187

IMPROVEMENT IN CF OUTCOMES SINCE NEWBORN SCREENING IMPLEMENTATION IN THE UNITED STATES

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Background: Newborn screening (NBS) for CF was implemented in all US states by 2010. Quality improvement efforts supported by the Cystic Fibrosis Foundation (CFF) and other stakeholders have aimed to improve processes. We hypothesized that outcomes have improved over time as a result of these efforts.

Methods: We included participants in the CFF Patient Registry born 2010-2018 and diagnosed between at age 0-365 days of age. We assessed timeliness of evaluation (age at first event, AFE), age of center-reported diagnosis and key outcomes in 2010-2012 (cohort 1, C1), 2013-2015 (C2) and 2016-2018 (C3).

Results: Among 6354 infants, there were 2299 in C1, 2172 in C2 and 1883 in C3. Reported age at diagnosis was earlier than AFE. Across time periods, AFE decreased. Weight-for-age (WFA) and height-for-age (HFA) Z-scores at age 1 were close to 0 and not different between the cohorts. HFA Z-score at age 5 was better in C2 than C1. *Pseudomonas aeruginosa* (PA) infection rates decreased over time. Results are summarized in the Table.

Conclusion: Over the first 9 years of universal NBS in the US, median AFE and PA infection rates decreased and HFA at age 5 increased. While causality cannot be inferred, these data suggest that earlier AFE may be associated with improved CF outcomes.

Patient Characteristics	C1 2010-2012	C2 2013-2015	C3 2016-2018	P-value (test)
Age at diagnosis, median days (range)	15 (0-3149)	14 (0-1630)	14 (0-945)	0.439 (Kruskal-Wallis)
Age at first event, median days (range)	40 (0-365)	38 (0-365)	33 (0-33)	<0.001 (Kruskal-Wallis)
Age 1 WHO WFA Z-score, mean (SD)	0.05 (0.95)	0.08 (0.96)	0.015 (0.98)	0.15 (ANOVA)
Age 1 WHO HFA Z-score, mean (SD)	-0.59 (1.1)	-0.58 (1.1)	-0.66 (1.1)	0.10 (ANOVA)
Age 5 CDC WFA Z-score, mean (SD)	-0.04 (0.94)	-0.04 (1.0)	NA	0.06 (ANOVA)
Age 5 CDC HFA Z-score, mean (SD)	-0.19 (1.0)	-0.06 (0.99)	NA	0.003 (ANOVA)
PA, age 0-1 (%)	25	23	18	<0.001 (Chi-square)
PA, age 1-2 (%)	37	37	21	<0.001 (Chi-square)
PA, age 3-6 (%)	37	23	NA	<0.001 (Chi-square)

188▲

CRMS/CFSPID CHILDREN AT RISK TO RECLASSIFY TO CF

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Background: Extensive genotyping as part of newborn screening has led to an increasing number of children carrying *CFTR* mutations/variants of unknown significance. These children are asymptomatic in early life, a condition known as CFTR-related metabolic syndrome (CRMS/CFSPID). Predictors identifying CRMS/CFSPID children at risk of expressing CF symptoms have not been characterized. Our goal is to identify phenotype patterns seen in CRMS/CFSPID and genotypes that are associated with risk of CF diagnosis reclassification.

Methods: We recruited CRMS/CFSPID and CF children from two large CF centers in Southern California to collect genotype/phenotype information longitudinally. Measurements included: sweat chloride test, standard pulmonary function test, and lung clearance index (LCI). A selected group of subjects also had human nasal epithelial (HNE) cells collected and shipped to Cincinnati Children's Hospital. HNE cells were grown in air-liquid interface and ion transport (I_{sc}) measured at baseline in Ussing chambers.

Results: 1. LCI: a total of 33 subjects (age 4 to 10 years old) completed LCI testing (CRMS/CFSPID n= 20, CF n = 13); An existing group of healthy controls (n=26, 3 to 19 years old) was used to establish the upper limit of normal at 8.02. Although mean LCI values were different across groups (p=0.0002), 35% of CRMS/CFSPID and 38% of CF had abnormal LCI values. 2. Genotypes seen in CF reclassification: Sixty-four subjects completed research visits: CRMS/CFSPID n=44 and CF=20, of which 6 were reclassified prior to enrollment. Reclassification criteria included sweat chloride ≥ 60 mmol/L and/or signs and symptoms such as persistent cough, and/or colonization with *Pseudomonas aeruginosa*. Most common mutations seen in reclassified subjects were: R117H/7T, D1152H, and 5T-13TG. 3. HNE assay: All 11 nasal brush samples collected had viable cells upon overnight shipping across the country; 5 (45%) required re-sampling due to fungal contamination (n=3) or not growing at satisfactory quality to perform the assay (n=2). Results are summarized in the Table.

Conclusion and Future Directions: Ongoing recruitment seeks to evaluate for trends associated with a higher risk of reclassification and, in a subset, whether the addition of HNE assay associates with phenotype. Our goal is to better understand the full spectrum of *CFTR* mutations/variants, which will facilitate prevention and treatment strategies to all people with the disease.

Acknowledgment: Supported by the CF Foundation.

Patient age (gender)	CFTR mutations	Sweat Chloride Tests	CFTR function Baseline (%)*	CRMS/CFSPID to CF reclassification?
9 yo (F)	G542X and 5T-13TG	28 - 42 - 52 - 55- 64	7.5	Y
8 yo (M)	G542X and 5T-12TG	21 - 28 - 32 - 44 - 67	30	Y
4 yo (F)	F508del and 5T-12TG	31 - 22- 17 - 31	27	N
4 yo (M)	F508del and 5T-12TG	28 - 46 - 45 - 49	67	N
1 yo (F)	W1282X and R117H/7T	29 - 29 - 24	34	N
1 yo (M)	F508del and R117H/7T	36 - 41 - 25	67	N
6 yo (M)	3849+10kbC>T and R117H/7T and R668C	14 - 16 - 21 - 40	28	N

*Measured as Isc in planar cultures from brushed HNE cells; results presented as % of healthy control function.

189

PREDICTING CLINICAL TRAJECTORIES IN CF USING AUTOMATED LONGITUDINAL SELECTION OF DEEP LEARNING MODELS

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Introduction: Accurate forecasting of clinical outcomes for individuals with CF could provide the opportunity to deliver truly personalised care. One of the challenges of using machine learning to develop outcome predictors is the fact that the optimal model itself may vary over time at both individual and population level. For example: risk factors for adverse outcomes will change from the beginning to the end of a patient's hospital admission or with the adoption of new CFTR modulator therapy. While such phenomena are common in medicine, they are rarely addressed explicitly by current methods, potentially giving rise to suboptimal prediction performance. We therefore propose a novel Bayesian approach to optimizing model selection in a stepwise fashion which treats the performance at each time step as its own black-box function (Figure) and solves the resulting multiple black-box function optimization problem jointly and efficiently by using deep kernel learning (DKL). We call our novel method Stepwise Model Selection via Deep Kernel Learning (SMS-DKL).

Methods: We took retrospective longitudinal annual metadata from the UK CF Patient Registry between 2008–2015. We use SMS-DKL to optimize the model selection for sequence predictions on the basis of 90 temporal variables, focusing on three important clinical outcomes: 1-year mortality (1YM) and the development of allergic bronchopulmonary aspergillosis (ABPA), and *E. coli* infection.

Results: Our method, SMS-DKL, outperforms the existing model selection methods not only using standard performance metrics but also in terms of speed of finding the optimal model. Our method makes correct predictions on >200 patients more than the benchmark methods. Such a result shows that our method can enhance the predictive power and reliability of machine learning models in real practice.

Conclusions: The benefit of SMS-DKL is that optimal models are automatically selected over time without requiring domain-specific engineering to explicitly model time-varying relationships. We are thus able to provide unprecedented forecasting for individuals with CF by automatically selecting the most appropriate deep learning model at each point in time.

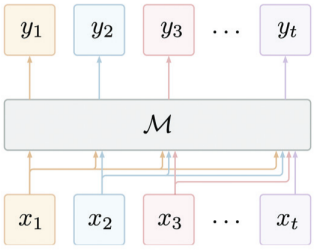

Figure. Diagram of SMS-DKL: M is model, x is input, and y is output.

190▲

DISEASE PROGRESSION IN F508DEL HOMOZYGOUS PERSONS WITH CYSTIC FIBROSIS TREATED WITH LUMACAFTOR/IVACAFTOR: INTERIM RESULTS OF A LONG-TERM SAFETY STUDY USING DATA FROM THE US CF FOUNDATION PATIENT REGISTRY

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Objectives: This ongoing 5-year safety surveillance study evaluates CF disease progression in F508del-homozygous (F/F) persons with CF treated with lumacaftor/ivacaftor (LUM/IVA) in the real-world setting.

Methods: This interim analysis focused on 2,287 F/F persons with CF in the US CF Foundation Patient Registry (CFFPR) treated with LUM/IVA for an average of 2.9 years (range: 1.2 to 4.0 years) by the end of Study Year 3 (2018). Outcomes were compared to a concurrent comparator (COMP) population of 3,527 phenotypically similar persons with CF (genotype F508del/minimal function) with no prior history of CFTR modulator use. Outcomes included percent predicted FEV_1 (ppFEV$_1$), BMI, and pulmonary exacerbations (PEx). Means and percentages were compared between LUM/IVA and COMP cohorts as appropriate; for continuous outcomes, change from pretreatment baseline in 2014 (BL) through 2018 was calculated.

Results: Mean change from BL (95% CI) in ppFEV$_1$ was smaller in the LUM/IVA vs COMP cohort (-3.7 percentage points [pp] [-4.2 to -3.3 pp] vs -6.9 pp [-7.2 to -6.5 pp], respectively). Among those <18 years old, BMI percentile increased by 1.7 pp (95% CI: 0.5 to 2.8 pp) in LUM/IVA but declined by 3.8 pp (95% CI: 2.9 to 4.7 pp decline) in COMP cohort. Among adults, BMI (95% CI) increased more in the LUM/IVA vs COMP cohort (+0.8 kg/m^2 [0.7 to 0.9 kg/m^2] vs +0.2 kg/m^2 [0.1 to 0.3 kg/m^2], respectively). The percentage of LUM/IVA persons with CF with at least one PEx remained stable (≈37%) but increased among the COMP cohort (39.8% in 2014 to 48.3% in 2018). The mean number of PEx/year/person also remained stable among the LUM/IVA cohort (≈0.6) but increased among the COMP cohort (0.7 in 2014 to 1.0 in 2018).

Conclusions: This interim analysis identified no new safety concerns with LUM/IVA and showed that, relative to untreated COMP, LUM/IVA persons with CF had favorable changes over time in lung function, BMI, and PEx. These data support the potential for LUM/IVA to modify CF disease progression with long-term use.

Acknowledgment: Sponsor: Vertex Pharmaceuticals Incorporated. This abstract was previously submitted to the 2020 ECFS annual meeting and has been published in J Cyst Fibros.

191

AI-BASED HYPOTHESIS TESTING IN INDIVIDUALS WITH CF

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Introduction: The rate of progression of lung function decline and response to treatments are heterogenous across CF individuals. Robust methods that could identify subgroups with differing lung function trajectories or responses to treatments would deliver enormous insights into the pathophysiology of CF and provide opportunities for personalised therapy. While standard hypothesis testing can be used to define such significant differences, most tests are restricted to static data and cannot test difference between trajectories themselves. We have therefore developed an AI-based hypothesis test designed to compare irregularly sampled time series to solve this problem.

Methods: Our test is designed to encode the uncertainty between observations by interpreting the lung function trajectory of each patient as a probability distribution and makes comparisons between these probability distributions to provably recover significant differences in the lung function of different groups (illustrated in the Figure). We then took retrospective longitudinal data from the UK Cystic Fibrosis Registry to systematically test for differences in lung function decline. The Registry contains regular measurements of lung function as well as clinical metadata for nearly all CF individuals in the UK. Our analysis partitioned the population into subgroups defined by these variables and compared their respective lung progression.

Results: We demonstrate gains in power (ie, the proportion of correctly rejected differences in two synthetically generated populations) of up to 50% compared to tests that do not capture the uncertainty between observations, but rather consider each trajectory as a fixed vector of observations. We use synthetic data to quantitatively evaluate our test because the ground truth aetiology of CF is most often unknown. Using real CF data, our method identifies several important subgroups (some already recognised) and detects significant differences in disease progression between these newly defined groupings.

Conclusions: Our new method provides a principled comparison method to systematically analyse patient progression and enlighten our understanding of the variable effect of new drugs such as ivacaftor, on future lung progression.

Acknowedgment: Work supported by the UK CF Trust.

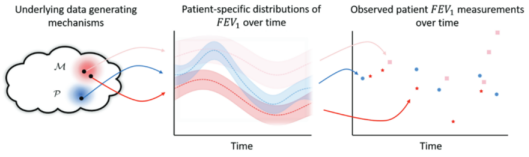

Figure 1. Illustration of hypothesis testing with lung function trajectories of CF patients. On the right-most panel we show the actual observed measurement of lung function for three patients. Because of the uncertainty between observations and potential measurement errors, we interpret each trajectory as a distribution of potential FEV1 measurements over time, as shown in the middle panel. The problem then becomes comparing sets of distributions rather than individual measurements. For example, one may compare two groups of patients, groups M and P in the left-most panel, to determine whether there are significant differences in patient trajectory.