Patient Registry Annual Data Report
Technical Supplement

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For questions about the Patient Registry, please contact reghelp@cff.org.

For information on how to request Patient Registry data for research projects, please go to: cff.org/Research/Researcher-Resources/Tools-and-Resources/Patient-Registry-Data-Requests/.

About the CF Foundation Patient Registry Annual Data Reports

Each year, the Cystic Fibrosis Foundation creates two complementary reports — the comprehensive Annual Data Report, and a shorter, corresponding Highlights Report.

The purpose of this technical user guide is to help readers interpret the data in the Annual Data Reports, including information about:

- Who is included in the reports
- Limitations of Registry data and how they impact the interpretation of data
- An explanation of figures included in the report
- The rationale and impact for changes in methods for reporting data over time

Our goal in creating and sharing these reports is to inform and educate the wider cystic fibrosis community about CF as a disease and describe trends in key health outcomes. It is our hope that this information will help people with CF and their families, clinicians, researchers, and policymakers work together to continuously improve the quality of CF care and ensure that it is accessible to all individuals with CF. Both the comprehensive Annual Data Report and the Highlights Report are publicly available on cff.org.

If you are interested in data about a specific CF care center, key metrics are available on cff.org. You can also ask your CF care center for this information from their center report, which describes the center's patient population, the care they provide their patients and the health outcomes in greater detail.

Inclusion and Exclusion Criteria

The Annual Data Report is based on data entered in the CF Foundation Patient Registry through our online portal, PortCF©, for the previous year. Each year, CF care centers have until February to enter all data from the previous calendar year. The database is then locked, and these data are used to generate annual reports.

The Annual Data Report contains data from individuals diagnosed with CF who: a) have consented to participate in the Registry, and b) were seen in a CF care center during the year, or were born, were diagnosed, or died in the year. Data from individuals with a diagnosis of CF transmembrane conductance regulator (CFTR)-related metabolic syndrome (CRMS), CF screen positive inconclusive diagnosis (CFSPID), or CFTR-related disorders are excluded from all figures except for one, which is specifically related to new diagnoses in the present year.

For Annual Data Reports prior to 2017, data from individuals who received a lung transplant were excluded from chapters related to pulmonary function and exacerbations, pulmonary therapies, pulmonary complications, and microbiology. In the 2017 Annual Data Report, data from individuals who have received a lung transplant are also excluded from chapters on guidelines, nutrition, and all therapies and complications. As a result of this change, some CF complications that are common among individuals post-transplant (i.e., CF-related diabetes and osteoporosis) are less prevalent than in data reports from years prior. In future years, we will be enhancing the data collection on individuals with advanced lung disease and who are post-transplant to better report on these populations.

The included populations represented in the figures vary and are based on the eligibility criteria described in the title and/or footnotes for the figure.

Figures presenting data on center-level variation include only those centers that are reporting on at least 10 eligible patients. Exceptions to this are figures showing center-level variation for infants, people with a G551D mutation, people with CF-related diabetes (CFRD), and people who had a pulmonary exacerbation. For these figures, centers reporting on five or more eligible patients are included.

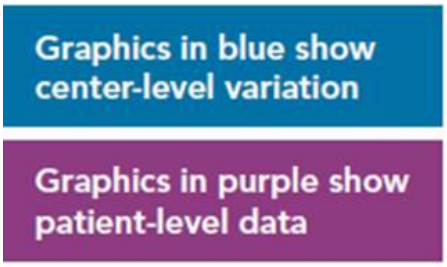
Interpretation of Figures

Figures are either cross-sectional (present year data only) or longitudinal (data over several years). When possible, longitudinal graphs include data from 1986 through the present year. However, for some figures, data from different ranges of years are included. In some cases, it is because the variable was added to the Registry later than 1986. In others, the way in which the variable was collected was modified or enhanced at a point and we can only show trends after the modification or enhancement. However, it is important to note that longitudinal graphs include the individuals participating in the Registry in a particular year, so each year can have a different subset of the population.

Registry data are updated and processed every year. As such, we encourage you to compare a given year's data with the adjusted results from previous year's data displayed within that given year's report instead of referring to numbers published in previous Annual Data Reports.

Guide to Tables, Figures, and Plots

To help readers determine the population included in the figures, the titles of the figures are either in blue or purple.



Box-and-Whisker Plots

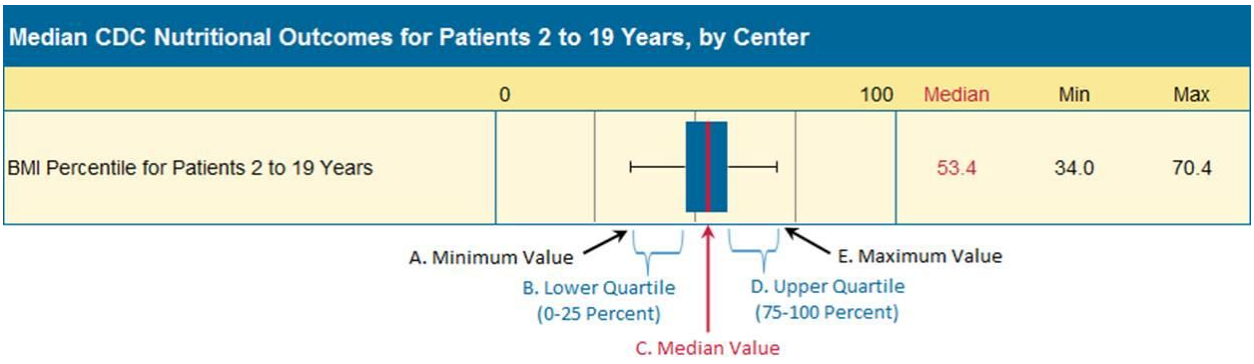
Annual Data Reports contain both patient-level and center-level data. All box-and-whisker charts, graphs, and tables outlined in blue in this report depict center-level variation. All charts and graphs outlined in purple represent patient-level data. The difference in the granularity of the results can cause some variation in the reported measures.

For example, at the patient level, the percentage of patients seen by a dietitian is calculated by dividing the number of patients seen by a dietitian by the total number of patients. In contrast, at the center level, the percentage of patients seen by a dietitian is calculated for each center. Then, the percentage from each center is aggregated, with the distribution of the percentages by center displayed in the box-and-whisker plot.

In general, there is much more variation seen for patient-level measures than center-level measures as indicated by larger boxes on the box-and-whisker plots.

Plots with no shading show data for all patients	Plots with yellow shading show data for children
Plots with gray shading show data for infants	Plots with blue shading show data for adults

As an example, the box-and-whisker plot below shows the median body mass index (BMI) percentile among individuals aged 2 to 19 years across all centers:



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

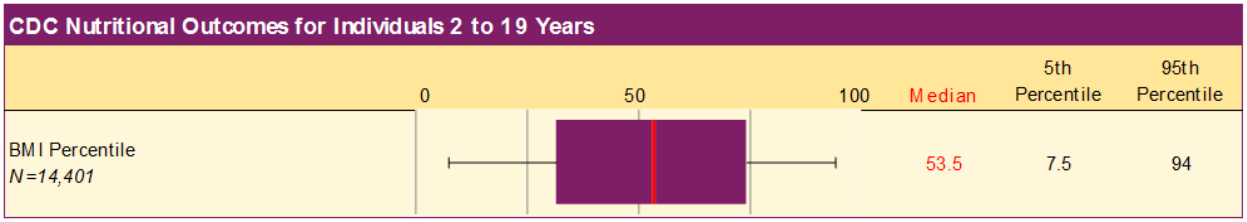
Box-and-whisker plots provide the following information as noted in the figure above:

A: Minimum Value: The lowest median BMI percentile at any center (left "whisker").
B: 0-25th Percentile: 25 percent of centers' observations fall below this value.
C: Median Value: 50 percent of observations fall below and 50 percent fall above this value. Median values, shown by a red line, are preferable to mean values because they are not skewed by extreme values.
D: "Box": 25th to 75th percentile values.
E: 75-100th Percentile: 75 percent of centers' observations fall below this value.
F: Maximum Value: The highest median BMI percentile of all centers (right "whisker").

There are a few things to look for when reading these plots. First, the width of the box indicates the amount of variation in the outcome across care centers — the wider the box, the more variation. Second, the position of the box indicates the values where most

care centers fall on that particular measure. In addition, the shading of the chart area indicates the age group examined. An advantage of the compactness of box-and-whisker plots is that we can display a group of plots together on the same page, allowing for a comparison in both the width and position of the boxes across related outcomes or in different subgroups of the population.

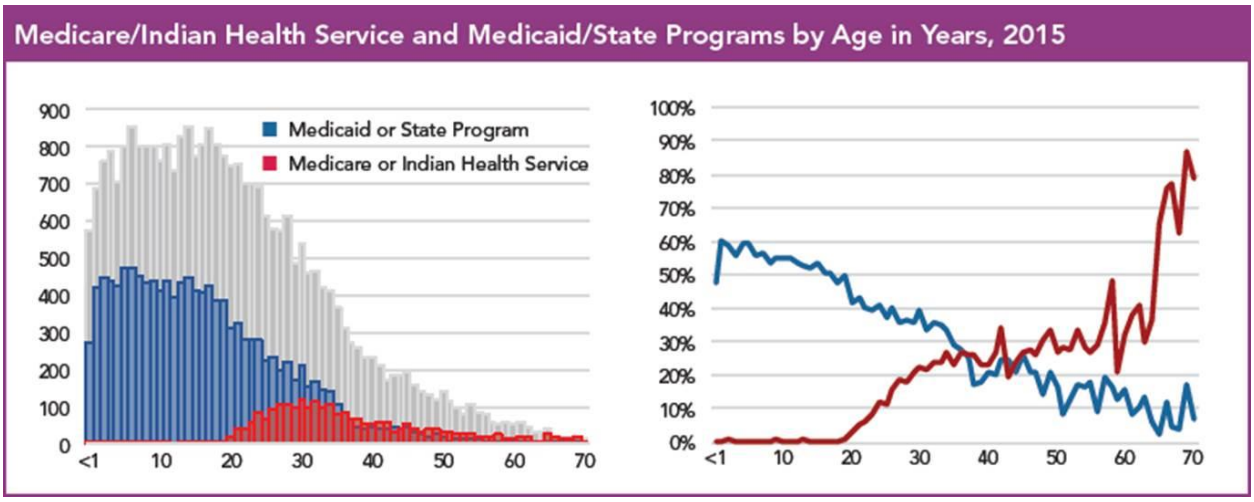
In addition to center-level data, box-and-whisker plots are used to show the distribution of population-level variations for outcomes and process measures. An example is the figure below, which also displays the variation in BMI percentile among individuals aged 2 to 19 years in the 2015 reporting year.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



Combined Data Charts to Display Selected Attributes by Age (Age Distribution)

Combined data charts display selected attributes or health outcomes for people with CF by age. On the left, histograms show raw patient counts, while on the right, line charts show the percentage of total individuals by age. For figures where the age group of over 70 years is not indicated, the group was removed because there were less than 10 individuals in any age group over 70 years. For consistency across the report and to allow comparisons across different attributes, the light gray bars in the background always represent the total number of people with CF, in that age cohort, in the given year's Registry data. Bars of other colors are used to show the number of people with a selected attribute (e.g., a complication).

As an example, in the following figure, the histogram on the left shows the number of people who reported Medicaid or another state-based program as a form of insurance in blue, and the number of people who reported Medicare or Indian Health Service as a form of insurance in red. The line graph on the right shows the percentage of people who selected each insurance type, with the percentage lines using the same color scheme as the bar chart. These charts provide insight into how attributes change across age groups in a given year's Registry data.



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

Information on the limitations of these charts and how to interpret them is provided in the section below on survival bias and newborn screening.

Validity of Data

Since 2012, an independent audit of the PortCF© data has been routinely conducted to evaluate data completeness and accuracy by comparing data in the Registry to information from medical records.

The initial audit included data from 28 centers of varying sizes and geographic locations. Results of this audit were published in Knapp et al.[1] The audit reviewed data for 1,606 patients, including 8,247 clinic visits and 1,471 hospitalizations. For key information, such as demographic, microbiological, treatment, and hospitalization variables, data entered for a patient in the Registry were compared with the data in their electronic medical record (EMR) and evaluated for completeness and accuracy.

Overall, the Registry contained 96.5 percent of clinic visits and 89.7 percent of hospitalizations recorded in EMRs. Among key variables examined, the accuracy of Registry data was over 95 percent for date of birth, sex, and CFTR mutations. Microbiology was recorded accurately for 93.1 percent of cultures, and medications were recorded accurately with some variability by type — with high accuracy observed for dornase alfa and azithromycin (over 95 percent), hypertonic saline and aztreonam (over 90 percent), but decreasing accuracy for cyclical inhaled medication including tobramycin (over 85 percent). We have used similar methodology in subsequent years, selecting different centers to be audited each year with comparable findings regarding completeness and accuracy of Registry data over time.

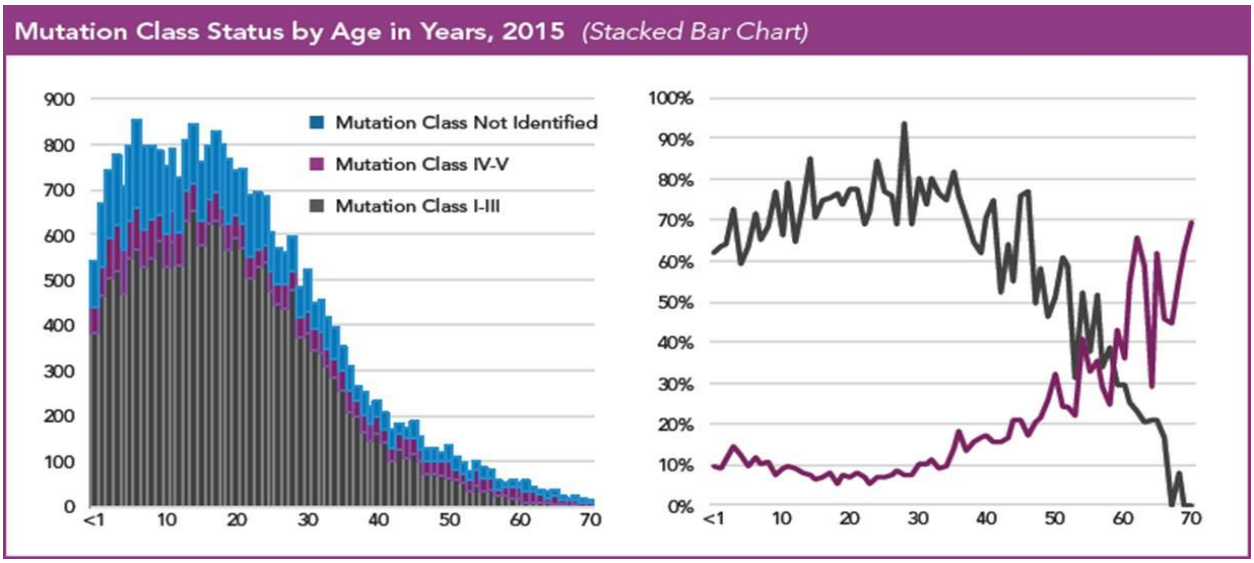
Data Interpretation

Each year, the Registry report includes individuals who consented to share their information in the Registry and who were seen in a CF care center, or were born, were diagnosed, or died during that year. Each year, new children and adults with CF are added or return to the Registry, while others are no longer captured in the Registry due to death or loss to follow-up. These year-to-year changes impact the overall profile of the patient population in the Registry. Of those in the 2008 cohort who were, to the best of our knowledge, alive in 2012, 91 percent were included in the Registry in 2012, and 87 percent of the cohort were included in the Registry for all five years. Among patients without five years of data, 36 percent returned to the Registry after a one-year gap, and an additional 9 percent returned after a two- or three-year gap.

To understand trends in outcomes over time and the impact of the disease at different ages, it is helpful to display figures that show change over time or by age. However, caution must be used when interpreting the data in these charts because there have been changes over time in the diagnosis, treatment, and survival of people with CF. Specifically, universal newborn screening for CF has been in place in the United States since 2010 and was implemented even earlier in many states. Therefore, the diagnostic and clinical characteristics of very young individuals included in the Registry in recent years are different than those of similarly aged individuals previously included in the Registry. Prior to newborn screening, most infants were diagnosed because of clinical symptoms. Now, asymptomatic and potentially healthier infants are being diagnosed with CF and included in the Registry earlier than they previously would have been.

Conversely, at older ages, there is potential for survival bias to impact the observed data. Survival bias occurs because older patients currently in the Registry have survived and are likely healthier, and, therefore, are not representative of other patients who were in their birth cohort at younger ages.

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



We must keep these and other potential biases in mind when interpreting the data. To prevent distorted interpretation of data due to survival bias, starting with the 2013 report, we removed figures that had previously displayed outcomes by age. Nevertheless, the potential for survival bias to lead to misrepresentation of results needs to be kept in mind when reviewing the data in the Annual Data Report, particularly for adult populations. Figures that include all adults or all patients are less likely to be impacted by survival bias because the “older” patients represent a relatively small proportion of the population.

Determining Data Values and Classifications

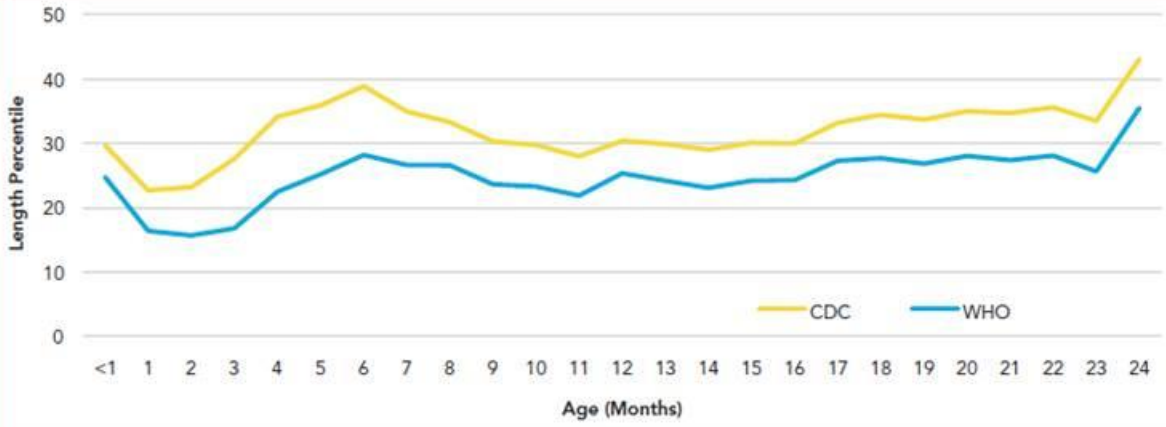
Rationale and Impact of Using World Health Organization (WHO) Compared to Centers for Disease Control and Prevention (CDC) Percentiles for Children Under Age 2

Height, weight, and weight-for-length percentiles for children under the age of 2 were based on percentiles developed by the Centers for Disease Control and Prevention (CDC) prior to 2013. Starting in 2013, we continued to use the CDC growth charts for individuals aged 2 to 19, and we switched to World Health Organization (WHO) growth charts for individuals younger than age 2. The WHO growth charts were developed from the WHO Multicentre Growth Reference Study.[2] This change from CDC growth charts to WHO growth charts for individuals aged 2 and under was precipitated by a recommendation by the CDC.[3]

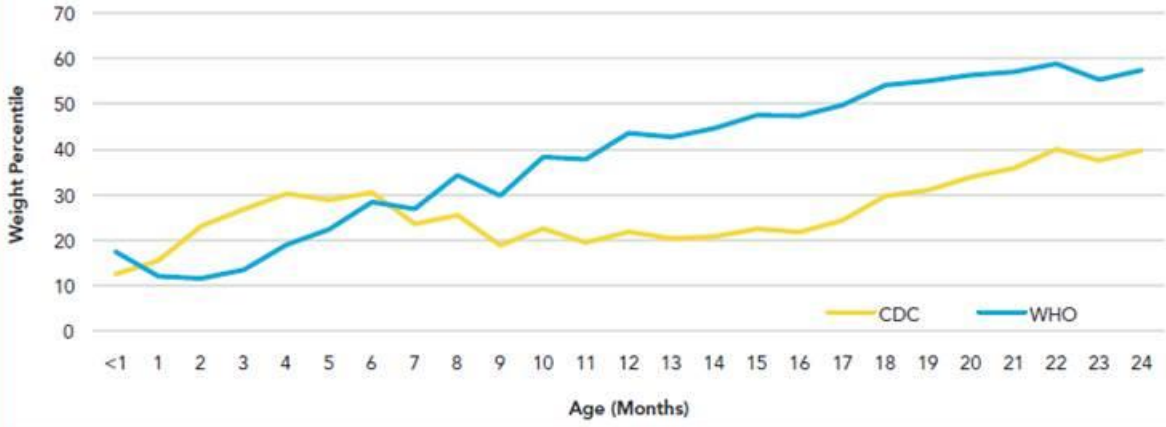
The rationale for the CDC's recommendation was based on both the methodology that WHO used in the Multicentre Growth Reference Study to collect their data to develop their reference equations and its larger sample size and more complete data. The CDC growth charts are based on data of how children in the United States grow as they age. In contrast, WHO charts are based on the physiology of how infants and toddlers should grow, and are based on children aged 0 to 2 years living in environments that are believed to support what WHO researchers view as the optimal growth of children in six countries throughout the world, including the U.S. The distribution shows how infants and young children grow under these optimal conditions, rather than how they grow in environments that may not support optimal growth.[3] Furthermore, the WHO charts use the growth of breastfed infants as the norm.

To understand the impact of using WHO growth charts to calculate length, weight, and weight-for-length percentiles, we used data from 9,790 encounters that occurred in 2013 among individuals with CF under the age of 2. For each measure by age, we calculated the median value using CDC growth charts and WHO growth charts. For length, percentiles using WHO growth charts are consistently lower than those using CDC growth charts. For weight, percentiles are lower using WHO growth charts for the first six months of life, and higher after the second six months. Weight-for-length percentiles are generally comparable during the first year of life and increasingly diverge in the second year of life, with WHO percentiles being consistently higher.

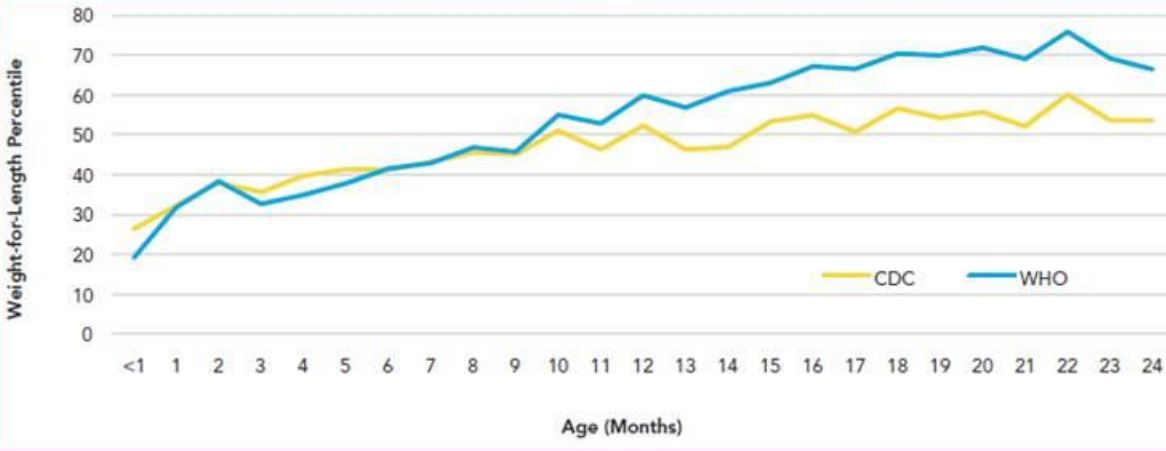
Median Length Percentile by Age — CDC and WHO Reference Equations



Median Weight Percentile by Age — CDC and WHO Reference Equations



Median Weight-for-Length Percentile by Age — CDC and WHO Reference Equations



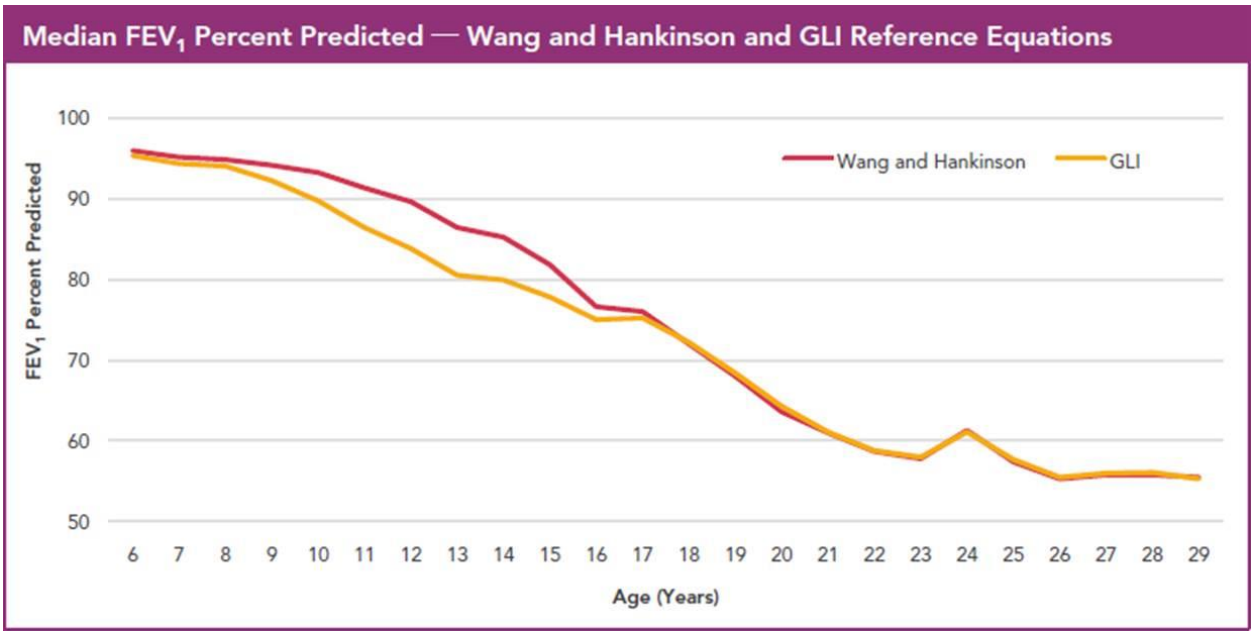
Rationale and Impact of Switching From Wang and Hankinson to Global Lung Initiative (GLI) Reference Equations

There have been improvements in reference equations used to compare lung function measures among individuals with CF to expected measures among individuals of the same age, sex, race, ethnicity, and height. The Registry primarily reports forced expiratory volume (FEV_1) percent predicted, but it also includes forced vital capacity (FVC) percent predicted and the FEV_1 / FVC ratio percent predicted.

Originally, predicted measures were calculated using the Knudson equations. Between 2004 and 2012, predicted measures included in Annual Data Reports were based on the Wang and Hankinson reference equations. In 2012, the Global Lung Initiative (GLI) released updated lung function reference equations, which have advantages over Wang and Hankinson reference equations. Specifically, GLI reference equations were developed using data obtained from healthy, non-smoking individuals around the world between the ages of 3 and 95, thus eliminating the need to use separate pediatric and adult equations.[4] As a result, starting with the 2013 annual data report, all percent predicted measurements are based on GLI reference equations.[4]

To understand the impact of using GLI reference equations to calculate lung function, we used data from 85,105 encounters that occurred in 2013 among individuals with CF aged 6 to 29 years with valid spirometry test results entered into the Registry.

The figure below displays the mean FEV_1 percent predicted for individuals aged 6 to 29 using Wang and Hankinson reference equations and GLI reference equations. The graph indicates that there is no clinically meaningful difference in FEV_1 percent predicted between the two reference equations for adults with CF. The patients most impacted by the change in reference equations are preteens, for whom the FEV_1 percent predicted using GLI equations is lower on average than that obtained from Wang and Hankinson equations. Our findings are comparable to those reported in a study by Stanojevic et al. using data from individuals with CF in the United Kingdom.[5]



Examining the Validity and Generalizability of Using Global Lung Initiative (GLI) Reference Equations in Children Ages 3-5 in the CF Foundation Patient Registry

Unlike previous reference equations that began at age 6, The Global Lung Initiative (GLI) reference equations can be used to evaluate lung function beginning at age 3.[4] We examined FEV_1 percent predicted using GLI equations for children ages 3 to 5 in the CF Foundation Patient Registry to help inform our decision on reporting measures taken at younger ages.

Specifically, we wanted to determine:

- The proportion of children with recorded pulmonary function test (PFT) measures
- Whether children with PFT measures are representative of the total population of children
- Validity of these early PFT measurements

The table below displays summary characteristics for children ages 3 to 5 in 2016, stratified by whether they ever had pulmonary function test measures for FEV_1 percent predicted, calculated using GLI equations. Those grouped in 'GLI Ever' had at least one PFT measurement reported during ages 3-5. Those grouped in 'GLI Never' did not have any reported PFT measurements during ages 3-5. The table indicates that, in 2016, about 45 percent of children ages 3 to 5 had at least one PFT measurement reported. Children with PFT data are significantly older than children without reported PFT data. There is no strong indicator of meaningful differences in disease severity measures between the two groups.

Table 1. Selected Summary Characteristics for Children Ages 3-5

Variable	**Total** (n=2820)	**GLI Ever** (n=1271) (45%)	**GLI Never** (n=1549) (55%)
Age on 12/31/ 2016 (mean)	5.0 (1.1)	5.7 (0.8)	4.4 (0.9)
Age on 12/31/2016 (in years)			
3	651	24 (2%)	627 (40%)
4	791	245 (19%)	546 (35%)
5	1378	1002 (79%)	376 (24%)
Sex			
Female	1385	637 (50%)	748 (48%)
Male	1435	634 (50%)	801 (52%)
Mode of Diagnosis			
Meconium Ileus	153	76 (6%)	77(5%)
Respiratory Abnormalities	78	34 (3%)	44 (3%)
Newborn Screening	2260	1006 (79%)	1254 (81%)
Other	329	155 (12%)	174 (11%)
Mutation Class			
I — III	1917	896 (71%)	1021 (66%)
IV — V	335	130 (10%)	205 (13%)
Undetermined	534	229 (18%)	305 (20%)
Missing	34	16 (1%)	18 (1%)
MRSA[A]			
Yes	482	214 (17%)	268 (17%)
No	2338	1057 (83%)	1281 (83%)
MSSA[B]			
Yes	1815	841 (66%)	974 (63%)
No	1005	430 (34%)	575 (37%)
H. influenzae			
Yes	884	412 (32%)	472 (31%)
No	1924	857 (68%)	1067 (69%)
P. Aeruginosa			
Yes	541	237 (19%)	304 (20%)
No	2267	1032 (81%)	1235 (80%)
Dornase Alfa			
Yes	2089	1026 (81%)	1063 (69%)
No	729	244 (19%)	485 (31%)
Pancreatic Enzyme Replacement Therapy			
Yes	2412	1108 (87%)	1304 (84%)
No	407	162 (13%)	245 (16%)
Height Percentile	45.7 (27.9)	46.1 (27.9)	45.4 (28.0)
Weight Percentile	51.1 (26.8)	51.0 (26.5)	51.1 (27.1)

BMI Percentile	59.4 (24.7)	60.0 (24.1)	59.0 (25.2)

There was concern that measures done in young children who are still learning to perform PFTs may not accurately reflect their lung function. We compared the distribution of lung function in children aged 3 to 5 in 2016 with those aged 6 to 8 and observed that the distribution did not differ dramatically between the two age groups.

Table 2. Comparative Lung Function Distribution Across Age Groupings

FEV_1 Percent Predicted	**Children aged 3 – 5 (n=1100)**	**Children aged 6 – 8 (n=1899)**
≥121	59 (5%)	101 (5%)
111 – 120	154 (14%)	285 (15%)
101 – 110	228 (21%)	432 (23%)
91 – 100	255 (23%)	448 (24%)
81 – 90	179 (16%)	308 (16%)
71 – 80	115 (10%)	152 (8%)
61 – 70	65 (6%)	86 (5%)
51 – 60	26 (2%)	43 (2%)
≤50	19 (2%)	44 (2%)

In addition, we looked at lung function measures within the same children over time to look at changes. Using data from the CF Foundation Patient Registry beginning in 2010, we compared patient PFT data in the first year available to the average of their maximum FEV_1 percent predicted at ages 6, 7, and 8. This distribution is shown below.

Based on this distribution, it appears that for over 40 percent of children, early PFTs are underestimating FEV_1 percent predicted and should not be used in reporting. Consequently, the CF Foundation has decided not to include this data in the Annual Data Report at this time. We will continue to monitor early PFT data in future years.

Table 3. Comparative Distribution of Averaged PFT Data

Absolute change in FEV_1	**N (%)**
<-5	578 (19%)
-5 = <0	543 (18%)
0 – <5	611 (20%)
5 – <10	508 (17%)
10 – <20	568 (19%)
20+	213 (7%)

Survival

Beginning with the 2015 Annual Data Report, we revised our methodology for calculating median predicted survival based on updated best practices in calculating median predicted survival. These best practices were published by researchers from the United States and Canada[6] (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. So, 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 assume that mortality rate will not change over time. **Therefore, they do not account for 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 the 2016 Annual Data Report:

Median Predicted Survival

Estimated median predicted survival age is the age beyond which we expect 50 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.

Median Conditional Predicted Survival

The definition of estimated median conditional predicted survival age is similar to median predicted survival. The difference is that 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, median conditional predicted survival for those who are currently 20 years old is the age beyond which we expect 50 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 average as compared to median age. Because the CF population is relatively small, it was determined that median is a more valid metric than average.

It should be noted that despite the difference in calculation of average and median, this difference is small, which is why the reference to "life expectancy" may be used as the more familiar term within the wider CF community.

Mortality Rate

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

Median Age at Death

This calculation includes only individuals who died during the calendar year, and therefore should not be used to predict survival in the entire CF population. This metric is the age at which exactly half of the deaths of individuals with CF were below and half were above.

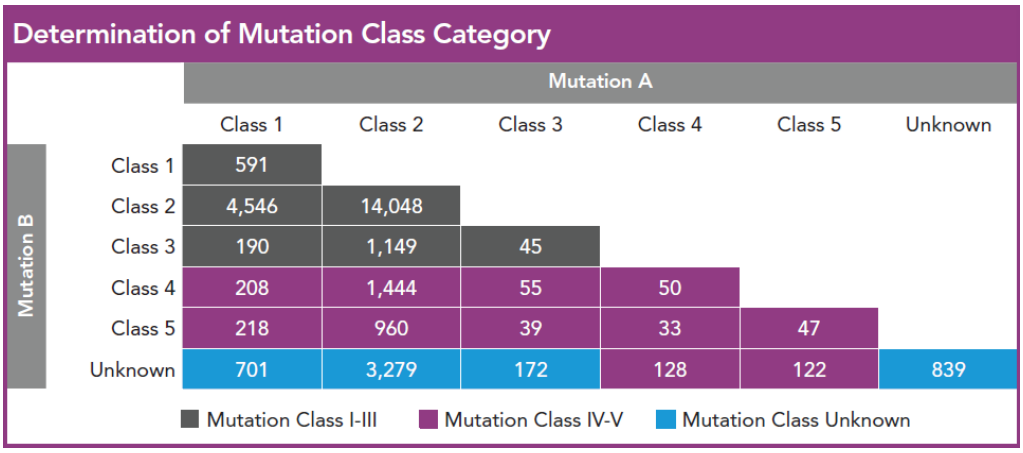
Mutation Class

The chapter on CFTR gene mutations in the 2016 Annual Data Report includes a figure showing classification of mutations based on the impact of the mutation on the function of the CFTR protein. The system has five classes, with smaller numbers reflecting a 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 sixth mutation class for mutations that lead to increased turnover of the CFTR channel and the cell surface, but this class is not used in the 2016 Annual Data Report or the analyses. To date, not all mutations have been studied and the mutation class of some mutations remains unknown.

Each individual has two alleles, and each can have different mutations. When the two mutations have different classes, it is necessary to use an algorithm to combine the information on the two alleles into one mutation class grouping for the individual. Based on data presented in the 2016 Annual Data Report 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 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 in class 1, 2 or 3 and the other mutation does not have a mutation classification, they are included in the **Class Unknown** grouping.
4. If both of a person's mutations are classified as unknown, they are included in the **Class Unknown** grouping.



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