Received: 10 October 2023 | Revised: 12 December 2023 | Accepted: 17 January 2024

DOI: 10.1002/pst.2365

WILEY

MAIN PAPER

Assessing the performance of group-based trajectory modeling method to discover different patterns of medication adherence

Awa Diop[1,2] | Alind Gupta[3] | Sabrina Mueller[4] | Louis Dron[5] | Ofir Harari[1] | Heather Berringer[1,6] | Vinusha Kalatharan[1] | Jay J. H. Park[1,7] | Miceline Mésidor[2,8] | Denis Talbot[2,8]

[1]Core Clinical Sciences Inc., Vancouver, British Columbia, Canada

[2]Département de médecine sociale et préventive, Université Laval, Québec, Canada

[3]Department of Epidemiology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada

[4]GIPAM GmbH, Wismar, Germany

[5]Cascade Outcomes Research Inc., Vancouver, British Columbia, Canada

[6]Department of Mathematics and Statistics, University of Victoria, Victoria, British Columbia, Canada

[7]Department of Health Research Methodology, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[8]Axe santé des populations et pratiques optimales en santé, Centre de recherche du CHU de Québec – Université Laval, Québec, Canada

Correspondence
Awa Diop, Laval University, CHU de Québec, Québec, Canada.
Email: awa.diop.2@ulaval.ca

Abstract

It is well known that medication adherence is critical to patient outcomes and can decrease patient mortality. The Pharmacy Quality Alliance (PQA) has recognized and identified medication adherence as an important indicator of medication-use quality. Hence, there is a need to use the right methods to assess medication adherence. The PQA has endorsed the proportion of days covered (PDC) as the primary method of measuring adherence. Although easy to calculate, the PDC has however several drawbacks as a method of measuring adherence. PDC is a deterministic approach that cannot capture the complexity of a dynamic phenomenon. Group-based trajectory modeling (GBTM) is increasingly proposed as an alternative to capture heterogeneity in medication adherence. The main goal of this paper is to demonstrate, through a simulation study, the ability of GBTM to capture treatment adherence when compared to its deterministic PDC analogue and to the nonparametric longitudinal K-means. A time-varying treatment was generated as a quadratic function of time, baseline, and time-varying covariates. Three trajectory models are considered combining a cat's cradle effect, and a rainbow effect. The performance of GBTM was compared to the PDC and longitudinal K-means using the absolute bias, the variance, the c-statistics, the relative bias, and the relative variance. For all explored scenarios, we find that GBTM performed better in capturing different patterns of medication adherence with lower relative bias and variance even under model misspecification than PDC and longitudinal K-means.

KEYWORDS

GBTM, KML, medication adherence, PDC, trajectory analysis

1 | INTRODUCTION

Medication adherence is an important determinant of patient outcomes, their quality of life, and overall healthcare utilization.[1] Gaining a better understanding of the drivers of medication adherence is crucial in ensuring treatment success, particularly for chronic conditions, or multimorbid patients who may suffer from treatment fatigue.[2] Identifying prevalent adherence patterns and the corresponding population groups may assist decision-makers in targeting these populations and tailoring interventions to enhance medication adherence. For example, in a meta-analysis conducted by Lewey et al,[3] it was discovered that non-white patients exhibit lower adherence rates to statin treatment. Such findings are valuable for guiding future research and interventions aimed at improving adherence within these specific subgroups. Additionally, in randomized controlled trials (RCTs), many patients fail to complete their intended treatment due to drug-related toxicity.[4] Adherence studies can play a crucial role in this context by identifying the patient profiles associated with incomplete treatment and their distinguishing characteristics.

Adherence can be measured in a number of ways. The Pharmacy Quality Alliance (PQA) organization has endorsed the use of the proportion of days covered (PDC) as the primary method of measuring adherence.[5,6] Defined as the number of fill days divided by the number of days between the index date (first fill) and the end of the follow-up perio,[5] PDC has been increasingly recommended over the medication possession rate (MPR), where the number of supplies is considered, mostly because it can account for the timing of medication refills.[5,6]

While PDC is easy to calculate, there are several drawbacks to using it as the primary measure of medication adherence. There is no universally accepted threshold for "adequate" PDC. While the PQA reports clinical evidence supporting a PDC threshold of 80%, they note that this may instead be 90% for antiretroviral medications for management of HIV.[7] Further, they specify that PDC is a poor capture for acute therapies of shorter duration, such as for hepatitis C treatment. There is a lack of quantitative evidence regarding this cut-off, and it is important to recognize that there is no ideal threshold that can be universally applied.[8] PDC, as a deterministic measure, may not be able to capture the complexity of the dynamic nature of medication adherence.[9,10]

Longitudinal clustering approaches may be better suited to capture the dynamic nature of behaviors associated with medication adherence. For example, group-based trajectory modeling (GBTM) consists of finite mixture modeling that can be useful in identifying latent subgroups within the population that may not be readily observable.[11,12] It is useful in summarizing developmental patterns of a time-varying phenomena,[12] achieved by clustering similar profiles into homogeneous subgroups. Diverse applications of GBTM, highlighting its significance in healthcare, are evident in the literature.[9,13–16] Alternatively, we may use k-means for longitudinal data (KML).[17] KML has the ability to recover latent subgroups by using metrics such as the Euclidean distance to assign individuals to trajectory groups. Like PDC, KML requires no model specification for the trajectories. In the literature, several applications of KML exist.[18–20] Although an exploratory approach contrary to GBTM which is a probabilistic-based modeling approach, there are advantages in considering KML as a longitudinal clustering method. KML is less computationally extensive than GBTM and is more scalable.[21] Indeed, its algorithmic simplicity can make it easier to implement and faster to execute.[21] Formalized statistical comparisons are lacking to compare the performance of GBTM in capturing medication adherence to that of other approaches, such as PDC and KML. This paper intends to do so systematically, through a comprehensive simulation study that encompasses various sample sizes, functional time-varying treatment representations, follow-up periods, and treatment-covariate relationships. To the best of our knowledge, this paper presents the first comprehensive simulation study to measure GBTM's performance in assessing medication adherence.

The paper is organized as follows. In Section 2, we review PDC, KML, and GBTM in greater detail. In Section 3, we review model selection criteria for GBTM, that will be put to use in Sections 4 and 5, where we outline the technical details of our simulation study and its results, respectively. We conclude the paper with a discussion in Section 6.

2 | APPROACHES TO STUDYING MEDICATION ADHERENCE

In this section, we will provide the reader with a brief introduction to the medication adherence measurement methods that will be our subject of investigation later in the paper.

2.1 | Proportion of days covered

PDC has enjoyed growing popularity in measuring medication adherence in medical research.[10] PDC refers to a percentage of days that a patient has a supply of medication available within a specified time frame. In practice, PDC is commonly estimated using claims data with the prescription fill dates and number of supply days for each prescription.[5] More specifically,

$$\text{PDC} = \frac{\text{Number of days covered with the drug during the follow} - \text{up period}}{\text{Number of days in the follow} - \text{up period after the index date}} \tag{1}$$

As seen in (1), the denominator represents the number of days between the first fill and the end of the follow-up period, while the numerator represents the total number of days covered by prescription fills during that same time frame.[5,10] Let $\overline{A}_{it} = (A_{i1}, \ldots A_{it})$ be the observed binary treatment sequence (or treatment trajectory) up to time $t = 1, \ldots, K$ of the i^{th} individual, $i = 1, \ldots, n$, where n is the sample size. When there is no stockpiling, meaning patients are taking their drug without anticipation or delay, we can define the PDC for the i^{th} individual as follows:

$$\text{PDC} = \frac{\sum_{t=1}^{K} I(A_{it} = 1)}{K}, \tag{2}$$

where $I(A_{it} = 1)$ is an indicator of whether or not the i^{th} individual took their treatment at time t. PDC is a deterministic metric that ranges between 0 and 1. It is typically categorized based on an arbitrary threshold. Most commonly, the threshold of 80% is used to classify individuals as adherent $(\geq 80\%)$ or non-adherent $(< 80\%)$. PDC cannot account for the dynamic nature of treatment patterns (trajectory) over time, as it simply measures the proportion of days that are covered with the drug prescription over the total follow-up period. Moreover, as a straightforward metric to assess medication adherence, PDC is not designed to handle the complexity of claims data and might lead to measurement errors.[22] Such measurement errors can mislead interpretations of the groups and exacerbate biases in subsequent analyses, particularly when the goal is to assess the association between medication adherence groups and endpoints outcomes.

In this paper, we categorized the adherence variable using PDC quantiles, to allow for more granularity. This approach is similar to the one employed in previous GBTM studies.[9]

2.2 | Longitudinal K-means

The k-means adaptation for longitudinal data (KML) utilizes traditional distance metrics, such as the Euclidean distance (also known as the L_2 norm) to cluster individuals into different trajectory groups.[17] It generalizes the standard k-means method to the case of longitudinal data. Here, the k-means algorithm, usually applied to cross-sectional data, is repeatedly applied at each measurement time point. In the initial step of KML, centers of each trajectory group are computed, followed by the assignment of observations to their nearest trajectory group and a subsequent calculation of some measure of within-group variability (meant to be minimized), averaged over the different trajectory groups. This iterative process continues until convergence is achieved.[17] In KML, the formula for calculating the Euclidean distance between two data points that represent treatment trajectories in a multidimensional space can be written as:

$$d(A_i, A_{i'}) = \sqrt{\frac{1}{K}\sum_{t=1}^{K} (A_{it} - A_{i't})^2}. \tag{3}$$

In this context, d is a distance metric, A_i and $A_{i'}$ represent the i^{th} and $i^{'\text{th}}$ individuals. Different distance metrics d will yield different partitions. For instance, k-medians employs the Manhattan distance, also referred to as the L_1 norm.[21] On the other hand, k-modes that utilize the mode as the central point for partitioning is the preferred choice for handling categorical data. In the simulation study appearing in this paper, the R package kml was used to perform KML.[23]

2.3 | Group-based trajectory modeling

In GBTM, we model the data to follow a mixture distribution whose components are linked to latent classes in the population.[12] The model assumes J distinct groups, each characterized by its own mean trajectory.[24] The i^{th} patient's likelihood contribution is then

$$P(\overline{A}_{iK}) = \sum_{j=1}^{J} \pi_j \prod_{t=1}^{K} P(A_{it}|z_i = j). \tag{4}$$

where π_j, also called the j^{th} mixture proportion, denotes the marginal probability that a random individual belongs to the j^{th} trajectory group, $j = 1,...,J$, and z_i denotes the group-membership or trajectory group for the i^{th} individual. It is a common practice to model the trajectory groups as a polynomial function of time.[12] For example, if we assume a quadratic relation, we could use the logistic regression model

$$\text{logit}P(A_{it}|z_i = j) = \theta_0^j + \theta_1^j t + \theta_2^j t^2,$$

where the parameters θ^j, $j = 1,...,J$, describe the treatment trajectory over time for the j^{th} group. We can also add covariates in the model:

$$\text{logit}P(A_{it}|z_i = j) = \theta_0^j + \theta_1^j t + \theta_2^j t^2 + \theta_3^j V_i + \theta_4^j L_{it},$$

where V_i and L_{it} are the baseline and time-varying covariates for the i^{th} individual. The main assumption of the model (4) is local independence, that is, treatment at different time-points $A_{i1},...,A_{iK}$ are assumed to be mutually independent conditional on group membership[16,25]: $A_{\text{it}} \amalg A_{it'} \,|\, z_i = j,\ t \neq t', j = 1,\cdots,J$.

In practice, when fitting a GBTM, both the groups' polynomial order and the number of groups must be specified. It is common practice to first estimate the model parameters, then to assign individuals to a trajectory group using their highest probability of belonging to that group, namely

$$\widehat{z}_i = \underset{j=1,...,J}{\text{argmax}}\ P\left(z_i = j|\overline{A}_{iK}, \widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\pi}}\right),$$

where

$$P\left(z_i = j|\overline{A}_{iK}, \widehat{\boldsymbol{\theta}}, \widehat{\boldsymbol{\pi}}\right) = \frac{\widehat{\pi}_j P\left(\overline{A}_{iK}|z_i = j, \widehat{\theta}_j\right)}{\sum_{j'=1}^{J} \widehat{\pi}_j' P\left(\overline{A}_{iK}|z_i = j', \widehat{\theta}_j\right)} \tag{5}$$

and the "hat" notation stands for the maximum likelihood estimator.

Choice of a sufficient number of periods for identifying groups can be guided by the identifiability conditions applicable to a binary variable. Formally, in the context of binomial distributions with repeated measures, it has been demonstrated that trajectory groups become identifiable when the number of repetitions for an individual, denoted as K is strictly greater than $2J - 1$, that is, $J < (K+1)/2$.[26,27]

To ensure proper reporting of results from GBTM analyses, one may employ the guidelines for reporting on latent trajectories analysis (GRoLTS) checklist.[28] This checklist includes 16 items that serve as valuable guidelines to improve the reproducibility of trajectory analyses. For continuous endpoints, the distinction is often made with latent class growth analysis (LCGA).[29] Seeing as this paper's focus is the modeling of a binary time-varying treatment, we will not attempt to differentiate between GBTM and LCGA. To perform GBTM in R, the package flexmix is used.[30]

3 | STATISTICAL CRITERIA FOR MODEL SELECTION

One main advantage of GBTM is that, as a probabilistic-based approach, it can be subjected to various goodness of fit and model selection criteria, to assist with the task of selecting model hyperparameters (i.e., the number of trajectories and the polynomial degree).[28,29] Similar criteria do not exist for PDC. As for KML, certain criteria do exist to choose the number of groups, such as the Calinski-Harabasz Index,[17] also known as the variance ratio criterion (VRC). This index is commonly employed to assess the quality of clusters in cluster analyses, and serves as a valuable tool for assessing the degree of separation between groups, thus offering an alternative or complementary approach to the elbow method[31] for identifying the optimal number of clusters.

3.1 | The Bayesian information criterion

When performing GBTM, the GRoLTS guidelines recommend using the Bayesian information criterion (BIC) for model selection. BIC balances model fit and complexity, thus enhancing robustness and interpretability of results in trajectory analysis.[28,32] The BIC criterion is defined by Nagin[12] as follows

$$\mathrm{BIC} = \log L\left(\widehat{\pi},\widehat{\theta}\right) - 0.5p\log(n), \tag{6}$$

where p is the number of parameters of the model (increasing with the number of groups and the polynomial degree), n the number of patients and $L\left(\widehat{\pi},\widehat{\theta}\right)$ the likelihood of the model, evaluated at the maximum likelihood estimates.[12] It is noteworthy that the BIC for model selection tends to favor more complex models, such as those with a higher number of groups. Given this inclination, the reliability of BIC can sometimes be questioned. As a result, alternative approaches like cross-validation error or bootstrapping[33,34] have been suggested in the literature to choose the number of groups and the polynomial form.

3.2 | Average posterior probability of assignment and odds of correct classification

Other classification statistics include the average posterior probability of assignment (APPA) and the odds of correct classification (OCC).[29] These statistics are useful in assessment of model adequacy whose primary focus is goodness of fit. The j^{th} group APPA is

$$\mathrm{APPA}_j = \frac{1}{n_j}\sum_{i=1}^{n_j} P\left(z_i = j|\overline{A}_{iK},\widehat{\boldsymbol{\theta}},\widehat{\boldsymbol{\pi}}\right), \tag{7}$$

where n_j is the sample size for the j^{th} group, $P\left(z_i = j|\overline{A}_{iK},\widehat{\boldsymbol{\theta}},\widehat{\boldsymbol{\pi}}\right)$ is given in (5), representing the degree of confidence in the assignment of subjects to trajectories. The j^{th} group OCC is then given by

$$\mathrm{OCC}_j = \frac{\mathrm{APPA}_j/\left(1-\mathrm{APPA}_j\right)}{\widehat{\pi}_j/\left(1-\widehat{\pi}_j\right)}. \tag{8}$$

This can be thought of as the ratio of the odds assignment to this group for members of this group to the odds of random assignment to this group. Larger values of both APPA and OCC indicate better goodness of model fit. An APPA value greater than 0.7 is generally considered acceptable.[29] An OCC value greater than 5 is seen as an evidence that the model is effective in its classification task.[29,32]

3.3 | The entropy information criterion

The inclusion of the entropy information criterion (EIC) in the reporting of trajectory analysis results is also recommended by the GroLTS. The EIC, given by

$$\text{EIC} = \sum_{i}^{n} \sum_{j}^{J} P\left(z_i = j|\overline{A}_{iK}\right) \log P\left(z_i = j|\overline{A}_{iK}\right). \tag{9}$$

is a measure of the degree of separation between groups.[29]

4 | SIMULATION STUDY

In the upcoming sections, our goal is to evaluate the performance of GBTM in capturing medication adherence, compared to its deterministic PDC counterpart and the non-parametric KML approach. We investigate various factors that could influence these methods, including different sample sizes, varying lengths of follow-up periods, the functional relationship between treatment and covariates, diverse levels of medication adherence, and scenarios where the boundaries between trajectory groups are not distinct.

4.1 | Data generating mechanism

To adopt a realistic data generating mechanism, we assumed that the time-varying treatment is a function of baseline and time-varying covariates alone, and is only dependent on time through the change in these covariates' values. Specifically for GBTM, this will give a better understanding of the impact of including covariates when modeling the treatment, and the impact of modeling the treatment as solely a polynomial function of time. Based on the identifiability conditions described in Section 4, the follow-up periods for 3, 4, and 5 groups have been chosen to be 6, 8, and 10, respectively. These are the minimum time points required to reliably identify the trajectory groups. We also explored longer follow-up periods, specifically 24, 100, and 365 measures for $n = 1000$, to assess their impact on biases when comparing GBTM and KML. Figure 1 depicts the possible causal relationship between these variables for a study with $K = 3$ time points, using a directed acyclic graph (DAG). The same principle is applied to $K = 8$ and $K = 10$ time points when modeling four and five trajectory groups.

Baseline covariates, time-varying covariates and time-varying treatment for the j^{th} group are generated as follows

$$\begin{cases} V \sim \mathcal{N}(0,1), \\ L_{j,1} \sim \mathcal{B}\left(1, \text{expit}\left(p_j + V\right)\right), \text{and} \\ A_{j,1} \sim \mathcal{B}\left(1, \text{expit}\left(p_j + V\right)\right), \end{cases}$$

where p_j, $j = 1,...,J$, are arbitrary probabilities chosen to simulate the treatment and covariate values at baseline, and $\text{expit}(x) = \exp(x)/(1+\exp(x))$. Note that A_j and L_j indicate here the treatment trajectory and covariate values for the j^{th} group.

For $t = 2,...,K$, we set

$$\begin{cases} L_{j,t} \sim \mathcal{B}\left(1, p = \text{expit}\left(0.5L_{j,t-1} + 0.25A_{j,t-1} + V\right)\right) \text{and} \\ A_{j,t} \sim \mathcal{B}\left(1, p = \text{expit}\left(\beta_{j,0} + \beta_{j,1}L_{j,t} + \beta_{j,2}L_{j,t}^2 + \beta_{j,3}A_{j,t-1} \times L_{j,t} + \beta_{j,4}A_{j,t-1} + V\right)\right), \end{cases}$$

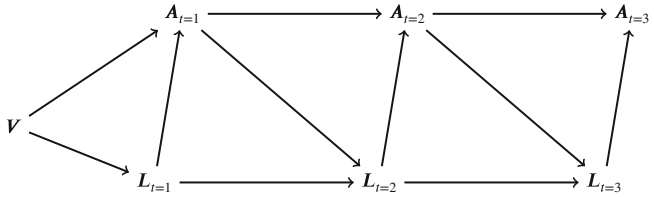


FIGURE 1 Directed acyclic graph representing the data-structure with a time-varying treatment A, time-varying covariates L, V baseline characteristics, and $K = 3$ time points.

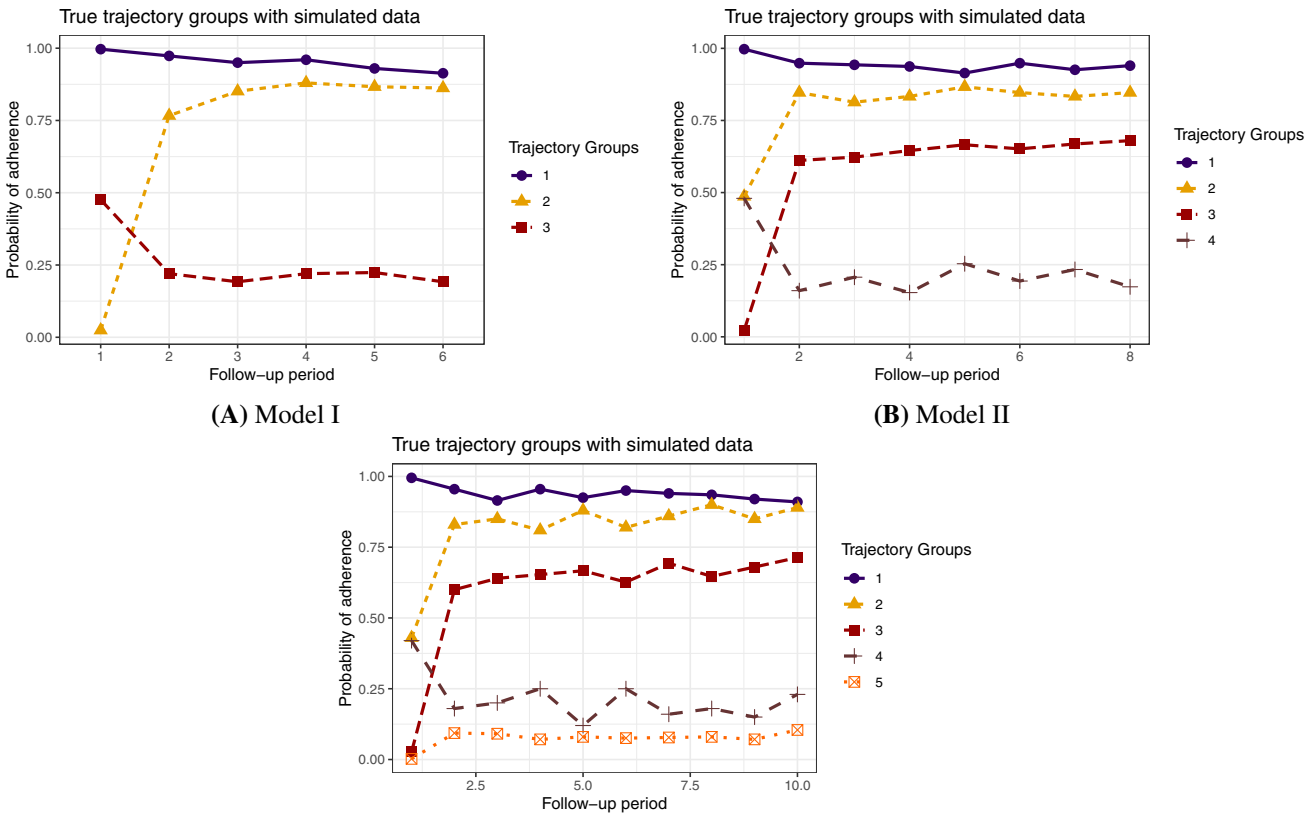
where $L_{j,t}$ is the j^{th} group's covariate value at time t, $A_{j,t}$ is the j^{th} group's treatment at time t, and $\beta_{j,0},...,\beta_{j,4}$ parameterize the trajectory for the j^{th} group. For three trajectory groups, we used $\beta_{1,0} = \cdots = \beta_{1,4} = 1.42$, $\beta_{2,0} = \cdots = \beta_{2,4} = 0.83$, and $\beta_{3,0} = \cdots = \beta_{3,4} = -0.67$. For four and five trajectory groups, we additionally used $\beta_{4,0} = \cdots = \beta_{4,4} = 0.25$ and $\beta_{5,0} = \cdots = \beta_{5,4} = -1.42$.

4.2 | Scenarios

To provide different perspectives on how treatment is modeled, we considered three scenarios, allowing for a comprehensive assessment of various factors.

- *Scenario I*: Modeling of the treatment does not involve covariates. Only a polynomial function of time is estimated.
- *Scenario II*: Modeling of the time-varying treatment includes only baseline values. No time-varying covariates are considered.
- *Scenario III*: Both baseline values and time-varying covariates are incorporated in the treatment model.

Data for this study were generated by considering fixed numbers of three, four, and five trajectory groups, which represent models I, II, and III, respectively. The goal is to identify these groups using PDC, KML, and GBTM. Moreover, we aimed to address both the *cat's cradle effect* and the *rainbow effect*.[35] The cat's cradle effect refers to GBTM's tendency to identify four distinct groups across different settings, including low and high adherence as well as increasing and decreasing adherence patterns, as observed in prior research.[35] The rainbow effect, on the other hand, occurs when the boundaries between trajectory groups become less clear.[35] Figure 2 reveals the average treatment adherence over time for the different groups in the labelled data as it was generated. The reader can notice the existence of low and high adherence patterns in all three scenarios. Models II and III in particular, also contain increasing and decreasing



(A) Model I

(B) Model II

(C) Model III

FIGURE 2 Trajectory models considered for the simulation study.

adherence patterns. In all three models, trajectories 1 and 2 were hard to disentangle at later time points, while in model III, trajectories 4 and 5 also very nearly overlap.

The time-varying treatment variable was generated using a binary distribution, indicating whether or not a patient took the treatment at each time point during the follow-up period. Alternatively, we can think of it as the presence or absence of a claim date in the database. Crucially, the data was generated without allowing for stockpiling, which can occur in real-world scenarios. Time-varying covariate was also generated using a binary distribution, while the baseline covariate followed a normal distribution. Various treatment models were explored, including linear, quadratic, and cubic functions of time, as well as models that incorporated baseline and time-varying covariates. Note that this was only done for GBTM. Indeed, PDC is deterministic and KML is not designed for modeling variables as functions of others.

4.3 | Performance measures

To evaluate the performance of different medication adherence approaches, we considered different metrics. The main quantity of interest is the absolute bias, which is used in the calculation of other metrics. The absolute bias is computed as the difference between the true treatment adherence and the estimated treatment adherence. True adherence is defined as the proportion of the observed treatment within each group initially chosen when generating the data, while estimated treatment adherence is defined as the proportion of the observed treatment within each group identified using either PDC, KML, or GBTM.

1. Absolute Bias (AB)

$$\mathrm{AB} = P_{\mathrm{true}}(\mathrm{Adherence}) - P_{\mathrm{estimated}}(\mathrm{Adherence}). \tag{10}$$

2. Relative Bias (RB): the bias of one method relative to another. For example

$$\mathrm{RB}_{\mathrm{PDC/GBTM}} = \mathrm{AB}_{\mathrm{PDC}}/\mathrm{AB}_{\mathrm{GBTM}}. \tag{11}$$

3. Relative Variance (RV): the relative difference in variance between two methods. For example

$$\mathrm{RV}_{\mathrm{PDC/GBTM}} = \mathrm{Var}_{\mathrm{PDC}}/\mathrm{Var}_{\mathrm{GBTM}} \tag{12}$$

4. C-statistics: The overall predictive accuracy for predicting adherence is defined as the area under the receiver operating characteristic (ROC) curve.[36] Higher C-statistic values signify superior discrimination.
5. Monte Carlo Error: The Monte Carlo standard error for the bias is estimated by

$$\mathrm{Var}_{\mathrm{Method}}/\sqrt{B}, \tag{13}$$

where $\mathrm{Var}_{\mathrm{Method}}$ is the variance of the adherence estimates using GBTM, KML, or PDC and B the number of replications for the simulation study.[37]

These metrics provide a comprehensive assessment of the model's performance by quantifying the accuracy of adherence probability estimation and the variability between different models.

5 | SIMULATION RESULTS

Tables 1–3 display the results of the simulation study for all three scenarios: modeling the treatment in GBTM as a function of time alone, time and baseline covariates, and time and time-varying covariates, for 3,4, and 5 trajectory groups. The results are presented for various sample sizes (n = 100, 500, 1000, and 5000) and polynomial degree to model the treatment in GBTM: linear, cubic, quadratic, quadratic with baseline, and quadratic with baseline and time-varying covariates. For each simulation, we performed 1000 replications.

Overall for most of the trajectory groups, GBTM demonstrated lower relative bias, even when models were misspecified. For instance in Table 1, in Scenario I, the relative bias for trajectory groups 1 and 2 was two to three times higher in PDC compared to GBTM with a quadratic function of time. Similarly, for KML, the adherence estimates for trajectory group 2 were almost three times more biased than those obtained with GBTM. In terms of variance of the adherence estimates, PDC and KML exhibited lower overall variance compared to GBTM. This result is expected as these approaches cannot fully capture the heterogeneity present in the data compared to a probabilistic approach such as GBTM.

In Table 4, where we compared GBTM and KML across longer follow-up periods, we found that extending the follow-up period did not seem to impact GBTM's performance. We noted that the biases in GBTM remained relatively consistent for longer follow-up periods of 24, 100, and 365 days. The accuracy of predictions measured with the C-statistics was good for both GBTM and KML, even for a period of 365 days, with nearly 1 for GBTM and 0.97 for KML.

In Models I–III, we included trajectory groups that were close enough to simulate a lack of variability within the data. When the separation between trajectory groups was minimal, all methods yielded biased adherence estimates, particularly for trajectory groups 1 and 2 for all models (see Figure 2). In such scenarios, GBTM faces difficulties in accurately identifying the trajectory groups, as also demonstrated in Reference 32 However, GBTM produced for most of the trajectory groups the least biased estimates. Interestingly, including both baseline and time-varying covariates in the treatment model did not appear to enhance the trajectory model's ability to capture adherence patterns (see Figure 3). As the sample size increased, we observed a reduction in both bias and variance. These results held true for

TABLE 1 Relative bias and variance when comparing PDC and KML to GBTM for three trajectory groups.

		Scenario I				Scenario II				Scenario III			
		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2	
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 100$	Group 1	0.78	0.91	0.39	0.94	0.8	0.87	0.41	0.95	0.30	0.08	0.69	0.20
	Group 2	3.41	0.14	3.08	0.82	3.2	0.14	2.95	0.85	1.47	0.05	1.24	0.42
	Group 3	3.79	0.36	1.12	0.36	3.5	0.37	1.05	0.39	14.07	0.74	3.50	0.52
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 500$	Group 1	0.74	0.60	0.42	0.81	0.73	0.61	0.40	0.76	0.78	0.47	0.44	0.64
	Group 2	3.52	0.04	2.94	1.18	3.65	0.05	3.06	1.16	3.54	0.02	2.87	0.75
	Group 3	2.83	0.12	0.85	0.24	2.93	0.13	0.88	0.21	3.30	0.08	0.97	0.17
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 1000$	Group 1	2.65	0.06	0.79	0.20	2.63	0.07	0.78	0.21	3.04	0.05	0.94	0.15
	Group 2	3.47	0.03	2.96	1.62	3.49	0.03	2.91	1.65	3.52	0.02	3.01	0.90
	Group 3	0.73	0.44	0.41	0.80	0.73	0.46	0.40	0.81	0.76	0.38	0.42	0.64
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 5000$	Group 1	2.19	0.01	0.73	0.19	2.25	0.01	0.74	0.18	2.49	0.01	0.81	0.12
	Group 2	3.02	0.01	2.58	1.76	3.16	0.01	2.69	1.76	3.26	0.00	2.73	1.05
	Group 3	0.75	0.15	0.43	0.66	0.74	0.12	0.42	0.59	0.75	0.11	0.43	0.54

Note: Scenario I: In GBTM, the treatment is modeled with only a function of time; Scenario II: In GBTM, the treatment is modeled with a function of time and baseline covariates; Scenario III: In GBTM, the treatment is modeled with a function of time, baseline and time-varying covariates.
Abbreviations: GBTM2, group-based trajectory modeling with a quadratic function of time; KML, K-means longitudinal; PDC, proportion of days covered.

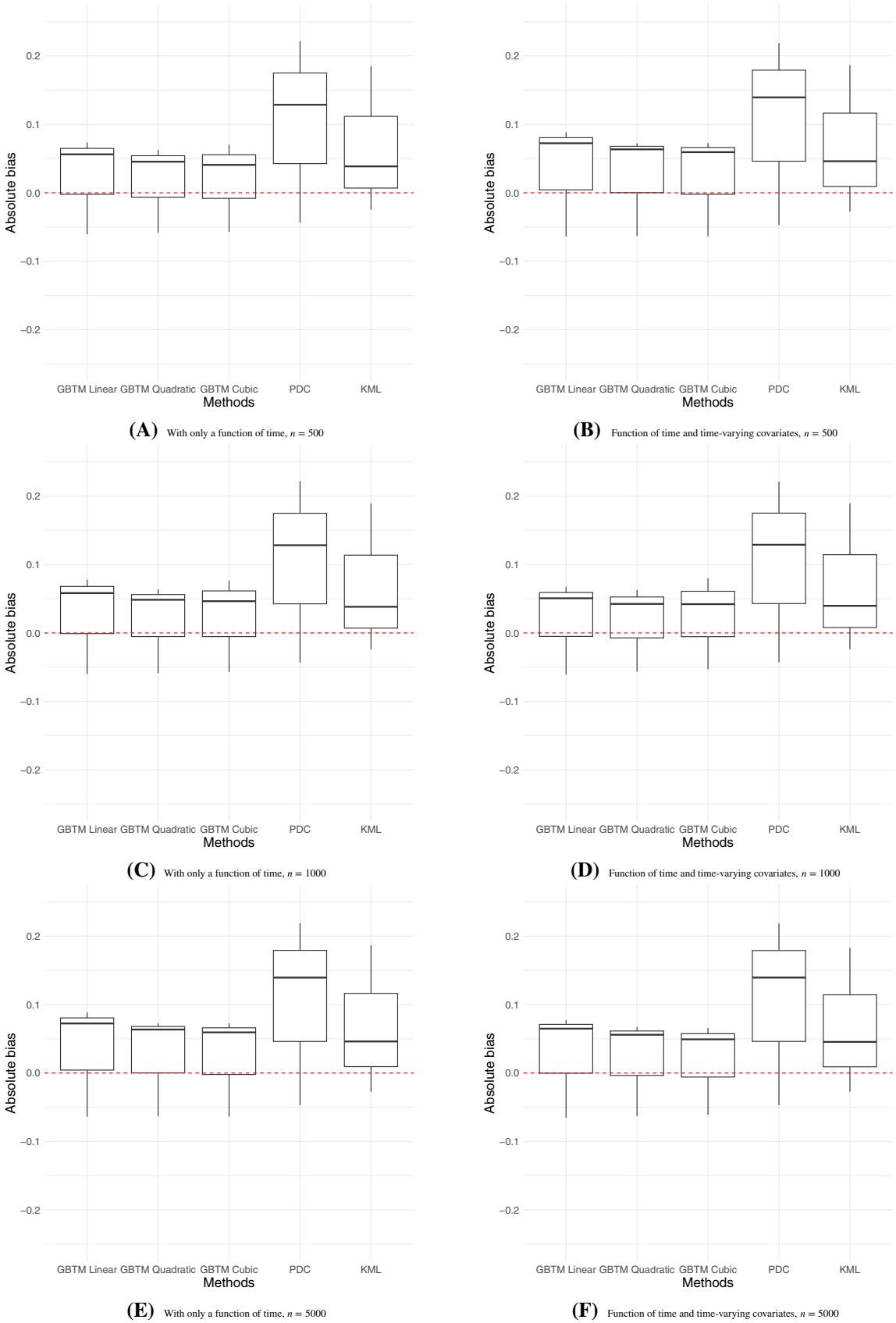


FIGURE 3 Absolute bias with three trajectory groups and different model for the treatment. GBTM, group-based trajectory modeling; KML, K-means longitudinal; PDC, proportion of days covered.

TABLE 2 Relative bias and variance when comparing PDC and KML to GBTM for four trajectory groups.

		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2	
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 100$	Group 1	2.50	0.02	0.63	0.01	−0.44	0.10	−0.11	0.05	−0.31	0.06	1.43	0.13
	Group 2	7.39	0.12	−0.13	0.03	5.10	0.14	−0.12	0.05	2.32	0.20	2.00	1.00
	Group 3	5.02	0.36	−2.83	0.19	3.04	0.23	−1.68	0.12	1.75	0.17	3.51	0.60
	Group 4	2.58	0.29	−5.85	0.27	−2.25	0.26	5.12	0.26	−4.47	0.56	−0.45	0.69
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 500$	Group 1	0.41	0.02	0.02	0.01	−1.31	0.03	−0.01	0.01	−0.65	0.23	0.63	0.88
	Group 2	5.19	0.15	−2.97	0.04	−3.62	0.07	2.08	0.02	−10.76	0.03	−17.34	0.27
	Group 3	5.09	0.03	−0.02	0.01	8.58	0.05	−0.06	0.02	2.94	0.13	1.34	2.27
	Group 4	2.52	0.09	−5.18	0.09	49.80	0.38	−101.28	0.38	13.70	0.98	4.93	1.70
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 1{,}000$	Group 1	0.39	0.01	0.00	0.01	−1.26	0.03	−0.04	0.01	−0.53	0.20	0.27	1.01
	Group 2	6.10	0.09	−3.55	0.02	−1.89	0.05	1.11	0.01	−2.99	0.02	−4.77	0.24
	Group 3	3.73	0.01	−0.02	0.01	10.10	0.05	−0.02	0.01	3.68	0.10	1.45	2.86
	Group 4	2.40	0.05	−4.84	0.05	13.58	0.36	−27.38	0.36	8.82	0.84	3.50	1.78
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 5{,}000$	Group 1	0.36	0.34	0.00	0.15	−1.11	0.01	−0.01	0.00	−0.42	0.12	0.11	1.92
	Group 2	9.04	0.02	−5.27	0.01	−1.26	0.02	0.73	0.00	−1.09	0.01	−1.73	0.53
	Group 3	3.89	0.00	0.00	0.00	55.84	0.02	−0.02	0.01	5.23	0.07	1.95	10.11
	Group 4	2.75	0.02	−5.52	0.02	7.29	0.17	−14.57	0.19	7.78	1.00	3.09	4.89

Note: Scenario I: In GBTM, the treatment is modeled with only a function of time; Scenario II: In GBTM, the treatment is modeled with a function of time and baseline covariates; Scenario III: In GBTM, the treatment is modeled with a function of time, baseline and time-varying covariates.
Abbreviations: GBTM2, group-based trajectory modeling with a quadratic function of time; KML, K-means longitudinal; PDC, proportion of days covered.

different numbers of trajectory groups (see Tables 2, 3 and Figures 4, 5). We observed that for three trajectory groups, biases were generally low for GBTM compared to PDC and KML. However, as we increased the model's complexity—by raising the number of trajectory groups to 4 and 5 and including covariates—there was a noticeable decline in GBTM's performance relative to PDC and KML small sample sizes ($n = 100$). Notably, in the scenario of five groups, the model failed to converge when both baseline and time-varying covariates were incorporated into the GBTM model. Despite these challenges, GBTM demonstrated overall robustness in identifying trajectory groups even in the presence of a small sample size.

The Monte Carlo error ranged from 0.0004 to 0.001 overall. The accuracy of prediction (C-statistic) was high when dealing with three trajectory groups, approaching a value of 1. However, as the number of trajectory groups increased, the accuracy of prediction decreased for KML. For instance, the accuracy of prediction reached 0.61 when the number of trajectory groups was 5, and $n = 5000$. GBTM and PDC maintained a level of accuracy of prediction between 0.98 and 1 for 5 trajectory groups, and $n = 5000$.

5.1 | Illustration of three trajectory groups from a single dataset

Here, we wish to provide a clear illustration of the different methods in use. A dataset of size $n = 1000$ was generated, featuring three trajectory groups using the data-generating mechanism defined in Section 4.1. The true trajectory groups are depicted in Figure 6A. These groups consist of a highly adherent group (Group 1), a group of individuals who progressively adhere to the treatment (Group 2), and a third group of individuals with the lowest adherence to the treatment (Group 3). The treatment was modeled with GBTM using various functions of time, including linear, quadratic, cubic, quadratic with baseline, and time-varying covariates, as well as the KML and PDC methods.

TABLE 3 Relative bias and variance when comparing PDC and KML to GBTM for five trajectory groups.

		Scenario I				Scenario II				Scenario III			
		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2		PDC/GBTM2		KML/GBTM2	
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 100$	Group 1	−0.14	0.01	0.20	0.01	−0.24	0.06	0.35	0.02	NA	NA	NA	NA
	Group 2	0.85	0.20	3.45	0.58	0.60	0.24	2.45	0.67	NA	NA	NA	NA
	Group 3	0.32	0.16	1.31	0.51	0.58	0.16	1.99	0.49	NA	NA	NA	NA
	Group 4	4.08	0.13	6.11	0.75	1.37	0.08	2.23	0.45	NA	NA	NA	NA
	Group 5	0.09	0.08	−0.77	0.27	−0.16	0.08	1.53	0.27	NA	NA	NA	NA
n = 500	Group 1	0.14	0.03	0.00	0.20	−0.24	0.03	−0.06	0.24	−1.25	0.06	0.30	0.45
	Group 2	1.73	0.04	1.34	0.61	0.75	0.02	0.56	0.32	2.01	0.03	1.54	0.61
	Group 3	0.46	0.04	2.15	0.52	12.54	0.06	60.79	0.75	0.37	0.05	1.63	0.68
	Group 4	1.49	0.08	4.88	1.00	1.47	0.10	4.74	1.23	0.53	0.05	1.64	0.64
	Group 5	−0.26	0.00	0.07	0.00	−1.44	0.01	0.26	0.03	−1.47	0.03	0.29	0.07
		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
$n = 1{,}000$	Group 1	0.13	0.02	0.22	0.28	−0.18	0.02	−0.17	0.32	−1.12	0.05	−2.01	0.84
	Group 2	1.72	0.02	0.89	0.51	0.70	0.01	0.36	0.30	2.10	0.03	1.00	0.58
	Group 3	0.48	0.02	2.47	0.66	5.42	0.03	26.62	0.94	0.33	0.02	1.68	0.69
	Group 4	2.48	0.05	5.97	1.31	2.39	0.05	5.62	1.11	0.57	0.03	1.33	0.61
	Group 5	−0.24	0.00	−0.02	0.00	−1.48	0.00	−0.22	0.01	−1.25	0.01	−0.14	0.03
$n = 5{,}000$		RB	RV	RB	RV	RB	RV	RB	RV	RB	RV	RB	RV
	Group 1	0.20	0.01	0.88	0.44	−0.94	0.00	−0.38	0.01	−1.69	0.02	−7.28	1.71
	Group 2	1.42	0.01	0.63	0.39	−6.31	0.01	−8.74	0.73	2.19	0.01	0.98	0.46
	Group 3	0.54	0.01	3.18	0.68	1.79	0.01	10.19	0.84	0.30	0.00	1.71	0.52
	Group 4	29.21	0.02	41.43	1.54	0.75	0.00	0.34	0.30	0.81	0.00	1.15	0.38
	Group 5	−0.25	0.00	−0.10	0.00	−0.23	0.01	−1.02	0.40	−1.03	0.00	−0.41	0.01

Note: Scenario I: In GBTM, the treatment is modeled with only a function of time; Scenario II: In GBTM, the treatment is modeled with a function of time and baseline covariates; Scenario III: In GBTM, the treatment is modeled with a function of time, baseline and time-varying covariates. Here, NA stands for non-available.

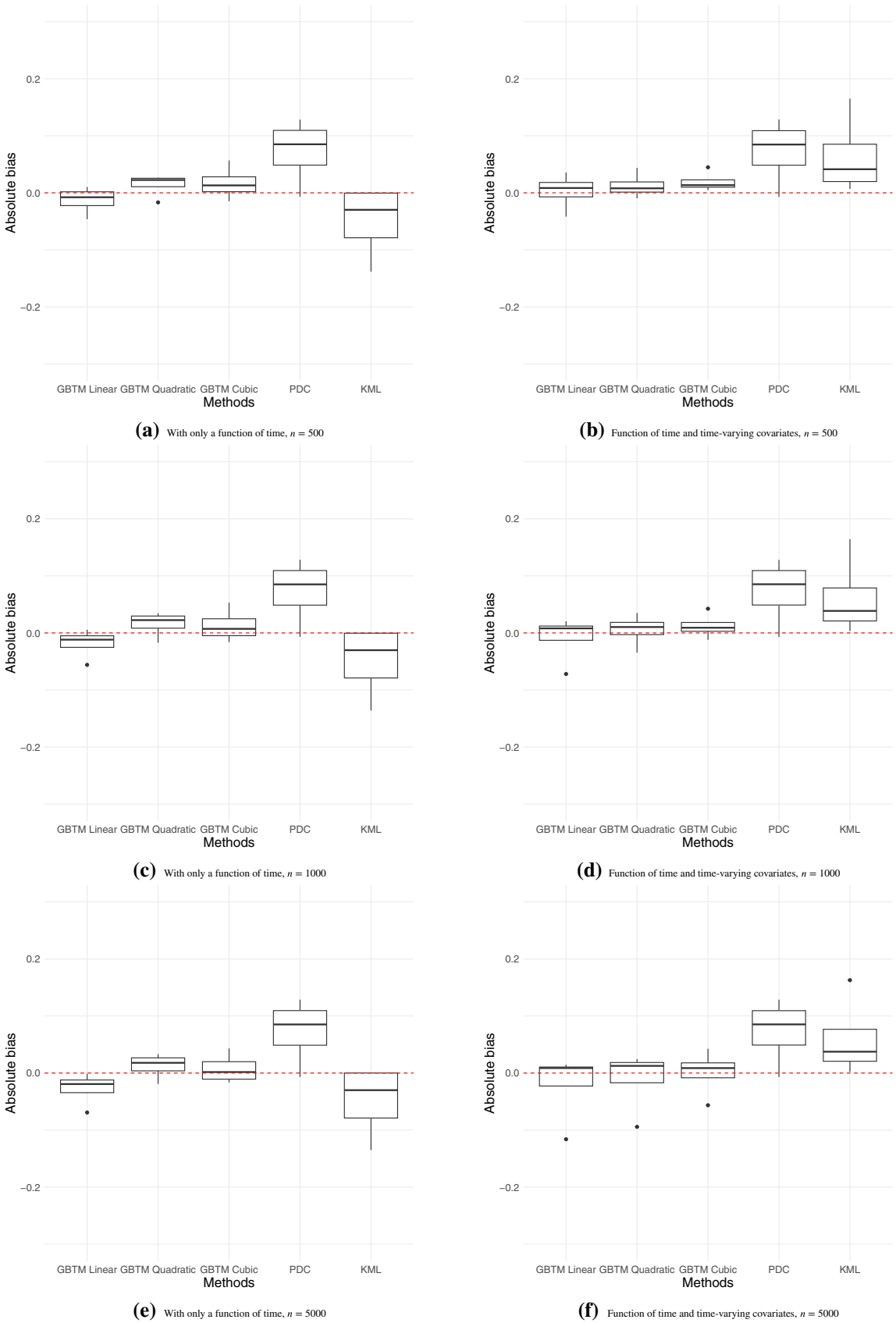
Abbreviations: GBTM2, group-based trajectory modeling with a quadratic function of time; KML, K-means longitudinal; PDC, proportion of days covered.

TABLE 4 Comparison of GBTM and KML in terms of absolute bias for longer follow-up periods and $n = 1000$.

	24 periods		100 periods		365 periods	
	GBTM	KML	GBTM	KML	GBTM	KML
Group 1	−0.094	−0.075	−0.109	−0.090	−0.108	−0.090
Group 2	0.011	0.152	0.016	0.143	0.011	0.127
Group 3	0.005	0.024	0.006	0.017	0.004	0.012

Abbreviations: GBTM, group-based trajectory modeling with a linear function of time; KML, K-Means longitudinal.

In this illustration of a single simulated dataset, GBTM with quadratic and cubic functions of time appeared to capture the true trajectory groups the best. This observation aligns with the fact that the data was simulated using a quadratic function of time-varying covariates. It is important to note that these results may vary when fitting other GBTM or KML models, even with the same dataset. Indeed, the parameters of a mixture model are typically estimated using an iterative method based on the maximum likelihood principle, such as the expectation–maximization (EM) algorithm.[38] Consequently, the estimation is influenced by the initial starting points, and there is no guarantee of finding the global maximum.[38] This entails that a local maximum might be identified, which provides a solution



(a) With only a function of time, $n = 500$

(b) Function of time and time-varying covariates, $n = 500$

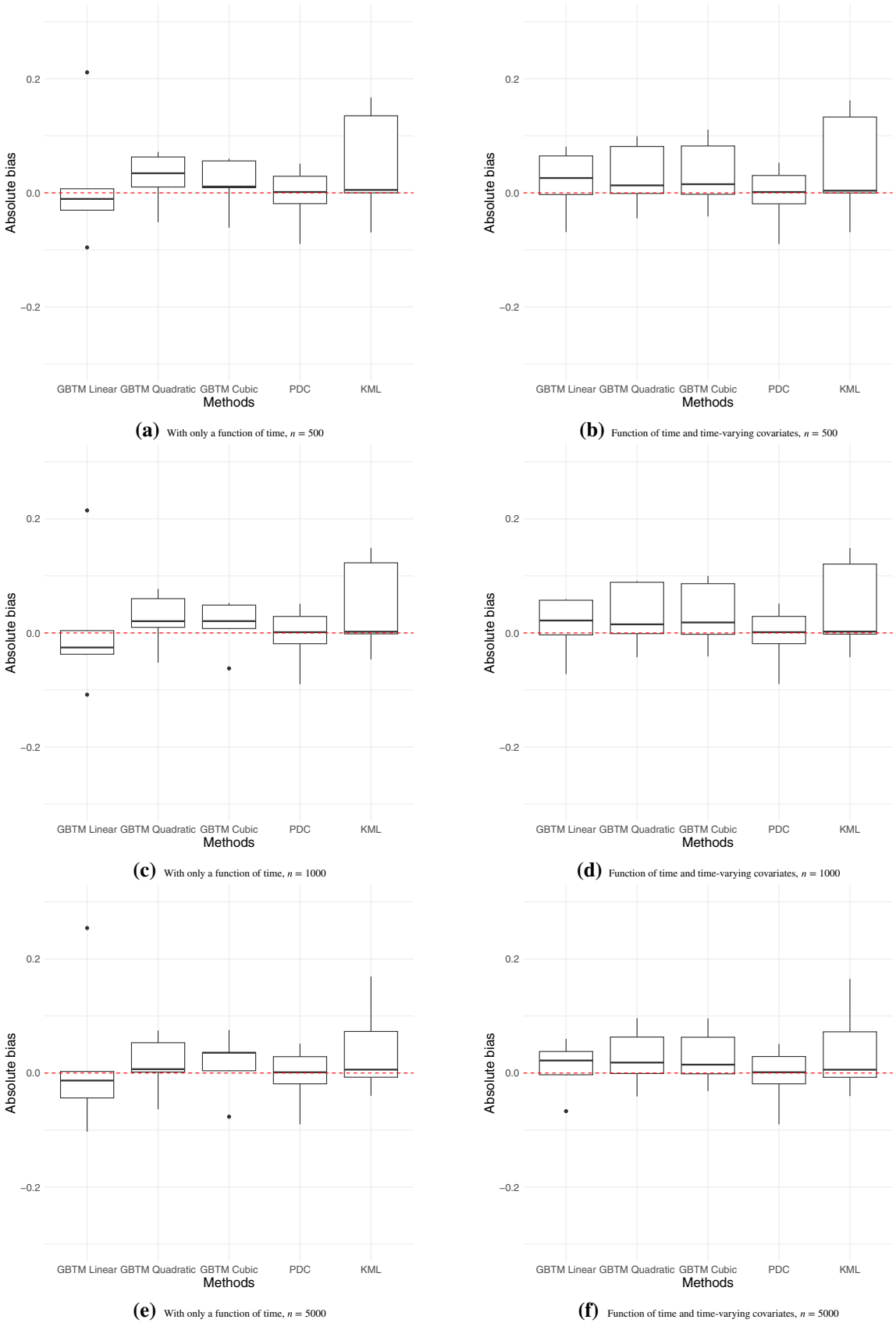
(c) With only a function of time, $n = 1000$

(d) Function of time and time-varying covariates, $n = 1000$

(e) With only a function of time, $n = 5000$

(f) Function of time and time-varying covariates, $n = 5000$

FIGURE 4 Absolute bias with four trajectory groups and different model for the treatment. GBTM, group-based trajectory modeling; KML, K-means longitudinal; PDC, proportion of days covered.



(a) With only a function of time, $n = 500$

(b) Function of time and time-varying covariates, $n = 500$

(c) With only a function of time, $n = 1000$

(d) Function of time and time-varying covariates, $n = 1000$

(e) With only a function of time, $n = 5000$

(f) Function of time and time-varying covariates, $n = 5000$

FIGURE 5 Absolute bias with five trajectory groups and different model for the treatment. GBTM, group-based trajectory modeling; KML, K-means longitudinal; PDC, proportion of days covered.

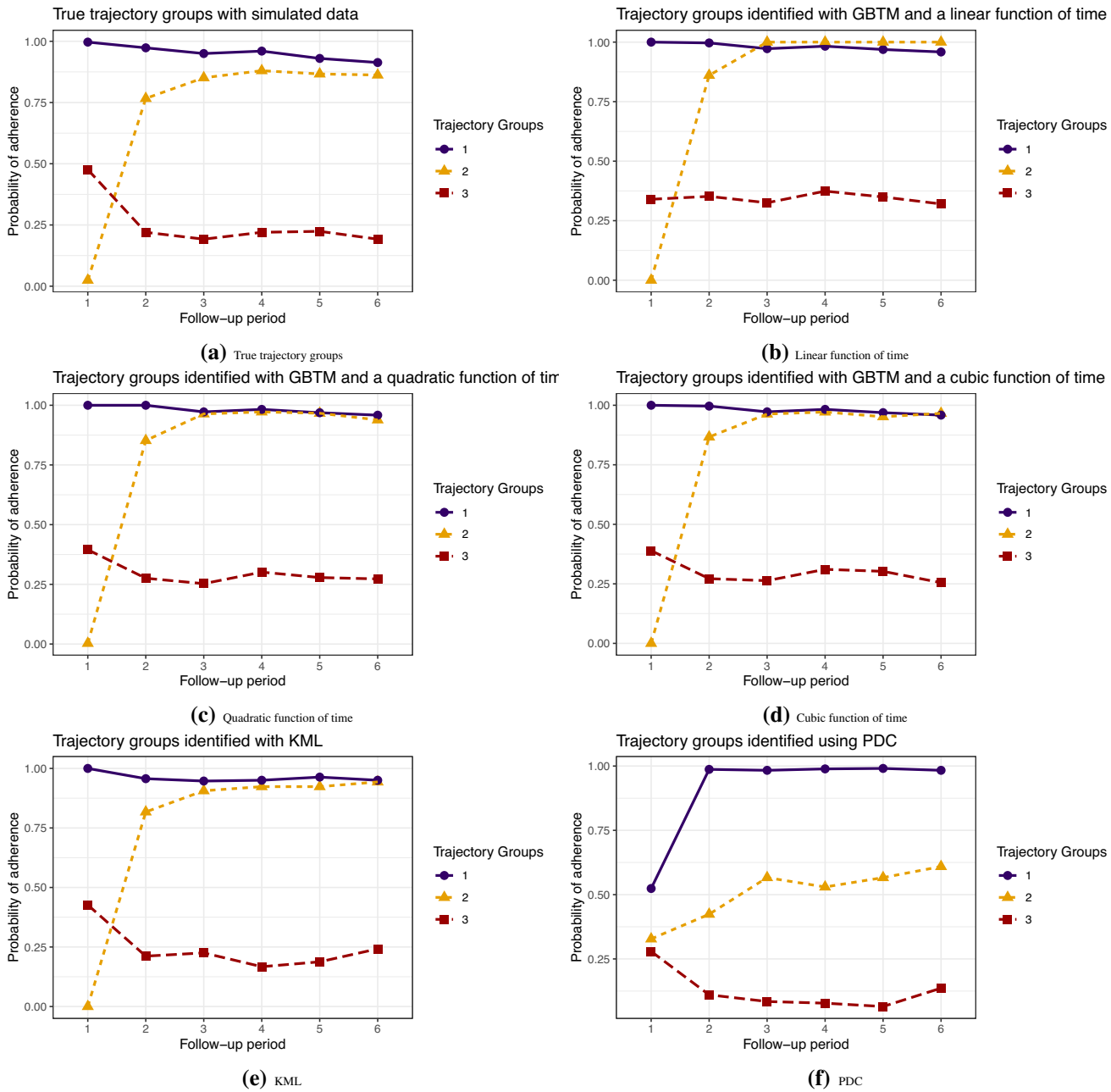


FIGURE 6 Ability of GBTM, KML and PDC to capture medication adherence through visualization. GBTM, group-based trajectory modeling; KML, K-means longitudinal; PDC, proportion of days covered.

TABLE 5 Choice of the best GBTM model.

	BIC	EIC	APPA	OCC
Linear	13,147	0.98	≥0.99	> 500
Quadratic	12,972	0.99	≥0.99	> 1100
Cubic	13,075	1.00	∼1.00	> 1000
Quadratic + Time-varying Covariates	13,002	0.99	∼1.00	> 500

Abbreviations: APPA, average posterior probability of assignment; BIC, Bayesian criterion information; EIC, entropy information criterion; GBTM, group-based trajectory modeling; OCC, odds of correct classification.

confined to a specific neighborhood of the overall distribution. Such a solution may not necessarily have the highest likelihood, as would be the case with a global maximum. Consequently, the solutions might vary with each iteration, even when using the same dataset. This is also true for other clustering algorithms, such as KML. PDC, however, remains consistent as it does not rely on any specific modeling assumptions.

For GBTM, metrics such as BIC, EIC, APPA, and OCC can be calculated to select the best model. In Table 5, the GBTM model with a quadratic function of time emerges as the best choice. Specifically, this model exhibits the lowest BIC, the highest OCC, and relatively good and comparable EIC and APPA scores when compared to other modeling options.

5.2 | Guidance for practitioners

In this section, we outline guidance on how to use GBTM in practice and cases where KML can be considered.

5.2.1 | Model selection and adequacy

When performing GBTM, we recommend that practitioners go beyond the BIC and entropy and explore other metrics such as APPA or OCC for model selection and adequacy assessment. Our findings indicate that when using GBTM the accuracy of predictions was not affected by the number of groups considered or the length of the follow-up period. In contrast, the accuracy of KML was impacted by the number of groups. These results highlight the fact that GBTM is a robust approach for summarizing patterns in treatment trajectories.

5.2.2 | Model specification and inclusion of covariates

In our simulations, inclusion of covariates did not significantly improve GBTM's ability to identify different trajectory groups. GBTM primarily aims at identifying groups of individuals with similar patterns over time. Including covariates can make the interpretation of trajectories more complex due to the interactions between the time-varying variable and the covariates. Moreover, GBTM focuses on identifying clusters of individuals following similar temporal patterns. Using solely a polynomial function of time to model treatment trajectories enables the model to capture each group's inherent trajectory based on observed data points. This method prioritizes trajectory shapes, often the primary interest in such analyses. Polynomial functions offer flexibility in modeling a wide range of trajectory shapes, including linear, quadratic, or cubic trends, allowing the model to fit complex patterns over time without additional covariates. Our findings suggested that a relatively simple model specification for GBTM, such as a polynomial function of time, can be sufficient for identifying hidden trajectory groups with relatively low biases.

5.2.3 | Sample sizes

Overall, GBTM performed better than PDC and KML for three trajectory groups but showed reduced performance as model complexity increased. Based on our findings, GBTM model achieved adequate performance and convergence with small sample sizes. This result holds when the number of trajectory groups is limited, and a low degree of the polynomial function is chosen.

5.2.4 | Optimal follow-up period

The optimal follow-up period necessary for identifying the number of groups can be computed based on the identifiability conditions. It is noteworthy that additional factors such as clinical relevance and insights from existing literature, should be considered, when determining the optimal length of follow-up periods.

5.2.5 | Role of covariates in predicting medication adherence

Covariates play an important role in mapping patient health status to their adherence probability, understanding different adherence profiles, and predicting adherence probability. We recommend a two-step approach. In a first step, trajectory groups can be identified using a polynomial function of time. Then, association between groups and covariates can be investigated using a descriptive or predictive method. This approach allows to separate the identification step of trajectory groups from the groups' characterization.

5.2.6 | Computational challenges

GBTM can pose computational challenges when handling large datasets or when dealing with numerous groups with high polynomial degrees. For example, with $n = 50{,}000$ and 6 periods, GBTM, using a simple linear function of time, required 387 s (6.45 min), whereas KML took approximately 121.8 s (2.03 min). For $n = 1000$ and 365 periods, GBTM needed 10.45 s, compared to KML's 3.53 s. Consequently, performing GBTM with large datasets can be demanding. In presence of large datasets, KML can be considered for a first assessment of trajectory groups.

6 | DISCUSSION

In this paper, we compared GBTM with PDC and KML methods for their performance in modeling medication adherence. This comparison takes into account various factors, including different follow-up periods, the number of groups, and the functional forms of time and covariates. To the best of our knowledge, our study represents the first study that assessed the performance of GBTM in identifying medication adherence groups. Under the scenarios explored in our study, we found the GBTM to stand out in terms of bias in the estimation of adherence, whereas the PDC approach showed the highest degree of bias. This finding highlights the limitations of PDC in capturing the complexities of dynamic (time-varying) medication adherence. For GBTM, our findings suggest that employing a relatively simple model specification such as a polynomial function of time is sufficient for identifying with relatively low biases hidden trajectory groups, if they exist. In other words, directly including baseline and time-varying covariates in the group-based trajectory model does not seem to improve its ability to capture medication adherence. However, covariates are useful for mapping patient health status to their adherence probability, in understanding the different adherence profiles and in predicting adherence probability.

This study has its own limitations. Despite GBTM performing the best, it still produced considerable bias in the adherence estimates. This points to the need for more methodological research to improve the way GBTM is used to model and study medication adherence. While we showed in this study the superiority, on average, of GBTM compared to PDC and KML, the identified trajectory groups may lack clear clinical significance or interpretation. Nonetheless, GBTM takes a more rigorous approach in selecting thresholds than situations where choices may be made arbitrarily, as can occur with PDC. Indeed, the use of checklists such as GRoLTS and numerous metrics for assessing adherence modeling quality in GBTM can improve the quality of future applications. GBTM operates within a statistical framework that allows for the testing of hypotheses about the number and nature of the trajectory groups, as well as the inclusion of covariates and the examination of group membership probabilities. This provides a rich interpretive framework for understanding the groups. In contrast, KML clustering is more of a descriptive, data-driven approach. It is useful for exploratory data analysis but lacks the statistical underpinning for hypothesis testing or probabilistic interpretation of group membership.

In future directions, Bayesian variants of GBTM that can incorporate prior knowledge about trajectory groups should be further explored, to see if these approaches can lower the observed bias in the adherence estimates. Although this work offers significant contributions to understanding the performance of GBTM and its practical applications, further research is needed to explore the remaining possibilities encountered when using GBTM. Investigation of alternative approaches specifying the dynamic relationship between the time-varying treatment adherence and time-varying covariates could be examined to see if bias in adherence estimation could be mitigated. It would be also interesting to investigate how to improve the scalability of GBTM in the presence of large datasets.

Improving the understanding of medication adherence is critical for improving patient outcomes and also to improve the optimization of healthcare resource utilization. Our study illustrates the potential to enhance medication

adherence practices by shedding light on utilizing GBTM and facilitating more tailored interventions. Our research contributes to the existing literature by providing a more thorough understanding of how GBTM models should be used in practice.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Awa Diop https://orcid.org/0000-0002-8646-5305
Ofir Harari https://orcid.org/0000-0002-2901-0558
Miceline Mésidor https://orcid.org/0000-0001-5788-4984

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How to cite this article: Diop A, Gupta A, Mueller S, et al. Assessing the performance of group-based trajectory modeling method to discover different patterns of medication adherence. *Pharmaceutical Statistics*. 2024;23(4): 511-529. doi:10.1002/pst.2365