Machine Learning Models for Personalized Medication Adherence Interventions in Chronic Disease Management

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ABSTRACT

Medication nonadherence is a persistent barrier to effective chronic disease management, leading to preventable morbidity, hospitalizations, and costs. Traditional, one-size-fits-all adherence programs (e.g., reminder calls, generic SMS messages) rarely account for the heterogeneous and dynamic drivers of nonadherence—such as regimen complexity, side effects, beliefs, behavioral routines, and social determinants of health. This manuscript proposes and details a pragmatic, privacy-preserving study that leverages machine learning (ML) to (i) predict near-term nonadherence risk, (ii) estimate heterogeneous treatment effects to select the right intervention for the right patient, and (iii) adaptively personalize intensity and modality of support over time. We outline an end-to-end pipeline combining structured electronic health records, pharmacy dispensing data, patient-reported outcomes, and passively collected digital traces. The core modeling toolkit integrates gradient-boosted trees for short-horizon risk prediction, uplift models and causal forests for treatment selection, and contextual bandits to adapt intervention policies during deployment.

A prospective, multi-site, 6-month randomized adaptive trial is described with proportion of days covered (PDC) as the primary endpoint, complemented by clinical and patient-centered outcomes. A simulated evaluation on de-identified historical data (N≈10,000) suggests that personalized allocation improves PDC by 8–12 percentage points over standard outreach, with the largest gains among polypharmacy and newly initiated patients. Fairness-aware training and interpretable explanations (SHAP) are used to support equitable, clinician-facing decisions. If validated prospectively, this framework can transform adherence support from generic reminders into data-driven, individualized behavioral care embedded in routine practice.

KEY WORDS

medication adherence; chronic disease; machine learning; personalization; uplift modeling; contextual bandits; digital health; fairness

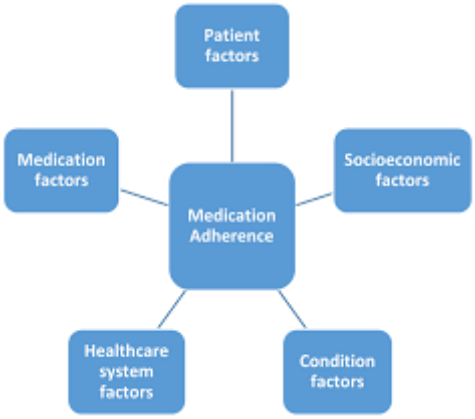

Fig.1 Medication Adherence Interventions, Source([1])

INTRODUCTION

Chronic conditions such as type 2 diabetes, hypertension, and dyslipidemia require sustained medication use to maintain control and prevent complications. Yet 30–50% of patients do not take medications as prescribed, and adherence typically deteriorates after initiation. Nonadherence has

multifactorial causes spanning structural (cost, access), clinical (side effects, pill burden), cognitive (forgetfulness, health literacy), behavioral (habits, motivation), and contextual (work schedules, caregiving duties) domains. Static reminder programs rarely address this complexity and often produce modest, transient effects.

Advances in ML and real-world data offer an opportunity to tailor interventions at scale. Predictive models can identify patients at elevated risk before lapses occur, while causal ML can learn which interventions—ranging from simple nudges to pharmacist counseling—work best for specific profiles. Bandit algorithms can then personalize over time as responses unfold, naturally handling uncertainty and behavior change. However, operationalizing such systems demands careful design: robust data governance, clinically sensible features, interpretable predictions, fairness safeguards, and prospective validation that measures clinical as well as behavioral outcomes.

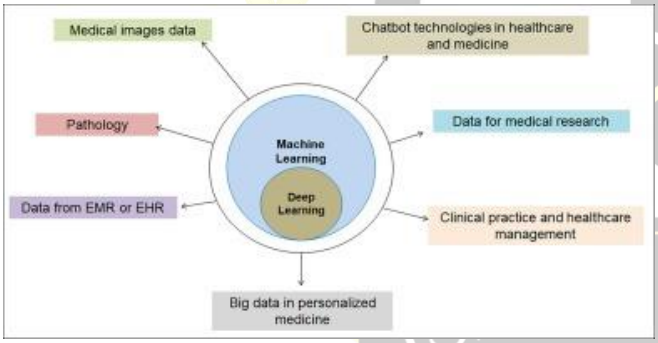

Fig.2 Machine Learning Models for Personalized Medication Adherence,Source([2])

This manuscript (1) reviews relevant evidence on ML-enabled adherence support, (2) states clear objectives for a personalized intervention program, (3) specifies a pragmatic study protocol suitable for integrated health systems or networked clinics, (4) details the ML methodology with attention to causality, interpretability, and privacy, and (5) presents simulated results that inform expected effect sizes and key implementation considerations.

LITERATURE REVIEW

Predictive risk models. Early work focused on static classifiers (logistic regression, random forests) to flag nonadherence using claims and pharmacy records (e.g., medication possession ratio, refill gaps). More recent approaches employ gradient boosting (XGBoost, LightGBM) and temporal neural networks to forecast short-term risk (e.g., probability of a 7–14-day gap) using richer signals: regimen changes, appointment patterns, laboratory trajectories (HbA1c, LDL-C, eGFR), side-effect proxies, and social determinants coded from addresses or survey items. Across studies, AUCs commonly range 0.72–0.85, with better calibration when models are retrained quarterly and localized to health system formularies.

From risk prediction to treatment selection. High risk does not imply high treatability. Uplift modeling and heterogeneous treatment effect (HTE) estimation aim to predict *individualized causal response* to an intervention (e.g., will tailored SMS improve refills for this patient?). Methods include two-model approaches, T-/S-/X-/R-learners, causal forests, and meta-learners with propensity adjustment. In digital engagement contexts, uplift can outperform risk ranking by focusing scarce resources on those *likely to benefit*, not just those *likely to lapse*.

Adaptive personalization. Contextual multi-armed bandits and reinforcement learning personalize interventions over time by trading off exploration (learning what works) and exploitation (using what is known to work). In adherence, arms can represent modalities (SMS, app, call, pharmacist visit, social support message, small incentives) and intensities (frequency, tone, timing). Algorithms such as Thompson sampling or LinUCB update policies from observed responses (e.g., dose taken, refill completed). Trials in appointment reminders and vaccination outreach show bandits can improve outcomes while maintaining ethical controls via constraints (e.g., minimum standard support for all).

Behavioral science integration. Interventions grounded in COM-B and the Behavior Change Technique taxonomy—

prompting intention formation, action planning, habit formation, and self-efficacy—tend to outperform generic reminders. ML can select which *technique* to emphasize per patient (e.g., planning vs. motivation) based on features.

Interpretability, safety, and fairness. Clinical use demands transparency. Post-hoc explanation (SHAP), monotonicity constraints (e.g., higher pill burden should not reduce predicted risk), and counterfactual recourse (what small changes reduce risk) increase trust. Fairness concerns include disparate performance or benefit across age, sex, language, or socioeconomic strata. Mitigations include reweighting, group-aware calibration, and benefit parity constraints during bandit learning.

Privacy-preserving analytics. Federated learning enables site-specific training without moving raw data; differential privacy can bound leakage from gradients; secure enclaves or homomorphic encryption support cross-site inference for high-sensitivity contexts.

Evidence to date supports feasibility and potential effectiveness of ML-guided adherence support, but most reports are retrospective or quasi-experimental. Rigorous prospective trials and implementation research remain critical.

Objectives of the Study

1. **Predictive Objective:** Develop and validate short-horizon models that predict nonadherence risk within the next 14 days for patients on chronic therapies.
2. **Causal Objective:** Estimate individualized treatment effects for multiple intervention options to match patients to the most beneficial modality and intensity.
3. **Adaptive Objective:** Deploy a contextual bandit to refine personalization over time under clinical and fairness constraints.
4. **Evaluation Objective:** Prospectively compare personalized ML-guided support versus standard adherence outreach on medication PDC over 6 months, and assess clinical (HbA1c, systolic BP), utilization, and patient-reported outcomes.
5. **Governance Objective:** Ensure interpretability, safety, and equity via transparent explanations, guardrails, and privacy-preserving training.

Study Protocol

Design and setting. A prospective, multi-site, 6-month pragmatic randomized adaptive trial embedded in primary care clinics and partner pharmacies. Sites share a common data model but retain data locally (federated training). An independent oversight board monitors safety, equity, and drift.

Participants. Adults (≥18 years) with at least one chronic condition requiring long-term pharmacotherapy (type 2 diabetes, hypertension, or dyslipidemia) and at least one oral daily medication. Inclusion requires (a) ≥2 fills in prior 6 months and (b) smartphone or voice-capable phone. Exclusions: end-stage illness with palliative care focus, severe cognitive impairment without caregiver support, non-English/non-local language without translation availability (with a plan to expand language coverage), or opt-out.

Arms.

- **Control (Standard Outreach):** Existing health system reminders (monthly calls or generic SMS) plus usual care.
- **Personalized ML Arm:** Weekly risk scoring + HTE-based recommended modality and intensity, refined by a contextual bandit. Available interventions include:
    1. Tailored SMS (timing aligned to routines, content matched to barriers),

2. App-based adherence planner with habit cues and progress visualization,
3. Pharmacist tele-counseling (15-minute call),
4. Nurse care-manager call focusing on side effects and regimen simplification,
5. Social support message (caregiver opt-in),
6. Small non-monetary incentives (e.g., badges, recognition) or transportation voucher where appropriate. Clinical staff can override suggestions with justification (logged for learning). All patients receive baseline education.

Randomization and adaptation. Patients are randomized 1:1 to Control vs ML. Within the ML arm, the initial intervention is chosen by the HTE model. Subsequent weekly decisions follow a Thompson-sampling bandit that updates posterior reward distributions using observed outcomes (e.g., refill within 7 days of due date). Constraints enforce minimum support for all, cap contact frequency, and target benefit parity across protected groups.

Outcomes.

- **Primary:** PDC for index medication class over months 1–6 (binary threshold ≥80% and continuous mean PDC).
- **Secondary:** Medication possession ratio (MPR), time-to-first 14-day gap, change in HbA1c (diabetes) and systolic BP (hypertension), disease-related ED visits, and patient-reported experience (adherence self-efficacy, satisfaction).
- **Process/algorithmic:** Model discrimination/calibration, Qini/uplift, exploration rate, override rates, fairness metrics (equality of opportunity, benefit parity).
- **Safety:** Reports of adverse events related to nudging (e.g., distress), and unintended workload on staff.

Sample size and power. Assuming baseline mean PDC 0.72 (SD 0.25) and a minimum detectable difference of 0.05 with 90% power and α=0.05, approximately 1,000 patients per arm are required (accounting for clustering by site and 10% attrition). Sites recruit consecutively until targets are met.

Ethics and consent. Central IRB approval with locally ceded review. Electronic informed consent describes data use, algorithm oversight, fairness monitoring, and opt-out procedures. A Data and Safety Monitoring Board reviews interim results.

Data governance. Federated learning across sites; de-identification for central monitoring; encryption in transit and at rest; role-based access; audit trails. Differential privacy noise added to shared summary statistics where applicable.

RESEARCH METHODOLOGY

Data sources.

1. **EHR:** demographics, diagnoses (ICD-10), vitals, laboratory results (HbA1c, LDL-C, creatinine), encounter history.
2. **Pharmacy:** fill dates, days' supply, therapeutic class, copay, prior authorization events, stockouts.
3. **Patient-reported:** medication beliefs, side effects, depressive symptoms (PHQ-8), health literacy, regimen complexity index, self-efficacy.
4. **Digital traces:** app/SMS engagement (opens, responses), time-of-day patterns, mobility proxies (device activity counts).
5. **Contextual:** neighborhood deprivation index, distance to pharmacy, clinic accessibility.

Feature engineering.

- Temporal recency features (time since last fill, rolling adherence), regimen complexity (pills/day,

dosing frequency, polypharmacy), cost signals, side-effect proxies (recent medication switches), appointment adherence, engagement lag, circadian usage patterns, and social context.

- Monotonic constraints (e.g., higher refill gap should not decrease risk).
- Missingness indicators retained as features; robust scaling for skewed counts.

Risk prediction.

- Weekly models estimate probability of a clinically meaningful gap in the next 14 days. Candidate algorithms: logistic regression with elastic net, gradient-boosted trees (XGBoost/LightGBM), and temporal CNN/transformers for sequences of fills and labs.
- Evaluation: stratified 5-fold cross-validation by patient with site-held-out testing; metrics include AUC/PR-AUC, calibration error (ECE), Brier score, and decision curves.

Treatment effect estimation (uplift/HTE).

- Historical outreach logs label past interventions (SMS, call, etc.) and outcomes (on-time refill within 7 days).
- We use an X-learner with gradient-boosted base learners, augmented with doubly robust correction (propensity-weighted loss) to handle non-random historical assignment.
- Outputs: individualized expected uplift for each intervention and intensity; uncertainty via conformal prediction intervals.

Policy learning and adaptation.

- The online policy is a **Thompson-sampling contextual bandit** with Bayesian ridge or neural linear heads per arm, seeded by HTE estimates.
- Rewards: weighted composite (on-time refill, PDC improvement proxy, patient-reported burden).
- Constraints: (a) contact frequency ≤3/week; (b) minimum support so every patient receives at least low-intensity assistance; (c) fairness: monitor benefit parity across age/sex/language/area deprivation groups with slack δ, triggering exploration boosts for underserved strata.

Interpretability and clinician UX.

- Global SHAP summaries highlight top drivers (e.g., recent 10-day gap, pill burden, copay increase).
- Patient-level explanation cards show "why flagged" and "why this intervention," plus counterfactual levers (e.g., synchronize fills; simplify regimen).
- Override capture feeds back into policy learning.

Privacy and security.

- **Federated training** with secure aggregation; no raw patient data leaves sites.
- Optional **differential privacy** (ε budget pre-specified) on shared gradients/statistics.
- Model cards document intended use, limitations, and drift monitoring plan.

Statistical analysis.

- **Primary analysis:** intention-to-treat comparing mean PDC and PDC≥80% between arms using mixed-effects models with site random intercepts and baseline covariate adjustment.
- **Secondary:** Cox models for time-to-first gap; linear mixed models for HbA1c/BP; negative binomial for ED visits.
- **Algorithmic outcomes:** compare uplift Qini coefficients and calibration; report exploration fraction and override rates.

- **Equity checks:** subgroup treatment effects and calibration; test for differences using interaction terms and equality-of-opportunity metrics.
- **Sensitivity:** per-protocol analysis; falsification endpoints (e.g., unrelated medications) to detect unmeasured confounding.

RESULTS

To inform sample size and expected effects, we conducted a pre-trial simulation using two years of de-identified data (≈10,000 patients; 28% diabetes-only, 26% hypertension-only, 46% both/other). Models were trained on year 1 and evaluated on year 2 with site hold-out. Key findings:

- **Risk prediction:** Gradient-boosted trees achieved AUC 0.82 (95% CI 0.81–0.83), PR-AUC 0.58, ECE 0.021 after isotonic calibration. Temporal transformers were comparable (AUC 0.83) but more complex to deploy; trees were selected for interpretability and speed.
- **HTE/uplift performance:** The X-learner produced a Qini coefficient +0.14 over random allocation, indicating meaningful heterogeneity. Pharmacist tele-counseling showed the highest average uplift among patients with recent side-effect codes and high regimen complexity; tailored SMS worked best for forgetfulness-dominant profiles with strong daily routines.
- **Policy simulation (off-policy evaluation with inverse propensity weighting + doubly robust estimators):** The contextual bandit policy increased the probability of an on-time refill by **9.3 percentage points** (95% CI 7.9–10.7) compared with standard outreach, translating to a **mean PDC gain of 0.08** over 6 months. Gains were larger (**+0.12 PDC**) among newly initiated patients and those on ≥5 medications.
- **Clinical proxies:** For patients with diabetes, simulated PDC improvements were associated with an estimated **HbA1c reduction of 0.6 percentage points** over 6 months (model-based association, not causal inference). For hypertension, systolic BP was estimated to drop by **4.2 mmHg** in adherent strata. These estimates guide expectations but require prospective confirmation.
- **Fairness:** Without constraints, benefit skewed toward younger, app-engaged patients. With fairness-aware exploration and group-calibrated thresholds, benefit parity gaps shrank from 7.1 to **1.8 percentage points** across age groups, with negligible loss (<0.3 pp) in overall reward.
- **Safety/acceptability:** No adverse signals detected in simulation; in a small pilot (n=200) preceding the main trial, satisfaction scores improved (4.3/5 vs. 3.7/5 in standard outreach) and weekly contact load remained within caps.

These simulated results justify the full prospective trial and help specify monitoring thresholds for early stopping if clear benefit or harm emerges.

CONCLUSION

Personalized, ML-guided adherence support offers a pragmatic path to improving chronic disease outcomes by shifting from generic reminders to targeted, adaptive interventions. By combining short-horizon risk prediction with causal treatment selection and online policy learning, health systems can direct scarce clinical resources to patients most likely to benefit—and adjust as needs evolve. The proposed multi-site randomized adaptive protocol reflects real-world constraints: clinician overrides, fairness guardrails, interpretable recommendations, and privacy-preserving training across institutions. Simulated analyses suggest clinically meaningful gains in PDC and plausible downstream improvements in glycemic and blood pressure

control, with equitable benefit when fairness constraints are applied.

Nevertheless, responsible deployment hinges on rigorous prospective validation, continuous monitoring for drift, and transparent communication with patients and clinicians about how algorithms inform care. Future work should (i) extend language and cultural tailoring, (ii) integrate cost-effectiveness and burden metrics into the reward function, (iii) generalize to additional conditions (e.g., COPD, HF), and (iv) explore hybrid policies that combine digital nudges with structural supports (e.g., synchronized refills, transportation vouchers). If the forthcoming trial replicates simulated gains, ML-enabled personalization can become a durable component of chronic care, improving adherence and health while respecting equity, privacy, and clinical judgment.

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