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Cystic Fibrosis

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Summary

Clinical characteristics

Cystic fibrosis (CF) is a multisystem disease affecting epithelia of the respiratory tract, exocrine pancreas, intestine, hepatobiliary system, and exocrine sweat glands. Morbidities include recurrent sinusitis and bronchitis, progressive obstructive pulmonary disease with bronchiectasis, exocrine pancreatic deficiency and malnutrition, pancreatitis, gastrointestinal manifestations (meconium ileus, rectal prolapse, distal intestinal obstructive syndrome), liver disease, diabetes, male infertility due to hypoplasia or aplasia of the vas deferens, and reduced fertility or infertility in some women. Pulmonary disease is the major cause of morbidity and mortality in CF.

Diagnosis/testing

The diagnosis of CF is established in a proband with:

- Elevated immunoreactive trypsinogen on newborn screen, signs and/or symptoms suggestive of CF, or family history of CF; AND
- Evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function: sweat chloride ≥60 mmol/L on sweat chloride testing, biallelic *CFTR* CF-causing pathogenic variants, or nasal transmembrane epithelial potential difference measurement consistent with CF.

Management

Targeted therapy: CFTR modulator therapy is available for individuals with responsive *CFTR* variants.

Supportive care: Newborns: management by a CF specialist or CF care center; airway clearance instruction; encouraging feeding with breast milk; routine vaccinations; contact precautions with every encounter; antibiotics for bacterial suppression and treatment; nutrition management; pancreatic enzyme replacement;

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nutrient-dense food and supplements; fat-soluble vitamin supplements; laxative treatment as needed with surgical management for bowel obstruction; and salt and water supplementation.

After the newborn period: airway clearance; pulmonary treatment (bronchodilator, hypertonic saline, dornase alfa, airway clearance, inhaled corticosteroids and/or long-acting beta agonist, and aerosolized antibiotic); standard treatments for pneumothorax or hemoptysis; double lung transplant for those with advanced lung disease; routine vaccinations including influenza; contact precautions; antibiotics for bacterial suppression and treatment; antibiotics and/or surgical intervention for nasal/sinus symptoms; nutrition management; pancreatic enzyme replacement; nutrient-dense food and supplements; fat-soluble vitamin supplements; laxative treatment as needed with surgical management for bowel obstruction; standard treatments for gastroesophageal reflux disease; oral ursodiol for biliary sludging/obstruction; liver transplant when indicated; management of CF-related diabetes mellitus by an endocrinologist; assisted reproductive technologies (ART) for infertility; salt and water supplementation; standard treatments for associated mental health issues.

Surveillance: Frequent assessment by a CF specialist to monitor for new or worsening manifestations; pulmonary function testing frequently after age five years; chest x-ray or chest CT examination to assess for bronchiectasis every two years or as needed; cultures of respiratory tract secretions at least every three months; non-tuberculosis mycobacterium culture and serum IgE annually or as indicated; annual CBC with differential; annual ENT assessment; monitoring growth and GI manifestations at each visit; fecal elastase as needed; annual serum vitamin A, D, E, and PT (as a marker of vitamin K); annual liver function tests; annual random glucose, annual two-hour glucose tolerance test beginning at age ten years; DXA scan as needed in adolescence; infertility assessment as needed; annual electrolytes, BUN, and creatinine; annual assessment of depression and anxiety.

Agents/circumstances to avoid: Environmental smoke, exposure to respiratory infections, dehydration.

Evaluation of relatives at risk: Molecular genetic testing of at-risk sibs (if the pathogenic variants in the family are known) or sweat chloride testing of at-risk sibs (if the pathogenic variants in the family are not known) to identify as early as possible those who should be referred to a CF center for initiation of early treatment.

Genetic counseling

CF is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *CFTR* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants. Once the *CFTR* pathogenic variants have been identified in an affected family member, targeted heterozygote testing for at-risk relatives and prenatal/preimplantation genetic testing for CF are possible.

Diagnosis

Consensus clinical diagnostic criteria for cystic fibrosis (CF) have been established [Farrell et al 2017a, Farrell et al 2017b, Sosnay et al 2017].

Suggestive Findings

Scenario 1: Abnormal newborn screening (NBS) result

- NBS for CF is based on quantification of immunoreactive trypsinogen (IRT) and subsequent molecular testing including either *CFTR* targeted analysis or sequence analysis on dried blood spots.
- Elevated IRT values with or without the presence of *CFTR* pathogenic variants are considered out of range and require diagnostic sweat chloride testing.

Scenario 2: Symptomatic individual not diagnosed during the newborn period. NBS was not universal in the United States until 2010; individuals not diagnosed following NBS may have: (1) been born prior to NBS implementation; (2) not had NBS for other reasons; (3) had a false negative NBS result; or (4) had caregivers who did not follow up with recommended diagnostic testing after abnormal NBS.

Suggestive clinical and laboratory findings in symptomatic individuals include:

- **Clinical findings** [Rosenfeld et al 2016]
  - Sinopulmonary: chronic wet or productive cough, recurrent pneumonia, bronchiectasis, nasal polyposis
  - Musculoskeletal: digital clubbing
  - Infectious: respiratory infection with *Pseudomonas aeruginosa* or other atypical gram-negative organisms, allergic bronchopulmonary aspergillosis
  - Nutritional/metabolic: poor weight gain, growth deficiency
  - Pancreatic: exocrine pancreatic insufficiency, recurrent pancreatitis
  - Intestinal: meconium ileus, rectal prolapse, distal intestinal obstructive syndrome, steatorrhea
  - Hepatic: protracted neonatal jaundice, biliary cirrhosis
  - Genitourinary: obstructive azoospermia
- **Laboratory findings**
  - Hyponatremia, hypochloremia, hypokalemia, hypoproteinemia, chronic metabolic alkalosis
  - Deficiency of fat-soluble vitamins (vitamins A, D, E, and K)

Establishing the Diagnosis

The diagnosis of CF **is established** in a proband with one of the following:

- Positive newborn screen (NBS) for CF (elevated immunoreactive trypsinogen [IRT])
- Signs and/or symptoms suggestive of CF (See Suggestive Findings.)
- Family history of CF in a first-degree relative (typically a sib)

AND one of the following:

- Elevated sweat chloride value ≥60 mmol/L on sweat chloride testing
- Identification of biallelic *CFTR* CF-causing pathogenic (or likely pathogenic) variants on molecular genetic testing
- Nasal transmembrane epithelial potential difference measurement consistent with CF (See Nasal Transmembrane Epithelial Potential Difference.)

Note: (1) A sweat chloride value ≥60 mmol/L establishes the diagnosis; however, an intermediate sweat chloride of 30-59 mmol/L should prompt further evaluation with a CF specialist. (2) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include any likely pathogenic variants. (3) Identification of biallelic *CFTR* variants of uncertain significance (or of one known CF-causing *CFTR* variant and one *CFTR* variant of uncertain significance) does not establish or rule out the diagnosis (see Nasal Transmembrane Epithelial Potential Difference).

Newborn Screening (NBS)

NBS for CF has been universal in the United States since 2010; IRT is measured in a blood sample in all newborns born in the US. Infants with CF have increased IRT levels as a result of inspissated secretions in pancreatic ducts leading to an increase of trypsinogen in the blood. Further testing for newborns with elevated IRT varies by state NBS program; follow-up testing may include a second IRT, targeted DNA analysis for

common CF-causing *CFTR* variant(s), or sequence analysis of *CFTR*. Infants with an elevated IRT should have a sweat chloride test [Rosenfeld et al 2016].

Sweat Chloride Testing

Sweat chloride testing, the gold standard for diagnosis of CF, requires appropriate techniques; within the US, it should be performed at a center accredited by the CF Foundation [LeGrys et al 2007]. Sweat chloride testing in an infant with an elevated IRT should be completed before 28 days of life to ensure prompt treatment of affected infants. A normal sweat chloride is <30 mmol/L; an intermediate sweat chloride is 30-59 mmol/L; an elevated sweat chloride diagnostic of CF is ≥60 mml/L.

Molecular Genetic Testing

Approaches include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *CFTR* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no CF-causing variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: Targeted analysis for pathogenic variants can be performed first in individuals of Amish, Ashkenazi Jewish, Faroe Islander, Hutterite, or Zuni ancestry (see Table 7).

- **A multigene panel** that includes *CFTR* and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Molecular Genetic Testing Used in Cystic Fibrosis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
CFTR	Sequence analysis [3]	97%-98% [4]
	Gene-targeted deletion/duplication analysis [5]	≤2%-3% [4]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Lucarelli et al [2016] and data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Nasal Transmembrane Epithelial Potential Difference (NPD)

NPD provides an indirect measurement of CFTR function in nasal epithelium. Currently, NPD is only performed in specialized testing centers [Sermet-Gaudelus et al 2010]. An abnormal NPD can establish the diagnosis in individuals with inconclusive sweat chloride and/or molecular genetic testing.

Clinical Characteristics

Clinical Description

Cystic fibrosis (CF) affects the epithelia in several organs resulting in a complex, multisystem disease primarily involving the respiratory, gastrointestinal, genitourinary, and endocrine systems and the sweat glands.

Table 2. Cystic Fibrosis: Frequency of Select Features

Feature	% of Persons w/Feature [1]	Comments
Lung disease	100%	
Chronic sinus disease	~38%	
Pancreatic insufficiency	~85%	
Pancreatitis	~1%	More common in persons w/PS *CFTR* variants
Liver disease	~6%-8%	
Diabetes	18%	
Depression &/or anxiety	~15%	

CF = cystic fibrosis; PS = pancreatic sufficient
1. Cystic Fibrosis Foundation Patient Registry [2020]

Respiratory

Pulmonary. Lung disease is the major cause of morbidity and mortality in people with CF. Without adequate ion transport out of the respiratory epithelium via the cystic fibrosis transmembrane conductance regulator (CFTR) chloride channel, the airway surface layer is not well hydrated. The resulting thickened airway surface layer attracts bacteria; subsequent white blood cell reaction leads to bronchiectasis (an abnormal dilatation of the airways). Bronchiectasis may be detected in infants as early as age ten weeks [Sly et al 2013]. Allergic bronchopulmonary aspergillosis, caused by a hypersensitivity reaction to *Aspergillus fumigatus*, is monitored by testing of serum IgE. Additional complications from airway damage include hemoptysis and pneumothorax. Progression to severe lung disease occurs in many people with CF, in whom lung transplantation is a treatment option.

Infections. Specific to CF, gram-negative bacteria infections (e.g., *Pseudomonas aeruginosa*) are especially common. People with CF can also have infections from *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Stenotrophomonas maltophilia*, *Alcaligenes xylosoxidans*, *Hemophilus influenzae,* and other bacteria in their airways. Bacterial infections accelerate CF lung disease. When the bacterial load is elevated, pulmonary exacerbations occur, characterized by increased cough and sputum production, decreased lung function, and worsening overall clinical outcomes [Zemanick & Hoffman 2016]. Pulmonary exacerbations contribute to the decline in lung function over time [Waters et al 2012]. Transmission of bacteria between people with CF has been documented; thus, contact precautions should be used when treating all people with CF [Saiman et al 2014].

Otolaryngology. Many people with CF have nasal and sinus complications. Anatomic differences in individuals with CF (e.g., sinus hypoplasia, medial bowing of the lateral nasal wall, lower fovea ethmoidalis) and thickened nasal secretions lead to chronic rhinosinusitis and diffuse pansinusitis, both of which can affect quality of life.

Additionally, nasal polyps can lead to nasal obstruction. Hearing loss is more common in individuals with CF as a result of medication side effects (e.g., intravenous aminoglycosides) and is not directly related to disease pathophysiology.

Pancreatic

Exocrine pancreatic insufficiency. Inspissated secretions within the pancreatic ducts block passage of the pancreatic enzymes into the intestines, where they aid in nutrient digestion. Instead, the enzymes autodigest the pancreas, with ultimate interstitial fibrosis leading to pancreatic insufficiency (PI). As a result of inadequate absorption of protein and fat, the clinical manifestations of PI are steatorrhea, excessive gassiness, malnutrition, poor weight gain, and growth deficiency [Sathe & Freeman 2016].

Pancreatitis. Pancreatitis is more likely to occur in individuals with milder *CFTR* pathogenic variants classified as pancreatic sufficient (PS; 10.3%) versus individuals with pancreatic insufficient (PI; 0.5%) *CFTR* variants (see Genotype-Phenotype Correlations) [Sathe & Freeman 2016]. Pancreatitis can be a presenting feature of CF in both children and adults.

Gastrointestinal

Bowel manifestations. People with CF can have decreased stomach and bowel transit time, which can contribute to bowel blockage. In the newborn period, inspissated meconium may cause ileus, which often requires surgical intervention. After the newborn period, inspissated stool leads to primarily left-sided stool retention and constipation. Progression to intestinal obstruction syndrome may require significant laxative treatment or surgical intervention [Sathe & Freeman 2016]. Inspissated secretions may also lead to appendiceal obstruction, intussusception, and rectal prolapse. Celiac disease and inflammatory bowel disease have increased prevalence in individuals with CF; the incidence of gastrointestinal cancers is also elevated (23-fold increased lifetime risk) [Sathe & Freeman 2016, Hadjiliadis et al 2018].

Gastroesophageal reflux disease (GERD). People with CF have an increased incidence of GERD compared to those without CF. However, despite approximately 50% of children with CF having evidence of reflux on pH impedance evaluation, close to two thirds had no symptoms [Sathe & Freeman 2016].

Liver disease. CF-associated liver disease includes a wide range of hepatobiliary complications, from transient elevations in liver function tests to focal biliary cirrhosis. In those that develop cirrhotic liver disease, complications include esophageal and gastric varices with or without associated gastrointestinal bleeding, splenomegaly, hypersplenism, encephalopathy, and ascites; liver transplantation is needed in some individuals [Sathe & Freeman 2016]. Liver disease, both cirrhotic and noncirrhotic, occurs in 3.1% and 3.6%, respectively, and is the cause of mortality in 3.2% of individuals with CF [Cystic Fibrosis Foundation Patient Registry 2020].

Endocrine

Diabetes. Cystic fibrosis-related diabetes (CFRD) increases in prevalence with age; approximately 20% of adolescents and 50% of adults have CFRD [Moran et al 2009, Moran et al 2014]. CFRD is distinct from type 1 and type 2 diabetes. Glucose metabolism in CFRD is impaired due to: a loss of islet cells leading to absence of insulin and glucagon; fluctuating insulin resistance secondary to inflammation; need for high caloric intake; gut abnormalities; altered intestinal motility; and liver disease [Moran et al 2014, Moran et al 2018].

Additional endocrine-related complications in individuals with CF include delayed puberty and delayed linear growth with reduced adult height [Blackman & Tangpricha 2016].

Musculoskeletal

Osteopenia and osteoporosis develop in individuals with CF as a result of multiple contributing factors (e.g., nutritional deficiencies, inflammation, altered sex steroids) [Blackman & Tangpricha 2016].

Clubbing is apparent when the finger- and toenail beds become convex, leading to a "club"-shaped distal digit. Hypertrophic osteoarthropathy characterized by a combination of clubbing, increased periosteal reaction of tubular bones, arthralgia, and synovial effusions also occurs as a result of CF-related pulmonary disease.

Additional musculoskeletal manifestations include arthritis and thoracic postural defects (e.g., thoracic kyphosis, scoliosis) [Botton et al 2003].

Genitourinary

Fertility is altered in both men and women with CF.

Men with CF often have congenital bilateral absence of the vas deferens (CBAVD) [Yu et al 2012]. This congenital hypoplasia or aplasia usually occurs bilaterally but may occur unilaterally. When the vas deferens are absent, atrophic, or fibrotic, men will have obstructive severe oligospermia or azoospermia. CFTR has also been shown to play a role in spermatogenesis; reduced CFTR expression in men with CBAVD undergoing sperm retrieval has been associated with low sperm count and concentration, decreased motility, decreased bicarbonate sensitivity, and lower fertilization rates. However, most men with CF are infertile but not sterile because testicular development and spermatogenesis can be normal [Shteinberg et al 2021]. Based on this pathophysiology, men with CF are often still able to have biological children through assisted reproductive technology.

Women with CF are typically fertile. However, abnormal, pH imbalanced, and thickened cervical mucus contribute to reduced fertility and infertility in some women with CF [Shteinberg et al 2019, Jain et al 2022]. Women with severe illness, malnutrition, and reduced body mass index may be anovulatory [Shteinberg et al 2021]. Until recent years, pregnancy rates in people with CF had remained relatively stable. With the introduction of highly effective CFTR modulator therapy, the rate of pregnancies has increased; more than 600 pregnancies were reported in women with CF (ages 14 to 45 years) in 2020 and 2021, which was more than twice the pregnancies reported in 2019 [Cystic Fibrosis Foundation Patient Registry 2020, Cystic Fibrosis Foundation Patient Registry 2021].

Salt Loss Syndrome

People with CF are at increased risk for excessive sodium chloride loss across various epithelial surfaces. This is particularly true during infancy and during episodes of sweating, vomiting, or diarrhea. Infants are at increased risk during the transition from human milk or infant formulas to baby food because of the lack of added salt in commercially available baby foods. Because of increased salt losses, people with CF are at increased risk for developing hyponatremic, hypochloremic dehydration. Chronically depleted levels of total body sodium can lead to chronic metabolic alkalosis. Children, adolescents, and adults must monitor dietary salt intake particularly in hot and humid climates and during periods of increased sweating (e.g., physical exercise, illness).

Mental Health

Anxiety and depression are increasingly recognized as major complications of CF. Elevated levels of anxiety have been reported in as high as 22% of the adolescent population and 32% of the adult population, while depression has been reported in as high as 10% of the adolescent population and 19% of the adult population. These rates of increased depression and anxiety are two to three times higher than community samples [Quittner et al 2014].

Palliative care in CF focuses on reducing physical and emotional symptoms and improving quality of life [Kavalieratos et al 2021]. Palliative care occurs alongside usual treatments and is individualized according to the unique goals, hopes, and values of each person [Dellon et al 2018]. One specific area that palliative care can aid in improving the quality of life for people with CF is related to pain, since 60%-89% of children and adults in various studies have reported pain [Masson et al 2017].

Prognosis

Among people with CF born between 2017 and 2021, the median predicted survival is to age 53 years – an increase of ten years compared to those born between 2012 and 2016 [Cystic Fibrosis Foundation Patient Registry 2021].

Heterozygotes

Individuals with bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, chronic rhinosinusitis / nasal polyposis, atypical mycobacterial infections, and aquagenic palmoplantar keratoderma are more likely to be heterozygous for a *CFTR* pathogenic variant [Hsu et al 2013, Gamaletsou et al 2018, Raynal et al 2019, Çolak et al 2020, Izquierdo et al 2022]. Approximately 15% of individuals with acute recurrent pancreatitis (24/155 individuals) or chronic pancreatitis (22/146 individuals) were heterozygous for a *CFTR* pathogenic variant [Kumar et al 2016].

Genotype-Phenotype Correlations

The Clinical and Functional Translation of CFTR website provides genotype-phenotype information for *CFTR* pathogenic variants including sweat chloride, lung function, pancreatic status, and pseudomonas infection rates.

The strongest genotype-phenotype correlations have been identified in the context of pancreatic function. The most common *CFTR* pathogenic variants have been classified as pancreatic sufficient (PS) or pancreatic insufficient (PI). Individuals who are PS usually have one or two PS alleles, indicating that PS alleles are dominant with respect to pancreatic phenotype [Rueda-Nieto et al 2022].

Beyond pancreatic function, genotype does not consistently predict phenotype. Pulmonary disease severity varies widely among individuals with identical genotypes (see Molecular Genetics, Genetic Modifiers).

CFTR pathogenic variants associated with protein trafficking, channel gating, and channel conductance have approved targeted therapies. See Table 5a and Jia & Taylor-Cousar [2023].

Prevalence

CF affects at least 100,000 individuals worldwide, with 40,000 individuals in the US [Guo et al 2022]. CF affects individuals of all ages, with more than 50% of people with CF in the US being older than age 18 years [Cystic Fibrosis Foundation Patient Registry 2020].

The incidence of CF is increased in several populations (e.g., Amish, Ashkenazi Jewish, Hutterite) due to the presence of pathogenic founder variants (see Table 7). However, CF occurs in individuals of all ethnicities.

Genetically Related (Allelic) Disorders

Cystic fibrosis-related metabolic syndrome / cystic fibrosis screen positive indeterminate diagnosis (CRMS/CFSPID). The diagnosis of CRMS (in the US) and CFSPID (in Europe), now known as CRMS/CFSPID, is given to asymptomatic infants with an elevated trypsinogen on newborn screening and either [Barben et al 2021]:

- A normal sweat chloride (<30 mmol/L) and biallelic *CFTR* variants including at least one variant of uncertain significance; OR
- An intermediate sweat chloride (30-59 mmol/L) and heterozygous or no CF-causing *CFTR* variant(s) identified.

Individuals with CRMS/CFSPID need to be monitored for features of CF by a CF specialist, as some individuals will become symptomatic and/or develop an elevated sweat chloride test and require treatment for CF [Borowitz et al 2009a, Bombieri et al 2011, Ren et al 2017].

***CFTR*-related disorders (*CFTR*-RD)** include disorders associated with biallelic *CFTR* pathogenic variants but without additional clinical manifestations of CF.

- ***CFTR*-related isolated congenital bilateral absence of the vas deferens (*CFTR*-CBAVD)** is the most common *CFTR*-RD. Isolated CBAVD usually results from compound heterozygosity for a severe loss-of-function *CFTR* variant with a non-CF-causing variant (e.g., c.1210-12T[5]) or two non-CF-causing variants (see Molecular Genetics, Genetic Modifiers). A small percentage of individuals diagnosed with isolated *CFTR*-CBAVD develop adult-onset respiratory or pancreatic disease [Cui et al 2020, Fedder et al 2021, Cai & Li 2022].
- ***CFTR*-related pancreatitis.** Biallelic *CFTR* pathogenic variants have been identified in a minority of individuals with acute recurrent pancreatitis or chronic pancreatitis and no additional features of CF (see Pancreatitis Overview).
- ***CFTR*-disseminated bronchiectasis.** Bronchiectasis is an abnormal dilatation of the airways leading to recurrent infections, cough, and mucopurulent sputum. An increased incidence of *CFTR* pathogenic variants has been reported in individuals with bronchiectasis, especially c.1210-12T[5] (IVS8-5T). However, no specific *CFTR* variants appear to be more common in those with *CFTR*-disseminated bronchiectasis [Bombieri et al 2011].

Differential Diagnosis

Genetic disorders of interest in the differential diagnosis of cystic fibrosis (CF) are summarized in Table 3.

Table 3. Genetic Disorders in the Differential Diagnosis of Cystic Fibrosis

Gene(s)	Disorder	MOI	Key Features	Comment / Distinguishing Features
~45 genes incl: *CCDC39* *CCDC40* *CCDC103* *DNAH5* *DNAH11* *DNAI1* *ODAD2* (*ARMC4*) *ODAD3* (*CCDC151*) *SPAG1* *ZMYND10*	Primary ciliary dyskinesia (PCD)	See footnote 1.	• Abnormal ciliary structure & function (→ retention of mucus & bacteria in respiratory tract) & abnormal flagellar structure (→ abnormal sperm motility); • Respiratory distress in infancy; cough & sputum production w/ recurrent pneumonias that may progress to chronic bronchiectasis; *Pseudomonas aeruginosa* or other opportunistic bacterial pathogens; chronic sinus disease	• Situs inversus is present in 50% of persons w/PCD. • Steatorrhea & poor weight gain are not assoc w/PCD. • 20%-30% of persons w/ well-characterized PCD do not have identifiable pathogenic variants in any known PCD-related genes.
BTK	X-linked agammaglobulinemia (XLA)	XL	• Recurrent bacterial infections in affected males in 1st 2 yrs of life – most commonly recurrent otitis media • Conjunctivitis, sinopulmonary infections, diarrhea, & skin infections are also frequently seen.	Persons w/XLA are also prone to life-threatening infections (e.g., meningitis, sepsis, cellulitis, or septic arthritis) not specifically seen in CF.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Key Features	Comment / Distinguishing Features
C2 [2] *CARD11* [3] *CD19* [4] *CD81* [5] *CR2* (*CD21*) [6] *CTLA4* [7] *CXCR4* [8] *ICOS* [9] *IKZF1* [10] *IL21* [11] *IRF2BP2* [12] *LRBA* [13] *MS4A1* [14] *NFKB1* [15] *NFKB2* [16] *PLCG2* [17] *PRKCD* [18] *SKIC3* (*TTC37*) [19] *STAT3* [20] *TNFSF12* [21] *TNFRSF13B* [22] *TNFRSF13C* [23] *TRNT1* [24]	Common variable immunodeficiency	AD AR	• Recurrent lung, sinus, & ear infection; recurrent lung infections can lead to chronic lung disease (bronchiectasis). • Diarrhea & impaired nutrient absorption	Recurrent or chronic Giardia lamblia infection of small intestine; lymphadenopathy; splenomegaly; ↑ risk of cancer of lymphatic tissues & gastric cancer; granular inflammatory nodules w/in skin, lung spleen, & liver
CA12	Isolated hyperchlorhidrosis (OMIM 143860)	AR	↑ sweat chloride levels, poor weight gain, growth deficiency	Can lead to severe infantile hyponatremic dehydration & hyperkalemia
DNAJC21 *EFL1* *SBDS* *SRP54*	Shwachman-Diamond syndrome (SDS)	AR AD [25]	Exocrine pancreatic dysfunction w/malabsorption, malnutrition, & growth failure	SDS can be distinguished from CF by presence of hematologic abnormalities w/single- or multilineage cytopenias, susceptibility to MDS & AML, & skeletal abnormalities.
IL2RG	X-linked severe combined immunodeficiency (X-SCID)	XL	• Typical X-SCID: w/ universal NBS for SCID, common presentation is asymptomatic, healthy-appearing male infant. • Atypical X-SCID: usually not detected by NBS; can manifest in 1st yrs of life or later w/recurrent upper & lower respiratory tract infections w/ bronchiectasis	• Persons w/X-SCID are also prone to nonrespiratory infections (e.g., otitis media, cellulitis) not specifically assoc w/CF. • Other features may incl, e.g., hepatosplenomegaly, lymphadenopathy, lymphopenia.

Table 3. continued from previous page.

Gene(s)	Disorder	MOI	Key Features	Comment / Distinguishing Features
NR3C2 *SCNN1A* *SCNN1B* *SCNN1G*	Pseudohypoaldosteronism type I (OMIM 177735 & 264350)	AR AD [26]	• Defect in epithelia sodium channel or mineralcorticoid receptor protein • ↑ sweat chloride in some persons • Chronic bronchitis, bronchiectasis, recurrent pulmonary infections	Normal exocrine pancreatic function

AD = autosomal dominant; AML = acute myelogenous leukemia; AR = autosomal recessive; CF = cystic fibrosis; MDS = myelodysplasia syndrome; MOI = mode of inheritance; NBS = newborn screening; XL = X-linked

1. PCD is usually inherited in an autosomal recessive manner. *PIH1D3*-related PCD and *OFD1*-related PCD are inherited in an X-linked manner. *FOXJ1*-related PCD is inherited in an autosomal dominant manner.

2. Seligmann et al [1979], Soto et al [2000]

3. Ma et al [2020]

4. van Zelm et al [2006], Kopecký & Lukesová [2007]

5. van Zelm et al [2010]

6. Thiel et al [2012]

7. Sun & Heimall [2019]

8. Hernandez et al [2003]

9. Salzer et al [2004], Abolhassani et al [2020]

10. Kuehn et al [2016]

11. Salzer et al [2014]

12. Keller et al [2016]

13. Charbonnier et al [2015], Ren et al [2021]

14. Kuijpers et al [2010]

15. Schipp et al [2016]

16. Aird et al [2019]

17. Bogaert et al [2016], Novice et al [2020]

18. Salzer et al [2013], de Valles-Ibáñez et al [2018]

19. Christiansen et al [2020]

20. Russell et al [2018]

21. Wang et al [2013]

22. Salzer et al [2005]

23. Warnatz et al [2009], Kermode et al [2022]

24. Bisgin et al [2021]

25. SDS caused by pathogenic variants in *DNAJC21*, *EFL1*, or *SBDS* is inherited in an autosomal recessive manner. SDS caused by pathogenic variants in *SRP54* is inherited in an autosomal dominant manner.

26. Pseudohypoaldosteronism caused by pathogenic variants in *SCNN1A*, *SCNN1B,* or *SCCN1G* is inherited in an autosomal recessive manner. Pseudohypoaldosteronism caused by pathogenic variants in *NR3C2* is inherited in an autosomal dominant manner.

Other Disorders

Primary dysphagia with chronic descending tracheal aspiration and **primary gastroesophageal reflux (GER) with or without ascending tracheal aspiration.** Both conditions can cause chronic cough in infancy and may be associated with poor weight gain and growth deficiency. However, in infants with primary dysphagia or primary GER, the cough is often temporally associated with feedings; steatorrhea is not associated with primary dysphagia or primary GER.

Asthma. CF and asthma both present with chronic cough and persistent wheeze following respiratory viral infections, allergen exposure, or exertion. However, individuals with asthma typically improve on asthma

therapy, do not experience recurrent pneumonia, are not colonized with CF-related bacteria, have normal growth and weight gain, and do not have steatorrhea.

Congenital airway anomalies, like CF, can cause chronic cough and wheezing during infancy. Gastrointestinal or nutritional manifestations that are typically present in infants with CF are not seen in children with congenital airway anomalies.

Primary biliary atresia. Rarely, individuals with CF may present in infancy with symptoms of biliary obstruction without other clinically apparent GI or respiratory manifestations. Serum levels of immunoreactive trypsinogen and stool levels of elastase should be normal in infants with primary biliary atresia, whereas CF liver disease is invariably associated with evidence of pancreatic duct obstruction.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in a newborn diagnosed with cystic fibrosis (CF), the evaluations summarized in Table 4a (if not performed as part of the evaluation that led to the diagnosis) are recommended. For those individuals diagnosed after the newborn period, the evaluations summarized in Table 4b are recommended [Borowitz et al 2009b, Lahiri et al 2016].

Table 4a. Recommended Evaluations Following Initial Diagnosis of Cystic Fibrosis in Newborn Period

System/Concern	Evaluation	Comment
General	• Assess growth (weight, length, head circumference). • Refer to CF specialist.	
Pancreatic	Fecal elastase measurement	Can be obtained while on pancreatic enzyme replacement therapy
Genetic counseling	Genetic counseling by genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of CF to facilitate medical & personal decision making [2]

CF = cystic fibrosis; MOI = mode of inheritance
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse
2. Langfelder-Schwind et al [2022]

Table 4b. Recommended Evaluations Following Initial Diagnosis of Cystic Fibrosis After the Newborn Period

System/Concern	Evaluation	Comment
General	• Assess growth (weight, length, head circumference). • Refer to CF specialist.	
Pulmonary	• Pulmonary function testing • Respiratory culture for CF-specific pathogens by expectorated sputum or deep oropharyngeal swab	
Pancreatic	Assess fat-soluble vitamin levels (vitamins A, E, & D, & PT as a marker of vitamin K).	
	Fecal elastase	Can be obtained while on pancreatic enzyme replacement therapy
Liver	Liver function tests: AST, ALT, alk phos, GGT, bilirubin, albumin	
Electrolytes / Salt loss	Serum electrolytes, BUN, & creatinine	

Table 4b. continued from previous page.

System/Concern	Evaluation	Comment
Genetic counseling	Genetic counseling by genetics professionals [1]	To inform affected persons & families re nature, MOI, & implications of CF to facilitate medical & personal decision making [2]

alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CF = cystic fibrosis; GGT = gamma-glutamyl transferase; MOI = mode of inheritance; PT = prothrombin time
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse
2. Langfelder-Schwind et al [2022]

Treatment of Manifestations

Targeted Therapy

In GeneReviews, a targeted therapy is one that addresses the specific underlying mechanism of disease causation (regardless of whether the therapy is significantly efficacious for one or more manifestation of the genetic condition); would otherwise not be considered without knowledge of the underlying genetic cause of the condition; or could lead to a cure. —ED

There is no cure for CF. However, cystic fibrosis transmembrane conductance regulator (CFTR) modulator targeted therapy is available to mitigate manifestations (see Table 5a).

Table 5a. Targeted Therapy for Cystic Fibrosis

CFTR Modulator Therapy	Indications [1]
Ivacaftor	In those age ≥4 mos w/at least 1 responsive *CFTR* pathogenic variant [2]
Lumacaftor/ivacaftor	In those age ≥1 yr & homozygous for p.Phe508del
Tezacaftor/ivacaftor	In those age ≥6 yrs & homozygous for p.Phe508del
Elexacaftor/tezacaftor/ivacaftor	In those age ≥6 yrs & heterozygous for p.Phe508del & a minimal function variant [3] or other known responsive pathogenic variant

CFTR = cystic fibrosis transmembrane conductance regulator
1. Ren et al [2018], Jia & Taylor-Cousar [2023]
2. CFTR variants that are responsive to ivacaftor include variants that result in a CFTR protein that reaches the cell surface but ion channel opening is impaired (i.e., gating pathogenic variants; see Genotype-Phenotype Correlations and Table 7).
3. Minimal function variants are *CFTR* pathogenic variants that result in little to no functional protein [Jia & Taylor-Cousar 2023].

Supportive Care

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 5b and Table 5c).

Table 5b. Treatment of Manifestations in a Newborn with Cystic Fibrosis

Manifestation/Concern	Treatment	Considerations/Other
General	Refer to CF specialist / CF care center.	
Pulmonary	Teach parent/caregiver airway clearance (typically postural drainage & percussion) to aid in mucus clearance.	

Table 5b. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Infection	• Encourage feeding w/breast milk. • Routine vaccinations	
	Use contact precautions (gown & gloves) for every encounter by every clinician.	Assume all people w/CF have transmissible bacteria.
	• Antibiotics (oral, inhaled, or IV) for chronic suppression & to treat pulmonary exacerbations • Treat identified bacteria in affected person & bacteria common in CF. [1]	Eradication attempts are recommended for *Pseudomonas aeruginosa*. [2]
Exocrine pancreatic insufficiency	• Consult nutritionist w/experience in CF. • Pancreatic enzyme replacement therapy • Nutrient-dense food & supplements • Fat-soluble vitamin supplements	
Meconium ileus & distal intestinal obstructive syndrome	• If obstructed, consult surgery for intervention. • If not obstructed, treat w/laxatives.	
Salt loss syndromes / Dehydration	• Salt supplementation • Extra salt & water for hydration & salt loss in situations w/salt loss (e.g., ↑ heat/humidity, exercise)	

CF = cystic fibrosis
1. Flume et al [2009a], Goetz & Singh [2016]
2. Mogayzel et al [2014]

Table 5c. Treatment of Manifestations in Individuals with Cystic Fibrosis

Manifestation/ Concern	Treatment	Considerations/Other
Pulmonary	Airway clearance to aid in mucus clearance [1]	
	Chronic pulmonary medications to open airway, ↓ sputum viscosity, promote expectoration of secretions, & deliver anti-inflammatory & antimicrobial medications [2]	Recommended sequence for inhaled medications: • Bronchodilator • Hypertonic saline • Dornase alfa • Airway clearance • Inhaled corticosteroids &/or long-acting beta agonist (for select persons) • Aerosolized antibiotic
	Standard treatments for pneumothorax or hemoptysis [3]	
	Consider double lung transplant for those w/advanced lung disease. [4]	
Infection	Routine childhood vaccinations incl annual influenza vaccine	
	Use contact precautions (gown & gloves) for every encounter by every clinician.	Assume all people w/CF have transmissible bacteria.
	• Antibiotics (oral, inhaled, or IV) for chronic suppression & to treat pulmonary exacerbations • Treat identified bacteria in affected persons & bacteria common in CF. [5]	Eradication attempts are recommended for *Pseudomonas aeruginosa*. [6]

Table 5c. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
ENT	• Standard treatments for rhinosinusitis • Referral to ENT specialist w/CF experience as needed • Sinus surgery as needed to widen ostia &/or clear impacted secretions • Polypectomy as needed for obstructive nasal polyps	If needed, evaluate w/sinus CT; but often reserved for pre-surgical planning or unresolved symptoms despite maximal therapy.
Exocrine pancreatic insufficiency	• Consult w/nutritionist w/experience in CF. • Pancreatic enzyme replacement therapy • Nutrient-dense food & supplements • Fat-soluble vitamin supplements	• Consider zinc supplementations. • Consider gastrostomy tube. [7]
Distal intestinal obstructive syndrome	• If obstructed, consult w/surgeon for intervention. • If not obstructed, use laxatives. [8]	
Gastroesophageal reflux disease	Standard treatments	
Liver disease	• Persistent elevations in liver function tests are treated w/ ursodiol. [9] • Refer to hepatologist w/CF experience.	May progress to need for liver transplant.
Diabetes (CFRD)	• Refer to endocrinologist familiar w/CFRD. • Treat CFRD w/glucose monitoring & insulin therapy. [10]	
Infertility	• Counseling regarding partner testing & preimplantation genetic testing • ART, sperm donation, surrogacy, & adoption	Invasive procedures & cost of aspiration/ extraction followed by IVF may be prohibitive for many. [11]
	Males: • Ultrasound to assess for absence of vas deferens • ART involves eval by urologist. 2 techniques are widely used: microsurgical epididymal sperm aspiration or testicular biopsy & sperm extraction. • Once sperm is obtained, IVF w/intracytoplasmic sperm injection is necessary as sperm counts & concentration are often too low for intrauterine insemination. [11]	Female partners of men w/CF will also need to undergo medical procedures assoc w/IVF regardless of underlying fertility status.
	Females: • ↓ fertility or infertility can be treated by several options available through ART. [12] There are no currently established guidelines as to which modality should be used. • While intrauterine insemination combined w/ gonadotropin ovulation induction can be used, IVF is more co mmonly used. [11]	IVF offers ability of preimplantation genetic testing.
Salt loss syndromes / Dehydration	• Salt supplementation • Extra salt & water for hydration & salt loss in situations w/salt loss (e.g., ↑ heat/humidity, exercise)	

Table 5c. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Mental health	Standard treatments using age-appropriate psychotherapy & pharmacotherapy [13]	

ART = assisted reproductive technology; CF = cystic fibrosis; CFRD = cystic fibrosis-related diabetes; GERD = gastroesophageal reflux disease; IVF = in vitro fertilization

1. Flume et al [2009b]
2. Flume et al [2007], Mogayzel et al [2013]
3. Flume et al [2010]
4. Ramos et al [2019], Kapnadak et al [2020]
5. Flume et al [2009a], Goetz & Singh [2016]
6. Mogayzel et al [2014]
7. Schwarzenberg et al [2016], Turck et al [2016], McDonald et al [2021]
8. Colombo et al [2011]
9. Cheng et al [2017]
10. Moran et al [2014]
11. Shteinberg et al [2021].
12. Shteinberg et al [2021], Jain et al [2022]
13. Quittner et al [2016]

Surveillance

To monitor existing manifestations, the individual's response to targeted therapy and supportive care, and the emergence of new manifestations, partnership with a CF specialist is critical in addition to the following recommended surveillance.

Table 6. Recommended Surveillance in Individuals with Cystic Fibrosis

System/Concern	Evaluation	Frequency
General	Clinical assessment w/CF specialist to assess for new &/or worsening manifestations	• Monthly until age 6 mos • Every 2 mos from age 6-24 mos • Every 3 mos beginning at age 2 yrs • More frequently as indicated
Pulmonary	Pulmonary function tests (PFTs)	PFTs are done frequently after age 5 yrs to monitor disease status.
	Chest radiograph or chest CT to assess for bronchiectasis	Every 2 yrs or as needed
	Respiratory culture for CF-specific pathogens: expectorated sputum or deep oropharyngeal swab	At least every 3 mos
	• Non-tuberculosis mycobacterium culture • Serum IgE to assess for allergic bronchopulmonary aspergillosis [1]	Annually & as indicated w/worsening pulmonary disease
	Bronchoscopy w/bronchoalveolar lavage	If recommended by pulmonologist; used to evaluate lower airway microbiology & inflammation
Infection	CBC w/differential	Annually & as indicated
ENT	Assess for clinical signs/symptoms of rhinosinusitis or polyps.	Routine imaging not indicated

Table 6. continued from previous page.

System/Concern	Evaluation	Frequency
Pancreatic disease	Assess anthropometrics using percentiles or z scores: • Weight & height • Weight for length (in those age <2 yrs) • BMI (in those age ≥2 yrs)	At each visit
	Fecal elastase	If change in signs/symptoms develop
	Serum vitamin A, D, & E, PT (as a marker of vitamin K)	Annually & as indicated
Gastrointestinal manifestations	Assess for signs/symptoms of GI concerns.	At each visit
	Colon cancer screening	Per standard population screening schedule in adults [2]
Liver disease	Liver function tests (AST, ALT, alk phos, GGT, bilirubin, albumin)	Annually
	Liver ultrasound w/doppler & if available elastography	Only if evidence of persistent elevation in liver function tests for >6 mos or other signs/ symptoms of liver disease
Diabetes (CFRD)	Random blood glucose measurement	Annually
	2-hour oral glucose tolerance test (fasting serum glucose, glucose load, & 2-hour serum level)	• Annually beginning at age 10 yrs • Note: Hgb A1C & fructosamine are not indicated in CF.
Osteopenia/ Osteoporosis	DXA to assess bone mineral density	In adolescence if risk factors present [3]
Infertility	Males: evaluation by urologist for congenital absence of vas deferens	As needed in men of childbearing age, based on preference & family planning
	Males & females: counseling on importance of safe & protected sexual practices	
Salt loss & hydration status	Serum electrolytes, BUN, & creatinine	Annually & as indicated
Depression & anxiety	Assess using PHQ-9 & GAD-7 scales.	Annually [4]

alk phos = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BUN = blood urea nitrogen; CBC = complete blood count; CF = cystic fibrosis; CFRD = cystic fibrosis-related diabetes; DXA = dual-energy x-ray absorptiometry; GAD-7 = General Anxiety Disorder-7; GGT = gamma-glutamyl transferase; PHQ-9 = Patient Health Questionnaire-9; PT = prothrombin time

1. Stevens et al [2003]
2. Hadjiliadis et al [2018]
3. Aris et al [2005]
4. Quittner et al [2016]

Agents/Circumstances to Avoid

Avoid the following:

- Environmental smoke
- Exposure to respiratory infections
- Dehydration

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband and at-risk relatives to identify as early as possible those who should be referred to a CF center for initiation of treatment. Evaluations can include the following:

- If the pathogenic variants in the family are known, molecular genetic testing can be used to clarify the genetic status of at-risk sibs.
- If the pathogenic variants in the family are not known, sweat chloride testing can be used to clarify the disease status of at-risk sibs.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Women with CF tolerate pregnancy well. Key factors for an optimal pregnancy include nutrition management, pulmonary clearance treatments, aggressive management of infections, and treatment by a multidisciplinary care team, especially in women with mild-to-moderate disease [Shteinberg et al 2021]. In all studies published to date, the most important predictors of pregnancy outcome are the severity of maternal pulmonary impairment and nutritional status. Women with more severe disease, such as cystic fibrosis-related diabetes (CFRD) and poor pulmonary function (FEV1 <50% predicted) should undergo pregnancy with caution [Taylor-Cousar 2020]. Increased rates of pulmonary exacerbations can be observed, and deterioration during pregnancy may precipitate preterm delivery [Shteinberg et al 2021]. Additionally, case reports of women with *Burkholderia cepacia* have been associated with more rapid rates of lung function decline during pregnancy [Jain et al 2022]. Pregnancy is not associated with long-term negative effects on pulmonary and nutritional outcomes or an increased risk of death [Schechter et al 2013, Taylor-Cousar 2020].

Preconception

- Females with CF of reproductive age should receive preconception counseling and take steps to optimize health prior to pregnancy.
- Maternal and fetal complications are high in women with CF who have received lung transplantation. Open and extensive discussions should be held between the transplant recipient and her care team prior to conception [Jain et al 2022].
- As in pregnancies of women with other forms of diabetes mellitus, fetal outcome is optimized when glycemic control is achieved prior to pregnancy.

During pregnancy

- The management of pregnancy and the immediate postpartum period for a woman with CF requires a maternal fetal medicine specialist, CF pulmonologist, dietician, and other members of the CF team [Jain et al 2022].
- Special attention should also be paid to supplementation of the fat-soluble vitamin A during pregnancy, as supratherapeutic levels may be teratogenic. Iron and folate supplementation recommendations in pregnant women with CF are similar to those in women without CF [Jain et al 2022].
- While there are no concerning signals in animal reproductive models for CFTR modulator therapy, human data are currently limited to case reports and physician surveys [Nash et al 2020, Taylor-Cousar 2020]. Risks and benefits of continuing CFTR modulator therapy during pregnancy should be discussed with a CF specialist [Taylor-Cousar 2020]. The multicenter prospective observational study entitled Maternal and Fetal Outcomes in the Era of Modulators (MAYFLOWERS; NCT04828382) is currently enrolling subjects to further address the effect of CFTR modulators on pregnancy and postpartum outcomes.

- Maternal nutritional status and weight gain should be monitored and optimized aggressively, and pulmonary exacerbations should be treated early.
- Gestational diabetes is common in pregnancies of women with CF. Traditional screening paradigms for gestational diabetes mellitus may not be useful in pregnancies of women with CF; therefore, screening at each trimester of pregnancy has been suggested to improve the detection of diabetes mellitus [Jain et al 2022]. Insulin is the first-line agent for glycemic control in CFRD and in gestational diabetes in women with CF [Jain et al 2022].

Delivery

- Mode of delivery is based on usual obstetric indications, with vaginal delivery being the most common mode of delivery in women with CF [Shteinberg et al 2021].
- During the postpartum period, it is important to support early mobilization and maintain good airway clearance practices, which can continue to be challenging with the demands of childcare [Taylor-Cousar 2020, Shteinberg et al 2021]. Adequate pain management and airway clearance must also be a focus for women who deliver by cesarean section.

Breastfeeding

- Review medications for risk of transfer in breast milk. Most medications used in the long-term management of CF are considered safe. The major exceptions to this are immunosuppressants (importantly, in transplant recipients), azoles, and tetracyclines. Animal reproductive models have shown the presence of modulators in the breast milk of lactating animals [Taylor-Cousar 2020].
- Women with CF will need to consider the choice of breastfeeding based on the ability to maintain weight in the face of the high caloric demands associated with breastfeeding and the need to resume medications that may be transferred to the infant through breast milk [Taylor-Cousar 2020].

Therapies Under Investigation

Therapeutic interventions for CF are continually evolving (see cff.org). Restoration of CFTR function continues to advance with improved modulators and gene therapy. Modulator therapy studies include using approved medications in individuals of younger ages and testing new modulators, once-daily dosing, and new combination therapies.

Therapies under study that focus specifically on the approximately 10% of individuals who are not eligible for current therapy due to nonsense or rare variants that do not produce any CFTR protein include read-through agents and gene therapy. Read-through agents are particularly interesting as a treatment for those with nonsense variants. Gene therapy is an area of active research, ranging from DNA based (both integrating and nonintegrating), RNA therapy, gene editing (such as CRISPR), and antisense oligonucleotide therapy.

The Infection Research Initiative from the Cystic Fibrosis Foundation is investigating a range of topics, including understanding CF-specific microorganisms, improving diagnosis and detection, optimizing current treatment, developing new antimicrobials, and evaluating the long-term effects of antimicrobial use. One exciting area of infection research related to bacteriophage therapy is the use of viruses to target difficult-to-treat bacteria.

Many other areas of CF research are also under way, such as mucociliary clearance modalities, anti-inflammatory agents, and nutritional treatments.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Cystic fibrosis (CF) is inherited in an autosomal recessive manner.

Risk to Family Members of a Proband with CF

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *CFTR* pathogenic variant.
- Molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *CFTR* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband not detected by sequence analysis that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes are at increased risk for bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, chronic rhinosinusitis / nasal polyposis, aquagenic palmoplantar keratoderma, acute recurrent pancreatitis, chronic pancreatitis, atypical mycobacterial infections, and bronchiectasis [Hsu et al 2013, Gamaletsou et al 2018, Raynal et al 2019, Çolak et al 2020, Izquierdo et al 2022, Polgreen & Comellas 2022]. (See Clinical Description, Heterozygotes.)

Sibs of a proband

- If both parents are known to be heterozygous for a *CFTR* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygotes are at increased risk for bronchiectasis, allergic bronchopulmonary aspergillosis, asthma, chronic rhinosinusitis / nasal polyposis, aquagenic palmoplantar keratoderma, acute recurrent pancreatitis, chronic pancreatitis, atypical mycobacterial infections, and bronchiectasis [Hsu et al 2013, Gamaletsou et al 2018, Raynal et al 2019, Çolak et al 2020, Izquierdo et al 2022, Polgreen & Comellas 2022]. (See Clinical Description, Heterozygotes.)

Offspring of a proband

- An individual with CF will transmit a *CFTR* pathogenic variant to all offspring. The risk that offspring will inherit a second *CFTR* pathogenic variant depends on the genetic status of the reproductive partner.
- If the reproductive partner of a proband is heterozygous for a *CFTR* pathogenic variant, offspring are at a 50% risk of being affected and a 50% risk of being heterozygous.

- It is appropriate to offer carrier testing to the reproductive partner of an individual with CF (see Population Screening).

  Note: While CF occurs in individuals of all ethnicities, the incidence of CF is increased in several populations (e.g., Amish, Ashkenazi Jewish, Hutterite) due to the presence of pathogenic founder variants (see Table 7).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *CFTR* pathogenic variant.

Heterozygote Detection

Targeted heterozygote testing for at-risk relatives requires prior identification of the *CFTR* pathogenic variants in the family.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on testing at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of carrier testing, potential risks to offspring, and reproductive options) to young adults who are affected, are carriers (heterozygotes), or are at risk of being carriers.
- Females with CF of reproductive age should receive preconception counseling and take steps to optimize health prior to pregnancy (see Pregnancy Management).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Population Screening

Carrier screening for CF is offered to all women who are pregnant.

Per NSGC Practice Guidelines, carrier (heterozygote) testing for CF should also be offered preconceptionally to women of all ancestries who are of reproductive age, to the reproductive partners of individuals who are heterozygous for a *CFTR* pathogenic variant or who are affected with CF, and to family members of an individual with CF.

A core panel of 23 *CFTR* pathogenic variants has been recommended by the ACMG for pan ethnic targeted carrier screening. Comprehensive CF testing can also be considered for pan ethnic carrier screening, particularly for individuals of non-northern European descent [Deignan et al 2020].

Prenatal Testing and Preimplantation Genetic Testing

High-risk pregnancies. Once the *CFTR* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing for CF are possible [Kessels et al 2020].

Note: Noninvasive prenatal testing for CF is also becoming more common.

Low-risk pregnancies. The finding of fetal echogenic bowel and/or intestinal loop dilatation and nonvisualization of the fetal gallbladder (NVFGB) on ultrasound examination is associated with an increased risk for CF in a pregnancy previously not known to be at increased risk for CF. The risk for CF ranges from 0.5% to 9.9% in fetuses with hyperechogenic bowel [Ameratunga et al 2012, Masini et al 2018, D'Amico et al 2021]. Fetuses with NVFGB and associated anomalies have a 16-fold higher risk for CF [Di Pasquo et al 2019]. In this situation, genetic counseling of the parents regarding the risk for CF is appropriate, followed by *CFTR* molecular genetic testing of the parents and/or the fetus, depending on the gestational age of the pregnancy and the decision of the parents.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Cystic Fibrosis Canada**
  Canada
  Phone: 800-378-2233
  www.cysticfibrosis.ca
- **Cystic Fibrosis Foundation**
  Phone: 800-344-4823; 301-951-4422
  Email: info@cff.org
  www.cff.org
- **Genetic Disorders of Mucociliary Clearance Consortium**
  www1.rarediseasesnetwork.org/cms/gdmcc
- **MedlinePlus**
  Cystic Fibrosis
- **Newborn Screening in Your State**
  Health Resources & Services Administration
  www.newbornscreening.hrsa.gov/your-state

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Cystic Fibrosis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar

Table A. continued from previous page.

CFTR	7q31.2	Cystic fibrosis transmembrane conductance regulator	CFTR2 Cystic Fibrosis Mutation Database Locus Specific Mutation Database Directory	CFTR	CFTR

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for Cystic Fibrosis (View All in OMIM)

219700	CYSTIC FIBROSIS; CF
602421	CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR; CFTR

Molecular Pathogenesis

CFTR encodes cystic fibrosis transmembrane conductance regulator (CFTR), an integral membrane protein that functions as a regulated chloride channel located at the apical membrane of epithelia, transporting chloride ions into and out of cells. Once chloride is transported out of the cell, sodium will join, forming sodium chloride (salt), which attracts water. CFTR maintains the balance of salt and water. CFTR is important in many organs, most specifically the respiratory, gastrointestinal, genitourinary, and endocrine systems and the sweat ducts.

Loss-of-function *CFTR* variants disrupt transepithelial chloride transport. Without chloride, sodium will not form salt and water will not be attracted. In most organs, this leads to excessively thick secretions and tissue damage. For example, in the lungs, thick mucus is an excellent milieu for bacteria, which the body attempts to fight with inflammation, leading to the vicious cycle of mucus production, infection, inflammation, and pulmonary damage (e.g., bronchiectasis). In the pancreas, thick secretions block the exocrine pancreatic ducts, preventing passage of pancreatic enzymes and creating pancreatic insufficiency. Secretion blockage causes pathology in many organs (e.g., liver disease, infertility/subfertility, bowel obstruction, pansinusitis).

The CFTR chloride channel is unique in the sweat glands, as it is reversed. In a person unaffected by CF, the CFTR chloride channel in sweat glands helps to reabsorb chloride (and thus salt and water). In people with CF, the channel is not functional, chloride is not reabsorbed, and the sweat is salty (resulting in an abnormal sweat test).

Mechanism of disease causation. Loss of function

***CFTR*-specific laboratory technical considerations.** Intronic variants including the poly T and poly TG tract in intron 8, c.2657+5G>A, and c.3718-2477C>T are included in the ACMG 23-variant panel. Deep intronic variants are not typically detected by exome sequencing. If deep intronic variants are not detected by the laboratory's methodology, additional testing to identify these variants should be performed [Deignan et al 2020].

Table 7. Notable *CFTR* Variants

Reference Sequences	DNA Nucleotide Change (Alias [1])	Predicted Protein Change	Comment [Reference]
NM_000492.4 NP_000483.3	c.350G>A	p.Arg117His	See Genotype-Phenotype Correlations.
	c.1364C>A	p.Ala455Glu	
	c.1521_1523delCTT	p.Phe508del	Most common pathogenic variant in individuals of Northern European ancestry; founder variant in Amish, Ashkenazi Jewish, Faroe Islander, & Hutterite populations.
	c.1652G>A	p.Gly551Asp	Gating variant responsive to ivacaftor; see Genotype-Phenotype Correlations.
NM_000492.4	c.2657+5G>A	--	Intronic pathogenic variant incl in ACMG 23-variant panel (See ***CFTR*-specific laboratory technical considerations**.)
NM_000492.4 NP_000483.3	c.3302T>A	p.Met1101Lys	Founder variant in Hutterite population [Zielenski et al 1993, Chong et al 2012, Triggs-Raine et al 2016]
NM_000492.4	c.3718-2477C>T	--	Intronic pathogenic variant incl in ACMG 23-variant panel (See ***CFTR*-specific laboratory technical considerations**.)
NM_000492.4 NP_000483.3	c.3846G>A	p.Trp1282Ter	Founder variant in Ashkenazi Jewish population [Scott et al 2010, Lazarin et al 2013]
	c.3484C>T	p.Arg1162Ter	Founder variant in Zuni population [Kessler et al 1996]
NM_000492.3	c.1210-12T[5_9] (5T/7T/9T)	--	See Genetic Modifiers, ***CFTR* poly T tract**.
	c.1210-34TG[11_13] (11TG/12TG/13TG)	--	See Genetic Modifiers, ***CFTR* poly TG tract**.

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.
1. Variant designation that does not conform to current naming conventions

Genetic Modifiers

***CFTR* poly T tract.** A poly T tract, a string of thymidine bases located in intron 8 of *CFTR*, can be associated with *CFTR*-related disorders depending on its size. The three common variants of the poly T tract are 5T, 7T, and 9T. Both 7T and 9T are benign variants, and 5T is a variably penetrant variant. The 5T variant is predicted to decrease the efficiency of intron 8 splicing, such that approximately 50% of full-length CFTR is produced (compared to almost 75% of full-length CFTR in those with 7T and 9T alleles) [Nykamp et al 2021]. The 5T variant is further modified by the TG tract.

***CFTR* poly TG tract.** A TG tract lies just 5' of the poly T tract. It consists of a short string of TG (thymidine-guanine) repeats that commonly number 11, 12, or 13. The number of TG repeats modulate phenotype in individuals with a 5T allele. Individuals with a longer TG tract (12 or 13 TG repeats) *in cis* with a shorter poly T tract (5T) have a full-length CFTR reduction to approximately 25%, which has the strongest adverse effect on proper intron 8 splicing [Salinas et al 2016, Nykamp et al 2021].

Chapter Notes

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References

Published Guidelines / Consensus Statements

Barben J, Castellani C, Munck A, Davies JC, de Winter-de Groot KM, Gartner S, Kashirskaya N, Linnane B, Mayell SJ, McColley S, Ooi CY, Proesmans M, Ren CL, Salinas D, Sands D, Sermet-Gaudelus I, Sommerburg O, Southern KW, et al. Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). J Cyst Fibros. 2021;20:810-9. [PubMed]

Borowitz DS, Grant RJ Durie PR. Use of pancreatic enzyme supplements for patients with cystic fibrosis in the context of fibrosing colonopathy. Consensus Committee. J Pediatr. 1995;127:681-84. [PubMed]

Cystic Fibrosis Foundation, Borowitz D, Parad RB, Sharp JK, Sabadosa KA, Robinson KA, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane

conductance regulator-related metabolic syndrome during the first two years of life and beyond. J Pediatr. 2009;155:S106-16. [PubMed]

Cystic Fibrosis Foundation, Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009;155:S73-93. [PubMed]

Floto RA, Olivier KN, Saiman L, Daley CL, Herrmann JL, Nick JA, Noone PG, Bilton D, Corris P, Gibson RL, Hempstead SE, Koetz K, Sabadosa KA, Sermet-Gaudelus I, Smyth AR, van Ingen J, Wallace RJ, Winthrop KL, Marshall BC, Haworth CS. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations for the management of non-tuberculous mycobacteria in individuals with cystic fibrosis. Thorax. 2016;71:i1-22. [PubMed]

Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416. [PubMed]

Moran A, Becker D, Casella SJ, Gottlieb PA, Kirkman MS, Marshall BC, Slovis B, et al. Epidemiology, pathophysiology, and prognostic implications of cystic fibrosis-related diabetes: a technical review. Diabetes Care. 2010;33:2677-83. [PubMed]

Moran A, Brunzell C, Cohen RC, Katz M, Marshall BC, Onady G, Robinson KA, Sabadosa KA, Stecenko A, Slovis B, et al. Clinical care guidelines for cystic fibrosis-related diabetes: a position statement of the American Diabetes Association and a clinical practice guideline of the Cystic Fibrosis Foundation, endorsed by the Pediatric Endocrine Society. Diabetes Care. 2010;33:2697-708. [PubMed]

Robinson KA, Saldanha IJ, McKoy NA. Management of infants with cystic fibrosis: a summary of the evidence for the Cystic Fibrosis Foundation Working Group on care of infants with cystic fibrosis. J Pediatr. 2009;155:S94-S105. [PubMed]

Sosnay PR, Salinas DB, White TB, Ren CL, Farrell PM, Raraigh KS, Girodon E, Castellani C. Applying cystic fibrosis transmembrane conductance regulator genetics and CFTR2 data to facilitate diagnoses. J Pediatr. 2017;181S:S27-S32.e1. [PubMed]

Stallings VA, Stark LJ, Robinson KA, Feranchak AP, Quinton H, et al. Evidence-based practice recommendations for nutrition-related management of children and adults with cystic fibrosis and pancreatic insufficiency: results of a systematic review. J Am Diet Assoc. 2008;108:832-9. [PubMed]

Literature Cited

Abolhassani H, El-Sherbiny YM, Arumugakani G, Carter C, Richards S, Lawless D, Wood P, Buckland M, Heydarzadeh M, Aghamohammadi A, Hambleton S, Hammarström L, Burns SO, Doffinger R, Savic S. Expanding clinical phenotype and novel insights into the pathogenesis of ICOS deficiency. J Clin Immunol. 2020;40:277–88. PubMed PMID: 31858365.

Aird A, Lagos M, Vargas-Hernández A, Posey JE, Coban-Akdemir Z, Jhangiani S, Mace EM, Reyes A, King A, Cavagnaro F, Forbes LR, Chinn IK, Lupski JR, Orange JS, Poli MC. Novel heterozygous mutation in NFKB2 Is associated with early onset CVID and a functional defect in NK cells complicated by disseminated CMV infection and severe nephrotic syndrome. Front Pediatr. 2019;7:303. PubMed PMID: 31417880.

Ameratunga DM, Said JM, Reidy K, Palma-Dias R. Perinatal outcomes following the ultrasound diagnosis of echogenic bowel: an Australian perspective. Fetal Diagn Ther. 2012;31:179–84. PubMed PMID: 22378220.

Aris RM, Merkel PA, Bachrach LK, Borowitz DS, Boyle MP, Elkin SL, Guise TA, Hardin DS, Haworth CS, Holick MF, Joseph PM, O'Brien K, Tullis E, Watts NB, White TB. Guide to bone health and disease in cystic fibrosis. J Clin Endocrinol Metab. 2005;90:1888–96. PubMed PMID: 15613415.

Barben J, Castellani C, Munck A, Davies JC, de Winter-de Groot KM, Gartner S, Kashirskaya N, Linnane B, Mayell SJ, McColley S, Ooi CY, Proesmans M, Ren CL, Salinas D, Sands D, Sermet-Gaudelus I, Sommerburg O, Southern KW, et al. Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID). J Cyst Fibros. 2021;20:810–9. PubMed PMID: 33257262.

Bisgin A, Sonmezler O, Boga I, Yilmaz M. The impact of rare and low-frequency genetic variants in common variable immunodeficiency (CVID). Sci Rep. 2021;11:8308. PubMed PMID: 33859323.

Blackman SM, Tangpricha V. Endocrine disorders in cystic fibrosis. Pediatr Clin North Am. 2016;63:699–708. PubMed PMID: 27469183.

Bogaert DJ, Dullaers M, Lambrecht BN, Vermaelen KY, De Baere E, Haerynck F. Genes associated with common variable immunodeficiency: one diagnosis to rule them all? J Med Genet. 2016;53:575–90. PubMed PMID: 27250108.

Bombieri C, Claustres M, De Boeck K, Derichs N, Dodge J, Girodon E, Sermet I, Schwarz M, Tzetis M, Wilschanski M, Bareil C, Bilton D, Castellani C, Cuppens H, Cutting GR, Drevínek P, Farrell P, Elborn JS, Jarvi K, Kerem B, Kerem E, Knowles M, Macek M Jr, Munck A, Radojkovic D, Seia M, Sheppard DN, Southern KW, Stuhrmann M, Tullis E, Zielenski J, Pignatti PF, Ferec C. Recommendations for the classification of diseases as CFTR-related disorders. J Cyst Fibros. 2011;10:S86–102. PubMed PMID: 21658649.

Borowitz D, Parad RB, Sharp JK, Sabadosa KA, Robinson KA, et al. Cystic Fibrosis Foundation practice guidelines for the management of infants with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome during the first two years of life and beyond. J Pediatr. 2009a;155:S106–16. PubMed PMID: 19914443.

Borowitz D, Robinson KA, Rosenfeld M, Davis SD, Sabadosa KA, et al. Cystic Fibrosis Foundation evidence-based guidelines for management of infants with cystic fibrosis. J Pediatr. 2009b;155:S73–93. PubMed PMID: 19914445.

Botton E, Saraux A, Laselve H, Jousse S, Le Goff P. Musculoskeletal manifestations in cystic fibrosis. Joint Bone Spine. 2003;70:327–35. PubMed PMID: 14563459.

Cai Z, Li H. Congenital bilateral absence of the vas deferens. Front Genet. 2022;13:775123. PubMed PMID: 35222530.

Charbonnier LM, Janssen E, Chou J, Ohsumi TK, Keles S, Hsu JT, Massaad MJ, Garcia-Lloret M, Hanna-Wakim R, Dbaibo G, Alangari AA, Alsultan A, Al-Zahrani D, Geha RS, Chatila TA. Regulatory T-cell deficiency and immune dysregulation, polyendocrinopathy, enteropathy, X-linked-like disorder caused by loss-of-function mutations in LRBA. J Allergy Clin Immunol. 2015;135:217–27. PubMed PMID: 25468195.

Cheng K, Ashby D, Smyth RL. Ursodeoxycholic acid for cystic fibrosis-related liver disease. Cochrane Database Syst Rev. 2017;9:CD000222. PubMed PMID: 28891588.

Chong JX, Ouwenga R, Anderson RL, Waggoner DJ, Ober C. A population-based study of autosomal-recessive disease-causing mutations in a founder population. Am J Hum Genet. 2012;91:608–20. PubMed PMID: 22981120.

Christiansen M, Offersen R, Jensen JMB, Petersen MS, Larsen CS, Mogensen TH. Identification of novel genetic variants in CVID patients with autoimmunity, autoinflammation, or malignancy. Front Immunol. 2020;10:3022. PubMed PMID: 32047491.

Çolak Y, Nordestgaard BG, Afzal S. Morbidity and mortality in carriers of the cystic fibrosis mutation CFTR Phe508del in the general population. Eur Respir J. 2020;56:2000558. PubMed PMID: 32398304.

Colombo C, Ellemunter H, Houwen R, Munck A, Taylor C, Wilschanski M, et al. Guidelines for the diagnosis and management of distal intestinal obstruction syndrome in cystic fibrosis patients. J Cyst Fibros. 2011;10:S24–8. PubMed PMID: 21658638.

Cui X, Wu X, Li Q, Jing X. Mutations of the cystic fibrosis transmembrane conductance regulator gene in males with congenital bilateral absence of the vas deferens: reproductive implications and genetic counseling. Mol Med Rep. 2020;22:3587–96. (Review) PubMed PMID: 33000223.

Cystic Fibrosis Foundation Patient Registry. 2020. 2020 Patient Registry Annual Data Report. Bethesda, Maryland. Available online. Accessed 11-2-22.

Cystic Fibrosis Foundation Patient Registry. 2021. 2021 Cystic Fibrosis Foundation Patient Registry Highlights Report. Bethesda, Maryland. Available online. Accessed 11-2-22.

D'Amico A, Buca D, Rizzo G, Khalil A, Silvi C, Makatsariya A, Nappi L, Liberati M, D'Antonio F. Outcome of fetal echogenic bowel: a systematic review and meta-analysis. Prenat Diagn. 2021;41:391–9. PubMed PMID: 31981377.

de Valles-Ibáñez G, Esteve-Solé A, Piquer M, González-Navarro EA, Hernandez-Rodriguez J, Laayouni H, González-Roca E, Plaza-Martin AM, Deyà-Martínez Á, Martín-Nalda A, Martínez-Gallo M, García-Prat M, Del Pino-Molina L, Cuscó I, Codina-Solà M, Batlle-Masó L, Solís-Moruno M, Marquès-Bonet T, Bosch E, López-Granados E, Aróstegui JI, Soler-Palacín P, Colobran R, Yagüe J, Alsina L, Juan M, Casals F. Evaluating the genetics of common variable immunodeficiency: monogenetic model and beyond. Front Immunol. 2018;9:636. PubMed PMID: 29867916.

Deignan JL, Astbury C, Cutting GR, Del Gaudio D, Gregg AR, Grody WW, Monaghan KG, Richards S, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22:1288–95. PubMed PMID: 32404922.

Dellon EP, Goggin J, Chen E, Sabadosa K, Hempstead SE, Faro A, Homa K. Defining palliative care in cystic fibrosis: a Delphi study. J Cyst Fibros. 2018;17:416–21. PubMed PMID: 29097163.

Di Pasquo E, Kuleva M, Rousseau A, Vitucci A, Sonigo P, Chardot C, Salomon LJ, Ville Y. Outcome of non-visualization of fetal gallbladder on second-trimester ultrasound: cohort study and systematic review of literature. Ultrasound Obstet Gynecol. 2019;54:582–8. PubMed PMID: 30809885.

Farrell PM, White TB, Howenstine MS, Munck A, Parad RB, Rosenfeld M, Sommerburg O, Accurso FJ, Davies JC, Rock MJ, Sanders DB, Wilschanski M, Sermet-Gaudelus I, Blau H, Gartner S, McColley SA. Diagnosis of cystic fibrosis in screened populations. J Pediatr. 2017a;181S:S33-S44.e2.

Farrell PM, White TB, Ren CL, Hempstead SE, Accurso F, Derichs N, Howenstine M, McColley SA, Rock M, Rosenfeld M, Sermet-Gaudelus I, Southern KW, Marshall BC, Sosnay PR. Diagnosis of cystic fibrosis: consensus guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017b;181S:S4-S15.e1.

Fedder J, Jorgensen MW, Engvad B. Prevalence of CBAVD in azoospermic men carrying pathogenic CFTR mutations - evaluated in a cohort of 639 non-vasectomized azoospermic men. Andrology. 2021;9:588–98. PubMed PMID: 33095972.

Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. Am J Respir Crit Care Med. 2009a;180:802–8. PubMed PMID: 19729669.

Flume PA, Mogayzel PJ Jr, Robinson KA, Rosenblatt RL, Quittell L, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: pulmonary complications: hemoptysis and pneumothorax. Am J Respir Crit Care Med. 2010;182:298–306. PubMed PMID: 20675678.

Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, Bujan J, Finder J, Lester M, Quittell L, Rosenblatt R, Vender RL, Hazle L, Sabadosa K, Marshall B, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2007;176:957–69. PubMed PMID: 17761616.

Flume PA, Robinson KA, O'Sullivan BP, Finder JD, Vender RL, Willey-Courand DB, White TB, Marshall BC, et al. Cystic fibrosis pulmonary guidelines: airway clearance therapies. Respir Care. 2009b;54:522–37. PubMed PMID: 19327189.

Gamaletsou MN, Hayes G, Harris C, Brock J, Muldoon EG, Denning DW. F508del CFTR gene mutation in patients with allergic bronchopulmonary aspergillosis. J Asthma. 2018;55:837–43. PubMed PMID: 29035608.

Goetz DM, Singh S. Respiratory system disease. Pediatr Clin North Am. 2016;63:637–59. PubMed PMID: 27469180.

Guo J, Garratt A, Hill A. Worldwide rates of diagnosis and effective treatment for cystic fibrosis. J Cyst Fibros. 2022;21:456–62. PubMed PMID: 35125294.

Hadjiliadis D, Khoruts A, Zauber AG, Hempstead SE, Maisonneuve P, Lowenfels AB, et al. Cystic fibrosis colorectal cancer screening consensus recommendations. Gastroenterology. 2018;154:736–745.e14. PubMed PMID: 29289528.

Hernandez PA, Gorlin RJ, Lukens JN, Taniuchi S, Bohinjec J, Francois F, Klotman ME, Diaz GA. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet. 2003;34:70–4. PubMed PMID: 12692554.

Hsu J, Avila PC, Kern RC, Hayes MG, Schleimer RP, Pinto JM. 2013. Genetics of chronic rhinosinusitis: state of the field and directions forward. J Allergy Clin Immunol 131:977-93, 993.e1-5..

Huang SJ, Amendola LM, Sternen DL. Variation among DNA banking consent forms: points for clinicians to bank on. J Community Genet. 2022;13:389–97. PubMed PMID: 35834113.

Izquierdo ME, Marion CR, Moore WC, Raraigh KS, Taylor-Cousar JL, Cutting GR, Ampleford E, Hawkins GA, Zein J, Castro M, Denlinger LC, Erzurum SC, Fahy JV, Israel E, Jarjour NN, Mauger D, Levy BD, Wenzel SE, Woodruff P, Bleecker ER, Meyers DA, Ortega VE. DNA sequencing analysis of cystic fibrosis transmembrane conductance regulator gene identifies cystic fibrosis-associated variants in the Severe Asthma Research Program. Pediatr Pulmonol. 2022;57:1782–8. PubMed PMID: 35451201.

Jain R, Kazmerski TM, Zuckerwise LC, West NE, Montemayor K, Aitken ML, Cheng E, Roe AH, Wilson A, Mann C, Ladores S, Sjoberg J, Poranski M, Taylor-Cousar JL. Pregnancy in cystic fibrosis: review of the literature and expert recommendations. J Cyst Fibros. 2022;21:387–95. PubMed PMID: 34456158.

Jia S, Taylor-Cousar JL. Cystic fibrosis modulator therapies. Annu Rev Med. 2023;74:413–26. PubMed PMID: 35973718.

Jónsson H, Sulem P, Kehr B, Kristmundsdottir S, Zink F, Hjartarson E, Hardarson MT, Hjorleifsson KE, Eggertsson HP, Gudjonsson SA, Ward LD, Arnadottir GA, Helgason EA, Helgason H, Gylfason A, Jonasdottir A, Jonasdottir A, Rafnar T, Frigge M, Stacey SN, Th Magnusson O, Thorsteinsdottir U, Masson G, Kong A, Halldorsson BV, Helgason A, Gudbjartsson DF, Stefansson K. Parental influence on human germline de novo mutations in 1,548 trios from Iceland. Nature. 2017;549:519–22. PubMed PMID: 28959963.

Kapnadak SG, Dimango E, Hadjiliadis D, Hempstead SE, Tallarico E, Pilewski JM, Faro A, Albright J, Benden C, Blair S, Dellon EP, Gochenour D, Michelson P, Moshiree B, Neuringer I, Riedy C, Schindler T, Singer LG, Young D, Vignola L, Zukosky J, Simon RH. Cystic Fibrosis Foundation consensus guidelines for the care of individuals with advanced cystic fibrosis lung disease. J Cyst Fibros. 2020;19:344–54. PubMed PMID: 32115388.

Kavalieratos D, Georgiopoulos AM, Dhingra L, Basile MJ, Rabinowitz E, Hempstead SE, Faro A, Dellon EP. Models of palliative care delivery for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed consensus guidelines. J Palliat Med. 2021;24:18–30. PubMed PMID: 32936045.

Keller MD, Pandey R, Li D, Glessner J, Tian L, Henrickson SE, Chinn IK, Monaco-Shawver L, Heimall J, Hou C, Otieno FG, Jyonouchi S, Calabrese L, van Montfrans J, Orange JS, Hakonarson H. Mutation in IRF2BP2 is responsible for a familial form of common variable immunodeficiency disorder. J Allergy Clin Immunol. 2016;138:544–550.e4. PubMed PMID: 27016798.

Kermode W, De Santis D, Truong L, Della Mina E, Salman S, Thompson G, Nolan D, Loh R, Mallon D, Mclean-Tooke A, John M, Tangye SG, O'Sullivan M, D'Orsogna LJ. A novel targeted amplicon next-generation sequencing gene panel for the diagnosis of common variable immunodeficiency has a high diagnostic yield: results from the Perth CVID cohort study. J Mol Diagn. 2022;24:586–99. PubMed PMID: 35570134.

Kessels SJM, Carter D, Ellery B, Newton S, Merlin TL. Prenatal genetic testing for cystic fibrosis: a systematic review of clinical effectiveness and an ethics review. Genet Med. 2020;22:258–67. PubMed PMID: 31467445.

Kessler D, Moehlenkamp C, Kaplan G. Determination of cystic fibrosis carrier frequency for Zuni native Americans of New Mexico. Clin Genet. 1996;49:95–7. PubMed PMID: 8740921.

Kopecký O, Lukesová S. Genetic defects in common variable immunodeficiency. Int J Immunogenet. 2007;34:225–9. PubMed PMID: 17627754.

Kuehn HS, Boisson B, Cunningham-Rundles C, Reichenbach J, Stray-Pedersen A, Gelfand EW, Maffucci P, Pierce KR, Abbott JK, Voelkerding KV, South ST, Augustine NH, Bush JS, Dolen WK, Wray BB, Itan Y, Cobat A, Sorte HS, Ganesan S, Prader S, Martins TB, Lawrence MG, Orange JS, Calvo KR, Niemela JE, Casanova JL, Fleisher TA, Hill HR, Kumánovics A, Conley ME, Rosenzweig SD. Loss of B cells in patients with heterozygous mutations in IKAROS. N Engl J Med. 2016;374:1032–43. PubMed PMID: 26981933.

Kuijpers TW, Bende RJ, Baars PA, Grummels A, Derks IA, Dolman KM, Beaumont T, Tedder TF, van Noesel CJ, Eldering E, van Lier RA. CD20 deficiency in humans results in impaired T cell-independent antibody responses. J Clin Invest. 2010;120:214–22. PubMed PMID: 20038800.

Kumar S, Ooi CY, Werlin S, Abu-El-Haija M, Barth B, Bellin MD, Durie PR, Fishman DS, Freedman SD, Gariepy C, Giefer MJ, Gonska T, Heyman MB, Himes R, Husain SZ, Lin TK, Lowe ME, Morinville V, Palermo JJ, Pohl JF, Schwarzenberg SJ, Troendle D, Wilschanski M, Zimmerman MB, Uc A. Risk factors associated with pediatric acute recurrent and chronic pancreatitis: lessons from INSPPIRE. JAMA Pediatr. 2016;170:562–9. PubMed PMID: 27064572.

Lahiri T, Hempstead SE, Brady C, Cannon CL, Clark K, Condren ME, Guill MF, Guillerman RP, Leone CG, Maguiness K, Monchil L, Powers SW, Rosenfeld M, Schwarzenberg SJ, Tompkins CL, Zemanick ET, Davis SD. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. Pediatrics. 2016;137:e20151784. PubMed PMID: 27009033.

Langfelder-Schwind E, Raraigh KS, Parad RB, et al. Genetic counseling access for parents of newborns who screen positive for cystic fibrosis: consensus guidelines. Pediatr Pulmonol. 2022;57:894–902. PubMed PMID: 34964558.

Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, Marshall JR, Seltzer WK, Patrizio P, Evans EA, Srinivasan BS. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15:178–86. PubMed PMID: 22975760.

LeGrys VA, Yankaskas JR, Quittell LM, Marshall BC, Mogayzel PJ Jr, et al. Diagnostic sweat testing: the Cystic Fibrosis Foundation guidelines. J Pediatr. 2007;151:85–9. PubMed PMID: 17586196.

Lucarelli M, Bruno SM, Pierandrei S, Ferraguti G, Testino G, Truglio G, Strom R, Quattrucci S. The impact on genetic testing of mutational patterns of CFTR gene in different clinical macrocategories of cystic fibrosis. J Mol Diagn. 2016;18:554–65. PubMed PMID: 27157324.

Ma J, Fu L, Gu H, Chen Z, Zhang J, Zhao S, Zhu X, Liu H, Wu R. Screening for genetic mutations for the early diagnosis of common variable immunodeficiency in children with refractory immune thrombocytopenia: a retrospective data analysis from a tertiary children's center. Front Pediatr. 2020;8:595135. PubMed PMID: 33425813.

Masini G, Maggio L, Marchi L, Cavalli I, Ledda C, Trotta M, Pasquini L. Isolated fetal echogenic bowel in a retrospective cohort: The role of infection screening. Eur J Obstet Gynecol Reprod Biol. 2018;231:136–41. PubMed PMID: 30388607.

Masson A, Kirszenbaum M, Sermet-Gaudelus I. Pain is an underestimated symptom in cystic fibrosis. Curr Opin Pulm Med. 2017;23:570–3. PubMed PMID: 28806187.

McDonald CM, Alvarez JA, Bailey J, Bowser EK, Farnham K, Mangus M, Padula L, Porco K, Rozga M. Academy of Nutrition and Dietetics: 2020 Cystic Fibrosis Evidence Analysis Center evidence-based nutrition practice guideline. J Acad Nutr Diet. 2021;121:1591–1636.e3. PubMed PMID: 32565399.

Mogayzel PJ Jr, Naureckas ET, Robinson KA, Brady C, Guill M, Lahiri T, Lubsch L, Matsui J, Oermann CM, Ratjen F, Rosenfeld M, Simon RH, Hazle L, Sabadosa K, Marshall BC, et al. Cystic Fibrosis Foundation pulmonary guideline. Pharmacologic approaches to prevention and eradication of initial Pseudomonas aeruginosa infection. Ann Am Thorac Soc. 2014;11:1640–50. PubMed PMID: 25549030.

Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjiliadis D, Hoag JB, Lubsch L, Hazle L, Sabadosa K, Marshall B, et al. Cystic fibrosis pulmonary guidelines. Chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187:680–9. PubMed PMID: 23540878.

Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care. 2009;32:1626–31. PubMed PMID: 19542209.

Moran A, Pillay K, Becker D, Granados A, Hameed S, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2018: management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2018;19:64–74. PubMed PMID: 30094886.

Moran A, Pillay K, Becker DJ, Acerini CL, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Management of cystic fibrosis-related diabetes in children and adolescents. Pediatr Diabetes. 2014;15:65–76. PubMed PMID: 25182308.

Nash EF, Middleton PG, Taylor-Cousar JL. Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators - an international survey. J Cyst Fibros. 2020;19:521–6. PubMed PMID: 32151568.

Novice T, Kariminia A, Del Bel KL, Lu H, Sharma M, Lim CJ, Read J, Lugt MV, Hannibal MC, O'Dwyer D, Hosler M, Scharnitz T, Rizzo JM, Zacur J, Priatel J, Abdossamadi S, Bohm A, Junker A, Turvey SE, Schultz KR, Rozmus J. A germline mutation in the C2 domain of PLCgamma2 associated with gain-of-function expands the phenotype for PLCG2-related diseases. J Clin Immunol. 2020;40:267–76. PubMed PMID: 31853824.

Nykamp K, Truty R, Riethmaier D, Wilkinson J, Bristow SL, Aguilar S, Neitzel D, Faulkner N, Aradhya S. Elucidating clinical phenotypic variability associated with the polyT tract and TG repeats in CFTR. Hum Mutat. 2021;42:1165–72. PubMed PMID: 34196078.

Polgreen PM, Comellas AP. Clinical phenotypes of cystic fibrosis carriers. Annu Rev Med. 2022;73:563–74. PubMed PMID: 35084992.

Quittner AL, Abbott J, Georgiopoulos AM, Goldbeck L, Smith B, Hempstead SE, Marshall B, Sabadosa KA, Elborn S, et al. International Committee on Mental Health in Cystic Fibrosis: Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus statements for screening and treating depression and anxiety. Thorax. 2016;71:26–34. PubMed PMID: 26452630.

Quittner AL, Goldbeck L, Abbott J, Duff A, Lambrecht P, Solé A, Tibosch MM, Bergsten Brucefors A, Yüksel H, Catastini P, Blackwell L, Barker D. Prevalence of depression and anxiety in patients with cystic fibrosis and

parent caregivers: results of The International Depression Epidemiological Study across nine countries. Thorax. 2014;69:1090–7. PubMed PMID: 25246663.

Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, Tallarico E, Faro A, Rosenbluth DB, Gray AL, Dunitz JM, et al. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. J Cyst Fibros. 2019;18:321–33. PubMed PMID: 30926322.

Raynal C, Girodon E, Audrezet MP, Cabet F, Pagin A, Reboul MP, Dufernez F, Fergelot P, Bergougnoux A, Fanen P, Ferec C, Bienvenu T. CFTR gene variants: a predisposition factor to aquagenic palmoplantar keratoderma. Br J Dermatol. 2019;181:1097–9. PubMed PMID: 31310009.

Ren CL, Borowitz DS, Gonska T, Howenstine MS, Levy H, Massie J, Milla C, Munck A, Southern KW. 2017. Cystic fibrosis transmembrane conductance regulator-related metabolic syndrome and cystic fibrosis screen positive, inconclusive diagnosis. J Pediatr 181S:S45-S51.e1.

Ren CL, Morgan RL, Oermann C, Resnick HE, Brady C, Campbell A, DeNagel R, Guill M, Hoag J, Lipton A, Newton T, Peters S, Willey-Courand DB, Naureckas ET. Cystic Fibrosis Foundation pulmonary guidelines. Use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. Ann Am Thorac Soc. 2018;15:271–80. PubMed PMID: 29342367.

Ren Y, Xiao F, Cheng F, Huang X, Li J, Wang X, Lang W, Zhou X, Lan J, Tong H. Whole exome sequencing reveals a novel LRBA mutation and clonal hematopoiesis in a common variable immunodeficiency patient presented with hemophagocytic lymphohistiocytosis. Exp Hematol Oncol. 2021;10:38. PubMed PMID: 34120644.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24. PubMed PMID: 25741868.

Rosenfeld M, Sontag MK, Ren CL. Cystic fibrosis diagnosis and newborn screening. Pediatr Clin North Am. 2016;63:599–615. PubMed PMID: 27469178.

Rueda-Nieto S, Mondejar-Lopez P, Mira-Escolano MP, Cutillas-Tolin A, Maceda-Roldan LA, Arense-Gonzalo JJ, Palomar-Rodriguez JA. Analysis of the genotypic profile and its relationship with the clinical manifestations in people with cystic fibrosis: study from a rare disease registry. Orphanet J Rare Dis. 2022;17:222. PubMed PMID: 35698092.

Russell MA, Pigors M, Houssen ME, Manson A, Kelsell D, Longhurst H, Morgan NG. A novel de novo activating mutation in STAT3 identified in a patient with common variable immunodeficiency (CVID). Clin Immunol. 2018;187:132–6. PubMed PMID: 29180260.

Saiman L, Siegel JD, Lipuma JJ, Brown RF, Bryson EA, Chambers MJ, Downer VS, Fliege J, Hazle LA, Jain M, Marshall BC, O'Malley C, Pattee SR, Potter-Bynoe G, Reid S, Robinson KA, Sabadosa KA, Schmidt HJ, Tullis E, Webber J, Weber DJ, et al. Infection prevention and control guideline for cystic fibrosis: 2013 update. Infect Control Hosp Epidemiol. 2014;35:S1–S67. PubMed PMID: 25025126.

Salinas DB, Azen C, Young S, Keens TG, Kharrazi M, Parad RB. Phenotypes of California CF newborn screen-positive children with CFTR 5T allele by TG repeat length. Genet Test Mol Biomarkers. 2016;20:496–503. PubMed PMID: 27447098.

Salzer E, Kansu A, Sic H, Májek P, Ikincioğullari A, Dogu FE, Prengemann NK, Santos-Valente E, Pickl WF, Bilic I, Ban SA, Kuloğlu Z, Demir AM, Ensari A, Colinge J, Rizzi M, Eibel H, Boztug K. Early-onset inflammatory bowel disease and common variable immunodeficiency-like disease caused by IL-21 deficiency. J Allergy Clin Immunol. 2014;133:1651–9.e12. PubMed PMID: 24746753.

Salzer E, Santos-Valente E, Klaver S, Ban SA, Emminger W, Prengemann NK, Garncarz W, Müllauer L, Kain R, Boztug H, Heitger A, Arbeiter K, Eitelberger F, Seidel MG, Holter W, Pollak A, Pickl WF, Förster-Waldl E,

Boztug K. B-cell deficiency and severe autoimmunity caused by deficiency of protein kinase C delta. Blood. 2013;121:3112–6. PubMed PMID: 23319571.

Salzer U, Chapel HM, Webster AD, Pan-Hammarström Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schäffer AA, Hammarström L, Grimbacher B. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet. 2005;37:820–8. PubMed PMID: 16007087.

Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W, Grimbacher B. ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol. 2004;113:234–40. PubMed PMID: 15507387.

Sathe MN, Freeman AJ. Gastrointestinal, pancreatic, and hepatobiliary manifestations of cystic fibrosis. Pediatr Clin North Am. 2016;63:679–98. PubMed PMID: 27469182.

Schechter MS, Quittner AL, Konstan MW, Millar SJ, Pasta DJ, McMullen A, et al. Long-term effects of pregnancy and motherhood on disease outcomes of women with cystic fibrosis. Ann Am Thorac Soc. 2013;10:213–19. PubMed PMID: 23802817.

Schipp C, et al. Specific antibody deficiency and autoinflammatory disease extend the clinical and immunological spectrum of heterozygous NFKB1 loss-of-function mutations in humans. Haematologica. 2016;101:e392–e396. PubMed PMID: 27365489.

Schwarzenberg SJ, Hempstead SE, McDonald CM, Powers SW, Wooldridge J, Blair S, Freedman S, Harrington E, Murphy PJ, Palmer L, Schrader AE, Shiel K, Sullivan J, Wallentine M, Marshall BC, Leonard AR. Enteral tube feeding for individuals with cystic fibrosis: Cystic Fibrosis Foundation evidence-informed guidelines. J Cyst Fibros. 2016;15:724–35. PubMed PMID: 27599607.

Scott SA, Edelmann L, Liu L, Luo M, Desnick RJ. Kornreich. Experience with carrier screening and prenatal diagnosis for 16 Ashkenazi Jewish genetic diseases. Hum Mutat. 2010;31:1240–50. PubMed PMID: 20672374.

Seligmann M, Brouet JC, Sasportes M. Hereditary C2 deficiency associated with common variable immunodeficiency. Ann Intern Med. 1979;91:216–7. PubMed PMID: 313733.

Sermet-Gaudelus I, Girodon E, Roussel D, Deneuville E, Bui S, Huet F, Guillot M, Aboutaam R, Renouil M, Munck A, des Georges M, Iron A, Thauvin-Robinet C, Fajac I, Lenoir G, Roussey M, Edelman A. Measurement of nasal potential difference in young children with an equivocal sweat test following newborn screening for cystic fibrosis. Thorax. 2010;65:539–44. PubMed PMID: 20522854.

Shteinberg M, Lulu AB, Downey DG, Blumenfeld Z, Rousset-Jablonski C, Perceval M, Colombo A, Stein N, Livnat G, Gur M, Bentur L, Mussaffi H, Blau H, Sarouk I, Dagan A, Kerem E, Aviram M, Picard E, Aliberti S, Álvarez A, Miranda JP, Polverino E, Durieu I, Stuart Elborn J, Cohen-Cymberknoh M. Failure to conceive in women with CF is associated with pancreatic insufficiency and advancing age. J Cyst Fibros. 2019;18:525–9. PubMed PMID: 30366850.

Shteinberg M, Taylor-Cousar JL, Durieu I, Cohen-Cymberknoh M. Fertility and pregnancy in cystic fibrosis. Chest. 2021;160:2051–60. PubMed PMID: 34284004.

Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, Murray CP, Stick SM, et al. Risk factors for bronchiectasis in children with cystic fibrosis. N Engl J Med. 2013;368:1963–70. PubMed PMID: 23692169.

Soto ME, Cordera F, Reyes PA. Congenital C2 (type I) deficiency associated with common variable immunodeficiency. Ann Intern Med. 2000;132:597. PubMed PMID: 10744610.

Sosnay PR, White TB, Farrell PM, Ren CL, Derichs N, Howenstine MS, Nick JA, De Boeck K. 2017. Diagnosis of cystic fibrosis in nonscreened populations. J Pediatr 181S:S52-S57.e2.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197–207. PubMed PMID: 32596782.

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, et al. Allergic bronchopulmonary aspergillosis in cystic fibrosis--state of the art: Cystic Fibrosis Foundation Consensus Conference. Clin Infect Dis. 2003;37:S225–64. PubMed PMID: 12975753.

Sun D, Heimall J. Disorders of CTLA-4 expression, how they lead to CVID and dysregulated immune responses. Curr Opin Allergy Clin Immunol. 2019;19:578–85. PubMed PMID: 31573993.

Taylor-Cousar JL. CFTR modulators: impact on fertility, pregnancy, and lactation in women with cystic fibrosis. J Clin Med. 2020;9:2706. PubMed PMID: 32825766.

Thiel J, Kimmig L, Salzer U, Grudzien M, Lebrecht D, Hagena T, Draeger R, Voelxen N, Bergbreiter A, Jennings S, Gutenberger S, Aichem A, Illges H, Hannan JP, Kienzler AK, Rizzi M, Eibel H, Peter HH, Warnatz K, Grimbacher B, Rump JA, Schlesier M. Genetic CD21 deficiency is associated with hypogammaglobulinemia. J Allergy Clin Immunol. 2012;129:801–810.e6. PubMed PMID: 22035880.

Triggs-Raine B, Dyck T, Boycott KM, Innes AM, Ober C, Parboosingh JS, Botkin A, Greenberg CR, Spriggs EL. Development of a diagnostic DNA chip to screen for 30 autosomal recessive disorders in the Hutterite population. Mol Genet Genomic Med. 2016;4:312–21. PubMed PMID: 27247959.

Turck D, Braegger CP, Colombo C, Declercq D, Morton A, Pancheva R, Robberecht E, Stern M, Strandvik B, Wolfe S, Schneider SM, Wilschanski M. ESPEN-ESPGHAN-ECFS guidelines on nutrition care for infants, children, and adults with cystic fibrosis. Clin Nutr. 2016;35:557–77. PubMed PMID: 27068495.

van Zelm MC, Reisli I, van der Burg M, Castaño D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patiño PJ, van Dongen JJ, Franco JL. An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med. 2006;354:1901–12. PubMed PMID: 16672701.

van Zelm MC, Smet J, Adams B, Mascart F, Schandené L, Janssen F, Ferster A, Kuo CC, Levy S, van Dongen JJ, van der Burg M. CD81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. J Clin Invest. 2010;120:1265–74. PubMed PMID: 20237408.

Wang HY, Ma CA, Zhao Y, Fan X, Zhou Q, Edmonds P, Uzel G, Oliveira JB, Orange J, Jain A. Antibody deficiency associated with an inherited autosomal dominant mutation in TWEAK. Proc Natl Acad Sci U S A. 2013;110:5127–32. PubMed PMID: 23493554.

Warnatz K, Salzer U, Rizzi M, Fischer B, Gutenberger S, Böhm J, Kienzler AK, Pan-Hammarström Q, Hammarström L, Rakhmanov M, Schlesier M, Grimbacher B, Peter HH, Eibel H. B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. Proc Natl Acad Sci U S A. 2009;106:13945–50. PubMed PMID: 19666484.

Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, Ratjen F. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2012;40:61–6. PubMed PMID: 22135280.

Yu J, Chen Z, Ni Y, Li Z. CFTR mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis. Hum Reprod. 2012;27:25–35. PubMed PMID: 22081250.

Zemanick ET, Hoffman LR. Cystic fibrosis: microbiology and host response. Pediatr Clin North Am. 2016;63:617–36. PubMed PMID: 27469179.

Zielenski J, Fujiwara TM, Markiewicz D, Paradis AJ, Anacleto AI, Richards B, Schwartz RH, Klinger KW, Tsui LC, Morgan K. Identification of the M1101K mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and complete detection of cystic fibrosis mutations in the Hutterite population. Am J Hum Genet. 1993;52:609–15. PubMed PMID: 7680525.

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