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ANNUAL REPORT

BELGIAN CYSTIC FIBROSIS REGISTRY BCFR 2021

BELGISCH MUCOVISCIDOSE REGISTER
REGISTRE BELGE DE LA MUCOVISCIDOSE

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ABPA – Allergic Bronchopulmonary Aspergillosis

BCFA – Belgian Cystic Fibrosis patient's Association

BCFR – The Belgian Cystic Fibrosis Registry

BMI – Body mass index is a measure of relative weight based on an individual's mass and height. It is defined as the individual's body mass divided by the square of their height – with the value universally being given in units of kg/m2.

BMR-RBM – Belgisch Mucoviscidose Register – Registre Belge de la Mucoviscidose

Bronchoalveolar lavage – is a medical procedure in which a bronchoscope is passed through the mouth or nose into the lungs and fluid is squirted into a small part of the lung and then collected for examination.

CDC – The Centers for Disease Control and Prevention is the leading national public health institute of the United States. Its main goal is to protect public health and safety through the control and prevention of disease, injury, and disability.

CDC growth charts – These consist of a series of percentile curves that illustrate the distribution of selected body measurements in children.

CF – Cystic Fibrosis

CFRD – Cystic Fibrosis Related Diabetes refers to a form of diabetes as a direct consequence of having cystic fibrosis.

CFTR – Cystic Fibrosis Transmembrane Conductance Regulator

CFTRm – Cystic Fibrosis Transmembrane Conductance Regulator Modulator

ConsultRN – a module of the eHealth platform that allows for the extraction of demographic data from the national registry database

Dual energy X-ray absorptiometry – (DXA, previously DEXA) is a means of measuring bone mineral density (BMD).

ECFSPR – European Cystic Fibrosis Society Patient Registry

eHealth – As public institution, the eHealth platform promotes and supports the exchange of electronic information between all stakeholders in health care. eHealth also acts as a Trusted Third party for coding and pseudonymising personal health-related data.

FEV_1 – Forced Expiratory Volume in one second is the volume of air that can forcibly be blown out in one second, after full inspiration

FVC – Forced Vital Capacity is the volume of air that can forcibly be blown out after full inspiration, measured in litres.

INAMI – Institut national d'assurance maladie-invalidité

P.A (*Pseudomonas aeruginosa*) – is the most important pathogen in the CF airway. *P. aeruginosa* is acquired from environmental reservoirs and can cause both acute and chronic infections, depending on the clinical context.

rhDNase – Recombinant human deoxyribonuclease is an enzyme that breaks down DNA strands in airway secretions, hydrolyzes the DNA present in sputum/mucus of CF patients, reducing viscosity in the lungs and promoting clearance of secretions.

RIZIV – Rijksinstituut voor ziekte- en invaliditeitsverzekering

NPD – Transepithelial nasal potential difference is the voltage across an epithelium, and is the sum of the membrane potentials for the outer and inner cell membranes used in CF diagnosis

VUB – Vrije Universiteit Brussel

ACKNOWLEDGMENTS

The annual data report of the Belgian Cystic Fibrosis Registry for the year 2021 is ready.

After the transition to a GDPR-compliant software at our public health institute, and limited time available to analyse the registry data, we are now glad to share the results on the cystic fibrosis situation in Belgium in 2021. Thank you all for your continued patience and collaboration.

We would like to most sincerely thank all our partners for their hard work: the physicians, nurses, administrative staff, physiotherapists and social workers who have spent long hours to complete the required registry data, without which the data collection and reporting would not be possible. We also thank the National Institute for Health and Disability Insurance (RIZIV-INAMI) for their continued financial support and the CF reference centres and their multidisciplinary teams of health care professionals for their continued support to the registry and care to the patients. Finally, we also thank the patients and their parents or care givers for their willingness to participate in the annual data collection process.

This report, and the outcomes of various research questions, enhances the continued monitoring of CF disease by providing a better understanding of disease progression to researchers while stimulating ideas for research into novel treatments and disease management strategies.

Our cover picture reflects on hope, first thanks to the regained freedom of the population and particularly the patients at risk of severe SARS-CoV-2 infection, and secondly, with the upcome of reimbursed CFTR modulators for a majority of patients.

The registry team

SUMMARY

This report presents the data collected in 2021. It is our hope that the analysis of the registry data will provide readers with information on various aspects of CF and continue to provide an important tool for monitoring the patient's quality of care and trends.

Since its establishment in 1999, the Belgian CF Registry (BCFR) has grown steadily and had 1367 patients registered in 2021. This number excludes one patient whose diagnosis for CF was revoked and eleven others without a confirmed diagnosis. There were 33 newly diagnosed patients in 2021, among them four adults, with a median age at diagnosis of 0.7 months and age range from prenatal to 53 years. All the newly diagnosed patients were genotyped; 31 had sweat chloride values, with 28 > 60 mmol/L ; 2 had no sweat chloride value yet by December 2021.

Among the patients followed-up in 2021, 52.6% were male and 65.8% adults, and the median age was 24.5 years. At inception of the registry, 22 years ago, 39.0% were adults, and the median age was 14.9 years, showing changes in demographics over the years. 44.6% of the patients are homozygous for the F508del mutation and 41.0% are F508del heterozygous. The main reasons for diagnosis of CF are acute or recurrent respiratory problems (41.4%) and failure to thrive (24.6%). About 21.8% of all patients were diagnosed via neonatal screening, but 78.8% of new diagnosis were based on neonatal screening, with a regional program started in Flanders in January 2019, and in Wallony in January 2020. Some local initiatives ongoing before the large scale implementation explain that some patients had a positive NBS even before 2019. Within the year, eleven deaths were reported (six of them among transplanted patients) with age at death ranging from 34 to 70 years. Six patients received a transplanted organ (2 lung transplantations), and 14.4% of the patients in the registry are living with a transplanted organ.

Among the adults, the proportion of underweight patients (BMI < 18.5 kg/m^2), continues to decline from about 31.2% in 1998 to 16.7% in 2010 and 7.8% in 2021. This decline was noted also amongst the F508del homozygous patients; 32.8% in 2000, 21.9% in 2010, and 7.9% in 2021. Amongst the patients up to 20 years, the proportion with BMI below the tenth percentile has also been declining over the years. The results above suggest better nutritional and global management in the patients. The patient population continues to record an improvement in lung function expressed as the mean percentage of predicted FEV_1. Among the F508del homozygous patients, 27.6% of the children and

3.5% of the adults had $FEV_1 \geq 90.0\%$ of predicted in 1998 compared to 49.5% and 8.4% in 2010 and 56.9% and 21.0% respectively among the children and adults in 2021.

The overall annual prevalence of *Pseudomonas aeruginosa* reported in 2021 was 33.3%. This is in line with the general decline observed from 42.4% in 2012 to 37.5% in 2016. There has also been a steady increase in the prevalence of *Achromobacter xylosoxidans* from 5.9% in 2009, stabilizing at prevalence levels of about 10.0% since 2012, with 8.6% in 2021. The prevalence of the *Burkholderia cepacia* complex on the other hand remains at about 3.5% over the years since 2014, with 3.1% in 2021.

Thanks to improved disease management and novel treatments, the life expectancy and the quality of life of patients with CF has improved significantly when compared to CF cohorts a decade or two ago. Cystic fibrosis is no longer a paediatric disease, however this progress is also accompanied by various challenges, expectations and disease-related complications. In 2021, CF-related diabetes had a prevalence of 4.1% and 28.3% in children and adults respectively (excluding transplanted patients). Other reported complications include early osteoporosis and CF related arthritis/arthropathy. These require specialized care in the adult CF patients.

CHAPTER 1.
BACKGROUND

This section briefly describes CF care in Belgium, the history, role and objectives of the Belgian CF Registry (BCFR) and the important contributions of the Belgian CF Patients' Association (BCFA), the National Institute for Health and Disability Insurance (INAMI - RIZIV) and the CF reference centres in the provision of care and management of CF.

1.1 WHAT IS CYSTIC FIBROSIS?

Cystic fibrosis (CF) is the most prevalent autosomal recessive disorder in the Caucasian population. Only people who have inherited two disease-causing mutations - one from each parent - are affected. Parents who are both carriers of a CF-causing mutation in the CFTR gene have a 1 in 4 chance of having a child with CF, in each pregnancy. CF occurs in 1/2850 live births in Belgium [1]. The earliest clear medical descriptions of CF date from the 1930s [2,3]. CF obviously existed prior to this dates even though it remained largely unrecognized and so went undiagnosed.

The disease is caused by an alteration (mutation) in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene which is located on the long arm of chromosome 7. More than 2000 (http://www.genet.sickkids.on.ca/SearchPage.html) mutations have been identified in the CFTR gene since its discovery in 1989 [4], but not all are causing CF. The CFTR gene codes for the CFTR protein. This is an ion channel involved in the regulation of chloride transport across the cell membrane. It is mainly found in the cell membranes of the respiratory and digestive tract, the sweat glands and the reproductive tract. The dysfunction of the CFTR protein leads to the production of sweat with a high salt content and mucus secretions with an abnormal viscosity causing dysfunction of many organs such as the lungs, pancreas and liver.

In the respiratory tract, thick mucus production results in persistent cough caused by chronic infection and inflammation, leading to severe bronchial obstruction and finally lung destruction. In the pancreas, the sticky exocrine pancreatic secretions lead to obstruction and blocking of the ducts, with secondary damage to the secretory gland tissue. Diminished secretion of

pancreatic enzymes leads to fat and protein malabsorption causing steatorrhea (fatty stools) and failure to thrive. Fat malabsorption also causes deficiency of fat soluble vitamins (A, D, E and K).

Most of the children with CF have a history of recurrent chest infections, steatorrhea and failure to thrive. About 1 in 10 new-borns with CF is affected by meconium ileus: intestinal obstruction with vomiting, abdominal distension and delay in passing the first meconium stools. The spectrum of presenting features is very wide and can vary with age at time of clinical presentation. The diagnosis is usually made in early childhood but in some patients, with late or milder symptoms, it can occur later into adulthood.

There is a national coverage for neonatal CF screening program in Belgium from 2020. For note, the national coverage is based on an official regional program from January 2019 in Flanders, and from January 2020 in Wallonia [5,6], based on the same national protocol. Infants with CF can be identified in the first weeks of life by assessing their blood immunoreactive trypsin (IRT), combined with detecting the most frequent CFTR mutations. The sweat test remains the gold standard for the diagnosis of CF. In the majority of patients with typical features, the sweat test is diagnostic. It will reveal an excessive quantity of chloride (salt) (> 60 mmol/L). In atypical forms, the sweat test chloride levels can fall into the intermediate range (30-60 mmol/L).

It is advised to perform genotyping in all patients with CF to identify the CF-causing mutations. F508del is the most common mutation, not just in the Belgian CF population but also worldwide.

Today standard treatments available to most patients in Belgium are based on respiratory management (e.g. physiotherapy, mucolytics, antibiotics, anti-inflammatories), digestive and nutritional management (e.g. pancreatic enzymes and hypercaloric diet). Due to medical progress and intensification of the care for patients with CF, the quality of life and the life expectancy have increased, with almost all patients reaching the adult age.

However, to further improve the life expectancy and quality of life, new and more effective treatments are now available for most patients to target the molecular defects and act upstream on the cause rather than on the symptoms resulting from the CFTR defect. Research is still ongoing to target the genetic defects, mainly for patients not eligible to the CFTR modulators.

More than 2000 mutations of the CFTR gene have been reported. They are grouped in six classes according to their functional defect: Class I: defect of protein synthesis; Class II: default of protein folding with premature degradation, which interferes with the protein trafficking to the cell surface; Class III (gating mutations): responsible for deficient channel opening; Class IV: decrease of CFTR channel conductance; Class V: decreased amount of CFTR protein synthesis; and Class VI: decreased stability of CFTR protein at the cell

membrane. Some CFTR mutations, such as F508del have characteristics of more than one mutation class [7] and, for many mutations, it is not known to what mutation class they belong.

CFTR modulating therapies are therapies that target the basic defect. They are small-molecule pharmacologic agents that correct the immature CFTR protein or potentiate the functioning of the defective CFTR channel. They do not correct the default in the gene itself. They are specific to certain mutations or class of mutations and thus effective only in patients carrying those specific mutations. There are different types of CFTR modulators: amplifiers, potentiators, and correctors.

Currently four of those CFTR modulators are approved in the USA and in Europe for clinical use, for different age groups. The European Medicines Agency approved: ivacaftor (Kalydeco®) for patients carrying a class III (gating) mutation (G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R) and those carrying the R117H mutation [8]; lumacaftor in association with ivacaftor (Orkambi®) for patients homozygous for the F508del mutation [9]; and tezacaftor/ivacaftor (Symkevi®) for patients homozygous for the F508del mutation or heterozygous for that mutation together with one of the fourteen residual function mutation (P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A- >G, S945L, S977F, R1070W, D1152H, 2789+5G- >A, 3272 26A- >G, or 3849+10kbC- >T) [10], and elexacaftor/tezacaftor/ivacaftor (Kaftrio®) for patients carying at least one F508del mutation [11].

Clinically, ivacaftor (a potentiator) has been shown to improve the lung function and the BMI, to reduce the sweat chloride concentrations and improve the quality of life in patients aged 12 years or older with G551D and non-G551D gating mutations [12–20]. The efficacy and good tolerance of ivacaftor has also been documented in children from 4 months with a gating mutation [21–24].

In Belgium, ivacaftor is reimbursed for patients older than 6 years carrying one of the nine gating mutations since February 2016, for children aged 2 - 5 years since October 2017, and for children from 4 months old from February 2023 [25]. Patients who received a lung transplant are not eligible for this treatment.

For patients carrying two copies of the F508del mutation, the combination of ivacaftor and lumacaftor (a corrector) (Orkambi®) has been shown to induce a modest yet significant improvement in the FEV_1% predicted (2.6 - 4.0%) [26]. Orkambi® was approved by the European Medicine Agency (EMA) in September 2015 for patients from 12 years old, extended to children 6-11y from November 2017, 2-5y from November 2018, and 1-2y from April 2023. The drug is theoretically available since October 2016 in Belgium, with reimbursement from April 2021 only for children 2-11y (and no lung transplant) [27,28].

Similarly, for patients carrying both copies of the F508del mutation, but also patients carrying one F508del mutation and one of the fourteen residual

function mutation, the combination of ivacaftor and tezacaftor (Symkevi®) was approved by the EMA in October 2018, thanks to a 6-7% improvement in FEV_1% predicted and no significant adverse events [29, 30], for patients older than 12 years (extended in September 2020 to 6-11y), with reimbursement in Belgium as of April 2021 for patients older than 12y, and August 2022 for 6-11y (and no lung transplant) [31].

Furthermore, the use of the triple combination, with elexacaftor added to ivacaftor and tezacaftor (Kaftrio®) was approved in June 2020 by the EMA for patients older than 12y and homozygous for the F508del mutation or with a F508del mutation and a minimal function mutation (i.e. a thousand mutations concerned, though no official list is published) (extended in November 2021 to 6-11y). Studies showed a FEV_1% increase of 10-11% for homozygous patients, and 13.9% for patients with a minimal mutation (compared to 0.4% in the placebo group) [32, 33]. In Belgium, the use of that medication was authorized from June 2020 in a FAGG approved Medical Need Program for CF patients homozygous for the F508del mutation or with a F508del mutation and a minimal function mutation with a poor pulmonary status waiting for a lung transplantation [34, 35]. From September 2022, it started being reimbursed for patients with at least one copy of the F508del mutation, from 12 years old, extended in February 2023 to 6-11y (with no lung transplant) [36].

Other CFTR modulating therapies and mutation-specific approaches are currently in development and are being evaluated in several on-going clinical trials. For more information about new therapies we refer to the review articles of Chaudary, Strug, Clancy, and Southern [37–40].

1.2 CF PATIENT CARE IN BELGIUM

Since 1999, 7 CF reference centres have been accredited by the National Institute for Health and Disability Insurance (INAMI - RIZIV) and receive financial support. An annual care and revalidation agreement (CF convention) for patients with CF is signed between each of the 7 CF reference centres and the RIZIV-INAMI [41, 42]. Each centre has specific expertise in CF care and ensures multidisciplinary follow-up of the patients in order to provide optimal medical, paramedical, psychological and social care to the patients and their relatives. Most of the persons with CF in Belgium are followed in one of the national CF reference centres and are registered in the national CF Registry (BMR-RBM, also known as the Belgian Cystic Fibrosis Registry BCFR).

1.3 THE BELGIAN CYSTIC FIBROSIS REGISTRY (BCFR)

The intent of a registry is to include, in a single database, the entire population of people with a given condition (or meeting a certain criteria), say chronic illness, within a defined geographical area.

The BMR-RBM was started in 1999 as a scientific project initiated by the Medical Committee of the Belgian Cystic Fibrosis Association and the seven CF-reference centres in Belgium collecting data of 1998. It was coordinated by the Vrije Universiteit Brussel (VUB) and co-sponsored by the CF Patient's Association and the Fund Alfonse and Jean Forton of the King Baudouin Foundation. The VUB covered the overheads. After 5 years, the scientific project came to an end in need of new sponsorship.

In 2006, the RIZIV-INAMI became the principal sponsor, and the registry was transferred to the section of Public Health and Surveillance of the Scientific Institute of Public Health (WIV-ISP, now known as Sciensano since April 2018). Since then, Sciensano ensures the collection and management of the data under the supervision of the board of the BCFR and the guidance of a scientific steering group. The board consists of a physician from each CF centre, a representative of the patients' association and the scientific collaborators of Sciensano. The scientific steering group holds all stakeholders (representatives of the INAMI-RIZIV, patients' association, CF centres and scientific collaborators of Sciensano).

The Belgian CF Registry lies since 2006 within the framework of the CF convention described above. Participation in collection of data for the CF registry is one of the obligatory tasks of the CF reference centres.

1.4 OBJECTIVES OF THE CF PATIENT REGISTRY

The aims of the CF patient registry are to study epidemiological aspects of the disease among people with CF in Belgium and to provide a tool for the assessment of the management and quality of care for patients with CF. It also provides a database for scientific research to CF researchers, and for analysis provided to the pharmaceutical industry (numbers of patients eligible for clinical trials, and reimbursement procedures)[1]. The registry also participates in activities organized by the European Cystic Fibrosis Society Patient Registry (ECFSPR) [43] and other international projects.

1 BCFA: Mucovereniging – Association Muco

CHAPTER 2.
POPULATION AND METHODOLOGY

In this section, we describe the target population and methodology used. We briefly describe the data collection procedures and its evolution over the years, and give the general structure of the database by listing some of its components. We look at the reporting procedures and use a flow chart to summarize the entire process.

2.1 STUDY POPULATION

The target population for the registry is people with CF who are cared for in Belgium. In 2021, there were 1367 patients reported in the registry. At the moment, the registry is estimated to have a coverage of more than 90% of all people with CF living or being cared for in Belgium.

Prior to the registration, the physicians (at the accredited CF reference centre) provide each patient and/or their parents (or legal representative) information about the objectives of the registry. The patients are only included in the registry after signing an informed consent. They are identified by their national registry number at the centre level. This number is then pseudonymised into a unique code by a trusted third party (eHealth) before the data are transmitted to the registry. The patients' names are never transferred to the registry.

2.2 DATA COLLECTION

The clinical and demographic data are collected for all patients once each year by the treating physician from medical records, and consists of more than 200 recorded items.

These data are divided into two sections:

a) The core data which contain demographic data, age at CF diagnosis and initial symptoms, genotype (mutations), sweat test and nasal transepithelial potential difference results, including information on neonatal screening.

These data are collected when the patient enters the registry and are updated if necessary during follow-up years.

b) Yearly follow-up sheets collect clinical data (height, weight), lung function (forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), forced expiratory flow 25-75% (FEF_{25-75})), complications that occurred or are still active during the registration year, microbiology results, treatments and medications taken as well as social data.

2.3 SOFTWARE

trusted third party (eHealth) was then used for data collection 2011 until 2013. A new data collection, validation and analysis tool was developed in collaboration with the Healthdata.be platform and used for the first time for data collection 2014. The digital questionnaire is provided in the appendix.

2.4 FEEDBACK

Physicians and team members from each of the seven reference centres receives a copy of the national annual report. Since 2006, they receive a centre report based on the data from patients within the individual centre. Starting 2008, a feedback report has been provided with analyses that compare the results of each centre with data from the other centres so that the quality of care provided can be improved for points that score weaker in a centre, e.g. BMI. This method to optimize the care to the patients is called benchmarking. These analyses are corrected for some known factors such as patient age and gender with further corrections planned as more confounding data are collected by the registry, including socioeconomic data.

Physicians from the centres and researchers can submit research questions to the BMR-RBM, and, currently, a number of research questions are being analysed. While some studies are still on-going, abstracts have been presented at national or international conferences [A1-A15] and several articles have been published [P1-P8].

2.5 INTERNATIONAL COLLABORATION

The Belgian CF registry participates in the European CF patient Registry (ECFSPR). A subset of variables with similar definitions among several European countries is sent each year to the ECFSPR. Their annual reports, at-a-glance reports and publications are available on their website [43].

The Belgian CF Registry has also contributed data to the CFTR2 project (https://www.cftr2.org). The objective of the CFTR2 project is to define the disease-liability of CFTR variants by means of a multistage process which involves clinical (sweat chloride average), functional (expression in cell-based systems) and epidemiological (mutation analysis in healthy obligate heterozygotes[2]) steps [44, 45]. The CFTR2 website provides information for patients, researchers, and the general public about specific variants in the CFTR gene.

2.6 ETHICS AND PRIVACY

The Belgian CF Registry has been approved by the Ethics Committees of all participating CF reference centres and clinics. The BCFR has also received the authorisation of the Privacy Commission (currently known as the Information Security Committee) for the treatment of coded data[3].

2.7 DATA FLOW

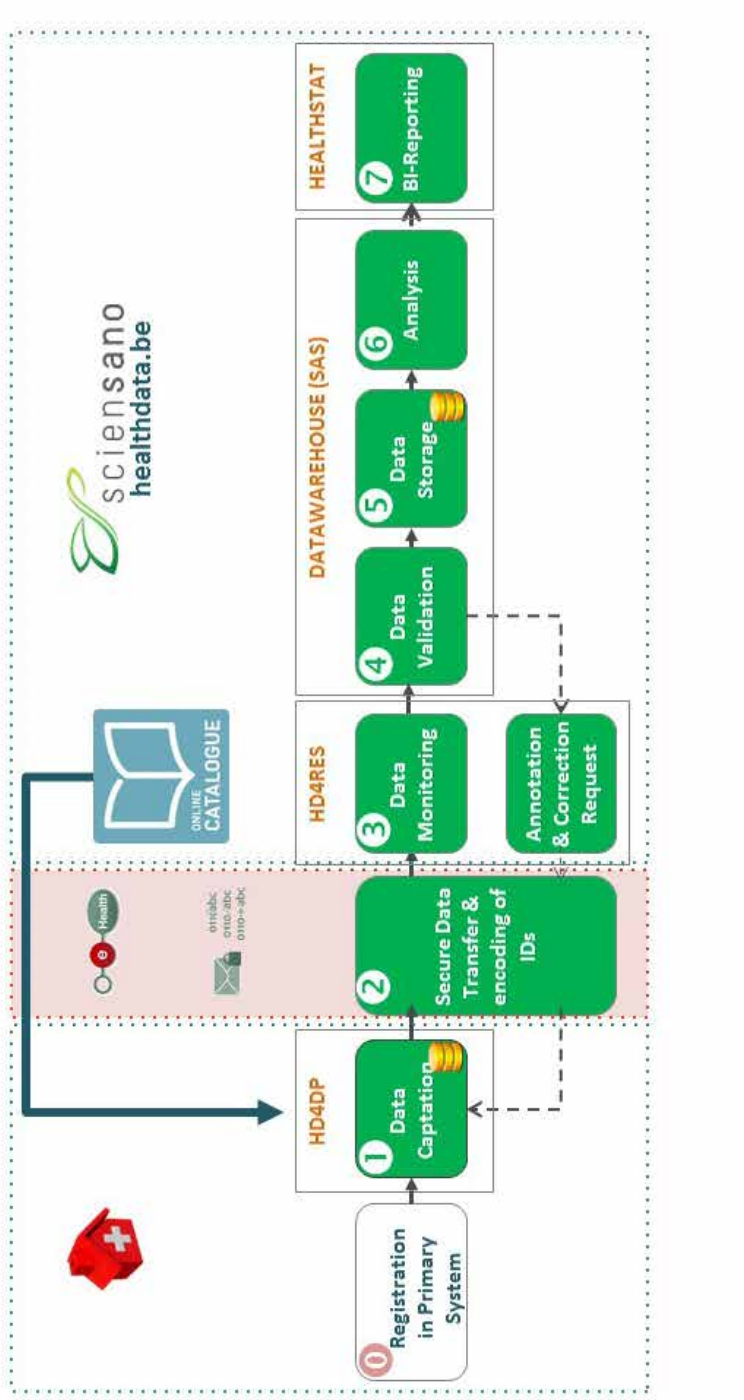
The development and use of a new data collection tool on the HealthData.be[4] platform, has improved the data collection and validation procedures. It has also facilitated communication between the researchers and the data providers and enhanced the data verification and error correction. The first data via this system were collected for registry year 2014. The scheme in figure 1 shows various stages from data entry and processing to reporting and publication.

2 An individual in a family who is proven to carry one copy of a recessive allele by having had affected progeny who inherited two copies of the mutant allele, one from each parent

3 FR: https://www.ehealth.fgov.be/ehealthplatform/file/view/AWh_M6EWnF_Mkwg-mL11?filename=10-084-f020-registre%20belge%20de%20la%20mucoviscidose-modifi%C3%A9e%20le%2015%20janvier%202019.pdf
NL: https://www.ehealth.fgov.be/ehealthplatform/file/view/AWh_Nt4ZgwvToiwBkfz2?filename=10-084-n020-Belgisch%20Mucoviscidoseregister-gewijzigd%20op%2015%20januari%202019.pdf

4 The mission of Healthdata is to facilitate the data exchange between healthcare professionals and researchers to increase public health knowledge and to adjust health care policy in Belgium, with respect for the privacy of the patient, the healthcare professional and the medical confidentiality.

Figure 1 | Data flow chart



a) Data collection (1)

A software called HD4DP (HealthData for Data Providers) is installed locally by the data providers in the hospital. This software contains the electronic form to fill in all the requested data. Data that are present in the primary system of the hospital (e.g. in patient electronic files) can also be extracted and uploaded via a .csv file in HD4DP. This means that the system allows for manual data entry in the electronic form or via uploading a .csv file. In the same registration year, both modalities can be used. Several validation rules (ranges, logical checks…) have been implemented in the software at this stage of the process to minimise data entry errors.

b) Data transfer (2)

When the registration forms have been completed, they are sent to the researchers in a secure way. The identifiers of the patients (national registry number) and the encrypted medical data are put in a digitally encrypted envelope. The envelope is sent to the "eHealthbox codage" of eHealth. The envelope is then opened. eHealth pseudonymises the identifiers but cannot read the encrypted medical data. After pseudonymisation of the identifiers, all the data are put again in an encrypted envelop and sent via the eHealthbox to Healthdata.be at Sciensano. The reopened envelope contains identifiers that are pseudonymised and medical data that will be decrypted to make them readable for the researchers. The result is a set of registrations with all necessary medical information but unrecognizable patient data.

c) Data validation (3-4)

The data arrive to Sciensano in the HD4RES (HealthData for RESearchers) software, for validation by the researchers. The data are loaded into the system and each observation get a time-stamp of the date and time when they were actually received. During validation, if a registration needs to be sent back to the data provider for verification or correction, the process of decoding and pseudonymisation is done in the opposite direction so that the data provider knows which patient it concerns, and which data need to be checked. The newly corrected data are then sent again to HD4RES as a separate record via the described process above, and will be assigned a new time stamp when loaded. No data sent by the data provider are changed or replaced including those initially sent with errors. Each record is stored as it was received.

d) Data storage (5)

After validation, all the data, including those with errors and the new ones received from the data providers after correction, are stored in the data warehouse.

e) Analysis (6)

The data used for the analysis are then populated based only on the valid records in the exploration environment. All old records that had been sent back for correction are excluded, and only the new ones, that replaced them, are retained. Specific tables can then be populated for ad hoc analyses and stored in this environment. An external analysis environment is also available for storage of the data tables sent to third parties such as the European CF Registry or used by other authorized researchers.

f) Reporting (7)

A new reporting tool is under development and will be available on Heathstat.be. This environment will be divided in two sections: a public section with information accessible for all users, and a secured section accessible only for authorized persons after identification by their electronic identification card (eID). In the latter section, benchmarking reports will be available.

SUMMARY OF REGISTRY REPORTS 2018 - 2021

Table 1 | Demographic and diagnosis data

	2018	2019	2020	2021
Number of CF patients	1327	1372	1353	1379
Number of CF patients with complete records	1299	1298	1334	1367
Number of CF patients without observation[1]	28	74	19	12
Number of CF patients with a transplant n (%)	189 (14.1%)	202 (14.6%)	203 (14.6%)	197 (14.1%)
Number of CF patients with a lung transplant	180	193	193	186
Number of CF patients who were not seen	31	67	12	11
New CF diagnoses[2]	22	33	29	33
Number of adults among the newly diagnosed patients	5	6	2	4
Number of patients without a confirmed diagnosis by physicians[3]	9	11	33	18
Number of patients without a confirmed diagnosis according to the ECFSPR	67	76	49	49
Number of patients with a revoked diagnosis[4]	2	1	17	1
Median patient age in years (range)[5]	23.5 (0.2 - 77.5)	23.6 (0.1 - 78.5)	24.2 (0.0 - 85.1)	24.5 (0.1 - 86.1)
Median patient age male (range)[5]	22.8 (0.2 - 65.4)	23.6 (0.1 - 66.4)	23.6 (0.0 - 85.1)	24.1 (0.1 - 86.1)
Median patient age female (range)[5]	23.8 (0.7 - 77.5)	23.9 (0.1 - 78.5)	24.6 (0.1 - 79.5)	25.4 (0.2 - 80.4)
Males (%)	687 (51.8%)	709 (51.7%)	706 (52.2%)	726 (52.6%)
Adults ≥ 18 years (%)	850 (64.1%)	889 (64.8%)	880 (65.0%)	907 (65.8%)
Median age at diagnosis (months)	5.2	5.0	4.6	4.4
Age range at diagnosis (years)[6]	- 0.4 - 70.6	- 0.4 - 75.5	- 0.4 - 82.6	- 0.4 - 82.6
Median age at diagnosis, male (months)	5.2	5.0	4.5	4.3
Age range at diagnosis, male (years)	-0.2 - 59.5	-0.2 - 59.5	-0.2 - 82.6	-0.2 - 82.6
Median age at diagnosis, female (months)	5.1	5.0	4.6	4.5
Age range at diagnosis, female (years)	-0.4 - 70.6	-0.4 - 75.5	-0.4 - 75.5	-0.4 - 75.5
Median age at diagnosis for new cases, months (range)	9.8 (0.1 - 846.6)	4.8 (0.0 - 707.0)	0.8 (0.1 - 410.8)	0.7 (-4.3 - 636.3)
Median age at diagnosis new cases in years (range)	0.8 (0.0 - 70.6)	0.4 (0.0 - 58.9)	0.1 (0.0 - 34.2)	0.1 (-0.4 - 53.0)
Number of transplants performed	17	20	9	6
Total number of deaths reported	16	6	10	10
Median age at death in years (range)	44.1 (20.4 - 70.2)	45.6 (29.6 - 60.1)	47.8 (19.4 - 72.4)	43.2 (34.4 - 69.9)
Number of deaths among transplant patients	9	4	7	6

1. Patients without at least four filled-in clinical items, postulated alive or registered as deceased in the collection year, are not used in the analysis of clinical data.
2. The new CF diagnoses are patients with the earliest diagnosis date from amongst the clinical diagnosis date, NPD date, genotype date or the sweat test date done within the registry data year.
3. Patients without a confirmed diagnosis are not included in the total number of CF patients.
4. Patients with a revoked diagnosis are not included in the total number of CF patients.
5. Patient's age at the last consultation.
6. Prenatal diagnosis is considered without setting to zero the age at diagnosis allowing negative values.

Table 2 | Spirometry, anthropometry, bacteriology and complications data

	2018	2019	2020	2021
SPIROMETRY: FEV_1% PREDICTED[1]				
Mean (SD) FEV_1% predicted, Last of year	78.0 (24.6)	78.5 (24.0)	79.6 (23.3)	81.3 (22.8)
male	79.2 (24.2)	79.9 (23.8)	80.7 (22.8)	83.3 (22.0)
female	76.7 (25.0)	77.0 (24.2)	78.4 (23.9)	79.0 (23.6)
children	91.1 (18.5)	92.2 (18.8)	92.3 (18.0)	93.3 (18.0)
adults	70.4 (24.5)	72.6 (23.7)	72.9 (23.1)	75.2 (22.6)
Mean (SD) FEV_1% predicted, Best of year	82.3 (23.8)	82.8 (23.4)	83.4 (23.0)	85.3 (22.6)
male	83.3 (23.4)	84.0 (23.1)	84.5 (22.4)	87.1 (21.8)
female	81.2 (24.2)	81.5 (23.7)	82.1 (23.6)	83.2 (23.3)
children	96.4 (17.1)	97.1 (17.1)	96.4 (16.8)	98.0 (16.7)
adults	74.1 (23.3)	76.5 (23.0)	76.5 (22.8)	78.9 (22.4)
Mean (SD) FEV_1% predicted z-score, Last of year	-1.7 (1.9)	-1.7 (1.9)	-1.6 (1.8)	-1.5 (1.8)
male	-1.6 (1.9)	-1.6 (1.8)	-1.5 (1.8)	-1.3 (1.7)
female	-1.8 (2.0)	-1.8 (1.9)	-1.7 (1.9)	-1.6 (1.8)
children	-0.7 (1.5)	-0.6 (1.6)	-0.6 (1.5)	-0.6 (1.5)
adults	-2.3 (1.9)	-2.1 (1.8)	-2.1 (1.8)	-1.9 (1.7)
Mean (SD) FEV_1% predicted z-score, Best of year	-1.4 (1.9)	-1.3 (1.8)	-1.3 (1.8)	-1.1 (1.8)
male	-1.3 (1.8)	-1.2 (1.8)	-1.2 (1.8)	-1.0 (1.7)
female	-1.5 (1.9)	-1.4 (1.9)	-1.4 (1.9)	-1.3 (1.8)
children	-0.3 (1.4)	-0.2 (1.4)	-0.3 (1.4)	-0.2 (1.4)
adults	-2.0 (1.8)	-1.8 (1.8)	-1.8 (1.8)	-1.6 (1.7)
ANTHROPOMETRY: BMI, HEIGHT AND WEIGHT (using CDC references)[2]				
Median (range) BMI Z-score (last of year)	-0.4 (-3.3 - 2.6)	-0.3 (-3.2 - 2.6)	-0.2 (-3.2 - 2.6)	-0.2 (-4.7 - 2.3)
Median (range) Weight Z-score (last of year)	-0.5 (-4.7 - 2.7)	-0.5 (-4.9 - 2.7)	-0.4 (-3.9 - 2.2)	-0.4 (-4.9 - 2.1)
Median (range) Height Z-score (last of year)	-0.4 (-3.5 - 2.6)	-0.4 (-4.8 - 2.4)	-0.4 (-3.9 - 2.8)	-0.3 (-3.2 - 3.4)

	2018	2019	2020	2021
INFECTIONS AND BACTERIOLOGY[3]				
Pseudomonas aeruginosa	417 (37.9%)	391 (35.4%)	375 (33.6%)	386 (33.3%)
Burkholderia cepacia complex	33 (3.0%)	38 (3.4%)	31 (2.8%)	36 (3.1%)
Methicillin Resistant *Staphylococcus Aureus* (MRSA)	68 (6.2%)	65 (5.9%)	73 (6.5%)	58 (5.0%)
Haemophilus influenzae	272 (24.7%)	279 (25.2%)	188 (16.8%)	212 (18.3%)
Stenotrophomonas maltophilia	141 (12.8%)	135 (12.2%)	132 (11.8%)	140 (12.1%)
Achromobacter xylosoxidans	111 (10.1%)	98 (8.9%)	92 (8.2%)	100 (8.6%)
Aspergillus spp.	370 (33.6%)	309 (28.0%)	283 (25.4%)	292 (25.2%)
Atypical Non-tuberculous Mycobacterium (NTM)	17 (1.5%)	29 (2.6%)	24 (2.2%)	21 (1.8%)
SARS-CoV-2 test performed this year			575 (50.9%)	674 (57.6%)
COVID-19			41 (7.1%)	120 (17.8%)
Chronic *Pseudomonas aeruginosa*	266 (24.2%)	266 (24.1%)	248 (22.2%)	259 (22.4%)
Chronic *Burkholderia Cepacia* complex	24 (2.2%)	25 (2.3%)	24 (2.2%)	23 (2.0%)
Chronic Stenotrophomonas maltophilia	44 (4.0%)	37 (3.3%)	29 (2.6%)	32 (2.8%)
Chronic *Achromobacter xylosoxidans*	70 (6.4%)	63 (5.7%)	62 (5.6%)	61 (5.3%)
Chronic MRSA	47 (4.3%)	40 (3.6%)	38 (3.4%)	37 (3.2%)
COMPLICATIONS				
Allergic Bronchopulmonary Aspergillosis (ABPA)	97 (8.5%)	105 (9.0%)	101 (8.8%)	93 (7.9%)
Haemoptysis requiring embolization	4 (0.4%)	4 (0.3%)	12 (1.0%)	6 (0.5%)
Pancreatic Insufficiency	964 (72.8%)	1071 (78.7%)	1112 (82.6%)	1131 (82.2%)
CF related diabetes (CFRD)	250 (18.9%)	253 (18.6%)	330 (24.5%)	345 (25.1%)
Bronchiectasis[4]	329 (78.1%)	327 (73.8%)	366 (75.9%)	344 (74.9%)
RESPIRATORY THERAPY[5]				
Regular chest physiotherapy	1109 (97.7%)	1116 (96.1%)	1130 (98.8%)	1170 (99.2%)
Oral Antibiotics only	471 (41.5%)	498 (42.9%)	524 (45.8%)	567 (48.1%)
IV Antibiotics only	23 (2.0%)	23 (2.0%)	32 (2.8%)	30 (2.5%)
Oral and IV Antibiotics	415 (36.6%)	395 (34.0%)	331 (28.9%)	277 (23.5%)
Other inhaled Antibiotics	618 (54.4%)	591 (50.9%)	593 (51.8%)	579 (49.1%)
RhDnase	941 (82.9%)	950 (81.8%)	970 (84.8%)	1003 (85.0%)
Other mucolytics	152 (13.4%)	146 (12.6%)	89 (7.8%)	103 (8.7%)
Hypertonic saline	746 (65.7%)	743 (64.0%)	790 (69.1%)	789 (66.9%)
Corticosteroids	569 (50.1%)	587 (50.6%)	601 (52.5%)	617 (52.3%)
Bronchodilators	863 (76.0%)	868 (74.8%)	852 (74.5%)	882 (74.7%)
Oral anti-inflammatories	683 (51.6%)	683 (50.2%)	636 (47.2%)	653 (47.5%)
Oral Azithromycin	608 (53.6%)	600 (51.7%)	597 (52.2%)	624 (52.9%)
Oral Systemic Corticosteroids	54 (4.8%)	33 (2.8%)	32 (2.8%)	29 (2.5%)
Oral NSAID	32 (2.8%)	41 (3.5%)	40 (3.5%)	29 (2.5%)
Oxygen Therapy	32 (2.8%)	26 (2.2%)	33 (2.9%)	22 (1.9%)

	2018	2019	2020	2021
GASTRO-INTESTINAL AND NUTRITIONAL THERAPY				
Pancreatic enzymes	967 (73.0%)	970 (71.3%)	1116 (82.9%)	1137 (82.6%)
Proton pump Inhibitors + H2 blocker	598 (45.2%)	620 (45.6%)	736 (54.6%)	742 (53.9%)
Enteral feeding	22 (1.7%)	32 (2.4%)	38 (2.8%)	35 (2.5%)
Parenteral feeding	5 (0.4%)	4 (0.3%)	7 (0.5%)	5 (0.4%)
Gastrotomy tube	50 (3.8%)	53 (3.9%)	56 (4.2%)	49 (3.6%)
OTHER TREATMENTS				
Ursodeoxycholic acid	225 (17.0%)	228 (16.8%)	277 (20.6%)	274 (19.9%)
Insulin therapy	193 (14.6%)	190 (14.0%)	271 (20.1%)	284 (20.6%)
Oral Therapy for Diabetes	37 (2.8%)	40 (2.9%)	48 (3.6%)	34 (2.5%)
Bisphosphonates	22 (1.7%)	28 (2.1%)	62 (4.6%)	63 (4.6%)
Anti-conceptive therapy (females 12 and over)[6]	150 (30.1%)	165 (32.2%)	171 (34.7%)	175 (34.2%)
CFTR MODULATING THERAPY				
CFTR Modulating Therapy[7]	155 (13.7%)	167 (14.4%)	236 (20.6%)	635 (53.8%)
Kalydeco® (Ivacaftor)	51 (4.5%)	51 (4.4%)	48 (4.2%)	46 (3.9%)
Orkambi® (Lumacaftor/ivacaftor)	68 (6.0%)	57 (4.9%)	64 (5.6%)	152 (12.9%)
Symkevi® (Tezacaftor/ivacaftor)	12 (1.1%)	19 (1.6%)	12 (1.0%)	271 (23.0%)
Kaftrio® (Elexacaftor/tezacaftor/ivacaftor)	8 (0.7%)	23 (2.0%)	101 (8.8%)	159 (13.5%)
Other or Blinded clinical trial	16 (1.4%)	17 (1.5%)	11 (1.0%)	7 (0.6%)

1. Spirometry data for patients aged 3 years and over based on Global Lung Initiative reference equations [46]. Lung transplant patients are excluded from the spirometry analysis.
2. CDC references allow calculating z-score for children up to 20y. Data from patients > 20y are therefore not included in the anthropometry z-scores. Lung transplant patients are excluded from anthropometry the analysis.
3. Only patients who had a culture or sample taken are included in the infection analysis. Lung transplant patients are excluded from the infection analysis.
4. Only patients who had a CT scan done during the year were considered in the case of Bronchiectasis.
5. Transplant patients are excluded from physiotherapy, inhalation therapy, anti-inflammatories and antibiotics treatments except for the intranasal steroids, oral anti-inflammatories, and Oxygen therapy analysis.
6. Only female patients aged 12y and above were considered in the case of anti-conceptive therapy.
7. Transplant patients are excluded from the CFTR modulating therapy analysis, where only the eligible patients (including if not seen) are used as denominator.

CHAPTER 3.
DEMOGRAPHIC DATA

In this section, the age at the end of the year by gender is presented in five-year categories. Information on the district of residence is provided, including maps of residence districts with estimated prevalence of CF based on the Belgian population in January 2021.

3.1 AGE ON DECEMBER 31 2021

Table 3 | Age on December 31 2021 by gender

	Males			Females			All Patients		
Age years (on 31 Dec 2021)	n	cum n	cum %	n	cum n	cum %	n	cum n	cum %
0 -< 5	56	56	7.7	49	49	7.5	105	105	7.6
5 -< 10	77	133	18.3	63	112	17.2	140	245	17.8
10 -< 15	67	200	27.5	63	175	26.8	130	375	27.2
15 -< 20	67	267	36.8	78	253	38.7	145	520	37.7
20 -< 25	108	375	51.7	66	319	48.9	174	694	50.3
25 -< 30	80	455	62.7	68	387	59.3	148	842	61.1
30 -< 35	61	516	71.1	65	452	69.2	126	968	70.2
35 -< 40	58	574	79.1	65	517	79.2	123	1091	79.1
40 -< 45	50	624	86.0	45	562	86.1	95	1186	86.0
45 -< 50	47	671	92.4	34	596	91.3	81	1267	91.9
≥ 50	55	726	100.0	57	653	100.0	112	1379	100.0
Total	**726**			**653**			**1379**		

The median age on 31, December 2021 was 24.2 and 25.6 years for male and female patients respectively.

The figure 2 compares the age distribution by gender for 2000 and 2021 data, observing an increase in the number of patients above age 40 years: 20.5% in 2021 compared to 1.3% in 2000.

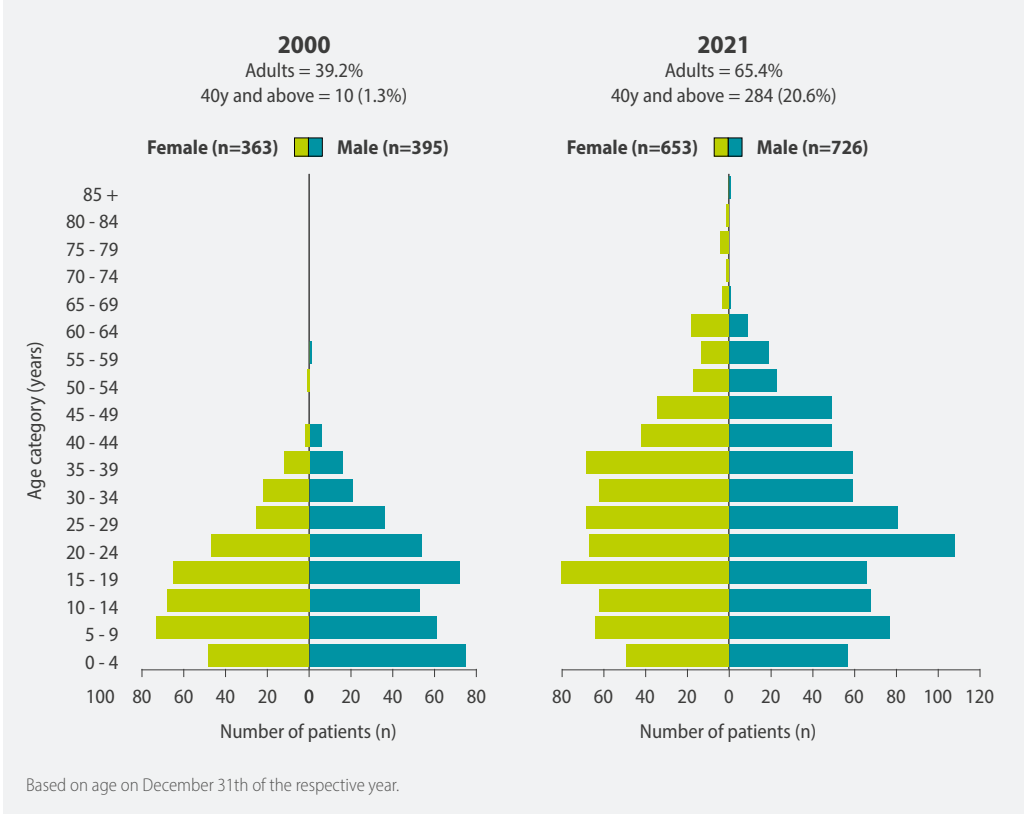


Figure 2 | Age distribution by gender in 2000 (left) and 2021 (right)
Based on age on December 31st of the respective year.

3.2 DISTRICT OF RESIDENCE

The table 4 shows the number of patients in the registry according to their district of residence. Most of the patients reside in Belgium. There are however some patients who reside in neighbouring countries.

Table 4 | District of residence

	District / Arrondissement	n	%
B11	Antwerpen	123	9.0
B12	Mechelen	60	4.4
B13	Turnhout	72	5.3
B21	Brussel Hoofdstedelijk Gewest - Région Bruxelles Capitale	109	8.0
B23	Halle-Vilvoorde	83	6.1
B24	Leuven	60	4.4
B25	Nivelles	58	4.2
B31	Brugge	22	1.6
B32	Diksmuide	12	0.9
B33	Ieper	12	0.9
B34	Kortrijk	34	2.5
B35	Oostende	24	1.8
B36	Roeselare	22	1.6
B37	Tielt	9	0.7
B38	Veurne	11	0.8
B41	Aalst	37	2.7
B42	Dendermonde	19	1.4
B43	Eeklo	10	0.7
B44	Gent	75	5.5
B45	Oudenaarde	15	1.1
B46	Sint-Niklaas	30	2.2
B51	Ath	18	1.3
B52	Charleroi	29	2.1
B53	Mons	29	2.1
B54	Doornik- Mouscron	20	1.5
B55	Soignies	8	0.6
B56	Thuin	16	1.2
B58	La Louvière	22	1.6
B61	Huy	25	1.8
B62	Liège	87	6.4
B63	Verviers	28	2.0
B64	Waremme	11	0.8
B71	Hasselt	50	3.7
B72	Maaseik	21	1.5
B73	Tongeren	16	1.2
B81	Arlon	4	0.3
B82	Bastogne	3	0.2
B83	Marche-en-Famenne	9	0.7
B84	Neufchâteau	10	0.7
B85	Virton	7	0.5
B91	Dinant	18	1.3
B92	Namur	30	2.2
B93	Philippeville	9	0.7
	Subtotal	**1367**	
	Foreign country/ unknown	12	0.9
	TOTAL	**1379**	

3.3 PREVALENCE OF CF PER DISTRICT OF RESIDENCE

The map below (Figure 3) illustrates the prevalence of CF in each district of residence in Belgium based on the population as at the beginning of 2021. The numbers on the map refer to the district codes. A list with the district names and exact number of people with CF residing in each district is provided in Table 4 above. The white circles represent the geographical position of the seven reference centres, i.e. ten clinic sites.

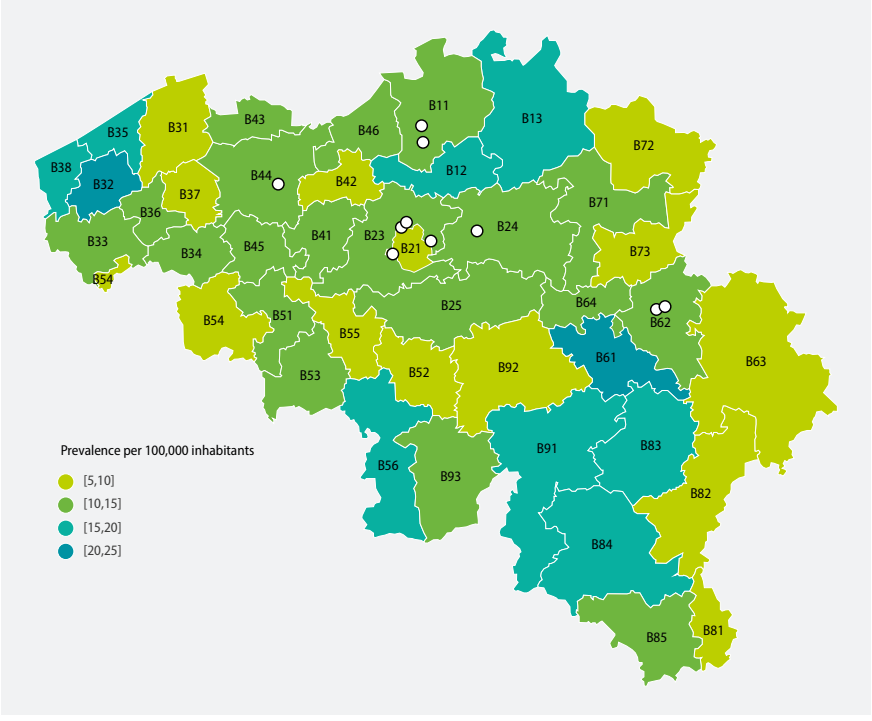


Figure 3 | Prevalence per 100,000 inhabitants by district of residence in January 202

The top three districts with the highest prevalence are Diksmuide (Dixmude, code 32) with prevalence 23.2 per 100,000 inhabitants, and population 51,774; Huy (Hoei, code 61) with prevalence 21.9 and population of 114,293; and Veurne (code 38) with prevalence 17.8 and population 61,947 at the beginning of the year respectively. The bottom three districts with the lowest prevalence are Charleroi (code 52) with prevalence 7.3 and population 395,832; Arlon (Aarlen, code 81) with prevalence 6.3 and population 63,546; and lastly Bastogne (Bastenaken, code 82) which had the lowest prevalence of 6.1 and population 49,352.

3.4 PATIENTS WITH CF UNDER FOLLOW-UP PER DISTRICT OF RESIDENCE

The figure 4 illustrates the number of CF patients resident in each district in Belgium at the beginning of 2021. The numbers on the map refer to the district codes. A list with the district names and exact number of people with CF residing in each district is provided in Table 4 above. The white circles represent the geographical position of the seven reference centres, i.e. ten clinic sites.

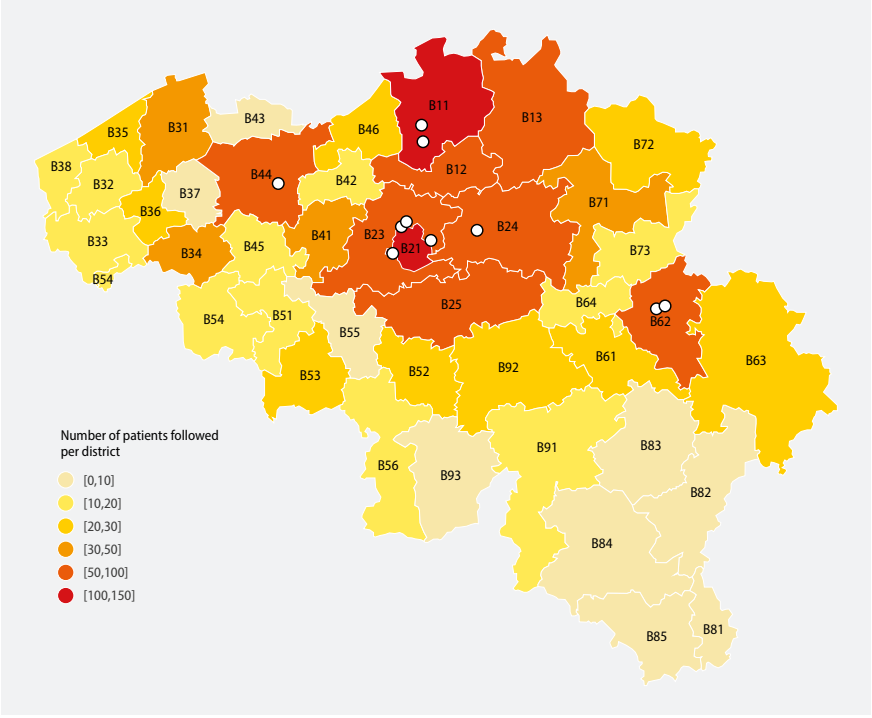


Figure 4 | Number of patients with CF per district of residence in January 2021

We see more patients concentrated in the central and northern sides of the country. Due to their populous nature though, Antwerp (Antwerpen/Anvers, code 11), with 123 patients in a population of about 1.060 million, had a prevalence of 11.6 in 100,000 inhabitants, and the capital city Brussels (Brussel/Bruxelles, code 21) coming second with 109 patients in 1.220 million inhabitants and a prevalence of 8.9. The districts with the fewest patients were Arlon (Aarlen, code 81) and Bastogne (Bastenaken, code 82), with 4 and 3 patients respectively, and prevalence 6.3 and 6.1.

CHAPTER 4.
DIAGNOSIS

In this section, we present the symptoms and clinical reasons suggesting a CF diagnosis. We also present a table of the procedure used for CF diagnosis which classifies the people with CF into two groups depending on whether or not they meet the conditions set for inclusion into the European Cystic Fibrosis Society Patient Registry (ECFSPR). Also presented is the age at diagnosis and the mutations found after genotyping.

4.1 SYMPTOMS AND CLINICAL REASONS SUGGESTING CF

In a patient with suggestive symptoms, a family history of CF or a positive neonatal screening test, the diagnosis of CF is confirmed by an abnormal sweat test (chloride > 60 mEq/L) and/or the identification of two mutations in the CFTR gene. Even though Belgium had no existing national neonatal screening program implemented before 2019, some children were screened for CF via local initiatives. Diagnosis by neonatal screening is expected to progressively increase, with a systematic program implemented in Flanders from January 2019, and Wallonia from January 2020. Most patients present with a combination of respiratory and/or gastrointestinal symptoms. Chronic cough, recurrent chest infections and chronic sinusitis are the most common presenting respiratory signs. Common gastrointestinal symptoms include meconium ileus (obstruction of the bowel with sticky secretions in the newborn infant), chronic diarrhoea and failure to thrive due to malabsorption. Less frequently, salt loss, jaundice or a rectal prolapse are the first diagnostic signs. In some cases, the diagnosis of CF is delayed until adulthood. Most of these patients are expected to have had a milder clinical course, or to present with limited symptoms, such as only infertility.

The diagnostic signs or clinical presentation are illustrated in table 5. The Belgian CF Registry collects and reports more than one diagnosis sign or symptom from the same patient. Over the years, the most common clinical presentation of CF remains acute or recurrent respiratory problems. Other common features on presentation were failure to thrive, chronic diarrhea / steatorrhea and meconium ileus. About 22% of all the patients were diagnosed via neonatal screening test.

Table 5 | Symptoms and clinical reasons for CF diagnosis

	All patients		Newly diagnosed			
			2020		2021	
	n	%	n	%	n	%
Acute or recurrent respiratory problems	546	41.4	5	17.2	5	15.2
Failure to thrive	325	24.6	4	13.8	1	3.0
Chronic diarrhea/steatorrhea/ malabsorption	216	16.4	1	3.4	1	3.0
Neonatal screening test	288	21.8	21	72.4	26	78.8
Meconium ileus	185	14.0	3	10.3	2	6.1
Family history	136	10.3	2	6.9	4	12.1
Nasal polyposis / chronic sinusitis	68	5.2	2	6.9	3	9.1
Rectal prolapse / Intestinal obstruction (other than meconium ileus)	54	4.1	0	0.0	0	0.0
Prenatal diagnosis	36	2.7	0	0.0	1	3.0
Dehydration / electrolyte imbalance / Neonatal jaundice / Prolonged icterus	36	2.7	1	3.4	0	0.0
Infertility	19	1.4	0	0.0	0	0.0
Diagnosis other	72	5.5	1	3.4	0	0.0
No diagnosis reasons given	60	4.5	0	0.0	0	0.0

The overall percentages are based on 1319, 60 patients did not have information on any of the above reasons given in the 2021 data and were excluded from the calculations.
There were 29 newly diagnosed in 2020, percentages are based on 29 patients.
There were 33 newly diagnosed in 2021, percentages are based on 33 patients.
Note: Reasons for diagnosis are not mutually exclusive, so total % may be higher than 100%

4.2 DOCUMENTATION OF CF AT DIAGNOSIS

According to the European Cystic Fibrosis Society Patient Registry (ECFSPR), for a patient to be included, he/she must meet at least one of the following three criteria below. We have used those criteria to explore the documentation of the diagnosis of the patients in our registry. These data are presented in the table 6.

Inclusion criteria for patients into the European CF Society Patient Registry (ECFSPR)
For a patient to be included in the ECFSPR, at least one of the following three criterions must be met:
1) two sweat tests returning results of sweat chloride > 60 mmol/L
2) one sweat test with chloride > 60 mmol/L and DNA Analysis/Genotyping done where two disease causing CF mutations are identified
3) if sweat chloride value is ≤ 60 mmol/L then at least two of the conditions below should be fulfilled: i. A DNA Analysis/Genotyping where two disease causing CF mutations are identified ii. A Transepithelial (Nasal) Potential Difference value – Consistent with a diagnosis of CF iii. Clinical Presentation at diagnosis – Where typical features of CF are identified

Table 6 | Documentation of CF diagnosis

Procedure	All patients		New diagnoses 2021	
	n	%	n	%
Patients meeting the European CF Society Patient Registry criteria				
Clinical symptoms and/or family history, sweat test and genotyping	709	51.4	2	6.1
Clinical symptoms and/or family history, sweat test, genotyping and abnormal TEPD	44	3.2		
Clinical symptoms and/or family history and sweat test	76	5.5	3	9.1
Clinical symptoms and/or family history, sweat test and abnormal TEPD	8	0.6		
Clinical symptoms and/or family history and genotyping	119	8.6	1	3.0
Clinical symptoms and/or family history, genotyping and abnormal TEPD	6	0.4		
Neonatal screening test, sweat test and genotyping	156	11.3	18	54.5
Neonatal screening test, sweat test, genotyping and abnormal TEPD	7	0.5		
Clinical symptoms and/or family history, neonatal screening test, sweat test and genotyping	81	5.9	3	9.1
Sweat test and genotyping	45	3.3		
Clinical symptoms, Neonatal screening, Sweat test, genotyping and abnormal TEPD	1	0.1		
Sweat test, genotyping and abnormal TEPD	2	0.1		
Neonatal screening test and sweat test	7	0.5	1	3.0
Sweat test only	3	0.2		
Clinical symptoms and/or family history, neonatal screening test and genotyping	6	0.4	1	3.0
Clinical symptoms and/or family history, neonatal screening test and sweat test	7	0.5	1	3.0
Clinical symptoms and/or family history and abnormal TEPD	14	1.0		
Genotyping only	24	1.7		
Sweat test and abnormal TEPD	1	0.1		
Neonatal screening test and genotyping	14	1.0		
Total	**1330**	**96.4**	**30**	**90.9**
Patients not meeting the European CF Society Patient Registry criteria				
Clinical symptoms and/or family history only	36	2.6	1	3.0
Neonatal screening test only	6	0.4	2	6.1
Clinical symptoms and/or family history and neonatal screening test	3	0.2		
Abnormal or Positive TEPD only	3	0.2		
Missing	1	0.1		
Total	**49**	**3.6**	**3**	**9.1**

Important Information: The data in the table above refer to documentation of CF at diagnosis. The clinical diagnosis was considered if at least one of a set of symptoms was identified (see Table 5; excluding neonatal screening); the sweat chloride if it resulted in values greater than 60 mmol/L, and genotyping was considered confirmatory if two CF-causing mutations were reported based on the CFTR2 Mutation list of 7April2023 [47]. The results of an abnormal or evocative Transepithelial Nasal Potential Difference (NPD) test are also included in the documentation.

4.3 AGE AT DIAGNOSIS

Figure 5 gives the number of patients and the cumulative percentage of age at diagnosis for patients alive in data 2021. The median age at diagnosis was 4.4 months; 4.3 months for male and 4.5 months for female patients. At the age of 18 years, 89.8% of the patients had been diagnosed. The age at diagnosis ranges from five months before birth, due to prenatal diagnosis, to 82 years. The median age at diagnosis was 2.4 months for the F508del homozygous patients, 7.8 months for the F508del heterozygous, and 6.0 months for patients with other mutations.

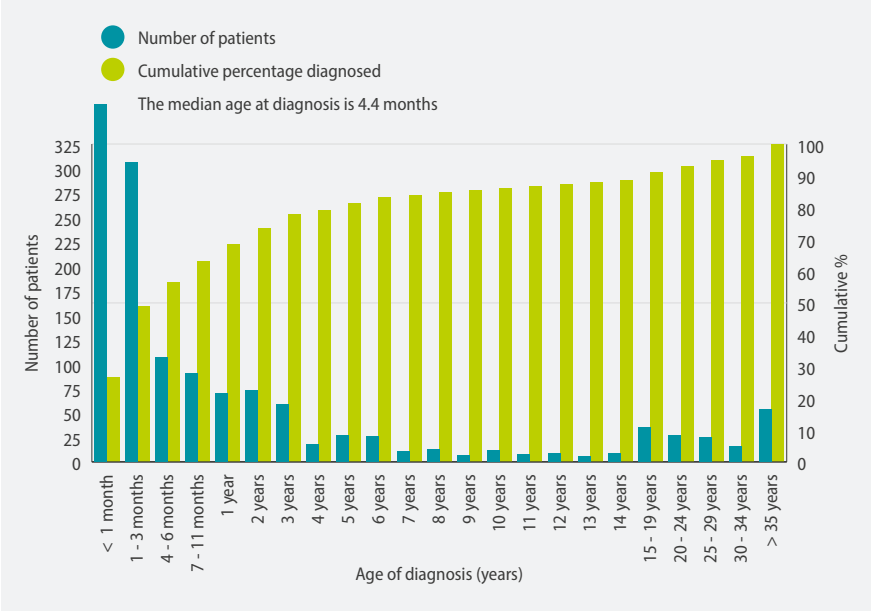


Figure 5 | Age at diagnosis

The median age at diagnosis for the 33 newly diagnosed patients in 2021 was 0.7 months; 0.7 months for male and 0.7 months for female patients, with range from before birth to 53.0 years. There were four adult patients amongst the newly diagnosed (three males and one female).

4.4 GENOTYPE

All 1379 patients have undergone genetic analysis. Almost half (44.6%) were homozygous for F508del (table 7), and 85.6% of the patients had this mutation on at least one of their alleles (table 8). However, 17 patients (1.2%) had at least one non-identified mutation. The mutation list included 143 different alleles present in at least one patient.

Table 7 | Mutation classification by disease liability and general broader categories

MUTATION 1	MUTATION 2											
	DC		NONCF		UCS		VCC		NI		OVERALL	
	n	%	n	%	n	%	n	%	n	%	n	%
F508del Homozygous												
DC	615	44.6%									615	44.6%
F508del Heterozygous												
DC	466	33.8%	3	0.2%	46	3.3%	41	3.0%			556	40.3%
F508del---NI												
DC									10	0.7%	10	0.7%
OTHER---OTHER												
DC	133	9.6%	1	0.1%	25	1.8%	19	1.4%			178	12.9%
VCC					1	0.1%	5	0.4%			6	0.4%
UCS					6	0.4%					6	0.4%
NONCF			1	0.1%							1	0.1%
	133	9.6%	2	0.1%	32	2.3%	24	1.7%			191	13.9%
OTHER---NI												
DC									1	0.1%	1	0.1%
VCC									1	0.1%	1	0.1%
NONCF									2	0.1%	2	0.1%
									4	0.3%	4	0.3%
NI---NI												
NI									3	0.2%	3	0.2%
	1214	88.0%	5	0.4%	78	5.7%	65	4.7%	17	1.2%	1379	100.0%

The table above shows the broad classification of mutations by disease liability for patients seen in the year 2021.
The categories are based on the CFTR list 7April2023 [47].

LEGEND:
DC = Disease Causing, VCC = Varying Clinical Consequence, UCS = Unknown Clinical Significance, NONCF= Non-CF-Causing,
NI = Not Identified, MISSING = Missing data on mutation.

Table 8 | Number and proportion of patients by CF allele or mutation

	patients		alleles	
Mutation	**n**	**%**	**n**	**%**
F508del	1181	85.6	1813	65.7
G542X	66	4.8	75	2.7
N1303K	66	4.8	72	2.6
3272-26A->G	58	4.2	58	2.1
S1251N	38	2.8	38	1.4
1717-1G->A	36	2.6	36	1.3
A455E	34	2.5	34	1.2
2789+5G->A	30	2.2	31	1.1
L927P	26	1.9	28	1.0
R117H*	26	1.9	29	1.1
R553X	25	1.8	25	0.9
3849+10kbC->T	22	1.6	22	0.8
2183AA->G	18	1.3	18	0.7
W1282X	18	1.3	18	0.7
D1152H*	12	0.9	13	0.5
R1162X	12	0.9	18	0.7
G178R	10	0.7	10	0.4
5T;TG12*	9	0.7	9	0.3
E60X	9	0.7	9	0.3
I507del	9	0.7	9	0.3
1002-1113_1110delGAAT**	8	0.6	8	0.3
306insA	8	0.6	8	0.3
3659delC	8	0.6	8	0.3
711+1G->T	8	0.6	11	0.4
G85E	8	0.6	8	0.3
G970R	8	0.6	8	0.3

	patients		alleles	
Mutation	**n**	**%**	**n**	**%**
R117C	8	0.6	8	0.3
R334W	8	0.6	8	0.3
W401X	8	0.6	8	0.3
3120+1G->A	7	0.5	8	0.3
394delTT	7	0.5	8	0.3
Q493X	6	0.4	6	0.2
2118del4	5	0.4	5	0.2
4218insT	5	0.4	5	0.2
5T;TG13*	5	0.4	5	0.2
621+1G->T	5	0.4	5	0.2
L165S	5	0.4	5	0.2
L227R	5	0.4	9	0.3
L927P; 1002-1113_1110delGAAT	5	0.4	5	0.2
Y913C**	5	0.4	5	0.2
1677delTA	4	0.3	6	0.2
5T*	4	0.3	4	0.1
CFTRdele2,3	4	0.3	6	0.2
G551D	4	0.3	5	0.2
Q1313X	4	0.3	4	0.1
R347H	4	0.3	4	0.1
Others	191	14.0	203	7.4
Not identified	17	1.2	20	0.7
Total			**2758**	

The mutations detected in less than four patients were all summarized into the "others" category for this purpose.
According to the CFTR2 database – list 7April2023 - https://cftr2.org/ [47], the mutations listed above are CF causing with few exceptions:
* = mutation with varying clinical consequence, while the one marked ** is not yet annotated in the CFTR2 database.

CHAPTER 5.
ANTHROPOMETRY (HEIGHT, WEIGHT AND BMI)

Persons with CF are known to be prone to nutritional deficiencies. Because of thick mucus, the pancreas is unable to produce digestive enzymes or they fail to reach the gut. This leads to poor absorption of proteins, fats and fat soluble vitamins, resulting in poor weight gain and growth. Nutritional care is of great importance for patients with CF. Maintaining or achieving a better nutritional status has a positive impact on lung function. For this reason, close follow-up of height, weight and BMI is standard practice in all CF care centres.

We present classifications of the patients into BMI, height and weight percentiles, compared to their healthy peers. The analysis of the height, weight and BMI z-scores is based on CDC and Cachera reference equations [48, 49]. An evolution of BMI and height data from selected years is also presented by age category.

In this section, data from **185 patients with a lung transplant (83 males, 102 females; 1 child, 184 adults) were excluded** from the analysis.

5.1 BMI PERCENTILES USING CACHERA REFERENCE VALUES

Cachera equations cover BMI z-scores for ages 0.0 - 58.0 years for male (56.0 for female) patients. In 2021, data from 467 children were analysed. The figure 6 shows a general trend for better median BMI percentile in children after 2000, mainly for the teenagers.

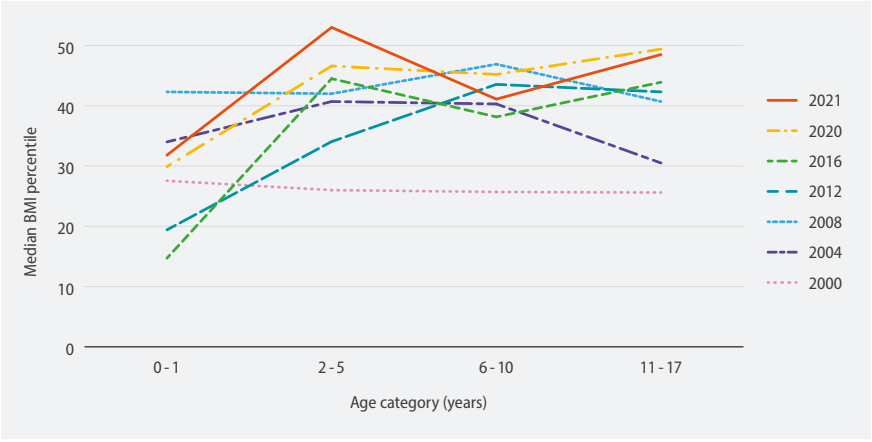


Figure 6 | Median BMI percentile by age group and year (children)

Considering the absolute value of BMI, most adults (70.5%) had a BMI within normal range (18.5 to 25 kg/m^2) (Table 9). The proportion of overweight patients was higher than those underweight, mainly for male patients.

Table 9 | Number and proportion of adult patients (≥ 18y) per BMI categories

	MALES		FEMALES		OVERALL	
	n	%	n	%	n	%
BMI < 18.5	24	6.1	31	10.0	55	7.8
18.5 ≤ BMI < 25	264	67.2	232	74.6	496	70.5
25 ≤ BMI < 30	91	23.2	29	9.3	120	17.0
BMI ≥ 30	13	3.3	19	6.1	32	4.5
BMI unknown	1	0.3			1	0.1
	393	100.0	311	100.0	704	100.0

5.2 BMI PERCENTILES USING THE CDC GROWTH CHARTS

CDC growth charts cover BMI for ages 2.0 – 20.0 years. The trend depicted is quite similar to the Cachera references shown previously. In 2021, data from 472 patients were analysed. Figure 7 displays the proportion in each percentile category. The proportion of patients with a BMI between the 25th and the 75th percentile (considered normal, expected 50%) was adequately between 52% and 58% for all the children age categories, but lower for the young adults ([18-20y] 38%). However, a higher proportion than expected (32-33%) was below the 25th percentile for children ≥ 6y old, and 47% for young adults.

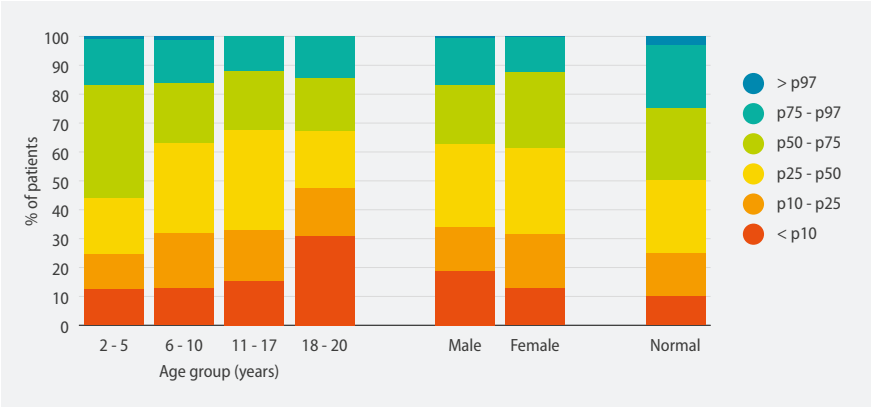


Figure 7 | **CDC BMI percentiles by age**

5.3 HEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover height from 0.0 – 20.0 years. No extrapolation was made for patients older than 20.0 years. In 2021, data from 522 patients were analysed. Figure 8 indicates the proportion in each percentile category. The proportion of patients with a height between the 25th and the 75th percentile was adequately between 43% and 53% for each category below 18y, but higher in the young adults. Moreover, a high proportion (40.5%) of teenagers (11-17y) had a height below the 25th percentile. The proportion in the < 10th percentile was higher than 15% for most age categories (except 2-5y and 18-20y).

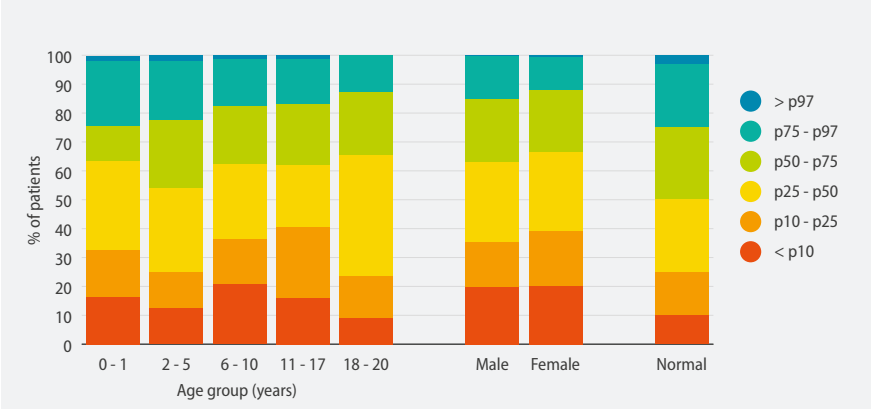


Figure 8 | **CDC Height percentiles by age**

5.4 WEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover weight from 0.0 – 20.0 years. In 2021, data from 522 patients were analysed. The figure 9 indicates the proportion in each percentile category. The proportion of patients with a weight between the 25th and the 75th percentile was adequately between 44% and 56% for each category but only 32.7% for infants (<1y). Moreover, a high proportion with weight for age below the 10th percentile was observed for all age categories, even higher than 20% for infants (0-1y) and for 11-20y.

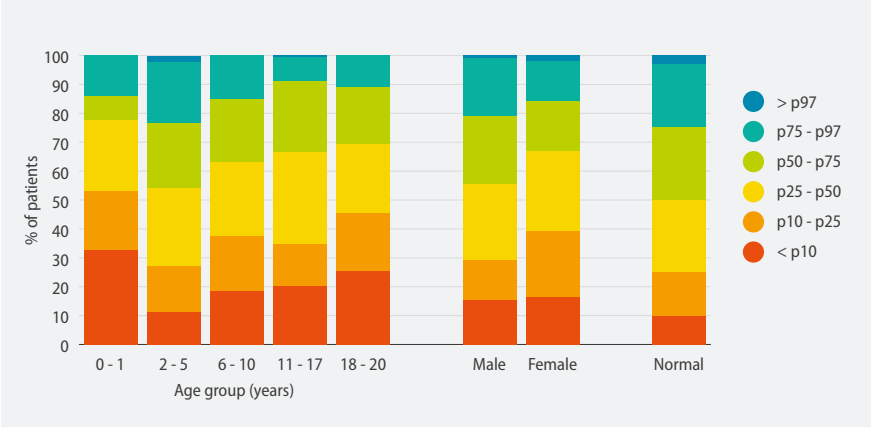


Figure 9 | CDC Weight percentiles by age

CHAPTER 6.
SPIROMETRY (LUNG FUNCTION)

The forced expiratory volume in one second (FEV_1) is the amount of air that a person is able to expire forcefully in one second, following full inspiration. It is expressed as a percentage of the predicted value for a reference population with same age, gender and height.

The percentage of predicted FEV_1 is a clinical parameter to monitor lung function impairment. The FEV_1 partly determines the prognosis [50]. Because most patients with CF develop progressive pulmonary disease, measures of pulmonary involvement, in particular FEV_1, are used to follow up the lung disease. However, considerable heterogeneity exists in prognosis and severity, even among patients of the same genotype [51].

For this analysis, FEV_1% predicted values are divided in four classes for the CF population corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) impairment.

Since lung function prediction is not available or reliable **below the age of 6 years**, data from those 139 children were excluded from the lung function analysis. **Those with a lung transplant (1 child and 184 adults) were also excluded.**

The values obtained at the last consultation of the year, pre- or post-bronchodilator, were analysed. An evolution of lung function from selected years by age category is also presented.

6.1 PERCENTAGE OF PREDICTED FEV_1

The predicted lung function was calculated with the Global Lung Initiative's equations for patients from 3 years onwards [46].

In 2021, data from 1043 patients were analysed. The overall mean FEV_1% predicted was 81.3% (SD = 22.8). The mean FEV_1% predicted was 83.3% (SD = 22.0) and 79.0% (SD = 23.6) respectively for 562 male and 485 female patients. The mean FEV_1% predicted was 93.3% (SD = 18.0) and 75.2% (SD = 22.6) respectively for 354 children and 693 adult patients.

Amongst the 450 F508del homozygous patients, the means were 79.2% (SD = 22.5) and 80.7% (SD = 21.9) respectively for the 238 male and 212 female patients. The means were 92.8% (SD = 16.8) and 71.7% (SD = 21.7) respectively for the 160 children and 290 adults homozygous for the F508del mutation.

The figure 10 shows a scatter plot of the FEV (in litres) with the means calculated by age and gender and with a 95% confidence band.

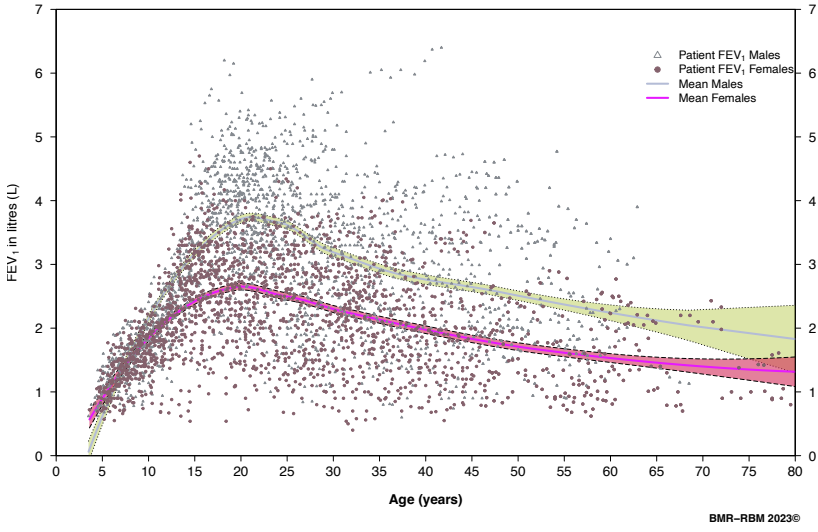


Figure 10 | Mean FEV_1 in litres by age and gender

In figure 11, the scatter plot shows the percentage of predicted FEV_1 with mean profiles and a 95% confidence band according to age and gender, based on GLI reference equations [46].

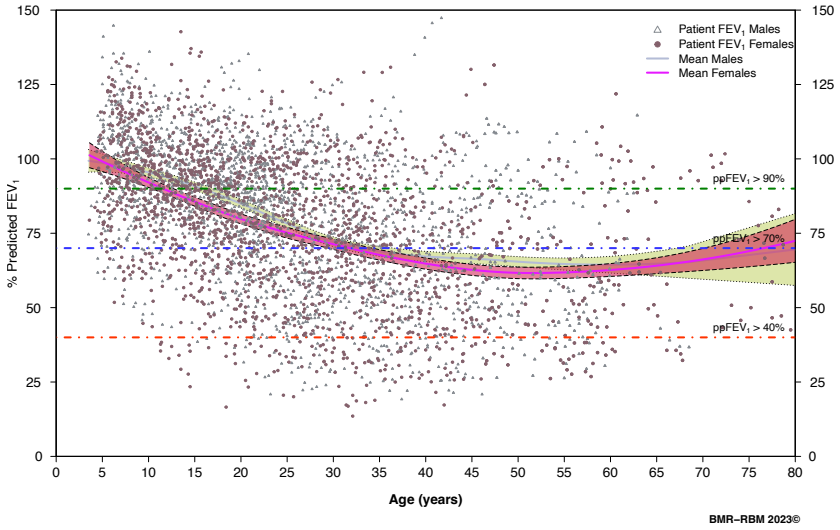


Figure 11 | Mean FEV_1% predicted by age and gender

The figure 12 shows lung function as z-scores of FEV_1.

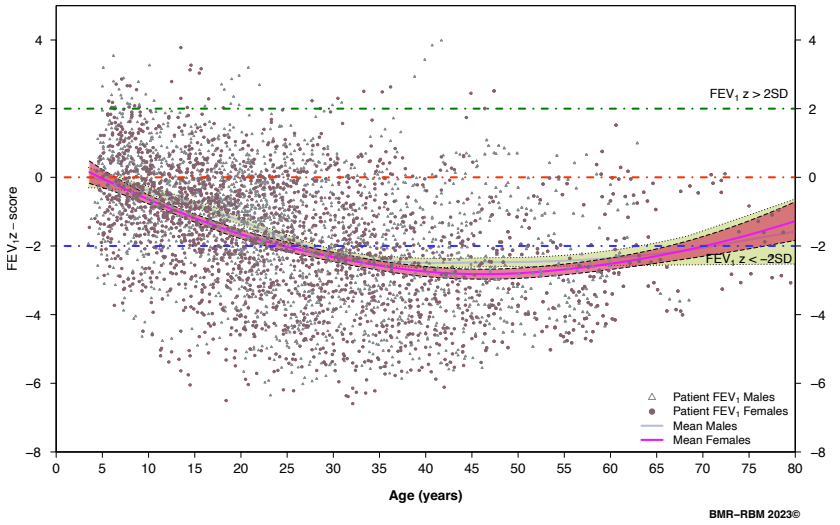


Figure 12 | Mean FEV_1 z-score by age and gender

6.2 FEV_1 CATEGORIES BY AGE GROUP

FEV_1% predicted values were divided in four classes, corresponding to different degrees of lung function impairment: normal lung function (≥ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) lung function impairment. The table 10 shows the classification for children and adults based on the data collected in 2021.

Table 10 | Proportions in each FEV_1 severity category for children and adults

Group	Children (6-17) years		Adults (≥ 18) years		Total	
	n	%	n	%	n	%
≥ 90% predicted	197	59.9	195	27.7	392	37.9
70% - 89% predicted	91	27.7	214	30.4	305	29.5
40% - 69% predicted	28	8.5	244	34.7	272	26.3
< 40% predicted	4	1.2	40	5.7	44	4.3
Missing*	9	2.7	11	1.6	20	1.9
Subtotal	*329*	*100.0*	*704*	*100.0*	*1033*	*99.9*
< 6 years	*139*				*139*	
Transplants	1		184		185	
Total	**469**		**888**		**1357**	

* Missing data number includes patients not seen

The FEV_1 was 70.0% of predicted or higher in 67.4% of the patients: in 87.6% of the children (6 – 17 years) and 58.1% of the adults (18 years and above). About 2.0% had missing FEV_1 data; mostly because the patient was not seen in 2021.

In figure 13, the mean FEV_1% predicted calculated cross-sectionally shows improving lung function in all age categories over the years.

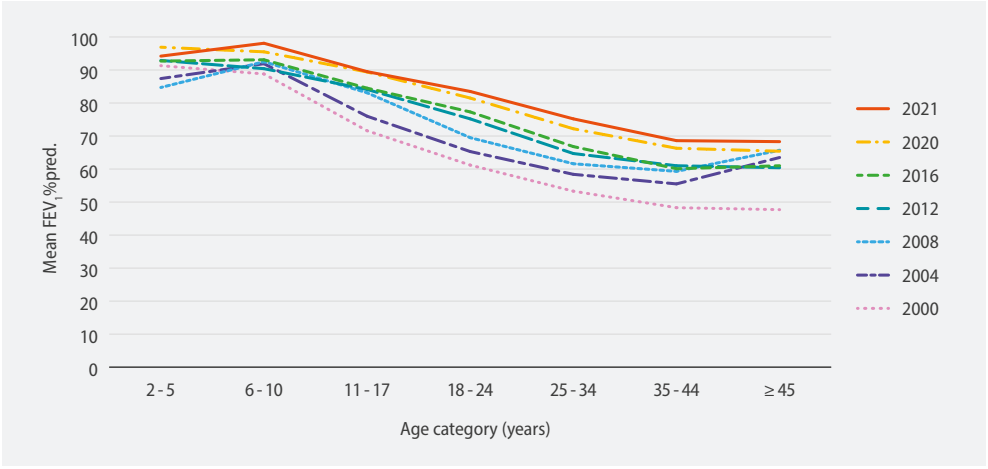


Figure 13 | Mean percentage of predicted FEV_1 by age group for selected years

In the following figure (Figure 14), the proportion of patients in each severity group over selected years is presented for children and adults separately. There has been a general increase in the proportion of children with lung function at least 90%, peaking-off in 2012, with a trend towards improvement in 2021. 59.9% of the children and 27.7% of the adults patients had FEV_1 of at least 90% in 2021. The proportion of adults with lung function > 90% has increased steadily from 11.9% in 2000 to 25.2% in 2018 and 27.7% in 2021. On the contrary, the proportion of adults with lung function below 40% has decreased since 2000, with a further decrease to 5.7% in 2021, after a plateau at about 14-15% since 2008.

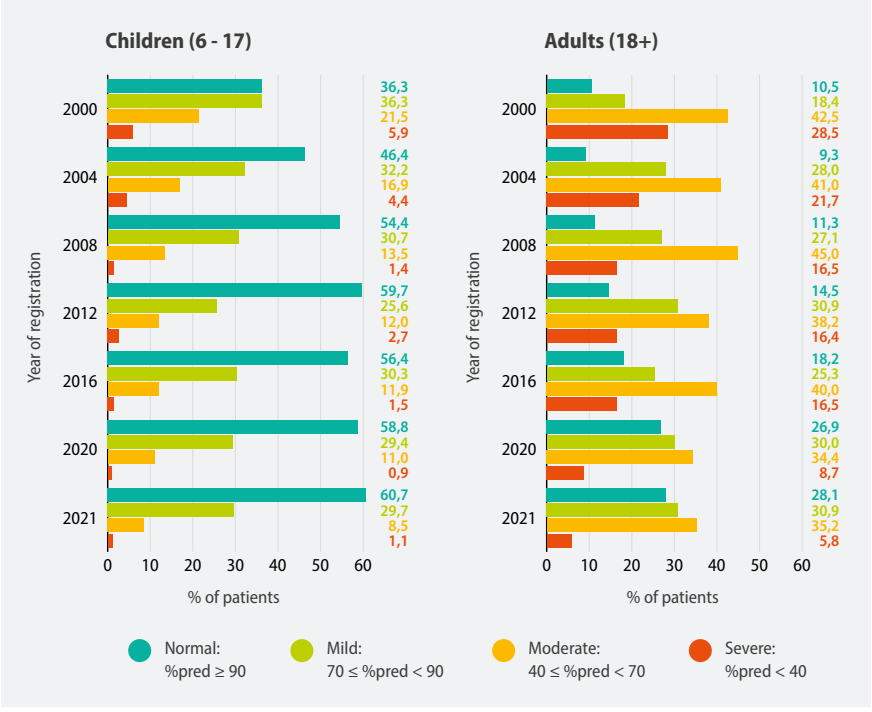


Figure 14 | FEV_1% predicted groups in children and adults for selected years

CHAPTER 7.
MICROBIOLOGY

The presence of thick mucus and impaired bacterial killing leads to inflammation and infection, and is responsible for progressive lung damage.

Bacterial colonisation occurs very early in the natural history of the disease. In children, common bacteria such as *Staphylococcus aureus* and *Haemophilus influenzae* infect the lungs [52]. Infection by *Pseudomonas aeruginosa* and sometimes *Burkholderia cepacia* complex and other gram-negative pathogens occur at a later age. The airways of patients with CF may also be chronically infected by fungi like *Aspergillus fumigatus* [53].

One of the main goals of CF care is to prevent, postpone or eradicate by all possible means, infections with the above named pathogens and to reduce the risk of chronic infection which increases respiratory morbidity and treatment burden.

In this section, we present the annual prevalence of recorded pathogens including the prevalence of chronic infections. Data from **186 transplant patients were excluded** from the respiratory microbiology analysis.

The analysis presented is based on the pathogens found at least once during the whole year (annual prevalence). The prevalence is also compared over a selected period in children and adults or by age category.

7.1 ANNUAL PREVALENCE OF ISOLATED PATHOGENS

During the year 2021, 467 children and 691 adults, i.e. 99.0% of the 1171 non-lung transplant patients, had at least one culture done. The largest proportion of those patients (81.8%) had at least four exploitable months during the year, so four culture results to identify chronic infections. Sputum samples were done in 845 patients, and throat or nose swabs in 533 patients, while 42 patients had a broncho-alveolar lavage.

The prevalence shown in table 11 and 12 refers to pathogens ever found during the year, compared between children and adults (Table 11) or with previous years (Table 12).

Table 11 | Isolated pathogens in 2021

	Children		Adults		All patients	
	n	%	n	%	n	%
Methicillin Sensitive *Staphylococcus aureus* (MSSA)	296	63.4	439	63.5	735	63.5
Haemophilus influenzae	129	27.6	83	12.0	212	18.3
Pseudomonas aeruginosa	90	19.3	296	42.8	386	33.3
Methicillin Resistant *Staphylococcus aureus* (MRSA)	9	1.9	49	7.1	58	5.0
Stenotrophomonas maltophilia	59	12.6	81	11.7	140	12.1
Achromobacter xylosoxidans	29	6.2	71	10.3	100	8.6
Burkholderia cepacia complex	8	1.7	28	4.1	36	3.1
Aspergillus spp	73	15.6	219	31.7	292	25.2
Scedosporium prolificans	1	0.2	3	0.4	4	0.3
Atypical / Non – tuberculous mycobacteria (NTM)	4	0.9	17	2.5	21	1.8
Other pathogens	199	42.8	253	39.7	452	41.0
Tested for Covid	286	61.2	388	55.1	674	57.6
Covid infection	41	14.3	79	20.4	120	17.8

Percentages are based on 1158 patients , with a culture in 2021; 467 children and 691 adults. For covid testing, all patients were used as denominator, while for covid infections, percentages are based on those who were tested.

Table 12 | Isolated pathogens 2017 - 2021

	2017		2018		2019		2020		2021	
	n	%	n	%	n	%	n	%	n	%
Methicillin Sensitive *Staphylococcus aureus* (MSSA)	701	64.1	710	64.6	697	63.2	688	61.6	735	63.5
Haemophilus influenzae	272	24.9	272	24.7	279	25.3	188	16.8	212	18.3
Pseudomonas aeruginosa	428	39.1	416	37.9	390	35.4	375	33.6	386	33.3
Methicillin Resistant *Staphylococcus aureus* (MRSA)	76	6.9	68	6.2	65	5.9	73	6.5	58	5.0
Stenotrophomonas maltophilia	133	12.2	141	12.8	135	12.2	132	11.8	140	12.1
Achromobacter xylosoxidans	124	11.3	110	10.0	98	8.9	92	8.2	100	8.6
Burkholderia cepacia complex	32	2.9	33	3.0	38	3.4	31	2.8	36	3.1
Aspergillus	339	31.0	370	33.7	310	28.1	283	25.4	292	25.2
Scedosporium spp.	10	0.9	7	0.6	3	0.3	4	0.4	4	0.3
Atypical / Non – tuberculous mycobacteria (NTM)	19	1.7	17	1.5	29	2.6	24	2.2	21	1.8
Other pathogens	358	32.7	354	32.2	452	41.0	439	39.3	465	40.2
Tested for Covid (YN)							575	50.8	674	57.6
Covid infection (YN)							41	7.1	120	17.8

Percentages are based on 1094 (2017), 1099 (2018), 1103 (2019), 1116 (2020) and 1158 (2021) patients with a culture respectively.

While the infection rate of MSSA remains quite high in all age categories, the prevalence of *Haemophilus influenzae* is higher among young children and decreases with age. As expected, the *Pseudomonas aeruginosa* infection rate increases with age, though the proportion of adults infected has decreased over the years. The prevalence of *Stenotrophomonas maltophilia* has oscillated at about 12.0% since 2012. In 2021, it was 12.1%. There had been a steady increase of the prevalence of *Achromobacter xylosoxidans* from 5.9% in 2009 to 10.7% in 2012, stabilized at about 10.0% since then - but up to 11.3% in 2017, fortunately decreasing again from 2019, with 8.6% in 2021. Similarly, despite a higher prevalence of Non-tuberculous mycobacteria in 2019, that pathogen remains infrequent, and reducing now (1.8% in 2021). Despite a higher prevalence of '*Other pathogens*' since 2019, no particular new pathogen was identified. In 2021, 674 patients (57.6%) were tested for SARS-CoV-2, from which 120 (17.8%) were infected.

The prevalence of various pathogens may differ according to the age of the patients. In the following figures, the annual prevalence of various pathogens and that of some chronic infections is presented by age category. This analysis is for those patients who had at least one culture analysed or sample taken during the year. The transplanted patients are excluded. The values may, however, be affected by low denominator in the lower age category (49 children 0 - 1y).

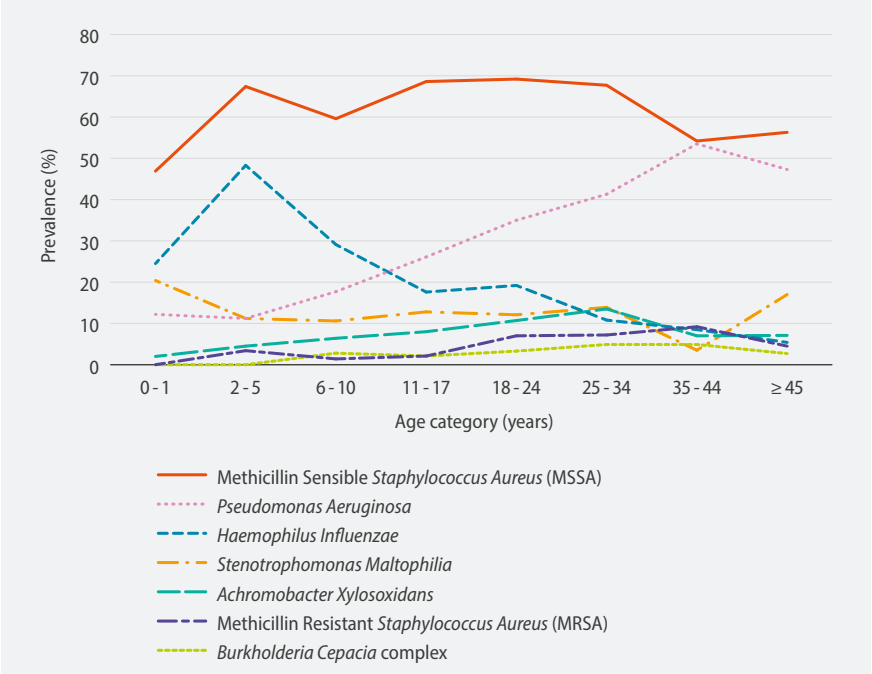


Figure 15 | Annual prevalence of selected pathogens by age group

Figures 16 - 18 show the annual prevalence of infections over selected periods. The prevalence presented is based on any positive culture for a given pathogen among those collected during the year.

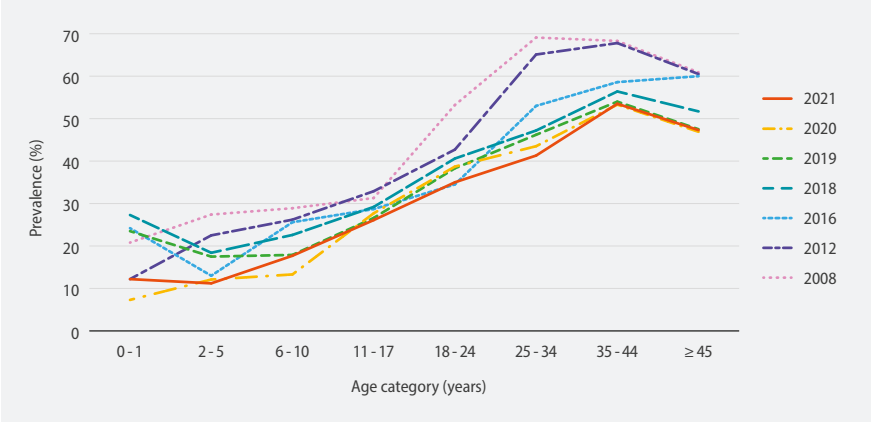


Figure 16 | Prevalence of *Pseudomonas aeruginosa* infections by year and age

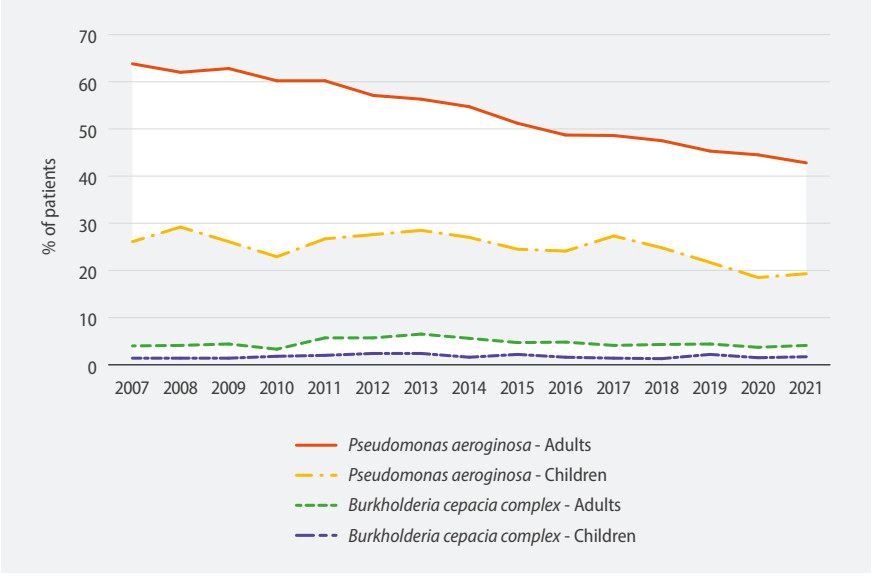


Figure 17 | Prevalence of *P. aeruginosa* and *B. cepacia* complex infections by age group and year

Note: The white area is the difference in the prevalence of *Pseudomonas aeruginosa* between children and adults. While the prevalence in children seems to be stable, the gap between prevalence in adults and children seems to be reducing.

The increase previously observed for the pathogen *Achromobacter xylosoxidans* was fortunately reversed (figure 18), with prevalence fluctuating across most age categories over the years, but still increasing among the young children.

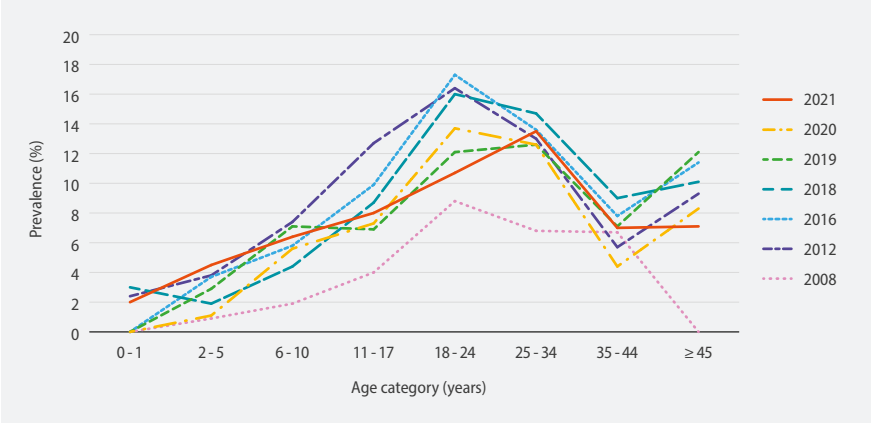


Figure 18 | Prevalence of *Achromobacter xylosoxidans* infections by age group and year

7.2 ANNUAL PREVALENCE OF CHRONIC INFECTIONS

Prevalence of chronic infection is shown in table 13, and in Figure 19 for the different age categories. About 6.9% of the children (n = 32) and 32.9% of the adults (n = 227) had chronic *Pseudomonas aeruginosa* infection.

Table 13 | Chronic infections 2017 - 2021

	2017		2018		2019		2020		2021	
	n	%	n	%	n	%	n	%	n	%
Chronic *Pseudomonas aeruginosa*	277	25.3	266	24.2	266	24.1	248	22.2	259	22.4
Chronic *Burkholderia cepacia* complex	25	2.3	24	2.2	25	2.3	24	2.2	23	2.0
Chronic *Stenotrophomonas maltophilia*	41	3.7	44	4.0	37	3.4	29	2.6	32	2.8
Chronic *Achromobacter xylosoxidans*	68	6.2	69	6.3	63	5.7	62	5.6	61	5.3
Chronic MRSA	49	4.5	47	4.3	40	3.6	38	3.4	37	3.2

Percentages are based on 1094 (2017), 1099 (2018), 1103 (2019), 1116 (2020) and 1158 (2021) patients with a culture respectively.

Chronic infection was defined according to modified Leeds criteria [54, 55]: >50% of the sputum samples positive, collected during the last 12 months, with at least 4 sputum samples during that period (taken on different calendar months). For *P. aeruginosa*, presence of anti-pseudomonas antibodies was also taken into account for determining the chronic infection status.

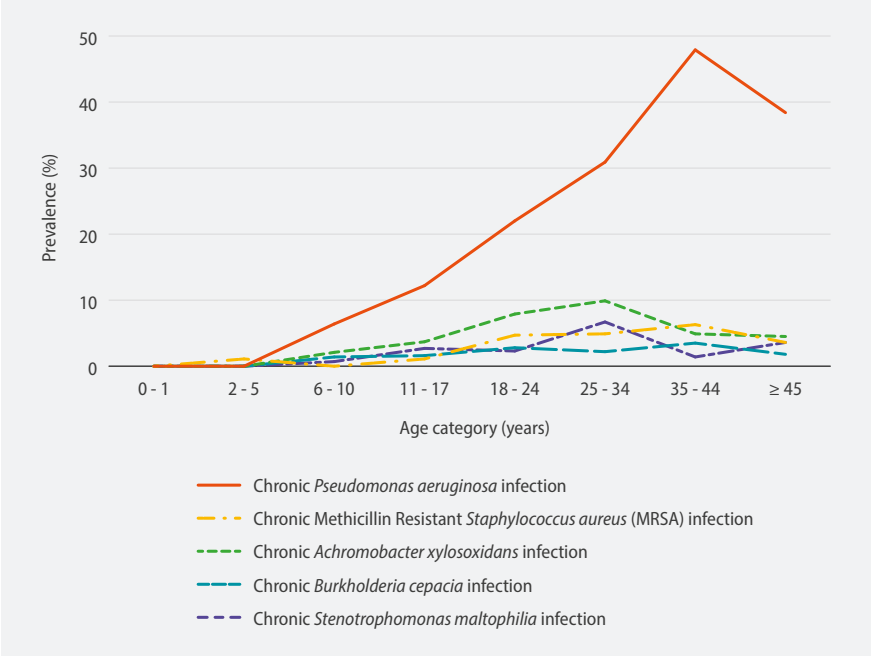


Figure 19 | Prevalence of chronic infections by age group

CHAPTER 8.
COMPLICATIONS

The defective chloride channel in CF causes a range of disturbances within the human body. Chloride channels are needed to regulate fluid exchanges at the surface of the epithelial cells. In CF, the transport through the cell wall of chloride, other ions and water are disturbed. Cystic fibrosis affects the respiratory [56], digestive [57, 58], and reproductive [59, 60] systems with variable degrees of severity. Complications in CF are mainly found in organs where mucus linings are needed (airways, intestines) and glands which need fluid to excrete their substances (pancreas, testes…).

In this section we cover the most frequent complications recorded during the year by age category. The overall prevalence is compared to the prevalence reported in previous years.

Data from 186 transplant patients were excluded from the analysis of complications.

8.1 RESPIRATORY COMPLICATIONS

Bronchiectasis is a permanent enlargement and obstruction of the airway walls, visible on a CT scan.

Nasal polyps (requiring surgery): In patients with CF, chronic infections of the upper airways (chronic sinusitis) may cause the formation of nasal polyps or mucosal overgrowths. They are responsible for nasal obstruction.

Allergic bronchopulmonary aspergillosis (ABPA): ABPA is an allergic reaction to *Aspergillus fumigatus*, a fungus that can colonize the airways of people with CF [61]. Diagnosis is not always straightforward as many symptoms of ABPA (cough, wheezing, shortness of breath and decline in lung function) are common symptoms of CF lung disease. Diagnosis relies on a combination of the clinical picture, blood tests, lung function and imaging.

Haemoptysis: When the tissue damage within the bronchi includes a blood vessel, the person with CF is coughing up blood. Haemoptysis is mild in

most cases, but sometimes the bleeding is so massive (> 250 cc/24h) that a therapeutic embolization of the bleeding vessel may be indicated.

A **pneumothorax** occurs when air reaches the vacuum of the pleural space, mainly caused by destruction of the alveoli causing the leakage of air. This complication is more common in adults who have more advanced lung disease [62, 63].

Table 14 | Prevalence of respiratory complications

Complication	2017		2018		2019		2020		2021	
	n	%	n	%	n	%	n	%	n	%
Bronchiectasis*	311	72.0	329	78.1	326	73.8	366	75.9	344	74.9
Nasal polyps	190	16.7	134	12.1	55	4.9	106	9.4	97	8.3
Allergic Bronchopulmonary Aspergillosis (ABPA)	80	7.0	97	8.7	104	9.3	101	8.9	93	7.9
Massive haemoptysis	5	0.4	10	0.9	9	0.8	20	1.8	16	1.4
Massive haemoptysis requiring embolization	3	0.3	4	0.4	4	0.4	12	1.1	6	0.5
Pneumothorax	2	0.2	4	0.4	4	0.4	1	0.1	1	0.1

Percentages are based on 1136 (2017), 1112 (2018), 1114 (2019), 1131 (2020) and 1171 (2021) non-transplant patients respectively.
*Only for patients with a CT scan done (161 children and 298 adults for 2021).

In this analysis, complications data from 467 children and 704 adults were used. Bronchiectasis was reported in 79 (49.1%) children and 265 (88.9%) adults who had a CT scan during the year. ABPA is also one of the most frequent major respiratory complications. In 2021, ABPA was reported in 24 (5.1%) children and 69 (9.8%) adults.

8.2 GASTRO-INTESTINAL AND ENDOCRINOLOGIC COMPLICATIONS

Exocrine pancreatic insufficiency: Pancreatic enzymes are needed to digest fat and proteins. Pancreatic insufficiency is the inability of the pancreas to produce and transport enough enzymes to the duodenum to digest fat and proteins resulting in malabsorption with steatorrhea (fatty stools), malnutrition and a shortage of fat-soluble vitamins (ADEK). A small proportion of patients with CF remain pancreatic sufficient (10-15%); acute pancreatitis may occur.

CF-related diabetes (CFRD) and Impaired Glucose Tolerance (IGT): Insulin is produced in the endocrine part of the pancreas. It is a hormone which maintains the balance of sugar in blood. The malfunctioning of the endocrine part of the

pancreas by fibrosis leads to an insufficiency of the secretion of insulin, leading to impaired glucose tolerance, which may lead to diabetes.

Liver disease: CF patients also present with defective CFTR protein in their biliary tract, and gall stones may develop. Some patients develop liver disease leading to cirrhosis (replacement of the liver tissue by fibrosis). **Cirrhosis** may be complicated by **portal hypertension** and, in rare cases, a liver transplant is required.

Distal intestinal Obstruction syndrome (DIOS): The intestinal epithelial cells featuring defective chloride channels produce thick intestinal mucus which, in combination with stools and undigested food residues, can cause intestinal obstruction. DIOS is especially found in the terminal ileum and caecum. It can cause acute abdominal pain and, if left untreated, it can progress to a complete bowel obstruction with vomiting. DIOS usually responds to medical treatment but in a few cases a surgical intervention may be required.

***Clostridium difficile* infection** may occur after repeated antibiotic treatments, and consecutive destruction of the normal intestinal flora, causing diarrhoea or colitis.

Table 15 | Prevalence of gastro-intestinal and endocrine complications

Complication	2017		2018		2019		2020		2021	
	n	%	n	%	n	%	n	%	n	%
Exocrine pancreatic Insufficiency	917	80.7	901	81.0	895	80.3	920	81.3	946	80.8
Acute pancreatitis	14	1.2	11	1.0	12	1.1	14	1.2	10	0.9
CF-related diabetes (CFRD)	212	18.7	208	18.7	203	18.2	203	17.9	218	18.6
Impaired Glucose Tolerance (IGT)	72	6.3	57	5.1	108	9.7	95	8.4	89	7.6
OGTT this year*							304	26.9	333	28.4
Cirrhosis with portal hypertension	40	3.5	46	4.1	51	4.6	46	4.1	51	4.4
Intestinal obstruction (surgery)	6	0.5	5	0.4	9	0.8	40	3.5	47	4.0
Intestinal obstruction (no surgery)	57	5.0	27	2.4	32	2.9	9	0.8	3	0.3
Clostridium infection (treatment needed)	11	1.0	9	0.8	12	1.1	15	1.3	9	0.8

Percentages are based on 1136 (2017), 1112 (2018), 1114 (2019), 1131 (2020) and 1171 (2021) non-transplant patients respectively.

In non-transplant patients, the data shows that 401 (85.9%) children and 545 (77.4%) adults are pancreatic insufficient. CFRD was reported in 19 (4.1%) children and 199 (28.3%) adults. IGT on the other hand was reported in 13 (2.8%) children and 76 (10.8%) adults.

8.3 MISCELLANEOUS COMPLICATIONS

Osteopenia and osteoporosis: Osteopenia and osteoporosis which is the result of a progressive loss of the bone mass are more frequent and are seen earlier in people with CF due to various risk factors like malabsorption of vitamins D, use of glucocorticoids, chronic inflammation… Osteopenia is diagnosed as the lowest z-score on Dual X-ray absorptiometry (DXA) between -1.0 and -2.5, and Osteoporosis with the lowest z-score on DXA < -2.5.

CF-related arthritis/arthropathy: Patients with advanced lung disease sometimes develop painful inflammation of joints. The exact cause is not known and regression of joint symptoms is usually seen when respiratory disease is stabilized.

Cancer: Patients with CF are at increased risk of gastrointestinal cancer.

Table 16 | Other complications reported

	2017		2018		2019		2020		2021	
Complication	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Osteopenia*	151	32.7	173	34.9	222	42.1	222	41.0	246	42.2
Osteoporosis*	49	10.6	43	8.7	39	7.4	43	7.9	47	8.1
CF-related arthritis / arthropathy	20	1.8	21	1.9	25	2.2	39	3.4	25	2.1
Cancer	3	0.3	3	0.3	3	0.3	6	0.5	6	0.5
Hypertension requiring treatment	24	2.1	29	2.6	37	3.3	43	3.8	40	3.4
Others	122	10.7	113	10.2	133	11.9	208	18.4	232	19.8

Percentages are based on 1136 (2017),1112 (2018), 1114 (2019), 1131 (2020)and 1171 (2021) non-transplant patients respectively.
*Only for patients with a DXA within last five years (95 children and 481 adults for 2021).

CHAPTER 9.
THERAPY, MEDICATION AND HOSPITALIZATION

To date, despite advances in the development of CFTR therapy, no definitive treatment for CF exists. Treatment of the disease is therefore mostly based on preventing or reducing symptoms in order to avoid complications or to stabilize them. Thanks to those preventive and symptomatic treatments, a steady improvement of the health status is obtained together with a better life expectancy.

In this section, the most common treatments and therapy used in 2021 are presented. An evolution of the proportion of patients hospitalized by age category for selected years is also presented. **This analysis excludes data from the transplant patients.**

Except for anti-conceptive therapy, the percentages are based on 467 children and 704 adults from a total of 1171 non transplant patients.

9.1 VISITS TO CF CARE CENTERS AND HOSPITALIZATION

In 2021, most of the patients (1065, 90.1%) (444 children, 94.7%; 621 adults, 87.2%) had a minimum of the four recommended visits to a CF reference centre during the year.

Every year, about half of the patients with CF are hospitalized, mostly for the treatment of a worsening pulmonary status (pulmonary exacerbations) requiring intravenous antibiotics.

The figure 20 shows the number of days of hospitalization. In 2021, 57.1% of the patients were not hospitalized: 61.8% of the children (n = 288) and 53.7% of the adults (n = 348). A small proportion (24 patients, 2.2%), was hospitalized for over two months. The median duration of hospitalization was about two weeks for both adults and children.
While the proportion of adults hospitalized more than two weeks keeps decreasing over the years, from 32.7% in 2000 to 12.8% in 2021, this started to be the case for children too, from 19.2% in 2000, and 16.9% in 2019, to 11.3% in 2021 (Figure 21).

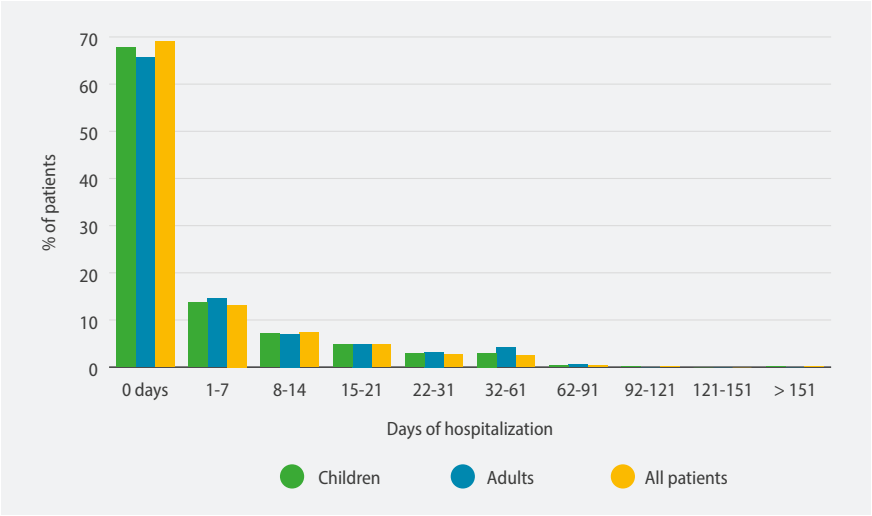


Figure 20 | Number of hospitalization days

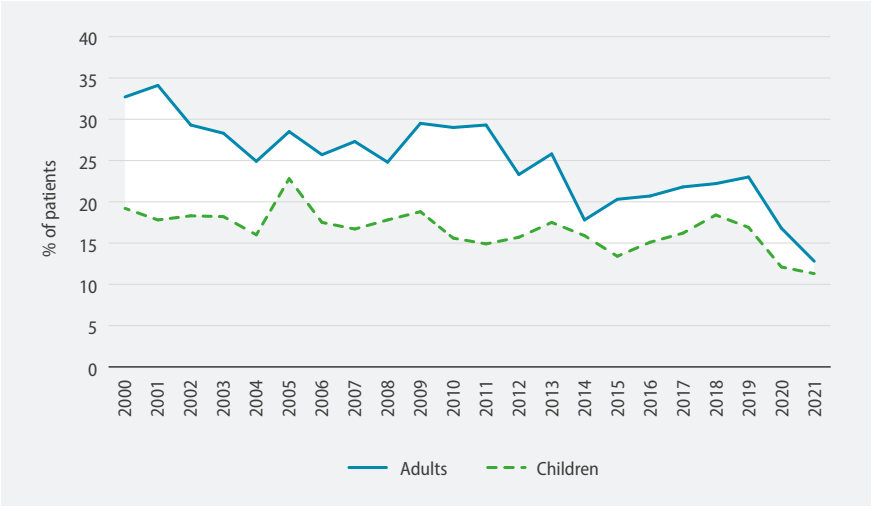


Figure 21 | Proportion hospitalized for more than two weeks by age and year

9.2 RESPIRATORY THERAPIES

To prevent and treat respiratory infections: Because mucus is stuck within the bronchi, evacuating mucus is one of the most important interventions. This is the reason why a person with CF has regular chest physiotherapy. Most patients also learn the technique of autogenic drainage where the patients, through breathing techniques, perform drainage by themselves.

Different types of inhaled medication are used to treat the symptoms of CF. Maintenance inhaled medications include mucolytics that thin the sticky airway secretions. These therapeutic agents include rhDNase (Dornase α) or hypertonic saline. Bronchodilators are given to dilate the bronchi. Inhaled antibiotics are used to treat, but also prevent or postpone infection. In advanced lung disease, oxygen is needed [64].

Inflammation caused by repeated infections plays an important role in the progression of lung injury. This explains the use of anti-inflammatories such as azithromycin, inhaled corticoids or other anti-inflammatory drugs as complementary treatment.

Table 17 | Physiotherapy, inhalation therapy, oral anti-inflammatories and antibiotics

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Regular chest physiotherapy	467	100.0	703	99.9	1170	99.9
Antibiotics	401	85.9	550	78.1	951	81.2
Oral only	285	61.0	282	40.1	567	48.4
IV only	6	1.3	24	3.4	30	2.6
Oral and IV	105	22.5	172	24.4	277	23.7
Inhaled antibiotics	196	42.0	383	54.4	579	49.4
Inhalation therapy (excluding antibiotics)	462	98.9	660	93.8	1122	95.8
RhDNase	418	89.5	585	83.1	1003	85.7
Other mucolytics	50	10.7	53	7.5	103	8.8
Hypertonic saline	319	68.3	470	66.8	789	67.4
Bronchodilators	343	73.4	539	76.6	882	75.3
Corticosteroids	175	37.5	442	62.8	617	52.7
Oral anti-inflammatories	223	47.8	430	61.1	653	55.8
Azithromycin	213	45.6	411	58.4	624	53.3
Systemic corticosteroids	4	0.9	25	3.6	29	2.5
NSAID	3	0.6	26	3.7	29	2.5
Leucotriens	30	6.4	102	14.5	132	11.3
Oxygen therapy	4	0.9	18	2.6	22	1.9

The percentages are based on 467 children and 704 adults for a total of 1171 non-transplant patients.

9.3 GASTRO-INTESTINAL AND NUTRITIONAL THERAPIES

Optimizing the nutritional status: The nutritional status of a patient is strongly correlated with disease severity. Therefore, every person with CF should maintain a well-balanced high-calorie and high-fat diet. Most individuals with CF are pancreatic insufficient [57] and must take pancreatic enzymes with each meal to sufficiently digest food. ADEK vitamin supplements are also administered routinely. Some people with CF can only achieve an adequate nutritional status by receiving supplemental feedings given by a tube placed into the stomach (enteral feeding) or intravenously (parenteral feeding). Medications that inhibit the gastric acid secretion (proton pump inhibitors or H2 blockers) are given to treat symptoms of gastro-oesophageal reflux or to improve the efficacy of pancreatic enzymes in a higher pH environment. Prokinetics are medications that increase the tone of the lower oesophagus sphincter and enhance the gastrointestinal motility resulting in an acceleration of gastric emptying.

Table 18 | Digestive and nutritional therapies

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Pancreatic enzymes	401	85.9	549	78.0	950	81.1
Proton pump inhibitor and/or H2 receptor blocker	206	44.1	354	50.3	560	47.8
Ursodeoxycholic acid	89	19.1	135	19.2	224	19.1
Enteral feeding	24	5.1	9	1.3	33	2.8
Parenteral feeding	2	0.4	1	0.1	3	0.3
Gastrotomy tube	33	7.1	12	1.7	45	3.8

The percentages are based on 467 children and 704 adults for a total of 1171 non-transplant patients.

9.4 OTHER TREATMENTS

Monitoring onset of complications and appropriate therapeutic interventions: Possible complications of the disease need to be regularly monitored. When clinical, biological or imaging findings point towards liver disease, ursodeoxycholic acid is started. This hydrophilic bile acid normally present in human bile stimulates the biliary secretion so that the bile is less thick. Depending on complications, other medications are prescribed such as insulin therapy when a patient develops CF related diabetes, or bisphosphonates for osteoporosis. The treatment burden for CF patients is high. Most CF patients several hours every day performing therapies. This imposes a substantial burden on their personal life [65].

Table 19 | Other treatments

Treatment	Children		Adults		Total	
	n	%	n	%	n	%
Insulin therapy	16	3.4	142	20.2	158	13.5
Oral Therapy for Diabetes	1	0.2	31	4.4	32	2.7
Diet only for Diabetes	13	2.8	98	13.9	111	9.5
Bisphosphonates			28	4.0	28	2.4
Anti-conceptive therapy (females 12 and over)	13	16.7	130	46.6	143	40.1
CFTR Modulating Therapy	196	42.0	433	61.5	629	53.7

The percentages are based on 467 children and 704 adults for a total of 1171 non-transplant patients.
* The percentages are based on 91 children and 311 adults for a total of 402 female patients aged 12y and above.

Note: Out of 1171 non-transplant patients, 225 had CFRD. Among these, 149 (66.2%) used insulin therapy only, 15 (10.3%) used only oral therapy for diabetes while 13 (5.7%) patients used both oral therapy for diabetes and insulin therapy. In 49 (21.8%) patients with CFRD, treatment was based on diet only.

In Table 20, the frequency of use for the specific drugs currently on the market is based on the number of patients eligible based on CFTR mutations and age, as defined in the EMA approval in December 2021. It doesn't take contraindications or personal situation into account.
A little bit more than half of the patients eligible for ivacaftor were using it (59.0%), or participated in a blinded clinical trial. Among the patients not taking it while eligible in theory, most were <2y, had a transplant, and/or R117H, that are exclusion criteria for reimbursement of Kalydeco® in Belgium.
The frequency of use for lumacaftor/ivacaftor (17.7% of eligible patients) and tezacaftor/ivacaftor (48.9%) increased due to both drugs being reimbursed from April 2021; Orkambi® only for children 2-11y, and Symkevi® from 12y

onwards. The use of elexacaftor/tezacaftor/ivacaftor was no more limited to open label studies, as the medicine was authorized for compassionate use in Belgium from 2020 though not yet widely available to all eligible patients.

Table 20 | CFTR modulators

CFTR modulator	Children		Adults		Total	
	n	n eligible	n	n eligible	n	n eligible
Kalydeco® (Ivacaftor)	16	61.5	30	57.7	46	59.0
Orkambi® (Lumacaftor / Ivacaftor)	119	63.3	33	11.3	152	31.7
Symkevi® (Tezacaftor / Ivacaftor)	51	30.9	220	58.4	271	50.0
Kaftrio® (Elexacaftor / Tezacaftor / Ivacaftor)	10	3.7	149	24.7	159	18.2
Blinded clinical trial			7		7	

*For specific CFTR modulators, % is based on the number of patient eligible in theory, based on the European Medicines Agency authorisation conditions on 31/12/2021), with mutations and age at 31/12/2021: Ivacaftor (Kalydeco®) for patients with gating mutations from 4 months [8]. Lumacaftor/ivacaftor (Orkambi®) for patients homozygous for F508del, from 2y [9]. Tezacaftor/ivacaftor (Symkevi®) for patients homozygous for F508del or heterozygous F508del with a residual func-tion mutation, from 6y [10]. Elexacaftor/tzeacaftor/ivacaftor for patients with at least one F508del mutation, from 6y [11].
There were 78 patients eligible for Kalydeco®; 26 children and 52 adults, 479 eligible for Orkambil®; 188 children and 291 adults, 542 eligible for Symkevi®; 165 children and 377 adults, and 873 eligible for Kaftrio®; 270 children and 603 adults.

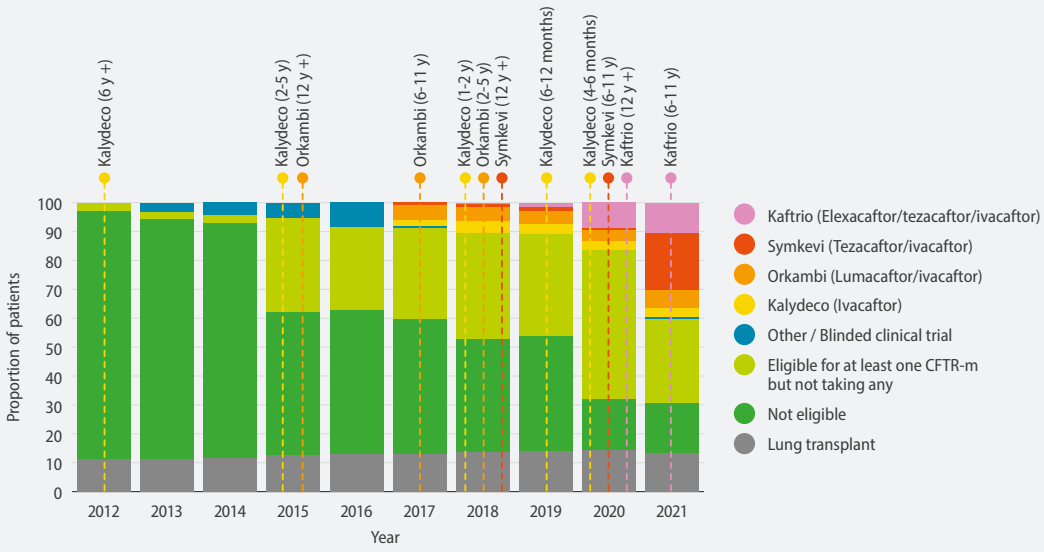


Figure 22 | Proportion that used and/or are eligible to CFTR modulators

Eligibility criteria based on the European Medicines Agency authorisation conditions on 31/12/year.
No data was collected for use of CFTRm in 2012; in 2013-2016, only use of any CFTRm was collected, so CFTRm use is included as "Other / Blinded clinical trial".

9.5 INTRAVENOUS ANTIBIOTICS

In 2021, 26.0% (n = 305) of the 1171 non-transplant patients received IV antibiotics; 23.3% (n = 109) of the children and 27.8% (n = 196) of the adults. Figure 22 shows the proportion that received IV antibiotics at home and/or in hospital in 2020 (top) compared to 2021 (bottom). IV antibiotics administered at home was rare in children younger than 10 years. Around a quarter (23.3%) of the adults received IV antibiotics in the hospital (either in hospital only or both at home and in hospital). A minority of the patients (15.5%) used IV antibiotics for over two weeks, much less than in 2019 (24.5%). This was slightly lesser in children (12.4%) than in adults (17.7%).

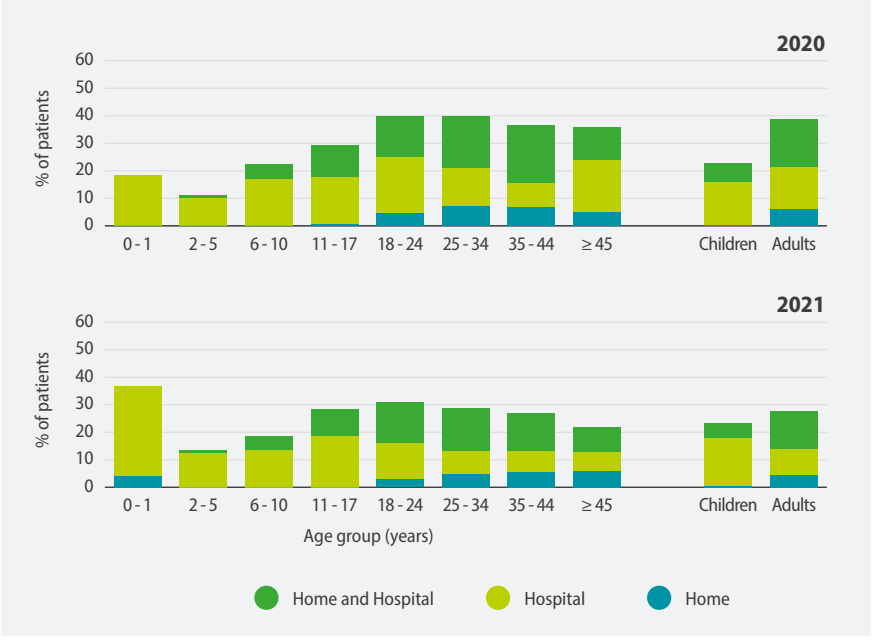


Figure 23 | Proportion that used IV antibiotic treatment by age category

9.6 ORAL ANTIBIOTICS

Figure 23 shows the cumulative days of oral antibiotics used in 2020 (top) and compared to 2021 (bottom). Unknown days or missing data were excluded from this analysis. In 2021, 27.8% of the patients did not take any oral antibiotics; 16.5% of the children (n = 77) and 35.3% of the adults (n = 248). Around a quarter of both the children (24.0%) and the adults (23.2%) used oral antibiotics for over six months (excluding azithromycin).

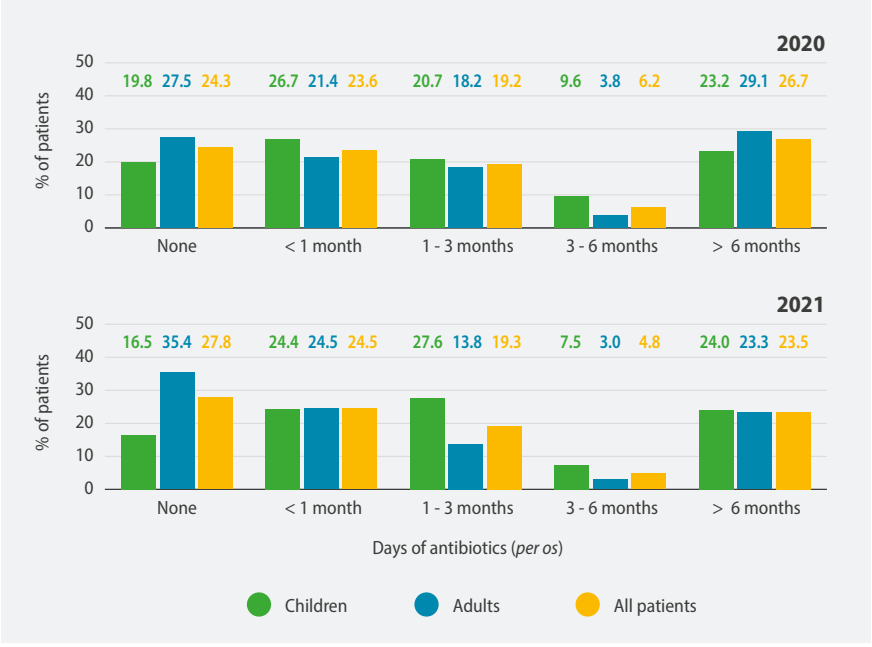


Figure 24 | Days of oral antibiotics

CHAPTER 10.
TRANSPLANTS AND CF

When a patient with CF develops severe and progressive lung disease, lung transplantation may become an option. However, like other major surgeries, lung transplantation involves significant risks. A lung transplant is indicated only for patients who have exhausted all other forms of conventional medical treatment and whose short term survival is compromised. For these patients, lung transplantation may offer prolonged survival and an improved quality of life; in some cases even a 'new' life.

The actuarial survival after lung transplantation for CF is steadily improving. At present the reported actuarial survival rate is more than 70% at 3 years and more than 45% at 10 years after primary transplant [66]. The longest surviving patients in the registry were transplanted more than 20 years ago.

The first (heart)-lung transplant in a Belgian patient with CF was performed in 1988. Since this time about 324 patients with CF[5] (286 reported in the CF registry) have received a (heart/liver/kidney)-lung transplant and approximately 15 lung transplants are now performed for CF each year, with a decrease during the COVID-19 pandemic. A few patients with CF will need other types of transplantations such as liver transplantation for end-stage CF-related liver cirrhosis, or renal transplantation for end-stage renal disease because of diabetes, antibiotic toxicity or the toxicity of immunosuppressive drugs required after lung transplantation.

This is a short analysis of data concerning the transplant patients. It includes a table with all transplants ever reported in the registry. This table shows the type and year of transplant and also the number of patients presumed alive by the time of data collection 2021, categorized by the year of first transplant.

5 Source: Communication from Eurotransplant International Foundation

10.1 TRANSPLANT STATUS

Our records show that since inception of the registry in 1998, at least **307** patients, **146** males and **161** females, have benefited from transplantation; lung and/or other organ, either single or multiple. In 2021, 21 patients were on the waiting list (1 of them with already a transplant), 20 had been evaluated but were not on the list, 3 patients declined the transplant while 2 patients were refused by the transplant centre.

The age at the first transplant was estimated using the last consultation in the year of transplant where available or the last day of the year if the former was missing. The mean (SD) and median (range) age of the transplant patients in the year of the first transplant was 29.1 (10.3) and 28.0 years (0.7 – 60.6) respectively. About 10.1% (31 patients) had their first transplant done before age 18 years.

In 2021, there were **200** patients reported living with a transplant. The mean (SD) and median (range) age of the transplant patients reported or assumed as alive in January 2021 was 40.3 (10.3) and 40.1 (2.6 – 69.1) years respectively at the end of 2021. 93 were male while 107 were female, while 98.5% of the transplanted patients in the 2021 data were adults. Four transplanted patients died in 2021.

The data presented in table 20 concern all recorded transplants in the registry and also data of patients reported alive by January 2021 (the numbers in the far right column). Slight differences may be noted with previous reports as we seek to consolidate the transplant data yearly. In the table, the numbers of transplants performed do not add up to the number of patients, as a patient can have several transplantations.

Multiple transplants are counted as separate transplant occasions. A total of 351 transplants in 307 patients are so far reported in the registry. There are 39 patients who had a transplant on more than one occasion, for a lung re-transplantation or for a second organ.

In figure 24, the total number of patients recorded each year is presented as a proportion of children and adults, with and without a transplant. While the proportion of adults is increasing, so is the number of adult patients living with a transplant.

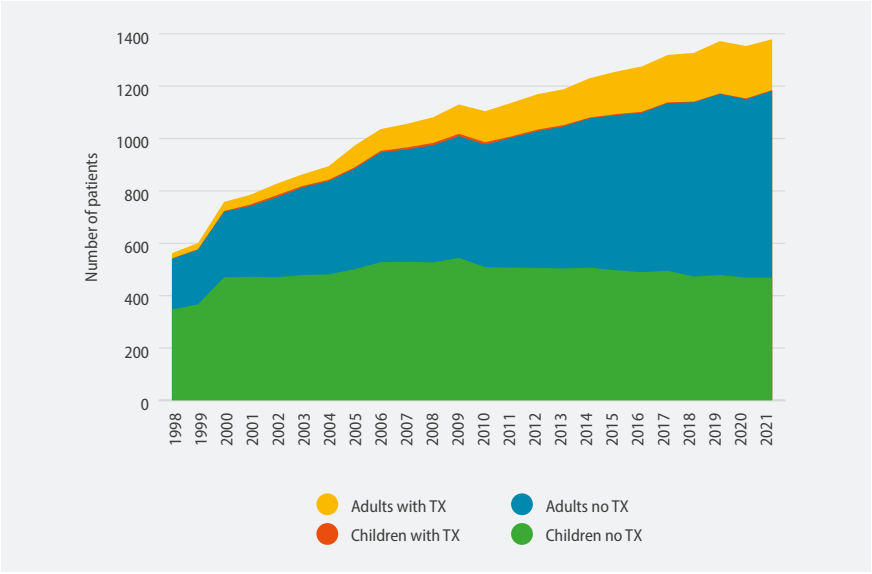


Figure 25 | Number of patients by age and transplant status

10.2 TYPE OF TRANSPLANT

The most frequent transplant done is the lung transplant, either alone or in combination with a liver or heart. So far, 275 isolated lung transplants have been carried out.

Table 21 | Type of transplant by year

	Type of transplant									Totals	
Year	Lung	Lung-Heart	Lung-Liver	Liver	Kidney	Liver-Kidney	Lung-Kidney	Heart	Lung-Liver-Kidney	Transplants performed	Patients Alive*
1991		2								2	
1992											
1993		2								2	
1994		3								3	1
1995	3	3		1						7	3
1996		1								1	
1997	1	3								4	
1998	9	1								10	1
1999	5									5	2
2000	10									10	2
2001	13		1	4						18	7
2002	10			2						12	3
2003	9			1						10	4
2004	11									11	4
2005	10		1	3						14	8
2006	13			1	1			1		16	6
2007	16			1	1					18	5
2008	16				3					19	11
2009	10			1		1				12	9
2010	13		2	1						16	10
2011	15				1		1			17	12
2012	12									12	8
2013	13				3					16	10
2014	7				4					11	11
2015	15		2		1		1			19	17
2016	18			2						20	18
2017	10			1	2		1			14	11
2018	12		2		3					17	17
2019	16		3	1						20	17
2020	6			1	1				1	9	9
2021	**2**			**1**	**2**	**1**				**6**	**6**
Total	**275**	**15**	**11**	**21**	**22**	**2**	**3**	**1**	**1**	**351**	
Alive**	**170**	**1**	**8**	**13**	**17**	**2**	**1**		**1**	**-**	**212**

* Number of patients assumed alive by beginning of 2021 by transplant year considering the first transplant; including 12 patients with an history of transplantation but without a record in 2021.
**Number of patients assumed alive by beginning of 2021 considering type of first transplant; including 12 patients with an history of transplantation but without a record in 2021.

CHAPTER 11.
REPORTED DEATHS

This section has a summary of data on the deaths reported to the registry since inception in 1998. The number of deaths is also classified into age groups with information on the primary cause of death given in the latter part. Note that the listed causes of death are not mutually exclusive.

The data are updated each year from centre reports with delays of up to two years noted in the confirmation of some data. In some centres, this background data are automatically updated using the ConsultRN module by linking the CF registry data collection to the national registry database. The numbers may thus differ slightly from those previously reported due to this automatic update.

11.1 AGE AT DEATH

The data in the registry show that there have been 220 reported deaths since inception of the registry, 114 male and 106 female. Twenty (9.1%) of the deaths were in children (below 18 years) while 9 (4.1%) of the deaths were in children younger than ten years. The mean (SD) and median (IQR) age at death for all reported cases is 33.0 (14.3) and 30.4 (17.9) respectively, with the youngest at 0.6 years and the oldest case at 76.9 years. The table below shows the year by age category at death for confirmed cases. In the last ten years, 11.0% of the deaths were reported in children and young adults (up to 20y); it is lower than in the earlier years (29.8% for the deaths in 1998 - 2008).

Table 22 | Categorized age at death

Year	Age at death																
	0 - 4	5 - 10	11 - 14	15 - 20	21 - 24	25 - 30	31 - 34	35 - 40	41 - 44	45 - 50	51 - 54	55 - 60	61 - 64	65 - 70	71 - 74	75 - 80	Total
1998	1			2		1	1										5
1999				5	2	4		1									12
2000				1	2	1	3	2									9
2001		2		1	3	2		2									10
2002					1	3	4	2				1					11
2003		1	1	3	4	3	1	1		1							15
2004				2	2	3	1		1								9
2005	1				1	1											3
2006	1			2				2	1								6
2007		1	1	1		2		1	1	1							8
2008				2		3				1							6
2009			1	1	2	2	2		1	1							10
2010					3		2				1	1					7
2011		1			2	3	1		1	1							9
2012		1		1	1	2	2	2	1		1						11
2013				1	2	3											6
2014			1			2	1	4						1		1	10
2015					1	3	2	3	1	1	1	3					15
2016				2		3	1	1	2								9
2017			1	1		2		1						1			6
2018				1		2	2	1	2	2	2	2		2			16
2019						1		1	1	2		1					6
2020				2			1	1	1		2	1			2		10
2021							**2**	**1**	**3**	**2**		**1**		**2**			**11**
Total	**3**	**6**	**5**	**28**	**26**	**46**	**26**	**26**	**16**	**12**	**7**	**10**		**6**	**2**	**1**	**220**

The figure 25 shows the number of reported and confirmed deaths in the CF registry since 1998. Most of the deceased patients were in the age category 25 – 30 years.

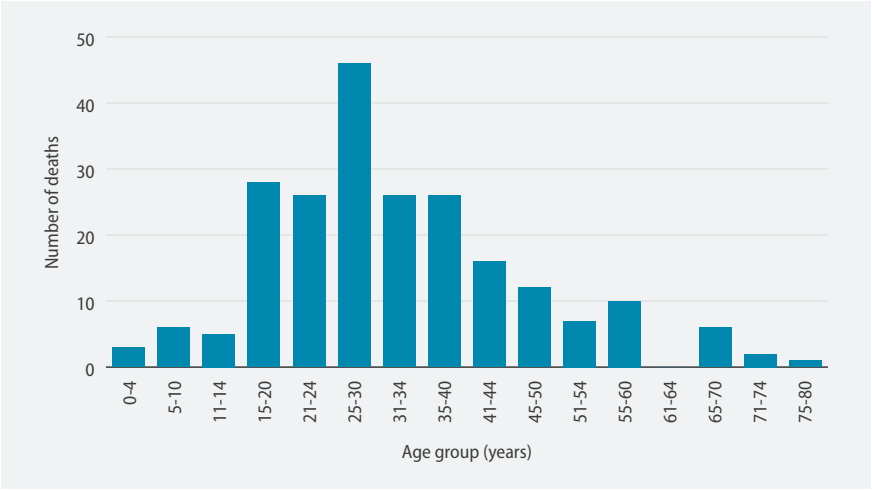


Figure 26 | Reported deaths by age category

11.2 PRIMARY CAUSE OF DEATH

Most of the reported deaths are attributable to multiple causes, some not listed in the table 23. The most common primary causes of death are associated with the respiratory system or are as a result of post-transplant complications. The other CF-related causes of death include and are not limited to: septic shock, multi-organ failure, terminal renal insufficiency, intoxication, hypoglycaemic coma, and euthanasia.

Table 23 | Primary causes of death for reported cases

Cause of death	n	%*
Respiratory	97	44.1
Transplant	55	25
Other	34	15.5
Cancer	10	4.5
Cardiac	9	4.1
Liver	6	2.7
Kidney	6	2.7
Suicide	3	1.4
Trauma	2	0.9
Other non-CF	2	0.9
Other CF related	2	0.9
Unknown + missing	33	15

*based on the total reported deaths.
Causes of death are not mutually exclusive and these percentages are attributable to the specific cause of death.

CHAPTER 12.
EDUCATION AND EMPLOYMENT

People with CF continue to live longer. According to the registry data, the median patient age has increased from 14.9 years in 1998 to about 24.5 years in 2021 suggesting better life expectancy. This introduces new challenges and expectations alike. Despite their therapy burden, they are now studying, graduating and taking up a career either part-time or even full-time. They are thus taking up roles in society that were previously less attainable.

This section contains a summary of social and economic data, including education level of the people with CF registered in 2021. It also gives information on social allowances and employment status. All patients with substantial data, including those with a transplant are included in this analysis.

12.1 EDUCATION

School attendance includes traditional school as well as hospital or home lessons, for temporary or long-term programs. Less than 3% of school-aged children (≥ 3 years) were not schooled at all in 2021, with most being <5 years, so no mandatory school), and there were similarly very few adults who left school before 18y without their diploma.

Table 24 | Education level

	Children		Adults		Total	
Education level	**n**	**%**	**n**	**%**	**n**	**%**
Below school attendance age*	69	14.7			69	5.1
No school	12	2.6	7	0.8	47	3.5
Regular school / education attendance	387	82.7**	163	18.3	550	40.5
Has finished school/education			718	79.2	690	50.8
Unknown			3	0.3	2	0.1
Missing	4		17		21	
Total	**472**	**100.0**	**907**	**100.0**	**1379**	**100.0**

* Children below age 3 years were considered below school attendance age.
** 97.0% of children > 3y with information on school status.

12.2 SOCIAL ALLOWANCES AND EMPLOYMENT

Patients can benefit from financial support from various sources. Care givers of children recognized with a disability can receive an additional child allowance. Adults without income or unable to have sufficient income can get income support from the government (if recognized as disable), or a disability allowance from the social security (if recognized as ill, after being professionally active). After retirement age (usually 65y), they perceive a pension like any other retiree. The integration allowance is an additional support for increased daily costs linked to the disability. The preferential tariff allows a reduction on health care costs and other various public services, and is attributed to people with income from some social security sources.

Table 25 | Social allowances or benefits and employment

	Children		Adults	
	n	%	n	%
DESCRIPTION				
Additional child allowance	417	88.3	104	11.5
Income support (in adults)			205	22.6
Disability allowance	1	0.2	197	21.7
Pension allowance (in adults)			16	1.8
Integration support (in adults)			378	41.7
Preferential tariff (in adults)			538	59.3
EMPLOYMENT*				
Yes	2	3.0	421	47.1
No	64	97.0	472	52.9

* data include 163 adults still in school.

Amongst the 423 patients who said they were employed, 246 (58.4%) worked full time, 161 (38.2%) part-time, and unknown for 14 patients.

CHAPTER 13.
CF AND FERTILITY

With the improving trend in life-expectancy for people with CF, it is increasingly clear that social life and expectations other than education and employment come into play. Infertility in men with CF mainly arises from the failure of the vas deferens to develop properly [67]. A very small number (2 – 3%) are fertile [68, 69]. Many men with CF have moved into adolescence without being counselled on their probable infertility [70]. This issue, including other aspects of their sexual functioning, could be included and discussed openly during adolescence or, at the latest, in a transition care program as they move from the paediatric clinic to the adult clinic. Regular reproductive health education and a sperm analysis should be offered once they are followed in the adult clinic. Men can have children via assisted reproduction techniques including Percutaneous Epididymal Sperm Aspiration (PESA) or Testicular Sperm Aspiration (TESA) which are then used in either Intracytoplasmic Sperm Injection (ICSI) or in *in vitro* fertilization (IVF).

Despite the fact that most children with CF nowadays achieve near normal to normal growth, puberty and onset of other related physiological developments, such as menstruation for girls, is often delayed by one to two years. This is thought to be a reflection of disease severity as especially poor weight [71], general ill health or CFRD contribute to delayed onset of puberty. Most girls with CF have normal menstrual cycles albeit with a higher incidence of missed (amenorrhea) or irregular periods. When an egg is released, the thick mucus in the cervix may act as a barrier to sperm penetration leading to reduced fertility. Nevertheless, most women with CF could become pregnant. Therefore, the use of contraception is advised to prevent unplanned pregnancies. Fertility issues in women with CF should however be dealt with as for any other woman.

Pregnant women with CF are more likely to have pre-gestational diabetes, deliver preterm and have a primary caesarean delivery [72]. Issues of persistent decrement in lung function have also been documented. Pre-conception care aimed at improving pulmonary function, eliminating pulmonary infections and exacerbations, improving the nutritional status as well as routine screening for signs of CFRD, including during gestation, will improve fertility before conception and the pregnancy outcome [73].

As some patients may have children via medical assistance including gamete donor, we cannot strictly talk about them having "biological children". In addition, some chose to grow their family via adoption. Therefore, since the data collection 2020, we consider any child born/adopted by a person with CF to assess their family status.

13.1 NUMBER OF CHILDREN REPORTED

Data from the registry show that by 2021, there were at least 391 children reported from 239 patients (194 of them alive in 2021). More than half of those who have children were female (135, 56.5%). Among the CF patients with children, 43 (18.0%) were transplanted. There were 102 (42.7%) parents homozygous for the F508del mutation. The mean age at which they had the first child was 29.9 years (median 30.0 years) with a range 16.0 – 49.2 years. The mean (median) was 32.0 (32.2) and 28.1 (28.1) years respectively for the male and female parents.

The mean number of children in CF patients reported to have children was 1.6 (median 1.0, range 1 – 5). 120 patients (50.2%) had one child while 92 (38.5%) had two children and 27 (11.3%) had three children or more. Nineteen parents have twins. There were three patients who have had a child before their 18th birthday. In 2021, seventeen new births/adoption were reported.

Consistently more children were born/adopted up to 2010 when compared to the years before, with now constant numbers, which reflects the improving health status and increased life expectancy of CF patients. The figure 26 shows the total number of births among CF patients.

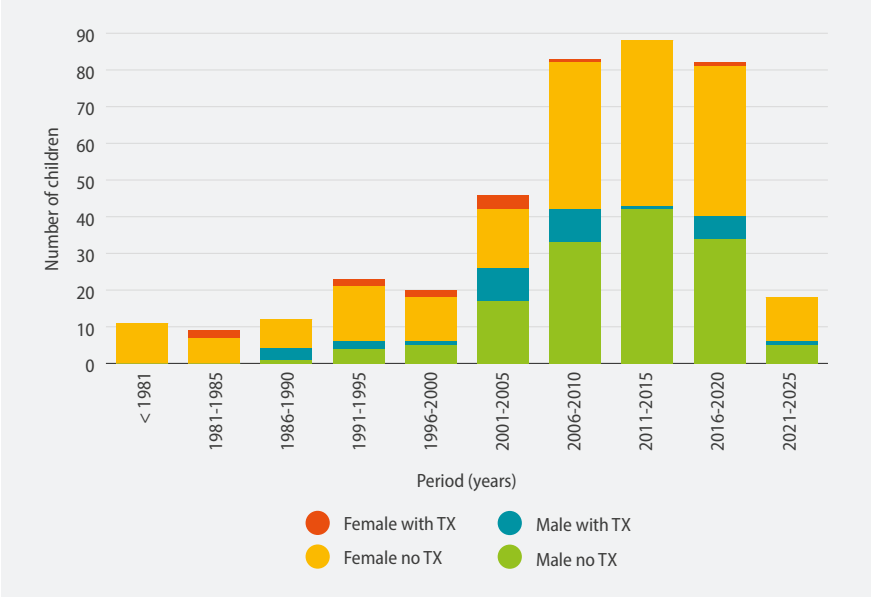


Figure 27 | Number of reported children by period*

*5-year periods except for 2021 (single year)

CHAPTER 14.
DATA QUALITY

Each year, the registry collates data from the seven Cystic Fibrosis reference centres in Belgium for the purposes of research and monitoring quality of care. It doesn't need to be emphasized that good quality of what is provided to the registry needs to be upheld. Good quality data will ensure that the research work done and results that emanate from the said data are accurate, trustworthy, valid, reliable and can be generalized to the specific population. The data present a true picture of those being studied.

Data quality involves checking and confirming the data entries before they are reported to the registry. It also involves looking at the previous records to confirm that indeed any new entries meet the subjects profile, and where there are deviations, corrections be made or that the said data be re-checked and confirmed as indeed valid and accurate reflections of the current status. In most recent times, a random sample can also be selected for purposes of a data audit. In this audit, it is checked, verified and confirmed that indeed the records provided can be traced back into the primary data storage system, the electronic patient records at the clinic, and that indeed the records are as reported.

However, research output and their conclusions are often affected by the completeness of the data collection as well. High proportions of missing data affect the validity and generalisability of any research outcomes. This is an important issue which must be addressed by the data providers so as to avoid a wastage of resources where a special request has to be made by researchers to collect data which was previously not complete, in order to proceed with a given research question.

In this section, we focus mainly on incomplete or missing data, with the total number of missing data per variable as presented in the previous chapters, so the interpretation on generalizing is accessible to all readers of this report. In addition, the results and tables of this exercise are detailed per centre in a special report to the data providers. In doing this, each data provider can reflect on their practise, with the aim reducing to the bare minimum missing values, in subsequent data collections.

14.1 MISSING DATA

The tables in this section present the proportion of missing data for patients with confirmed CF diagnosis and who were seen in 2021. It includes the data with no value reported, reported as "unknown" or "missing", or as "not identified" (for genotype), whatever the reason. The tables are provided in six categories, quite similar to the order in the Cystic Fibrosis Registry Questionnaire.

The field with the highest proportion of missing values under diagnosis was the sweat test chloride, 10.9% (Table 26). This has an impact on the number of patients with confirmed diagnosis according to the European Cystic Fibrosis Society – Patient Registry guidelines (cfr. Table 6).

For annually collected fields, missing height and weight could imply that for these patients, the evaluation of nutrition on the basis of standardized z-scores including the BMI is not possible. This affects the total analysis on nutritional status. Missing values for height and FEV_1 mean that the calculation of the percentage of predicted is not done making the evaluation of lung function severity and progression of lung disease difficult.

Missing information on prevalence of infections leads to an underestimation of the true age-related prevalence of the affected pathogens. It also makes the monitoring of changes and detection of emerging infections very difficult leading to possible late detection of outbreaks and interventions.

It is well known that CF is a progressive disease. This also means that monitoring of disease progression includes reports on complications. A high number of missing values for the complications leads to an underestimation of the true prevalence, needless to say that the reported prevalence could be in stark difference with reported values in other registries among patients of comparable demographics. Such data could be misleading.

People with cystic fibrosis generally have a high burden of medications and spend several hours each day on therapy. Often, issues of non-compliance are also reported. This means that while there have been advances in treatment options and general care in the field of CF, monitoring and keeping record of the therapy and medications currently being used is important. If one would wish to perform a retrospective study on long term effects of a said medication, the least they would expect is that missing data would be the problem that makes their findings inconclusive.

CF ceased being a paediatric-only disease in Belgium more than a decade ago! This means that, since the year 2008, when the median patient age for CF patients living in Belgium surpassed 18 years (it was 18.1 years), the proportion of adult patients has only been higher each year, with over 65.8% in 2021. But this also means that since the patients are living longer with CF, then they also

seek to be integrated into the larger Belgian society. Some simple factors to estimate activity level despite burden of disease are the school (among children up to 18) and work status (among adults). The incomplete data on these fields gives us little insight into what our patient population is doing and whether their activity levels are comparable to CF cohorts in other countries.

Table 26 | Missing data on demographic, diagnosis anthropometry, spirometry, and chronic infections

Description	ALL clinics
DEMOGRAPHIC AND DIAGNOSTIC INFORMATION	
No diagnosis symptoms given	60 (4.4%)
Mutation 1	3 (0.2%)
Mutation 2	16 (1.2%)
Sweat test chloride	149 (10.9%)
Date diagnosis	30 (2.2%)
ANTHROPOMETRY AND SPIROMETRY	
Height values	1 (0.1%)
Weight values	1 (0.1%)
FEV_1 values *	24 (1.8%)
CHRONIC INFECTIONS**	
Chronic *Pseudomonas Aeruginosa* infection	8 (0.7%)
Chronic *Burkholderia Cepacia* Complex infection	7 (0.6%)
Chronic *Stenotrophomo-nas Maltophilia* infection	7 (0.6%)
Chronic MRSA infection	7 (0.6%)
Chronic *Achromobacter Xylosoxidans* infection	7 (0.6%)

This summary includes only files from patients seen over the period indicated. Patients with revoked diagnosis, without a confirmed diagnosis, without observation (without at least four filled-in clinical items, postulated alive or registered as deceased), or who have not been seen, are excluded from the totals. Empty field = no missing data.
* The summary of FEV_1 excludes children below 6y.
** The summary of infections excludes lung transplanted patients and patients who had no culture or sample taken during the year.

Table 27 | Missing data on respiratory, gastro-intestinal, and miscellaneous complications

Description of item with missing or no info	ALL clinics
RESPIRATORY COMPLICATIONS*	
Allergic Bronchial Pulmonary *Aspergillosis*	5 (0.4%)
Pneumothorax	3 (0.3%)
Nasal Polyps	3 (0.3%)
Massive haemoptysis	5 (0.4%)
Bronchiectasis	1 (0.1%)
GASTRO-INTESTINAL COMPLICATIONS	
Pancreatic sufficiency status	3 (0.2%)
Acute pancreatitis	3 (0.2%)
CFRD or IGT	214 (15.7%)
Cirrhosis with portal hypertension	5 (0.4%)
Intestinal obstruction (no surgery)	3 (0.2%)
Intestinal obstruction (with surgery)	4 (0.3%)
Clostridium infection (Treated)	3 (0.2%)
MISCELLANEOUS COMPLICATIONS	
CF related Arthri-tis/arthropathy	206 (15.1%)
Cancer	3 (0.2%)
Osteopenia or Osteoporosis	12 (0.9%)
Hypertension (treated)	3 (0.2%)
Other complications	5 (0.4%)

This summary includes only files from patients seen over the period indicated. Patients with revoked diagnosis, without a confirmed diagnosis, without observation (without at least four filled-in clinical items, postulated alive or registered as deceased), or who have not been seen, are excluded from the totals. Empty field = no missing data.
* The summary of respiratory complications, surgery and general anaesthesia excludes transplanted patients.

Table 28 | Missing data on therapy and medication

Description of item with missing or no info	ALL clinics
PHYSIOTHERAPY, INHALATION THERAPY, ORAL-ANTI-INFLAMATORY AND ANTIBIOTICS	
Number of visits to clinic	1 (0.1%)
Number of exploitable months	196 (14.3%)
Days of hospitalization	1 (0.1%)
Systemic antibiotics*	2 (0.2%)
Home Oxygen therapy	2 (0.1%)
DIGESTIVE AND NUTRITIONAL THERAPY	
Pancreatic enzymes	1 (0.1%)
Ursodeoxycholic acid	5 (0.4%)
Tube feeding	1 (0.1%)
Gastrostomy	1 (0.1%)
Parenteral feeding	1 (0.1%)
OTHER THERAPY AND MEDICATION	
Insulin therapy	1 (0.1%)
Oral therapy for diabetes	2 (0.1%)
Bisphosphonates	2 (0.1%)
Anticonceptive therapy (females 12 and over)	50 (9.8%)
PPI + H2 receptor blocker	2 (0.1%)
CFTR modulating therapy*	1 (0.1%)

This summary includes only files from patients seen over the period indicated. Patients with revoked diagnosis, without a confirmed diagnosis, without observation (without at least four filled-in clinical items, postulated alive or registered as deceased), or who have not been seen, are excluded from the totals. Empty field = no missing data.
* The summary of physiotherapy, inhalation therapy, oral anti-inflammatory, systemic antibiotics and CFTR therapy excludes transplanted patients.

Table 29 | Missing data on school, work, and social allowances

Description of item with missing or no info	ALL clinics
SCHOOL, SOCIAL AND EMPLOYMENT INFORMATION	
School attendance in children aged 3 - 18 years	6 (1.5%)
Child allowance for children under 18 years	20 (4.2%)
Income support for adults	73 (8.0%)
Disability allowance for adults	168 (18.5%)
Preferential tariff for adults	29 (3.2%)
Integration allowance for adults	196 (21.6%)
Employment for adults not attending school	32 (4.5%)

This summary includes only files from patients seen over the period indicated. Patients with revoked diagnosis, without a confirmed diagnosis, without observation (without at least four filled-in clinical items, postulated alive or registered as deceased), or who have not been seen, are excluded from the totals. Empty field = no missing data.

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REGISTRY RELATED PUBLICATIONS AND ABSTRACT PRESENTATIONS

ABSTRACTS AND PRESENTATIONS

[P1] J. Dewulf, M. Vermeulen, M. Thomas, S. Wanyama, and K. De Boeck, "Treatment burden in patients with CF and at least one class 4 or 5 mutation.," presented at the 37th ECFS Conference, Gothenburg, Sweden, 2014, vol. 13, pp. S8-.

[P2] F. De Baets *et al.*, "ABPA in CF: effect on FEV_1 decline and infectious exacerbations, a case control study," presented at the Belgische Vereniging Kindergeneeskunde (BVK-SBP), Belgium, 2014, vol. 16, p. 439.

[P3] F. De Baets *et al.*, "ABPA syndrome (ABPAs) in CF : FEV_1 decline, infectious exacerbations and BMI before and after the year of diagnosis (index year), a case control study.," presented at the 37th ECFS Conference, Gothenburg, Sweden, 2014, vol. 13S2, p. S86.

[P4] F. De Baets *et al.*, "ABPA syndrome (ABPAs) in CF: FEV_1 decline, infectious exacerbations and BMI before and after the year of diagnosis (index year), a case control study," presented at the ERS International Congres 2014, Munich, Germany, 2014, vol. 16, pp. 439-.

[P5] M. Thomas *et al.*, "How different is the cohort of young CF children included in national registries of countries with and without newborn screening ?," presented at the 37th ECFS Conference, Gothenburg, Sweden, 2014, vol. 13S2, p. S8.

[P6] J. Willekens, S. Wanyama, M. Thomas, E. De Wachter, I. De Schutter, and A. Malfroot, "CF patients with a declining FEV_1: at risk for acquisition of *Burkholderia cepacia* complex infection?," presented at the 38th ECFS Conference, Brussels, Brussels, Belgium, 2015, vol. 14, p. S74.

[P7] J. Willekens, S. Wanyama, M. Thomas, E. De Wachter, I. De Schutter, and A. Malfroot, "*Burkholderia cepacia* complex acquisition: a threat in all CF patients ?," presented at the 38th ECFS Conference, Brussels, Belgium, 2015, vol. 14, p. S54.

[P8] E. De Wachter, M. Thomas, S. Wanyama, E. Vanderhelst, I. De Schutter, and A. Malfroot, "Characterizing Belgian CF-registry (BCFR)-patients with a rare CFTR-mutation (RM): topwards better identification of the role of RM in disease liability.," presented at the 39th ECFS Conference, Sevilla, Spain, 2019, vol. 15S1, p. S35.

[P9] D. Libeert *et al.*, "The impact of tube feeding in children and adults with cystic fibrosis.," presented at the 39th ECFS Conference, Sevilla, Spain, 2019, vol. 16S1, p. S9.

[P10] D. Libeert *et al.*, "Impact of tube feeding on pulmonary function in children and adults with cystic fibrosis.," presented at the 39th ECFS Conference, Sevilla, Spain, 2019, vol. 16S1, p. S10.

[P11] D. Libeert *et al.*, "Characteristics at baseline of tube-fed cystic fibrosis (CF) patients with matched controls: a registry study.," presented at the 39th ECFS Conference, Sevilla, Spain, 2019, vol. 16, p. S147.

[P12] D. Libeert, S. Wanyama, D. Declercq, M. Thomas, F. De Baets, and S. Van Biervliet, "Impact of tube feeding on pulmonary function in children and adults with cystic fibrosis (CF): a registry study," presented at the Acta Gastroenterol Belg, Belgium, 2019, vol. 80, p. H06.

[P13] D. Libeert, S. Wanyama, D. Declercq, M. Thomas, F. De Baets, and S. Van Biervliet, "Impact of tube feeding on nutritional status in children and adults with cystic fibrosis (CF): a registry study.," presented at the Acta Gastroenterol Belg, Belgium, 2019, vol. 80, p. H07.

[P14] D. Libeert, S. Wanyama, D. Declercq, M. Thomas, F. De Baets, and S. Van Biervliet, "Characteristics at baseline of tube fed cystic fibrosis (CF) patients with matched controls: a registry study.," presented at the Acta Gastroenterol Belg, Belgium, 2019, vol. 80, p. H09.

[P15] M. Thomas *et al.*, "Demography and clinical outcomes in cystic fibrosis lung transplant recipients in Belgium.," presented at the 40th ECFS Conference, Belgrade, Serbia, 2019, vol. 17S3, p. S47.

[P16] J.L. Vandekerckhove *et al.*, "Impact of COVID-19 on the disease course in CF in Belgium ? A registry-based study", ePS4.02, presented at the 45th ECFS Conference, Rotterdam, The Netherlands, 2022, vol. 21S1, p. S52.

[P17] M. Thomas *et al.*, "Clinical outcomes and long-term survival in cystic fibrosis lung transplant recipients in Belgium", WS03.03, presented at the 46th ECFS Conference, Vienna, Austria, 2023, vol. 22S2, p. S56.

[P18] S. Wanyama *et al.*, "Review of diagnostic labels for patients with unconfirmed CF diagnosis using registry data", P142, presented at the 46th ECFS Conference, Vienna, Austria, 2023, vol. 22S2, p. S108.

[P19] G. Daneau *et al.*, "COVID pandemic in the Belgian cystic fibrosis patients compared with the international CF patients and the general Belgian population", P146, presented at the 46th ECFS Conference, Vienna, Austria, 2023, vol. 22S2, p. S109.

ARTICLES

[A1] K. De Boeck, F. Vermeulen, S. Wanyama, M. Thomas, and members of the Belgian CF Registry, "Inhaled corticosteroids and lower lung function decline in young children with cystic fibrosis," *Eur. Respir. J.,* vol. 37, no. 5, pp. 1091–1095, May 2011, doi: 10.1183/09031936.00077210.

[A2] M. Thomas *et al.*, "Is there evidence for correct diagnosis in cystic fibrosis registries?," *J.Cyst.Fibros.*, vol. 13, no. 3, pp. 275–280, May 2014.

[A3] J. Dewulf *et al.*, "Treatment burden in patients with at least one class IV or V CFTR mutation.," *Pediatr.Pulmonol.*, vol. 50, no. 12, pp. 1230–1236, Nov. 2017.

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[A5] B. Bosch *et al.*, "Ethnicity impacts the cystic fibrosis diagnosis: A note of caution.," *J.Cyst.Fibros.*, vol. 16, no. 4, pp. 488–491, Nov. 2017.

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[A8] F. De Baets *et al.*, "Risk factors and impact of allergic bronchopulmonary aspergillosis in *Pseudomonas aeruginosa*-negative CF patients," *Pediatr Allergy Immunol*, vol. 29, no. 7, pp. 726–731, 2018, doi: 10.1111/pai.12953.

[A9] N. Rodriguez Mier *et al.*, "Clinical evolution and disease burden in Belgian cystic fibrosis patients: effect of newborn screening ?" *Belgian Journal of Pediatrics*, vol. 23, no. 4, pp. 292–297, 2021.

APPENDIX

APPENDIX I:
BCFR 2021 DIGITAL QUESTIONNAIRE NON TRANSPLANT PATIENTS

BMR-RBM-BCFR 2021 – non-transplant patients

1. Background

Patient code (BMR-RBM) : ……
Year of collection : .....
Treating physician : .....
I confirm that an informed consent has been signed: ❑ No ❑ Yes

1.1 - Identification

Patient ID (Pseudo NISS) : .....
Date of birth : . . / . . / . . . .
Gender : ❑ Female ❑ Male ❑ Unknown
Deceased? ❑ No ❑ Yes Date of death : . . / . . / . . . .
Place of residence : .....
Order in the family : .....
Country of origin mother : .....
Country of origin father : .....
Height father (cm) : ..... measured : ❑ Yes ❑ No
Height mother (cm) : ..... measured : ❑ Yes ❑ No
Received transplant : ❑ No ❑ Yes Received lung transplant : ❑ No ❑ Yes
Diagnosis confirmed : ❑ No ❑ Yes ❑ To be confirmed ❑ Unknown

1.2 - Diagnosis

Date of clinical diagnosis . . / . . / . . . .
Symptoms
Respiratory problems ❑
Nasal polyposis/chronic sinusitis ❑
Chronic dia-steatorrhea/malabsorption ❑
Meconium ileus ❑
If Yes, treatment: ❑ With surgery ❑ Without surgery ❑ Unknown if surgery
Intestinal obstruction (other than meconium ileus) ❑
Rectal prolapse ❑
Dehydration/electrolyte imbalance ❑
Failure to thrive ❑
Prenatal diagnosis ❑
Neonatal screening test ❑
Prolonged icterus ❑
Family history ❑
Infertility ❑
Other ❑
Specify other.....
Missing data ❑

Neonatal screening test ❑ unknown ❑ not done ❑ performed positive ❑ performed negative ❑ performed result unknown ❑ missing data

1.3 - Sweat test

Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.4 - Genotype

Date of initial genotype : . . / . . / . . . .

Legacy name

Chromosome 1 :
Chromosome 1 other : .....
T status 1 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data

cDNA name

Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data

Protein name

Chromosome 1 : .....
Chromosome 1 other : .....
Chromosome 2 : .....
Chromosome 2 other : .....

1.5 - Nasal Transepithelial Potential Difference

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal ❑ Inconclusive ❑ Missing data
Date : . . / . . / . . . .

1.6 - Sweat test performed during the registration year

Sweat test done ❑ No ❑ Yes
Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.7 - New genotype test performed after diagnosis

New genotype test performed after diagnosis ? ❑ No ❑ Yes
Date of last genotype : . . / . . / . . . .

2. Observation

2.1 - Patient status

Patient status
- ❑ First registration in this center
- ❑ Not seen patient
- ❑ Moved to other center/other country
- ❑ Lost to follow-up
- ❑ In follow-up
- ❑ Revoked diagnosis
- ❑ No information
- ❑ Revoked consent

2.2 - Cause of death

- Cardiac ❑
- Respiratory ❑
- Hepatic- gastrointestinal ❑
- Trauma ❑
- Suicide ❑
- Associated with cancer ❑
  - (type) .....
- Associated with organ transplant ❑
  - (type)
    - ❑ Chronic Lung Allograft Dysfunction (CLAD)
    - ❑ Infection
    - ❑ Other
- Other cause (CF-related) ❑
  - (type) .....
- Other cause (not CF-related) ❑
  - (type) .....
- Cause unknown ❑

2.3 - Last consultation of the year

Date consultation : . . / . . / . . . .

Anthropometry

- Weight (kg) : .....
- Height (cm) : .....

Lung function

- Executed : ❑ No ❑ Yes ❑ Impossible ❑ Missing data
- FVC (L) : .....
- FEV_1 (L) : .....
- FEF25-75 (L/s) : .....

2.4 - The best lung function of the year

- Date of best LungFx : . . / . . / . . . .
- FVC (L) : .....
- FEV_1 (L) : .....
- FEF25-75 (L/s) : .....
- Weight (kg) : .....
- Height (cm) : .....

2.6 - LCI 2.5% performed during the registration year

Has the lung clearance index (LCI) 2.5% been evaluated this year? ❑ No ❑ Yes ❑ Unknown

Date of LCI : . . / . . / . . . .

Lowest value : .....

Type of device
- ❑ Ecomedics Exhalyzer D N2-Washout
- ❑ Ecomedics Exhaler SF6 (Tracergas 4%)
- ❑ NDD Easyone Pro
- ❑ Other

3. Microbiology

3.1 - Microbiology: all cultures of the registration year

Microbiology executed	❑ Executed	❑ Not executed	❑ Missing data
Swabs	❑		
Sputum	❑		
Broncho-alveolar lavage (BAL)	❑		
Missing values	❑		

3.2 - Pathogen ever found during the registration year

Pseudomonas aeruginosa	❑
Burkholderia cepacia complex	❑
Stenotrophomonas maltophilia	❑
Achromobacter xylosoxidans (Alcaligenes)	❑
Methicillin resistant *Staphylococcus aureus* (MRSA)	❑
Methicillin sensible *Staphylococcus aureus* (MSSA)	❑
Haemophilus influenzae	❑
Aspergillus	❑
Scedosporium prolificans	❑
Atypical Mycobacterium (NTM)	❑
Other	❑
No pathogens	❑
Missing values	❑

3.3 - Colonisation

Number of exploitable months	❑ 0	❑ <4	❑ >=4	❑ Missing data
Pseudomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Burkholderia cepacia complex colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Stenotrophomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Achromobacter xylosoxidans colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
MRSA colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
MSSA colonization	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Haemophilus influenza colonization	❑ No	❑ Yes	❑ Unknown status	❑ Missing data

3.4 - SARS-CoV-2 test performed this year

SARS-CoV-2 test	❑ No	❑ Yes, negative	❑ Yes, positive	❑ Unknown

4. Complications

4.1 - Respiratory causes

Allergic bronchopulmonary aspergillosis ❑ No ❑ Yes ❑ Missing data
ABPA Treated ❑ No ❑ Yes ❑ Missing data
Treatment for ABPA ❑ Oral steroids
(more than 1 response possible) ❑ Pulse steroids
❑ Oral antifungal therapy
❑ Inhaled antifungal therapy
❑ Omalizumab
❑ Anti-IL5
❑ Intravenous antifungal therapy
❑ Other
Pneumothorax ❑ No ❑ Yes ❑ Missing data
Pneumothorax treatment ❑ Treated with chest drain
❑ Observation only
❑ Treatment unknown
Nasal polyps (having required/requiring therapy) ❑ No ❑ Yes ❑ Missing data
Massive haemoptysis ❑ No ❑ Yes ❑ Missing data
Requiring embolization ❑ No ❑ Yes ❑ Missing data
Bronchiectasis ❑ No CT scan this year ❑ CT scan done, no bronchiectasis
❑ CT scan done, bronchiectasis ❑ CT scan done, result unknown ❑ Missing data

4.2 - Digestive causes

CF diabetes ❑ No ❑ IGT ❑ CFRD ❑ Missing data
OGTT done this year ❑ No ❑ Yes ❑ Missing data
Acute pancreatitis ❑ No ❑ Yes ❑ Missing data
Cirrhosis with portal hypertension ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : requiring surgery ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : not requiring surgery ❑ No ❑ Yes ❑ Missing data
Clostridium ❑ No ❑ Yes ❑ Missing data

4.3 - Other complications

CF related arthritis / arthropathy ❑ No ❑ Yes ❑ Missing data
Osteopenia / Osteoporosis ❑ z-score≥-1 ❑ z-score<-1 and >-2.5
❑ z-score≤-2.5 ❑ Not done ❑ Missing data
Date of most recent DEXA: . . / . . / . . . .
Salt loss syndrome ❑ No ❑ Yes ❑ Missing data
Cancer ❑ No ❑ Yes ❑ In remission ❑ Missing data
❑ Colorectal cancer ❑ Small bowel cancer ❑ Lymphoid leukemia ❑ Testicular cancer
❑ Breast cancer ❑ Thyroid gland cancer ❑ Other
Specify : .....
Hypertension treated ❑ No ❑ Yes ❑ Missing data
Other complications ❑ No ❑ Yes ❑ Missing data
Type : .....

5. Therapy

5.1 - Therapy received during the registration year

Number of consultations ❑ 0 ❑<4 ❑ ≥4 ❑ Missing data
Days in hospital .....
Days in revalidation center .....

5.2 - Respiratory system

Systemic antibiotics ❑ No ❑ per os ❑ iv ❑ per os+iv ❑ Missing data
Days per os ❑ < 1 month ❑ 1-3 mths ❑ 3-6 mths ❑ > 6 mths ❑ Missing
Days iv at home .....
Days iv in revalidation center .....
Days iv in hospital .....
Inhaled antibiotics ❑ No ❑ Yes ❑ Missing data
Home O2-therapy ❑ No ❑ At night ❑ Day&Night ❑ Day/On demand ❑ Missing data
Continuous NIPPV ❑ No ❑ CPAP ❑ BiPAP ❑ CPAP+BiPAP ❑ Unknown
Inhalation therapy (except antibiotics) ❑ No ❑ Yes ❑ Missing data
RhDnase ❑ No ❑ Yes
Mucolytics ❑ No ❑ Yes
Bronchodilators ❑ No ❑ Yes, Short-acting only
❑ Yes, Long-acting only ❑ Yes, Short- and Long-acting
Corticosteroids ❑ No ❑ Yes
Hypertonic saline ❑ No ❑ Yes
Antiinflammatories p.o. ❑ No ❑ Yes ❑ Missing data
NSAID ❑ No ❑ Yes
Systemic Corticoids ❑ No ❑ Yes
Azithromycine/macrolide ❑ No ❑ Yes
Anti-leucotriens ❑ No ❑ Yes
Other ❑ No ❑ Yes
Specify : .....

5.3 - Digestive system

Pancreatic sufficient ❑ No ❑ Yes ❑ Missing data
Pancreatic enzymes ❑ No ❑ Yes ❑ Missing data
Ursodeoxycholic acid ❑ No ❑ Yes ❑ Missing data
Tube feeding ❑ No ❑ Yes ❑ Missing data
Gastrostomy ❑ No ❑ Yes ❑ Missing data
Parenteral feeding ❑ No ❑ Yes ❑ Missing data

5.4 - Miscellaneous

Oral therapy for diabetes ❑ No ❑ Yes ❑ Missing data
Insulin therapy ❑ No ❑ Yes ❑ Missing data
Diet only (for diabetes) ❑ No ❑ Yes ❑ Missing data
PPI + H2 receptor blocker ❑ No ❑ Yes ❑ Missing data
Anticonceptive therapy (only for females) ❑ No ❑ Yes ❑ Missing data
Biphosphonates ❑ No ❑ Yes ❑ Missing data
Randomised drug trial ❑ No ❑ Yes ❑ Missing data
CFTR modulating therapy ❑ No ❑ Yes ❑ Missing data
If yes, ❑ ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown
❑ lumacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

5.4 - Miscellaneous (2)

❑ tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown
❑ elexacaftor/tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown
❑ blinded clinical trial Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
❑ other Other, specify: …….. Start date : . . / . . / . . . .
Ongoing ❑ No ❑ Yes Stop date : . . / . . / . . . .

Regular chest physiotherapy ❑ No ❑ Yes ❑ Missing data

6. Transplantation

Transplant status ❑ Not evaluated ❑ Refused by transplant center ❑ Waiting list
❑ Evaluated but not on waiting list ❑ Refused by patient
❑ Missing data

7. Social data

7.1 - Pregnancy / Paternity

Parenthood this year ❑ No ❑ Yes ❑ Missing data
Pregnancy this year (*for females)* ❑ No ❑ Yes ❑ Missing data
If Yes, pregnancy status ❑ Ongoing (on Dec 31th) ❑ Life birth ❑ Still birth
❑ Therapeutic abortion ❑ Spontaneaous abortion ❑ Unknown
Congenital anomalies ❑ No ❑ Yes ❑ Unknown ❑ Missing data
If yes, specify : ……

Delivery/adoption date of the children for this patient:
Child(ren) 1 : . . / . . . . (month/year)
Child(ren) 2 : . . / . . . . (month/year)
Child(ren) 3 : . . / . . . . (month/year)
Child(ren) 4 : . . / . . . . (month/year)
Child(ren) 5 : . . / . . . . (month/year)
Child(ren) 6 : . . / . . . . (month/year)

7.2 - School

School status ❑ Unknown ❑ Regular school/education attendance
❑ No school ❑ Has finished school/education ❑ Missing data

7.3 - Employment data

Patient works ❑ No ❑ Yes ❑ Missing data
Percentage ❑ Unknown ❑ Fulltime ❑Parttime ❑ Missing data

7.4 - Financial benefits

Additional child allowance ❑ No ❑ Yes ❑ Missing data
Integration support ❑ No ❑ Yes ❑ Missing data
Disability allowance ❑ No ❑ Yes ❑ Missing data
Preferential tariff ❑ No ❑ Yes ❑ Missing data
Pension ❑ No ❑ Yes ❑ Missing data
Income support ❑ No ❑ Yes ❑ Missing data

7.4 - Financial benefits (2)

Disability recognition requested ❑ No ❑ Yes ❑ Unknown
If yes, year of request : . . . . .
Parking card requested ❑ No ❑ Yes
Parking card granted ❑ No ❑ Yes ❑ Unknown
Decision made ❑ On paper ❑ With consultation ❑ Unknown
Place of decision ❑ Antwerpen ❑ Brabant wallon ❑ Brussels ❑ Hainaut
❑ Liège ❑ Luxembourg ❑ Namur
❑ Oost-Vlaanderen ❑ Vlaams Brabant ❑ West-Vlaanderen
For a child:
Number of points granted : . .
Pilar 1 : .
Pilar 2 : .
Pilar 3 : .
Part-time by any parent ❑ No ❑ Yes ❑ Unknown
For an adult:
Working disability ❑ No ❑ Yes ❑ Unknown
Independence - number of points granted : . .
Section 1 (Movement) : .
Section 2 (Cooking) : .
Section 3 (Hygiene) : .
Section 4 (Household) : .
Section 5 (Reaction) : .
Section 6 (Communication) : .
Duration ❑ Limited ❑ Unlimited

7.5 - Family composition

Household composition ❑ Unchanged ❑ Changed
❑ First registration ❑ Missing data
Number of siblings including the patient .....
Number of siblings with CF .....
Number of siblings deceased from CF .....

General remark .....
.....

APPENDIX II:
BCFR 2021 DIGITAL QUESTIONNAIRE LUNG TRANSPLANT PATIENTS

BMR-RBM-BCFR 2021 – lung transplant patients

1. Background

Patient code (BMR-RBM) : ……
Year of collection : .....
Treating physician : .....
I confirm that an informed consent has been signed: ❑ No ❑ Yes

1.1 - Identification

Patient ID (Pseudo NISS) : .....
Date of birth : . . / . . / . . . .
Gender : ❑ Female ❑ Male ❑ Unknown
Deceased? ❑ No ❑ Yes Date of death : . . / . . / . . . .
Place of residence : .....
Order in the family : .....
Country of origin mother : .....
Country of origin father : .....
Height father (cm) : ..... measured : ❑ Yes ❑ No
Height mother (cm) : ..... measured : ❑ Yes ❑ No
Received transplant : ❑ No ❑ Yes Received lung transplant : ❑ No ❑ Yes
Diagnosis confirmed : ❑ No ❑ Yes ❑ To be confirmed ❑ Unknown

1.2 - Diagnosis

Date of clinical diagnosis . . / . . / . . . .
Symptoms
Respiratory problems ❑
Nasal polyposis/chronic sinusitis ❑
Chronic dia-steatorrhea/malabsorption ❑
Meconium ileus ❑
If Yes, treatment: ❑ With surgery ❑ Without surgery ❑ Unknown if surgery
Intestinal obstruction (other than meconium ileus) ❑
Rectal prolapse ❑
Dehydration/electrolyte imbalance ❑
Failure to thrive ❑
Prenatal diagnosis ❑
Neonatal screening test ❑
Prolonged icterus ❑
Family history ❑
Infertility ❑
Other ❑
Specify other.....
Missing data ❑

Neonatal screening test ❑ unknown ❑ not done ❑ performed positive
❑ performed negative ❑ performed result unknown ❑ missing data

1.3 - Sweat test

Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.4 - Genotype

Date of initial genotype : . . / . . / . . . .

Legacy name

Chromosome 1 :
Chromosome 1 other : .....
T status 1 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data

cDNA name

Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data

Protein name

Chromosome 1 : .....
Chromosome 1 other : .....
Chromosome 2 : .....
Chromosome 2 other : .....

1.5 - Nasal Transepithelial Potential Difference

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal ❑ Inconclusive ❑ Missing data
Date : . . / . . / . . . .

1.6 - Sweat test performed during the registration year

Sweat test done ❑ No ❑ Yes
Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.7 - New genotype test performed after diagnosis

New genotype test performed after diagnosis ? ❑ No ❑ Yes
Date of last genotype : . . / . . / . . . .

2. Observation

2.1 - Patient status

Patient status
- ❑ First registration in this center
- ❑ Not seen patient
- ❑ Moved to other center/other country
- ❑ Lost to follow-up
- ❑ In follow-up
- ❑ Revoked diagnosis
- ❑ No information
- ❑ Revoked consent

2.2 - Cause of death

- Cardiac ❑
- Respiratory ❑
- Hepatic- gastrointestinal ❑
- Trauma ❑
- Suicide ❑
- Associated with cancer ❑
  - (type) .....
- Associated with organ transplant ❑
  - (type)
    - ❑ Chronic Lung Allograft Dysfunction (CLAD)
    - ❑ Infection
    - ❑ Other
- Other cause (CF-related) ❑
  - (type) .....
- Other cause (not CF-related) ❑
  - (type) .....
- Cause unknown ❑

2.3 - Last consultation of the year

Date consultation : . . / . . / . . . .

Anthropometry

Weight (kg) : .....

Height (cm) : .....

Lung function

Executed : ❑ No ❑ Yes ❑ Impossible ❑ Missing data

FVC (L) : .....

2.4 - The best lung function of the year

Date of best LungFx : . . / . . / . . . .

FVC (L) : .....

FEV_1 (L) : .....

FEF25-75 (L/s) : .....

Weight (kg) : .....

Height (cm) : .....

2.5 - Best post-transplantation lung function (time interval between the 2 functions ≥ 3 weeks)

Date lung function 1	: . . / . . /	Date lung function 2	: . . / . . / . . . .
Weight (kg)	:	Weight (kg)	: .....
Height (cm)	:	Height (cm)	: .....
FVC (L)	:	FVC (L)	:.....
FEV_1 (L)	:	FEV_1 (L)	: .....

3. Microbiology

3.4 - SARS-CoV-2 test performed this year

SARS-CoV-2 test ❑ No ❑ Yes, negative ❑ Yes, positive ❑ Unknown

4. Complications

4.2 - Digestive causes

CF diabetes ❑ No ❑ IGT ❑ CFRD ❑ Missing data
OGTT done this year ❑ No ❑ Yes ❑ Missing data
Acute pancreatitis ❑ No ❑ Yes ❑ Missing data
Cirrhosis with portal hypertension ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : requiring surgery ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : not requiring surgery ❑ No ❑ Yes ❑ Missing data
Clostridium ❑ No ❑ Yes ❑ Missing data

4.3 - Other complications

Osteopenia / Osteoporosis ❑ z-score≥-1 ❑ z-score<-1 and >-2.5
❑ z-score≤-2.5 ❑ Not done ❑ Missing data
Date of most recent DEXA . . / . . / . . . .
Salt loss syndrome ❑ No ❑ Yes ❑ Missing data
Cancer ❑ No ❑ Yes ❑ In remission ❑ Missing data
❑ Colorectal cancer ❑ Small bowel cancer ❑ Lymphoid leukemia ❑ Testicular cancer
❑ Breast cancer ❑ Thyroid gland cancer ❑ Other
Specify : .....
Hypertension treated ❑ No ❑ Yes ❑ Missing data
Other complications ❑ No ❑ Yes ❑ Missing data
Type : .....

4.4 - Renal function

Renal Function (last consultation of the year)

Date : . . / . . / . . . . Creatinine (mg/dl): ……..……

Renal Function (1 month post-transplantation)

Date : . . / . . / . . . . Creatinine (mg/dl): ……..……

4.5 - Post-transplantation complications

Chronic lung allograft dysfunction (CLAD)
❑ No
❑ Bronchiolitis Obliterans Syndrome (BOS) : ❑ BOS 0-p
❑ BOS 1
❑ BOS 2
❑ BOS 3
❑ Restrictive allograft syndrome (RAS)
❑ Not possible to classify

Post-transplant lympho-proliferative disease ❑ No ❑ Yes ❑ In remission ❑ Missing data

5. Therapy

5.1 - Therapy received during the registration year

Number of consultations ❑ 0 ❑<4 ❑ ≥4 ❑ Missing data
Days in hospital .....
Days in revalidation center .....

5.2 - Respiratory system

Home O2-therapy ❑ No ❑ At night ❑ Day&Night ❑ Day/On demand ❑ Missing data
Continuous NIPPV ❑ No ❑ CPAP ❑ BiPAP ❑ CPAP+BiPAP ❑ Unknown
Azithromycine/macrolide ❑ No ❑ Yes ❑ Missing data

5.3 - Digestive system

Pancreatic sufficient ❑ No ❑ Yes ❑ Missing data
Pancreatic enzymes ❑ No ❑ Yes ❑ Missing data
Ursodeoxycholic acid ❑ No ❑ Yes ❑ Missing data
Tube feeding ❑ No ❑ Yes ❑ Missing data
Gastrostomy ❑ No ❑ Yes ❑ Missing data
Parenteral feeding ❑ No ❑ Yes ❑ Missing data

5.4 - Miscellaneous

Oral therapy for diabetes ❑ No ❑ Yes ❑ Missing data
Insulin therapy ❑ No ❑ Yes ❑ Missing data
Diet only (for diabetes) ❑ No ❑ Yes ❑ Missing data
PPI + H2 receptor blocker ❑ No ❑ Yes ❑ Missing data
Anticonceptive therapy (only for females) ❑ No ❑ Yes ❑ Missing data
Biphosphonates ❑ No ❑ Yes ❑ Missing data
Randomised drug trial ❑ No ❑ Yes ❑ Missing data
CFTR modulating therapy ❑ No ❑ Yes ❑ Missing data

If yes, ❑ ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ lumacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ elexacaftor/tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ blinded clinical trial Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .

❑ other Other, specify: ..... Start date : . . / . . / . . . .
Ongoing ❑ No ❑ Yes Stop date : . . / . . / . . . .

5.5 - Immunosuppressive treatments (> 3 months)

Calcineurin inhibitors			
Cyclosporine	❑ No	❑ Yes	❑ Missing data
Tacrolimus	❑ No	❑ Yes	❑ Missing data
Cell cycle inhibitors			
Azathioprine	❑ No	❑ Yes	❑ Missing data
Mycophenolate mofetil (MMF)	❑ No	❑ Yes	❑ Missing data
Other immunosuppressive treatments			
Steroids	❑ No	❑ Yes	❑ Missing data
Everolimus	❑ No	❑ Yes	❑ Missing data

Other immunosuppressive therapy, specify .....

6. Transplantation

Transplant status ❑ Refused by transplant center ❑ Waiting list (w transplant)
❑ Received transplant ❑ Evaluated but not on waiting list
❑ Refused by patient ❑ Missing data

Transplant 1

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart ❑ Kidney ❑ Lung-liver
❑ Lung-Kidney ❑ Liver-Kidney ❑ Pancreas ❑ Liver-pancreas
❑ Lung-liver-kidney ❑ Lung-liver-pancreas ❑ Missing data

Year of transplant : . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Transplant 2

Precise date of Tx : . . / . . / . . . .

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart ❑ Kidney ❑ Lung-liver
❑ Lung-Kidney ❑ Liver-Kidney ❑ Pancreas ❑ Liver-pancreas
❑ Lung-liver-kidney ❑ Lung-liver-pancreas ❑ Missing data

Year of transplant : . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Precise date of Tx : . . / . . / . . . .

Transplant 3

Type of transplant ❑ Lung ❑ Lung-Heart ❑ Liver ❑ Heart ❑ Kidney ❑ Lung-liver
❑ Lung-Kidney ❑ Liver-Kidney ❑ Pancreas ❑ Liver-pancreas
❑ Lung-liver-kidney ❑ Lung-liver-pancreas ❑ Missing data

Year of transplant : . . . .

Precise date of entering the Tx waiting list : . . / . . / . . . .

Precise date of Tx : . . / . . / . . . .

7. Social data

7.1 - Pregnancy / Paternity

Parenthood this year ❑ No ❑ Yes ❑ Missing data
Pregnancy this year *(for females)* ❑ No ❑ Yes ❑ Missing data
If Yes, pregnancy status ❑ Ongoing (on Dec 31th) ❑ Life birth ❑ Still birth
❑ Therapeutic abortion ❑ Spontaneaous abortion ❑ Unknown
Congenital anomalies ❑ No ❑ Yes ❑ Unknown ❑ Missing data
If yes, specify : ……
Delivery/adoption date of the children for this patient:
Child(ren) 1 : . . / . . . . (month/year)
Child(ren) 2 : . . / . . . . (month/year)
Child(ren) 3 : . . / . . . . (month/year)
Child(ren) 4 : . . / . . . . (month/year)

7.2 - School

School status ❑ Unknown ❑ Regular school/education attendance
❑ No school ❑ Has finished school/education ❑ Missing data

7.3 - Employment data

Patient works ❑ No ❑ Yes ❑ Missing data
Percentage ❑ Unknown ❑ Fulltime ❑Parttime ❑ Missing data

7.4 - Financial benefits

Additional child allowance ❑ No ❑ Yes ❑ Missing data
Integration support ❑ No ❑ Yes ❑ Missing data
Disability allowance ❑ No ❑ Yes ❑ Missing data
Preferential tariff ❑ No ❑ Yes ❑ Missing data
Pension ❑ No ❑ Yes ❑ Missing data
Income support ❑ No ❑ Yes ❑ Missing data

Disability recognition requested ❑ No ❑ Yes ❑ Unknown
If yes, year of request : . . . .
Parking card requested ❑ No ❑ Yes
Parking card granted ❑ No ❑ Yes ❑ Unknown
Decision made ❑ On paper ❑ With consultation ❑ Unknown
Place of decision ❑ Antwerpen ❑ Brabant wallon ❑ Brussels ❑ Hainaut
❑ Liège ❑ Luxembourg ❑ Namur
❑ Oost-Vlaanderen ❑ Vlaams Brabant ❑ West-Vlaanderen
For a child:
Number of points granted : . .
Pilar 1 : .
Pilar 2 : .
Pilar 3 : .
Part-time by any parent ❑ No ❑ Yes ❑ Unknown

APPENDIX III:
BCFR 2021 DIGITAL QUESTIONNAIRE NON-LUNG TRANSPLANT PATIENTS

BMR-RBM-BCFR 2021 – non-lung-transplant patients

1. Background

Patient code (BMR-RBM) : ……
Year of collection : .....
Treating physician : .....
I confirm that an informed consent has been signed: ❑ No ❑ Yes

1.1 - Identification

Patient ID (Pseudo NISS) : .....
Date of birth : . . / . . / . . . .
Gender : ❑ Female ❑ Male ❑ Unknown
Deceased? ❑ No ❑ Yes Date of death : . . / . . / . . . .
Place of residence : .....
Order in the family : .....
Country of origin mother : .....
Country of origin father : .....
Height father (cm) : ..... measured : ❑ Yes ❑ No
Height mother (cm) : ..... measured : ❑ Yes ❑ No
Received transplant : ❑ No ❑ Yes Received lung transplant : ❑ No ❑ Yes
Diagnosis confirmed : ❑ No ❑ Yes ❑ To be confirmed ❑ Unknown

1.2 - Diagnosis

Date of clinical diagnosis . . / . . / . . . .
Symptoms
Respiratory problems ❑
Nasal polyposis/chronic sinusitis ❑
Chronic dia-steatorrhea/malabsorption ❑
Meconium ileus ❑
If Yes, treatment: ❑ With surgery ❑ Without surgery ❑ Unknown if surgery
Intestinal obstruction (other than meconium ileus) ❑
Rectal prolapse ❑
Dehydration/electrolyte imbalance ❑
Failure to thrive ❑
Prenatal diagnosis ❑
Neonatal screening test ❑
Prolonged icterus ❑
Family history ❑
Infertility ❑
Other ❑
Specify other.....
Missing data ❑

Neonatal screening test ❑ unknown ❑ not done ❑ performed positive ❑ performed negative ❑ performed result unknown ❑ missing data

1.3 - Sweat test

Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.4 - Genotype

Date of initial genotype : . . / . . / . . . .

Legacy name

Chromosome 1 :
Chromosome 1 other : .....
T status 1 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 ❑ None ❑ 5T ❑ 7T ❑ 9T ❑ Missing data

cDNA name

Chromosome 1 : .....
Chromosome 1 other : .....
T status 1 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data
Chromosome 2 : .....
Chromosome 2 other : .....
T status 2 : ❑ None ❑ c.1210-12T(5) ❑ c.1210-12T(7) ❑ c.1210-12T(9) ❑ Missing data

Protein name

Chromosome 1 : .....
Chromosome 1 other : .....
Chromosome 2 : .....
Chromosome 2 other : .....

1.5 - Nasal Transepithelial Potential Difference

Nasal transepithelial potential difference : ❑ Not executed ❑ Normal ❑ Evocative/Abnormal ❑ Inconclusive ❑ Missing data
Date : . . / . . / . . . .

1.6 - Sweat test performed during the registration year

Sweat test done ❑ No ❑ Yes
Date of sweat test : . . / . . / . . . .
Type of sweat test ❑ Unknown ❑ Titration ❑ Conductivity ❑ Missing data
Chloride : .....
Sodium : .....

1.7 - New genotype test performed after diagnosis

New genotype test performed after diagnosis ? ❑ No ❑ Yes
Date of last genotype : . . / . . / . . . .

2. Observation

2.1 - Patient status

Patient status
- ❑ First registration in this center
- ❑ Not seen patient
- ❑ Moved to other center/other country
- ❑ Lost to follow-up
- ❑ In follow-up
- ❑ Revoked diagnosis
- ❑ No information
- ❑ Revoked consent

2.2 - Cause of death

- Cardiac ❑
- Respiratory ❑
- Hepatic- gastrointestinal ❑
- Trauma ❑
- Suicide ❑
- Associated with cancer ❑
  - (type) .....
- Associated with organ transplant ❑
  - (type)
    - ❑ Chronic Lung Allograft Dysfunction (CLAD)
    - ❑ Infection
    - ❑ Other
- Other cause (CF-related) ❑
  - (type) .....
- Other cause (not CF-related) ❑
  - (type) .....
- Cause unknown ❑

2.3 - Last consultation of the year

Date consultation : . . / . . / . . . .

Anthropometry

- Weight (kg) : .....
- Height (cm) : .....

Lung function

- Executed : ❑ No ❑ Yes ❑ Impossible ❑ Missing data
- FVC (L) : .....
- FEV_1 (L) : .....
- FEF25-75 (L/s) : .....

2.4 - The best lung function of the year

- Date of best LungFx : . . / . . / . . . .
- FVC (L) : .....
- FEV_1 (L) : .....
- FEF25-75 (L/s) : .....
- Weight (kg) : .....
- Height (cm) : .....

2.6 - LCI 2.5% performed during the registration year

Has the lung clearance index (LCI) 2.5% been evaluated this year? ❑ No ❑ Yes ❑ Unknown

- Date of LCI : . . / . . / . . . .
- Lowest value : .....
- Type of device
  - ❑ Ecomedics Exhalyzer D N2-Washout
  - ❑ Ecomedics Exhaler SF6 (Tracergas 4%)
  - ❑ Innovision Innocor
  - ❑ NDD Easyone Pro
  - ❑ Other
  - ❑ Unknown

3. Microbiology

3.1 - Microbiology: all cultures of the registration year

Microbiology executed	❑ Executed	❑ Not executed	❑ Missing data
Swabs	❑		
Sputum	❑		
Broncho-alveolar lavage (BAL)	❑		
Missing values	❑		

3.2 - Pathogen ever found during the registration year

Pseudomonas aeruginosa	❑
Burkholderia cepacia complex	❑
Stenotrophomonas maltophilia	❑
Achromobacter xylosoxidans (Alcaligenes)	❑
Methicillin resistant *Staphylococcus aureus* (MRSA)	❑
Methicillin sensible *Staphylococcus aureus* (MSSA)	❑
Haemophilus influenzae	❑
Aspergillus	❑
Scedosporium prolificans	❑
Atypical Mycobacterium (NTM)	❑
Other	❑
No pathogens	❑
Missing values	❑

3.3 - Colonisation

Number of exploitable months	❑ 0	❑ <4	❑ >=4	❑ Missing data
Pseudomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Burkholderia cepacia complex colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Stenotrophomonas colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
Achromobacter xylosoxidans colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data
MRSA colonisation	❑ No	❑ Yes	❑ Unknown status	❑ Missing data

3.4 - SARS-CoV-2 test performed this year

SARS-CoV-2 test	❑ No	❑ Yes, negative	❑ Yes, positive	❑ Unknown

4. Complications

4.1 - Respiratory causes

Allergic bronchopulmonary aspergillosis ❑ No ❑ Yes ❑ Missing data
ABPA Treated ❑ No ❑ Yes ❑ Missing data
Treatment for ABPA (more than 1 response possible)
❑ Oral steroids
❑ Pulse steroids
❑ Oral antifungal therapy
❑ Inhaled antifungal therapy
❑ Omalizumab
❑ Anti-IL5
❑ Intravenous antifungal therapy
❑ Other

Pneumothorax ❑ No ❑ Yes ❑ Missing data
Pneumothorax treatment
❑ Treated with chest drain
❑ Observation only
❑ Treatment unknown

Nasal polyps (having required/requiring therapy) ❑ No ❑ Yes ❑ Missing data
Massive haemoptysis ❑ No ❑ Yes ❑ Missing data
Requiring embolization ❑ No ❑ Yes ❑ Missing data
Bronchiectasis ❑ No CT scan this year ❑ CT scan done, no bronchiectasis
❑ CT scan done, bronchiectasis ❑ CT scan done, result unknown ❑ Missing data

4.2 - Digestive causes

CF diabetes ❑ No ❑ IGT ❑ CFRD ❑ Missing data
OGTT done this year ❑ No ❑ Yes ❑ Missing data
Acute pancreatitis ❑ No ❑ Yes ❑ Missing data
Cirrhosis with portal hypertension ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : requiring surgery ❑ No ❑ Yes ❑ Missing data
Intestinal obstruction : not requiring surgery ❑ No ❑ Yes ❑ Missing data
Clostridium ❑ No ❑ Yes ❑ Missing data

4.3 - Other complications

Osteopenia / Osteoporosis ❑ z-score≥-1 ❑ z-score<-1 and >-2.5
❑ z-score≤-2.5 ❑ Not done ❑ Missing data
Date of most recent DEXA . . / . . / . . . .
Salt loss syndrome ❑ No ❑ Yes ❑ Missing data
Cancer ❑ No ❑ Yes ❑ In remission ❑ Missing data
❑ Colorectal cancer ❑ Small bowel cancer ❑ Lymphoid leukemia ❑ Testicular cancer
❑ Breast cancer ❑ Thyroid gland cancer ❑ Other
Specify : .....
Hypertension treated ❑ No ❑ Yes ❑ Missing data
Other complications ❑ No ❑ Yes ❑ Missing data
Type : .....

4.5 - Renal function

Renal Function (last consultation of the year)

Date : . . / . . / . . . . Creatinine (mg/dl): .....

Renal Function (1 month post-transplantation)

Date : . . / . . / . . . . Creatinine (mg/dl): .....

4.6 - Post-transplantation complications

Post-transplant lympho-proliferative disease ❑ No ❑ Yes ❑ In remission ❑ Missing data

5. Therapy

5.1 - Therapy received during the registration year

Number of consultations ❑ 0 ❑<4 ❑ ≥4 ❑ Missing data
Days in hospital .....
Days in revalidation center .....

5.2 - Respiratory system

Systemic antibiotics ❑ No ❑ per os ❑ iv ❑ per os+iv ❑ Missing data
Days per os ❑ < 1 month ❑ 1-3 mths ❑ 3-6 mths ❑ > 6 mths ❑ Missing
Days iv at home .....
Days iv in revalidation center .....
Days iv in hospital .....
Inhaled antibiotics ❑ No ❑ Yes ❑ Missing data
Home O2-therapy ❑ No ❑ At night ❑ Day&Night ❑ Day/On demand ❑ Missing data
Continuous NIPPV ❑ No ❑ CPAP ❑ BiPAP ❑ CPAP+BiPAP ❑ Unknown
Inhalation therapy (except antibiotics) ❑ No ❑ Yes ❑ Missing data
RhDnase ❑ No ❑ Yes
Mucolytics ❑ No ❑ Yes
Bronchodilators ❑ No ❑ Yes, Short-acting only
❑ Yes, Long-acting only ❑ Yes, Short- and Long-acting
Corticosteroids ❑ No ❑ Yes
Hypertonic saline ❑ No ❑ Yes
Azithromycine/macrolide ❑ No ❑ Yes ❑ Missing data

5.3 - Digestive system

Pancreatic sufficient ❑ No ❑ Yes ❑ Missing data
Pancreatic enzymes ❑ No ❑ Yes ❑ Missing data
Ursodeoxycholic acid ❑ No ❑ Yes ❑ Missing data
Tube feeding ❑ No ❑ Yes ❑ Missing data
Gastrostomy ❑ No ❑ Yes ❑ Missing data
Parenteral feeding ❑ No ❑ Yes ❑ Missing data

5.4 - Miscellaneous

Oral therapy for diabetes ❑ No ❑ Yes ❑ Missing data
Insulin therapy ❑ No ❑ Yes ❑ Missing data
Diet only (for diabetes) ❑ No ❑ Yes ❑ Missing data
PPI + H2 receptor blocker ❑ No ❑ Yes ❑ Missing data
Anticonceptive therapy (only for females) ❑ No ❑ Yes ❑ Missing data
Biphosphonates ❑ No ❑ Yes ❑ Missing data
Randomised drug trial ❑ No ❑ Yes ❑ Missing data
CFTR modulating therapy ❑ No ❑ Yes ❑ Missing data
If yes, ❑ ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown
❑ lumacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

5.4 - Miscellaneous (2)

❑ tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ elexacaftor/tezacaftor/ivacaftor Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .
Reason for stop: ❑ Side effect ❑ Contraindication ❑ End clinical trial
❑ Switch to another CFTR molecule ❑ Other ❑ Unknown

❑ blinded clinical trial Start date : . . / . . / . . . . Ongoing ❑ No ❑ Yes
Stop date : . . / . . / . . . .

❑ other Other, specify: ……. Start date : . . / . . / . . . .
Ongoing ❑ No ❑ Yes Stop date : . . / . . / . . . .

Regular chest physiotherapy ❑ No ❑ Yes ❑ Missing data

5.5 - Immunosuppressive treatments (> 3 months)

Calcineurin inhibitors
Cyclosporine ❑ No ❑ Yes ❑ Missing data
Tacrolimus ❑ No ❑ Yes ❑ Missing data
Cell cycle inhibitors
Azathioprine ❑ No ❑ Yes ❑ Missing data
Mycophenolate mofetil (MMF) ❑ No ❑ Yes ❑ Missing data
Other immunosuppressive treatments
Steroids ❑ No ❑ Yes ❑ Missing data
Everolimus ❑ No ❑ Yes ❑ Missing data
Other immunosuppressive therapy, specify

6. Transplantation

Transplant status ❑ Refused by transplant center ❑ Waiting list (with transplant)
❑ Received transplant ❑ Evaluated but not on waiting list
❑ Refused by patient ❑ Missing data

Transplant 1

Type of transplant ❑ Liver ❑ Heart ❑ Kidney ❑ Liver-Kidney ❑ Pancreas
❑ Liver-pancreas ❑ Missing data
Year of transplant : . . . .
Precise date of entering the Tx waiting list : . . / . . / . . . .
Precise date of Tx : . . / . . / . . . .

Transplant 2

Type of transplant ❑ Liver ❑ Heart ❑ Kidney ❑ Liver-Kidney ❑ Pancreas
❑ Liver-pancreas ❑ Missing data
Year of transplant : . . . .
Precise date of entering the Tx waiting list : . . / . . / . . . .
Precise date of Tx : . . / . . / . . . .

7. Social data

7.1 - Pregnancy / Paternity

Parenthood this year ❑ No ❑ Yes ❑ Missing data
Pregnancy this year *(for females)* ❑ No ❑ Yes ❑ Missing data
If Yes, pregnancy status ❑ Ongoing (on Dec 31th) ❑ Life birth ❑ Still birth
❑ Therapeutic abortion ❑ Spontaneaous abortion ❑ Unknown
Congenital anomalies ❑ No ❑ Yes ❑ Unknown ❑ Missing data
If yes, specify : ……
Delivery/adoption date of the children for this patient:
Child(ren) 1 : . . / . . . . (month/year)
Child(ren) 2 : . . / . . . . (month/year)
Child(ren) 3 : . . / . . . . (month/year)
Child(ren) 4 : . . / . . . . (month/year)

7.2 - School

School status ❑ Unknown ❑ Regular school/education attendance
❑ No school ❑ Has finished school/education ❑ Missing data

7.3 - Employment data

Patient works ❑ No ❑ Yes ❑ Missing data
Percentage ❑ Unknown ❑ Fulltime ❑Parttime ❑ Missing data

7.4 - Financial benefits

Additional child allowance ❑ No ❑ Yes ❑ Missing data
Integration support ❑ No ❑ Yes ❑ Missing data
Disability allowance ❑ No ❑ Yes ❑ Missing data
Preferential tariff ❑ No ❑ Yes ❑ Missing data
Pension ❑ No ❑ Yes ❑ Missing data
Income support ❑ No ❑ Yes ❑ Missing data

Disability recognition requested ❑ No ❑ Yes ❑ Unknown
If yes, year of request : . . . .
Parking card requested ❑ No ❑ Yes
Parking card granted ❑ No ❑ Yes ❑ Unknown
Decision made ❑ On paper ❑ With consultation ❑ Unknown
Place of decision ❑ Antwerpen ❑ Brabant wallon ❑ Brussels ❑ Hainaut
❑ Liège ❑ Luxembourg ❑ Namur
❑ Oost-Vlaanderen ❑ Vlaams Brabant ❑ West-Vlaanderen
For a child:
Number of points granted : . .
Pilar 1 : .
Pilar 2 : .
Pilar 3 : .
Part-time by any parent ❑ No ❑ Yes ❑ Unknown

7.4 - Financial benefits (2)

For an adult:

Working disability ❑ No ❑ Yes ❑ Unknown

Independence - number of points granted : . .

Section 1 (Movement) : .

Section 2 (Cooking) : .

Section 3 (Hygiene) : .

Section 4 (Household) : .

Section 5 (Reaction) : .

Section 6 (Communication) : .

Duration ❑ Limited ❑ Unlimited

7.5 - Family composition

Household composition ❑ Unchanged ❑ Changed
❑ First registration ❑ Missing data

Number of siblings including the patient .....

Number of siblings with CF .....

Number of siblings deceased from CF .....

General remark .....
.....

NOTES

MORE INFORMATIONS

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