New-Onset Diabetes Assessment Using Artificial Intelligence-Enhanced Electrocardiography

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Abstract

Objectives. To determine if an artificial intelligence (AI)-enhanced electrocardiogram (ECG) can improve the assessment of a patient’s likelihood of new-onset diabetes.

Design. A neural network to estimate HbA1c using a 12-lead ECG and readily available demographics (ECG model) and evaluated its ability to screen for new-onset diabetes in the complete outpatient population.

Setting. Outpatient settings at an academic medical center based in New York City.

Cohort Definition. Patients (aged ≥ 18 years) with paired 12-lead, 10-second ECG and HbA1c test acquired during an outpatient encounter at a major academic health system.

Main outcome measures. Main outcome measures: The performance of the AI-enhanced ECG at classifying new-onset diabetes (HbA1c ≥ 6.5% in patients without a prior history of diabetes), which was assessed using the area under the receiver operator curve (AUC) and positive predictive value (PPV) at the sensitivity defined by the ADA risk test, with 95% bootstrap CIs.

Results. Our training and validation set consisted of 198,857 ECGs from 160,788 patients, and our test set comprised 34,106 ECGs from 30,593 patients, recorded between January 1, 2013 and September 17, 2021. The test set consisted of patients without a prior history of diabetes. The prevalence of new-onset diabetes (HbA1c ≥ 6.5) in this population was 4.9%. The ECG model achieved the best performance (AUC, 0.80 [95% CI, 0.80-0.81]), outperforming scores based on using the ADA Risk test (AUC, 0.69 [95% CI, 0.69-0.70]; p-value < 0.01) and QDiabetes-2018 risk calculator (AUC, 0.69 [95% CI, 0.68-0.70]; p-value < 0.01). The ADA Risk test recommends follow-up testing for patients with a score ≥ 5, at which point (70.4% true positive rate) the ECG model significantly outperforms (PPV, 0.13 [95% CI, 0.12-0.14]) the ADA Risk test (PPV, 0.09 [95% CI, 0.08-0.09]; p-value < 0.01). Subsetting the test set to those without diabetes, the group identified as high risk by the ECG Model presented higher three-fold increase in future risk of diabetes in one year compared to the low-risk group (High risk cumulative incidence, 0.12 [95%CI, 0.09-0.14]; low risk cumulative incidence, 0.04 [95%CI, 0.03-0.05]; p-value < 0.005). We found that two clinical electrophysiologists underperformed a deep neural network model that only uses ECGs (AUC 0.82), achieving AUCs of 0.58 and 0.61 when assessed on a class balanced subset of 100 randomly sampled ECGs from the test set.

Conclusions. An AI-enhanced ECG can automate the identification of patients who are likely to have new-onset diabetes with fewer false positives than questionnaire-based assessment. This conclusion applies to single-lead ECGs, commonly found on wearable devices, which opens a door for community-wide diabetes assessment.
Introduction

Diabetes mellitus affects 37.3 million Americans, 95% of whom have type 2 diabetes, and is one of the leading causes of illness in the United States[1]. Due to its long asymptomatic period, early diagnosis requires screening, which allows for interventions that reduce diabetic complications[2]. Several tests allow for the discovery of diabetes in asymptomatic people, the most popular of which is the measurement of glycated hemoglobin (HbA1c). Yet, even with current screening efforts, 1 in 5 people are not aware of their diabetes[1]. To address this, public health agencies such as the American Diabetes Association (ADA) have promoted the use of risk tests. The ADA Risk test uses simple-to-collect patient information, such as family history and body mass index (BMI), to identify high-risk patients[3]. Artificial intelligence (AI), however, has created the possibility of improving diabetes assessment by making use of easily-queryable, high-dimensional biosignals like the electrocardiogram (ECG). ECGs are simple to collect, even in the community setting, because of ECG-enabled mobile fitness trackers.

AI-enhanced ECG systems have performed tasks that are imperceptible by humans, such as identifying age, sex[4], and left ventricular systolic dysfunction[5]. Analogously, we hypothesized that the ECG could be an effective tool to identify people who are likely to have diabetes and require additional testing.

Preliminary evidence suggests that a relationship between ECGs and diabetes exists. A deep learning system using ECG data was able to detect nocturnal hypoglycemic events[6]. Most recently, researchers used an AI-enabled ECG system to estimate HbA1c, where the estimates were associated with many complications of diabetes such as chronic kidney diseases and heart failure[7]. A limitation of this previous work is that the population investigated includes many patients with long-standing diabetes, as they are more likely to have their A1c measured. Patients with long-standing diabetes often develop cardiovascular diseases; therefore, it is less surprising that the ECG can help identify such patients. Instead, we focus on detecting new-onset diabetes in patients without a history of diabetes.

In this study, we trained a deep learning model to estimate HbA1c using a 12-lead/10 second ECG and readily available demographic information and evaluated its ability to screen for new-onset diabetes in the general or complete outpatient population. To do so, we used retrospective data where patients have both an HbA1c and ECG measured. However, such patients may not be representative of the complete outpatient population, so we generated a pseudo-population that better represents the general outpatient population, as visualized in Figure 1. This procedure is important because the AI-enhanced system must perform well on those eligible for diabetes assessment, not only those with contemporaneous ECG and HbA1c measurements.

Methods

Study Population

We considered all outpatient encounters within NYU Langone Health system, an academic medical center based in New York City with more than 300 locations. Encounters between January 1, 2013 and September 17, 2021 with the following types: physicals, wellness, annual exam, walk-ins, follow-up, and prenatal were considered. We referred to this cohort as the Outpatient Cohort. The Outpatient Cohort was used to model the probability of acquiring an HbA1c and ECG measurement. Patients in the Outpatient Cohort were split into train and test set with 4:1 ratio. Within the Outpatient Cohort test set, encounters with at least one digital, standard 12-lead/10s resting ECG measured during the encounter were defined as the ECG cohort. The ECG Cohort was used to evaluate the efficacy of diabetes detection in the population of outpatients with an ECG. Within the Outpatient cohort, encounters with both standard 12-lead/10s ECG and an HbA1c obtained were defined as the HbA1c-ECG Cohort. For patients with multiple 12-lead/10s ECG and HbA1c measurements, we paired the earliest HbA1c with the ECG most proximal in time. We referred to this cohort as the HbA1c-ECG Cohort. The HbA1c-ECG Cohort was used to train and evaluate models for HbA1c estimation and the detection of diabetes. HbA1c-ECG Cohort derived from the Outpatient Cohort train set were further split into train and validation with 3:1 ratio. Finally, we subsetted the test set of HbA1c-ECG Cohort to those without prior history of diabetes, which we defined as the absence of a diagnosis for diabetes.
Goal
Evaluate how well the ECG assesses a patient’s likelihood of diabetes (HbA1c ≥ 6.5%).

Problem
Some individuals don’t receive an ECG and HbA1c test. Those who do receive an ECG/HbA1c may be more likely to have cardiovascular disease or diabetes.

Figure 1: Diagram of pseudo-population construction. The electronic health record provides a large amount of data with which to train and evaluate an AI-enhanced ECG to estimate HbA1c. However, for many patients ECGs or HbA1c tests are not performed. In order to understand how well the AI-enhanced ECG will work in practice, one needs to estimate the performance on the complete population. This diagram shows that by modeling the probability of ordering an ECG and HbA1c, the observed population can be re-weighted to represent the complete population.

Data
Encounter data were collected from the electronic health record (EHR) system for NYU Langone Health (Epic Systems, Verona, WI) and ECG were retrieved from MUSE (GE Healthcare, Chicago, IL). ECGs were measured at sampling rates of either 250 or 500 Hz. For each encounter, we extracted the patient’s demographics as well as the most recent set of diagnoses (from ICD-10 codes), medications, and laboratory results, including their HbA1c values, prior to the encounters (S. Table 1). Diagnoses covered risk factors for diabetes/cardiovascular disease, disease complications, or medications for the treatment of diabetes/cardiovascular diseases. HbA1c measured at encounter was discretized into four bins for classification: <5.7%, 5.7-6.4%, 6.5-7.9%, and ≥ 8.0%. Variables with missing values were imputed by multivariate imputation with chained equations using the scikit-learn package.

Probability of Measurement Model
To model the mechanism of data acquisition, we considered the full set of variables summarized in S. Table 1 that would inform a physician’s decision to acquire an ECG and HbA1c and labeled the data with whether or not both an ECG and HbA1c were obtained. Any variables with missing values were imputed to mimic a clinician’s ability to make decisions with the available information about a patient. We trained an XGBoost model on the Outpatient Cohort to classify whether or not an ECG and HbA1c were acquired. We tuned the XGBoost algorithm’s hyperparameters and selected the best performing model (the one with the highest area under the precision-recall curve (AUPRC)) using 5-fold cross-validation. To ensure the model generalized to the test set and produced calibrated probabilities, we measured the expected calibration error (ECE) and
Figure 2: Flow diagram describing the study design. After exclusion based on age and visit type, patients were split into train and hold-out test datasets, ensuring that no patient was included in both sets. These splits were conserved as the inclusion criteria were applied to generate the ECG and HbA1c-ECG Cohorts. For the HbA1c-ECG Cohort, the set of patients in the train set was split by patient into a train and validation set used to train the HbA1c estimation models. Further details and a description of how each of the data sets was used are described in the Methods.

plotted a calibration curve. Calibration is important because the model’s outputs must serve as probabilities. Additionally, we randomly selected a single encounter for each patient in the ECG Cohort, and repeated the steps mentioned above to build another XGBoost model to estimate the probability of measuring the HbA1c given that an ECG was obtained.

Inverse Probability Adjustment
The probability of acquiring an ECG and HbA1c was obtained by running each sample through the probability of measurement model. To reduce the variability in downstream inverse probability weighted estimates, the most extreme probabilities were truncated to the [0.02-0.98] range. Expanding this range to [0.005-
where less than 10% of the probabilities are truncated, does not significantly affect the estimated model performances. Inverse probability weighting re-weighs each encounter by the inverse probability of acquiring both an ECG and HbA1c. By up-weighting patients that were less likely to have an ECG and HbA1c acquired, greater emphasis was placed on the type of patients for whom we less frequently get to observe ECG and HbA1c values. The inverse probability weighted estimator is described in detail in the Supplement. Further, for training, each encounter was down-weighted for patients with multiple encounters in the dataset by dividing by the number of encounters to ensure that each patient had equal representation in the dataset.

Model Architecture
We implemented a convolutional neural network (CNN) to learn a concise 1-dimensional representation of the ECG time series. This representation was fused with the tabular data then fed through a fully-connected neural network with a softmax output layer to generate the probability of each class. The CNN architecture was based on the current state of the art for arrhythmia detection[8] and is a 34-layer ResNet CNN consisting of 16 residual connections as depicted in S.Figure 6. The input to the network was an 8 x 2,500 matrix, representing the 8 measured leads (lead III and the augmented leads are arithmetically computed) by 10-second duration sampled at 250 Hz (ECGs sampled at 500Hz were down-sampled to 250 Hz).

Model Training and Hyperparameter Tuning
We trained the models using an Adam optimizer for 25 epochs to minimize the categorical cross-entropy loss. After each epoch, we evaluated the models on the validation set. We used a learning rate scheduler that multiplies the learning rate by 0.8 after two epochs of no validation loss improvement. Early stopping was triggered after the validation loss ceased to improve for five epochs.

We used the validation set to select the best network architecture and hyperparameter configuration. We selected the model with the highest inverse-weighted micro-averaged area under the precision-recall curve (AUPRC). We examined the effect of varying the number and dimensionality of the fully-connected layers, considering 1, 2, or 3 layers of dimension 100 or 1000. We considered the effect of temporal dimensionality reduction by modifying the stride lengths to reduce the input 2,500-dimensional vector to either a 10-dimensional vector or an 80-dimensional vector. We also tuned the batch size (32, 64, 128) and learning rate (10^{-5}, 10^{-4}, 10^{-3}). We implemented only the fully-connected portion of the neural network for the Questionnaire model. Analogously, using the inverse-weighted AUPRC on the validation set, we tuned the number and dimensionality of the fully-connected layers as well as the batch size, and learning rate.

Model Evaluation
We used the New-Onset Diabetes Assessment Cohort to assess new-onset diabetes classification. We labeled each encounter with whether the HbA1c measured was ≥ 6.5%, indicating diabetes. We obtained the scores outputted by each model and re-weighted each encounter by their inverse probability of ECG/HbA1c measurement. We constructed the receiver-operator (ROC) and precision-recall (PRC) curves and calculated the area under the ROC (AUC) and PRC (AURPC). We set up three baselines for diabetes screening: 1) the ADA Risk test, 2) the Questionnaire model where we trained a fully-connected Deep Neural Network (DNN) using information easily queried (see S.Table 1) from a patient, and 3) QDiabetes-2018[9]. The Questionnaire model serves as a stronger baseline than the ADA Risk test, representing the performance of an AI-enhanced questionnaire tailored to the population under study. Additionally, the Questionnaire model helps to disentangle the effect of using AI on the demographic features from the additional information provided by including ECG data, such that if the ECG model outperforms the Questionnaire model, then its superior performance cannot simply be attributed to the application of AI to the demographic features. We also considered QDiabetes-2018, a diabetes risk calculator developed for the United Kingdom population, to evaluate the generalizability on a global scale. We did not include additional features added to 2018 version of the QDiabetes risk score because prior validations showed similar performance to prior version of the risk score[9]. QDiabetes-2018 scores were generated using the “QDiabetes” R package.
To evaluate each model against the ADA Risk Test, we binarized the ADA Risk Test score at each level from 1 to 7 and computed the true positive rate (TPR). We then calculated model thresholds that correspond to each ADA Risk Test score TPR, which is used to binarize the model output. We finally assessed the positive predictive value (PPV) at each TPR for all models. In similar fashions, we also calculated model thresholds that correspond to each ADA Risk Test score True Negative Rate (TNR), then assessed the negative predictive value (NPV) at each TNR for all models. As the ADA recommends that people with ADA risk score $\geq 5$ should follow up with their doctor, we paid particular attention to the performance across models at this level. To evaluate the impact on current clinical practice, we utilized the ECG Cohort comprised of patients for whom an ECG was acquired and looked at the percentage of patients for whom an HbA1c test was performed. We calculated the percentage of high-likelihood patients with an HbA1c test at each ADA Risk test derived TPR threshold. Again, we estimated the inverse probability weighted PPV at each threshold. The idea is that if testing rates are low in patients with a high estimated likelihood of diabetes, where the likelihood is indicated by the PPV, then there is an opportunity to improve the quality of care. For all evaluation metrics in this section, we adopted the bootstrap method to calculate confidence intervals as well as p-values when comparing models. We bootstrapped for 100 rounds for each metric, thus p-values have a resolution of $\frac{1}{10^3}$.

**Sensitivity Analysis**
The inferences in the complete outpatient cohort rely on assumptions about the mechanism controlling the acquisition/missingness of both HbA1c and ECG data – that they are missing at random (MAR) given the set of observed risk factors (S.Table 1). Violations of this assumption may arise due to recording errors in the electronic health record or other bits of patient information that goes unrecorded. They can be reflected in the degree to which the probability for inverse weighting differs using the recorded information from the true probability that would render the data MAR. Therefore, we defined a range over which the probabilities are subject to change and examined how the results change in the worst-case scenario, using an approach inspired by Zhao et al.[10]. To compare the models, we thresholded each model using the TPR corresponding to the ADA Risk Test score of $\geq 5$. We then minimized the difference in F1-score, the harmonic mean of the PPV and TPR, between the ECG model and the baseline models. To minimize this difference, all the encounters where the ECG model produced an incorrect classification were up-weighted, while the correctly classified encounters were down-weighted. This procedure causes the estimated performance of the ECG model to decline to a greater extent than that of the baseline models. To put these in context, we examined the effect of significant violations to the MAR assumption — ignoring the contribution of age or the inverse weight entirely (unweighted).

**Prospective Analysis**
We hypothesized the false positives identified by the model still present a higher risk of developing diabetes in the future. To evaluate the model on a longer time horizon, we followed up patients within the New-Onset Diabetes Assessment Cohort who did not develop diabetes at the time, and collected any HbA1c measurements or diabetes diagnoses within one year since the original measurements. We stratified these patients by ADA risk score and the ECG model, and those with ADA risk score $\geq 5$ or the ECG model score greater than the threshold at ADA $\geq 5$ were defined as high risk. We then generated Kaplan-Meier curves and compare the cumulative incidence of future diabetes between group identified by high risk and low risk. The curves were generated using the lifelines Python package. Confidence intervals were calculated using Greenwood’s exponential formula and log-rank tests were used to compute p-values.

**Ethics Statement and Declaration of Interests**
This study was approved by the Institutional Review Board (IRB) of NYU Grossman School of Medicine under IRB protocol ID#120-00348. The study did involve human subjects. The authors declare no competing financial or non-financial interests.

**Patient and Public Involvement**
No patients/public were involved in the research.
Figure 3: **New-onset diabetes assessment results.** (a) The ECG model is more discriminative of new-onset diabetes as indicated by the IPW receiver operator curve (ROC). (b) The ECG model has a higher positive predictive value (PPV) for detecting new-onset diabetes at the true positive rate (TPR) corresponding to the ADA’s Risk Test threshold of ≥5. (c) Among patients who receive an ECG in the clinic, most patients identified as highly likely to have new-onset diabetes (bottom) do not receive an HbA1c test (top). (d) The ECG model is robust to inaccuracies in estimating the probability of ECG/HbA1c acquisition, requiring relatively large re-weighting schemes to invalidate the superiority of the ECG model in terms of the F1-score (left) and PPV (right). The sensitivity weight determines the multiple by which the inverse probability weights can be altered. The ECG model’s performance (F1-score) is selectively minimized as the sensitivity weight increases. The effect of extreme inaccuracies, omitting the contribution of age or the inverse weight entirely (unweighted), is provided as context to indicate that an invalidating re-weighting scheme would be implausible.

**Results**
**Study Population**
A single encounter was randomly selected for each patient in the Outpatient Cohort, yielding 2,479,891 encounters. Both an ECG and HbA1c were acquired in 1.0% of these encounters. The patient characteristics of the data set can be found in S.Table 3. We would expect that the patient characteristics do not differ significantly across sets, though due to random chance they may appear significantly different. The ECG-HbA1c Cohort, which contained encounters from the Outpatient Cohort with both ECG and HbA1c obtained, consisted of 248,725 encounters across 200,985 unique patients. HbA1c values taken at encounter were <5.7% in 132,518 encounters (53.3%), 5.7-6.4% in 62,691 encounters (25.2%), 6.5-7.9% in 37,045 encounters, and >8.0% in 16,471 encounters (6.6%). S.Table 2 describes the patient characteristics for each partition. The New-Onset Diabetes Assessment Cohort consists of 34,106 encounters involving 30,593 patients, of which 4.9% have an HbA1c ≥ 6.5% (S.Table 4)

**Model Performance**
Diabetes screening was evaluated on the New-Onset Diabetes Assessment Cohort. The results are shown in Figure 3. The ECG model, which takes in age, sex, race, ethnicity, BMI, and ECG, achieved the best performance (Figure 3a) AUC, 0.80 [95% CI, 0.80-0.81]), outperforming scores based on using the ADA Risk test (AUC, 0.69 [95% CI, 0.69-0.70]), Questionnaire model (AUC, 0.76 [95% CI, 0.75-0.77]), and QDiabetes-2018 AUC, 0.69 [95% CI, 0.68-0.70]) Comparing positive predictive value (PPV) across models (Figure 3b), especially at ADA ≥ 5 (TPR 70.5%), the ECG model showed significantly superior precision (PPV, 0.13 [95% CI, 0.12-0.14]; p-value < 0.01) than ADA Risk Test (PPV, 0.09 [95% CI, 0.08-0.09]; p-value < 0.01) and other baselines (the Questionnaire model (PPV, 0.11 [95% CI, 0.10-0.11]; p-value < 0.01); QDiabetes-2018 (PPV, 0.08 [95% CI, 0.08-0.09]; p-value < 0.01)), and is consistent with prior assessment of the ADA Risk Test[11].

The Negative Predictive Value (NPV) comparisons are shown in Figure 4. Again at ADA ≥ 5 (TNR 58.7%), the ECG model also had superior NPV (NPV, 0.99 [95% CI, 0.99-0.99]) than ADA Risk Test (NPV, 0.97 [95% CI, 0.97-0.97]; p-value < 0.01) and other baselines (the Questionnaire model (NPV, 0.98 [95% CI, 0.98-0.98]; p-value < 0.01); QDiabetes-2018 (PPV, 0.97 [95% CI, 0.97-0.97]; p-value < 0.01))

Using the same model thresholds, we evaluated how well the ECG model can automatically screen patients that receive an ECG. We generated a pseudo-population that represents the ECG Cohort, where an ECG was acquired for patients without a prior history of diabetes. We found that the ECG model outperformed (PPV 14.8% [95% CI, 13.7-15.7%]) the ADA Risk test (PPV 8.5% [95% CI, 8.0-8.7%]) (Figure 3c). Of the 112,580 patients in the ECG Cohort, 95,629 patients were not assessed with an HbA1c test. The ECG model identified 36,355 of these patients as highly likely to have diabetes. The estimated PPV implies that 14.8% of this cohort or 5,380 additional patients would have been newly diagnosed with diabetes had the ECG been applied clinically to this cohort.

S.Figure 7 plots the calibration curve for measurement probability model on the held-out test set, which shows the measurement probability model is well-calibrated.

**Sensitivity Analysis**
Figure 3d depicts that in the worst-case scenario, where the performance (F1-score; harmonic mean of the TPR and PPV[12]) of the ECG model is selectively minimized, the importance placed on each incorrectly classified encounter would have to be increased by a factor of 1.25 and decreased by a factor of 0.8 for each correctly identified encounter to invalidate the results. To put these in context, we examined the effect of significant violations to the MAR assumption — ignoring the contribution of age or the inverse weight entirely (unweighted). We found that neither re-weighting altered the performance of the ECG model nearly as much, suggesting that such an invalidating re-weighting scheme is implausible.
Comparison with Cardiac Electrophysiologists

Lastly, we compared the AI system to human interpretation of the ECG data. Two cardiac electrophysiologists screened 100 randomly sampled ECGs from the New-Onset Diabetes Assessment Cohort and estimated the likelihood of diabetes on a scale from 1 to 5. We enriched the dataset such that 50% of the ECGs belonged to patients with diabetes (HbA1c ≥6.5%) to increase the difficulty of screening and the statistical power, as is typical for such studies[13]. We found that the physicians, with AUCs of 0.58 and 0.61, underperformed a deep neural network model that only uses ECGs (AUC 0.82), suggesting that the task is beyond the current understanding of the cardiac electrophysiologists.

Prospective Analysis

Kaplan-Meier curves were generated on the subset of the New-Onset Diabetes Assessment Cohort who did not develop diabetes at the time (Figure 5). The groups with ADA ≥ 5 or the ECG model score higher than the threshold set at same TPR at ADA ≥ 5 were defined as high-risk, and the rest were low-risk. Looking one year after the encounter, groups identified as high risk by either the ECG Model or the ADA Risk Test presented higher cumulative incidence of developing diabetes within one year than low-risk group. Groups identified as high risk by the ECG Model presented higher three-fold increase in future risk of diabetes compared to the low-risk group (ECG Model high risk cumulative incidence, 0.12 [95%CI, 0.09-0.15]; ECG Model low risk cumulative incidence, 0.04 [95%CI, 0.03-0.05]; p-value < 0.005). Group identified as high risk by the ECG Model had significant higher cumulative incidence of future diabetes than high risk group identified by ADA ≥ 5 in one year (ADA high risk cumulative incidence, 0.08 [95%CI, 0.07-0.11]; p-value 0.01). On the other hand, low risk groups identified by either model had similar cumulative incidence levels and were lower compared to high-risk groups (ECG Model cumulative incidence, 0.04 [95%CI, 0.03-0.05]; ADA low-risk cumulative incidence, 0.03 [95%CI, 0.02-0.05]; p-value 0.93). This suggested patient who did not have diabetes at the time of prediction and identified by the model as high risk presented higher rated of future onset compared to those who were not identified.

![Figure 4: Negative Predictive Value Comparisons](image)

At ADA ≥ 5, the ECG model also had superior NPV (NPV, 0.99 [95% CI, 0.99-0.99]) than ADA Risk Test (NPV, 0.97 [95% CI, 0.97-0.97]; p-value <0.01) and other baselines (the Questionnaire model (NPV, 0.98 [95% CI, 0.98-0.98]; p-value <0.01); QDiabetes-2018 (PPV, 0.97 [95% CI, 0.97-0.97]; p-value < 0.01))
Figure 5: **Kaplan-Meier Curves comparing the ECG Model and ADA Risk Test** The curves were generated on a subset of the New-Onset Diabetes Assessment Cohort who did not have diabetes at the time of encounter. Patients were grouped as high-risk if their ADA Risk Test $\geq 5$ or the ECG Model score is greater than the threshold at the TPR that matches ADA $\geq 5$. High-risk group defined by both ADA Risk Test and the ECG Model presented higher incidence for future diabetes onset in one year compared to the low risk group. High-risk group identified by the ECG Model showed significant higher cumulative incidence compared to the high-risk group identified by the ADA Risk Test (ECG Model high risk cumulative incidence, 0.12 [95%CI, 0.09-0.15]; ADA high risk cumulative incidence, 0.08 [95%CI, 0.07-0.11]; p-value 0.01)

**Discussion**

Undiagnosed diabetes leads to increased morbidity and a higher overall burden on the healthcare system[14, 15]. The capacity to screen for diabetes is primarily limited by the frequency of patient interactions with the healthcare system. Improving this capacity requires better use of existing patient interactions in clinical settings and an improved capacity to screen for diabetes in the community. Such improvements will be crucial for identifying the 8.5 million US adults with undiagnosed type 2 diabetes[1].

This work demonstrates how diabetes assessment benefits from the incorporation of ECGs. We show that ECG-based assessment outperforms questionnaire-based assessment, achieving a higher PPV (13% vs. 9% for the ADA risk score; p-value <0.001) at the desired TPR (70.5%). The higher PPV implies that using the ECG reduces false alerts relative to the ADA risk score. We also show that when applied in the outpatient setting, the ECG model would improve the quality of clinical care and screening for diabetes, where 83% of high-likelihood patients did not have their HbA1c assessed. Community-wide AI-enhanced ECG diabetes assessment can be carried out via mobile devices that collect single-lead (Lead-I) ECGs. We found that an AI-enabled single-lead ECG (Lead I) retains much of the discriminate performance relative to the 12-lead ECG model (AUC, 0.78 [95% CI, 0.77-0.79] vs. 0.80 [95% CI, 0.80-0.81]). These findings suggest that an AI-enabled ECG system could be utilized both at the community level and within outpatient clinics to automate the identification of patients who are likely to have diabetes. With the improved capacity for
diabetes screening enabled by the ECG-based assessment, more diabetes would be captured and the rate of undiagnosed diabetes would go down.

A strength of our study lies in our methodology for training a model to screen for diabetes in yet unseen populations, recently described as integrative modeling[16]. Practitioners require a large amount of data to train deep learning models; therefore, studies rely on retrospective study designs. Researchers look for patient encounters in a retrospective dataset where the input variable (i.e., ECGs) can be paired with an outcome variable (i.e., HbA1c)[4, 7]. Yet, it is likely that patient risk factors influence the measurement of these variables. This influence means evaluations under the retrospective population, where both the input and output are known, do not match evaluations under the complete population of interest.

In our work, we generated a pseudo-population representative of the complete outpatient population using IPW. This procedure ensured that we optimized over the intended population during training and evaluated our models’ ability to screen the general outpatient population for diabetes. Lastly, we evaluated the sensitivity of our results to changes in the pseudo-population assessed to understand the degree to which the results would have to change to invalidate our findings. These steps help ensure that further prospective evaluation would yield similar results. The framework we layout for handling missing data using IPW during model training and evaluation will be of use in other domains that make use of retrospective data to build AI models[17, 18].

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Author contributions statement

N.J. and R.R. conceived the study. N.J. and H.Z. designed the data processing and model training pipeline. N.J., H.Z and A.P. performed the sensitivity analysis. L.J. and L.G. provided clinical expertise and manually reviewed the data. Y.A. provided advise for model evaluation. N.J., H.Z and R.R. wrote the manuscript with inputs from all authors.

Data Availability

Due to specific institutional requirements governing privacy protection, data used in this study will not be available.

Code Availability

Code for model development and evaluation is available upon reasonable request.

Appendix

The results were reported following the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) Statement.[19].
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## Suppement

### Clinical Variables

| Covariate                        | Source   | ECG Model | Questionnaire Model | QDiabetes-2018 | Propensity Score Models |
|----------------------------------|----------|-----------|---------------------|----------------|-------------------------|
| **Demographics (During or prior to Encounter)** |          |           |                     |                |                        |
| Age                              | Epic     | ✓         |                     |                | ✓                       |
| Sex                              | Epic     | ✓         |                     |                | ✓                       |
| Race                             | Epic     | ✓         |                     |                | ✓                       |
| Ethnicity                        | Epic     | ✓         |                     |                | ✓                       |
| **Vital Signs (During or prior to Encounter)** |          |           |                     |                |                        |
| BMI                              | Epic     | ✓         |                     |                | ✓                       |
| Blood Pressure                   | Epic     | ✓         |                     |                | ✓                       |
| **Personal History (During or prior to Encounter)** |          |           |                     |                |                        |
| Physical Activity                | ICD-10 (E72.3) | ✓         |                     |                | ✓                       |
| Smoking History                  | Patient Dim |          |                     |                |                         |
| Diabetes                         | Epic     | ✓         |                     |                |                         |
| Cardiovascular Diseases          | Epic     | ✓         |                     |                |                         |
| Labs (Prior to Encounter)        |          |           |                     |                |                         |
| HbA1c                            | Epic     | ✓         |                     |                |                         |
| LDL                              | Epic     |           |                     |                |                         |
| TG                               | Epic     |           |                     |                |                         |
| **Diagnoses (Prior to Encounter)** |          |           |                     |                |                         |
| Type 1 Diabetes                  | ICD-10 (E10) |          |                     |                |                         |
| Type 2 Diabetes                  | ICD-10 (E11) |          |                     |                |                         |
| Gestational diabetes             | ICD-10 (O24.4) |          |                     |                |                         |
| PCOS                             | ICD-10 (E28.2) |          |                     |                |                         |
| Atherosclerosis                  | ICD-10 (I70,175) |          |                     |                |                         |
| Ischemic Heart disease           | ICD-10 (I20-26) |          |                     |                |                         |
| Heart Failure                    | ICD-10 (I50) |          |                     |                |                         |
| Cerebrovascular disease          | ICD-10 (I60-69) |          |                     |                |                         |
| Peripheral vascular disease      | ICD-10 (I73) |          |                     |                |                         |
| Arrhythmia                       | ICD-10 (I48.49) |          |                     |                |                         |
| Hypertension                     | ICD-10 (I10.16) |          |                     |                |                         |
| Hypercholesterolemia             | ICD-10 (E78.0) |          |                     |                |                         |
| Hyperlipidemia                   | ICD-10 (E78.2-78.6) |          |                     |                |                         |
| Hyperglycemia                    | ICD-10 (E78.1,R73) |          |                     |                |                         |
| **Diabetic Complications (Prior to Encounter)** |          |           |                     |                |                         |
| Retinopathy                      | ICD-10 (E11.3) |          |                     |                |                         |
| Neuropathy                       | ICD-10 (E11.4) |          |                     |                |                         |
| Nephropathy                      | ICD-10 (E11.2) |          |                     |                |                         |
| Other diabetic complications     | ICD-10 (E13) |          |                     |                |                         |
| **Acute Conditions (During Encounter)** |          |           |                     |                |                         |
| Polydipsia                       | ICD-10 (R64.1) |          |                     |                |                         |
| Polyuria                         | ICD-10 (R55) |          |                     |                |                         |
| Polyphagia                       | ICD-10 (R63.2) |          |                     |                |                         |
| Weight Loss                      | ICD-10 (R63.4) |          |                     |                |                         |
| Chest pain                       | ICD-10 (R07.1,R07.8-9) |          |                     |                |                         |
| SOB                              | ICD-10 (R06) |          |                     |                |                         |
| Dizziness                        | ICD-10 (R42) |          |                     |                |                         |
| **Diabetic Medications (Currently Prescribed)** |          |           |                     |                |                         |
| Insulins                         | Epic     |           |                     |                |                         |
| Amylinomimetic                   | Epic     |           |                     |                |                         |
| Biguanides                       | Epic     |           |                     |                |                         |
| Alpha-glucosides inhibitors      | Epic     |           |                     |                |                         |
| DPP-4 inhibitors                 | Epic     |           |                     |                |                         |
| GLP-1 receptor agonists          | Epic     |           |                     |                |                         |
| Meglitinides                     | Epic     |           |                     |                |                         |
| SGLT 2 inhibitors                | Epic     |           |                     |                |                         |
| Sulfonylureas                    | Epic     |           |                     |                |                         |
| Thiazolidinediones               | Epic     |           |                     |                |                         |
| **Cardiovascular Medications (Currently Prescribed)** |          |           |                     |                |                         |
| ACE inhibitors                   | Epic     |           |                     |                |                         |
| A-H Receptor Blockers            | Epic     |           |                     |                |                         |
| Beta blockers                    | Epic     |           |                     |                |                         |
| Cholesterol lowering             | Epic     |           |                     |                |                         |
| Calcium Channel Blockers         | Epic     |           |                     |                |                         |
| Diuretics                        | Epic     |           |                     |                |                         |
| Vasodilators                     | Epic     |           |                     |                |                         |
| Digitalis Preparations           | Epic     |           |                     |                |                         |
| Antiplatelet                     | Epic     |           |                     |                |                         |
| Anticoagulants                   | Epic     |           |                     |                |                         |
| Antihypertensives                | Epic     |           |                     |                |                         |
| Corticosteroids                  | Epic     |           |                     |                |                         |

Table 1: List of Covariates. For each covariate, the data source is provided. For each model, the set of inputs are identified. The covariate grouping and the corresponding collection period are defined.
| Patient Characteristics | Missing | Overall | Test | Train | Validation | P-Value |
|-------------------------|---------|---------|------|-------|------------|---------|
| Age, median [Q1,Q3]     | 381     | 248723  | 49866| 149334| 49523      | 0.736   |
| Sex, n (%)              | 1908    | 61.4 [50.1,71.6] | 61.3 [50.1,71.6] | 61.4 [50.1,71.6] | 61.3 [50.1,71.7] | 0.149   |
| Smoking, n (%)          | 23813   | 125064 (50.3) | 24914 (50.0) | 75101 (50.3) | 25049 (50.6) | 0.292   |
| Race, n (%)             | 52861   | 155687 (79.5) | 31473 (79.9) | 93267 (79.4) | 30947 (79.4) | 0.083   |
| Ethnicity, n (%)        | 194395  | 4830 (8.9) | 977 (9.0) | 2865 (8.8) | 988 (9.1) | 0.538   |
| BMI, median [Q1,Q3]     | 28805   | 124.0 [116.0,136.0] | 124.0 [116.0,136.0] | 124.0 [116.0,136.0] | 124.0 [116.0,136.0] | 0.769   |
| Hypertension, n (%)     | 135563  | 716289 (47.8) | 17819 (47.8) | 71453 (47.8) | 23656 (47.8) | 0.925   |
| Glycated hemoglobin, n (%) | 125429 | 31.0 [25.0,32.9] | 31.0 [25.0,32.9] | 31.0 [25.0,32.9] | 31.0 [25.0,32.9] | 0.835   |
| Gestational diabetes, n (%) | 107265 | 93.0 [71.0,119.0] | 93.0 [71.0,119.0] | 93.0 [71.0,119.0] | 93.0 [71.0,119.0] | 0.392   |
| Polycystic ovarian syndrome, n (%) | 99613 | 109.0 [78.0,157.0] | 109.0 [78.0,157.0] | 109.0 [78.0,157.0] | 109.0 [78.0,157.0] | 0.837   |
| eGFR > 60 mL/min/1.73m^2, n (%) | 83811 | 141407 (85.7) | 28304 (85.7) | 84834 (85.7) | 28269 (85.9) | 0.650   |

Table 2: Patient Characteristics for the HbA1c-ECG Cohort Stratified by Data Split.
### Table 3: Patient Characteristics for the Outpatient Cohort used to build the probability of HbA1c/ECG acquisition model stratified by whether both an ECG and HbA1c were measured.

| Missing Overall | Missing ECG or HbA1c | HbA1c/ECG Measured | P-Value |
|-----------------|----------------------|--------------------|---------|
| n               | 2479891              | 2454992            | 243899  |
| Age, median [Q1,Q3] | 51.4 [35.6,65.8]     | 51.4 [35.6,65.8]   | 53.3 [41.6,64.3] | <0.001 |
| Sex, n (%)      | Female               | 1281721 (51.7)     | 1270130 (51.7)   | 11591 (46.6) | <0.001 |
| Smoking, n (%)  | Never                | 1306192 (67.9)     | 1290412 (67.9)   | 15780 (66.8) | <0.001 |
| Current         | 451381 (23.5)        | 445723 (23.5)      | 5658 (24.0)      |            |
| Race, n (%)     | White                | 1226853 (80.1)     | 1212840 (80.2)   | 14013 (78.7) | <0.001 |
|                | Black                | 228995 (15.0)      | 226132 (14.9)    | 2863 (16.1)  |            |
|                | Asian                | 64723 (4.2)        | 63910 (4.2)      | 813 (4.6)    |            |
|                | Pacific Islander     | 5090 (0.3)         | 5062 (0.3)       | 28 (0.2)     |            |
|                | Multiracial          | 5081 (0.3)         | 4995 (0.3)       | 86 (0.5)     |            |
| Ethnicity, n (%)| Hispanic             | 32060 (10.1)       | 32942 (10.1)     | 258 (10.1)   | 1.000      |
|                | BMI, median [Q1,Q3]  | 26.1 [22.4,30.5]   | 26.1 [22.4,30.4] | 27.7 [24.3,32.0] | <0.001 |
|                | Sys. BP (mmHg), median [Q1,Q3] | 120.0 [110.0,130.0] | 120.0 [110.0,130.0] | 122.0 [112.0,133.0] | <0.001 |
|                | Dia. BP (mmHg), median [Q1,Q3] | 74.0 [68.0,80.0]   | 74.0 [68.0,80.0] | 78.0 [70.0,82.0] | <0.001 |
|                | HbA1c (%), median [Q1,Q3] | 5.6 [5.3,6.0]      | 5.6 [5.3,6.0]    | 5.6 [5.3,6.0] | <0.001 |
|                | eGFR > 60 mL/min/1.73m², n (%) | 1776336             | 630131 (90.6)    | 637768 (90.6) | 7637 (92.2) | <0.001 |
|                | Type 1 DM, n (%)     | 16253 (0.7)        | 16048 (0.7)      | 205 (0.8)    | 0.001      |
|                | Polycystic ovarian syndrome, n (%) | 16594 (0.7)       | 16488 (0.7)     | 106 (4.4)    | 0.001      |
|                | Lack of physical activity, n (%) | 597 (0.0)         | 593 (0.0)       | 4 (0.0)      | 0.540      |
|                | Hypertension, n (%)  | 492337 (19.9)      | 485875 (19.8)    | 6462 (26.0)  | <0.001     |
|                | Hypercholesterolemia, n (%) | 172665 (7.0)       | 169899 (6.9)    | 2766 (11.1)  | <0.001     |
|                | Hyperlipidemia, n (%) | 417523 (16.8)      | 411109 (16.7)   | 6414 (25.8)  | <0.001     |
|                | Cardiovascular disease, n (%) | 54639 (2.2)        | 54221 (2.2)     | 418 (1.7)    | <0.001     |
|                | Heart failure, n (%) | 54059 (2.2)        | 53521 (2.2)     | 538 (2.2)    | 0.852      |
|                | Ischemic heart disease, n (%) | 179823 (7.3)       | 177698 (7.2)    | 2125 (8.5)   | <0.001     |
|                | Peripheral vascular disease, n (%) | 48818 (2.0)       | 48225 (2.0)    | 593 (2.4)    | <0.001     |
|                | Arrhythmia, n (%)    | 151163 (6.1)       | 149755 (6.1)    | 1408 (5.7)   | 0.004      |
|                | Atherothrombosis, n (%) | 47156 (1.9)         | 46647 (1.9)     | 509 (2.0)    | 0.102      |
|                | Cerebrovascular disease, n (%) | 87432 (3.5)        | 86447 (3.5)     | 985 (4.0)    | <0.001     |
|                | Polyuria, n (%)      | 1355 (0.1)         | 1353 (0.1)      | 2 (0.0)      | 0.002      |
|                | Polydipsia, n (%)    | 170 (0.0)          | 164 (0.0)       | 6 (0.0)      | 0.008      |
|                | Polyphagia, n (%)    | 3345 (0.1)         | 3353 (0.1)      | 2 (0.0)      | 0.002      |
|                | Polyuria, n (%)      | 12725 (0.5)        | 12161 (0.5)     | 564 (2.3)    | <0.001     |
|                | Weight loss, n (%)   | 1341 (0.2)         | 1344 (0.2)      | 124 (0.5)    | <0.001     |
|                | Chest pain, n (%)    | 25046 (1.0)        | 23787 (1.0)     | 1259 (5.1)   | <0.001     |
|                | Dyspnea, n (%)       | 45807 (1.8)        | 44844 (1.8)     | 1323 (5.3)   | <0.001     |
|                | Dizziness, n (%)     | 15651 (0.6)        | 14575 (0.6)     | 476 (1.9)    | <0.001     |
|                | Diabetic retinopathy, n (%) | 11832 (0.5)      | 11687 (0.5)     | 145 (0.6)    | 0.018      |
|                | Diabetic nephropathy, n (%) | 16734 (0.7)       | 16511 (0.7)     | 223 (0.9)    | <0.001     |
|                | Diabetic neuropathy, n (%) | 19458 (0.8)        | 19207 (0.8)     | 251 (1.0)    | <0.001     |
|                | Other diabetic complications, n (%) | 11809 (0.5)       | 11608 (0.5)    | 201 (0.8)    | <0.001     |
|                      | Missing | Overall                | Diabetic | Normal                | P-Value |
|----------------------|---------|------------------------|----------|-----------------------|---------|
| **n**                | 34106   | 1682                   | 32424    |                       | <0.001  |
| **Age, median [Q1,Q3]** | 65      | 65.0 [53.6,71.4]       | 57.1 [45.4,67.6] |                       | <0.001  |
| **Sex, n (%)**       | 17713   | 736 (43.8)             | 16977 (52.4) |                       | <0.001  |
| **Smoking, n (%)**   | 21425   | 965 (59.3)             | 20460 (64.4) |                       | <0.001  |
| **Race, n (%)**      | 21539   | 896 (70.2)             | 20643 (81.3) |                       | <0.001  |
| **BMI, median [Q1,Q3]** | 576     | 70.0 [67.9]            | 57.1 [45.4,67.6] |                       | <0.001  |
| **Sys. BP (mmHg), median [Q1,Q3]** | 11882   | 122.0 [114.0,134.0]    | 122.0 [112.0,133.0] |                       | <0.001  |
| **Dias. BP (mmHg), median [Q1,Q3]** | 19267   | 80.0 [71.0,85.0]       | 80.0 [71.0,85.0] |                       | <0.001  |
| **HbA1c (%), median [Q1,Q3]** | 17101   | 9.0 [7.5,8.2]          | 9.0 [7.5,8.2] |                       | <0.001  |
| **Prior HbA1c (%), median [Q1,Q3]** | 15892   | 11.0 [9.0,14.0]        | 11.0 [9.0,14.0] |                       | <0.001  |
| **Tot. chol. (mg/dL), median [Q1,Q3]** | 14058   | 185.0 [159.0,211.0]    | 185.0 [159.0,211.0] |                       | 0.011   |
| **HDL (mg/dL), median [Q1,Q3]** | 124     | 54.0 [45.0,66.0]       | 54.0 [45.0,66.0] |                       | <0.001  |
| **LDL (mg/dL), median [Q1,Q3]** | 90      | 55.0 [46.0,67.0]       | 55.0 [46.0,67.0] |                       | <0.001  |
| **eGFR > 60 mL/min/1.73m2, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **FHx cardiovascular disease, n (%)** | 1167    | 91 (5.4)               | 91 (5.4) |                       | <0.001  |
| **FHx heart failure, n (%)** | 1167    | 91 (5.4)               | 91 (5.4) |                       | <0.001  |
| **Ischemic heart disease, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Peripheral vascular disease, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Arrhythmia, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Atherosclerosis, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Cerebrovascular disease, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Polyuria, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Weight loss, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Chest pain, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Diabetes retinopathy, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Diabetic nephropathy, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |
| **Other diabetic complications, n (%)** | 229     | 665 (39.0)             | 665 (39.0) |                       | <0.001  |

Table 4: Patient Characteristics for the New-Onset Diabetes Assessment Cohort stratified by whether the patient is newly diagnosed with diabetes (HbA1c >6.4).
|                                | Missing     | Overall     |
|--------------------------------|-------------|-------------|
| n                              | 112580      |             |
| Age, median [Q1, Q3]           | 2192        | 58.4 [45.5, 70.2] |
| Sex, n (%)                     | Female 60348 (53.6) |         |
| Smoking, n (%)                 | Never 67237 (62.5) |         |
|                                | Former 32301 (30.0) |         |
|                                | Current 8025 (7.5) |         |
| Race, n (%)                    | White 73702 (83.8) |         |
|                                | Black 11033 (12.5) |         |
|                                | Asian 2736 (3.1) |         |
|                                | Multiracial 276 (0.3) |         |
|                                | Pacific Islander 172 (0.2) |         |
| Ethnicity, n (%)               | Hispanic 1906 (9.1) |         |
| BMI, median [Q1, Q3]           | 14027       | 27.1 [23.7, 31.2] |
| Systolic BP (mmHg), median [Q1, Q3] | 5264       | 122.0 [112.0, 134.0] |
| Diastolic BP (mmHg), median [Q1, Q3] | 5264       | 76.0 [70.0, 80.0] |
| HBa1c (%), median [Q1, Q3]     | 94245       | 5.5 [5, 5.2, 5.8] |
| Prior HBa1c (%), median [Q1, Q3] | 76015       | 5.5 [5, 5.2, 5.8] |
| Total cholesterol (mg/dL), median [Q1, Q3] | 60588      | 185.0 [158.0, 212.0] |
| HDL (mg/dL), median [Q1, Q3]   | 80698       | 55.0 [45.0, 67.0] |
| LDL (mg/dL), median [Q1, Q3]   | 73681       | 102.0 [80.0, 126.0] |
| TG (mg/dL), median [Q1, Q3]    | 70639       | 99.0 [71.0, 141.0] |
| eGFR > 60 mL/min/1.73m2, n (%) | 58586       | 49006 (90.8) |
| Hyperglycemia, n (%)           | 18111       | 16.1 (16.1) |
| FHx cardiovascular disease, n (%) | 46175       | 41.0 (41.0) |
| FHx Diabetes, n (%)            | 25960       | 23.1 (23.1) |
| Gestational Diabetes, n (%)    | 253         | 0.2 (0.2)  |
| Polycystic ovarian syndrome, n (%) | 668         | 0.6 (0.6)  |
| Poor diet, n (%)               | 16          | 0.0 (0.0)  |
| Lack of physical activity, n (%) | 26          | 0.0 (0.0)  |
| Hypertension, n (%)            | 41980       | 37.3 (37.3) |
| Hypercholesterolemia, n (%)    | 17520       | 15.6 (15.6) |
| Hyperlipidemia, n (%)          | 38101       | 33.8 (33.8) |
| Cardiovascular disease, n (%)  | 4816        | 4.3 (4.3)  |
| Heart failure, n (%)           | 5147        | 4.6 (4.6)  |
| Ischemic heart disease, n (%)  | 17335       | 15.4 (15.4) |
| Peripheral vascular disease, n (%) | 3825       | 3.4 (3.4)  |
| Arrhythmia, n (%)              | 15661       | 13.9 (13.9) |
| Atherosclerosis, n (%)         | 4239        | 3.8 (3.8)  |
| Cerebrovascular disease, n (%) | 7875        | 7.0 (7.0)  |
| Polydipsia, n (%)              | 11          | 0.0 (0.0)  |
| Polyphagia, n (%)              | 41          | 0.0 (0.0)  |
| Polyuria, n (%)                | 1303        | 1.2 (1.2)  |
| Weight loss, n (%)             | 351         | 0.3 (0.3)  |
| Chest pain, n (%)              | 5711        | 5.1 (5.1)  |
| Dyspnea, n (%)                 | 6305        | 5.6 (5.6)  |
| Dizziness, n (%)               | 2083        | 1.9 (1.9)  |
| Diabetic retinopathy, n (%)    | 52          | 0.0 (0.0)  |
| Diabetic nephropathy, n (%)    | 177         | 0.2 (0.2)  |
| Diabetic neuropathy, n (%)     | 179         | 0.2 (0.2)  |
| Other diabetic complications, n (%) | 216         | 0.2 (0.2)  |

Table 5: Patient Characteristics for the ECG Cohort used to evaluate the utility of the ECG for estimating the likelihood of diabetes.
Figure 6: Diagram of the ECG model architecture.
Probability of Measurement Modeling

Inverse Probability Weighted Estimator

Let $y \in \{0, 1, 2, 4\}$ be a categorical variable indicating that a patient’s HbA1c is <5.7%, 5.7-6.4%, 6.5-7.9%, or >8.0%. Let $x$ represent a patient’s ECG, $z$ represent a patient’s clinical factors driving the acquisition of an HbA1c and ECG, and $m \in \{0, 1\}$ indicate whether or not an ECG and HbA1c were acquired. ECG and HbA1c are observed only when acquired by a physician, indicated that access to samples $y, x, z \sim p(x, y, z | m = 1)$ are available. However, we want to estimate the model performance (the mean of some loss function $f$) on the complete distribution $p(x, y, z); \mathbb{E}_{x,y,z \sim p(x,y,z)}[f(x,y)]$. To achieve this using samples from only from $p(x, y, z | m = 1)$, we express the expectation on the complete distribution as a weighted expectation on the observed distribution.

First, as $f(x,y)$ does not depend on $m$, $\mathbb{E}_{x,y,z \sim p(x,y,z)}[f(x,y)] = \mathbb{E}_{x,y,z \sim p(x,y,z,m)}[f(x,y)]$. The latter expectation can be expanded using the law of total expectation when conditioning on the missingness indicator $m$ as follows:

$$\mathbb{E}_{x,y,z \sim p(x,y,z,m)}[f(x,y)] = \mathbb{E}_{z \sim p(z|m=0)} \mathbb{E}_{x,y \sim p(x,y|z,m=0)} [f(x,y) | m = 0] p(m = 0)$$

$$+ \mathbb{E}_{z \sim p(z|m=1)} \mathbb{E}_{x,y \sim p(x,y|z,m=1)} [f(x,y) | m = 1] p(m = 1)$$

The first expectation on the right hand side is with respect to the observed data distribution and therefore can be directly estimated using the observed data. Focusing instead on the second expectation on the left hand side, we make the MAR assumption that $y, x \perp m | z$ and expand it as follows:

$$\mathbb{E}_{x,y,z \sim p(x,y,z,m)}[f(x,y) | m = 0] p(m = 0) = \mathbb{E}_{z \sim p(z|m=0)} \mathbb{E}_{x,y \sim p(x,y|z,m=0)} [f(x,y) | m = 0, z] p(m = 0)$$

$$= \mathbb{E}_{z \sim p(z|m=0)} \mathbb{E}_{x,y \sim p(x,y|z,m=0)} [f(x,y) | m = 0] p(m = 0)$$

$$= \int x, y \sim p(x,y|z) \left[ \frac{p(m = 0 | z)p(z)}{p(m = 1 | z)p(z)} f(x,y) | z \right] p(m = 0)dz$$

$$= \int x, y \sim p(x,y|z) \left[ \frac{p(m = 0 | z)p(z)}{p(m = 1 | z)p(z)} f(x,y) | z \right] p(m = 1)dz$$

Combining the two terms results in the following:

$$\mathbb{E}_{x,y,z \sim p(x,y,z,m)}[f(x,y)] = \mathbb{E}_{x,y,z \sim p(x,y,z,m)} [f(x,y) | m = 1] p(m = 1)$$

$$+ \mathbb{E}_{x,y,z \sim p(x,y,z,m)} \left[ \frac{p(m = 0 | z)}{p(m = 1 | z)} f(x,y) \right] p(m = 1)$$

$$= \mathbb{E}_{x,y,z \sim p(x,y,z,m)} \left[ \frac{1 + p(m = 0 | z)}{p(m = 1 | z)} f(x,y) \right] p(m = 1)$$

$$= \mathbb{E}_{x,y,z \sim p(x,y,z,m)} \left[ \frac{p(m = 1 | z)}{p(m = 1 | z)} + \frac{p(m = 0 | z)}{p(m = 1 | z)} f(x,y) \right] p(m = 1)$$

$$= \mathbb{E}_{x,y,z \sim p(x,y,z,m)} \left[ \frac{1}{p(m = 1 | z)} f(x,y) \right] p(m = 1)$$
The estimator above is known as the inverse probability weighted (IPW) estimator. We parametrically model \( p(m = 1 \mid z) \) and use the IPW estimator in order to estimate the expected performance in the complete population using only the data observed.

Calibration

Figure 7: Calibration curve for the probability of measurement model on held-out test data. The probability estimates outputted by the model plotted against the true frequency of the positive label for binned probabilities. Plotted below the curve is a histogram depicting the number of encounters included in each bin. The low calibration error and similarity to a perfectly calibrated curve indicate that the model is well-calibrated. Further, bins with small calibration errors tend to have more samples.
Figure 8: Area under the receiver operator curve (AUROC) for a model using single lead ECGs. The AUROCs are plotted for each method, with the results for a model using single-lead ECGs plotted in purple. These results indicate that the single-lead ECG model outperforms both the ADA Risk test and the Questionnaire model; however, it under-performs the 12-Lead ECG model when estimating the likelihood of new-onset diabetes.