A NEW ERA IN CYSTIC FIBROSIS CARE:

HIGHLY EFFECTIVE MODULATOR THERAPIES

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Objectives

Become familiar with the underlying cause of Cystic Fibrosis (CF) and the resultant clinical manifestations

Review selected key therapies in CF lung care

Gain an understanding the impact of highly effective modulator therapy (HEMT) on CF lung health

Disclosures

- Clinical Trial investigator: *Vertex Pharmaceuticals*

Brief overview of cystic fibrosis

- Cystic Fibrosis (CF) is a life-limiting genetic disease most commonly affecting the respiratory and GI tract

- ~105,000 individuals with CF worldwide

Guo J et al. J Cyst Fibros 21 (2022) 456-462
Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report

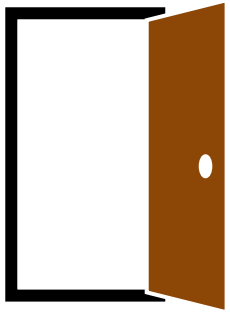
Brief overview of cystic fibrosis

- Autosomal recessive disorder that results in abnormal ion transport due to CFTR (Cystic Fibrosis Transmembrane Regulator) protein dysfunction
  - To date, over 700 gene variants identified that cause CF
  - Most common gene mutation is F508del

- CFTR protein is found in epithelial cells of various tissues and organs

The Clinical and Functional TRanslation of CFTR (CFTR2) http://cftr2.org

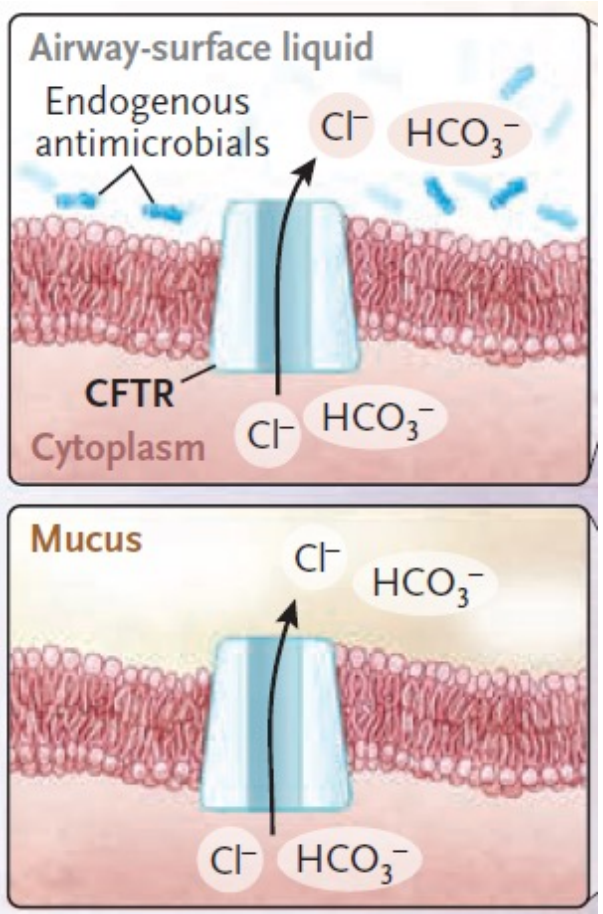
Pathophysiology of CF lung disease



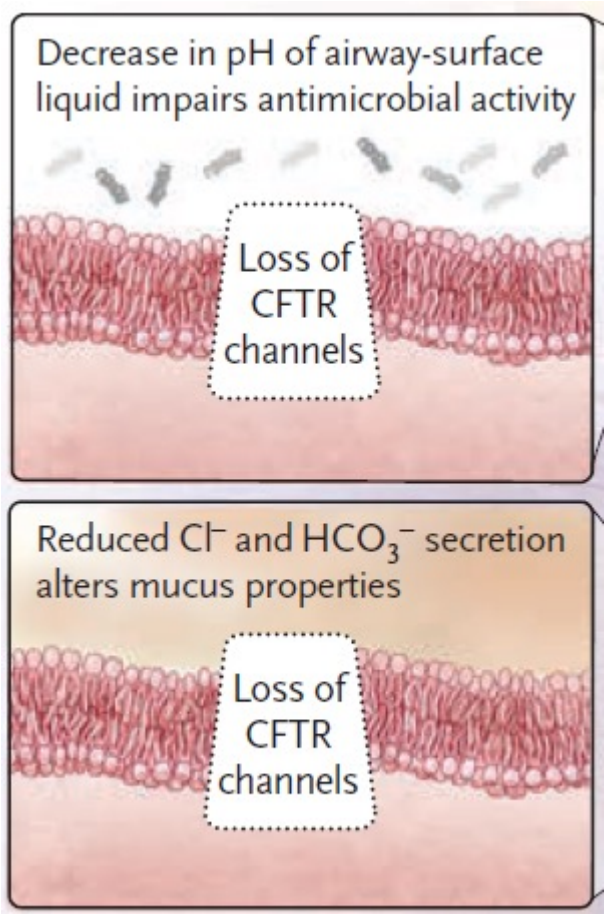
Airway lumen

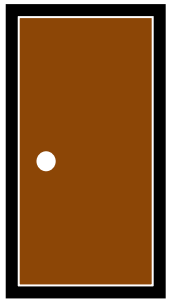
Inside of epithelial cell

Healthy Airway

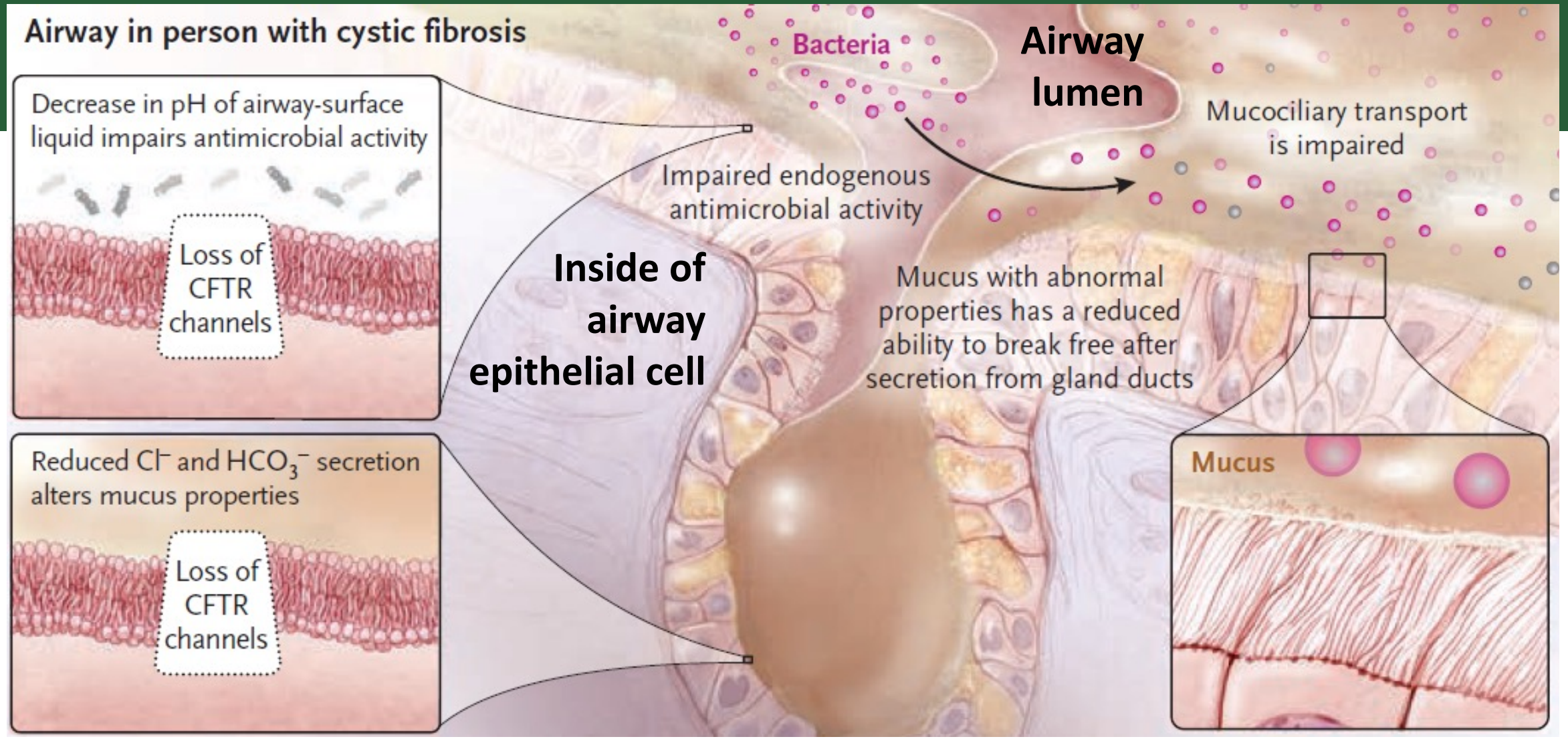


CF Airway

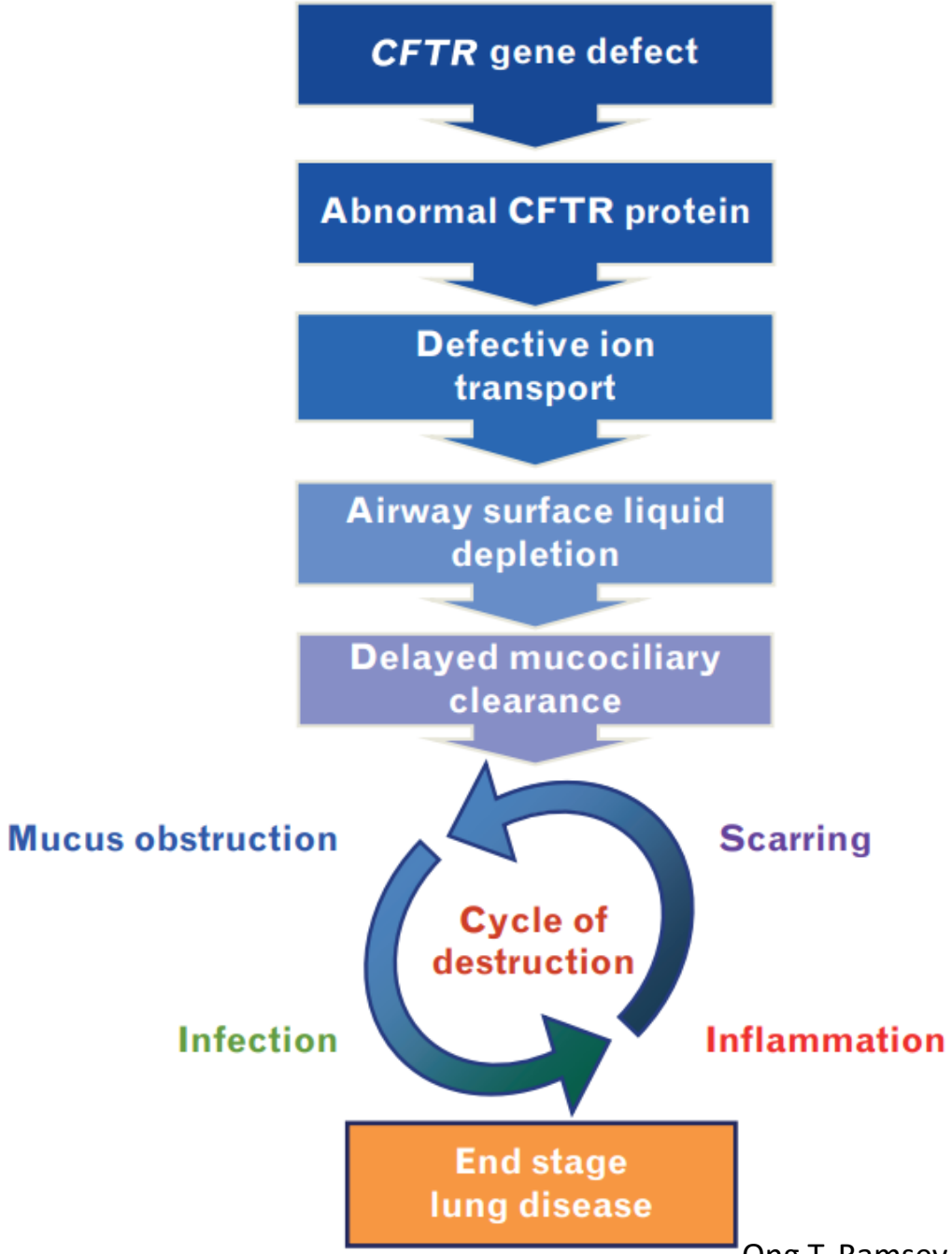




Stoltz DA et al. N Engl J Med 2015; 372: 351-362



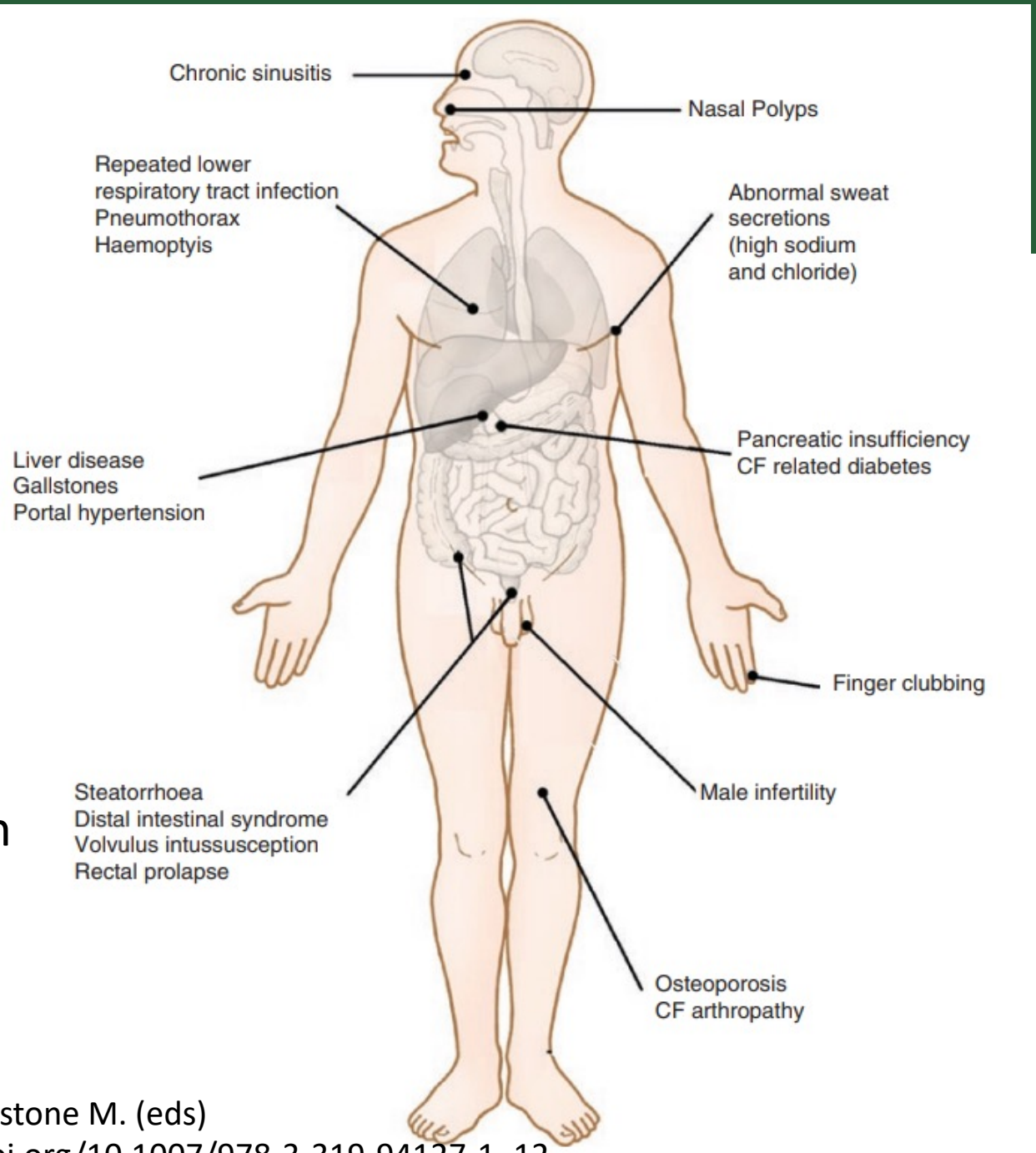
Stoltz DA et al. N Engl J Med 2015; 372: 351-362



Ong T, Ramsey BW. Curr Op Pulm Med 2013. 19(6):645-51

Common clinical features of CF

- Other manifestations and comorbidities:
  - Bronchiectasis
  - ABPA (Allergic bronchopulmonary aspergillosis)
  - Nephrolithiasis, nephrocalcinosis, hyperoxaluria
  - Mental health – anxiety/depression



Peckham D., Whitaker P. (2018) Cystic Fibrosis. In: Hart S., Greenstone M. (eds) Foundations of Respiratory Medicine. Springer, Cham. https://doi.org/10.1007/978-3-319-94127-1_12

Lung therapies in CF

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CF care over time

Life expectancy:

1930s: ~ 6 months

1950s: 4-5 years

1970s: 11 years

1990s: early 30s

2000s: late 30s/ early 40s

1938: CF identified as a disease entity

1959: Standardization of Sweat test for CF diagnosis

1950s: establishment of CF centers for comprehensive care -nutrition, lung health

1970s: -new antibiotics, especially for gram-negative bacteria -Digestive enzymes for absorption of nutrients

1988: improved pancreatic enzyme formulation

Late 1980s: lung transplant

1989: CF gene discovered

1993: inhaled tobramycin

1994: inhaled DNase

2003: low-dose azithromycin

Davis PB. Am J Respir Crit Care Med 2006. Vol 173. 475–482
McBennett KA et al. Pediatr Pulmonol 2022. 57(S1):S5-S12

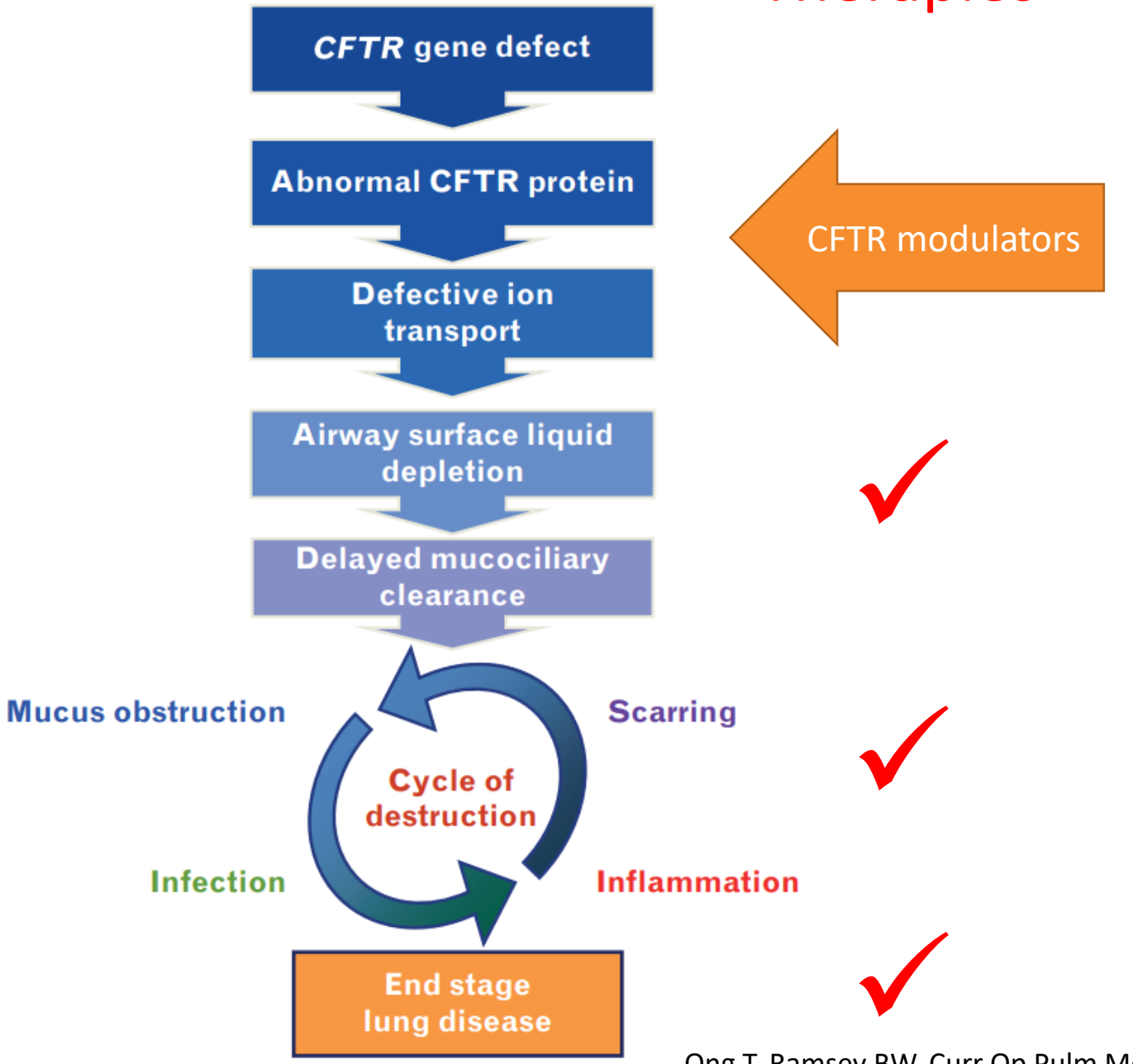
Impact on lung health from therapies

	Goal	Impact on FEV1*	Impact on pulmonary exacerbations*
Dornase alfa (DNase)	Improve sputum clearance	↑ 5.6-5.8%	↓ Pulmonary Exacerbation risk by 22-34%
Inhaled Tobramycin	Treatment and chronic suppression of *pseudomonas aeruginosa* in the lung	↑ 9.7-12%	↓ hospitalization risk by 26% ↓IV antibiotic risk by 36%
Low-dose oral azithromycin	Anti-inflammatory	↑ 6.2%	↓ Pulmonary Exacerbation risk by 35%

* Compared to placebo

Fuchs HJ et al. NEJM 1994; 331:637-42
Ramsey B et al. NEJM 1993; 328:1740-46
Ramsey B et al. NEJM 1999; 340:23-30
Saiman L et al. JAMA 2003; 290:1749-56

Therapies

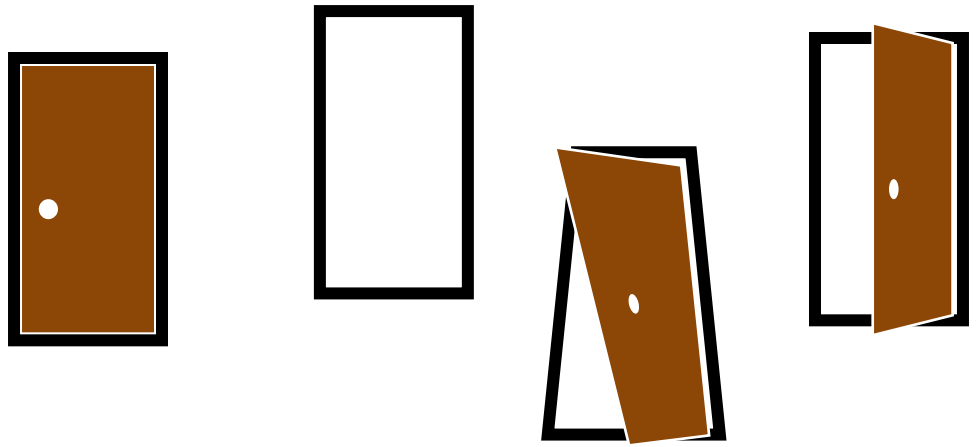


Ong T, Ramsey BW. Curr Op Pulm Med 2013. 19(6):645-51

CFTR modulator therapy

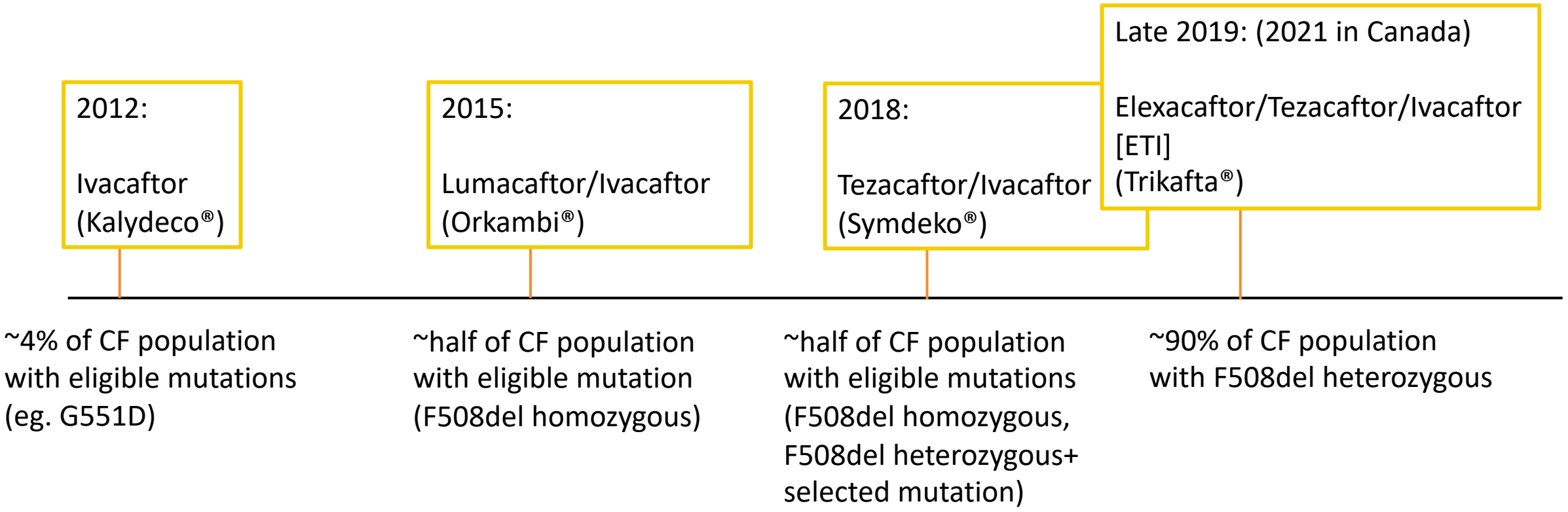
CFTR modulator therapy

- Medications that improve the function of the dysfunctional CFTR protein
  - Multiple ways that CFTR malfunctions
  - Caused by different CFTR gene mutations



- Current CFTR modulator therapies are effective for people with specific CFTR mutations

Currently available* CFTR modulators



*First available approval for commercial use in adults. Approval for pediatric use dependent on availability of pediatric studies

CFTR modulators – lung outcomes

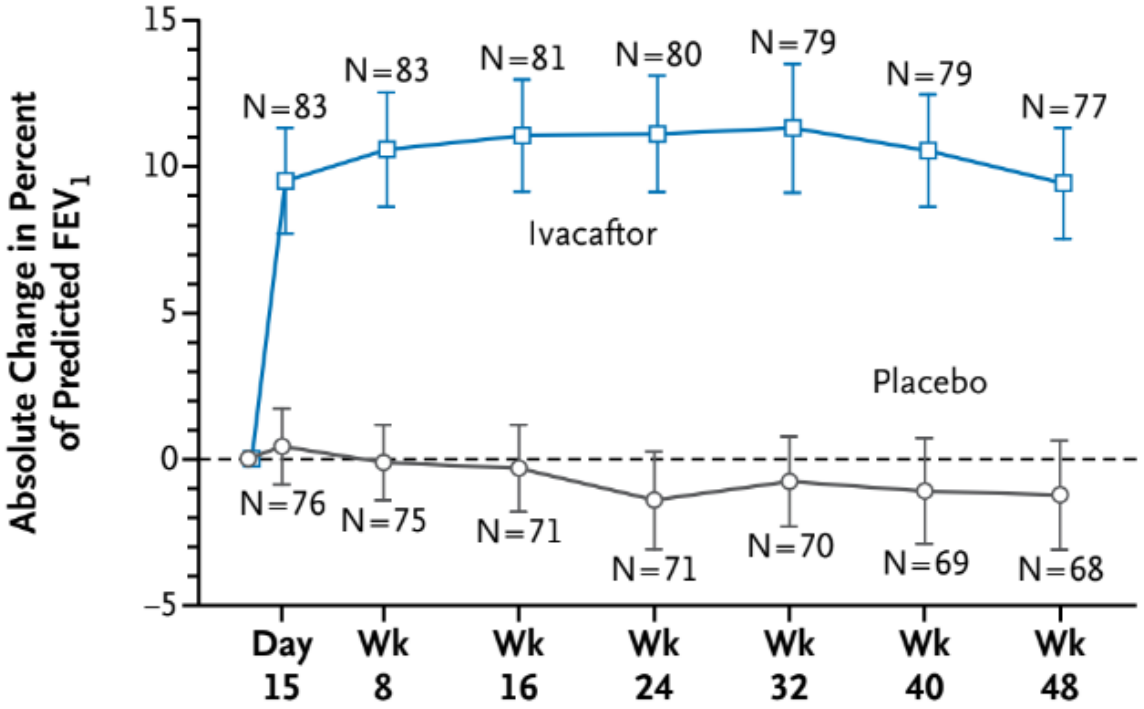
Drug	Mutations	Health Canada Approval	FEV1 effect	Pulmonary exacerbation rate
Ivacaftor (Kalydeco®)	G551D Other gating mutations	Yes (4 months+)	↑ 10%	↓ Pulmonary Exacerbation rate by 55%
Lumacaftor/Ivacaftor (Orkambi®)	F508del Homozygous	Yes (1 years+)	↑ 2.6 – 4%	↓ Pulmonary Exacerbation rate by 30-39%
Tezacaftor/ivacaftor (Symdeko®)	F508del Homozygous F508del Heterozygous + selected other mutation	Yes (12 years+)	↑ 4%	↓ Pulmonary Exacerbation rate by 36%
Elexacaftor/Tezacaftor/ Ivacaftor (Trikafta®)	F508del Homozygous F508del Heterozygous	Yes (6 years+)	↑ 10-13.8%	↓ Pulmonary Exacerbation rate by 63%

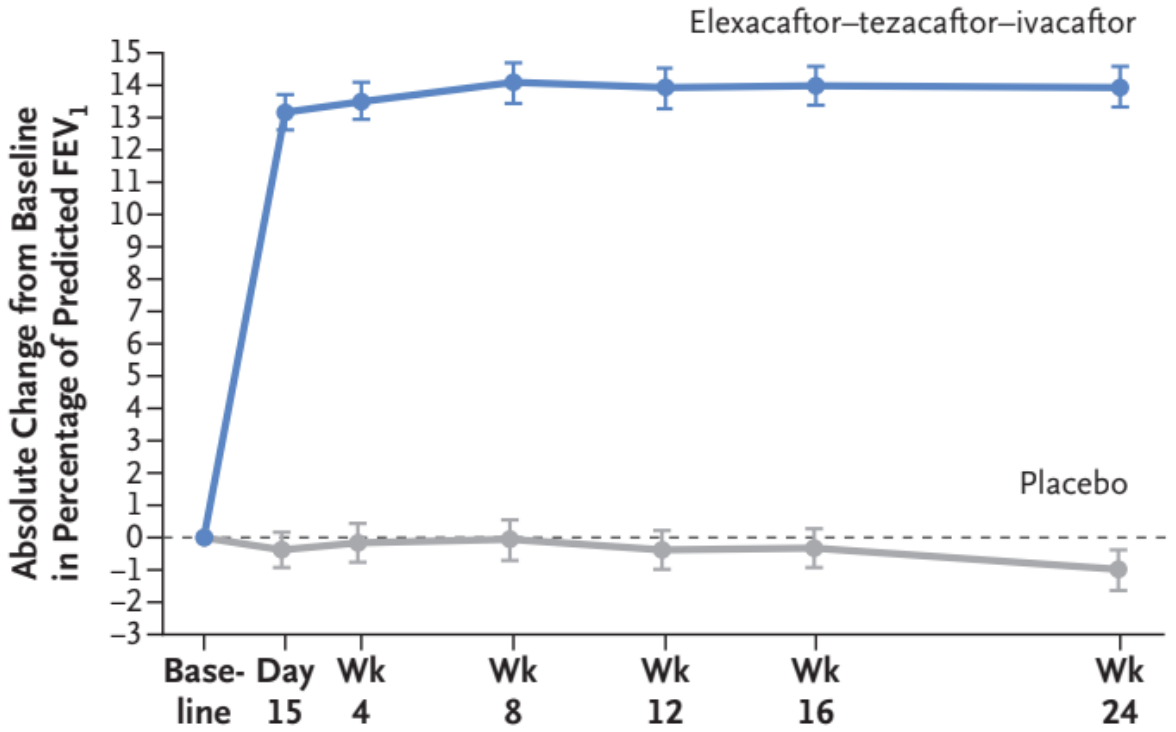
Highly Effective Modulator Therapy (HEMT)

NEJM 2011. 365:1663-72; NEJM 2015. 373(3):220
NEJM 2017. 377(21) 2024-35; NEJM 2017. 377(21) 2013
Lancet 2019, vol 394.p1940; NEJM 2019, 381(19) 1809

Highly Effective Modulator Therapy

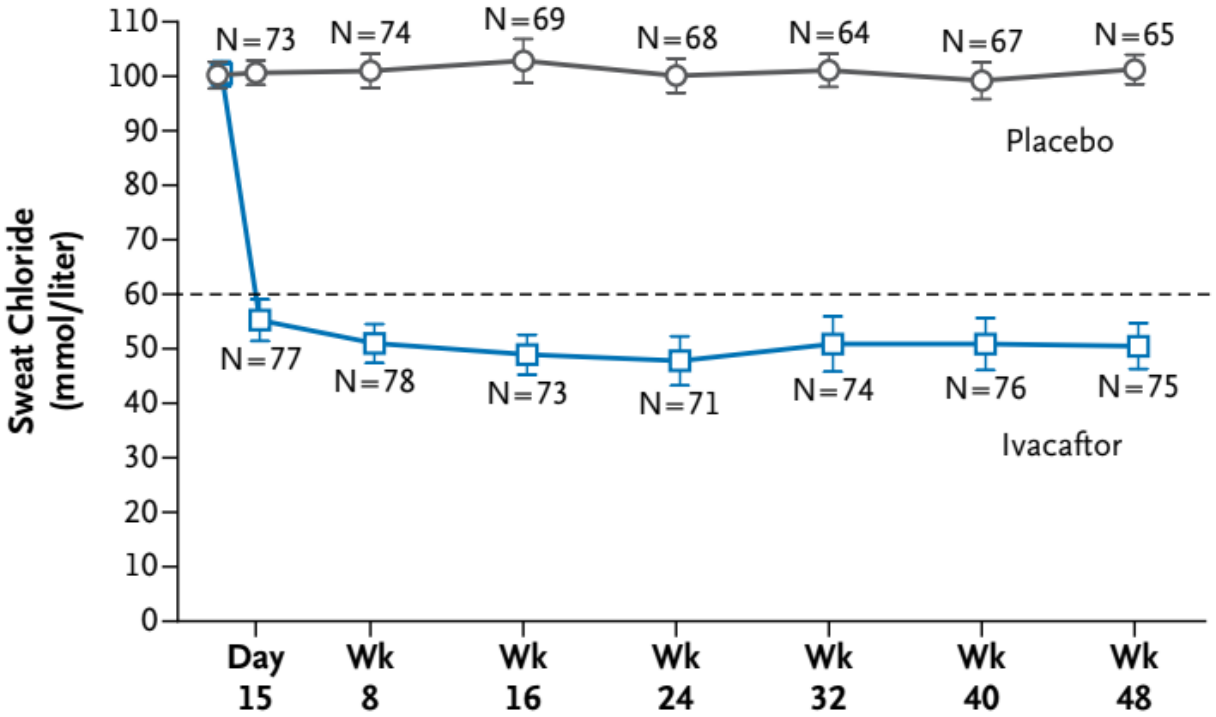
FEV1 increase occurs by Day 15 of HEMT initiation

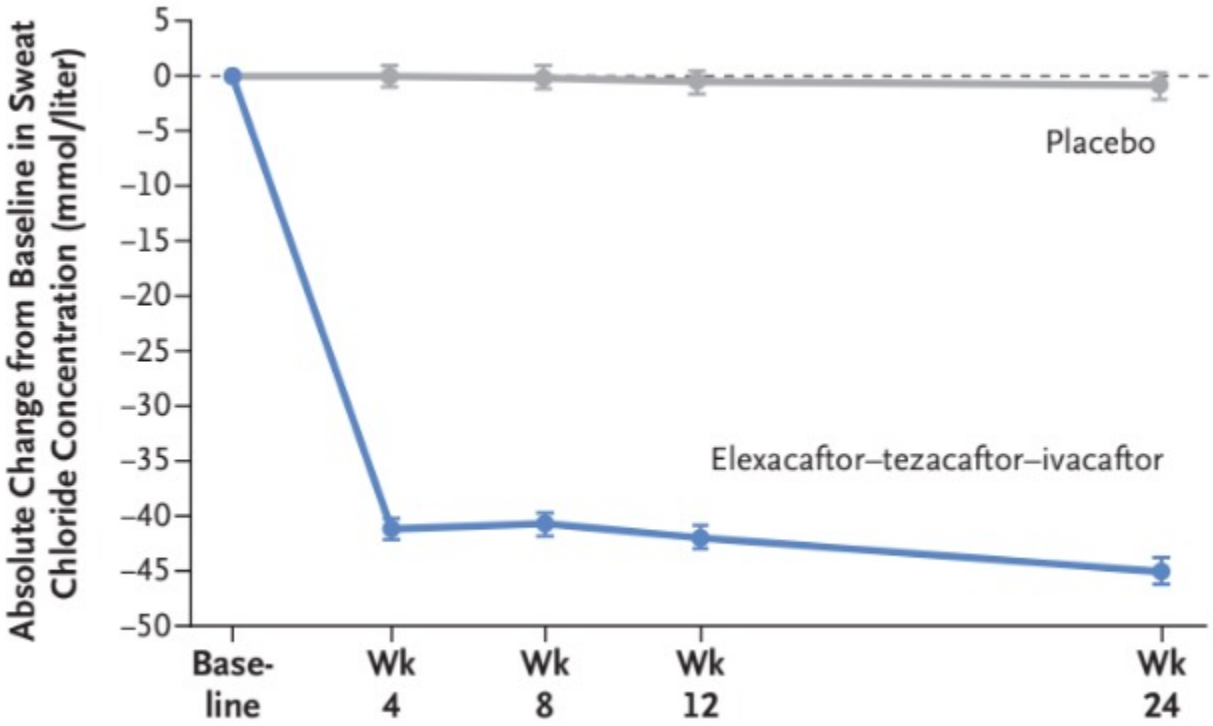




NEJM 2011. 365:1663-72; NEJM 2019, 381(19) 1809

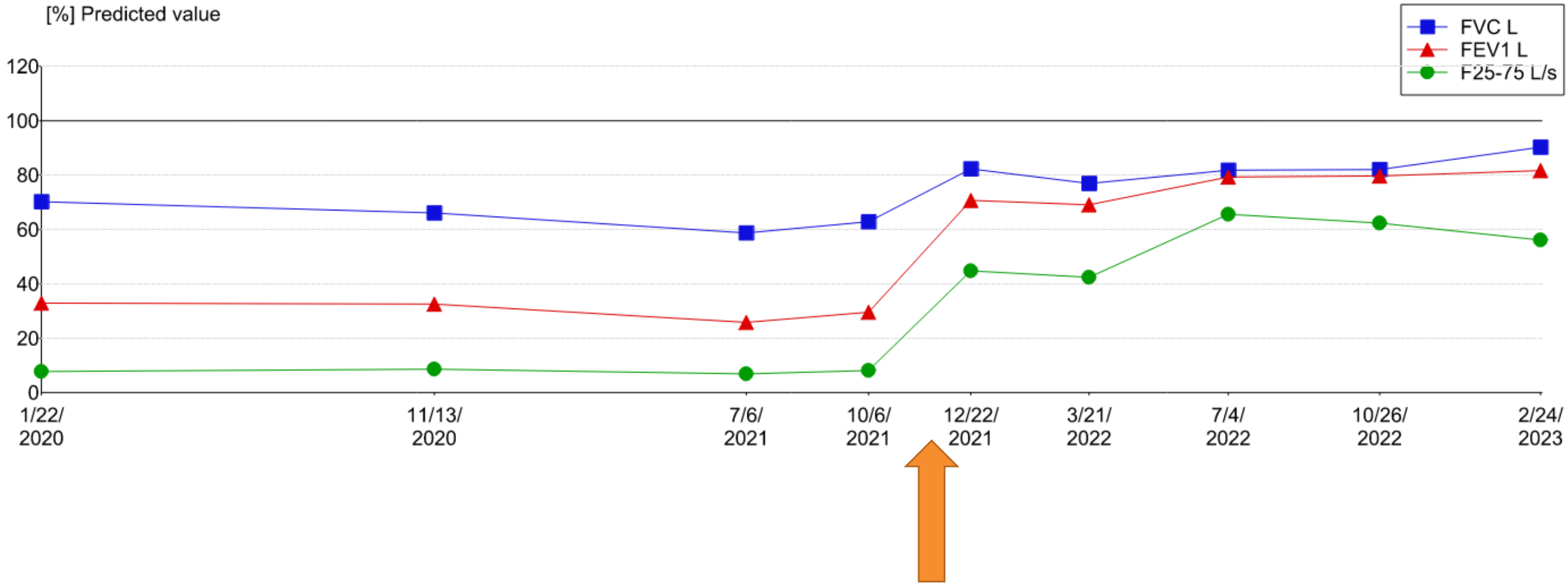
Improved CFTR protein function with HEMT





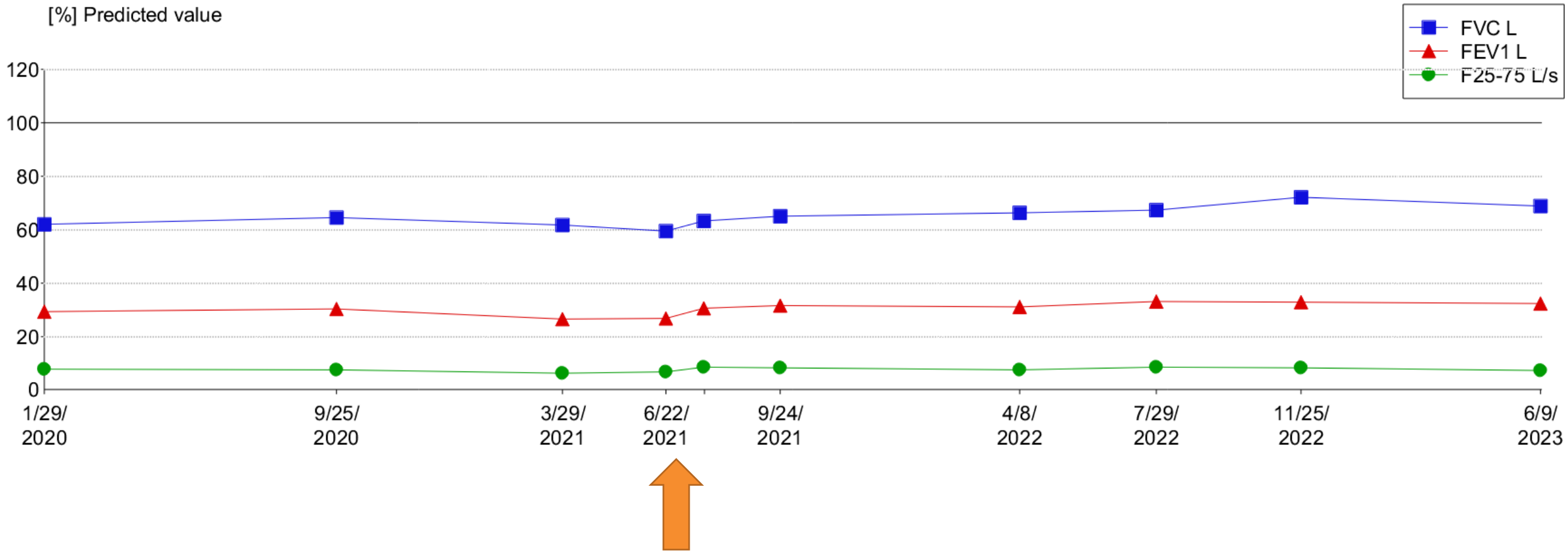
NEJM 2011. 365:1663-72; NEJM 2019, 381(19) 1809

27 yo F



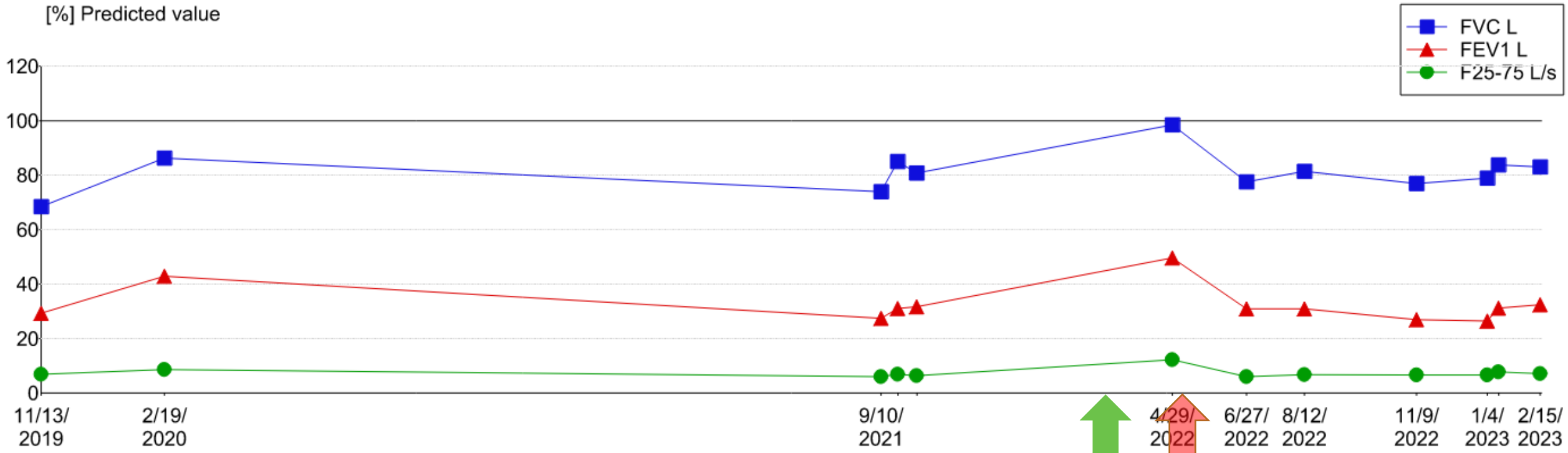
ETI started Nov 2021

42 yo M



ETI started Jun 2021

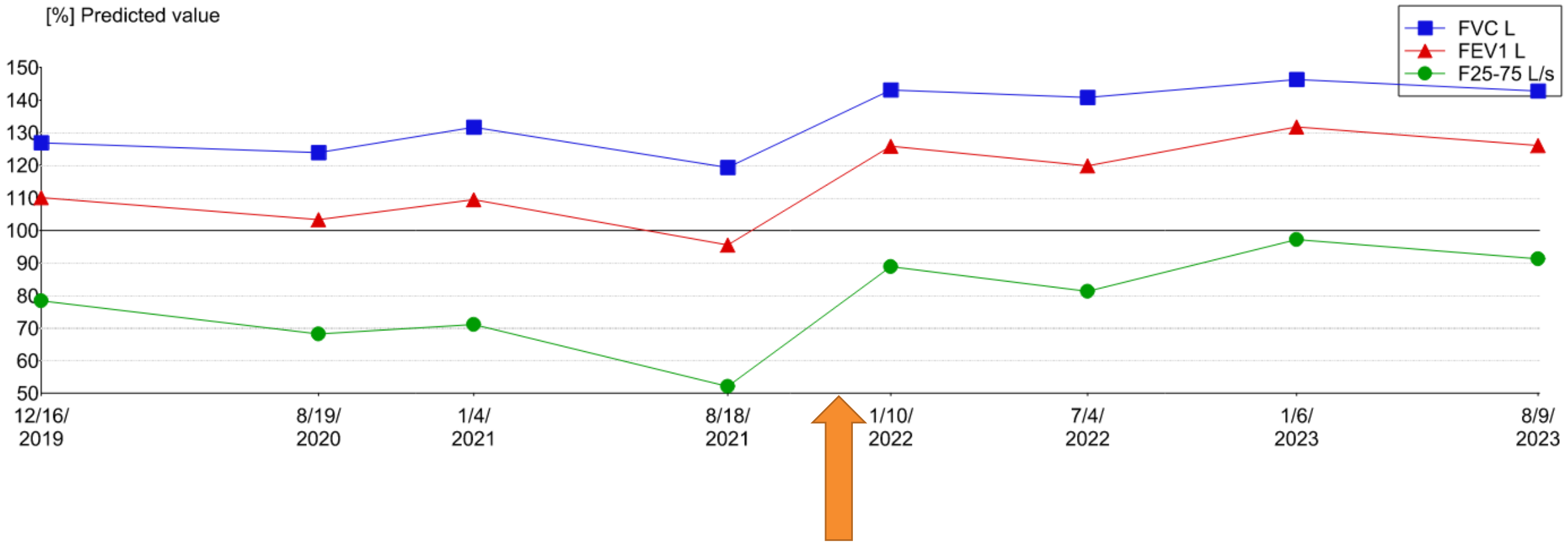
39 yo M



ETI started March 2022

ETI stopped late April due to significant rise in liver enzymes

23 yo F



ETI started Dec 2021

Impact of HEMT beyond the lungs

- Improved nutritional status (as measured by body mass index)
- Improved chronic rhinosinusitis symptoms
- Improved glycemic control
- Improved quality of life scores
- Enhanced fertility in women
- Reduction in abdominal symptoms

NEJM 2011, 365:1663-72; Lancet 2019, 394:1940-8; NEJM 2019, 381(19) 1809;
J Cyst Fibros 2021, 20(3):460-3; J Cyst Fibros 2021, 20(3):399-401;
J Clin Transl Endocrinol 2022, 27:100286; J Cyst Fibros 2022, 21(2):258-63
Front Pharmacol 2022 Jun 3 13:877118

Our local trends

- More “well” clinic appointments (vs “sick” appointments)
- Less hospitalizations and IV antibiotics
- 4 pregnancies in women on their first year of taking ETI
- Increase in body mass index

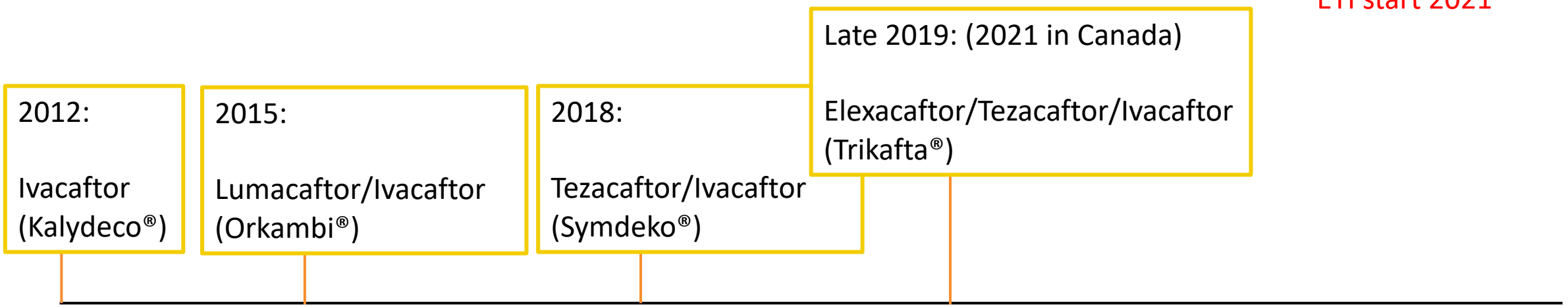
- Emerging health issues? – obesity, cardiovascular disease
- New life goals - Family, career, travel etc
- Psychosocial considerations
- Financial considerations of longer life

Survival in CF

Estimated median age of survival in Canada:

2012:	2015:	2018:	2020:	2021:	2025:	2030:
49.7 years	52.1 years	52.1 years	55.4 years	57.3 years	62.5 years	67.5 years

Projected median age of survival following ETI start 2021



Cystic Fibrosis Canada. (2023). The Canadian Cystic Fibrosis Registry 2021 Annual Data report, and Annual data reports 2012, 2015, 2018, 2020
Stanojevic S. et al. J Cyst Fibros 2021. 20:243-49

What does the future hold?

- Shift in CF care aspects
  - Nutrition goals
  - Simplification of CF lung treatments
  - Preventative health (similar to general population)
  - Psychosocial supports
  - Care for aging population

- CF research continues
  - for treatments for individuals with mutations that do not benefit from current CFTR modulators
  - for the impact of current CFTR modulators for younger CF individuals

Conclusion

- Highly effective modulator therapy has vastly improved the health of individuals with CF
- CF care continues to evolve
  - Healthier lungs and nutrition status
  - Shift in focus of care to other CF care aspects and preventative health
- Research continues to look for therapies that can benefit those whose CFTR mutations do not benefit from current CFTR modulators

Thank you!