APPLICATION OF AN ARTIFICIAL INTELLIGENCE MODEL TO DETECT ALPHA-1 ANTITRYPSIN DEFICIENCY: MODEL PERFORMANCE

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INTRODUCTION

- The genetic condition alpha-1 antitrypsin deficiency (AATD) remains under-recognized despite decades of detection efforts.[1]
  - Previous estimates suggest that at least 90% of patients with genotypes that cause severe AATD remain unidentified.[2]
- Patients with AATD are predisposed to chronic obstructive pulmonary disease and/or liver disease.[3]
- Patient identification can be challenging because it is difficult to distinguish the signs and symptoms of chronic obstructive pulmonary disease and/or liver disease associated with AATD from those seen in other lung/liver disorders.[4,5]
- Machine learning models can be applied to large clinical datasets to identify patients with rare diseases. We previously developed a machine learning model using a large Komodo US claims database to identify undiagnosed, symptomatic patients with AATD.[6]

OBJECTIVE

- To calibrate, refine, and evaluate the AATD diagnostic performance of the machine-learning model on de-identified patient data from the Cleveland Clinic electronic medical record (EMR).

METHODS

- De-identified patient records from January 1, 1998, to August 15, 2024, were retrospectively sourced from the Cleveland Clinic EMR.
  - This study was processed under expedited review and approved by the Cleveland Clinic Institutional Review Board (#24-469).
- Patients were divided into two cohorts based on the presence or absence of a confirmed AATD diagnosis (**Table 1**). Patients with fewer than five medical record entries were excluded from this analysis.
- For the AATD-positive cohort, only data obtained before the first AATD diagnosis or treatment were included in this analysis. Patients with a diagnosis code for another disease that made AATD unlikely (e.g. Wilson's disease or Hepatitis B) were excluded from this cohort.

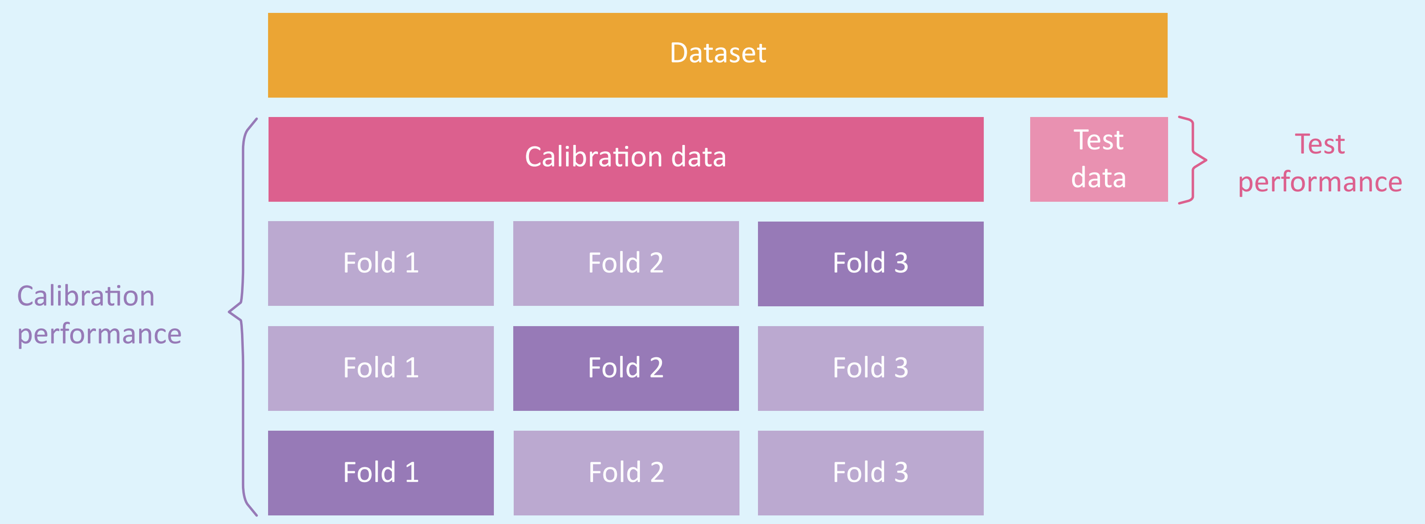
TABLE 1. PATIENTS WERE GROUPED BASED ON THE PRESENCE OF A CONFIRMED AATD DIAGNOSIS

Category	AATD diagnosis status
AATD-positive	Patients with an AATD diagnosis code and confirmed diagnosis either by genetic testing[a] or by serum AAT levels[b]
AATD-negative	Patients who had symptoms and comorbidities similar to AATD but no records of AATD diagnosis or treatments[c]

[a]Diagnosis of AATD was based on the identification of biallelic pathogenic variants (SS, ZZ, II, FF or compound heterozygotes of these alleles) in *SERPINA1*. [b]Mild deficiency: AAT serum level 57–90 mg/dL; severe deficiency: AAT serum level < 57 mg/dL. [c]Randomly selected control patients were also included in this cohort.
AAT, alpha-1 antitrypsin; AATD, alpha-1 antitrypsin deficiency.

- Patient data were split into calibration and test subsets, comprising 80% and 20% of the data, respectively (see **Figure 1** for a schematic representation).
  - The calibration subset was used to refine the model using a 3-fold cross-validation method.
  - The test subset was reserved to assess model performance on data that were unseen during calibration.
- The features used by the model included patient demographics (age and gender), diagnosis and medication codes, as well as test and procedure orders. The results of tests and procedures were not used for model calibration.

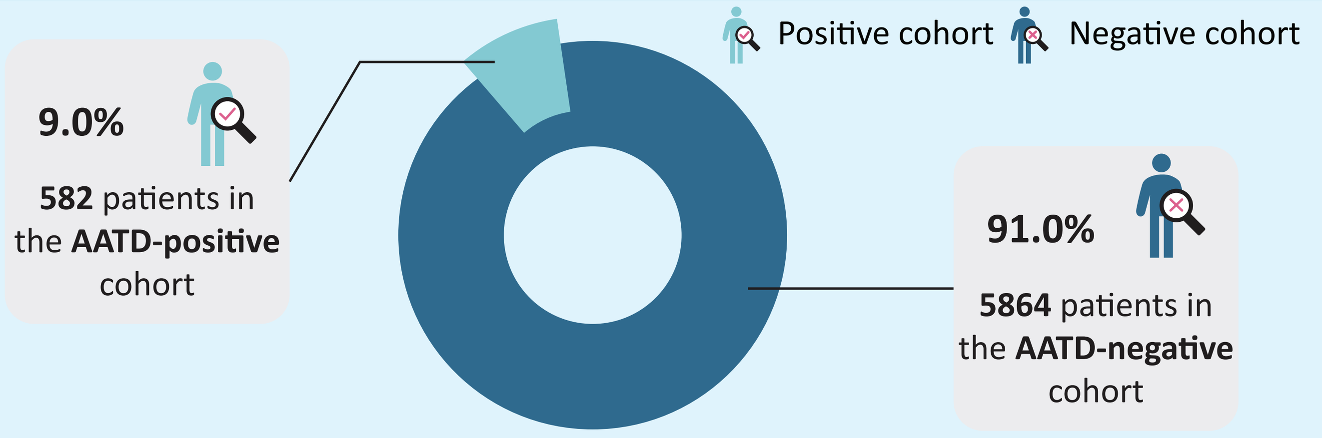
FIGURE 1. SCHEMATIC REPRESENTATION OF MODEL CALIBRATION AND TESTING METHODOLOGY



Class-revealing features (e.g. AATD diagnostic and treatment codes) were excluded.

- Of the 21,166 records analyzed, 582 patients fulfilled the inclusion criteria for the AATD-positive cohort. The AATD-negative cohort comprised 5864 patients who had symptoms and comorbidities similar to AATD but no records of AATD diagnosis or AATD-specific treatments (**Figure 2**).
  - Of the AATD-positive patients, 290 had a confirmed AATD diagnosis via genetic testing; among the AATD-negative patients, 1112 were confirmed not to have AATD based on normal serum alpha-1 antitrypsin levels or a PI*MM genotype.

FIGURE 2. OF THE 6446 PATIENT RECORDS INCLUDED, 9.0% (582) WERE AATD-POSITIVE PATIENTS AND 91.0% (5864) WERE AATD-NEGATIVE CONTROLS



AATD, alpha-1 antitrypsin deficiency.

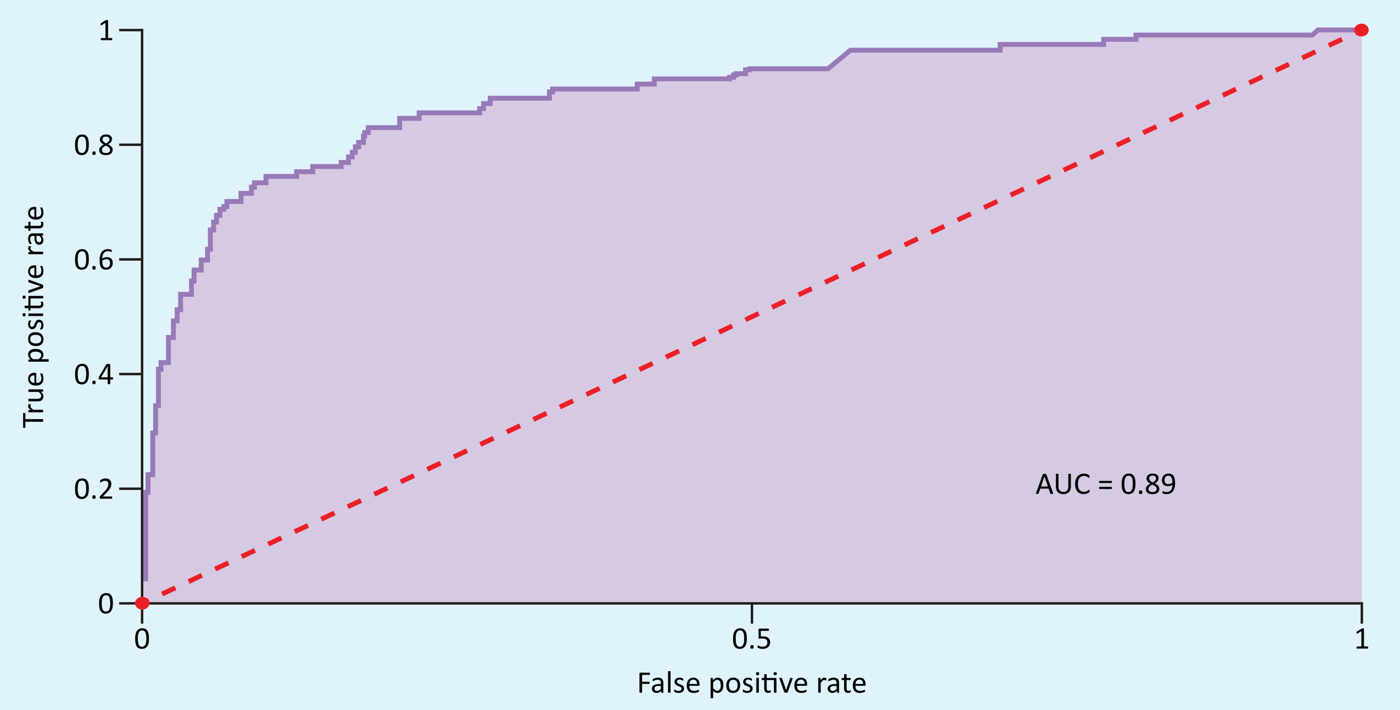
- The areas under the curve (AUC) for receiver operating characteristic and precision-recall curves were generated to evaluate model performance.
  - The receiver operating characteristic curve evaluated the overall diagnostic performance of the model by plotting the true positive rate (recall or sensitivity) against the false positive rate (1−specificity) at varying decision threshold values.
  - The precision-recall curve aided in the evaluation of the imbalanced dataset (number of patients in the AATD-positive vs AATD-negative cohorts) by illustrating the trade-off between precision (positive predictive value) and recall (finding all relevant instances).
- Sensitivity, specificity, and balanced accuracy values were calculated based on confusion-matrix quantities (true positives, true negatives, false positives, and false negatives) from the test data subset.
- A final evaluation assessed concordance between clinical experts (authors: JKS and UH) and the model in a subset of patients who the model classified as having the highest likelihood of AATD but who were not currently diagnosed with AATD and had not been tested for AATD.
  - Each clinician reviewed 20 unique records as well as an additional 10 overlapping records independently and assigned a likelihood score based on how likely they thought it was that the patient might have AATD or should be tested for AATD.

RESULTS

Receiver operating characteristic curve

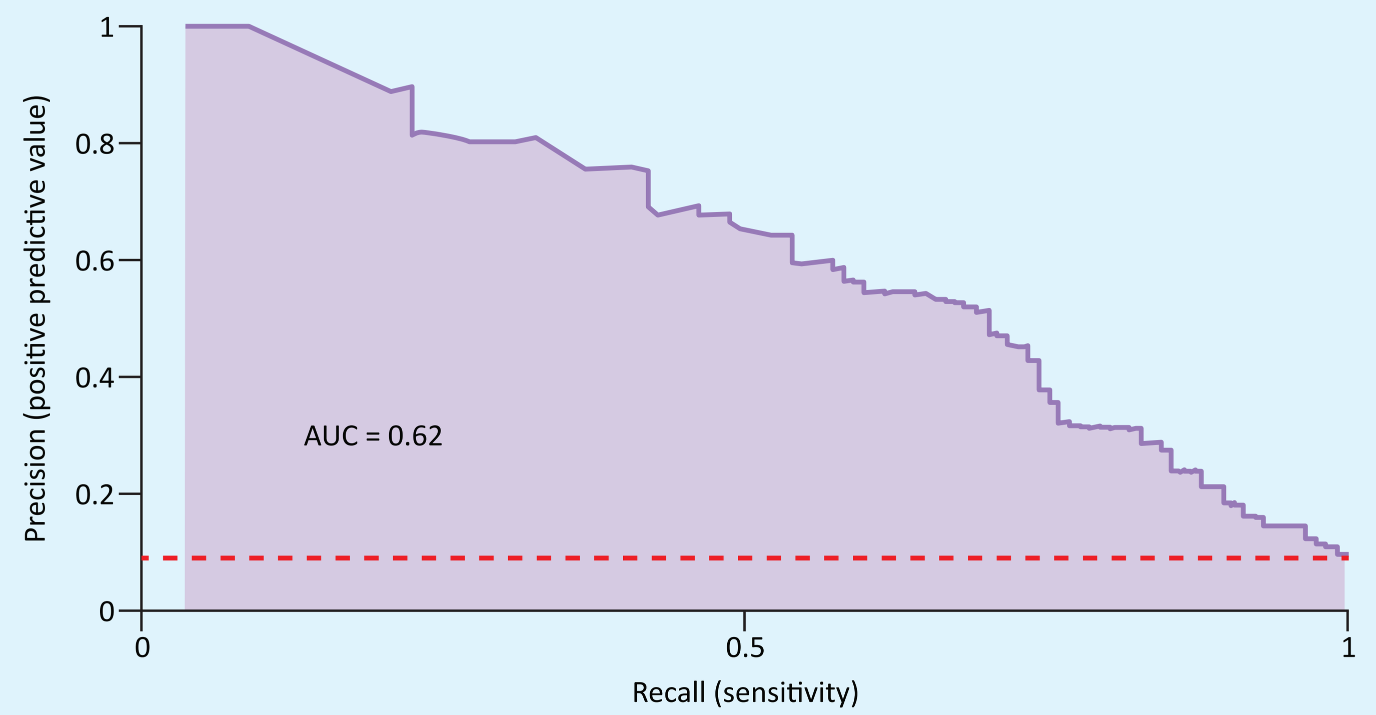
- The calibrated model achieved a receiver operating characteristic AUC of 0.89 (**Figure 3**).
  - This indicates that the model can distinguish AATD-positive from AATD-negative patients with a high level of precision.
  - The calibrated model maintained high performance (receiver operating characteristic AUC of 0.92) when evaluated on patients with genetically confirmed AATD and those with confirmed negative results.
- A higher AUC indicates better model discrimination between positive and negative cases; 1 is equivalent to perfect discrimination and 0.5 is equivalent to random guessing.

FIGURE 3. THE RECEIVER OPERATING CHARACTERISTIC CURVE OF THE AATD MODEL



The red dotted line indicates the performance expected based on random guessing.
AATD, alpha-1 antitrypsin deficiency; AUC, area under the curve.

FIGURE 4. THE PRECISION-RECALL CURVE OF THE AATD MODEL



The red dotted line indicates the minority class ratio (the proportion of AATD-positive patients in the dataset).
AATD, alpha-1 antitrypsin deficiency; AUC, area under the curve.

Precision-recall curve

- A precision-recall AUC substantially higher than the minority class ratio (i.e. number of patients in the AATD-positive cohort divided by the total number of patients) represents a well-performing model.
- The calibrated model achieved a precision-recall AUC of 0.62, which was substantially higher than the minority class ratio, as shown in **Figure 4**.
  - This indicates that the model continued to perform strongly, despite the imbalanced dataset.
  - The precision-recall AUC remained high (0.83) when evaluated on patients with genetically confirmed AATD and those with confirmed negative results.
- When thresholding the patient prediction scores above the value of 0.90, the model achieved high sensitivity (0.70), high specificity (0.92), and balanced accuracy (0.81).
- For the 20 highest-scoring currently undiagnosed patients, clinician assessment agreed with 80% of model-predicted cases that these patients were likely to have AATD.

CONCLUSIONS

- A previously developed machine learning model for identifying patients with AATD was successfully calibrated and validated using patient data from the Cleveland Clinic EMR.
- This model achieved high levels of performance as measured by receiver operating characteristic AUC and precision-recall AUC on clinical data that were not used to calibrate the model.
- The model could distinguish patients with AATD from patients with similar conditions without AATD or randomly selected controls with high sensitivity, specificity, and accuracy.
- The current study suggests that artificial intelligence could be used as an effective and generalizable tool to enhance detection of AATD. To fully optimize and utilize artificial intelligence in patient identification, future validation work using real-time EMR will be important.

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DISCLOSURES

JKS has received royalties from Elsevier and UpToDate; has served as a consultant for 4DMT, 23andMe, Dicerna, Grifols, Insmed, Korro, Sanofi, Takeda, and UpToDate; and serves on the Medical and Scientific Advisory Committee for the Alpha-1 Foundation. **NK**, **CB**, **MK**, and **JH** are employees of Takeda Pharmaceuticals USA, Inc., and are Takeda shareholders. **VL**, **AM**, and **CR** are employees of Volv Global SA. **LJ** and **JS** have no relevant conflicts of interest to report. **UH** receives royalties from UpToDate as a section editor and author for COPD. He has provided *ad hoc* consulting services to CITI Pharma.

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ACKNOWLEDGMENTS
This research was sponsored by Takeda Pharmaceuticals USA, Inc., Cambridge, MA, USA. Under the direction of the authors, medical writing services were provided by Jessica Boles, PhD, Oxford PharmaGenesis Inc., and were funded by Takeda Pharmaceuticals USA, Inc., Cambridge, MA, USA.

Presented at American Thoracic Society International Conference, May 18–21, 2025, San Francisco, CA, USA

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