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Original Article

Year to year change in FEV_1 in patients with cystic fibrosis and different mutation classes

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Abstract

In patients with cystic fibrosis, most treatments addressing the underlying basic defect are mutation or mutation class specific. These treatments are disease modifying if they lower the year to year change in lung function. We therefore calculated the current loss of lung function, measured by year to year change in forced expired volume in 1 s in 11,417 patients included in the European Cystic Fibrosis Society Patient Registry. Whereas patients with at least one mutation of class IV or V have on average a lower year to year change, we did not find a difference between patients with a stop codon mutation, homozygous for F508del or at least one class III mutation. These data are useful background information to discuss the impact of different disease modifying treatments.

Keywords: Cystic fibrosis; Mutation class; Lung function; Age distribution

1. Introduction

More than 2000 different mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene have been reported in patients with cystic fibrosis (CF) or in subjects with CF like symptoms [1]. Many of these mutations can be grouped in classes according to their main deleterious effect on *CFTR* protein synthesis or function: no synthesis (class I), protein degradation (class II), defective protein channel gating (class III), defective protein channel conductance (class IV), decreased protein synthesis (class V) and reduced membrane stability (class VI) [2]. In recent years several clinical trials with mutation or mutation class specific drugs have been performed [3–6] and many new ones are ongoing or planned. Some of these trials have already led to drug approval in patients with specific *CFTR* mutations [3–5]. Thereby, we have entered the era of personalized medicine for CF.

Longstanding CF registries provide ample information about the longitudinal course of lung function in patients with CF [7–10]. However, apart from — on average — milder disease [11–13] and lower treatment burden [14] in patients with class IV and V mutations, there is little information whether lung function decline differs between subjects with classes I to III mutations. Still, to interpret the relative benefit of the very costly mutation class specific therapies, knowledge about the average year to year change in lung function in different mutation classes is informative. On theoretical grounds alone, patients with at least one class I mutation could be assumed to have an on average worse disease course than patients with at least one class II or class III mutation. Indeed, whereas the former have no full length CFTR protein synthesis, patients with class II mutations have limited presence of CFTR protein at the cell membrane mutations and in patients with class III mutations, the CFTR protein is present but the channel opening is disturbed. From *CFTR* mutation classes to patients is however a big step: patients have by definition 2 *CFTR*

Abbreviations: CF, Cystic fibrosis; CFTR, Cystic fibrosis transmembrane conductance regulator; ECFSPR, European Cystic Fibrosis Society Patient Registry; FEV_1, Forced expired volume in 1 s.

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mutations, not necessarily of the same mutation class. In addition, modifier genes and environment further influence disease expression. However, limited clinical information also points towards worse lung disease in patients with class I mutations. In a Swedish CF clinic, patients with 2 class I mutations had worse lung function than subjects with 2 class II mutations [15]. In addition, in the phase 3 ataluren placebo controlled trial in patients with a class I stop codon mutation, the FEV_1 decline in the placebo group was rather high [6] especially when compared to the decline seen in studies in patients homozygous for F508del [5]. However, year to year change in forced expiratory volume in 1 s (FEV_1) is known to have a large variability [16]. Therefore, we explored the year to year change in FEV_1 according to mutation class in the European Cystic Fibrosis Society Patient Registry (ECFSPR) [17].

2. Methods

We analysed the data of patients with CF included in the 2008–2009–2010 data set (the most recent data available at the time of the analysis). The ECFSPR is a large CF database with information on more than 35,000 subjects from 15 national registries as well as from more than 50 centres in 12 countries. Data collection methods have been described in detail elsewhere [18].

To study the influence of mutation class, we classified the *CFTR* mutations — where possible — in one of the 5 *CFTR* mutation classes as reported previously [19]. We then grouped the patients as how they will qualify for mutation class specific treatment: at least one stop codon mutation, F508del homozygous, at least one class III mutation, at least one class IV mutation, at least one class V mutation (Table 1). Since at present only subjects with a stop codon mutation are targeted by therapy, only this subgroup of class I was included. Other possible genotype combinations than the ones listed were also not considered e.g. patients compound heterozygous stop codon/class III or IV or V.

We compared the cumulative age between patients in the different genotype groups, comparing the median age of each group with the Kruskal–Wallis test.

Table 1
Genotype groups considered for the analysis.

Genotype group[a]	I allele	II allele
A F508del homozygous	F508del	F508del
B at least one stop codon mut	Stop codon mut	Class I[b], class II, unknown
C at least one class III mut	Class III	Class I, class II, class III, unknown
D at least one class IV mut	Class IV	Class I, class II, class IV, unknown
E at least one class V mut	Class V	Class I, class II, class V, unknown

[a] Patients with genotype that belongs to more than one of these groups were not considered (e.g. patient with one allele in class III and the other in class IV can belong both to groups C and D).

[b] Stop codon mutation belongs to class I, therefore a patient stop codon homozygote belongs to this group.

To study the influence of genotype on lung function and on lung function year to year change, we included subjects older than 6 years, without lung transplant and with lung function data available in at least two years. The ECFSPR asks to report the best lung function in the year and this is done in most countries; for details on deviations in specific countries we refer to the ECFSPR web pages [17] and the 2008 to 2010 ECFSPR annual reports [20]. Lung function data were expressed as percentage of predicted values (FEV_1%) using the Global Lung Function Initiative equations [21].

We compared the proportion of patients with baseline FEV_1% predicted (year 2008 or 2009) in different severity categories (<40% predicted, 40–90% predicted and >90% predicted) between genotype groups by chi square test. We also fitted a linear regression model to evaluate the effect of genotype on FEV_1% predicted at baseline adjusting for age at baseline (in age categories of 6 years: 6–11, 12 to 17, 18–24 etc. until 42 plus).

We studied the year to year change in FEV_1% in the entire group as well as in patients with a baseline FEV_1 between 40 and 90% of predicted, the usual target group in clinical trials, and with baseline above 90% of predicted. The year to year change in FEV_1% was calculated as the difference between FEV1% in 2010 and FEV1% in 2008 divided by 2 ((fev2(2010) − fev0(2008)) / 2). For those patients with measures only in 2008 and 2009 or 2009 and 2010, we considered the difference of FEV1% measure in the two consecutive years. We fitted a linear regression model to evaluate the effect of genotype on the year to year change adjusting the model for the age at baseline (year 2008 or 2009, depending on the year to year change computed, in age categories of 6 years).

Results are expressed as proportions, median, 10th and 90th centile, and means and 95% confidence intervals (CI). For multiple comparison adjustment of the p-values for the differences of least square means estimated from the models, we considered the Tukey–Kramer method.

3. Results

For years 2008–2009–2010, the ECFSPR collected data on 35,259 patients. 33,820 patients underwent DNA analysis and 32,329 patients had at least one *CFTR* mutation identified: 21,608 of these could be classified in the genotype groups as defined in Table 1 (14,839 (68.7%) F508del homozygous patients, 3979 (18.4%) patients with at least one stop codon mutation, 1145 (5.3%) patients with at least one class III mutation, 1008 (4.7%) patients with at least one class IV mutation, 637 (3.0%) patients with at least one class V mutation). The median and the inter-quartile range (IQR) of the age of these subjects was lowest in the group of patients with at least stop codon mutation (15.1 (7.8–24.1) years), than the group of patients homozygous for F508del (16.0 (8.0–24.2) years), the group of patients with at least one class III mutation (17.1 (9.2–26.2) years), the group of patients with at least one class IV mutation (17.6 (6.7–31.4) years) and the patients with at least one class V mutation (24.3 (12.39–37.4) years) (Fig. 1) ($p < 0.0001$ Kruskal–Wallis).

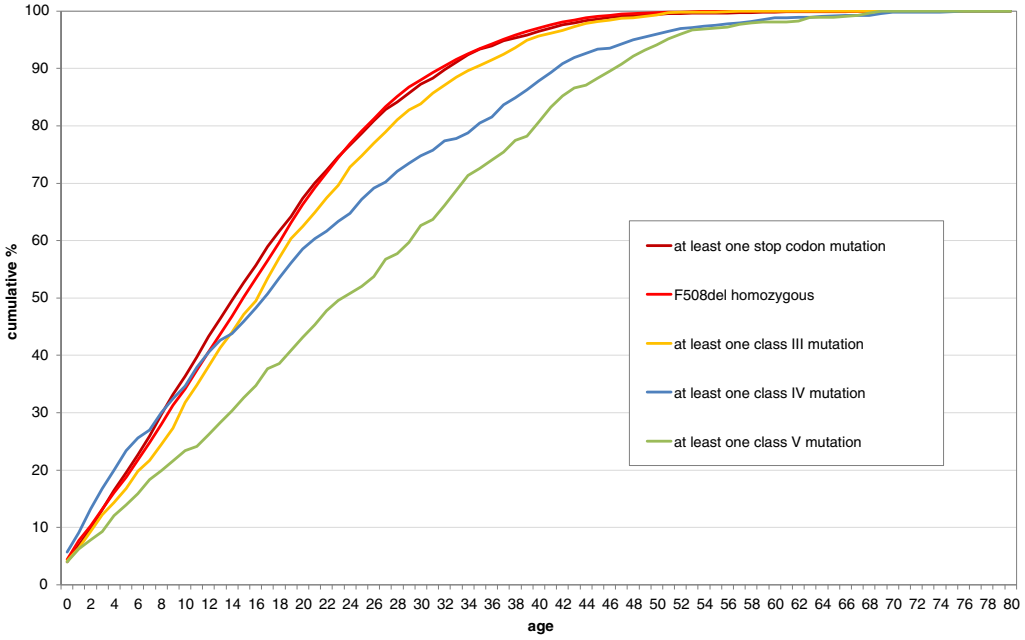

Fig. 1. Cumulative distribution of age by genotype group.

For lung function analyses, 11,417 patients above 6 years, without lung transplant and with at least two lung function measurements were included (Fig. 2): 1959 (17.2%) in the stop codon mutation group; 8152 (71.4%) homozygous for F508del; 553 (4.8%) in the class III mutation group; 463 (4.1%) in the class IV mutation group and 290 (2.5%) in the class V mutation group. Because they had a lung transplant or no information on lung transplant or because of missing lung function criteria 10,191 patients had been excluded: 2020 (19.8%) in the stop codon mutation group; 6687 (65.6%) homozygous for F508del; 592 (5.8%) in the class III mutation group; 545 (5.3%) in the class IV mutation group; 347 (3.4%) in the class V mutation group. The proportion of excluded subjects in each mutation class is thus proportional to the relative frequency of each mutation class. Table 1 suppl. reports details of the included patients' genotype and of those patients older than 6 years, not transplanted and with at least two FEV_1 measurements that were excluded because their genotype can be classified in two different genotype groups among those selected for this analysis.

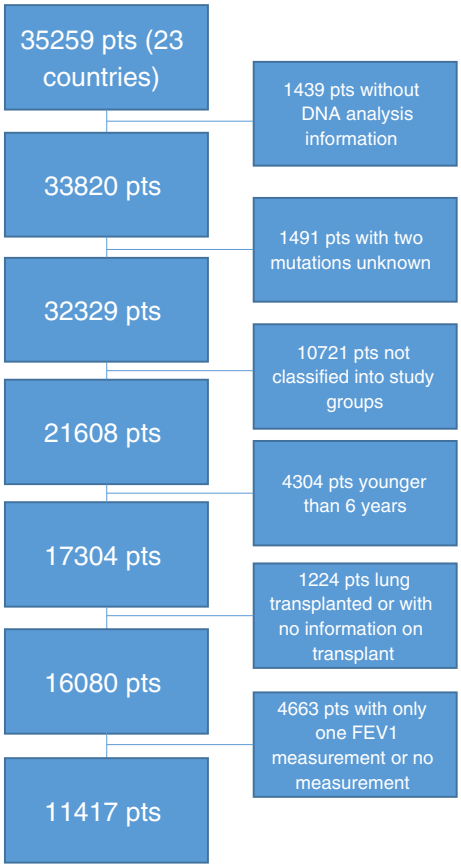

Fig. 2. Flow chart of patient selection.

Table 2
Percentages of patients with baseline FEV_1% predicted in different severity categories <40%, 40–90%, >90% by genotype group.

Genotype group, N(%)	FEV_1% predicted			
	<40	40–90	>90	Total
At least one stop codon mutation	218 (11.1)	1196 (61.1)	545 (27.8)	1959
F508del homozygous	1003 (12.3)	5001 (61.3)	2148 (26.4)	8152
At least one class III mutation	71 (12.8)	343 (62.0)	139 (25.1)	553
At least one class IV mutation	31 (6.7)	250 (54.0)	182 (39.3)	463
At least one class V mutation	26 (9.0)	174 (60.0)	90 (31.0)	290
Total	1349 (11.8)	6964 (61.0)	3104 (27.2)	11,417

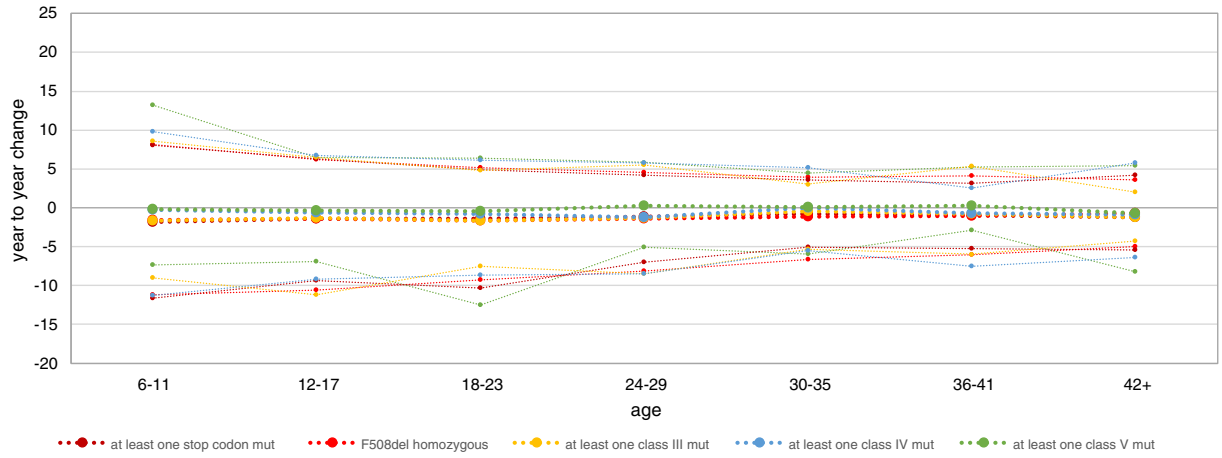

Fig. 3. 10th and 90th centiles (thin lines) and median (bold line) of the year to year change by age category for the 5 genotype groups. Connecting the cross-sectional points with dotted lines does not imply year-to-year relationships: this needs only to help the reader following the pattern of points.

Distribution of baseline lung function severity differed between the group of patients with at least one class IV and class V mutation, and patients in groups F508del homozygous, at least one stop codon mutation and at least one class III mutation ($p < 0.00001$, chi square in Table 2). The groups of patients with at least one class IV and class V mutation have a lower proportion of patients in the most severe category (FEV1 < 40% of predicted) and a higher proportion of patients in the >90% category.

As expected, mean baseline FEV_1% predicted (suppl. Fig. 1) decreased with age in all genotype groups. Mean baseline FEV_1% predicted was significantly higher ($p < 0.0001$) in groups of patients with at least one class IV and V mutation, but did not differ between the groups stop codon, F508del homozygous, and class III ($p = 0.13$). The same decrease of FEV_1% predicted with advancing age as well as slightly higher FEV_1% baseline in groups of patients with at least one class IV and V mutation was seen when only patients with baseline FEV_1% between 40 and 90% were considered (suppl. Fig. 2). The term of interaction between age and genotype was not considered into the models because they are not statistically significant.

The year to year change centiles (10th, median and 90th) by genotype groups and age categories are reported in Figs. 3–5. For the three subsequent analyses, the term of interaction between age and genotype was not considered into the model because it was not significant. When considering all patients, the year to year change in FEV_1% did not differ by age categories ($p = 0.05$), but an effect of genotype groups was observed ($p = 0.01$): however, when each genotype group was tested against another, controlling for the multiple comparison, no differences were observed. Only testing the groups of patients with at least one class IV and class V mutation against

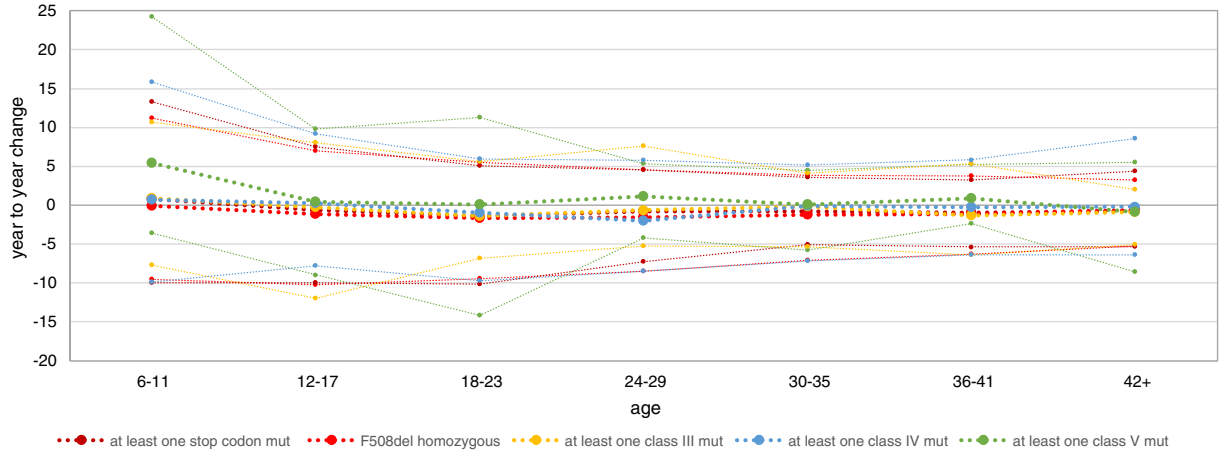

Fig. 4. 10th and 90th centiles (thin lines) and median (bold line) of the year to year change by age category for the 5 genotype groups; patients with baseline FEV_1 between 40 and 90% of predicted only. Connecting the cross-sectional points with dotted lines does not imply year-to-year relationships: this needs only to help the reader following the pattern of points.

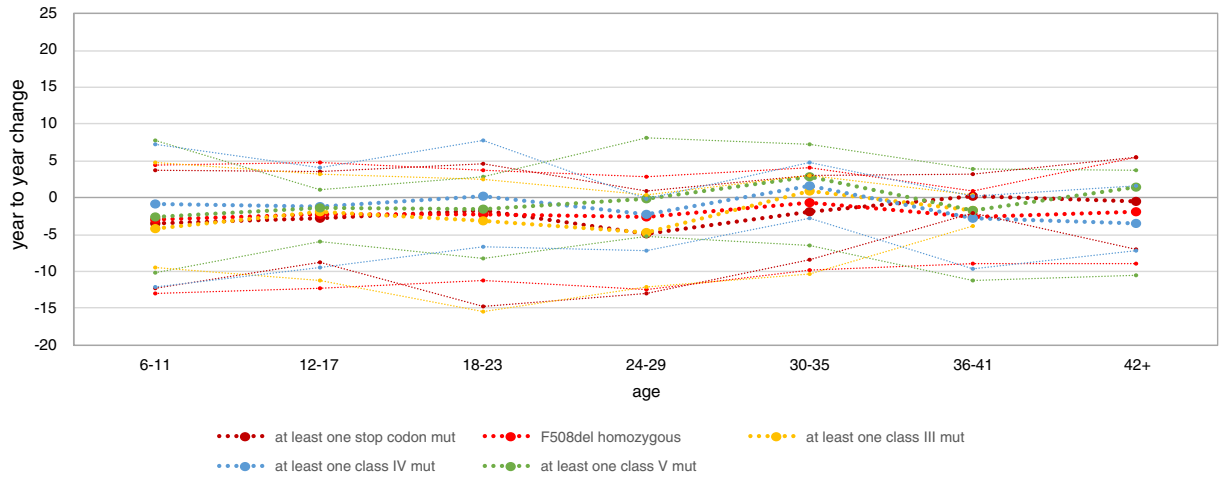

Fig. 5. 10th and 90th centiles (thin lines) and median (bold line) of the year to year change by age category for the 5 genotype groups; patients with baseline FEV_1 above 90% of predicted only. Connecting the cross-sectional points with dotted lines does not imply year-to-year relationships: this needs only to help the reader following the pattern of points.

the other three groups of patients a slight difference of 0.88% points in the year to year change was observed ($p = 0.004$). The means of the year to year changes per genotype group, estimated by the linear regression model, are reported in Table 3.

When only patients with baseline FEV_1% between 40 and 90% were considered, the year to year change in FEV_1% differed by age classes ($p < 0.0001$) and between genotype groups ($p = 0.002$). When each genotype group was tested against another, controlling for the multiple comparison, no differences was observed. Only testing the groups of patients with at least one class IV and class V mutation against the other three groups of patients a slight difference of 0.90% points in the year to year change was observed ($p = 0.02$). The means of the year to year change per genotype group, estimated by the linear regression model, are reported in Table 4.

The mean year to year change in FEV_1 was much lower in patients with baseline FEV_1 between 40 and 90% than in patients with baseline FEV_1 above 90%. This difference was striking in the 3 genotype groups. The means of the year to year change in patients with baseline FEV_1 above 90% in the genotype groups, estimated by the linear regression model, are reported in Table 5.

Table 3
Least square mean and 95% CI year to year changes in FEV_1% predicted in the 5 genotype groups.

Genotype group	Year to year change		
	Mean	95% CI	
At least one stop codon mutation	−1.35	−1.70	−0.99
F508del homozygous	−1.52	−1.72	−1.31
At least one class III mutation	−1.24	−1.87	−0.61
At least one class IV mutation	−0.62	−1.30	0.06
At least one class V mutation	−0.35	−1.21	−1.0

Table 4
Least square mean and 95% CI year to year changes in FEV_1% predicted in the 5 genotype groups; patients with baseline FEV_1 between 40 and 90% predicted only.

Genotype group	Year to year change		
	Mean	95% CI	
At least one stop codon mutation	−0.70	−1.14	−0.26
F508del homozygous	−1.22	−1.48	−0.97
At least one class III mutation	−0.51	−1.29	0.26
At least one class IV mutation	−0.08	−0.99	0.82
At least one class V mutation	0.25	−0.83	1.33

4. Discussion

Using the data from the ECFSPR, we found slight differences in age distribution of subjects grouped according to genotype, with the youngest median age in the stop codon group and the highest median in subjects in group class V. On the whole, lung disease severity expressed as FEV_1% predicted at baseline or FEV_1% year to year change, did not differ between the groups stop codon mutation, F508del homozygous and class III. Year to year decline in FEV_1 was highest in subjects with a baseline FEV_1 above 90% predicted.

Table 5
Least square mean and 95% CI year to year changes in FEV1% predicted in the 5 genotype groups; patients with baseline FEV_1 above 90% predicted only.

Genotype group	Year to year change		
	Mean	95% CI	
At least one stop codon mutation	−4.28	−5.15	−3.40
F508del homozygous	−4.00	−4.66	−3.33
At least one class III mutation	−4.28	−5.71	−2.85
At least one class IV mutation	−1.88	−3.07	−0.69
At least one class V mutation	−1.78	−3.44	−0.12

The subtle lower median age in the group with stop codon mutation could point towards a difference in disease severity. Indeed, if survival is worse in certain mutation classes, there will be underrepresentation of older individuals in that group. Indeed, a longitudinal analysis from one centre [22] pointed towards worse disease course in subjects with class I mutations. However, in our data set, many confounders can also be responsible for this difference. The prevalence of stop codon mutations is higher in south east Europe. We know there are differences in outcome between countries within Europe: more northern and western countries in Europe report a higher proportion of adults with CF [23]. In addition, in several south-eastern European countries national CF registries do not exist, but individual centres, the majority being paediatric, contribute data to the ECFSPR registry [20]. Hence a true representation of all subjects from these regions can be questioned. The wide IQR in class IV genotype age distribution probably mirrors the early detection and 'overrepresentation' of mutation R117H via newborn screening [24] as well as the milder disease course [11–13].

Although worse outcome and worse disease course seem plausible on theoretical grounds [2,15], we did not find age specific lower lung function in patients with stop codon mutations and also no larger year to year change in FEV_1%. This is thus in contrast with longitudinal data from the single centre [22]. Hence, differences may exist but they are unlikely large, since not found in this large dataset. Indeed, FEV_1 rate of decline is a very variable outcome measure. More statistical power in the analysis can be gained from a long follow up period [25] as done in the studies of Konstan et al. evaluating the effect of ibuprofen [26] and of Sanders et al. studying risk factors for progression of lung disease [22] or from a very large dataset as done in the current study. The ECSFPR is indeed the largest patient registry available. Still, using this large data collection, and comparing outcome in more than 10,000 patients, differences were not found.

The higher year to year change in FEV_1 in subjects with a baseline FEV_1 above 90% predicted than in patients with baseline FEV_1 between 40 to 90% is compatible with previous findings in patient registries [27,28]. The reasons are not known but patients with preserved lung function may be at risk of receiving less aggressive treatment. Hence preventing lung function loss in patients with a high lung function disease is of major importance and probably still insufficiently exploited [29]. Indeed, even patients with baseline lung function above 90% predicted can greatly benefit from treatment with *CFTR* modulators [30].

Like any registry study this study has limitations. The registry collects FEV_1% best of the year, hence the time between measurements in different years is not necessarily one year. One would however expect this to even out in a large data set. In addition, we analysed 2 years of FEV_1 and also from that analysis a difference between groups did not emerge. Although the data set is large, difference in definitions and outcome between countries and centres and differences in prevalence of mutation classes between countries could obscure true differences between groups. A within large country analysis could resolve some of these shortcomings: however, by these analyses conclusions did not change (results not shown). From the large dataset of the ECFSPR only about a third of the subjects could eventually be included in the FEV_1 analysis; many because of missing data but the largest proportion (N = 10,721) because the patients could not be categorized to one the predefined mutation classes (Fig. 2). The majority of these patients were F508del heterozygous with another class II mutation on the second allele. In addition, less than 300 of the more than 2000 different *CFTR* mutations reported have been fully characterized [31]. Therefore, we are confident that the results from this analysis are generalizable. We included subjects with a second mutation unknown, but also when the analysis was limited to the patients with F508del on the second allele (marked in italic in suppl Table 1; total N 10474/11,417 hence 91% of the total group) a difference was not found (results not shown).

The largest subset of data concerns the groups homozygous for F508del and the group stop codon mutations. The mean year to year change in FEV_1% predicted was similar in both groups: it was −1.52% points (95% CI −1.72; −1.31, IQR −5.09;1.99) in F508 del homozygous and −1.35% points (95% CI −1.70; −0.99, IQR −4.89;1.96) in the stop codon group. The average loss of about 3.1% points of FEV_1 over a year in the placebo group in the ataluren trial [6] was thus within the IQR for year to year change FEV_1% seen in the stop codon group in the ECFSPR.

In conclusion, using the data of the ECFSPR we did not find differences in age or lung disease severity between patient groups stop codon mutation, F508del homozygous or class III. The on average less severe disease in patients with class IV and V mutations, reflected by a higher median age and a lower proportion of subjects with severe FEV_1 impairment was confirmed.

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Appendix A. Supplementary data

Supplementary table and graphs can be found online at http://dx.doi.org/10.1016/j.jcf.2016.09.009.

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