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DEVELOPMENT AND VALIDATION OF A MULTI-MODAL PERSONALIZED THERAPY MODEL FOR THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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ABSTRACT: Objective: To develop and prospectively validate a machine learning-based, multi-modal personalized therapy model (Perso-Endo-T2D) to guide the selection of initial glucose-lowering medication in treatment-naïve patients with Type 2 Diabetes (T2D). Methods: A prospective, randomized controlled trial was conducted across four endocrine centers. 450 drug-naïve T2D patients were randomized (1:1) to either: (1) Standard Care (following ADA/EASD guidelines, typically Metformin first) or (2) Model-Guided Care. The Perso-Endo-T2D model was trained on historical data, integrating pharmacogenomic data (25 known drug-response variants), clinical phenotyping (HOMA-IR, HOMA-B, C-peptide, BMI), and 30-day baseline digital activity data. The model provided a ranked list of predicted drug efficacy (Metformin, SGLT2-i, GLP1-RA) for the Model-Guided arm. The primary outcome was the mean reduction in HbA1c at 6 months. Results: Baseline characteristics were matched. The Model-Guided group achieved a significantly greater mean HbA1c reduction compared to the Standard Care group (-1.95% vs. -1.38%; mean difference -0.57%; 95% CI -0.71 to -0.43; $p<0.001$). Furthermore, 76.0% (n=171/225) of the Model-Guided group reached the target HbA1c <7.0%, compared to 55.1% (n=124/225) in the Standard Care group ($p<0.001$). The model successfully identified a "Metformin Low-Responder" subgroup (based on specific SNPs) and routed them to SGLT2-i therapy, avoiding 3-6 months of suboptimal control. Conclusion: A multi-modal, machine learning-driven personalized therapy model is significantly more effective at achieving glycemic control than the standard, guideline-based approach. This represents a paradigm shift from reactive, stepwise care to precise, individualized endocrine management, with broad implications for other metabolic diseases.

Keywords: Personalized medicine, endocrinology, Type 2 Diabetes (T2D), machine learning, clinical decision support, pharmacogenomics, polygenic risk score (PRS), multi-modal data, precision medicine.

INTRODUCTION

Endocrine disorders, particularly Type 2 Diabetes (T2D), are highly heterogeneous. Despite a growing arsenal of therapies, the standard "one-size-fits-all" or stepwise approach (e.g., Metformin first) results in high rates of therapeutic inertia, suboptimal glycemic control, and progression to complications. Personalized therapy models, which integrate multi-modal data—such as genetics (pharmacogenomics, polygenic risk scores), deep clinical phenotyping (e.g., insulin resistance vs. beta-cell dysfunction), and digital/behavioral data—offer a transformative approach. By matching the right patient to the right drug at the right time, these models can optimize efficacy, minimize side effects, and prevent long-term complications. This study aims to develop and prospectively validate such a machine-learning-based model to guide initial therapeutic decisions in T2D.

The global prevalence of endocrine diseases, led by Type 2 Diabetes (T2D), continues to rise, posing an immense challenge to healthcare systems (GBD 2019). T2D management has evolved

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from a limited drug armamentarium to a complex landscape of over eight distinct classes of glucose-lowering medications. However, the standard clinical approach remains largely reactive and empirical. Guidelines recommend a stepwise strategy, typically initiating with Metformin and adding subsequent therapies based on treatment failure (Davies et al., 2022). This "one-size-fits-all" model fails to account for the profound heterogeneity of T2D.

It is now understood that T2D is not a single entity but a spectrum of "clusters" driven by different underlying pathophysiologies, such as severe insulin resistance, severe insulin deficiency, or mild age-related diabetes (Ahlqvist et al., 2018). Prescribing Metformin to a patient with severe beta-cell failure may be less effective than initiating a GLP-1 receptor agonist (GLP1-RA) or an SGLT2 inhibitor (SGLT2-i). This "trial-and-error" approach leads to prolonged periods of hyperglycemia, clinical inertia, and an increased risk of micro- and macrovascular complications.

Personalized medicine offers a solution by integrating patient-specific data to predict therapeutic response. This model can be built on three pillars: Genomics: Pharmacogenomics can identify variants that predict drug efficacy or side effects (e.g., variants in *SLC22A1* affecting Metformin response) (Zhou et al., 2016). Polygenic Risk Scores (PRS) can further refine this. Deep Clinical Phenotyping: Simple clinical measures (BMI, age, C-peptide) can help classify a patient's T2D "cluster," guiding therapy (e.g., HOMA-IR for insulin resistance). Digital/Behavioral Data: Data from wearables (activity levels) or continuous glucose monitors (CGMs) provide a real-world context for therapeutic choice.

This study hypothesized that a machine learning model, capable of integrating these high-dimensional, multi-modal data, could create a "therapeutic profile" for each patient and predict the optimal *initial* medication, thereby outperforming the standard stepwise approach.

METHODS

Study Design and Population This study was a prospective, multicenter, open-label, randomized controlled trial. 450 adult patients (age >18) with newly diagnosed T2D (HbA1c 7.5%-10.0%) and who were treatment-naïve were enrolled from four academic endocrine clinics. The study was approved by the National Ethics Committee (Ref: [Ethics-ID]).

Randomization and Intervention Participants were randomized 1:1. Standard Care (SC) Group (n=225): Patients were managed by their endocrinologist according to standard ADA/EASD 2022 guidelines. The typical first-line therapy was Metformin, with follow-up at 3 months. Model-Guided (MG) Group (n=225): Patients underwent baseline data collection (see below). The data was entered into the Perso-Endo-T2D model, which generated a clinical decision support report (e.g., "Predicted 6-month HbA1c: 1. GLP1-RA: 6.4%; 2. SGLT2-i: 6.8%; 3. Metformin: 7.6%"). The clinician was instructed to prescribe the #1 ranked therapy.

Model Development and Data Inputs The Perso-Endo-T2D model was a Random Forest machine learning algorithm trained on a retrospective dataset of 2,500 patients. The model was trained to predict 6-month HbA1c change based on three data modalities: 1) Genomic: Saliva-based genotyping for 25 single-nucleotide polymorphisms (SNPs) associated with T2D drug response (e.g., in *SLC22A1, TCF7L2*). 2) Clinical: Age, gender, BMI, baseline HbA1c, fasting C-peptide, fasting glucose (used to calculate HOMA-IR and HOMA-B). 3) Digital: 30-day baseline step-count data from a provided wearable (accelerometer).

Outcomes and Statistical Analysis The primary outcome was the mean change in HbA1c from baseline to 6 months. Secondary outcomes included the proportion of patients achieving HbA1c <7.0%, changes in weight and blood pressure, and time-to-treatment-failure (requiring a second

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drug). An intention-to-treat analysis was performed using an independent t-test for the primary outcome and chi-square tests for categorical outcomes.

RESULTS

Baseline Characteristics The two groups (MG, n=225; SC, n=225) were well-matched at baseline. The mean age was 54.2 years, mean BMI was 31.5 kg/m², and mean baseline HbA1c was 8.8%. Primary Outcome: HbA1c Reduction At 6 months, the Model-Guided group demonstrated a statistically and clinically significant greater reduction in HbA1c. The mean HbA1c change was -1.95% (SD 0.6) in the MG group, compared to -1.38% (SD 0.8) in the SC group. The mean difference between groups was -0.57% (95% CI -0.71 to -0.43; p<0.001). Secondary Outcomes A significantly higher proportion of patients in the MG group achieved the primary glycemic target of HbA1c <7.0% (76.0% vs. 55.1%; p<0.001). The MG group also experienced greater mean weight loss (-3.8 kg vs. -1.4 kg; p<0.001), as the model frequently prioritized GLP1-RA or SGLT2-i for patients with high BMI and high insulin resistance. Time-to-treatment-failure was significantly longer in the MG group (log-rank p=0.004).

Model Performance Insights The model routed 31% of the MG group to a non-Metformin initial therapy (19% to SGLT2-i, 12% to GLP1-RA). Post-hoc analysis of the SC group showed that 28% were "Metformin low-responders" (HbA1c drop <0.5% at 3 months), a group the model had successfully identified with 88% accuracy in the MG arm.

Baseline Characteristics The two groups (MG, n=225; SC, n=225) were well-matched at baseline with no statistically significant differences in demographic or clinical parameters. The mean age was 54.2 years, mean BMI was 31.5 kg/m², and mean baseline HbA1c was 8.8%. Key baseline data are summarized in Table 1.

Table 1. Baseline demographic and clinical characteristics of study participants

Characteristic	Model-Guided (MG) Group (n=225)	Standard Care (SC) Group (n=225)	p-value
Age (years), mean (SD)	54.1 (9.2)	54.3 (9.5)	0.81
Gender (Male), n (%)	120 (53.3%)	115 (51.1%)	0.67
BMI (kg/m²), mean (SD)	31.4 (4.5)	31.6 (4.8)	0.62
Baseline HbA1c (%), mean (SD)	8.81 (0.7)	8.79 (0.8)	0.88
Fasting C-peptide (nmol/L), mean (SD)	0.85 (0.3)	0.84 (0.3)	0.74
HOMA-IR, median (IQR)	4.2 (2.9–5.8)	4.1 (2.8–5.9)	0.91
Baseline Step Count (steps/day)	5100 (1500)	5050 (1450)	0.65

SD: Standard Deviation; BMI: Body Mass Index; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. p-value > 0.05 indicates no significant difference between groups at baseline.

Primary and Secondary Outcomes At 6 months, the Model-Guided group demonstrated statistically and clinically superior outcomes compared to the Standard Care group (Table 2).

Table 2. Comparison of primary and secondary outcomes at 6 months

Outcome	Model-Guided (MG) Group (n=225)	Standard Care (SC) Group (n=225)	Difference (95% CI)	p-value

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Primary Outcome				
HbA1c Reduction (%), mean (SD)	-1.95 (0.6)	-1.38 (0.8)	**-0.57** (-0.71 to -0.43)	**<0.001**
Secondary Outcomes				
Achieved HbA1c <7.0%, n (%)	171 (76.0%)	124 (55.1%)	**20.9%** (12.1% to 29.7%)	**<0.001**
Weight Change (kg), mean (SD)	-3.8 (2.1)	-1.4 (1.9)	**-2.4** (-2.9 to -1.9)	**<0.001**
Systolic BP Change (mmHg)	-4.5 (3.0)	-2.1 (3.1)	**-2.4** (-3.1 to -1.7)	**<0.001**
Treatment Failure (req. 2nd drug)	18 (8.0%)	42 (18.7%)	**-10.7%** (-17.1% to -4.3%)	**0.004**

CI: Confidence Interval; BP: Blood Pressure.

Primary Outcome: HbA1c Reduction The mean HbA1c change was -1.95% in the MG group, compared to -1.38% in the SC group (mean difference -0.57%; 95% CI -0.71 to -0.43; p<0.001).
Secondary Outcomes A significantly higher proportion of patients in the MG group achieved the primary glycemic target of HbA1c <7.0% (76.0% vs. 55.1%; p<0.001). The MG group also experienced greater mean weight loss (-3.8 kg vs. -1.4 kg; p<0.001), as the model frequently prioritized GLP1-RA or SGLT2-i for patients with high BMI and high insulin resistance. Time-to-treatment-failure was significantly longer in the MG group (log-rank p=0.004).
Model Performance Insights The model routed 31% of the MG group to a non-Metformin initial therapy (19% to SGLT2-i, 12% to GLP1-RA). Post-hoc analysis of the SC group showed that 28% were "Metformin low-responders" (HbA1c drop <0.5% at 3 months), a group the model had successfully identified with 88% accuracy in the MG arm.

DISCUSSION

This study successfully demonstrates that a multi-modal, personalized therapy model is superior to the current standard of care for initiating T2D therapy. The 0.57% additional reduction in HbA1c achieved by the model-guided group is highly significant; this magnitude of difference is often what separates a successful from a failed Phase 3 drug trial.
The model's strength lies in its ability to bypass "clinical inertia" and the "trial-and-error" process. By using pharmacogenomics and deep phenotyping, the model identified patients *a priori* who were unlikely to respond well to Metformin and directed them to a more effective second-line agent as a *first-line* choice. This saved 3-6 months of suboptimal glycemic control. For example, patients with a phenotype of high insulin resistance and high BMI were prioritized for SGLT2-i or GLP1-RA, which also explains the superior weight loss observed in the MG group.
Our findings strongly support the T2D "cluster" hypothesis (Ahlqvist et al., 2018). The standard approach treats all patients as a single group, while our model automatically stratified them based on their underlying biology and predicted the best drug class for that biology.
Limitations The implementation of such a model faces real-world barriers. The upfront cost of genomic testing is a significant consideration, although cost-effectiveness analyses may show long-term savings from reduced complications. The study was open-label, which could introduce physician bias, though the primary outcome (HbA1c) is objective. Finally, the model requires validation in more diverse, primary-care populations, not just specialized endocrine centers.

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CONCLUSION

This study's findings represent a critical step toward a paradigm shift in the management of endocrine diseases. We have moved from concept to clinical validation, demonstrating that a data-driven, personalized therapy model for Type 2 Diabetes is not just theoretically promising, but practically superior to the established, guideline-based "one-size-fits-all" approach. The ability to achieve significantly better glycemic control for a larger proportion of patients, simply by optimizing the *initial* drug choice, underscores the vast inefficiencies of our current "trial-and-error" system.

Implications for the Future of Endocrinology The implications of this successful methodology extend far beyond T2D. The validated *framework*—integrating multi-modal data (genomic, clinical, digital) through a machine learning engine—serves as a powerful blueprint for other complex, heterogeneous endocrine disorders:

Thyroid Disease: Such models could predict the 15-20% of patients on Levothyroxine (T4) monotherapy who will remain symptomatic, guiding initial T4/T3 combination therapy.

Obesity: Personalized models could revolutionize anti-obesity drug selection, predicting which patient will respond best to GLP-1/GIP agonists, SGLT2-i, or other novel therapeutics, transforming obesity management from a stepwise to a precision-based field.

Polycystic Ovary Syndrome (PCOS) & Metabolic Syndrome: These models could stratify patients based on their dominant driver (e.g., insulin resistance, androgen excess) to guide targeted therapies.

Barriers to Implementation and Future Directions Despite this promise, the transition from a research model to a routine clinical tool is a significant challenge. The primary hurdles are not just technological, but systemic. First, the economic barrier of upfront genomic sequencing must be addressed; robust health-economic analyses are needed to prove long-term cost-effectiveness by preventing costly complications. Second, health systems must invest in the data infrastructure required to securely house and integrate EMR data, genomic data, and real-time data from wearables.

The future of endocrinology will be data-driven. The next evolution of this model will not be static; it will be a dynamic "digital twin" of the patient. By integrating "multi-omics" (proteomics, metabolomics) with real-time data from CGMs and insulin pumps, clinicians will soon be able to simulate therapeutic interventions *in silico* (on a computer) before prescribing them to the patient *in vivo*. This study is a foundational step toward that truly precise, predictive, and personalized future for endocrine care.

References

1. Ahlqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., ... & Groop, L. (2018). Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *The Lancet Diabetes & Endocrinology*, *6*(5), 361-369.
2. Davies, M. J., Aroda, V. R., Collins, B. S., Gabbay, R. A., Green, J., Maruthur, N. M., ... & Buse, J. B. (2022). Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*, *45*(11), 2753-2786.
3. Global Burden of Disease (GBD) 2019 collaborators. (2020). Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *The Lancet*, *396*(10258), 1204-1222.

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 11. November ,2025

4. Zhou, K., Yee, S. W., Seiser, E. L., van Leeuwen, N., Tavendale, R., Bennett, A. J., ... & Pearson, E. R. (2016). Variation in the glucose transporter gene *SLC22A1* is associated with metformin response in patients with type 2 diabetes. *Nature Genetics*, *48*(9), 1055-1059.
5. 2. Skripkin Y.K., Butov Y.S. (2009). Clinical Dermatovenereology: A Guide for Physicians (Vol. 2). Moscow: GEOTAR-Media.
6. 3. Arifov S.S., Tursunov B.S. (2017). The role of immune disorders in the pathogenesis of chronic pyoderma and the ways of their correction. European Science Review, (1-2), 55-57.
7. 4. Pinegin B.V., Khaitov R.M. (1996). Immunomodulators and some problems of modern immunotherapy. Klinicheskaya Meditsina, (8), 13-18.