Application of Obtainable Biological Agent Characteristics in Efficacy Stratification of Oral Anti-Obesity Drugs

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Article

Application of Obtainable Biological Agent Characteristics in Efficacy Stratification of Oral Anti-Obesity Drugs

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Abstract

The aim of this study is to develop a "patient-friendly, accurate screening application for oral anti-obesity medicines" (AOMs). It transforms gut microbiome information from high-cost mechanistic research into an optional add-on input and constructs a surrogate feature system that remains functional without omics testing. We followed 260 obese individuals who were treated orally/injected with AOMs (mainly GLP-1 agonists) for 16 weeks, collecting baseline fecal 16S/metagenomic data, continuous glucose monitoring (CGM), lipid metabolism indices, and patient reported outcomes (PROs). First, we constructed a microbiota-metabolic pathway, and further refined the surrogate variables under "non-omics conditions" (dietary structure questionnaire, postprandial blood glucose fluctuations, history of gastrointestinal symptoms, sleep/activity characteristics). The app implemented a two-layer model: the baseline layer predicts treatment response using only low-burden features; the enhanced layer calibrates prediction confidence and refines population stratification when omics data is available.Results demonstrated: the baseline layer predicted a 12 – 16 week reduction of 7% or more (AUC = 0.82), whereas the enhanced layer, including the microbial-pathway score, raised AUC to 0.87 and significantly reduced uncertainty in borderline samples (18% reduction in ECE) .This study showed that microbiome information was more suitable as an "enhanced module" for the application, which improved the reliability and interpretability of precise screening without compromising patient availability.

Keywords: AOMs; patient-friendly app; microbiome-enhanced module; proxy features; confidence calibration; precision screening

1. Introduction

Antiobesity drugs (AOMs) have emerged as a key therapeutic tool for the treatment of complex obesity. Given their significant efficacy variability, personalized screening strategies have garnered increasing research attention. Jeon et al [1] pointed out that although more than one AOMs have been used in clinical practice in recent years, the significant differences in the proportion of patients◎body weight response indicate that the outcome of treatment is affected by a variety of metabolic and physiological factors.Regarding the mechanism and treatment approach, Alharbi [2] emphasized that GLP-1 receptor agonists have shown significant efficacy in the treatment of obesity by regulating appetite and energy metabolism. Podder et al. [3] Furthermore, it has been suggested that multiple agonists such as incretin may be the main orientation of the treatment of obesity. At the same time, the concept of precision medicine is becoming more and more integrated in metabolic research. Shannon et al.[4] suggests that the identification of individual metabolic phenotypes increases the accuracy of metabolic interventions; Gangwal and Lavecchia [5] emphasize the potential use of AI in predicting drug reactions and developing personalized therapy strategies.Although current research continues to advance the research of obesity from a pharmacological and data-analysis point of view,

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the high cost of omics testing limits its availability in routine clinical screening. How to reduce the barriers of data collection while keeping the prediction reliability is still a challenge. In order to solve these problems, we build an accessible biosurrogate system and build a two-tier effectiveness forecasting model to evaluate the efficacy of oral anti-obesity drugs.

2. Study Population and Multi-Source Data Collection

Obese participants were recruited from the MCD cohort, all of whom met the BMI criteria (BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² with metabolic abnormalities). The cohort included 260 subjects who underwent 16 weeks of pharmacological treatment and monitoring for obesity, mainly involving GLP-1 receptor agonists, while baseline metabolic status and lifestyle characteristics were systematically recorded [6]. Although the present study focuses on screening strategies for oral anti-obesity medications, the real-world treatment cohort also contained individuals receiving injectable GLP-1 receptor agonists, which were included because the modeling framework aims to predict treatment response rather than drug-delivery route.Gut microbiome data were obtained through fecal 16S rRNA sequencing and metagenomic sequencing. The dynamics of glucose metabolism were captured using continuous glucose monitoring (CGM) systems. Metabolic biochemical parameters were measured from fasting blood samples, while behavioral and dietary information was collected using standardized patient-reported questionnaires.Metabolic stability was characterized by a postprandial glucose fluctuation index, defined a:

$$G_{var}=\sqrt{\frac{1}{T}\sum_{t=1}^{T}\left(g_t-\bar{g}\right)^2} \quad (1)$$

whereG_{var} denotes the glycemic fluctuation intensity index;g_t represents the continuous glucose monitoring value at time point$t$;$\bar{g}$ indicates the average blood glucose level during the monitoring period; and$T$ signifies the number of valid sampling time points. The CGM device recorded glucose concentrations at 5-minute intervals, generating approximately 288 measurements per day. The monitoring window used for the calculation ranged from 3–7 consecutive days prior to treatment, resulting in approximately 864–2016 observations for each participant. This index quantifies the magnitude of postprandial glucose variability and provides an input variable for subsequent proxy feature learning.Multi-source data were paired at the sample level using unified identifiers to ensure stable mapping relationships among microbiome features, metabolic indicators, and behavioral variables.

Table 1. Multi-source Data Collection Structure for the Research Cohort.

Data Type	Data Source	Primary Metric
Gut Microbiome	Fecal 16S/Metagenomic Sequencing	Species Abundance, Functional Pathways
Blood Glucose Dynamics	CGM Continuous Glucose Monitoring	Postprandial blood glucose, variability index
Metabolic Markers	Blood Biochemical Testing	TG, HDL, HOMA-IR
Behavioral Characteristics	Patient-Reported Outcome Measures	Dietary Patterns, Sleep, Activity

3. Constructing Therapeutic Efficacy Prediction Models Using Accessible Biological Proxies

3.1. Construction of Microbiome Metabolic Pathway Features

Characterization of gut microbiome metabolic functions depends on systematic mapping of microbial abundance and functional annotation data.As illustrated in Figure 1, the species abundance matrix obtained from sequencing is first annotated with pathways through a functional database to

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form a microbial metabolic pathway association matrix. This structure measures the contribution of specific microorganisms to metabolic pathway activity and provides functional biomarkers for future effectiveness forecasting models.This study constructs species relative abundance vectors by normalization and maps them to metabolic pathways [7]. Pathway activity scores are calculated via weighted aggregation, expressed as follows:

$$P_k = \sum_{i=1}^{N} \omega_{ik} \cdot R_i \quad (2)$$

where P_k denotes the composite activity score for the k th metabolic pathway; R_i denotes the standardized relative abundance of the i th microbial species in the sample; ω_{ik} represents the functional contribution weight of species i in metabolic pathway k , calculated from the species-pathway association frequency in functional annotation databases; N denotes the number of species participating in pathway metabolic reactions. To ensure comparability of different pathway features in the statistical space, the pathway scores undergo scale normalization during the study process, expressed as:

$$S_k = \frac{P_k - \mu_k}{\sigma_k} \quad (3)$$

where S_k denotes the normalized pathway feature value; μ_k represents the mean of pathway k across the sample set; and σ_k indicates the standard deviation of the corresponding pathway score.The normalized pathway feature matrix is used to characterize individual metabolic microbiome differences and provides a functional reference for the subsequent learning process of available bioproxy features [8].

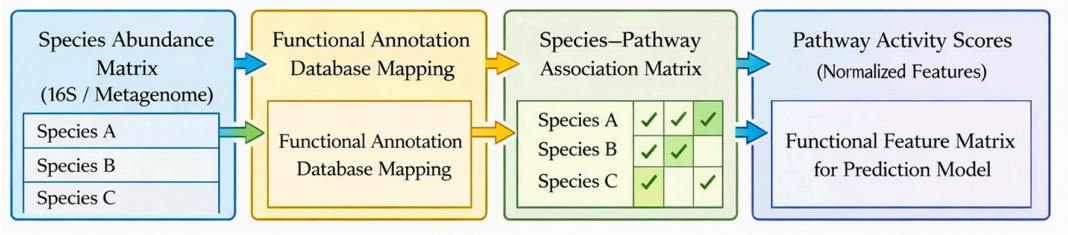

Figure 1. Schematic diagram of the microbial species-metabolic pathway functional mapping structure.

3.2. Learnable Biological Surrogate Feature Methodology

Metabolic pathway features reflect functional states of the gut microbiome, yet clinical environments cannot sustain routine omics testing. Therefore, a surrogate feature system is introduced to infer microbial metabolic functions from low-burden observable variables. Behavioral and metabolic indicators are standardized to construct candidate proxy variables. Dietary composition indicators are encoded using measures such as fibre intake proportion, carbohydrate ratio, and lipid intake balance. Continuous glucose monitoring data characterize metabolic responses through postprandial glucose dynamics. Information on gastrointestinal symptoms and sleep–activity patterns is transformed into behavioral variables through standardized scoring procedures [9].The surrogate feature learning process establishes a mapping between low-cost observable variables and microbial pathway activity using an L1-regularized sparse regression model, whose objective function is expressed as:

$$L(\theta) = \frac{1}{M} \sum_{j=1}^{M} \left(U_j - \hat{U}_j\right)^2 + \lambda \sum_{q=1}^{Q} |\theta_q| \quad (4)$$

Where, $L(\theta)$ denotes the optimization objective function of the surrogate learning model; U_j represents the true pathway activity indicator for the j th sample; $\hat{U}_j$ denotes the pathway estimate predicted by the surrogate model; M indicates the number of samples; θ_q signifies the regression weight for the q th surrogate variable; Q represents the number of surrogate variables; and λ denotes the sparse regularization coefficient. Although nonlinear machine-learning models such as random forest can capture complex feature interactions, the sparse regression framework is adopted

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here because the primary objective of the proxy system is interpretability and feature stability. The L1 regularization encourages the selection of a compact subset of behavioral and metabolic indicators that best approximate microbial pathway activity while reducing overfitting risk in moderate sample sizes.The surrogate pathway estimate is obtained through a weighted combination of normalized proxy variables:

$$\hat{U}_j = \sum_{q=1}^{Q} \theta_q \cdot Z_{jq} \quad (5)$$

where Z_{jq} denotes the normalized value of the j th sample on the q th proxy variable. This mapping enables dietary patterns, blood glucose fluctuations, and behavioral variables to approximate microbial metabolic functions without omics testing, providing stable, low-cost input features for subsequent efficacy prediction models.

3.3. Construction of the Two-Layer Efficacy Prediction Model

After metabolic proxy variables are established, a stable decision framework is required to support efficacy prediction under different data availability conditions. The proposed forecasting framework adopts a two-layer hierarchical model structure, and Figure 2 illustrates the overall workflow. In the first layer, low-burden behavioral and metabolic proxy features are used to construct a baseline prediction module. This module adopts a logistic regression classifier to estimate the probability that an individual reaches the predefined weight-loss threshold during the treatment cycle. The prediction function is defined a:

$$R_i = \frac{1}{1+\exp\left(-\sum_{h=1}^{H} \alpha_h \cdot W_{ih}\right)} \quad (6)$$

where R_i denotes the probability of therapeutic response for the i th subject; W_{ih} represents the value of the i th sample on the h th proxy feature; α_h indicates the corresponding feature weight parameter; and H denotes the number of proxy variables. When omics data are available, microbial metabolic pathway characteristics are further incorporated to calibrate the baseline prediction results [10]. The enhanced layer adjusts the predicted probability through a confidence calibration function defined as:

$$C_i = R_i + \beta \cdot \sum_{k=1}^{K} \delta_k \cdot S_{ik} \quad (7)$$

where C_i denotes the calibrated efficacy prediction probability; S_{ik} represents the normalized score of the i th sample on the k th metabolic pathway; δ_k indicates the pathway contribution coefficient; K denotes the number of pathways; and β signifies the calibration weight factor. This dual-layer modeling strategy enables efficacy prediction under low-data conditions while allowing prediction confidence and accuracy to improve when microbial functional information becomes available.

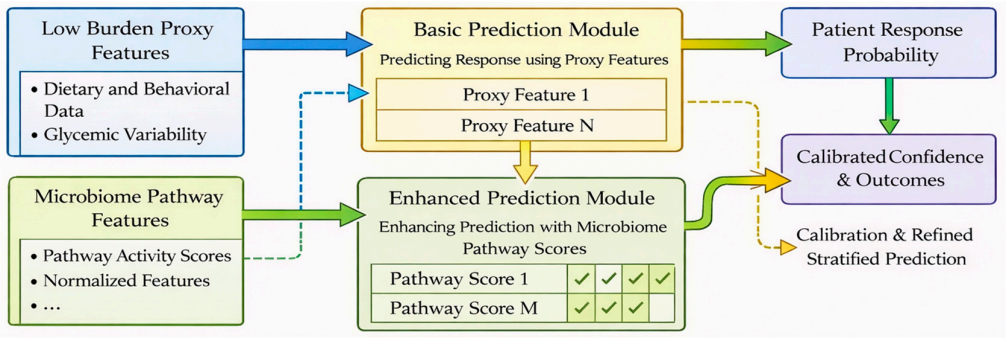

Figure 2. Schematic diagram of the AOMs dual-layer efficacy prediction model.

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4. Experimental Design and Results Analysis

4.1 Experimental Setup

The trial design focused on the relationship between the multiple sources of baseline data and 16 weeks of follow up, using the percentage of weight change as the efficacy criterion. The study cohort recorded participants◎metabolic indices, behavioral characteristics, and microbial functions before treatment, and continued monitoring of body weight and metabolism throughout the duration of the intervention. In order to characterize the individual state trajectories during therapy, a patient state evolution structure (as illustrated in Figure 3) was constructed to describe the process by which a participant moved from a baseline metabolic status to a final treatment outcome via drug intervention.Experimental labels were constructed on the basis of a 16-week loss percentage. Samples were classified as responders if they achieved or exceeded 7% in body weight and otherwise as non-responders. Data partitioning employed a stratified sampling strategy to maintain a consistent response ratio, with an independent partition at the subject level to prevent information from leaking from multiple data sources. The basic module uses low-burden proxy variables, such as diet patterns, blood sugar levels, and lifestyle behaviors, to predict effectiveness. The enhanced module further incorporates microbial metabolic pathway features within the same data framework for probability calibration and hierarchical refinement. The performance of the model is assessed using the AUC for discrimination and the consistency of the prediction probability calibration with ECE.

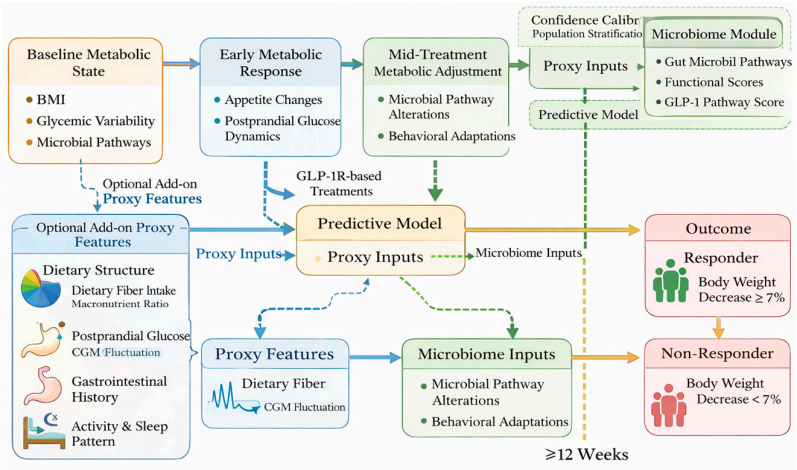

Figure 3. Evolution of patient status during AOM treatment.

4.2. Fitting Effectiveness of Proxy Features on Microbial Pathway Scores

A model establishing behavioral and metabolic proxy variables, the model training process first validated the fitting capability of these proxies for microbial metabolic pathway scores. Behavioral characteristics and continuous glucose dynamics measures of 260 participants were mapped to the respective pathway activity spaces, and the training set learned the approximate capacity of proxy variable combinations for pathway characteristics. The Pearson correlation coefficient between the predicted value and the actual pathway score was 0.71, the bile acid metabolic pathway was 0.68, and the branched-chain amino acid degradation pathway was 0.64. Postprandial GSD showed a high contribution to the proxy characteristic set, accounting for 18.4% of the characteristic significance weights, and the percentage of dietary fibre intake and sleep duration accounted for 16.1% and 12.7% respectively, respectively. These results suggest that low load behaviors and metabolic variables can be used to approximate the function of microbial function in a statistical way, thus providing an alternative input for future effectiveness forecasting models.

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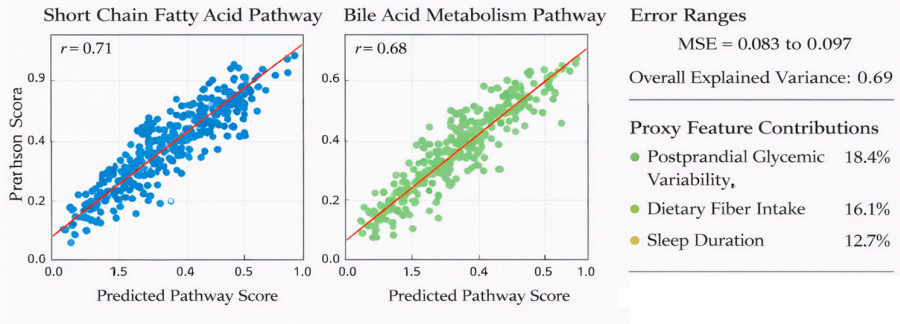

Figure 4. Schematic diagram of the fitting relationship between proxy features and pathway scores.

4.3. Efficacy Prediction Performance of the Baseline Model

After the surrogate variable system was established, the baseline prediction module evaluated responses to anti-obesity drug treatments without user input. Among the 260 subjects in the study, those achieving more than 7% weight loss during 16 weeks constituted 41.9% of the population, with subjects classified into responders and nonresponders according to the percentage of weight loss. The ability to discriminate was assessed on an independent test sample. The model outputs showed an average predicted probability of 0.74 for responders versus 0.36 for nonresponders, indicating a clear distinction between the two groups. The AUC of the test specimen was 0.82, the sensitivity was 0.78, the specificity was 0.75, and the F1 score was 0.76. The model demonstrated stable discrimination capability around a probability threshold of 0.50, with approximately 68% of samples◎predicted probabilities concentrated within the 0.30-0.80 range. The results show that behavioral and metabolic proxy variables are able to generate relatively stable performance forecasting capabilities without reliance on omics testing.

4.4. Predictive Performance Enhancement via Augmented Layer Models

During model training, microbial metabolic pathway features were included as enhanced inputs to the baseline prediction framework to assess the contribution of functional microbiome information to therapeutic discrimination. As shown in Figure 5, the addition of the path features significantly improved the overall recognition of the test sample, with an increase in the area below the operating characteristic curve from 0.82 to 0.87.The improved prediction model yielded an average prediction probability of 0.81 (from 0.74) and a nonresponse of 0.29 (lower from 0.36), widening the difference in probability distribution to 0.5. The sensitivity of the model increased from 0.78 to 0.83, the specificity increased from 0.75 to 0.80, and the total F1 score increased to 0.82. In addition, the prediction results show that there was a class change in about 21% of the samples, and 67% of the regraded samples were given a corrected true label.

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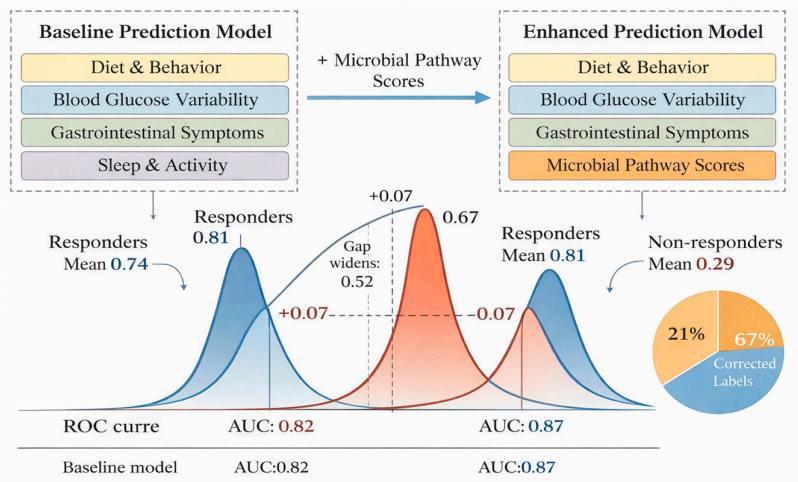

Figure 5. Enhanced Model Improves Treatment Response Prediction.

4.5. Analysis of Model Confidence Calibration Results

The reliability of predicted probabilities has a direct impact on the clinical interpretation of individual efficacy assessments, which requires consistency checks on prediction outcomes. An expected calibration error of 0.117 was observed in the baseline prediction model, with 27.3% of samples falling within the 0.40-0.60 probability range — indicating high uncertainty. The expected calibration error was reduced to 0.096, which is about 18% Probability Distribution Analysis showed that a sample with a predicted probability greater than 0.70 had a true response rate of 72.5%, and a true nonresponse rate of 76.8% for those with a probability lower than 0.30. These results suggest that the MBM is effective in reducing the uncertainty in the prediction boundary area and keeping the predicted efficacy probability consistent with the actual therapeutic outcome.

5. Conclusions

The issue of anti-obesity drug efficacy stratification was systematically explored by constructing an accessible biosurrogate feature system. Low load behavior and metabolism can approximate microbial metabolism to some degree, and it can support the steady running of effectiveness forecasting model. While maintaining patient accessibility, the dual-layer prediction structure enhances efficacy discrimination capability and probability calibration. However, this study remains constrained by sample size and population sources, and the cross-population stability of pathway functional characteristics needs to be confirmed. Future studies should combine larger, multicentre data with longitudinal microbial dynamics to improve the generalization of the model and the accuracy of screening.

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