German Cystic Fibrosis Register

Annual Report 2016

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Preface

PD. Dr. med. Lutz Nährlich

Medical Director
German CF Register

The introduction of the new-born screening for cystic fibrosis as of 01.09.2016 and the approval of the CFTR-Modifier Lumacaftor/Ivacaftor (20th November 2015) for F508del-homozyogous patients over 12 years of age represent important changes in the diagnosis and treatment in the year 2016. The German Cystic Fibrosis Register represents an important source of information for the evaluation of the effects on the health condition of the patients.

We are particularly looking forward to introducing the results of the data records extended since 2015/2016 in this Report. In the Microbiology section, you will find information on further relevant bacteria and chronic bacterial infections. Furthermore, we are able to throw light on a multitude of new aspects regarding accompanying illnesses and treatments. Outpatient support and exacerbations are to supplement the report over the coming years. The reference values for evaluation of the lung function have been converted within the scope of the international harmonisation by Wang and Hankinson to those of the Global Lung Initiative. In order to facilitate the comparison with previous years, we shall be presenting both analyses during a period of transition.

In this Report, the data from 5720 patients from 92 outpatient departments is presented. The proportion of adult patients lies at 56.8%, and the median age at 20 years. A CFTR genotyping

which is of importance in this era of mutation-specific treatment is available for 99.4% of all patients. Both mutations are known for 92.7%. 71% of the children and adolescents and 78% of the adults have a normal nutritional status. At the age of 16-17 years, 58% of the adolescents have a FEV1%pred of ≥80%. A chronic Pseudomonas aeruginosa infection has been found in 11.3% of the children and adolescents and 52.3% of the adults.

This would not have been possible without the trust placed in us by yourselves. In particular the extended data records represented a challenge which we have successfully mastered together. I would like to thank all the outpatient teams and patients most cordially for your assistance. I also wish to thank the AG Register, Axaris (Ms Jaumann, Mr Müller, Mr Volk) and the Data Management Team at the MH Hannover (Ms Dipl. Math. Wiese, Ms Usascheva, Ms Mamone, Ms Oey). I would especially like to extend my thanks to Mr Burkhart from the Mukoviszidose Institut (Cystic Fibrosis Institute) for his untiring work in the project management. Please continue to support the Register.

Gießen, November 2017
PD. Dr. Lutz Nährlich

Collective description

For the reporting year 2016, the progressive data records of 5720 patients have been integrated into the evaluations. A informed consent declaration of consent is available for these patients, or they died before a new consent could be obtained. Regarding the evaluation of the lung function, those patients are excluded who had a lung transplant in the year 2016 or before, and who are under 6 years old or have not had any lung function measurements, meaning that 4654 data records are available. In total, 86 values (1.5%) are missing for the evaluation of the nutritional status. Information on complications is lacking for 114 (2015:502) patients.

The progressive data records are documented once per year in the so-called stage 1 outpatient departments as the status for the entire calendar year, or aggregated from the visit-related data records from the so-called stage 2 outpatient departments. In 2016, the examination date for patients ≥ 6 years who have undergone a lung function measurement is selected as the examination time with the best FEV1%pred and the associated body measurements. In case of a missing FEV1 value, and for children under 6, the last available body measurements for the reporting year have been drawn upon. A complication occurring at least once per year or a microbiological verification determines the manifestation for the entire reporting year. If progressive data records are available from several outpatient departments, these are also aggregated according to the abovementioned rules to form a data record for the Report.

The Mortality analysis contains all those patients who died during the respective reporting year, independently of whether a progressive data record is available or not. However, those patients are excluded who withdraw their consent prior to their death. The age of the patients was calculated for patients not recorded as deceased to the end of the respective reporting year in complete years. In the case of deceased persons who died after the end of the reporting year, the age was calculated as for those still living. For those patients who died in the reporting year, the age at the time of death was calculated in complete years. In the case of deceased persons for whom no date of death has been recorded, the age has been calculated in complete years at the end of the reporting year.

The lung function was calculated and presented using the reference values acc. Wang et al (Pediatr Pulmonol 1993; 15: 793) for boys between 6-18 years and girls between 6-15 years and acc. Hankinson et al (Am Respir Crit Care Med 1999; 159:179) for men ≥ 18 years, women ≥ 16 years, and for the first time also acc. the Global Lung Initiative reference.

For the BMI, the reference study acc. the KiGGS Study (Robert-Koch Institute: Reference percentile for the anthropometric measured values and blood pressure from the study on the health of children and adolescents (KiGGS); Berlin: RKI-Hausdruckerei; 2013) was used, and for children under 4 months, the reference values acc. Kromeyer-Hauschild (Monatsschr Kinderheilkd (Paediatric Monthly Report) 2001; 149: 807) were used.

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Map of participating CF sites within Germany in 2016

Fig. 1: Map of the participating CF sites within Germany in 2016

The map shows all 92 CF sites participating in the Register in 2016. Please report to us if your CF sites is not represented: register@muko.info. The CF site in Innsbruck is participating in the quality assurance measures for the Mukoviszidose-Registers (Cystic Fibrosis Register). The data thus collected is not taken into consideration in this evaluation.

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Brief overview

	2014	2015	2016
Data status	2016-10-28	2016-10-28	2017-09-11
Participating facilities	90	90	92
Participating patients with progressive data[1]	5187	5331	5720
Age in year; median[1]	19	20	20
Proportion of adults (≥ 18 years); %[1]	55.4%	56.5%	56.8%
Male patients in %[1]	51.8%	51.8%	51.9%
New diagnoses[1,2]	135	140	162
Age for new diagnoses in years; Median[1,2]	0.59	0.62	0.5
of these, diagnosis through new-born screening	24.4%	22.4%	22.8%
Cases of death; number and % of all patients[1]	72 (1.4)	80 (1.5)	63 (1.1)
Age of death in median years; (25.-75.P)[1]	33 (25-40)	32 (24-38)	33 (23-41)
Transplantations[1,2]:	27	28	40
of these, lung transplantations	24	25	36
of these, liver transplantations	4	5	2

Table 1: Brief overview CF Germany 2016

1: The information refers to patients with progressive data and valid informed consent in the reporting year and those deceased in the reporting year (if applicable without updated declaration of consent, which has not been withdrawn.

2: The information refers to those diagnosed in the reporting year or those who had transplants

Age structure

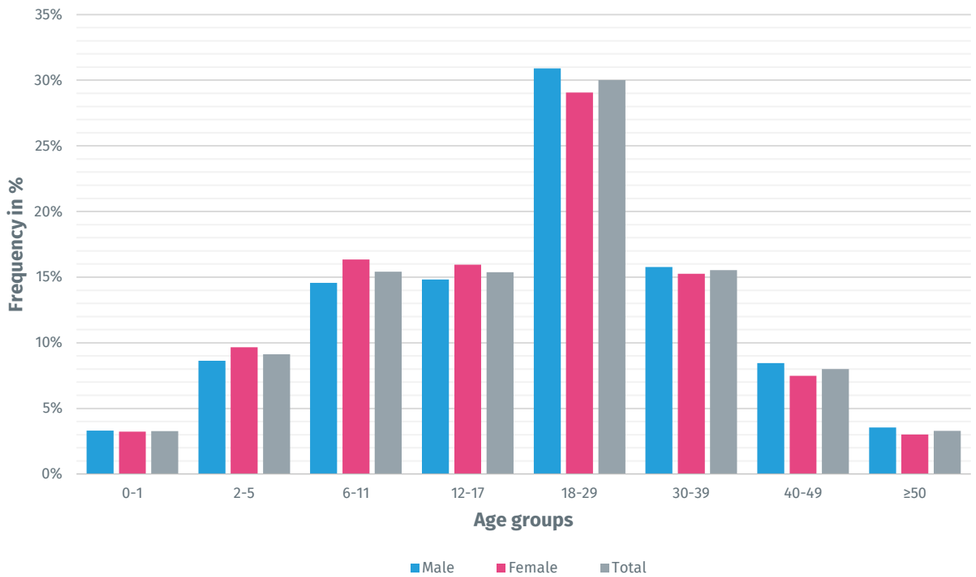

Fig. 2: Age distribution of those suffering from CF in 2016

	Male	Female	Total
Number	2967	2753	5720
Mean value [years]	22.0	21.0	21.5
Median [years]	20	19	20
Minimum [years]	0	0	0
Maximum [years]	78	74	78
Percentile 25 [years]	11	10	11
Percentile 75 [years]	31	30	30
Number < 18 years	1226	1244	2470
Number ≥ 18 years	1741	1509	3250

Table 2: Age distribution of those suffering from CF in 2016

Age structure

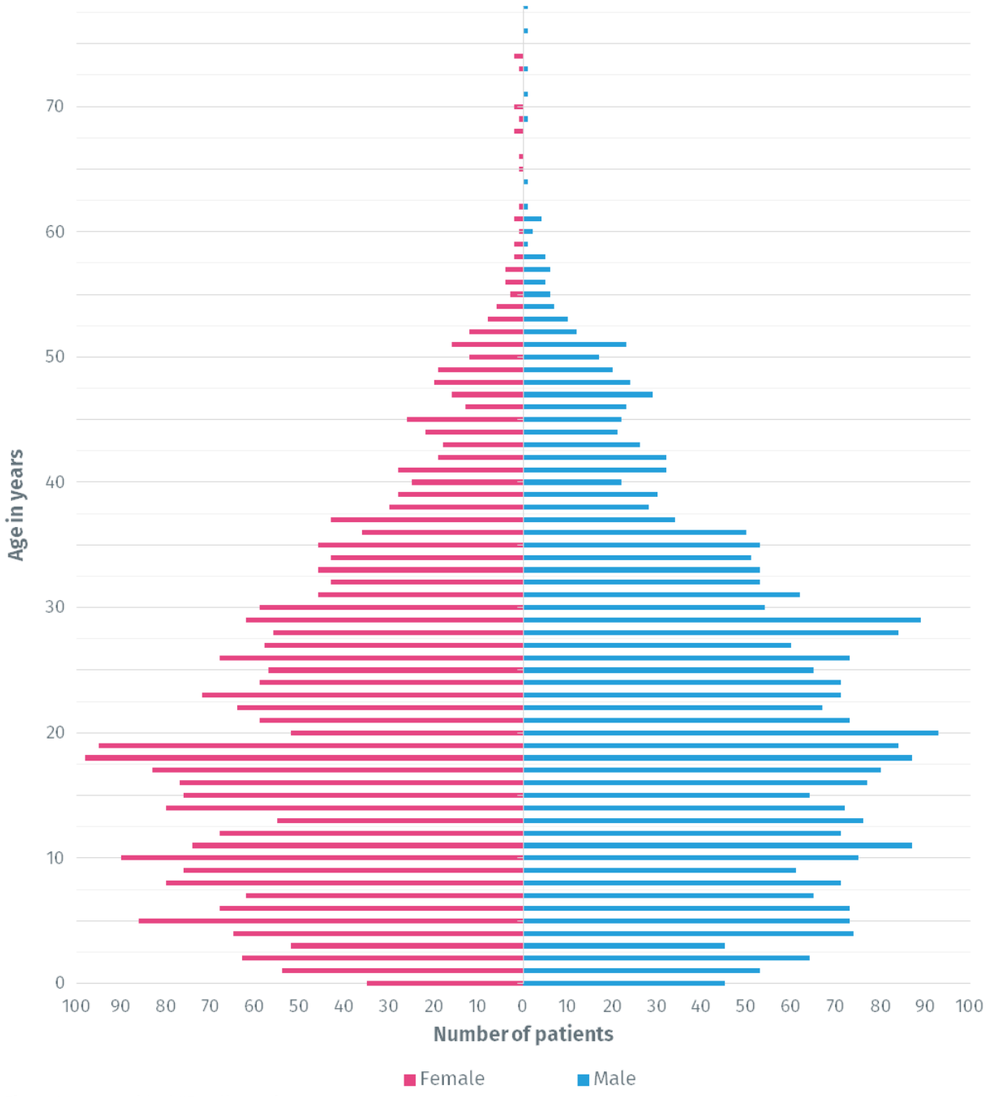

Fig. 3: Age pyramid of CF sufferers in

CF diagnosis

4a. Diagnoses in 2016

162 patients were diagnosed in the year 2016. of these, 22.8% were diagnosed via a new-born screening and 14.8% via a meconium ileus. The age distribution of the diagnosed patients is presented in the following tables:

Mean value	Median	Minimum	Maximum	Percentile 25	Percentile 75
4.69	0.50	0.00	60.92	0.08	3.83

Table 3: Age of diagnosed patients at the time of diagnosis in 2016

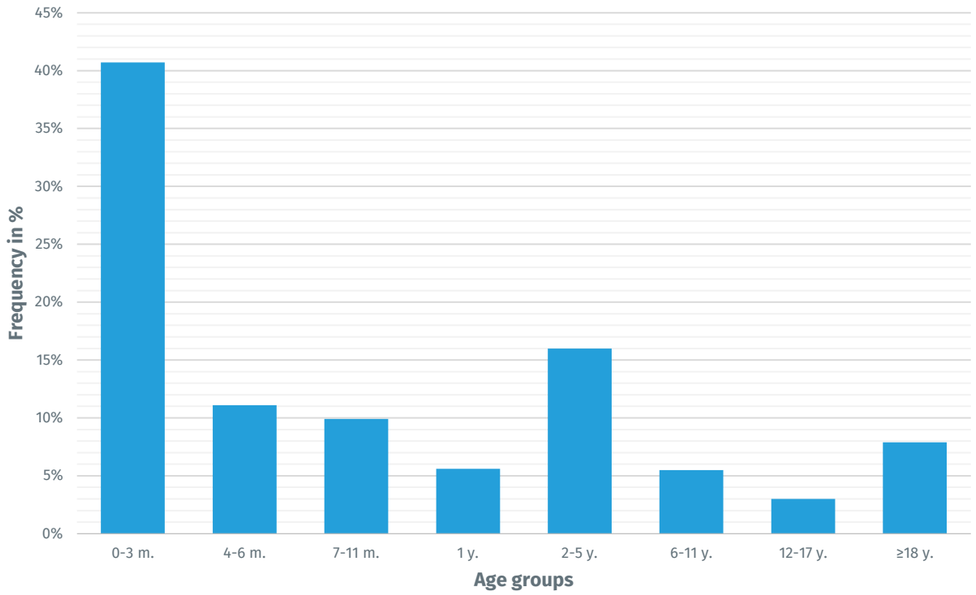

Fig. 4: Age-related frequencies in % of the diagnosed patients in 2016

CF diagnosis

4a. Diagnoses in 2016

Age on diagnosis	Frequency	Percent	Accumulated percentages
0-3 months	66	40.7	40.7
4-6 months	18	11.1	51.8
7-11 months	16	9.9	61.7
1 year	9	5.6	67.3
2-5 years	26	16.0	83.3
6-11 years	9	5.5	88.8
12-17 years	5	3.0	91.8
≥ 18 years	13	7.9	100.0
Total	162	100.0	

Table 4: Age of diagnosed patients at time of diagnosis in 2016

CF diagnosis

4b. Age at time of diagnosis

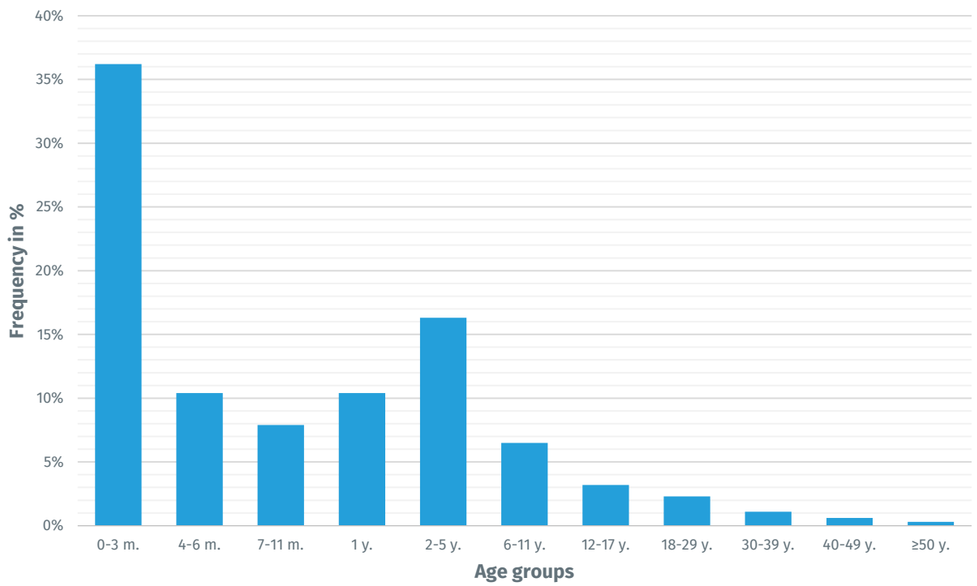

Fig. 5: Age-related frequencies in % age on diagnosis, 2016

Age on diagnosis	Frequency	Percent	Accumulated percentages
0-3 months	2061	36.2	36.2
4-6 months	593	10.4	46.6
7-11 months	451	7.9	54.5
1 year	592	10.4	64.9
2 years	374	16.3	81.2
3 years	261	6.5	87.7
4 years	166	3.2	90.9
5 years	128	2.3	93.2
6-11 years	370	1.1	94.3
12-17 years	183	0.6	94.9
≥ 18 years	252	0.3	95.2
Not known	260	4.6	100.0

Table 5: Age on diagnosis, 2016

CF diagnosis

4c. Genotyping

A genotyping is available for 5668 (99.4%) of all patients. Of the remaining cases, no genotyping has been carried out up to now for 9 (0.1%) or has been stated as unknown for a further 28 (0.5%).

	Frequency	Percent
F508del homozygous	2658	46.9
F508del heterozygous: Second mutation identified	1977	34.9
F508del heterozygous: No second mutation identified	276	4.9
No verification of F508del: Both mutations identified	619	10.9
No verification of F508del: Only one mutation identified	71	1.3
No verification of F508del: No mutations identified	67	1.2
Total	5668	100.0

Table 6: Mutation combinations 2016

The frequencies for the individual alleles are presented below, whereby only those with an absolute frequency of at least 50 are to be individually presented:

	Frequency	Percent
F508del(p.Phe508del,c.1521_1523delCTT)	7569	66.8
G542X(p.Gly542X,c.1624G>T)	223	2.0
R553X(p.Arg553X,c.1657C>T)	218	1.9
N1303K (p.Asn1303Lys ,c.3909C>G)	216	1.9
G551D(p.Gly551Asp,c.1652G>A)	206	1.8
CFTRdele2,3(p.Ser18ArgfsX16,c.54-5940_273+10250del21kb)	156	1.4
R347P(p.Arg347Pro,c.1040G>C)	148	1.3
3849+10kbC->T(No protein name,c.3717+12191C>T)	122	1.1
1717-1G->A (No protein name,c.1585-1G>A)	93	0.8
2789+5G->A (No protein name,c.2657+5G>A)	79	0.7
W1282X (p.Trp1282X ,c.3846G>A)	79	0.7
2183AA->G(p.Lys684SerfsX38 ,c.2051_2052delAAinsG)	71	0.6
R117H(p.Arg117His,c.350G>A)	50	0.4
Other mutation	1625	14.3
Unknown and/or not identified	478	4.2
Total	11333	100.0

Tabelle 7: CFTR Genotypisierung 2016

Nutritional status

5a. Nutritional status for children and adolescents under 18 years

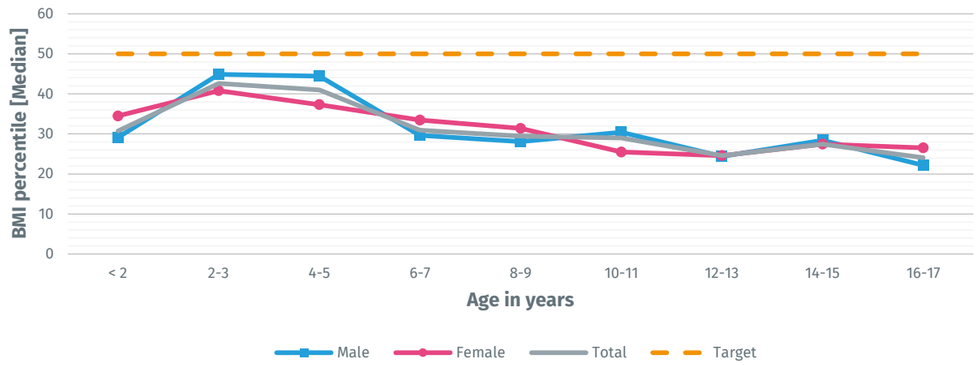

Fig. 6: Nutritional status for children and adolescents under 18 years in 2016

	All			Male			Female		
Age	N	Median	25.-75.P	N	Median	25.-75.P	N	Median	25.-75.P
< 2	193	30.7	12.0-61.8	98	29.1	10.2-59.4	95	34.5	13.4-69.1
2-3	227	42.6	15.8-70.5	110	44.9	15.8-74	117	40.8	16.2-69.6
4-5	294	41.0	18.6-64.6	141	44.4	20.5-69	153	37.3	18.6-60.4
6-7	310	30.9	17.8-51.4	160	29.7	18.4-49	150	33.4	16.1-53.1
8-9	292	29.4	14.3-51.4	134	28.1	13.5-50.8	158	31.4	16.3-51.7
10-11	321	29.0	12.3-51.2	164	30.4	12.4-54.9	157	25.5	12.1-49.1
12-13	264	24.6	9.2-47.7	144	24.4	9.2-43	120	24.6	9.3-53.9
14-15	307	27.4	10.2-46.9	138	28.4	10.3-45.5	169	27.4	10.2-48.7
16-17	362	24.1	8.7-46.6	181	22.2	8.1-47.2	181	26.5	9.5-42.9
Total	2570	30.5	12.5-54.5	1270	29.9	12.0-55.5	1300	30.7	12.6-54.1

Table 7: BMI percentile for children and adolescents under 18 years 2016 (Reference: KIGSS study or 0-3 months old, Kromeyer-Hauschild)

	Male	Female	Total
< 3rd percentile (%)	8.4	7.8	8.1
< 15th percentile (%)	29.9	29.0	29.5
≥ 50th percentile (%)	28.7	29.0	28.9

Table 8: Nutritional status for children and adolescents under 18 years: BMI percentile <3, <15 & ≥50; 2016

Nutritional status

5b. Nutritional status for adults from 18 years:

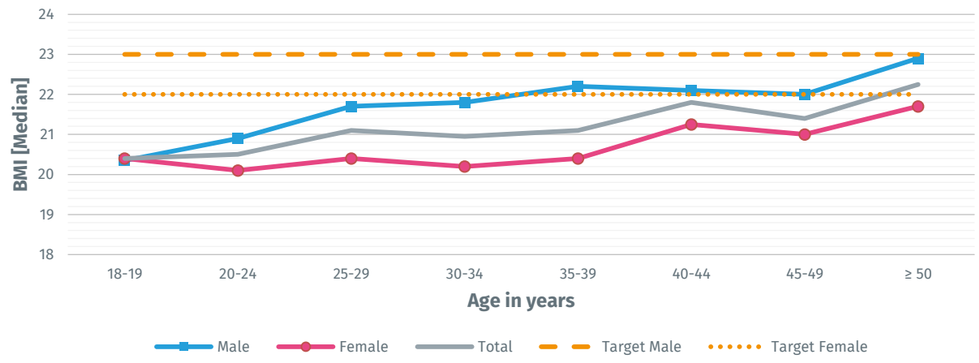

Fig. 7: Nutritional status for adults from 18 years 2016

	All			Male			Female		
Age	N	Median	25.-75.P	N	Median	25.-75.P	N	Median	25.-75.P
18-19	312	20.4	18.7-22.2	160	20.4	18.4-22.3	152	20.4	18.9-22.2
20-24	643	20.5	18.6-22.5	344	20.9	18.7-22.9	299	20.1	18.5-22.1
25-29	669	21.1	19.2-23.3	360	21.7	19.9-23.8	309	20.4	18.7-22.6
30-34	476	21.0	19.4-23.1	260	21.8	20-24.1	216	20.2	18.9-22.1
35-39	349	21.1	19.3-23.5	176	22.2	19.9-24.3	173	20.4	18.9-22.2
40-44	243	21.8	19.9-23.5	135	22.1	20.1-23.7	108	21.3	19.8-23.1
45-49	200	21.4	20.0-24.0	111	22.0	20.4-24.6	89	21.0	19.8-22.6
≥ 50	172	22.3	19.9-24.7	94	22.9	20.9-24.7	78	21.7	19.5-24.5
Total	3064	21.1	19.2-23.2	1640	21.6	19.6-23.8	1424	20.4	18.9-22.4

Table 9: BMI for adults from 18 years in 2016

	Male	Female	Total
< 18.5 kg/m² (%)	13.3	19.7	16.3
< 19 kg/m² (%)	19.0	25.4	22.0
≥ 22 kg/m² (%)	---	29.7	29.7
≥ 23 kg/m² (%)	32.9	---	32.9

Table 10: Nutritional status for adults: BMI < 18.5 kg/m2, < 19 kg/m2 nd target BMI 2016

Lung function FEV1%

Wang & Hankinsonvs. GLI 2016 (without lung transplant)

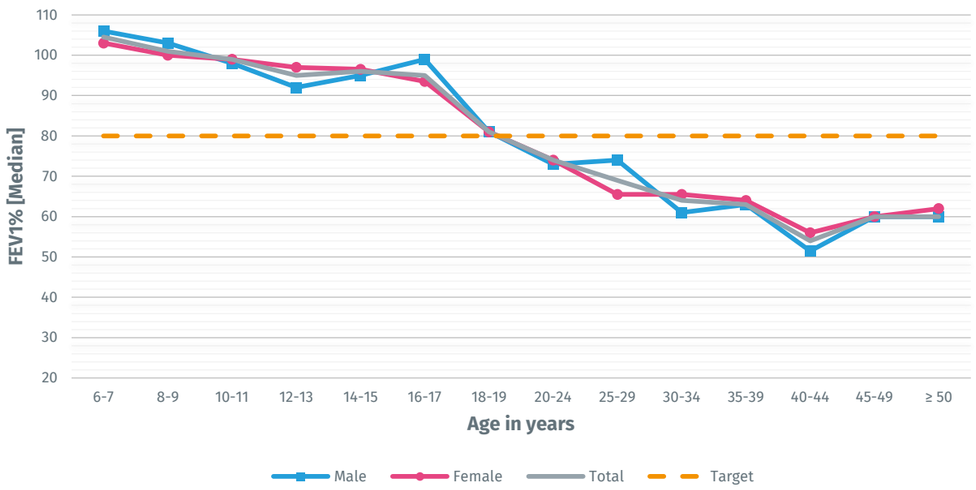

Fig. 8: FEV1% value acc. Wang and Hankinson 2016

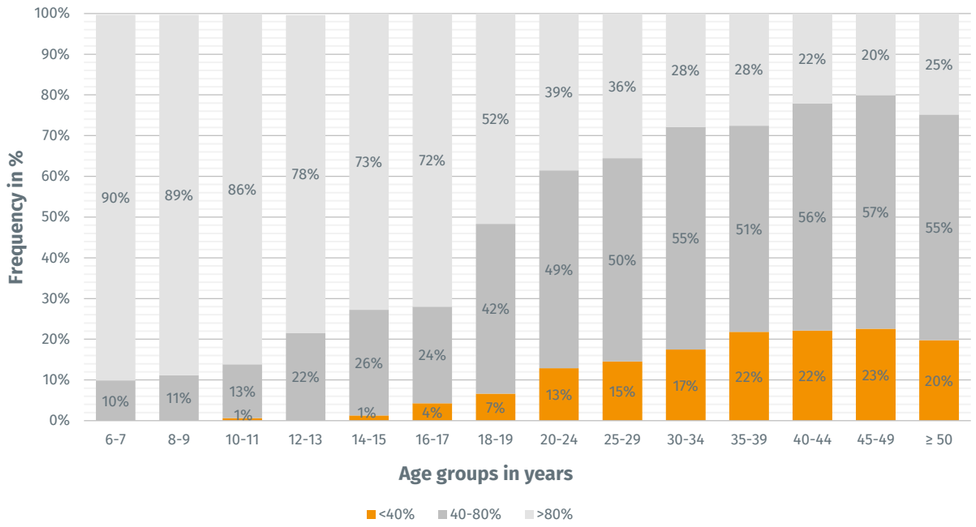

Fig. 9: Age-related frequencies of the degrees of severity of the FEV1% (categories >80%, 40-80% &< 40%) 2016 acc. Wang und Hankinson

Lung function FEV1%

Wang & Hankinsonvs. GLI 2016 (without lung transplant)

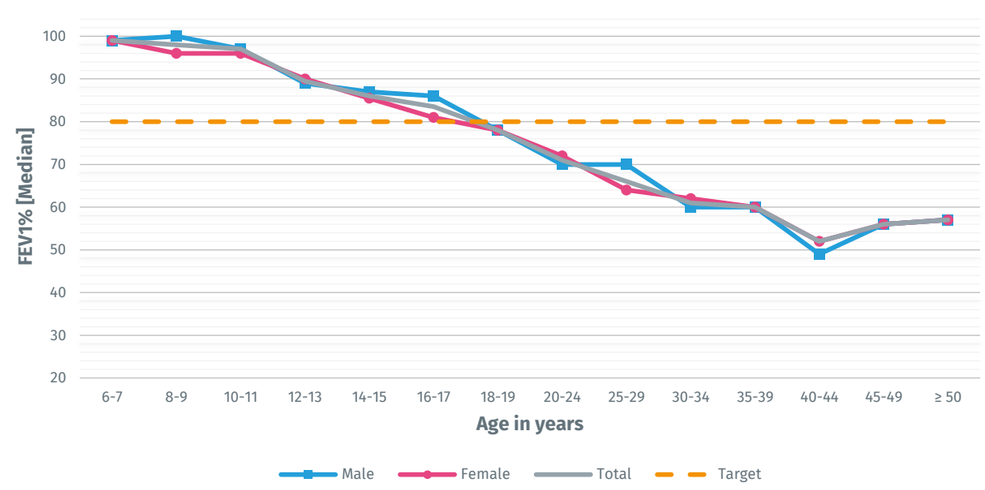

Fig. 10: FEV1% value acc. Global Lung Initiative 2016

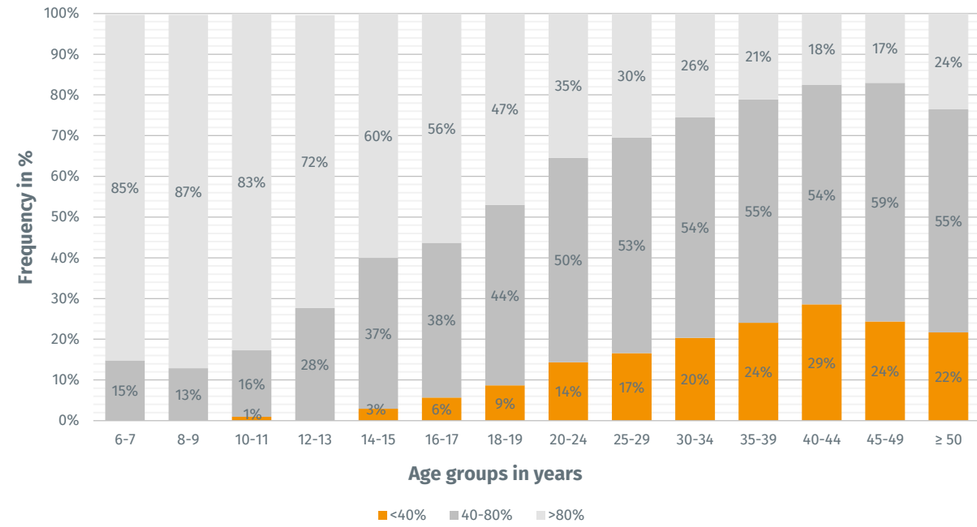

Fig. 11: Age-related frequencies of the degrees of severity of the FEV1% (categories >80%, 40-80% &< 40%) 2016 acc. Global Lung Initiative

Lung function FEV1%

Wang & Hankinsonvs. GLI 2016 (without lung transplant)

	All			Male			Female		
Age	N	Median	25.-75.P	N	Median	25.-75.P	N	Median	25.-75.P
6-7	304	105	95-114	159	106	96-115	145	103	94-113
8-9	287	101	91-110	131	103	91-111	156	100	90-110
10-11	318	99	87-108	159	98	86-107	159	99	87-110
12-13	264	95	83-104	145	92	83-101	119	97	82-105
14-15	305	96	79-108	139	95	81-106	166	97	75-110
16-17	350	95	78-110	174	99	84-110	176	94	74-110
18-19	300	81	64-99	154	81	66-101	146	81	61-98
20-24	620	74	51-93	335	73	51-92	285	74	52-94
25-29	633	69	49-88	351	74	54-90	282	66	45-86
30-34	423	64	25-76	233	61	25-76	190	66	25-76
35-39	312	63	43-82	161	63	40-85	151	64	44-81
40-44	217	54	41-74	124	52	40-74	93	56	42-76
45-49	164	60	42-77	91	60	40-79	73	60	48-75
≥ 50	157	60	45-79	86	60	39-81	71	62	49-79
Total	4654	83	58-101	2442	83	57-101	2212	82	59-101

Table 11: FEV1% value acc. Wang and Hankinson 2016

Lung function FEV1%

Wang & Hankinsonvs. GLI 2016 (without lung transplant)

	All			Male			Female		
Age	N	Median	25.-75.P	N	Median	25.-75.P	N	Median	25.-75.P
6-7	304	99	89-108	159	99	90-109	145	99	88-107
8-9	287	98	88-106	131	100	88-108	156	96	88-105
10-11	318	97	85-104	159	97	86-105	159	96	84-104
12-13	264	90	79-98	145	89	80-99	119	90	75-96
14-15	305	86	71-98	139	87	73-99	166	86	65-97
16-17	350	84	67-96	174	86	71-97	176	81	63-93
18-19	300	78	62-95	154	78	63-96	146	78	58-93
20-24	620	71	50-90	335	70	49-90	285	72	50-90
25-29	633	66	47-85	351	70	51-86	282	64	43-83
30-34	423	61	25-76	233	60	25-76	190	62	25-76
35-39	312	60	40-78	161	60	39-81	151	60	42-76
40-44	217	52	38-70	124	49	38-70	93	52	39-72
45-49	164	56	40-73	91	56	37-75	73	56	45-70
≥ 50	157	57	43-75	86	57	37-78	71	57	46-74
Total	4654	78	54-95	2442	79	54-96	2212	77	55-95

Table 12: FEV1% value acc. Global Lung Initiative 2016

Lung infections
(without lung transplant)

7a. Annual verification at least once

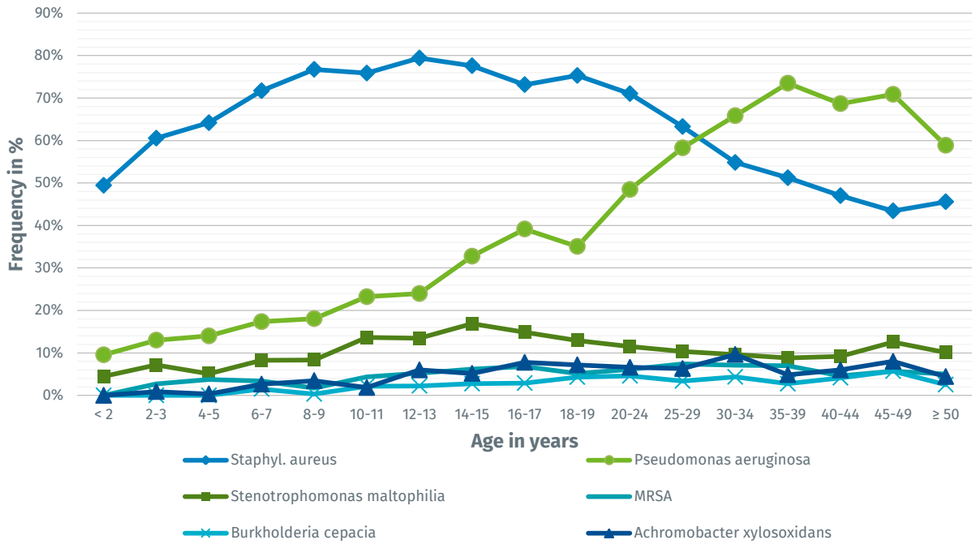

Fig. 12: Age-related frequency in % of patients with bacterial verification occurring at least once, 2016

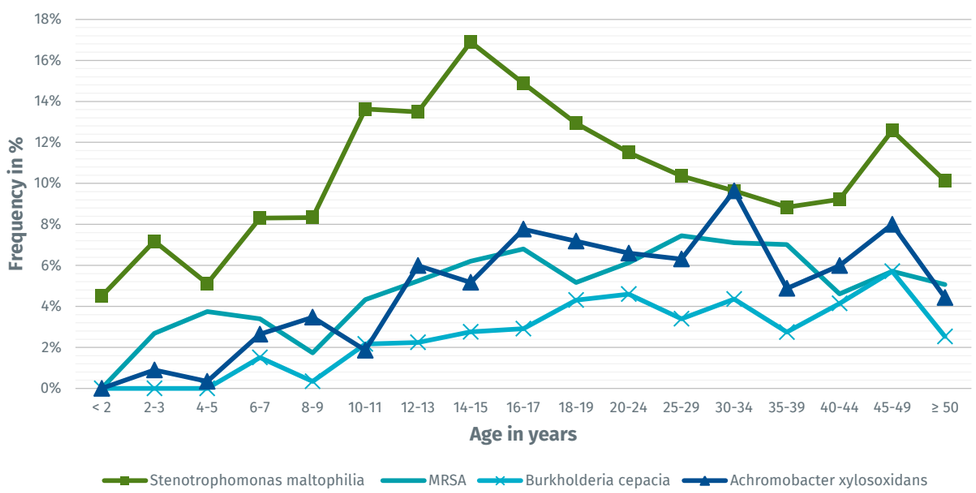

Fig. 13: Age-related frequency in % of patients with bacterial verification occurring at least once, without Pseudomonas aeruginose and Staphylococcus aureus 2016

Lung infections
(without lung transplant)

7a. Annual verification at least once

Age of patients	Staph. aureus	MRSA	Pseudomonas aeruginosa	Burkholderia cepacia	Stenotrophomonas maltophilia	Achromobacter xylosoxidans
< 2	49.4	0.0	9.6	0.0	4.5	0.0
2-3	60.5	2.7	13.0	0.0	7.2	0.9
4-5	64.2	3.8	14.0	0.0	5.1	0.3
6-7	71.7	3.4	17.4	1.5	8.3	2.6
8-9	76.7	1.7	18.1	0.3	8.3	3.5
10-11	75.9	4.3	23.2	2.2	13.6	1.9
12-13	79.4	5.2	24.0	2.2	13.5	6.0
14-15	77.6	6.2	32.8	2.8	16.9	5.2
16-17	73.1	6.8	39.2	2.9	14.9	7.8
18-19	75.3	5.2	35.1	4.3	12.9	7.2
20-24	71.0	6.1	48.5	4.6	11.5	6.6
25-29	63.3	7.4	58.3	3.4	10.4	6.3
30-34	54.8	7.1	65.8	4.4	9.6	9.6
35-39	51.2	7.0	73.5	2.7	8.8	4.9
40-44	47.0	4.6	68.7	4.1	9.2	6.0
45-49	43.4	5.7	70.9	5.7	12.6	8.0
≥ 50	45.6	5.1	58.9	2.5	10.1	4.4
Total	65.3	5.3	41.6	2.8	10.7	5.2
< 18 years	71.0	4.0	22.2	1.4	10.7	3.3
≥ 18 years	60.5	6.3	57.7	4.0	10.7	6.8

Table 13: Frequency in % of patients with bacterial verification occurring at least once, 2016

Lung infections
(without lung transplant)

7b. Chronic lung infection

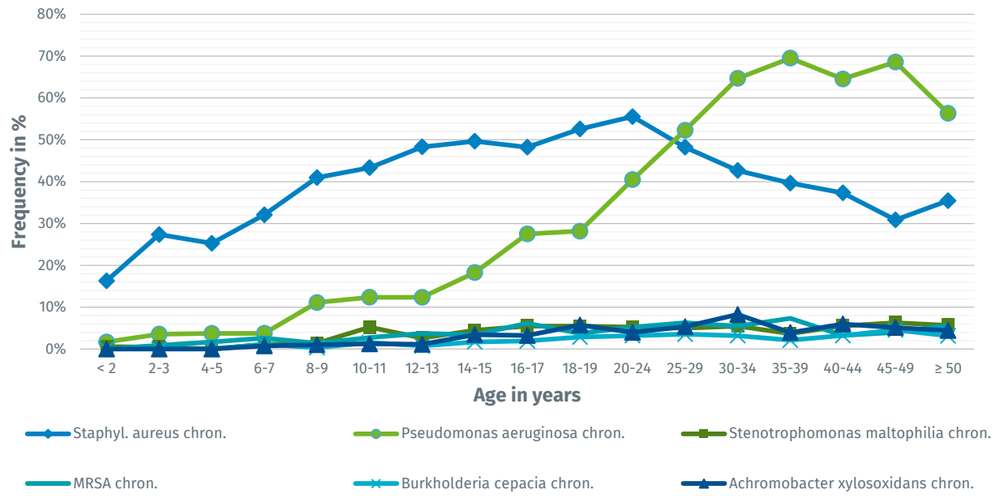

Fig. 14: Age-related frequency in % of chronic lung infections, 2016

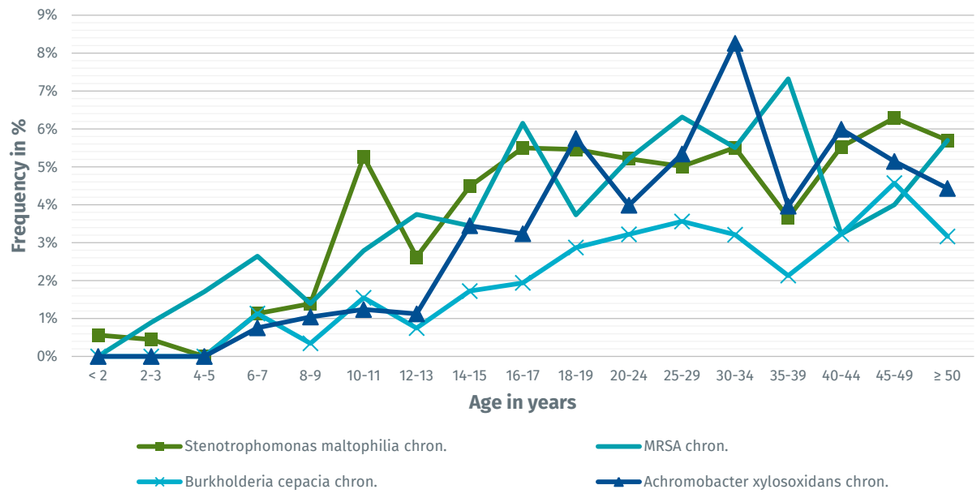

Fig. 15: Age-related frequency in % of chronic lung infections without Pseudomonas aeruginose and Staphylococcus aureus 2016

Lung infections
(without lung transplant)

7b. Chronic lung infection

Age of patients	Staph. aureus	MRSA	Pseudomonas aeruginosa	Burkholderia cepacia	Stenotrophomonas maltophilia	Achromobacter xylosoxidans
< 2	16.3	0.0	1.7	0.0	0.6	0.0
2-3	27.4	0.9	3.6	0.0	0.4	0.0
4-5	25.3	1.7	3.8	0.0	0.0	0.0
6-7	32.1	2.6	3.8	1.1	1.1	0.8
8-9	41.0	1.4	11.1	0.3	1.4	1.0
10-11	43.3	2.8	12.4	1.5	5.3	1.2
12-13	48.3	3.7	12.4	0.7	2.6	1.1
14-15	49.7	3.4	18.3	1.7	4.5	3.4
16-17	48.2	6.1	27.5	1.9	5.5	3.2
18-19	52.6	3.7	28.2	2.9	5.5	5.7
20-24	55.5	5.2	40.5	3.2	5.2	4.0
25-29	48.2	6.3	52.3	3.6	5.0	5.3
30-34	42.7	5.5	64.7	3.2	5.5	8.3
35-39	39.6	7.3	69.5	2.1	3.7	4.0
40-44	37.3	3.2	64.5	3.2	5.5	6.0
45-49	30.9	4.0	68.6	4.6	6.3	5.1
≥ 50	35.4	5.7	56.3	3.2	5.7	4.4
Total	42.5	4.2	33.9	2.2	4.0	3.5
< 18 years	38.1	2.7	11.3	0.9	2.6	1.3
≥ 18 years	46.0	5.7	52.7	3.2	5.2	5.4

Table 14: Frequency in % of patients with a chronic lung infection, 2016

Lung infections
(without lung transplant)

7c. Atypical mycobacteria (at least once in the reporting year)

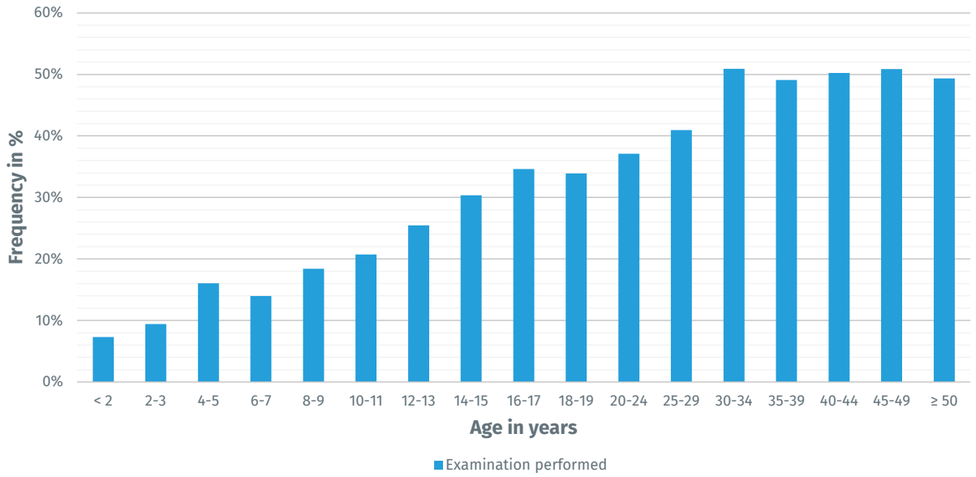

Fig. 16: Age-related frequency in % of examinations conducted, atypical mycobacteria, 2016

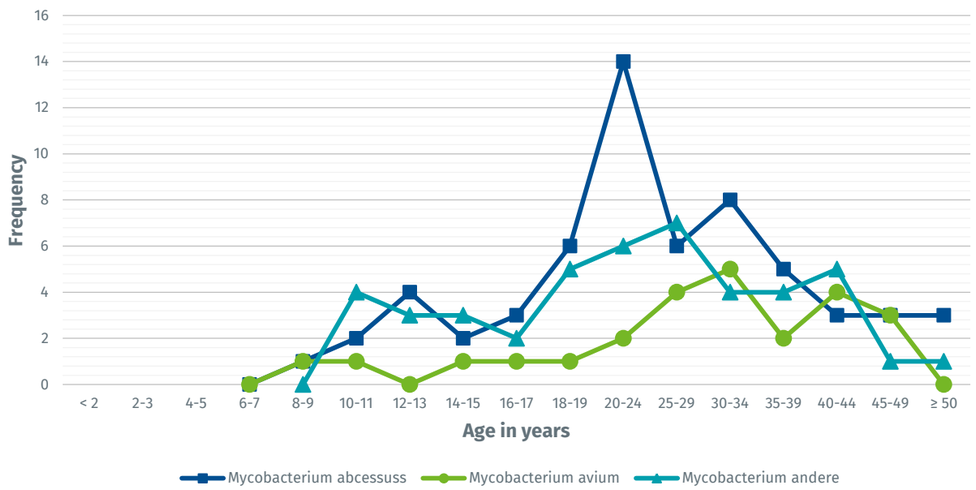

Fig. 17: Age-related frequency in % of patients of mycobacterial verification occurring at least once, 2016

Lung infections
(without lung transplant)

7c. Atypical mycobacteria (at least once in the reporting year)

Age of patients	Examination conducted	Mycobacterium abcessuss	Mycobacterium avarium	Mycobacterium, other
< 2	7.3	0.0	0.0	0.0
2-3	9.4	0.0	0.0	0.0
4-5	16.0	0.0	0.0	0.0
6-7	14.0	0.0	0.0	0.0
8-9	18.4	1.9	1.9	0.0
10-11	20.7	3.0	1.5	6.0
12-13	25.5	5.9	0.0	4.4
14-15	30.3	2.3	1.1	3.4
16-17	34.6	2.8	0.9	1.9
18-19	33.9	5.1	0.8	4.2
20-24	37.1	5.8	0.8	2.5
25-29	40.9	2.4	1.6	2.8
30-34	50.9	3.6	2.3	1.8
35-39	49.1	3.1	1.2	2.5
40-44	50.2	2.8	3.7	4.6
45-49	50.9	3.4	3.4	1.1
≥ 50	49.4	3.8	0.0	1.3
Total	33.0	3.4	1.4	2.5
< 18 years	20.6	2.4	0.8	2.4
≥ 18 years	43.4	3.8	1.7	2.6

Table 15: Frequency in % of patients with examination for mycobacteria and at least one verification of mycobacteria in 2016

Complications extended

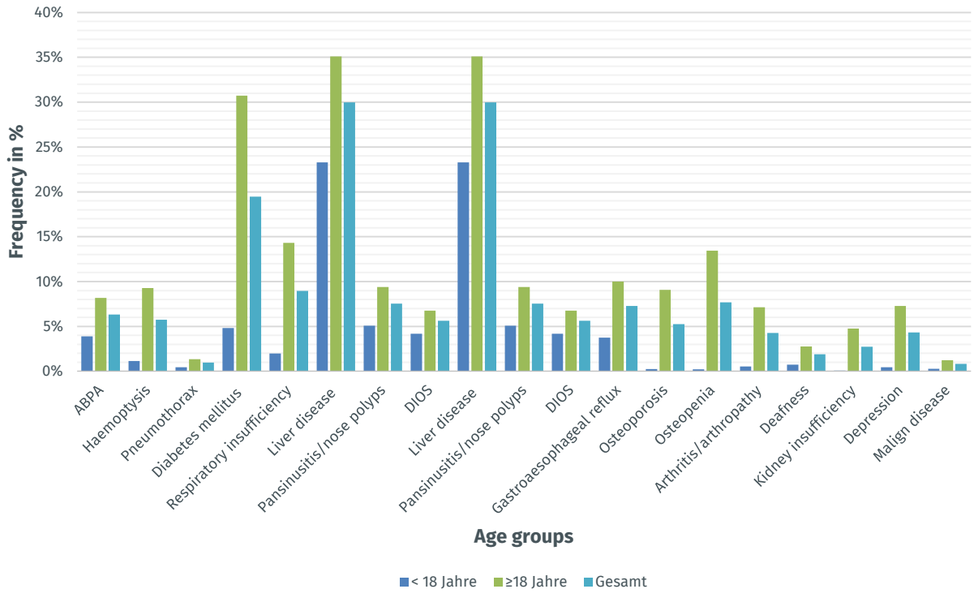

Fig. 18: Frequency in %, complication <18 and ≥18 years, 2016

Complications extended

	< 18 years (n=2435)	**≥18 years** (n=3171)	**Total** (n=5606)
ABPA (*)	3.9	8.2	6.3
Haemoptysis	1.1	9.3	5.7
of these, severe cases	4.2	5.1	5.0
Pneumothorax	0.5	1.4	1.0
of these, requiring drainage	70.0	48.6	53.3
Respiratory insufficiency	2.0	14.3	9.0
of these, partial insufficiency	87.8	79.1	79.9
of these, global insufficiency	12.2	20.9	20.1
Exocrine pancreatic insufficiency	84.9	83.2	83.9
Diabetes mellitus (*)	4.8	30.7	19.5
of these, Type III	93.0	97.0	96.6
of these, not Type III	7.0	3.0	3.4
DIOS (*)	4.2	6.7	5.6
Liver disease (*)	23.3	35.1	30.0
of these, liver cirrhosis	21.6	26.9	25.1
of these, without portal hypertension	7.0	10.2	9.2
of these, with portal hypertension	6.2	8.9	8.0
Gastroaesophageal reflux	3.7	10.0	7.3
Bone disease			
Osteopenia	0.2	13.4	7.7
Osteoporosis	0.2	9.1	5.2
Arthritis/arthropathy	0.5	7.1	4.3
Pansinusitis/nose polyps, operation in reporting year	5.1	9.4	7.5
Deafness	0.7	2.8	1.9
Kidney insufficiency	0.1	4.8	2.7
Depression (*)	0.5	7.3	4.3
Malign disease Frequencies of ICD 10 codes	0.3	1.2	0.8

Table 16: Frequencies in % complications <18 or >18 years 2016

Therapies

9a. Basic treatment

9a.i. Children and adolescents

	0-5 years	6-11 years	12-17 years	Total
DNAse	20.3	52.8	67.7	48.8
Mannitol	0.3	0.6	2.7	1.3
Hypertonic saline solution	87.4	98.9	85.0	87.4
of these 3-5.7%	44.3	32.7	28.1	34.5
of these ≥5.8%	55.7	67.3	71.9	65.5
Beta sympathomimetics				
Short-term effect (SABA)	71.9	72.1	71.3	71.8
Long-term effect (LABA)	8.6	21.1	32.5	21.5
Anticholinergic drugs	14.0	14.6	14.5	14.4
Anti-staphylococci treatment	7.6	10.9	14.2	11.1
Steroids				
Nasal	8.8	19.6	21.3	17.1
Oral	0.4	2.5	6.1	3.2
Inhalative	12.4	25.2	31.0	23.6
Vitamins				
Vitamin A	77.7	76.1	80.1	78.0
Vitamin D	93.2	93.3	93.7	93.4
Vitamin E	76.7	72.9	78.3	75.9
Vitamin K	65.5	59.6	66.5	63.8

Table 17: Frequencies in % basic treatments <18 years, 2016

Therapies

9a. Basic treatment

9a.ii. Adults

	18-29 years	30-39 years	≥ 40 years	Total
DNAse	60.6	47.7	45.8	54.2
Mannitol	10.0	10.3	8.3	9.8
Hypertonic saline solution	72.9	68.3	59.3	69.0
of these 3-5.7%	26.7	27.8	29.9	27.5
of these ≥5.8%	73.7	72.2	70.1	72.5
Beta sympathomimetics				
Short-term effect (SABA)	64.2	62.8	64.5	63.9
Long-term effect (LABA)	49.7	59.3	65.7	55.5
Anticholinergic drugs	29.9	44.5	53.2	38.5
Anti-staphylococci treatment	12.3	11.6	9.3	11.5
Steroids				
Nasal	19.4	17.4	19.0	18.8
Oral	11.8	18.8	21.6	15.6
Inhalative	40.7	49.6	55.3	46.0
Vitamins				
Vitamin A	67.5	56.4	48.8	60.8
Vitamin D	88.8	87.2	84.7	87.6
Vitamin E	65.2	55.8	46.7	59.0
Vitamin K	51.3	41.8	37.0	45.9

Table 18: Frequencies in % basic treatments ≥ 18 years, 2016

9b. Indication therapy

9b.i. Children and adolescents

	0-5 years	6-11 years	12-17 years	Total
Ivacaftor* *in case of gating mutation*	68.4 (2-5 years)	74.3	76.2	69.6
Lumacaftor/Ivacaftor *in case of F508del/F508del*	0.0	0.8	16.7	6.8
Inhalative antibiotics *in case of chronic pseudomonas infection*	68.2	89.0	92.6	89.6
Azithromycin *in case of chronic pseudomonas infection*	0.0	15.9	33.1	25.4
Ursodeoxycholic acid *in case of liver disease*	92.2	88.5	89.0	89.2
Dietary measures for CFRD *in case of Diabetes mellitus*	0.0	41.7	24.5	26.4
Insulin treatment *in case of Diabetes mellitus*	0.0	62.5	70.3	69.2
Oral antidiabetics *in case of Diabetes mellitus*	0.0	6.3	12.9	12.0
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	99.0	98.5	98.9	98.8
Additional nutrition *in case of being underweight*	43.2	48.3	51.0	48.2
Oral supplementary food	40.8	43.5	46.8	44.3
PEG	2.4	7.8	8.4	6.8
Proton pump inhibitors *in case of gastroesophageal reflux*	100.0	85.7	77.5	83.5
Polyenthylene glycol *in case of DIOS*	59.3	74.1	52.1	59.8
Calcium *in case of osteopenia/osteoporosis*	0.0	0.0	22.2	20.0
Oxygen treatment *in case of respiratory insufficiency*	11.1	57.1	48.0	43.8

Table 19: Frequencies in % indication treatments < 18 years, 2016

* Ivacaftor is approved in Germany from the second year of age for the gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. and, from the 18th year of age, for R117H.

9b. Indication therapy

9b.ii. Adults

	18-29 years	30-39 years	≥ 40 years	Total
Ivacaftor* *in case of gating mutation*	79.5	68.8	81.8	77.6
Lumacaftor/Ivacaftor *in case of F508del/F508del*	18.1	20.8	20.6	19.3
Inhalative antibiotics *in case of chronic pseudomonas infection*	87.6	87.3	86.2	87.2
Azithromycin *in case of chronic pseudomonas infection*	38.7	41.4	47.0	41.5
Ursodeoxycholic acid *in case of liver disease*	82.4	76.2	82.2	80.8
Dietary measures *in case of Diabetes mellitus*	22.1	19.9	22.2	21.4
Insulin treatment *in case of Diabetes mellitus*	71.5	78.7	78.5	75.8
Oral antidiabetics *in case of Diabetes mellitus*	7.0	7.9	9.6	8.0
Pancreatic enzymes *in case of exocrine pancreatic insufficiency*	96.6	98.2	94.8	96.7
Additional nutrition *in case of being underweight*	56.3	54.3	41.4	53.9
Oral supplementary food	48.6	50.3	36.8	47.5
PEG	11.4	5.2	1.1	8.5
Proton pump inhibitor *in case of gastroesophageal reflux*	82.2	83.9	85.4	83.6
Polyenthylene glycol *in case of DIOS*	44.0	40.4	43.8	43.0
Calcium *in case of osteoporosis/osteopenia*	44.6	53.4	50.7	49.6
Biphosphonate *in case of osteoporosis*	11.9	19.4	29.7	21.2
Oxygen treatment *in case of respiratory insufficiency*	67.2	63.2	59.3	63.9
Non-invasive ventilation *in case of respiratory global insufficiency*	47.5	30.4	42.9	41.7

Table 20: Frequencies in % indication treatments ≥ 18 years 2016

* Ivacaftor is approved in Germany from the second year of age for the gating mutations: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R. and, from the 18th year of age, for R117H.

Mortality

In the reporting year 2016, 63 patients (31 girls/women and 32 boys/men) died. The main causes of death were cardiopulmonary (69.0%), hepato-intestinal (6.9%) and malign diseases (6.9%). 8.6% respectively were other or unknown causes. The age at time of death is distributed as follows:

	Number	Mean value	Median	Minimum	Maximum	Percentile 25	Percentile 75
Age at time of death; in complete years	63	33.21	33	9	57	23	41

Table 21: Age of death in 2016

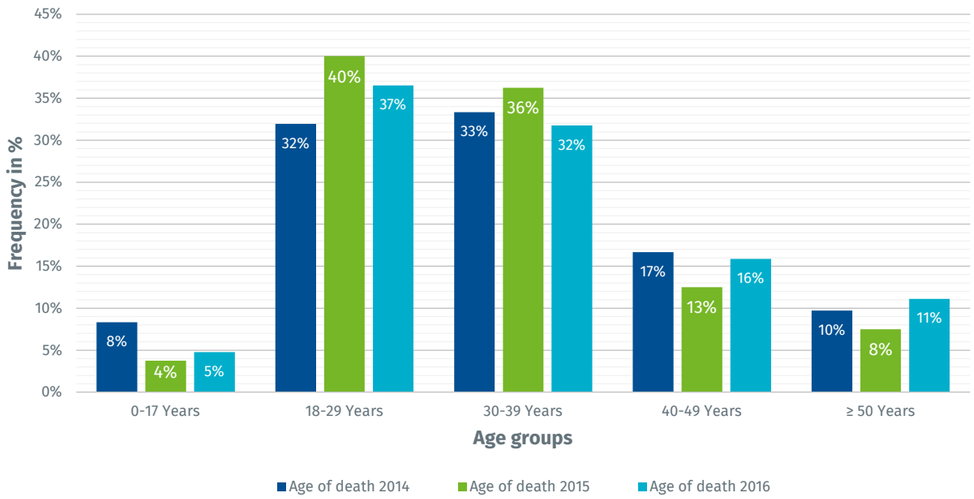

Fig. 19: Frequencies in % of deceased patients acc. age groups in 2016

	Number	Percent
0-17 years	<5	4.8
18-29 years	23	36.5
30-39 years	20	31.7
≥ 40 years	10	15.9
≥ 50 years	7	11.1
Total	63	100.0

Table 22: Frequency of deceased patients acc. age groups in 2016

10

Mortality

Note to readers:
Extended data and graphs on mortality statistics will be updated regularly until the beginning of 2018 in a second edition of the annual report 2016.

Structure of care

In the reporting year 2016, 92 facilities participated in the Cystic Fibrosis Register. 50 facilities care for less than 50 patients, and 42 facilities care for more than 50 patients. Over 80% of the patients documented in the Register are cared for in the 42 outpatient departments.

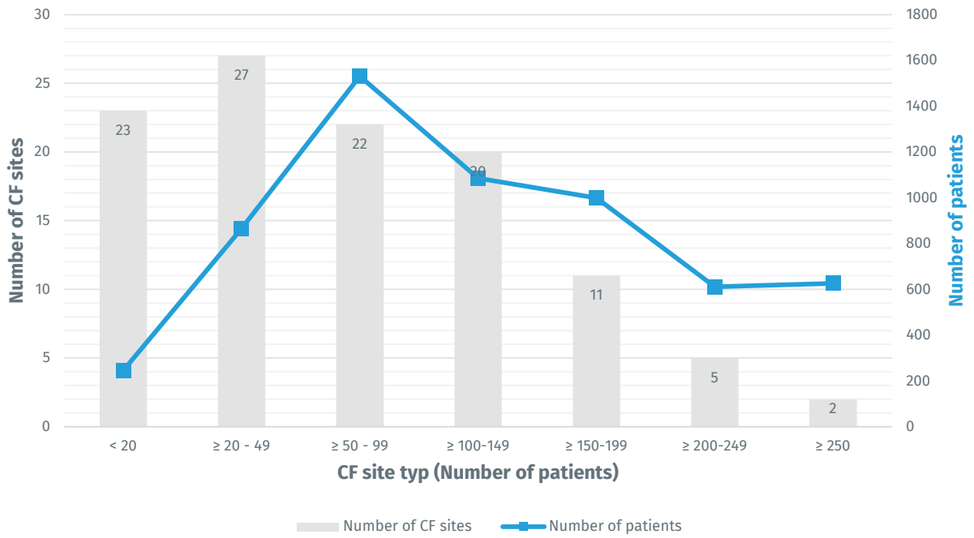

Fig. 20: Number of documented patients and number of CF sites in 2016

Glossary

ABPA (Allergic bronchopulmonary aspergillosis)	When a person develops an allergic reaction to Aspergillus fumigatus.
Anticholinergic drugs	An anticholinergic medicine has a relaxant effect on the smooth musculature and inhibits secretion.
Arthritis	A condition which causes pain and inflammations in the joints.
Arthropathy	A condition which causes pain in the joints.
Pancreas	An organ in the digestive system which produces insulin and digestive enzymes.
Beta sympathomimetics	Beta sympathomimetics are drugs Drug substanceswhich stimulate the Beta receptors of the Sympathetic nervous system .
BMI (Body Mass Index)	A measured value for the assessment of the body weight of a person in relation to its body size
Burkholderia cepacia	Burkholderia cepacia is one of a species of bacteria in the Burkholderia genus. Several of these bacteria are a potential threat to the health of people with cystic fibrosis.
CF - Cystic fibrosis	Cystic fibrosis
CFTR (Regulator of the transmembrane conductivity in case of cystic fibrosis)	A protein on the cell surface which controls the saline and water levels in a cell. The gene which causes cystic fibrosis is the blueprint for the CFTR protein. Every person has two copies of the gene for CFTR. In order for someone to be born with cystic fibrosis, both CFTR genes must be affected by a mutation causing CF.
Enzymes	Biological molecules present in the body which support complex reactions such as the digestion of foods.
FEV1 (one-second capacity)	The FEV1 (Forced Expiratory Pressure in 1 Second) is the largest-possible quantity of air which you can force out of your lungs within 1 second. The FEV1 value is a part of the lung function, and can be measured within the scope of a lung function test.
FEV1% predicted	The FEV1% is the percent value of the average FEV1 which healthy people of the same age, gender and length can achieve. Normally, this lies between 80-120%.
Gastroesophageal reflux disease	A chronic symptom of damage through stomach acid which rises up from the gastric mucosa.
Genotype	A characteristic part of the genetic structure of a cell, an organism or an individual.
GLI equations	The equation of the Global Lung Initiative takes into consideration the following factors for calculation of the FEV1%: absolute FEV1, age, gender, size and ethnicity
Haemophilus influenzae	Haemophilus influenza is a bacterium which can cause severe illness.
Haemoptysis	Coughing up blood.

Frequency	Number of people who have been newly diagnosed in the respective year.
Hepatobiliary disease	A liver or bilious disease
Heterozygous	Everyone who lives with cystic fibrosis has two mutations of the gene for CFTR. One mutation is inherited from the mother, and one from the father. If the two mutations (or genotypes) are different, then the person is heterozygous.
Homozygous	Everyone who lives with cystic fibrosis has two mutations of the gene for CFTR. One mutation is inherited from the mother, and one from the father. If the two mutations (or genotypes) are the same, then the person is homozygous.
IQR (Interquartile range)	The interquartile range is a dispersion measure in descriptive statistics. If we sort the spot checks according to their size, this range states how wide the interval is in which the average % of the spot check elements lie. It shows the difference between the upper and lower quartile: IQR = Q3 - Q1.
Confidence interval	An expectation range in order to express how certain we are regarding our statistical estimations of a clinical measurement value. It shows a series of results which probably also include the correct values for the examined population. A narrow confidence interval indicates a more precise estimation. A wide confidence interval indicates a large uncertainty over and above the exact value of the measurement value - frequently because only a small group of patients have been examined.
Gastrointestinal tract (GI)	The gastrointestinal tract is the main part of the digestive system which extends from the oesophagus down to the anus. The GI is an organ system which is responsible for the digestion of nutrients, the adsorption of nutrients and the excretion of faeces.
Median	The middle number when all numbers are arranged from the smallest to the largest number.
Median survival prognosis	A mathematical formula, using which a forecast can be made as to what age half of the people born with CF today will reach. e.g.: 50% of the people born today will reach the age of at least 47. The other 50% of these people will probably die before they have reached this age.
Mean value	An average value calculated by adding up all the values and dividing by the number of values.
Average age of death	The average age of death is based on those people with CF who died in one year.
MRSA	Methicillin-resistant Staphylococcus aureus is a type of bacteria which is resistant to a series of widely-used antibiotics.

Mutation	A mutation is an alteration to a gene. If both parents of a child bear a mutation which causes CF, there is a 25% chance that the child will have cystic fibrosis. There are over 1,400 different mutations of the CFTR gene.
Nose polyps	Small, sack-shaped growths caused through chronic inflammations of the nasal mucosa.
New-born screening	The new-born screening is an examination of new-born babies in order to detect congenital diseases such as cystic fibrosis at an early stage.
Non-tuberculous mycobacteria (NTM)	A mycobacteria which does not trigger tuberculosis but can still be the cause of respiratory infections. Several types are known.
Osteopenia	A less severe disease than osteoporosis, through which the mineral content of bones is reduced.
Osteoporosis	A condition in which the bones become brittle due to the loss of tissue.
Percentile	A percentile indicates where a value is relative to the rest of the data. If a value lies higher than 90% of the remaining data, we speak of the 90th percentile.
Pneumothorax	A collection of air in the cavity between the lung and the chest wall which can lead to a collapsed lung on the affected side.
Prevalence	The total number of people with this disease over the past 12 months.
Pseudomonas aeruginosa	A tenacious bacterial strain which seldom affects healthy people, but which can lead to a multitude of infections in case of a weakened immune system.
Liver cirrhosis	A chronic liver disease.