

COME CAMBIA IL REFERRAL AL TRAPIANTO DOPO L'ARRIVO DEI MODULATORI DEL CFTR

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CONFLITTO DI INTERESSE

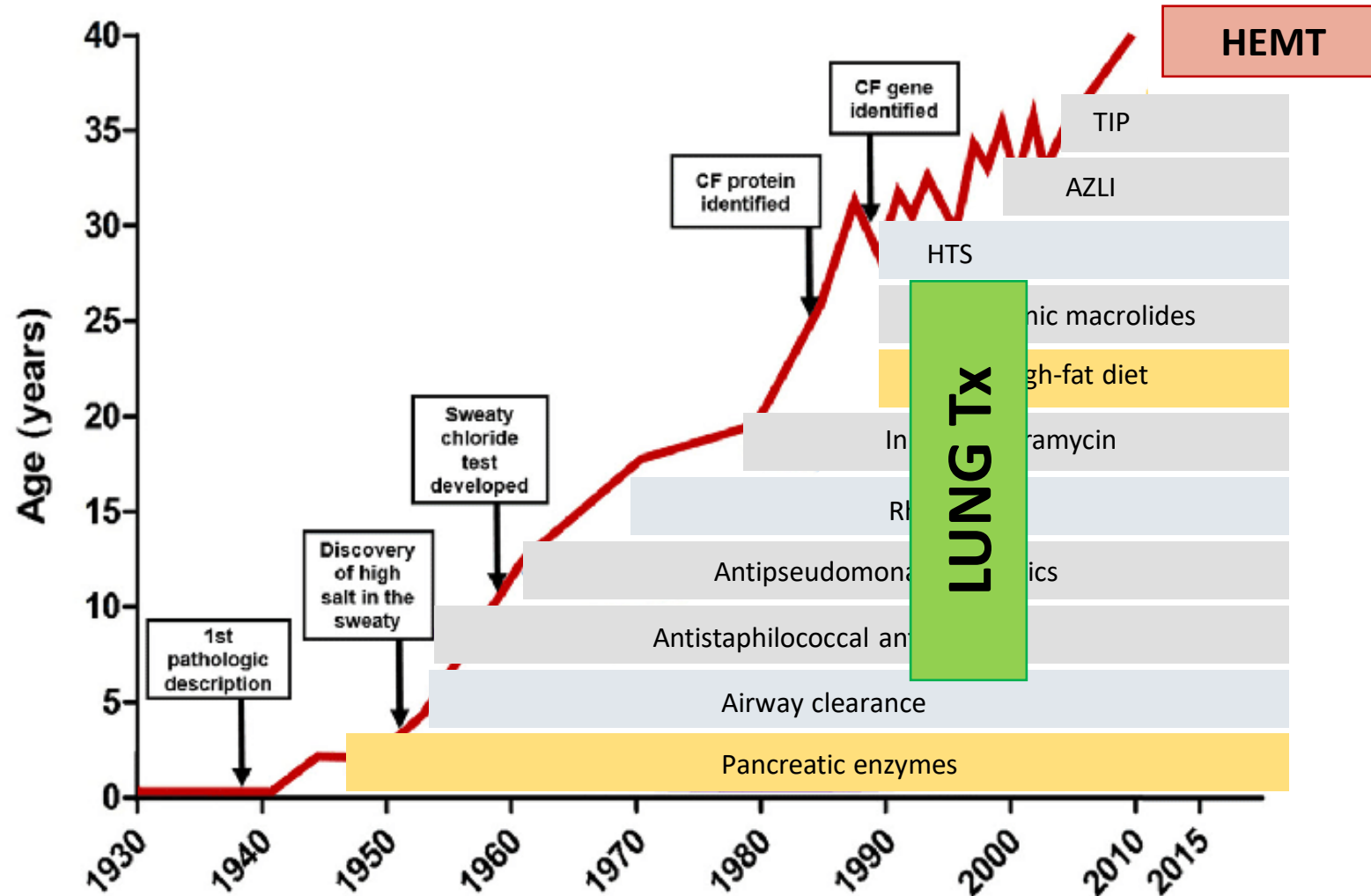
DICHIARAZIONE AI SENSI DELLA LEGGE 24 Nov 2003, N. 326- ART 48 comma 25 AUTOCERTIFICAZIONE 2020

Ai sensi dell'art. 76.4 sul Conflitto di Interessi dell'Accordo Stato-Regione del 2 febbraio 2017,

DICHIARO i seguenti rapporti anche di finanziamento con soggetti portatori di interessi commerciali in campo sanitario avuti dal 2018 a oggi:

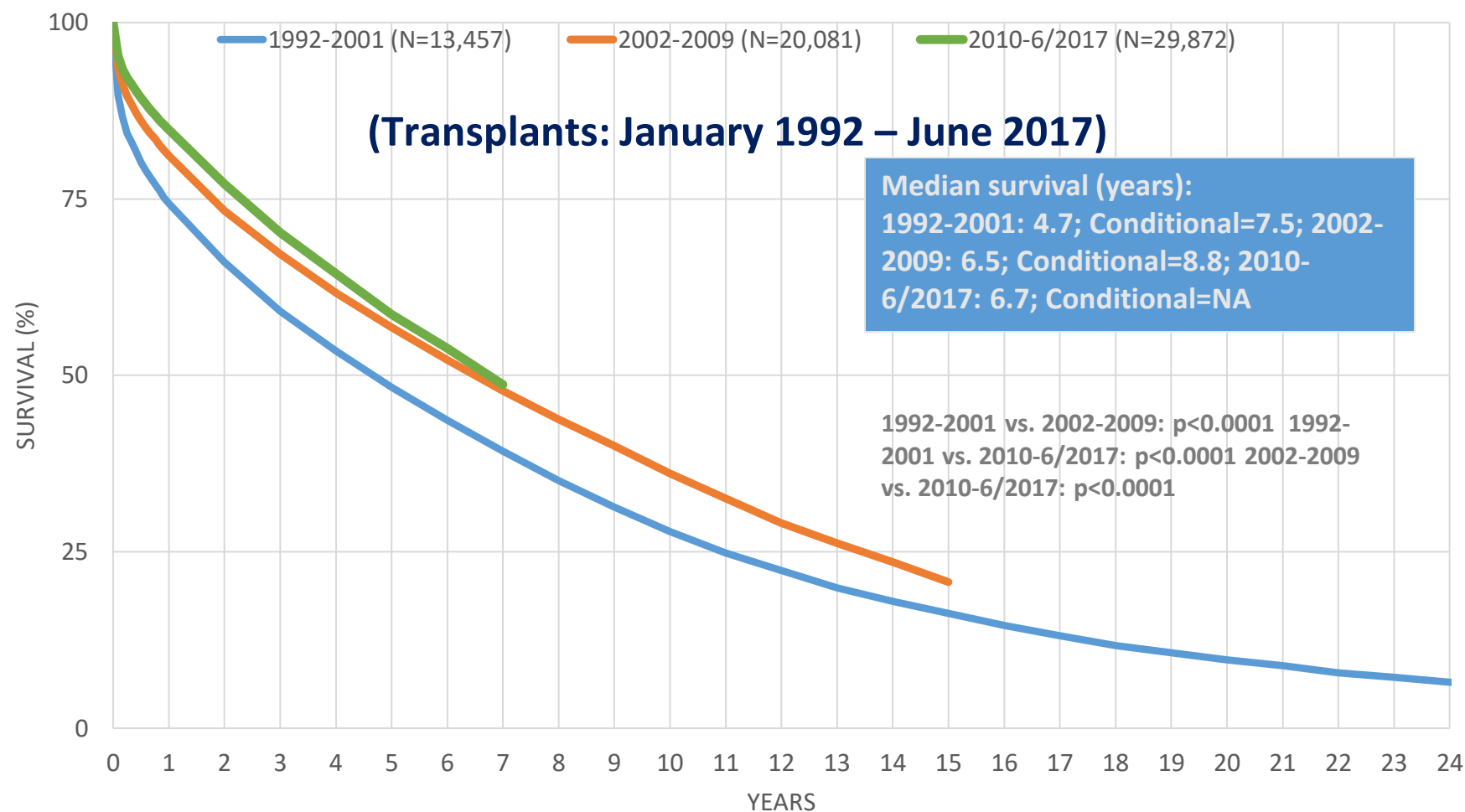
- travel grant per congressi: *Actelion, Biotest, Neupharma*
- lecture fee: *Biotest, Vertex*

Un paradigma terapeutico in continua evoluzione

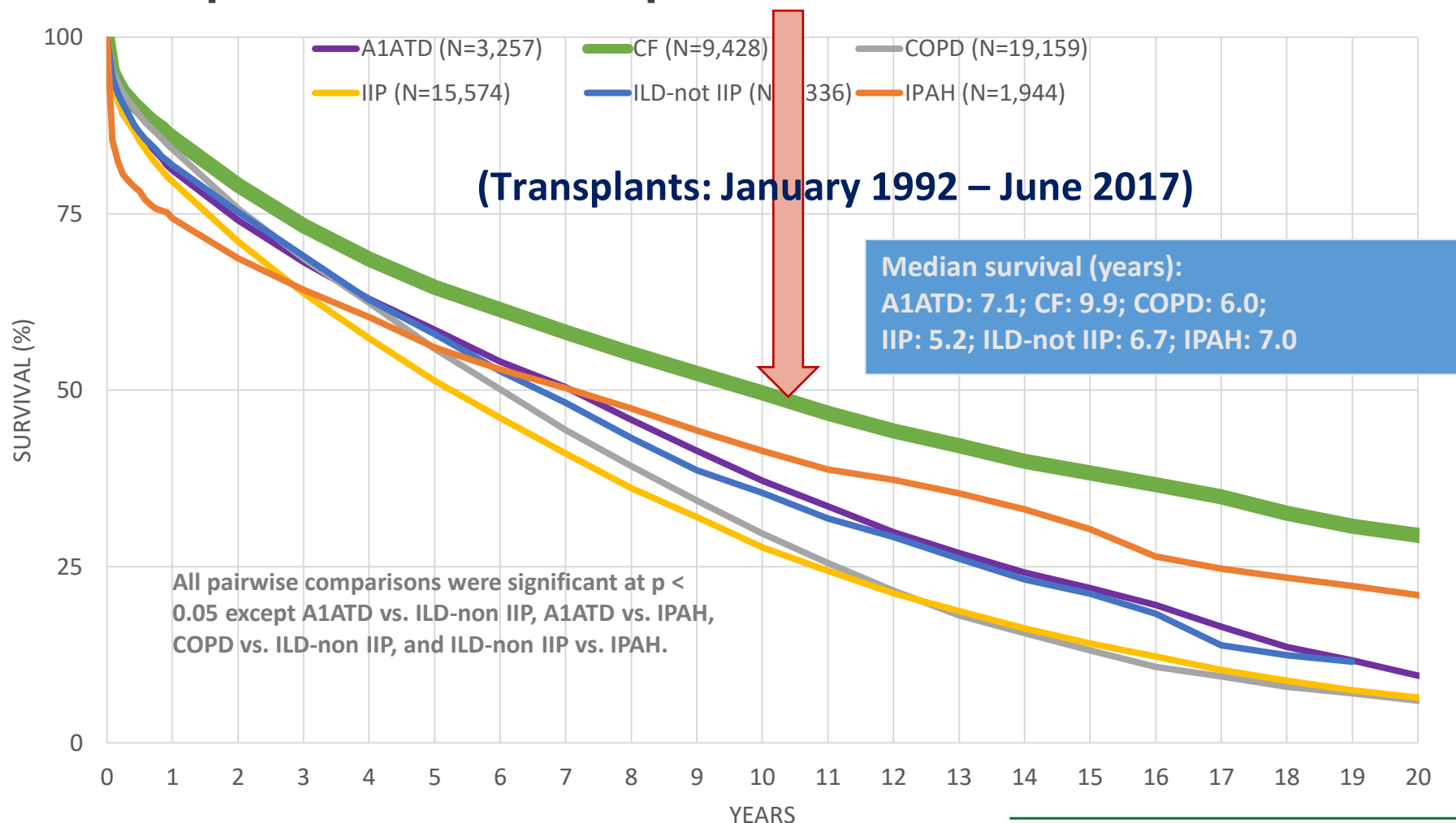


Courtesy of a famous friend of mine, Andrea Gramegna, MD, Milano

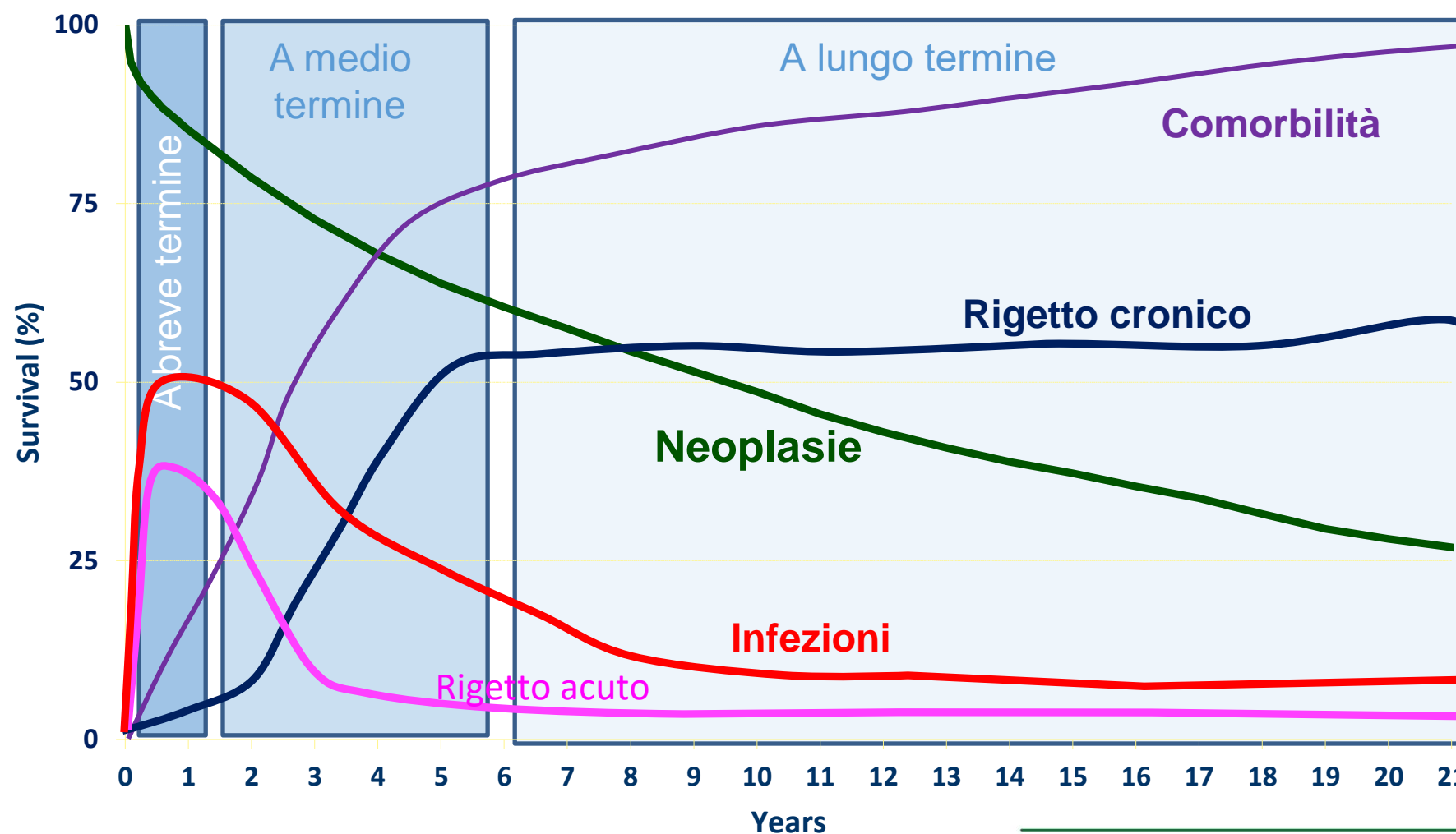
LuTx – Sopravvivenza per era



LuTx – Sopravvivenza per indicazione



LuTx - Complicanze



Modified from JHLT. 2019 Oct; 38(10): 1015-1066



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Regione
Lombardia

Candidati al LuTx per FC

ARTICLE IN PRESS

Indicazioni generali - Adulti con end stage lung disease con i seguenti criteri:

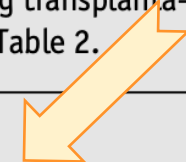
- Alto rischio di mortalità (> 50%) nei successivi 2 anni
- Alta probabilità (>80%) di sopravvivenza a 5 anni da un eventuale trapianto in caso di adeguata funzione del graft polmonare.

Table 2 Risk factors for poor post-transplant outcomes

Risk factors can change over time and may not be a contraindication for referral, but when present at the time of listing or while listed for lung transplantation may increase risk for poor transplant outcomes. There was 100% consensus (24 committee members) for the content of the entirety of Table 2.

ABSOLUTE CONTRAINDICATIONS:

- Candidates with these conditions are considered too high risk to achieve successful outcomes post lung transplantation.
 - Factor or condition that significantly increases the risk of an adverse outcome post-transplant and /or would make transplant most likely harmful for a recipient.
 - Most lung transplant programs should not transplant patients with these risk factors except under very exceptional or extenuating circumstances.
- [...]
1. Lack of patient willingness or acceptance of transplant
 2. Malignancy with high risk of recurrence or death related to cancer
 3. Glomerular filtration rate < 40 mL/min/1.73m² unless being considered for multi-organ transplant
 4. Acute coronary syndrome or myocardial infarction within 30 days (excluding demand ischemia)
 5. Stroke within 30 days
 6. Liver cirrhosis with portal hypertension or synthetic dysfunction unless being considered for multi-organ transplant




Accertamenti minimi per il referral

Relazione clinica dettagliata, che contenga

- 1) Stato funzionale (ultime PFR disponibili e andamento nel tempo)
- 2) Accertamenti per valutazione scambi gassosi
 - EGA
 - 6MWT e SN
- 3) Dati microbiologici:
 - Batteri
 - Miceti
 - NTM
- 4) Storia di riacutizzazioni; precedenti embolizzazioni e/o PNX
- 5) Ecocardio con studio camere destre
- 6) TC torace con immagini
- 7) Comorbilità e stato nutrizionale





**THE TIMES
THEY ARE
A-CHANGIN'
BOB
DYLAN**

THE LONESOME DEATH OF RATTIE CARRON
BOOTS OF SPANISH LEATHER
RESTLESS FAREWELL / WITH GOD ON OUR SIDE
THE TIMES THEY ARE A-CHANGIN'
ONLY A PAIR IN THEIR GAME
WHEN THE SUN COMES IN / ONE TOO MANY MORNINGS
BALLAD OF HOLDS BROWN / NORTH COUNTRY BLUES

The line it is drawn
The curse it is cast
The slow one now
Will later be fast
As the present now
Will later be past
The order is
Rapidly fadin'
And the first one now
Will later be last

For the times they are a-changin'.

The times they are a-changin'



REVIEW
CYSTIC FIBROSIS



CrossMark

Impact of CFTR modulator use on outcomes in people with severe cystic fibrosis lung disease

Michal Shteinberg ^{1,2} and Jennifer L. Taylor-Cousar³

The CFTR modulators IVA, LUM/IVA, TEZ/IVA and ELX/TEZ/IVA have a beneficial effect not only in individuals with mild to moderate CF, but also in individuals with advanced pulmonary disease, including candidates for lung transplantation.

Shteinberg M, Taylor-Cousar JL, Eur Respir Rev 2020; 29: 190112



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Ivacaftor & LuTx

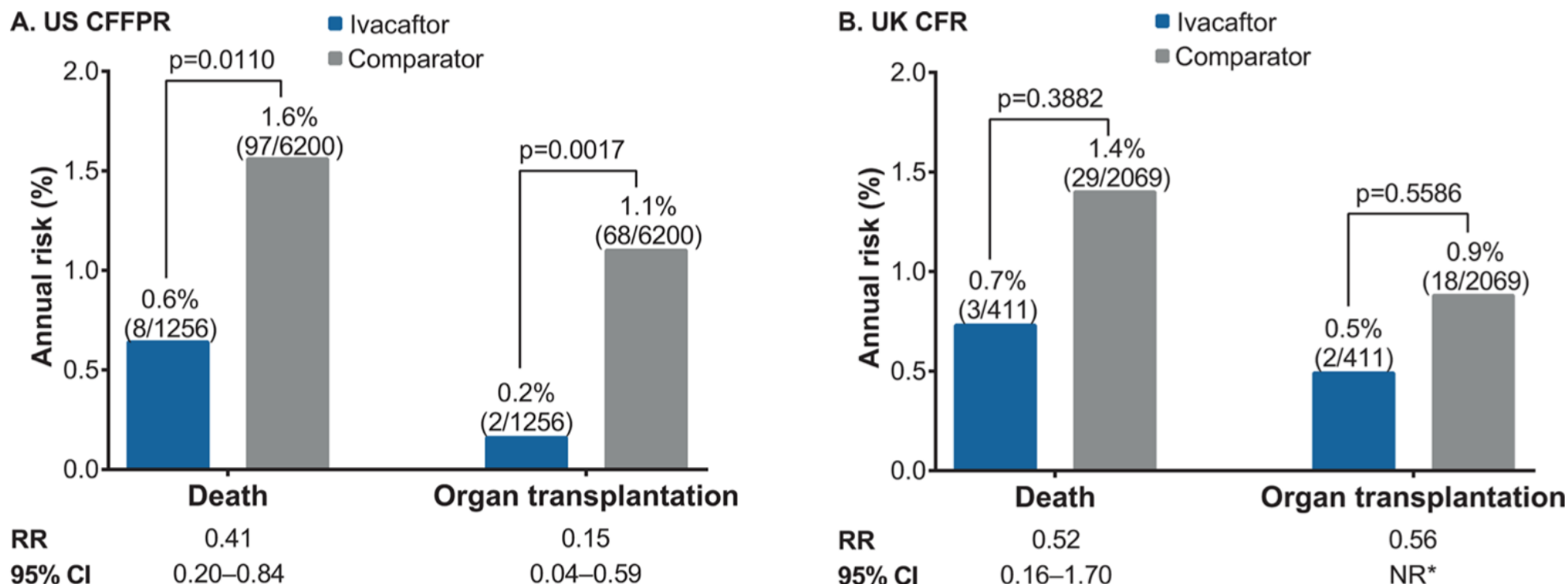


Figure 3 Death and organ transplantation, 2014 ivacaftor and comparator cohorts, (A) US CFFPR and (B) UK CFR. *Fisher's exact p values are shown when the expected value is <5 in at least one cell of the contingency table. CFFPR, Cystic Fibrosis Foundation Patient Registry; CFR, Cystic Fibrosis Registry;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

Ivacaftor & LuTx

«These data support the conclusion that highly effective CFTR modulation with ivacaftor leads to **disease modification**, consistent with the multisystem benefits observed in clinical trials.»

A lower risk of transplant was observed relatively early on and remained consistent each year

Table 2 Summary of key safety outcomes across US and UK annual analyses of ivacaftor versus comparator safety cohorts

Relative risk (95% CI)/ Fisher's exact <i>P</i> value ^a	2012	2013	2014	2015	2016
US CFFPR					
Death	0.43 (0.17, 1.07)	0.37 (0.15, 0.93)	0.41 (0.20, 0.84)	0.18 (0.07, 0.44)	0.41 (0.20, 0.86)
Organ transplants	0.22 (0.05, 0.89)	0.19 (0.05, 0.76)	0.15 (0.04, 0.59)	0.55 (0.27, 1.09)	0.29 (0.13, 0.67)
Pulmonary exacerbation	0.70 (0.62, 0.78)	0.62 (0.56, 0.69)	0.64 (0.58, 0.70)	0.69 (0.63, 0.76)	0.72 (0.66, 0.79)
Hospitalizations ^b	0.67 (0.60, 0.76)	0.59 (0.53, 0.66)	0.64 (0.58, 0.70)	0.66 (0.60, 0.72)	0.67 (0.62, 0.73)
UK CFR					
Death	NA	0.45, <i>P</i> = 0.41	0.52 (0.16, 1.70)	0.75 (0.27, 2.15)	0.47, <i>P</i> = 0.41
Organ transplants	NA	0.76, <i>P</i> = 1.00	0.56, <i>P</i> = 0.56	NA, <i>P</i> = 0.06	0.24, <i>P</i> = 0.20
Pulmonary exacerbation	NA	0.89 (0.79, 1.00)	0.61 (0.53, 0.70)	0.61 (0.53, 0.70)	0.58 (0.50, 0.67)
Hospitalization due to pulmonary exacerbation	NA	0.87 (0.75, 1.01)	0.57 (0.48, 0.68)	0.62 (0.53, 0.73)	0.57 (0.48, 0.67)

NA not applicable

^a Fisher's exact *P* values are shown when the expected value is < 5 in ≥ 1 cell of the contingency table

^b Reasons for hospitalization included pulmonary exacerbation, pulmonary complication, gastrointestinal complication, transplant related, sinus infection, nontransplant surgery, and other

ELX/TEZ/IVA & LuTx

American Journal of Respiratory and Critical Care Medicine



Rapid Improvement After Starting Elexacaftor-tezacaftor-ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary Disease

Pierre-Régis Burgel ; Isabelle Durieu , Raphaël Chiron , Sophie Ramel , Isabelle Danner-Boucher , Anne Prevotat , Dominique Grenet , Christophe Marguet , Martine Reynaud-Gaubert , Julie Macey , Laurent Mely , Annlyse Fanton , Sébastien Quetant , Lydie Lemonnier , Jean-Louis Paillasseur , Jennifer Da Silva , Clémence Martin ; , French Cystic Fibrosis Reference Network study group... [Show less](#)

Burgel PR, et al. Blue J Feb 2021

ELX/TEZ/IVA & LuTx

Metodi:

- TUTTI i centri FC di Francia (47 centri)
- Studio osservazione prospettico
- GOAL: to obtain real-world data in CF patients with advanced respiratory disease
- Criteri per l'early access program:
 - A) età ≥ 12 aa
 - B) almeno una mutazione Phe508del
 - C) compromissione respiratoria avanzata, caratterizzata da $FEV1 < 40\%$ del predetto e/o candidati al trapianto di polmone (almeno referral).

ELX/TEZ/IVA & LuTx

RISULTATI:

- PERIODO: 24 dicembre 2019 >> 7 agosto 2020
- 245 pazienti (228 adulti) iniziano elexacaftor-tezacaftor-ivacaftor in Francia
- Aumento FEV1 +15.1% (+13.8; 16.4), $p < 0.0001$
- Aumento peso + 4.2 Kg (+3.9; +4.6) $p < 0.0001$
- Fabbisogno di OTLT ridotto del 50%
- Necessità di NIV ridotta del 30%
- Necessità di SNG/EN ridotta del 50%

- TRAPIANTI:
 - all'inizio 16 pazienti in lista e 37 riferiti ...
 - al termine del follow up 2 pazienti trapiantati, 1 deceduto, 5 in lista

ELX/TEZ/IVA & LuTx

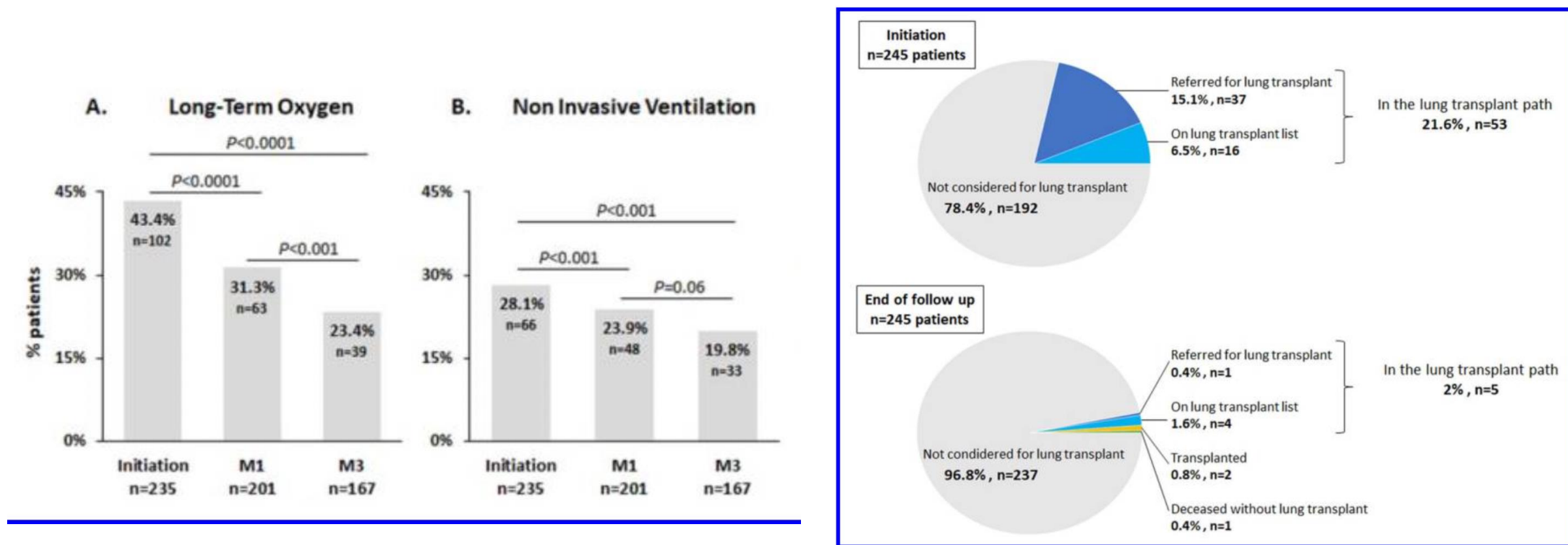


Figure 2. Vital status and lung transplantation candidate status at initiation of elexacaftor-tezacaftor-ivacaftor and at the end of the follow-up period.

Come cambia il centro trapianti?

Table 4. Numbers of lung transplantation in France by underlying disease comparing 2020 to 2018-2019.

	2018	2019	2020	Variation 2020 vs. 2018/2019
Cystic fibrosis	72	80	33	-56.5 %
Pulmonary hypertension	29	22	24	-5.8 %
Pulmonary fibrosis	97	89	82	-11.8 %
COPD	127	136	90	-31.5 %
Alpha 1 antitrypsin deficiency	6	2	3	-25 %
Other diseases	27	36	33	+4.7%
All indications	358	365	265	-26.4%

COPD: chronic obstructive pulmonary disease

Burgel PR, et al. Blue J Feb 2021

Come cambia il centro trapianti?

UK – Harefield

A Ottobre 2020:

di 25 iscritti in lista, solo 7 (28%) ancora attivi in attesa
gli altri 18: miglioramento mediano del FEV1 + 10% (0; 24%)

Referral medi nel 2020: 22/anno

Referall medi nel 2017-2019: 37/anno

Dave K et al. ISHLT Meeting April 2021



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Candidati al LuTx per FC - REFERRAL



Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation

The Journal of
Heart and Lung
Transplantation

<http://www.jhltonline.org>

Lorriana E. Leard, MD,^a Are M. Holm, MD, PhD,^b Maryam Valapour, MD, MPP,^c

Referral for lung transplantation should occur for an individual with CF meeting any of the following criteria despite optimal medical management including a trial of ELX/TEZ/IVA if eligible:

- FEV1 < 30% pred (o < 40% nei bambini)
- FEV1 < 40% pred (o < 50% nei bambini) e almeno uno dei seguenti:
 - 6MWT < 400 mt
 - pCO₂ > 50 mmHg
 - Ipossiemia
 - Ipertensione polmonare (PAPs stimata > 50 mmHg all'ecocardio o disfz VDx)
 - Malnutrizione ingravesciente nonostante supplementi
 - 2 riacutizzazioni/anno con necessità di ATB e.v. nous antibiotics
 - Emottisi massiva (> 240 mL) con necessità di embolizzazione
 - PNx
- FEV1 < 50% predetto e in rapido declino o progressivo peggioramento condizioni respiratorie
- Almeno una riacutizzazione con necessità di NIV

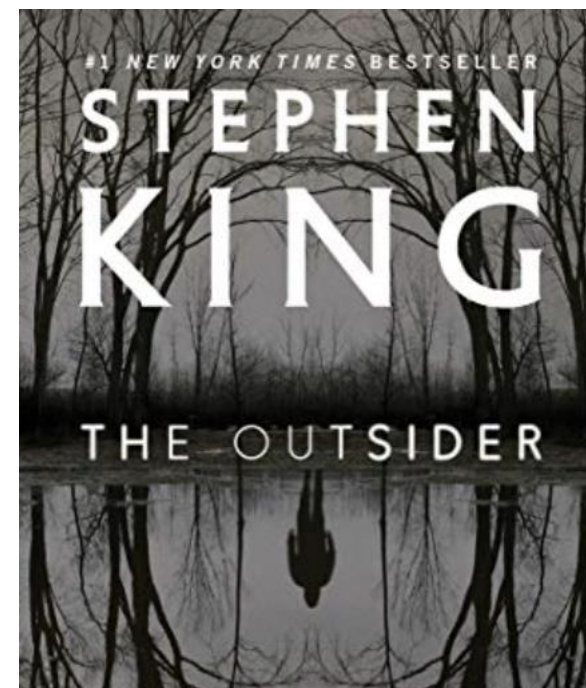
Il pdv del clinico: la sospensione dalla lista – tre scenari



Il pdv del clinico: Chi è rimasto fuori dalla lista

Modulatori come mezzo di trattamento per chi non possiamo trapiantare!

- Controindicazione extra respiratorio: e.g. malnutrizione
- Controindicazione microbiologica: BCC, NTM non controllati



Il pdv del clinico: Chi rimane in lista – tre scenari



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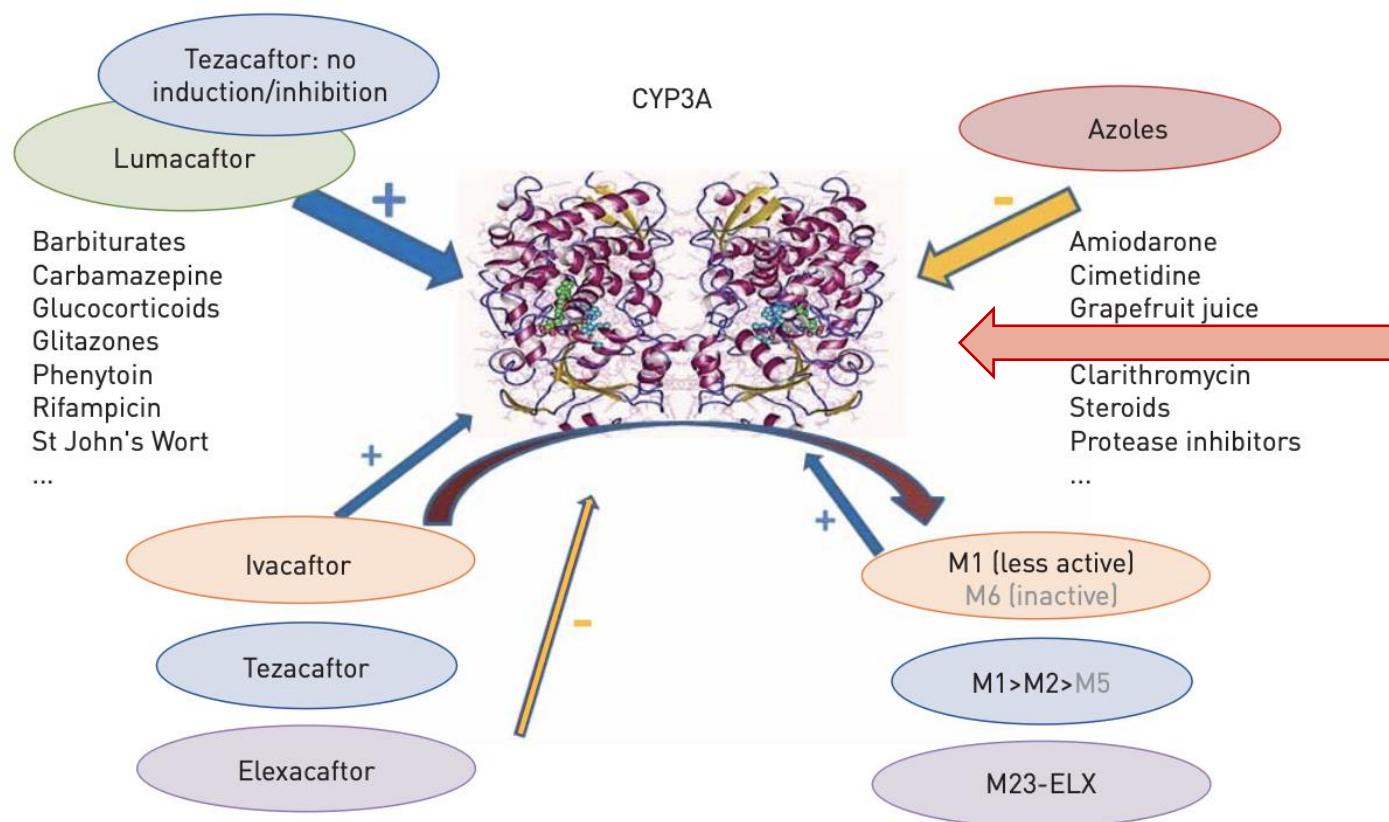
Changing candidates...



As a consequence, patients might only develop end-stage lung disease later in life, leading to a more elderly CF population being referred for lung transplantation. A change in referral demographics in patients with additional confounding factors, secondary to a different ageing-related profile, may have an adverse impact on transplantation outcomes.

Rang C et al.; ERJ 2020; 55: 1902443

Modulatori post SOT?



**CNI – inibitori
della calcineurina
(FK506 oppure CSA)**

FIGURE 1 A summary of interactions between cystic fibrosis transmembrane regulator modulators and other drugs/compounds and cytochrome P450 3A4 [CYP3A]. Blue arrows: induction of the cytochrome; yellow arrow: inhibition of the cytochrome; curved arrow: metabolism of a drug by the cytochrome. Adapted from [28–32].

Shteinberg M, Taylor-Cousar JL, Eur Respir Rev 2020; 29: 190112

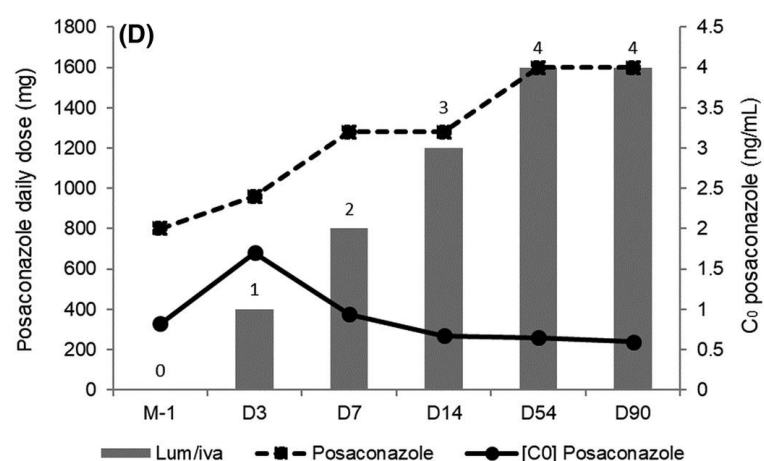
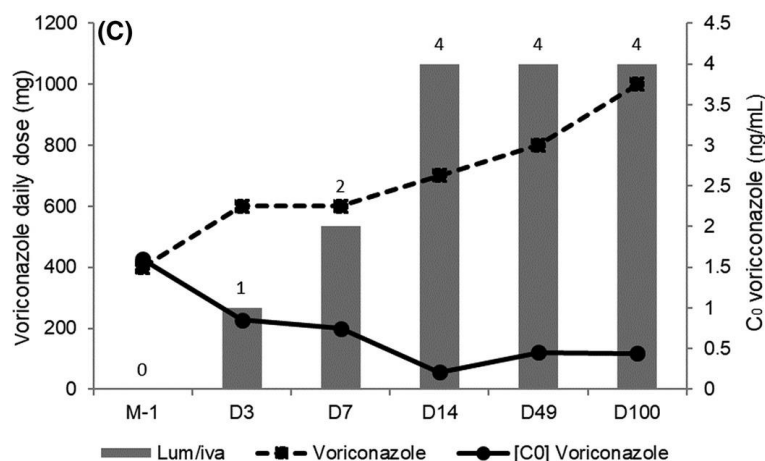
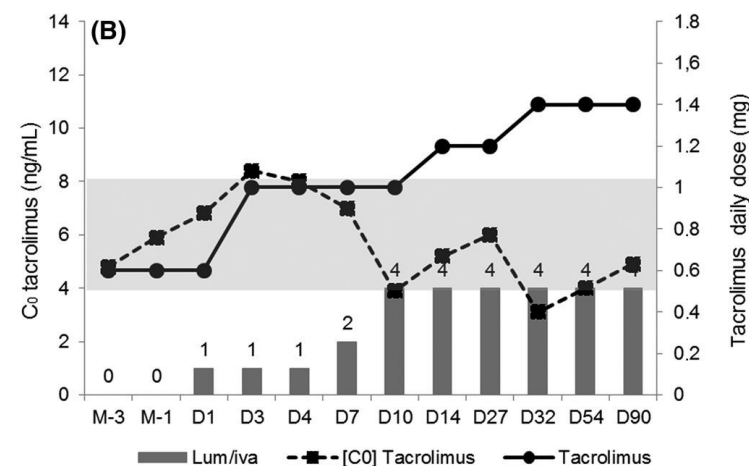
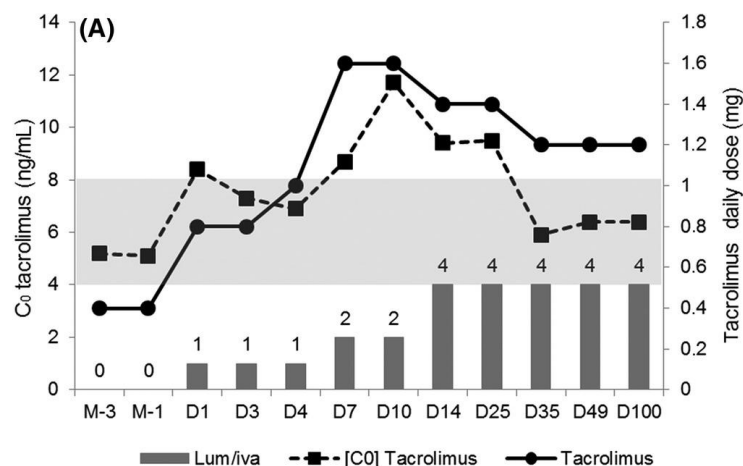


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Modulatori post SOT?

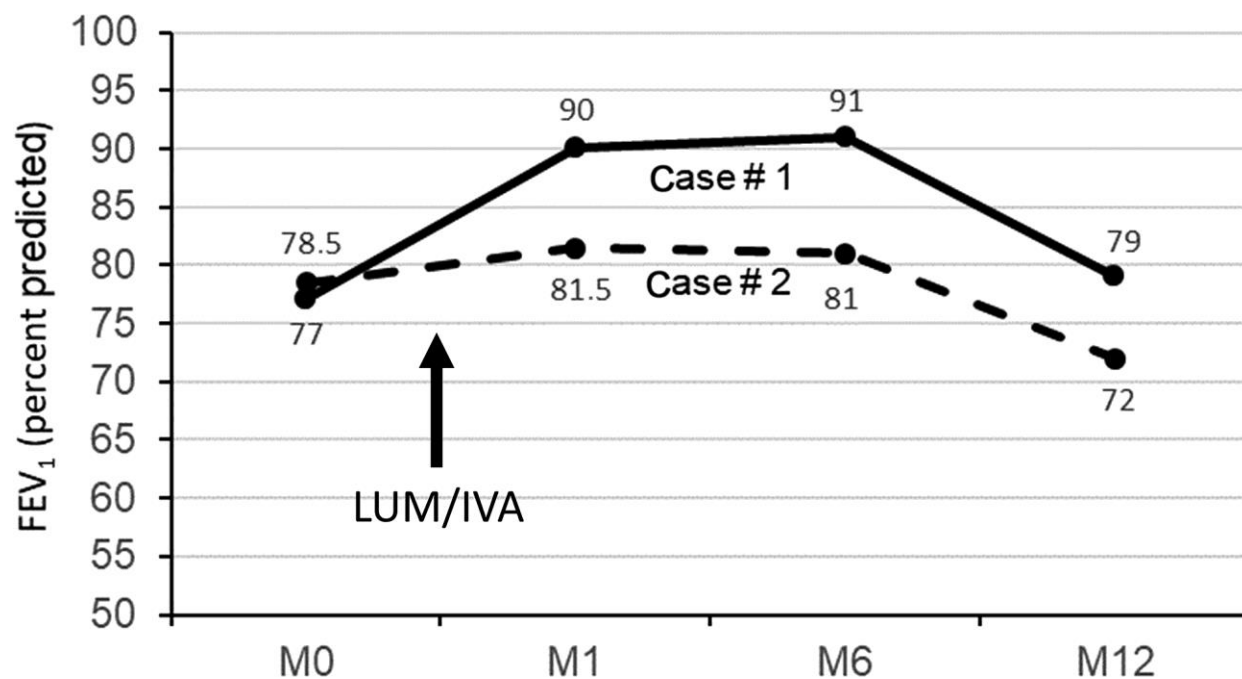


Chouchane I, et al. Clin Case Rep. 2019 Feb 17;7(4):616-618.



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Modulatori post SOT?



«We report the initiation of CFTR modulator lumacaftor/ivacaftor combination (LUM/IVA) in two adolescents with cystic fibrosis who were treated with antifungal azoles (AZO) and tacrolimus (TCS) for liver transplantation. Despite multiple drug-drug interactions, maintaining therapeutic TCS levels was achievable. During the following year, LUM/IVA was well tolerated, providing clinical benefits.»

Chouchane I, et al. Lumacaftor/ivacaftor initiation in two liver transplantation patients under tacrolimus and antifungal azoles. Clin Case Rep. 2019 Feb 17;7(4):616-618.

Modulatori post SOT?

TABLE 1 Characteristics of LTx recipients with CF who received CFTR modulator therapy

Patient	Age (years)	Initiation of CFTR therapy	CFTR therapy (length of therapy)	BMI (kg/m ²)	Post-LTx period (years)	Current Post-LTx FVC (% predicted)	Current Post-LTx FEV1 (% predicted)	Number ACR episodes (worse ISHLT grade)	Extrapulmonary effects of CFTR therapy (clinical improvements)
1	16	Pre-LTx	Tezacaftor/ivacaftor (1.5 years)	17.5	1	82%	78%	1 (A2B0C0)	Nutritional status (BMI improvement – initial 13.9 kg/m ²), CF-related diabetes (reduction in insulin requirement), depression (reduction in anti-depressant requirement)
2	16	Pre-LTx	Tezacaftor/ivacaftor (1.5 years)	20.4	1	100%	101%	2 (A2B0C0)	Nutritional status (BMI improvement – initial 13.6 kg/m ²), osteoporosis (improvement in bone density)
3	17	Pre-LTx	Tezacaftor/ivacaftor (1.5 years)	19.8	1.25	110%	102%	1 (A2B0C0)	CF-liver disease (reduction in hepatic transaminases), chronic rhinosinusitis (reduced symptoms)
4 ^a	16	Post-LTx	Elexacaftor/tezacaftor/ivacaftor (0.5 years)	17.8	1	95%	90%	2 (A2B0C0)	Chronic rhinosinusitis (reduced symptoms), nutritional status (BMI improvement – initial 14.2 kg/m ²),
5	21	Post-LTx	Elexacaftor/tezacaftor/ivacaftor (0.75 years)	16.1	1.5	72%	70%	1 (A3B1RC0)	Chronic rhinosinusitis (reduced symptoms), nutritional status (BMI improvement – initial 13.1 kg/m ²)

Note: All five patients have two copies of F508del mutation.

BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ISHLT, International Society for Heart and Lung Transplantation.

^aMild elevation in hepatic transaminases which has resolved.

Hayes D et al. To treat or not to treat: CFTR modulators after lung transplantation. *Pediatr Transplant*. 2021;25:e14007.

Modulatori post SOT?

1 | PROS

1. Potential extrapulmonary benefits may include improvement in nutritional status, CF-related diabetes, chronic rhinosinusitis, osteoporosis, gastroesophageal reflux, CF-associated liver disease, and depression
2. Achievable therapeutic immunosuppressive drug levels with CFTR modulator therapy

2 | CONS

1. Administration of CFTR modulators requires taking with fat-containing food to enhance drug absorption
2. Drug-drug interactions
3. Medication dose adjustments for both CFTR modulators and other transplant-related medications
4. Cost of CFTR modulators

Hayes D et al. To treat or not to treat: CFTR modulators after lung transplantation. *Pediatr Transplant.* 2021;25:e14007.



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Modulatori post SOT?



Review

Challenges in the use of highly effective modulator treatment for cystic fibrosis

Kathleen J. Ramos^{a,*}, Joseph M. Pilewski^b, Jennifer L. Taylor-Cousar^c

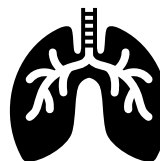
OLT:



- PROs: migliorare i sintomi e la malattia respiratoria
- CAVE: tossicità epatica e livelli terapeutici dei farmaci

Ramos KJ et al. JCF 2021

LUTX



- Non più malattia respiratoria FC relata
- Ruolo dubbio per:
 - Sinusopatia
 - Malnutrizione
 - Prevenzione del rischio di neoplasia GIT e PTLD (ruolo tumor suppressor della CFTR protein)
 - MRGE
- CAVE: tossicità epatica e livelli terapeutici dei farmaco

Modulatori post SOT?

BRIEF COMMUNICATION

CFTR modulator use in post lung transplant recipients

Lauryn A. Benninger, DO, Cesar Trillo, MD, and Jorge Lascano, MD

5 pazienti:

- 3 in CS + FK + MMF
- 1 in CS + FK + AZA
- 1 in CS + FK

RISULTATI:

- Miglioramento CFRD e BMI
- No effetti collaterali

Benninger LA et al. JHLT 2021

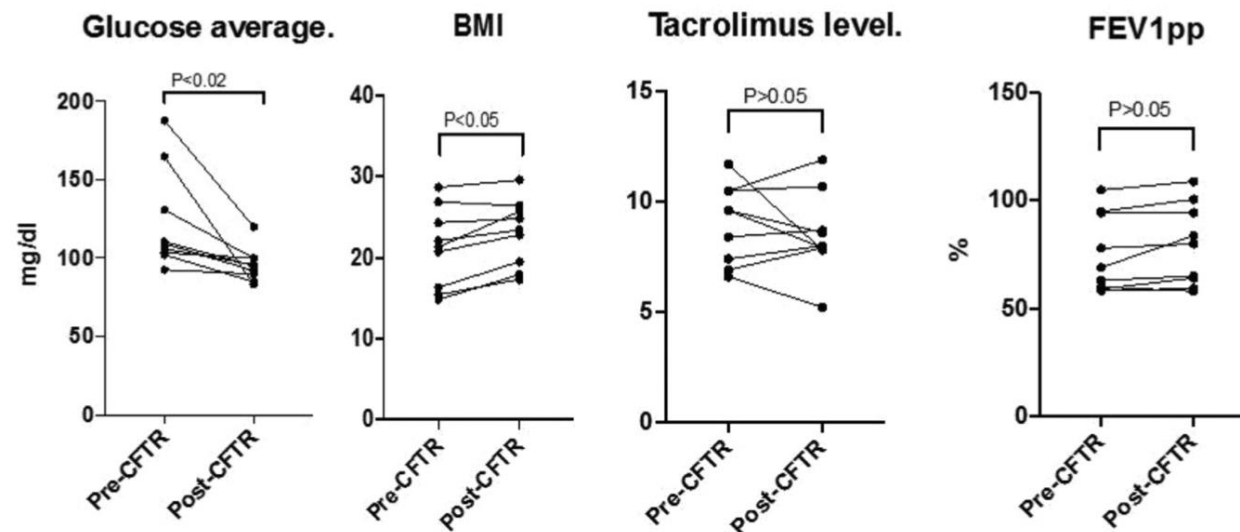
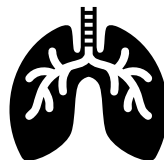
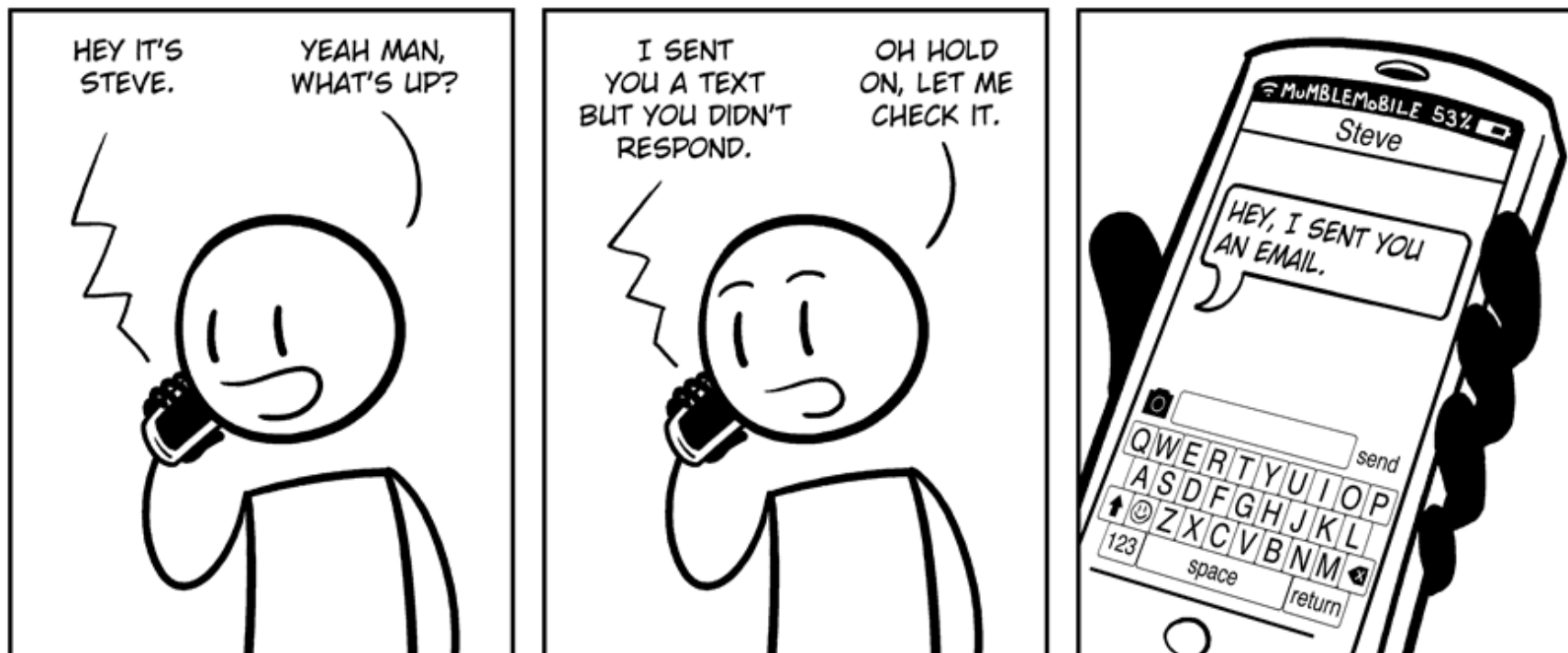


Figure 1 Comparison between mean values per patient for fasting glucose level, body mass index (BMI), tacrolimus level and forced expiratory volume in 1 second as expressed by percent predicted (FEV1) pre- and post-Trikafta. We used *t*-test to compare these variables pre- and post-Trikafta use. A *p* value < 0.05 was considered statistically significant. Statistical analysis was performed using GraphPad (Version 8; San Diego, CA).

Take home message



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Cure palliative

Riflessioni insieme alla Commissione Adulti

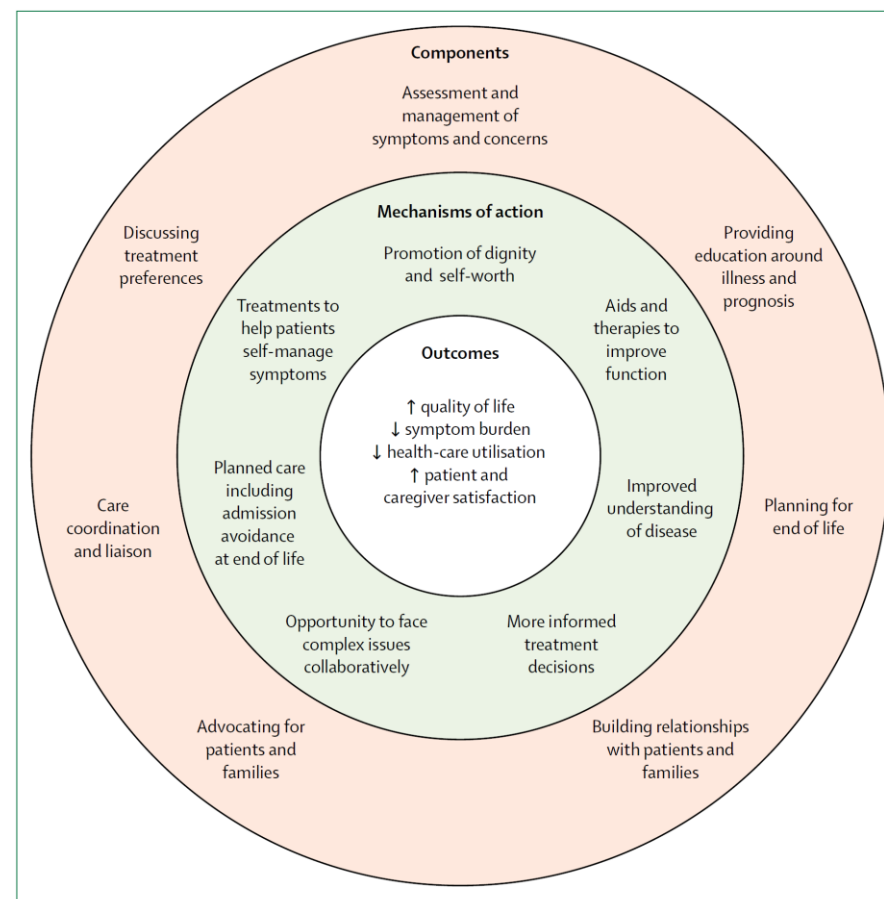
Cure palliative

Palliative care → an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering

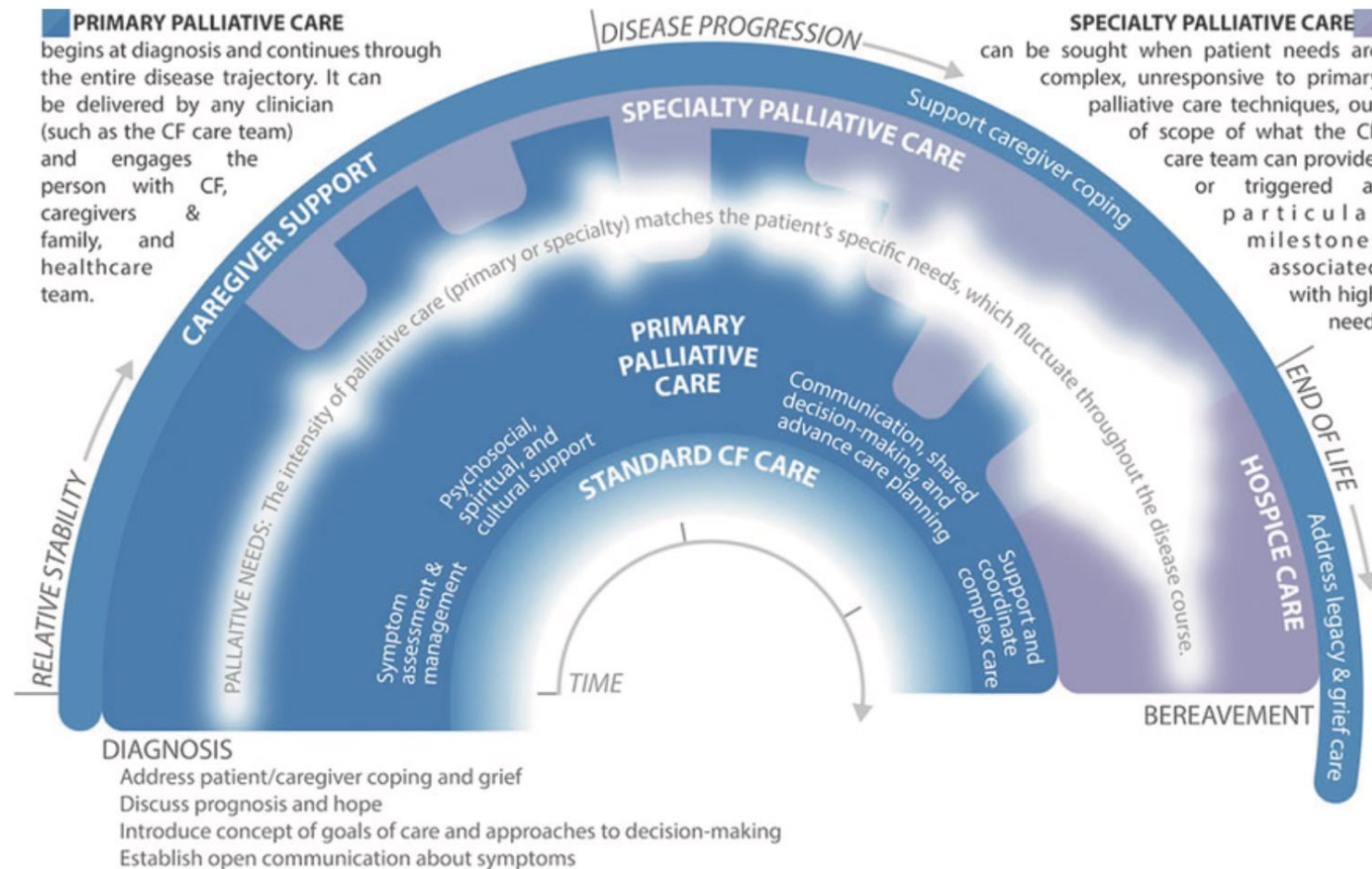
Seymour, ERJ 2010

[patients and caregivers] felt that PC is underutilized for CF, and that people with CF may miss out on the benefits of PC.

Basile M, J of Pall Med, Apr 2021



Cure palliative in FC



Cure palliative in FC

When referring for lung transplant evaluation, consider simultaneous referral to palliative care to provide decision support and treatment selection that is consistent with goals of care throughout the transplant evaluation, listing, surgery, and post-transplant.

ARTICLE IN PRESS



ELSEVIER

The Journal of
Heart and Lung
Transplantation

<http://www.jhltonline.org>

CONSENSUS STATEMENT

Consensus document for the selection of lung transplant candidates: An update from the International Society for Heart and Lung Transplantation

Loriana E. Leard, MD,^a Are M. Holm, MD, PhD,^b Maryam Valapour, MD, MPP,^c



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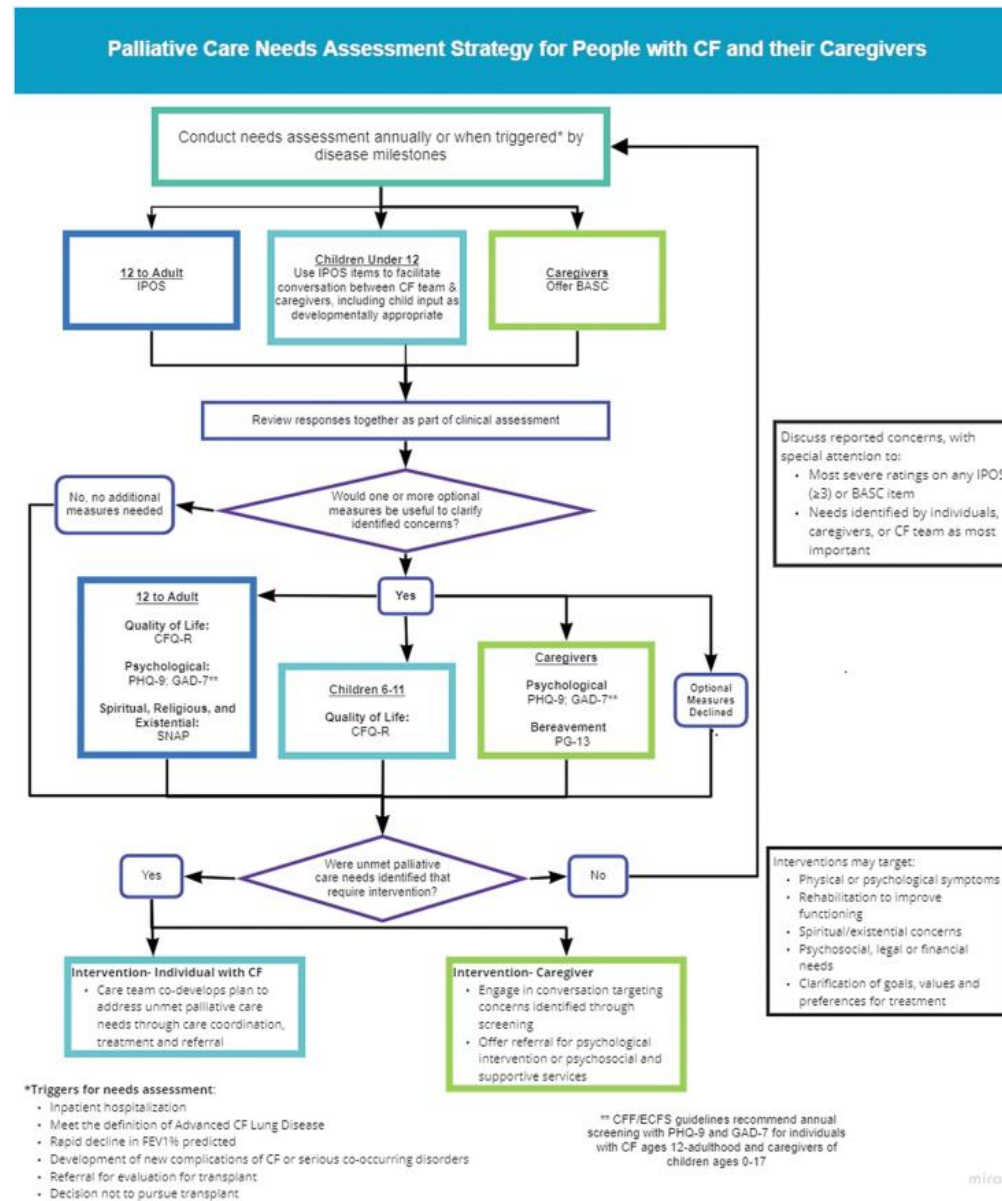


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Cure palliative – risultati di una chiacchierata

- Pazienti con fase avanzata di malattia, in cui sia (quasi) stato raggiunto il tetto di cura
- Pazienti che rifiutano alcune strategie terapeutiche ma chiedono sollievo dai loro sintomi
- Pazienti non candidabili all'iscrizione in lista d'attesa di trapianto
- Pazienti iscritti in lista d'attesa con sintomatologia non controllata:
 - Dolore
 - Dispnea
 - Tolleranza ai presidi (es. NIV)

Cure palliative



mira


Cure palliative – post LuTx

Systematic Review

An Integrative Review of the Role of Palliative Care in Lung Transplantation

Patricia C. Pawlow, PhD, ACNP-BC¹ ,
Caroline L. Doherty, MSN, AGACNP-BC, AACCC¹,
Nancy P. Blumenthal, DNP, ACNP-BC, CCTC¹,
Lea Ann Matura, PhD, RN, FAAN¹, Jason D. Christie, MD, MSCE²,
and Mary Ersek, PhD, RN, FPCN^{2,3,4}

PROGRESS in TRANSPLANTATION

Progress in Transplantation
2020, Vol. 30(2) 147-154
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DOI: 10.1177/1526924820913512
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Seven articles were included in the review. Most were single-center, descriptive studies. Two studies used qualitative and 5 used quantitative methodologies. Collectively, these studies suggest that palliative care is typically consulted for physical and psychological symptom management, although consultation is uncommon and often occurs late in the lung transplant process. We found no studies that systematically assessed palliative needs. Misperceptions about palliative care, communication challenges, and unrealistic patient/family expectations are identified barriers to the integration.



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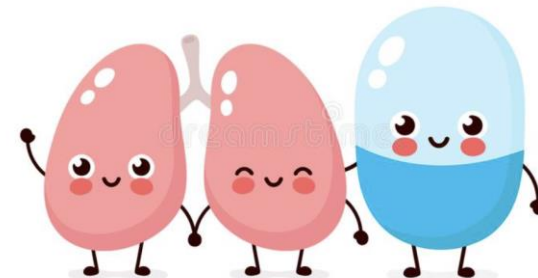


Regione
Lombardia

“Every accomplishment starts with a decision to try.” JFK



Grazie dell'attenzione



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