Improving Detection of Rapid Cystic Fibrosis Disease Progression—Early Translation of a Predictive Algorithm into a Point-of-Care Tool

Rhonda D. Szczesniak1,2*, Cole Brokamp1, Weiji Su1, Gary L. McPhail2, John Pestian3, and John P. Clancy2

ABSTRACT The clinical course of cystic fibrosis lung disease is marked by acute drops of lung function, defined clinically as rapid decline. As such, lung function is monitored routinely through pulmonary function testing, producing hundreds of measurements over the lifespan of an individual patient. Point-of-care technologies aimed at improving detection of rapid decline have been limited. Our aim in this early translational study is to develop and translate a predictive algorithm into a prototype prognostic tool for improved detection of rapid decline. The predictive algorithm was developed, validated and checked for 6-month, 1-year and 2-year forecast accuracies using data on demographic and clinical characteristics from 30,879 patients aged 6 years and older who were followed in the US Cystic Fibrosis Foundation Patient Registry from 2003-2015. Predictions of rapid decline based on the algorithm were compared to a detection algorithm currently being used at a CF center with 212 patients who received care between 2012-2017. The algorithm was translated into a prototype web application using RShiny, which resulted from iterative development and refinement based on clinician feedback. The study showed that the algorithm had excellent predictive accuracy and earlier detection of rapid decline, compared to the current approach, and yielded a prototype platform with the potential to serve as a viable point-of-care tool. Future work includes implementation of this clinical prototype, which will be evaluated prospectively under real-world settings, with the aim of improving the pre-visit planning process for CF point of care. Likely extensions to other point-of-care settings are discussed.

INDEX TERMS Decision support systems, longitudinal data analysis, patient monitoring, predictive algorithms, user centered design

I. INTRODUCTION

The most common and deadliest inherited disease that affects Caucasians is cystic fibrosis (CF). Currently there are nearly 30,000 individuals in the US and 70,000 individuals worldwide who are living with CF [1]. The leading cause of death in CF is respiratory failure [2]; therefore, maintaining lung function is essential for survival. Acute drops in lung function over the clinical course of CF have been clinically termed “rapid decline” (Fig. 1). Further adding to the complexity of identifying rapid decline at its onset is the lack of a clear definition [3].

Numerous epidemiologic studies by these authors [4] and others [5] [6] [7] have employed various statistical approaches to estimate trajectories of lung function decline. These trajectories exhibit nonlinearity over the lifespan with substantial variation both between subjects and within an individual subject over time. Despite unique approaches, each study has demonstrated that the most severe bouts of rapid decline tend to occur during adolescence and early adulthood. Indeed, recent work suggests that, although there are distinct patterns or phenotypes of rapid decline, those individuals with the highest lung function initially are at risk for the most severe declines early in life [8]. In addition, adults with CF experience rapid decline [9], suggesting that this requires clinical monitoring throughout the lifespan.

A. CF Point-of-Care Technologies

While numerous therapeutic advancements and quality improvement initiatives have extended life expectancy, point-of-care algorithms and technologies that harness well-developed epidemiologic findings regarding prediction—as opposed to explanation—as of rapid decline within the individual CF patient are limited. Efforts to translate

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statistical innovations into CF point of care began with spirometric reference equations [10] [11], which initially were separated by children and adults but have recently been extended through advanced methodology [12].

Treating rapid decline from the clinician perspective typically includes a series of treatment decisions in response to decline. Real-time clinical data availability and utilization, along with implementing evidence-based prescribing algorithms, have been shown to improve lung function in CF [13]. Furthermore, clinical algorithms that retrospectively identify rapid decline have been successfully implemented to trigger interventions and slow lung function loss [14].

B. Recent Advances

Home spirometry has been studied, in which patients’ FEV1 data were monitored for onset of acute respiratory events known as pulmonary exacerbations [15, 16]. This study involved more frequent FEV1 collection and elucidated the variation in FEV1, which has been shown to be a significant predictor of subsequent FEV1 decline [17], and it also shows the difficulty in developing a medical monitoring intervention in CF. On the other hand, a recent diagnostic tool development highlights the feasibility of CF point-of-care technologies for diagnosis [18], but does not address routine care and clinical surveillance that are necessary to treat rapid disease progression.

C. Aim of the Study

The aim of this study was to translate a flexible algorithm to accurately detect rapid lung function decline within the individual patient into a clinical prototype for CF point of care. Clinician feedback and prototype refinements were performed iteratively based on application mock-ups of clinical dashboards. Earlier developments were presented and reported as conference proceedings [19].

II. METHODS AND PROCEDURES

The Institutional Review Board at the Cincinnati Children’s Hospital Medical Center (CCHMC) approved the study (IRB No. 2017-7763). The request for patient registry data access subsequently underwent a separate review process, and approval was granted by the Cystic Fibrosis Foundation Patient Registry Committee (Request No. PRR088).

A. Data

Data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) were used to develop the longitudinal model and resulting algorithm. The timeframe included data from January 1, 2003, until December 31, 2015, in order to reflect the most modern era of CF care from the available data. This registry has been tracking outcomes on patients with CF for nearly 50 years; detailed descriptions of its contents have been provided [20]. For model development in this study, we utilized forced expiratory volume in 1 s of % predicted (hereafter, FEV1) as a marker of lung function, and included data on patients aged ≥ 6 years in order to obtain reliable pulmonary function from the FEV1 measure.

Other clinical and demographic characteristics from the CFFPR, which were used as model inputs, included static variables: sex (male or female), genotype (copies of F508del alleles coded as heterozygous, homozygous, or none), birth cohort (a categorical variable defined as birth year < 1981, 1981-1988, 1989-1994, 1995-1998, 1999-2005, ≥ 2006), chronic infection with Pseudomonas aeruginosa (Pa, defined as ≥ 4 positive cultures over time), persistent methicillin-resistant Staphylococcus aureus (MRSA, defined as ≥ 4 positive cultures over time); time-varying variables: age (in years), low socioeconomic status (defined as having received federal/state insurance). These variables were chosen based on existing CF epidemiologic literature on modeling FEV1, which has been summarized in a recent review article [21].

B. Algorithm Development and Validation

A longitudinal model was developed to fit age-related FEV1 progression and account for its nonlinearity by expanding an established method that has been successfully used to monitor markers of renal disease progression [22]. The expanded model used in this paper was presented at the 40th European Cystic Fibrosis Society Meeting.

Let $Y_{ij}$ be a random variable representing the longitudinal process of FEV1 taken on the $i$th patient at the $j$th time point ($i = 1, \ldots, N; j = 1, \ldots, n_i$); here, let time be represented by age (in years). The longitudinal model can be expressed as:

$$Y_{ij} = f(t_{ij}) + X_i'β + U_i + W_i(t_{ij}) + ε_{ij}. \quad (1)$$

In Equation (1), the function $f(\cdot)$ is used to depict nonlinear FEV1 progression over time $t_{ij}$, which is expressed as age (in years); $f(\cdot)$ is represented using natural splines with knots located at ages 11.3, 16.0, 21.2 and 29.8 years; the term $X_i'β$ represents the patient-specific vector of covariates defined previously and corresponding coefficients; $U_i \sim N(0, σ_U^2)$ are random intercepts allowing FEV1 trajectories to be shifted across individual that follow a normal distribution with mean 0 and variance $σ_U^2$; $W_i(t_{ij})$ are independent realizations of a zero-mean, continuous-time stochastic process known as...
obtained based on AIC). Each model was fitted using the ‘imemrpp’ package available in R.

Two types of validation were performed on each model through a stratified split sample of the CFFPR cohort (Fig. 2). Patients were randomly split into development and validation sub-cohorts (80% and 20%, respectively). Within the development cohort, a forecast validation sub-cohort was created by randomly selecting roughly 20% of patients and masking the last two years of their data. Metrics included mean absolute error (MAE), root mean square error (RMSE) and mean absolute % error (MAPE), in order to assess the degree to which FEV1 as predicted by the algorithm was similar to observed FEV1. These metrics were calculated using the actual data held out from either the primary validation sub-cohort or the forecast validation sub-cohort. Over the two-year window for the forecast validation sub-cohort, overall and h-step ahead forecasts were computed; steps included 0.5 years, 1 year and 2 years for clinical horizons.

C. Clinically Defining Rapid Decline

In the analysis cohort used to develop the predictive algorithm, there were \( N = 30,879 \) patients “at risk” of rapid decline with a total of \( \sum_{i=1}^{N} n_i = 6,19,960 \) observed FEV1 data points and \( j = 1, ..., n_i \leq 89 \) visits per patient. Age range during follow up was 6 to 83 years. The covariate history on patient \( i \) up to time \( t \) can be denoted as \( H_i(t) = \{ x_i(t), y_i(t), \gamma_i(t) : t_i < t \} \).

The first derivative of Equation (1) may be used as an estimate of rate of change in FEV1. A threshold of -1.5% predicted/year was selected based on clinical judgment and graphical inspection (Fig. 3). In order to identify periods in which a given patient is at risk of rapid decline based on this threshold, the following probability needs to be estimated.

\[
P \left( \frac{d}{dt} Y_i(t) < -1.5 \right | H_i(t) \right) \tag{2}
\]

This probability in Equation (2) corresponds to the risk of rapid decline for patient \( i \) based on his or her information history, which includes clinical and demographic data as well as past FEV1. By conditioning probabilities on this information, more accurate risk predictions are expected.

D. Prototype Development and Refinement

Clinician feedback was sought at various points in Phase II of the study (Fig. 4), which focused on translating the predictive algorithm into a clinical prototype for point of care use. A combination of convenience and purposive sampling was used to acquire preliminary feedback from clinician researchers and care providers at CF Data and Chart Review Conferences at CCHMC. The predictive algorithm approach was described, attendees were prompted to review and comment on a basic web application translating the algorithm (Fig. 5, upper panel). This preliminary dashboard shows observed FEV1 (black dots, top graph) for a female CF patient with data available beginning at 6.1 years of age. Her risk of rapid decline (bottom graph) is elevated around 10-12 years of age (see red arrow). Other patients can be
selected (see black arrow). Several refinements were made to improve upon the base application. An interim dashboard is shown (Fig. 5, lower panel) for another female patient, including additional covariate inputs.

E. Comparison to Currently Employed Algorithm

Prior to the algorithm described in this study, a local center study was conducted to develop and implement a systematic algorithm specific to rapid decline in pediatric patients [14]. Those patients whose peak FEV1 in the prior 3 months was not within 10% predicted of their highest FEV1 in the prior 12 months were classified as high-risk “Red Zone” patients. Modifiable risk factors for this degree of FEV1 decline included untreated/newly identified infectious organisms, gaps in or failure to prescribe pulmonary therapies, gastroesophageal reflux disease, unrecognized allergic bronchopulmonary aspergillosis and infrequent clinic follow up.

The local Red Zone algorithm to identify rapid decline was compared to the algorithm described in this paper with respect to age at which rapid decline was first identified using a retrospective analysis of 212 patients (age range: 6-22.3 years) who received care based on the Red Zone algorithm at CCHMC (2012-2015). Age at which the algorithm first estimated probability of rapid decline to be ≥ 0.80 was considered high risk.

III. Results

A. Algorithm Performance

Patients in the development and first-level validation cohorts were similar in age at entry, length of follow up, sex, and genotype, as well as other morbidity and mortality characteristics that have been identified as risk factors of rapid decline (results not shown). Parameter estimates for the covariate associations and statistics for goodness of fit are shown in the Appendix (Table E1). Associations between included covariates and FEV1 were similar across static, full and reduced models. In the final reduced model, having two F508del alleles, being male and born into an older cohort, and having MRSA, CFRD and more frequent pulmonary exacerbations in the prior year corresponded to lower overall FEV1, while having Pa more clinic visits were associated with higher overall FEV1. More rapid FEV1 decline was associated with having fewer F508del alleles, being female and born into an older cohort, and not having CFRD. Each model similarly decomposed sources of variation in FEV1, with the largest source estimated as residual error, followed by between-patient heterogeneity. The full model, which included all candidate covariates, performed similarly to the reduced model omitting socioeconomic status and the

TABLE 1

<table>
<thead>
<tr>
<th>Predictive Performance and Forecast Accuracy</th>
<th>Models*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=6,175)</td>
<td>Full</td>
</tr>
<tr>
<td>RMSE, % pred</td>
<td>7.745</td>
</tr>
<tr>
<td>MAE, % pred</td>
<td>5.535</td>
</tr>
<tr>
<td>MAPE, %</td>
<td>8.989</td>
</tr>
<tr>
<td>Forecast Accuracy</td>
<td>(n=4,490)</td>
</tr>
<tr>
<td>RMSE, % pred</td>
<td></td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>MAE, % pred</td>
<td></td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
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<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
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<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>MAPE, %</td>
<td></td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
<tr>
<td>Clinical horizon, years</td>
<td>0.5</td>
</tr>
</tbody>
</table>

MAE = mean absolute error; MAPE = mean absolute percentage error; RMSE = root mean-square error. *Each model was developed using the unmasked data from the development cohort (Fig. 2). Metrics calculated for the "held-out validation cohort and for "last two years of follow-up for data that were masked from patients in the development cohort. Clinical horizons are duration (in years) after the last observed (unmasked) FEV1 and covariate values included in the model development dataset. Model estimates are provided in the Appendix (Table E2).
interaction between MRSA and age. However, this reduced model had better fit than the full model (LRT statistic: 12, \( P = 0.007 \)). The static model had the poorest fit, compared to the full and reduced models (LRT statistics: 2526 and 2514, respectively, both \( P < 0.001 \)).

The held-out validation cohort exhibited predictive performance that was similar across the models (Table 1), indicating that the static model provided reasonable accuracy for patients who were excluded from the model development cohort. In the forecasting of data that were masked from patients whose earlier data had been included in model development, the static model had the highest RMSE, MAE and MAPE, suggesting some loss of prediction if measures over time could not be incorporated into the models. The full and reduced models performed similarly over the forecasting term. As expected, forecasting errors increased over the clinical window; however, MAPE values at two years out were within range of held-out validation estimates (8.9%).

B. Clinician Feedback and Prototype Improvements

The interim dashboard (Fig. 5, lower panel) served as a key interim point in the clinical evaluation of the displays. Compared to the base dashboard, we included 95% confidence bands to provide a measure of uncertainty about the trajectory estimations. There was also a desire to view a snapshot of covariate information, ranging from genotype to time-varying inputs, such as infection statuses. As a result, we decided to build the app using the full model, which included all covariate inputs that were considered. Although this model suffered from a lack of parsimony, it had similar predictive accuracy to its counterparts with fewer parameters (Table 1) and had improved clinical utility.

At this point in Phase II, dashboards were constructed using Microsoft PowerPoint slides. These slides were shown to conference attendees, who provided input on data visualization and clinical relevance of various thresholds of rapid decline (e.g., -1.5% predicted per year, Fig. 3) as well as degree of predictive probability that constitutes rapid decline (e.g., 0.80 or higher). Clinicians were also interested in having forecast intervals or horizons of up to 2 years ahead. The interim dashboard as shown represented an improvement from the base dashboard; however, clinicians preferred vertical stacking of the graphs depicting observed FEV1, rate of change in FEV1 and predictive probability distributions. In addition, value was placed on having normative data across patients and patient subgroups, in order to provide context for clinical status of an individual patient relative to his or her peers in the data. Clinician preferences were subsequently programmed into the web application using RShiny. A look-up table was used to display data points in each sub-graphic. Dynamic medians calculated at quarterly intervals over age were used to create patient normative data, with display enabled through checkbox functions.

The finalized prototype includes de-identified data from the forecast validation sub-cohort (Fig. 6). As shown below, a given patient can be selected using the scroll-down selection bar on the leftmost pane. This pane also includes features to toggle patient selection based on age and FEV1 at entry. Other factors are provided for selection, ranging from sex to birth cohort. A bookmark feature is available to save a particular patient and feature combination from the app. The middle panel shows observed FEV1 (black dots) versus age, and it includes the estimated FEV1 trajectory based on observed data (gray line). Forecast regions are provided in red for the last two years of follow up, which also illustrate predictive accuracy of the model for the masked data. Similarly, information is provided for rate of FEV1 decline over age in the middle graph. Finally, the risk of rapid decline is graphed using the predictive probability distribution. As shown, the gray shaded area shows real-time risk of rapid decline, while the red shaded area shows predictive risk of rapid decline. Having these features was deemed important by clinicians, as it is sometimes desirable to look retrospectively at a patient’s FEV1 progression. A third panel is available measuring covariate information using a heat map for frequency variables and a dichotomous color scheme (red/gray) for present/absent characteristics, such as having CFRD.

The patient shown in the final prototype graphic is a male F508del heterozygote, whose first available FEV1 was 84% pred and was taken at 6.1 years of age. He was born during 1999-2005. His FEV1 declines in a nonlinear fashion, as shown by the observed FEV1 and estimated rate of decline. His risk of rapid decline increases over age, becoming high risk around 12 years of age. Based on the covariate snapshot, he appears to have developed MRSA infection around this time and was affected by Pa infection around age 10 years. His other information shows relatively few pulmonary exacerbations and a slight increase in clinic visits over age. He is reported as using state/federal insurance, which has been associated previously with accelerated FEV1 decline [23]: he does not, however, have CFRD. A comparison of his data to overall norms, as provided by the app, suggests that his progression is relatively similar to others in the population. Using check boxes to subset normative data to individuals with his same covariate inputs, we see that this progression is slightly above the normative data (see website and video file in Section E2 of the Appendix).

C. Comparison to Currently Employed Algorithm

There were 212 patients aged 6-22 years old who contributed 3,846 observations over the timeframe at the single CF care center. The prediction model and center-level algorithm both identified 120 patients (57%) experiencing rapid decline over the study period. Mean (range) of the timing of rapid decline based on the predictive algorithm and center-level algorithm was 12.2 (6 to 19.5) and 12.75 (6.3 to 20.7), respectively. For these patients, rapid decline was identified earlier using the prediction model, compared to the clinical algorithm (mean difference: 0.65 years, 95% CI: 0.41 to 0.89, \( P < 0.0001 \)). The prediction model detected a similar subgroup of patients experiencing rapid decline to those identified using the standard clinical algorithm (sensitivity: 83%) but detected a distinct subgroup of patients who were classified as not experiencing rapid decline (specificity: 25%).
IV. Discussion

The ultimate aim of this study was to develop a predictive algorithm to identify rapid lung function decline and create a corresponding prototype for CF point of care. The algorithm to identify rapid lung function decline and create a prototype for CF point of care could be expanded to enable shared decision making between the provider and patient, enabling the patient to view her accrued data and risk of rapid decline. Real-time updating could be accomplished by integrating the application with electronic health record data as it is accrued at the center level. The prognostic utility of the model could be compared to current clinical algorithms for the treatment of rapid decline in a prospective study. The algorithm used as a comparator in this study has shown effectiveness of using decision rules to identify rapid decline.

A. Clinical Utility

We have developed and translated a novel point-of-care prognostic algorithm for improving early detection and forecasting of rapid pulmonary decline in CF. A series of models were examined, and all relied upon covariates that are routinely obtained during clinic visits and contributed by over 200 accredited centers to a patient registry, providing individualized predictions drawn from a broad national cohort. We found that predictive accuracy was robust across a series of models ranging from a basic collection of static covariates to a comprehensive collection of time-varying measures, and that a reduced model including genotype, sex, infection with MRSA or *Pa*, diagnosis of CFRD, birth cohort and rolling covariates for frequencies of clinical visits and pulmonary exacerbations was the most accurate of all models considered. Predictive accuracy was excellent in the held-out validation cohort, indicating that future FEV<sub>1</sub> data for newly diagnosed patients could be predicted within 8.7% of actual values. The model exhibited viable clinical utility for looking ahead at rapid decline over 6 months, 1-year and 2-year intervals, forecasting FEV<sub>1</sub> within margins of 5.6%, 6.9% and 8.6%, respectively, for patients with existing data. Root mean-square errors for the forecast intervals (Table 1) approached the estimated within-patient SD that has been reported in a Danish CF registry study (6.3% predicted) that employed a similar covariance structure[24], suggesting that our algorithm’s predictive performance falls within the natural FEV<sub>1</sub> variation experienced by a given patient over time.

By translating this model into a point-of-care tool, there are several implications for clinical care and shared decision making. Having substantial risk of rapid decline (e.g., predictive probability > 0.80) could serve as a trigger to initiate more frequent clinical visits, assessments for infections or mobile reporting of cough symptoms. The approach could complement methods to monitor patients outside the clinical setting, such as aforementioned efforts made to collect at-home spirometry. The web application

![FIGURE 6. Finalized prototype web application (see text for patient profile explanations). Detailed description and video illustration available in the Appendix materials (see section E2).](image)

B. Considerations for Personalized Care

Our prognostic model has implications for other clinical/translational research into point of care. With the dawn of CFTR modulators and novel biomarkers taken on the microbiome and proteome level [25], accurate prediction of readily available clinical outcomes, like FEV<sub>1</sub>, augmented with other markers will be paramount to CF precision medicine. The structure of the predictive algorithm and point-of-care platform could be expanded to assess performance of novel markers and therapies as additional model inputs. However, other considerations would be needed to incorporate/evaluate treatment effectiveness given the confounding-by-indication bias that has been shown to exist in the CFFPR[26].

C. Limitations

This study has some limitations. Medication use was not incorporated in the predictive algorithm, although comparative effectiveness of specific medications over a subset of eligible patients could be further assessed with some careful attention to the aforementioned indication bias that is pervasive in patient registries [27]. It is possible that CFTR modulators could impact future predictions; however, it is unlikely that this impact was significant in the current study as therapeutics such as Orkambi were not available until 2015. There is a loss to death as shown in a previous study [4], which could impact the reliability of predictions during adulthood. Additional considerations would be needed to incorporate this potential survivor bias into the prediction model and assess performance. It is possible that intensity of patient follow-up is affected by disease severity, as shown by the significant association between number of clinic visits in the prior year and decline in FEV1 (Table E1); however, results from this model are similar to previous studies using nonlinear curves but relying on quarterly FEV1 as the outcome [28].

D. Future Work

Upcoming project phases include a formal clinician focus group study, in order to optimize the prototype for CF point of care. This future work will involve setting up realistic scenarios in parallel with real-time clinical care, which are meant to elicit clinician adjudication regarding the use of the prediction tool in confirming rapid decline. Additional work should be done to assess how clinicians discuss rapid decline in care management teams and with patients and families.
It will be essential in later-stage translation to discuss among researchers, clinicians, engineers and informaticists how to integrate the finalized prediction application into point of care given the existing electronic health systems, which vary across CF centers. Another consideration is where to embed the application. Discussions with clinicians and informaticists have included division-specific intranets, medical electronic health record programs and applications allowing for cell phone accessibility.

Once the prototype application has been evaluated in a real-world clinic setting, its extension to other centers and evaluation of efficacy will require additional considerations related to healthcare systems and clinical management practices. Although CF care has been standardized through various pulmonary and nutritional guidelines [29] [30] [31], variation in care still exists among CF centers [32]. These variations may necessitate customizable dashboards, allowing users to customize interfaces in real time [33].

V. CONCLUSION

This study demonstrates the power of utilizing routinely collected clinical data for point-of-care prediction technologies. Registries like the CFFPR not only can be used to describe prior events and associations but can predict current course as well as future events in clinical settings in a way that can be generalized to a broad spectrum of patients. Predictive data on rapid decline and its clinical translation to the patient had been a critical missing piece in CF care, and now collectively provide capacity to arm caregivers with information needed to personalize patient prescribing and identify those requiring intervention in real time. External validation in international CF cohorts and prospective evaluation as a prognostic tool for timely treatment of rapid decline are needed.

APPENDIX

E1. Model parameter estimates resulting from predictive algorithm.

<table>
<thead>
<tr>
<th>TABLE E1</th>
<th>POINT ESTIMATES AND MODEL FITS IN DEVELOPMENT COHORT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td>Full</td>
</tr>
<tr>
<td>F508del alleles (Reference: None)</td>
<td></td>
</tr>
<tr>
<td>Homozygous</td>
<td>-1.421 [-2.064 to -0.778]</td>
</tr>
<tr>
<td>Birth Cohort</td>
<td></td>
</tr>
<tr>
<td>FEV&lt;sub&gt;1&lt;/sub&gt; at baseline</td>
<td>0.812 [0.804 to 0.820]</td>
</tr>
</tbody>
</table>

AIC = Akaike Information Criterion; CF = cystic fibrosis; FEV<sub>1</sub> = forced expiratory volume in the first second; -2LL = -2 times the loglikelihood.

*Results are presented as point estimates of coefficients with 95% CI; age-related spline coefficient estimates are included but not shown. *Coefficient estimates with P > 0.05; all other estimates are significant (i.e., P < 0.05).

Variance estimates from stochastic modeling approach (see Methods).

TABLE 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (Standard Error)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socioeconomic status</td>
<td>-0.217 [0.366 to -0.068]</td>
</tr>
<tr>
<td>Positive culture</td>
<td></td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0.598 [0.398 to 0.798]</td>
</tr>
<tr>
<td>Methicillin-resistant</td>
<td>-0.243 [0.468 to 0.018]</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>-0.435 [0.977 to 0.025]</td>
</tr>
<tr>
<td>CF-related diabetes mellitus</td>
<td>-1.037 [-1.294 to -0.790]</td>
</tr>
<tr>
<td>Outpatient visits in last year</td>
<td>0.121 [0.111 to 0.131]</td>
</tr>
<tr>
<td>Acute exacerbations in last year</td>
<td>-0.739 [-0.770 to -0.708]</td>
</tr>
<tr>
<td>F508del alleles (Reference: None) x age</td>
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<tr>
<td>Homozygous</td>
<td>0.191 [0.105 to 0.277]</td>
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<tr>
<td>Heterozygous</td>
<td>0.412 [0.290 to 0.534]</td>
</tr>
<tr>
<td>Male sex x age</td>
<td>0.244 [0.166 to 0.322]</td>
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<tr>
<td>Birth Cohort (Reference: &lt; 1981) x age</td>
<td></td>
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<tr>
<td>1981-1994</td>
<td>-1.064 [-1.268 to -0.860]</td>
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<tr>
<td>1995-1998</td>
<td>-1.704 [-1.924 to -1.484]</td>
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<tr>
<td>2005</td>
<td>-1.834 [-2.048 to -1.620]</td>
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<tr>
<td>Socioeconomic status (Reference: Low) x age</td>
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<tr>
<td>F508del alleles (Reference: None) x age</td>
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<td>Homozygous</td>
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<td>Heterozygous</td>
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<td>CF-related diabetes mellitus x age</td>
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<tr>
<td>Male sex x age</td>
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<td>Variance components</td>
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<td>Between-patient</td>
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<td>Within-patient</td>
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<td>Residual error</td>
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<tr>
<td>-2LL</td>
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</tbody>
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E2. Detailed description of point-of-care prototype and video narrative.

Rapid_decline Prototype.mp4: Video illustrating the RShiny web application of the prototype point-of-care platform. The figures below describe corresponding sections of the app.
FIGURE E2a. Leftmost panel on web application, depicting patient selection, which can be modified according to toggles for age and/or FEV1 at entry. Additional variables for which the cohort can be subset include sex, birth cohort, genotype, chronic infection with Pa or MRSA. The application can also be bookmarked based on selections.

FIGURE E2b. Bottom section of the web application, providing baseline input information on the selected patient.

FIGURE E2c. Middle panel of web application, displaying three plots corresponding to FEV1 (% predicted), rate of decline in FEV1 (% predicted/year), and predictive probability of rapid decline, all over age.

FIGURE E2d. Rightmost panel on web application, showing observed inputs over time for the selected patient. The top two graphs show number of pulmonary exacerbations in year prior to the given clinical visit and a similar metric for number of clinic visits. The frequencies are marked using a heat map index pictured on the right. The remaining four graphs are dichotomous inputs observed at each clinical encounter, showing status of MRSA infection, state/federal insurance use, CF-related diabetes, and Pa infection.

FIGURE E2e. Displaying normative data on the middle panel of web application. This feature overlays dynamic medians for FEV1 and rate of change in FEV1 (see brown dashed lines). As shown in the video, the dynamic medians can be displayed based on subsets of patient characteristics by de-selecting items on the leftmost panel of the app (see Figure E2a: Show Population Norms?).

To access the online application in prototype form, visit: http://cfpopd.amazon-shiny.duckdns.org. Please see the About tab for additional information.

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Cole Brokamp is an Assistant Professor in the Division of Biostatistics & Epidemiology at Cincinnati Children’s Hospital Medical Center interested in geoinformatics, environmental health, statistical computing, population health, and statistical inference for machine learning. I completed my PhD in Biostatistics & Bioinformatics in the Department of Environmental Health at the University of Cincinnati and did my postdoctoral training at Cincinnati Children’s in Biostatistics & Epidemiology. Currently, I am evaluating the heterogeneous causal effects of environmental exposures on childhood health outcomes, testing and implementing causal inference methods for random forest, creating statistical computing tools for geocoding and environmental exposure assessment, and designing interactive web applications for exploring the social determinants of health.

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Dr. Clancy is a Professor of Pediatric Pulmonary Medicine at Cincinnati Children’s Hospital Medical Center, and recently joined the Cystic Fibrosis Foundation as the Senior Director of Clinical Research. His research program focuses on airway epithelial biology, pulmonary imaging, and new outcome measures for clinical and translational research. Specifically, the goals of his research program are 1) to examine strategies to restore activity to mutant, disease-causing CFTR mutations in preclinical model systems and in human subjects, 2) to develop new biomarkers of CFTR activity, and 3) to advance novel techniques to monitor CF lung disease. He utilizes these themes to provide research training platforms to future physician-scientists, focusing on translational research across model systems to human subjects. This is accomplished through the design and execution of studies in cell-based model systems, patient-derived tissues and specimens, and human subjects. Dr. Clancy has been the primary or co-mentor of >20 fellows, graduate students and junior faculty. He has published > 250 peer reviewed publications, and regularly provides leadership in clinical and translational research through the international CF research community.

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Dr. Pestian’s research focuses on developing advanced technology for the care of neuropsychiatric illness. Using artificial intelligence, his team integrates analyses of trait and state characteristics for early identification of both neurological and psychiatric illness. His lab developed and implemented an automated, electronic health record surveillance system that processes clinician notes to identify epilepsy surgery candidates up to two years earlier than traditional approaches. The lab also focuses on earlier identification of individuals at risk of suicide, depression, and bipolar and anxiety disorders using verbal and nonverbal language. His current projects include fusion of linguistic, acoustic, and visual cues that are being tested in selected Cincinnati Public Schools and Cincinnati Children’s clinics. Dr. Pestian and his lab have 18 issued patents and he is active in the entrepreneurial community. This activity has yielded over 500 jobs and one-half billion in revenue have been created. One invention, Processing Text With Domain-Specific Spreading Activation Methods, is a platform for neuropsychiatric research. Another, Optimization and Individualization of Medication Selection and Dosing, has been used for optimal mental health drug selection on more than 420,000 people. He and his colleagues have published more than 80 peer reviewed publications that focus on applied and translational sciences apropos to artificial intelligence.

REFERENCES


