UNIVERSITY
CHILDREN'S HOSPITAL
ZURICH
Children's Research Center CRC

Personalized Medication for Cystic Fibrosis:

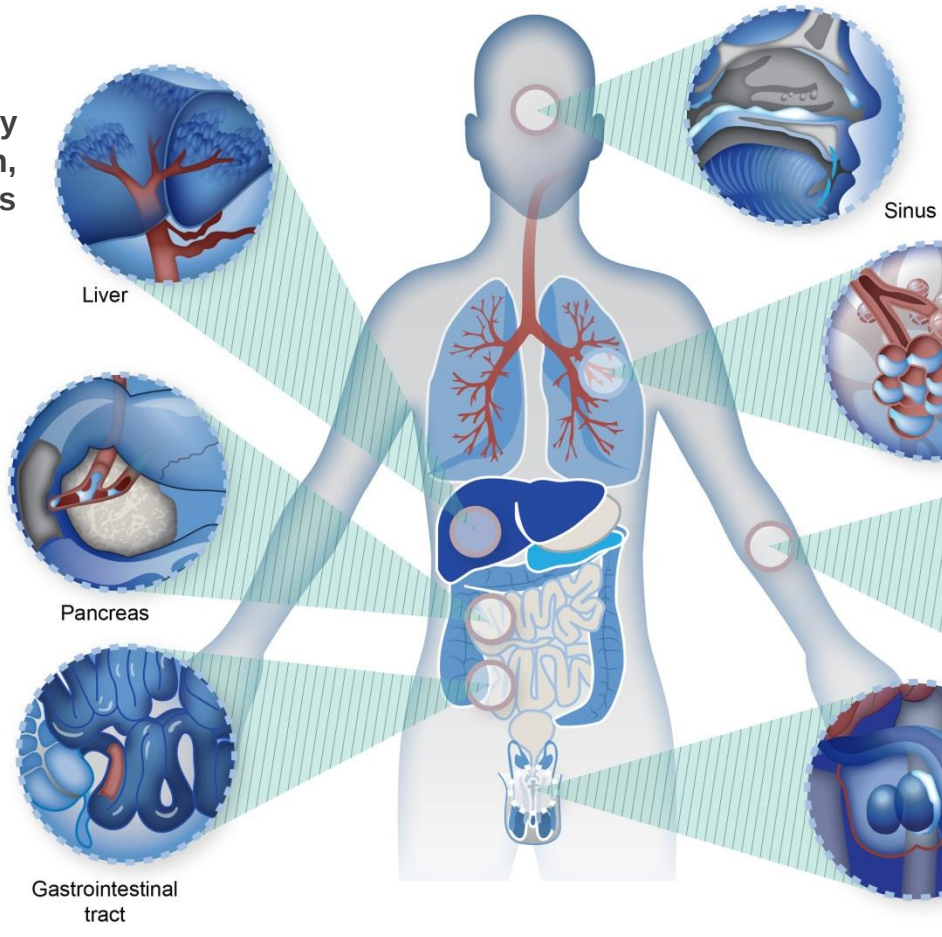
A new era

Dr. med. Andreas Jung

Consultant in Paediatric Pulmonology / Cystic Fibrosis

Diagnosing CF

Cystic Fibrosis (CF): A genetic, multiple organ disease



Cholestase, biliary duct obstruction, liver fibrosis/cirrhosis

Chronic rhinosinusitis, nasal polyps

Reduced lung function, bacterial airway infection, progressive lung damage; ABPA

Exocrine pancreatic insufficiency and malnutrition; failure to thrive; endocrine pancreatic insufficiency (CFRD)

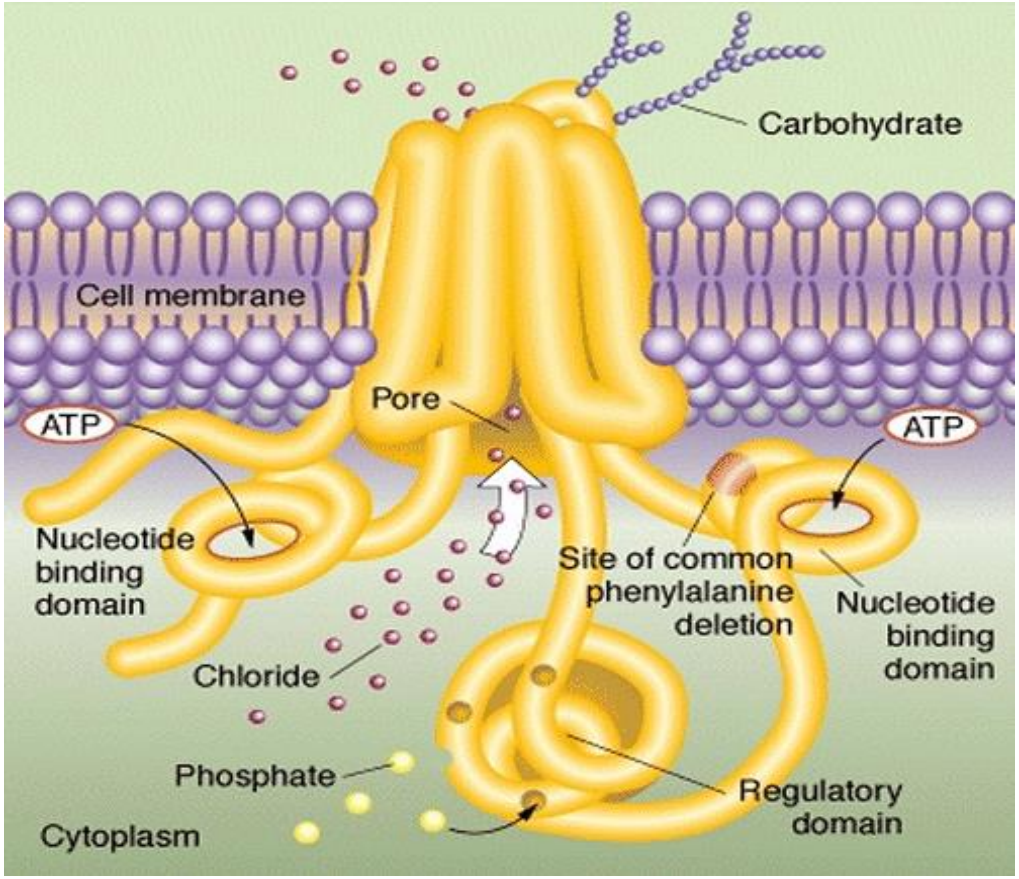
Salt loss syndrome (Pseudo Bartter`s syndrome)

Intestinal obstruction / coprostasis (DIOS)

Infertility in males (CBAVD)

O'Sullivan, Lancet 2009
Westaby, Prog Respir Res.2006

Basic defect in Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) = chloride channel



Cystic Fibrosis: Epidemiology

- Autosomal recessive inheritance, gene locus 7q3.1, CFTR-Gen
- Incidence in CH 1:3600, carrier frequency ca. 1:25
- >70% dF508-Mutation (compound heterozygous or homozygous)
- >2000 mutations known, ca.15% disease causing
- Some mutations of undetermined clinical consequence

- “Classic” CF vs. CFTR-related disorder („atypical“ or mild CF)
- “CFSPID”: CF screening positive, inconclusive diagnosis

- CF registry 2021: n = 1053 people with CF in CH, 57% ≥ 18 Jahre
- Age at diagnosis: Median 4 months
- National CF newborn screening since 1.01.2011

Early diagnosis is essential

- Optimal nutritional status and growth
- Improved mental developement (vitamin E)
- Increased survival

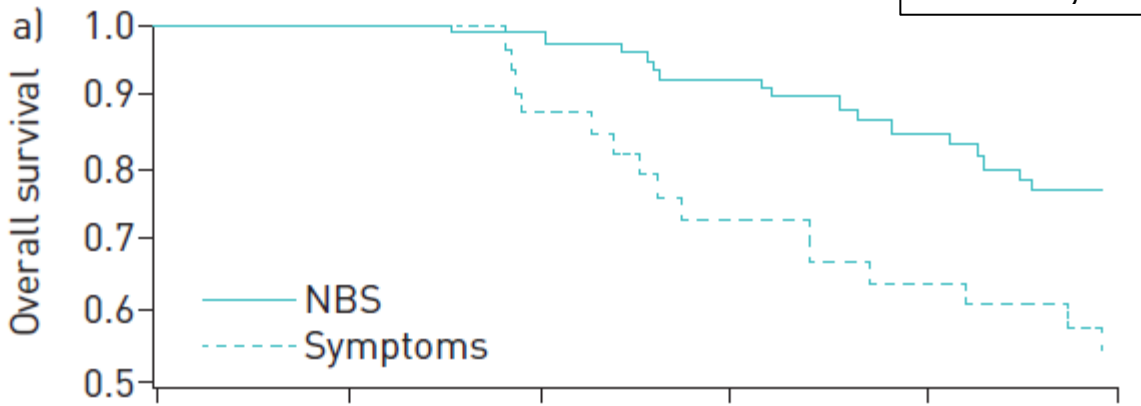
- Shorter period of fear and suffering
- Family planning

- Increased overall prognosis

Newborn screening increases survival

N=586
NBS=342
Clinical=244
Verona, 1971-2014

Severe group
≥3 hosp./year



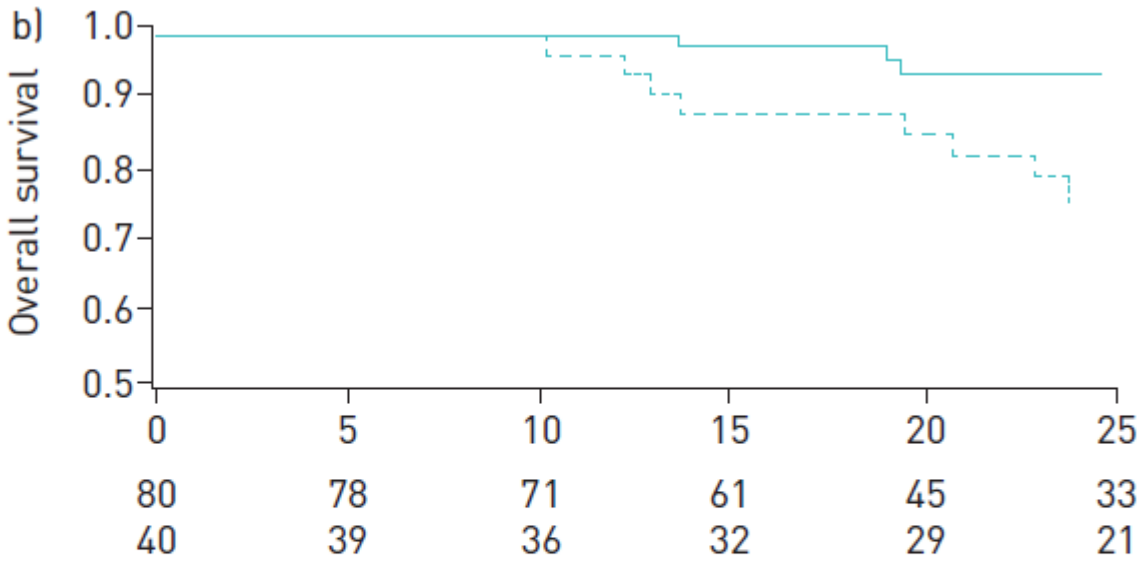
	Patients n	Events n	HR (95% CI)	20 years OS (95% CI)	p-value
NBS	95	23	1.00	84.93 (74.29–91.41)	0.007
Symptoms	34	21	2.23 (1.23–4.03)	63.64 (44.95–77.46)	

Tridello et al., ERJ Open Res 2018

Newborn screening increases survival

N=586
NBS=342
Clinical=244
Verona, 1971-2014

Moderate group
1-2 hosp./year

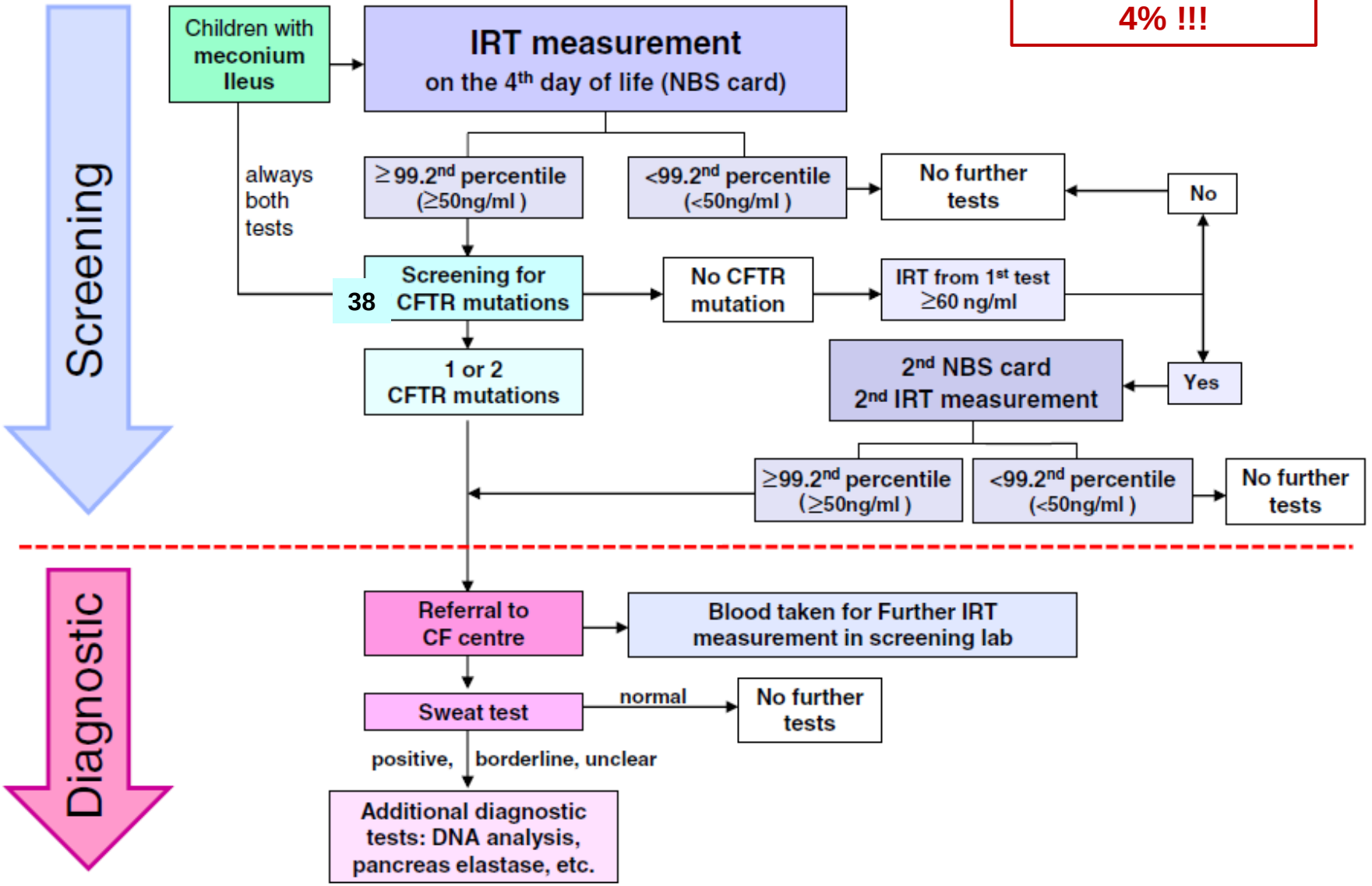


	Patients n	Events n	HR (95% CI)	20 years OS (95% CI)	p-value
NBS	80	4	1.00	94.48 (83.72–98.20)	0.016
Symptoms	40	21	3.86 (1.21–12.38)	85.93 (69.41–93.89)	

Tridello et al., ERJ Open Res 2018

Newborn screening in Switzerland

Screening failure 4% !!!



CFSPID

CF ccreen positive, inconclusive diagnosis

Increased IRT in NBS

and

a) Normal sweat test & 2 CFTR mutations (at least one of them with undetermined clinical consequence)

or

a) Intermediate sweat test with one or no CFTR mutation

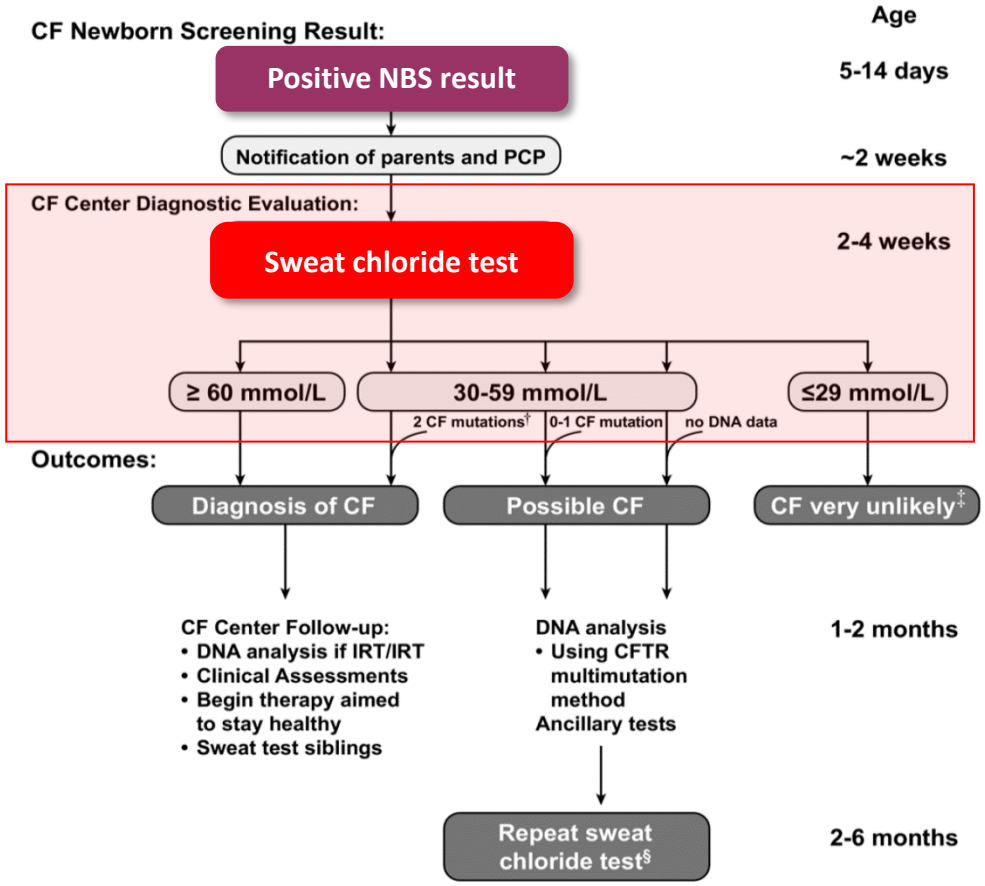
(intermediate / pathological sweat test and 2 CF causing mutations = CF)

Risk to develope mild CF / CF-related disorder in later life

Barben & Suthern, Curr Opin Pulm Med 2016

Guidelines for Diagnosis of Cystic Fibrosis in Newborns through Older Adults: Cystic Fibrosis Foundation Consensus Report

Philip M. Farrell, MD, PhD, Beryl J. Rosenstein, MD, Terry B. White, PhD, Frank J. Accurso, MD, Carlo Castellani, MD, Garry R. Cutting, MD, Peter R. Durie, MD, FRCP, Vicky A. LeGrys, DrA, CLS, John Massie, MBBS, FRACP, PhD, Richard B. Parad, MD, MPH, Michael J. Rock, MD, and Preston W. Campbell, III, MD



- Positive NBS
- Positive family history
- One or more typical clinical feature of CF

AND

- Sweat chloride ≥ 60 mmol/l on at least two occassions

OR

- Two CF-causing mutations

* 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.

Farrell, J Pediatr 2008

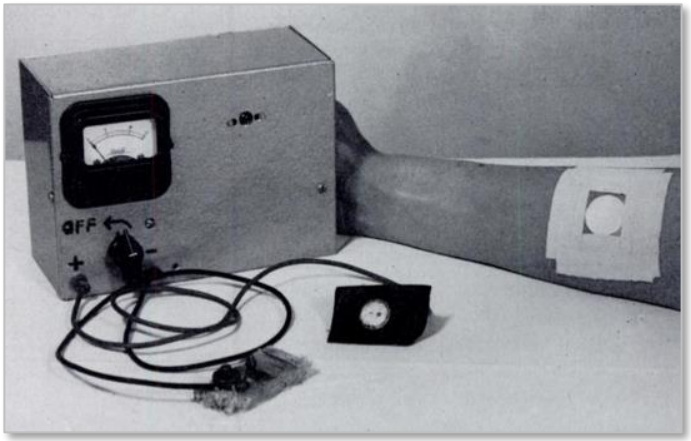
Woe to that child which when kissed on the forehead tastes salty – he is bewitched and soon must die.

Observation of midwifes in the 17th century

A TEST FOR CONCENTRATION OF ELECTROLYTES IN SWEAT IN CYSTIC FIBROSIS OF THE PANCREAS UTILIZING PILOCARPINE BY IONTOPHORESIS

By Lewis E. Gibson, M.D., *and* Robert E. Cooke, M.D.

Department of Pediatrics, Johns Hopkins Medical School, Johns Hopkins University



THE DISCOVERY OF Darling and coworkers[1,2] that there is a high concentration of sodium and chloride in the sweat of patients with cystic fibrosis of the pancreas has been widely applied in the diagnosis of the disease. When these authors tested 43 patients with this disease, they found that all of the patients had concentrations of chloride in sweat above 60 meq/l, with a mean value of 106 meq/l; 50 controls all had values below 80 meq/l and only 3 were above 60 meq/l. In many clinics the sweat test is performed by placing the patient's body in a plastic bag to stimulate sweating as suggested by Shwachman *et al.*[3]

tion is obviously painful. The oral administration of cholinergic drugs has not been recommended as a diaphoretic stimulus for this test; such a procedure would be dangerous because of systemic effects.

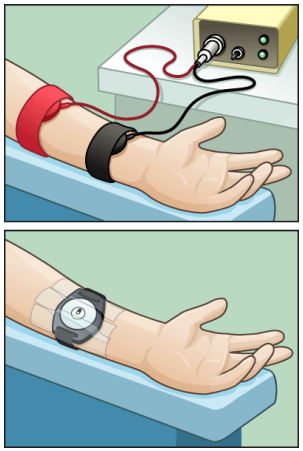
The method to be described obviates these difficulties by avoiding both the danger of heat stress and the pain of injection. Pilocarpine is introduced into the skin by iontophoresis where it produces localized sweating. The process of iontophoresis is almost completely painless and requires only 5 minutes. Rapid sweating continues for about 30 minutes after stimulation, during which time an adequate collection can be made.

Still the gold standard!

Gibson & Cooke, Pediatrics 1959

Sweat test: Accepted methods and cut-off values

	Chlorid Titration	Conductivity
Normal	< 30 mmol/l	< 50 mmol/l
Intermediate	30 – 59 mmol/l	50 – 79 mmol/l
CF	≥ 60 mmol/l	≥ 80 mmol/l
Sweat volume	≥ 15 µL (Macroduct®)	≥ 3 µL (Nanoduct®)
Sweat rate	n.a.	≥ 1.0 g/m^2/min



Managing CF care

CF management: a multidisciplinary approach

Social workers

Genetics

Rehabilitation

CF specialists (pulmonologists)

Lung function lab

Transition / Transplantation

Physiotherapists

Dieticians

Psychologists

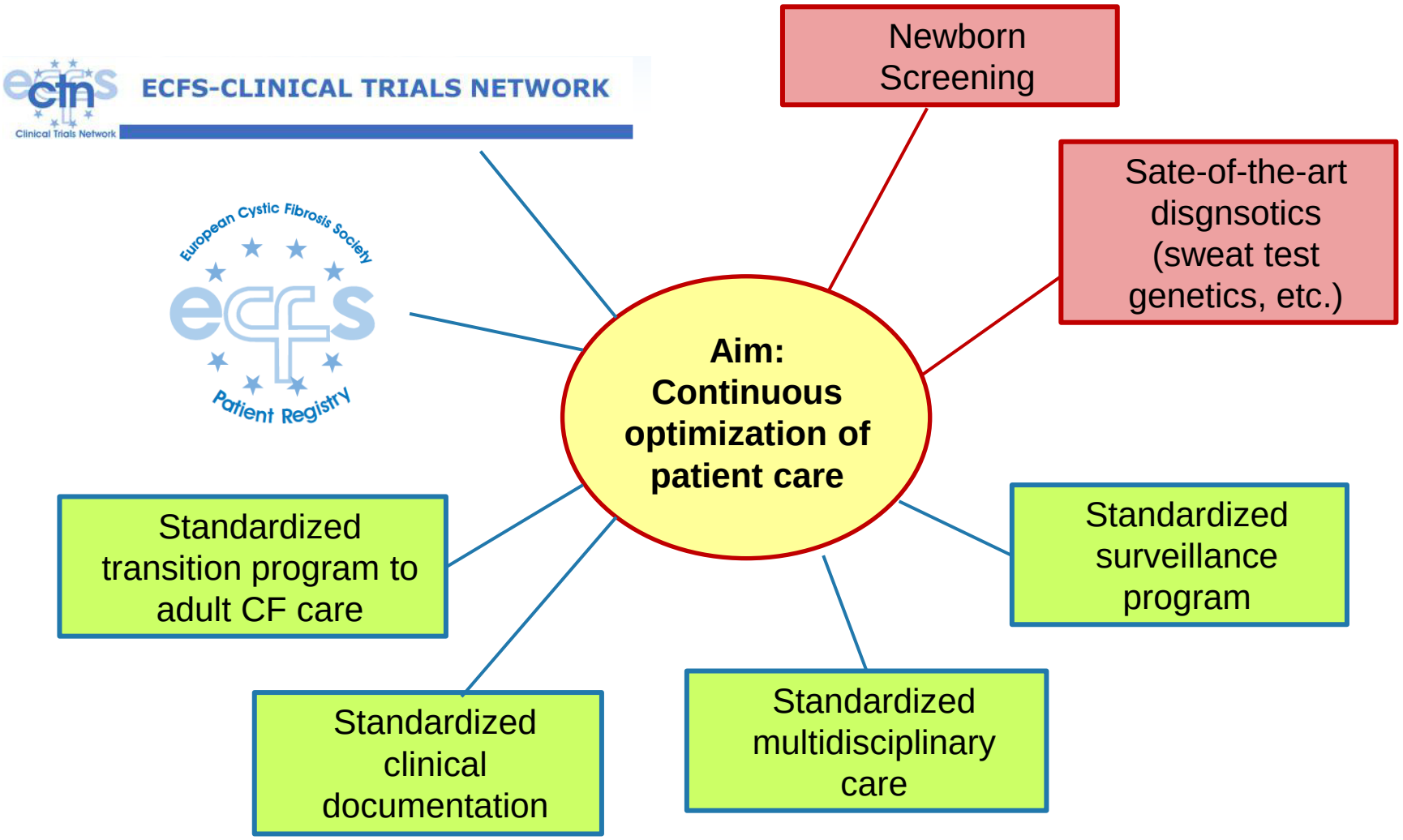
Specialists:
Gastroenterology
Diabetology
ENT
Radiology
Infectious Diseases

Patient Registry

Research

CF nurse

Standards of a paediatric CF centre in Europe today



Standards of care of the European CF society (ECFS)

ELSEVIER

Journal of Cystic Fibrosis 4 (2005) 7–26

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Standards of care for patients with cystic fibrosis: a European consensus

Eitan Kerem*, Steven Conway, Stuart Elborn, Harry Heijerman

For the Consensus Committee[1]

Department of Pediatrics and CF center, Mount Scopus, Jerusalem 91240, Israel

ELSEVIER

Check for updates

Journal of Cystic Fibrosis 17 (2018) 153–178

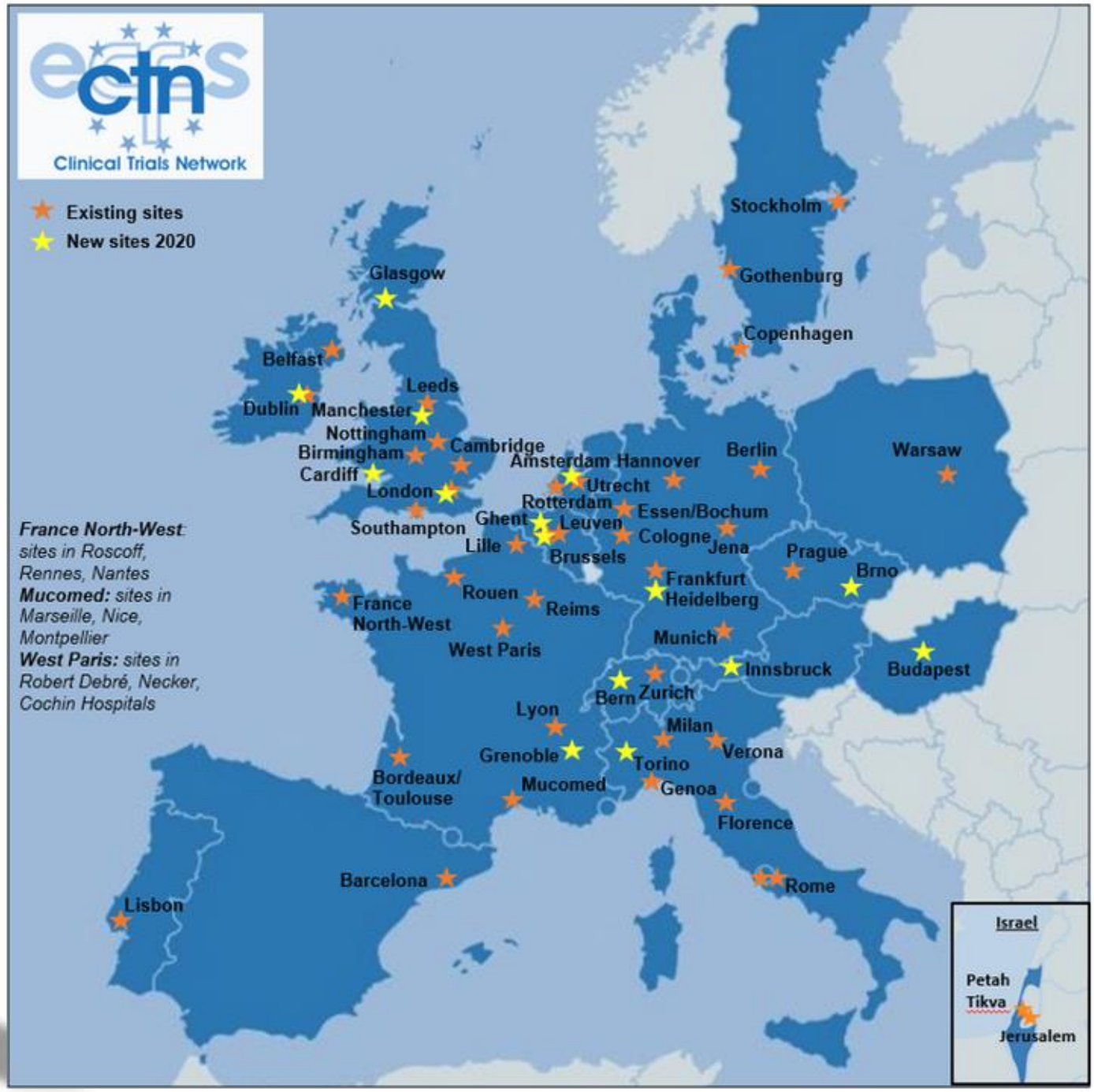
Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Review

ECFS best practice guidelines: the 2018 revision

Carlo Castellani [a,b], Alistair J.A. Duff [c,d,*], Scott C. Bell [e], Harry G.M. Heijerman [f], Anne Munck [g], Felix Ratjen [h], Isabelle Sermet-Gaudelus [i], Kevin W. Southern [j], Jurg Barben [k], Patrick A. Flume [l], Pavla Hodková [m], Nataliya Kashirskaya [n], Maya N. Kirszenbaum [o], Sue Madge [p], Helen Oxley [q], Barry Plant [r], Sarah Jane Schwarzenberg [s], Alan R. Smyth [t], Giovanni Taccetti [u], Thomas O.F. Wagner [v], Susan P. Wolfe [w], Pavel Drevinek [x]



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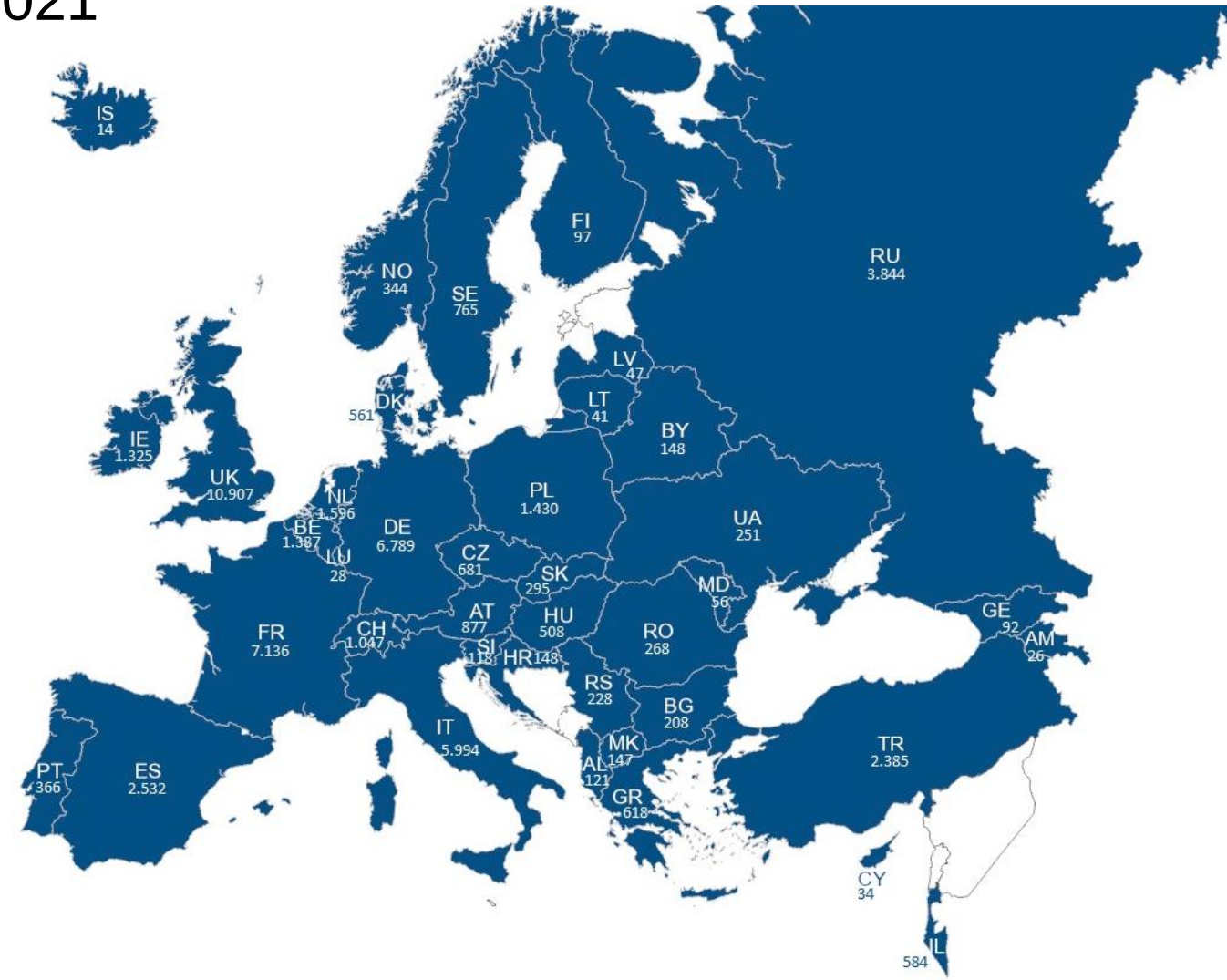
ECFS Patient Registry (ECFSPR): Annual Report 2021

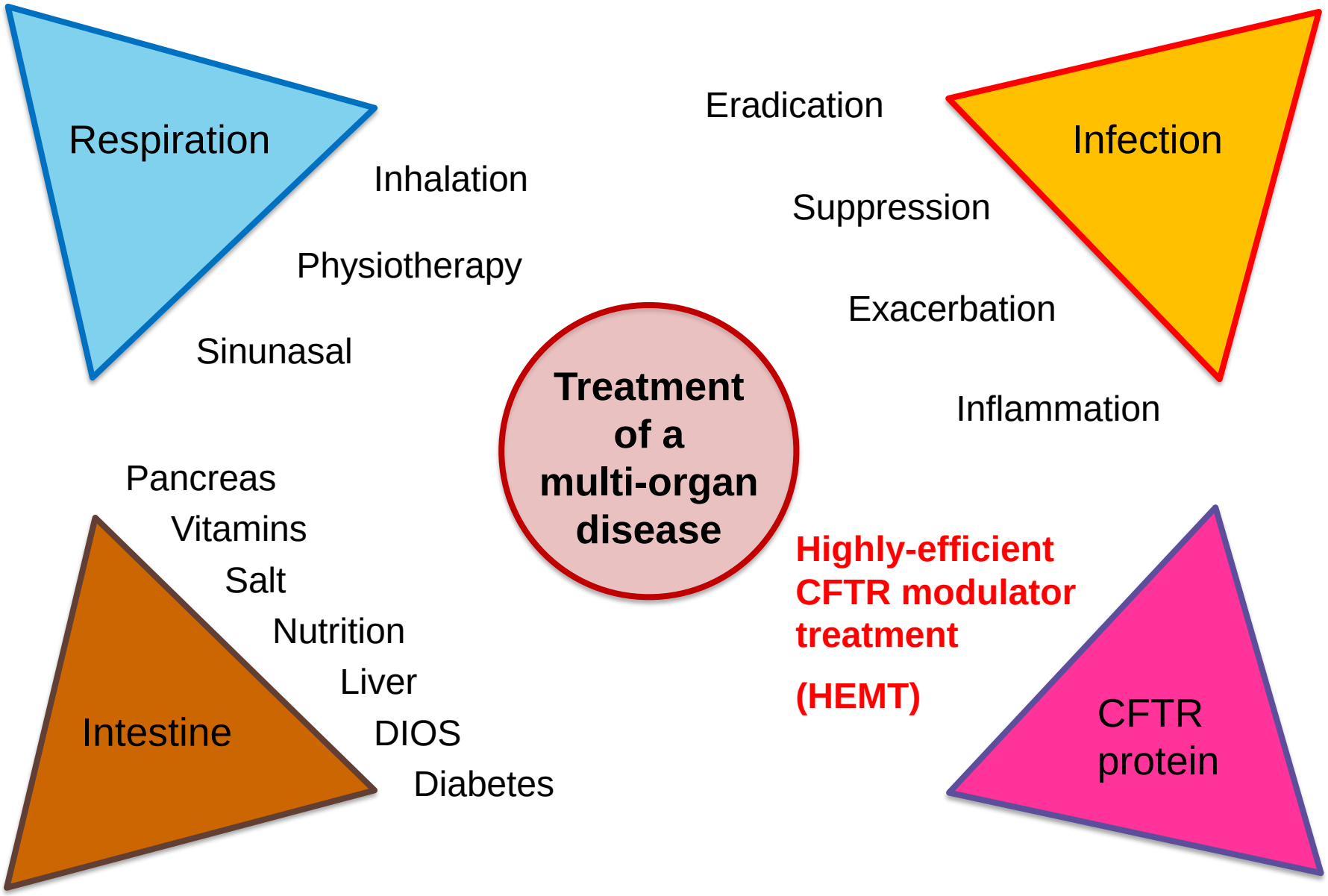
40 countries

54.043 patients

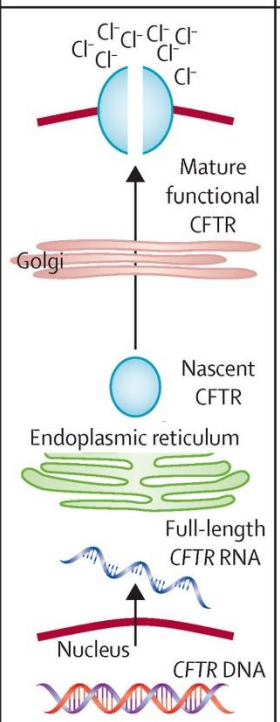
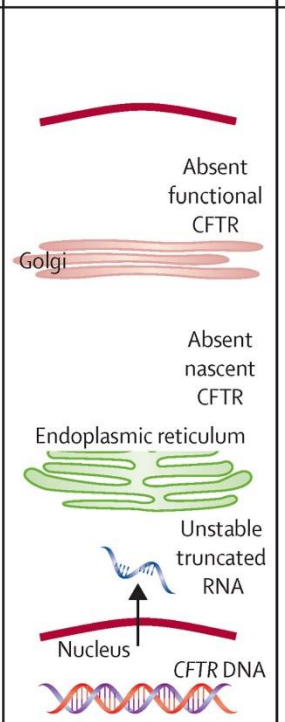
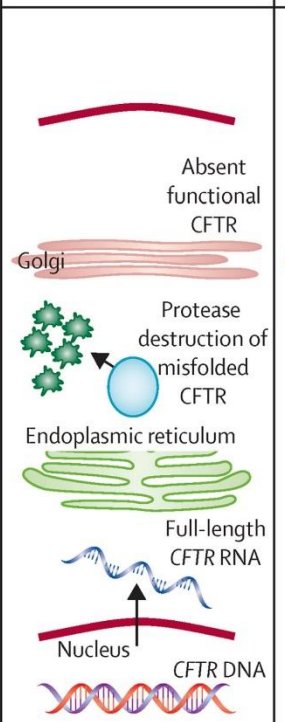
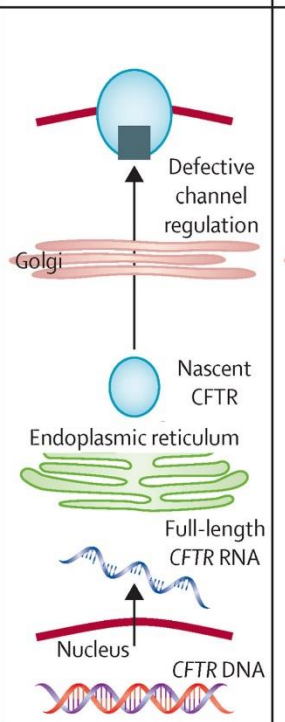
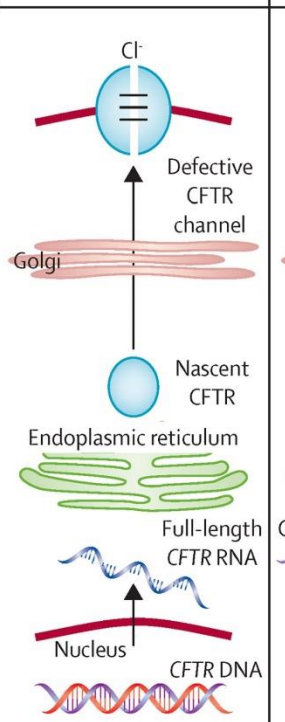
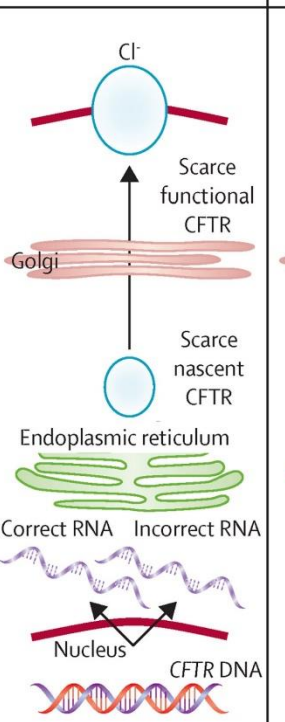
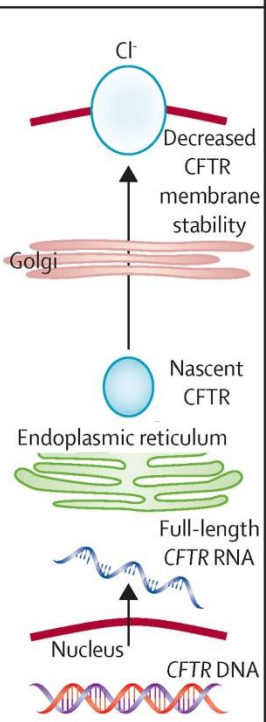
Longitudinal data 2008-2021



Treating CF

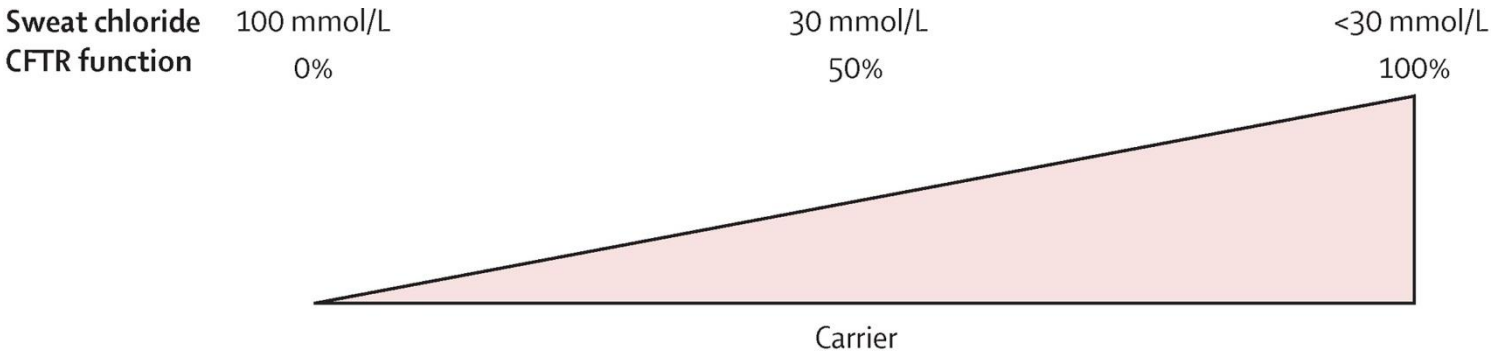

Respiration
Inhalation
Physiotherapy
Sinunasal
Eradication
Infection
Suppression
Exacerbation
Inflammation
Treatment of a multi-organ disease
Pancreas
Vitamins
Salt
Nutrition
Liver
DIOS
Diabetes
Intestine
Highly-efficient CFTR modulator treatment
(HEMT)
CFTR protein

CFTR mutation classes

Normal	I	II	III	IV	V	VI
						
CFTR defect	No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations	Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples	Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Elborn, Lancet 2016

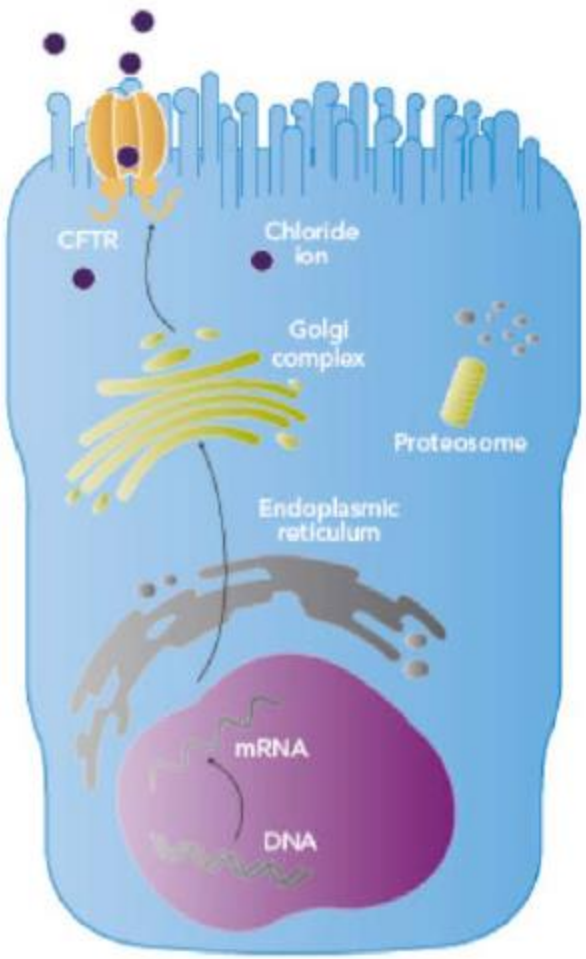
CFTR function and clinical phenotype



Sweat chloride	100 mmol/L	30–60 mmol/L	<30 mmol/L
Lung phenotype	Bronchiectasis	Airway wall thickening	Normal airways
Bacteriology	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Normal microbiome
Pancreatic function	None	50% pancreatic insufficiency	Normal pancreatic function
Male fertility	Infertile	Infertile	Fertile
Typical mutations	Gly542X Phe508del Gly551Asp	Arg117His (5T) Arg334Trp Ala55Glu	
	Class I–III mutations	Class IV–VI mutations	Healthy
			Heterozygote carrier

Elborn, Lancet 2016

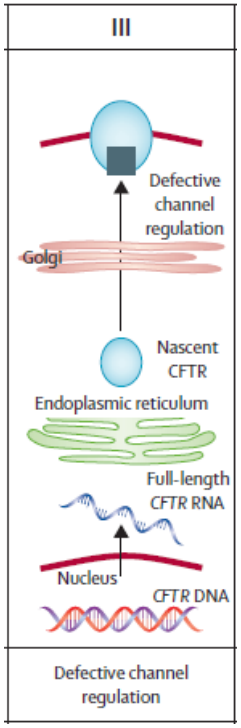
Personalized medicine in CF: CFTR modulators



Biological Problem	Therapeutic Approach
Defective CFTR Function	**Potentiators** Increase function of CFTR at cell surface
Defective CFTR Processing and Trafficking	**Correctors** Increase delivery of CFTR to cell surface
Increase mutant CFTR (mRNA level)	**Amplifiers** Increase substrate for potentiators / correctors
Defective Protein Synthesis	**Genetic Approaches** Produce normal CFTR by altering DNA or RNA

Courtesy Vertex, modified

Ivacaftor (IVA, Kalydeco®)

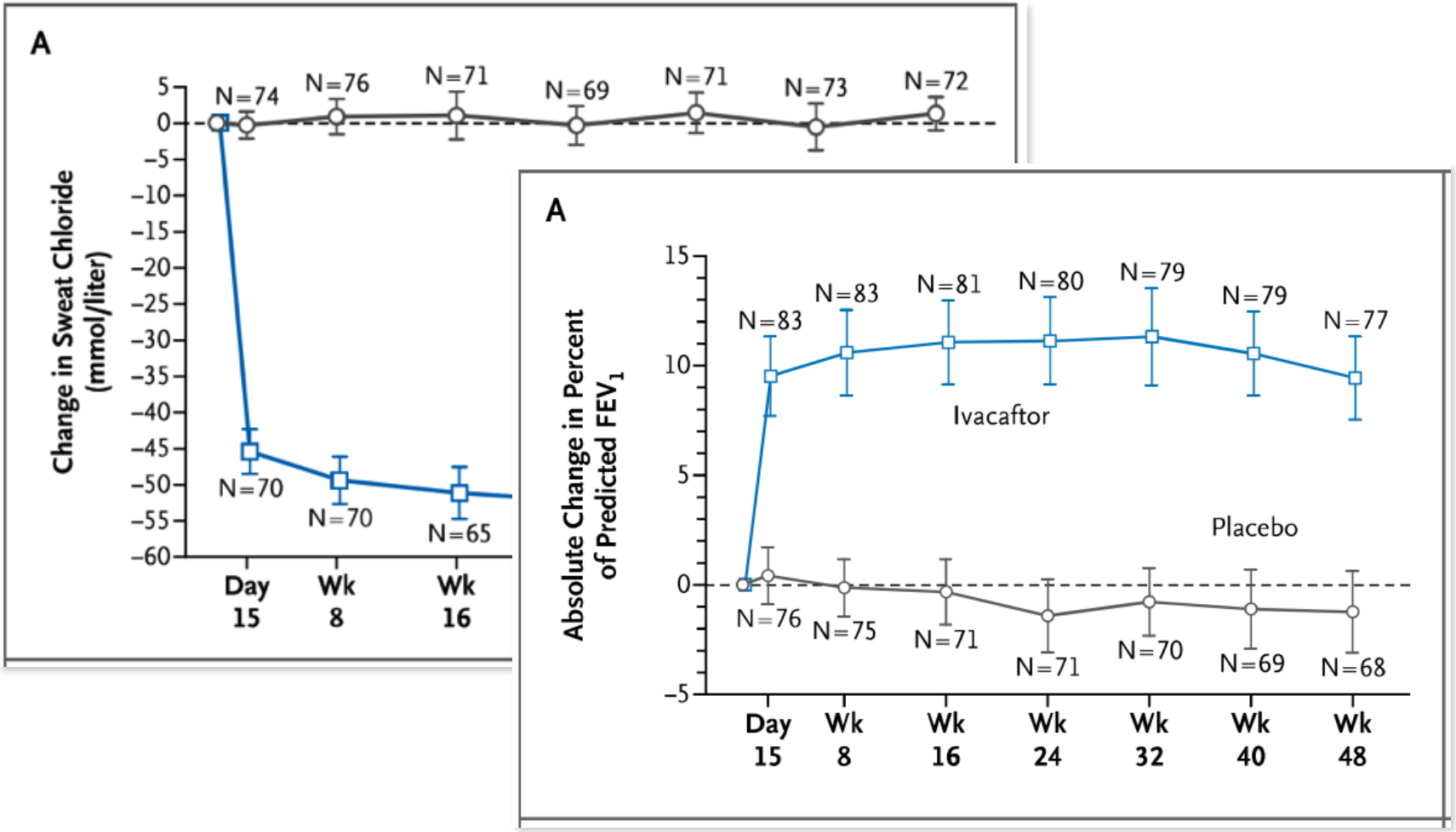


- VX-770: CFTR potentiator
- Class III mutations (gating mutations)
- Opens CFTR channel

- Licence (from 12 months)
  - EMA & Swissmedic: Gating mutations
  - G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R

- Price around 100.000 – 200.000 CHF / EUR per year

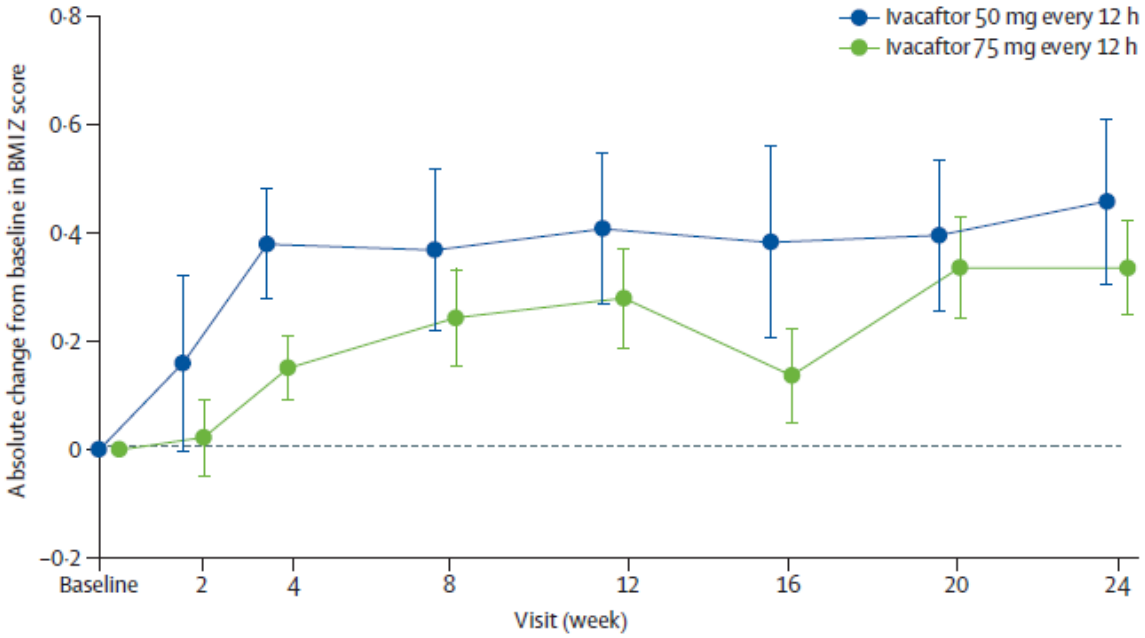
Ivacaftor



Ramsey B. & Davies J., NEJM 2011

Ivacaftor

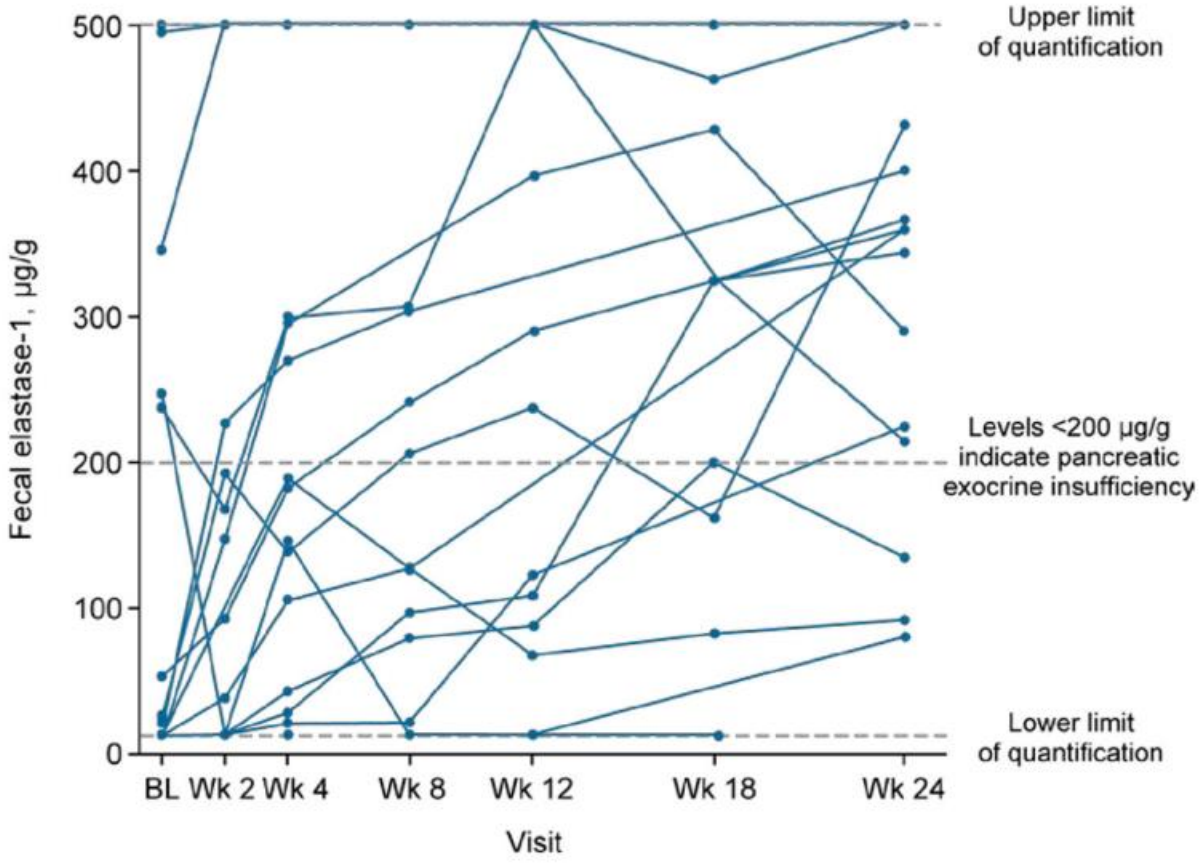
G551D mutation, age 2-5 years



Davies, Lancet Respir Med 2016

Ivacaftor

Gating mutation, age 12-24 months



Rosenfeld M et al., Lancet Respir Med 2018

Real world evidence: **Ivacaftor**
UK & US CF registry

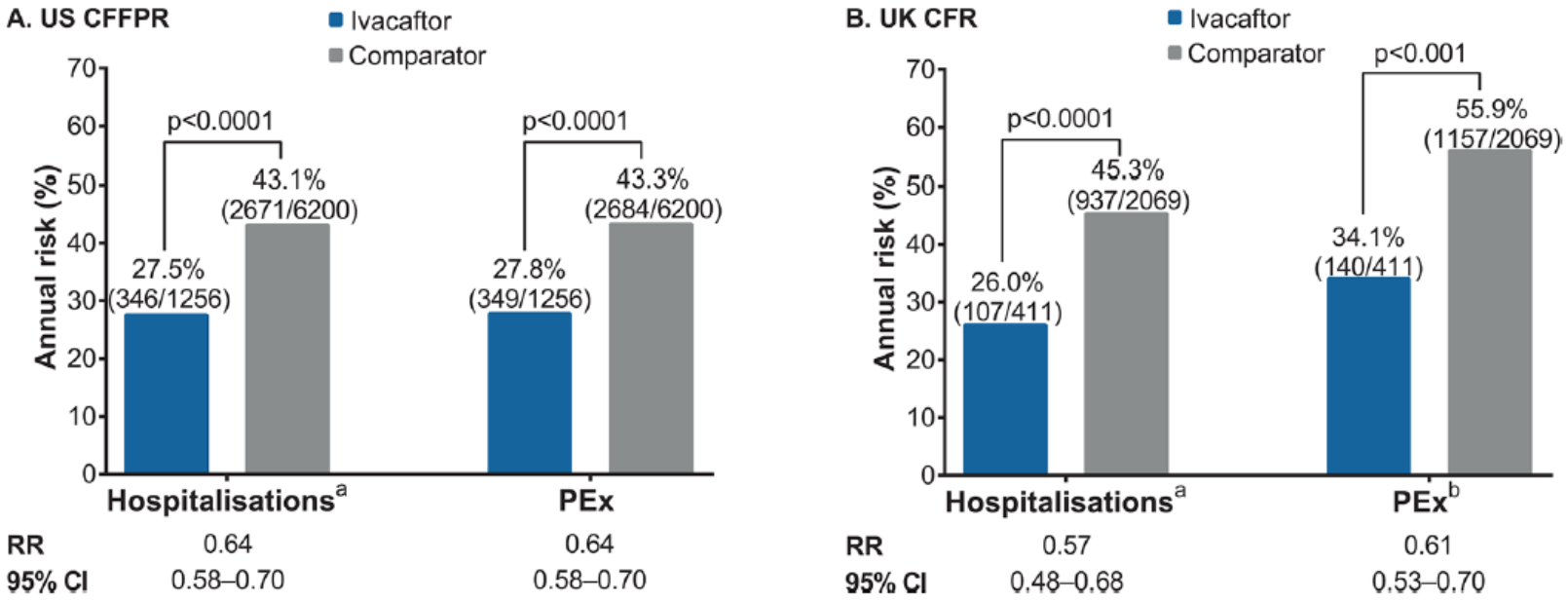
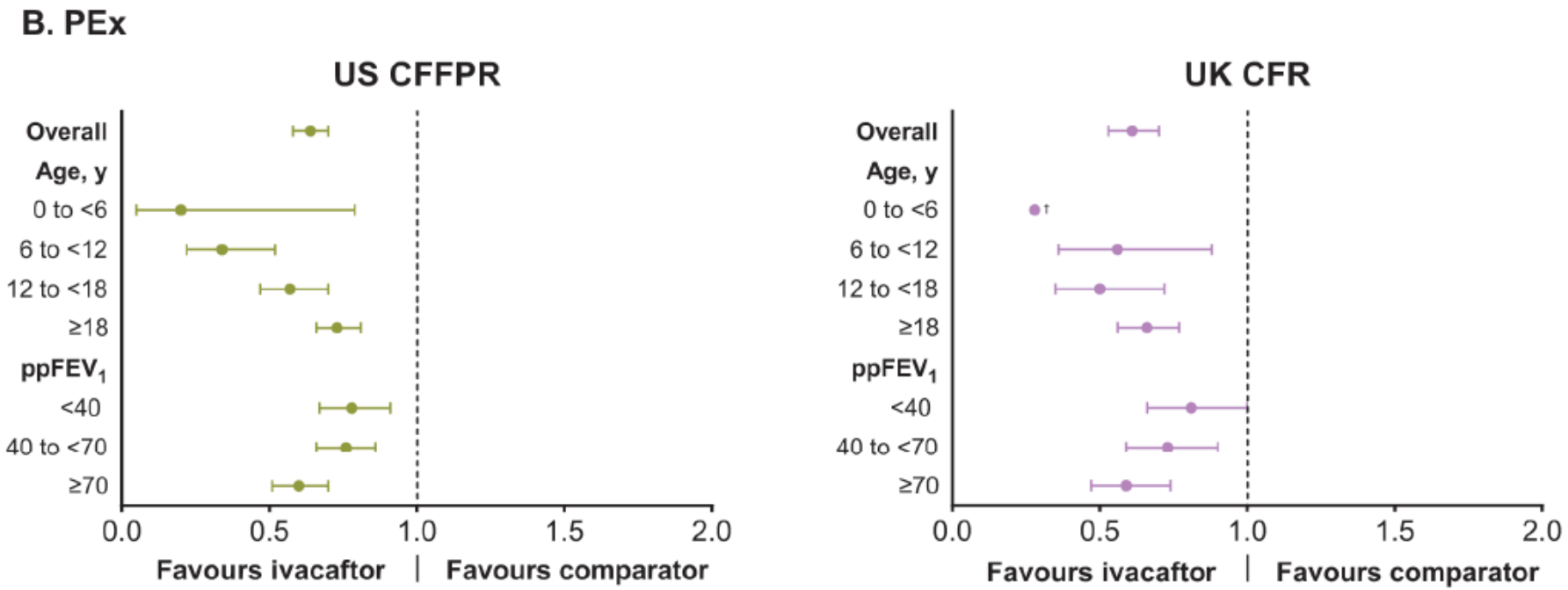


Figure 1 Hospitalisations and pulmonary exacerbations, 2014 ivacaftor and comparator cohorts, (A) USA and (B) UK. [a]Hospitalisation due to any reason in the US CFFPR and for PEx in the UK CFR. [b]In the UK CFR, PEx were defined as the requirement of intravenous antibiotic use at home or in the hospital. CFFPR, Cystic Fibrosis Foundation Patient Registry; CFR, Cystic Fibrosis Registry; PEx, pulmonary exacerbations; RR, relative risk.

Bessonova et al., Thorax 2018

Real world evicende: **Ivacaftor**
UK & US CF registry



Hospitalisations similar

Bessonova et al., Thorax 2018

Real world evidence: **Ivacaftor**
UK & US CF registry

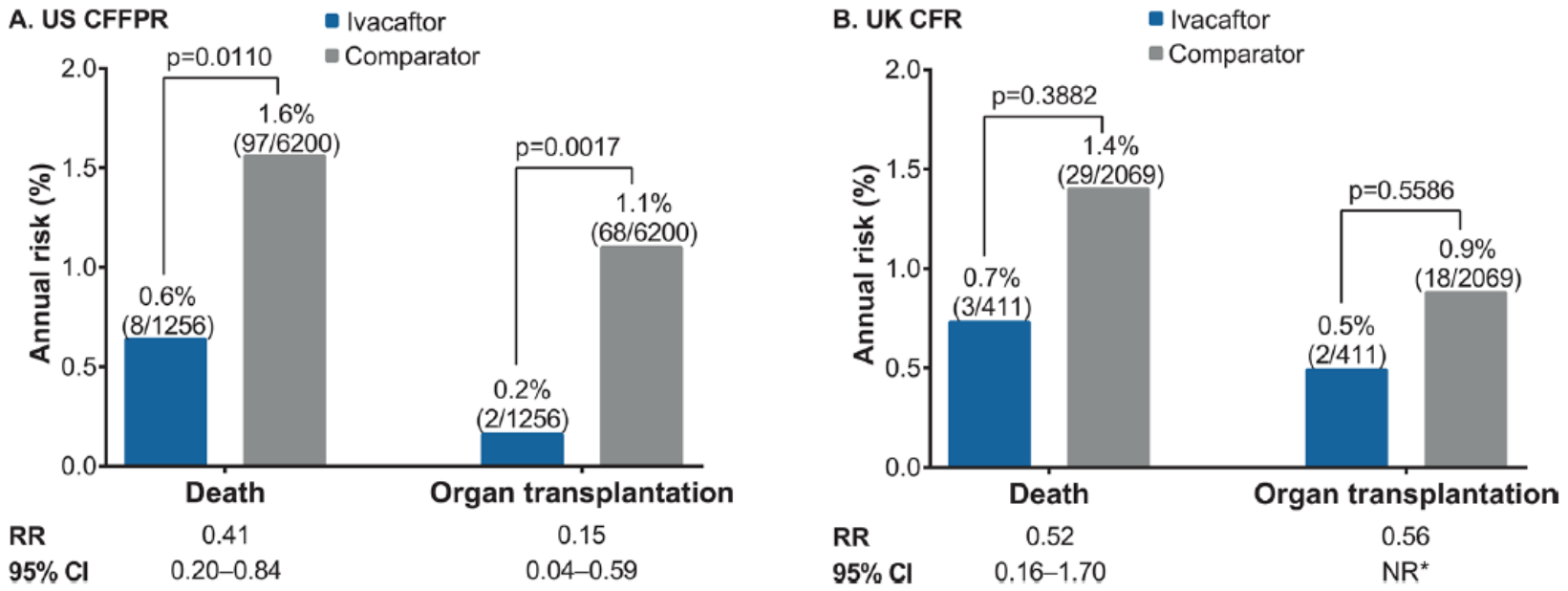
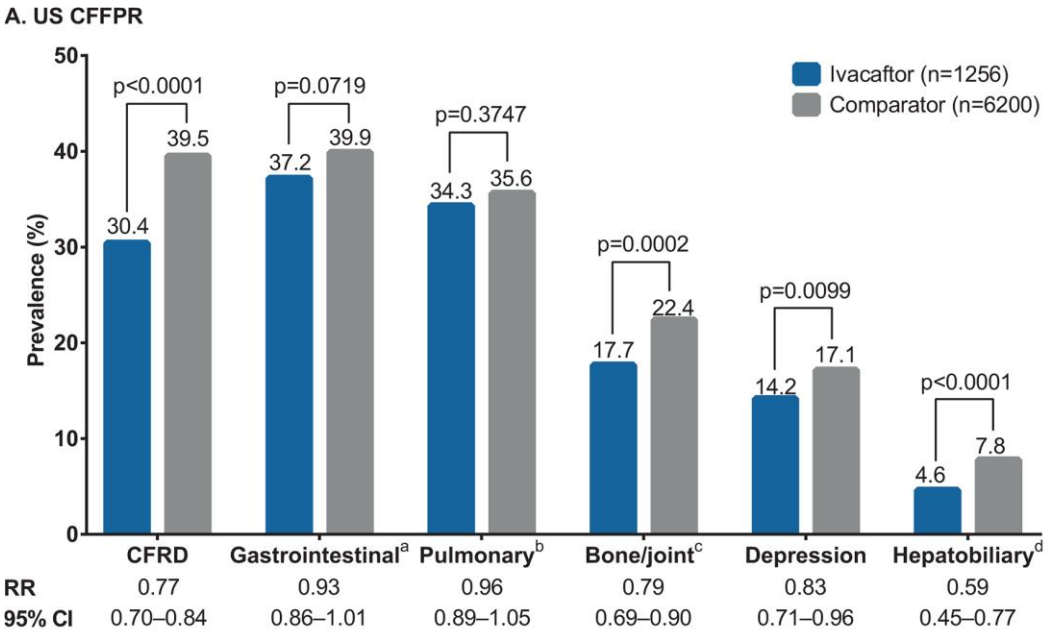
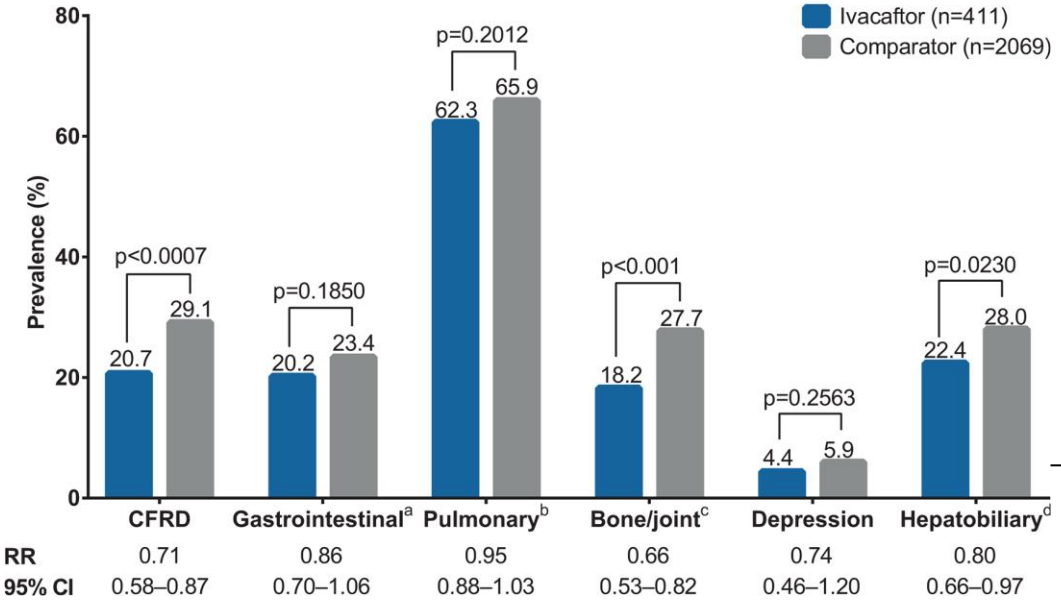


Figure 3 Death and organ transplantation, 2014 ivacaftor and comparator cohorts, (A) US CFFPR and (B) UK CFR. *Fisher's exact p values are shown when the expected value is <5 in at least one cell of the contingency table. CFFPR, Cystic Fibrosis Foundation Patient Registry; CFR, Cystic Fibrosis Registry; NR, not reported; RR, relative risk.

Bessonova et al., Thorax 2018





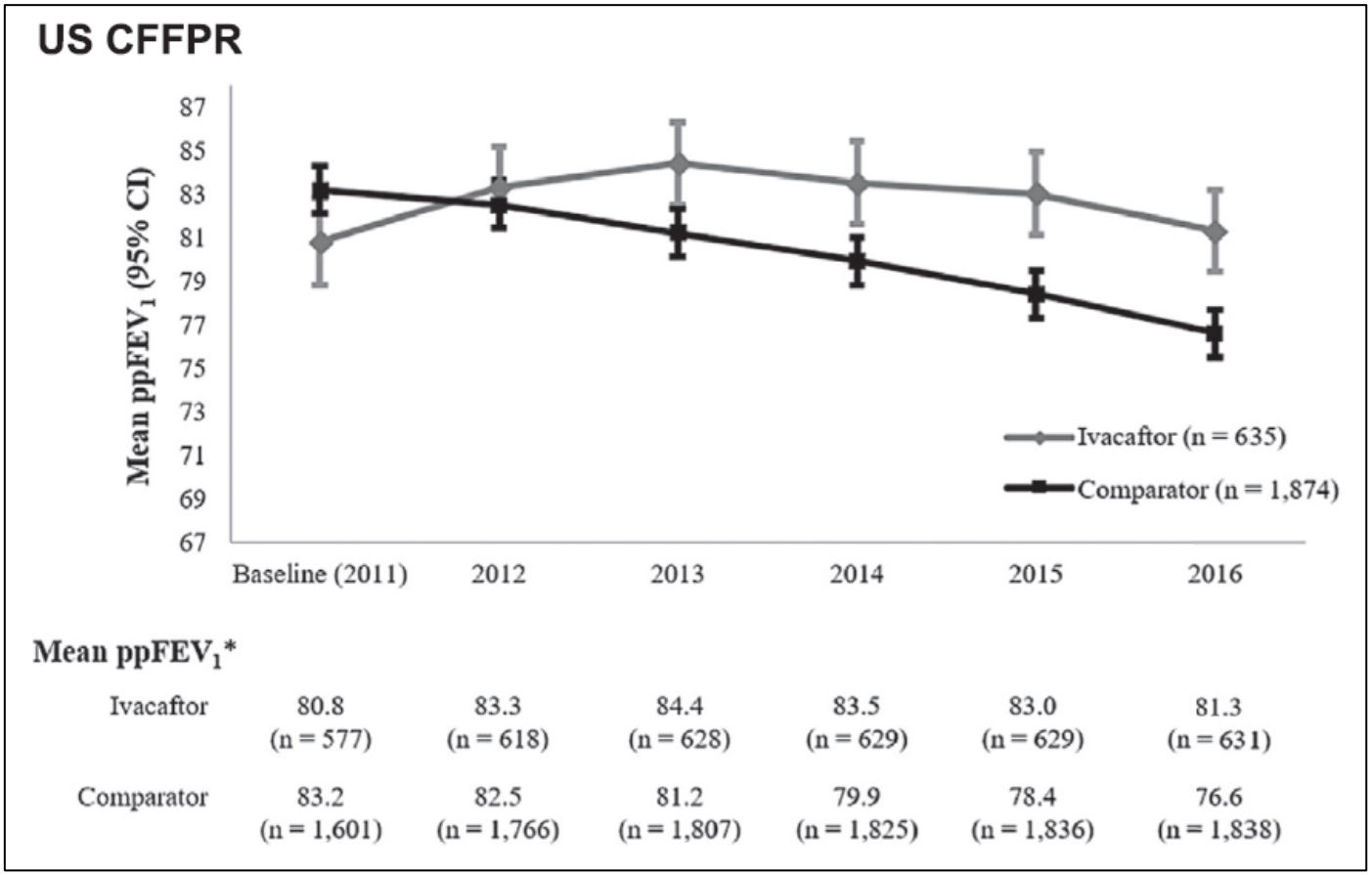
Real world evidence: Ivacaftor

CF complications / drug safety

Bessonova et al., Thorax 2018

Real world evidence: **Ivacaftor** UK & US CF registry

US n=635 (IVA) vs 1874
UK n=247 (IVA) vs 1230



Mean ppFEV$_1$*

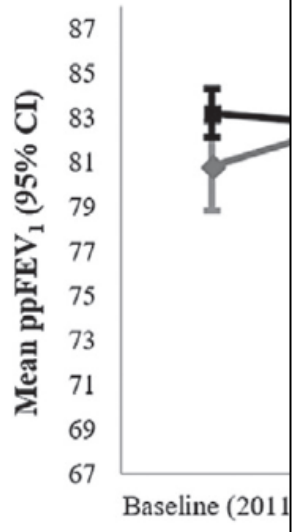
	Baseline (2011)	2012	2013	2014	2015	2016
Ivacaftor	80.8 (n = 577)	83.3 (n = 618)	84.4 (n = 628)	83.5 (n = 629)	83.0 (n = 629)	81.3 (n = 631)
Comparator	83.2 (n = 1,601)	82.5 (n = 1,766)	81.2 (n = 1,807)	79.9 (n = 1,825)	78.4 (n = 1,836)	76.6 (n = 1,838)

Volkova et al., J Cystic Fibros 2020

Real world evidence: **Ivacaftor** UK & US CF registry

US n=635 (IVA) vs 1874
UK n=247 (IVA) vs 1230

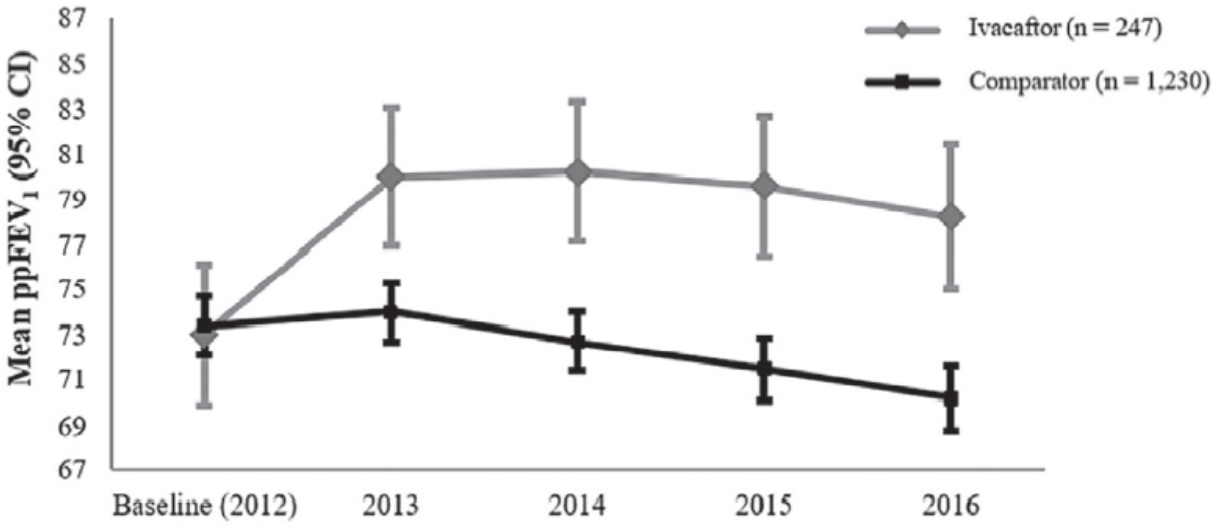
US CFFPR



Mean ppFEV$_1$*

Ivacaftor	80.8 (n = 577)
Comparator	83.2 (n = 1,601)

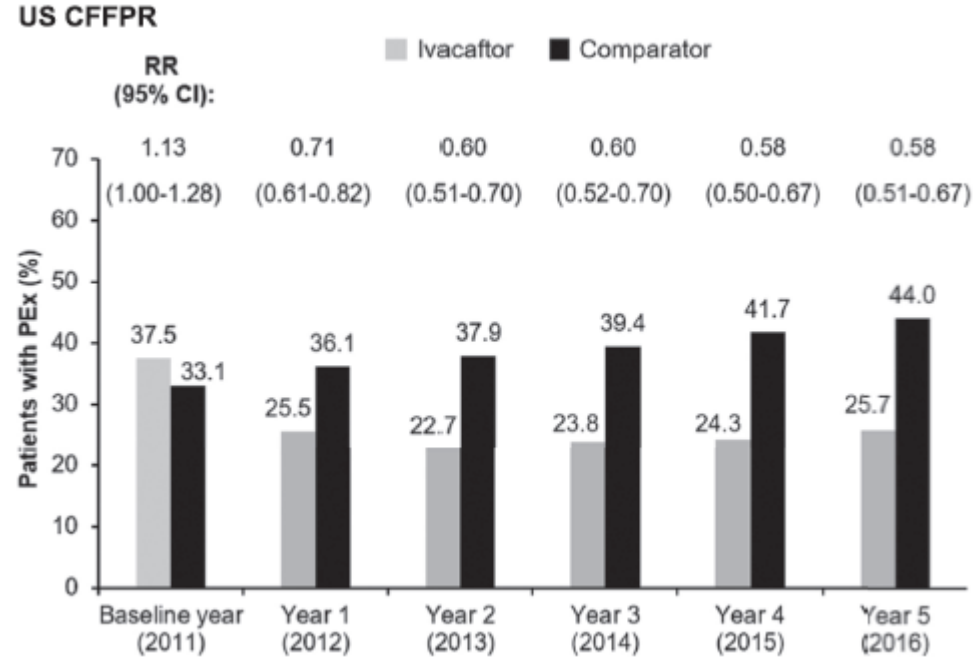
UK CFR

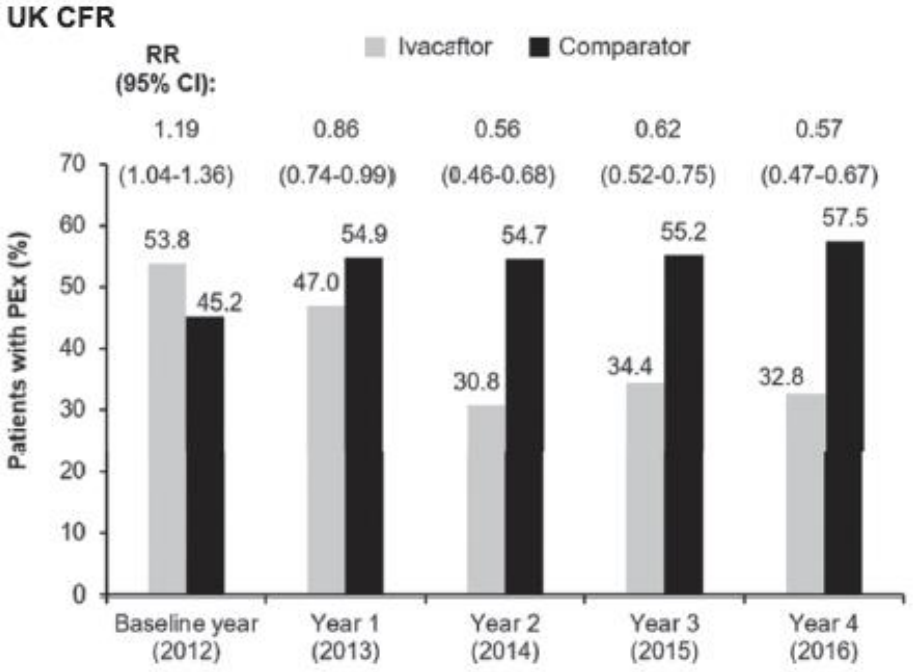


Mean ppFEV$_1$*

	Baseline (2012)	2013	2014	2015	2016
Ivacaftor	73.0 (n = 227)	80.0 (n = 242)	80.2 (n = 243)	79.6 (n = 243)	78.2 (n = 235)
Comparator	73.4 (n = 1,127)	74.0 (n = 1,169)	72.7 (n = 1,193)	71.5 (n = 1,193)	70.2 (n = 1,183)

Volkova et al., J Cystic Fibros 2020





Improvement over time also for

- Hospitalization rate
- CFRD
- *P. aeruginosa* prevalence

Volkova et al., J Cyst Fibros 2020

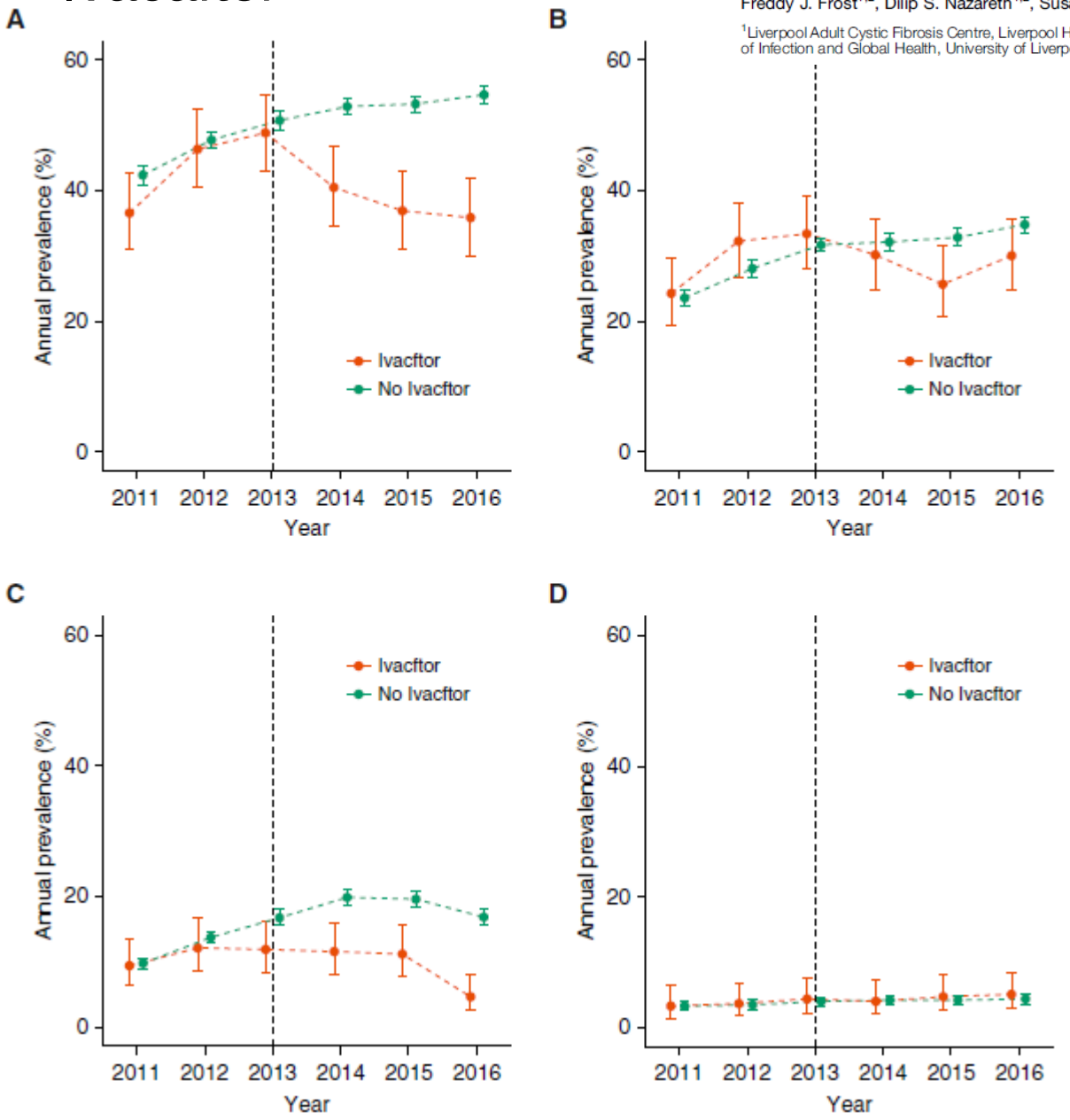
Real world evidence: Ivacaftor

Ivacaftor Is Associated with Reduced Lung Infection by Key Cystic Fibrosis Pathogens

A Cohort Study Using National Registry Data

Freddy J. Frost[1,2], Dilip S. Nazareth[1,2], Susan C. Charman[3], Craig Winstanley[2], and Martin J. Walshaw[1,2]

[1]Liverpool Adult Cystic Fibrosis Centre, Liverpool Heart and Chest Hospital NHS, Foundation Trust, Liverpool, United Kingdom; [2]Institute of Infection and Global Health, University of Liverpool, Liverpool, United Kingdom; and [3]Cystic Fibrosis Trust, London, United Kingdom



Positive respiratory culture for

A) *P. aeruginosa*

B) *S. aureus*

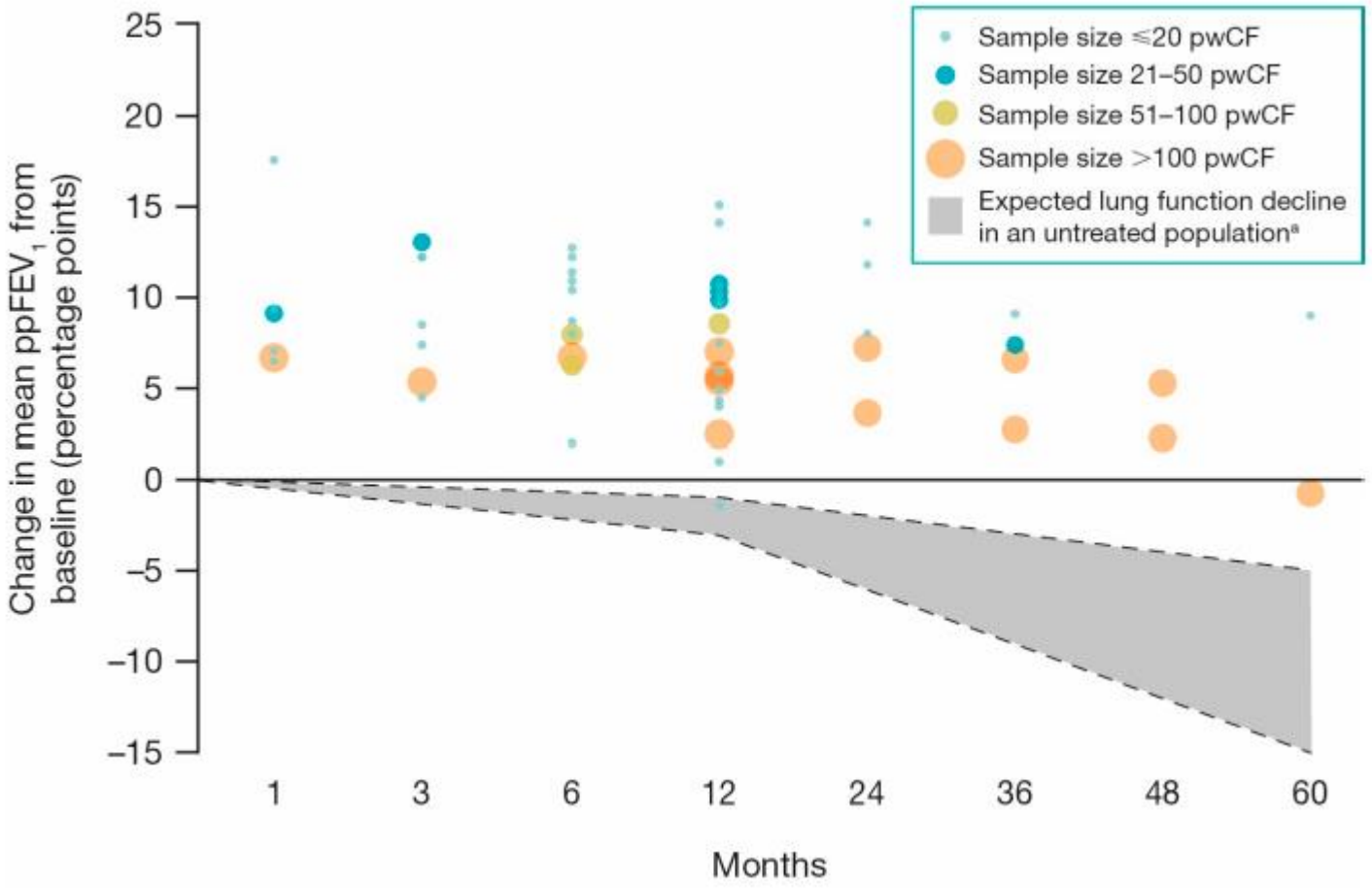
C) *A. fumigatus*

D) *B. cepacia*

Frost et al., Annals ATS 2019

Real world evidence: Ivacaftor

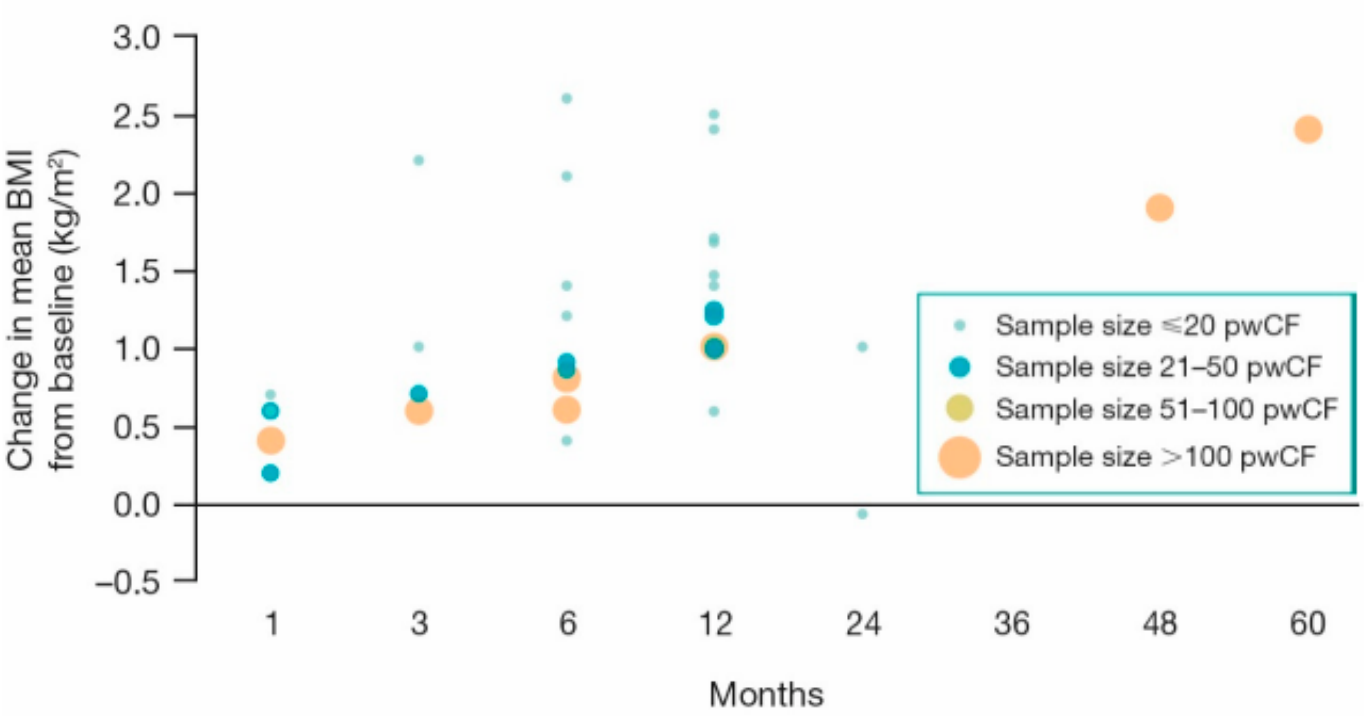
Meta analysis
31 studies incl. registry data



Duckers et al., J Clin Med 2021

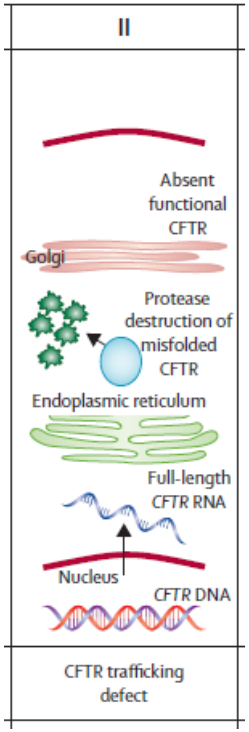
Real world evidence: Ivacaftor

Meta analysis
17 studies incl. registry data



Duckers et al., J Clin Med 2021

Elexacaftor/Ivacaftor/Tezacaftor (ELX/TEZ/IVA, Trikafta®, Kaftrio®)



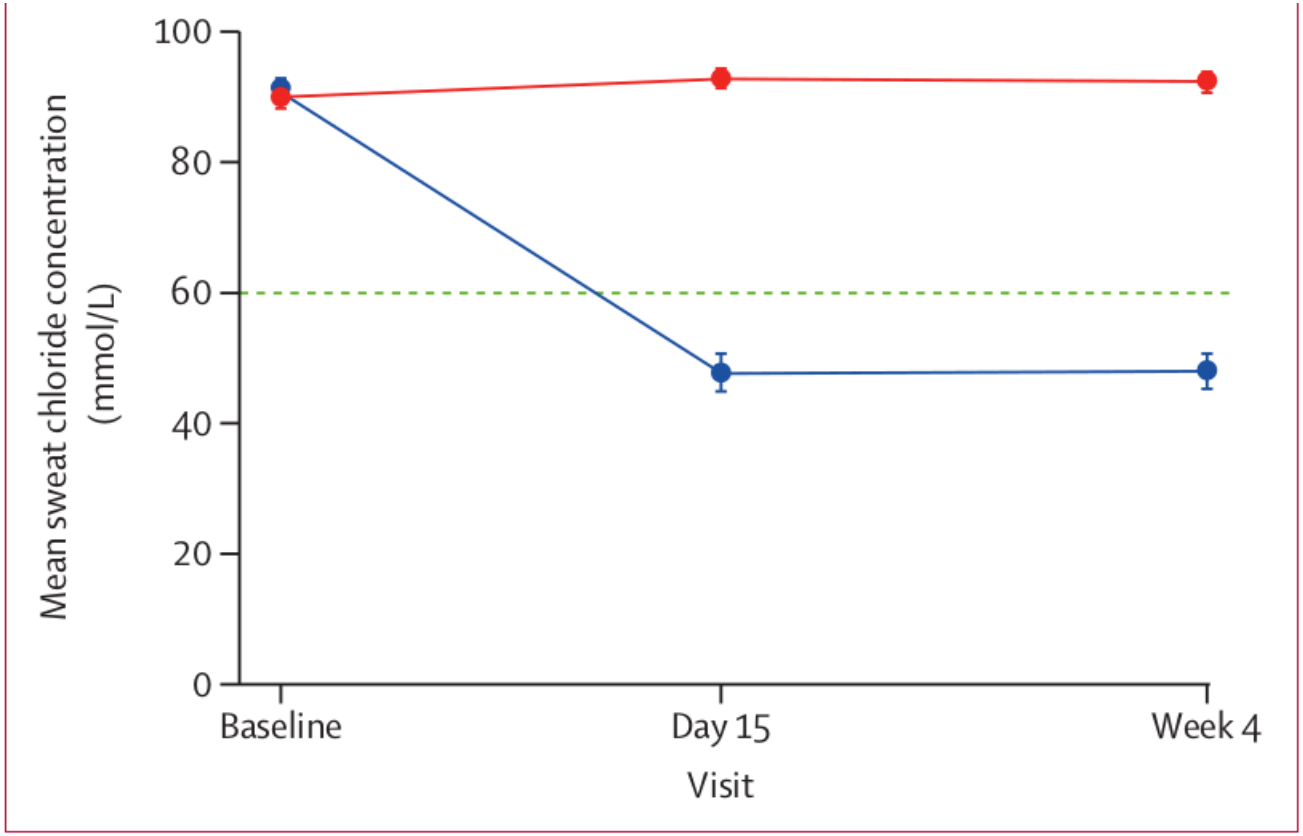
- Combination of two correctors and a potentiator
- mostly class II mutations
- Optimizes CFTR protein maturation and activity

- Potentially 75% to >90% of all patients (depending on region)

- Licence (from 6 years)
  - EMA & Swissmedic: F508del homozygous / any other CFTR mutation

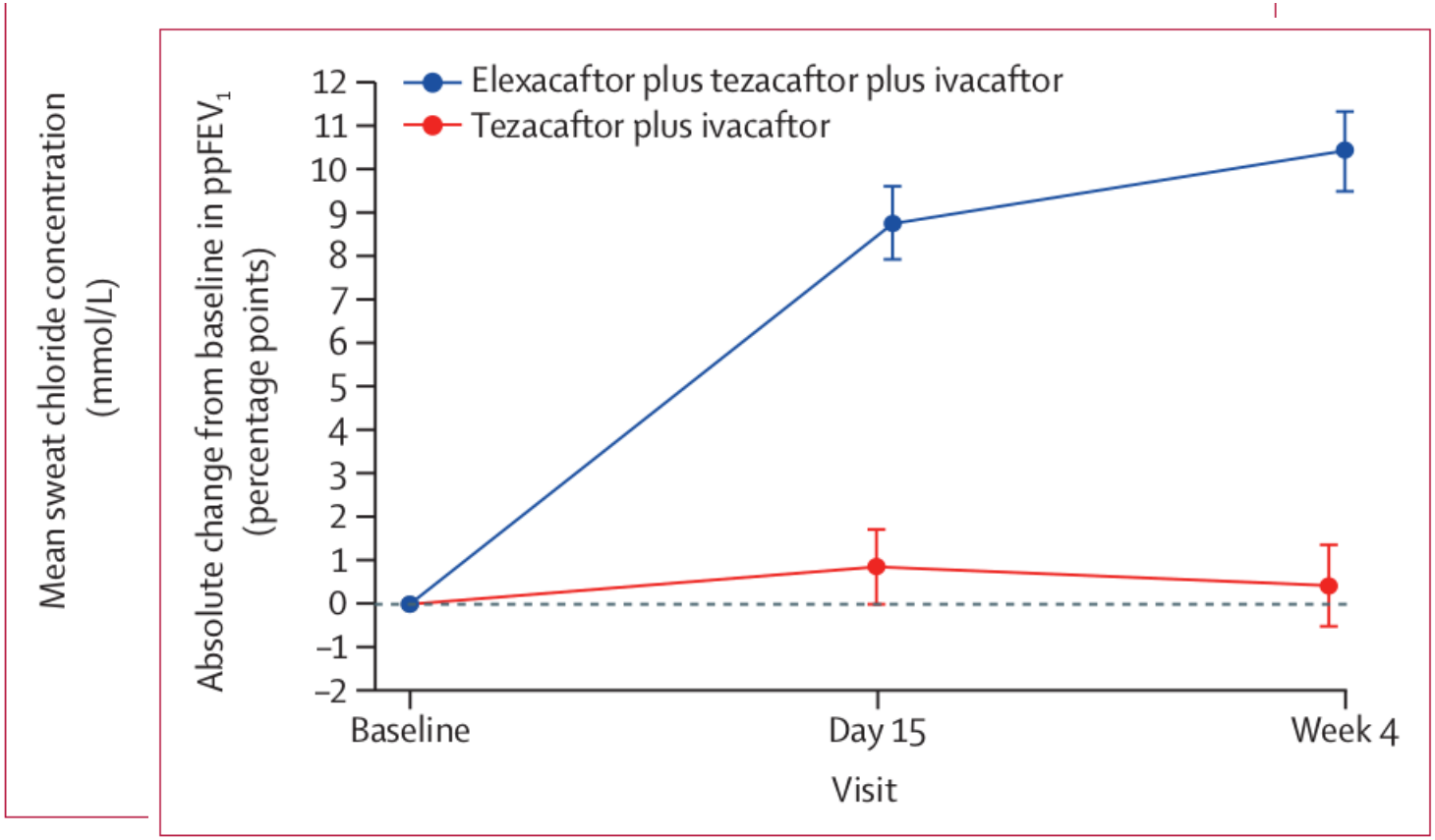
- Price around 100.000 – 200.000 CHF / EUR per year

ELX/TEZ/IVA:
Patients homozygous for F508del



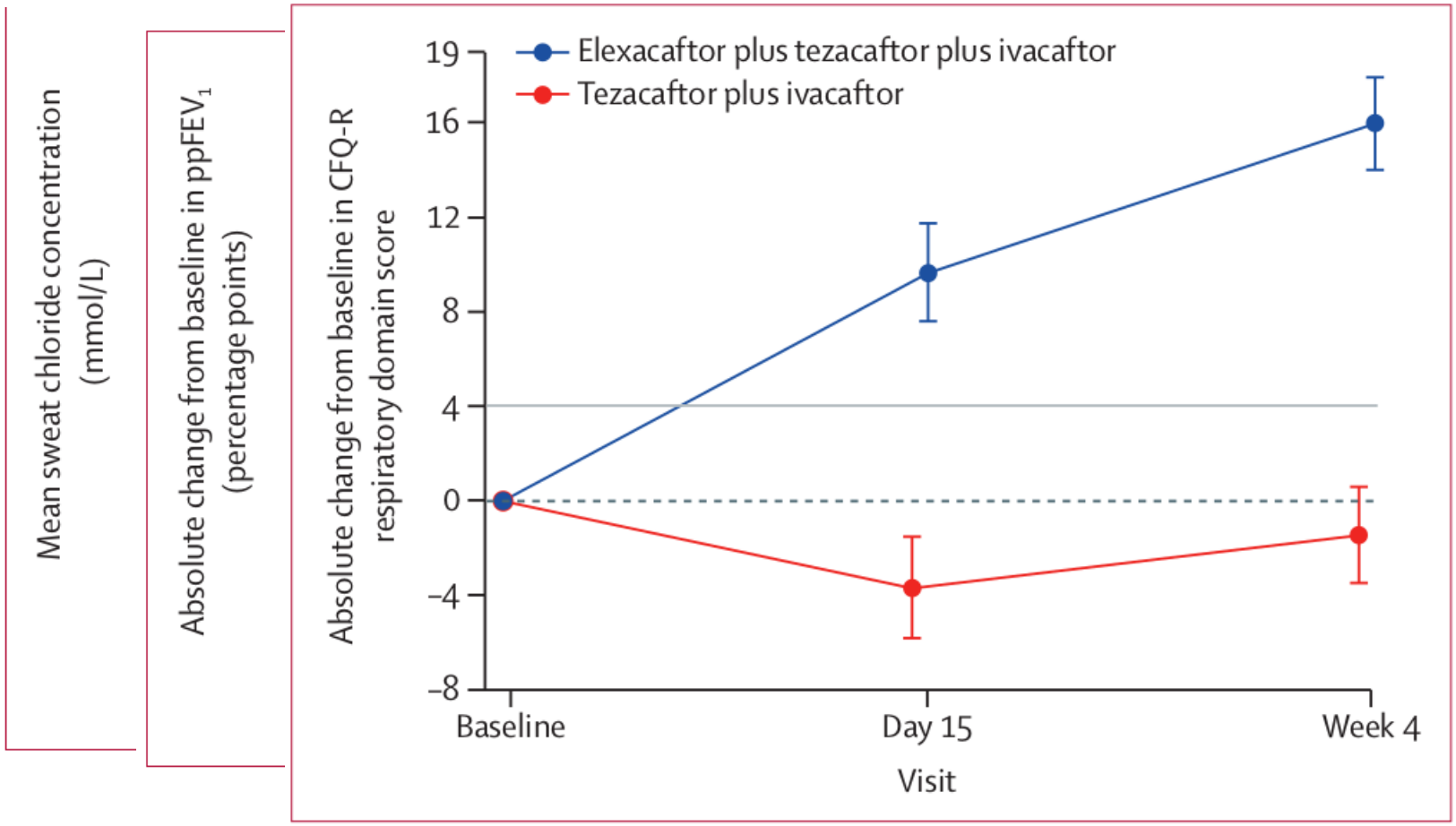
Heijerman et al. Lancet 2019

ELX/TEZ/IVA:
Patients homozygous for F508del



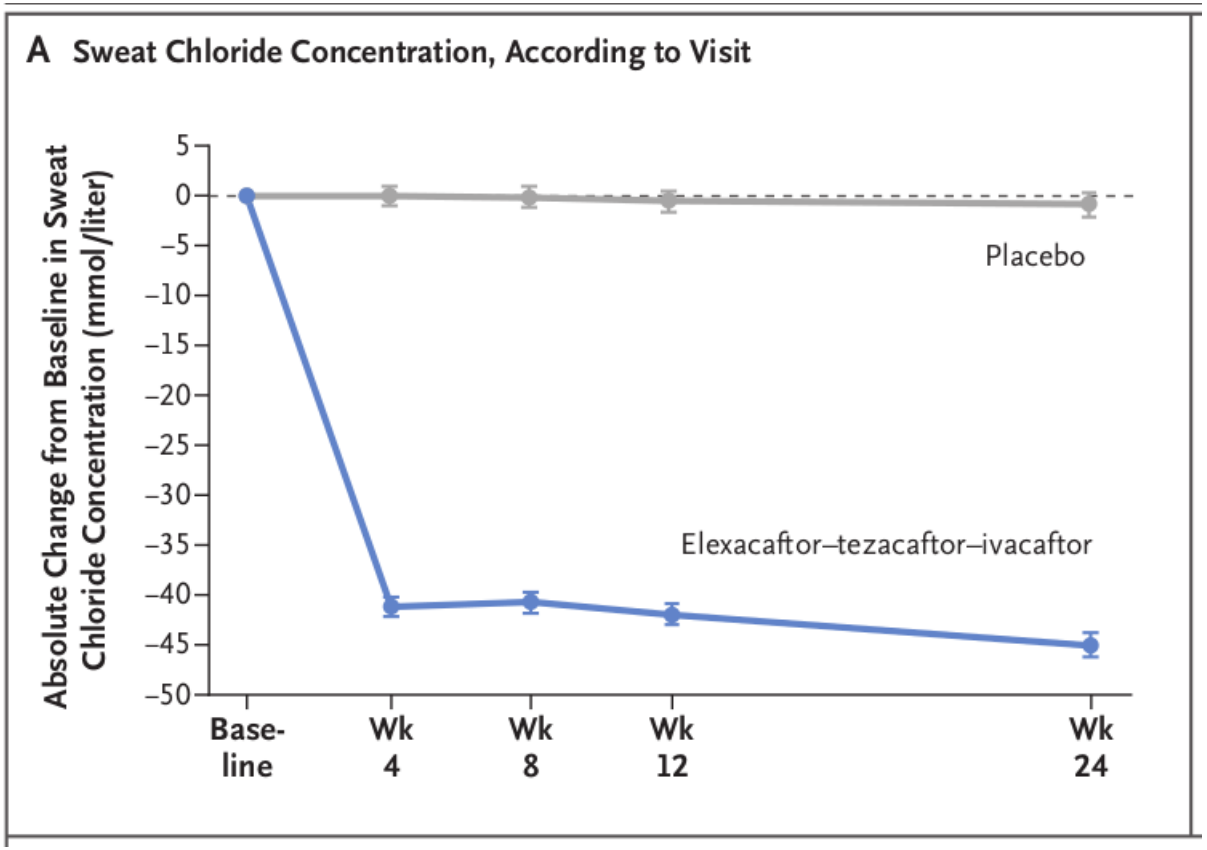
Heijerman et al. Lancet 2019

ELX/TEZ/IVA:
Patients homozygous for F508del



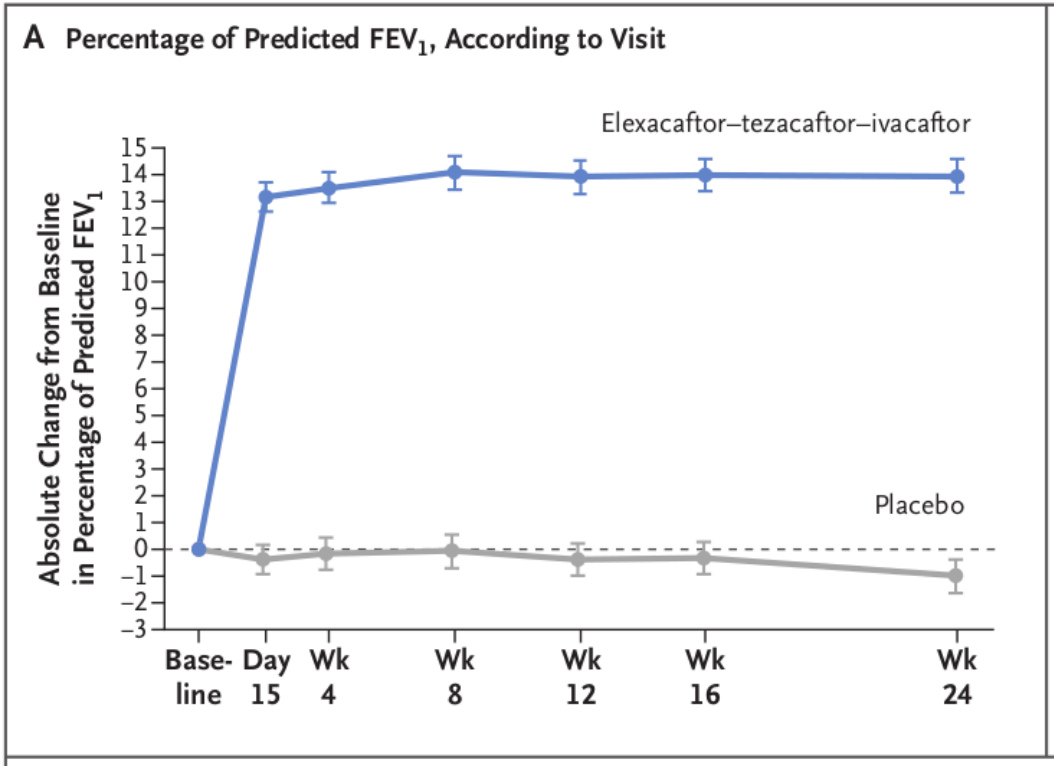
Heijerman et al. Lancet 2019

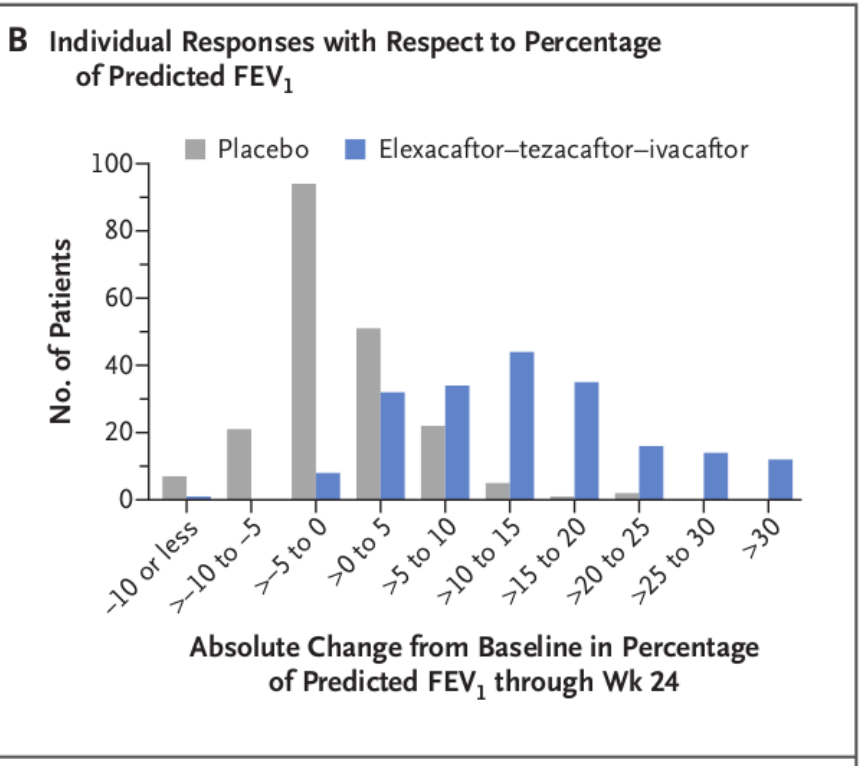
ELX/TEZ/IVA:
Patients with F508del and a minimal function mutation



Middleton et al. NEJM 2019

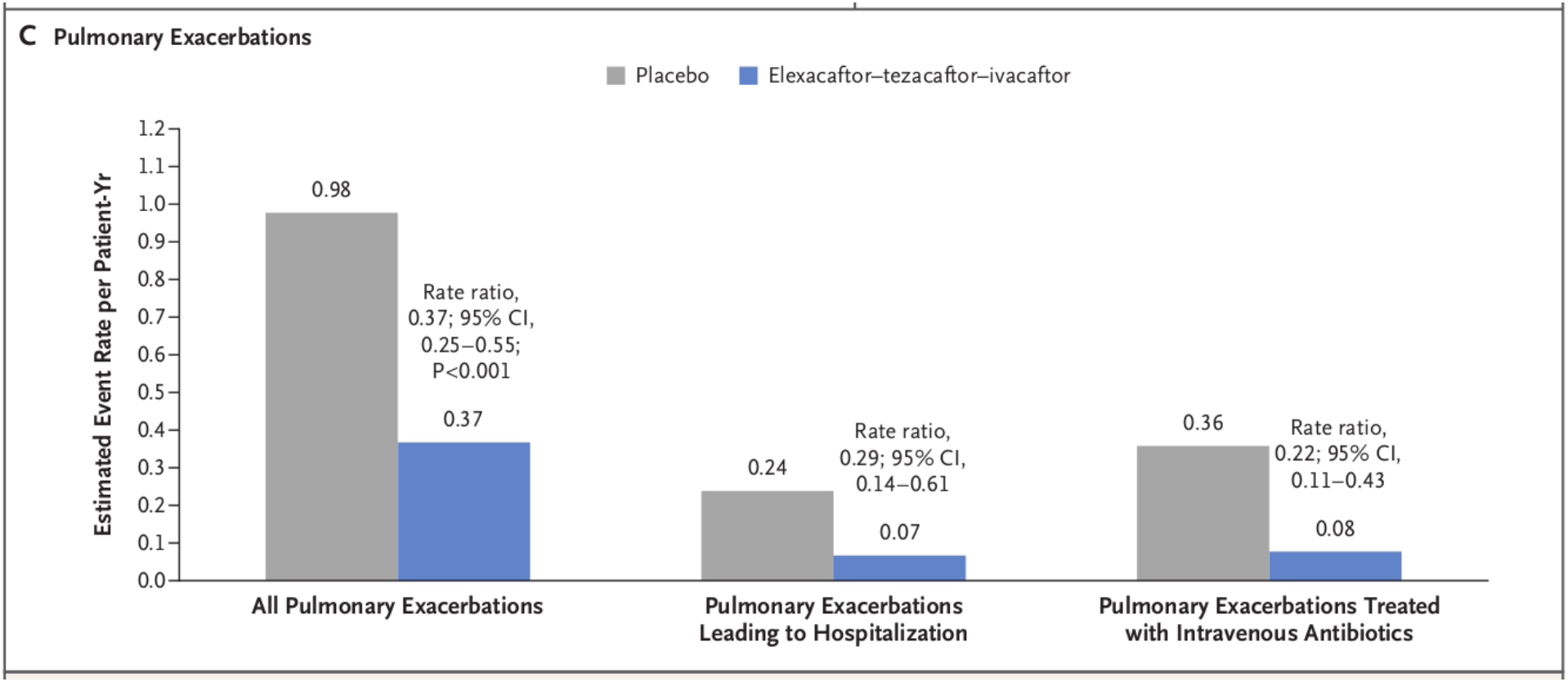
ELX/TEZ/IVA:
Patients with F508del and a minimal function mutation





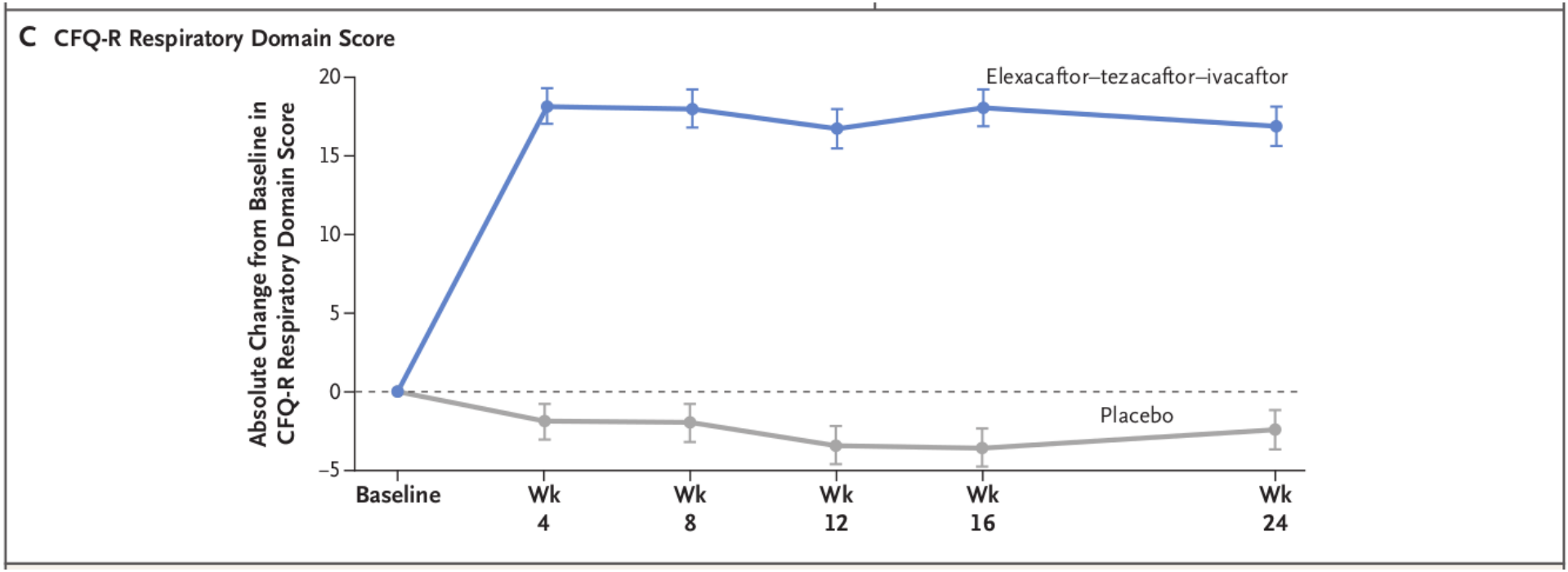
Middleton et al. NEJM 2019

ELX/TEZ/IVA:
Patients with F508del and a minimal function mutation



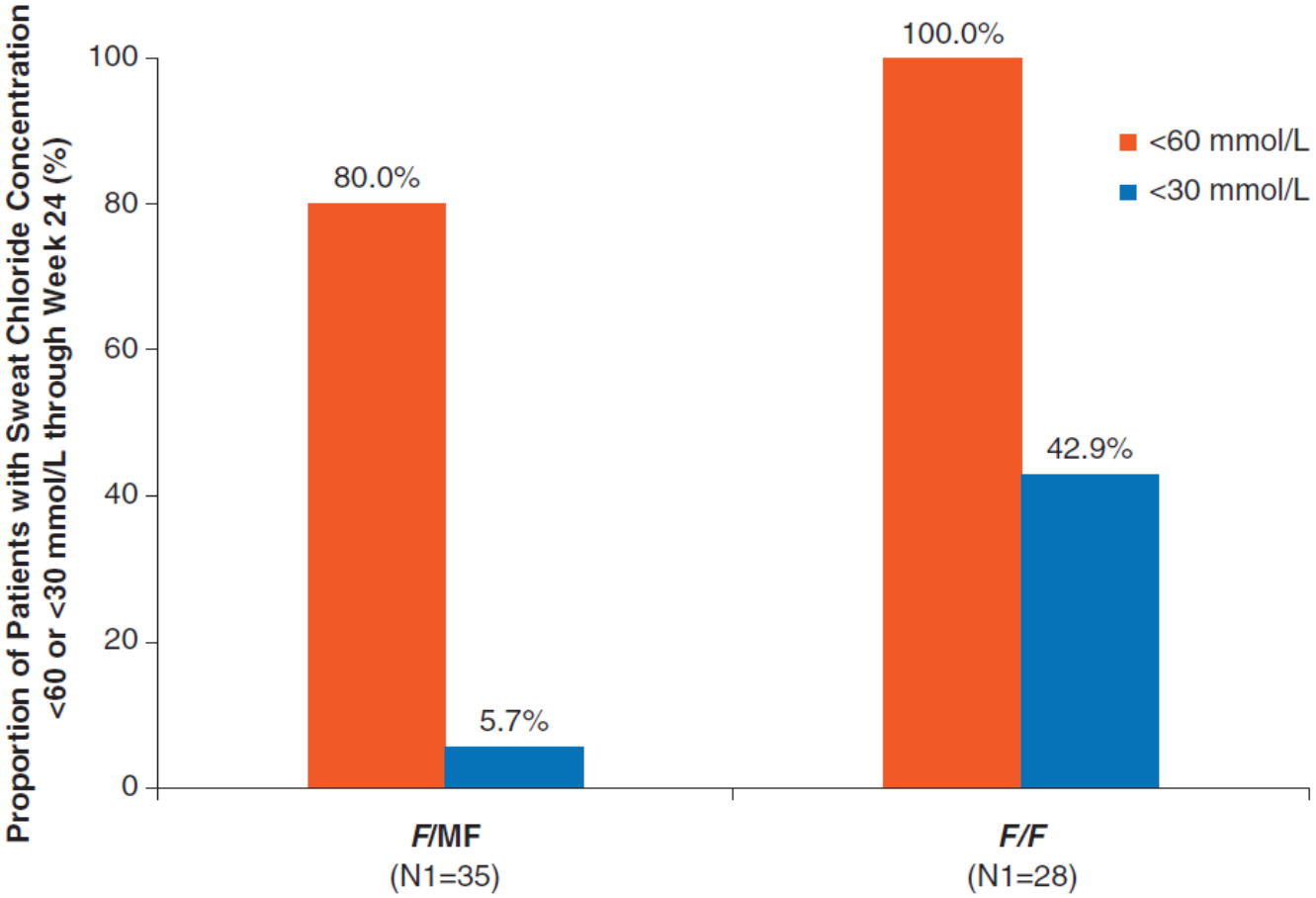
Middleton et al. NEJM 2019

ELX/TEZ/IVA:
Patients with F508del and a minimal function mutation



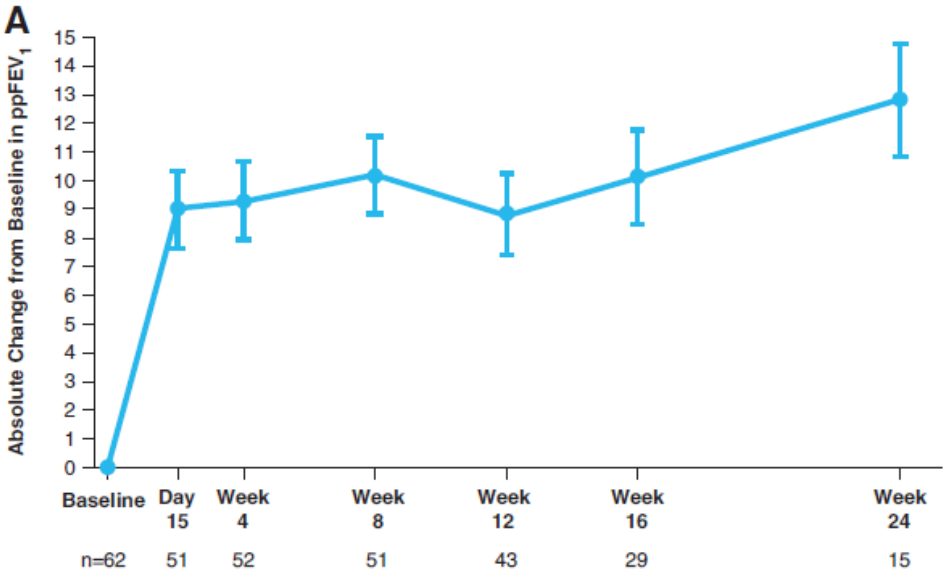
Middleton et al. NEJM 2019

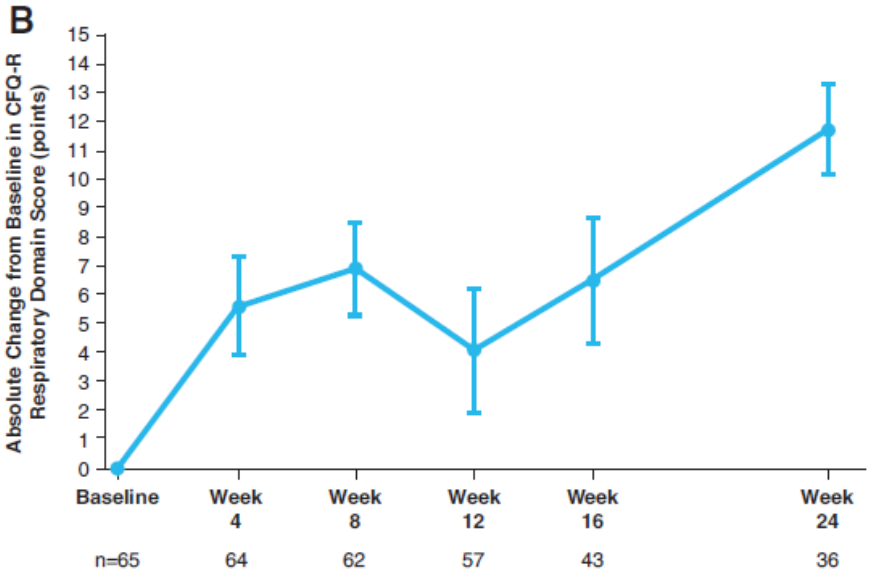
ELX/TEZ/IVA:
Children 6-11 yrs with F508del / Any



Zemanick et al. AJRCCM 2021

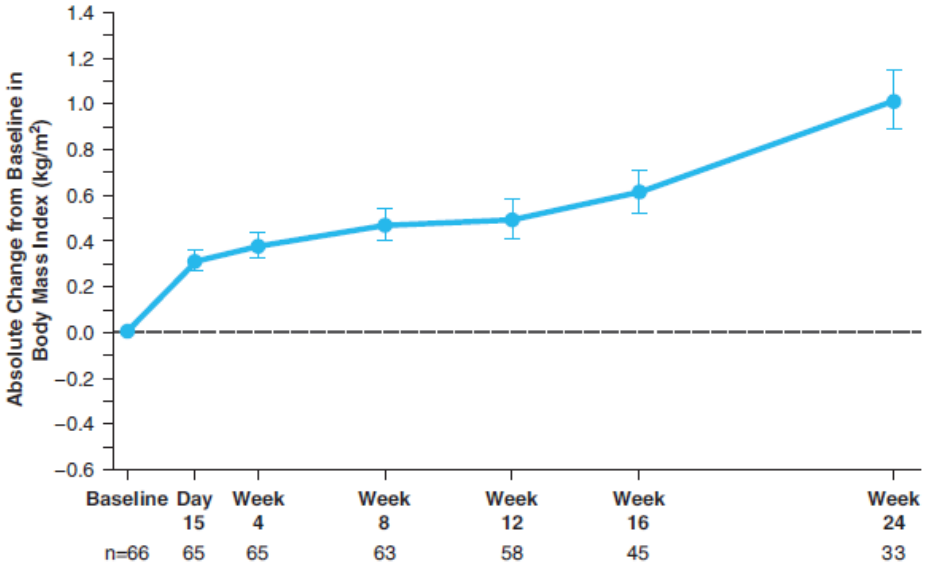
ELX/TEZ/IVA:
Children 6-11 yrs with F508del / Any

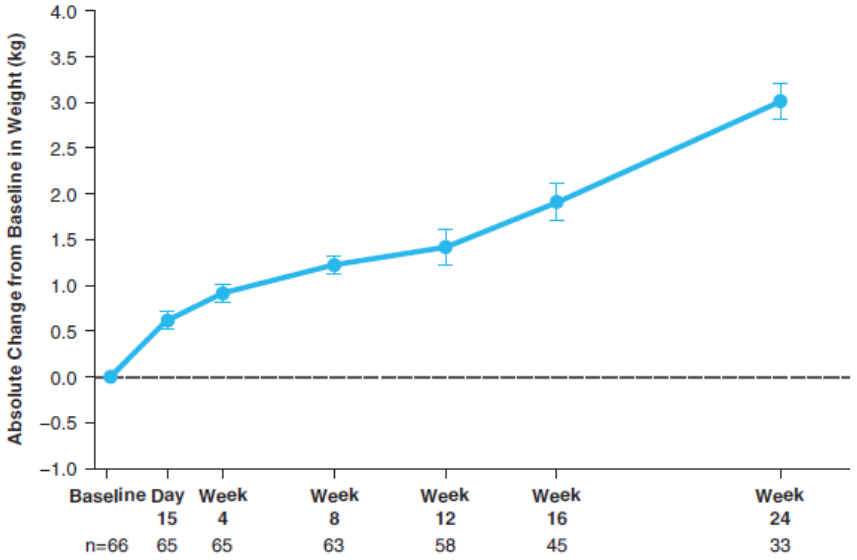




Zemanick et al. AJRCCM 2021

ELX/TEZ/IVA:
Children 6-11 yrs with F508del / Any

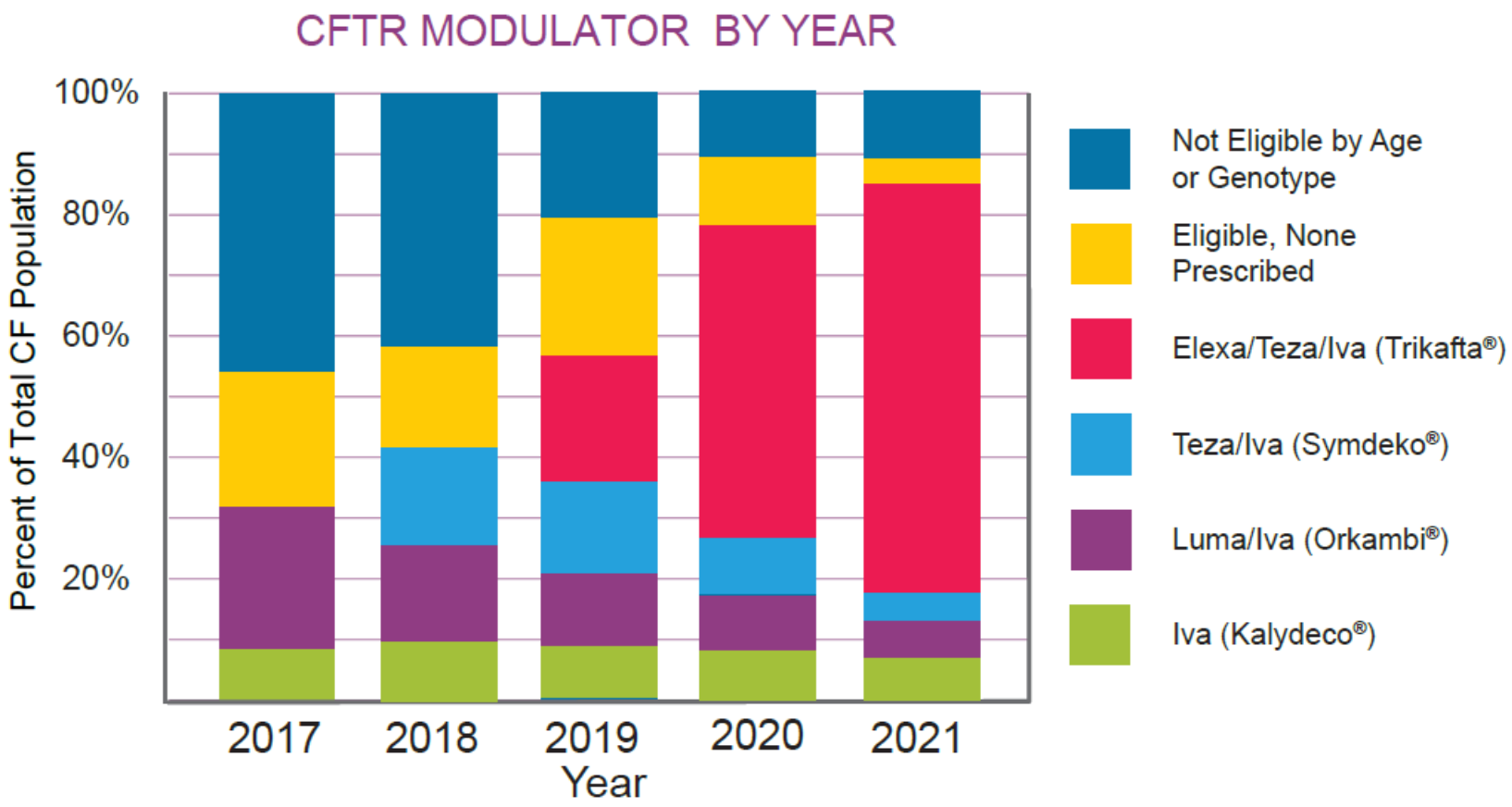




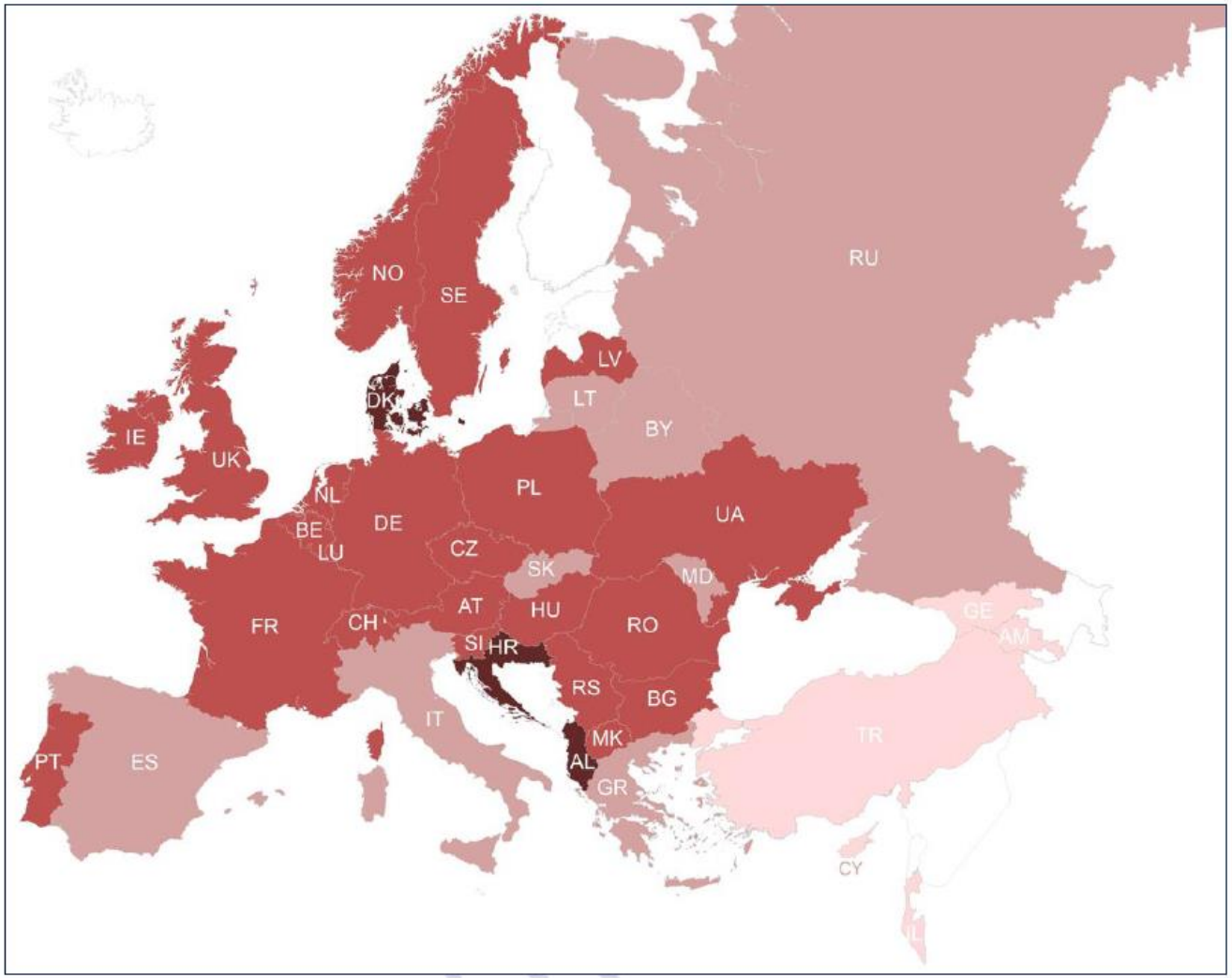
Zemanick et al. AJRCCM 2021

Monitoring of efficacy and safety: Registry-based pharmacovigilance studies

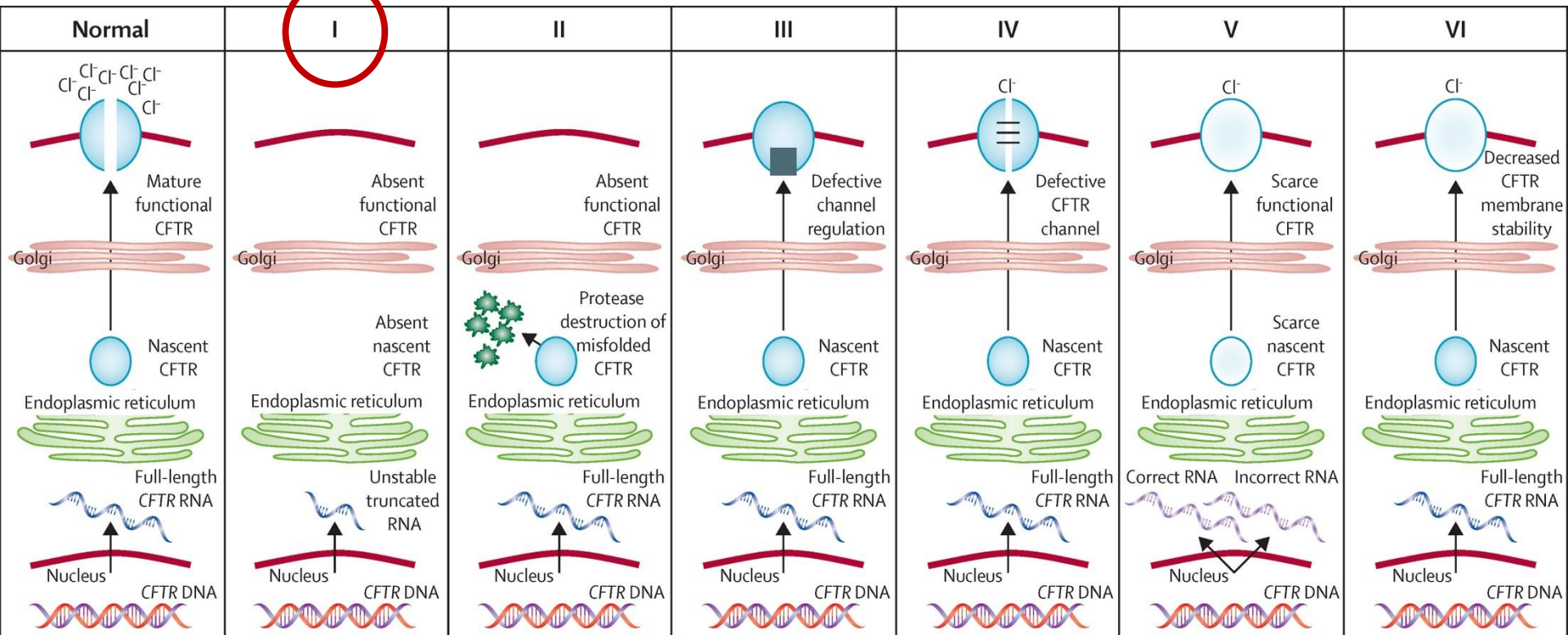
Increasing proportion of patients eligible for CFTR modulators



Prevalence of F508del in Europe: 80%

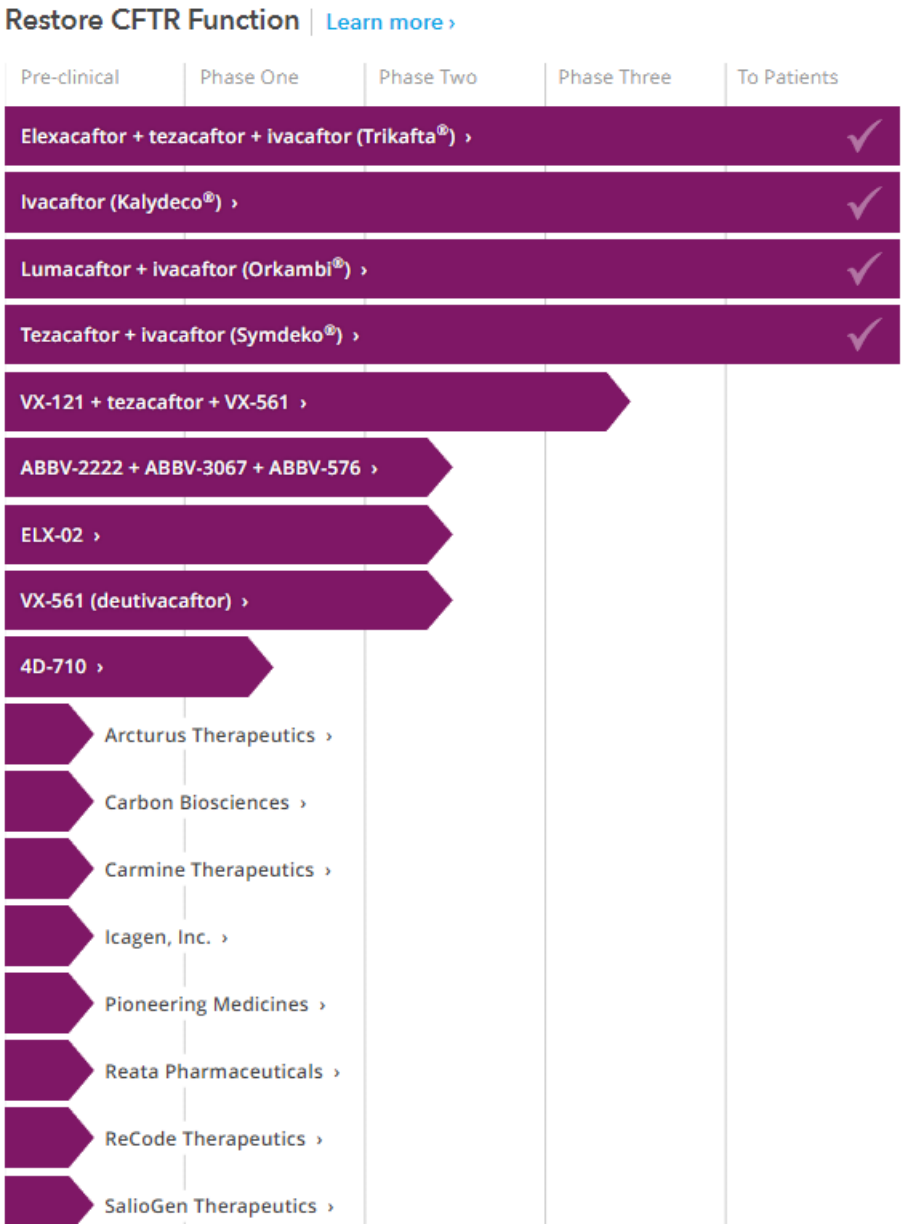


CFTR mutation classes: No CFTR modulators for class I



	Normal	I	II	III	IV	V	VI
CFTR defect		No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations		Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples		Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Elborn, Lancet 2016



https://www.cff.org/Trials/pipeline

VERTEX

ELO
Eloxx Pharmaceuticals

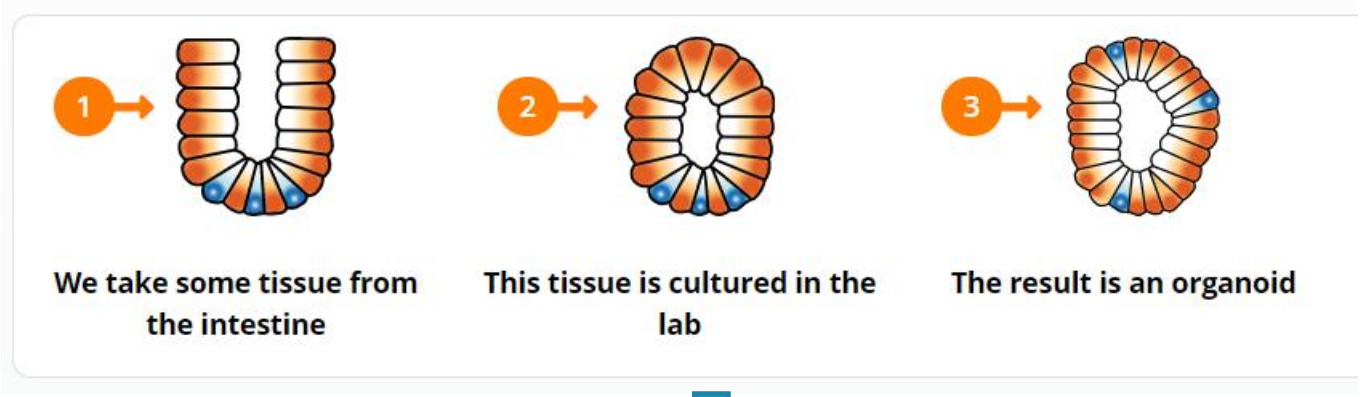
abbvie

4DMT

TranslateBIO

HIT-CF Europe: Rare non-F508del mutations

WWW.HITCF.ORG

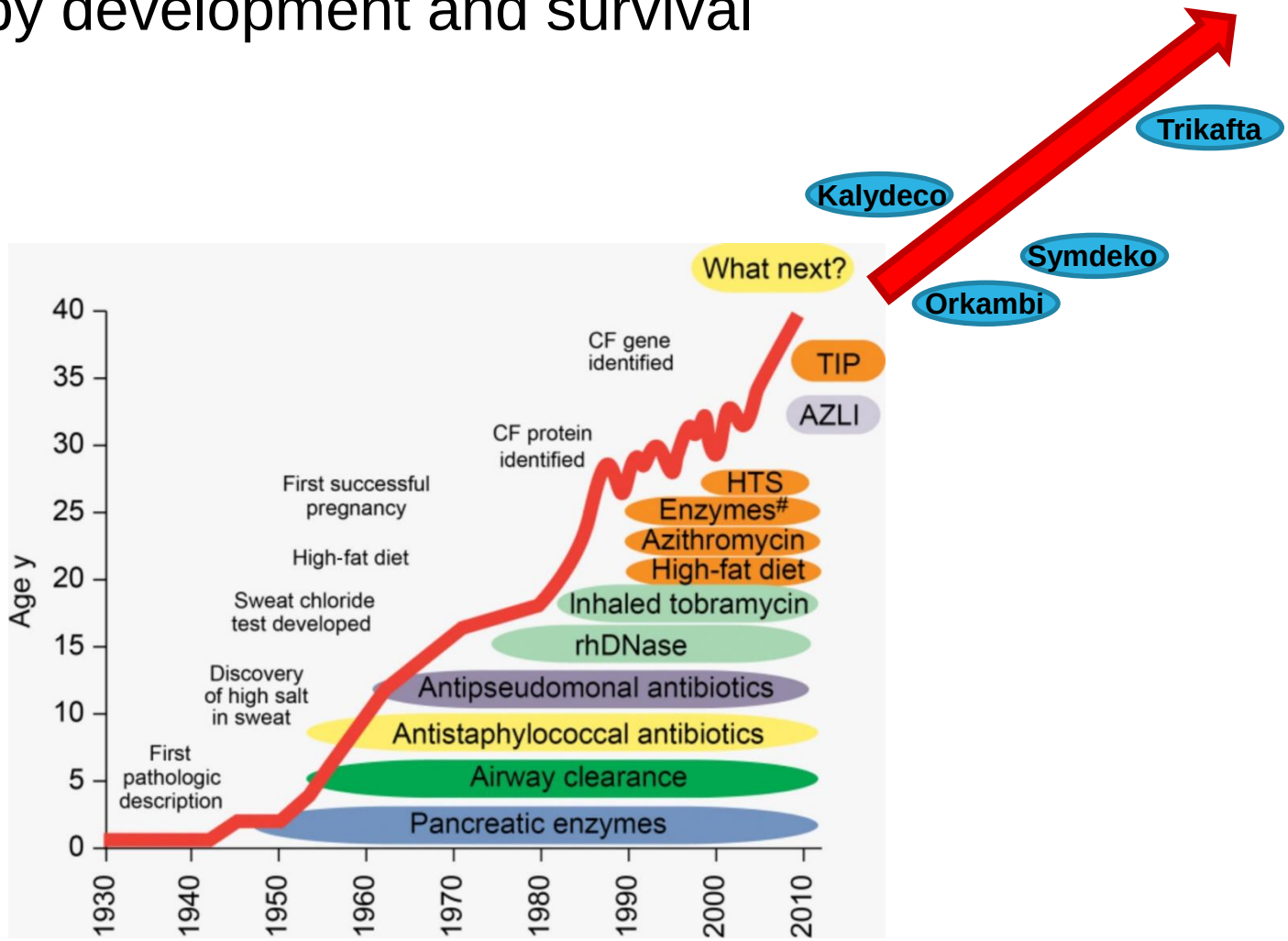


Clinical Trials Network

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 755021

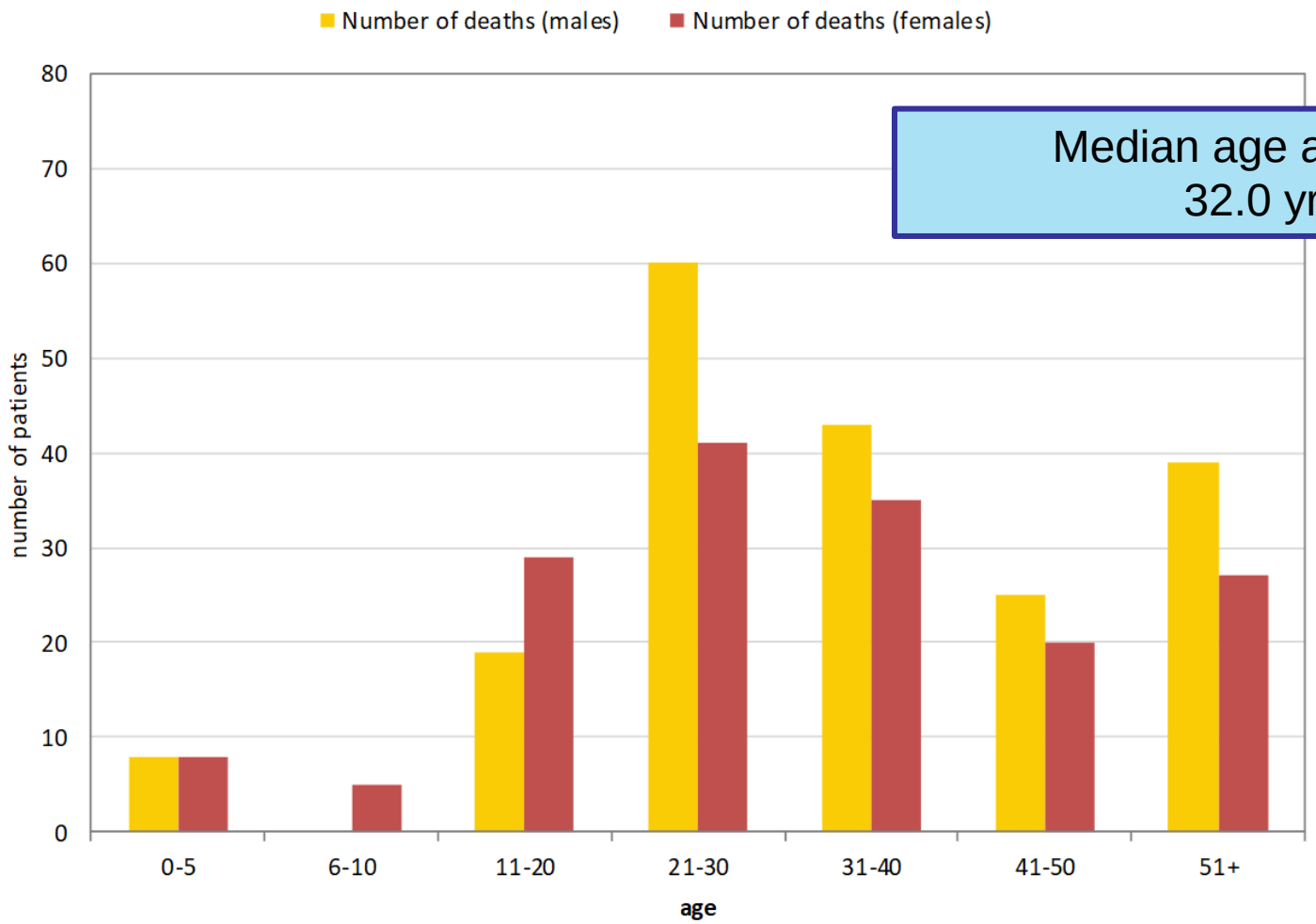
Surviving CF

Therapy development and survival



De Boeck, Acta Paediatr 2020

Age at death



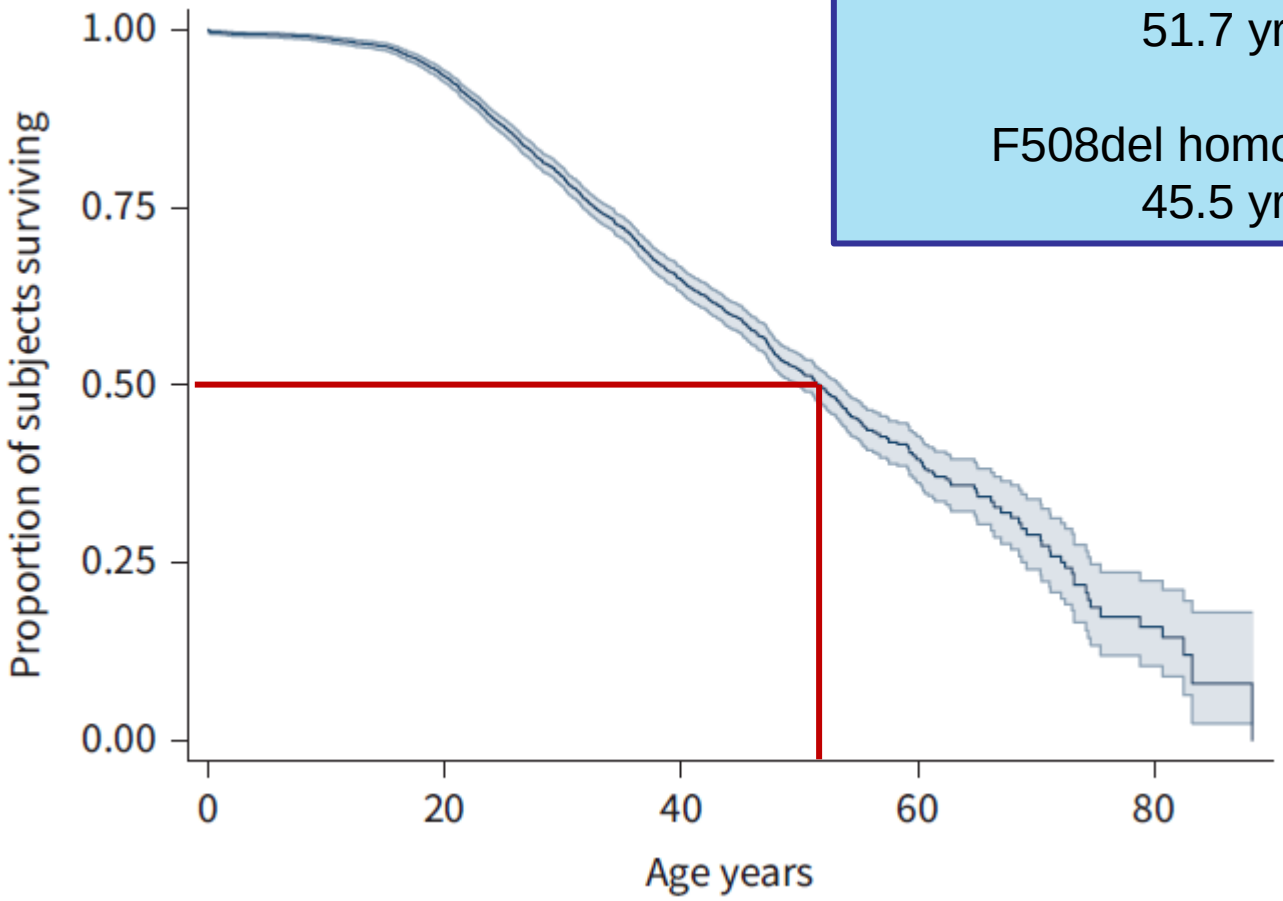
Median age at death:
32.0 yrs

Survival in Europe

Median estimated life expectancy
(without modulator effect)

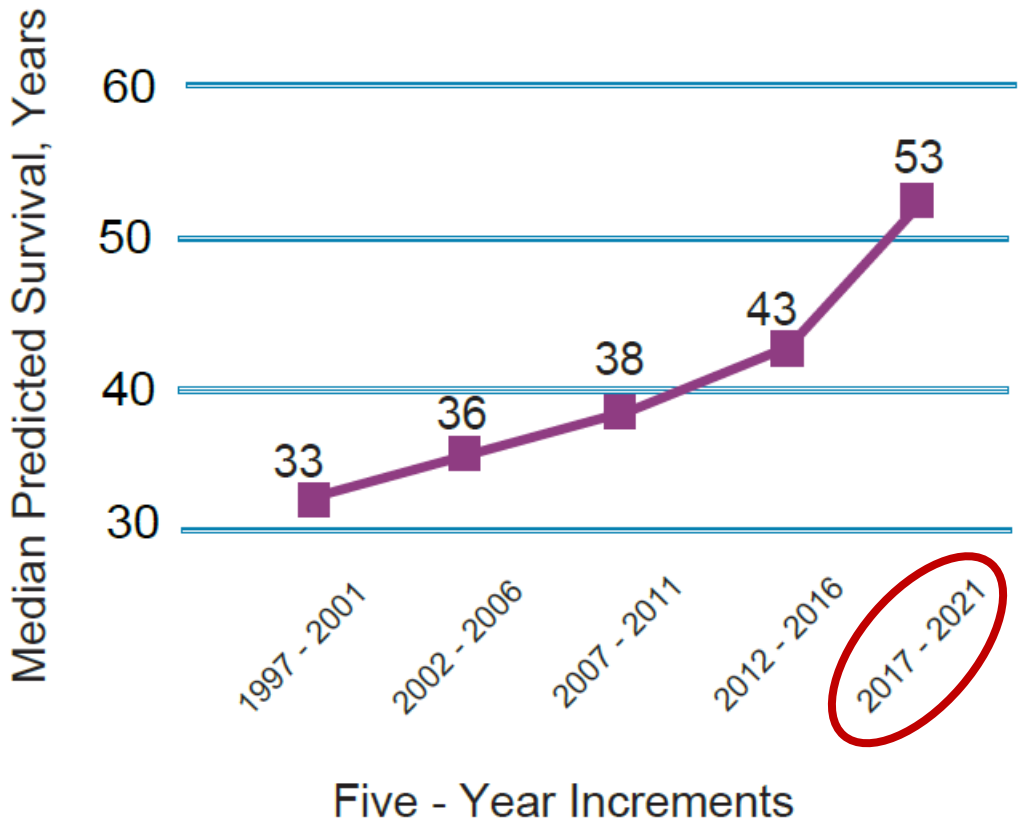
in a newborn child:
51.7 yrs

F508del homozygous:
45.5 yrs

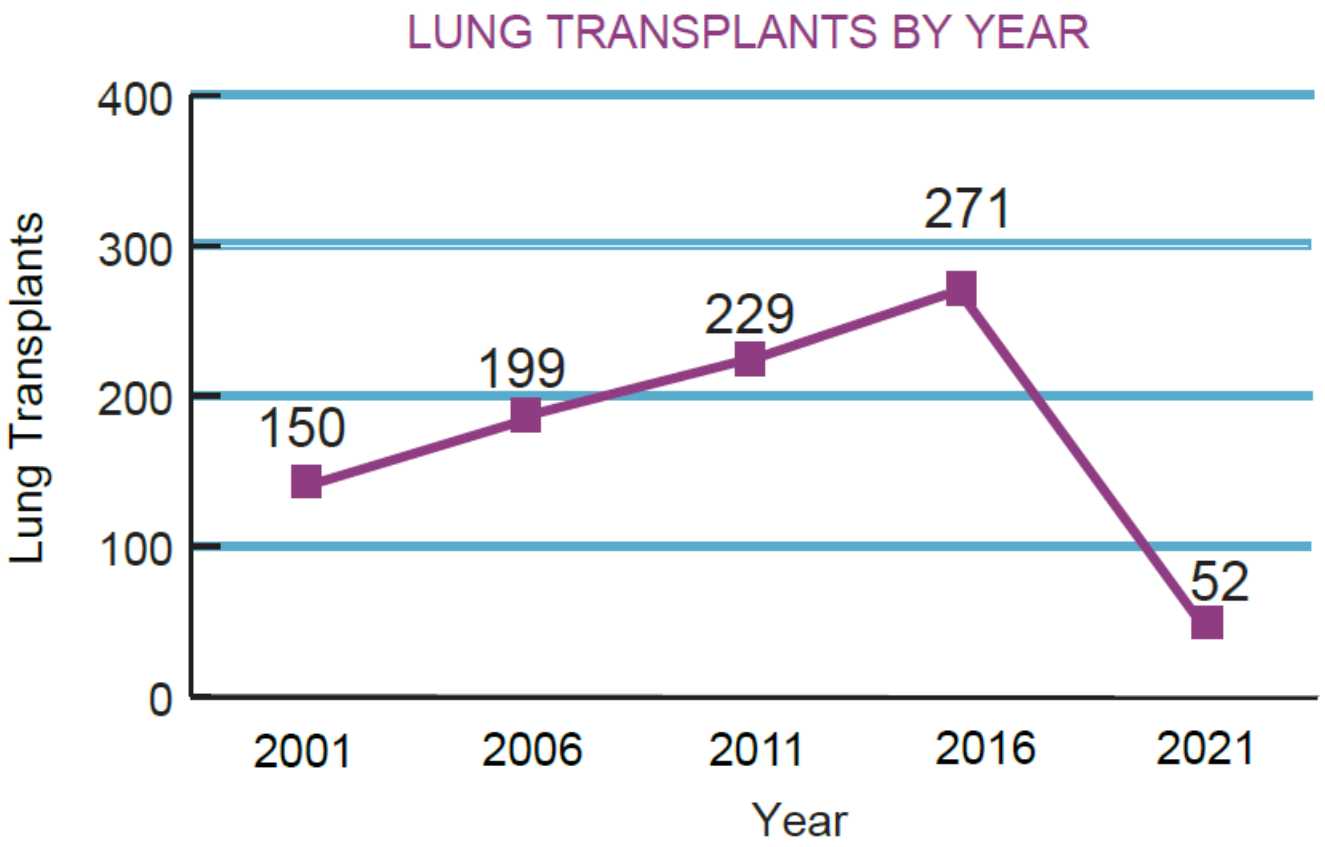


McKone et al., Eur Respir J 2021

Improvement of survival since CFTR modulator age

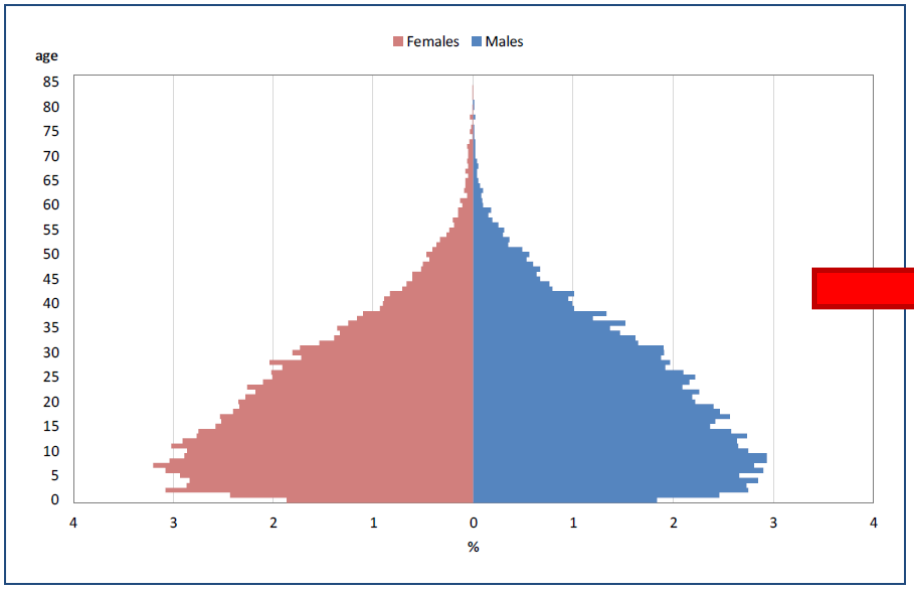


Decrease of lung transplantation

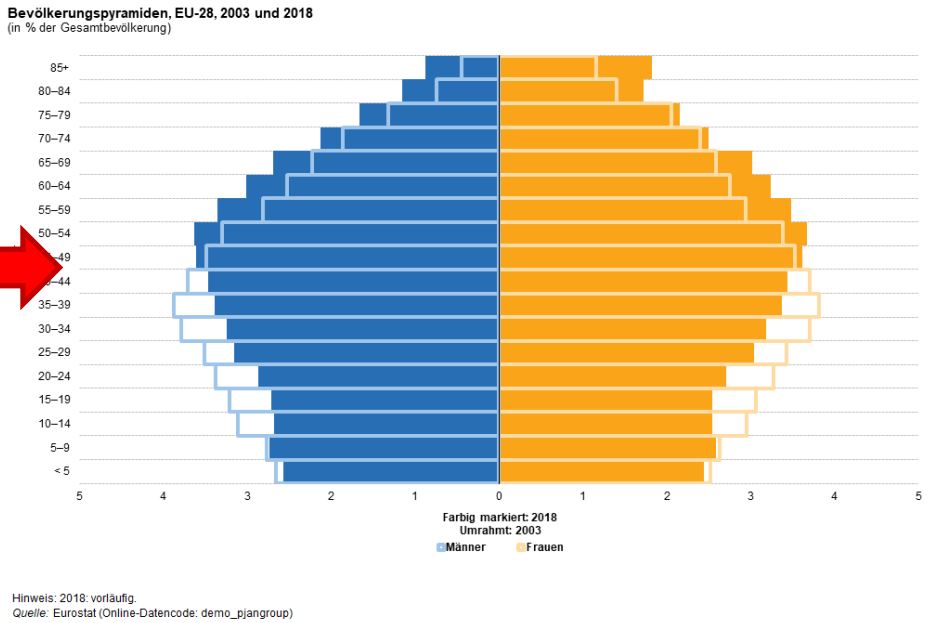


Registries: monitoring demographic development

CF



healthy

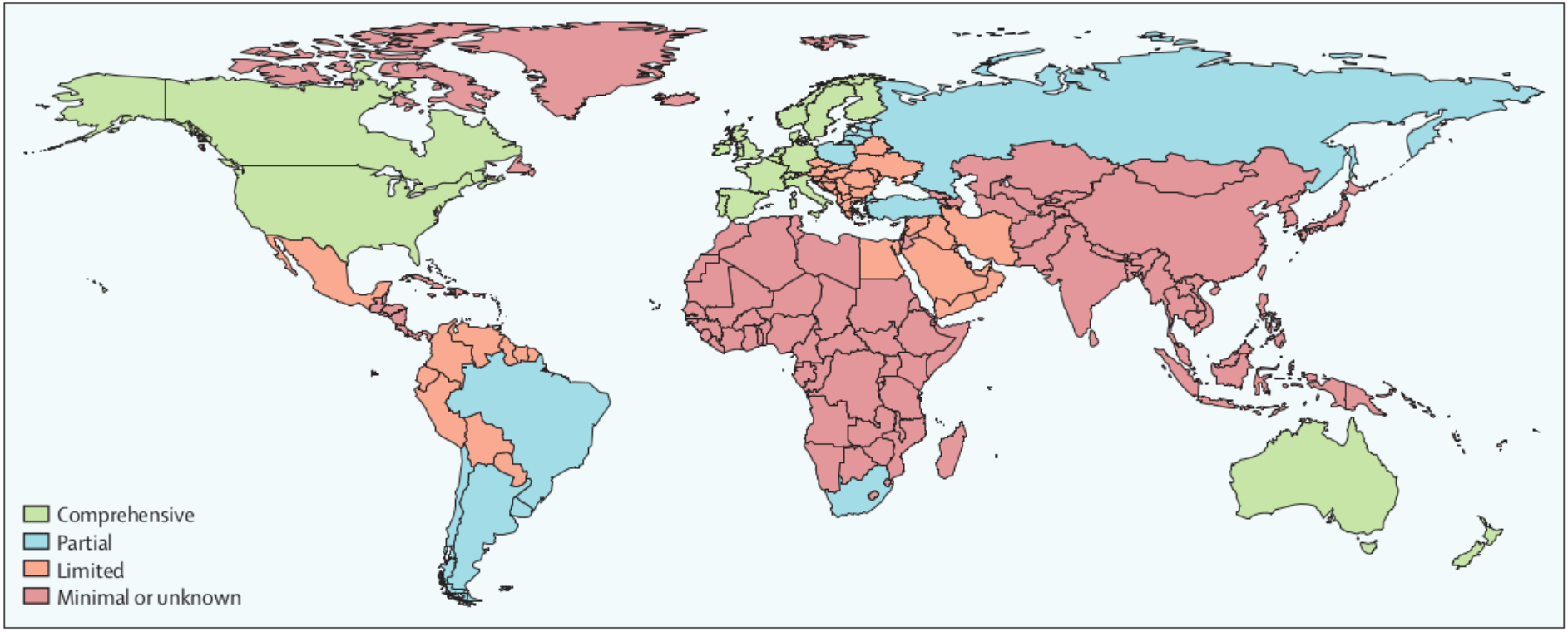


Hinweis: 2018: vorläufig.
Quelle: Eurostat (Online-Datencode: demo_pjangroup)

eurostat

Public health planning? (e.g. adult CF care)

Worldwide standards of CF care



Bell CS et al., Lancet Respir Med 2019

Personalized Medication in CF: Take home messages

- A new era of highly efficient CFTR-modulators has begun
- These drugs target specific mutation classes and restore CFTR function

- They are a game changer for >80% of all pwCF
- Dramatic improvement of health and QoL are observed

- Significant improvement of survival can be expected
- This needs to be accompanied by public health planning

- Long-term efficacy and safety to be monitored in registries
- Unmet needs are patients ineligible for HEMT and costs of treatment