PATIENT REGISTRY

ANNUAL DATA REPORT

2015

CYSTIC FIBROSIS FOUNDATION

ADDING TOMORROWS

MISSION OF THE
CYSTIC FIBROSIS FOUNDATION
The mission of the Cystic Fibrosis Foundation is to cure cystic fibrosis and to provide all people with the disease the opportunity to lead full, productive lives by funding research and drug development, promoting individualized treatment and ensuring access to high-quality, specialized care.

SOURCE OF DATA
Cystic fibrosis patients under care at CF Foundation-accredited care centers in the United States, who consented to have their data entered.

SUGGESTED CITATION
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2015 Annual Data Report
Bethesda, Maryland

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CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

August 2016

Dear Friends and Colleagues:

It is a pleasure to share the 2015 Patient Registry Annual Data Report with you. The impact of the Cystic Fibrosis Foundation Patient Registry continues to grow and inform many important initiatives, including: quality improvement, clinical trial design, "real world" observational research, and safety and effectiveness studies of newly approved therapies.

I call your attention to a recent publication, "Cystic Fibrosis Foundation Patient Registry: Design and Methods of a National Observational Disease Registry,"[1] which describes the history of the CF Foundation Patient Registry from its inception in the 1960's to the present, the patient population, and the methods for collection, security, and processing of the data. Of note, the journal editor commented: "The article this month by Knapp and colleagues features one of the most fully developed disease registries in all of medicine. The current publication offers a benchmark and roadmap for the development of other observational patient registries."

I hope that all of you are proud of your contributions to the tremendous success of the registry. It would not be possible without the vital contributions of many, most notably the individuals with CF and their families who generously agree to share their data and the Registry coordinators and care team members who collect and enter the data. The audit studies confirm the high degree of completeness and accuracy of the Registry data. We are deeply grateful to all who have helped make the Registry an indispensable tool in our shared endeavors to help those with CF enjoy the best health and quality of life.

This year's report includes an update to the survival section and information on the uptake of CFTR modulators (over 5,500 people with CF in the registry were prescribed a CFTR modulator in 2015). In addition, we continue to see the year-over-year incremental improvements in key metrics such as pulmonary function and nutritional status that bode well for the future.

We hope you find this report interesting and that it sparks discussions among members of the CF community. As always we are open to your comments and suggestions for improvement.

This is a truly exciting time in CF, with advances in health care delivery and new therapeutics that have transformative potential. Together, we will track these and other important developments in the Registry.

Thank you all for your hard work throughout the year and your commitment to the CF Foundation's mission.

Bruce C. Marshall, M.D.
Senior Vice President of Clinical Affairs
Cystic Fibrosis Foundation

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Summary of the Cystic Fibrosis Foundation Patient Registry, 2000-2015

Demographics	2000	2005	2010	2014	2015
People with CF (n)	22,201	23,082	26,366	28,680	28,983
Newly diagnosed individuals (n)[A]	972	938	1,112	923	853
Detected by newborn screening (%)	8.1	18.6	54.9	63.1	59.6
Mean age at diagnosis (years)	3.1	3.2	3.5	3.8	3.8
Median age at diagnosis (months)	6	6	5	4	4
Mean age (years)	16.9	17.8	19.2	20.5	20.9
Median age (years)	14.8	15.8	17.2	18.2	18.6
Adults ≥ 18 years (%)	38.7	42.7	47.5	50.7	51.6
Race (not mutually exclusive)					
White (%)	95.4	95.1	94.3	93.9	93.8
African American (%)	3.9	3.9	4.3	4.6	4.6
Other race (%)	1.4	2.1	2.8	3.1	3.3
Hispanic (any race) (%)	5.3	6.3	7.2	8.2	8.5
Males (%)	52.9	52.0	51.7	51.5	51.6
Mortality					
Total deaths (n)	422	358	420	467	448
Annual mortality rate (per 100)	1.9	1.5	1.6	1.6	1.5
Predicted median survival (years)	33.3	37.9	39.0	40.0	41.7
95% confidence interval (years)	31.0-35.1	34.7-40.8	36.4-41.6	38.2-42.1	38.5-44.0
Median age at death (years)	26.2	26.5	27.5	29.4	30.1
GI/Nutrition					
BMI percentile, individuals 2 to 19 years (median)	40.3	45.6	50.2	53.4	54.2
Percent weight < 10th CDC percentile	25.2	19.2	15.2	12.8	12.4
Percent height < 5th CDC percentile	16.2	14.0	11.3	10.4	9.9
BMI, individuals 20 to 40 years (median)	21.0	21.5	22.1	22.3	22.4
Pancreatic enzyme replacement therapy (%)	96.1	94.6	87.4	87.4	87.1
Supplemental feeding - tube (%)	8.8	10.0	11.2	11.5	11.7
Supplemental feeding - oral only (%)	27.9	37.4	40.9	44.4	43.9
Pulmonary					
FVC % predicted (mean)[B]	81.5	84.4	86.9	87.6	87.8
FEV_1 % predicted (mean)[B]	70.6	73.6	75.6	76.2	76.4
FEV_1/FVC ratio (mean)	73.6	74.7	74.8	74.6	74.5
Respiratory Microbiology					
P. aeruginosa (PA) (%)[C]	58.8	56.5	51.4	47.6	47.5
Multidrug-resistant PA (%)[D]	3.7	8.7	9.1	8.6	9.2
B. cepacia complex (%)	3.2	3.1	2.5	2.5	2.6
S. aureus (SA) (%)[E]	49.8	63.6	67.0	70.0	70.6
Methicillin-sensitive *S. aureus* (MSSA) (%)	45.3	51.7	50.4	53.2	54.0
Methicillin-resistant *S. aureus* (MRSA) (%)	6.1	17.4	25.8	25.8	26.0
S. maltophilia (%)	6.9	12.5	13.9	13.3	13.6
Mycobacterial species (%)[F]	-	-	10.1	12.2	11.9

Table continues on the next page

Summary of the Cystic Fibrosis Foundation Patient Registry, 2000-2015 *continued*

Health Care Utilization and Pulmonary Exacerbations[G]	2000	2005	2010	2014	2015
Outpatient visits to CF centers reported per year (mean)	5.4	4.2	4.7	4.5	4.4
Treated with IV antibiotics for a pulmonary exacerbation (%)	-	34.6	34.3	34.9	34.9
Number of pulmonary exacerbations per year (mean)	-	0.6	0.6	0.7	0.7
Number of days of treatment for pulmonary exacerbation per year (mean)[H]	-	30.6	30.5	31.6	31.1
Number of days of home IV treatment for exacerbations per year (mean)[H]	-	13.5	11.7	11.6	10.8
Number of days of hospitalization for pulmonary exacerbation per year (mean)[H]	-	17.1	18.8	20.0	20.3
Pulmonary Therapies[I]					
Dornase alfa (≥ 6 years) (%)	60.1	71.6	81.8	86.1	86.9
Inhaled tobramycin (PA+ and ≥ 6 years) (%)[J]	65.1	69.0	70.6	69.8	70.2
Inhaled aztreonam (PA+ and ≥ 6 years) (%)	-	-	22.5	42.5	42.7
Azithromycin (PA+ and ≥ 6 years) (%)[K]	-	-	69.3	67.5	66.6
Hypertonic saline (≥ 6 years) (%)	-	-	52.0	65.7	68.6
Ivacaftor (≥ 6 years with G551D mutation) (%)	-	-	-	89.3	90.4
Ivacaftor/Lumacaftor (≥ 12 years and F508del Homozygous) (%)	-	-	-	-	41.3
Oxygen (%)[L]	-	-	10.8	11.3	11.1
Non-invasive ventilation (%)	-	-	2.3	2.9	2.9
Transplants					
Lung (all procedures) (n)	168	154	193	207	216
Liver (n)	21	15	17	16	15
Kidney (n)	0	4	7	13	8
Lost to Follow Up[M]					
Lost to follow up (per 100 individuals)	2.5	4.1	2.8	2.8	2.5

[A] *We anticipate that additional 2015 diagnoses will be entered into the Registry in 2016.*

[B] *Pulmonary function data throughout this report reflect the use of GLI equations[2] for both children and adults.*

[C] *Includes PA and multidrug-resistant PA, found in any culture during the year.*

[D] *Defined as resistant to all antibiotics tested in two or more classes.*

[E] *Includes MSSA and MRSA and reflects the prevalence of* S. aureus *among individuals who had a bacterial culture during the year. The percentages for MSSA and MRSA individually are greater than the total* S. aureus *percentage because MSSA and MRSA are not mutually exclusive.*

[F] *Percentage of individuals with one or more mycobacterial species isolated out of those individuals who had a mycobacterial culture during the year. This includes* M. tuberculosis *as well as nontuberculous mycobacteria (NTM) species.*

[G] *Defined as a period of treatment with intravenous (IV) antibiotics in the hospital and/or at home.*

[H] *Among those with one or more pulmonary exacerbations in the year.*

[I] *Percent of individuals on therapy at any encounter in the year. All individuals noted as intolerant or having an allergy to a specific therapy were excluded.*

[J] *Includes TOBI®, TOBI® Podhaler™ and Bethkis® in 2014 and 2015. In prior years, only TOBI® was available.*

[K] *Individuals were considered eligible if they met the selection criteria used in the U.S. azithromycin trial.[3]*

[L] *Includes continuous, nocturnal or with exertion.*

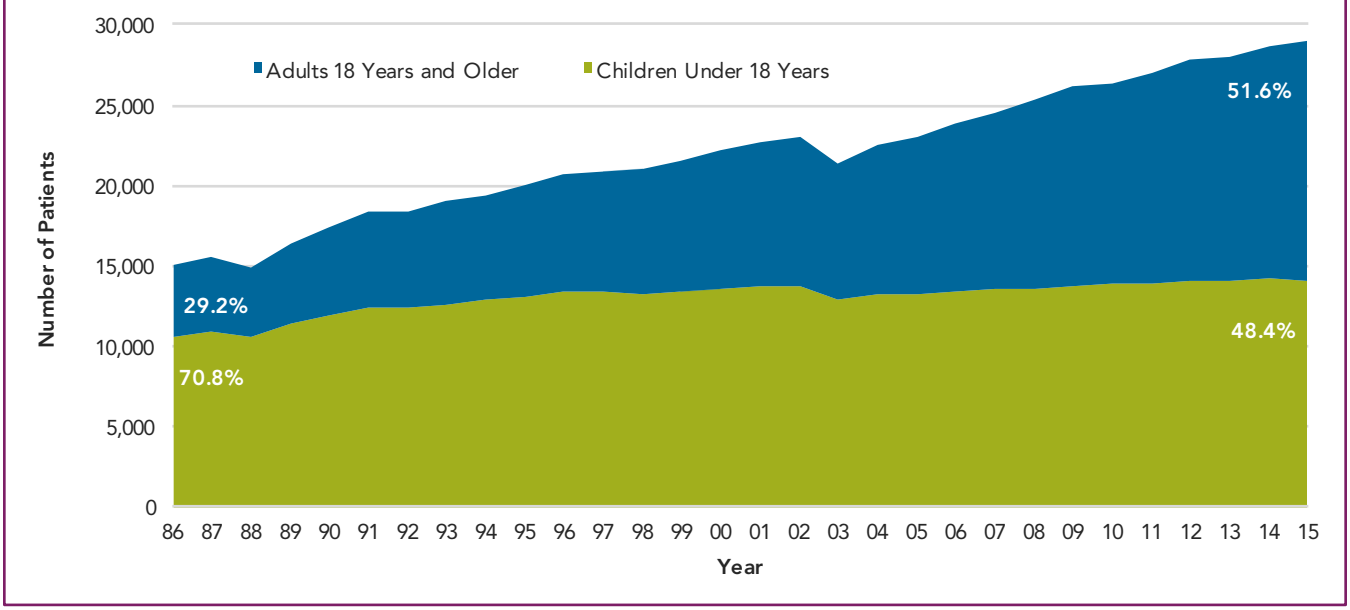
[M] *Defined as individuals seen in the previous reporting year (2014) but not the current reporting year (2015).*

DEMOGRAPHICS

The Registry contains data on people with CF from 1986 to 2015. During that time, substantial changes in specialized CF care have led to improved survival. This section shows the current and longitudinal distribution of demographic characteristics of individuals with CF in the Registry.

In 2015, there were 28,983 individuals with CF in the Registry. The number of adults with CF continues to increase, while the number of children has remained relatively stable. In 2015, adults constituted 51.6 percent of the CF population, compared with 29.2 percent in 1986.

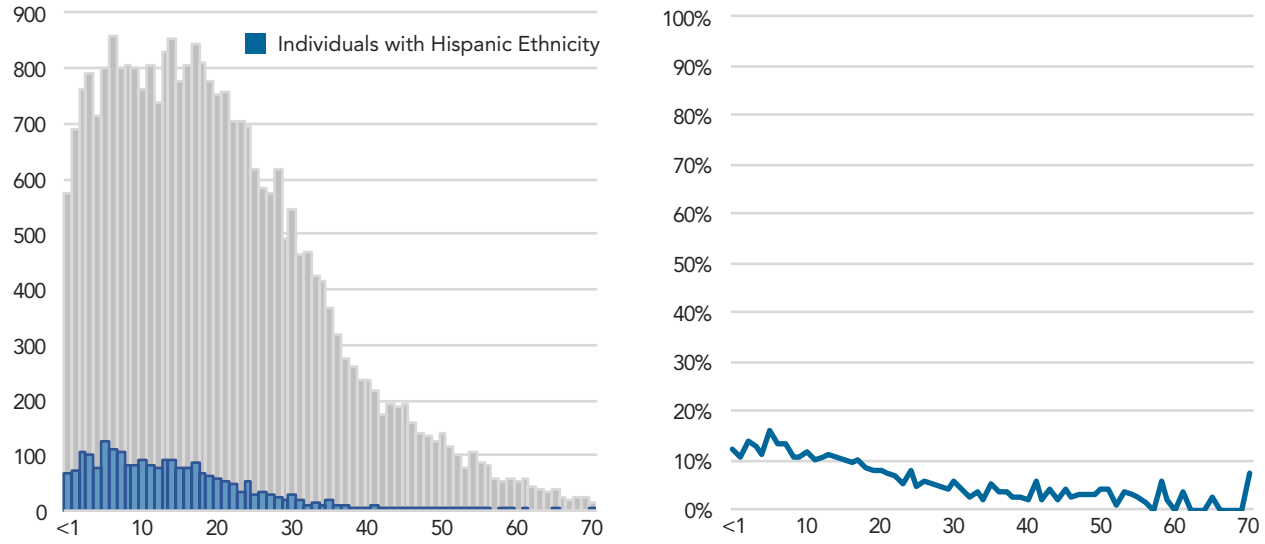
Number of Children and Adults with CF, 1986–2015



The decrease in the number of individuals in 2003 is due to a delay in obtaining informed consent forms before the close of the calendar year at some CF care centers.

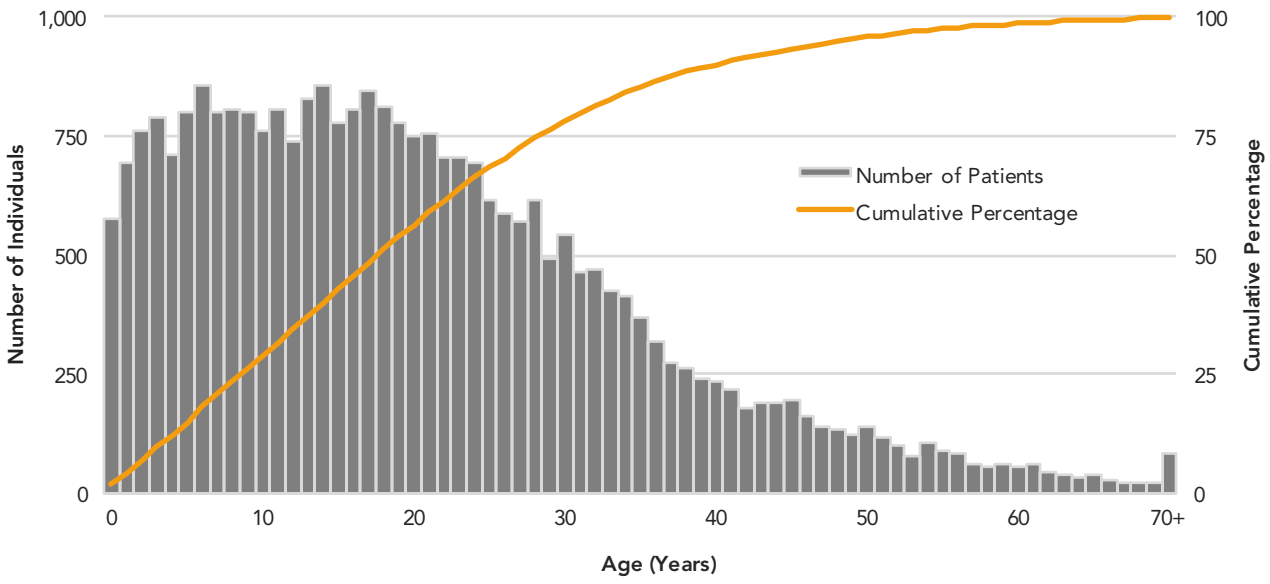
Currently, 8.5 percent of the individuals in the Registry have reported as Hispanic. There has been a steady increase over the past 15 years, reflecting national population trends.[4] Hispanics with CF tend to be younger than the overall CF population, with a median age of 12.8 years.

Hispanic Ethnicity by Age in Years, 2015



The median age of people with CF currently in the Registry is 18.6 years. The range is from birth to 87.2 years. Despite gains in survival, the age distribution remains markedly skewed toward younger ages.

Age Distribution of the CF Population in 2015



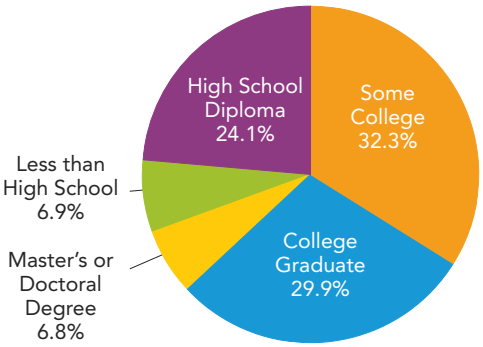
Throughout this report, there are a number of age distribution charts used to display particular characteristics of individuals in the Registry. Each of these charts will include the grey bars seen in the chart above to display the total number of individuals in the Registry in 2015. More information on these charts is available in the Appendix.

Characteristics of Adults with CF

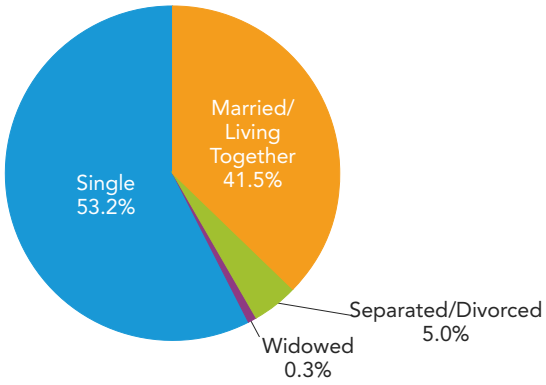
As a growing number of individuals with CF enter adulthood, it is encouraging to note that many are pursuing higher education and employment, and are in committed relationships and having children of their own. About two-thirds of adults with CF are either studying or working.

Socioeconomic Characteristics of Adults 18 Years and Older with CF, 2015

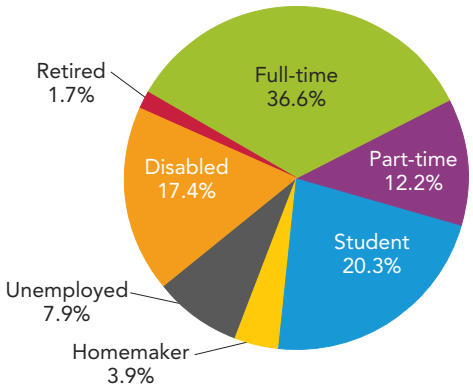
Education



Marital Status

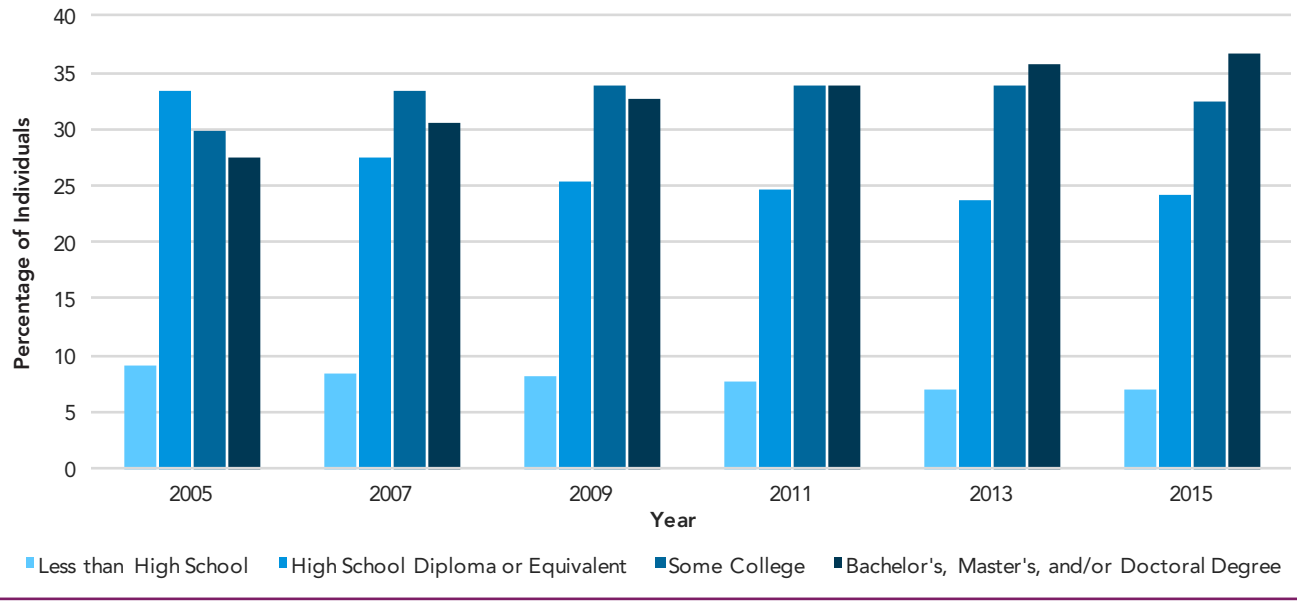


Employment



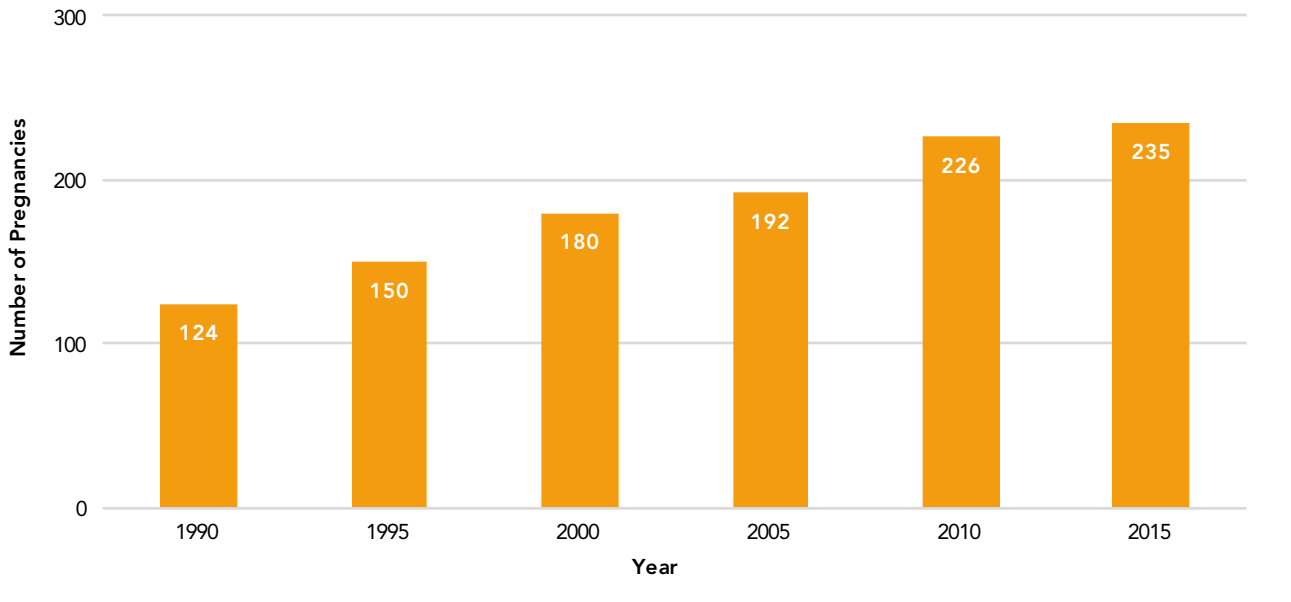
Since 1994, the percentage of adults with CF who report being married or living with a partner has increased by almost 10 percentage points. About 37 percent of adults in the Registry are college graduates, representing an increase of almost 10 percentage points.

Educational Attainment of Individuals with CF 18 Years and Older, 2005–2015



The number of pregnancies among women with CF has increased steadily since the 1990s. Registry data show that 235 women with CF were pregnant in 2015. The overall pregnancy rate among women with CF has remained relatively constant, in contrast to the pregnancy rate in the general U.S. population, which has declined during this time.[5]

Number of Pregnancies in Women 14 to 45 Years with CF, 1990–2015



Health Insurance Information

Access to insurance coverage for specialized care and treatments is a challenge for some individuals with CF. About half of the individuals in all age groups in the Registry receive at least some component of their health insurance through federal or state-funded programs. Registry data show that in 2015 a majority of people with CF who were age 18 to 25 received health insurance through their parents' plan.

Insurance Coverage in 2015

	Under 18 Years	18 to 25 Years	26 Years and Older	All
Number of individuals (n)	13,854	5,698	8,935	28,487
Private Health insurance (%)	53.0	65.3	65.9	59.5
Medicare/Indian Health Services (%)	0.5	6.0	26.1	9.6
Medicaid/state programs (%)	55.5	43.8	28.9	44.8
TriCare or other military health plan (%)	3.0	2.4	1.5	2.4
Other (%)	1.3	1.2	1.1	1.2
No health insurance (%)	0.4	1.3	0.9	0.7

"Insurance coverage" reflects coverage at any point during the year, thus these categories are not mutually exclusive (except for the "no health insurance" option).

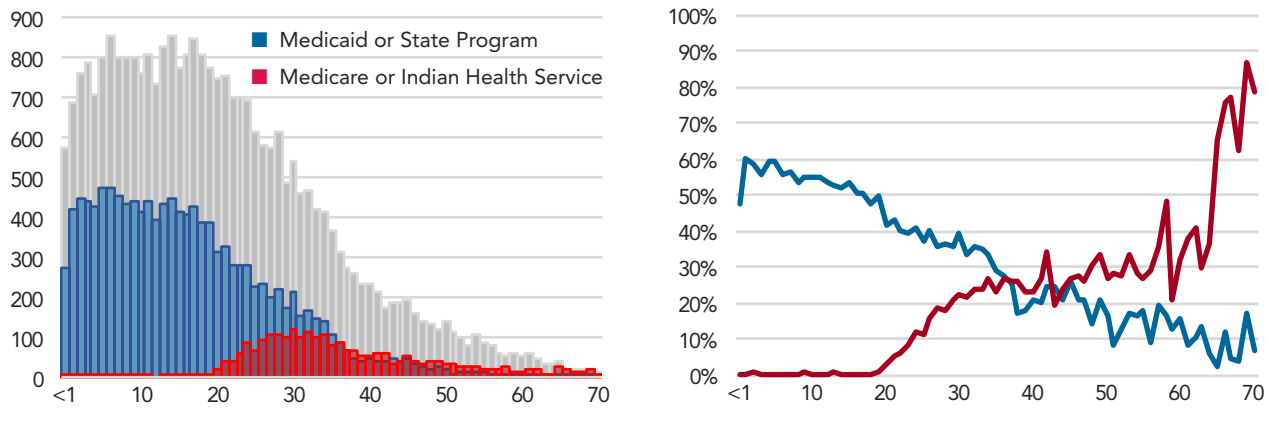
Additional Insurance Information in 2015

Individuals who participated in a patient assistance program (%)	30.9
Individuals 18 to 25 years covered under parent's insurance (%)	56.2

"Patient assistance program" refers to any program that provides free medication or co-pay assistance.

A large proportion of children with CF use Medicaid or state programs, including 57 percent of children under age 10. Though the overall prevalence of Medicare use is low, the program covers between 20 and 40 percent of adults age 30 to 65. Individuals under age 65 who receive Medicare have met the federal criteria for disability.

Medicare/Indian Health Service and Medicaid/State Programs by Age in Years, 2015



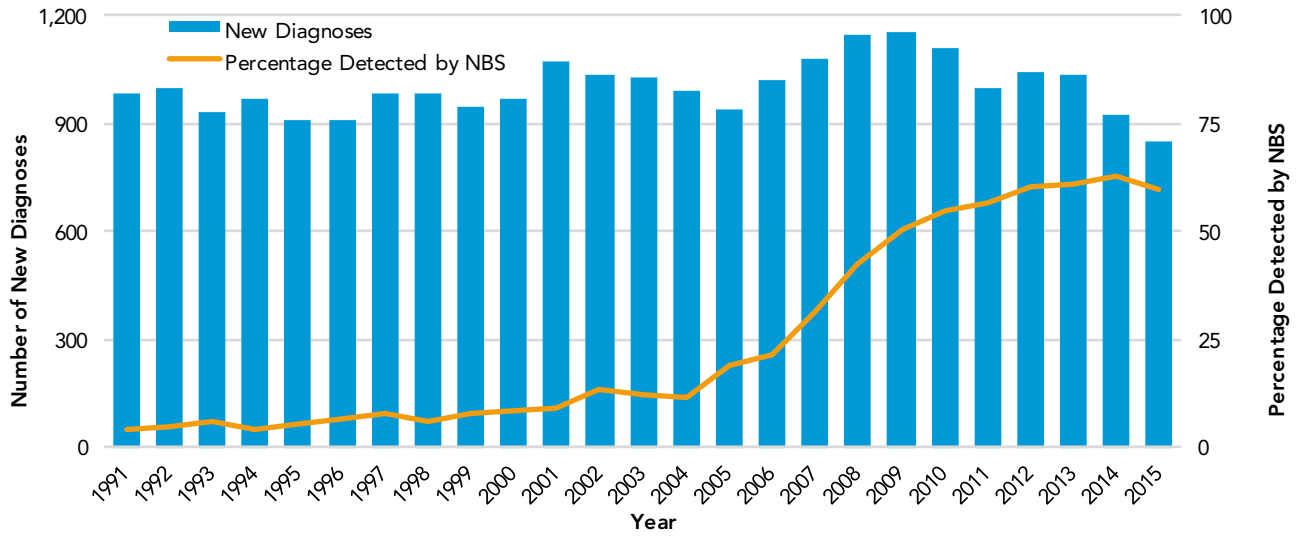
DIAGNOSIS

Characteristics of Diagnoses among Individuals with CF

This section examines characteristics of individuals diagnosed with CF, as well as trends over time for two key diagnostic tests: genotyping and sweat test.

In 2015, 59.6 percent of new diagnoses were detected by newborn screening (NBS). There is evidence that individuals diagnosed prior to the onset of symptoms have better lung function and nutritional outcomes later in life.[6] Diagnosis in the newborn period also represents an important opportunity for CF care centers to partner with community physicians and families to ensure the best possible care and outcomes for infants with CF.

Number of New CF Diagnoses, 1991–2015



The implementation of a screening program is typically associated with an increase in the number of newly diagnosed individuals. This is known as lead time bias since individuals who would have presented with symptoms later in life are detected earlier by a screening program. Thus, lead time bias is potentially the explanation for the increase in new cases during 2005-2010. In recent years, we see a decrease in the number of individuals newly diagnosed with CF. Some of the decrease observed in 2015 is the result of infants born late in 2015 who were not seen at a CF care center before the close of the reporting year; therefore, their data are not yet included in the Registry. Future reports will be adjusted to include these individuals for the 2015 diagnosis year.

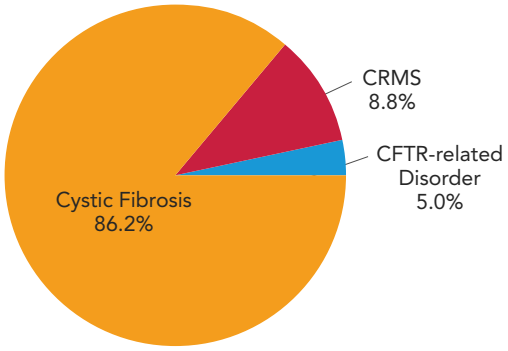
The cystic fibrosis transmembrane conductance regulator (CFTR) gene was discovered in 1989. According to CF Foundation guidelines, infants with a positive NBS who have inconclusive sweat test results and/or less than two CF-causing genetic mutations should be diagnosed with CFTR-related metabolic syndrome[7] (CRMS). CRMS was added to the Registry as a diagnostic option in 2010.

In 2015, data were entered for 614 individuals diagnosed with CRMS, 87 of whom were given this diagnosis during 2015. Entry of a diagnosis of CF versus CRMS into the Registry is a clinical decision; there is no validation that individuals meet published diagnostic criteria for CF or

CRMS. A comparison of clinical diagnoses of CF and CRMS in 2010 and 2011 showed that 41 percent of infants (n=126) who met the published diagnostic criteria for CRMS were entered into the Registry with a diagnosis of CF.[8] Analyses involving this cohort of people with CF must account for this misclassification.

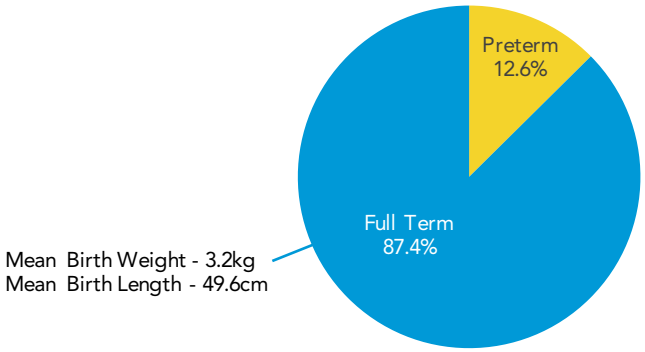
In addition to CRMS, individuals can be diagnosed with a CFTR-related disorder. This option has been available in the Registry since 2010. Individuals with this diagnosis do not meet diagnostic criteria for CF or CRMS but are affected by CF-related conditions such as congenital bilateral absence of the vas deferens (CBAVD) and often have mutations in the CFTR gene.[9] Collection and analysis of data from these individuals will provide new and important information for these distinct populations.

CF, CRMS and CFTR-related Disorder Diagnoses, 2015



In 2015, 613 newborn infants were diagnosed with CF. Of those with a known gestational age at birth, 87.4 percent were born full term, comparable with the figure for the general U.S. population.[10] The mean birth weight for full-term infants with CF is also about the same as for the U.S. population,[11] suggesting that infants with CF do not initially show nutritional deficiencies. The graph does not include the 109 infants who were born and diagnosed with CF in 2015 who did not have a gestational age recorded in the Registry (17.8 percent).

Gestational Age of Infants Born and Diagnosed with CF in 2015



"Preterm" refers to infants born at a gestational age less than 37 weeks. "Full term" refers to infants born at a gestational age greater than or equal to 37 weeks.

The majority of those diagnosed in their first year are asymptomatic or minimally symptomatic at time of diagnosis. Among the 13.3 percent of infants diagnosed in 2015 under age 1 with meconium ileus (or other intestinal obstruction), 31.7 percent had bowel perforation. Those diagnosed after age 1 often present with acute or persistent respiratory abnormalities.

Symptoms Reported at CF Diagnosis

	Diagnosed in 2015 (%)	Diagnosed in 2015 Age < 1 (%)	Diagnosed in 2015 Age ≥ 1 (%)	All Individuals (%)
Number of Individuals	**853**	**613**	**240**	**28,983**
Asymptomatic				
DNA Analysis	17.8	17.5	18.8	10.8
Family history	12.2	9.8	18.3	15.1
Newborn (neonatal) screening	59.6	81.1	4.6	22.1
Prenatal Screening (CVS[A], Amniocentesis)	3.5	4.6	0.8	2.3
Symptomatic				
Meconium ileus/other intestinal obstruction	9.8	13.4	0.8	18.1
Acute or persistent respiratory abnormalities	18.1	2.1	58.8	38.3
CBAVD[B] or Infertility/GU[C] abnormalities	2.2	0.0	7.9	0.4
Digital clubbing	1.8	0.0	6.3	0.5
Edema	0.1	0.0	0.4	0.6
Electrolyte imbalance	0.4	0.3	0.4	3.4
Failure to thrive/malnutrition	7.4	5.7	11.7	30.1
Liver problems	0.7	0.2	2.1	1.1
Nasal polyps/sinus disease	3.8	0.0	13.3	3.6
Rectal prolapse	0.2	0.0	0.8	2.9
Steatorrhea/abnormal stools/malabsorption	5.0	4.1	7.5	23.2
Other	5.6	2.6	13.3	4.5

Data are not mutually exclusive. We anticipate that additional 2015 diagnoses will be entered into the Registry in 2016.

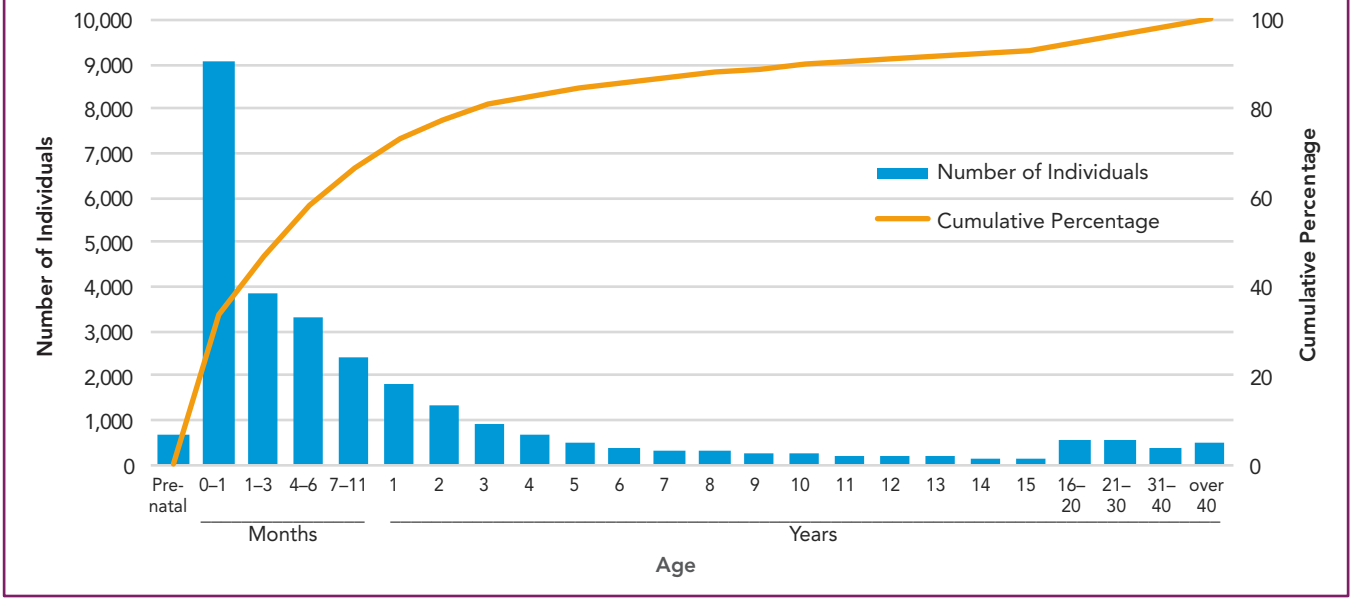
[A]*Chorionic villus sampling*

[B]*Congenital bilateral absence of the vas deferens*

[C]*Genitourinary abnormalities*

Previous figures in this section refer to infants born or diagnosed in 2015; the following figure includes all individuals followed in the Registry in 2015.

Age at Diagnosis of All Individuals with CF Seen in 2015



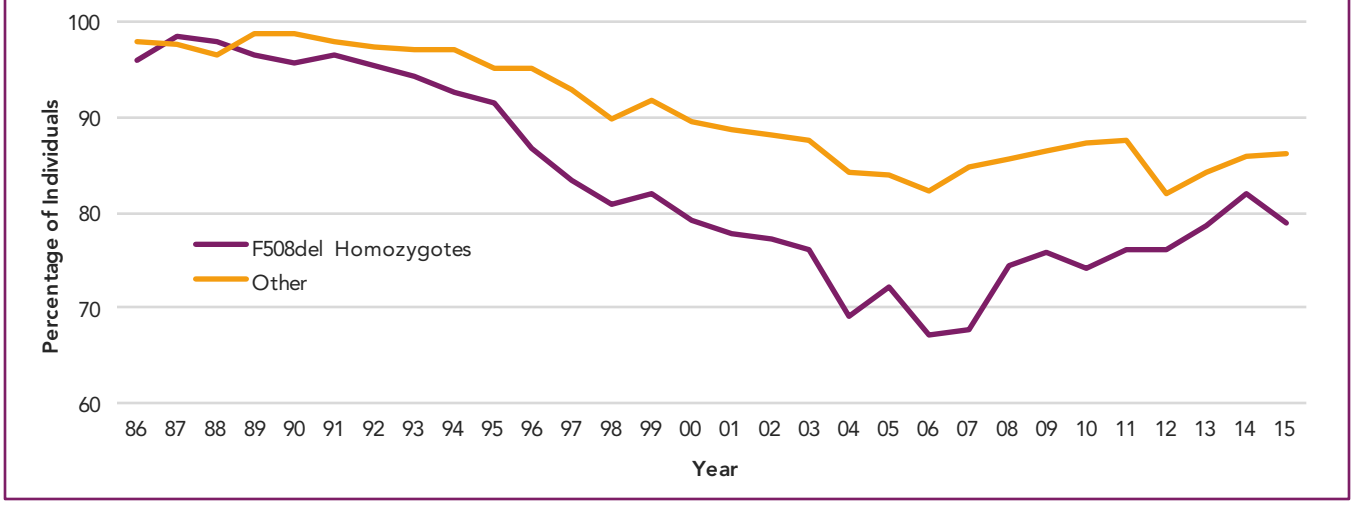
Among all individuals in the Registry in 2015, 66.8 percent were diagnosed in the first year of life.

Diagnostic Tests

Sweat Chloride Testing

Sweat chloride testing is an important diagnostic test recommended for all individuals regardless of genotype.[12] In 2015, 86.4 percent of individuals in the Registry had a sweat chloride test result recorded. The downward trend in the reporting of sweat chloride test results through the 1990s and early 2000s appears to have plateaued. Individuals who are homozygous for F508del, the most common CF-causing genetic mutation, are less likely to have sweat chloride values in the Registry than those with other mutations. Baseline sweat chloride tests are becoming more important as changes in sweat chloride are now viewed as indicators of the physiological effects of CFTR modulators.

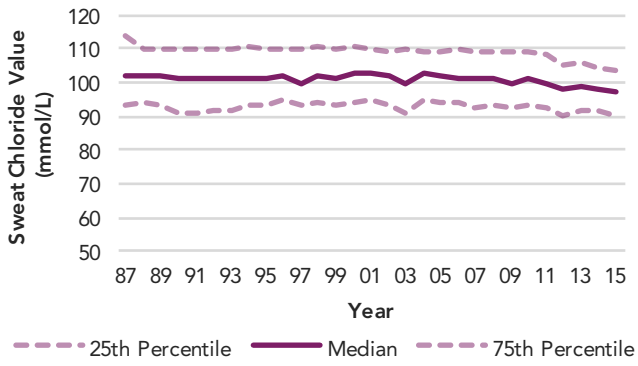
Percentage of Individuals with a Sweat Chloride Test Reported by Year of Diagnosis, 1986-2015



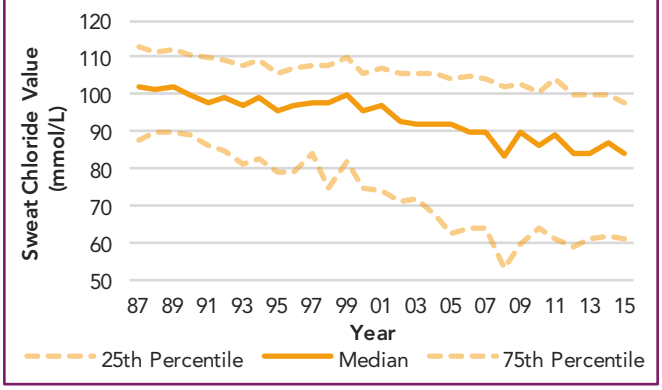
Some individuals diagnosed in 2015 may not have had a sweat chloride test result entered in the Registry before the close of the reporting year.

Individuals may have two F508del mutations (homozygous), one F508del mutation (heterozygous) or no F508del mutations. Median sweat chloride test results remain consistent for individuals who are F508del homozygous. In contrast, there has been a steady decline in median sweat chloride values among individuals who are not homozygous for F508del, suggesting that more individuals with "less severe" genotypes are being entered into the Registry.

Sweat Chloride Value of F508del Homozygous Patients by Year of Diagnosis, 1987-2015



Sweat Chloride Value of Patients Not Homozygous for F508del by Year of Diagnosis, 1987-2015



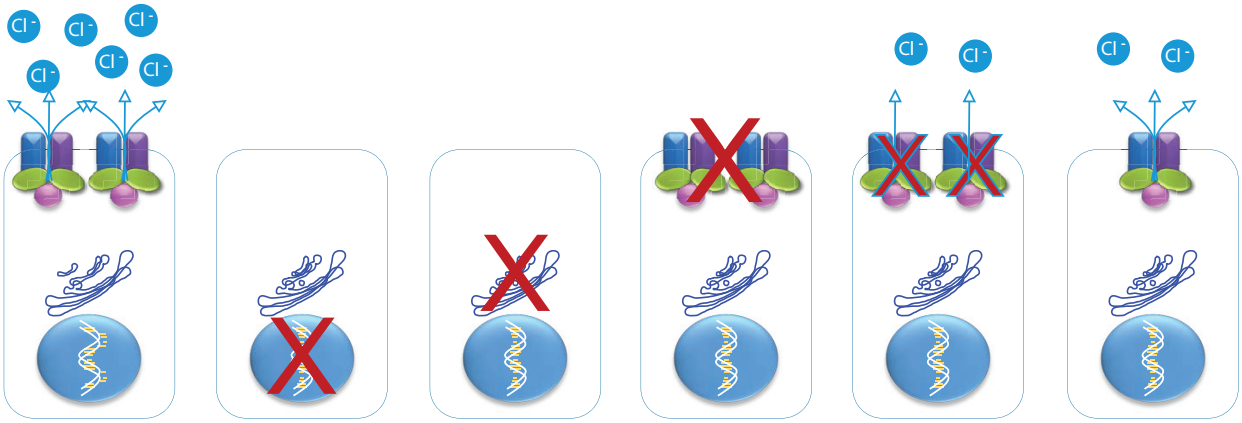
Genotyping

The cystic fibrosis transmembrane conductance regulator (CFTR) gene and the most prevalent CF causing mutation (F508del) were discovered in 1989. Since then, genotyping has been a key component of the diagnostic work-up. In addition, with the introduction of CFTR modulators, genotyping all people with CF is increasingly important to research and clinical care. In 2015, 97.8 percent of individuals (n=28,341) in the Registry had been genotyped. Among those, 5.1 percent have one or more alleles entered as "Unknown."

CFTR GENE MUTATIONS

To date, more than 1,800 mutations have been found in the CFTR gene.[13] Some mutations result in virtually no CFTR function and others are associated with some residual function. To help categorize CF disease-causing mutations on the basis of their resulting functional impact, researchers have created five classes.[14-16] This classification schema is an oversimplification as some mutations lead to more than one defect in CFTR function. For example, the R117H mutation results in both gating and conductance defects in CFTR. In addition, functional status has not been determined for all mutations. As a result, we use the term "class not identified" to refer to individuals who have been diagnosed with CF and genotyped but have one or more mutations whose functional consequences have not yet been determined.

One Way of Classifying CFTR Mutations



	Normal	Class I	Class II	Class III	Class IV	Class V
DESCRIPTION	CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.	No functional CFTR created.	CFTR protein is created, but misfolded, keeping it from reaching the cell surface.	CFTR protein is created and reaches cell surface, but the gate does not function properly.	The opening in the CFTR protein ion channel is faulty.	CFTR is created in insufficient quantities.
EXAMPLES		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F R117H	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

The most common CFTR mutation is F508del: 86.4 percent of individuals in the Registry have at least one copy of this mutation. There is a substantial drop in prevalence from F508del to the next most common mutations. No other mutation is currently found in more than 5 percent of the population with CF.

Prevalence of the 25 Most Common CFTR Mutations in People with CF Seen in 2015

CFTR Mutation			Number of Individuals	Percent of All People with CF
Legacy Name	cDNA Name	Protein Name		
F508del	c.1521_1523delCTT	p.Phe508del	24,487	86.4
G542X	c.1624G>T	p.Gly542X	1,314	4.6
G551D	c.1652G>A	p.Gly551Asp	1,245	4.4
R117H		p.Arg117His	816	2.9
N1303K	c.3909C>G	p.Asn1303Lys	692	2.4
W1282X	c.3846G>A	p.Trp1282X	652	2.3
R553X	c.1657C>T	p.Arg553X	514	1.8
1717-1G->A	c.1585-1G>A		450	1.6
621+1G->T	c.489+1G>T		467	1.6
3849+10kbC->T	c.3717+12191C>T		449	1.6
2789+5G->A	c.2657+5G>A		384	1.4
3120+1G->A	c.2988+1G>A		291	1.0
I507del	c.1519_1521delATC	p.Ile507del	232	0.8
D1152H	c.3454G>C	p.Asp1152His	225	0.8
R1162X	c.3484C>T	p.Arg1162X	211	0.7
3659delC	c.3528delC	p.Lys1177SerfsX15	202	0.7
1898+1G->A	c.1766+1G>A		199	0.7
G85E	c.254G>A	p.Gly85Glu	184	0.6
R347P	c.1040G>C	p.Arg347Pro	170	0.6
R560T	c.1679G>C	p.Arg560Thr	161	0.6
2184insA	c.2052_2053insA	p.Gln685ThrfsX4	170	0.6
A455E	c.1364C>A	p.Ala455Glu	153	0.5
R334W	c.1000C>T	p.Arg334Trp	152	0.5
Q493X	c.1477C>T	p.Gln493X	131	0.5
E60X	c.178G>T	p.Glu60X	115	0.4

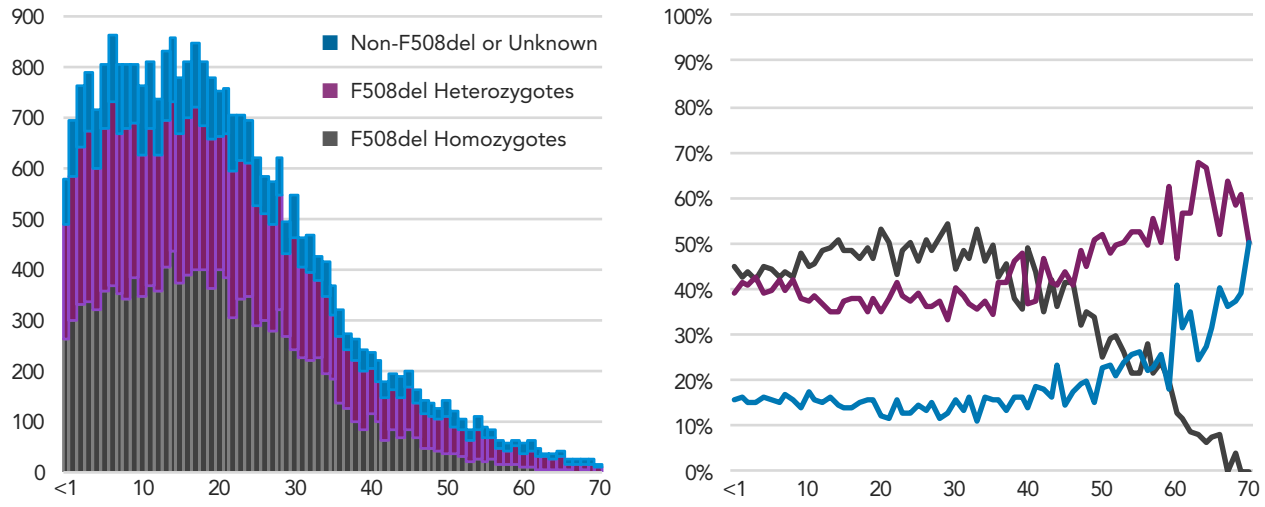
The number and percent of individuals with a given mutation include those with one or two copies of the mutation.

F508del Mutation Prevalence

F508del Mutation	Percent of All People with CF
Homozygous F508del	46.1
Heterozygous F508del	40.3
Neither F508del or Unknown	13.6

Since F508del is the most common mutation, we examined the distribution of individuals by age and F508del status: two F508del mutations (homozygote), one F508del mutation (heterozygote) or no F508del mutations. A decrease in the proportion of F508del homozygotes in older age groups is likely due to a survivor bias for individuals with "milder" genotypes. Late diagnosis of individuals with "milder" genotypes may also contribute to this trend.

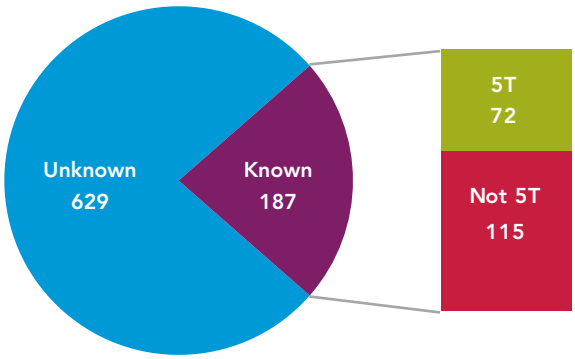
F508del Mutation Status by Age in Years, 2015 *(Stacked Bar Chart)*



Among less common mutations, the number of individuals with an R117H mutation has increased over the years. Among those genotyped in 1993, less than 1 percent had an R117H mutation, compared with almost 5 percent of those genotyped in 2015. This may be due to the inclusion of R117H in newborn screening algorithms. Of note, 84 (10.3%) of the 816 individuals with an R117H mutation and CF diagnosis had a sweat chloride value less than 30 mmol/L.

The clinical significance of the R117H mutation depends in part on the poly-T tract variant on the chromosome. Research indicates that a shorter poly-T tract is associated with a higher likelihood of having CF.[17, 18] Unfortunately, the Registry has incomplete information on the poly-T tract for the majority of individuals diagnosed with CF with the R117H mutation.

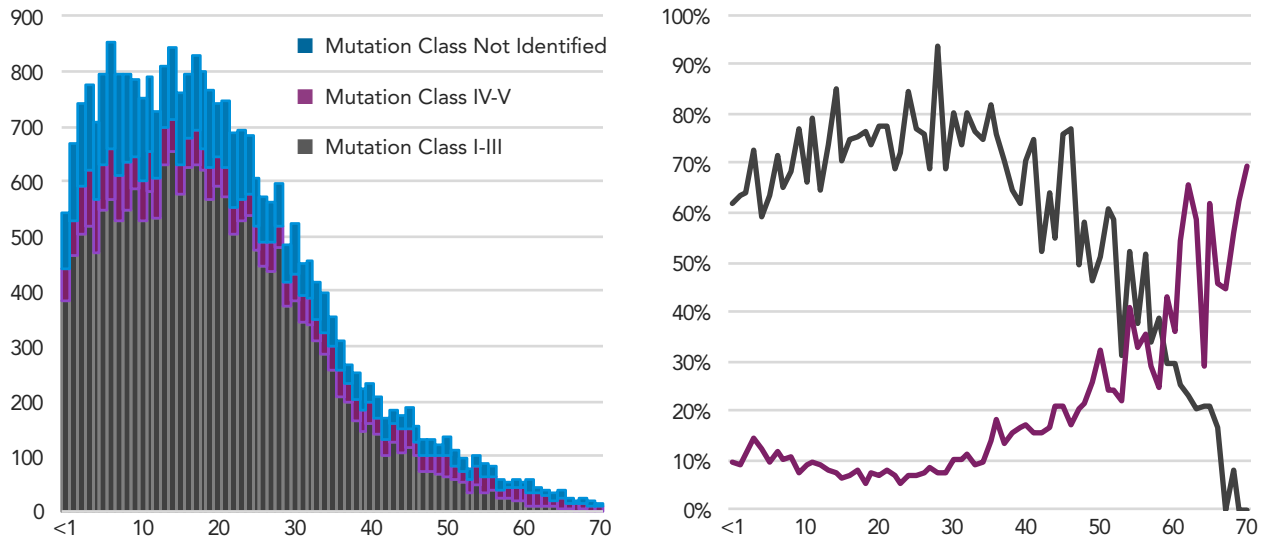
Poly-T Tract Status of Individuals with an R117H Mutation Seen in 2015



Throughout this report, we use mutation class categories. Individuals with two mutations in classes I, II or III are grouped together because these mutations typically lead to little or no CFTR function. Individuals with one or two mutations in classes IV or V are grouped together because these mutations are typically associated with residual CFTR function. Research has shown that this grouping of classes is associated with meaningful clinical differences between the groups.[14, 16]

The majority of children and young adults with CF have genetic mutations in classes I-III. The number and proportion of individuals in this group decreases in older ages. Conversely, we see a greater number of individuals with genotypes in classes IV-V who are under age 10, and older ages. This is likely due to the implementation of NBS and survivor bias, respectively.

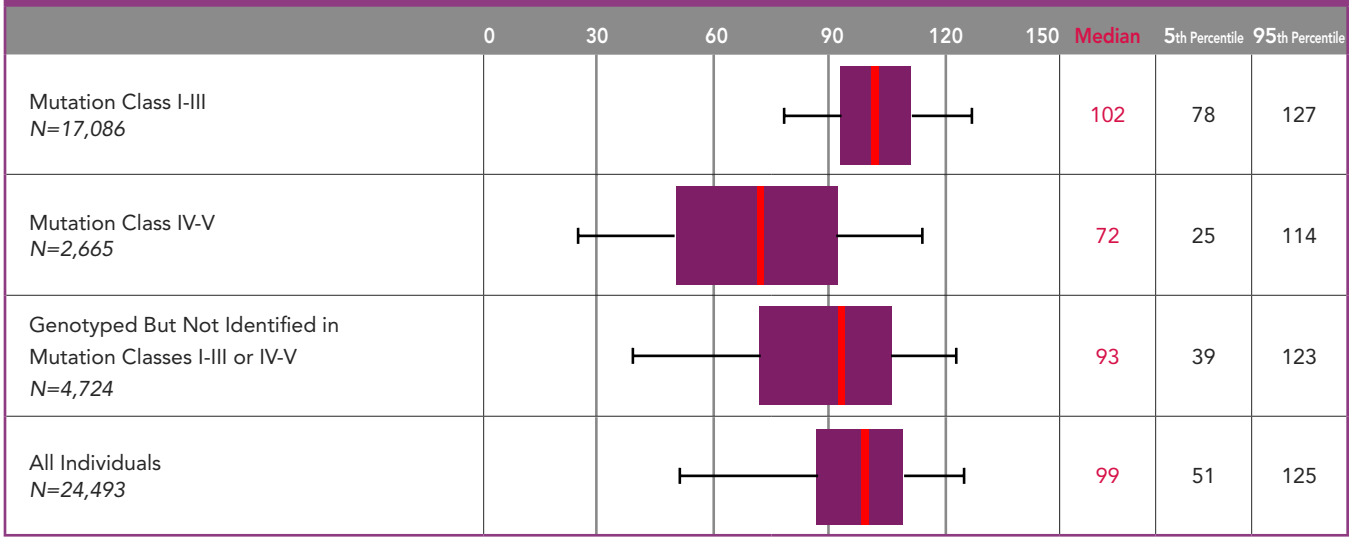
Mutation Class Status by Age in Years, 2015 *(Stacked Bar Chart)*



Of all individuals who were genotyped, 71.2 percent were classified in the class I-III group, 10.9 percent were classified in the class IV-V group and 17.9 percent could not be classified. As expected, individuals in the class I-III group are younger and are more likely to be prescribed pancreatic enzyme replacement therapy (98.6 percent of whom are taking PERT) than individuals with a mutation in the class IV-V group (38.2 percent of whom are taking PERT).

As expected, higher sweat test values are observed among individuals in classes I-III than in classes IV-V.

Sweat Chloride Value (mmol/L), by Mutation Class Group



These charts use the most recent sweat test value reported to the Registry. There is the potential that for some individuals, this value reflects sweat chloride values after initiation of CFTR modulator therapy.

GUIDELINES: CARE, SCREENING AND PREVENTION

The CF Foundation has developed clinical practice guidelines for routine care and screening for individuals with CF during infancy, childhood and adulthood.[19-21] In accordance with guidelines for people with CF over age six,[20, 21] many CF care centers report four office visits, two pulmonary function tests and at least one microbiology culture annually for the majority of their CF patients. Similarly, among children age 2 to 5, the majority have at least four visits and at least one culture.

However, adherence to the recommendation that CF care centers perform quarterly respiratory cultures continues to be lower and more variable across the CF care center network.[22] CF care centers report that respiratory therapists/physical therapists, dietitians/nutritionists and social workers evaluate most of their patients at least once per year, as recommended.[23]

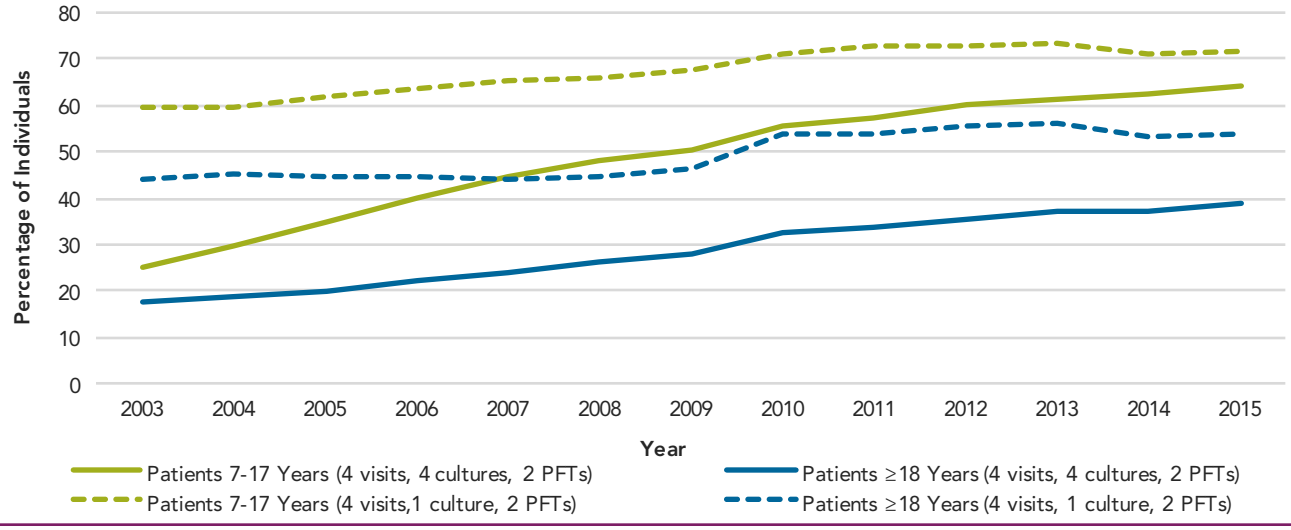
There is significant variation by CF care center in several key screening measures, including measurement of immunoglobulin E (IgE) for allergic bronchopulmonary aspergillosis (ABPA) and dual-energy X-ray absorptiometry (DXA) scan for osteopenia/osteoporosis. The influenza vaccination rate for people with CF age 6 months and older remains high across the CF care center network. Smoking and secondhand smoke exposure remain challenges, particularly for infants and young adults.

Patient Care Guidelines

The percentage of individuals receiving care that meets CF Foundation care guidelines has increased in recent years. Because individuals should be able to perform reliable pulmonary function tests (PFTs) at age 6 and older, we use guidelines criteria for those age 7 and older to ensure that individuals were eligible to perform a reliable PFT for the entire year.

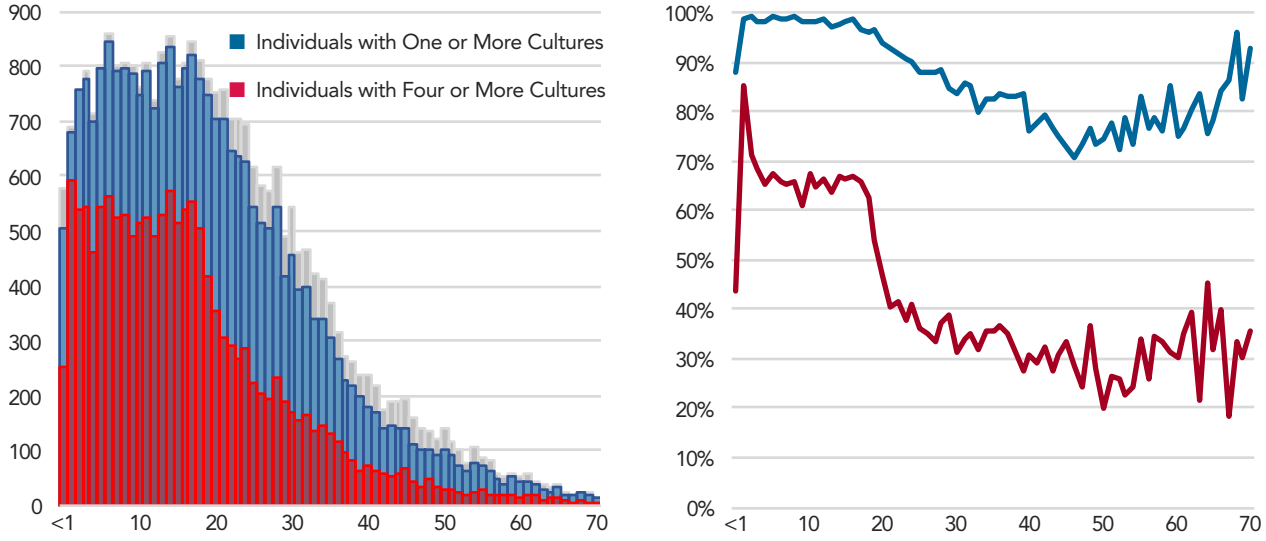
Over the past decade, the number of children and adults receiving at a minimum the recommended four visits, four respiratory cultures and two PFTs has doubled.[21, 22] The percentage of adults who receive care that meets guidelines criteria remains lower than that observed in children. However, over half of adults are being seen at least four times, complete two or more PFTs and are cultured at least once during the year.

Percentage of Patients Meeting Guidelines for Visits, Cultures and PFTs, 2003–2015



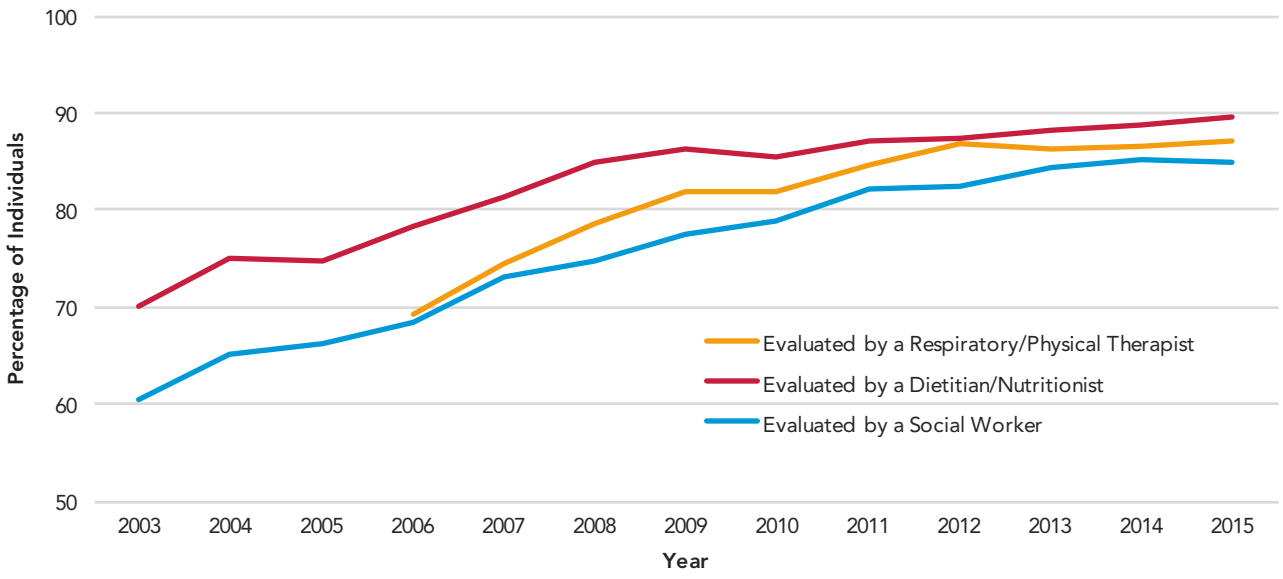
The guidelines on infection prevention and control recommend that individuals with CF have quarterly respiratory cultures.[22, 24] Nearly 98 percent of individuals received at least one culture in 2015, and 54.9 percent of individuals had four or more respiratory cultures. Those under age 18 were more likely to meet the recommendation for four cultures.

Number of Cultures by Age in Years, 2015



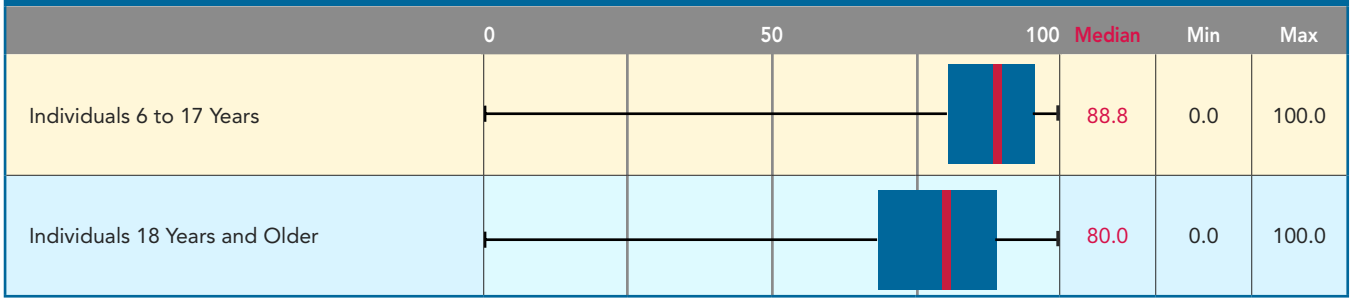
The multidisciplinary care team plays an important role in CF care. Over time, there has been an increase in the number of individuals with CF who receive at least an annual evaluation from their respiratory therapist, dietitian and social worker. In 2015, 70.9 percent of individuals were evaluated by all three specialists.

Percentage of Patients Evaluated by Multidisciplinary Care Team Members, 2003–2015



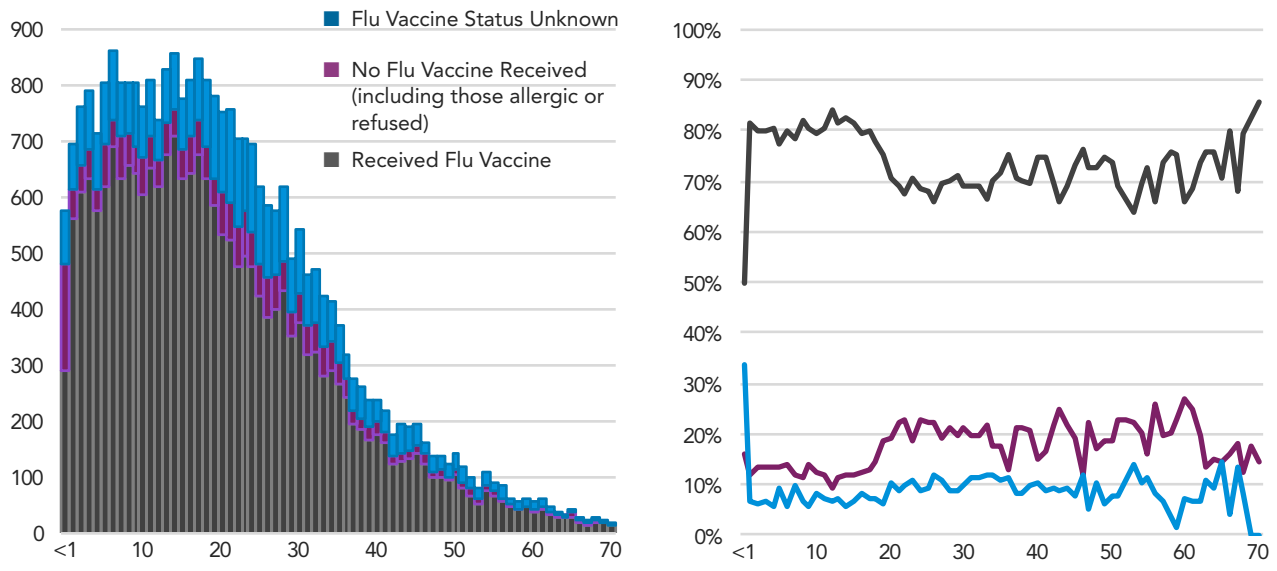
The CF Foundation's consensus statement on ABPA recommends screening individuals 6 years and older for ABPA by annual measurement of total serum IgE concentration.[25]

Percentage of Individuals with an IgE Measurement, by Center



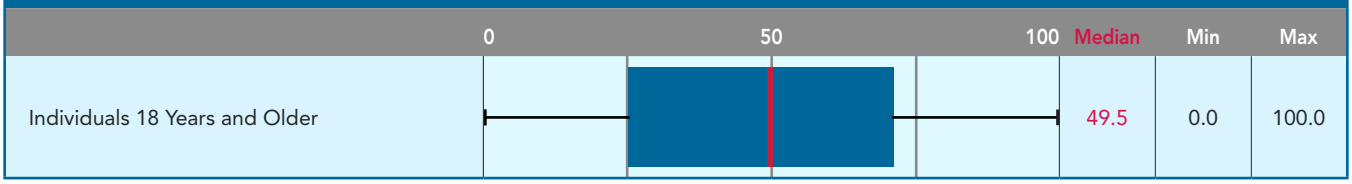
The Centers for Disease Control and Prevention's Advisory Committee on Immunization Practices recommends influenza vaccination for all individuals with CF age 6 months and older.[26] The influenza vaccination rate of people with CF 6 months and older is about 75 percent of the total population and 90 percent of those with a known vaccination status (excluding the 16 percent with unknown status).

Flu Vaccine Status by Age in Years, 2015 *(Stacked Bar Chart)*



The CF Foundation consensus statement on bone health and disease recommends screening all adults with CF with a DXA scan and subsequent follow-up based on the findings of the baseline scan.[27] Annual screenings are recommended only for individuals with DXA z-scores that are lower than two standard deviations below the mean, with less frequent screening recommended for those with higher values. Therefore, in the figure below we group five years of data.

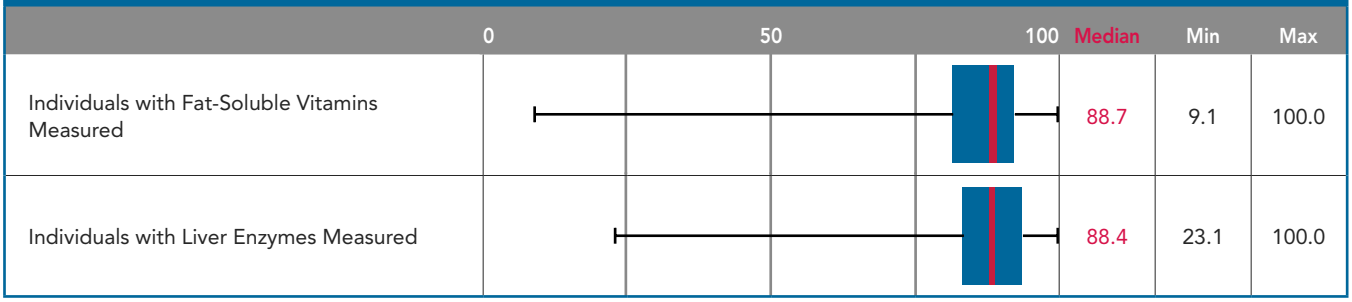
Percentage of Individuals with a DXA Scan in the Past Five Years, by Center



Includes any DXA scans performed during 2011–2015. Previously, we reported the percentage that had a DXA scan within the Registry reporting year.

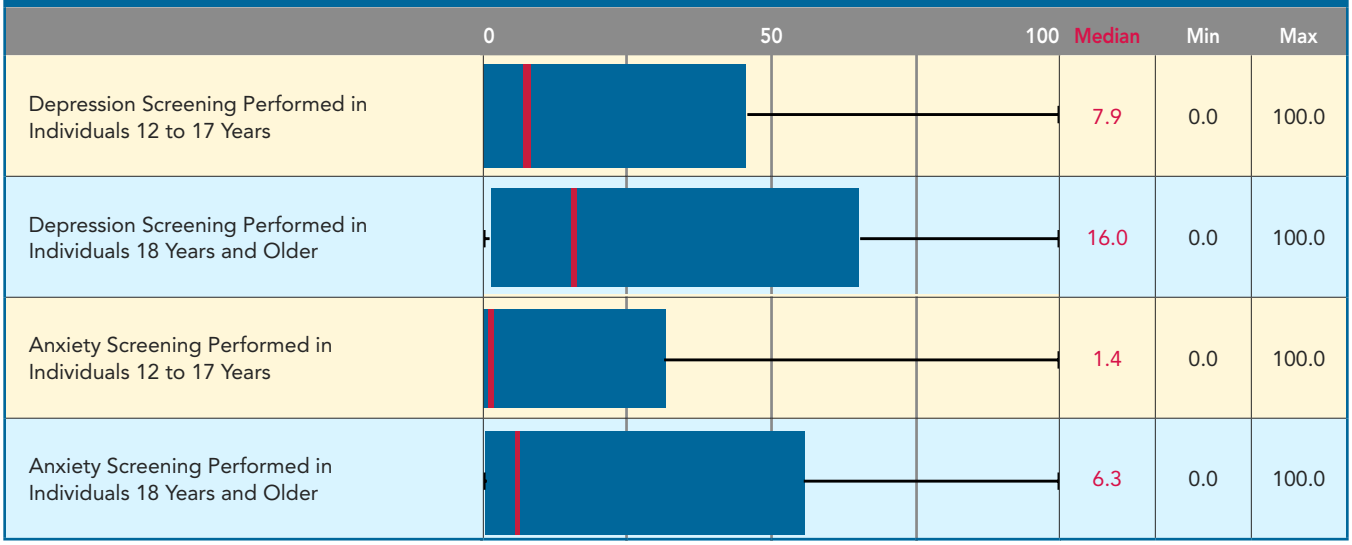
CF Foundation guidelines recommend annual measurement of fat-soluble vitamins to screen for vitamin deficiency.[21, 28] The CF Foundation Hepatobiliary Disease Consensus Group recommends a yearly panel of liver blood tests for all people with CF to screen for possible liver disease. Registry data suggest that these tests are being done on the majority of individuals.[29]

Percentage of Individuals Screened by or Monitored with Annual Labs, by Center



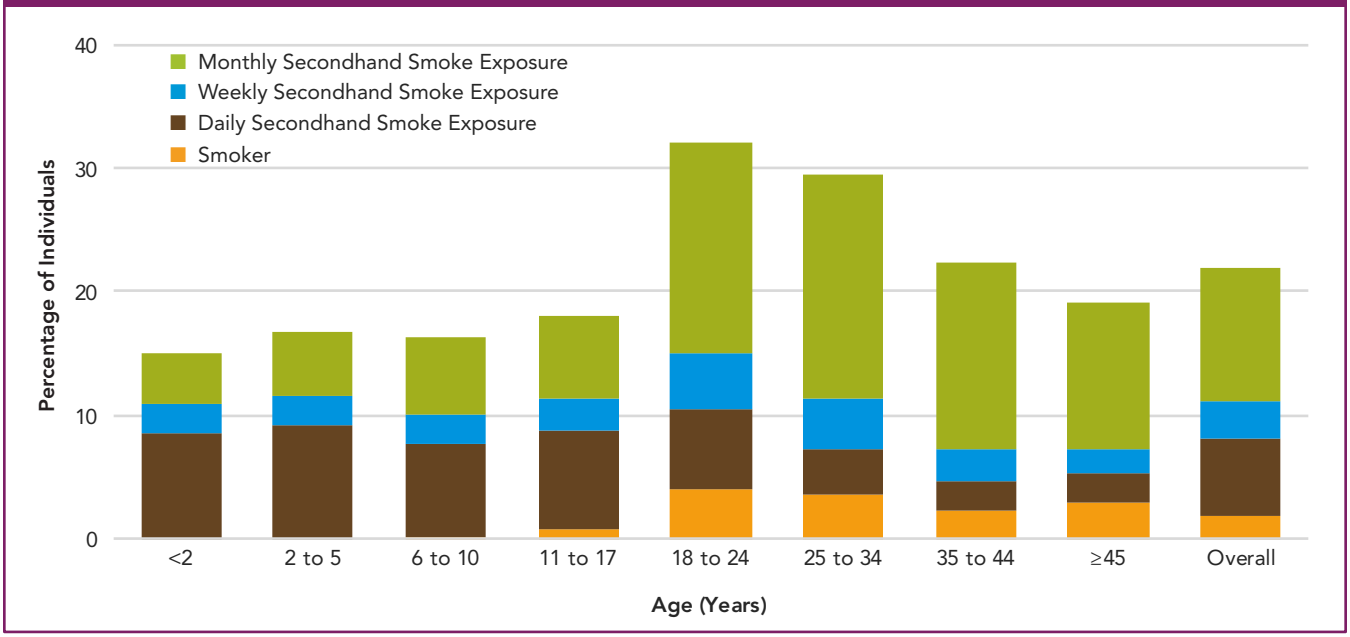
In 2015, the CF Foundation and the European CF Society jointly released the first guidelines on screening for depression and anxiety among individuals with CF and caregivers of children with CF. Annual screening is recommended for all individuals with CF who are age 12 and older, as well as caregivers of children with CF. The chart below shows some preliminary data from 2015, the first year that data on screening of individuals with CF were collected in the Registry. There is currently wide variation in screening across the CF care center network, with more screening for depression than for anxiety. Data on caregiver screening are not included in the Registry at this time.

Percentage of Individuals with Mental Health Screening, by Center



Of additional concern for individuals with CF is exposure to tobacco smoke. In 2015, 21.8 percent of individuals with CF reported monthly or more frequent exposure to tobacco smoke, either secondhand or as a smoker. Exposure to tobacco smoke is a substantial problem that causes disease and premature death in children and adults.[30] Cigarette smoking prevalence is lower in the CF population than in the general U.S. population — only 3.4 percent of adults with CF are smokers, compared with 16.8 percent in the general population in 2014.[31] However, smoking and secondhand smoke exposure remain significant concerns, especially for infants and young adults. Smoke exposure was unknown for 38.4 percent of individuals with CF, who were excluded from the analyses.

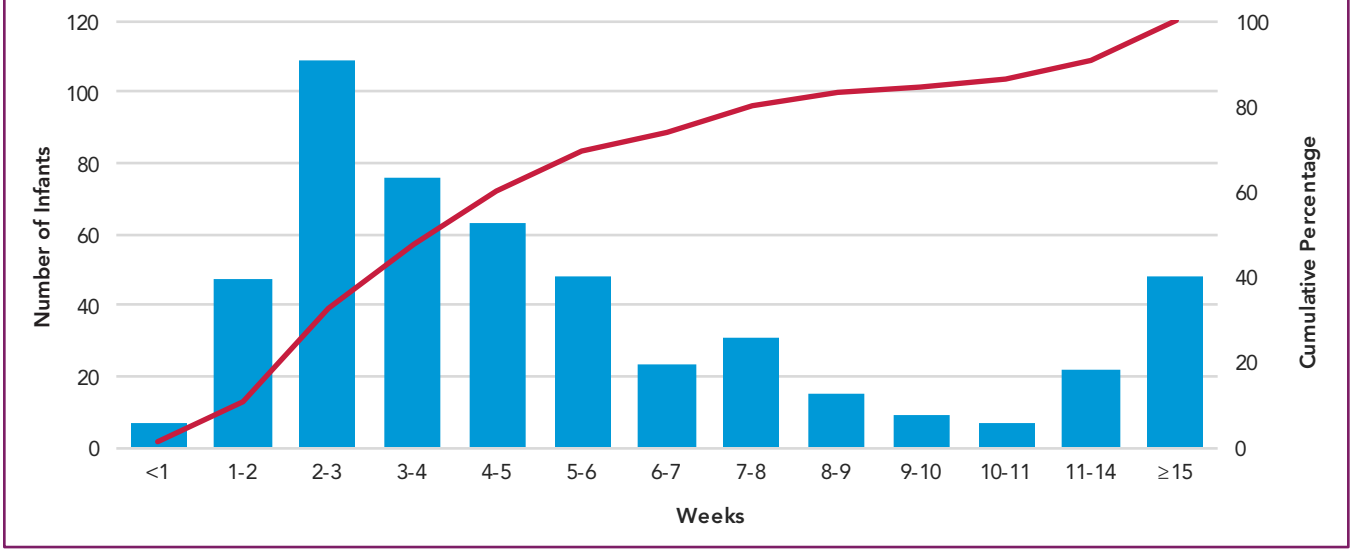
Tobacco Smoke Exposure by Age in 2015



Infant Care Guidelines

The CF Foundation guidelines for diagnosis of CF recommend that infants with a positive newborn screen undergo a sweat chloride test. It is important to make a definitive diagnosis as quickly as possible so families can be educated about the disease and treatment can be started.[6]

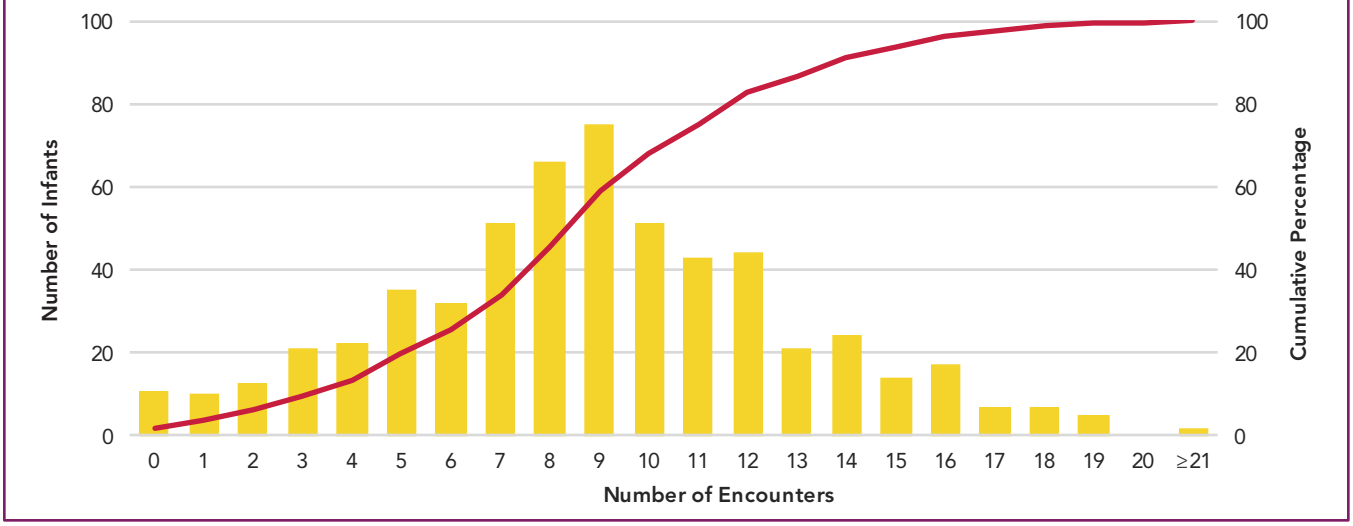
Time from Birth to First Recorded Sweat Test for Infants with CF Born in 2014 and Detected by Newborn Screening (n=505)



The chart shows data for children born in 2014 because a full year of data is available for these individuals. Median time to first sweat test for these individuals is 30 days. In 2014, 77 infants (13.2 percent) who were detected by NBS did not have a sweat chloride test reported to the Registry by the end of 2015 and thus are not included in this analysis.

The CF Foundation infant care guidelines recommend monthly CF care center visits during the first 6 months of life and every 1 to 2 months in the second 6 months.[6] Therefore, we expect infants with CF, detected by NBS, to have 9 to 12 visits in the first year of life. There is marked variation in the number of encounters for individuals in the first year of life across the CF care center network.

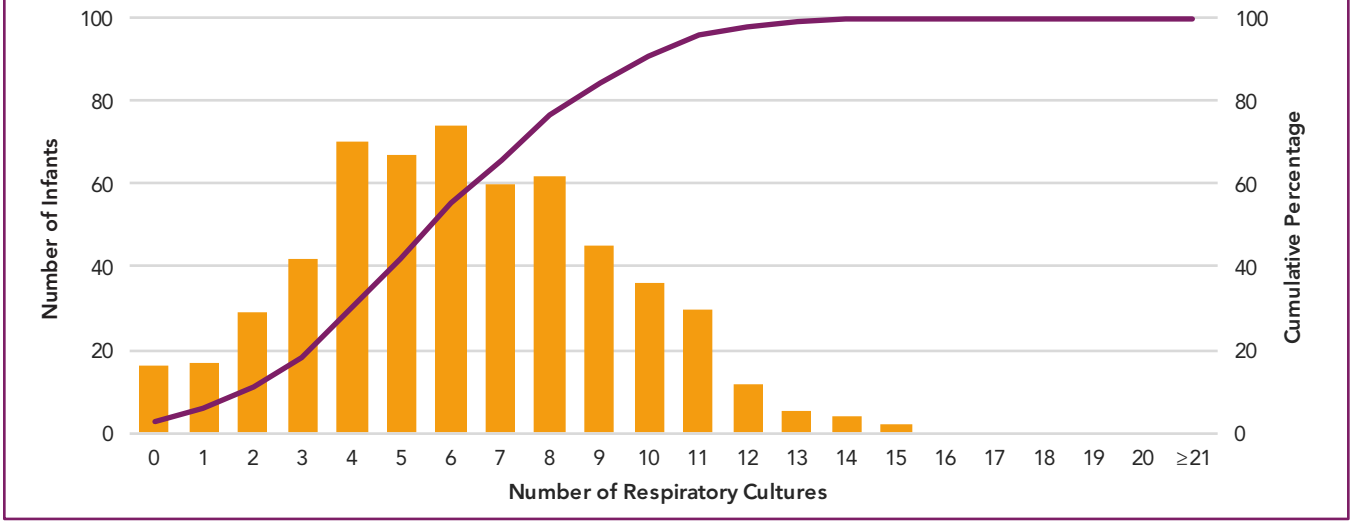
Number of Encounters in the First Year of Life for Infants with CF Born in 2014 and Detected by Newborn Screening (n=571)



The chart shows data for children born in 2014 because a full year of data is available for these individuals. The median number of visits in the first year of life is eight.

Respiratory cultures are being collected at the majority of clinic visits for infants with CF. Guidelines recommend that cultures be performed at least quarterly during the first 2 years of life.[6]

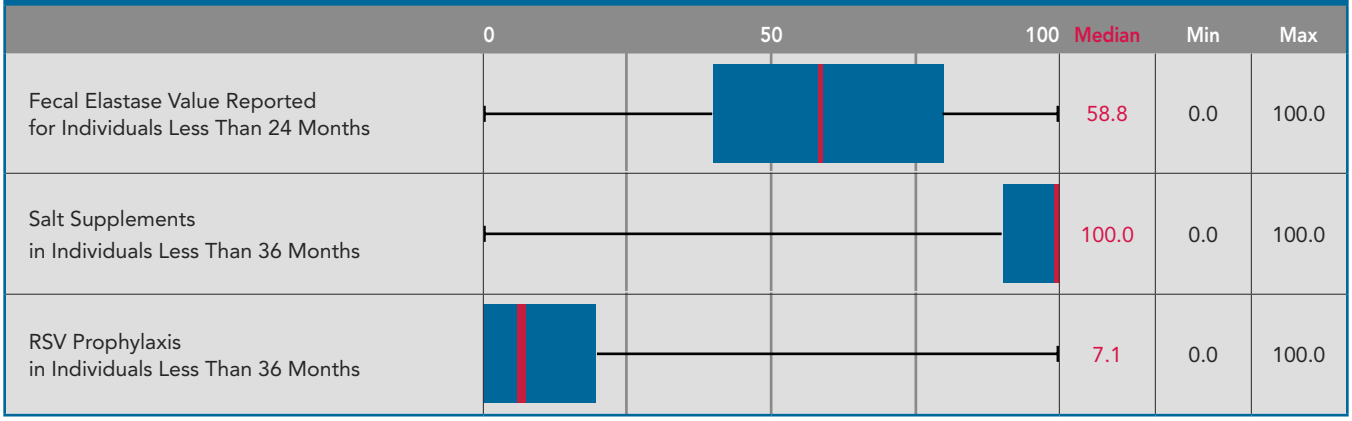
Number of Respiratory Cultures in the First Year of Life for Infants with CF Born in 2014 and Detected by Newborn Screening (n=571)



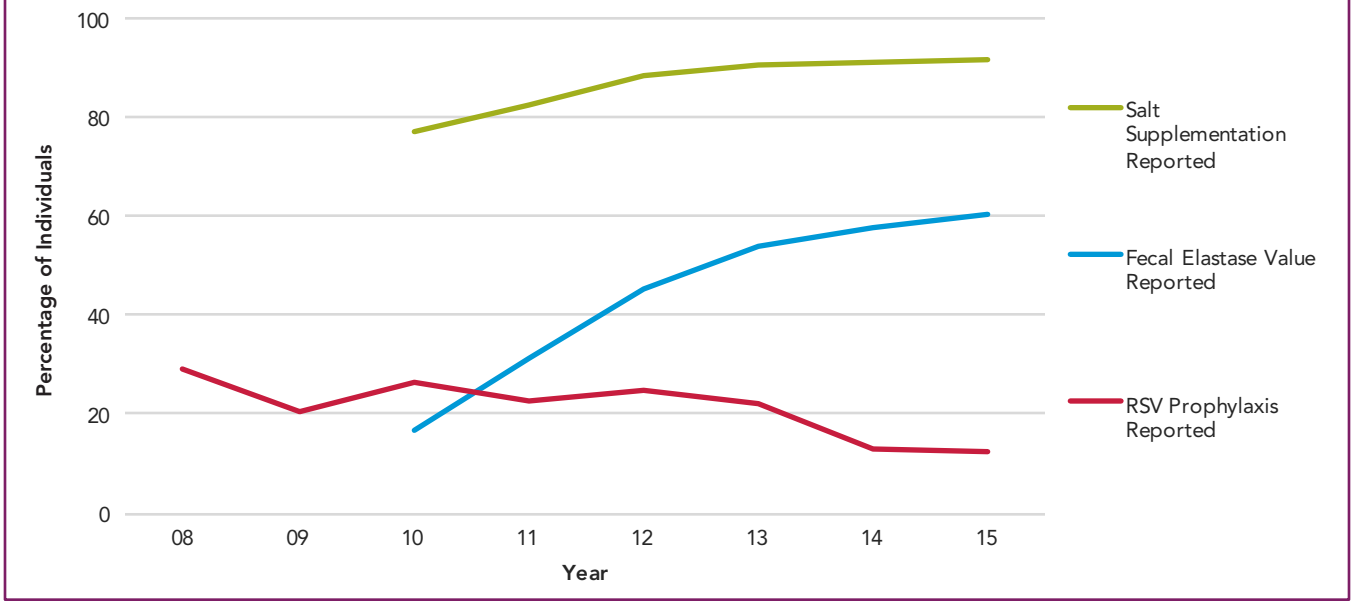
The chart shows data for children born in 2014 because a full year of data is available for these individuals. The median number of cultures is five.

Fecal elastase testing, which provides an objective measure of pancreatic function, is recommended in the infant care guidelines.[6] There is marked variation in the use of this test across the CF care center network. The guidelines also recommend that infants begin salt supplementation after diagnosis, and this is widely followed across the CF care center network. We observe substantial variation in the utilization of palivizumab (respiratory syncytial virus, or RSV, prophylaxis) with a downward trend since 2008. The current American Academy of Pediatrics recommendation is that palivizumab should not be routinely used in individuals with CF. The CF Foundation infant care guidelines recommend that its use be considered for infants with CF.[6] Nearly all CF care centers are prescribing the therapy for some infants with decreased use in recent years.

Infant Care Guidelines, by Center



Testing and Therapies for Individuals Under 24 Months of Age, 2008-2015



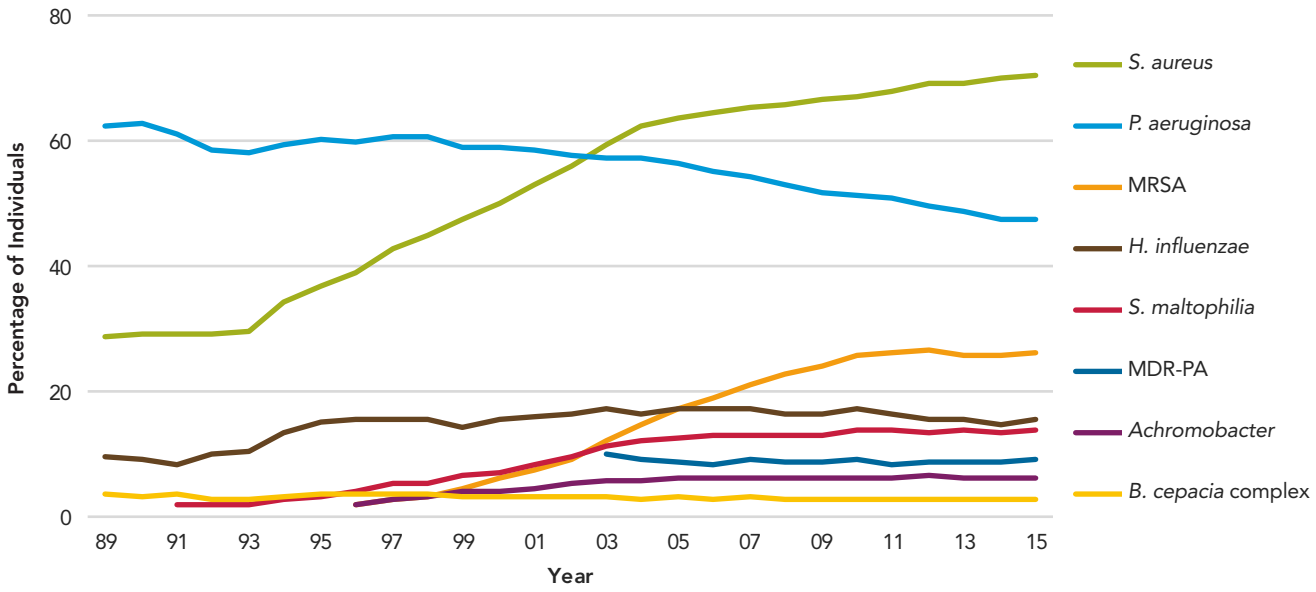
MICROBIOLOGY

Bronchiectasis with chronic pulmonary infections represents a serious problem for most individuals with CF. This section provides information on trends in CF pathogens over time and by age group. Updated infection prevention and control guidelines provide current best practices for reducing exposure to CF pathogens in the health care setting and in everyday life.[24]

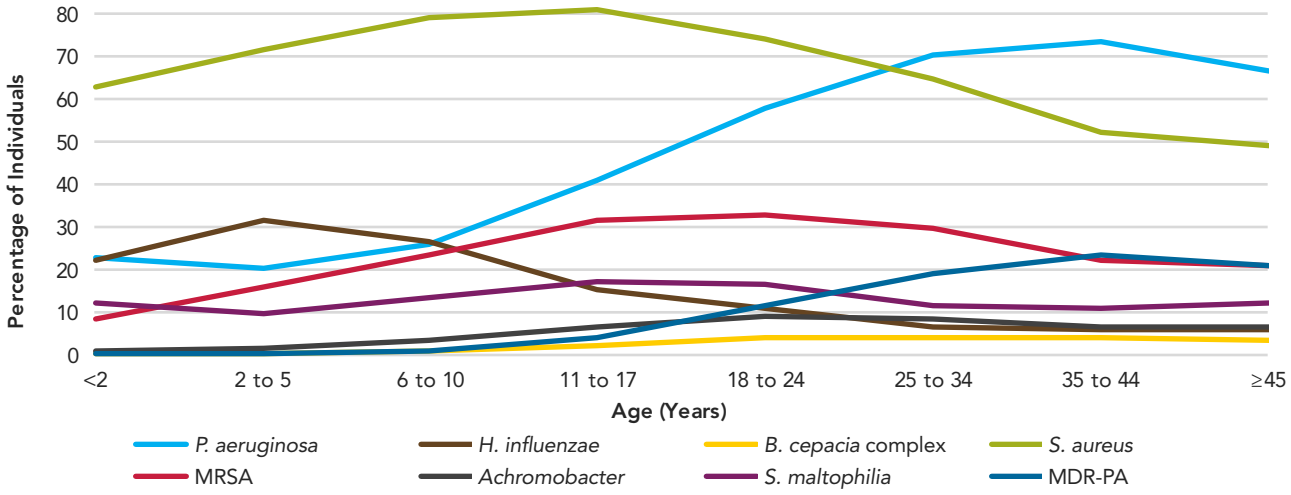
The prevalence of *Pseudomonas aeruginosa* (*P. aeruginosa* or *PA*) continues to decrease. This may in part relate to widespread implementation of therapy to eradicate initial acquisition.[24, 32]

Some of the increase in *Staphylococcus aureus* may be due to improved microbiologic practices for detection of Gram-positive organisms. From 2000 to 2015, there was about a five-fold increase in the numbers of individuals with CF with a culture positive for MRSA. Since 2010, prevalence appears to have plateaued. Research has shown that about two-thirds of individuals with MRSA had strains associated with hospital-acquired infections while one-third had strains associated with community-acquired infections.[33-35] The stabilization of prevalence is potentially due to increased awareness and infection prevention and control strategies.

Prevalence of Respiratory Microorganisms, 1989–2015



Prevalence of Respiratory Microorganisms by Age Cohort, 2015



The graph above provides a snapshot of the individuals who cultured positive for a microorganism during 2015. The table below displays that information, along with median age in years at first positive culture for the microorganism. Overall, *S. aureus* and *H. influenzae* are typically first cultured in young children and other microorganisms are first cultured during adolescence and young adulthood.

Microbiology Results for Individuals Seen and Cultured in 2015

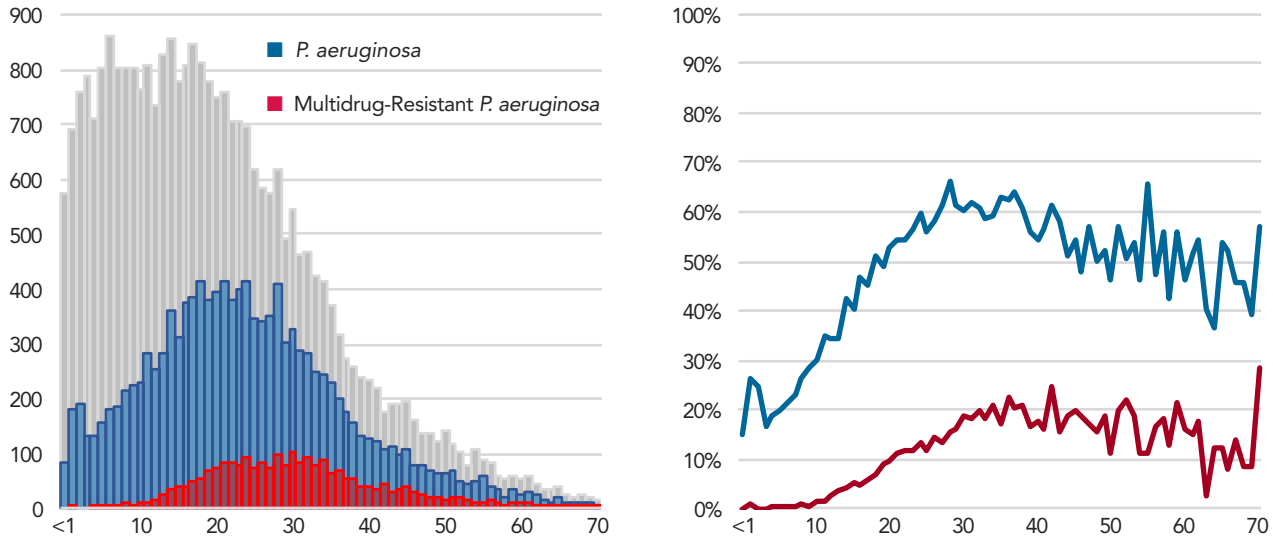
	Percent with Infection	Median Age at First Infection
S. aureus	70.6	3.6
P. aeruginosa	47.5	5.5
MRSA	26.0	11.9
H. influenzae	15.5	2.6
S. maltophilia	13.6	10.0
MDR-PA	9.2	22.4
Achromobacter	6.1	14.3
B. cepacia complex	2.6	19.9

Pseudomonas aeruginosa

The percentage of individuals who cultured positive for *P. aeruginosa* has continued to decline over time, with the largest decrease observed among individuals younger than 18 years (50.7 percent had a positive culture in 1995 compared with 30.4 percent in 2015). Many individuals with CF now transition to adult care without *P. aeruginosa* in their respiratory tract.

Rates of multidrug-resistant *P. aeruginosa* (MDR-PA) infection are most notable in older adolescents and adults with CF. These findings likely reflect cumulative exposure to antibiotics. The clinical significance of this drug resistance is unclear. In 2015, 9.2 percent of individuals with a bacterial culture were reported to have MDR-PA and 19.4 percent of individuals with a *P. aeruginosa* infection were reported to have MDR-PA.

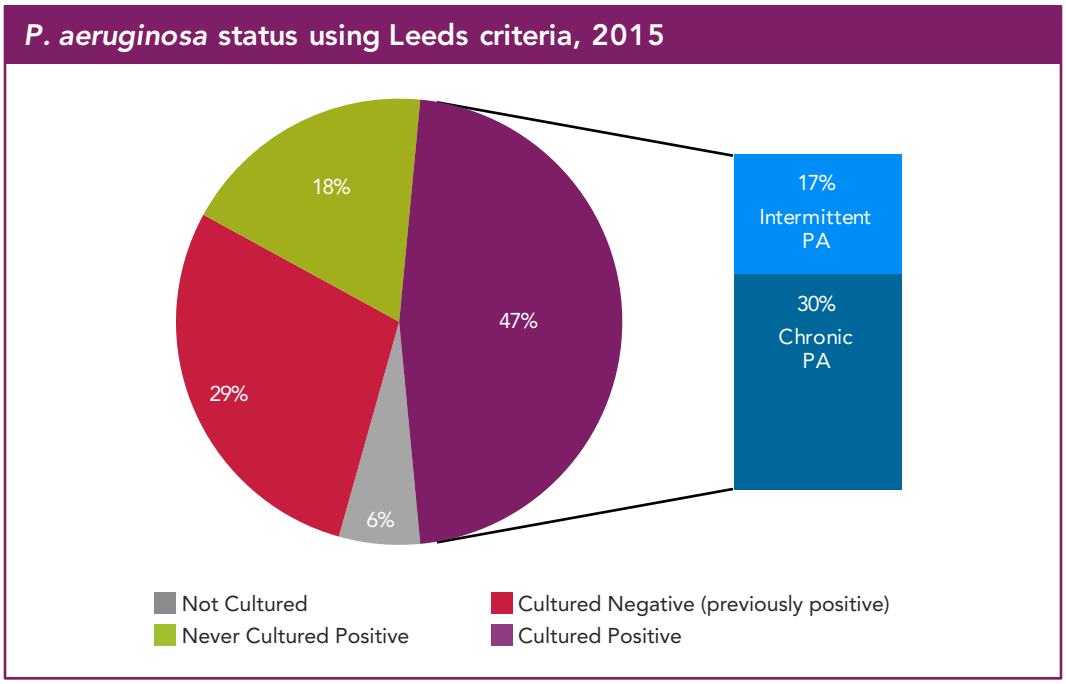
P. aeruginosa and Multidrug-Resistant _P. aeruginosa_ by Age in Years, 2015



Multidrug resistance is defined as resistance to all antibiotics tested in two or more classes in a single culture.

Researchers have developed a classification system, known as the Leeds criteria, to categorize individuals on the basis of *P. aeruginosa* infection status. The categories are "never having a positive *P. aeruginosa* culture," "free of a positive *P. aeruginosa* culture in the past 12 months," "intermittent infection" (less than 50 percent of their cultures in the past year were positive for *P. aeruginosa*) and "chronic infection" (more than 50 percent of their cultures in the past year were positive for *P. aeruginosa*). In 2015, 18 percent of individuals in the Registry had never had a positive culture for *P. aeruginosa* . In addition, another 29 percent of individuals had cultures that were negative for *P. aeruginosa* during the entire calendar year but had a positive culture in a previous year. Some 47 percent of individuals had at least one positive culture in 2015, of which 30 percent were categorized as having chronic infection, and 17 percent as having intermittent infection.

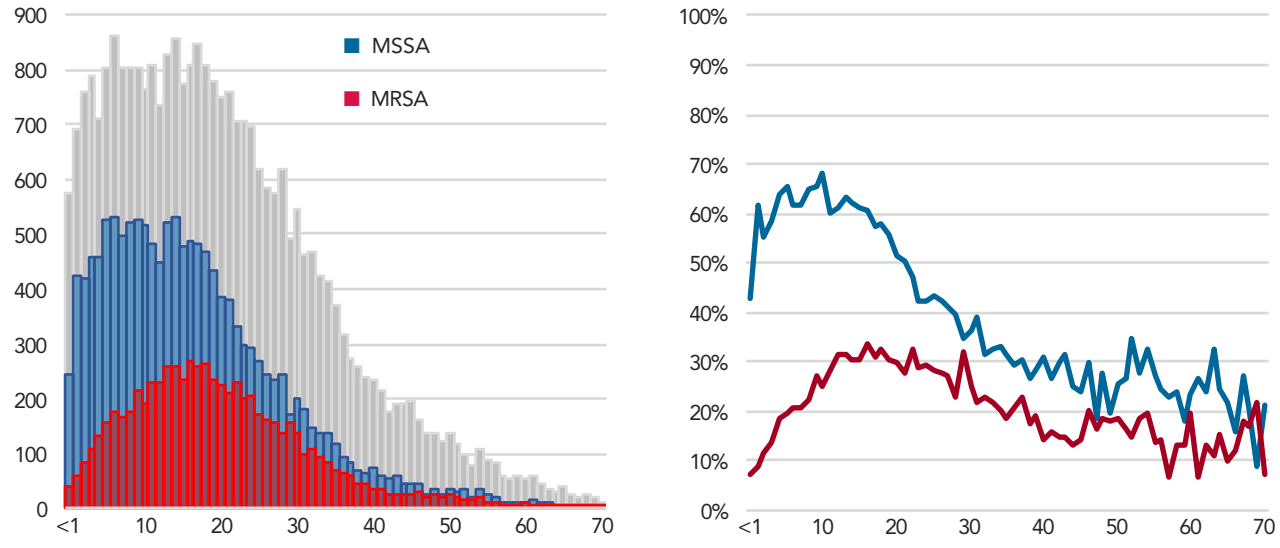
P. aeruginosa status using Leeds criteria, 2015



Staphylococcus aureus

The prevalence of MRSA has markedly increased over the last 25 years, which reflects secular trends. This chart shows that the highest prevalence of MRSA occurs in individuals between the ages of 10 and 30.

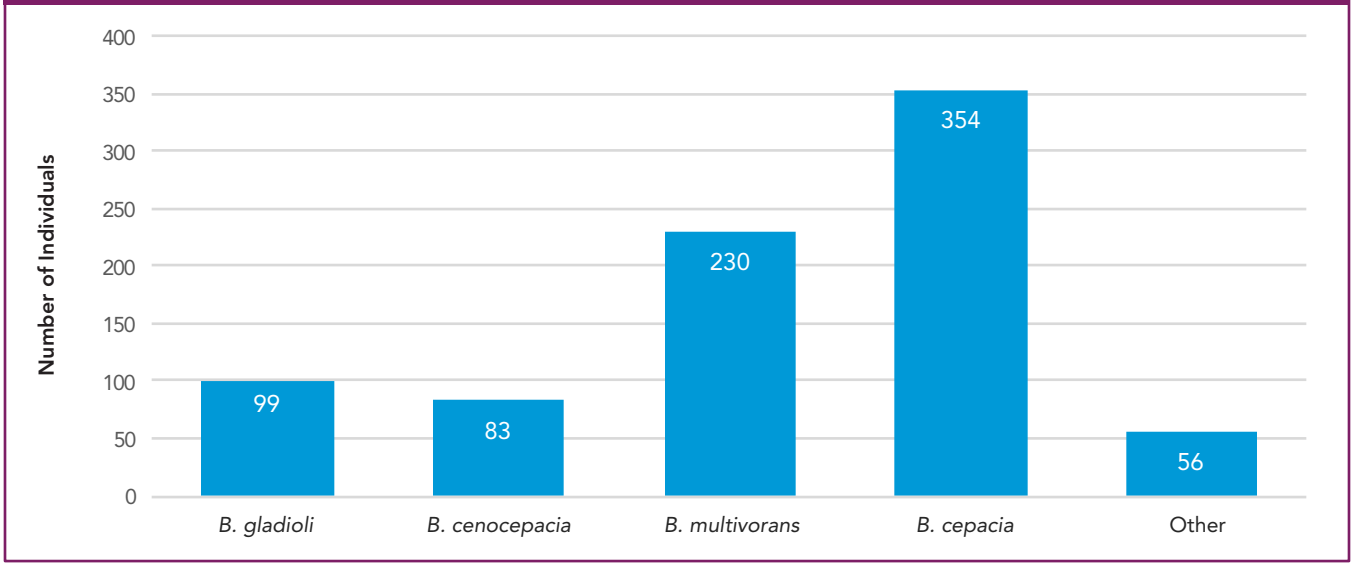
MSSA and MRSA by Age in Years, 2015



Burkholderia cepacia complex

In 2015, 664 people with CF had a culture positive for *Burkholderia cepacia* (*B. cepacia*) complex: 93.6 percent of those isolates were confirmed at the CF Foundation *B. cepacia* Research Laboratory and Repository at the University of Michigan.

Burkholderia Species Confirmed at the *B. cepacia* Research Lab, 2015



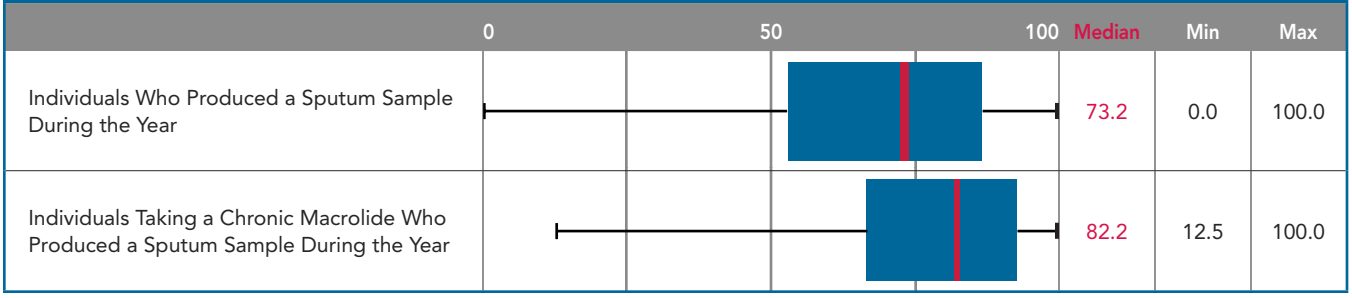
Data are not mutually exclusive. Some individuals had more than one species isolated in 2015. Note that B. gladioli *is not part of the* B. cepacia *complex. Due to changes in data processing the values are higher than those reported in 2014 and earlier. However, there is no significant increase in the prevalence of* Burkholderia *species in the CF population.*

Nontuberculous Mycobacteria

The prevalence of nontuberculous mycobacteria (NTM) infections is increasing in the general population.[36] Since 2010, the Registry has collected more robust information on mycobacterial cultures and NTM infections.

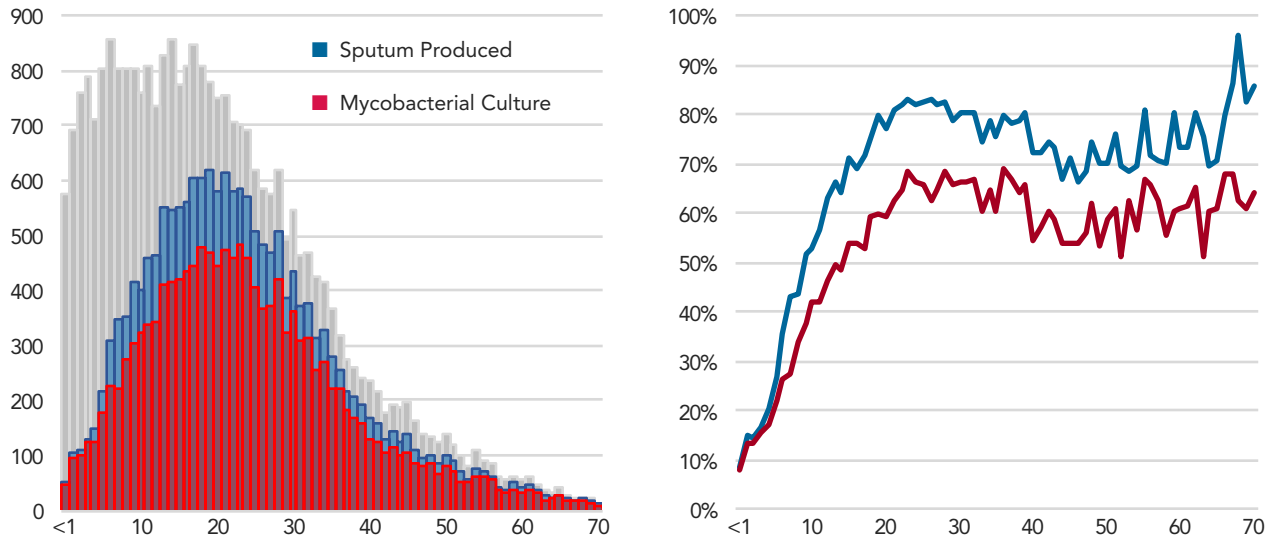
The CF Foundation/European Cystic Fibrosis Society Guidelines recommend that individuals with CF who are able to expectorate be cultured for NTM infections annually.[37] Individuals should also be screened before and six months after beginning azithromycin and annually thereafter.[3] The data show improvement in screening rates over time, but wide variation by CF care center persists in these measures.

Percentage of Individuals with a Mycobacterial Culture, by Center



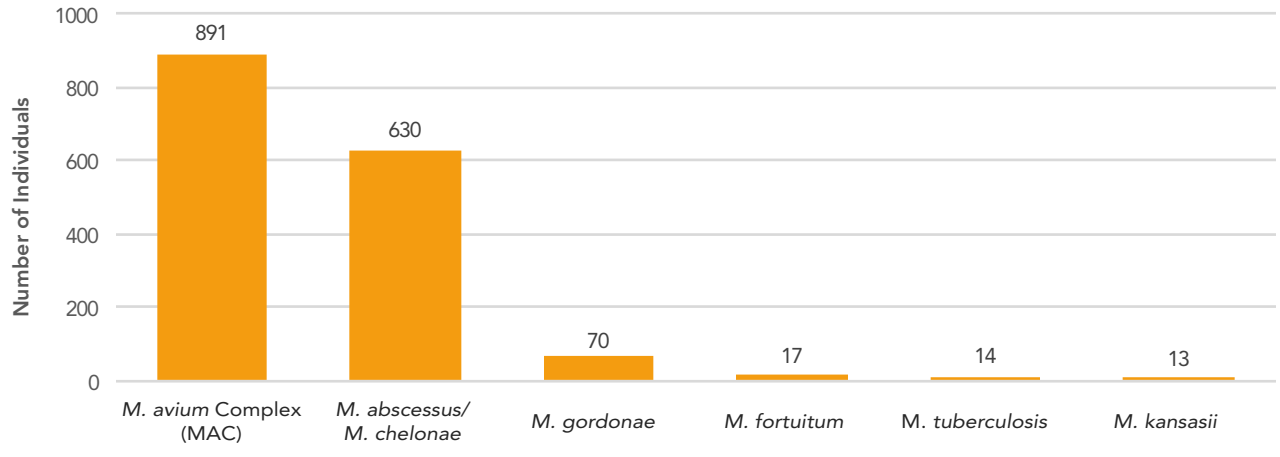
A throat swab is insufficient for a mycobacterial culture, so a patient must be able to produce sputum in order for this culture to be performed. As shown in the chart below, a majority (71.1%) of the individuals who produced a sputum culture for a bacterial culture also had a mycobacterial culture performed during the year.

Sputum Produced and Mycobacterial Cultures by Age in Years, 2015



Of the 14,225 individuals who had a mycobacterial culture performed in 2015, 1,692 (11.9 percent) had a mycobacterial species isolated one or more times. The relative proportion of *M. abscessus* isolated in 2015 is higher than reported over a decade ago in a CF Foundation-supported multicenter prevalence study.[38]

Mycobacterial Species Isolated in 2015



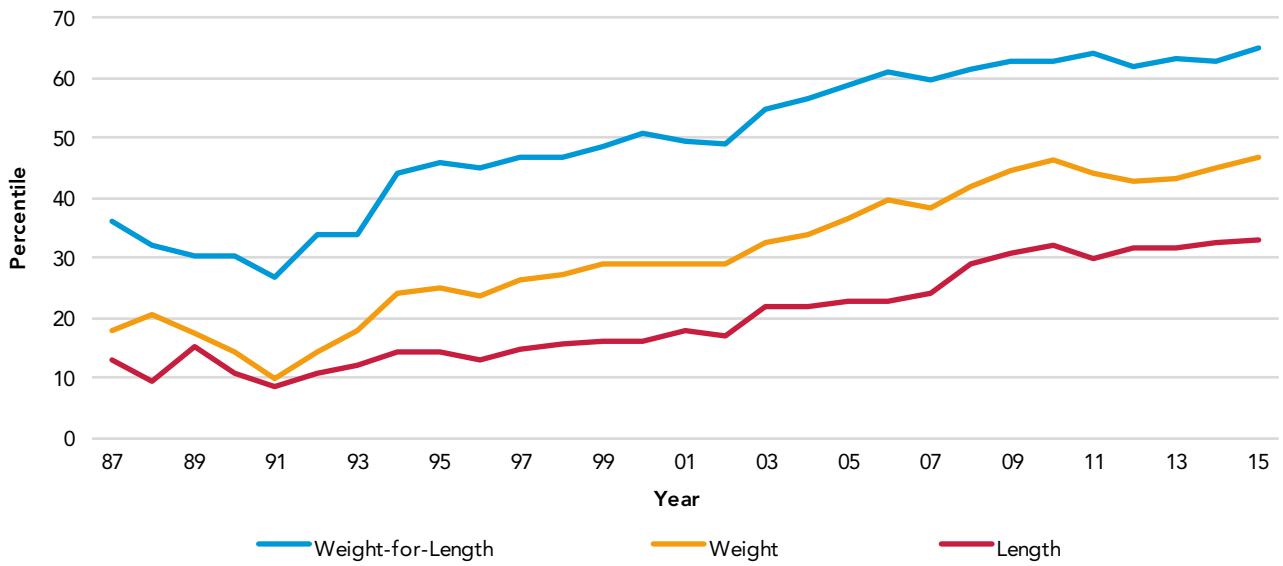
Data are not mutually exclusive. Some individuals have more than one species.

Because individuals may not have a mycobacterial culture each year, data from 2011 to 2015 were combined to allow a more robust analysis of mycobacterial species prevalence among people with CF. Among the 21,898 individuals who were cultured in this time period, 4,161 had one or more mycobacterial species isolated (19.0 percent).

NUTRITION

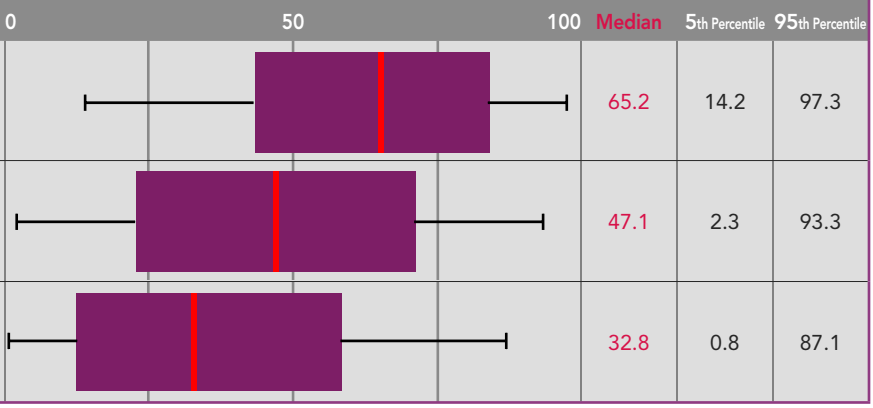
Nutritional outcomes are a key measure of health in people with CF. As there is no consistent nutritional measurement that can be used across the lifespan, this section is divided into three age groups: infants younger than 2 years, children 2 to 19 years and adults 20 years and older. We show the data in that order.

Median WHO Nutritional Outcome Percentiles for Patients Under 24 Months, 1987–2015



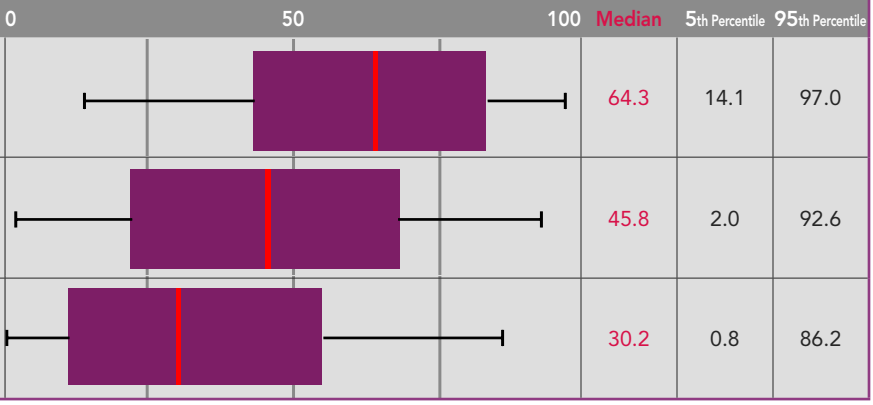
The charts below show the population-level variation in each age group for World Health Organization (WHO) weight-for-length, weight percentile and height percentiles in three groups: all individuals, those in mutation class I-III, and those in classes IV-V. All three groups show a median weight-for-length value well above the 50th percentile; however, individuals in the I-III group have lower weight and substantially lower height percentiles than individuals in the IV-V group. Although this suggests that growth is not optimal in these infants, trends do show improvement.

All Individuals, WHO Nutritional Outcomes for Individuals Under 24 Months



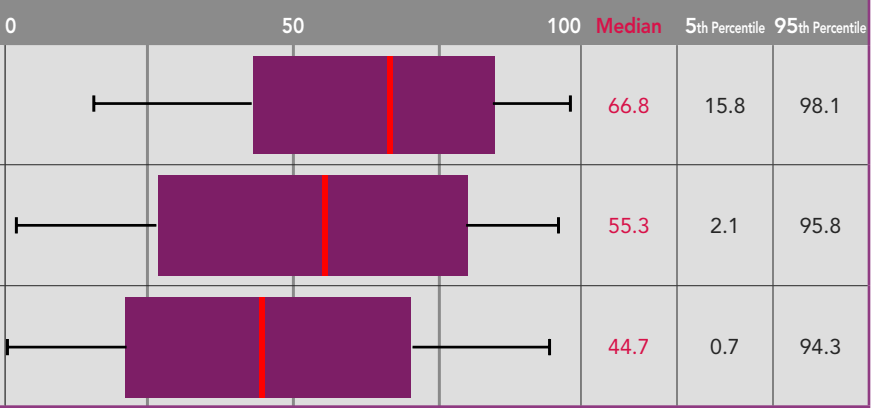
	Median	5th Percentile	95th Percentile
Weight-for-Length *N=1,801*	65.2	14.2	97.3
Weight Percentile *N=1,808*	47.1	2.3	93.3
Height Percentile *N=1,803*	32.8	0.8	87.1

Mutation Class I-III, WHO Nutritional Outcomes for Individuals Under 24 Months



	Median	5th Percentile	95th Percentile
Weight-for-Length *N=1,259*	64.3	14.1	97.0
Weight Percentile *N=1,262*	45.8	2.0	92.6
Height Percentile *N=1,260*	30.2	0.8	86.2

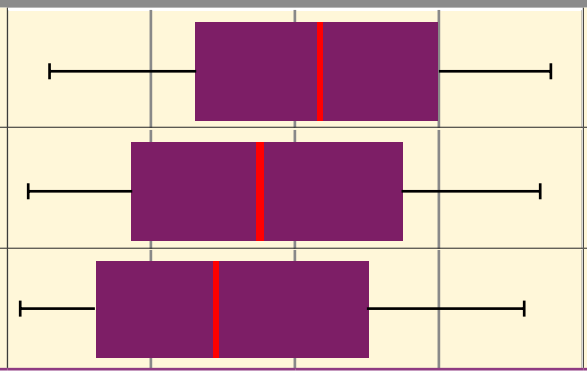
Mutation Class IV-V, WHO Nutritional Outcomes for Individuals Under 24 Months



	Median	5th Percentile	95th Percentile
Weight-for-Length *N=187*	66.8	15.8	98.1
Weight Percentile *N=189*	55.3	2.1	95.8
Height Percentile *N=187*	44.7	0.7	94.3

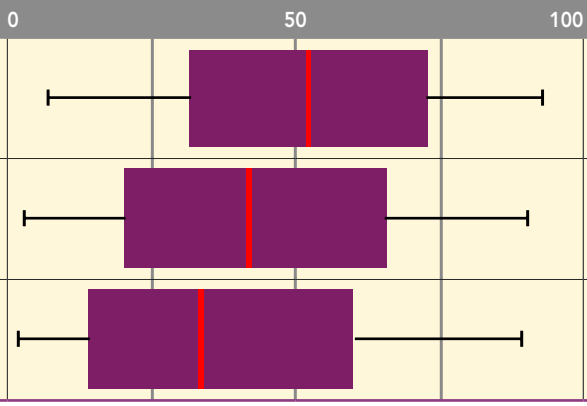
The goal established by the CF Foundation nutrition guidelines for children age 2 to 19 years is a BMI at or above the 50th percentile.[28] The median BMI percentile is above the 50th percentile for this age group. The median weight percentile is approaching the recommendation, but the median height percentile still has room for improvement.

All Individuals, CDC Nutritional Outcomes for Individuals 2 to 19 Years



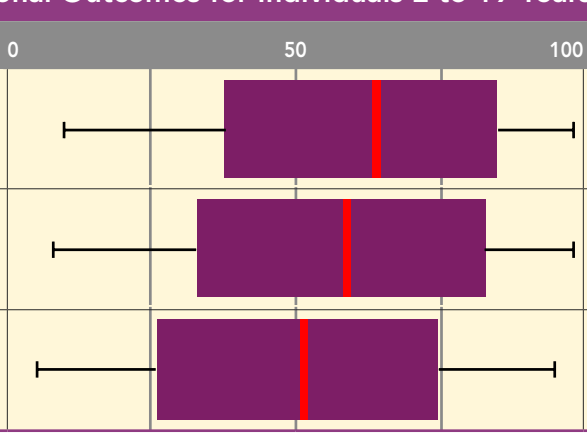
	Median	5th Percentile	95th Percentile
BMI Percentile *N=14,432*	54.1	7.4	94.4
Weight Percentile *N=15,091*	43.9	3.6	92.5
Height Percentile *N=15,085*	36.3	2.2	89.9

Mutation Class I-III, CDC Nutritional Outcomes for Individuals 2 to 19 Years



	Median	5th Percentile	95th Percentile
BMI Percentile *N=10,525*	52.1	7.2	92.3
Weight Percentile *N=10,910*	41.7	3.2	89.8
Height Percentile *N=10,915*	33.8	2.0	88.7

Mutation Class IV-V, CDC Nutritional Outcomes for Individuals 2 to 19 Years

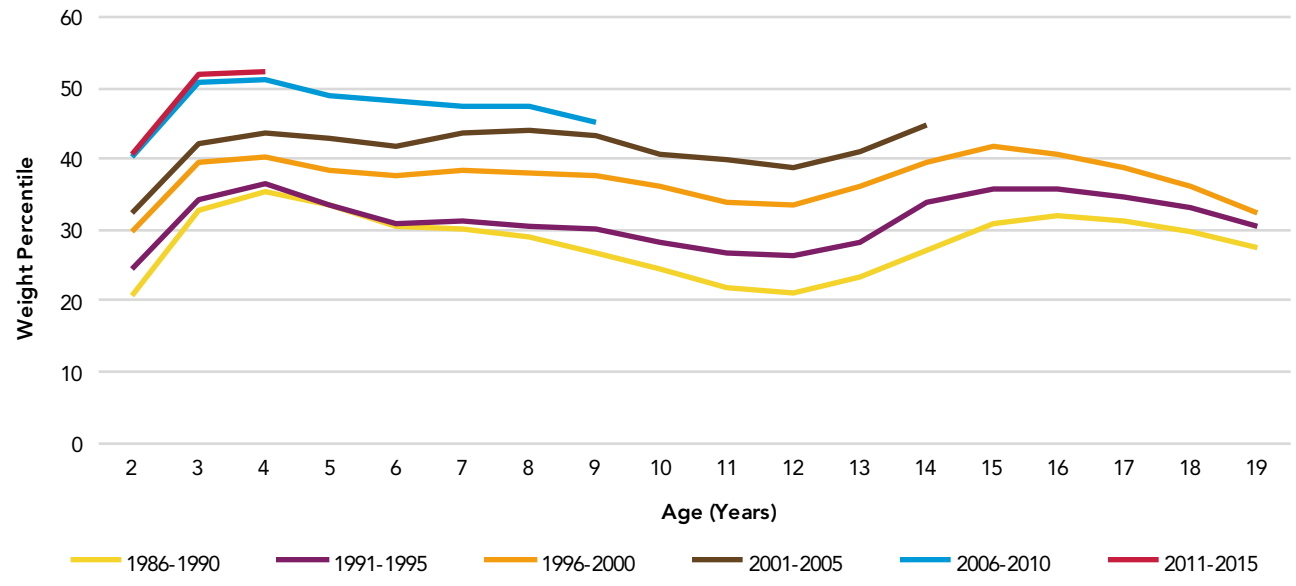


	Median	5th Percentile	95th Percentile
BMI Percentile *N=1,296*	64.0	10.4	97.9
Weight Percentile *N=1,393*	58.9	8.4	97.9
Height Percentile *N=1,389*	51.5	5.5	94.5

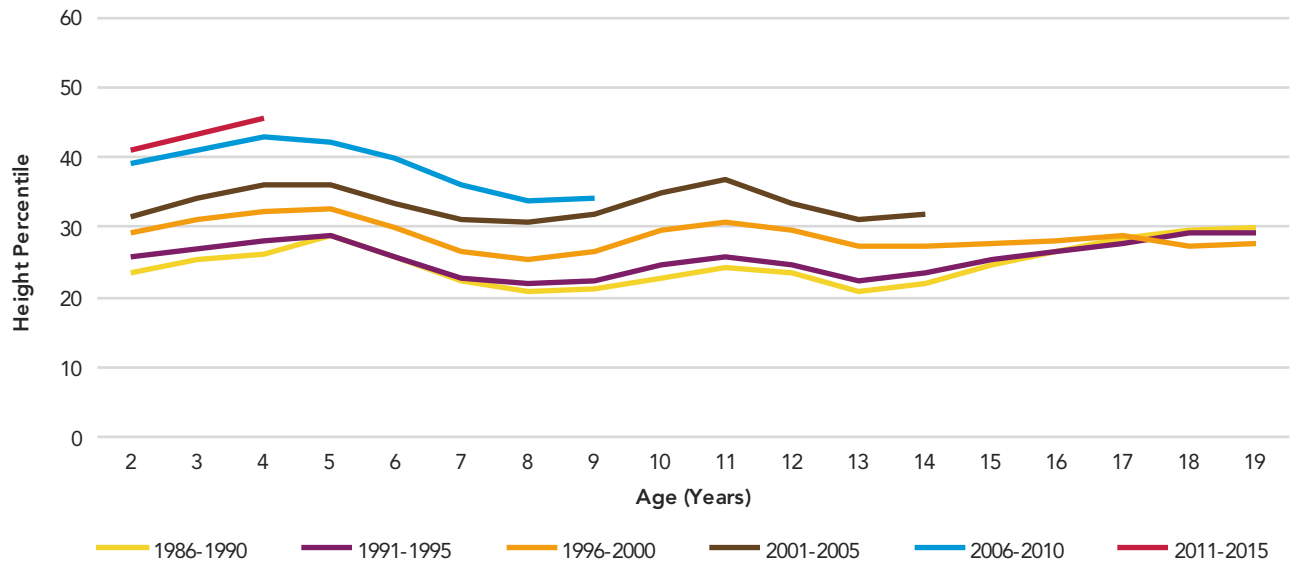
People with CF age 2 to 19 in the IV-V group have higher BMI percentiles than those in the I-III group, but there is substantial variation in the outcomes and significant overlap in outcomes between the two.

Successive birth cohorts show improved weight and height percentiles, most notably in the youngest cohorts. Multiple factors may be contributing to improvements in the youngest cohorts, including implementation of NBS with early intervention.

Median CDC Weight Percentile, by Age and Birth Cohort

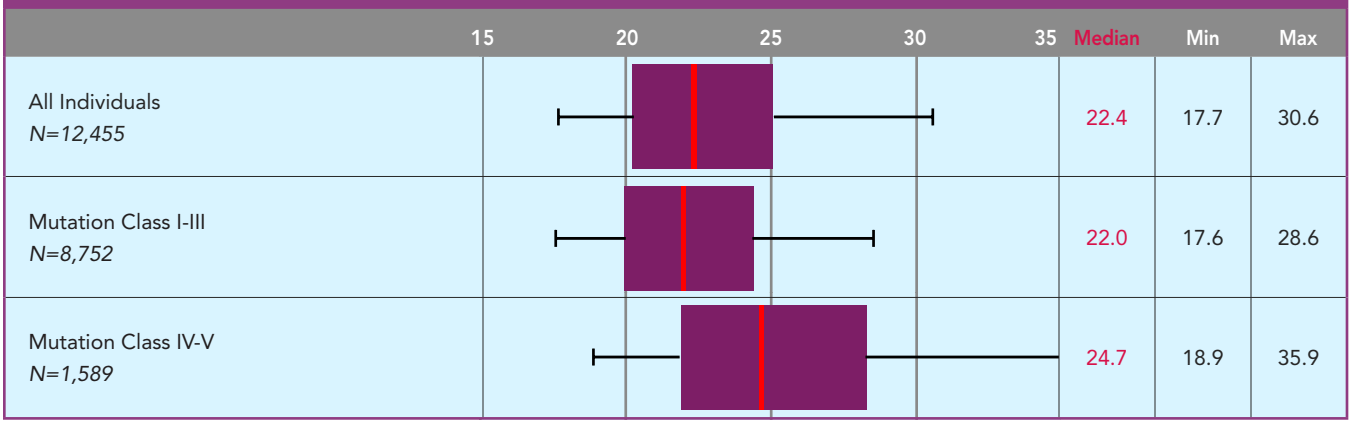


Median CDC Height Percentile, by Age and Birth Cohort



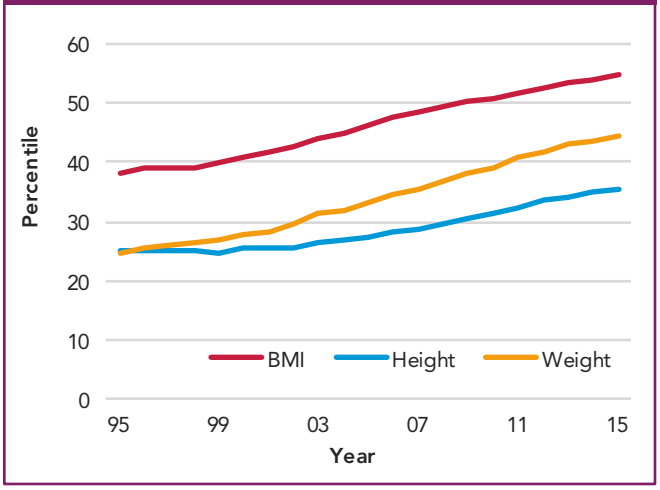
The BMI goal established by the CF Foundation nutrition guidelines is at or above 22 for females and 23 for males age 20 years and older.[28] Among individuals in the mutation class I-III group, median BMI is below the goal, whereas individuals in the class IV-V group have a median BMI above the goal. Considerable variation in BMI exists within each genotype group, with significant overlap between individuals in the I-III group and the IV-V group. Of note, a substantial proportion of those in the IV-V group are overweight (BMI of 25 to 29.9), and some are obese (BMI of 30+).

BMI Value for Individuals 20 Years and Older, by Mutation Class

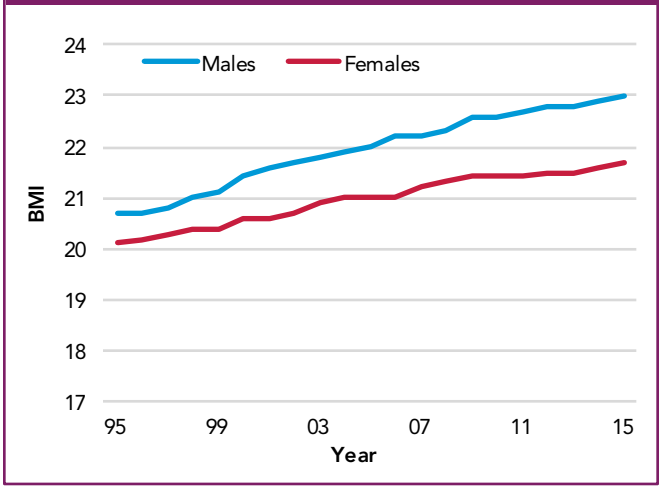


Since the 1980s, significant progress in nutritional outcomes has been made for both pediatric and adult CF populations. Since 2008, the median BMI percentile of individuals with CF age 2 to 19 has met the CF Foundation goal of the 50th percentile. Aging of the CF population and a greater number of late diagnoses with genotypes associated with milder disease may also be contributing to this trend in adults.

Median Nutritional Outcomes Percentiles for Individuals 2 to 19, 1995–2015



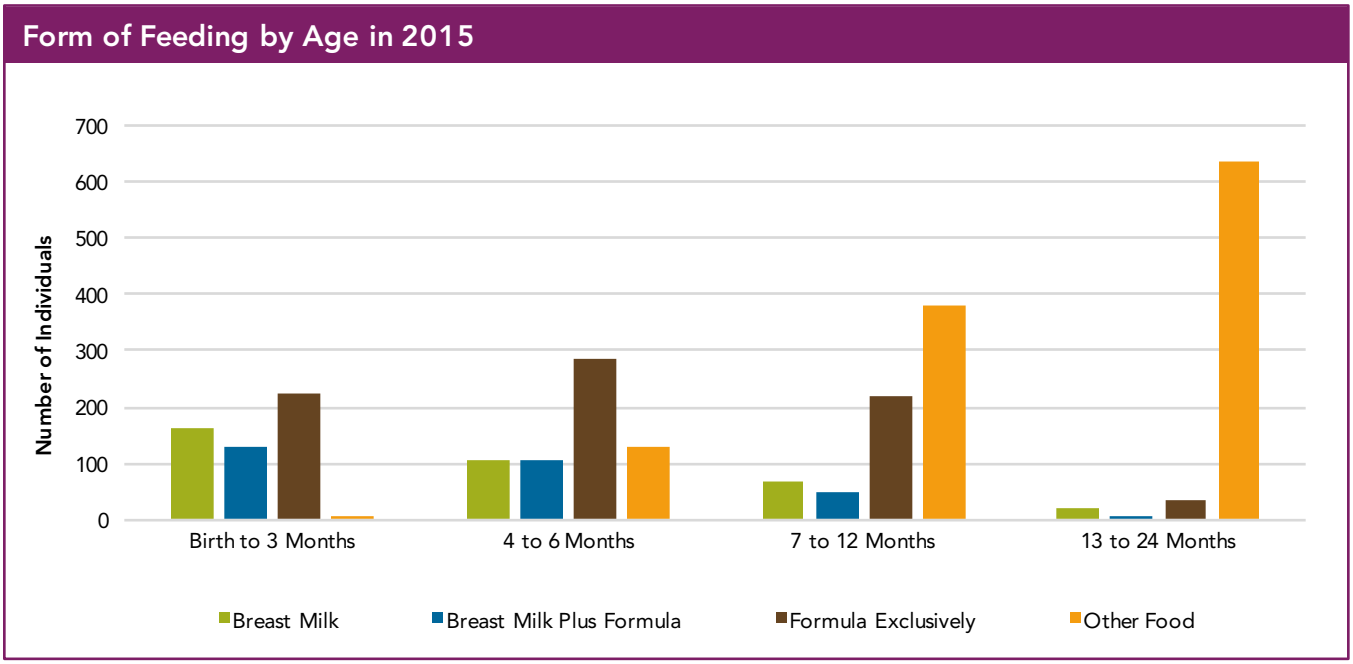
Median BMI Values for Individuals 20 Years and Older, 1995–2015



Infant Feeding

The majority of infants with CF receive formula feeding as the primary form of feeding or as a supplement to breast-feeding. Cow's milk-based formula with the standard caloric density of 20 calories per ounce is the most common feeding used from birth to age 3 months. More calorie-dense formulas are used after 3 months of age. CF Foundation infant care guidelines recommend human breast milk or standard infant formula as the initial form of feeding. Fortified human breast milk, calorie-dense formulas or complementary foods are recommended if the infant is failing to gain weight adequately.[6]

Form of Feeding by Age in 2015



Infants may be included in more than one age category. They may also be counted more than once within an age category if different forms of feeding were recorded during separate clinic visits while within the same age category.

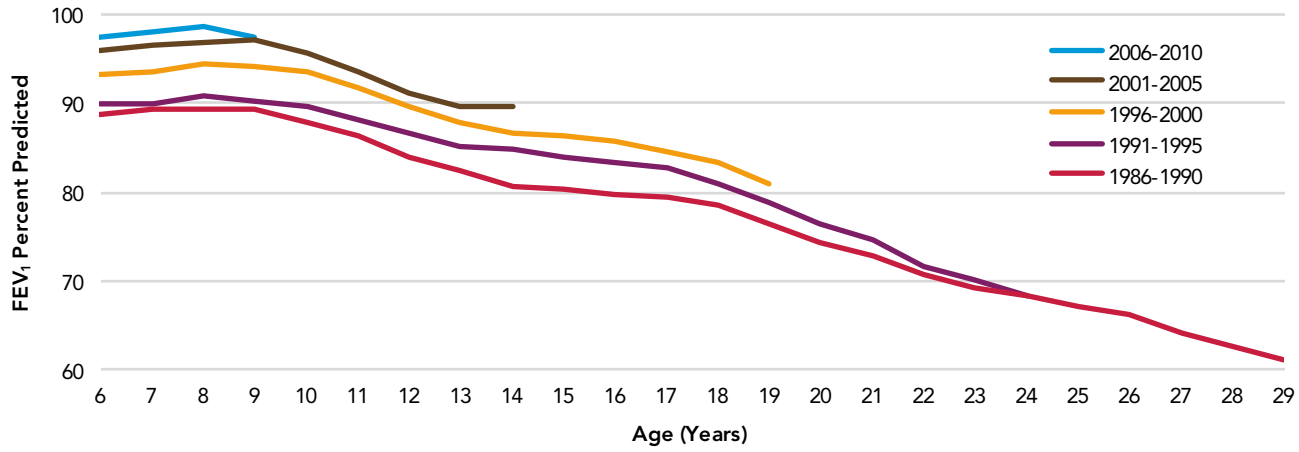
PULMONARY FUNCTION

Pulmonary function is an important clinical indicator of the health of individuals with CF. This section provides information on trends in pulmonary function by age, as well as variations in pulmonary function across CF care centers and by mutation class groups. Pulmonary function is measured using the FEV_1 percent predicted and calculated using the GLI reference equations.[2]

Successive birth cohorts show improved pulmonary function, and cross-sectional analyses from 1994 to 2015 show improvement in the FEV_1 percent predicted across all ages. The majority of those age 18 — a typical age of transition to adult care — now have normal lung function or mild obstruction, defined as an FEV_1 percent predicted greater than or equal to 70.

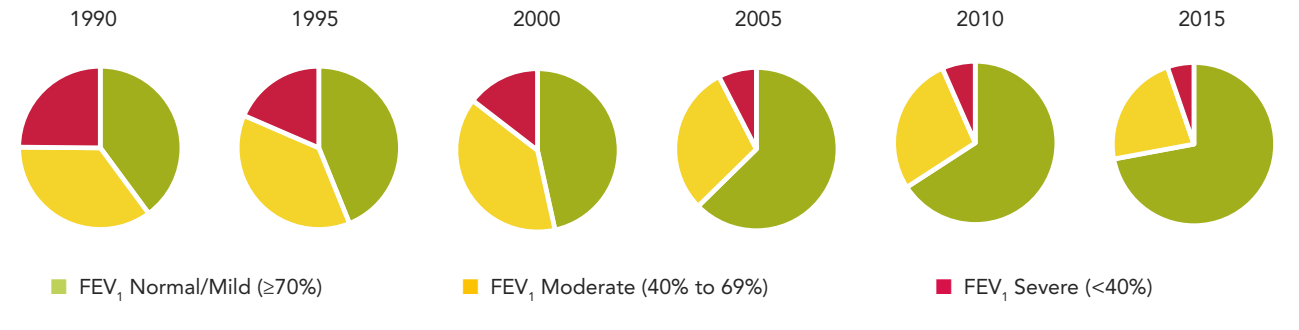
FEV_1 percent predicted is steadily improving and currently is above 90 percent predicted into early adolescence.

Median FEV_1 Percent Predicted, by Age and Birth Cohort



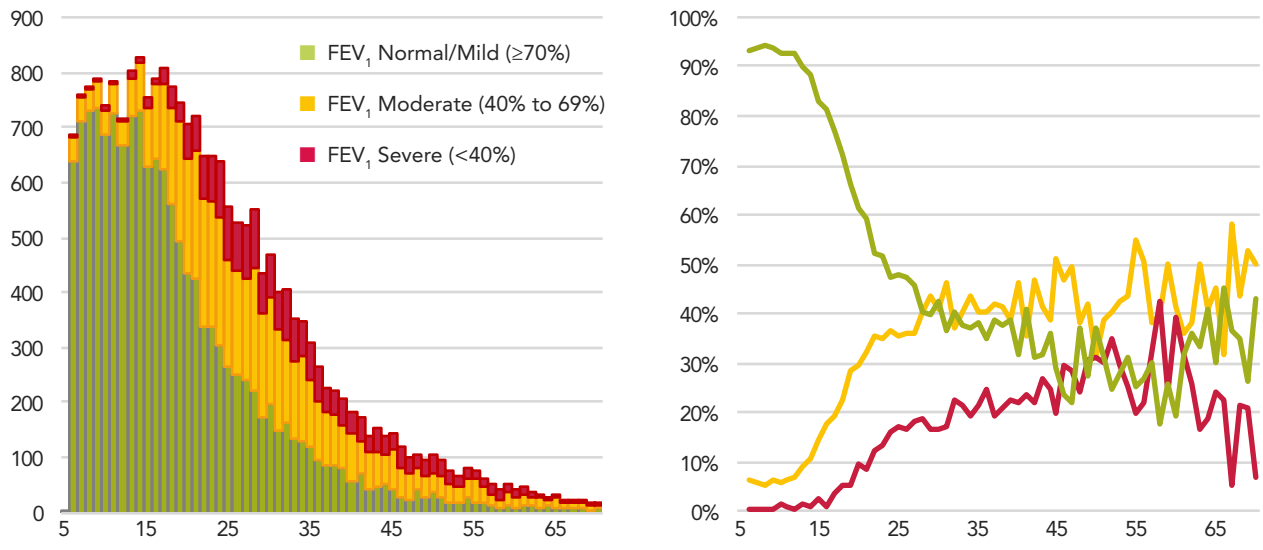
The proportion of people with CF age 18 who are in the normal/mild category (FEV_1 ≥70 percent predicted) has increased from 39.9 percent in 1990 to 72.1 percent in 2015, while the proportion in the severe category (FEV_1 <40 percent predicted) has decreased from 24.9 percent to 5.3 percent.

Median FEV_1 Percent Predicted in 18-Year-Olds, 1990–2015



It is important to point out that spirometry is not a sensitive measure of early lung disease in CF. With that caveat in mind, the vast majority of children have normal or "mild" impairment in pulmonary function. This proportion decreases with age until age 45, when the population has nearly equal proportions of individuals with mild, moderate and severe lung disease.

Pulmonary Function Impairment by Age in Years, 2015 *(Stacked Bar Chart)*

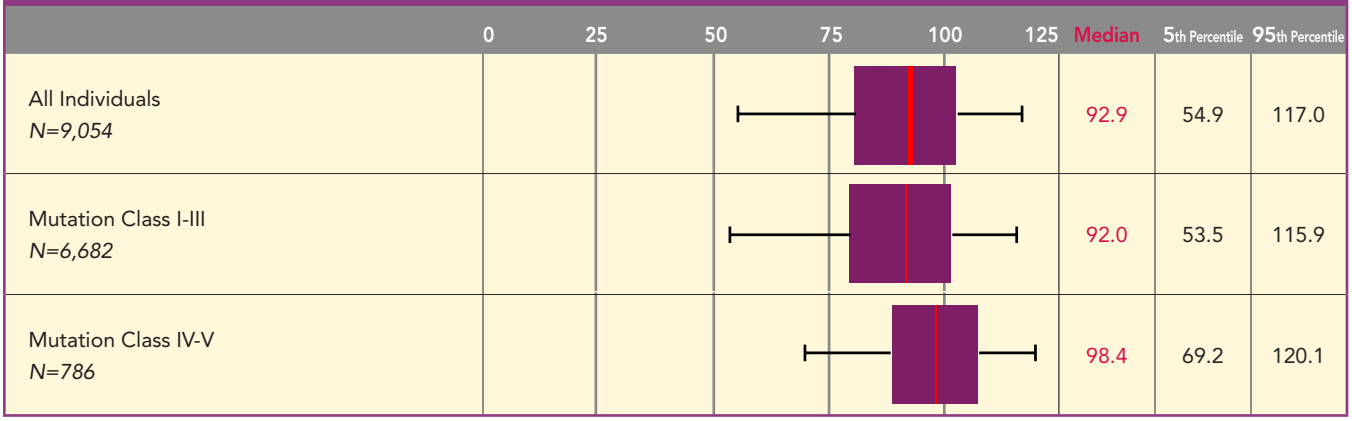


Variation in FEV_1 Outcomes by Mutation Class

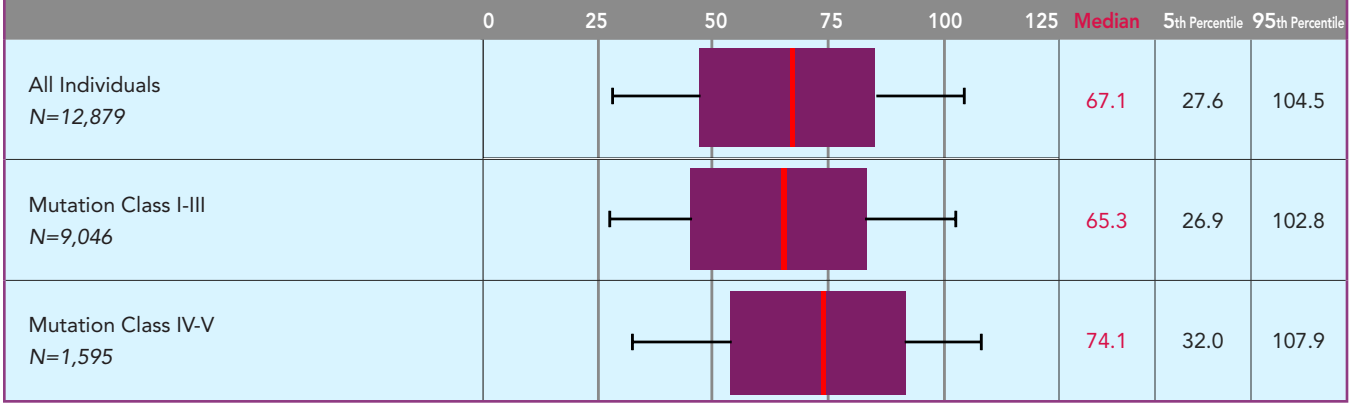
As the majority of individuals with CF are in the class I-III group of mutations (70.7 percent of those genotyped), the outcomes of this group drive national values.

In children and adults with CF, median lung function is lower among individuals in the I-III group than in individuals in the IV-V group (6.4 percent lower in children and 8.8 percent lower in adults). However, there is considerable variation among individuals within each mutation class group and substantial overlap between the two groups.

FEV_1 Percent Predicted for Individuals 6 to 17 Years, by Mutation Class Group



FEV_1 Percent Predicted for Individuals 18 Years and Older, by Mutation Class Group



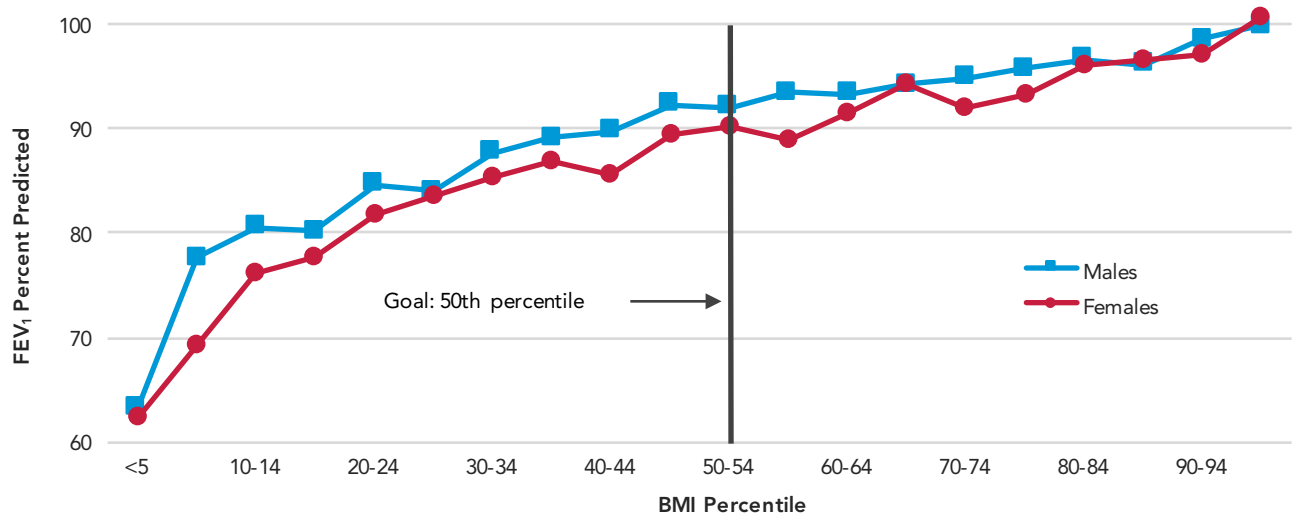
FEV_1 AND BMI OUTCOMES

Pulmonary and nutritional outcomes are two key metrics of health among individuals with CF and are therefore the main focus of quality improvement work within the CF care center network. The data show that for both children and adults with CF, pulmonary function and nutrition status are related and improvements in one metric are associated with improvements in the other.

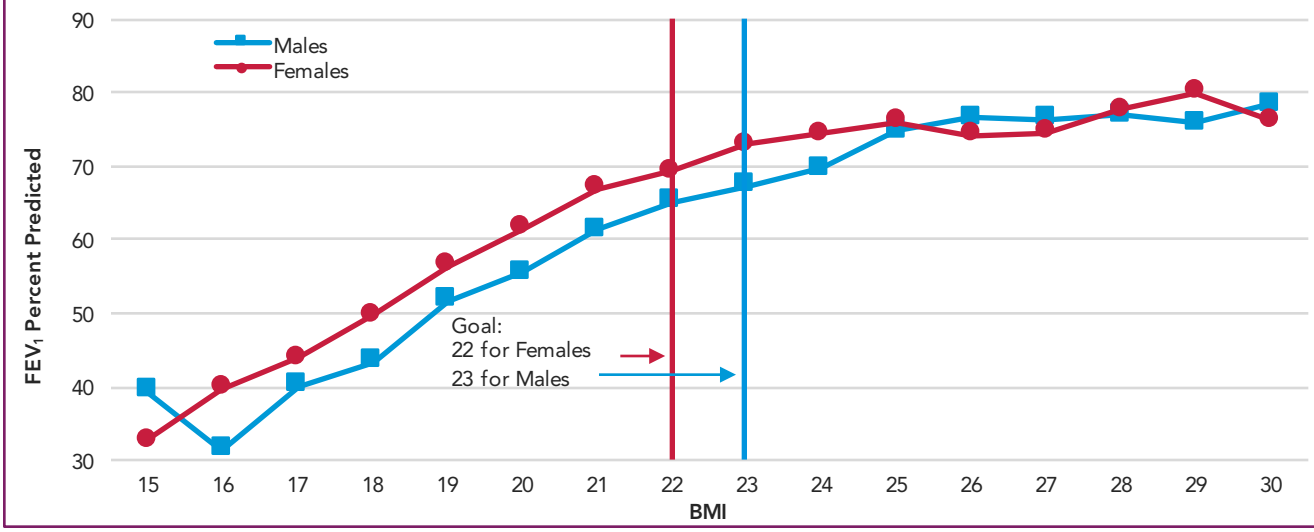
The pulmonary and nutritional goals are as follows:

- *For children, FEV_1 percent predicted greater than or equal to 100 and BMI percentile meeting or exceeding the 50th percentile.*
- *For adults, FEV_1 percent predicted greater than or equal to 75 and BMI greater than or equal to 22 for females and 23 for males.*[28]

FEV_1 Percent Predicted vs. BMI Percentile for Children 6 to 19 Years in 2015

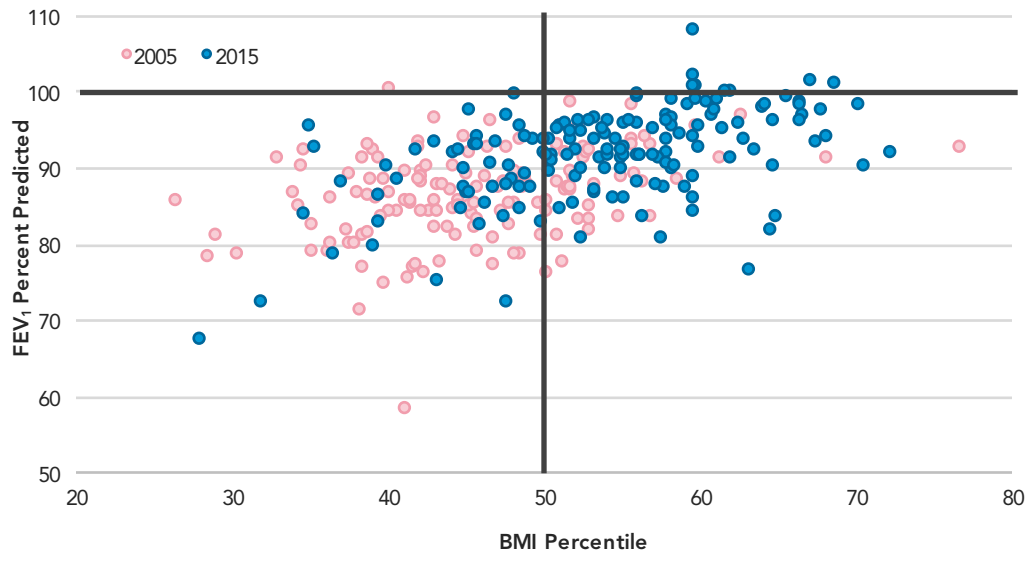


FEV_1 Percent Predicted vs. BMI Value for Adults 20 to 40 Years in 2015



The figures below show the distribution of CF care centers with regard to their median nutritional and pulmonary outcomes and changes in distribution between 2005 and 2015. Each dot in the figure represents a value from an accredited CF care center or affiliate program. Ideally, CF care centers would be in the upper right quadrant of the graph, which represents centers that meet both pulmonary function and nutritional goals. In 2015, the majority of pediatric CF care centers met nutritional guidelines and showed improvements in median pulmonary function during the preceding 10 years.

Median FEV_1 Percent Predicted vs. Median BMI Percentile for Individuals 6 to 17 Years, 2005 and 2015



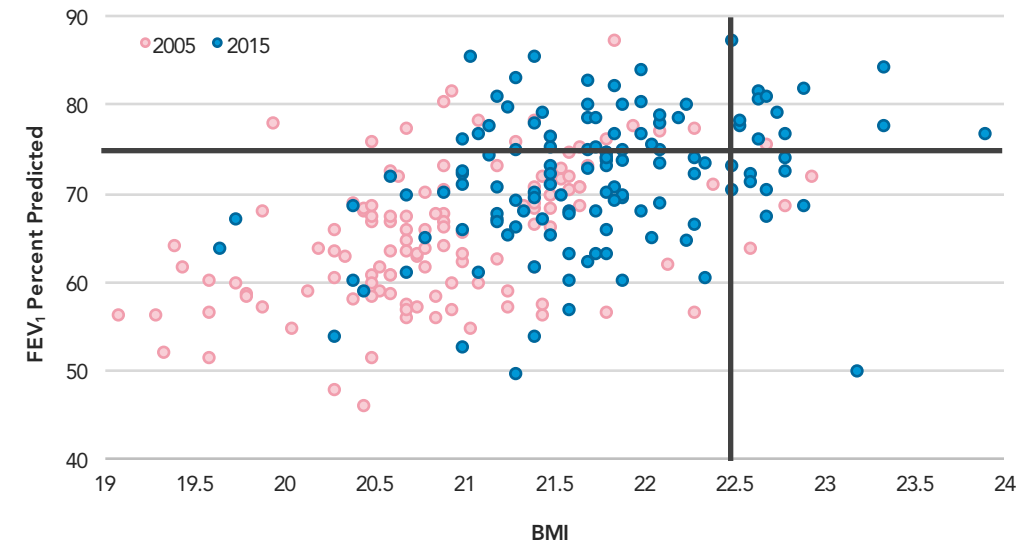
Goals:	
FEV_1 % predicted	100.0
BMI percentile	50.0

2005 Medians:	
FEV_1 % predicted	86.9
BMI percentile	45.3

2015 Medians:	
FEV_1 % predicted	92.0
BMI percentile	54.3

Among adult CF care centers, 33.1 percent are meeting pulmonary function goals for individuals. The data show progress toward more CF care centers meeting nutritional goals.

Median FEV_1 Percent Predicted vs. Median BMI Value for Individuals 18 to 30 Years, 2005 and 2015



Goals:	
FEV_1 % predicted	75.0
BMI	22.5

2005 Medians:	
FEV_1 % predicted	65.9
BMI	20.9

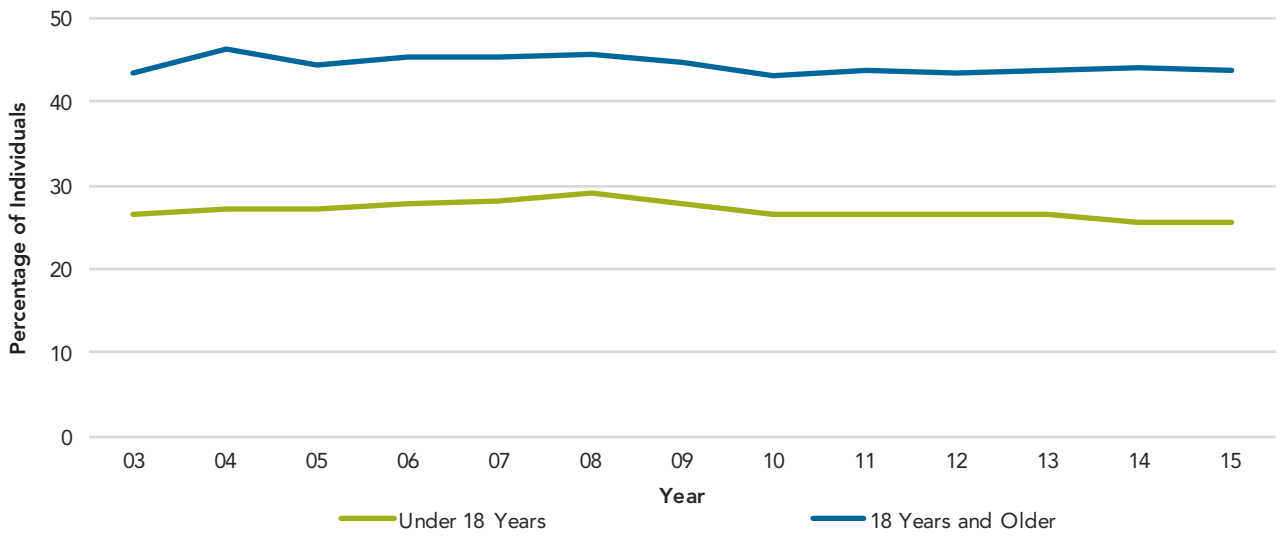
2015 Medians:	
FEV_1 % predicted	72.4
BMI	21.8

PULMONARY EXACERBATIONS

Pulmonary exacerbations, characterized by intravenous (IV) antibiotic treatment in the hospital or at home, are associated with morbidity, mortality and decreased quality of life. They are also a major driver of health care costs. This section displays trends in the rate of pulmonary exacerbations over time and by age group, as well as variation in exacerbation rates and treatment characteristics by CF care center.

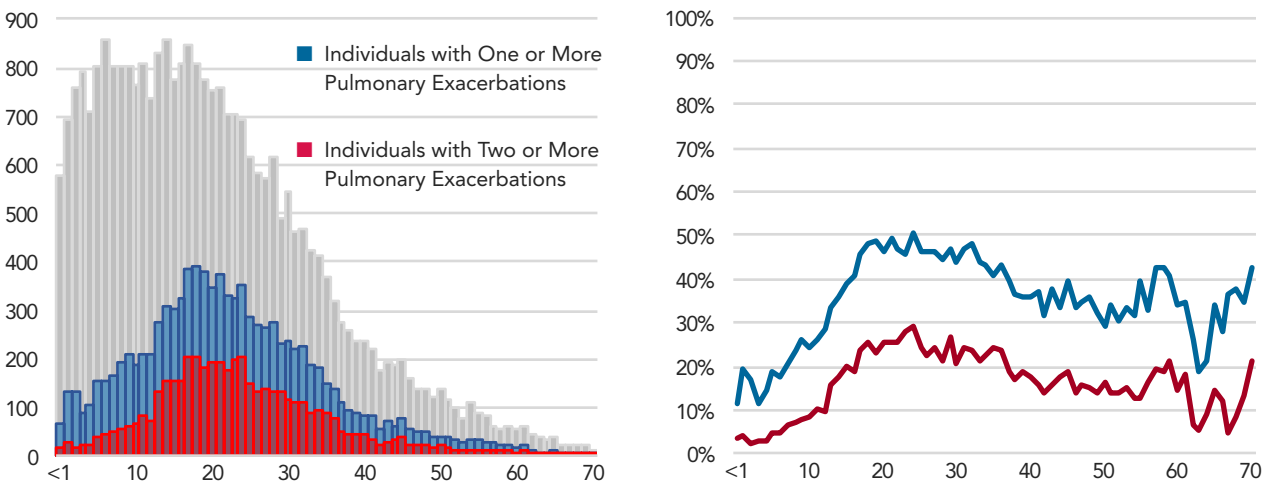
Despite notable improvements in pulmonary function and nutritional status over the years, there has been no reduction in the proportion of individuals with CF who are treated with IV antibiotics for pulmonary exacerbations. This suggests that clinicians' threshold for prescribing IV antibiotics may have changed over time.

Patients Treated with IV Antibiotics for a Pulmonary Exacerbation, 2003–2015



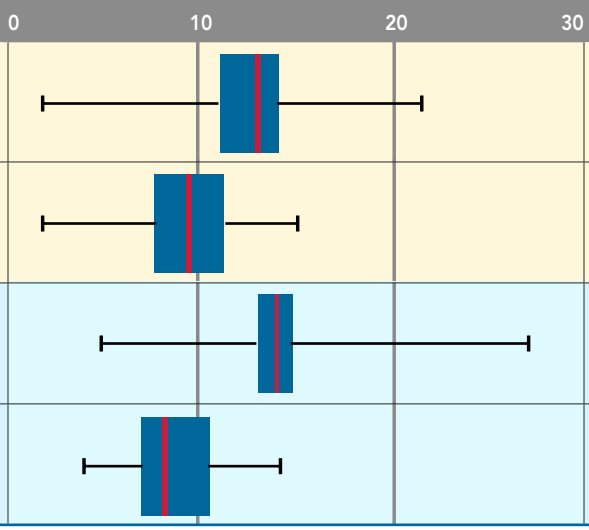
Individuals with CF who are between ages 15 and 30 are more likely than those in other age groups to experience a pulmonary exacerbation during the year.

Pulmonary Exacerbations by Age in Years, 2015



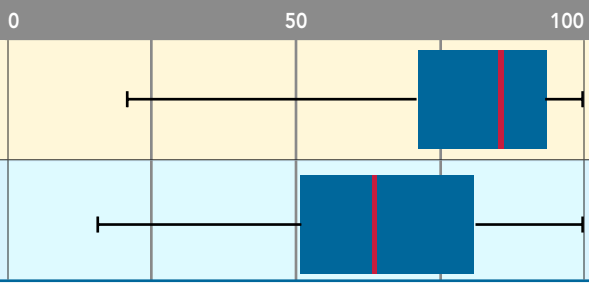
When the CF Foundation developed guidelines for the treatment of pulmonary exacerbations in 2009, little published literature or data were available upon which to base recommendations.[39] Current practice within the CF Foundation care center network indicates a median treatment duration of about 2 weeks, with adults more likely to complete some of their treatment at home. Further research is underway to develop evidence for best practices in the treatment of pulmonary exacerbations.

Duration of Pulmonary Exacerbation Treatment in Days, by Center



	Median	Min	Max
Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals Less than 18 Years	13.0	2.0	21.5
Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals Less than 18 Years	9.5	2.0	15.0
Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals 18 Years and Older	14.0	5.0	27.0
Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals 18 Years and Older	8.3	4.0	14.3

Percentage of Total Pulmonary Exacerbation Treatment Duration in Hospital, by Center



	Median	Min	Max
Individuals Less Than 18 Years	85.4	21.0	100.0
Individuals 18 Years and Older	63.9	15.9	100.0

THERAPIES

Gastrointestinal (GI) Therapies

The CF Foundation infant care guidelines recommend that pancreatic enzyme replacement therapy (PERT) be started for all infants with two CFTR mutations associated with pancreatic insufficiency, a fecal elastase below 200µg/g of stool and/or signs of malabsorption.[6]

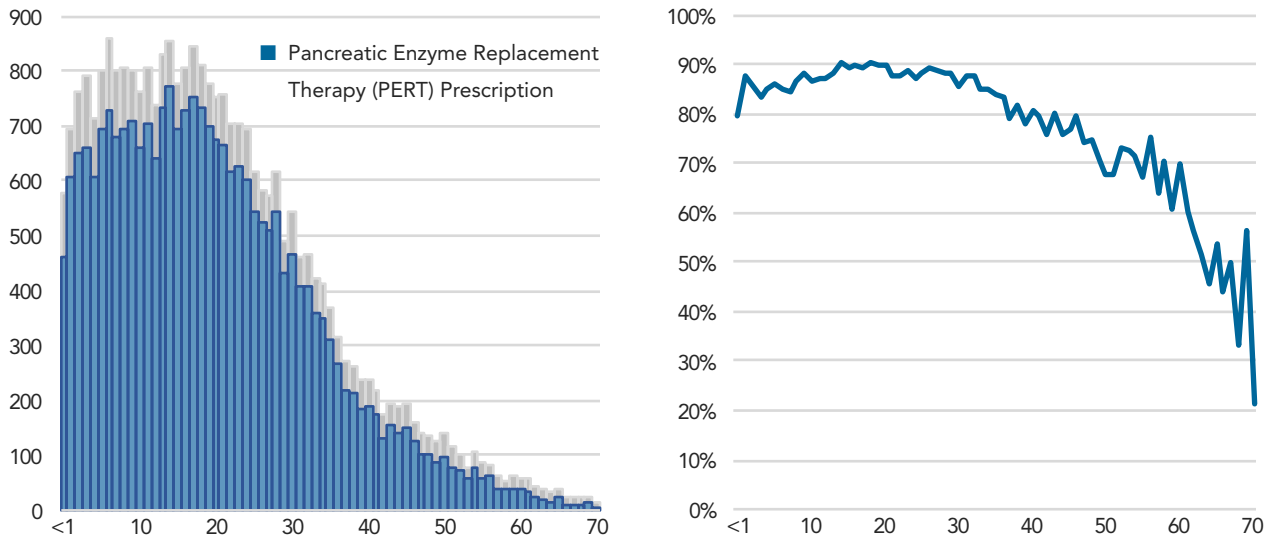
For infants with CF under age 2, the guidelines recommend assessment of pancreatic functional status by measurement of fecal elastase.[6] Data on fecal elastase test results have been collected in the Registry since 2010, with an increase in the number of individuals with a fecal elastase test. Almost 60 percent of infants were tested in 2015. Some 745 individuals under age 24 months did not have a fecal elastase value reported, 89% of which were on PERT in 2015. Almost all individuals with a fecal elastase value of less than 200 have been prescribed PERT. Approximately one-quarter of individuals with fecal elastase values greater than 200 were also prescribed PERT.

Pancreatic Enzyme Use by Fecal Elastase Value in Individuals Under 24 Months in 2015

Pancreatic Enzyme Replacement Therapy	Fecal Elastase Value <200	Fecal Elastase Value ≥ 200
On PERT	918	56
Not on PERT	16	142

A large proportion of individuals of all ages are prescribed PERT: the proportion remains over 80 percent until age 40, when the proportion in each age cohort begins to decrease. The decrease in the proportion of older CF individuals prescribed PERT is most likely due to survivor bias.

Pancreatic Enzyme Replacement Therapy (PERT) Prescription by Age in Years, 2015

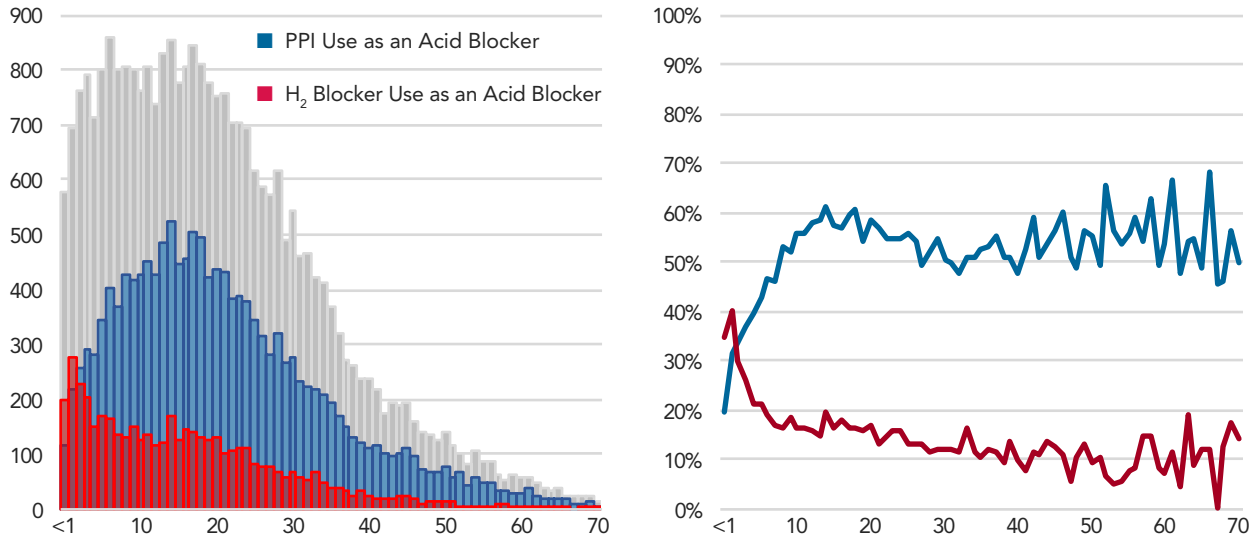


Infants with evidence of pancreatic insufficiency are recommended to receive 2,000 to 5,000 lipase units per feeding (total lipase dose), with adjustments as the infant grows.[6] The Registry data show that the mean highest dose of lipase among children younger than 2 years is 14,006 total lipase units per largest meal.

For individuals age 2 years and older, the recommended upper limit for enzyme dosing is 2,500 lipase units/kg/meal and a total of 10,000 lipase units/kg/day.[28] The mean dose of lipase units/kg/meal for individuals 2 to 19 years is 1,856 and for individuals 20 years and older is 1,773.

Acid blockers are commonly prescribed for people with CF to treat gastroesophageal reflux disease (GERD) and/or to decrease the acidity of the stomach to increase the effectiveness of PERT. Overall, proton pump inhibitors (PPIs) are prescribed more often (51.4 percent of individuals) than H2 blockers (16.6 percent of individuals). H2 blockers are used more frequently in younger individuals and their use tapers among older individuals. In contrast, use of PPIs is lowest among younger individuals and consistently about 50 percent among individuals age 20 and older.

PPI and H_2 Blocker Use by Age in Years, 2015



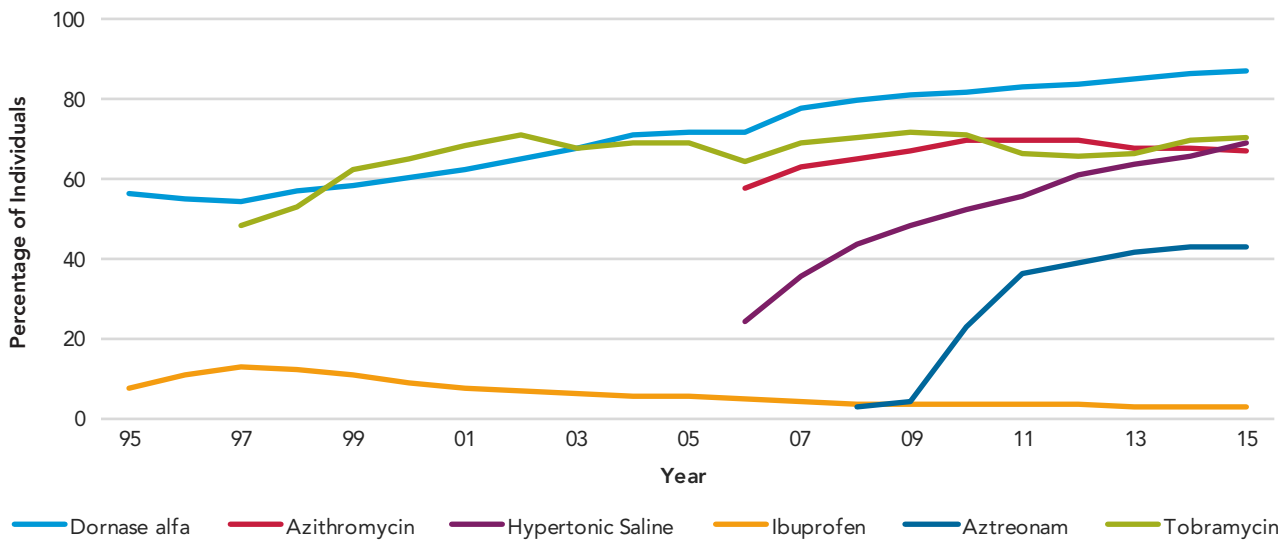
CF-specific vitamins also play an important role in the overall regimen of GI therapies for individuals with CF. In 2015, almost 92 percent of individuals age 2 to 19 and nearly 80 percent of individuals age 20 and older were prescribed CF-specific vitamins.

Pulmonary Therapies

Chronic pulmonary therapies are a major component of the treatment regimen for individuals with CF. This section provides data on the uptake of and trends in the prescription of pulmonary medications recommended for chronic use by the CF Foundation pulmonary guidelines committee. Data are also provided on medications that are not recommended and on those for which the committee did not find sufficient evidence to recommend for or against chronic use.[40]

Typically between 60 to 80 percent of the eligible population uses CF therapies and the use of most therapies has increased over time. Over the last few years, additional formulations of inhaled tobramycin have become available, so the chart below includes all formulations. Chronic oral antibiotics are used infrequently (by 14.7 percent of the CF population). The availability of multiple pulmonary therapies for CF is beneficial; however, it also contributes to treatment complexity and overall burden on individuals with CF and their caregivers.

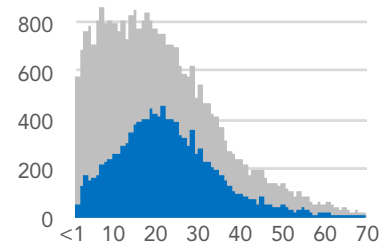
Chronic Medication Prescription in Eligible Patients, 1995-2015



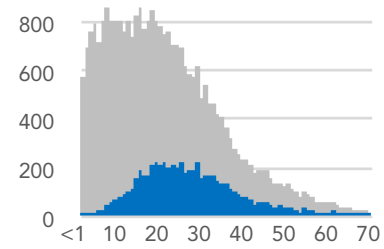
Pulmonary Medication Prescriptions by Age

There are three classes of inhaled antibiotics for treatment of *P. aeruginosa* infections. Tobramycin is used most frequently, followed by aztreonam and colistin. For all medications, peak use occurs during adolescence and young adulthood.

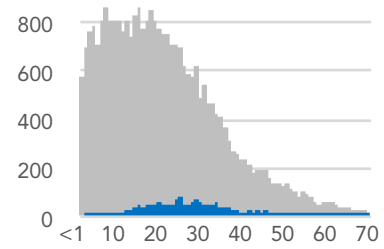
Any Tobramycin



Aztreonam

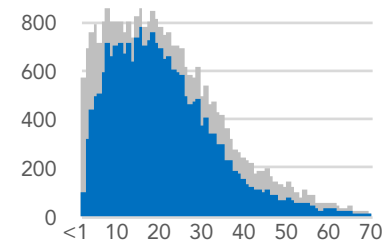


Colistin

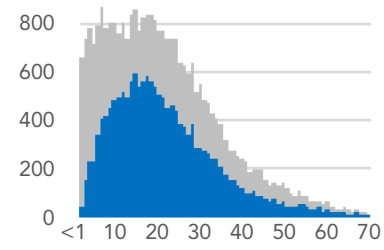


Dornase alfa is prescribed for the majority of individuals with CF. More than half of them are prescribed hypertonic saline either in place of, or in addition to, dornase alfa. Azithromycin is also widely used, with peak use occurring at slightly older ages than for use of dornase alfa and hypertonic saline.

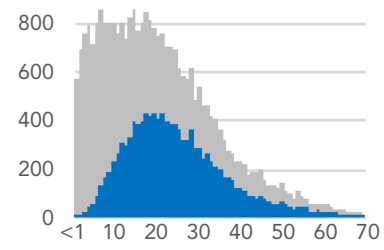
Dornase Alfa



Hypertonic Saline

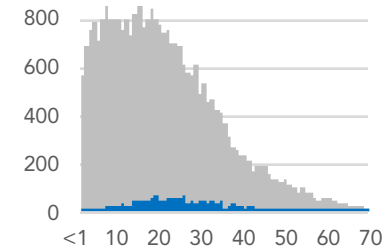


Azithromycin

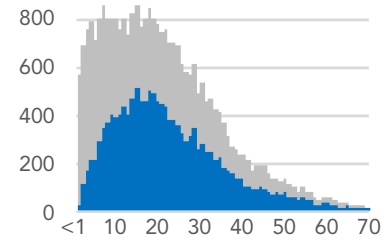


A substantial proportion of individuals with CF are prescribed inhaled corticosteroids and, to a lesser degree, leukotriene modifiers.

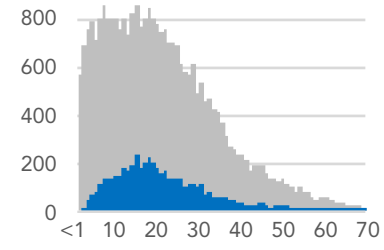
Oral Corticosteroids



Inhaled Corticosteroid

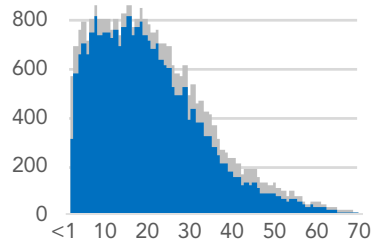


Leukotriene Modifiers

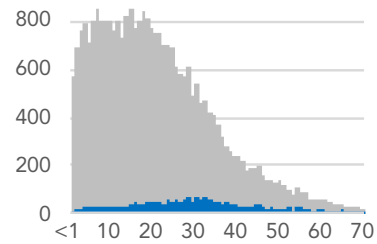


Bronchodilators are used extensively among individuals with CF. Almost all people with CF are prescribed beta agonists, except for a very small percentage who are prescribed anticholinergics.

Inhaled Beta Agonist

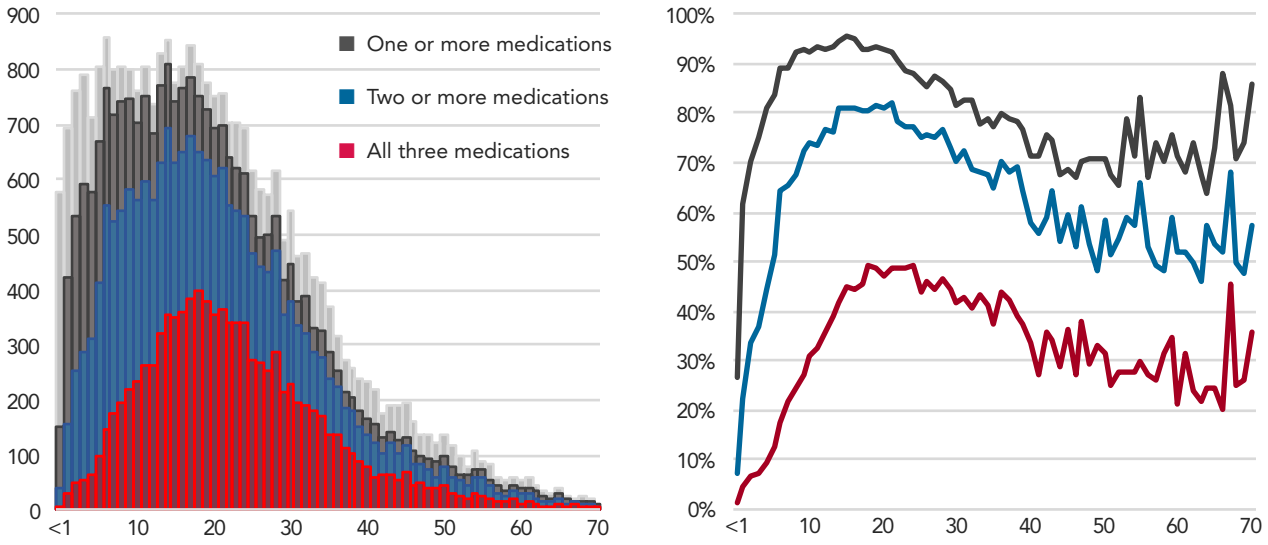


Inhaled Anticholinergic



Multiple pulmonary therapies are available for individuals with CF. Inhaled medications are effective treatments for pulmonary disease, but they require time to prepare, administer and clean after treatment. All people with CF are eligible for dornase alfa and hypertonic saline prescriptions. Those with *P. aeruginosa* infection are typically prescribed inhaled antibiotics. Almost all individuals are prescribed at least one inhaled medication, and over half of those age 10 and older are prescribed two or more of these therapies.

Inhaled Medication (Dornase Alfa, Hypertonic Saline, Inhaled Antibiotic) **Prescription by Age in Years, 2015**

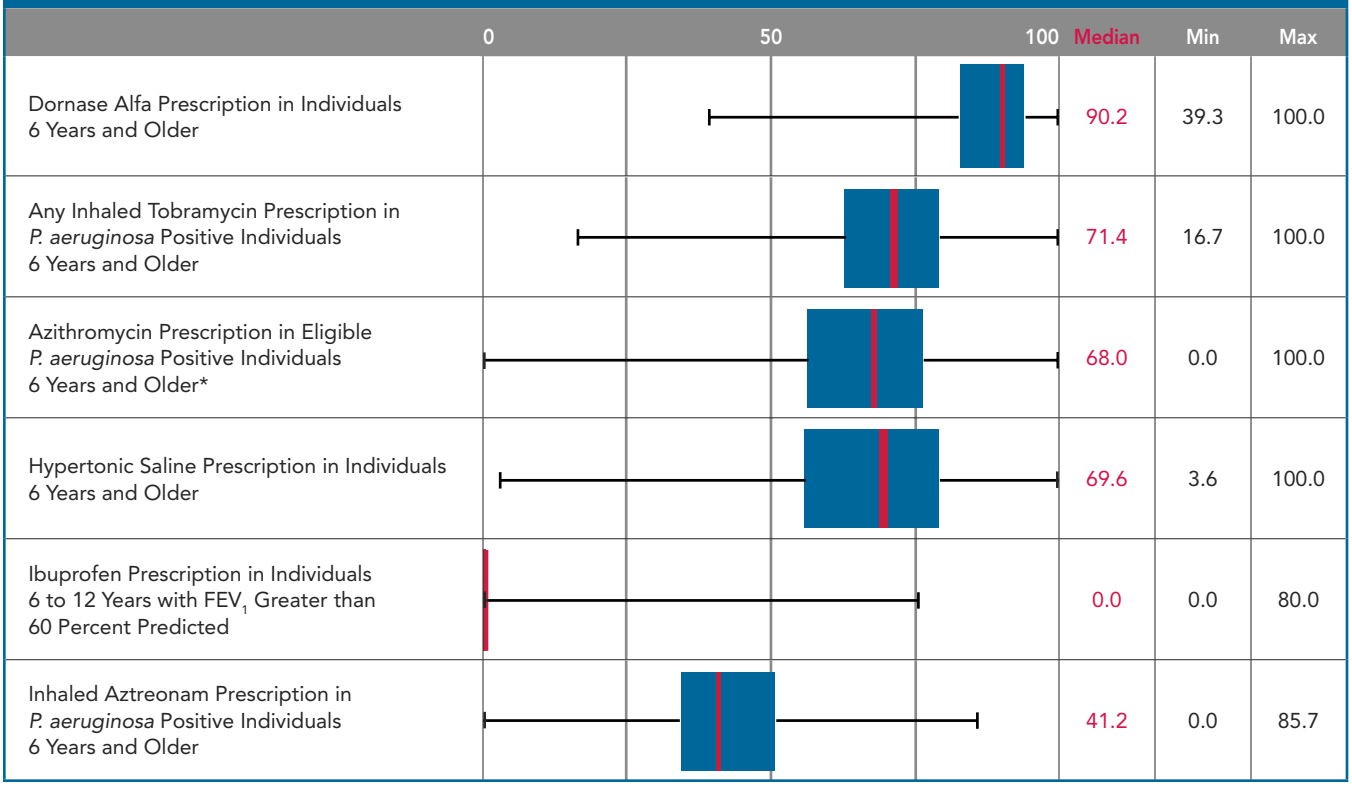


Inhaled antibiotic use includes the use of tobramycin, aztreonam, colistin or other aminoglycosides.

Medications Recommended for Chronic Use

Recommended therapies are widely prescribed, with the exception of ibuprofen; however, there is considerable variation across the CF Foundation care center network. Increasingly, individuals with CF are using multiple inhaled antibiotics for the treatment of *P. aeruginosa* infections.

Pulmonary Therapies Recommended for Chronic Use, by Center

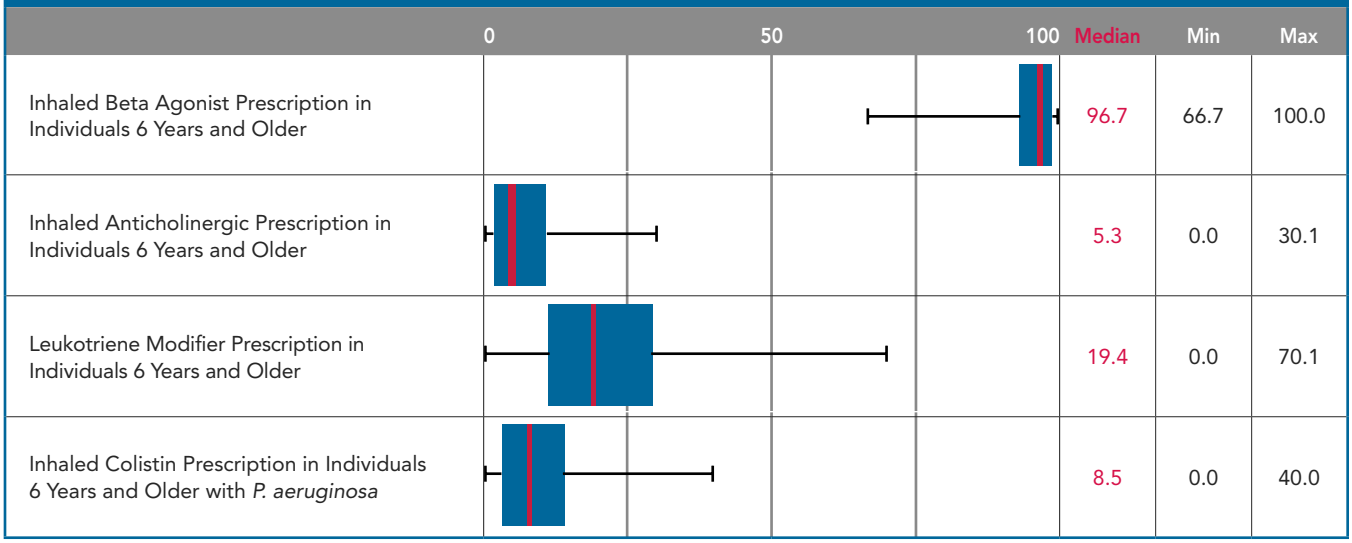


**Individuals were considered eligible if they met the selection criteria used in the U.S. azithromycin trial.[3]*

Medications with Insufficient Evidence to Recommend For or Against Chronic Use

In 2013, the CF Foundation pulmonary guidelines committee determined that there was insufficient evidence to recommend for or against the chronic use of inhaled beta agonists, inhaled anticholinergics, leukotriene modifiers and inhaled colistin to improve lung function, reduce exacerbations or improve quality of life.[40] Inhaled beta agonists are used consistently across the CF care center network for the vast majority of individuals with CF. Use of colistin has decreased in recent years. The other medications are used infrequently.

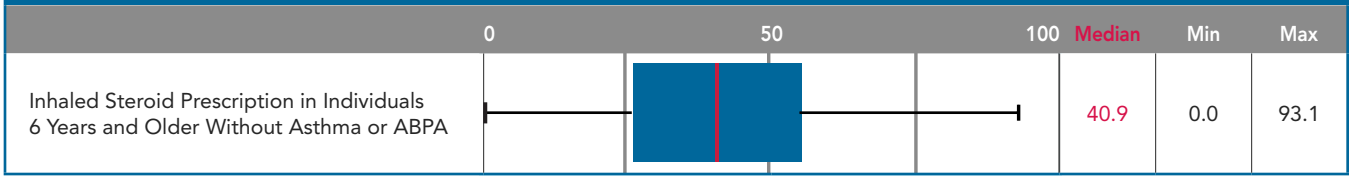
Pulmonary Therapies with Insufficient Evidence to Recommend for or Against Chronic Use, by Center



Medications Not Recommended for Chronic Use

Inhaled steroids continue to be commonly prescribed, despite the recommendation against their chronic use in the absence of asthma or allergic bronchopulmonary aspergillosis (ABPA).

Pulmonary Therapies Not Recommended for Chronic Use, by Center



Medication Use in Young Children

Recently, the CF Foundation released the first set of guidelines focusing on the preschool timeframe from ages 2 to 5.[19] Although the results of rigorous efficacy trials are not available for this age group, the guidelines recommend that dornase alfa and hypertonic saline be selectively offered to individuals on the basis of individual circumstances. The chart below shows the use of these medications among children younger than age 6.

Medication Use in Individuals Under 6 Years, 2015

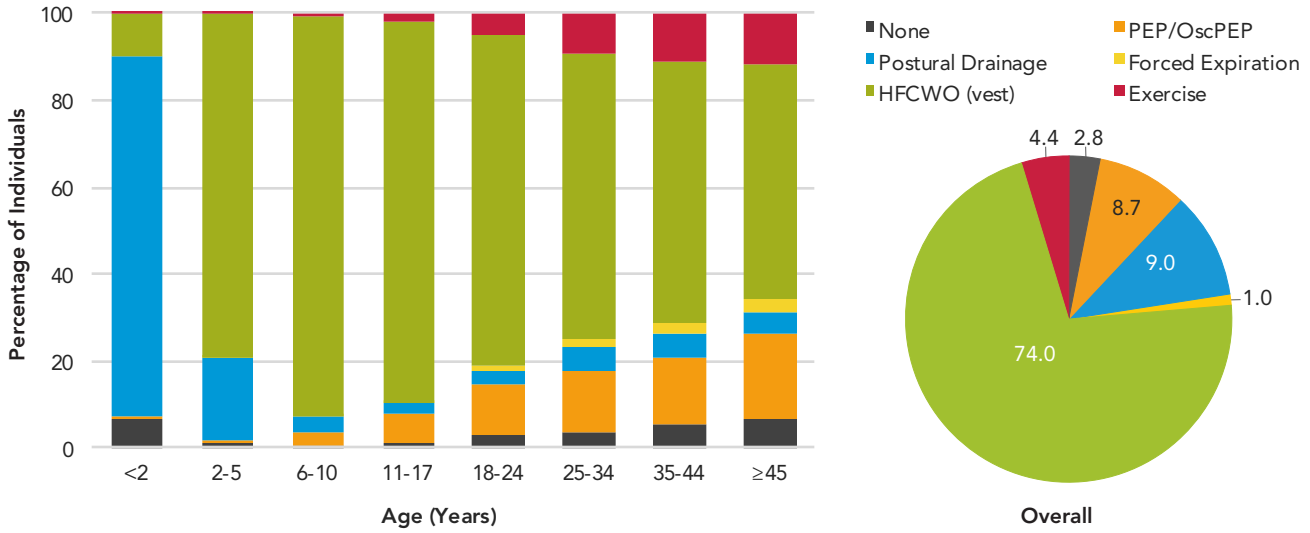
	Individuals Under 3 Years (%)	Individuals 3 to 5 Years (%)
Number of Individuals (n)	1,980	2,287
Dornase alfa	43.5	69.9
Hypertonic saline	21.5	41.9
Inhaled bronchodilators	79.0	92.9
Inhaled corticosteroids	15.7	31.3
Inhaled tobramycin	15.9	18.6
Azithromycin	2.0	8.1
Inhaled aztreonam	1.1	2.8

Most children under age 6 are prescribed inhaled bronchodilators. Dornase alfa is prescribed in 43.5 percent of children younger than age 3 and in almost 70 percent of children ages 3 to 5.

Airway Clearance Techniques

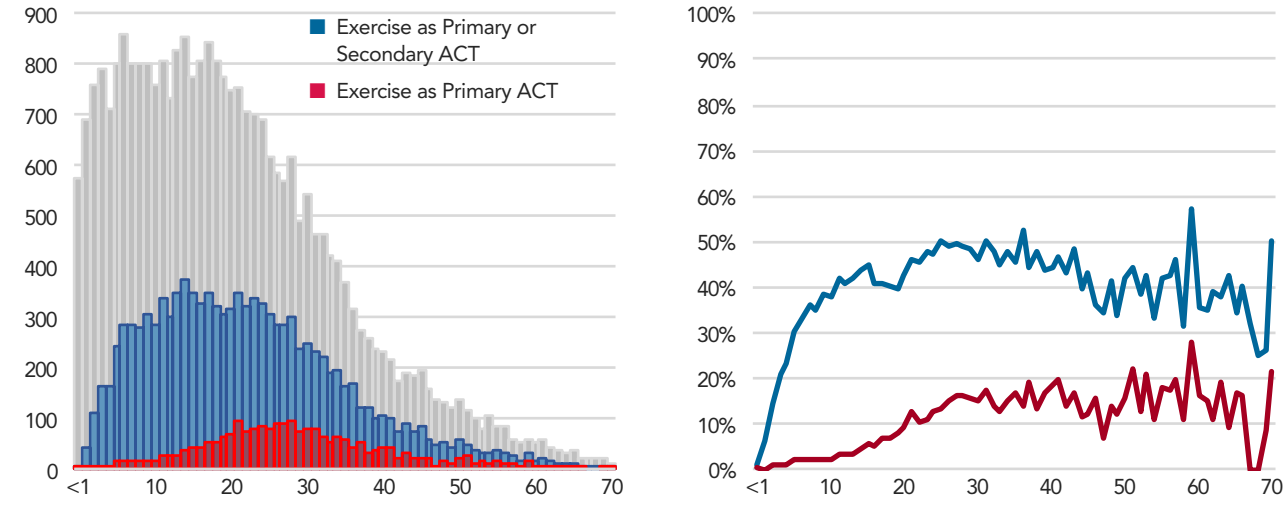
The CF Foundation pulmonary guidelines recommend airway clearance for all individuals with CF.[41] A high-frequency chest wall oscillation (HFCWO) vest is the most widely used airway clearance technique in persons with CF after infancy.

Primary Airway Clearance Techniques by Age and Overall, 2015



The CF Foundation pulmonary guidelines recommend aerobic exercise as an adjunct therapy for airway clearance and for its additional benefits to overall health.[41] Many individuals with CF report exercising in addition to their primary method of airway clearance, with 32.6 percent of children and 45.2 percent of adults identifying exercise as one of their methods of airway clearance.

Exercise as an Airway Clearance Technique by Age in Years, 2015

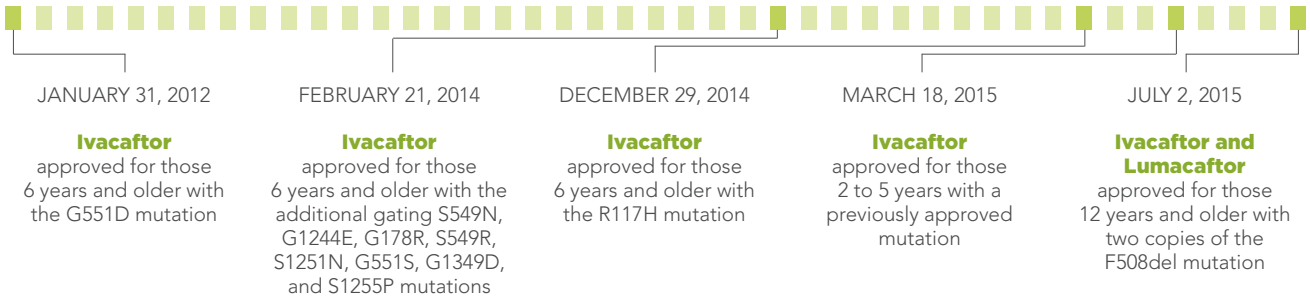


CFTR Modulator Therapies

CFTR Modulators

In 2012, the U.S. Food and Drug Administration approved Ivacaftor for individuals with at least one G551D mutation ages 6 and older. Since then there have been label extensions for other mutations and for younger patients. In 2015, Ivacaftor in combination with Lumacaftor was approved for individuals age 12 and older who are homozygous for the F508del mutation.

Timeline of CFTR Modulator Approvals



Ivacaftor

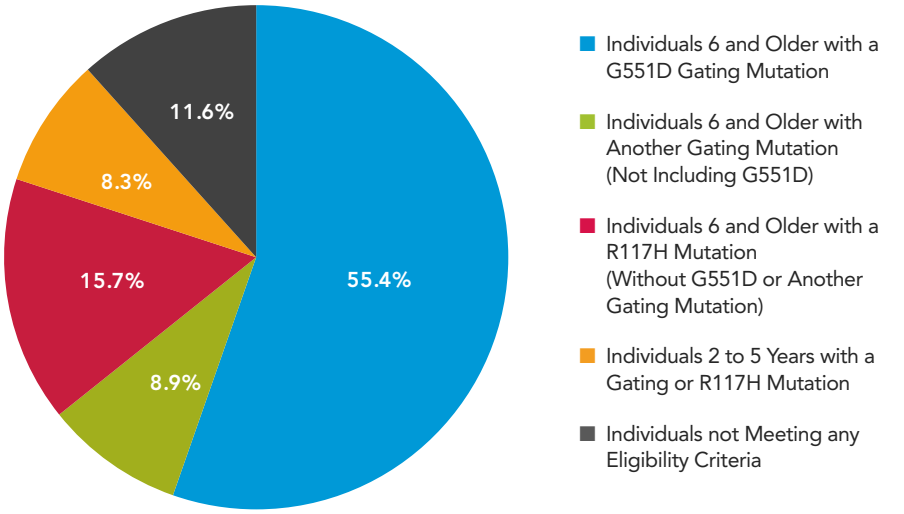
In 2015, among 2,176 eligible individuals in the Registry, 1,526 (70 percent) were prescribed Ivacaftor. For all individuals currently eligible, the percentage prescribed Ivacaftor is highest (89 percent) among individuals age 6 and older with a G551D mutation, and is lowest (43 percent) among individuals with an R117H mutation. An additional 201 individuals were prescribed Ivacaftor during one or more clinic visits in 2015 who did not meet the label eligibility criteria.

The percentage of individuals age 6 and older with a G551D mutation who were prescribed Ivacaftor increased from 77 to 89 percent from 2012 to 2015.

Ivacaftor Use in Individuals by Eligibility Cohort, 2015

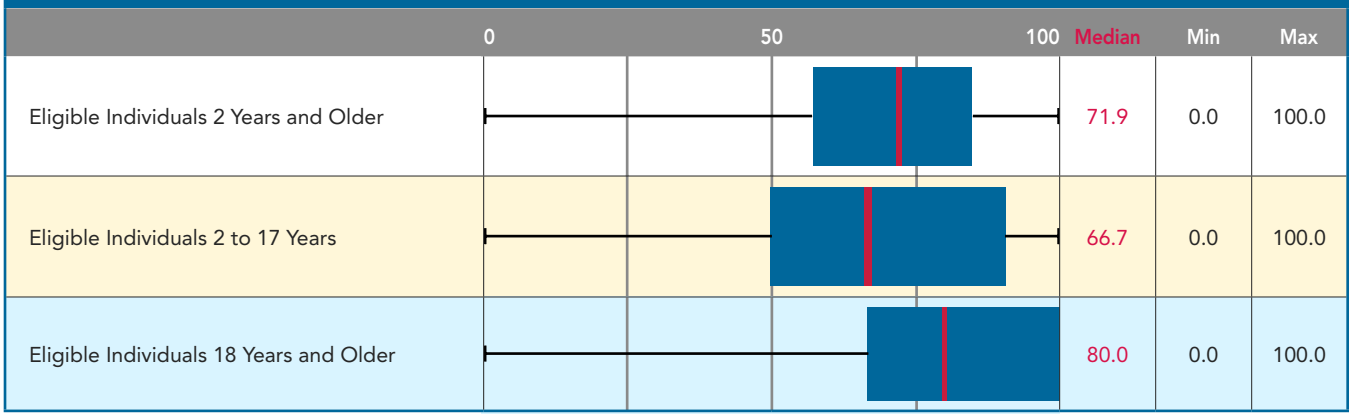
	Date Eligibility Added	Number Eligible	On Ivacaftor	Percentage
Patients 6 and Older with a G551D Gating Mutation	January 2012	1,071	956	89.3%
Patients 6 and Older with Another Gating Mutation *(Not including G551D)*	February 2014	208	154	74.0%
Patients 6 and Older with a R117H Mutation *(Without G551D or Another Gating Mutation)*	December 2014	631	272	43.1%
Patients 2 to 5 Years with a Gating or R117H Mutation	March 2015	266	144	54.1%

Ivacaftor Prescription by Eligibility Criteria



Among all Ivacaftor-eligible individuals, the median proportion of individuals receiving a prescription for the medication is 72 percent, with an interquartile range from 57 to 85 percent. For those younger than 18 years, the median percentage of individuals who received an Ivacaftor prescription is 67 percent compared with 80 percent of individuals age 18 and older; more variation in prescription rates across centers is observed among those younger than 18 than among those age 18 and older.

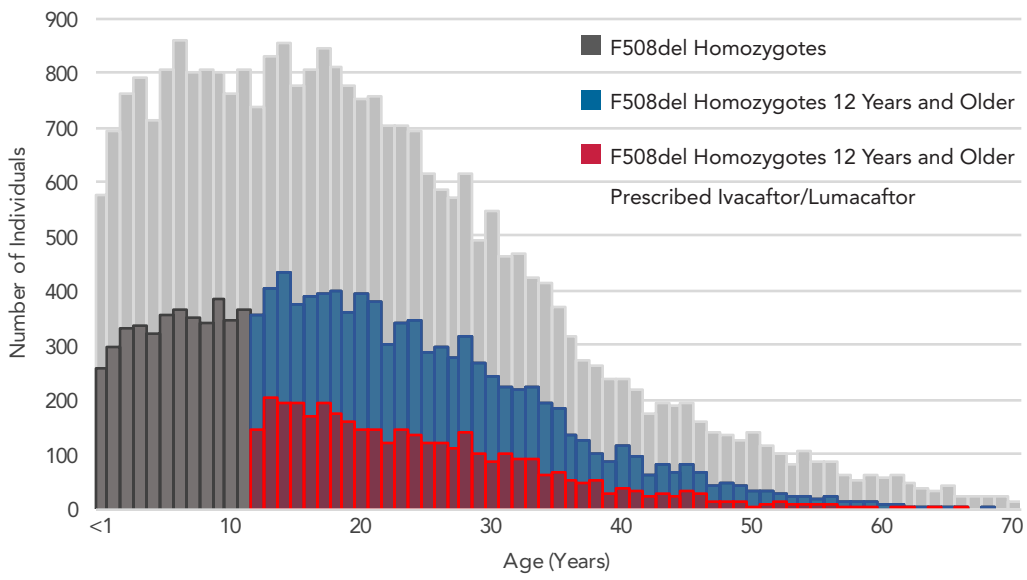
Ivacaftor Prescription in Individuals with an Eligible Mutation, by Center



Ivacaftor / Lumacaftor

In 2015, Ivacaftor/Lumacaftor was prescribed for 3,708 individuals, or 45 percent of the eligible population of individuals age 12 and older who are homozygous for the F508del mutation (47 percent of those age 12 to 17 and 40 percent of those age 18 and older). It is important to note that Ivacaftor/Lumacaftor combination therapy was not commercially available to individuals with CF until July 2015. There does not appear to be substantial variation in the proportion of eligible individuals receiving a prescription for Ivacaftor/Lumacaftor across age groups.

Ivacaftor/Lumacaftor Eligibility and Prescription by Age in Years, 2015

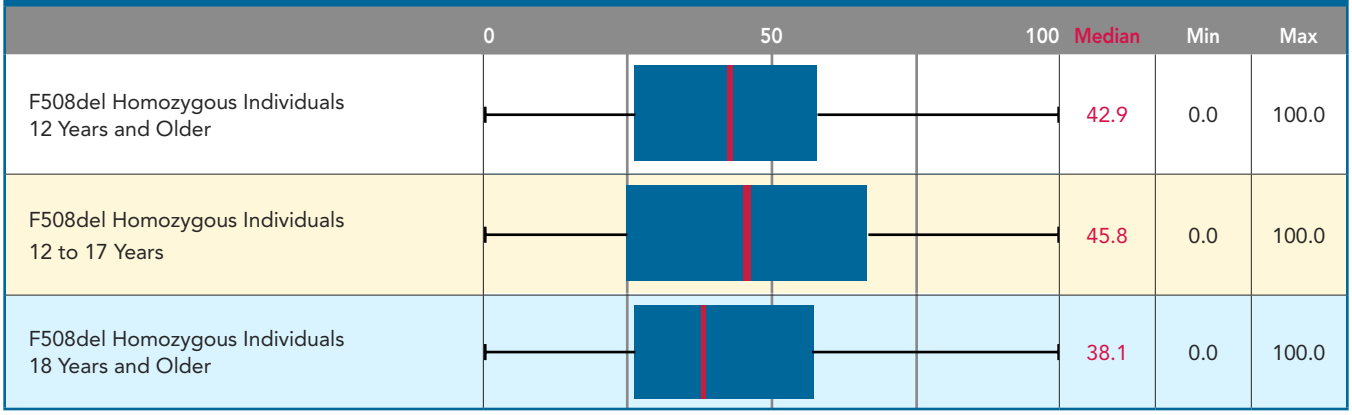


Ivacaftor/Lumacaftor Use in F508del Homozygous Individuals 12 and Older by FEV_1, 2015

	Number Eligible	On Ivacaftor/Lumacaftor	Percentage
All	8,248	3,708	45.0%
FEV_1 Less than 40% Predicted	1,119	530	47.4%
FEV_1 40% to 69% Predicted	2,577	1,252	48.6%
FEV_1 70% to 89% Predicted	2,528	1,113	44.0%
FEV_1 90% Predicted or Higher	1,922	799	41.6%
FEV_1 Unknown in 2015	102	14	13.7%

The box and whisker plots below show variation across the CF care center network with regard to the number of individuals prescribed Ivacaftor/Lumacaftor therapy. The variation is greater among individuals age 12 to 17 than individuals age 18 and older.

Ivacaftor/Lumacaftor Prescription in F508del Homozygous Individuals, by Center



COMPLICATIONS

Management of complications secondary to CF is important for maintaining an individual's health and quality of life. Complications of CF can affect many different organ systems; they can be the direct result of the malfunction of the CFTR protein or a downstream effect of the disease or its treatment.

Cystic fibrosis-related diabetes (CFRD) remains an important and highly prevalent complication that greatly affects a person's quality of life and is associated with increased morbidity and mortality. Bone disease, sinus disease and depression are other complications of CF that are more common among older adults.

Complications of CF in 2015

	< 18 (%)	≥ 18 (%)	All (%)
Number of Individuals (#)	14,018	14,965	28,983
Percent with no complications	21.7	3.8	12.5
Percent with complications not reported[A]	1.4	2.5	1.9
Cystic Fibrosis-Related Diabetes			
Cystic fibrosis-related diabetes (CFRD)[B]	6.4	34.9	21.0
Hepatobiliary			
Gall stones	0.2	0.8	0.5
Gall stones requiring surgery/procedure	0.2	1.2	0.7
Liver disease, cirrhosis[C]	2.3	3.1	2.7
Liver disease, non-cirrhosis	5.5	5.5	5.5
Hepatic steatosis	0.5	0.8	0.6
Liver disease, other	3.6	3.5	3.5
Bone/Joints			
Arthritis/arthropathy	0.5	5.9	3.3
Bone fracture	0.3	0.4	0.3
Osteopenia	1.8	21.5	11.9
Osteoporosis	0.6	9.4	5.1
Pulmonary			
Allergic bronchopulmonary aspergillosis (ABPA)	3.1	7.7	5.4
Asthma	29.9	31.7	30.8
Hemoptysis	0.4	4.1	2.3
Hemoptysis, massive	*0.1*	*1.8*	*0.9*
Pneumothorax requiring chest tube	0.1	0.8	0.5
GI			
Distal intestinal obstruction syndrome (DIOS)	5.2	5.9	5.5
Gastroesophageal reflux disease (GERD)	34.2	38.2	36.3
GI bleed requiring hospitalization (non-variceal)	0.1	0.2	0.1
Pancreatitis	0.8	2.7	1.8
Peptic ulcer disease	0.0	0.2	0.1
Rectal prolapse	1.3	0.3	0.8

Table continues on the next page

Complications of CF in 2015 (continued)			
Other Complications	< 18 (%)	≥ 18 (%)	All (%)
Anxiety disorder	2.7	14.5	8.8
Cancer confirmed by histology	0.1	1.0	0.6
Depression	3.0	24.1	13.8
Hearing loss	1.0	3.0	2.0
Hypertension	0.5	7.8	4.2
Kidney stones	0.2	2.4	1.4
Nasal polyps requiring surgery	4.2	4.9	4.6
Renal failure requiring dialysis[D]	0.0	0.3	0.2
Sinus disease	21.8	49.2	35.9

[A] *Individuals who did not have a complications case report form completed were considered to not have any complications, as in previous years.*
[B] *See table on page 68 for secondary complications.*
[C] *See table below for secondary complications.*
[D] *Cause other than CFRD.*

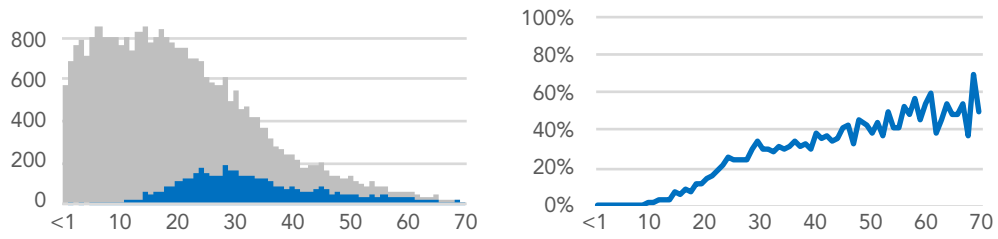
The table below highlights the prevalence of the clinical manifestations of portal hypertension among individuals with cirrhosis.

Complications of Liver Disease, Cirrhosis in 2015 (n=764)				
	All (n)	All (%)	< 18 (%)	≥ 18 (%)
Esophageal varices	186	24.3	22.0	25.9
Gastric varices	43	5.6	5.1	6.0
GI bleed related to varices	14	1.8	1.6	2.0
Splenomegaly	262	34.3	39.6	30.6
Hypersplenism	80	10.5	11.2	10.0
Ascites	47	6.2	4.2	7.5

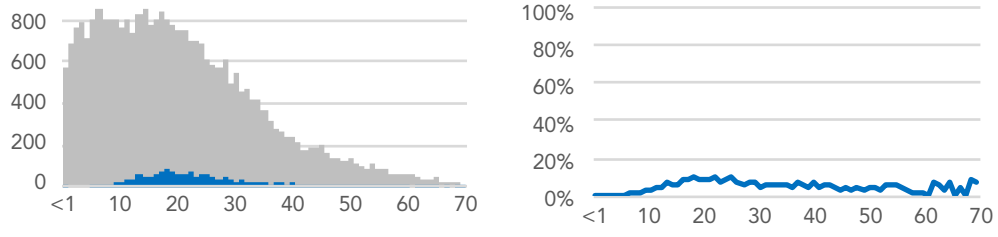
CF Complications by Age, 2015

Addressing complications of CF is an increasingly important component of treatment and care for people with CF. The prevalence of bone disease and GERD is higher among older age groups. Sinus disease, asthma and depression are higher among older children and adolescents, but stable among adults of all ages. The prevalence of CFRD peaks at about age 45. ABPA, DIOS, and anxiety are less prevalent and appear to remain consistent across all age groups. Liver disease is more prevalent in children.

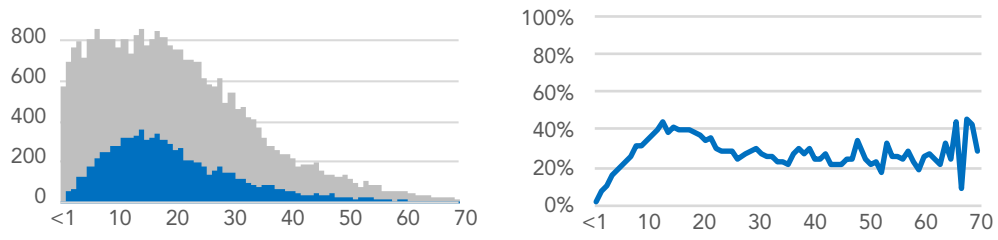
Bone Disease (Osteopenia, Osteoporosis or Bone Fracture)



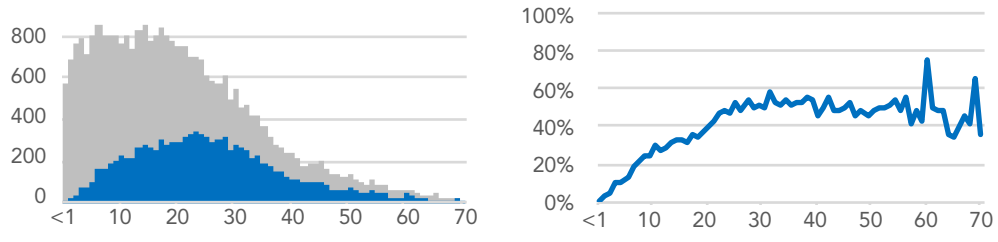
Allergic Bronchopulmonary Aspergillosis (ABPA)



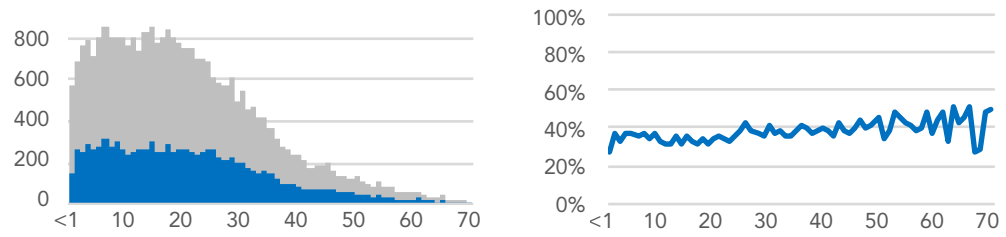
Asthma



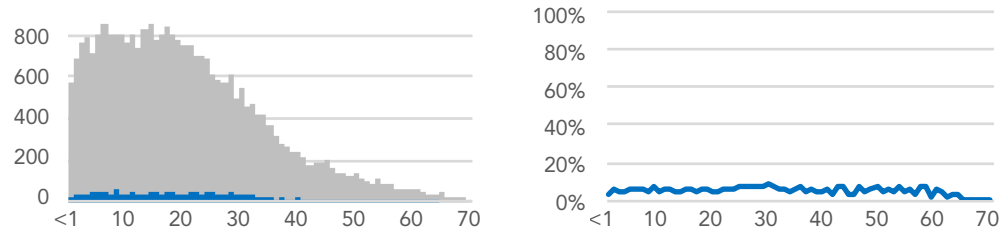
Sinus Disease



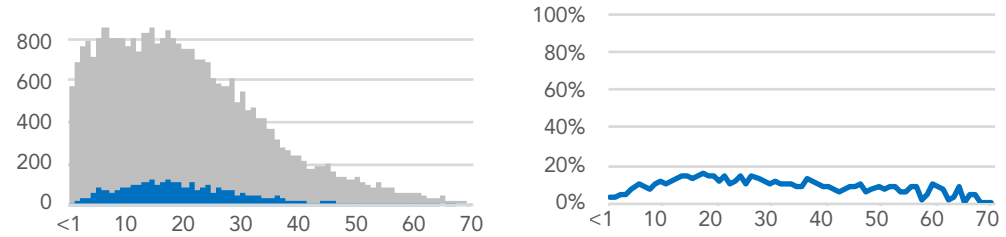
Gastroesophageal Reflux Disease (GERD)



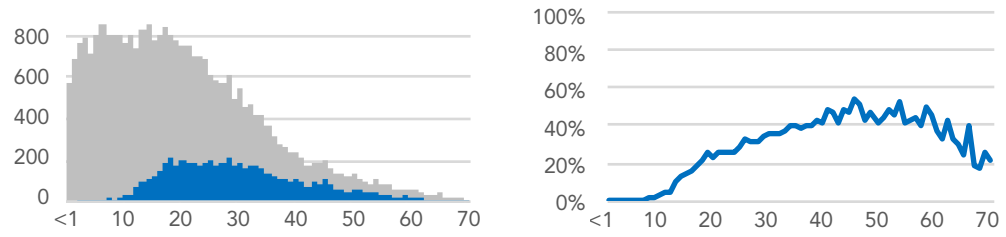
Distal Intestinal Obstruction Syndrome (DIOS)



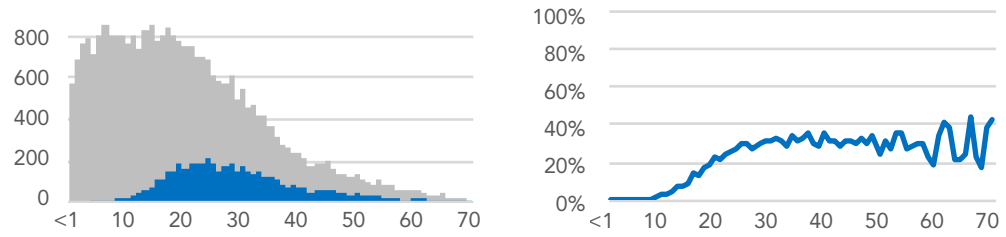
Liver Disease



Cystic Fibrosis Related-Diabetes (CFRD)

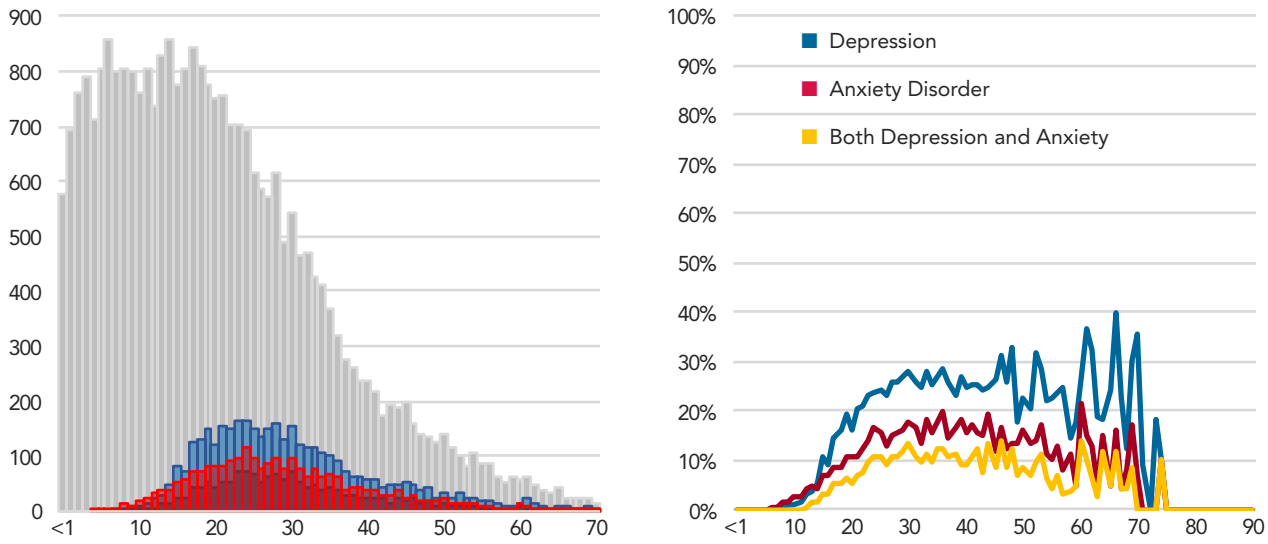


Depression or Anxiety



Addressing the mental health of all individuals with CF is critical to maintaining their overall health and quality of life. Substantial proportions of individuals living with CF report anxiety and/or depression. The prevalence reported to date is likely an underestimate as mental health screenings have not been consistently performed across the CF care center network. With the publication of guidelines on depression and anxiety,[42] we anticipate that more systematic screening will uncover a higher prevalence of these complications. Data regarding screening for depression and anxiety can be found in the earlier section of this report (page 24) that discusses CF care guidelines. Prevalence is highest in early adulthood, a time when lung disease often worsens. Almost 10 percent of people with CF report having both depression and anxiety.

Depression and Anxiety by Age in Years, 2015



The table on the opposite page displays complications by mutation class groups. Over time, the percentage of individuals reporting no complications has decreased. This observation is potentially the result of improved screening for complications, more consistent reporting of these complications in the Registry and improved survival. CFRD, liver disease, meconium ileus and DIOS are more prevalent among individuals in mutation classes I-III. In contrast, pancreatitis is more common among individuals in mutation classes IV-V. It is interesting to note that the prevalence of anxiety and depression does not differ by mutation class.

Complications of CF in 2015, by Mutation Class Group

	Mutation Class I-III (%)	Mutation Class IV-V (%)
Number of Individuals (#)	**20,157**	**3,100**
Percent with no complications	10.6	18.2
Percent with complications not reported[A]	1.5	2.8
Cystic Fibrosis-Related Diabetes		
CFRD[B]	24.6	6.8
Hepatobiliary		
Gall stones	0.6	0.4
Gall stones, requiring surgery/procedure	0.7	0.8
Liver disease, cirrhosis[C]	3.1	0.6
Liver disease, non-cirrhosis	6.5	1.7
Hepatic Steatosis	0.7	0.3
Liver disease, other	4.2	1.3
Bone/Joints		
Arthritis/Arthropathy	3.4	3.7
Bone fracture	0.4	0.3
Osteopenia	12.2	12.1
Osteoporosis	5.2	5.9
Pulmonary		
Allergic bronchopulmonary aspergillosis (ABPA)	5.7	4.1
Asthma	31.6	29.3
Hemoptysis, massive	1.0	0.8
Pneumothorax requiring chest tube	0.5	0.3
GI		
Distal intestinal obstruction syndrome (DIOS)	6.4	2.0
Gastroesophageal reflux disease (GERD)	38.7	28.7
GI bleed requiring hospitalization (non-variceal)	0.1	0.1
Pancreatitis	0.4	8.5
Peptic ulcer disease	0.1	0.2
Rectal prolapse	0.9	0.2
Other Complications		
Anxiety disorder	8.9	8.1
Cancer confirmed by histology	0.5	0.9
Depression	14.2	13.2
Hearing loss	2.0	2.4
Hypertension	3.9	5.8
Kidney stones	1.5	1.0
Nasal polyps requiring surgery	5.1	2.4
Renal failure requiring dialysis[D]	0.2	0.1
Sinus disease	36.1	38.1

[A] *Individuals who did not have a complications case report form completed were considered to not have any complications, as in previous years.*

[B] *See table on page 68 for secondary complications.*

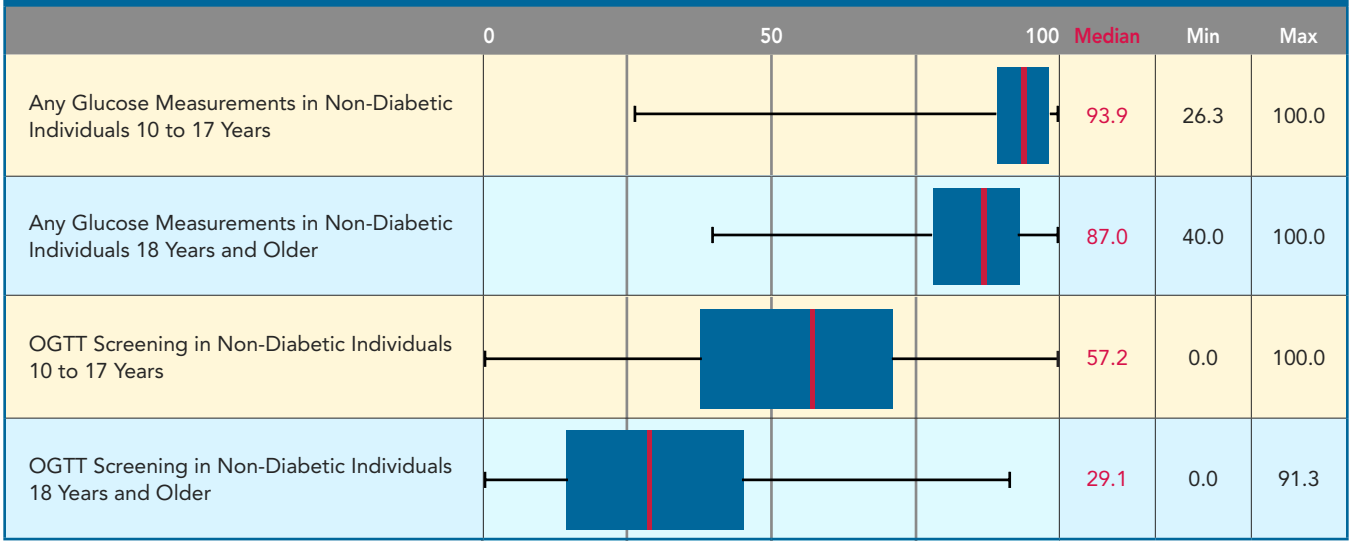
[C] *See table on page 61 for secondary complications.*

[D] *Cause other than CFRD.*

Cystic Fibrosis-Related Diabetes (CFRD)

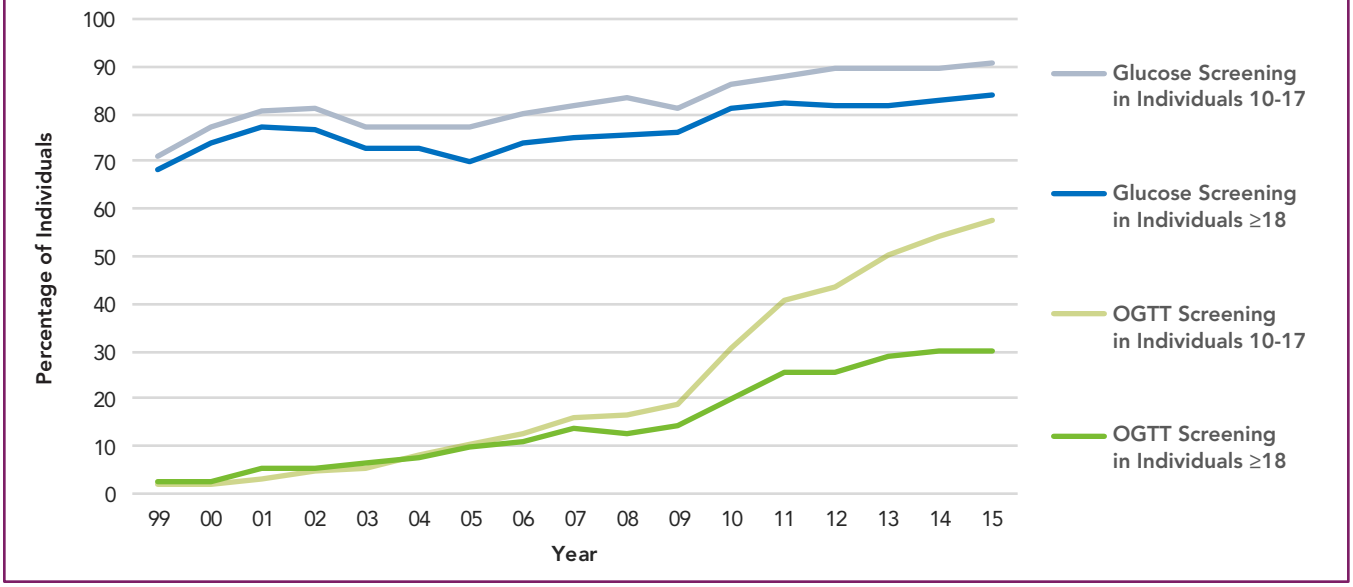
CFRD is associated with weight loss, lung function decline and increased mortality.[43] Early diagnosis and treatment may minimize the impact of CFRD. The CF Foundation CFRD guidelines recommend screening all individuals annually, starting at age 10, with an oral glucose tolerance test (OGTT).[43]

Percentage of Non-Diabetic Individuals Receiving Glucose Testing, by Center



CFRD screening using blood glucose tests is routinely performed at the vast majority of CF care centers. However, there is not as much use of the recommended OGTT test, and substantial variation across CF care centers.

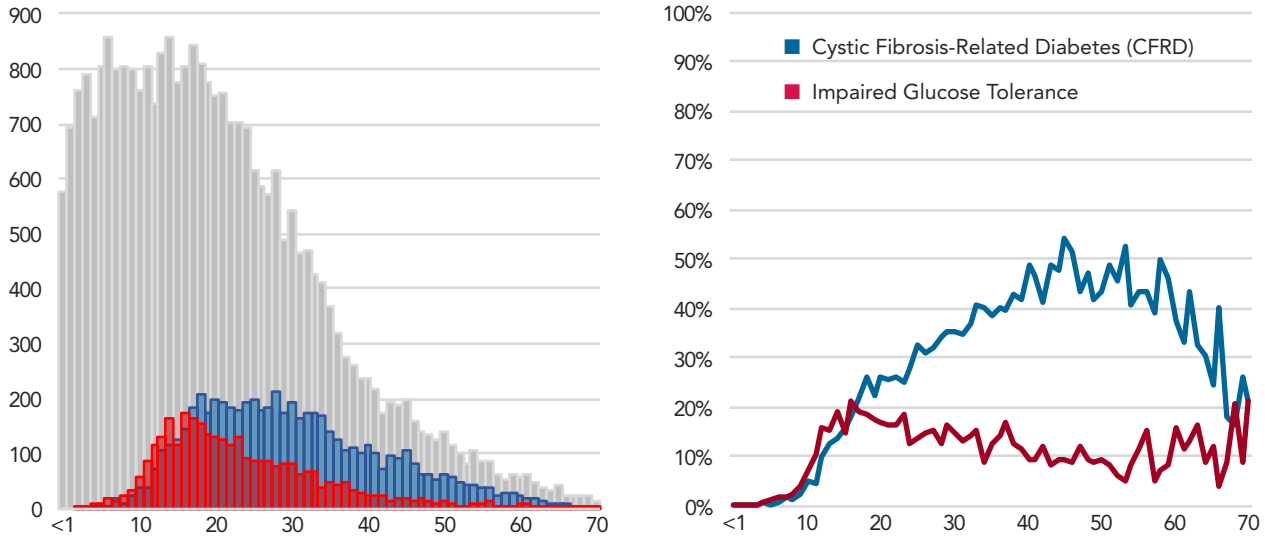
Blood Glucose and OGTT Screening for Individuals without CFRD, 1999–2015



It is encouraging to note that rates of screening adolescents for CFRD using the OGTT have increased since the publication of the CF Foundation CFRD guidelines in 2010.[43]

The prevalence of CFRD is higher among adults with CF than among children with CF. Impaired glucose tolerance is most prevalent in adolescence; these individuals are at increased risk for developing CFRD and may benefit from increased monitoring.

CFRD and Impaired Glucose Tolerance by Age in Years, 2015



The vast majority of individuals who were diagnosed with CF-related diabetes are noted in the Registry as being treated with insulin, as recommended in the CF Foundation guidelines.[43]

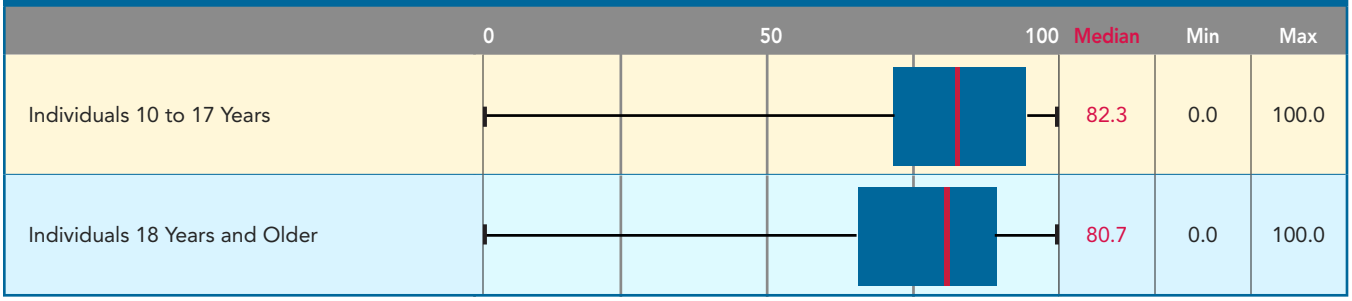
CFRD Treatment in 2015

	Percent of People with CFRD on Treatment
Dietary change	20.0
Oral hypoglycemic agents	4.3
Intermittent insulin (with illness, steroids, etc.)	5.5
Chronic insulin	77.6
No Treatment Noted in Reporting Year	8.2

The data are not mutually exclusive and represent CFRD treatment at any point during the year.

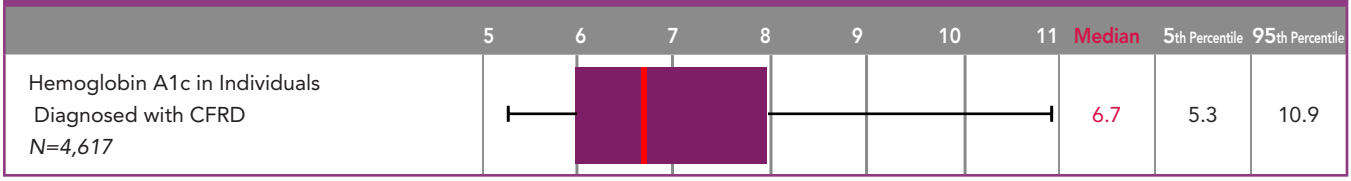
The CFRD guidelines recommend regular hemoglobin A1c (HgbA1c) measurements for individuals with CFRD.[43] There is variation by CF care center in the percentage of individuals with CFRD with one or more HgbA1c measurement during the year, but a majority of centers are testing their patients at least annually.

Percent of Individuals with CFRD with at Least One Hemoglobin A1c Measurement, by Center



The goal established by the CF Foundation CFRD guidelines is an HgbA1c less than 7.0 percent for individuals with CFRD.[43] More than half of individuals with CFRD are meeting this guideline.

Hemoglobin A1c Lab Values Reported, 2015



Rates of secondary complications of CFRD, including retinopathy, microalbuminuria, kidney disease and neuropathy, remain low. As the CF population continues to age, adult CF care providers should continue to screen individuals for these complications, as recommended by the CFRD guidelines.[43]

Complications of CFRD in 2015 (n=5,811)

	All (n)	All (%)	Age < 18 years (%)	Age ≥ 18 years (%)
Retinopathy	46	0.8	0.3	0.8
Microalbuminuria	111	1.9	0.3	2.1
Chronic renal insufficiency	252	4.2	0.2	4.9
Chronic renal failure requiring dialysis	29	0.5	0.0	0.6
Peripheral neuropathy	62	1.0	0.1	1.2
Any episodes of severe hypoglycemia	236	5.3	3.5	5.6

TRANSPLANTATION

Lung transplantation remains an option for some individuals with severe lung disease. The annual number of lung transplant procedures for individuals with CF fluctuates yearly, with an overall upward trend. Bilateral lung transplant is by far the most common procedure.

There were 1,552 individuals in the Registry in 2015 who were reported to have received a lung, kidney, heart or liver transplant.

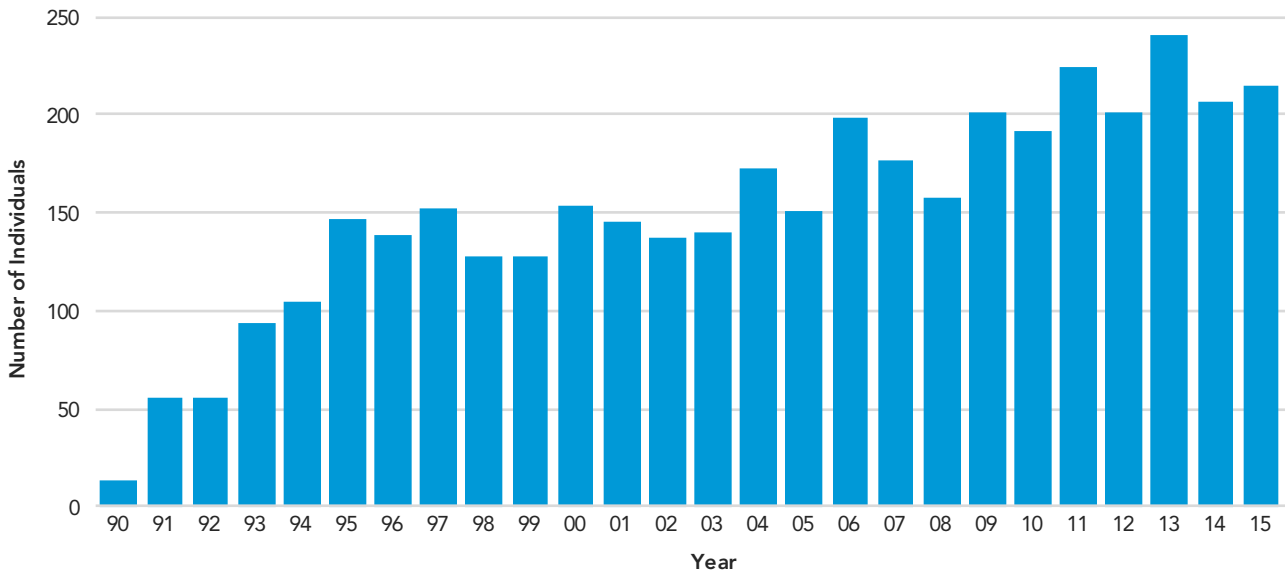
Transplant Status of People with CF in 2015 (All organs)

	Number of Individuals
Accepted, on waiting list	180
Evaluated, final decision pending	365
Evaluated, rejected	102
Received transplant in 2015	237
Received transplant in prior years	1,315

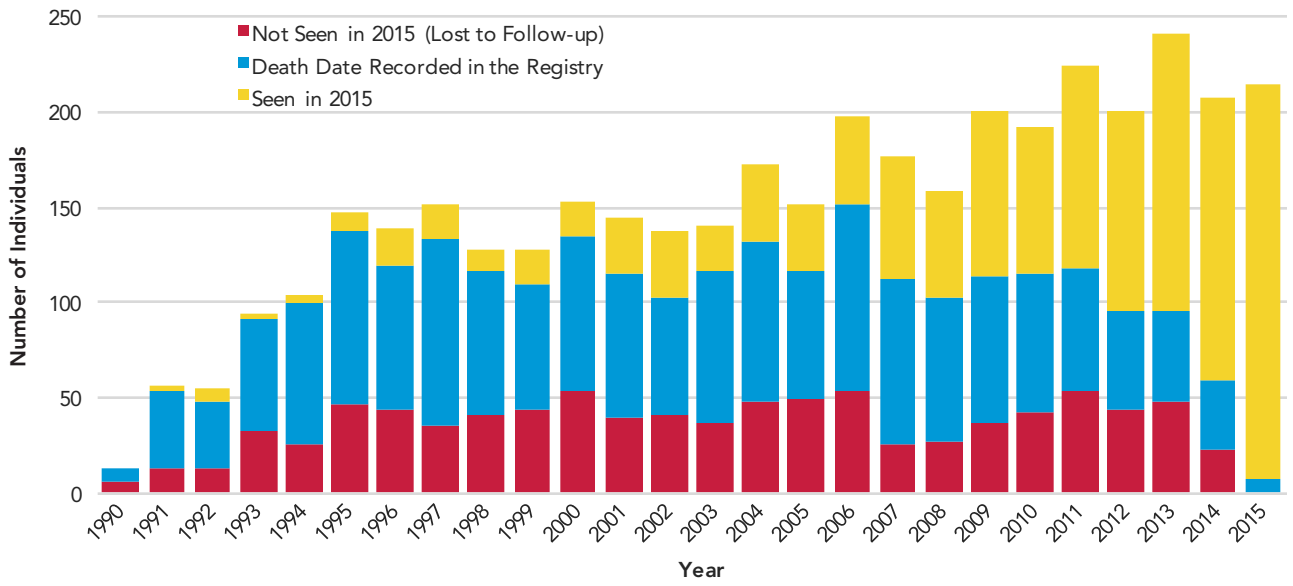
Lung Transplantation

There were 1,388 individuals in the Registry in 2015 who were reported to have ever had a lung transplant. This includes 212 individuals who were reported to have received a lung transplant in 2015.

Number of Patients Receiving a Lung Transplant, 1990–2015



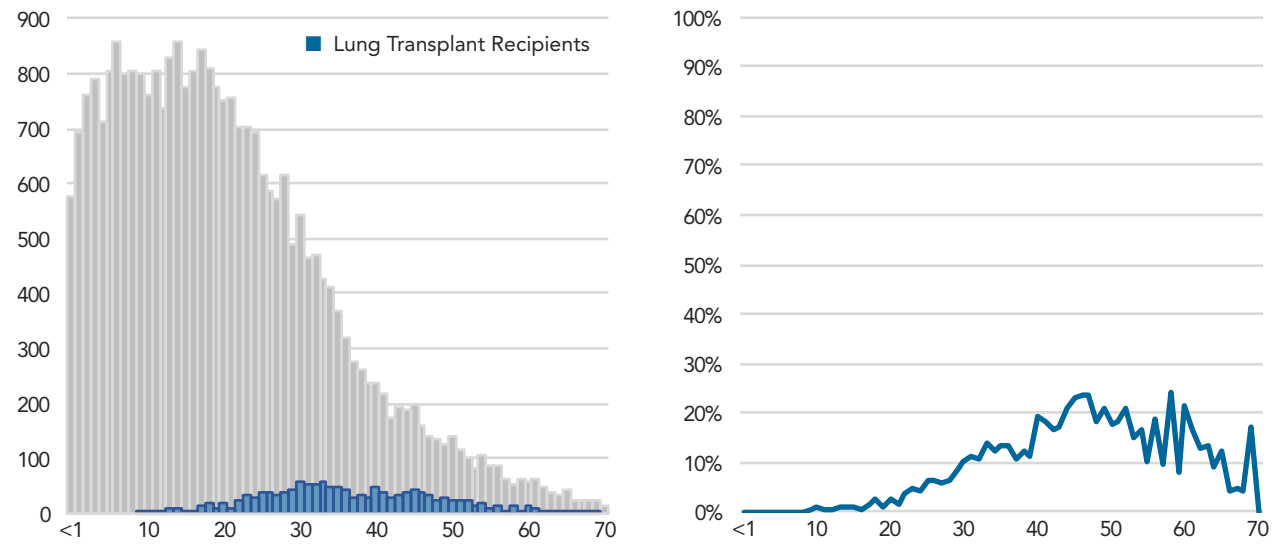
2015 Status of Lung Transplant Recipients by Year of Transplant, 1990–2015



Incomplete Registry data on post-transplant individuals receiving all of their care at a transplant center may affect survival calculations.

Overall, lung transplant recipients are a small proportion of individuals included in the Registry; the majority are age 30 and older.

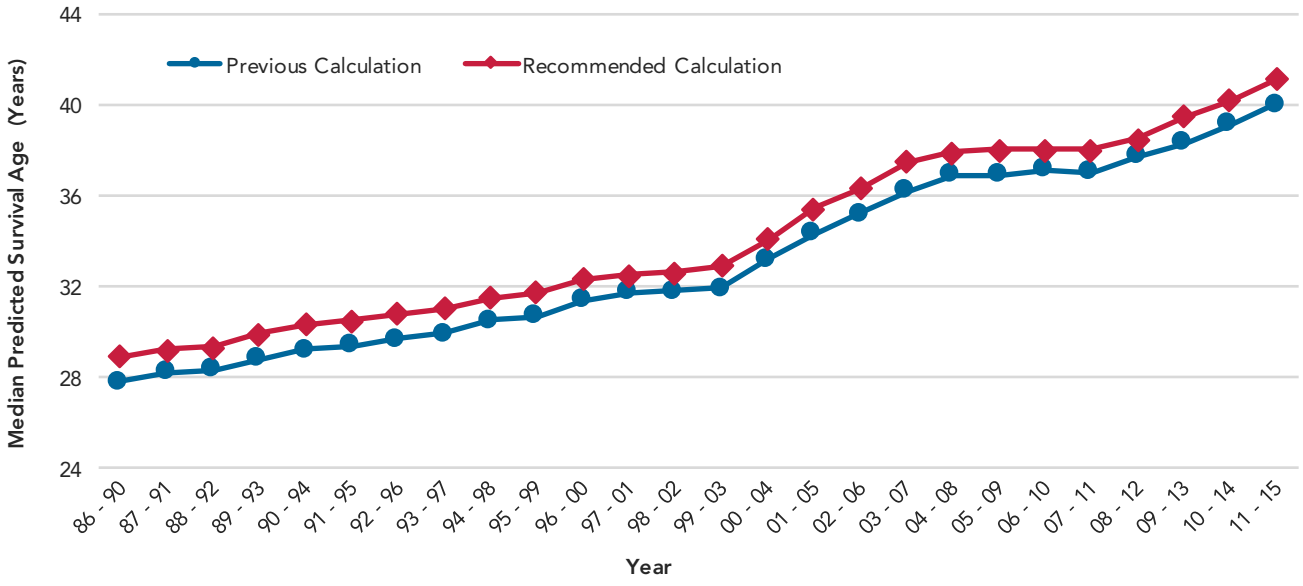
Lung Transplant Distribution in People with CF Seen in 2015



SURVIVAL

Researchers from the United States and Canada recently published an article with recommendations for best practices in calculating median predicted survival.[44] Beginning this year, the CF Foundation has adopted these recommendations. The figure below shows that estimates of median predicted survival using the recommended method (red) are higher than the method previously used (blue). The main reason is that the previous method looked only at an individual's status during a specific year. If an individual was not seen at a CF care center during a year or their data was not entered in the Registry that year, they were excluded from the analysis. In contrast, the recommended method includes individuals who were not in the Registry during a specific year but subsequently returned to a CF care center; such individuals are included in the calculation during all intervening years since their last data was entered in the Registry, thereby providing a more accurate estimate of predicted survival among individuals with CF.

Median Predicted Survival Age, 1986–2015 In 5-Year Increments



Survival Metrics

The following metrics are included in this year's report:

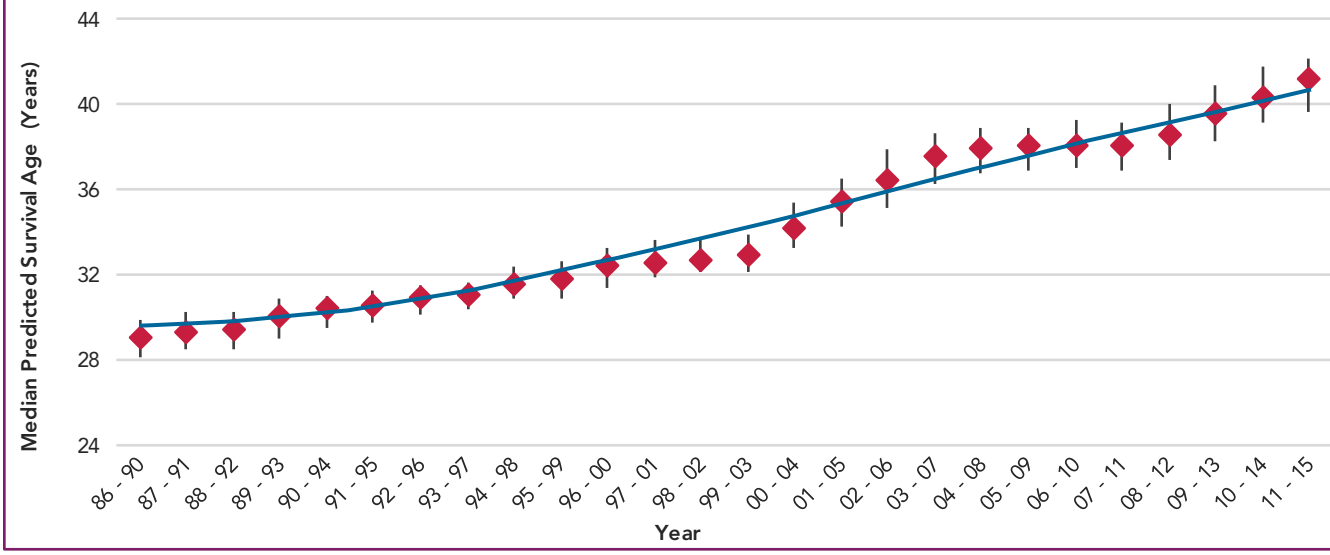
1) Median Predicted Survival: All individuals currently in the Registry are included in this calculation. It reports the age at which 50 percent of the current population is expected to survive, given the current age distribution of the population and assuming that mortality rates do not change. This is a key survival metric that we have reported for many years.
2) Mortality Rate: The number of deaths in the calendar year divided by the number of individuals in the Registry during that calendar year.
3) Life Expectancy: All individuals currently in the Registry are included in this calculation. This metric is an estimate of the **average additional years of life for individuals at a specific age**.[45] Therefore there is no single measure of life expectancy for the entire CF population.
4) Median Age at Death: This calculation includes only individuals who died during the calendar year and therefore should not be used to predict survival in the entire CF population. This metric is the age at which exactly half of the deaths of individuals with CF were below that age and half were above that age.

All metrics that use current data to predict survival make the assumption that the mortality rate will not change over time. **Therefore, they do not take into account any potential benefits from newly available CFTR modulators and other improvements in clinical care.**

Median Predicted Survival

The median predicted survival age in 2015 is 41.6 years (95 percent confidence interval: 38.5–44.0 years). This estimate increased from 40.0 in 2014. Annual estimates are imprecise because of the relatively low number of deaths in a given year, so we grouped the data into 5-year increments. The graph below shows gains in median predicted survival from 1986 to 2015 in 5 year increments. The median predicted survival age between 2011 to 2015 was 41.1 years (95 percent confidence interval: 39.6–42.1 years).

Median Predicted Survival Age, 1986–2015 In 5-Year Increments

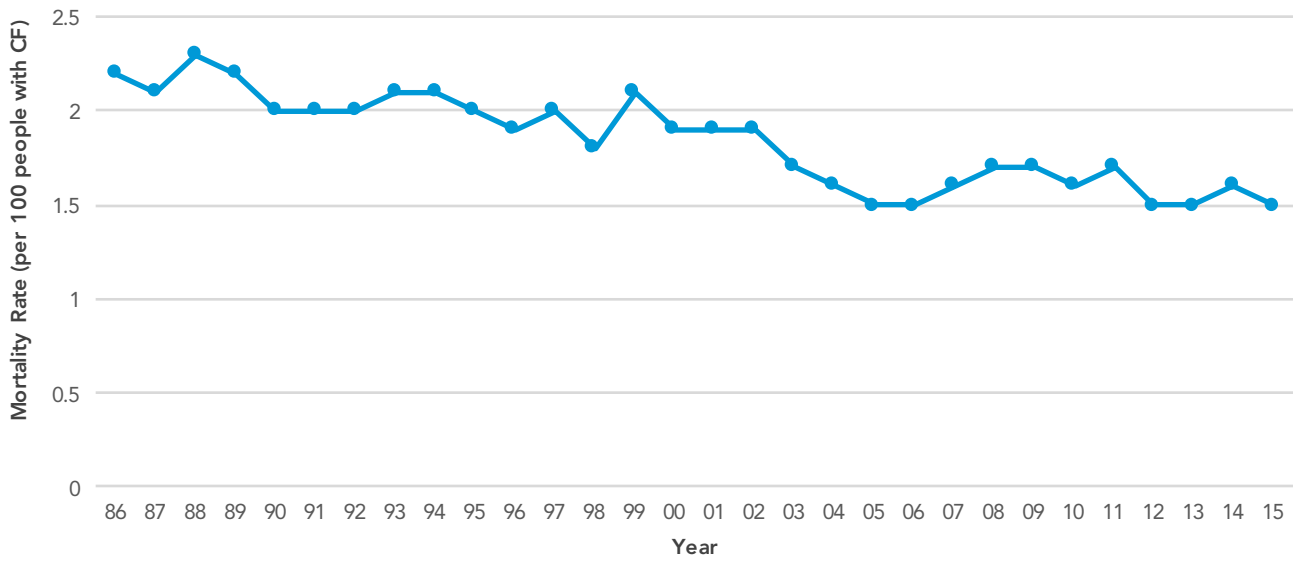


Using the currently recommended method for calculation median predicted survival.

Mortality Rate

The mortality rate in 2015 is 1.5 deaths per 100 individuals with CF in the Registry. Over time, there has been a decrease in the mortality rate. This is encouraging given that the median age of individuals in the Registry has increased from 11.6 years in 1986 to 18.6 years in 2015.

Annual Mortality Rate (per 100 people with CF), 1986–2015

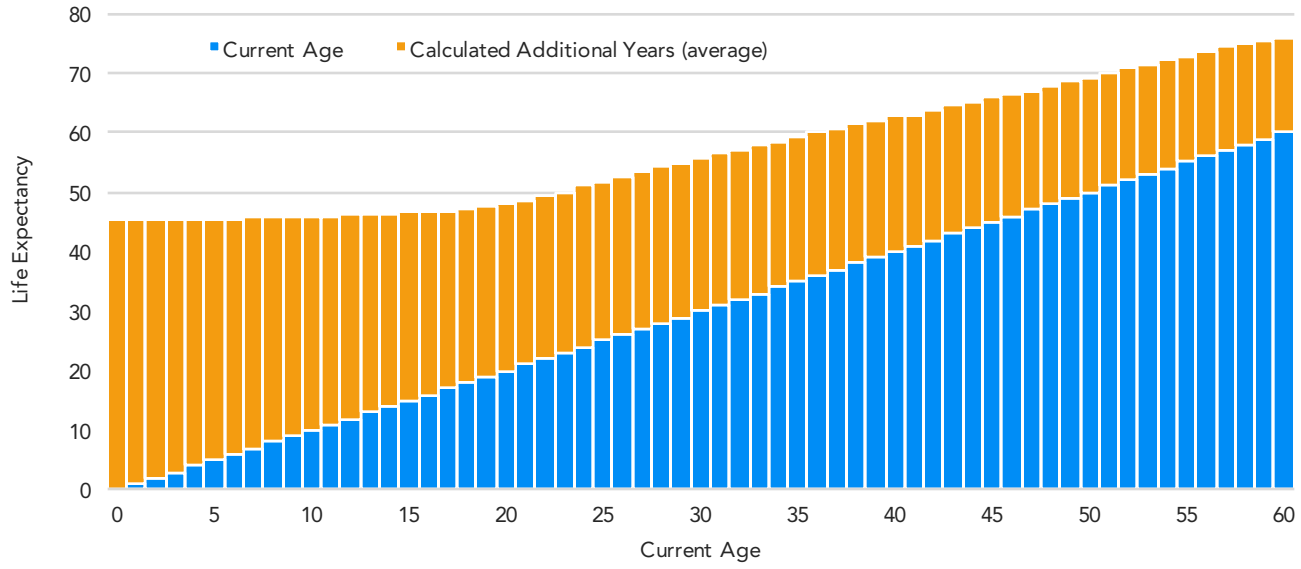


Life Expectancy

Life expectancy at specific ages is another metric to help understand changes in survival over time. However, this metric reflects population-based averages for all individuals of a given age and does not take into consideration the characteristics of individuals. Also, note that the older patient population likely reflects a survivor bias for those with milder genotypes (see page 19).

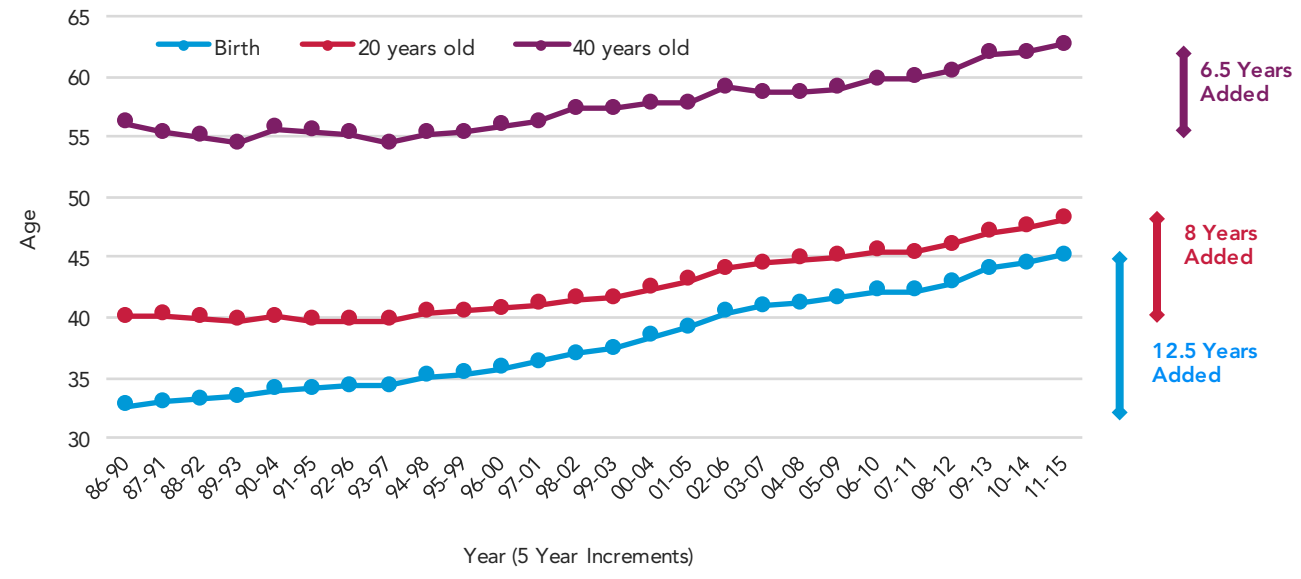
The calculations indicate that infants born in 2015 have an estimated average life expectancy of 45.2 years. Life expectancy is similar for those with an attained age up to 20 years. Individuals who have attained 30 and 40 years of age have an estimated average life expectancy of 55.6 and 62.6 years, respectively. Because the number of individuals in the Registry with attained ages of 60 and older is small, they were not included in the figure.

Life Expectancy Based on Current Age, 2015



Examining the data over time, life expectancy at birth was 34.0 years during 1991–1995, then increased to 39.2 years during 2001–2005, then rose to 45.2 years during 2011–2015. This is the age group with the largest observed increase in life expectancy (12.5 years). During the same time period, the life expectancy at birth for the entire US population increased by 4.0 years. Life expectancy for 20 year olds remained at about 40 years until 1997–2001. It has risen steadily since then to 48.1 years. Smaller but consistent increases have also been observed among those who are age 40.

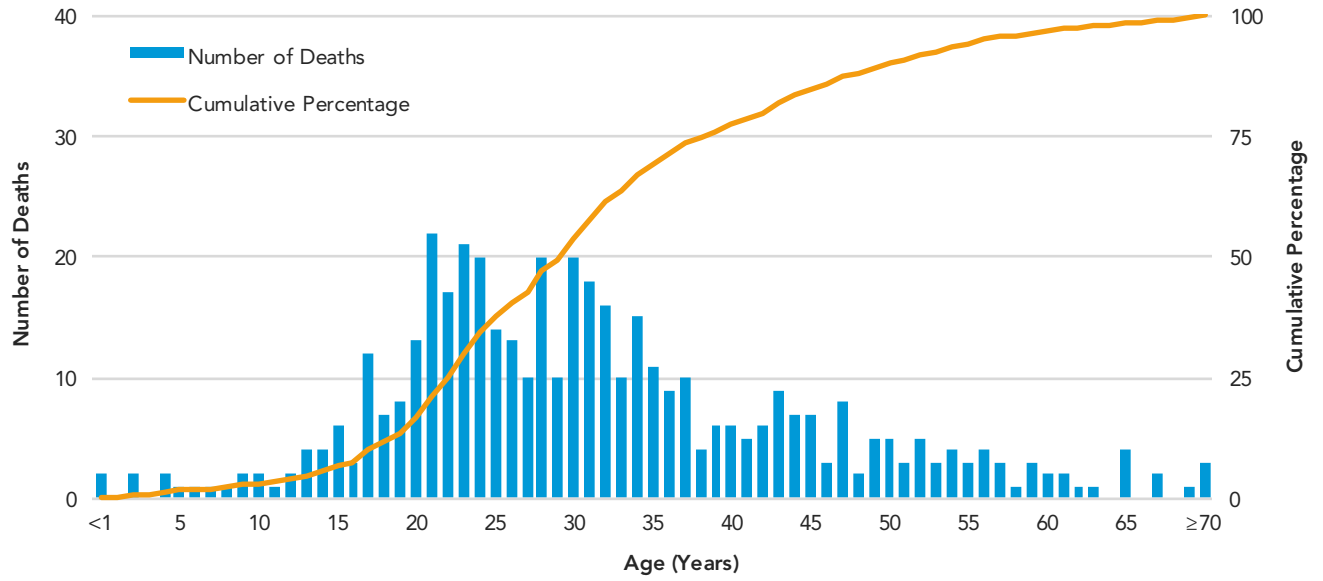
Life Expectancy by Age, 1986-2015 In 5-Year Increments



Median Age at Death

The median age at death for the 448 deaths of people with CF reported in 2015 is 29.1 years. Overall, 5 percent of deaths occur in individuals younger than age 13. Half of the deaths occur between age 22 and 39. Over time, the increase in the median age at death has been more modest than that observed in the median predicted survival, but it has increased steadily from a median age of death of 22 years in 1995 to 25 years in 2005. As noted previously, the median age of death cannot be used to predict survival in the entire population.

Age at Death in 2015



Causes of Death

Among the 448 deaths in 2015, the primary causes were respiratory/cardiorespiratory and transplant-related, similar to previous years. Over 50 percent of deaths among individuals in the Registry occurred among people with CF who were F508del homozygotes. Although less than 5 percent of individuals in the Registry population are living after organ transplant, transplant recipients represent 19 percent of all reported deaths.

Primary Cause of Death in 2015

Cause	Number of Individuals	Percent
Respiratory/cardiorespiratory	289	64.5
Transplant-related:	86	19.2
Bronchiolitis obliterans	*34*	*7.6*
Other	*52*	*11.6*
Other	35	7.8
Unknown	19	4.2
Liver disease/liver failure	15	3.3
Suicide or Trauma	<5	<1.0

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2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

DEMOGRAPHIC DATA

Demographics

CFF Patient Number: _____
Last Name: _____
Last Name at Birth (if different): _____
First Name: _____
Middle Name: _____
Last 4 digits of SSN: _____
Date of Birth: (MM/DD/YYYY)
State of Birth: _____
Gender: ○ Male ○ Female
Current Zip: _____
Is patient residing in the US permanently?
○ Yes ○ No
Emergency Phone: _____
Email: _____

Race/Ethnicity Information

Race:
○ White
○ Black or African American
○ American Indian or Alaska Native
○ Asian
○ Native Hawaiian or Other Pacific Islander
○ Some other race
○ Two or more races
If two or more races, specify Mixed Race components:
☐ White
☐ Black or African American
☐ American Indian or Alaska Native
☐ Asian
☐ Native Hawaiian or Other Pacific Islander

Is the Patient of Hispanic Origin?
○ Yes ○ No ○ Unknown

Death Information

Date of Death: (MM/DD/YYYY)

Check if date of death is approximate: ☐

Primary Cause of death:
○ Respiratory/cardiorespiratory
○ Liver Disease/Liver Failure
○ Trauma
○ Suicide
○ Transplant related: Bronchiolitis obliterans
○ Transplant related: Other
○ Other
○ Unknown

Additional Information

Additional Information: _____

CF DIAGNOSIS

History of patient diagnosis*

Date of Diagnosis: (MM/DD/YYYY)
Date is an approximation: ☐

Diagnosis:
○ Cystic Fibrosis
○ CFTR-related metabolic syndrome
○ CFTR-related disorder
○ CF, CRMS and CFTR-related disorder all ruled out

Patient was diagnosed with CF after false negative result by newborn screening:
○ Yes ○ No ○ Unknown

Diagnosis Suggested by the following:
☐ Acute or persistent respiratory abnormalities
☐ CBAVD (absent vas deferens) or related abnormalities
☐ Digital clubbing
☐ DNA Analysis
☐ Edema
☐ Electrolyte imbalance
☐ Elevated immunoreactive trypsinogen (IRT) at CF newborn screening
☐ Failure to thrive/malnutrition
☐ Family history
☐ Infertility/GU abnormalities
☐ Less than 2 identified disease causing mutations
☐ Liver problems
☐ Meconium ileus/other intestinal obstruction (provide details below)
○ meconium ileus with perforation
○ meconium ileus without perforation
Other neonatal bowel obstruction: _____
☐ Nasal polyps/sinus disease
☐ Newborn (neonatal) screening
☐ Non-diagnostic sweat chloride value(<60 mmol/L)
☐ Pancreatitis (not explained by other etiologies)
☐ Persistent respiratory colonization/infection with a typical CF pathogen(s) (e.g., Pseudomonas aeruginosa)
☐ Prenatal screening (CVS, amnio)
☐ Pulmonary mycobacterial infection
☐ Rectal prolapsed
☐ Repeat Normal Sweat Testing
☐ Steatorrhea/abnormal stools/malabsorption
☐ Transepithelial potential differences
☐ Other, specify: _____
☐ Unknown

Date & value of documented positive quantitative pilocarpine iontophoresis sweat test (Chloride)*

Date of Test: MM/DD/YY
Value (mmol/L): _____
Quantity Not Sufficient: ☐

If sweat test value <=60, CF diagnosis was suggested by:
☐ DNA Analysis/genotyping
☐ Transepithelial potential differences
☐ Clinical presentation (pancreatic fxn tests, Microbiology, etc.)
☐ Unknown

Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

*repeated entries can be recorded
[ ] indicates values calculated by the registry

2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

Parents' Information *(information not required for patients 21 years of age and older)*
Not available: ☐
Mother height: _____ ○ cm ○ inches
Father height: _____ ○ cm ○ inches

Birth Measurements
Baby delivered:
○ Full term (>= 37 weeks gestational age)
○ Premature (< 37 weeks gestational age)
○ Unknown

Specify gestational age(only if premature):_____
Birth length: _____ ○ cm ○ inches
Birth weight:_____ ○ kg ○ lb

Genotype Information
For a list of mutation options, please contact reghelp@cff.org
Has this patient been genotyped? ___ Yes ___ No
Date: (MM/DD/YYYY) Date is an approximation: ☐

Select Mutation 1: _____ Other genotype: _____
Poly T tract: ○ 5T ○ 7T ○ 9T ○ Unknown
Poly TG repeats: ○ 9 ○ 10 ○11 ○12 ○13
○ Other/unknown/not done

Select Mutation 2: _____ Other genotype: _____
Poly T tract: ○ 5T ○ 7T ○ 9T ○ Unknown
Poly TG repeats: ○ 9 ○ 10 ○11 ○12 ○13
○ Other/unknown/not done

Select Mutation 3: _____ Other genotype: _____

Additional information about genotype not captured above:_____

ENCOUNTER DATA

Vital Signs/Encounter Start

Encounter date: (MM/DD/YYYY)
Location: ○ Clinic ○ Hospital ○ Home IV
Non-clinic start date: (MM/DD/YYYY)
Non-clinic end date: (MM/DD/YYYY)
Height : _____ ○ cm ○ inches
[Height Percentile _____]
Weight : _____ ○ kg ○ lb
[Weight Percentile _____]
[BMI value: _____]
[BMI Percentile: _____]
[Weight for Length percentile: _____]

Exacerbation Assessment
What was your assessment regarding pulmonary exacerbation at this visit?
○ Absent
○ Mild exacerbation
○ Moderate exacerbation
○ Severe exacerbation
Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

○ Don't know/unable to answer

If you determined that an exacerbation was present, please select the treatment course prescribed to treat the exacerbation:
☐ Increased airway clearance, exercise, and/or bronchodilators
☐ Oral NON-quinolone antibiotic (e.g. azithromycin, Bactrim, Augmentin, etc.)
☐ Oral quinolone antibiotic (e.g. ciprofloxacin (Cipro), levofloxacin)
☐ Inhaled antibiotic
☐ Inhaled antibiotic PLUS Oral NON-quinolone antibiotic
☐ Inhaled antibiotic PLUS an oral quinolone antibiotic
☐ None of the above
If none of the above, the specify:_____
(Note: if you elected to treat with hospital or home IV antibiotics, please start a care episode and enter the requested data.)

Social Worker Consultation
☐ Patient consulted with a Social Worker at this visit

Nutritional
☐ Patient was seen by a Dietitian/Nutritionist at this visit

Pulmonary
☐ Patient was seen by a Respiratory therapist/physical therapist at this visit

Other
Record any additional information about this encounter:
Custom field 1:_____
Custom field 2:_____
Custom field 3: _____

Respiratory Microbiology

Bacterial Culture
Bacterial culture done? ☐
Date of Culture: (MM/DD/YYYY)
Type of Specimen:
○ sputum ○ induced sputum
○ throat/nasal ○ bronchoscopy

Culture Results:
○ Microorganisms ○ Normal flora
○ No growth/sterile culture

Staphylococcus aureus: ☐
○ MRSA (methicillin resistant Staph aureus)
○ MSSA (methicillin sensitive Staph aureus)

Haemophilius influenzae (any species): ☐

Pseudomonas aeruginosa: ☐
☐ mucoid ☐ non mucoid ☐ mucoid status unknown

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2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

Susceptibility Testing *(Please use the most resistant PA strain. If multiple PA strains are resistant to the same number of classes of antibiotics then use the following schema: Beta lactams> Quinolones>Aminoglycosides).*

Resistant to All Aminoglycosides Tested (e.g., tobramycin, gentamicin, amikacin):
○ Yes ○ No ○Testing not done

Resistant to All Quinolones Tested (e.g., ciprofloxacin, levofloxacin, moxifloxacin):
○ Yes ○ No ○ Testing not done

Resistant to All Beta Lactams Tested (e.g., ceftazidime, imipenem, meropenem, piperacillin/tazobactam (Zosyn), ticarcillin/clavulanic acid (Timentin), aztreonam):
○Yes ○ No ○ Testing not done

Burkholderia species: ☐
☐ B. gladioli
☐ B. cenocepacia
☐ B. multivorans
☐ Burkholderia – other
☐ B. cepacia ☐ B. stabilis ☐ B. vietnamiensis
☐ B. dolosa ☐ B. anthina ☐ B. ambifaria
☐ B. pyrrocinia ☐ B. ubonensis ☐ B. arboris
☐ B. latens ☐ B. lata ☐ B. metallica
☐ B. seminalis ☐ B. contaminans
☐ B. diffusa ☐ B. pseudomallei

Was the identification of the Burkholderia species confirmed at the CFF reference lab? ○ Yes ○ No ○ Unknown

Other microorganisms:
☐ Alcaligenes (Achromobacter) xylosoxidans
☐ Stenotrophomonas (Xanthomonas)/Maltophilia
☐ Other types:
☐ Acinetobacter baumannii ☐ Acinetobacter species -other*
☐ Agrobacterium species ☐ Bordetella species
☐ Brevundimonas species ☐ Chryseobacterium species
☐ Cupriadidus metallidurans ☐ Cupriavidus pauculus
☐ Cupriavidus respiraculi ☐ Delftia acidivordans
☐ Delftia species - other* ☐ Enterobacter species
☐ Exophilia dermatitidis ☐ Herbaspirillum frisingense
☐ Herbaspirillum seropedicae ☐ Inquilinus limosus
☐ Klebsiella pneumoniae ☐ Klebsiella species - other*
☐ Ochrobacterum species ☐ Pandoraea apista
☐ Pandoraea norimbergensis ☐ Pandoraea pulmonicola
☐ Pandoraea sputorum ☐ Pandoraea species - other*
☐ Pseudomonas mendocina
☐ Pseudomonas pseudoalcaligenes
☐ Pseudomonas putida ☐ Pseudomonas stutzeri
☐ Pseudomonas species - other*
☐ Ralstonia insidiosa ☐ Ralstonia pickettii
☐ Ralstonia species - other* ☐ Serratia marcescens
☐ Streptococcus milleri

Fungal/Yeast:
☐ Aspergillus (any species) ☐ Candida (any species)
☐ Scedosporium species

Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

Other bacterial or fungal species: ☐
Specify: _____

Mycobacterial culture
Was Mycobacterial culture done? ☐
Date of Culture: (MM/DD/YYYY)

Type of Specimen:
○ sputum ○ induced sputum ○ bronchoscopy

AFB Smear:
○ Positive ○ Negative ○ Not done

Culture Results:
○ Microorganisms
○ Normal flora
○ No growth/sterile culture

Mycobacterial Species:
☐ Mycobacterial tuberculosis
☐ Mycobacterium abscessus/chelonae
☐ Mycobacterium avium complex (MAC)
☐ Mycobacterium fortuitum group
☐ Mycobacterium gordonae
☐ Mycobacterium kansasii
☐ Mycobacterium marinum
☐ Mycobacterium terrae
☐ Other
Specify: _____
Please note: The option Mycobacterium avium complex (MAC) includes M. avium subsp. Avium, M. avium subsp. Hominissuis, M. avium subsp paratuberculosis, and M. intracellulare.

Medications

Not on Medications
This patient is not on any of the pulmonary medications below: ☐

Pulmonary Medication
Chronic Antibiotics (i.e. not prescribed to treat an exacerbation) – inhaled and/or oral
Tobramycin solution for inhalation (i.e. TOBI): ☐
Frequency: ○ 300 mg BID alternate month schedule
○ 300 mg BID continuous
○ Other regimen (different dose or freq)

Tobi Podhaler (Tobramycin Inhalation Powder): ☐
Frequency: ○ Four 28mg capsules BID alternate month
○ Other regimen (different dose or freq)

Bethkis: ☐
Frequency: ○ 300 mg BID alternate month
○ Other regimen (different dose or freq)

Other inhaled aminoglycoside (e.g. gentamcin, amikacin, or tobramycin preparation): ☐
Frequency: ○ Alternate Month
○ Continuous
○ Other regimen (different dose or freq)

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Colistin: ☐
Frequency: ○ Alternate Month
○ Continuous
○ Other regimen (different dose or freq)

Aztreonam – Inhaled: ☐
Frequency: ○ 75 mg TID Alternate Month Schedule
○ 75 mg TID Continuous
○ Other Regimen

Chronic oral macrolide antibiotic: ☐
☐ azithromycin (Zithromax)
☐ clarithromycin (Biaxin)

Other chronic oral antibiotic: ☐
☐ Quinolone (Cipro, Levaquin, gatifloxacin, etc.)
☐ Cephalosporin (cephalexin, Keflex, cefixime, etc.)
☐ Sulfa (Bactrim, Septra, etc.)
☐ Amoxicillin (Augmentin, etc.)
☐ Tetracycline (doxycycline, Vibramycin, minocycline, etc.)
☐ Other

CFTR Modulators
Ivacaftor (e.g. Kalydeco, VX-770): ☐
Frequency: ○ 50 mg BID
○ 75 mg BID
○ 150mg BID
○ Other Regimen (different dose or freq)

Ivacaftor/Lumacaftor (e.g. Kalydeco/VX-809): ☐
Frequency: ○ Full dose BID
○ Half dose BID
○ Other Regimen (different dose or freq)

Other Medications
Dornase alfa (i.e. Pulmozyme): ☐
Frequency: ○ 2.5 mg QD
○ 2.5 mg BID
○ Other regimen (different dose or frequency)
Acetylcysteine or Mucomist: ☐
High-dose ibuprofen (e.g. 25-30 mg/kg): ☐
Total (mg/dose): _____
Hypertonic saline: ☐
Concentration (%):○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10
Frequency: ○ QD ○ BID ○ Other

Bronchodilators (oral):
☐ Beta agonist (e.g. Proventil Repetabs, Volmax, etc.)
☐ Theophylline product (e.g. Theodur, Slo-bid, Uniphyl)

Bronchodilators (inhaled)
☐ Short acting beta agonist (e.g. albuterol, Proventil, Ventolin, Xopenex, etc.)
☐ Long acting beta agonist (e.g. salmeterol, Serevent, Foradil, Brovana, etc.)
☐ Short acting anticholinergic (e.g. ipratroprium, Atrovent)
☐ Long acting anticholinergic (e.g. tiotroprium, Spiriva, etc.)
Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

☐ Combination beta agonist and anticholinergic (e.g. Combivent, DuoNeb, etc.)

Corticosteriods:
☐ Oral (e.g. prednisone)
☐ Inhaled (e.g. fluticasone, Flovent, budesonide, Pulmicort, etc.)
☐ Inhaled in combination with a bronchodilator (e.g. Advair, Symbicort)

Other:
☐ Leukotriene modifiers (e.g. montelukast, Singulair, zafirlukast, Accolate, zileuton, Zyflo, etc.)
☐ Mast cell stabilizers (e.g. cromolyn, Intal, nedocromil, Tilade, etc.)
☐ Antifungals (e.g. itraconazole, Sporanox) Note: exclude topical agents for skin conditions and agents used for oral thrush)

Drug Intolerance/Allergies:
☐ Dornase alfa (i.e. Pulmozyme)
☐ Tobramycin solution for inhalation (i.e. TOBI)
☐ Aztreonam
☐ Colistin
☐ Macrolide antibiotics
☐ High-dose ibuprofen
☐ Hypertonic saline

GI/Nutrition/Endrocrine Medications
This Patient is on enzyme medications: ○ Yes ○ No
For all enzymes, "capsules per largest meal" options are:
○ .5 ○ 1 ○ 2 ○ 3 ○ 4 ○ 5 ○ 6 ○ 7 ○ 8 ○ 9 ○ 10 ○ 10+
"Total capsules per day" is a numeric free text field.

Enzymes
Creon
Creon 1203: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Creon 1206: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Creon 1212: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Creon 1224: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Creon 1236: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____

Pancreaze
Pancreaze MT4: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Pancreaze MT10: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____

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Pancreaze MT16: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Pancreaze MT20: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____

Ultresa
Ultresa 14: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Ultresa 20: ☐
Number of capsules per largest meal of the day:____
Total capsules per day:____
Ultresa 23: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____

Pancrecarb
Pancrecarb MS-4: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Pancrecarb MS-8: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Pancrecarb MS-16: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____

Zenpep
Zenpep 3: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Zenpep 5: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Zenpep 10: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Zenpep 15: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Zenpep 20: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Zenpep 25: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____

Viokace
Viokace 10: ☐
Number of capsules per largest meal of the day: ____
Total capsules per day: ____
Viokace 20: ☐
Number of capsules per largest meal of the day:____
Total capsules per day: ____

Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

Other Enzymes
Please specify if other enzymes: _____

Acid Blocker
Acid Blocker (Daily use. Check all that apply since last visit):
☐ H2 Blocker (e.g. Zantac, Pepcid, etc.)
☐ Proton Pump Inhibitor (e.g. Prilosec, Nexium, etc.)
☐ Unknown

GI other
Ursodeoxycholic acid: ☐

Pulmonary

Pulmonary Function Tests (PFTs)
Unable to Perform test: ☐
Reason why PFTs have not been done: _____

FVC measure (L): _____
[Predicted value:_____]
[Reference equation:_____]
[% Predicted:_____]
[Relative change since previous measurement:_____]
[Days since last measured:____]
FEV1 measure (L): _____
[Predicted value:_____]
[Reference equation:_____]
[% Predicted:_____]
[Relative change since previous measurement:_____]
[Days since last measured:____]
FEF25-75 measure (L): _____
[Predicted value:_____]
[Reference equation:_____]
[% Predicted:_____]
[CF Specific FEV 1 percentile (ages 6-21):]

GI/Nutrition

Assessment of Oral Intake: ○ Done ○ Not done
Is patient currently receiving supplemental feeding?
○ Yes ○ No ○Unknown
Feeding:
☐ oral supplementation (Scandishakes, Pediasure, Instant Breakfast, etc.)
☐ nasogastric tube (NG)
☐ gastrostomy tube/button (G-Tube)
☐ jejunal tube (J-tube)
☐ total parenteral nutrition (TPN)

CF specific vitamins (i.e. with additional vitamins A, D, E, and K): ○ Yes ○ No

Infants under 2 years of age
Salt supplementation: ○ Yes ○ No

Select type of feeding:
○ Breast milk ○ Breast milk plus formula
○ Formula exclusively ○ Other food
○ Unknown

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[ ] indicates values calculated by the registry

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If receiving any formula feeding, select type of formula and caloric density:

○ Cow's milk ○ Soy milk
○ Predigested ○ Other

Caloric Density:

○ 20 cal/oz ○ 22 cal/oz
○ 24 cal/oz ○ 27 cal/oz
○ 30 cal/oz ○ Other, specify:_____

Complications

Patient does not have any complications: ☐

CFRD Status

○ Impaired Glucose Tolerance (FBG < 126, 2-h PG 140-199)
○ CFRD with or without fasting hyperglycemia
CFRD secondary complications:
☐ Retinopathy
☐ Microalbuminuria
☐ Chronic renal insufficiency
☐ Chronic renal failure requiring dialysis
☐ Peripheral neuropathy

Hepatobiliary

☐ Gall stones
☐ Gall stones, requiring surgery/procedure
☐ Liver disease, cirrhosis
Please specify complications related to cirrhosis:
☐ Esophageal varices
☐ Gastric varices
☐ GI bleed related to varices
☐ Splenomegaly
☐ Hypersplenism (i.e., WBC <3.0 or platelets <100,000)
☐ Ascites
☐ Encephalopathy
☐ Liver disease, non- cirrhosis
☐ Acute Liver Failure (No underlying liver disease, ALT>3X ULN, INR>2, not responsive to vitamin K)
☐ Hepatic Steatosis
☐ Liver disease, other: _____

Acute Hepatitis (ALT > 5X ULN and duration of illness < 6 months) ☐
☐ Infectious (Hepatitis A,B,C,EBV,CMV or other known infectious cause)
☐ Non-infectious (Autoimmune, Drug Induced, Alcohol or other known cause)
☐ Unknown

Bones/Joints

☐ Arthritis/Arthropathy
☐ Bone fracture
☐ Osteopenia
☐ Osteoporosis

Pulmonary

☐ Allergic Bronchial Pulmonary Aspergillosis (ABPA)
☐ Asthma
☐ Hemoptysis
Please specify selection of hemoptysis:
☐ Hemoptysis, massive
☐ Hemoptysis, other
☐ Pneumothorax requiring chest tube

GI

☐ Distal intestinal obstruction syndrome (DIOS, Meconium ileus equiv.)
☐ Fibrosing colonopathy/colonic stricture (report incidence only)
☐ GERD (Gastro-Esophageal Reflux Disease)
☐ GI Bleed req hosp non variceal
☐ History of intestinal or colon surgery
☐ Pancreatitis
☐ Peptic ulcer disease
☐ Rectal prolapse

Other Complications

☐ Absence of Vas Deferens
☐ Anxiety Disorder
☐ Cancer confirmed by histology
☐ Depression
☐ Hearing loss
☐ Hypertension
☐ Kidney Stones
☐ Nasal polyps requiring surgery
☐ Renal failure requiring dialysis (cause other than CFRD)
☐ Sinus Disease (symptomatic)

Complications not listed above

Enter additional complications: _____

Lab

Blood counts

WBC count x1,000/microL(typical clinical value: 3.0 to 30.0): _____
Platelet Count x1,000/microL(typical clinical value: 100 to 500):_____
Hemoglobin (grams per deciliter):_____

Serum Creatinine

Serum Creatinine Level (mg/dL): _____

Liver Function Tests (LFTs)

Alanine Aminotransferase (ALT or SGPT), IU/L: _____
GGTP (gamma glutamyl transpeptidase), IU/L: _____
Aspartate Aminotransferase (AST), IU/L: _____
Alkaline phosphatase (ALP), IU/L: _____
Total Bilirubin, mg/dL: _____

Glucose Test

Random blood glucose (mg/dL):_____
Fasting blood glucose (mg/dL):_____

If OGTT performed:
OGTT Fasting glucose level (mg/dL):_____
2 hour (mg/dL):_____

Key:

FORM NAME

○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

*repeated entries can be recorded
[ ] indicates values calculated by the registry

2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

Hemoglobin A1C (Hgb A1C)
Hgb A1C value, %:_____

Fecal Elastase
Fecal Elastase Value (microg/g of stool):_____

Act/Exercise

Primary Airway Clearance Technique (ACT)
○ Positive Expiratory Pressure (PEP)
○ Postural drainage with clapping (CPT)
○ Forced expiratory techniques (e.g. autogenic drainage, huff cough, active cycle breathing)
○ Oscillating PEP (e.g. Flutter, acapella, IPV)
○ High frequency chest wall oscillation (e.g. Vest)
○ Exercise
○ None
○ Other
Specify if other technique:_____

Secondary Airway Clearance Technique (ACT)
☐ Positive Expiratory Pressure (PEP)
☐ Postural drainage with clapping (CPT)
☐ Forced expiratory techniques (e.g. autogenic drainage, huff cough, active cycle breathing)
☐ Oscillating PEP (e.g. Flutter, acapella, IPV)
☐ High frequency chest wall oscillation (e.g. Vest)
☐ Exercise

CARE EPISODE

Care Episode Segment*

Start date: (MM/DD/YYYY)
End date: (MM/DD/YYYY)
Location: ○ Hospital ○ Home IV
Reasons:
☐ Pulmonary Exacerbation
☐ Pulmonary Complication Other than exacerbation
☐ GI Complications
☐ Transplant related
☐ Sinus infection
☐ Non-transplant surgery
☐ Other
Please specify reason: _____

Care Episode Measurements

At the beginning of Care Episode:
FVC (L):_____
FEV1 (L):_____
FEF25-75 (L):_____
Height: _____ ○ cm ○ inches
Weight: _____ ○ kg ○ lb
Date recorded: (MM/DD/YYYY)
Check if data were impossible to measure: ☐

At the end of Care Episode:
FVC (L):_____
FEV1 (L):_____
FEF25-75 (L):_____
Height: _____ ○ cm ○ inches
Weight: _____ ○ kg ○ lb
Date recorded: (MM/DD/YYYY)
Check if data were impossible to measure: ☐

Comments:_____

Key:
FORM NAME
○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

ANNUAL REVIEW

Annual Review Year: (YYYY)

Patient Statistics
Number of Encounters recorded by Center: [ ]
Number of Encounters recorded by other Care Centers: [ ]
[Number of Care Episodes recorded by Care Center: [ ]
Number of Care Episodes recorded by Other Care Centers: [ ]

Demographics Update
Current Zip: _____
Patient is: [alive or dead]

Pulmonary
Did this patient use oxygen therapy during the reporting year?
○ Yes, Continuously
○ Yes, Nocturnal and/or with exertion
○ Yes, During exacerbation
○ Yes, prn
○ No
○ Unknown

Did this patient use non-invasive ventilation during the reporting year (i.e., assisted breathing, BiPap, CPAP, etc)
○ Yes ○ No ○ Unknown

Was a Chest X Ray performed during the reporting year?
○ Yes ○ No ○ Unknown

Did the patient receive an influenza vaccination this season (Sept through Jan)?
○ Yes ○ No ○ Unknown

Mycobacterial Culture
[According to the encounters a Mycobacterial culture has been performed during this reporting year: ○ Yes ○ No]
Please check to confirm the above is correct: ☐
Was treatment INITIATED for a pulmonary mycobacterial infection during this reporting year?
○ Yes ○ No ○ Unknown

Was an IgE screening for ABPA performed in this reporting year? ○ Yes ○ No ○ Unknown

Did this patient smoke cigarettes during the reporting year?
○ No
○ Occasionally
○ Yes, Regularly, less than 1 ppd
○ Yes, Regularly, 1 ppd or more
○ Declined to answer
○ Not Known

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2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

○ Not Applicable

Does anyone in the patient's household smoke cigarettes?
○ Yes ○ No ○ Unknown

During the reporting year, how often was this patient exposed to secondhand smoke?
○ Daily
○ Several Times Per Week
○ Several Times Per Month or less
○ Never
○ Declined to answer
○ Not Known

Liver

[According to the encounters data liver function tests were done in this reporting year ○ Yes ○ No]

Please check to confirm that information about liver function tests above is correct. If it is incorrect, please return to the encounter forms and enter correct information into the lab section of the encounter form: ☐

Growth and Nutrition

Fat soluble vitamin levels measured?
○ Yes ○ No ○ Unknown

Has this patient been on growth hormone in the reporting year? ○ Yes ○ No ○ Unknown

Was a DEXA scan for bone density performed in the reporting year? Please enter findings of osteoporosis or osteopenia into the complications section of last patient encounter. ○ Yes ○ No ○ Unknown

Results of DEXA Scan:
○ Normal ○ Osteopenia
○ Osteoporosis ○ Other
○ Unknown

Update on CFRD Status

Status from recent encounter [does or does not] indicate CFRD.

○ Normal Glucose Metabolism (includes normal, random, fasting, or OGTT)
○ Impaired Glucose Tolerance (FBG < 126, 2-h PG 140-199)
○ CF-related diabetes with or without fasting hyperglycemia (2-h PG >= 200)

Was a retinal eye exam performed by an opthalmologist in this reporting year? ○ Yes ○ No ○ Unknown

Was a spot urine sent for albumin/creatinine ratio in this reporting year? ○ Yes ○ No ○ Unknown

Was the patient prescribed treatment for CFRD?
○ Yes ○ No

Select all that apply:
☐ Dietary change
☐ Oral hypoglycemic agents
☐ Intermittent insulin (with illness, steroids, etc.)
☐ Chronic insulin

Key:

FORM NAME

○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

Did the patient experience any episodes of severe hypoglycemia (became unconscious or required help to resolve) during the reporting year?
○ Yes ○ No ○ Unknown

Transplantation

What is the transplantation status of the patient currently? If the patient had transplantation in previous years please select or keep "Had transplantation" option.
○ Not pertinent
○ Accepted, on waiting list
○ Evaluated, final decision pending
○ Evaluated, rejected
○ Had transplantation

Transplant

☐ Lung: Bilateral
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Heart/lung
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Lung: Lobar/Cadaveric
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Lung: Lobar/living donor
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Liver
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Kidney
Number this year:__ Date of last transplant: (MM/DD/YYYY)
☐ Other
Number this year:__ Date of last transplant: (MM/DD/YYYY)
Specify transplant type: _____

Were there post transplant complications? ☐
Select those that apply:
☐ Bronchiolitis obliterans syndrome
☐ Lympho-proliferative disorder
☐ Other
Specify other complication: _____

Clinical Trials

Has this patient participated in any interventional (drug) studies? ○ Yes ○ No ○ Unknown

Has this patient participated in any observational studies?
○ Yes ○ No ○ Unknown

Health Insurance Coverage

It is important for us to have accurate numbers of patients who have specific types of coverage:
☐ Health Insurance Policy (e.g. Private Insurance)
☐ Medicare
☐ Medicaid
☐ State special needs program, e.g., BCMH, CCS, CRS, GHPP, etc.
☐ TriCare or other military health plan
☐ Indian Health Service
☐ Other
Specify if other insurance:_____

Patient has no health insurance: ☐

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2015 Cystic Fibrosis Foundation Patient Registry Questionnaire

Was patient covered under parent's health insurance plan?
○ Yes ○ No ○ Unknown

Did patient receive free medicine or co-pay/deductible assistance from a Patient Assistance Program?
○ Yes ○ No ○ Unknown

Socio-economic Status

Education of Patient:
○ Less than High School
○ High School diploma or equivalent
○ Some College
○ College Graduate
○ Masters/Doctoral level degree
○ Unknown/Not applicable

Education of father of patient:
○ Less than High School
○ High School diploma or equivalent
○ Some College
○ College Graduate
○ Masters/Doctoral level degree
○ Unknown/Not applicable

Education of mother of patient:
○ Less than High School
○ High School diploma or equivalent
○ Some College
○ College Graduate
○ Masters/Doctoral level degree
○ Unknown/Not applicable

Education of spouse of patient:
○ Less than High School
○ High School diploma or equivalent
○ Some College
○ College Graduate
○ Masters/Doctoral level degree
○ Unknown/Not applicable

What was the total combined income of the household before taxes where the patient resided for the majority of the reporting year?
○ <$10,000 ○ $10,000 to $19,999
○ $20,000 to $29,999 ○ $30,000 to $39,999
○ $40,000 to $49,999 ○ $50,000 to $59,999
○ $60,000 to $69,999 ○ $70,000 to $79,999
○ $80,000 to $89,999 ○ >$90,000
○ Unknown or Prefer not to Answer

How many people currently live in the patient's household (including the patient)?
○ 1 ○ 2 ○ 3 ○ 4
○ 5 ○ 6 ○ 7 ○ 8
○ 9 ○ 10 ○ 11 ○ 12 or more
○ Unknown

Mental Health

Was the patient screened for symptoms of classic depression using Patient Health Questionnaire (PHQ-9) or other valid depression screening tools?
○ Yes ○ No ○ Unknown

Was the patient screened for the anxiety disorder using Generalized Anxiety Disorder Tool (GAD-7 or similar)?
○ Yes ○ No ○ Unknown

Age 18 and Older

Marital Status:
○ Single (never married)
○ Living Together
○ Married
○ Separated
○ Divorced
○ Widowed
○ Unknown

Employment:
☐ Part Time
☐ Full time homemaker
☐ Full time employment
☐ Unemployed
☐ Student
☐ Disabled
☐ Retired
☐ Unknown

Pregnancy

Was patient pregnant during the reporting year?
○ Yes ○ No ○ Unknown

If Yes, indicate outcome:
○ Live Birth
○ Still Birth
○ Spontaneous Abortion
○ Therapeutic Abortion
○ Undelivered
○ Unknown

Age 2 and Younger

Did the patient attend day care during this reporting year?
○ Yes ○ No ○ Unknown

Did the family receive genetic counseling this reporting year?
○ Yes ○ No ○ Unknown

Was the patient given palivizumab (Synagis) this season (Sept through January)?
○ Yes ○ No ○ Unknown

Other

Please use this field to record any additional information about this patient: _____

Key:

FORM NAME

○ radio buttons (select one option only)
☐ check box (multiple selections allowed)

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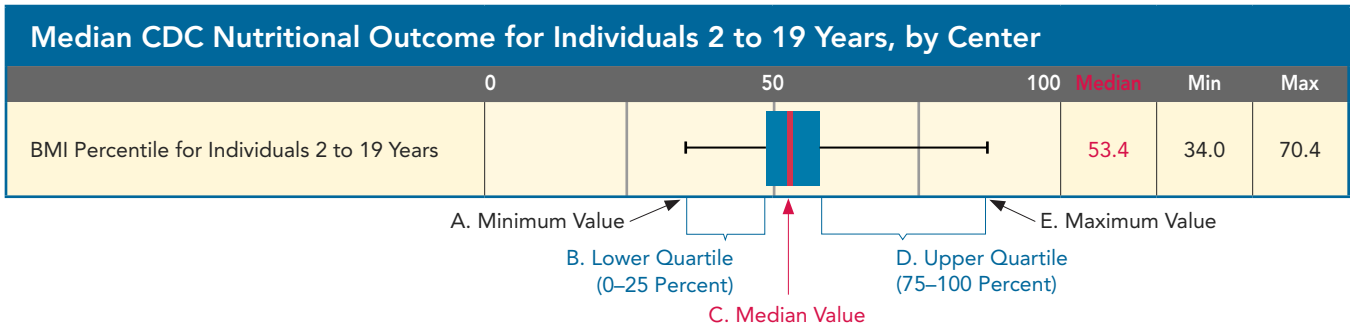
APPENDIX

Box-and-Whisker Charts to Show Center-Level and Population-Level Variation

Throughout the report, box-and-whisker plots are used in two ways: to show center-level and population-level variation. For example, the box-and-whisker plot below shows the median body mass index (BMI) percentile among individuals ages 2 to 19 years across all centers:



Center-level box and whisker plots are constructed by first determining the median value for individuals at each center, then creating the box-and-whisker plots using the summary numbers from each center.

Box-and-whisker plots provide the following information as noted in the figure above:

A. Minimum: The lowest median BMI percentile at any center (left "whisker").

B. 0-25th percentile: 25 percent of centers' observations fall below.

C. Median: 50 percent of observations fall below and 50 percent fall above. Median values, shown by a red line, are preferable to mean values because they are not skewed by extreme values.

D. "Box": 25th to 75th percentile values.

E. 75th – 100th percentile: 75 percent of centers' observations fall below.

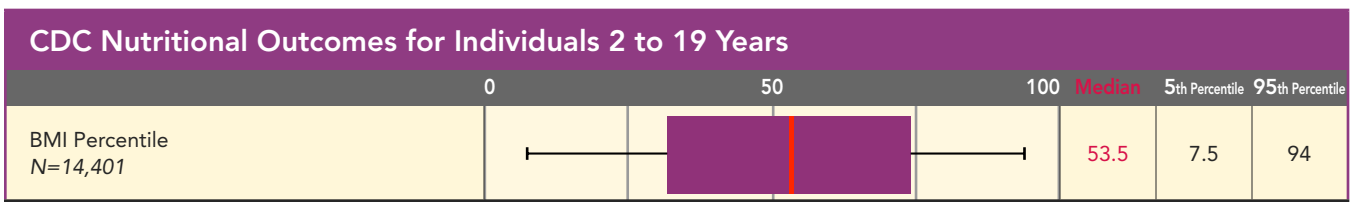
F. Maximum: The highest median BMI percentile of all centers (right "whisker").

Plots with no shading show data for all individuals

Plots with yellow shading show data for children

Plots with blue shading show data for adults

In addition, box-and-whisker plots are used to show the distribution of population-level variations for outcomes and process measures. An example is the figure below, which also displays the variation in BMI percentile among individuals ages 2 to 19 years in the 2015 reporting year. In this case, each individual's data is included in the box-and-whisker plot. As a result, the median value is nearly identical but there is much wider variation in the population-level plot as compared to the center-level.

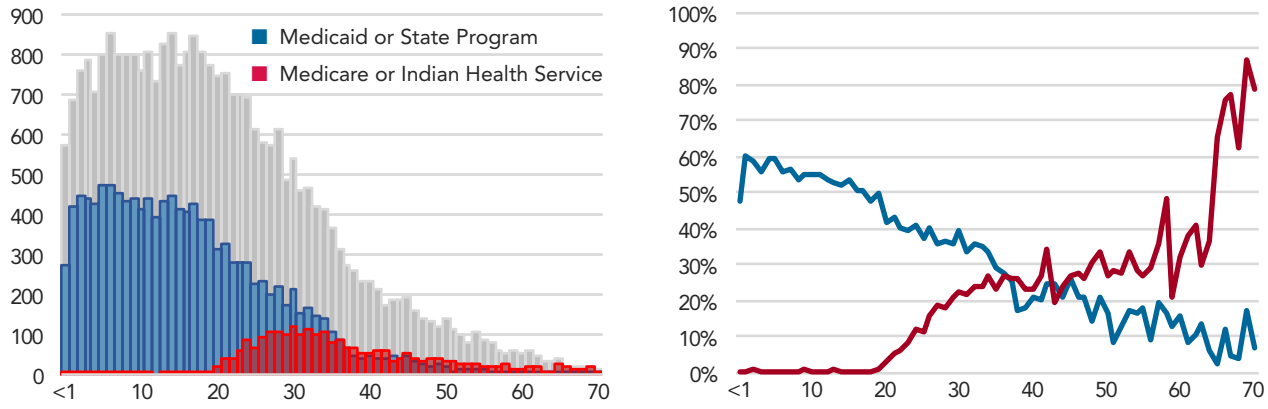


Using Combined Data Charts to Display Selected Attributes, by Age

Throughout this report, combined data charts are used to display selected attributes or health outcomes by age for people with CF; histograms are used for raw patient counts and line charts are used for percentage of total individuals by age. Within these charts, the figure on the left shows the total number of people with CF at each age, as well as the number with the attribute displayed. The figure on the right shows the percentage of people with CF at each age with the attribute. We removed those over 70 years for this display because there were less than 10 individuals in any age group over 70 years. For consistency across the report and to allow comparisons across different attributes, the light gray bars in the background always represent the total number of people with CF, in that age cohort, in the 2015 Registry data. Bars of other colors are used to show the number of people with a selected attribute (e.g., a complication).

In the figure below, the histogram on the left shows the number of people who reported Medicaid as a form of insurance in blue and the number of people who reported Medicare as a form of insurance in red. The line graph on the right shows the percentage of people who selected each insurance type with the percentage lines using the same color scheme as the bar chart. These charts provide insight into how attributes change across age groups in the 2015 Registry data.

Medicare/Indian Health Service and Medicaid/State Programs by Age in Years, 2015

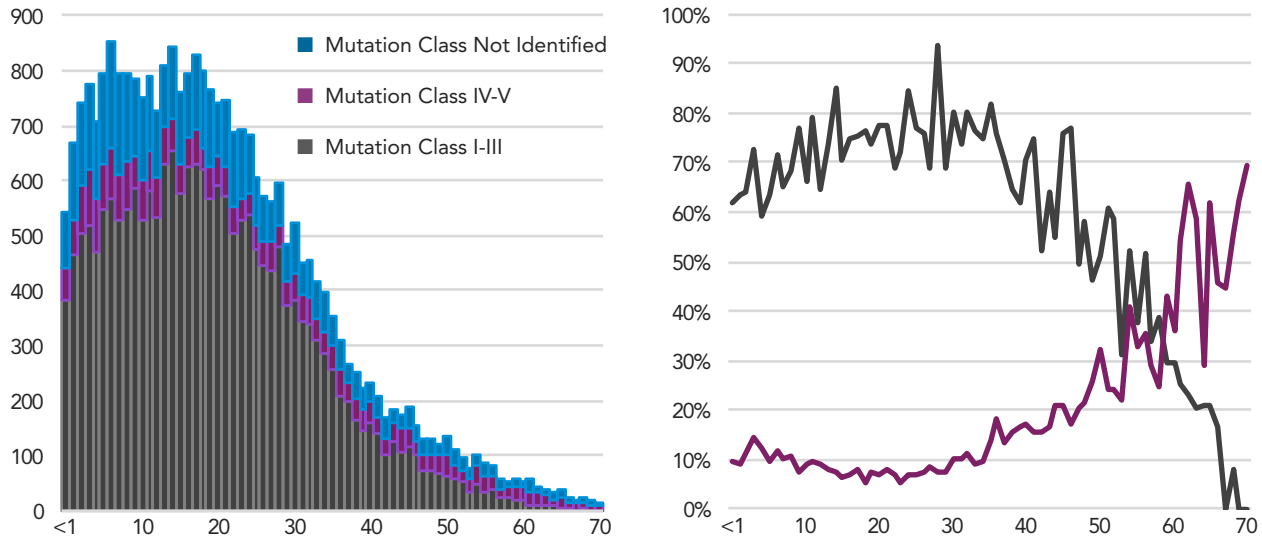


In most cases where this type of display is used, the categories are not mutually exclusive, so an individual can be counted in more than one of the categories. In cases where the attributes are mutually exclusive, such as mutation class or lung function cohorts, a stacked bar is shown.

Caution must be used when interpreting the data in these charts because there have been changes over time in the diagnosis, treatment and survival of people with CF. Specifically, universal newborn screening for CF has been in place in the United States since 2010 and was implemented even earlier in many states. Therefore, the diagnostic and clinical characteristics of very young individuals included in the Registry in recent years are different than those of similarly aged individuals previously included in the Registry. Prior to newborn screening, most infants were diagnosed because of clinical symptoms. Now, asymptomatic and potentially healthier infants are being diagnosed with CF and included in the Registry earlier than they previously would have been. Within older ages, we see an effect referred to as survivor bias, which is particularly evident in cross-sectional data. Older individuals currently in the Registry have survived and are likely healthier, and are therefore not representative of other people with CF who were included in the same birth cohort for analysis done at younger ages. We must keep these and other potential biases in mind when interpreting the data.

These two specific biases can be seen in the chart below. Individuals with a genotype with two mutations within classes I to III are typically associated with a severe phenotype and are assigned to the mutation class I-III group. Individuals with one or more mutations within classes IV or V are typically associated with a milder phenotype and are assigned to the mutation class IV-V group. We see a modest increase in number and percentage of individuals with class IV and V mutations among those ages 5 years and younger, i.e., children born in the era of universal newborn screening for CF. At older ages, the greater proportion of individuals observed with a genotype consisting of one or more mutations from classes IV or V is the result of survivor bias.

Mutation Class Status by Age in Years, 2015 *(Stacked Bar Chart)*



NOTES

CYSTIC FIBROSIS FOUNDATION
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