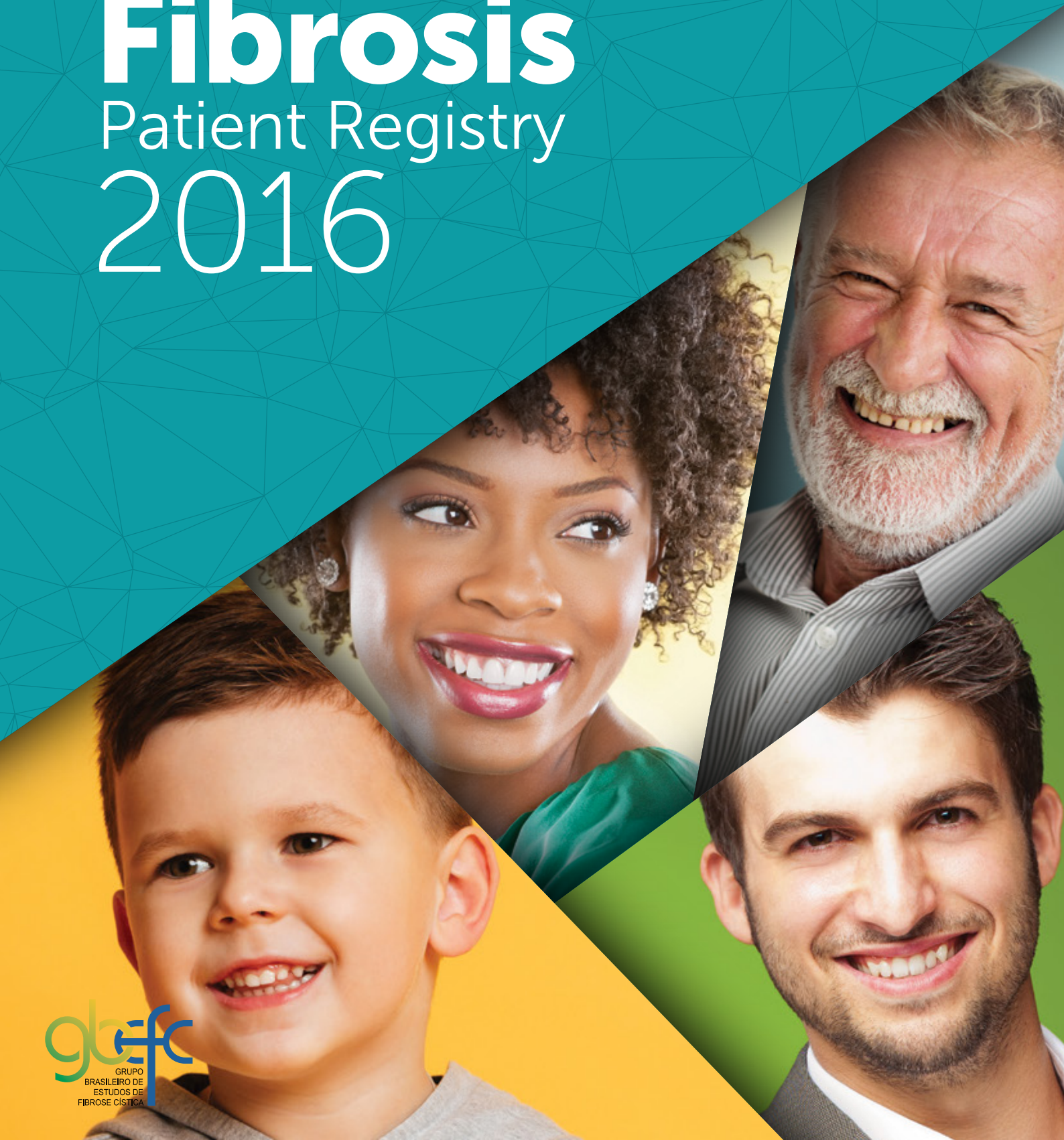
The Brazilian

Cystic Fibrosis

Patient Registry 2016



GRUPO BRASILEIRO DE ESTUDOS DE FIBROSE CÍSTICA

ANNUAL REPORT 2016

The Brazilian Cystic Fibrosis Registry (REBRAFC) contains demographic data on the diagnosis and treatment of patients with cystic fibrosis (CF) in Brazil, with the aim of improving the attention given to this disease in our country. With the publication of this report, this initiative completes eight years, with growing participation by colleagues and an increasing number of CF Centers operating in the country. For the first time in the history of CF in Brazil, we have achieved a great leap in knowledge of the genetics of our patients, thanks to the sponsorship of a pharmaceutical company, the quick action of a private laboratory in São Paulo, and the coordination of the Brazilian Cystic Fibrosis Study Group (GBEFC). However, there is still much to do for Brazilian patients who lack access to diagnostic and therapeutic resources in several regions of the country. The continuity and integrity of REBRAFC are of paramount importance in this scenario because the registry represents the main documented resource for the current situation of CF patients in Brazil and their evolution over the years, thus demonstrating how CF is being diagnosed and treated in the country.

We continue to believe that this initiative can contribute to changes in the public agenda, resulting in better health assistance for individuals with CF in Brazil

CYSTIC FIBROSIS AND GBEFC:

Cystic fibrosis (CF) is an autosomal recessive disease with multisystem involvement (respiratory, gastrointestinal, hepatic, and genitourinary systems). It is a complex disease with progressive and potentially lethal features that remain little known in Brazil, despite the existence of various centers and professionals dedicated to the study and care of patients over many years. Treatment is also complex and involves high-cost drugs, some of which are subsidized by the Ministry of Health and others by state health secretariats; however, access to drugs is not uniform troughout the country.

The Brazilian Cystic Fibrosis Study Group (GBEFC) is a non-profit organization, created on November 5, 2003, and composed of health professionals working in the area of CF. The activities of the GBEFC include dissemination of research, training of personnel, assistance with the establishment of centers for the treatment of CF in Brazil, the organization of congresses in the country on CF and working with the Ministry of Health to define a national protocol for the treatment of CF.

In addition to the recent publication of the Brazilian Guidelines on the Diagnosis and Treatment of Cystic Fibrosis, the GBEFC has been acting intensively, promoting technical visits to Centers in several States and promoting the improvement of the diagnosis of CF, both through the recent genotyping initiative and the expansion of access to a good quality sweat test by providing chloridometers to some important Brazilian Care Centers for patients with CF.

The GBEFC maintains a website (www.gbefc.org.br) that provides information on cystic fibrosis; the present and previous reports are available as free downloads on the site in Portuguese and English versions.

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01. INTRODUCTION

This report describes data from the Brazilian Cystic Fibrosis Registry (REBRAFC), which contains demographic, diagnostic, and treatment data of patients with cystic fibrosis (CF) in Brazil. Data on patients followed up during 2016 and that were included during the year of 2017 are presented. By the time these data were generated for analysis, 4,654 patients had been registered in the database, of which 4,258 (91.5%) had some follow-up data.

The number of records and follow-ups has been increasing annually, as shown in Figure 1. In 2017, 848 new cases were registered, a significant number when compared to the previous year. The annual number of follow-ups did not increase in the same proportion as the records but continues to increase as shown in Figure 1.

Even with the increase in the number of records, more than 60% of patients have at least three years of follow-up, and 76.5% have at least 2 years of follow-up (Table 1). These data clearly illustrate the continuous updating of the REBRAFC database regarding the follow-up of registered cases.

FIGURE 1

Number of registrations and follow-ups between 2009 and 2016.

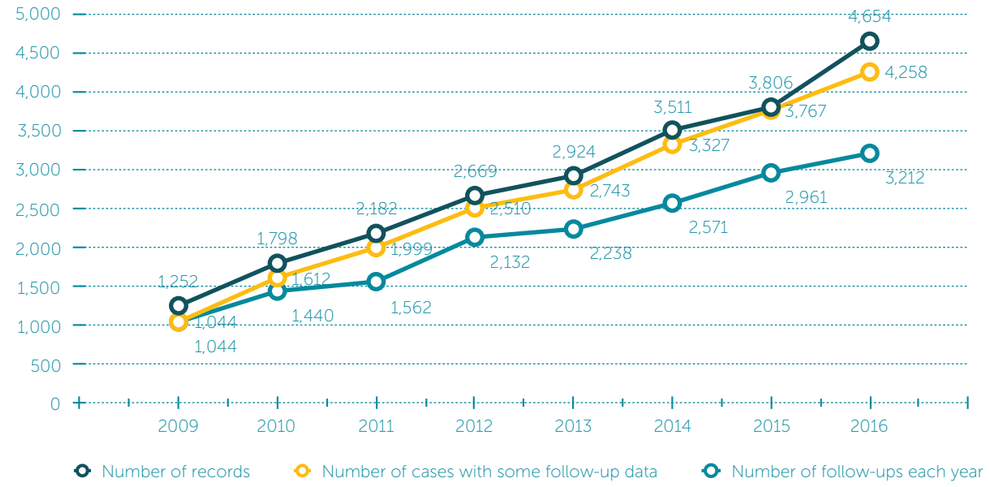


TABLE 1

Distribution of patients according to follow-up time.

FOLLOW-UP TIME	n	%	ACCUMULATED %
8 years	380	8.2%	8.2%
7 years	425	9.1%	17.3%
6 years	408	8.8%	26.1%
5 years	478	10.3%	36.3%
4 years	498	10.7%	47.0%
3 years	665	14.3%	61.3%
2 years	705	15.1%	76.5%
1 year	699	15.0%	91.5%
No follow-up	396	8.5%	100.0%
TOTAL	**4654**	**100%**	

In the description of personal and diagnostic data, all registered patients (n = 4,654) were considered. For analysis of the follow-up data, only data of 2016 (inserted in 2017), which included data of a total 3,212 patients, were considered.

02. DEMOGRAPHIC DATA

TABLE 2

Distribution of patients according to state of birth, 2016.

STATE OF BIRTH	n	%	STATE OF BIRTH	n	%
São Paulo	1185	25.5	Sergipe	45	1.0
Minas Gerais	527	11.3	Rio Grande do Norte	32	0.7
Rio Grande do Sul	463	9.9	Alagoas	31	0.7
Bahia	451	9.7	Maranhão	21	0.5
Rio de Janeiro	389	8.4	Paraíba	19	0.4
Paraná	295	6.3	Amazonas	11	0.2
Santa Catarina	234	5.0	Tocantins	11	0.2
Espírito Santo	158	3.4	Piauí	10	0.2
Pará	158	3.4	Rondônia	9	0.2
Ceará	115	2.5	Amapá	5	0.1
Goiás	94	2.0	Acre	3	0.1
Distrito Federal	80	1.7	Roraima	3	0.1
Pernambuco	76	1.6	Não informado	124	2.7
Mato Grosso do Sul	54	1.2			
Mato Grosso	51	1.1	**TOTAL**	**4,654**	**100**

n = number of patients.

FIGURA 3

Distribution of patients according to state of birth, 2016.

TABLE 3

Distribution of patients according to region of birth, 2016.

REGION OF BIRTH	n	%
Southeast	2,259	48.5%
South	992	21.3%
Northeast	800	17.2%
Midwest	279	6.0%
North	200	4.3%
Not reported	124	2.7%
TOTAL	**4,654**	**100%**

TABLE 4

Distribution of patients according to state of the care center, 2016.

STATE OF CENTER	n	(%)	STATE OF CENTER	n	(%)
São Paulo	1,269	27.3	Pernambuco	73	1.6
Minas Gerais	538	11.6	Mato Grosso do Sul	50	1.1
Rio Grande do Sul	506	10.9	Sergipe	40	0.9
Bahia	445	9.6	Mato Grosso	39	0.8
Rio de Janeiro	389	8.4	Rio Grande do Norte	32	0.7
Paraná	331	7.1	Alagoas	31	0.7
Santa Catarina	211	4.5	Maranhão	18	0.4
Espírito Santo	169	3.6	Paraíba	14	0.3
Pará	161	3.5	Amazonas	3	0.1
Distrito Federal	127	2.7	**TOTAL NUMBER OF PATIENTS**	**4,654**	**100%**
Ceará	117	2.5			
Goiás	91	2.0			

n = number of patients.

TABLE 5

Distribution of patients according to sex and ethnic group, 2016.

SEX	n (%)
Male	2,421 (52.0%)
Female	2,233 (48.0%)
TOTAL NUMBER OF PATIENTS	**4,654 (100%)**

ETHNIC GROUP	n (%)
White	3,186 (68.5%)
Mulatto	1,162 (25.0%)
Black	293 (6.3%)
Asian	10 (0.2%)
Indigenous	3 (0.1%)
TOTAL NUMBER OF PATIENTS	**4,654 (100%)**

n = number of patients.

The Brazilian Cystic Fibrosis Patient Registry 2016

02. DEMOGRAPHIC DATA

FIGURE 3

Distribution of patients according to state of the care center, 2015 and 2016.

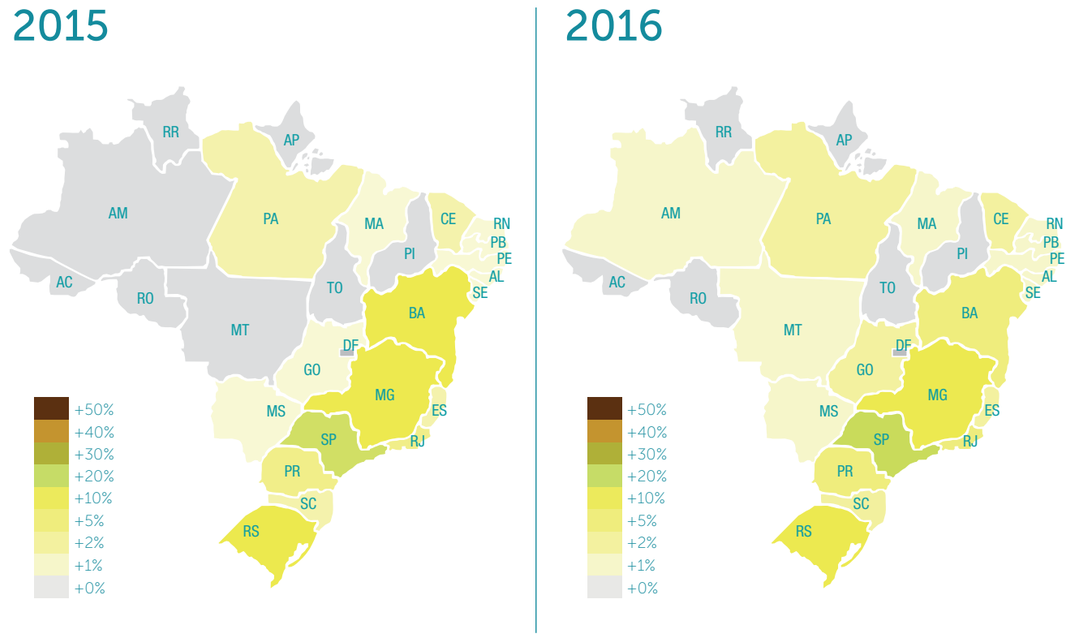


TABLE 6

Description of patients according to current age, 2016.

AGE (YEARS)	
Mean (standard deviation)	13.84 (11.37)
Median (p25-p75)	12.53 (5.75-18.38)
TOTAL NUMBER OF PATIENTS WITH KNOWN AGE	**3,126**
PATIENTS WHO DIED	**59**
PATIENTS WITHOUT SPIROMETRY/ANTHROPOMETRY	**27**
TOTAL NUMBER OF PATIENTS WITH FOLLOW-UP IN 2016	**3,212**

n = number of patients; p25 = 25th percentile, p75 = 75th percentile.

FIGURE 4

Distribution of patients according to current age (N = 3126), 2016.

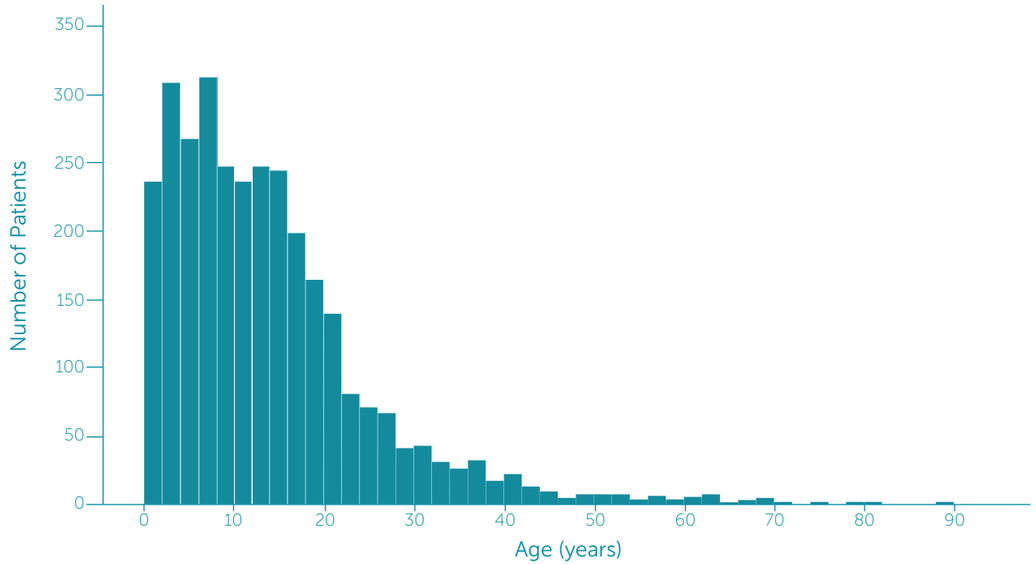
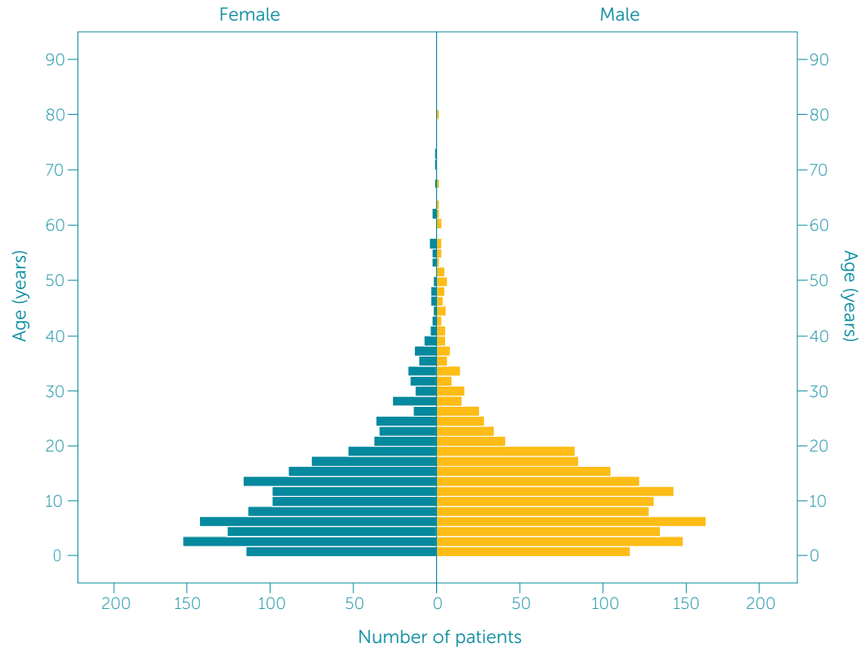


FIGURE 5

Distribution of patients according to current age and sex (N = 3126), 2016.



The Brazilian Cystic Fibrosis Patient Registry 2016

02. DEMOGRAPHIC DATA

TABLE 7

Distribution of patients according to current age group, 2016.

AGE GROUP	n (%)
Up to 5	679 (21.7%)
> 5 to 10	696 (22.3%)
> 10 to 15	614 (19.6%)
> 15-20	479 (15.3%)
> 20-25	256 (8.2%)
> 25-30	144 (4.6%)
> 30 to 35	86 (2.8%)
> 35 to 40	63 (2.0%)
> 40 to 45	38 (1.2%)
> 45 to 50	18 (0.6%)
> 50 years	53 (1.7%)
TOTAL NUMBER OF PATIENTS	**3,126 (100%)**

AGE GROUP (PEDIATRIC, ADULT)	n (%)
Less than 18 years	2,241 (71.7%)
18 years or older	885 (28.3%)
TOTAL NUMBER OF PATIENTS	**3,126 (100%)**

n = number of patients.

FIGURE 6

Evolution of median age from 2009 to 2016.

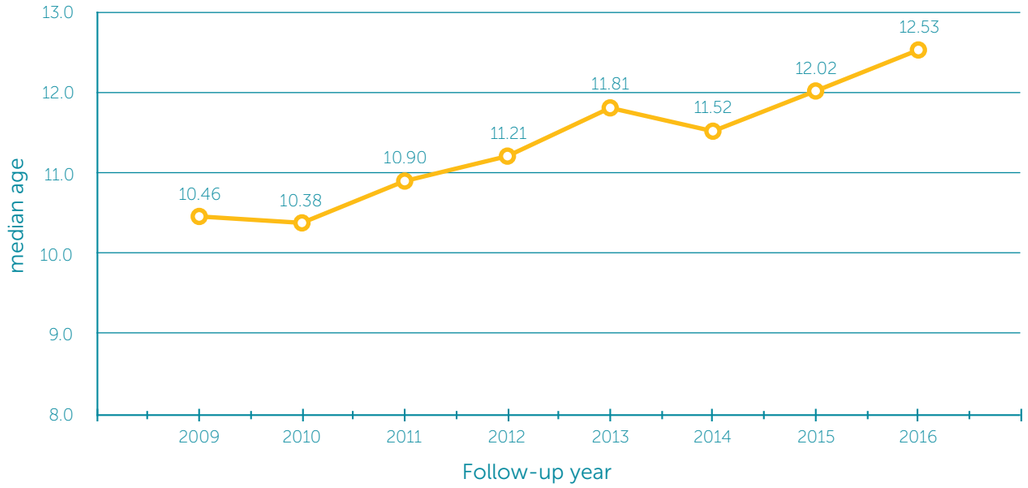
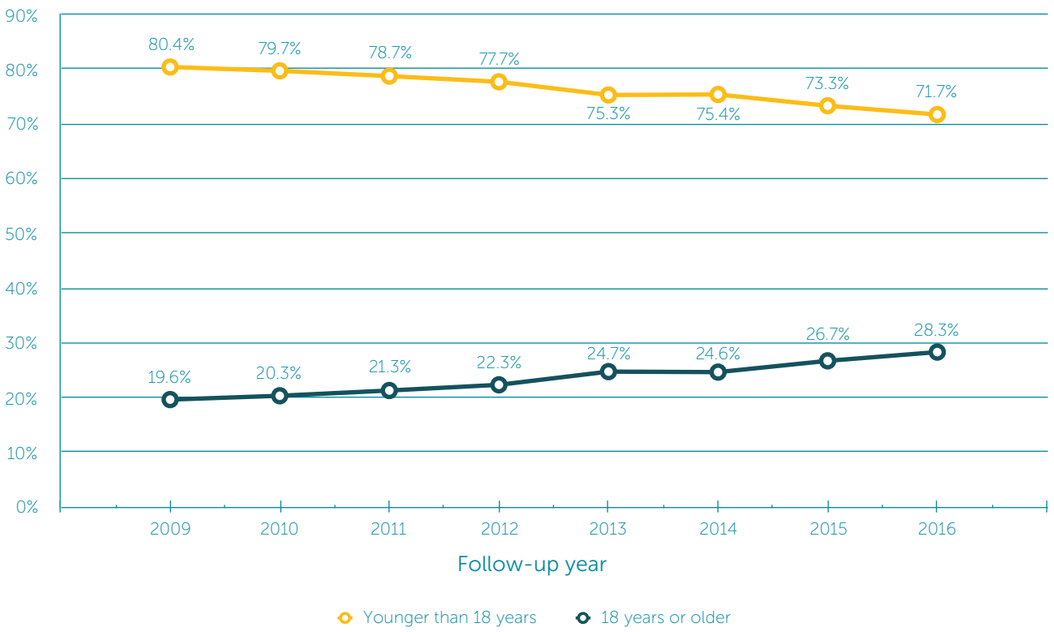


FIGURE 7

Distribution of patients according to pediatric age group from 2009 to 2016.



03. DIAGNOSIS DATA

TABLE 8

Description of patients according to age at diagnosis.

AGE (YEARS)	
Mean (standard deviation)	6.03 (10.69)
Median (p25; p75)	1.13 (0.20 - 7.64)
TOTAL NUMBER OF PATIENTS	**4,646**
PATIENTS WITH NO INFORMATION*	**8**

n = number of patients; p25 = 25th percentile, p75 = 75th percentile.
** Birthdates/diagnosis incorrectly completed*

FIGURE 8

Distribution of patients according to age at diagnosis.

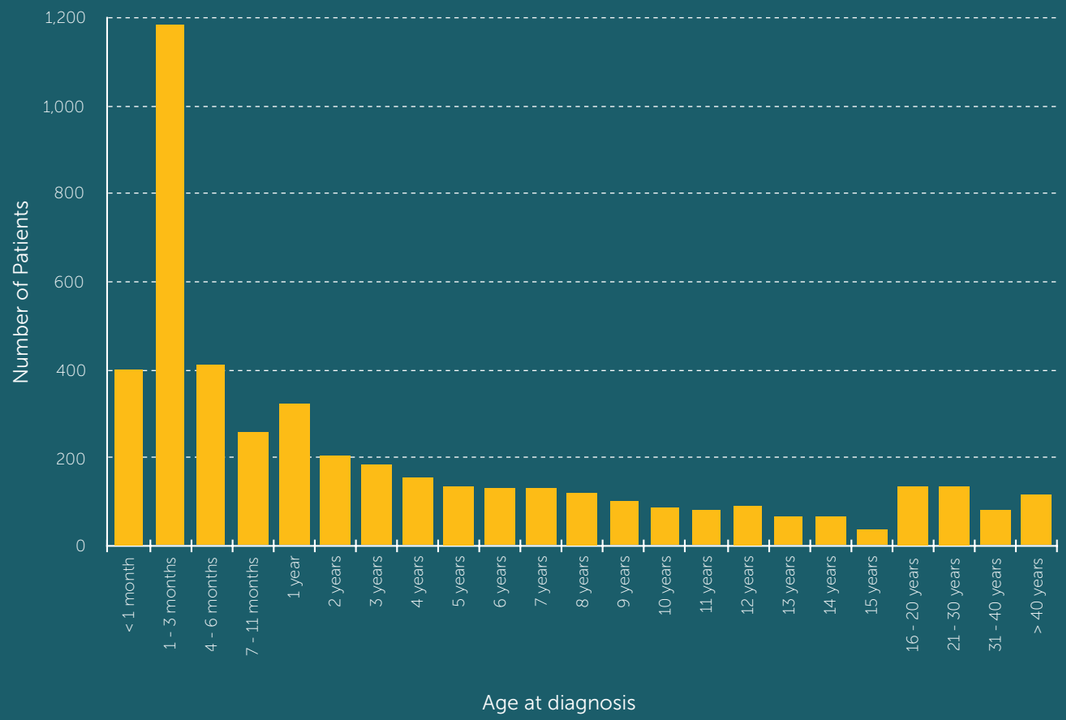


Figure 9 shows the median age at diagnosis according to the year in which cases were diagnosed, for the period between 2009 and 2016. It can be observed in the graph that in the last 4 years, the median has remained below 6 months of age.

FIGURE 9

Variations in age at diagnosis over the years.

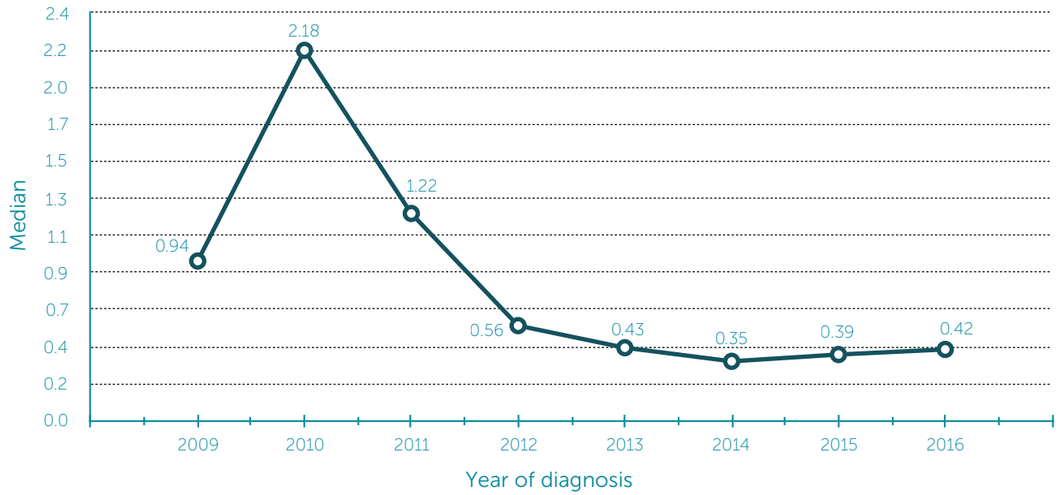


TABLE 9

Distribution of patients according to conditions for diagnosis.

CONDITIONS FOR DIAGNOSIS	n	(%)
Persistent respiratory symptoms	2,777	59.7%
Growth deficit/malnutrition	1.741	37.4%
Steatorrhea or malabsorption	1.583	34.0%
Neonatal screening (IRT)	1,471	31.6%
Family history	391	8.4%
Clinical or surgical meconium ileus	345	7.4%
Sinus disease and/or nasal polyp	291	6.3%
Metabolic disorder	270	5.8%
Edema/anemia	178	3.8%
Prolonged jaundice	46	1.0%
Rectal prolapse	39	0.8%
Infertility	23	0.5%
Other	232	5.0%
Unknown condition	113	2.4%
TOTAL NUMBER OF PATIENTS	**4,654**	**100%**

n = number of patients.

TABLE 10

Description of patients according to sweat test results.

	CHLORIDE (mEq/l)	MASS (mg)	CONDUCTIVITY (mmol/l)
Mean (standard deviation)	90.06 (26.77)	146.83 (79.11)	101.5 (20.9)
Median (p25-p75)	90.00 (71.0-105.50)	135.00 (100-187)	104.0 (93.5-114)
TOTAL NUMBER OF PATIENTS	**3,946**	**2,739**	**624**

n = number of patients; p25 = 25th percentile, p75 = 75th percentile.
For chloride and mass, the means of the 2 measurements were considered

TABLE 11

Diagnosis by neonatal screening with immunoreactive trypsinogen (IRT).

IMMUNOREACTIVE TRYPSINOGEN (IRT) DOSAGE (ng/ml)	1st TEST	2nd TEST
Mean (standard deviation)	199.5 (120.8)	200.4 (129.2)
Median (p25-p75)	171.0 (120-249)	169.0 (116-247)
TOTAL NUMBER OF PATIENTS	**1,271**	**975**

TABLE 12

Other diagnostic tests reported.

	n (%)
Measurement of nasal potential difference	113 (2.4%)
Rectal biopsy	77 (1.7%)
TOTAL NUMBER OF PATIENTS	**4,654 (100%)**

n = number of patients

As in previous years, it was found that the age at diagnosis is significantly lower among patients who underwent neonatal screening (p<0.001, Table 13 and Figure 10).

TABLE 13

Description of patients in relation to age at diagnosis according to neonatal screening.

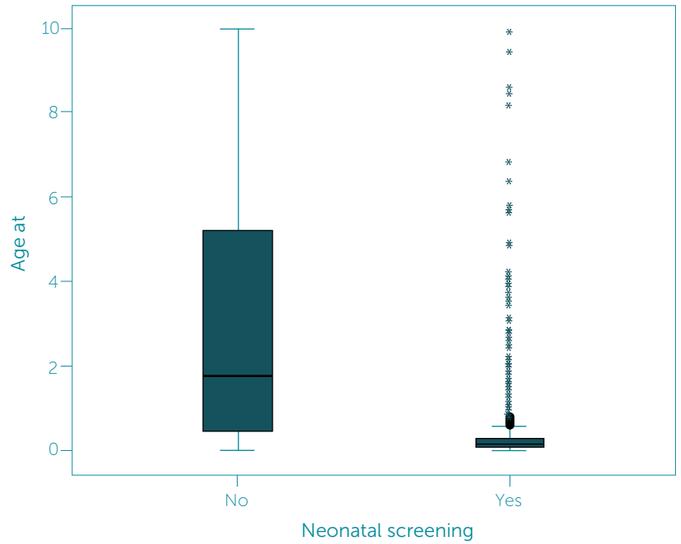
	NEONATAL SCREENING		
AGE AT DIAGNOSIS (YEARS)	**NO**	**YES**	**TOTAL**
Mean (standard deviation)	8.62 (12.06)	0.44 (1.21)	6.03 (10.69)
Median (p25-p75)	4.38 (0.76-11.13)	0.14 (0.09-0.29)	1.13 (0.20 - 7.64)
TOTAL NUMBER OF PATIENTS	**3,176**	**1,470**	**4,646**
PATIENTS WITH NO INFORMATION	**7**	**1**	**8**

p25 = 25th percentile, p75 = 75th percentile.

The Brazilian Cystic Fibrosis Patient Registry 2016
03. DIAGNOSIS DATA

FIGURE 10

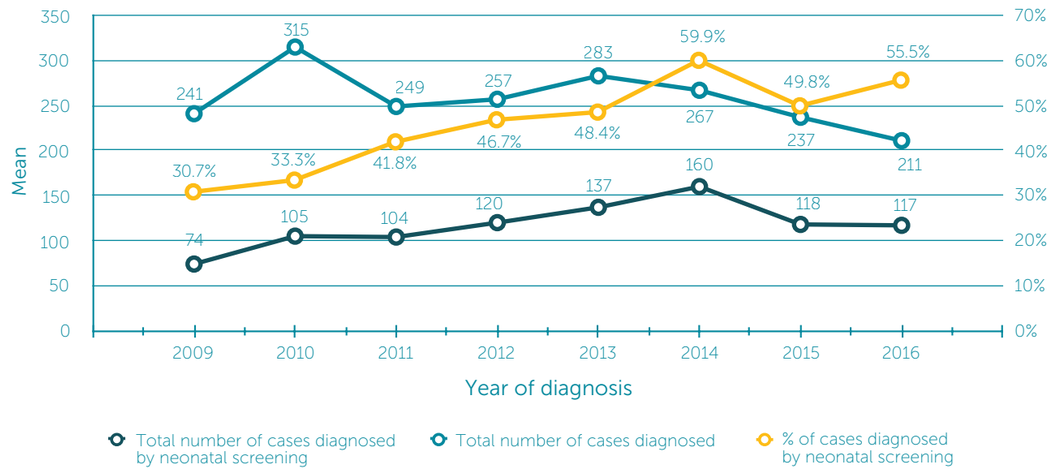
Distribution of patients according to age at diagnosis and whether neonatal screening was performed - considering only patients diagnosed up to 10 years of age.



A total of 2,208 cases of cystic fibrosis were diagnosed between 2009 to 2016, of which, 1,004 (45.5%) were diagnosed by neonatal screening

FIGURE 11

Diagnosis by neonatal screening between 2009 and 2016.



04. GENETIC DATA

The genetic data presented in this report include part of the results of the recent Brazilian initiative of sequencing the exons (in addition to juxtaposed intronic regions) of the CFTR gene in all patients with undefined genotype. Consequently, more than 1,200 cases were examined between March and October 2017 and had their results included in the REBRAFC database. The data were extracted in November 2017. Due to this initiative, there was a large increase in the number of patients that had their genotype analyzed, reaching almost 70% of all recorded cases (Table 14, Figure 12).

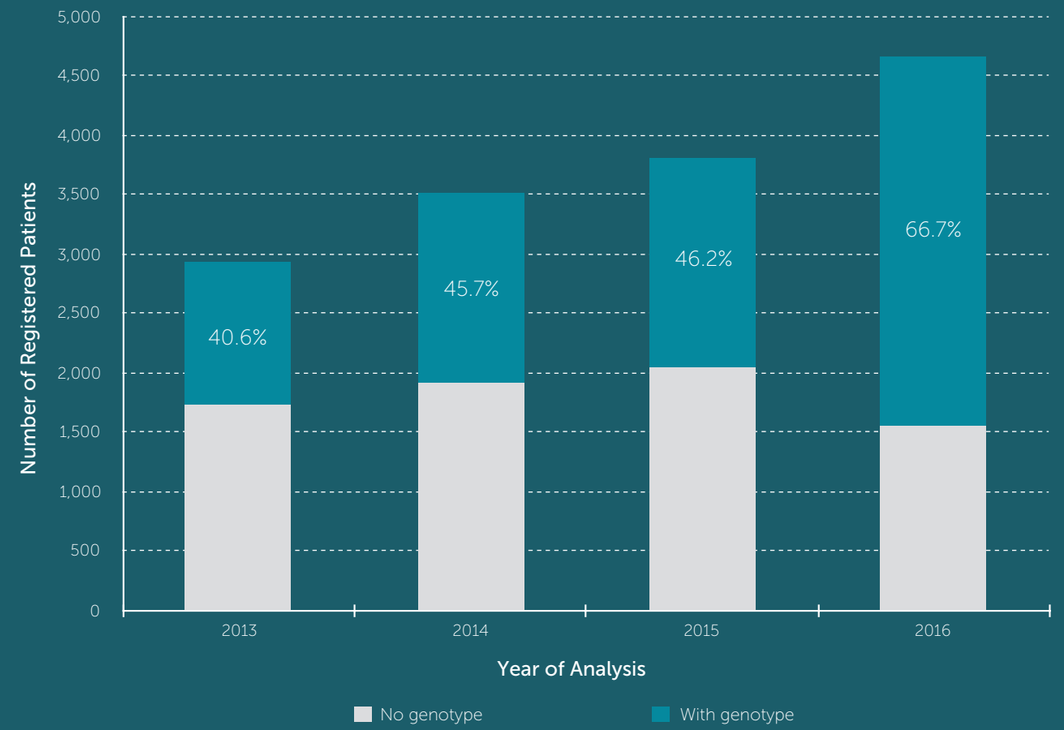
TABLE 14

Description of patients according to genetic study from 2013 to 2016 (including examinations conducted until October 2017).

GENOTYPE PERFORMED	2013 N (%)	2014 N (%)	2015 N (%)	2016 N (%)
No	1,737 (59.4%)	1,907 (54.3%)	2,046 (53.8%)	1,550 (33.3%)
Yes	1,187 (40.6%)	1,604 (45.7%)	1,760 (46.2%)	3,104 (66.7%)
TOTAL NUMBER OF PATIENTS	**2,924 (100%)**	**3.511 (100%)**	**3,806 (100%)**	**4,654 (100%)**

FIGURE 12

Total number of patients and proportion of patients with genotyping over the years.



When analyzing the proportion of patients according to **region of birth**, it was observed that there was a significant increase in all Brazilian regions, with only the North region having less than 50% of patients with genotyping performed (Table 15).

TABLE 15

Description of patients according to genotype analysis by region of birth (including examinations conducted until October 2017).

REGION OF BIRTH	2013 (%)	2014 (%)	2015 (%)	2016 (%)
Southeast	39.2%	47.7%	47.6%	68.6%
South	54.7%	55.9%	57.2%	73.7%
Northeast	31.0%	32.9%	33.2%	54.5%
Midwest	47.6%	41.0%	45.6%	73.1%
North	19.0%	40.0%	39.3%	45.5%
TOTAL	**40.6%**	**45.7%**	**46.2%**	**66.7%**

Analyzing CF genotyping results, 64.5% of the cases had a positive result, i.e., were homozygous or heterozygous with the identification of two or more pathogenic mutations, and 24.4% of the cases were inconclusive, with the identification of only one mutation or one pathogenic mutation and the other of uncertain significance. About 11% of the patients had negative results, with no mutations identified (Table 16).

TABLE 16

Description of genotyping results of patients who underwent genetic testing.

RESULTS OF THE GENETIC EXAMINATION	n (%)
Positive	2,002 (64.5%)
Inconclusive	757 (24.4%)
Negative	345 (11.1%)
TOTAL NUMBER OF PATIENTS WITH GENOTYPING	**3,104 (100%)**

Negative: unidentified/inconclusive mutation: only one mutation or one pathogenic mutation and one of uncertain significance; Positive: homozygous or heterozygous with the identification of two or more pathogenic mutations.

The Brazilian Cystic Fibrosis Patient Registry 2016

04. GENETIC DATA

Most patients (88.4%) had at least one mutation identified and in 10 cases, three mutations were identified (Table 17).

TABLE 17

Number of genetic mutations identified in patients who underwent genetic testing.

NUMBER OF MUTATIONS IDENTIFIED	n (%)
None	345 (11.1%)
One	757 (24.4%)
Two	1,994 (64.2%)
Three	8 (0.3%)
TOTAL NUMBER OF PATIENTS WITH GENOTYPING	**3,104 (100%)**

The distribution of the results according to region of birth indicated that North and Northeast regions had the highest proportion of negative cases with no mutations identified (Table 18, Figure 13).

TABLE 18

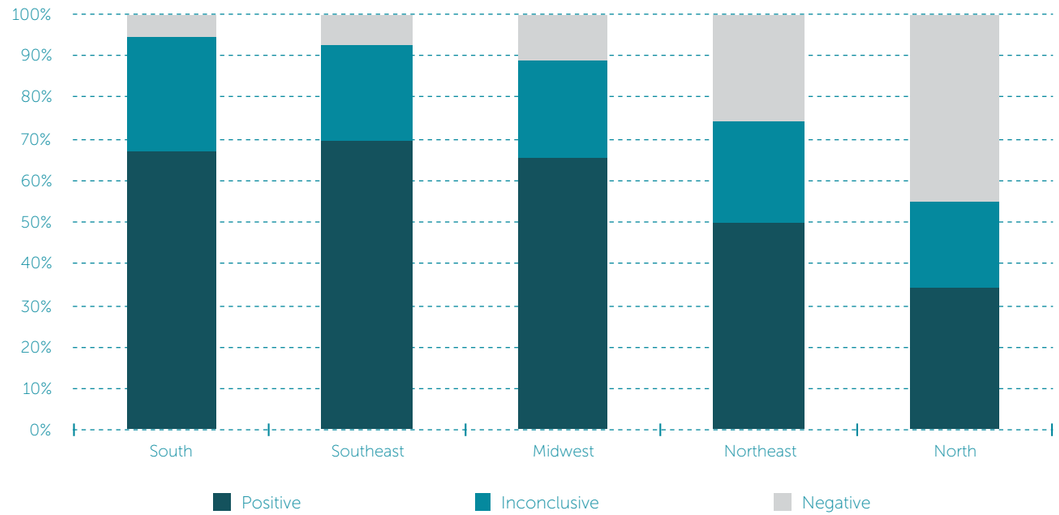
Description of genotyping results according to region of birth.

GENOTYPING RESULT	MIDWEST % (n)	NORTHEAST % (n)	NORTH % (n)	SOUTHEAST % (n)	SOUTH % (n)
Positive	65.2% (133)	49.5% (216)	34.1% (31)	69.7% (1079)	66.8% (488)
Inconclusive	23.5% (48)	24.5% (107)	20.9% (19)	22.8% (353)	27.9% (204)
Negative	11.3% (23)	25.9% (113)	45.1% (41)	7.6% (117)	5.3% (39)
TOTAL	**100% (204)**	**100% (436)**	**100% (91)**	**100% (1,549)**	**100% (731)**

Note: 93 patients did not have information on their home state .

FIGURE 13

Distribution of genotyping results according to region of birth of patients (n = 3,104).



These results indicate that the clinical diagnosis of CF may not be entirely reliable due to inadequate diagnostic tests - after all, it is unlikely that this negative population has such a large proportion of intronic mutations or other types of complex genetic mutations not identified by using the new generation sequencing method.

Analyzing the genotyping results, we observed that 50% of the cases have at least one copy of the F508del mutation, and half of them (25% of all patients) are homozygous for this mutation (Table 19, Figure 14).

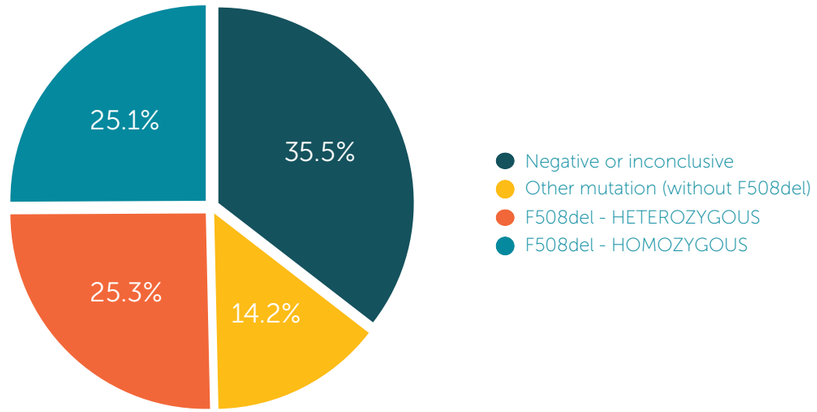
TABLE 19

Description of genotyping results for the identified mutations, focusing on the frequency of the most frequent mutation, F508del.

GENOTYPE - DESCRIPTION	n (%)
F508del - HOMOZYGOUS	778 (25.0%)
F508del - HETEROZYGOUS	784 (25.3%)
Other mutations (without F508del)	440 (14.2%)
Negative or inconclusive	1,102 (35.5%)
TOTAL NUMBER OF PATIENTS WITH GENOTYPING RESULTS	**3,104 (100%)**

FIGURE 14

Distribution of patients according to genotyping results, focusing on the frequency of the most frequent mutation, F508del (n = 3,104 patients).



Analyzing the distribution of genotype categories based on the preponderant mutation by region of origin, we observed that the proportion of homozygotes for F508del does not show substantial variation, but the proportion of heterozygous and negative/inconclusive cases is very different in the North and Northeast regions, when compared to the rest of the country. It is interesting to note that these differences can also be observed in the proportion of cases in which other genetic mutations were identified (Table 20, Figure 15).

TABLE 20

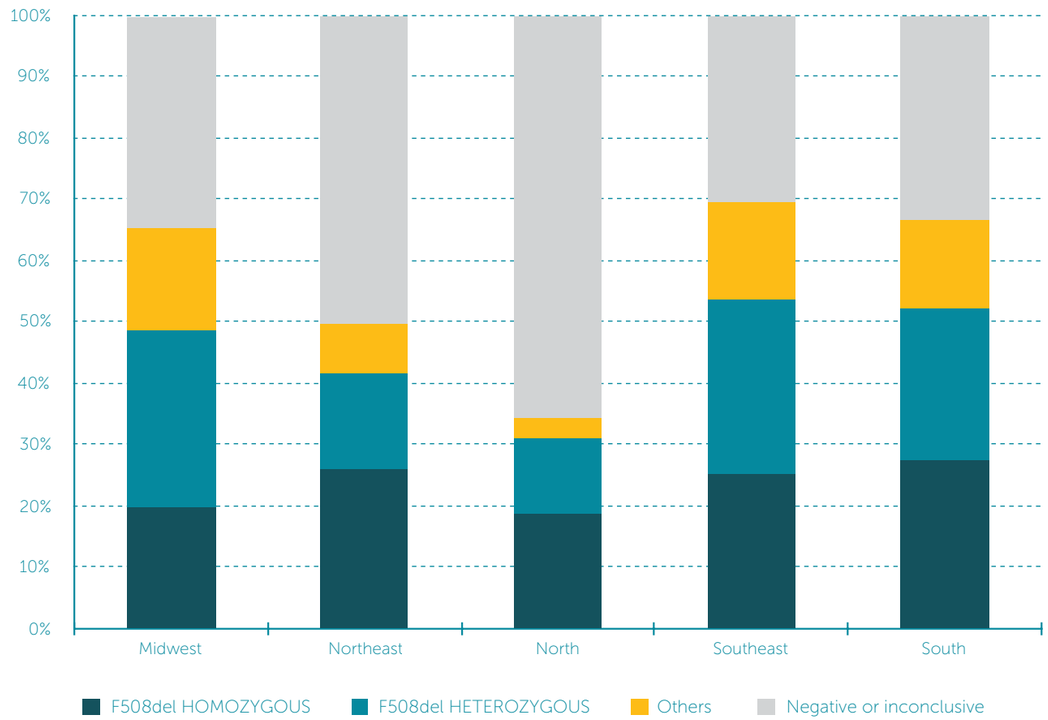
Description of genotyping results for the identified mutations, focusing on the frequency of the most frequent mutation (F508del), according to region of birth (n = 3,011 patients).

GENOTYPE CATEGORY	MIDWEST % (n)	NORTHEAST % (n)	NORTH % (n)	SOUTHEAST % (n)	SOUTH % (n)
F508del - HOMOZYGOUS	19.6% (40)	25.9% (113)	18.7% (17)	25.0% (387)	27.2% (199)
F508del - HETEROZYGOUS	28.9% (59)	15.6% (68)	12.1% (11)	28.6% (443)	25.0% (183)
Other mutations (without F508del)	16.7% (34)	8.0% (35)	3.3% (3)	16.1% (249)	14.5% (106)
Negative or inconclusive	34.8% (71)	50.5% (220)	65.9% (60)	30.3% (470)	33.2% (243)

Note: 93 patients did not have information on their home state

FIGURE 15

Distribution of patients according to genotyping results, focusing on the frequency of the most frequent mutation, F508del, according to region of birth (n = 3,104 patients).



A total of 160 mutations were identified among the patients as shown in Table 21. The percentage in relation to the total of alleles and the mutation final determination by the CFTR2 website (https://www.cftr2.org/) are also shown. Figure 16 shows the frequency distribution of the 15 most frequent mutations identified in the population of CF patients from the Registry.

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04. GENETIC DATA

TABLE 21

Description of mutations identified in the 3,104 patients who underwent genetic testing (6,208 alleles).

RANKING	MUTATION*	NUMBER OF ALLELES	% IN RELATION TO TOTAL OF ALLELES	ANNOTATION BY THE CFTR2#
1	F508del	2,854	45.97%	CF-causing
2	G542X	415	6.68%	CF-causing
3	3120+1G>A	164	2.64%	CF-causing
4	R334W	117	1.88%	CF-causing
5	R1162X	112	1.80%	CF-causing
6	G85E	101	1.63%	CF-causing
7	N1303K	79	1.27%	CF-causing
8	R1066C	58	0.93%	CF-causing
9	S4X	52	0.84%	CF-causing
10	3272-26 A>G	46	0.74%	CF-causing
11	S549R	43	0.69%	CF-causing
12	Y1092X	35	0.56%	CF-causing
13	W1282X	33	0.53%	CF-causing
14	2184delA	32	0.52%	CF-causing
14	A561E	32	0.52%	CF-causing
15	5T	26	0.42%	Varying clinical consequence
16	1812-1G>A	25	0.40%	CF-causing
16	P205S	25	0.40%	CF-causing
17	R553X	24	0.39%	CF-causing
18	2184insA	19	0.31%	CF-causing
19	1717-1G>A	18	0.29%	CF-causing
20	2789+5G>A	17	0.27%	CF-causing
20	I507del	17	0.27%	CF-causing
20	S466X	17	0.27%	CF-causing
21	711+1G>T	16	0.26%	CF-causing
22	L206W	15	0.24%	CF-causing
23	2183AA>G	14	0.23%	CF-causing
24	3849+10kbC>T	13	0.21%	CF-causing
25	A559T	12	0.19%	CF-causing
26	711+5G>A	11	0.18%	CF-causing
26	D1152H	11	0.18%	Varying clinical consequence
26	G551D	11	0.18%	CF-causing
27	1078delT	7	0.11%	CF-causing
27	c.1052C>G	7	0.11%	Missing on CFTR2
27	c.3874-1G>A	7	0.11%	Missing on CFTR2
27	CFTRdele19-21	7	0.11%	CF-causing
27	R347H	7	0.11%	CF-causing
27	R347P	7	0.11%	CF-causing
28	3120G>A	6	0.10%	CF-causing
28	621+1G>T	6	0.10%	CF-causing
28	c.1083_1084insTATGA	6	0.10%	Missing on CFTR2
28	R1066H	6	0.10%	CF-causing
28	S1255X	6	0.10%	CF-causing
29	2143delT	5	0.08%	CF-causing
29	2347delG	5	0.08%	CF-causing
29	3132delTG	5	0.08%	CF-causing
29	c.487delA	5	0.08%	Missing on CFTR2
29	L1077P	5	0.08%	CF-causing
30	124del23bp	4	0.06%	CF-causing
30	1898+3A>G	4	0.06%	CF-causing
30	2307insA	4	0.06%	CF-causing

RANKING	MUTATION*	NUMBER OF ALLELES	% IN RELATION TO TOTAL OF ALLELES	ANNOTATION BY THE CFTR2#
30	CFTRdele2,3	4	0.06%	CF-causing
30	D614G	4	0.06%	Varying clinical consequence
30	R1158X	4	0.06%	CF-causing
30	V201M	4	0.06%	Unknown meaning
30	W1089X	4	0.06%	CF-causing
31	3659delC	3	0.05%	CF-causing
31	4005+1G>A	3	0.05%	CF-causing
31	4016insT	3	0.05%	CF-causing
31	c.1399C>T	3	0.05%	Missing on CFTR2
31	c.2552G>T	3	0.05%	Missing on CFTR2
31	c.2997_3000dateAATT	3	0.05%	Missing on CFTR2
31	E92X	3	0.05%	CF-causing
31	G576A	3	0.05%	Non CF-causing
31	Q220X	3	0.05%	CF-causing
31	R117C	3	0.05%	CF-causing
31	R764X	3	0.05%	CF-causing
31	S549N	3	0.05%	CF-causing
31	Y275X	3	0.05%	CF-causing
32	1898+1G>A	2	0.03%	CF-causing
32	3791delC	2	0.03%	CF-causing
32	4428insGA	2	0.03%	CF-causing
32	541delC	2	0.03%	CF-causing
32	711+3A>G	2	0.03%	CF-causing
32	7T	2	0.03%	Non CF-causing
32	991del5	2	0.03%	CF-causing
32	A455E	2	0.03%	CF-causing
32	c.2555_2556insT	2	0.03%	Missing on CFTR2
32	c.3067_3072delATAGTG	2	0.03%	Missing on CFTR2
32	c.326A>G	2	0.03%	Missing on CFTR2
32	c.3607A>G	2	0.03%	Missing on CFTR2
32	c.3746G>A	2	0.03%	Missing on CFTR2
32	c.4333G>A	2	0.03%	Missing on CFTR2
32	c.743+1G>A	2	0.03%	Missing on CFTR2
32	c.952T>A	2	0.03%	Missing on CFTR2
32	CFTRdele17a-18	2	0.03%	CF-causing
32	CFTRdele2	2	0.03%	CF-causing
32	E585X	2	0.03%	CF-causing
32	G1244E	2	0.03%	CF-causing
32	H1054D	2	0.03%	CF-causing
32	I1234V	2	0.03%	CF-causing
32	I148T	2	0.03%	Non CF-causing
32	L997F	2	0.03%	Non CF-causing
32	M1101K	2	0.03%	CF-causing
32	Q715X	2	0.03%	CF-causing
32	R117H	2	0.03%	Varying clinical consequence
32	R75Q	2	0.03%	Non CF-causing
32	R851X	2	0.03%	CF-causing
32	S1235R	2	0.03%	Non CF-causing
32	V754M	2	0.03%	Non CF-causing
32	D1270N	2	0.04%	Varying clinical consequence
32	R74W	2	0.04%	Varying clinical consequence
33	1161delC	1	0.02%	CF-causing
33	1248+1G>A	1	0.02%	CF-causing
33	1341+1G>A	1	0.02%	CF-causing
33	1465_1466insTAAT	1	0.02%	Missing on CFTR2
33	1609delCA	1	0.02%	CF-causing

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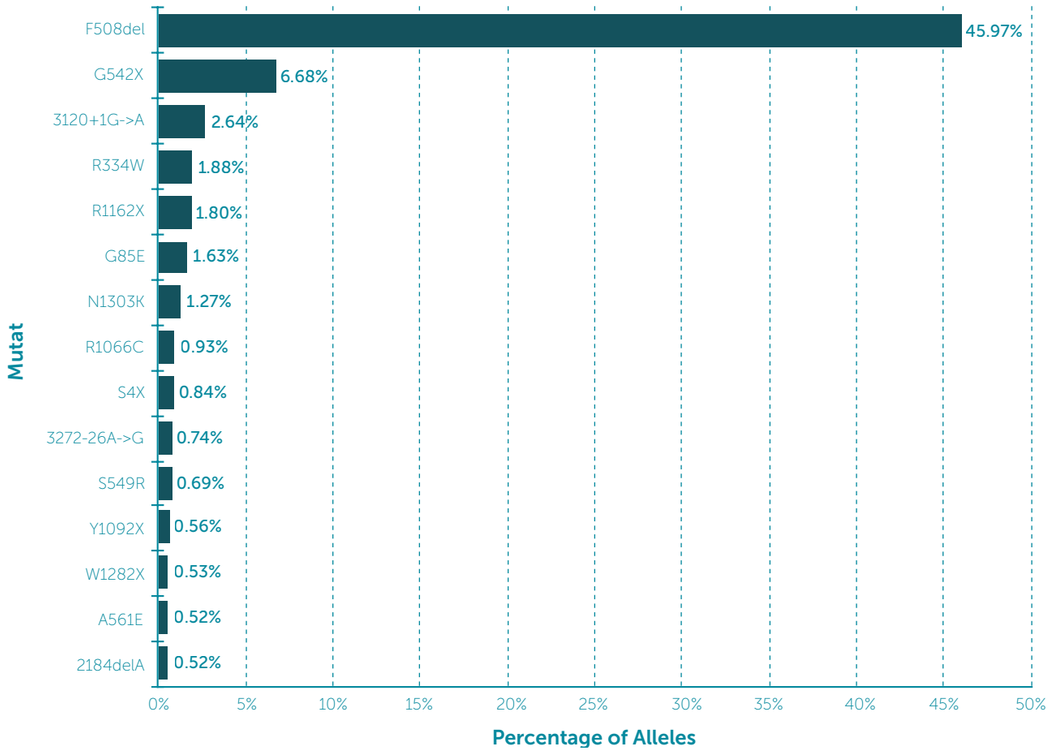
04. GENETIC DATA

RANKING	MUTATION*	NUMBER OF ALLELES	% IN RELATION TO TOTAL OF ALLELES	ANNOTATION BY THE CFTR2#
33	1717-8G>A	1	0.02%	CF-causing
33	1782delA	1	0.02%	CF-causing
33	185+1G>T	1	0.02%	CF-causing
33	2372del8	1	0.02%	CF-causing
33	2711delT	1	0.02%	CF-causing
33	2789+2insA	1	0.02%	Unknown significance
33	2869insG	1	0.02%	CF-causing
33	2942insT	1	0.02%	CF-causing
33	2991del32	1	0.02%	CF-causing
33	3121-1G>A	1	0.02%	CF-causing
33	3600+2insT	1	0.02%	CF-causing
33	3600G>A	1	0.02%	CF-causing
33	4218insT	1	0.02%	Unknown significance
33	4374+1G>T	1	0.02%	CF-causing
33	4382delA	1	0.02%	CF-causing
33	5T; TG13	1	0.02%	Varying clinical consequence
33	c.1043T>A	1	0.02%	Missing on CFTR2
33	c.1317T>G	1	0.02%	Missing on CFTR2
33	c.137C>T	1	0.02%	Missing on CFTR2
33	c.1409_1418del	1	0.02%	Missing on CFTR2
33	c.147_150delATCT	1	0.02%	Missing on CFTR2
33	c.1654C>A	1	0.02%	Missing on CFTR2
33	c.1687T>C	1	0.02%	Missing on CFTR2
33	c.2057C>A	1	0.02%	Missing on CFTR2
33	R709X	1	0.02%	CF-causing
33	R792X	1	0.02%	CF-causing
33	W1098X	1	0.02%	CF-causing
33	Y913X	1	0.02%	CF-causing
33	c.2375G>A	1	0.02%	Missing on CFTR2
33	c.241delT	1	0.02%	Missing on CFTR2
33	c.2658-2A>G	1	0.02%	Missing on CFTR2
33	c.2706C>G	1	0.02%	Missing on CFTR2
33	c.274-6T>C	1	0.02%	Missing on CFTR2
33	c.2879_2882delCTAT	1	0.02%	Missing on CFTR2
33	c.319G>C	1	0.02%	Missing on CFTR2
33	c.325T>C	1	0.02%	Missing on CFTR2
33	c.3569_3570delTT	1	0.02%	Missing on CFTR2
33	c.490-1G>T	1	0.02%	Missing on CFTR2
33	c.51delC	1	0.02%	Missing on CFTR2
33	c.675T>A	1	0.02%	Missing on CFTR2
33	D579G	1	0.02%	Varying clinical consequence
33	E831X	1	0.02%	CF-causing
33	F1052V	1	0.02%	Varying clinical consequence
33	G1069R	1	0.02%	Varying clinical consequence
33	L732X	1	0.02%	CF-causing
33	P67L	1	0.02%	CF-causing
33	Q2X	1	0.02%	CF-causing
33	Q493X	1	0.02%	CF-causing
33	Q552X	1	0.02%	CF-causing
33	Q98X	1	0.02%	CF-causing
33	R1070Q	1	0.02%	Varying clinical consequence
33	R117H-7T	1	0.02%	Varying clinical consequence
33	R668C	1	0.02%	Non CF-causing

** The names of the mutations are represented by the legacy name where available; otherwise, they are represented by the cDNA name*
 # Annotation by the CFTR2: information in the North American database CFTR2 (https://www.cftr2.org/), according to the worksheet of December 8, 2017, containing data from 89,052 patients, characterizing 374 mutations.

FIGURE 16

Frequency of the 15 most identified mutations among CF patients in REBRAFC (3,104 patients, 6,208 alleles).



In the distribution of the frequency of mutations according to region of birth, there is a decreasing frequency of the F508del mutation as it moves from the South to the North. Moreover, the frequency of the G542X mutation is higher in the South and Southeast. The 3120+1G>A mutation, which is of African origin, is more frequent in the Southeast, Midwest, and Northeast regions, which indicates high racial miscegenation in these regions.

TABLE 22

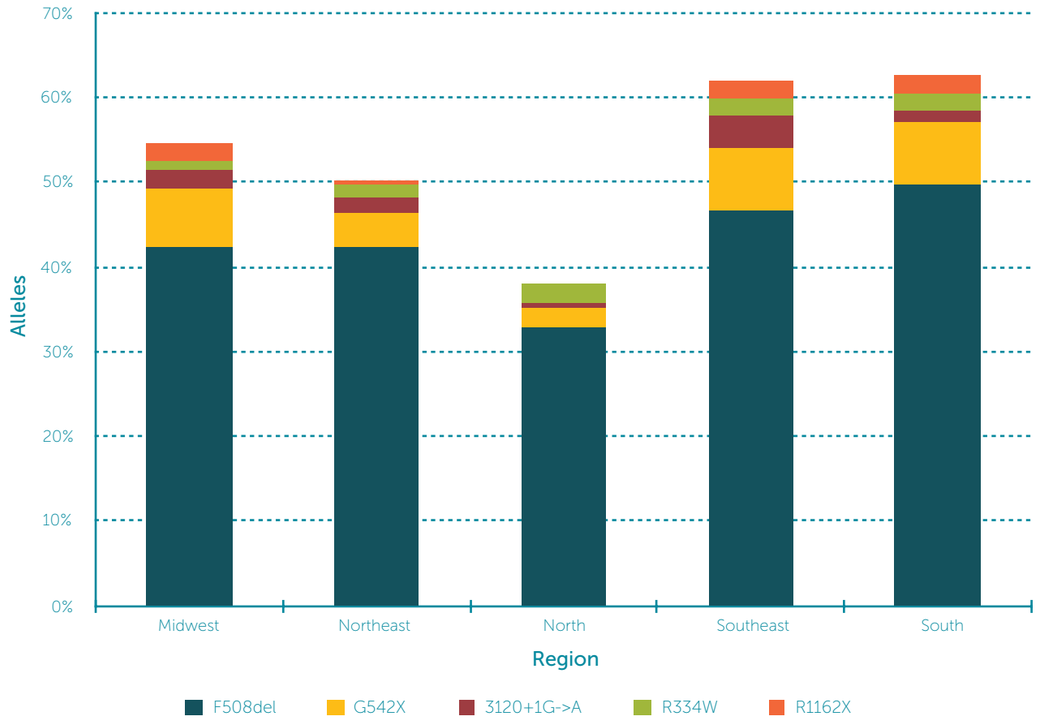
Description of the 32 most identified mutations, according to region of birth (n = 3,011 patients).

	CENTER WEST		NORTHEAST		NORTH		SOUTHEAST		SOUTH	
MUTATION	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
F508del	173	42.4%	370	42.4%	60	33.0%	1,443	46.6%	726	49.7%
G542X	28	6.9%	35	4.0%	4	2.2%	231	7.5%	110	7.5%
3120+1G->A	9	2.2%	15	1.7%	1	0.5%	115	3.7%	18	1.2%
R334W	4	1.0%	15	1.7%	4	2.2%	62	2.0%	30	2.1%
R1162X	8	2.0%	4	0.5%			64	2.1%	33	2.3%
G85E	7	1.7%	2	0.2%			74	2.4%	15	1.0%
N1303K	8	2.0%	3	0.3%	1	0.5%	29	0.9%	34	2.3%
R1066C	13	3.2%	2	0.2%	0	0.0%	37	1.2%	5	0.3%
S4X	9	2.2%	2	0.2%	2	1.1%	28	0.9%	8	0.5%
3272-26A->G	6	1.5%	12	1.4%			26	0.8%	2	0.1%
S549R	2	0.5%	6	0.7%			34	1.1%	1	0.1%
Y1092X	1	0.2%	3	0.3%			24	0.8%	7	0.5%
W1282X	3	0.7%	2	0.2%	2	1.1%	21	0.7%	5	0.3%
2184delA	4	1.0%					11	0.4%	13	0.9%
A561E			1	0.1%			25	0.8%	5	0.3%
5T	1	0.2%	7	0.8%	1	0.5%	11	0.4%	4	0.3%
1812-1G->A							14	0.5%	8	0.5%
P205S	3	0.7%	5	0.6%	1	0.5%	12	0.4%	3	0.2%
R553X	4	1.0%					15	0.5%	5	0.3%
2184insA			3	0.3%	1	0.5%	7	0.2%	8	0.5%
1717-1G->A	2	0.5%					9	0.3%	6	0.4%
2789+5G->A							6	0.2%	11	0.8%
I507del	1	0.2%	1	0.1%			9	0.3%	6	0.4%
S466X	4	1.0%	3	0.3%			7	0.2%	1	0.1%
711+1G->T	2	0.5%					10	0.3%	4	0.3%
L206W	3	0.7%	3	0.3%			6	0.2%	2	0.1%
2183AA->G	0	0.0%					10	0.3%	4	0.3%
3849+10kbC->T	1	0.2%					9	0.3%	3	0.2%
A559T			4	0.5%			4	0.1%	4	0.3%
711+5G->A							2	0.1%	8	0.5%
D1152H			5	0.6%			3	0.1%	3	0.2%
G551D							3	0.1%	7	0.5%
TOTAL OF ALLELES	**408**	**100.0%**	**872**	**100.0%**	**182**	**100.0%**	**3,098**	**100.0%**	**1,462**	**100.0%**

Note: 93 patients did not have information on their home state

FIGURE 17

Frequency of the 5 most identified mutations among patients, according to region of birth (n = 3,011 patients, 6,022 alleles)



In the analysis of the frequency of mutations according to ethnic group (defined according to IBGE, 2013), it is observed that the F508del mutation is more frequent among white individuals, and the 3120+1G>A mutation is more frequent among black individuals (Table 23).

TABLE 23

Description of frequency of the most identified mutations according to ethnic group (n = 3,104 patients).

	ETHNIC GROUP							
MUTATION	YELLOW		WHITE		MULATTO		BLACK	
F508del	5	31.3%	2,273	50.0%	456	35.1%	120	34.5%
G542X	2	12.5%	330	7.3%	65	5.0%	18	5.2%
3120+1G->A			89	2.0%	47	3.6%	28	8.0%
R334W			81	1.8%	31	2.4%	5	1.4%
R1162X			89	2.0%	18	1.4%	5	1.4%
G85E			71	1.6%	22	1.7%	8	2.3%
N1303K			72	1.6%	4	0.3%	3	0.9%
R1066C			41	0.9%	12	0.9%	5	1.4%
S4X			42	0.9%	7	0.5%	3	0.9%
3272-26A->G			33	0.7%	10	0.8%	3	0.9%
S549R			27	0.6%	13	1.0%	3	0.9%
Y1092X			29	0.6%	4	0.3%	2	0.6%
W1282X			26	0.6%	5	0.4%	2	0.6%
2184delA			28	0.6%	4	0.3%		
A561E			28	0.6%	3	0.2%	1	0.3%
5T			13	0.3%	11	0.8%	2	0.6%
1812-1G->A			20	0.4%	5	0.4%		
P205S			14	0.3%	7	0.5%	4	1.1%
R553X			21	0.5%	3	0.2%		
2184insA			14	0.3%	5	0.4%		
1717-1G->A			18	0.4%				
2789+5G->A			16	0.4%	1	0.1%		
I507del			14	0.3%	3	0.2%		
S466X			13	0.3%	4	0.3%		
711+1G->T			12	0.3%	3	0.2%	1	0.3%
L206W			9	0.2%	6	0.5%		
2183AA->G			13	0.3%	1	0.1%		
3849+10kbC->T			13	0.3%				
A559T			7	0.2%	4	0.3%	1	0.3%
711+5G->A			11	0.2%				
D1152H			8	0.2%	2	0.2%	1	0.3%
G551D			10	0.2%	1	0.1%		
TOTAL ALLELES	**14**	**100.0%**	**4,544**	**100.0%**	**1,298**	**100.0%**	**348**	**100.0%**

Note: the only indigenous individual that underwent genetic testing was negative for mutations.

Similarly, genotype categories show a higher frequency of F508del homozygotes among white individuals and a greater proportion of negative or inconclusive results among yellow and indigenous individuals (Table 24).

TABLE 24

Description of the frequency of genotype categories, focusing on the frequency of the most frequent mutation (F508del), according to ethnic group (n = 3,104 patients).

GENOTYPE CATEGORY	YELLOW		WHITE		INDIGENOUS		MULATTO		BLACK	
	n	%	n	%	n	%	n	%	n	%
F508del HOMOZYGOUS			631	27.8%			113	17.4%	34	19.5%
F508del HETEROZYGOUS	2	25%	609	26.8%			138	21.3%	35	20.1%
Others			329	14.5%			83	12.8%	28	16.1%
Negative or inconclusive	6	75%	703	30.9%	1	100%	315	48.5%	77	44.3%
TOTAL NUMBER OF PATIENTS	**8**	**100%**	**2.272**	**100%**	**1**	**100%**	**649**	**100%**	**174**	**100%**

FOLLOW-UP DATA

Only the year 2016 was considered (N = 3,212) to describe the follow-up data.

05. ANTHROPOMETRIC DATA

Anthropometric data were obtained on the day of the pulmonary function exam or the last visit of the year in situations where the pulmonary function test was not performed.

In the calculation of percentiles and Z-scores of the anthropometric data, data of the US Centers for Disease Control and Prevention (CDC) were used as a reference (available at http://www.cdc.gov/growthcharts/).

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TABLE 25

Description of patients according to anthropometric data.

WEIGHT	NCHS PERCENTILE	Z-SCORE
Mean (standard deviation)	34.24 (29.57)	-0.65 (1.22)
Median (p25; p75)	25.00 (7; 58)	-0.62 (-1.46, 0.19)
TOTAL NUMBER OF PATIENTS	**2,330**	**2,330**

HEIGHT	NCHS PERCENTILE	Z-SCORE
Mean (standard deviation)	34.41 (28.65)	-0.60 (1.13)
Median (p25; p75)	27.00 (9; 56)	-0.62 (-1.32, 0.15)
TOTAL NUMBER OF PATIENTS	**2,333**	**2,333**

BMI (KG/M2)	NCHS PERCENTILE (PATIENTS UNDER 18 YEARS OF AGE)	ABSOLUTE VALUE (PATIENTS AGED 18 YEARS OR OLDER)
Mean (standard deviation)	43.09 (31.51)	21.54 (4.22)
Median (p25; p75)	39.00 (15; 69)	22.5 (18.93; 23.32)
TOTAL NUMBER OF PATIENTS	**1,635**	**806**

p25 = 25th percentile, p75 = 75th percentile.

FIGURE 18

Evolution of median percentiles of weight, height, and BMI according to age, among patients 2-18 years of age, 2016.

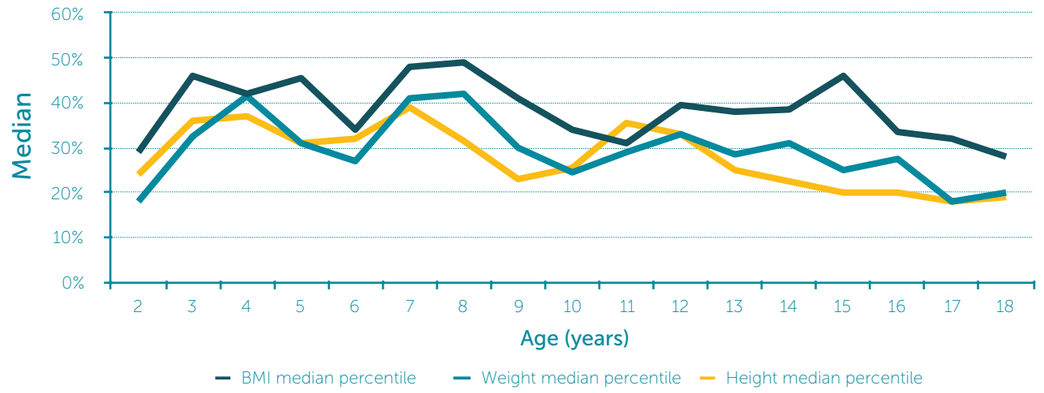


FIGURE 19

Evolution of Z-scores for weight and height according to age, among patients 2-18 years old, 2016.

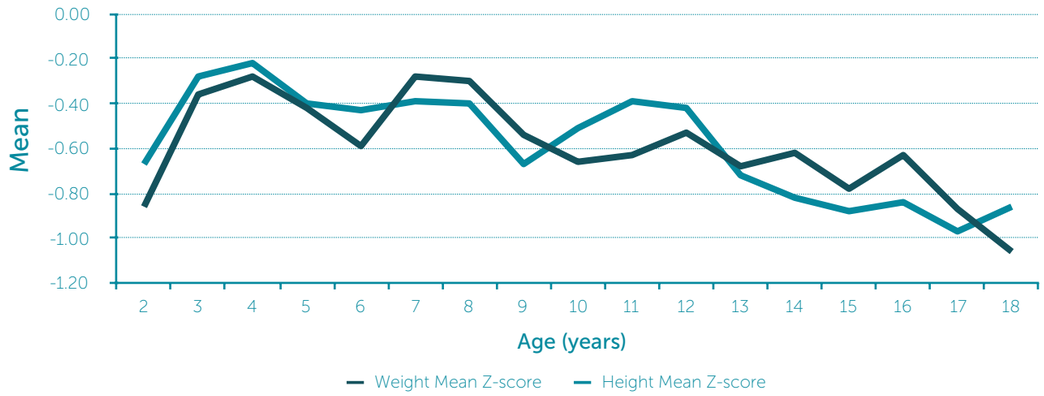
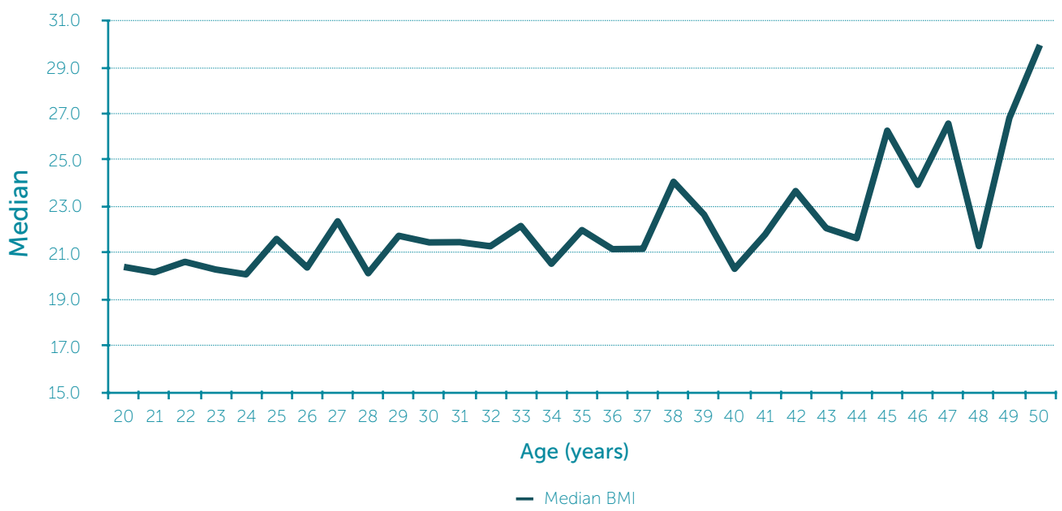


FIGURE 20

Evolution of body mass index (median BMI) according to age, among patients 20-50 years old, 2016.



06. PULMONARY FUNCTION DATA

Spirometry data were available for 1,619 patients (50.4%). In the case of patients with more than one lung function test in the year, test data with the best pulmonary function values were reported. The predicted lung function values used as reference were from Stanojevic et al., Spirometry Centile Charts for Young Caucasian Children: The Asthma UK Collaborative Initiative. American Journal of Respiratory and Critical Care Medicine 2009;180(6):547-552.

TABLE 26

Description of patients according to pulmonary function data.

Z-SCORE, FVC	
Mean (standard deviation)	-1.18 (2.25)
Median (p25; p75)	-0.97 (-2.59, 0.27)
TOTAL NUMBER OF PATIENTS	**1,562**

Z-SCORE, FEV1	
Mean (standard deviation)	-1.84 (2.32)
Median (p25; p75)	-1.67 (-3.65, -0.19)
TOTAL NUMBER OF PATIENTS	**1,562**

PERCENTAGE OF PREDICTED FVC	
Mean (standard deviation)	86.45 (26.54)
Median (p25; p75)	88.25 (69.13, 103.38)
TOTAL NUMBER OF PATIENTS	**1,562**

PERCENTAGE OF PREDICTED - FEV1	
Mean (standard deviation)	76.81 (28.87)
Median (p25; p75)	79.96 (54.58, 97.79)
TOTAL NUMBER OF PATIENTS	**1,562**

FEV1/FVC	
Mean (standard deviation)	0.77 (0.13)
Median (p25-p75)	0.79 (0.69-0.87)
TOTAL NUMBER OF PATIENTS	**1,619**

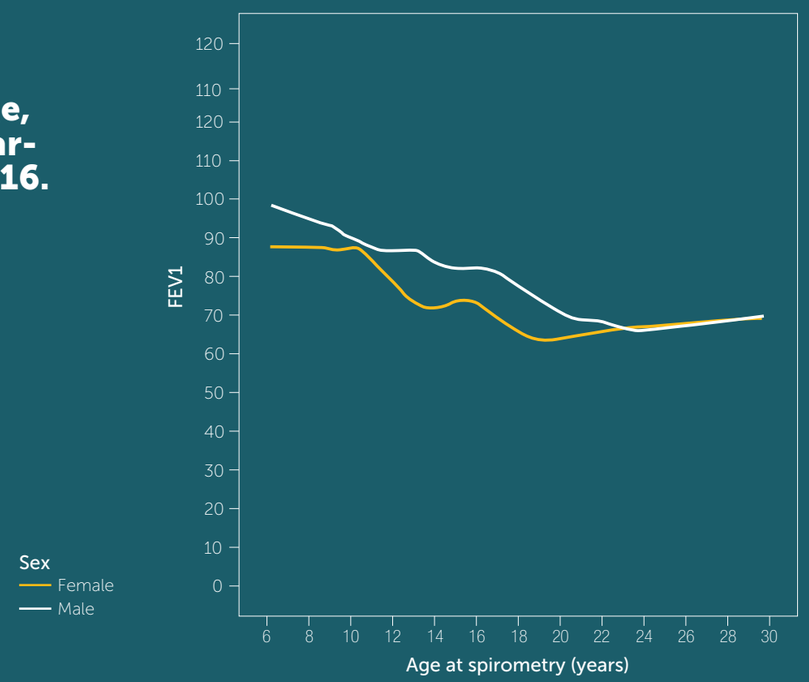
Z-SCORE - FEV1/FVC	
Mean (standard deviation)	-1.41 (1.48)
Median (p25; p75)	-1.50 (-2.49, -0.34)
TOTAL NUMBER OF PATIENTS	**1,562**

n = number of patients; p25 = 25th percentile; p75 = 75th percentile; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 second.

Analyzing the pulmonary function data by age, there is a progressive and marked decrease in the values of FEV1 according to age.

FIGURE 21

Percentage of predicted FEV1 according to age, among 6-30 year-old patients, 2016.



In the age group of 6 to 17 years, a significant proportion of patients with established functional impairment is observed (about 30% of patients with predicted FEV1 less than 70%). However, greater functional loss occurs in adults, in which about 60% of patients have a moderate or severe airflow obstruction.

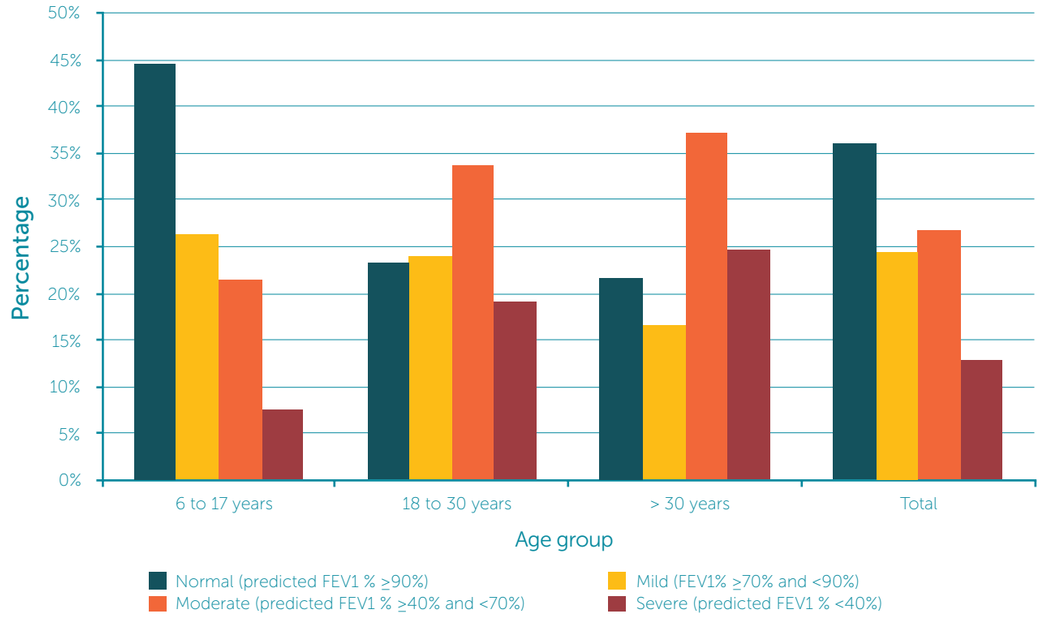
TABLE 27

Degree of airflow obstruction according with age group, 2016.

DEGREE OF AIRFLOW OBSTRUCTION	AGE GROUP			
	6 - 17 YEARS	18 - 30 YEARS	> 30 YEARS	TOTAL
Normal (predicted FEV1 % ≥90%)	422 (44.5%)	98 (23.3%)	42 (21.6%)	562 (36.0%)
Normal / mild (predicted FEV1 % ≥70% and <90%)	250 (26.4%)	101 (24.0%)	32 (16.5%)	383 (24.5%)
Moderate (predicted FEV1 % ≥40% and <70%)	204 (21.5%)	141 (33.6%)	72 (37.1%)	417 (26.7%)
Severe (predicted FEV1% <40%)	72 (7.6%)	80 (19.0%)	48 (24.7%)	200 (12.8%)
TOTAL NUMBER OF PATIENTS	**948 (100%)**	**420 (100%)**	**194 (100%)**	**1,562 (100%)**

FIGURE 22

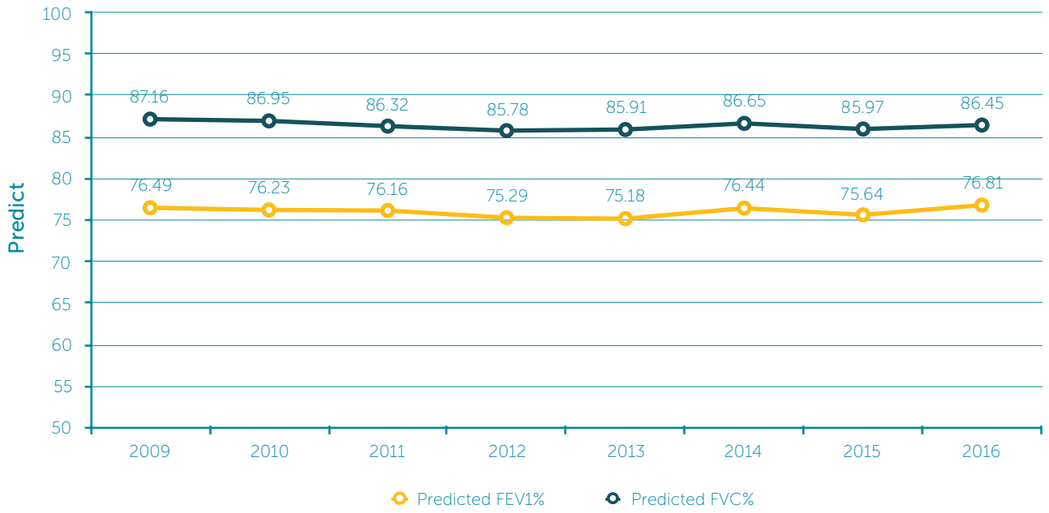
Degree of airflow obstruction according with age group, 2016.



Analyzing the evolution of pulmonary function over the years (2009 to 2016), we observed that mean values of FEV1 and FVC varied little over the years (Figure 23).

FIGURE 23

Variations in the percentages of FVC and FEV1 predicted values from 2009 to 2016.



The Brazilian Cystic Fibrosis Patient Registry 2016

06. PULMONARY FUNCTION DATA

The following graphs (Figures 24 and 25) show the relationship between nutritional indexes and lung function, both in the pediatric age group (BMI percentile x FEV1 values), and in adults (BMI value x FEV1).

FIGURE 24

FEV1 predicted percentage according with BMI percentile among patients aged 6-18 years old, 2016.

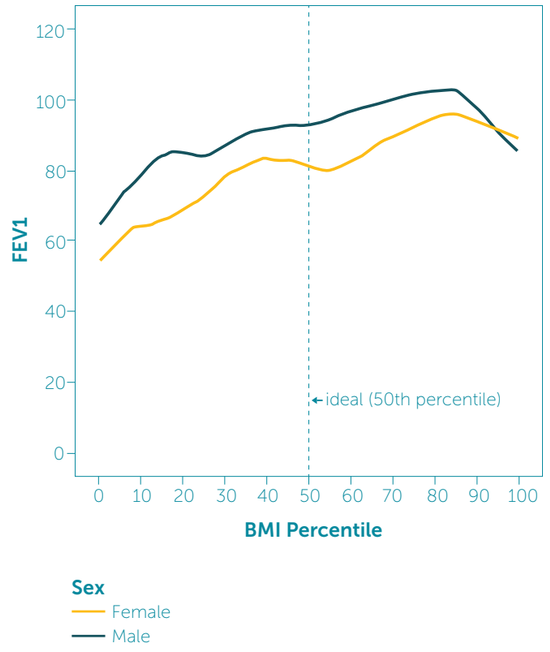
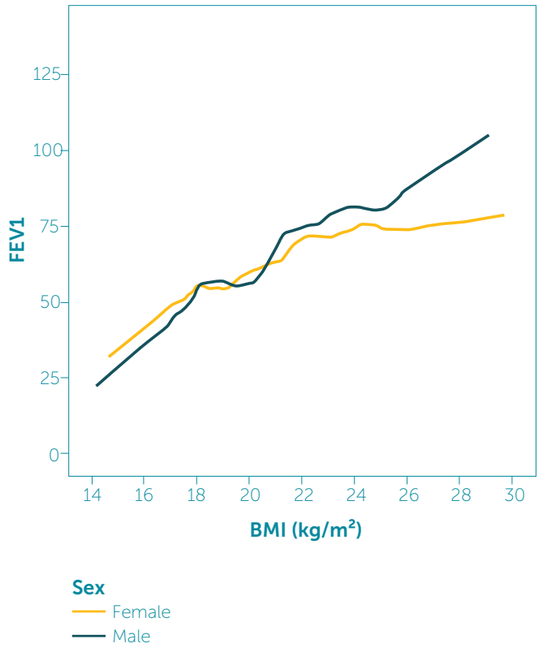


FIGURE 25

FEV1 predicted percentage according with BMI among patients aged 20-40 years old, 2016.



07. MICROBIOLOGICAL DATA

The registry includes microbiological data from patients with at least one respiratory tract culture in the year of follow-up. As there is no standardization regarding the techniques of processing and culturing of respiratory tract samples from patients with CF in Brazil, these data should be interpreted with caution.

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TABLE 28

Description of microorganisms identified in 2016.

MICROORGANISMS IDENTIFIED	n	%
Staphylococcus aureus Oxacillin-sensitive	1,937	60.3%
Pseudomonas aeruginosa	1,329	41.4%
Non-mucoid Pseudomonas aeruginosa	949	29.5%
Mucoid Pseudomonas aeruginosa	593	18.5%
Burkholderia cepacia complex	257	8.0%
Haemophilus influenzae	242	7.5%
Staphylococcus aureus Oxacillin-resistant (MRSA)	224	7.0%
Stenotrophomonas maltophilia	158	4.9%
Candida sp.	148	4.6%
Klebsiella pneumoniae	109	3.4%
Aspergillus fumigatus	95	3.0%
Achromobacter sp.	63	2.0%
Serratia sp.	52	1.6%
Other *Pseudomonas*	49	1.5%
Escherichia coli	54	1.7%
Nontuberculous mycobacteria	17	0.5%
Mycobacterium tuberculosis	8	0.2%
TOTAL NUMBER OF PATIENTS	**3,212**	**100%**

TABLE 29

Microorganisms identified according to age group.

AGE GROUP	MICROORGANISMS IDENTIFIED						
	S. aureus Oxacillin-sensitive	*P. aeruginosa*	*H. influenzae*	*B. cepacia complex*	*S. aureus Oxacillin-resistant (MRSA)*	*S. maltophilia*	n*
Up to 5 years	65.7%	35.1%	12.0%	6.5%	6.7%	5.9%	673
> 5-10	71.5%	35.7%	10.7%	7.9%	8.4%	5.9%	694
> 10-15	67.5%	39.0%	8.1%	8.3%	7.0%	5.7%	618
> 15-20	59.5%	48.6%	5.0%	10.0%	6.9%	4.0%	479
> 20-25	46.1%	45.7%	2.0%	7.1%	5.9%	3.9%	254
> 25-30	42.4%	54.7%	2.2%	12.2%	6.5%	0.7%	139
> 30-35	40.2%	55.2%	1.1%	16.1%	10.3%	4.6%	87
> 35 years	30.2%	53.3%	1.8%	4.1%	7.1%	4.7%	169

**Total: 3,113 patients (99 patients had no information on age)*

FIGURE 26

Prevalence of pathogens identified, according to age group in 2016.

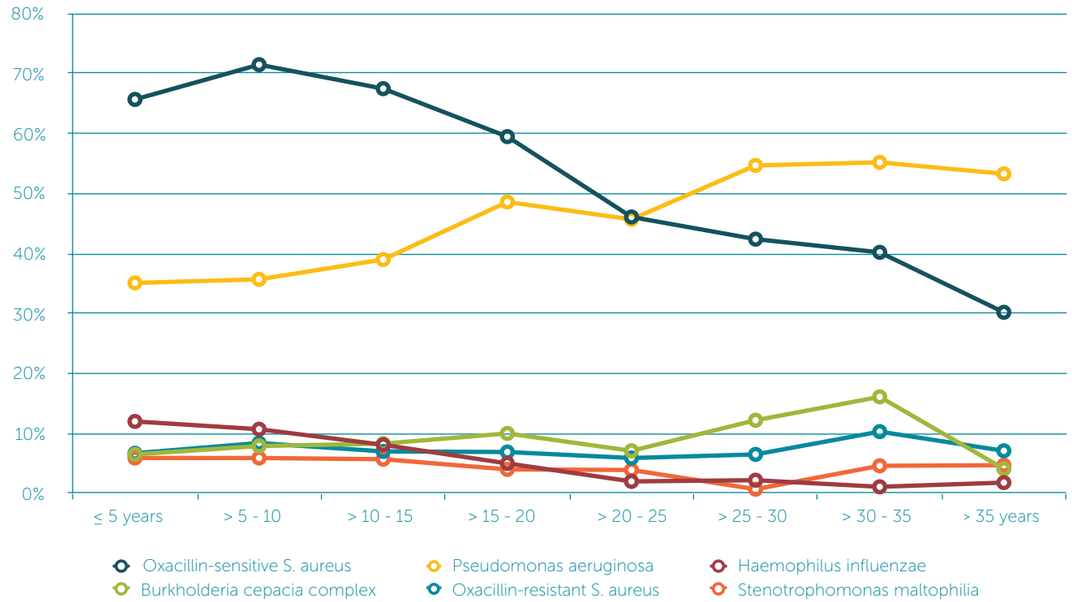
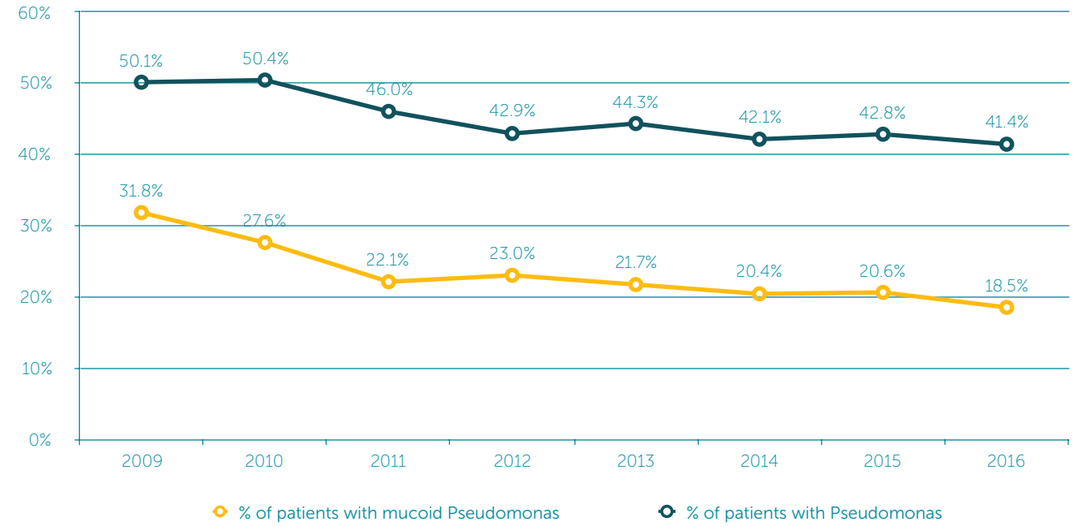


FIGURE 27

Percentage of patients with Pseudomonas aeruginosa, from 2009 to 2016.



08. CLINICAL TREATMENT DATA

In 2016, 13,507 healthcare visits were carried out, with a median of 4 encounters per patient.

FIGURE 28

Distribution of patients according to the number of healthcare visits in 2016.

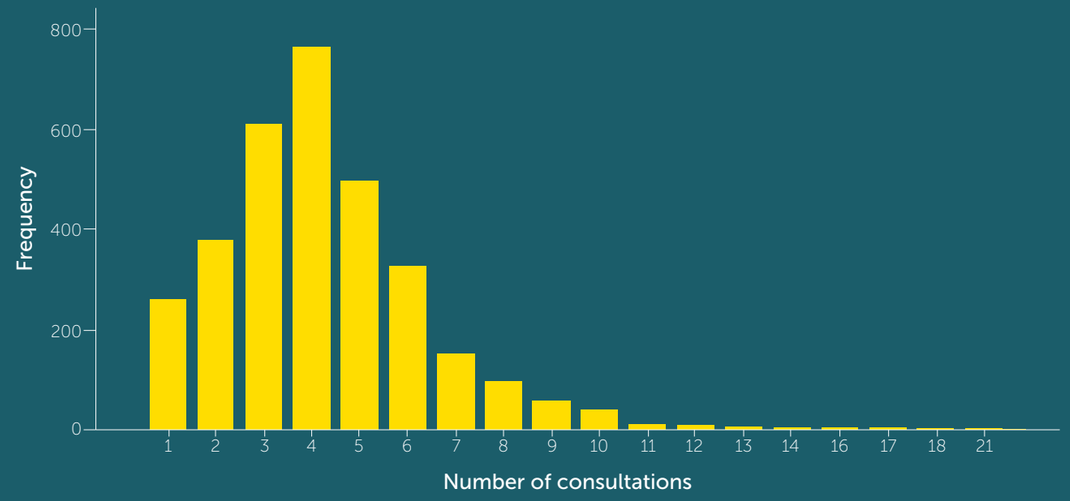


TABLE 30

Deaths

DEATH	n (%)
No	3,154 (98.2%)
Yes	58 (1.8%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

AGE AT DEATH (YEARS)	
mean (standard deviation)	18.7 (14.8)
median (p25-p75)	14.6 (9.9-24.9)
Minimum-maximum	0.6-76.59

Note: In this report and previous reports, the percentage of deaths was calculated by considering only the total number of patients followed-up in the reference year. This estimate does not represent patient survival. It should be emphasized that the adequate analysis of deaths is the one that uses median survival curves.

CAUSE OF DEATH	n	%
Respiratory Cause	47	81.0%
Transplantation complications	4	6.9%
Gastrointestinal-hepatic cause	4	6.9%
Cardiovascular cause	1	1.7%
Accidental or violent	1	1.7%
Unknown		1.7%
TOTAL	**58**	**100%**

TABLE 31

Total Shwachman-Kulczycki score according with age group (patients up to 18 years old, n = 1,727)

	AGE GROUP (YEARS)				
TOTAL SCORE	**UP TO 5**	**> 5 TO 10**	**> 10 TO 15**	**> 15 TO 18**	**TOTAL**
Severe (≤40)	2 (0.4%) -	10 (1.9%)	15 (3.2%)	11 (4.4%)	38 (2.2%)
Moderate (41-55)	11 (2.3%)	23 (4.4%)	48 (10.1%)	30 (12.0%)	112 (6.5%)
Medium (56-70)	38 (7.9%)	90 (17.2%)	91 (19.2%)	64 (25.6%)	283 (16.4%)
Good (71-85)	131 (27.3%)	174 (33.3%)	188 (39.6%)	87 (34.8%)	580 (33.6%)
Excellent (86-100)	298 (62.1%)	225 (43.1%)	133 (28.0%)	58 (23.2%)	714 (41.3%)
TOTAL NUMBER OF PATIENTS	**480 (100%)**	**522 (100%)**	**475 (100%)**	**250 (100%)**	**1,727 (100%)**

FIGURE 29

95% Confidence intervals (CI) for mean Shwachman-Kulczycki scores according with age group (patients <18 years old).

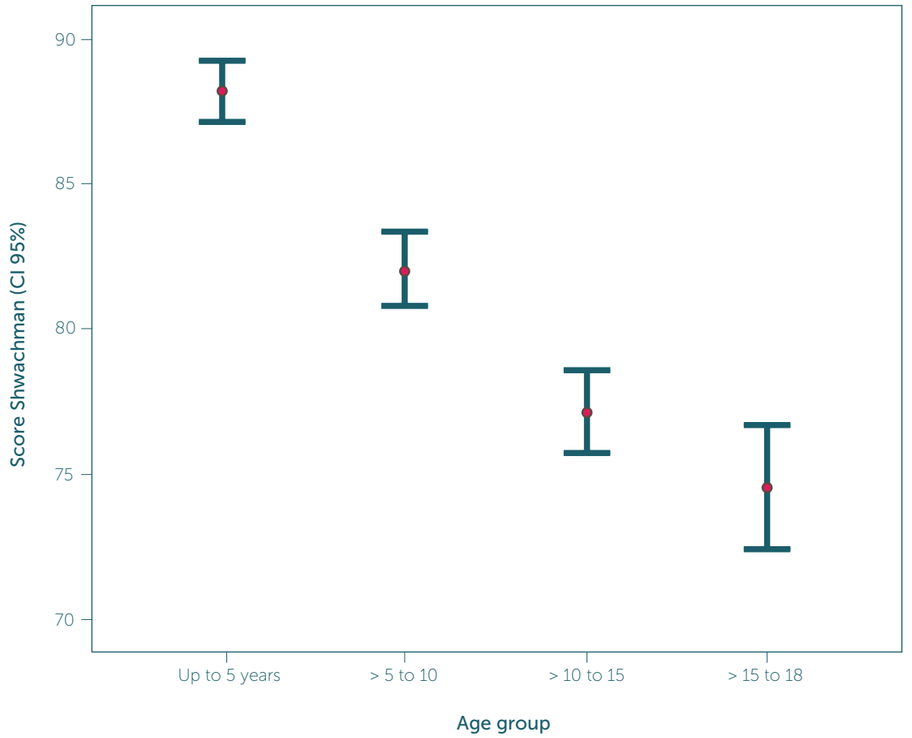


TABLE 32

Complications/Comorbidities in the previous year

COMPLICATIONS/ COMORBIDITIES IN THE PREVIOUS YEAR	n (%)
Asthma	416 (13.0%)
Evidence of hepatic impairment	273 (8.5%)
Gastroesophageal Reflux Disease	226 (7.0%)
Nasal Polyposis	187 (5.8%)
Diabetes	130 (4.1%)
Hemoptysis	129 (4.0%)
Osteopenia/Osteoporosis	98 (3.1%)
Chronic Atelectasis	80 (2.5%)
Cholelithiasis	46 (1.4%)
Allergic bronchopulmonary aspergillosis	29 (0.9%)
Pulmonary Hypertension/Cor pulmonale	28 (0.9%)
Distal Intestinal Obstruction Syndrome	27 (0.8%)
Cirrhosis with Portal Hypertension	23 (0.7%)
Pancreatitis	19 (0.6%)
Pneumothorax	16 (0.5%)
Hematemesis	3 (0.1%)
Intestinal Invagination	1 (0.1%)
Colonic stenosis	1 (0.03%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

n=número de pacientes.

TABLE 33

Transplants received

TRANSPLANTATION	n (%)
Pulmonary transplantation	40 (1.25%)
Deceased donor	37
Living donor	3
Liver transplantation	1 (0.03%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

TABLE 34

Oxygen therapy

OXYGEN THERAPY	n (%)
No	3,083 (96.0%)
Yes	129 (4.0%)
Continuous	76 (2.4%)
Nocturnal	53 (1.7%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

TABLE 35

Insulin

USE OF INSULIN	n (%)
No	3,061 (95.3%)
Yes	151 (4.7%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

TABLE 36

Inhaled therapies used by CF patients

BRONCHODILATORS	n (%)
Short-acting beta-2 agonist	1,212 (37.7%)
Long-acting beta-2 agonist	747 (23.3%)
Anticholinergic	123 (3.8%)
ANTIBIOTICS	**n (%)**
Inhaled Tobramycin 300 mg	1,188 (37.0%)
Colimycin	591 (18.4%)
Amikacin	27 (0.8%)
Gentamicin	27 (0.8%)
Injectable tobramycin	19 (0.6%)
Vancomycin	8 (0.2%)
Aztreonam	8 (0.2%)
Others	64 (2.0%)
MUCOLYTICS	**n (%)**
Dornase alfa	2,348 (73.1%)
N-acetyl Cysteine	104 (3.2%)
SALINE SOLUTIONS	**n (%)**
Saline solution 0.9%	498 (15,5%)
Hypertonic saline solution 3%	217 (6,8%)
Hypertonic saline solution 5%	207 (6,4%)
Hypertonic saline solution 7%	638 (19,9%)
TOTAL NUMBER OF PATIENTS	**3.212 (100%)**

n = number of patients.

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08. CLINICAL TREATMENT DATA

TABLE 37

Oral medications used by CF patients

	n (%)
PANCREATIC ENZYMES	**2,551 (79.4%)**
less than 5,000 U/kg/day	840 (32.9%)
5,000-10,000 U/kg/day	1465 (57.4%)
greater than 10,000 U/kg/day	223 (8.7%)
Unknown	23 (0.9%)
NUTRITION SUPPLEMENTS	**1,987 (61.9%)**
Oral	1,741 (87.6%)
Gastrostomy	70 (3.5%)
Probe	11 (0.6%)
Unknown	165 (8.3%)
Azithromycin	1.238 (38.5%)
Proton Pump Inhibitors	769 (23.9%)
Ursodeoxycholic acid	565 (17.6%)
Corticosteroid	245 (7.6%)
H2 Blockers	206 (6.4%)
Ibuprofen or other NSAIDs (Arthropathy)	14 (0.4%)
Ibuprofen (Pulmonary Disease)	4 (0.1%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

*n = number of patients. * percentages relative to enzyme doses or supplement use were calculated based on the subgroup(s) using enzymes/supplements*

TABLE 38

Intravenous treatments and hospitalizations

INTRAVENOUS TREATMENT	n (%)
Home care	131 (18.1%)
Hospital care	557 (76.9%)
Home and hospital care	36 (5.0%)
TOTAL NUMBER OF PATIENTS ON TREATMENT	**724 (100%)**

** percentage of total number of patients on treatment*

CYCLES/YEAR	
mean (standard deviation)	1.70 (1.26)
median (p25-p75)	1 (1-2)
TOTAL NUMBER OF PATIENTS	**689**

DAYS/YEAR	
mean (standard deviation)	26.84 (25.12)
median (p25-p75)	17 (14-30)
TOTAL NUMBER OF PATIENTS	**681**

CATHETER IMPLANTED	n (%)
No	3,179 (99.0%)
Yes	33 (1.0%)
TOTAL NUMBER OF PATIENTS	**3,212 (100%)**

TABLE 39

Treatment for P. aeruginosa eradication

TREATMENT FOR *P. AERUGINOSA ERADICATION*	n (%)
Yes	724 (22.5%)
No	2,488 (77.5%)
TOTAL NUMBER OF PATIENTS	**2,961 (100%)**

TABLE 40

Intravenous antibiotics: Days of hospitalization per year according to age group.

	AGE GROUP (YEARS)					
DAYS / YEAR	**UP TO 5**	**> 5 TO 10**	**>10 TO 15**	**>15 TO 20**	**>20 YEARS**	**TOTAL**
Mean (SD)	23.0 (21.8)	22.9 (17.3)	30.0 (28.0)	28.0 (23.5)	30.5 (30.7)	27.0 (25.3)
median (p25-p75)	14 (14-26)	16.5 (14-28)	19 (14-37)	21.0 (14-32)	21.0 (14-30)	18 (14-30)
TOTAL NUMBER OF PATIENTS	**123**	**118**	**131**	**127**	**163**	**662**

TABLE 41

Intravenous antibiotics used by CF patients.

DRUGS USED	n	(%)
Ceftazidime	409	12.7%
Amikacin	372	11.6%
Oxacillin	238	7.4%
Imipenem/Meropenem	173	5.4%
Sulfa-Trimethoprim	163	5.1%
Ciprofloxacin	159	5.0%
Cefepime	104	3.2%
Tobramycin	91	2.8%
Vancomycin	86	2.7%
Gentamicin	68	2.1%
Piperacillin/Tazobactam	52	1.6%
Linezolid	26	0.8%
Colimycin	21	0.7%
Cefuroxime	19	0.6%
Aztreonam	2	0.1%
Ticarcillin/Piperacillin	2	0.03%
Chloramphenicol	1	0.03%
Others	64	2.0%
TOTAL NUMBER OF PATIENTS	**3,212**	**100%**

n = number of patients.

TABLE 42

Specific data on the adult population.

	SEX		
	MALE	FEMALE	TOTAL
Azoospermia/Hypospermia *	49 (11.5%)	-	49
Pregnancy	-	15 (3.6%)	15
Oral or injectable contraceptive	-	65 (15.5%)	65
Stable relationship	69 (16.2%)	112 (26.7%)	181 (21.4%)
Employed	138 (32.4%)	100 (23.8%)	238 (28.1%)
TOTAL NUMBER OF PATIENTS AGED ≥ 18 YEARS	**426**	**420**	**846**

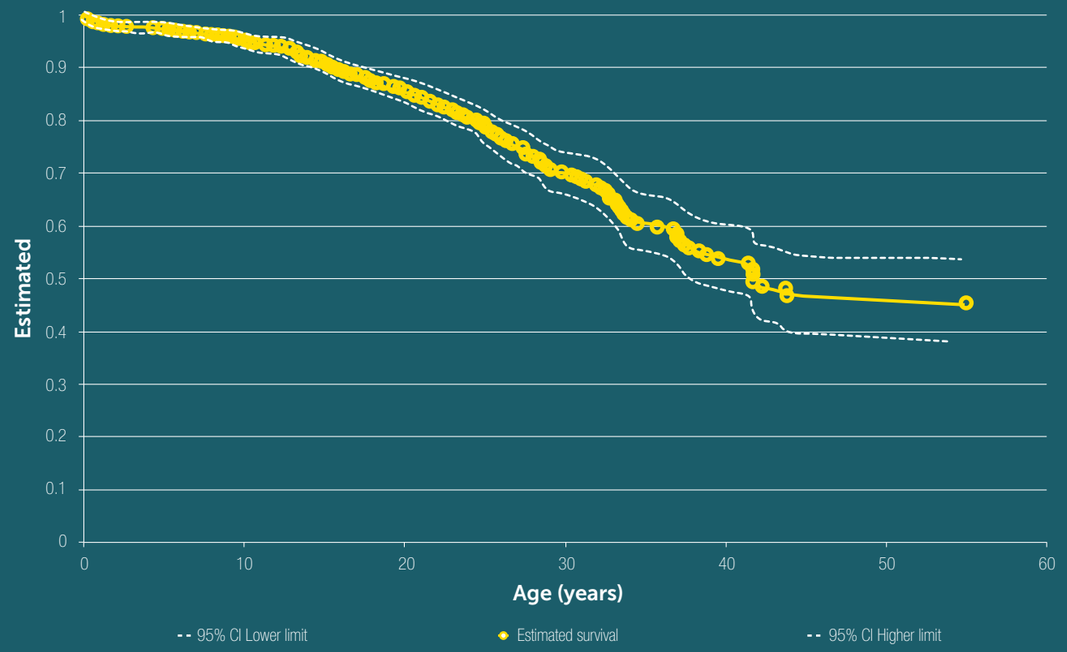
** Patients who have undergone infertility testing*

09. SURVIVAL

Between 2009 and 2016, 249 deaths were observed (5.8%). However, 10 of them were excluded from the survival analysis because they were due to unrelated causes (osteosarcoma of the femur, septicemia due to piercing use, accidental death, unknown cause, acute myocardial infarction, acute death, viral myocarditis, aspiration of foreign bodies, car accident, and violent death). Figure 26 shows the survival curve considering all patients observed during this period using the same methodology adopted by the American organization, the Cystic Fibrosis Foundation (CFF). **Median survival was 41.7 years**, with a lower limit of 37.7 years (the age at which the confidence interval crosses the line representing 50% probability of survival).

FIGURE 30

Survival curve by the Cox method for the total number of patients from 2009 to 2016.



ACKNOWLEDGMENTS

This work would not have been possible without the support of the pharmaceutical companies listed below, who financially supported the initiative in an ethical and enthusiastic manner, with no privileged data collection or marketing space in the document.

- Vertex Farmacêutica do Brasil Ltda.
- Produtos Roche Químicos e Farmacêuticos S. A.

We would also like to thank all the health professionals involved in the treatment of cystic fibrosis for their cooperation in this initiative, which we are certain will bring great benefit to Brazilian patients with cystic fibrosis

HOSPITAL	CITY	STATE	NUMBER OF FOLLOW-UPS IN 2016	DIRECTOR
PAM Codajás	Manaus	AM	1	Cláudia Mello Gonçalves
Hospital Especializado Otavio Mangabeira	Salvador	BA	146	Maria Angélica Santana
Hospital Universitario Prof. Edgard Santos	Salvador	BA	65	Edna Lúcia Santos de Souza
Hospital Infantil Albert Sabin	Fortaleza	CE	85	Cláudia de Castro e Silva
Hospital da Criança de Brasilia Jose Alencar	Brasília	DF	73	Luciana de Freitas Velloso Monte
Hospital de Base do Distrito Federal	Brasília	DF	28	Clarice Guimarães de Freitas
Hospital Infantil N Sra da Gloria	Vitória	ES	92	Roberta de Cássia Melotti
Hospital Dr Dorio Silva ES	Vitória	ES	38	Daniele Menezes Torres
Hospital das Clinicas da UFGO	Goiânia	GO	36	Lusmaia Damaceno Camargo Costa
APAE Anápolis	Anápolis	GO	29	Eliane Pereira dos Santos
Hospital Universitário Materno-Infantil de São Luis	São Luis	MA	15	Dra Denise Haidar
Centro Geral de Pediatria	Belo Horizonte	MG	160	Alberto Andrade Vergara
Hospital das Clínicas da UFMG	Belo Horizonte	MG	110	Elizabet Vilar
Hospital Julia Kubitschek	Belo Horizonte	MG	66	Marina Nishi
Hospital Universitario da UFJF	Juiz de Fora	MG	38	Marta Cristina Duarte
Hospital das Clinicas da UFMG - adultos	Belo Horizonte	MG	23	Marcelo de Fuccio
Consultorio Francisco Reis	Belo Horizonte	MG	19	Francisco José Caldeira Reis
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Hospital Universitário João de Barros Barreto	Pará	PA	140	Valéria de Carvalho Martins
Hospital Universitario Lauro Wanderley	João Pessoa	PB	1	Constantino Cartaxo
Instituto Materno Infantil de Pernambuco	Recife	PE	39	Murilo Carlos Amorim de Britto
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Hospital Pequeno Principe	Curitiba	PR	71	Paulo Kussek
Hospital das Clinicas da UFPR - Adultos	Curitiba	PR	44	Mariane Martynychen
Instituto Fernandes Figueira	Rio de Janeiro	RJ	168	Tania Wrobel Folescu
Hospital Universitario Pedro Ernesto - UERJ	Rio de Janeiro	RJ	58	Agnaldo J. Lopes
Hospital dos Servidores do Estado Rio de Janeiro	Rio de Janeiro	RJ	35	Daniela de Souza Paiva Borgli

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HOSPITAL	CITY	STATE	NUMBER OF FOLLOW-UPS IN 2016	DIRECTOR
Centro de Referencia em Fibrose Cistica do RN	Natal	RN	26	Vera Maria Dantas
Hospital de Clinicas de Porto Alegre - Adultos	Porto Alegre	RS	114	Paulo de Tarso Roth Dalcin
Hospital de Clinicas de Porto Alegre	Porto Alegre	RS	103	Paulo Cauduro Maróstica
Hospital São Lucas	Porto Alegre	RS	89	Leonardo Araújo Pinto
Santa Casa de Porto Alegre	Porto Alegre	RS	44	Gilberto Bueno Fischer
Hospital Infantil Joana de Gusmao	Florianópolis	SC	95	Norberto Ludwig Neto
Hospital Nereu Ramos	Florianópolis	SC	18	Concetta Esposito
Hospital Infantil Jeser Amarante Faria	Joinvile	SC	17	Tiago Neves Veras e Rafaela C. Benvenutti da Costa
Hospital Santa Isabel	Blumenau	SC	10	Glaunir Maria Foletto
Hospital Universitario da Univ Federal de Sergipe	Aracaju	SE	38	Daniela Gois Meneses
Santa Casa	São Paulo	SP	174	Neiva Damaceno
Instituto da Criança	São Paulo	SP	161	Joaquim Carlos Rodrigues
Unicamp	Campinas	SP	153	Antonio Fernando Ribeiro
Hospital das Clinicas da FMUSP - adultos	São Paulo	SP	108	Rodrigo Athanazio e Samia Rached
Hospital das Clinicas da USP Ribeirao Preto	Ribeirão Preto	SP	103	Lidia Alice Gomes M. M. Torres
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