FUNDACJA POMOCY RODZINOM I CHORYM NA MUKOWISCYDOZĘ

# Zborník prednášok z V4-CF konferencie

SLOVENSKÁ ASOCIÁCIA CYSTICKEJ FIBRÓZY

# Book of Presentations from V4-CF Conference

3rd CONFERENCE

# V4-CF

19 - 20 November 2021
Kraków

## V4 future CF?

MINISTERSTVO ZDRAVOTNÍCTVA SLOVENSKEJ REPUBLIKY

**Vladimír Lengvarský**
minister zdravotníctva SR






V4-CF



UNIWERSYTET JAGIELLOŃSKI
COLLEGIUM MEDICUM
W KRAKOWIE





UNIVERSITAS IAGELLONICA


FUNDACJA POMOCY RODZINOM I CHORYM NA MUKOWISCYDOZĘ

# Zborník prednášok z V4-CF konferencie

SLOVENSKÁ ASOCIÁCIA CYSTICKEJ FIBRÓZY

# Book of Presentations from V4-CF Conference


**SCIENTIFIC COMMITTEE**

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

# OBSAH

*Ladies and gentlemen,*

*at the outset, I would like to thank everyone who has supported us and without whom today's meeting would not have been possible.*
*My thanks go to the* ***Jagiellonian University*** *authorities, our host* ***professor Tomasz Grodzicki****, for letting us use the historic Aula for our meeting. It is a great honor to deliberate in such beautiful spaces of the Jagiellonian University.*

*I would also like to thank our foundation staff and volunteers for their work in organizing the conference.*
*However, my greatest thanks go to the person without whom this conference would not take place, our partner Katarina Stepankova, she is the one who made us meet here today.*
*Finally, let me extend my thanks to all the guests, representing 12 countries, for their involvement and readiness to participate and share their experiences and achievements.*

*Ladies and gentlemen,*
*We meet in difficult times after months of isolation. For all of us it is a fantastic opportunity to meet in person, but also to talk, not in the virtual world, about cystic fibrosis, a topic so important for our environment.*

*However, for the safety of ourselves and others, during our meeting, let's remember the rules - Distance, Disinfect, Mask.*

*Krakow hosts the conference already for the 3rd time. When we met in 2017, none of us anticipated that the next few years would be so groundbreaking for cystic fibrosis patients around the world. We are facing a challenge: what is the future of cystic fibrosis for the people in our countries and, above all, when will this future come? Everything is in our hands, our ability to organize, to negotiate, but above all, our ability to convince everyone of the need for change. After all, less than 4% of rare diseases can count on disease management, and cystic fibrosis is among them as of late. Nevertheless, we should not forget about such an important thing as the surroundings of the sick person, as well as medical and social facilities. Without it, even the best medicine will not succeed.*
*I hope that here, working together, we can answer the questions that bother us and find solutions for equal access to treatment for all patients, in all countries and for all possible therapies for cystic fibrosis patients.*

*On behalf of the organizers I wish you a fruitful meeting and a pleasant visit to our Royal City of Krakow.*

*Welcome to the V4 CF conference "V4 future CF"*
*Welcome to Malopolska. Welcome to Krakow*

*Pawel Wojtowicz*

# NEW ERA IN CYSTIC FIBROSIS

*Dorota SANDS*
*President of Polish Cystic Fibrosis Society, POLAND*

Rethinking care for an ageing community

**Patients clearly are living longer**

Before modulation became an option for the majority

An increase in the overall number of CF patients by **2025**, by approximately 50% corresponds to an **increase** by 20% and by **75%** in children and **adults**, respectively.

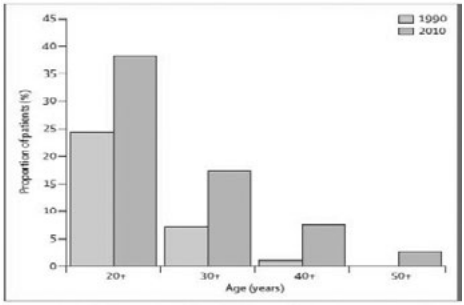



***Figure 1:*** **Proportions patients with cystic fibrosis in the USA by age, 1990 and 2010**
Data are from the Cystic Fibrosis Foundation patient registry data report 2010.[2]

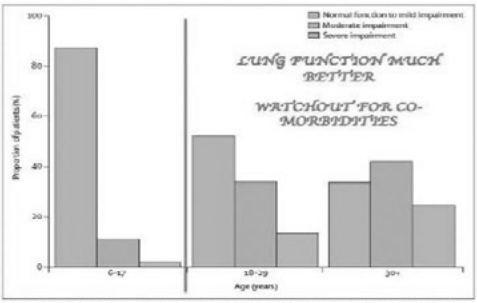
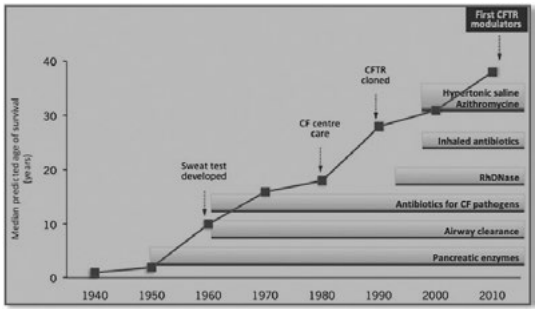
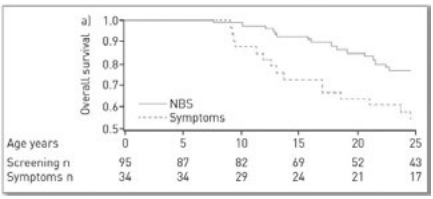


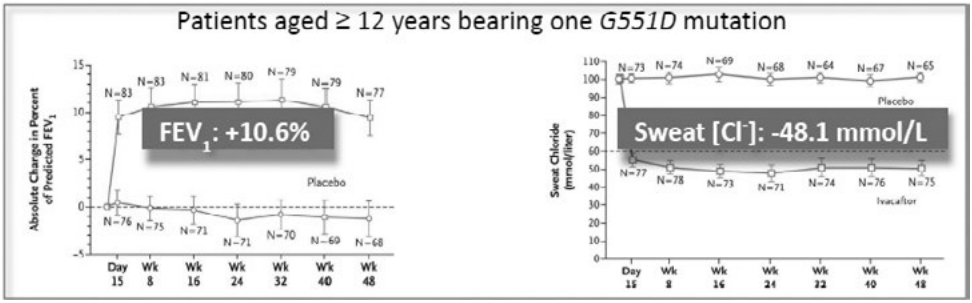

***Figure 2:*** **Severity of lung function impairment by age group in patients with cystic fibrosis in the USA, 2011**
Normal function to mild impairment is defined as forced expiratory volume in 1 s ($FEV_1$) that is 70% of predicted or higher; moderate impairment is $FEV_1$ of 40–69% of predicted; severe impairment is $FEV_1$ of less than 40% of predicted. Reproduced from reference 11, by permission of the Cystic Fibrosis Foundation.

**Improved outcomes of cystic fibrosis over 70 years**

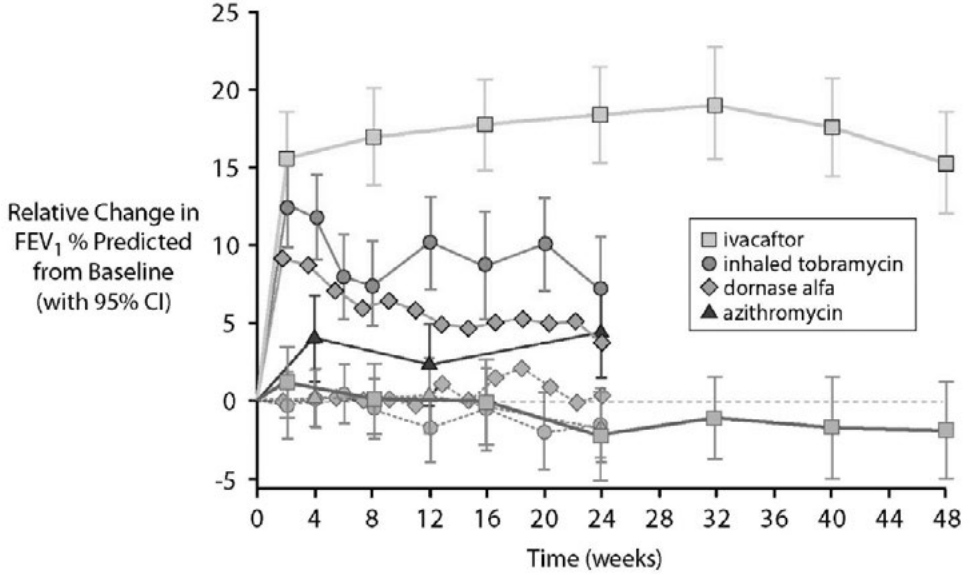


**In 2012, the first CFTR modulator was approved for a few patients**

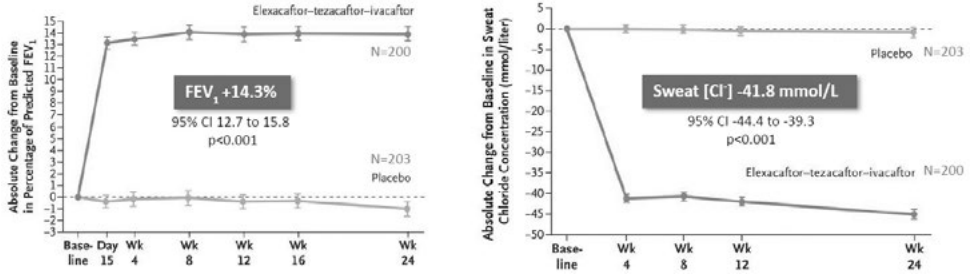



**Phase 3 Results of CF Therapies**



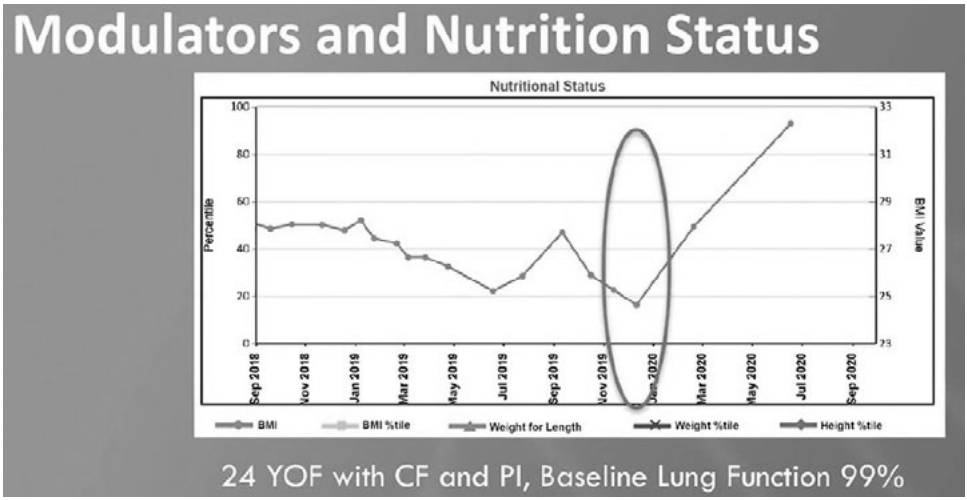

**New CFTR modulator regimen has been approved and 80 – 90% of patients are eligible**

Patients aged 12 years and older bearing one F508del mutation and one minimal function mutation

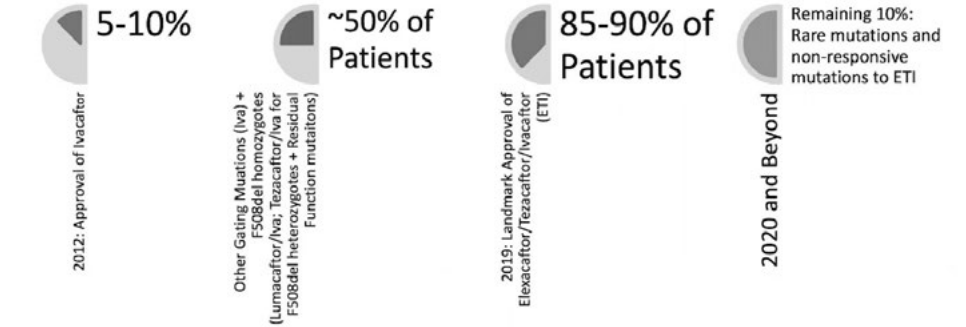


**Elexacaftor-Tezacaftor-Ivacaftor: Safety**

- The safety profile of ELX/TEZ/IVA was generally similar across all subgroups of patients, including analysis by age, baseline ppFEV1 and geographical regions
- Adverse events more common in the treatment group vs placebo included headache, diarrhoea and the two adverse events leading to discontinuation were rash and portal hypertension with pre-existing cirrhosis
- Adverse events more common in the ELX/TEZ/IVA treatment group vs TEZ/IVA included cough and nasopharyngitis

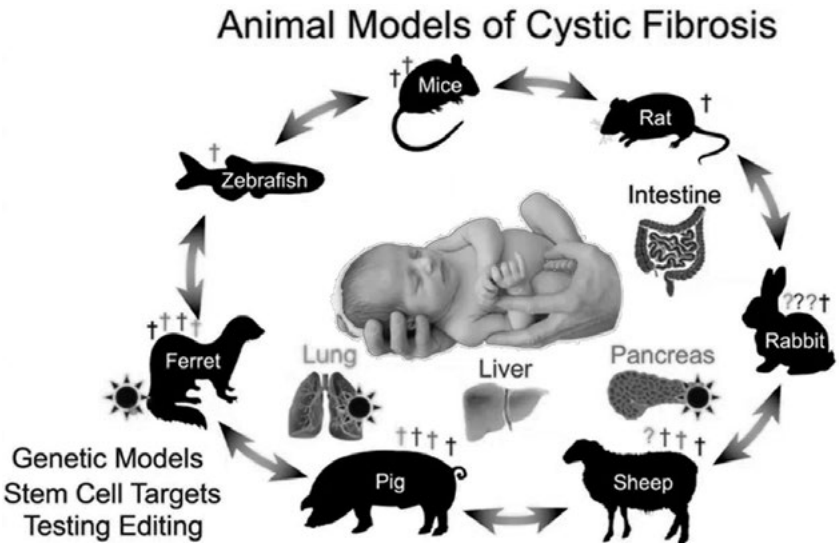



**CFTR modulators**

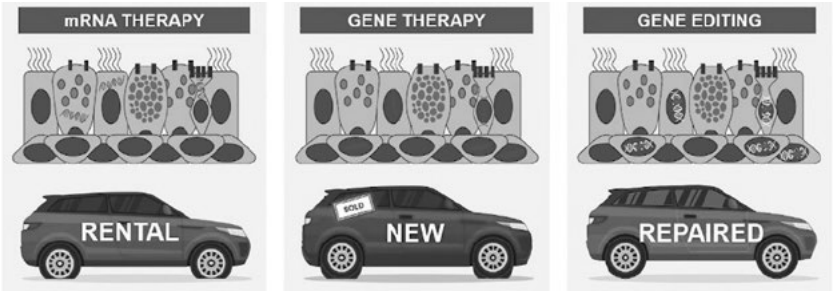



**Potential impact**

- Massive transition period / life change
- Education
- Work / pensions
- Financial / psychological stress




**Genetic therapies for CF**




**Is equity new in CF care?**

- The goal of the CF community is to let **ALL PEOPLE WITH CF** live the **HIGHEST** quality of life.
- As new therapies are developed, we do **NOT** withold them from those eligible, but work to **EXPAND** coverage and **OPPORTUNITES** to **ALL** patients.

**Planning for a sustainable future**

**What may better equity in CF care look like?**

Flexible focus on those with higher needs
- Assessing and responding locally to patients and community barriers to care

Empower patients for self management
- Responsibility for remote monitoring of health

Reimagine CF guidelines
- SIMPLIFY and other withdrawal studies underway
- Reshape to better reflect variable treatment options and responses

**How is the CF team evolving?**

**TRADITIONAL CF TEAM**
- Pulmonologists
- Nurses/APPs
- Registered dietitians
- Respiratory therapists
- Social workers
- Program coordinators
- Pharmacists
- Physical therapists

**EXTENDED CF TEAM**
- Primary care physicians
- Research coordinators
- Endocrinologists
- Gastroenterologists
- Otolaryngologists
- Psychiatrists
- Lung transplant team

**EXPANDED CF TEAM**
- Urologists
- Reproductive endocrinology/infertility
- Obstetricians
- Cardiologists
- Geriatricians
- ??

**How may the role of CF care teams be changing?**

Growing adult CF population with longer life expectancy
- More people … new health challenges

Role of the CF team may be evolving
- Many people with CF are attaining healthier lives WITHOUT as many admissions/interventions
- Consultation services/hybrid model of care for inpatients/outpatients

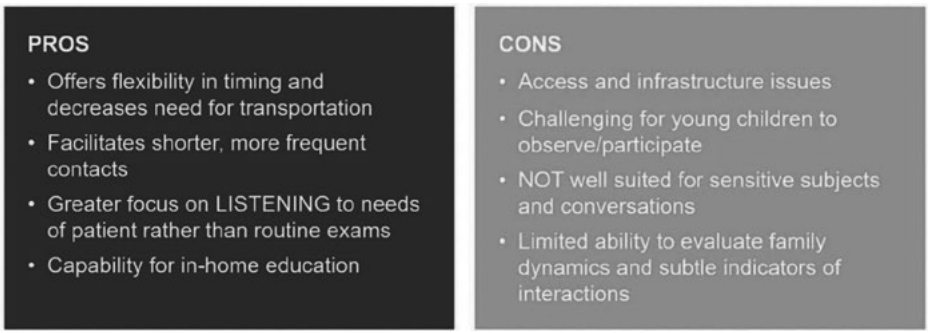
**What CF resources are needed?**

**SPACE & MATERIALS**
- Clinic/office space
- Telehealth equipment
- Spirometry & labs
- Medications
- RT equipment

**DATA & INFORMATICS**
- Registry data
- Patient data
- EHR capabillities
- Patient reported outcomes

**PEOPLE POWER**
- Clinical staff
- FTE or % effort
- Administrative support
- Access to experts

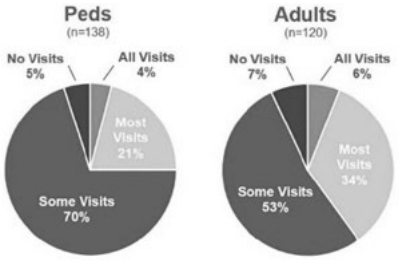
**Learning to incorporate telehealth**

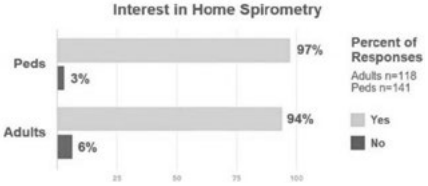


# TELEHEALTH

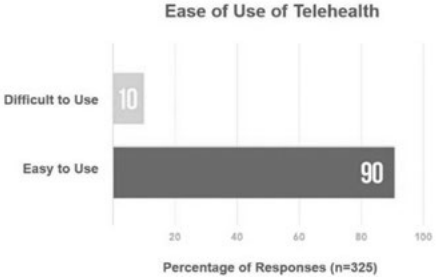
## Is there a role for telehealth and remote monitoring in the future?

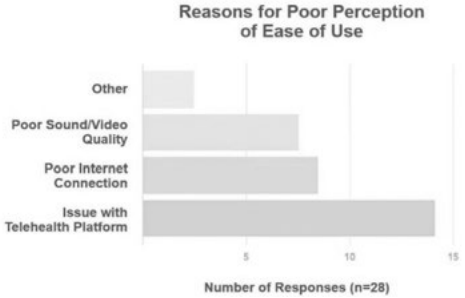
- Ongoing role for telehealth for AT LEAST SOME visits in the future
- Majority of patients (94-97%) are interested in home spirometry



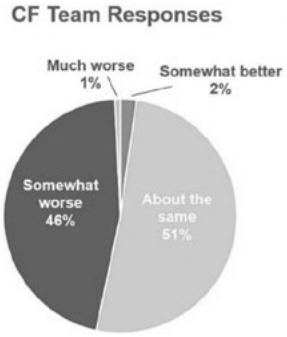



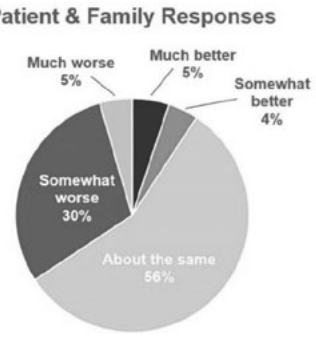

## Was telehealth easy for people to use?




## How did care teams and patients feel about telehealth compared to in-person care?



**Overview**
- Change in healthcare needs
- Reassess the effectiveness of past therapies
- Delivering remote healthcare
- Innovate
- Focus on education and employment
- Psychological support
- Non-cf care

**Personalized CF Regimens**
Maximize CFTR function
  - Initially based on the patient's CFTR mutations
  - Ultimately a personalized response may be used

Symptomatic therapies will be utilized as needed
  - Infants and young children with excellent CFTR restoration may not need other therapies
  - Understanding impact of various levels of CFTR restoration will help us determine what additional therapies are needed to maintain health

**Older patients with established disease will probably continue to need other therapies**

**What may be the future for adults on effective CFTR modulator therapeutic regimen?**

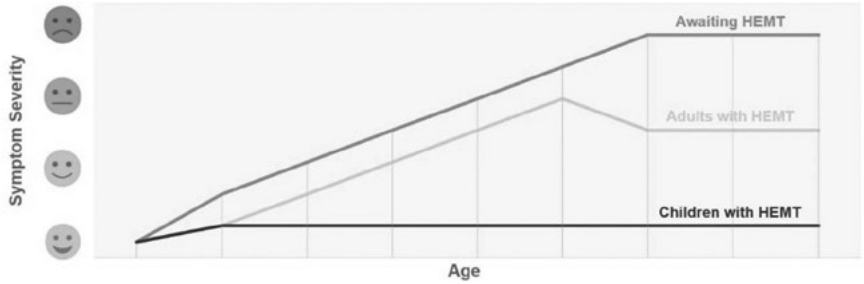
**We can speculate from what we have already observed with ivacaftor**
**Over the years, we may observe:**
- Less severe respiratory disease
- Fewer exacerbations
- Fewer hospitalisations
- Less prevalence of Pseudomonas aeruginosa
- Less prevalence of CFTR-related diabetes

**How CF care may change?**
- Lower burden of care
- Less IV antibiotic treatment
- Less routine appointments
- Development of at-home monitoring: symptoms and FEV1+++
- Need of patients' education for awareness of symptoms or FEV1 limits triggering contact with centre

**What may be the future for very young patients on effective CFTR modulator therapeutic regimen?**

**If around 2027 – 2030: approval of effective CFTR modulator therapy for 80–90% of patients:**
- Nearly no respiratory disease at onset of treatment1
- No or very mild respiratory disease over the years?
- Recovery from pancreatic insufficiency?

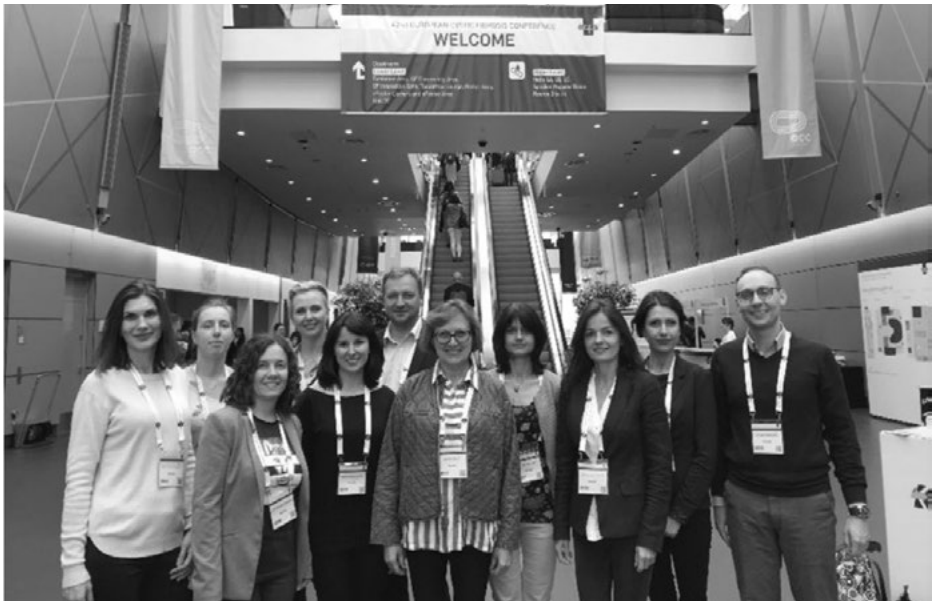
**How might we see CF care in the future?**




**Let's not get ahead of ourselves!**
**- #10% of patients are not eligible to CFTR modulators: their disease will stay the same**
**- CF disease is very diverse and responses to treatment differ**
**- We don't know if CFTR modulators effects will last through the whole life**
**- A multidisciplinary team will still be needed: let's not lose our skills!**
**- Approval is not Access!**

***Delayed access is to be expected in many countries***

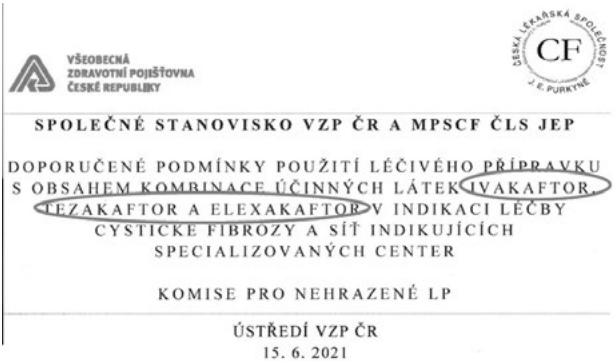
**The Future**
- Ongoing high-quality collaborative research
- New and better therapies **for all**
- An era of more clinical stability
- Response to changing health care needs
- Integration of non-CF primary and secondary care services
- Retain the personal touch!
- The unknown



# INTRODUCTION OF NOVEL THERAPIES - THE COUNTRY PERSPECTIVE

*Pavel DŘEVÍNEK*
*Department of Medical Microbiology, Prague CF Centre*
*2nd Medical Faculty, Charles University, Motol University Hospital, Prague, CZECH REPUBLIC*

**Access to CFTRm in Czech Republic**



VŠEOBECNÁ ZDRAVOTNÍ POJIŠŤOVNA ČESKÉ REPUBLIKY

ČESKÁ LÉKAŘSKÁ SPOLEČNOST J. E. PURKYNĚ

CF

SPOLEČNÉ STANOVISKO VZP ČR A MPSCF ČLS JEP

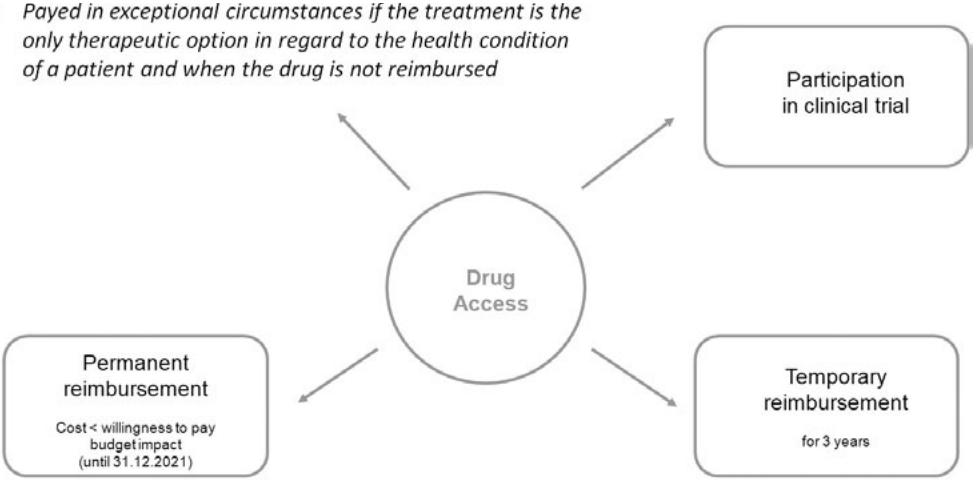
DOPORUČENÉ PODMÍNKY POUŽITÍ LÉČIVÉHO PŘÍPRAVKU S OBSAHEM KOMBINACE ÚČINNÝCH LÁTEK IVAKAFTOR, TEZAKAFTOR A ELEXAKAFTOR V INDIKACI LÉČBY CYSTICKÉ FIBRÓZY A SÍŤ INDIKUJÍCÍCH SPECIALIZOVANÝCH CENTER

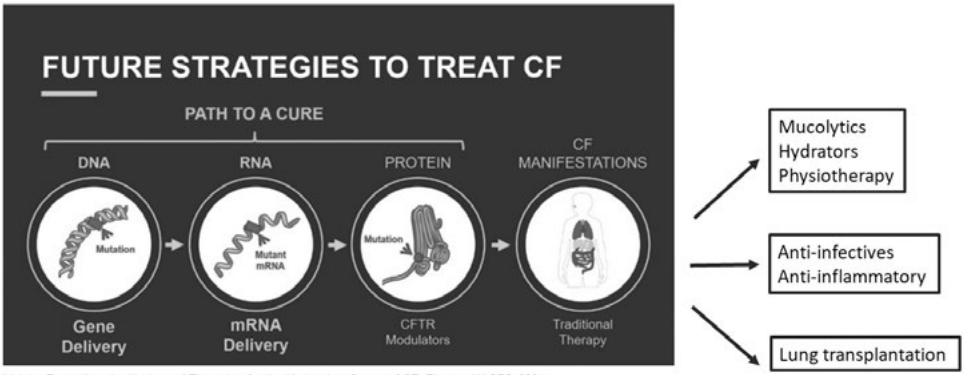
KOMISE PRO NEHRAZENÉ LP

ÚSTŘEDÍ VZP ČR
15. 6. 2021

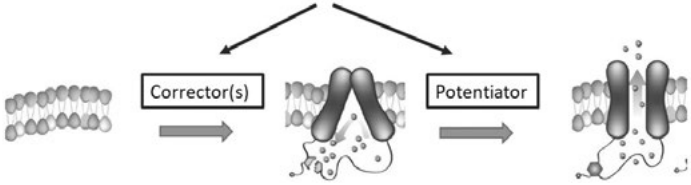
**Public Health Insurance Act (No 48/1997)** **§16: Individual reimbursement, exceptional**

- *Payed in exceptional circumstances if the treatment is the only therapeutic option in regard to the health condition of a patient and when the drug is not reimbursed*



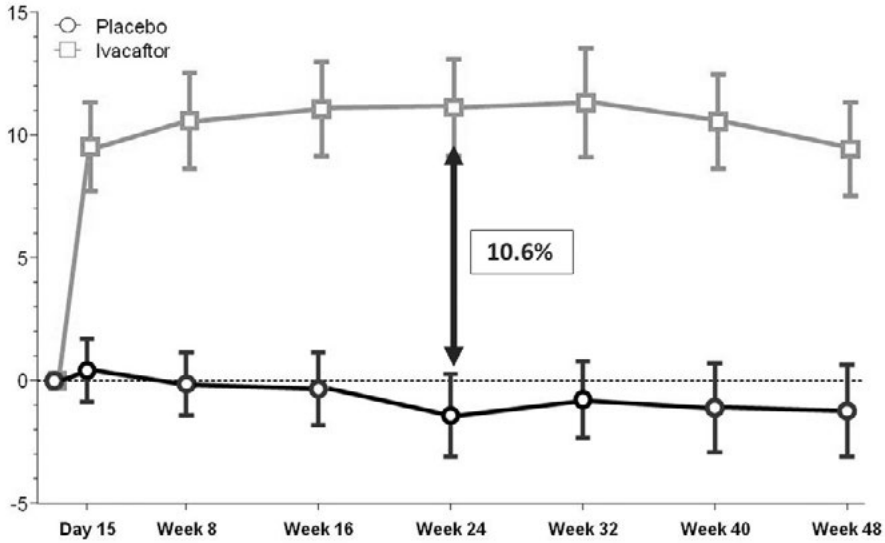



M Jain: Expanding the Horizon of Therapies for the Underlying Cause of CF. Plenary NACFC 2021.




**KALYDECO**

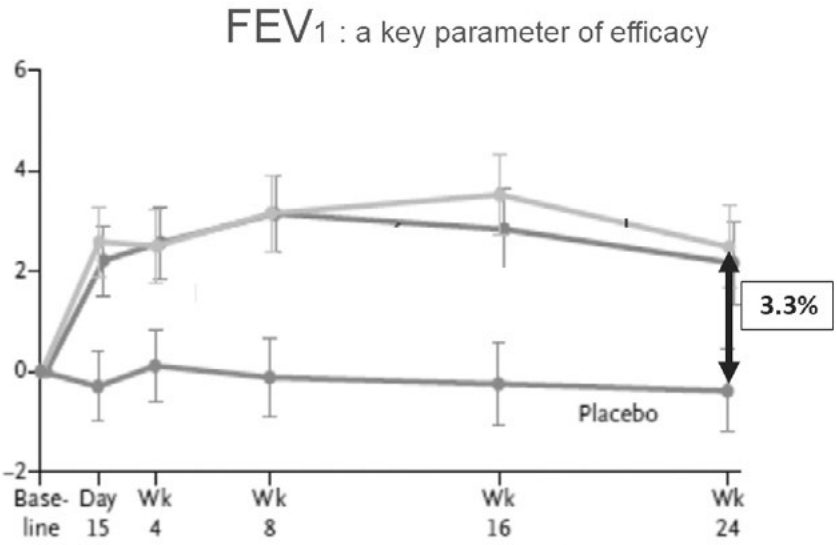
## FEV1 : a key parameter of efficacy




Ramsey et al. N Engl J Med 2011.

| | | | |
|---|---|---|---|
| **G551D** | G551S | S549N | R117H |
| G1349D | S1251N | S549R | |
| G178R | S1255P | G1244E | |

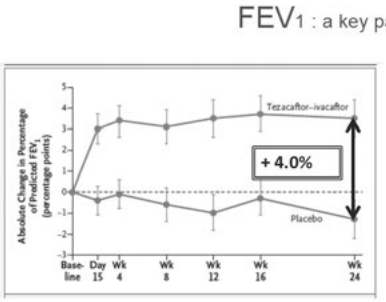
**ORKAMBI**




| F508del/F508del |
|---|
| |
| |

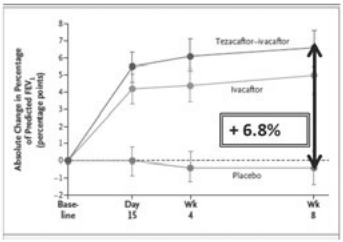
Wainwright et al. N Engl J Med 2015.

**SYMKEVI**




Taylor-Cousar et al. N Engl J Med 2017.

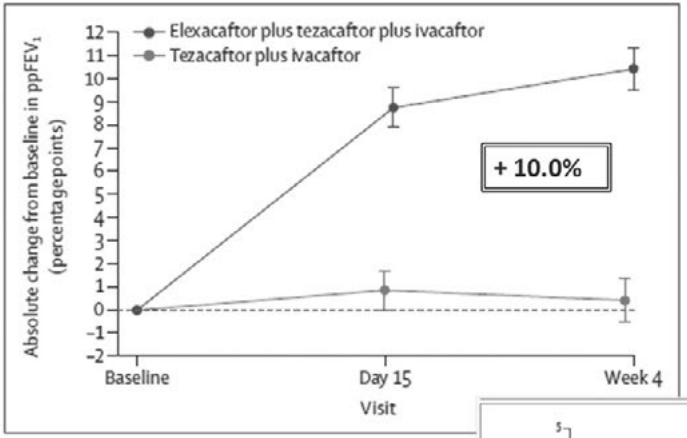
| F508del/F508del |
|---|
| |
| |



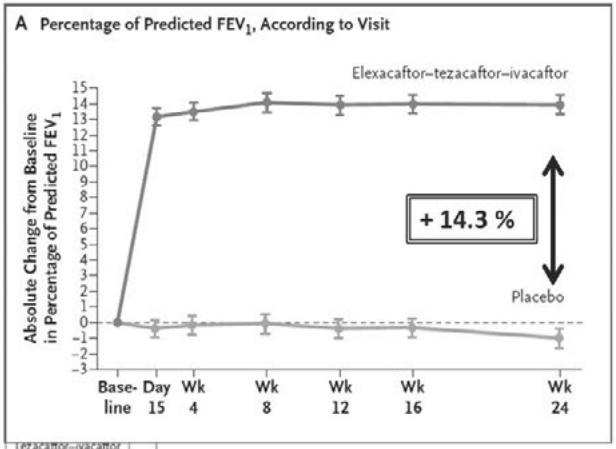

Rowe et al. N Engl J Med 2017.

| F508del/and: | D1152H | 2789+5G→A | 3272-26A→G | 3849+10kbC→T |
|---|---|---|---|---|
| P67L | R117C | L206W | R352Q | A455E |
| D579G | 711+3A→G | S945L | S977F | R1070W |

**KAFTRIO**

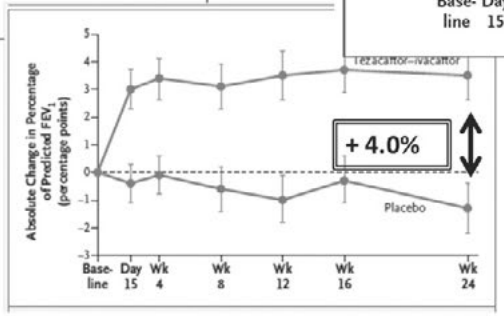



Lancet, Oct 31 2019




N Eng J Med, Oct 31 2019

treated with Symkevi prior to Day 1:

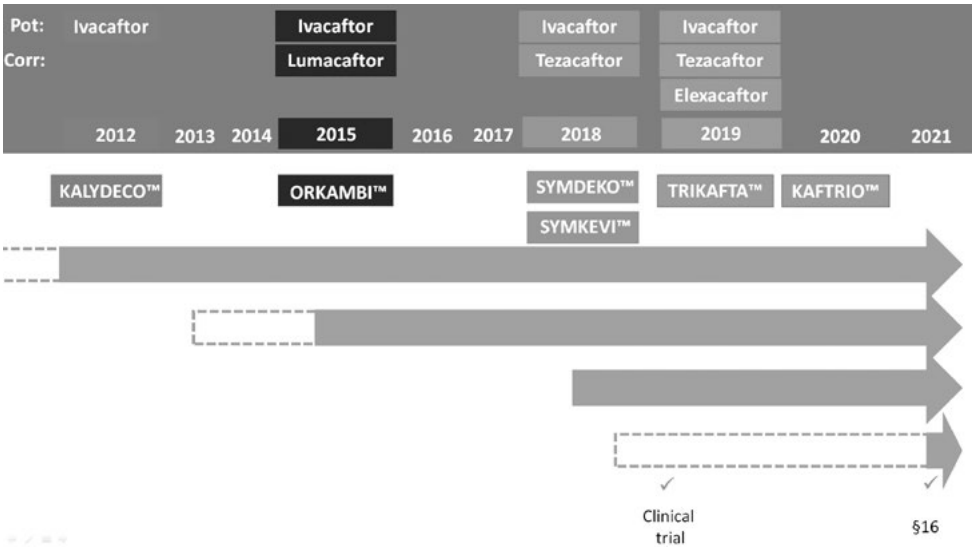



Taylor-Cousar et al. N Engl J Med 2017.

| F508del/F508del |
|---|
| |
| |

| F508del/and: |
|---|
| ANY OTHER MUTATION |
| |

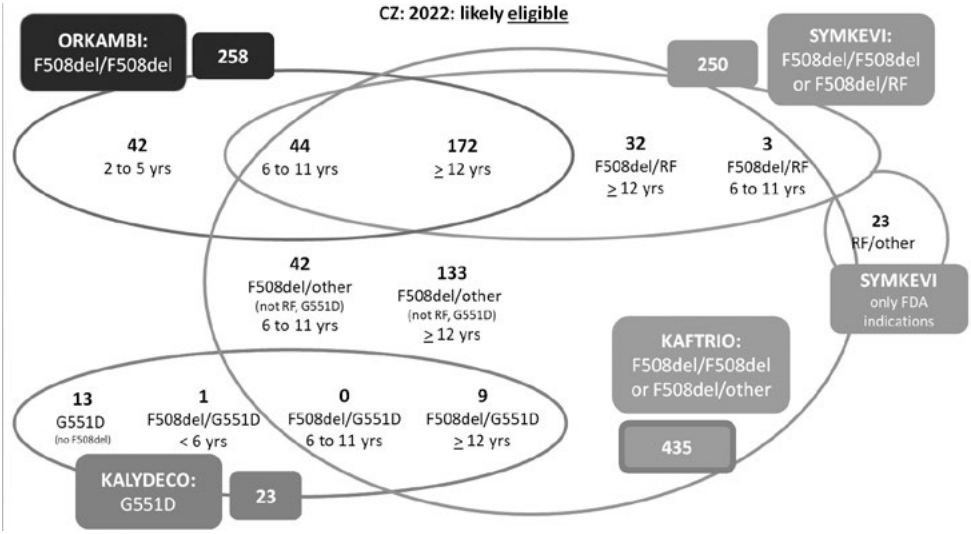
**Pathway to the CFTRm access in the Czech Republic**




| Eligible patients | | Treated patients with | | | |
|---|---|---|---|---|---|
| | | Kalydeco | Orkambi | Symkevi | Kaftrio |
| G551D (no F508del) | 13 | 13 | | | |
| G551D/F508del | 10 | 9 | | | 1 |
| F508del/F508del (< 12 years) | 86 | | 69 | 1 | |
| F508del/F508del (≥ 12 years) | 172 | | 13 | 4 | 99 |
| F508del/RF (< 12 years) | 3 | | | | |
| F508del/RF (≥ 12 years) | 32 | | | 16 | 6 |
| F508del/ANY (excl. G551D, RF) | 133 | | | | 65 |

In Total: **449** (66% of Czech CF population)

In Total: **296** (66 % of eligible patients)




**What next?**

- **to carry on prescribing CFTRm to new patients and to switch from 1st generation modulators to Kaftrio**
- **to remember that CFTR modulators = hugely dynamic environment:**
  - **changes of indications (age groups, genotypes, new drugs on the market)**
    **–> functional national registry and administrative support are absolutely essential**

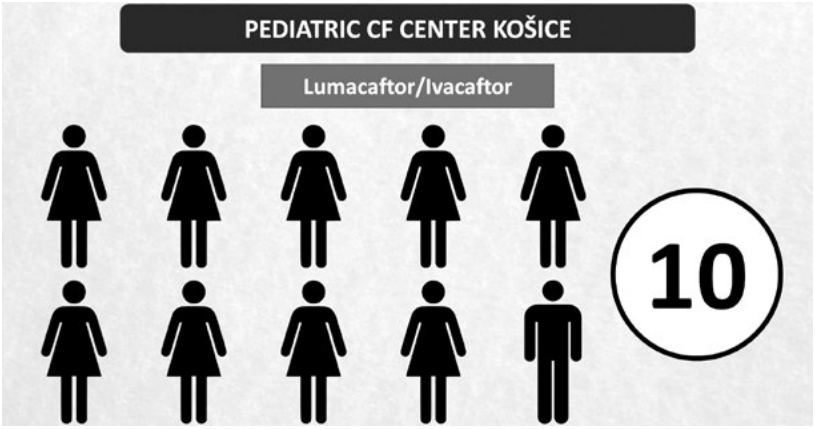
český registr
cystické fibrózy

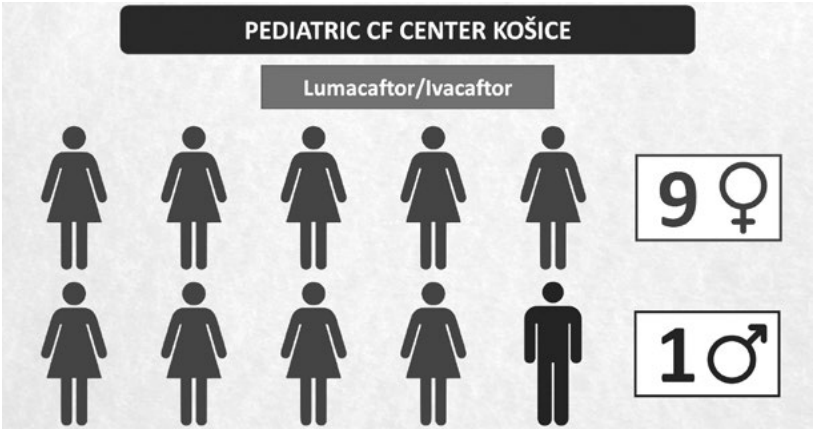
Alena Bilkova
Dr. Marek Turnovec
Prof. Milan Macek
Simona Zabranska
Dr. Miriam Mala
Dr. Lukas Homola

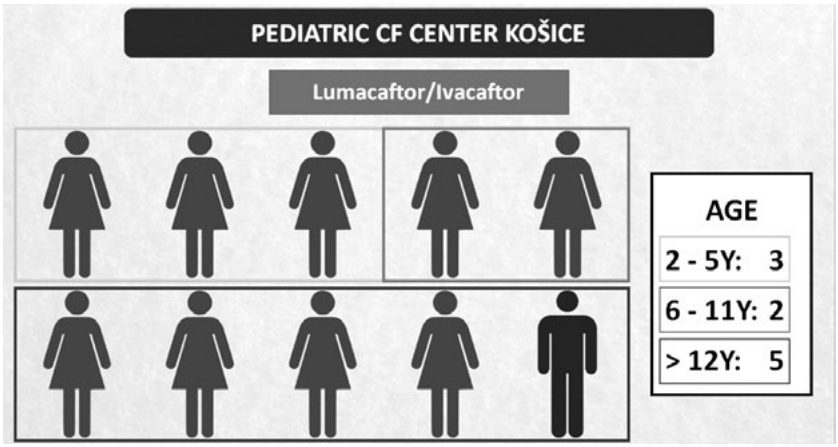
# CFTR MODULATOR THERAPY IN SLOVAKIA

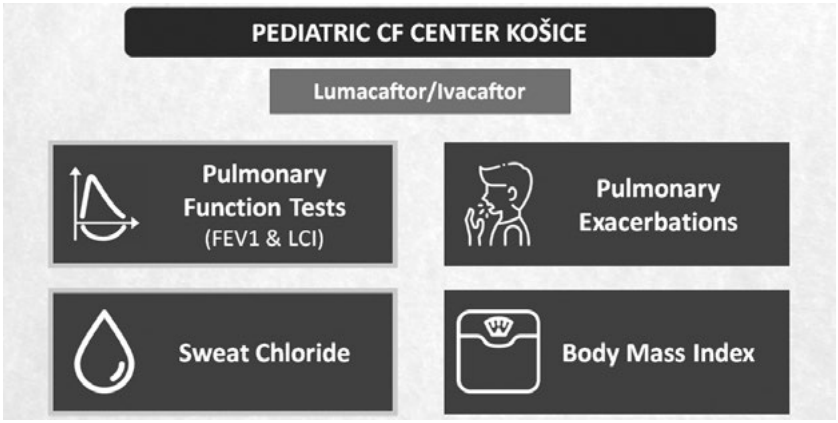
*Zuzana HRIBÍKOVÁ & Anna FEKETEOVÁ*
*DFN Košice, SLOVAKIA*

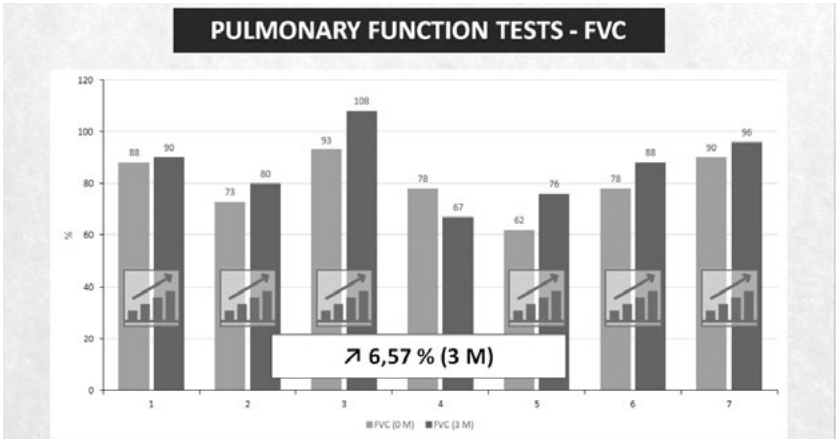
Currently, we have 87 patients taking CFTR modulator therapy in Slovakia this year. Most of them, 82, are on lumacaftor/ivacaftor. 49 of those are adults or children 12 years old and more, 17 are in 6 - 11 years category and 16 fall into range of 2 to 5 years of age.
3 other patients are taking the newest combination of elexacaftor/tezacaftor/ivacaftor, 1 is using tezacaftor/ivacaftor and 1 is solely on ivacaftor.



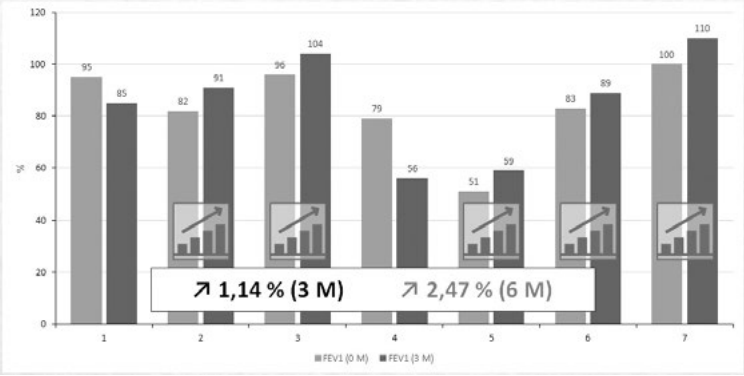




PEDIATRIC CF CENTER KOŠICE
Lumacaftor/Ivacaftor
AGE
2 - 5Y: 3
6 - 11Y: 2
> 12Y: 5

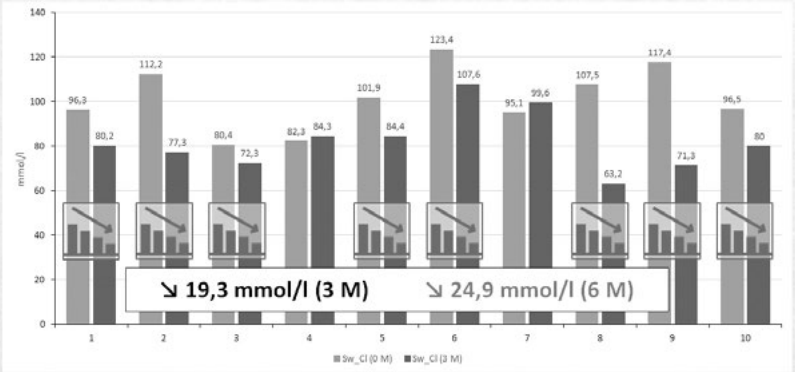

PEDIATRIC CF CENTER KOŠICE
Lumacaftor/Ivacaftor
Pulmonary Function Tests (FEV1 & LCI)
Pulmonary Exacerbations
Sweat Chloride
Body Mass Index


PULMONARY FUNCTION TESTS - FVC
%
120
100
80
60
40
20
0
88
90
73
80
93
108
78
67
62
76
78
88
90
96
1
2
3
4
5
6
7
↗ 6,57 % (3 M)
FVC (0 M)
FVC (3 M)

## PULMONARY FUNCTION TESTS - FEV1




## SWEAT CHLORIDE TESTS



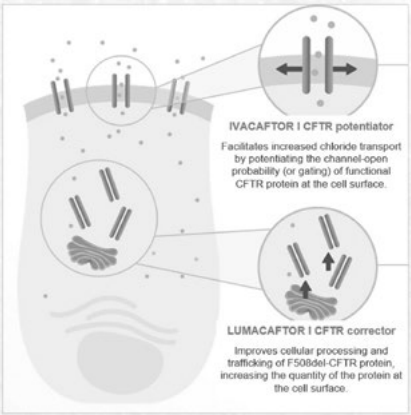

## PEDIATRIC CF CENTER KOŠICE

### Summary

- Improvement in PFTs
- Decrement in levels of sweat chloride
- Only 2 patients experienced side effects (Chest tightness)
- NEW DATA (9 M) - Less frequent pulmonary exacerbations
- NEW DATA (9 M) - Improvement in BMI

## CFTR MODULATORS

- Potentiators
- Correctors
- Amplifiers
- Stabilizers
- Read-through agents (Production correctors)




Coulthard, K. P. (2018). Cystic fibrosis: Novel therapies, remaining challenges. Journal of Pharmacy Practice and Research, 48(6), 569-577

## POTENTIATORS

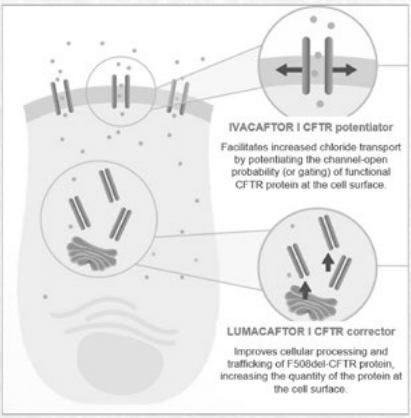
Increase channel-opening probability (channel gating) of CFTR at the cell surface

↑ **FUNCTION**

## CORRECTORS

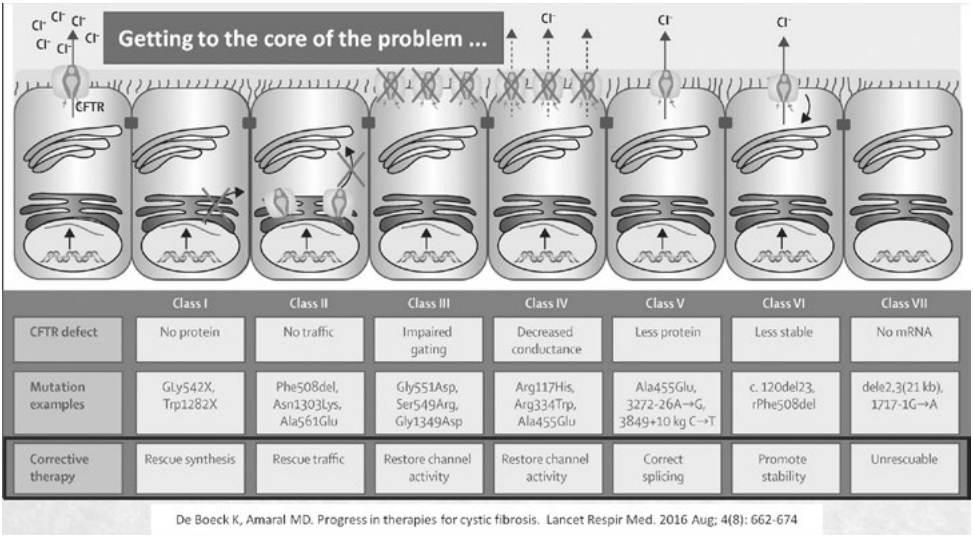
Improve processing and trafficking of CFTR to the cell surface

↑ **AMOUNT**



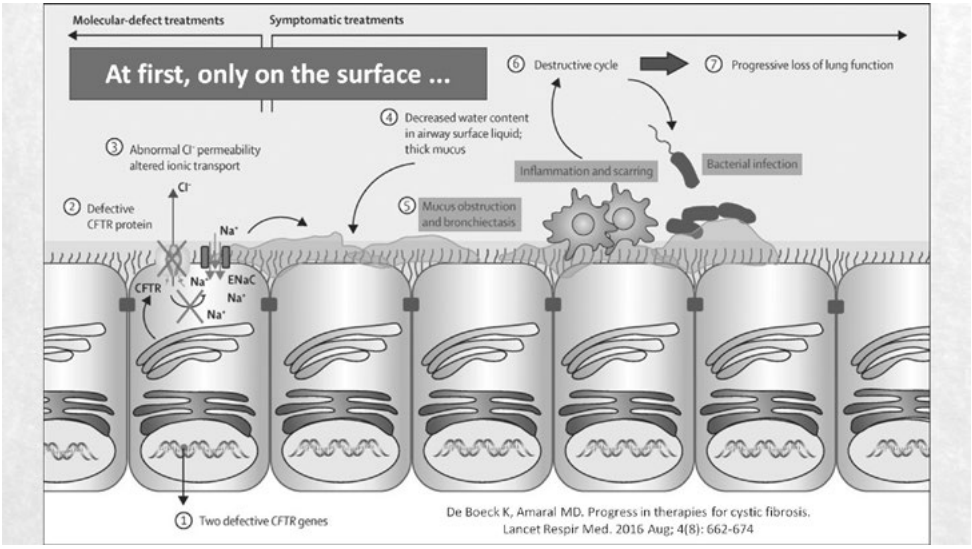

Coulthard, K. P. (2018). Cystic fibrosis: Novel therapies, remaining challenges. Journal of Pharmacy Practice and Research, 48(6), 569-577

| | | | |
|---|---|---|---|
| **2012** | **IVACAFTOR** (Kalydeco®) | G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R R117H | **SEPTEMBER 2021** |
| **2015** | **LUMACAFTOR/IVACAFTOR** (Orkambi®) | F508del/F508del | **SEPTEMBER 2020** |
| **2018** | **TEZACAFTOR/IVACAFTOR** (Symkevi®) | F508del/F508del *or* F508del + P67L / R117C / L206W / R352Q / A455E / D579G / 711+3A→G / S945L / S977F / R1070W / D1152H / 2789+5G→A / 3272-26A→G / 3849+10kbC→T | |
| **2020** | **ELEXACAFTOR/TEZACAFTOR/IVACAFTOR** (Kaftrio®) | F508del + Any other mutation | **SEPTEMBER 2021** |




| | Class I | Class II | Class III | Class IV | Class V | Class VI | Class VII |
|---|---|---|---|---|---|---|---|
| CFTR defect | No protein | No traffic | Impaired gating | Decreased conductance | Less protein | Less stable | No mRNA |
| Mutation examples | Gly542X, Trp1282X | Phe508del, Asn1303Lys, Ala561Glu | Gly551Asp, Ser549Arg, Gly1349Asp | Arg117His, Arg334Trp, Ala455Glu | Ala455Glu, 3272-26A→G, 3849+10 kg C→T | c. 120del23, rPhe508del | dele2,3(21 kb), 1717-1G→A |
| Corrective therapy | Rescue synthesis | Rescue traffic | Restore channel activity | Restore channel activity | Correct splicing | Promote stability | Unrescuable |

De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016 Aug; 4(8): 662-674




De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. Lancet Respir Med. 2016 Aug; 4(8): 662-674

# ROLE OF PATIENT ORGANISATIONS IN THE PROCESS OF ACCESS TO NEW THERAPIES FOR CF

*Jacquelien NOORDHOEK*
*President of CF Europe*

**Focus on CFTR Modulators**

Access to **Kaftrio / Trikafta**
Large variation in access in different continents and countries
FDA 2 years ago plus reimbursement
EMA august 2020...

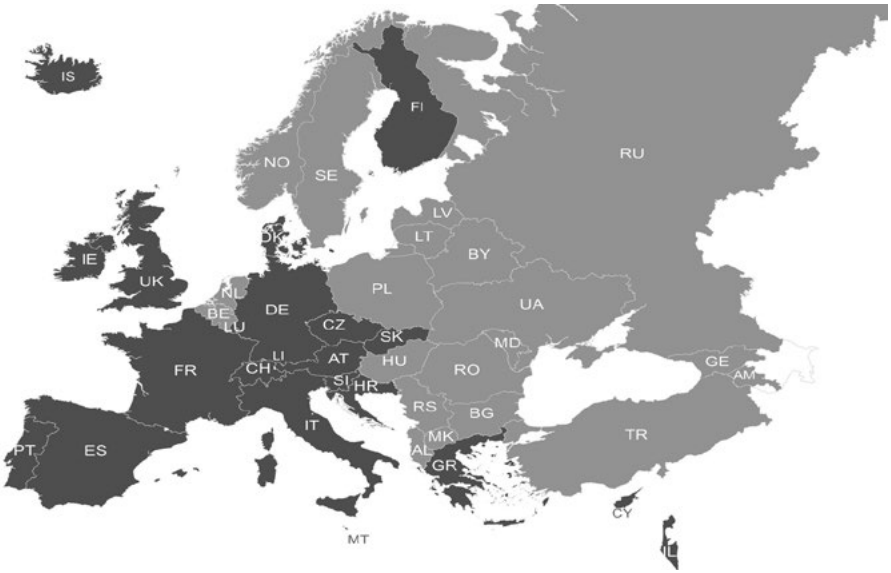
**After approval for the market**

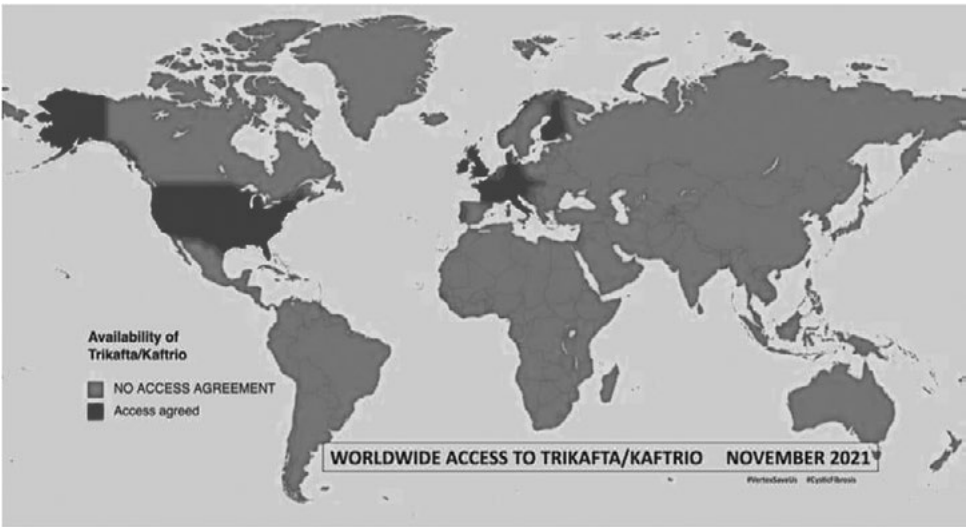
Apply in every separate country
Subsequently: pricing is the issue
Negotiations about different aspects

**Introduction to CF Europe**

Cystic Fibrosis Europe is the federation of national CF Patient Associations in Europe. 39 European countries are member of CF Europe.


**Countries having access to Kaftrio in Europe**






**So what can be done ?**
- Collecting information on a national level
- 'Activism'(?)
- Media attention / campaigning
- Connecting with governmental bodies
- Connecting with politicians
- Connect to clinics
- Collect data

**Depending on…**
- Culture
- Political situation
- Economics
- Professionality
- Infrastructure for data
- Ethical issues

**Most important: "Be a nice stakeholder" / "Be impressive"**

# V4 COUNTRY REPORT´S

*ARELLANESOVÁ Anička, ZÁBRANSKÁ Simona, 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 | **691** | **344** | **1 350** | **500** |
| CF children | **330** | **140** | **896** | **254** |
| CF adults | **361** | **204** | **454** | **246** |
| CF Centers for children | **5** | **3** | **16** | **15** |
| CF Centers for adults | **5** | **3** | **3** | **3** |

*Poland:*

*A. 9 Competence centers (2 for adults)*
*B. 3 Regional Centers (only for kids)*
*C. 7 Other Centers (1 for adults)*

*Hungary:*

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

**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**

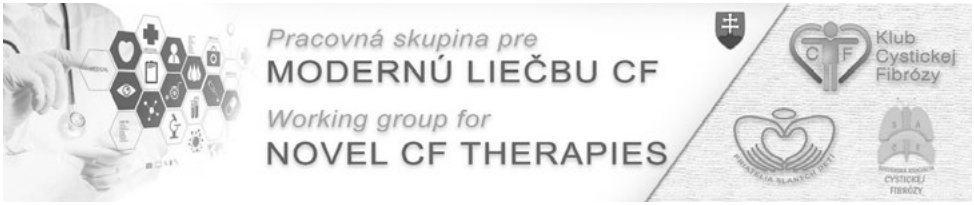
Klub cystické fibrózy

## 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**

MUKOKOALICJA

**HU**
**1**
Cisztás Fibrózis Magyarország
(Assotiation of Cystic Fibrosis Patients)

Betegek Egyesülete

**1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2021. Access to standard medicines and therapies.**

| | KALYDECO | ORKAMBI | SYMKEVI | KAFTRIO | Total |
|---|---|---|---|---|---|
| CZ | 22 | 82 | 21 | 171 | 296 |
| SK | 1 | 71 | 1 | 26 | 99 |
| PL | 1 | 24 | 3 | 5 | 33 |
| HU | 0 | 137 | 0 | 7 | 144 |
| UA | 0 | 1 | 0 | 1 | 2 |
| LATVIA | 0 | 0 | 0 | 0 | 0 |
| BG | 4 | 16 | 0 | 7 | 27 |
| RU | 0 | 600 | 0 | 92 | 692 |

## CZ

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

Modulators: 296 patients (from 449 indicated patients).
Clinical trials, §16: Individual reimbursement, exceptional.

| | |
|---|---|
| **Kalydeco** | **22** |
| **Orkambi** | **82** |
| **Symkevi** | **21** |
| **Kaftrio** | **171** |

**Big success!!**
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 and KAFTRIO since 15. July 2021

| | |
|---|---|
| **Kalydeco** | **1** |
| **Orkambi** | **71** |
| **Symkevi** | **1** |
| **Kaftrio** | **26** |

Standard therapy:
**For free:**
- pancreatic enzymes
- antibiotics – p.o., i.v., inhaled
- some mucolytics (ACC, Pulmozyme)
- nebulisers, physiotherapy devices, Simeox
- 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**

- February 2021 - start of the reimbursement procedure
- June 2021 - negative opinion of the Polish HTA agency (the main complaint was the price)
- November 2021 - waiting for the decision of the Minister of Health

| | |
|---|---|
| **Kalydeco** | **1** |
| **Orkambi** | **24** |
| **Symkevi** | **3** |
| **Kaftrio** | **5** |

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 - fix price below 1 EUR.
Tobramycin is limited. Available as part of drug programs with high entry barriers.
Pulmozyme is reimbursed - fix price below 1 EUR
Pancreatic enzymes: KREON 10,000 / 50pcs - not reimbursed
KREON 25,000 / 50pcs reimbursed fix price below 3 EUR,
LIPANCREA 16 000 / 60pcs – for free).
Nutrients: Fortimel MAX flat fee 0.85 EUR / 4 bottles 300ml to 18 years old

## HU

**ORKAMBI** therapy has been introduced to 137 patients in Hungary since March 2021. The therapy is totally free for the phe508del homozygous patients. It is provided at the three largest centers. To get CFTR modulator therapy the patient and the doctor must apply for **financial support to the National Health Insurance.**
**KAFTRIO** is still under negotiation.
Kaftrio therapy has been introduced to 7 adults in Hungary since July 2021. All patients take the drug without complaint. We are waiting for the positive assessment of several applications for the financial support for phe508del heterozygous patients (20 000 US dollars/month).

| | |
|---|---|
| **Kalydeco** | **0** |
| **Orkambi** | **137** |
| **Symkevi** | **0** |
| **Kaftrio** | **7** |

| | |
|---|---|
| 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 |

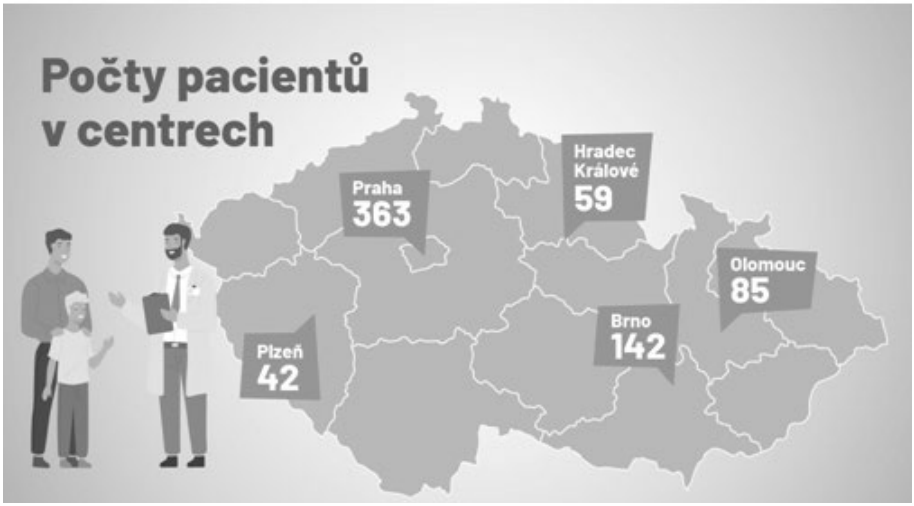
**2. Does actual National CF Registry exist in your country? Is it part of ECFSPR?**

## CZ

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

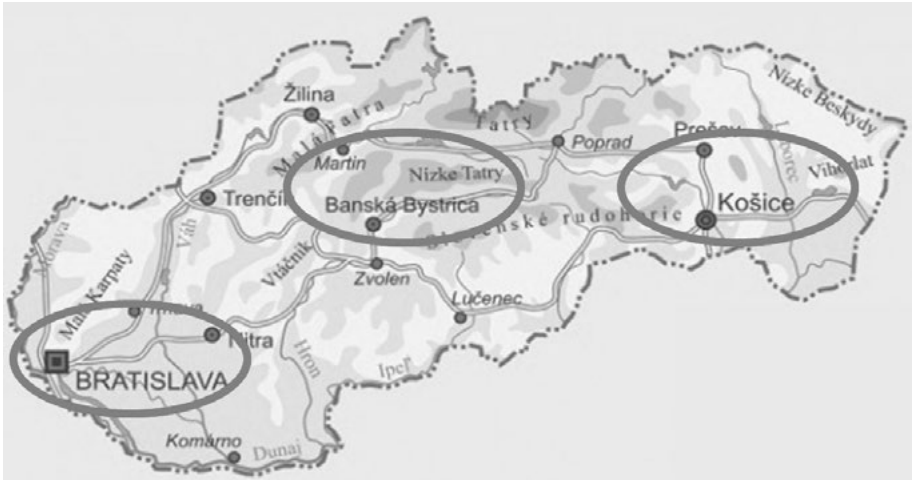
**Czech At-a-glance report 2021**

- 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**

13 Centers are parts of ECFSPR since **2021.**

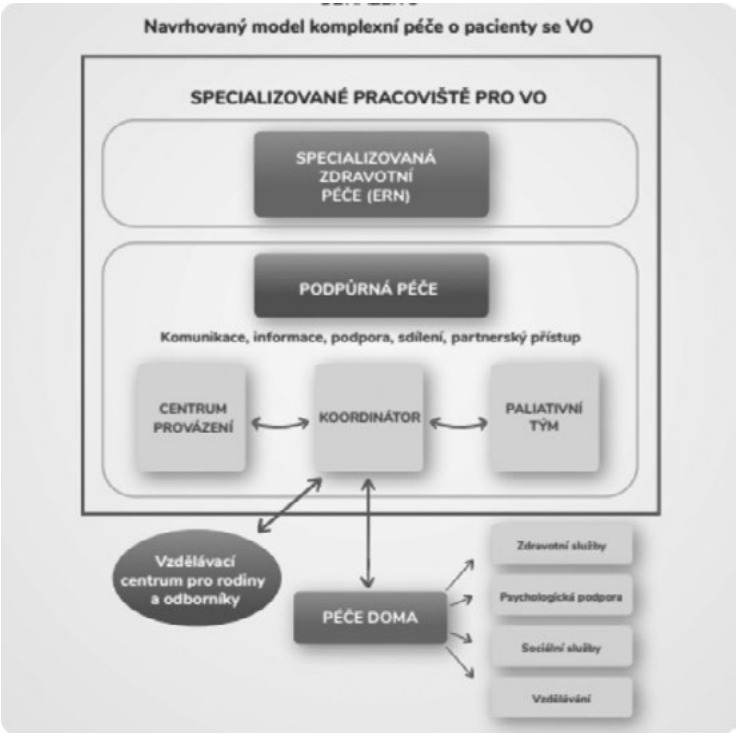

**HU**

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

### 3. Do you have National standards of CF care?

## 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.**

**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.

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

## HU
Yes

### 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 (200 – 400E/month)
- Pension for disable adult person (200 – 300E/month)
- Nutrition (30 EUR/month)
- Hygiene (30 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

Basic support EUR 55.

Extended (if parent resigns from work) EUR 434.

## 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

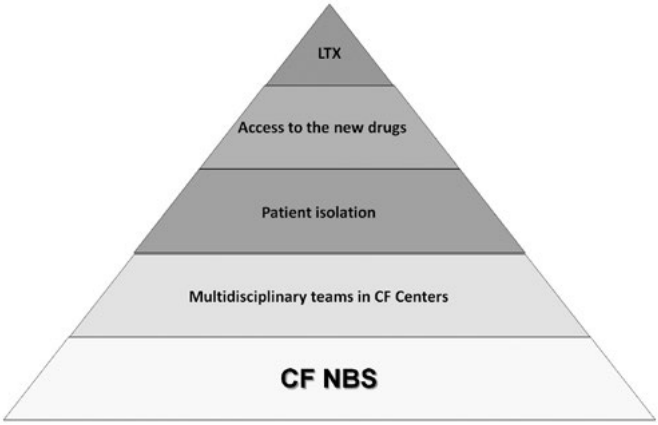
## SK

- **Lung transplantations (Prague, Vienna)**
- 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 and Symkevi:**
**- patients must collect funds and set up fund-raisers on Internet**
**- many families left Poland for countries where drugs are reimbursed**
**- Improve care for adult CF patients. Not enough CF center for adults.**
- Reduction of hospital stays:
- Improve outpatient care
- Improve home care - intravenous antibiotics and physiotherapy given at home
- Telemedicine - possible online consultation
- None reimbursed for:
**1. Kaftrio and Symkevi**
2. Devices supporting physiotherapy (The Vest, Simeox)
3. Mesh Inhalators (Pari e-flow)




## 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:**


***CZ***
***Klub nemocných cystickou fibrózou, z.s.***
*Kudrnova 22/95*
*150 00, Praha 5*
*info@cfklub.cz*
*+420 257 211 929*
*www.klubcf.cz*

***PL***
***MATIO Fundacja Pomocy Rodzinom i Chorym na Mukowiscydoze***
*ul. Celna 6, 30 - 507 Kraków*
*www.mukowiscydoza.pl*
*+48 12 292 31 80*
*p.wojtowicz@mukowiscydoza.pl*

***SK***
***Slovak Cystic Fibrosis Association***
*Park Angelinum 2, 040 01 Košice*
*www.cfasociacia.sk*
*+421 903 608 455*
*cfasociacia@gmail.com*

***HU***
***Cisztás Fibrózis Magyarország (CFBE)***
*2040 - Budaörs, Felsőhatár út 65*
*www.cisztasfibrozis.hu*
*cisztasfibrozis@gmail.com*

# UKRAINE
# COUNTRY REPORT

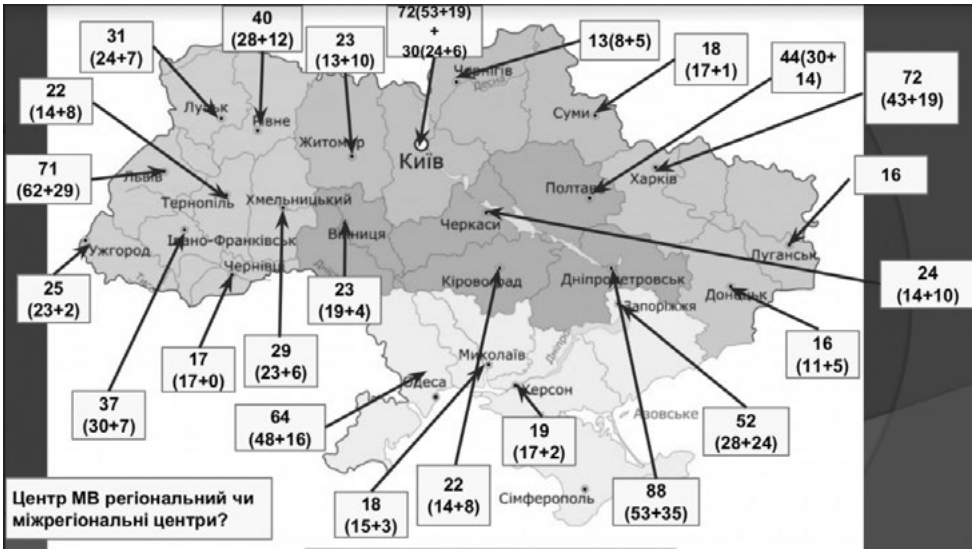
*VOLOSHYNA Larysa, ALL - Ukrainian Association of care of patients with cystic fibrosis»*
*MAKUKH Halyna, Institute of Hereditary Pathology of Ukrainian Academy of Medical Sciences, Lviv*

| | |
|---|---|
| Number of inhabitants | **41,9 mil** |
| Number of CF patients | **903** |
| CF children | **668** |
| CF adults | **235** |
| CF Centers for children | **4** |
| CF Centers for adults | **2** |
| Mixed | **2** |

Expected frequency **1 : 3 364**
**143** Cystic Fibrosis children are expected to be born every year

2500 - 4000 CF patients are expected to be exist in Ukraine ~ 903 – are registered
**24 oblasts** children's hospitals (pulmonology, pediatrician, gastroenterology departments)
4 CF centers for children (>50 patients), 2 mixed centers
**No official recognition of term "CF center"**

**Number of CF patients**




**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?**

***ALL - Ukrainian Association of care of patients with cystic fibrosis»***

## 1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2021. Access to standard medicines and therapies.

| KALYDECO | ORKAMBI | SYMKEVI | KAFTRIO | Total |
|---|---|---|---|---|
| 0 | 1 | 0 | 1 | 2 |

We were held several meetings with Vertex and the next one is planned for December 9, 2021 together with the leadership of CF Europe and medical experts of the Ministry of Health of Ukraine.

**BUT**

**CF patients do not have access to targeted therapy yet.**

2 patients receive the treatment in Italy.

**The National Program for Cystic Fibrosis in Ukraine:**

Creon 10 000
Creon 25 000
Pulmozym (Dornaza Alfa)
Colomicyn (Colistin)

Financing:

2015 y. - 8,000 mln.grn. = 302 000 $
2021 y. - 139,155 mln.grn. = 5,2 mln. $

Providing standard therapy for patients with CF in Ukraine:

- **National programme**
- **Regional Programme**
- **City Programme**
- **Free recepies**

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

At the state level, we do not yet have a national register, but we are working on it every day and hope that thanks to the adopted laws and approval of the action plan for the implementation of the Concept, we will have a national register in the nearest future. In this way, all regions will be able to be connected to the European register ECFSPR.
Currently, only **2 regions**, out of 24 (**Lviv** and **Ivano-Frankivsk**) are connected to the ECFSPR.

## 3. Do you have National standards of CF care?

The new version of **Guidelines for CF treatment in Ukraine** is being developed (the development of the National Treatment Guideline includes 17 best doctors of Ukraine and our patient organization), the old version was in **2016**.

Structural units of health care of Ukraine:

- Ministry of Health
- National Health Service of Ukraine
- Regional Departments of Health
- Etc.

The **Guidelines for CF treatment in Ukraine** is updating in 2021 - 2022.

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

**Law on Rare Diseases** adopted in **2014** which ensures that says:

*The State of Ukraine guarantees to local RD patients:*

- *uninterrupted,*
- *free of charge and*
- *life-long*

*treatment and support with essential medicines and relevant nutritional products.*

Managed Entry Agreements (MEA) - finally got the green light in Ukraine MEA legislation was adopted this year.

**The National Concept of Rare Diseases in Ukraine 2021 - 2026** was adopted on **April 28, 2021**. On **November 11, 2021**, the Cabinet of Ministers of Ukraine approved an **Action plan for the implementation of the Concept on Rare Diseases.**

The LIST of Orphan diseases which are included in the List of the Ministry of Health of Ukraine:

| | |
|---|---|
| **Orphanet** | **7000 diseases** |
| **Ukrainian list** | **312 diseases** |

**16 diseases including cystic fibrosis have a national program**

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

Social system is at the beginning of development of support of RD patients.

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

- **COVID-19**
- **CFTR modulators are not registered in Ukraine**
- **There are no CF national registry**
- **No interest from representatives of targeted therapy to work with Ukraine**
- **Not all antibiotics are accessed (Generics!)**
- **Patients should commonly pay for flutter, nebulizers, vitamins, etc.**
- **The CF centers mainly do not have specialist CF dieticians, psychologists, physiotherapists.**
- **Not sutisfied knowledge about CF among specialist, luck of CF adult specialist**
- **Higher incidence of lung infection, low body mass index.**
- **Many CF patients died too early.**

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

*“The action does not always lead to happiness, but only the action can lead to happiness!”*

**CONTACT:**

***ALL -Ukrainian Association of care of patients with cystic fibrosis***
*https://www.youtube.com/channel/UC4BiW-mJL91LO90Z_ItOIWg*
*+390 987 339 233 Larysa Voloshyna*
*uacpcf@gmail.com*

ВГО «ВСЕУКРАЇНСЬКА АСОЦІАЦІЯ ДОПОМОГИ ХВОРИМ НА МУКОВІСЦИДОЗ»

# LATVIA
# COUNTRY REPORT

*BELINSKA Alla, Cystic Fibrosis Society*
*ALEKSEJEVA Elina, Children's Clinical University Hospital, Riga*

| | |
|---|---|
| Number of inhabitants | **1,9 mil** |
| Number of CF patients | **56** |
| CF children | **41** |
| CF adults | **15** |
| CF Centers for children and adults | **1** |


**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?**

Latvia has **1** CF patients Association.

Mission: Develope and improve CF patients quality of life.

- to promote the improvement of the health care and social system for cystic fibrosis patients in Latvia
- get gowernmental attention to problems for CF patients and parents
- to cooperate with Latvian and foreign public organizations, state institutions, medical organizations and institutions, mass media, as well as other persons

**1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2021. Access to standard medicines and therapies.**

| KALYDECO | ORKAMBI | SYMKEVI | KAFTRIO | Total |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |

The Plan for Rare Diseases for years 2017 - 2020 was made to provide Orkambi medicine to **28 CF patients** in Latvia. All these years, the Latvian Cystic Fibrosis Society has been working hard to implement this planned activity. In October 2021, it was announced that 4.2 million euro would be allocated for orphan drugs (rare diseases budget) in the 2022 budget. Patients with cystic fibrosis starting from **2022** will receive innovative therapy with the drug **Orkambi, which will be reimbursed by state** for all patients with appropriate mutations.

Therapy with other innovative medicines are planned to be included into next Plan for Rare Diseases 2022 - 2024. We hope that it will only take a year and drug **Kaftrio** will also be available to Latvian CF patients. We are currently working on making CFTR modulators available in LV. Continuing to work on Kaftrio being registered.

**Standard therapy:**
**All CF patients receive state-paid treatment.**
**Riga Children's Clinical University Hospital** have special budget for CF patients treatment. Patients receive more prescribed medicine in Children`s Hospital where CF consulting-room is located. General practitioners are available by the place of residence.
Pari Boy SX inhaler also provides patients for physiotherapy devices (the acapella and the flutter) and nebulisers. Vibro vests are available for patients in hospital as well as for outpatients, if prescribed by a physiotherapist. Mannitol and CFTR modulators are currently not available in LV. Feeding with the PEG probe is available. Home IV antibiotic treatment initiated since 2019.

**For free for all CF patients:**
- pancreatic enzymes 10 000 and 25 000
- all required antibiotics - oral, inhaled (tobramycine (+TOBI), aztreonam, colomycine), and intra-venous
- NaCL 5, 85%
- Pulmozyme
- other special drugs for CF
- vitamin K, D, E, antifungals
- Pari Boy SX nebuliser
- nutritional products - all CF patients are providedved with medical food and this service has paid from the state budget, products included. In addition, there has been developed a procedure for BKUS (allergist-gastroenterologist council) by which a special medical nutrition (amino acid mixture) is granted, and a procedure for receiving and delivery directly to patient's home in any place of Latvia.
-from **2018 lung transplantation** is paid from the state budget.

**Not paid by Latvia state:**
- **Aquadeks Multivitamin and Mineral Supplement** - Patients' parents buy them from their own finances. Latvia Cystic Fibrosis Society helps CF patients' parents to purchase them from Netherlands company Alveolus Biomedical B.V.
- CF patients receive support from the Latvian Cystic Fibrosis Society by receiving **free-to-use sterilizer** to sterilize the inhalation component, thanks to the support of Latvian donors.

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

Latvian CF Registry is a part of ECFSPR since **2015**.

We have **national registry for all rare diseases**, supervised by the Rare Diseases Coordination Center of Children`s Clinical University Hospital, Riga.
Rare Diseases Coordination Center, which is subsidiary of Riga Children`s Clinical University Hospital, is responsible for maintain and developing National CF Registry. It is coordinated by the Centre's pulmonologists together with the Coordinator of the Center for Rare Diseases. Coordinator is responsible for all rare diseases patient registries in general.

## 3. Do you have National standards of CF care?

Latvian CF standards of care **„CF care standards, principles of therapy"**, reviewed in **2021**, have been available since **2014** and adapted from "'European Cystic Fibrosis Society Standards of Care: Best Practice guidelines", 2014. "Treatment guidelines for children with CF "have been available since 2014, reviewed in 2020, adapted from Royal Brompton and Harefield hopsitals " Clinical guidelines: Care of children with cystic fibrosis", 2020.

**CF Center in Latvia**
For treatment and care of CF patients is a granteds with special budget. The CF Center has been in Riga Children`s Clinical University Hospital since **1994** within the Rare Diseases Coordination Centre where is located **CF consulting-room**.
All CF patients are seen by a multidisciplinary team regularly (every 2 - 3 month,up to 1 year of age - every month, once a year on annual review): CF doctor, nurse, physiotherapist, nutritionist, CF consultants - ENT, gastroenterologists, psychologist, social worker etc.
The centre provides CF services for children and adults. The transition to an adult clinic has not yet taken place, CF team training is currently underway. CF patients have access to all necessary diagnostic tests (Macroduct and Nanoduct sweat testing, expanded molecular diagnostic tests).

Starting from July 1, **2019**, Latvia implemented state-paid **screening for newborn** genetic diseases. 8 CF patients were diagnosed within two years.

On February 28, **2018**, the **Rare Diseases Coordination Center** was established at the **Riga Children's Clinical University Hospital**.
Patients with rare diseases are provided with the opportunity to receive state-funded molecular genetic examinations, multidisciplinary councils also recommend therapies for rare diseases for which treatment in Latvia was not possible so far, as well as coordinated monitoring of health status in dynamics.

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

**Plan for Rare Diseases for period 2017 - 2020** for Latvia was approved in Latvia on October 23, **2017**. The plan sets out the priority tasks and measures to be taken to improve the early diagnosis of rare diseases, treatment. In particular, it is intended to ensure that genetic examinations are available not only to children but also to adult patients in appropriate indications to allow early detection and treatment.
The Ministry of Health responsible for managing, coordinating and monitoring the implementation of the plan. Unfortunately this plan **expired** since the end of 2020.
This year were discussed and were started development of a new Rare Diseases Plan for the next period 2022 - 2024. Unfortunatelly plan still not completed yet.

**Latvian Alliance of Rare Diseases**
Since 2014, the Latvian Alliance of Rare Diseases has been operating in Latvia, which unites various organizations representing the interests of rare disease patients. The Alliance's mission is to improve quality of life conditions for people with rare and chronic diseases in Latvia. The Latvian Cystic Fibrosis Society is a member of the Alliance Board.

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

All CF patients (children and adults) receive treatment and investigation free of charge at the hospital and at the outpatient clinic. For adult patients, the patient co-payment is funded by the Children's Hospital Foundation.Since the diagnosis is set up, all patients receive a state benefit (disability).

At present, **adult CF** patients with severe health disorders with **level 1 disability** are exempted from the fee for hospital treatment and for each visit to doctors and examinations in Latvia.
Adult CF patients with **level 2 and 3 disabilities** pay by themselves, including a visit to a CF doctor. Everything is free for children under 18. The Children's Hospital Foundation provides support for adult CF patients by paying for their examinations and treatment.
The proposal of the Latvian Cystic Fibrosis Society was included in the Plan for Rare Diseases 2017 - 2020 to exempt Rare Disease patients from patient fees in hospitals after the age of 18, but unfortunately it was not yet accepted by the country government.
We hope very much that in accordance with the provisions of the Latvian Health Care Financing Law, from January 1, 2022, Rrare Disease patients with a level II disability will be included in the list of persons who will be exempted from making a patient's co-payment.

- After the age of 18, patients diagnosed with CF acquire a level 2 or 3 disability status.
- **Adults with disability level 1** receive at least EUR 217.60 per month. In turn, patients with a degree of disability from childhood receive not less than 260.80 EUR
- **Adults with level 2 disability** receive not less than 190.40 EUR per month. In turn, patients who have been diagnosed with a degree of disability since childhood receive not less than 228.20 EUR
- **Adults with disability level 3** receive 136 EUR per month. In turn, patients who have been diagnosed with a degree of disability since childhood receive 163 EUR.

**Children** diagnosed with CF receive disability status for the first time for 2 to 5 years. At the end of this period, the disability specialist commission does repeated examination and status prolongs until the age of 18.

**Parents** who take care of a child with a disability status receive 106.72 EUR per month. In turn, a child who has a certain disability and has been issued an opinion on the need for special care – receives an additional 313.43 EUR per month.
Thus, the state support provided to families can reach 420.15 EUR per month.

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

- **Doctors need to be trained and a team of multidisciplinary specialists for the treatment of adult CF patients needs to be formed. That process takes place very slowly in Latvia.**
- **The transition to an adult clinic also needs to be developed.**
- **Exempt adult patients with CF from the age of 18 for hospital treatment, each visit to doctors and examinations**
- **In 2022, work is planned to CF patients in Latvia start treatment with Kaftrio drugs. To make up for this from health care system there will be the need to work hard to find funding for it.**
- **Latvia is one of the few countries in the European Union that has not joined any of the international organ transplantation networks.** The state plans to change it and work is being done at it underway.

  **Lung transplantation not performed in Latvia.** Donor organs are missing. Legislative changes are needed to increase the number of potential donors. Latvia plans to introduce consent for the use of organs for transplantation in the unified electronic system of the health sector from the February 1, 2022.

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

Thanks to the introduced newborn screening, the number of CF patients in Latvia is growing, and it is necessary to think not only about strengthening the existing CF consulting-room. The creation of a CF center with a team of disciplinary doctors working full-time only with CF patients and adequate remuneration for them, relieving them of other workloads, should be considered.

*„Our main goal and a step forward:*
*to provide treatment with new innovative medicines*
*for every patient with this rare and devastating disease".*

**CONTACT:**

***Latvian Cystic Fibrosis Society***
*Kalku 1, LV - 5237 VIESITE*
*LATVIA*
*cistiskafibroze.lv.info@gmail.com*
*+371 29 161 629*

# BULGARIA
# COUNTRY REPORT

*YANKOV Yanko, PETROVA Guergana*
*Bulgarian CF Association*

| | |
|---|---|
| Number of inhabitants | **6,9 mil** |
| Number of CF patients | **220** |
| CF children | **126** |
| CF adults | **94** |
| CF Centers for children | **4** |
| CF Centers for adults | **0** (4) – we don't have specialized adult center so children centers work with adult patients also |

- Population 6 876 495 (as of 17 Nov 2021)
- Area 110 994 km2
- Average life expectancy - 74.8 years (EU 80.99)
- Ethnicity - Bulgarian 70%, turks 15%, 10% romani
- Religion - $^{3}/_{4}$ orthodox christians, 10% muslims and others
- EU country since 2007
- Poverty line - 157 EUR → 1,6 mil. People in BG (22,29%) (EU average 17%)
- Internet users - 54.6%

**How many non-governmental CF organisations are there in your country?**
1
**„Asociacia Mucoviscidoza“, https://lifewithcf.org/**
It is patient organization (initially it was doctor-patient one, but currently it is strictly patient one – maintained and directed by patients and parents of patients.

**What is their mission?**
- Help and support to CF families.
- Improving care for CF in Bulgaria
- Different charity causes including individual support for a patient in need or hospital support for the centers (like fixing specialized CF-rooms or buying LCI machine) or support for every patient (like providing PEP masks for everyone)

**Is there any common platform or other form of cooperation?**
Facebook, webpage, Association is the best partner for CF centers

## 1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2021. Access to standard medicines and therapies.

| KALYDECO | ORKAMBI | SYMKEVI | KAFTRIO | Total |
|---|---|---|---|---|
| 4 | 16 | 0 | 7 | 27 |

**Yes, after very difficult fight, name patient list covered by NHIF (National Health Insurance Fund).**
It all started in 2016 November. The first patient with **Ivacaftor** started on 31st of December **2019**. All our patient´s are currently on patient name basis (something like article 16) payd from NHIF (National Health Insurance Fund).

**Currently**
- **4 children on ivacaftor**
- **16 ivacaftor/lumacaftor**
- **4 children on ivacaftor/elexacaftor/tezacaftor**
- **3 adults on Kaftrio, who are on lung transplant waiting list** (one dF/dF; and the other two dF/any) **– their therapy would be covered only during the state of emergency due to COVID19**. As the name patient therapy is available only for children in Bulgaria

**Standard therapy:**
**NHIF covers:**
- **Enzymes** - for all patients (only one brand, 2 strengths - 25 000 and 35 000 - we don't have suitable formula for very small babies - we open the capsule and divide it roughly)
- **Dornase alfa** - for all patient over the age of 5 yrs.
- **Inhaled colistin** - for all patients with chronic Pseudomonas aeruginosa (two forms – DPI and solution)
- **Inhaled tobramycin** for all patients over the age of 7 years with chronic Pseudomonas aeruginosa (two forms - DPI and solution)
- **Inhaled levofloxacin** - for all patients over the age of 18 years with chronic Pseudomonas aeruginosa (solution) - since April 2021
- **CFTRm** - ivacaftor monotherapy on a patient name basis
  - for the other modulators see above

**NHIF is not covering (patients have to pay):**

- Two inhaled antibiotics for one patient (we have to choose only one)
- Ursodeoxyholic acid!
- Bronchodilators (unless for adult patients labeled additionally as COPD !)
- Inhaled corticosteroids (unless the patients are labeled additionally as asthma)
- Vitamins
- Antibiotics (unless the patient is in the hospital and under 18 yrs, for some adults have to pay even in the hospital)
- Nutritional support
- PPI and H2 blockers, other gastrointestinal support medications (macrogol and others)

**We don't have in Bulgaria (have to be imported):**

- Special formula of vitamins for CF
- Inhaled aztreonam, amikacin (the patients use the i.v. form to do inhalations if needed)
- Properly working transplant program

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

- on a national level – we have one "unofficial"
- **2 CF Centers** are included in ECFSPR **(Sofia** and **Varna)**
- more than **80%** of all patient´s coverage

## 3. Do you have National standards of CF care?

We have **translated the ECFS standards from 2005**, and are on the webpage of MH - rare diseases section, but honestly not so many doctors are following them :(
It was translated with the aid of CF Bulgarian Association, who did sue the MH to change the policy for CF patients.
Every "center" decides what standards we should follow.
In Sofia – Royal Brompton Hospital guidelines 2020 are followed.

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

- yes, we have a nice program on paper
- and a lot is done for some rare diseases
- for CF there are still a lot work - i.e., implementing NBS – when? how?

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

In some extent:

- 14% under poverty line
- 46% live with less than 250 EUR/family member/month
- 36% spend – roughly 250 EUR for treatment/month
- 34% spend – roughly 150 EUR
- 11% spend – over 250 EUR

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

From the **physician's point of view**:

- lack of some medications (like AquaADEK)

- lack of specialized medicine formulas – i.e. liquid Ursofalk
- lack of specialized adult centers (CF is not appealing to our internal medicine specialists)
- lack of transplantation program
- lack of national children's hospital for easier and better team care
- lack of sustained governmental policy for CF (the country was in 3 elections in a row for a year…. Even now we still don't have updated national budget… With all the COVID19 pandemic problems it is hard)

From **patient's point of view**:
- I need an extra job, our expenses are too high and my salary is low.
- Have problems to take a sick leave
- All medications and nutritional supplements should be covered by NHI
- Most social workers don't know what is CF - disability evaluation on every 3 years, like I could be healed?
- When my kid has to be admitted due to pulmonary exacerbation, local hospital rejects us be cause of her CF
- Lack of free of charge transport to and from the hospital for patients
- Difficult to find a job when you have CF
- There is no adequate evaluation for practical needs of CF patients
- People don't know what is CF – when my child coughs or expectorates sputum she receives very strange looks.
- She is worried when she has to take Creon at school
- There is no psychological support even on the hospitals
- Old information in some doctors – when the diagnosis is confirmed you are told the child will live up to 13 years only

*THERE IS NO CENTER AS DESCRIBED IN THE STANDARDS OF CARE*

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

- Complicated, but better for we had obtained NHIF reimbursement CFTRm from next year for most of the eligible patients…..
- As of 4th January 2022, it was confirmed triple therapy would be available from NHIF for every eligible patient over 12 years of age and double therapy also but for children 6 and older.
- I hope to have NBS in the next 5 years
- I dream for a National Children's hospital for better team care
- I hope to have an adult center
- But again, it is money talk

**CONTACT:**

***Асоциация Муковисцидоза България***
*www.lifewithcf.org*
*+359 888 80 26 40, chairman: Anton Alexiev*
*e-mail: info@lifewithcf.org*

Асоциация Муковисцидоза България

# RUSSIA
# COUNTRY REPORT

*MIASNIKOVA Irina, "Help to CF patients"*

| | |
|---|---|
| Number of inhabitants | **144,1 mil** |
| Number of CF patients | **4 227** |
| CF children | **2 944** |
| CF adults | **1 283** |
| CF Centers for children | **53** (these are mostly in-patient clinics with Specialised CF beds, Not multidisciplinery CF teams) |
| CF Centers for adults | **6** (1 federal CF center in Moscow, regional in St.Petersburg, Yaroslavl, Novosibirsk, Omsk, Tomsk) |

Prevalence: 1 x 34,09 thousand of population
CF patients live in **84 regions** of Russia (out of 85), but not found in Chukcha region.


**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?**
**"Help to CF patients"**

- Opened - July, 1997 by parents of children with CF
- Aim - to help families with CF patients
- Subdivisions in **62 regions of Russia** (out of 85)
- Members: parents of CF children + grown-up patients + volunteers
- member of the **Board of Trustees of the "Circle of Good" Foundation**

What we do:

- We keep in touch with patients from 62 subjects of the **Russian Federation**
- Cooperation: legislative power of the Russian Federation (amendments to draft laws, participation in working groups) executive power: we are members of the Council for the Protection of Patients' rights of the Ministry of Health, Roszdravnadzor, MHD,
- We have cooperation agreement with Roszdravnadzor
- We organize events: Conferences, trainings for patients, Information support: **www.mucoviscidoz-russia.ru**
- Google is a group that unites regional representatives, different groups in social media

There are also several separate regional CF patients NGOs (Moscow, Moscow region, Yaroslavl, Novosibirsk).

## 1. Access to novel CF therapies (CFTR modulators,....) in your country until 31.12.2021. Access to standard medicines and therapies.

| KALYDECO | ORKAMBI | SYMKEVI | KAFTRIO | Total |
|---|---|---|---|---|
| 0 | 600 | 0 | 92 | 692 |

**ORKAMBI**

- registered in Russia in **2020** including infant formula
- in 2021 included into the **essential and vital drugs list**
- for all children from 2 years old to 18 years old with 2 copies of delF508 mutations without complex alelle - for about **600 children** (financed from the **state fund "Circle of good"**; CF adults with disability status can get the drug financed from local budgets starting 2022 .

**TRIKAFTA**

- not registered in Russia, but Trikafta was submitted for registration in Russia December, 24, **2021**
- for about **92 children** with severe CF disease age 12 years and older with 1 copy of delF508 mutation

*President Vladimir Putin started special state foundation for rare diseases. The foundation buys Orkambi for 600 Russian CF children and Trikafta for 92 children with most severe condition since October 2021. The foundation is planning to buy Orkambi (about 600 CF children) and Tricafta (for about 700 CF patients) for all Russian CF children with suitable mutations in 2022.*

**Reimbursed CF Drugs in Russia:**

Kreon
Dornaze Alfa
Ursodezoxycholic acid
Colistine for inhalation
Tobramicine for inhalation
IV antibiotics (in clinics)
Drugs from essential and vital drugs list (for individual cases)
Specialized CF medical nutrition products (for CF children only)

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

We have a CF registry, but it does not belong to the state, it`s scientific non-profit organization property. It`s part of ECFSPR
Russian Ministry of Health conducts a registry of CF patietns who get Dornase Alfa included into „High cost nozologies program“
**Neonatal screening** since **2006**.

## 3. Do you have National standards of CF care?

We have Russian clinical recomendations for chilren and adults with CF approved by the Russian Ministry of Health

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

No, we don`t have

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

The majority of CF patients have disability status, they receive a pension, free medicines (from essential and vital drugs list) and social benefits

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

- **To give access of innovative drugs to all CF patients including adults**
- **To achieve full availability of medical supplies with all vital drugs in all regions of Russia: inhalation drugs and IV ATB, innovative drugs**
- **To create a system of outpatient dispensary supervision in the regions of Russia**
- **To achieve Specialized Medical care for children and adults in all regions of the Russian Federation with sufficient compulsory health insurance rates**
- **Organize home care – IV ATB**
- **To achieve the adoption of updated standards and clinical recommendations**
- **To minimize the risks of cross-infection**
- **To achieve stability of social assistance: disability, TSR**
- **To achieve free diagnosis of CF – DNA**

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

***I hope all patients will have acceess to innovative care !***

**CONTACT:**

***NGO “Help to CF patients”***
*Member of the Board of Trustees of the “Circle of Good” Foundation*
***Irina Miasnikova**, chair person*
*Tel +7-916-313-81-53*
*E-mail miv20@mail.ru*
*www.rare-dieases.ru*
***www.mucoviscidoz-russia.ru***

# GENETICS OF CYSTIC FIBROSIS: AN UPDATE 2021

*Milan MACEK*
*Ústav biologie a lékařské genetiky*
*Univerzita Karlova v Praze a Fakultní nemocnice v Motole, CZECH REPUBLIC*

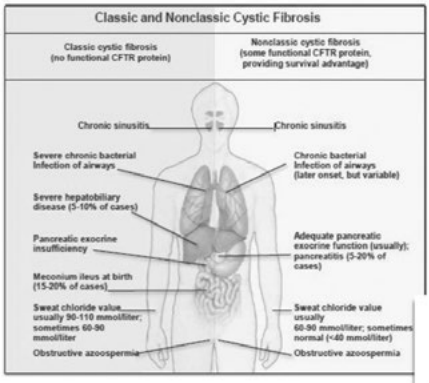
**The genetic diagnostics challenge in the era of next generation sequencing**

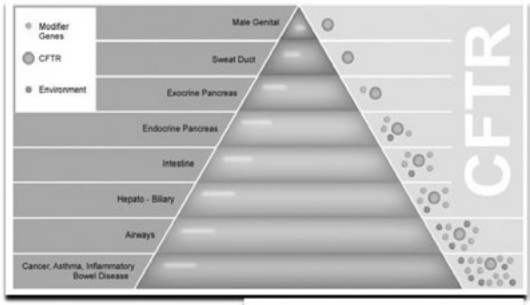
Over **5000 Mendelian "rare" phenotypes** with known causative gene (*OMIM.org; Orpha.net*)

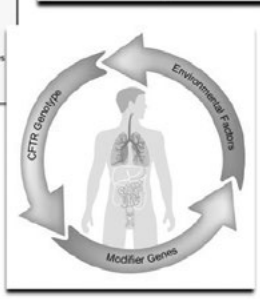
- **Allelic heterogeneity** is the rule
- Genes have >100 mutations
- **Disease implications**
- Known (usually) for common mutations
- Variably known for low frequency mutations (<5%)
- Unknown (usually) for rare mutations (<1%)

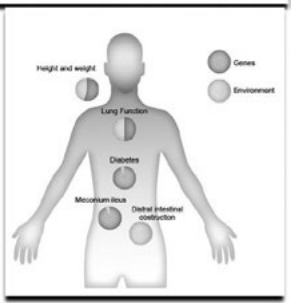
Clinical diagnostic **DNA sequencing** identifies all 3 types of mutations (**disease associated variants**)

**Cystic fibrosis is a multisystemic genetic syndrome!**



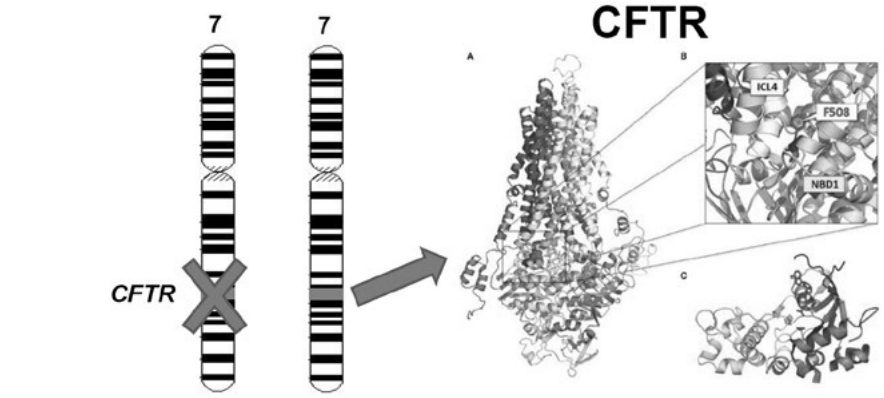




**Need for accurate assessment of diseaseliability (penetrance) of variants**

- Diagnosis of (postnatal) clinical cases
- **Newborn screening (bioch. phenotype)**
- **Carrier screening**
- Pregnancy decisions **(PGT M)**
- Variant (mutation) - specific therapies **(e.g. CFTR modulating therapies)**

**Gene therapy ?!**

**Milder CFTR mutation determines the phenotype in recessive syndromes**




**Need for accurate assessment of disease-liability of *CFTR* mutations and their tissue specific expression**

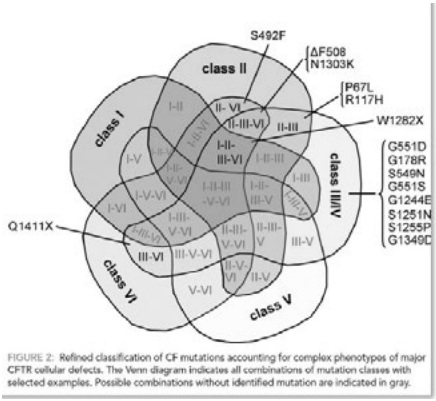
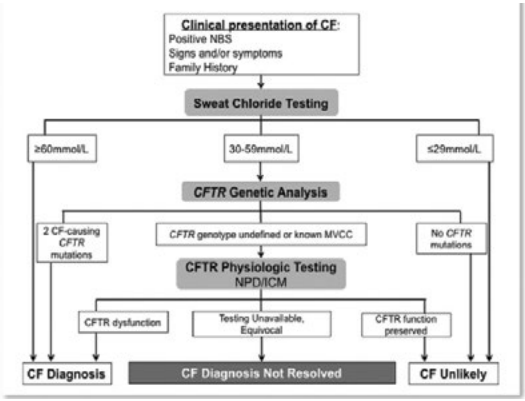
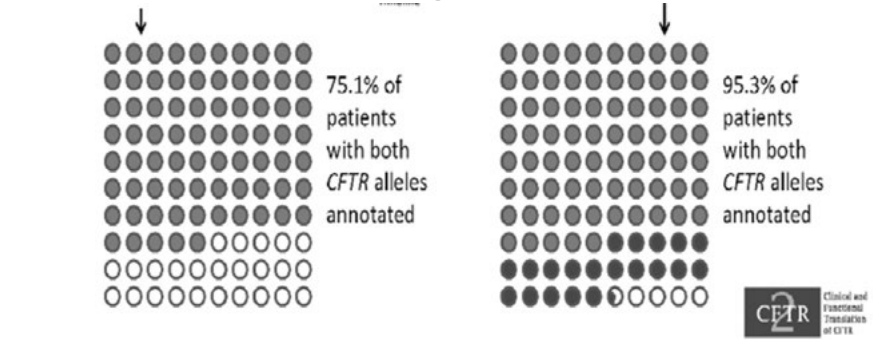



FIGURE 2: Refined classification of CF mutations accounting for complex phenotypes of major CFTR cellular defects. The Venn diagram indicates all combinations of mutation classes with selected examples. Possible combinations without identified mutation are indicated in gray.



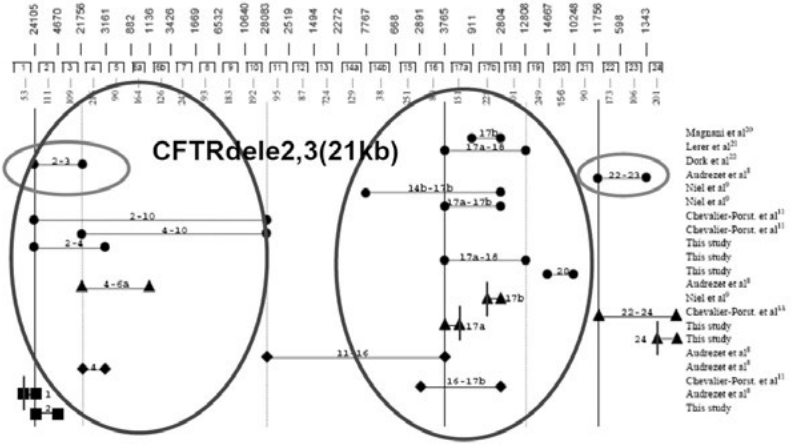

www.ncbi.nlm.nih.gov/pmc/articles/PMC3874936/#SD6

**International collaboration and CFTR2.org**




„Complete CFTR gene sequencing in 5,058 individuals with CF identified at least one DNA variant in 99.6% of the cohort that is targetable by current molecular or emerging gene-based therapeutic technologies “

**CFTR intragenic rearrangements (+3 % of non F508del alleles)**




S. Europe and the Middle East >25% mutations still u n known

**Carrier screening**

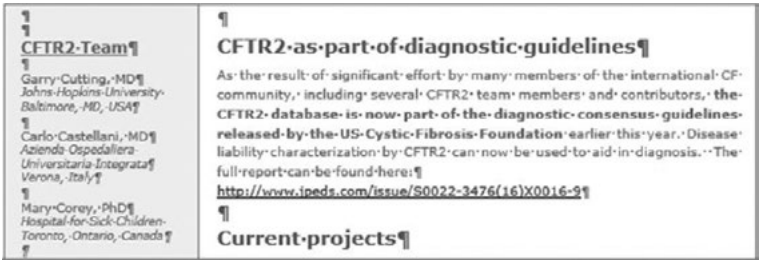
## What genes and mutations are investigated with the CarrierTest?

**CarrierTest** examines hidden transmission of more than 2000 frequent -„**key**"- mutations of 80 recessive genes that cause more than 75 genetic diseases and conditions which may affect the offspring of healthy carriers. They include cystic fibrosis, spinal muscular atrophy, congenital defects in metabolism (such as phenylketonuria), visual and hearing disorders, musculoskeletal disorders and skin diseases.

Mutations of another group of genes may be of importance for the treatment of fertility disorders (thrombophilia profile, congenital response to hormone treatment of infertility) or they can manifest themselves as a result of lifestyle (hemochromatosis, alpha-1 antitrypsin deficiency).

https://www.psmarketresearch.com/marketanalysis/carrier screening market

**CFTR2 - part of diagnostic guidelines**



CFTR2-Team

Garry Cutting, MD
*Johns Hopkins University, Baltimore, MD, USA*

Carlo Castellani, MD
*Azienda Ospedaliera Universitaria Integrata, Verona, Italy*

Mary Corey, PhD
*Hospital for Sick Children, Toronto, Ontario, Canada*

**CFTR2 as part of diagnostic guidelines**

As the result of significant effort by many members of the international CF community, including several CFTR2 team members and contributors, **the CFTR2 database is now part of the diagnostic consensus guidelines released by the US Cystic Fibrosis Foundation** earlier this year. Disease liability characterization by CFTR2 can now be used to aid in diagnosis. The full report can be found here:

http://www.jpeds.com/issue/S0022-3476(16)X0016-9

**Current projects**

**Basic principles –„Exploratory population genetic study"**

1) **Unrestricted charitable academic contribution e.g . EuroCareCF, CFNetwork, Eurogentest, Snip2Chip, Techgene , 3Gb test)**
2) **„No strings attached"** - serves underte sted and untested CF populations,
3) Complete analysis of the **entire CFTR coding region (plus introns)** by MPS massively parallel sequencing (Devyser) and MLPA analysis of CNVs / positive s independently verified by DNA Sanger sequencing

**Academic principles**

1) Joint authorship, patient / regulatory consent ( EU 28 regulations )
2) Entry of clinical data into the **ECFS registry** where allowed collaborators
3) Entry of novel CFTR mutations into **CFTR1** Prague
4) Entry of annotated clinical data into **CFTR2.org** Prague+collaborators
5) Confidentiality agreements, cases patients included at the discretion of collaborators **anonymously**
6) Further studies based on verification of cilnical phenotype (1 or both muts.)

**Caveats**

1) Tested cohorts are may not be not representative, comprising cases with one or both CFTR mutations remained unidentified after local initial screen or where there was no testing at all usually in countries which also do not have routine sweat testing . Sweat chloride at least over 40mM bearing in mind uncertainty of testing / inexperience / phenotype
2) **CFTR DNA testing is the easy part... logistics, legal issues, trust..., complementing concurrent ECFS initiative**

*(www.ecfs.eu/content/complete-cftr-gene-mutation-analysis-european -patients-cystic-fibrosis)*

**„Cascade" testing strategy (ISO15189:2013)**

**„Negative" patients likely do not have CF Introns / complex alleles, CNVs, pathogenetic reanalysis of VUS**

**Czechia**

ELSEVIER

Journal of Cystic Fibrosis 12 (2013) 532–537

Journal of Cystic Fibrosis
www.elsevier.com/locate/jcf

Short Communication

Distribution of *CFTR* mutations in the Czech population: Positive impact of integrated clinical and laboratory expertise, detection of novel/*de novo* alleles and relevance for related/derived populations☆

Petra Křenková [a], Tereza Piskáčková [a], Andrea Holubová [a], Miroslava Balaščaková [a], Veronika Krulišová [a], Jana Čamajová [a,b], Marek Turnovec [a], Malgorzata Libik [a], Patricia Norambuena [a], Alexandra Štambergová [a], Lenka Dvořáková [a], Veronika Skalická [c], Jana Bartošová [c], Tereza Kučerová [c], Libor Fila [d], Dana Zemková [c], Věra Vávrová [c], Monika Koudová [a,c], Milan Macek, Sr. [a], Alice Krebsová [a,f], Milan Macek Jr. [a,*]

[a] Department of Biology and Medical Genetics, 2nd Faculty of Medicine of Charles University Prague and University Hospital Motol, Prague, Czech Republic
[b] Regional Authority of Public Health, Banská Bystrica, Slovak Republic
[c] Department of Pediatrics, 2nd Faculty of Medicine of Charles University Prague and University Hospital Motol, Prague, Czech Republic
[d] Department of Pneumology, 2nd Faculty of Medicine of Charles University Prague and University Hospital Motol, Prague, Czech Republic
[e] GHC Genetics Ltd., Prague, Czech Republic
[f] Department of Cardiology, Humboldt University, Virchow Klinikum Charité, Berlin, Germany

Received 15 October 2012; received in revised form 30 November 2012; accepted 2 December 2012
Available online 29 December 2012

| Protocol | Sensitivity | Specificity PPV | Avoiding detection of patients with equivocal diagnosis | Avoiding carrier detection |
|---|---|---|---|---|
| IRT/IRT | ++ | + | +++ | +++ |
| IRT/DNA limited panel | ++ | +++ | ++ | ++ |
| IRT/DNA extended panel | +++ | +++ | + | + |
| IRT/DNA/EGA | +++ | ++++ | - | - |
| IRT/DNA/IRT | +++ | +++ | ++ | +++ |
| IRT/IRT/DNA | + | +++ | + | + |
| IRT/PAP | ++ | - | +++ | +++ |
| IRT/PAP/DNA | ++ | +++ | ++ | ++ |
| IRT/PAP/DNA/EGA | ++ | ++++ | + | ++ |

# GENETICS OF CF IN POLAND
# GENETYKA W MUKOWISCYDOZIE

*Karolina KOWALCZYK, Agnieszka SOBCZYŃSKA-TOMASZEWSKA*
*MedGen Medical Centre, POLAND*

**Genetic testing in Poland:**

**OBLIGATORY**

- Genetic tests applied in medicine are performed in a medical laboratory registered in KIDL
- Each test is authorized by a laboratory diagnostician (not by a doctor, biologist, biotechnologist or pharmacist
- The laboratory has to work in accordance with the Polish Ministry of Health regulations on quality standards for genetic testing

**RECOMMENDED**

- The laboratory should take part in the external quality control (CF Network/EMQN)
- Polish Society of Human Genetics certifies medical laboratories in Poland
- ISO (9001, 15189) is not required but appreciated
- If the test is ordered during a visit in a outpatient clinic, it can be reimbrused by the National Health Fund (but only up to a fixed amount ). Expensive tests, such as WES, can be reimbrused during patient hospitalization
- Genetic tests can be ordered and financed by a patient himself

**How we should call defects in the CFTR gene?**

**Understanding between: patient/physician/laboratory**

| Traditional classification |
|---|
| mutation |
| polymorphism |

| CF recommendations [2008] | CFTR2 |
|---|---|
| CF causing mutations, disease causing mutations | |
| CFTR-related mutations | Variable consequence mutations |
| Non causing mutations, non pathogenic mutation | |
| Mutations of unknown clinical significance | |

| ACMG recommendation (Genet Med. 2015 May; 17(5): 405–424. ) |
|---|
| Pathogenic variant (null variant like: nonsense, frameshift, canonical +/−1 or 2 splice sites, initiation codon, single or multi-exon deletion) in a gene where loss of function (LOF) is a known mechanism of disease), Same amino acid change as a previously established pathogenic variant regardless of nucleotide change, de novo |
| Likely Pathogenic |
| VUS (variants of uncertain significance) |
| Likely Benign |
| Benign (Allele frequency is above 5% in Exome Sequencing Project, 1000 Genomes, or ExAC) |

**Traditional genotype and genotype according to HGVS recommendation should be included into genetic results:**

**Wynik / RESULT**

| | |
|---|---|
| Nazwa genu / loci | CFTR |
| Genotyp | -/- |
| Genotyp zgodny z HGVS v.2 (na poziomie cDNA) | LRG_663 t1(NM_000492.3): c.[=];[=] |
| Genotyp zgodny z HGVS v.2 (na poziomie białka) | NP_000483.3: p.[=];[=] |
| Wynik badania | prawidłowy |

**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 |

Data from Matio Foundation database

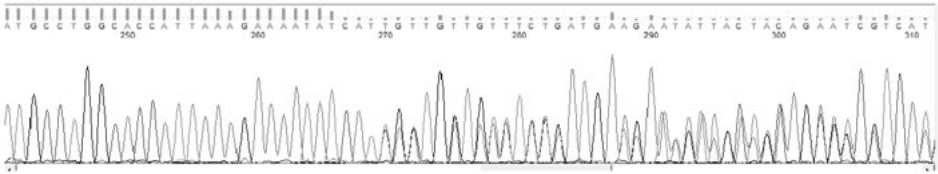
| | number | % |
|---|---|---|
| Total of CF patients/alleles | 1370/2740 | 100% |
| ?/? or m/? | 151 | 11% |
| F508del/F508del | 572 | 42% |
| Rare variants or variants not identified | 336 | 12% |
| Age >18 | 466 | 38% |
| Age <18 | 777 | 62% |

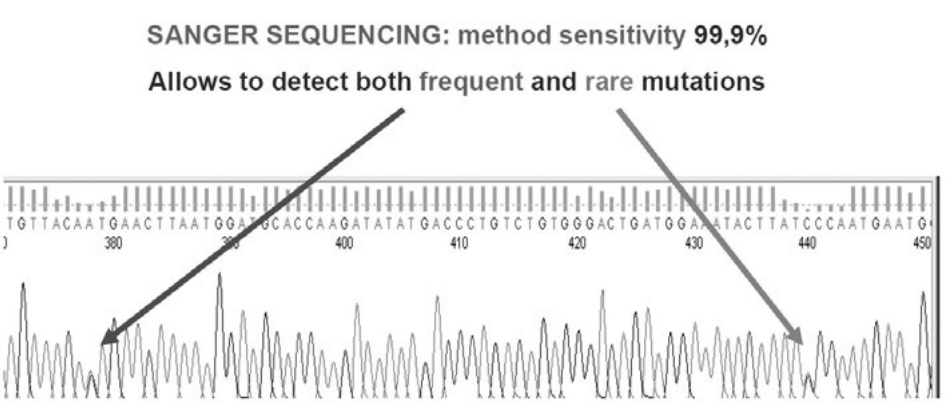
Typical for the Polish population mutations were not be included into commercial diagnostic assay

Sequencing DNA strategy for diagnostic testing

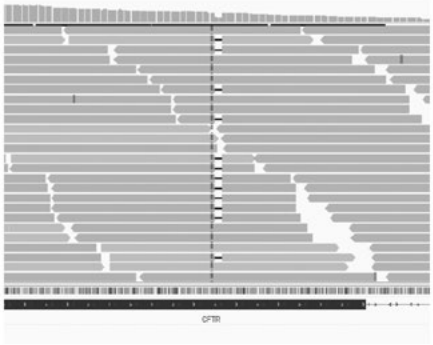
| Variant | Allele number | % |
|---|---|---|
| F508del | 1729 | 71,9 |
| dele2,3(21kb) | 101 | 4,2 |
| N1303K | 58 | 2,4 |
| G542X | 56 | 2,3 |
| 3849+10kbC>T | 53 | 2,2 |
| 2143delT | 42 | 1,7 |
| 2184insA | 41 | 1,7 |
| R553X | 39 | 1,6 |
| R553X | 38 | 1,6 |
| 1717-1G>A | 34 | 1,4 |
| 2183AA>G | 31 | 1,3 |
| W1282X | 27 | 1,1 |
| 3272-26A>G | 19 | 0,8 |
| R334W | 17 | 0,7 |
| K710X | 17 | 0,7 |
| 3600+2insT | 14 | 0,6 |
| D1152H | 13 | 0,5 |
| R347P | 12 | 0,5 |
| R117H+7T | 12 | 0,5 |
| 3659delC | 10 | 0,4 |
| 1898+1G>A/C | 10 | 0,4 |
| 711+3A>G | 5 | 0,2 |
| G551D | 4 | 0,2 |
| R792X | 4 | 0,2 |
| c.1392+1G>A | 3 | 0,1 |
| 2721del11 | 3 | 0,1 |
| 621+1G>T | 3 | 0,1 |
| c.1392+1G>A | 3 | 0,1 |
| c.164+1G>T | 3 | 0,1 |
| E585X | 3 | 0,1 |
| Σ= | 2404 | 100,0 |

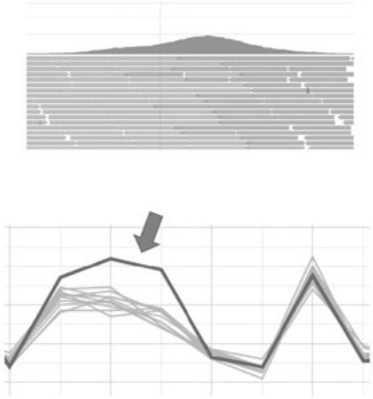
## POSZUKIWANIE MUTACJI RZADKICH, ULTRARZADKICH i DE NOVO
## SEARCHING FOR RARE, ULTRARARE and DE NOVO MUTATIONS






**SEARCHING FOR RARE, ULTRA RARE AND DE NOVO MUTATION**
**NEXT GENERATION SEQUENCING/SEKWENCJONOWANIE NOWEJ GENERACJI (NGS)**



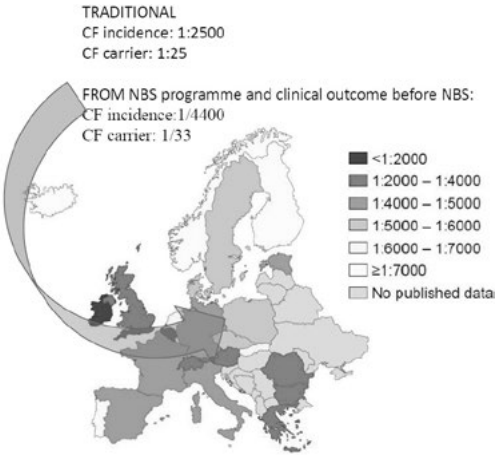



Matio Foundation database

| Variant | Allele number | % |
|---|---|---|
| F508del | 1729 | 71,9 |
| dele2,3(21kb) | 101 | 4,2 |
| N1303K | 58 | 2,4 |
| G542X | 56 | 2,3 |
| 3849+10kbC>T | 53 | 2,2 |
| 2143delT | 42 | 1,7 |
| 2184insA | 41 | 1,7 |
| R553X | 39 | 1,6 |
| R553X | 38 | 1,6 |
| 1717-1G>A | 34 | 1,4 |
| 2183AA>G | 31 | 1,3 |
| W1282X | 27 | 1,1 |
| 3272-26A>G | 19 | 0,8 |
| R334W | 17 | 0,7 |
| K710X | 17 | 0,7 |
| 3600+2insT | 14 | 0,6 |
| D1152H | 13 | 0,5 |
| R347P | 12 | 0,5 |
| R117H+7T | 12 | 0,5 |
| 3659delC | 10 | 0,4 |
| 1898+1G>A/C | 10 | 0,4 |
| 711+3A>G | 5 | 0,2 |
| G551D | 4 | 0,2 |
| R792X | 4 | 0,2 |
| c.1392+1G>A | 3 | 0,1 |
| 2721del11 | 3 | 0,1 |
| 621+1G>T | 3 | 0,1 |
| c.1392+1G>A | 3 | 0,1 |
| c.164+1G>T | 3 | 0,1 |
| E585X | 3 | 0,1 |
| Σ= | 2404 | 100,0 |

Newborn screening in Poland
from 2012

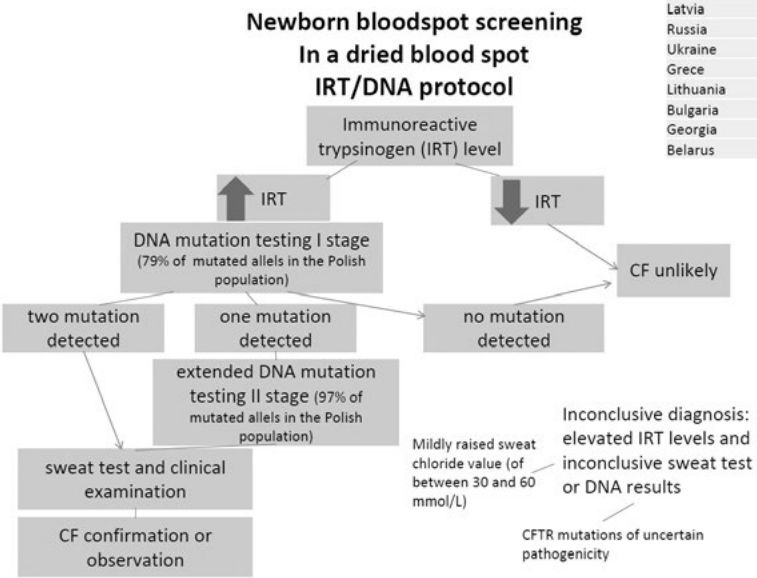
| | |
|---|---|
| F508del | 54,3% |
| dele2,3(21kb) | 4,2% |
| 3849+10kbC>T | 3,0% |
| Phe1052Val | 2,5% |
| Gly542Ter | 2,3% |
| Asn1303Lys | 2,0% |
| IVS8-5T(TG)12 | 1,9% |
| Asp1152His | 1,9% |
| Arg553Ter | 1,6% |
| Arg117His+IVS8-7T | 1,6% |
| 1717-1G>A | 1,4% |
| 2143delT | 1,3% |
| 2184insA | 1,2% |
| Trp1282Ter | 1,1% |
| 3272-26A>G | 0,9% |
| 2143delt | 0,8% |
| Arg297Gln | 0,8% |
| Pro750Leu | 0,8% |
| Arg347Pro | 0,7% |
| Asp806Gly | 0,6% |
| 2183AA>G | 0,7% |
| Arg334Trp | 0,5% |
| Lys710Ter | 0,4% |
| Gly1069Arg | 0,4% |
| IVS8-5T(TG)13 | 0,3% |
| Tyr301Cys | 0,3% |
| Gln685ThrfsTer4 | 0,3% |
| Met952Ile | 0,3% |
| Tyr1092Ter | 0,3% |


**Screening tests in Poland and other countries**

CH, CAH, CF, PKU, MSUD, HCY, TYR 1, TYR 2, ASA, CIT1/2, ARG, GA1, IVA, 3MCC, PA, MMA, BKT, 3HMG, GA2, MCAD, LCHAD, VLCAD, CPT1, CPT2, CACT, CUD, GAL*, BIOT, SCID*, SMA = 29+1

| Country | national | pilot |
|---|---|---|
| Italy | 31 | 4 |
| Poland | 29 | 1 |
| Hungary | 26 | 1 |
| Austria | 26 | |
| Slovakia | 25 | 2 |
| Sweden | 25 | |
| Portugal | 24 | |
| Netherlands | 20 | 2 |
| Demark | 19 | 1 |
| Slovenia | 19 | 1 |
| Estonia | 19 | |
| CzechRep | 18 | |
| Belgium | 17 | 3 |
| Germany | 17 | 2 |
| UK | 9 | |
| Croatia | 8 | |
| Spain | 7 | 26 |
| France | 6 | |
| Latvia | 6 | |
| Russia | 6 | |
| Ukraine | 4 | 24 |
| Grece | 4 | |
| Lithuania | 4 | |
| Bulgaria | 3 | |
| Georgia | 3 | |
| Belarus | 2 | |



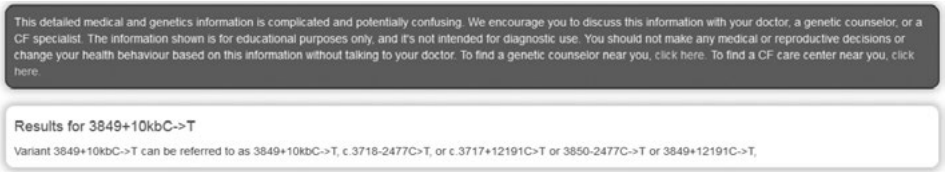
**Diagnostic dilemma...**
**abnormal screening tests (elevated IRT ) + inconclusive sweat tests and/or DNA results**

**CRMS (CFTR related metabolic syndrome in the USA**
**Cystic Fibrosis Screen Positive, Inconclusive Diagnosis in Europe**

- An asymptomatic infant with a positive NBS result for CF and either a sweat chloride value <30 mmol /L and two CFTR variants at least one of which has unclear phenotypic consequences OR an intermediate sweat chloride value (30 59 mmol /L) and one or zero CF causing variants
- ICD-9: 277.9, ICD 10: E88.9: niespecyficzna choroba metaboliczna /nonspecific metabolic disease/
- 17% of newborn in USA registry after NBS have diagnosed CRMS
- F508del/R117H is the most frequent genotype among CRMS patients
- CRMS /SPID one year clinical observation is necessary

**The CFTR-2 project has collected information from over 89 000 CF patients.**

***www.cftr2.org***




As of the most recent file (24 September 2021), a total of 466 variants are annotated on the CFTR2 website:
- CF causing: 382
- Variants of varying clinical consequence: 49
- Non CF causing: 24
- Variants of unknown significance: 11

According to the information on the CFTR-2 website, it shoud be used for educations purposes only

In the recommendations: „Diagnosis of Cystic Fibrosis in Screened Populations“ there are information that CFTR-2 website shoud be use to aid with CF diagnosis.

## Diagnosis of Cystic Fibrosis in Screened Populations

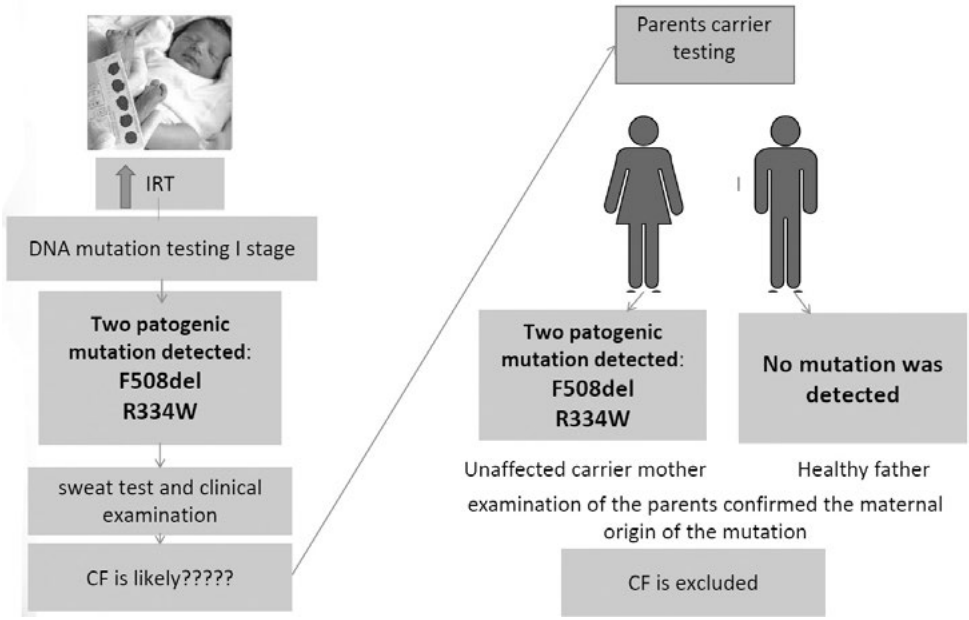
Philip M. Farrell, MD, PhD[1], Terry B. White, PhD[2], Michelle S. Howenstine, MD[3], Anne Munck, MD[4], Richard B. Parad, MD, MPH[5], Margaret Rosenfeld, MD, MPH[6], Olaf Sommerburg, MD[7], Frank J. Accurso, MD[8], Jane C. Davies, MBChB, FRCPCH, MD[9], Michael J. Rock, MD[1], Don B. Sanders, MD, MS[10], Michael Wilschanski, MBBS[11], Isabelle Sermet-Gaudelus, MD, PhD[12], Hannah Blau, MBBS[13], Silvia Gartner, MD[14], and Susanna A. McColley, MD[15]

**Objective** Cystic fibrosis (CF) can be difficult to diagnose, even when newborn screening (NBS) tests yield positive results. This challenge is exacerbated by the multitude of NBS protocols, misunderstandings about screening vs diagnostic tests, and the lack of guidelines for presumptive diagnoses. There is also confusion regarding the designation of age at diagnosis.
**Study design** To improve diagnosis and achieve standardization in definitions worldwide, the CF Foundation convened a committee of 32 experts with a mission to develop clear and actionable consensus guidelines on diagnosis of CF with an emphasis on screened populations, especially the newborn population. A comprehensive literature review was performed with emphasis on relevant articles published during the past decade.
**Results** After reviewing the common screening protocols and outcome scenarios, 14 of 27 consensus statements were drafted that apply to screened populations. These were approved by 80% or more of the participants.
**Conclusions** It is recommended that all diagnoses be established by demonstrating dysfunction of the CF transmembrane conductance regulator (CFTR) channel, initially with a sweat chloride test and, when needed, potentially with newer methods assessing membrane transport directly, such as intestinal current measurements. Even in babies with 2 CF-causing mutations detected via NBS, diagnosis must be confirmed by demonstrating CFTR dysfunction. The committee also recommends that the latest classifications identified in the Clinical and Functional Translation of CFTR project [http://www.cftr2.org/index.php] should be used to aid with CF diagnosis. Finally, to avoid delays in treatment, we provide guidelines for presumptive diagnoses and recommend how to determine the age of diagnosis. *(J Pediatr 2017;181S:S33-44).*

Mutation status is not fixed

| Variant cDNA name (ordered 5' to 3') | Variant protein name | Variant legacy name | rsID | # alleles in CFTR2 | Allele frequency in CFTR2 (of 142,036 identified variants)* | % pancreatic insufficient (patients with variant in trans with 5/5T/9 TG variant, with variant in homozygosity, or with another variant expected to lead to no CFTR protein production) | Variant final determination 31 July 2020 (previous version) | Variant final determination 24 September 2021 (current version) | Change from previous version? |
|---|---|---|---|---|---|---|---|---|---|
| c.[4C>T;7A>T] | p.[Gln2X;Arg3Trp] | Q2X;R3W | not found | 4 | 0,00003 | 100% | | CF-causing | Yes |
| c.54-5842_489+401del | No protein name | IVS1-5842_IVS4+401del | not found | 4 | 0,00003 | 100% | | CF-causing | Yes |
| c.168delA | p.Glu56AspfsX35 | 300delA | rs397508269 | 8 | 0,00006 | 100% | | CF-causing | Yes |
| c.[273+1_274-1]_(1584+1_1585-1)del | No protein name | CFTRdele4-10 | not found | 18 | 0,00013 | 100% | | CF-causing | Yes |
| c.346G>A | p.Glu116Lys | E116K | rs397508571 | 8 | 0,00006 | 100% | | CF-causing | Yes |
| c.424delA | p.Ile142PhefsX11 | 556delA | rs387906363 | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.580-2A>G | No protein name | 712-2A->G | rs193922730 | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.653T>A | p.Leu218X | L218X | rs397508777 | 36 | 0,00025 | 100% | | CF-causing | Yes |
| c.744-2A>G | No protein name | 876-2A->G | rs1057516646 | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.761delA | p.Lys254ArgfsX7 | 892delA | not found | 4 | 0,00003 | 100% | | CF-causing | Yes |
| c.935_937delTCT | p.Phe312del | F312del | rs121908768 | 28 | 0,00020 | 57% | | Varying clinical consequence | Yes |
| c.1210-33_1210-6GT[11]T[4] | No protein name | 5T;TG11 | not found | 35 | 0,00025 | 23% | Varying clinical consequence | Non CF-causing | Yes |
| c.1210-2A>C | No protein name | 1342-2A->C | rs397508179 | 9 | 0,00006 | 67% | | CF-causing | Yes |
| c.1330_1331delAT | p.Ile444X | 1460delAT | rs397508190 | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.1820_1903del84 | p.Met607_Gln634del | 1949del84 | rs121908777 | 24 | 0,00017 | 100% | | CF-causing | Yes |
| c.1911delG | p.Gln637HisfsX26 | 2043delG | rs1554389296 | 8 | 0,00006 | 100% | | CF-causing | Yes |
| c.2502dupT | p.Asp835X | 2634insT | not found | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.2797A>G | p.Arg933Gly | R933G | rs397508436 | 7 | 0,00005 | 29% | | Varying clinical consequence | Yes |
| c.2822delT | p.Leu941GlnfsX27 | 2954delT | rs762844777 | 7 | 0,00005 | 33% | | CF-causing | Yes |
| c.3067_3072delATAGTG | p.Ile1023_Val1024del | 3199del6 | rs121908767 | 75 | 0,00053 | 98% | | CF-causing | Yes |
| c.3103C>T | p.Gln1035X | Q1035X | rs397508496 | 5 | 0,00004 | 100% | | CF-causing | Yes |
| c.3382A>T | p.Arg1128X | R1128X | not found | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.3600delA | p.Asp1201MetfsX10 | 3732delA | not found | 4 | 0,00003 | 100% | | CF-causing | Yes |
| c.3822G>A | p.Trp1274X | W1274X | rs397508613 | 3 | 0,00002 | 100% | | CF-causing | Yes |
| c.3929G>A | p.Trp1310X | W1310X | rs397508645 | 3 | 0,00002 | 100% | | CF-causing | Yes |

**Patient from NBS programme with two known patogennic variants located in one allele (*in cis*)**




***CONTACT/KONTAKT***
*Laboratorium Badań Genetycznych i Poradnia Genetyczna*
*ul. Wiktorii Wiedeńskiej 9a, Warszawa*
*diagnostyka@medgen.pl*

***dr Agnieszka Sobczyńska-Tomaszewska***
*506 069 568; ast@medgen.pl, office@medgen.pl*

# NBS PROGRAM AND DIAGNOSTIC PROCESS IN UKRAINE

*Halyna MAKUKH[1], Vira MURONENKO[1], Lyudmyla BOBER[2], Marta TYRKUS[1], Nadiya HELNER[1]*
*1 - Institute of Hereditary Pathology of National Academy of Medical Sciences, Lviv, UKRAINE*
*2 - Western Ukrainian Specialized Children's Medical Centre, Lviv, UKRAINE*

- In Ukraine CF care is not as good as than generally in Europe and many CF patients died to early.
- **903 CF** patients are registered in Ministry of Health Care.
- The expected frequency of cystic fibrosis in Ukraine is **1 in 3364** newborns according to the estimated frequency of CFTR gene mutations heterozygous carriers.
- Taking into account the population **2500 to 4000** CF patients should exist in Ukraine.

The CF NBS by two steps IRT/IRT was started in the whole country in 2012 and was discontinued in 2015 – 2016.

**In 2012 - 2015 IRT – IRT CF - NBS**

- the CF NBS protocol was integrated into the current blood spot screening program.
- the cut-off for Immunoreactive Typsinogen was set
  **IRT-1 at 70 ng/ml**
  **IRT-2 - 40 ng/ml.**
- next step was sweat testing followed by DNA test in case of sweat Cl level was over 30 mmol/l.

**The incidence of IRT-1, IRT-2 positive cases and CF in different districts (West regions)**

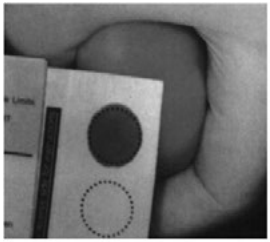
| Districts | All newborns screened 2012 - 2015 | Positive IRT-1 tests (>70 ng/ml) | | Positive IRT-2 tests (>40 ng/ml) | | CF diagnosis confirmed | Cystic fibrosis incidence |
|---|---|---|---|---|---|---|---|
| | | N | N, per 10 000 newborns | N | N, per 10 000 newborns | | |
| Lviv | 70554 | 244 | 31 | 36 | 5 | 15 | 1: 4703 |
| Zakarpattya | 59435 | 535 | 93* | 75 | 13 | 7 | 1:8491 |
| Khmelnytsky | 42958 | 282 | 67 | 52 | 12 | 10 | 1:4296 |
| Chernivtsy | 34158 | 233 | 78 | 37 | 12 | 3 | 1:11386 |
| All screened newborns | 207109 | 1294 (0.6%) | | 200 (0.1%) | | 35 | 1:5917 |

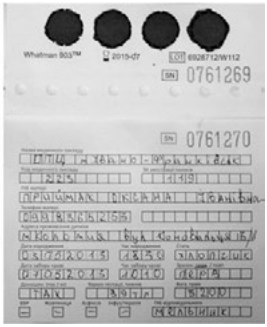
**Higher IRT level among Gypsy origin newborns**

- there are many Gypsy origin newborns in Zakarpattya which were informed to have higher IRT level (S. Dluholucky, 2013).
- newborns of Gypsy origin have an elevated IRT level in NBS but no one case of CF was confirmed.

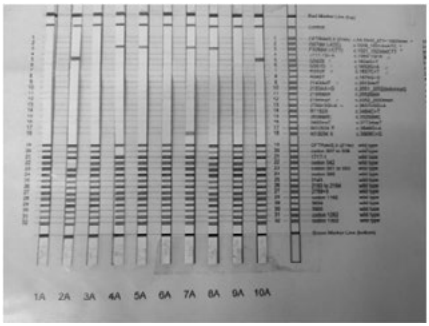
**In 2018 IRT – IRT - DNA CF - NBS restarted in Ukraine**

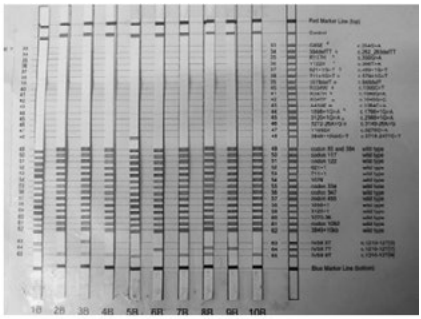
- one of four conditions to screen in newborns
  - 14 sites for IRT testing over the country
  - 2 sites for DNA testing (Kyiv, Lviv)
- CF StripAssay for 32 CFTR mutations
- next step - sweat testing and CF diagnosis.






**DNA - CF StripAssay from 2-nd blood spot**

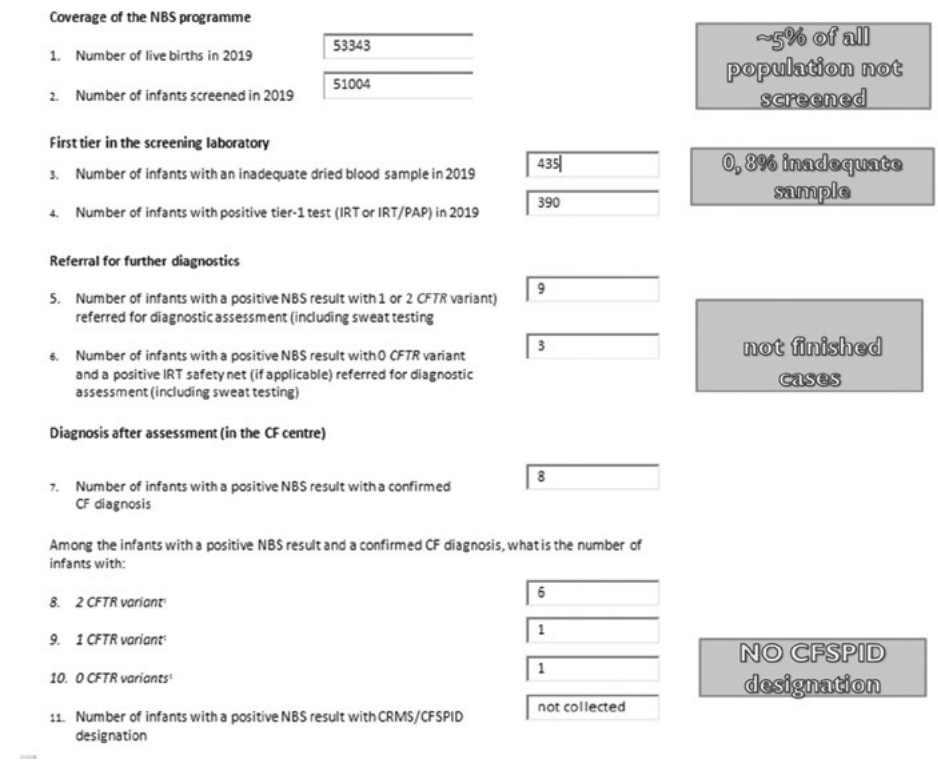




Assay for the identification of cystic fibrosis conductance regulator (CFTR) gene mutations

**The incidence of IRT-1, IRT-2 positive cases and CF in different districts of West Ukraine**

| Districts | All newborns screened 2019 – 2020 | Positive IRT-1 tests (>65 ng/ml, *> 80 ng/ml for GP) | | Positive IRT-2 tests (>50 ng/ml) | | CF diagnosis confirmed | Cystic fibrosis Incidence in NBS |
|---|---|---|---|---|---|---|---|
| | | N | N, per 10 000 newborns | N | N, per 10 000 newborns | | |
| Lviv | 43 851 | 273 | 62 | 13 | 3 | 7 | 1: 6242 |
| Zakarpattya* | 24 603 | 153 | 62 | 7 | 3 | 4 | 1:6150 |
| Khmelnytsky | 16 864 | 105 | 63 | 5 | 3 | 3 | 1:5561 |
| Chernivtsy | 15 713 | 98 | 62 | 2 | 1.3 | 1 | 1:15713 |
| All screened newborns | 101031 | 629 (0.6%) | | 27 (0.03%) | | 15 | 1:6735 |




**The incidence of CF 1:6735 with NBS**

- The estimated incidence of CF 1:6735 screened newborns.
- Not all the positive IRT tests were analyzed/confirmed on the next stages because of unwilling of parents (information, organisation)
- In three cases newborn screening failed. One child has normal IRT-1 (32 ng\ml), one case of child with meconium ileus and one was premature infant.

**Detection of one CFTR mutation in the heterozygous is a challenge**

Mutation detected !! - It's a cystic fibrosis. In heterozygous !! - it's healthy.

**Mutations** **Heterozygous**

CFSPID designation

**CF diagnosis**

CF diagnosis - By the sum of clinical and paraclinical data in CF center.

**Cystic Fibrosis Center - an institution where trained professionals work. (There are more than 50 patients with cystic fibrosis, 100 for Western Europe)**

- Among Screening positive cases many IVS 5T allele carriers.
- There are cases of not-accepting CF diagnosis.
- No practice of CFSPID

**DNA - CF StripAssay (32 mutations) from IRT2 positive (2-nd blood spot)**

| | |
|---|---|
| Two CFTR pathogenic variants identified among IRT-2 positive cases (21/90) -23% | |
| F508del/ F508del | 7 |
| F508del / CFTRdele2,3 | 3 |
| F508del / G542X | 3 |
| F508del /W1282X | 1 |
| F508del / 2184insA | 1 |
| 2184insA /5 T | 1 |
| 2184insA /CFTRdele2,3 | 1 |
| F508del /621+1G->T | 1 |
| F508del/ 1717+1>A | 1 |
| F508del/ N1303K | 1 |
| G542X/ G542X | 1 |
| One CFTR pathogenic variant identified (13/90) – 14% | |
| F508del | 8 |
| G542X | 3 |
| 3849+10kbC->T | 1 |
| CFTRdele2,3 | 2 |
| No one CFTR pathogenic variants identified (46/90) – 51% | |
| Unidentified | 46 |
| 5 T alleles identified (9/90) – 10 % | |
| 5 T alleles in homozygous | 1 |
| 5 T alleles in heterozygous | 8 |

| CFTR mutation | Number of allele (CF patient in ECFPR ) | Frequency % |
|---|---|---|
| F508del | 186 | 61.59 |
| 2184insA | 39 | 12.91 |
| N1303K | 12 | 3.97 |
| G542X | 10 | 3.31 |
| CFTRdele2,3 | 8 | 2.65 |
| Inidentified | 7 | 2.32 |
| 1898+1G->A | 4 | 1.32 |
| 3272-11A->G | 3 | 0.99 |
| 3849+10kbC->T | 3 | 0.99 |
| R347H | 3 | 0.99 |
| 185+1G->T | 2 | 0.66 |
| 3131delI15 | 2 | 0.66 |
| R553X | 2 | 0.66 |
| S466X | 2 | 0.66 |
| S945L | 2 | 0.66 |
| 1609delCA | 1 | 0.33 |
| 2183AA->G | 1 | 0.33 |
| 296+1G->A | 1 | 0.33 |
| 4163_4167delTAAAA | 1 | 0.33 |
| 4375-36delT | 1 | 0.33 |
| 621+1G->T | 1 | 0.33 |
| E831X | 1 | 0.33 |
| I336K | 1 | 0.33 |
| K598X | 1 | 0.33 |
| Q1412X | 1 | 0.33 |
| Q493X | 1 | 0.33 |
| R75X | 1 | 0.33 |
| S1347PfsX13 | 1 | 0.33 |
| W1282X | 1 | 0.33 |
| Y362X | 1 | 0.33 |

**NBS program in conditions of not established CF care system**

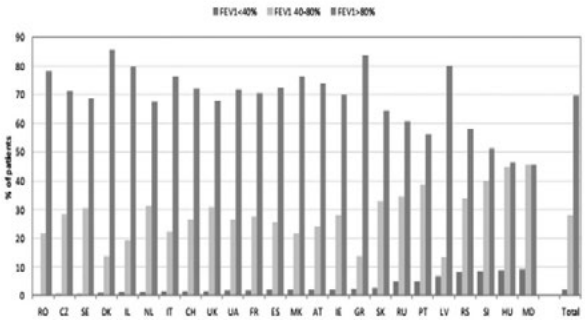
**Minuses**

No proper care in some cases, Missed diagnosis, Anxiety for not CF patient.

**Pluses**

Early diagnosis, Less severe cases, General knowledge increases, CF is treatable, More diagnosed cases, Positive attitude to CF-NBS program from doctors who organize the CF patient's treatment

**Since 2011 data are included in ECFSPR (Two Centers)**




**Compare to ECFSPR data**

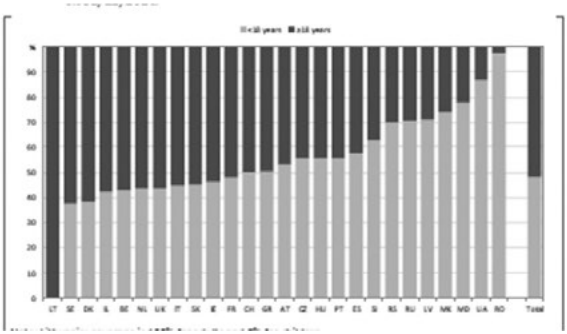
**Lover BMI,**

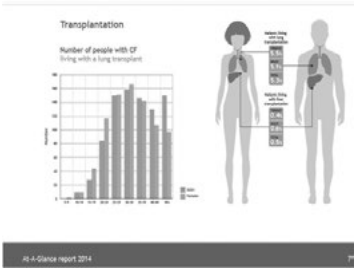
**Higher incidence of infection Ps.aeruginosa**

The oldest CF patient is 38.

**Ratios CF patients <18 years and > 18 years (79 : 21)**

In 2020, the average age of CF patients from Ukraine is **10.7** years, European average age - 17.8






**Conclusions**

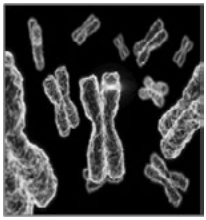
- to decrease the CF false positivity rate among newborns of Gypsy origin the IRT-1 cut off level increased and blood spots should be marked additionally with ethnic data.
- CFSPID should be included into the classification and national guidelines have to be adapted
- the positive outcomes of CF-NBS include decreasing of CF diagnosis age, starting care of CF children without symptoms, increasing attention to CF problems among specialists and community.
- the educational activities should be done to improve the benefits and justify the financial costs of CF-NBS program.
- the experience and support of EU country are crucial for CF patients surviving rate improving in UA.

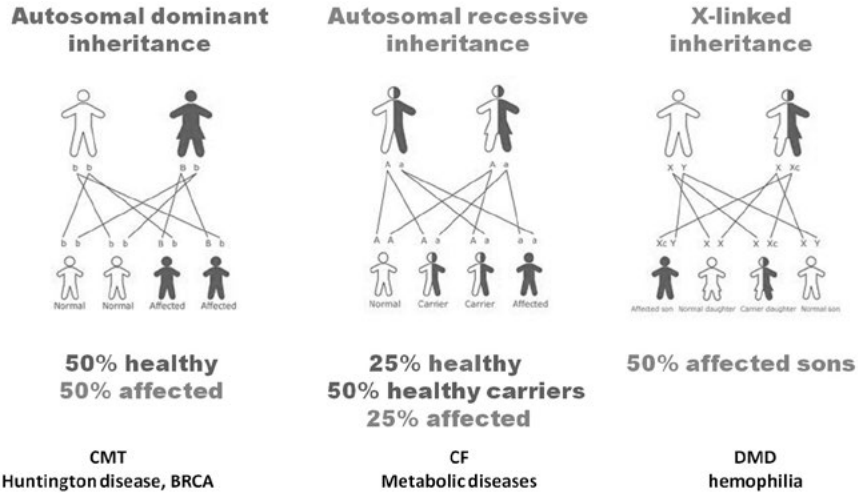
# PRECONCEPTION GENETIC SCREENING OF CYSTIC FIBROSIS AND OTHER SINGLE GENE DISORDERS

*I. ČERNÁKOVÁ, R. PETROVIČ*
*Genetic lab ReproGen, Bratislava, SLOVAKIA*

## Single gene disorders

- Clinical presentations are caused by the mutation in one gene
- Mendelian type of inheritance
- Rare occurance
- 7 000 single gene disorders
  **WHO: Common prevalence 1 : 100**
- 20% of children mortality in developed countries
- 1 300 single gene disorders with recessive inheritance






## Diagnostic opportunities of single gene disorders in Slovakia

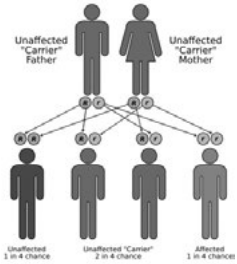
**1. Preconception testing**
- preconception carrier genetic screening
- preimplantation genetic testing (PGT-M)

**2. Prenatal diagnostics**
- amniocentesis, chorionic villi sampling
- NIPT – CF, de novo single gene disorders

**3. Newborn biochemical screening** - 13 single gene disorders

**4. Postnatal diagnostics**
- family/person with detected single gene disorders or carrier
- oocyte/sperm donors – CF SMA, non-syndromic deafness

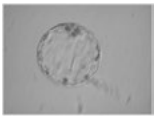
## Single gene disorders




| | Carriers | |
|---|---|---|
| **Cystic fibrosis** | **1 : 25** | **4 %** |
| **Spinal muscular atrophy** | **1 : 50** | **2 %** |
| **Non-syndromic deafness** | **1 : 48** | **2 %** |

**80% of children** with recessive disorder is born in the healthy family without previous occurance of single gene disorder

## Preconception genetic screening of single gene disorders



**For whom?**
Before natural conception
Before assisted conception
Oocyte and sperm donors

**Preimplantation genetic testing (PGT-M)**
**1 : 100 1 : 100 000**
Risk of the delivery of the child affected by single gene disorder

Pacients and donors of oocytes (2 570 persons):
**84 % of pacients has at least 1 pathogenic variant** (AR or XR)
2.3 pathogenic variant/person (1 - 7)
15 % of persons are negative for tested disorder
**5 - 8% of couples has mutation in the same gene - genetic incompatibility**
**2 % of women are carriers of X-recessive disorder**

**Our experience**
- panel of **300 or 550 genes**, analysis using NGS
- high risk of transmission of disease **with recessive inheritance (AR or X-linked)** to the next generation

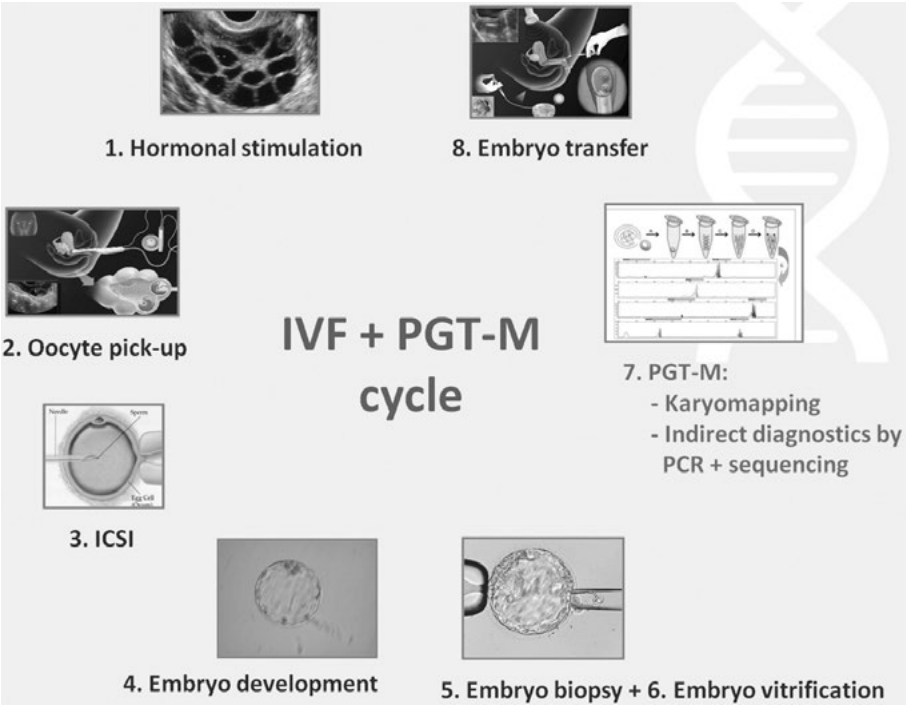
| Indication | No. couples | Carriership in couples | Genetic incompatibility | Reproductive decission |
|---|---|---|---|---|
| Consanquinity | 1 | both | 1 | PGT-M |
| Healthy couple without *a priori* risk | | | | |
| Infertility – before IVF | 15 | 4 | 2 | 2 couples – PGT-M |
| Before IVF - one healthy child | 1 | 1 partner | no | End of reproduction |
| Familiar anamnesis | | | | |
| Before IVF - PGT-M | 1 | both | CFTR, CD2AP | PGT-M 2x |
| | 1 | 1 partner – AD both - AR | IT15, REN | PGT-M 2x |
| Mukopolysacharidosis, unknown type | 1 | 1 partner | no | IVF |
| Infertility + translocation | 1 | 1 partner | + translocation | Voluntary childless |

**Genetic testing of oocyte and sperm donors**
Period: 10/2018 – 16.8.2021

| | Total persons | CFTR gene | SMN1 gene | GJB2 gene |
|---|---|---|---|---|
| Total persons | 265 | 253 | 252 | 186 |
| Patholog. variants | 23 | 10 | 7 | 6 |
| % | 8.68 | 3.95 | 2.7 | 3.2 |

| Multiple findings | Number |
|---|---|
| 47,XXX + CFTR (5T variant) | 1 |
| CFTR (ΔF508) + GJB2 (c.101C>T) | 1 |
| GJB2 (c.101C>T) + CFTR (5T variant) | 1 |

**Reproductive options of couples with genetic incompatibility:**
**- Preimplantation genetic testing (PGT-M)**
**- Prenatal diagnostics – amniocentesis, chorionic villi sampling**
**- NIPT – CF**
- Gamete donation
- Adoption of child



**PGT-M**

**- Genetic counselling before PGT-M**

**- Preparation for PGT-M:**

Haplotype analysis of 5 fully informative DNA markers
WGA – whole genome amplification
PCR haplotype analysis
Sanger sequencing – verification of results
Report

**- Genetic counselling after PGT-M**

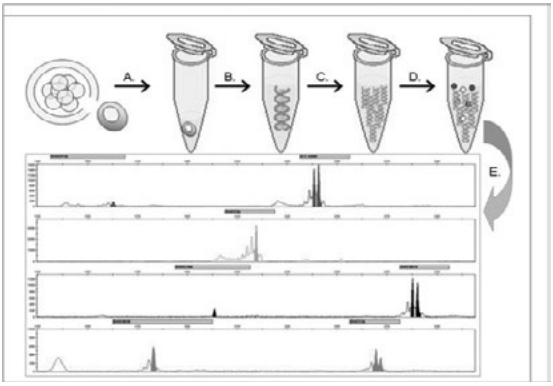
**PCR – PGT-M**

A. Biopsy of blastocyst. Transfer of cells to test tube.

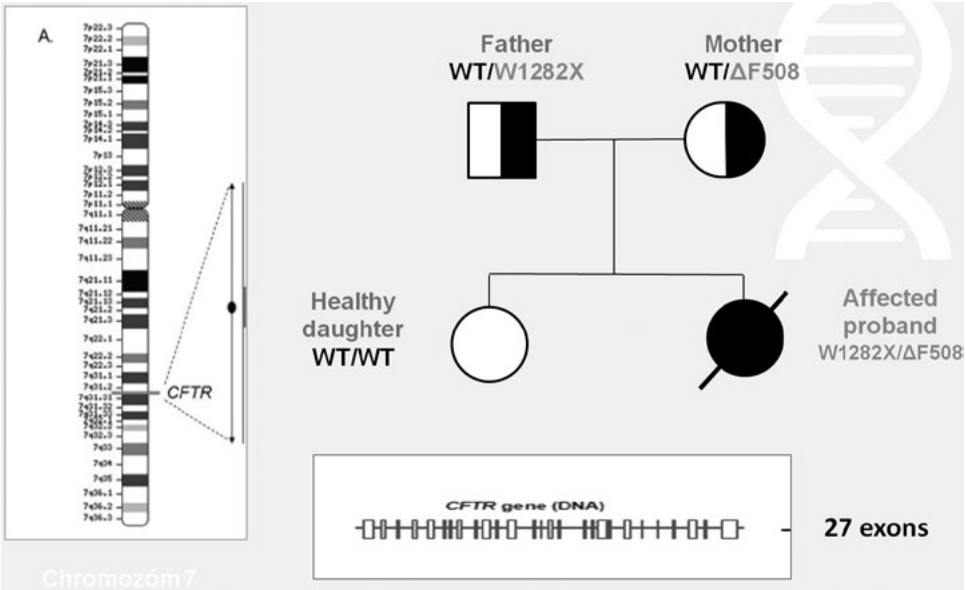
B. Whole genome amplification - WGA.

C. Amplificatmultiplexion of WGA products by fluorescence PCR - detection of specific DNA markers linked to the mutation.

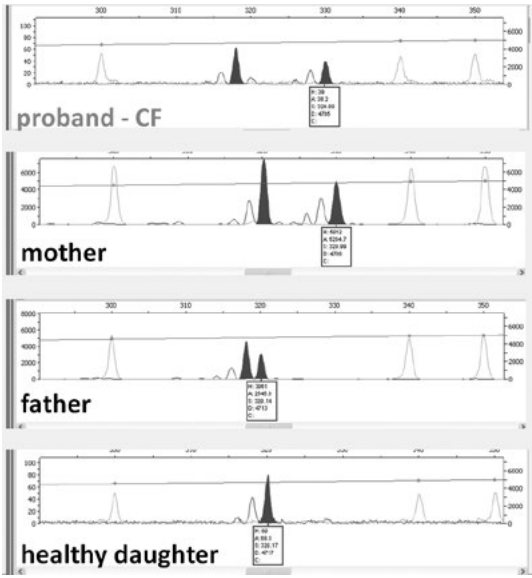
D. Detection of embryo genotype using fragmentation analysis. Verification of mutation by Sanger sequencing.




**Cystic fibrosis family**



**Haplotype analysis in family**




Marker – IVS10CA

| IVS10CA | Allele 1 | Allele 2 |
|---|---|---|
| proband | 318 | 330 |
| mother | 320 | 330 |
| father | 318 | 320 |
| healthy daughter | 320 | 320 |

12 markers analyzed inside of *CFTR* gene, in front and behind *CFTR* gene

## The reasons of PGT-M failures:

**Human failure**

- Unprotected sexual intercourse
- No appropriate identification (of embryos, test tubes, documents ...) and interpretation of results
- Transfer of no appropriate embryo
- No appropriate DNA primer design

**Technical failure**

- DNA Contamination (maternal, paternal, genetic staff, DNA of former analysis)
- Failure DNA of primers, PCR
- Allelic drop-out – elimination by blastocyst biopsy

**Single gene disorders can´t be cured, but they can be prevented**

**Primary prevention of occurence of single gene disorders in family**
**- Preimplantation genetic testing – PGT-M**
**- Preconception carrier screening of single gene disorders**

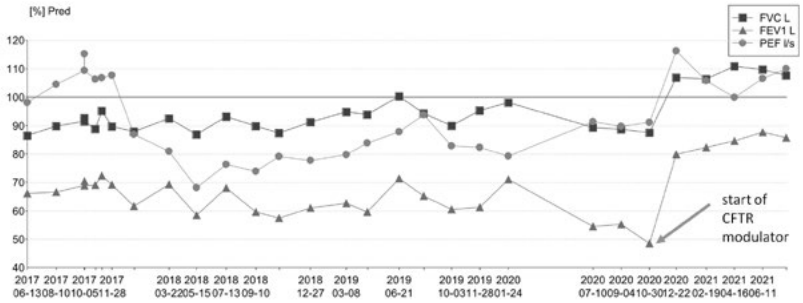
# CYSTIC FIBROSIS REGISTRY IN POLAND
# THE DISEASE AND DATA MANAGEMENT

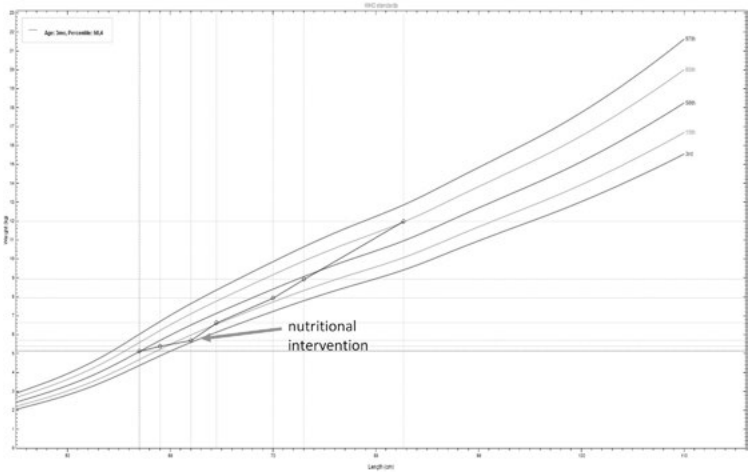
*Lukasz WOZNIACKI*
*Warsaw Cystic Fibrosis Centre, Dziekanow Lesny Paediatric Hospital, POLAND*

**Computerization of the healthcare system – a game changer**
- significantly improves the quality of medical records
- records are easy to read
- searchable, immediate result
- transmittable
- changes beneficial for:
  patients, caregivers, medical professionals, payer, insurer

**Computerization of the healthcare system**
- e - prescriptions
- e - referrals
- e - medical records

**Disadvantages**
- increase in complexity
- high cost
- requires integration of mulitple systems



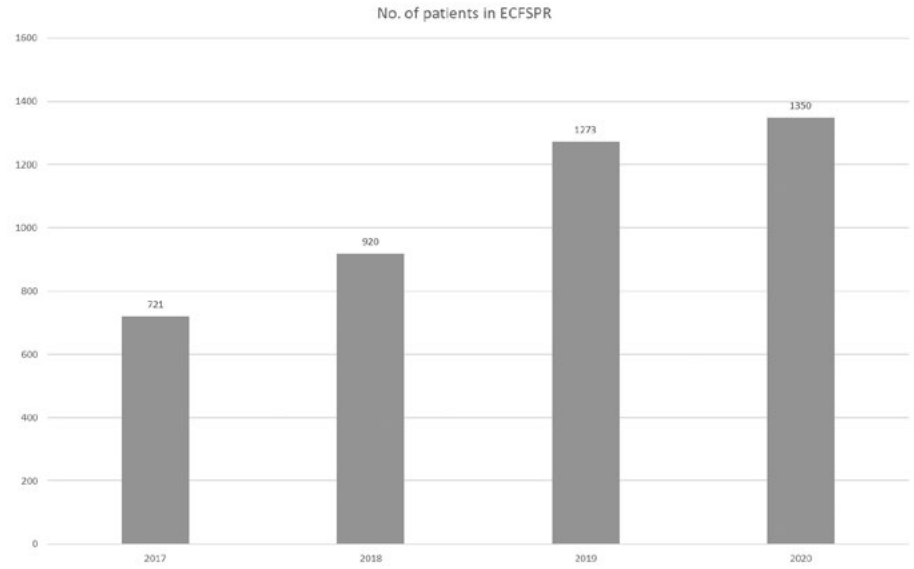



***Data is important, but its adequate presentation and clinical interpretation are even more important.***

## Variables in ECFSPR

| Demographics | Diagnosis | Complications | Microbiology |
|---|---|---|---|
| CF centre code | Diagnosis confirmed | Allergic broncho-pulmonary aspergillosis this year | Chronic *Pseudomonas aeruginosa* |
| Patient code | Age at diagnosis | Diabetes treated this year | Chronic *Staphylococcus aureus* |
| Year of follow-up | Sweat test type and value | Pneumothorax this year | Chronic *Burkholderia cepacia complex* |
| Date of birth (year and month) | Electrolytes | Distal intestinal obstruction syndrome (DIOS) this year | *Haemophilus influenzae* this year |
| Gender | Chloride value | Salt loss syndrome this year | *Stenotrophomonas maltophilia* this year |
| Status of patient | Meconium ileus | Liver disease this year | *Nontuberculous mycobacteria* this year |
| Cause of death | Nasal Potential Difference (NPD) | Haemoptysis major over 250 ml this year | *Achromobacter spp* this year |
| Date of death | CF-typical NPD | Pancreatic status: faecal elastase | *MRSA* this year |
| | Date of NPD | Pancreatic status: faecal fat | Total days on iv antibiotics at home and in hospital |
| | Intestinal current measurement (ICM) | Occurrence of malignancy this year | Total days on iv in hospital |
| | CF-typical ICM | | Total days in hospital |
| | Date of ICM | | |
| | Neonatal screening | | |

| Genotype | Therapy (this year) | Follow-up | Transplant |
|---|---|---|---|
| First mutation | Inhaled continuous hypertonic NaCl | Date of best $FEV_1$ recorded this year | Liver transplant |
| Second mutation | Inhaled continuous Mannitol | Value of best $FEV_1$ recorded this year | Year of latest liver transplant (if occurred before or during this year) |
| | Inhaled continuous antibiotic | Value of best FVC recorded this year | Lung transplant |
| | Inhaled continuous bronchodilators | Date of lowest LCI 2.5% recorded this year | Year of latest lung transplant (if occurred before or during this year) |
| | In Oxygen therapy | Value of lowest LCI 2.5% recorded this year | Kidney transplant |
| | Use of continous non-invasive positive pressure ventilation this year | Type of device for LCI measurement | Year of latest kidney transplant (if occurred before or during this year) |
| | Use of rhDNase | Height measured at date of best $FEV_1$ (or in case of no $FEV_1$ last height of the year) | Other transplant |
| | Use of continuous Inhaled steroids | Weight measured at date of best $FEV_1$ (or in case of no $FEV_1$ last height of the year) | |
| | Use of continuous Oral steroids | | |
| | Use of continuous azithromycin (or other macrolide) | | |
| | Use of ursodeoxycholic acid | | |
| | Use of pancreatic enzymes | | |
| | Use of proton pump inhibitors | | |
| | Use of CFTR modulator therapy | | |



## Number of patients registered in year 2020 by diagnosis and status

Table of diagnosis by status

| diagnosis(Diagnosis confirmed) | status(Status of patient) | | | | |
|---|---|---|---|---|---|
| Frequency | Deceased | Alive | Not seen during the year of follow-up | Lost to follow-up | Total |
| Yes | 9 | 1195 | 137 | 9 | 1350 |
| Total | 9 | 1195 | 137 | 9 | 1350 |

## Cause of death

Cause of death

| death_cause | Frequency | Percent |
|---|---|---|
| Respiratory | 5 | 55.56 |
| Liver-GI | 1 | 11.11 |
| Suicide | 1 | 11.11 |
| Transplantation | 1 | 11.11 |
| Cancer | 1 | 11.11 |

| age_dthl | Frequency | Percent |
|---|---|---|
| 21-30 | 5 | 55.56 |
| 31-40 | 2 | 22.22 |
| 41-50 | 2 | 22.22 |

Median death age 25.6, avarage 31.6

Proportion of children (<18 years) and adults (>=18 years). Patients alive, also not seen, on 31/12/2020

| age_fupl | Frequency | Percent |
|---|---|---|
| <18 | 889 | 66.74 |
| >=18 | 443 | 33.26 |

Frequency Missing = 9

Age at follow-up: descriptive statistics. Patients alive, also not seen, on 31/12/2020

Analysis Variable : age_fup

| N | Mean | Minimum | 25th Pctl | Median | 75th Pctl | Maximum |
|---|---|---|---|---|---|---|
| 1332 | 15.1 | 0.1 | 7.1 | 13.2 | 20.8 | 60.5 |

Sex distribution. Patients alive, also not seen, on 31/12/2020

Gender

| Gender | Frequency | Percent |
|---|---|---|
| M | 667 | 50.08 |
| F | 665 | 49.92 |

Age at diagnosis: descriptive statistics. All patients seen in 2020

Analysis Variable : age_dia0

| N | N Miss | Mean | Minimum | 25th Pctl | Median | 75th Pctl | Maximum |
|---|---|---|---|---|---|---|---|
| 1189 | 15 | 2.92 | 0.00 | 0.10 | 0.20 | 1.90 | 54.10 |

Proportion of patients diagnosed when younger than 1 year, when older than 18 years and in between. All patients seen in 2020

| age_dia0 | Frequency | Percent |
|---|---|---|
| <1 | 828 | 69.64 |
| 1-18 | 316 | 26.58 |
| >18 | 45 | 3.78 |

Frequency Missing = 15

Proportion of patients who underwent neonatal screening. All patients seen in 2020

Neonatal screening

| neo_scree | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 62 | 5.15 |
| Not done | 521 | 43.27 |
| Performed | 621 | 51.58 |

Proportion of patients who underwent neonatal screening. Patients 5 years old or younger seen in 2020

Neonatal screening

| neo_scree | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 10 | 3.98 |
| Not done | 2 | 0.80 |
| Performed | 239 | 95.22 |

Patients with meconium ileus by age. All patients seen in 2020

Table of agel by ileus

| agel | ileus(Meconium ileus) | | | | | |
|---|---|---|---|---|---|---|
| Frequency Row Pct | Missing/Unknown | No | Yes, operated | Yes, not operated | Yes, I don't know if operated | Total |
| <=10 | 19 | 403 | 84 | 7 | 0 | 513 |
| | 3.70 | 78.56 | 16.37 | 1.36 | 0.00 | |
| >10 | 51 | 572 | 57 | 9 | 2 | 691 |
| | 7.38 | 82.78 | 8.25 | 1.30 | 0.29 | |
| Total | 70 | 975 | 141 | 16 | 2 | 1204 |

**Proportion of alleles which underwent DNA analysis**

| DNA_test | Frequency | Percent |
|---|---|---|
| done | 2404 | 99.83 |
| not done/missing | 4 | 0.17 |

**Number of patients for whom both mutations were identified and number of patients for whom at least one mutation was unknown**

| mut_ident | Frequency | Percent |
|---|---|---|
| both identified | 1131 | 94.09 |
| at least one unknown | 71 | 5.91 |

Frequency Missing = 2

**Proportion of identified mutations**

| mut_cat | Frequency | Percent |
|---|---|---|
| identified | 2309 | 96.05 |
| unknown | 95 | 3.95 |

Frequency Missing = 4

**Prevalence of F508del homozygous and heterozygous patients. All patients seen in 2020**

| df | Frequency | Percent |
|---|---|---|
| F508del heterozygote | 501 | 41.68 |
| F508del homozygote | 514 | 42.76 |
| Not F508del | 187 | 15.56 |

Frequency Missing = 2

**FEV1% of predicted: descriptive statistics by age group. All patients seen in 2020 aged 6 years or older have never had a transplant**

Analysis Variable : FEV1_pp

| age_fevl | N Obs | N | N Miss | Mean | Minimum | 25th Pctl | Median | 75th Pctl | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| 6-9 | 205 | 168 | 37 | 98.8 | 32.7 | 90.8 | 101.9 | 108.5 | 134.6 |
| 10-14 | 231 | 219 | 12 | 87.8 | 34.4 | 78.4 | 91.9 | 101.2 | 136.3 |
| 15-19 | 163 | 154 | 9 | 79.0 | 20.4 | 59.9 | 85.1 | 95.0 | 127.7 |
| 20-24 | 90 | 79 | 11 | 65.0 | 17.8 | 45.5 | 67.8 | 83.9 | 115.0 |
| 25-29 | 63 | 59 | 4 | 63.2 | 22.3 | 45.6 | 56.5 | 86.8 | 130.4 |
| 30-34 | 33 | 29 | 4 | 66.7 | 26.6 | 58.5 | 64.2 | 75.6 | 119.8 |
| 35-39 | 25 | 23 | 2 | 53.2 | 22.6 | 35.7 | 52.1 | 73.8 | 101.7 |
| 40-44 | 12 | 12 | 0 | 60.2 | 15.3 | 40.9 | 63.1 | 79.7 | 101.6 |
| 45+ | 9 | 8 | 1 | 45.6 | 17.4 | 32.7 | 49.0 | 54.3 | 75.8 |

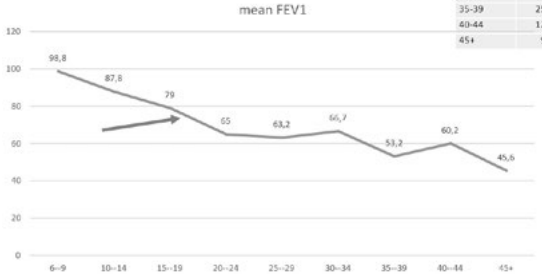



Table of age_fevl by FEV1_pp

| age_fevl Frequency Row Pct | FEV1_pp <40 | 40-80 | >80 | Total |
|---|---|---|---|---|
| 6-17 | 19<br>3,80 | 109<br>21,80 | 372<br>74,40 | 500 |
| 18-29 | 28<br>15,64 | 89<br>49,72 | 62<br>34,64 | 179 |
| 30+ | 13<br>18,06 | 49<br>68,06 | 10<br>13,89 | 72 |
| Total | 60 | 247 | 444 | 751 |

Frequency Missing = 80

**LCI, lung clearance index**

Analysis Variable : lci Value of lowest LCI 2.5%%

| age_lcil | N Obs | N | N Miss | Mean | Minimum | 25th Pctl | Median | 75th Pctl | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| 0-5 | 45 | 45 | 0 | 8.3 | 6.4 | 7.4 | 7.9 | 8.9 | 12.4 |
| 6-17 | 228 | 228 | 0 | 10.0 | 5.9 | 7.5 | 8.9 | 11.2 | 29.5 |
| 18-29 | 8 | 8 | 0 | 20.0 | 10.9 | 17.1 | 19.7 | 23.6 | 28.0 |
| 30+ | 3 | 3 | 0 | 11.5 | 10.1 | 10.1 | 11.3 | 13.1 | 13.1 |

**Chronic Pseudomonas aeruginosa**

Table of agel by pseudo

| agel Frequency Row Pct | pseudo(Chronic Pseudomonas aeruginosa) Missing/Unknown | No | Yes | Total |
|---|---|---|---|---|
| <18 | 9<br>1.09 | 723<br>87.21 | 97<br>11.70 | 829 |
| >=18 | 31<br>8.91 | 135<br>38.79 | 182<br>52.30 | 348 |
| Total | 40 | 858 | 279 | 1177 |

**Chronic Burkholderia cepacia complex**

Table of agel by burkho

| agel<br>Frequency<br>Row Pct | burkho(Chronic Burkholderia cepacia complex)<br>Missing/Unknown | No | Yes | Total |
|---|---|---|---|---|
| <18 | 12<br>1.45 | 809<br>97.59 | 8<br>0.97 | 829 |
| >=18 | 31<br>8.91 | 300<br>86.21 | 17<br>4.89 | 348 |
| Total | 43 | 1109 | 25 | 1177 |

**Prevalence of non tuberculous mycobacteria infection**

Table of agel by myco

| agel<br>Frequency<br>Row Pct | myco(Nontuberculous mycobacteria)<br>Missing/Unknown | No | Yes | Total |
|---|---|---|---|---|
| <18 | 227<br>27.38 | 599<br>72.26 | 3<br>0.36 | 829 |
| >=18 | 44<br>12.64 | 301<br>86.49 | 3<br>0.86 | 348 |
| Total | 271 | 900 | 6 | 1177 |

**Prevalence of Achromobacter species**

Table of agel by achro

| agel<br>Frequency<br>Row Pct | achro(Achromobacter species this year)<br>Missing/Unknown | No | Yes | Total |
|---|---|---|---|---|
| <18 | 12<br>1.45 | 799<br>96.38 | 18<br>2.17 | 829 |
| >=18 | 32<br>9.20 | 287<br>82.47 | 29<br>8.33 | 348 |
| Total | 44 | 1086 | 47 | 1177 |

**Prevalence of Methicillin-resistant Staphylococcus infection**

Table of agel by MRSA

| agel<br>Frequency<br>Row Pct | MRSA(Methicillin-resistant Staphylococcus Aureus this year)<br>Missing/Unknown | No | Yes | Total |
|---|---|---|---|---|
| <18 | 12<br>1.45 | 794<br>95.78 | 23<br>2.77 | 829 |
| >=18 | 32<br>9.20 | 294<br>84.48 | 22<br>6.32 | 348 |
| Total | 44 | 1088 | 45 | 1177 |

**Total days on intravenous antibiotics (for CF-related reasons), at home + in hospital**

Analysis Variable : ivDaysTotal Total days on intravenous antibiotics (for CF-related reasons), at home + in hospital, this year

| agel | N Obs | N | N Miss | Mean | Minimum | 25th Pctl | Median | 75th Pctl | Maximum |
|---|---|---|---|---|---|---|---|---|---|
| 0-4 | 214 | 208 | 6 | 3.3 | 0.0 | 0.0 | 0.0 | 0.0 | 80.0 |
| 5-9 | 249 | 243 | 6 | 3.1 | 0.0 | 0.0 | 0.0 | 0.0 | 46.0 |
| 10-14 | 249 | 241 | 8 | 9.6 | 0.0 | 0.0 | 0.0 | 14.0 | 234.0 |
| 15-19 | 176 | 167 | 9 | 13.7 | 0.0 | 0.0 | 0.0 | 25.0 | 120.0 |
| 20-24 | 110 | 100 | 10 | 17.8 | 0.0 | 0.0 | 12.0 | 22.5 | 197.0 |
| 25-29 | 80 | 75 | 5 | 19.3 | 0.0 | 0.0 | 13.0 | 28.0 | 275.0 |
| 30-34 | 43 | 42 | 1 | 13.0 | 0.0 | 0.0 | 12.5 | 15.0 | 62.0 |
| 35-39 | 31 | 29 | 2 | 19.6 | 0.0 | 0.0 | 11.0 | 15.0 | 239.0 |
| 40-44 | 13 | 13 | 0 | 11.8 | 0.0 | 0.0 | 14.0 | 15.0 | 33.0 |
| 45+ | 12 | 12 | 0 | 12.7 | 0.0 | 0.0 | 14.0 | 22.5 | 37.0 |

**Use of pancreatic enzymes**

Use of pancreatic enzymes this year

| enzymes | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 25 | 2.12 |
| No | 141 | 11.98 |
| Yes | 1011 | 85.90 |

**Prevalence of allergic broncho-pulmonary aspergillosis in patients seen in 2020**

ABPA this year

| ABPA | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 32 | 2.72 |
| No ABPA this year | 1122 | 95.33 |
| Yes, current ABPA | 23 | 1.95 |

**Prevalence of diabetes in patients seen in 2020**

Table of agel by Diabetes

| agel | Diabetes(CF related diabetes and type of treatment this year) | | | | | |
|---|---|---|---|---|---|---|
| Frequency<br>Row Pct | Missing/Unknown | No diabetes | Yes, treated with daily insulin | Yes, treated with oral hypoglycaemic agents | Yes, dietary advice only | Total |
| <18 | 5<br>0.60 | 758<br>91.44 | 29<br>3.50 | 0<br>0.00 | 37<br>4.46 | 829 |
| >=18 | 27<br>7.76 | 247<br>70.98 | 51<br>14.66 | 3<br>0.86 | 20<br>5.75 | 348 |
| Total | 32 | 1005 | 80 | 3 | 57 | 1177 |

**Prevalence of hemoptysis**

Hemoptysis major over 250 ml this year

| hemo | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 35 | 2.97 |
| No | 1094 | 92.95 |
| Yes | 48 | 4.08 |

**Prevalence of liver disease**

Liver disease this year

| liver | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 32 | 2.72 |
| No | 735 | 62.45 |
| Cirrhosis with hypertension/hypersplenism | 40 | 3.40 |
| Cirrhosis without hypertension/hypersplenism | 6 | 0.51 |
| Cirrhosis, hypertension unknown | 4 | 0.34 |
| Liver disease without cirrhosis | 358 | 30.42 |
| Variceal bleeding | 2 | 0.17 |

4,42%

**Continuous use of inhaled antibiotics**

Inhaled antibiotic this year

| Antibiotic | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 28 | 2.38 |
| No | 831 | 70.60 |
| Yes | 318 | 27.02 |

**Use of oxygen therapy**

In oxygen therapy this year

| Oxygen | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 33 | 2.80 |
| No | 1093 | 92.86 |
| Yes | 51 | 4.33 |

**Continuous use of NIPPV**

Continuous NIPPV this year

| NIPPV | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 31 | 2.63 |
| No | 1142 | 97.03 |
| Yes - BiPAP (Bilevel Positive Airways Pressure) | 4 | 0.34 |

**Continuous use of inhaled steroids**

Continuous inhaled steroids this year

| steroid_inhaled | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 30 | 2.55 |
| No | 932 | 79.18 |
| Yes | 215 | 18.27 |

**Continuous use of proton pump inhibitors**

Continuous use of proton pump inhibitors this year

| PPI | Frequency | Percent |
|---|---|---|
| Missing/Unknown | 30 | 2.55 |
| No | 967 | 82.16 |
| Yes | 180 | 15.29 |

**Number of patients living in 2020 with transplanted lungs**

Table of age_fupl by Gender

| age_fupl | Gender(Gender) | | |
|---|---|---|---|
| Frequency | M | F | Total |
| 10-14 | 0 | 1 | 1 |
| 15-19 | 5 | 0 | 5 |
| 20-24 | 4 | 1 | 5 |
| 25-29 | 2 | 2 | 4 |
| 30-34 | 1 | 0 | 1 |
| 35-39 | 2 | 0 | 2 |
| 45+ | 3 | 0 | 3 |
| Total | 17 | 4 | 21 |

# Poland & ECFSPR


## Introduction

The European Cystic Fibrosis Society Patient Registry collects demographic and clinical data from consenting people with cystic fibrosis (CF) in Europe, in accordance with agreed inclusion criteria and definitions. The information is used to measure, survey and compare aspects of CF and its treatment in participating countries, to deepen our understanding of CF, to improve standards of care, to provide data for epidemiological research and to facilitate public health planning.

The Registry's database includes data from more than 48,000 people with CF, from 35 participating countries, and longitudinal data from 2008 to 2017. It is a unique resource reflecting the reality of CF across Europe.

For more information about the Registry *www.ecfs.eu/projects/ecfs-patient-registry/project*

# PANCREATIC ENZYME THERAPY IN CF PATIENTS - OLD AND NEW

*Halina WOŚ*
*POLAND*

Exocrine pancreatic insufficiency (EPI) is characterised by the maldigestion of macronutrients and micronutrients as a result of inadequate intraduodenal pancreatic exocrine enzyme delivery

**Manifestations of EPI**

**Steatorrhea**
**Deficiency in microelements and vitamins**
**Abdominal discomfort**
**Bloating**
**Metabolic bone disease**
**Significant decrease in the quality of life**
**MALNUTRITION**

**Nutritional status is positively associated with the lung function and survival in pediatric patients and young adults**

BMI>50 percentile in the 4th year of life

↑improved lung function
↓in CF- related complications
↓in hospitalisations
↓in mortality in the 18th year of life

**Pancreatic function**

- the production of pancreatic juice at 1200 - 3000 ml/day
- pancreatic enzymes: amylase, lipase, trypsin, chymotrypsin, elastase, kallikrein
- the production of bicarbonates neutralizing acidic gastric contents
- maintenance of the acid-base balance

**Function of the pancreas controlled by the hormones of the digestive tract**

- secretin –> secretion of bicarbonates
- CCK: bile release from the gallbladder, secretion of pancreatic juice
- acetylcholine –> motility and secretion of pancreatic juice
- digestive disorders <10% of the normal secretion
- carbohydrate digestion already started in the mouth (salivary amylase) and the stomach
- fat digestion, mainly in the proximal part of the small intestine

**Diagnosis of EPI**

**72-hour fecal testing** (93% of dietary fat is absorbed) = normal 3 days stool collection (difficult or impossilbe in a routine clinical seeting)

**Elastaze levels** in stool samples

**<100mcq/g – pancreatic insufficiency**
**>200mcq/g – normal**

Stool consistency
Chronic kidney disease
Diabetes mellitus

**The exocrine function of the pancreas**
85% - 90% of CF patients develop EPI
Genotype
SIBO (small intestine bacterial overgrowth)
Low pH of gastric juice
    Precipitation of bile acids
Abrupt secretion of gastric juice
    Drop in duodenal pH
    Denaturation of enzymes
Digestive disorders <10% of the normal secretion

**Pancreatic secretion**
**900 000 IU of lipase / meal (10% is required)**
    **90 000 iu of lipase/meal in adults**
    **but the following is sufficient in CF**

    **40 000 - 50 000 IU of lipase/meal**
    **20 000 - 25 000 IU of lipase/snack**
**Half of the pills to be taken after a few bites, the remaining ones shortly before finishing the meal.**

**Supplementation of pancreatic enzymes**
in all patients with exocrine pancreatic insufficiency and malnutrition prevents deficiencies in micronutrients, fat-soluble vitamins, ferritin and prealbumin

2000 - 4000 IU lipase / 120ml blend/fed
1000 IU lipase / kg b.w./meal < 4 year of life
 500 IU lipase / kg b.w./ meal > 4 year of life

**max dose 10 000 IU lipase / kg b.w. / day**
**2 500 IU lipase / kg b.w. / meal**
**Supplementation of pancreatic enzymes per gram of fat intake 2000 – 4000 j IU lipase**

**Clinical effectivenes**
steatorrhea improvement
↑ in fat soluble vitamin levels
↑ in retinol binding protein
↑ in muscle strength
↑ in the quality of life
↑ in the level of nutrition

**Pancreatic enzyme preparations approved by FDA (after April 2010)**
**Creon** *(Abbott Laboratories, Hanover, Germany)*
**Zenpep** *(Aptalis Pharmaceuticals, Milan, Italy)*
**Pancreaze** *(Janssen Pharaceuticals, Uetersen, Germany)*
**Ultresa** *(Aptalis Pharmaceuticals, Pessano, Italy)*
**Viokace** *(Aptalis Pharmaceutocals, St. Hubert, Canada)*
**Pertzye** *(Digestive Care, Inc, Bethlehem PA)*

**Pancreatic enzyme preparations available in Poland**

Table C.15-2. Contents and presentation of pancreatin preparations available in Poland

| Prepartion | Form | Contents | | | Dispensing category |
|---|---|---|---|---|---|
| | | Lipase (u.Ph.Eur.) | Amylase (u.Ph.Eur.) | Protease u.Ph.Eur.) | |
| Kreon 25 000 | Enteric capsules (minimicrospheres) | 25 000 | 18 000 | 1000 | PD |
| Kreon 40 000 | Enteric capsules, hard (minimicrospheres) | 40 000 | 25 000 | 1600 | PD |
| Kreon Travix | Enteric capsules (minimicrospheres) | 10 000 | 8000 | 600 | OTC |
| Pangrol 10 000 | Capsules (mini tablets) | 10 000 | 9000 | 500 | OTC |
| Pangrol 25 000 | Capsules (mini tablets) | 25 000 | 22 500 | 1250 | OTC |
| Neo-Pancreatinum Forte | Enteric capsules (pellets) | 10 000 | 8000 | 500 | PD |

u.Ph.Eur. – dosage units as per the European Pharmacopoeia; OTC – over the counter; PD – prescription drug

**Pancreatic enzymes**

The enteric capsules release the lipase in the duodenum pH >5,5

microspheres 1,0 - 1,2 mm

macrospheres 1,8 – 2,0 mm

***To be swallowed! Not to be chewed! Not to be crushed!***

(optionally to be mixed with soft acidic foods or liquids)

Forms: powder, granules, tablets, microspheres,

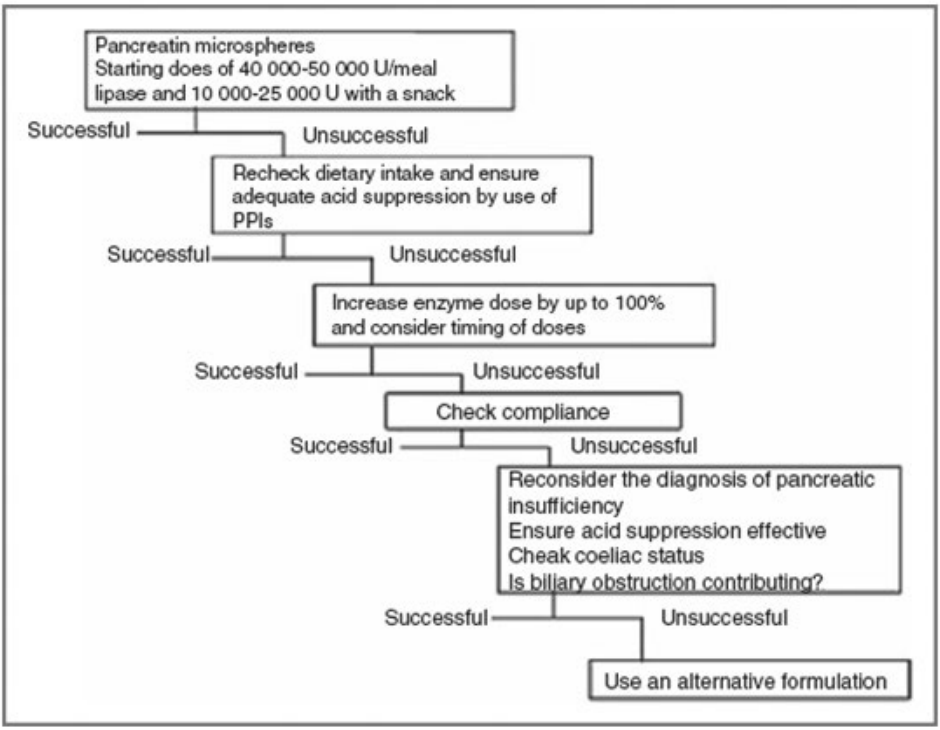
ORIGINAL ARTICLES www.jpeds.com • The Journal of Pediatrics

## Pancreatic Enzyme Replacement Therapy Dosing and Nutritional Outcomes in Children with Cystic Fibrosis

Mark E. Haupt, MD[1,*], Mary J. Kwasny, ScD[2], Michael S. Schechter, MD, MPH[3], and Susanna A. McColley, MD[1]

1755 IU lipase /kg b.w./meal vs 1628 IU lipase

| | | | |
|---|---|---|---|
| weight BMI | 50,7 | vs | 39,6 |
| height BMI | 40,4 | vs | 31,6 |
| b.w. deficiency | 37% | vs | 45% |
| steathorea | 26% | vs | 39,5% |
| FEV1 | 90,3 | vs | 81,3 |




**Lack of efficacy of PERT**

- inadequate dosage
- storage of enzymes at too high temperatures
- failure to follow the recommendations
- low pH in the duodenum – inactivation of lipase pH <4 blockage of enzyme release from the shell
- bacterial overgrowth in the small intestine
- unconducive diet
  rich in fiber: absorption of pancreatic enzymes delayed absorption
  rich in Ca and Mg: increased precipitation of bile acids
- consider MCT fats: absorption in the small intestine without lipase, colipase and bile

**Side effects of PERT use**

Nausea
Bloating
Feeling full
Intestinal cramps
Too high doses combined with fibrosing colonopathy

***OPTIMAL DOSE IS NOT KNOWN FOR ALL PATIENTS***

Lack of knowledge of the optimum introduction time of PERT and the appropriate dosage for the different degrees of pancreatic insufficiency, especially in infants

**Another form of enzymes**
Insoluble form in the intestine
Necessity to use together with IPP - enzymes can be deactivated in the stomach (not available in Poland)

**Liprotomase**
Nonporcine PERT
Biotechnology – Yarroia lipolytica
Crystal lipase 32 500 IU
Crystal protease 25 000 IU
Amylase 3 750 IU

Dosage: 2 500 IU/kg /meal for up to 17 y.o.
3 750 IU/kg /meal for adults

**Nutritional treatment**
1. **Dietary intervention to increase the calorie intake**, including oral dietary supplementation
2. **Enteral nutrition through a nasogastric tube or PEG**
3. **Parenteral** nutrition

**NIGHT ENTERAL NUTRITION COMPLETES THE DAILY CALORIE INTAKE AND DOES NOT REPLACE NORMAL MEALS (~ 30%)**

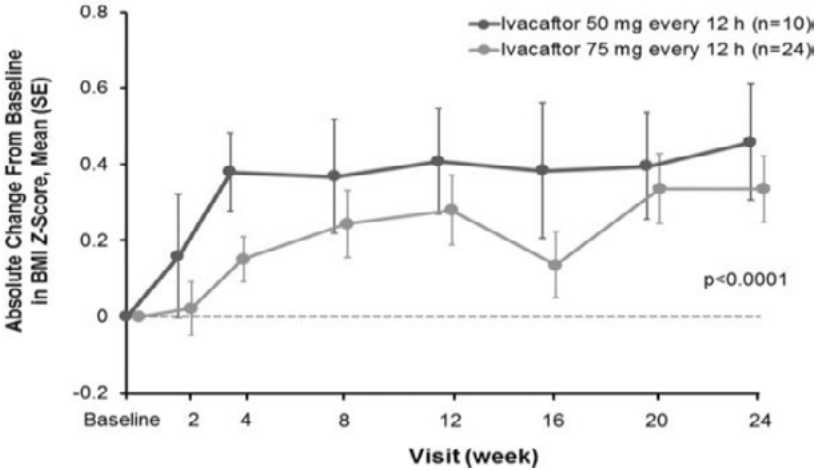
**Enzyme therapy during enteral feeding**
Calculate the enzyme dose per 1 gram of fat
orally $^3/_4$ of the dose at the beginning of the supplementation, and $^1/_4$ towards the end
**Enzymes - enteric form** – microspheres dissolve in natrium bicarbonate or $^1/_4$ - $^1/_2$ a teaspoon of soda + 30ml $H_2O$, dissolved enzymes after 15 - 30' to be added to the feeding bag
**Enzymes - insoluble form in the intestine** - mash and add to the nutritional bag (note: the powder is not to be inhaled and eyes to be protected)

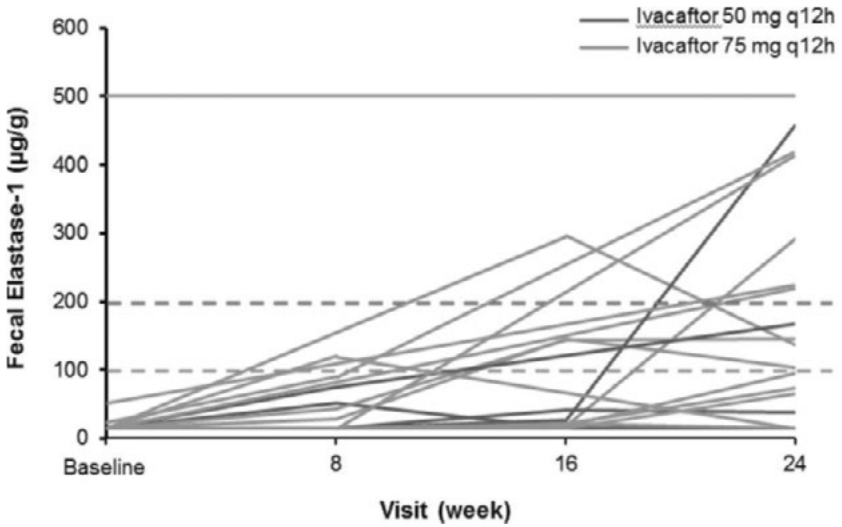
**Pancreating enzyme replacement therapy for people with CF**
14 studies assessing the impact of PERT on weight, height and BMI – obvious improvement
2 studies have indicated improved absorption of fat
Reduced discomfort
Reduced frequency of defecation linked to the use of minimicrospheres
1 study has indicated better absortion of fat when non-porcine enzymes have been used

**Therapy with modulators and the standard PERT therapy**
Improvement in lung function
Improvement in the level of nutrition
Reduced frequency of hospitalisations
Reduced concentration of sweat chlorides
Improvement in the quality of life
**Exocrine pancreatic activity??**

It is commonly believed that EPI is irreversible due to the complete destruction of the pancreatic ducts and the acinar cells

**BUT – an increased secretion of elastase in faeces has been observed, which leads to improved BMI**




**Treating patients with CF in the era of modulators or maybe the conventional treatment?**
Reversible pancreatic insufficiency – if so, when??
Hepatic dysfunction
10% of patients with CF – insufficient indication for the use of modulators
Cost of treatment PLN ~311 000/year

**Modulators in the treatment of CF**

- ↑ **improved lung function**
- ↑ **BMI**
- ↑ **elastase in faeces (mainly in the youngest patients)**
- ↓ **in sweat chlorides**
- ↑ **the quality of life**
- **And what about PERT??**

***www.mukowiscydoza.pl***

# DAMAGE TO THE LIVER AND BILE DUCTS IN CF WITH REGARD TO LIVER AND PANCREAS TRANSPLANTATION.

*Sabina WIĘCEK*
*Department of Paediatrics, Faculty of Medical Sciences, Medical University of Silesia, Katowice, POLAND*
*Upper Silesian Child Health Centre, Katowice, POLAND*

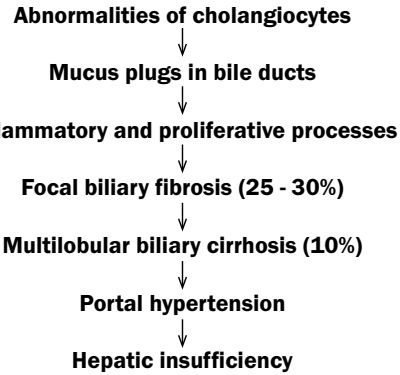
**Hepatic lesions concern only 5 - 20% of patients with diagnosed cystic fibrosis (CF). They increase the level of fatalities, shorten the survival rate and impair the quality of life.** Liver diseases are the most common, non-pulmonary cause of death among patients with cystic fibrosis. (2 - 5% of overall CF mortality). They most often occur in the first decade of life. Cirrhosis is detected in about 10% of CF children under the age of 18 compared to 2% of adults with the same condition. The average age of the detection of cystic fibrosis liver disease is about 10 years.

**Cystic fibrosis liver disease (CFLD) epidemiology:**

- Nonspecific increase in transaminases are observed 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 injure in CF only 1.7%
- Abnormal hepatic histopathology in patients with CF 27 - 41%
- 5 - 10% of children with CF develop cirrhosis before or during puberty

**Etiopathogenis of cystic fibrosis liver disease :**

- 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
- Role of translocation of bacteria into the portal circulation
- **Changes to the bile acids** (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, induction of pro-inflammatory chemokines -> biliary fibrogenesis)
- **Genetic factors** - so far, no specific mutation relating solely to liver damage in the course of cystic fibrosis has been discovered. The delta 508 mutation plays a particular role in the development of hepatic lesions in the course of cystic fibrosis due to its stimulation of an increased loss of bile acids with stools and the fact that it leads to the formation of more hydro phobic bile acids. Cirrhosis typically occurs in patients with severe mutations – class I - III. Hepatic lesions co-occuring with cystic fibrosis in patients with the 3849+10kB C->T mutation have not yet been the subject of interest. However, the clinical course in patients with diagnosed cystic fibrosis and the same mutation of the CFTR gene tends to vary. There is no strict phenotype-genotype correlation.
- **Immunological factors**: role of chemokines - activation of stellate cells (source: hepatic macrophages, endothelial cells, bile duct epithelial cells, lymphocytes, blood platelets and hepatocytes), 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).




Patogenesis of hepatic lesions the course of cystic fibrosis according to Colombo.
*Colombo C. et all. J.Pediatr.Gastroenterol.Nutr. 2006;43:49-55.*

**Clinical picture of Cystic fibrosis liver disease:**

**Risk factors of the development of liver diseases in cystic fibrosis :**
- Male gender – $^{3}/_{4}$ of patients with CFLD are boys. Protective role of estrogens in women ?
- Co-existing meconium ileus
- Significant malnutrition
- Pancreatic insufficiency
- Severe genotype (delta F508)
- CF- related diabetes

**Role of malnutrition.** Children with diagnosed cystic fibrosis and liver damage have lower body mass, height, circumference of the upper arm and BMI, They also have significantly lower levels of linoleic (LA), docosahexaenoic (DHA) and docosapentaenoic (DPA) acids. The influence have parenteral nutrition, antioxidant, vitamin, essential fatty acids and choline deficiency.

**The role of the hepatotoxic effect of medications:**
- Abnormal functions of oxidases and P450, CYP2C8, CYP2C9, CYP3A4 cytochromes.
- The dose of beta lactame should be reduced by 20%
- The doses of aminoglycosides should be decided upon depending on the level of the medication in the blood serum
- Increased microsomal metabolism relating to theophylline and methylxanthine through the affected 1st phase of the biotransformation of the medications
- Increased hepatic clearance of the 2nd phase, which may be reflected in the abnormal metabolism of furosemide, lorazepam and ibuprofen

**Defects of gall blader and bile ducts:**
- In about 30% of patients with cystic fibrosis, atrophic gall bladder or the lack there of, also its defects and/or of bile ducts is reported.
- No correlation between cirrhosis and abnormalities in the gall bladder and/or bile ducts has been observed.
- Gallbladder hydrops and lithiasis are significantly statistically more commonly observed in patients with cystic fibrosis compared to the healthy population.
- The narrowing of the distal regions of the bile ducts is frequent and may occur in even 90% of CF patients and contribute to the formation of gallstones.

**Clinical presentation of CFLD:**

**1. Preclinical disease** no evidence of liver disease - based on clinical exam, imaging or laboratory test

**2. CFLD without cirrhosis and portal hypertension.**

- Persistent AST, ALT, GGT > 2 times
- Steatosis
- Fibrosis
- Cholangiopathy

**3. CFLD with cirrhosis and portal hypertension**

**HEPATIC LESIONS IN THE COURSE OF CF**

1. Focal hepatic fibrosis 72%
2. Focal biliary cirrhosis 20 - 30%
3. Multilobular biliary cirrhosis 5 - 15%
4. Portal hypertension 2 - 5%
5. Small atrophic gallbladder and narrowing of bile ducts 15 - 45%
6. Cholelithiasis 14 - 24%
7. Steatosis 25 - 60%
8. Cholestasis in newborns <10%
9. Primary sclerosing cholangitis rarely
10. Cholangiocarcinoma rarely
11. Drug-induced, toxic liver damage

In most CF patients, the course of hepatic complications is symptomless. Pruritus sometimes occurs and jaundice in patients whose condition is advanced. Accidentally diagnosed hepatomegaly is usually the first symptom. In newborns, steatosis may be accidentally discovered in a routine abdominal ultrasound. 53 - 93% of patients with CF have at least one abnormal value of ALT or AST 30% have abnormal levels of gamma glutamyl - transferase.

**STEATOSIS OF LIVER IN CF**

- Etiology mulitifactorial
- Role nutritional deficiences - particulary essential fatty acids
- Common – the 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 finding
- Management – optimise nutrition, exclude 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.

**IDIOPATHIC NONCIRRHOTIC PORTAL HYPERTENSION (INCPH) pathogenesis:**

1. Immunological disorders
2. Chronic infections - vasculitis, endothelialitis.
3. Pulmonary infections
4. Intestinal infections - SIBO, Escherichia coli
5. Exposure to drugs and toxins
6. Genetic diseases
7. Prothrombotic conditions (50% CF patients), platelet activation

**Cardiac cirrhosis in patients with CF:**

1. Clinical signs of cor pulmonale
2. Dilated hepatic veins
3. AST and ALT are mildly elevated (<2 - 3x)
4. Treatment - optimize cardiopulmonary function and avoid hypoxia

**DEBRAY CRITERIA AND KOH´S CRITERIA OF CFLD**

| Parameters | Debray criteria[8] | Koh's new criteria[41] |
|---|---|---|
| Diagnosis of CFLD should be considered if one of the following categories is present: | Not included | Liver biopsy indicating pathology or radiologic evidence of diffuse liver disease or cirrhosis |
| Diagnosis of CFLD should be considered if two or more of the following categories are present: | | |
| Physical examination | X | Not included |
| Blood tests | X | X |
| Imaging | X | X |
| Transient elastography | Not included | X |
| Histology | X | As above |
| Noninvasive biomarkers | Not included | X |

## Diagnosis of hepatic lesions in the course of cystic fibrosis:

**1. Cilinical symptoms**
- hepatomegaly, splenomegaly symptoms of portal hypertension
- very frequent symptomless course

**2. Periodic laboratory tests** (the levels of AlAT, AspAT, GGTP, bilirubin and bile acids, the APRI index and Fibrotest)
- it is believed that 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.

**3. Abdominal ultrasound and a Doppler test** - 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** - seems to be a non-invasive examination useful in detecting early liver changes and monitoring of progression in paediatric patients with diagnosed cystic fibrosis, ahead of changes in laboratory tests.

**4. Liver biopsy with histopathological assessment** – apart from being painful, it is invasive, prone to side-effects and sampling errors.

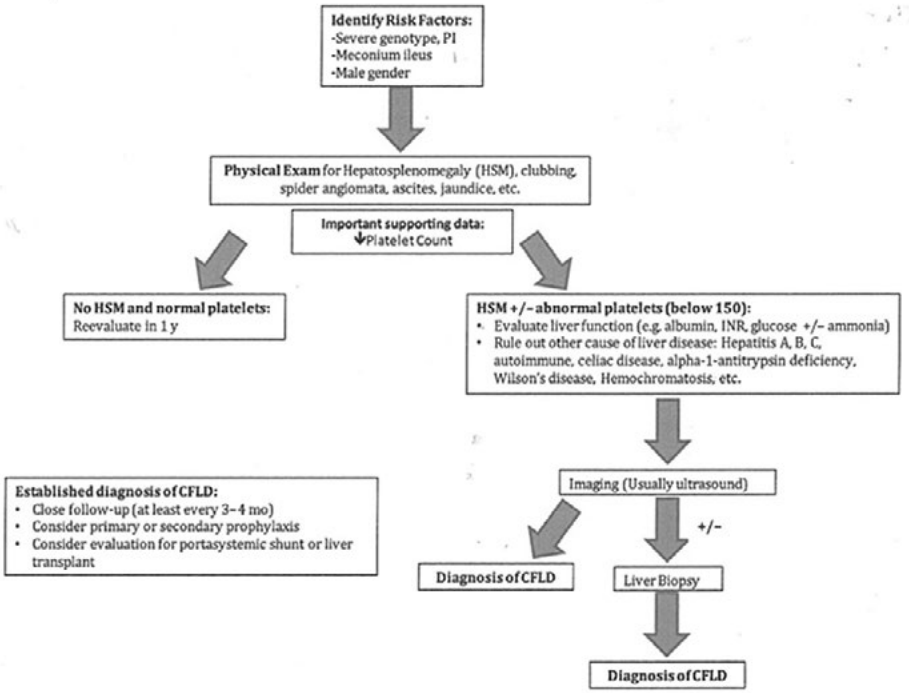
**5. Non-invasive parameters of liver fibrosis** (Fibroindex, amino peptides of type III procollagen, collagen I, collagen IV, laminine, hyaluronic acid, cytokines and chemokines relating to the process of fibrosis, cytokeratin 18) - during clinical trials.

**DIFFERENTIAL DIAGNOSIS OF CFLD :**

- Drug induced liver injury (DILI)
- Viral hepatitis A,B,C, EBV
- Autoimmune hepatitis
- Wilson disease
- Celiac disease
- Alpha1-antitripsin deficiency
- Metabolic syndrome NAFLD/NASH – diabetes or glucose intolerance, obesity, hypertension, hypertriglycerydemia

**Algorithm for diagnosis, evaluation and management of CFLD**

*Sathe M, Freeman A.: Gastrontestinal, pancreatic and hepatobiliary manifestations of cystic fibrosis. Pediatr Clin N Am 2016;63:679-698.*




**THE TREATMENT OF CYSTIC FIBROSIS LIVER DISEASE:**

**1. Background therapy of cystic fibrosis**

**2. Diet therapy** - Prevention of malnutrition in cystic fibrosis. Feeding tube or PEG nutrition recommended.

**3. Ursodeoxycholic acid**

- has cytoprotective effect on the cell membranes of cholangiocytes,
- stimulates the secretion of chloride ions through calcium-dependent 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.
- has anti-apoptopic effect and reduces the toxic effects of hydrophobic bile acids.
- anti-inflammatory effects.

*Present data suggesting that UDCA when started before severe liver damage is present, might be able to prevent the progression of CFRLD and might even induce a reversal of fibrosis.* The use of UDCA in CFLD has become a standard treatment, although the scientific basis for this requires more reliable data especially for efficacy endpoints in middle and long term use. Nevertheless, UDCA appears to be beneficial, especially when started early and against the background of lacking therapeutic alternatives.

**4. The treatment of portal hypertension** (obligatory than PLT<120*$10^9$/L)

- Beta- blockers
- Endoscopic methods for the treatment of esophageal/gastric varices – band - ligation
- Portosystemic shunts
- Liver transplantation

**5. Liver transplant**

**Advancing** dysfunction of the liver, progressing ascites and jaundice, recurrent bleeding from esophageal varices and hepatopulmonary syndrome

a. Only liver

b. Combined with a lung and/or pancreas - difficulty of the procedure and the high risk for complications

c. Heart - Lung - Liver transplantation - multiorgan failure

Posttransplantation survival in CFLD patients is lower than in other patients. Increased risk of other CF-related complications such as diabetes.

Patient with CFLD should be reffered to a transplant center early in the course of liver disease. Patients who are candidates for an isolated liver transplant should not have severe pulmonary disease. FVC in the vicinity of 75% of predictive value and FEV1 in the vicinity of 70% indicate satisfactory lung function in a transplant candidate.

In patients with diagnosed cystic fibrosis following isolated liver transplantation, there is an increased risk of pulmonary complications (severe infections).

It seems that an FEV1<50% was associated with poor outcomes in isolated liver transplantation, and thus patients with poor lung function should be considered for combined lung-liver transplantation.

For isolated liver transplantation, if the FEV1 is <40%, patients are listed with their MELD/PELD score plus a 10% mortality equivalent.

If listed for a combined liver-lung transplantation with an FEV1 <40%, the liver listing starts with a MELD of 40.

d. **Experimental treatments**

- Nor – UDCA – synthetic homolog UDCA. Induces bile flow by increasing bicarbonate secretion. Anti-inflammatory, antifibrotic, anti-proliferactive.
- Obeticholic acid- semisynthetic bile acid analog, functions as a potent farnesoid X-receptor (FXR) receptor – increased due to intestinal bile acid malabsorption. Anti-inflammatory effects.
- PGF1 - improved hepatic inflammation, steatosis and damage in leptin – deficient and choline - deficient mice.
- Vit D receptor- prevent hepatic fibrosis involving TGFB1 signaling via profibrotic genes.
- CF transmembrane regulator modulators ? Hepatotoxic side effects. Metabolised through cytochrome p-450 enzymes. Some drug interactions (cyclosporine, tacrolimus).

**European recommendations for the treatment of with cystic fibrosis and hepatic lesions:**

1. **Biochemical tests (AlAT, AspAT,GGTP, FA, prothrombin time, blood platelets) every 6 months.**
2. **Imaging tests – abdominal ultrasound + doppler, elastography - alternatively annual CT or MR.**
3. **Ursodeoxycholic acid at 20mg /kg daily**
4. **Panendoscopy performed every 2 - 3 years is necessary in patients with cirrhosis and or splenomegaly in order to exclude esophageal verices.**
5. **Assessment of the hepatopulmonary syndrome – assessment of intrapulmonary shunts as they intensify hypoxemia.**
6. **In the case of cirrhosis – assesment of the levels of alpha-fetoprotein (AFP) every 6 months.**
7. **Mild esophageal varices – non selective beta blockers? Levels 2 - 3 varices – endoscopic treatment or intrahepatic portosystemic shunts.**
8. **Prevention of malnutrition (via feeding tube or PEG).**

**EFFECTS OF CFTR MODULATORS ON CFLD**

- UNCLEAR – benefits in CFLD unknown but in 5 - 15% hepatoxicity
- **IVACAFTOR – increase ALT (13.2%), AST (9.6%), bilirubin (2.4%) 2x - 8x elevated**
- Some evidence that CFTR modulators might have a beneficial effect on the liver.
- Less hepatic steatosis in MRI
- Influence on cholesterol metabolism
- Ivacaftor has therapeutic potential in an in vitro model of PFIC2
- **CFTR modulators show a certain therapeutic potential in CFLD but there is a long way to go...**

**SUMMARY**

1. **The etiopathogenesis of hepatic lesions in the course of cystic fibrosis is very complex and not yet fully explained.**
2. **The clinical symptoms of CFLD are not characteristic and the clinical picture is often symptomless or limited.**
3. **Further studies into the causes of hepatic lesions in cystic fibrosis are necessary, which will contribute to the reduction in the number of deaths, extended survival rate.**

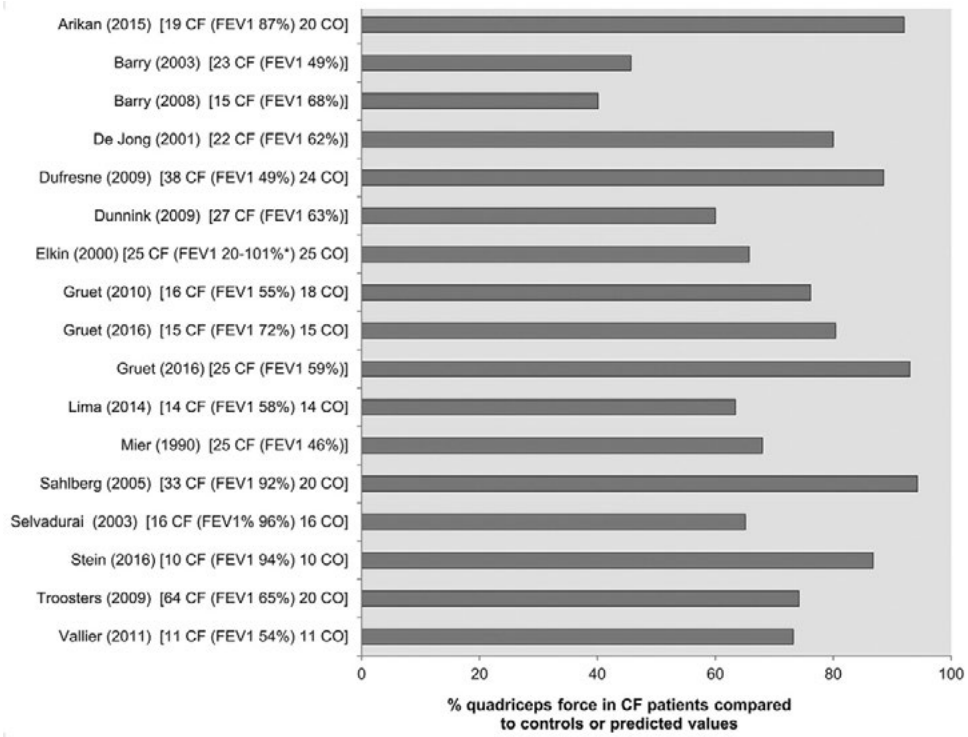
# THE INTEREST OF MUSCLES MANAGEMENT IN CYSTIC FIBROSIS

*Hughes GAUCHEZ, Claire BEHAGUE*
*FRANCE*

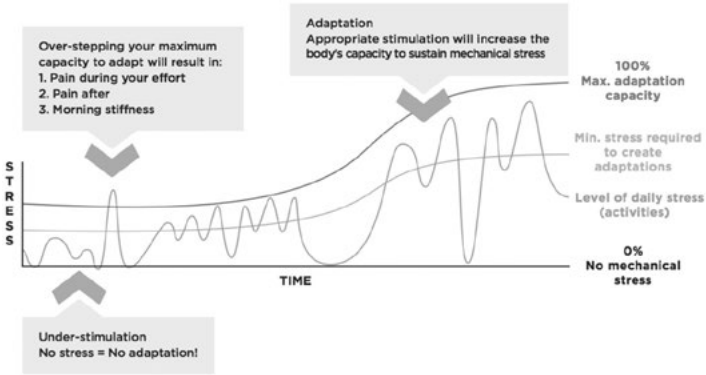
**Common sense advices:**
- Reassure and train the teams
- Motivate the patient
- Integrate physical activity into daily life
- Eat well to build muscles

**Keys of success:**
- Science
- Knowledges
- Experience
- Passion
- Empathy
- Motivation

**Peripheral muscle abnormalities in cystic fibrosis: Etiology, clinical implications and response to therapeutic interventions.**



## Mechanical stress quantification



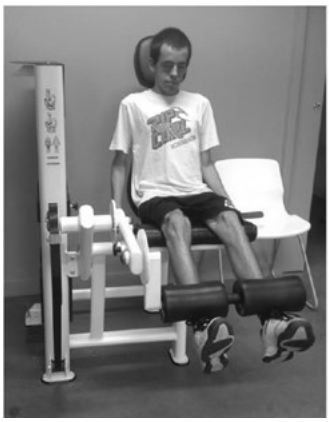

VOLUME

X

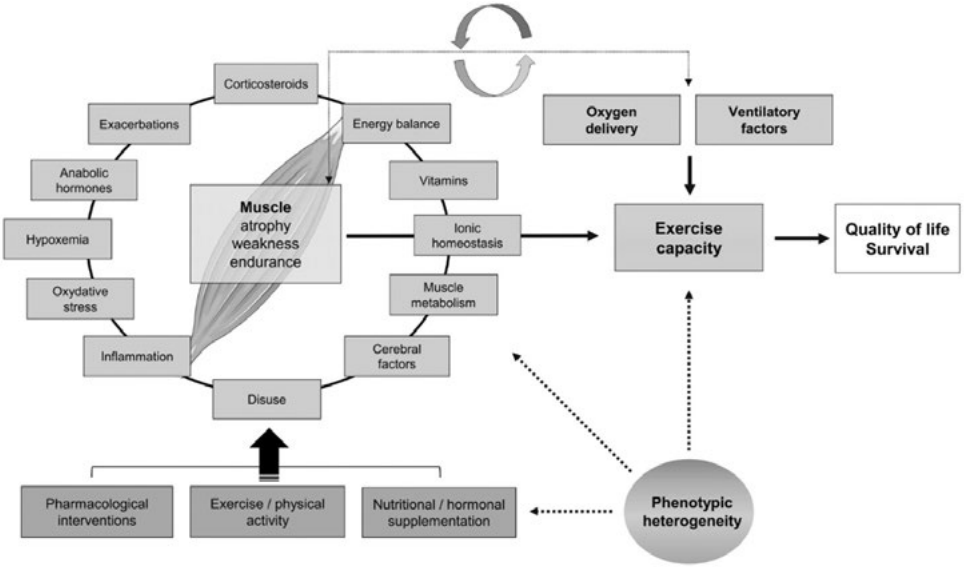
REPETITIONS

X

CHARGE



**Estimation of the 1 RM (Repetition Maximum)**



*« Behind each patient, there is a team »*

# PHYSIOTHERAPY IN CYSTIC FIBROSIS

*Natalia JENERALSKA*
*Centrum Leczenia Mukowiscydozy, Szpital w Dziekanowie Leśnym, POLAND*

**Physiotherapy is considered as one of the most important elements in the standard treatment of cystic fibrosis.**

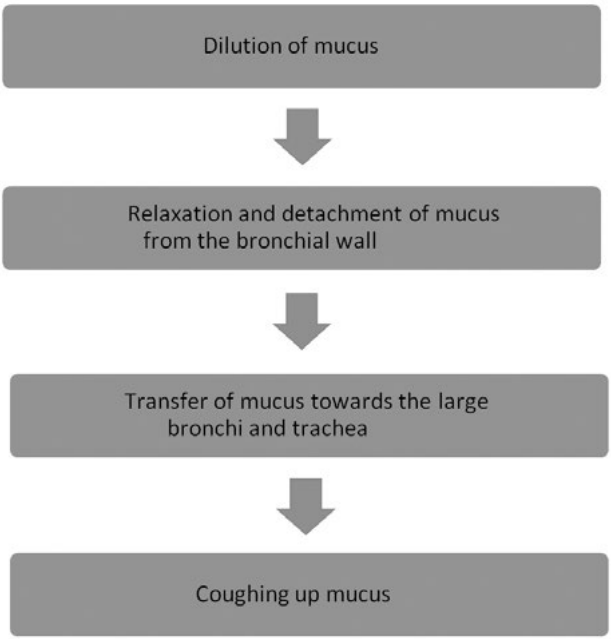
Comprehensive physiotherapy should be implemented as soon as the disease is diagnosed and carried out on a daily basis even in case of patients who do not show respiratory symptoms.

Early implementation of physiotherapy may delay disease progression.

The main reason for early physiotherapy is to teach the parents and the patient how to systematically perform.

**Aims of respiratory physiotherapy**

- Systematic bronchial drainage of lingering mucus.
- Development of a level of physical fitness appropriate to age and stage of disease
- Keeping the proper mobility of the chest
- Maintaining a correct body posture
- Keeping skeletal muscles strong and resistant
- Reduce lung disease related symptoms
- Preventing complications that are related to inadequate lung ventilation
- Improving the quality of life



**Respiratory physiotherapy**
- Cleansing of the upper airways
- Nebulisation therapy
- Drainage of the bronchial tree
- Non-invasive ventilation
- Physical activity and corrective exercises

**Cleansing of the upper airways**
- Sinus irrigation - starting already in infants and young children
- Sinus inhalations - in well-cooperating patients

**Nebulisation therapy**
- Nebulisation therapy plays major role in the treatment of cystic fibrosis
- It is used throughout the patients' lives, starting from infancy
- Besides airway clearance techniques, it is an important part of both bronchial tree physiotherapy (mucolytic drugs) and pharmacological treatment (inhaled antibiotic therapy)

**Drainage of the bronchial tree**
It should be individually adapted to the patient's needs:
- autogenic drainage,
- active breathing cycle,
- forced expiration technique,
- positive expiratory pressure (PEP),
- oscillating positive expiratory pressure (OPEP),
- breathing exercises,
- use of aid mechanical devices

**Autogenic drainage**
Autogenic drainage is an airway clearance technique which utilises controlled breathing at different lung volumes to loosen, mobilise and move secretions in three stages towards the larger central airways. The technique aims to maximise expiratory airflow, while avoiding dynamic airway collapse.

**Assisted Autogenic Drainage**
Assisted autogenic drainage is based on the principles of autogenic drainage and is used for infants and uncooperative patients.

During exhalation, we gently follow the patient's breathing moves. We lengthen the exhalation and thus move the secretion from the peripheral bronchi to the central bronchi.

No chest compressions or excessive force is applied, which could lead to resistance reactions on the part of the patient.

**The Active Cycle of Breathing Techniques**
The Active Cycle of Breathing Techniques (ACBT) is an active breathing technique performed by the patient and can be used to mobilise and clear excess pulmonary secretions and to generally improve lung function. It is a flexible method of treatment that can be used in conjunction with positioning and adapted for use with most patients.

**Positive Expiratory Pressure - PEP**
- Dilates the peripheral bronchi and facilitate their cleaning.
- Prevents the phenomenon of bronchial collapse.
- Can be used already in infants

**Oscillating PEP**
- Combines increased exhalation pressure with oscillation.
- The vibrations produced by the device help to detach, break up and loosen secretions.
- Creates variable bronchial pressure.
- Can be used already in 3-4 years old children

**Alpha 300 (IPPB)**
- Helps clear mucus - increased inspiratory volume improves expiratory flow and cough efficiency.
- Improves respiratory function - by increasing the patient's inspiratory rate, it is possible to improve lung vital capacity.
- Increases lung ventilation - ventilation of poorly ventilated or non-ventilated lung areas.
- Helps patients breathe slowly and deeply while reducing respiratory effort

**Simeox**
- Thins and liquefies thick mucus.
- Displaces secretions from the smallest bronchioles during the exhalation phase.
- Generates consecutive low-frequency vacuum vibrations to agitate the secretions and remove them from the airways.
- The inhalation phase is active and performed by the patient

**Non-invasive ventilation (NIV)**
- Reduces respiratory effort
- Facilitates evacuation of secretions
- Reduces work of respiratory muscles (respiratory muscles rest)
- Stabilises lung function
- Increases exercise tolerance
- Reduces desaturation during the exercise
- Allows passive expansion of the chest (increase in tidal volume)

**Physical activity and corrective exercises**
- General development training
- Exercises to increase muscle strength and endurance
- Stretching of the chest, back and shoulder girdle muscles
- Prevention of the posture defects

# OUR EXPERIENCE WITH SIMEOX IN CF

*Eva BÉREŠOVÁ, Jana BÉREŠOVÁ*
*University Hospital F.D. Roosevelt CF Center for adult patient Department of pneumology, Regional Authority of Public Health Department of epidemiology, Banská Bystrica, SLOVAKIA*

**SIMEOX**
**Innovative device which helps remove mucus from the airways - mucus is liquefied, transported and removes by coughing**

**Indications:** cystic fibrosis, chronic obstructive pulmonary disease, asthma and bronchiectasis

**Relative contraindications:** pneumothorax, unstable cardiovascular pathology and massive hemoptysis


**We have two devices at:**
- the pneumological outpatient clinic
- the department of pneumology and phtiseology

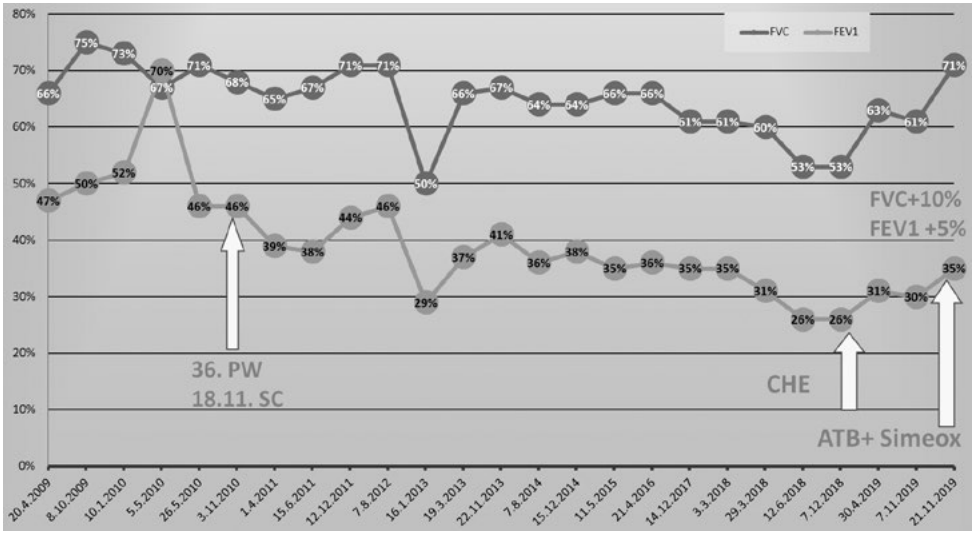
**Case Report**
**32 years old CF patient (born 1989) F 508del homozygous**
- CF was diagnosed at 3 months of age
  03/91 colonisation with Ps. Aeruginosa
  05/2005 DIOS, 10/2005 sepsis Acinetobacter
  AA: Gentamycin
  FA: the patient's brother is after a lung transplantation for cystic fibrosis

- The patient was transferred to our adult CF center in 2009
- 18.11.2010 SC - she gave birth to a healthy boy
- Regular monitoring,treatment with oral and parenteral antibiotic treatment
- Intermitent inhalation antibiotic Colimycine and Tobramycine
- The follow-up of an immunoallergologist for pollen allergy, food allergy, reduction of B lymphocyte subpopulations, NK cells
- Osteopenia, **CT of lung**: diffuse varicose bronchiectasis

- **Deterioration of condition - December 2018** - multiple cholecystolithiasis and choledocholithiasis sonographically verified, ERCP, PS, duodenobiliary drain
- **Weight 48 kg, BMI: 18,7, non smoker**
  very severe obstructive ventilation disorder with **FEV1 26 %**
- **After stabilisation - March 2019 - cholecystectomy laparoscopica under epidural anesthesia and sedation**

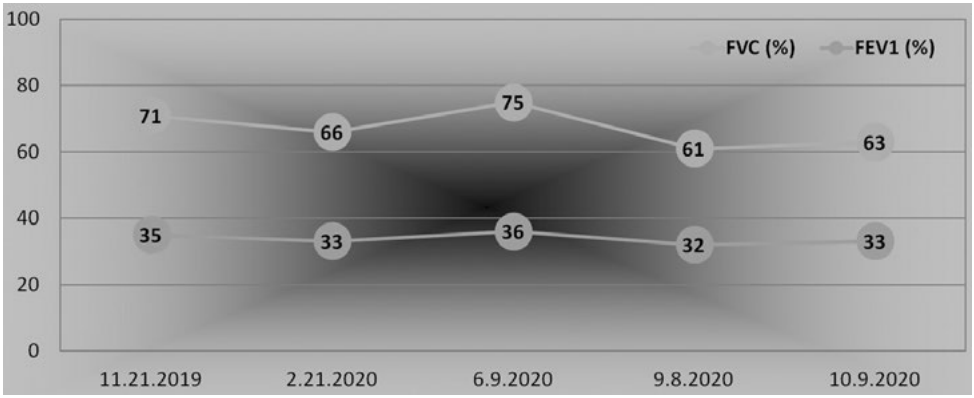
- **November 2019** - Consideration to enroll her on a **waiting list before LTx – 1st time**
- Hospitalization in the pulmonary department, antibiotic treatment and rehabilitation with **Simeox-clinical condition improved and FEV1 increased from 30% do 36%**

**Development of lung function 2009 - 2019**




**November 2019 - October 2020**

- Improvement of clinical condition, weight increased to 51 kilograms, no need 02
- During the COVID-19 pandemic the patient bought Simeox and rehabilitates every day at home
- Maintanance of spirometric value from 32 to 36% FEV1 from November 2019 to October 2020

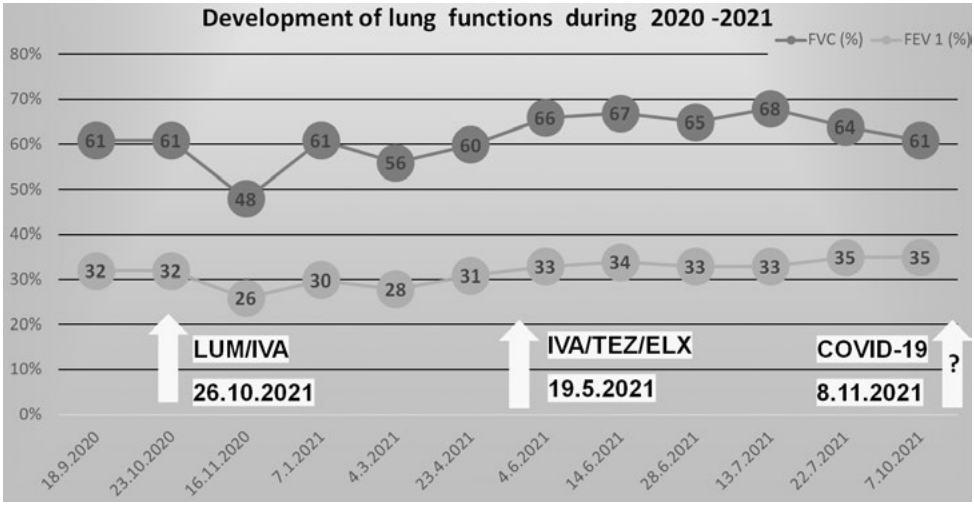



- **26. 10. 2020** start of half dose of **the innovative treatment with ivacaftor and lumacaftor (outpatient)**
- **Patient did not tolerate the treatment very well**
- **Hospitalization** (ATB i.v., O2, Simeox, full dose of ivacaftor and lumacaftor)
- Relatively stable clinical condition: **FEV1 30%**
- **Preparation for inclusion on the waiting list before lung transplantation /2nd time/**

**January 2021 until now..**

- **January - February 2021 – ivacaftor/lumacaftor** therapy continued, condition deteriorated, weight decreased to **46 kg, FEV1 28%** recurrent hemoptysis, insulin therapy
- Control **chloride sweat test**: significant decrease in chloride sweat test from **112.87 mmol/l** after six month of therapy to **60.75 mmol/l**
- We asked **the insurance company to approve an exemption for the treatment of Tezacaftor / ivacaftor / elexacaftor**
  *(that time the drug was not categorized in Slovakia)*

- **Tezacaftor / ivacaftor / elexacaftor was approved for an exemption and the patient began treatment on 19th of May 2021**
- After 6 months her condition improved significantly, **weight 56 kg, FEV1 35%**, cough is significantly reduced, without hemoptysis for 6 months, good tolerantion, no need for oxygen inhalation, rehabilitation daily with Simeox , jumping on the trampoline for 30 minutes a day
- Due to the improved condition, the patient will not yet be included in the waiting list before lung transplantation.




- Admission to the hospital 2.11.2021- intravenous antibiotic treatment and intensive rehabilitation, PCR COVID- 19 negative
- regular PCR monitoring - **PCR COVID-19 positive**
- 3 days mild symptoms, headache, difficult expectoration, no temperature, not need oxygen

## COVID-19 SITUATION IN SLOVAKIA

**Total number of lab-confirmed cases (PCR)**
***578 208*** Last increase: ***8342***

**Total number of lab-confirmed cases (antig.)**
***453 058***
Last increase: ***1 959***
**Number of COVID-19 associated deaths**
***13 687***, Last increase: ***43***

**Number of patients in hospitals confirmed with COVID-19**
***2 879***
**of which in intensive care: *253***
**on ventilation: *246***

**Number of fully vaccinated persons**
***2 429 477*****,** Last increase: ***1508***
***44.5 %***

**COVID-19 in adult CF pt in Banská Bystrica**
- **15** patients overcame COVID-19 infection
- **13** of them had mild symptoms
- **1 patient was hospitalized with hypoxemia, infection**, she was in good condition during 10 days
- Our pacient from case report is the **second to be hospitalized**, but at first she was not hospitalized due to a COVID-19 infection.

***I hope that the COVID-19 infection will not worsen our patient condition***

***I think that not only excellent medications, but also rehabilitation and physical exercise have contributed to the current stabilization of the condition***

***I hope that she will be in such good condition for as long as possible***

# CF HERO

**Application for kids with cystic fibrosis**
CF Hero mobile app helps young patients with cystic fibrosis to improve their adherence to prescribed treatment.

The application CF Hero was originally created in 2019 in the Czech Republic within the Czech Cystic Fibrosis Association. We currently operate in the Czech Republic and Slovakia. In the first quarter of 2022, the CF Hero application will be released in Poland and Ukraine.

## How does the CF Hero app help cystic fibrosis patients?

**Motivation**
Thanks to the gamification, the CF Hero application encourages young patients to follow the inhalation plan and surpass previous results.

**Breathing technique**
The application leads to the correct breathing technique during inhalation and respiratory physiotherapy.

**Playful learning**
With funny and educational comic stories, the CF Hero app breaks down taboos of everyday life with CF.

**Building habits**
CF Hero app uses a playful design so that teenagers are more willing to follow the prescribed therapy and, most importantly, they know why they are doing it.

**Taking over responsibility**
The application helps to transfer the responsibility for the treatment from parents to patients.

## Get more insight about the patient's treatment thanks to CF Hero:

**Inhalation and respiratory therapy**
Physiotherapists and physicians have the opportunity to help patients to set up the right breathing pattern that will accompany them during inhalation and respiratory rehabilitation with the application.

**Sharing results**
Users of the application can share their results with their doctor or physiotherapist by using the diary. The diary records performed inhalations and respiratory rehabilitations with the application, the rewards obtained and together achieve a better result.

## Why are we doing this?

From our own experience we know how difficult it is to follow the daily routine for CF patients. Although the progression is often unpredictable, patients themselves can positively influence it by adhering to treatment and lifestyle choices. The goal of CF Hero application is to make the long everyday inhalations and respiratory rehabilitations more efficient and entertaining at the same time.

## Experts and patients participated in the creation of the mobile application CF Hero

Physicians, physiotherapists and psychologists from CF centers participated in the mechanics of the CF Hero application, as well as multiple experts on habit building and human centered design. All major features were also discussed and tested by CF patients and their feedback is being incorporated in future design of the application.

CF Hero
therappy Fun

# RESPILON

**About Us**

RESPILON is a Czech company active on the international market since 2013. It researches and develops nanofiber products. Its mission to find novel applications for the specific properties of nanofiber to help people live better and healthier lives. Their products range from nanofiber respiratory protection and nanofiber window and door screens to functional nanofiber textiles for sport and outdoor clothing. RESPILON has branch offices in Spain, USA, UK, and China. It partners with the world's top manufacturers of nanofibers, with research centers and universities. RESPILON has its own production capacities in the Czech Republic, as well as using the time-tested production capacities of its partners abroad, which helps to satisfy international demand. RESPILON is in long-term cooperation with a number of non-profit organizations that support children and adults with compromised immunity, seriously-ill patients, and other people in need. A percentage of its sales regularly goes to such NGOs. "We are not involved in solely commercial activities. As our mission statement says: we make products that help people live better and heathier lives. We help, educate, care, think, change, influence, learn and never stop...
because Life's worth it. Yours, ours, the whole planet!"

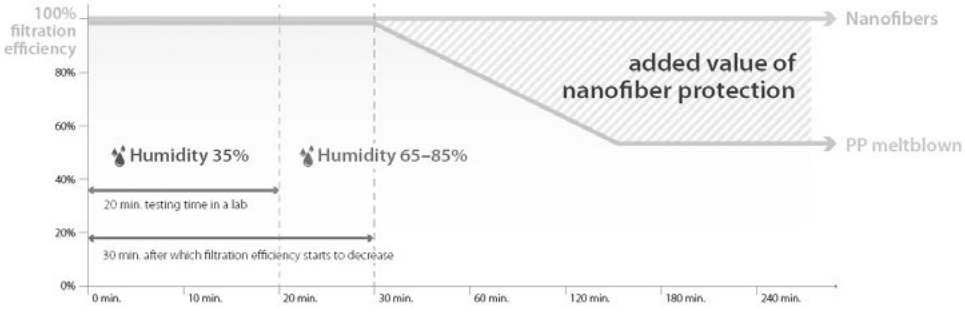
*Jana Zimová, RESPILON Head for Foundations & CSR.*

**The Advantages of Nanofiber**

Ordinary respirators may seem to provide effective protection against viruses and bacteria, but they are not as effective as they should be. And that is why we developed nanofiber respirators that offer the maximum protection you need. Their effectivity relies on the mechanical principle of filtration, which is why they perform well even when in contact with moisture and humidity, for example the human breath.

Even when put to simple use, the level of protection offered by an ordinary respirator is compromised – the moment you put it on and breathe through it. A typical respirator starts to lose its protective function after a mere 30 minutes, due to the moisture of coming into contact with human breath. Nanofiber respirators, on the other hand – thanks to their mechanical filtration – maintain a constant high level of filtration performance. They even work in both directions: they protect not only the wearer, but also those around them.

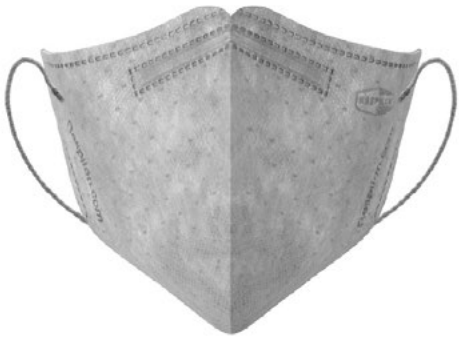
Nanofiber is also permeable and light. Therefore, nanofiber products for respiratory protection are very light and comfortable.



**VK Respirators – How They Work and What Is Unique About Them**

Double protection against viruses. These are the words that first come to mind if you know the VK product line, or have at least heard about it. These respirators boast a nanofiber membrane that works as a protective filter in both directions. Thus they protect the wearer and those around them at the same time. The inner and outer layer of the respirator are enriched with accelerated copper. Between them is situated the nanofiber filter, blocking out 99.9% of all viruses and bacteria, which are then all deactivated by the accelerated copper. In other words, it eliminates not only those pathogens from the outside, but also any that that may be coming from you in case you have been infected. This process is what allows us to call the VK respirators self-sterilizing. It means that you can wear them repeatedly – without any maintenance – for a whole week, or 168 hours cumulatively. What is more, they come in various shapes and sizes to fit almost everyone.

There are two types of respirators in the VK line, with diff erent shapes. Both are comfortable, light, and off er maximum protection thanks to their nanofi ber membrane.
Their nanofi bers are up to a thousand times thinner than the human hair. Because they are so thin, they can form a perfect, dense sieve which blocks out even the most minute particles, such as viruses and bacteria.



VK respirators are certifi ed in accordance with the EN 149:2001+A1:2009 norm and have an embedded nanofi ber membrane that captures 99.9% of viruses and bacteria, smog, dust, pollen, allergens, molds, and other pathogens. Their unique feature is accelerated copper, which secures their self-sterilizing eff ect. VK respirators are maintenance-free and can be worn repeatedly. They have fl exible ear loops and are manufactured in the Czech Republic.

The VK RespiPro is C-shaped and thus follows the contours of your face. It is available in sizes M and L. The elongated shape of the VK RespiRaptor might be likened to a fish. This shape ensures that when it is put on, its wearer is better understood when speaking. It is also suitable for men with beards and people with glasses. It is available in sizes S and M/L. Size S also fi ts children.

We really enjoyed the feedback that we got from our customer Jana: “Our daughter is in love with your VK respirator! She says that if everyone wore it we could wipe out all viruses. At last, she can wear her size-S RespiRaptor to school. She says it doesn’t chafe or rub and that she can fi nally breathe! Sometimes she even forgets to take it off when I pick her up at school. We are really satisfied.”

**Protecting Yourself from Viruses and Bacteria with the R-shield Neck Gaiter**

R-shield bears no resemblance to a standard medical protective device, yet it is an ideal compromise between functionality and design. It boasts a special nanofiber membrane that captures up to 99.9% of viruses and bacteria. It is sewed in the area that covers the wearer's nose and mouth so it won't let any smog, dust, pollen or other allergens pass through it. It is available in both classic and Light versions. The tubular shell of the R-shield Light is made from a lighter textile, and so it is even more breathable, making it suitable even for warmer days and for sports.

The idea of a neck gaiter was conceived back in the days when wearing a face mask in public anywhere in Europe might earn its wearer questioning looks and/or undesirable reactions from passers-by.

We launched the product based on feedback from our client-patients. Due to their illnesses, they had to wear respiratory protection in public long before COVID. That is why we decided to "conceal" a nanofiber face mask that effectively blocks out viruses and bacteria into a neck gaiter. This helped them to better "blend in with the crowd".

And how does R-shield work? The RESPILON® membrane, which is sewed in the area that covers the wearer's nose and mouth, is a part of each neck gaiter. This membrane is made up from an extremely dense network of nanofibers which can mechanically capture even the smallest viruses and bacteria. What's more, it works in both directions, and thus protects both its wearer and also the people around them.

R-shield is made from a flexible material which provides outstanding elasticity, it wicks moisture, and is resistant against molds. Its special, close-fitting tubular design, embedded nose clip, and cord lock which lets you adjust the size or width of your R-shield, ensure no uncomfortable tightness nor headaches. It also fits almost every face type and face size. It is washable and needs no changing of filters.

There is no need to worry about choosing the right size. Thanks to the cord lock at the back of your R-shield you can always readjust its size to make it fit to your face more closely. It is also available in a children's size. The adjustable nose clip also helps inhaled air to travel through the nanofiber membrane.

R-shield is an ideal companion in the mountains, in polluted areas and in places with airborne allergens, for sports, in crowded cities during flu season, in public transport, on busses, trains, or for sports and trips. A handy case that will protect your R-shield from getting dirty, torn, or cross-contaminated, is also available.

To support the Czech Cystic Fibrosis Association, we created the limited edition R-shield Parrot with a parrot pattern. We asked children to draw the design of an R-shield they would like to wear every day and everywhere. More than 100 children participated, and the author of the final design was then 14-year-old Karolína. She said that her drawing was inspired by her own parrot. Children and adults all around the world now wear the neck gaiter with her own design. What is more, RESPILON donates $1 from the sales of every R-shield Parrot to the Czech Cystic Fibrosis Association.

**Clean and Safe Air in Your Homes**

Since clean air indoors is also important for us, we developed a universal protective air conditioner filter as well. It adsorbs bacteria, and its antimicrobial properties prevent their further growth inside the A/C unit. The filter also eliminates odors, harmful gases, and protects your space from dust. It can be installed in every room fitted with an air conditioner, be it a living room, office, or doctor's office.

How does the RESPILON® A/C filter work? First, it is important to realize how home air conditioners work. An indoor air conditioner draws in air from the room, heats it or cools it, and then lets it back into the room. Because of that, the air which was already in the room circulates. The RESPILON® A/C Filter attaches to the vents through which the air conditioner draws in air. The air is filtered at the intake through the nano membrane, which rids it of undesirable particles such as dust, pollen, bacteria, and gases responsible for unpleasant odors.

Purified air at a required temperature then comes out of the air conditioner. The versatility of the filter is a big advantage – it doesn't matter whether you have a wall-mounted, a ceiling-mounted (so-called cassette), or a mobile air conditioner, it doesn't even matter what brand it is. RESPILON® A/C can be installed in any A/C unit.

Its universal applicability is a great advantage, just like its antimicrobial effect, not to mention its deodorizing zeolite core – which not only adsorbs odors, but also prevents their growth on the filter. It is also maintenance-free and easy to install. It is certified by independent institutions, and holds four test reports from the accredited FITI Testing & Research Institute.

All our nanofiber products help to improve the quality of life for both the healthy and the sick. As Jana Zimová says: "We understand how important it is to help patients with cystic fibrosis to protect themselves from harmful particles which can be mortally dangerous. And how difficult it can be for them to do everyday activities. We believe that with our solutions we can help them better protect themselves against viruses and bacteria, and bring more comfort into their lives."

If you want to learn more about RESPILON and our products, please go to **www.respilon.com**. And if you think that our products may help you and make your life easier, please visit our online store at **www.shop.respilon.com**.


UNIWERSYTET JAGIELLOŃSKI
W KRAKOWIE
www.krakow.pl


CF
UKRAINE
CF

**MAIN ORGANISERS:**

Polish CF Foundation MATIO
Paweł Wójtowicz
phone: +48 603 751 001, +48 12 292 31 80
ul. Celna 6, 30-507 Kraków, POLAND
e-mail: krakow@mukowiscydoza.pl
www.mukowiscydoza.pl

Slovak Cystic Fibrosis Association
MUDr. Katarina Štěpánková
phone: +421 903 608 455
Park Angelinum 2, 040 01 Košice, SLOVAKIA
e-mail: cfasociacia@gmail.com
www.cfasociacia.sk

**GOLD SPONSORS:**

VERTEX™

**SPONZORS:**

NUTRICIA METABOLICS
LIFE-TRANSFORMING NUTRITION

Chiesi

MATIO MED
SKLEP ZE SPRZĘTEM REHABILITACYJNYM

VIATRIS™

RESPILON
LIFE'S WORTH IT

**PARTNERS:**

MEDGEN
Centrum Medyczne

reprogen
INTERNATIONAL

STOWARZYSZENIE ZDROWYCH DZIAŁ. POLSKICH

Editor: Slovenská CF Asociácia, Park Angelinum 2, 040 01 Košice, SLOVAKIA
Polish CF Foundation MATIO, ul. Celna 6, 30-507 Kraków, POLAND
Editorial board: Katarína Štěpánková, Paweł Wójtowicz

ISBN SK: 978-80-974191-0-3, ISBN PL: 978-83-964593-0-5

Deadline: 31.3.2022, printing 1000 pcs.
Pre-press: RESULT reklamná agentúra s.r.o. & RESULT PRODUCTION, s.r.o.
Press: TECHNET sp. z o.o.

RESULT reklamná agentúra

RESULT PRODUCTION

9 788097 419103


UNIWERSYTET JAGIELLOŃSKI
COLLEGIUM MEDICUM


Member of
EURORDIS
Rare Diseases Europe


MAŁOPOLSKA
Marszałek Województwa Małopolskiego
Witold Kozłowski


Kraków
Prezydent Miasta Krakowa
Jacek Majchrowski


TVP3
KRAKÓW


medycyna praktyczna


MATIO


kraków.pl


TOK FM
Pierwsze
Radio
Informacyjne


MATIO
FUNDACJA POMOCY
RODZINOM I CHORYM
NA MUKOWISCYDOZĘ


Betegek
Egyesülete


Klub
cystické
fibrózy


SLOVENSKÁ ASOCIÁCIA
CYSTICKEJ
FIBRÓZY