2020 Annual Report

CF Registry of Ireland

Preface

During 2020 the Registry's activities were strongly influenced by the COVID-19 pandemic. Various periods of lockdown prevented our Research Associates from accessing CF Centres. As the year progressed there was a trend towards virtual clinics. As a result, we made changes to our software where we could distinguish between a virtual and a routine clinic visit.

When data collection was not possible, the team allocated time to data cleaning exercises. In addition, considerable time was devoted to the testing of various aspects of our next generation registry platform. Time was also devoted to the processing of ethics amendments around GDPR compliant Patient Consent Forms.

In 2020 CFRI participated in a number of research projects that included; C-FORMS (Children's Follow up Orkambi Real world MBW Study; RECOVER (Real world clinical outcomes with novel modifier therapy combinations in children with CF); and ICOS part2 (Irish Comparative Outcome Study of CF – Evaluation of the clinical, psychological and economic effects of the Cystic Fibrosis Newborn Screening Programme. The Registry continues to contribute summary tables that are used in post-authorisation safety studies that are submitted to the European Medicines Authority.

CFRI continues to participate in the CFTR2 Project – Clinical and Functional Translation of CFTR. This international project has made great progress where the vast majority of individuals with CF should now be able to find information about at least one of their variants on the CFTR2 website (www.cftr2.org).

In 2020 CFRI reported a total of 1,256 patients currently contributing appropriate clinical data to the registry, representing 88 % of the total Irish CF population. CFRI cannot overstress the importance of this data in driving research to improve patient outcomes. CFRI continues to collaborate with the European Cystic Fibrosis Society Patient Registry (ECFSPR). In 2019 ECFSPR reported that it now contains pseudonymised demographic and clinical data of 50,902 consenting CF patients from 38 countries.

CFRI is pleased to report that the registry is currently well resourced by core funding, commissioned research and unrestricted grants from industry. Our financials are summarised at the back of this report.

We would like to thank the various committees that contributed to the review of CFRI's extensive governance documentation. In addition, we would like to thank our board members for their guidance and support during the year. Our staff continue to work tirelessly to collect and prepare quality data that drives research, you dedication to CFRI is very much appreciated.

We would also like to thank the multi-disciplinary CF care teams across the country for their dedication and professionalism particularly during the COVID-19 pandemic. Without their active participation it would be impossible to maintain a quality registry. In addition, without the generosity of the patients who give explicit consent to access their data there would be no registry. We thank you all for your valued contribution.

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Cover Image: Altamont Gardens, Co Carlow. Photo courtesy of Laura Kirwan.

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Summary registry data, 2010-2020

The table below provides general summary information about people living with cystic fibrosis (CF) consenting to participate in the Cystic Fibrosis Registry of Ireland (CFRI).

Since the inception of the CFRI in 2002, 1,560 individuals with CF have consented to join the registry. In 2020, 25 individuals were registered, of whom 5 were newly diagnosed with CF. Importantly, the median age of people with CF has increased by three years since 2010, and now stands at 21.9 years, with 12.5% of people over the age of forty.

Summary of the CF Registry of Ireland, 2010-2020				
	2010	**2015**	**2019**	**2020**
Cumulative no. of registered individuals[1]	1,130	1,391	1,535	**1,560**
Living registered individuals[2]	1,024	1,181	1,254	**1,256**
Deceased registered individuals	93	182	236	**244**
Lost to follow up	13	28	45	**60**
Newly consented individuals	32	49	32	**25**
Newly diagnosed individuals consented	13	14	20	**5**
Median age (years)	18.9	19.6	21.4	**21.9**
IQR[3]	10.5-26.9	10.4-30.3	11.8-33.1	**12.3-33.8**
Median age at diagnosis (years)	0.35	0.33	0.27	**0.26**
Children (<18 years)	488	546	508	**497**
%	47.7%	46.2%	40.5%	**39.6%**
Adults (≥18 years)	536	635	746	**759**
%	52.3%	53.8%	59.5%	**60.4%**
Adults (≥40 years)	45	92	148	**157**
%	4.4%	7.8%	11.8%	**12.5%**
Females	436	502	522	**528**
%	42.6%	42.5%	41.6%	**42.0%**
Males	588	679	732	**728**
%	57.4%	57.5%	58.4%	**58.0%**
Number of deaths	16	17	11	**8**
%	1.5%	1.4%	0.9%	0.6%

[1] Living, deceased and lost to follow-up. Note that the number of registered individuals reported in a given year may change between annual reports due to de-notifications and diagnosis reversals.
[2] Registered, alive and not lost to follow-up on the last day of the reporting year.
[3] Interquartile range (IQR) is a measure of the spread of data. It shows the mid-spread or middle fifty percent of the data, or the difference between the upper (Q3) and lower quartiles (Q1).

Registry coverage of the CF population

The CFRI operates on an opt-in basis, whereby individuals living with CF are not registered prior to informed consent being obtained. Adults living with CF and parents/guardians of children living with CF are invited to participate. The registry collects information about consenting participants' CF care from medical records and compiles this with information on other registry participants before analysing the data. This information can be used to develop a better understanding of the health of all people in Ireland with CF and the treatment they are receiving.

The introduction of the General Data Protection Regulation (GDPR) in 2018 gave us all more control over how our personal data is stored and used. As a result, we are required to ask all patients to re-confirm their consent for CFRI to collect their information. Our new consent forms are fully GDPR compliant and have passed a review process with the ethics committee of each CF Centre. CFRI are currently undertaking a programme of re-consenting all participants in our national registry.

At the beginning of each year the Cystic Fibrosis Registry of Ireland conducts a census of all people with CF (PWCF) attending CF Centres in Ireland. The primary aim of this is to calculate the CFRI's rate of coverage of the CF population in Ireland at a given time period.

According to CFRI's most recent estimate, 1,466 individuals were receiving CF care in Irish hospitals in 2020. Of the 1,466 listed individuals, 1,289[1] were registered with the CFRI, representing 88% of people receiving care for CF in Ireland in 2020. This rate of coverage has dropped from previous years, largely due to the burden of the programme of re-consent that we are undertaking.

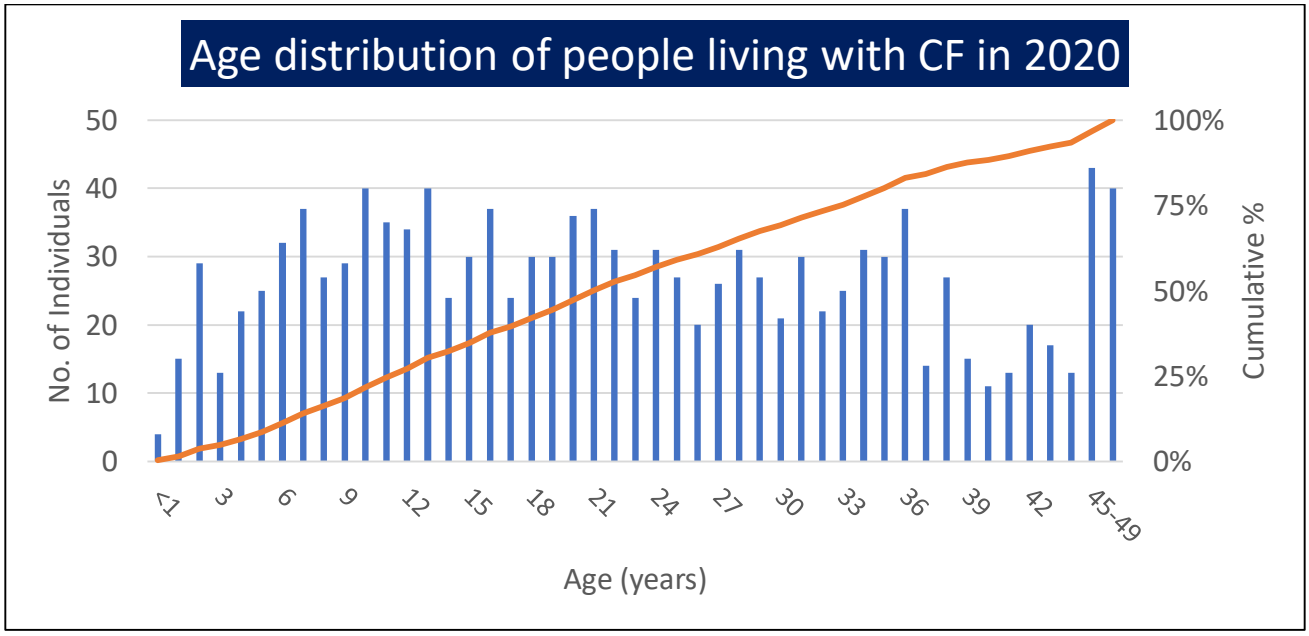
Participation with the registry is voluntary and is encouraged. Registration with the CFRI is open to anyone currently living with CF in the Republic of Ireland. If you are an individual with CF, or a parent/guardian of a child(ren) with CF, and wish to participate with the registry, you can contact the CFRI (contact details are available on the last page of this report) or your CF care team.

[1] Note that this includes patients that were consented to CFRI in 2021 before the annual patient survey was carried out, and so does not match the 1,256 patients alive and consented to the registry on the last day of 2020.

Demography

Since 2002, the registry has collected information on people living with CF in Ireland. This section provides demographic information of people living with CF in 2020, including age, gender, and geographical distribution.

In 2020, there were more adults (aged 18 years or older) living with CF in Ireland than children. By the end of the year, 1256 people were alive in the registry, of whom 497 were children and 759 were adults. The median age of people living with CF in Ireland is 21.9, meaning half of the CF population was under the age of 21.9 and half was over the age of 21.9. The age of individuals alive in the registry ranged from birth to over 73 years old, of whom 157 (12.5%) were 40 years or older.

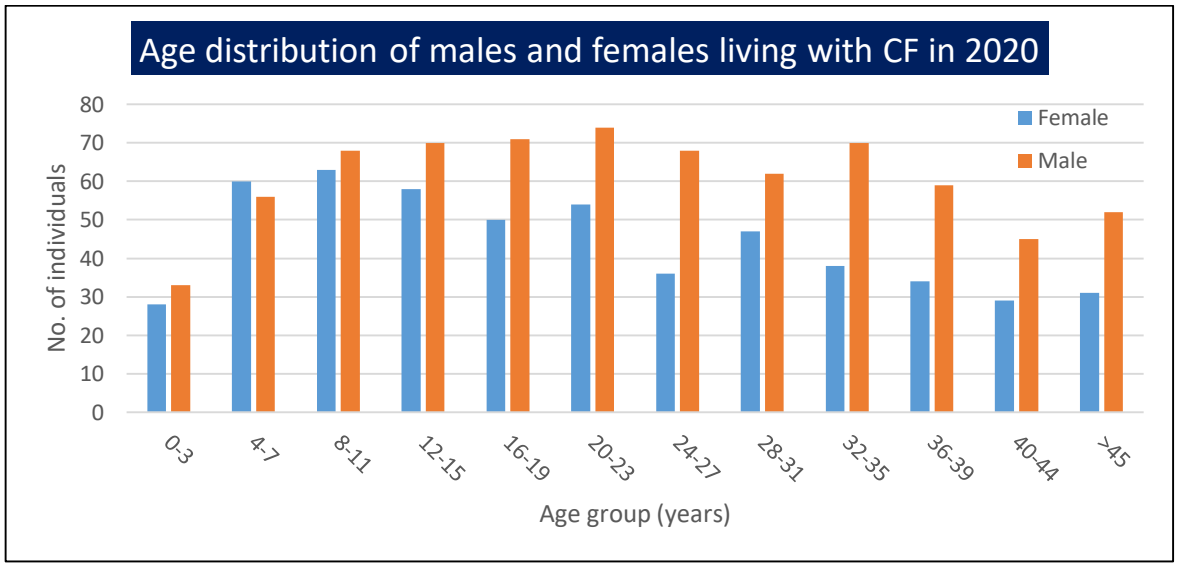


As reported in other years, there were more males (58%) living with CF than females (42%). This is due in part to poorer survival of females with CF in Ireland[2]. Similar discrepancies have also been observed in other countries.

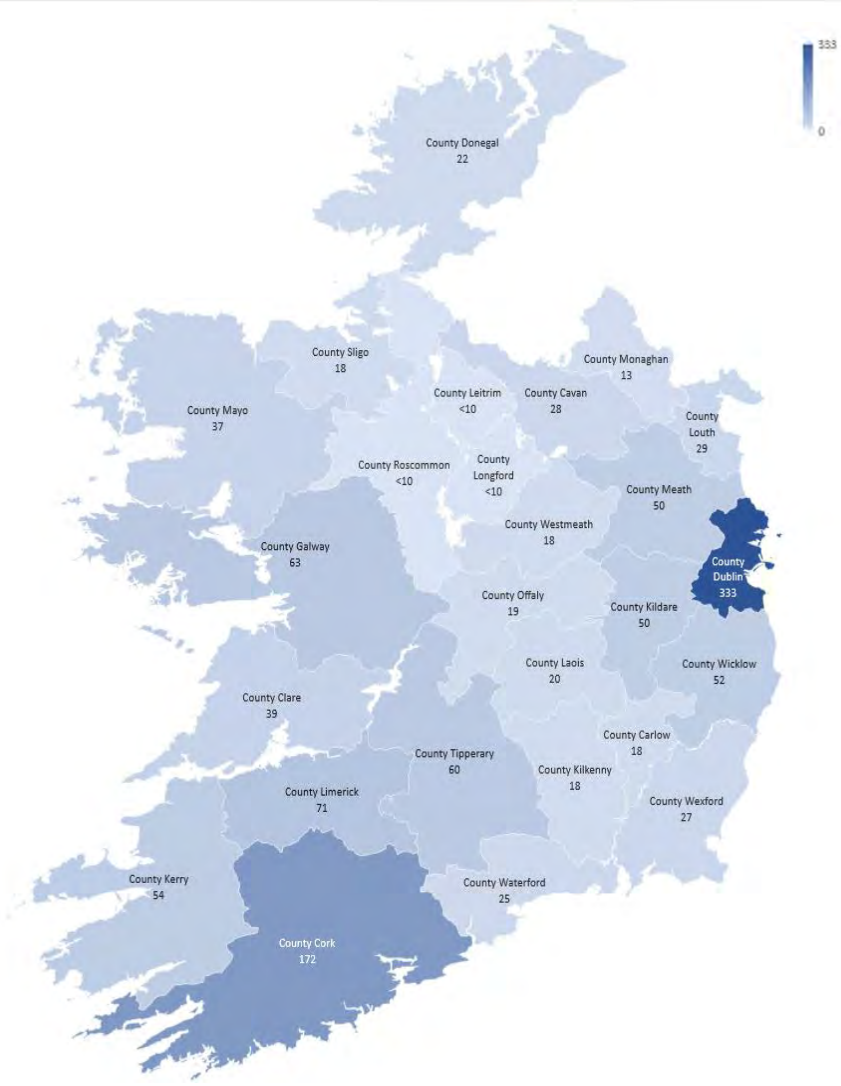
The median age for females was 20.4 years (IQR 11.0-32.0) and 23.7 years for males (IQR 13.1-34.8). The difference in median age between the sexes was statistically significant (p=0.003).

[2] Jackson AD et al, Validation and use of a parametric model for projecting cystic fibrosis survivorship beyond observed data: a birth cohort analysis. Thorax 2011; 66:674-679.

In order to further analyse the distribution of CF across age groups, individuals under 45 years were grouped into four-year age bands (0-3 years old, 4-7 years old, etc.). The age-band with the greatest number of individuals was the 8-11 year old category (n=131), followed by the 12-15 (n=128) and 20-23 year old categories (n=128). The number of males exceeded females across all age bands, with the exception of the 4-7 category (n=60 females; n=56 males).



Distribution of the number of people living with CF, registered with CFRI by county in 2020



When comparing the distribution of individuals living with CF and registered with CFRI across the four provinces in the Republic of Ireland, over half (51%) were located in Leinster. One third of individuals lived in Munster, with the remaining 15.4% in either Connaught or Ulster.

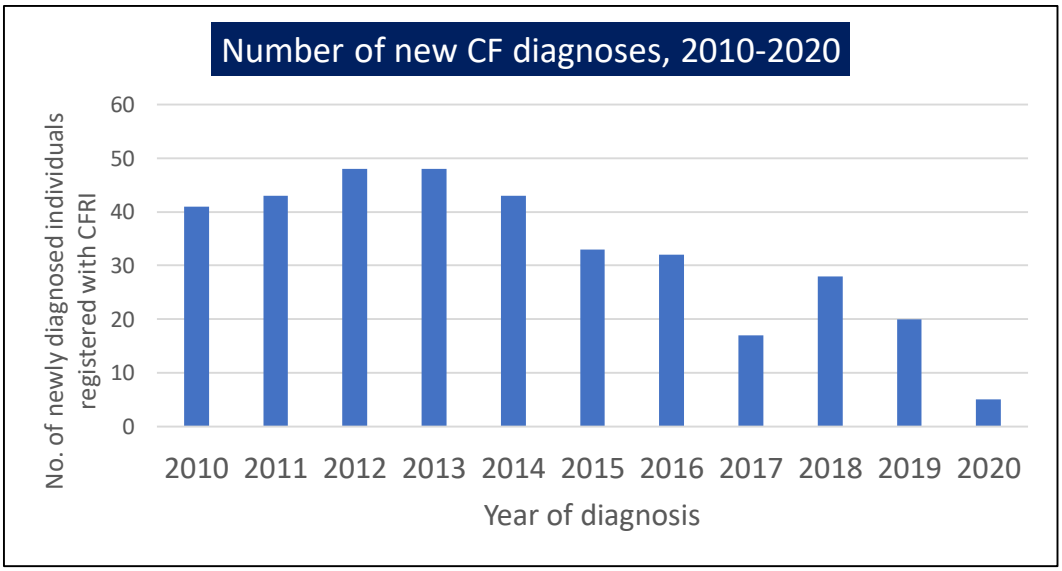
Distribution of people registered with CFRI by province in 2020		
	Number	%
Connaught	130	10.4%
Leinster	641	51.0%
Munster	421	33.5%
Ulster	63	5.0%
Unknown	1	0.1%

The counties with the largest numbers of individuals included Dublin (n=333), Cork (n=172), Limerick (n=71), Galway (n=63) and Tipperary (n=60). These figures reflected the county of home residence. The home address provided by individuals at registration was updated to reflect this where possible.

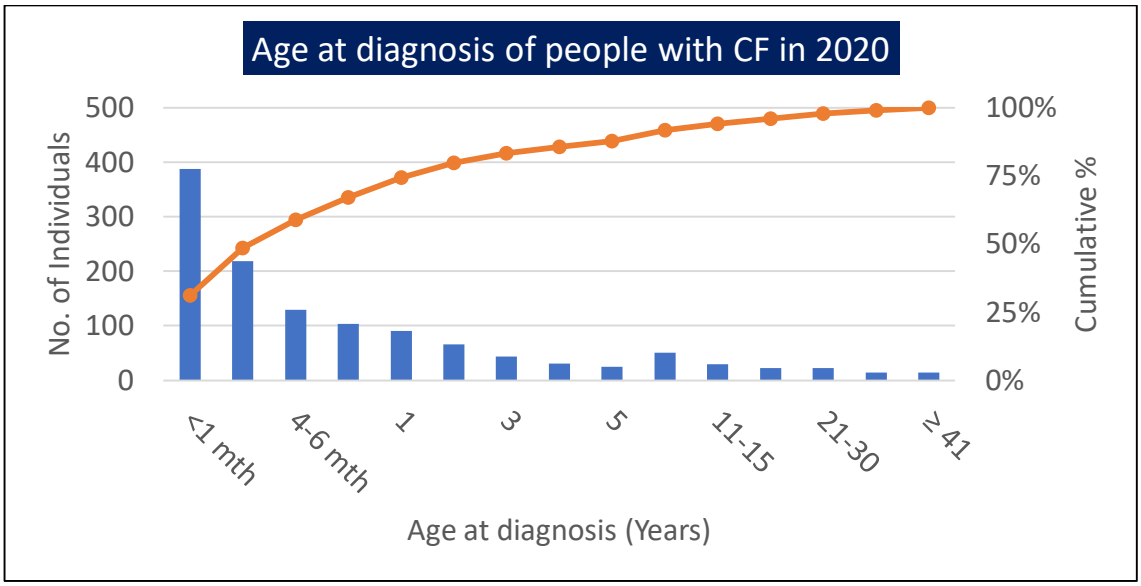
Diagnosis

Early diagnosis of CF provides opportunities for earlier medical intervention. Providing infants with the best possible care may result in better nutritional and lung function outcomes later in life. In this section, we examine how and when individuals are diagnosed with CF, and how these trends compare to previous years.

On average, 33 individuals newly diagnosed with CF were registered with CFRI each year between 2010 and 2020, with a range of 5 to 48 new diagnoses annually across the decade. Five individuals registered with the CFRI were diagnosed with CF in 2020 out of a total of 30 reported by the National Newborn Bloodspot Screening Programme. However, this represents an underestimation of the total number of individuals diagnosed in 2020. Delays were encountered when inviting newly diagnosed individuals to participate in the registry. Reports in subsequent years are adjusted as necessary to include those participants. As such, the number of individuals registered with the CFRI who were diagnosed with CF in 2019 is 20, having been reported as 15 in the previous year's report.



Routine newborn screening for CF was first introduced in July 2011. As such, the majority of individuals registered with the CFRI were diagnosed prior to its introduction. Early diagnosis of CF is vital for planning future management of the condition. Seven hundred and thirty-six (58.6%) individuals were diagnosed with CF in their first six months of life, although 255 (20.3%) were diagnosed after their third birthday.



There are numerous symptoms and circumstances which can lead to a diagnosis of CF. Although some may have exhibited a number of symptoms prior to their diagnosis, newborn screening has assisted in identifying 241 individuals with CF in Ireland. Newborn screening tended to lead to a diagnosis earlier in life, along with those who had a meconium ileus, irrespective of its management. More than one-third of individuals experienced respiratory symptoms leading to a diagnosis of CF. However, those individuals had a median age at diagnosis of over 1 year of age.

Modes and median age of diagnosis of individuals living with CF in 2020

	Frequency[1]	% of individuals living in 2020 (n=1,256)	Median age at diagnosis (years)	IQR
Respiratory symptoms	439	35.0%	1.17	(0.4 - 5)
Failure to thrive/malnutrition	278	22.1%	0.44	(0.2 - 1.4)
Family history	269	21.4%	0.14	(0.04 - 0.94)
Steatorrhea +/- abnormal stools +/- malnutrition	249	19.8%	0.88	(0.2 - 3.1)
Newborn screening (in Ireland/other country)	241	19.2%	0.05	(0.03 - 0.07)
Meconium ileus:				
treated surgically	108	8.6%	0.04	(0.02 - 0.08)
medically managed	63	5.0%	0.04	(0.02 - 0.11)
management unknown	12	1.0%	0.08	(0.05 - 0.32)
Other[2]	168	13.4%	1.55	(0.1 - 7.7)

[1] Multiple categories may apply to a single individual.
[2] Includes sinus disease, rectal prolapse, other neonatal intestinal/bowel obstruction, heaptorbiliary disease, prenatal screening, prolonged jaundice, pancreatitis, electrolyte imbalance/dehydration, diabetes, infertility/genito-urinary abnormalities, clubbing.

In 2020, 22.1% of people living with CF and registered with CFRI failed to thrive prior to their diagnosis. Furthermore, 21.4% of individuals had a family history of CF and 19.8% reported experiencing steatorrhea, with or without abnormal stools and malnutrition.

Thirty individuals were identified as part of the National Newborn Bloodspot Screening Programme (NNBSP), leading to a diagnosis of CF in 2020. By the end of that year, 5 of those individuals were registered with the CFRI through consent from their parents or guardians. The statistics from the NNBSP are reported below.

National Newborn Bloodspot Screening Programme outcomes, 2020[1]					
	2016, N(%)	**2017, N(%)**	**2018, N(%)**	**2019, N(%)**	**2020, N(%)**
Number of newborns[2] screened	64076	62084	61319	59591	57019
Number of samples with raised IRT sent to National Centre for Medical Genetics (NCMG)	789 (1.23%)	742 (1.19%)	759 (1.23%)	759(1.27%)	659(1.15%)
Number of newborns with one mutation identified	68	68	69	51	80
Number of newborns with two mutations identified	19	14	35	20	22
Number of newborns referred to a CF Specialist Centre	87	82	103	71	102
Number of initial sweat tests performed	88	80	103	70	102
Number of sweat test failures	23	20	15	17	21
Number of newborns with positive sweat test	17	10	29	17	20
Number of newborns with negative sweat test	45	44	51	32	57
Number of newborns with borderline sweat test	3	6	8	4	4
Number of newborns requiring repeat sweat test	3	4	8	2	25
Number of newborns diagnosed with CF	25	16	41	26	30
Number of newborns diagnosed with variant CF	1	3	2	0	1
Number of newborns diagnosed as carriers	62	63	60	44	71
Number of newborns without definitive diagnosis[3]					

[1]Source: National Newborn Screening Laboratory, Children's Health Ireland at Temple Street

[2] Figures reported here are based on baby's date of birth.

[3] Awaiting sweat results.

Since its introduction in July 2011, 269 individuals have been identified as a result of the NNBSP, leading to a diagnosis of CF.

Summary of National Newborn Screening Programme outcomes, July 2011-2020	
	Number of screened newborns diagnosed with CF
2011 (Jul-Dec)	16
2012	28
2013	34
2014	32
2015	21
2016	25
2017	16
2018	41
2019	26
2020	30
Total	269

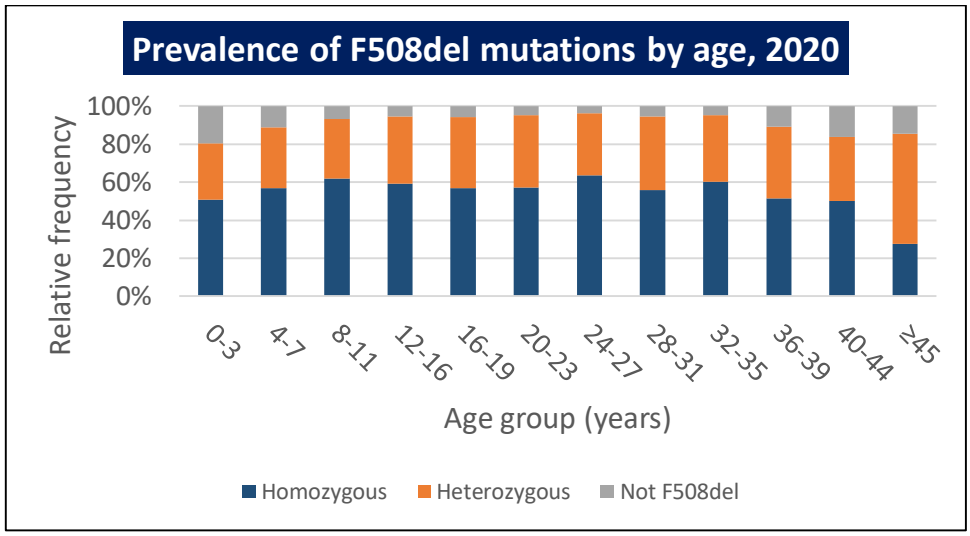
CFTR gene mutations

CF is a genetic condition, whereby individuals inherit one copy of a defective cystic fibrosis transmembrane conductance regulator (CFTR) gene off each of their parents. To date, approximately 2,000 CFTR gene mutations have been identified, each of which may cause varying levels and severities of CF disease. Vital information has been provided through genetic testing, which has assisted in diagnosing and treating CF and CF-related complications. This section examines the most frequently identified CFTR gene mutations in Ireland.

The F508del mutation was the most frequently identified CFTR gene mutation in people living with CF in 2020. In fact, 91.8% of individuals had at least one copy of this particular mutation. Other common mutations in Ireland include the G551D mutation (14.8%) and the R117H mutation (6.3%). All other CFTR mutations affect less than 4% of the Irish CF population. CFTR allele frequencies are shown below.

CFTR allele frequency, 2020			
Legacy name	**cDNA name**	**Protein name**	**% Allele frequency N=2,512**
F508del	.1521_1523delCTT	p.Phe508del	73.44%
G551D	c.1652G>A	p.Gly551Asp	8.25%
R117H	-	p.Arg117His	3.23%
R560T	c.1679G>C	p.Arg560Thr	1.63%
621+1G->T	c.489+1G>T	-	1.12%
1717-1G->A	c.1585-1G>A	-	1.00%
G542X	c.1624G>T	p.Gly542X	0.68%
V520F	c.1558G>T	p.Val520Phe	0.64%
I507del	c.1519_1521delATC	p.Ile507del	0.56%
Other			7.81%
Unknown			1.90%

In 2020, 55.4% of people living with CF in Ireland were F508del homozygous, meaning they had one copy of the F508del mutation on each allele. For European and neighbouring countries, the ECFS reported[3] that for 2019, 40% were F508del homozygous. Furthermore, 36.4% of the Irish CF population were F508del heterozygous, meaning they carried the F508del on one allele only. This compares with 41% in Europe. The remaining 8.2% of individuals had no copies of the F508del mutation on either allele. The prevalence of the F508del mutation among people living with CF across four-year age-bands is shown below.



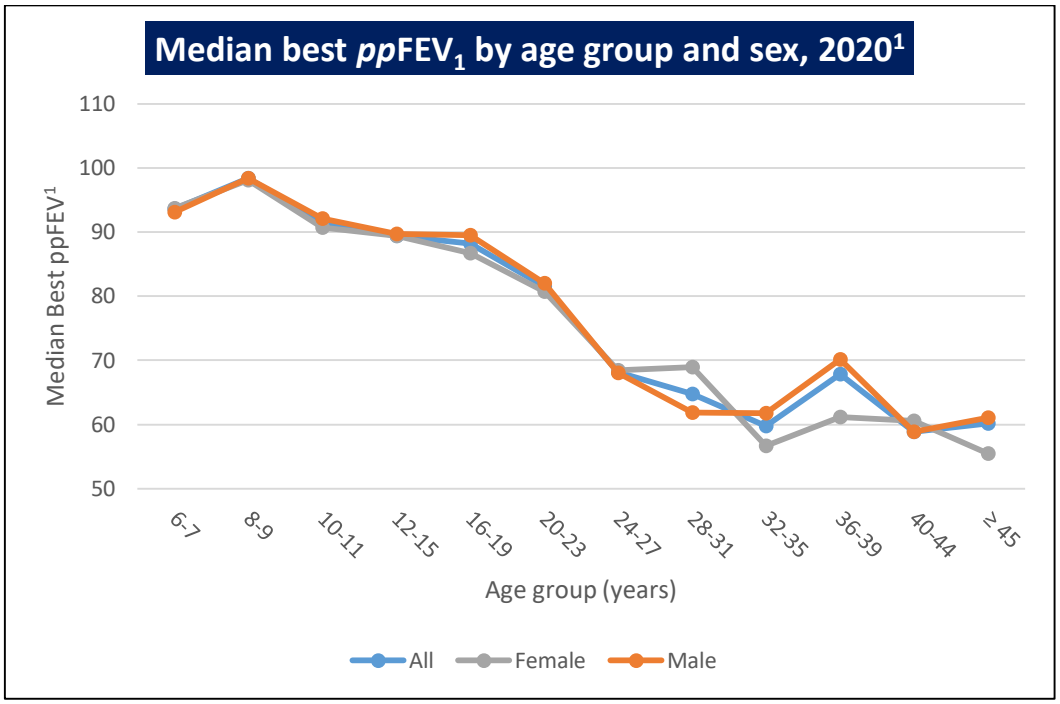
[3] 2019 Annual Report from the European Cystic Fibrosis Society Patient Registry (ECFSPR). https://www.ecfs.eu/sites/default/files/general-content-images/working-groups/ecfs-patient-registry/ECFSPR_Report_2019_v1_23Dec2021.pdf

Lung function

Cystic fibrosis is a multi-organ disease. However, individuals' lungs are particularly impacted due to the failure of mucociliary clearance, mucus plugging and secondary infection. As a result, the health of the lungs is an important indicator of the overall condition of a person with CF. This is routinely measured using the Forced Expiratory Volume of air in the first second of an exhaled breath (FEV_1). Although this is measured in litres, it is often expressed as a percentage of the expected value from people without cystic fibrosis of the same age, gender, height, and ethnicity.

In order to standardise the collection, presentation, and interpretation of registry data, international CF registries have agreed that the Global Lung Function Initiative (GLI) should be used to predict lung function relative to the general population. This harmonises the global reporting of data and allows for comparisons between countries. For this reason, CFRI data on lung function is recorded in FEV_1 (litres) and then converted to FEV_1 percent predicted (*pp*FEV_1) using the GLI equations. Lung function tests completed by individuals under the age of six years old, or after a lung transplant are unreliable, and therefore not reported here.

Overall, 2,860 lung function measurements were recorded from 874 individuals aged 6 years or older with no lung transplant in the CFRI. This compares with 5,397 (47% reduction) lung function measurements recorded from 1,001 (13% reduction) patients for the same group in 2019. The lung function recorded for individuals in Ireland compares similarly to those reported in 2019 by ECFS for European and neighbouring countries[2]. For individuals aged 6-18 years, the median *pp*FEV_1 of best lung function measurement was 91.5% (IQR: 82.0-100.8%). This compares with a median of 92.8% (IQR: 80.6-102.9%) in the European data. For individuals aged over 18 years, the median *pp*FEV_1 of best lung function measurement was 66.3% (IQR: 47.5-84.6%). This compares with a median of 69.7% (IQR: 49.3-87.8%) reported in the European data.



[1]Among individuals aged 6 years and older who have not had a lung transplant

In 2020, females living with CF had a median best *pp*FEV$_1$ of 80.6% (IQR: 57.2-92.4%). This compared to 78.8% (IQR: 57.7-92.7%) in males. An independent samples median test of *pp*FEV$_1$ showed no significant difference between males and females (p=0.783).

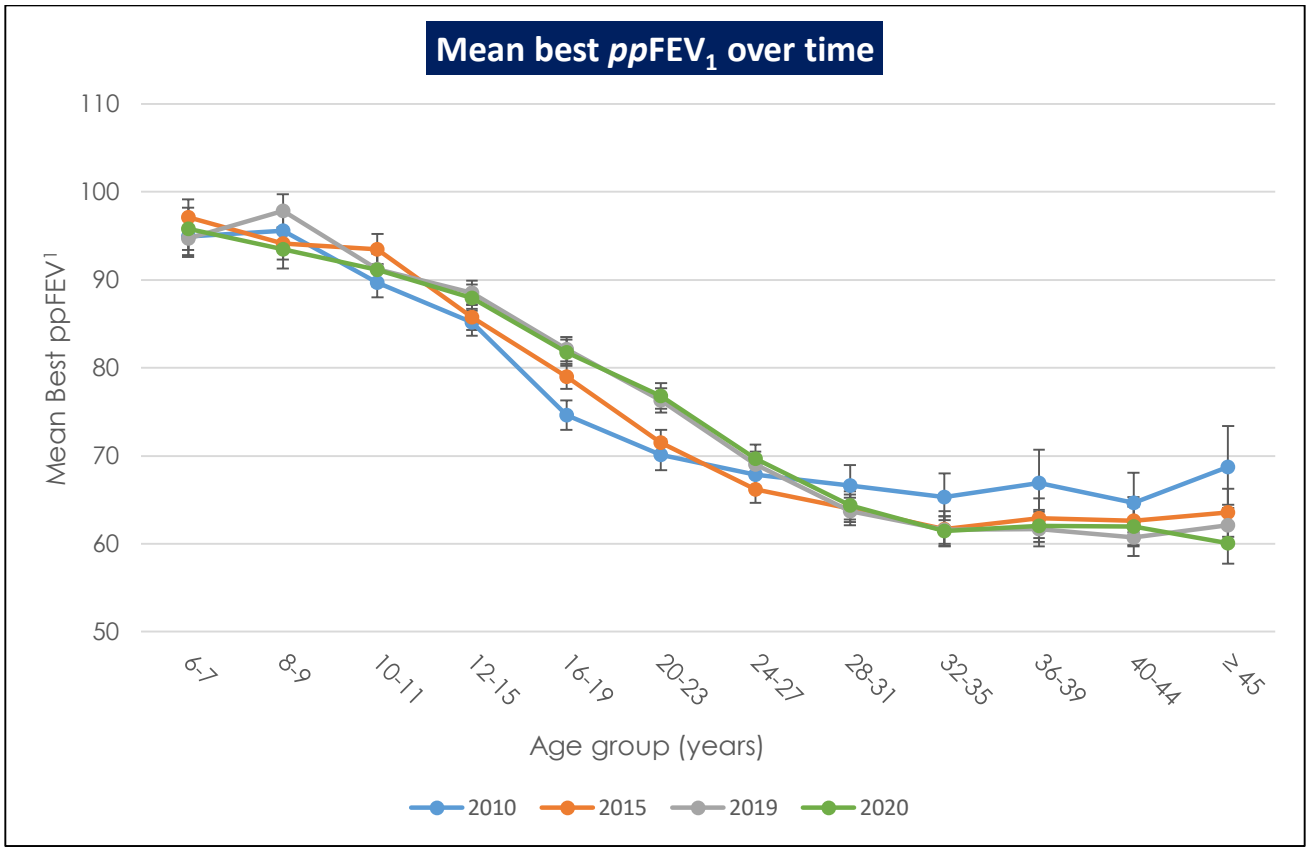
Cystic fibrosis is a chronic, progressive disease, which tends to become more severe as individuals get older. As such, both females' and males' median best *pp*FEV$_1$ decreases with age. Individuals living with CF between the ages of six and eleven had a median best *pp*FEV$_1$ between 91.6% and 98.5%. However, individuals over the age of 45 had a median best *pp*FEV$_1$ of 60.1%.

Median best *pp*FEV$_1$ by age and gender, 2020									
	All			Female			Male		
Age	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**
6-7	47	93.6	(86.5 , 103.7)	25	93.8	(91 , 104.3)	22	93.1	(86.5 , 100.8)
8-9	41	98.5	(90.7 , 105.4)	22	98.1	(85.5 , 105.4)	19	98.5	(92.4 , 107.6)
10-11	61	91.6	(83.6 , 100.8)	31	90.7	(83.6 , 106.9)	30	92.1	(83.3 , 100.1)
12-15	103	89.4	(83.3 , 100.6)	51	89.4	(79.9 , 98.6)	52	89.7	(83.5 , 103.7)
16-19	94	88.2	(71.7 , 96.9)	39	86.8	(67.8 , 94)	55	89.5	(74.7 , 99.2)
20-23	103	81.6	(64.8 , 92.3)	46	80.7	(66.2 , 87)	57	82.0	(61.3 , 101.6)
24-27	82	68.2	(53.4 , 84.7)	33	68.5	(56.2 , 84.7)	49	68.1	(48.4 , 81.9)
28-31	88	64.8	(46 , 82.5)	39	68.9	(46.9 , 85.4)	49	61.9	(45.2 , 80.6)
32-35	79	59.8	(44.8 , 75.1)	26	56.7	(44.1 , 65.8)	53	61.8	(47.5 , 78.8)
36-39	68	67.9	(44.3 , 81.7)	29	61.2	(43.8 , 81.3)	39	70.1	(45.5 , 82.2)
40-44	49	58.8	(39.4 , 79)	20	60.6	(46.7 , 90.8)	29	58.8	(39.4 , 72.5)
≥ 45	59	60.1	(43.4 , 75.3)	26	55.5	(46.2 , 71.7)	33	61.1	(39.4 , 79.3)
Total	874	80.0	(57.5 , 92.6)	387	80.6	(57.2 , 92.4)	487	78.8	(57.7 , 92.7)

Lung disease can typically be categorised according to an individuals' *pp*FEV$_1$: *pp*FEV$_1$ <40% is severe; *pp*FEV$_1$ 40-69% is moderate; and *pp*FEV$_1$ ≥70% is mild or normal. In 2020, 88.4% of children had best lung function measurements in the normal to mild lung disease range. This compares to 45.8% in adults (≥18 years). Over 16% of adults with CF had severe lung disease, compared to just over 2% of children.

Severity of lung disease, 2020			
	Severe *pp*FEV1 <40%	**Moderate ppFEV1 40-69%**	**Mild/normal *pp*FEV1 ≥70%**
Children (6-17 years)	2.0%	9.5%	88.4%
Adult (≥18 years)	16.9%	37.3%	45.8%
All	11.0%	26.3%	62.7%

Over the past decade, significant improvements in individuals' lung health have been observed in certain age categories. Increases in *pp*FEV$_1$ have been recognised in young people with CF between the ages of sixteen and twenty-three years. For this age group, mean best *pp*FEV$_1$ was on average 7% higher in 2020 compared to the mean best *pp*FEV$_1$ in 2010.



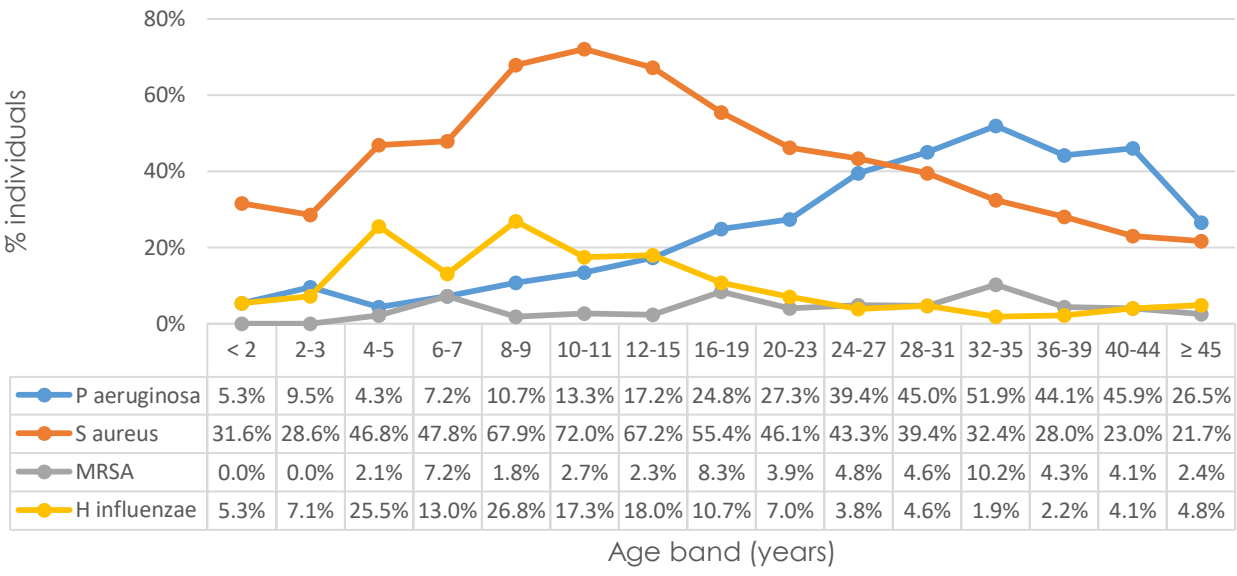
Mean best *pp*FEV$_1$ over time	6-7	8-9	10-11	12-15	16-19	20-23	24-27	28-31	32-35	36-39	40-44	≥ 45
2010	94.9	95.6	89.7	85.2	74.6	70.1	67.9	66.6	65.3	66.9	64.7	68.7
2015	97.2	94.2	93.5	85.8	79.0	71.5	66.2	64.0	61.7	62.9	62.6	63.6
2019	94.7	97.8	91.2	88.5	82.1	76.3	69.0	63.7	61.6	61.7	60.7	62.1
2020	95.8	93.5	91.1	88.0	81.7	76.8	69.7	64.3	61.5	62.1	61.9	60.1
p-values *	0.432	0.975	0.729	0.149	**0.001**	**0.002**	0.275	0.693	0.290	0.471	0.518	0.093

*If the p-value is below 0.05, then there is a statistically significant linear trend over time in *pp*FEV$_1$. Significant values are highlighted in bold.

Microbiology

One of the most notable characteristics of CF is recurrent exacerbations of lung infections. Due to thickened mucus in the lungs, bacteria may not be cleared easily. This may result in individuals with CF developing lung infections. Although a large range of organisms may contribute to these infections, there are a number of bacteria that are particularly prevalent.

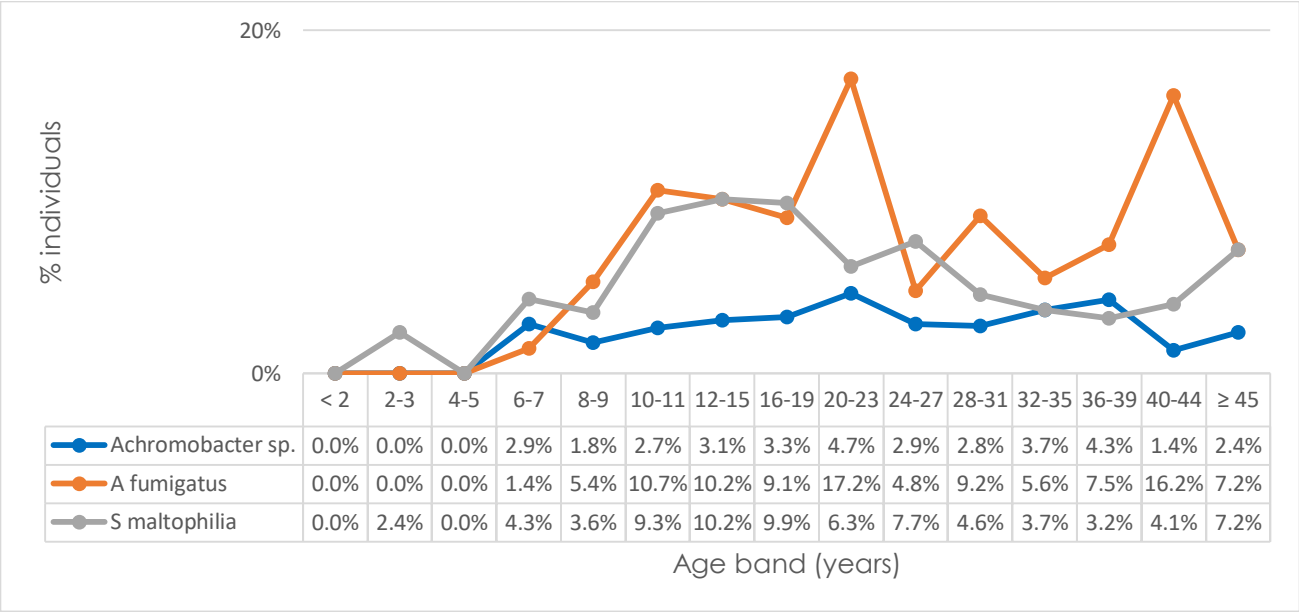
The graph below shows the organisms detected in the airways of individuals living with CF in 2020. *Staphylococcus aureus* was found most frequently in sputum cultures from children, with prevalence's of 57.1%. In 2020 *Haemophilus influenza* was found in 16.0% of children. This has fallen dramatically from 31% in 2019, and may have been impacted by the COVID-19 public health guidelines on restricted movement. *Pseudomonas aeruginosa* was more frequently found in adults than in children. In fact, *Pseudomonas aeruginosa* was detected in at least one respiratory sample of 39.8% of adults in 2020. This compares to 49.3% in 2019.



	< 2	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24-27	28-31	32-35	36-39	40-44	≥ 45
P aeruginosa	5.3%	9.5%	4.3%	7.2%	10.7%	13.3%	17.2%	24.8%	27.3%	39.4%	45.0%	51.9%	44.1%	45.9%	26.5%
S aureus	31.6%	28.6%	46.8%	47.8%	67.9%	72.0%	67.2%	55.4%	46.1%	43.3%	39.4%	32.4%	28.0%	23.0%	21.7%
MRSA	0.0%	0.0%	2.1%	7.2%	1.8%	2.7%	2.3%	8.3%	3.9%	4.8%	4.6%	10.2%	4.3%	4.1%	2.4%
H influenzae	5.3%	7.1%	25.5%	13.0%	26.8%	17.3%	18.0%	10.7%	7.0%	3.8%	4.6%	1.9%	2.2%	4.1%	4.8%

Age band (years)

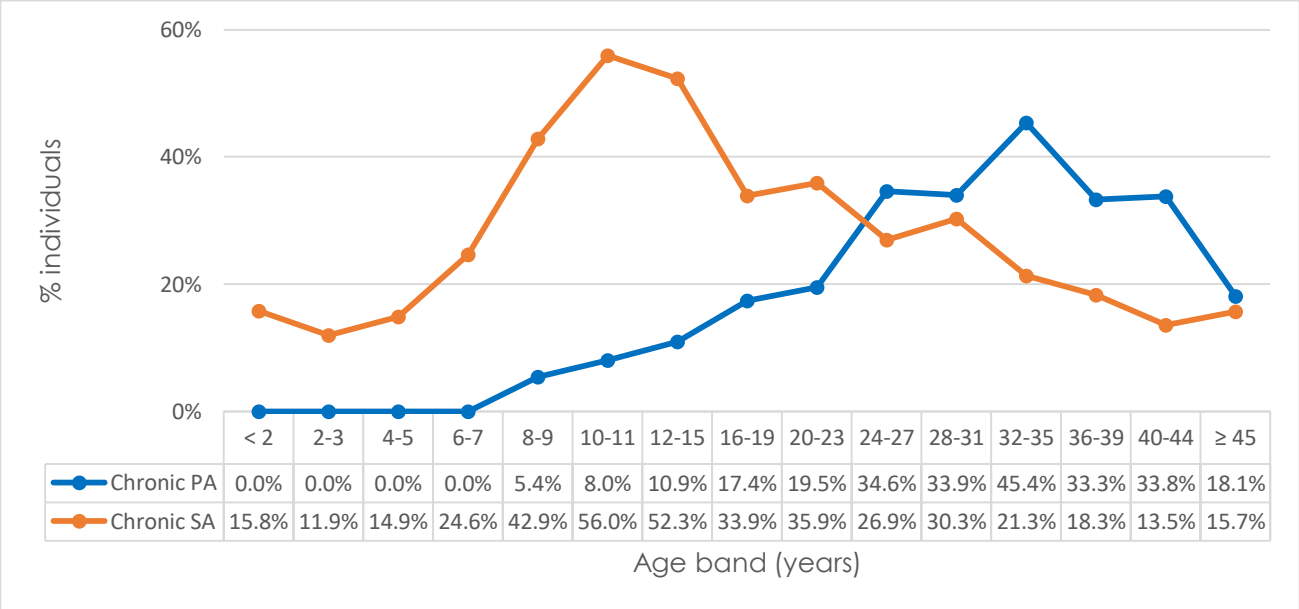
Other less frequently identified organisms found in the sputum cultures of people living with CF in Ireland in 2020 included *Burkholderia cepacia* and non-tuberculous mycobacteria species. *Burkholderia cepacia* was detected in 31 people (2.5%), while non-tuberculous *Mycobacteria* species (*M. abscessus, M. avium, M. chelonae)* were found in 17 individuals (1.4%).



	< 2	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24-27	28-31	32-35	36-39	40-44	≥ 45
Achromobacter sp.	0.0%	0.0%	0.0%	2.9%	1.8%	2.7%	3.1%	3.3%	4.7%	2.9%	2.8%	3.7%	4.3%	1.4%	2.4%
A fumigatus	0.0%	0.0%	0.0%	1.4%	5.4%	10.7%	10.2%	9.1%	17.2%	4.8%	9.2%	5.6%	7.5%	16.2%	7.2%
S maltophilia	0.0%	2.4%	0.0%	4.3%	3.6%	9.3%	10.2%	9.9%	6.3%	7.7%	4.6%	3.7%	3.2%	4.1%	7.2%

Lung infections caused by *Pseudomonas aeruginosa* and *Staphylococcus aureus* may become chronic. Chronic infections have a reduced likelihood of being removed from the lung, and often require long-term maintenance antibiotics. Furthermore, they may cause an irreversible reduction in lung function. Chronic status is defined as having three or more positive reports in the 12-month period preceding the last reported positive culture in the reporting year.

In 2020, 218 (31.2%) adults and 44 (7.9%) children had a chronic *Pseudomonas aeruginosa* infection. This compares to 43.8% of adults and 12.8% of children in the European data[2]. Chronic *Staphylococcus aureus* infection was reported in 170 (24.3%) adults and 206 (37.0%) children.

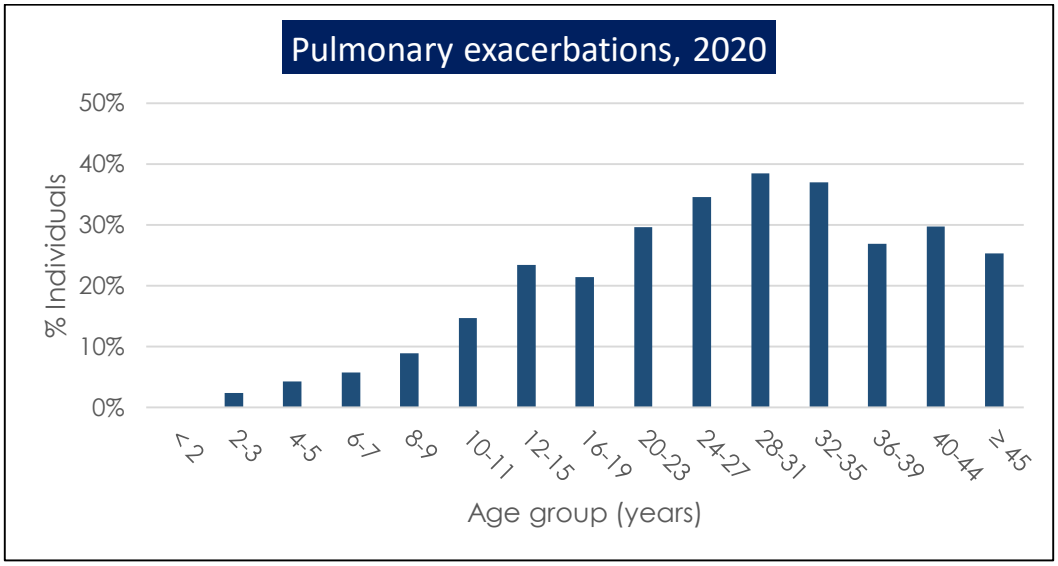


	< 2	2-3	4-5	6-7	8-9	10-11	12-15	16-19	20-23	24-27	28-31	32-35	36-39	40-44	≥ 45
Chronic PA	0.0%	0.0%	0.0%	0.0%	5.4%	8.0%	10.9%	17.4%	19.5%	34.6%	33.9%	45.4%	33.3%	33.8%	18.1%
Chronic SA	15.8%	11.9%	14.9%	24.6%	42.9%	56.0%	52.3%	33.9%	35.9%	26.9%	30.3%	21.3%	18.3%	13.5%	15.7%

Pulmonary exacerbations

A pulmonary exacerbation (PEx) is the development of a new symptom(s) or the worsening of existing symptoms, requiring treatment with intravenous (IV) antibiotics at home or in hospital.

Three hundred and three (24.1%) individuals had at least one pulmonary exacerbation which required treatment with IV antibiotics in 2020. This compares with 34.7% in 2019. Of these, 64 (12.9%, compared with 22.4% in 2019) were children and 239 (31.5%, compared with 43.0% in 2019) were adults.



Of the 303 individuals who experienced at least one pulmonary exacerbation in 2020, 141 (46.5%) had two or more. Although pulmonary exacerbations are a common characteristic of CF, the majority of individuals do not require IV antibiotics. In fact, 87.1% of children and 68.5% of adults required no IV antibiotics. This is an increase on 2019, where 77.6% of children and 57.0% of adults required no IV antibiotics.

Recurrence of pulmonary exacerbations, 2020			
Courses of IV antibiotics	Children N=407	Adults N=759	All N=1,256
0	87.1%	68.5%	75.9%
1	7.0%	16.7%	12.9%
2	2.8%	7.2%	5.5%
≥3	3.0%	7.5%	5.7%

Overall, individuals living with CF spent 9,517 cumulative days on IV antibiotics (in hospital or at home) for a pulmonary exacerbation in 2020. This compares with 12,476 in 2019. The mean cumulative duration of pulmonary exacerbation treatment over the course of the year was 31.4 days (SD=±35.3) and median cumulative duration was 22 days (IQR: 15-42 days). Children generally had a similar amount of average time per IV antibiotic as adults (14.1 days vs 16 days), although cumulatively, adults had a greater mean total duration over the year. The overall average duration per pulmonary exacerbation was 15.6 days (SD=±12.2), with a median duration per pulmonary exacerbation of 15 days (IQR: 14-17 days).

Duration of pulmonary exacerbation (PEx) treatment, 2020			
	Children N=64	**Adults N=239**	**All N=303**
Cumulative days on IV antibiotics	1,618	7,899	9,517
Mean cumulative duration of PEx treatment (SD)	25.3 (16.4)	33.1 (38.7)	31.4 (35.3)
Median cumulative duration of PEx treatment (IQR)	18.5 (15 - 36)	23 (15 - 42)	22 (15 - 42)
Mean duration per PEx treatment (SD)	14.1 (5.3)	16 (13.5)	15.6 (12.2)
Median duration per PEx treatment (IQR)	14.3 (12.6 - 15)	15 (15 - 17.2)	15 (14 - 17)

Hospitalisations

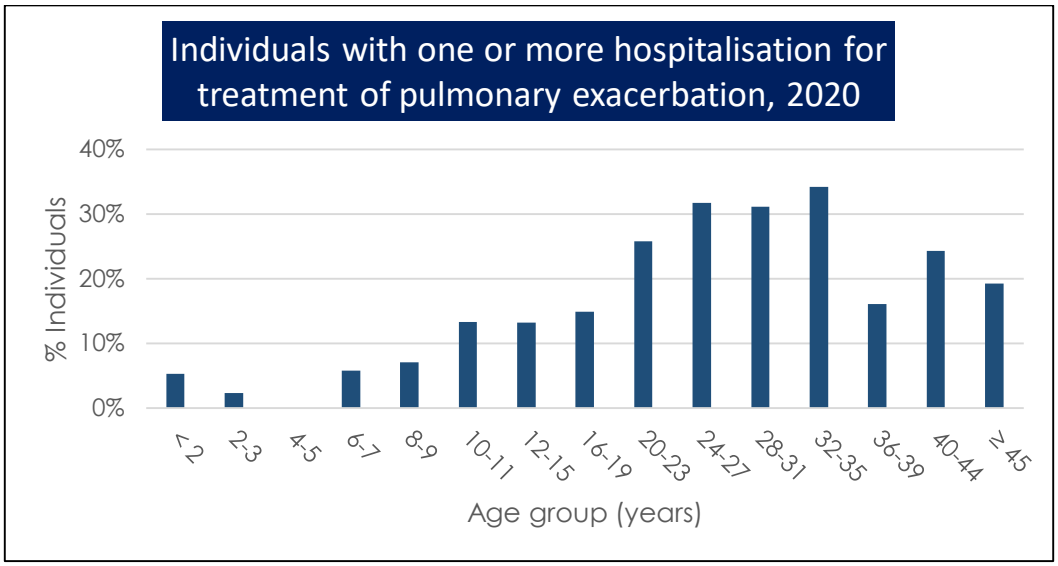
While some courses of IV antibiotic treatment for pulmonary exacerbations may be administered at home, some individuals may need to be admitted to hospital for additional care. While pulmonary exacerbations are the most common reason for individuals requiring hospitalisation, records in the registry reflect admissions for a variety of reasons, both CF and non-CF related.

In 2020, 353 individuals required hospitalisation. Overall, 707 hospitalisations were recorded for these individuals. This represents a 44% decline on the previous year. Sixty-seven percent of hospitalisations in 2020 were for the purpose of treating a pulmonary exacerbation, compared with 59% in 2019. There was a large decline in the number of CF patients being hospitalised for non-CF related reasons, from 20% of the hospitalisations in 2019 to only 7% in 2020.

Number (%) of hospitalisations				
Reason for hospitalisation	**2019**		**2020**	
CF pulmonary exacerbation	735	(58.7%)	473	(66.9%)
Other - CF related*	219	(17.5%)	142	(20.1%)
Other - not CF related	245	(19.6%)	51	(7.2%)
Unknown	53	(4.2%)	41	(5.8%)
Total	1252		707	

*Most common other CF-related hospitalisations included: planned elective admission for IV antibiotics, day case admissions for bronco-alveolar lavage, bronchoscopy, insertion/change/ removal of gastrostomy tube, port-a-cath, haemoptysis and pneumothorax, amongst other reasons.

Two-hundred and forty-one individuals (19.2%) were hospitalised for the treatment of a pulmonary exacerbation over the course of 2020 (473 hospitalisations altogether). Of these, only 43 (8.7%) were children and 198 (26.1%) were adults. Individuals in the 24-35-year-old age group had the highest proportion of hospitalisations, while a very low proportions of children required hospitalisation for pulmonary exacerbations, until their teenage years.



Of the 241 individuals hospitalised for the treatment of a pulmonary exacerbation in 2020, 100 (41.5%) were admitted to hospital two or more times in the year. Despite this, the majority of people living with CF required no hospitalisation for pulmonary exacerbations. In fact, 91.3% of children and 73.9% of adults were not admitted for pulmonary exacerbations.

Frequency of hospitalisation for pulmonary exacerbation, 2020			
Frequency of hospitalisation per patient	**Children N=497**	**Adults N=759**	**All N=1,256**
0	91.3%	73.9%	80.8%
1	6.2%	14.5%	11.2%
2	1.6%	6.3%	4.5%
≥3	0.8%	5.3%	3.5%

Overall, individuals living with CF spent 7,325 cumulative days in hospital for treatment of a pulmonary exacerbation; 778 days for paediatric care and 6,547 days for adult care. The mean cumulative duration of hospital stays for treatment of pulmonary exacerbations over the course of the year was 30.4 days (SD=±39.7) and median cumulative duration was 17 days (IQR=13-34). Children generally spent less time in hospital for treatment than adults (8 days vs 14.4 days), and had a mean cumulative duration of just 18.1 days compared to 33.1 days in adults. The average duration of hospital stays was 14.9 days (SD=±17.9), with a median duration per hospital stay of 12.8 days (IQR: 8-16).

Duration of hospital stay for pulmonary exacerbation treatment, 2020			
	Children N=43	**Adults N=198**	**All N=241**
Cumulative days hospitalisation	778	6,547	7,325
Mean cumulative duration of hospitalisation (SD)	18.1 (24.1)	33.1 (41.9)	30.4 (39.7)
Median cumulative duration of hospitalisation (IQR)	15 (6 - 20)	19 (14 - 37)	17 (13 - 34)
Mean duration per hospitalisation (SD)	9.2 (7.5)	16.1 (19.2)	14.9 (17.9)
Median duration per hospitalisation (IQR)	8 (3 - 13)	14.4 (8.6 - 17)	12.8 (8 - 16)

Outpatient hospital visits

Further to being admitted to hospital for treatment, individuals living with CF require regular outpatient visits to monitor the progression of their disease. The National Clinical Programme's Model of Care for Ireland recommends that medically stable individuals be reviewed by a specialist team every three months in an outpatient or day-care setting. The registry collects information on care delivered to individuals in a hospital outpatient setting.

In 2020, 6,907 outpatient visits by 1,256 individuals living with CF to CF specialist centres and CF clinics across the country were recorded. Sixty percent of these encounters were outpatient appointments or day-clinic reviews.

In 2020, the COVID-19 pandemic impacted on patient access to in-person hospital visits. With many clinic visits and communication with healthcare professionals happening remotely, we adapted our registry software to allow us to distinguish between a virtual and a routine clinic visit. In 2020 17% of CF encounters happened virtually, either by phone or online.

Number and type of outpatient hospital visits

	2019		2020	
Outpatient appointment	3282	(41.4%)	2519	(36.5%)
CF day-unit review/drop-in	2859	(36.1%)	1621	(23.5%)
Virtual encounter	0	(0.0%)	1176	(17.0%)
Other*	999	(12.6%)	1083	(15.7%)
Annual assessment	746	(9.4%)	488	(7.1%)
Unknown	41	(0.5%)	20	(0.3%)
Total	7927		6907	

*Most common other visits included: review of annual assessment results, first dose or level-check of IV or nebulised medication, gastrointestinal issues, pulmonary function testing, weight check, physiotherapy review and port-a-cath flush.

Long-term medications

Certain medications are recommended for long-term use (typically for more than three months), to maintain health. These include long-term inhaled antibiotics for chronic lung infections and medications for CF-related complications, such as pancreatic insufficiency.

In 2020, the most commonly prescribed medications for regular use by individuals living with CF were bronchodilator (71.3%) and mucolytic (71.1%). Furthermore, 61% of individuals used azithromycin (or other macrolide) and 64% of adults used inhaled antibiotics. Pancreatic enzyme replacement therapy (PERT), a common treatment for pancreatic insufficiency, was the most frequently prescribed long-term medication, with 86% of individuals taking PERT in 2020.

Long-term medications, 2020				
	Children <6 years N=108	Children 6-17 years N=389	Adult N=759	All N=1,256
Pulmonary				
Macrolides	67.5%	42.2%	69.4%	60.8%
Inhaled antibiotic	2.8%	21.9%	64.0%	45.7%
Mucolytic	58.3%	91.8%	62.3%	71.1%
Bronchodilator	37.0%	70.7%	76.4%	71.3%
Inhaled steroid	8.3%	18.5%	36.8%	28.7%
Oral Steroid	0.9%	2.6%	15.8%	10.4%
Gastrointestinal				
Proton pump inhibitors	20.4%	29.0%	62.6%	48.6%
Pancreatic Insufficiency				
Pancreatic enzyme replacement therapy (PERT)	73.1%	90.0%	85.8%	86.0%

CFTR modulators have revolutionized the treatment of CF, from only using medications to treat symptoms, such as antibiotics, bronchodilators and mucolytic medications, to mechanism-targeting therapies. Currently, four modulators, are authorized in Ireland, Kalydeco® (ivacaftor), Orkambi® (lumacaftor/ivacaftor), Symkevi® (tezacaftor/ivacaftor) and Kaftrio® (elexacaftor/tezacaftor/ivacaftor.

CFTR modulator therapy, 2020				
	<6 years N=108	6-17 years N=389	Adult N=759	All N=1,256
CFTR therapy				
Ivacaftor (% population)	13.9%	16.7%	18.3%	17.4%
Ivacaftor (% of those eligible)	65.2%	89.0%	73.9%	77.1%
Lumacaftor/ivacaftor (% population)	38.0%	53.7%	23.1%	33.8%
Lumacaftor/ivacaftor (% of those eligible)	87.5%	88.9%	40.0%	59.1%
Tezacaftor/ivacaftor (% population)	0.0%	1.5%	19.6%	12.3%
Tezacaftor/ivacaftor (% of those eligible)		4.6%	32.8%	27.3%
Elexacaftor/tezacaftor/ivacaftor (% population)	0.0%	14.1%	25.8%	20.0%
Elexacaftor/tezacaftor/ivacaftor (% of those eligible)		35.9%	34.5%	34.8%
Any Modulator therapy (%population)	51.9%	77.1%	65.6%	68.0%
Any Modulator therapy (% of those eligible)	80.1%	89.0%	71.1%	77.2%
Not eligible for Modulator therapy	35.2%	13.4%	7.8%	11.9%

In 2020, Kalydeco® was used as a monotherapy to treat cystic fibrosis in patients aged 4 months and above with one of the following mutations in the gene for a protein called 'cystic fibrosis transmembrane conductance regulator' (CFTR): R117H, G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N and S549R. Overall, in 2020 Kalydeco® was prescribed for 17.4% of Irish individuals with CF. This represents 77% of individuals who were eligible by age and genotype to receive the therapy.

In 2020, ivacaftor was used in combination with lumacaftor (Orkambi®) for the treatment of individuals aged 2 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. In 2020, 34% of Irish individuals with CF received Orkambi®, representing 59% of those eligible. The percentage of those eligible who were prescribed Orkambi® was greater in children (88%) than adults (40%). This was due to the alternative CFTR modulators available to older individuals in 2020.

In 2020, Symkevi® was used as a combination regimen with tezacaftor/ivacaftor for the treatment of individuals aged 12 years and older who are homozygous for the F508del mutation, or who are heterozygous for the F508del mutation and have one residual mutations in the CFTR gene. Overall, in 2020 Symkevi® was prescribed for 12.3% of Irish individuals with CF. This represents 27% of individuals who were eligible by age and genotype to receive the therapy.

Kaftrio® is a combination regimen with elexacaftor/ tezacaftor /ivacaftor. In 2020 it became available to individuals aged 12 years and older with one F508del mutation and

one minimal function mutation or two F508del mutations in the CFTR gene. Therefore, this is the first annual report from the CFRI to report on this particular CFTR modulator. Twenty percent of all Irish individuals with CF were prescribed Kaftrio® 2020, representing 34.8% of those eligible.

In 2020 some individuals were eligible to receive more than one CFTR modulator therapy. Many individuals switched therapy during the year and 190 patients received more than one modulator therapy during 2020.

In 2020 68% of individuals with CF in Ireland received a CFTR modulator therapy. At that time, 88% of individuals were eligible according to age and genotype to receive a modulator therapy, with 18% of children and 8% of adults ineligible.

Airway clearance

Airway clearance is a vital element in the ongoing management of CF disease. There are a number of different airway clearance techniques which can be adopted by individuals. The primary aim of these techniques is to clear secretions from the lungs.

Airway clearance techniques are often age-specific. The most frequently adopted airway clearance technique (ACT) by adults is autogenic drainage, a breathing technique with varying levels of shallow to deep breaths. In children, positive expiratory pressure (PEP) is the most common ACT.

Airway clearance techniques, 2020			
	Children N=497	Adults N=759	All N=1,256
Autogenic drainage	**18.5%**	**63.9%**	**45.9%**
Autogenic drainage	3.6%	63.2%	39.6%
Assisted autogenic drainage	1.8%		0.7%
Drop huffs	14.1%	1.7%	6.6%
Active cycle of breathing technique	**6.4%**	**6.3%**	**6.4%**
Active cycle of breathing technique	4.0%	2.6%	3.2%
Breathing control			
Thoracic expansion exercises	0.2%		0.1%
Forced expiration technique	3.0%	4.0%	3.6%
Positive expiratory pressure (PEP)	**93.2%**	**58.2%**	**72.1%**
Pari PEP	2.6%	2.5%	2.5%
Bubble PEP	4.6%		1.8%
Thera PEP	8.2%		3.3%
PEP mask	50.9%	36.2%	42.0%
Other PEP	1.8%		0.7%
Acapella	28.0%	18.1%	22.0%
Aerobika	39.8%	5.1%	18.9%
Cornet			
Flutter	0.6%	2.0%	1.4%
Passive techniques	**7.0%**	**0.7%**	**3.2%**
HFCWO (Vest)	2.2%	0.5%	1.2%
Postural drainage			
Percussion	6.0%	0.1%	2.5%
Vibrations			
Exercise (i.e., trampoline, etc.)	**3.8%**	**0.3%**	**1.7%**
Other	**16.5%**	**0.1%**	**6.6%**

Occasionally, in cases of severe CF disease, individuals may require oxygen therapy to maintain sufficient oxygen levels. Oxygen prescriptions may be given to individuals for different scenarios, such as while sleeping, exercising, or even for continuous use. Just over 10% of adults living with CF in 2020 required oxygen therapy at home. Non-invasive positive pressure ventilation, such as BiPAP or CPAP, may also be used by people with CF. These techniques are occasionally used for airway clearance.

Oxygen and non-invasive ventilation, 2020			
	Child	**Adult**	**All**
	N=497	N=759	N=1,256
Home oxygen therapy	1.0%	10.0%	6.5%
Non-invasive positive pressure ventilation	2.4%	10.9%	7.6%

Lung transplant

Lung transplant is an established treatment for some people with severe or end-stage lung disease. Outcomes for people with lung transplantation continue to improve. In fact, ten-year survival rates are approaching 50%[4]. The Irish National Lung Transplant Programme operates out of the Mater Misericordiae University Hospital.

The vast majority of lung transplant procedures for people living with CF in Ireland take place at the Mater Misericordiae hospital. In 2020 one individual underwent a bilateral lung transplant. This compares with seven in 2019 and 20 in 2014, the year in which the most bilateral lung transplants took place in the last decade.

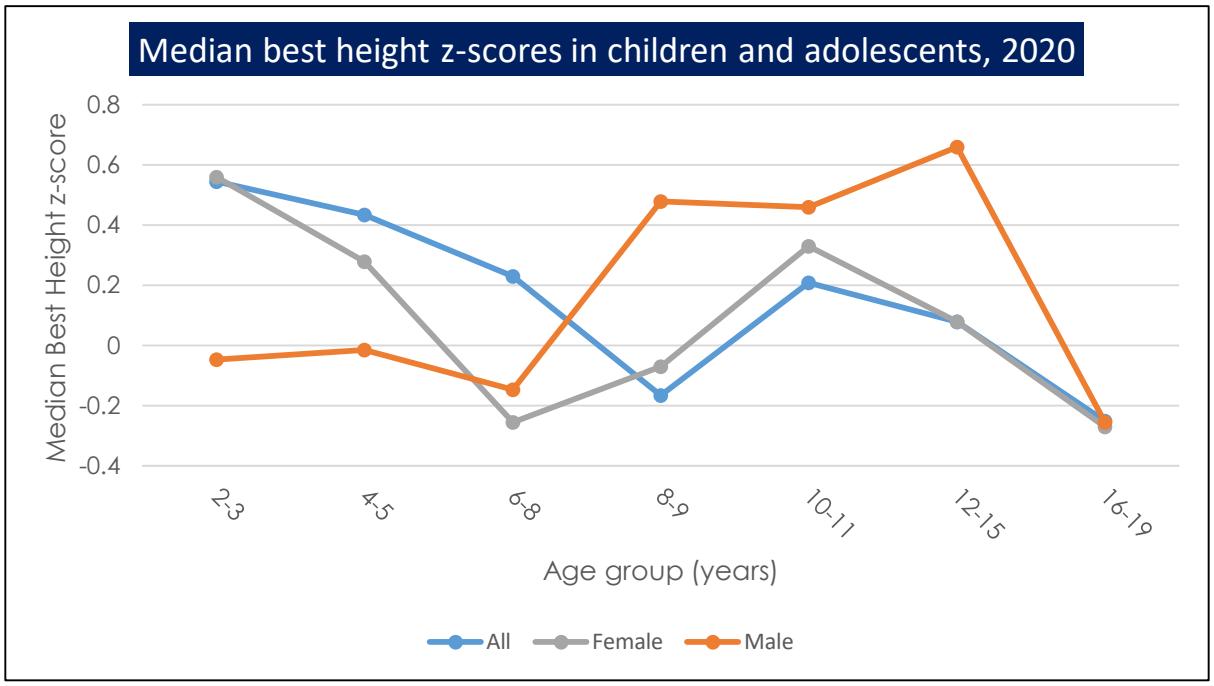
Individuals with Cystic Fibrosis receiving a bilateral lung transplant	
2011	6
2012	7
2013	10
2014	20
2015	10
2016	7
2017	10
2018	8
2019	7
2020	1
Total	76

[4] Stephenson AL et al, Clinical and demographic factors associated with post-lung transplantation survival in individuals with cystic fibrosis. J Heart Lung Transplant 2015; 34:1139-1145

Nutrition

Nutritional outcomes such as height, weight, and BMI are an important measure of health in people with CF and can be expressed using a Z-score. The Z-score is a measurement of the relationship between an individual's height, weight or BMI, and that of the average of a group of people living without cystic fibrosis. Nutritional status has a strong correlation with pulmonary function and survival in people with CF[5]. Ensuring adequate growth and nutritional status in children with CF is a major goal for CF specialist teams[6].

In order to examine the profile of nutritional health of individuals living with CF in 2020, the highest measurements of height recorded in the year were considered.

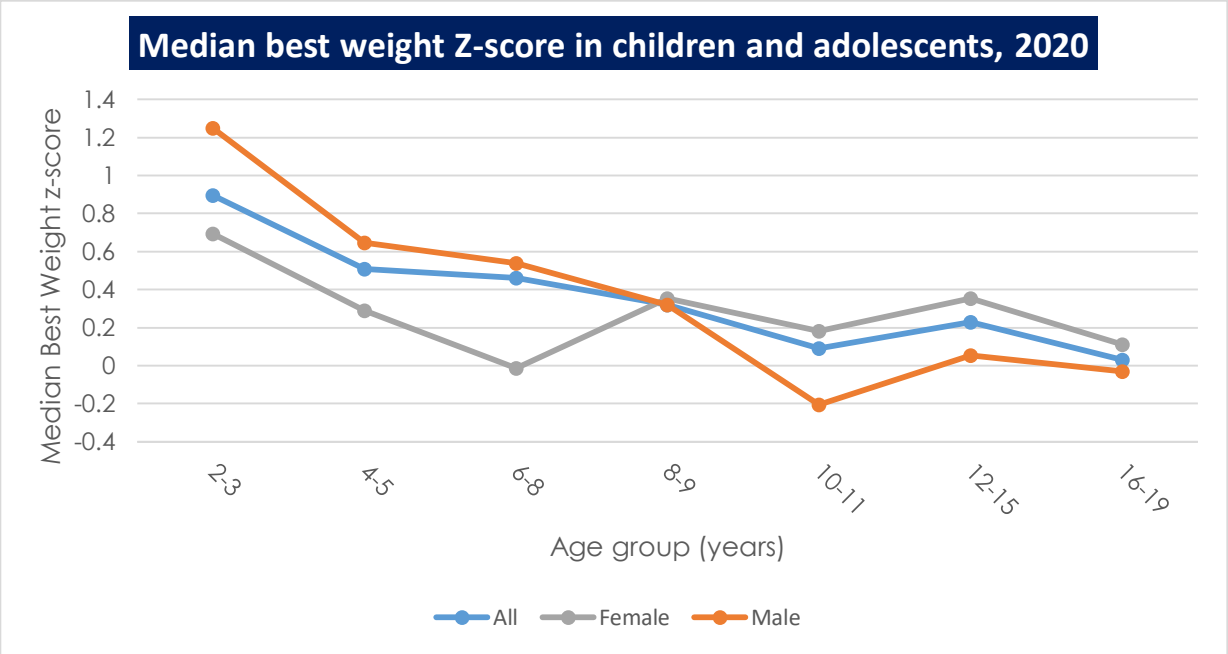


Children living with CF generally had median height Z-scores similar to the that among children without CF. The exception was the 16-19 years age group, which was below the average but still within one standard distribution from the mean.

[5] Kerem E et al, Factors associated with FEV_1 decline in cystic fibrosis: analysis of the ECFS patient registry. Eur Respir J 2014; 43:125-133.
[6] Castellani C et al, ECFS best practice guidelines: the 2018 revision. J Cyst Fibros 2018; 17:153-178

Median best height Z-scores in children and adolescents, 2020									
	All			Female			Male		
Age	N	Median	IQR	N	Median	IQR	N	Median	IQR
2-3	40	0.55	(-0.1 , 1)	19	0.56	(0.2 , 1.2)	38	-0.045	(-0.8 , 0.8)
4-5	46	0.44	(-0.1 , 1.2)	20	0.28	(-0.5 , 1.3)	70	-0.015	(-0.7 , 0.7)
6-7	69	0.23	(-0.5 , 0.9)	40	-0.26	(-0.7 , 0.5)	68	-0.145	(-0.8 , 0.3)
8-9	56	-0.17	(-0.7 , 0.6)	26	-0.07	(-0.6 , 0.7)	21	0.48	(-0.2 , 0.9)
10-11	75	0.21	(-0.6 , 0.7)	37	0.33	(-0.5 , 0.7)	26	0.46	(0.1 , 1)
12-15	127	0.08	(-0.6 , 0.7)	57	0.08	(-0.5 , 0.6)	29	0.66	(0.2 , 1.1)
16-19	115	-0.25	(-0.8 , 0.2)	47	-0.27	(-0.9 , 0.2)	30	-0.255	(-0.9 , 0.5)
All	528	0.08	(-0.6 , 0.7)	246	0.08	(-0.6 , 0.6)	282	0.05	(-0.6 , 0.7)

Interestingly, children with CF in Ireland in 2020 had median weight Z-scores which were higher than the mean, although mostly remaining within one standard deviation. This indicates adequate maintenance in nutritional status in people with CF under the age of 18.

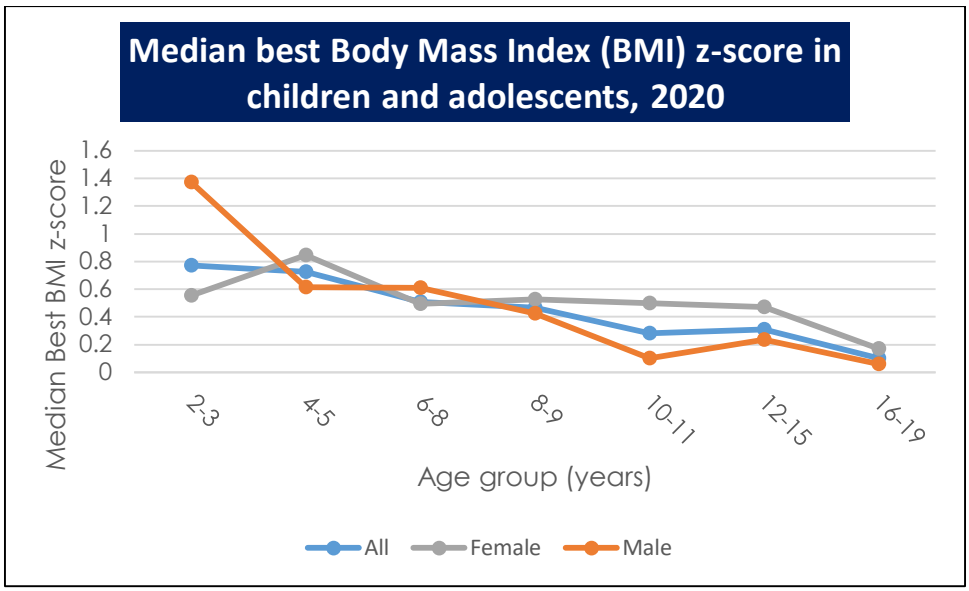


Median best weight Z-score in children and adolescents, 2020									
	All			Female			Male		
Age	N	Median	IQR	N	Median	IQR	N	Median	IQR
2-3	42	0.90	(0.4 , 1.5)	20	0.70	(0.3 , 1.2)	22	1.25	(0.6 , 2)
4-5	46	0.51	(-0.1 , 1.1)	20	0.29	(-0.4 , 1.1)	26	0.65	(0 , 1.1)
6-7	69	0.46	(-0.2 , 0.9)	40	-0.02	(-0.4 , 0.8)	29	0.54	(0.3 , 1)
8-9	56	0.32	(-0.3 , 0.7)	26	0.36	(-0.4 , 1)	30	0.32	(-0.3 , 0.6)
10-11	75	0.09	(-0.4 , 0.8)	37	0.18	(-0.3 , 1)	38	-0.21	(-0.5 , 0.7)
12-15	128	0.23	(-0.4 , 0.8)	58	0.36	(-0.3 , 1.1)	70	0.06	(-0.4 , 0.8)
16-19	118	0.03	(-0.5 , 0.7)	49	0.11	(-0.5 , 0.8)	69	-0.03	(-0.4 , 0.7)
All	534	0.28	(-0.3 , 0.9)	250	0.28	(-0.4 , 0.9)	284	0.26	(-0.3 , 0.8)

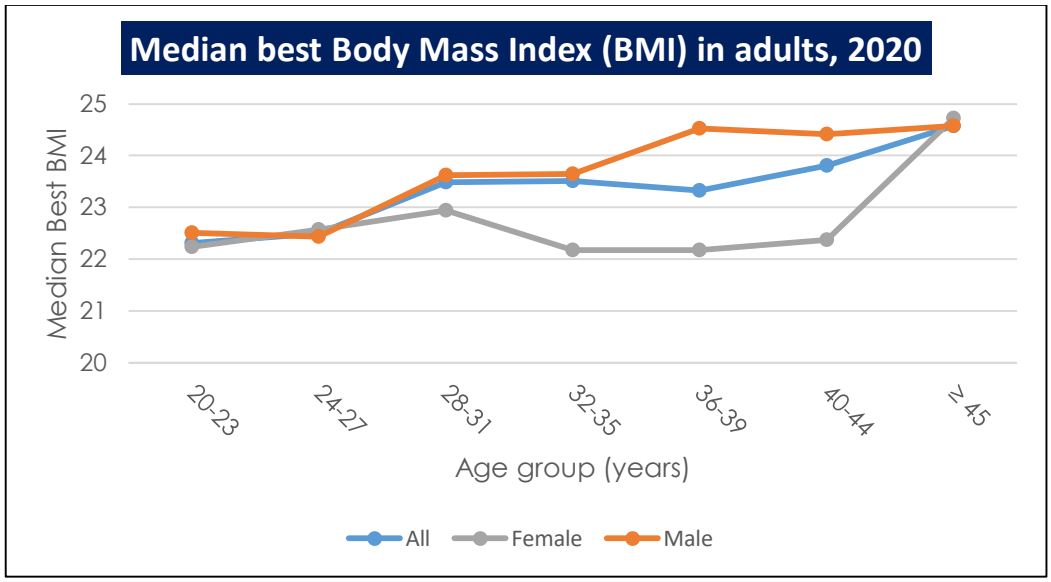
Body mass index (BMI) describes the weight/height relationship and is considered a good measure of nutritional status. In order to examine the profile of nutritional health of individuals living with CF in 2020, the highest measurements of BMI recorded in the year were considered.

In 2020, children living with CF in Ireland had median BMI Z-score higher than the mean. However, similar to median weight Z-score, the median BMI Z-score was mostly within one standard deviation of the mean.

Median best Body Mass Index (BMI) Z scores in children and adolescents, 2020									
	All			Female			Male		
Age	N	Median	IQR	N	Median	IQR	N	Median	IQR
2-3	34	0.77	(0.5 , 1.5)	18	0.56	(-0.6 , 0.8)	16	1.38	(0.8 , 2.2)
4-5	46	0.73	(0 , 1.2)	20	0.85	(0 , 1.2)	26	0.62	(0.1 , 1.1)
6-7	69	0.51	(0 , 1)	40	0.50	(0 , 1)	29	0.61	(0.1 , 1)
8-9	56	0.47	(-0.1 , 1)	26	0.53	(-0.2 , 1.1)	30	0.43	(-0.1 , 0.9)
10-11	75	0.28	(-0.3 , 1)	37	0.50	(-0.1 , 1.1)	38	0.10	(-0.4 , 0.6)
12-15	127	0.31	(-0.3 , 0.9)	57	0.47	(-0.1 , 1)	70	0.24	(-0.3 , 0.8)
16-19	113	0.10	(-0.4 , 0.7)	46	0.17	(-0.1 , 0.9)	67	0.06	(-0.5 , 0.7)
All	520	0.41	(-0.1 , 1)	244	0.48	(-0.1 , 1)	276	0.37	(-0.3 , 0.9)



The ECFS Standards of Care[7] recommend a BMI of greater than 20 kg/(m^2) in adults living with CF. In 2020, the median BMI of adults aged 20 years or older was 23.2 (IQR: 21.4-25.5). This is in line with the ECFS recommendation.



[7] Smyth AR ET AL, ECFS standards of care: best practice guidelines. J Cyst Fibros 2014; 13:S23-S42.

Median best Body Mass Index (BMI) in adults, 2020									
	All			Female			Male		
Age	N	Median	IQR	N	Median	IQR	N	Median	IQR
20-23	112	22.3	(20.7 , 24.6)	49	22.2	(21.1 , 23.5)	63	22.5	(20.5 , 25)
24-27	92	22.5	(21.2 , 23.8)	34	22.6	(21.1 , 24.8)	58	22.4	(21.3 , 23.7)
28-31	103	23.5	(21.5 , 25.4)	45	22.9	(21 , 24.5)	58	23.6	(21.9 , 25.6)
32-35	101	23.5	(21.2 , 25.9)	34	22.2	(20.2 , 24)	67	23.6	(22.4 , 26.3)
36-39	85	23.3	(21.6 , 25.8)	34	22.2	(20.1 , 23.9)	51	24.5	(22.5 , 26.4)
40-44	64	23.8	(21.9 , 26.5)	28	22.4	(20.4 , 24.5)	36	24.4	(23.1 , 27.2)
≥ 45	77	24.6	(22.2 , 26.9)	30	24.7	(21.2 , 27)	47	24.6	(22.9 , 26.9)
All	634	23.2	(21.4 , 25.5)	254	22.4	(20.7 , 24.6)	380	23.6	(21.8 , 25.8)

In 2020, 67% of adults and 71% of children were in the normal weight category based on BMI and BMI z-scores. Almost 34% of adult males were in the overweight category, compared with 23% of adult females. Only 3.6% of adults and 7.2% of children were in the underweight category.

Nutrition Categories based on BMI (adults) and BMI z-score (children), 2020						
	All		Female		Male	
Age	Children	Adults	Children	Adults	Children	Adults
Underweight	7.2%	3.6%	6.6%	5.1%	7.7%	2.6%
Normal weight	71.0%	66.9%	68.7%	72.0%	73.1%	63.4%
Overweight	21.8%	29.5%	24.7%	22.8%	19.2%	33.9%

In order to maintain or improve individuals' nutritional status, supplemental feeding may be required. Guidelines recommend differing interventions depending on the level of malnutrition[7], ranging from reinforcement of adherence to diet for anticipatory guidance, to feeding via NG or gastronomy tubes in severe cases of malnutrition. In 2020, over 44% of individuals with CF required supplemental feeding. Although most took oral supplements, one in ten required gastronomy tubes. Multiple approaches were adopted by some individuals in the reporting year.

Supplemental feeding, 2020 (n=1,256)			
	Any supplemental feeding	Oral supplements	Gastrostomy tube/button
<2	10.5%	0.0%	10.5%
2-3	14.3%	11.9%	4.8%
4-5	36.2%	34.0%	0.0%
6-7	50.7%	42.0%	5.8%
8-9	55.4%	50.0%	10.7%
10-11	53.3%	46.7%	6.7%
12-15	53.1%	44.5%	12.5%
16-19	49.6%	30.6%	20.7%
20-23	47.7%	35.9%	16.4%
24-27	56.7%	48.1%	11.5%
28-31	43.1%	35.8%	11.9%
32-35	49.1%	40.7%	11.1%
36-39	33.3%	30.1%	6.5%
40-44	37.8%	32.4%	6.8%
≥ 45	25.3%	22.9%	1.2%
All	44.5%	36.4%	10.4%

Complications

Individuals living with CF may develop a variety of complications. Complications of CF affect many organ systems, and can interfere with a person's health and quality of life. These complications often occur through the build-up of thick mucus in particular organs such as the digestive system, similar to the effects on the lungs.

Gastro-oesophageal reflux disease was the most frequently reported complication in both adults and children living with CF in 2020, affecting 55.1% of adults and 25.4% of children. Sinus disease (40.2%), CF-related diabetes (30.3%), and osteoporosis (20.6%) were also common among adults. As CF is a progressive disease, fewer children tend to suffer CF-related complications than adults. Sinus disease (6.2%), liver disease (5.0%), and allergic bronchopulmonary aspergillus (ABPA) (4%) were the most common complications among children with CF in 2020.

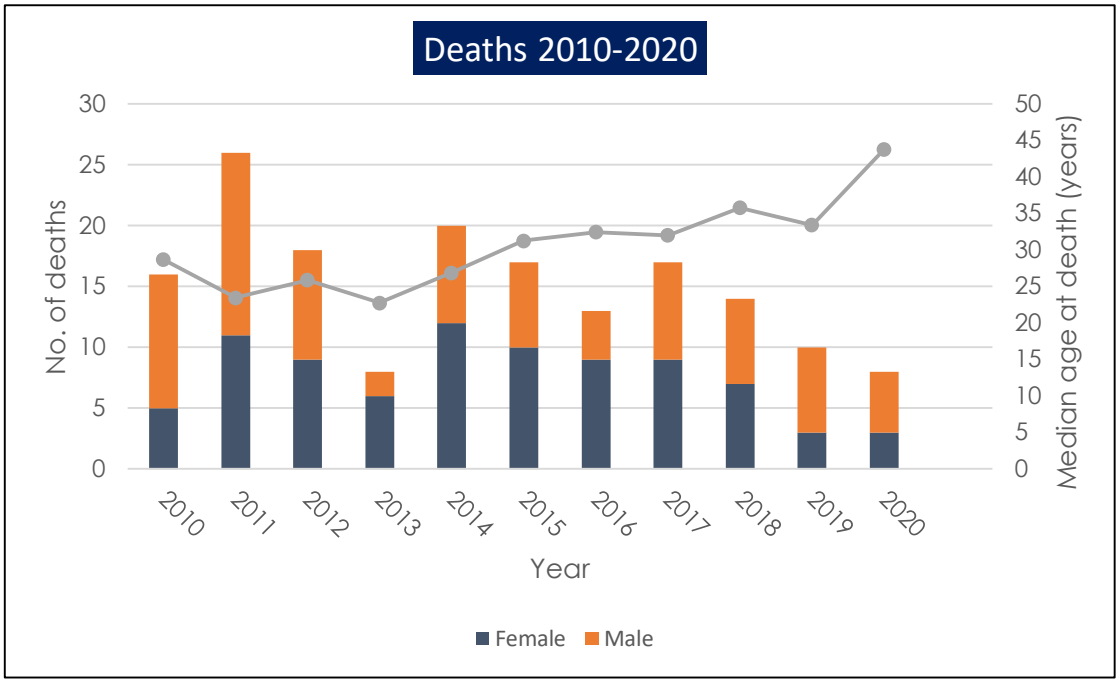
Complications, 2020			
	Child N=497	Adult N=759	All N=1,256
Respiratory related			
Allergic Bronchopulmonary Aspergillosis	4.0%	8.2%	6.5%
Nasal polyps	3.4%	6.5%	5.3%
Asthma	2.2%	13.4%	9.0%
Symptomatic sinus disease	6.2%	40.2%	26.8%
Hepatobiliary & pancreas			
Elevated liver enzymes	0.4%	0.0%	0.2%
Liver disease other than cirrhosis	5.0%	11.2%	8.8%
Cirrhosis with portal hypertension	0.8%	5.3%	3.5%
Cirrhosis without portal hypertension /hypertension status unknown	0.6%	0.7%	0.6%
Impaired OGT	3.6%	8.4%	6.2%
CF related diabetes (CFRD)	3.4%	30.3%	19.7%
Gastrointestinal			
Gastro-oesophageal reflux	25.4%	55.1%	43.3%
Distal intestinal obstructive syndrome	1.0%	5.4%	3.7%
Musculo-skeletal			
Osteopenia	0.8%	16.9%	10.5%
Osteoporosis	1.0%	20.6%	12.8%
Arthritis/arthropathy	0.4%	3.4%	2.2%
Other			
Depression	0.8%	7.9%	5.1%

Survival

As a result of developments in the management of CF disease, survival among individuals has improved dramatically. However, unfortunately, people living with CF still die younger than the national average, mostly as a result of respiratory failure[5]. The number of deaths varies from year to year. Since 2010, an average of 15 individuals have died annually (range: 8-26).

In 2020, nine individuals living with CF sadly passed away (three female; six male), of which eight were registered with CFRI. All of these individuals died between the ages of 21 and 86 years old, with a median age of death of 43.8 years. As median age of death is based solely on the length of life in people with CF who died during the year, it is an underestimate of how long those alive will continue to live.

Of the nine deaths in 2020, four (50%) were due to respiratory or cardiopulmonary causes and one (12.5%) from liver failure. The cause of death in the remaining four individuals was not known to the registry.



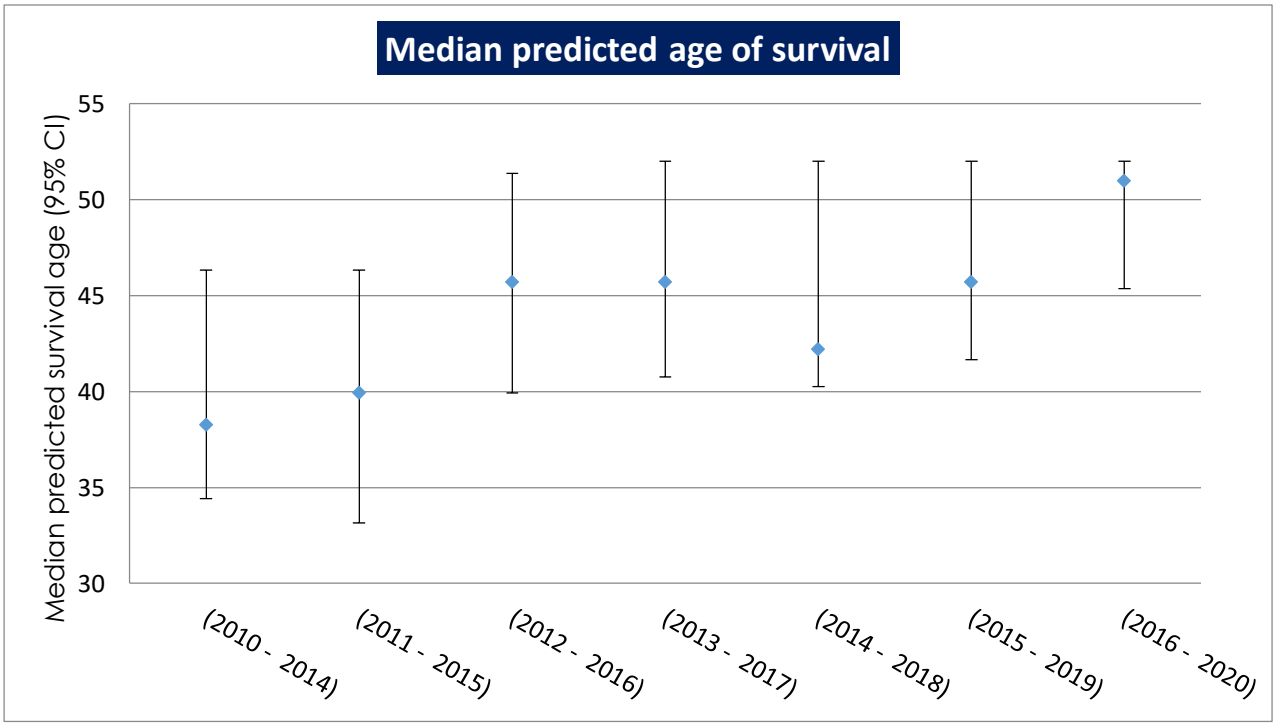
*This graph includes only the individuals registered with the CFRI

Of the registered CF population, 0.6% died in 2020. This compares to 0.8%[2] in Europe in 2019 and 0.8%[8] in the US in 2020. The calculation of median predicted survival is based on people with CF who are recorded in the registry as alive in the given year. The median predicted survival age predicts how long we can expect half of people with CF born today

[8] CF Foundation 2020 Patient Registry Annual Data Report. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf

to live. The age to which individuals living with CF born today are predicted to live to is at least 51 years. This assumes that current age-specific mortality rates will not change for the rest of their lives. As such, the approach does not take into account any potential benefits from improved CF care.

Data from single years can show large variations in predicted median survival age. A rolling five-year predicted age of survival has been predicted and is presented below, as grouping together several years of data gives more robust estimates.



Median predicted age of survival				
	Total	Deaths	Median predicted survival age	95% CI
(2010 - 2014)	1273	88	38.3	(34.4 , 46.3)
(2011 - 2015)	1298	89	39.9	(33.1 , 46.3)
(2012 - 2016)	1300	76	45.7	(39.9 , 51.4)
(2013 - 2017)	1313	75	45.7	(40.8 , 52.0)
(2014 - 2018)	1321	81	42.2	(40.3 , 52.0)
(2015 - 2019)	1328	70	45.7	(41.7 , 52.0)
(2016 - 2020)	1332	61	51.0	(45.4 , 52.0)

Applications for CFRI data

One of the CF registry's founding principles is to promote and facilitate the use of clinical data in approved research projects.

Requests for information held by the registry are assessed by the registry's scientific committee. If approved, data provided to third parties are anonymised (all identifiable data such as name, date of birth, home address, is removed). The data is summarised by the CFRI statistician and a report is prepared for the requester. This means that individuals in the registry cannot be identified from the data shared with third parties. In 2020, 5 data applications were approved. See https://cfri.ie/data-applications-2/ for details.

The Irish CF registry contributes annually to the European CF Society Patient Registry (ECFSPR). The ECFSPR Annual Reports can be accessed here: https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports

Research papers & presentations in 2020

CFRI publications

AD Jackson, L Kirwan, S Gibney, P Jeleniewska, G Fletcher, G Doyle (2020) Associations between health literacy and patient outcomes in adolescents and young adults with cystic fibrosis. European journal of public health 30 (1), 112-118

ECFSPR publications

Naehrlich L, Orenti et al. Incidence of SARS-CoV-2 in people with cystic fibrosis in Europe between February and June 2020. Journal of Cystic Fibrosis 2021; April 17. DOI: https://www.cysticfibrosisjournal.com/article/S1569-1993(21)00099-0/fulltext#seccesectitle0022

McKone EF, Ariti C, Zolin A, on behalf of the ECFSPR, Survival estimates in European cystic fibrosis patients and the impact of socioeconomic factors: a retrospective registry Cohort study. https://erj.ersjournals.com/content/58/3/2002288.

Kotnik Pirš A, Krivec U, Trebušak Podkrajšek K. The c.3140-26A>G Variant of the CFTR Gene in homozygous state causes mild cystic fibrosis Overview of longitudinal clinical data of the patient managed in our centre and review of the literature. Acta Chimica Slovenica 2020;67:666-673. https://dx.doi.org/10.17344/acsi.2019.5677.

Financial information

Financial information for Cystic Fibrosis Registry of Ireland CLG, 2020 January - December		
Income & Expenses		2020 €
Income		
Core Funding		140,000
Special Projects Grants		510,000
Unrestricted Grants		775
Commissioned Research		16,133
Data Request Fees		
Sundry income		600
	Total income	667,508
Expenses		
Wages & salary		261,462
Employer's PRSI		22,694
Staff training		
Rent payable		6,073
Insurance		762
Computer network & server costs		12,526
Telephone, fax and video conferencing		767
Printing, postage and stationery		4,144
Travelling & subsistence		8,766
Legal Fees		5,068
Staff Welfare		2,600
Audit		3,690
Bank charges		5
Sundry expenses		4,445
	Total expenses	333,002
	(Deficit)/Surplus	334,506

The full audited accounts were prepared by Hayden Brown, Chartered Accountants, Grafton Buildings, Grafton Street, Dublin 2 and copies are available upon written request to CFRI

Acknowledgements

There are many individuals and groups that have contributed to and supported the work of the Cystic Fibrosis Registry of Ireland during this reporting year.

First we would like to thank all those who have financially supported the registry. This includes the HSE (through our Service Level Agreement), Cystic Fibrosis Ireland, our industry partners who have provided us with unconditional grants, and other funded researchers who have included us in their research grant applications. Without your support CFRI could not survive.

Most importantly we would like to thank each person with CF and/or their guardian for consenting for their medical data to be collected and used in a de-identified form to drive research into the development of new treatments and models of care for cystic fibrosis patients nationally and internationally.

We would also like to thank every member of the CF multi-disciplinary teams in every centre who assist our Research Associates in collecting data and assist in the patient consent process.

Our CFRI staff, Mr Sam Babu, Dr Huw Rees, Dr Megan Rice, Dr Abi Jackson and Dr Laura Kirwan deserves special thanks for working tirelessly in the collection and preparation of quality data that contributes so much to CF research, service and treatment development, and quality management. Particularly for the extra work that had to be done to assist with the development of the new registry technology.

Our management committee have been very supportive during the year and are always available when any assistance is required. We thank our research committee for their input during the year.

We would also like to thank UCD for supplying us with affordable accommodation through the sponsorship of the School of Public Health, Physiotherapy and Sport Science. We appreciate the support and mentorship of Prof Kelleher and her colleagues who have made an invaluable contribution to our own internal research programme.

The HSE's Health Intelligence Unit have been particularly supportive and special thanks go to Dr H Johnson and Dr F Donohue.

We would to thank the National Bloodspot Screening Programme Governance Group (NNBSPGG) for confirming the numbers of infants detected in 2020 by the National Newborn Bloodspot Screening Programme screening programme.

Finally, we thank Dr Laura Kirwan and colleagues for preparing this report.

Appendix 1: Abbreviations

Abbreviation	
AA	Annual Assessment
ABPA	Allergic Bronchopulmonary Aspergillosis
ACT	Airway Clearance Technique
ADULT	Aged 18 years or older (≥18)
AMCNH	Adelaide and Meath Hospital Inc. the Children's National Hospital
BMI	Body Mass Index
BMT	Beaumont Hospital
CFRD	Cystic fibrosis-related diabetes
CFRI	Cystic Fibrosis Registry of Ireland
CFTR	Cystic Fibrosis Transmembrane conductance Regulator (mutation)
CHILD	Aged under 18 years (<18)
CRA	Clinical Research Associate
DIOS	Distal Intestinal Obstruction Syndrome
ECFS	European Cystic Fibrosis Society
FEV_1	Forced Expiratory Volume in one second
$ppFEV_1$	FEV1 percent predicted
HSE	Health Service Executive
IRT	Immunoreactive trypsinogen
IV	Intravenous
IQR	Interquartile range
MRSA	Methicillin Resistant Staphylococcus aureus
NBS	Newborn screening
NCMG	National Centre for Medical Genetics
OLCH	Our Lady's Children's Hospital, Crumlin
PAEDIATRIC	Aged under 18 years (<18)
PEP	Positive expiratory pressure
PERT	Pancreatic enzyme replacement therapy
PEx	Pulmonary exacerbation
RCSI	Royal College of Surgeon's Ireland
SVUH	St Vincent's University Hospital
TCD	Trinity College Dublin
UCD	University College Dublin
UHG	University Hospital Galway
UHL	University Hospital Limerick

Appendix 2: Technical notes

Data collection sites

In 2020, the CFRI gathered data from the eight HSE-designated CF specialist centres (Beaumont Hospital, St Vincent's University Hospital, CHI (Children's Health Ireland) group (including National Children's Hospital, Tallaght, Our Lady's Children's Hospital, Crumlin, Temple Street Children's University Hospital), University Hospital Galway, Cork University Hospital and University Hospital Limerick), five CF clinics (Cavan General Hospital, Mayo University Hospital, Our Lady of Lourdes Hospital, Drogheda, Sligo University Hospital, and University Hospital Waterford) and the Irish National Lung Transplant Programme at the Mater Misericordiae University Hospital Dublin.

Lung function

As spirometry cannot reliably be performed until the age of 6 years, only reported values for CF individuals aged 6 and older were considered. For individuals who were reported to have had a lung transplant in or before 2020, their FEV1% predicted values in the year of transplant and post-transplant were excluded. The best value of the year was considered. The Global Lung Function Initiative equations described by Quanjer PH *et al.* [8] was used.

Nutrition

Heights and weights recorded at the patient's best FEV1% predicted of the year were included in the analysis. Where no spirometry was performed, the nutrition record with the best weight measurements in the year was considered. The reference group used to estimate Z scores was the Centre for Disease Control (CDC) 2000 reference charts. [9]

Z scores are a statistical measurement of the relationship between an individual's height/weight/BMI, and the mean of a group of reference individuals. A z-score of 0 means that the measurement (e.g. height/weight/BMI) is equal to the mean measurement of individuals of the same age and sex in the reference (i.e. healthy population). A z-score of -2 means that the value is two standard deviations below the mean of people of the same age and sex in the reference population, and a score of +2 means that the value is two standard deviations. The average score for a healthy population is typically zero.

[8] Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations'. Report of the Global Lung Function Initiative (GLI), ERS Task Force to establish improved Lung Function Reference Values, Eur Respir J. 2012; 40(6): 1324–43.
[9] Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC Growth Charts for the United States.

Appendix 3: Members of the Board of Directors 2020

Prof Ed McKone	Chairperson	Consultant in Respiratory Medicine St. Vincent's University Hospital, Dublin
Prof Cedric Gunaratnam	Vice Chairperson	Consultant in Respiratory Medicine Beaumont Hospital, Dublin
Dr Marion Rowland	Secretary	Lecturer UCD School of Medicine & Medical Sciences, Dublin
Mr John Coleman	Treasurer	CF Ireland
Prof Gerry McElvaney		Professor of Medicine, Royal College of Surgeons in Ireland & Consultant in Respiratory Medicine Beaumont Hospital, Dublin
Prof Peter Greally		Consultant in Paediatric Respiratory Medicine Tallaght University Hospital, Dublin
Prof Paul McNally		Consultant in Paediatric Respiratory Medicine Our Lady's Children's Hospital, Crumlin
Dr Barry Linnane		Adjunct Associate Professor, University of Limerick School of Medicine, Paediatric Respiratory Consultant, University Hospital Limerick, Limerick
Prof Barry Plant		Consultant in Respiratory Medicine Cork University Hospital, Cork
Mr Philip Watt		Chief Executive CF Ireland, Dublin

Cystic fibrosis is an inherited condition that affects many body functions such as breathing, digestion, and reproduction. This lifelong condition usually becomes more severe with age and affects both males and females in equal proportions. The symptoms and severity of cystic fibrosis vary from person to person. The majority of people have both respiratory and digestive problems. There is no cure for cystic fibrosis. Life expectancy has increased steadily over the past 20 years, and today cystic fibrosis is no longer exclusive to childhood.

Better treatment strategies help to improve the length and quality of life of people with CF by controlling their symptoms. Improved treatments can be developed using patient registries. Cystic fibrosis registries gather information on all aspects of a patient's condition. They act as information storehouses for infection and treatment statistics. Detailed analysis of this information can yield significant findings about the most effective treatments for CF. It is through these analyses that better management of CF may be achieved.

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Company Number: 635291

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