# Genomic Breakthroughs in the Diagnosis and Treatment of Cystic Fibrosis

The nursing implications of recent genetic discoveries and technologic advances.

**OVERVIEW:** Cystic fibrosis (CF) is an autosomal recessive disorder that was long considered a terminal illness. Recent genetic discoveries and genomic innovations, however, have transformed the diagnosis, classification, and treatment of this multisystem condition. For affected patients, these breakthroughs offer hope for significantly greater longevity and quality of life and, perhaps, for a future cure. This article reviews empirical research on CF, filling a critical gap in the nursing literature regarding recent findings in the study of CF genetics and their implications for patient teaching, diagnosis, and treatment.

**Keywords:** cystic fibrosis, cystic fibrosis transmembrane conductance regulator gene, genetics, genomics, patient education

Cystic fibrosis (CF) is the second most common potentially life-shortening genetic disorder affecting U.S. children.[1] Like sickle cell disease, the most common serious inherited disorder of childhood onset, CF is an autosomal recessive disorder. Although CF occurs in most racial and ethnic groups, it is most common among white Americans, with an incidence of one per 2,500 live births in this population, and both ethnic and geographic distribution vary widely (see Table 1[1-3]).[4-6] Currently, there is no cure for CF, but recent advances in genomic technology have given rise to treatments that increase life expectancy and quality of life for people with CF. In the 1930s, infants born with CF seldom lived past four months of age. Today, patients with CF can be expected to live beyond the fourth or fifth decade. At many CF centers, the number of adult patients exceeds the number of pediatric patients.[7] As a result, nurses are now more likely to encounter patients with CF in a variety of settings, including adult and pediatric primary care centers, specialty clinics, tertiary care settings, and schools. To optimize the care of these patients, nurses need to understand CF genetics, CF manifestations, and recent genomic developments that have advanced CF treatment.

This article describes recent genetic discoveries in the area of CF; the spectrum of genetic variants and phenotypic clinical presentations; the impact of new genomic advances on CF diagnosis and treatment; and implications for nursing practice, education, and research. It summarizes findings from salient research of the past 10 years, as well as from earlier seminal articles in the CF literature, and provides a glossary of common genetic terms (see Table 2).

## PATHOPHYSIOLOGY OF CF

CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which regulates the hydration of epithelial cells throughout the body by controlling chloride and sodium transport. Defects in the chloride channel alter the transport of electrolytes across the cell membrane, resulting in excessive secretion of chloride and sodium in the sweat and abnormally thick secretions in exocrine glands, most notably, the lungs, pancreas, and reproductive organs. Consequently, the most common

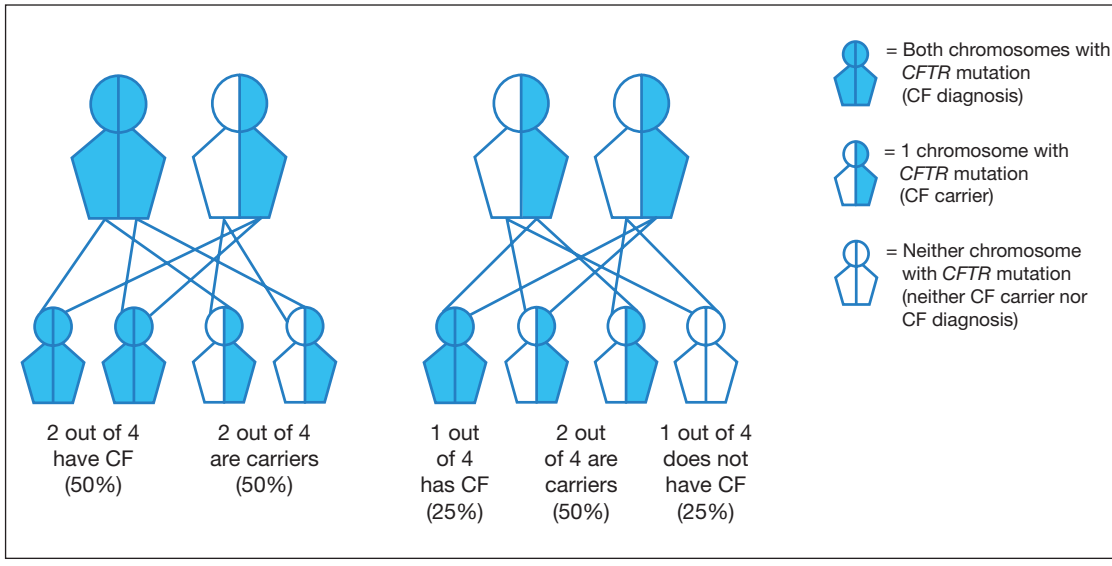


**Figure 1.** The Autosomal Recessive Inheritance Pattern in Cystic Fibrosis. CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator.

problems associated with CF are chronic bacterial infections in the lungs and progressive obstructive pulmonary disease, both resulting from decreased mucociliary clearance, and malnutrition resulting from pancreatic insufficiency. Men tend to be infertile owing to congenital bilateral absence of the vas deferens. Although many women with CF can become pregnant, CF may thicken cervical mucus, thereby obstructing the sperm's entry and reducing fertility.

## GENETIC IMPLICATIONS

Because CF is inherited in an autosomal recessive pattern, a person must inherit two mutations in the *CFTR* gene, one from each parent, in order to manifest symptoms. Those who inherit only one mutation are classified as carriers and are not expected to develop CF symptoms. A child has a one in four chance of having CF if both parents are carriers, and a one in two chance if one parent has CF and the other is a carrier (see Figure 1). For a given couple, the risk of inheritance remains the same with each pregnancy.

**The *CFTR* gene** is located on the long arm of chromosome 7. As of this writing, genomic advances have led to the identification of 1,965 *CFTR* mutations, though the number continues to rise.[8] There is evidence that 127 mutations sufficiently impair CFTR function to produce CF symptoms.[9] Of the remaining mutations, 225 are known to produce no symptoms, and the others are of unknown clinical significance.[10] A project called the Clinical and Functional Translation of CFTR (www.cftr2.org) is dedicated to documenting all *CFTR* mutations and associated clinical presentations.

**Symptom-causing mutations** interfere with the protein responsible for transporting chloride across the cell membrane. Based on the means by which they disrupt CFTR protein production or function, there are six classes of CF mutations, which are not mutually exclusive (see Table 3[8, 11-14]). Patients with class I and II mutations, which result in very limited or no CFTR protein production, are more likely to manifest typical CF symptoms, including pulmonary disease and pancreatic insufficiency, in infancy or early childhood. Patients with classes III, IV, V, and VI mutations have some protein production. Patients who have class IV mutations, in which protein production is normal, tend to have milder symptoms than patients with two class I or II mutations, even if they also have a single class I or II mutation.[12]

Although information on the correlation between patients' genotype and phenotype is limited, clinical symptoms usually reflect the degree to which CFTR protein function is lost.[12] Clinical presentation of CF, particularly pulmonary symptoms, varies widely, even among patients who have the same *CFTR* gene mutations. These variations suggest that environmental factors such as medical treatment and adherence to prescribed recommendations, or genetic factors such as modifier genes (non-*CFTR* alleles that can

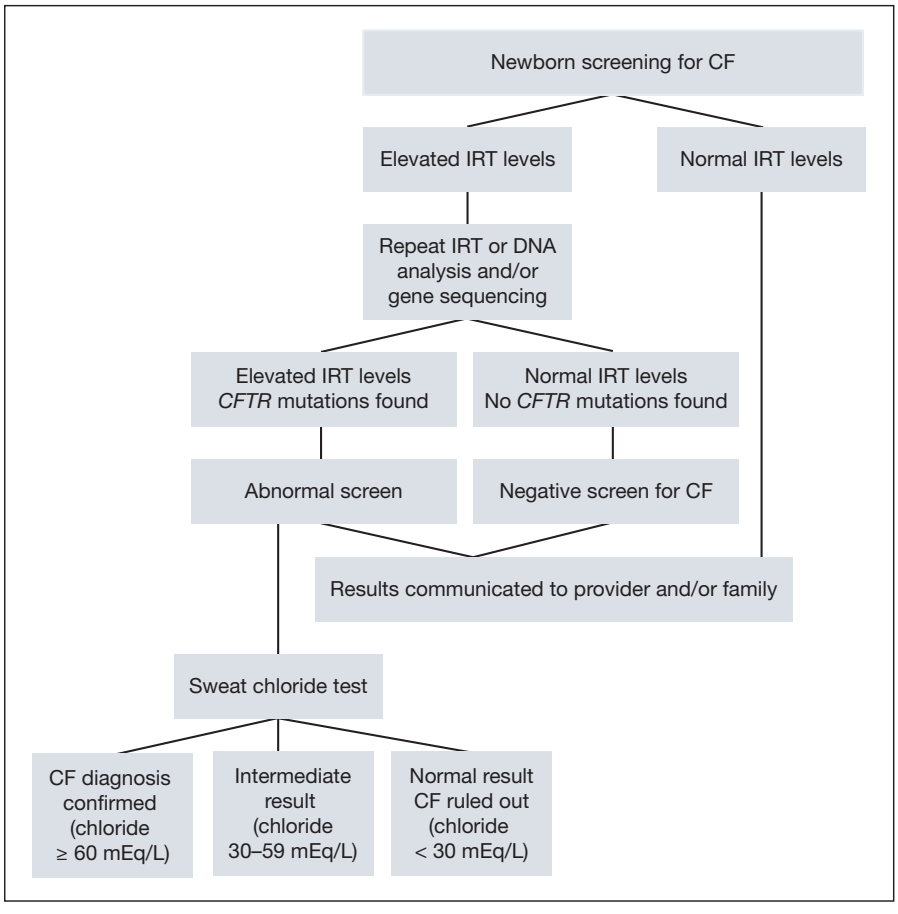


**Figure 2.** A Cystic Fibrosis Newborn Screening Algorithm.[5, 10, 17, 18] CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; IRT = immunoreactive trypsinogen.

affect CFTR function), may play a significant role in symptom manifestation and disease progression.[5, 15, 16]

## NEWBORN SCREENING AND DIAGNOSIS

Newborn screening for CF was first introduced as a pilot project—in Colorado in 1982 and in Wisconsin in 1985.[1] These early screening programs measured the pancreatic enzyme immunoreactive trypsinogen (IRT), which is usually elevated in CF, to identify infants at risk. With the discovery of the CF gene in 1989 and related advances in molecular genetics, DNA analysis was added to the screening procedure. In 1991, DNA analysis for F508del, the gene mutation responsible for most cases of CF, was added to the newborn screening panel in Wisconsin. This milestone marked the first time DNA testing had been applied to population-based newborn screening in the United States. Later, additional CF symptom-causing mutations were added to screening panels. Today, throughout the United States and in most industrialized countries, newborns are screened for CF. Research has shown that early diagnosis and prompt treatment improve nutrition and growth and can thus be expected to improve overall health and survival.

Newborn screening involves obtaining a blood specimen through a heel prick and sending it to a CF-screening laboratory for analysis. Most such laboratories screen for CF by measuring IRT, and if levels are elevated, following up with a second test that may include repeating the IRT measurement or analyzing DNA for *CFTR* mutations. Algorithms for CF newborn screening vary by state or jurisdiction (for one example, see Figure 2[5, 10, 17, 18]). The Cystic Fibrosis Foundation recommends that newborn screening panels include the 23 most common symptom-causing mutations.[10] Since the ethnic composition of the population screened affects the frequency and distribution of mutations, gene panels may vary by geographic region. For example, the screening panel recommended by the American College of Medical Genetics for screening white Americans identifies only 68.5% of mutations that are associated with CF in Hispanic Americans.[10] The frequency of F508del mutation in people with CF is 72% among white Americans, only 31% to 44% among black Americans, and 18% among Iranians.[19]

Newborn screening is considered positive (abnormal) if the IRT is elevated and the DNA analysis indicates one or two symptom-causing *CFTR* mutations. Positive screening is followed by a diagnostic sweat test. When multimutation panels are used, about 97% of infants found to have only one CF mutation through newborn screening have normal sweat test results, indicating that they do not have CF.[17] Because of the ethnically diverse population of California, the state's newborn screening procedure includes three steps: IRT and DNA analysis followed by gene sequencing, which searches for *CFTR* mutations not on the screening panel. Consequently, only infants found to have two mutations are referred for a confirmatory sweat test in California.[5] Genetic counseling is recommended for all families with infants found to have one or two *CFTR* mutations, regardless of the screening algorithm used.[20]

A CF diagnosis requires the presence of clinical symptoms and evidence of a *CFTR* defect, which is reflected in elevated sweat chloride levels, or the

confirmation of CF-causing mutations on both alleles. A sweat test that uses pilocarpine iontophoresis is considered the gold standard for diagnosis. A sweat chloride value of 60 mEq/L or higher confirms a CF diagnosis in all age groups; a value between 30 and 59 mEq/L in infants younger than six months, or between 40 and 59 mEq/L in children and adults, is considered an "intermediate" result, which is inconclusive; and a value below 30 mEq/L in infants younger than six months, or 39 mEq/L or lower in children and adults, rules out a CF diagnosis.[10] If sweat test results are intermediate, the test may be repeated and additional DNA analysis may be performed to establish the individual's diagnostic status.

## THE CF SPECTRUM

With the implementation of genetic testing in newborn screening came the inevitable consequence of identifying infants in the intermediate range of CF diagnosis. Clinical evidence, diagnostic test results, and the number and type of *CFTR* mutations determine where a patient's diagnosis falls along the CF spectrum (see Figure 3[10, 15, 21, 22]). The classifications within the spectrum guide clinicians in determining the treatment and frequency and type of monitoring the patient requires.

Those with a clear CF diagnosis have evidence of two symptom-causing mutations confirmed by the presence of pulmonary involvement, pancreatic insufficiency, or both, as well as diagnostic sweat chloride levels in the clinical range.[15, 23] Patients with CF may or may not have a family history of CF.

Some people do not meet these diagnostic criteria but have evidence of multisystem disease in addition to an intermediate sweat chloride value or a *CFTR* mutation that may or may not have known clinical relevance. These patients are classified as having CFTR-related disease (CFTR-RD). They tend to have some CFTR function and present atypically compared with patients who have a clear CF diagnosis.[15, 23] These patients usually have less severe lung disease and are less likely to have pancreatic insufficiency. Conditions that can be associated with CFTR-RD include congenital bilateral absence of the vas deferens, disseminated bronchiectasis, and recurrent acute pancreatitis or chronic pancreatitis.[15, 23]

**It is important to assure parents that genetics alone do not determine their child's prognosis.**

CFTR-related metabolic syndrome (CRMS) is indicated by fewer than two CF-causing *CFTR* mutations and an intermediate sweat chloride value, or two *CFTR* mutations, of which no more than one is CF causing, and a normal sweat chloride value.[22] This classification is generally associated with a more favorable prognosis and less need for aggressive treatment than a CF diagnosis. Even so, affected patients should be followed closely because they may develop clinical symptoms of CF.

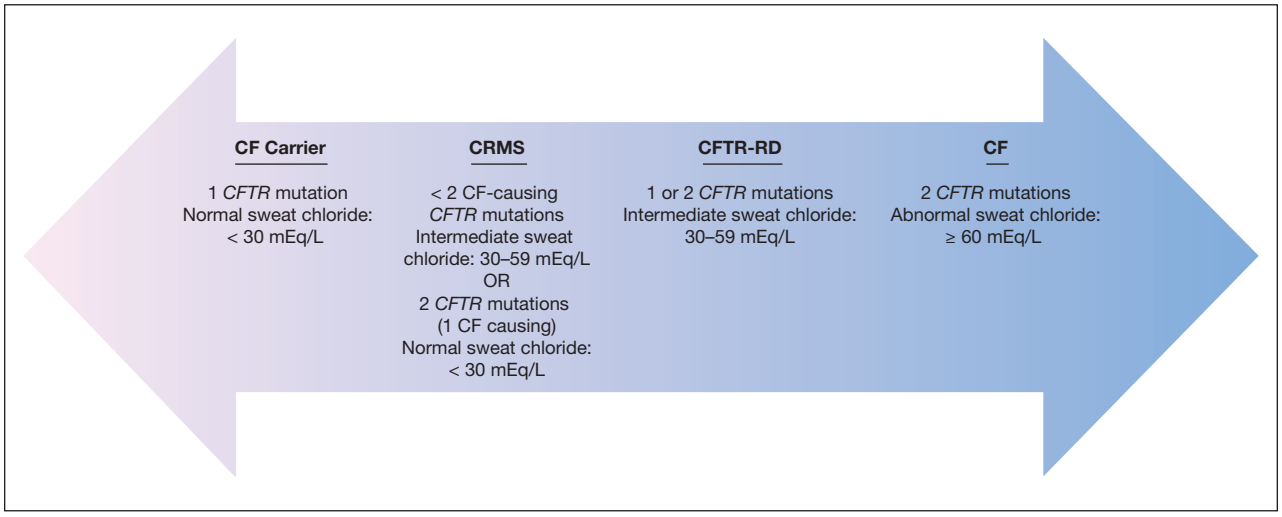


**Figure 3.** The Cystic Fibrosis Diagnostic Spectrum.[10, 15, 21, 22] CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator; CFTR-RD = CFTR-related disease; CRMS = CFTR-related metabolic syndrome.

Although carriers of one *CFTR* mutation are not expected to develop CF symptoms, questions have been raised about the presence of symptoms in heterozygous CF carriers. One survey documented chronic sinusitis in CF carriers.[24] Two other studies found that the presence of a single *CFTR* mutation, usually a CF-causing mutation, can be associated with chronic pancreatitis.[25, 26]

## NEW GENETIC TREATMENTS

Until recently, improvement in patient outcomes was largely attributed to multidisciplinary treatment, regular patient assessment in specialty clinics, early diagnosis through newborn screening, aggressive therapies for pulmonary infection exacerbations, and nutritional support. The goal of these interventions has been to manage symptoms and minimize complications.

Today, however, genetics research and genomic advances in CF have led to the development of pharmacotherapies that act at the cellular level to correct the malfunctioning chloride channel. Preliminary results of clinical trials evaluating the efficacy of mutation-specific therapies show that they have great promise in reducing chloride levels and improving CFTR function.[14, 27, 28] These therapies offer great hope for significant symptom reduction and treatment breakthroughs.

One such new drug, ivacaftor (Kalydeco or VX-770), was approved by the U.S. Food and Drug Administration in January 2012 for patients with CF who have at least one G551D mutation and are at least six years of age. This orally administered drug is a CFTR potentiator that increases the ability of affected CFTR proteins to transport ions across the cell membrane at the cell surface. Ivacaftor has been shown to counteract cell surface dehydration by reducing sodium and fluid absorption and improving ciliary mobility.[27] In some studies, ivacaftor has been associated with improved lung function and CFTR ion-channel transport.[27] Two other oral drugs in the pipeline, VX-809 and VX-661, are CFTR correctors, which promote the movement of the CFTR protein to the appropriate location on the cell surface. In doing so, they make more CFTR chloride channels available.[29] Clinical trials are under way to evaluate both ivacaftor–VX-809 and ivacaftor–VX-661 combination treatments for CF patients with the class II mutation F508del.[30] Such drug regimens, tailored to specific genotypes, are likely to become the norm for genetic conditions like CF.

**Nurses who work in maternal–child health services can help parents of newly diagnosed infants to understand how screening and sweat test results are interpreted.**

## IMPLICATIONS FOR NURSING

Multidisciplinary care is essential for patients with CF, and nurses are likely to have more interaction with patients and their families than any other health care provider. Nurses caring for patients with CF or counseling the parents of a child with CF have many opportunities to correct misconceptions about CF genetics, offering remedial education or referral to genetics specialists.

**Table 1.** Incidence of Cystic Fibrosis in the United States by Race/Ethnicity[1-3]

| Race/Ethnicity | CF Diagnosis/Live Births | Carrier Frequency |
|---|---|---|
| Non-Hispanic whites | 1/2,500–3,500 | 1/29 |
| Hispanics | 1/4,000–10,000 | 1/46 |
| Non-Hispanic blacks | 1/15,000–20,000 | 1/60–65 |
| Native Americans | 1/3,970 (Pueblo); 1/1,500 (Zuni) | NA |
| Asian Americans | 1/32,100 | 1/90 |

CF = cystic fibrosis; NA = not available.

**Table 2.** Definitions of Common Genetic Terms

| Term | Definition |
|---|---|
| Allele | A specific variant of a particular gene; for example, R117H is an allele for the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. |
| Carrier | A person who has two variants of an allele for a particular condition, in which one functions normally but the other does not. The person doesn't have signs and symptoms of the disorder, but she or he can pass either a functioning or a nonfunctioning allele on to any child conceived. |
| Chromosome | A cellular structure consisting of condensed DNA that is replicated in cell division. |
| DNA | Molecules that store inheritable information. DNA is made of different combinations of four chemicals, called "bases": adenine, cytosine, guanine, and thymine. The sequence of these bases determines physical characteristics and physiologic functioning. |
| Heterozygous | Having two different alleles of a particular gene (for example, having mutations F508del and G551D of the *CFTR* gene) or one mutant gene and one commonly found, normally functioning (wild type) gene. |
| Homozygous | Having two of the same alleles of a particular gene (for example, having two F508del mutations of the *CFTR* gene). |
| Mutation | A change in the base DNA or RNA sequence of a particular gene that may take a number of forms, including deletion, duplication, insertion, frame shift, missense (base substitution), nonsense (production of an unfinished protein product), or repeat expansion (an increase in the number of times a sequence is repeated, resulting in production of an abnormally functioning protein). |
| Phenotype | The observable physical manifestation of one or more genes. |

**Patient teaching.** In one study, parents who were found to be CF carriers mistakenly attributed the CF gene mutation to family histories of miscarriages, birth defects, respiratory illnesses, and digestive problems unrelated to CF.[31] Education is central to enhancing patients' and family members' understanding of emerging genetic discoveries that can improve the quality of their lives. Therefore, nurses should remain informed about the spectrum of CF diagnostic classifications and related available genetic treatments.

Families of newly diagnosed infants may take comfort in learning about new lines of drug therapies designed for specific genotypes. It is also important to assure parents that genetics alone do not determine their child's prognosis. The environment parents provide for children with CF can play a significant role in the child's health and future. Patients who adhere to prescribed medication regimens have better lung function, fewer pulmonary exacerbations, and fewer hospitalizations than those who do not.[32] Nurses can empower families with information about CF and how to keep their children as healthy as possible, so as new therapies become available, their children will derive maximum benefit.

For example, when one of us (SJN) shadowed an NP working in a CF clinic, she observed the routine evaluation of an adolescent who was homozygous for the F508del mutation. (Identifying details of this case have been omitted to protect patient privacy.) Despite that such a genetic profile is generally associated with severe symptoms, this patient had developed, with the support of her family, the self-care skills needed to manage her home treatments effectively and maintain overall good health. She presented as a typical teenager who was energetic, involved in sports, academically successful, and socially active.

Nurses who work in maternal–child health services can help parents of newly diagnosed infants to understand how screening and sweat test results are interpreted, discuss options for genetic testing and counseling, and explain reproductive implications for family members. They can also offer parents guidance in discussing the diagnosis and genetics of CF with relatives.

By the time children reach fifth or sixth grade, most have developed the cognitive ability to understand aspects of genetics. Nurses can help parents assess their children's readiness to learn about the

**Table 3.** Classification of Cystic Fibrosis[8, 11-14, a]

| Classification | Mechanism of dysfunction | Worldwide frequency in CF population | Example of a mutation | CFTR protein production | Chloride transport | Clinical presentation |
|---|---|---|---|---|---|---|
| Class I | Little to no protein is produced | 5%–10% | G542X | Little or none | None | Typical CF symptoms |
| Class II | Defective protein is destroyed before it reaches cell membrane | 40%–50% | F508del[b] | Very limited | Almost none | Typical CF symptoms |
| Class III | Protein cannot be turned on to conduct chloride (gating defect) | 5% | G551D | Normal/ reduced | Greatly reduced | Typical CF symptoms |
| Class IV | Protein conducts chloride less effectively | Unknown | R117H | Normal | Diminished | Mild symptoms or delayed onset of typical symptoms |
| Class V | Abnormal RNA splicing results in decreased functional protein | Unknown | 3849+ 10kbC->T | Reduced | Diminished | Mild symptoms or delayed onset of typical symptoms |
| Class VI | Functional protein present at membrane for a shorter than normal period | Unknown | Q1412X | Normal | Diminished | Mild symptoms or delayed onset of typical symptoms |

CF = cystic fibrosis; CFTR = cystic fibrosis transmembrane conductance regulator.
[a] The authors acknowledge Patrick Sosnay, MD, of Johns Hopkins University for reviewing this table on behalf of the CFTR2 project.
[b] Most common *CFTR* mutation; at least one copy is found in approximately 90% of CF cases worldwide.

heritability of CF and the ramifications for affected children and their siblings, who may be carriers. Adolescents with CF can benefit from family planning counseling. It's important for female patients to understand that they can become pregnant, so they will be prepared to make informed reproductive decisions. Although 98% of men with CF are sterile, it is essential that they have reproductive testing rather than assume they fall within the majority. If they prove to be sterile, assisted reproductive methods are available.

As patients transition to adulthood, they may need guidance in managing self-care while attending college or trade school and when making career choices. Although most patients today are diagnosed through newborn screening, about 30% of people with CF, particularly those born before the advent of newborn screening, are diagnosed as adults. Nurses who work in adult care settings may encounter patients with CF who are in need of information about all aspects of the condition and related care. The Cystic Fibrosis Foundation Web site (www.cff.org) offers excellent resources for adults with CF as well as for their health care providers.

**Continuing education.** To be able to provide patients with accurate information, nurses must first have a good understanding of genetics. The study of genetics should be integrated into undergraduate and graduate nursing programs. A foundation in genetics enables nurses to explain genetic test results accurately, interpret clinically relevant research, and communicate effectively with genetics specialists.

**Research.** Recent genetic discoveries related to CF raise issues that call for additional nursing research. The widespread use of newborn screening allows parents to learn a child's carrier status in infancy. Little is known about the optimal time or way in which to inform children that they are CF carriers. There is also a dearth of information on the effects of the new CF diagnostic classifications on parents' perceptions of their children's health or on their parenting styles. Some data, for example, suggest that parents of children found to be CF carriers through newborn screening might view their children as being more susceptible to illness or more "fragile" than noncarriers.[33] One of us (AT) is currently collecting data for a study that will shed light on this issue. Empirical evidence will be critical in identifying the most effective approaches to communicating genetic test results and educating patients and their families. ▼

For five additional continuing nursing education activities on genomics topics, go to www.nursingcenter.com/ce.

*Stephanie J. Nakano is a staff nurse in the Department of Nursing and Patient Services and works in the pediatric ICU of American Family Children's Hospital, Madison, WI. Audrey Tluczek is an associate professor at the University of Wisconsin–Madison School of Nursing. Contact author: Audrey Tluczek, atluczek@wisc.edu.* *The authors and planners have disclosed no potential conflicts of interest, financial or otherwise.*

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