Supplementary Digital Content for the manuscript entitled:

Aspergillus and progression of lung disease in children with cystic fibrosis

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ABBREVIATIONS IN TEXT

ACFBAL	Australasian Cystic Fibrosis Bronchoalveolar Lavage
ACFDR	Australian Cystic Fibrosis Data Registry
BAL	bronchoalveolar lavage
BSV	between-subject variability
CF	cystic fibrosis
CI	confidence interval
FEV_1%	forced expiratory volume in 1-second percent
HR	hazard ratio
HRCT	high-resolution computed tomography
IQR	interquartile range
NONMEM	non-linear mixed effects modelling software package
OFV	objective function value
OR	odds ratio

ASPERGILLUS AND LUNG STRUCTURE AT AGE 5-YEARS

Culture method

In the Australasian Cystic Fibrosis Bronchoalveolar Lavage (ACFBAL) study, the colony count in the bronchoalveolar lavage (BAL) fluid samples was determined by adding the BAL fluid samples by the spread plate method.[1] This involved 500µL of BAL fluid being serially diluted from 10^{-1} to 10^{-5} in sterile phosphate buffered saline for quantitative colony counts and 100µL of undiluted BAL fluid and 100µL from each of the serial dilutions were added to six different selective and non-selective media: (1) horse blood agar (HBA), (2) mannitol salt agar, (3) MacConkey agar, (4) chocolate bacitracin agar (CBA), (5) cetrimide or *Pseudomonas* agar and (6) *Burkholderia cepacia* agar. Plates were then incubated in air at 37^0C (in 5%CO_2 for CBA plates) and read at 24- and 48-hours. The colony count for BAL fluid was determined by choosing whichever plate contained between 30 and 100 individual colonies. Respiratory bacterial pathogens were identified by standard methods.

Five of eight centres also included Sabouraud dextrose agar with gentamicin routinely as selective media to isolate fungal organisms. The plates were incubated in air at 35^0C for up to 7-days for the primary isolation of moulds. When mould was found growing on either selective or non-selective media (eg. HBA agar), *Aspergillus* species were identified by their colonial and microscopic appearance.

The children with at least one positive *Aspergillus* BAL culture and the timing of these events in the first 5-years of life in children from the BAL-directed therapy arm is shown in Figure E1.

Explanatory variables tested in cross-sectional analysis

Data using the subject's genotype were not tested in this analysis as all participants in the ACFBAL study met the criteria of classical cystic fibrosis (CF) based on having two or more of the following: two CFTR mutations, sweat chloride level >60mmol/L, pancreatic insufficiency, or meconium ileus. Similarly, data on pancreatic status were not tested as most of the children in ACFBAL study were

already pancreatic insufficient. Finally, there was no ACFBAL study arm effect, as assignment was by randomisation.

Cross-sectional analysis

Logistic regression uses linear predictor function to predict the probability of outcomes of chest high-resolution computed tomography (HRCT) scan scores in children with CF at age 5-years with z^{th} observation, as shown in the equation below:

$$f(k,z) = \beta_{0,k} + \beta_{1,k}x_{1,i} + \beta_{2,k}x_{2,i} + \cdots + \beta_{m,k}x_{m,i} \quad \text{Equation E1}$$

where $\beta_{m,k}$ is a regression coefficient associated with the m^{th} explanatory variable and the k^{th} outcome. Odds ratios (OR) were obtained from the exponential of the regression coefficient

$OR = e^{\beta_{m,k}}$.

Results

Figure E2 displays the distribution of total chest HRCT scores at 5-years of age in children with cystic fibrosis (CF) included in the ACFBAL study. The proportion of subjects at the time of their age 5-year bronchoscopy with positive BAL *Aspergillus* cultures is shown in Table E1. Detailed results of a multivariable model on structural lung changes at age 5-years are presented in Table E2 below.

Table E1. Number and percentage of subjects with positive BAL *Aspergillus* cultures at age 5-years by study site.

ACFBAL study site	Number and proportion of subjects with positive BAL *Aspergillus* cultures at age 5-years/total subject number at each study site (%)
New South Wales	6/32 (18.8%)
Northern Territory	1/1 (100%)
Queensland	10/56 (17.9%)
South Australia	0/3 (0%)
Victoria	3/33 (9.01%)
New Zealand	8/31 (25.8%)

Table E2 Results for the multivariable model investigating the influence of subject characteristics and explanatory variables obtained in the first 5-years of life on the bronchiectasis, airway wall thickening, mucous plugging, parenchymal disease and air trapping scores at 5-years of age.

Factors tested/ Reference score: 0%	**Bronchiectasis score Score >0%**		**Airway wall thickening score >0%**		**Mucous Plugging score >0%**		**Parenchymal disease scores >0%**		**Air trapping score >0%**	
	OR [95%CI OR]	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***
Intercept	29.3	0.06	0.47 (1.61)	0.78	0.87	0.92	2.83	0.49	0.69	0.80
Aspergillus at age 5-years[b]	1.14 [0.39-3.34]	0.81	2.79 [0.93-7.82]	0.07	1.51 [0.59-3.86]	0.39	2.28 [0.84-6.21]	0.11	5.53 [2.35-10.82]	0.003
Male	0.48 [0.21-1.09]	0.08	1.04 [0.44-2.47]	0.93	1.07 [0.51-2.24]	0.86	0.72 [0.34-1.49]	0.38	0.73 [0.34-1.57]	0.42
Having MI at birth	2.23 [0.82-1.18]	0.11	0.99 [0.34-2.91]	0.99	1.37 [0.56-3.36]	0.49	0.87 [0.36-2.44]	0.78	0.59 [0.23-1.54]	0.28
BMI- Z score	0.60 [0.38-0.97]	0.03	0.61 [0.35-1.06]	0.08	1.15 [0.74-1.78]	0.52	0.82 [0.53-1.28]	0.38	0.76 [0.48-1.21]	0.24
P. aeruginosa at age 5-years[a]	3.93 [1.02-15.23]	0.04	9.33 [2.34-36.51]	0.001	2.91 [0.89-9.46]	0.08	2.32 [0.66-8.18]	0.19	1.09 [0.51-2.35]	0.83
Cum. IV tobramycin, other than for ET	1.0 [0.99-1.0]	0.49	1.0 [0.99-1.0]	0.44	0.99 [0.99-1.00]	0.08	1.0 [0.99-1.0]	0.11	1.0 [0.99-1.0]	0.02
Cum. IV tobramycin for ET	1.0 [0.99-1.0]	0.97	1.0 [0.99-1.0]	0.93	1.0 [0.99-1.0]	0.09	1.002 [0.995-1.01]	0.61	1.0 [0.99-1.0]	0.92
Cum. inh. tobramycin for ET	1.0 [0.99-1.0]	0.92	1.0 [0.99-1.0]	0.78	1.0 [0.99-1.0]	0.20	1.002 [0.995-1.01	0.61	1.0 [0.99-1.0]	0.23
Cum. IV and inh. tobramycin for ET	1.0 [0.99-1.0]	0.87	1.0 [0.99-1.0]	0.86	1.0 [0.99-1.0]	0.22	1.005 [0.995-1.01]	0.61	1.0 [0.99-1.0]	0.27

Factors tested/ Reference score: 0%	Bronchiectasis score Score >0%		Airway wall thickening score >0%		Mucous Plugging score >0%		Parenchymal disease scores >0%		Air trapping score >0%	
	OR [95%CI OR]	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***	**OR [95%CI OR]**	***P***
Cum. Macrolide	1.0 [0.99-1.0]	0.21	1.0 [0.99-1.0]	0.28	1.0 [0.99-1.0]	0.49	1. [0.99-1.0]	0.23	1.0 [0.99-1.0]	0.77
Cum. Gentamicin	1.0 [0.99-1.0]	0.56	1.0 [0.96-1.0]	0.06	1.0 [0.99-1.0]	0.59	1.0 [0.99-1.0]	0.10	1.0 [0.99-1.0]	0.15
Max. Temperature	0.92 [0.82-1.01]	0.13	0.95 [0.85-1.06]	0.32	1.02 [0.93-1.12]	0.66	0.98 [0.89-1.08]	0.74	1.0 [0.99-1.1]	0.98
Min. Temperature	0.98 [0.92-1.05]	0.59	0.97 [0.91-1.03]	0.35	0.98 [0.93-1.04]	0.66	1.02 [0.96-1.07]	0.57	1.02 [0.38-2.68]	0.27
Number of hospitalisations secondary to PE	1.01 [0.88-1.16]	0.95	1.00 [1.0-1.0]	0.98	1.02 [0.87-1.18]	0.83	1.14 [0.95-1.36]	0.18	0.87 [0.77-0.99]	0.01
Staphylococcus aureus at baseline[a]	0.64 [0.23-1.78]	0.39	1.10 [0.38-3.16]	0.86	0.82 [0.31-2.19]	0.69	0.93 [0.36-2.45]	0.89	1.01 [0.38-2.68]	0.98
Received anti-staphylococcal prophylaxis in the first-year of life	0.38 [0.05-3.11]	0.37	0.37 [0.11-1.19]	0.07	0.59 [0.21-1.59]	0.29	1.03 [0.39-2.64]	0.96	1.63 [0.63-4.20]	0.31

[a]BAL culture $\geq 10^3$ colony-forming units/mL; [b]Any growth in BAL cultures; [c]$p<0.05$ and [95%CI OR] does not include 1.0. BAL, bronchoalveolar lavage; BMI, body-mass Index; cum., Cumulative dosage (mg) of drugs prior to chest high-resolution computed tomography (HRCT); ET, *Pseudomonas aeruginosa* eradication therapy received prior to age 5-years; inh., inhaled tobramycin; IV, intravenous; max. Temperature, maximum annual temperature of geographic region of birth (^{0}C); MI, meconium ileus at birth; min. Temperature, mminimum annual temperature of geographic region of birth (^{0}C); OR, odds ratio; *p*, *P*-value; PE, pulmonary exacerbations requiring hospitalisation during the 1st 5-years of life

ASPERGILLUS AND LUNG FUNCTION AT AGE 5-YEARS AND SUBSEQUENT LUNG FUNCTION PROGRESSION

Explanatory variables tested in longitudinal analysis

Other explanatory variables tested, besides *Aspergillus,* included the categorical variables such as sex, meconium ileus at birth, and *Pseudomonas aeruginosa* BAL cultures $\geq 10^3$ colony-forming units (cfu)/mL during the first 5-years of life. In addition, *P. aeruginosa* grown in sputum (any growth) or BAL ($\geq 10^3$ cfu/mL) between the current and the last forced expiratory volume in 1-second percent (FEV_1%) predicted measurement and hospitalisation secondary to pulmonary exacerbation at the time of FEV_1% predicted measurement were also included. Time-varying continuous covariates included body-mass index (BMI) z-score at the time of the FEV_1% predicted measurement, interval between two FEV_1% predicted measurements, *Aspergillus* and *P. aeruginosa* positive BAL or sputum cultures between the current and the last FEV_1% predicted measurement, hospitalisation secondary to pulmonary exacerbation at the time of FEV_1% predicted measurement, and duration (days) of hospitalisation secondary to pulmonary exacerbation between the current and the last FEV_1% predicted measurement. As in the cross-sectional analysis, data using the subject's genotype were not tested in this analysis as all participants in the ACFBAL study met the criteria of classical CF. Similarly, data on pancreatic status were not tested as most of the children in ACFBAL study were already pancreatic insufficient. Finally, as expected there was no ACFBAL study arm effect, since assignment was by randomisation.

The relationship between *P. aeruginosa* and CF lung function changes with age was tested by examining the association of (i) recurrent *P. aeruginosa* positive BAL cultures ($\geq 10^3$ cfu/mL) in the first 5-years of life and FEV_1% predicted at age 5-years; and (ii) *P. aeruginosa* positive sputum or BAL cultures any time between 5-14 years of age and the current and previous FEV_1%

predicted measurements and changes of FEV_1% predicted with age. A subsequent new positive culture of *P. aeruginosa* was defined as recurrent if the previous respiratory culture had not grown this organism.

Longitudinal analysis

Software

The nonlinear mixed-effect disease modelling was conducted using NONMEM® v7.4[2], Intel FORTRAN compiler and PsN® 4.1.0.[3] Model diagnostics were performed using Xpose (v4.4.0, http://xpose.sourceforge.net)[4] in R[5].

Model building

A linear and a nonlinear structural model were initially selected to describe the population average progression of FEV_1% predicted over age. The linear model assumed a constant rate of FEV_1% predicted decline over age from an initial estimated baseline. The nonlinear model assumed a nonlinear decline, with $\Delta max_{FEV_1\%}$ fixed to literature values as no data were observed to support its estimation.[6] The typical population parameter for $\Delta max_{FEV_1\%}$ was fixed to a population average decrease of 40% in FEV_1 %predicted over a lifetime and was allowed to vary between individuals.

To describe individual lung function progressions, an exponential (Equation E2) stochastic model was used to describe between-subject variability (BSV) for the parameter $t_{50\%max}$. A proportional stochastic model was used to describe the BSV (Equations E3) for parameters α, $\Delta\max_{FEV_1}\%$ and γ. Utilising a proportional model for α and γ allowed the direction of the FEV_1% predicted progression to change in both positive and negative directions and therefore facilitated both, an improvement and decline of FEV_1% predicted over a subject's lifetime

respectively. The use of a proportional model for $\Delta\max_{\mathrm{FEV}_1}\%$ allowed negative and positive changes of the parameter value over a subject's lifetime, as some showed an improved lung function status compared to their baseline lung function status at some stage during the observation period. Both proportional and exponential models were tested to describe BSV for $\mathrm{FEV}_1\%_{\mathrm{baseline}}$.

$$P_i = P_{TV} \times e^{\eta_{i,P}} \quad \text{Equation E2}$$

$$P_i = P_{TV} \times \left(1 + \left(\eta_{i,P}\right)\right) \quad \text{Equation E3}$$

Here, P_i represents the estimate of a parameter P for the i^{th} subject, given a typical population parameter value (P_{TV}) and $\eta_{i,\mathrm{P}}$, which is a random variable distributed with a mean value of 0 and variance of ω^2_{P}, which represents the BSV around P in the population. Given Equation E2, P_i will be log-normal distributed around P_{TV} and given Equation E3, P_i will be normally distributed around P_{TV}. The covariance between different parameters was examined using a full or reduced variance-covariance matrix.

Residual unexplained variability was estimated using an additive, proportional and combined error models according to Equations (E4) to (E6), respectively,

$$FEV_1\%_{obs} = FEV_1\%_{pred} + \varepsilon_{add} \quad \text{Equation E4}$$

$$FEV_1\%_{obs} = FEV_1\%_{pred} \times \left(1 + \varepsilon_{prop}\right) \quad \text{Equation E5}$$

$$FEV_1\%_{obs} = FEV_1\%_{pred} \times \left(1 + \varepsilon_{prop}\right) + \varepsilon_{add} \quad \text{Equation E6}$$

where $FEV_1\%_{obs}$ represent the observed $\mathrm{FEV}_1\%$ predicted value and $FEV_1\%_{pred}$ are the individual predicted values of $\mathrm{FEV}_1\%$ predicted. ε_{add} and ε_{prop} are the additive and the proportional error terms on $\mathrm{FEV}_1\%$predicted values with a mean value of 0 and variance of Σ^2.

Available patient characteristics and clinical information were screened initially for potential significant explanatory variables-parameter relationships via graphical inspection. Continuous explanatory factors were centred to their median values in the data set and were included in the model using linear, exponential and power functions, when appropriate. Categorical and continuous explanatory variables were included in a multiplicative manner on the parameter.[7]

Results

Structural models

The nonlinear base model (4 degrees of freedom) resulted in a lower objective function value (OFV) value by 20.5 points compared to the base linear model (2 degrees of freedom), which indicates a significantly better fit of the model to the data. Residual errors for linear and nonlinear models were best described by an additive model. Parameter estimates for nonlinear progression models of FEV_1% predicted over age are presented in Table E3.

Explanatory factors

Of the explanatory factors added to the nonlinear model, BMI z-score was associated with $FEV_1\%_{baseline}$ (F_{BMI_B}, ΔOFV = -47.6). With every 1-standard deviation increase in BMI away from the mean BMI z-score of zero, $FEV_1\%_{baseline}$ increased by 3.82% and vice versa. Being hospitalised secondary to pulmonary exacerbation at the time of a FEV_1% predicted measurement reduced $\Delta max_{FEV_1\%}$ from 40% to 31.2% ($F_{HPE\_\Delta max_{FEV_1\%}}$, ΔOFV = -54.5) and reduced $t_{50\%max}$ from 8.38 to 6.41-years ($F_{HPE\_t_{50\%max}}$, ΔOFV = -16). The estimated value for $\Delta max_{FEV_1\%}$ was the same before and after hospitalisation secondary to a pulmonary exacerbation. Hospitalisation was associated with a faster onset of lung function loss ($\theta_{\text{HPE on }\Delta\text{max}_{FEV_1\%}}$, $\theta_{\text{HPE on }t_{50\%max}}$), which may be explained by the correlation between the two parameters, $\Delta max_{FEV_1\%}$ and $t_{50\%max}$. Of the HRCT scan components at age 5-years, air

trapping was found to be significantly associated with lung function progression (see main manuscript). The changes in OFV values for each of the variables included during the model building are shown in Table E4.

Table E3: Parameter estimates of the base and final nonlinear lung function progression model, including bootstrap median and 95% confidence intervals (CI).

Parameter	**Units**	**Base model [bootstrap median; 95% CI]**	**Final model [bootstrap median; 95% CI]**
OFV		15106.3	14949.2
$FEV_1\%_{\text{baseline}}$	% predicted	91.3 [91.2; 86.7, 94.6]	99.7 [98.8; 94.28, 105.91]
Maximal change in lung function ($\Delta max_{FEV_1\%}$) (fixed)	% predicted	40	40
Age at which 50% of the maximal change in lung function occurs ($t_{50\%max}$)	years	15.3 [15.8; 13.5, 21.8]	8.38 [8.19; 7.19, 9.35]
Hill coefficient (γ)	-	2.4 [2.5; 0.9, 4.0]	3.08 [3.09; 2.15, 4.16]
$\theta_{\text{BMI on baseline}}$	-	-	0.038 [0.039; 0.028, 0.051]
$\theta_{\text{air trapping on baseline}}$	-	-	-0.04 [-0.031; -0.089, -0,011]
$\theta_{\text{HPE on }\Delta max_{FEV_1\%}}$	-	-	-0.22 [-0.214; -0.443, -0.064]
$\theta_{\text{HPE on }t_{50\%max}}$	-	-	-0.24 [-0.26; -0.33, -0.09]
BSV $FEV_1\%_{\text{baseline}}$	%	14.3 [14.3;9.6, 17.6]	13.3 [12.9; 9.64, 16.2]
BSV $\Delta max_{FEV_1\%}$	%	104.8 [109.6;17.5,151.1]	63.64 [61.8; 2.05, 98.3]
BSV$t_{50\%max}$	%	28.3 [31.8; 10.5,60.7]	30 [30.7; 14.5, 53.2]
Covariance between $\Delta max_{FEV_1\%}$ and $t_{50\%max}$	-	0.08 [0.23; -0.29, 0.27]	0.15 [0.15; -0.09, 0.48]
BSV $_{\text{Hill coefficient}}$	%	55.0 [48.8; 13.1, 60.9]	52.5 [51.4; 37.03, 67.93]
Additive residual error	$FEV_1\%$	9.6 [9.5; 8.5, 10.3]	9.32 [9.27; 8.64, 9.96]

BMI, Body mass index z-score; BSV, between-subject variability; HPE, hospitalisation because of a pulmonary exacerbation; OFV, objective function value;

PE, pulmonary exacerbation; t, age in years; FEV1% baseline, baseline FEV1% predicted at 5-years [%]; $\Delta\max_{FEV_1\%}$, the typical maximum change in lung function over the subject's lifetime from 5-years until end of life [%]; $t_{50\%max}$, age at which half of the maximal change in lung function occurs [years];

γ, Hill coefficient, which determines the steepness of FEV1% predicted changes over age; $\theta_{\text{present of Air trapping at baseline}}$, the fractional change in $FEV_1\%_{baseline}$ for a patient with an air trapping score of greater than zero; $\theta_{\text{BMI on baseline}}$, the fractional change in $FEV_1\%_{baseline}$ per BMI z-score unit different from 0;

$\theta_{\text{HPE on }\Delta\max_{FEV_1\%}}$, the fractional change in $\Delta\max_{FEV_1\%}$ when a patient is hospitalised secondary to pulmonary exacerbation; $\theta_{\text{HPE on }t_{50\%max}}$, fractional change in $t_{50\%\max}$ when a patient is hospitalised because of a pulmonary exacerbation; TV, Typical population value for a given parameter

Abbreviations for the final nonlinear model:

Nonlinear lung function progression base model according to the method section (see Equation 1):

$$FEV_1\%(t) = \text{FEV1\% baseline} - \left[\frac{\Delta\max_{FEV_1\%} \times t^{\gamma}}{t_{50\%max}{}^{\gamma} + t^{(\gamma)}}\right]$$

Structural parameters after inclusion of the influencing factors (final model parameters shown in Table E3):

- FEV1% baseline = *TV*_FEV1% baseline * (1+ $\theta_{\text{presence of air trapping on baseline}}$)*(1+ $\theta_{\text{BMI on baseline}}$*(BMI-0))

  FEV1% baseline = 99.7* (1+(-0.042)) *(1+0.038*(BMI z score-0)));

- $\Delta\max_{FEV_1\%}$ = *TV_*E_{MAX}* (1+ $\theta_{\text{HPE on }\Delta\max_{FEV_1\%}}$)

  $\Delta\max_{FEV_1\%}$ = 40* (1 + (-0.22));

- $t_{50\%max}$ = *TV_*E_{MAX}* (1+$\theta_{\text{HPE on }t_{50\%max}}$)

  $t_{50\%max}$ = *8.38** (1+(−0.24));

- γ = *TV_* γ

  γ = *3.08*;

Model evaluation

Figure E3 provides a visualisation of the data available for the lung function progression study, model evaluation and diagnostic comparison. Goodness-of fit plots shown in Figure E4 reveal the conditional weighted residuals are evenly distributed around zero, indicating a good model fit.

Table E4: Steps involved in building the nonlinear model of lung function progression

Model No	Influential Factor tested	Parameter-Factor relationship	ΔOFV	p-value	Model Comparison
Univariate inclusion of tested factors					
1. Base model	$FEV_1\%(t) = FEV_1\%_{baseline} + \frac{\Delta\max_{\mathrm{FEV}_1}\% \times t^{\gamma}}{t_{50\%max}{}^{\gamma} + t^{\gamma}}$		15106.3	-	
2.	$\theta_{\text{BMI on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$	-47.6	< 0.001	1
3.	$\theta_{\text{sex on baseline}}$	$TV\_FEV_1\%_{baseline} * (1 + \theta_{\text{sex on baseline}})$	-0.49	NS	1
4.	$\theta_{\text{MI on baseline}}$	$TV\_FEV_1\%_{baseline} * (1 + \theta_{\text{MI on baseline}})$	-0.29	NS	1
5.	$\theta_{Aspergillus\ 0-5\ \text{on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + \theta_{Aspergillus\ 0-5\ \text{on baseline}}\right)$	-0.05	NS	1
6.	$\theta_{Pseudomonas\ 0-5\ \text{on baseline}}$	$TV\_FEV_1\%_{baseline} * (1 + \theta_{Pseudomonas\ 0-5\ \text{on baseline}})$	-3.22	NS	1
7.	$\theta_{\text{air trapping on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + \theta_{\text{air trapping on baseline}}\right)$	-12.01	< 0.001	1
8.	$\theta_{\text{bronchiectasis on baseline}}$	$TV\_FEV_1\%_{baseline} * (1 + \theta_{\text{bronchiectasis on baseline}})$	-2.01	NS	1
9.	$\theta_{\text{airway wall thickening on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + \theta_{\text{airway wall thickening on baseline}}\right)$	-0.11	NS	1
10.	$\theta_{\text{parenchymal disease on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + \theta_{\text{parenchymal disease on baseline}}\right)$	-3.01	NS	1
11.	$\theta_{\text{mucuos plugging on baseline}}$	$TV\_FEV_1\%_{baseline} * \left(1 + \theta_{\text{mucuos plugging on baseline}}\right)$	-3.12	NS	1
12.	$\theta_{\text{BMI on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \left(\theta_{\text{BMI on }\Delta\max_{\mathrm{FEV}_1}\%} * [\text{BMI} - 0]\right)\right)$	-3.54	NS	1
13.	$\theta_{\text{sex on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{sex on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-1.20	NS	1
14.	$\theta_{\text{MI on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{MI on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-0.30	NS	1
15.	$\theta_{\text{HPE on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{HPE on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-38.5	< 0.001	1
16.	$\theta_{Aspergillus\ 5-14\ \text{on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{Aspergillus\ 5-14\ \text{on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-2.99	NS	1
17.	$\theta_{Pseudomonas\ 5-14\ \text{on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{Pseudomonas\ 5-14\ \text{on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-3.32	NS	1
18.	$\theta_{\text{air trapping on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{air trapping on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-3.26	NS	1
19.	$\theta_{\text{bronchiectasis on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{bronchiectasis on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-2.60	NS	1
20.	$\theta_{\text{airway wall on }\Delta\max_{\mathrm{FEV}_1}\%}$	$TV\_\Delta\max_{\mathrm{FEV}_1}\% * \left(1 + \theta_{\text{airway wall on }\Delta\max_{\mathrm{FEV}_1}\%}\right)$	-3.02	NS	1

21.	$\theta_{\text{parenchymal disease on } \Delta\max_{FEV_1}\%}$	$TV\_\Delta\max_{FEV_1}\% * \left(1 + \theta_{\text{parenchymal disease on } \Delta\max_{FEV_1}\%}\right)$	-3.01	NS	1
22.	$\theta_{\text{mucuos plugging on } \Delta\max_{FEV_1}\%}$	$TV\_\Delta\max_{FEV_1}\% * \left(1 + \theta_{\text{mucuos plugging on } \Delta\max_{FEV_1}\%}\right)$	-3.10	NS	1
23.	$\theta_{\text{BMI on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \left(\theta_{\text{BMI on } t_{50\%max}} * [\text{BMI} - 0]\right)\right)$	-2.31	NS	1
24.	$\theta_{\text{sex on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{sex on } t_{50\%max}}\right)$	-3.54	NS	1
25.	$\theta_{\text{MI on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{MI on } t_{50\%max}}\right)$	-2.04	NS	1
26.	$\theta_{\text{HPE on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{HPE on } t_{50\%max}}\right)$	-10.35	< 0.001	1
27.	$\theta_{Aspergillus\ 5-14 \text{ on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{Aspergillus\ 5-14 \text{ on } t_{50\%max}}\right)$	-0.49	NS	1
28.	$\theta_{Pseudomonas\ 5-14 \text{ on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{Pseudomonas\ 5-14 \text{ on } t_{50\%max}}\right)$	-0.37	NS	1
29.	$\theta_{\text{air trapping on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{air trapping on } t_{50\%max}}\right)$	-3.45	NS	1
30.	$\theta_{\text{bronchiectasis on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{bronchiectasis score on } t_{50\%max}}\right)$	-3.01	NS	1
31.	$\theta_{\text{airway wall on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{airway wall on } t_{50\%max}}\right)$	-3.30	NS	1
32.	$\theta_{\text{parenchymal disease on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{parenchymal disease on } t_{50\%max}}\right)$	-3.02	NS	1
33.	$\theta_{\text{mucuos plugging on } t_{50\%max}}$	$TV\_t_{50\%max} * \left(1 + \theta_{\text{mucuos plugging on } t_{50\%max}}\right)$	-3.01	NS	1
34.	$\theta_{\text{BMI on } \gamma}$	$TV\_\gamma * \left(1 + \left(\theta_{\text{BMI on } \gamma} * [\text{BMI} - 0]\right)\right)$	-0.078	NS	1
35.	$\theta_{\text{sex on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{sex on } \gamma}\right)$	-3.20	NS	1
36.	$\theta_{\text{MI on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{MI on } \gamma}\right)$	-2.14	NS	1
37.	$\theta_{\text{HPE on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{HPE on } \gamma}\right)$	-3.74	NS	1
38.	$\theta_{Aspergillus\ 5-14 \text{ on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{Aspergillus\ 5-14 \text{ on } \gamma}\right)$	-0.46	NS	1
39.	$\theta_{Pseudomonas\ 5-14 \text{ on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{Pseudomonas\ 5-14 \text{ on } \gamma}\right)$	-2.28	NS	1
40.	$\theta_{\text{air trapping on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{air trapping on } \gamma}\right)$	-3.44	NS	1
41.	$\theta_{\text{bronchiectasis on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{bronchiectasis on } \gamma}\right)$	-3.20	NS	1
42.	$\theta_{\text{airway wall on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{airway wall on } \gamma}\right)$	-3.25	NS	1
43.	$\theta_{\text{parenchymal disease on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{parenchymal disease on } \gamma}\right)$	-3.52	NS	1
44.	$\theta_{\text{mucuos plugging on } \gamma}$	$TV\_\gamma * \left(1 + \theta_{\text{mucuos plugging on } \gamma}\right)$	-3.22	NS	1

Inclusion of significant factors					
45.	$\theta_{\text{BMI on baseline}} + \theta_{\text{HPE on } \Delta\max_{FEV_1\%}}$	FEV1% baseline = $TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $\Delta\max_{FEV_1\%} = TV\_\Delta\max_{FEV_1\%} * \left(1 + \theta_{\text{HPE on } \Delta\max_{FEV_1\%}}\right)$	-54.5	<0.001	2
46.	$\theta_{\text{BMI on baseline}} + \theta_{\text{air trapping on baseline}}$	FEV1% baseline = $TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $* \left(1 + \theta_{\text{air trapping on baseline}}\right)$	-8.20	< 0.05	2
47.	$\theta_{\text{BMI on baseline}} + \theta_{\text{HPE on } t_{50\%max}}$	FEV1% baseline = $TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $t_{50\%max} = TV\_t_{50\%max} * \left(1 + \theta_{\text{HPE on } t_{50\%max}}\right)$	-28.6	< 0.001	2
48.	Model 45 + $\theta_{\text{HPE on } t_{50\%max}}$	FEV1% baseline = $TV_{FEV_1\%_{baseline}} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $\Delta\max_{FEV_1\%} = TV_{\Delta\max_{FEV_1\%}} * \left(1 + \theta_{\text{HPE on } \Delta\max_{FEV_1\%}}\right)$ $t_{50\%max} = TV\_t_{50\%max} * \left(1 + \theta_{\text{HPE on } t_{50\%max}}\right)$	-14.5	<0.001	45
49.	Model 45 + $\theta_{\text{air trapping on baseline}}$	FEV1% baseline = $TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $* \left(1 + \theta_{\text{air trapping on baseline}}\right)$ $\Delta\max_{FEV_1\%} = TV_{\Delta\max_{FEV_1\%}} * \left(1 + \theta_{\text{HPE on } \Delta\max_{FEV_1\%}}\right)$	-39.0	< 0.001	45
50.	Model 49 + $\theta_{\text{HPE on } t_{50\%max}}$	**Final model** FEV1% baseline = $TV\_FEV_1\%_{baseline} * \left(1 + (\theta_{\text{BMI on baseline}} * [\text{BMI} - 0])\right)$ $* \left(1 + \theta_{\text{air trapping on baseline}}\right)$ $\Delta\max_{FEV_1\%} = TV_{\Delta\max_{FEV_1\%}} * \left(1 + \theta_{\text{HPE on } \Delta\max_{FEV_1\%}}\right)$ $t_{50\%max} = TV\_t_{50\%max} * \left(1 + \theta_{\text{HPE on } t_{50\%max}}\right)$	-16.0	< 0.001	49

BMI, Body mass index z-score; HPE, hospitalisation because of a pulmonary exacerbation; MI, meconium ileus; OFV, objective function value; NS: non-significant; TV: typical value; γ, hill coefficient; t, age in years; FEV1% baseline, baseline FEV1% predicted at 5-years [%]; $\Delta\max_{FEV_1\%}$, the typical maximum change in lung function over the subject's lifetime from 5-years until end of life [%]; $t_{50\%max}$, age at which half of the maximal change in lung function occurs [years]; γ, Hill coefficient, which determines the steepness of FEV1% predicted changes over age; $\theta_{\text{BMI on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ per BMI z-score unit different from 0; $\theta_{\text{sex on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ of being male; $\theta_{\text{MI on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ in patient with MI at birth; $\theta_{Aspergillus\ 0-5\ \text{on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ when patient had recurrent positive *Aspergillus* culture in the first five years of life; $\theta_{Pseudomonas\ 0-5\ \text{on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ when patient had recurrent positive *Pseudomonas* culture in the first five years of life; $\theta_{\text{air trapping on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ for a patient with an air trapping score of greater than zero; $\theta_{\text{bronchiectasis on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ for a patient with a bronchiectasis score of greater than zero; $\theta_{\text{presence of airway wall thickening score on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ for a patient with an airway wall thickening score of greater than zero; $\theta_{\text{parenchymal disease on baseline}}$: the fractional change in

$FEV_1\%_{baseline}$ for a patient with a parenchymal disease score of greater than zero; $\theta_{\text{mucuos plugging on baseline}}$: the fractional change in $FEV_1\%_{baseline}$ for a patient with a mucous plugging score of greater than zero; $\theta_{\text{BMI on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ per BMI z-score unit different from 0; $\theta_{\text{sex on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ of being male; $\theta_{\text{MI on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ in patient with MI at birth; $\theta_{\text{HPE on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ when a patient is hospitalised secondary to pulmonary exacerbation; $\theta_{Aspergillus\ 5-14\text{ on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ when patients had a positive *Aspergillus* culture between the current and the last $FEV_1\%$ predicted measurement at any time from 5-14 years of age; $\theta_{Pseudomonas\ 5-14\text{ on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ when patients had a positive *Pseudomonas* culture between the current and the last $FEV_1\%$ predicted measurement at any time from 5-14 years of age; $\theta_{\text{air trapping on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ for a patient with an air trapping score of greater than zero; $\theta_{\text{bronchiectasis on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ for a patient with a bronchiectasis score of greater than zero; $\theta_{\text{airway wall thickening on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ for a patient with a airway wall thickening score of greater than zero; $\theta_{\text{parenchymal disease on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ for a patient with a parenchymal disease score of greater than zero; $\theta_{\text{mucuos plugging on }\Delta\max_{FEV_1\%}}$: the fractional change in $\Delta\max_{FEV_1\%}$ for a patient with a mucous plugging score of greater than zero; $\theta_{\text{BMI on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ per BMI z-score unit different from 0; $\theta_{\text{sex on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ of being male; $\theta_{\text{MI on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ in patient with MI at birth; $\theta_{\text{HPE on }t_{50\%max}}$: the fractional change in $t_{50\%max}$ when a patient was hospitalised secondary to pulmonary exacerbation; $\theta_{Aspergillus\ 5-14\text{ on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ when patient had a positive *Aspergillus* culture between the current and the last $FEV_1\%$ predicted measurement at any time from 5-14 years of age; $\theta_{\text{air trapping on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ for a patient with an air trapping score of greater than zero; $\theta_{\text{bronchiectasis on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ for a patient with a bronchiectasis of greater than zero; $\theta_{\text{airway wall thickening on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ for a patient with an airway wall thickening of greater than zero; $\theta_{\text{parenchymal on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ for a patient with a parenchymal disease score of greater than zero; $\theta_{\text{mucuos plugging score on }t_{50\%max}}$: the fractional change in $t_{50\%\max}$ for a patient with a mucous plugging score of greater than zero; $\theta_{\text{BMI on }\gamma}$: the fractional change in hill coefficient per BMI z-score unit different from 0; $\theta_{\text{sex on }\gamma}$: the fractional change in hill coefficient of being male; $\theta_{\text{MI on }\gamma}$: the fractional change in hill coefficient in patient with MI at birth; $\theta_{\text{HPE on }\gamma}$: the fractional change in hill coefficient when a patient is hospitalised secondary to pulmonary exacerbation; $\theta_{Aspergillus\ 5-14\text{ on }\gamma}$: the fractional change in Hill coefficient when patient positive *Aspergillus* culture between the current and the last $FEV_1\%$ predicted measurement at any time from 5-14 years of age; $\theta_{Pseudomonas\ 5-14\text{ on }\gamma}$: the fractional change in hill coefficient when patients had positive *Pseudomonas* culture between the current and the last $FEV_1\%$ predicted measurement at any time from 5-14 years of age; $\theta_{\text{air trapping on }\gamma}$: the fractional change in hill coefficient for a patient with an air trapping score of greater than zero; $\theta_{\text{bronchiectasis on }\gamma}$: the fractional change in hill coefficient for a patient with a bronchiectasis score of greater than zero; $\theta_{\text{airway wall thickening on }\gamma}$: the fractional change in hill coefficient for a patient with a airway wall thickening score of greater than zero; $\theta_{\text{parenchymal disease on }\gamma}$: the fractional change in hill coefficient for a patient with a parenchymal disease score of greater than zero; $\theta_{\text{mucuos plugging on }\gamma}$: the fractional change in hill coefficient for a patient with a mucous plugging disease score of greater than zero;

NMTRAN model codes

NMTRAN code for the final nonlinear model including the final model estimates

```
$PROBLEM Disease Progression nonlinear final model
$INPUT   ID DAT1=DROP TIME DV MDV EVID FLAG HOSPRA BMI ATS5C
$DATA   101.CSV IGNORE=#
; Comments:
; ID = Patient's ID
; DAT1 = date of FEV1 observation
; TIME = time of observation
; DV = FEV1pp observation using GLI Equation
; HOSPRA= hospitalisation at the time of FEV1% predicted measurement; 0=no, 1=yes
; BMI = body-mass index
; AT = present of air trapping at age 5

; ------------------------------------------------------------------------------------------------------
$ABBREVIATED DERIV2=NOCOMMON
$PRED

; ------------- EXPLANATORY FACTORS ON BASELINE-----------------------------------------
BASEBMI=1+ (THETA (6)*(BMI-0))

; ----------------------- EXPLANATORY FACTORS ON Δmax_FEV1% ------------------------------
IF (HOSPRA.EQ.0) EMAXHOSPRA= 1
IF (HOSPRA.EQ.1) EMAXHOSPRA = (1+THETA (7))
EMAXCOV=EMAXHOSPRA

; ----------------------- EXPLANATORY FACTORS ON t_50%max ---------------------------------
IF (HOSPRA.EQ.0) EC50HOSPRA=1
IF (HOSPRA.EQ.1) EC50HOSPRA=1+THETA (8)
EC50COV=EC50HOSPRA

IF (ATS5C.EQ.0) BASEAT=1
IF (ATS5C.EQ.1) BASEAT= (1+THETA (9))        ; presence of air trapping

BASECOV=BASEAT*BASEBMI
TIME1= ((TIME/24)/365)                       ; change time from hour to years
TVBASE=THETA (1)                             ; population baseline FEV1%predicted
TVBASE= TVBASE*BASECOV                       ; individual baseline FEV1%pred
BASE=TVBASE*(1+ETA(2))                       ; individual baseline FEV1%pred

TVEMAX=THETA (2)                             ; population Δmax_FEV1%
TVEMAX=EMAXCOV*TVEMAX                        ; added Δmax_FEV1%factors
EMAX=TVEMAX*(1+ (ETA (3)))                   ; individual Δmax_FEV1%

TVEC50=THETA (3)                             ; population t_50%max
EC50=TVEC50*EC50HOSPRA*(EXP(ETA(4)))         ; added t_50%maxfactors
```

```
TVHILL=THETA (4)                    ; population hill coefficient
HILL=TVHILL*(1+ (ETA(1))            ; individual hill coefficient

DP=BASE-((EMAX*(TIME1**HILL))/((EC50**HILL)+(TIME1**HILL)))   ;   nonlinear progression model

; ------------------ RESIDUAL ERROR ----------------------------------------------------------------
IPRED=DP
IRES=DV-IPRED
W=THETA (5)
IWRES=IRES/W
Y=IPRED+W*EPS (1)

; ------------------ ESTIMATES----------------------------------------------------------------

$THETA (0, 99.7)        ; population baseline FEV1% predicted
$THETA 40 FIX           ; population Δmax_FEV1%
$THETA 8.38             ; population t_50%max
$THETA 3.08             ; population hill coefficient
$THETA 9.32             ; residual error
$THETA 0.0382           ; BMI Z-score on baseline FEV1% predicted
$THETA -0.22            ; hospitalisation secondary to pulmonary exacerbation on Δmax_FEV1%
$THETA -0.235           ; hospitalisation secondary to pulmonary exacerbation on t_50%max
$THETA -0.0417          ; present of Air trapping on baseline FEV1% predicted

$OMEGA 0.272            ; between subject variability for hill coefficient
$OMEGA 0.0172           ; between subject variability for baseline FEV1%predicted
$OMEGA BLOCK (2)        ; correlation between Δmax_FEV1% and t_50%max
0.405                   ; between subject variability for Δmax_FEV1%
0.15 0.09               ; between subject variability for t_50%max
```

FIGURE LEGENDS

Figure E1 Occurrence of initial and recurrent *Aspergillus* positive bronchoalveolar lavage (BAL) cultures according to subject's age for those in the BAL arm of the Australasian Cystic Fibrosis Bronchoalveolar Lavage study. Subjects were sorted according to identification (ID) numbers in the study and age at recurrent positive *Aspergillus* cultures.

Figure E2 Frequency of total chest high-resolution computed tomography scan scores for children with positive (red) and negative (black) *Aspergillus* bronchoalveolar lavage cultures at age 5-years.

Figure E3 Prediction and variability corrected visual predictive check of the nonlinear model for lung function progression. Observed data are represented as grey triangles. Top, middle and bottom black lines represent 95^{th}, 50^{th} and 5^{th} percentiles of the observations. Top, middle and bottom red dashed lines represent 95^{th}, 50^{th} and 5^{th} percentiles of the simulated data with the red shaded areas presenting the 90% confidence intervals.

Figure E4 Goodness-of-fit for the final nonlinear model, observed forced expiratory volume in 1-second percent (FEV_1%) predicted versus population-predicted FEV_1% predicted, observed FEV_1% predicted versus individual-predicted FEV_1% predicted, Conditional weighted residuals versus age (years). The red solid lines are smooths through the data.

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