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Profiling the response to lumacaftor-ivacaftor in children with cystic between fibrosis and new insight from a French-Italian real-life cohort

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Abstract

Introduction: Clinical trials for CFTR modulators consider mean changes of clinical status at the cohort level, and thus fail to assess the heterogeneity of the response. We aimed to study the different response profiles to lumacaftor-ivacaftor according to age in children with cystic fibrosis (CF).

Methods: A mathematical framework, including principal component analysis, data clustering, and data completion, was applied to a multicenter cohort of 112 children aged 6–18 years, treated with lumacaftor-ivacaftor. Studied parameters at baseline and 6 months included body mass index (BMI), number of days of antibiotics (ATB), Sweat test (ST), forced expiratory volume in 1 s expressed in percentage predicted ($ppFEV_1$), forced vital capacity (ppFVC), and forced expiratory flow at 25%–75% of FVC ($ppFEF_{25-75}$).

Results: Change in $ppFEV_1$ was the most significant parameter in characterizing response heterogeneity among the 12–18-year-old patients. Patients with minimal changes in $ppFEV_1$ were further separated by change in BMI and ATB course. In the 6–12-year-old children both BMI and $ppFEV_1$ evolution were the most relevant. ST change was not associated with a clinical response.

Conclusions: Change in $ppFEV_1$, BMI, and ATB course are the most relevant outcomes to discriminate clinical response profiles in children treated with lumacaftor-ivacaftor. Prepubertal and pubertal children display different response profiles.

Vincenzina Lucidi, Véronique Stoven, and Isabelle Sermet-Gaudelus are co-last authors.

KEYWORDS
children, lumacaftor-ivacaftor, principal component analysis

1 | INTRODUCTION

CFTR modulators are expected to rapidly improve baseline condition of people with cystic fibrosis (CF). Clinical trials and real-world studies show improvement of pulmonary function tests (PFTs).[1–3] Other outcomes are also considered, including sweat chloride concentration, pulmonary exacerbations, and nutritional status. Importantly, these parameters cannot be considered independently as they all reflect the consequences of CFTR dysfunction on different target tissues. We aimed to determine which combination of outcomes, collected on a routine clinical basis, might be the most relevant to assess the global heterogeneity of the response to CFTR modulators in children treated with lumacaftor-ivacaftor, and to characterize different profiles of response based on the evolution of these clinical outcomes in a 6-months span.

We focused on a cohort of children older than 6 years treated with the combo therapy lumacaftor-ivacaftor and followed-up in different pediatric centers in France and in Italy. We considered the parameters usually measured in patients treated with CFTR modulators, including PFT, body mass index (BMI), sweat test (ST), and antibiotic courses, and studied their evolution during the first 6 months of treatment. Independent parameters characterizing the response variability were identified with principal component analysis (PCA). PCA provides a mathematical framework to integrate various parameters, identifies principal components (PCs) that explain most of the variability in the data, which variables contribute the most to each component, and whether they vary together. It was also used as a dimension reduction method. We took advantage of this functionality in our study, as k-means clustering was performed on the minimum number of PCs explaining 70% of the variance of the sample.

2 | MATERIALS AND METHODS

2.1 | Cohorts and data description

This study is a retrospective analysis of data collected during routine follow-up of patients. Data from children above 6 years homozygous for p.Phe508del and treated with lumacaftor-ivacaftor were collected from four centers: Necker Enfants Malades, Paris, France; Ospedale pediatrico Bambino Gesu, Rome, Italy; Hospices Civils de Lyon, Lyon, France; and Centre Hospitalier Universitaire de Nantes, Nantes, France. Patients were enrolled before starting lumacaftor-ivacaftor therapy and were evaluated at 6 months according to the standard of care. The following outcomes were measured at treatment initiation (M0) and at six months (M6), according to the standard of care guidelines: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25%–75% of FVC (FEF_{25-75}), all expressed as percentage predicted (pp) values for normal values[4]; chloride concentration by ST; days of antibiotics in the previous 6 months as a treatment of pulmonary exacerbation, including both IV treatment and oral therapy (ATB); BMI, expressed as BMI *Z*-score.[5] Clinical data were part of a French and Italian real-life study (IRB Comité d'Ethique de la Recherche APHP.5, nber 0011928; IRB Ospedale Pediatrico Bambino Gesu, nber 1534).

We studied their absolute change between M0 and M6: $\Delta ppFEV_1$, ΔppFVC, $\Delta ppFEF_{25-75}$, ΔBMI, ΔATB, ΔST where "Δ" stands for "absolute variation from baseline to 6 months."

All patients initiating lumacaftor-ivacaftor combination were enrolled in the study. Patients were included between 2017 and 2020.

2.2 | Principal component analysis (PCA) algorithm and imputation of missing data

We used PCA to describe our data set.[6] If patients are described by *n* initial clinical parameters, PCA determines *n* new variables that are linear combinations of the initial parameters, called principal components (PC) 1 to *n* (PC1 to PC*n*). The PCs define *n* new orthogonal (i.e., independent or non-redundant) variables along which patients are best dispersed, such that the percentage of variance captured along the corresponding directions decreases from PC1 to PC*n*. Initial parameters with strong coefficients in the same PC are correlated. Conversely, initial parameters that never appear together with strong coefficients in any component are essentially independent. Using PCA, it is also possible to view the PCs as linear combinations of the initial parameters, showing which parameters contribute the most to each PC. This information is available in loading matrixes: the higher the loading of an initial parameter in a given PC, the more it contributes to this PC, and therefore, to the variance along this PC direction. Loadings are similar to correlations, which can also be calculated and represented graphically to visualize relationships between initial parameters and PCs.[7]

In our study, six PCs were determined, named PC1 to PC6. As PCs are ordered by the percentage of overall variance explained, PC1 describes the major part of the variance of the data, followed by PC2, and so forth. Thus, parameters included in the first PCs are the most relevant to discriminate patient response. In particular, those associated with PC1 are the most important. On the contrary, the last PCs carry little to no information and can be regarded as uninformative. In this study, we thus only considered the PCs explaining most of the global variance (at least two-thirds of the variance when taken together). Their correlation with the six outcome parameters was studied and represented graphically in two-dimensional (2D) space to ease interpretation. Each vector (represented by an arrow) represents an initial parameter, that is, one

of the monitored outcomes. The more a vector is aligned with a PC, the longer the arrow, the more it is correlated to the PC, and thus contributes to the variance captured by this PC.

To remove potential bias of PCA towards parameters with larger variations, data for each outcome parameter were normalized after aggregation, before running the algorithm. Missing values were imputed before running the PCA algorithm, using the missForest R package.[8]

2.3 | Patient clustering

Clustering was performed by Kmeans algorithm. This method allows to separate the samples in clusters of equal variances and to provide an informative and interpretable description of the data. The optimal number of clusters was determined using the *C*-index criterion.[9] The clusters were compared based on the six outcome variables considered in the study to better characterize the associated profiles of response and understand what differentiate them from each other. To take advantage of the dimension reduction feature of PCA, patient clustering was performed based on the minimum number of PCs necessary to account for 70% of the variance of the sample.

2.4 | Statistical evaluation

Analyses were conducted in R.[10] Data are presented as mean (IQR). A p value of <0.05 was considered statistically significant. As normality assumption could not be verified for all parameters, comparisons between values from patients in the 6–12-year-old cohort and values from patients in the 12–18-year-old cohort, as well as comparisons between values from patients in different subgroups of the same age group, were performed by Wilcoxon signed-rank test. Values from patients in the same age group at baseline and after 6 months of treatment were compared by paired Wilcoxon signed-rank test. Correlation between variables was assessed by Spearman correlation test. Benjamini–Hochberg corrections were applied to account for multiple testing.

3 | RESULTS

3.1 | Patient characteristics

Characteristics of the 112 F508del homozygous children are summarized in Supporting Information: Table 1. Patients had a mild lung disease, as assessed by a mean ppFEV$_1$ of 87% at M0. Similarly, most of the patients had a normal nutritional status with a mean BMI *Z*-score at M0 of −0.6. Six- to 12 year-old patients ($n = 24$) had a significantly better respiratory status than 12–18-year-old patients ($n = 88$), as shown by a significantly higher ppFEV$_1$ ($p < 10e{-}3$) and ppFEF$_{25-75}$ ($p = 0.01$). Therefore, the two cohorts were analyzed separately.

Overall, in both cohorts, there was a significant improvement in BMI and ST at 6 months lumacaftor-ivacaftor, in contrast to ppFEV$_1$ and ppFEF$_{25-75}$ which were not significantly changed.

Forty-two values were missing in the 12–18-year-old cohort (4.0% of the data) and 9 in the 6–12-year-old cohort (3.1%). Most of them involved the ST. Removing all patients with at least one missing value would have led to discard 43 patients in the PCA analysis. We thus performed missing values imputation, as described in Supporting Information. No significant change in data interpretation was observed upon potential data imputation errors after performing bootstrap-based multiple imputations using repeated random patient removal, which provides evidence for the robustness of the data imputation method[11] (Supporting Information: Table 1 and Figure 1A).

3.2 | PCA of clinical parameters and patient clustering in the 12–18 years children cohort

PCA analysis determined six PCs, PC1 to PC6. PCA was robust to data reduction, as shown by PCA calculation after repeated random data removal (Supporting Information: Figure 1B). The amount of variance explained by each component is shown in Supporting Information: Table 2. We focused on the first three PCs in the following analysis (PC1, PC2, and PC3), as they accounted for more than 70% of the whole variance of the sample (respectively 38%, 19%, and 17%; Supporting Information: Table 2).

Evolution of the three PFT parameters (ΔppFEV$_1$, ΔppFVC, ΔppFEF$_{25-75}$) were the strongest contributors to PC1, as shown by their correlation with this PC (Figure 1 andSupporting Information: Table 2) and their value in the loading matrix (Supporting Information: Table 3). ΔppFVC and ΔppFEF$_{25-75}$ carried redundant information with ΔppFEV$_1$, as assessed by their similar loadings in PC1 (Supporting Information: Table 3). ΔST was also correlated to PC1, although to a lesser degree, as shown by less alignment of its vector to PC1 and a smaller loading (Figure 1 and Supporting Information: -Tables 2 and 3). ΔATB and ΔBMI were strongly correlated to PC2 (Figure 1 and Supporting Information: Table 2). As expected, these two parameters pointed in opposite directions; for example, when BMI increased, the number of ATB courses in the six previous months decreased. ΔST and ΔATB were the most significant contributors to PC3 (Figure 1 and Supporting Information: Table 2).

Clustering was then performed to characterize profiles of response to treatment. Patient clustering was performed based on the first three principal components. An optimal number of four clusters was determined by the *C*-index criterion. Two-dimensional (2D) visualization of the patients within clusters in the PC space is shown in Figures 2 and 3 and Supporting Information: Figure 2. Partition of Cluster 1 and Cluster 4 was based on respiratory outcomes. Cluster 1 was characterized by an improvement in all three pulmonary function parameters (Figure 3 and Supporting Information: Table 4). ΔppFEV$_1$ change in Cluster 1 was significantly higher than in any other cluster, as indicated by an absolute increase of 21%

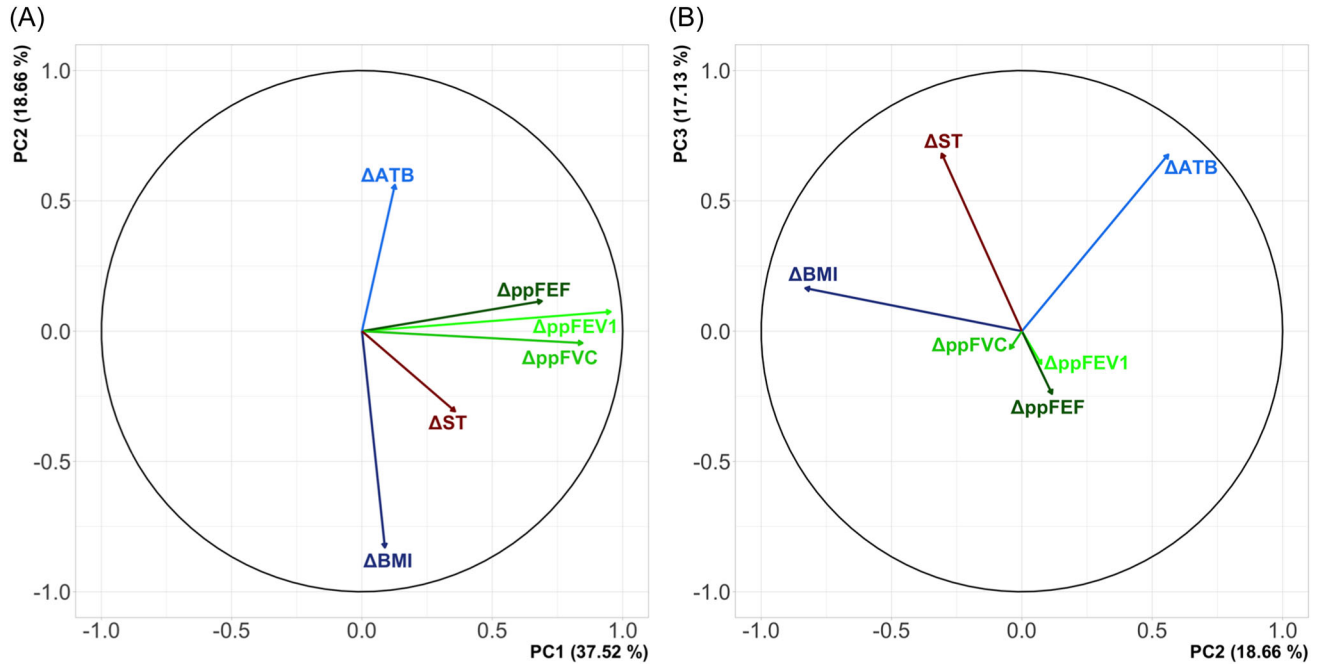

FIGURE 1 Circle of correlation between clinical parameters and the first three PCA components for patients aged 12 years and older. (A) Graphical representation of PC1 and PC2. (B) Graphical representation of PC2 and PC3. Each parameter is represented by a vector whose abscissa and ordinate provide its correlation with PCA components. % of explained overall variance of the data are displayed alongside the PC they correspond to. ATB, days of antibiotics in the last 6 months; BMI, body mass index; ppFEF, percent predicted forced expiratory flow between 25% and 75% of FVC; PC, principal components; PCA, principal component analysis; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; ppFVC, percent predicted forced vital capacity; ST, sweat test.

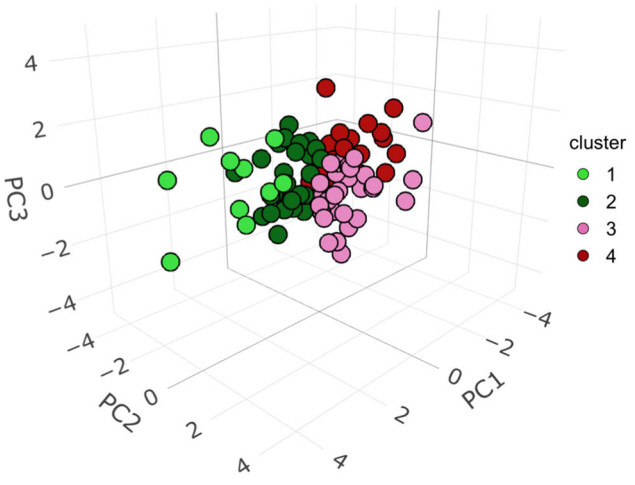

FIGURE 2 Projection of the patients on the three-dimensional space with coordinates of the first three principal components (PC1, PC2, and PC3). Each point corresponds to one patient and each color corresponds to a cluster. Coordinates for each patient were obtained by a linear combination of the outcome parameters contributing to the PCs, according to PCA methodology. PC, principal components; PCA, principal component analysis.

(9) points, while it was significantly lower in Cluster 4 than in any other cluster (absolute decrease of 10% (6) points) (Supporting Information: Table 4). A similar pattern was observed for ΔppFVC or $\Delta ppFEF_{25-75}$, although to a lesser degree. In particular, $\Delta ppFEF_{25-75}$ was not significantly higher in Cluster 1 compared to Clusters 2 or 3. A combination of $\Delta ppFEV_1$ with ΔppFVC and $\Delta ppFEF_{25-75}$ within PC1 (Figure 3) did not improve the separation between clusters, further supporting the fact that $\Delta ppFEV_1$, ΔppFVC, and $\Delta ppFEF_{25-75}$ carry redundant information. Interestingly, patients from Cluster 1 had a significantly lower ppFVC at treatment initiation compared to any other cluster, and a significantly lower ppFEV1, as compared to Cluster 4. Patients in Cluster 1 also displayed the smallest decrease in ST (−1.6 (20)). Those in Clusters 2 and 3 displayed an intermediate change in respiratory parameters and were further differentiated by their respective change in ATB course, BMI *Z*-score, and ST. Patients in Cluster 2 displayed the greatest decrease in ATB. Patients in Cluster 3 had a significantly higher ST at M0 than any other cluster, displayed the greatest decrease in ST (−37 (18)) and, in contrast to all other clusters, experienced a decrease in BMI *Z*-score.

3.3 | PCA of clinical parameters and patient clustering in the 6–12 years children cohort

In children below 12 years of age, the two first components of the PCA summarized 66% of the total variance, PC1 alone accounting for 44% (Supporting Information: Table 5). We therefore focused on the first two PCs. Given the small number of patients, we did not perform clustering analysis.

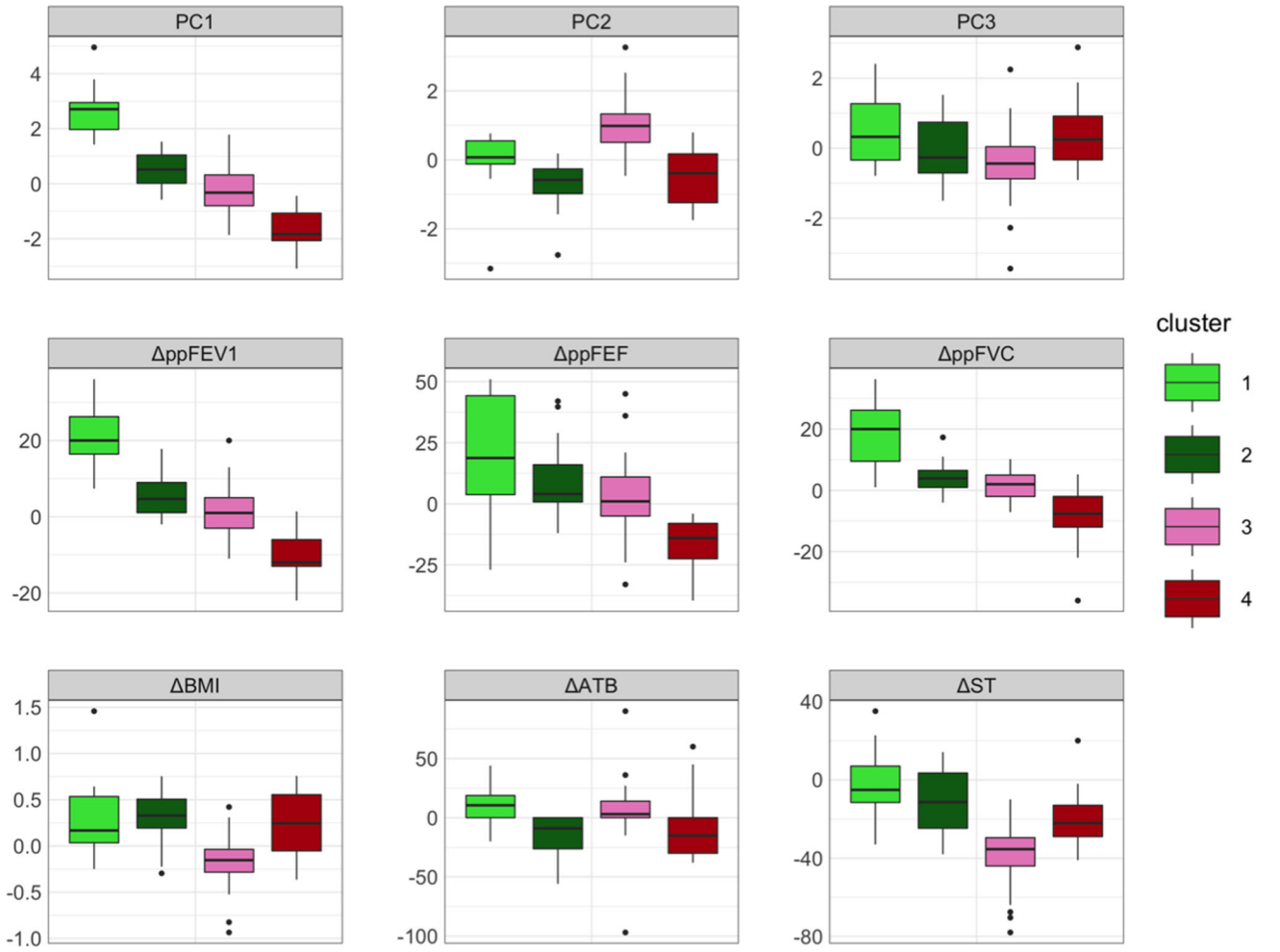

FIGURE 3 Distribution of parameters in the four clusters for 12–18-year-old patients. Values for the first three PCs were obtained by a linear combination of the outcome parameters contributing to the PCs, according to PCA methodology. ATB, days of antibiotics in the last 6 months; BMI, body mass index; PC, principal components; PCA, principal component analysis; ppFEF, percent predicted forced expiratory flow between 25% and 75% of FVC; $ppFEV_1$: percent predicted forced expiratory volume in 1 s; ppFVC, percent predicted forced vital capacity; ST, sweat test.

Similarly to the 12–18-year-old cohort, PC1 was correlated to the three respiratory function parameters (Figure 4 and Supporting Information: Table 5). ΔppFEF and ΔppFVC remained highly correlated with ΔppFEV1, as assessed by their similar loadings (Supporting Information: Table 6). Conversely, unlike the 12–18-year-old cohort, ΔBMI was also a strong contributor to PC1 ($r = 0.67$, $p = 0.0003$) (Supporting Information: Table 5). ΔST and ΔATB were the two main contributors to PC2 (Figure 4 and Supporting Information: Tables 5 and 6).

4 | DISCUSSION

This study aimed at characterizing the heterogeneity of the response to lumacaftor-ivacaftor in children enrolled in a "real-life" study and at deciphering different profiles of response to treatment. We used a mathematical framework based on PCA to identify nonredundant variables and random forests to impute missing values.

This also enabled to show the relationships between the evolution of outcome parameters in a 6-month span, highlighting specific response patterns. Nutritional outcome, as assessed by BMI, was an important response parameter in the 6–12-year-old patients, in contrast to the 12–18-year-old cohort.

Given the efficiency of CFTR modulators, an increasing number of children will benefit from these therapies as it is anticipated that if started early in life, they might at least slow down the evolution of the disease.[12] However, the fact that children present a very mild disease or are even asymptomatic makes evaluation in real-life studies very challenging.[13] This is why outcomes such as Lung Clearance Index are currently being tested to characterize the response.[14] However, such investigations cannot be performed in all centers. We investigated whether outcomes collected routinely in all European centers

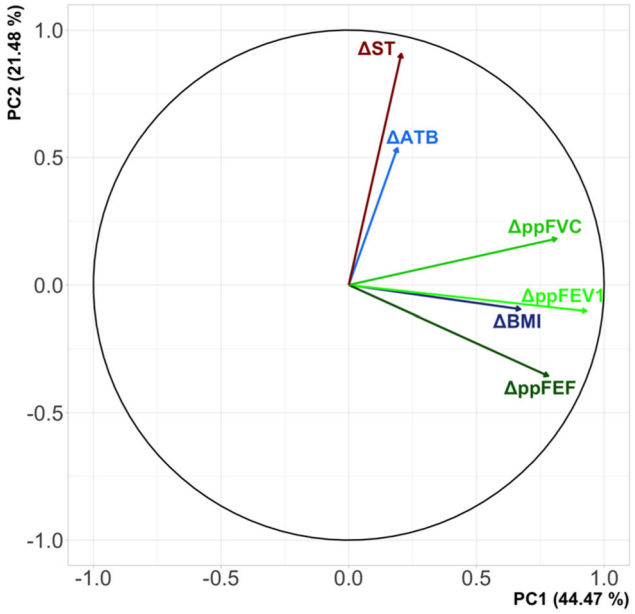

FIGURE 4 Circle of correlation between clinical parameters and the first two PCA components, for patients younger than 12 years old. Each parameter is represented by a vector whose abscissa and ordinate provide its correlation with PCA components. % of explained overall variance of the data are displayed alongside the PC they correspond to. ATB, days of antibiotics in the last 6 months; BMI, body mass index; PC, principal components; PCA, principal component analysis; ppFEF, percent predicted forced expiratory flow between 25% and 75% of FVC; $ppFEV_1$, percent predicted forced expiratory volume in 1 s; ppFVC, percent predicted forced vital capacity; ST, sweat test.

and in a standardized way might differentiate specific response patterns. In contrast to previous studies where the effect of a treatment was evaluated in terms of a mean response of the whole cohort, we focused on the heterogeneity of the response in real-life follow-up. We used PCA to reduce the number of variables to a smaller number of principal components without losing too much information and for later clustering. We assessed the redundancy between the outcome parameters to define a core data set of the response of the pediatric patients. Therefore, our analysis differs from those performed usually by understanding which parameters vary similarly in response to a treatment. Not only did we assess which factors are implicated in cohort heterogeneity, but we also aimed at finding a combination of variables that explain most of the variability in a given data set. Moreover, we defined different profiles of response thanks to clustering analysis. To our knowledge, a single other study focused on the heterogeneity of the response to treatment in patients with bronchiectasis, and also concluded that the response was highly heterogeneous.[15] These observations reinforce the need to understand how multiple factors participate to the response.

Importantly, the methodology we propose in this study can be applied to other studies. In particular, following the advent of the triple combination therapy to treat patients with CF,[16] it would be interesting to apply this methodology to a cohort of patient treated with elexacaftor-tezacaftor-ivacaftor.

The main limitation of our study is the small number of patients. We thus challenged the statistical soundness of our results based on a random resampling approach, assessing how much PCA results would have changed upon removal of part of our data. In addition, there were missing data in this real-life study. Although only a few results were missing (around 4%), ignoring patients with partial information would have led to discard around 38% of the patients, which is critical in already small cohorts. We implemented a methodology of data imputation and assessed whether the results of the PCA could change with respect to potential data imputation errors. We found that the PCA results were stable regarding both resampling and potential imputation errors. Therefore, our methodology is statistically robust despite the small size of the cohort and our results are reliable.

An other limitation is the absence of follow-up beyond 6 months. Although this time range is similar to the one used in clinical studies[17,18] and allows to unveil significant heterogeneity in response to treatment, the possible long-term effects of the treatment and long-term heterogeneity cannot be assessed by the current study.

In the 12–18-year-old cohort, clustering of the patients unveiled two response levels. First, even if it was not significant at the whole sample level, the evolution of $ppFEV_1$ allowed to characterize "Good Respiratory Responders" with significant improvement (Cluster 1), "Bad Respiratory Responders" with significant deterioration (Cluster 4) and clusters with minimal change, within the intrinsic variability of this respiratory test.[19] This provides evidence that $ppFEV_1$ evolution is of crucial significance to discriminate response of pediatric patients aged 12–18 years treated with lumacaftor-ivacaftor. Moreover, neither ΔppFVC nor $\Delta ppFEF_{25-75}$ improved this cluster characterization, suggesting that they were redundant with $\Delta ppFEV_1$ and did not provide additional information. Interestingly, patients in Cluster 1 (those who improved the most) had the worse $ppFEV_1$ at baseline and a significantly lower ppFVC. This suggests that in a pediatric population, patients with lower PFT, and in particular $ppFEV_1$, have a higher potential for improvement. This is supported by similar data from adolescents, which showed an improvement of $ppFEV_1$ in those with low baseline $ppFEV_1$,[20,21] while increase in $ppFEV_1$ was not detected in patients with normal $ppFEV_1$.[1,22] Overall, $ppFEV_1$ evolution in this cohort underlines the importance of considering subgroups of patients. Indeed, considering the mean evolution of $ppFEV_1$ at the sample level would have led to the conclusion that there is no significant improvement. On the contrary, the subgroups analysis highlights a significant improvement in specific subpopulations of the cohort and underlines the heterogeneity of the response to the treatment. The patients benefiting the most were those with a significantly lower ppFVC at treatment initiation compared to any other cluster and a significantly lower $ppFEV_1$ as compared to Cluster 4.

To further characterize the response of the patients with no significant change in $ppFEV_1$ (Clusters 2 and 3), the second level

of response testing (i.e., PC2) included change in ST, BMI *Z*-score, and ATB courses. Cluster 2 was characterized by an increase in BMI and a decrease in ATB consumption (i.e., less pulmonary exacerbations). This highlights a specific profile of patients experiencing concomitant improved nutrition and infection in contrast to minimal change in $ppFEV_1$. The emergence of ATB courses as an independent factor of the response in pediatric cohorts was also evidenced in other cohorts with normal $ppFEV_1$.[23,24] This may reflect improved pulmonary inflammation and innate immunity, based on improved antimicrobial activity and immune cell function.[25,26] This highlights the potential benefit of those therapies even in patients with normal lung function. This aspect is crucial in the pediatric population who displays a "silent" disease in a perspective of preventative care. Similar to our cohort, a significant improvement in BMI has been reported in the 12–18-year-old children treated with lumacaftor-ivacaftor.[1,20] This may reflect not only an increased caloric intake but also an improved pancreatic status, and possibly a systemic effect of increased anabolism due to improved inflammation.[27] Unexpectedly, we also identified a group of patients who worsened their BMI (Cluster 3). We have no clear explanation for this, but the fact that these patients displayed neither improvement in $ppFEV_1$ nor in ATB course shows that they were not clinically improved at all by the modulator therapy. Interestingly, these patients also displayed the most important decrease in ST, while patients with the best respiratory response displayed the smallest decrease in ST. This demonstrates that, even though sweat chloride concentration improves at the level of the overall cohort, its evolution is not indicative of a clinical benefit at the individual level in the pediatric population. This is in line with previous studies in adults showing that sweat chloride concentration decreases in response to treatment with CFTR modulators, although there was no correlation with $ppFEV_1$ evolution.[27–29] Patients in this cluster had a significantly higher ST value than those in any other cluster, thus they might have had a larger margin of improvement for this parameter.

The 6–12-year-old cohort was analyzed separately because they had a significantly better respiratory function at baseline as compared to the 12–18-year-old adolescents ($p = 0.002$). In this younger cohort, $ppFEV_1$ did not significantly improve, as already reported in studies conducted with lumacaftor-ivacaftor and tezacaftor-ivacaftor in a similar age group (6–11-year-olds).[17,18,22] Most importantly, the PCA profile was different from the 12–18-year-old cohort, as PC1 was not only correlated to change in $ppFEV_1$ but also in BMI. This shows that in this younger sample with normal respiratory function, BMI captures a part of the response and is an important parameter, independently of the respiratory function. This is indirectly confirmed by the fact that in most of the studies in this age group, BMI is consistently improved in contrast to $ppFEV_1$.[17,30] BMI evolution is usually considered as a secondary endpoint. Here, we show that BMI evolution is an important endpoint in young patients to discriminate responders from nonresponders.

5 | CONCLUSION

We propose a global mathematical framework suited to real-life studies that could be translated to currently ongoing studies.

In the present case, it highlighted that changes in $ppFEV_1$, BMI, and ATB course numbers explain most of the heterogeneity in children's response to lumacaftor-ivacaftor. In particular, BMI is the cornerstone of the heterogeneity of the response in the 6–12-year-old children with a normal respiratory function. Improvements in lung function, BMI, exacerbation frequency, and ST are dissociated in children with CF. Studying heterogeneity of the response will help reassess how we measure treatment response to CFTR modulators in this population, who will be the target of the future trials with CFTR modulators.

AUTHOR CONTRIBUTIONS

Matthieu Cornet: Conceptualization; methodology; software; visualization; validation; writing – original draft; formal analysis. **Geneviève Robin**: Methodology; conceptualization, writing – original draft. **Fabiana Ciciriello**: Data curation; writing – review & editing; investigation. **Tiphaine Bihouee**: Data curation; investigation; writing – review & editing. **Christophe Marguet**: Data curation; investigation; writing – review & editing. **Valérie Roy**: Conceptualization; methodology. **Muriel Lebourgeois**: Investigation; writing – review & editing; data curation. **Frédérique Chedevergne**: Data curation; investigation. **Anne Sophie Bonnel**: Data curation; investigation; writing – review & editing. **Mairead Kelly**: Writing – review & editing. **Philippe Reix**: Data curation; writing – review & editing; investigation. **Vincenzina Lucidi**: Data curation; supervision; writing – review & editing; investigation. **Véronique Stoven**: Conceptualization; methodology; supervision; writing – original draft. **Isabelle Sermet-Gaudelus**: Writing – original draft; resources; data curation; project administration; supervision; conceptualization; investigation; funding acquisition; writing – review & editing; methodology.

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CONFLICT OF INTEREST

ISG has participated to scientific Board of Vertex Therapeutics and received Academic Funding from Vertex Therapeutics. The other authors do not declare any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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