FUNDACJA POMOCY RODZINOM I CHORYM NA MUKOWISCYDOZĘ

SLOVENSKÁ ASOCIÁCIA CYSTICKEJ FIBRÓZY

Zborník prednášok z V4-CF konferencie

Book of Presentations from V4-CF Conference & Twinning Project

4th CONFERENCE

V4-CF

22 - 23 November 2024

Kraków-Wieliczka

On The Other Side of The Bridge

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4 CONFERENCE

V4-CF

21 - 23 November 2024
Kraków, Wieliczka

On the other side of the bridge

SCIENTIFIC COMMITTEE

Prof. dr hab. n. med. Dorota SANDS
Prof. Dr hab. n. med. Halina WOŚ
Prof. Dr hab. n. med. Tomasz GRODZICKI
MUDr. Katarina ŠTĚPÁNKOVÁ
Dr n. med. Agnieszka SOBOCZYŃSKA-TOMASZEWSKA

CONTENT

TWINNING PROJECT – CF CENTERS:

TWINNING PROJECT – PATIENT´S ORGANISATIONS:

I would like to express my sincere gratitude to all participants of the 4th International V4-CF Conference "On the Other Side of the Bridge" for their creative contributions and for fostering such a remarkable atmosphere of mutual respect, collaboration, and openness.
The conference brought together over 100 participants from 17 countries, and for the first time, it was combined with a meeting of centers involved in the "Twinning" project.
In these challenging times, for many delegations, this was the first opportunity to meet their partner centers in person. This occasion brought with it numerous emotional and joyful moments.
I trust that, re-energized by the positive and creative energy shared during the event, we will continue to pass it on to our colleagues and patients.

I look forward to our next meeting.

Prof. Dorota Sands

Dear Sirs,

It is with great pleasure that I hand into your hands the publication summarising the 4th V4 CF Scientific Conference, which took place in such unique places as Krakow and Wieliczka. It is an honour for me to co-create this event with our Slovak partner. The conference is a unique opportunity to exchange knowledge and experience, to build solutions together and to address new challenges that can improve the quality of life of CF patients and support them in their daily life.
My words of gratitude go to the Scientific Committee, staff and volunteers whose daily work and commitment made this conference possible. Heartfelt thanks are also due to the patrons, sponsors, and our partners.

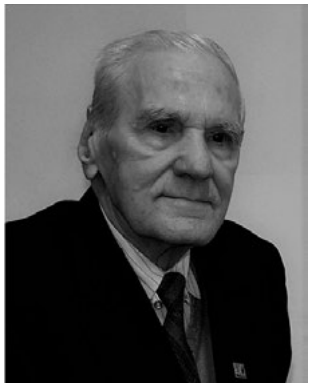
The meeting in Wieliczka, at this special UNESCO World Heritage site, also had a symbolic dimension. The salt mine - as a symbol of centuries of history, hard work and determination - reminds us of the hardships that accompany the journey to a better life with cystic fibrosis. The symbol of salt, which has been associated with the disease for years, today becomes part of history. Thanks to modern medicines and therapies, we can proudly say that this symbol is becoming a thing of the past. However, we still face challenges - we have already crossed a certain shore, but on the other side of the bridge there are new goals waiting for us, new barriers to overcome and new hopes. During the conference, we looked at these challenges, shared our knowledge and experiences, and worked together to find solutions to make life easier and more fulfilling for cystic fibrosis patients around the world.

Many thanks are due to the speakers, who came from 17 countries to discuss the present and future of cystic fibrosis patients, but also registries and the TWINING project, which was prominently and deservedly highlighted at the conference.

Thanking you once again, I'm inviting you to read our publication.

Paweł Wójtowicz
MATIO Polish CF Foundation

STANISŁAW SITKO AWARD *(1926 - 2020) IN MEMORY*



Nestor of the Polish Cystic Fibrosis Community.

The contributions of Stanisław Sitko to CF Patients are so numerous that it is impossible to list them all. However, it is important to mention that his efforts have gone far beyond accepted frameworks and norms. He is a remarkable individual whose actions have permanently transformed the lives of Polish patients with cystic fibrosis.

His dedication and passion are truly inspiring, making him a beacon of hope for many. The impact of his work is invaluable, and he deserves immense recognition for his tireless commitment to improving the lives of others.

To honor the life's work of Stanisław Sitko, the Matio Foundation has established a medal awarded to individuals who have made significant contributions to the cystic fibrosis community in Poland. This medal serves as a recognition of dedication and commitment to improving the lives of those affected by this condition. It highlights the importance of advocacy and support within the community. Each recipient of the medal embodies the spirit of compassion and resilience that Stanisław Sitko exemplified throughout his life. The foundation aims to inspire others to follow in his footsteps and continue the fight against cystic fibrosis. By celebrating these individuals, the Matio Foundation fosters a sense of unity and hope among patients and their families. This initiative not only honors Stanisław's legacy but also encourages ongoing efforts in research and support. The medal symbolizes the collective strength of the cystic fibrosis community in Poland. It is a powerful reminder of the impact one person can have on many lives. Through this recognition, the foundation aims to keep the spirit of Stanisław Sitko alive for future generations.

Prof. Dorota Sands is a distinguished expert in cystic fibrosis, whose extensive training and experience have significantly advanced patient care in Poland. With a background that includes prestigious fellowships at renowned institutions like the Royal Brompton Hospital and the University of Leuven, she has gained invaluable knowledge that she shares with her multidisciplinary team. Since 2017, she has led the Cystic Fibrosis Treatment Center in Dziekanów Leśny, establishing it as a model facility for cystic fibrosis care. Prof. Sands has authored over 100 publications, contributing to the global understanding of the disease. As a co-author of European treatment standards, she has implemented best practices that enhance patient outcomes. Her dedication to research and clinical excellence, along with her recognition through awards like the Silver Cross of Merit, exemplifies her commitment to improving the lives of cystic fibrosis patients. She truly embodies the spirit of compassion and innovation that Stanisław Sitko represented.

V4 COUNTRY REPORT´S

ZÁBRANSKÁ Simona, ARELLANESOVÁ Anička, DŘEVÍNEK Pavel, CZECH REPUBLIC
ŠTĚPÁNKOVÁ Katarína, FEKETEOVÁ Anna, SLOVAKIA
MARSZALEK Przemyszlaw, SANDS Dorota, POLAND
MARSAL Géza, HALÁSZ Adrien, HUNGARY




	CZ	SK	PL	HU
Number of inhabitants	10,7	5,6	38,5	9,8
Number of CF patients	**728**	**308**	**1 732**	**550**
CF children	**323**	**146**	**998**	**270**
CF adults	**405**	**162**	**734**	**280**
CF Centers for children	**5**	**3**	**18**	**15**
CF Centers for adults	**5**	**3**	**3**	**3**

Czech Republic:
5 CF Centers
Prague, Brno, Hradec Králové, Olomouc, Pilsen

Poland:
A. 9 Competence centers (2 for adults)
B. 3 Regional Centers (only for kids)
C. 9 Other Centers (1 for adults)

- Cooperation between CF Centers & POs is at a very good level.
- The organizations are participants in national scientific conferences.Representatives of CF centers actively support conferences and workshops organized by organizations.
- In CF centers, patients are informed about the possibility of using the help from the organization.
- Organizations actively support CF Center (financing educational materials, funding medical equipment)

Hungary:
- *>100 patients treated - 1 center*
- *>50 patients treated - 2 centers*
- *<50 patients treated - 12 centers (?)*

Heim Pál National Pediatric Insitute - Budapest
Pulmonology Hospital - Törökbálint
National Korányi Institute of Pulomology - Budapest

How many non-governmental CF organisations are there in your country?
What is their mission? Is there any common platform or other form of cooperation?

CZ

1

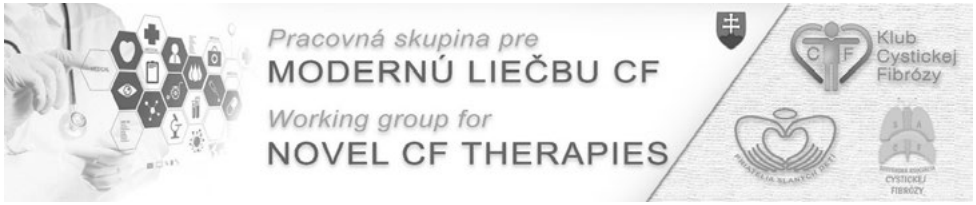
Klub cystické fibrózy

SK

3

Klub cystickej fibrózy
Priatelia slaných detí
Slovenská Asociácia Cystickej Fibrózy

Working group for novel CF therapies
- common platform of all 3 organisations



PL

5

Yes. 5 patient organizations created a common platform for cooperation called: **Muko Coalition, www.mukokoalicja.pl**

HU

1

Cisztás Fibrózis Magyarország

Hungarian Association of Cystic Fibrosis Patients (CFBE)

Main objectives:

- to improve the length and the quality of life of every patient with CF in Hungary
- supports the patients and their families, specialized for their needs
- to encourage the CF patients to continously studying in high schools and universities
- to provide social support to find the proper job and to have successful carreer
- build and maintain the Hungarian CF Registry and provide the required reports and data for the professional needs
- collaboration with ECFS, ECFSPR and other international teams

Website: http://www.cisztasfibrozis.hu
Facebook page: https://www.facebook.com/CisztasFibrozisMagyarorszag/
Facebook group: https://www.facebook.com/cf.hungary/

Achievements

Support CF Care Units -	OKPI CF részleg, HOGYI , Törökbálint
Educational events -	CF Nagyokos, Specialized Dental Care for CF Webinar
International conferences -	Participating CF Events, Better together 2017
Figyelemfelketlés, jótékonyság -	6 feet apart Fundarising
Novel therapies -	CFTR modulators

Patient Organization

Social Media, Online presence

www.cisztasfibrozis.hu
Facebook: Cisztás Fibrózis Magyarország
cisztasfibrozis@googlegroups.com
cisztasfibrozis@gmail.com

Education

International CF Day, Publications, guidelines, CF Nagyokos, CF – Better together 2017, CSIBE – Csoportos Internetes Beszélgetés

Quality of life, social events

Social events during the summer, Supplements, tools for devices, Tenders for patients, E-flow, 30k EUR

Financial support for CF care units

Raising funds for supporting the major CF centers and caregivers in HU

Heim Pál Országos Gyermekgyógyászati Intézet
Országos Korányi Pulmonológiai Intézet
Törökbálinti Tüdőgyógyintézet
SOTE Tüdőklinika

1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2024. Access to standard medicines and therapies.

CZ

In the Czech Republic, standard and modern therapies are available for CF patients – mucolytics, ATB, and modulators...

Kalydeco	**15**
Orkambi	**7**
Symkevi	**12**
Kaftrio	**492**

Modulators: 526 patients.
Clinical trials, §16: Individual reimbursement, exceptional.
Thanks to patient advocacy, a new legislation (**Act on public health insurance**) is effective since January 2022.

WHAT is new?

- Orphan drugs will enter into reimbursement via **new way**
- **Patients will be part of evaluation and decision making**
- Special emphasis will be on **soft criteria, such as quality of life** and **not** the price

SK

Vertex came to Slovakia in October 2018. Today we have access to CFTR modulators in SK. Modulators are the part of **List of reimbursed drugs of MoH SR** and reimbursed by **Insurance companies** (3). ORKAMBI since 26. June 2020 from 2 years old and KAFTRIO since 15. July 2021 from 12 years old.

Kalydeco	**0**
Orkambi	**31**
Symkevi	**0**
Kaftrio	**132**

This year Vertex strated negotiations for extended use of Kaftrio for more mutations and for children from 2 years old.

Standard therapy:

For free:

- pancreatic enzymes
- antibiotics – p.o., i.v., inhaled
- some mucolytics (ACC, Pulmozyme)
- nebulisers, physiotherapy devices, Simeox (Pari boy SX is free once every 10 years)
- nutritional supplements
- CFTR modulators

Special EXCEPTION for diagnosis CF - the recepies have to be written by doctor in CF Center.
Special drugs for CF - patient´s name administration.

Still the CF patients have to pay many other drugs or services, **but it is some way acceptable with social support from government.**

PL

Kalydeco - reimbursement from November 2020

Kafrio and Symkevi

- March 2022 – reimbursement >12 years old
- November 2023 – fail to reimbursement >6 years old
- November 2024 - waiting for the decision of the Minister of Health for reimbursement >2 years old

Patients must collect funds and set up fundraisers on Internet.

Many families left Poland for countries where drugs are reimbursed (150 ??).

Compassionate use (50 ??).

Most antibiotics are reimbursed

Tobramycin is limited. Available as part of drug programs with high entry barriers.

Pulmozyme is reimbursed

Pancreatic enzymes: KREON 10,000 - not reimbursed
KREON 25,000 - reimbursed
LIPANCREA 16 000 / 60pcs – for free).

Nutrients: Fortimel MAX flat fee 0.85 EUR / 4 bottles 300ml to 18 years old

Are the medicaments free for CF?

Medical devices	Amount of public funding	The period of use
Nebulizers (Pari LC Sprint, LC Sprint Star, Aeroeclipse, etc.)	100 PLN/ 23 EUR	once a month
Head for membrane inhaler (eFlow head, etc.)	150 PLN/ 35 EUR	once every 6 months
Pneumatic inhaler (Pari Boy Junior, Pari Boy Classic, AP30 etc.)	400 PLN / 93 EUR	once a year
Membrane inhaler (Twister Mesh, eFlow, etc.)	800 PLN/ 186 EUR	once a year
Equipment for individual respiratory physiotherapy – drainage devices producing elevated or variable exhaust pressure (PEP System, Areobika with a pressure gauge, Flutter, etc.)	470 PLN (hardware with a pressure gauge) 109 EUR 250 PLN (kits without a pressure gauge) 58 EUR	once a year

HU

Lumacaftor/ivacaftor (LUM/IVA)

2021 February - from 2024, for patients aged 1 year and older.

ORKAMBI®: Orkambi granules/tablets are indicated for the treatment of cystic fibrosis (CF) in patients aged 1 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Elexacaftor/tezacaftor/ivacaftor (ETI)

2022 November - from 2024, for patients aged 2 year and older.

KAFTRIO®: Kaftrio, in combination with ivacaftor tablets, is indicated as a combination treatment for patients aged 2 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

KALYDECO®: As part of a combination treatment with ivacaftor/tezacaftor/elexacaftor tablets, it is indicated for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Kalydeco	**0**
Orkambi	**71**
Symkevi	**0**
Kaftrio	**251**

Free medication: CFTR modifying therapy
Pulmozyme
inhaled antibiotics
enzyme substitution
insulin

Mostly covered: dietary supplements
for personal application Pari Boy family nebuliser

Fully covered: hospital treatment including iv. antibiotics
transplantation

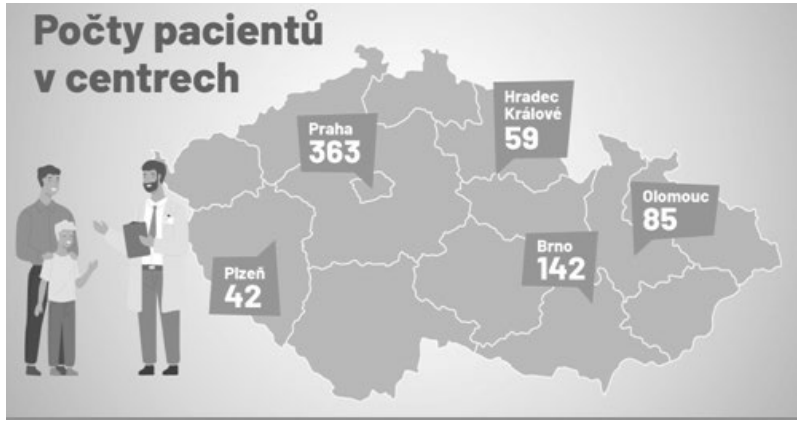
2. Does actual National CF Registry exist in your country? Is it part of ECFSPR?

CZ

Czech CF registry since **2002 provides data for ECFS database**.

Czech At-a-glance report 2021

- supported by Czech CF Association,
- to be introduced at Czech expert conference ***Recyf 2021*** in December 2021
- published on CF Association website and in Czech CF Registry
- 5 CF Centers: Praha (363), Brno (142), Hradec Králové (59), Plzeň (42), Olomouc (85)



SK

All 6 CF Centers in SK (3 for children + 3 for adult) are part of ECFSPR since **2010**. Every year doctors from CF Centers upload their own data. We dont have special Slovak CF registry.

PL

18 Centers are parts of ECFSPR since **2023.**

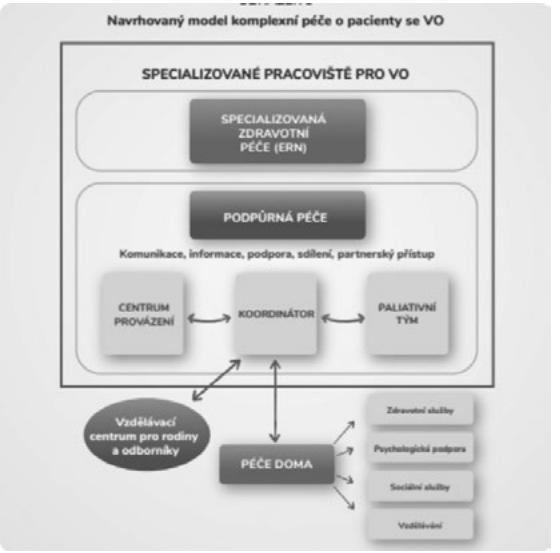
HU

Yes, since **2008** we are participating in the ECFSPR.

3. Do you have National standards of CF care & neonatal screening ?

CZ

- **ECFS Standards of care** are adopted in the CF Centers – prof. Dřevínek was a leader of The standards of care working group at the time
- preparations to have **Highly Specialized Centers of Care for Rare Diseases** according to new legislation 372/2011 on Health-care services (as of January 2021)
- new methodology will be introduced which will impact the functioning of centers and mainly its financing
- emphasis on **multidisciplinary and holistic care**



SK

2021, 1. October - Ministry of Health adopted standard:
„Štandardné diagnostické, terapeutické postupy pre pacientov s cystickou fibrózou“

2010, 20. December - Slovak Ministry of Health adopted recommendation document:
„Odborné usmernenie MZ SR o poskytovaní zdravotnej starostlivosti o pacienta s cystickou fibrózou“
Translation of ECFS document from 2004 adapted on the Slovak healthcare system and laws.
Not fully accepted by hospitals, it is only recommendation.

How is the chest physiotherapy provided to CF patients?

1. Parents after a child’s diagnosis receive instruction on rehabilitation.
2. Every three months during check-ups - a patient should be consulted - but not in every center this is done due to the lack of funding for this service.
3. In the case of long hospital stays - the physiotherapist is normally available
4. Rehabilitation outside of hospitalization is possible on prescription ten times in a row, or once every 6 weeks (recommended for young children who change quickly).
5. For children and their parents, the CF Club prepared educational videos on rehabilitation and the use of aids during the pandemic with the help of a grant. The videos are available in the BodyFix application and access is based on a code that the club will provide to patients upon request. Currently, efforts are being made to prepare videos for adult patients as well.
6. Pediatric patients have the opportunity to stay at the diagnostic center of the National Institute of Pediatric Tuberculosis and Respiratory Diseases, n.o., where they are examined and undergo intensive rehabilitation for 3 weeks.

How is mental health care provided?
In the area of mental health, active care is provided in the Bratislava children’s center in the form of sessions for older children and parents. Active cooperation with a psychologist is also established in the Banská Bystrica center for adults.

Neonatal screening – since **2009**.

PL

In Poland, we operate according to European Standards. The ECFS standards are translated into Polish and do not have the status of binding law.
Patients have no option to demand treatment according to the standards. Their implementation depends on the determination and commitment of doctors, decision makers in the CF centers, financial opportunities.
In Poland exist public health insurance for and medical service covered by public health system.
There is no national health care system/plan strictly for CF patients.
Of course, there is also a private sector where you can get help for a fee.

How is the chest physiotherapy provided to CF patients?

1. Parents after a child’s diagnosis receive instruction on rehabilitation.
2. Every three months during check-ups - a patient should be consulted - but not in every center this is done due to the lack of funding for this service.
3. In the case of long hospital stays - the physiotherapist is normally available.
4. A big problem is the lack of reimbursement for rehabilitation outside hospital stays. Patients have to pay extra for them.
5. Patient organizations organize training for parents and patients with physiotherapy.
6. Sometimes organizations also get grants for free home visits.

How does the nutrition counselling work?

1. This area works quite well.
2. Almost every visit there is a dietary consultation.
3. Patient organizations run infolines and workshops with the participation of dieticians.
4. There are several cookbooks with recipes especially for CF patients.
5. A big problem is the lack of reimbursement of nutrients for adults. Of course, it does not apply to patients with modulators.
6. Home Enteral Nutrition (HEN) is available for CF patients

Neonatal screening:
1999 – pilot regional CF NBS
2009 – national CF NBS

HU

Yes
2022 January - Neonatal screening

4. Do you have National programms for Rare diseases in your country?

CZ

2nd National strategy for Rare Diseases (2021 - 2030) introduced to new Czech government (prepared by RD experts and patients)

1st National Action Plan for Rare Diseases (2022 - 2224)

Working group for Rare Diseases at Health Ministry (patients are members)

European Reference Networks (ERNs) - Czech Republic has members in 22 out of 24 networks.

ERN-LUNG (faculty hospitals in Prague and Brno)

SK

Slovenská Aliancia Zriedkavých Chorôb (SAZCH)
12.12.2011 (patient´s organisation)
National strategy for the development of healthcare for patient´s with RD in SK
24.10.2012
National program for the development of care for patient´s with RD in SK
12.05.2021 - 12.05.2030 with Action plan for 2 years

PL

Since 2009 we are still waiting for a realistic plan for rare diseases in Poland.
August 2021 - the government will allocate over PLN 128 million to a comprehensive model of care for patients with rare diseases. The plan envisages improving the monitoring of morbidity and treatment of this type of diseases, with the visualization of the patient in the health care system using the Passport of a Patient with a Rare Disease and the Polish Register of Rare Diseases. The plan does not include Integrated social assistance for patients with rare diseases and their families. Aaccording to the recommendation of the European Union, this should be included.

HU
Yes

5. What are the possibilities of support from your social system for CF patients and their families?

CZ
CF patients take advantage of the Czech social welfare system
- Support in care allowance (4 stages)
- Disability support
- Support from foundations such as „Good angel“ or „Golden fish“

Problems we face:
People with CF look healthy for the social welfare system, no physical handicaps: that causes problems to receive social support.

SK
Cystic Fibrosis is accepted as disability disease and CF families usually receive social support:
- Social support for person giving care (600 – 800EUR/month)
- Pension for disable adult person (300 – 500EUR/month)
- Nutrition (50 EUR/month)
- Hygiene (50 EUR/month)
- Transport – travel cost
- Car – very rare

Card for disabled persons – some advantages.
It is voluntary not obligatory, complicate subjective administrative process. **Changes in rules very often – not transparent.**

PL
186 EUR – monthly for each child in Poland
220 EUR – one time for CF newborn
55 EUR – monthly basic support for CF
694 EUR – monthly extended support for CF (if one parent resigns from work)

Do you have any social workers? What are their responsibilities?
There are social workers who are working within state and self-government units (social help for poor and disabled people) and in non-government organisations (including CF organisations). There are no state social workers dedicated strictly to CF patients.

HU
- reimbursed drugs and devices
- increased financial support to the families in some cases

6. What are the main problems in CF care in your country? What would you need to change?

CZ
- CF Centers lack experts and other multidisciplinary care team members, specifically for adults
- training of new experts, more support from hospital management, more financial support for centers for the expertise...
- we hope this will be solved thanks to the new legislation on health-care services

SK
- **Acces to Kaftrio for all eligible CF patients (extend mutations and from 2 years old)**
- **Lung transplantations (Prague)**
- E-Flow – patients have to buy it
- Hypertonic saline, ADEKs – patient´s have to buy it
- In many cases there is the need to ask for exception – a lot of paper work (CFTR modulators, Simeox, flutters, nutrition,...)
- **Create the real CF Centers with real CF teams**, where all members have defined real responsibilities with regular **CF team meetings**
- Implement the standards of care in the existing system
- Create better healthcare and social services for CF families
- There is a lack of profound motivation for young CF doctors
- **Access to new clinical trials**
- **Discrimination of sick persons in many fields - better definition of disabillity and needs of social support for CF families**
- Low financial support for CF families and CF adults
- Discrimination of parents who decided to stay at home and take care about their sick CF children – in many levels – tax system, stop their professional growth, holidays, no social security,... - **social status of parents taking care about their CF children without discrimination**

PL
-– No access to Kaftrio for 2 yars old
– Not enough CF center for adults

Cystic Fibrosis One Disease Two Lives
Still a group of patient:
-Does not have access to therapy
-Does do not have therapy !!!

HU
Our CF care system is too fragmented, it needs to be more centralized in order to optimize the performance and the cost effectiveness.
Our tasks:
- to reorganize CF centers - at medical schools and existing 3 large CF Centers
- to obtain financial support
- establish an accreditation committee
- to organize further trainings for the teams of the new centers
- to accreditate the new centers
- to organize regular audits of the centers

7. How you see the Future of CF in your country?

CZ

- CF Centers as part of National network of centers for rare diseases within ERNs
- Improving care for children and adults according to Standards of care
- International collaboration
- Functioning multidisciplinary teams
- Participation in clinical trials

„Our disease is invisible .... but your help can be .... (visible)“

SK

Very optimistic - access to new therapies – new future

Unsecure:

- Collaps of healthcare system ?
- Existence of real CF Centers acctepting the standards?
- Longterm reimbursement of expensive therapies for all CF patients ?
- Covid-19 on the same places as the CF Centers?

PL

CF patient´s needs

„The best way to predict the future, is to create it“
Peter Druker

HU

CF therapies changings incredeably fast, so we are constantly fighting for accessing the novel therapies and better care system.

CONTACTS:

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COLLABORATION BETWEEN PATIENT ORGANIZATIONS AND CF CENTERS

Mgr. Adéla ODRIHOCKÁ, Mgr. Simona ZÁBRANSKÁ, Prof. MUDr. Pavel DŘEVÍNEK, KLUB CF CZECH REPUBLIC



Centers of highly specialized care for individuals with CF

5 CF Centers:
Prague, Brno, Hradec Králové, Olomouc, Pilsen

Number of patients

Total number of patients:	**713**
Children under 18 years old:	**333**
Adults:	**380**

Number of newly diagnosed 17 of which, from neonatal screening 16

Innovative treatment

Patients on treatment: 468 *(of those eligible for treatment – if non-eligible patients and those in clinical trials were included, the total would be 501)*
Eligible for treatment: 553

Klub cystické fibrózy

A partner and advocate for patients.
A partner for healthcare providers and the professional community.
An essential third party in discussions between professional societies and government institutions.

Activities of the czech cf association (patient organization)

- Educational activities:
- Meetings for parents and grandparents.
- Publishing brochures and books about CF.
- Raising public awareness about CF.

Support for families and patients:
- Providing social services.
- Providing medical equipment on loan (e.g., inhalers, oxygen concentrators).
- Financial assistance (3,000 CZK/year; Social Support Fund).

Support for CF Centers:
- Offering guidance to families during educational stays.
- Providing equipment and devices for CF centers.
- Financial support for professional development: internships and participation in conference.

Public engagement:
Fundraising
Public events

Education for the newly diagnosed
The Czech CF Association plays a key role in the educational initiatives at Motol University Hospital and Brno University Hospital.

Starter Kit for Families:
Covers initial expenses and provides a starter kit, including a sterilizer, disinfectant, and masks.

Buddy System („Parent Patrons“):
Each family is paired with a “buddy“, an experienced parent who offers guidance and support.

Support for CF Center Staff:
The Czech CF Association funds the salary costs of CF center nurses during educational stays.

Support for CF Center research
Purchase of a Ussing Chamber:
A Ussing chamber was purchased for the research laboratory at Motol University Hospital. This equipment facilitates research on the effects of CFTR modulators and mutations responsible for cystic fibrosis.

Financial Support for the CAR CF Project:
Funding is provided for the CAR CF registry, which collects and analyzes patient data to improve understanding of disease progression, evaluate treatment efficacy, and enhance patient care in general.

Transitioning from childhood to adulthood in cystic fibrosis care
- With innovative treatments, the lifespan of individuals with CF is increasing, children with CF are now thriving into adulthood, necessitating a holistic approach to lifelong care.

- In response to these changing dynamics, CF Club partnered with the CF Center at the Motol University hospital to develop a Standard Operating Protocol (SOP) for transition into adulthood

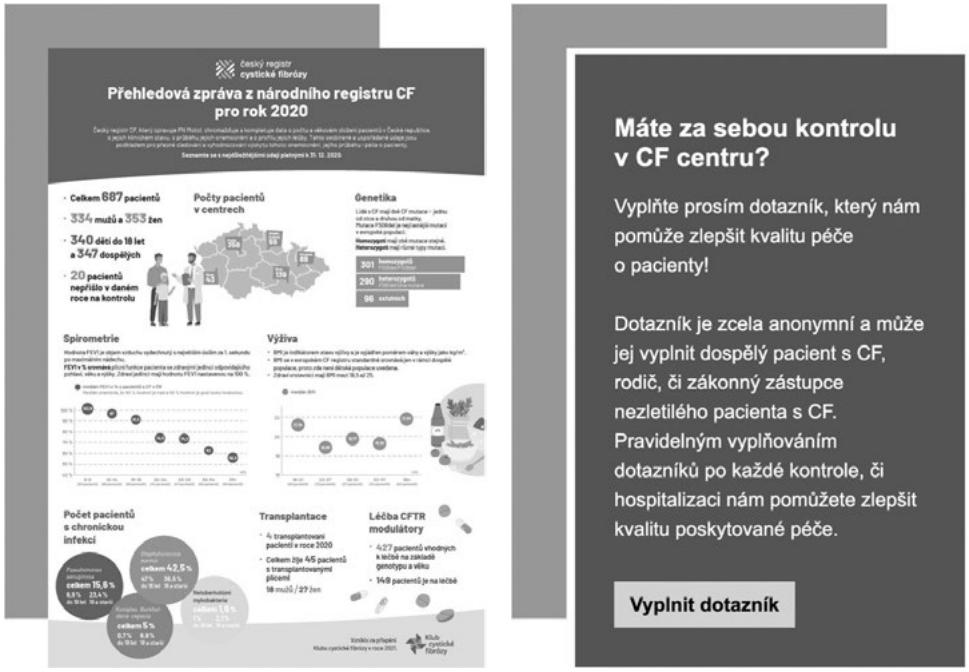
- Transitioning into adulthood represents new challenges and opportunities, including education, career, relationships, and managing complex health needs.

The SOP:
- Systematic process of preparing the young individual for adult life
- Describes the transition process from pediatric to adult care.
- Focuses on physical, emotional, and social support.
- Engages multidisciplinary teams to provide comprehensive care.

The CF Club also created materials, such as a brochure, to support the transition process.

With this partnership, we ensure that every person with CF receives the support they need to achieve the best possible quality of life in adulthood.

Monitoring the quality of patient care



Patient advocacy

- Engagement in administrative proceedings:
- Participating in administrative proceedings, together with expert societies, including conducting socio-economic surveys of patients and their families.

- Collaboration on guidelines:
  Working together to establish and implement recommended protocols and best practices.

Zákon č. 48/1997 Sb
Zákon o veřejném zdravotním pojištění o změně a doplnění některých souvisejících zákonů

„§ 39da

Zásady pro úhradu léčivých přípravků určených k léčbě vzácných onemocnění

(1) Je-li to ve veřejném zájmu podle § 17 odst. 2 a není-li podána pro stejnou indikaci žádost o stanovení dočasné úhrady podle § 39d ani Žádost o stanovení výše a podmínek úhrady v řízení podle § 39g, Ústav rozhodne o výši a podmínkách úhrady léčivého přípravku určeného k léčbě vzácného onemocnění. Za léčivý přípravek určený k léčbě vzácného onemocnění se považuje léčivý přípravek, který byl stanoven jako takový podle přímo použitelného předpisu Evropské unie o léčivých přípravcích pro vzácná onemocnění[64]). Řízení lze samostatně vést také ohledně léčivého přípravku určeného k léčbě vzácného onemocnění, u kterého je pro jinou indikaci vedeno současně řízení o stanovení, změně nebo zrušení maximální ceny nebo výše a podmínek úhrady, nebo hloubková nebo zkrácená revize.

(2) Žádost o stanovení výše a podmínek úhrady léčivého přípravku určeného k léčbě vzácného onemocnění mohou podat držitel rozhodnutí o registraci takového léčivého přípravku nebo zdravotní pojišťovna. Na náležitosti žádosti podané držitelem rozhodnutí o registraci se použije § 39f odst. 1, 5 a 6. Na náležitosti žádosti podané zdravotní pojišťovnou se použije § 39f odst. 1 a 5; k žádosti dále přiloží základní údaje o nákladech stávající léčby, odhad dopadů posuzovaného léčivého přípravku na prostředky zdravotního pojištění, odhad spotřeby léčivého přípravku a odhad počtu pacientů. Účastníkem řízení jsou zdravotní pojišťovny a držitel rozhodnutí o registraci léčivého přípravku určeného k léčbě vzácného onemocnění. Účastníkem řízení je také příslušná odborná společnost, sdružující odborníky zabývající se léčbou onemocnění, které může být posuzovaným přípravkem ovlivněno, a pacientská organizace podle zákona o zdravotních službách sdružující pacienty s onemocněním, jejichž léčba může být posuzovaným přípravkem ovlivněna, (dále jen „příslušná pacientská organizace").

(3) V řízení o stanovení výše a podmínek úhrady se u léčivého přípravku určeného k léčbě vzácného onemocnění posuzují

a) jeho terapeutická účinnost a bezpečnost,

b) závažnost onemocnění, k jehož léčbě je určen,

c) jeho nahraditelnost jinými léčebnými postupy hrazenými z prostředků zdravotního pojištění,

d) celospolečenský význam možnosti terapeutického ovlivnění onemocnění, k jehož léčbě je určen, a dopady léčby na systém zdravotního pojištění a sociálního zabezpečení,

e) jeho prokazatelný přínos na zlepšení kvality života pacienta,

f) reálné možnosti pro zajištění poskytování úspěšné a efektivní léčby v síti poskytovatelů zdravotních služeb,

g) doporučené postupy odborných institucí a příslušných odborných společností,

h) podmínky jeho úhrady z prostředků zdravotního pojištění navržené v žádosti, včetně případných smluv uzavřených držitelem rozhodnutí o registraci a zdravotními pojišťovnami omezujících dopad na prostředky zdravotního pojištění nebo upravujících sdílení rizik souvisejících s účinností tohoto léčivého přípravku v podmínkách klinické praxe,

i) analýza nákladové efektivity, avšak bez zohlednění jejího výsledku v podobě poměru inkrementálních nákladů a přínosů, a

j) předpokládaný dopad do rozpočtu zohledňující veřejný zájem podle § 17 odst. 2.

Access to innovative treatments

CF CARE IN HUNGARY

Géza MARSAL, Andrea PÁRNICZKY, MD, PhD
HUNGARY

16 centers
3 of them are country wider

550 patients
Total number of patients in 2022

49 - 51%
Child / adult ratio

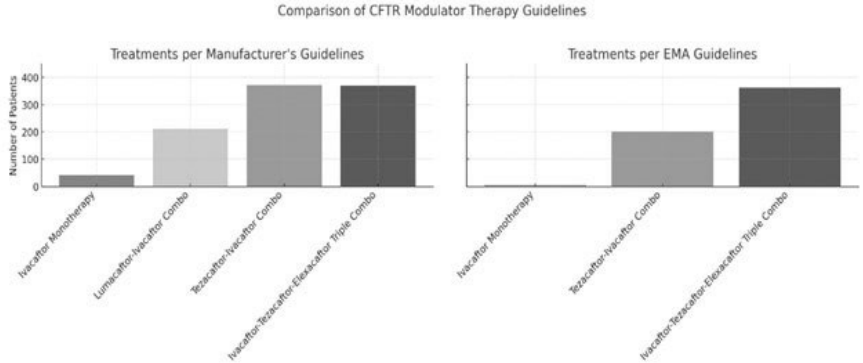
CFTR modulator therapy- theoretically
449 patients (genetic screening and revision)

Manufacturer's Guidelines:

Ivacaftor Monotherapy:	42 patients (9.4%).
Lumacaftor-Ivacaftor:	211 patients (47%).
Tezacaftor-Ivacaftor:	372 patients (82.9%).
Ivacaftor-Tezacaftor-Elexacaftor:	370 patients (82.4%).

EMA Guidelines:

Ivacaftor Monotherapy:	4 patients (0.9%).
Tezacaftor-Ivacaftor:	201 patients (44.8%).
Ivacaftor-Tezacaftor-Elexacaftor:	361 patients (80.4%)



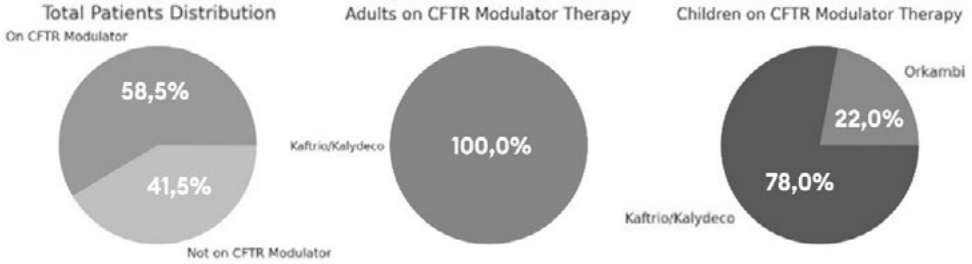
CFTR modulator therapy

Lumacaftor/ivacaftor (LUM/IVA)
2021 February - From 2024, for patients aged 1 year and older.
ORKAMBI®: Orkambi granules/tablets are indicated for the treatment of cystic fibrosis (CF) in patients aged 1 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

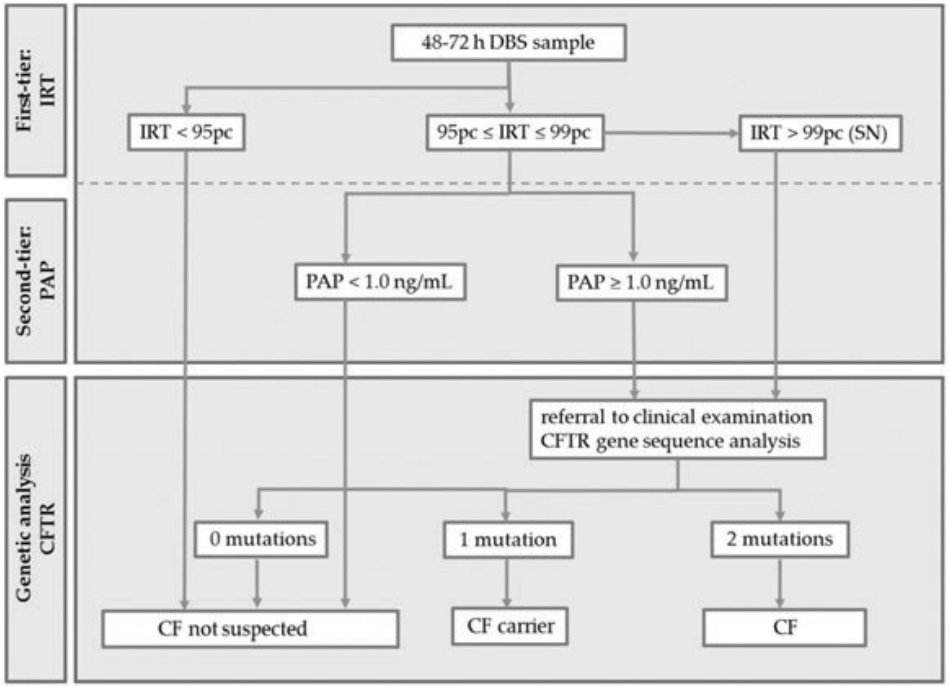
Elexacaftor/tezacaftor/ivacaftor (ETI)
2022 November - From 2024, for patients aged 2 year and older.
KAFTRIO®: Kaftrio, in combination with ivacaftor tablets, is indicated as a combination treatment for patients aged 2 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

KALYDECO®: As part of a combination treatment with ivacaftor/tezacaftor/elexacaftor tablets, it is indicated for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

CFTR modulator therapy in reality



Neonatal CF screening program - From 2022 January



Hungarian NBS Programme results from the first year

Screening for CF characteristics	**IRT/IRTxPAP/IRT + SN**
Infants screened for CF	88400
Infants with CF + CFSPID (% of infants screened)	15+3 (0.02%)
CF screen-positive results (% of infants screened)	256 (0.29%)
Infants referred to CF centre for sweat test	406
Detected cases with CF (% of infants with CF +CFSPID)	13 (72%)
False-positive cases (% of infants screened)	240 (0.27%)
Detected CF +CFSPID related to CF screen-positives	~1:16
CF screen-negative results (% of infants screened)	87994 (99.5%)
True-negatives (% of infants screened)	87992 (99.5%)
False-negative results (% of infants with CF +CFSPID)	2 (11%)
Sensitivity	87%
Specificity	99.7%
PPV	5.2%

CF Centers in Hungary
>100 patients treated - 2 center
>50 patients treated - 1 centers
<50 patients treated - 12 centers

Heim Pál National Pediatric Insitute - Budapest
Pulmonology Hospital - Törökbálint
National Korányi Institute of Pulomology - Budapest

Patient Organization
Hungarian Association of Cystic Fibrosis Patients (CFBE)

Main objectives:
- to improve the length and the quality of life of every patient with CF in Hungary
- supports the patients and their families, specialized for their needs
- to encourage the CF patients to continously studying in high schools and universities
- to provide social support to find the proper job and to have successful carreer
- build and maintain the Hungarian CF Registry and provide the required reports and data for the professional needs
- collaboration with ECFS, ECFSPR and other international teams

Website: http://www.cisztasfibrozis.hu
Facebook page: https://www.facebook.com/CisztasFibrozisMagyarorszag/
Facebook group: https://www.facebook.com/cf.hungary/

Achievements

Support CF Care Units -	OKPI CF részleg, HOGYI , Törökbálint
Educational events -	CF Nagyokos, Specialized Dental Care for CF Webinar
International conferences -	Participating CF Events, Better together 2017
Figyelemfelketlés, jótékonyság -	6 feet apart Fundarising
Novel therapies -	CFTR modulators

Patient Organization

Social Media, Online presence

www.cisztasfibrozis.hu
Facebook: Cisztás Fibrózis Magyarország
cisztasfibrozis@googlegroups.com
cisztasfibrozis@gmail.com

Education

International CF Day, Publications, guidelines, CF Nagyokos, CF – Better together 2017, CSIBE – Csoportos Internetes Beszélgetés

Quality of life, social events

Social events during the summer, Supplements, tools for devices, Tenders for patients, E-flow, 30k EUR

Financial support for CF care units

Raising funds for supporting the major CF centers and caregivers in HU

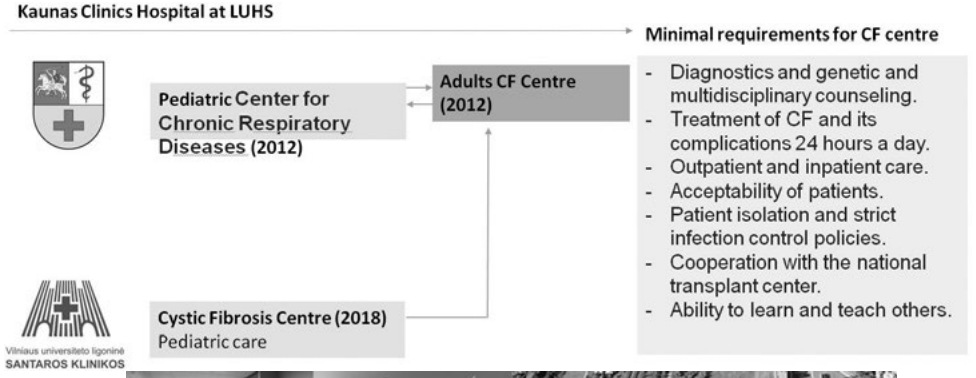
Heim Pál Országos Gyermekgyógyászati Intézet
Országos Korányi Pulmonológiai Intézet
Törökbálinti Tüdőgyógyintézet
SOTE Tüdőklinika

CF CARE IN LITHUANIA FROM THE PERSPECTIVE OF HEALTHCARE PROFESSIONALS

Valdone MISEVICIENE, MD
The Centre of Pediatric Chronic Respiratory Diseases
Lithuanian University of Health Science Hospital Kaunas Clinics, LITHUANIA

The Hospital of Lithuanian University of Health Sciences Kaunas Clinics

Cystic Fibrosis Care Centers in Lithuania



Countries Referring Data to the ECFS Patient Registry
CF is a Very Rare Disease in Lithuania

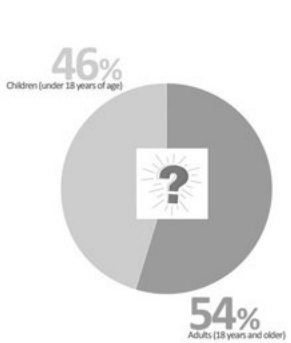
- **Prevalence:**
  < 1:10 000
  (≈ 80 patients at all)
- **Incidence:**
  5-6 new cases/year
  Or
  1:6000 births
  Or
  < 1:200 000 population

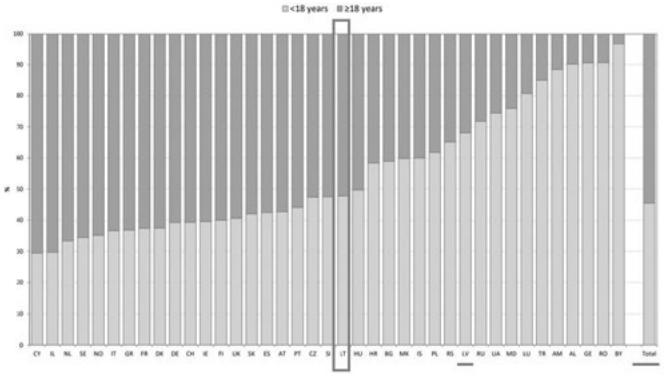
ECFS PATIENT REGISTRY

Lithuania	2 individual centres:	Kęstutis Malakauskas
	Hospital of theLithuanian University of Health Sciences Kauno Klinikos, Adult Cystic Fibrosis Centre, Kaunas	Kęstutis Malakauskas Virginija Kalinauskaitė - Žukauskė
	Hospital of Lithuanian University of Health Sciences Kauno Klinikos, Centre of Pediatric Chronic Respiratory Diseases, Kaunas	*Valdone Misevičiene*

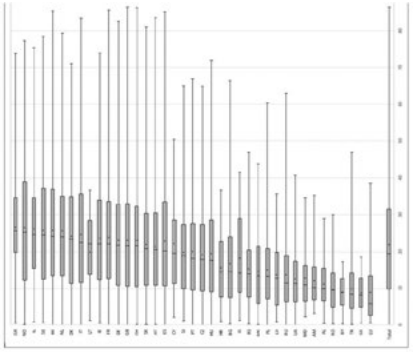
The Registry's database includes data from more than 50,000 people with CF, from 39 participating countries, and longitudinal data from 2008 to 2022. It is a unique resource reflecting the reality of CF across Europe.

Proportion of Children and Adults by Country and Overall





Distribution of Patients by Age at Follow-up Among European Countries



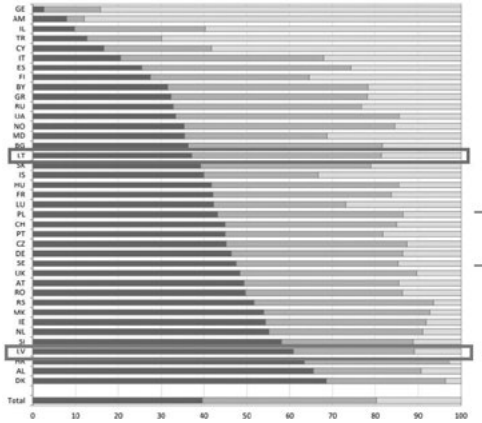
Median age in Lithuania – 18.9 y/o.
Min – 0.8 y/o, max – 38.5 y/o.

ECFSPR Annual Report 2022, Zolin A, Adamoli A, Bakkeheim E, van Rens J et al, 2024.

Diagnostics of CF in Lithuania

- In EU most patients are currently diagnosed by the age of 4 months old.
- NBS – was the main factor contributing to an early diagnosis.
- **NBS started since 2023.**
- Unrecognized CF symptoms lead to a delayed diagnosis, because patients are not sent to the centers.
- Acceptance of the Dx is a long and challenging process for the patients and families.

Distribution of Patients According to Prevalence of F508del Mutations



In 93, 35% of Lithuanian patients CF is confirmed genetically

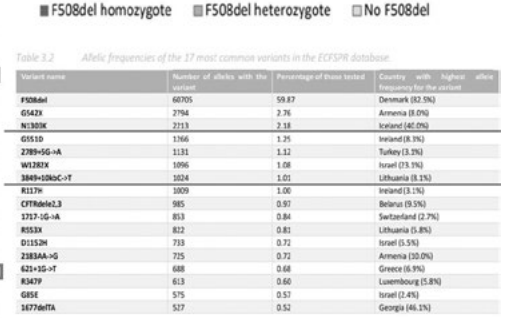
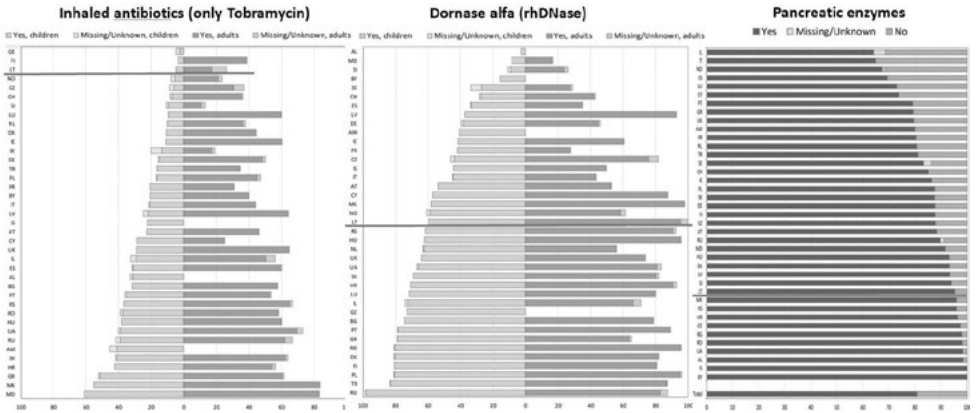


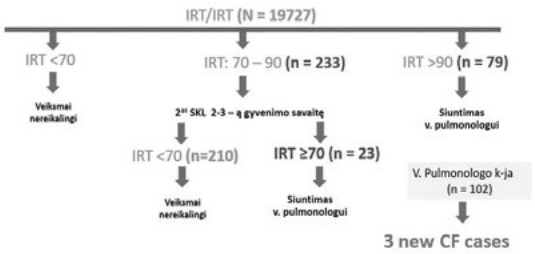
Table 3.2 Allelic frequencies of the 17 most common variants in the ECFSPR database.

Variant name	Number of alleles with the variant	Percentage of those tested	Country with highest allele frequency for the variant
F508del	60705	59.87	Denmark (82.5%)
G542X	2794	2.76	Armenia (8.0%)
N1303K	2113	2.18	Iceland (40.0%)
G551D	1266	1.25	Ireland (8.1%)
2789+5G->A	1131	1.12	Turkey (3.3%)
W1282X	1096	1.08	Israel (73.1%)
3849+10kbC->T	1024	1.01	Lithuania (8.1%)
R117H	1009	1.00	Ireland (3.1%)
CFTRdele2,3	985	0.97	Belarus (9.5%)
1717-1G->A	853	0.84	Switzerland (2.7%)
R553X	822	0.81	Lithuania (5.8%)
D1152H	733	0.72	Israel (5.5%)
2383AA->G	725	0.72	Armenia (10.0%)
621+1G->T	688	0.68	Greece (6.9%)
R347P	613	0.60	Luxembourg (5.8%)
G85E	575	0.57	Israel (2.4%)
1677delTA	527	0.52	Georgia (46.1%)

Therapies available and reimbursed in Europe and Lithuania



2023 is the start of CF Newborn Screening in LT
IRT/IRT/DNA Algorithm



N ≈ 12 975 (till 2024 08 mėn.)

↑ IRT n = 67
(consulted by pulmonologist)

7 new cases

2023m. CF incidence: ≈1:6500

2024m. CF incidence: ≈1:1850

2023-2024m. CF incidence in LT ≈ 1:3500

New CF cases found during NBS

CF CASES	CF VARIANT (I)	CF VARIANT (II)
5	II CLASS (F508del)	II CLASS (F508del)
1	II CLASS (F508del)	I CLASS
1	I CLASS	III CLASS
1	I CLASS	IV CLASS
2	IV CLASS	V CLASS

The Journey to CFTR Modulators in Lithuania

The first applications for reimbursement of treatment with CFTR modulators

A lot of queries, documents, meetings.

Discussions at the Parlament and Ministry of Health in various working groups

27/12/2021 → 05/02/2022 -24/11/2022 → 01/12/2022 – 2024 ?

Initiatives of Lithuanian CF Association

Patients on Treatment with ITE therapy before CFTR modulators reimbursement

2022 December – 1 adult	ITE therapy initiated in severely sic, intubated patient in ICU.
2023 April – 1 adolescent	ITE therapy initiated in severe condition (FEV1 – 27proc.) during exacerbation treatment in the hospital. CF was deteriorating quickly despite all treatment prescribed.
2023 October – 1 adolescent	Treatment initiated in the hospital because of quickly deteriorating disease and severe CF exacerbation (FEV1 – 34 proc.).
2024 July – 3 adults	Severe patients , treated for exacerbation in the hospital with progressing course of the disease and chronic respiratory failure.

Our Findings about ITE therapy in Severe Patients

- Treatment with ITE is effective and safe even in critically ill patients.
- The positive effect is notable already after 1-4 weeks of treatment.
- Sweat chloride is significantly decreased already after 1 month after initiation of ITE therapy.
- Clinical effects:
  - Less CF symptoms and no need for oxygen.
  - Better nutrition and gaining weight.
  - Less and milder or no exacerbations.
  - Better quality of life.
- Mild effect on lung function (+10 - 15 proc.) and radiological findings if the disease is far-advanced.

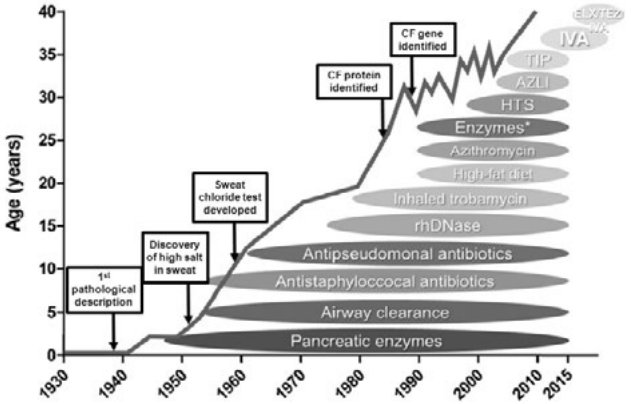
CFTR modulators are reimbursement to all eligible patients from 2y.
52 patients are on treatment

CYSTIC FIBROSIS IN A NEW ERA - CF MONITORING

Prof. dr hab. n. med. Dorota SANDS
Institute of Mother and Child , Warsaw, POLAND

Advances in treatment approaches have led to improvements in life expectancy

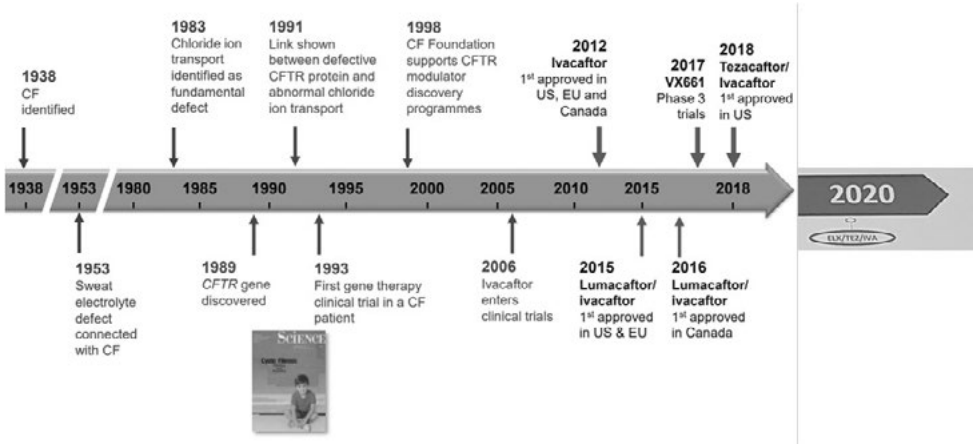
Effect of different therapies on the life expectancy of patients with CF



Schematic illustration.

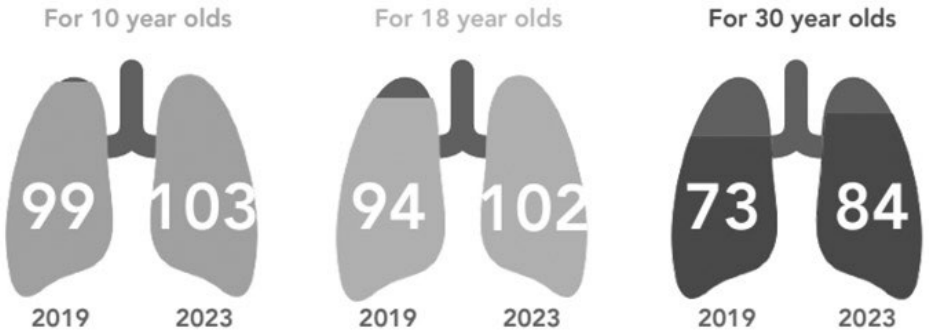
AZLI, aztreonam; HTS, high throughput screening; IVA, ivacaftor; LUM, lumacaftor; rhDNase, recombinant human deoxyribonuclease; TIP, tobramycin.

CF Research milestones



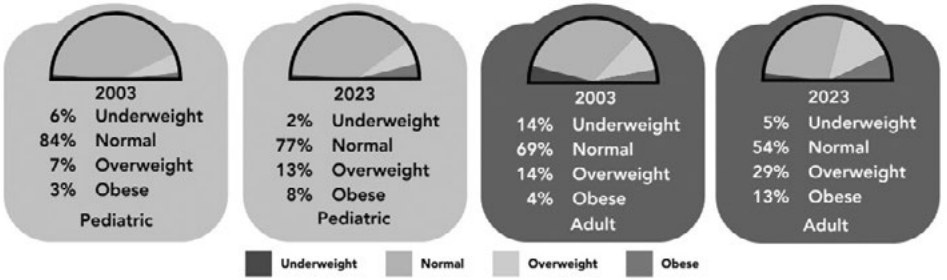
LUNG FUNCTION

Median FEV_1 Percent Predicted

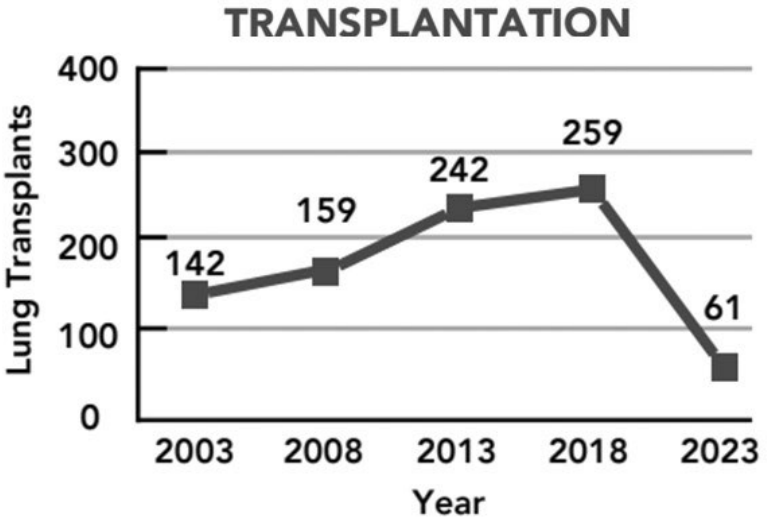


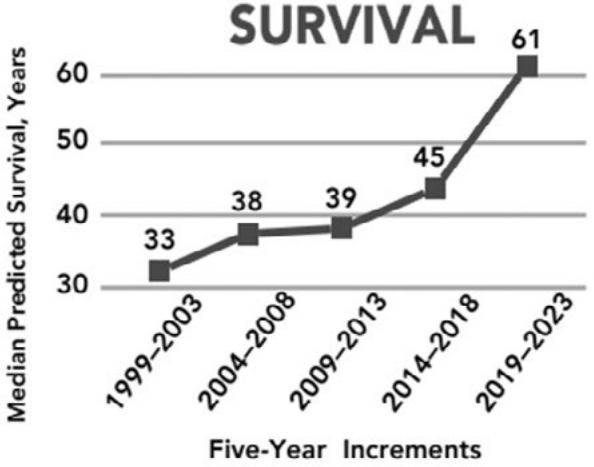
NUTRITIONAL STATUS

Over the last 20 years, the percentage of people with CF who are overweight or obese has increased — from 10% to 21% among children with CF and from 18% to 42% among adults.



TRANSPLANTATION



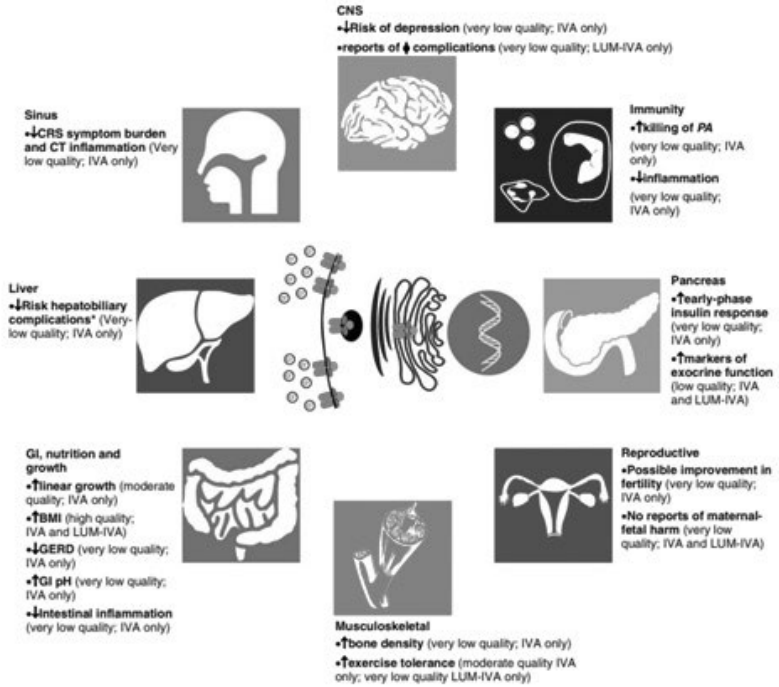


Check for updates

FOCUSED REVIEW

The Extrapulmonary Effects of Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Cystic Fibrosis

Valentine Sergeev[1], Frank Y. Chou[1], Grace Y. Lam[2,3], Christopher Michael Hamilton[4], Pearce G. Wilcox[2,3], and Bradley S. Quon[2,3]



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☆

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Odczucia pacjentów

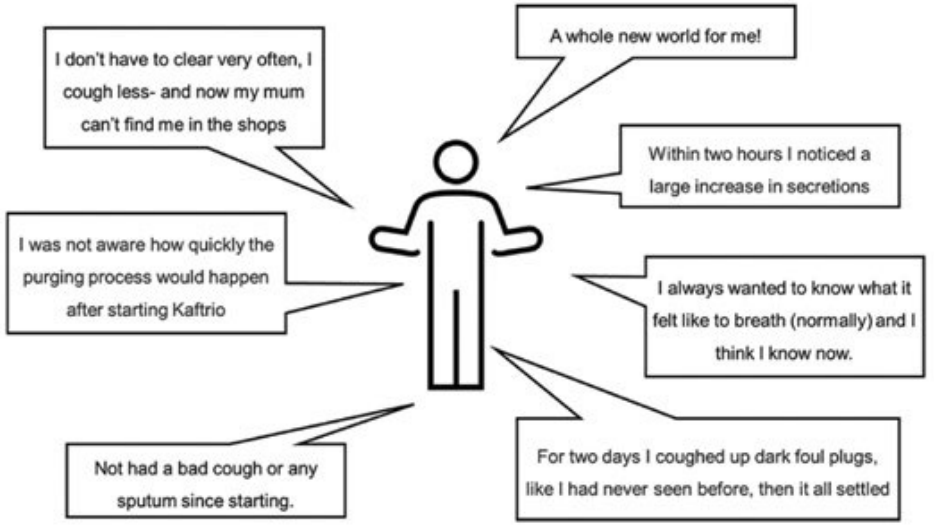
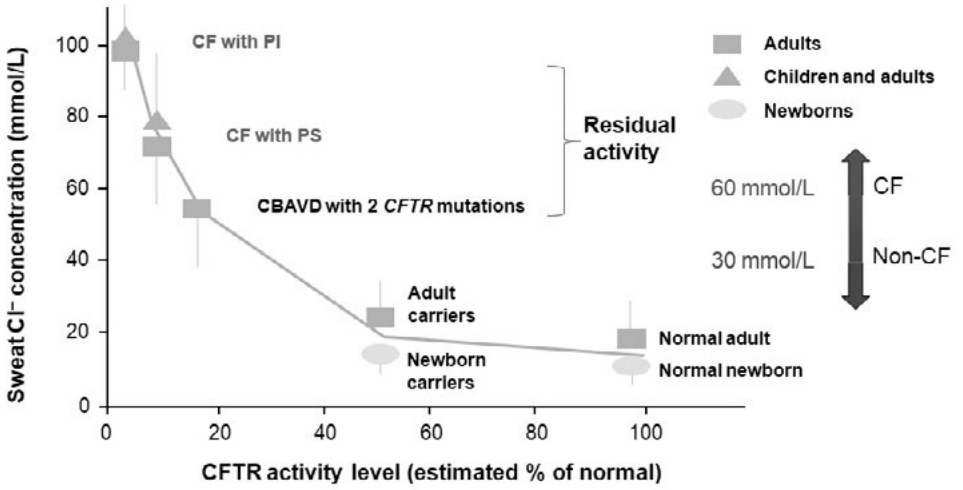


Fig. 2. Comments from pwCF upon starting VST.

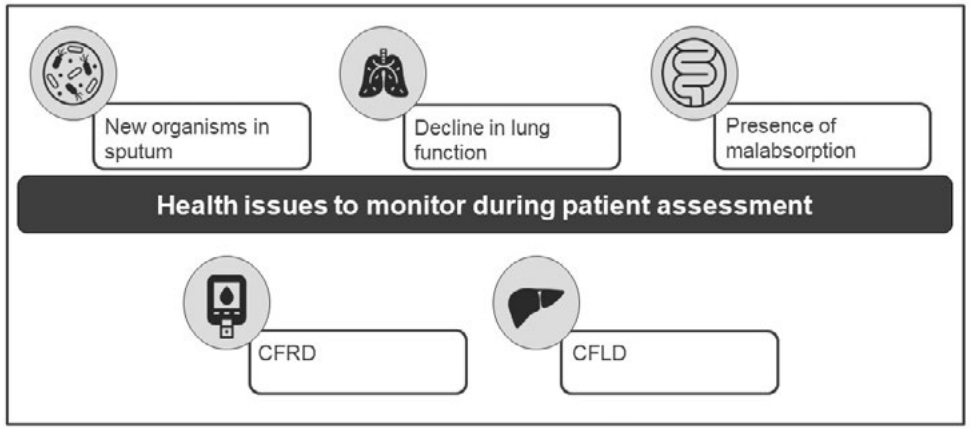
Sweat Cl – and pancreatic status are indicators of CFTR activity



Note: Three important assumptions are made: (1) sweat Cl– levels vs predicted CFTR activity; (2) normal individuals are assumed to have 100% CFTR activity; (3) carriers are assumed to have 50% CFTR activity.

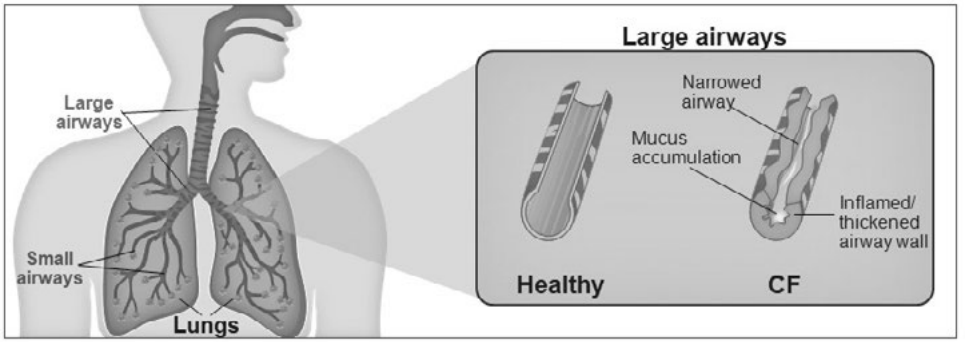
Ongoing monitoring facilitates early detection and management of CF-related health issues

Periodic evaluation of patients with CF ~every 3 months allows for early detection and prompt intervention of disease-associated health problems



FEV1 is the cornerstone of pulmonary function testing

- FEV1 = volume of air forcefully expelled from the lungs in the first second1
- The most widely used method for clinical monitoring of CF lung function in children, adolescents and adult CF patients
- FEV0.5 can be used for infants and young children unable to exhale for 1 full second
- Strong correlation with airway wall thickness and mucus plugging, both features of larger airway obstruction



FEV1 is not sensitive to early lung disease and is difficult to perform in young children, limiting its value in the young CF population

Strengths

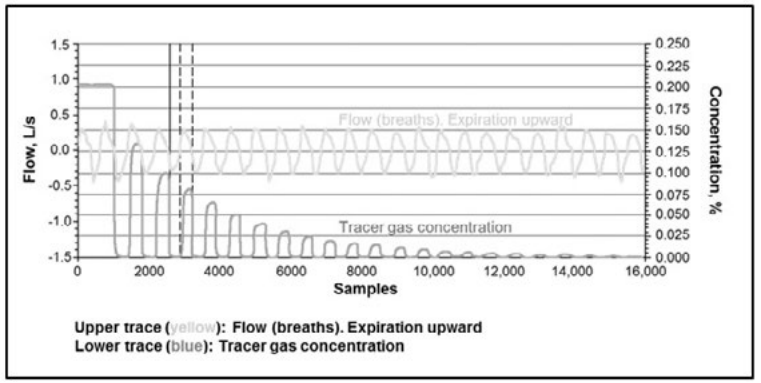
- Widely used in the clinic and in clinical trials[1,2]
- When expressed as percent predicted, FEV1 is the most useful objective measure of pulmonary status[3]
- Validated prognostic indicator of lung disease progression and survival time in CF[2,4]
- Recognised as a primary outcome by the FDA and EMA[5]

Limitations

- Not sensitive to small airway damage that occurs earlier in CF lung disease[6,7]
- Not sensitive to mild lung disease[6,7]
- FEV1 values often do not correlate with more detailed assessments of pulmonary disease severity such as CT imaging[8,9]
- Spirometry can be difficult for young children to perform[10]
- Spirometry measurements are dependent on patient cooperation and effort[10]

1. De Benedictis FM, et al. Eur J Clin Pharmacol. 2010;67(suppl 1):49–59; 2. Liou TG, et al. Am J Epidemiol. 2001;153(4):345–52; 3. Yankaskas JR, et al. Chest. 2004;125(suppl 1):1S–39S; 4. Corey M. Proc Am Thorac Soc. 2007;4(4):334–7; 5. Kent L, et al. J Cyst Fibros. 2014;13(2):123–38; 6. Gustafsson PM, et al. Thorax. 2008;63(2):129-34; 7. Horsley A & Siddiqui S. Respirology. 2015;20(1):33–45; 8. Brody AS, et al. J Paediatr. 2004;145(1):32–8; 9. de Jong PA, et al. Eur Respir J. 2004;23(1):93–7; 10. Aurora P, et al. Am J Respir Crit Care Med. 2004;169(10):1152–9.

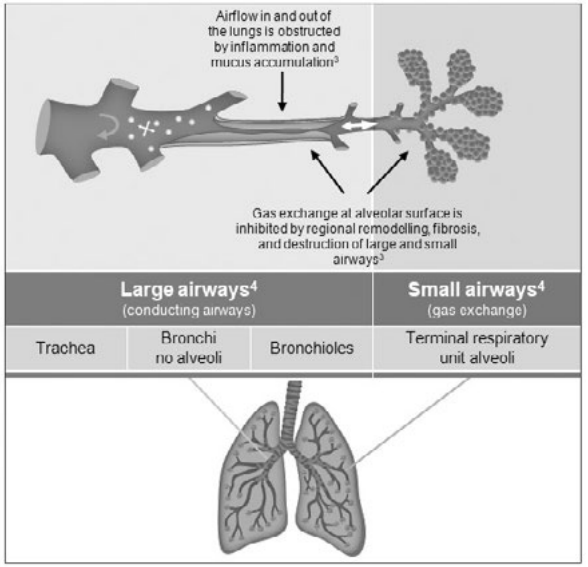
LCI is a measurement of lung function capable of detecting early airway disease in CF



- Multiple breath washout (MBW) tests measure the tidal breaths needed to remove an inert tracer gas present in the lungs
- LCI is a numerical value derived from MBW test data
  - Represents the number of breaths needed to reduce the tracer gas to a predefined concentration

LCI is sensitive to damage in both large and small airways, enabling detection of early airway disease in CF

Why more breaths are required to clear tracer gas from CF lungs



LCI is an indication of ventilation heterogeneity, based on how many breaths it takes to wash a tracer gas out of the lungs during tidal breathing[1]

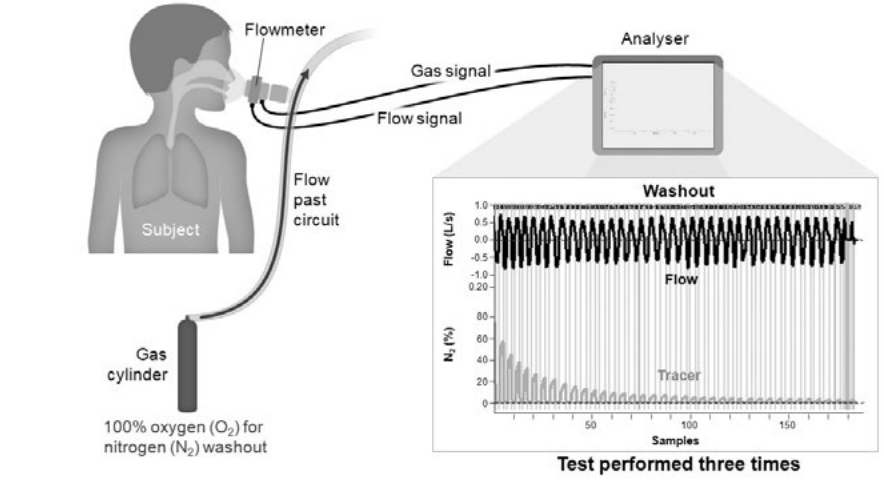
LCI is sensitive to damage in both large and small airways[2]

LCI values increase with lung disease severity[1]

LCI can detect early lung diseasebefore a noticeable drop in spirometry measurements occurs[1]

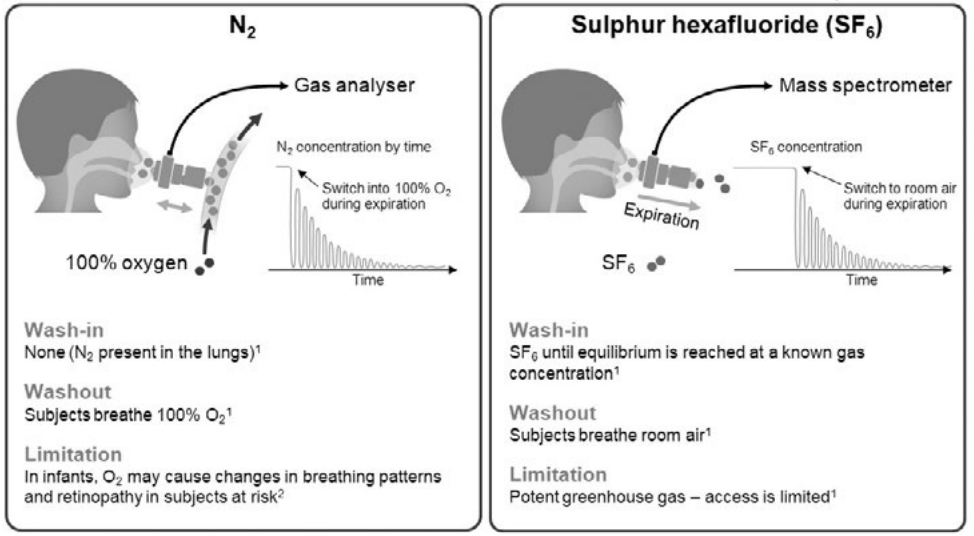
1. Horsley A. Respir Med. 2009;103(6):793–9; 2. Verbanck S, et al. J Appl Physiol. 2012;112(5):782–90; 3. Horsley A & Siddiqui S. Respirology. 2015;20(1):33–45; 4. The Human Respiratory System. In: Tu J, et al. Computational Fluid and Particle Dynamics in the Human Respiratory System. Springer, 2013; Chap. 2.

Performing a MBW test [1,2]



1. Horsley A. Respir Med. 2009;103(6):793–9; 2. Subbarao P, et al. Ann Am Thorac Soc. 2015;12(6):932–9.

Tracer gas selection



1. Subbarao P, et al. Ann Am Thorac Soc. 2015;12(6):932–9; 2. Schultzke SM & Frey U. Eur Respir J. 2013;41(3):500–2.

LCI can be performed in infants and young children without the need for sedation and mechanical manipulation

Strengths

- Sensitive to early airway disease before noticeable FEV1 decline[1,2]
- Requires only passive tidal breathing (vs forceful exhalation)[2]
- Can be performed in infants and young children without the need for sedation and mechanical manipulation[2,3]
- Correlates with high-resolution computed tomography (HRCT) detection of lung structural changes[4]
- Correlates with risk for pulmonary exacerbation in patients with CF[5]
- Worsens with FEV1 decline in patients with early and moderate lung disease[6]

Limitations

- Few centres have incorporated MBW into routine clinical practice[7]
- Longitudinal data are limited[7]
- Lack of guidelines and normative data to assist with interpreting results[7]
- Limited standardisation for staff training, equipment, and analysis software[7]
- Minimum clinically important difference not yet established[8]
- Not practical for patients with advanced lung disease (ppFEV1 <60%) due to profound ventilation heterogeneity and extended wash-in and washout periods[8]

1. Aurora P, et al. Thorax. 2004;59(12):1068–73; 2. Robinson PD, et al. Eur Respir J. 2013;41(3):507–22; 3. Lum S, et al. Thorax. 2007;62(4):341–7; 4. Ellemunter H, et al. Respir Med. 2010;104(12):1834–42; 5. Vermeulen F, et al. Thorax. 2014;69(1):39–45; 6. Kraemer R, et al. Am J Respir Crit Care Med. 2005;171(4):371–8; 7. Subbarao P, et al. Ann Am Thorac Soc. 2015;12(6):932–9; 8. Horsley A & Siddiqui S. Respirology. 2015;20(1):33–45.

Warsaw CF Team Experience with LCI

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ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

WILEY

Change in lung clearance index with microbiological status in children with cystic fibrosis

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LCI vs microbiological status in CF children

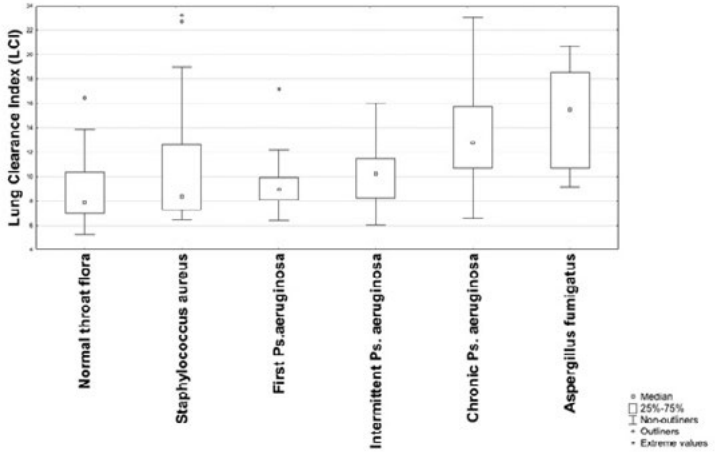

FIGURE 2 Median Lung Clearance Index (LCI) values (interquartile range) for CF subjects with different microbiologic status (*Staphylococcus aureus* (n-27)-median 8,39 [7,28;12,9]; *Pseudomonas aeruginosa* (n-70) first time (n-27)-median 8,71 [7,98; 9,84], intermittent (n-9)-median 10.58 [8,77;11.48], and chronic (n-34)-median 12.90 [10.82;16.12]; *Aspergillus fumigatus* (n-6)-median 15.53 [11.26; 19.07]; normal throat flora (n-33)-median 7.84 [6.94; 10.34].)

Journal of *Clinical Medicine*

MDPI

Article

Lung Clearance Index in Children with Cystic Fibrosis during Pulmonary Exacerbation

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LCI vs pulmonary exacerbations in CF children

Figure 1. FEV_1 results: (**A**) FEV_1 % predicted and (**B**) FEV_1 z-score for subjects with CF in stable condition, before and after treatment of pulmonary exacerbation.

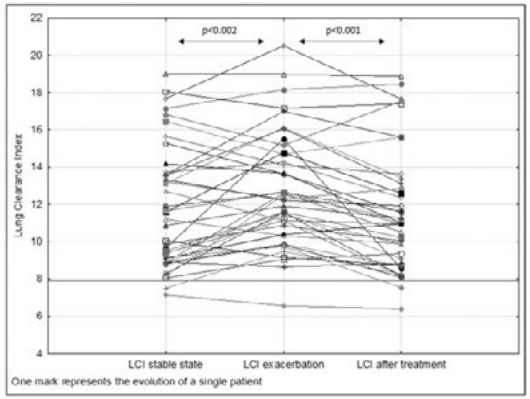


Figure 2. Lung clearance index (LCI) values for CF subjects in stable condition, before and after treatment of pulmonary exacerbation. For LCI, the upper limit of 7.91 was presented according to normative data for healthy children [19].

Guidelines recommend systematic screening for CFRD in all patients

- CFRD is often clinically silent and associated with weight loss, protein catabolism, lung function decline, and increased mortality[1]
- Periodic screening for CFRD should be done in all CF patients[1,2]
  - Annual screening should begin by age 10 in all CF patients who do not have CFRD

Screening for CFRD should be performed using 2 h 75 g oral glucose tolerance test (OGTT) except in CF patients:[3]

With acute pulmonary exacerbation requiring intravenous antibiotics and/or systemic glucocorticoids: *Monitor fasting and 2-hour postprandial plasma glucose levels for the first 48 hours*

On continuous enteral feedings, at the time of gastrostomy tube feeding initiation, and then monthly at home: *Measure mid- and immediate post-feeding plasma glucose levels*

Elevated glucose levels detected by self-monitoring of blood glucose (SMBG) must be confirmed by a certified laboratory[2]

1. O'Sullivan BP & Freedman SD. Lancet. 2009;373(9678):1891–904; 2. Castellani C, et al. J Cyst Fibros. 2018;17(2):153–78;3. Moran A, et al. Diabetes Care. 2010;33(12):2697–708.

Continuous glucose monitoring system for detection and monitoring of CFRD in patients with CF

- The continuous glucose monitoring system (CGMS) is a useful and valid tool in defining glucose metabolism in children and adults affected by CF with early glucose derangements[1]
- CGMS provides 24-hour monitoring to determine glycaemic trends[1]
- CGMS is able to predict the development of CFRD and has been shown to reveal early glucose tolerance abnormalities that were not detected by OGTT in paediatric patients[1]
- Some centres now use CGMS as part of the diagnostic process[2]

1. Schiaffini R, et al. Eur J Endocrinol. 2010;162(4):705–10; 2. Castellani C, et al. J Cyst Fibros. 2018;17(2):153–78.

Nutritional status monitoring forms part of routine CF care

- Close monitoring of nutrition and growth is essential for paediatric and adult CF patients[1]
- Optimal nutritional status is associated with better clinical outcomes[1,2]
- However, achieving and maintaining optimal nutritional status can be difficult[1]
- Nutritional status should be assessed every month during first year of life and then every three months[1]
- Frequency of nutritional assessments should increase if nutritional status becomes suboptimal[1]

Nutritional status assessments[1]

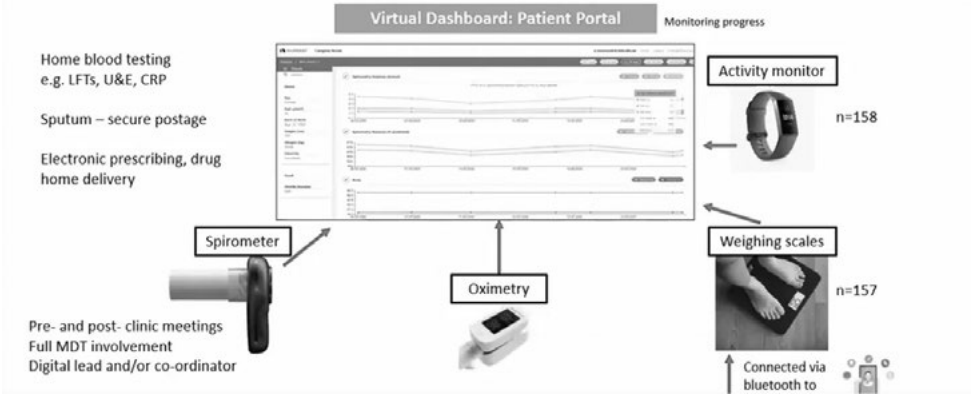
CF patient group	Assessment components
Children ≤2 years	Weight, height, weight-for-length percentiles
Children ≥2 years and adults	BMI

Nutritional goals[2–4]

CF patient group	Goal
≤2 years	Weight-for-length ≥50%ile for age
2–5 years	BMI ≥50%ile for age Weight ≥10%ile
>5–18 years	BMI ≥50%ile for age

1. Sullivan JS & Mascarenhas MR. J Cyst Fibros. 2017;16(suppl 2):S87–93; 2. Yen EH, et al. J Paediatr. 2013;162(3):530–5.e1; 3. Stallings VA, et al. J Am Diet Assoc. 2008(5);108:832–9; 4. Lahiri T, et al. Paediatrics. 2016;137(4):e20151784.

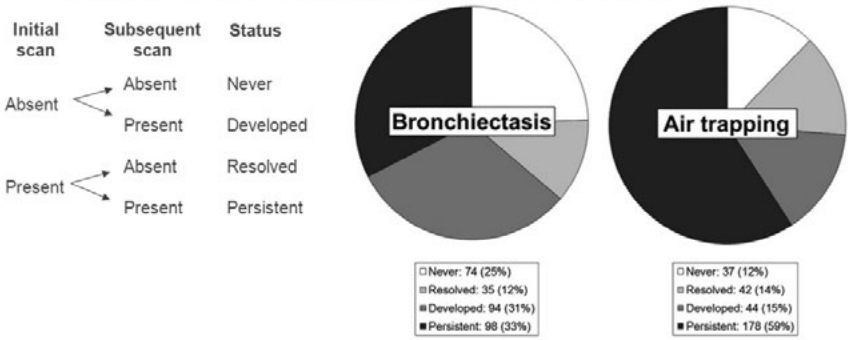
A new model of care? (example provided by RBH, London)



Structural lung disease progresses even in early life

143 children aged 0.2–6.5 years with CF from a NBS population contributed 444 limited slice annual chest CT scans for analysis that were scored for bronchiectasis and air trapping and analysed as paired scans one year apart

Bronchiectasis and air trapping status after initial and subsequent scans



CT and magnetic resonance imaging can be used to detect structural lung changes

CT[1]

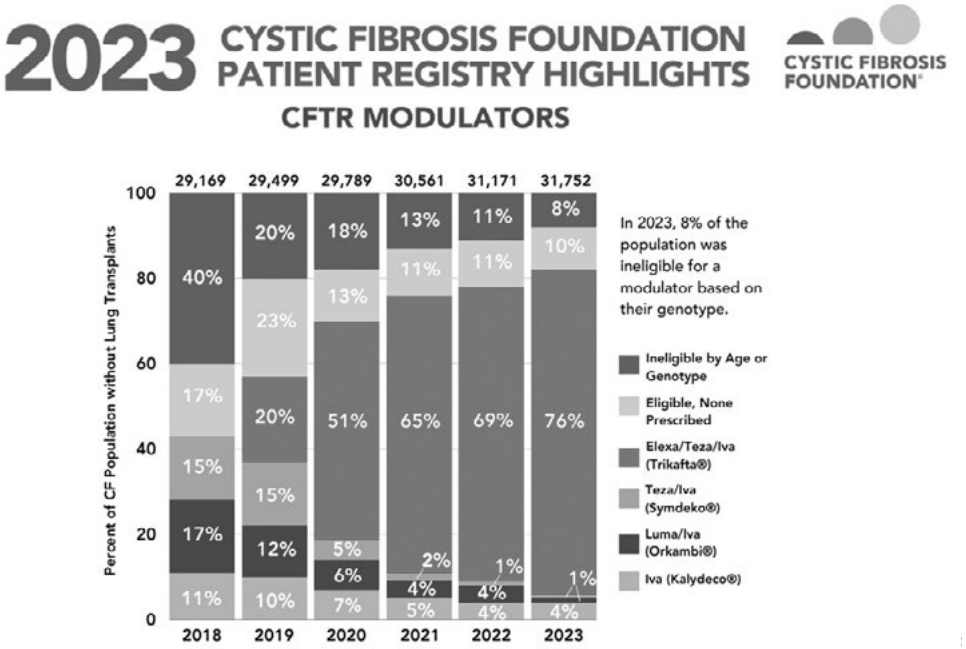
- 'Gold standard' for assessment of morphological changes of the airways and lung parenchyma
- Can be performed extremely fast, even in very young and critically ill children
- Can be used to detect early CF lung disease
- Major disadvantage is the use of radiation
- The cumulative radiation dose for lifelong repeated CT scans has limited its use for CF patients as their life expectancy increases

Magnetic resonance imaging (MRI)[1,2]

- Radiation-free
- Comparable to CT for detection of morphological changes in the CF lung
- Less sensitive than CT to detect small airways
- Superior to CT for assessment of functional and structural changes such as:
  - Altered pulmonary perfusion
  - Bronchiectasis/bronchial wall thickening
  - Mucus plugging
- Sufficiently sensitive to detect changes associated with pulmonary exacerbation and response to standard antibiotic therapy following such exacerbations

1. Eichinger M, et al. J Magn Reson Imaging. 2010;32(6):1370–18; 2. Wielpütz MO, et al. Am J Respir Crit Care Med. 2014;189(8):956–65.

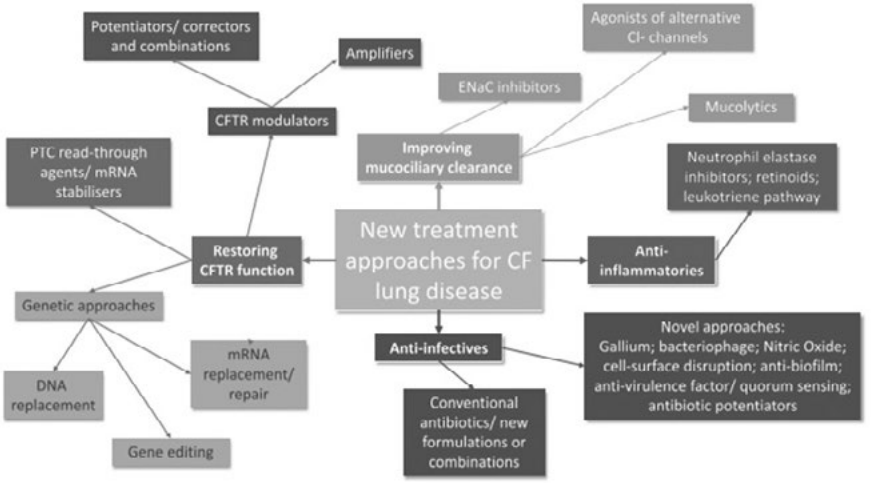
Maintaining adherence



https://www.cff.org/medical-professionals/patient-registry

Perspective https://doi.org/10.1038/s41467-023-36244-2

Future therapies for cystic fibrosis

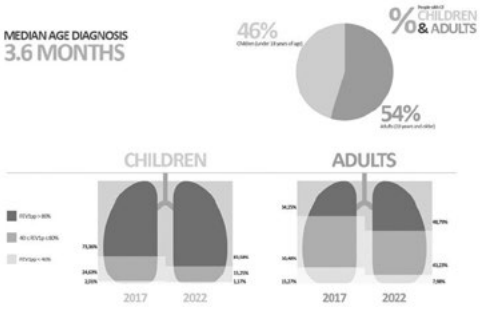


FRYDERYK CHOPIN

EUROPEAN CYSTIC FIBROSIS SOCIETY PATIENT REGISTRY (ECFSPR)

Egil BAKKEHEIM, MD, PhD
Director ECFSPR, Head of the Oslo CF-centre, NORWAY

2022 Annual Report:
39 countries
54.546 patients
Longitudinal data 2008-2022
Annual Report 2022 was published in June 2024



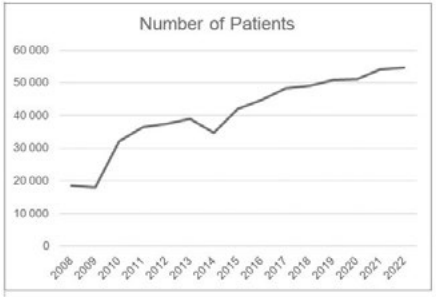
Objectives of the ECFSPR
Strategic Plan
- Publish annual reports 12 - 18 months after data-collection year
- Ensure high data quality
- Increase visibility and usage of data
- Increase number of scientific publications
- Maintain ECFSTracker's relevance
- Strengthen collaboration with patient organisations
- Foster relationships with ECFS-CTN and ECFS working groups
- Recruit new countries and increase national coverage to ≥80%

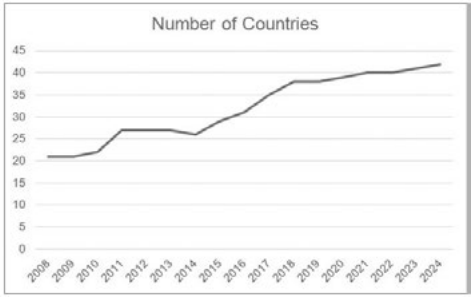
Data Collection - Software
A platform for the collection of CF data for all purposes
Excel-file uploaded >> WEBSERVER >> Manual Data-Entry
- Web-based and open source
- Custom designed for the collection of CF data
- User friendly
- Available for free to participating countries
- Service Desk
- Data Quality checks & controls, Statistical validation
- Add on modules (clinical trials, specific data collection, etc.)

2024 data collection
New variables and changes to existing variables:
- Information on aging in CF: cardiovascular disease, cancer, osteopenia, clinical trial participation
- Pharmacovigilance: Reasons for stopping after initiation of CFTRm (cataract, liver chemistries)

Planning:
- New Data Coding document ready for national registries
- Collection from 2024 data (in 2025) onwards

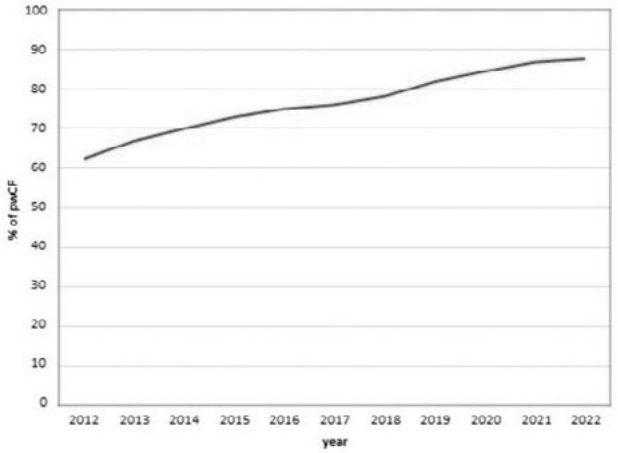
Facts and Figures 2022 - Coverage and participation





AR 2022: Newborn screening in Europe - rate increases to almost 90%

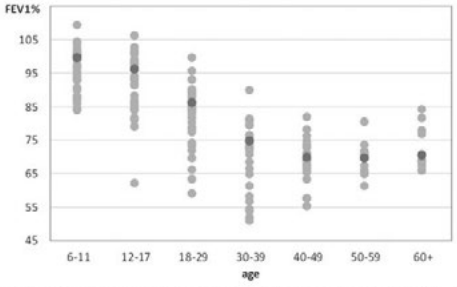
Neonatal screening in children with CF aged 5 years or younger in the years from 2012 to 2022.



In this graph data over time is presented using cross sectional data per year of children with a confirmed CF diagnosis. Children with CF who are alive, deceased, or not seen during the year of follow-up were included and those who were lost to follow-up and/or transplanted (lung and/or liver) were excluded. When computing the yearly prevalence, where the information was missing for a child it was excluded from the total number.

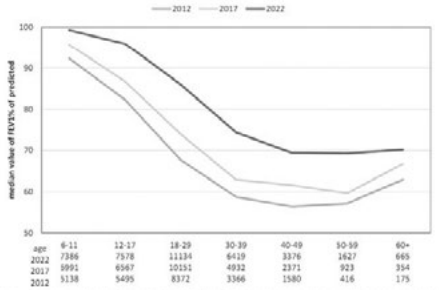
AR2022: 2022 and longitudinal data for FEV1

Median FEV_1% of predicted by age group and by country.



Note: We excluded from the graph those age groups where the number of individuals was <10.

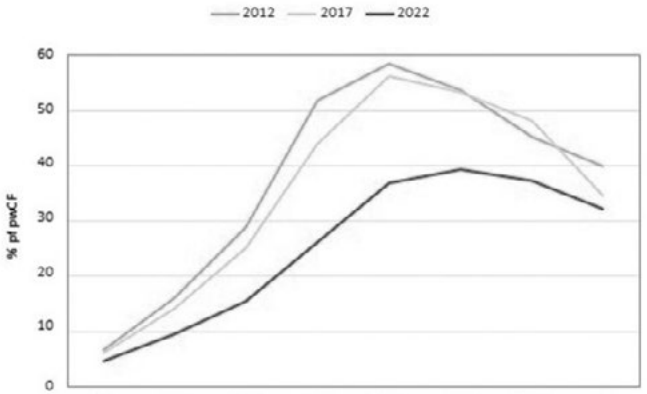
Median FEV_1% of predicted by age group in 2012, 2017 and 2022.



Note: People with CF aged 6 years or more at lung function measurement, who have never had a lung or liver transplant.

Ar 2022: Microbiology - chronic P. Aeruginosa infection decreases

Prevalence of chronic *Pseudomonas aeruginosa* infection in people with CF, by age group, in 2012, 2017 and 2022.

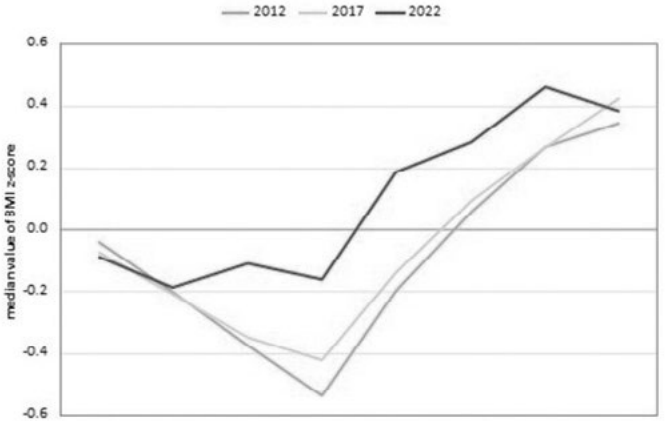


age	0-5	6-11	12-17	18-29	30-39	40-49	50-59	60+
2022	7806	8285	7761	11322	6416	3309	1588	653
2017	8336	7682	6780	10404	4882	2366	912	357
2012	5396	4880	4838	7387	2841	1285	370	163

In this graph we present data over time using cross sectional data per year of people with a confirmed CF diagnosis. All people with CF alive, deceased, or not seen during the year of follow-up were included. Exclusion criteria were people who were lost to follow-up and/or transplanted individuals (lung and/or liver), and people with missing values.

Ar 2022: BMI has improved

Median z-score for BMI by age group in 2012, 2017 and 2022.

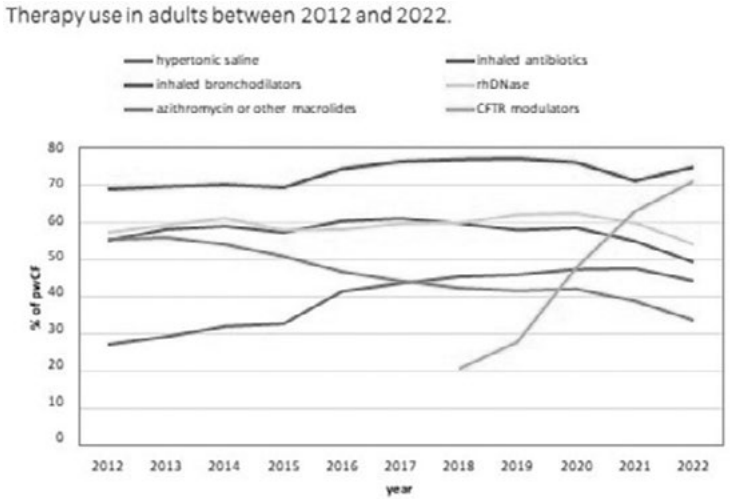


age	2-5	6-11	12-17	18-29	30-39	40-49	50-59	60+
2022	4933	8328	7962	11375	6516	3379	1623	668
2017	5213	7756	6952	10502	5039	2408	940	361
2012	3567	5560	5716	8590	3422	1587	422	179

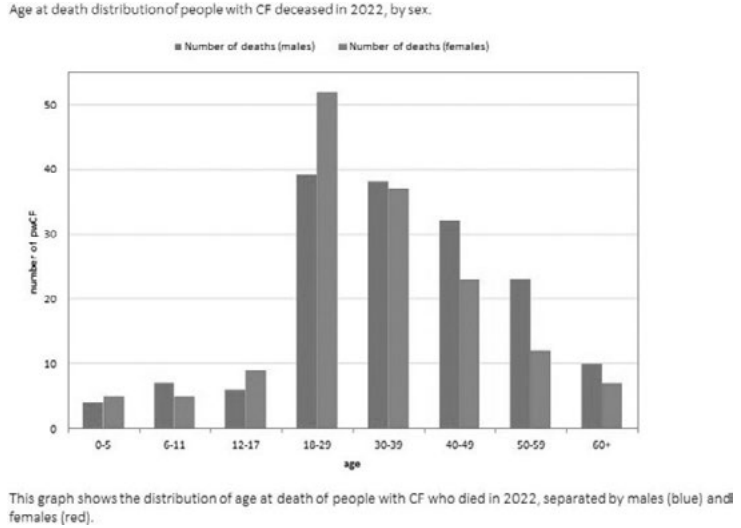
Note: Only people with CF aged 2 years or more at measurements and who have never had a lung or liver transplant.

In this graph we present data over time using cross sectional data per year of people with a confirmed CF. All people with CF alive, deceased, or not seen during the year of follow-up were included. Exclusion criteria were people who were lost to follow-up, and transplanted individuals (lung and/or liver). Also, people with missing values are excluded when computing the yearly prevalence for each variable.

Treatment trends in Adults: CFTR modulators in > 70% of pwCF



Mortality in Europe in 2022 – CF disease is still a matter of concern



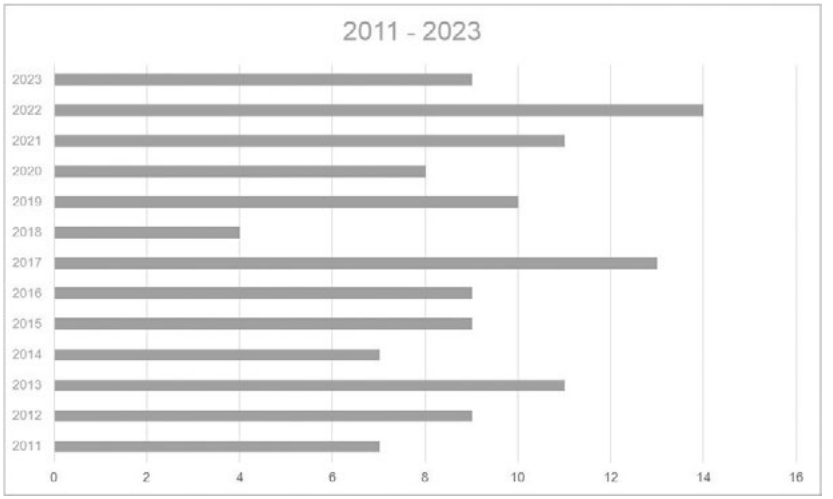
This graph shows the distribution of age at death of people with CF who died in 2022, separated by males (blue) and females (red).

Structure of ECFSPR: Scientific committee

Siobhán Carr, Pierre-Régis Burgel, Anders Lindblad, Milan Macek jr.,
Elise Lammerlyn (CF Europe), Anna Zolin, Annalisa Orenti, Egil Bakkeheim (liaison Exec. Com.)
Lutz Naehrlich, Jacqui van Rens, Panagiota Gkolia

- 4 - 8 meetings per year
- Oversight and Review of Data Requests
  - Scientific rigor
  - Data availability
  - Advice to researcher
  - Capacity to help with analysis
- Review progress of approved projects
- Initiate research ideas
- Collaboration with other CF-registries worldwide

Research - Data Requests



PAES Project

POST AUTHORISATION SAFETY AND EFFICACY STUDIES - Pharmacovigilance
2 pharmacovigilance (PMV) studies in 2024
- PAES study for use of lumacaftor/ivacaftor in 1–5-year-old children at therapy initiation
- PASS study on Real-World Effects and Utilisation Patterns of elexacaftor/tezacaftor/ivacaftor combination therapy
- ECFS grant applications: annually from 2021
- Ensure high data quality
- Around 80% of the income from the PMV-studies is given back to the ECFSPR participating countries through direct and indirect grants

Data Quality
- High-quality data is essential!
- Validation visits to 23 centres in 14 countries in 2023
- Many visits have been performed in 2024
- Introduction of the Validation Programme in 5 countries with a national registry (BE, CZ, DE, IE & NL)

New Projects:

CFSPID-registry under establishment
- Joint project of ECFSPR, Neonatal Screening WG & Standards of Care
- ECFS board had decided to put the governance at the ECFSPR.
- Chair: **Andreas Jung**
- Other members: Kevin Southern (SoC), Jürg Barben (Neonatal Screening WG) ++ other interested ECFS members.

- Working plan:
  - Concept Sheet (including CFTR-RD) 06/2022
  - Variables & definitions ready
  - Harmonization with national registries (cont.)
  - Establish a ECFSPR Working Group, Meet in Brussels January 2025
  - Secure funding (Funded through ECFS and ECFSPR)
  - Create ECFSTracker module in 2025 and start data collection from 2025

ENRICH

ENRICH the ECFSPR with Structural Lung data from Chest computed tomography scans
- Automated image analysis of CT scans

- Scores included in ECFSTracker

- Pilot project: ECFSTracker module, limited no. of CTN sites, larger no. of variables to be tested

- Funding by CFF

- Rotterdam CF centre: Harm Tiddens, Daan Caudri
- ECFSPR: Andreas Jung, Pierre-Régis Burgel
- CTN: Damian Downey, Hettie Janssens

Joint Projects with CFS Clincal Trials Network
Research topics :
- Inhaled ATB withdrawal in PwCFTR modulators
- Complex infections: Statement
- Impact of CFTR modulators
- Aging of PwCF / Changing of CF
- Transplantation
- New or variables or adapt variables
- Eligibility for clinical trials

Executive Committee ECFSPR
Egil Bakkeheim, Norway, Director ECFSPR
Laura Kirwan, Ireland
Uros Krivec, Slovenia
Lutz Naehrlich, Germany, Pharmacovigilance Study Manager
Kerry Laidlaw, UK, Patient Representative
Domenique Zomer, The Netherland

Non-Voting Members:
Christine Dubois, ECFS Executive Coordinator
Lieven Dupont, ECFS-CTN Representative
Jacqui Van Rens, ECFSPR Representative

POLAND IN ECFS PATIENT REGISTRY

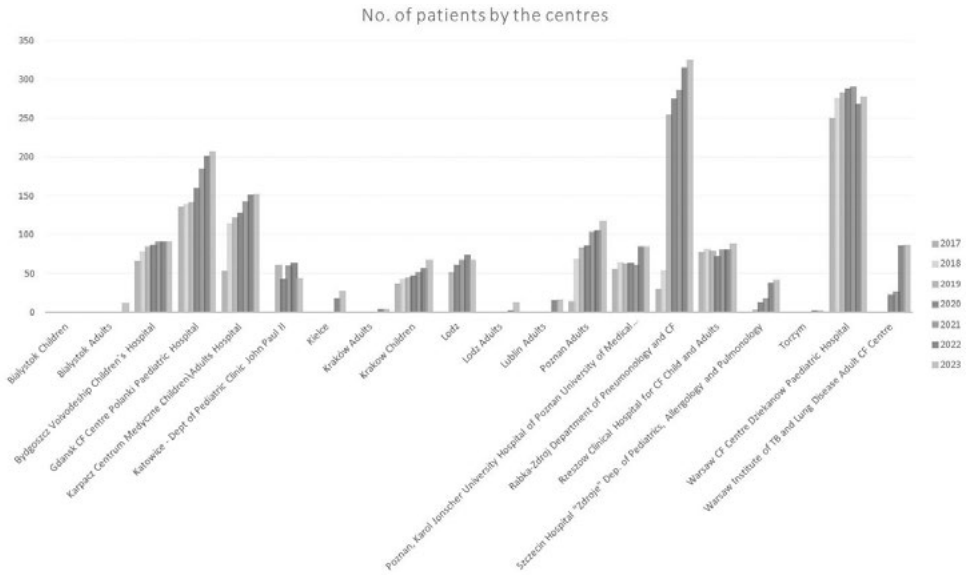
Prof. dr hab. n. med. Dorota SANDS
Institute of Mother and Child , Warsaw, POLAND, President of Polish CF Society

Dane za rok 2023

Odsetek dorosłych		
18+	**734**	42%
child	**998**	58%
Suma końcowa	**1732**	100%

All CF patients	
Ages 0 to <12mos	9
Ages 1 to <2	27
Ages 2 to <6	212
Ages 6 to <12	363
Ages 12+	1121

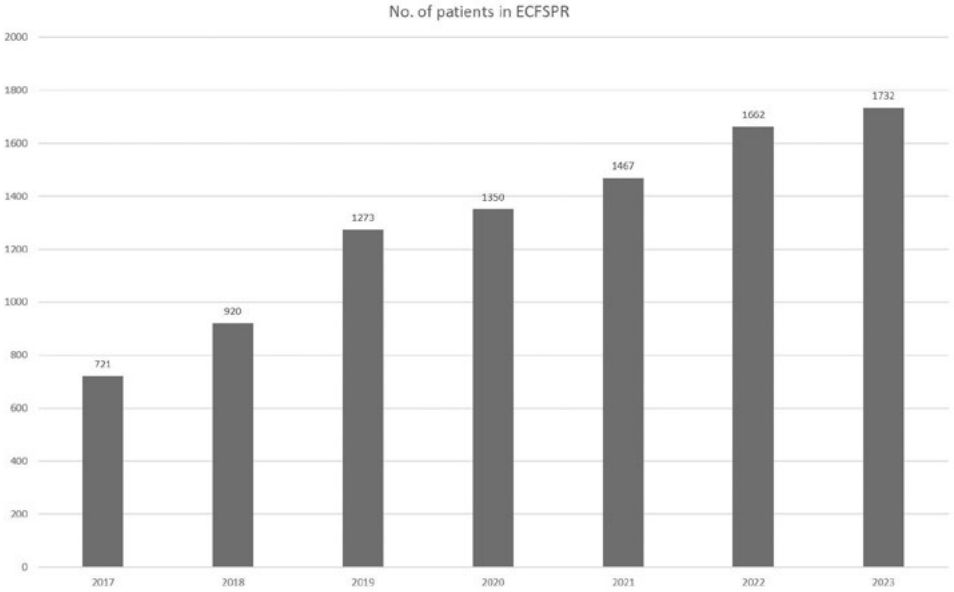
18 CF Centers are part of ECFSPR in 2023



Wiek		**Patients with at least 1 f508del mutation**	
Średnia	17,7	**F508del on ≥ 1 allele**	**Number of Patients**
Mediana	15,7		
Odchylenie standardowe	11,1	Ages 0 to <12mos	6
Wariancja próbki	124,2	Ages 1 to <2	25
Kurtoza	0,7	Ages 2 to <6	187
Skośność	0,9	Ages 6 to <12	296
Zakres	63,5	Ages 12+	972
Minimum	0,8		
Maksimum	64,2	Total	1486
Licznik	1732	**Total aged > 2**	**1455 (84%)**

Allelic frequencies of mutations

mut	**Frequency**	**Percent**
F508del	1974	64,81
CFTRdele2,3	131	4,30
3849+10kbC->T	120	3,94
unknown	67	2,20
G542X	65	2,13
N1303K	54	1,77
2143delT	53	1,74
R553X	47	1,54
1717-1G->A	36	1,18
2184insA	36	1,18
W1282X	34	1,12



Załącznik **B.112**

LECZENIE CHORYCH NA MUKOWISCYDOZĘ
(ICD-10: E84)

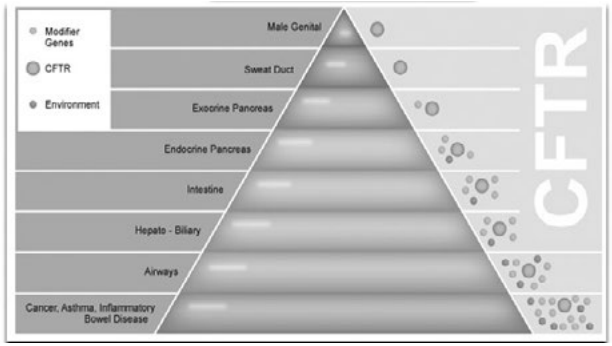
kalydeco iwakaftor	KALYDECO®
ORKAMBI lumakaftor/iwakaftor	ORKAMBI®
symkevi tezakaftor/iwakaftor + kalydeco iwakaftor	SYMKEVI® + KALYDECO®
kaftrio eleksakaftor/tezakaftor/iwakaftor + kalydeco iwakaftor	KAFTRIO® + KALYDECO®

From 01.04.2025,
the drug program has been expanded
and all patients from 2 years of age
with al least one F508del mutation will receive Kaftrio.

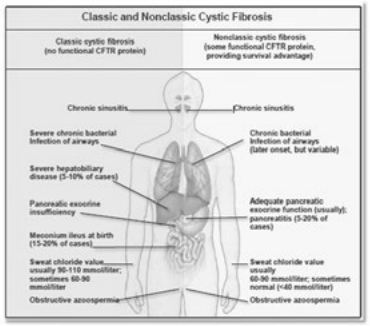
NEW DIRECTIONS IN GENETIC RESEARCH

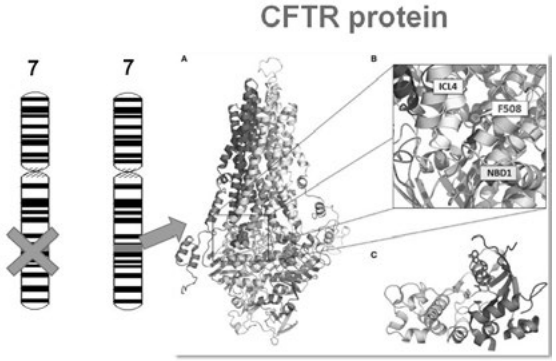
prof. MUDr. Milan MACEK, DrSc.
Department of Biology and Medical Genetics , Charles University and University Hospital Motol, Prague, CZECHIA

CFTR is expressed in an organ specific manner



„CF syndrome“ is recessive Mendelian syndrome caused by pathogenic variants in the CFTR gene (MIM:602421)

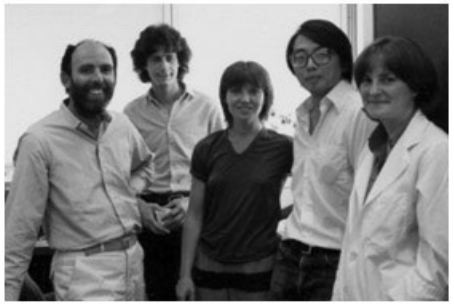




www.nejm.org/doi/pdf/10.1056/NEJMe020070

doi.org/10.3389/fphar.2012.00160

CFTR1: locus specific database since 1990 (>2,200 variants)



Basics of CF pathogenesis

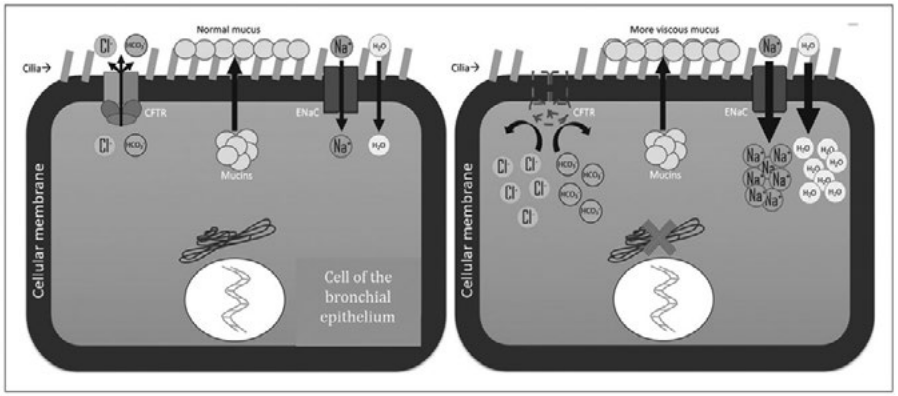
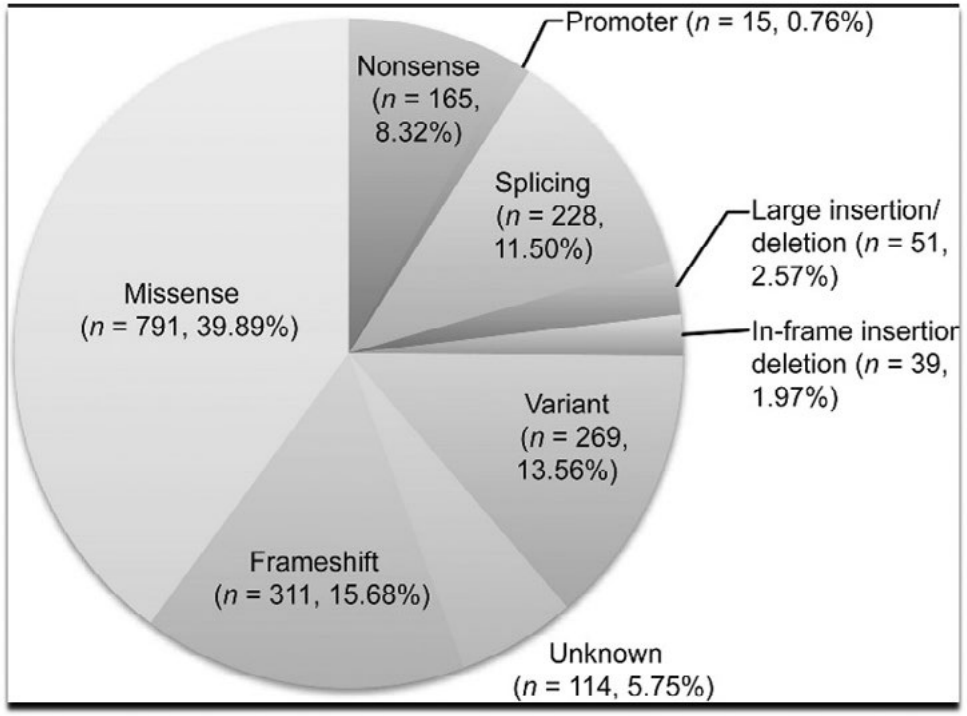


Figure 2. The function of the CFTR channel, the function of the ENaC channel, and mucin secretion for the formation of normal airway surface fluid are illustrated. **A.** Cell dynamics in a healthy context. **B.** Cell dynamics in CF in the context of the p.F508del mutation. The intradomain defect affects full-length CFTR protein assembly and post-translational stability, whereby deletion of phenylalanine at position 508 in NBD1 leads to a CFTR trafficking defect.
CFTR, cystic fibrosis transmembrane conductance regulator; ENaC, epithelial sodium channel.

Types of CFTR mutations: molecular pathology

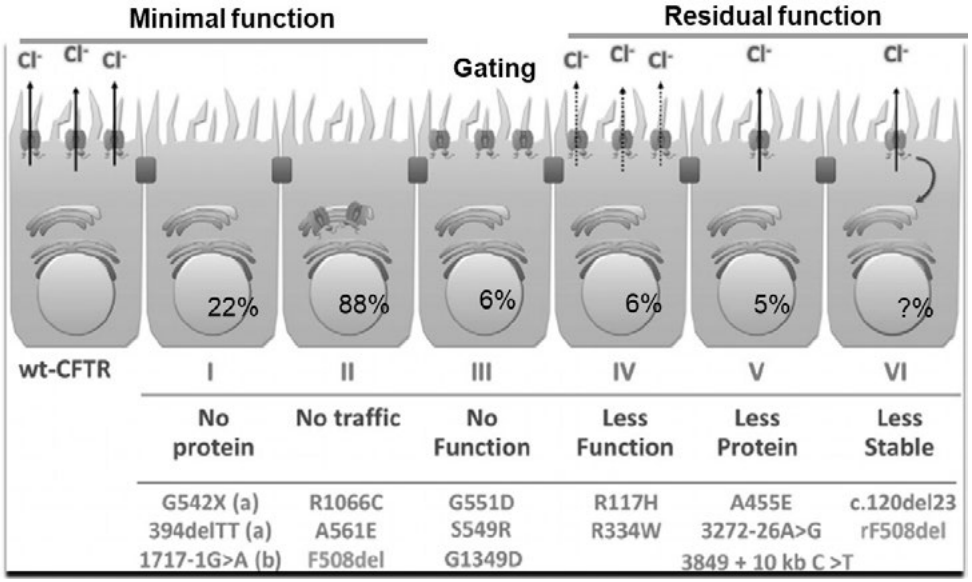


„Genomics“ HUGO/HGVS vs. „Legacy“ CFTR1/CFTR2: pitfalls of variant nomenclature

Type of change	HUGO/HGVS		*CFTR* mutation database	
	DNA	Protein*	DNA	Protein*
deletion	c.3659delC	p.Thr1220fs	3791delC	
deletion	c.3527delC	p.Thr1176fs	3659delC	

Identical mutations could have different „names“
„Legacy nomenclature“
(c.1521_1523delCTT x F508del x p.Phe508del x ΔF508)

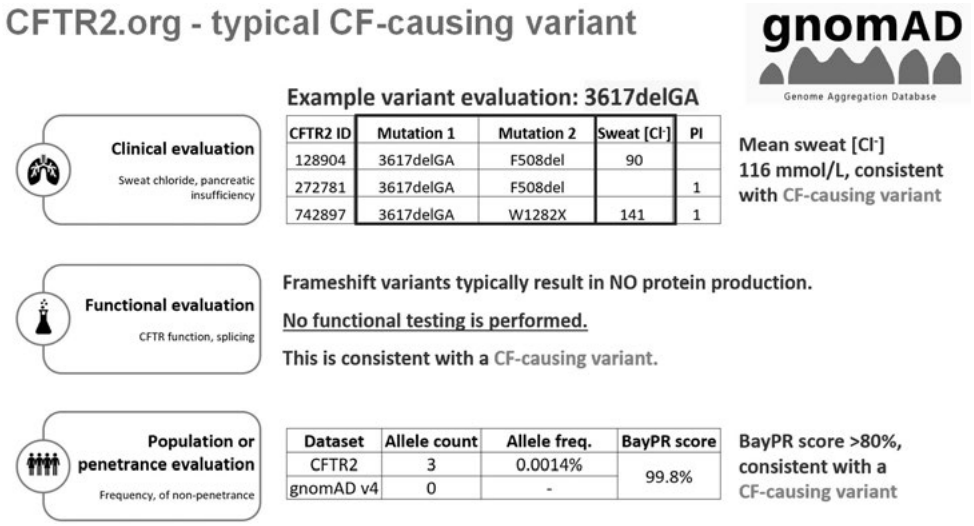
Classes of CFTR variants – „correctors versus potentiators“



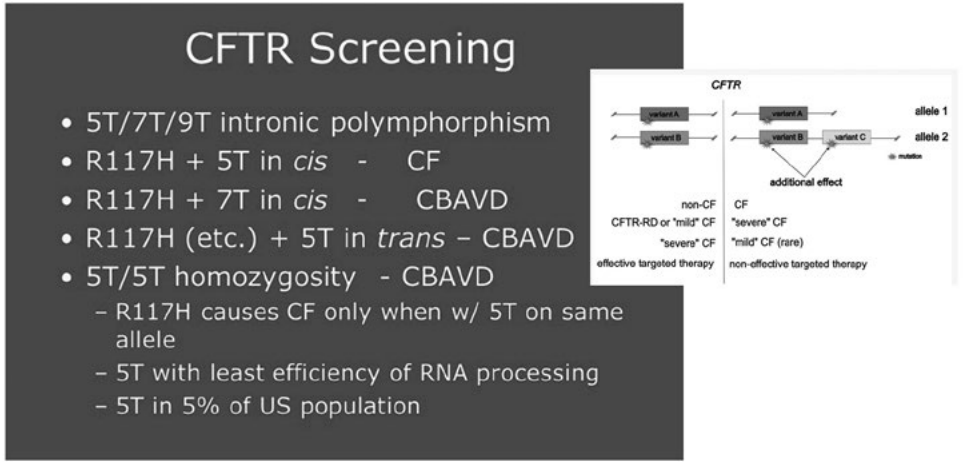
Approx. 10% Threshold Note: Class VII no mRNA
dx.doi.org/10.1016/j.pharmthera.2014.06.005; DOI 10.3389/fphar.2024.1476331; % = relative incidence; pwCF with variants in two classes are counted twice

CFTR – genetic modifiers per organ system- research vs. diagnostics

Objective assessment of CFTR pathogenesis and eligibility for variant-specific therapies



„Nineties Oldies but Goldies“ 5/7/9 T /IVS-8 T(n)/ issue



Theratyping

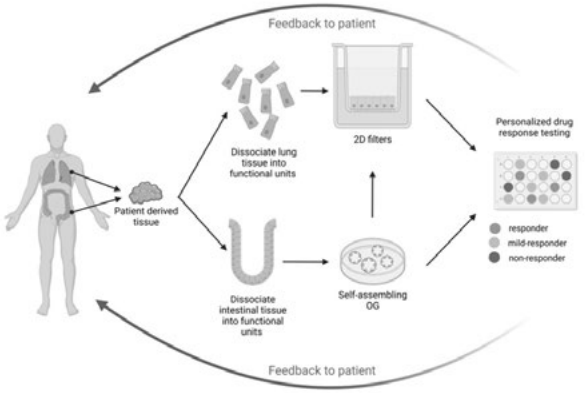


Figure 2. Theratyping strategies. Nasal and intestinal biopsies can be collected and utilized to derive long-term cultures that can be utilized for functional assays measuring CFTR function, as described in the text. The results can inform the clinician on the response of the specific CFTR variants and combinations expressed by the proband thus providing directions on the choice of the most appropriate treatment.

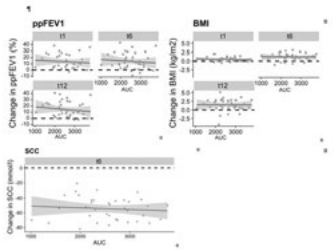
Table 1
Theranostics vs theratyping.

	Challenges	Advantages	Disadvantages
Theratyping	- Limited physiological relevance - Hurdles in translation to human therapy - Species-specific differences - Genetic instability for long-term use - Relies on supplier theratyping - Requires phase III trials (large cohorts) to demonstrate efficacy (new drugs)	- Easy to use - Cost-effective for common variants - Low technical requirements - Feasible standardization - FDA approved for label extension	- Misses patient-specific responses - Treatment optimization by drug screening not possible - False results for some variants - False negatives for some genotypes (e.g., 2 low responder variants)
Theranostics	- Technical complexity - Access to patients' samples - Requires centre accreditation - Inter-patient variability	- Human-relevant disease modelling - Personalized/precision medicine - Amenable to optimize treatment by drug screening - Amenable to shipping and biobanking - Cost-effective for rare variants - Accepted in some countries for access to drugs - Allow 'basket trials' for rare variants - Pre-identifies responders for trials of novel drugs and also non-responders avoiding false expectations	- Resource intensive - Limited access to pwCF-derived samples

Theranostics – CZ experience

EUROPEAN RESPIRATORY JOURNAL
RESEARCH LETTER
E. FURSTOVA ET AL.

Precision medicine in cystic fibrosis: predictive role of forskolin-induced swelling assay



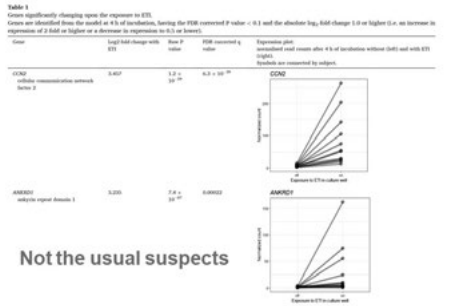
The FIS assay generally indicates responsiveness to CFTRm, but cannot discriminate between high and low responders within the F508del homozygotes. Higher FIS response in intestinal organoids did not predict better clinical outcomes.

Short Communication

Gene expression profile of intestinal organoids from people with cystic fibrosis upon exposure to elexacaftor/tezacaftor/ivacaftor

Ondrej Cinek[a,b,*], Eva Furstova[b], Stepanka Novotna[b], Klara Hubackova[a], Tereza Dousova[b], Lucie Borek-Dohalska[a], Pavel Drevinek[a]

[a] Department of Medical Microbiology, Second Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czechia
[b] Department of Paediatrics, Second Faculty of Medicine Charles University and Motol University Hospital, Prague, Czechia



Not the usual suspects

Upregulation inflammatory response!

Table 2. List of CFTR mutations eligible for the treatment with Ivacaftor and approved by the FDA. Available from https://www.vertexgps.com, accessed on 14 November 2022.

711 + 3A→G	D1152H	G194R	I807M	Q237H	R553Q	S1159F
2789 + 5 G→A	D1270N	G314E	I1027T	Q359R	R668C	S1159P
3272–26A→G	E56K	G551D	I1139V	Q1291R	R792G	S1251N
3849 + 10kbC→T	E193K	G551S	K1060T	R74W	R933G	S1255P
A120T	E822K	G576A	L206W	R75Q	R1070Q	T338I
A234D	E831X	G970D	L320V	R117C	R1070W	T1053I
A349V	F311del	G1069R	L967S	R117G	R1162L	V232D
A455E	F311L	G1244E	L997F	R117H	R1283M	V562I
A1067T	F508C	G1249R	L1480P	R117L	S549N	V754M
D110E	F508C/S1251N	G1349D	M152V	R117P	S549R	V1293G
D110H	F1052V	H939R	M952I	R170H	S589N	W1282R
D192G	F1074L	H1375P	M952T	R347H	S737F	Y1014C
D579G	G178E	I148T	P67L	R347L	S945L	Y1032C
D924N	G178R	I175V	Q237E	R352Q	S977F	

TI

Table 3. List of CFTR mutations eligible for the treatment with Tezacaftor/Ivacaftor and approved by the FDA. Patients should carry F508del mutation in both alleles or at least one copy of the mutations listed here. Available from https://www.vertexgps.com, accessed on 14 November 2022.

546insCTA	D1152H	G126D	I601F	P5L	R334L	S912L
711 + 3A→G	D1270N	G178E	I618T	P67L	R334Q	S945L
2789 + 5 G→A	E56K	G178R	I807M	P205S	R347H	S977F
3272–26A→G	E60K	G194R	I980K	Q98R	R347L	S1159F
3849 + 10kbC→T	E92K	G194V	I1027T	Q237E	R347P	S1159P
A120T	E116K	G314E	I1139V	Q237H	R352Q	S1251N
A234D	E193K	G551D	I1269N	Q359R	R352W	S1255P
A349V	E403D	G551S	I1366N	Q1291R	R553Q	T338I
A455E	E588V	G576A	K1060T	R31L	R668C	T1036N
A554E	E822K	G576A/R668C	L15P	R74Q	R751L	T1053I
A1006E	E831X	G622D	L206W	R74W	R792G	V201M
A1067T	F191V	G970D	L320V	R74W/D1270N	R933G	V232D
D110E	F311del	G1069R	L346P	R74W/V201M	R1066H	V562I
D110H	F311L	G1244E	L967S	R74W/V201M/D12	R1070Q	V754M
D192G	F508C	G1249R	L997F	R75Q	R1070W	V1153E
D443Y	F508C/S1251N	G1349D	L1324P	R117C	R1162L	V1240G
D443Y/G576A/R668C	F508del	H939R	L1335P	R117G	R1283M	V1293G
D579G	F575Y	H1054D	L1480P	R117H	R1283S	W1282R
D614G	F1016S	H1375P	M152V	R117L	S549N	Y109N
D836Y	F1052V	I148T	M265R	R117P	S549R	Y161S
D924N	F1074L	I175V	M952I	R170H	S589N	Y1014C
D979V	F1099L	I336K	M952T	R258G	S737F	Y1032C

ETI

Table 4. List of CFTR mutations eligible for the treatment with Ivacaftor/Tezacaftor/Elexacaftor and approved by the FDA. Patients should carry at least one copy of the mutations listed here. Available from https://www.vertexgps.com, accessed on 14 November 2022.

3141del9	E193K	G551D	I980K	P574H	R352W	S1255P
546insCTA	E403D	G551S	I1027T	Q98R	R553Q	T338I
A46D	E474K	G576A	I1139V	Q237E	R668C	T1036N
A120T	E588V	G576A/R668C	I1269N	Q237H	R751L	T1053I
A234D	E822K	G622D	I1366N	Q359R	R792G	V201M
A349V	F191V	G628R	K1060T	Q1291R	R933G	V232D
A455E	F311del	G970D	L15P	R31L	R1066H	V456A
A554E	F311L	G1061R	L165S	R74Q	R1070Q	V456F
A1006E	F508C	G1069R	L206W	R74W	R1070W	V562I
A1067T	F508C/S1251N	G1244E	L320V	R74W/D1270N	R1162L	V754M
D110E	F508del	G1249R	L346P	R74W/V201M	R1283M	V1153E
D110H	F575Y	G1349D	L453S	R74W/V201M/D1270	R1283S	V1240G
D192G	F1016S	H139R	L967S	R75Q	S13F	V1293G
D443Y	F1052V	H199Y	L997F	R117C	S341P	W361R
D443Y/G576A/R668C	F1074L	H939R	L1077P	R117G	S364P	W1098C
D579G	F1099L	H1054D	L1324P	R117H	S492F	W1282R
D614G	G27R	H1085P	L1335P	R117L	S549N	Y109N
D836Y	G85E	H1085R	L1480P	R117P	S549R	Y161D
D924N	G126D	H1375P	M152V	R170H	S589N	Y161S
D979V	G178E	I148T	M265R	R258G	S737F	Y563N
D1152H	G178R	I175V	M952I	R334L	S912L	Y1014C
D1270N	G194R	I336K	M952T	R334Q	S945L	Y1032C
E56K	G194V	I502T	M1101K	R347H	S977F	
E60K	G314E	I601F	P5L	R347L	S1159F	
E92K	G463V	I618T	P67L	R347P	S1159P	
E116K	G480C	I807M	P205S	R352Q	S1251N	

+ French compassionate programme

Table 5: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA

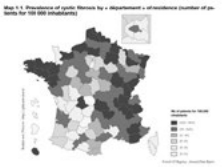
3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del**	*H939R*	*M152V*	*R347H*	*S1255P*
A534E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1054I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G453V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)]*.
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Expanded access to ETI

- 6 years, w/o F508del
- 47 FR CF centres
- 4–6 week trial
- response was determined by a centralised committee based on the evolution of clinical data, lung function, and sweat Cl^-.

N1303K, R334W, R1066C,
2789+5G>A, 3849+10kbC>T,
3272-26A>G, **3041-15T>G**



> 10% -> „compassionate“ programme using the „French model“

Table 2b: Borderline responsive variants (colored in grey in Fig. 4C)

Mean (Fsk) Baseline Function (%WT)	Mean Response to ELX/TEZ/IVA (%WT)	**Variant (# of CFTR genes carrying the variant)** variants are separated by comma, variants for complex alleles (with two or three *in cis* variants) are separated by semicolon
<10	<10	H147del (NA), A155P (1), S308P (1), S341P (23), V456F (4), K464E (4), T465N (2), A559V (2), R560K (15), Y563N (33), L633P (1), V1020E (1), M1137K (1), 3761T->G (1), I1234Vdel (NA), G1265V (3), R1283M (7), N1303K (2226), 4193T->G (1), I1366N (5)
	≥10	L15P;L1253F (1), R74Q;V201M;D1270N (1), R74W;V201M;L997F (2), P99L (7), R117H (1852), R117L;L997F (4), R117P (5), H146R (2), G149R;G576A;R668C (1), M150K (2), Y161C (1), H199Y (22), G226R (1), R334L (15), T338I (52), R347P (528), V392G (5), V456A (27), G480D (1), I502T (16), F508del;N1148S (1), D513G (8), I521S (1), S549R
Mean (Fsk) Baseline Function (%WT)	Mean Response to ELX/TEZ/IVA (%WT)	**Variant (# of CFTR genes carrying the variant)** variants are separated by comma, variants for complex alleles (with two or three *in cis* variants) are separated by semicolon
≥10	<10	(T->G) (11), R555G (2), Y563H (2), Y569C (4), F587I (2), G628R (11), S912L;G1244V (3), Y914C (1), D993A (4), D993G (2), D993Y (2), G1003E (2), A1025D (1), G1061R (24), E1104K (1), E1104V (1), M1210K (3), G1249E (1), D1270Y (1), W1282R (6), R1283G (1), R1283S (5), 4209TGTT->A (6), I1398S (2)
	≥10	I1366T (3)
		R31C (23), R74W;D1270N (22), P140S (4), Q151K (1), M152V* (5), Q237H (4), G253R (1), A309D (3), V322M (1), R334Q (8), I336L (1), R347H (195), R347L (3), G424S (3), G451V (1), G461R (1), A534E (1), G545R (1), D565E(T->G) (1), G576A;S1359Y (1), S589N* (9), D651H (1), R709Q (2), R792G (3), S902R (1), S912L (6), Y919C (2), V920L (2), V944A (1), L967F;L1096R (1), S977F (13), S977F;R1438W (1), L1011S (2), G1047R (2), R1048G (2), A1081V (1), T1086A (1), Y1092H (1), M1137V (2), R1162Q (1), I1203V (1), E1228K (1), V1240G (3), V1293I (1), A1374D (1), Y1381H (1), S1426F (1), D1445N (4), A1466S (1)

* May affect splicing

Table 2c: Non-responsive variants (colored in red in Fig. 4C)

Mean (Fsk) Baseline Function (%WT)	Mean Response to ELX/TEZ/IVA (%WT)	**Variant (# of CFTR genes carrying the variant)** variants are separated by comma, variants for complex alleles (with two or three *in cis* variants) are separated by semicolon
<10	<10	M1K (1), M1L (2), M1T (9), M1V (27), 149del84 (2), W57G (10), W57R (8), A72D (2), L73P (1), G85E (610), G85R (1), G85V (3), V93D (1), K95E (1), 420del9 (3), L102P (1), L102R (4), L102R;F1016S (1), L127fsdup (1), L137R (2), H147P (1), 591del18 (3), M156R (3), T164P (2), H199R (7), L227R (29), W277X (NA), R334W (425), 1140-1151dup (2), R352W (6), S364P (8), 1234insACAAAA (2), M394R (1), Q452P (4), 1491-1500del (2), G458R (1), G458V (5), L467P (38), S489P (NA), c.1493-1507del15 (1), T501I (1), I506S (6), I506T (12), I507del (647), Y517C (3), V520F (156), C524R (5), L558S (34), A559E (3), A559P (2), A559T (91), R560G (1), R560S (6), R560T (343), A561E (17), Y563D (7), Y569D (45), L571S (5), D572N (1), D579Y (2), C590Y (1), L594P (2), I601T (1), T604I (3), 1949del84 (25), H609R (10), L610S (1), A613T (7), L617del (1), L619S (3), E815X (NA), G832X (NA), Y913C (7), Y913S (2), Y917C (1), G921E (NA), 2949del84 (2), 3131del15 (5), I1005R (5), 3199del6 (74), I1023R (1), R1066C (220), R1066L (2), 3410T->C (2), W1098R (11), Q1100P (14), M1101R (4), M1105R (1), A1319E (4), L1324P (4), L1335P (19)

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but legal/liability issues…

Table 8. Additional *CFTR* Variants Responsive to VNZ/TEZ/D-IVA

3195del6	A561E	G149R	I1234Vdel6aa	L1065P	Q1100P	R1066L	R560S	V520F
3199del6	A613T	G91R	I1398S	M1101R	Q452P	R1066M	R560T	Y569C
A559T	A72D	H199R	I506T	P99L	R1066C	R516G	T604I	Y913C
A559V	D513G	H609R	L102R					

Challenges of gene therapy

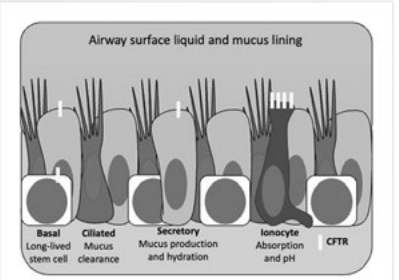


FIGURE 3
Surface airway target cell types for CFTR gene therapy based on distribution of functional tasks. Basal stem cells (white) repopulate the airway and express low levels of CFTR (yellow). Secretory cells (green) produce mucus and antimicrobial peptides and also express low levels of CFTR which functions to hydrate airway surface liquid. Ciliated cells (red) sweep hydrated mucus from the airway and produce little to no CFTR. Ionocytes (purple) express high CFTR which functions in pH balance and is thought to mediate bacterial killing. Given that multiple cell types perform CFTR functional tasks, basal stem cells would be the ideal target for a durable gene therapy so that CFTR can be retained in all daughter cells.

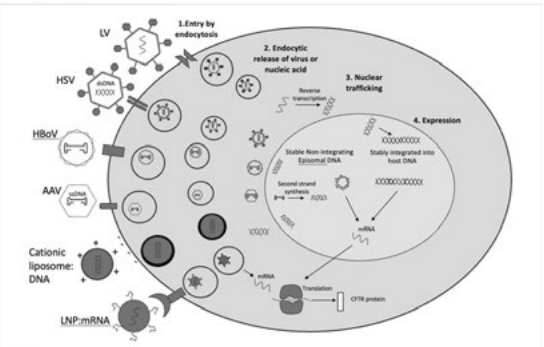


FIGURE 4
Entry mechanisms and post-entry processing of viral and non-viral vectors considered for CFTR gene therapy. In step 1, vectors bind to cell surface receptors or molecules or fuse directly to the plasma membrane (Cationic liposome: DNA) and are endocytosed. In Step 2, viral particles or nucleic acids are released into the cytoplasm. This is a rate limiting step for some viruses which need an expression enhancer such as doxorubicin to improve endocytic release and nuclear trafficking. In step 3, vectors containing DNA are trafficked to the nucleus while mRNA cargos are translated in the cytoplasm. In step 4, some cargos are integrated into the host chromosome (lentivirus cargo) while others remain episomal. Integrated cargos will be retained after every division while episomal cargos will be diluted out with cell division. mRNA cargos will be transient in transduced cell.

Personalised medicine in CF – CFTRm questions for further research

Points for clinical practice

- CFTR modulators partially restore ion transport and lead to a rapid and major improvement in respiratory symptoms and lung function.
- CFTR modulators may also improve pancreatic insufficiency in young children.
- CFTR modulators may improve diabetes control.
- CFTR modulators improve fertility in females.
- CFTR modulators improve chronic rhinosinusitis.

Questions for future research

- What will be the extent of improved survival on CFTR modulators?
- What will be the long-term progression of lung function on CFTR modulators?
- What will be the long-term effect of CFTR modulators on airway pathogens and inflammation?
- What will be the CF disease of pwCF when CFTR modulators are started in infancy or early childhood?
- How will the usual complications of CF evolve on CFTR modulators?

Classification of *CFTR* variants

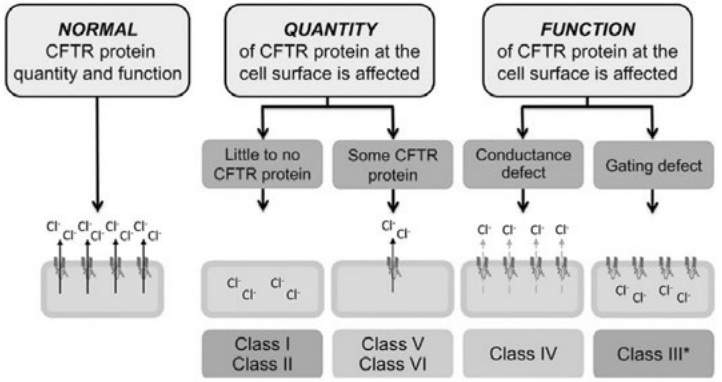
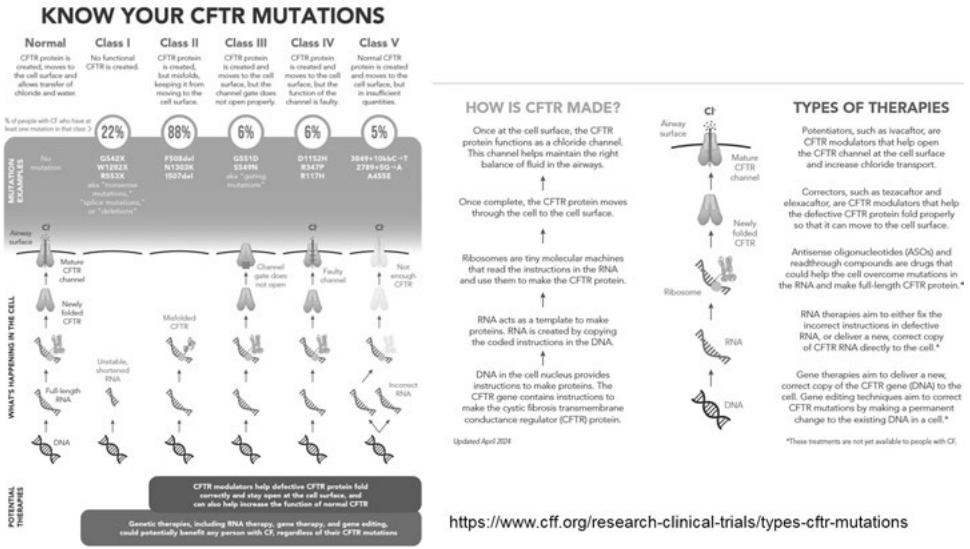


Fig. 1. A functional classification of CFTR gene variants (Adapted from Foil et al. [24]).



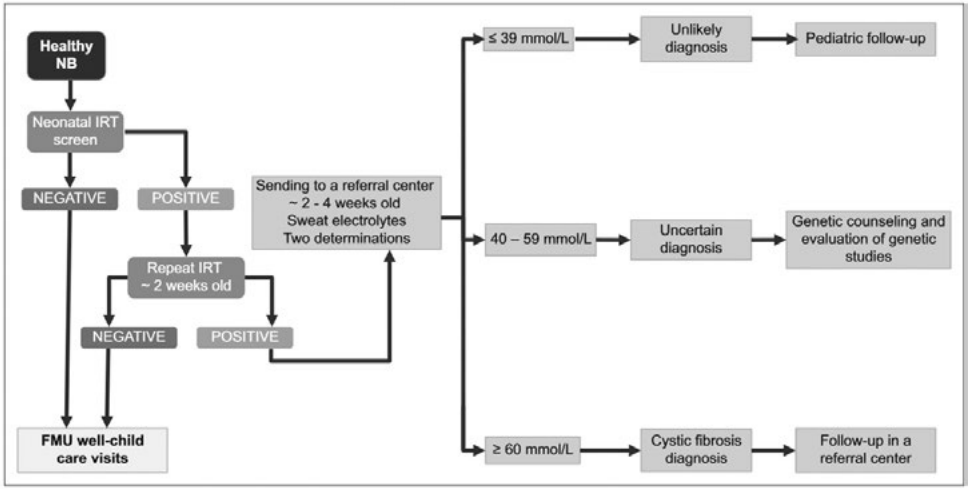


Figure 4. Cystic fibrosis diagnosis algorithm.
NB, newborn; FMU, family medicine unit; IRT, immunoreactive trypsin.

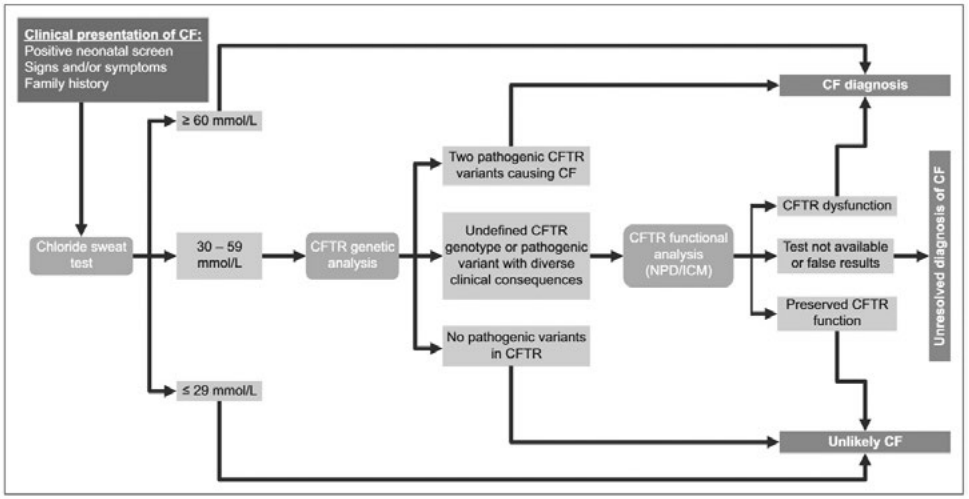


Figure 3. Diagnostic algorithm for individuals with high suspicion of cystic fibrosis.
CFTR, CF transmembrane conductance regulator; NPD, nasal potential difference; ICM, intestinal current measurement.

Conclusions

- **The changing demography and epidemiology of CF world-wide requires a robust and reliable CFTR sequencing by MPS(NGS)**

- **Introduction of CFTR sequencing at a global level, especially in less resourced countries, where sequencing of the entire gene establishes CF diagnosis and „leapfrogs" the gradual development of CF diagnostics and care.**

- **CFTR sequencing could foster development of newborn screening programs when CF at birth prevalence is decreasing due to preconception screening in Europe and N. America.**

- **CFTR sequencing leads to the adjustment of the current diagnostic algorithms, mainly optimized for European-derived populations and support accurate diagnosis in "emerging" CF populations with different CF presentations/phenotypes.**

- **CFTR sequencing improves knowledge on the correlation between CFTR genotype and clinical phenotype for less frequent CFTR variants, including the role of genetic modifiers that could negatively affect CFTR modulator therapies**

WHAT INFORMATION DOES GENETIC TESTING IN CYSTIC FIBROSIS PROVIDE US ?

Kamila CZERSKA, MD, Mgr. Karolina KOWALCZYK
POLAND

Chromosome 7
27 exons
250 000 base pairs (bp)

The CFTR protein is called an ion channel and helps to maintain the balance of salt and water on many surfaces in the body. CF occurs when CFTR protein is either not made correctly, or not made at all.

Traditional genotype and the genotype according to HGVS (The Human Genome Variation Society) recommendations should be included in results of genetic tests:

Wynik / RESULT

Nazwa genu / loci	CFTR
Genotyp	Phe508del/Phe508del
Genotyp zgodny z HGVS v.2 (na poziomie cDNA)	LRG_663 t1(NM_000492.3): c.1521_1523delCTT(;)(1521_1523delCTT)
Genotyp zgodny z HGVS v.2 (na poziomie białka)	NP_000483.3: p.(Phe508del)(;)(Phe508del)
Wynik badania	nieprawidłowy

DNA level c.1521_1523delCTT
Protein p.Phe508del
Legacy name F508del

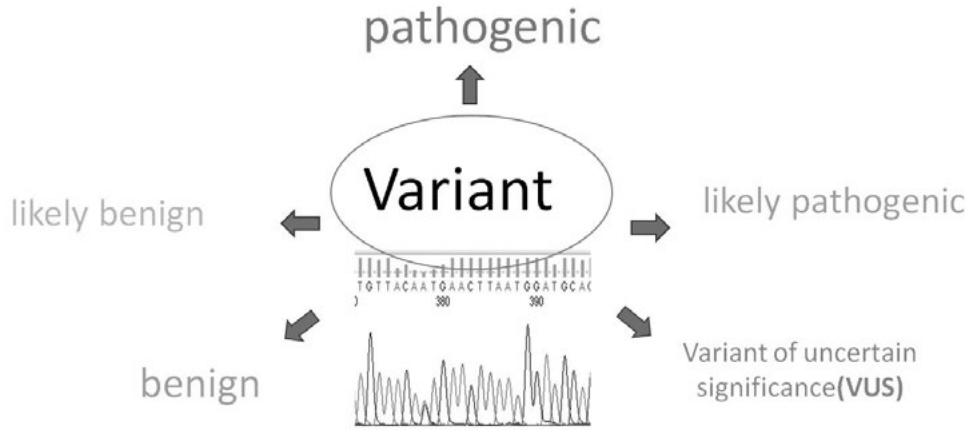
Databases are used to evaluate the clinical significance of variants

CFTR2 contains information from more than 88,000 patients from the United States, Canada and Europe, which was collected by the CFTR2 team from national cystic fibrosis patient registries

CFTR France contains information from about 6,000 individuals. Variants are gathered from 10 laboratories from all over FRANCE with a particular focus on phenotypes.

All variants	1 167	989	4 151
CF-causing	1 085	499	P,LP: 1 388
Non CF-causing	27	63	B,LB: 1 067
VUS	11	427	VUS: 1 696
VVCCs	55	-	-

CF- causing variant - F508del; dele2,3(21kb);G542X, N1303K
Non CF-causing variant - R31C; I148T; L997F, R1161L
Variant of varying clinical consequence - F1052V; R117H,7T, D1152H, R334Q, P750L
Variant of uncertain significance - 296+28A>G; R153K; R31L



Classification of genetic variants according to ACMG

Classification of variants based on their effect on protein
missens: single nucleotide change leads to amino acid change :p.N1303K, p.F1052V, p.R334W, p.D1152H

nonsens: insertion of the STOP codon causes premature termination of the protein:p.G542X, p.W1282X, p.K710X, p.R1162X

insertion/deletion or insdel: insertion or deletion of nucleotides leads to a change or no change in the reading frame:
inframe: deletion/insertion of one amino acid: p.F508del
frameshift: change of all other amino acids : c.2184insA
splice site: disruption of the splicing process : c.1717-1G>A
Identification of the type of variants allows the choice of treatment

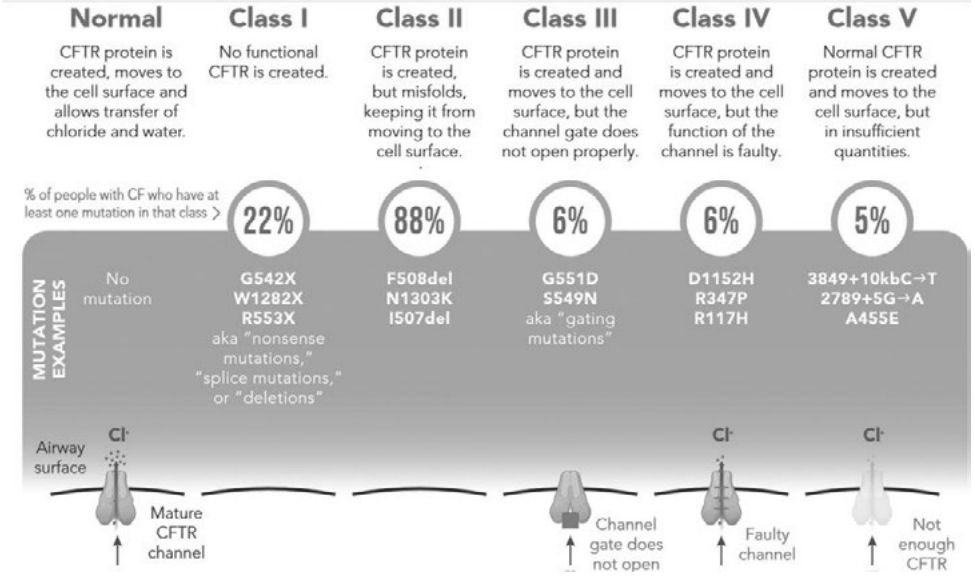
Genotype-phenotype correlation
The genotype-phenotype correlation shows how different variants of the CFTR gene contribute to the clinical variability of cystic fibrosis.

GENotype – combination of pathogenic variants
FENotype – features present in the patient (e.g. symptoms)

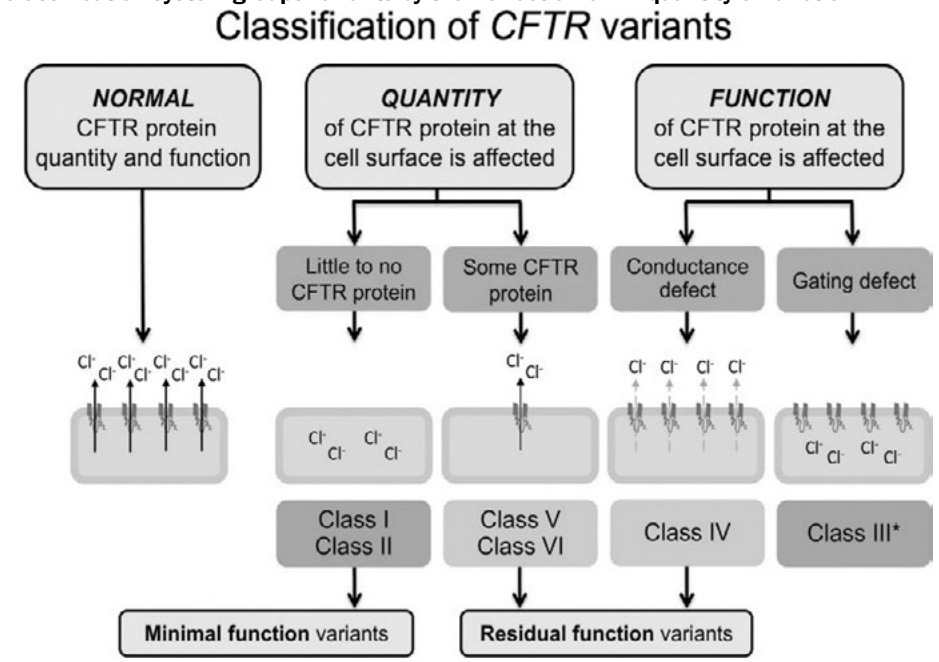
severe – mild lung disease
PI-PS (assessment of pancreatic function)

However, it is important to remember that CF is characterized by high phenotypic variability occurring even in patients with the same genotype. This is due to the intervention of modifier genes that interact with both the CFTR gene and environmental factors.

Classification system that groups variants according to the problems they cause in the production of the CFTR protein



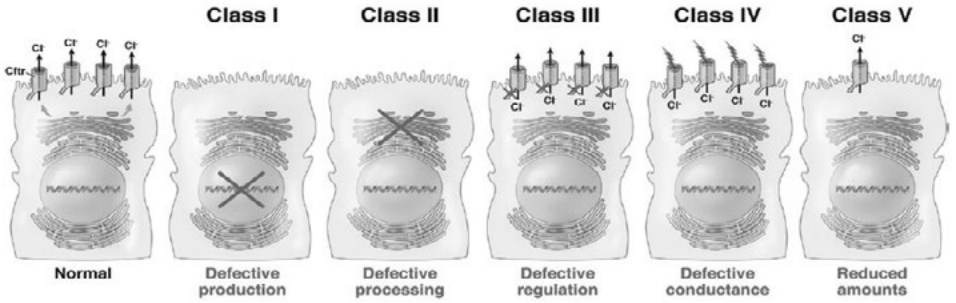
Classification system groups variants by their effect on CFTR quantity or function



A functional classification of CFTR gene variants. *Foil KE, Powers A, Raraigh KS, Wallis K, Southern KW, Salinas D. The increasing challenge of genetic counseling for cystic fibrosis. J Cyst Fibros 2019;18:167–74. doi:10.1016/j.jcf.2018.11.014*

CFTR modulators adress various problems caused by diffrent types of the CFTR variants
The drug ivacaftor helps people with gating mutations by forcing the gate on the CFTR channel to stay open. This enables chloride to move through the channel and reduces the symptoms of CF.

The drug combination elexacaftor/tezacaftor/ivacaftor works by enabling CFTR protein with an F508del mutation to fold in a more correct shape, and then activates the protein to allow more chloride to pass through.



nonsense variants - do we have treatment??
- About 10 - 15 percent of people with CF have a combination of two nonsense or nonsense + another rare mutation that do not produce an active CFTR protein.

- **Such patients cannot benefit from CFTR modulators**. They need therapy to fix the cause of their disease.

- Nonsense mutations (also known as “X” or “stop” mutations):e.g., p.G542X, p.W1282X, c.2184insA, c.2143delt cause premature termination of CFTR protein production.

- Strategies for restoring CFTR activity in people with nonsense or rare mutations - RNA therapy, gene editing, gene therapy.

Conclusion
Genetic testing is an important part of diagnosing cystic fibrosis. It helps identify and classify variants in the CFTR gene, which not only confirms the diagnosis but also helps choose the right treatment, such as CFTR modulators. These treatments target specific problems caused by certain mutations.

Genetic tests are also used in The Newborn Screening Program, which enables early detection of cystic fibrosis cases and quick start of treatment, improving the health of patients.

ADVANCES IN THE RESTORATION OF CFTR IN CHILDREN (AND PWCF WITH "MILD"DISEASE)

Prof. Malena COHEN-CYMBERKNOH, MD
Hadassah-Hebrew University Medical Center, Jerusalem, ISRAEL

Growing up with CF

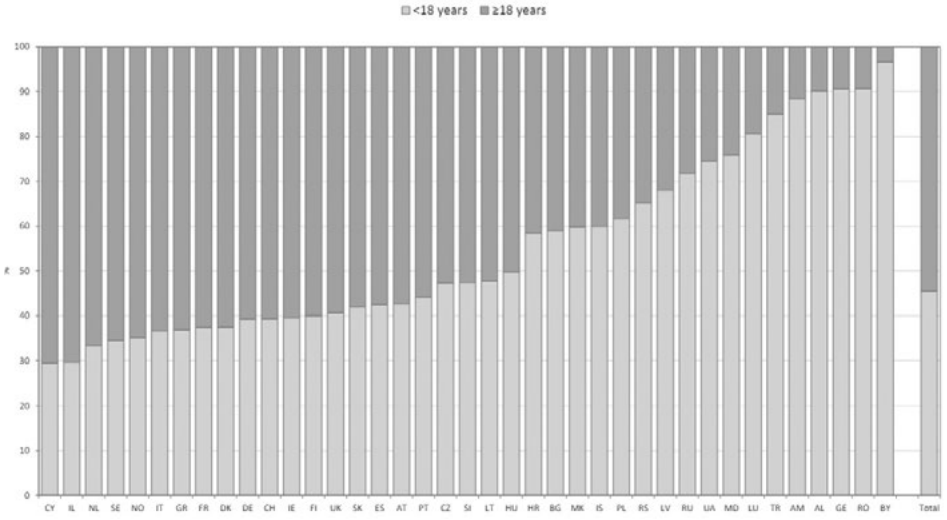
CF is a progressive disease, meaning that symptoms tend to worsen over time in people with CF (pwCF)

Aggressive management and advances in treatment may delay, but do not prevent progression of lung disease

In children and young people, the disease may be less severe initially, and they may have fewer complications

However, as they age, lung function may decline, and they may experience more frequent and severe respiratory infections, more pulmonary exacerbations (PEx) and lung deterioration

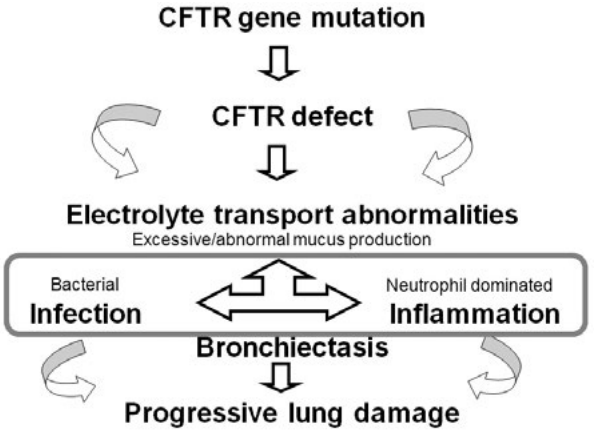
Proportion of children (<18 years) and adults (≥18 years) **52% adults, 48% children**



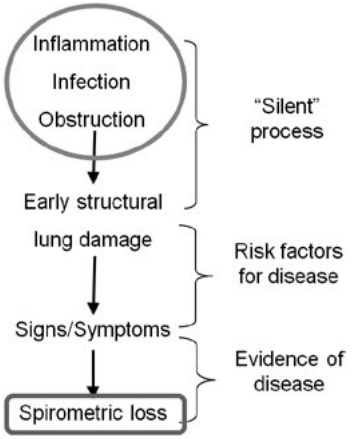
Early CF pulmonary inflammation - how early does it start ?

- Inflammation was shown to be present in infants as young as 4 weeks and with no bacterial colonization
- Colonization by CF pathogens enhances the inflammatory response
- Bronchiectasis are present even in infants and preschool children who were diagnosed with CF by NBS

CF Pathogenesis



Stages of CF Lung Damage



Airway inflammation in cystic fibrosis: molecular mechanisms and clinical implications

Thorax 2013

Table 1 Methods of assessing inflammation in the cystic fibrosis airways: pros and cons

Parameter	Method	Advantage	Disadvantage
Lung function	Spirometry	Non-invasive Reproducible	Poor correlation with inflammation Does not localise disease Special equipment required for small children
	Multiple breath washout (MBW)	Non-invasive and reproducible Identifies early small airway disease Applicable to small children	Requires special equipment Less sensitive in severe disease
Respiratory samples	Sputum	Simple and accessible sample	Questionable reproducibility Limited correlation with clinical disease severity
	Exhaled breath condensate (EBC)	Simple and non-invasive	Requires special equipment Questionable reproducibility
	Bronchoalveolar lavage (BAL)	Directlmeasurement of inflammation	Invasive Limited reproducibility Focal sampling
	Endobronchial biopsy (EBB)	Direct evaluation of level of inflammation	Invasive May not represent all the areas in the lungs Being used for research purposes only
Imaging	High-resolution CT (HRCT)	Sensitive for early structural changes	Radiation exposure Does not distinguish old structural changes (scarring) from active inflammation
	Positron emission tomography (PET-CT)	Directly measures neutrophilic activity May distinguish between active inflammation and old structural changes (scarring)	Radiation exposure Needs validation Being used for research purposes only

M. Cohen-Cymberknoh, et al. Airway inflammation in Cystic fibrosis: Molecular mechanisms and clinical implications. Thorax 2013; 68(12):1157-62

How abnormal is the normal? Clinical characteristic of CF patients with normal FEV1

Aim: to investigate disease severity in patients with "normal" FEV1 (≥80%) according to demographic and clinical parameters:

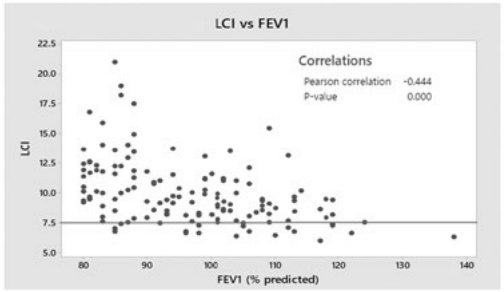
Data from pwCF from 2 CF Centers:

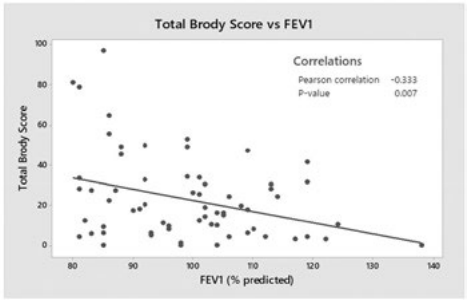
- Hadassah Medical Center, Jerusalem, Israel
- Vall d'Hebron Hospital, Barcelona, Spain
- ≥6 years
- FEV1 ≥80% predicted
- Clinically stable, with no PEx in the previous 4 weeks

- Age
- Gender
- CFTR mutations
- Pancreatic status (PI/PS)
- CF-related diabetes (Y/N)
- BMI
- LCI
- HRCT- Brody's score
- 6-min-distance walking (6MWD) test
- Sputum cultures
- PEx 1 year before
- PO/IV Abx treatment (days) 1 year before

Correlation between FEV1 and LCI and Brody scores

N= 147 FEV1 and LCI at the same day





From 147 FEV1 "normal" tests (≥80 % pred.), 83% (122/147) LCI were "abnormal"

Most of the patients had structural abnormalities, as expressed by abnormally high Total Brody Score, despite having normal FEV1

**A high correlation was found between LCI and HRCT*

M. Cohen-Cymberknoh, et al. How abnormal is the normal? Clinical characteristics of CF patients with normal FEV1. Pediatr Pulmonol 2021;56(7):2007-2013.

Pseudomonas aeruginosa in CF

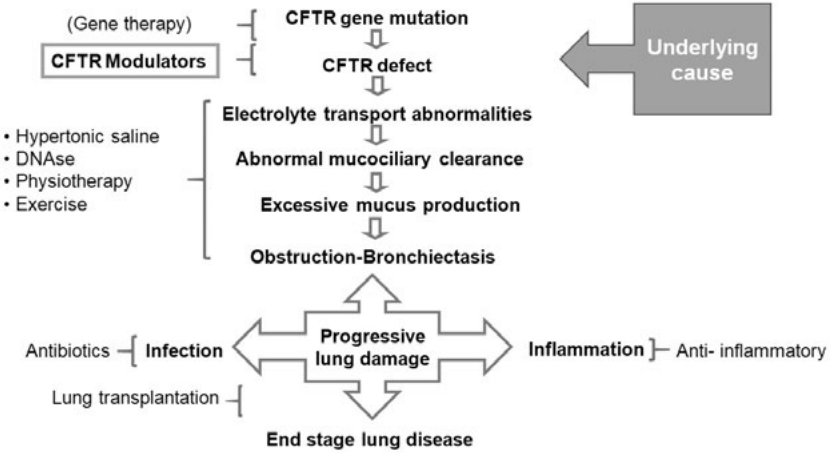
- Respiratory infection with P. aeruginosa (PA) is well recognized as a leading cause of morbidity and mortality in patients with CF
- Chronic infection with PA in the airways is associated with decline in pulmonary function, worsening nutritional status, more hospital admissions and shorter life expectancy
- Early eradication therapy is associated with increased survival
- Aggressive early eradication therapy have to be initiated as soon as the pathogen is detected, which can delay the onset of chronic infection

The "Ten Golden Rules" of CF Care

- **Maintain good nutrition and correct nutritional deficiencies**
- **Daily chest physiotherapy**
- **Enhance mucociliary clearance (inhaled hypertonic saline & Dornase alfa)**
- **Avoid and early treat new acquisition of pseudomonas infection**
- **Suppression of chronic pseudomonas infection (inhaled antibiotics)**
- **Early and aggressive treatment of pulmonary exacerbation**
- **Anti-inflammatory therapy**
- **Early identification and treatment of complications**
- **Centered care with frequent regular visits**
- **Strict adherence to all the above therapies**

M.Cohen-Cymberknoh et al, Standards of Care for patients with CF. Eur Respir Monogr 2014

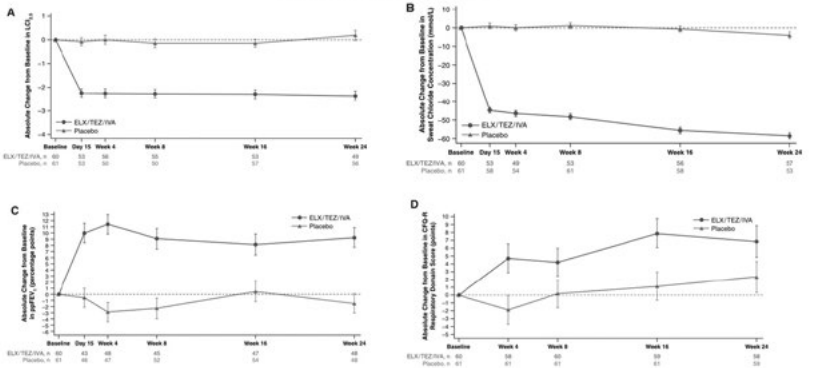
CF Pathophysiology and Treatment



Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for *F508del* and a Minimal Function Mutation

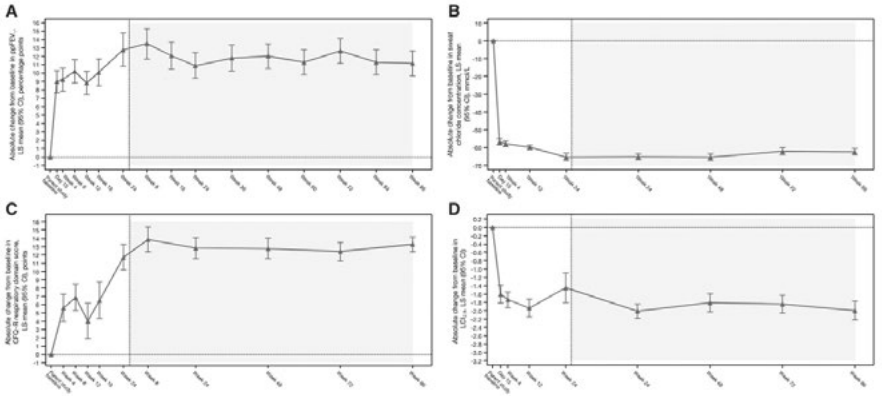
A Phase 3b, Randomized, Placebo-controlled Study

Absolute change in LCI2.5, sweat chloride concentration, ppFEV$_1$ and in the CFQ-R respiratory domain score in each clinic visit



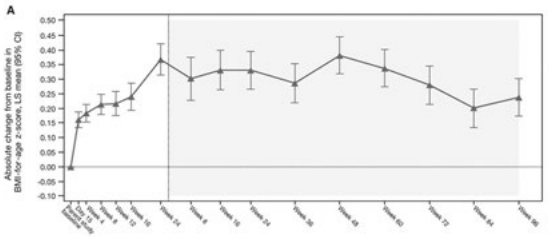
Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged ≥6 Years with Cystic Fibrosis and at Least One *F508del* Allele
A Phase 3, Open-Label Clinical Trial

Absolute change in ppFEV$_1$, sweat chloride concentration, CFQ-R respiratory domain score and LCI2.5, at each clinic visit

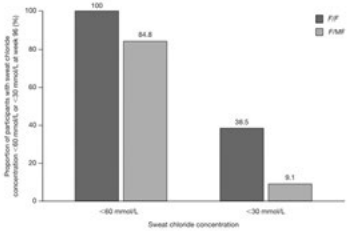


Long-Term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged ≥6 Years with Cystic Fibrosis and at Least One *F508del* Allele
A Phase 3, Open-Label Clinical Trial

Absolute change in BMI-for-age z-score from baseline at each visit



Responder analysis for sweat chloride concentration by genotype group

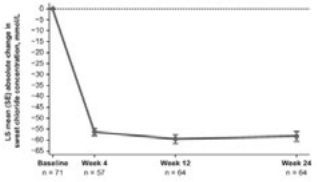


ELX/TEZ/IVA continued to be generally safe and well tolerated in children aged >6 years through an additional 96 weeks of treatment

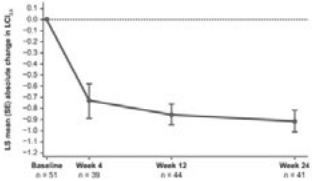
Phase 3 Open - Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children aged 2 through 5 years with Cystic Fibrosis and at least one F508del allele

- N=75 children (2-5 years) with at least one F508del allele enrolled; 74 completed the study, 71 entered in the open-label extension study
- ELX/TEZ/IVA treatment was well tolerated, safe, and led to improvements in CFTR function and lung function, and was associated with stable nutritional status, over a 24-week treatment period
- These results support the use of ELX/TEZ/IVA in children with CF >2 years of age

Mean (SE) change from baseline in sweat chloride concentration is shown for each visit



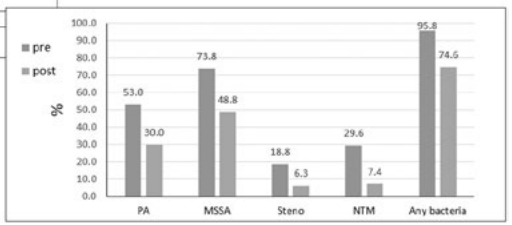
Mean (SE) change from baseline in LCI2.5 is shown for each visit



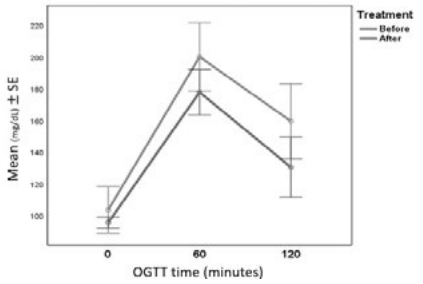
Variables before and after ETI treatment

Variable	Pre ETI	Post ETI	p value
Variables in the total cohort (n=91)			
BMI Kg/m^2 (mean±SD)			
Adults (n=52)	22.6±2.8	23±2.6	**0.001**
Children percentile _(n=39)	40.3±30.5	45.6±26.7	**0.035**
Sweat Cl (mEq/L) (mean±SD) (n=54)	98.8±23.8	54.4±24.5	**0.001**
PFT (mean±SD)			
FEV$_1$ %	91.7±11.9	98±11.5	**0.001**
FVC %	99±13.8	102±11.9	**0.001**
FEF25-75%	77.6±26.7	91.7±28.5	**0.001**
LCI (mean±SD) (n=31)	11±4.7	8.9±2	**0.001**
Range	6-24	6-14.5	

N=91; FEV$_1$>70%
Bacterial and fungal colonization before and after ETI treatment



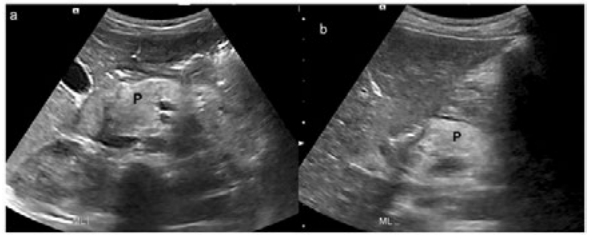
- Observational retrospective study, 15 pwCF, followed at the Hadassah CF Center
- OGTT prior to CFTRm was compared with last OGTT
- Treatment duration 3-81 months (mean 28 m.)
- OGTT 120-minute glucose values were significantly lower after starting CFTRm treatment (P<0.046)
-Glucosemonitoringisrecommendedaftertheinitiationof CFTRm in order to adjust the insulin dose



A.Cohen et al. Long-term therapy with CFTR modulators consistenly improves glucose metabolism in adolescents and adults with cystic fibrosis. Respiratory Medicine 228 (2024) 107664

Two siblings CF-PI (F508del/S549R) who presented with acute pancreatitis shortly after commencing ETI therapy

Both were treated with IVA for 5 years prior to ETI initiation, but had no previous episodes of acute pancreatitis



Abdominal US showing increased echogenicity of the enlarged pancreas (P) head and body in sibling a and of the pancreatic body in the other (b)

We suggest that HEMT may restore additional pancreatic acinar activity, resulting in the development of acute pancreatitis in the interim until ductal flow is improved

I. Sadras, et al. Acute pancreatitis in pancreatic-insufficient cystic fibrosis patients treated with CFTR modulators. J Cyst Fibros. 2023 ;22(4):777-779

Published data suggest that:
"People taking ETI have rates of depression-related adverse events that are consistent with background epidemiology of depression in the CF population and do not suggest a causal relationship between ETI treatment and depression-related adverse events"

Take home messages

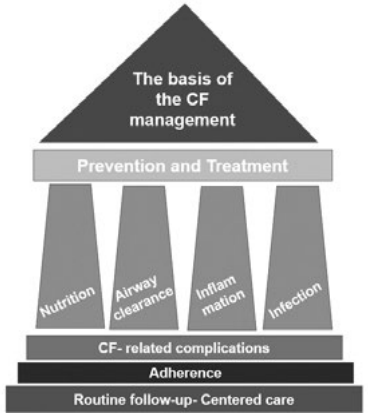
Aggressive management and advances in treatment may delay, but do not prevent lung disease progression

Most pwCF with normal FEV1 already have evidence of lung disease

More clinical tools are needed to better assess the evolution of lung disease

CTRF modulators can alter the progression of lung disease, making it essential to begin treatment as soon as possible

The basic treatment is still crucial!



ACCESS TO MODULATORS IN EUROPE

ACCESS STATUS OF ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN EUROPEAN COUNTRIES

This document was developed by Vertex and is shared upon request of CF Europe.

- This table provides an overview of the access status for elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor (ETI) in European countries where Vertex is currently active.
- Vertex is fully committed to making our CF medicines available to as many eligible patients as possible around the world, and our teams are working with governments and communities every day to expand access.
- Beyond the countries in this table, including in lower-income countries, we continue to work on pathways to access that promise the fastest route in each country to enable long-term sustainable access to our medicines.

KEY:
Grey cells = official reimbursement
 # = Broad access via exceptional reimbursement, tenders, broad named patient sales

COUNTRY	ETI 2 - 5 years	ETI 6 - 11 years	ETI ≥ 12 years
Albania			
Andorra			
Armenia			
Austria			
Azerbaijan			
Belarus			
Belgium			
Bosnia		Limited access via tender since mid-2022	
Bulgaria			
Croatia			
Cyprus		#	#
Czechia	#		
Denmark			
Estonia			
England			
Finland			
France	EAP		
Georgia			
Germany			
Greece			
Hungary	#	#	#

Iceland		#	#
Ireland			
Italy			
Israel			
Latvia			
Liechtenstein			
Lithuania			
Luxembourg			
Malta			
Moldova			
Montenegro		**Limited access via NPS since early 2023**	
Netherlands			
Northern Ireland			
North Macedonia		**Broad scale access via NPS since early 2023**	
Norway			
Poland			
Portugal			
Russia		**Several hundred patients <18 years old access via Circle of Goodness since 2021**	
Romania			
Scotland			
Serbia		**Limited access via NPS since late 2021**	
Slovakia			
Slovenia			
Spain			
Sweden			
Switzerland			
Turkey		**Limited access via NPS since late 2021**	
Ukraine		**Donation pilot program in Lviv & Kiev**	
Wales			

THE GASTROINTESTINAL SYSTEM IN THE COURSE OF CYSTIC FIBROSIS IN THE ERA OF MODULATOR TREATMENT

dr hab. n. med. Sabina WIĘCEK
Department of Paediatrics, Medical University of Silesia, Katowice, POLAND

Pancreatic changes before modulator therapy

- Pancreatic changes – impaired secretion of water, bicarbonates, chloride ions – > precipitation, obstruction of the pancreatic ducts
- Secretion of zymogen by pancreatic cells-> closure of the efferent ducts-> inflammation-> fibrosis
- Chronic pancreatic insufficiency – malabsorption/digestion syndromes – chronic fatty diarrhoea, abdominal pain, weight loss
- Acute pancreatitis – 10% of patients with CF
- Chronic pancreatitis
- Diabetes melitus
- Chronic pancreatic insufficiency – 70 - 90% of patients with CF
- Symptoms from the first weeks of life
- Full-blown exocrine pancreatic insufficiency develops within 2 - 12 months of life

Alimentary tract in cystic fibrosis

ESOPHAGUS STOMACH	SMALL AND LARGE INTESTINE	PANCREAS	LIVER AND BILE DUCTS
Reflux gastroesophageal Ulceration of stomach/duodenum Motylity disorders Eosinophilic esophagitis Esophageal adenocarcinoma	Maldigestion/malabsorption Polyps DIOS CF-enteropathy Constipation Fibrosing colopathy Rectal prolapse Intussusception of the intestines Colon cancer	Pancreatic failure Acute pancreatitis Chronic pancreatitis Fatty diarrhoea Diabetes mellitus	Preclinical hypertransaminazemia Cholestatis Focal hepatic fibrosis 72% Focal biliary cirrhosis 20-30% Multilobular biliary cirrhosis 5-15% Portal hypertension 2-5% Small atrophic gallbladder and narrowing of bile ducts 15-45% Cholelithiasis 14-24% Steatosis 25-60% Cholestasis in newborns <10% Primary sclerosing cholangitis - rare Cholangiocarcinoma - rare Drug-induced, toxic liver damage

Malnutrition in cystic fibrosis pathogenesis

- Pancreatic failure/endocrine and exocrine insufficiency- steatorrhea- fat malabsorption 85%
- Poor absorption of fat-soluble vitamins A D E K
- Gastroesophageal reflux
- Poor lung function
- Greater energy expenditure
- Loss of appetite - lower energy intake
- Enteric inflammation
- Bacterial overgrowth
- Cholestasis

Pancreatic changes after modulator therapy

Weight gain after modulator therapy has been evaluated in several studies. In a phase 3 study of elexacaftor/tezacaftor/ivacaftor in F508del heterozygotes, the absolute change from baseline in body weight after 24 weeks of treatment was +3.4 kg compared to+0.5 kg for placebo, with a +2.9 kg difference between groups (95% CI, 2.3 to 3.4).

(Middleton P, Mall M, Dřevínek, P. Elexacaftor–tezacaftor–ivacaftor for cystic fibrosis with a single Phe508del allele. N. Engl. J. Med. 2019, 381,1809–1819)

In patients receiving ivacaftor for G551D mutations, the mean (standard deviation, SD) weight significantly increased from 52.1 (20.4) kg to 54.2 (20.8) kg after 3 months ($p < 0.001$).

(Guimbellot J, Baines A, Paynter T et al.. GOAL-e2 Investigators. Long term clinical effectiveness of ivacaftor in people with the G551D CFTR mutation. J. Cyst. Fibros. 2021, 20, 213–219)

The albumin level was also significantly increased after one year in patients treated with lumacaftor/ivacaftor ($p < 0.001$).

(Misgault B, Chatron, E, Reynaud Q al. Effect of one-year lumacaftor–ivacaftor treatment on glucose tolerance abnormalities in cystic fibrosis patients. J. Cyst.Fibros. 2020, 19, 712–716)

MODULATOR	AUTHOR YEAR	DURATION	NUMBER	NUTRITIONAL CHANGES	DELTA CFQ-R SCORE
Ivacaftor	Ramsey 2011	48 weeks	167	Weight +2.7kg	+8.6
	De Boeck 2014	8 weeks	39	BMI +0.7kg/m2	+9.6
	Moss 2015	24 weeks	69	BMI +0.26kg/m2	+8.4
Ivacaftor + Lumacaftor	Wainwright 2015	24 weeks	1108	BMI + 0.28kg/m2	+3.1
Ivacaftor + Tezacaftor + Elexacaftor	Heijerman 2019	4 weeks	107	BMI +0.6kg/m2 Weight +1.6kg	+17.4
	Middleton 2019	24 weeks	403	BMI +1.4kg/m2	+20.2

Effect of modulator therapies on nutritional risk index in adults with cystic fibrosis: a prospective cohort study.

Yalcun N, Akman E, Karcioglu O et al. Nutrients.2024;16:1811

VARIABLES	MODULATOR THERAPY GROUP (N=50)	NON-MODULATOR THERAPY GROUP (N=57)	P VALUE
Pancreatic insufficiency	40/50 (80%)	54/57 (94.7%)	0.020
CF-related diabetes melitus	9/50 (18%)	7/57 (12.3%)	0.408
CF- related liver disease	10/50 (20%)	14/57 (24.6%)	0.572
Oral nutritional supplements	23/50 (46%)	30/57 (52.6%)	0.494
Albumin (g/dl) 12 –week period	4.08 vs 4.25	4.26 vs 4.13	0.029
BMI 12-week observation	19.88 vs 21.02	20.72 vs 20.36	0.121
Nutritional risk factors -12 –week period	100.65 vs 104.18	104.10 vs 102.58	0.044
Modulator therapy Elexacaftor/tezacaftor/ivacaftor or Ivacaftor			

Elexacaftor –tezacaftor- ivacaftor - occurrence of side effects:

Abdominal pain 14% vs 9% placebo
Diarrhoea 13% vs 7% placebo

TRIKAFTA (elexacaftor, tezacaftor and ivacaftor tablets) Boston MA-Vertex Pharmaceuticals Inc 2019

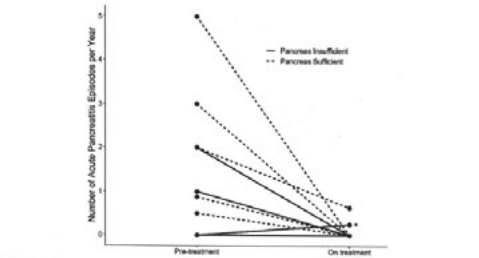
CFTR modulators and the pancreas

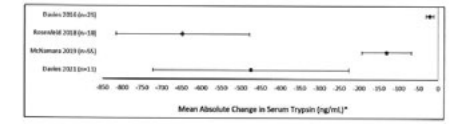
(Ramsey M et al. J Cyst Fibros.2023;22(2):193-200. Doi: 10.1016/j.jcf.2022.08.008)

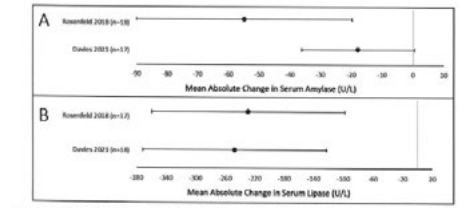
CFTR modulators reduced the incidences of acute pancreatitis by 85%, with a greater effect in the subgroup with pancreatic insufficiency

Decrease serum trypsin (565ng/ml), increased elastase in stool (>200ug/g), decreased amylase (by 38.2 U/l), decreased lipase (by232.2 U/l)

CFTR modulators and the pancreas *(Ramsey M, Li S, Lara L J Cyst Fibros 2023;22:193-200)*







Impact of LUM/IVA on glucose tolerance abnormalities- prospective study

(Misgault B, Chatron E, Reynaud Q et al. Effect of one-year lumacaftor-ivacaftor treatment on glucose tolerance abnormalities in cystic fibrosis patients. J Cyst Fibros. 2020;19:712-716)

- N-40 person, duration-12 months, age 12 - 61years
- Proportion of patients with glucose intolerance decreased from 78% to 40%
- Proportion of patients with diabetes decreased from 22% to10%
- Improved glucose tolerance in 57.3% with a significant decrease in both 1-h and 2-h OGTT glycemia

Intestinal inflammation (fecal calprotectin concentrations) in CF adolescents treated with LUM/IVA

(Tetard C, Mittaine M, Bui S et al. Reduced intestinal inflammation with Lumacaftor/Ivacaftor in adolescents with cystic fibrosis. J Gastroenterol Nutr. 2020;71:778-781)

- N-15, duration -336 days, age-12-16 years
- Significant decrease in fecal calprotectin concentrations from 713 mg/1g stool to 102mg/1g stool.
- Significant decrease in intestinal inflammation.
- Decrease of intestinal inflammation not correlated with respiratory function changes.

Liver and biliary ducts in cystic fibrosis CFLD

- Hepatic lesions concern only 5-20% of patients with diagnosed cystic fibrosis (CF).
- They increase the level of fatalities, shorten the survival rate and impair the quality of life.
- The average age of the detection of cystic fibrosis liver disease is about 10 years.
- Liver diseases are the most common, non-pulmonary cause of death among patients with cystic fibrosis. (2-5% of overall CF mortality).
- Nonspecific increase in transaminases is observed in more than 50% infants with CF
- CFLD – 2.5/100 patient-years during the first 10 years of life but CF Foundation National Registry liver injury in CF only 1.7%
- Abnormal hepatic histopathology in patients with CF 27-41%
- 10% of children with CF develop cirrhosis before or during puberty

Liver and biliary ducts in cystic fibrosis CFLDethiopathogenesis

- A combination of complex processes of fibrosis, inflammation, re-modelling, apoptosis and cholestasis
- A consequence of the abnormal functioning of the CFTR protein, immunologic reactions and response to oxidative stress

Abnormalities of cholangiocytes >> Mucous plugs in bile ducts >> Inflammatory and proliferative processes >> Focal biliary fibrosis (25-30%) >> Multilobular biliary cirrhosis (10%) >> Portal hypertension >> Hepatic insufficiency

Risk factors of the development of liver diseases in cystic fibrosis :

- Male gender – $^{3}/_{4}$ of patients with CFLD are boys. Protective role of oestrogens in women ?
- Co-existing meconium ileus
- Significant malnutrition
- Pancreatic insufficiency
- Severe genotype (delta F508)
- CF- related diabetes

Liver and biliary ducts in cystic fibrosis CFLD

- Preclinical disease no evidence of liver disease- based on clinical exam, imaging or laboratory test
- CFLD without cirrhosis and portal hypertension.
  - Persistent AST, ALT, GGT>2 Times
  - Steatosis
  - Fibrosis
  - Cholangiopathy
- CFLD with cirrhosis and portal hypertension

CHANGES TO THE BILE ACIDS	GENETIC FACTORS	IMMUNOLOGICAL FACTORS	CHANGES IN THE MICROBIOM
Changes to the components of the bile -abnormal water and electrolyte contents and change to the pH of the bile, changes to the profile of bile acids – to hydrophobic. Abnormal transportation of the bile, retention of toxic bile acids - taurocholic acid.	Severe mutations – class I-III. No correlation genotype -> fenotype Different associated mutations eg. SERPINA	Induction of pro-inflammatory chemokines activation of stellate cells monocyte chemotactic protein (MCP1), macrophage inflammatory protein beta 1 (MITGF-beta), TNF-alfa, Platelet-derived growth factor (PDGF), Interleukins – IL-1,IL-6, IL-10, Activation of the tyrosine kinase Src -> regulation toll-like receptor 4 (TLR-4).	Translocation of bacteria into the portal circulation

HEPATIC LESIONS IN THE COURSE OF CF

- Focal hepatic fibrosis 72%
- Focal biliary cirrhosis 20-30%
- Multilobular biliary cirrhosis 5-15%
- Portal hypertension 2-5%
- Small atrophic gallbladder and narrowing of the bile ducts 15-45%
- Cholelithiasis 14-24%
- Steatosis 25-60%
- Cholestasis in newborns <10%
- Primary sclerosing cholangitis - rare
- Cholangiocarcinoma - rare
- Drug-induced, toxic liver damage

Steatosis of the liver

- Mulitifactorial etiology
- Role of nutritional deficiencies - essential fatty acids in particular
- Common – higher number of patients with obesity (BMI for patients with CF has increased by 3 points over the past 20 years)
- Soft hepatomegaly or incidental USG findings
- Management – nutritional optimisation, exclusion of other hepatotoxins, diabetes
- Hepatic steatosis was observed in 77% children with CF after liver transplantation (mean age 17 years). Factors : metabolic syndrome, changes in the gut microbiota, antibiotics, pancreatic insufficiency, nutritional factors, immunosuppressive treatment

Cardiac liver cirrhosis in patients with cystic fibrosis

- Clinical signs of cor pulmonale

- Dilated hepatic veins
- AST and ALT are mildly elevated (<2-3x)
- Treatment- optimisation of cardiopulmonary function and prevention of hypoxia

Diagnosis of cystic fibrosis liver disease

DIAGNOSIS OF CFLD	
Clinical symptoms	- Hepatomegaly, splenomegaly; symptoms of portal hypertension - Very frequent symptomless course
Laboratory tests (AIT, AST, GGTP, bilirubine, AF, bile acids, albumine)	- Elevated levels of at least 2 hepatic parameters above the norm within at least 3 months is an indication of advancing hepatic lesions. - Low sensitivity and specificity - Most patients with multifocal cirrhosis have normal test results. - Isolated elevation of aminotransferases with concurrent normal GGTP index may indicate steatosis.
Abdominal and Doppler ultra-sound	- Assessment of the level of steatosis, - Symptoms of portal hypertension and cirrhotic transformation of the liver. - Inexpensive and non-invasive test. - Normal imaging of the liver does not exclude the ongoing process of fibrosis.
Elastography	- Non-invasive examination useful in detecting early liver fibrosis changes and monitoring of progression
Liver biopsy and histopathological examination	- Apart from being painful, it is an invasive, prone to side-effects and sampling errors examination

Liver and biliary ducts in cystic fibrosis CFLD - differential diagnosis
- Drug induced liver injury (DILI)
- Viral hepatitis A,B,C, EBV
- Autoimmune hepatitis
- Wilson's disease
- Coeliac disease
- Alpha1-antitripsin deficiency
- Metabolic syndrome MAFLD – diabetes or glucose intolerance, obesity, hypertension, hypertriglicerydemia

Liver and biliary ducts in cystic fibrosis CFLD - Treatment
- Background therapy of cystic fibrosis
- Diet therapy - Prevention of malnutrition in cystic fibrosis. Feeding tube or PEG nutrition recommended.
- Ursodeoxycholic acid
  - Has cytoprotective effect on the cell membranes of cholangiocytes,
  - Stimulates the secretion of chloride ions through calcium-dependent the chloride channel.
  - Increases hepatocellular and cholangiocellular secretion.
  - Reduces the ratio of cholic acid in bile (less than 5%), reduces its synthesis and lowers its overall volume.
- The treatment of portal hypertension (obligatory than PLT<120*109/L)
  - Beta- blockers
  - Endoscopic methods for the treatment of esophageal/gastric varices – band -ligation

  - Portosystemic shunts
- Liver transplantation

It was before modulator therapy for the treatment of cystic fibrosis...and.....what's the situation now?
Conceptual outcomes in the natural history of CFLD with impact of CFTR modulator use:
- Prevention of CFLD –evolution
- Reduced severity of CFLD natural history
- Change natural history of CFLD

- Reduce biliary obstruction
- Effects on the microbiom and inflammation

- Liver function test abnormalities occurred at similar frequencies in the ivacaflor and placebo groups.
- Activity ALT, AST, GGTP and bilirubin is recommended every 3 months during the first year of therapy with modulators

- Lumacaftor is a strong inducer of CYP5A-> a liver enzyme commonly involved in drug metabolism -> drug –drug interactions with common agents such as antifungal therapies and oral contraceptive drugs (Kalydeco (Ivacaftor). Cambridge MA VERTEX Pharnaceuticals Inc 2012, ORCAMBI (Lumacaftor/Ivacaftor). Boston MA VERTEX Pharnaceuticals Inc .2015

Steatosis of liver and CFTR modulators
- Liver steatosis – about 70% of children undergoing liver biopsy
- Association with diabetes mellitus, medication exposure
- Malnutrition, essential fatty acid or carnitine deficiency -> metabolic dysfunction-associated fatty liver disease (MASLD)
- Increased rates of MASLD in patients treated with CFTR modulator.

In USCFF Patient Registry, 7000 patients treated with CFTR modulators: No difference in the rates of aminotransferase abnormalities 3ULN vs 5ULN vs 8ULN after treatment with ETI for 20 months

In patients treated with tezacaftor-ivacaftor, similar rates of serum aminotransferase values elevated more than three times the upper limit of normal have been observed compared with placebo at 3.4%

Drummond D et al. (2022) did not show Lumacaftor-ivacaftor treatment, no hepatic adverse reactions were documented and no patients developed liver failure. Serum levels ALT, AST and GGT (especially) decreased significantly following initiation of lumacaftor-ivacaftor- during 12 months treatment.Beneficial - may improve liver fibrosis (Levitte)

(Drummond D et al. Lumacaftor-ivacaftor effects on cystic fibrosis – related liver involvement in adolescents with homozygous F508 del-CFTR. J Cyst Fibros.2022;21(2):212-219

Levitte S eta l. Effects of CFTR modulators on serum biomarkers of liver fibrosis in children with cystic fibrosis. AASLD. www.hepcommjournal.com)

STUDY AND DESIGN (ELEXACAFTOR/ IVACAFTOR/TEZACAFTOR ETI)	AMINOTRASFERASES > 3X ULN	AMINOTRANSFERASES >5X ULN
Mall et al. 2022 Aged 6-11 years Randomized, double-blind, placebo-controlled study	13,6% vs placebo 4.9%	5.1% vs placebo 1,6%
Midleton et al. 2019 Randomized, double-blind, placebo-controlled study	7,9% vs placebo 5.5%	2.5% vs placebo 1,5%
Heijerman et al. 2019 Randomized, double-blind, placebo-controlled multi-centre study	7.0% vs placebo 0%	4% vs placebo 0%
Sutharsan et al. Randomized, double-blind, placebo-controlled study	7% vs placebo 0%	4.5% vs placebo 0%
Barry et al. 2021 Randomized, double-blind, placebo-controlled study	3.2% vs placebo 0.8%	0.9% vs placebo 0%

Liver and modulator therapy

- Tezacaftor, ivacaftor, elexacaftor all undergo predominantly hepatic metabolism-> in the setting of established hepatic impairment-> higher serum drug concentration
- Liver dysfunction Child-Pugh class B or greater- ETI dose reduction by up to 50% is recommended.
- ETI should be avoided in severe hepatic dysfunction- cirrhosis and/or portal hypertension

(Viswanathan L et al. Eur J.Drug Meatab Pharmacokinet 2022;47(6):817-825)

Modulators after liver transplantation

- Freeman et al. recommend early but cautious reintroduction of CFTR modulators post orthotopic liver transplantation due to the beneficial effects on lung function and nutrition.
- Several case reports and case series describing no adverse effects with early drug reintroduction.
- Optimal dosing of CFTR modulators post OLT has not been established.
- Antimicrobials and anti-rejection immunosuppression agents (tacrolimus) may interact (substrate for CYP3A4/5 and CYP3A). Reduced serum tacrolimus concentrations may be seen in association with increased ETI concentrations.

Freeman A et al. Liver Transpl. 2019;25(4):40-57
Ragan H et al. Pediatr Pulmonol 2022;57(2):411-7
Mc Kinzie C et al. J Cyst Fibros. 2022;21(2):227-9

BUT ...

- A recent single –centre study suggested advanced liver disease should not always preclude ETI treatment.
- 27 patients with cirrhosis and /or portal hypertension had no differences in change of liver tests compared to patients without CFLD with ETI

Eldredge J, Olivier M, Ooi C. Cystic fibrosis liver disease in the new era of cystic fibrosis transmembrane conductance regulator (CFTR) modulators. Ped Res Rev.https://doi.org/10.1016/j.prrv.2023.12.005

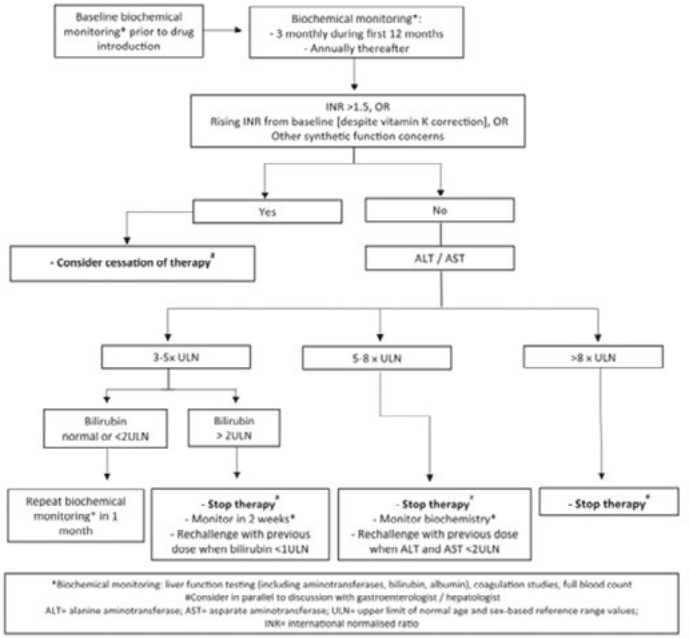


Fig. 1. Suggested biochemical and synthetic function monitoring prior to and during treatment with CFTR modulator, and recommended action with aminotransferase, bilirubin and synthetic functioning monitoring.

Meconium ileus *(Chu T, Kormakar J, Haggie P et al. Selective isoxazolopyrimidine PAT1 (SLC26A6) inhibitors for therapy of intestinal disorders. Med. Chem., 2023, 14,2342*

- Simple (intraluminal occlusion by stick meconium)
- Complex - with volvulus, atresia, necrosis, perforation, meconium peritonitis, and pseudocyst formation

Meconium ileus – on changes before and after ....but

- 10 - 18% of newborns with cystic fibrosis
- Meconium in the ileum -> ileo-cecal section -> mechanical obstruction of the gastrointestinal tract-> meconium peritonitis
- 98% meconium obstruction – cystic fibrosis
- Meconium peritonitis in the fetal period – > calcifications in the abdomen/peritoneum
- Risk factors: prematurity, sepsis, hypothyroidism, Hirschprung's disease, hypotonia, hypermagnesaemia
- F508del homozygous diagnosed by amniocentesis at gestational age 18 weeks
- 23 weeks gastation- in ultrasonography – single loop of dilated bowel
- Mother has got ETI therapy from 32 weeks gestation
- After birth multiple stools on the first day of life, abdominal X-ray no bowel obstruction, has started oral feeding with pancreatic enzyme replacement therapy.

(Szentpetery S, Foil K, Hendrix S et al. A case report of CFTR modulator administration via carrier mother to treat meconium ileus in a F508del homozygous fetus. J Cyst Fibros.2022;21(4):721-724)

DIOS – Distal Intestinal Obstruction Syndrome before modulator therapy

- Recurrent colic abdominal pain located in the right lower abdomen
- Most often in children over the age of 3 years
- Symptoms become apparent with age
- 80% of recurrent symptoms
- 90% of patients with DIOS have exocrine pancreatic insufficiency

Predisposing factors:
- Genetic predisposition
- Incorrect enzyme supplementation
- Improper diet, dehydration
- Use of drugs that inhibit gastrointestinal motility

TRIAD DIOS:
- Paroxysmal, severe abdominal pain
- Noticeable resistance in the right lower abdomen
- Radiological changes in the deposition of fecal masses in the distal ileum and ascending colon

Other symptoms:
- Constipation, bloating
- Diarrhoea, high-volume stools
- Symptoms of mechanical obstruction

DIOS – Distal Intestinal Obstruction Syndrome before modulators treatment

Procedures in exacerbation:
- Compensation of water-electrolyte disturbances
- Rectal infusions with: N-acetylcysteine, lactulose
- Surgical treatment

Preventive measures:
- Treatment of the underlying disease – treatment with modulators ???
- Proper enzyme supplementation
- Avoiding constipation – macrogols, lactulose
- Avoiding medications that inhibit bowel motility

DIOS – Distal Intestinal Obstruction Syndrome after modulators treatment

I have 3 children in the Gastroenterology Outpatients Clinic (8, 11 and 12 years old) with DIOS symptoms (reccurent subileus) now they are treated with modulators-> now nobody has any symptoms of subileus !!!

Since meconium ileus and DIOS mainly affect the ileum, the distal portion of the small intestine, by blocking Cl - and fluid absorption, PAT1 inhibition can hydrate the luminal contents independent of CFTR for treatment of CF-associated small intestinal disorders.

SIBO- small intestinal bacterial overgrowth- risk factors

- Presence of not fully digested and not fully absorbed nutrients in the intestine
- Presence of thick, glycoprotein-rich mucus
- Gastrointestinal motility disorders
- Antibiotic therapy used

Rectal prolapse

- 3 - 20% of patients with cystic fibrosis
- Most often before the age of 5 (max 12 - 36 months)

Contributing factors:
- Constipation, diarrhoea
- Malnutrition
- Severe cough – participation of abdominal press
- Incorrect enzyme therapy

Sometimes surgical treatment necessary

Polyps of the alimentary tract in cystic fibrosis

- Adenomatous polyps develop more frequently in patients with CF
- For nontransplanted patients, colonoscopy should begin at 40 years of age, with rescreening at 5-year intervals; the screening interval should be shortened to 3 years if adenomatous polyps are discovered.
- For transplanted patients, screening should start at 30 years of age, or within 2 years of the transplant operation.
- The risk of developing colorectal cancer (CRC) in CF is 5–10-fold higher compared with age-matched individuals without CF, and the risk of CRC increases up to 30 times post solid organ transplant.

Gastroesophageal reflux in cystic fibrosis before modulator therapy

25 - 80% of patients with cystic fibrosis

Risk factors for the development of GERD:
- From the respiratory side
  - Increased cough
  - Lung distension
  - Physiotherapy – strenuous inhalations and exhalations, Trendelenburg position
  - Medications used – e.g. B-agonists, euphylline
- Gastrointestinal motility disorders (including a high-fat diet, medications)

Symptoms of gastroesophageal reflux:
- Abdominal pain, heartburn, dysphagia
- Retrosternal pain
- Recurrent vomiting, regurgitation
- Reluctance to eat
- Recurrent wheezing, coughing
- Recurrent respiratory infections

Gastroesophageal reflux in cystic fibrosis after modulator therapy

- Less severe respiratory symptoms – > less severe gastroesophageal reflux
- Less strenuous physiotherapy > less severe gastroesophageal reflux

Time will tell ?
- More often obesity – a risk factor for gastroesophageal reflux

Summary

Long-term data on the safety and effectiveness of CFTR modulators on alimentary tract needed.

Impact of CFTR modulators on emerging complications of CF such as liver cirrhosis, colorectal cancer remains unknown, and should be examined in the coming years.

NUTRITION IN THE ERA IN THE ERA OF MODULATOR TREATMENT

Monika MIELUS, PhD, CF dietitian
Institute of Mother and Child, Cystic Fibrosis Department, Warsaw, POLAND,
Dziekanow Lesny Hospital, Cystic Fibrosis Center, Dziekanow Lesny, POLAND

Nutrition suport in CF

Nutrition Assessment	Fat Soluble Vitamins
Nutrition Education	Minerals
Macronutrients – diet quality	Pancreatic Enzyme Replacement
Sodium Replacement	Therapy
Undernutrition	Cystic Fibrosis Related Diabetes
Behavioural Modification	Bone Health
Strategies	Pregnancy
Oral Nutrition Supplements	Lung Transplantation
Appetite Stimulants	
Enteral Feeding	Gastrointestinal and Hepatobiliary
Parenteral Nutrition	Considerations

In the 1960s - a low-fat diet to manage steatorrhea -> severe malnutrition and growth failure
In the 1980s - a high-fat diet with aggressive pancreatic enzyme replacement therapy (PERT) -> improved growth and survival

Unrestricted high-calorie, high-fat diets with PERT to meet gender specific body mass index (BMI) goals

Current CF diet evidence in 21st century

- Overconsumption energy-dense, nutrient-poor foods, particularly foods high in added sugars and refined carbohydrates that have a high glycemic index

- Overconsumption energy-dense, nutrient-poor foods, particularly foods high in added sugars and refined carbohydrates that have a high glycemic index .

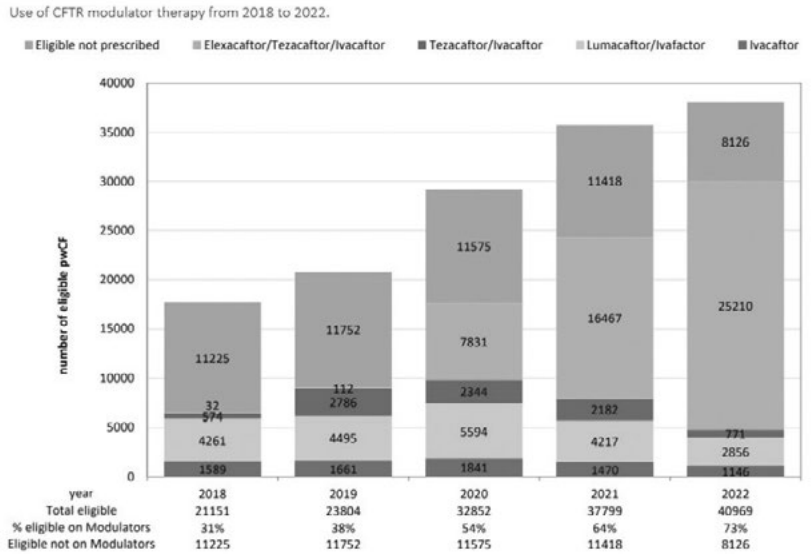
- CF Participants had a lower proportion of calories from protein than their healthy peers.

- The poor dietary quality of adults with CF with excessive fat intake and reliance on energy-dense, nutrient-poor foods.

CFTR modulator therapy in Europe in 2022

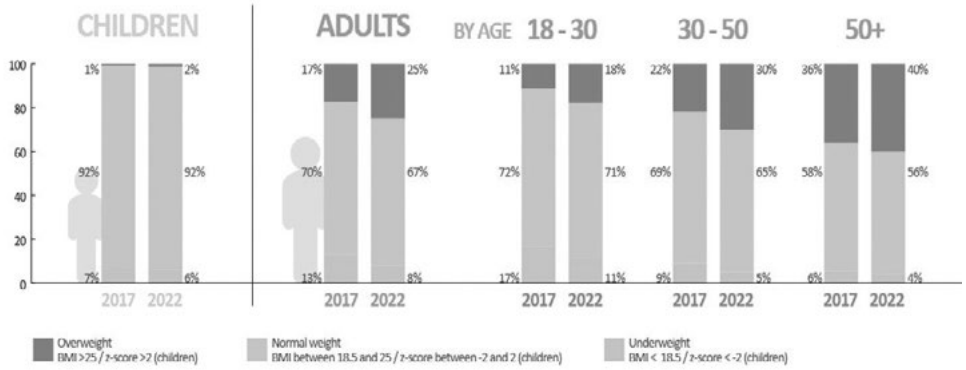
Children - almost 50% receive CFTR modulators
Adults - >70% receive CFTR modulators

Increased usage of CFTR modulator therapy over the years, but there are still patients not receiving it despite eligibility



The percentage of people with CF who are overweight increased in all age groups between 2017 and 2022.

Fewer people are underweight in 2022 than in 2017.



Concequences of excess weight in CF population
Adults patients who are overweight (BMI≥25-27 kg/m2) - better pulmonary function, but also present adverse cardiometabolic risk factor trends
- higher blood presurre, total and LDL cholesterol, elevated insulin secretion

Overweight (BMI ≥ 25) and obesity (BMI ≥30) are associated with higher total cholesterol and triglyceride levels.

Academy of Nutrition and Dietetics guidelines

Difficulties with transitioning to a diet that emphasizes healthy foods, especially if the individual has historically focused intake on a high-fat, high energy diet.

General guidance for food intake		
Food and supplement intake	For all individuals with CF, it is reasonable for the RDN or international equivalent to advise an age-appropriate, healthy diet that emphasizes culturally appropriate foods associated with positive health outcomes in the general population, including vegetables, fruits, whole grains, seafood, eggs, beans and peas, nuts and seeds, dairy products, and meats and poultry, as tolerated and preferred by the individual with CF, because there is no evidence to suggest that routine modification from a well-balanced, healthy diet is associated with improved outcomes. It is reasonable to advise supplementation with energy- and/or protein-dense foods or oral or enteral supplements, as needed to achieve or maintain normal growth (pediatrics) or BMI status (adults).	***Consensus*** *Conditional*
Dietary patterns	For all individuals with CF, it is reasonable for the RDN or international equivalent to consider advising a dietary pattern, individualized for dietary preferences and nutrient needs, that promotes consumption of nutrient-dense foods, including healthy fats and micronutrients.	***Consensus*** *Imperative*

Era of CFTR modulators

- The impact of CFTR modulators on nutrition is significant, although the precise mechanisms remain unclear.
- Ivacaftor or elexacaftor-tezacaftor-ivacaftor treatments have shown notable enhancements in weight, height, and BMI compared to dual CFTR modulator therapy.
- When concerning trends in weight, BMI, or body composition arise, it's crucial to prioritize dietary quality over quantity.
- Close collaboration with dietitians and the CF healthcare team supports individuals with CF in maintaining a healthy weight, BMI, and body composition while following a balanced, nutritious diet.

European nutrition guidelines

Nutrition and CFTR modulator therapy

Recommendation 77

Appropriate dietary counselling should be provided for pwCF starting on CFTR modulator therapy, this should include advice about limiting and managing weight gain

Recommendation 78

The nutritional status and dietary intake of pwCF on CFTR modulator therapy including salt intake and fat-soluble vitamin status should continue to be regularly reviewed and modifications recommended according to changes observed

Recommendation 79

Gastrointestinal symptoms should be closely monitored following the initiation of CFTR modulator therapy and this should continue as part of routine CF care

Recommendation 80

In view of the fact that CFTR modulators may improve beta cell function and insulin secretion, blood glucose levels should be monitored regularly to avoid hypoglycemia when assuming the same insulin dose prescribed before starting modulators.

Recommendation 81

PwCF on CFTR modulator therapy should have their blood pressure routinely monitored three months after commencing therapy and at least annually and appropriate medical management started if clinically indicated.

Recommendation 82

PwCF on CFTR modulator therapy may have their lipid profiles checked annually and appropriate dietary advice and medical management should be given if required.
Grade of recommendation GPP - Strong consensus 92 % agreement

Definitions of overweight and obesity in people with CF

Adults

Overweight
BMI 25–29.9 kg/m2
Obesity
BMI ≥30 kg/m2

Children (2 years and older)

Overweight
BMI between 85th-94.9th percentile OR
BMI >1 SD (84th percentile) above the WHO Growth reference median for sex and age)
Obesity
BMI ≥95th percentile obesity OR
BMI z-score >2 SD (98th percentile) above the WHO Growth Reference median for sex and age for

A CF Fundation position paper

Table 1
Interdisciplinary Team's role in weight management and food insecurity assessment.

Collaboration between team members is essential to address all issues and ensure consistent messaging.	
Team Member	Role in Weight Management and Food Insecurity Assessment
Patient and Family	1. Provide input on food preferences, cultural food practices, and access to nutrient-dense foods 2. Participate in shared decision making
Dietitian	1. Perform diet recalls identifying opportunities for optimizing dietary intake 2. Recommend strategies to enhance diet quality 3. Review labs and provide recommendations on micronutrients (both deficiency and excess) 4. Evaluate for manifestations of malabsorption and adjustment of pancreatic enzyme dosage 5. May perform body composition measurements in the clinic (bioelectrical impedance analysis), and alternative measures of nutritional assessment (skin fold thickness, hand-grip strength etc.) 6. Provide education for PwCF and family 7. Provide supportive counseling around body image and weight stigma 8. Screen for food insecurity
Social Worker/ Clinical Psychologist/Mental Health Coordinator	1. Provide psychosocial support around body image and weight stigma and implementing behavioral change strategies 2. Screen for depression, anxiety, disordered eating, and food insecurity 3. Provide resources and interventions for patients with positive screening 4. Follow up after the clinical visit to ensure resources provided were helpful
Pulmonologist/ Physician/Advanced Practice Providers (primary care physician may play a shared role for certain conditions)	1. Evaluate/provide referral for CF-related comorbidities which may increase with obesity (eg CFRD) 2. Evaluate/provide referral for obesity-related comorbidities such as obstructive sleep apnea, hypertension, and cardiovascular disease 3. Reinforce importance of healthy diet and exercise with PwCF, assess access to adequate nutrient rich foods
Gastroenterologist	1. Evaluate and manage gastrointestinal comorbidities of obesity (e.g., gastroesophageal reflux disease, cholelithiasis, hepatic steatosis) 2. Evaluate and manage CF-related or obesity related liver disease 3. Evaluate pancreatic function and manage pancreatic insufficiency 4. Managing gastrointestinal/hepatic manifestations of E/T/I (85)
Nurse Coordinator/Research Nurse	1. Encourage communication between the PwCF and the team, facilitate coordination between team members in issues related to weight management.
Endocrinologist/ Obesity Specialist	1. Evaluate and manage dyslipidemia 2. Evaluate the need for medical/surgical management for obesity 3. Discuss the effect of medical/surgical management of obesity on CF-related diabetes and malabsorption
PhysicalTherapist/ Physiotherapist	1.Measure functional ability: stamina, endurance, and ADLs 2.Provide customized exercise program aimed at integrating physical activities into a healthy lifestyle and optimize lean body mass
Pharmacist	1. Assess drug-nutrient and drug-drug interactions, including weight loss drugs.

Dietitian role in weight management and food insecurity assessment
- Recommend strategies to enhance diet quality
- Provide education for PwCF and family
- Provide supportive counseling around body image and weight stigma

Weight Neutral Approaches

Focus on optimizing health outcome measures rather than promoting weight loss to treat overweight and obesity

New challenges in pediatric clinical practice

Improvement in nutritional status:
- Increased or uncontrolled appetite -> rapid weigh gain
- More prevalent issue among girls than boys
- There's a desire to be "slim" like before using CFTR modulators

Increased appetite does not necessarily translate to improved dietary habits
- Changing long-established habits is very challenging
- Pediatric patients „depend on" parents - difficult to alter approaches to implementing "healthy eating."
- Not all parents want to collaborate with dietary changes – new actions = effort

Importance of morning/evening meals
- Skipping breakfast (ubiquitous among adolescents)
- „Lack of time for breakfast", „I'm not hungry"
- Inappropriate fat content (also too low)
- Difficult to stop ONS – even optimal nutritional statsus achieved

Experimentation with keto/low-calorie diets
- Also parents inquiring about potential implementation

Self-decreasing PERT doses
- Not adjusting doses when fat intake increases

Not all patients taking CFTR modulators improve their nutritional status, leading to disappointment for both patients and parents.

Those who have experienced rapid weight gain have concerns about taking it.

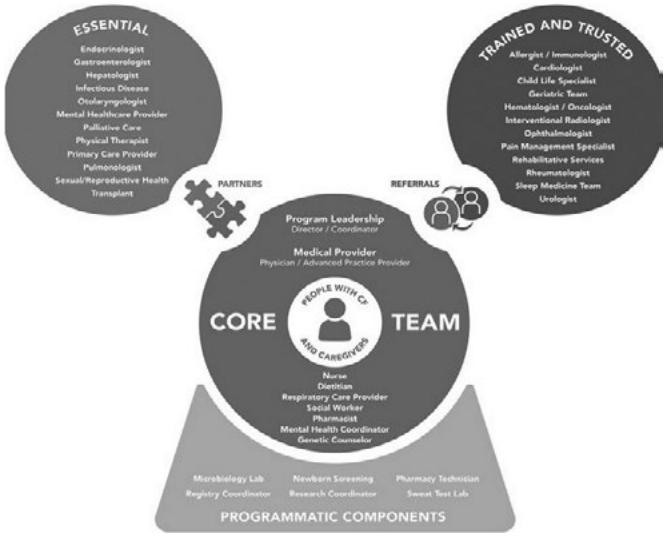
Challanges for dietitians
- How to optimise vitamins and salt supplementation?
- Not in all CF centres labolatory assessment is available

If Kaftrio has decreased sweat chloride to <30, then you should not need salt supplementation routinely. Extra salt on the food is also not indicated.

If CI is in the 30-60 range, then a reduction in salt supplementation is recommended but may still be needed in the summer.

Longer living - changing co-morbidities

Newer complications and co-morbidities >> Cancer >> Obesity as an independent risk factor >> >> Heart disease >> New challenges for CF MDT



Conclusion
- Awareness about current existing guidelines is essential.
- Monitoring all aspects of nutrition – an individualized approach for implementing dietary guidelines
- Reshaping entrenched "nutrition bad habits" is a gradual process.
- Education is crucial in promoting healthier eating habits, beginning as early as possible to alter the "CF legacy" diet.
- A renewed effort is necessary for dietitians and the entire CF team.
- Collaboration with the CF team and a unified message are essential for success.

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ADULTS WITH CF – CURRENT SITUATION IN POLAND

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Institute of TB and Lung Diseases, Warsaw, POLAND

ADULTS IN CF CENTERS

More than 100 patients:
Poznań, Warszawa (IGiChP), Rabka

100 – 50 patients:
Gdańsk

Less than 30 patients:
Białystok, Karpacz, Kielce, Kraków, Warszawa (Attis), Łódź, Lublin, Rzeszów, Szczecin, Torzym

PROPER CF CENTER ... MDT

PULMONOLOGIST ... all in one ... NOT ANYMORE !!!

CHRONIC INFECTIONS

Pseudomonas aeruginosa	31%
Achromobacter spp.	2,7%
MRSA	1,7%
BCC	0,8%

NEBULISED ANTIBIOTICS

- Colistimethate sodium
- Tobramycin (limited acces)
- Levofloxacin (limited acces)

117 patients at the age of 16 - 18 years

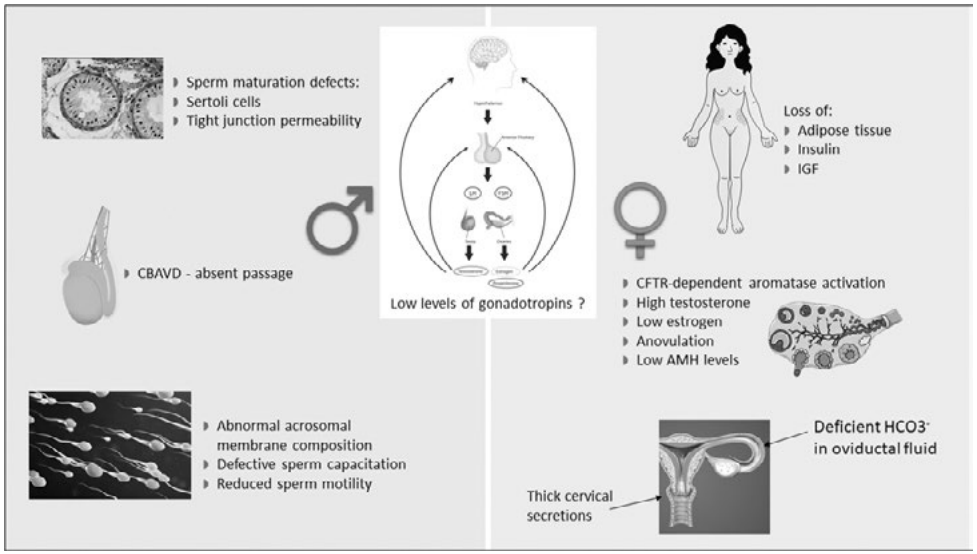
PREGNANCY AND BREASTFEEDING IN CF

Prof. Malena COHEN-CYMBERKNOH, MD
Hadassah-Hebrew University Medical Center, Jerusalem, ISRAEL

No relationships related to this presentation to disclose

Infertility in women with Cystic Fibrosis (wwCF)

- 1973 - 1st report of reduced fertility in wwCF- thick cervical mucus due to low water content
- 1986 - WwCF successfully treated with intrauterine insemination
- Causes are multi-factorial: nutritional, chronic inflammation, altered mucous and uterine bicarbonate secretion
- Anovulation: Insulin deficiency mediated?
- CFTR is expressed in multiple female reproductive tissues as well as the hypothalamic-pituitary-gonadal axis
- Decreased ovarian reserve (DOR) has been proposed as a possible cause, but limited data is available to support this
- AMH (anti-mullerian hormone), a marker of ovarian reserve, is not recommended as a screening test for the general population



- Reproductive-age wwCF were recruited during routine visits at the Hadassah-CF Center, Jerusalem. Participants signed inform consent
- Blood was drawn for anti-Mullerian hormone (AMH) levels and for routine CF blood tests
- A trans-vaginal ultrasound was performed by a senior gynecologist in non-virgin, non-pregnant subjects to ascertain the antral follicular count (AFC)
- Demographic, clinical, and laboratory results, as well as gynecological and obstetric data was collected

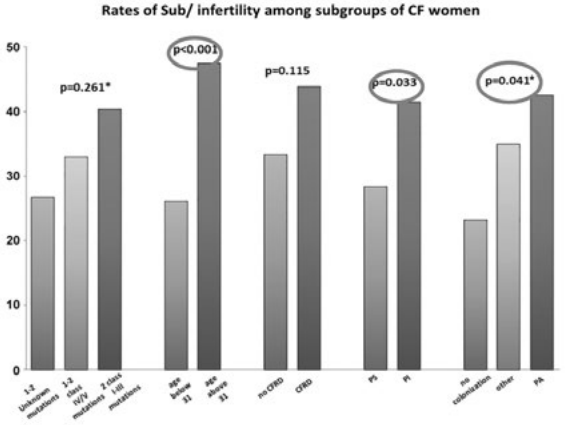
- Twenty-three wwCF, aged 19-40 years (median age 27 years) were enrolled; 14/23 expressed a desire to have children
- Subfertility was found in 5/14 (36%), who performed work-up and/or fertility treatments; 3/5 had conceived and given birth to ≥1 children
- All but one wwCF had an AMH level between the 5th and 95th% for age
- No correlations between CF disease severity, serum inflammatory parameters, AMH values or the use of HEMT were found
- Overall, wwCF in our cohort had born 22 children, with a range of 1-4 children per woman
  - 6 more spontaneous pregnancies post recruitment and sampling

Our results do not support the hypothesis that decreased ovarian reserve plays a major role in subfertility/infertility in wwCF

- Aim- to determine the prevalence and factors associated with subfertility* in wwCF
- A retrospective-multinational study including women with CF from 11 CF Centers [Israel (7), France, Spain, Italy, UK]
- Demographic and clinical data were collected from patients' files: genetics, PI/PS, CFRD, FEV1, BMI, sputum culture, and rate of pulmonary exacerbations (PEx)

Failure to conceive in wwCF is associated with pancreatic insufficiency and advancing age

- 621 women were screened, 605 included
- 241/605 attempted conception
- Prevalence of subfertility among wwCF (35%), higher than the expected in the general population (5-15%)
- Older age and PI are associated with subfertility; a trend in pseudomonas+
- FEV1, BMI, CFRD, severe mutations and number of PEx in the year prior to fertility attempts were not associated with subfertility



Pregnancies in wwCF

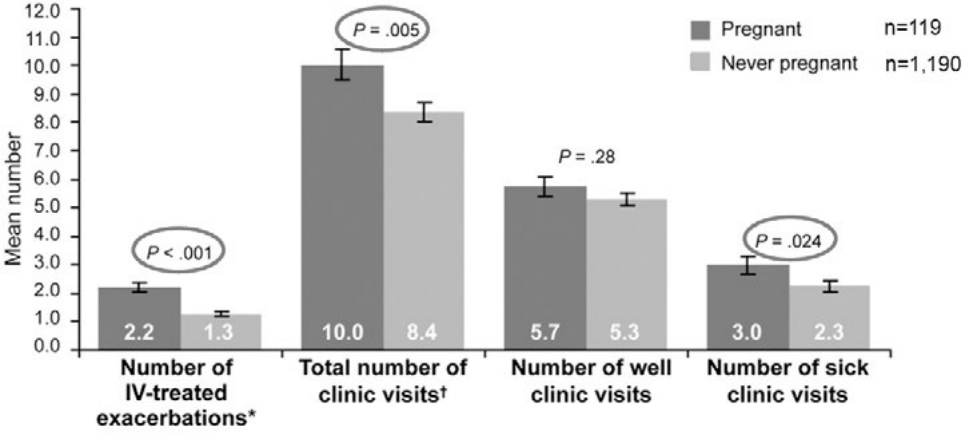
- The first pregnancy in a wwCF was reported in 1960. The woman laboured prematurely and died 6 weeks postpartum
- The number of pregnancies in wwCF has been rising during the last decades
- In general, successful outcomes and without long-term implications on maternal health or survival

Physiologic changes during pregnancy

- Hormonal changes
- Increased uterine size
- Changes in pulmonary function
- Increase in oxygen consumption
- Cardiac changes

In wwCF:
Risks during Pregnancy and Delivery?
Maternal long-term outcome?
Complications in the neonates?

Comparison of wwCF who had reported a pregnancy to those who had notHealth care use (2004 to 2005)



Although, no significant deterioration in PFTs or BMI during the years after pregnancy

Medical and obstetric complications among pregnant wwCF

TABLE 4
Obstetric events present at time of delivery among women with CF

Condition, n (%)[a]	CF n = 1119	No CF n = 12,627,627	OR (95% CI)	*P* value
Cesarean delivery	351 (31.4)	4,041,005 (32.0)	1.0 (0.9–1.1)	.67
Operative vaginal delivery	100 (8.9)	792,143 (6.3)	1.5 (1.2–1.8)	.0002
Multiple gestation	39 (3.5)	267,193 (2.1)	1.7 (1.2–2.3)	.0013
GDM	148 (13.2)	714,940 (5.7)	2.5 (2.1–3.0)	< .0001
Preeclampsia, eclampsia, gest HTN	76 (6.8)	931,154 (7.4)	0.9 (0.7–1.1)	.48
Preterm labor	209 (18.7)	1,051,494 (8.3)	2.5 (2.2–2.9)	< .0001
Abruption	16 (1.4)	136,053 (1.1)	1.3 (0.8–2.2)	.22
Fetal growth restriction	29 (2.6)	271,882 (2.2)	1.2 (0.8–1.8)	.26
Postpartum hemorrhage	15 (1.3)	321,959 (2.5)	0.5 (0.3–0.9)	.012
Chorioamnionitis	36 (3.2)	323,531 (2.6)	1.3 (0.9–1.8)	.17

CF, cystic fibrosis, *CI*, confidence interval; *GDM*, gestational diabetes; *gest HTN*, gestational hypertension; *NIS*, Nationwide Inpatient Sample; *OR*, odds ratio.

[a] The NIS does not allow reporting the number of cases when the cell frequency is less than or equal to 10. There were 10 or fewer cases of fetal demise and placenta previa among women with CF.

Patel. Cystic fibrosis in pregnancy. Am J Obstet Gynecol 2015.

TABLE 5

Multivariable logistic regression model for complications among women with CF

Maternal condition	Adjusted OR (95% CI)	*P* value
Death	76.0 (31.6–183)	< .0001
Mechanical ventilation	18.3 (10.8–31.2)	< .0001
Transfusion	1.68 (1.01–2.81)	.045
Pneumonia	56.5 (43.2–74.1)	< .0001
Acute respiratory failure	20.3 (10.5–39.0)	< .0001
Acute renal failure	17.3 (9.1–32.6)	< .0001
Composite CF outcome	28.1 (21.8–36.3)	< .0001
Preterm labor	2.2 (1.9–2.6)	< .0001

Multivariable logistic regression analysis for the listed outcomes among women with CF at delivery while controlling for age, race/ethnicity, diabetes, hypertension, gestational diabetes, preeclampsia, multiple gestation, and mode of delivery.

CF, cystic fibrosis; *CI*, confidence interval; *OR*, odds ratio.

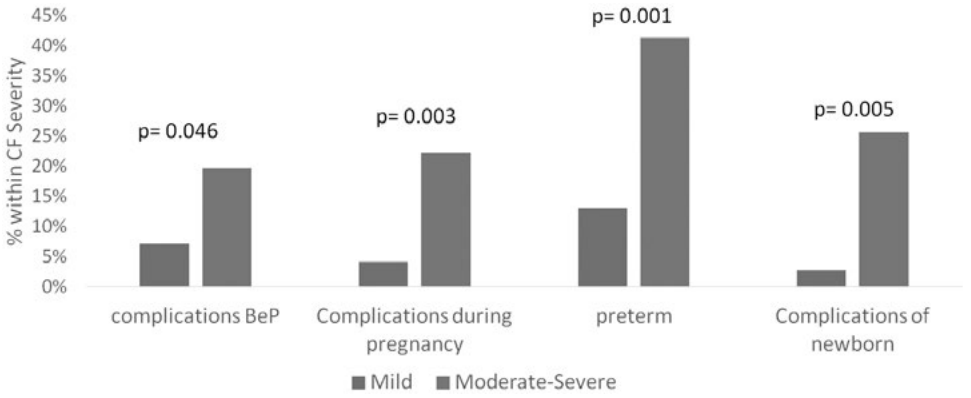
Patel. Cystic fibrosis in pregnancy. Am J Obstet Gynecol 2015.

- Aims: to analyze the effect of pregnancy on CF disease severity, complications and risks for mother and fetus
- We collected data on pregnancies and deliveries from 10 CF Centers: Israel (6), Barcelona, Milan, Chile and JHH (USA)
- Data analyzed before, during and up to 1 year post delivery:
  - FEV1, BMI, CFRD, chronic pseudomonas, PI/PS, number of pulmonary exacerbations
  - complications of mother, fetus and newborn
- Pregnancies compared according to CF disease severity:
  - mild disease: FEV1 >60% pred. + BMI >21 kg/m2
  - moderate-severe disease: FEV1 ≤60% pred and/or BMI ≤21 kg/m2

Demographic data

	Total		Mild	Moderate-Severe	p-value
Number of Pregnancies	**171**		57	70	-
PI/PS (n, %)	123	PI	19 33.9%	38 **56.7%**	**0.012**
		PS	37 56.1%	29 43.9%	
CFRD (n, %)	163	Yes	9 15.8%	18 26.1%	0.161
		No	48 48.5%	51 51.5%	
Ps. Aeruginosa (n, %)	126	Yes	30 52.6%	45 65.2%	0.15
		No	27 52.9%	24 47.1%	
BMI (before pregnancy) mean	22.8±3.9		**25.6±3.7**	**20.4±2.2**	**<0.001**
FEV_1% pred. (before pregnancy) mean	73±21.3		**84.7±15.8**	**61.1±19.2**	**<0.001**

Relationship between CF severity and pregnancy outcomes



Baseline disease severity, pseudomonas infection and PI have an adverse impact on infant outcomes, but do not impact significantly on disease progression during and after pregnancy
In general, outcomes appear to be successful, and without long-term implications on maternal health or survival

- Multinational-multicenter (n=18) retrospective cohort study
- N=141 wwCF patients that had been pregnant between 1973 and 2020
- 41/141 (29%) had ≥3 pregnancies
- Data was collected on 246 pregnancies - 108 from Israel, 74 from Europe, 30 from the US and 34 from South America
- Overall, 69 pregnancies (28%) were multigravid pregnancies

Subgroup analysis

- A greater decline in FEV1 following pregnancies in multiparous wwCF, mainly in wwCF with two severe CFTR mutations and CF-PI

- A trend but not significant effect on the rate of PEx

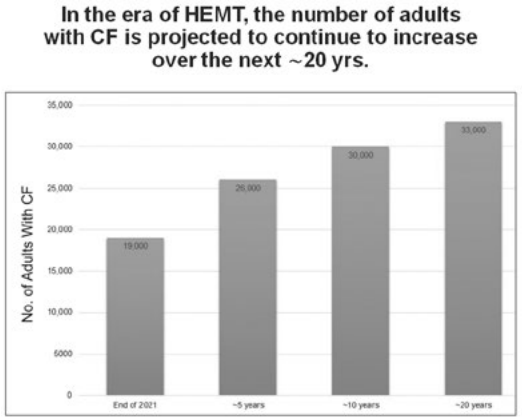
- Higher rates of prematurity and newborn complications in multiparous wwCF >30 years old

Table 2
Within patient analysis of pregnancy outcomes.

	1st & 2nd Pregnancies		≥3 Pregnancies		
	N	Mean/% within	N	Mean/% within	P-Value
Change in ppFEV1	12	2·5 ± 5·6	12	7·8 ± 6·7	***0·003***
Percent Change in ppFEV1, pre-post pregnancy	12	2·8 ± 8·1	12	11·0 ± 7·4	***0·001***
Number of days on PO Abx, During Pregnancy	18	6·6 ± 11·9	18	12·7 ± 20·5	*0·23*
Number of days on IV Abx, During Pregnancy	19	3·8 ± 7·8	19	13·2 ± 25·9	*0·10*
Number of mild PEx (during)	18	0·5 ± 0·9	18	0·8 ± 1·1	*0·35*
Number of severe PEx (during)	21	0·3 ± 0·6	21	0·7 ± 1·0	*0·07*
Weight gain during pregnancy (kg.)	13	10·0 ± 5·1	13	7·6 ± 5·3	*0·07*
Gestational age (weeks)	21	39·1 ± 1·5	21	37·3 ± 3·5	***0·04***
Weight at birth (kg)	19	3·0 ± 0·5	19	3·0 ± 0·7	*0·10*
Newborn complications	29	10·3%	29	6·90%	*1·00*

Table 2- Within patient analysis. The comparison of a single patient's 1st or 2nd pregnancy with her multigravid pregnancy (≥3). In each pregnancy, change was defined as between the year prior to the year after pregnancy. N- number, PO- per os, IV- intravenous, Abx-antibiotics, ppFEV1- percent predicted forced expiratory volume in 1 s, BMI- body mass index, PEx-pulmonary exacerbations.

What do you know about the impact of CFTR modulators both in pregnant wwCF and in the fetus, and during lactation?



- Fertility may improve in wwCF who are taking modulators
- Most drugs used to treat CF are considered safe in pregnancy and lactation, including the limited data regarding safety of modulator's therapy during conception, pregnancy, and lactation.."

- Currently literature suggest minimal risk to pregnant pwCF and breastfed infants with continued CFTRm therapy
- Discontinuing CFTRm therapy may pose more of risk to the pregnant pwCF
- For developing fetus' with US findings suggestive of CF or if CF is confirmed by genetic testing, CFTRm therapy exposure may help treat CF-related complications present during pregnancy and even delay additional complications that typically occur postpartum

- Data on pregnancies from 2010 to 2021 were collected from 11 US adult CF centers
- N= 307 pregnancies, mean age at conception was 28.5 years (range, 17-42 years)
- 114/307 pregnancies (37%) had CFTRm exposure during pregnancy
- Mean change in ppFEV1 from pre-pregnancy to during pregnancy was −2.36 in the unexposed group and 2.60 in the CFTRm group, with no significant change 1 year post-pregnancy
- In the HEMT group PEx decreased, and BMI increased from pre-pregnancy to during pregnancy in all groups but with no significant change post-pregnancy

Key Points- Pregnancies in CF
- Improvements in CF care and survival have resulted in an increase in the number of wwCF that are considering parenthood
- Chronic maintenance therapies are widely used throughout all trimesters of pregnancy and lactation in wwCF
- CFTR modulator use throughout pregnancy and lactation has generally been well-tolerated but requires further study. Ophthalmologic follow-up for the neonate is recommended
- Close follow up for the pregnant wwCF by a multidisciplinary team is mandatory

RESPIRATORY PHYSIOTHERAPY

Natalia JENERALSKA, MSC
Center for Cystic Fibrosis Treatment, Hospital in Dziekanów Leśny, POLAND

Key objectives in the physiotherapy of patients with chronic lung diseases include:
- Systematic clearing of the bronchi from retained secretions.
- Reducing symptoms related to lung diseases, such as dyspnea, cough, and exercise intolerance.
- Preventing complications associated with insufficient lung ventilation.
- Developing physical fitness levels appropriate for the patient's age and disease progression.
- Maintaining proper chest mobility.
- Preserving adequate skeletal muscle strength and endurance.
- Improving quality of life.

These objectives are often perceived by patients as exhausting, restrictive, and yielding mixed results.

Respiratory physiotherapy:
- Upper respiratory airway clearance
- Inhalation therapy
- Bronchial tree drainage
- Physical activity - general training

Dilution of mucus —> Relaxation and detachment of mucus from the bronchial wall —> Transfer of mucus towards the large bronchi and trachea —> Coughing up mucus

Upper Airway Clearance:
Sinus irrigation:
Sinus irrigation helps to remove accumulated secretions, allergens, and other debris that collect in the nasal cavity with each breath.

Sinus inhalation:
The Jet-type inhaler additionally produces aerosol pulsation, allowing it to penetrate the paranasal sinuses—exactly where it is needed. The blocked mucus and secretions are loosened.

Inhalation therapy
In addition to airway clearance techniques, it is an important part of bronchial tree physiotherapy (mucolytic drugs) as well as very important pharmacological treatment (inhaled antibiotic therapy)

When selecting an appropriate inhalation device, consider:
- The form of the medication
- Characteristics of the nebulizer and aerosol
- The patient's age
- The patient's ability to synchronize inhalation with the device
- The severity of the lung disease, including complications (e.g., hemoptysis, pneumothorax)
- The availability of the device
- The patient's acceptance

Positive Expiratory Pressure (PEP)
- Prevents bronchial collapse syndrome
- Dilate the peripheral bronchi and facilitate their cleansing

Oscillatory Positive Expiratory Pressure (O-PEP)
- They combine increased exhalation pressure with oscillation (vibration)
- The vibrations produced by the device help to detach, break up and loosen secretions
- Generates oscillating bronchial pressure
- Can be used for children as young as 3-4 years old

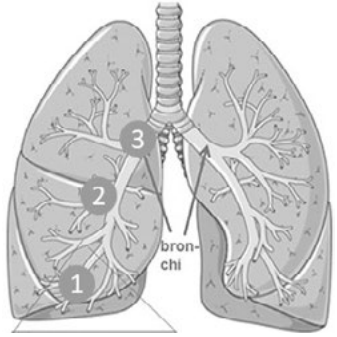
Autogenic Drainage

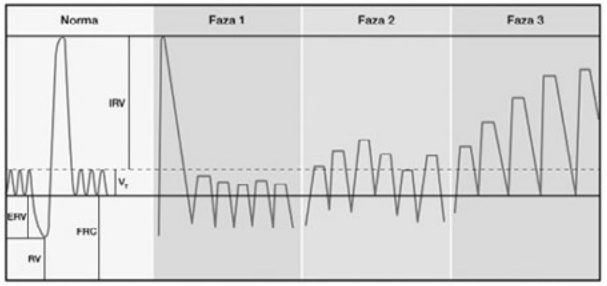
Breathing at so-called three volumes corresponding to specific phases:

Phase I - Low volume: Loosening secretions in peripheral bronchi. The patient continues exhaling until reaching the expiratory reserve volume (ERV) - positioning the chest in the expiratory position.
Loosening secretions in peripheral bronchi.

Phase II - Medium volume: Gathering secretions in large bronchi. The patient breathes within the deepened tidal volume (TV) - positioning the chest in the resting position.
Gathering secretions in large bronchi.

Phase III - High volume: Transporting secretions from large bronchi toward the throat. The patient performs a quick exhalation and expectorates the secretions - positioning the chest in the inspiratory position.
Transporting secretions from large bronchi toward the throat.



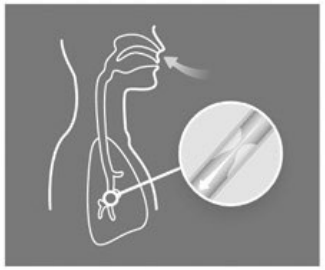


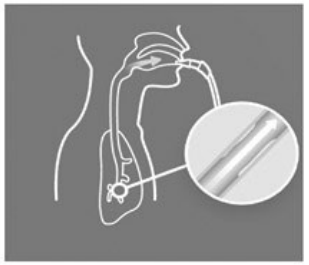
Assisted autogenic drainage
- Used for uncooperative patients.
- Drainage performed with the assistance of a physiotherapist.
- It is carried out in a gentle and gradual manner.
- Uses manual techniques of the thorax to achieve adequate airflow depending on the phase of drainage and the location of the secretions.

During exhalation, we gently mimic the patient's breathing movements without applying chest pressure or excessive force. In reality, the physiotherapist's hands placed on the patient's chest gradually limit the level of inhalation to encourage a slightly larger and longer exhalation. This

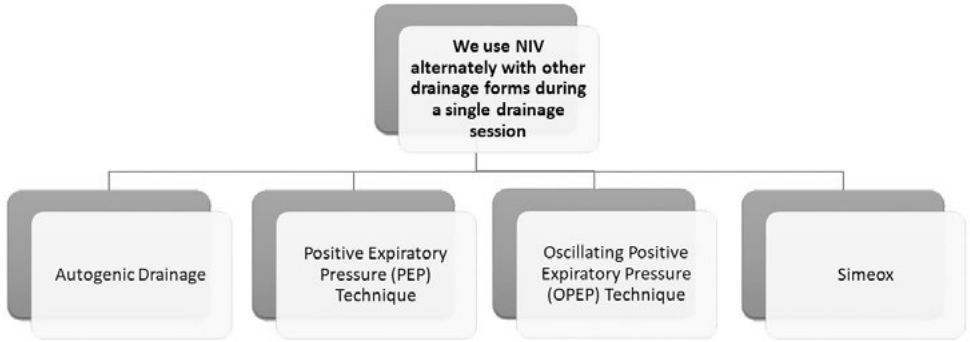
helps move secretions from the peripheral bronchioles to the central bronchi, optimizing the respiratory system's function and enabling the respiratory muscles to work more properly and efficiently

Simeox
- A device utilizing the generation of short-term negative variable pressures in the airways
- Thins and liquefies thick secretions
- Moves secretions from the smallest bronchioles during the exhalation phase
- Generates successive low-frequency negative pressure vibrations to loosen and remove secretions from the airways
- The inhalation phase is active and performed by the patient





Non-invasive mechanical ventilation (NIV)
- Lowers the paCO2 pressure in the blood
- Reduces respiratory effort
- Facilitates secretion evacuation
- Decreases the work of respiratory muscles (respiratory muscles rest)
- Stabilizes lung function
- Increases exercise tolerance
- Reduces desaturation during exercise
- Allows passive expansion of the chest (increase in tidal volume)



A GLOBAL EFFORT TO ASSESS EMOTIONAL WELL-BEING IN YOUNG CHILDREN WITH CF

Sonia GRAZIANO
Psychology Unit, Child & Adolescent Psychiatry Unit, Pneumology and Cystic Fibrosis Unit, Bambino Gesu Children's Hospital, IRCCS, Rome, ITALY

NO HEALTH WITHOUT MENTAL HEALTH

Benefits of Mental Health Screening (MH)

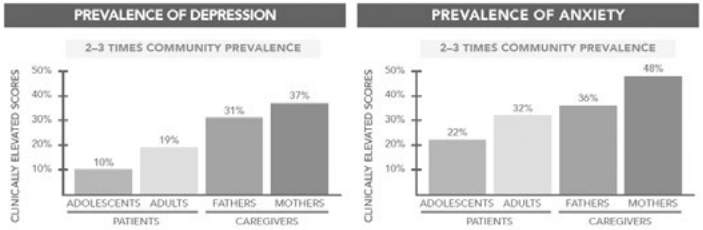
MH seen as an intervention itself and provides motivation to pursue MH support

CF patients and caregivers view MH screening as an important part of CF care

TO RECOGNIZE MH CHALLEGES HELPS TO ADRESS THE NEEDS OF PWCF!

TIDES The International Depression/Anxiety Epidemiological Study

The International Depression/Anxiety Epidemiological Study (TIDES)



Landmark study screening:

6088 teens and adults with CF in 9 countries - 4102 caregivers

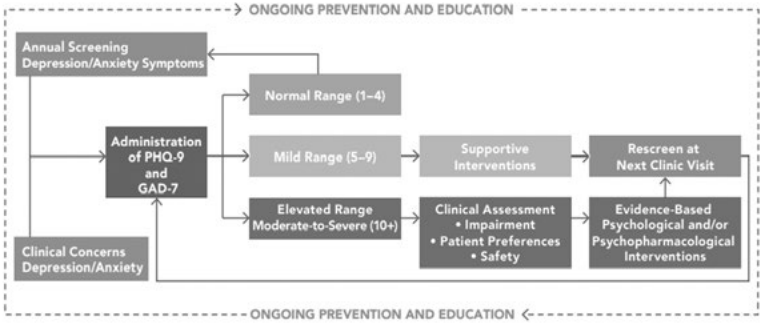
OPEN ACCESS

ORIGINAL ARTICLE

International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety

Alexandra L Quittner,[1] Sonia Abbott,[2] Anna M Georgopoulos,[3] Lutz Goldbeck,[4] Beth Smith,[5] Sarah E Hempstead,[6] Bruce Marshall,[7] Kathryn A Sabadosa,[8] Stuart Elborn,[9] the International Committee on Mental Health

ASSESSING AND TREATING DEPRESSION AND ANXIETY



Screening Measure: PHQ-9 & GAD-7

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

pwCF ≥12 years

GAD-7

Over the last 2 weeks, how often have you been bothered by the following problems? (Use "✔" to indicate your answer)	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3

SCORING
- Score 1-4 = No Symptoms
- Score 5-9 = Mild
- Score 10-14 = Moderate
- Score >15 = Severe

OPEN ACCESS

ORIGINAL ARTICLE

International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety

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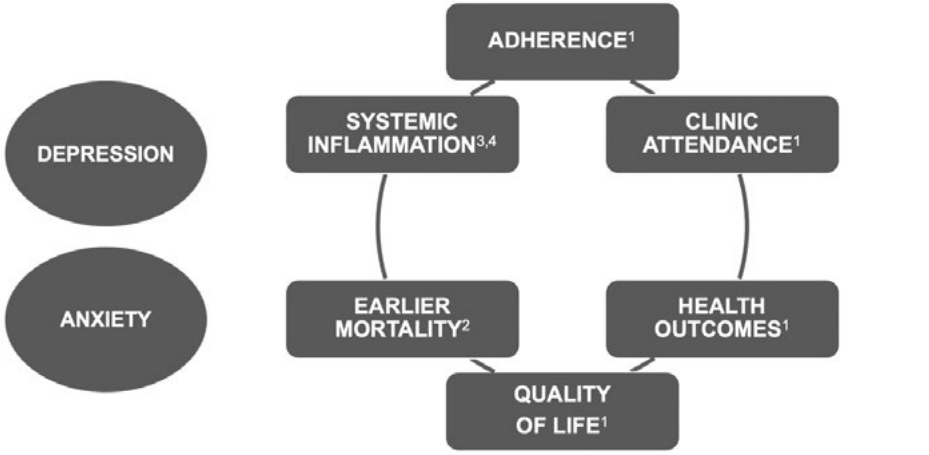
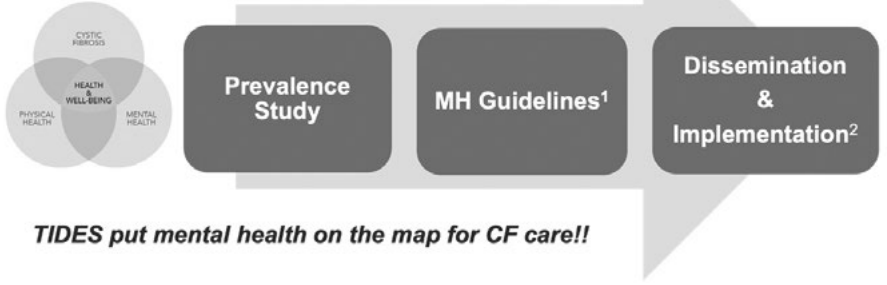


International Dissemination & Implementation

TIDES The International Depression /Anxiety Epidemiolgical Study



TIDES put mental health on the map for CF care!!

NEW MODULATORS – NEW CHALLEGES IN MENTAL HEALTH

Standard of care for CFTR variant-specific therapy (including modulators) for pwCF[1]
Standards for the care of people with cystic fibrosis; establishing and maintaining health[2]

1	2	3	4
Neuropsychiatric side effects have been reported for all available CFTR modulator therapies Alterations in mood, anxiety, sleep and neurocognition, as well as suicidal ideation/attempts	Pharmacovigilance Risk Assessment Committee (PRAC) for the European Commission: recently determined that there is at least a reasonable possibility of a causal relationship between ETI and depression	PwCF and their families should be encouraged to report both positive and adverse experiences to the CF team, regardless of presumed causality	MH should be monitored in accordance with CFF/ECFS guidelines, including screening for depression and anxiety before and no later than 3 months after initiating modulators

Systematic Screening & Follow-up

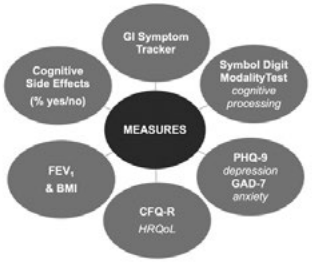
Case series & reports of unique experiences – Adolescents and adults

Study	n
Tindell et al. (2020), Psychosomatics	1
Heo et al. (2022), J Cyst Fibrosis	6
Lyman et al. (2022), Pediatric Pulm.	1
Spoletini et al. (2022), J Cyst Fibrosis	19
Ibrahim et al. (2023), Frontiers in Pharma.	10
Baroud et al. (2023), Pediatric Pulm.	16
Arslan et al. (2023), J Cyst Fibrosis	2
McKinzie et al. (2024), The Lancet.	6

Chest Infections Original Research | CHEST

Longitudinal Effects of Elexacaftor/Tezacaftor/Ivacaftor

Multidimensional Assessment of Neuropsychological Side Effects and Physical and Mental Health Outcomes in Adolescents and Adults



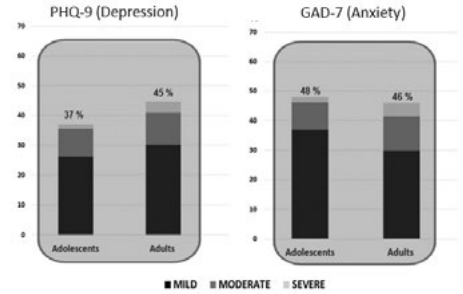
Significant improvements

- FEV_1
- BMI
- Depression
- Cognitive processing
- Some GI symptoms
- Most HRQoL domains

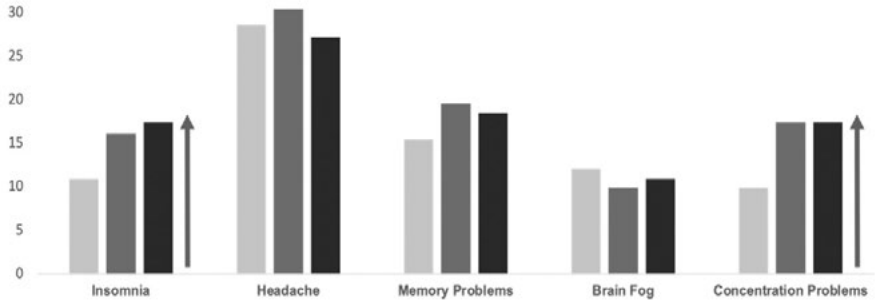
Depression & Anxiety

Table A. PHQ-9, GAD-7 scores

		T0	T1	T2	T3
PHQ-9, mean (SD)		3.7 (3.5)	2.8 (2.8)	2.7 (3)	2.7 (2.6)
- No symptoms *n (%)*		66 (71.7)	71 (77.2)	70 (76.1)	74 (80.4)
- Mild, *n (%)*	28%	18 (19.6)	18 (19.6)	18 (19.6)	16 (17.4)
- Moderate, *n (%)*		6 (6.5)	2 (2.2)	3 (3.3)	1 (1.1)
- Severe, *n (%)*		2 (2.2)	1 (1.1)	1 (1.1)	1 (1.1)
- Item #9, *n (%)*		4 (4.3)	3 (3.3)	4 (4.3)	2 (2.2)
GAD-7, mean (SD)		3.6 (3.4)	3.1 (2.6)	3.5 (3.9)	3.3 (3.2)
- No symptoms, *n (%)*		58 (63)	67 (72.8)	66 (71.7)	70 (76.1)
- Mild, *n (%)*	37%	26 (28.3)	21 (22.8)	19 (20.7)	15 (16.3)
- Moderate, *n (%)*		7 (7.6)	4 (4.3)	4 (4.3)	6 (6.5)
- Severe, *n (%)*		1 (1.1)	0 (0)	3 (3.3)	1 (1.1)

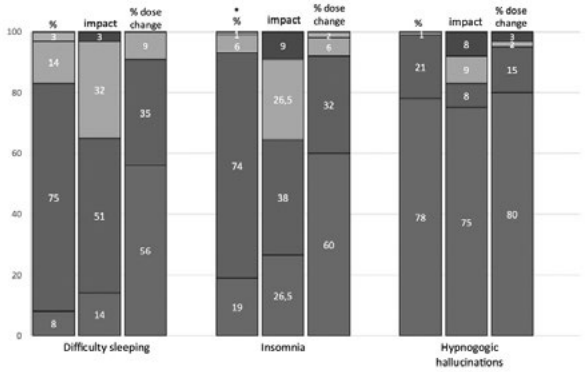


Neuropsychological side-effects occurred in 10-29% with no improvement over time!



Women reported more side-effects than men!

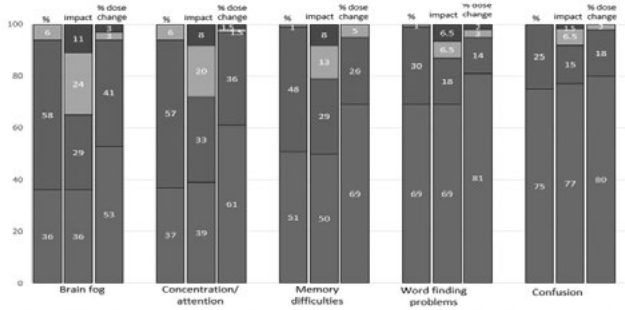
Most Common Effects on Sleep



- Sleep difficulties and insomnia occurring in 1-24%
- Impact is slight to moderate
- Can lead to changes in dosing in 40-44%
- Hypnogogic hallucinations occurring in 1-24%
- Sleep problems *significantly* more common in adult *vs.* pediatric patients

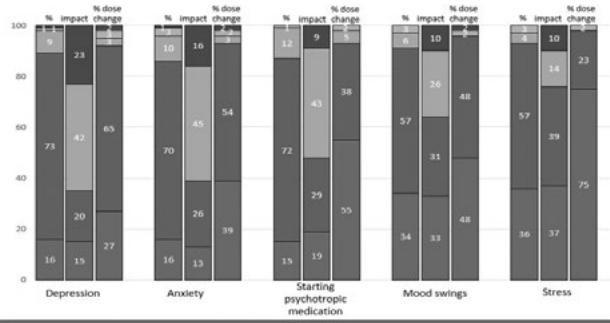
National survey of providers at 75 US CF Centers

Most Common Effects on Cognition



- More than half of clinicians reported brain fog, problems with concentration/attention and memory in 1-24% (another 12% report occurrence in 25-49% of pwCF)
- Word finding and confusion observed in one-third
- Substantial impact on majority of pwCF
- Leads to dose changes in about one-third

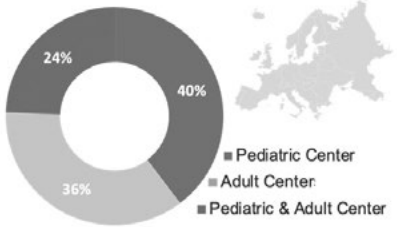
Most Common Effects on Mental Health



- Worsening depression and anxiety 1-24% or more; 10-13% reported worsening mood in 25-49%
- *Moderate impact* in 42-45%
- New antidepressant medication in 1-24%
- Reason for dose changes in majority
- No adult *vs* pediatric differences

78 respondents - 21 countries

Primarily Physicians (61.5%)
A majority of providers had >10 years of experience on a CF team (52.6%) compared to US (36.3%)

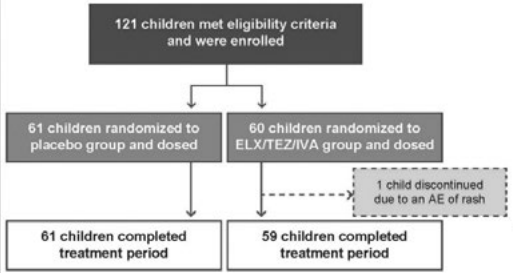


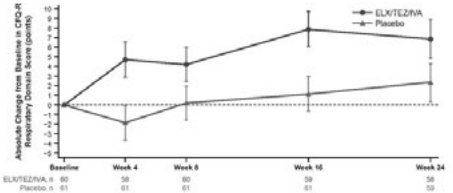
Respondents: Social Worker, Psychologist, Nurse, Respiratory Therapist, Physiotherapist, Centr/Program Director, MD Clinician, Pharmacist

- Lower percentage of side-effects related to sleep in EU *vs* US
- Similar rates of side-effects of ETI (e.g., mood swings) were reported by clinicians in EU and the US
- Fewer negative mental health effects (e.g., increased depression, suicidal ideation) and concerns about the future (e.g., food insecurity), were reported in EU *vs* US.

These results may be explained by differences in the healthcare systems and social safety nets

Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for *F508del* and a Minimal Function Mutation: A Phase 3B, Randomized, Placebo-Controlled Study[1]





International Mental Health

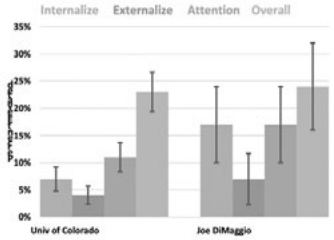
Table 1 Consensus statements

Recommendation statement	Consensus (%)
Prevention	
1. For all individuals with CF and caregivers, the CFF/ECFS International Committee on Mental Health in CF (ICMH) recommends that ongoing education and preventative, supportive interventions, such as training in stress management and the development of coping skills, aligned with appropriate developmental stage and disease events be offered.	100
2. For all individuals with CF undergoing medical procedures, the ICMH recommends that behavioural approaches be used to reduce the risk of distress.	100
Screening	
3. The ICMH recommends that children with CF ages 7–11 be clinically evaluated for depression and anxiety when caregiver depression or anxiety scores are elevated, or when significant symptoms of depression or anxiety in the child are reported or observed by patients, caregivers or members of the CF multidisciplinary team.	100
4. The ICMH recommends annual screening for depression and anxiety with the PHQ-9 and GAD-7 for adolescents and adults with CF (ages 12–adulthood).	100

- **10 years ago, no national guidelines on screening for children < 12 years**
- **2022, US Preventive Taskforce recommended screening *all children* for anxiety at age 8**
- **With introduction of ETI for young children, concerns have emerged about side-effects (e.g., sleep, emotional and behavioral concerns, cognition)**

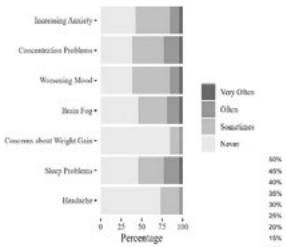
New mood and neurocognitive findings – Preliminary results

Pediatric Symptom Checklist: Results in 2 Pediatric Centers [1]



Colorado $N = 137$ Joe DiMaggio $N = 39$

Side-effects Checklist [2]
(Graziano & Quittner)

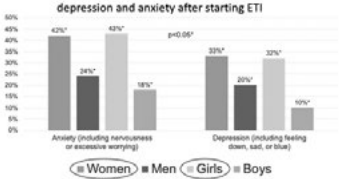


Well-Me Survey [3]

Table 1: Mental Health Adverse Events (N=571 currently taking ETI) Percent Reported Worsening post-ETI

Anxiety	**32%**
Feelings of stress	**31%**
Agitation or irritability	**28%**
Thinking clearly (brain fog)	**28%**
Depression	**28%**
Sleep difficulties	**26%**

Figure 4. Gender differences in worsening depression and anxiety after starting ETI



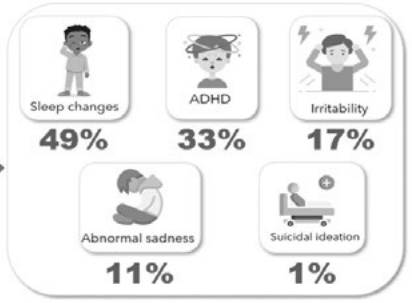
New mood and neurocognitive findings - Preschool Children

MODUL-CF (n=197, ages 2-5)[1]

47% had behavioral changes within

ONE MONTH

85% had no previously documented behavioral or sleep issues



New mood and neurocognitive findings – Adolescents & Children

31 adolescents (aged 10-18 years)[1]

10% anxiety/depression concerns

10% sleep concerns

6 MONTHS

149 children/adolescents (aged 6-11 years) (72%) children[2]

No significant changes in mental health, or sleep. Neuropsychiatric symptoms in 12% of children.

BEFORE ETI & 1 MONTH AFTER

TIDES 2.0

Aim 1	Aim 2	AIM 3
* Estimate national prevalence in 600 children with CF * Children ages 18 months thru 11 years	* Identify Best Screener * Compare Pediatric Symptom Checklist with PROMIS Measures	* Mixed methods, qualitative approach to characterizing modulator AEs * Parent and child interviews (onset, frequency, severity, impact)

Hurray!
TIDES 2.0 – FOUNDED BY CFF

Sampling (600 children 18 mos-11 yrs)

- Cluster-randomized sampling will be used with 16 pediatric CF centers selected across 6 regions of the US
- Within each center, stratified random sampling will be used to oversample racial and ethnic minorities to promote equity in CF research and clinical care

Map of Selected CF Centers

TIDES 2.0: Variations on the US Protocol

	Measures: Ages 18 mos thru 5 yrs	Measures: 6 thru 11 yrs	Time
US Protocol* Longitudinal: 3 assessments	PARENT REPORT: BASC {111 items}, PSC-preschool {18 items}, PROMIS {26 items} CFQ-R Parent, Well-Me	PARENT REPORT: BASC {156 items}, PSC 17, PROMIS {23 items}, CFQ-R Parent, CF Procedural Anxiety, Well-Me	40 min
	CHILD REPORT: Preschool CFQ-R (on a tablet/computer)	CHILD REPORT: PSC-Y-17 {17 items}, CES-DC {20 items} SCARED-Short form {5 items}, PROMIS {16 items}, CFQ-R	20 min
	Qualitative interviews-ETI side-effects	Qualitative interviews-ETI side-effects	
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min
Variation #1 Longitudinal: 3 assessments	PARENT REPORT: PSC-preschool {18 items}, PROMIS {26 items}, CFQ-R	PARENT REPORT: PSC-17 {23 items}, PROMIS {23 items}, CFQ-R	20 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items}, PROMIS {16 items}, CFQ-R	15 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min
	OPTIONAL: Well-Me, qualitative interviews	OPTIONAL: CF Procedural Anxiety, Well-Me, qualitative interviews	
Variation #2 Cross-sectional (1 time)	PARENT REPORT: BASC {105 items}, PSC-preschool {18 items}, PROMIS {26 items}, CFQ-R	PARENT REPORT: BASC {156 items}, PSC 17, PROMIS {23 items}, CFQ-R Parent	40 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items}, CES-DC {20 items} SCARED-Short form {5 items}, PROMIS {16 items}, CFQ-R	15 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min
	OPTIONAL: Well-Me, qualitative	OPTIONAL: CF Procedural Anxiety, Well-Me, qualitative	
Variation #3: shortest protocol Cross-sectional (1 time)	PARENT REPORT: PSC-preschool {18 items}, PROMIS {26 items}	PARENT REPORT: PSC 17 {17 items}, PROMIS {23 items}	15 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items}, PROMIS {16 items}	15 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min

TIDES 2.0: Variation #1

	Measures: Ages 18 mos - 5 yrs	Measures: 6 thru 11 yrs	Time
Variation #1 Longitudinal: 3 assessments	PARENT REPORT: PSC-preschool {18 items} PROMIS {26 items} CFQ-R	PARENT REPORT: PSC-17 {23 items} PROMIS {23 items} CFQ-R	20 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items} PROMIS {16 items}, CFQ-R	15 min 10 min 12 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min
	OPTIONAL: Well-Me qualitative interviews	OPTIONAL: CF Procedural Anxiety Well-Me qualitative interviews	

TIDES 2.0: Variation #2

	Measures: Ages 18 mos - 5 yrs	Measures: 6 thru 11 yrs	Time
Variation #2 Cross-sectional (1 time)	PARENT REPORT: BASC {105 items} PSC-preschool {18 items} PROMIS {26 items} CFQ-R	PARENT REPORT: BASC {156 items} PSC 17 PROMIS {23 items} CFQ-R Parent	40 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items} BASC-Depression BASC-Anxiety PROMIS {16 items} CFQ-R	10 min 10 min 10 min 10 min 12 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min
	OPTIONAL: Well-Me qualitative	OPTIONAL: CF Procedural Anxiety Well-Me qualitative	

TIDES 2.0: Variation #3

	Measures: Ages 18 mos - 5 yrs	Measures: 6 thru 11 yrs	Time
Variation #3: shortest protocol Cross-sectional (1 time)	PARENT REPORT: PSC-preschool {18 items}, PROMIS {26 items}	PARENT REPORT: PSC 17 {17 items}, PROMIS {23 items}	15 min
	CHILD REPORT: Preschool CFQ-R	CHILD REPORT: PSC-Y-17 {17 items}, PROMIS {16 items}	15 min 12 min
	PARENT ASSESSMENT: PHQ-8, GAD-7	PARENT ASSESSMENT: PHQ-8, GAD-7	5 min

Minimum for TIDES 2.0 inclusion in international dataset

HEALTH LITERACY OF THE CHRONIC AND CF PATIENTS AND ITS IMPACT ON THE HEALTH OUTCOMES

Mgr. Peter KOLARČIK, PhD.
Department of Health Psychology and Research Methodology,
Faculty of Medicine, P.J. Šafárik University in Košice, SLOVAKIA

... literacy concept
very simply – ability to write and read

content and context specific – we know different literacies, e.g.:
- financial literacy,
- consumer literacy,
- reading literacy
- IT literacy (computer literacy),
- health literacy

What do we understand by health literacy (HL) ?
Narrow understanding:
- Ability to read and understand written health information

Broader understanding:
- The ability to search for, comprehend and use/apply health information from various sources

HL is not only an individual personality trait, but also a characteristic of families, communities and organizations (hospitals, healthcare centers, patient associations, ...)

WHO HL definition
"Health literacy represents the cognitive and social skills which determine the motivation and ability of individuals to gain access to, understand, and use information in ways which promote and maintain good health"

It is a degree to which individuals have the capacity to obtain, process and understand basic health information and services needed to make appropriate health decisions.

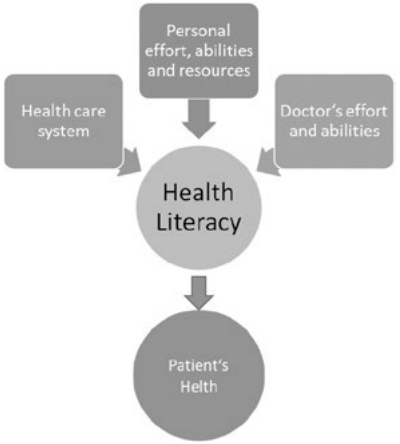
"Health literacy means more than being able to read pamphlets and make appointments. By improving peoples' access to health information and their capacity to use it effectively, health literacy is critical to empowerment (of individuals)."

HL dimensions
1. Feeling understood and supported by healthcare providers
2. Having sufficient information to manage my health
3. Actively managing my health
4. Social support for health
5. Appraisal of health information
6. Ability to actively engage with healthcare providers
7. Navigating the healthcare system
8. Ability to find good health information
9. Understanding health information well enough to know what to do

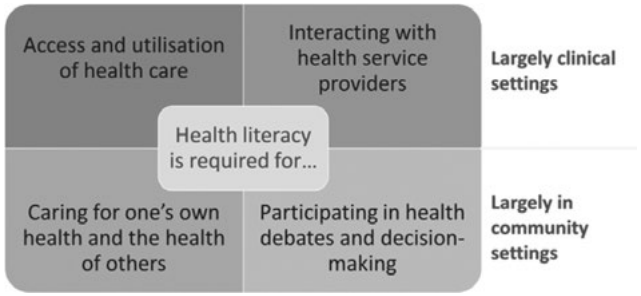
What affects HL of an individual?

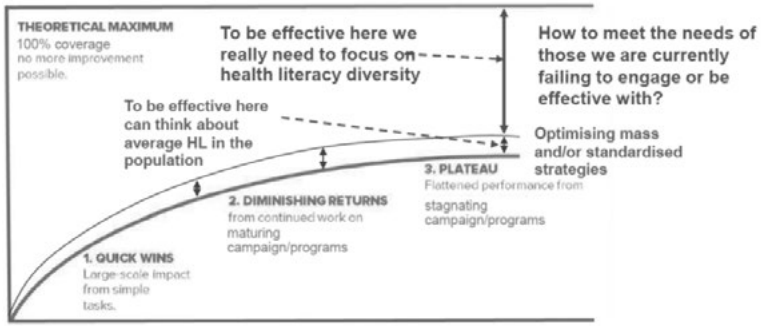
Client:
- Socioeconomic status
- Literacy (ability to read and write)
- Education
- Health status (physical and mental)
- Motivation
- Social support
- Experience with health care

Healthcare provider:
- Communication skills
- Complexity of health information
- Nature of the health care system
- Realtionship of healthcare provider with client



HL importance





Patients with CF & low HL

Cystic fibrosis is a serious genetic disease that primarily affects the lungs and digestive system. When combined with low health literacy in the patient or their caregiver, the situation can become significantly more complicated.

Health literacy enables a patient/caregiver to:
- Understand their disease and its consequences
- Cooperate with the doctor in treatment
- Adhere to the treatment regimen
- Recognize and respond to symptoms of worsening condition

The most common complications related to low health literacy
- Non-adherence to the treatment regimen:
  - Neglect of respiratory physiotherapy.
  - Irregular medication use.
  - Improper diet.
- Delayed seeking of medical help:
  - Neglecting symptoms of infection.
  - Late recognition of serious complications.
- Deterioration of lung function:
  - Recurrent respiratory infections.
  - Increased occurrence of exacerbations (attacks).
- Malabsorption of nutrients:
  - Insufficient intake of calories and nutrients.
  - Decreased weight.
  - Vitamin and mineral deficiencies.
- Psychological problems:
  - Depression, anxiety.
  - Social isolation.
- Decreased quality of life:
  - Limitation of physical activity.
  - Pain.
  - Fatigue.

Improving HL not only in CF Patients

Patient-Centered Communication
- Clear and Concise Language: Avoid medical jargon and use plain language.
- Active Listening: Encourage patients to ask questions and express concerns.
- Teach-Back Method: Ask patients to explain information in their own words to ensure understanding.
- Visual Aids: Utilize diagrams, charts, and videos to simplify complex concepts.

Tailored Education Materials
- Readability Assessments: Use tools like the Flesch-Kincaid Grade Level to ensure materials are appropriate for the patient's reading level.
- Cultural Sensitivity: Adapt materials to the patient's cultural background and language preferences.
- Interactive Tools: Develop interactive tools like mobile apps and games to make learning engaging.

Supportive Interventions
- Support Groups: Facilitate peer-to-peer support and knowledge sharing.
- Counseling Services: Address emotional and psychological needs.
- Community Outreach: Collaborate with community organizations to provide resources and education.

Technology-Based Solutions
- Telehealth: Utilize telehealth for remote consultations and education.
- Mobile Health Apps: Develop apps for medication reminders, symptom tracking, and educational content.
- Online Resources: Provide access to reliable online information and educational materials.

Empowering Patients
- Shared Decision-Making: Involve patients in treatment decisions.
- Self-Management Education: Teach patients how to manage their condition independently.
- Skill-Building Workshops: Offer workshops on topics like nutrition, exercise, and stress management.

Evaluating Health Literacy
- Health Literacy Assessments: Use validated tools to measure patients' health literacy levels.
- Feedback Mechanisms: Regularly seek feedback from patients to identify areas for improvement.

Conclusion
- **Health literacy is important factor of succesful treatment and adherence of the patient**
- **Consider patient's/caregiver's HL level**
- **Accommodate your actions and provided information and treatment accordingly**
- **Develop patient's/caregiver's HL related skills and abilities**
- **Develop your repertoire of actions based on patient's/caregiver's HL level**
- **Support patients' communities, organisations/associations, societies on local, national or international level in order to promote community health literacy**

TWINNING PROJECT

Prof. Pavel DREVINEK
Department of Medical Microbiology, Prague CF Centre
Second Faculty of Medicine, Charles University
and Motol University Hospital
Prague, CZECH REPUBLIC

2020: ECFS and CFE launched the Twinning project

Long-term centre-to-centre partnership
- a mentor (i.e. an ECFS-CTN site) coaches, advises and supports a mentee site
- to address specific needs of a mentee site
- mutual visits

2014: ECFS Standards of Care

Review

European Cystic Fibrosis Society Standards of Care: Best Practice guidelines

Review

European Cystic Fibrosis Society Standards of Care: Framework for the Cystic Fibrosis Centre

Review

European Cystic Fibrosis Society Standards of Care: Quality Management in cystic fibrosis

Inequalities in standards of care across Europe

12. Challenges relating to developing health services in low income countries

The aim of the ECFS Standards of Care Guidelines is to improve the quality of care for patients with CF and to establish

Immediate implementation of these guidelines may prove difficult for less economically advantaged countries where CF services are absent or inadequate.

Framework Coordination Action project identified a persisting wide difference in the standards of care across Europe, with some Eastern European countries having very basic or no recognizable

The likely reason for such dramatic inequalities has been the absence of appropriate funding, a lack of staff recruitment and training, and also a lack of political prioritization.

Organization of CF centres in Eastern Europe

Survey 2015 - 2016: answers from CF physicians from 16 countries

Specialist CF centres. Data from 12 countries included (4 additional countries reported no specialist CF centres). CF physicians answered on existence of CF centres, multidisciplinary teams (MDT) and population size in their largest CF centres.

Recognition by healthcare authorities	6 countries
Adult CF care centres	6 countries
More than one CF centre nationally	7 countries
MDT representation	
Paediatrician	12 countries
Physiotherapist	11 countries
Dietitian	10 countries
Social worker	9 countries
Clinical Geneticist	9 countries
Nurse specialist	8 countries
Clinical Microbiologist	8 countries
Clinical Psychologist	8 countries
Database Coordinator	7 countries
Pharmacist	6 countries
Secretary	4 countries

Walicka - Serzysko et al. Insights into the CF care in Eastern Europe: Results of survey. J Cyst Fibros. 2018.

- a lack of financial resources
- only 6 of 12 recognized by health authorities
- a lack of access to diagnostics and therapies

The beginnings of European twinning

Eastern Europe and the access to CFTR modulators

	Patients in CF registry (as of Nov 2021)	Patients eligible to CFTRm (%) as of Nov 2021*	IVA		LUM/IVA		TEZ/IVA		ELX/TEZ/IVA		Treated (%) out of all eligible patients	
			Nov 2021	May 2022	Nov 2021	May 2022	Nov 2021	May 2022	Nov 2021	May 2022	Nov 2021	May 2022
Bulgaria	220	129 (59%)	4	4	16	32	0	0	7	33	21%	53%
Czech Rep	691	449 (65%)	22	20	82	71	21	11	171	276	66%	84%
Hungary	500	340 (68%)	0	0	117	126	0	0	0	11	34%	40%
Latvia	45	39 (87%)	0	0	0	27	0	0	0	0	0%	69%
Poland	1473	881 (59%)	4	4	22	16	3	3	52	78	9%	11%
Slovakia	344	216 (63%)	1	1	71	50	1	0	26	81	46%	61%
Ukraine	903	605 (67%)	0	0	1	4	1	1	1	3	0.5%	1.3%

Survey 2021 - 2022, 7 countries, percentage of eligible patients on therapy EMA approval ELX/TEZ/IVA: 21-Aug-2020

ECFS-Clinical Trials Network (CTN)

57 CF centres from 17 countries (as of 2024)

ELSEVIER

Journal of Cystic Fibrosis 17 (2018) 475–477

Journal of Cystic Fibrosis

www.elsevier.com/locate/jcf

Short Communication

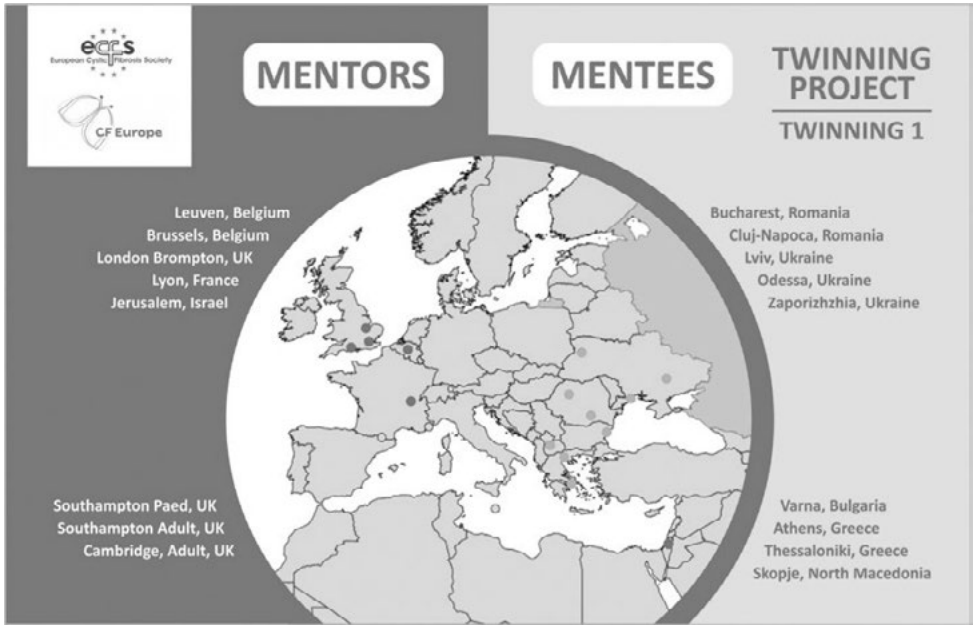
Insights into the cystic fibrosis care in Eastern Europe: Results of survey

Katarzyna Walicka-Serzysko [a,b], Monika Peckova [c], Jacquelien J. Noordhoek [d], Dorota Sands [a,b], Pavel Drevinek [e,*]

„There is a key need to support CF healthcare providers in Eastern Europe in terms of team training and ongoing professional development, supporting access to therapies and support approaches to government authorities."

December 2020: Twinning Project

9 mentees, 8 mentors



Specific needs of mentee sites (self-assessment):

- the setup and organisation of the team
- roles of the team members (especially nurses, physiotherapists)
- how to run a CF ward and CF clinics
- infection control
- monitoring of infections
- microbiological testing and antimicrobial stewardship
- monitoring of nutritional status
- genetic testing
- how to become a clinical trial site

December 2020 > > > April 2022 - Covid 19
A key activity of the project:
A visit to a mentee site and the start of the partnership

Instead of travelling:
- online meetings
- video conferences
- emails

2024: Twinning Expansion Project
- a project ambassador (a liaison officer for mentee sites)
- translation and dissemination of ECFS learning materials translation into 8 languages in 2024
- networking between CF centres and patient organisations (within a country and between coutries)

March 2024: 21 mentees, 19 mentors
27 twins! from 25 countries

2024: Twinning Project activities
- zoom introductory meetings (04/2024)
- meetings at the CFE booth in Glasgow (06/2024)
- South Eastern European CF conference in Cluj-Napoca (10/2024)
- Twinning at various national (Riga 09/2024) or international events (Krakow right now)

(My personal) overall aim: collaboration and friendship

Prof. Elke De Wachter, CF Centre Brussel
Dr. Csilla Szabo, CF Centre Cluj-Napoca

Leuven - Bucharest
Southampton - Athens
Brussel - Cluj - Napoca
Cambridge - Skopje, Kozle
Rotterdam - Sofia
Berlin - Skopje
Montpellier - Vinnytsia
Leeds – Ankara, Paed

Twinning Project and deliverables
- visits
- other forms of contact between mentors and mentees (including patient organizations)
- the level of involvement of CF centre team members
- achievement of three main objectives

Twinning Site Progress report (twinning call 1): Mar 2023 - Feb 2025
Twinning Expansion Site Progress Report (twinning call 2): Mar 2024 - Feb 2025

Conclusions
The Twinning program has been running since 2020: (despite very unfortunate external circumstances)
- many sites have made contacts (at least online)
- many online meetings have taken place
- some site visits have taken place or are in preparation

The Twinning team is here to help and support your pair
- travel budget
- educational materials
- assistance

A mentor team is here to help and support their mentee

THE TWINNING EXPANSION PROJECT
THE INVOLVEMENT OF THE PATIENT COMMUNITY

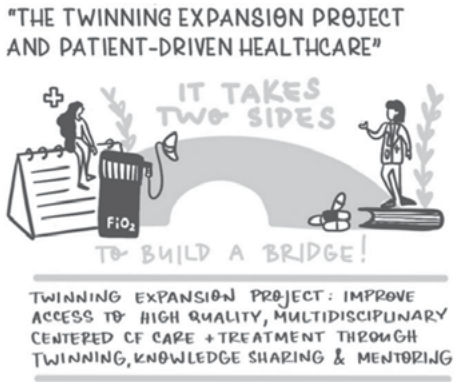
Claire FRANCIS
CFE/ECFS Twinning project coordinator

The Twinning Expansion Project (TEP) is a three-year (2024 - 2026) collaboration between CFE and ECFS, building on the ECFS Twinning Project (2020) which aimed to improve access to high quality, multidisciplinary CF care and optimal treatment.

The aim of TEP is to address discrepancies in clinical outcome for people with CF across Europe. Building long-term collaborative partnerships between mentors and mentee sites and addressing specific needs of the mentee sites, TEP will optimise patients' clinical outcomes.

TEP opened applications for new CF Centres to twin in December 2023 and we had a remarkable number of applications. 21 new pairs (30 in total) are now recruited.

The new aspect of the TEP is that it will also **engage patient organisations (POs)**, who play a pivotal role in identifying and addressing unmet needs (e.g. access to therapies, adult care, trained healthcare professionals), facilitating communication, and signalling possible mentee sites. Well-resourced POs with advanced advocacy, digital expertise and capabilities will provide guidance to those POs needing more support or training. As well as the twinned pairs building their partnership, the project also aims to support and facilitate networking between POs and CF centres participating in the project.



Twinned Patient Organisations

Albania	- Italy	Estonia	- United Kingdom	North Macedonia	- Germany
Armenia	- Switzerland	Georgia	- Germany	Romania	- Belgium
Bulgaria	- Netherlands	Kosovo	- Netherlands	Slovakia	- United Kingdom
Croatia	- Denmark	Latvia	- France	Ukraine	- France
Cyprus	- Italy				

Aims of TEP
1. Establish new CF centre mentor and mentee sites with the aim of facilitating collaborations and exchanges between the twinned pairs.
2. Identify unmet needs in CF care in the mentee sites and formulate feasible goals.
3. Grant access to ECFS learning resources to participating CF centres and translating these resources into relevant languages.
4. Facilitate knowledge sharing and networking opportunities between CF centres and patient organisations in different regions.

How will the twins work together?
- Getting to know each other through zoom and visits
- Devising one or two objectives to work on together in 2025
- Devising an action plan together to achieve these objectives

Knowledge sharing and networking
- Central learning resources
- The Southeastern European conference (Pristina, Kosovo in 3 - 5 April 2025)
- Encourage twins (POs and CF Centres) to meet at ECFS conference
- Project Ambassador visits

How friendships will be built
It is expected of the new twinning pairs that the mentor site will organise at least one visit to the mentee site in 2024/25 (if geopolitical conditions allow it). The visit will include a CF physician and possibly a CF nurse and/or other CF team members (physiotherapist, nutritionist, psychologist,...). The aim of the visit is to establish a partnership, get an overview of the mentee site, discuss unmet needs and opportunities, and build on this knowledge to develop further twinning. The duration of TEP for new sites is one year. After one year, a summary report will be prepared and submitted jointly by both sites and will serve as the basis for the continuation of the funding.

The Twinning Project is governed by a Steering Committee made up of clinicians and patient organisation representatives and is led by Hilde De Keyser and Prof. Pavel Drevinek. The Project Team includes Claire Francis, Project Coordinator, Helen Chadwick, ECFS Twinning Coordinator and ECFS Education Coordinator, Katarína Štepánková, Project ambassador and Oxana Igonchenkova, Team Coordinator.

Project Ambassador visits
With so many new applicants for TEP, we have a detailed programme of visits by the Project Ambassador, Katarina Stepankova to mentee sites. Once the applicants were approved as twins and officially announced in early 2024, Katarina surveyed the needs of each mentee country and assessed which countries need further support from a central ambassador.
The criteria for visits are:
- Mentee country has yet to set up a CF Centre or has specific issues that need to be addressed
- Lack of patient organisation
- Patient organisation has requested further support from CF Europe

The following table outlines the itinerary including visits that have happened and those that are planned.

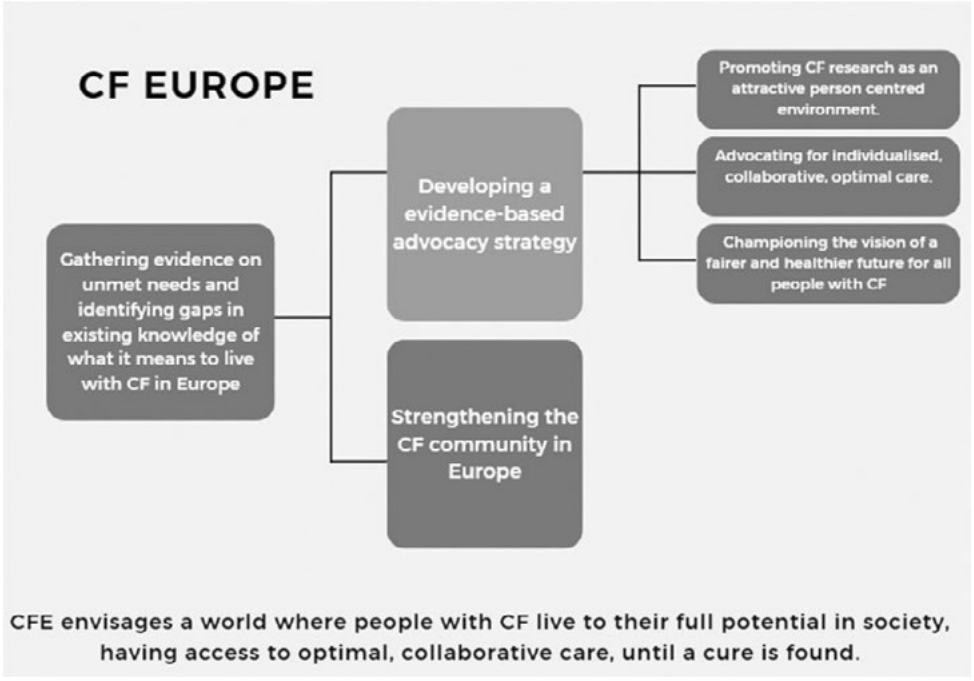
Ambassador Visits

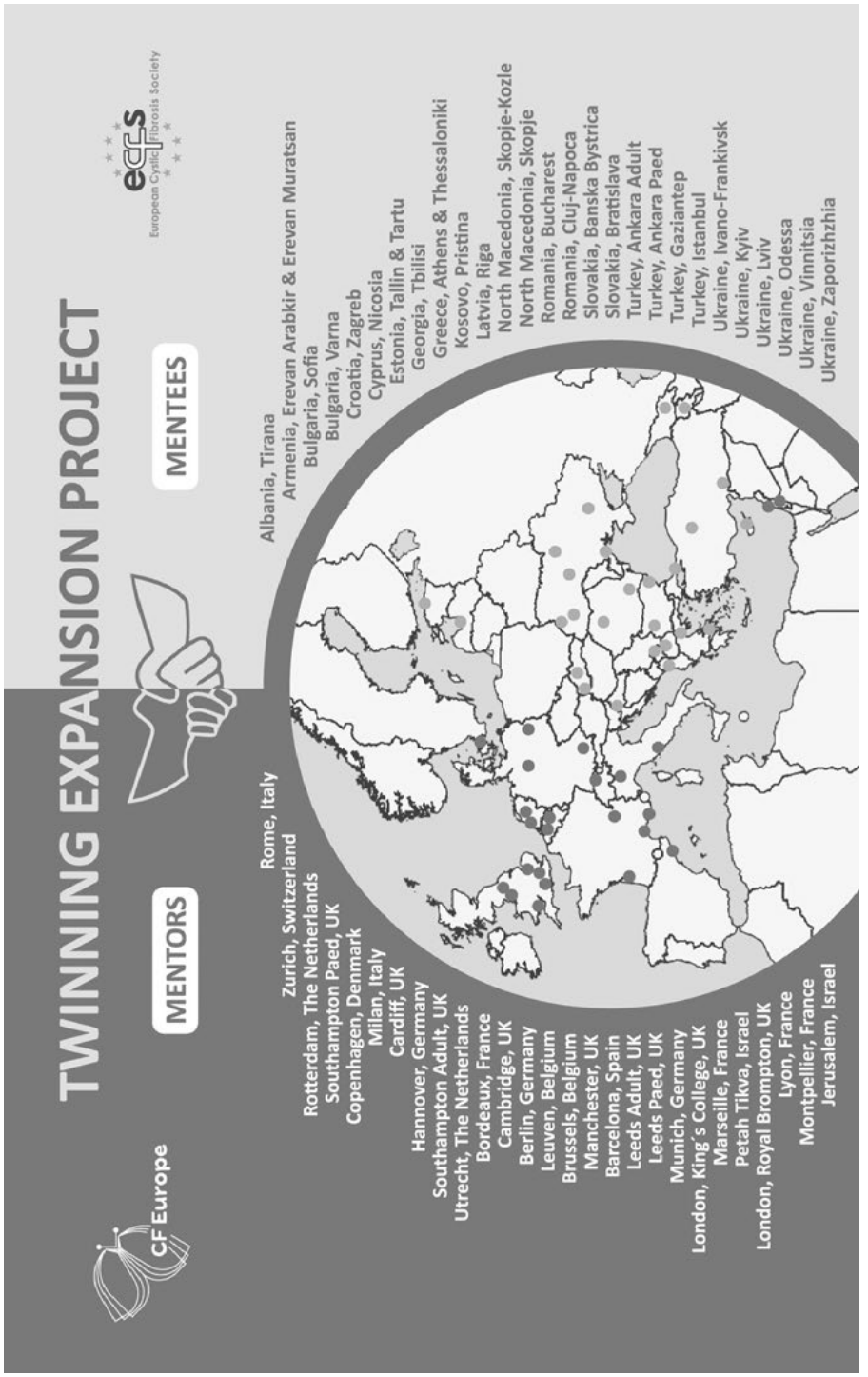
COUNTRY	DATE	STATUS
SLOVAKIA	2023	DONE
UKRAINE	DECEMBER 2023	DONE
ALBANIA	AUGUST 2024	DONE
KOSOVO	AUGUST 2024	DONE
LATVIA	SEPTEMBER 2024	DONE
ROMANIA	OCTOBER 2024	DONE
ARMENIA	APRIL 2025	DONE
GEORGIA	APRIL 2025	DONE
BULGARIA	JULY 2025	PLANNED
CYPRUS	SEPTEMBER 2025	PLANNED
ESTONIA	MAY 2026	PLANNED
MACEDONIA	AUGUST 2026	PLANNED

Visits in 2024
Albania

Republic of Kosovo

Strengthening the CF Community in Europe together





TWINNING PROJECT
ALBANIA, TIRANA + ITALY, ROME

Irma TASHI + Fabio MAJO

Mentee: University Lung Deparment, Rajonal Hospital of Tirana Shefqet Ndroqi, Adult CF Center, Tirana
Mentor: Bambino Gesú Children's Hospital, Rome

Gaps
- The absence of a standardized protocol approved by the Ministry of Health which can significantly impact the quality of care provided to patients with Cystic Fibrosis.
- Gaps in specialized training for auxiliary staff, Efforts to enhance education and skill development are needed.
- Limited Access to Specialized Nutritional Support
- Restricted Availability of Modulator Medications
- Essential treatments, such as alpha dornase and Tobramycin inhalers, are currently insufficient. Efforts are ongoing to secure a more consistent supply.
- Insufficient Sociopsychological Support

Visit in Tirana, January 15th to 18th
- Discussing cases of pwCF
- Sharing educational material
- Shadowing clinic
- Meeting patient representatives
- Networking
- visit to University Hospital Mother Teresa Prof. ass. Irena Kasmi

Challenges:
False start: burocratic issue with permissions

Objectives for 2025
- Onsite visit of the mentee staff in Rome
- Remote training for mentee staff
- Support in decision-making for pwCF
- Support in internal guidelines writing
- ...more networking!

TWINNING PROJECT
BULGARIA, SOFIA + NETHERLANDS, ROTTERDAM

Guerguana PETROVA-STOYANOVA + Hettie JANNSENS

Mentee: CF Center, Pediatric center, Alexandrovska University Hospital, Sofia
Mentor: CF Center-Sophia Erasmus University Medical Center-Sophia Children's Hospital, Rotterdam

Aims for Sofia CF Center:
1. Improve follow-up program for patients
2. To increase knowledge of CF care for staff
3.To establish a smooth transition program

Activities till now:
- Patient discussion via teams
- Meeting with CF team Rotterdam and Dr Petrova and Bulgarian representative of CF patient organization at ECFS
- Visit CF team Rotterdam to Sofia 25th of October.

Visit of adult clinic Sofia:
- Patient discussion
- Discussion on ways to improve care for adult CF patients: what is needed?
- Finance problem: adult ambulant care not reimbursed
- No government

Impression of visit Pediatric Clinic:
- **One doctor doing all the work for CF patients**
- **Taking care of 140 patients all on her own (children and adults)**
- **Follow-up is not possible to do more frequently than every 6 months**
- **Investigations like chest-CT's cannot be done routinely.**
- **Restrictions on medication budget**
- **One gastro-enterologist available and dedicated to CF**
- **One physiotherapist, one lungfunction technician, one nurse: but not specifically for CF.**
- **Lack of nurses.**

Plans:
- Help in education material for patients (video's, flyers, website)
- Education staff: possibility for 3 staff members to go to ECFS for free (ask ECFS)
- Monthly Teams meeting to discuss patients, education staff members.
- Talk with health authorities as soon as a government is in place...

TWINNING PROJECT
CROATIA, ZAGREB + DENMARK, COPENHAGEN

Duška TJEŠIĆ-DRINKOVIĆ, Andrea VUKIČ DUGAĆ + Tavs QUIST

Mentee: Cystic Fibrosis Centre Pediatrics and Adults University Hospital Centre Zagreb, Croatia
Mentor: Cystic Fibrosis Centre, Copenhagen

Gaps
- 2020 - earthquake in Zagreb
- UHC Zagreb - reduced hospital capacity to 1/3
- PARI inhalers - not on the positive list of health insurance
- Airway clearance devices (PEP, Flutter, Aerobika...) - not on the positive list of health insurance
- NO National newborn screening program for cystic fibrosis in Croatia!!!!

What was done
- several zoom meetings
- Zoom meeting of patient CF organizations
- March 27th – 29th 2025: Mentor – Mentee meeting in Zagreb
- Visit of CF Centre Copenhagen to CF centre Zagreb

Danish team's visit, we organized:
- workshop for physiotherapists led by a Danish physiotherapist,
- mini CF symposium with engaging lectures, and
- hybrid meeting with patients and their family members.

Objectives for 2025
- Visit CF centre Zagreb to CF Centre Copenhagen – autumn 2025
- Setting grounds for the NBS program in Croatia using the Danish model
- Collaboration in scientific research, publication

TWINNING PROJECT
ESTONIA, TARTU, TALLIN + UNITED KINGDOM, CARDIFF

Maire VASAR + Julian FORTON, Jamie DUCKERS

Mentor: Tartu University Hospital, Tartu, SA Tallinna Lastehaigla, Tallinn
Mentor: Children´ s Hospital for Wales, Cardiff

Visits:
Estonia, 9. – 12. October 2023
- Julian Forton, Katherine Ronchetti (physiotherapist) and Hannah Morgan (physiotherapist)

Cardiff, June 2024
Tallinn: Dr. Silvi Plado, Elise Kukk (nurse), Cristina Lõokene (physiotherapist)
Tartu: Dr. Anneli Viidebaum, Katri Paavel (nurse), Kaari Käsper (nutritionist).
- Annual assesement
- Experience with modulator therapies
- Transition to adult services
- Afternoon lectures
- Visit to the Adult CF service for transition clinic

Current Priorities:
1. Establish Annual Assessments in Estonia as standard of Care
2. Develop virtual support network between Twin services
   - Ad Hoc virtual meetings to discuss difficult cases, virtual meetings between therapists
   - Sharing of educational materials and protocols via website shared page
   - Formal virtual educational meetings
   - Emphasis on managing patients on Modulator therapy
3. Expand collaboration to incorporate Adult CF Teams
   - Combined Paediatric/Adult Visit to Estonia planned for December 2024 (Forton/Duckers)
   - Hospital visits in Tartu and Tallinn, meeting of colleagues, sharing of ideas, lectures, planning future
   - Emphasis on managing patients on Modulator therapy
4. Organise Estonian Adult team Visit to Cardiff 2025

TWINNING PROJECT
KOSOVO, PRISHTINA + NETHERLAND, UTRECHT

Vlora NIMANI + Marit van OIRSCHOT-van de VEN

Mentee: Pediatric Clinic, Cystic Fibrosis Center, Prishtina
Mentor: Pediatric Pulmonology, Cystic Fibrosis Center, University Medical Center Utrecht

Gaps
- Not enough rooms to support the admission of patients at once
- Still no complete multidisciplinary team (lacking nutrition and physio)
- No modulators to treat patients, low income country
- Need more nurses to support the daily tasks with CF patients

What we done
- Regular zoom meetings
- Discussing old and new CF cases with the multidisciplinary CF team in Utrecht
- Trying to start a online training of nurses to assess and treat CF patients

Challenges
First challenges faced starting the zoom meetings on regular bases
- we used personalized e-mails on disscussing cases, on times we couldn't make the zoom meeting

Objectives for 2025
- Visit of CF Center in Prishtina, from the Dutch team
- Visit on site the respective CF Centers, 7 April – 2 nurses
- Train nurses and doctors on basic nutrition until a nutritionist added to the team
- Sharing the Dutch Steps to take after a positive Newborn screening for cystic fibrosis (CF)
- Sending to Kosovo educational materials and picture books about cystic fibrosis (CF) for parents and their children

TWINNING PROJECT
LATVIA, RIGA + FRANCE, BORDEAUX

Elina ALEXEJEVA + Stephanie BUI

Mentee: Children's Clinical University Hospital, Latvia
Mentor: Centre Hospitalier Universitaire de Bordeaux, France

Cystic fibrosis will not win because we will never stop fighting.
Together we will make a difference

Activities:
- Communication via email.
- Two remote meetings were held on the Webex platform with the CF multidisciplinary team (MDT) from the Bordeaux CF Center and the CF team of the (LV) Children's Clinical University Hospital.

A complex clinical case was discussed at the meetings on:
- plan of investigations and treatment;
- consultations with other specialists
- infectionists, microbiologists.

Result:
- quick involvement and responsiveness,
- exchange of experience between two national specialists on specific clinical cases,
- very valuable recommendations that have contributed to a good result.

Action plan:
for achieving goals, tasks and priorities in the coming years:
- Meetings in Riga, Latvia. The Bordeaux team was invited to the Baltic CF Conference, which will take place in October 2025.
- To get acquainted with the activities and organization of the CF center
- To supplement the knowledge of the CF team
- To train CF-related services - microbiologists, radiologists
- To acquire additional knowledge in the field of functional diagnostics (LCI, etc.)
- To assist in the development of an adult CF transition program and team training
- To evaluate diagnostic and CF newborn screening algorithms

Challenges of the cooperation:
- active involvement occurred in the initial stage, which has now decreased,
- MDK meetings are not held (once a month) according to the plan,
- it is difficult for the mentor and the team to find additional time for cooperation,
- the next meeting is expected on 19/DEC/2024

TWINNING PROJECT
NORTH MACEDONIA, KOZLE + UK, CAMBRIDGE

Tatjana JAKJOVSKA MARETTI + Charles HAWORTH, Donna McSHANNE

Mentee: University Clinic for Respiratory Diseases in children, Kozle, North Macedonia
Mentor: Royal Papworth Hospital and Addenbrooke's Hospital, Cambridge, UK

Gaps
- CT scan at the Clinic (CT scan at the Pulmonology Clinic, monthly joint clinic with the radiologists)
- Fiber scan at the Clinic (fiber scan at the GIT Clinic, monthly joint clinic with the hepatologist to manage CF liver disease)
- Monthly joint clinic with diabetologist to manage CF related diabetes.
- Reintroduce Fecal elastase test (malfunction device)
- bigger budget

Activities done
- High level strategic discussions with hospital management, Minister of Health and First lady of North Macedonia in support of the CF service
- Onsite visits of Mentor team to Skopje x 3
- Onsite visit of Mentee team to Cambridge x 1
- Review of patients
- Discussions / teaching of MDT – particularly in relation to CFTR modulators
- Lectures at conferences in Macedonia x 2

Chalenges
- Face to Face visits help to build relationships between the teams and to better understand the resource constraints / training requirements
- Meeting at the ECFS conference and other events is beneficial between face-to-face meetings
- Online discussions have proved difficult due to poor internet speed and language
- WhatsApp is very useful for rapid advice!

Objectives for 2025
- Arrange further on-site visits when time allows
- Continue to meet at ECFS conference in June and at other conferences such as ERS
- Provide on-line support as and when needed (WhatsApp)
- Provide strategic support in relation to Hospital Management / Ministry of Health

TWINNING PROJECT
NORTH MACEDONIA, SKOPJE + GERMANY, BERLIN

Valentina CVEJOSKA CHOLAKOVSKA, Stojka FUSTIKJ + Mirjam STAHL, Zulfiya SYUNYAEVA

Mentee: University Children's Clinic, Skopje, North Macedonia
Mentor: Charité – Universitätsmedizin, (University Hospital), Berlin, Germany

Gaps
- Lung clearance index (Multiple-breath-washout Analyzer)
- Nasal potential difference (Voltmeter)

Activities done
- Visit of the mentee team in Berlin – June 2024
- Doctors
- Nurse
- Physiotherapist
- Online meetings – firstly to get knew each other
- Regular contact via e-mail and online meetings
- Monthly online patient discussion round
- Exchange of experience with CFTR modulator therapy in children and adults
- Exchange of SOPs

Challenges
- Mutual trust and personal compatibility form the strongest foundation for ongoing collaboration and meaningful support wherever possible.
- The exchange of experiences and regular dialogue—especially in this new era of treatment—are invaluable.
- Developing a strong and connected network for CF care is essential.
- Deep dedication holds tremendous value and can inspire creative, alternative approaches that help us achieve our goals - even making the seemingly impossible, possible.

Objectives for 2025
- Mentor-Mentee Meeting at SEEC 2025, Pristina, Kosovo
- Mentor-Mentee Meeting at ECFS 2025 Conference, Milan, Italy
- Scheduled Visit to the Mentee Site at University Children's Clinic CF Center, Skopje in 07/2025
- Visit to the Mentor Site, Charite, during the autumn
- Ongoing Regular Patient Discussion Meetings
- Continued Collaboration on Specific Questions and Challenges at the Mentee Site

TWINNING PROJECT
ROMANIA, BUCHAREST + BELGIUM, LEUVEN

Simona MOSESCU + Mieke BOON

Mentee: Emergency Children's Hospital, Bucharest, Romania
Mentor: University Hospital, Leuven, Belgium

Setting goals:
- Build up partnership
- Working in a CF team
- Managing severe respiratory cases
- Become CF clinical trial site

Online meetings:
9 Online meetings from January 2021
- Online physiotherapy clinics: coach patients, parents and physiotherapists
- Online psychologists meeting: supporting newly diagnosed case

Visits:
Bucharest, November 2022
- Pediatric Pulmonologist and physiotherapist went to Bucharest for 3 days
- Medical education, live medical teaching, suggestions for training
- Onsite physiotherapy training sessions, focusing on self-treatment

Leuven, April 2023
- junior Pediatric Pulmonologist came to Leuven for 5 days
- Programme in function of specific needs
- Bedside teaching on CF
- Attending MDT activities: outpatient and inpatient clinics
- Specific topics addressed by MDT
  - Physiotherapy
  - Nutrition
  - Psychological support
  - Social support
  - Nurse aspects of CF care
  - Lung function
  - CF research
- Case discussions

Spread the word...POSTER on ECFS conference 2023

Conclusions
No large gaps in medical treatment
- CFTR modulators similar to Belgian situation

Main gaps in MDT
- Training in CF physiotherapy
- Developing focus on nutrition

Organisation of health care has impact

Way forward
- Hard work and dedication
- Scientific training and education

TWINNING PROJECT
ROMANIA, CLUJ-NAPOCA + BELGIUM, BRUSSELS

Csilla Enikő SZABO + Elke de WACHTER

Mentee: Pediatric Clinic I, Clinical Emergency Children's Hospital, Cluj-Napoca, Romania
Mentor: CF Clinic, Pediatric Pulmonology and allergy clinic, Brussels, Belgium

What is Twinning project?

Connects leading experts from Brussels and Cluj - Napoca to improve the quality of care for patients with CF by exchanging knowledge, skills, and resources.

Our Journey

- September 2020 – Centre application for the Twinning project
- December 2020 – Receiving the results of evaluation and selection
- January 2021 - First virtual Twinning project meeting Brussels-Cluj-Napoca
- 15. – 17. May 2023 – First visit of Belgium's team in Cluj-Napoca
- June 2023 – In-person meeting at the Vienna CF conference

1st online meeting - to get to know the teams – Experieces:

- Connection problems
- Emergency in clinic
- Language barrier
- the first meetings to get to know the teams:
  - sharing the organizational structure of the departments
  - discussing difficult cases
  - sharing the improvement of communication with parents and patients
  - learning new Physiotherapy and airway clearance techniques

- The first meeting was exploratory
  ...certain shyness that was difficult to break due to the virtual nature of the encounter
  -> More online meetings to get a personal connection
  ...sharing birthdays (23 and 24 jan)

More online meetings...

- Always with Csilla
- With different members of CF Team UZ Brussels -> specific topics
- Discussing Standards of care (2014-2018) – identifying barriers
  multidisciplinary team
- Plans to meet in person

What we learnt

- Trust and a personal match is the best basis for further collaboration and to support each other where needed / possible
- Ideal world is often far away, but it opens your perspective and can lead to interesting alternative ways to achieve your goal
- Dedication is precious and valuable

Long-term vision

- Visit UZ Brussels ...in 2025
- Establish a standardized protocol for CF treatment in our centers (challenges, pitfalls)
- Discussion of complex cases remains important
- Building a Strong Network of CF Care
- Strengthen relationship between our CF centers, for future collaborations

TWINNING PROJECT
SLOVAKIA, BRATISLAVA + SPAIN, BARCELONA

Zuana RENNEROVÁ, Nina BLIŽNÁKOVÁ + Silvia GARTNER



Mentee: CF Centrum NÚDCH Bratislava
Mentor: CF Unit Barcelona Hospital Universitari Vall d´Hebron, Barcelona

Chalenges in Slovakia:
- Ivacaftor / Tezacaftor / Elexacaftor for children from 2 years of age
- teamwork between individual specialists
- access to clinical trials
- availability of LCI
- ERN-CF

Expectations from Twinning project:
- to learn as much as possible
- to improve patients managment - nutrition evaluation and management, better monitoring and treatment of CFRD, follow up with LCI measurement
- to discuss clinical cases
- to improve organisation of CF center, collaboration with patients organisations
- to have opportunity to participate to international clinical studies

Visit:
- on Sunday 10th November we met with a pleasant and healthy meal in city Modra
- visit in the hospital Monday and Tuesday (**11th - 12th November**)
- hospital tour with Dr. Zuzana Rennerová and Dr.Nina Bliznáková – ward, out patients clinic, kinesiology department, different specialist

- Out-patient clinic:
  - see pwCF
  - discuss different protocols (PA infection-erradication, etc)
  - ABPA
  - CFSPID
  - NBS strategies
  - talk about special cases

- Specialists
  - Kinesiology
  - ORL
  - Psychologist
  - Parent's association

Meeting with the director of the hospital:
- needs to be covered (budget!)
- important role of CF associations
- financial support for treatment
- new CF Unit
- new spaces and new device for diagnosis

PLAN:
- **Monthly zoom meetings**
- **Visit CF unit Hospital Vall d´Hebron.Barcelona in 2025 - Meet multidisciplinary CF team (Ped-adults)**
- **Educational talks**
- **Discuss**
  - **patients**
  - **protocols**
  - **follow –up patients**
  - **different specialists**
  - **parent / pwCF association**
  - **special patient for intestinal organoids - identifying patients suitable for treatment through intestinal organoids**

TWINNING PROJECT
UKRAINE, IVANO-FRANKIVSK + FRANCE, MARSEILLE

Monika MAKIAN, Nadyia FOMENKO + Natalie STREMLER

As part of the Twinning project, we would like to achieve:

1. **Practice training and workshops;**
2. **Helping in mananging difficult patients.**
   Modern aspects of treatment: targeted therapy, possibly gene therapy.
3. **Psychological support of patients and their families.**
   Professional burnout.

Activities:

- As part of the project, we hold monthly online meetings, during which our mentors give answers to questions that interest us.
- share the experience regarding treatment, early diagnosis of complications and management tactics of patients with cystic fibrosis.
- A trip to the hospital to our mentors is also planned in order to achieve the set goals.

TWINNING PROJECT
UKRAINE, KYIV + ISRAEL, PETAH TIKVA

Natalyia SAMONENKO, Yulia OSTAPYSHENA + Dario PRAIS, Meir MEI-ZAHAV

Activities:

1. zoom meeting 11/9/24: Team presentation and introduction

2. zoom meeting 6/11/24:

- General discussion
- Case presentation: 17-ys-old patient with severe lung disease and coagulopathy
- **Multidisciplinary discussion**
  - Physicians
  - Dietician
  - Clinical pharmacologist
  - Social worker
  - Physiotherapist
  - Nurses
  - Psychologist

Supporting material

- Contact details of all the Schneider team submitted
- Translated mental health questionaries supplied

Future plans

- “plenary” periodical meetings
- Direct contact between teams based on a professional/discipline basis
- To understand what the needs are
- To translate more protocols and worksheets (funding needed)
- Who knows? To visit each other in the future…

Challenges:

"Hello everyone! As you know, both Israel and Ukraine are facing unique challenges. But, just like cystic fibrosis care, our spirit of collaboration and resilience keeps us pushing forward. Despite the missiles and sirens, our centers continue to work together, proving that determination knows no borders."

The Common Mission Theme: "Good day! In times like these, every challenge is amplified, and yet so is our commitment. Despite obstacles that might seem impossible, our Israeli and Ukrainian centers have chosen to stand together, showing that even when the world around us feels uncertain, our mission to help patients remains unwavering."

The Shared Strength and Humor: "Hello everyone! Working in healthcare, we're no strangers to challenges—even those that come with sirens and difficult news. Yet, here we are, united and determined. The Israeli and Ukrainian teams, while separated by distance, are bound by a shared resilience—and maybe even a stubborn optimism—that we can make things better for our patients."

The 'Why We're Here' Connection: "Thank you for joining. In Israel and Ukraine, we've both faced days where hospitals themselves come under threat, yet our work for cystic fibrosis patients goes on. I'm here to share how we've stayed connected through this journey, holding strong to our shared vision for better care, regardless of the obstacles."

TWINNING PROJECT
UKRAINE, LVIV + UNITED KINGDOM, BROMPTON

Lyudmyla BOBER, Halyna MAKUKH + John KING

Twinning project - "mark 1"
Ian Balfour Lynn and Su Madge
- Challenging clinical cases
- Shared educational resources and guidelines
- Plans for online CF course

Resources:
- Email
- Zoom and Teams meetings
- Royal Brompton Paediatric CF Guidelines

ABPA Disease Course in a Patient with Cystic Fibrosis (observation from 05.2019 to 09.2021)

Challenges:
Lviv.: War, Financial, Travel visas for visits etc
Royal Brompton: Sue and Ian leaving the project, Handover

Reset - new relationships and planning for the future:
- Meeting in Glasgow 2024 for discussion the most helpful way to support.
- Ongoing lectures online for important topics
- Discussion of complex clinical cases by email/zoom
- Visit to the UK

Goals:
1. Implementation of clear medical leadership and chain of command, the roles and responsibilities in the team
2. Improving specialised care for children with cystic fibrosis
3. Organization of NBS care for patients with maximum anti-infective protection, improvement of infection control in general.
4. Improving the support of patients with pulmonary complications and portal hypertension, psychological problems and socially vulnerable families.

Plans of joint activities:

- The case discussions for adult and pediatric patients accordingly to desired topics for discussion
- Online meetings and talks on desired topics, particularly relating to management of complications of Trikafta
- Visit to the UK Brompton CF centre in 2025

Topics for discussion and shared education:

- Talks online – lead by Dr Barbara Belkarty
- Proposals of the Lviv Cystic Fibrosis Team:
  - Complications of mCFTR in adults with CF
  - Changing the methods of physiotherapeutic support in CF against the background of therapy with modulators
  - Nutritional support of people with CF on the background of taking mCFTR
  - Hypoglycemia in people with CF - a complication of mCFTR or undiagnosed diabetes?
  - Hypoglycemia in diabetes associated with cystic fibrosis on the background of taking chlorine channel modulators
  - The importance of taking fat-soluble vitamins during the period of taking mCFTR - a rational approach, recommendations, justification.
  - Cystic fibrosis and chronic infection in the era of mCFTR: diagnosis, tactics, strategy

Visit to the UK Royal Brompton Hospital, London:

- Likely 2 weeks visit
- Plan for series of talks and likely 'in house' CF course
- Role specific partnerships for parallel learning
- Timing alongside the well respected King John Price Paediatric Respiratory Conference
- Resources needed: translation
- Challenges expected: funding, accommodation, visas
- Support from RBH charity and our hospital HR teams

All our plans that arose in Glasgow, were discussed in Krakow and implemented in London. 24. March – 6. April 2025 CF team from Lviv visited he Royal Brompton Hospital. 9 specialists from Lviv, as part of the Twinning project, with the support of the CFE (European Cystic Fibrosis Association), co-financing by the CF Trust and our joint efforts, underwent training, familiarization with the system of providing medical care to cystic fibrosis patients in the UK, visited the congress, met with incredible people - legends of British medicine.

Plans for the future:

- **New relationships starting in the past year only due to explained challenges**
- **Real start of work next year, so everything presented today determines the long-term vision**

TWINNING PROJECT
UKRAINE, VINNYTSIA + FRANCE, MONTPELLIER

Nataliya SINCHUK + Raphael CHIRON

How are you developing your relationship?

- First there was correspondence
- Then an online meeting

Visit:
Montpellier CF center, August 2024
-lots of exchanges and a real friendly time!

A hot week with the multidiscipliary team!

What we did:

- Sharing our practices
- Participation in multidisciplinary consultations
- Presentation of the research team integrated into the clinical team and we shared our experience in clinical research

What we decided to do:

- **Gain a better understanding of our cohorts and compare them in order to identify opportunities for improving care for patients and their carriers.**
  Project development (in progress)
  Objective: Compare our pediatric cohorts (Montpellier and Vinnytsia) to identify differences and needs
  Method: Comparative descriptive study

- Following the observations of our discussions, we identified 3 areas requiring urgent action:
  - Nutrition and diabetes management: screening, treatment and therapeutic education action: diet connection!
  - Physiotherapy: training in collaboration with Hugues Gauchez
  - Antibiotic strategies: planned remote medical consultations

- Clinical research:
  The Vinnytsia team is highly motivated, when Montpellier team has experience in CF CTs
  Objective: to be ready for research when sponsors will able to conduct studies in Ukraine

"I believe that we also complement each other within the framework of our joint collaboration and look towards the future - helping doctors and families of children with CF.
The next station is Vinnytsia!"

The road to future goals: Thank you for the meeting in Krakow where we have opportunity to discuss our future activities.

TWINNING PROJECT
UKRAINE, ZAPORYZHYA + ISRAEL, JERUSALEM

Tanya OKUL, Elena FOLUMENOVA + Malena COHEN-CYMBERKNOH

Can you share a challenge you've encountered so far in working with your twin, and how you approached it?

Our initial plan was:

- to establish open communication between the two CF centers
- to assess the needs of the CF team in Zaporizhzhia
- to invite the Zaporizhzhia's staff to our CF Center in Jerusalem for hands-on training
- to visit the Zaporizhzhia CF Center to provide on-site training for their team

Unfortunately, the situation during the last years is as follows:

- 3 / 2020 - COVID Pandemic
- February 22nd 2022 **War started in Ukraine**
- October 7th, 2024 **War started in Israel**

Therefore, the "original" project was adapted upon the current situation:

We have been in contact virtually by zoom meetings, been more fluid since 2024:
February 19, May 29, September 11, October 30, December 4

Objectives for the near future:

Establish a Sustainable CF Program: to enhance CF care and support for patients and caregivers
Maintain Knowledge Transfer: Set up regular virtual follow-ups, mentorship, and continuous training resources to ensure ongoing skills development (hopefully not only "virtual")
Implement Monitoring and Quality Protocols: Guide the team in creating protocols for monitoring outcomes, quality assurance, and data-driven improvements (e.g., GI guidelines for colorectal cancer- last meeting)
Provide Insights on Advanced CF Therapies: Share the latest CF treatments (e.g., advancements in airway clearance, covered in prior zoom meeting by the physiotherapist from Hadassah in a previous virtual meeting)
Promote Inter-Professional Collaboration: Foster teamwork among physicians, nurses, physiotherapists, dietitians, and social workers to meet the comprehensive needs of CF patients

TWINNING PROJECT: PATIENTS ORGANIZATIONS
ALBANIA + ITALY

Fjorza MULLAHAJ + Silvia RANOCCHIARI

ALBANIA

Current situation

- Lack of information
- Lack of institutional cooperation
- Lack and difficulty in treatments

Visit – January 2025 Italian CF team in Albania

- Information and clarification on the progress and treatments of patients by the team of doctors of the CF center of "Bambino Gesu"
- Fruitful collaboration regarding the most contemporary methods and techniques for the treatment of patients
- Coordination on the statute and policies for the creation of the CF Albania association

Achievements

- Registration of the "CF Albania" association
- Organization of parents and CF patients

Objectives

- Activating the association
- Creating awareness and information activities
- Creating a registry with complete statistics about patients and genotypes
- Creating communication and information facilities between patients and doctors through an electronic system

Expectations

- Coordination and information about the way to organize awareness activities
- Designing projects
- Better structuring of the internal organization of the association

ITALY

Vision
- Patient-centered care and rights
- Research focused on improving patients' lives
- Coordination of all stakeholders in the CF world
- Strong, united CF community
- Partnership to support the development of a strong CF patient organization in Albania
- Shared experience, knowledge, and good practices

First steps
- Already started: First meetings and exchanges, together towards a common goal
- Initial online meetings completed
- Needs analysis underway
- Shared priorities identified
- Planning next steps for building the Albanian CF association

What we can offer as a mentor
- Share our organizational model and best practices
- Training for leaders and volunteers
- Support advocacy initiatives
- Facilitate networking with CF organizations
- Participate in online and in-person meetings
- Co-create strategies tailored to Albania's needs

What we cannot do
- We cannot interfere with healthcare institutions or clinical centers
- We cannot provide direct financial support (except for specific shared projects)
- We are mentors, not decision-makers for Albania's future association

Next steps
- Continue online workshops and meetings
- Organize training sessions
- Support advocacy efforts with local institutions
- Strengthen the community of Albanian families and patients
- Long-term vision: A self-sufficient and recognized CF patient association in Albania

Conclusion
Patient associations represent a fundamental resource in the fight against chronic diseases, offering multidimensional support that goes beyond the clinical aspect and addresses the emotional, informational, and social needs of patients.

- Building a better future for people with CF in Albania
- Sharing experience and creating new opportunities.

We are here to walk this path together, step by step.

TWINNING PROJECT: PATIENTS ORGANIZATIONS ARMENIA + SWITZERLAND

Narine MOVSYSYAN + Reto WEIBEL

ARMENIA

Existing issues
- Different care delivery in capital and rural regions
- Low social economic status of families living in rural areas, Armenian refugees (forcibly displaced) from Nagorno Karabakh
- Cultural issues, problems with heading to kinder garden, in schools
- Limited or No access to - inhaled antibiotics, DEKA's, nutritional supplements, expensive modern antibiotics (Linezolid, Piperacillin tazobactam etc.)
- No access to gene modulators
- No adult CF service

What we expect
- Strong collaboration between
  - CF health caregivers and CF community in Armenia
  - CF community and Armenian governmental policymakers and decision makers
  - CF Armenian community/doctors and Switzerland-Zurich University Hospital and patient association
  - Zurich Uni clinic and local authorities in Armenia, Yerevan State Medical University, "Arabkir'' MC, Ministry of Health of Armenia i.e neonatal screening project

Resources and support needed
- training and education of physicians (online sessions, case discussions, problem solution meetings, adiology discussions, in person trainings etc.)
- education of parents, funding for translation service, newsletters, manuals
- Implementation of good quality physiotherapy service
- on site audit of needs

SWITZERLAND

Twinnig project
- Thoughts from our perspective on how we can get involved!
- Is it worth getting involved in a twinning project?
- Are we properly positioned for this path?

Expectations…?
- How do I develop a strong PO?
- What is possible? What is not possible?
- What challenges do we face in the time of Trikafta?
- What role should CF patient organizations in Western European countries play?

What we can offer
- Experience in setting up a PO!
- Advice on questions …
- Information material / brochures that can be adopted and adapted to the country
- Training / self-help
- Cooperation with ECFS / Klinik

What we cannot
- Direct financial support offer:
- Developing projects in the country
- Medication deliveries

How do I form a strong PO?
- Motivated CF parents + PWCF
- Leaders, people with specialist skills, stakeholders with a view to needs,
- Fundraising possible…?
- Political activity.

Together we are successful !

Gap in supply

The difference between East and West concerns us all

With Triakfta, the difference has become even greate

TWINNING PROJECT: PATIENTS ORGANIZATIONS BULGARIA + NETHERLANDS

Tsvetelina IVANOVA + Jacquelien NOORDHOEK

Unmet needs

Despite recent progress, unmet needs include:
- Reimbursement for home-use inhalers, oral antibiotics, mucolytics, specialized vitamins, and medical foods.
- Provision of oxygen therapy machines for home use.
- Establishment of adult CF centers with multidisciplinary teams.

What has been done?
- No formal meetings between patient organizations yet.
- Medical team visits conducted. Mentor team visited Bulgaria in October 2024.
- Strong collaboration at the medical level (presented at Krakow Conference, November 2024).

Priorities
1. Care for adult CF patients: Lack of specialists for 18+ age group. Pediatricians struggle to refer adult patients.
2. Volunteer recruitment: Need for more active contributors to the association's work.
3. Patient and family education: Development of materials to improve understanding of CF management.

Action Plan - Next Steps:
- Initiate communication between POs for experience exchange.
- Organize online meetings and/or in-person visits (to be discussed).

Planned Visits:
- Mentee to Mentor: In May 2025, Bulgarian doctors will visit the CF center in Rotterdam. Efforts will be made to include a PO representative.
- Mentor to Mentee: Potential PO-level visits to be discussed with the mentor country.

Resources and Support Needed:
- Collaboration with Chris Smith (Director of Education, ECFS) for CF educational lectures.
- Translation of materials into Bulgarian to improve patient education.
- Guidance on addressing challenges to better strategize for achieving goals.

Challenges:
- Bureaucratic obstacles: Slow or stalled progress due to legislative roadblocks.
- Lack of national CF standards: No official treatment protocols or adult CF centers.
- Political instability: Disrupts communication with institutions.
- Limited financial support: Reliance on pharmaceutical companies and individual donors for critical medical supplies.
- Low patient engagement: Many hesitate to speak publicly about CF or participate in advocacy efforts.

Long-term Vision:
- Raise public awareness of CF.
- Advocate for national CF treatment standards.
- Establish adult CF centers with specialized care.
- Improve access to essential medicines and medical foods.
- Secure partial or full reimbursement for medical equipment and daily therapies.

TWINNING PROJECT: PATIENTS ORGANIZATIONS ESTONIA + UNITED KINGDOM

Madli KADAJAS + Ellie DAVIES

Identified priorities:
1) Information/guide for new parents
2) Engaging the Estonian CF community in volunteer work for the organisation and be more active
3) Facilitate meeting between UK clinicians and Estonian families

Planned actions:
1) Translate Cystic Fibrosis Trust's new diagnosis pack into Estonian
2) Host workshop with Cystic Fibrosis Trust's communications, marketing and engagement teams to share expertise on community building

Potential challenges:
1) Resourcing/capacity of both organisations
2) Understanding the current environment in Estonia and applicability of Cystic Fibrosis Trust resources to their context

Next steps:
- **Arrange regular meetings between patient organisations**
- **Host workshop with Cystic Fibrosis Trust's communications, marketing and engagement teams to share expertise on community building**
- **Learn more about the Estonian CF context and patient organisation**
- **Pilot resource translation**

TWINNING PROJECT: PATIENTS ORGANIZATIONS KOSOVO + NETHERLANDS

Adthe RAMA + Jacquelien NOORDHOEK

KOSOVO

Advocacy
- Raising awareness
- Fundraising activities, through Culture and Sport
- Urgent need for KAFTRIO

Challenges
- Lack of an up-to-date national cystic fibrosis registry.
- Digitalization in hospitals
- Multidisciplinary Teams: Necessity of a complete team including nutritionists, psychologists and physiotherapist.
- Physiotherapists: No specialized physiotherapists in Kosovo for CF patients
- Access to KAFTRIO

Objectives of twinning project
1. Improving materials and resources for CF Kosovo
2. Specialized training and workshops (for medical staff and association)
3. Study visits between both states

Collaboration Opportunities
Beyond the partnership with twin organization of the Netherlands, here are some key local and international collaboration opportunities:
- Ministry of Health
- University Clinical Center of Kosovo
- Pharmaceutical Companies in Kosovo
- Cystic Fibrosis Europe (CF Europe)
- Educational and Awareness Collaborations
- Non-Governmental Organizations (NGOs)

Resources and Support Needed
CF Kosovo and CF Netherlands
1. Improving Materials and Resources for CF Kosovo
Develop and distribute educational resources tailored to CF patients and families in Kosovo, based on materials used in the Netherlands but adapted to local needs and language.

2. Specialized Training and Workshops
Medical Training: Provide training and workshops for healthcare professionals in Kosovo, focusing on advanced CF treatments. Dutch experts could lead these workshops, sharing their expertise.
Workshops for Association Development: Conduct workshops for CF Kosovo staff on effective advocacy, fundraising, and patient support programs, based on CF Netherland's successful models.

3. Study Visits Between Both States
Exchange Programs: Organize reciprocal study visits where medical staff and association leaders from Kosovo can visit CF treatment centers in the Netherlands, and vice versa. This will allow for first-hand observation of best practices and foster deeper collaboration.

Challenges
1. One of the main challenges encountered in working with our twin organization, CF Netherlands, could be been adapting advanced treatment protocols to the local healthcare infrastructure in Kosovo.
2. While CF Netherlands has access to cutting-edge technology and well-established healthcare systems, Kosovo's healthcare infrastructure is more limited, especially in terms of available equipment and innovative medications.

Long-Term Vision
1. Create a comprehensive support network for CF patients and their families, including psychosocial support, educational resources, and advocacy for better healthcare policies.
2. Develop a well-organized advocacy platform for CF Vision for the collaboration between CF Kosovo and CF Netherlands is to establish a sustainable, high-quality cystic fibrosis care model in Kosovo.

NETHERLANDS

How to be an impactful patient organization?

5 pillars of the Dutch PO
1. **Advocacy**
2. **Peer to peer contact**
3. **Information, Education**
4. **Research**
5. **Quality of care**

What works for you?
- **Start small, take your time**
- **Volunteers and professionals**
- **Be inspiring and deliver**
- **Be the leader of your own process**
- **Be a trustworthy stakeholder**

TWINNING PROJECT: PATIENTS ORGANIZATIONS LATVIA + FRANCE

Alla BELINSKA + Thierry NOUVEL

Activities

- We are developing our relationships
- Communicating by e-mail, zoom meetings

Visit

Paris, 27. 9. – 2. 10. 2024:

Latvian Cystic Fibrois Society visited Vaincre La Mucoviscidose, the mentor in Paris

Participation in VIRADE DE L'ESPOIR DE PARIS:

3 km, 6 km, 10 km - each participant has their own race throughout Paris and other activities.

Goal was fundraising for 4 priority missions:

- support research projects
- support for training and engagement of CF center specialists
- increasing awareness of CF and related activities
- financial support for CF families

Meeting with persons:

- Responsible for the animation of the volunteer network (Marianne Namysl)
- Responsible for the organization of fundraising events (Gautier Le Mouel)
- Responsible for the digital collection (Ana Grecu)
- Volunteers responsible for the organization of fundraising events
- Director of the Coordination and Events Center (Laure Brogliolo)

Together with a social worker (Pauline Besse), representatives of the Latvian community **visited the CF center of the Cochin Hospital in Paris**, which specializes in the treatment of cystic fibrosis.

Having meeting with Professor Pierre-Régis Burgel and other doctors of the center. Later, in October of this year, Professor Bergel and Thierry Nouvel helped the Latvian Cystic Fibrosis Society and **an interview was given to Latvian television about the innovative therapy and its impact on health.**

What is our long-term vision for working with in next year ?

In the long term, the work carried out between Vaincre la Mucoviscidose and the Latvian association should meet two main objectives:

- better care for cystic fibrosis patients through training and awareness-raising about the disease
- the structuring of the Latvian association to enable it to become the main interlocutor of public institutions and thus defend the rights of CF patients

What are our goals, objectives and priorities in the next year ?

Our mentoring system will focus on several topics:

- support in structuring the association: attracting volunteers, motivating them, training them, etc.
- support in setting up fundraising events: providing tools, helping to organize the fundraising event, discussing digital fundraising, etc.
- support in raising awareness about cystic fibrosis
- training healthcare professionals: training physiotherapists in cooperation with the French association AMK

Specific partnership steps. What does it include ?

- **Visit of the French Vaincre La Mucoviscidose Association to Latvia in July 2025**
- Video conferencing training on volunteer management, fundraising and digital fundraising development
- Financial support for training missions organized by the French association AMK
- Providing and supporting the development of awareness-raising and therapeutic education tools (e.g. awareness-raising tools for children)

What specific resources or support do we need to effectively implement the partnership action plan?

- Financial support is needed;
- Within Vaincre la Mucoviscidose, the CEO, Thierry Nouvel is particularly involved in this action and one person is in charge of coordinating the actions implemented internationally;
- Employees who work on fundraising and volunteer management will also be involved

„Thank You Vaincre La Mucoviscidose and CF Europe !

The Vaincre La Mucoviscidose team community led by excellent leaders.
Parents and patients of CF patients from all over France motivated us a lot.
A large and friendly are involved in the events and their organization.
They help to collect donations for the activities of their organization.
They build their community thanks to the professional staff and leaders!

I want to say a big thank you to Thierry Nouvel and his team for welcoming us and sharing their experiences !"

TWINNING PROJECT: PATIENTS ORGANIZATIONS ROMANIA + BELGIUM

Oana VOIVOD + Stephan JORIS

Our Vision

- Strengthening Partnerships for Better CF Care
- The collaboration between Together for Patrick and the Belgian Patient Organization provides an opportunity to exchange expertise and resources to improve cystic fibrosis (CF) care in Romania.
- Beyond our twin collaboration, we see potential for engaging with: creating sustainable and impactful networks of support

Our Mission

- Facilitate the exchange of priorities and progress between organizations.
- Builds strong relationships between organizations and countries.
- Improve collaboration and support between patient and clinician organizations.
- Promote the exchange of knowledge and best practice in cystic fibrosis care
- Focus on joint initiatives between the Romanian and Belgian CF organisations.
- Sharing knowledge on best practices for CF care, especially in areas like respiratory physiotherapy, patient education, and psychosocial support

Resources and Support Needed

To implement our action plan effectively and improve CF care in Romania, we need the following resources and support:

Specialized Training:

1. Ongoing education and training programs for parents and caregivers
2. Educational workshops or online training
3. Establishing a mentorship program where Romanian patient organisations can benefit from the expertise of Belgian patient organisation
4. Mentoring programes between organizations
5. To learn how to organise national awareness campaigns to educate the public and policymakers about CF and the need for improved care standards.
6. Learn from their experience how to become one voice

Challenges

Budget and resource constraints

- How to implement our projects locally using the resources currently available to us.
- Adjust our resources to meet current needs and address challenges effectively

Barriers

- Healthcare system barriers: The bureaucratic nature of Romania's healthcare system makes it difficult to introduce new CF care practices and innovations.
- Awareness and education gaps: Many families in Romania still struggle to understand CF management, and increasing awareness is critical for improving patient outcomes.

Approaches to Solving Challenges

1. Mentor's experience can guide us in adapting and enhancing our resources, as well as improving our implementation methods
2. Identifying and mobilizing additional resources. Developing flexible and adaptable strategies for collaboration.
3. Constant and transparent communication between partners.

Long-Term Vision

Strategy

- Expand Twinning to include more patient organizations.
- Creating a strong network of support and collaboration between organizations.

Objectives

- Develop sustainable projects that have a positive long-term impact on Patient Community
- Advocate for necessary resources and policy changes.

Evaluation

- Promote continuous exchange of knowledge and best practice.
- Benefits of sharing knowledge and building strong relationships.

Performance

- Encouraging active participation and exchange of ideas between participants

TWINNING PROJECT: PATIENTS ORGANIZATIONS UKRAINE + FRANCE

Larysa VOLOSHYNA + Tierry NOUVEL

Our difficulties are WAR !

Our plans are to survive the blackout !

Our goal is to survive !

Our dreams to win !

We should not been pitied, we need help and support.

Support for UA twin clinicians:

Kyiv Okhmatyd + Israel, Petah Tikva - zoom meeting
Vinnytsia + France, Montpellier: 5 zoom meetings
5 - days training at the CF Center in Montpellier

Our goals: VICTORY

1. Increasing life expectancy and quality of life
2. Training of doctors, physiotherapists
3. Development of the field of assistance +18
4. Scientific projects
5. Equipping the centers with equipment and medicines
6. Assistance to patients: medicines, devices, vitamins, material assistance, involvement in clinical trials

What we need to succed:

- Training
- Financing
- Mentoring
- Support
- Help with medicines, vitamins

ACCESS STATUS OF CFTR MODULATORS - 31.12.2024

	KALYDECO	ORKAMBI	SYMKEVI	KAFTRIO TRIKAFTA	TOTAL	NUMBER OF CF PATIENTS
CZECHIA	15	7	12	492	526	728
SLOVAKIA	0	31	0	132	163	308
HUNGARY	0	71	0	251	322	550
UKRAINE	0	0	0	317	317	501
BULGARIA	9	49	0	127	185	290
ROMANIA	5	38	0	337	380	560
LATVIA	0	21	0	19	40	53
LITHUANIA	0	0	0	52	52	71
ESTONIA	0	0	0	44	44	62

Flaem NebulAir+

NebulAIR+ je mimoriadne výkonný a odolný inhalačný prístroj pre ľudí s respiračnými ochoreniami. Zariadenie je navrhnuté s maximálnym tlakom 3,5 baru na časté používanie je preto vhodný aj pre nemocnice. S priloženým nebulizérom RF7+ sa vytvára veľmi jemné a pľúcne kompatibilné spektrum častíc.

NebulAIR+ je plne hradený poisťovňou K72241

Flaem Nuova - AirFeel

PEP A OPEP V JEDNOM ZARIADENÍ

Prenosný, ergonomický a extrémne ľahký AirFeel je nástroj, ktorý pomáha pacientovi uvoľniť dýchacie cesty prostredníctvom respiračnej gymnastiky. Umiestnenie krúžkovej matice umožňuje výber medzi dvoma rôznymi typmi použitia: PEP a OPEP.

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