Cystic Fibrosis 2023 National Indicator Report

TOOL DEVELOPMENT AND SURVEILLANCE WORKGROUP

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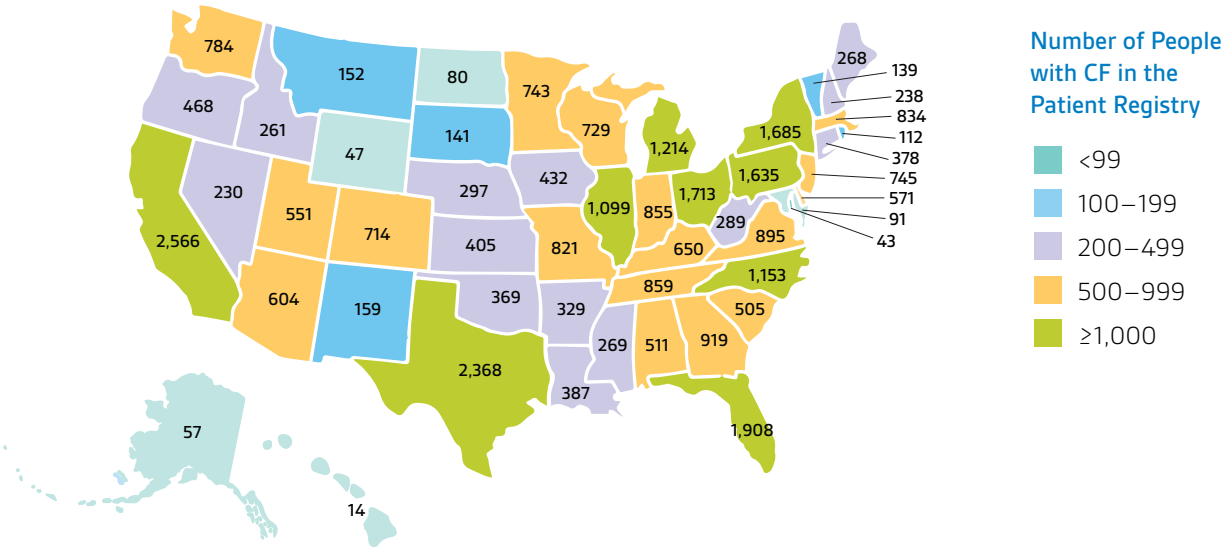
Introduction

BACKGROUND

The *Cystic Fibrosis Indicator Report* provides information on cystic fibrosis (CF), including diagnosis, treatment and health outcomes in the United States. It reports key national and state trends, including demographic information, nutrition and lung health. Because people with CF are healthier when they are diagnosed within the first weeks of life, we emphasize the importance of early and accurate diagnosis of CF through newborn screening. Public health professionals, health care practitioners, individuals and communities can use this data to build and strengthen knowledge of CF, improve practice and work together so everyone with CF has a rapid and accurate diagnosis, the proper treatment and the longest and healthiest life possible.



CYSTIC FIBROSIS OVERVIEW

Cystic fibrosis (CF) is a genetic disease that affects breathing and digestion, impacting about 40,000 children and adults in the United States. It occurs in people from all backgrounds and ancestries.

CF causes abnormal movement of salt and water to surfaces of cells that make up tube- or pipe-like structures in body organs. This makes the usually thin and watery secretions become dry, thick and sticky instead. This leads to:

- Blockage of the airways, which leads to lung infections and damages the lungs
- Impaired digestion, decreasing the body's ability to absorb nutrients from food
- Increased salt in sweat, which causes imbalances in the bloodstream and dehydration
- Abnormalities in other parts of the body, including the sinuses and genital tract

The pancreas, an organ that makes enzymes that break down food in the intestines, and the respiratory system are severely affected in most people with CF. The first signs of CF in babies and children are often poor growth and/or digestive problems. Symptoms include abdominal pain (stomach aches) and frequent, large or oily stools.

Thick and sticky secretions in the airways cause cough and infection in the lungs that increase over time and can cause wheezing or pneumonia. The liver, reproductive organs and sweat glands are also affected. The sweat gland abnormality causes excessive salt loss (sodium and chloride) through sweat. This can cause dehydration and salt loss in the body, resulting in serious illness or death. The salt loss is why a sweat test, which measures sweat chloride, is the diagnostic test for CF. Sweat tests can be done in babies as young as two days old.

CF Genetics: The Basics

When a baby inherits a CF-causing variant (previously called a mutation) of the cystic fibrosis transmembrane conductance regulator (CFTR) gene from each of their biological parents, the baby has cystic fibrosis. People who can pass on the gene are called "CF carriers." This means they have one normal copy and one defective copy of the CFTR gene.

The chance of two carrier parents having a child with CF is one in four for each pregnancy. This inheritance pattern is called "recessive", and the CF-causing gene variant can be passed down through families for many generations before a baby with CF is born.

It is recommended that people who plan to become, or are already, pregnant be tested for gene variants that cause CF. If the person who intends to get pregnant, or is pregnant, carries an CF-causing gene variant, the other parent can be tested to see if they also carry a CF-causing gene variant. If both parents are carriers, prenatal testing can be done to see if the fetus has CF and whether there are signs of intestinal problems that may affect care after birth. Not all parents choose carrier testing, and sometimes the test does not detect carriers due to the many types of changes in the CFTR gene that can cause CF.

NEWBORN SCREENING FOR CF

In the United States, CF can be detected through newborn screening. All states test for CF and other conditions that should be treated early in life before symptoms occur. Each state decides on how screening for CF is done, and all states use at least two steps. The first step, done in all states, measures immunoreactive trypsinogen (IRT), which is increased in the blood of infants with CF. States use different definitions of what is considered a high IRT level. A few states do a second IRT test if the first level is high. When IRT is increased, states test for CFTR variants. How testing is done, and which variants are detected, differs between states. In most states, the discovery of at least one CFTR variant leads to the test being called abnormal, positive, or out-of-range, and testing for CF is recommended. A few states do additional CFTR variant testing if only one variant is found, and only recommend follow-up for infants with two variants. Follow-up includes a sweat chloride test, the most widely used diagnostic test for CF. When infants have two CFTR variants known to cause CF, a CF diagnosis can be made, and treatment started immediately, but a sweat test should still be done. Infants without two CFTR variants, but who have symptoms of CF, should also be treated if a sweat test is not quickly available or if the sweat test does not collect enough for analysis.

Sometimes a sweat chloride is above the normal range but below the level that is diagnostic for CF, and sometimes one or two CFTR variants whose consequences are unknown are discovered. These findings are called CFTR-related metabolic syndrome/CF screen positive, inconclusive diagnosis (CRMS/CFSPID). Infants with CRMS/CFSPID should be followed by a CF specialist for further testing and monitoring.

In people with CF symptoms that start later in life, a CF diagnosis can be made when symptoms are present, sweat chloride is elevated and/or two disease-causing CFTR variants are found. There are also CFTR variants that can cause isolated signs or symptoms. For example, some men are born without a vas deferens, which are thin tubes that carry sperm to the urethra and outside a man's body, and can be infertile as a result. This is called CFTR-related disorder and does not progress to CF.

The Importance of Early Diagnosis and Treatment of CF

CF is a progressive disease. The main cause of sickness and early death in CF is lung disease, which can be detected during the first months of life. Good nutrition early in life is associated with better lung function and longer survival.

DIAGNOSIS OF CF

When CF was first described in 1938, it was usually fatal in early life. Fortunately, with improvements in diagnosis and treatment, most people with CF can live well into middle age. Newborn screening was fully implemented in all U.S. states and Washington, DC in 2010, a significant advancement.

All babies with any abnormal newborn screening test need follow-up testing quickly. Babies who have an abnormal CF newborn screening test should be evaluated through a program with expertise in CF diagnosis and care. The Cystic Fibrosis Foundation accredits more than 130 CF care centers throughout the United States, with strict standards for diagnosis and all aspects of care. Babies with CF who are evaluated at a CF center in the first weeks of life are healthier during infancy and childhood than babies who are evaluated in the second month of life or later. In research reports, this is referred to as Age at First Event (AFE), marking the first time a test or visit at a CF center occurs. Early treatment with pancreatic enzymes allows infants to absorb nutrients from breast milk or formula, and giving infants supplemental table salt can avoid dehydration. Starting preventive treatment for lung disease, providing frequent monitoring and offering support for psychological and social needs are also very important so that babies with CF, and their families, can thrive.

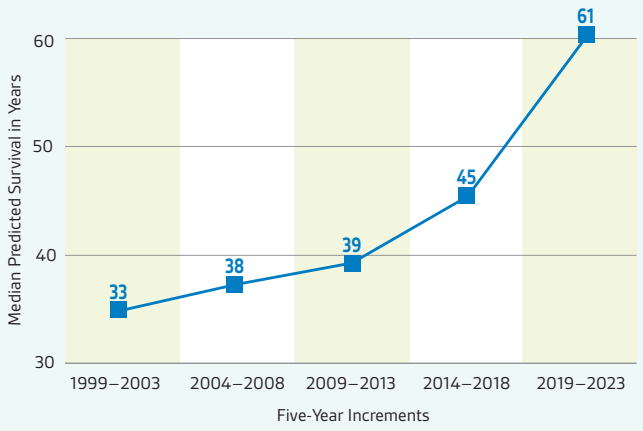
SURVIVAL

61 YEARS

2019–2023

Among people with CF born between 2019 and 2023, half are predicted to live to 61 years of age or more.

This does not reflect individual variability in survival among people with CF.



Infants with abnormal CF newborn screening results are referred for diagnostic evaluation. The sweat test is performed by stimulating sweat glands using a medicine and a very low voltage electrical current that drives the medicine into the sweat gland. About one in 10 babies with CF does not produce enough sweat for a valid test during the first few weeks of life. Babies who have an abnormal newborn screening test and symptoms of CF, or two CFTR variants on their newborn screening test, should be treated as soon as possible. Pancreatic enzyme and salt treatment are safe for babies who do not have CF.

Usually, the sweat test clearly indicates that CF is present or is not present. Sometimes, a sweat test is "indeterminate," meaning that the salt level is higher than it is in healthy people but not as high as it is in most people with CF. This can be caused by the presence of a CFTR variant that causes a less

IDENTIFYING CF EARLIER

MEDIAN AGE AT FIRST CF EVENT*

2013: 24 days
2019: 22 days
2023: 21 days

*Measure for timeliness inclusive of sweat test, clinic visit and/or hospitalization.

severe problem with salt and water transport across cells. If there are two CFTR variants that are known to cause CF, it is diagnosed. Sometimes there are CFTR variants with unknown significance, or that cause CF in some people, but not others. These findings are called "CFTR-related metabolic syndrome (CRMS)" or "CF screen positive, inconclusive diagnosis (CFSPID)." Babies with these findings need ongoing evaluation, which may be needed over months or even years since CF signs and symptoms can start at a later age. There is ongoing research to learn more about CFTR variants whose significance isn't fully understood yet.

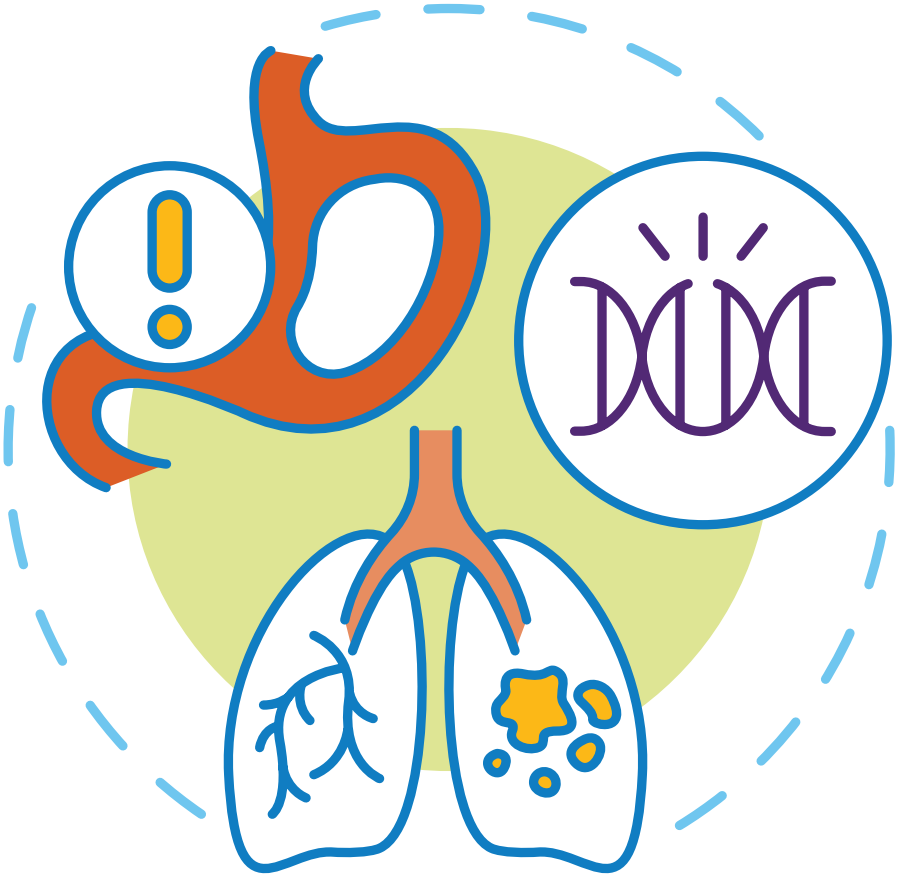
SIGNS AND SYMPTOMS OF CF

A newborn screening test is sometimes normal, even when a baby has CF (false negative test). Babies who have symptoms of CF should be evaluated quickly by specialists who are CF experts. Treatment may be recommended before the CF diagnosis is confirmed, especially when a baby is not gaining weight. Because symptoms are not always apparent early in life, all people with CF symptoms should be evaluated for the disease, even if they start having symptoms as teenagers or adults.

There are many symptoms of CF. Not everyone with CF has all of the symptoms, which include:

- Salty-tasting skin
- Cough that is frequent or doesn't go away
- Cough that produces thick mucus, which can be coughed up
- Wheezing
- Frequent lung or sinus infections
- Nasal polyps (growths in the nose that can be visible and/or cause blocked nasal passages)
- Poor weight gain
- Abdominal pain or stomach aches, sometimes severe
- Large, frequent, greasy or oily, bad smelling stools
- Severe or daily constipation
- Infertility in men

Although CF is a severe disease, health and life expectancy continue to improve. There are more adults than children with CF in the United States. Many adults with CF have completed college, work full time and are parents.



Treatment and Management of CF

Early diagnosis and treatment are important regardless of the age at which symptoms appear. The goal is to manage the condition effectively, prevent complications and improve the individual's quality of life. Most people with CF need to take pancreatic enzyme replacement therapy before meals and snacks to assist with the digestion of food. People with CF need to take medication that thins the thick, sticky airway secretions and implement measures to effectively remove these secretions from the lungs. These medicines are often inhaled. Antibiotics are used to treat airway infections with CF. Some infections can be persistent and harmful, so antibiotics may be prescribed to rid the airways of infection even when the person with CF feels well. The most common reason for hospitalization is a "pulmonary exacerbation", an increase in airway infection that requires intravenous antibiotics and other care. Antibiotics may also be used to suppress infections, often by administering on an every-other-month schedule.

For over a decade, very effective medicines called CFTR modulators have been developed. These medicines change the CFTR protein to improve salt transport across cell membranes and improve nutrition and lung function. These medicines work for people with specific CFTR variants determined by genetic testing. While most modulators can't be given until after the first or second birthday, one is now available for infants as young as four weeks old who have specific variants, and more studies are underway. About one in 10 people with CF in the United States do not benefit from modulator treatment because they do not have at least one CFTR variant that responds to a modulator. Some people can't take modulators due to side effects or other medical conditions. Research is underway to find new treatments that are very effective in all people with CF.

Cystic fibrosis impacts multiple organs and requires daily care. Frequent monitoring by CF experts can detect complications early and is important to maintain health. Multidisciplinary teams that are equipped to diagnose CF and provide the specialty care needed for infants, children and adults with CF are accredited through the **Cystic Fibrosis Foundation**, which provides oversight and funding to assure that standards of care are met. Accredited centers have physicians and other providers, nurses, social workers, respiratory therapists, physical therapists and pharmacists with special training on the needs of people with CF and their families. Many also conduct research that improves knowledge and treatment of CF.

Currently, there is no cure for cystic fibrosis. The hope of a cure is driving research that is focused on permanently correcting the genetic abnormality that causes CF. Many researchers are working toward this goal, and both governmental agencies and non-profit foundations support and conduct this research.

What's New in CF?

CF NEWBORN SCREENING

There are many positive outcomes of nationwide newborn screening for CF.

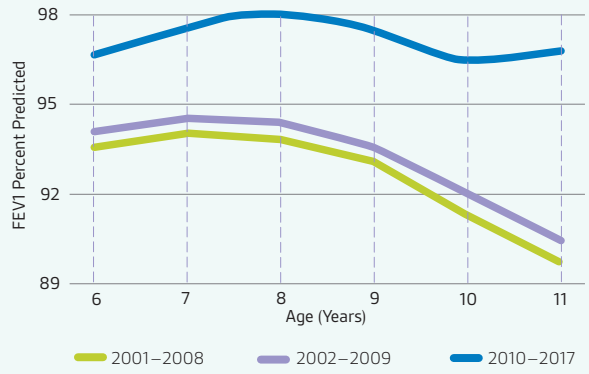
- Cystic fibrosis newborn screening has led to most babies with CF being diagnosed in the first month of life.
- Childhood nutrition and lung function have improved since newborn screening started.
- Earlier evaluation for CF is associated with better early life nutrition. Infants evaluated at a median age of 10 days had higher weight-for-age percentiles up to one year and higher height-for-age percentiles up to five years compared to infants evaluated later.

IMPROVEMENT IN KNOWLEDGE AND PRACTICE IS NEEDED TO BE SURE THAT ALL BABIES WITH CF ARE DIAGNOSED AS SOON AS POSSIBLE

- One of every eight infants with CF born between 2010 and 2018 were evaluated at a cystic fibrosis center after two months of age, and more than one of 10 were not evaluated at a center until after 6 months of age.
- Babies with CF who are diagnosed in the first two weeks of life have better nutrition at 1 and 5 years of age than babies who are diagnosed during the second month of life.
- Babies who are Black or African American, Hispanic, Asian, Hawaiian/Pacific Islander or Indigenous (American Indian/ Native Alaskan) are evaluated at a later age than babies who are White and not Hispanic.
- Black or African American and Asian infants are most likely to have a false negative newborn screening test, meaning a test is normal when CF is present. This is because CF-causing gene variants differ by ancestry, and there are more rare variants, not tested for on newborn screening panels, in people from these backgrounds.
- The false belief that CF is a disease of White and European, or "Caucasian" people likely contributes to delayed diagnosis in babies from other groups.

Lung Function Has Improved Since NBS Implementations in 2010

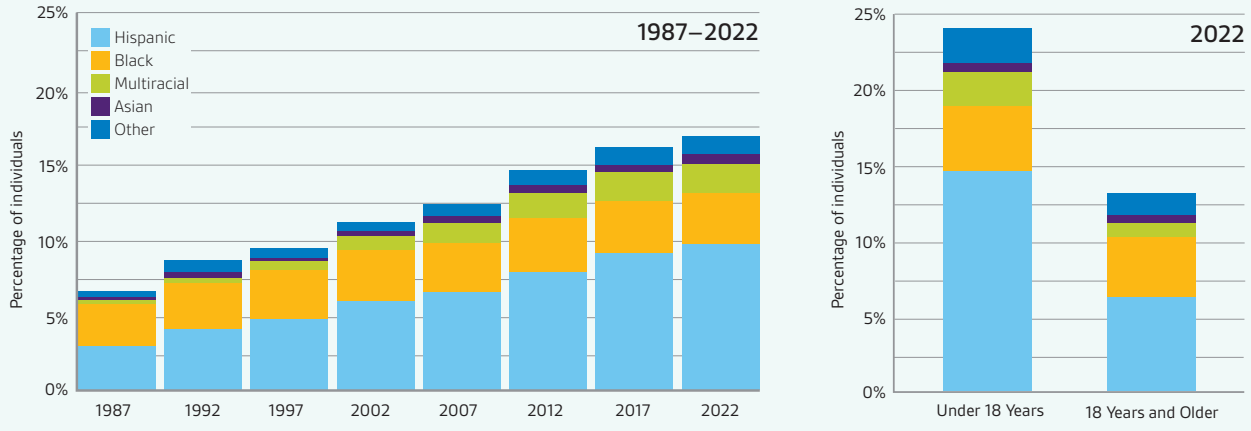
Mean FEV1 Percent Predicted in Children with CF by Birth Cohort*



During 2023, new standards for calculating FEV1pp were used, which can affect evaluation of year-over-year lung function changes.

Diversity in the CF Population

The CF population as reported to the Registry is growing more diverse every year. In 2022, over 15 percent of people with CF were identified as either Hispanic Black, Multiracial, Asian, or other than White. This trend toward increased diversity will likely continue, as it is being driven by younger individuals with CF.



LOOKING AHEAD

Timely evaluation and treatment improves health outcomes.

Newborns with a positive NBS should be be referred for evaluation of CF immediately and be evaluated at no later than 28 days (4 weeks) of age. Sweat testing can be done if weight is at or greater than 2 kilograms (4.4 pounds).

Infants can have CF even with a negative NBS. Infants with clinical concerns should be referred for further evaluation.

False negative NBS or the detection of zero or one variant on a positive NBS test can occur in infants from all backgrounds. Many babies with CF will have only one genetic variant found in newborn screening because not all variants are found through the screening test. Infants showing clinical signs, including bowel obstruction and failure to thrive, should be referred for evaluation, even with a negative NBS or detection of only one variant.

Clear communication among providers and caregivers reduces misconceptions and improves understanding of risk and outcomes.

There are long-held misconceptions that CF only affects infants of European ancestry. All infants can have CF. Ensuring that health providers and caregivers understand this and the benefit of earlier diagnosis is essential.

RESOURCES

- 2023 CFFPR Highlights Report: https://www.cff.org/media/33636/download
- CF NBS key findings infographics for providers and public health professionals:
  - https://d31hzlhk6di2h5.cloudfront.net/20230606/8a/bd/f4/bd/d8e201ad07c4b3b2e1e1cb41/Digital_Cystic_Fibrosis_Key_Findings_2023_Care_Providers.pdf
  - https://d31hzlhk6di2h5.cloudfront.net/20230606/b2/31/a4/ca/d76038ddcdc064d4c648f64f/Digital_Cystic_Fibrosis_Key_Findings_2023_Public_Health_Professionals.pdf
- These organizations have expertise in CF and provide valuable resources for people with CF and their family members:
  - Cystic Fibrosis Foundation: https://www.cff.org/
  - National Organization of African Americans with Cystic Fibrosis: https://noaacf.org/
  - Cystic Fibrosis Research Institute: https://www.cfri.org/
  - NewSTEP's: https://www.newsteps.org/index.php/
  - The Bonnell Foundation: https://thebonnellfoundation.org/
  - Center for Latinos with Cystic Fibrosis: https://latinoswithcysticfibrosis.org/
  - Baby First Test: https://www.babysfirsttest.org/
  - Emily's Entourage: https://www.emilysentourage.org/about-cystic-fibrosis/?gad_source=1&gclid=CjwKCAiA_5WvBhBAEiwAZtCU7zVIOh6WdrrM5jM2ahDiGpNQWGqh9g3MtVD8FzUG5w7gc5nTPZCePxoCDkAQ

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