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
Cystic Fibrosis Foundation Patient Registry
2016 Annual Data Report
Bethesda, Maryland
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PHOTOGRAPHY BY
Michael Barley and Joe McNally

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Ase Sewall
Deena Loeffler
Kristofer Petren
Thomas O’Neil
Samar Rizvi
August 2017

Dear Friends and Colleagues:

It is a pleasure to share the 2016 Patient Registry Annual Data Report with you. The Cystic Fibrosis Foundation Patient Registry remains a very important resource to the CF community, contributing to clinical trial design, “real world” observational research including safety and effectiveness studies of newly approved therapiest, and quality improvement.

Many thanks to each and every one of you who contribute to the success of the Registry. It would not be possible without the vital contributions of many, most notably the people 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. We hope that you feel a sense of pride as you read through this report.

I call your attention to a few highlights in the 2016 data. First the good news is that median predicted survival as well as pulmonary function and measures of nutritional status continue to show trends upwards. Also of note, over 7,500 individuals were prescribed a CFTR modulator drug.

The data also show us that much work remains. Nearly one third of people with CF require one or more courses of intravenous antibiotics for treatment of a pulmonary exacerbation. The treatment burden remains high, with approximately 35 percent of people with CF prescribed three or more inhaled medications as well as other standard therapies. Complications such as anxiety and depression are highly prevalent. On a positive note, the screening rates for anxiety and depression show marked improvement in 2016, an important first step in identifying people who might benefit from support and therapeutic interventions.

This is a truly exciting time in CF, with advances in health care delivery and new therapeutics that have transformative potential. Together, we will continue to 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, 2001-2016

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</tr>
</thead>
<tbody>
<tr>
<td>People with CF (n)</td>
<td>22,619</td>
<td>23,898</td>
<td>27,000</td>
<td>29,057</td>
<td>29,497</td>
</tr>
<tr>
<td>Newly diagnosed individuals (n)^</td>
<td>1,070</td>
<td>1,016</td>
<td>995</td>
<td>977</td>
<td>892</td>
</tr>
<tr>
<td>Detected by newborn screening (%)</td>
<td>9.2</td>
<td>21.1</td>
<td>56.2</td>
<td>57.8</td>
<td>62.4</td>
</tr>
<tr>
<td>Mean age at diagnosis for all people with CF (years)</td>
<td>3.2</td>
<td>3.4</td>
<td>3.6</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Median age at diagnosis for all people with CF (years)</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>17.1</td>
<td>18.3</td>
<td>19.6</td>
<td>20.9</td>
<td>21.3</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>15.0</td>
<td>16.3</td>
<td>17.5</td>
<td>18.5</td>
<td>19.0</td>
</tr>
<tr>
<td>Adults ≥ 18 years (%)</td>
<td>39.4</td>
<td>44.2</td>
<td>48.4</td>
<td>51.5</td>
<td>52.7</td>
</tr>
</tbody>
</table>

### Race (not mutually exclusive)

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>White (%)</td>
<td>95.4</td>
<td>95.0</td>
<td>94.3</td>
<td>93.7</td>
<td>93.7</td>
</tr>
<tr>
<td>African American (%)</td>
<td>3.9</td>
<td>4.0</td>
<td>4.4</td>
<td>4.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Other race (%)</td>
<td>1.6</td>
<td>2.0</td>
<td>2.9</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>Hispanic (any race) (%)</td>
<td>5.4</td>
<td>6.1</td>
<td>7.2</td>
<td>8.2</td>
<td>8.5</td>
</tr>
<tr>
<td>Males (%)</td>
<td>52.8</td>
<td>52.0</td>
<td>51.8</td>
<td>51.6</td>
<td>51.5</td>
</tr>
</tbody>
</table>

### Mortality

| Total deaths (n)           | 420    | 370    | 459    | 450    | 373    |
| Annual mortality rate (per 100) (%) | 1.9 | 1.5    | 1.7    | 1.5    | 1.3    |
| Predicted median survival (years) | 33.9 | 36.9   | 37.2   | 41.2   | 47.7   |
| 95% confidence interval (years) | 32.0-37.0 | 34.6-40.9 | 35.5-40.9 | 38.2-43.9 | 45.6-51.1 |
| Median age at death (years) | 24.7   | 25.5   | 27.0   | 30.1   | 29.6   |

### GI/Nutrition

| BMI percentile in individuals 2 to 19 years (median) | 41.0 | 46.9 | 51.1 | 54.1 | 55.1 |
| Weight < 10th CDC percentile (%)                      | 24.4 | 18.2 | 14.7 | 12.4 | 11.5 |
| Height < 5th CDC percentile (%)                        | 15.5 | 13.6 | 11.0 | 9.9  | 9.8  |
| BMI in individuals 20 to 40 years (median)            | 21.2 | 21.7 | 22.1 | 22.5 | 22.6 |
| Pancreatic enzyme replacement therapy (%)             | 95.8 | 92.4 | 87.3 | 86.9 | 86.5 |
| Supplemental feeding - tube (%)                       | 8.5  | 10.5 | 11.2 | 11.7 | 11.5 |
| Supplemental feeding - oral only (%)                  | 30.9 | 39.9 | 41.2 | 44.0 | 44.9 |

### Pulmonary

| FVC % predicted (mean)\^ | 82.3  | 85.5  | 87.4  | 88.2  | 88.7  |
| FEV₁ % predicted (mean)\^ | 71.2  | 74.9  | 76.2  | 77.1  | 77.4  |
| FEV₁/FVC ratio (mean)\^  | 73.7  | 75.2  | 74.6  | 74.5  | 74.3  |

### Respiratory Microbiology

| P. aeruginosa (PA) (%)\^ | 58.7  | 55.1  | 50.9  | 47.5  | 46.4  |
| Multidrug-resistant PA (%)\^ | 4.2   | 8.3   | 8.4   | 9.2   | 8.2   |
| B. cepacia complex (%)     | 3.1   | 2.9   | 2.6   | 2.5   | 2.7   |
| S. aureus (SA) (%)\^       | 52.9  | 64.5  | 68.0  | 70.6  | 71.1  |
| Methicillin-sensitive S. aureus (MSSA) (%)            | 47.5  | 51.5  | 50.8  | 54.2  | 55.0  |
| Methicillin-resistant S. aureus (MRSA) (%)            | 7.3   | 19.0  | 26.0  | 26.0  | 26.0  |
| S. maltophilia (%)         | 8.5   | 12.8  | 14.0  | 13.7  | 13.1  |
| Mycobacterial species (%)\^ | -     | -     | 10.8  | 11.9  | 12.7  |

Table continues on the next page
### Health Care Utilization and Pulmonary Exacerbations (PEX)<sup>g</sup>

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Outpatient visits to CF centers reported per year (mean)</strong></td>
<td>5.5</td>
<td>4.2</td>
<td>4.7</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>Treated with IV antibiotics for a pulmonary exacerbation (%)</strong></td>
<td>-</td>
<td>35.4</td>
<td>34.9</td>
<td>34.6</td>
<td>33.8</td>
</tr>
<tr>
<td><strong>Number of pulmonary exacerbations per year (mean)</strong>*</td>
<td>-</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Number of days of treatment for all PEX per year (mean)</strong>&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>30.6</td>
<td>30.2</td>
<td>31.0</td>
<td>28.9</td>
</tr>
<tr>
<td><strong>Number of days of home IV treatment for all PEX per year (mean)</strong>&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>12.8</td>
<td>11.2</td>
<td>10.7</td>
<td>8.8</td>
</tr>
<tr>
<td><strong>Number of days of hospitalization for all PEX per year (mean)</strong>&lt;sup&gt;h&lt;/sup&gt;</td>
<td>-</td>
<td>17.8</td>
<td>19.0</td>
<td>20.2</td>
<td>20.1</td>
</tr>
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</table>

### Pulmonary Therapies<sup>i</sup>

<table>
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</thead>
<tbody>
<tr>
<td><strong>Dornase alfa (≥ 6 years) (%)</strong></td>
<td>60.2</td>
<td>71.2</td>
<td>82.7</td>
<td>87.0</td>
<td>87.5</td>
</tr>
<tr>
<td><strong>Inhaled tobramycin (PA+ and ≥ 6 years) (%)</strong>&lt;sup&gt;j&lt;/sup&gt;</td>
<td>66.8</td>
<td>63.9</td>
<td>66.2</td>
<td>69.3</td>
<td>69.4</td>
</tr>
<tr>
<td><strong>Inhaled aztreonam (PA+ and ≥ 6 years) (%)</strong></td>
<td>-</td>
<td>-</td>
<td>35.9</td>
<td>42.7</td>
<td>43.2</td>
</tr>
<tr>
<td><strong>Azithromycin (PA+ and ≥ 6 years) (%)</strong>&lt;sup&gt;k&lt;/sup&gt;</td>
<td>-</td>
<td>58.3</td>
<td>70.8</td>
<td>67.2</td>
<td>65.5</td>
</tr>
<tr>
<td><strong>Hypertonic saline (≥ 6 years) (%)</strong></td>
<td>-</td>
<td>24.2</td>
<td>55.7</td>
<td>68.7</td>
<td>70.7</td>
</tr>
<tr>
<td><strong>Ivacaftor (≥ 6 years with G551D mutation) (%)</strong></td>
<td>-</td>
<td>-</td>
<td>11.0</td>
<td>90.0</td>
<td>90.7</td>
</tr>
<tr>
<td><strong>Ivacaftor/Lumacaftor (≥ 12 years and F508del Homozygous) (%)</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>44.4</td>
<td>60.1</td>
</tr>
<tr>
<td><strong>Oxygen (%)</strong></td>
<td>-</td>
<td>9.9</td>
<td>11.0</td>
<td>11.1</td>
<td>10.4</td>
</tr>
<tr>
<td><strong>Non-invasive ventilation (%)</strong></td>
<td>-</td>
<td>1.8</td>
<td>2.3</td>
<td>2.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

### Transplants

<table>
<thead>
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</thead>
<tbody>
<tr>
<td><strong>Lung (all procedures) (n)</strong></td>
<td>152</td>
<td>200</td>
<td>225</td>
<td>215</td>
<td>265</td>
</tr>
<tr>
<td><strong>Liver (n)</strong></td>
<td>20</td>
<td>15</td>
<td>13</td>
<td>15</td>
<td>18</td>
</tr>
<tr>
<td><strong>Kidney (n)</strong></td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

### Lost to Follow Up<sup>m</sup>

<table>
<thead>
<tr>
<th>Lost to follow up (per 100 patients) (%)</th>
<th>2001</th>
<th>2006</th>
<th>2011</th>
<th>2015</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow up</td>
<td>1.8</td>
<td>4.4</td>
<td>3.4</td>
<td>2.5</td>
<td>2.6</td>
</tr>
</tbody>
</table>

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<sup>A</sup> We anticipate that additional 2016 diagnoses will be entered into the Registry in 2017.

<sup>B</sup> Pulmonary function data throughout this report reflect the use of Global Lung Initiative (GLI) equations<sup>j</sup> for both children and adults.

<sup>C</sup> Includes PA and multidrug-resistant PA, found in any culture during the year.

<sup>D</sup> Defined as resistant to all antibiotics tested in two or more classes.

<sup>E</sup> 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.

<sup>F</sup> Percentage of people with CF with one or more mycobacterial species isolated out of those who had a mycobacterial culture during the year. This includes *M. tuberculosis* as well as nontuberculous mycobacteria (NTM) species.

<sup>G</sup> Defined as a period of treatment with IV antibiotics in the hospital and/or at home.

<sup>H</sup> Among those with one or more pulmonary exacerbations in the year.

<sup>I</sup> Percent of people with CF on therapy at any clinical visit in the year. All individuals noted as intolerant or having an allergy to a specific therapy were excluded.

<sup>J</sup> Includes TOBI<sup>R</sup>, TOBI<sup>™</sup> Podhaler<sup>™</sup> and Bethkis<sup>™</sup> in 2015 and 2016. In prior years, only TOBI<sup>R</sup> was available.

<sup>K</sup> Individuals were considered eligible if they met the selection criteria used in the U.S. azithromycin trial.<sup>2</sup>

<sup>L</sup> Includes continuous, nocturnal or with exertion.

<sup>M</sup> Defined as individuals seen in the previous reporting year (2015) but not the current reporting year (2016).
DEMOGRAPHICS

The Registry contains data on people with CF from 1986 to 2016. 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 2016, there were 29,497 individuals with CF in the Registry. The number of adults with CF continues to increase, while the number of children remains relatively stable. In 2016, adults were 52.7 percent of the CF population, compared with 29.2 percent in 1986.

Currently, 8.5 percent of the individuals in the Registry have identified themselves as Hispanic. There has been a steady increase over the past 15 years, reflecting national population trends. Hispanics with CF tend to be younger than the overall CF population, with a median age of 12.9 years.
The median age of people with CF currently in the Registry is 19.0 years. The range is from birth to 86.7 years. Despite gains in survival, the age distribution remains markedly skewed toward younger ages.

Throughout this report, a number of age distribution charts are used to display particular characteristics of individuals in the Registry. Each of these charts includes the gray bars seen in the chart above to display the total number of individuals in the Registry in 2016.
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, are in committed relationships, and having children of their own. About two-thirds of adults with CF are either studying or working.
Over the last ten years, there has been almost a doubling of the number of people who are married or living together and the number with a college degree.

The number of pregnancies among women with CF has increased steadily since the 1990s. Registry data show that 270 women with CF were pregnant in 2016. 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.4
Health Insurance Information

Access to insurance coverage for specialized care and treatments is a challenge for some individuals with CF. Across all age groups, about half of the individuals in the Registry receive at least some component of their health insurance through federal or state-funded programs. Registry data show that in 2016, a majority of people with CF who were age 18 to 25 were covered under their parents’ health insurance plan.

Insurance Coverage in 2016

<table>
<thead>
<tr>
<th></th>
<th>Under 18 Years</th>
<th>18 to 25 Years</th>
<th>26 Years and Older</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of individuals (n)</td>
<td>13,741</td>
<td>5,742</td>
<td>9,412</td>
<td>28,895</td>
</tr>
<tr>
<td>Health insurance policy (e.g. private insurance) (%)</td>
<td>52.6</td>
<td>64.9</td>
<td>66.2</td>
<td>59.5</td>
</tr>
<tr>
<td>Medicare/Indian Health Services (%)</td>
<td>0.7</td>
<td>5.7</td>
<td>26.1</td>
<td>9.9</td>
</tr>
<tr>
<td>Medicaid/state programs (%)</td>
<td>54.8</td>
<td>43.0</td>
<td>27.3</td>
<td>43.5</td>
</tr>
<tr>
<td>TriCare or other military health plan (%)</td>
<td>3.0</td>
<td>2.6</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Other (%)</td>
<td>1.0</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>No health insurance (%)</td>
<td>0.4</td>
<td>1.1</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*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 2016

<table>
<thead>
<tr>
<th></th>
<th>37.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals who participated in a patient assistance program (%)</td>
<td></td>
</tr>
<tr>
<td>Individuals 18 to 25 years covered under parents’ insurance (%)</td>
<td>55.1</td>
</tr>
</tbody>
</table>

*Patient assistance program” refers to any program that provides free medication or copay assistance.

A large proportion of children with CF use Medicaid or state programs, including 56.0 percent of children under age 10. Though the overall prevalence of Medicare use is low, among adults age 30, 20.0 percent report Medicare coverage. This increases to 40.0 percent among adults in their early 60’s. Individuals under age 65 who receive Medicare have met the federal criteria for disability.
DIAGNOSIS

Diagnostic Characteristics of 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 2016, 62.4 percent of total new diagnoses and 86.0 percent of diagnoses among those less than 6 months old 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.\(^5\) 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.

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 2016 is the result of a yearly issue that infants born late in the year (i.e. late 2015) 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 2016 diagnosis year.

With the widespread use of newborn screening for CF, it was necessary to develop terminology for individuals with a positive NBS who have inconclusive sweat test results and/or less than two CF-causing genetic mutations. In the United States, this is referred to as CFTR-related metabolic syndrome\(^6\) (CRMS); other countries use the term CF screen positive, inconclusive diagnosis (CFSPID). Recently released diagnosis guidelines harmonized the criteria for CRMS/CFSPID.\(^7\) CRMS was added to the Registry as a diagnostic option in 2010. In 2016, data were entered for 688 individuals diagnosed with CRMS, 86 of whom were given this diagnosis during 2016.
Entry of a diagnosis of CF versus CRMS into the Registry is a clinical decision; there is no requirement 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 41.0 percent of infants (n=126) who met the published diagnostic criteria for CRMS were entered into the Registry with a diagnosis of CF. Analyses involving this cohort of patients must account for this apparent misclassification.

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

In 2016, 619 newborn infants were diagnosed with CF. Of those with a known gestational age at birth, 88.7 percent were born full-term, comparable with the figure for the general U.S. population. The mean birthweight for full-term infants with CF is also about the same as for the U.S. population, suggesting that babies born with CF do not initially show nutritional deficiencies. The graph does not include the 122 infants who were born and diagnosed with CF in 2016, who did not have a gestational age recorded in the Registry (19.7 percent).

"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 11.3 percent of infants diagnosed in 2016 under age one with meconium ileus (or other intestinal obstruction), 24.0 percent had bowel perforation. Those diagnosed after age one often present with acute or persistent respiratory abnormalities.

<table>
<thead>
<tr>
<th>Symptoms Reported at CF Diagnosis</th>
<th>All Patients (%)</th>
<th>Diagnosed in 2016 (%)</th>
<th>Diagnosed in 2016 Age &lt; 1 (%)</th>
<th>Diagnosed in 2016 Age ≥ 1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Individuals (n)</td>
<td>29,497</td>
<td>892</td>
<td>661</td>
<td>231</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA Analysis</td>
<td>11.3</td>
<td>21.2</td>
<td>20.1</td>
<td>24.2</td>
</tr>
<tr>
<td>Family history</td>
<td>14.8</td>
<td>11.0</td>
<td>10.4</td>
<td>12.6</td>
</tr>
<tr>
<td>Newborn (neonatal) screening</td>
<td>23.6</td>
<td>62.4</td>
<td>83.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Prenatal Screening (CVS, Amniocentesis)</td>
<td>2.3</td>
<td>3.1</td>
<td>4.2</td>
<td>N/A</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meconium ileus/other intestinal obstruction</td>
<td>17.6</td>
<td>8.6</td>
<td>11.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Acute or persistent respiratory abnormalities</td>
<td>37.3</td>
<td>16.4</td>
<td>2.7</td>
<td>55.4</td>
</tr>
<tr>
<td>CBAVD or infertility/GU abnormalities</td>
<td>0.5</td>
<td>2.1</td>
<td>0.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Digital clubbing</td>
<td>0.5</td>
<td>1.7</td>
<td>0.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Edema</td>
<td>0.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Electrolyte imbalance</td>
<td>3.1</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Failure to thrive/malnutrition</td>
<td>29.1</td>
<td>6.6</td>
<td>6.4</td>
<td>7.4</td>
</tr>
<tr>
<td>Liver problems</td>
<td>1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Nasal polyps/sinus disease</td>
<td>3.6</td>
<td>3.4</td>
<td>0.0</td>
<td>13.0</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>2.8</td>
<td>0.6</td>
<td>0.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Steatorrhea/abnormal stools/malabsorption</td>
<td>22.4</td>
<td>4.5</td>
<td>4.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Other</td>
<td>4.6</td>
<td>6.2</td>
<td>2.4</td>
<td>16.9</td>
</tr>
</tbody>
</table>

Data are not mutually exclusive. We anticipate that additional 2016 diagnoses will be entered into the Registry in 2017.

A  Chorionic villus sampling  
B  Congenital bilateral absence of the vas deferens  
C  Genitourinary abnormalities
Among all individuals in the Registry in 2016, 66.9 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. In 2016, 88.5 percent of individuals in the Registry had a sweat chloride test result recorded. 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.
Median sweat chloride test results have remained consistent over time 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” mutations are being entered into the Registry.

**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 become a key component of the diagnostic work-up. In addition, with the introduction of CFTR modulators, genotyping all people with CF is becoming more important for research and clinical care. In 2016, 97.7 percent of individuals (n=28,804) in the Registry had been genotyped.
CFTR GENE MUTATIONS

To date, more than 1,800 mutations have been found in the CFTR gene. 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. 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.

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

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 U.S. CF population.

### Prevalence of the 25 Most Common CFTR Mutations in People with CF Seen in 2016

<table>
<thead>
<tr>
<th>CFTR Mutation</th>
<th>Mutation Class</th>
<th>Number of Individuals</th>
<th>Percent of All People with CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>2</td>
<td>24,901</td>
<td>86.4</td>
</tr>
<tr>
<td>G542X</td>
<td>1</td>
<td>1,342</td>
<td>4.7</td>
</tr>
<tr>
<td>G551D</td>
<td>3</td>
<td>1,280</td>
<td>4.4</td>
</tr>
<tr>
<td>R117H</td>
<td>4</td>
<td>865</td>
<td>3.0</td>
</tr>
<tr>
<td>N1303K</td>
<td>2</td>
<td>703</td>
<td>2.4</td>
</tr>
<tr>
<td>W1282X</td>
<td>1</td>
<td>658</td>
<td>2.3</td>
</tr>
<tr>
<td>R553X</td>
<td>1</td>
<td>527</td>
<td>1.8</td>
</tr>
<tr>
<td>1717-1G-&gt;A</td>
<td>1</td>
<td>456</td>
<td>1.6</td>
</tr>
<tr>
<td>3849+10kbC-&gt;T</td>
<td>5</td>
<td>435</td>
<td>1.5</td>
</tr>
<tr>
<td>621+1G-&gt;T</td>
<td>1</td>
<td>431</td>
<td>1.5</td>
</tr>
<tr>
<td>2789+5G-&gt;A</td>
<td>5</td>
<td>361</td>
<td>1.3</td>
</tr>
<tr>
<td>3120+1G-&gt;A</td>
<td>1</td>
<td>267</td>
<td>0.9</td>
</tr>
<tr>
<td>D1152H</td>
<td>4</td>
<td>248</td>
<td>0.9</td>
</tr>
<tr>
<td>I507del</td>
<td>2</td>
<td>234</td>
<td>0.8</td>
</tr>
<tr>
<td>ST</td>
<td>5</td>
<td>224</td>
<td>0.8</td>
</tr>
<tr>
<td>R1162X</td>
<td>1</td>
<td>220</td>
<td>0.8</td>
</tr>
<tr>
<td>3659delC</td>
<td>1</td>
<td>203</td>
<td>0.7</td>
</tr>
<tr>
<td>G85E</td>
<td>2</td>
<td>186</td>
<td>0.6</td>
</tr>
<tr>
<td>1898+1G-&gt;A</td>
<td>1</td>
<td>185</td>
<td>0.6</td>
</tr>
<tr>
<td>2184insA</td>
<td>1</td>
<td>174</td>
<td>0.6</td>
</tr>
<tr>
<td>R347P</td>
<td>4</td>
<td>173</td>
<td>0.6</td>
</tr>
<tr>
<td>A455E</td>
<td>5</td>
<td>162</td>
<td>0.6</td>
</tr>
<tr>
<td>R560T</td>
<td>2</td>
<td>160</td>
<td>0.6</td>
</tr>
<tr>
<td>R334W</td>
<td>4</td>
<td>160</td>
<td>0.6</td>
</tr>
<tr>
<td>L206W</td>
<td>4</td>
<td>148</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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

### F508del Mutation Prevalence

<table>
<thead>
<tr>
<th>F508del Mutation</th>
<th>Percent of All People with CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous F508del</td>
<td>45.8</td>
</tr>
<tr>
<td>Heterozygous F508del</td>
<td>40.7</td>
</tr>
<tr>
<td>Neither F508del or Unknown</td>
<td>13.5</td>
</tr>
</tbody>
</table>
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 2016. This may be due to the inclusion of R117H in newborn screening algorithms. Of note, 102 (11.8 percent) of the 865 patients with an R117H mutation 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.\textsuperscript{16,17} Unfortunately, the Registry has incomplete information on the poly-T tract status for the majority of individuals (66.0 percent) who are reported as having a diagnosis of CF and an R117H mutation. Of the 285 individuals with poly-T tract status recorded in the Registry, 108 (38.0 percent) are classified as having 5T.

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.\textsuperscript{14,15} The majority of patients in the Registry are in the mutation class I-III grouping. More information about how alleles are grouped into classes is provided in the Appendix (page 78).
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.

Individuals in the class I-III group are younger and more likely to be prescribed pancreatic enzyme replacement therapy (PERT) than individuals in the class IV-V group (97.0 percent of individuals in the class I-III group and 35.6 percent in the class IV-V group are taking PERT).
In relation to disease severity, higher sweat test values are observed among individuals in classes I-III than in classes IV-V.

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>150</th>
<th>Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation Class I-III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>102.0</td>
<td>77.0</td>
<td>127.0</td>
<td></td>
</tr>
<tr>
<td>N=17,562</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation Class IV-V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70.0</td>
<td>25.0</td>
<td>113.0</td>
<td></td>
</tr>
<tr>
<td>N=2,633</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotyped But Not Identified in Mutation Classes I-III or IV-V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.0</td>
<td>36.0</td>
<td>122.0</td>
<td></td>
</tr>
<tr>
<td>N=4,807</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Individuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>99.0</td>
<td>50.0</td>
<td>125.0</td>
<td></td>
</tr>
<tr>
<td>N=25,002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

These charts use the most recent sweat test value reported to the Registry. For some individuals, this value may reflect sweat chloride values after initiation of CFTR modulator therapy.
GUIDELINES: CARE, SCREENING AND PREVENTION

The CF Foundation has sponsored the development of clinical practice guidelines to promote high quality physical and mental health care for individuals with CF during infancy, childhood, and adulthood.18-20 In accordance with guidelines for people with CF over age six,20 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.21 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.22

There is significant variation by CF care center in several key screening measures, including dual-energy X-ray absorptiometry (DXA) scans 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 annual recommended four office visits, four respiratory cultures and two PFTs20,21 has doubled. The percentage of adults who receive care that meets guidelines criteria remains lower than that observed in children. However, the percent of those meeting guidelines continues to rise. Currently, 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. While we strive for all patients to meet guideline recommendations, we acknowledge that many factors outside of the control of CF care centers may impact metrics.
The guidelines on infection prevention and control recommend that individuals with CF have quarterly respiratory cultures.\textsuperscript{21-23} Nearly 98 percent of individuals received at least one culture in 2016, and 55.3 percent of individuals had four or more respiratory cultures. Those under age 18 were more likely to meet the recommendation for four cultures.

The multidisciplinary care team plays an important role in CF care.\textsuperscript{20} Over time, there has been an increase in the number of individuals with CF who receive at least an annual evaluation from a respiratory/physical therapist, dietitian/nutritionist, and social worker. In 2016, 72.1 percent of individuals were evaluated by all three specialists.
The CF Foundation recently supported the inclusion of mental health professionals as part of the CF care team. Information on screening for anxiety and depression is included in the Complications section (page 69).

The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices recommends influenza vaccination for all individuals with CF age six months and older.\textsuperscript{24} The influenza vaccination rate of people with CF who are six months and older is 74.6 percent of the total population and 89.5 percent of those with a known vaccination status (excluding 16.6 percent with unknown status).
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. 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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100 Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals 18 Years and Older</td>
<td></td>
<td></td>
<td>55.3</td>
<td>0.0</td>
<td>93.1</td>
</tr>
</tbody>
</table>

Includes any DXA scans performed during 2012–2016. 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. 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.

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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100 Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals with Fat-Soluble Vitamins Measured</td>
<td></td>
<td></td>
<td>88.1</td>
<td>30.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Individuals with Liver Enzymes Measured</td>
<td></td>
<td></td>
<td>88.8</td>
<td>33.3</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Tobacco smoke and secondhand smoke exposure remain significant concerns, especially for infants and young adults. In 2016, 20.0 percent of individuals with CF reported monthly or more frequent exposure to tobacco smoke, either secondhand or as a smoker. Cigarette smoking prevalence is lower in the CF population than in the general U.S. population; only 2.1 percent of adults with CF are smokers, compared with 17.5 percent in the general population in 2015. Smoke exposure was unknown for 35.2 percent of individuals with CF, who were excluded from the analyses.
Infant Care Guidelines

The CF Foundation recommends that evaluation and treatment of infants detected by newborn screening should be done at an CF Foundation-accredited care center. Infants with CF should have an initial visit at an accredited care center within 24 - 72 hours. 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. Encouragingly, 88.6 percent of infants diagnosed have their first clinic encounter, genotyping, or sweat test within 30 days of birth.

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. 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.

The chart shows data for children born in 2015 because a full year of data is available for these individuals. Median time to first sweat test for these individuals is 27 days. Of individuals with CF born in 2015, 63 infants (12.5 percent) who were detected by NBS did not have a sweat chloride test reported to the Registry by the end of 2016 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. 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.
Respiratory cultures are being collected at the majority of clinic visits for infants with CF. Infant care guidelines recommend that cultures be performed at least quarterly during the first two years of life.5

The chart shows data for children born in 2015 because a full year of data is available for these individuals. The median number of visits in the first year of life is nine.

The chart shows data for children born in 2015 because a full year of data is available for these individuals. The median number of cultures in the first year of life is six.
Fecal elastase testing, which provides an objective measure of pancreatic function, is recommended in the infant care guidelines. 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) across the CF care center network, 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.

### Infant Care Guidelines, by Center

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal Elastase Value Reported</td>
<td></td>
<td></td>
<td></td>
<td>62.5</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>for Individuals Less Than 24 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salt Supplements</td>
<td></td>
<td></td>
<td></td>
<td>100.0</td>
<td>40.0</td>
<td>100.0</td>
</tr>
<tr>
<td>in Individuals Less Than 36 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSV Prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td>10.8</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>in Individuals Less Than 36 Months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Testing and Therapies for Individuals Under 24 Months of Age, 2009-2016

- **Salt Supplementation Reported**
- **Fecal Elastase Value Reported**
- **RSV Prophylaxis Reported**
MICROBIOLOGY

Bronchiectasis with chronic pulmonary infections represents a serious problem for most individuals with CF. This section provides information on trends in CF airway 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.\(^31\)

The prevalence of *Pseudomonas aeruginosa* (*P. aeruginosa* or PA) continues to decrease. This may relate in part to widespread implementation of therapy to eradicate initial acquisition.\(^23,31\) Despite this, the prevalence of infection with multidrug-resistant *P. aeruginosa* (MDR-PA) has remained constant.

Some of the increase in *Staphylococcus aureus* (*S. aureus*) may be due to improved microbiologic practices for detection and reporting of Gram-positive organisms. From 2000 to 2010, there was a significant increase in the numbers of individuals with CF with a positive culture for methicillin-resistant *S. aureus* (MRSA). Since 2010, prevalence appears to have plateaued. The stabilization of prevalence is potentially due to increased awareness and infection prevention and control strategies.

The graph shows the proportion of individuals in various age groups who cultured positive for the bacterial species indicated during 2016.
A note about the reporting of *Burkholderia* species: in 2016, 721 people with CF were reported in the Registry as having had a culture positive for *Burkholderia cepacia* (*B. cepacia*) complex. A preliminary comparison of the *Burkholderia* species entered in the Registry as compared to those reported by the CF Foundation *B. cepacia* Research Laboratory and Repository at the University of Michigan shows discordant results. Further investigation is needed on the reporting practices for these variables before figures on *B. cepacia* complex sub-species can be included in the report.

The table below displays prevalence of the key respiratory microorganisms in 2016 along with median age at first positive culture for the species.
Pseudomonas aeruginosa

The percentage of individuals with a positive culture for *P. aeruginosa* has continued to decline over time, with the largest decrease observed among individuals younger than 18 years (49.8 percent had a positive culture in 1996 compared with 29.1 percent in 2016). Many individuals with CF now transition to adult care without *P. aeruginosa* in their respiratory tract.

Rates of MDR-PA infection are greatest in older adolescents and adults with CF. These findings likely reflect cumulative exposure to antibiotics. The clinical significance of this drug resistance is unclear. Among the individuals with CF who had at least one bacterial culture in 2016, 8.0 were reported to have MDR-PA. 17.7 percent of individuals with a *P. aeruginosa* infection were reported to have MDR-PA.

A classification system known as the Leeds criteria is used to categorize individuals on the basis of *P. aeruginosa* infection status. The Leeds criteria 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 2016, 19.7 percent of individuals in the Registry had never had a positive culture for *P. aeruginosa*. Another 30.0 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 46.9 percent of individuals had at least one positive culture, of which 29.1 percent were categorized as having chronic infection, and 17.8 percent as having intermittent infection.
**Staphylococcus aureus**

*S. aureus* is currently the most common microorganism reported among individuals with CF. Overall, more than half of individuals had at least one culture positive for methicillin-sensitive *S. aureus* (MSSA) in 2016. This chart shows that the highest prevalence of MRSA occurs in individuals between the ages of 10 and 30, while MSSA peaks among those younger than 10.
Nontuberculous Mycobacteria

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

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

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 (78.1 percent) of the individuals who produced a sputum culture for a bacterial culture also had a mycobacterial culture performed during the year.
Of the 14,501 individuals who had a mycobacterial culture performed in 2016, 1,846 (12.7 percent) had a mycobacterial species isolated one or more times. The relative proportion of *M. abscessus* isolated in 2016 is higher than reported over a decade ago in a CF Foundation-supported multicenter prevalence study.\textsuperscript{15}

### Mycobacterial Species Isolated in 2016

<table>
<thead>
<tr>
<th>Mycobacterial Species</th>
<th>Number of Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. avium</em> Complex (MAC)</td>
<td>922</td>
</tr>
<tr>
<td><em>M. abscessus</em>/<em>M. chelonae</em></td>
<td>713</td>
</tr>
<tr>
<td><em>M. gordonae</em></td>
<td>70</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>32</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>13</td>
</tr>
<tr>
<td><em>M. tuberculosis</em></td>
<td>8</td>
</tr>
</tbody>
</table>

Data are not mutually exclusive. Some individuals had more than one species isolated in 2016.

Because individuals may not have a mycobacterial culture each year, data from 2012 to 2016 were combined to allow a more robust analysis of mycobacterial species prevalence among people with CF. Among the 22,502 individuals who were cultured in this time period, 4,505 (20.0 percent) had one or more mycobacterial species isolated.
NUTRITION

Nutritional outcomes are a key measure of health in people with CF. This section is divided into three age groups to report nutrition metrics: infants younger than 2 years, children 2 to 19 years, and adults 20 years and older. Overall improvements in nutritional metrics are observed for all ages. Recent CF Foundation evidence-informed guidelines recommend enteral tube feeding as a means to improve age-dependent anthropometrics and nutrition in individuals with CF who are unable to consume adequate nutrition to meet nutritional goals.36

CF Foundation weight-for-length and BMI percentile goals for children are based on CDC growth curves. However, in accordance with the American Academy of Pediatric recommendations, World Health Organization (WHO) growth curves are more frequently utilized in patients less than 24 months of age37 and are reported as such below.

![Median WHO Nutritional Outcome Percentiles for Infants Under 24 Months, 1992–2016](image-url)
The charts below show the population-level variation in infants for WHO weight-for-length, weight percentile, and height percentiles in three groups: all individuals, those in classes I-III (typically considered more severe mutations), 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.

### All Individuals, WHO Nutritional Outcomes for Individuals Under 24 Months

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight-for-Length</td>
<td></td>
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<tr>
<td>N=1,784</td>
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<tr>
<td></td>
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<td></td>
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<td>64.4</td>
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<td>96.7</td>
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<td>31.4</td>
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<td>86.7</td>
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### Mutation Class I-III, WHO Nutritional Outcomes for Individuals Under 24 Months

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<td>29.2</td>
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<td>84.9</td>
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### Mutation Class IV-V, WHO Nutritional Outcomes for Individuals Under 24 Months

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<th>100</th>
<th>Median</th>
<th>5th Percentile</th>
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</thead>
<tbody>
<tr>
<td>Weight-for-Length</td>
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<td>53.7</td>
<td>7.4</td>
<td>92.9</td>
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<td>Length Percentile</td>
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<tr>
<td>N=184</td>
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<td></td>
<td>42.6</td>
<td>3.5</td>
<td>87.0</td>
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</table>
The goal established by the CF Foundation nutrition guidelines for children age 2 to 19 years is a BMI percentile at or above 50 using CDC growth curves. The median BMI percentile is above the 50th percentile for this age group, regardless of mutation class. Children in the IV-V group have higher BMI percentiles than those in the I-III group. Children with a BMI at or above the 50th percentile and with significant stunting of linear growth may also benefit from advanced nutritional management.

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

<table>
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<tr>
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<th>50</th>
<th>100 Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
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<tr>
<td><strong>BMI Percentile</strong></td>
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<tr>
<td><strong>Weight Percentile</strong></td>
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<tr>
<td><strong>Height Percentile</strong></td>
<td>N=15,056</td>
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</table>

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

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<th>0</th>
<th>50</th>
<th>100 Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
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</thead>
<tbody>
<tr>
<td><strong>BMI Percentile</strong></td>
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<tr>
<td><strong>Weight Percentile</strong></td>
<td>N=10,948</td>
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<tr>
<td><strong>Height Percentile</strong></td>
<td>N=10,058</td>
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</table>

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

<table>
<thead>
<tr>
<th></th>
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<th>100 Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
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<tr>
<td><strong>BMI Percentile</strong></td>
<td>N=1,243</td>
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<tr>
<td><strong>Weight Percentile</strong></td>
<td>N=1,341</td>
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<tr>
<td><strong>Height Percentile</strong></td>
<td>N=1,340</td>
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</table>
Successive birth cohorts show improved weight and height percentiles, most notably in the youngest cohorts. Multiple factors may contribute to improvements in the youngest cohorts, including implementation of NBS with early intervention.\textsuperscript{38,39}
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. Among individuals in the 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 mutation class, with significant overlap between individuals in the I-III group and the IV-V group. Of note, 31.1 percent of those in the IV-V group are overweight (BMI of 25 to 29.9), and 18.3 are obese (BMI of 30+).

<table>
<thead>
<tr>
<th>Mutation Class Group</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
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<tbody>
<tr>
<td>All Individuals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.5</td>
<td>17.8</td>
<td>31.1</td>
</tr>
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<td>N=12,292</td>
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</tr>
<tr>
<td>Mutation Class I-III</td>
<td></td>
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<td></td>
<td>22.1</td>
<td>17.7</td>
<td>28.9</td>
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<tr>
<td>Mutation Class IV-V</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24.9</td>
<td>19.0</td>
<td>35.8</td>
</tr>
<tr>
<td>N=1,586</td>
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</table>

Significant progress in nutritional outcomes continues for all people with CF. Aging of the CF population and a greater number of late diagnoses with genotypes associated with milder disease may contribute to improvements in adult nutritional outcomes shown below.
Infant Feeding

The majority of infants with CF receive formula feeding as the primary form of feeding or as a supplement to breastfeeding. 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.\(^5\)

*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\textsubscript{1} percent predicted and calculated using the GLI reference equations.\textsuperscript{1}

Successive birth cohorts show improved pulmonary function across all ages. The majority of those age 18 — a typical age of transition to adult care — now have an FEV\textsubscript{1} percent predicted greater than or equal to 70.

FEV\textsubscript{1} percent predicted is steadily improving and currently is above 90 percent predicted into early adolescence.

The proportion of people with CF age 18 who are in the normal/mild category (FEV\textsubscript{1} ≥70 percent predicted) has increased from 31.9 percent in 1986 to 73.9 percent in 2016. The proportion in the severe category (FEV\textsubscript{1} <40 percent predicted) has decreased from 30.2 percent in 1986 to 4.0 percent in 2016.
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.
Variation in Pulmonary Function by Mutation Class

A majority of people with CF are in the class I-III group of mutations (71.3 percent of those genotyped), and the clinical outcomes of this group drive national averages.

Median lung function is lower among individuals in the I-III group than in individuals in the IV-V group (7.2 percent lower in children and 9.1 percent lower in adults). However, there is considerable variation among individuals within each mutation class group and substantial overlap between the two groups.

<p>| FEV₁ Percent Predicted for Individuals 6 to 17 Years, by Mutation Class Group |</p>
<table>
<thead>
<tr>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>Median</th>
<th>5th Percentile</th>
<th>95th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Individuals</td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>Mutation Class I-III</td>
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<tr>
<td>Mutation Class IV-V</td>
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</table>

<p>| FEV₁ Percent Predicted for Individuals 18 Years and Older, by Mutation Class Group |</p>
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<tr>
<th>0</th>
<th>25</th>
<th>50</th>
<th>75</th>
<th>100</th>
<th>125</th>
<th>Median</th>
<th>5th Percentile</th>
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</thead>
<tbody>
<tr>
<td>All Individuals</td>
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<td></td>
<td></td>
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</table>
PULMONARY AND NUTRITIONAL OUTCOMES

Pulmonary and nutritional outcomes are two key measures of CF health. These metrics are the primary focus of quality improvement work within the CF care center network. The data show that for all people with CF, pulmonary function and nutrition status are related, and improvements in one metric are associated with improvements in the other.

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 value greater than or equal to 22 for women and 23 for men.

![FEV$_1$ Percent Predicted vs. BMI Percentile for Children 6 to 19 Years in 2016](image)

![FEV$_1$ Percent Predicted vs. BMI Value for Adults 20 to 40 Years in 2016](image)
The figures below on the left show median BMI percentile and FEV₁ percent predicted values for each center in 2016. The figures on the right show how median values for all centers have improved over the last 30 years.
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 a minimal 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.

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.
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. 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.

<table>
<thead>
<tr>
<th>Duration of Pulmonary Exacerbation Treatment in Days, by Center</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>---------------------------------</td>
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<tr>
<td>Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals Less than 18 Years</td>
</tr>
<tr>
<td>Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals Less than 18 Years</td>
</tr>
<tr>
<td>Median Total Duration of IV Antibiotic Treatment for a Pulmonary Exacerbation in Individuals 18 Years and Older</td>
</tr>
<tr>
<td>Median Duration of Hospital Stay for Treatment of a Pulmonary Exacerbation in Individuals 18 Years and Older</td>
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<table>
<thead>
<tr>
<th>Percentage of Total Pulmonary Exacerbation Treatment Duration in Hospital, by Center</th>
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<tr>
<td>0</td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Individuals Less Than 18 Years</td>
</tr>
<tr>
<td>Individuals 18 Years and Older</td>
</tr>
</tbody>
</table>
THERAPIES

Gastrointestinal (GI) Therapies

The CF Foundation infant clinical 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 value below 200μg/g of stool, and/or signs of malabsorption.5

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

![Pancreatic Enzyme Replacement Therapy (PERT) Prescription by Age in Years, 2016](chart)

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.26 The mean dose of lipase units/kg/meal for individuals 2 to 19 years is 1,908 and for individuals 20 years and older, the mean dose is 1,771.

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.5 Registry data show that the mean highest dose of lipase among children younger than 2 years is 1,562 total lipase units per kilogram per meal.

For infants with CF under age 2 years, the infant clinical care guidelines recommend assessment of pancreatic functional status by measurement of fecal elastase.1 Data on fecal elastase test results have been collected in the Registry since 2010, with an increased number of individuals undergoing fecal elastase testing. About 60 percent of infants were tested in 2016. Among individuals under age 2 years in 2016, 534 did not have a fecal elastase value reported, and 76 percent were on PERT. Almost all individuals with a known fecal elastase value of less than 200μg/g of stool were prescribed PERT. Approximately 30 percent of individuals with fecal elastase values greater than 200μg/g of stool were also prescribed PERT.
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 percent of individuals) than H₂ blockers (17 percent of individuals). H₂ blockers are used more frequently in younger individuals and their use tapers among older individuals. Use of PPIs increases with age until age 20 and then is prescribed to approximately 50% of individuals age 20 and older.

In 2016, 93.0 percent of individuals age 2 to 19 and 83.0 percent of individuals age 20 and older were prescribed CF-specific vitamins, including vitamins A, D, E, and K. Additionally, ursodeoxycholic acid is most commonly prescribed to adolescents and young adults with abnormal liver function tests or suspected CF liver disease.
Pulmonary Therapies

Chronic pulmonary therapies are a major component of the treatment regimen for individuals with CF. This section provides data on 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.42

Many of the CF therapies are used by between 60 to 80 percent of the eligible population. The use of most therapies has increased over time. In recent years, additional formulations of inhaled tobramycin have become available, and they are included in the chart below. Dornase alfa, which is recommended for all individuals with CF, is used by the vast majority of people and its use continues to rise. Use of chronic inhaled antibiotics seems to have plateaued. The availability of multiple pulmonary therapies for CF is beneficial; however, this also contributes to treatment complexity and overall burden on individuals with CF and their caregivers.

![Medication Prescription in Eligible Patients, 1996-2016](image-url)

*Tobramycin includes all available formulations of inhaled tobramycin. Dornase alfa was approved by the FDA in 1994.*
**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 then colistin. For all medications, peak use occurs during adolescence and young adulthood.

Dornase alfa and hypertonic saline are each prescribed for the majority of individuals with CF.Azithromycin is also widely used, with peak use occurring at slightly older ages than for use of dornase alfa and hypertonic saline.

A substantial proportion of individuals with CF are prescribed inhaled corticosteroids and, to a lesser degree, leukotriene modifiers. Oral corticosteroids are used infrequently.
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. The vast majority of those prescribed beta agonists are on short-acting formulations.

Multiple pulmonary therapies are available for individuals with CF. Inhaled medications are effective treatments for pulmonary disease, and they require time to prepare, administer, and clean equipment after treatment. All people with CF are eligible for dornase alfa and hypertonic saline prescriptions. Those with *P. aeruginosa* infection or colonization are typically prescribed inhaled antibiotics. Almost all individuals are prescribed at least one inhaled medication, and over half of those age 15 and older are prescribed two or more of these therapies.

<table>
<thead>
<tr>
<th>Inhaled Beta Agonists</th>
<th>Inhaled Anticholinergics</th>
</tr>
</thead>
</table>

Inhaled medication includes dornase alfa, hypertonic saline, and inhaled antibiotic. 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. CFTR modulators are discussed in a separate chapter (p. 57).

### Pulmonary Therapies Recommended for Chronic Use, by Center

<table>
<thead>
<tr>
<th>Therapy Description</th>
<th>0</th>
<th>50</th>
<th>100 Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dornase Alfa Prescription in Individuals 6 Years and Older</td>
<td></td>
<td></td>
<td>89.9</td>
<td>42.4</td>
<td>100.0</td>
</tr>
<tr>
<td>Any Inhaled Tobramycin Prescription in <em>P. aeruginosa</em> Positive Individuals 6 Years and Older</td>
<td></td>
<td></td>
<td>70.6</td>
<td>34.8</td>
<td>100.0</td>
</tr>
<tr>
<td>Azithromycin Prescription in Eligible <em>P. aeruginosa</em> Positive Individuals 6 Years and Older*</td>
<td></td>
<td></td>
<td>65.1</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Hypertonic Saline Prescription in Individuals 6 Years and Older</td>
<td></td>
<td></td>
<td>71.5</td>
<td>6.5</td>
<td>100.0</td>
</tr>
<tr>
<td>Ibuprofen Prescription in Individuals 6 to 17 Years with FEV1 Greater than 60 Percent Predicted</td>
<td></td>
<td></td>
<td>0.0</td>
<td>0.0</td>
<td>75.6</td>
</tr>
<tr>
<td>Inhaled Aztreonam Prescription in <em>P. aeruginosa</em> Positive Individuals 6 Years and Older</td>
<td></td>
<td></td>
<td>41.2</td>
<td>0.0</td>
<td>83.3</td>
</tr>
</tbody>
</table>

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

---

*Annual Data Report 2016  Cystic Fibrosis Foundation Patient Registry*
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, inhaled colistin, and ibuprofen for adults to improve lung function, reduce exacerbations, or improve quality of life. Inhaled beta agonists are used consistently across the CF Foundation 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. Ibuprofen use in adults is used very rarely, in less than two percent of adults.

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

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled Beta Agonist Prescription in Individuals 2 Years and Older</td>
<td></td>
<td></td>
<td></td>
<td>96.3</td>
<td>69.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Inhaled Anticholinergic Prescription in Individuals 2 Years and Older</td>
<td></td>
<td></td>
<td></td>
<td>5.7</td>
<td>0.0</td>
<td>36.8</td>
</tr>
<tr>
<td>Leukotriene Modifier Prescription in Individuals 2 Years and Older</td>
<td></td>
<td></td>
<td></td>
<td>17.9</td>
<td>0.0</td>
<td>66.7</td>
</tr>
<tr>
<td>Inhaled Colistin Prescription in Individuals 6 Years and Older with <em>P. aeruginosa</em></td>
<td></td>
<td></td>
<td></td>
<td>9.5</td>
<td>0.0</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Pulmonary Therapies Not Recommended for Chronic Use, by Center

<table>
<thead>
<tr>
<th>Medication Type</th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled Steroid Prescription in Individuals 6 Years and Older Without Asthma or ABPA</td>
<td></td>
<td></td>
<td></td>
<td>38.9</td>
<td>0.0</td>
<td>90.3</td>
</tr>
</tbody>
</table>
Medication Use in Young Children

The CF Foundation recently released the first set of guidelines focusing on the preschool timeframe from ages 2 to 5. 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 these patients on the basis of individual circumstances. The chart below shows the use of medications among children younger than age 6.

<table>
<thead>
<tr>
<th>Medication Use in Individuals Under 6 Years, 2016</th>
<th>Age &lt; 3 Years (%)</th>
<th>Age 3 to 5 Years (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Individuals (n)</td>
<td>1,948</td>
<td>2,273</td>
</tr>
<tr>
<td>Dornase alfa</td>
<td>41.5</td>
<td>70.7</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>23.7</td>
<td>43.1</td>
</tr>
<tr>
<td>Inhaled bronchodilators</td>
<td>80.4</td>
<td>92.8</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>16.5</td>
<td>30.0</td>
</tr>
<tr>
<td>Inhaled tobramycin</td>
<td>15.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>1.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Inhaled aztreonam</td>
<td>1.7</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Airway Clearance Techniques

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

The CF Foundation pulmonary guidelines recommend aerobic exercise as an adjunct therapy for airway clearance and for its additional benefits to overall health. Many individuals with CF report exercising in addition to their primary method of airway clearance, with 33.4 percent of children and 45.3 percent of adults identifying exercise as one of their methods of airway clearance.

Exercise as an Airway Clearance Technique by Age in Years, 2016
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 to other mutations and to younger patients. In 2015, ivacaftor in combination with lumacaftor was approved for individuals age 12 and older who are homozygous for the F508del mutation; in 2016, the age limit was reduced to age 6.

Ivacaftor

In 2016, among 2,287 eligible individuals in the Registry, 1,650 individuals (72.0 percent) were prescribed ivacaftor. For all individuals currently eligible, the percentage prescribed ivacaftor is highest among individuals age 6 and older with a G551D mutation, and is lowest among individuals with an R117H mutation. The prescription of ivacaftor among individuals with an R117H mutation is associated with age, with the highest reported rate among individuals age 18 and older. An additional 208 individuals were prescribed ivacaftor during one or more clinic visits in 2016, but 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 75.1 percent to 89.2 percent from 2012 to 2016.

### Timeline of CFTR Modulator FDA Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 31, 2012</td>
<td>Ivacaftor approved for those 6 years and older with the G551D mutation</td>
</tr>
<tr>
<td>December 29, 2014</td>
<td>Ivacaftor approved for those 6 years and older with the R117H mutation</td>
</tr>
<tr>
<td>March 18, 2015</td>
<td>Ivacaftor approved for those 2 to 5 years with a previously approved mutation</td>
</tr>
<tr>
<td>July 2, 2015</td>
<td>Ivacaftor and Lumacaftor approved for those 12 years and older with two copies of the F508del mutation</td>
</tr>
<tr>
<td>September 28, 2016</td>
<td>Ivacaftor and Lumacaftor approved for those 6 to 11 years with two copies of the F508del mutation</td>
</tr>
</tbody>
</table>

### Ivacaftor Use or Prescription in Individuals with a Gating Mutation, 2016

<table>
<thead>
<tr>
<th>Individuals 6 and Older with a G551D Gating Mutation</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 2012</td>
<td>1,099</td>
<td>980</td>
<td>89.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals 6 and Older with Another Gating Mutation (Not including G551D)</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2014</td>
<td>216</td>
<td>163</td>
<td>75.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals 2 to 5 Years with G551D or Another Gating Mutation</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2015</td>
<td>152</td>
<td>116</td>
<td>76.3</td>
<td></td>
</tr>
</tbody>
</table>

### Ivacaftor Use or Prescription in Individuals with a R117H Mutation, 2016

<table>
<thead>
<tr>
<th>Individuals 18 and Older with a R117H Mutation</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2014</td>
<td>404</td>
<td>208</td>
<td>51.5</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals 6 to 17 with a R117H Mutation</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 2014</td>
<td>268</td>
<td>123</td>
<td>45.9</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Individuals 2 to 5 Years with a R117H Mutation</th>
<th>Date Eligibility Added</th>
<th>Number Eligible</th>
<th>On Ivacaftor</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2015</td>
<td>120</td>
<td>42</td>
<td>35.0</td>
<td></td>
</tr>
</tbody>
</table>
There is substantial uniformity across centers with regard to prescription of ivacaftor for individuals with gating mutations, with the majority of centers reporting a prescription for all their eligible patients. There is considerable variability in reported prescription for individuals with a R117H mutation.

### Ivacaftor Prescription in Individuals with an Eligible Mutation, by Center

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100 Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Years and Older with a Currently Approved Gating Mutation</td>
<td></td>
<td></td>
<td>92.6</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>2 Years and Older with a R117H Mutation</td>
<td></td>
<td></td>
<td>50.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>2 to 18 Years with a Currently Approved Gating Mutation</td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>2 to 18 Years with a R117H Mutation</td>
<td></td>
<td></td>
<td>33.3</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>18 Years and Older with a Currently Approved Gating Mutation</td>
<td></td>
<td></td>
<td>100.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>18 Years and Older with a R117H Mutation</td>
<td></td>
<td></td>
<td>60.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Ivacaftor / Lumacaftor**

In 2016, ivacaftor/lumacaftor was prescribed for 5,569 individuals, or 52.5 percent of the eligible population of individuals age 6 and older who are homozygous for the F508del mutation (45.0 percent of those age 6 to 17 and 57.9 percent of those age 18 and older). There does not appear to be substantial variation in the proportion of eligible individuals receiving a prescription for ivacaftor/lumacaftor across age groups or lung function. It is important to note that ivacaftor/lumacaftor was not approved for those age 6 to 11 with two copies of the F508del mutation until September 28, 2016.
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.
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 or deficiency of the CFTR protein or a downstream effect of the disease or its treatment. 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 increased overall survival.

Cystic fibrosis-related diabetes (CFRD) remains an important and highly prevalent complication that greatly impacts quality of life and is associated with increased morbidity and mortality. As the population ages, a larger proportion of individuals are reporting complications typically seen in older adults, including bone and joint disease and sinus disease. Furthermore, along with the recent publication and implementation of mental health screening guidelines, an increase in the reporting of anxiety and depression has been observed.

<table>
<thead>
<tr>
<th>Complications of CF, 2016</th>
<th>Age &lt; 18 (%)</th>
<th>Age ≥ 18 (%)</th>
<th>All (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Individuals (n)</strong></td>
<td>13,944</td>
<td>15,553</td>
<td>29,497</td>
</tr>
<tr>
<td><strong>Percent with no complications</strong></td>
<td>21.6</td>
<td>3.6</td>
<td>12.1</td>
</tr>
<tr>
<td><strong>Percent with complications not reported</strong></td>
<td>0.9</td>
<td>2.0</td>
<td>1.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Cystic Fibrosis-Related Diabetes</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic fibrosis-related diabetes (CFRD)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Hepatobiliary</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gall stones</td>
</tr>
<tr>
<td>Gall stones, requiring surgery/procedure</td>
</tr>
<tr>
<td>Liver disease, cirrhosis</td>
</tr>
<tr>
<td>Liver disease, non-cirrhosis</td>
</tr>
<tr>
<td>Acute hepatitis</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>Liver disease, other</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Bone/Joints</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis/arthropathy</td>
</tr>
<tr>
<td>Bone fracture</td>
</tr>
<tr>
<td>Osteopenia</td>
</tr>
<tr>
<td>Osteoporosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pulmonary</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic bronchopulmonary aspergillosis (ABPA)</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Hemoptysis</td>
</tr>
<tr>
<td>Hemoptysis, massive</td>
</tr>
<tr>
<td>Pneumothorax requiring chest tube</td>
</tr>
</tbody>
</table>

Table continues on the next page
The table below highlights the prevalence of clinical manifestations of portal hypertension among individuals with cirrhosis.

<table>
<thead>
<tr>
<th>Complications of Cirrhosis, 2016 (n=799)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (n)</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Esophageal varices</td>
</tr>
<tr>
<td>Gastric varices</td>
</tr>
<tr>
<td>GI bleed related to varices</td>
</tr>
<tr>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Hypersplenism</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Ascites</td>
</tr>
</tbody>
</table>
CF Complications by Age, 2016

Reported complications differ in their distribution by age. Some are relatively stable over ages while others increase with age. The prevalence of bone disease and GERD is higher among older age groups. The prevalence of sinus disease, asthma, and depression are higher among older children and adolescents, and stable among adults of all ages. The prevalence of CFRD peaks at about age 45. ABPA, DIOS, and anxiety are less prevalent and appear consistent across all age groups. Liver disease is more prevalent in children.
CF Complications by Mutation Class

The table below displays complications by mutation class groups. For more information about mutation classes and groups, see page 88. Many complications do not differ between mutation classes. CFRD, liver disease, meconium ileus and DIOS are more prevalent among individuals in mutation class I-III, typically associated with more severe disease. In contrast, pancreatitis is more common among individuals in mutation class IV-V. It is interesting to note that the prevalence of anxiety and depression does not differ by mutation class.

<table>
<thead>
<tr>
<th>Complications of CF in 2016, by Mutation Class Group</th>
<th>Mutation Class I-III (%)</th>
<th>Mutation Class IV-V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Individuals (n)</td>
<td>20,569</td>
<td>3,054</td>
</tr>
<tr>
<td>Percent with no complications</td>
<td>10.1</td>
<td>19.3</td>
</tr>
<tr>
<td>Percent with complications not reported</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Cystic Fibrosis-Related Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cystic fibrosis-related diabetes (CFRD)</td>
<td>25.2</td>
<td>7.0</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gall stones</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Gall stones, requiring surgery/procedure</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Liver disease, cirrhosis</td>
<td>3.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver disease, non-cirrhosis</td>
<td>4.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Acute hepatitis</td>
<td>0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Liver disease, other</td>
<td>2.3</td>
<td>0.5</td>
</tr>
<tr>
<td>Bone/Joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthritis/arthropathy</td>
<td>3.4</td>
<td>3.2</td>
</tr>
<tr>
<td>Bone fracture</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>12.0</td>
<td>11.7</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>5.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic bronchopulmonary aspergilosis (ABPA)</td>
<td>5.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Asthma</td>
<td>32.1</td>
<td>28.9</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>3.5</td>
<td>2.9</td>
</tr>
<tr>
<td>Hemoptysis, massive</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Pneumothorax requiring chest tube</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>GI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal intestinal obstruction syndrome (DIOS)</td>
<td>2.8</td>
<td>1.0</td>
</tr>
<tr>
<td>Fibrosing colonopathy/colonic stricture</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease (GERD)</td>
<td>40.1</td>
<td>27.9</td>
</tr>
<tr>
<td>GI bleed requiring hospitalization (non-variceal)</td>
<td>&lt;0.1</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>History of intestinal or colon surgery</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0.4</td>
<td>4.8</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>0.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Rectal prolapse</td>
<td>0.4</td>
<td>&lt;0.1</td>
</tr>
</tbody>
</table>

Table continues on the next page
### Complications of CF in 2016, by Mutation Class Group

<table>
<thead>
<tr>
<th></th>
<th>Mutation Class I-III (%)</th>
<th>Mutation Class IV-V (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mental Health</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>11.0</td>
<td>10.5</td>
</tr>
<tr>
<td>Depression</td>
<td>15.2</td>
<td>14.3</td>
</tr>
<tr>
<td><strong>Other Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer confirmed by histology&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2.2</td>
<td>2.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.1</td>
<td>5.7</td>
</tr>
<tr>
<td>Kidney stones&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Nasal polyps requiring surgery&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Renal failure requiring dialysis&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Sinus disease</td>
<td>37.9</td>
<td>38.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Individuals who did not have a complications case report form recorded were considered to not have any complications, as in previous years.

<sup>b</sup> See table on page 68 for secondary complications.

<sup>c</sup> At the end of 2015, the data entry for complications was revised such that acute complications would no longer carry forward from one encounter to the next. We hypothesize that this is the reason for the decrease in the observed number of reported acute complications, compared to prior years, most notably DIOS.

<sup>d</sup> See table on page 61 for secondary complications.

<sup>e</sup> Cause other than CFRD.
Cystic Fibrosis-Related Diabetes (CFRD)

CFRD is associated with weight loss, lung function decline, and increased mortality. Early diagnosis and treatment may minimize the impact of CFRD. The CF Foundation/American Diabetes Association clinical practice guidelines for CFRD recommend screening all individuals annually, starting at age 10, with an oral glucose tolerance test (OGTT). Blood glucose testing is routinely performed at most CF care centers. The recommended OGTT test is used less frequently and there is substantial variation across CF care centers. It is encouraging to note that rates of screening adolescents for CFRD using the OGTT continues to increase since the CF Foundation clinical care guidelines for CFRD were published in 2010, but use among adults is increasing more slowly.

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

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>50</th>
<th>100</th>
<th>Median</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Glucose Measurements in Non-Diabetic Individuals 10 to 17 Years</td>
<td></td>
<td></td>
<td></td>
<td>93.8</td>
<td>21.9</td>
<td>100.0</td>
</tr>
<tr>
<td>Any Glucose Measurements in Non-Diabetic Individuals 18 Years and Older</td>
<td></td>
<td></td>
<td></td>
<td>86.9</td>
<td>28.6</td>
<td>100.0</td>
</tr>
<tr>
<td>OGTT Screening in Non-Diabetic Individuals 10 to 17 Years</td>
<td></td>
<td></td>
<td></td>
<td>59.5</td>
<td>2.4</td>
<td>97.3</td>
</tr>
<tr>
<td>OGTT Screening in Non-Diabetic Individuals 18 Years and Older</td>
<td></td>
<td></td>
<td></td>
<td>29.8</td>
<td>0.0</td>
<td>89.3</td>
</tr>
</tbody>
</table>

### Blood Glucose and OGTT Screening for Individuals without CFRD, 2000–2016

- **Glucose Screening in Individuals 10-17**
- **Glucose Screening in Individuals ≥18**
- **OGTT Screening in Individuals 10-17**
- **OGTT Screening in Individuals ≥18**

![Graph showing blood glucose and OGTT screening trends from 2000 to 2016](image-url)
Prevalence of CFRD is higher among adults as compared to 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.

The vast majority of individuals who were diagnosed with CFRD are noted in the Registry as being treated with insulin, as recommended in the CF Foundation CFRD clinical care guidelines. 44

<table>
<thead>
<tr>
<th>CFRD and Impaired Glucose Tolerance by Age in Years, 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Graph showing prevalence of CFRD and impaired glucose tolerance by age." /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CFRD Treatment in 2016</th>
<th>Percent of People with CFRD on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary change</td>
<td>19.5</td>
</tr>
<tr>
<td>Oral hypoglycemic agents</td>
<td>3.9</td>
</tr>
<tr>
<td>Intermittent insulin (with illness, steroids, etc.)</td>
<td>5.9</td>
</tr>
<tr>
<td>Chronic insulin</td>
<td>76.3</td>
</tr>
<tr>
<td>No Treatment Noted in Reporting Year</td>
<td>8.2</td>
</tr>
</tbody>
</table>

The data are not mutually exclusive and represent CFRD treatment at any point during the year.
The clinical practice guidelines recommend regular hemoglobin A1c (HbA1c) measurements for individuals with CFRD. Variation by CF care centers in the percentage of individuals with CFRD with one or more HbA1c measurements during the year shows that a majority of centers test their patients at least annually.

<table>
<thead>
<tr>
<th>Complications of CFRD in 2016 (n=6,204)</th>
<th>All (n)</th>
<th>All (%)</th>
<th>Age &lt; 18 (%)</th>
<th>Age ≥ 18 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>46</td>
<td>0.7</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>111</td>
<td>1.8</td>
<td>0.2</td>
<td>2.1</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>213</td>
<td>3.4</td>
<td>&lt;0.1</td>
<td>4.0</td>
</tr>
<tr>
<td>Chronic renal failure requiring dialysis</td>
<td>24</td>
<td>0.4</td>
<td>&lt;0.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>67</td>
<td>1.1</td>
<td>0.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Any episodes of severe hypoglycemia</td>
<td>295</td>
<td>4.8</td>
<td>3.4</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Depression and Anxiety

Addressing the mental health of all individuals with CF is critical to maintaining their overall health and quality of life. In 2015, the CF Foundation and the European CF Society jointly published guidelines on screening and treatment for depression and anxiety among individuals with CF and caregivers of children with CF. These guidelines recommend annual screenings for all individuals with CF who are age 12 and older, as well as caregivers of children with CF.

It is encouraging to note the more than doubling in the number of people who were screened for depression or anxiety in 2016, potentially due to the release of the mental health guidelines and the support for their implementation.

Of note, 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.

<table>
<thead>
<tr>
<th>Percentage of Individuals with Mental Health Screening, by Center</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Depression Screening Performed in Individuals 12 to 17 Years</strong></td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>21.4%</td>
</tr>
</tbody>
</table>

| **Depression Screening Performed in Individuals 18 Years and Older** |
| 0 | 50 | 100 | Median | Min | Max |
| 17.6% | 19.5% | 76.0 | 0.0 | 100.0 |

| **Anxiety Screening Performed in Individuals 12 to 17 Years** |
| 0 | 50 | 100 | Median | Min | Max |
| 24.1% | 57.7% | 69.1 | 0.0 | 100.0 |

| **Anxiety Screening Performed in Individuals 18 Years and Older** |
| 0 | 50 | 100 | Median | Min | Max |
| 19.5% | 53.0% | 69.9 | 0.0 | 100.0 |
Prevalence of both anxiety and depression peaks in early adulthood, a time when lung disease often worsens. There is substantial overlap in individuals who report both anxiety and depression; among individuals who report anxiety or depression, 35.8 percent report both conditions.
TRANSPLANTATION

Lung transplantation remains an option for some individuals with severe lung disease. The 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.

In 2016, there were 1,642 individuals in the Registry who were reported to have ever received a lung, kidney, heart, or liver transplant.

<table>
<thead>
<tr>
<th>Transplant Status of People with CF in 2016 (All organs)</th>
<th>Number of Individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accepted, on waiting list</td>
<td>151</td>
</tr>
<tr>
<td>Evaluated, rejected</td>
<td>126</td>
</tr>
<tr>
<td>Received transplant this year</td>
<td>289</td>
</tr>
<tr>
<td>Received transplant in a prior year</td>
<td>1,353</td>
</tr>
</tbody>
</table>

Lung Transplantation

There were 1,478 post-transplant individuals in the Registry in 2016, including 265 individuals who were reported to have received a lung transplant in 2016. The increase in CF transplants mirrors the overall increase in lung transplants in 2016 (2,327) compared to 2015 (2,057) as reported by UNOS. Overall, 6.2 percent of CF transplants performed in 2016 were among individuals younger than age 18.
Overall, lung transplant recipients are a relatively small proportion of individuals included in the Registry; the majority are age 30 years and older.

While most CF care occurs within CF Foundation-accredited care centers, transplant and post-transplant care typically occurs at transplant centers and therefore some of these individuals are lost to follow-up in the Registry. Optimal care for CF transplant recipients should include periodic follow-up at a CF Foundation-accredited care center.

### 2016 Status of Lung Transplant Recipients by Year of Transplant, 1990–2016

- **Not Seen in 2016 (Lost to Follow-up)**
- **Death Date Recorded in the Registry**
- **Seen in 2016**

![Graph showing lung transplant distribution in people with CF seen in 2016](image-url)
SURVIVAL

Over time, there have been substantial improvements in the survival of people with CF. In the 2015 Annual Data Report, we used a number of metrics to describe survival of people living with CF in the United States. Definitions for these metrics are provided in the Appendix (page 77).

Median Predicted Survival

In 2016, the median predicted survival age of those born in 2016 was 47.7 years (95 percent confidence interval: 45.6-51.1 years) as compared to 41.2 in 2015 (95 percent confidence interval: 38.2-43.9). This is a larger one-year increase than has previously been observed. Estimates of median predicted survival for the next few years are needed to establish if this is a trend that continues. There were 373 reported deaths in 2016, compared to 448 deaths in 2015. The process for reporting and validating deaths has not changed and the percent of people lost to follow-up in 2016 did not differ from 2015. Several potential factors may contribute to the decreased number of deaths and the related increase in median predicted survival. In 2016, 289 people reported an organ transplant, compared to 238 people in 2015. Furthermore, over time, there has been a small and potentially important increase in the number of people first entering the Registry at older ages, with some entering at age 60 and older. Lastly, some of the decrease in deaths may be due to the entry of CFTR modulators into clinical practice.

Given the instability of annual survival estimates due to the relatively low number of deaths in a given year, we group the data into five year increments. The graph below shows gains in median predicted survival from 1986 to 2016 in five year increments.* Between 2012 to 2016, the median predicted survival age was 42.7 years (95 percent confidence interval: 41.7-43.9 years). This means that half of individuals born from 2012 to 2016 are predicted to live beyond 42.7 years of age. This prediction assumes no further improvement in mortality rate and thus does not take into account the potential impact of CFTR modulators and other improvements in clinical care.

*Using the currently recommended method for calculating median predicted survival.
Median Conditional Predicted Survival

Median conditional predicted survival at specific ages is another metric to help understand changes in survival over time that considers an individual’s current age. This metric reflects the population-based median for all individuals of a specific attained age and does not take individual characteristics into consideration. The figure ends at age 40 because the number at older ages are currently too small to accurately predict survival. As for median predicted survival, this metric assumes no further improvement in mortality rate.

**Median Conditional Predicted Survival Based on Attained Age, 2012 - 2016**

Mortality Rate

The mortality rate in 2016 was 1.3 deaths per 100 individuals with CF in the Registry. There has been a steady decrease in the mortality rate over the last thirty years. This is encouraging, given that the median age of individuals in the Registry has increased from 11.6 years in 1986 to 19.0 years in 2016.

**Annual Mortality Rate (per 100 People with CF), 1986–2016**
Median Age at Death

The median age at death was 29.6 years for the 373 people with CF reported to have died in 2016. About 20.0 percent of deaths occurred before 20 years of age. Comparing the cumulative percentage for age at death between 1986 and 2016 shows a substantial shift of the curve towards the right and a less steep curve, indicating that deaths are occurring at older ages and are spread across a wider age range. The median age at death reflects the current situation and cannot be used to predict survival of the entire population.

Causes of Death

Among the 373 deaths in 2016, the primary causes were respiratory/cardiorespiratory and organ transplant-related, similar to previous years. About 50.0 percent of deaths occurred in people who are F508del homozygotes, reflecting their distribution in the Registry. While 5.0 percent of people in the Registry are post-transplant, 93 deaths (24.9 percent) occurred in transplant recipients.
APPENDIX

Survival

Beginning with the 2015 Annual Data Report, we revised our methodology for calculating median predicted survival after researchers from the United States and Canada published an article with recommendations for best practices in calculating median predicted survival46 (see figure on page 71 of the 2015 Annual Data Report). 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 specific year or their data were not entered in the Registry that year, they were excluded from analysis. In contrast, the newer recommended method includes individuals who were not in the Registry during a specific year, then subsequently returned to a CF care center and provided data to the Registry. These individuals are included in the calculation during all intervening years since their last data were entered in the Registry, thereby providing a more accurate estimate of predicted survival among individuals with CF. In this year’s Annual Data Report (and all subsequent reports) we have used the recommended calculation.
Survival Metrics

All metrics that use current data to predict survival make the assumption that 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.** Furthermore, the median predicted survival age refers to a population and not an individual; it does not account for individual features such as genotype which impact survival, and should not be used to make decisions at the patient level.

The following survival metrics are included in this year’s report:

1. **Median Predicted Survival**

   The estimated median predicted survival age is the age beyond which we expect 50.0 percent of infants with CF born in the present day to live, under the assumption that recent age-specific mortality rates will hold for the rest of their lives. This calculation includes all individuals currently in the Registry. This is a key survival metric that we have reported for many years.

2. **Median Conditional Predicted Survival**

   The definition of the estimated median conditional predicted survival age is similar to the median predicted survival. The difference is this calculation is done for people who are currently a specific age and does not necessarily relate to those born recently. It can be calculated for individuals of any current age. For example, the definition of the median conditional predicted survival for those currently age 20 years is the age beyond which we expect 50.0 percent of those individuals to live, under the assumption that current age-specific mortality rates will hold for the rest of their lives. This metric is similar to life expectancy. The difference is that life expectancy refers to the average as compared to the median age. Because the CF population is relatively small, it was determined that median is a more valid metric than the average.

3. **Mortality Rate**

   The number of deaths in a calendar year divided by the number of individuals in the Registry during that calendar year.

4. **Median Age at Death**

   This calculation includes only individuals who died during the calendar year and therefore should not be used to reflect 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.
Mutation Class

The chapter on CFTR Gene Mutations includes a figure (page 18) showing classification of mutations based on impact of the mutation on function of the CFTR protein. The system has five classes, with smaller numbers reflecting larger impact of the mutation on the protein development and function, and typically less CFTR function in the cell. It has been proposed that there should be a mutation class 6 for mutations that lead to increased turnover of the CFTR channel and the cell surface, but this class is not used in this report or the analysis. To date, not all mutations have been studied and the mutation class of some mutations remains unknown. To learn more about CFTR mutations, please visit CFTR2.org.

Each individual has two alleles, and each can have different mutations. When the two mutations have different classes, it is necessary to create an algorithm to combine the information on the two alleles into one mutation class grouping for the individual. Based on literature showing a clinical difference in disease severity between mutation classes I-III and IV-V, we created two mutation class groupings.

Rules for determining mutation class groupings are as follows:

1. If a person has at least one mutation that is in class 4 or 5, they are included in the Class IV-V grouping.
2. If a person has two mutations in class 1, 2 or 3 they are included in the Class I-III grouping.
3. If a person has one mutation that is in class 1, 2 or 3 but the other mutation does not have a mutation classification, they are included in the Class Unknown grouping.
4. If both a person’s mutations are classified as unknown, they are included in the Class Unknown grouping.

<table>
<thead>
<tr>
<th>Determination of Mutation Class Category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Mutation A</strong></td>
</tr>
<tr>
<td>Class 1</td>
</tr>
<tr>
<td>Class 1</td>
</tr>
<tr>
<td>Class 2</td>
</tr>
<tr>
<td>Class 3</td>
</tr>
<tr>
<td>Class 4</td>
</tr>
<tr>
<td>Class 5</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
</tbody>
</table>

- Mutation Class I-III
- Mutation Class IV-V
- Mutation Class Unknown
# 2016 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
  - [ ] Unknown
- **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

---

*repeated entries can be recorded

[ ] indicates values calculated by the registry

---

**Key:**
- [ ] radio buttons (select one option only)
- [ ] check box (multiple selections allowed)
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:
☐ 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.)

Consultations with Care Team Members
☐ Patient consulted with a Social Worker at this visit
☐ Patient was seen by a Dietitian/Nutritionist at this visit
☐ Patient was seen by a Physical therapist at this visit
☐ Patient was seen by a Respiratory therapist at this visit
☐ Patient consulted with a Pharmacist at this visit

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

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)
Haemophilus influenzae (any species):  ☐
Pseudomonas aeruginosa:  ☐
☐ mucoid  ☐ non mucoid  ☐ mucoid status unknown
### 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**

### Other microorganisms:

- **B. gladioli**
- **B. cenocepacia**
- **B. multivorans**
- **Burkholderia – other**
  - **B. cepacia**
  - **B. stabilis**
  - **B. vietnamiensis**
  - **B. dolosa**
  - **B. anthina**
  - **B. ambifaria**
  - **B. pyrrococina**
  - **B. ubonensis**
  - **B. arboris**
  - **B. latens**
  - **B. lata**
  - **B. metallica**
  - **B. seminalis**
  - **B. contaminans**
  - **B. diffusa**
  - **B. pseudomallei**

### Fungal/Yeast:

- **Aspergillus (any species)**
- **Candida (any species)**
- **Scedosporium species**

### 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 kansasi
- **☐** Mycobacterium marinum
- **☐** Mycobacterium terrae
- **☐** Other
  Specify: ____________

*Please note: The option Mycobacterium avium complex (MAC) includes M. avium subsp. Avium, M. avium subsp. Hominis, M. avium subsp. paratuberculosis, and M. intracellulare.*

### Medications

**Not on Medications**

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

### Pulmonary Medications

**Antibiotics – inhaled and/or oral**

**Tobramycin Based Medications**

**Tobramycin solution for inhalation (i.e. TOBI):**
- **☐** 300 mg BID alternate month schedule
- **☐** 300 mg BID continuous
- **☐** Other regimen (different dose or freq)
- **☐** Eradication

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

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

**Other inhaled aminoglycoside (e.g. gentamicin, amikacin, or tobramycin preparation):**
- **☐** Frequency: Alternate Month
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- Continuous
- Other regimen (different dose or freq)
- Eradication

**Colistin:** □
**Frequency:** □ Alternate Month
- Continuous
- Other regimen (different dose or freq)
- Eradication

**Aztreonam – Inhaled:** □
**Frequency:** □ 75 mg TID Alternate Month Schedule
- 75 mg TID Continuous
- Other Regimen
- Eradication

**Other inhaled antibiotics:** □

- **Comments:**

**Oral macrolide antibiotic:** □
- azithromycin (Zithromax)
- clarithromycin (Biaxin)

**Other oral antibiotic:** □
- Quinolone (Cipro, Levaquin, gatifloxacin, etc.)
- Cefpodoxim Pericon (cecphelexin, 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 (i.e. Orkambi):** □
**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):**
- β-agonist (e.g. Proventil, Reptabs, Volmax, etc.)

**Key:**
- □ radio buttons (select one option only)
- □ check box (multiple selections allowed)

- □ Theophylline product (e.g. Theodur, Slo-bid, Uniphyl)

**Bronchodilators (inhaled):**
- Short acting β-agonist (e.g. albuterol, Proventil, Ventolin, Xopenex, etc.)
- Long acting β-agonist (e.g. salmeterol, Serevent, Foradil, Brotvane, etc.)
- Short acting anticholinergic (e.g. ipratropium, Atrovent)
- Long acting anticholinergic (e.g. tiotropium, Spiriva, etc.)
- Combination β-agonist and anticholinergic (e.g. Combivent, DuoNeb, etc.)

**Corticosteroids:**
- 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, Tilde, 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)
- TOBI or other aminoglycoside
- Aztreonam
- Colistin
- Macrolide antibiotics
- High-dose ibuprofen
- Hypertonic saline
- Ivacaftor (i.e. Kalydeco)
- Ivacaftor Lumacaftor (i.e. Orkambi)

**GI/Nutrition/Endocrine Medications**
This Patient is on enzyme medications: □ Yes ○ No
For all enzymes, "capsules per largest meal" options are:
□ 0.5 ○ 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:**

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

**Pertzye (Pancrecarb)**
- Pertzye 4000: __
  - Number of capsules per largest meal of the day: ____
  - Total capsules per day: ____
- Pertzye 8000: __
  - Number of capsules per largest meal of the day: ____
  - Total capsules per day: ____
- Pertzye 16000: __
  - Number of capsules per largest meal of the day: ____
  - Total capsules per day: ____
- Pertzye 25000: __
  - Number of capsules per largest meal of the day: ____
  - Total capsules per day: ____

**Zenpep**
- 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: ____

**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: ____

**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)**

**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/sec):**
- [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.)] __

*repeated entries can be recorded
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- 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

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: □

Diabetes Status
○ Impaired Glucose Tolerance (FBG < 126, 2-h PG 140-199)
○ CFRD with or without fasting hyperglycemia
○ Type 1 Diabetes
○ Type 2 Diabetes

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: _______________

Key:
□ radio buttons (select one option only)
□ check box (multiple selections allowed)

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

Bone/Joints
□ Arthritis/Arthropy
□ 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 10.0): ___________
Platelet Count x1,000/microL (typical clinical value: 100 to 500): ___________
Hemoglobin (grams per deciliter): ___________

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

**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
Key:

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

**Care Episode Measurements**
At the beginning of Care Episode:
FVC (L):_______
FEV1 (L):_______
FEF25-75 (L):_______
Height: ____ o cm o inches
Weight: ____ o kg o 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: ____ o cm o inches
Weight: ____ o kg o lb
Date recorded: (MM/DD/YYYY)
Check if data were impossible to measure: □

Comments:___________________________

**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, pm
○ No
○ Unknown

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

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

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

A indicates values calculated by the registry
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**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
○ 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?
○ Yes ○ No ○ Unknown

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

**Diabetes Status**

Key:

<table>
<thead>
<tr>
<th>FORM NAME</th>
</tr>
</thead>
<tbody>
<tr>
<td>○ radio buttons (select one option only)</td>
</tr>
<tr>
<td>□ check box (multiple selections allowed)</td>
</tr>
</tbody>
</table>

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)
○ CFRD with or without fasting hyperglycemia (2-h PG >= 200)
○ Type 1 Diabetes
○ Type 2 Diabetes

Was a retinal eye exam performed by an ophthalmologist 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

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

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

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

Key:
- ○ radio buttons (select one option only)
- □ check box (multiple selections allowed)

*repeated entries can be recorded
[ ] indicates values calculated by the registry
2016 Cystic Fibrosis Foundation Patient Registry Questionnaire

**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: _______________________________


