Clinical and Translational Science

ARTICLE OPEN ACCESS

Machine Learning-Based Prediction of Drug-Induced QTc Changes in a Large Finnish Biobank Cohort

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Received: 21 December 2025 | **Revised:** 7 March 2026 | **Accepted:** 20 April 2026

Keywords: biobank research | drug safety | machine learning | polygenic risk score | QT interval

ABSTRACT

Prolongation of the QT interval is a known precursor to serious arrhythmias and sudden cardiac death, often triggered by medication use. Current medication risk evaluation platforms rely on literature-based synthesis and may lag behind real-world developments. We aimed to evaluate whether a machine learning (ML) model trained on real-world genomic and medication data can identify associations between drug use and QTc duration, potentially enabling automated risk detection in clinical workflows. We included 10,208 individuals from the FinnGen biobank Expansion Area 3 substudy, integrating prescription records, clinical variables, and genetic information. We applied a nested-cross-validation approach to develop an ML framework to predict QTc duration using clinical characteristics, recent medication purchases, and polygenic score for QTc duration. We performed conventional linear regression analyses to estimate the robustness of the findings. Only a minority of ML-detected drug–QTc associations aligned with known effects listed in expert-curated reference. Several apparent false positives were observed, and effect sizes for true positives, such as amiodarone, were small and likely interpreted as clinically not meaningful (+1 ms in ML vs. +49 ms in linear regression). These findings highlight challenges in using ML to detect meaningful drug effects on ECG. ML models did not reliably identify medications associated with QT-interval prolongation. Consequently, risk quantification using QTc as an intermediate marker of electrophysiological vulnerability was limited in this framework. While new approaches continue to develop in medication safety assessment, a systematic evidence review conducted by clinical pharmacology experts is unlikely to be supplanted in the foreseeable future.

1 | Introduction

Prolongation of the QT interval on electrocardiograms (ECGs) is a critical marker that can herald devastating outcomes such as torsades de pointes tachycardia and sudden cardiac death [1]. Most instances of prolonged QT are acquired, often triggered by factors such as electrolyte imbalances or certain medications—including commonly prescribed agents like certain antiarrhythmics, antibiotics, and antipsychotics [2]. Patients with congenital long QT syndrome (LQTS) are particularly vulnerable, as their underlying genetic makeup magnifies the arrhythmic risk associated with these external factors [3]. LQTS contributes to thousands of deaths annually, not due to a lack of treatment options, but because early diagnosis remains difficult [4].

Study Highlights

- What is the current knowledge on the topic?
  - Drug-induced QT prolongation is a major safety concern, and clinicians rely on evidence-based resources to assess medication risk. Recent studies have used ML to predict QT prolongation in specific clinical settings, but its ability to detect medication effects directly from real-world data remains uncertain.
- What question did this study address?
  - Whether ML models trained on genomic, clinical, and medication data could be used to automatically detect medications associated with QTc duration.
- What does this study add to our knowledge?
  - In more than 10,000 FinnGen participants, ML models identified few known QT-prolonging drugs and frequently highlighted medications without established effects. Detected effect sizes were small and inconsistent with conventional regression, showing a high risk of false positives and limited ability to capture meaningful drug–QTc relationships.
- How might this change clinical pharmacology or translational science?
  - These findings suggest that broad, data-driven ML approaches are not yet reliable for detecting and quantifying the magnitude of ECG changes that may indicate QT-risk and serve as early indicators of impending arrhythmic events for clinicians. Expert-curated evaluation of medication-related QT risk by clinical pharmacologists and other expert clinicians remains indispensable.

Risk mitigation in individuals vulnerable to QTc prolongation—whether due to congenital predisposition or acquired factors—depends on frameworks that enable timely identification of high-risk medications. Current medical risk assessment systems, such as INXBASE by Medbase, are invaluable tools in reporting adverse drug reactions, including events such as drug-induced QT prolongation [5]. However, these tools are inherently constrained by the pace of scientific research and publication.

We hypothesized that recent advancements in machine learning (ML) could provide a novel framework for identifying medication use patterns that increase the risk of QT interval prolongation using register data. If an ML-based framework could first be trained within a hospital district and subsequently applied on a case-by-case basis, clinicians investigating patients identified as high-risk for QT prolongation could receive a prompt from the electronic health record system to record an ECG.

To explore this concept, we sought to understand how ML models perform in predicting corrected QT interval duration (QTc) on resting ECG. We leveraged the extensive genomic and clinical data available through the FinnGen registry for building these proof-of-concept models.

2 | Methods

2.1 | Participants

The FinnGen study is a research partnership involving Finnish universities, biobanks, hospital districts, and international pharmaceutical companies [6]. It includes samples from six regional hospital biobanks, representing a wide spectrum of specialized healthcare patients; a private healthcare biobank, which contributes individuals typically underrepresented in specialized care; and the Blood Service Biobank, which enriches the cohort with healthier individuals. The present study utilized data from the Expansion Area 3 substudy ($n = 40{,}809$) of FinnGen, which was designed to enrich the dataset with clinical information relevant to heart failure research. Notably, inclusion in this cohort was independent of a heart failure diagnosis and was based solely on the availability of echocardiography data. A total of 10,208 individuals from this sub-cohort had a standard 12-lead resting ECG and other covariate data available, with variable-specific missingness detailed in Table 1.

2.2 | Variable Definitions

QTc was calculated using Bazett's formula: $QTc = QT/\sqrt{RR}$, based on the earliest available ECG. Age was defined as the age at the time of the ECG recording. Sex was imputed from genetic data.

Prevalent medical conditions were identified using International Classification of Diseases (ICD) codes versions 9 and 10 from the national hospital discharge register, Anatomical Therapeutic Chemical (ATC) codes for medication purchases, Nordic Medico-Statistical Committee (NOMESCO) codes for surgical procedures, and special reimbursement codes from the national drug reimbursement register. Chronic kidney disease was defined by ICD codes N18, Y84.1, Z99.2, 585, and special reimbursement codes 137 and 138. Coronary artery disease was defined using hospital discharge codes I20.0, I21, I22, 410, and 4110, as well as operation codes for coronary artery bypass grafting and coronary angioplasty. Diabetes was defined by hospital discharge codes E10, E11, E12, E13, E14, and 250, medication expense reimbursement codes E11, E12, E13, and E14, and medication purchase code A10B. Heart failure was defined using hospital discharge codes I11.0, I13.0, I13.2, I50, 4029B, 428, 42,700, 42,710, 428, and 7824; medication expense reimbursement code 201; and medication purchase codes C03CA01 and C03EB01.

2.3 | Definition of Medication Usage

Medication use was determined from drug purchase records obtained from the Social Insurance Institution of Finland's medicinal products database. A medication was classified as used if purchased within the 3 months preceding the first available resting ECG measurement. In accordance with FinnGen's privacy regulations, all ATC codes with fewer than five users were excluded. Additionally, antibiotics were excluded due to their generally short treatment durations.

TABLE 1 | Characteristics of the study population.

Characteristic	Mean SD/*N* (%)	Missing values
N	10,208	
Age (years)	60.0 (14.5)	
Women	6025 (59.0%)	166 (1.6%)
Chronic kidney disease	115 (1.1%)	
Coronary artery disease	797 (7.8%)	
Diabetes	1570 (15.4%)	
Heart failure	317 (3.1%)	
Polygenic score for QTc	0.0403 (0.992)	965 (9.5%)
QTc (ms)	432 (28.9)	

Note: Values are means ± standard deviations for continuous data and numbers and percentages for categorical data. QTc, Bazett-corrected QT interval.

2.4 | Polygenic Score

Genetic data from 391,124 European UK Biobank participants were utilized to define a polygenic score (PGS) for QTc [7]. At the UK Biobank assessment center, QT intervals were measured from a single resting 12-lead ECG using Cardiosoft ver. 6 (GE Healthcare, Chicago, IL, USA), with QTc calculated using Bazett's formula. The PGS was subsequently derived by applying penalized linear regression to 490,392 genetic variants, with adjustments made for age, birth date, sex, Townsend deprivation index, and the first 16 genetic principal components.

2.5 | Statistical Methods

Linear regression models were fitted to assess the association between QTc and various medications, adjusting for PGS for QT interval, age, sex, chronic kidney disease, coronary artery disease, diabetes, and heart failure. Covariates were selected a priori based on established clinical risk factors associated with cardiovascular disease, and PGS for QT interval was included to account for the heritable component of QTc duration. Multiple testing correction was applied using the Benjamini–Hochberg method [8].

A nested cross-validated gradient boosting ML platform was constructed to evaluate the simultaneous contribution of different medications to QTc using R package xgboost [9]. Threefold cross-validation was applied in both the inner and outer loops, with the entire procedure repeated 20 times to ensure robustness. We used Bayesian optimization to tune model hyperparameters using R package mlrMBO [10]. The tuned hyperparameters were boosting rounds (10–500), learning rate (0.001–0.1), minimum loss reduction (0–5), L2 regularization (0–10), and L1 regularization (0–10), maximum tree depth (2–5), minimum child weight (5–100), subsample ratio (0.6–0.9), and column subsample ratio per tree (0.6–0.9). A minimal model predicted QTc based on the PGS, age, sex, chronic kidney disease, coronary artery disease, diabetes, and heart failure, while a full model additionally included all medications. Twenty control features, generated from a binomial distribution with success probabilities randomly sampled from a uniform distribution, were incorporated alongside model covariates. Model performance was assessed using root-mean-square error (RMSE) and the coefficient of determination (R^2), calculated as $R^2 = \sum (y-\hat{y})^2 / \sum (y-\bar{y})^2$, where y denotes observed values, $\bar{y}$ their mean, and $\hat{y}$ the predicted values. Point estimates of RMSE were used without prespecifying a minimum clinically important difference. Our aim was descriptive comparison of relative predictive performance rather than formal hypothesis testing; therefore, we did not compute confidence intervals for differences in RMSE. Feature importance was quantified using gain, which reflects the improvement in model performance at each decision tree split. Features with a mean gain lower than that of control features were deemed to have negligible predictive value. Additionally, Shapley values were employed to interpret feature contributions to individual predictions. Marginal effects of binary variables on QTc were estimated by calculating the mean difference in model predictions when the variable was toggled between true and false, with other features held constant.

All analyses were conducted using R version 4.4.3 (R Core Team, Vienna, Austria).

2.6 | Ethics

The FinnGen study protocol was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa. All participants gave written informed consent for voluntary participation in biobank research.

3 | Results

The study population included 10,208 individuals (mean age 60.0 ± 14.5 years), of whom 59.0% were female (Table 1). Registry data identified drug purchases spanning 368 distinct ATC codes within 3 months prior to ECG recording (Table S1). The proportion of individuals using any single medication ranged from < 0.1% to 14.4%.

3.1 | Linear Regression Analyses of Clinical and Medication Effects on QTc Interval

In a linear regression model including only clinical covariates (Table S2), heart failure was associated with a 22.1 ms longer QTc interval (95% CI: 18.7–25.5; $p < 0.001$), female sex with a 4.4 ms longer QTc (95% CI: 3.2–5.6; $p < 0.001$), and each 1-standard deviation increase in PGS with a 4.5 ms longer QTc (95% CI: 3.9–5.1; $p < 0.001$) (Figure 1). Eight prescription medications were significantly associated with QTc duration after adjustment for clinical covariates. Acyclovir and the norethisterone–estrogen combination were linked to shorter QTc durations, while amiodarone, fenofibrate, flecainide, leuprolide, spironolactone, and warfarin were associated with longer QTc intervals (Figure 2).

3.2 | Machine Learning Analyses of Clinical and Medication Associations With QTc

In ML models using only clinical covariates (Table S3), the R^2 was 4.5% and the RMSE was 28.3. Model performance improved slightly when data from 368 distinct ATC codes were included (Table S4): in the full model, the R^2 increased to 4.9% and the RMSE decreased to 28.2. Clinical covariates consistently accounted for 30%–50% of the model's performance, while the addition of the PGS alone accounted for 20%–30% (Figure 3). Warfarin was the only medication consistently associated with QTc across gain, Shapley values, and conventional linear regression (Figure 3). Most medications highlighted by Shapley values were treatments for cardiovascular conditions such as atrial fibrillation, heart failure, and coronary artery disease. Using model gain—which is a less stringent importance metric—we also identified several non-cardiovascular medications, including acyclovir, estradiol, fenofibrate, levocetirizine, paracetamol, quetiapine, leuprolide, and liraglutide, as significantly associated with QTc duration.

4 | Discussion

In this moderate to large registry-based study, we examined ML models incorporating clinical and medication data to explore their potential for identifying individuals at risk of QTc prolongation. As a benchmark, we conducted parallel analyses using conventional linear regression to validate and contextualize the findings. Consistent with previous knowledge, our analysis confirmed established links between heart failure [11], female sex [12], and polygenic risk with longer QTc intervals [13]. However, even when applying less stringent feature importance metrics, only 18 prescription medications were associated with QTc duration in the ML models. Most of these medications have not been traditionally linked to QT interval effects, highlighting the limited promise of

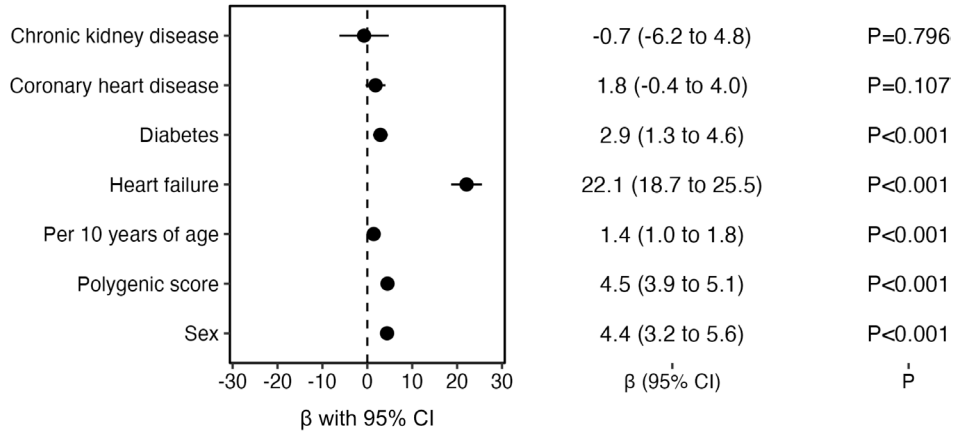

FIGURE 1 | Associations between clinical covariates and QTc interval in a linear regression model.

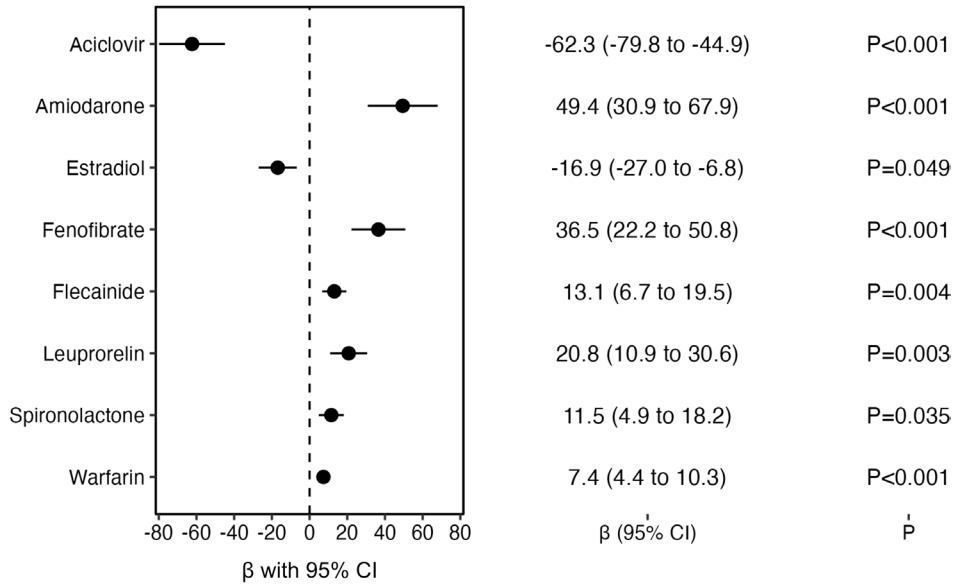

FIGURE 2 | Prescription medications significantly associated with QTc in linear regression models adjusted for clinical covariates. Clinical covariates included polygenic score, age, sex, chronic kidney disease, coronary artery disease, diabetes, and heart failure. Associations were corrected for multiple testing using the Benjamini–Hochberg method.

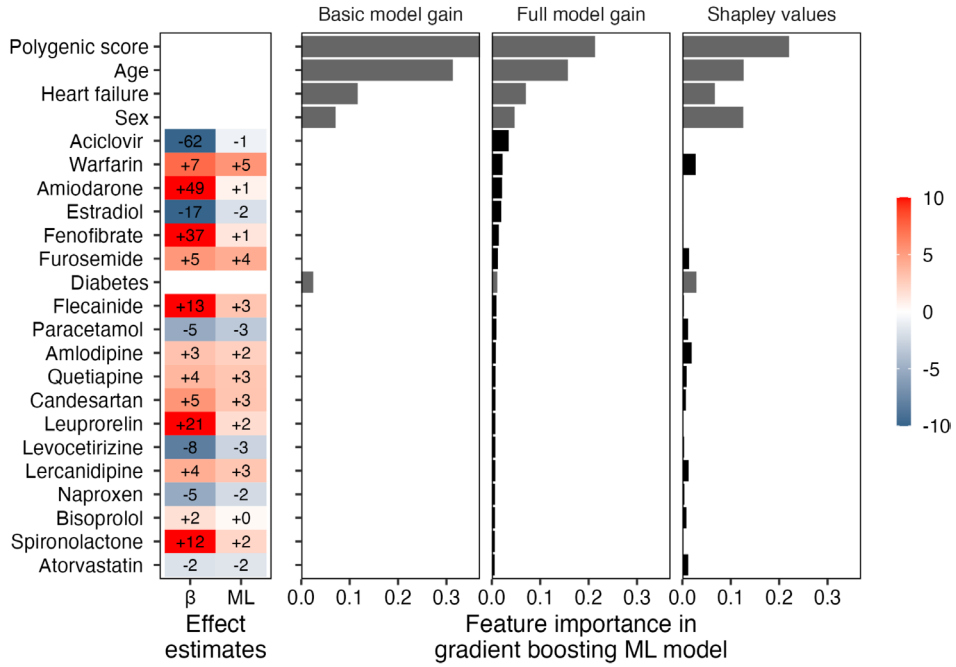

FIGURE 3 | Importance metrics and effect size estimates for clinical covariates and prescription medications associated with QTc, comparing linear regression and machine learning models. Only prescription medications with predictive value exceeding randomly generated control variables according to the full machine learning model gain are depicted. The chart displays feature importance from basic and full machine learning models (gain and Shapley values) alongside effect size estimates from linear regression and machine learning analyses, presented as numbers on colored backgrounds—blue indicating negative effects and red indicating positive effects—enabling direct comparison of their contributions to QTc variation. β, linear regression; ML, machine learning.

this approach for identifying meaningful drug–QTc associations. Notably, warfarin was the only medication consistently associated with QTc duration across all analytic methods, despite lacking known effects on QT interval, underscoring the challenges and potential for false positives when using ML to detect pharmacological influences on QTc.

Current medication risk assessment systems, such as INXBASE by Medbase, are built on established scientific evidence and provide invaluable guidance to clinicians on potential drug interactions [5]. However, their scope is limited by the pace of scientific publication. Because these tools depend on published research, they reflect only what has already been studied, written up, and peer-reviewed—leaving potential gaps in assessing newer or less well-characterized pharmacological risks. In this context, we sought to examine whether ML could contribute to this arduous task by uncovering drug–QTc associations. By first training an ML model with real-world data, this strategy could potentially enable real-time detection directly within clinical workflows through integration with electronic health record systems.

Of the 18 medications identified by the ML models in the present study, only four—amiodarone, flecainide, quetiapine, and leuprolide—are listed in INXBASE as having a known effect on QT interval duration. One could argue that a larger sample size might have uncovered more true positives. Nevertheless, the real limitation might lie in the number of apparent false positives in the present study. Amlodipine serves as a representative example: rather than being a causal agent, it is more likely a marker of underlying hypertension, a factor known to prolong the QT interval on resting ECG [14]. A similar explanation may apply to warfarin, which is frequently prescribed for atrial fibrillation, which is often a consequence of longstanding hypertension [15]. Conversely, medications such as haloperidol and amitriptyline could have been expected to yield detectable signals given their known associations with QTc effects [16]; however, their low exposure prevalence (0.1%–0.3%) might have attenuated signal detection in this cohort. Of note, regression analysis also revealed some unexpected findings. Acyclovir demonstrated a negative association with QTc, not supported by prior literature; given the very small exposure numbers, chance remains a plausible explanation. By contrast, fenofibrate showed a positive association with QTc, a novel observation for which residual confounding—reflecting underlying cardiovascular disease—may be the most likely interpretation.

Another key challenge highlighted by our findings is the very modest effect sizes detected by the ML analyses, even for medications recognized as true positives. For example, while amiodarone is a well-established QT-prolonging drug, the ML model estimated its effect on QTc duration to be only around +1 ms—an increase unlikely to hold clinical significance. In stark contrast, the linear regression model indicated a much larger effect size of +49 ms for amiodarone, which aligns more closely with clinical expectations [17]. This discrepancy highlights the potential limitations of ML approaches for risk quantification within this context.

Other studies, using more narrowly defined exposure criteria, have shown stronger predictive performance. In a large inpatient cohort, an ML model trained on diagnostic and medication data predicted prolonged QTc intervals (defined as QTc

> 500 ms) with reasonable accuracy, with a black-box approach outperforming an interpretable, more conventional statistical method (concordance index 0.78 vs. 0.65) [18]. Similar predictive performance (concordance index 0.80) was observed in an outpatient cohort, where a convolutional neural network was applied to clinical and ECG data collected within 6 months of initiating medication [19]. Another study demonstrated that ML models incorporating laboratory, ECG, and clinical data significantly outperformed traditional methods (82.4% vs. 62.0%) in forecasting QTc prolongation within 24–48 h of exposure to interacting medications [20]. A key methodological difference compared to our study lies in how drug exposure was defined. Prior studies restricted their analyses to medications with established QT-prolonging potential—either focusing on a curated list of high-risk drugs [18, 19] or on specific drug–drug interactions known to increase QTc duration [20]. This targeted approach likely enhanced the models' ability to detect meaningful associations. In contrast, our study adopted a broader, hypothesis-generating strategy by including all prescription medications, regardless of known QT risk. While this design increases generalizability and may uncover novel associations, it may introduce noise, potentially diluting the signal from true QT-prolonging agents and contributing to the limited predictive performance observed.

The main advantages of the ML approach include its ability to handle missing data, manage collinearity and non-linearity, and capture complex interactions among variables [21]. Nested cross-validation provides a robust method for obtaining unbiased performance estimates and minimizing overfitting [22]. Compared to conventional statistical methods, which offer human-interpretable summary statistics, ML techniques have the potential to fully leverage the complexity of the data—particularly when working with well-justified continuous covariates such as age and PGS. Despite the promising potential of such ML models in risk prediction, several challenges remain. The complexity of ML algorithms often raises concerns regarding their interpretability and clinical applicability. As noted in the review by Black et al., while ML models can outperform traditional statistical methods, their 'black box' nature may hinder acceptance in clinical practice [23]. For this reason, we chose to focus on an intermediate marker—QT interval on the resting ECG—as the outcome, since within this framework clinicians could verify or rule out the predicted risk by obtaining an ECG, making it a practical decision point.

Strengths of this study include the large and relatively unfiltered sample from the FinnGen cohort, comprehensive medication data integration, and cross-validation of ML analyses with linear regression and INXBASE searches. Limitations involve the observational design, potential residual confounding from unmeasured factors, and the inherent challenge of achieving a sufficiently large sample size to detect associations between medication and QT time. Although we did not have a pre-medication ECG available, this limitation was likely partially mitigated by the inclusion of the PGS. Additionally, due to the nature of the register data, most information available to our models was binary, which likely reduced the comparative advantage in statistical power of the ML methods over conventional statistical approaches. This limitation may be particularly evident in scenarios involving low-prevalence features—such as those ranging from absent to less than one-fifth of the study population. In such cases, even features with potentially strong effects may have little influence on model performance due to their rarity. Finally, while our data reflects medication purchases, it only serves as a proxy for actual use, with adherence often imperfect—ranging from 10% to 70% depending on regimen complexity [24].

This study should be regarded as a novel proof of concept. Certain improvements in data quality and model design might enhance the performance of ML models aimed at predicting QTc duration on resting ECG. For instance, the availability of structured prescription data—such as standardized dosage entries (e.g., mg/day)—could allow explanatory variables to be modeled as multi-class or semi-continuous inputs. To support the implementation of such or similar enhancements, we have made our code and tools openly accessible via Zenodo, encouraging continued research in this area.

In conclusion, the concept of using ML models trained on real-world data to automatically detect QTc-prolonging drug effects was not supported by our findings. Indeed, it seems unlikely that a methodological silver bullet—whether ML-based or otherwise—will emerge any time soon to replace the painstaking, drug-by-drug evaluation currently undertaken by clinical pharmacology researchers. The systematic work of gathering evidence from diverse studies and carefully synthesizing it into trusted medication risk assessment platforms remains irreplaceable. Amidst the current hubris surrounding artificial intelligence, ML, and related technologies, this may not be an entirely unwelcome conclusion. The enduring need for expert judgment and systematic evidence appraisal serves as a reminder that not all aspects of clinical decision-making can—or should—be automated.

Acknowledgments

Open access publishing facilitated by Turun yliopisto, as part of the Wiley - FinELib agreement.

Author Contributions

V.L. and J.P. wrote the manuscript; V.L., A.W., K.T., T.P., J.L., FG, A.M., T.J.N., and J.P. designed the research, V.L., A.W., K.T., T.P., J.L., A.M., T.J.N., and J.P. performed the research; J.P. analyzed the data.

Funding

V.L. was supported by a grant from the State Research Funding of the Wellbeing Services County of Southwest Finland. K.T. has received research grants from The Finnish Foundation for Cardiovascular Research, The Finnish Medical Foundation, and The Finnish Foundation for Alcohol studies. J.P. was funded by Paavo Nurmi Foundation and the Finnish Medical Foundation. The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. This study used FinnGen data, which is funded by two grants from Business Finland (HUS 4685/31/2016 and UH 4386/31/2016) and 14 industry partners: AbbVie Inc., AstraZeneca UK Ltd., Biogen MA Inc., Bristol Myers Squibb (including Celgene Corporation & Celgene International II Sàrl), Genentech Inc., Merck Sharp & Dohme LCC, Pfizer Inc., GlaxoSmithKline Intellectual Property Development Ltd., Sanofi US Services Inc., Maze Therapeutics Inc., Johnson&Johnson Innovative Medicine Inc., Novartis AG, Boehringer Ingelheim International GmbH and Bayer AG. Biobank samples were provided by Auria Biobank, THL Biobank, Helsinki Biobank, Biobank Borealis of Northern Finland,

Finnish Clinical Biobank Tampere, Biobank of Eastern Finland, Central Finland Biobank, Finnish Red Cross Blood Service Biobank, Terveystalo Biobank, and Arctic Biobank; all Finnish biobanks are members of the BBMRI.fi infrastructure, coordinated by the Finnish Biobank Cooperative (FINBB).

Conflicts of Interest

V.L. has received a lecture honorarium from Boehringer Ingelheim, unrelated to the present study. All other authors declared no competing interests for this work.

Data Availability Statement

The analysis codes for this study have been deposited in the Zenodo repository with the following DOI 10.5281/zenodo.15223007.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Characteristics for medicines used within 3 months of ECG. **Table S2:** Linear regression results for QTc time. **Table S3:** Feature importance for basic XGBoost model. **Table S4:** Feature importance for full XGBoost model.