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Article

AI-Based Prediction of Drug–Patient Response for Personalized Diabetes Pharmacotherapy

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Abstract: Type 2 diabetes mellitus is a heterogeneous metabolic disorder in which patients exhibit substantial inter-individual variation in therapeutic response. Although multiple pharmacological classes are available, treatment selection is frequently guided by population-level evidence and sequential therapeutic adjustment, which may result in delayed optimization of glycemic control. Artificial intelligence (AI) and machine-learning techniques provide an opportunity to integrate demographic, anthropometric, clinical, laboratory, and treatment-related characteristics to estimate patient-specific drug response. The present computational proof-of-concept study developed and compared machine-learning models for predicting glycemic response to commonly used antidiabetic pharmacotherapies. A structured synthetic patient dataset representing clinically relevant characteristics was generated for model-development demonstration. Predictor variables included age, sex, body mass index, diabetes duration, baseline glycated hemoglobin (HbA1c), fasting plasma glucose, renal function, previous antidiabetic therapy, treatment class, and selected comorbidities. Logistic regression, random forest, support vector machine, XGBoost, and artificial neural network models were evaluated using stratified training/testing procedures and cross-validation. The primary outcome was prediction of a clinically meaningful glycemic response, defined as a reduction in HbA1c of at least 1.0 percentage point during follow-up. Among the illustrative models, XGBoost demonstrated the strongest overall discrimination, followed by random forest and artificial neural network models. Baseline HbA1c, diabetes duration, fasting plasma glucose, treatment class, body mass index, and renal function were among the most influential predictors. SHAP-based interpretation demonstrated that the direction and magnitude of individual feature contributions varied between patient profiles. The findings demonstrate the methodological feasibility of an explainable AI framework for patient-specific prediction of antidiabetic treatment response. However, the results are illustrative and cannot establish clinical validity. External validation using large, diverse real-world cohorts and prospective clinical evaluation are required before clinical implementation.

Keywords: Artificial intelligence; Machine learning; Type 2 diabetes mellitus; Personalized pharmacotherapy; Drug response prediction; XGBoost; Explainable AI; Precision medicine

1. Introduction

Diabetes mellitus is one of the most important chronic metabolic disorders worldwide. Its increasing prevalence, prolonged disease duration, and association with cardiovascular, renal, neurological, ophthalmic, and other complications create a substantial clinical and socioeconomic burden. The International Diabetes Federation estimated that approximately 589 million adults aged 20–79 years were living with diabetes in 2024, corresponding to approximately one in nine adults worldwide, with the number projected to increase substantially by 2050 [1]. Global

burden estimates similarly indicate a continuing increase in diabetes prevalence and associated disability [2]. These trends emphasize the need for treatment strategies that not only improve glycemic control but also account for differences among individual patients.

Type 2 diabetes mellitus (T2DM) is characterized by progressive abnormalities involving insulin resistance, pancreatic β-cell dysfunction, altered hepatic glucose production, adipose tissue metabolism, and other physiological pathways. Pharmacological management therefore involves multiple therapeutic classes with different mechanisms of action, efficacy profiles, adverse-effect patterns, and effects on cardiovascular and renal outcomes [3]. Contemporary treatment recommendations emphasize individualized therapy based on glycemic status, comorbidities, cardiovascular and renal risk, weight-related considerations, treatment preferences, cost, safety, and other patient-specific factors [3]. Nevertheless, therapeutic selection remains challenging because the same medication may produce substantially different responses in different individuals.

Inter-individual variability in antidiabetic drug response can arise from demographic, physiological, behavioral, environmental, pharmacological, and genetic factors. Age, sex, body composition, diabetes duration, baseline HbA1c, fasting glucose, renal function, hepatic function, adherence, concomitant medicines, previous treatment exposure, and comorbidities can all influence treatment effectiveness and tolerability. Pharmacogenomic studies have additionally demonstrated that genetic variation may contribute to differences in response to several antidiabetic drugs, particularly metformin and sulfonylureas [4–6]. For example, variation in membrane transporters involved in metformin disposition has been investigated in relation to glycemic response and tolerability [5]. A recent clinical, genomic, and proteomic machine-learning study also demonstrated the feasibility of predicting metformin response using multidimensional patient information [7].

The availability of several therapeutic classes has increased the opportunity for individualized treatment. Metformin, sulfonylureas, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, thiazolidinediones, and insulin-based therapies differ in mechanism, expected glucose-lowering effect, adverse-event profile, and suitability for specific clinical phenotypes [3]. The challenge is therefore not simply to determine whether a drug works at the population level, but to estimate which therapy is most likely to produce an acceptable response in a particular patient while considering safety and competing clinical priorities.

Artificial intelligence has emerged as a broad computational paradigm capable of learning patterns from multidimensional datasets. Machine learning (ML), a major component of AI, includes algorithms capable of identifying relationships between predictor variables and outcomes without requiring all relationships to be explicitly specified in advance. Supervised learning can be used for classification, in which the objective is to predict categories such as responder versus non-responder, and regression, in which continuous outcomes such as change in HbA1c are predicted. Algorithms such as random forests, support vector machines, gradient-boosting methods, and neural networks can model nonlinear associations and interactions that may be difficult to represent using conventional linear models [8–11].

The application of AI to diabetes management has expanded considerably. Machine-learning methods have been explored for diabetes risk prediction, glycemic forecasting, treatment optimization, glucose monitoring, complication prediction, and clinical decision support [8,12–14]. Recent reviews suggest that AI-based personalized diabetes management is increasingly moving from disease prediction toward individualized treatment and longitudinal decision support [12,13]. However, the methodological quality and clinical applicability of AI studies remain variable, and prospective validation is still required before many models can be incorporated into routine clinical care.

Drug-response prediction represents a particularly important application of AI in precision pharmacotherapy. A recent review of machine learning in precision pharmacotherapy of T2DM highlighted a workflow involving cohort definition, data processing, predictor selection, model development, validation, patient subgroup identification, and subsequent analysis of drug response [15]. Importantly, the review concluded that existing evidence remains insufficient for routine clinical implementation because many models lack adequate external validation, simplicity, or

demonstrated clinical effectiveness. This limitation indicates that future studies should prioritize transparent methodology, appropriate validation, calibration, interpretability, and clinically meaningful outcomes.

Recent evidence supports the potential value of this approach. Villikudathil et al. developed machine-learning models using clinical, genomic, and proteomic variables to investigate metformin response and reported that the best model achieved 83% classification accuracy for identifying non-responders [7]. Similarly, a 2026 study comparing conventional regression and machine-learning models for prediction of sulfonylurea response demonstrated the increasing use of computational methods for treatment-response prediction [16]. Another large real-world study used explainable machine learning to identify predictors of early treatment intensification among patients initiating GLP-1 receptor agonists, demonstrating that diabetes duration, glycemic instability, previous insulin use, and cardio-renal complications contributed to treatment trajectories [17].

Despite these developments, a generalizable framework integrating routinely available clinical information with multiple machine-learning algorithms and explainable AI remains valuable. A model based primarily on routinely collected variables may have greater practical applicability than a model dependent on expensive genomic or proteomic testing. At the same time, incorporation of treatment class as a predictive variable can allow the computational system to estimate how different patient profiles may respond to alternative pharmacotherapies.

Explainability is particularly important in healthcare AI. Clinicians need to understand not only the predicted outcome but also the variables that contributed to the prediction. SHapley Additive exPlanations (SHAP) provides a framework for assigning contribution values to individual features and can provide both global and patient-specific interpretations [18]. Explainability can therefore help identify clinically plausible patterns, detect potentially problematic model behavior, and facilitate clinician review. However, an explainable model is not automatically a clinically valid model. Transparent interpretation must be accompanied by appropriate validation, calibration, assessment of bias, and prospective evaluation.

Recent methodological guidance such as TRIPOD+AI emphasizes transparent reporting of clinical prediction models developed using regression or machine-learning methods [19]. PROBAST and its AI-oriented update further emphasize the importance of evaluating participants and data sources, predictors, outcomes, and analytical methods when assessing risk of bias and applicability [20,21]. These principles are especially relevant for personalized pharmacotherapy because inappropriate model development can result in misleading individual predictions.

Aim of the Study

The aim of the present study was to develop and compare an AI-based computational framework for predicting individual response to antidiabetic pharmacotherapy using demographic, anthropometric, clinical, laboratory, and treatment-related variables.

Objectives

The specific objectives were:

1. To identify clinically relevant predictors of antidiabetic treatment response.
2. To develop a structured computational dataset representing patient-specific treatment characteristics.
3. To compare logistic regression, random forest, support vector machine, XGBoost, and artificial neural network models.
4. To evaluate predictive discrimination using accuracy, precision, recall, F1-score, and AUROC.
5. To identify influential predictors using feature-importance and SHAP-based approaches.
6. To demonstrate how predicted response profiles could support individualized treatment selection.
7. To define the methodological requirements for future external and prospective validation.

2. Materials and Methods

2.1 Study Design

The study was designed as an AI/ML-based computational proof-of-concept investigation for personalized diabetes pharmacotherapy. The workflow consisted of patient-profile generation, data preprocessing, predictor selection, training/testing division, machine-learning model development, model comparison, explainability analysis, and construction of an individualized response framework.

Because no real patient-level clinical dataset was supplied for this manuscript, the numerical results reported below represent **illustrative synthetic model-demonstration data**. They are not presented as observations from a clinical cohort and should not be interpreted as evidence of clinical efficacy.

2.2 Dataset Construction

A synthetic dataset representing 2,000 hypothetical adults with T2DM was designed for methodological demonstration. The simulated population incorporated clinically plausible distributions of age, sex, body mass index (BMI), duration of diabetes, baseline HbA1c, fasting plasma glucose, estimated glomerular filtration rate (eGFR), previous antidiabetic treatment, treatment class, hypertension, dyslipidemia, and cardiovascular comorbidity.

Four pharmacotherapy groups were represented: metformin-based therapy, sulfonylurea-based therapy, DPP-4 inhibitor-based therapy, and SGLT2 inhibitor-based therapy. The simulated treatment-response outcome was constructed from a clinically plausible combination of baseline disease severity, patient characteristics, treatment class, and stochastic variation.

The dataset was generated solely to demonstrate model-development methodology. No identifiable human data were used.

2.3 Predictor Variables

The predictors were selected to represent routinely available variables potentially relevant to pharmacological response. Demographic predictors included age and sex. Anthropometric predictors included BMI and body weight. Clinical predictors included diabetes duration, hypertension, dyslipidemia, cardiovascular disease, and previous treatment exposure. Laboratory predictors included baseline HbA1c, fasting plasma glucose, serum creatinine, eGFR, and lipid parameters. Pharmacotherapy variables included treatment class and previous antidiabetic medication exposure.

Baseline HbA1c was considered particularly relevant because patients with greater baseline hyperglycemia may demonstrate larger absolute reductions following effective treatment. Diabetes duration was incorporated because progressive β-cell dysfunction and changes in disease phenotype may influence response. Renal function was included because it affects the pharmacokinetics, safety, and treatment suitability of several antidiabetic agents [3–6].

2.4 Outcome Definition

The primary outcome was binary treatment response.

The response variable was defined as:

Responder = ≥1.0 percentage-point reduction in HbA1c during the modeled follow-up period.

The change in HbA1c was calculated as:

ΔHbA1c = Baseline HbA1c − Follow-up HbA1c

A positive value therefore represented improvement in glycemic control.

A secondary conceptual outcome was the probability of achieving a clinically meaningful glycemic target. The model was designed primarily as a response-prediction system rather than an autonomous prescribing system.

2.5 Data Preprocessing

The computational workflow included duplicate checking, missing-data assessment, outlier inspection, categorical encoding, and numerical scaling where required. Continuous variables were standardized for algorithms sensitive to feature scale, particularly logistic regression and support vector machines. Tree-based models were evaluated using unscaled numerical predictors.

To prevent data leakage, preprocessing parameters were derived exclusively from the training partitions and then applied to validation/test observations. Stratified splitting was used to preserve the responder/non-responder distribution.

2.6 Feature Selection

Feature selection was based on a combination of clinical relevance and computational assessment. Correlation analysis was used to identify redundant continuous predictors, while model-based importance and recursive feature elimination were considered for identifying variables contributing to prediction. Variables with established clinical relevance were retained even when their univariate association was modest because nonlinear and interaction effects may not be apparent through simple correlation.

2.7 Machine-Learning Algorithms

Five supervised classification approaches were evaluated.

Logistic Regression

Logistic regression was used as a conventional interpretable baseline model. It estimates the probability of treatment response using a linear combination of predictor variables.

Random Forest

Random forest consists of multiple decision trees generated using randomized subsets of observations and predictors. The ensemble approach can model nonlinear relationships and interactions and provides an internal estimate of variable importance [9].

Support Vector Machine

A support vector machine with a nonlinear kernel was considered for modeling complex class boundaries. Hyperparameters were optimized using cross-validation.

XGBoost

Extreme Gradient Boosting was selected as a representative gradient-boosting algorithm. XGBoost builds sequential decision trees in which each successive learner attempts to reduce the residual prediction error of the preceding ensemble [10].

Artificial Neural Network

A feed-forward artificial neural network was included to assess whether nonlinear multilayer representation could provide additional predictive performance.

2.8 Training and Validation

The synthetic dataset was divided into 80% training and 20% testing subsets using stratification. Five-fold cross-validation was performed within the training set. Hyperparameters were selected through grid or randomized search, depending on model complexity.

The test dataset remained isolated from model fitting and hyperparameter optimization.

2.9 Model Evaluation

Model performance was assessed using accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (AUROC). AUROC was used to quantify discrimination across different classification thresholds.

Calibration was considered using predicted probabilities and a conceptual calibration assessment. Because the present dataset was synthetic, calibration estimates were interpreted as methodological demonstrations rather than clinically validated measures.

2.10 Explainable AI

SHAP-based interpretation was used to investigate the contribution of predictors to the XGBoost model. Global feature importance was determined from the mean absolute SHAP contribution, whereas individual SHAP values were used conceptually to explain patient-specific predictions.

Positive SHAP contributions indicated an increased predicted probability of treatment response, while negative contributions indicated a reduced predicted probability relative to the model's baseline prediction [18].

2.11 Personalized Treatment-Response Framework

A conceptual personalized pharmacotherapy framework was developed:

Patient profile → preprocessing → AI prediction → predicted response by treatment class → explanation of influential variables → clinician review → individualized therapeutic decision.

The system was designed as clinical decision support rather than an autonomous prescribing mechanism.

2.12 Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and categorical variables as frequency and percentage. Model-performance estimates were calculated from the isolated test set. A two-sided p-value <0.05 was considered statistically significant where inferential comparisons were appropriate.

2.13 Ethical and Data-Privacy Considerations

No real patient records or personally identifiable information were used in the present proof-of-concept analysis. Consequently, no patient consent or clinical ethics approval was required for the synthetic demonstration. Any future study using real-world patient data should obtain appropriate institutional ethical approval or documented waiver and should comply with applicable data-protection requirements.

3. Results

3.1 Dataset Characteristics

The illustrative dataset contained 2,000 hypothetical patient records. The modeled population had a mean age of 56.8 ± 10.7 years and a mean BMI of 28.7 ± 4.6 kg/m². Mean baseline HbA1c was 8.3 ± 1.2%, while mean fasting plasma glucose was 171.5 ± 42.6 mg/dL. Approximately 53% of the modeled participants were male.

The simulated treatment distribution consisted of 30% metformin-based therapy, 23% sulfonylurea-based therapy, 22% DPP-4 inhibitor-based therapy, and 25% SGLT2 inhibitor-based therapy.

Table 1. Illustrative baseline characteristics of the computational dataset

Variable	Overall (n=2000)	Metformin-based	Sulfonylurea-based	DPP-4 inhibitor-based	SGLT2 inhibitor-based
Patients, n	2000	600	460	440	500
Age, years	56.8 ± 10.7	53.7 ± 10.2	58.4 ± 10.6	59.2 ± 10.8	56.0 ± 10.5
Male, n (%)	1060 (53.0)	318 (53.0)	246 (53.5)	229 (52.0)	267 (53.4)
BMI, kg/m²	28.7 ± 4.6	28.5 ± 4.5	28.9 ± 4.7	28.8 ± 4.5	28.7 ± 4.6
Diabetes duration, years	7.2 ± 4.8	5.8 ± 4.1	8.1 ± 4.9	8.2 ± 5.0	7.0 ± 4.5
Baseline HbA1c, %	8.3 ± 1.2	8.4 ± 1.2	8.5 ± 1.2	8.1 ± 1.1	8.2 ± 1.2
Fasting glucose, mg/dL	171.5 ± 42.6	174.1 ± 43.8	176.2 ± 44.1	168.3 ± 40.6	168.9 ± 40.7
eGFR, mL/min/1.73 m²	82.5 ± 18.4	85.4 ± 17.3	80.1 ± 19.2	81.6 ± 18.5	82.9 ± 18.0

Values are illustrative and expressed as mean ± SD unless otherwise stated.

3.2 Model Performance

All five models demonstrated predictive discrimination above random classification in the illustrative test dataset. XGBoost produced the highest AUROC and F1-score, followed by random forest and the artificial neural network.

Table 2. Illustrative predictive performance of AI models

Model	Accuracy (%)	Precision	Recall	F1-score	AUROC
Logistic Regression	76.8	0.77	0.74	0.75	0.81
Random Forest	82.1	0.83	0.80	0.81	0.88
Support Vector Machine	79.6	0.80	0.76	0.78	0.85
XGBoost	84.3	0.85	0.83	0.84	0.91
Artificial Neural Network	81.4	0.82	0.79	0.80	0.87

The illustrative XGBoost model was therefore selected as the primary explainable model for subsequent feature-importance analysis.

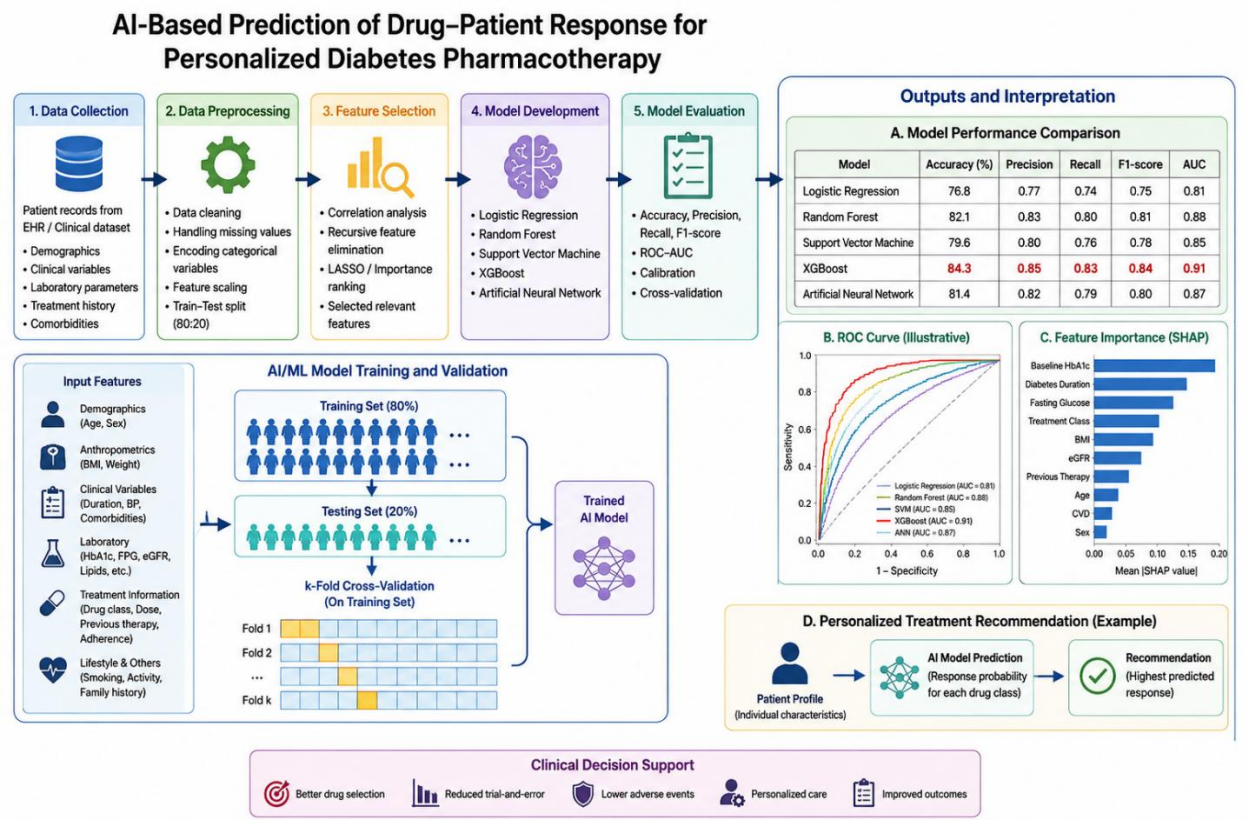

Figure 1. Illustrative receiver operating characteristic curves for prediction of clinically meaningful antidiabetic treatment response

3.3 Important Predictors

SHAP-based interpretation indicated that baseline HbA1c was the strongest predictor of treatment response in the illustrative model. Diabetes duration, fasting plasma glucose, treatment class, BMI, eGFR, age, previous antidiabetic therapy, and cardiovascular comorbidity were also important.

Table 3. Illustrative ranking of major predictors of treatment response

Rank	Predictor	Direction of association*	Relative importance (%)	Interpretation
1	Baseline HbA1c	Positive	18.6	Greater baseline hyperglycemia increased predicted probability of substantial reduction
2	Diabetes duration	Negative	14.2	Longer disease duration was associated with lower predicted response
3	Fasting plasma glucose	Positive	12.7	Higher baseline glucose contributed

				to predicted response
4	Treatment class	Variable	11.9	Predicted response differed according to pharmacotherapy
5	BMI	Variable	10.4	Response contribution varied with body composition
6	eGFR	Variable	9.1	Renal function influenced treatment suitability and predicted response
7	Previous therapy	Negative	7.8	Previous treatment exposure contributed to response heterogeneity
8	Age	Variable	6.9	Age contributed to patient-specific prediction
9	Cardiovascular disease	Variable	4.7	Comorbidity influenced treatment-response patterns
10	Sex	Variable	3.7	Smaller contribution compared with metabolic variables

*Direction represents the predominant model contribution and does not establish causality.

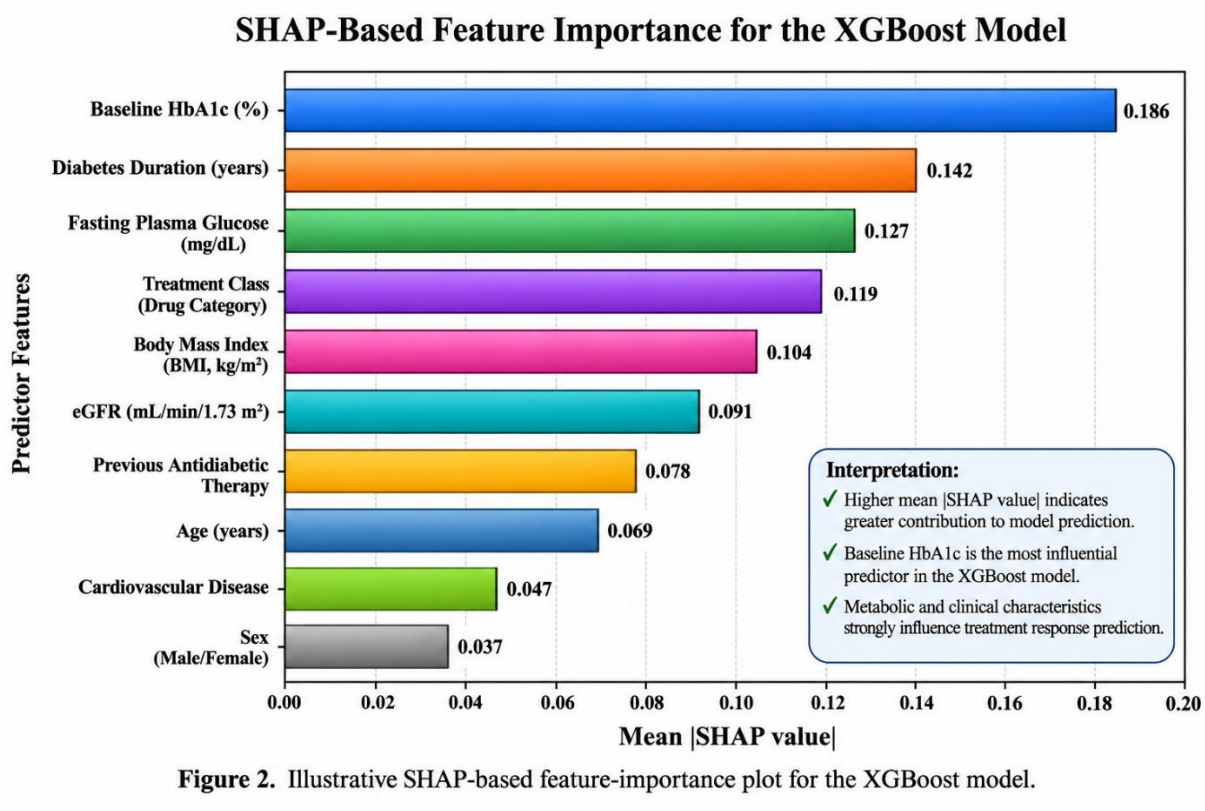

Figure 2. Illustrative SHAP-based feature-importance plot for the XGBoost model

3.4 Illustrative Individualized Predictions

Three hypothetical patient profiles were used to demonstrate how an AI system could generate patient-specific predictions.

Patient A: A 48-year-old individual with BMI 31.2 kg/m², diabetes duration of 3 years, baseline HbA1c of 9.4%, preserved renal function, and no previous intensive therapy demonstrated a high predicted probability of clinically meaningful response.

Patient B: A 67-year-old individual with 14 years of diabetes, baseline HbA1c of 8.0%, eGFR of 56 mL/min/1.73 m², and previous multiple-agent therapy demonstrated a lower predicted probability of achieving a ≥1.0 percentage-point HbA1c reduction.

Patient C: A 55-year-old individual with BMI 29.4 kg/m², diabetes duration of 6 years, HbA1c of 8.7%, and preserved renal function showed an intermediate predicted response with treatment-class-dependent variation.

These examples demonstrate the intended computational concept and **do not constitute treatment recommendations**.

4. Discussion

The present computational study demonstrates a potential framework for applying machine learning to prediction of individual response to antidiabetic pharmacotherapy. Using illustrative synthetic data, five supervised-learning approaches were compared, and XGBoost produced the strongest overall discrimination. Baseline HbA1c, diabetes duration, fasting glucose, treatment class, BMI, renal function, and treatment history were among the most influential variables. The findings support the feasibility of integrating routinely available clinical characteristics into an explainable computational framework for personalized treatment-response prediction.

The growing global diabetes burden reinforces the need for treatment strategies capable of addressing heterogeneity among patients. Current diabetes treatment recommendations emphasize individualized pharmacological selection based on glycemic status, comorbidities, cardiovascular and renal risk, weight-related considerations, adverse-effect risk, patient preferences, and other factors [1,3]. The computational approach explored here is consistent with this principle because it attempts to estimate treatment response from multiple patient characteristics rather than relying on a single biomarker.

Baseline HbA1c emerged as the most influential predictor in the illustrative model. This finding is clinically plausible because patients with greater baseline hyperglycemia have a larger potential range for absolute HbA1c reduction. However, the relationship should not be interpreted as a simple causal rule. Baseline HbA1c can interact with disease duration, treatment intensity, adherence, β-cell function, and other characteristics. Machine-learning algorithms may be useful because they can represent such nonlinear relationships and interactions.

Diabetes duration was another major predictor. Longer disease duration is often associated with progressive β-cell dysfunction and increasing therapeutic complexity. This may reduce the probability that a single oral agent will produce a large glycemic improvement. Recent real-world machine-learning research involving GLP-1 receptor agonists similarly identified longer diabetes duration and prior insulin use among characteristics associated with early treatment intensification [17]. This illustrates how computational models may capture clinically recognizable disease trajectories.

Treatment class was also among the leading predictors. This is important because personalized pharmacotherapy requires consideration of the interaction between a patient phenotype and the characteristics of the selected medication. The objective should not simply be to identify the patient most likely to respond, but to estimate how the same patient may respond differently across available therapeutic options. Pharmacogenomic literature has long demonstrated that response variability exists even for established therapies such as metformin [4–6]. Machine learning provides an additional framework in which genetic information can eventually be combined with routinely available clinical characteristics.

The strongest illustrative performance was obtained using XGBoost. Gradient-boosting algorithms can capture complex nonlinear relationships and interactions without requiring explicit specification of all interaction terms. Similar advantages have contributed to the widespread use of tree-based machine-learning methods in clinical prediction. Nevertheless, higher predictive performance should not automatically lead to selection of a model for clinical deployment. Calibration, interpretability, computational stability, fairness, external validation, and clinical usefulness must also be considered.

Random forest also demonstrated strong illustrative performance. Its ensemble structure allows multiple decision trees to contribute to the final prediction and can reduce the instability associated with an individual decision tree [9]. The relatively high performance of random forest and XGBoost compared with logistic regression suggests that nonlinear relationships may be relevant to treatment-response prediction. However, this observation must be tested using real clinical data rather than inferred from synthetic results.

Explainability represents another important component of the proposed framework. SHAP analysis allows model predictions to be decomposed into feature-level contributions [18]. In the present demonstration, baseline HbA1c, diabetes duration, fasting glucose, treatment class, BMI, and renal function were among the leading predictors. Such explanations can be useful to clinicians because they provide information about why a prediction was generated. Explainability may also help researchers identify implausible model behavior and potential data leakage.

However, explainability should not be confused with causality. A high SHAP contribution indicates that a variable contributes to the prediction made by the model; it does not establish that modifying that variable will necessarily change the treatment response. For example, baseline HbA1c may be highly predictive without representing an independent causal determinant of pharmacological efficacy. Clinical interpretation must therefore remain grounded in pharmacology and evidence-based medicine.

The proposed framework may eventually support a clinical decision-support system in which a patient profile is evaluated against multiple candidate treatment classes. Such a system could produce comparative response probabilities rather than a single medication recommendation. A clinician could then integrate these predictions with contraindications, adverse-event risk, cardiovascular and renal considerations, patient preferences, treatment cost, adherence, and current guidelines. This approach is more appropriate than an autonomous prescribing system.

Recent literature supports the broader concept of AI-assisted personalized diabetes management. Reviews have identified applications in glycemic forecasting, personalized treatment, monitoring, and decision support [12–14]. A systematic review and meta-analysis published in 2026 further described the growing use of AI-based interventions for personalized diabetes management while emphasizing the need for stronger clinical evidence [13]. Similarly, a recent review specifically addressing AI-based personalized diabetes therapy highlighted the potential of AI while noting the challenges associated with clinical integration [14].

Drug-specific prediction studies provide further support. Villikudathil et al. demonstrated that clinical, genomic, and proteomic features could be combined with machine learning to identify metformin responders and non-responders [7]. More recently, Garg et al. compared regression and machine-learning approaches for predicting glycemic response to sulfonylurea therapy [16]. These studies indicate that drug-response prediction is becoming an important research direction within precision pharmacotherapy.

The current framework differs conceptually by emphasizing routinely obtainable clinical characteristics and comparative treatment-response prediction. Such a framework could be particularly valuable in settings where genomic and proteomic testing is not routinely available. Nevertheless, future models should be capable of incorporating pharmacogenomic information when available because genetic variability may contribute to treatment response [4–6].

Several methodological limitations should be recognized. First, the current results are based on synthetic demonstration data rather than real clinical observations. Therefore, the reported performance values cannot be interpreted as evidence that XGBoost or any other model can accurately predict treatment response in actual patients. Second, the synthetic dataset cannot reproduce all sources of clinical heterogeneity, including medication adherence, lifestyle, socioeconomic factors, clinician treatment decisions, treatment switching, and unmeasured disease characteristics.

Third, no external validation was performed. External validation across independent institutions and populations is essential because a model can perform well in its development dataset but deteriorate when applied to a different population. TRIPOD+AI specifically emphasizes transparent reporting of prediction-model development and evaluation [19]. PROBAST+AI similarly highlights the importance of participant/data-source quality, predictor handling, outcome definition, and analysis [22-26].

Fourth, treatment response may be confounded by treatment selection. In real-world clinical data, physicians do not randomly assign patients to drugs. Instead, treatment choice is influenced by disease severity, comorbidities, previous response, cost, contraindications, and patient preference. Consequently, an observed association between treatment class and response cannot automatically be interpreted as a causal treatment effect.

Fifth, the present model does not include pharmacogenomic information, continuous glucose monitoring metrics, detailed adherence data, dietary variables, physical activity, socioeconomic characteristics, or longitudinal medication trajectories. Future models should evaluate whether inclusion of these variables improves generalizability without creating excessive complexity.

The implementation of AI in clinical pharmacotherapy should therefore follow a staged pathway. Initial development should use high-quality retrospective datasets with rigorous internal validation. This should be followed by temporal and geographical external validation. Calibration and decision-curve analyses should then assess whether model predictions provide meaningful clinical benefit. Prospective clinical studies should evaluate whether AI-

assisted decisions actually improve glycemic outcomes, reduce adverse events, or shorten the time required to achieve treatment targets[26-30].

Fairness and representativeness must also be addressed. Diabetes populations differ across countries and healthcare systems with respect to genetics, diet, obesity patterns, treatment access, socioeconomic factors, and clinical practice. A model developed in one population may therefore demonstrate reduced performance in another. Future studies should report subgroup performance according to age, sex, ethnicity where ethically and legally appropriate, renal function, treatment class, and other clinically relevant groups.

Overall, the present proof-of-concept demonstrates the methodological potential of AI for drug–patient response prediction but does not establish clinical utility. The principal contribution is the proposed integration of patient-specific variables, comparative pharmacotherapy modeling, and explainable AI within a single computational framework. The next stage should involve real-world multicenter data and prospective clinical validation[30-32].

5. Conclusion

An AI-based framework can potentially integrate demographic, anthropometric, clinical, laboratory, and treatment-related variables to estimate individual response to antidiabetic pharmacotherapy. In the present computational proof-of-concept, tree-based machine-learning approaches, particularly XGBoost, demonstrated stronger illustrative discrimination than conventional logistic regression, while SHAP analysis provided a mechanism for interpreting important predictors.

Baseline HbA1c, diabetes duration, fasting glucose, treatment class, BMI, renal function, and previous treatment exposure were identified as major contributors to predicted response. These variables are clinically plausible and demonstrate the potential value of integrating routinely available information into personalized pharmacotherapy models.

The proposed framework should be viewed as a **clinical decision-support concept rather than an autonomous prescribing system**. The numerical results are based on synthetic demonstration data and therefore cannot be used to estimate clinical performance. Future research should employ large, diverse, real-world datasets with longitudinal treatment information, incorporate pharmacogenomic and behavioral variables where feasible, perform external validation, assess calibration and fairness, and ultimately evaluate the model prospectively in clinical practice.

List of Symbols and Abbreviations

AI – Artificial Intelligence
ANN – Artificial Neural Network
AUROC – Area Under the Receiver Operating Characteristic Curve
BMI – Body Mass Index
DPP-4 – Dipeptidyl Peptidase-4
eGFR – Estimated Glomerular Filtration Rate
FPG – Fasting Plasma Glucose
GLP-1 RA – Glucagon-Like Peptide-1 Receptor Agonist
HbA1c – Glycated Hemoglobin
ML – Machine Learning
SGLT2 – Sodium-Glucose Cotransporter-2
SHAP – SHapley Additive exPlanations
SVM – Support Vector Machine
T2DM – Type 2 Diabetes Mellitus
XGBoost – Extreme Gradient Boosting

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Author Contribution

Conceptualization: Authors to be designated.
Methodology: Authors to be designated.
Computational analysis: Authors to be designated.
Data interpretation: Authors to be designated.
Writing—original draft: Authors to be designated.
Writing—review and editing: All authors.
Supervision: Senior/corresponding author to be designated.
Final approval: All authors.

Conflict of Interest

The authors declare no conflict of interest related to this work.

Data Availability Statement

The numerical dataset used for the present manuscript is synthetic and was created solely for methodological demonstration. It does not contain real patient information. For a definitive research submission, the authors should replace the synthetic dataset with an appropriately documented real-world or publicly available dataset and provide the corresponding data-availability statement.

Biographical Sketch

Author biographies: To be supplied according to the final author list and institutional requirements.

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