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CFTR-Related Disorders

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Summary

Disease characteristics. *CFTR*-related disorders include cystic fibrosis (CF) and congenital absence of the vas deferens (CAVD). Cystic fibrosis affects epithelia of the respiratory tract, exocrine pancreas, intestine, male genital tract, hepatobiliary system, and exocrine sweat glands, resulting in complex multisystem disease. Pulmonary disease is the major cause of morbidity and mortality in CF. Affected individuals have lower airway inflammation and chronic endobronchial infection, progressing to end-stage lung disease characterized by extensive airway damage (bronchiectasis, cysts, and abscesses) and fibrosis of lung parenchyma. Meconium ileus occurs at birth in 15%-20% of newborns with CF. Pancreatic insufficiency with malabsorption occurs in the great majority of individuals with CF. More than 95% of males with CF are infertile as a result of azoospermia caused by absent, atrophic, or fibrotic Wolffian duct structures. CAVD occurs in men without pulmonary or gastrointestinal manifestations of CF. Affected men have azoospermia and are thus infertile.

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 on **one** of the following: presence of two disease-causing mutations in the *CFTR* gene **or** two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L) **or** transepithelial nasal potential difference (NPD) measurements characteristic of CF. The *CFTR* mutation detection rate varies by test method and ethnic background. In some symptomatic individuals, only one or neither disease-causing mutation is detectable; in some

carriers, the disease-causing mutation is not detectable. The diagnosis of *CFTR*-related CAVD is established in males with azoospermia, low volume of ejaculated semen, absence of vas deferens on clinical or ultrasound examination, and at least one disease-causing mutation in *CFTR*.

Management. *Treatment of manifestations:* treatment/prevention of pulmonary complications using oral, inhaled, or IV antibiotics, bronchodilators, anti-inflammatory agents, mucolytic agents, and chest physiotherapy; lung or heart/lung transplantation in selected patients; topical steroids, antibiotics, and/or surgical intervention for nasal/sinus symptoms; special infant formulas to enhance weight gain; oral pancreatic enzyme replacement with meals in those who are pancreatic insufficient; supplemental feeding, often with an indwelling gastric feeding catheter to increase caloric intake; additional fat-soluble vitamins and zinc; oral ursodiol for biliary sludging/obstruction; management of CF-related diabetes mellitus (CFRD) by an endocrinologist; assisted reproductive technologies (ART) for male infertility. *Prevention of secondary complications:* airway clearance using chest physiotherapy (CPT) and a variety of airway clearance techniques (ACTs); antibiotics to eradicate initial airway infection and prevent chronic airway infection; immunizations. *Surveillance:* regularly scheduled visits to CF care providers to monitor for subtle changes in physical examination, pulmonary function studies, chest radiographs, specific blood and urine tests; cultures of respiratory tract secretions at least four times yearly in patients who are not yet chronically infected with *P. aeruginosa*; random serum glucose concentration measured annually to screen for CFRD; assessment of bone density starting in adolescence. *Agents/circumstances to avoid:* respiratory irritants (smoke, dust); respiratory infectious agents (especially viruses); dehydration. *Testing of relatives at risk:* sweat chloride testing of sibs and mothers of affected individuals to determine if they may have mild or not yet symptomatic forms of CF. *Therapies under investigation:* antibiotic agents/treatment schedules to delay chronic respiratory tract infection.

Genetic counseling. *CFTR*-related disorders are inherited in an autosomal recessive manner. Sibs of a proband with cystic fibrosis and brothers of a proband with CAVD have a 25% chance of being affected, a 50% chance of being asymptomatic carriers, and a 25% chance of being unaffected and not carriers. 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 increased risk for *CFTR*-related disorders if the disease-causing mutations in the family are known.

Diagnosis

Clinical Diagnosis

Cystic fibrosis (CF). Phenotypic features of CF include but are not limited to the following:

- **Chronic sinopulmonary disease** (chronic cough and sputum production, chronic wheeze and air trapping, obstructive lung disease on lung function tests, persistent colonization with pathogens commonly found in individuals with CF, chronic chest radiograph abnormalities, chronic pansinusitis, digital clubbing)
- **Gastrointestinal/nutritional abnormalities** (meconium ileus, rectal prolapse, malabsorption/pancreatic insufficiency, steatorrhea, hypoproteinemia, fat-soluble vitamin deficiencies, failure to thrive, distal intestinal obstructive syndrome, recurrent pancreatitis, biliary sludging, elevation of transaminases and gamma-glutamyl transferase, direct hyperbilirubinemia, chronic hepatobiliary disease)
- **Obstructive azoospermia**
- **Salt-loss syndromes** (acute salt depletion, chronic metabolic alkalosis, hyponatremic hypochloremic dehydration)

The diagnosis of CF is established in individuals with the following:

- One or more characteristic phenotypic features of CF

  and

- Evidence of an abnormality in cystic fibrosis transmembrane conductance regulator (CFTR) function based on **one** of the following:
  - Presence of two disease-causing mutations in the *CFTR* gene

    or
  - Two abnormal quantitative pilocarpine iontophoresis sweat chloride values (>60 mEq/L)

    or
  - Transepithelial nasal potential difference (NPD) measurements characteristic of CF

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

- 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 2002, 12.8% of newly diagnosed individuals were identified through newborn screening [CFF Patient Registry 2003].
- In utero diagnosis by presence of two disease-causing mutations in the *CFTR* gene. In 2002, 4.0% of newly diagnosed individuals were identified by prenatal diagnosis [CFF Patient Registry 2003].

Congenital absence of the vas deferens (CAVD). The diagnosis of *CFTR*-related CAVD is established in males with the following:

- Azoospermia (absence of sperm in the semen)
- 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* alleles [Dork et al 1997]

Additional features that may be seen include the following:

- A low volume of ejaculated semen (<2 mL; normal: 3-5 mL) with a specific chemical profile
- Evidence of abnormalities of seminal vesicles or vas deferens on rectal ultrasound examination

Testing

Cystic Fibrosis—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. This test is positive in more than 90% of individuals with CF.

- A minimum sweat weight of 75 mg must be collected during a 30-minute period to assure a sweat rate of 1 g/M ^{2}/min.

- A chloride concentration greater than 60 mEq/L in sweat on two separate occasions is diagnostic.

Note: Sweat chloride levels higher than 160 mEq/L are not physiologically possible and should be attributed to technical error. (2) False positive sweat chloride results may be associated with other conditions, most notably mucopolysaccharidosis type 1 (Hurler syndrome). (3) False negative sweat chloride results may occur in the setting of acute CF-related salt losses. (4) When CF is suspected in an individual with hyponatremia and hypochloremia, sweat testing should be deferred until electrolyte balance has been restored and fluid status stabilized.

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. The protocol for NPD measurements in individuals older than age six years is well described, standardized, and safely performed in many specialized CF centers worldwide [Schuler et al 2004, Standaert et al 2004].

Individuals with CF have the following:

- A raised (more negative) baseline NPD reflecting enhanced sodium absorption across a relatively chloride-impermeable membrane
- A greater change in NPD during perfusion of the nasal mucosa with amiloride, an inhibitor of sodium channel activity
- Minimal change in NPD in response to perfusion with amiloride/low chloride/beta-agonist, as a measure of cAMP-mediated chloride transport via CFTR

Newborn screening. Newborn screening using immunoreactive trypsinogen (IRT) assays performed on blood spots has been implemented in most of the United States [National Newborn Screening Status Report (pdf)]. Trypsinogen is synthesized in the pancreas; in CF, its release into the circulation appears to be enhanced by abnormal pancreatic duct secretions. Thus, IRT levels are elevated in cystic fibrosis. The benefits of newborn screening across various populations have been reviewed [Wagener et al 2004, Grosse et al 2006].

- In keeping with the use of IRT as a screening test, the definition of a positive result favors sensitivity over specificity, resulting in a decreased positive predictive value and a significant false positive rate when IRT is used by itself. Some states in the US utilize serial IRT testing to improve sensitivity and specificity [Sontag et al 2005].
- Abnormal IRT results are therefore evaluated through sweat testing and/or molecular genetic testing of *CFTR* [Gregg et al 1997, Pollitt 1998, Wilcken & Wiley 2003].

CAVD—Semen analysis. Additional findings of the semen of men with CAVD include the following [Holsclaw et al 1971]:

- Low pH (pH <7; normal: pH >8)
- Elevated citric acid concentration (>2000 mg/100 mL; normal: 400-1500 mg/100 mL)
- Elevated acid phosphatase concentration (760-1140 mμ/mL; normal: 140-290 mμ/mL)
- Low fructose concentration (30-80 mg/100 mL; normal: 250-720 mg/100 mL)
- Failure to coagulate

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory *by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.*—ED.

Molecular Genetic Testing—Gene. *CFTR* is the only gene known to be associated with the *CFTR*-related disorders, CF and CAVD.

Clinical uses

- Diagnosis in symptomatic individuals
  - With CF
  - With CAVD
- Carrier testing
  - In at-risk relatives and their reproductive partners
  - In population screening programs for CF
- Prenatal diagnosis
  - For pregnancies at increased risk for CF
  - For pregnancies in which fetal echogenic bowel has been identified
- Preimplantation genetic diagnosis for pregnancies at increased risk for CF

Clinical testing

- **Targeted mutation analysis**

Mutation panels. Several panels are available. In 2004, the American College of Medical Genetics (ACMG) decreased the recommended mutation panel from 25 to 23 mutations [Watson et al 2004]. The mutation detection rate for the 23-mutation panel (Table 8) varies with ethnic background (Table 1) [Richards et al 2002].

5T/TG tract analysis

- The poly T tract, a string of thymidine bases located in intron 8 of the *CFTR* gene, 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 considered polymorphic variants and 5T is considered a variably penetrant mutation. The 5T variant is thought to decrease the efficiency of intron 8 splicing. Poly T testing is appropriate as a reflex test when an R117H mutation is detected or an adult male is being evaluated for CAVD.
- The TG tract lies just 5' of the poly T tract. It consists of a short string of TG repeats that commonly number 11, 12, or 13. A longer TG tract (12 or 13) in conjunction with a shorter poly T tract (5T) has the strongest adverse effect on proper intron 8 splicing [Cuppens et al 1998, Groman et al 2004].
- Males with CAVD or suspected CAVD, individuals with non-classic CF, or adult carriers of 5T who wish to further refine their reproductive risks are all appropriate for 5T/TG tract typing.

Table 1 summarizes molecular genetic testing for this disorder.

Table 1. Molecular Genetic Testing Used in *CFTR*-Related Disorders

Test Method	Mutations Detected	Mutation Detection Frequency by Population Group		Test Availability
Targeted mutation analysis	*CFTR* mutations using the original 25-mutation panel [1]	Ashkenazi Jewish	97% [2]	Clinical Testing
		Non-Hispanic Caucasian	88.3% [3]	
		African American	69% [2]	
		Hispanic American	57% [2]	
		Asian American	Unknown	
Deletion analysis	*CFTR* exonic and whole-gene deletions	All populations	Unknown	
Sequence analysis	*CFTR* sequence variants	All populations	98.7% [4]	

1. The original 25-mutation panel recommended by the American College of Medical Genetics [Grody et al 2001] included the 23 mutations listed in Table 8, 1078delT, and I148T. The 23-mutation panel recommended in 2004 is expected to have a similar mutation detection rate [Watson et al 2004]. Other panels may have significantly different mutation detection rates.
2. Grody et al 2001
3. Palomaki et al 2002
4. Using an assay to sequence all the coding sequences, splice donor and acceptance sites, the promotor region, and two intronic sequences [Strom et al 2003]

Interpretation of test results used in diagnosis of individuals suspected of having CF

- For issues to consider in interpretation of sequence analysis results, click here.
- The number of abnormal alleles detected (two, one, or none) (Table 2) depends on the mutation detection rate (Table 1).

Table 2. Expected Percentage of Abnormal Alleles Detected in Individuals with CF Based on the Detection Frequency of the Test Method Used

Mutation Detection Frequency of Test Method	Percentage of Individuals with CF for which a Given Number of Abnormal Alleles is Identified		
	Two Abnormal Alleles	One Abnormal Allele	No Abnormal Allele
98%	96%	4%	0%
95%	90%	10%	0%
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%

Calculated using Hardy-Weinberg Rule

Interpretation of test results used in diagnosis of individuals suspected of having CAVD. The percentage of mutant *CFTR* alleles and 5T variant alleles detected in males with CAVD is summarized in Table 3.

Table 3. Percentage of Abnormal Alleles Detected in Males with CAVD

Number of Mutant *CFTR* Alleles		%
Other than 5T	5T	
2	0	26%
0	2	2%
1	1	26%
1	0	17%
0	1	8%
0	0	22%

Based on pooled data from Dork et al 1997, Mak et al 1999, Casals et al 2000, Wang et al 2002

Interpretation of results of CF carrier testing. It is recommended that in population screening programs cystic fibrosis carrier testing be performed using the ACMG 23-mutation panel (Table 8).

- 5T and TG tract typing should not be included in a routine carrier screen.
  - If an individual has the R117H mutation, reflex testing for the variants 5T/7T/9T is recommended.
  - If the individual has the 5T allele, family studies are recommended to determine if the 5T allele is in cis configuration or trans configuration with the R117H allele.
- The 5T/TG tract analysis is not able to provide a specific risk figure for developing symptoms or having a child who develops symptoms of non-classic CF or CAVD; it is able to assign risk as "increased" or "decreased."
  - A person with ΔF508 (Phe508del) and 5T/11TG is less likely to develop non-classic CF, but it is still possible.
  - An individual with ΔF508 and 5T/12TG or ΔF508 and 5T/13TG is more likely, though not certain, to develop CAVD or non-classic CF [Groman et al 2004].

Testing Strategy

Cystic fibrosis. In most circumstances, the following strategy is indicated:

- Quantitative pilocarpine iontophoresis for sweat chloride concentrations (remains the primary test for the diagnosis of CF, accurately diagnosing >90% of cases)
- Molecular genetic testing of *CFTR* for diagnostic purposes if sweat chloride testing is unavailable or uninformative *(CFTR* molecular genetic testing for prognostic and epidemiologic purposes is appropriate for individuals diagnosed with CF based on sweat chloride testing.)
- Transepithelial nasal potential difference (NPD) measurements to confirm the diagnosis of CF in symptomatic individuals with borderline or nondiagnostic sweat tests in whom only one or no *CFTR* disease-causing mutation has been detected

In the following special circumstances, *CFTR* molecular genetic testing is the initial diagnostic test:

- Prenatal testing in a high-risk fetus

- Prenatal diagnosis in low-risk fetus with echogenic bowel
- Newborn screening
- Symptomatic infants (i.e., those with meconium ileus) who are too young to produce adequate volumes of sweat
- Testing of symptomatic sibs of an affected individual in whom both *CFTR* mutations have been identified

CAVD. The diagnosis of CAVD is generally made in three steps:

1 **Evaluation of infertility.** A male with severe oligospermia (<5 million), azoospermia, or very low volume of semen (<2 mL) proceeds to Step 2.

2 **Clinical evaluation by a urologist.** If absence of the vas deferens is diagnosed by palpation, the workup proceeds to Step 3. (Imaging may be used but is not usually necessary if the clinical examination is consistent.)

3 **Molecular genetic testing** for *CFTR* mutations

Genetically Related (Allelic) Disorders

An increased prevalence of *CFTR* mutations has been noted in individuals with idiopathic pancreatitis, bronchiectasis, allergic bronchopulmonary aspergillosis, and chronic rhinosinusitis. The reader is referred to the following references for further information: Cohn et al 1998, Luisetti et al 1998, Mickle & Cutting 1998, Wang et al 2000, Cohn et al 2004, Cohn et al 2005, Nick & Rodman 2005, Weiss et al 2005.

At present, DNA testing is of unknown and unclear utility for these conditions.

Clinical Description

Natural History

Cystic Fibrosis—Cystic fibrosis (CF) affects the epithelia in several organs resulting in a complex, multisystem disease that includes the exocrine pancreas, intestine, respiratory tract, male genital tract, hepatobiliary system, and exocrine sweat glands. Disease expression varies by severity of *CFTR* mutations [De Braekeleer et al 1997], genetic modifiers [Drumm et al 2005, Blackman et al 2006, Vanscoy et al 2007], and environmental factors [Goss et al 2004]. The range extends from early childhood death as a result of progressive obstructive lung disease with bronchiectasis, to pancreatic insufficiency with gradually progressive obstructive lung disease during adolescence and increasing frequency of hospitalization for pulmonary disease in early adulthood, to recurrent sinusitis and bronchitis or male infertility in young adulthood.

The great majority of individuals with CF are pancreatic insufficient. Individuals with CF and 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 overall median survival is 36.5 years (95% confidence intervals, 33.7-40.0 years) [CFF Patient Registry 2006]. A gender difference is present in CF, with greater median survival in males than in females [CFF Patient Registry 1999].

Respiratory. Pulmonary disease remains the major cause of morbidity and mortality in CF [CFF Patient Registry 2006]. Affected individuals have lower airway inflammation and chronic endobronchial infection. Failure of lung defenses leads 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 15%-20% of newborns diagnosed with CF.

Pancreatic insufficiency with malabsorption occurs in the great majority of individuals with CF. Exocrine pancreatic insufficiency is caused by inspissation of secretions within the pancreatic ducts and ultimately interstitial fibrosis. The clinical manifestations are steatorrhea and poor growth related to fat malabsorption and hemolytic anemia, defective coagulation, or skin rashes related to deficiencies of fat-soluble vitamins and zinc. Acute or chronic recurrent pancreatitis can be a presenting manifestation of CF, and is much more common among those with pancreatic sufficiency (10% prevalence) than those with pancreatic insufficiency (0.5% prevalence) [De Boeck et al 2005].

Cystic fibrosis-related diabetes mellitus (CFRDM) may present in adolescence. It is diagnosed in 7% of those age 11 to 17 years [CFF Patient Registry 2006]. The prevalence increases in adulthood. 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 serum concentration of liver enzymes in school-age children, infrequently progresses to biliary cirrhosis in adolescents and adults. Prevalence of liver disease varies based on definition, with the overall rate reported as 6.1% in the 2003 CFF Patient Registry. As liver disease progresses, portal hypertension and varices develop. Liver disease is second to pulmonary disease (plus organ transplantation complications) as a cause of mortality in CF (1.7% of deaths) [CFF Patient Registry 2003].

Fertility. More than 95% of males with CF are infertile as a result of azoospermia caused by altered vas deferens, 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 that may contribute to infertility. The rate of live births among females with CF age 13-45 years is 1.9 per 100 [CFF Patient Registry 2003].

Pregnancy. The survival of individuals with CF has improved considerably over the past few decades. Currently, the average median survival is approximately 37 years and pregnancy in women 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 have been 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 improved 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, Gillet et al 2002, Cheng et al 2006]. In these women, the risk factors for

deteriorating health and early death after pregnancy are the same as for the non-pregnant adult population. In a recent study, Goss et al (2003) adjusted for FEV(1) percent predicted, weight, height, and pulmonary exacerbation rate per year and found that pregnancy was not associated with an increased risk of death. In fact, pregnancy did not appear to be harmful even in a subset of women with diabetes mellitus or with FEV(1) less than 40% of predicted. Important predictors of pregnancy outcome for the fetus are the severity of maternal pulmonary impairment and nutritional status, in that deterioration during pregnancy may precipitate preterm delivery.

The risk for congenital anomalies in the fetus is not increased over background.

Breastfeeding is possible.

Congenital Absence of the Vas Deferens (CAVD)—Men without clinically apparent pulmonary or gastrointestinal manifestations of CF may have CAVD. Hypoplasia or aplasia of the vas deferens and seminal vesicles may occur either bilaterally or unilaterally. CAVD does not pose a health risk per se to the affected male. Testicular development and function and spermatogenesis are usually normal.

CAVD is generally identified during evaluation of infertility or as an incidental finding at the time of a surgical procedure, such as orchidopexy.

Genotype-Phenotype Correlations

Probands—Cystic fibrosis. The best correlation between genotype and phenotype is seen in the context of pancreatic function. The most common mutations have been classified as pancreatic sufficient or pancreatic insufficient. Individuals with pancreatic sufficiency usually have either one or two PS alleles, indicating that PS alleles are dominant with respect to pancreatic phenotype.

In contrast, genotype-phenotype correlation is generally poor for pulmonary disease in CF. Pulmonary disease among individuals with identical genotypes varies widely, a finding that may be accounted for in part by genetic modifiers or environmental factors (see Cutting 2005, Drumm et al 2005, Braun et al 2006).

- Compound heterozygotes with the ΔF508/A455E mutations have better pulmonary function than individuals who are homozygous for ΔF508 [De Braekeleer et al 1997].
- The severity of lung disease in individuals with one or two R117H mutations depends on the presence of a variation in the poly T tract of intron 8 [Massie et al 2001]. Individuals with a *CFTR* disease-causing mutation plus the 5T variant in cis configuration with the R117H mutation usually develop the lung disease of CF, but those individuals with R117H and the 7T variant or the 9T variant have a highly variable phenotype that can range from no symptoms to mild lung disease [Kiesewetter et al 1993, Chmiel et al 1999].
- Because A455E and R117H mutations are associated with pancreatic sufficiency, the less severe lung disease seen in individuals with these mutations could be the consequence of better nutritional status.

CAVD. CAVD usually results from the combination of one severe CF mutation on one chromosome with either a mild CF mutation or the 5T allele on the other chromosome (Table 3). However, some overlap exists between the CAVD phenotype and a very mild CF phenotype, with some fraction of individuals with CAVD also reporting respiratory or pancreatic problems [Dork et al 1997,Gilljam et al 2004]. Moreover, the 5T allele may be associated with lung

disease in adult females with CF-like symptoms [Noone et al 2000]. Thus, caution must be exercised in attempting to use genotype to predict the future course of individuals initially diagnosed with CAVD only.

At-risk individuals. Genotype-phenotype correlations are most relevant for genetic counseling of two carriers who have not had an affected child but who have been detected either through evaluation of at-risk family members or screening programs. The considerations in predicting the phenotype of potential offspring are the same as described above for probands with CF or CAVD.

- In general, prediction of severity of pancreatic disease on the basis of genotype is most reliable, while prediction of the severity of respiratory disease is less reliable.
- Prediction of the risk of CAVD from genotype is reasonably reliable, but couples should be aware that mild respiratory and/or pancreatic disease can also occur in individuals with genotypes usually associated with CAVD. The mechanism of partial penetrance of the 5T allele for CAVD appears to be variation in the length of the adjacent TG tract (estimated at 60% in one study) [Groman et al 2004] (see Table 4).

Table 4. Genotype-Phenotype Correlations

CFTR Genotype [1]		Range of Phenotypes [2]
First Allele	Second Allele (or Homozygous)	
Classic (e.g., ΔF508)	Classic	Classic >> non-classic
Mild (e.g., A455E)	Classic or mild	Non-classic > classic
R117H/5T	Classic or mild	Non-classic > classic
R117H/7T	Classic or mild	Asymptomatic female or CAVD > non-classic
5T/TG13 or TG12	Classic or mild	CAVD or non-classic CF >> asymptomatic carrier
5T/TG11	Classic or mild	Asymptomatic > CAVD
7T or 9T	Classic or mild	Asymptomatic
7T or 9T	7T or 9T	Asymptomatic

1. Patterns reflect dominant effect of "milder" alleles in compound heterozygotes. Classic alleles generally refer to Class I-III mutations; mild alleles refer to Class IV-V mutations exclusive of R117H and 5T alleles (see Table 10).

2. Data derived from Kiesewetter et al 1993, Witt et al 1996, Brock et al 1998, Cuppens et al 1998, Mak et al 1999, Wang et al 2002, McKone et al 2003, Groman et al 2004

Nomenclature

Outdated or alternative nomenclature for cystic fibrosis appears in the literature very infrequently.

- In Europe, CF is sometimes referred to as mucoviscidosis.
- "Atypical CF" is still used to denote mild CF or CF-like illness. Use of this confusing term is strongly discouraged; it should be replaced with classic CF versus non-classic CF.

Prevalence

CF is the most common life-limiting autosomal recessive disorder in the Caucasian population. The disease incidence is 1:3200 live births among Caucasians [Rosenstein & Cutting 1998]. Approximately 30,000 affected persons live in the US.

CF occurs with lower frequency in other ethnic and racial populations (1:15,000 African-Americans, and 1:31,000 Asian Americans) [Rosenstein & Cutting 1998].

In the Caucasian population, the heterozygote frequency is one in 22-28 (see Table 5).

Table 5. Carrier Frequency for Mutant *CFTR* Alleles

Population Group	Approximate Carrier Frequency	Reference
Ashkenazi Jewish	1:29	Kerem et al 1997
North American Caucasian	1:28	Hamosh et al 1998
African American	1:61	Hamosh et al 1998

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Disorders in the differential diagnosis of cystic fibrosis (CF) include the following:

- **Dysphagia with chronic descending tracheal aspiration** and **gastroesophageal reflux (GER) with or without ascending tracheal aspiration**
  - **Similarities.** Chronic cough in infancy; may be associated with failure to thrive; either of these conditions may present as secondary complications in individuals with CF lung disease during infancy, or in the case of GER, later in childhood.
  - **Differences.** Chronic aspiration is typically associated with focal densities in the lower lobe of the right lung; cough is often temporally associated with feedings; steatorrhea is not associated with primary dysphagia and primary GER.
- **Immunologic abnormalities (especially severe combined immunodeficiency)**
  - **Similarities.** May present with recurrent respiratory infections and chronic diarrhea in infancy
  - **Differences.** These individuals are also prone to non-respiratory infections (e.g., otitis media, cellulitis) not specifically associated with CF.
- **Airway anomalies**
  - **Similarities.** Chronic cough and wheezing during infancy
  - **Differences.** GI or nutritional manifestations that are typically present in individuals with CF with respiratory symptoms during infancy are not associated with these anomalies.
- **Primary ciliary dyskinesia (PCD)**
  - **Similarities.** Cough and sputum production during infancy; *Pseudomonas aeruginosa* or other opportunistic bacterial pathogens may be cultured from airway secretions; chronic sinus disease; may progress to chronic bronchiectasis.
  - **Differences.** Situs inversus occurs in about 50% of persons with PCD; steatorrhea and failure to thrive are not associated with PCD; associated with mutations in multiple genes encoding different structural components of cilia.

- **Shwachman-Diamond syndrome** (congenital lipomatosis of pancreas; Shwachman-Bodian syndrome; Shwachman-Bodian-Diamond syndrome)
  - **Similarities.** Pancreatic insufficiency, steatorrhea, and failure to thrive; respiratory symptoms may occur during infancy as a result of hypoplasia of the chest wall.
  - **Differences.** Chronic neutropenia, anemia, thrombocytopenia, or pancytopenia; additional hematologic abnormalities (myelodysplasia) with increased risk of leukemic transformation; skeletal abnormalities (metaphyseal dysostosis type); caused by autosomal recessive mutation of the *SBDS* gene.
- **Biliary atresia**
  - **Similarities.** Rarely, individuals with CF may present in infancy with symptoms of biliary obstruction, but without other clinically apparent GI or respiratory manifestations.
  - **Differences.** Serum levels of immunoreactive trypsinogen and stool levels of elastase should be normal in primary biliary atresia, whereas CF liver disease is invariably associated with evidence of pancreatic duct obstruction.

Recent investigations have shown that mutations at genetic loci other than *CFTR* can produce CF-like phenotypes that are clinically indistinguishable from non-classic CF caused by *CFTR* mutations [Groman et al 2002]. For example, mutations in the gene encoding the beta subunit of the epithelial sodium channel can mimic CFTR deficiency [Sheridan et al 2005].

Disorders in the differential diagnosis of CAVD. CAVD accounts for 1.2%-1.7% of male infertility. Approximately 80% of men with CAVD have at least one mutation in *CFTR* [Mak et al 1999].

CAVD may be part of a syndrome or may be an isolated finding.

CAVD is part of the differential diagnosis of obstructive azoospermia, caused by obstruction to sperm outflow from the testes or ductular system. Syndromes with obstructive azoospermia include the following:

- Young syndrome, a progressive obstruction of the epididymis by inspissated secretions in males with chronic sinopulmonary infection. Males with Young syndrome do not have malformations of the vas deferens or epididymis. Genetic testing of individuals with Young syndrome indicates that this disorder is not associated with *CFTR* mutant alleles and thus is probably not an alternative presentation of CAVD [Friedman et al 1995].
- 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.

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with cystic fibrosis (CF), the following evaluations are recommended:

Pancreatic insufficiency

- Fecal elastase (most helpful)
- Fecal fat content based on 72-hour stool collection
- Vitamin A, D, and E serum concentrations
- Prothrombin time and international normalized ratio (INR)
- Serum carotene concentration in children older than age six months
- Esophago-gastro-duodenoscopy (EGD) with pancreatic duct cannulation, to measure stimulated enzyme secretion (available at some research centers)

Upper and lower respiratory tracts

- Sinus CT to assess for pansinusitis in individuals with non-classic presentations or intermediate sweat tests
- Pulmonary function testing (including infant PFTs at specialized centers)
- Chest x-ray or possibly chest computed tomography (CT)
- Sputum culture in patients who can expectorate a sputum sample, or culture of deep oropharyngeal swab in those who cannot
- Bronchoscopy with bronchoalveolar lavage to evaluate lower airway microbiology and inflammation

Overall clinical status / extent of disease

- CBC with differential cell count
- Serum electrolytes, BUN, creatinine, random glucose
- ALT, gamma-glutamyltransferase
- Urinalysis

Treatment of Manifestations

Respiratory

- 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; Gibson, Burns et al 2003; Bradley et al 2006].
- Lung or heart/lung transplantation is an option for selected individuals 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 and sometimes zinc to prevent the development of deficiencies. Among persons with CF age two to 20 years with body-mass index (BMI) less than 50th percentile followed at CF centers in the US, about 62% receive routine nutritional supplementation, often via an indwelling gastric feeding catheter; the comparable use of nutritional supplements among persons with CF age 20 years or older is 44.5% [CFF Patient Registry 2006].

- Pancreatic insufficiency is treated with oral pancreatic enzyme replacement with meals.
- Biliary sludging or frank obstruction, and associated hepatic inflammation, are treated with oral ursodiol.

Endocrine

- CF-related diabetes mellitus (CFRD) may develop during teenage years or later. This form of diabetes mellitus is distinct from both juvenile-onset (type I) and adult-onset (type II) diabetes mellitus; however, some affected individuals do require routine insulin therapy for optimal management [Onady & Stolfi 2005].
- Casual (random) glucose levels are measured annually in individuals with CF as part of routine management starting at age ten years [Allen et al 1998].
  - If this level is below 126 mg/dL (7.0 mM), it is unlikely that fasting hyperglycemia is present and no further work-up is necessary unless symptoms of CFRD are present.
  - Fasting glucose levels should be measured on all individuals with casual glucose levels ≥126 mg/dL (7.0 mM). A fasting glucose level ≥126 mg/dL (7.0 mM) is diagnostic for CFRD with fasting hyperglycemia when confirmed by a second fasting glucose test or if it occurs in association with a casual glucose level >200 mg/dL (11.1 mM).
  - In individuals with fasting glucose below 126 mg/dL but possible symptoms of diabetes mellitus, an oral glucose tolerance test (OGTT), in which plasma glucose is measured two hours after an oral glucose load of 1.75 g/kg, or 75 g maximum, should be strongly considered to distinguish among normal glucose tolerance (2-hr glucose level <140 mg/dL), impaired glucose tolerance (2-hr glucose level 140-199 mg/dL), and CFRD without fasting hyperglycemia (2-hr glucose level≥200 mg/dL) [Moran et al 1999].
- Input from endocrinology consultants in the management of CFRD is recommended.

Pregnancy

- Ideally, a woman with CF of reproductive age should receive preconception counseling and take steps to optimize her health prior to pregnancy.
- The management of pregnancy for a woman with CF requires a multidisciplinary team that includes a dietician, members of the CF team, and an obstetrician.
- Maternal nutritional status and weight gain should be monitored and optimized aggressively and pulmonary exacerbations should be treated early.
- The improved survival of women with CF has resulted in an increasing number of women with CFRD contemplating pregnancy. As in pregnancies of women with other forms of diabetes mellitus, fetal outcome is optimized when glycemic control is achieved prior to pregnancy.
- Traditional screening paradigms for gestational diabetes mellitus are not useful in pregnancies of women with CF; therefore, screening at each trimester of pregnancy has been suggested to improve the detection of diabetes mellitus.
- Only one pregnancy following lung transplantation in a woman with CF has been reported to date [Gyi et al 2006].

CAVD. The main issues relate to management of infertility that results from obstruction of sperm outflow through the ductal system. Assisted reproductive technologies (ART) to manage infertility include microscopic sperm aspiration from the epididymal remnant in conjunction with in vitro fertilization or artificial insemination using donor sperm.

Physical activity, exercise, and conditioning. A regular exercise program is important to all individuals in maintaining overall health. For persons with CF, regular exercise has the added benefits of maintaining bone health and improving airway clearance. Although exercise improves clearance of airway secretions, it should be used more as an adjunct rather than as a replacement for the individual's prescribed airway clearance regimen.

Prevention of Primary Manifestations

Pancreatic insufficiency and malnutrition. Historically (i.e., in the era prior to newborn screening), about half of all patients with CF presented with failure to thrive and/or steatorrhea during infancy. If untreated, this would typically progress to hypoproteinemia, edema, and severe cachexia. These primary nutritional manifestations of CF can be prevented through prompt institution of pancreatic enzyme replacement and supplementation of fat-soluble vitamins in CF patients with evidence of pancreatic insufficiency. In addition, some patients benefit from high-calorie, high-fat nutritional supplements, which may be recommended based on consultation with a nutritionist specializing in CF.

Biliary cirrhosis. Individuals with CF are also at risk for biliary sludging and obstruction, the first indications of which may be elevation of hepatic enzymes such as gamma-glutamyl transferase (GGT) and amino-acid transaminases (ALT and AST). Individuals with higher levels of endogenous ursodeoxycholic acid appear to be at lower risk for progression to CF liver disease [Smith et al 2004], and chronic oral administration of exogenous ursodiol can reverse focal biliary obstruction at least transiently [Nousia-Arvanitakis et al 2001]. However, whether chronic ursodiol therapy can prevent progression to biliary cirrhosis in the subset of CF patients who are at risk for this complication is uncertain [Brigman & Feranchak 2006].

Prevention of Secondary Complications

Airway clearance

- Chest physiotherapy (CPT), which can be accomplished through a variety of airway clearance techniques (ACTs), is used to mobilize airway secretions, thereby minimizing the development of airway obstruction as well as the risk of acute exacerbations of airway infection. Several different ACTs are recognized as effective, including manual chest percussion with postural drainage, hand-held devices (e.g., flutter valve, or Acapella®), and inflatable vest therapy devices that vibrate the chest wall. These treatments are most effective when performed at least twice daily.
- Additional therapies that are helpful in mobilizing airway secretions include once-daily inhalation of DNase (dornase alfa), a mucolytic that can increase cough productivity during CPT. In addition, inhalation of hypertonic saline (3%-7%) has recently been introduced as a maintenance "airway hydration" therapy in patients with CF [Donaldson et al 2006, Elkins et al 2006].
- CPT is typically performed in conjunction with administration of any inhaled medications that have been prescribed, given in a standard sequence:

Before CPT

1. Bronchodilator
2. Hypertonic saline

3 DNase

After CPT

4 Inhaled corticosteroid and/or long-acting beta-agonist

5 Inhaled antibiotics

The rationale for this sequence is to open the airway, decrease sputum viscosity, promote expectoration of secretions, and then deliver anti-inflammatory treatments and/or antibiotics as widely and deeply as possible within the bronchial tree.

Eradication of initial airway infection and prevention of chronic airway infection. The clinical approach to initial CF airway infection has intensified over the past 20 years, with many CF care providers now advocating aggressive antibiotic treatment at the time of first isolation of *Pseudomonas aeruginosa* from cultured airway secretions. The goal of such treatment is eradication of the initial *P. aeruginosa* infection and prevention of chronic *P. aeruginosa* airway infection. Clinical trials of various regimens of inhaled and oral antibiotics have indicated that this organism may be rendered at least transiently undetectable in airway secretions in most cases of initial infection, although recrudescence or re-infection is a common occurrence [Littlewood et al 1985; Frederiksen et al 1997; Gibson, Emerson et al 2003; Gibson et al 2007] (see Therapies Under Investigation).

Immunization

- All routine immunizations should be given at the recommended times.
  - Especially important are vaccines that protect against microorganisms associated with pulmonary manifestations, including pertussis, measles, varicella, *Haemophilus influenzae* type B, and *Streptococcus pneumoniae*.
  - Influenza vaccine should be administered each year as well.

    Note: (1) Because the influenza vaccine may not be fully protective, some experts recommend immunizing a patient's entire family. (2) Some CF care providers prescribe anti-viral medications targeted toward influenza A and B for patients to keep on hand. Patients are instructed to take these medications promptly at the first sign of fever and cough during influenza season.
- Most children now receive the heptavalent conjugated pneumococcal vaccine (Prevnar®); administration of the 23-valent polysaccharide pneumococcal vaccine (Pneumovax®) later in childhood or adulthood is more controversial because pneumococcal pneumonia is uncommon in CF. However, considering the risks/benefits of vaccine administration and the increased incidence of resistant organisms in CF, its use is reasonable.
- Infection with respiratory syncytial virus (RSV) is an especially serious problem in younger patients with CF. Unfortunately, there is no safe and effective vaccine. Passive immunization with an anti-RSV monoclonal antibody (Synagis®) is available; however, this requires monthly subcutaneous injections for the duration of the local RSV season, and no convincing studies have been published to demonstrate efficacy (or lack thereof) in treating CF. Pending the availability of such data, passive immunization of young CF patients against RSV is considered by many CF care providers.

Surveillance

Respiratory

- Patients should have regularly scheduled visits to their CF care providers to monitor for subtle changes in physical examination that are not yet manifest as symptoms.
- Patients who are not yet chronically infected with *P. aeruginosa* should have cultures of respiratory tract secretions at least four times yearly. Some patients may benefit from more frequent visits and respiratory tract surveillance cultures (see Therapies Under Investigation).
- Affected individuals are regularly followed with pulmonary function studies, chest radiographs, and specific blood and urine laboratory tests.

Gastrointestinal/Endocrine

- There are also increased risks of osteopenia related to vitamin D and calcium deficiencies that require screening of bone density starting in adolescence.
- Casual (random) glucose levels are measured annually in individuals with CF as part of routine management starting at age ten years [Allen et al 1998]. Casual glucose levels ≥126 mg/dL (7.0 mM) require further evaluation (see Treatment of Manifestations).

Agents/Circumstances to Avoid

- Respiratory irritants (smoke, dust)
- Respiratory infectious agents (especially respiratory viruses)
- Dehydration (need to add extra salt to diet in hot, dry climates because of perspiration-related salt losses)

Testing of Relatives at Risk

Sweat chloride testing of sibs and mothers of affected individuals to determine if they may have mild or not yet symptomatic forms of CF is appropriate.

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

Therapies Under Investigation

Currently, studies are being performed in Europe and the United States to assess whether chronic respiratory tract infection can indeed be delayed, and if so, which antibiotic agents are most effective for this purpose.

- Continuous prophylactic antibiotic treatment for *Staphylococcus aureus* has not been shown to reduce the deterioration in lung function.
- One multicenter trial of continuous cephalexin administration demonstrated increased acquisition of *P. aeruginosa* in treated patients [Stutman et al 2002].
- Large multicenter randomized controlled trials are now underway to determine optimal strategies and regimens for eradication of *P. aeruginosa* and prevention of chronic infection.

New therapies for the treatment of cystic fibrosis lung disease that span the pathophysiologic cascade of CF are being investigated. 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 [Kerem 2005], use of small molecular modulators of CFTR [Verkman et al 2006], new anti-inflammatory agents, new IV and inhaled antibiotics, and antiproteases.

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 [Anson et al 2006].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Other

There has been much interest in developing active and passive immunization strategies against *Pseudomonas aeruginosa*. However, an effective vaccine against *P. aeruginosa* has not yet been developed.

Genetics clinics are a source of information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section (below) may include disease-specific and/or umbrella support organizations.

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, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory.

Mode of Inheritance

CFTR-related disorders are inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband with cystic fibrosis (CF)

- The unaffected parents are obligate carriers (heterozygotes) and have an alteration in one copy of the *CFTR* gene.
  - If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test parents by molecular genetic testing.
- Carriers are generally asymptomatic.
- On rare occasions, a parent may be diagnosed as affected subsequent to the diagnosis of the child.

Sibs of a proband with CF

- At conception, each full sib of an affected individual has a 25% chance of being affected, a 50% chance of being an asymptomatic 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.

- For an at-risk sib who is known to be unaffected but has not yet undergone molecular genetic testing, the risk of being a carrier is 2/3.
  - If the disease-causing *CFTR* alleles have been identified in the proband, it is most informative to test sibs by molecular genetic testing.
- Carriers are asymptomatic.

Offspring of a female proband with CF

- Females with CF can be 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 on her reproductive partner's carrier status. *CFTR* molecular genetic testing should be offered to her reproductive partner to determine his carrier status. The specific molecular genetic testing panel that is used should be based on the reproductive partner's ethnicity and family history.
  - If the reproductive partner is a carrier, the offspring will be at risk for CF or CAVD.

Offspring of a male proband with CF

- Males with CF may conceive children through assisted reproductive technologies (ART).
  - An affected male will transmit one mutant *CFTR* allele to each of his offspring.
  - The risk that his child will inherit a second disease-causing *CFTR* allele depends on his reproductive partner's carrier status. *CFTR* molecular genetic testing should be offered to his reproductive partner to determine her *CFTR* carrier status. The specific molecular genetic testing panel that is used should be based on the reproductive partner's ethnicity and family history.
  - If the reproductive partner is a carrier, the offspring will be at risk for CF or CAVD

Parents, sibs, and offspring of a proband with CAVD

- Males with CAVD may conceive children through assisted reproductive technologies (ART).
- The risk to the relatives of a proband with CAVD depends on the parental genotypes and cannot readily be predicted without this information.
- Molecular genetic testing is most informative when the CAVD-causing *CFTR* alleles have been identified in the proband. Men with CAVD sometimes have only one identifiable *CFTR* mutation, complicating the testing and interpretation of results in their family members.

Other family members. Each sib of a known *CFTR* mutation carrier is at a 50% risk of being a carrier. Even if the carrier has no known affected sibs, a residual risk remains that both parents could be carriers and thus could conceive an affected offspring.

Carrier Detection

The following situations may arise when carrier detection is pursued for at-risk relatives of individuals with CF or CAVD and their reproductive partners:

- **Both disease-causing alleles of a proband are known.** If both disease-causing alleles have been identified in the proband, the at-risk maternal and paternal relatives can be tested for their family-specific mutation following genetic counseling.
- **Only one disease-causing allele of a proband is known.** As mutation detection rates improve, one should consider performing additional molecular genetic testing for identifiable mutations in probands. Molecular genetic testing should be informative for relatives related through the parent with the identifiable mutation. Molecular genetic testing will not be informative for relatives related through the carrier parent who does not have an identifiable mutation if the relatives are only tested for mutations in the proband's test panel. Linkage analysis may be helpful for these relatives.
- **Neither disease-causing allele of a proband is known.** As mutation detection rates improve, one should consider performing additional molecular genetic testing for identifiable mutations in probands. Molecular genetic testing of relatives will not be informative if the relatives are only tested for mutations in the proband's test panel. Linkage analysis may be helpful for these relatives.

Table 6. Residual Risk (%) of a Relative Being a *CFTR* Mutation Carrier if Molecular Genetic Testing Does Not Detect a Mutation

Prior Risk of Being a Carrier	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. Unaffected sib of a proband
2. Unaffected sib of a carrier
3. Unaffected cousin of a proband

Click here (Table 6a) for residual risk of being a carrier for other values of prior risk.

- **Cis configuration and trans configuration of 5T variant with a disease-causing allele is not known.** Additional family members may need molecular genetic testing to establish phase for informative interpretation of results.
- **A person has a reproductive 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 molecular genetic testing to the reproductive partners of those who are found to be carriers, with the understanding that failure to detect a mutation reduces but does not eliminate the risk of being a carrier (See Table 7).

Related Genetic Counseling Issues

Family planning. The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal testing is before pregnancy.

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). The ACMG Subcommittee on Cystic Fibrosis Screening recommends that CF carrier screening be offered to non-Jewish Caucasians and Ashkenazi

Jews, and made available to other ethnic and racial groups through appropriate counseling regarding risks, testing options, detection rates, and informed consent. The Committee recommends use of a pan ethnic, 23-mutation panel that includes the majority of CF-causing mutations with an allele frequency of greater than 0.1% in the general US population (Table 8) [Watson et al 2004]. Screening panels may be supplemented with other mutations to improve sensitivity for specific ethnic groups. Implementation of population-based newborn screening programs for CF generally includes plans to address increased demands on genetic counseling resources.

Carrier testing at the time of newborn screening follow-up. Lagoe et al (2005) found that providing genetic counseling and offering carrier testing to parents at the time their newborn was undergoing sweat testing for a positive newborn screening result led to greater use of these services than when parents were offered genetic counseling and carrier testing by phone at the time the sweat tests results were relayed.

5T/TG tract. The 5T/TG tract analysis should not be included in a routine carrier screen. It is an appropriate test in males with CAVD or suspected CAVD, individuals with non-classic CF, or adult carriers of 5T who wish to further define their reproductive risks. 5T/TG tract analysis can increase or decrease risk, but no specific risk figures are associated with test results.

Residual risk after carrier testing. Individuals with no family history of CF who test negative for a panel of *CFTR* mutations can have their carrier risk reduced (though not eliminated) based on their ethnicity. The residual risk of being a carrier depends on the carrier frequency and the mutation detection rate. Table 7 provides calculations of residual risk based on the mutation detection rate of the test method used and the individual's a priori risk of being a carrier. For example, an individual with no known family history of CF has a 1/30 a priori risk of being a carrier. If the individual does not have one of the mutations in a test panel with a mutation detection rate of 95%, his/her (residual) risk of being a carrier is 1/500.

Table 7. Residual Risk (%) of an Individual with No Family History of a *CFTR*-Related Disorder of Being a *CFTR* Mutation Carrier if Molecular Genetic Testing Does Not Detect a Mutation

Prior Risk of Being a Carrier	Mutation Detection Rate									
	30%	40%	50%	60%	70%	75%	80%	85%	90%	95%
1/28 (3.57%)	2.5%	2.2%	1.8%	1.5%	1.1%	0.9%	0.7%	0.6%	0.4%	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%

DNA banking. DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, mutations, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals. DNA banking is particularly relevant when the sensitivity of currently available testing is less than 100%. See Testing for a list of laboratories offering DNA banking.

Prenatal Testing

High-risk pregnancies. Prenatal testing for pregnancies at increased risk is possible by molecular genetic testing of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15-18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing mutations of the *CFTR* gene must be identified in both parents before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

Indeterminate-risk pregnancies. When 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 to clarify the status of the fetus is available. 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 & Abuhamad 1996, Ghose et al 2000]. 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. Based on the mutation detection rate of the test method used, 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].

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutations have been identified. This requires coordination between the genetic counselor, specialists in reproductive endocrinology and fertility (REI), and the molecular genetics laboratory. For laboratories offering PGD, see Testing.

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of CFTR-Related Disorders

Gene Symbol	Chromosomal Locus	Protein Name
CFTR	7q31.2	Cystic fibrosis transmembrane conductance regulator

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

Table B. OMIM Entries for CFTR-Related Disorders

219700	CYSTIC FIBROSIS; CF
277180	VAS DEFERENS, CONGENITAL BILATERAL APLASIA OF; CBAVD
602421	CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR; CFTR

Table C. Genomic Databases for CFTR-Related Disorders

Gene Symbol	Locus Specific	Entrez Gene	HGMD
CFTR	CFTR	1080 (MIM No. 602421)	CFTR

For a description of the genomic databases listed, click here.

Note: HGMD requires registration.

Normal allelic variants: The *CFTR* gene is 230 kb long and contains 27 coding exons. It produces a 6.5-kb mRNA product.

Pathologic allelic variants: More than 1000 mutations are known; almost all are point mutations or small (1-84 bp) deletions. The most common mutation is ΔF508 (Phe508del), accounting for an estimated 30%-80% (depending on the ethnic group) of mutant alleles. Table 8 lists the panel of 23 alleles recommended by the American College of Medical Genetics for routine diagnostic and carrier testing [Watson et al 2004]. Table 9 lists ten of the most common *CFTR* mutations and shows their most typical phenotypic effect when present in affected individuals.

Table 8. Recommended Core Mutation Panel for General Population CF Carrier Screening

3120+1G>A	A455E	G85E	R334W	1717-1G>A
3659delC	ΔF508	R347P	1898+1G>A	3849+10kbC>T
ΔI507	N1303K	R553X	2184delA	621+1G>T
G542X	R1162X	R560T	2789+5G>A	711+1G>T
G551D	R117H	W1282X		

Table 9. Ten Most Common *CFTR* Mutations in Caucasians with Related Phenotypic Expression

Mutation	Relative Frequency	Mutation Functional Class [1]	Phenotype [2]
ΔF508	66.0%	II	Classic [3]
G542X	2.4%	I	
G551D	1.6%	III	
N1303Lys	1.3%	II	
W1282X	1.2%	I	
R553X	0.7%	I	
621+1G>T	0.7%	I	
1717-1G>A	0.6%	I	
R117H	0.3%	IV	Non-classic
R1162X	0.3%	Not clear [4]	Classic

Based on www.genet.sickkids.on.ca and McKone et al (2003)

1. See Table 10 below.

2. At a recent European Cystic Fibrosis Society Consensus Conference (*Interpretation of Genetic Analysis for CF*, Garda Lake, Italy, March 23-24, 2007), it was decided that mutation class is useful from a molecular biology perspective but that it should not be used clinically. A manuscript summarizing the results of this consensus conference is in preparation [Garry R Cutting, personal communication].

3. There are numerous exceptions to the correlation between mutation effect and phenotype (e.g., A455E is Class II but associated with mild lung disease and pancreatic sufficiency).

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

Normal gene product: Cystic fibrosis transmembrane conductance regulator (CFTR) is 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 10 provides one classification scheme for the functional consequences of *CFTR* mutations.

Table 10. 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 & Tsui 1995 (Figure 3) and Welsh et al 2001

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. Information that appears in the Resources section of a GeneReview is current as of initial posting or most recent update of the GeneReview. Search GeneTests*for this disorder and select* Resources *for the most up-to-date Resources information.*—ED.

Canadian Cystic Fibrosis Foundation
2221 Yonge Street Suite 601
Toronto M4S 2B4
Canada
Phone: 800-378-2233 (Toll free from Canada only); 416-485-9149
Fax: 416-485-0960
Email: info@cysticfibrosis.ca
www.ccff.ca

Cystic Fibrosis Foundation
6931 Arlington Road 2nd Floor
Bethesda MD 20814-5200
Phone: 800-FIGHTCF (800-344-4823); 301-951-4422
Fax: 301-951-6378
Email: info@cff.org
www.cff.org

Medline Plus
Cystic Fibrosis

National Library of Medicine Genetics Home Reference
Cystic fibrosis

NCBI Genes and Disease
Cystic fibrosis

Cystic Fibrosis Foundation Patient Registry Annual Report
CF Foundation Patient Registry

Genetic Diseases Of Mucocilliary Clearance Consortium Registry
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Genetic Diseases Of Mucocilliary Clearance Consortium Registry

Teaching Case-Genetic Tools

Cases designed for teaching genetics in the primary care setting.

Case 12. Failure to Thrive: Workup Results in Diagnosis of Cystic Fibrosis

Case 13. Parents Concerned about Risk of Having a Child with Cystic Fibrosis

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Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. PubMed

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Chapter Notes

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Revision History

- 19 February 2008 (me) Comprehensive update posted to live Web site
- 24 August 2005 (cd) Revision: changes to ACMG-recommended mutation panel
- 24 August 2004 (me) Comprehensive update posted to live Web site
- 26 March 2001 (me) Review posted to live Web site
- 6 October 1998 (jt) Original submission

Table 6a. 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
1/8 (12.5%)	9.1	7.9	6.7	5.4	4.1	3.4	2.8	2.1	1.4	0.7
1/16 (6.3%)	4.5	3.8	3.2	2.6	2.0	1.6	1.3	1.0	0.7	0.3
1/20 (5.0%)	3.6	3.1	2.6	2.1	1.6	1.3	1.0	0.8	0.5	0.3
1/25 (4.0%)	2.8	2.4	2.0	1.6	1.2	1.0	0.8	0.6	0.4	0.2
1/30 (3.3%)	2.4	2.0	1.7	1.4	1.0	0.9	0.7	0.5	0.3	0.2
1/35 (2.9%)	2.0	1.7	1.4	1.2	0.9	0.7	0.6	0.4	0.3	0.1
1/40 (2.5%)	1.8	1.5	1.3	1.0	0.8	0.6	0.5	0.4	0.3	0.1
1/50 (2.0%)	1.4	1.2	1.0	0.8	0.6	0.5	0.4	0.3	0.2	0.1
1/60 (1.7%)	1.2	1.0	0.8	0.7	0.5	0.4	0.3	0.3	0.2	0.1
1/70 (1.4%)	1.0	0.9	0.7	0.6	0.4	0.4	0.3	0.2	0.1	0.1
1/80 (1.3%)	0.9	0.8	0.6	0.5	0.4	0.3	0.3	0.2	0.1	0.1
1/90 (1.1%)	0.8	0.7	0.6	0.4	0.3	0.3	0.2	0.2	0.1	0.1
1/100 (1.0%)	0.7	0.6	0.5	0.4	0.3	0.3	0.2	0.2	0.1	0.1

Last update: 3-23-01

1. sib of proband
2. sib of parent
3. cousin of proband