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CFTR modulators and the impact on nutritional status

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Overview

- Background to cystic fibrosis (CF) and nutritional management
- What are CFTR modulators?
- Impact of CFTR modulators on nutritional status
- Implications for clinical practice and future considerations

CFTR, cystic fibrosis transmembrane conductance regulator

Background

CF caused by variants in the gene for **CFTR protein,** responsible for chloride transport across cell surface

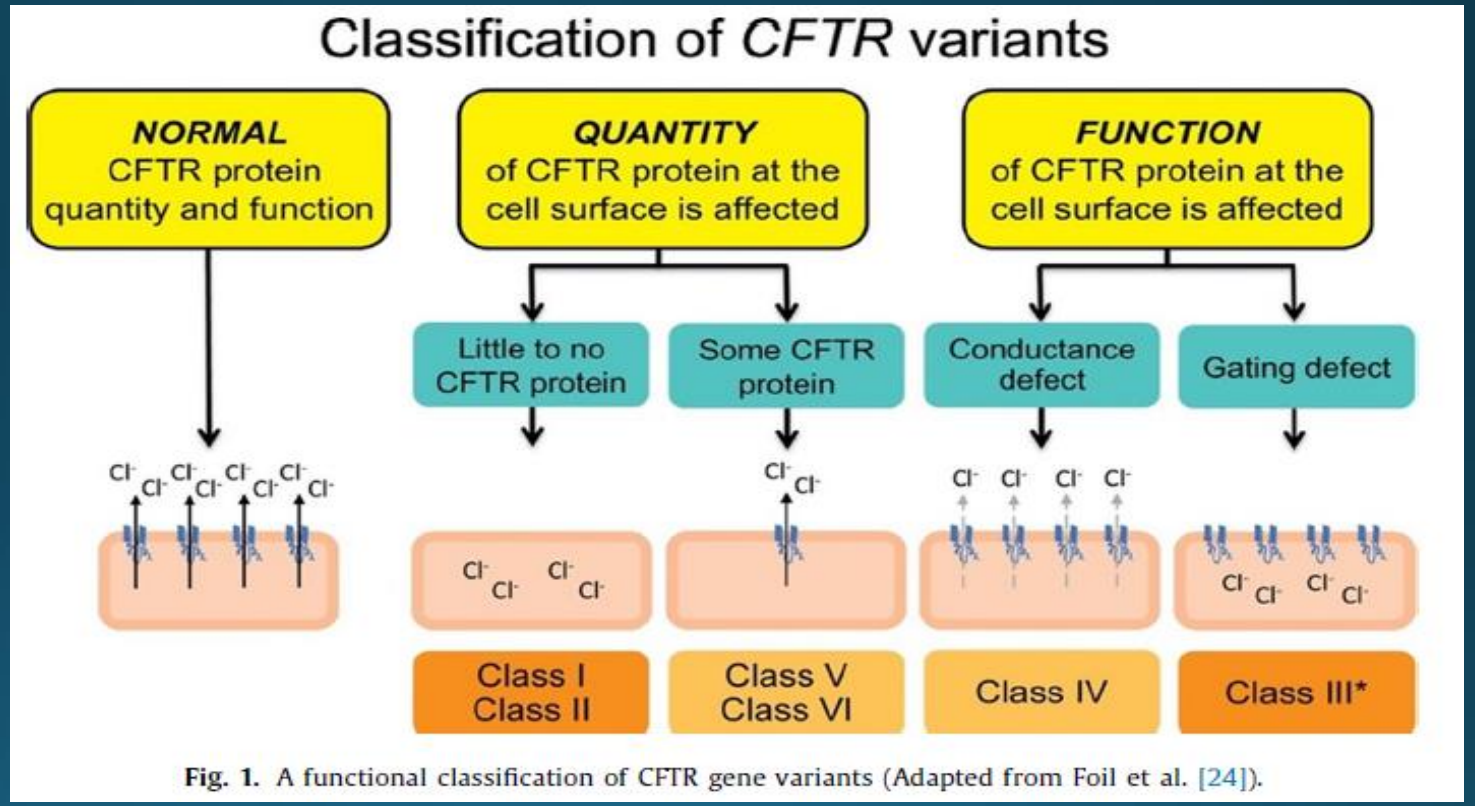


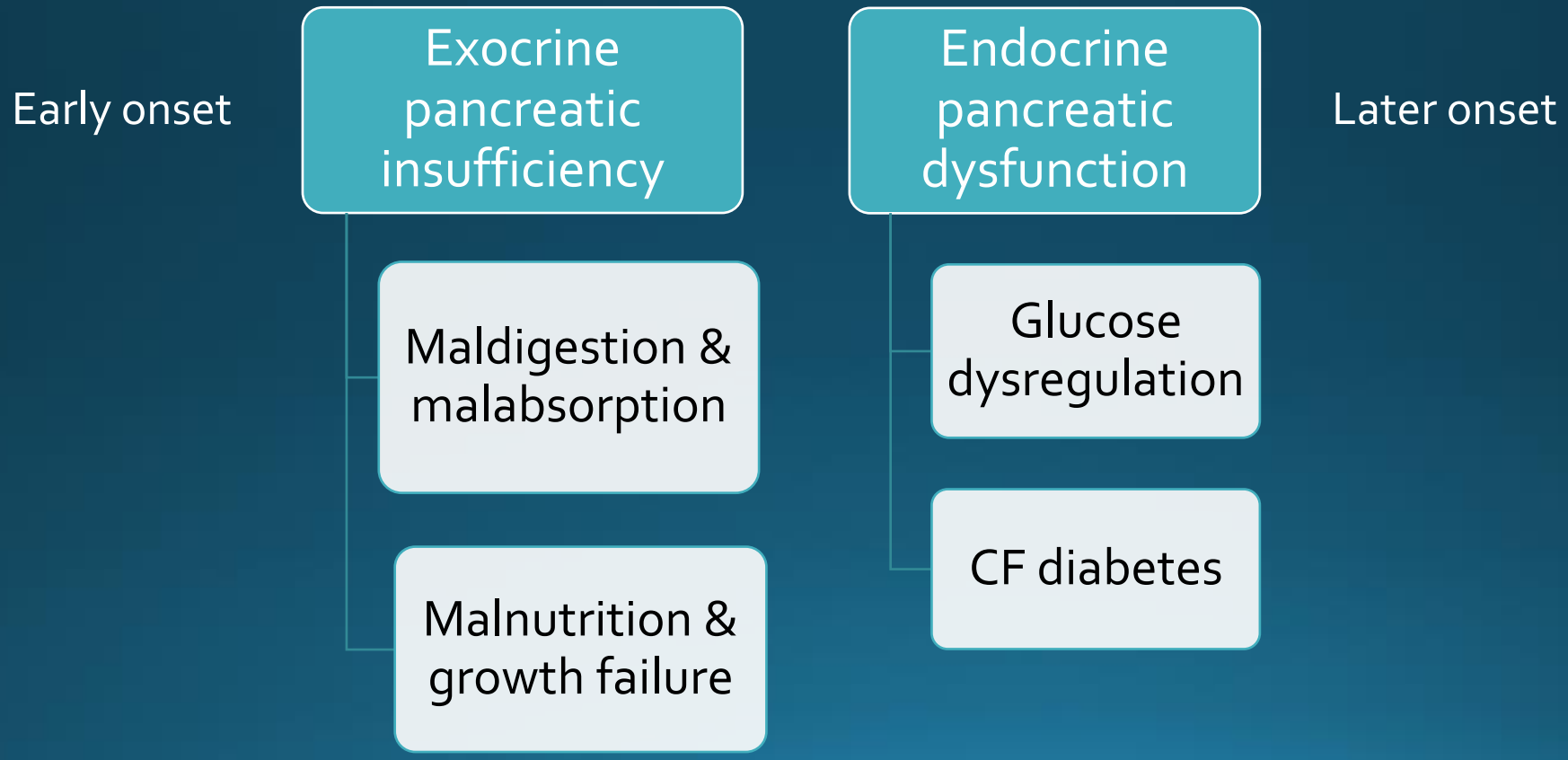
Fig. 1. A functional classification of CFTR gene variants (Adapted from Foil et al. [24]).

Source: Southern et al, JCF. 2022

CFTR, cystic fibrosis transmembrane conductance regulator

Non-pulmonary symptoms of CF

- First described as 'cystic fibrosis of the pancreas' in 1938 *(Andersen)*



Nutritional management

Treatments have targeted **symptoms of CFTR dysfunction**

- Pancreatic enzyme replacement therapy
- High calorie, high fat "CF legacy diet"
- Oral/enteral nutritional support
- Fat-soluble vitamin & mineral supplementation

→ Improved growth, pulmonary function and survival *(Corey et al)*

Corey et al, Ped Pulm. 1988

What are CFTR modulators?

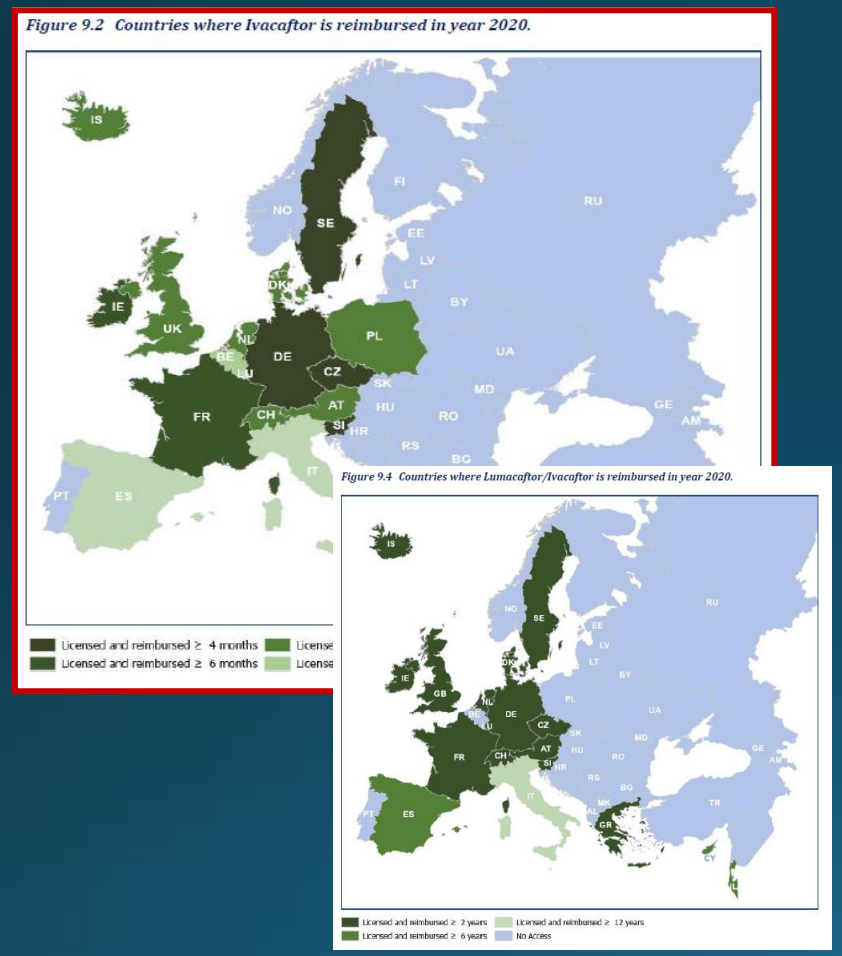
- Small molecule agents which target the **underlying CFTR defect** by improving **function** and increasing **quantity** of CFTR protein
- These agents are either a **potentiator** or a combination of both potentiator and **corrector/s**
- Oral medications taken 12 hourly with fat-containing food and enzymes

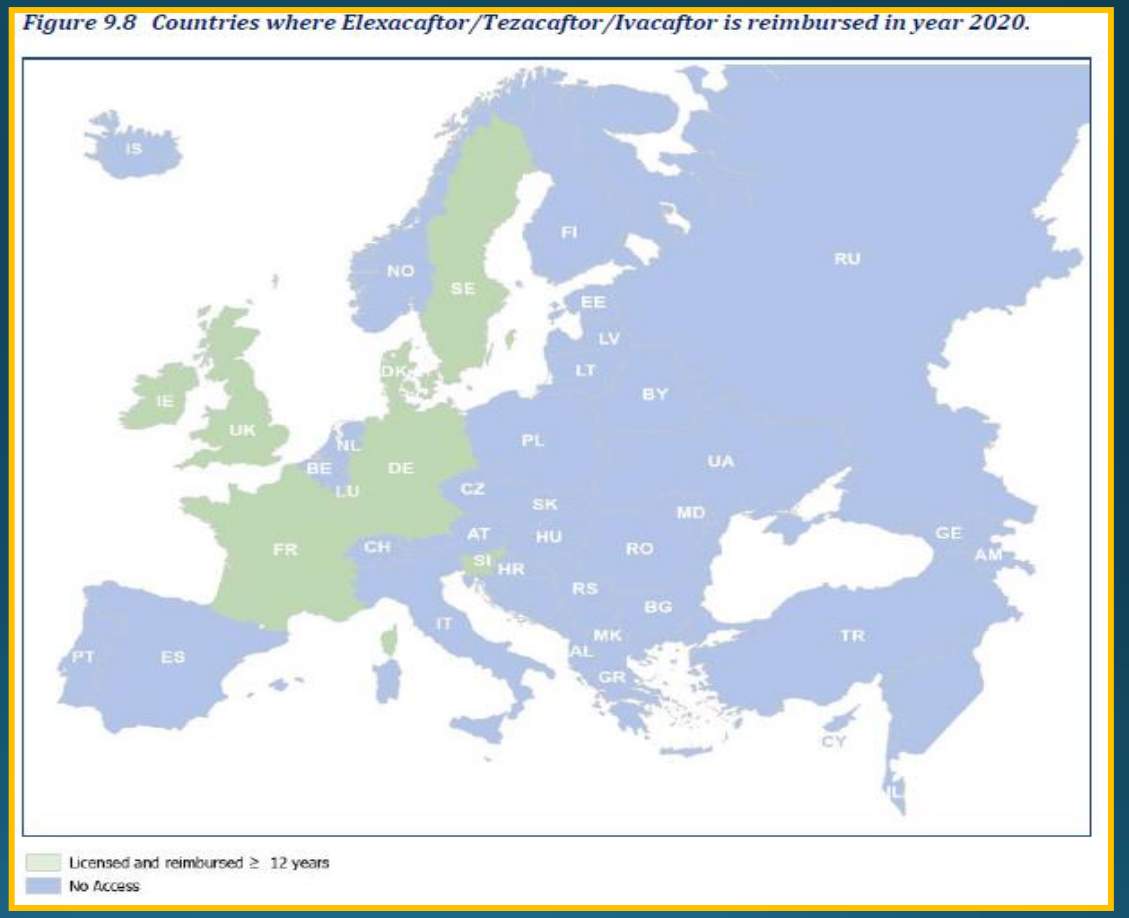
Types of CFTR modulators and eligibility

Modulator	Agent	Variants and class	Date licenced in UK
Ivacaftor* (Kalydeco®)	**Potentiator**	**Gating (e.g. G551D) Class III-V**	**Infants ≥4m since 2020 Children ≥12y & adults since 2013**
Lumacaftor/Ivacaftor (Orkambi®)	**Potentiator & corrector**	**dF508 homozygous Class II**	**Children ≥2y since 2020 Children ≥12y & adults since 2015**
Tezacaftor/Ivacaftor (Symkevi®)	Potentiator & corrector	dF508 heterozygous Class II-V	Children 6-11y since 2021 Children ≥12y & adults since 2019
Elexacaftor/Tezacaftor/ Ivacaftor* (Kaftrio®)	**Potentiator & correctors**	**dF508 homozygous dF508 heterozygous Class II-V**	**Trials in children 1-2y due to start Trials in 2-5y awaiting approval Children 6-11y since 2022 Children ≥12y & adults since 2020**

* IVA and ELX/TEZ/IVA are described as **highly effective modulator therapies**

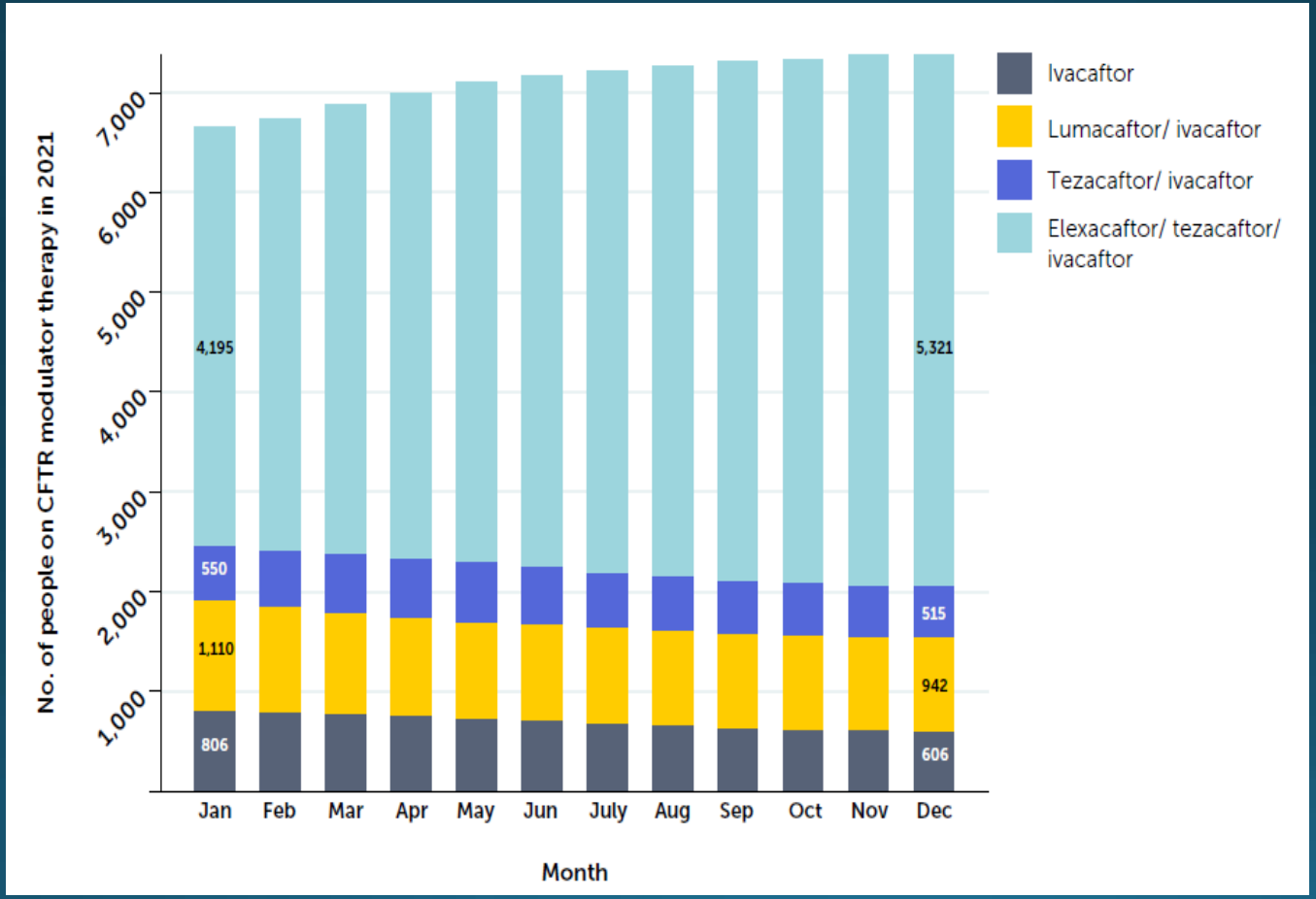
European registry data: modulator use





ECFS Patient Registry Annual Report 2020, published 2022

UK registry data: modulator use



UK CF Patient Registry 2021 Annual Report, CF Trust 2022

European registry data: nutritional status

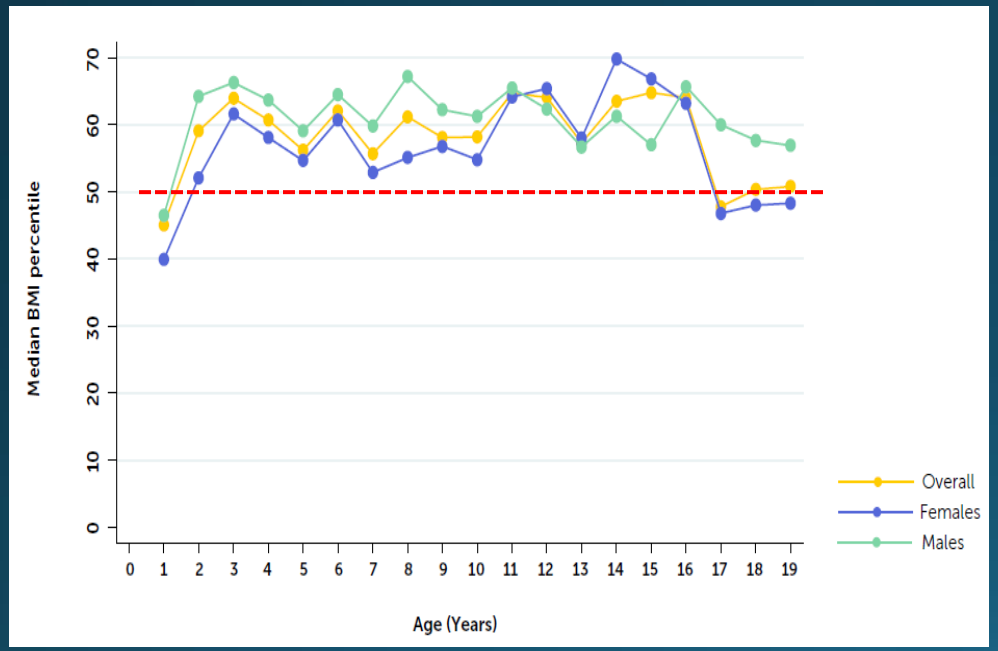
Children 2-17y	Median BMIp	% underweight	% overweight	% obese
2008	38.6	18.74	5.75	1.96
2018	40.9	18.33	7.32	2.96

Adults ≥18y	Median BMI	% underweight	% overweight	% obese
2008	20.9	20.5	9.11	1.89
2018	21.6	14.67	14.11	3.35

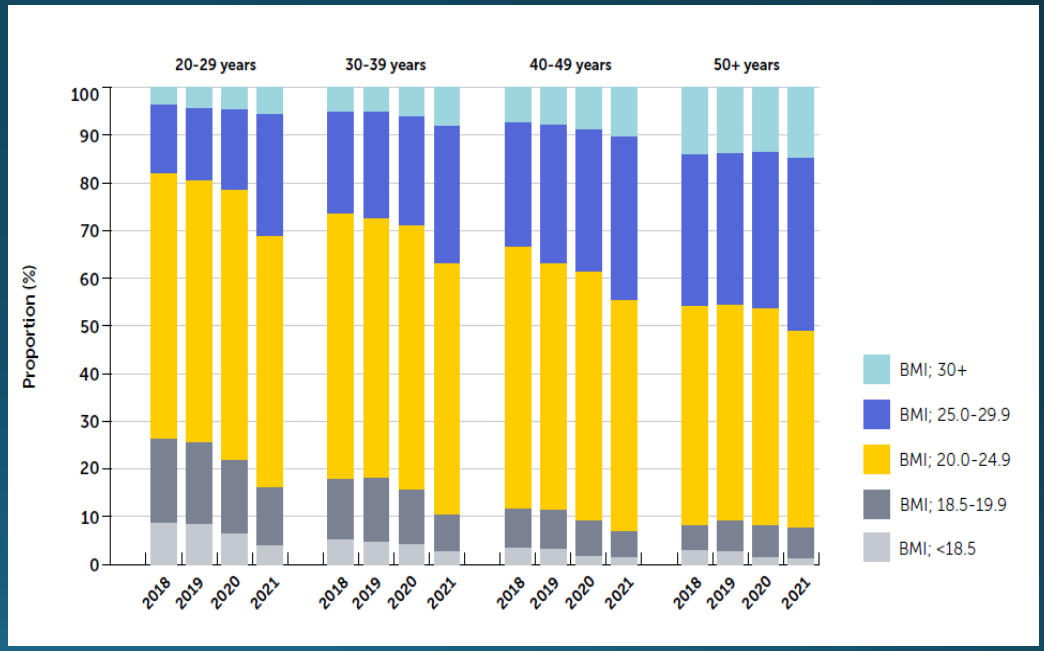
Zolin et al, ECFSPR 2020. Reproduced with permission

UK registry data: nutritional status

Median BMI percentiles in children & young people



BMI in adults 2018-2021



↑ overweight / ↓ underweight

UK CF Patient Registry 2021 Annual Report, CF Trust 2022

Impact on nutritional status

Table 1. Summary of the effects of highly effective CFTR modulators on markers of growth, nutritional status and gastrointestinal health.

Outcome	Ivacaftor	ELEX-TEZ-IVA
Weight-Z	Increased	Increased
Height-Z	Increased in youth	To be determined
BMI-Z	Increased	Increased
Fat Mass	Increased	To be determined
Fat-Free Mass	Unchanged to increased	To be determined
Bile Acid Metabolism	Increased FGF-19 and decreased C4	To be determined
CF Liver Disease	To be determined, case reports of improved steatosis	To be determined
Exocrine Pancreatic Insufficiency	Increased fecal elastase at younger ages	To be determined
Bicarbonate Secretion	Decreased time to reach pH 5.5	To be determined
Energy Expenditure	Decreased	To be determined
GI Microbiome	Changes in intestinal flora and decreased calprotectin	To be determined

Bass, Brownell and Stallings, Nutr. 2021

Impact on anthropometry

Effect of CFTR Modulators on Anthropometric Parameters in Individuals with Cystic Fibrosis: An Evidence Analysis Center Systematic Review

Julianna Bailey, MS, RDN, LD; Mary Rozga, PhD, RDN; Catherine M. McDonald, PhD, MS, RDN, CSP; Ellen K. Bowser, MS, RDN, LDN, RN, FAND; Kristen Farnham, MSH, RD, CSP, LDN; Mark Mangus; Laura Padula, MS, RD, LDN, CSP; Kathleen Porco, MS, CDCES; Jessica A. Alvarez, PhD, MS, RDN

Modulator	Parameters	Follow up	Results
IVA Children ≥6y ≥1 G551D	WFA and BMI z-scores	8 to 48 wk	Mean baseline WFA -0.292 and BMI -0.199. ↑ WFA and BMI z-scores by 0.35 and 0.39 respectively compared to placebo
IVA Adults ≥1 G551D	Wt and BMI	4 to 48 wk	Optimal or low mean BMI at baseline, ↑ wt and BMI by 2.9kg and 0.58-1.2 respectively
ELX/TEZ/IVA ≥12y dF508 homozygous	BMI	24 wk	Baseline nutritional status not reported. Mean change in BMI 1.04
ELX/TEZ/IVA ≥12y dF508 heterozygous	Wt and BMI	4 wk	Baseline nutritional status not reported. Mean change in BMI 0.6. Mean change in wt 1.6kg

WFA, Weight-for-age

Bailey et al, J Acad Nutr Diet. 2020

Long term impact on anthropometry: IVA

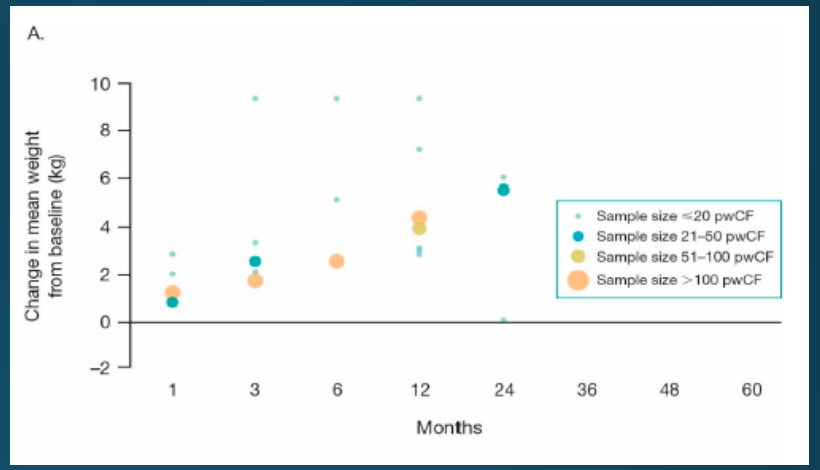
Review

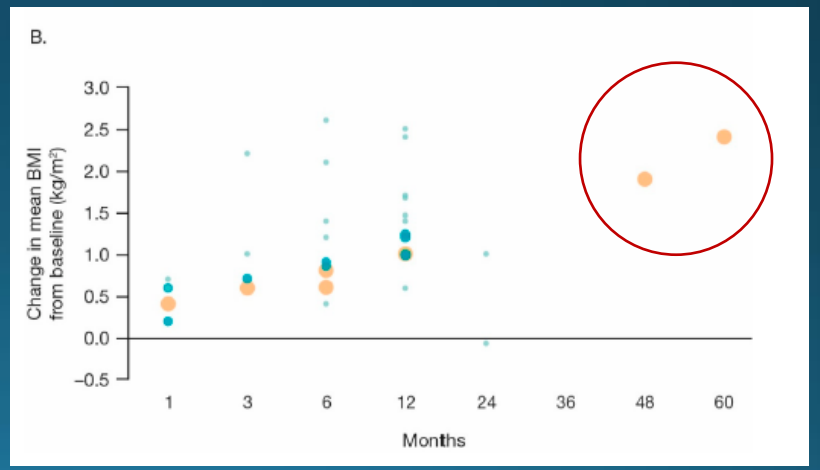
Real-World Outcomes of Ivacaftor Treatment in People with Cystic Fibrosis: A Systematic Review

Jamie Duckers [1,*], Beth Lesher [2], Teja Thorat [3], Eleanor Lucas [2], Lisa J. McGarry [3], Keval Chandarana [3] and Fosca De Iorio [4]

57 studies 2012-2019 (children & adults)

Highly **consistent** & **sustained** clinical benefit in both pulmonary & non-pulmonary outcomes, including nutritional markers after 5y





Duckers et al , J Clin Med. 2021

Impact on anthropometry: ELX/TEZ/IVA

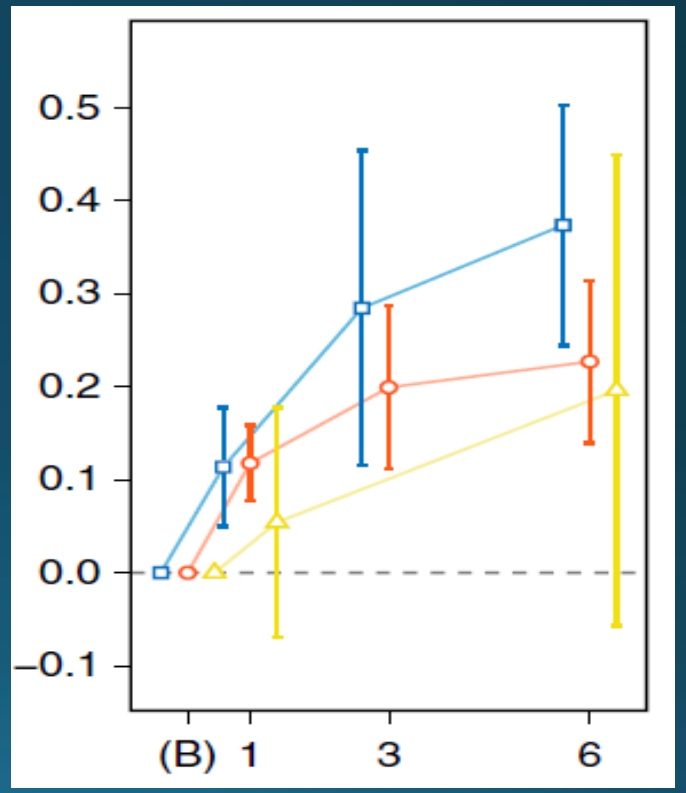
Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis
A Clinical Trial

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

'PROMISE' n=487, US adolescents & adults ≥12y

At 6m ↑ BMI percentile to 65th in adolescents, 24.5kgm$_2$ in adults (even after FEV1 plateaued)

Change in BMI percentile



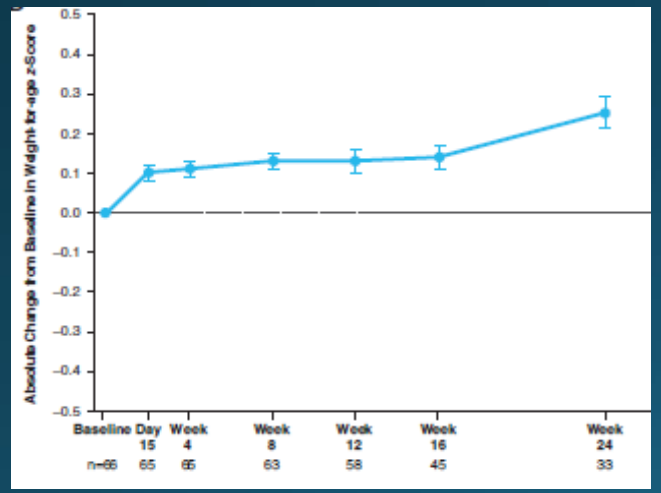
Nichols et al, Am J Resp Crit Care Med. 2021

Impact on growth: ELX/TEZ/IVA

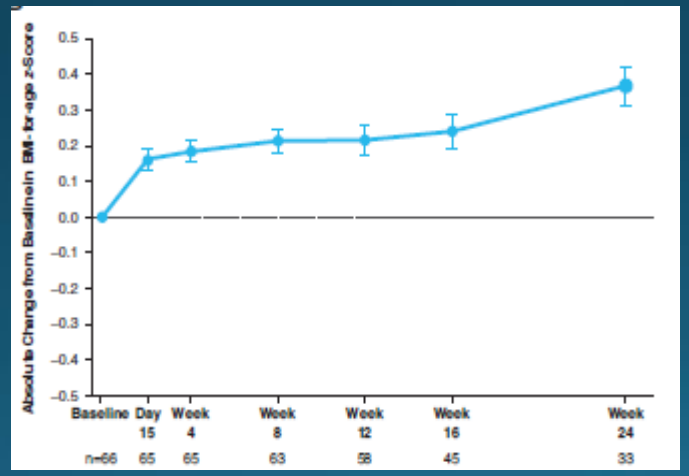
A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One *F508del* Allele

Edith T. Zemanick[1*], Jennifer L. Taylor-Cousar[2,3*], Jane Davies[4], Ronald L. Gibson[5], Marcus A. Mall[6,7,8], Edward F. McKone[9], Paul McNally[10], Bonnie W. Ramsey[5‡], Jonathan H. Rayment[11], Steven M. Rowe[12], Elizabeth Tullis[13], Neil Ahluwalia[14], Chenghao Chu[14], Thang Ho[14], Samuel M. Moskowitz[14], Sabrina Noel[14], Simon Tian[14], David Waltz[14], Tanya G. Weinstock[14], Fengjuan Xuan[14], Claire E. Wainwright[15§], and Susanna A. McColley[16,17§]; for the VX18-445-106 Study Group

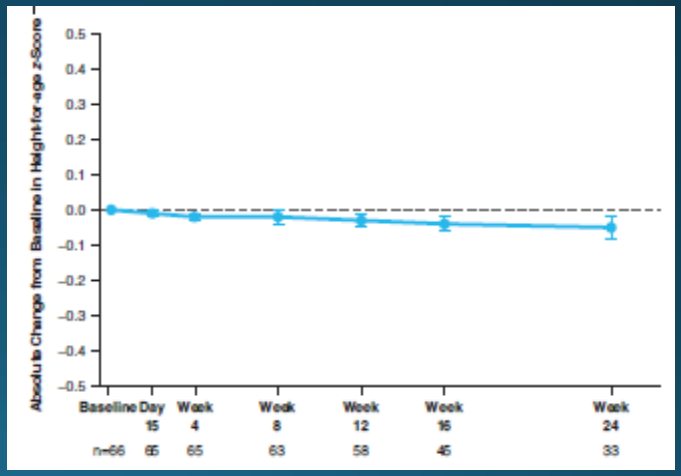
n=66 children 6-11y
↑ wt & BMI z-scores at 24wks,
ht z-score maintained



Wt z-score



BMI z-score



Ht z-score

Zemanick et al, Am J Resp Crit Care Med. 2021

Impact on body composition: IVA

Body composition and weight changes after ivacaftor treatment in adults with cystic fibrosis carrying the G551 D cystic fibrosis transmembrane conductance regulator mutation: A double-blind, placebo-controlled, randomized, crossover study with open-label extension

Susannah J. King Ph.D. [a,b,c,*,1], Audrey C. Tierney Ph.D. [a,b,c,d,1], Deirdre Edgeworth B.M.B.B., B.A.O. Dominic Keating M.D. [b,f], Elyssa Williams B.Sc., R.N. [b], Tom Kotsimbos M.D. [b,f], Brenda M. Button John W. Wilson M.B.B.S., Ph.D. [b,f]

n=20 adults
After 28d: ↑ wt, BMI & FFM
After 6m: ↑ fat mass, plateaued at 2.5y

At baseline: 20% overweight / 5% obese
After 6m: ↑ to 25% overweight / 10% obese

King et al, Nutr. 2021

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Energy Balance and Mechanisms of Weight Gain with Ivacaftor Treatment of Cystic Fibrosis Gating Mutations

Virginia A. Stallings, MD[1,2], Nina Sainath, MD[1], Megan Oberle, MD[3], Chiara Bertolaso, MD[4], and Joan I. Schall, PhD[1]

n=23 children & adults (5-61y)
At 3 m: ↑ wt, BMI, fat mass & FFM

Stallings et al, J Ped. 2018

FFM, Fat-free mass

Impact on pancreatic function: IVA

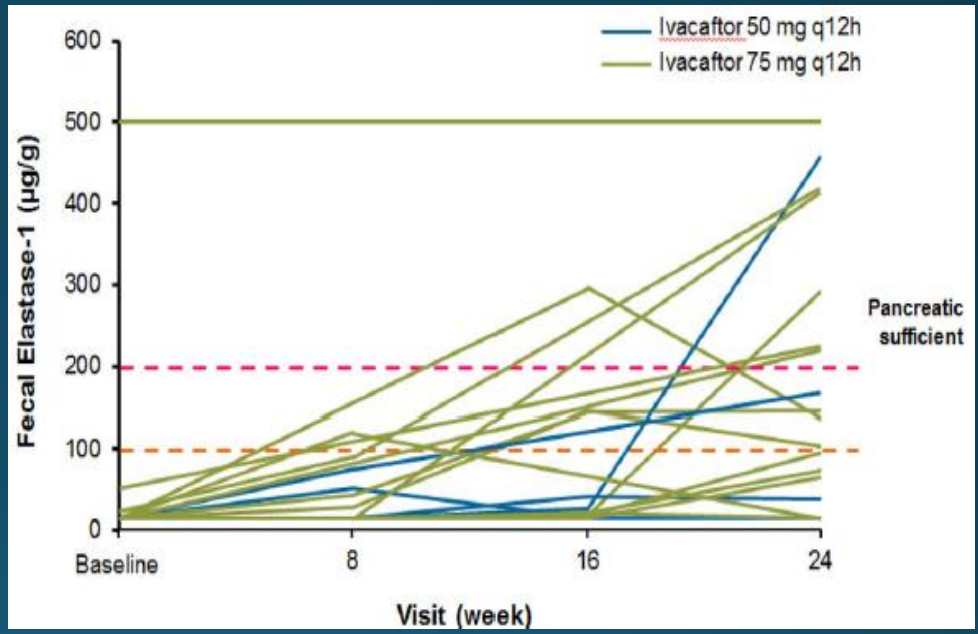
Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study.

Jane C. Davies, MD[1,2], Steve Cunningham, MBChB[3], William T. Harris, MD[4], Allen Lapey, MD[5], Warren E. Regelmann, MD[6], Gregory S. Sawicki, MD[7], Kevin W. Southern, MBChB[8], Sarah Robertson, PharmD[9], Yulia Green, MBChB[10], Jon Cooke[10], Margaret Rosenfeld, MD[11], KIWI Study Group

'KIWI' study, n=34 young children 2-5y

- Improvement pancreatic function (n=27): ↑elastase, ↓IRT

- Wt & BMI z-scores ↑ by wk 2, sustained to wk 24, ht z-score similar from baseline to wk 24



Similar results shown in 'ARRIVAL' study children aged 1-2y with ≥1 gating variant
Rosenfeld et al, Lancet Resp Med. 2018

IRT, immunoreactive trypsin

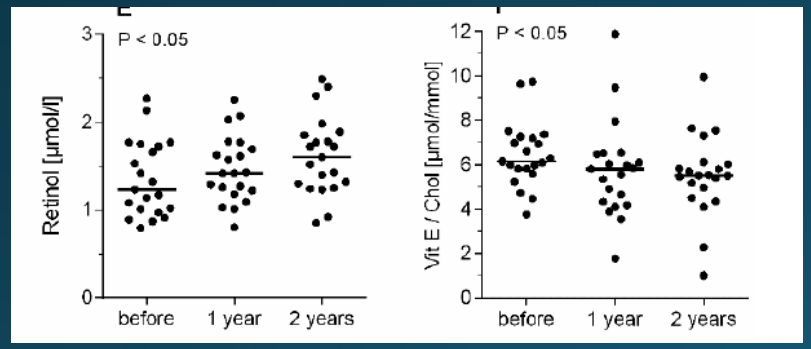
Davies et al, Lancet Resp Med. 2016

Impact on fat-soluble vitamin status

Article

CFTR Modulator Therapy with Lumacaftor/Ivacaftor Alters Plasma Concentrations of Lipid-Soluble Vitamins A and E in Patients with Cystic Fibrosis

Olaf Sommerburg [1,2], Susanne Hämmerling [1,2], S. Philipp Schneider [2], Jürgen Okun [3], Claus-Dieter Langhans [3], Patricia Leutz-Schmidt [2,4], Mark O. Wielpütz [2,4], Werner Siems [5], Simon Y. Gräber [6,7,8], Marcus A. Mall [6,7,8,*] and Mirjam Stahl [6,8,*]



n=41 (2-21y), ↑ in plasma vitamin A, ↓ in vitamin E, within normal ranges

Sommerburg et al, Antioxid. 2021

Real-Life Safety and Effectiveness of Lumacaftor–Ivacaftor in Patients with Cystic Fibrosis

Pierre-Régis Burgel[1,2,3], Anne Munck[4], Isabelle Durieu[3,5,6], Raphaël Chiron[7], Laurent Mely[8], Anne Prevotat[9], Marlene Murris-Espin[10], Michele Porzio[11], Michel Abely[12], Philippe Reix[13,14], Christophe Marguet[15], Julie Macey[16], Isabelle Sermet-Gaudelus[3,17,18], Harriet Corvol[19,20], Stéphanie Bui[21], Lydie Lemonnier[22], Clémence Dehillotte[22], Jennifer Da Silva[1,3,23], Jean-Louis Paillasseur[24], and Dominique Hubert[2,3]; for the French Cystic Fibrosis Reference Network Study Group

n=845 adolescents & adults, no ↑ in serum vitamin A, E or D after 1y

Burgel et al, Am J Resp Crit Care. 2020

Case reports of raised ICP & **mild hypervitaminosis A** in children after starting ELX/TEZ/IVA

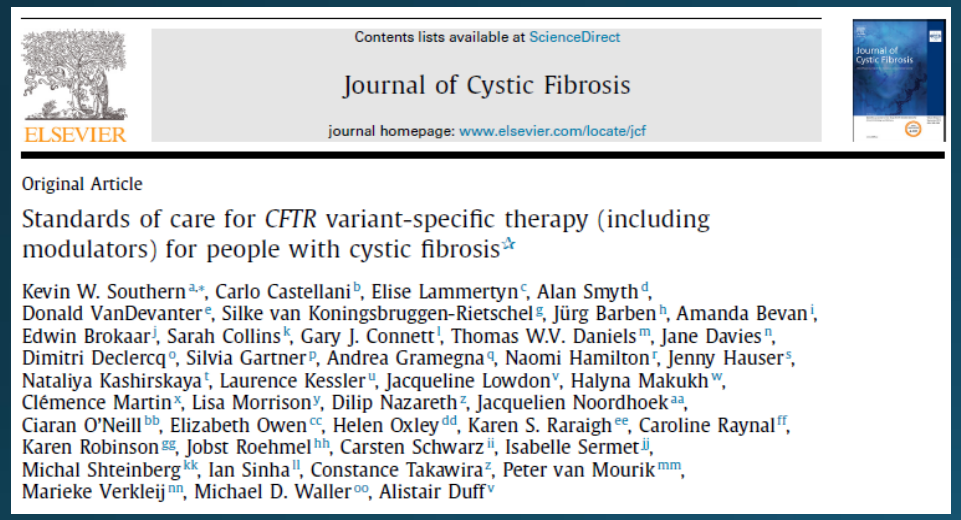
Miller & Foroozan, Can J Ophthal. 2022;
Wisniewski et al, JCF. 2022

ICP, intracranial pressure

Re-thinking nutritional management

- Nutritional assessment to include **body composition** markers in addition to anthropometry
- Dietary management to focus on **quality,** rather than **quantity**
- May be able to reduce/discontinue enzymes in younger children?
- Review frequency of fat-soluble vitamin monitoring, with adjustment of supplementation

ECFS SOC for CFTR modulators



Contents lists available at ScienceDirect

Journal of Cystic Fibrosis

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

Original Article

Standards of care for *CFTR* variant-specific therapy (including modulators) for people with cystic fibrosis☆

Kevin W. Southern[a,*], Carlo Castellani[b], Elise Lammertyn[c], Alan Smyth[d], Donald VanDevanter[e], Silke van Koningsbruggen-Rietschel[g], Jürg Barben[h], Amanda Bevan[i], Edwin Brokaar[j], Sarah Collins[k], Gary J. Connett[l], Thomas W.V. Daniels[m], Jane Davies[n], Dimitri Declercq[o], Silvia Gartner[p], Andrea Gramegna[q], Naomi Hamilton[r], Jenny Hauser[s], Nataliya Kashirskaya[t], Laurence Kessler[u], Jacqueline Lowdon[v], Halyna Makukh[w], Clémence Martin[x], Lisa Morrison[y], Dilip Nazareth[z], Jacquelien Noordhoek[aa], Ciaran O'Neill[bb], Elizabeth Owen[cc], Helen Oxley[dd], Karen S. Raraigh[ee], Caroline Raynal[ff], Karen Robinson[gg], Jobst Roehmel[hh], Carsten Schwarz[ii], Isabelle Sermet[jj], Michal Shteinberg[kk], Ian Sinha[ll], Constance Takawira[z], Peter van Mourik[mm], Marieke Verkleij[nn], Michael D. Waller[oo], Alistair Duff[v]

"(15) Regular monitoring of nutritional status & dietary intake, according to changing energy requirements"

"(16) Frequency of support of nutritional assessment should be individualised, depending on age, clinical status & modulator therapy"

Southern et al, JCF. 2022

Summary

- CFTR modulators have transformed CF care, moving from treating the symptoms of CFTR dysfunction → targeting the underlying defective CFTR protein
- CFTR modulators have a significant impact on nutritional status, the extent to which is variant-specific & depends on the type of modulator used
- **Nutritional assessment & dietary management are evolving, becoming more individualised & focusing on optimising long term health**

Thank you for listening

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