Published in final edited form as:

Med Decis Making. 2019 February ; 39(2): 137–151. doi:10.1177/0272989X18817521.

DEVELOPMENT AND VALIDATION OF THE REAL-WORLD PROGRESSION IN DIABETES (RAPIDS) MODEL

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Abstract

INTRODUCTION: To develop and validate the first real-world-data based Type II diabetes progression model (RAPIDS) employing econometric techniques that can study the comparative effects of complex dynamic patterns of glucose-lowering drug use.

METHODS: The US Department of Veterans Affairs (VA) EMR and claims databases were used to identify over 500,000 diabetes patients in 2003 with up to 9-year follow-up. The RAPIDS model contains interdependent first-order Markov processes over quarters for each of the micro and macro-vascular events, hypoglycemia, and death, and predictive models for eight biomarker levels. Model parameters varied by static demographic factors, and dynamic factors, such as age, duration of diabetes, thirteen-possible glucose –lowering treatment combinations, any blood pressure, and any cholesterol-lowering medications, and cardiovascular history. To illustrate model capabilities, a simple comparative study was set up to compare observed treatment use patterns to alternate patterns if perfect adherence is assumed following initiating the use of any of these medications.

RESULTS: Data were randomly split into 307,288, 105,195, and 105,081 patients to perform estimation, out-of-sample calibration, and validation respectively. Model predictions in the validation sample closely aligned with the observed longitudinal trajectory of biomarkers and outcomes. Perfect adherence among initiators increased proportion-of-days covered by only six months. Most of this increase came from increased adherence to monotherapies and did not lead to meaningful changes in any of the outcomes over the 9-year period.

CONCLUSION: Future value of increasing medication adherence among VA patients with diabetes may lie among those who never initiate treatment or are late in initiating treatment. The

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first-of-its-kind real-world data based model has the potential to carry out many complex CER studies of dynamic glucose-lowering drug regimens.

INTRODUCTION

In type 2 diabetes, a core component of care is glycemic control, which reduced the long-term risk of microvascular and cardiovascular risks among the newly diagnosed in the UK Prospective Diabetes Study (UKPDS). The maintenance of intensive glucose control typically requires the use of multiple glucose-lowering agents including insulin.¹ Over the past decade, the number of available glucose-lowering agents has expanded creating more options and more uncertainty regarding the optimal approach to glucose control.^{2,3}

This uncertainty is heightened by concerns regarding possible adverse effects of glucose-lowering agents and associated patterns of intensive glucose lowering. In 2008, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial,⁴ the ADVANCE (Action in Diabetes and Vascular Disease) trial,⁵ and the VADT (Veterans Affairs Diabetes Trial),⁶ each aiming to reduce glucose levels to very low levels with the intention of reducing cardiovascular events, released conflicting results. The ACCORD trial demonstrated excessive deaths in the very intensive glucose control arm.⁴ On the other hand, the VADT and ADVANCE trials showed no statistically significant harm of very intensive glucose control but also showed no clear cardiovascular or mortality benefits.^{5,6} The rates of excess deaths in the ACCORD trial in comparison to the VADT and ADVANCE trial have been attributed to the combination and patterns of drugs used, the pace of glucose lowering, as well as distinct risk/benefit profiles for selected patient groups.⁷ In post-trial follow-up of both ACCORD and VADT, cardiovascular benefits of intensive glucose control appeared to emerge.^{8,9} Newer glucose-lowering agents such as the GLP-1 receptor agonists and SGLT-2 inhibitors have been found in drug vs. placebo trials to reduce cardiovascular events and mortality in relatively short timelines among very high-CVD-risk participants.^{10,11} Beyond recommendations to use metformin as first-line therapy, there is considerable uncertainty regarding optimal choice of second or third-line therapy.¹² In real-world clinical practice, physicians continue to use a variety of combinations of older and newer glucose-lowering drugs that are not easily studied in trials.

The extent to which concerns regarding drug combinations, the pace of treatment, and changes in treatment and associated outcomes are relevant for real-world practice remains unknown. In fact, longitudinal patterns of glucose-lowering medications and their associations with diabetes outcomes have not been well studied. To do so will require an understanding of patterns of care seeking that influence the frequency of treatment decisions as well as statistical approaches that capture the details and variability of dynamic treatment decisions. In turn, accounting for selection bias in clinical encounters and treatment decisions will require methods such as instrumental variables. Moreover, establishing these patterns and related outcomes can help define the baseline against which future innovations in diabetes care can be compared. It can inform the relevance of monitoring biomarker levels beyond HbA1c to prescribe the combination of medications and achieving desired outcomes.

In this paper, we describe the development and validation of the first real-world data based progression in Type 2 diabetes model (RAPIDS). The model can evaluate the impact of different dynamic combinations of glucose-lowering drugs on a variety of micro- and macro-vascular outcomes as a function of eight underlying biomarkers for patients with diabetes obtaining care through the US Veterans Affairs (USVA). To illustrate the range of complicated questions that RAPIDS model would be able to answer, we perform a simple comparative analysis to compare observed treatment use patterns to alternate patterns if perfect adherence is assumed among patients who select to initiate treatment using any of these medications.

DATA

Our real-world data consist of all patients with diabetes who were at least 40 years old and treated in the Veterans Affairs (VA) healthcare system in 2003. Patients were identified as having diabetes if they received at least one prescription for a diabetes medication in VA or Medicare data in 2002 or if two or more International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 250.xx were present in any in-patient or out-patient records in 2001 – 2002.¹³ Patients were followed from January 1, 2003, until death or study completion, December 31, 2011. The nine-year study was divided into 90-day periods. Initial quarter of follow-up period for each patient was determined by the first 90-day period where all the biomarkers levels can be inferred (see BIOMARKER section). At least 80% of the patients in our sample had at least one prescription of glucose lowering drug between January 2001 and the first quarter of follow-up period.

The cohort was constructed using data from the VA National Patient Care Database, the VA Decision Support System Pharmacy Datasets, and the Centers for Medicare and Medicaid Services Medicare claims files, including Medicare Part D Event files, available through the VA Information Resource Center.

Data were randomly split into three parts – PART A, B, and C, to carry out different out-of-sample validation exercises as described below.

TREATMENTS

Detailed use of glucose-lowering (GLC) drugs, cholesterol (CHL) lowering drugs and blood pressure (BP) lowering drugs for each patient were extracted from the pharmacy claims databases. For each type of drugs, use was defined as possession of at least a 30-day supply during a 90-day period. If a patient filled a prescription at the end of a period, the remaining days' supply was rolled over to the next period. For this analysis, no distinction between individual CHL drugs or BP drugs was made; they were represented as two broad categories defined by the receipt of any CHL drug and any BP drug. For GLC drugs, use drugs were categorized into twelve categories: 1) NO THERAPY; 2) MONOTHERAPIES: metformin only, sulfonylurea only, thiazolidinediones (TZD) only, and insulin only; 3) DUO-THERAPIES: metformin and sulfonylurea, metformin and TZD, metformin and insulin, sulfonylurea and TZD, sulfonylurea and insulin, and TZD and insulin; 4) TRIPLE THERAPIES AND OTHER – where all combinations beyond duo therapies and any newer

therapies such as DPP-4 inhibitors or GLP-1 agonists were grouped into one category. This last category was combined due to the relatively infrequent use of these regimens in practice during our time period of study (e.g., Table 2).

BIOMARKERS

Data from VA Laboratory Results database and Corporate Data Warehouse vitals database were used to obtain levels of eight different biomarkers for each patient over time. These biomarkers are: hemoglobin A1c, body mass index, HDL and LDL cholesterol, total cholesterol, triglycerides, systolic and diastolic blood pressure. If persons had multiple measurements of these biomarkers within a 90-day period, we used their average values. As typical for most real-world health care systems, these measurements were not recorded for every period. We implement linear interpolation of values between measurements across two periods with missing periods in between. For every patient, the first period where all biomarker levels are either directly measured or inferred based on interpolation marks the index quarter of that patient in our analyses. Thus, the baseline period could be chronologically different for a different patient.

OTHER EXPLANATORY VARIABLES

The following variables were assessed at the beginning of 2003 and were modeled as time-invariant: sex, race/ethnicity, baseline marital status and veteran status. Factors that were allowed to vary over each quarter were age, duration of diabetes (capped at five years before January 1 2003), and histories of myocardial infarction, unstable angina, stroke, and hypoglycemia.

OUTCOMES

A variety of outcomes were identified within each 90-day period. They included events such as: myocardial infarction, unstable angina, stroke, and hypoglycemic episode. In addition, we identified the incidence of congestive heart failure, advanced eye disease, end-stage renal disease (ESRD), lower extremity amputation, and death.

In identifying these conditions, we created a combined list of all ICD-9-CM and CPT-9 codes from both VA and Medicare data files. The list of these codes is shown in online Table A6, linked in the Appendix. The first dates these conditions were recorded were taken as the dates of incidence. For conditions that were recorded only once in the outpatient file throughout the entire follow-up were treated as a rule-out condition and were not identified as an incident condition. ESRD was an exception to this rule. Patients with a minimum of six instances of dialysis-related treatment (see Table A6) along with at least one diagnosis or procedure code of ESRD or outpatient dialysis were taken as evidence of ESRD. We separately identified all patients who have experienced any of these conditions before the baseline for exclusion in the analysis of each outcome separately.

METHODS

Model Development

The RAPIDS model is illustrated in Figure 1. At its heart, it contains a series of first-order Markov processes, one for each of the micro and macro-vascular events, hypoglycemia, and death over subsequent quarters. The transitions in each of these Markov processes are modeled to vary by static demographic risk factors as well as dynamic factors, such as age, duration of diabetes, treatments, cardiovascular history, and all biomarker levels and interactions with age. These factors were also used to predict the biomarker levels in the next period.

The methodological plan to develop parameter estimates for the RAPIDS model is grouped into three parts- Sections I, II and III and summarized in the infographic in Figure 2.

Section I: Causal estimation of treatment effects and validation of subsequent quarter prediction model

Treatment effect models were estimated using Part A data where each of the biomarker and outcome levels in a quarter was modeled as a function of all their levels in the previous quarter, demographics and treatment categories (Table 1 lists all the variables used). To address the selection biases associated with treatment choices in an observational setting, instrumental variables (IV) approach was used. Selection biases would be especially strong in our case since we only adjust for factors that are necessary for the diabetes simulation model. National variation in the clinic-level use-rate of a specific treatment during the year before the previous quarter was used as an instrumental variable to exploit exogenous variation in the treatment choice.¹⁴ A two-stage residual inclusion approach using Anscombe residuals was used for the instrumental variable methods so that the estimated coefficients can be used to obtain estimates of Average Treatment Effects.¹⁵

First-stage (fixed-effect linear model):

$$E(D_{jit}) = a0_i + a1 * X_{i(t-1)} + a2 * Z_{j(t-1)} + a3 * Z_{j(t-1)} * Age_{i(t-1)} \quad (1)$$

j=Treatment indicator, i = individual, t = quarter.

D_{jit} =Indicator for each of the thirteen glucose lowering treatment options, one for any blood-pressure lowering treatment, and another for any cholesterol-lowering treatment	<u>Glucose lowering treatment options</u> Monotherapy: Metformin, Sulfonylurea, Thiazolidinediones (TZD) Duo-therapy: Metformin+Sulfonylurea, +TZD, Metformin+Insulin, Sulfonylurea+TZD, Sulfonylurea+Insulin TZD+Insulin Triple-therapy/others Ref: No treatment
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$X_{i(t-1)}$ = Vector of Age, biomarker, outcome levels, cardiovascular history and treatment use in the previous quarter. (Table A1)

$Z_{j(t-1)}$ = Instrumental variable, VA-clinic-level variation in treatment-specific use rates in the year previous to that quarter. An F-test is conducted using a likelihood-ratio test for including versus excluding Z in the first stage regressions.¹⁶

Results available in Table A2

Second Stage (Non-linear Generalized linear models^{17,18})

$$E(Y_{kit}) = g_k(b_0 + b_2 * W_i + b_3 * X_{i(t-1)} + \sum_j b_{4j} * D_{jit(t-1)} + \sum_j b_{5j} * D_{jit(t-1)} * (Age_{i(t-1)} - 65) + \sum_j b_{6j} * (D_{jit} - \hat{D}_{jit}) + \sum_j b_{7j} * (D_{jit} - \hat{D}_{jit}) * (Age_{i(t-1)} - 65)) \quad (2)$$

k = outcome indicator, W_i = non-time varying patient characteristics, e.g. racial categories, $\hat{D}_{jit}$ = predicted values from first stage regressions, $(D_{jit} - \hat{D}_{jit})$ = treatment-specific first-stage residuals.

Y_{kit} = Levels of biomarker or indicator for each outcome

$g()$: Link Function, see Table A3.

Normalization of predictions based on second stage regression coefficients conditional of $(D_{jit} - \hat{D}_{jit}) = 0$ and validation in Part B data.—

Next, prediction models were developed based on the coefficients from the treatment effects models to predict the subsequent quarter's biomarker and outcome values conditional on previous quarter's levels of all the covariates in the model.¹ Since prospective application of these prediction models would not have values of the IV residuals to condition on, the prediction models were calibrated on Part A data using constant multipliers (β_k), holding all the treatment-specific residuals to zero.

¹Goodness of fit for individual regressions estimators applied to Part A data were assessed both in Part A and in out-of-sample Part B. Hosmer-Lemeshow goodness-of fit tests were used to assess fit. No systematic lack of fit was detected for any of the final regression

$$E(Y_{kit}) = \beta_k * g_k(\hat{b}_0 + \hat{b}_2 * W_i + \hat{b}_3 * X_{i(t-1)} + \sum_j \hat{b}_{4j} * D_{ji(t-1)} + \sum_j \hat{b}_{5j} * D_{ji(t-1)} * (Age_{i(t-1)} - 65)) \quad (3)$$

Finally, these regression-based prediction models were validated using part B data, where each quarter's biomarker levels and outcomes were predicted based on demographics, previous quarter's levels, and treatments.

Results are shown in Table A3

Modeling residual variances for each biomarker—In addition, residual variances for each biomarker from these prediction models were modeled as a function of its mean. These variance model are meant to allow for heteroscedasticity in our micro-simulation model described below.

$$E\{(Y_{kit} - \hat{Y}_{kit})^2\} = \exp(c_0 + c_1 * \ln(\hat{Y}_{kit})), \text{ where } \hat{Y}_{kit} = \hat{E}(Y_{kit}) \quad (4)$$

Results are shown in Table A4

Section II: Developing the RAPIDS microsimulation model

Armed with the prediction models from Section I, a microsimulation model was developed where, conditional on only the observed baseline quarter values of biomarkers and outcomes and the treatment pattern trajectory over 9 years, the prediction models were applied repeatedly over 36 quarters to predict the trajectory of biomarker values of outcomes for each patient in the Part B data. Unlike the validation of regression model predictions in Section I, here we use observed data only from the baseline period for each patient, which are then used to build predictions longitudinally for all future quarters. Note that the prediction model produced estimates of the expected value of a biomarker or outcome for a patient in any quarter. A random draw of individual-level value was then obtained based on the expected value and the modeled heteroscedasticity from Section 1 for continuous biomarkers and assuming Bernoulli distribution for binary outcome variables. These individual values were then used to predict next quarter's expected values using the prediction model. Thousand simulated trajectories over the 9-year period were generated for each patient and then averaged. A detailed pseudo-code on how the econometric regressions were integrated to develop the simulation model is provided in the Appendix.

It is common that a prediction model, which is meant to predict only the subsequent quarter, when applied over many quarters can produce a natural drift in the predicted outcomes from true values. Therefore, the average longitudinal predictions over all patients were fitted to the average observed values using an exponential drift model and an additional parameter was estimated to correct the drift effect by calibrating model predictions to observed values. The predicted values with additional parameter is given as

$$E(\hat{Y}_{kit}) = \hat{Y}_{kit} * \exp(\gamma_k * t) \quad (5)$$

The underlying rationale for such an approach is that it is very likely that the transitional matrices for each outcome will not be stationary over time. However, estimating time-specific transition parameters will lead to over parameterization of this problem, severe overfitting, and difficulty in projecting future trends. Therefore, we use an additional multiplicative factor for each outcome to allow the transitional matrices to be non-stationary over time, but at a constant rate. This approach is similar to introducing time-varying regressor in duration model to allow for non-stationary transitions.¹⁹

Results are shown in Table A5

Section III: Out-of-sample validation of the final RAPIDS micro-simulation model

The final RAPIDS microsimulation model (which combined the calibrated prediction models from Section I and the drift-correction model from Section II) was used to generate similar predictions as in Section II for the Part C data that were not used in any estimation or calibration of the RAPIDS model.

Comparative Assessment

To illustrate the value of the RAPIDS model in answering complex questions about how changing the treatment patterns of glucose-lowering drugs can impact outcomes, a simple comparative study was set up of alternative treatment patterns in Part C data. First, we assess treatment use rates based on total days supply for any glucose-lowering drug available to a patient in any given quarter. We express these use rate using the traditional adherence metric of Proportion of Days Covered (PDC), although 20% of our patients were not observed to initiate any treatment in the baseline period. We then assess how the fraction of this overall use rate is driven by those who do not initiate treatment at all versus those who become non-adherent after initiating treatment. This is important because for our comparative analysis we compared outcomes under observed treatment patterns to the predicted outcomes if patients continued to be adherent to the last glucose lowering drug that they initiate treatment during the follow-up period. So, our alternative treatment use patterns do not affect treatment choices for those who never initiate therapy during the follow-up period. They only affect patients who initiated any glucose-lowering drug such that, following that prescription fill, there was no gap in medication adherence until the end of the 9-year follow-up period. If the patient switched to another drug, they were assumed to continue on that new drug unless they switched again.

RESULTS

The IV analyses were carried out on Part A data on 307,228 individuals. On average, these individuals were followed over 23 quarters (Table 1). Descriptive statistics in the first quarter for these individuals and other parts of the data splits are given in Table 1. These patients, on average, were about 67 years old, 2% female, 65% married and 74% whites. The IVs were

significant predictors of actual treatment choices (F-statistics ranged from 210 to 1979). Goodness-of-fit tests carried out for each outcome model on both Part A and out-of-sample Part B data did not reveal any systematic lack of fit. Predictions from the outcomes models were made holding the IV residuals to zero since future prediction will not have information on these residuals. Additional goodness-of-fit tests were carried out in out-of-sample Part B data on 105,195 individuals with such calibrated outcomes model.

The microsimulation model based on these IV regression parameter estimates was developed and calibrated on Part B data. A multiplicative normalizing factor was added to the prediction model for each outcome in-order to achieve best model fit through calibration. These factors ranged from 0.8295 (ESRD) to 1.3201 (Advanced Eye disease). Most normalizing factors were close to 1 indicating substantial calibration were not required. Results from Section I and II were presented in detail in the online link given in the Appendix.

In Section III, the final microsimulation RAPIDS model was applied to Part C data on 105,081 individuals and its predictions compared with observed outcomes to demonstrate complete out-of-sample validation. We found that the RAPIDS model could consistently predict all biomarker levels (Figure 3), micro- and macrovascular events (Figure 4) and death (Figure 5). The y-axis scales for these figures represent two standard deviations of the corresponding outcome.

In our illustrative comparative study, we found the PDC for any glucose-lowering drug to be about 72.6% on average over the entire follow-up period. About 60.5% of patients had a PDC greater than or equal to 80%. However, this is not a true adherence measure as 10.8% of patients in our sample never initiated any therapy throughout the follow-up. Those who ever initiate therapy have an average PDC of 84.5% after initiation; over 72% achieve PDC 80%. In fact, among these patients, only 8% of patient-quarters over the remaining follow-up period are without any glucose-lowering drugs. This is in line with many other studies that have looked at adherence in patients with diabetes, although most studies have not looked at such a long follow-up.^{20,21,22}

For our analysis, we defined treatment use as having at least 30 days of supply to any glucose-lowering drug within a quarter, as explained under the Treatment definition. Using this criterion, those who were considered to have at least one glucose-lowering drug during a quarter, on average, had 87 (s.e. = 12) days of supply of glucose-lowering drugs. Those who were not identified as having any glucose-lowering drug in a quarter, on average, had 2.6 days (s.e. = 8.6) of supply of glucose-lowering drugs; 87.5% of these quarters have zero days of supply of glucose-lowering drugs.

Figure 6 shows how the patterns of treatments (identified based on whether they have or do not have a glucose-lowering drug in a given quarter) changes with alternative treatment use assumptions for 100 randomly selected patients. Note that although Figure 6 illustrates these changes by grouping monotherapies and duo-therapies, changes were implemented at the specific drug level within our model. Follow-up period remained constant under both treatment use profiles. Table 2 presents the extent of each treatment use under alternative

treatment use profiles. Compared to observed treatment uses, the mean number of quarters with any glucose-lowering drug increased only by two quarters or about six months (17.9 quarters to 20 quarters) under the alternative fully-adherent treatment-use profile. This increase aligns with the traditional adherence rates that we observed post-initiation and indicates that once individuals in this population initiate treatment, they adhere well to that treatment until a treatment switch occurs. In fact, most of the increase in treatment duration under the alternative adherence profile comes from increases in adherence to monotherapies across all the options.

Table 3 reports the consequences of these changed treatment use patterns on long-term outcomes. There were no substantial changes in any outcomes under the alternative treatment patterns. These results suggest that any additional intervention, beyond what is already employed currently, to improve adherence of glucose-lowering drugs in this population may not be valuable.

DISCUSSIONS

The long-term management of glucose control has always been fraught with uncertainty, and this uncertainty has been compounded by the arrival of new classes of glucose-lowering medicines. The questions that providers often face include questions regarding 1) the optimal timing of therapeutic changes and 2) the optimal selection of therapies for a given patient.

Neither one of these complex questions is readily addressed with traditional research methods. Randomized controlled trials of diabetes treatments are resource intensive, typically require prolonged follow-up to see changes in end-stage outcomes, and not flexible enough to evaluate dynamic changes. For example, the UKPDS required ten years of following for the original trial period and another ten years of post-trial follow-up to reveal the full benefits of intensive glucose control versus conventional control.²³ Typical observational pharmaco-epidemiological methods are also unable to address questions regarding the comparative effectiveness of dynamic treatment patterns. By its design, the RAPIDS model is a highly innovative analytic framework that helps to overcome the limitations of these methods.

The RAPIDS model is distinct from existing models of diabetes complications in at least three dimensions. First, many models of diabetes are based on an amalgamation of observations from diverse diabetes studies, and many rely heavily on the UKPDS cohort as a source of data.^{24,25,26} The UKPDS cohort is comprised of individuals willing to participate in a long-term clinical trial, and such individuals may have behaviors related to medication adherence and self-care that are fundamentally different from those of the majority of patients. The RAPIDS model is unique in that its source data come entirely from a real-world population. Second, RAPIDS is purposely designed to address comparative effectiveness questions. Most prior models did not even account for the presence of medications. RAPIDS accounts for the use of glucose and blood pressure lowering medicines as well as statins. Third, RAPIDS was developed with econometric techniques including the application of novel instrumental variables. The model accounts for selection

issues related to prescribing behaviors of physicians by exploiting the large variation in the use of alternative glucose-lowering medications across the clinics in VA and over time.

The RAPIDS model can be used for both clinical decision-making and also to evaluate population-level policies. As it currently stands, one of the unique future use of such a model is to predict trajectories of outcomes for individual patients with specific levels of baseline values under alternative glucose intensification patterns and also under the assumption of alternative treatment use patterns. It can help inform the physician/patient shared decision making on whether to switch treatment, intensify or maintain status quo at any point in time during the trajectory of care for patients with diabetes. It is this dynamic information that makes this model unique. We are in the process of making this model available as a web tool for carrying out such comparison, with the caveat that these results only pertain to VA patients.

The model can also be used to inform policy, such as cost-effectiveness, clinical guidance change, etc., at the population level, given that population-level treatment use patterns are well represented in the model. Any policy evaluation with this model would need to add a predictive component as to treatment use patterns will look like under a specific alternative policy. We delegate this to our future work.

The model we have constructed does have limitations. The model is based on retrospective observations of care, and due to secular changes in patterns of care, the model does not account for many of the newer glucose-lowering drugs that are now available. This limitation is shared by all other studies dependent on historical observations. The RAPIDS model was also constructed with data from the VA population which has limited representation by women. However, the data set used to develop RAPIDS was so large (1 million) that a significant number of women were still in the sample. Nevertheless, results from this analysis can only be used to project outcomes for patients with diabetes receiving care through the USVA. Future work should focus on validating these estimates against other population.

The model only accounts for cardiovascular history but no other comorbidities, as is typical in other diabetes models. Especially because our focus is on the dynamic nature of outcomes, conditioning on any additional comorbidity would require developing additional transition model for this comorbidity over time. This would result in an explosion of the parameter space.

Because of lack of retrospective data within the VA system before 1997, duration of diabetes in 2003 was capped at five years. Note that because of nine years of follow-up, our regression models do allow the coefficients to vary by 0 – 14 years of duration of diabetes. Moreover, UKPDS data shows that the risk of complication increases linearly with respect to duration of diabetes²⁵ and so it is possible to extrapolate these risks beyond the 14-year duration period.

Due to severe restrictions on CPU power and continuous CPU use on the VA servers, we have not been able to run bootstrap analysis on our estimation sample to get standard errors for our coefficients. Therefore, as it stands now, the RAPIDS model is a deterministic model

in terms of parameter or second-order uncertainty. The RAPIDS model still captures first-order uncertainty, can generate multiple random trajectories for a given individual, and allow summarizing the prediction error. Although this summarized predictions from our deterministic model appear to perform quite well in out of sample validation exercise, we are continuing to work of bootstrap exercises to convert RAPIDS into a probabilistic model.

Despite these limitations, we believe that RAPIDS provides a methodological framework for addressing increasingly complex treatment decisions that we face today. It is built keeping in mind the modeling guidelines laid out by the American Diabetes Association for a diabetes model.²⁷ It employs data on a much more diverse population than typically enrolled in clinical trials, has long follow-up, allows for interdependency in the progression to complications, and allows for treatment complexity. Further work to validate this model against heterogeneity defined by baseline factors, against external trial data, and other real-world population would be needed. As we become more successful in extending the lives of our patients by preventing complications and as the choice of therapeutic classes grows, we will face difficult decisions regarding glucose control for patients with long-standing diabetes. The framework used to develop RAPIDS could be applied to other real-world populations that may have different demographic characteristics, baseline risks, and distinctive utilization of glucose-lowering medications.

Acknowledgments:

We thank Dr. Nicholas Emanuele and Dr. Marylou Guihan at the Center of Innovation for Complex Chronic Healthcare (CINCCCH) at the Edward Hines, Jr. VA Hospital in Hines, IL for generous computer, data support, and guidance. We also thank four anonymous reviewers for their comments on earlier versions of the paper. This work was supported by the Agency for Healthcare Research and Quality (AHRQ) [grant number R01HS018542], and National Institutes of Health (NIH) [grant numbers UL1TR000427, R01HL126804]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH, AHRQ, or VA. The authors have no conflict of interest regarding this work.

APPENDIX

Detailed results from each part of the analysis are available in Tables at <https://www.dropbox.com/s/s3x5ahd71oua93k/APPENDIXTABLES.xlsx?dl=0>

A pseudo-algorithm to illustrate one Monte–Carlo random walk for one patient over the first-two quarters. To simply notation, we will mute subscript i , which is used for reflect patients. Bold-face will be used to reflect a vector of values.

Quarter 0:

Individual-level Data (observed):

$$\{(Y_{10}, \dots, Y_{K0}), \mathbf{W}, \mathbf{X}_{0^*} (D_{10}, \dots, D_{J0})\}$$

Quarter 1:

Predict Mean Y's:

for k in 1:k {

$$\hat{Y}_{k1} = \hat{E}(Y_{k1}) = g_k(\{Y_{10}, \dots, Y_{K0}\}, \mathbf{W}, \mathbf{X}_{0^*} (D_{10}, \dots, D_{J0})); \hat{a} \quad \# \# \text{ using Eq (3)}$$

If Y_k is a Biomarker {

$$\hat{V}_{k1} = E\{(Y_{k1} - \hat{Y}_{k1})^2\} = \exp(\hat{c0} + \hat{c1} * \ln(\hat{Y}_{k1})) \quad \# \# \text{ using Eq (4)}$$

$$(\hat{Y}_{k1})_i \sim \text{Normal}(\hat{Y}_{k1}, \hat{V}_{k1}) \quad \# \# \text{ Draw individual-level value for the current}$$

patient

Else if Y_k is a binary Outcome {

$$(\hat{Y}_{k1})_i \sim \text{Bernoulli}(\hat{Y}_{k1}) \quad \# \# \text{ Draw individual-level value for the current patient}$$

}

Update X deterministically (e . g age) or based on predicted Y (. e . g MI history)

$$\mathbf{X}_1 = f\{\mathbf{X}_{0^*}, ((\hat{Y}_{11})_i, \dots, (\hat{Y}_{K1})_i)\}$$

Individual – level Data

$$\{((\hat{Y}_{11})_i, \dots, (\hat{Y}_{K1})_i), \mathbf{W}, \mathbf{X}_1, (D_{11}, \dots, D_{J1})\}$$

Quarter 2:

Predict Mean Y's:

for k in 1:k{

$$\hat{Y}_{k2} = \hat{E}(Y_{k2}) = g_k(\{((\hat{Y}_{11})_i, \dots, (\hat{Y}_{K1})_i), \mathbf{W}, \mathbf{X}_1, (D_{11}, \dots, D_{J1})\}; \hat{a}) \quad \# \# \text{ using Eq (3)}$$

If Y_k is a Biomarker {

$$\hat{V}_{k2} = E\{(Y_{k2} - \hat{Y}_{k2})^2\} = \exp(\hat{c0} + \hat{c1} * \ln(\hat{Y}_{k2})) \quad \# \# \text{ using Eq (4)}$$

$$(\hat{Y}_{k2})_i \sim \text{Normal}(\hat{Y}_{k2}, \hat{V}_{k2}) \quad \# \# \text{ Draw individual-level value for the current}$$

patient

Else if Y_k is a binary Outcome {

$$(\hat{Y}_{k2})_i \sim \text{Bernoulli}(\hat{Y}_{k2}) \quad \# \# \text{ Draw individual-level value for the current patient}$$

}

Update X deterministically (e . g age) or based on predicted Y (. e . g MI history)

$$\mathbf{X}_2 = f\{\mathbf{X}_1, ((\hat{Y}_{12})_i, \dots, (\hat{Y}_{K2})_i)\}$$

Individual-level Data

$$\{((\hat{Y}_{12})_i, \dots, (\hat{Y}_{K2})_i), \mathbf{W}, \mathbf{X}_2, (D_{12}, \dots, D_{J2})\}$$

Quarter 3: Repeat**REFERENCES**

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Figure 1.
REAL-WORLD PROGRESSION IN DIABETES (RAPIDS) MODEL

Figure 2.
Infographic on methodological plan for RAPIDS model development

Figure 3.
Predicted trajectories and observed values of biomarkers in Part C – Validation Sample.
(Quarter 0 refers to the baseline quarter Oct – Dec 2012).

Figure 4. Predicted trajectories and observed values of micro (a-d) and macro-vascular (e-h) outcomes in Part C – Validation Sample. (Quarter 0 refers to the baseline quarter Oct – Dec 2012).

Figure 5. Predicted trajectories and observed values of cumulative all-cause mortality in Part C – Validation Sample. (Quarter 0 refers to the baseline quarter Oct – Dec 2012).

Figure 6. Comparative analysis: treatment patterns for 100 randomly selected patients with (a) observed treatment use pattern and (b) alternate treatment use pattern after assuming perfect adherence patterns to glucose-lowering drugs after initiation.

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D _{j<i>it</i>} =Indicator for each of the thirteen glucose lowering treatment options, one for any blood-pressure lowering treatment, and another for any cholesterol-lowering treatment	<u>Glucose lowering treatment options</u>
	Monotherapy: Metformin, Sulfonylurea, Thiazolidinediones (TZD)
	Duo-therapy: Metformin+Sulfonylurea, +TZD, Metformin+Insulin, Sulfonylurea+TZD, Sulfonylurea+Insulin TZD+Insulin
	Triple-therapy/others
	Ref: No treatment

Table 1:

Characteristics of patients in the first quarter across three randomly split data folds.

Characteristics Mean (SD)	Part A: Estimation Sample N = 307,228	Part B: Calibration Sample N = 105,195	Part C: Validation Sample N = 105,081
Age (in years)	66.9 (10.4)	67 (10.5)	67 (10.4)
Female	2.1% (14.4%)	2.1% (14.4%)	2.2% (14.6%)
Married	64.5% (47.8%)	64.6% (47.8%)	64.8% (47.8%)
Never married	9.9% (29.9%)	9.8% (29.8%)	9.9% (29.8%)
White	74.3% (43.7%)	74.4% (43.6%)	74.6% (43.5%)
Black	15.8% (36.5%)	15.7% (36.4%)	15.7% (36.4%)
Hispanic	8.4% (27.7%)	8.4% (27.7%)	8.2% (27.5%)
Veteran	94.9% (21.9%)	94.7% (22.4%)	94.9% (22%)
Duration with diabetes (in years)	4.33 (2.19)	4.34 (2.2)	4.34 (2.2)
Hemoglobin A1c (%)	7.23 (1.51)	7.23 (1.51)	7.24 (1.52)
High-density lipoprotein (mg/dL)	40.9 (11.5)	40.9 (11.5)	40.9 (11.5)
Low-density lipoprotein (mg/dL)	101 (31.7)	101 (31.7)	101 (31.8)
Total Cholesterol (mg/dL)	176 (37.3)	176 (37.3)	176 (37.4)
Triglyceride (mg/dL)	178 (106)	178 (106)	178 (106)
BMI	31 (5.97)	31 (5.96)	31 (5.98)
Systolic BP (mm Hg)	137 (17.1)	137 (17.2)	137 (17.1)
Diastolic BP (mm Hg)	73.4 (10.3)	73.4 (10.3)	73.4 (10.2)
Myocardial Infarction	0.8% (9.1%)	0.8% (9%)	0.8% (9.1%)
Any unstable angina	1% (10.2%)	1.1% (10.2%)	1% (10%)
Stroke	2.5% (15.7%)	2.4% (15.3%)	2.6% (15.8%)
Congestive heart failure	3.4% (18.2%)	3.5% (18.5%)	3.5% (18.5%)
Any hypoglycemia	2.7% (16.3%)	2.8% (16.6%)	2.8% (16.6%)
Advanced eye disease	5.7% (23.2%)	5.8% (23.4%)	5.7% (23.2%)
ESRD	1.1% (10.3%)	1.1% (10.2%)	1.1% (10.2%)
Lower extremity amputation	0.2% (4.2%)	0.2% (4.8%)	0.2% (4.7%)
History of myocardial infarction	4.6% (20.8%)	4.6% (20.9%)	4.6% (20.9%)
History of unstable angina	6.3% (24.2%)	6.4% (24.4%)	6.2% (24.2%)
History of stroke	7.9% (26.9%)	7.9% (27%)	8.1% (27.2%)
History of hypoglycemia	11% (31.3%)	11.1% (31.5%)	11.2% (31.5%)
Follow-up (in quarters)	23.1 (11)	23 (11)	23 (11)

Table 2:

Extent of treatment use during the follow-up period under alternate adherence profiles in Part C data.

Glucose-lowering Treatments (in quarters, mean (sd))	Observed adherence	Alternate adherence
Any treatment	17.9 (12.1)	20.0 (12.5)
Monotherapy	9.46 (9.49)	11.3 (10.7)
Metformin monotherapy	2.16 (5.58)	2.65 (6.58)
Sulfonylurea monotherapy	3.67 (6.88)	4.42 (7.99)
Thiazolidinediones (TZD) monotherapy	0.24 (1.49)	0.31 (1.98)
Insulin monotherapy	3.40 (7.27)	3.87 (8.07)
Duo-therapy	6.52 (8.42)	6.79 (8.64)
Metformin+Sulfonylurea	3.26 (6.48)	3.43 (6.72)
Metformin+TZD	0.18 (1.3)	0.19 (1.35)
Metformin+Insulin	1.29 (4.33)	1.32 (4.41)
Sulfonylurea+TZD	0.64 (2.68)	0.67 (2.76)
Sulfonylurea+Insulin	0.90 (3.15)	0.93 (3.22)
TZD+Insulin	0.25 (1.64)	0.26 (1.68)
Triple-therapy/others	1.92 (4.92)	1.96 (5)
No treatment	5.13 (8.32)	3.02 (7.5)

Table 3:

Results from comparative analysis of alternate adherence profiles using the RAPIDS model.

Outcomes	Observed treatment patterns	Alternate treatment patterns
Average levels per quarter:		
Hemoglobin A1c (%)	7.35	7.32
High-density lipoprotein (mg/dL)	40.49	40.45
Low-density lipoprotein (mg/dL)	89.92	89.55
Total cholesterol (mg/dL)	161.29	161.04
Triglycerides (mg/dL)	162.7	162.6
Body mass index	31.2	31.22
Systolic blood pressure (mm Hg)	133.81	133.61
Diastolic blood pressure(mm Hg)	71.58	71.84
Average number of quarters with events:		
Myocardial infarction	0.008	0.008
Unstable angina	0.008	0.008
Stroke	0.03	0.03
Hypoglycemia	0.034	0.036
Proportion of cohort with chronic endpoint at 9 years:		
Congestive heart failure	17.6%	17.5%
Advanced eye disease	31.8%	32.8%
End-stage renal disease	6.3%	6.1%
Lower extremity amputation	1.4%	1.4%
Death	18.1%	17.7%