Highly Effective Modulator Therapy in Cystic Fibrosis

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Presenter Disclosure

- I have the Relationships with commercial interests:
  - Speaker Fees: Vertex Pharmaceuticals Canada
- Speaking Fees for current program:
  - I have received no speaker’s fee for this learning activity

Commercial Support Disclosure

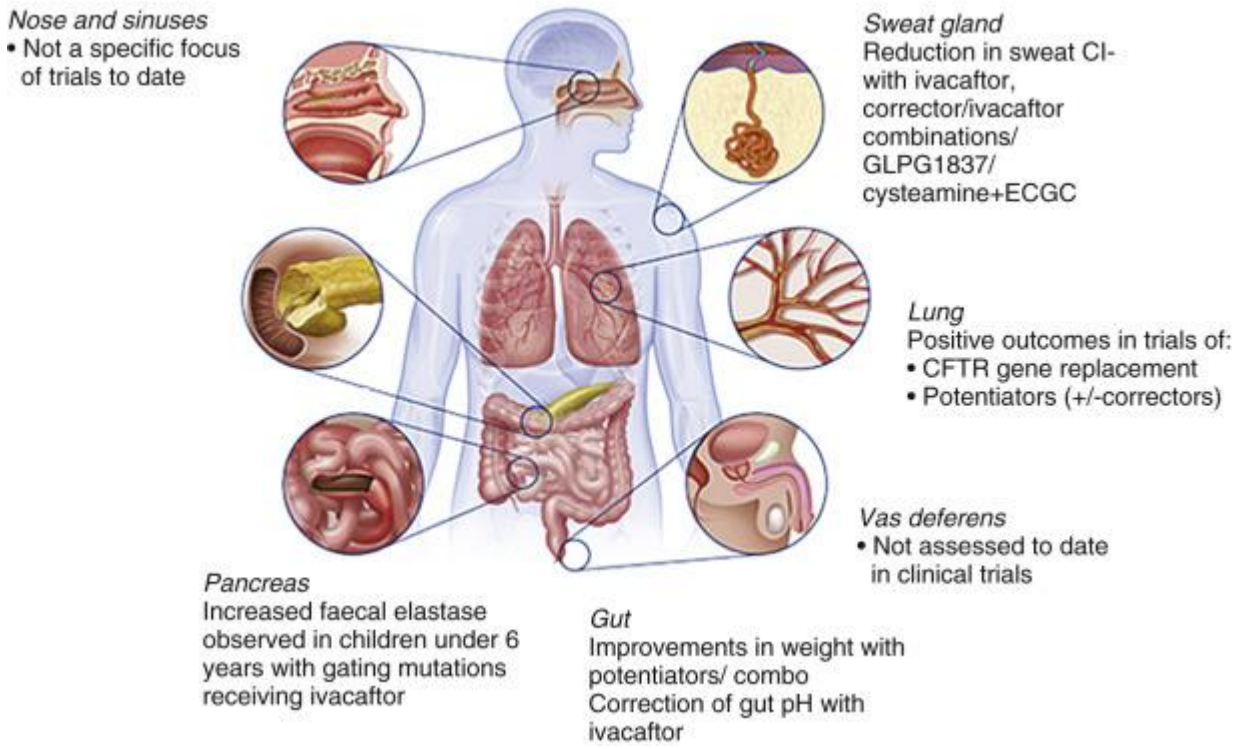
- This program has received no financial or in-kind support from any commercial or other organization

Learning Objectives

- By the end of this session participants should understand:
  - Molecular pathogenesis of Cystic Fibrosis
  - Mechanism of action of novel CFTR modulator drugs
  - Safety and efficacy of elexacaftor/tezacaftor/ivacaftor
  - Current accessibility of modulator drugs across Canada

Cystic Fibrosis

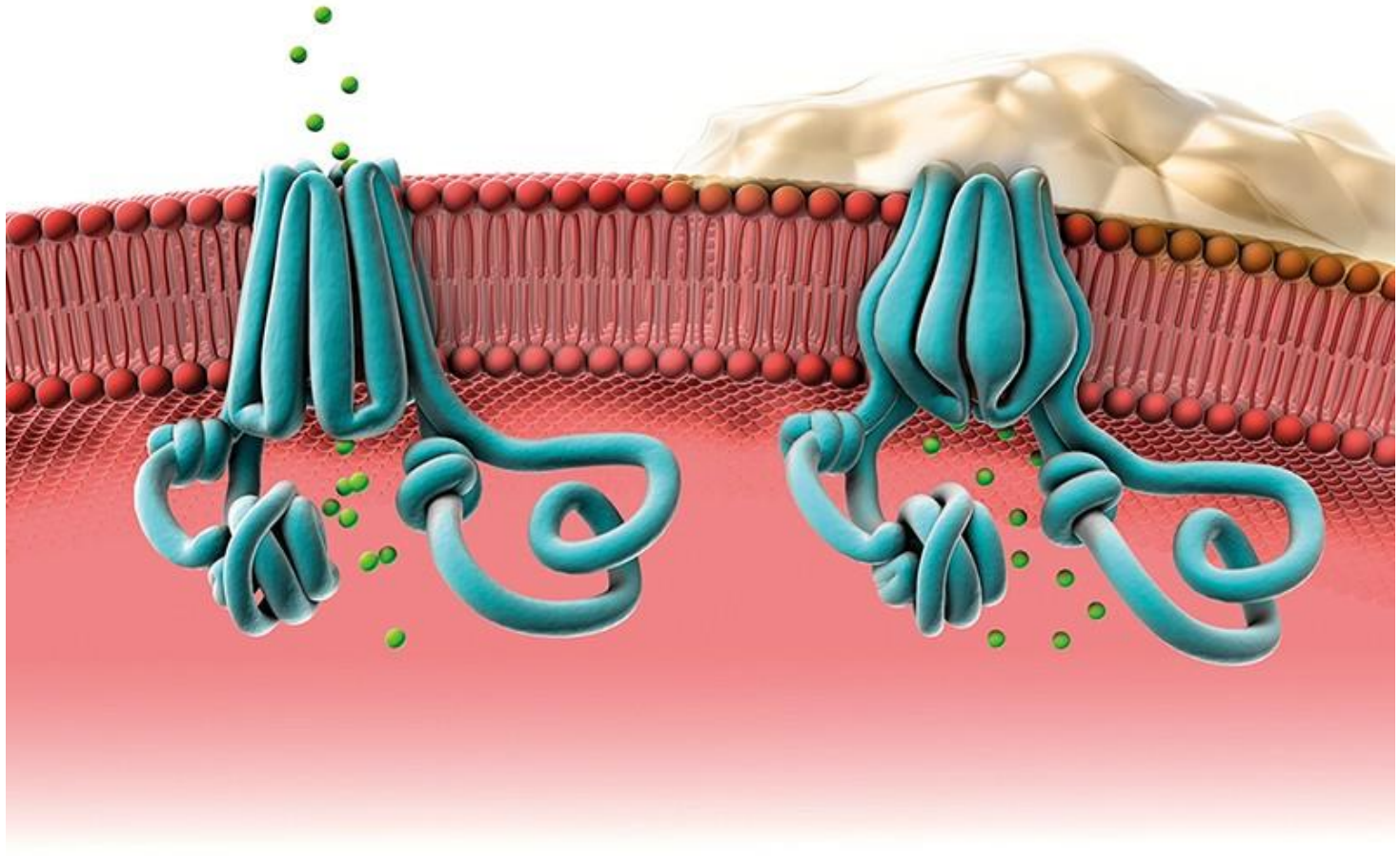
- Genetic disease resulting from mutation in cystic fibrosis transmembrane conductance regulator (CFTR) gene
- Multisystem disorder
  - **Lung**
  - Pancreas
  - Liver
  - Intestines
  - Reproductive organs
- Goals of therapy
  - Maintaining lung function
  - Maintaining growth and development



Davies, *Kendig's Disorders of the Respiratory Tract in Children* (2019)

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

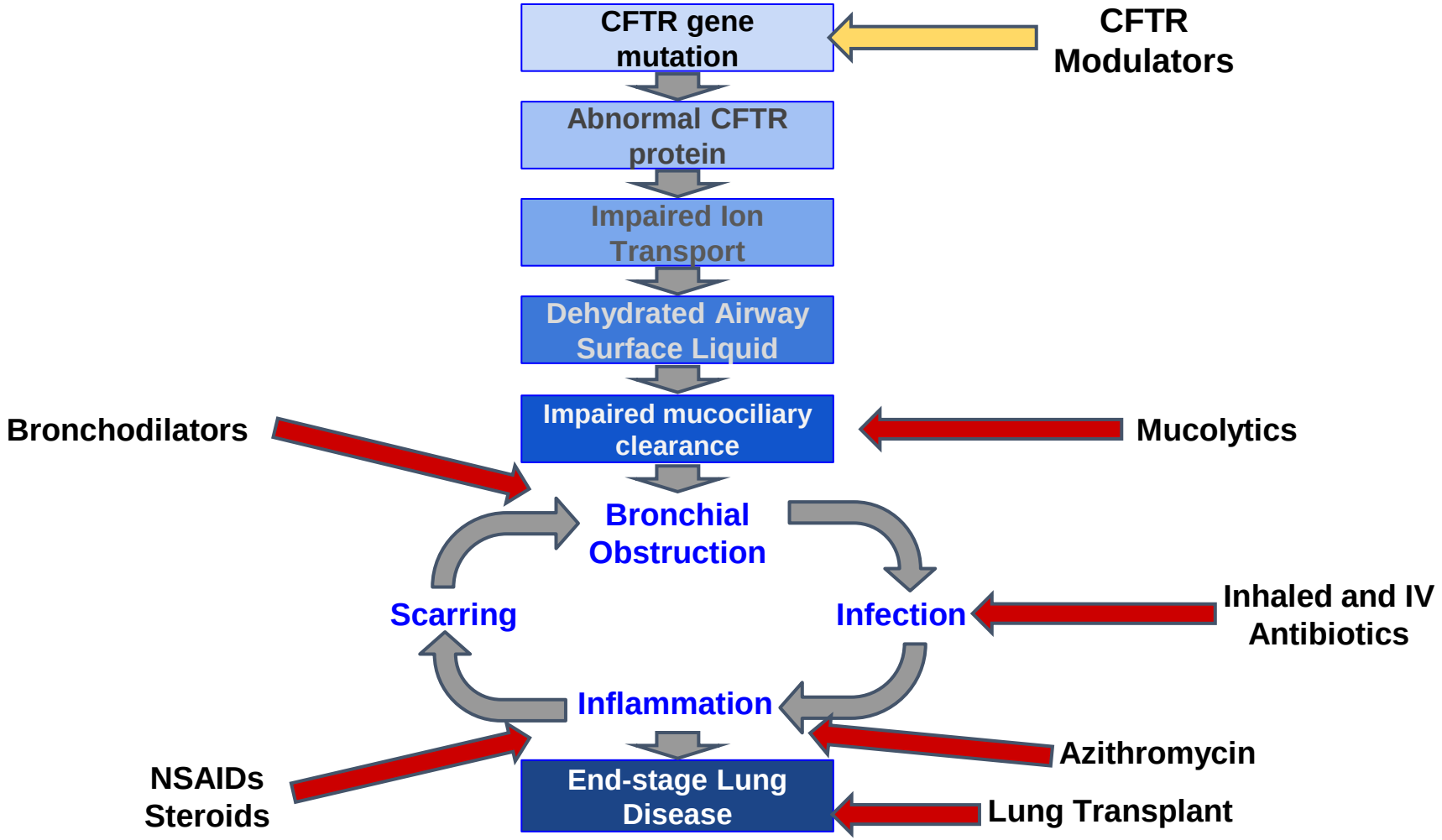
Normal CFTR Channel
Chloride ions move across membrane to outside of cell



Mutant CFTR Channel
Chloride ions do not move across membrane. Sticky mucus builds up outside of cell

Nature **583**, S17 (2020)

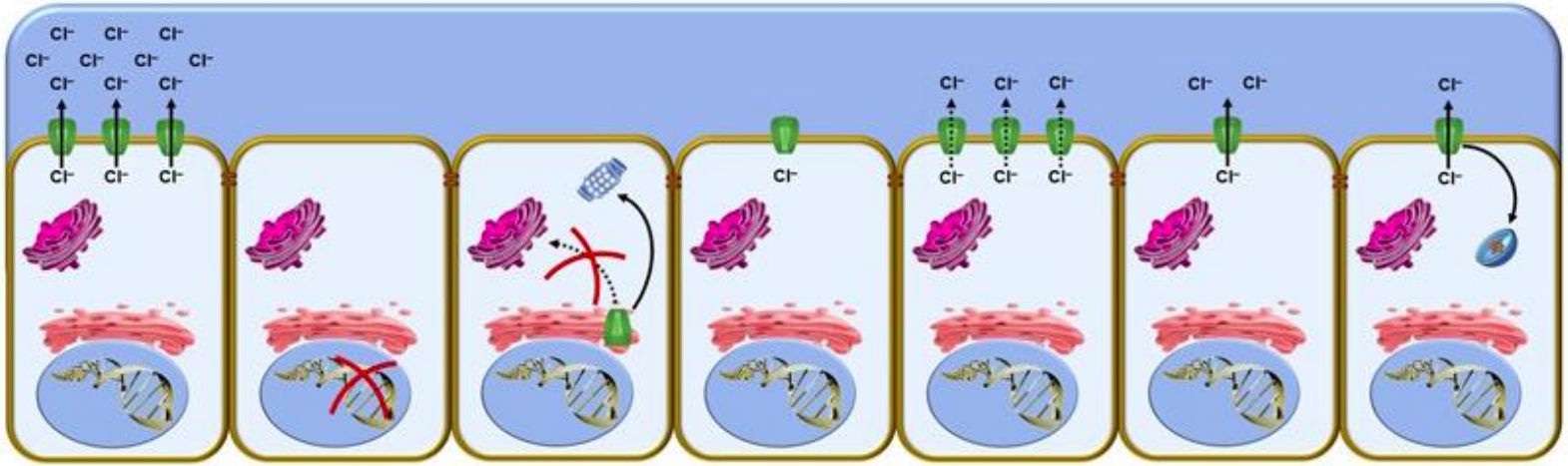
Treatment vs. Pathophysiology of CF Lung Disease



CFTR Modulators

- Drugs that act directly on CFTR to correct defects in production and/or structure
- Small molecules
- New drugs or existing drugs discovered by high throughput screening
- Categories of CFTR Modulators:
  - Read-through
  - **Correctors**
  - **Potentiators**
  - Stabilizers
  - Amplifiers

CFTR Mutations

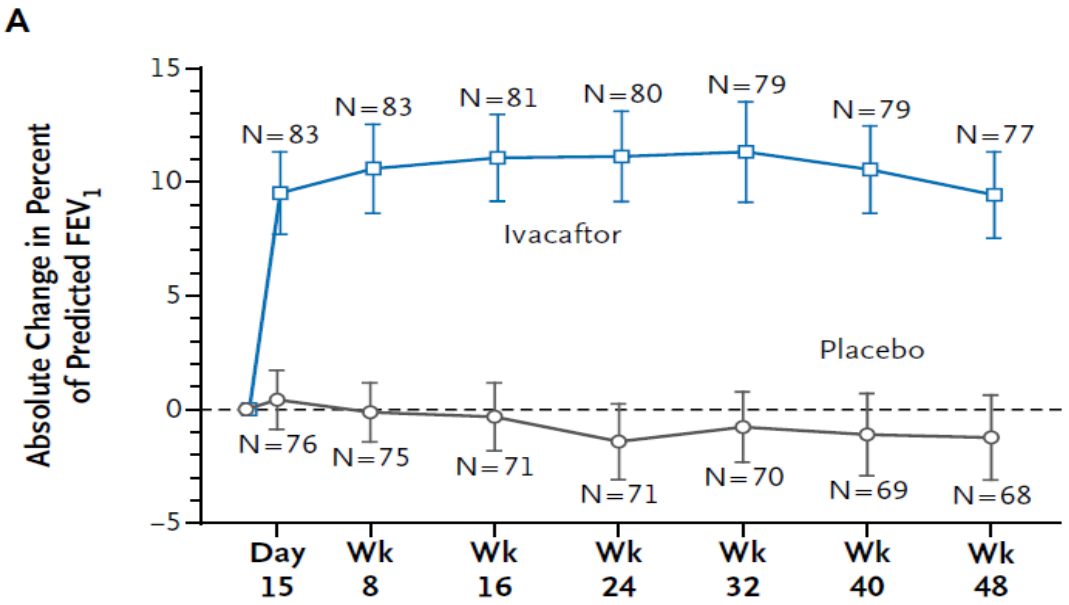


	wt-CFTR	I	II	III	IV	V	VI
Defect types		**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples		G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches		Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

Lopes-Pacheco, *Frontiers in Pharmacology* (2016)

Ivacaftor

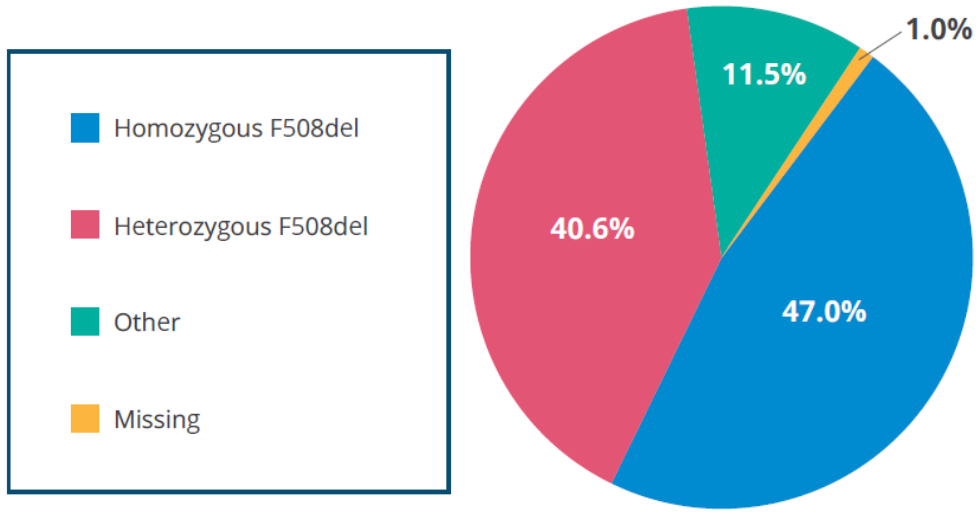
- Potentiator - Corrects gating defects in G551D (and others)
- Approved 2012 based on STRIVE, ENVISION
  - 10.6% increase in ppFEV1
  - 55% reduction in exacerbations
- Well tolerated, few drug interactions



Ramsay et al, NEJM (2011)

CFTR Genotypes

Genotype distribution of CF population (N = 4,332), 2020.

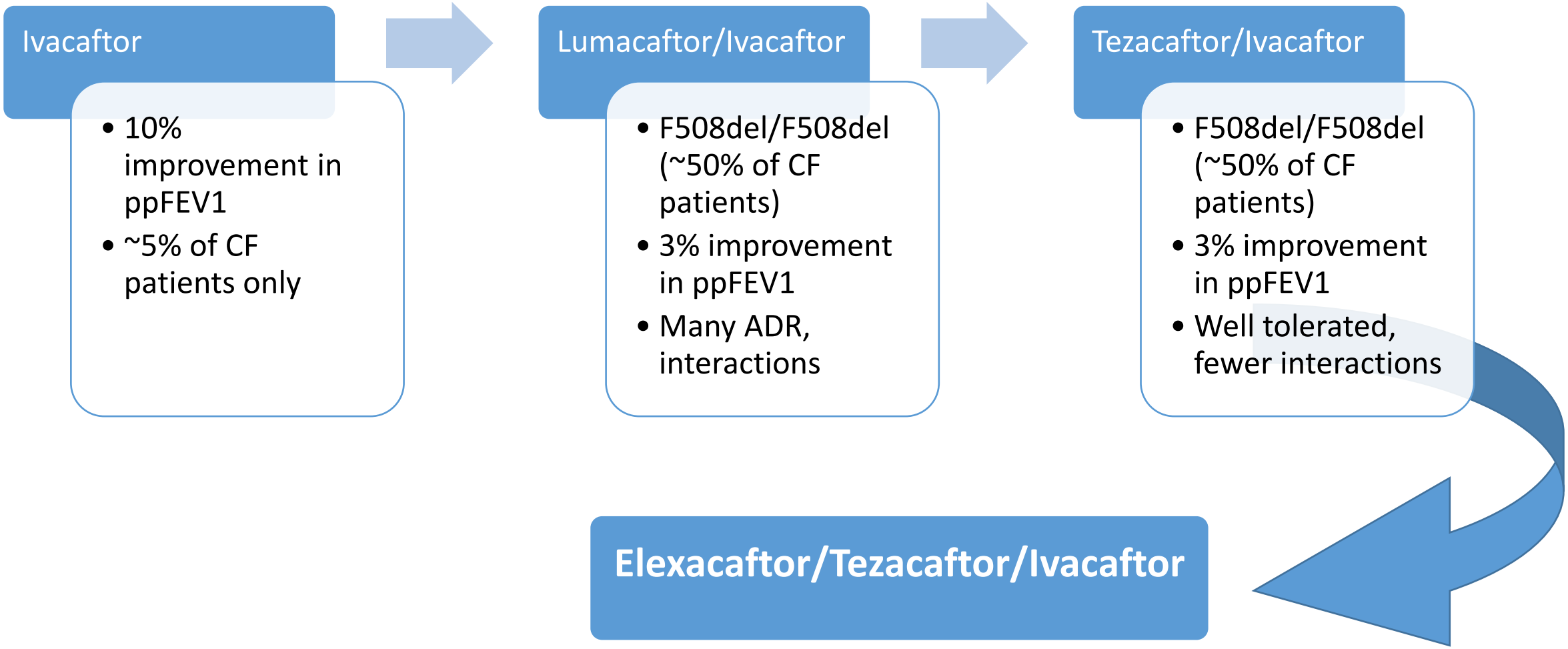


Frequency of the top 10 most common CFTR gene mutations on one or both alleles of cystic fibrosis individuals with recorded mutations (N = 4,290), 2020.

MUTATION	NUMBER	PERCENTAGE
F508del	3,791	88.4%
621+1G->T	259	6.0%
G542X	146	3.4%
G551D	136	3.2%
711+1G->T	118	2.8%
A455E	112	2.6%
L206W	110	2.6%
N1303K	91	2.1%
M1101K	69	1.6%
G85E	68	1.6%

The Canadian Cystic Fibrosis Registry 2020 Annual Data Report.

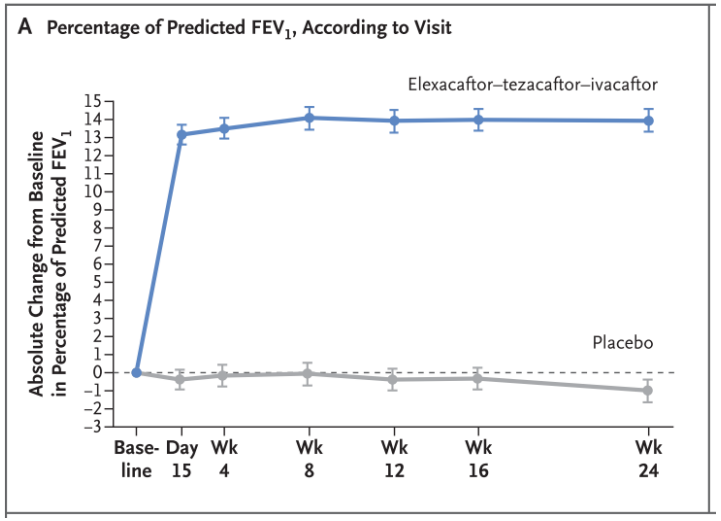
CFTR Modulator Development



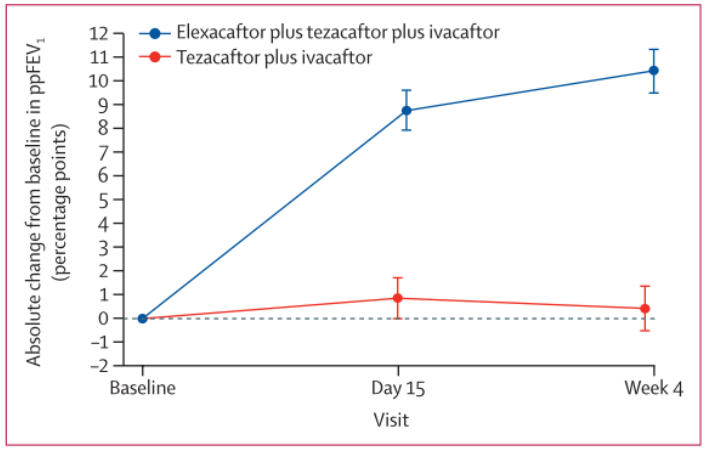
Elexacaftor/Tezacaftor/Ivacaftor

- Triple combination
  - Corrector/Corrector/Potentiator
- Studied in F508del homozygous or F508del/MF
- Phase III trial results published Oct. 2019
  - **13.8%** increase in FEV1 for F508del/MF
  - **10.0%** increase in FEV1 for F508del/F508del
    - Versus tezacaftor/ivacaftor alone
  - **63%** reduction in pulmonary exacerbations
- Approved in Canada 2021
  - For patients with one copy F508del (~90% of CF population)

MF = Minimal Function



F/MF



F/F

Middleton et al., NEJM (2019)
Heijerman et al., Lancet (2019)

Elexacaftor/Tezacaftor/Ivacaftor Side Effects

Side Effect	E/T/I	Placebo	Side Effect	E/T/I	Placebo
Headache	17%	15%	CPK increase	9%	4%
URTI	16%	12%	**AST increase**	**9%**	**2%**
Abdo Pain	14%	9%	Rhinorrhea	8%	3%
Diarrhea	13%	7%	Influenza	7%	1%
Rash	**10%**	**5%**	Sinusitis	5%	4%
ALT increase	**10%**	**3%**	**Increased bilirubin**	**5%**	**1%**
Nasal congestion	9%	7%			

- Post-marketing
  - Joint, muscle pain
  - Cognitive, psychiatric effects

Middleton et al., NEJM (2019)

Administration and Clinical Pearls

- Two tablets AM (elexacaftor/tezacaftor/ivacaftor), one tablet PM (ivacaftor)
- Medication must be taken with food
  - 10-15g fat minimum
- CYP450 and Pgp substrate
  - Interactions with azole antifungals, anti-seizure meds
- Close monitoring of liver function in first year
- Counsel on fertility, birth control
- Discuss discontinuation, plan for other chronic CF meds

Elexacaftor/Tezacaftor/Ivacaftor Coverage

- List price ~$300,000 per year
- Currently covered by all provincial public drug plans for patients over 6 years of age with one copy F508del
- Many private drug plans covering
- Clear demonstration of benefit required for renewal – baseline and follow-up monitoring required
  - Lung function
  - BMI
  - Exacerbations
  - CFQ-R

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