

Cystic Fibrosis

[CF, Mucoviscidosis. Includes: Congenital Bilateral Absence of the Vas Deferens (CBAVD)]

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Summary

Disease characteristics. Cystic fibrosis (CF) affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and the exocrine sweat resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. Patients have lower airway inflammation and chronic endobronchial infection, which progresses to end stage lung disease characterized by extensive airway damage (cysts/abscesses) and fibrosis of lung parenchyma. Meconium ileus occurs in 10-20% of newborns diagnosed with CF. Pancreatic insufficiency with malabsorption occurs in the great majority of patients with CF. More than 95% of males with CF are infertile due to azoospermia resulting from absent, atrophic or fibrotic Wolffian duct structures. Men without any pulmonary or gastrointestinal manifestations of CF may have congenital bilateral absence of the vas deferens (CBAVD) resulting in azoospermia.

Diagnosis/testing. Most commonly the diagnosis of cystic fibrosis (CF) is established in individuals with one or more characteristic phenotypic features of CF plus evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function based upon ONE of the following: presence of two disease-causing mutations in the *CFTR* (*ABCC7*) gene; OR two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60mEq/L); OR An abnormal value for the transepithelial nasal potential difference (NPD). Using the panel of 25 alleles recommended by the American College of Medical Genetics, the *CFTR* mutation detection rate varies with ethnic background. In some symptomatic individuals only one or neither mutation is detectable; in some carriers, the disease-causing mutation is not detectable.

Genetic counseling. Cystic fibrosis and CBAVD, caused by mutations in the *CFTR* gene, are inherited in an autosomal recessive manner. Sibs of a proband with cystic fibrosis and brothers of a proband with CBAVD have a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of being unaffected and not a carrier. Molecular genetic testing for disease-causing mutation(s) in the *CFTR* gene is used for carrier detection in population screening programs. Prenatal testing is available for pregnancies at 25% risk in which the disease-causing mutations of the *CFTR* gene have been identified in both parents and for pregnancies in which fetal echogenic bowel and/or dilated bowel is observed on ultrasound examination.

Diagnosis

Clinical Diagnosis

Cystic Fibrosis

The diagnosis of cystic fibrosis (CF) is established in individuals with:

- One or more characteristic phenotypic features of CF PLUS
- Evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function based upon ONE of the following:
 - Presence of two disease-causing mutations in the *CFTR* (*ABCC7*) gene; OR
 - Two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60mEq/L); OR
 - An abnormal value for the transepithelial nasal potential difference (NPD)

The diagnosis of CF may be made in the absence of phenotypic features of CF in the following settings:

- Confirmed diagnosis of CF in a sibling and an abnormal sweat chloride value or the presence of the same two disease-causing mutation in the *CFTR* gene as identified in an affected sibling

- Diagnosis in a newborn screening program (based on the presence of two disease-causing mutations in the *CFTR* gene OR abnormal sweat chloride value)
- In utero diagnosis by *CFTR* mutational analysis. 10.3% of newly diagnosed patients in 1999 were diagnosed by newborn screening (7.1%) or prenatal diagnosis (3.2%) [1999 CFF Patient Registry].

Phenotypic features of CF include, but are not limited to:

- **Chronic sino-pulmonary disease** (chronic cough and sputum production, chronic wheeze and air trapping, obstructive lung disease on lung function tests, persistent colonization with CF pathogens, chronic chest radiograph abnormalities, digital clubbing).
- **Gastrointestinal/nutritional abnormalities** (malabsorption/pancreatic insufficiency, distal intestinal obstructive syndrome, rectal prolapse, recurrent pancreatitis, meconium ileus, chronic hepatobiliary disease, failure to thrive, hypoproteinemia, fat soluble vitamin deficiencies).
- **Obstructive azoospermia**
- **Salt-loss syndromes** (acute salt depletion, chronic metabolic alkalosis)

Testing

Sweat chloride. The National Committee for Clinical Laboratory Standards has published guidelines for the appropriate performance of the quantitative pilocarpine iontophoresis procedure [Wayne 1994, Legrys 1996]. Centers accredited by the [Cystic Fibrosis Foundation](#) are required to adhere to this protocol; alternative sweat test procedures are not acceptable. A minimum sweat weight of 75 mg must be collected during a 30-minute period to assure a sweat rate of 1 g/M²/min. A chloride concentration of >60 mEq/L in sweat on two separate occasions is diagnostic. This test is positive in over 90% of patients with CF. Sweat chloride levels >160 mEq/L are not physiologically possible and should be considered a technical error.

Transepithelial nasal potential difference (NPD). Respiratory epithelia regulate ion transport and alter content of the airway surface fluid by active transport mechanisms. The absence of functional CFTR at the apical surface with resultant alterations in chloride efflux and sodium transport produces an abnormal electrical potential difference across epithelial surfaces. When compared to individuals who do not have CF, individuals with CF have 1) a raised (more negative) baseline NPD reflecting enhanced sodium absorption across a relatively chloride impermeable membrane; 2) a greater change in NPD during perfusion of the nasal mucosa with amiloride, an inhibitor of sodium channel activity; and 3) the lack of change in NPD in response to perfusion with amiloride/low chloride/beta-agonist, as a measure of cAMP-mediated chloride transport via CFTR. The protocol for NPD measurements in patients greater than 6 years of age is well described, standardized, and safely performed in many specialized CF centers worldwide [Knowles et al 1995].

Newborn screening. Newborn screening has been implemented in some states using immunoreactive trypsinogen (IRT) assays performed on blood spots. The levels are elevated in cystic fibrosis. Abnormal results are further evaluated with molecular genetic testing of the *CFTR* gene OR sweat testing after the child is at least two months of age if two disease-causing mutations are not identified [Gregg et al 1997, Pollitt 1998].

Molecular Genetic Testing

Molecular genetic testing for disease-causing mutation(s) in the *CFTR* gene (chromosomal locus 7q31) is used:

- **to establish or confirm the diagnosis of CF** in symptomatic individuals;
- **for carrier detection:**
 - in population screening programs
 - in at-risk relatives, their reproductive partners and in certain other individuals;
- **in prenatal testing** of at-risk pregnancies and for pregnancies in which fetal echogenic bowel has been identified; and

Diagnosis of cystic fibrosis in symptomatic individuals. Using the panel of 25 *CFTR* alleles recommended by the American College of Medical Genetics (Table 6), the mutation detection rate varies with ethnic background (Table 3). In some symptomatic individuals only one or neither mutation is detectable (Table 1).

Table 1. Molecular Genetic Testing Used in the Diagnosis of CF in a Symptomatic Individual

Mutation Detection Rate (%)	Percentage of Affected Individuals by Number of Disease-Causing Alleles Detected ¹			Test Availability
	2	1	0	
95	90	10	0	Clinical GENEtests
90	81	18	1	
85	72	26	2	
80	64	32	4	
75	56	38	6	
70	49	42	9	
60	36	48	16	
50	25	50	25	
40	16	48	36	
30	9	42	49	

1. Calculated according to Hardy-Weinberg rule

Table 2. Residual Risk of Being a Carrier (%) if Testing is Negative

Prior Risk of Carrier Status	Mutation Detection Rate									
	30%	40%	50%	60%	70%	75%	80%	85%	90%	95%
2/3 (66.7%) ¹	58.3	54.5	50.0	44.4	37.5	33.3	28.6	23.1	16.7	9.1
1/2 (50.0%) ²	41.2	37.5	33.3	28.6	23.1	20.0	16.7	13.0	9.1	4.8
1/4 (25.0%) ³	18.9	16.7	14.3	11.8	9.1	7.7	6.3	4.8	3.2	1.6
1/30 (33.3%)	2.4	2.0	1.7	1.4	1.0	0.9	0.7	0.5	0.3	0.2
1/60 (1.7%)	1.2	1.0	0.8	0.7	0.5	0.4	0.3	0.3	0.2	0.1

1. sib of a proband

2. sib of a parent

3. cousin of a proband

Click [here](#) for residual risk of being a carrier for other values of prior risk.

Testing strategy for individuals suspected to have CF.

- Quantitative pilocarpine iontophoresis for sweat chloride concentrations remains the primary test for the diagnosis of CF (accurately diagnoses >90% of cases).
- Transepithelial nasal potential difference measurements may be necessary to confirm the diagnosis of CF in symptomatic individuals with borderline/non-diagnostic sweat tests in whom it has not been possible to detect two *CFTR* disease-causing mutations.
- Special circumstances in which *CFTR* mutational analysis is the initial diagnostic test include:
 - Prenatal testing, in a high-risk fetus
 - Newborn screening
 - Symptomatic infants (i.e., those with meconium ileus) who are too young to produce adequate volumes of sweat.
 - Prenatal diagnosis in low-risk fetus with fetal echogenic bowel

Carrier detection for cystic fibrosis. It is recommended that carrier testing be performed using a standard [25-mutation panel](#) (Table 6). Mutation detection rates vary among different population groups (Table 3); of note, groups other than European Caucasians and Ashkenazi Jewish have significantly lower mutation detection rates. The residual risk of being a carrier depends upon the carrier frequency and the mutation detection rate (Table 2).

Table 3. Carrier Frequency and Mutation Detection Rates in Population Groups

Population Group	Approximate Mutation Detection Rate ¹	Reference	Approximate Carrier Frequency ²	Reference
Ashkenazi Jewish	95%		1/29	
North American Caucasian	88-89%	DeMarchi et al 1994 , Wall et al 1995	1/28	
Spanish	75%		---	
African American	64%		1/61	
Mexican	58%		---	
Colombian	46%		---	
Venezuelan	33%		---	
Other groups	Varies	See CFGAC 1994 , Estivill et al 1997	---	

- Using the panel of the 25 *CFTR* alleles specified by the American College of Medical Genetics ([Table 6](#))
- Numbers vary depending on study.

Testing strategy for detection of carriers of *CFTR* disease-causing alleles. If an individual is R117H mutation positive, reflex testing for the 5T/7T/9T variant is recommended. If the individual is 5T positive, family studies are recommended to determine if the 5T polymorphism is in cis (i.e., on the same chromosome) or trans (i.e., on the homologous chromosome) with the R117H allele. (The son of a carrier for the R117H allele and the 5T polymorphism in trans and a carrier for a CF disease-causing allele is at risk to inherit the R117H and the CF mutation and to have CBAVD. The offspring of a carrier for the R117H allele and the 5T polymorphism in cis and a carrier for a CF disease-causing allele is at risk to inherit the R117H allele with the 5T polymorphism and the CF mutation and to have CF).

CBAVD

The diagnosis of congenital bilateral absence of the vas deferens (CBAVD) caused by mutations of *CFTR* is established in males with:

- Azoospermia (absence of sperm in the semen)
- A low volume of ejaculated semen (< 2 ml; normal 3-5 ml) with a specific chemical profile
- Absence of the vas deferens on palpation. Rarely a thin fibrous cord representing a rudimentary vas deferens may be present.
- An identifiable mutation in one or both *CFTR* genes [[Dork et al 1997](#)]
- Evidence of abnormalities of seminal vesicles or vas deferens upon rectal ultrasound examination

Semen analysis. Additional findings in the semen of men with CBAVD include, low pH (pH< 7; normal is pH>8); elevated citric acid concentration (>2000 mg/100 ml; normal 400-1500 mg/100 ml); elevated acid phosphatase concentration (760-1140 mu/ml; normal 140-290 mu/ml); low fructose concentration (30-80 mg/100 ml; normal 250-720 mg/100 ml) and failure to coagulate [[Holsclaw et al 1971](#)].

Molecular genetic testing of men with isolated congenital absence of the vas deferens. Routine clinical test panels detect about 80% of the *CFTR* mutations that can be detected in patients with CBAVD identified in research studies using extensive laboratory screening methods [[Mak et al 1999](#)]. In addition, a variant called the 5T allele is frequently found in this patient population. The 5T allele, a variably penetrant mutant allele in which five thymidines occur near the 3' end of intron 8 in the *CFTR* gene, is observed in about 10% (5% allele frequency) of the general population and has been associated with mild CF. This variant alone does not cause cystic fibrosis, but can cause CBAVD in trans combination with disease-causing *CFTR* mutation.

Table 4. Molecular Genetic Testing Used in the Diagnosis of CBAVD

Approximate % of Patients ¹	Genetic Mechanism	Test Type	Test Availability ^{2,3}
19%	Two mutant <i>CFTR</i> alleles identified	DNA-based	Clinical/Research
33%	One mutant <i>CFTR</i> allele plus one 5T allele identified	DNA-based	Clinical/Research
20%	One mutant <i>CFTR</i> allele identified and no 5T allele identified	DNA-based	Clinical/Research
1%	Two 5T alleles identified	DNA-based	Clinical/Research
27%	No mutant <i>CFTR</i> allele and zero or one 5T allele identified	DNA-based	Clinical/Research

- Based on [Chillon et al 1995](#)
- In this patient population, routine clinical test panels detect about 80% of the *CFTR* mutant alleles that can be found by more extensive research screening methods [[Mak et al 1999](#)]
- Testing for the 5T allele found in intron 8 needs to be ordered separately in some clinical laboratories

Genetically Related Disorders

Although there is noted to be an increased prevalence of *CFTR* mutations in patients with idiopathic pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis, DNA-based testing is not routinely used in the evaluation of these patients. The reader is referred to the following references for further information: [Zielenski and Tsui 1995](#), [Cohn et al 1998](#), [Mickle et al 1998](#), and [Wang et al 2000](#).

Clinical Description

Cystic Fibrosis

CF affects epithelia in several organs resulting in complex, multi-system disease including the exocrine pancreas, intestine, respiratory tract, male genital tract, hepatobiliary system, and the exocrine sweat gland. Patients with pancreatic sufficiency (<10%) have a milder clinical course with greater median survival (i.e., 56 years [1995 CFF Patient Registry]) than those with pancreatic insufficiency. The great majority of patients are pancreatic-insufficient with overall median survival of 26.9 years [1999 CFF Patient Registry]. A gender gap is present in CF with median survival for females at 28.1 years versus 29.1 years for males [1999 CFF Data Registry]. There is a wide variability of disease expression due to varying severity of *CFTR* mutations [[Gan et al 1995](#), [De Braekeleer et al 1997](#)], genetic modifiers [[Garred et al 1999](#), [Zielenski et al 1999](#)], and environmental factors [[Rubin 1990](#)]. The range includes death in early childhood due to progressive obstructive lung disease with bronchiectasis, to children with pancreatic insufficiency with gradually progressive obstructive lung disease during adolescence with increasing frequency of hospitalization for pulmonary disease as they enter adulthood, to patients presenting as young adults with a history of recurrent sinusitis and bronchitis or male infertility.

Respiratory. Pulmonary disease is the major cause of morbidity and mortality in CF [1999 CFF Registry]. Patients have lower airway inflammation and chronic endobronchial infection. Failure of lung defenses lead to bacterial endobronchitis (most commonly *Staphylococcus aureus* and *Pseudomonas aeruginosa*) with resulting airway obstruction and intense neutrophilic inflammation. Early manifestations are chronic cough, intermittent sputum production, and exertional dyspnea. As the lung disease progresses as a result of chronic endobronchitis, structural injury to the airways occurs with resulting bronchiectasis. End stage lung disease is characterized by extensive damage to the airways (cysts/abscesses) and accompanying fibrosis of lung parenchyma adjacent to airways.

Gastrointestinal.

- Meconium ileus occurs in 10-20% of symptomatic newborns diagnosed with CF.
- Pancreatic insufficiency with malabsorption occurs in the great majority of patients with CF (>85%; 93% of patients with CF in the 1999 CFF Registry taking pancreatic enzyme supplements). Exocrine pancreatic insufficiency is caused by inspissation of secretions within the pancreatic ducts and ultimately interstitial fibrosis. The clinical manifestations are steatorrhea, poor growth, and potential deficiencies in fat-soluble vitamins.
- Cystic fibrosis related diabetes mellitus (CFRDM) may present in adolescence; 2.2% of children less than 18 years of age require insulin. The prevalence increases in adulthood with greater than 15% in patients older than 18 years of age requiring insulin [1999 CFF Patient Registry]. The etiology is a combination of reduced insulin secretion (secondary to fibrosis of the pancreas and reduced number of islet cells) and peripheral insulin-resistance [[Lanng 1996](#), [Hardin et al 1997](#)].
- Hepatobiliary disease with elevation of liver enzymes in serum in school-age children, and rarely progresses to biliary cirrhosis in adolescents and adults. Prevalence of liver disease varies based on definition, and is reported as 4.5% in the 1999 CFF Registry. As liver disease progresses, patients develop portal hypertension and varices. Liver disease is second to pulmonary disease (plus organ transplantation complications) as a cause of mortality in CF (1.6% of deaths) [1999 CFF Patient Registry].

Fertility.

- More than 95% of males with CF are infertile due to azoospermia resulting from altered Wolffian duct structures which may be absent, atrophic or fibrotic. The body and tail of the epididymis and seminal vesicles may be abnormally dilated or absent.
- Women with CF are fertile, although a few females have abnormal cervical mucus which may contribute to infertility.

Congenital Bilateral Absence of the Vas Deferens

Men without any pulmonary or gastrointestinal manifestations of CF may have CBAVD. Absence of the vas deferens does not pose a health risk per se to the affected male. Testicular development and function, and spermatogenesis are usually normal. Bilateral absence of the vas deferens is generally identified during evaluation of infertility or as an incidental finding at the time of a surgical procedure, such as orchiopexy. Hypoplasia or aplasia of the vas deferens and seminal vesicles may occur either bilaterally (CBAVD) or unilaterally (CAVD).

Genotype-Phenotype Correlations

Probands

Cystic fibrosis. The best correlation between genotype and phenotype occurs in the area of pancreatic sufficiency. The most common mutations have been classified as pancreatic-sufficient ("PS") or pancreatic-insufficient ("PI") (see [Table 7](#)

below). Patients with pancreatic sufficiency usually have either one or two PS alleles.

In contrast, genotype-phenotype correlation is generally poor for pulmonary disease in CF. There is a wide variability in pulmonary diseases for individuals with the identical genotype, which may be due in part to genetic modifiers or environmental factors. However, compound heterozygotes with delta F508/A455E have better pulmonary function than patients who are homozygous for delta F508 [Gan et al 1995, De Braekeleer et al 1997]. In addition, the severity of lung disease in patients with one or two R117H mutation depends upon the presence of a variation in the poly T tract of intron 8 [Kiesewetter et al 1993]. Patients with 5 thymidines in the poly T tract of intron 8 and the R117H mutation can develop the lung disease of CF, but those patients with R117H and the 7T and 9T variant in intron 8 generally have normal lung function. Because A455E and R117H mutations are associated with pancreatic sufficiency, the less severe lung disease for patients with this mutation could be the consequence of better nutritional status.

CBAVD. CBAVD usually results from the combination of a severe CF mutation on one chromosome with either a mild CF mutation or the 5T allele on the other chromosome (Table 4). However, there is some overlap between the CBAVD phenotype and a very mild CF phenotype, with some fraction of CBAVD patients also reporting respiratory or pancreatic problems [Dork et al 1997]. Thus, some caution should be exercised in attempting to use genotype to predict the future course of patients initially diagnosed only with CBAVD.

At-risk couples. Genotype-phenotype correlations are most relevant for genetic counseling of two carriers who have been detected through evaluation of at-risk family members or screening programs and who have not had an affected child. The considerations in predicting the phenotype of potential offspring are the same as described above for CF and CBAVD probands. In general, prediction of severity of pancreatic disease on the basis of genotype will be most reliable, while prediction of the severity of respiratory disease will be less reliable. Prediction of the risk of CBAVD from genotype is reasonably reliable, but couples should be aware that mild respiratory and/or pancreatic disease can also occur in patients with genotypes usually associated with CBAVD. In addition, the penetrance of the 5T allele for CBAVD is incomplete (estimated at 60% in one study [Zielenski et al 1995]).

Many mutations are sufficiently rare that genotype-phenotype predictions cannot be made on the basis of empirical studies of populations of patients. In this setting, the molecular type of the mutation (Table 6) can give some indication of the likely phenotype: mutations that completely prevent protein synthesis or expression are most likely to be severe, while missense mutations that alter channel function or regulation are more likely to be mild [Mickle et al 1998].

Prevalence

CF is the most common life-limiting autosomal recessive disorder in the Caucasian population. The disease incidence is one in 3200 live births in Caucasians [Rosenstein et al 1998], and approximately 30,000 affected persons in the US. In the Caucasian population, the heterozygote frequency is one in 22-28. Cystic fibrosis also occurs in other ethnic, religious, and racial populations, but it is less common (one in 15,000 African-Americans, and one in 31,000 Asian Americans) [Rosenstein et al 1998].

Differential Diagnosis

Cystic fibrosis needs to be considered in:

- Infants with meconium ileus
- Infants with hyponatremia of unknown etiology
- Infants with hypoproteinemia and anemia
- Children with rectal prolapse
- Children with failure to thrive, poor growth and weight gain, with nutritional problems, chronic diarrhea, or malabsorption
- Children with refractory asthma, particularly at a young age; recurrent pneumonia, recurrent sinusitis, and/or nasal polyps. Such children may have a spectrum of non-related disorders including immunologic abnormalities, ciliary dysfunction, bronchopulmonary anatomic abnormalities, and allergies.
- Adolescents or adults with recurrent pancreatitis
- Adults with recurrent sinusitis/bronchitis or bronchiectasis, nasal polyps, recurrent pancreatitis, and male infertility.

Congenital absence of the vas deferens accounts for 1.2-1.7% of male infertility. CBAVD is part of the differential diagnosis of obstructive azoospermia, caused by obstruction to sperm outflow from the testes or ductular system. CBAVD may be part of a syndrome or may be an isolated finding. Syndromes with obstructive azoospermia include:

- Young syndrome, a progressive obstruction of the epididymis by inspissated secretions in males with chronic sinopulmonary infection [Handelsman et al 1984]. Males with Young syndrome do not have malformations of the vas deferens or epididymis.
- Hereditary urogenital adysplasia, an autosomal dominant disorder of variable expressivity and reduced penetrance. Females have a range of uterine anomalies; males may have Wolffian duct anomalies including unilateral or bilateral absence of the vas deferens; males and females may have unilateral or bilateral renal agenesis [Biedel et al 1984].

Management

Cystic Fibrosis

Referral to a regional CF Center is strongly recommended for individuals known to have CF or those in whom the diagnosis is being considered. A local CF clinical care center can be identified by contacting the [CF Foundation](#). Most patients followed at a CF Center are evaluated quarterly by a multidisciplinary team consisting of physicians, nurses, respiratory therapists, dietitians, social workers and genetic counselors. Epidemiologic data show that patients followed on a regular basis in accredited CF centers have improved clinical outcome [Wohl et al, submitted data].

Respiratory. Patients are regularly followed with pulmonary function studies, chest radiographs, and specific blood and urine laboratory tests. Intervention to treat or prevent pulmonary complications may include oral, inhaled or IV antibiotics, bronchodilators, anti-inflammatory agents, mucolytic agents, and chest physiotherapy (postural drainage with chest percussion) [[Ramsey et al 1999](#)]. New therapies are being investigated for the treatment of cystic fibrosis lung disease that span the pathophysiologic cascade of CF. Additional research focuses on CFTR "bypass" therapy to augment alternative chloride channels (i.e., UTP), CFTR "protein assist" treatment to improve the trafficking and function of defective CFTR protein (i.e., butyrates), new anti-inflammatory agents, new IV and inhaled antibiotics, and anti-proteases. Lung or heart/lung transplantation is an option for selected patients with severe disease. Nasal/sinus symptoms may require topical steroids, antibiotics, and/or surgical intervention.

Gastrointestinal. Nutritional therapy may include special formulas for infants to enhance weight gain through improved intestinal absorption, supplemental feeding to increase caloric intake, and additional fat soluble vitamins to prevent the development of vitamin deficiencies. Pancreatic insufficiency is treated with oral pancreatic enzyme replacement with meals.

Pregnancy. The survival of individuals with CF has improved considerably over the past few decades. Currently, the average median survival is approximately 33 years and pregnancy in patients with CF has become an important issue. Early reports of such pregnancies were discouraging. Historically, the predictors of poor pregnancy outcome for mother and/or fetus was a forced vital capacity (FVC) of less than 50% of the predicted value and poor nutritional status. In fact, an FVC of less than 50% of the predicted value was an absolute contraindication to pregnancy. However, with increasingly better pulmonary treatment, aggressive management of infections with a greater variety of antibiotics, and improved nutrition, pregnancies today are well tolerated, especially in women with mild to moderate disease [[Edenborough et al 2000](#), [Gilljam et al 2000](#)]. In these women, the risk factors for deteriorating health and early death after pregnancy are the same as the general adult female population. Important predictors of pregnancy outcome for mother and fetus are the severity of pulmonary impairment and nutritional status. Other factors affecting long-term survival include the frequency of pulmonary infections/exacerbations, presence of diabetes, and presence of colonization with *Burkholderia cepacia*.

Ideally, a woman with CF of reproductive age should have preconception counseling and optimization of her health prior to pregnancy. The management of such a pregnancy requires a multidisciplinary teamwork approach which includes a dietician, members of the CF team, and an obstetrician. Maternal nutritional status and weight gain should be monitored, pulmonary exacerbations should be treated early and aggressively, and early screening for diabetes is recommended. The risk for congenital anomalies in the fetus is not increased and breastfeeding is possible.

Gene therapy. Gene therapy is in a research phase only. Gene therapy is not able to control or treat the symptoms related to CF at this time.

Congenital Bilateral Absence of the Vas Deferens

The main issues relate to management of infertility that results from obstruction of sperm outflow through the ductular system. Assisted reproductive technologies can be used to alleviate infertility. These include microscopic sperm aspiration from the epididymal remnant in conjunction with *in vitro* fertilization, or artificial insemination using donor sperm.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal or cultural issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see [GENETests](#). -ED.

Mode of Inheritance

Cystic fibrosis and CBAVD, caused by mutations in the *CFTR* gene, are inherited in an autosomal recessive manner.

Risk To Family Members

Parents of a proband. The unaffected parents are obligate carriers (heterozygotes) and have an alteration in one copy of the *CFTR* gene. Carriers are asymptomatic.

Sibs of a proband with cystic fibrosis. Sibs have a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of being unaffected and not a carrier. If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test sibs by molecular genetic testing. Otherwise, sweat chloride testing should be performed. The unaffected sibs of a proband who have not undergone molecular genetic testing have a 2/3 chance of being a carrier.

Sibs of a proband with CBAVD. The brothers of a proband with CBAVD have a 25% chance of being affected, a 50% chance of being an unaffected carrier, and a 25% chance of being unaffected and not a carrier. It is appropriate to offer genetic counseling to brothers of a man with CBAVD. Molecular genetic testing is most informative when the disease-causing *CFTR* alleles have been identified in the proband. Men with CBAVD typically have only one (if any) identifiable *CFTR* mutation, making testing and interpretation of results in their family members complicated.

Offspring of a proband. Females with CF are fertile. A woman with CF transmits one disease-causing *CFTR* allele to each of her children. The risk that her child will inherit a second disease-causing *CFTR* allele depends upon her partner's carrier status. It is essential that *CFTR* mutation analysis be offered to her partner to determine his carrier status.

Males with CF and males with CBAVD may conceive a child through assisted reproductive technologies. In this instance, the affected male will transmit one disease-causing *CFTR* allele to each of his children. It is essential that *CFTR* mutation analysis be offered to the partners of these men to determine their *CFTR* carrier status.

Other family members. When a known carrier has no affected sibs, the carrier's brothers and sisters each have a 50% risk of being a carrier.

Related Genetic Counseling Issues

Carrier detection. Carrier detection may be pursued under the following circumstances:

- **Both disease-causing alleles of a proband are known.** If the maternally inherited disease-causing allele and the paternally inherited disease-causing allele have been identified, the at-risk maternal and paternal relatives can be tested following genetic counseling.
- **The proband is deceased and no DNA testing was performed.** Under such circumstances, it is appropriate to attempt to obtain any available tissue samples for the purpose of DNA extraction and *CFTR* mutation analysis. If DNA cannot be obtained, then it is appropriate to test at-risk family members, following genetic counseling. Those family members who have a disease-causing *CFTR* mutation are carriers and follow up genetic counseling regarding testing of partners and pregnancy risks is advised. Those family members who test negative for a panel of *CFTR* mutations can have their carrier risk reduced, using Bayes Theorem, but not eliminated. (See also the National Society of Genetic Counselors [statement](#) on carrier testing for cystic fibrosis.)
- **A person has a partner who is a known carrier or is at risk based on family history.** At-risk partners should be offered *CFTR* molecular genetic testing. It is appropriate to offer testing to the partners of those who are found to be carriers, with the understanding that negative test results reduce, but do not eliminate, the risk to be a carrier.
- **Population screening.** Screening for CF carrier status is being offered to some couples as part of routine prenatal care in some centers [[Grody 1999](#)] (see [Statements and Guidelines Regarding Genetic Testing](#)). Individuals with no family history of CF who test negative for a panel of *CFTR* mutations can have their carrier risk reduced based on their ethnicity, but not eliminated.

DNA banking. DNA banking is the storage of DNA that has been extracted from white blood cells for possible future use. It is likely that testing methodologies and our understanding of genes, mutations, and diseases will improve in the future. Consideration should be given to banking an individual's DNA particularly when current molecular genetic testing is not informative. For laboratories offering DNA banking, see [GENETests](#).

Prenatal Testing

High-risk pregnancies. Prenatal testing is available for pregnancies at 25% risk in which the disease-causing mutations of the *CFTR* gene have been identified in both parents. DNA from fetal cells obtained by chorionic villus sampling (CVS) at 10-12 weeks' gestation or by midtrimester amniocentesis at 15-20 weeks' gestation is analyzed for the disease-causing mutations in the *CFTR* gene.

Preimplantation diagnosis using embryonic cells is available on a limited basis to couples at 25% risk of having a child with CF when the disease-causing mutations of the *CFTR* gene have been identified in both parents. Achievement of pregnancy is through assisted reproductive technology and requires coordination with specialists in fertility and endocrinology.

Indeterminant-risk pregnancies. In cases in which one parent is known to be a *CFTR* mutation carrier and the other parent has tested negative for a panel of *CFTR* alleles, no additional testing is available to clarify the status of the fetus. Although [Girodon-Boulandet et al \(2000\)](#) have suggested that assay of intestinal enzyme levels in amniotic fluid may be informative, these tests are not available in the United States and lack specificity and sensitivity.

Low-risk pregnancies. The finding of fetal echogenic bowel and/or dilated bowel 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 may be 2-3% with Grade 2 (moderate) echogenic bowel. For Grade 3 (severe) echogenic bowel, defined as echogenicity similar to or greater than that of surrounding fetal bone, and/or intestinal dilation, the reported incidence of CF has been 5-20% [[Corteville et al 1996](#), [Slotnick and Abuhamad 1996](#), [Ghose et al 2000](#)]. In this situation, genetic counseling of the parents regarding the risk for CF is appropriate, followed by *CFTR* mutational analysis on the parents and/or the fetus, depending on the gestational age of the pregnancy and the decision of the parents. Based on the detection rate of the panel of *CFTR* mutations used, the risk for CF when only one disease-causing allele is identified in the fetus can be calculated [[Bosco et al 1999](#) [Hodge et al 1999](#)].

Molecular Genetics

Table 5. Molecular Genetics of CF

Gene/Locus Name	Locus	Normal Gene Product	Genomic Databases
<i>CFTR</i> (<i>ABCC7</i>)	7q31	Cystic fibrosis transmembrane conductance regulator	OMIM LocusLink OMIM LocusLink OMIM CFTR

Molecular pathogenesis. CFTR forms a regulated cell membrane chloride channel.

- **Gene/locus name:** *CFTR* (*ABCC7*)
- **Chromosomal locus:** 7q31
- **Normal allelic variants:** 230 kilobases, contains 27 coding exons, produces a 6.5 kilobase mRNA product.
- **Disease-causing allelic variants:** Over 900 mutations are known; almost all are point mutations or small (1-84 bp) deletions. The most common mutation is F508, accounting for about 30-80% of mutant alleles depending on the ethnic group. [Table 6](#) lists the panel of 25 alleles recommended by the American College of Medical Genetics for routine diagnostic and carrier testing. [Table 7](#) lists ten of the most common *CFTR* mutations and shows their most typical phenotypic effect when present in affected individuals.

Table 6. Recommended Core Mutation Panel for General Population CF Carrier Screening

1078delT	3120+1G>A	A455E	G85E	xR334W
1717-1G>A	3659delC	DeltaF508	I148T	R347P
1898+1G>A	3849+10kbC>T	DeltaI507	N1303K	R553X
2184delA	621+1G>T	G542X	R1162X	R560T
2789+5G>A	711+1G>T	G551D	R117H	W1282X

Reflex Tests

Benign variants. These tests distinguish between CF mutations and the benign variants **I506V**, **I507V**, **F508C**. I506V, I507V, and F508C tests are performed only as reflex tests for unexpected homozygosity for F508 and/or I507.

5T/7T/9T. 5T is cis and can modify the R117H phenotype or can contribute to congenital bilateral absence of vas deferens (CBAVD); 5T analysis is performed only as a reflex text for R117H positives.

Table 7. Ten Most Common *CFTR* Mutations in Caucasians ¹ and their Phenotypic Expression

Mutation	Relative Frequency	Mutation Functional Class ²	Pancreatic Sufficient (PS)/Insufficient (PI) ³
DF508	66.0%	II	PI
G542X	2.4%	I	PI
G551D	1.6%	III	PI
N1303K	1.3%	II	PI
W1282X	1.2%	I	PI
R553X	0.7%	I	PI
621+1G->T	0.7%	I	PI
1717-1G->A	0.6%	I	PI
R117H	0.3%	IV	PS
R1162X	0.3%	Not clear ⁴	PI

1. Based on genet.sickkids.on.ca

2. See Table 8 below

3. Degree of pancreatic function in patients with cystic fibrosis. PS mutations are dominant to PI mutations; thus, patients with PS/PS and PS/PI genotypes are usually pancreatic-sufficient, whereas patients with PI/PI genotypes are usually pancreatic-insufficient.

4. Transcript is stable; truncated protein is probably misfolded; therefore, is likely Class II

- **Normal gene product:** Cystic fibrosis transmembrane conductance regulator (abbreviated CFTR), a 1480-amino acid integral membrane protein that functions as a regulated chloride channel in epithelia.
- **Abnormal gene product:** Mutations can affect the CFTR protein quantitatively, qualitatively, or both. Table 8 provides one classification scheme for the functional consequences of *CFTR* mutations [[Zielenski et al 1995](#)].

Table 8. Classification Scheme for *CFTR* Mutations

Mutation Class	Effect of Mutation on CFTR Protein	Mechanisms
I	Reduced or absent synthesis	Nonsense, frameshift, or splice-junction mutations
II	Block in protein processing	Missense mutations, amino acid deletions
III	Block in regulation of CFTR chloride channel	Missense mutations
IV	Altered conductance of CFTR chloride channel	Missense mutations

After [Zielenski and Tsui 1995](#) (Figure 3) and [Welsh et al 2001](#)

Resources

GeneClinics provides information about selected national organizations and resources for the benefit of the reader. *GeneClinics* is not responsible for information provided by other organizations. -ED.

- **Cystic Fibrosis Foundation**
6931 Arlington Road, 2nd Floor
Bethesda, MD 20814-5200
Phone: 301-951-4422; 800-344-4823 (800-FIGHTCF)
Fax: 301-951-6378
Email: info@cff.org
www.cff.org
- **CF-Web**
Email: cf-web@cf-web.org
www.cf-web.org
- **NCBI Genes and Disease Webpage**
www.ncbi.nlm.nih.gov/disease/CF.html

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Statements and Policies Regarding Genetic Testing

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- American College of Medical Genetics (2000) [Statement](#) on genetic testing for cystic fibrosis.
- National Society of Genetic Counselors (1999) [Statement](#) on carrier testing for cystic fibrosis.

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