Variables, Inclusion Criteria and References used by the ECFSPR (valid from 2024 YFU)

New variables introduced for the 2024 follow-up year are blue

Demographics

- CF centre code;
- Centre Patient code (optional);
- Year of follow-up;
- Year and month of birth;
- Sex (Previously "Gender") - Male, Female, Other/Prefer not to say;
- Ethnicity;
- Vital Status of patient;
- Cause of death;
- Date of death.

Diagnosis

- Age at diagnosis;
- Sweat test type and values (x2);
- First & second genetic CFTR variants in trans (possible to record complex variants in cis);
- Meconium Ileus;
- Neonatal screening;
- Nasal Potential Difference Measured? (NPD);
- CF-typical NPD measurement Yes/No;
- Date of NPD measurement;
- Intestinal current value measured? (ICM);
- CF-typical IC measurement Yes/No;
- Date of IC measurement.

Maintenance Therapy

- Inhaled continuous (≥ 3 months) hypertonic saline ≥3% ;
- Inhaled continuous (≥ 3 months) Mannitol;
- Inhaled antibiotic this year - continuous (≥ 3 months) or on/off for a total of (≥ 6months);
- Inhaled continuous (≥ 3 months) bronchodilators, long-acting or short-acting or both;
- Oxygen therapy ≥ 3 months during the year of follow-up (inc. 24h/day, night time, exercise). Does not need to be continuously but should be from a single prescription);
- Use of continuous (≥ 3 months) non-invasive positive pressure ventilation (NIPPV);
- Use of continuous (≥ 3 months) rhDNase this year;
- Use of continuous (≥ 3 months) Inhaled steroids;
- Use of continuous (≥ 3 months) Oral steroids;
- Use of continuous (≥ 3 months) azithromycin (or other macrolide) this year;
- Use of continuous (≥ 3 months) ursodeoxycholic acid this year;
- Use of continuous (≥ 3 months) pancreatic enzymes this year;
- Use of continuous (≥ 3 months) proton pump inhibitors (PPI);
- Use of CFTR Modulator Therapy (data for each of the following are collected: Ivacaftor, Lumacaftor/ Ivacaftor, Tezacaftor/Ivacaftor, Elexacaftor/Tezacaftor/Ivacaftor, Vanzacaftor/Texacafter/Deutivacaftor, Other CFTR modulator;
- Start and stop dates x 2 for each CFTR modulator (pause of <30 days not to be recorded);
- Sweat chloride values - before start & during (lowest of year) for each CFTR modulator;
- Principal reason for stopping CFTRm therapy (for each stop).

Lung function and nutrition follow-up

- Value of FEV1 in litres of highest FEV1% predicted of the year;
- Value of FVC in litres (from same spirometry as recorded FEV1);
- Height measured at date of best FEV1 (or if no available FEV1, last height of the year);
- Weight measured at date of best FEV1 (or if no available FEV1, last weight of the year);
- Date of recorded FEV1 or if no FEV1 recorded, date of recorded height and weight);
- Lowest LCI 2.5% of the year;
- Type of device used for LCI2.5 measurement;
- Date of lowest LCI 2.5% this year;
- Value of lowest LCI 2.5% this year.

Microbiology *(positive-chronic or positive-at least once/not chronic for all pathogens except Nontuberculous mycobacteria and Fungi)*

- Pseudomonas aeruginosa;
- MSSA - Methicillin-sensitive Staphylococcus aureus;
- MRSA - Methicillin-resistant Staphylococcus aureus;
- Burkholderia cepacia complex;
- Stenotrophomonas maltophilia;
- Achromobacter spp;
- Haemophilus influenza;
- Nontuberculous mycobacteria (tested for);
- Mycobacterium abscessus complex;
- Mycobacterium avium complex;
- Other mycobacteria;
- Nontuberculous mycobacteria treated this year;
- Fungi investigated;
- Aspergillus fumigatus;
- Scedosporium spp.

Hospitalisation, Pulmonary Exacerbations, IV Antibiotics

- Total days on iv antibiotics at home and in hospital this year (CF-related reasons);
- Total days on iv antibiotics in hospital this year (CF-related reasons);
- Total days in hospital this year (any reason);
- PEx treated with intravenous antibiotics yes/no etc.
- Number of PEx episodes treated with intravenous antibiotics during the year.

Complications

- ABPA (Allergic bronchopulmonary aspergillosis)
- Distal intestinal obstruction syndrome (DIOS) this year;
- Salt loss syndrome this year;
- Diabetes this year;
- Pneumothorax this year;
- Liver disease this year;
- Haemoptysis major volume of expectorate > 250ml in a day;
- Occurrence of malignancy (from 2024 YFU change to ICD10 codes C00 - C96)
- Pancreatic status: faecal elastase;
- Pancreatic status: faecal fat;
- Pregnancy this year;
- Pregnancy stopped this year - reason for stop;
- Pregnancy ongoing at 31/12.
- BMD (Bone mineral density): osteopoenia or osteoporosis in year of follow-up;
- BMD Diagnosis/status: was the diagnosis/status based on a DEXA scan?
- At least 1 episode of acute pancreatitis this year;
- Arterial hypertension treated with medication during the year of follow-up
- Hypercholesterolaemia treated with medication during the year of follow-up

Hospitalisation, Pulmonary Exacerbations, IV Antibiotics

- Total days on iv antibiotics at home and in hospital this year (CF-related reasons);
- Total days on iv antibiotics in hospital this year (CF-related reasons);
- Total days in hospital this year (any reason);
- PEx treated with intravenous antibiotics yes/no etc.
- Number of PEx episodes treated with intravenous antibiotics during the year.

Transplant

- Liver transplant at any time;
- Year of latest liver transplant (before or during this year);
- Lung transplant at any time;
- Year of latest lung transplant (before or during this year);
- Kidney transplant at any time;
- Year of latest lung transplant (before or during this year);
- Other transplant at any time;
- Year of latest other transplant (before or during this year).

Criteria and References used by the ECFS Patient Registry (valid for 2024 YFU)

1 Diagnosis / Reversal of Diagnosis: Criteria, References

A. **Diagnosis accepted if:**

Two sweat tests value > 59 mmol/L chloride;

OR

ii. One sweat test value > 59 mmol/L chloride + DNA Analysis/Genotyping with two identified disease-causing CF variants in trans

OR

iii. Sweat chloride value is less than or equal to 60 mmol/L or not reported **AND at least 2 of the following:**

a. DNA Analysis/Genotyping: two identified disease-causing CF variants in trans;

b. NPD (Transepithelial (Nasal) Potential Difference) or ICM (Intestinal current measurement): result consistent with a diagnosis of CF;

c. Clinical presentation: typical features of CF.

B. **Diagnosis reversal* - CF diagnosis should be reversed if any of the following is true:**

i. DNA Analysis has not identified any CF disease-causing variants;

ii. NPD (nasal potential difference) &/or ICM (intestinal current measurement): result not consistent with diagnosis of CF;

iii. Normal values from repeated sweat testing (never prescribed CFTR modulators & confirm with the clinical team).

**See also ECFSPR SOP (Standard Operating Procedure) 214 Reversal of Diagnosis - regarding reversal of diagnosis and previously submitted data (find it on the homepage of the data collection software ECFSTracker, together with other useful information).*

References

1) ECFS best practice guidelines: the 2018 revision
2) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

2 Demographics: Ethnicity, References

i. Ethnicity categories are based on the available Global Lung Function Initiative equations and are: Caucasian; Black; North East Asian; South East Asian; Mixed / Other (including Indian sub-continent); Unknown; Missing.

ii. **Group country/region**

Caucasian: Europe, Israel, Australia, USA, Canada, Mexican Americans, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria, Tunisia;
Black: African-American;
South East Asian: Thailand, Taiwan and China (including Hong Kong) south of the Huaihe River and Qinling Mountains;
North East Asian: Korea and China north of the Huaihe River and Qinling Mountains;
Mixed / Other: Indian Sub-continent and individuals not represented by one of the groups or who are of mixed ethnicity.

iii. In addition to the countries listed, it is reasonable to apply the same ethnicity to others with geographic or ethnic proximity. Thus the Caucasian equations could be used for any person having origins in any of the original peoples of Europe, the Middle East or North Africa and for any non-indigenous person of South America. Similarly, the South East Asian equations may be reasonably extended throughout that region.

References

1) Global Lung Function Initiative equations described by Quanjer PH et al. (Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343).
https://erj.ersjournals.com/content/40/6/1324

3 Sweat Test: Parameters, Values to be reported, References

i. Diagnostic standards: the quantity of sweat should indicate an adequate rate of sweat production;

ii. a. The sweat sample should be processed immediately after sweat collection;

b. Chloride concentration measurement is the preferred analysis for Diagnostic sweat tests. **For sweat tests in relation to CFTR modulator therapy, Chloride is the only accepted value;**

c. Chloride value: report the Chloride value in millimols per litre (mmol/L). If duplicate tests were completed on the same day, for Diagnostic sweat tests, **report the highest positive value;**

d. A sweat chloride value >59 mmol/L is consistent with a diagnosis of CF;

e. A sweat chloride value <30 mmol/L makes the diagnosis of CF unlikely (However, specific CF causing mutations can be associated with a sweat test below 30 mmol/L).

n.b. *The acceptable range for Chloride values is 1-160 mmol/L.* ***Anyone who has a Chloride value above 160 mmol/L should be re-tested;***

iii. As already mentioned above, the ECFSPR will consider only Titration/Chloride values in analyses.

References (links)

1) ECFS best practice guidelines: the 2018 revision
2) European Cystic Fibrosis Society Standards of Care: Best Practice guidelines (2013)

Criteria and References used by the ECFS Patient Registry (valid for 2024 YFU)

4 Nutrition: Method, Values and Dates to be reported, References.

i. The height and weight reported to the ECFSPR should be from the same day as the reported FEV1 (of hightest FEV1% predicted of the year);
If spirometry was not done the last weight and height measurements of the year, and the date they were measured, should be recorded.

ii. If spirometry was not done, the last weight and height measurements of the year, and the date they were measured, should be recorded.

iii. Height and weight should be measured in accordance with EuroCareCF guidelines:
Weight: removal of outer clothing, shoes and socks;
Height: removal of shoes and socks, stadiometer - top of head in contact with head board, slight pressure.

iv. Z-scores for height, weight & BMI are calculated with the CDC reference values [Kuczmarski et al (2002)].

References

1) Kromeyer-Hauschild K, Wabitsch M, Kunze D, Geller F, Geiss HC, Hesse V et al. Percentiles of body mass index in children and adolescents evaluated from different regional German studies. Monatsschr Kinderheilkd 2001; 149:807-818.
2) Lai H-C, Corey M, FitzSimmons S, Kosorok MR, Farrell M. Comparision of growth status of patients with cystic fibrosis between the United States and Canada. Am J Clin Nutr 1999; 69:531-538.
3) Public Use File BGS98, German National Health Interview and Examination Survey 1998, Robert-Koch-Institut, Berlin, Germany, 2000.
4) Wiedemann B, Paul KD, Stern M, Wagner TO, Hirche TO, on behalf of the German CFQA Group. Evaluation of body mass index percentiles for assessment of malnutrition in children with cystic fibrosis. Eur J Clin Nutr 2007; 61, 759-768.
5) Kuczmarski RJ, Ogden CL, Guo SS et al. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 2002; 11(246): 1-190.

5 Spirometry: Criteria, Method, Values to be reported, References.

- The ECFS Patient Registry collects data on spirometry values to obtain standardised data for comparison with other centres/countries and for use in specific epidemiological studies.
- **n.b.** Some of the conditions for this (see below) may not be met at every clinical visit for all patients and, **for the ECFSPR, only spirometry tests fulfilling the criteria should be recorded by centres or submitted by the National Registries.**

- We recommend a**ll spirometry tests are carried out in accordance with the ATS/ERS guidelines** (www.thoracic.org/statements/resources/pfet/PFT2.pdf) although a decision was taken by the ECFSPR Definitions group in 2022 to accept lung function values from spirometry tests carried out also post-bronchodilator.*

For the spirometry values reported to the ECFSPR the following criteria should be met:

i. **Pre-test preparation**
   a. All recorded spirometry tests should be pre-bronchodilator (but see above*);
      i. short-acting bronchodilators: at least 4 hours pre-test;
      ii. long-acting bronchodilators: at least 12 hours pre-test.
   b. Date of birth, gender and height should be recorded for calculation of predicted values. In addition, the ECFS Patient Registry asks for the weight and height to be measured at the same time, and recorded.

ii. **Values to report:**
   a. FEV1 in litres of best FEV1% predicted, pre- or post-bronchodilator (to 2 decimals), in accordance with local reference values;
   b. The FEV1 and FVC measurements must be reported in litres (L), to max 2 decimal points;
   c. FVC in litres: must be the FVC measured from the same test as recorded FEV1 (of the best FEV1% predicted of the year, pre- or post-bronchodilator) and it must be greater than or equal to the FEV1 measurement.
   d. For the reported spirometry values, the date of the test and the patient's height and weight at that date should also be recorded in order to calculate the percent of predicted values and other values;
   e. Only tests deemed valid according to ATS/ERS guidelines to be reported.

iii. **Calculation of percent of predicted values:**
   a. A common set of reference values - the Global Lung Function Initiative equations (See (1) below) - is used for calculations.

References

1) Global Lung Function Initiative equations described by Quanjer PH et al. (Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324–1343).
2) Miller et al. Standardisation of spirometry. Eur Respir J 2005; 26: 319–338 / Graham et al. Standardisation of spirometry 2019 update. Am J Respir Crit Care Med.2019 Oct 15;200(8):e70-e88.
3) Miller et al. General considerations for lung function testing. Eur Respir J 2005; 26: 153–161.
4) Rosenfeld et al. Task Force to Evaluate Choice of Spirometric Reference Equations for the National Patient Registry: Summary and Recommendations. Cystic Fibrosis Foundation Registry Committee; 2005.

Criteria and References used by the ECFS Patient Registry (valid for 2024 YFU)

6 Chronic infection in the lower airways: Definition, References.

i. Chronic Pseudomonas aeruginosa infection: A patient should be considered chronically infected if the modified Leeds criteria are met - (a) below - and/or anti-pseudomonas antibodies are detected - (b) below.

ii. A patient should be defined as chronically infected if he/she fulfils the criteria now, or has done so in recent years, and the physician has no reason to think that the status has changed.

a. **Modified Leeds criteria** - chronic infection: >50% of the samples (sputum/other) collected during the last 12 months should be positive; at least 4 samples collected.
b. Significantly raised levels of anti-pseudomonas antibodies according to local laboratories.

iii. Chronic infection with other gram-negative or gram-positive bacteria should meet the same criteria as described above.

References

1) Lee TWR, Brownlee KG, Conway SP, Denton M, Littlewood JM. Evaluation of a new definition for chronic Pseudomonas aeruginosa in cystic fibrosis patients. J Cystic Fibrosis
2) Proesmans M, Balinska-Miskiewiscz, Dupont L et al. Evaluating the "Leeds criteria" for Pseudomonas aeruginosa infection in a cystic fibrosis centre. Eur Resp J 2006;27:937-943.
3) Doring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. Eur Respir J 2000;16:749-767.

7 Allergic Broncho-pulmonary aspergillus - ABPA

i. Diagnostic criteria:

a. Acute or subacute clinical deterioration (cough, wheeze, exercise intolerance, exercise-induced asthma, change in pulmonary function, or increased sputum production) not attributable to another etiology.
b. Total IgE > 500 IU/ml.
c. Positive skin prick test for Aspergillus antigen (> 3 mm) or positive specific IgE for A. fumigatus.
d. Precipitins to A. fumigatus or in vitro demonstration of IgG antibody to A. fumigatus;
OR
new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (characteristic changes) that have not cleared with antibiotics and standard physiotherapy.

References

Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. Stevens DA, Moss RB, Kurup VP, Knutsen AP, Greenberger P, Judson MA, Denning DW, Crameri R, Brody AS, Light M, Skov M, Maish W, Mastella G; Participants in the Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis. 2003 Oct 1;37 Suppl 3:S225-64.

8 Liver Disease: Definitions

The ECFSPR has adopted the definitions for Liver Disease used by the Cystic Fibrosis Registry in the UK. These definitions discriminate patients with severe liver disease (with portal hypertension) from milder cases (cirrhosis without portal hypertension).

- **Cirrhosis with Hypertension**: scarring of the liver related to underlying CF, typically in a biliary pattern. Severe liver disease may include portal hypertension and/or hypersplenism;
- **Cirrhosis without Hypertension**: scarring of the liver related to underlying CF;
- **Liver disease without cirrhosis**: this includes fatty liver or viral hepatitis but not biliary cirrhosis.

Additional reference

A position statement regarding classification of CF hepatobiliary manifestations (CFHBI) was published in January 2024 and may provide further guidance for ECFSPR members when reporting on liver disease in people with CF.

Bodewes FAJA, Freeman AJ, Weymann A, Debray D, Scheers I, Verkade HJ, Narkewicz MR. Towards a Standardized Classification of the Hepatobiliary Manifestations in Cystic Fibrosis (CFHBI): A Joint ESPGHAN/NASPGHAN Position Paper. J Pediatr Gastroenterol Nutr. 2024 Jan;78(1):153-165. doi:

Criteria and References used by the ECFS Patient Registry (valid for 2024 YFU)

9 Pancreatic Status: Pancreatic Insufficiency, References

i. **Indicator of Pancreatic Insufficiency - Faecal Fat** (2 determinations are mandatory)
   a. Young children: Stool fat (van de Kamer) > 4-5 g/d;
   b. Children older than 10 years and adults: Stool fat (van de Kamer) >7g/d and/or faecal pancreatic elastase-1 < 200 ug/g.

Please note
- Faecal fat excretion values of infants below 3 months are contradictory.
- Other than pancreatic causes of steatorrhoea must have been excluded.

ii. **For the ECFSPR, pancreatic status will be assessed as follows:**
- Pancreatic insufficiency: Faecal elastase <200 µg/g (twice), and faecal fat high* (twice);
- Pancreatic sufficiency: Faecal elastase ≥200 µg/g (twice) and Faecal fat normal* (twice).

**see no. 1 Definition, above*

References

1) Sinaasappel M, Stern M, Littlewood J, Wolfe S, Steinkamp G, Heijerman HGM, Robberecht E, Döring G. Nutrition in patients with cystic fibrosis. A European consensus. J Cystic Fibrosis 2002; 1:51-75.
2) Walkowiak J, Nousia-Arvanitakis S, Henker J, Stern M, Sinaasappel M, Dodge JA. Invited review: Indirect pancreatic function tests in children. J Pediatr Gastroenterol Nutr 2005; 40:107-114.

10 Acute pancreatitis: Definition and References

The ECFSPR recommends: at least two of the following three criteria to be met:

i. An episode of moderate to sever upper abdominal pain with/without emesis (vomiting) compatible with acute pancreatitis;
ii. Amylase and/or lipase ≥ 3 × the upper level of normal (or elevated above the ranges established by local laboratory);
iii. Abdominal imaging consistent with pancreatitis.

References

- De Boeck K, Weren M, Proesmans M, Kerem E. Pancreatitis among patients with cystic fibrosis: correlation with pancreatic status and genotype. Pediatrics. 2005 Apr;115(4):e463-9. doi: 10.1542/peds.2004-1764. Epub 2005 Mar 16. PMID: 15772171.
- Banks PA, Bollen TL, Dervenis C, et alClassification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013;62:102-111.

11 Salt Loss Syndrome: Definition and Reference

All 3 of the following to be present:
'- Primary metabolic alkalosis with blood pH > 7.45;
- Serum sodium < 130 mmol/l;
- Serum chloride < 90 mmol/l.

Reference

1) Fustik S, Pop-Jordanova N, Slaveska N, Koceva S, Efremov G. Metabolic alkalosis with hypoelectrolytemia in infants with cystic fibrosis. Pediatr int 2002; 44: 289-92.

12 Malignancy diagnosed this year

Use the ICD10 (International Classification of Diseases, Tenth Revision) codes for malignant neoplasms (C00 to C96)
https://icd.who.int/browse10/2019/en#/C00-C97

13 Transplantation: Indications

i. For patients who had a transplant during the year of follow up:
   a. Use the best FEV1 before transplantation;
   b. Record therapy, complications and microbiology from before transplantation.

ii. For patients who had a transplant before the current follow-up year:
   a. Record all available information.