G.1 Diagnosis of cystic fibrosis

Review question: In infants, children, young people and adults (including those that have undergone newborn screening) when should cystic fibrosis be suspected?

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Grimaldi, C., Bremont, F., Berlioz-Baudoin, M., Brouard, J., Corvol, H., Couderc, L., Lezmi, G., Pin, I., Petit, I., Reix, P., Remus, N., Schweitzer, C., Thumerelle, C., Dubus, J. C., Sweat test practice in pediatric pulmonology after introduction of cystic fibrosis newborn screening, European Journal of Pediatrics, 174, 1613-20, 2015 Ref Id 449541	Sample size N=502 children presenting respiratory symptoms Asthma: n=358 Chronic cough: n=263 Lower airway infections: n=212 Bronchiectasis: n=35 Characteristics Mean age±SD (range): 36±28 months (1 month to 10 years) Gender: 282 boys (56.2%) No differences in the distribution of age and gender across hospitals Inclusion Criteria Children born in France after 1 January 2003 with a prior negative newborn screening test,	Tests Clinical symptoms: asthma chronic cough lower airway infections bronchiectasis No definitions given. Reference standard: sweat chloride test Thresholds for patients >6 months: Positive ST: ≥60 mmol/l. Intermediate ST: 40 to 59 mmol/l. Negative ST: ≤39 mmol/l. Thresholds for infants up to 6 months: Positive ST: ≥60 mmol/l. Intermediate ST: 29 to 59 mmol/l. Negative ST: ≤29 mmol/l.	Methods Sample selection: Retrospective, descriptive and multicentre study. Children identified from sweat test laboratories of each hospital. Procedure: Most children (94%) had 1 sweat test, 5.4% had 2 tests, and 3 children had ≥3 tests 538 sweat test performed in 502 children (this represents 15 to 25% of all sweat tests performed in each hospital) Number of sweat test per hospital ranged from 5 to 121 4 methods of sweat collection and sweat chloride dosage were used:	Results Clinical diagnosis of CF based on sweat test: In children with asthma: n=1; 0.3% In children with chronic cough: n=4; 1.5% In children with lower airway infections: n=4; 1.8% In children with bronchiectasis: n=2; 5.7% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Yes (All children had a negative CF newborn screening)

5

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out France Study type Descriptive Aim of the study To describe the current indications of sweat test prescription and to evaluate their interest in children with negative cystic fibrosis (CF) newborn screening referred to paediatricians specialized in respiratory diseases. Study dates January to December 2012 Source of funding Not reported.	for whom a paediatric pulmonologist prescribed a sweat test for respiratory symptoms between 1 January and 31 December 2012 Inpatient or outpatient Exclusion Criteria Patients born outside France Patients born before 1 January 2003 Patients without a newborn screening test If test was made to confirm a positive CF screening, or because of meconium illeus or a diagnosis of CF in siblings If the test was not prescribed by a hospital paediatric pulmonologist If the test result was unknown		Filter paper + Schales and Schales (3 hospitals) Exsupatch® + Exudose® (6 hospitals) Exsupatch® + Exudose® or Macroduct + Sweat Check® (2 hospitals) Macroduct coil + coulometric titration (3 hospitals) Definitions for symptoms not provided Data collection: Laboratory records Data analysis: Descriptive analysis. Critical confounders not taken into consideration.		2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). No (Definition for symptoms not provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted, and the thresholds for diagnosis)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low Other information Conflict of interest: the authors declare that they have no conflict of interest.

7

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					All children had a negative CF newborn screening.
Full citation Hubert, D., Fajac, I., Bienvenu, T., Desmazes-Dufeu, N., Ellaffi, M., Dall'ava-Santucci, J., Dusser, D., Diagnosis of cystic fibrosis in adults with diffuse bronchiectasis, Journal of Cystic Fibrosis, 3, 15-22, 2004 **Ref Id** 332804 **Country/ies where the study was carried out** France **Study type** Descriptive **Aim of the study** To assess retrospectively the contribution of the sweat test and	**Sample size** N=601 adults with diffuse bronchiectasis **Characteristics** N=601 patients referred for diffuse brochiectasis n=46 diagnosed with CF (7.6%) Gender: 24 males and 22 females Mean age (range): 31 years (18 to 56) **Inclusion Criteria** All adult patients who were referred to the Pulmonary Department with diffuse bronchiectasis and who were diagnosed with CF between 1992 and 2001. **Exclusion Criteria** Not reported	**Tests** Clinical symptom: diffuse bronchiectasis Diffuse bronchiectasis was defined as chronic mucopurolent sputum production and recurrent lower respiratory tract infection, were confirmed by high-resolution CT. Reference standard: sweat chloride test The pilocarpine iontophoresis test was performed on both arms with measurements of sweat weight. Concentrations were measured using Gibson and Cooke method. Thresholds: Diagnosis of CF: >60 mmol/l. Suggestive, but not diagnostic of CF: 40 to 60 mmol/l.	**Methods** Sample selection: As described in inclusion criteria Procedure: All suspected cases of bronchiectasis were sent for CF testing. Two sweat test were performed for each patient. Data collection: Data was collected retrospectively from medical records. Statistical analysis: Descriptive analysis. Critical confounders not taken into consideration.	**Results** Clinical diagnosis of CF based on sweat test: Confirmed CF diagnosis: n=37; 6.16% Borderline CF diagnosis: n=9; 1.50% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	**Limitations** The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. No (It is unknown whether these patients underwent newborn screening, but seems unlikely as newborn screening was implemented in France in 2002)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
genotyping in the diagnosis of cystic fibrosis (CF) in adults with diffuse bronchiectasis. Study dates 1992 to 2001 Source of funding Not reported					2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes(Definition for bronchiectasis provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted,

9

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					and the thresholds for diagnosis)

5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study)

6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis)
Overall quality: very low
Other information
Conflict of interest: not reported
It is unknown whether these patients |

10

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					underwent newborn screening, but seems unlikely as newborn screening was implemented in France in 2002 (Grimaldi 2015)
Full citation Lucidi, V., Alghisi, F., Dall'Oglio, L., D'Apice, M. R., Monti, L., De Angelis, P., Gambardella, S., Angioni, A., Novelli, G., The etiology of acute recurrent pancreatitis in children: a challenge for pediatricians, Pancreas, 40, 517-21, 2011

Ref Id 369280

Country/ies where the study was carried out Italy

Study type Descriptive

Aim of the study | **Sample size** N=78 infants, children and young people with acute recurrent pancreatitis

Characteristics Mean age ± SD (range): 8.8±5.1 years (4 months to 18 years) 60% of patients complained of abdominal pain suggestive of biliopancreatic origin All patients had pancreatic sufficiency 42.3% (n=33) patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test

Inclusion Criteria Paediatric patients affected by acute recurrent pancreatitis | **Tests** Clinical symptom: recurrent pancreatitis Defined as 2 or more separate documented episodes of acute pancreatitis with serum amylase and/ or lypase levels at least 3 times the upper reference limit

Reference standards: Sweat test Thresholds for diagnosis of CF not reported. CFTR mutation | **Methods** **Sample selection** Retrospective descriptive study All consecutive patients affected by acute recurrent pancreatitis referred to the centre during the period 2003 to 2008

Procedure All patients were submitted to endoscopic retrograde cholangiopancreatography to exclude biliopancreatic malformation All patients were tested for CF by a sweat chloride test according to Gibson and Cooke method Most patients were also searched for the following gene mutations: CFTR, PRSSI and SPINKI

Data collection | **Results** Clinical diagnosis of CF based on sweat test: Diagnosis of CF with ST: n=1; 1.3% Borderline diagnosis of CF with ST: n=7; 9%

Genetic test: CFTR mutation: 39.6% (data available for n=53) SPINKI mutation: 7.1% (data available for n=42) PRSSI mutation: 4.5% (data available for n=44)

Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable. | **Limitations** The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37)

1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Unclear (The authors indicate 42.3% of patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test. However it is |

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
To assess specific etiologies of acute recurrent pancreatitis at a single cystic fibrosis (CF) paediatric centre. Study dates 2003 to 2008 Source of funding Not reported.	Exclusion Criteria Not reported		Medical data was collected by reviewing clinical charts Data analysis Descriptive analysis. Critical confounders not taken into consideration.		unknown whether all these patients underwent newborn screening) 2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (Definition for pancreatitis provided) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Unclear

12

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					(The study gives details about how the sweat test was conducted, but it does not report the thresholds for diagnosis) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information Conflict of interest: not reported 42.3% (n=33) patients had a positive family history of chronic pancreatitis/ cystic fibrosis and/ or positive genetic testing and/ or altered sweat test. However it is unknown whether all these patients underwent newborn screening.
Full citation Ooi, C. Y., Dupuis, A., Ellis, L., Jarvi, K., Martin, S., Gonska, T., Dorfman, R., Kortan, P., Solomon, M., Tullis, E., Durie, P. R., Comparing the American and European diagnostic guidelines for cystic fibrosis: same disease, different language?, Thorax, 67, 618-24, 2012 Ref Id	Sample size N=208 people with single organ manifestations of CF People with idiopathic chronic sinopulmonary disease: n=72 People with idiopathic recurrent, acute or chronic pancreatitis: n=44 Men with infertility due to obstructive azoospermia: n=92 Characteristics People with idiopathic chronic sinopulmonary disease:	Tests Clinical symptoms: Idiopathic chronic sinopulmonary disease Idiopathic sinopulmonary disease was defined as recurrent or chronic sinusitis (including sinusoidal pain, nasal discharge, and postnasal drip), nasal polyps, recurrent or chronic bronchitis, recurrent pneumonia and/or bronchiectasis for at least 6 months. All enrolled subjects with sinopulmonary disease had three or more of these symptoms. If not	Methods Sample selection Participants were prospectively and consecutively enrolled into the study. Data collection Sweat testing was conducted following Gibson and Cooke or Macroduct methods. American and European diagnostic guidelines were used. Extensive genotyping was performed in all subjects. The 23 CFTR mutations recommended by ACMG	Results People with idiopathic chronic sinopulmonary disease Clinical diagnosis of CF: Classic CF: n=14; 19.4% CFTR dysfunction: n=3; 4.2% Inconclusive: n=1; 1.4% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable.	Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37) 1. The study sample represents the population of interest on key characteristics,

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
449720 Country/ies where the study was carried out Canada Study type Descriptive Aim of the study To evaluate the diagnostic outcomes of prospectively recruited undiagnosed individuals referred to CF clinics with single organ manifestations of CF. Study dates 1994 to 2008 Source of funding Research grants from the Canadian CF Foundation and Genome Canada	Mean age ± SD (range): 38.5±15.9 (9.9 to 66.7) years Gender: 70.8% (n=51) women People with idiopathic recurrent, acute or chronic pancreatitis: Mean age ± SD (range): 24.3±13.2 (7.9 to 59.9) years Gender: 59.1% (n=26) women Men with infertility due to obstructive azoospermia: Mean age ± SD (range): 34.8±5.3 (25.4 to 56.6) years Inclusion Criteria Undiagnosed individuals with single organ manifestations of CF. These included: idiopathic chronic sinopulmonary disease, idiopathic recurrent, acute or chronic pancreatitis or men with infertility due to obstructive azoospermia	done prior to referral, RESP subjects were tested for immunodeficiency, a-1-antitrypsin deficiency, allergic bronchopulmonary aspergillosis, non-tuberculous mycobacteria, and primary ciliary dyskinesia. Patients were also screened for conditions known to be associated with bronchiectasis (eg, rheumatoid arthritis, other collagen vascular diseases and inflammatory bowel disease). Patients diagnosed as having any of these disorders were excluded from the study. Idiopathic recurrent, acute or chronic pancreatitis A diagnosis of idiopathic recurrent acute pancreatitis was accepted following at least two episodes of abdominal pain associated with raised serum amylase and/or lipase (more than two times the upper limit of the reference range), and/or imaging evidence of acute pancreatitis such	were used as initial screening. Data analysis Descriptive analysis. Critical confounders not taken into consideration.	People with idiopathic recurrent, acute or chronic pancreatitis Clinical diagnosis of CF: Classic CF: n=2; 4.5% CFTR dysfunction: n=6; 13.6% Inconclusive: n=1; 2.3% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable. Men with infertility due to obstructive azoospermia Clinical diagnosis of CF: Classic CF: n=19; 20.7% CFTR dysfunction: n=21; 22.8% Inconclusive: n=9; 9.8% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable	sufficient to limit potential bias to the results. Unclear (It is unknown whether all these patients underwent newborn screening) 2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (Definition of symptom provided) 4. The outcomes of interest are adequately measured in study participants to

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	No patients were excluded on the basis of sex or race (defined by patient self report self report). Exclusion Criteria Not reported	as pancreatic oedema, haemorrhage or necrosis. Patients with chronic pancreatitis had chronic pain in association with pancreatic calcifications and/or characteristic ductal changes. Infertility due to obstructive azoospermia A diagnosis of obstructive azoospermia (congenital unilateral or bilateral absence of vas deferens) was confirmed by physical examination, transrectal ultrasound and evidence of azoospermia on two separate occasions. Reference standard: sweat test Thresholds for the diagnosis of CF according to European consensus recommendations.			sufficiently limit potential bias (outcome measurement). Yes (The study gives details about how the sweat test was conducted, and the thresholds for diagnosis) 5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Other information Conflict of interest: none It is unknown whether these patients underwent newborn screening.
Full citation Seear,M., Wensley,D., Chronic cough and wheeze in children: do they all have asthma?, European Respiratory Journal, 10, 342-345, 1997

Ref Id 208109

Country/ies where the study was carried out Canada

Study type Descriptive

Aim of the study The study aimed to answer two questions: do such diagnostic orphans exist? And if so, can | Sample size N=81 children with a history of >3 months of productive cough

Characteristics Not reported

Inclusion Criteria Children with productive or rattly cough, with or without wheezing, on most days for three consecutive months or more.

Exclusion Criteria Children with known causes of productive cough (cystic fibrosis, immunodeficiencies, bronchiectasis and bronchopulmonary dysplasia). | Tests Clinical symptom: productive cough No definition given. But just children with a history of >3 months of productive cough, of unknown cause, were included

Reference standard: sweat test

Thresholds for diagnosis of CF not reported. | Methods Sample selection Children referred to the respiratory clinic of British Columbia's hospital who fulfilled the inclusion criteria were prospectively recruited.

Procedure and data collection All children completed the following test; chest radiograph, pulmonary function tests (if old enough), Mantoux test, sweat chloride test, full blood count, and immunoglobulin levels. If clinically indicated, subsequent tests included chest computed tomography (CT)-scan, flexible or rigid bronchoscopy, expanded immune investigations and lung biopsy. | Results Clinical diagnosis of CF: Diagnosis of CF: n=1; 1.23% Sensitivity, specificity, LR+, LR-, PPV and NPV not reported and not calculable. | Limitations The quality of this study was assessed using the tool proposed by Hayden et al. (2006), as suggested by NICE methods manual (2014) (Full citation: Hayden JA, Cote P, Bombardier C (2006) Evaluation of the quality of prognosis studies in systematic reviews. Annals of Internal Medicine 144: 427–37)

1. The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results. Unclear (the study does not say if the participants had undergone newborn screening) |

17

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
they be classified in a clinically useful manner? Study dates December 1993 to December 1995 Source of funding Not reported			Data analysis Descriptive analysis. Critical confounders not taken into consideration.		2. Loss to follow-up (from sample to study population) is not associated with key characteristics, sufficient to limit potential bias (i.e., the study data adequately represent the sample) (study attrition). Unclear (the study does not indicate if data is available for all people) 3. The prognostic factor of interest is adequately measured in study participants to sufficiently limit potential bias (prognostic factor measurement). Yes (history of > 3 months of productive cough) 4. The outcomes of interest are adequately measured in study participants to sufficiently limit potential bias (outcome measurement). Unclear (the study does not give details on how sweat test was conducted)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					5. Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest (confounding measurement and account). No (the study does not indicate whether participants presented with other signs suggestive of CF. This is a very serious limitation of the study) 6. The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results (analysis). Yes (data analysis is not reported, but authors only conducted descriptive analysis) Overall quality: very low Other information Conflict of interest: not reported It is unknown whether these patients underwent newborn screening.

19