LIFC
Lega Italiana
Fibrosi Cistica

10° Forum italiano sulla Fibrosi Cistica

L'impatto dei modulatori sulla vita dei pazienti

Prof. Francesco Blasi

Dipartimento Fisiopatologia e Trapianti, Università di Milano;

Dipartimento di Medicina Interna, SC Pneumologia e Fibrosi Cistica,

Fondazione IRCCS Cà Granda Milano.

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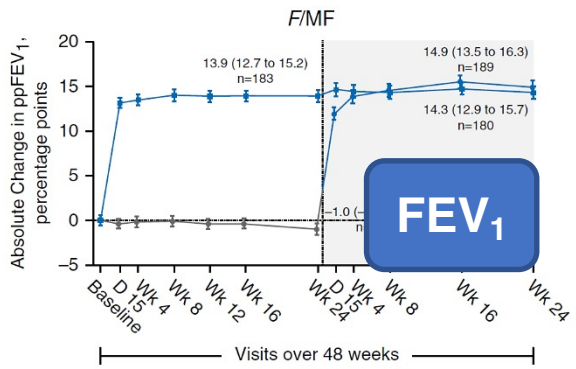
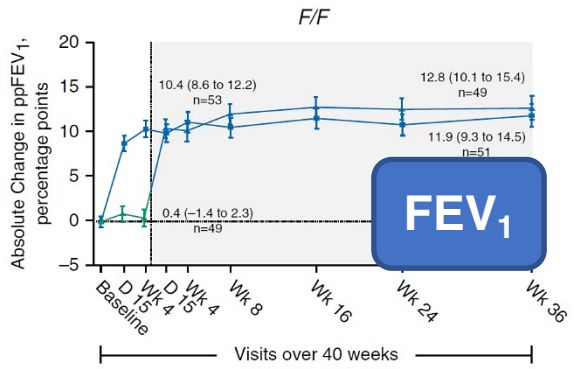
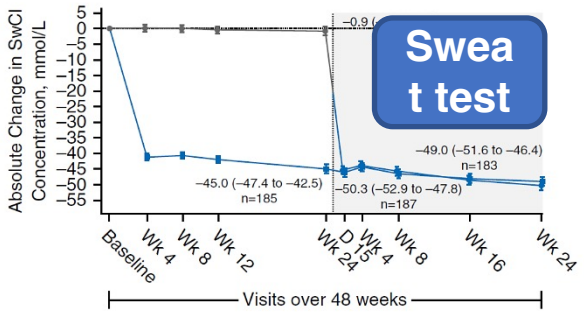
Check for updates

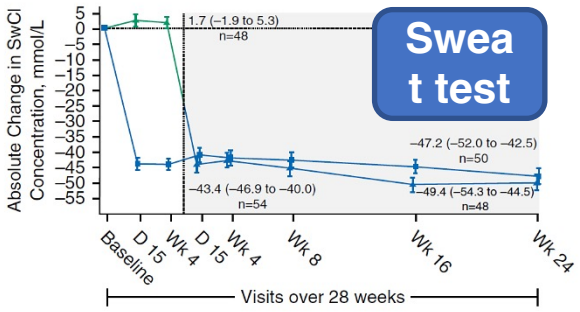
Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor for 24 Weeks or Longer in People with Cystic Fibrosis and One or More *F508del* Alleles: Interim Results of an Open-Label Phase 3 Clinical Trial

12 years and older, ppFEV$_1$ 40-90%
24 to 36 weeks









PBO→ELX/TEZ/IVA ELX/TEZ/IVA
The white shaded portion of the graph corresponds to the *F/MF* pivotal study and the gray shaded portion of the graph corresponds to the OLE.

TEZ/IVA→ELX/TEZ/IVA ELX/TEZ/IVA
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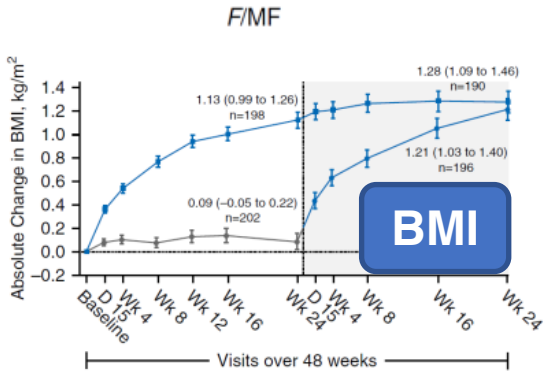

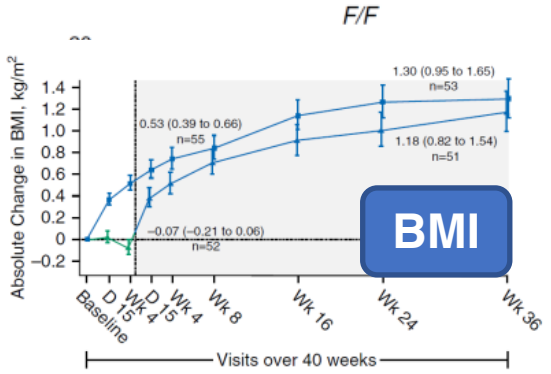

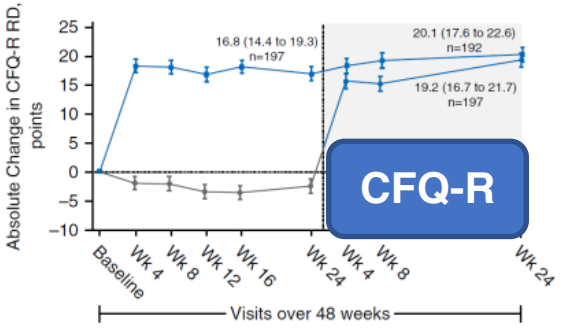

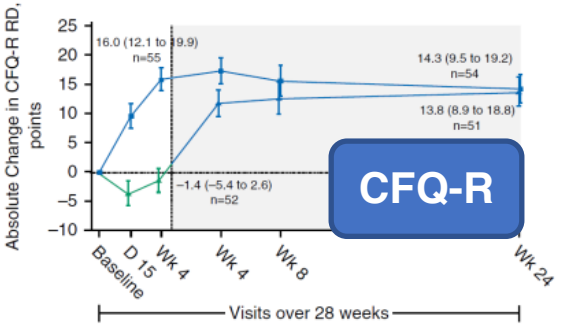

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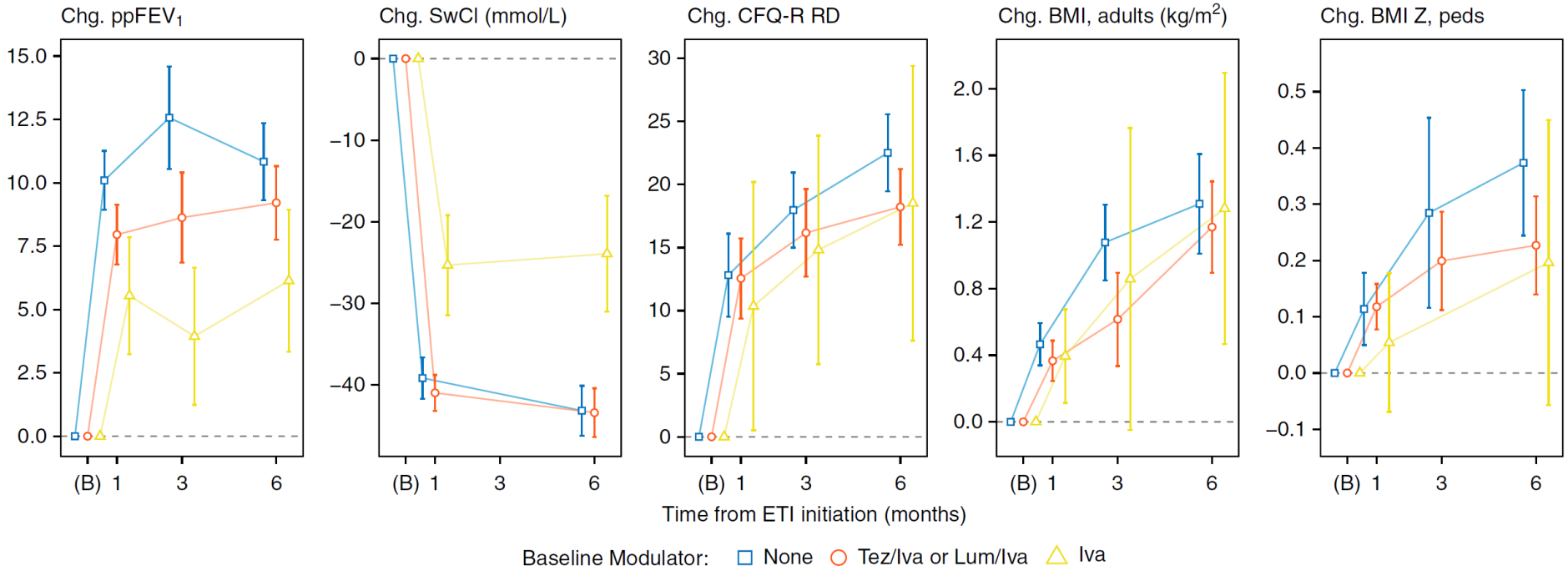
Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis

A Clinical Trial

David P. Nichols[1,2], Alex C. Paynter[2], Sonya L. Heltshe[1,2], Scott H. Donaldson[3], Carla A. Frederick[4], Steven D. Freedman[5], Daniel Gelfond[6], Lucas R. Hoffman[1,7], Andrea Kelly[8,9], Michael R. Narkewicz[10,11], Jessica E. Pittman[12], Felix Ratjen[13], Margaret Rosenfeld[1,14], Scott D. Sagel[15], Sarah Jane Schwarzenberg[16], Pradeep K. Singh[7], George M. Solomon[17,18], Michael S. Stalvey[18,19], John P. Clancy[20], Shannon Kirby[2], Jill M. Van Dalfsen[2], Margaret H. Kloster[2], and Steven M. Rowe[17,18,19]; for the PROMISE Study Group

487 people with CF age 12 years or older with at least one F508del allele starting ETI for the first time



Am J Respir Crit Care Med Vol 205, Iss 5, pp 529–539, Mar 1, 2022

Rapid Improvement after Starting Elexacaftor–Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease

Pierre-Régis Burgel[1,2,3], Isabelle Durieu[3,4,5], Raphaël Chiron[6], Sophie Ramel[7], Isabelle Danner-Boucher[8], Anne Prevotat[9], Dominique Grenet[10], Christophe Marguet[11], Martine Reynaud-Gaubert[12], Julie Macey[13], Laurent Mely[14], Annlyse Fanton[15], Sébastien Quetant[16], Lydie Lemonnier[17], Jean-Louis Paillasseur[18], Jennifer Da Silva[1,3,19], and Clémence Martin[1,2,3]; for the French Cystic Fibrosis Reference Network Study Group

	Not Treated with a CFTR Modulator ($n = 179$)		Treated with a CFTR Modulator ($n = 57$)		*P* Value
$ppFEV_1$					
At initiation	Missing, $n = 1$	29 (24–35)	Missing, $n = 0$	28 (24–33)	0.42
After 1 mo	Missing, $n = 35$	41 (34–50)	Missing, $n = 6$	41 (34–51)	0.87
After 3 mo	Missing, $n = 33$	43 (36–53)	Missing, $n = 19$	42 (35–50)	0.69
Absolute change from initiation, $ppFEV_1$					
After 1 mo	Missing, $n = 35$	+11 (7–17)	Missing, $n = 6$	+11 (8–17)	0.43
After 3 mo	Missing, $n = 34$	+12 (8–20)	Missing, $n = 19$	+13 (7–19)	0.77
After 1 and 3 mo (pooled)*	Missing, $n = 4$	+13 (8–20)	Missing, $n = 0$	+14 (8–20)	0.90
Weight					
At initiation	Missing, $n = 0$	52 (46–60)	Missing, $n = 0$	53 (47–60)	0.89
After 1 mo	Missing, $n = 28$	54 (49–62)	Missing, $n = 6$	56 (49–62)	0.87
After 3 mo	Missing, $n = 32$	58 (52–66)	Missing, $n = 18$	56 (49–63)	0.43
Absolute change from initiation, weight (kg)					
After 1 mo	Missing, $n = 28$	+2.0 (1.0–3.9)	Missing, $n = 6$	+2.0 (0.5–3.5)	0.62
After 3 mo	Missing, $n = 32$	+4.4 (2.7–6.5)	Missing, $n = 18$	+4.0 (2.5–6.0)	0.43
After 1 and 3 mo (pooled)	Missing, $n = 0$	+4.0 (2.0–6.0)	Missing, $n = 0$	+3.0 (2.0–5.0)	0.02

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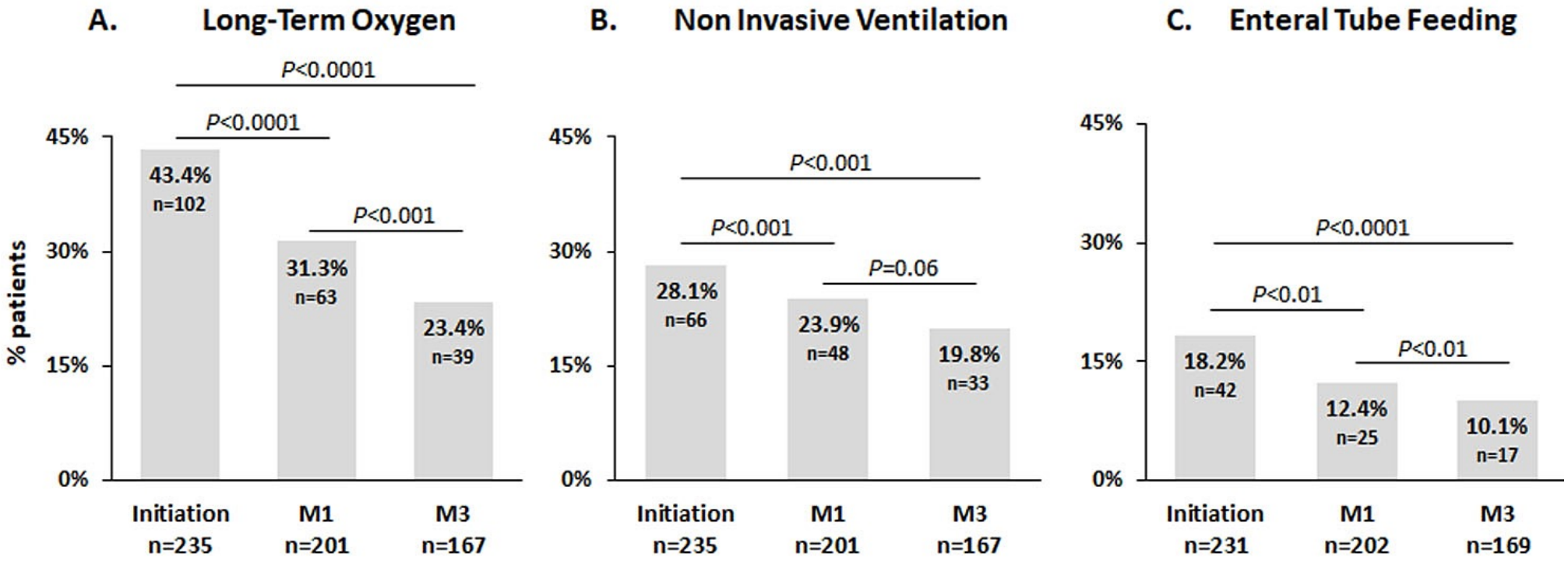
Rapid improvement after starting elexacaftor-tezacaftor-ivacaftor in patients with cystic fibrosis and advanced pulmonary disease

Discontinuation of selected therapies



Burgel et al. AJRCCM 2021; doi: 10.1164/rccm.202011-4153OC

Adverse effects possibly related to elexacaftor-tezacaftor-ivacaftor (n=236 patients)

Clinical manifestations

- Localized cutaneous rash : 17 patients (7.2%)
- Extensive cutaneous rash: 9 patients (3.8%)
- Headache: 10 patients (4.2%)
- Gastro-intestinal symptoms: 24 patients (10.2%)
- Myalgia/Arthralgia: 11 patients (4.7%)

Blood tests

- ALAT>3N: 6 patients (2.5%); including 2 patients ≥5N
- ASAT ≥3N: 2 patients (0.8%)
- Bilirubin ≥3N: 11 patients (4.7%)
- CPK ≥3N: 8 patients (3.4%) up to 11N

No elexacaftor-tezcafator-ivacaftor discontinuation

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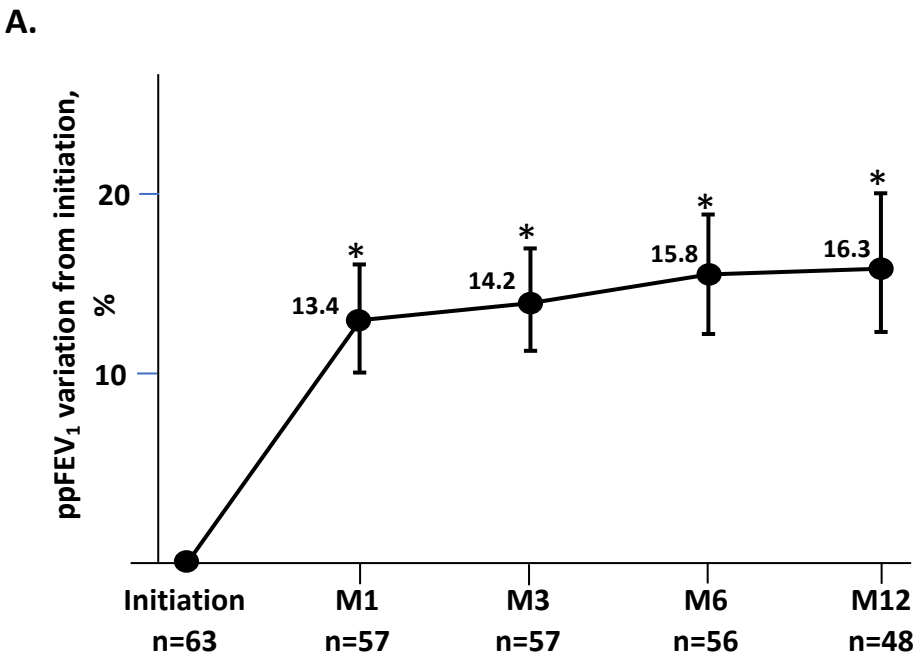
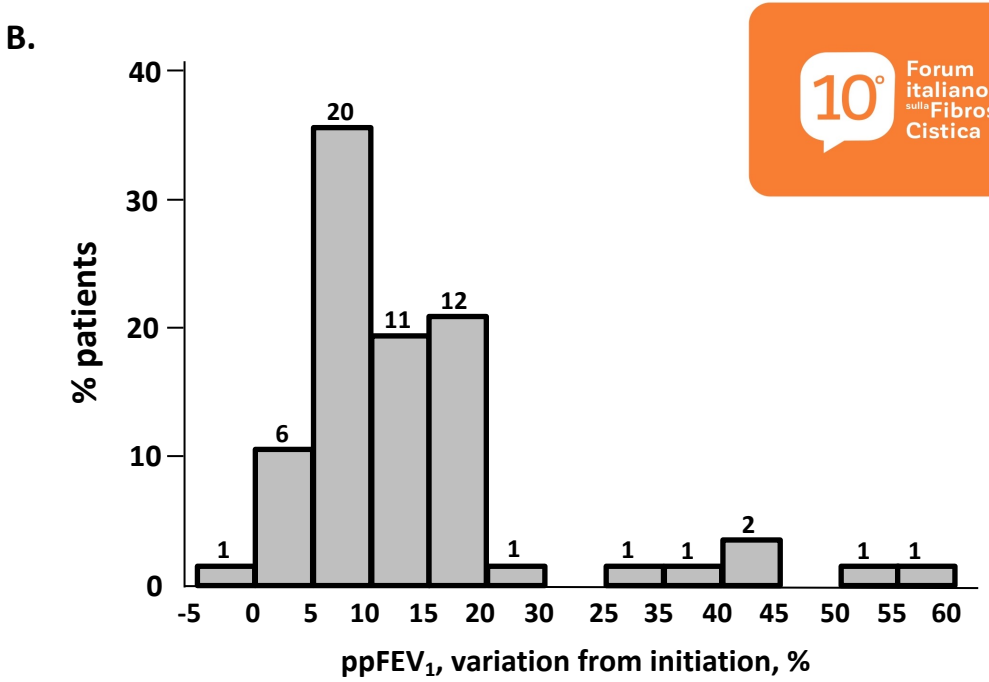
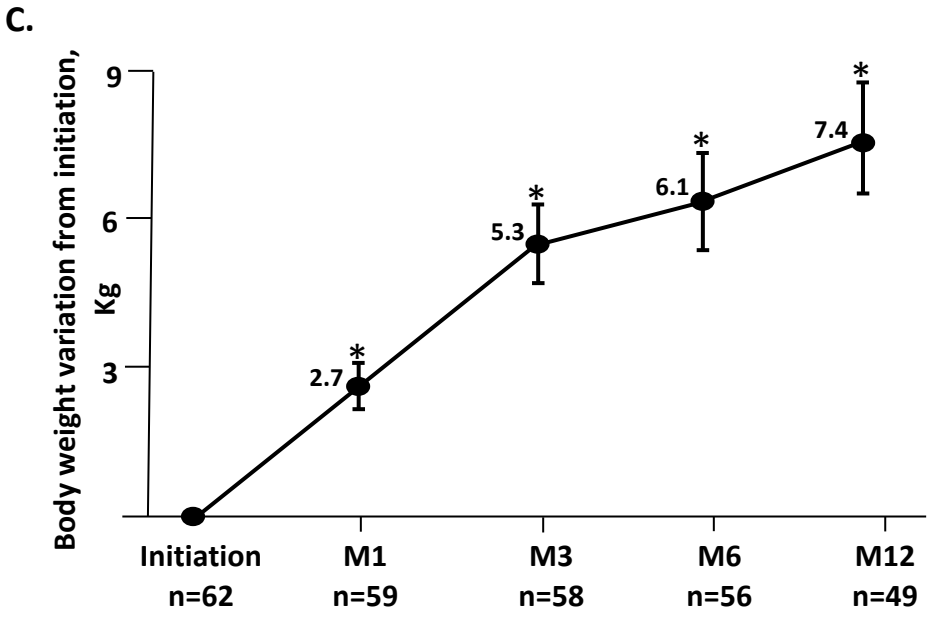
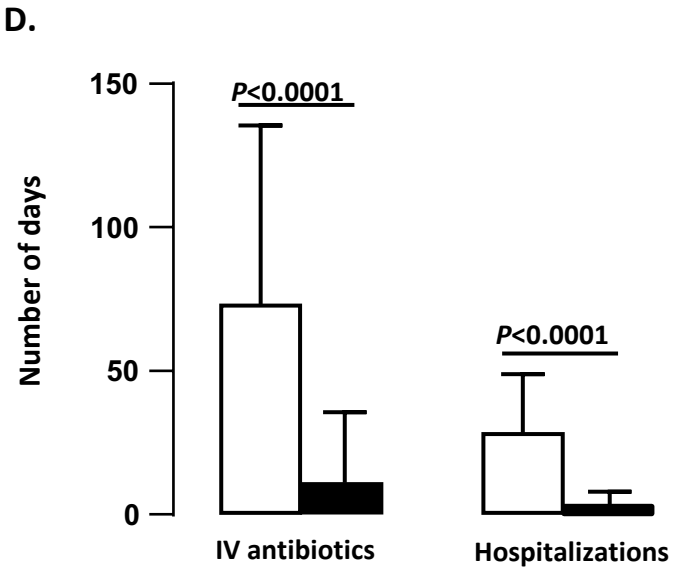
1 year of ELX-TEZ-IVA in patients with very severe respiratory disease (lung transplant candidates)

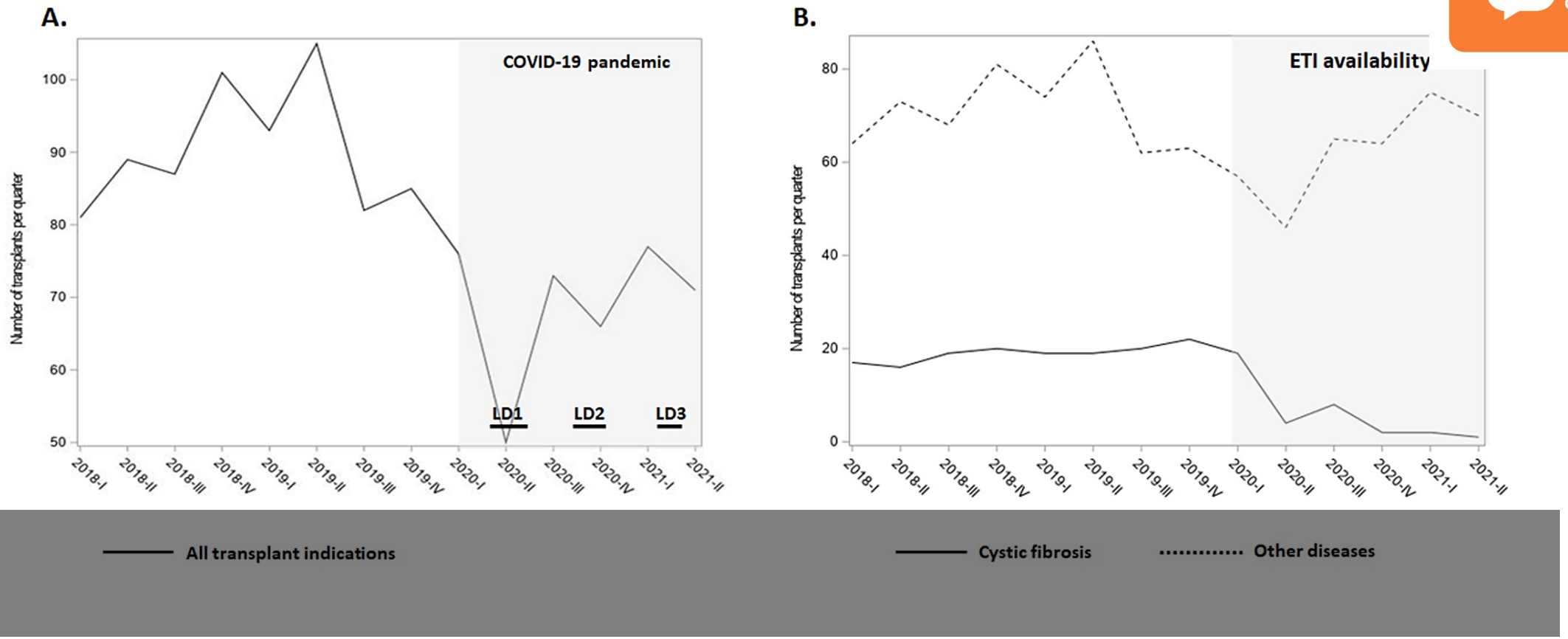








Martin et al. *J Cyst Fibrosis* 2022; in press



Martin C et al. *Am J Respir Crit Care Med* 2022; 205(5):584-586

Major decrease in lung transplantation in patients with CF in France: COVID-19 vs. ETI

Discontinuation of other therapies

Use of Four Chronic Daily Medications Assessed at Each Visit by Self-Report

Outcome	Visit	Using/Observed (%)	*P* Value
Inhaled antibiotics	Baseline	248/486 (51.0)	—
	1 mo	186/417 (44.6)	—
	3 mo	97/195 (49.7)	—
	6 mo	145/429 (33.8)	<0.005
Azithromycin	Baseline	238/486 (49.0)	—
	1 mo	206/417 (49.4)	—
	3 mo	94/195 (48.2%)	—
	6 mo	191/429 (44.5%)	0.01
Hypertonic saline	Baseline	368/486 (75.7%)	—
	1 mo	308/417 (73.9%)	—
	3 mo	148/195 (75.9%)	—
	6 mo	293/429 (68.3%)	<0.005
Dornase alfa	Baseline	424/486 (87.2%)	—
	1 mo	365/417 (87.5%)	—
	3 mo	166/195 (85.1%)	—
	6 mo	350/429 (81.6%)	<0.005

Nichols DP et al. *Am J Respir Crit Care Med* Vol 205, Iss 5, pp 529–539, Mar 1, 2022

Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Research letter: The impact of elexacaftor/tezacaftor/ivacaftor on adherence to nebulized maintenance therapies in people with cystic fibrosis

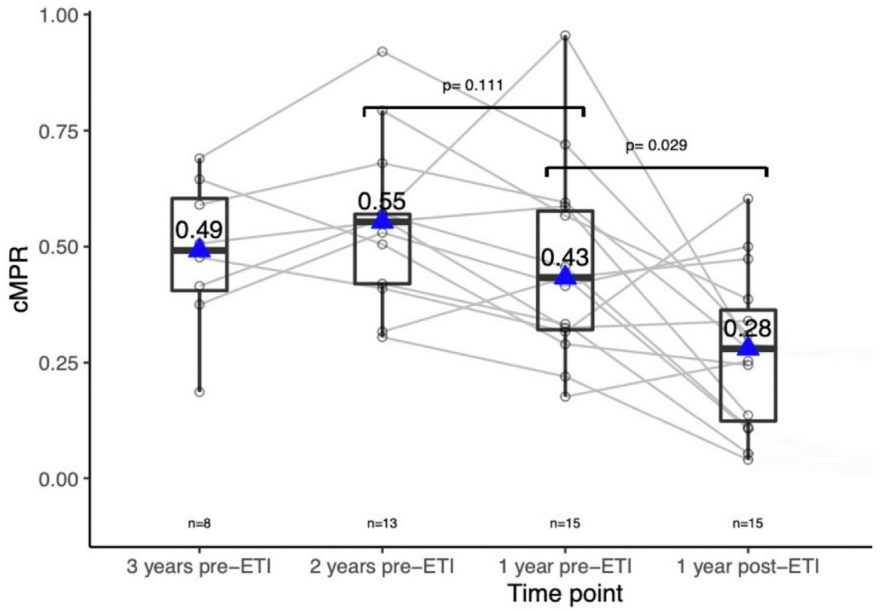
June 2022

Retrospective study in the **15 patients** that started ETI in Vancouver ppFEV1 38%;

$$\textit{Drug-specific MPR} = \frac{\textit{sum of all days of medication filled}}{\textit{number of days the medication was prescribed for}}$$

$$\textit{Composite MPR (cMPR)} = \textit{average of all drug-specific MPRs for each patient}$$

Drug	MPR pre ETI	MPR 1 yr ETI	P value
Dornase α	0.47	0.21	0.03
Hypertonic saline	0.45	0.14	0.014
Inhaled antibiotics	0.43	0.33	0.20
Azithromycin +PERT	0.57	0.43	0.18



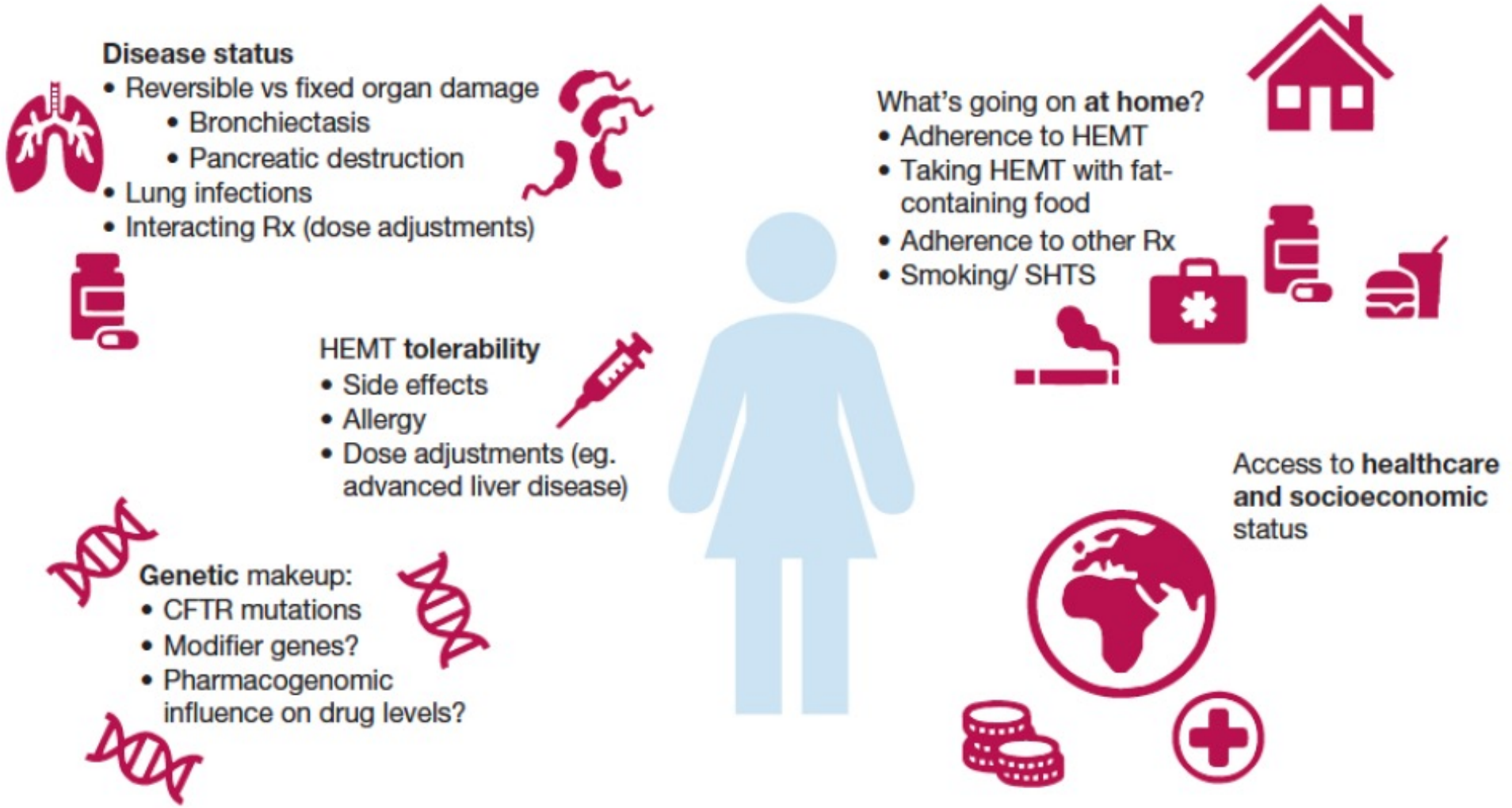
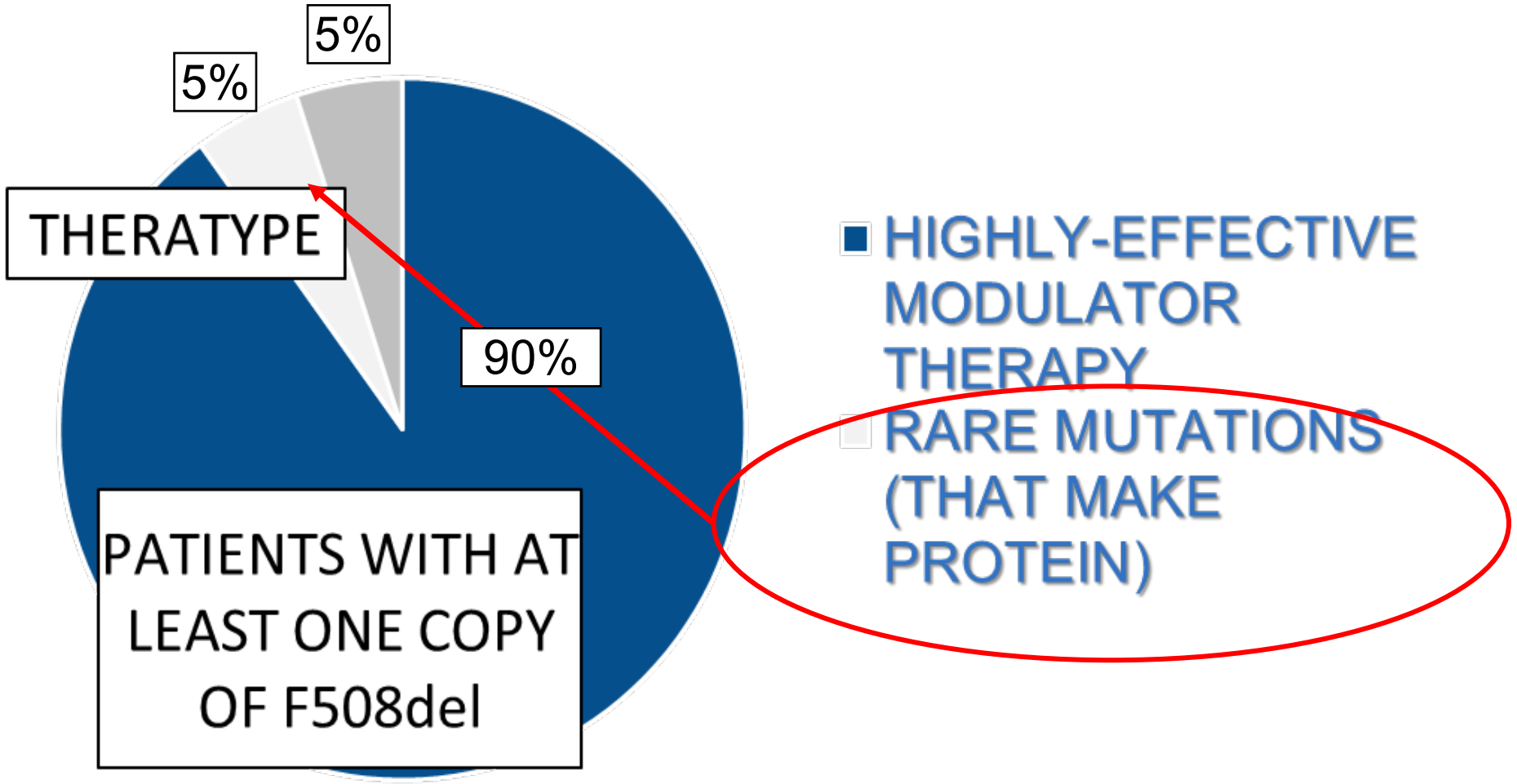


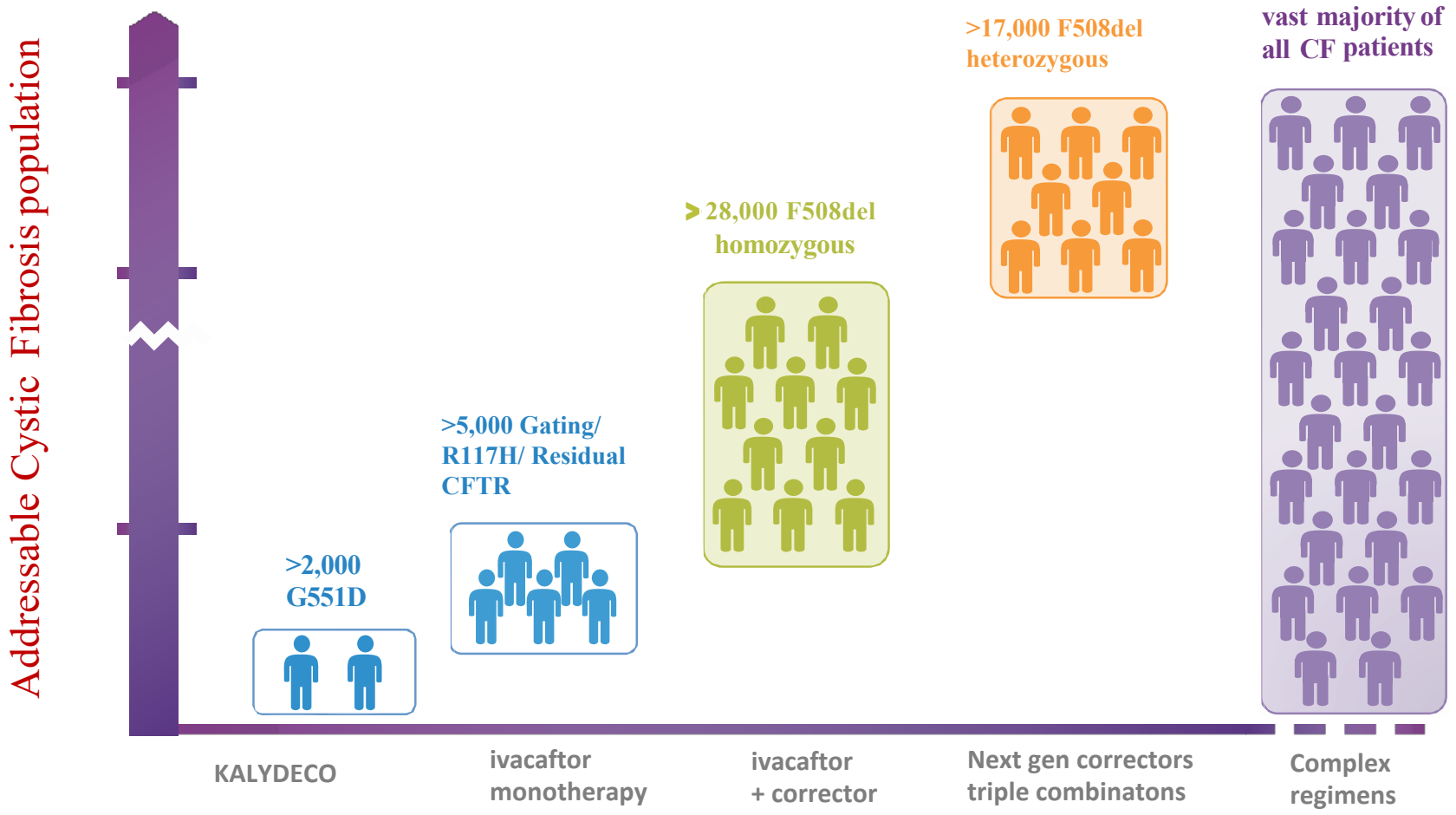
Figure 1 – *Individuals may respond differently to cystic fibrosis transmembrane regulator protein modulators, based on a huge number of factors. Many of these groups interact, for example, home environment, socioeconomic status, and disease status. When weighed against these cumulative impacts, any distinction between child and adult is arbitrary. CFTR = cystic fibrosis transmembrane regulator protein; HEMT = highly effective CFTR modulator therapy; Rx = therapies; SHTS = second-hand tobacco smoke.*

https://doi.org/10.1016/j.chest.2021.06.018

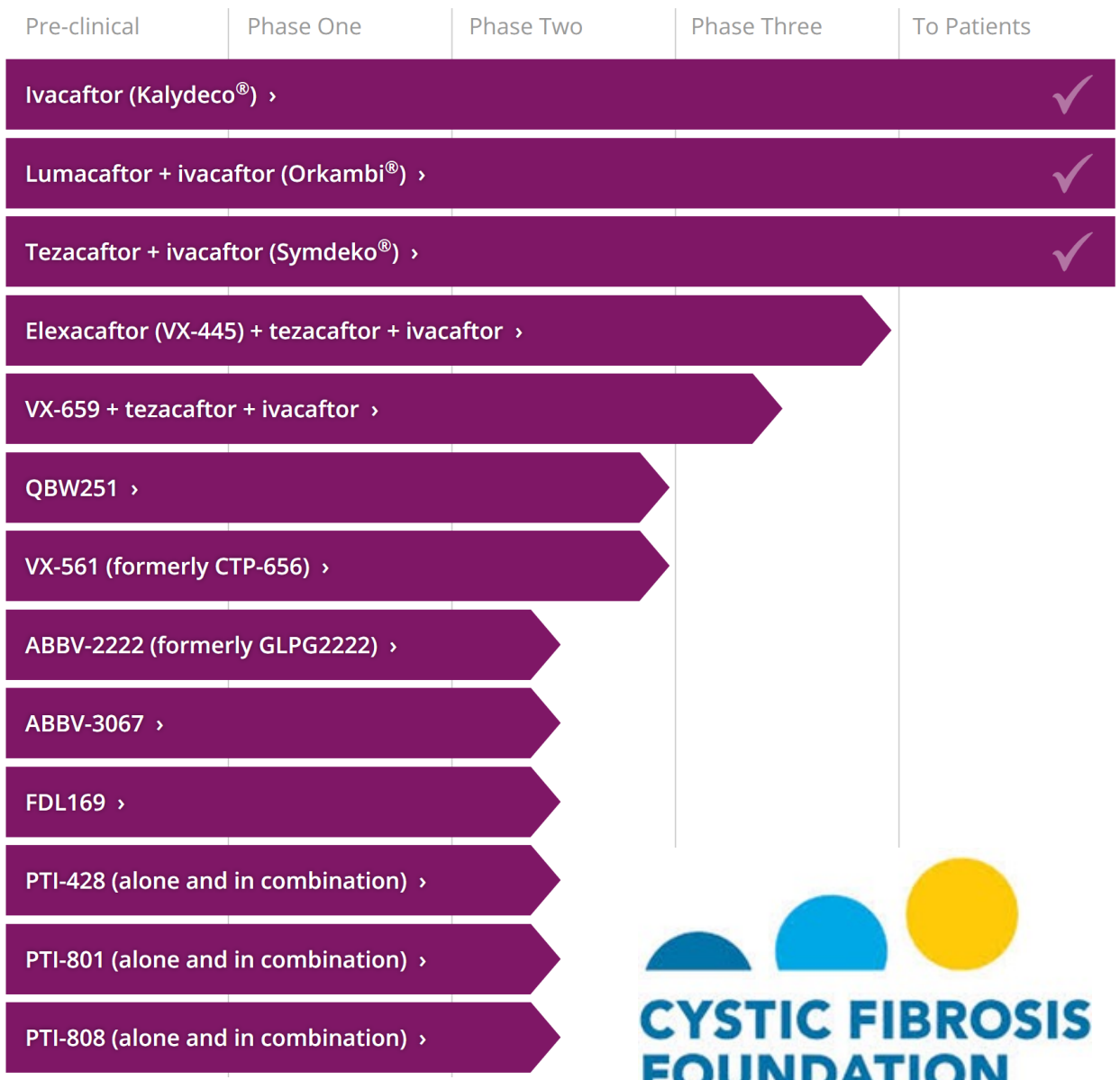
Therapeutics Coverage in 2022



CF Treatment



Restore CFTR Function | Learn more ›



CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

10° Forum italiano sulla Fibrosi Cistica

Developing Highly Effective Therapy for the Last 5-10%

- **Strategies: stop mutation readthrough, RNA delivery and repair, DNA delivery and expression, gene editing and stem cells**

Nonsense (PTC) mutations largest single group with unmet need:

- **Eloxx in phase I with gentamicin analog**
- **Partnership with Southern Research Institute/University of Alabama**
  - **Screening of 750,000 compounds for new readthrough agents**
- **CFFT Laboratory, Lexington, Mass.**

The unanswered questions?

- Long-term side effects
- Safety in pregnancy
- Best time to start
- Interactions
- Need for other medications
- Adherence to new drugs
- Adherence to other drugs
- Role in end stage disease or post-transplant

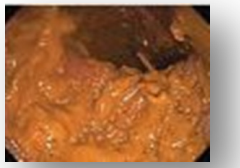
Emerging issues….RWE

- **Drug-related**
  - Renal disease – 42% adults (n = 80), [creat clearance <80][1]
  - Ototoxicity – 50.8% adults (n = 153), [varying severity][2]
  - Polypharmacy

- **Age related**
  - Obesity – 11% adults (n = 187), BMI>25[3]
  - Hypercholesterolemia – 24% (PI) and 43% (PS) adults (n = 334)[4]
  - ? Ischaemic heart disease – case reports

- **Drug/CF/age related ??**
  - Cancer – ↑GI malignancy (SIR 3.5; 95% CI 2.6–4.7)[5]
    - Colonoscopic screening programme; >40 y, FEV_1>40%
    - Cardiovascular disease

25% advanced adenomas and **3%** carcinoma



1. Al-Aloul M et al. *Pediatr Pulmonol.* 2005;39:15–20
2. Conrad DJ et al. *Pharmacogenet Genomics.* 2008;18:1095–1102
3. Coderre L et al. *J Cyst Fibros.* 2012;11:393–397
4. Rhodes B et al. *J Cyst Fibros.* 2010;9:24–28
5. Maisonneurve P et al. *J Natl Cancer Inst.* 2013;105:122-129
6. Niccum DE et al. *J Cyst Fibros.*2016;pii:S1569–1993(16)00009-6

Future Adult CF Outpatient care delivery model

Home care

- Home monitoring
  - Spiro/BMI/activity monitors/sputum surveillance/local dexa/remote bloods if necessary/audiology
  - Regular AHP led clinics at satellite clinic if required
    - All pts 2 yrly cross-sectional MRI to r/v progression
    - Annual review

Satellite care

- Combination home and satellite care

Designated CF centre local to pt run by CF staff visiting from central CF hub

- Homecare info reviewed pre clinic.

Pts triaged based on homecare info and nurse specialist to AHP driven clinic as required and Consultant

POC micro testing available at clinic

Central CF hub care

- Complex infection/low-lung function/complex co-morbidity requiring non-CF specialist input
- CF team /micro/ID/ Immunology/Radiologist/Gastro/liver/ENT/Audiology/Geneticist/Fertility/pall care/pharmacy etc
- Comprehensive immunoprofiling/immunogenetics + CF genetics
- Virtual/FtF clinics for pts from other OP groups that warrant further review.

Homecare info reviewed pre clinic.

Pts triaged based on homecare info and nurse specialist to AHP driven clinic as required and Consultant

Designated specialist AHP clinics for difficult pts (physio/dietician/Pysch) plus joint dietician/Pysch clinics

POC micro testing at clinic plus immune biomarker (?NE/HMGB-1)

Separate NTM clinics

The Future

- Large number of drugs in clinical development
- Pre-clinical pipeline is strong
- Challenges of how do we use them, when do we use them, what combinations will work best?
- The natural history of CF will alter
    - Likely rise in co-morbidities
    - Tailor drug therapies over time
- This is an unprecedented time of CF research