Foreword

This eighth report by the Dutch CF Registry (Nederlandse CF Registratie) has been made possible with the cooperation of a large group of Cystic Fibrosis (CF) patients and the efforts of many people in the CF centres. This report includes the data of 1521 of the estimated 1545 people with CF and CF-related disease in the Netherlands. This is 98% of all Dutch patients with CF.

CF is a complex illness, and there are many factors that influence the progress of the disease. The treatment is such a factor. To be able to compare and interpret the information on the treatment in different centres, the possible related factors have to be taken into account.

Since 2014, the data for the CF centres also include the name of the centre. This is done to promote transparency. Since 2014, data about the so-called indicators have also been added: figures and values which say something about aspects of the quality of care offered in the CF centres. But I would stress that the interpretation of the tables and diagrams must be done with great care. The quality of care in a CF centre is influenced by many factors and is hard to capture in one number or diagram. This means that a centre where, for example, the average pulmonary function is high, not automatically also offers the best care.

New in this report is the information about pregnant women with CF and about the use of Kalydeco and Orkambi. Kalydeco is the first drug which is available for patients with CF and certain class-III mutations, and which engages the basic cell problem in CF. Orkambi has been registered for patients with a dual F508del mutation.

This report presents the information for each centre separately and also at a national level. The CF centres have received an overview of their data in relation to the national averages. Every year, the Nederlandse Cystic Fibrosis Stichting organises meetings with the centres’ paediatric pulmonary specialists, pulmonary specialists, paediatric gastro-enterologists and paediatric nutritionists. At these meetings, the treatment, results and differences between the centres are discussed in an open and positive atmosphere. When relevant differences are found in a number of areas, these are further discussed and, where possible, guidelines are developed. In October 2016, the development of a new Guidelines and Standard of Care project has started, covering all aspects of the diagnosis, treatment and support of CF patients.

The shared ambition of the CF centres and the NCFS remains unchanged: Better care, resulting in a better and longer life for people with CF.

October 2016

Jacquelien Noordhoek, chair of the Dutch CF Registry steering group

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Summary

Key findings from the Dutch CF Registry 2015:

- In The Netherlands, there are approximately **1540 people with CF** or CF-related disease*.
- More than half of them are over 17 years of age. The oldest patient with CF in The Netherlands is 74 years old. The number of people aged over 50 with CF is 70 (59 in 2014).
- Almost half of the children were diagnosed before the age of 2 months. In 2010, this was 4 months. 7% of patients were diagnosed after they reached the age of 18 years.
- In The Netherlands, there are **more men** (52.7%) than women (47.3%) with CF.
- 88% has at least one **F508del mutation**.
- In 2015, 16 patients with CF underwent a lung transplant. There are 101 patients with CF in the Registry who underwent a lung transplant and who were alive in 2015.
- At the end of 2015, 24 patients with CF were on the waiting list for a lung transplant, a similar number to 2014 (22).
- In 2015, 12 adults and one child with CF passed away. Half of them were younger than 42 years of age.
- More than half of the children has a pulmonary function (FEV1) higher than 90% of the predicted value. Half of the adults has a pulmonary function (FEV1) higher than 66% of the predicted value. The pulmonary function of children and adults with CF has gradually improved over the past years.
- The nutritional condition (height to weight) of children with CF is, on average, comparable to that of healthy peers. On average, children with CF are less tall than their healthy peers. The average nutritional condition of adults with CF has remained the same over the past few years. The differences between the centres have decreased. The nutritional condition of children with CF has gradually improved over the past years.
- 50 % of children and 43% of adults with CF uses **food supplements**.
- A third of all patients has a chronic **Pseudomonas aeruginosa** infection. For adults, the percentage is 51%, and for children 13%.
- 20% of patients with CF has **CF-related liver disease**.
- **CF-related diabetes** occurs in 9% of the children and 32% of the adults.
- One in five children and one in three adults was given an intravenous course of antibiotics at the hospital in 2015. One in ten children was given an intravenous course of antibiotics at home. For adults, this was one in four.
- Of the adults, 62% has a **job**, studies or goes to school. One percent is retired.

* For the registry, the diagnosis CF is reserved for when two mutations are known which have been established to cause CF (according to the CFTR mutation database CFTR2); and/or when the chloride content in the sweat test is 60 mmol or higher. In 1409 (92.6%) of the 1521 registered patients, the diagnosis CF has been confirmed.
Introduction

The Nederlandse Cystic Fibrosis Stichting (NCFS) has coordinated, managed and financed the Dutch CF Registry since 2007, and publishes an annual report on the situation in the Netherlands. The Registry steering group is composed of representatives from all the CF centres and the NCFS. The steering group defines the policy of the Registry.

All information from the national registry is anonymised. The only person who can deduce the data to an individual patient is the patient's own doctor at the CF centre. Each CF centre enters the details of their own patients and keeps these updated to follow their progress. The quality of the data is being systematically monitored by the research coordinator at the NCFS, with automated checks in the software, and by the statisticians of the European Registry. Strict checks are carried out to ensure that patient data are not traceable by others. The Dutch and European laws and regulations are applicable.

The Dutch CF Registry has been registered with the Board of Dutch Data Protection (College Becherming Persoonsgegevens), which ensures that the privacy legislation is complied with. Patients with CF are informed about the Registry and have given their consent in writing for the recording of their (anonymous) data in the Registry. A small number of patients (20; 1.3%) refused to participate in the Registry.

CF registries are carried out in more than 30 countries, recording the medical details of patients with CF. The objective is to support scientific research and to improve the care and treatment of patients with CF. The Dutch CF Registry also provides information to the European CF Registry (http://www.ecfs.eu/projects/ecfs-patient-registry/intro). The NCFS is actively involved in the European CF Registration.

The Dutch CF Registry has adopted the definitions of the European CF Registry (http://www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions). The use of data from the Dutch or European Registry requires the approval of the Dutch steering group or the European review board. These consist of national or European CF specialists and experts in the field of legal and ethical aspects of the use of personal data, respectively. Requests for information from the Dutch or European Registry can be submitted via application forms which are available on the websites https://www.ncfs.nl/onderzoek/cf-registratie and http://www.ecfs.eu/. Annex 1 shows the requests for data from the registry from 2015.

Each year, a report is drawn up. These reports are available on the NCFS website: https://www.ncfs.nl/onderzoek/cf-registratie. The report can also be downloaded in English. If you have questions or comments, you can contact the NCFS research coordinator via info@ncfs.nl.
1 Methods

The Dutch CF Registry records the medical and personal details of patients with CF. The steering group of the Dutch Registry has determined which parameters with related definitions are to be recorded, and mainly bases this selection on the variables that are measured in the European Registry. This results in a database with the data of approximately 40,000 European patients with CF. The definitions applied to the parameters are almost identical to the definitions of the American CF registration; this contains the data of a further 28,000 patients with CF.

For the purposes of the 2015 report, the seven Dutch CF centres entered the data of approximately 150 variables into an Excel file. These data were collected during the year. For the pulmonary function, the highest value recorded in that year is recorded, in line with the European definitions. Some CF centres could not provide all the variables, as these are not recorded at the centre. Data on these variables are not included in this report.

As regards the pulmonary function, the same reference values are used for all centres, namely the international reference values in accordance with the Global Lung Function Initiative (GLI 2012; http://erj.ersjournals.com/content/early/2012/06/27/09031936.00080312.abstract?papetoc).

For the calculation of Z scores for the growth in children (weight to height and BMI), the Growth Analyzer application by the Stichting Kinderen Groei in Rotterdam was used. The reference values of the Dutch population from 2010 (Talma) are used.

Percentages and averages or medians are determined per centre for the various items. Important outcome parameters, such as the pulmonary function value FEV1 and Body Mass Index for the nutritional condition are displayed as an uncorrected value, only for patients with a confirmed diagnosis of CF and whom have not had a lung transplant. The FEV1 and Body Mass Index are also displayed per age group.

1.1 Outcome parameters and Confounder Analysis

Outcome parameters such as FEV1, BMI and weight to height say something about the quality of care patients receive. However, there are many factors that influence the FEV1, BMI and weight to height. Some of them can be influenced by the centre (for example the treatment), but others are not. These are also referred to as ‘confounders’. The steering group has identified the following possible confounders: sex, age, age at diagnosis, ethnic background, severity of the mutation class, meconium ileus, pancreatic insufficiency and historical lung transplant. The socio-economic status can be a confounder, but the Registry does not contain any data on this factor.

In consultation with a clinical epidemiologist of the Julius Centre in Utrecht, the differences per centre in FEV1, BMI, BMI Standard Deviation Score (SDS) and weight to height SDS are corrected for most confounders (sex, age, pancreatic sufficiency, meconium ileus, severity of the mutation class (1,2,3 versus 4,5) and ethnic background). The analyses were carried out separately for children and adults. Patients who underwent a lung transplant were not included in the analysis, because this would distort the picture.

The variable ‘age at diagnosis’ is not included in the analysis, because insufficient data were available in a number of centres. The median age at which the patients were diagnosed hardly differs from the centres for which data are available.

We looked at the differences between the centres with a multi-variable linear regression model, both for children and adults. The possible influence of confounders was examined by adding them to the model.
Differences between centres do not change significantly after correction (adjustment) for possible confounders. This is in line with the conclusions from the analysis of the American and English CF Registry. This provides room for a detailed analysis of possible predictors of differences between centres.
2 Demographic data

In the ‘Guidelines on diagnosis and treatment of CF’ (2007) and in the report ‘Centre Care’ (NCFS 2003), it is recommended that patients with CF visit a CF centre at least once a year. In 2015, the seven Dutch CF centres were treating approximately 1540 people with CF and CF-related disease. More than half of them (57%) are over 17 years of age. The number of adults is increasing gradually, while the number of children appears to remain reasonable constant in the last five years. The data of 1521 (98.7%) patients with CF (93%) and CF-related disease (7%) are included in the Registry for 2015. The analyses about the diagnosis, treatment and complications, only include the data of people with a confirmed diagnosis of CF. Twenty people (1.3%) did not give consent for their data to be included. Where adults are mentioned, these are understood to mean persons of 18 years of age or older.

In the presentation of the following summaries, the data for all registered patients are used.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of patients in the Registry</th>
<th>Number of adults (≥18 years)</th>
<th>Number of children (&lt;18 years)</th>
<th>Percentage of men</th>
<th>Percentage of women</th>
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<th>Median* age in years</th>
<th>Average age in years</th>
<th>Standard deviation</th>
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<td>9.4</td>
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* The median value indicates that half of the patients has a value which is higher than the median and the other half has a value that is lower.
### Number of patients in the Registry per centre

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<td>1374</td>
<td>1452</td>
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<td>1499</td>
<td>1521</td>
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</table>

**Figure 1. Number of children and adults per centre**
3 Diagnosis

The diagnosis CF is often made at a young age, but increasingly when patients have reached adulthood. Almost 50% of children were diagnosed before the age of 2 months. However, 7.1% of patients were diagnosed after they reached the age of 18 years.

3.1 Screening

In 25.8% of children, the diagnosis CF is made after the CF screening through the neonatal heel prick. Since 2008, newborns in a number of provinces have been screened for CF after birth through this heel prick as part of a trial. This screening was rolled out for all newborns in the Netherlands from May 1, 2011.

Figure 2 shows the number of children per year who are diagnosed with CF through the heel prick. It is very likely that a number of children born at the end of 2015 and diagnosed with CF a few weeks later were not included in the registry for 2015. These will be included in the registry for 2016.

It is well known that a small number of children are not immediately diagnosed with CF after the heel prick, but only at a later age. It is therefore important to remain alert to symptoms that may indicate the presence of CF.

![Number of children diagnosed after newborn screening per year](image)

Figure 2. Number of children diagnosed after the heel prick screening every year

3.2 Symptoms at the time of diagnosis

The symptoms that lead to the diagnosis of CF can vary immensely. In children born with an MI (meconium ileus, 19.4% of the children), the diagnosis CF is easily made. In 55% of cases, failure to thrive or bad nutritional condition leads to the diagnosis CF. In 38% of children, the diagnosis is made on occurrence of respiratory problems and in 15% because CF occurs in the family. Other symptoms and combinations are also found.
3.3 Mutations

In 97.6% of patients, the results of genetic tests is known. For children, this is 99.5%.
The percentage of patients with a F508del mutation on both chromosomes (homozygous) is 52.8%. In
children, this is 56.4%, while the figure for adults is 50.1%.
The percentage of patients with a F508del mutation on one chromosome and another mutation on the
other chromosome (heterozygous) is 35.4%. In children, this is 35.0%, while the figure for adults is
35.7%.
The percentage of patients with a non-F508del mutation on both chromosomes is 8.9%. In children,
this is 8.3%, while the figure for adults is 9.3%.
In 88.2% of patients, the F508del mutation occurs on at least one chromosome. The other mutations are much rarer. Table 1 shows the most frequent mutations (occurrence more than 0.5%) in patients which had their DNA tested. In the calculation of the percentages, both ‘arms’ (alleles) of the chromosomes were included.

<table>
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<tr>
<th>Mutation</th>
<th>Frequency (%)</th>
<th>Mutation class</th>
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<tbody>
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<td></td>
</tr>
<tr>
<td>Other known mutations</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100</strong></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Most frequent mutations.
The total percentage (100) comprises 1475 patients whose mutations have been analysed. For 46 patients, no mutation test was carried out or the results are not known.

At the moment, approximately 2000 mutations worldwide are known to lead to CF or a so-called CF-related disease. The type of mutations can be divided into ‘classes’. In each class, the nature of the deviation causing the mutation in the cells is different.

In the event of a class-1 mutation, no CFTR protein is formed, which means no chloride channels are created at the cell membrane.

The most common F508del mutation is a class-2 mutation. This results in a disruption in the transport of the CFTR protein to the surface of the cells, hindering the development of the chloride channels.

In class-3 mutations, chloride channels are formed, but they are not activated and therefore they don’t work.

In class-4 and -5 mutations, there are chloride channels, but there are only a few of them or they don’t function as well. As a group, these mutations are considered to be the ‘milder mutations’. However, no predictions can be made on the basis of this information about the prognosis of the individual CF patient.

For a large number of rare mutations, it is not clear what class they belong to. In addition, a number of patients shows mutations of which it is unclear whether they lead to ‘actual CF symptoms’. In that case, we talk about ‘CF-related disease’*. Among others, this often applies to patients with an R117H mutation, which is relatively common (2.6%, see table 1) and which is found in children a number times per year through the heel prick screening. Some patients with this mutation also show clear symptoms of CF. From 1-7-2016, children in which the screening indicated an R117H mutation, are no longer automatically referred to a CF centre.

* For the registry, the diagnosis CF is confirmed when two mutations are known which are established to cause CF (according to the CFTR mutation database CFTR2); and/or when the chloride content in the sweat test is 60 mmol or higher. In 1409 (92.6%) of the 1521 registered patients, the diagnosis CF has been confirmed.
Figure 5. Distribution by mutation class (percentage) of all patients
For the distribution in classes, the 'mildest' class was applied, where applicable.
For 2.4% of patients, no mutation test was carried out or the results are not known ('missing').
For 9.1% of patients, a mutation was found, but the exact class was not established ('unknown').
4 Overview children (under 18 years of age)

The overviews in this paragraph include the data of 610 children with a confirmed diagnosis of CF. The diagnosis was confirmed on the basis of CF mutations and/or a positive sweat test. For 42 children, this was not (yet) the case. The following diagrams show the centres in the same order. On the right-hand side, the total for all centres is shown in red. For all diagrams, the alphabetical order with the corresponding abbreviations of the centres is as follows:

Amst: CF centre Amsterdam (AMC and VUMC)
Gron: CF centre UMC Groningen
Haga: CF centre HagaZiekenhuis The Hague
Maas: CF centre Maastricht UMC
Nijm: CF centre Oost-Nederland (Nijmegen)
Rott: CF centre Erasmus MC Rotterdam
Utre: CF centre UMC Utrecht

4.1 Pulmonary function

The FEV1 value is the air volume that can be expelled in 1 second, and is an important indicator for the pulmonary function. The FEV1 value is given as a percentage of the predicted value (the reference value compared to healthy peers). The median value for children between 6 and 18 years of age is 92.5%. This means that 50% of the children has a value that is lower than 92.5% of the predicted value, and 50% has a higher value.

The median FEV1 value for children between 6 and 18 years of age is between 88 and 100% per centre, and is 92.5% for all child centres combined (this was 88.0% in 2014).

Figure 6 shows the FEV1 values per centre for 2013, 2014 and 2015.

The interquartile range for all centres combined is 23.5% and varies from 19 to 27% per centre. Per distribution, 4 quartiles can be distinguished. The first quartile is the value where below which 25% of the FEV1 values are found if all measured values are placed in order of size, the second below which 50% of the FEV1 values are found, etc. The interquartile range is a dispersion measure and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).
Figure 6. Median FEV1 percentage in relation to the reference values for healthy children per centre and total

Figure 7 shows the median FEV1 values per age group (6 to 12 and 12 to 18 years). Up to the age of 12 years, the median FEV1 value in all centres is well above the 90% of the predicted value and is almost 100% for all centres combined.

Figure 7. Median FEV1 percentage in relation to the reference values for healthy children per age category and per centre
Figure 8 shows the percentage of children per pulmonary category function (with a FEV1 less than 40%, between 40 and 70%, between 70 and 90% and more than 90%). This distribution has been selected because it is also used in other countries, which makes international comparison possible. The figure shows that more than half of the children up to 18 years has a pulmonary function more than 90%, and that the percentage of children with a worse pulmonary function is reducing.

Figure 8. Percentage of children per pulmonary function category
4.2 Micro-organisms

The airways of patients with CF show micro-organisms (bacteria and fungi) that lead to infection in varying degrees. The occurrence of a number of important micro-organisms in children is shown in Figure 9.

The definitions of the European CF Registry are followed. This means that a chronic infection with *Pseudomonas aeruginosa* (PA) is considered present if more than 50% of at least four sputum cultures in the last year came back positive and/or there is a significant increase in the number of anti-pseudomonas antibodies ("Modified Leeds criteria"). In addition, the specialist can, if there are not enough cultures, determine that there is no grounds to reassess an earlier-found chronic PA infection.

![Percentage micro-organisms children](image)

**Figure 9. Percentage of micro-organisms in children**

- **PA** Pseudomonas aeruginosa
- **BC** Burkholderia cepacia
- **SM** Stenotrophomonas maltophilia
- **SA** Staphylococcus aureus
- **MRSA** Methicillin-resistant Staphylococcus aureus
- **HI** Haemophilus influenzae
- **AF** Aspergillus fumigatus
- **NTM** Non-tuberculous Mycobacteria
- **AX** Achromobacter xylosoxidans

For many children with CF, *Pseudomonas aeruginosa* (PA) has a particular influence on the treatment and prognosis. Figure 10 shows the percentage of children with a chronic PA infection per centre. The differences between the centres are considerable. The identification and definition of a chronic PA infection remains difficult in practice, which can influence the registration. For the total group of children, the percentage of patients with a chronic PA infection is 12.9%. In 2013, this was 21.4%.

The percentage of children of 6 years and older with a chronic PA infection treated with inhalation antibiotics is 87%. In 2013, this was 73%.
Figure 10. Percentage of chronic *Pseudomonas aeruginosa* infection in children per centre
4.3 Nutritional Status

The optimisation of growth and weight is important in children with CF. The ratio between weight and height is one way to determine the nutritional condition. The Body Mass Index (BMI) is a different method. This index is calculated by dividing the weight (in kg) by the height (in m) squared.

In addition, the height for the age and weight for the age are shown.

All these units of measure can be expressed as a standard score, also called the Z score. A Z score with a value of 0 is average. The scores of 97% of healthy Dutch children are between -2 and +2.

The Registry records the values for height and weight measured at the time of the pulmonary function tests with the highest FEV1 value. For children who did not undergo a pulmonary function test, the values at the time of the annual examination were used.

Weight to height

The median Z scores for weight to height (Figure 11) vary between -0.06 and +0.5 per centre. The median value for all centres combined is +0.07 (+0.14 in 2014). This means that 50% of the children has a value that is lower than +0.07 and 50% has a higher value.

![Weight to Height (Z score) children](image)

**Figure 11. Median Z scores for weight to height per centre for the period 2013-2015**

Figure 12 shows the improvement of the median Z score for weight to height for all children for the period 2008-2015.
Figure 12. Median Z score for weight to height for the period 2008-2015

Broken down by age group (0 to 6 years, 6 to 12 years and 12 to 18 years), the median Z scores for weight to height are, respectively, +0.20, +0.19 and +0.09 (in 2013, they were +0.11, +0.29 and +0.02, respectively).

BMI

The median Z scores for the BMI (Figure 13) vary per centre between -0.05 and +0.29 (between -0.05 and +0.37 in 2014). The median value for all centres combined was +0.17 (+0.10 in 2014). Broken down by age group (0 to 6 years, 6 to 12 years and 12 to 18 years), the median Z scores for BMI are, -0.01, 0.16 and -0.03, respectively.

This means that the average nutritional condition of children with CF is even slightly better than that of healthy peers, and that the nutritional condition of children with CF has significantly improved since 2008 (Figure 14). The nutritional condition has again improved in 2015 compared to 2014.
**Figure 14.** Median Z scores for BMI for the period 2008-2015

**Weight and height to age**

Figure 15 and 16 show the Z scores for weight and height to age per centre and as a total. This shows that in particular the children with CF are, on average, less tall than healthy peers.

**Figure 15.** Median Z scores for weight to age per centre for the period 2013-2015
Figure 16. Median Z scores for height to age per centre for the period 2013-2015
4.4 Co-morbidity

A number of children with CF suffer from so-called ‘co-morbidity’. Examples are:

- ABPA: Allergic Bronchopulmonary Aspergillosis, an allergic reaction to Aspergillus spores.
- CFRD: CF-related diabetes. A number of patients develop a special CF-related type of diabetes.
  To discover CFRD at an early stage, the ‘Guideline diagnosis and treatment of Cystic Fibrosis’ (2007) recommends that children from the age of ten that do not have diabetes undergo an Oral Glucose Tolerance Test (OGTT) every year. 80% of all children that qualify underwent an OGTT (60% in 2013).
- DIOS: Distal Intestinal Obstruction Syndrome, a serious obstruction of the end of the small intestines, which is common in people with CF.
- Liver disease: Liver dysfunction/transaminase disorders develop gradually in some people with CF and can result in serious liver dysfunction.
  The CF Registry gives the following definition of liver disease: the existence of steatosis (fatty liver) and/or cirrhosis ( shrinkage).

![Specific co-morbidity children](image)

**Figure 17. Percentage of specific co-morbidity in children**

The percentage of children with ABPA varies per centre between 3 and 12%.
The percentage of children with CFRD varies per centre between 2 and 19%.
The percentage of children with DIOS varies per centre between 3 and 15%.
The percentage of children with liver disease varies per centre between 3 and 26%.
### 4.5 Treatment

Listed below are the percentages of various aspects of the treatment of children with a confirmed diagnosis CF (n=610).

<table>
<thead>
<tr>
<th></th>
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<tr>
<td>Use of pancreatic enzymes</td>
<td>89.3</td>
<td>89.5</td>
<td>85.8</td>
<td>92.1</td>
<td>89.8</td>
<td>91.2</td>
<td>88.7</td>
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<td>Use of antacids</td>
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<td>45.4</td>
<td>42.7</td>
<td>42.3</td>
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<td>Use of dietary supplements</td>
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<td>59.9</td>
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<td>48.2</td>
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<td>Energy-enriched fluid nutrition</td>
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<td>43.3</td>
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<td>37.2</td>
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<td>Enteral nutrition</td>
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<td>12.3</td>
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<td>13.0</td>
<td>11.5</td>
<td>11.9</td>
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<td>Use of ursodeoxylic acid</td>
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<td>26.8</td>
<td>27.5</td>
<td>28.6</td>
<td>26.8</td>
<td>27.4</td>
<td>25.1</td>
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<td>Mucus-loosening nebuliser</td>
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<td>RhDNase</td>
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<td>0.3</td>
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<td>0</td>
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<td>Hypertonic saline</td>
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<td>20.9</td>
<td>23.5</td>
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<td>20.8</td>
<td>28.8</td>
<td>28.5</td>
</tr>
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<td>Intravenous antibiotics</td>
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<td>Hospital-administered</td>
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<td>22</td>
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<td>6.0</td>
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<td>Maintenance antibiotics</td>
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<td>Tobramycin nebulised</td>
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<td>-</td>
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<td>1.7</td>
<td>2.6</td>
<td>0.7</td>
</tr>
<tr>
<td>Inhaled antibiotics total</td>
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<td>26.0</td>
<td>25.9</td>
<td>24.8</td>
<td>25.7</td>
<td>37.0</td>
<td>26.5</td>
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<td>Macrolides</td>
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<td>25.0</td>
<td>24.1</td>
<td>23.7</td>
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<td>25.8</td>
<td>19.5</td>
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<td>Corticosteroids</td>
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<td></td>
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<td>Oral</td>
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<td>7.1</td>
<td>8.1</td>
<td>8.4</td>
<td>12.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Inhalation drugs</td>
<td>19.7</td>
<td>19.4</td>
<td>14.4</td>
<td>20.4</td>
<td>25.2</td>
<td>28.3</td>
<td>33.7</td>
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<td>Bronchodilators</td>
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<tr>
<td>Inhalation drugs</td>
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<td>27.0</td>
<td>29.0</td>
<td>34.0</td>
<td>29.6</td>
<td>29.5</td>
<td>28.5</td>
</tr>
<tr>
<td>Use of extra oxygen</td>
<td>2.6</td>
<td>2.4</td>
<td>1.5</td>
<td>2.3</td>
<td>2.6</td>
<td>2.1</td>
<td>1.9</td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
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<td>0.3</td>
<td>0.6</td>
<td>1.1</td>
<td>0.7</td>
<td>0.3</td>
<td>0.5</td>
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<td>Kalydeco (number of users)</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Orkambi (number of users)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
</tbody>
</table>
4.6 Transplants in children

Shown below is the number of children that started a transplant process.

Liver transplant before 2015 0
Liver transplant on waiting list on 31/12/2015 0
Liver transplant in 2015 0

Lung transplant before 2015 4
Lung transplant on waiting list on 31/12/2015 1
Lung transplant in 2015 0

4.7 Number of deceased patients

In 2015, 1 child with CF passed away.
5 Adults (18 years and older)

The overviews in this paragraph include the data of 685 children without a lung transplant (n=114) and with a confirmed diagnosis of CF. The diagnosis was confirmed on the basis of CF mutations and/or a positive sweat test. For 70 adults, this was not (yet) the case. 15.5% of adults with CF were diagnosed after they reached the age of 18 years.

The following diagrams show the centres in the same order. On the right-hand side, the total for all centres is shown in red.

For all diagrams, the alphabetical order with the corresponding abbreviations of the centres is as follows:

Amst: CF centre Amsterdam (AMC)
Gron: CF centre UMC Groningen
Haga: CF centre HagaZiekenhuis The Hague
Maas: CF centre Maastricht UMC
Nijm: CF centre Oost-Nederland (Nijmegen)
Rott: CF centre Erasmus MC Rotterdam
Utre: CF centre UMC Utrecht

5.1 Pulmonary function

The FEV1 value is the air volume that can be expelled in 1 second, and is an important indicator for the pulmonary function. The FEV1 value is given as a percentage of the predicted value (the reference value compared to healthy peers).

The median value is 66.3%. This means that 50% of the adults has a value that is lower than 66.3% of the predicted value, and 50% has a higher value. In 2014, this median value was 65.9%.

The median FEV1 value of adults varies between 64 and 72% per centre (between 61 and 75% per centre in 2014).

Figure 18 shows the FEV1 values per centre for the period 2013-2015.

The interquartile range for all centres combined is 34 % and varies from 27 to 43 % per centre. Per distribution, 4 quartiles can be distinguished The first quartile is the value where below which 25% of the FEV1 values are found if all measured values are placed in order of size, the second below which 50% of the FEV1 values are found, etc. The interquartile range is a dispersion measure and indicates the difference between the third quartile (75% of all values) and the first quartile (25% of all values).
Figure 18. Median FEV1 percentage in relation to the reference values for healthy adults per centre

Figure 19 shows the percentage of adults per pulmonary category function (with a FEV1 less than 40%, between 40 and 70%, between 70 and 90% and more than 90%). This distribution has been selected because it is also used in other countries, which makes international comparison possible. It is a positive development that the groups with an FEV1 < 70% are gradually becoming smaller, and the groups with a higher FEV1 are gradually becoming bigger. The percentage of patients with an FEV1 < 40% varies between 12 and 19% per centre.

Figure 19. Percentage of adults per pulmonary function category
5.2 Micro-organisms

The airways of patients with CF show micro-organisms (bacteria and fungi) that lead to infection in varying degrees. The occurrence of a number of important micro-organisms in adults is shown in the figure below.

The definitions of the European CF Registry are maintained from 2010. This means that a chronic infection with *Pseudomonas aeruginosa* (PA) is considered present if more than 50% of the sputum cultures in the last year came back positive and/or there is a significant increase in the number of anti-pseudomonas antibodies ('Modified Leeds criteria'). In addition, the specialist can, if there are not enough cultures, determine that there is no grounds to reassess an earlier-found chronic PA infection.

**Figure 20. Percentage of micro-organisms in adults**

<table>
<thead>
<tr>
<th>Micro-organism</th>
<th>Percentage 2013</th>
<th>Percentage 2014</th>
<th>Percentage 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>PA</td>
<td>50</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>BC</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>SM</td>
<td>5</td>
<td>5</td>
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<td>SA</td>
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</tr>
<tr>
<td>MRSA</td>
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<td>0</td>
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</tr>
<tr>
<td>HI</td>
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<td>0</td>
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</tr>
<tr>
<td>AF</td>
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</tr>
<tr>
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<tr>
<td>AX</td>
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</tr>
</tbody>
</table>

The percentage of adults with a chronic *Pseudomonas* infection remains around the 50%

The percentage of adults with a Burkholderia, MRSA or Mycobacteria culture, remains low.
For many adults with CF, Pseudomonas aeruginosa (PA) has a particular influence on the treatment and prognosis. Figure 21 shows the percentage of adults with a chronic PA infection per centre. For the total group of adults, this is 51%.
The percentage of adults that is treated with inhalation antibiotics, which are generally used against PA, is 58.5%.
The percentage of adults with a chronic PA infection treated with inhalation antibiotics is 85%.

![Figure 21. Percentage of chronic Pseudomonas aeruginosa infection in adults per centre](image)
5.3 Nutritional Status

Maintaining or improving a good nutritional condition is important in adults with CF. The nutritional condition of adults is expressed as the Body Mass Index (BMI). The BMI is calculated by dividing the weight (in kg) by the height (in m) squared. The median BMI values vary per centre for adults (Figure 22) between 21.1 and 22.4 (between 20.8 and 22.1 in 2014). The total of all centres combined is 21.7 (21.6 in previous years) (Figure 23). This means that 50% of the adults has a value that is lower than 21.7. BMI values between 18.5 and 25 are considered to be normal.

![BMI adults](image)

**Figure 22. Median Z scores for BMI for adults per centre for the period 2013-2015**

![Median BMI Adults 2008-2015](image)

**Figure 23. Median Z scores for BMI for adults for the period 2008-2015**
5.4 Co-morbidity

A number of adults with CF suffers from so-called ‘co-morbidity’. Examples are:
- ABPA: Allergic Bronchopulmonary Aspergillosis, an allergic reaction to Aspergillus spores.
- CFRD: CF-related diabetes. In particular in adults, a special type of CF-related diabetes can develop. To discover CFRD at an early stage, the "Guideline diagnosis and treatment of Cystic Fibrosis” (2007) recommends that adults who do not have diabetes undergo an Oral Glucose Tolerance Test (OGTT) every year. 59 % of all adults that qualify underwent an OGTT. In 2014, this was 60%, in 2013: 50% and in 2012: 37%.
- DIOS: Distal Intestinal Obstruction Syndrome, a serious obstruction of the end of the small intestines, which is common in people with CF.
- Liver disease: Liver dysfunction/transaminase disorders develop gradually in some people with CF and can result in serious liver dysfunction.

The CF Registry gives the following definition of liver disease: the existence of steatosis (fatty liver) and/or cirrhosis (shrinkage).

![Diagram: Specific co-morbidity adults]

**Figure 24. Percentage of specific co-morbidity in adults**

The percentage of adults with ABPA varies per centre between 0 and 14%.
The percentage of adults with CFRD varies per centre between 15 and 48%.
The percentage of adults with DIOS varies per centre between 0 and 12%.
The percentage of adults with liver disease varies per centre between 5 and 39%.
5.5 Treatment

Listed below are the percentages of various aspects of the treatment of adults with a confirmed diagnosis CF.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Use of pancreatic enzymes</td>
<td>82.6</td>
<td>80.5</td>
<td>76.8</td>
<td>80.3</td>
<td>76.7</td>
<td>79.0</td>
<td>75.7</td>
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<tr>
<td>Use of antacids</td>
<td>47.1</td>
<td>48.8</td>
<td>46.5</td>
<td>48.8</td>
<td>53.0</td>
<td>53.8</td>
<td>49.8</td>
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<tr>
<td>Use of dietary supplements</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Use of dietary supplements</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Use of dietary supplements</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Energy-enriched fluid nutrition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral nutrition</td>
<td>12.3</td>
<td>9.2</td>
<td>7.5</td>
<td>7.8</td>
<td>7.3</td>
<td>5.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Use of ursodeoxylic acid</td>
<td>29.6</td>
<td>29.1</td>
<td>29.3</td>
<td>29.2</td>
<td>29.3</td>
<td>28.7</td>
<td>24.6</td>
</tr>
<tr>
<td>Mucus-loosening nebuliser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RhDNase</td>
<td>54.6</td>
<td>60.3</td>
<td>60.7</td>
<td>63.8</td>
<td>63.0</td>
<td>64.4</td>
<td>62.9</td>
</tr>
<tr>
<td>Acetyl cysteine</td>
<td>9.6</td>
<td>6.5</td>
<td>5.3</td>
<td>3.8</td>
<td>3.9</td>
<td>2.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Hypertonic saline</td>
<td>17.6</td>
<td>26.5</td>
<td>27.5</td>
<td>26.7</td>
<td>28.9</td>
<td>27.5</td>
<td>26.5</td>
</tr>
<tr>
<td>Intravenous antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-administered</td>
<td>-</td>
<td>-</td>
<td>24.0</td>
<td>22.4</td>
<td>22.5</td>
<td>23.4</td>
<td>32.2</td>
</tr>
<tr>
<td>Home treatment</td>
<td>-</td>
<td>-</td>
<td>25.0</td>
<td>22.4</td>
<td>22.7</td>
<td>21.8</td>
<td>26.9</td>
</tr>
<tr>
<td>Maintenance antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin nebuliser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin nebulised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry-powder antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam-lysine nebulised</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics inhaled total</td>
<td>54.4</td>
<td>52.8</td>
<td>56.1</td>
<td>58.8</td>
<td>58.7</td>
<td>59.7</td>
<td>58.5</td>
</tr>
<tr>
<td>Macrolides</td>
<td>63.8</td>
<td>64.4</td>
<td>63.7</td>
<td>69.3</td>
<td>64.1</td>
<td>67.9</td>
<td>62.4</td>
</tr>
<tr>
<td>Use of corticosteroids</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>17.2</td>
<td>14.8</td>
<td>16.4</td>
<td>12.3</td>
<td>19.4</td>
<td>12.6</td>
<td>9.2</td>
</tr>
<tr>
<td>Inhalation drugs</td>
<td>44.8</td>
<td>49.4</td>
<td>45.9</td>
<td>44.4</td>
<td>51.7</td>
<td>56.0</td>
<td>53.5</td>
</tr>
<tr>
<td>Use of bronchodilators</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation drugs</td>
<td>59.4</td>
<td>63.6</td>
<td>65.5</td>
<td>65.4</td>
<td>56.3</td>
<td>60.2</td>
<td>60.4</td>
</tr>
<tr>
<td>Use of extra oxygen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-invasive ventilation</td>
<td>8.2</td>
<td>8.1</td>
<td>7.2</td>
<td>5.3</td>
<td>5.1</td>
<td>5.4</td>
<td>5.8</td>
</tr>
<tr>
<td>Kalydeco (number of users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orkambi (number of users)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.6 Transplants in adults

Shown below is the number of adults that started a transplant process.

Liver transplant before 2015 5
Liver transplant on waiting list on 31/12/2015 0
Liver transplant in 2015 0

Lung transplant before 2015 97
Lung transplant on waiting list on 31/12/2015 23
Lung transplant in 2015 16

5.7 Number of deceased patients

In 2015, 12 adults with CF passed away.
5.8 Social situation

The following diagram shows the percentages for work/study for 729 adults.

<table>
<thead>
<tr>
<th>Work/study</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unemployed</td>
<td>7.8</td>
<td>10.8</td>
<td>14.9</td>
<td>10.4</td>
<td>12.3</td>
</tr>
<tr>
<td>Full-time employment</td>
<td>19.6</td>
<td>17.6</td>
<td>14.9</td>
<td>15.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Part-time employment</td>
<td>20.3</td>
<td>21.5</td>
<td>22.2</td>
<td>26.7</td>
<td>26.2</td>
</tr>
<tr>
<td>Full-time housewife/househusband</td>
<td>1.5</td>
<td>1.7</td>
<td>1.0</td>
<td>1.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Student</td>
<td>22.7</td>
<td>27.3</td>
<td>24.5</td>
<td>20.1</td>
<td>17.8</td>
</tr>
<tr>
<td>Retired</td>
<td>0.4</td>
<td>0.5</td>
<td>1.4</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Not able to work</td>
<td>13.7</td>
<td>13.2</td>
<td>10.7</td>
<td>12.8</td>
<td>12.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>14.0</td>
<td>7.4</td>
<td>10.4</td>
<td>11.9</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Civil status

The following diagram shows the percentages for the civil status for 725 adults.

<table>
<thead>
<tr>
<th>Civil status</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/never married</td>
<td>55.8</td>
<td>53.0</td>
<td>43.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Married/relationship</td>
<td>36.2</td>
<td>34.0</td>
<td>41.4</td>
<td>50.2</td>
</tr>
<tr>
<td>Divorced</td>
<td>1.1</td>
<td>1.4</td>
<td>1.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Widowed</td>
<td>0.1</td>
<td>0.3</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>6.8</td>
<td>11.3</td>
<td>13.8</td>
<td>7.7</td>
</tr>
</tbody>
</table>

Pregnancy

The Registry contains the data of a total of 365 adult women with CF.

In 2015, 11 women were pregnant in 2015 (data known for 320 women).

53 women had a child before 2015 (data known for 216 women).
5.9 Patients over 50 with CF

In 2015, 70 patients over the age of 50 years had a confirmed diagnosis of CF. Of those, 13 had a lung transplant. The oldest patient with CF in The Netherlands is 74 years old.

56% is male and 44% is female.
The percentage of patients with a F508del mutation on both chromosomes (homozygous) is 24.3%.
The percentage of patients with a F508del mutation on one chromosome and another mutation on the other chromosome (heterozygous) is 55.7%.
The percentage of patients with a non-F508del mutation on both chromosomes is 12.9%.
For 7.1%, the mutation is not known.
44% of the over-fifties has at least one class-4 or -5 mutation.

The median pulmonary function is 65% (64% without patients who received a lung transplant).
The BMI is 22.9 (23.1 without patients who received a lung transplant).

- 20% use extra dieterary supplements
- 36% has a chronic Pseudomonas infection
- 40% uses inhalation antibiotics
- 29% has CF-related diabetes (CFRD)
- 79% lives with a partner
- 45% works or has worked and is retired
- 33% of the women has at least one child
6 Pulmonary function in children and adults, men and women

Figure 25 shows the median FEV1 (percentage of the predicted value) per age group from 6 to 74 years, for the period 2013-2015. The reduced pulmonary function is smaller than before in almost all age groups. The median FEV1 for all age groups combined is 77.0%. In 2014, this was 76.1%.

Figure 25. Pulmonary function (median FEV1 % of predicted value) per age group

Figure 26 shows the median FEV1 (percentage of the predicted value) per age group from 6 to 74 years, for men and women. Up to the age of 21 years, the FEV1 is generally higher for boys. After that, the differences vary. In the over-60 group, the numbers are very small (6 women, 8 men) causing considerable median differences.

Figure 26. Pulmonary function (median FEV1 % of predicted value) per age group for men and women
7 Indicators

7.1 Introduction

On the basis of European and Dutch guidelines, a number of tools have been developed to give insight into the quality of care of patients with CF.

The NCFS Quality Mark assesses the quality of care on sixty criteria, from the perspective of patients with CF.

An important question is whether the introduction of a guideline actually has the desired effect on the quality of care. Indicators are used to measure this effect.

Indicators are measurable aspects of the care offered which provide an indication of the quality of that care. An indicator has a signal function: it is not a direct measure of quality, but does point at a particular aspect of care and may be a reason to investigate further. This hits the heart of the quality of care: the actual measurement of the quality of care and, on the basis of that measurement, the introduction of improvements with the objective of improving the quality of care.

A number of indicators is measured every year using the CF Registry. Until 2014, hospitals were required to provide this information to the organisation ‘Zichtbare Zorg (ZiZo)’. A large part of this information was also collected in the framework of the Dutch CF Registry.

To prevent double registration and to make the information more accessible to a wider audience, it was agreed that all information about the CF indicators would be included in the annual reports of the NCFS CF Registry from 2014 onwards.

Indicators allow caregivers more insight in the results of their own care process, support internal control and help improve it. The indicators that are used for this purpose are referred to as internal indicators. The indicators can also be used to compare the performance of the CF centres (benchmarking). Structural feedback on the results of the care offered and the introduction of benchmarking can ensure continuous process improvement.

The indicators can also serve another purpose. The government, Dutch Healthcare Inspectorate (IGZ) and patients/consumers want to assess whether healthcare providers offer sufficient quality of care and are looking for appropriate indicators. Indicators used for this purpose are called external indicators. The external indicators can also be used in negotiations on DTCs. The external indicators developed are already being used by Zorgverzekeraars Nederland for the the buying-in of care.

The following indicators for CF care are developed on the basis of recommendations in the Netherlands (2007) and European (2014) guidelines.

The following diagrams show the centres in the same order. On the right-hand side, the total for all centres is shown in red.

For all diagrams, the alphabetical order with the corresponding abbreviations of the centres is as follows:

- **Amst:** CF centre Amsterdam (AMC and VUMC)
- **Gron:** CF centre UMC Groningen
- **Haga:** CF centre HagaZiekenhuis The Hague
- **Maas:** CF centre Maastricht UMC
- **Nijm:** CF centre Oost-Nederland (Nijmegen)
- **Rott:** CF centre Erasmus MC Rotterdam
- **Utre:** CF centre UMC Utrecht
7.2 Outcome indicators

1 – Pulmonary function
Pulmonary function is an important measure of the severity of the disease and the prognosis for people with Cystic Fibrosis. The percentage of predicted FEV1 (forced expiratory volume in 1 second) is a good and frequently-used unit of measure.

The European Standards or Care Guidelines specifies that the pulmonary function is an important unit of measure in the assessment of the severity of the disease (morbidity) and mortality of CF. The FEV1 percentage of the predicted value is the strongest clinical predictor of mortality and is often used as a primary parameter in clinical trials (Kerem, 1992; Ramsey, 1994; Grasemann, 1995; Flume, 2007, Smith 2014).

Figure 6 (page 14) shows the median highest FEV1 value for children per centre and the total for all centres. Figure 18 (page 26) shows these values for adults.

2 – Nutritional condition
Approximately 80% of all patients with CF also have an exocrine pancreatic disorder. In addition, they have a high calorie need, sometimes up to 150% of what a healthy person needs. That is why the addition of pancreatic enzymes and well-balanced high-calorie nutrition with vitamin supplementation is important. In addition to the pulmonary function, the nutritional condition is an important indicator for the prognosis.

The optimisation of growth and weight is important in children with CF. The ratio between weight and height is one way to determine the nutritional condition. The Body Mass Index (BMI) is a different method. This index is calculated by dividing the weight (in kg) by the height (in m) squared. These units of measure can be expressed as a standard score, also called the Z score. A Z score with a value of 0 is average. The scores of 97% of healthy Dutch children are between -2 and +2.

The Registry records the values for height and weight measured at the time of the pulmonary function tests with the highest FEV1 value. For children who did not undergo a pulmonary function test, the values at the time of the annual examination were used.

Figure 11 (page 18) shows the median Z score for weight to height per centre.

Maintaining or improving a good nutritional condition is important in adults with CF. Figure 22 (page 29) shows the median BMI for adults per centre.

3 – Indicator for infrastructure
The members of a multidisciplinary care team need to build up sufficient experience and expertise to be able to care and treat patients with CF on a daily basis. For that reason, a minimum number of 50 children or adults with CF has to treated per centre, who are offered continuous/chronic care (Kerem, 2005; Conway, 2014). Due to the complexity of the disease, the centres require specialist CF teams. A CF centre can only offer added value if they have more expertise and more facilities than elsewhere. The centre has to have a minimum number of specialists. All specialists must have sufficient contact with patients and demonstrable take part in further training and instruction every year. The centre should be accessible, to ensure that patients with CF can easily make use of the expertise offered by the centre. In addition, the care offered by the centre has to be of a demonstrable high quality. There are protocols for diagnosis and treatment, and the implementation of care can be verified. The European Cystic Fibrosis Society (ECFS) provides guidelines the centre has to comply with (Kerem, 2005; Conway, 2014). The NCFS Quality Mark assessment tests the conditions for a good infrastructure of a CF centre.

The number of patients with CF per centre is recorded each year. Figure 27 shows the percentage of children and adults per centre.
4 – Process indicators
Routine examination of various parameters contributes to early detection of infections, deviations in
the nutritional condition, etc. This allows more effective care being offered, ultimately improving the
prognosis. In accordance with the guidelines, an outpatient’s check-up should take place at least four
times a year. This includes, in addition to a history and physical examination, a sputum sample /cough
on cotton and, from the age of six years, a pulmonary function test.

Figure 28 shows the percentage of children per centre who visited the outpatient’s clinic at least four
times a year.
Figure 29 shows the percentage of adults per centre who visited the outpatient's clinic at least four times a year.

![Bar Chart: Outpatient clinics at least 4 times percentage adults]

**Figure 29. Percentage of adults per centre who visited the outpatient’s clinic at least four times a year**

Figure 30 shows the percentage of children per centre who gave a sputum sample / cough on cotton at least four times a year.

![Bar Chart: Sputum culturing at least 4 times percentage children]

**Figure 30. Percentage of children per centre who gave a sputum sample / cough on cotton at least four times a year**
Figure 31 shows the percentage of adults per centre who gave a sputum sample / cough on cotton at least four times a year.

Figure 31. Percentage of adults per centre who gave a sputum sample / cough on cotton at least four times a year

Figure 32 shows the percentage of children per centre who underwent a pulmonary function test at least four times a year.

Figure 32. Percentage of children per centre who underwent a pulmonary function test at least four times a year
Figure 33 shows the percentage of adults per centre who underwent a pulmonary function test at least four times a year.

Children and especially adults can develop a special form of CF-related diabetes (CFRD). To discover CFRD at an early stage, the ‘Guideline diagnosis and treatment of Cystic Fibrosis’ (2007) recommends that children from the age of 10 that do not have diabetes undergo an Oral Glucose Tolerance Test (OGTT) every year. Figure 34 shows the percentage of children per centre who underwent an OGTT in 2015. The percentage is calculated on the basis of children from 10 years without CFRD and with pancreatic insufficiency.
Figure 35 shows the percentage of adults per centre who underwent an OGTT in 2015. The percentage is calculated on the basis of adults, who did not receive a lung transplant, without CFRD and with pancreatic insufficiency.

Figure 35. Percentage of adults per centre who underwent an OGTT in 2015
Annex 1: Publications and accepted applications in 2015 of data from the Dutch CF Registry

Request UMCU:
Data on growth and nutritional condition in children.
Status: Publication realised
*Height Assessment in the Dutch-Origin Pediatric Cystic Fibrosis Population.*
Woestenenk JW, Gulmans VA, van der Ent CK, Houwen RH.

Request MUMC:
Expansion of earlier request with data on the period 2009-2011: risk factors for loss of pulmonary function and pulmonary exacerbations in children.
Status: Publication in preparation.

Request CFTR2 mutation database:
Update of mutations in Dutch patients with CF.
Status: processed in database: [http://www.cftr2.org](http://www.cftr2.org)

Request Vertex:
Overview of F508del mutations in The Netherlands
Status: processed in the application to the Zorginstituut Nederland for reimbursement of Orkambi.

For a Dutch contribution to data requests from the European CF Registration, see: [https://www.ecfs.eu/projects/ecfs-patient-registry/overview-data-applications](https://www.ecfs.eu/projects/ecfs-patient-registry/overview-data-applications)