ANNUAL REPORT

# BELGIAN CYSTIC FIBROSIS REGISTRY BCFR 2020

## 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 $kg/m^2$.

**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

**pwCF** – People with Cystic Fibrosis

**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 pwCF, 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

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# SUMMARY

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This report presents the data collected in 2020. 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 quality of care provided to pwCF and trends.

Since its establishment in 1999, the Belgian CF Registry (BCFR) has grown steadily and had 1353 pwCF registered in 2020. This number excludes 17 people whose diagnosis for CF was revoked and 33 others without a confirmed diagnosis. There were 29 newly diagnosed pwCF in 2020, among them two adults, with a median age at diagnosis of one month and age range from birth to 34.7 years. All the newly diagnosed pwCF were genotyped; 26 had sweat chloride values > 60 mmol/L and two < 60mmol/L.

Among the pwCF followed-up in 2020, 52.2% were male and 65.0% adults, and the median age was 24.2 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. 45.5% of the pwCF are homozygous for the F508del mutation and 39.2 % are F508del heterozygous. The main reasons for diagnosis of CF are acute or recurrent respiratory problems (41.8%) and failure to thrive (24.8%). About 19.8% of all pwCF were diagnosed via neonatal screening. With regional New Born Screening (NBS) programs starting in the Dutch speaking Flanders in January 2019 and in the French speaking Wallonia in January 2020, about 72.4% of the new diagnoses were based on neonatal screening. Some local NBS initiatives in the previous years explain this difference in proportions. Within the year, ten deaths were reported (seven of them among transplanted pwCF) with age at death ranging from 20 to 72 years. Nine pwCF received a transplanted organ (7 lung transplantations). About 14.6% of the pwCF in the registry are living with a transplanted organ, a majority of these having had a lung transplantation.

Among the adults, the proportion of underweight pwCF (BMI < 18.5 kg/m$^2$), continues to decline from about 31.2% in 1998 to 16.7% in 2010 and 8.2% in 2020. This decline was noted also amongst the F508del homozygous pwCF; 32.8% in 2000, 21.9% in 2010, and 9.8% in 2020. Amongst the pwCF 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 management and certainly better care for pwCF. The CF population continues to record an improvement in lung function expressed as the mean percentage of predicted $FEV_1$. Among the F508del homozygous pwCF, 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 54.5% and 17.5% respectively among the children and adults in 2020.

The overall annual prevalence of *Pseudomonas aeruginosa* reported in 2020 was 33.7%. This is in line with the general decline observed from 42.4% in 2012 to 37.5% in 2016. The prevalence of *Achromobacter xylosoxidans* steadily increased from 5.9% in 2009 to a stable 10.0% since 2012, but now decreased to 8.3% in 2020. The prevalence of the *Burkholderia cepacia* complex on the other hand remains at about 3.5% over the years since 2014, with 2.8% in 2020.

Thanks to improved disease management and novel treatments, the life expectancy and the quality of life of pwCF 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 2020, CF-related diabetes had a prevalence of 3.8% and 28.7% in children and adults respectively (excluding transplanted pwCF). Other reported complications include early osteoporosis and CF related arthritis/arthropathy. These require specialized care for the adults with CF.

# BACKGROUND

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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 lethal 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 date 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 pwCF, with late or milder symptoms, it can occur later into adulthood.

The neonatal CF screening program has a national coverage in Belgium since 2020. Noteworthy is that the national coverage is based on two official regional programs, from January 2019 in Flanders, and from January 2020 in Wallonia [5,6], with the same screening 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 pwCF 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 pwCF to identify the CF-causing mutations. F508del is the most common mutation, not just in the Belgian CF population but also worldwide.

Today, the standard treatments available to most pwCF 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 advancements in CF care, including and not limited to multidisciplinary care and novel treatments, the quality of life and the life expectancy have increased, with almost all pwCF reaching the adult age. CFTR modulators are a new and more effective treatment that targets the molecular defects and act upstream on the cause rather than on the symptoms resulting from the CFTR defect. While these are now available for most PwCF, research is still ongoing targeting the genetic defects, mainly for the few pwCF still not eligible for the CFTR modulator therapy.

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 pwCF 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 pwCF 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 pwCF homozygous for the F508del mutation [9]; and tezacaftor/ ivacaftor (Symkevi®) for pwCF 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 pwCF carrying at least one F508del [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 pwCF 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 pwCF 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]. PwCF who received a lung transplant are not eligible for this treatment.

For pwCF 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 pwCF 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 pwCF carrying two copies of the F508del mutation, but also pwCF 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 pwCF older than 12 years (extended in September 2020 to 6-11y), with reimbursement in Belgium as of April 2021 for pwCF 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 pwCF 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 an $FEV_1$% increase of 10-11% for homozygous pwCF, and 13.9% for pwCF with a minimal mutation (compared to 0.4% in the placebo group) [32, 33].

The use of Kaftrio® in Belgium was first authorized in June 2020 in a FAGG approved Medical Need Program for pwCF homozygous for the F508del mutation or with a F508del mutation and a minimal function mutation, who have a poor pulmonary status, waiting for a lung transplantation [34, 35]. From September 2022, it started being reimbursed for pwCF 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

Disability Insurance (INAMI - RIZIV) and receive financial support. An annual care and revalidation agreement (CF convention) for pwCF 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 pwCF in order to provide optimal medical, paramedical, psychological and social care to the pwCF 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[1] 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 constitutes 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 aim of the CF registry is to study epidemiological aspects of the disease among pwCF in Belgium and to provide a tool for the assessment of the management and quality of care for pwCF. It also provides a database for scientific research to CF researchers, and for analysis provided to the pharmaceutical industry (numbers of pwCF eligible for clinical trials, and reimbursement procedures). The registry also participates in activities organized by the European Cystic Fibrosis Society Patient Registry (ECFSPR) [43] and other international projects.

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1    BCFA: Mucovereniging – Association Muco

# POPULATION AND METHODOLOGY

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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 2020, there were 1353 pwCF reported in the registry. Now, 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 pwCF and/or their parents (or legal representative) information about the objectives of the registry. The pwCF 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 names of pwCF are never transferred to the registry.

## 2.2 DATA COLLECTION

The clinical and demographic data are collected for all pwCF 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 person 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

Until 2010, the data were collected via an Access based computer application on CD-Rom. A web-based application which worked with a 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 receive a copy of the national annual report. Since 2006, they receive a centre report based on the data from pwCF 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 pwCF is called benchmarking. These analyses are corrected for some known factors such as the 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. 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 pwCF, 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

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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**

Global architecture
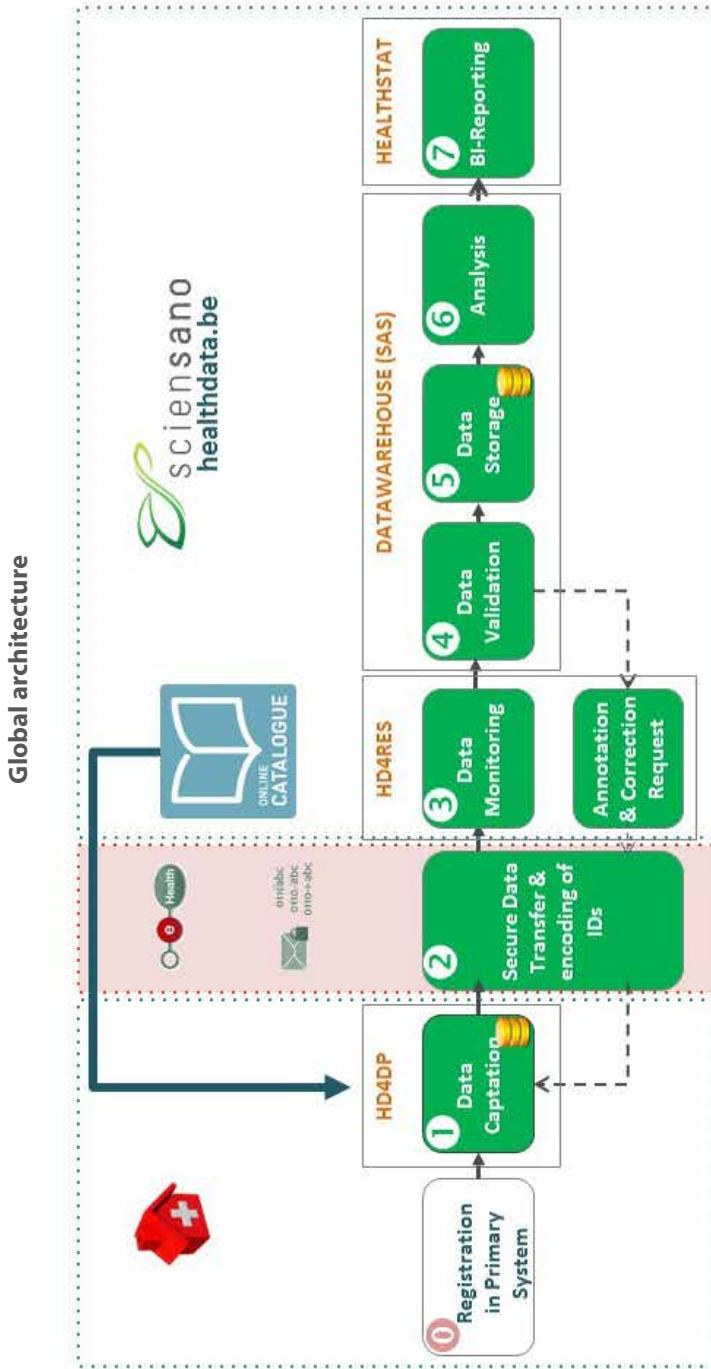
were collected for registry year 2014. The scheme in figure 1 shows various stages from data entry and processing to reporting and publication.

**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 pwCF (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 with unrecognizable individual 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 person 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 Healthstat. 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 2017 - 2020

### Table 1 | Demographic and diagnosis data

| | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| Number of people with CF (pwCF) | 1319 | 1327 | 1372 | 1353 |
| Number of pwCF with complete records | 1288 | 1299 | 1298 | 1334 |
| Number of pwCF without observation[1] | 31 | 28 | 74 | 19 |
| Number of pwCF with a transplant n (%) | 184 (13.8%) | 189 (14.1%) | 202 (14.6%) | 203 (14.6%) |
| Number of pwCF with a lung transplant | 172 | 180 | 193 | 193 |
| Number of pwCF who were not seen | 23 | 31 | 67 | 12 |
| New CF diagnoses[2] | 38 | 22 | 33 | 29 |
| Number of adults among the newly diagnosed pwCF | 2 | 5 | 6 | 2 |
| Number of pwCF without a confirmed diagnosis by physicians[3] | 14 | 9 | 11 | 33 |
| Number of pwCF without a confirmed diagnosis according to the ECFSPR | 69 | 67 | 76 | 49 |
| Number of pwCF with a revoked diagnosis[4] | 4 | 2 | 1 | 17 |
| Median age in years (range)[5] | 22.8 (0.2 - 76.5) | 23.5 (0.2 - 77.5) | 23.6 (0.1 - 78.5) | 24.2 (0.0 - 85.1) |
| Median age male (range)[5] | 22.4 (0.3 - 70.3) | 22.8 (0.2 - 65.4) | 23.6 (0.1 - 66.4) | 23.6 (0.0 - 85.1) |
| Median age female (range)[5] | 22.9 (0.2 - 76.5) | 23.8 (0.7 - 77.5) | 23.9 (0.1 - 78.5) | 24.6 (0.1 - 79.5) |
| Males (%) | 683 (51.8%) | 687 (51.8%) | 709 (51.7%) | 706 (52.2%) |
| Adults ≥ 18 years (%) | 821 (62.2%) | 850 (64.1%) | 889 (64.8%) | 880 (65.0%) |
| Median age at diagnosis (months) | 5.2 | 5.2 | 5.0 | 4.6 |
| Age range at diagnosis (years)[6] | -0.4 - 65.2 | - 0.4 - 70.6 | - 0.4 - 75.5 | - 0.4 - 82.6 |
| Median age at diagnosis, male (months) | 5.4 | 5.2 | 5.0 | 4.5 |
| Age range at diagnosis, male (years) | -0.2 - 59.5 | -0.2 - 59.5 | -0.2 - 59.5 | -0.2 - 82.6 |
| Median age at diagnosis, female (months) | 5.1 | 5.1 | 5.0 | 4.6 |
| Age range at diagnosis, female (years) | -0.4 - 65.2 | -0.4 - 70.6 | -0.4 - 75.5 | -0.4 - 75.5 |
| Median age at diagnosis for new cases, months (range) | 5.4 (0.0 - 724.5) | 9.8 (0.1 - 846.6) | 4.8 (0.0 - 707.0) | 0.8 (0.1 - 410.8) |
| Median age at diagnosis new cases in years (range) | 0.4 (0.0 - 60.4) | 0.8 (0.0 - 70.6) | 0.4 (0.0 - 58.9) | 0.1 (0.0 - 34.2) |
| Number of transplants performed | 14 | 17 | 20 | 9 |
| Total number of deaths reported | 6 | 16 | 6 | 10 |
| Median age at death in years (range) | 25.8 (11.8 - 70.4) | 44.1 (20.4 - 70.2) | 45.6 (29.6 - 60.1) | 47.8 (19.4 - 72.4) |
| Number of deaths among transplanted pwCF | 2 | 9 | 4 | 7 |

1. PwCF 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 people 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. PwCF without a confirmed CF diagnosis are not included in the total number of pwCF
4. PwCF with a revoked diagnosis are not included in the total number of pwCF
5. 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**

| | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| **SPIROMETRY: FEV$_1$% PREDICTED[1]** | | | | |
| Mean (SD) FEV$_1$ % predicted, Last of year | 76.8 (24.0) | 78.0 (24.6) | 78.5 (24.0) | 79.6 (23.3) |
| male | 78.2 (23.5) | 79.2 (24.2) | 79.9 (23.8) | 80.7 (22.8) |
| female | 75.3 (24.5) | 76.7 (25.0) | 77.0 (24.2) | 78.4 (23.9) |
| children | 89.7 (18.3) | 91.1 (18.5) | 92.2 (18.8) | 92.3 (18.0) |
| adults | 69.1 (23.6) | 70.4 (24.5) | 72.6 (23.7) | 72.9 (23.1) |
| Mean (SD) FEV$_1$ % predicted, Best of year | 81.1 (23.2) | 82.3 (23.8) | 82.8 (23.4) | 83.4 (23.0) |
| male | 82.4 (22.6) | 83.3 (23.4) | 84.0 (23.1) | 84.5 (22.4) |
| female | 79.7 (23.9) | 81.2 (24.2) | 81.5 (23.7) | 82.1 (23.6) |
| children | 94.2 (17.4) | 96.4 (17.1) | 97.1 (17.1) | 96.4 (16.8) |
| adults | 73.2 (22.7) | 74.1 (23.3) | 76.5 (23.0) | 76.5 (22.8) |
| Mean (SD) FEV$_1$ % predicted z-score, Last of year | -1.8 (1.9) | -1.7 (1.9) | -1.7 (1.9) | -1.6 (1.8) |
| male | -1.7 (1.8) | -1.6 (1.9) | -1.6 (1.8) | -1.5 (1.8) |
| female | -1.9 (1.9) | -1.8 (2.0) | -1.8 (1.9) | -1.7 (1.9) |
| children | -0.8 (1.5) | -0.7 (1.5) | -0.6 (1.6) | -0.6 (1.5) |
| adults | -2.4 (1.8) | -2.3 (1.9) | -2.1 (1.8) | -2.1 (1.8) |
| Mean (SD) FEV$_1$ % predicted z-score, Best of year | -1.5 (1.8) | -1.4 (1.9) | -1.3 (1.8) | -1.3 (1.8) |
| male | -1.4 (1.8) | -1.3 (1.8) | -1.2 (1.8) | -1.2 (1.8) |
| female | -1.6 (1.9) | -1.5 (1.9) | -1.4 (1.9) | -1.4 (1.9) |
| children | -0.5 (1.4) | -0.3 (1.4) | -0.2 (1.4) | -0.3 (1.4) |
| adults | -2.1 (1.8) | -2.0 (1.8) | -1.8 (1.8) | -1.8 (1.8) |
| **ANTHROPOMETRY: BMI, HEIGHT AND WEIGHT (using CDC references)[2]** | | | | |
| Median (range) BMI Z-score (last of year) | -0.4 (-4.0 - 2.6) | -0.4 (-3.3 - 2.6) | -0.3 (-3.2 - 2.6) | -0.2 (-3.2 - 2.6) |
| Median (range) Weight Z-score (last of year) | -0.4 (-4.5 - 2.6) | -0.5 (-4.7 - 2.7) | -0.5 (-4.9 - 2.7) | -0.4 (-3.9 - 2.2) |
| Median (range) Height Z-score (last of year) | -0.4 (-3.4 - 2.9) | -0.4 (-3.5 - 2.6) | -0.4 (-4.8 - 2.4) | -0.4 (-3.9 - 2.8) |

| | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| **INFECTIONS AND BACTERIOLOGY[3]** | | | | |
| *Pseudomonas aeruginosa* | 427 (39.1%) | 417 (37.9%) | 391 (35.4%) | 375 (33.6%) |
| *Burkholderia cepacia complex* | 31 (2.8%) | 33 (3.0%) | 38 (3.4%) | 31 (2.8%) |
| *Methicillin Resistant Staphylococcus Aureus* (MRSA) | 76 (7.0%) | 68 (6.2%) | 65 (5.9%) | 73 (6.5%) |
| *Haemophilus influenzae* | 272 (24.9%) | 272 (24.7%) | 279 (25.2%) | 188 (16.8%) |
| *Stenotrophomonas maltophilia* | 133 (12.2%) | 141 (12.8%) | 135 (12.2%) | 132 (11.8%) |
| *Achromobacter xylosoxidans* | 124 (11.3%) | 111 (10.1%) | 98 (8.9%) | 92 (8.2%) |
| *Aspergillus* spp. | 339 (31.0%) | 370 (33.6%) | 309 (28.0%) | 283 (25.4%) |
| *Atypical Non-tuberculous Mycobacterium* (NTM) | 19 (1.7%) | 17 (1.5%) | 29 (2.6%) | 24 (2.2%) |
| SARS-CoV-2 test performed this year | | | | 575 (50.9%) |
| COVID-19 | | | | 41 (7.1%) |
| Chronic *Pseudomonas aeruginosa* | 275 (25.2%) | 266 (24.2%) | 266 (24.1%) | 248 (22.2%) |
| Chronic *Burkholderia Cepacia complex* | 24 (2.2%) | 24 (2.2%) | 25 (2.3%) | 24 (2.2%) |
| Chronic *Stenotrophomonas maltophilia* | 41 (3.8%) | 44 (4.0%) | 37 (3.3%) | 29 (2.6%) |
| Chronic *Achromobacter xylosoxidans* | 68 (6.2%) | 70 (6.4%) | 63 (5.7%) | 62 (5.6%) |
| Chronic MRSA | 49 (4.5%) | 47 (4.3%) | 40 (3.6%) | 38 (3.4%) |
| **COMPLICATIONS** | | | | |
| Allergic Bronchopulmonary Aspergillosis (ABPA) | 80 (7.1%) | 97 (8.5%) | 105 (9.0%) | 101 (8.8%) |
| Haemoptysis requiring embolization | 3 (0.3%) | 4 (0.4%) | 4 (0.3%) | 12 (1.0%) |
| Pancreatic Insufficiency | 983 (74.9%) | 964 (72.8%) | 1071 (78.7%) | 1112 (82.6%) |
| CF related diabetes (CFRD) | 328 (25.0%) | 250 (18.9%) | 253 (18.6%) | 330 (24.5%) |
| Bronchiectasis[4] | 310 (71.9%) | 329 (78.1%) | 327 (73.8%) | 366 (75.9%) |
| **RESPIRATORY THERAPY[5]** | | | | |
| Regular chest physiotherapy | 1108 (98.1%) | 1109 (97.7%) | 1116 (96.1%) | 1130 (98.8%) |
| Oral Antibiotics only | 458 (40.6%) | 471 (41.5%) | 498 (42.9%) | 524 (45.8%) |
| IV Antibiotics only | 18 (1.6%) | 23 (2.0%) | 23 (2.0%) | 32 (2.8%) |
| Oral and IV Antibiotics | 413 (36.6%) | 415 (36.6%) | 395 (34.0%) | 331 (28.9%) |
| Other inhaled Antibiotics | 607 (53.8%) | 618 (54.4%) | 591 (50.9%) | 593 (51.8%) |
| RhDnase | 924 (81.8%) | 941 (82.9%) | 950 (81.8%) | 970 (84.8%) |
| Other mucolytics | 221 (19.6%) | 152 (13.4%) | 146 (12.6%) | 89 (7.8%) |
| Hypertonic saline | 703 (62.3%) | 746 (65.7%) | 743 (64.0%) | 790 (69.1%) |
| Corticosteroids | 593 (52.5%) | 569 (50.1%) | 587 (50.6%) | 601 (52.5%) |
| Bronchodilators | 831 (73.6%) | 863 (76.0%) | 868 (74.8%) | 852 (74.5%) |
| Oral anti-inflammatories | 658 (50.1%) | 683 (51.6%) | 683 (50.2%) | 636 (47.2%) |
| Oral Azithromycin | 579 (51.3%) | 608 (53.6%) | 600 (51.7%) | 597 (52.2%) |
| Oral Systemic Corticosteroids | 63 (5.6%) | 54 (4.8%) | 33 (2.8%) | 32 (2.8%) |
| Oral NSAID | 34 (3.0%) | 32 (2.8%) | 41 (3.5%) | 40 (3.5%) |
| Oxygen Therapy | 21 (1.9%) | 32 (2.8%) | 26 (2.2%) | 33 (2.9%) |

| | 2017 | 2018 | 2019 | 2020 |
|---|---|---|---|---|
| **GASTRO-INTESTINAL AND NUTRITIONAL THERAPY** | | | | |
| Pancreatic enzymes | 980 (74.6%) | 967 (73.0%) | 970 (71.3%) | 1116 (82.9%) |
| Proton pump Inhibitors + H2 blocker | 603 (45.9%) | 598 (45.2%) | 620 (45.6%) | 736 (54.6%) |
| Enteral feeding | 31 (2.4%) | 22 (1.7%) | 32 (2.4%) | 38 (2.8%) |
| Parenteral feeding | 7 (0.5%) | 5 (0.4%) | 4 (0.3%) | 7 (0.5%) |
| Gastrotomy tube | 49 (3.7%) | 50 (3.8%) | 53 (3.9%) | 56 (4.2%) |
| **OTHER TREATMENTS** | | | | |
| Ursodeoxycholic acid | 235 (17.9%) | 225 (17.0%) | 228 (16.8%) | 277 (20.6%) |
| Insulin therapy | 252 (19.2%) | 193 (14.6%) | 190 (14.0%) | 271 (20.1%) |
| Oral Therapy for Diabetes | 34 (2.6%) | 37 (2.8%) | 40 (2.9%) | 48 (3.6%) |
| Bisphosphonates | 24 (1.8%) | 22 (1.7%) | 28 (2.1%) | 62 (4.6%) |
| Anti-conceptive therapy[6] | 148 (30.6%) | 150 (30.1%) | 165 (32.2%) | 171 (34.7%) |
| **CFTR MODULATING THERAPY** | | | | |
| CFTR Modulating Therapy[7] | 124 (11.0%) | 155 (13.7%) | 167 (14.4%) | 236 (20.6%) |
| Kalydeco® (Ivacaftor) | 30 (2.7%) | 51 (4.5%) | 51 (4.4%) | 48 (4.2%) |
| Orkambi® (Lumacaftor/ivacaftor) | 65 (5.8%) | 68 (6.0%) | 57 (4.9%) | 64 (5.6%) |
| Symkevi® (Tezacaftor/ivacaftor) | 14 (1.2%) | 12 (1.1%) | 19 (1.6%) | 12 (1.0%) |
| Kaftrio® (Elexacaftor/tezacaftor/ivacaftor) | | 8 (0.7%) | 23 (2.0%) | 101 (8.8%) |
| Other or Blinded clinical trial | 15 (1.3%) | 16 (1.4%) | 17 (1.5%) | 11 (1.0%) |

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

# DEMOGRAPHIC DATA

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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 2020.

## 3.1 AGE ON DECEMBER 31 2020

**Table 3 |** Age on December 31 2020 by gender

| Age years (on 31 Dec 2020) | Males | | | Females | | | All Patients | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | cum n | cum % | n | cum n | cum % | n | cum n | cum % |
| 0 - < 5 | 56 | 56 | 7.9 | 52 | 52 | 8.0 | 108 | 108 | 8.0 |
| 5 - < 10 | 71 | 127 | 18.0 | 69 | 121 | 18.7 | 140 | 248 | 18.3 |
| 10 - < 15 | 69 | 196 | 27.8 | 60 | 181 | 28.0 | 129 | 377 | 27.9 |
| 15 - < 20 | 65 | 261 | 37.0 | 78 | 259 | 40.0 | 143 | 520 | 38.4 |
| 20 - < 25 | 112 | 373 | 52.8 | 66 | 325 | 50.2 | 178 | 698 | 51.6 |
| 25 - < 30 | 74 | 447 | 63.3 | 65 | 390 | 60.3 | 139 | 837 | 61.9 |
| 30 - < 35 | 57 | 504 | 71.4 | 66 | 456 | 70.5 | 123 | 960 | 71.0 |
| 35 - < 40 | 56 | 560 | 79.3 | 62 | 518 | 80.1 | 118 | 1078 | 79.7 |
| 40 - < 45 | 61 | 621 | 88.0 | 46 | 564 | 87.2 | 107 | 1185 | 87.6 |
| 45 - < 50 | 37 | 658 | 93.2 | 27 | 591 | 91.3 | 64 | 1249 | 92.3 |
| ≥ 50 | 48 | 706 | 100.0 | 56 | 647 | 100.0 | 104 | 1353 | 100.0 |
| **Total** | **706** | | | **647** | | | **1353** | | |

The median age on 31, December 2020 was 23.7 and 24.8 years for male and female pwCF respectively.

The figure 2 compares the age distribution by gender for 2000 and 2020 data, observing an increase in the number of pwCF above age 40 years: 19.7% in 2020 compared to 1.3% in 2000.



**2000**
Adults = 39.2%
40y and above = 10 (1.3%)

Female (n=363) ◼◻ Male (n=395)

**2020**
Adults = 65.0%
40y and above = 266 (19.7%)

Female (n=647) ◼◻ Male (n=706)

Based on age on December 31th of the respective year.
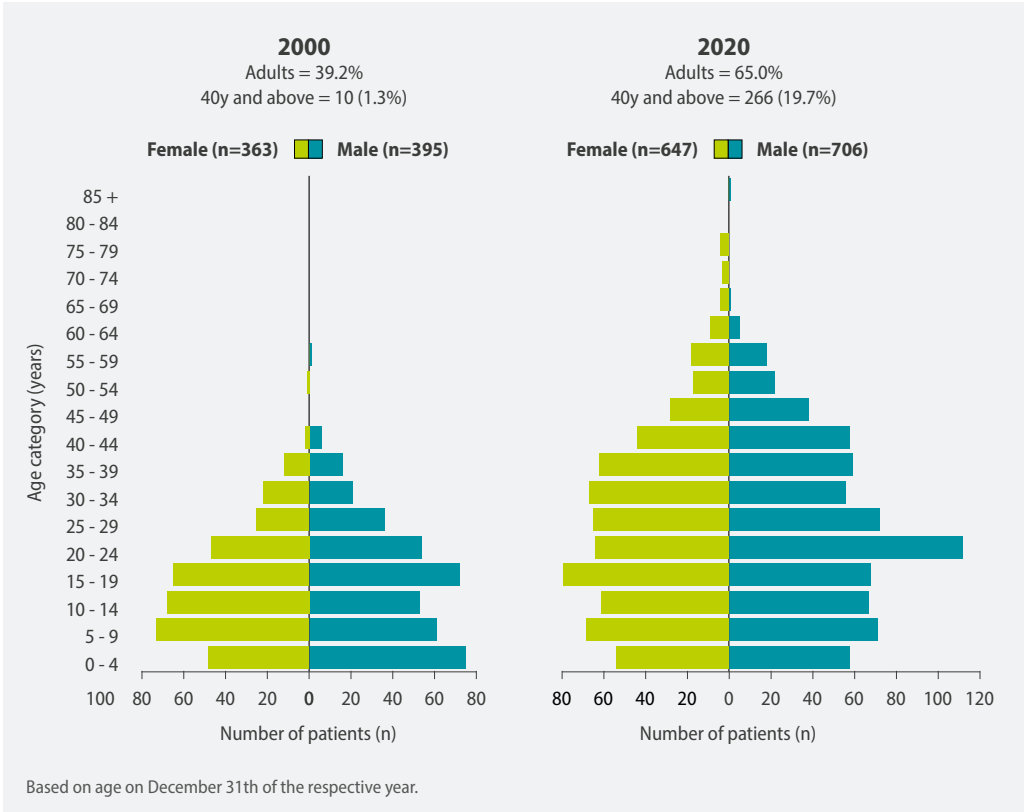
**Figure 2 |** **Age distribution by gender in 2000 (left) and 2020 (right)**
Based on age on December 31st of the respective year.

## 3.2    DISTRICT OF RESIDENCE

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

**Table 4 |    District of residence**

| | District / Arrondissement | n | % | | District / Arrondissement | n | % |
|---|---|---|---|---|---|---|---|
| B11 | Antwerpen | 122 | 9.1 | B53 | Mons | 29 | 2.2 |
| B12 | Mechelen | 59 | 4.4 | B54 | Tournai - Mouscron | 21 | 1.6 |
| B13 | Turnhout | 71 | 5.3 | B55 | Soignies | 8 | 0.6 |
| B21 | Brussel Hoofdstedelijk Gewest - Région Bruxelles Capitale | 108 | 8.1 | B56 | Thuin | 15 | 1.1 |
| | | | | B58 | La Louvière | 26 | 1.9 |
| B23 | Halle-Vilvoorde | 76 | 5.7 | B61 | Huy | 21 | 1.6 |
| B24 | Leuven | 59 | 4.4 | B62 | Liège | 89 | 6.7 |
| B25 | Nivelles | 59 | 4.4 | B63 | Verviers | 22 | 1.6 |
| B31 | Brugge | 23 | 1.7 | B64 | Waremme | 12 | 0.9 |
| B32 | Diksmuide | 14 | 1.0 | B71 | Hasselt | 46 | 3.4 |
| B33 | Ieper | 12 | 0.9 | B72 | Maaseik | 24 | 1.8 |
| B34 | Kortrijk | 31 | 2.3 | B73 | Tongeren | 16 | 1.2 |
| B35 | Oostende | 23 | 1.7 | B81 | Arlon | 4 | 0.3 |
| B36 | Roeselare | 22 | 1.6 | B82 | Bastogne | 3 | 0.2 |
| B37 | Tielt | 10 | 0.7 | B83 | Marche-en-Famenne | 9 | 0.7 |
| B38 | Veurne | 11 | 0.8 | B84 | Neufchâteau | 10 | 0.7 |
| B41 | Aalst | 37 | 2.8 | B85 | Virton | 7 | 0.5 |
| B42 | Dendermonde | 17 | 1.3 | B91 | Dinant | 17 | 1.3 |
| B43 | Eeklo | 10 | 0.7 | B92 | Namur | 28 | 2.1 |
| B44 | Gent | 71 | 5.3 | B93 | Philippeville | 9 | 0.7 |
| B45 | Oudenaarde | 16 | 1.2 | | **Subtotal** | **1339** | |
| B46 | Sint-Niklaas | 29 | 2.2 | | | | |
| B51 | Ath | 17 | 1.3 | | Foreign country/ unknown | 14 | 1.0 |
| B52 | Charleroi | 26 | 1.9 | | | | |
| | | | | | **TOTAL** | **1353** | |

## 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 2020. 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. The white circles represent the geographical position of the seven reference centres, i.e. ten clinic sites.
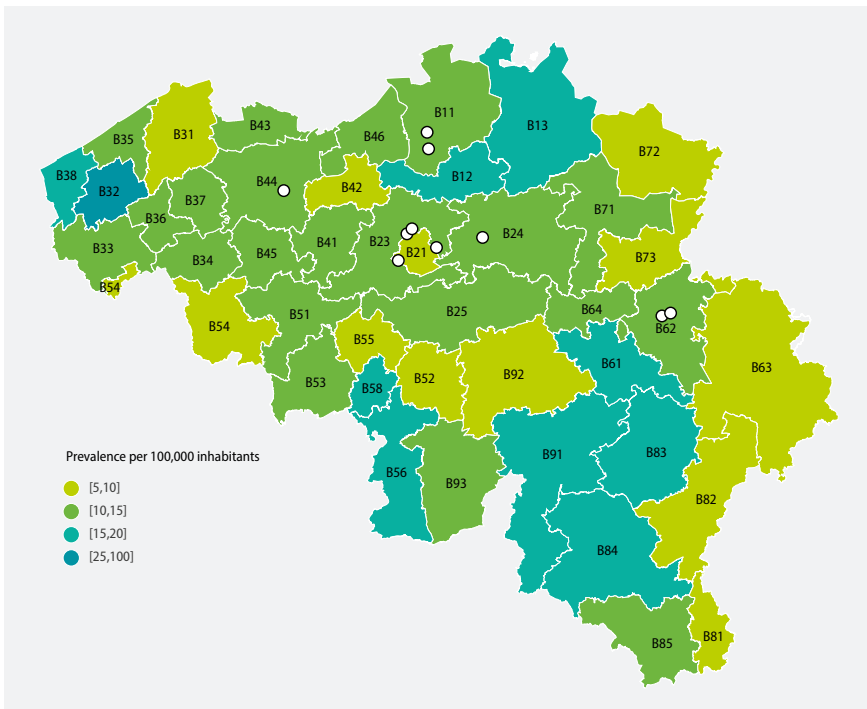


**Figure 3 |    Prevalence of CF per 100,000 inhabitants by district of residence in January 2020**

The top three districts with the highest prevalence are Diksmuide (Dixmude, code 32) with prevalence 27.1 per 100,000 inhabitants, and population 51,696; Huy (Hoei, code 61) with prevalence 18.4 and population of 113,869 ; and La Louvière (code 58) with prevalence 18.4 and population 141,470 at the beginning of the year respectively. The bottom three districts with the lowest prevalence are Charleroi (code 52) with prevalence 6.5 and population 396,962; Arlon (Aarlen, code 81) with prevalence 6.3 and population 62,996 and lastly Bastogne (Bastenaken, code 82) which had the lowest prevalence of 6.1 and population 49,083.

## 3.4    PEOPLE 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.
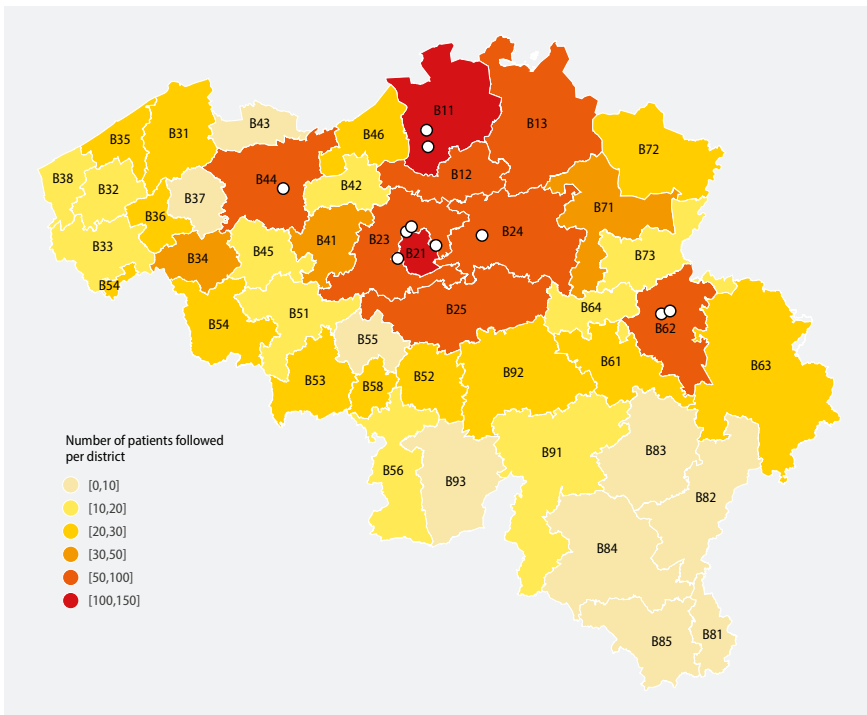


**Figure 4 |    Number of people with CF per district of residence in January 2020**

We see more pwCF concentrated in the central and northern sides of the country. Due to their populous nature though, Antwerp (Antwerpen/Anvers, code 11), with 122 pwCF in a population of about 1.060 million, had a prevalence of 11.5 in 100,000 inhabitants, and the capital city Brussels (Brussel/ Bruxelles, code 21) coming second with 108 pwCF in 1.220 million inhabitants and a prevalence of 8.7. The districts with the fewest pwCF were Arlon (Aarlen, code 81) and Bastogne (Bastenaken, code 82), with 4 and 3 pwCF respectively, and a prevalence of 6.3 and 6.1.

# DIAGNOSIS

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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 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 person 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 pwCF 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 new-born 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 pwCF 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 individual. 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 19.8% of all the pwCF were diagnosed via neonatal screening test.

**Table 5 |** **Symptoms and clinical reasons for CF diagnosis**

| | All pwCF | | Newly diagnosed | | | |
| | | | 2019 | | 2020 | |
| | n | % | n | % | n | % |
|---|---|---|---|---|---|---|
| Acute or recurrent respiratory problems | 542 | 41.8 | 11 | 35.5 | 5 | 17.2 |
| Failure to thrive | 322 | 24.8 | 8 | 25.8 | 4 | 13.8 |
| Chronic diarrhea / steatorrhea / malabsorption | 219 | 16.9 | 1 | 3.2 | 1 | 3.4 |
| Neonatal screening test | 257 | 19.8 | 12 | 38.7 | 21 | 72.4 |
| Meconium ileus | 188 | 14.5 | 5 | 16.1 | 3 | 10.3 |
| Family history | 135 | 10.4 | 2 | 6.5 | 2 | 6.9 |
| Nasal polyposis / chronic sinusitis | 64 | 4.9 | 3 | 9.7 | 2 | 6.9 |
| Rectal prolapse / Intestinal obstruction (other than meconium ileus) | 57 | 4.4 | 0 | 0.0 | 0 | 0.0 |
| Prenatal diagnosis | 35 | 2.7 | 0 | 0.0 | 0 | 0.0 |
| Dehydration / electrolyte imbalance / Neonatal jaundice / Prolonged icterus | 33 | 2.5 | 1 | 3.2 | 1 | 3.4 |
| Infertility | 19 | 1.5 | 2 | 6.5 | 0 | 0.0 |
| Diagnosis other | 75 | 5.8 | 3 | 9.7 | 1 | 3.4 |
| No diagnosis reasons given | 57 | 4.4 | 0 | 0.0 | 0 | 0.0 |

The overall percentages are based on 1296, 57 pwCF did not have information on any of the above reasons given in the 2020 data and were excluded from the calculations.
There were 31 newly diagnosed in 2019, percentages are based on 31 people.
There were 29 newly diagnosed in 2020, percentages are based on 29 people.
Note: Reasons for diagnosis are not mutually exclusive, implying a person may present more than one symptom hence counted more than once.

## 4.2    DOCUMENTATION OF CF AT DIAGNOSIS

According to the European Cystic Fibrosis Society Patient Registry (ECFSPR), for a person 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 pwCF in our registry. These data are presented in the table 6.

| **Inclusion criteria for PwCF into the European CF Society Patient Registry (ECFSPR)** |
|---|
| For a person 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:<br>**i.  A DNA Analysis/Genotyping where two disease causing CF mutations are identified**<br>**ii.  A Transepithelial (Nasal) Potential Difference value** – Consistent with a diagnosis of CF<br>**iii. Clinical Presentation at diagnosis** – Where typical features of CF are identified |

**Table 6 |**    **Documentation of CF diagnosis**

| Procedure | All pwCF | | New diagnoses 2020 | |
|---|---|---|---|---|
| | n | % | n | % |
| **PwCF meeting the European CF Society Patient Registry criteria** | | | | |
| Clinical symptoms and/or family history, sweat test and genotyping | 702 | 51.9 | 3 | 10.3 |
| Clinical symptoms and/or family history, sweat test, genotyping and abnormal TEPD | 42 | 3.1 | | |
| Clinical symptoms and/or family history and sweat test | 71 | 5.2 | 2 | 6.9 |
| Clinical symptoms and/or family history, sweat test and abnormal TEPD | 7 | 0.5 | | |
| Clinical symptoms and/or family history and genotyping | 141 | 10.4 | 3 | 10.3 |
| Clinical symptoms and/or family history, genotyping and abnormal TEPD | 6 | 0.4 | | |
| Neonatal screening test, sweat test and genotyping | 134 | 9.9 | 12 | 41.4 |
| 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 | 74 | 5.5 | 6 | 20.7 |
| Sweat test and genotyping | 38 | 2.8 | | |
| 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 | 6 | 0.4 | 2 | 6.9 |
| Sweat test only | 2 | 0.1 | | |
| Clinical symptoms and/or family history, neonatal screening test and genotyping | 7 | 0.5 | | |
| Clinical symptoms and/or family history, neonatal screening test and sweat test | 7 | 0.5 | 1 | 3.4 |
| Clinical symptoms and/or family history and abnormal TEPD | 15 | 1.1 | | |
| Genotyping only | 28 | 2.1 | | |
| Sweat test and abnormal TEPD | 1 | 0.1 | | |
| Neonatal screening test and genotyping | 13 | 1.0 | | |
| **Total** | **1304** | **96.4** | **29** | **100.0** |
| **PwCF not meeting the European CF Society Patient Registry criteria** | | | | |
| Clinical symptoms and/or family history only | 37 | 2.7 | | |
| Neonatal screening test only | 4 | 0.3 | | |
| Clinical symptoms and/or family history and neonatal screening test | 4 | 0.3 | | |
| Abnormal or Positive TEPD only | 3 | 0.2 | | |
| Missing | 1 | 0.1 | | |
| **Total** | **49** | **3.6** | | |

**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 pwCF and the cumulative percentage of age at diagnosis for people alive in data 2020. The median age at diagnosis was 4.6 months; 4.5 months for male and 4.6 months for females with CF. At the age of 18 years, 90.9% of the pwCF 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 those F508del homozygous, 8.2 months for the F508del heterozygous, and 6.4 months for people with other mutations.
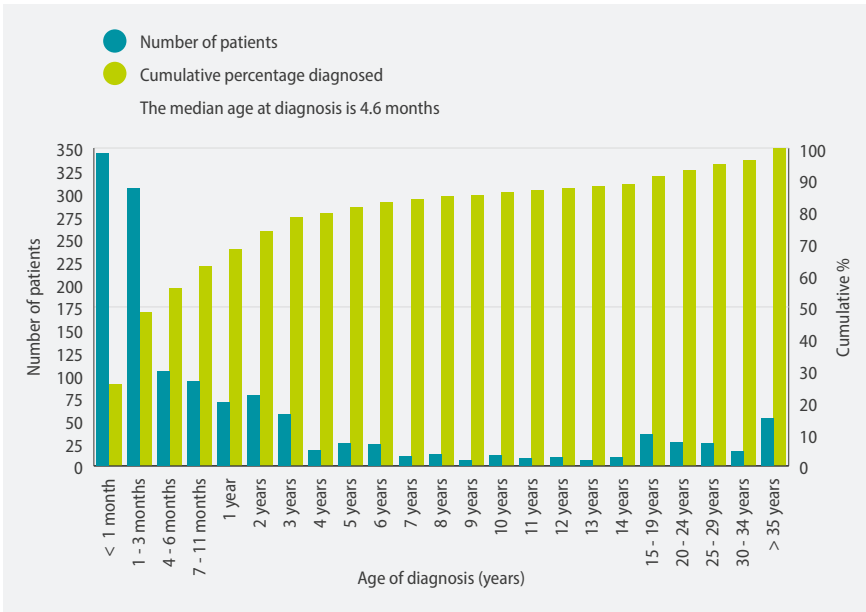


**Figure 5 |    Age at diagnosis**

The median age at diagnosis for the 29 newly diagnosed pwCF in 2020 was 0.8 months; 0.8 months for male and 1.0 months for female pwCF, with range from before birth to 34.2 years. There were two adult pwCF amongst the newly diagnosed.

## 4.4    GENOTYPE

All 1353 people have undergone extended genetic analysis. Almost half (45.5%) were homozygous for F508del (table 7), and 86.0% of the pwCF had this mutation on at least one of their alleles (table 8). However, 18 pwCF (1.3%) had at least one non-identified mutation. The mutation list included 143 different alleles present in at least one person.

**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 | 616 | 45.5% | | | | | | | | | 616 | 45.5% |
| **F508del Heterozygous** | | | | | | | | | | | |
| DC | 455 | 33.6% | 3 | 0.2% | 43 | 3.2% | 37 | 2.7% | | | 538 | 39.8% |
| **F508del---NI** | | | | | | | | | | | |
| DC | | | | | | | | | 10 | 0.7% | 10 | 0.7% |
| **OTHER---OTHER** | | | | | | | | | | | |
| DC | 124 | 9.2% | 1 | 0.1% | 24 | 1.8% | 20 | 1.5% | | | 169 | 12.5% |
| VCC | | | | | | | 4 | 0.3% | | | 4 | 0.3% |
| UCS | | | | | 6 | 0.4% | | | | | 6 | 0.4% |
| NONCF | | | 1 | 0.1% | 1 | 0.1% | | | | | 2 | 0.1% |
| | 124 | 9.2% | 2 | 0.1% | 31 | 2.3% | 24 | 1.8% | | | 181 | 13.4% |
| **OTHER---NI** | | | | | | | | | | | |
| DC | | | | | | | | | 2 | 0.1% | 2 | 0.1% |
| VCC | | | | | | | | | 1 | 0.1% | 1 | 0.1% |
| NONCF | | | | | | | | | 2 | 0.1% | 2 | 0.1% |
| | | | | | | | | | 5 | 0.4% | 5 | 0.4% |
| **NI---NI** | | | | | | | | | | | |
| NI | | | | | | | | | 3 | 0.2% | 3 | 0.2% |
| | 1195 | 88.3% | 5 | 0.4% | 74 | 5.5% | 61 | 4.5% | 18 | 1.3% | 1353 | 100.0% |

The table above shows the broad classification of mutations by disease liability for pwCF seen in the year 2020.
The categories are based on the CFTR list 29April2023 [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 PwCF by CF allele or mutation**

| Mutation | PwCF n | PwCF % | alleles n | alleles % | Mutation | PwCF n | PwCF % | alleles n | alleles % |
|---|---|---|---|---|---|---|---|---|---|
| F508del | 1164 | 085.6 | 1797 | 465.7 | 1002-1113_1110delGAAT** | 7 | 0.5 | 7 | 0.3 |
| G542X | 67 | 5.0 | 76 | 2.8 | 5T;TG12* | 7 | 0.5 | 7 | 0.3 |
| N1303K | 63 | 4.7 | 68 | 2.5 | E60X | 7 | 0.5 | 7 | 0.3 |
| 3272-26A->G | 56 | 4.1 | 56 | 2.1 | 3120+1G->A | 6 | 0.4 | 7 | 0.3 |
| 1717-1G->A | 35 | 2.6 | 35 | 1.3 | 394delTT | 6 | 0.4 | 7 | 0.3 |
| S1251N | 34 | 2.5 | 34 | 1.3 | 4218insT | 5 | 0.4 | 5 | 0.2 |
| A455E | 33 | 2.4 | 33 | 1.2 | 621+1G->T | 5 | 0.4 | 5 | 0.2 |
| 2789+5G->A | 29 | 2.1 | 30 | 1.1 | L165S | 5 | 0.4 | 5 | 0.2 |
| L927P | 24 | 1.8 | 26 | 1.0 | L227R | 5 | 0.4 | 9 | 0.3 |
| R117H* | 23 | 1.7 | 26 | 1.0 | L927P; 1002-1113_1110delGAAT | 5 | 0.4 | 5 | 0.2 |
| R553X | 23 | 1.7 | 23 | 0.8 | Q493X | 5 | 0.4 | 5 | 0.2 |
| 3849+10kbC->T | 21 | 1.6 | 21 | 0.8 | Y913C** | 5 | 0.4 | 5 | 0.2 |
| W1282X | 18 | 1.3 | 18 | 0.7 | 2118del4 | 4 | 0.3 | 4 | 0.1 |
| 2183AA->G | 17 | 1.3 | 17 | 0.6 | 5T;TG13* | 4 | 0.3 | 4 | 0.1 |
| D1152H* | 12 | 0.9 | 13 | 0.5 | C276X | 4 | 0.3 | 4 | 0.1 |
| R1162X | 11 | 0.8 | 16 | 0.6 | CFTRdele2,3 | 4 | 0.3 | 6 | 0.2 |
| G178R | 9 | 0.7 | 9 | 0.3 | G551D | 4 | 0.3 | 5 | 0.2 |
| I507del | 9 | 0.7 | 9 | 0.3 | L206W | 4 | 0.3 | 4 | 0.1 |
| 306insA | 8 | 0.6 | 8 | 0.3 | Q1313X | 4 | 0.3 | 4 | 0.1 |
| 3659delC | 8 | 0.6 | 8 | 0.3 | R347H | 4 | 0.3 | 4 | 0.1 |
| 711+1G->T | 8 | 0.6 | 11 | 0.4 | Others | 189 | 14.0 | 202 | 7.5 |
| G85E | 8 | 0.6 | 8 | 0.3 | Not identified | 18 | 1.3 | 21 | 0.8 |
| G970R | 8 | 0.6 | 8 | 0.3 | Total | | | 2706 | |
| R117C | 8 | 0.6 | 8 | 0.3 | | | | | |
| R334W | 8 | 0.6 | 8 | 0.3 | | | | | |
| W401X | 8 | 0.6 | 8 | 0.3 | | | | | |

The mutations detected in less than four pwCF were all summarized into the "others" category for this purpose.
According to the CFTR2 database – list 29April2023 - 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.

# ANTHROPOMETRY (HEIGHT, WEIGHT AND BMI)

PwCF are known to be prone to nutritional deficiencies. Because of thick mucus, the pancreas is unable to produce digestive enzymes or that 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 pwCF. 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 pwCF 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 **193 pwCF with a lung transplant (86 males, 107 females; 1 child, 192 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). In 2020, data from 471 children were analysed. The figure 6 shows a general trend for better median BMI percentile in children after 2000, mainly for the teenagers.
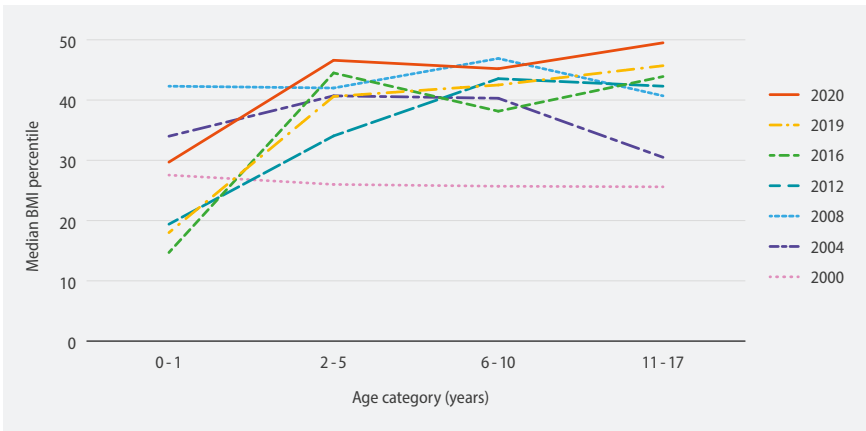
**Figure 6 |**   **Median BMI percentile by age group and year (children)**

Considering the absolute value of BMI, most adults (71.0%) had a BMI within the normal range (18.5 to 25 kg/m²) (Table 9). The proportion of overweight pwCF was higher than those underweight, mainly for male patients.

**Table 9 |**   **Number and proportion of adult PwCF (≥ 18y) per BMI category**

|  | MALES | | FEMALES | | OVERALL | |
|---|---|---|---|---|---|---|
|  | n | % | n | % | n | % |
| BMI < 18.5 | 23 | 6.2 | 32 | 10.7 | 55 | 8.2 |
| 18.5 ≤ BMI < 25 | 261 | 70.2 | 215 | 72.1 | 476 | 71.0 |
| 25 ≤ BMI < 30 | 69 | 18.5 | 36 | 12.1 | 105 | 15.7 |
| BMI ≥ 30 | 18 | 4.8 | 15 | 5.0 | 33 | 4.9 |
| BMI unknown | 1 | 0.3 |  |  | 1 | 0.1 |
| **Total** | **372** | **100.0** | **298** | **100.0** | **670** | **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 2020, data from 485 people was analysed. Figure 7 displays the proportion in each percentile category. The expected proportion of pwCF with a BMI between the 25th and the 75th percentile (considered normal, 50%) was met for all age categories (between 48.3% and 54.2%).
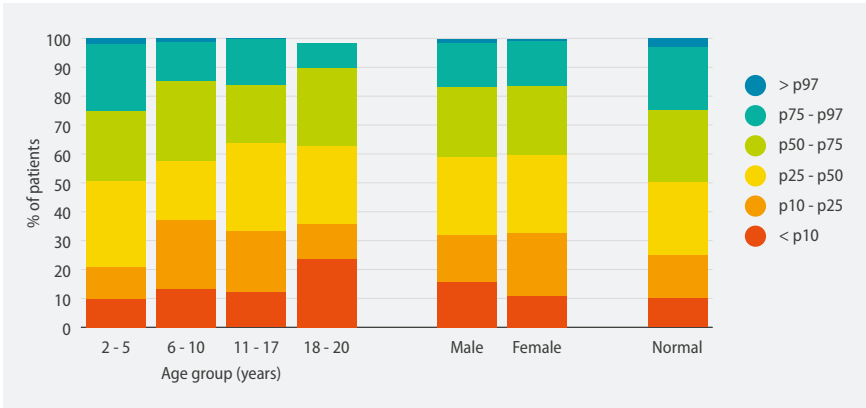
**Figure 7 |** **CDC BMI percentiles by age**

## 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 people older than 20 years. In 2020, data from 530 people was analysed. Figure 8 indicates the proportion in each percentile category. The proportion of people with a height between the 25th and the 75th percentile was between 42.7% and 56.1% for each age category below 20y. Nevertheless, a high proportion of children (37.0% - 40.7%) with a height below the 25th percentile was observed for all age categories but for the children aged 2-5y (19.8%).
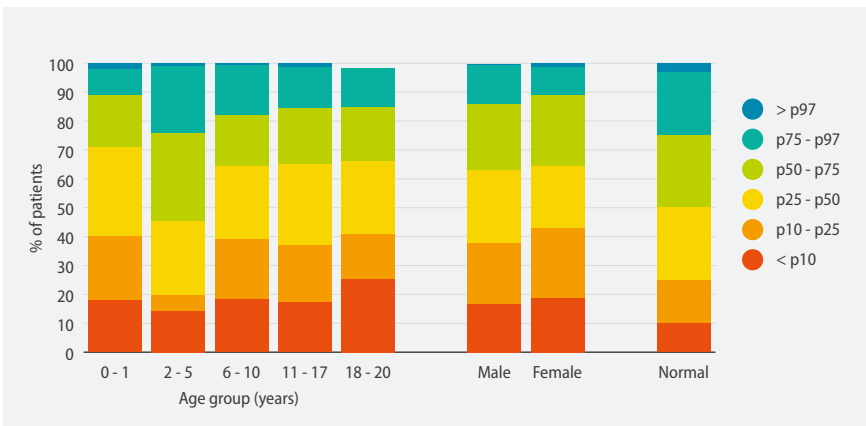


**Figure 8 |** **CDC Height percentiles by age**

## 5.4   WEIGHT PERCENTILES USING THE CDC GROWTH CHARTS

The CDC growth charts cover weight from 0.0 – 20.0 years. In 2020, data from 530 people was analysed. Figure 9 indicates the proportion in each percentile category. The proportion of pwCF with a weight between the 25th and the 75th percentile was between 35.6% and 56.1% for each category, lowest in infants (<1y, 35.6%). Moreover, a higher-than-expected proportion (> 10%) with weight for age below the 10th percentile was observed in all age categories, except in children aged 2-5y (8.8%).
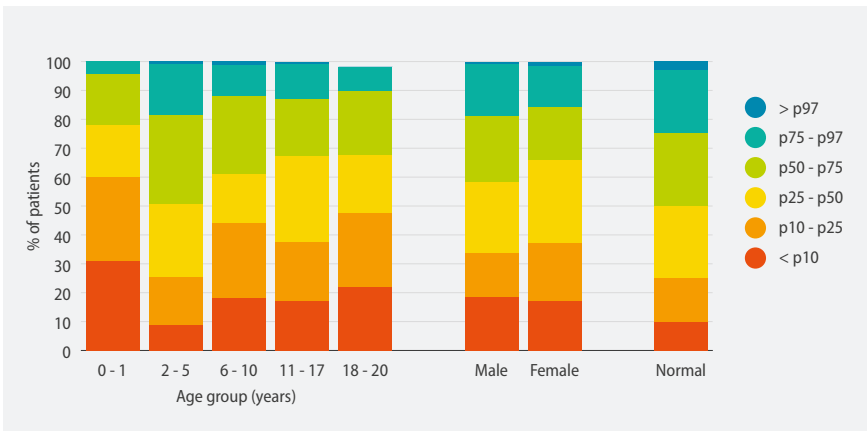


**Figure 9 |   CDC Weight percentiles by age**

# SPIROMETRY (LUNG FUNCTION)

The forced expiratory volume in one second ($FEV_1$) is the amount of air that a person can 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 pwCF develop progressive pulmonary disease, measures of pulmonary involvement, particularly $FEV_1$, are used to follow up the lung disease. However, considerable heterogeneity exists in prognosis and severity, even among people of the same genotype [51].

In this analysis, $FEV_1$% predicted values are divided in four classes corresponding to different degrees of lung function impairment: normal lung function ($\geq$ 90%), mild (70-89%), moderate (40-69%) and severe (< 40%) impairment.

While lung function prediction is not reliable below **the age of 6 years**, it was excluded from some of the analyses, but all available data was used in the plots. Data from 136 children was excluded from the severity analysis. Data from **people with a lung transplant (1 child and 192 adults) was excluded** from all lung function analyses.

The values obtained at the last consultation of the year, pre- or post-bronchodilator, were analysed. The 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 people from 3 years onwards [46].

In 2020, data from 993 people ≥ 6 years were analysed. The overall mean FEV$_1$% predicted was 79.2% (SD = 23.4). The mean FEV$_1$% predicted was 80.3% (SD = 23.0) and 77.9% (SD = 23.7) respectively for 531 males and 462 females. The mean FEV$_1$% predicted was 92.0% (SD = 18.2) and 72.9% (SD = 23.0) respectively for 328 children and 665 adults with CF.

Amongst the 428 PwCF homozygous for F508del, the means were 76.2% (SD = 23.1) and 76.0% (SD = 24.0) respectively for the 226 male and 202 female PwCF. The means were 91.3% (SD = 18.6) and 68.6% (SD = 22.0) respectively for the 142 children and 286 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.
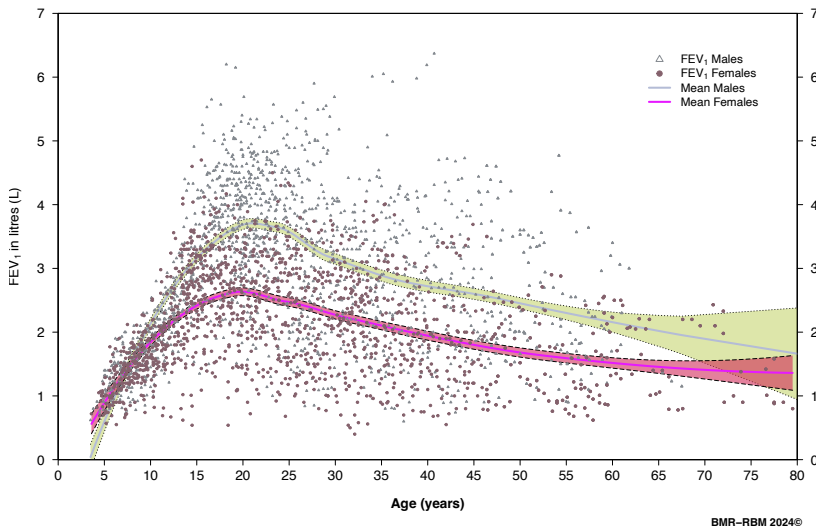


**Figure 10 |   Mean FEV$_1$ in litres by age and gender**

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].
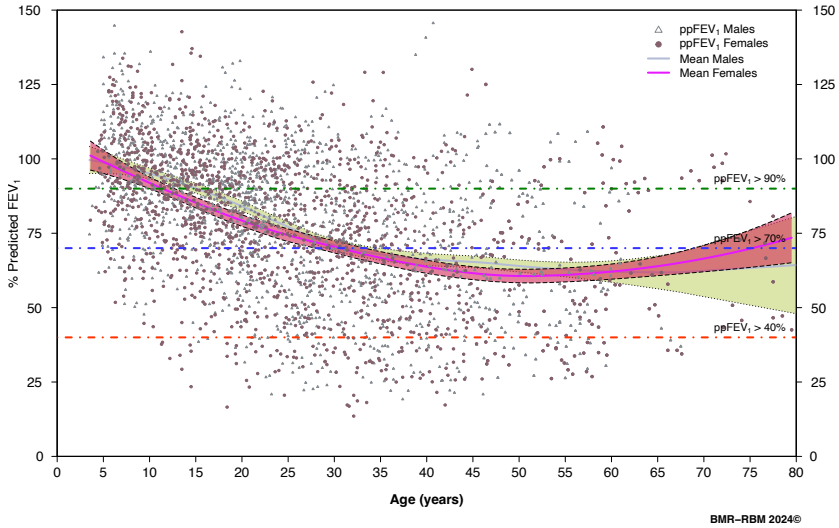


**Figure 11 |** **Mean FEV$_1$% predicted by age and gender**

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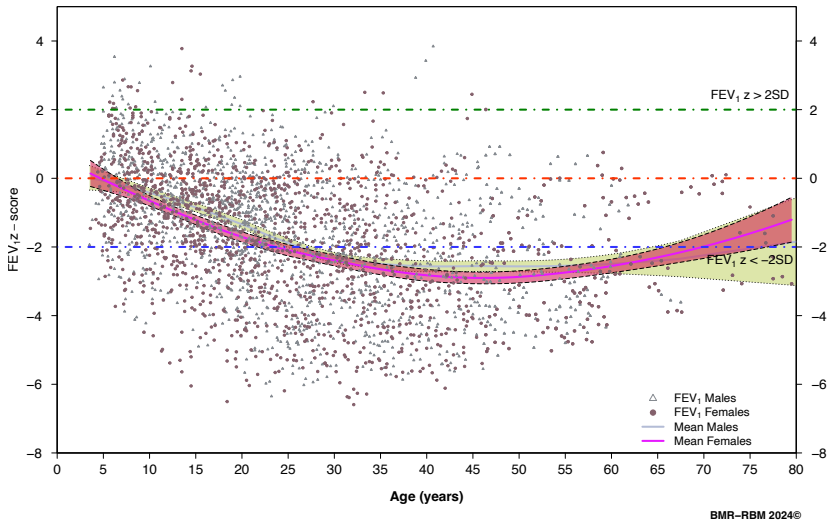


**Figure 12 |** **Mean FEV$_1$ z-score by age and gender**

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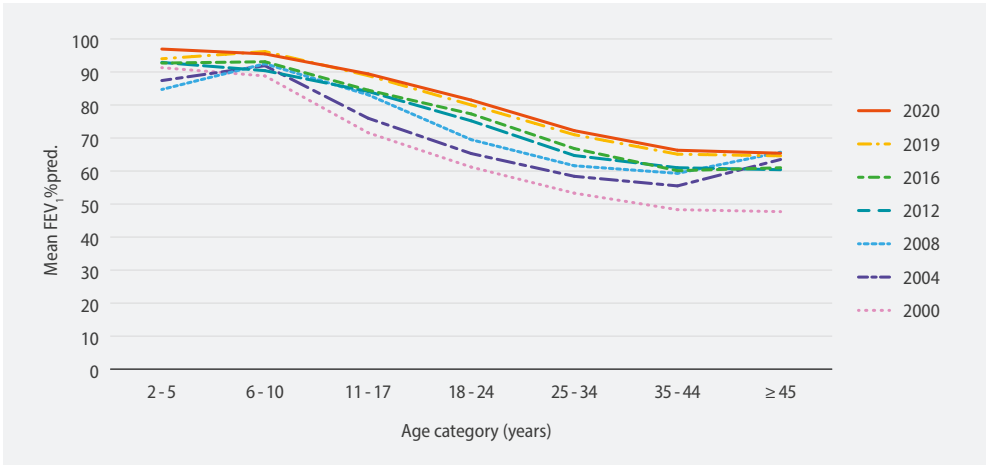


**Figure 13 |** **Mean percentage of predicted $FEV_1$ by age group for selected years**

## 6.2    $FEV_1$ CATEGORIES BY AGE GROUP

$FEV_1\%$ predicted ($ppFEV_1$) values were divided in four classes, corresponding to different degrees of lung function impairment: normal lung function ($\geq$ 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 2020.

**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 | 192 | 57.1 | 177 | 25.7 | 369 | 36.0 |
| 70% - 89% predicted | 95 | 28.3 | 201 | 29.2 | 296 | 28.9 |
| 40% - 69% predicted | 38 | 11.3 | 229 | 33.3 | 267 | 26.1 |
| < 40% predicted | 3 | 0.9 | 58 | 8.4 | 61 | 6.0 |
| Missing* | 8 | 2.4 | 23 | 3.3 | 31 | 3.0 |
| *Subtotal* | *336* | *100.0* | *688* | *99.9* | *1024* | *100.0* |
| *< 6 years* | *136* | | | | *136* | |
| Lung transplants | 1 | | 192 | | 193 | |
| **Total** | **473** | | **880** | | **1353** | |

\* Missing includes people not seen

The ppFEV$_1$ was 70.0% or higher in 64.9% of the pwCF: in 85.4% of the children (6 – 17 years) and 54.9% of the adults (18 years and above). About 3.0% had missing FEV$_1$ data; mostly because the person was not seen in 2020.

In Figure 14, the proportion 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 ppFEV$_1$ of at least 90%, peaking-off in 2012, with a trend towards improvement in 2020. 57.1% of the children and 25.7% of the adults with CF had ppFEV$_1$ of at least 90% in 2020.

The proportion of adults with lung function > 90% has increased steadily from 11.9% in 2000 to 25.7% in 2020. On the contrary, the proportion of adults with ppFEV$_1$ below 40% has decreased since 2000, with a further decrease to 8.4% in 2020, after a plateau at about 14-15% since 2008.
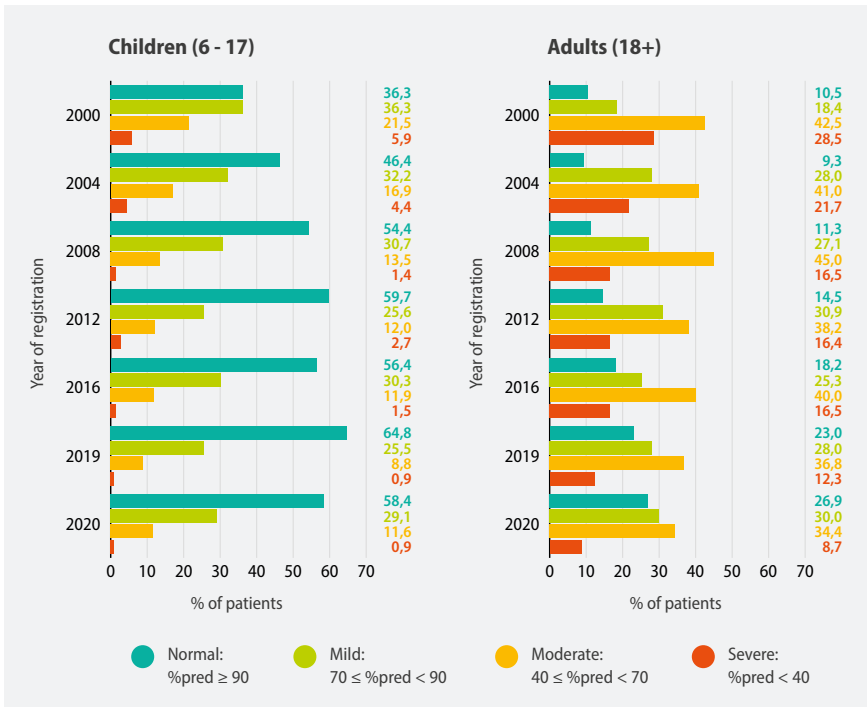


**Figure 14 |  FEV$_1$% predicted groups in children and adults for selected years**

# MICROBIOLOGY

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

Bacterial colonisation may occur early in the natural history of CF 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 pwCF 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 mentioned 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 **193 lung-transplanted pwCF was 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 2020, 468 children and 658 adults, i.e. 98.7% of the 1141 non-lung transplanted pwCF, had at least one culture done. The largest proportion of those (74.3%) had at least four exploitable months during the year, i.e. at least four cultures done with results to identify chronic infections. Sputum samples were done in 815 people, throat or nose swabs in 493 while 36 had a broncho-alveolar lavage.

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

**Table 11 |  Isolated pathogens in 2020**

| | Children | | Adults | | All pwCF | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Methicillin Sensitive *Staphylococcus aureus* (MSSA) | 296 | 63.2 | 396 | 60.2 | 692 | 61.5 |
| *Haemophilus influenzae* | 118 | 25.2 | 71 | 10.8 | 189 | 16.8 |
| *Pseudomonas aeruginosa* | 86 | 18.4 | 293 | 44.5 | 379 | 33.7 |
| Methicillin Resistant *Staphylococcus aureus* (MRSA) | 18 | 3.8 | 55 | 8.4 | 73 | 6.5 |
| *Stenotrophomonas maltophilia* | 50 | 10.7 | 83 | 12.6 | 133 | 11.8 |
| *Achromobacter xylosoxidans* | 23 | 4.9 | 71 | 10.8 | 94 | 8.3 |
| *Burkholderia cepacia complex* | 7 | 1.5 | 24 | 3.6 | 31 | 2.8 |
| *Aspergillus* spp | 65 | 13.9 | 222 | 33.7 | 287 | 25.5 |
| *Scedosporium prolificans* | 1 | 0.2 | 3 | 0.5 | 4 | 0.4 |
| Atypical / Non-tuberculous mycobacteria (NTM) | 4 | 0.9 | 20 | 3.0 | 24 | 2.1 |
| Other pathogens | 185 | 39.5 | 259 | 39.4 | 444 | 39.4 |
| Tested for Covid | 234 | 49.7 | 348 | 51.9 | 582 | 51.0 |
| Covid infection | 10 | 4.3 | 32 | 9.2 | 42 | 7.2 |

Percentages are based on 1126 people, with a culture in 2020; 468 children and 658 adults. For covid testing, all non-lung transplanted pwCF were used as denominator, while for covid infections, percentages are based on those who were tested.

**Table 12 |  Isolated pathogens 2017 - 2020**

| | 2017 | | 2018 | | 2019 | | 2020 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Methicillin Sensitive Staphylococcus aureus (MSSA) | 701 | 64.1 | 710 | 64.4 | 698 | 62.7 | 692 | 61.5 |
| *Haemophilus influenzae* | 272 | 24.9 | 272 | 24.7 | 280 | 25.2 | 189 | 16.8 |
| *Pseudomonas aeruginosa* | 427 | 39.1 | 418 | 37.9 | 396 | 35.6 | 379 | 33.7 |
| Methicillin Resistant Staphylococcus aureus (MRSA) | 76 | 7.0 | 68 | 6.2 | 65 | 5.8 | 73 | 6.5 |
| *Stenotrophomonas maltophilia* | 133 | 12.2 | 141 | 12.8 | 138 | 12.4 | 133 | 11.8 |
| *Achromobacter xylosoxidans* | 124 | 11.3 | 112 | 10.2 | 100 | 9.0 | 94 | 8.3 |
| Burkholderia cepacia complex | 31 | 2.8 | 33 | 3.0 | 39 | 3.5 | 31 | 2.8 |
| *Aspergillus* | 339 | 31.0 | 371 | 33.7 | 313 | 28.1 | 287 | 25.5 |
| *Scedosporium* spp. | 10 | 0.9 | 7 | 0.6 | 3 | 0.3 | 4 | 0.4 |
| Atypical / Non – tuberculous mycobacteria (NTM) | 19 | 1.7 | 17 | 1.5 | 29 | 2.6 | 24 | 2.1 |
| Other pathogens | 358 | 32.8 | 355 | 32.2 | 455 | 40.9 | 444 | 39.4 |
| Tested for Covid (YN) | | | | | | | 582 | 51.0 |
| Covid infection (YN) | | | | | | | 42 | 7.2 |

Percentages are based on 1093 (2017), 1102 (2018), 1113 (2019) and 1126 (2020) non-lung transplanted pwCF with a culture respectively. For covid testing, all non-lung transplanted pwCF were used as denominator, while for covid infections, percentages are based on those who were tested.

While the infection rate of MSSA remains quite high in all age categories, the prevalence of *Haemophilus influenza* 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 been decreasing over the years. The prevalence of *Stenotrophomonas maltophilia* has oscillated at about 12.0% since 2012. In 2020, it was 11.8%. There had been a steady increase of the prevalence of *Achromobacter xylosoxidans* from 5.9% in 2009 to 10.7 % in 2012 stabilizing at about 10 to 11.0% by 2017, since then a decreasing trend has been observed with 8.3% in 2020. Similarly, despite a prevalence ranging 1.5% – 2.0% for *Non-tuberculous mycobacteria* since 2017, this pathogen remains infrequent. While a high prevalence of '*Other pathogens*' was reported since 2019, no emerging pathogen was identified. In 2020, 582 pwCF (51.0%) were tested for SARS-CoV-2, among whom 42 (7.2%) were infected with the Covid-19 virus.

The prevalence of various pathogens may differ according to the age of the pwCF. 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 people who had at least one culture analysed or sample taken during the year. Data from lung-transplanted pwCF is excluded. The calculated values may, however, be affected by low denominator in the lower age category (45 children 0 - 1y).
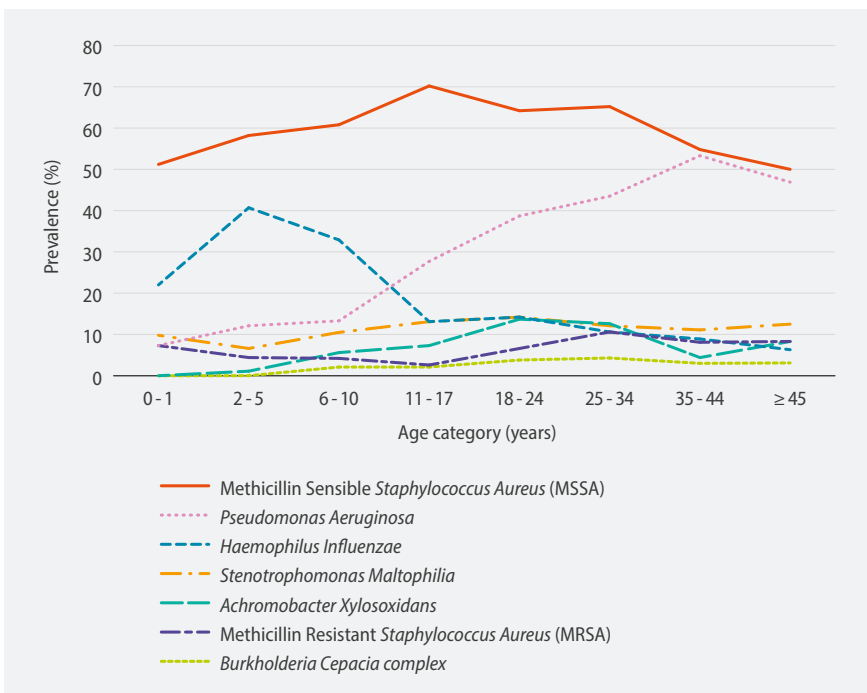


**Figure 15 |** **Annual prevalence of selected pathogens by age group**

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.
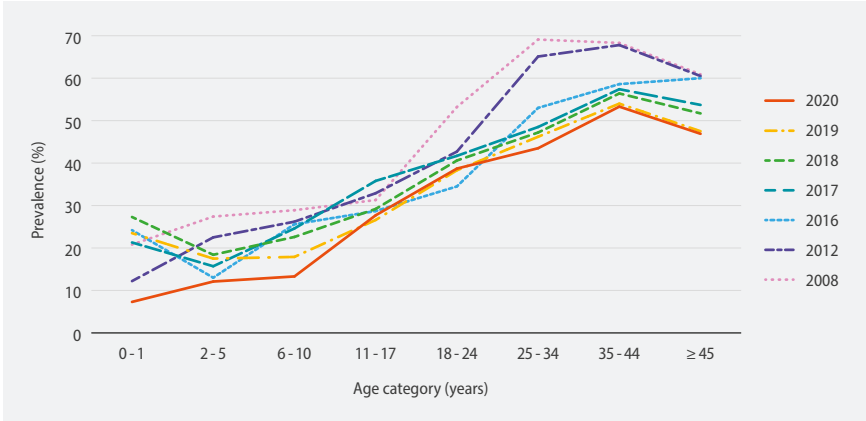


**Figure 16 |** **Prevalence of *Pseudomonas aeruginosa* infections by year and age**
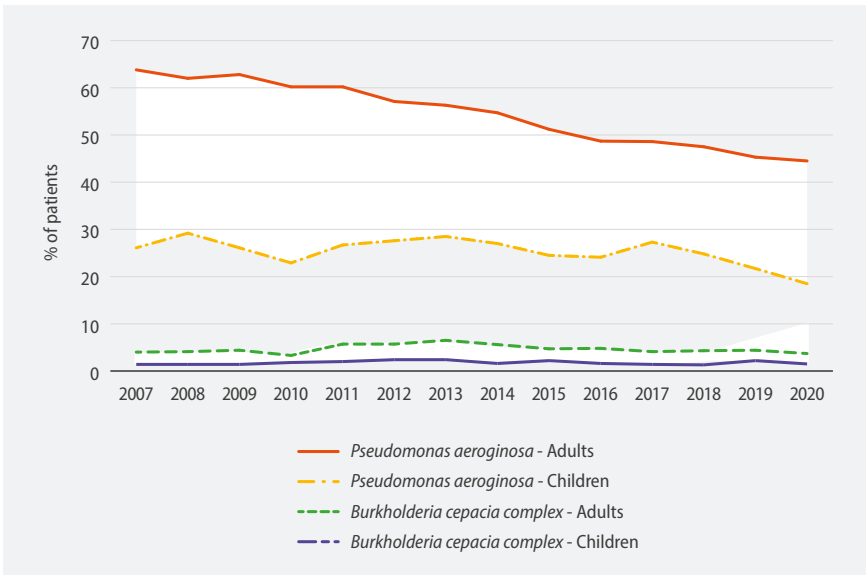


**Figure 17 |** **Prevalence of *P. aeruginosa* and *B. cepacia complex* infections by age group and year**

**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.
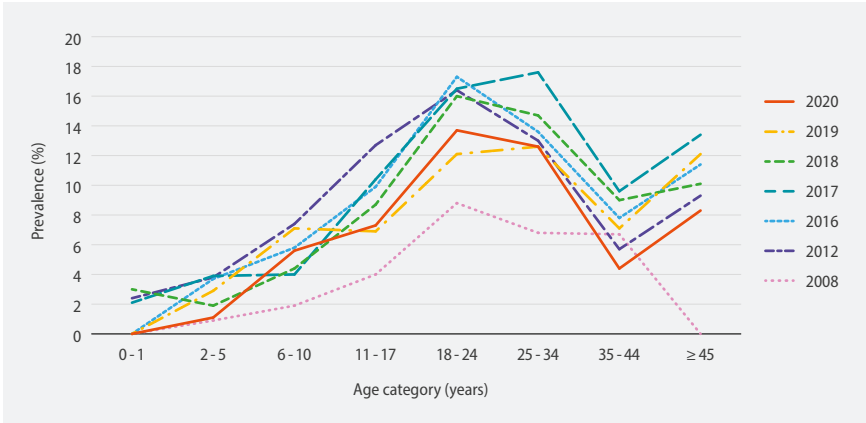


**Figure 18 |** **Prevalence of *Achromobacter xylosoxidans* infections by age group and year**

## 7.2    ANNUAL PREVALENCE OF CHRONIC INFECTIONS

The prevalence of chronic infections among non-lung transplanted pwCF is shown in table 13, and in Figure 19 for the different age categories. About 6.2% of the children (n = 29) and 33.9% of the adults (n = 252) had chronic *Pseudomonas aeruginosa* infection.

**Table 13 |** **Chronic infections 2017 - 2020**

|  | 2017 | | 2018 | | 2019 | | 2020 | |
|---|---|---|---|---|---|---|---|---|
|  | n | % | n | % | n | % | n | % |
| Chronic *Pseudomonas aeruginosa* | 275 | 25.2 | 267 | 24.2 | 268 | 24.1 | 252 | 22.4 |
| Chronic *Burkholderia cepacia complex* | 24 | 2.2 | 24 | 2.2 | 25 | 2.2 | 24 | 2.1 |
| Chronic *Stenotrophomonas maltophilia* | 41 | 3.8 | 44 | 4.0 | 37 | 3.3 | 29 | 2.6 |
| Chronic *Achromobacter xylosoxidans* | 68 | 6.2 | 71 | 6.4 | 65 | 5.8 | 64 | 5.7 |
| Chronic MRSA | 49 | 4.5 | 47 | 4.3 | 40 | 3.6 | 38 | 3.4 |

Percentages are based on 1093 (2017), 1102 (2018), 1113 (2019) and 1126 (2020) non-lung transplanted PwCF 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.
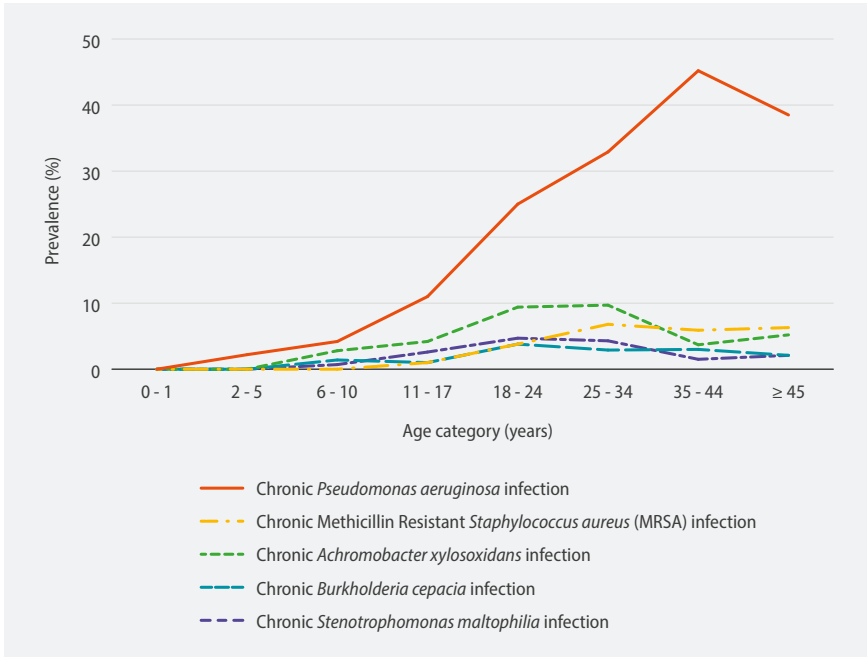


**Figure 19 |** **Prevalence of chronic infections by age group**

## 7.3    THE PANDEMIC AND ITS IMPACT

During the COVID-19 pandemic in 2020, individuals with cystic fibrosis (CF) may have faced several challenges in accessing regular and scheduled healthcare, including consultations and laboratory visits. This, among other factors, may also have had an impact on the estimate of overall microbial prevalence. Below are examples of challenges. However, this list is not complete.

1 **Susceptability and mental health impact**: People with cystic fibosis are susceptoible to respiratory infections, and COVID-19 primarily affects the respiratory system. This increased vulnerability to a significant health risk for pwCF and the stress and uncertainty associated with the pandemic, coupled with concerns about health and access to healthcare, may have impacted their mental health.

2 **Overlapping symptoms**: The symptoms of COVID-19, such as cough and shortness of breath, overlap with the typical symptoms of CF. This made it difficult to distinguish between a routine exacerbation of cystic fibrosis and a potential COVID-19 infection, which may have led to complexity in diagnosis and management.

3 **Disruption to regular healthcare and telemedicine**: Lockdowns, restrictions and fea of contracting the virus may have led to disruptions to regular healthcare services and the shift towards telemedicine. Many routine checkups, pulmonary function tests, and other important health appointments for pwCF may have been postponed or conducted remotely, affecting continuity of care and potentially the quality of care.

4 **Vaccine prioritization**: As vaccines became available, there were discussions about prioritizing high-risk populations, including those with underlying conditions such as CF An important consideration was ensuring timely access to vaccines for this vulnerable group.

It is important to note that these challenges may have varied by region and individual circumstances. Healthcare providers and organizations worked to adapt and address these challenges to ensure the well-being of people with cystic fibrosis during the pandemic. Many lessons were certainly learned.

# COMPLICATIONS

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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 **193 non-lung transplanted pwCF 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 pwCF, 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 pwCF cough 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 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Bronchiectasis* | 310 | 71.9 | 329 | 78.1 | 330 | 74.0 | 370 | 76.0 |
| Nasal polyps | 190 | 17.0 | 134 | 11.9 | 55 | 4.9 | 108 | 9.5 |
| Allergic Bronchopulmonary Aspergillosis (ABPA) | 80 | 7.1 | 97 | 8.6 | 105 | 9.3 | 101 | 8.9 |
| Massive haemoptysis | 5 | 0.4 | 10 | 0.9 | 9 | 0.8 | 21 | 1.8 |
| Massive haemoptysis requiring embolization | 3 | 0.3 | 4 | 0.4 | 4 | 0.4 | 13 | 1.1 |
| Pneumothorax | 2 | 0.2 | 4 | 0.4 | 4 | 0.4 | 1 | 0.1 |

Percentages are based on 1119 (2017), 1122 (2018), 1124 (2019) and 1141 (2020) non-lung transplanted pwCF respectively.
*Only for pwCF with a CT scan done (183 children and 304 adults for 2020).

In this analysis, data from 471 children and 670 adults were used. Bronchiectasis was reported in 98 (53.6%) children and 272 (89.5%) adults who had a CT scan during the year. ABPA, one of the most frequent major respiratory complications, was reported in 25 (5.3%) children and 76 (11.3%) adults in 2020.

## 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 pwCF 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**: PwCF also present with defective CFTR protein in their biliary tract, and gall stones may develop. Some people 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 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Exocrine pancreatic Insufficiency | 924 | 82.6 | 906 | 80.7 | 910 | 81.0 | 930 | 81.5 |
| Acute pancreatitis | 14 | 1.3 | 11 | 1.0 | 12 | 1.1 | 14 | 1.2 |
| CF-related diabetes (CFRD) | 212 | 18.9 | 209 | 18.6 | 208 | 18.5 | 210 | 18.4 |
| Impaired Glucose Tolerance (IGT ) | 72 | 6.4 | 57 | 5.1 | 109 | 9.7 | 96 | 8.4 |
| OGTT this year* | 317 | 28.3 | 295 | 26.3 | 343 | 30.5 | 305 | 26.7 |
| Cirrhosis with portal hypertension | 39 | 3.5 | 42 | 3.7 | 46 | 4.1 | 47 | 4.1 |
| Intestinal obstruction (surgery) | 58 | 5.2 | 27 | 2.4 | 33 | 2.9 | 41 | 3.6 |
| Intestinal obstruction (no surgery) | 6 | 0.5 | 6 | 0.5 | 9 | 0.8 | 10 | 0.9 |
| *Clostridium infection* (treatment needed) | 10 | 0.9 | 9 | 0.8 | 12 | 1.1 | 15 | 1.3 |

Percentages are based on 1119 (2017), 1122 (2018), 1124 (2019) and 1141 (2020) non-lung transplanted pwCF respectively.

In non-lung transplanted pwCF, the data shows that 406 (86.2%) children and 524 (78.2%) adults are pancreatic insufficient. CFRD was reported in 18 (3.8%) children and 192 (28.7%) adults. IGT on the other hand was reported in 17 (3.6%) children and 79 (11.8%) 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**: PwCF with advanced lung disease sometimes develop painful inflammation of joints. The exact cause is unknown and regression of joint symptoms is usually seen when respiratory disease is stabilized.

**Cancer: PwCF are at increased risk of gastrointestinal cancer.**

**Table 16 |**  **Other complications reported**

| Complication | 2017 | | 2018 | | 2019 | | 2020 | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Osteopenia* | 155 | 33.4 | 188 | 37.6 | 222 | 41.7 | 224 | 41.4 |
| Osteoporosis* | 49 | 10.6 | 43 | 8.6 | 42 | 7.9 | 43 | 7.9 |
| CF-related arthritis / arthropathy | 20 | 1.8 | 21 | 1.9 | 26 | 2.3 | 39 | 3.4 |
| Cancer | 3 | 0.3 | 3 | 0.3 | 3 | 0.3 | 6 | 0.5 |
| Hypertension requiring treatment | 26 | 2.3 | 31 | 2.8 | 38 | 3.4 | 46 | 4.0 |
| Others | 124 | 11.1 | 115 | 10.2 | 133 | 11.8 | 211 | 18.5 |

Percentages are based on 1119 (2017), 1122 (2018), 1124 (2019) and 1141 (2020) non-lung transplanted pwCF respectively.
* Only for people with a DXA within last five years (89 children and 452 adults for 2020).

Some other complications were directly related to CF disease or treatment, like pancreatitis, gastro-oesophageal reflux, pneumonia, renal insufficiency, but could also be hypothyroidy, allergies, otitis, psoriasis, alopecia, epilepsy, Alzheimer…

# 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 2020 are presented. An evolution of the proportion of pwCF hospitalized by age category for selected years is also presented. **Some analyses exclude data from people with a (lung) transplant.**

Except for contraceptive therapy, the percentages are based on 469 children and 662 adults from a total of 1131 non-transplanted pwCF.

## 9.1    VISITS TO CF CARE CENTERS AND HOSPITALIZATION

In 2020, most of the people (961, 84.2%) (422 children, 89.6%; 539 adults, 80.6%) had a minimum of the four recommended visits to a CF reference centre during the year. This is less than previous years, but expected in line with the COVID-19 pandemic and sanitary measures taken, including cancellation of non-urgent consultations. It may also been influenced by the fear of viral transmission when coming to the hospital.

Every year, about two in five of the people 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 2020, 62.8% of the people were not hospitalized: 64.8% of the children (n = 305) and 61.5% of the adults (n = 412). A small proportion (17 people, 1.5%), was hospitalized for over two months. The median duration of hospitalization was about two weeks (11 days - children and 14 days - adults). The proportion of adults hospitalized for more than two weeks has been decreasing over the years, from 32.7% in

2000 to 16.8% in 2020 among adults and from 19.2% in 2000 to 12.2% in 2020 among children (Figure 21).
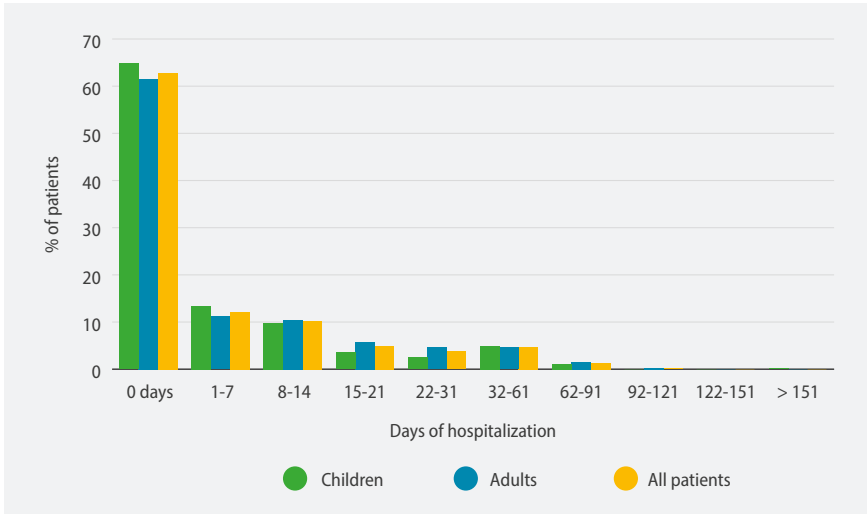


**Figure 20 |** **Number of hospitalization days**
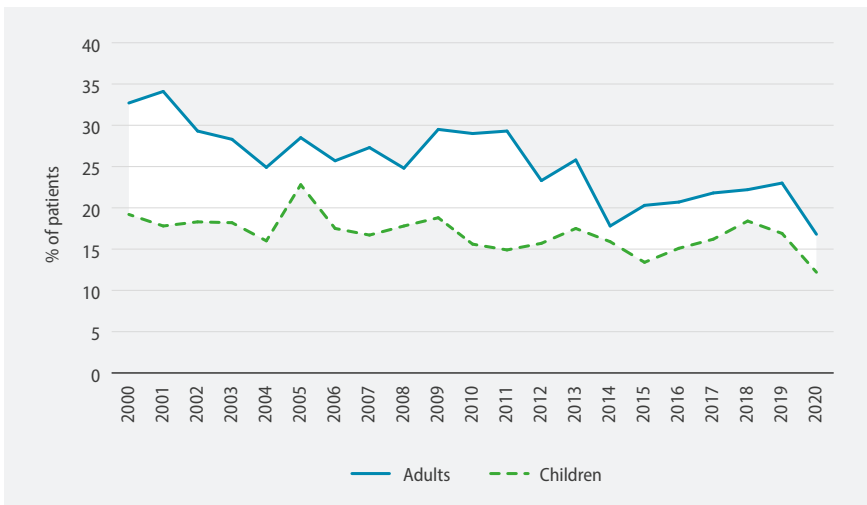


**Figure 21 |** **Proportion hospitalized for more than two weeks by age and year**

## 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 pw CF have regular chest physiotherapy. Most pwCF also learn the technique of autogenic drainage where they can perform drainage by themselves through breathing techniques.

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 corticosteroids 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 | 469 | 100.0 | 661 | 99.8 | 1130 | 99.9 |
| Antibiotics | 394 | 84.0 | 548 | 82.8 | 942 | 83.3 |
|     Oral only | 277 | 59.1 | 247 | 37.3 | 524 | 46.3 |
|     IV only | 7 | 1.5 | 25 | 3.8 | 32 | 2.8 |
|     Oral and IV | 99 | 21.1 | 232 | 35.0 | 331 | 29.3 |
|     Inhaled antibiotics | 201 | 42.9 | 392 | 59.2 | 593 | 52.4 |
| Inhalation therapy (excluding antibiotics) | 460 | 98.1 | 627 | 94.7 | 1087 | 96.1 |
|     RhDNase | 419 | 89.3 | 551 | 83.2 | 970 | 85.8 |
|     Other mucolytics | 46 | 9.8 | 43 | 6.5 | 89 | 7.9 |
|     Hypertonic saline | 340 | 72.5 | 450 | 68.0 | 790 | 69.8 |
|     Bronchodilators | 353 | 75.3 | 499 | 75.4 | 852 | 75.3 |
|     Corticosteroids | 182 | 38.8 | 419 | 63.3 | 601 | 53.1 |
| Oral anti-inflammatories | 202 | 43.1 | 434 | 65.6 | 636 | 56.2 |
|     Azithromycin | 191 | 40.7 | 406 | 61.3 | 597 | 52.8 |
|     Systemic corticosteroids | 7 | 1.5 | 25 | 3.8 | 32 | 2.8 |
|     NSAID | 5 | 1.1 | 35 | 5.3 | 40 | 3.5 |
|     Leucotriens | 23 | 4.9 | 93 | 14.0 | 116 | 10.3 |
| Oxygen therapy | 7 | 1.5 | 26 | 3.9 | 33 | 2.9 |

The percentages are based on 469 children and 662 adults for a total of 1131 non-transplanted pwCF

## 9.3    GASTRO-INTESTINAL AND NUTRITIONAL THERAPIES

**Optimizing the nutritional status:** The nutritional status of pwCF is strongly correlated with disease severity. Therefore, every person with CF should maintain a well-balanced high-calorie and high-fat diet. Most pwCF are pancreatic insufficient [57] and must take pancreatic enzymes with each meal to sufficiently digest food. ADEK vitamin supplements are also administered routinely. Some pwCF 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.

**Table 18 |    Digestive and nutritional therapies**

| Treatment | Children | | Adults | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Pancreatic enzymes | 408 | 87.0 | 515 | 77.8 | 923 | 81.6 |
| Proton pump inhibitor and/or H2 receptor blocker | 216 | 46.1 | 336 | 50.8 | 552 | 48.8 |
| Ursodeoxycholic acid | 92 | 19.6 | 127 | 19.2 | 219 | 19.4 |
| Enteral feeding | 22 | 4.7 | 12 | 1.8 | 34 | 3.0 |
| Parenteral feeding | 1 | 0.2 | 4 | 0.6 | 5 | 0.4 |
| Gastrotomy tube | 31 | 6.6 | 17 | 2.6 | 48 | 4.2 |

The percentages are based on 469 children and 662 adults for a total of 1131 non-transplanted PwCF

## 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 person develops CF related diabetes, or bisphosphonates for osteoporosis. The treatment burden for pwCF is high. Most pwCF spend 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 | 14 | 3.0 | 136 | 20.5 | 150 | 13.3 |
| Oral Therapy for Diabetes | | | 39 | 5.9 | 39 | 3.4 |
| Diet only for Diabetes | 10 | 2.1 | 72 | 10.9 | 82 | 7.3 |
| Bisphosphonates | | | 18 | 2.7 | 18 | 1.6 |
| Anti-conceptive therapy* | 13 | 18.1 | 111 | 42.4 | 124 | 37.1 |
| CFTR Modulating Therapy | 52 | 11.1 | 184 | 27.8 | 236 | 20.9 |

The percentages are based on 469 children and 662 adults for a total of 1131 non-transplanted pwCF.
* The percentages are based on 83 children and 295 adults for a total of 378 girls and women aged 12y and above.

**Note:**    Out of 1131 non-transplanted pwCF, 210 had CFRD. Among these, 140 (66.7%) used insulin therapy only, 18 (8.6%) used only oral therapy for diabetes while 14 (6.7%) pwCF used both oral therapy for diabetes and insulin therapy. In 44 (21.0%) of the people with CFRD, treatment was based on dietary intervention alone.

In Table 20, the frequency of use for the specific drugs currently on the market is based on the number of people eligible based on CFTR mutations and age, as defined in the EMA approval in December 2020. It doesn't take contraindications or personal situation into account. Around half of the pwCF eligible for ivacaftor were using it (94.0%). Among the people 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 use for lumacaftor/ivacaftor (13.0% of eligible pwCF) and tezacaftor/ ivacaftor (2.3%) was low due to absence of Orkambi® and Symkevi® reimbursement in Belgium in 2020. The use of elexacaftor/tezacaftor/ivacaftor was no more limited to open label studies, as Kaftrio® was authorized for

compassionate use in Belgium from 2020 though not yet widely available to all eligible pwCF.

**Table 20 |** **CFTR modulators**

| CFTR modulator | Children | | Adults | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Kalydeco® (Ivacaftor) | 16 | 100.0 | 32 | 94.1 | 48 | 96.0 |
| Orkambi® (Lumacaftor / Ivacaftor) | 18 | 9.5 | 46 | 16.4 | 64 | 13.6 |
| Symkevi® (Tezacaftor / Ivacaftor) | 6 | 3.6 | 6 | 1.7 | 12 | 2.3 |
| Kaftrio® (Elexacaftor / Tezacaftor / Ivacaftor) | 10 | 3.6 | 91 | 16.1 | 101 | 12.0 |
| Other or Blinded clinical trial | 2 | | 9 | | 11 | |

*For specific CFTR modulators, % is based on the number of people eligible in theory, based on the European Medicines Agency authorisation conditions on 31/12/2020, with mutations and age at 31/12/2020: Ivacaftor (Kalydeco®) for pwCF with gating mutations from 4 months [8]. Lumacaftor/ivacaftor (Orkambi®) for pwCF homozygous for F508del, from 2y [9]. Tezacaftor/ivacaftor (Symkevi®) for pwCF homozygous for F508del or heterozygous F508del with a residual function mutation, from 6y [10]. Elexacaftor/tzeacaftor/ivacaftor for pwCF with at least one F508del mutation, from 12y [11]. There were 50 people eligible for Kalydeco®; 16 children and 34 adults, 470 eligible for Orkambi®; 190 children and 280 adults, 527 eligible for Symkevi®; 169 children and 358 adults, and 700 eligible for Kaftrio®; 134 children and 566 adults.
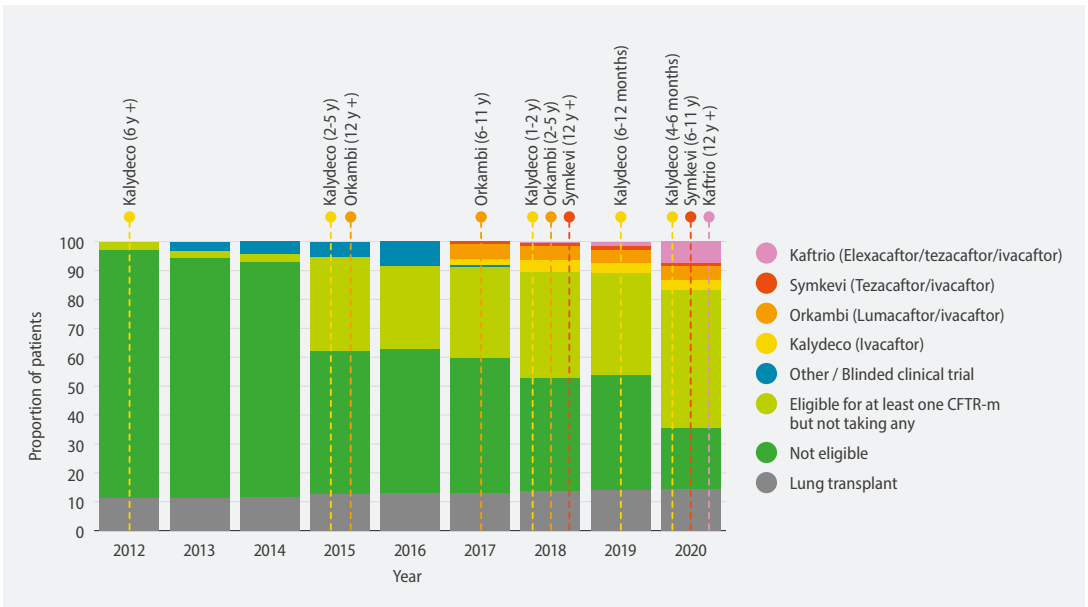


**Figure 22 |** **Proportion that used and/or are eligible to CFTR modulators**

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

## 9.5    INTRAVENOUS ANTIBIOTICS

In 2020, 31.9% (n = 361) of the 1131 non-transplanted pwCF received IV antibiotics; 22.6% (n = 106) of the children and 38.5% (n = 255) of the adults. Figure 23 shows the proportion who received IV antibiotics at home and/or in hospital in 2019 (top) compared to 2020 (bottom).

IV antibiotics administered at home was rare in children younger than 10 years. About one in five people (20.9%) received IV antibiotics treatment for over two weeks in 2020 compared to 24.5% in 2019. This was lower in children (11.7%) than in adults (27.4%).
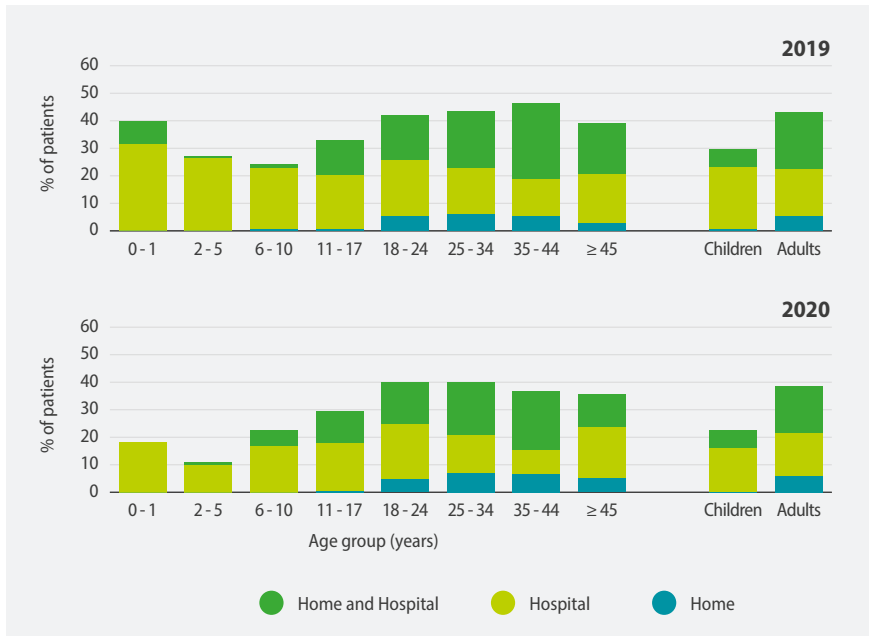


**Figure 23 |  Proportion that used IV antibiotic treatment by age category**

## 9.6    ORAL ANTIBIOTICS

Figure 24 shows the cumulative days of oral antibiotics used in 2019 (top) and compared to 2020 (bottom). Unknown days or missing data were excluded from this analysis. In 2020, 24.3% of the pwCF did not take any oral antibiotics; 19.8% of the children (n = 93) and 27.4% of the adults (n = 181). About a quarter of the people (26.7%; children - 23.2% and adults - 29.1%) used oral antibiotics, excluding azithromycin, for over six months.
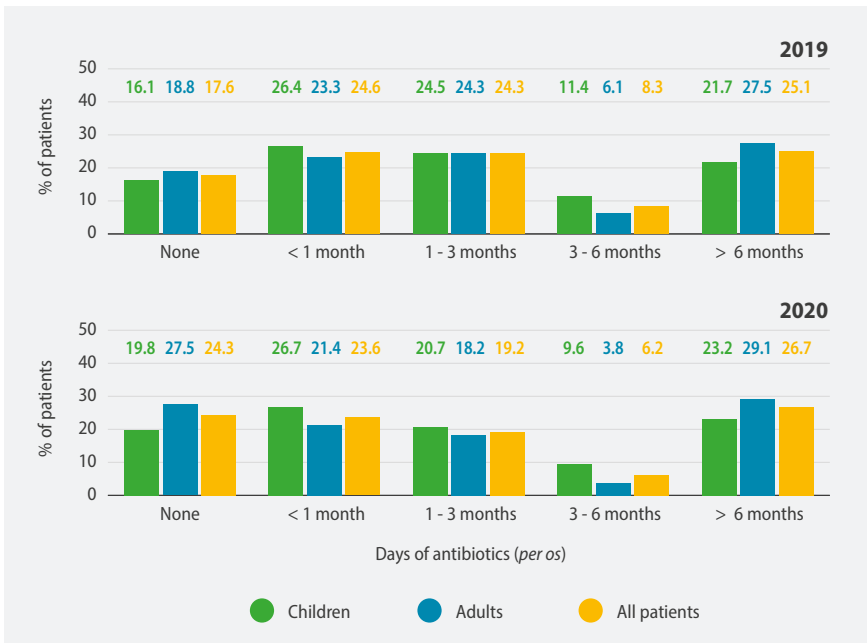


**Figure 24 |  Days of oral antibiotics**

# TRANSPLANTS AND CF

—

When a person 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 pwCF who have exhausted all other forms of conventional medical treatment and whose short term survival is compromised. For these people, lung transplantation may offer prolonged survival and an improved quality of 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 people in the registry were transplanted more than 20 years ago.

The first (heart)-lung transplant in a Belgian person with CF was performed in 1988. Since this time about 322 pwCF5 (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 due to a temporary stop in transplantation programs. A few people with CF 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 people with a transplant. It includes a table with all transplants ever reported in the registry. This table shows the type and year of transplant and the number of pwCF presumed alive by the time of data collection 2020, 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 **304** pwCF, **143** males and **161** females, have benefited from transplantation: lung and/or other organ, either single or multiple. In 2020, 18 people were on the waiting list (two of them with already a transplant), 19 had been evaluated but were not on the list, 3 declined the transplant while one was 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 transplanted pwCF in the year of the first transplant was 29.0 (10.2) and 27.9 years (0.7 – 60.6) respectively. About 10.2% (31 people) had their first transplant done before age 18 years.

In 2020, there were **216** people recorded living with a transplant. The mean (SD) and median (range) age of the transplanted pwCF reported or assumed as alive in January 2020 was 39.1 (11.0) and 38.8 years (1.7 – 71.8) respectively at the end of 2020. While 100 were male and 116 were female, about 97.7% of the transplanted pwCF reported in 2020 were adults.

The data presented in table 21 overleaf concerns all recorded transplants in the registry and also data of pwCF reported alive by January 2020 (last column, on the right). Slight differences may be noted with previous reports as we seek to consolidate the transplant data yearly. In table 21, the number of transplants performed do not add up to the number of people: - a person can have several transplants.

Multiple transplants are counted as separate transplant occasions. A total of 345 transplants in 304 people are so far reported in the CF registry. There are 37 people who had a transplant on more than one occasion, either for a lung re-transplantation or other organ.

In figure 25, the total number of people recorded each year is presented as a proportion of children and adults, with and without a transplant. While the proportion of adults living with CF is increasing, so is the number of adults living with a transplant.
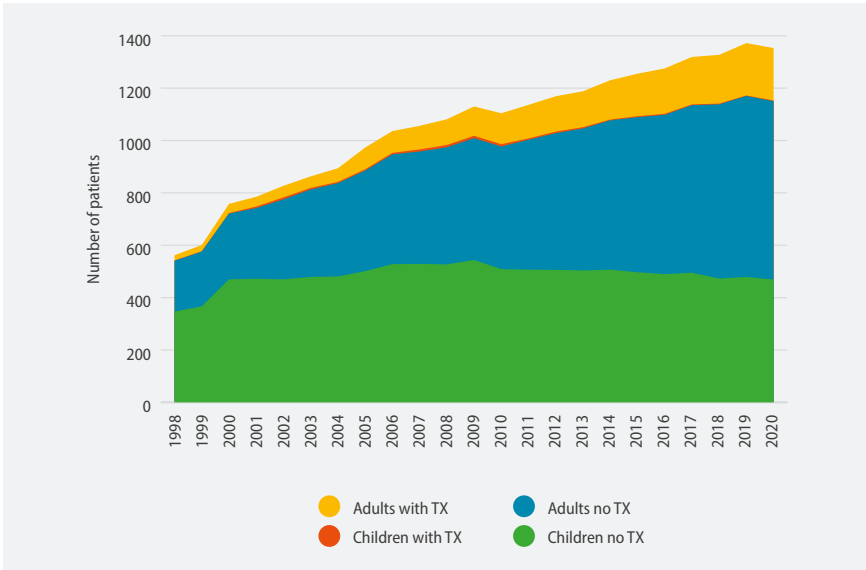
**Figure 25 |  Number of pwCF by age and transplant status**

## 10.2    TYPE OF TRANSPLANT

The most frequent transplant done is the lung transplant, either alone or in combination with a liver or heart. Thus far, 273 isolated lung transplants have been carried out.

**Table 21 |**   **Type of transplant by year**

| 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 | 1 |
| 1998 | 9 | 1 | | | | | | | | 10 | 3 |
| 1999 | 5 | | | | | | | | | 5 | 2 |
| 2000 | 10 | | | | | | | | | 10 | 2 |
| 2001 | 13 | | 1 | 4 | | | | | | 18 | 10 |
| 2002 | 10 | | | 2 | | | | | | 12 | 5 |
| 2003 | 9 | | | 1 | | | | | | 10 | 8 |
| 2004 | 11 | | | | | | | | | 11 | 6 |
| 2005 | 10 | | 1 | 3 | | | | | | 14 | 8 |
| 2006 | 13 | | | 1 | 1 | | 1 | | | 16 | 8 |
| 2007 | 16 | | | 1 | 1 | | | | | 18 | 7 |
| 2008 | 16 | | | | 3 | | | | | 19 | 12 |
| 2009 | 10 | | | 1 | | 1 | | | | 12 | 9 |
| 2010 | 13 | | 2 | 1 | | | | | | 16 | 10 |
| 2011 | 15 | | | | 1 | | 1 | | | 17 | 11 |
| 2012 | 12 | | | | | | | | | 12 | 10 |
| 2013 | 13 | | | | 3 | | | | | 16 | 7 |
| 2014 | 7 | | | | 4 | | | | | 11 | 5 |
| 2015 | 15 | | 2 | | 1 | | 1 | | | 19 | 16 |
| 2016 | 18 | | | 2 | | | | | | 20 | 18 |
| 2017 | 10 | | | 1 | 2 | | 1 | | | 14 | 10 |
| 2018 | 12 | | 2 | | 3 | | | | | 17 | 12 |
| 2019 | 16 | | 3 | 1 | | | | | | 20 | 17 |
| **2020** | **6** | | | **1** | **1** | | | | **1** | **9** | **9** |
| **Total** | **273** | **15** | **11** | **20** | **20** | **1** | **3** | **1** | **1** | **345** | |
| **Alive**** | **175** | **3** | **8** | **12** | **15** | **1** | **1** | | **1** | **-** | **216** |

\* Number of reported people alive by beginning of 2020 by transplant year considering the first transplant.
\*\* Number of reported people alive by beginning of 2020 considering type of first transplant.

# REPORTED DEATHS

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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 is 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 updates.

## 11.1   AGE AT DEATH

The data in the registry show that there have been 209 reported deaths since inception of the registry, 111 male and 98 female. Twenty (9.6%) of the deaths were in children (below 18 years) while 9 (4.3%) of the deaths were in children younger than ten years. The mean (SD) and median (IQR) age at death for all reported cases is 32.2 (14.0) and 29.9 (17.2) 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, 12.2% 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**

Legend (dot size): 1, 2, 3, 4, 5

| Year | Age at death | | | | | | | | | | | | | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 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 | ● | | | ● | | ● | ● | | | | | | | | | | 5 |
| 1999 | | | | ● | ● | ● | | ● | | | | | | | | | 12 |
| 2000 | | | | ● | ● | ● | ● | ● | | | | | | | | | 9 |
| 2001 | | ● | | ● | ● | ● | | ● | | | | | | | | | 10 |
| 2002 | | | | | ● | ● | ● | ● | | | | ● | | | | | 11 |
| 2003 | | ● | ● | ● | ● | ● | ● | ● | | ● | | | | | | | 15 |
| 2004 | | | | ● | ● | ● | ● | | ● | | | | | | | | 9 |
| 2005 | ● | | | | ● | ● | | | | | | | | | | | 3 |
| 2006 | ● | | | ● | | | | ● | ● | | | | | | | | 6 |
| 2007 | | ● | ● | ● | | ● | | ● | ● | ● | | | | | | | 8 |
| 2008 | | | | ● | | ● | | | | ● | | | | | | | 6 |
| 2009 | | | ● | ● | ● | ● | ● | | ● | ● | | | | | | | 10 |
| 2010 | | | | | ● | | ● | | | | ● | ● | | | | | 7 |
| 2011 | | ● | | | ● | ● | ● | | ● | ● | | | | | | | 9 |
| 2012 | | ● | | ● | ● | ● | ● | ● | ● | | ● | | | | | | 11 |
| 2013 | | | | ● | ● | ● | | | | | | | | | | | 6 |
| 2014 | | | ● | | | ● | ● | ● | | | | | | ● | | ● | 10 |
| 2015 | | | | | ● | ● | ● | ● | ● | ● | ● | ● | | | | | 15 |
| 2016 | | | | ● | | ● | ● | ● | ● | | | | | | | | 9 |
| 2017 | | | ● | ● | | ● | | ● | | | | | | ● | | | 6 |
| 2018 | | | | ● | | ● | ● | ● | ● | ● | ● | ● | | ● | | | 16 |
| 2019 | | | | | | ● | | ● | ● | ● | ● | | | | | | 6 |
| **2020** | | | | ● | | | ● | ● | ● | | ● | ● | | | ● | | **10** |
| Total | 3 | 6 | 5 | 28 | 26 | 46 | 24 | 25 | 13 | 10 | 7 | 9 | - | 4 | 2 | 1 | 209 |

The figure 26 shows the number of confirmed and reported deaths in the CF registry since 1998. Most of the deceased were in the age category 25 – 30 years.
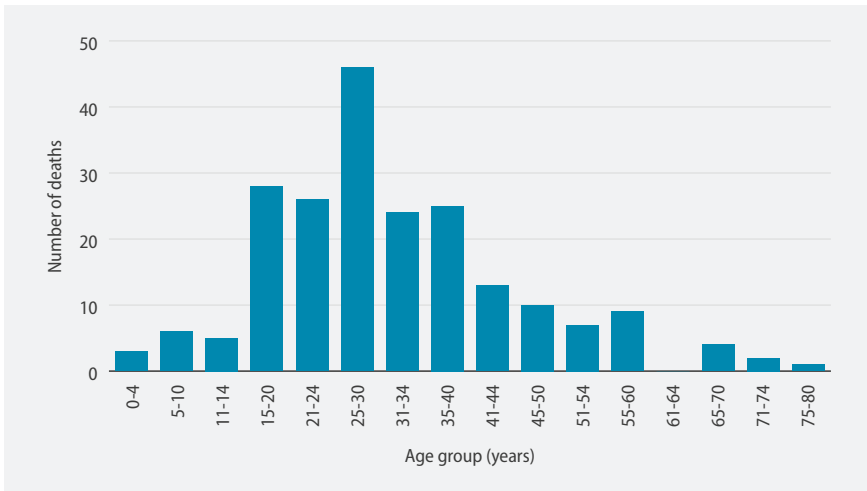
**Figure 26 |** **Reported deaths by age category**

## 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 either associated with the respiratory system or with post-transplant complications. The other CF-related causes of death include but are not limited to septic shock, multi-organ failure, terminal renal insufficiency, intoxication, hypoglycaemic coma, road accident, and euthanasia.

**Table 23 |**   **Primary causes of death for reported cases**

| Cause of death | n | %* |
|---|---|---|
| Respiratory | 93 | 44.5 |
| Transplant | 50 | 23.9 |
| Other | 34 | 16.3 |
| Cancer | 10 | 4.8 |
| Cardiac | 8 | 3.8 |
| Liver | 6 | 2.9 |
| Kidney | 4 | 1.9 |
| Suicide | 3 | 1.4 |
| Trauma | 2 | 1 |
| Other CF related | 1 | 0.5 |
| Unknown + missing | 33 | 15.8 |

* 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

—

PwCF continue to live longer. According to the registry data, the median age has increased from 14.9 years in 1998 to about 24.2 years in 2020 suggesting better life expectancy. This introduces new challenges and expectations alike. Despite their therapy burden, they continue 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 2020. It also gives information on social allowances and employment status. All people 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 2020, 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* | 64 | 13.7 | | | 64 | 4.8 |
| No school | 9 | 1.9 | 10 | 1.2 | 19 | 1.4 |
| Regular school / education attendance | 395 | 84.4** | 151 | 17.4 | 546 | 40.9 |
| Has finished school/education | | | 703 | 81.0 | 703 | 52.7 |
| Unknown | | | 2 | 0.2 | 3 | 0.2 |
| Missing | 5 | | 13 | | 18 | |
| **Total** | **473** | **100.0** | **880** | **100.0** | **1353** | **100.0** |

* Children below age 3 years were considered below school attendance age.
** 97.8% of children > 3y with information on school status.

## 12.2   SOCIAL ALLOWANCES AND EMPLOYMENT

PwCF 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 those getting insufficient income can request income support from the government (if recognized as having a disability), or a disability allowance from the social security (if recognized as ill, after being professionally active).

After retirement (usually 65y, with options for early retirement from 54y), one receives their pension. The integration allowance is additional support for increased costs linked to the disability while the preferential tariff allows for a reduction on health care costs and on various public services, and is available to people with income from certain social security sources.

**Table 25 |**   **Social allowances or benefits and employment**

|  | Children | | Adults | |
|---|---|---|---|---|
|  | **n** | **%** | **n** | **%** |
| **DESCRIPTION** | | | | |
| Additional child allowance | 436 | 92.2 | 111 | 12.6 |
| Income support (in adults) | | | 162 | 18.4 |
| Disability allowance | 1 | 0.2 | 175 | 19.9 |
| Pension allowance (in adults) | | | 15 | 1.7 |
| Integration support (in adults) | | | 349 | 39.7 |
| Preferential tariff (in adults) | | | 518 | 58.9 |
| **EMPLOYMENT*** | | | | |
| Yes | | | 384 | 43.6 |
| No | | | 496 | 56.4 |

* Data include 151 adults (and children from 16y) still in school.

Amongst the 384 pwCF who said they were employed, 212 (55.2%) worked full time, 161 (41.9%) part-time, and unknown for 11 people.

# CHAPTER 13.
# CF AND FERTILITY

—

With the improving trend in life-expectancy for pwCF, 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).

Even though most children with CF nowadays achieve near 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].

Some pwCF may have children via medical assistance including via gamete donation. In this sense, we cannot strictly talk about them (if male) having "biological children". In addition, some chose to grow their family via adoption. Therefore, since the data collection 2020, we assess family status by considering any addition to their family whether the child is biological or born/adopted by a person with CF.

## 13.1    NUMBER OF CHILDREN REPORTED

Data from the registry shows that by 2020, there were at least 359 children reported from 223 pwCF (206 (194 of them alive in 2020). These children could be biological or adopted. More than half of those who have children were female (125, 56.1%). Among those with children, 43 (19.3%) were living with a transplant while 94 (42.5%) parents were homozygous for the F508del mutation. The mean age at which they had the first child was 29.8 years (median 30.0 years) with a range 16.0 – 49.2 years. The mean (median) was 32.2 (32.0) and 27.9 (28.0) years respectively for the male and female parents with CF.

The mean number of children in pwCF reported to have children was 1.6 (median 1.0, range 1 – 5). 115 pwCF (51.6%) had one child, while 85 (38.1%) had two children and 23 (9.7%) had three children or more. Sixteen parents have twins. There were three pwCF who have had a child before their 18th birthday. In 2020, sixteen 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 pwCF. The figure 27 shows the total number of births among pwCF.
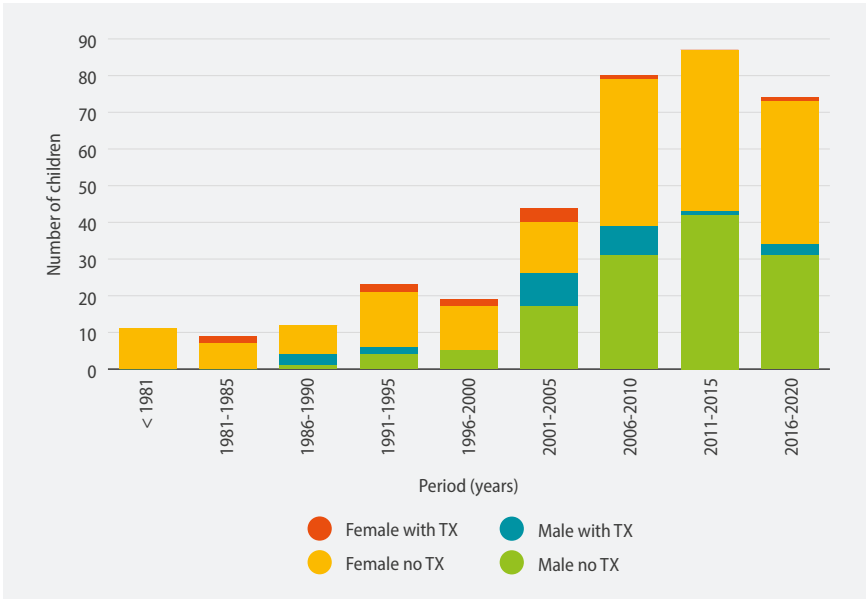
**Figure 27 |** **Number of reported children by period***

* 5-year periods

# 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 people with confirmed CF diagnosis and who were seen in 2020. It includes the data with no value reported, reported as "unknown" or "missing", or as "not identified" (for genotype), whatever the reason. People with a revoked diagnosis, those without a confirmed diagnosis, or without observation (without at least four filled-in clinical items, postulated alive or registered as deceased), or who were not seen at a CF center during the year, are excluded from the totals. The tables are provided in six categories, quite similar to the order of appearance in the Cystic Fibrosis Registry Questionnaire (see appendix).

The field with the highest proportion of missing values under diagnosis was the sweat test chloride, 13.1% (Table 26). This has an impact on the number of people 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 people, 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 pwCF with comparable demographics. Such data could be misleading.

PwCF 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 age for people with CF living in Belgium surpassed 18 years (it was 18.1 years), the proportion of adults has only been higher each year, with over 64.2% in 2020. But this also means that since the people 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 CF 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**

|  | ALL clinics | |
| --- | --- | --- |
|  | n | % |
| **DEMOGRAPHIC AND DIAGNOSTIC INFORMATION** | | |
| No diagnosis symptoms given | 55 | 4.1 |
| Mutation 1 | 3 | 0.2 |
| Mutation 2 | 17 | 1.3 |
| Sweat test chloride | 175 | 13.1 |
| Date diagnosis | 30 | 2.2 |
| **ANTHROPOMETRY AND SPIROMETRY** | | |
| Height values | 3 | 0.2 |
| Weight values | 3 | 0.2 |
| $FEV_1$ values * | 23 | 1.7 |
| **CHRONIC INFECTIONS \*\*** | | |
| Chronic *Pseudomonas Aeruginosa* infection | 11 | 1.0 |
| Chronic *Burkholderia Cepacia Complex* infection | 7 | 0.6 |
| Chronic *Stenotrophomonas Maltophilia* infection | 8 | 0.7 |
| Chronic MRSA infection | 7 | 0.6 |
| Chronic *Achromobacter Xylosoxidans* infection | 8 | 0.7 |

* The summary of $FEV_1$ excludes children below 6y.
6** The summary of infections excludes people with a lung transplant and those who had no culture or sample taken during the year. Empty field = no missing data.

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

| | ALL clinics | |
|---|---|---|
| | n | % |
| **RESPIRATORY COMPLICATIONS** | | |
| Allergic Bronchial Pulmonary Aspergillosis | 2 | 0.2 |
| Pneumothorax | 2 | 0.2 |
| Nasal Polyps | 19 | 1.7 |
| Massive haemoptysis | 4 | 0.4 |
| Bronchiectasis | 6 | 0.5 |
| **GASTRO-INTESTINAL COMPLICATIONS** | | |
| Pancreatic sufficiency status | 4 | 0.3 |
| Acute pancreatitis | 6 | 0.4 |
| CFRD or ITG | 198 | 14.8 |
| Cirrhosis with portal hypertension | 10 | 0.7 |
| Intestinal obstruction (no surgery) | 6 | 0.4 |
| Intestinal obstruction (with surgery) | 9 | 0.7 |
| Clostridium infection (Resection needed) | 8 | 0.6 |
| **MISCELLANEOUS COMPLICATIONS** | | |
| CF related Arthritis/arthropathy | 208 | 15.6 |
| Cancer | 5 | 0.4 |
| Osteopenia or Osteoporosis | 16 | 1.2 |
| Hypertension (treated) | 6 | 0.4 |
| Other complications | 9 | 0.7 |

\* The summary of respiratory complications excludes data from people with a transplant.

**Table 28 |**   **Missing data on therapy and medication**

| | ALL clinics | |
|---|---|---|
| | n | % |
| **PHYSIOTHERAPY, INHALATION THERAPY, ORAL-ANTI-INFLAMATORY AND ANTIBIOTICS[3]** | | |
| Number of visits to clinic | 3 | 0.2 |
| Number of exploitable months | 194 | 14.5 |
| Days of hospitalization | 3 | 0.2 |
| Systemic antibiotics* | 2 | 0.2 |
| Home Oxygen therapy | 33 | 2.5 |
| **DIGESTIVE AND NUTRITIONAL THERAPY** | | |
| Pancreatic enzymes | 3 | 0.2 |
| Ursodeoxycholic acid | 4 | 0.3 |
| Tube feeding | 5 | 0.4 |
| Gastrostomy | 5 | 0.4 |
| Parenteral feeding | 6 | 0.4 |
| **OTHER THERAPY AND MEDICATION** | | |
| Insulin therapy | 4 | 0.3 |
| Oral therapy for diabetes | 4 | 0.3 |
| Bisphosphonates | 8 | 0.6 |
| Anticonceptive therapy (females 12 and over) | 60 | 12.3 |
| PPI + H2 receptor blocker | 6 | 0.4 |
| CFTR modulating therapy* | 1 | 0.1 |

* The summary of physiotherapy, inhalation therapy, oral anti-inflammatory, systemic antibiotics and CFTR therapy excludes people living with a transplant.

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

| | ALL clinics | |
|---|---|---|
| | n | % |
| School attendance in children aged 3 - 18 years | 5 | 51.2 |
| Child allowance for children under 18 years | | |
| Income support for adults | 54 | 546.1 |
| Disability allowance for adults | 51 | 515.8 |
| Preferential tariff for adults | 44 | 445.0 |
| Pension for adults | | |
| Integration allowance for adults | 52 | 525.9 |
| Employment for adults not attending school | 34 | 344.8 |

Pension for adults considers only people aged 54 years and above. 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.

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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.

[A6]    E. De Wachter, M. Thomas, S. Wanyama, S. Seneca, and A. Malfroot, "What can the CF registry tell us about rare CFTR-mutations? A Belgian study.," *Orphanet.J.Rare.Dis.,* vol. 12, no. 1, pp. 142-, Nov. 2017.

[A7]    D. Libeert *et al.*, "The effect of enteral tube feeding in cystic fibrosis: A registry based study," *J. Cyst. Fibros.*, vol. 17, no. 2, pp. 264–270, 2018, doi: 10.1016/j.jcf.2018.01.004.

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# APPENDIX

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## BMR-RBM-BCFR 2020 – 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        ❑ Indeterminate sex        ❑ 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            : ................

## 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
- ❑ In follow-up
- ❑ Not seen patient
- ❑ Revoked diagnosis
- ❑ Moved to other center/other country
- ❑ No information
- ❑ Lost to follow-up
- ❑ 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          ❑ NDD Easyone Pro
                     ❑ Ecomedics Exhaler SF6 (Tracergas 4%)       ❑ 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

### 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 |
| 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 and Night ❑ 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 |
|     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

❑ 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

## 5.4 - Miscellaneous (2)

❏ 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 2020 DIGITAL QUESTIONNAIRE LUNG TRANSPLANT PWCF

# BMR-RBM-BCFR 2020 – 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     ❑ Indeterminate sex     ❑ 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      ❑ In follow-up
                 ❑ Not seen patient                        ❑ Revoked diagnosis
                 ❑ Moved to other center/other country    ❑ No information
                 <span style="color:red">❑ Lost to follow-up</span>                <span style="color:red">❑ Revoked consent</span>

### 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 <span style="color:red">(CF-related)</span> | ❑ |

    (type) ....................................................................................................................................

| | |
|---|---|
| Other cause <span style="color:red">(not CF-related)</span> | ❑ |

    (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 and Night | ❑ 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

### 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 : . . / . . / . . . .

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

### Transplant 2

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

## 7.4 - Financial benefits (2)

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 III:
## BCFR 2020 DIGITAL QUESTIONNAIRE NON-LUNG TRANSPLANT PWCF

# BMR-RBM-BCFR 2020 – 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      <span style="color:red">❑ Indeterminate sex      ❑ Unknown</span>
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 <span style="color:red">initial</span> 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            : ................

## <span style="color:red">1.7 - New genotype test performed after diagnosis</span>

<span style="color:red">**New genotype test performed after diagnosis ?**   ❑ No ❑ Yes</span>
    <span style="color:red">Date of last genotype : . . / . . / . . . .</span>

## 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. Complicatons

### 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 | | |

| | | | |
|---|---|---|---|
| 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 and Night ❑ 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

   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

## 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  ❑ 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 |

<span style="color:red">

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

</span>

### 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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## CONTACT

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