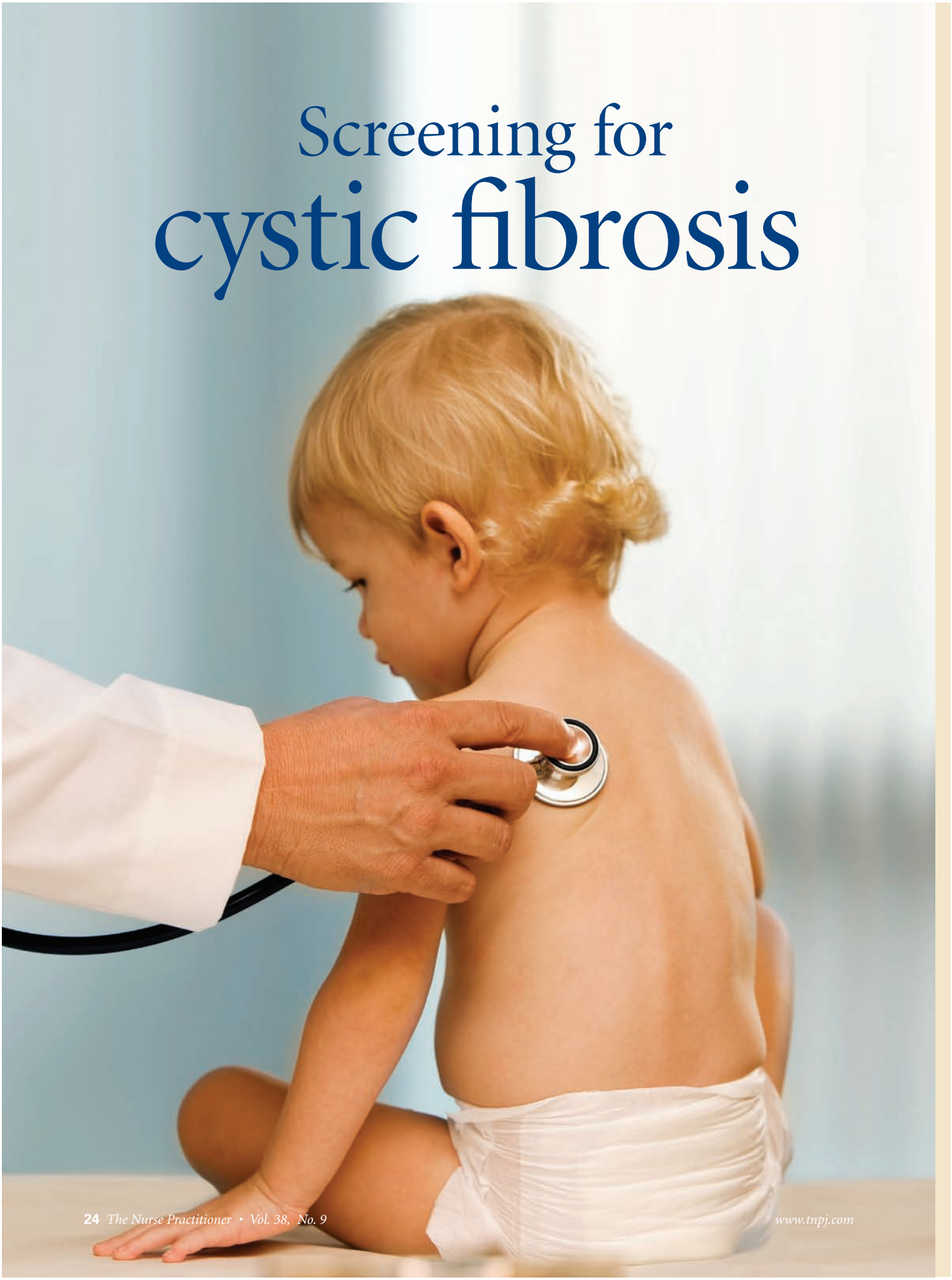
Screening for cystic fibrosis



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What every NP should know

Abstract: In a chronic childhood disease such as cystic fibrosis, it is important for nurse practitioners to be knowledgeable about the disease process, methods of mutation identification, and diagnostic criteria. Multiple studies have shown improved prognosis for patients diagnosed early.

By Krysta N. Nicholson, MS, CPNP

Nurse practitioners (NPs) play a role in the diagnosis and treatment of cystic fibrosis (CF). State newborn screening (NBS) programs, family history, or manifestation of clinical symptoms of CF can prompt the diagnostic process. It is essential that the provider be familiar with the NBS process, genetic testing, and its limitations. If a child presents to the provider with clinical signs of CF, it is important to include CF in the differential diagnosis regardless of the child's NBS or parental carrier results. Studies have shown that early identification during infancy and implementing interventions can prevent or delay complications and improve overall outcomes.[1,2] NPs can have an impact on these patients, their knowledge of CF, and the progression of their disease. This article will discuss CF pathophysiology, the diagnostic process, clinical signs, and early intervention strategies.

The prevalence of CF varies around the world depending on region and ethnicity. In the United States, the highest rate is 1 in 3,000 White births.[3] Improved technology has allowed screening of large populations for the disease. Since December 2009, NBS for CF has been adopted by all 50 states, the District of Columbia and can be found internationally.[4] The specific screening steps can vary from state to state (see *CF NBS protocol by state*). With these new strategies, patients are being diagnosed and beginning therapy at an early age. It is speculated that the life expectancy for those born with CF in the year 2000 may be as high as 50 years.[5]

Defining CF

Genetics. CF is an inherited genetic disorder. Located on chromosome 7, the CF transmembrane conductance regulator gene (CFTR) is the most common site of genetic mutation. A CF mutation can cause ineffective transport of chloride across the cell membrane, which changes the chloride concentration gradient and the direction of sodium transport.[6,7] This causes physiological dysfunction in the body and affects many organ systems.[6,7]

CF is an autosomal recessive disease. An individual with two mutations typically expresses symptoms of disease and is diagnosed with CF. Carriers have a single mutation and usually do not express physical manifestations.

As of April 2011, a total of 1,940 mutations have been discovered.[8] The mutation with the highest pathologic frequency is ΔF508, which occurs in 70% of Whites with CF.[6] Between regions and ethnicities, there is a high variation in mutation incidence, and not all of the mutations are pathologic.[9] Each new mutation discovered is placed into one of four categories: Group A, B, C, or D.[9] Group A mutations directly cause CF; group B mutations cause CFTR-related disorders, not CF; group C mutations are benign, lacking physiological consequence; and group D mutation effects are unknown.[9]

Mutations that cause CF (group A) can be further classified by mutation type and associated severity of disease.[9] (See *Classes of CFTR mutations and associated complications.*) Classification of CFTR mutations range from I to V and are correlated to specific mutations in the CFTR gene.[9]

Key words: cystic fibrosis, early diagnosis of cystic fibrosis, genetic screening for cystic fibrosis

CF NBS protocol by state

IRT Auto Delfia/IRT

- Alaska
- Delaware
- Hawaii
- Idaho
- Kentucky
- Maryland
- Missouri
- Montana
- New Mexico
- Oregon
- South Carolina
- Tennessee
- Virginia
- Washington
- Wyoming

IRT Auto Delfia/DNA

- Alabama
- Arizona
- California (38 mutations)
- District of Columbia
- Florida (43 mutations)
- Georgia
- Iowa (40 mutations)
- Kansas
- Louisiana
- Massachusetts (39 mutations)
- Minnesota (39 mutations)
- Mississippi
- Nebraska
- New Hampshire
- New Jersey
- New York (39 mutations)
- North Dakota (40 mutations)
- Ohio (23 mutations)
- Oklahoma (40 mutations)
- Pennsylvania
- Rhode Island
- South Dakota (40 mutations)
- West Virginia (46 mutations)
- Wisconsin (25 mutations)

IRT Auto Delfia/IRT/DNA

- Colorado
- Texas

Source: Adapted from Therrell B. Laboratory testing for CF in 2011. National Newborn Screening and Genetics Resource Center, University of Texas Health Science Center at San Antonio. 2011. IRT testing method by MPBioMedicals (ICN). National Newborn Screening and Genetics Resource Center, University of Texas Health Science Center at San Antonio.

Classes of CFTR mutations and associated complications

Class	Change in CFTR protein	Associated symptoms
I	Defective synthesis of protein	• Pancreatic insufficiency • Meconium ileus • Premature mortality • Early deterioration of lung function • Malnutrition • Liver disease
II	Defective processing and maturation	
III	Defective regulation	
IV	Defective conductance/ partial function	• Mild lung disease • Pancreatic sufficiency
V	Reduced function/ synthesis	

Source: Adapted from Castellani C, Cuppens H, Macek M, et al. Consensus on the use and interpretation of cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros.* 2008;7(3):76.

Adapted from Culling B, Ogle R. Genetic counseling issues in cystic fibrosis. *Paediatr Respir Rev.* 2010;11(2):187.

The variation creates a spectrum of CF severity depending on the specific defect caused by the mutation.[10] Class I–III mutations are more severe than class IV and V. Knowledge of the classification of mutations assists in predicting prognosis of a patient with CF.[9,10] The ΔF508 is a class II mutation and does not produce a CFTR protein due to a defect in processing. Individuals homozygous (two mutations) for ΔF508 have a higher severity of clinical disease than those who are heterozygous (one mutation). Having two ΔF508 mutations is the most severe CF-causing genotype.[9]

Pathophysiology. There is a spectrum of disease severity in CF due to the variation in gene mutations (see *Clinical features of CF*). Any tissue that has CFTR proteins in the epithelial membrane can be affected. Affected sites include the lungs, intestines, sweat glands, pancreas, vas deferens, and liver.[7]

In the lungs, the chloride channel is ineffective at moving the ions across the membrane.[7] Sodium moves into the cell, bringing along water and leaving the lungs dry with thick mucus. The viscosity of the mucus makes it difficult for the cilia to clear it. The cilia become flattened and ineffective at removing sputum.[7] This medium allows opportunistic infections to colonize and possibly trigger an inflammatory process that causes remodeling of the lung tissue. This can lead to lung damage.[3] Lung deterioration is the primary cause of death in 90% of CF patients.[7] A similar process occurs in the intestine, which prevents proper absorption of nutrients and causes a buildup of thick mucus.[3]

In the pancreas, the exocrine cells do not function properly and impair the secretion of bicarbonate and pancreatic enzymes.[3] These enzymes are essential for intestinal absorption and can cause deficiency in vitamins A, D, E, and K.[3] The buildup of products in the pancreas causes cell damage, which leads to pancreatic insufficiency. It can also cause CF-related diabetes mellitus.[3,7]

CF-related liver disease is caused by bile thickening in the gallbladder and subsequent obstruction.[3] Obstruction can lead to cell damage and trigger an inflammatory response that causes a range of problems from focal biliary cirrhosis to multilobular cirrhosis.[7,11]

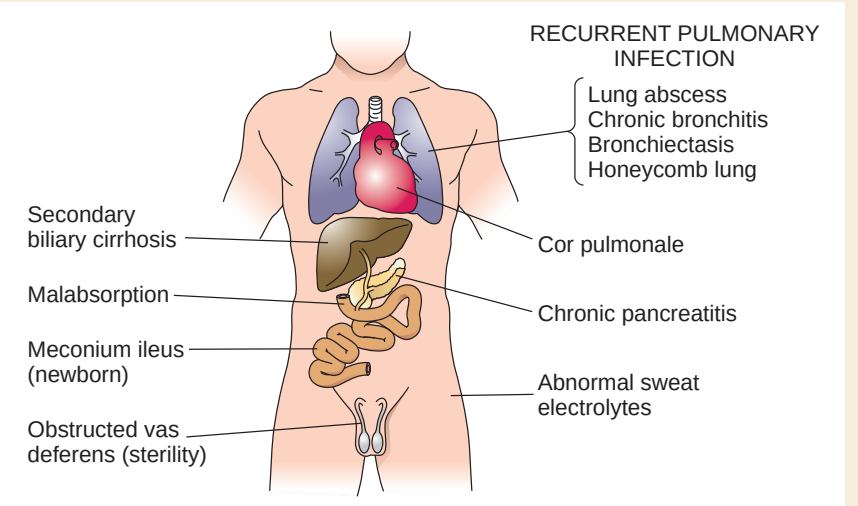
In all patients with CF, the sweat glands release large amounts of sodium and chloride. The defect prevents the uptake of sodium back into the epithelium. Excess excretion of these electrolytes can lead to hyponatremia, hypochloremia, and dehydration.[12] Infertility only affects males due to a congenital bilateral absence of the vas deferens.[13]

Screening and diagnosing CF

Genetic screening. Genetic testing has improved with the implementation of new technology and further discovery of CFTR mutations.[10] There are several types of genetic tests available, such as carrier testing, cascade screening,

prenatal testing, or NBS.[10] An ideal genetic screening panel will have a high detection rate for a mutation without having to test for all known mutations.[9] Each CF screening program has developed a specific protocol for the number and types of mutations on their panel.[14] In the United States, an average of 23 to 43 mutations will be screened for on each mutation panel.[6] The incidence of carriers for CF varies throughout the world; in Europe, carrier incidence can be as high as 1 in 20 individuals.[15] In the United States, the frequency of carriers is more prevalent in specific populations, the highest being of Ashkenazi Jewish decent and the least being of Asian Americans.[6] Carrier testing is not a standard test in the United States unless there are risk factors present. These risk factors include European ancestry, Ashkenazi Jewish ancestry, family history of a carrier, or diagnosis of CF.[7] Many couples are unaware of their carrier status until they have a child diagnosed with CF.[16]

Clinical features of CF



Source: Rubin R, Reisner HM, eds. Essentials of Rubin's pathology. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2009:105.

Carrier testing. According to the American College of Medical Genetics, carrier testing for individuals categorized as "at risk" should have a panel of the 25 most common mutations screened.[17] The screening often occurs in couples who are in the early stages of family planning.

If a mutation is detected, it is important that they receive proper counseling and emotional support to make informed decisions about family planning.[10] If both partners are known to have a mutation, with each pregnancy, there is a one in four chance of having a child with CF.[18] (See *Risk of carrier incidence and offspring with CF in a couple of North European decent.*) With a selective panel of the most common 25 mutations, there is still a risk that a mutation can go undetected.[18] Screening for a select panel of mutations will rule out those specifically screened for. Since not all mutations are screened, there is still a chance that the individual is a carrier of a rare mutation. Undergoing carrier testing decreases the risk of having a mutation from 1/25 to 1/250 for an individual of European descent.[18] The screening method has a high sensitivity, which means that when an individual is found to have a mutation, he or she is most likely a carrier. However, the specificity is lower and cannot guarantee that a negative test result means that the individual does not have a CFTR mutation.[18]

Once a couple knows their CF carrier status, there are various options for family planning. One option is in vitro fertilization, where an embryo can be screened before implantation; this is referred to as pre-implantation genetic diagnosis.[10] On days 3 to 5 post fertilization, a small sample of DNA can be obtained and tested.[10] Knowing the precise mutations of the parents, they are able to test for specific markers unique to those mutations—not the mutations themselves.[10] Since the specific mutations are unable to be detected at this stage, a diagnosis of CF cannot be absolutely ruled out.[10]

Prenatal testing. Partners that are known carriers and are expecting have the option to receive prenatal testing.[6] At 11 weeks gestation, a chorionic villus sample can be taken, or at 16 weeks, an amniocentesis is done. A DNA sample is obtained during the procedure and tested for known parental mutations.[10] Knowing the specific mutations allows definitive testing and diagnosis for the developing fetus.[6] This enables the couple to make informed decisions about their family's future and possibly ease some anxiety or hesitation that they may have.

Cascade testing. If an individual has been diagnosed with CF or identified as a carrier, the family should undergo genetic screening.[17] This is referred to as cascade testing, the genetic panel includes the specific mutation that was identified in the family member.[10] This gives the opportunity for family members to learn if they are carriers. If a mutation is not identified, they are still at risk, but the probability is reduced.[10]

It is not a guarantee that the mutation will be found during the screening process.[9] Culling and Ogle state that 1% to 5% of CFTR mutations are undetected in patients clinically

diagnosed with CF.[10] Due to the large number of mutations and varying incidences among populations, it can be difficult to create an accurate, cost-effective, genetic screening panel.[7]

Problems with genetic testing. With globalization, people are able to migrate around the world and blend families and backgrounds.[9] This makes it challenging to develop an accurate CFTR mutation panel reflective of the local population.[15] In the United States, a screening panel selection of the 23 most common mutations will only detect 94% of carriers that are of Ashkenazi Jewish descent, 88% of non-Hispanic White carriers, 72% of Hispanic American carriers, 65% of Black carriers, and 49% of Asian American carriers.[6] It is not feasible to create specific panels for each circumstance and background.[4] The purpose of genetic testing and the development of CFTR mutation panels is to reduce the risk of carrier status in those that are at greatest risk.[15] It would not be practical to screen for all of the CF mutations, which would result in increased costs.

Newborn screening

Each child in the United States has an NBS done within the first few days of life. It has been found that newborns with CF have elevated immunoreactive trypsinogen (IRT); this makes it an ideal marker to test in an NBS program.[19] There are two types of protocols used: the IRT/IRT and the IRT/DNA.[20] A number of studies have shown that current NBS protocols can effectively identify CF while keeping costs at a minimum.[21,22] The outcomes of early diagnosis and treatment are greatly beneficial. The Cystic Fibrosis Foundation published guidelines for implementing and running a successful NBS program.[20]

The immunoreactive trypsinogen/immunoreactive trypsinogen (IRT/IRT) protocol was the first to be developed.[23] In the first 24 to 72 hours of life, a blood sample is taken and analyzed.[20] Each laboratory determines the acceptable levels of IRT and the cutoff values.[20] If the infant has an elevated IRT level, a second blood sample is obtained at day 14 of life.[20] If the infant has two elevated IRT levels, the patient is referred for a sweat test.[20] According to Rock and colleagues, the IRT/IRT test protocol has 99% specificity and 87% sensitivity.[21]

Protocol IRT/DNA has the same steps as the IRT/IRT method, except that a DNA analysis is conducted instead of repeating the IRT level. A single sample is taken from the infant to test both the IRT and conduct a DNA analysis for CFTR mutations.[19] The number of mutations tested can vary from the single mutation to an extensive panel of 40 mutations; it is determined by each state's NBS program. IRT/DNA has a 99% specificity; when testing for a single CFTR mutation, it has a 94% sensitivity compared to a 99% sensitivity in a 25-mutation panel.[21] (See *Efficacy of NBS protocols.*)

Some newborns are thought to have CF before the test results of the NBS have been obtained. These infants have meconium ileus at birth, a clinical sign of CF.[24] There is a high incidence of infants with meconium ileus being diagnosed with CF. This can be a red flag for CF and prompts the patient to skip NBS protocol and receive a sweat test for a definitive diagnosis.[25]

Risk of carrier incidence and offspring with CF in a couple of North European decent

	Partner A carrier incidence	Partner B carrier incidence	Risk of offspring with CF per birth
Carrier status unknown	1/25	1/25	1/2,500
Both partners are carriers	1	1	1/4
Partner A is a known carrier	1	1/250	1/1,000
Both partners screened negative	1/250	1/250	1/250,000
Partner A has CF and partner B is a carrier	2	1	1/2

Source: Adapted from Shulman LP. Cystic fibrosis screening. *J Midwifery Womens Health.* 2005;50(3):207. With permission from Elsevier.

Diagnosis

There are several pathways to a diagnosis of CF; the most traditional is a patient with a positive sweat test supported by two known CFTR mutations that are associated with CF disease.[20] Current guidelines state that if a patient has two known diseases causing CF mutations, it is considered a diagnosis regardless of the sweat test results (see *Diagnosing CF*).[26] Patients can also have a single identified CF causing mutation associated with physical manifestations of CF, such as pancreatic insufficiency, acute/chronic bronchiectasis, or pancreatitis. Even with new clinical guidelines, patients can fall into an indeterminate category, such as an intermediate sweat test range or an unidentified mutation. In these types of cases, clinical judgment and referral to a geneticist are essential to the diagnosis.[26]

If there is any suspicion that a patient has CF, it is recommended that they have a sweat test and referral to a geneticist and CF center.[7] The most common ways of referral are a positive NBS, meconium ileus, or clinical signs of CF. Other reasons include a family history of CF or the parents are known carriers.

Sweat testing

The gold standard diagnostic test for CF has been a sweat test.[20] Gibson and Cooke pioneered a method that involves stimulating the body to sweat through application of pilocarpine on the skin.[27] A process called iontophoresis increases the rate of absorption of pilocarpine through the skin by applying a low electrical current.[27] Sweat is collected on gauze, and the sweat chloride concentration is determined. In a child 6 months or older, a value greater than 60 mEq/L is a positive for CF, and a range of 40 to 60 mEq/L is considered indeterminate; a repeat test should be done within 1 to 2 months.[20,26,28] Infant's 0 to 3 months of age can have a positive test at a much lower level.[26-28] There are several benefits to the sweat test, as it is cost-effective and can identify up to 99% of patients with CF.[7,29]

For the test to be accurate, the patient should be older than 48 hours and weigh at least 3 kg.[28,30] Taylor et al. recommend that if a patient tests negative or the result is at an indeterminate level, it is important to review the patient/family history and physical exam.[30] There may be clinical evidence, such as a history of failure to thrive, chronic anemia, diarrhea, steatorrhoea, rectal prolapse, or Vitamin E deficiency, that would give a clinical diagnosis of CF.[24]

The role of the NP

The NP can be the first contact that the patient and family have with a medical professional after leaving the hospital postpartum. The NP and local CF center are notified of the NBS results.[24] It is sometimes the role of the NP to order a sweat test based on NBS results, presence of clinical symptoms, and family history. Depending on the circumstances, the NP may be the individual who discusses the results with the family. It is important that the NP be equipped to discuss and answer questions about the testing process, interpretation of results, and disease. The Cystic Fibrosis Foundation is a resource for current guidelines and practices.[7]

Delayed diagnosis

Any CF patient who has not prompted the diagnostic process for CF through NBS, prenatal testing, or meconium ileus is considered to have a delay in diagnosis. These patients can present with clinical symptoms characteristic of CF. The common systems that show clinical signs and symptoms include the lungs, skin, and gastrointestinal system.[24] (See *Early signs and symptoms of CF.*)

CF can affect multiple systems and cause many complications, leading to the diagnosis of failure to thrive. It is common for the patients to have a growth curve below the 5th percentile for growth and weight.[3,24] With a thorough patient/family medical history and physical exam, an NP can have a high suspicion of CF. By recognizing this, the patient can be referred to a CF center for further evaluation, genetic testing, and confirmatory sweat test.

Efficacy of NBS protocols

Protocol	Sensitivity	Specificity	PPV
IRT/IRT	87%	99%	12.5%
IRT/DNA 1 mutation	94%	99%	10%
IRT/DNA 25 mutations	99%	99%	9%

Source: Adapted from Rock MJ, Hoffman G, Laessig RH, Kopish GJ, Litsheim TJ, Farrell PM. Newborn screening for cystic fibrosis in Wisconsin: Nine-year experience with routine trypsinogen/DNA testing. *J Pediatr.* 2005;147(suppl 3):S75. With permission from Elsevier.

Management of early CF

Patients diagnosed early in life through NBS often do not display clinical signs.[31] It is important that these patients receive routine management and care despite being asymptomatic. This patient population has a different treatment regimen and protocols than symptomatic patients.[12] The focus is on early intervention to reduce and prevent complications.[23] A referral to a locally certified CF center can help with the early management.

Effective monitoring and communication

The NP can help clarify the interpretation of results and educate the family on the outcomes. It is vital that NPs understand how to effectively monitor these patients and appropriately communicate with the CF center.[4]

Patients should maintain normal growth. The NP should regularly plot height, length, weight, and head circumference.[12] Ideally, the patient should be above the 50th percentile in weight for length.[12] If they fall below the 25th percentile, they should be closely monitored, and the CF center should be contacted.[12] At every visit, the provider should assess for any signs of respiratory change, such as coughing, wheezing, or pallor.[12] Symptoms that may be benign in a healthy child can indicate severe complications in a child with CF.[12]

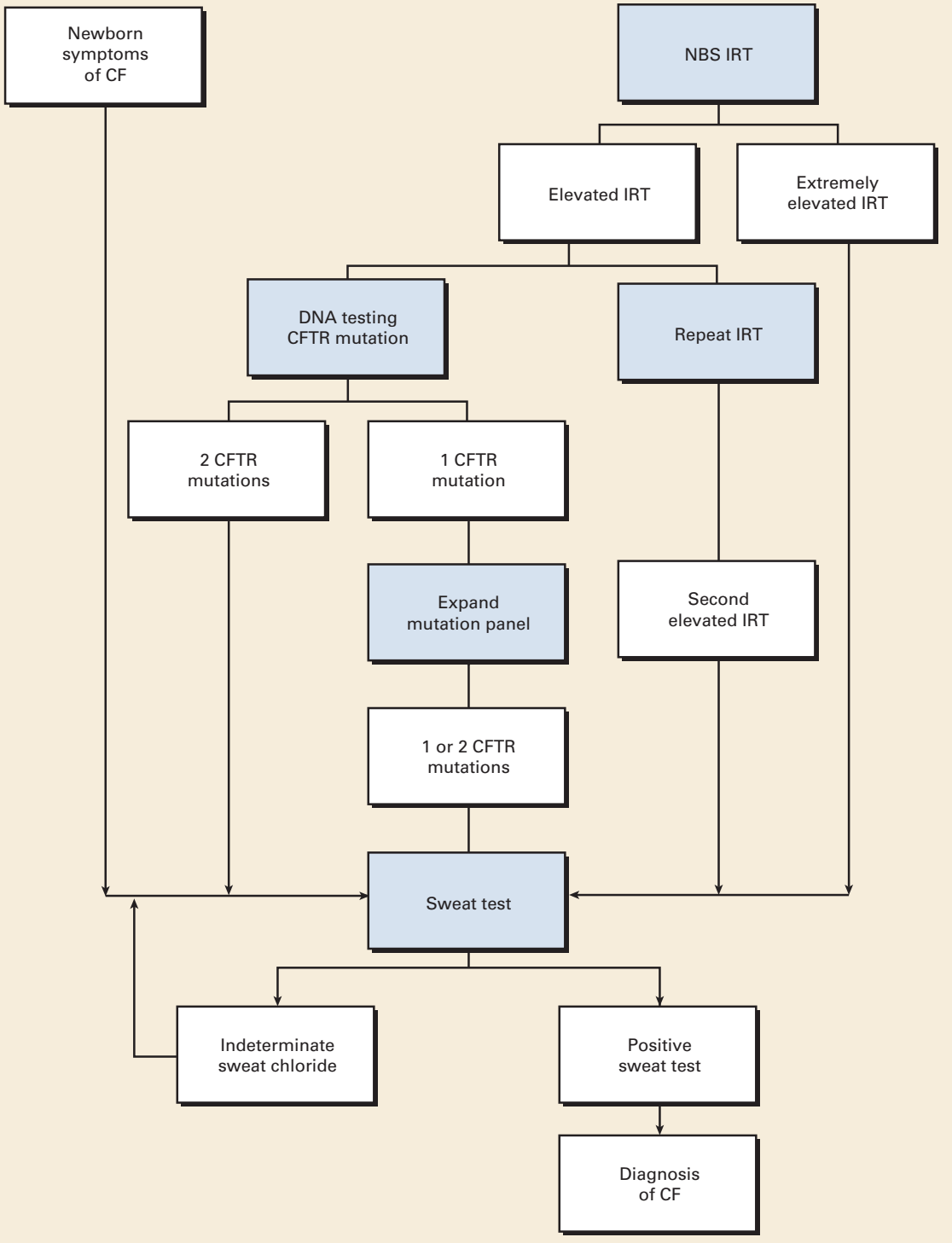
Infection control is important in keeping the patient healthy. Education for the patient and family regarding hand hygiene and up-to-date immunizations is essential. All age-appropriate immunizations should be given, including an annual influenza vaccine beginning at 6 months of age.[15] Children under 2 years of age should receive prophylaxis during respiratory syncytial virus season.[15]

Prognosis of CF with early identification

With early implementation of management strategies after diagnosis, there has been great improvement to CF patient

Diagnosing CF

Algorithm for diagnosis of CF. Actions are shown in shaded boxes; results are shown in the unshaded boxes.



Adapted from American College of Medical Genetics. Immunoreactive trypsinogen (IRT elevated)., Newborn Screening Confirmatory Algorithm. 2006. Adapted from Farrell PM, Rosenstein BJ, White TB, Accuroso FJ, Castellani C. Guidelines for diagnosis of cystic fibrosis in newborns through older adults: Cystic fibrosis foundation consensus report. *Pediatr.* 2008 ;153 :6. With permission from Elsevier.

outcomes. They can have longer life spans, improved nutrition, growth, and lung function.[32] Growth has improved with enhanced nutrition therapy. A common approach is a high-fat and calorie diet along with vitamin, salt, and enzyme supplements.[31,33] Stallings and Stark concluded that maintaining growth in the 50th percentile or higher for CF patients will lead to better pulmonary status, and a body mass index in the 50th percentile or higher is associated with higher FEV1 values, a measure of pulmonary status. Treatments to meet these goals involve behavioral therapy, nutritional counseling, oral or enteral supplementation, and pancreatic enzyme for those who are pancreatic insufficient.[33]

The future of CF

As technology and research advance, so will the detection capabilities and treatment of CF. Some of the latest research involves targeting the specific CFTR mutations. By targeting the specific classes of mutations, the protein can be corrected at a cellular level and ultimately prevent the consequences of CF. There has been progress in modifying the class I nonsense mutations. The mutation is modified by adding molecule PTC124 that suppresses the mutation. The change results in a functioning CFTR protein. Other classes of mutations have been a little more challenging to modify and need further evaluation before progressing. Gene therapy is another area of treatment research. The latest method involves inserting a copy of a normal-functioning CFTR gene into the DNA of affected epithelial cells, rendering them fully operational. The challenge involves finding suitable vectors that are able to insert the DNA into the cells.[3] In the future, some of these therapies may become standard practice and change the disease course of CF.

Moving forward

The diagnosis of CF has been transformed through the use of enhanced DNA analysis and laboratory techniques implemented through NBS. CF patients are not only living longer but are being diagnosed at an earlier age. Genetic testing can take many forms from parental carrier testing to offspring being tested in utero. Implementing a standardized strategy for screening aids practitioners in understanding their role in early identification and diagnosis.

Improved nationwide screening has caused a new CF population to emerge: the asymptomatic CF patient diagnosed early through NBS. These patients did not exist prior to the implementation of CF on NBS, and they can improve their growth, maturation, and life span through early management and health surveillance. The care is focused on prevention, enhanced nutrition, and delay of progression. The purpose is to optimize health and maturation while reducing the effects of disease. The NP has the ability to care for CF patients and their families by providing guidance, monitoring health parameters, and collaborating with the CF center. Together, the NP and CF center can enhance the lives and prognosis for patients with CF.

Early signs and symptoms of CF

Respiratory
- Wheezing
- Chronic cough
- Sputum production
- Colonization *Pseudomonas aeruginosa*
- Hemoptysis
- Pneumonia
- Chronic sinusitis
- Chest radiograph infiltrates

Gastrointestinal
- Meconium ileus
- Intestinal atresia
- Abdominal distention
- Chronic diarrhea
- Constipation
- Steatorrhoea
- Rectal prolapse
- Vitamin deficiency
- Anemia
- Failure to thrive

Integument
- Jaundice
- Excess salt

Source: Adapted from Steinraths M, Vallance HD, Davidson AGF. Delays in diagnosing cystic fibrosis: Can we find ways to diagnose it earlier?. *Can Fam Physician.* 2008;54(6):879. Adapted from O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet.* 2009;373(9678):1894.

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INSTRUCTIONS

Screening for cystic fibrosis: What every NP should know

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