




# Cystic Fibrosis: Utilizing Personalized Treatments and Addressing Health Disparities

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## Learning Objectives



At the end of this educational activity, participants should be able to:

- Describe CF and its different genetic etiologies.
- Explain how an individual's genetic profile can be utilized to develop a personalized CF treatment plan.
- Discuss the prevalence of CF in different racial and ethnic groups.
- Address health disparities among individuals with CF related to their socioeconomic status, residential geographic location and access to genetic evaluations and CF centers.
- Recognize other environmental factors that impact outcomes for individuals with CF.

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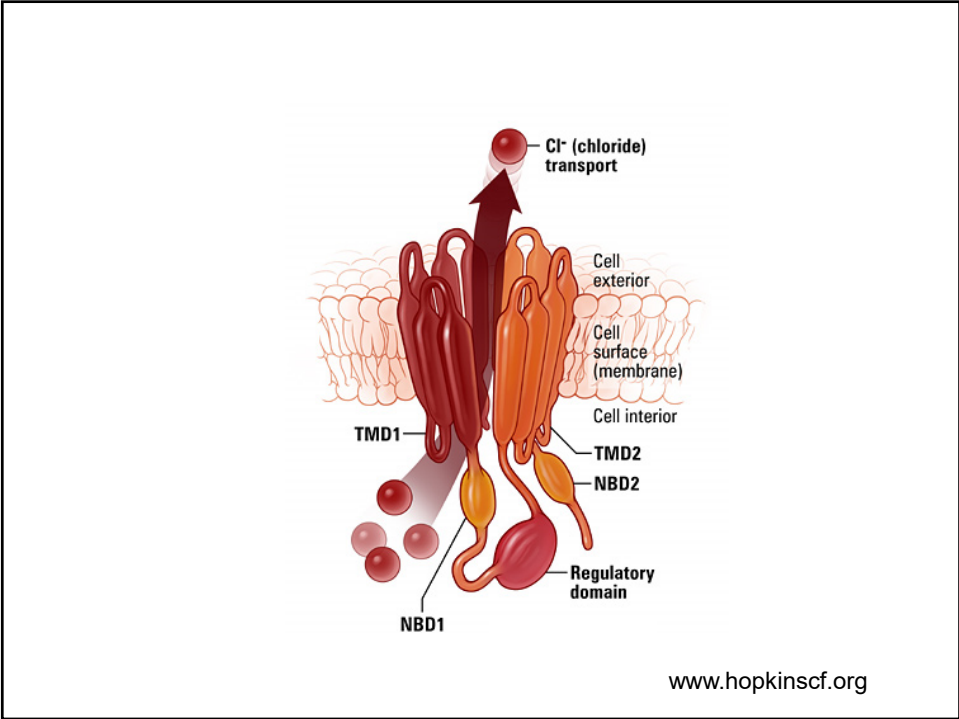
Peter J. Mogayzel, Jr, MD, PhD, MBA  
Menowitz/Rosenstein Professor of Pediatric Respiratory Sciences  
Johns Hopkins University School of Medicine  
Director, Eudowood Division of Pediatric Respiratory Sciences  
Director, Cystic Fibrosis Center  
Johns Hopkins Hospital

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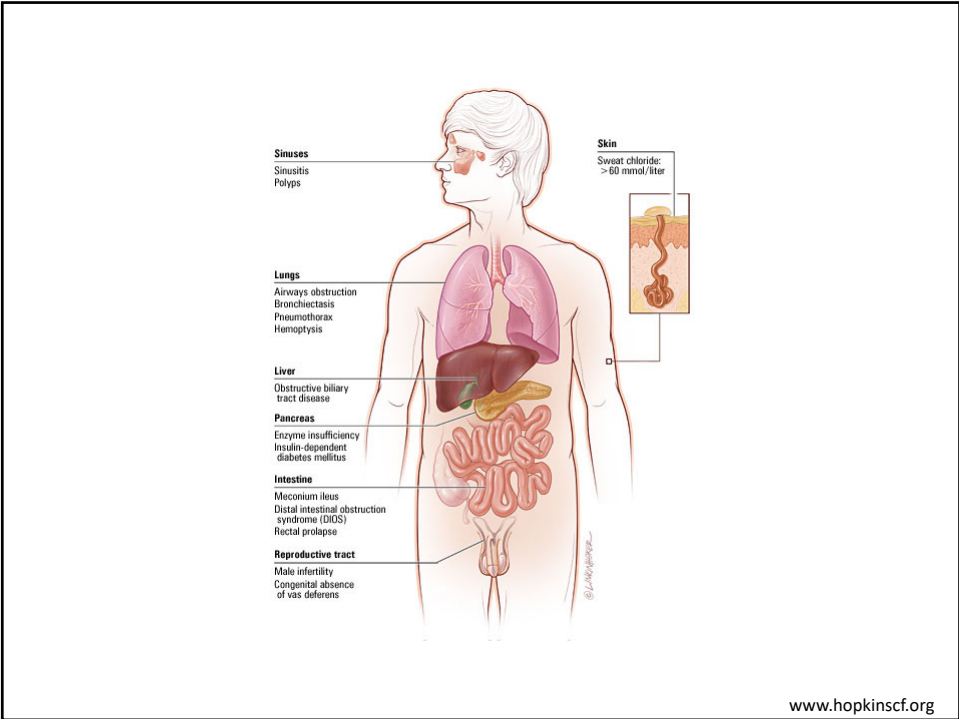
## Overview

- Cystic Fibrosis Pathogenesis
- Current Treatment
- Genetics
- Personalized Therapies
- Future Therapies

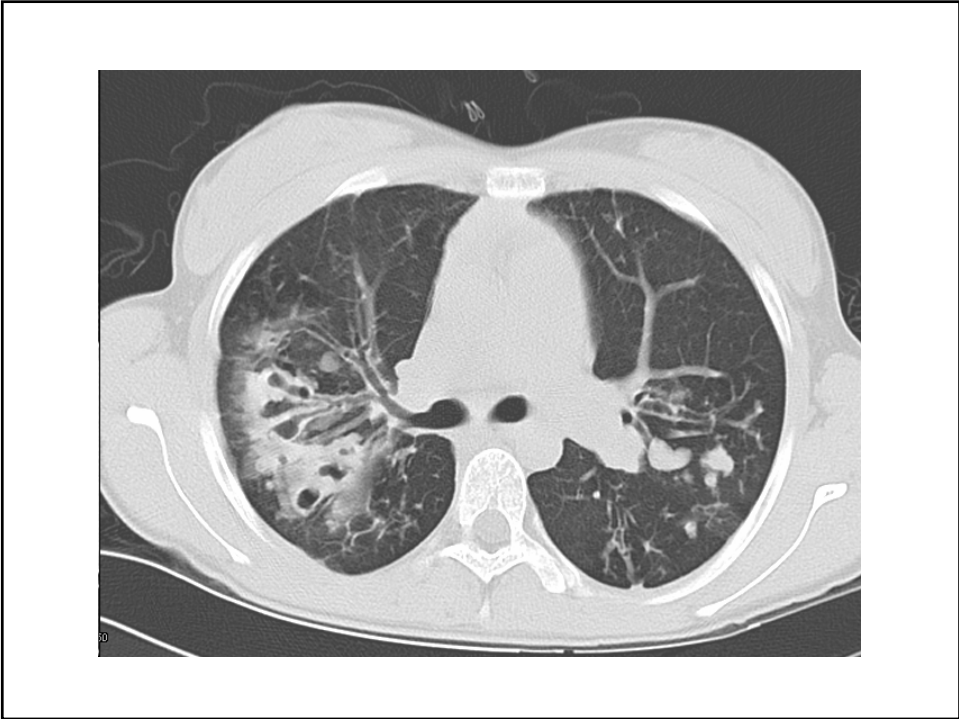
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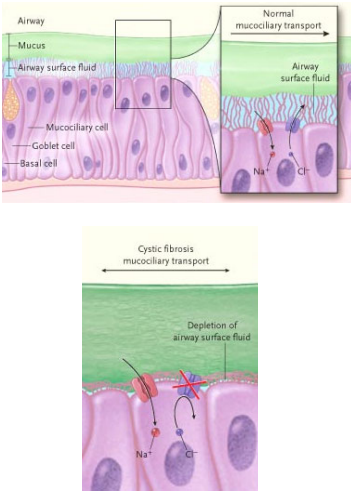


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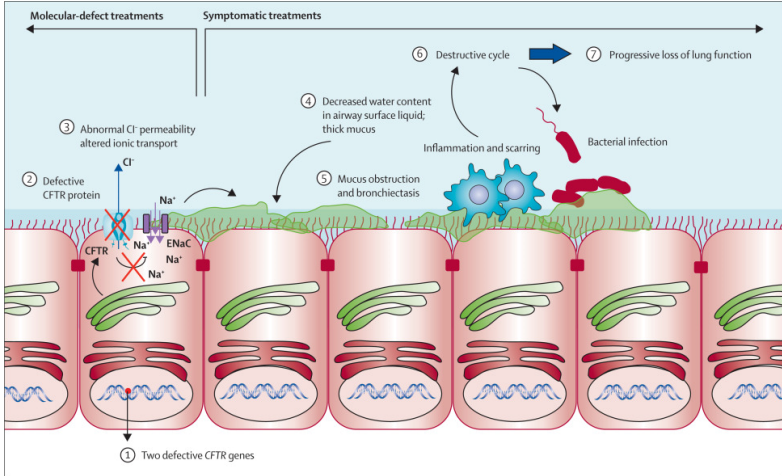
# Mucociliary Clearance



Ratjen, *New Engl J Med* 2006, 354: 291-293

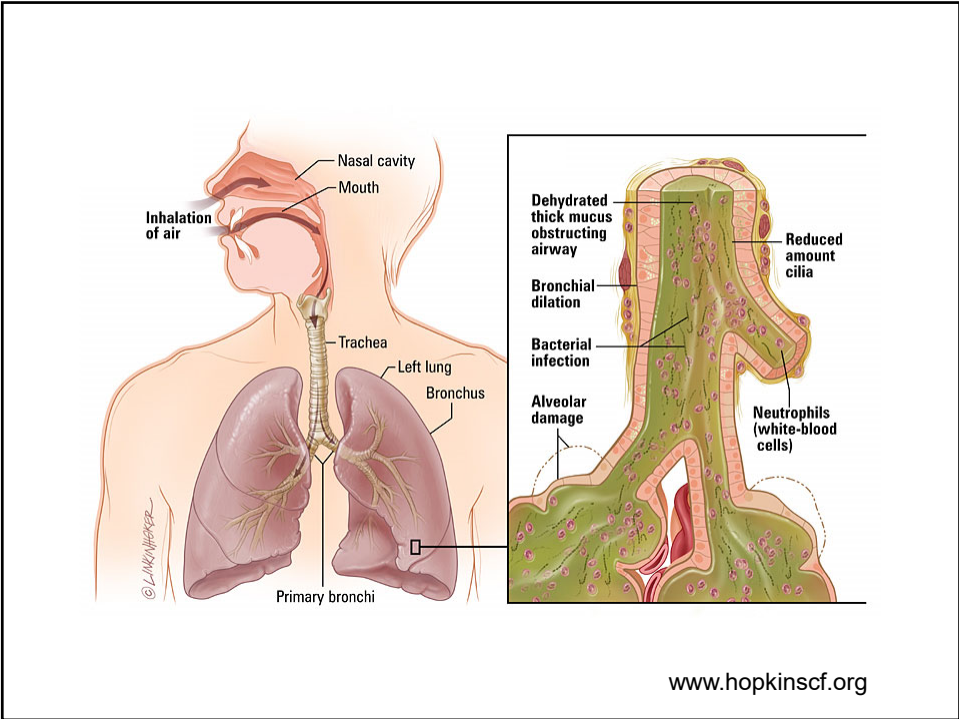
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# Therapeutic Mode of Action

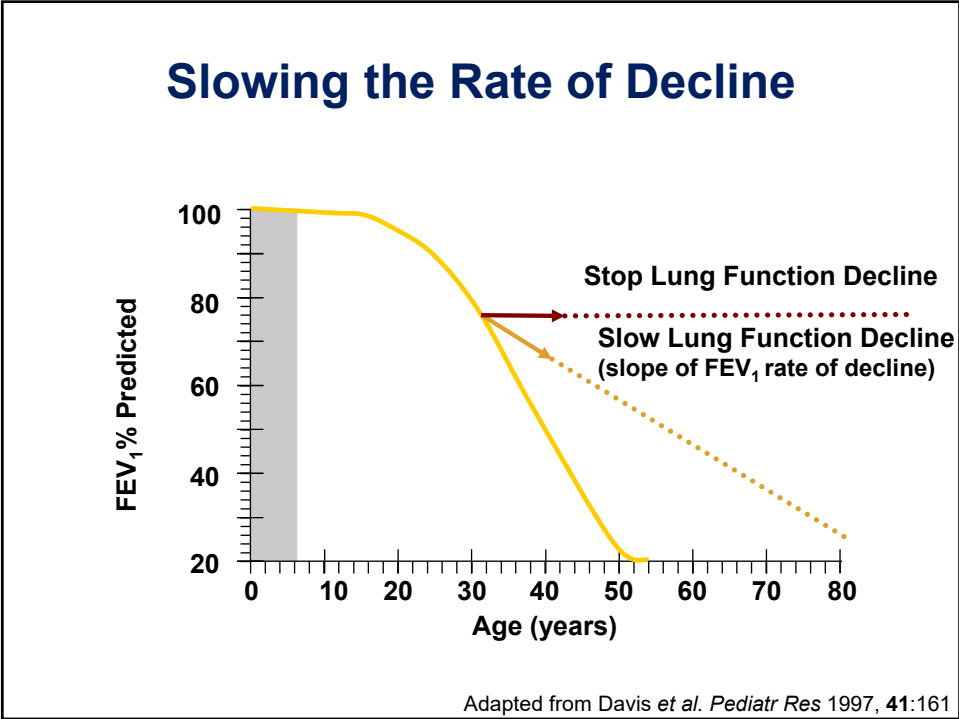


DeBoeck and Amaral. *Lancet Respiratory Medicine*. 2016;4(8):662-674

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### Pulmonary Therapies

- Airway Clearance
  - Manual percussion
  - Chest wall oscillation

Best wall oscillation

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## **Pulmonary Therapies**

- **Airway Clearance**
  - Manual percussion
  - PEP devices
  - High-frequency chest wall oscillation
- **Mucoactive Agents**
  - **Dornase alfa (rhDNase)**
  - **Hypertonic saline**
  - **Mannitol**

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## **Pulmonary Therapies**

- **Airway Clearance**
  - Manual percussion
  - PEP devices
  - High-frequency chest wall oscillation
- **Mucoactive Agents**
  - Dornase alfa (rhDNase)
  - Hypertonic saline
  - Mannitol
- **Inhaled Antibiotics**
  - **Tobramycin**
  - **Aztreonam**
  - **Colistin**

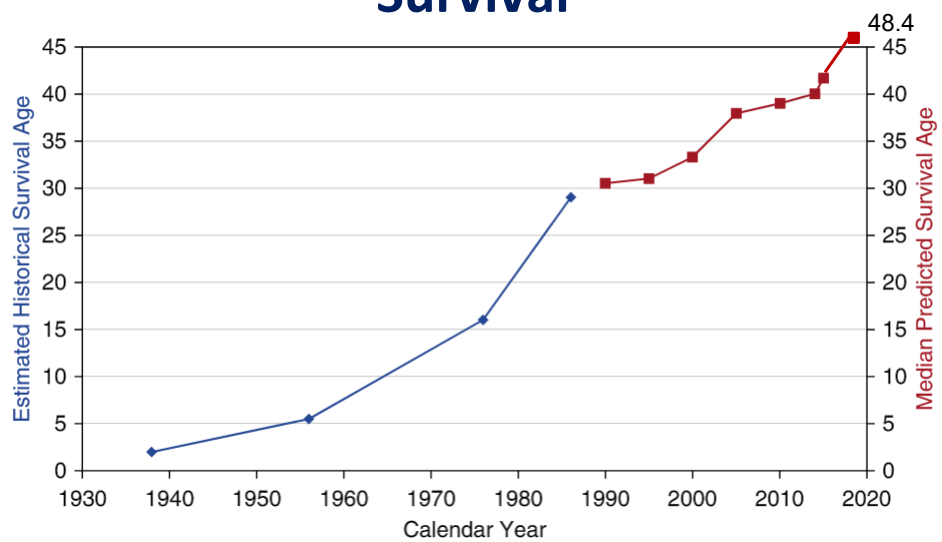
14

## Pulmonary Therapies

- Airway Clearance
  - Manual percussion
  - PEP devices
  - High-frequency chest wall oscillation
- Mucoactive Agents
  - Dornase alfa (rhDNase)
  - Hypertonic saline
- Inhaled Antibiotics
  - Tobramycin
  - Aztreonam
  - Colistin
  - Mannitol
- **Anti-inflammatory**
  - **Ibuprofen**
  - **Azithromycin**

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## Survival

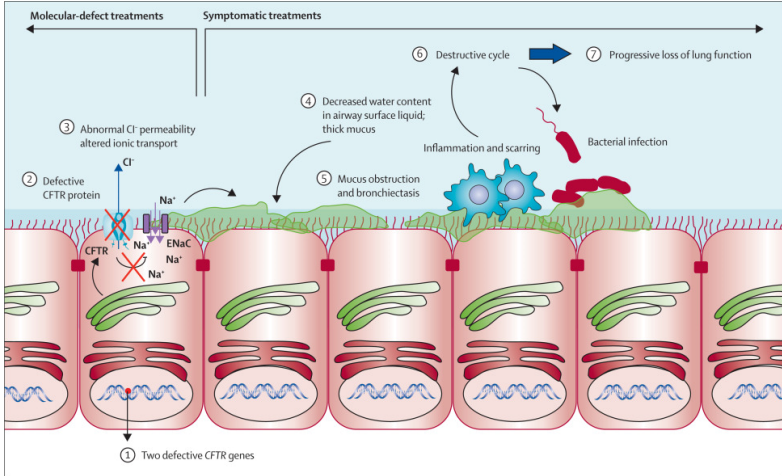


Adapted from Ramsey & Welsh. *Am J Respir Crit Care Med* 2017;195(9):1092-1099

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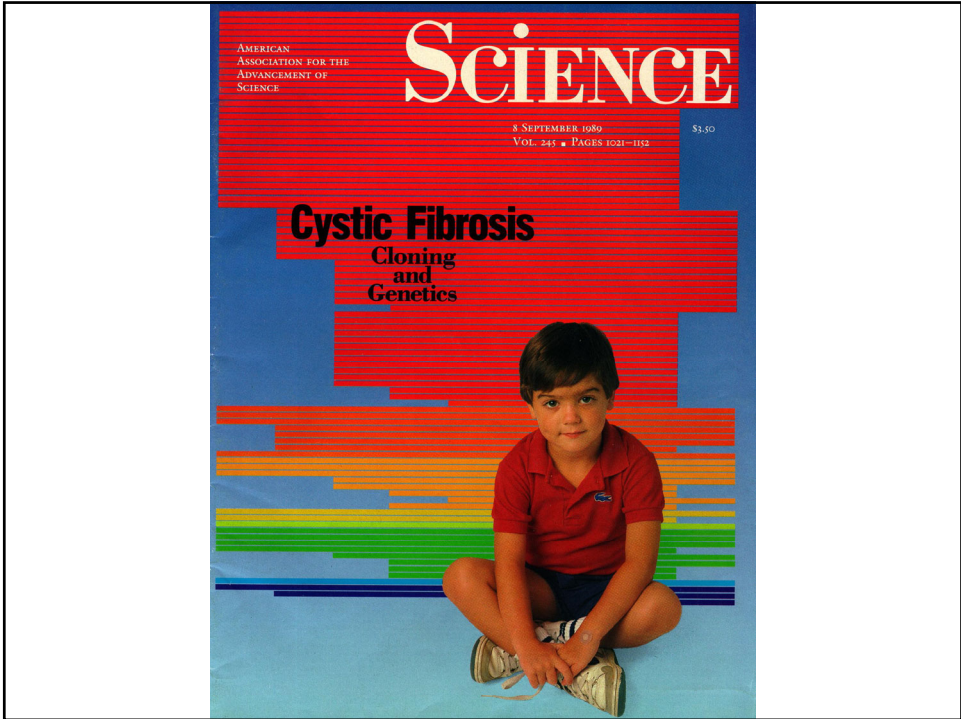


# Therapeutic Mode of Action



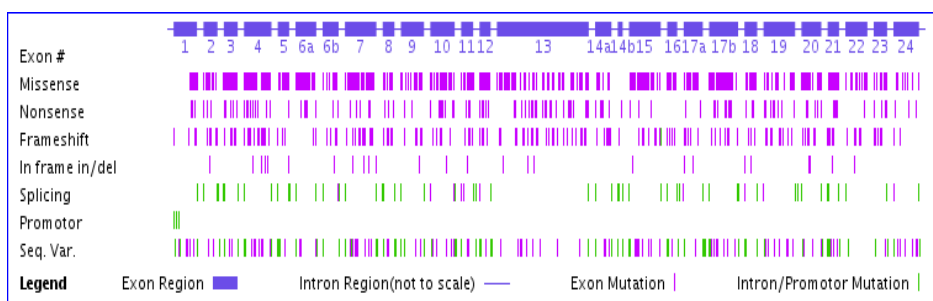
DeBoeck and Amaral. *Lancet Respiratory Medicine*. 2016;4(8):662-674

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## 2103 CFTR Mutations



www.genet.sickkids.on.ca/cftr - 1/26/2021

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## CFTR Mutations

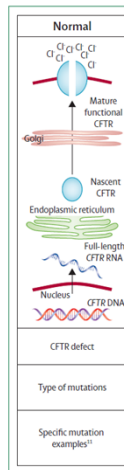
CFTR Mutation			Number of Individuals	Percent of Individuals
Legacy Name	cDNA Name	Protein Name		
F508del	c.1521_1523delCTT	p.Phe508del	26,626	85.3
G542X	c.1624G>T	p.Gly542X	1,418	4.5
G551D	c.1652G>A	p.Gly551Asp	1,365	4.4
R117H	c.350G>A	p.Arg117His	983	3.2
N1303K	c.3909C>G	p.Asn1303Lys	736	2.4
W1282X	c.3846G>A	p.Trp1282X	701	2.2
3849+10kbC->T	c.3718-2477C>T		573	1.8
R553X	c.1657C>T	p.Arg553X	548	1.8
1717-1G->A	c.1585-1G>A		498	1.6
621+1G->T	c.489+1G>T		493	1.6
2789+5G->A	c.2657+5G>A		456	1.5
3120+1G->A	c.2988+1G>A		377	1.2
D1152H	c.3454G>C	p.Asp1152His	321	1.0
5T	c.1210-12T[5]		307	1.0

44.4% - F508del / F508del  
40.8% - F508del / Other  
14.7% - Other / Other

CFF Patient Registry - 2019

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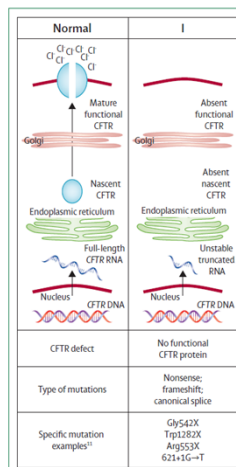
# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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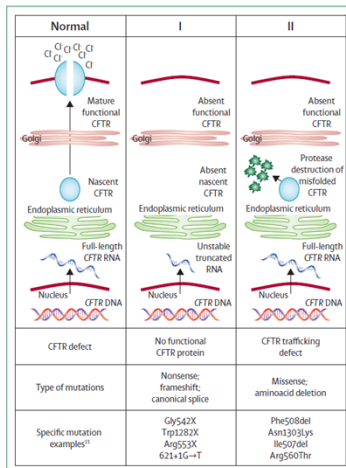
# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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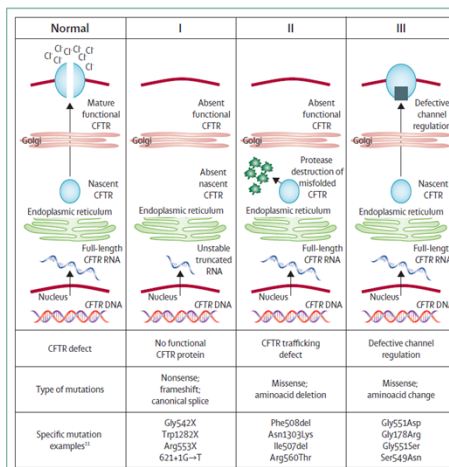
# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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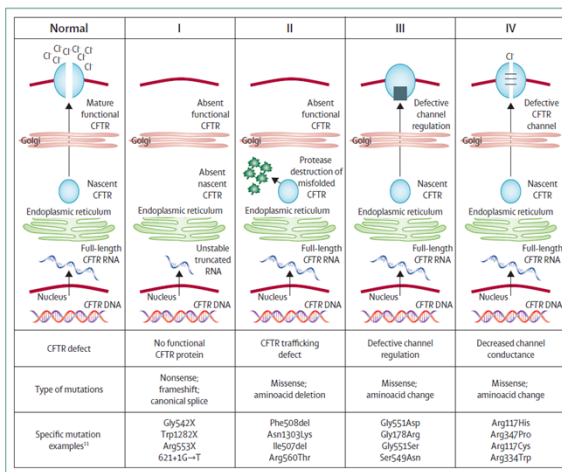
# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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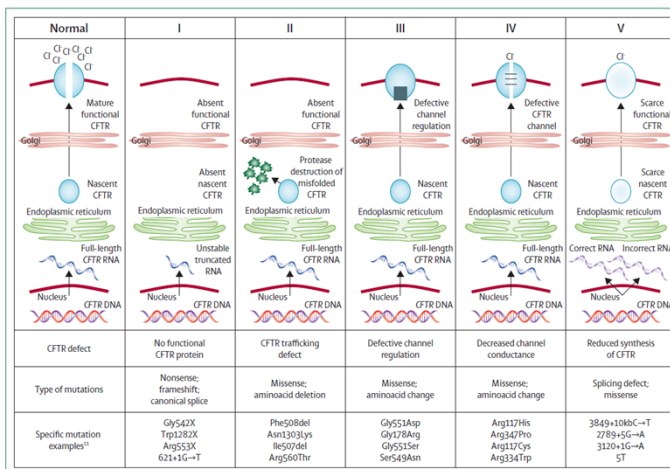
# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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# CFTR Mutation Classes



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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# CFTR Mutation Classes

Normal	I	II	III	IV	V	VI
<b>CFTR defect</b>	No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
<b>Type of mutations</b>	Nonsense; frameshift; canonical splice	Misense; aminoacid deletion	Misense; aminoacid change	Misense; aminoacid change	Splicing defect; missense	Misense; aminoacid change
<b>Specific mutation examples<sup>9</sup></b>	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly78Arg Gly551Ser Ser494Asn	Arg17His Arg347Pro Arg17Cys Arg334Trp	3849+104bc→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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# CFTR Mutation Classes

Normal	I	II	III	IV	V	VI
<b>CFTR defect</b>	No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
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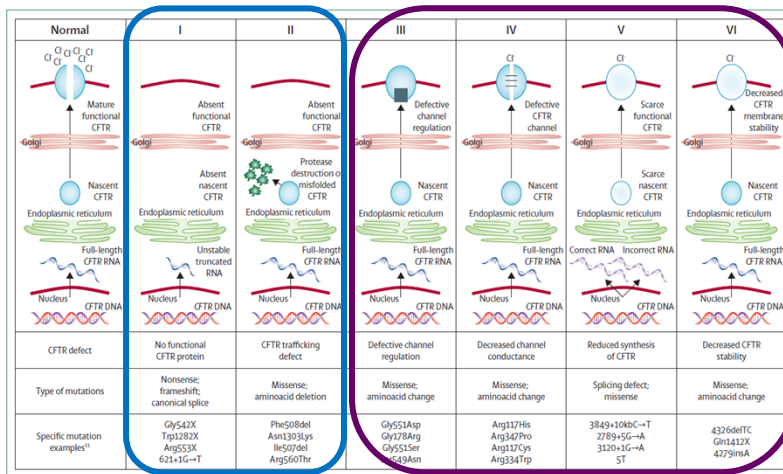
**Minimal Function**

**Residual Function**

Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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# CFTR Mutation Classes



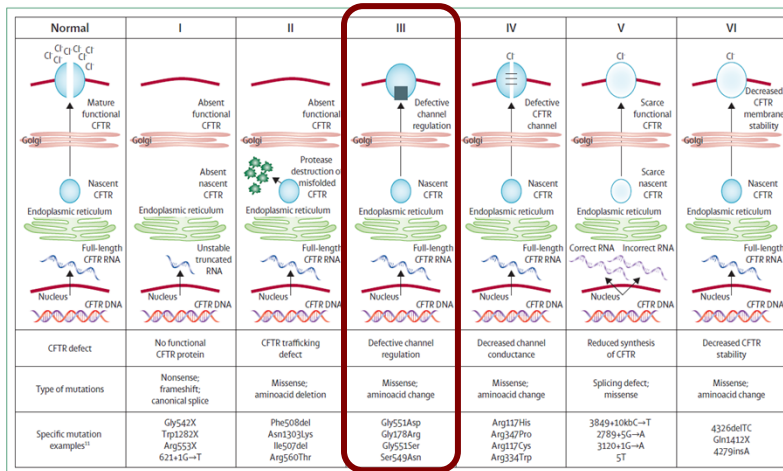
No CFTR at Surface

CFTR at the Surface

Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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# G551D



Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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*The* **NEW ENGLAND**  
**JOURNAL** *of* **MEDICINE**

ESTABLISHED IN 1812      NOVEMBER 3, 2011      VOL. 365 NO. 18

**A CFTR Potentiator in Patients  
with Cystic Fibrosis and the G551D Mutation**

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McElvaney, M.D., Elizabeth Tullis, M.D.,  
Scott C. Bell, M.B., B.S., M.D., Pavel Dřevinek, M.D., Matthias Griese, M.D., Edward F. McKone, M.D.,  
Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D.,  
Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, Ph.D.,  
Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group<sup>‡</sup>

**A**

Time Point	Ivacaftor (N)	Placebo (N)
Day 15	~10 (N=83)	~0 (N=76)
Wk 8	~10 (N=83)	~0 (N=75)
Wk 16	~10 (N=81)	~0 (N=71)
Wk 24	~10 (N=80)	~0 (N=71)
Wk 32	~10 (N=79)	~0 (N=70)
Wk 40	~10 (N=79)	~0 (N=69)
Wk 48	~10 (N=77)	~0 (N=68)

**B**

Week	Ivacaftor	Placebo
0	1.00	1.00
24	0.78	0.51
48	0.67	0.41

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## Ivacaftor – Sweat Chloride

**A**

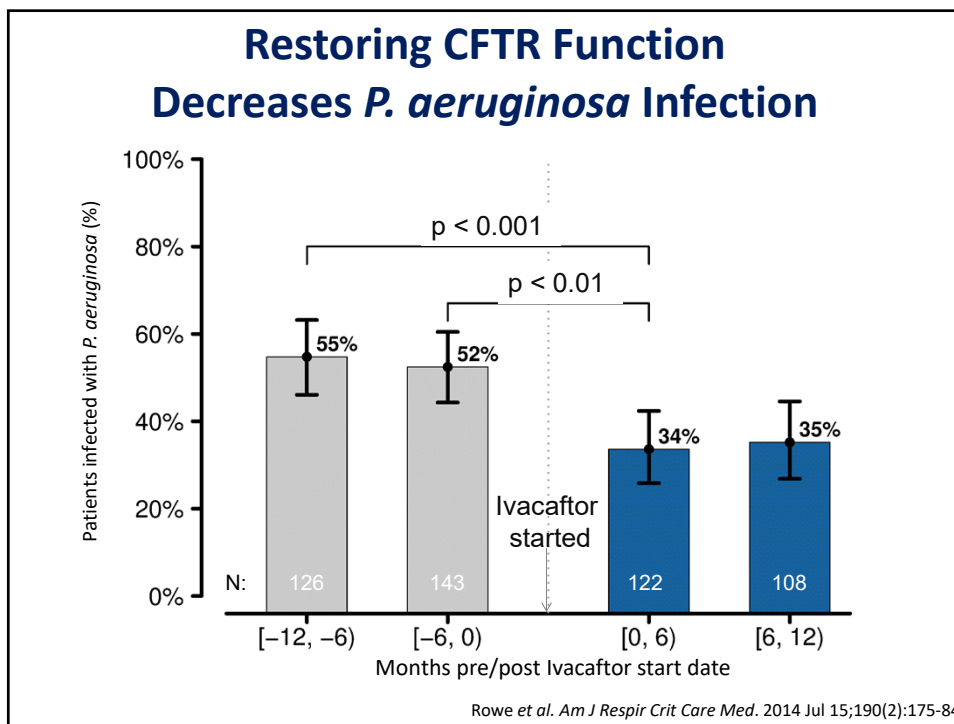
Time Point	Ivacaftor (N)	Placebo (N)
Day 15	~-45 (N=70)	~0 (N=74)
Wk 8	~-45 (N=70)	~0 (N=76)
Wk 16	~-45 (N=65)	~0 (N=71)
Wk 24	~-45 (N=66)	~0 (N=69)
Wk 32	~-45 (N=61)	~0 (N=71)
Wk 40	~-45 (N=63)	~0 (N=73)
Wk 48	~-45 (N=62)	~0 (N=72)

N=144

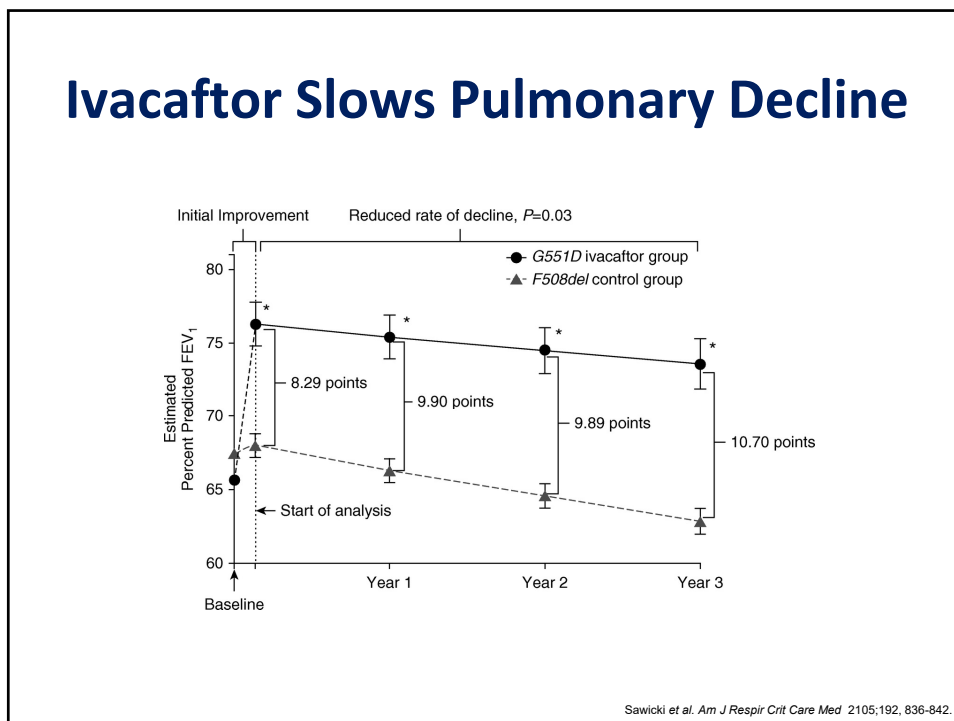
Ramsey BW et al. *N Engl J Med* 2011;365:1663-1672

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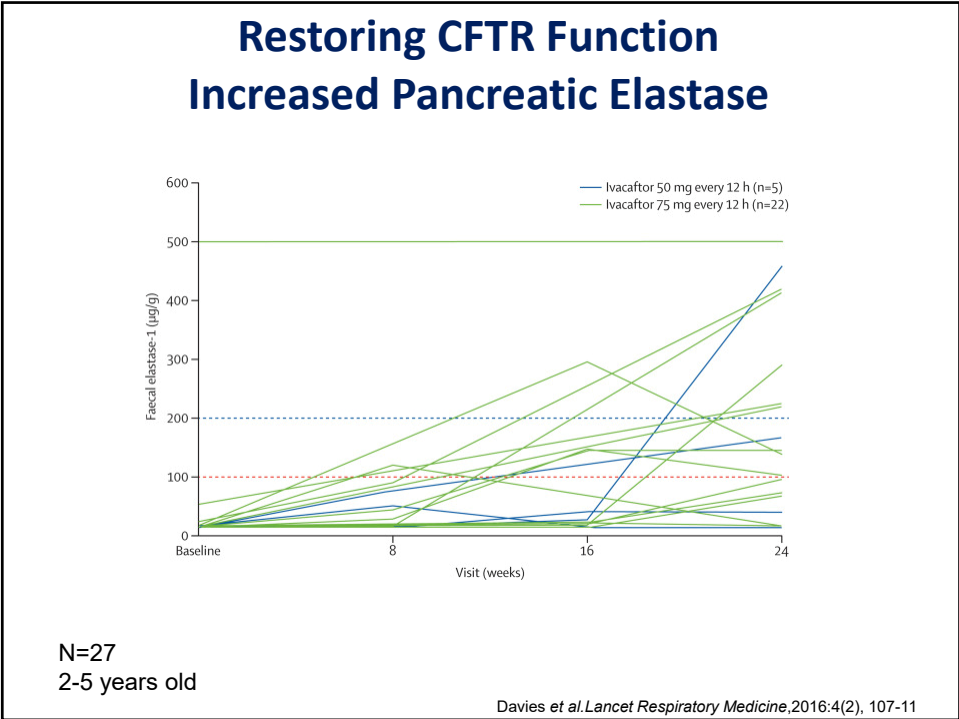
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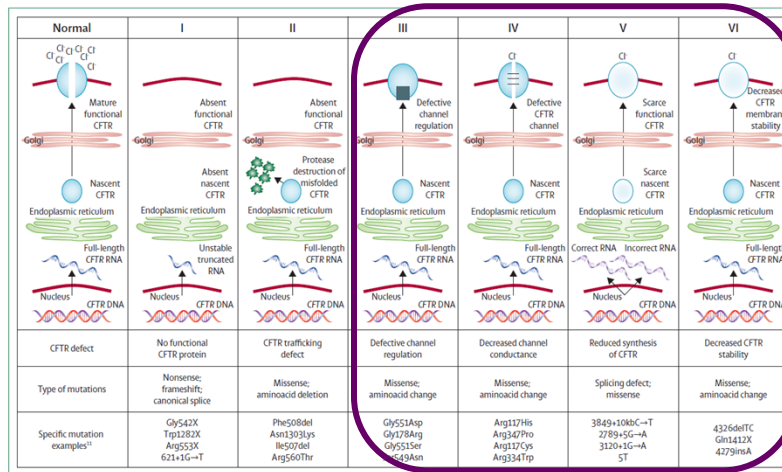


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# CFTR Mutation Classes



## CFTR at the Surface

Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

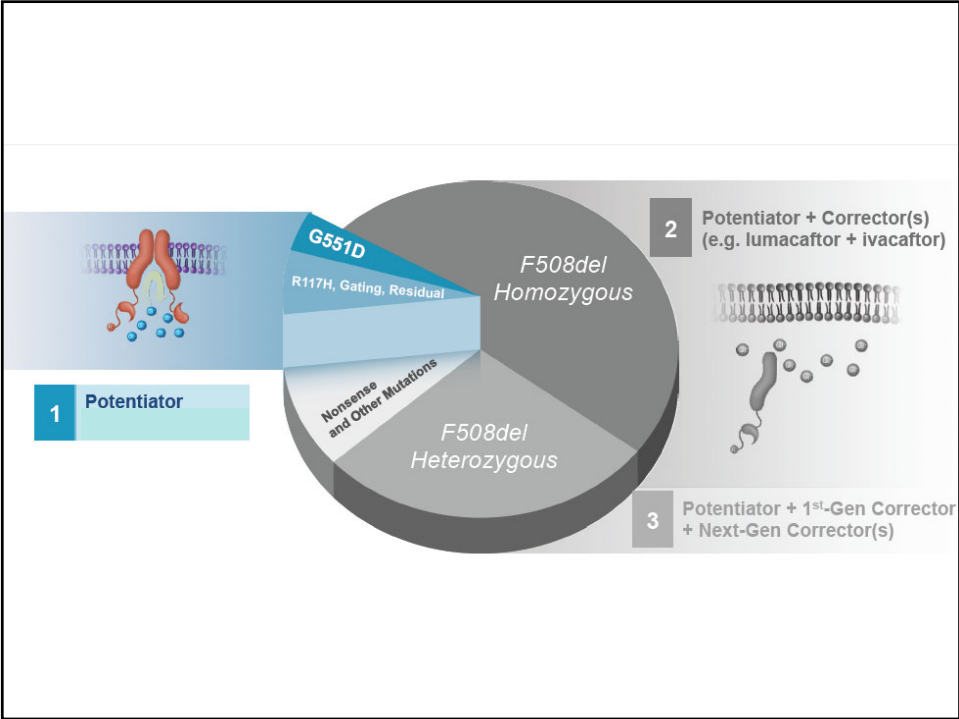
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# Ivacaftor FDA Indication

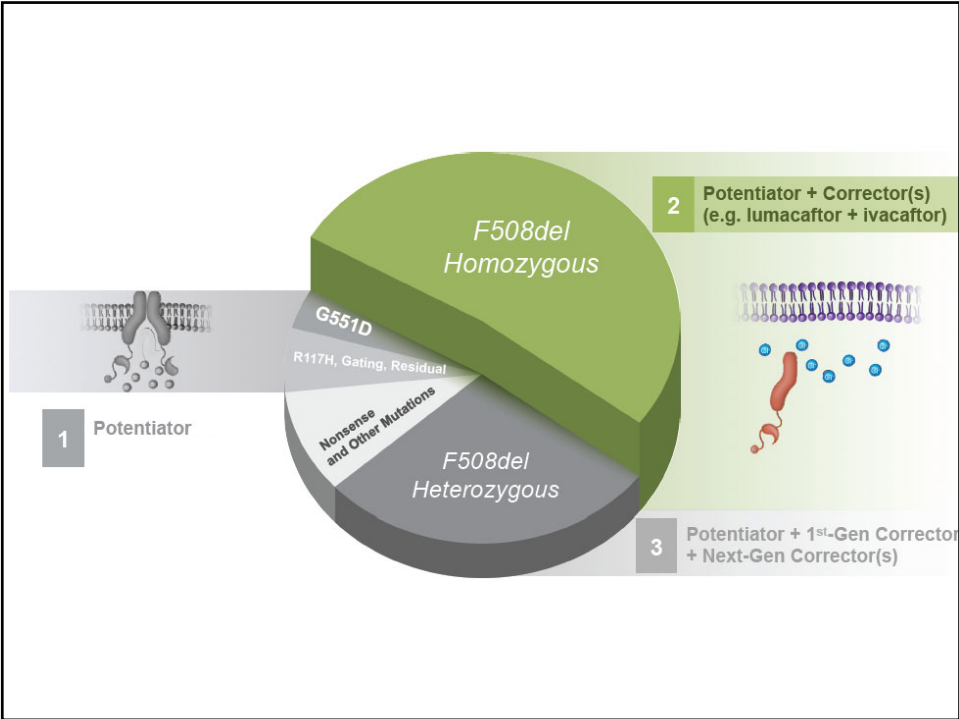
## INDICATIONS AND USAGE

KALYDECO is a cystic fibrosis transmembrane conductance regulator (CFTR) potentiator indicated for the treatment of cystic fibrosis (CF) in patients age 4 months and older who have one mutation in the CFTR gene that is responsive to ivacaftor based on clinical and/or in vitro assay data.

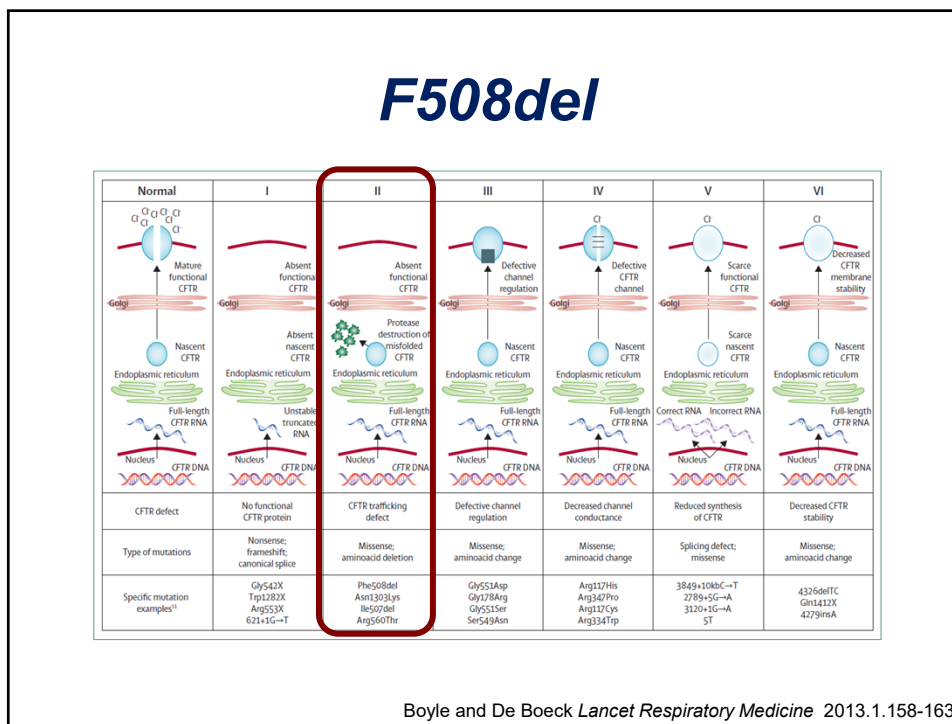
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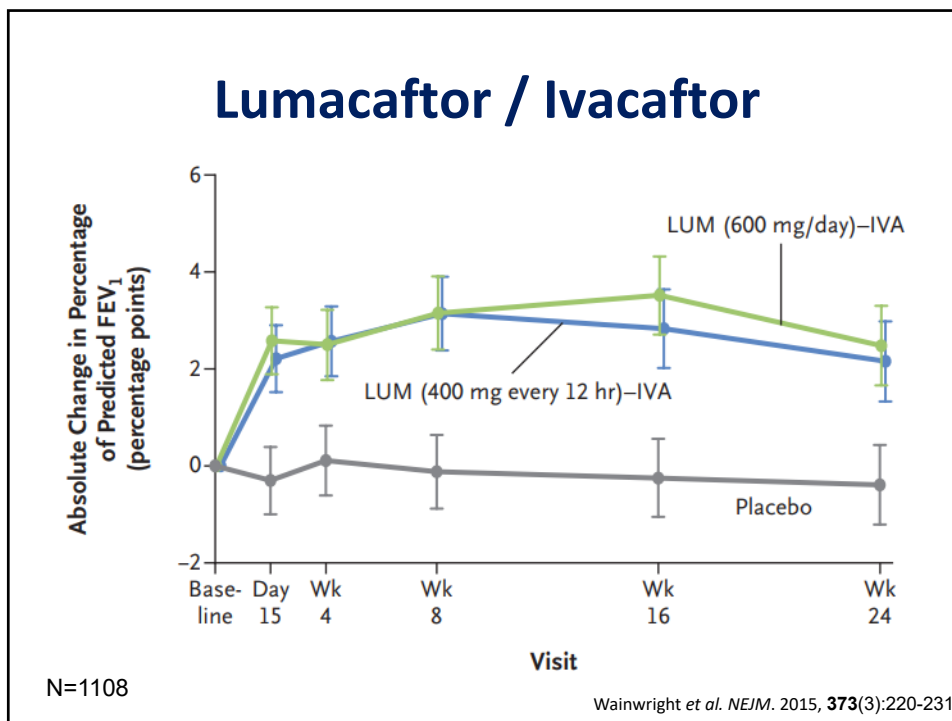
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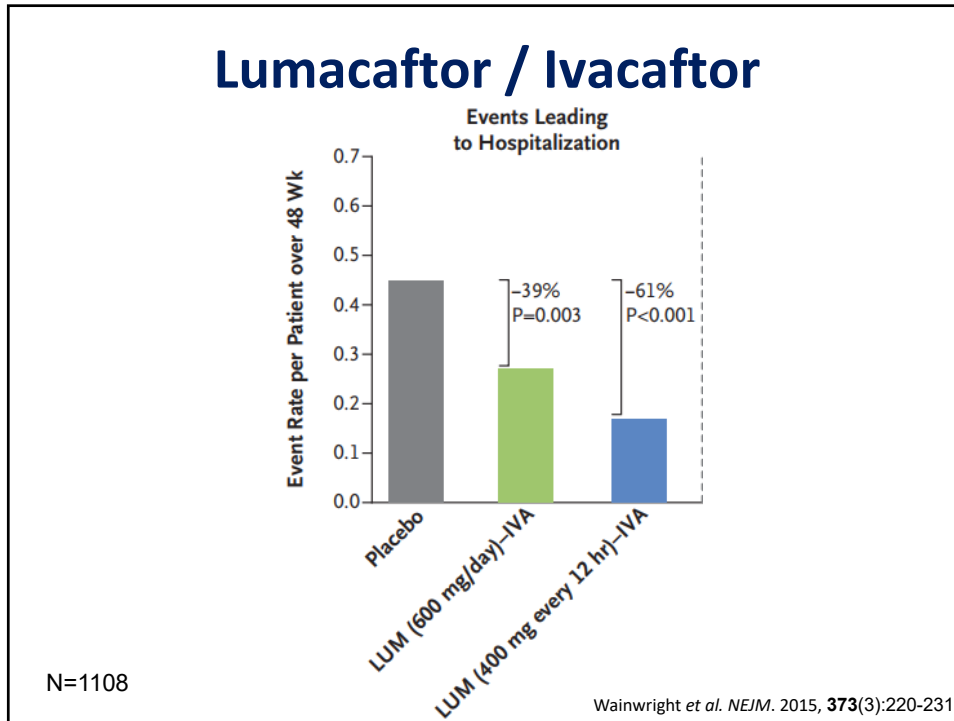
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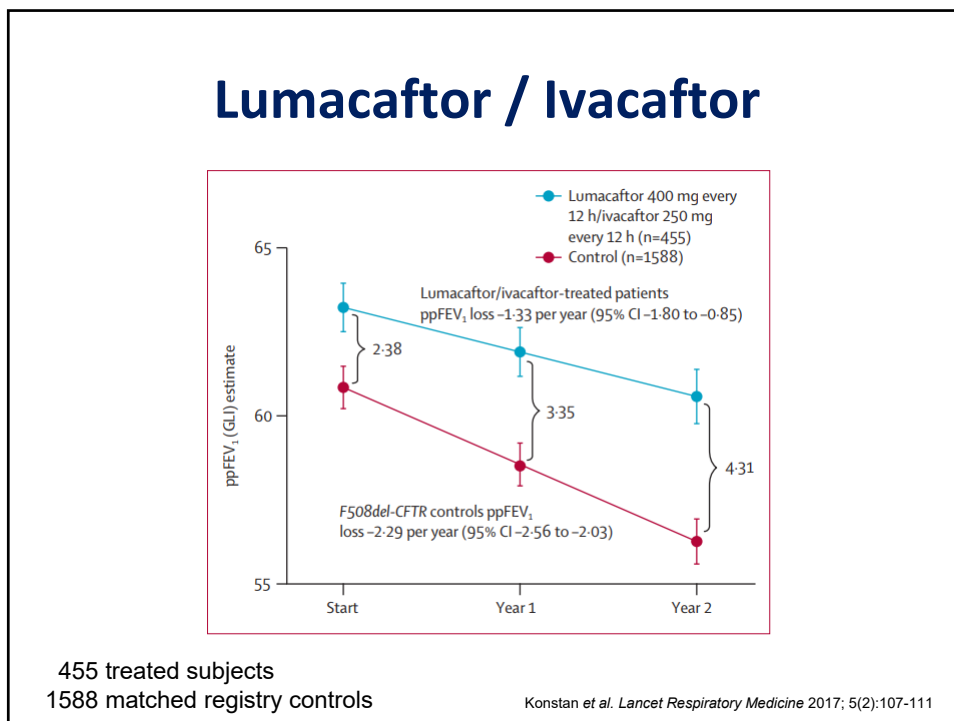
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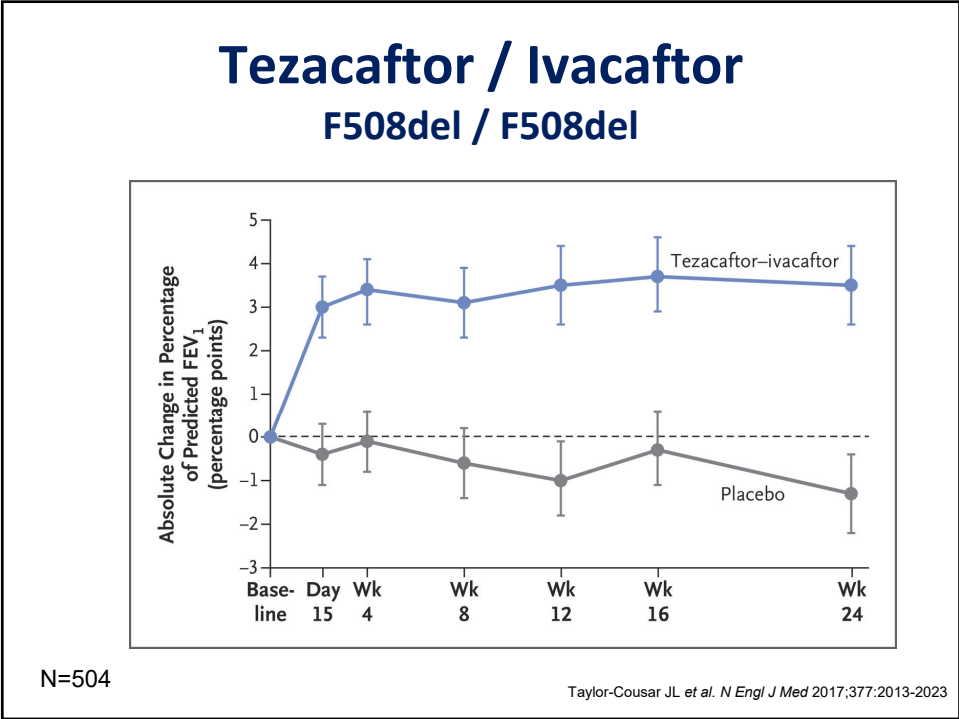
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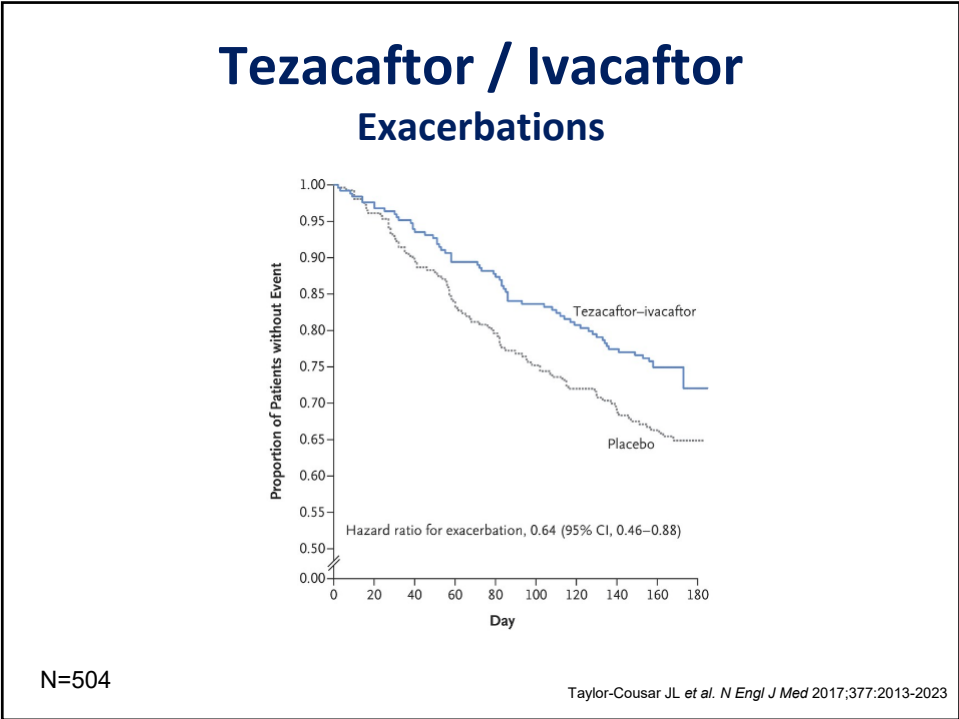
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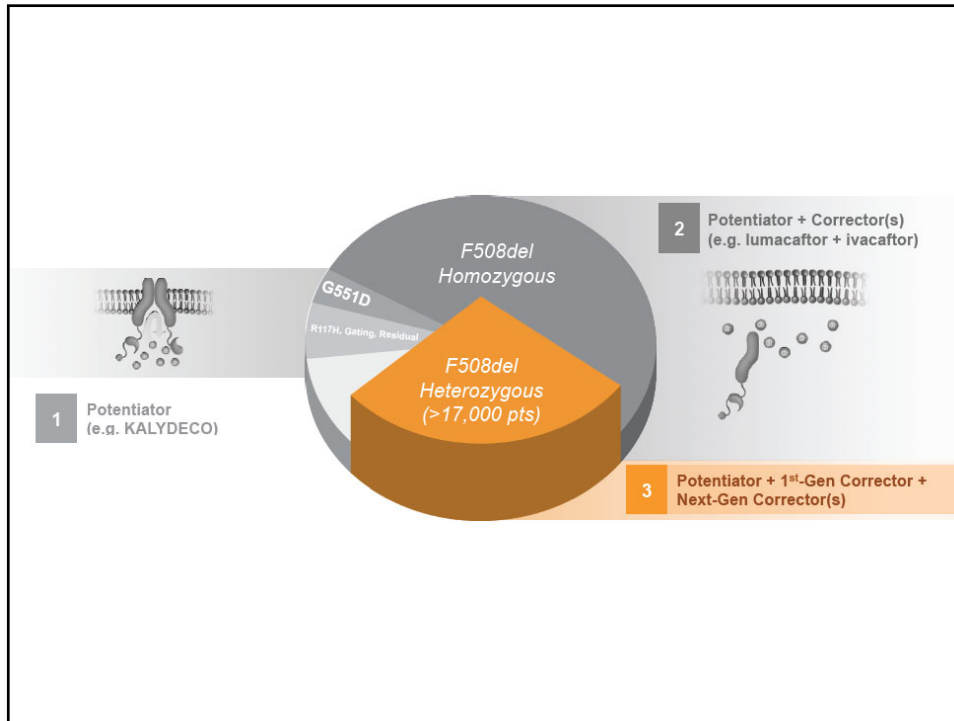
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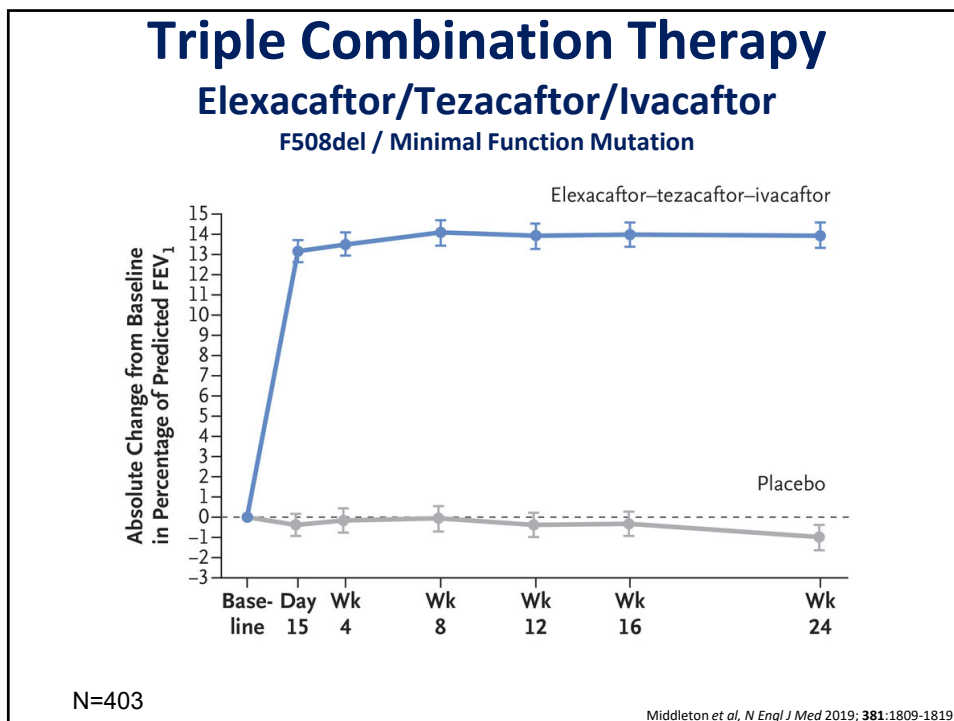
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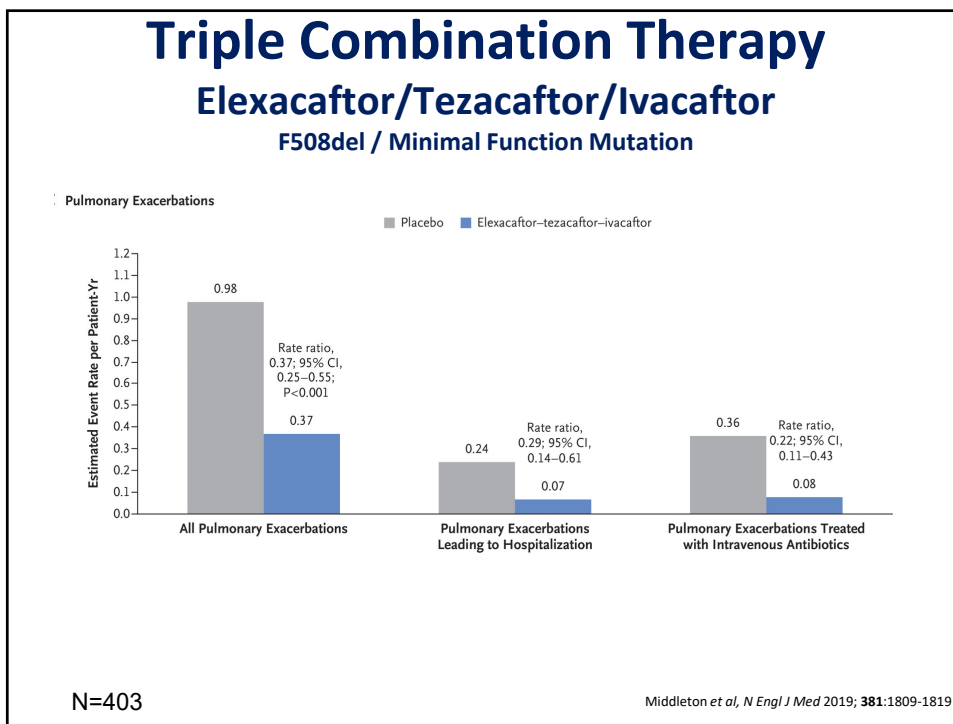


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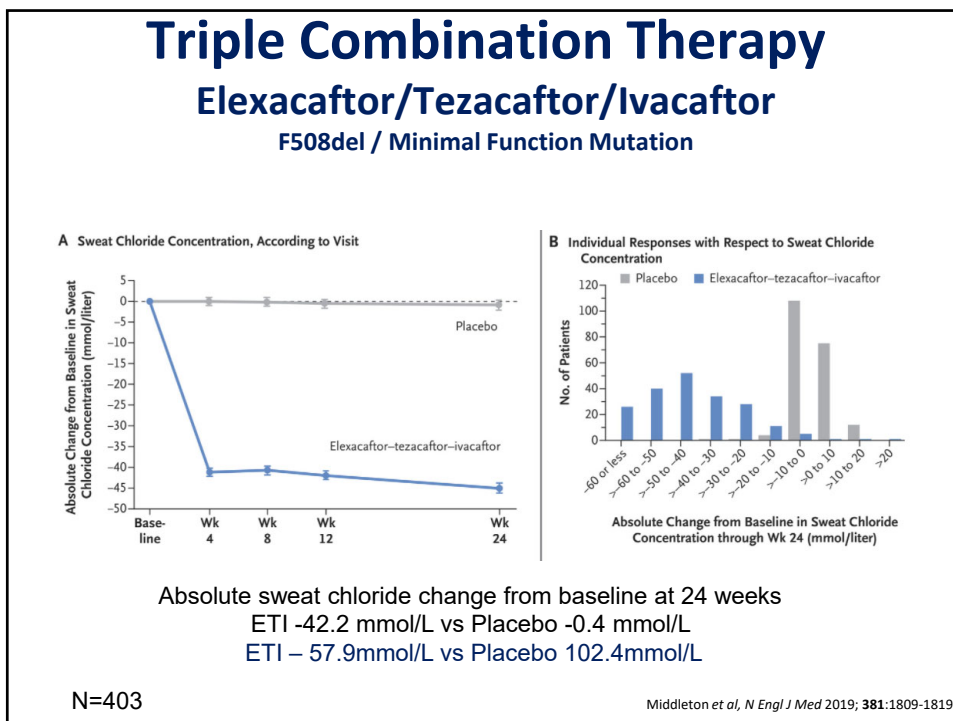


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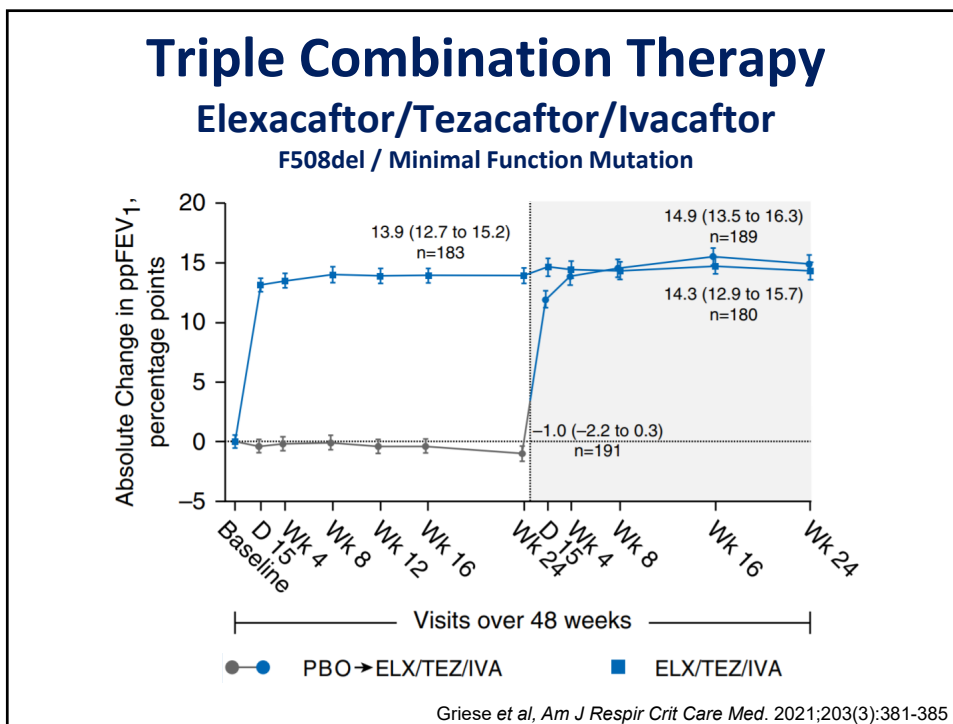




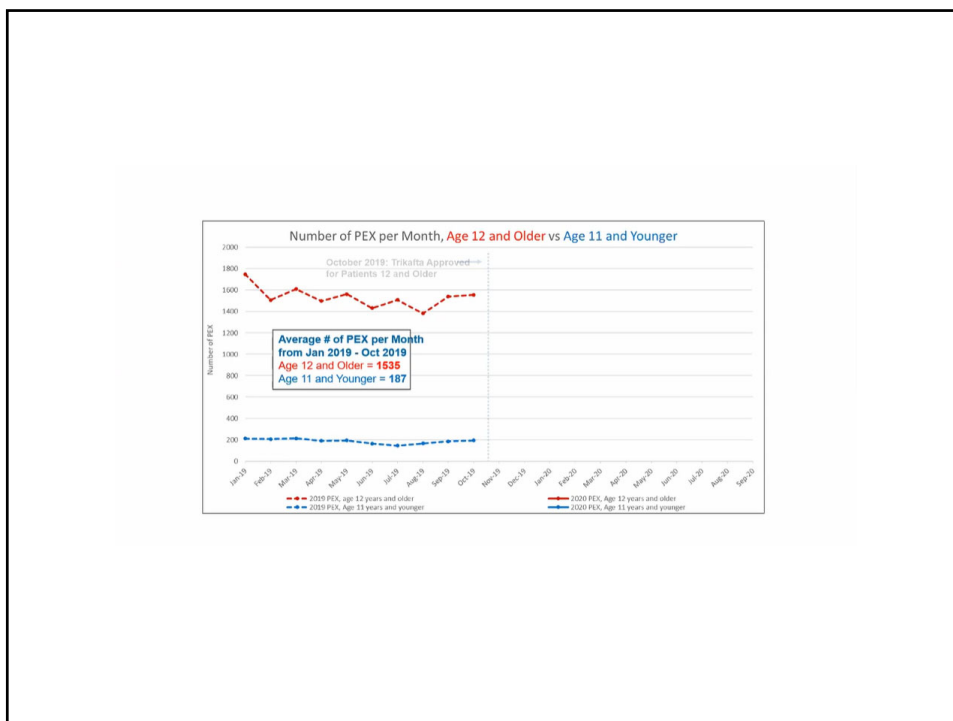
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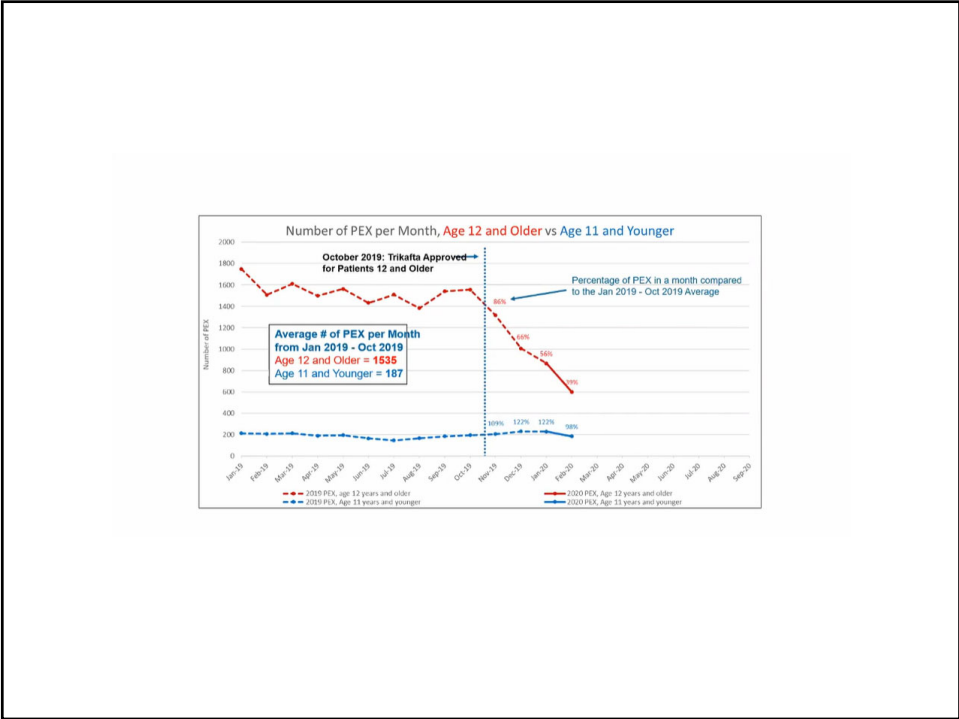
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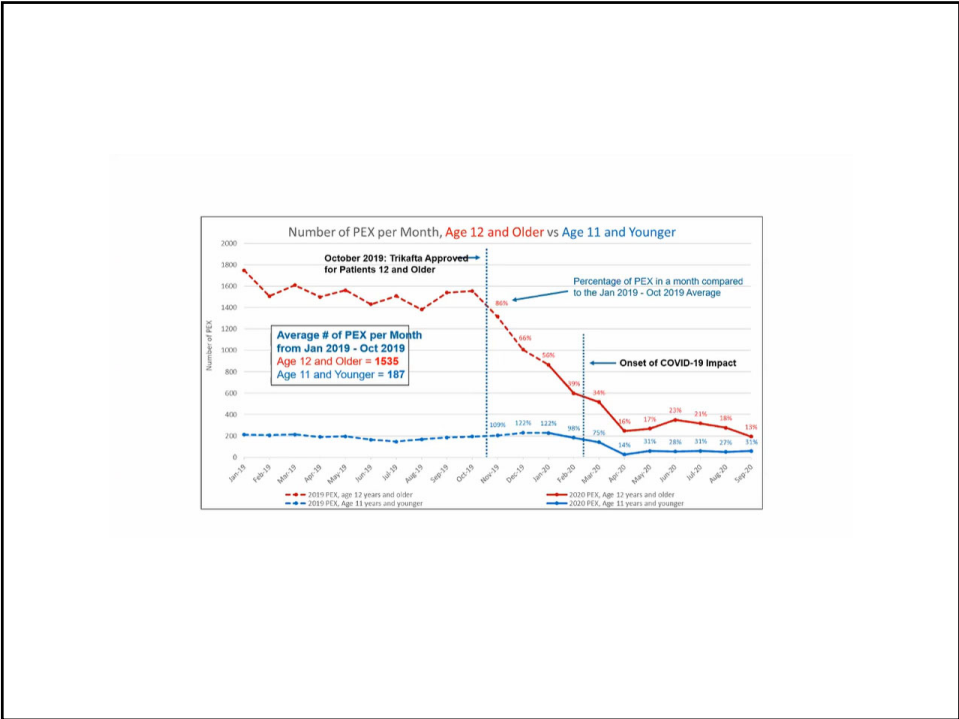
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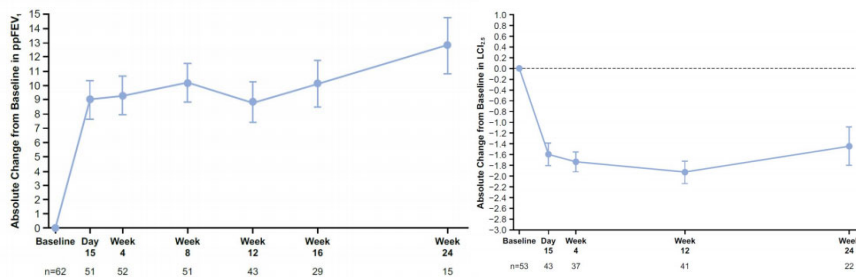


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## Elexacaftor/Tezacaftor/Ivacaftor 6-11 Year Olds



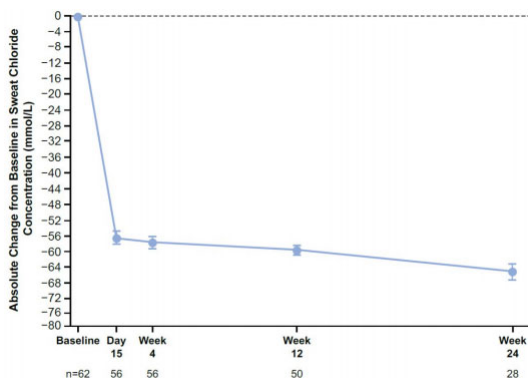
Mean change 10.2 (7.6-12.6)  
at 24 weeks

Mean change -1.71 (-2.11 to -1.30)  
at 24 weeks

*Zemanick et al. Am J Respir Crit Care Med*  
2021 Mar 18. doi: 10.1164/rccm.202102-0509OC.

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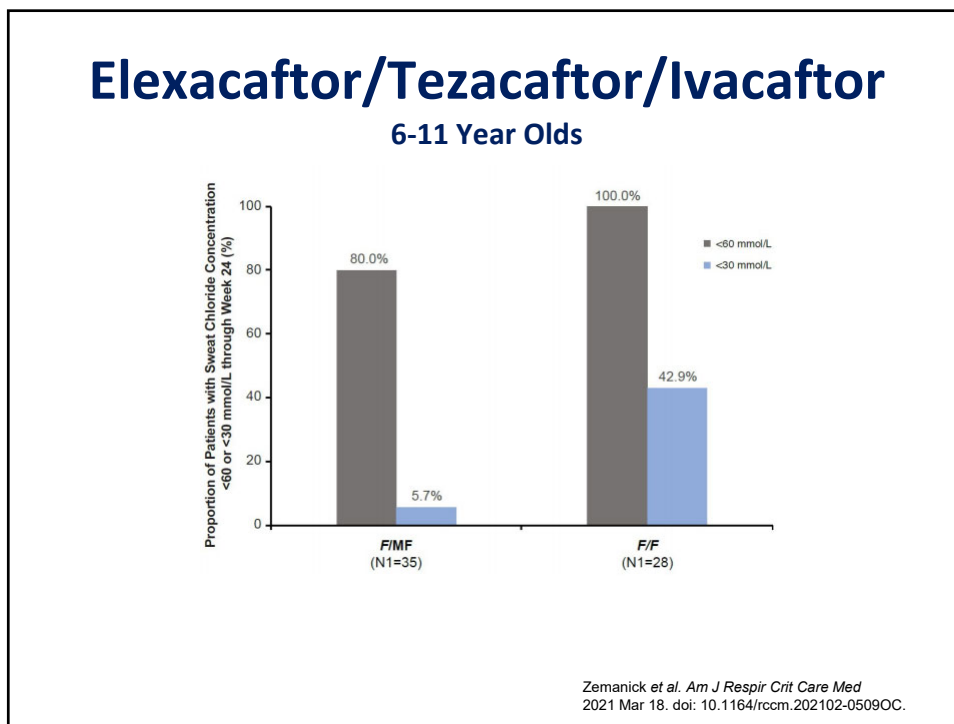
## Elexacaftor/Tezacaftor/Ivacaftor 6-11 Year Olds



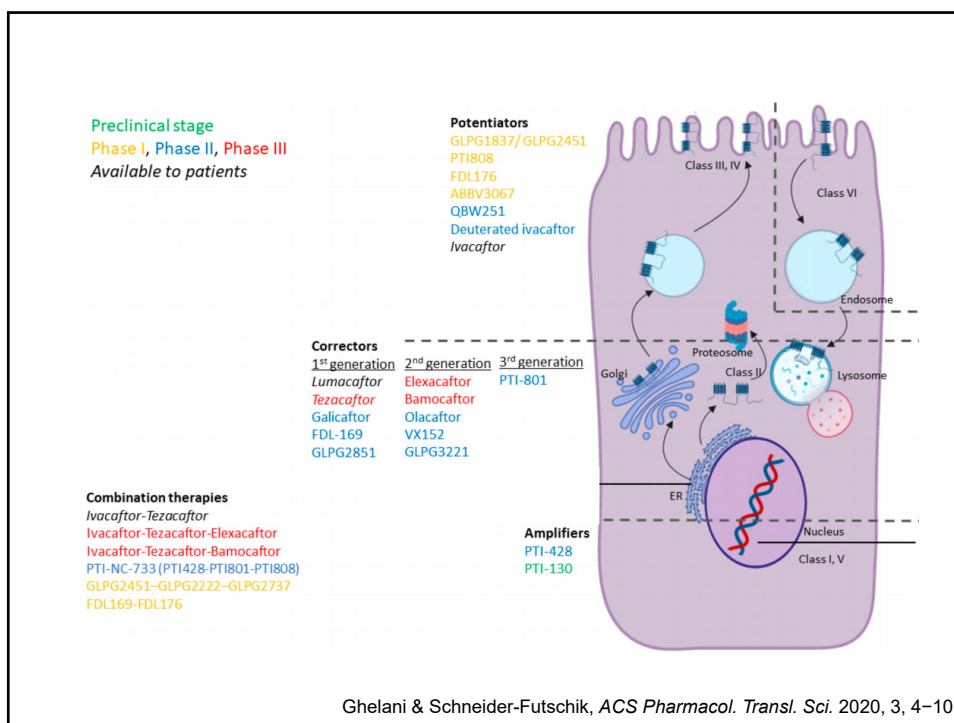
Mean change -60.9 mmol/L  
Final value mean 41.3 mmol/L

*Zemanick et al. Am J Respir Crit Care Med*  
2021 Mar 18. doi: 10.1164/rccm.202102-0509OC.

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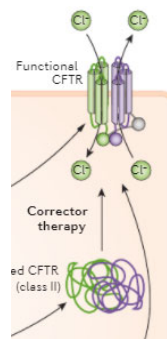


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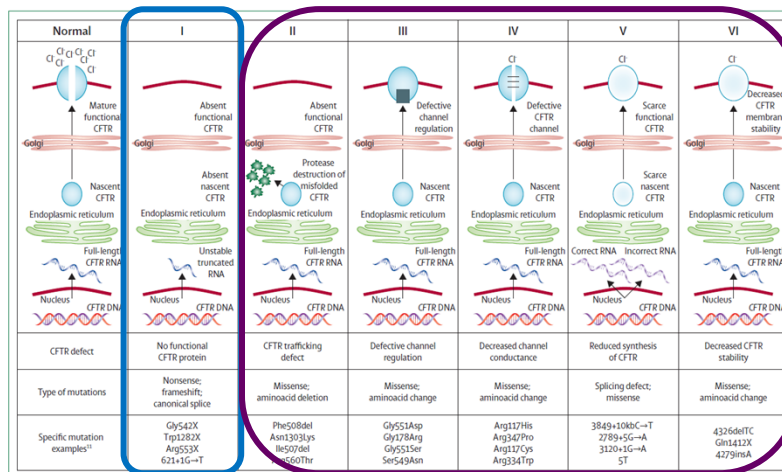
## CFTR Modulators



Ratjen et al. *Nature Reviews* 2015;1(1)1-19

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## CFTR Mutation Classes



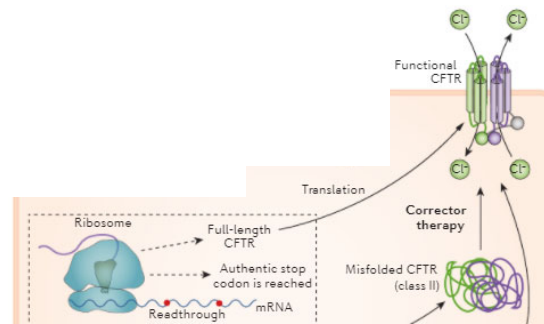
No CFTR protein

CFTR is produced

Boyle and De Boeck *Lancet Respiratory Medicine* 2013.1.158-163

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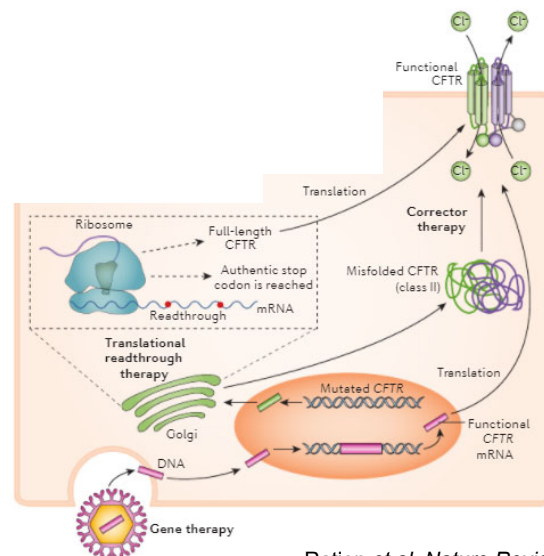
## Read Through & mRNA



Ratjen *et al. Nature Reviews* 2015;1(1)1-19

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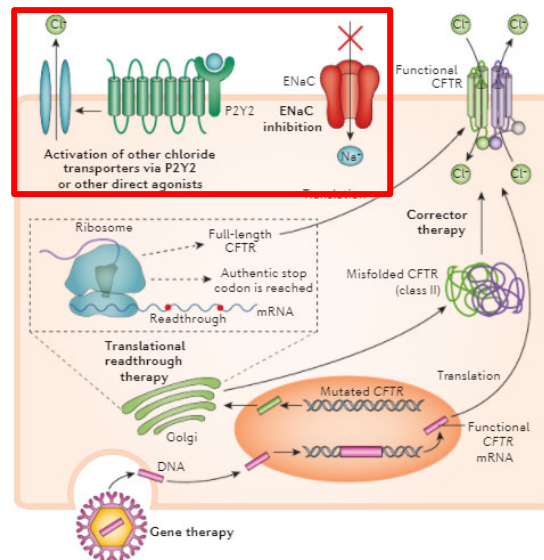
## Gene Therapy & DNA repair



Ratjen *et al. Nature Reviews* 2015;1(1)1-19

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## Alternative Ion Channels



Ratjen *et al.* *Nature Reviews* 2015;1(1)1-19

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## Summary

- Personalized therapies are available for people with CF
- Highly effective modulators can slow disease progression
- Novel approaches are under development for nonsense mutations
- Early intervention has the potential to prevent the manifestations of CF

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Michael J. Collaco, MD, MS, MBA, MPH, PhD  
Associate Professor of Pediatrics  
Johns Hopkins University School of Medicine

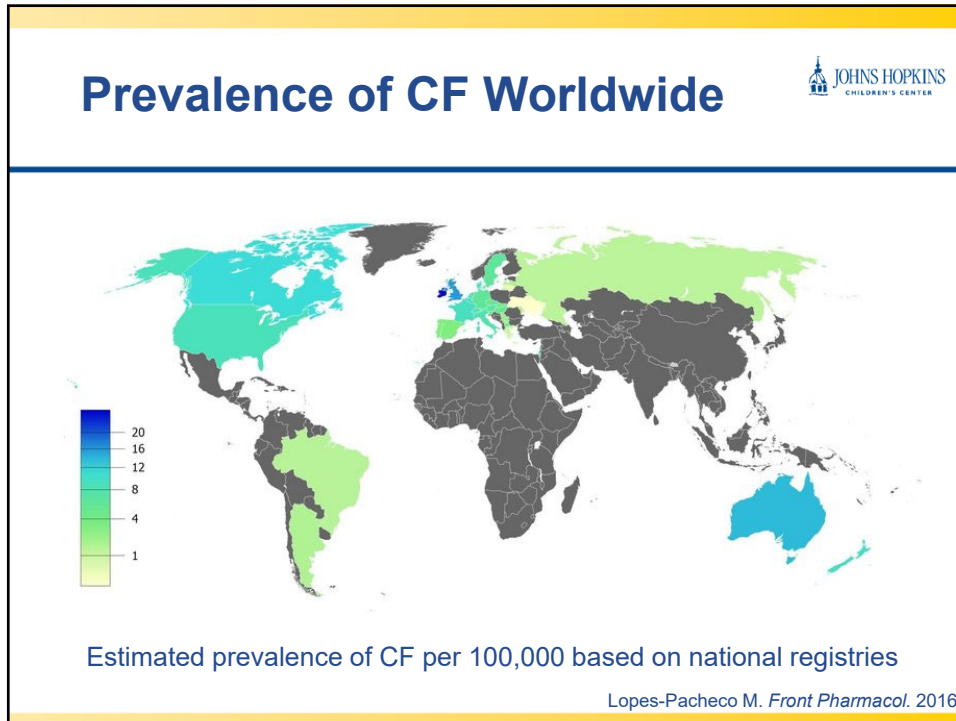
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## Outline



- **Prevalence of cystic fibrosis (CF)**
- Racial/ethnic health disparities in CF
- Other disparities

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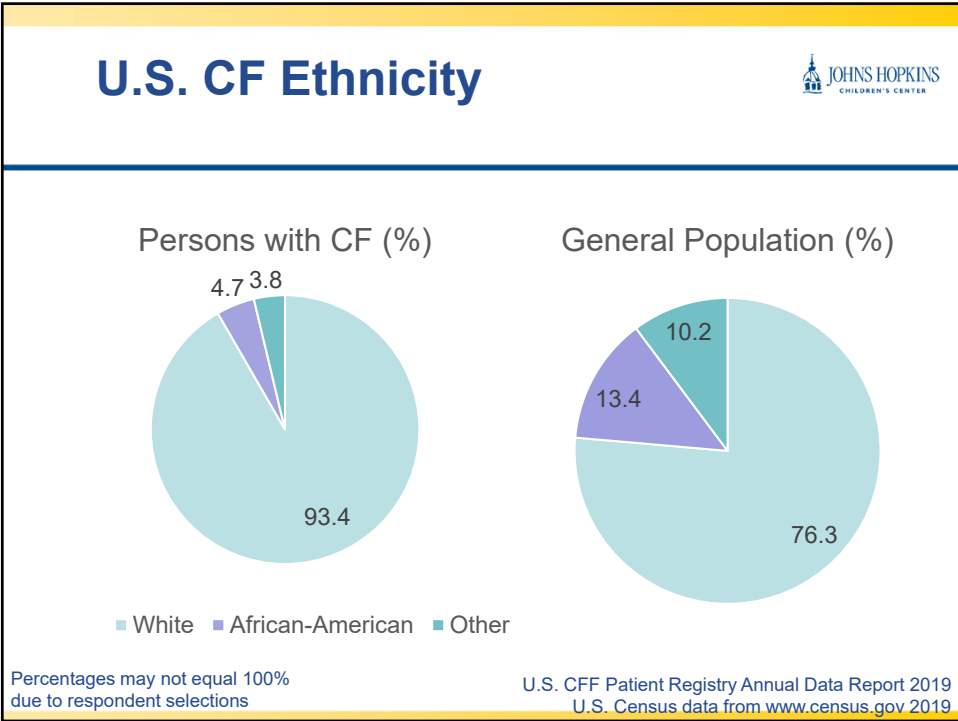
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## Country Statistics

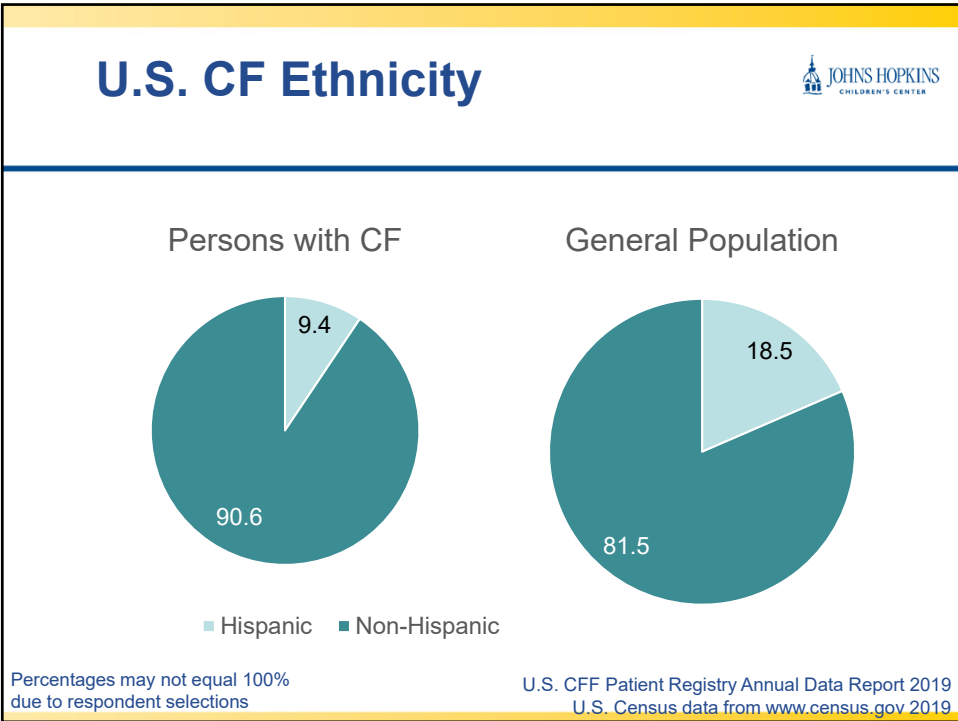
	Registered Patients	Per 100,000 Inhabitants
1	United States	Ireland
2	United Kingdom	United Kingdom
3	France	Australia
4	Germany	Canada
5	Italy	Belgium
6	Canada	New Zealand
7	Brazil	France
8	Australia	United States
9	Russia	Switzerland
10	Spain	Denmark

Lopes-Pacheco M. *Front Pharmacol.* 2016

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## Outline



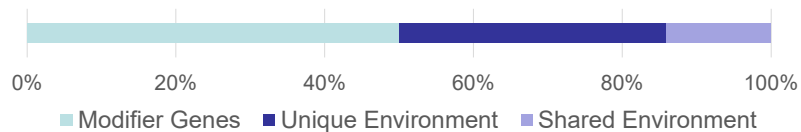
- Prevalence of CF
- **Racial/ethnic health disparities in CF**
- Other disparities

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## Environmental Contributions to CF



Contributions to Lung Function in CF



- Outcomes in CF can differ even with the same genotype
  - Half of the non-CF gene related variation is due to the environment
  - Disparities can affect patients on the individual and community levels

Kerem E et al. *NEJM*. 1990  
Collaco JM et al. *Pediatr Pulmonol*. 2010

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## Racial/Ethnic Disparities in CF

- Although the prevalence of CF is lower in minorities (but rising) than in whites in the U.S., health disparities have been reported for over 20 years
  - These disparities may persist in the future owing to differences in applying personalized medicine approaches
- It is difficult to parse the separate genetic and socio-cultural contributions of race/ethnicity to outcomes in CF

Oates GR, Schechter MS. *Ann Am Thorac Soc.* 2021  
Schechter MS et al. *AJRCCM.* 2001

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## Diagnosis

- 1960s
  - The diagnosis of CF was rarely considered in African-Americans
- 1990s
  - African-Americans were being diagnosed up to 7 months earlier
  - But had poorer nutritional status

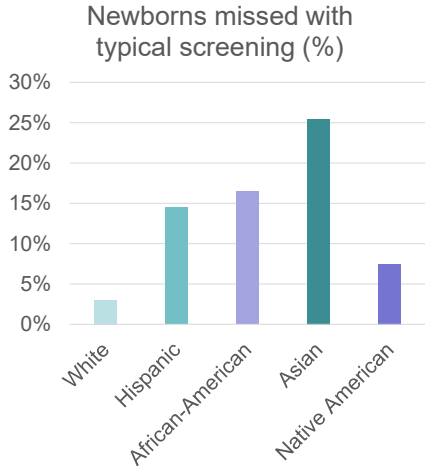
Hamosh A. et al. *J Pediatr.* 1998

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## Newborn Screening



- Newborn screening has been available in all 50 states since 2010
  - All states use 2 steps for screening
    - Most common: Immunoreactive trypsinogen, and if positive, a state-specific variant panel




Race	Percentage
White	~3%
Hispanic	~14%
African-American	~16%
Asian	~25%
Native American	~7%

Pique L. et al. Genet Med. 2017

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## Disparities (African-American)



- Adjusted mortality risk is 48% higher, but may not be different once adjusting for health insurance
- Lung function
  - No difference compared to white patients
- Nutrition
  - Lower weight and height percentiles
- Infection
  - No difference in Pseudomonas positive cultures

O'Connor GT et al. *Pediatr Pulmonol.* 2002  
 Schechter MS et al. *AJRCCM.* 2001  
 Hamosh A. et al. *J Pediatr.* 1998

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## Disparities (Hispanic)



- Adjusted mortality risk is 27% higher
- Lung function
  - 5.8% lower compared to non-Hispanic white patients
  - No difference in decline over time
- Nutritional status
  - Similar or better for all age groups
- Infection
  - Earlier acquisition of *Pseudomonas*

Rho J *et al. AJRCCM.* 2018  
McGarry ME *et al. Pediatr Pulmonol.* 2017  
Watts KD *et al. Pediatr Pulmonol.* 2009

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## Disparities (Asian)



- Studies are more limited
- Diagnosis is later
  - More patients are pancreatic sufficient
  - Lower sweat chloride given same variants
  - More variants not captured on screening panels
- Lung function does not differ

Bosch B *et al. J Cyst Fibros.* 2017

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## Modulator Therapy

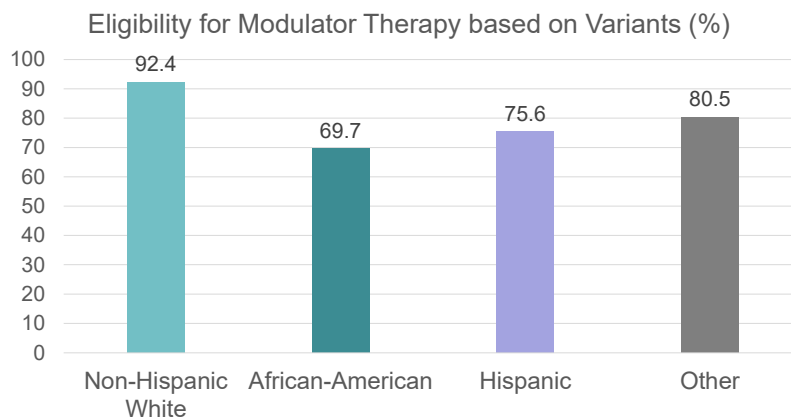


- Minority patients are underrepresented in modulator trials
- Minorities are less likely to have variants that are eligible for specific therapies (see next slide)
- Disparities in access to therapies has not been reported yet

McGarry ME, McColley SA. *Pediatr Pulmonol.* 2021

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## Modulator Therapy



McGarry ME, McColley SA. *Pediatr Pulmonol.* 2021

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## Outline



- Prevalence of CF
- Racial/ethnic health disparities in CF
- **Other disparities**

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## Household Income



- Minorities more likely to have lower household incomes
- Mortality
  - 44% increased risk in lowest bracket
- Lung function and nutritional status are worse with lower income brackets
- No differences in CF outcomes seen in Canadian study (lung function, BMI, etc.)

O'Connor GT *et al. Pediatrics.* 2003  
Schechter MS *et al. J Pediatr.* 2009  
Stephenson A *et al. Pediatr Pulmonol.* 2011

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## Health Insurance



- No insurance
  - Associated with a 6.1 year decrease in survival
- Public insurance
  - Minorities more likely to be covered by Medicaid
  - Associated with 9-12% difference in lung function
  - Higher risk of death (Hazard ratio 3.65)
  - 2.2-fold increased odds of growth failure
- Even individuals with some periods of public insurance may do worse than those with continuous private insurance

Curtis JR *et al.* *AJRCCM*. 1997  
Schechter MS *et al.* *J Pediatr*. 1998  
Schechter MS *et al.* *AJRCCM*. 2001  
Tumin D *et al.* *Ann Am Thorac Soc*. 2021

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## Secondhand Smoke (SHS)



- Minorities are more likely to be exposed to secondhand smoke
- SHS exposure in CF may result in:
  - Airway dysfunction as early as infancy
  - Reduced lung function in later life
  - Decreases in childhood growth

[www.cdc.gov](http://www.cdc.gov)  
Kopp BT *et al.* *Int J Environ Res Public Health*. 2016

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## Air Pollution



- Minorities, especially African-Americans are more likely to be exposed to pollution than whites
- Ambient air pollution
  - Short-term changes associated with risk of bronchitis/pneumonia (exacerbation)
  - Annual exposure linked to decrease in lung function
- Traffic
  - Closer proximity of home to major roadway associated with risk of exacerbation

www.epa.gov  
Goeminne PC *et al. Chest.* 2013  
Farhat SCL *et al. Chest.* 2013  
Goss CH *et al. AJRCCM.* 2004  
Jassal MS *et al. Int J Environ Health Res.* 2013

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## Access to Care



- In U.S. (and some other countries) CF care is coordinated through accredited CF centers
  - Distance to CF center not associated with lung function or presence of respiratory pathogens

Collaco JM *et al. PLoS One.* 2011  
Johnson B *et al. Pediatr Pulmonol.* 2018

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## Neighborhood Characteristics

- Area Deprivation Index (ADI) (census blocks)
  - Derived from 17 measures of income, education, employment, and housing quality
- Children living in areas with worse ADI:
  - Lower lung function
  - Higher risk of pulmonary exacerbations
  - Partially explained by overall child health in the state

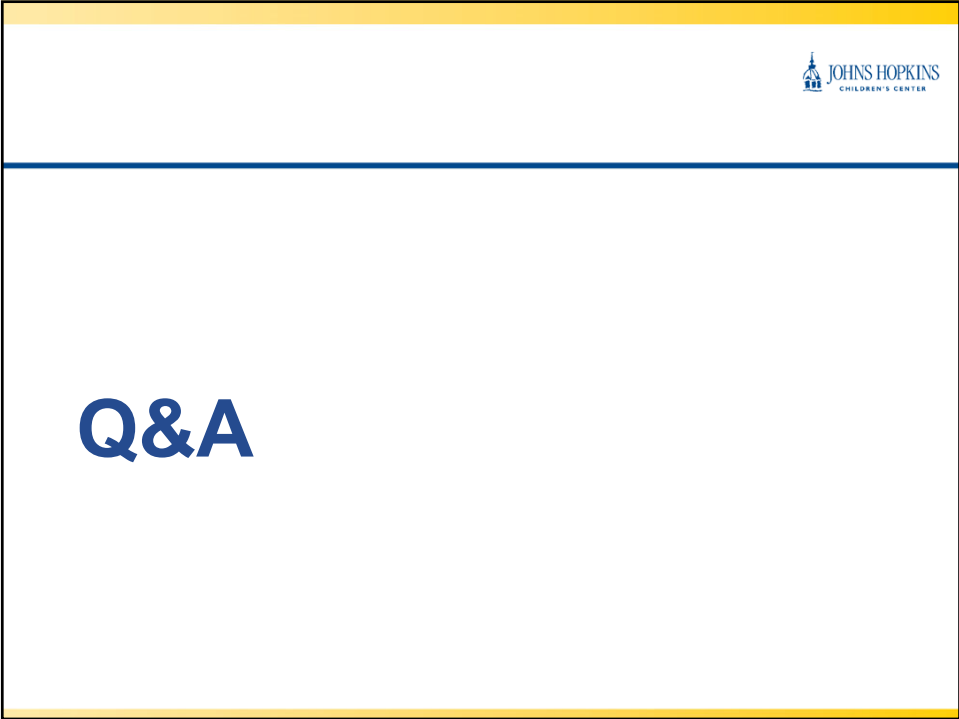
Oates G et al. *Pediatr Pulmonol*. 2020

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## Summary

- CF can occur in all racial/ethnic groups
- Similar to many other diseases, disparities also play a role in outcomes in CF
- These disparities will not necessarily resolve with the current CFTR modulator landscape

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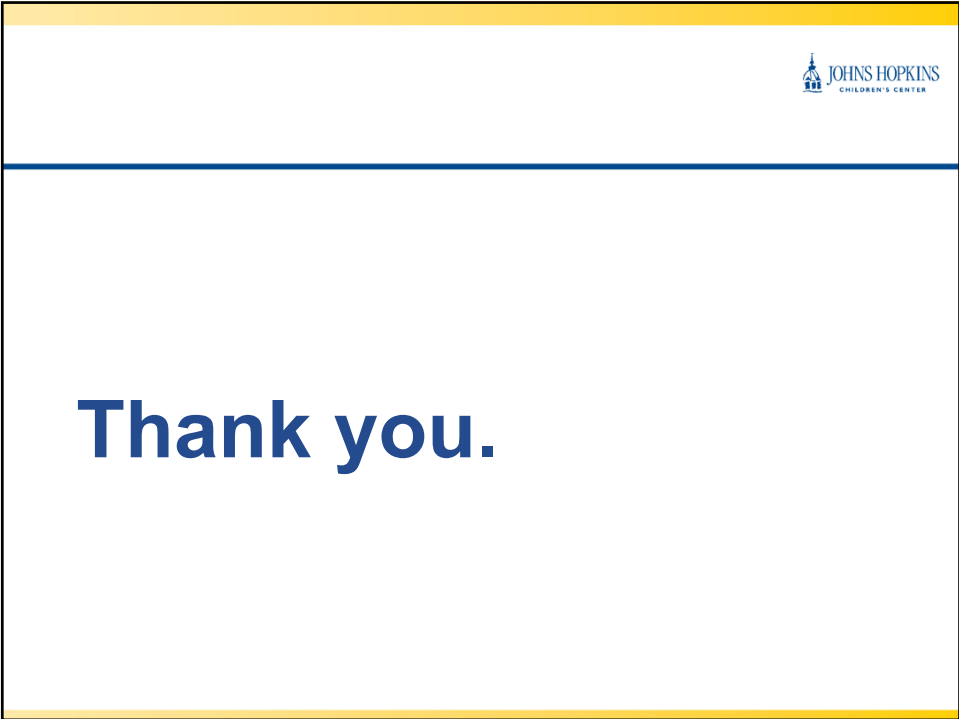


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CHILDREN'S CENTER

**Q&A**

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JOHNS HOPKINS  
CHILDREN'S CENTER

**Thank you.**

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