Interpretable AI-Based Risk Profiling of Metabolic Syndrome and Simulated Klotho Modulation Using Real-World NHANES Data (2007–2023)

MSR203

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INTRODUCTION

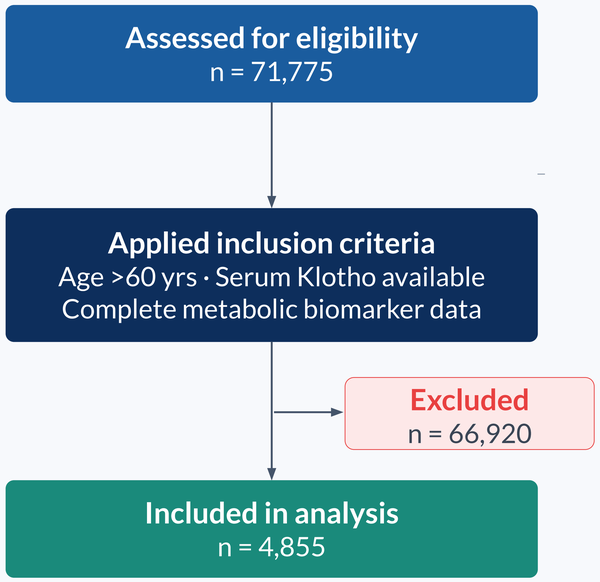
Metabolic Syndrome (MetS) is a heterogeneous condition linked to elevated cardiometabolic risk. Traditional models relying on isolated biomarkers often miss patient-level complexity relevant to clinical decisions and trial design. This study used interpretable artificial intelligence (AI) to identify key predictors of MetS in real-world data and to evaluate Klotho, a pleiotropic protein involved in metabolic and aging pathways, as a contextual modifier of metabolic risk.

OBJECTIVES

1. Identify patient-level predictors of MetS using real-world data
2. Specify clinically meaningful biomarker thresholds of MetS risk
3. Simulate Klotho modulation for evaluation as a contextual modifier

METHODS

A retrospective analysis was performed using National Health and Nutrition Examination Survey (NHANES) data from 2007–2023. Of 71,775 participants, 4,855 met inclusion criteria and were included in analysis.



An interpretable AI model was developed using KolateAI's precision-medicine platform to:

- Generate patient-level MetS risk predictions
- Rank biomarkers by feature importance with interpretable AI outputs
- Identify clinically meaningful risk thresholds
- Simulate counterfactual Klotho-related perturbations via digital-twin modeling

Simulations were intended for hypothesis generation and stratification rather than efficacy assessment. Future translational evaluation will use human-relevant New Approach Methodologies (NAMs).

RESULTS

Model Performance

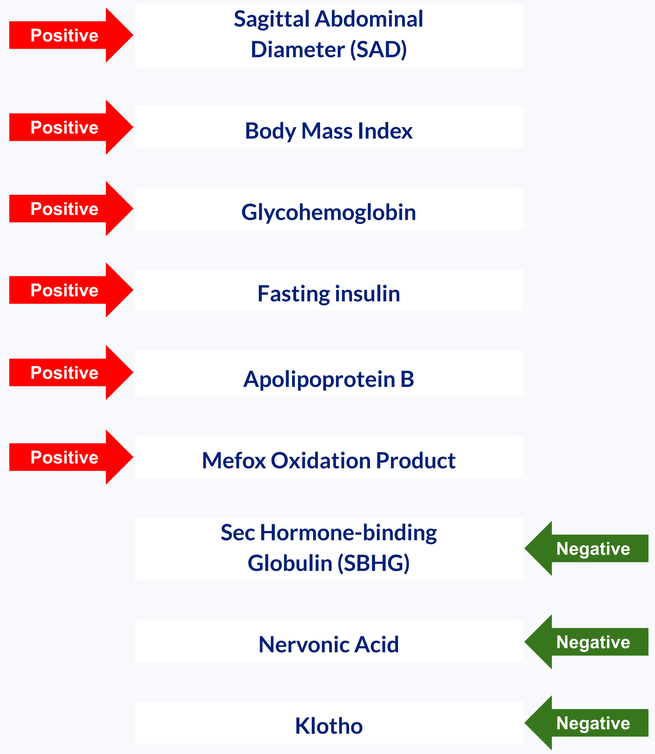
The model achieved an accuracy of 92% and AUC-ROC of 0.93 in predicting patient-level MetS risk from a set of clinically available biomarkers in a real-world cohort.

91.8%	0.93	91.7%
Accuracy	AUC-ROC	F1-score

91.7%	91.7%
Precision	Recall

Predictors of MetS

Various biomarkers revealed correlation with MetS risk by feature importance analysis. Shown below are the top eight, plus Klotho, which is a molecule of interest. **Positive** correlation indicates increased MetS risk with higher values; **negative** indicates decreased MetS risk with higher values.



***Klotho** - shown as a **negative correlate** of MetS risk - clustered with SHBG and nervonic acid among protective biomarkers, supporting its evaluation as a contextual modifier rather than a dominant predictor.*

RESULTS (CONTD.)

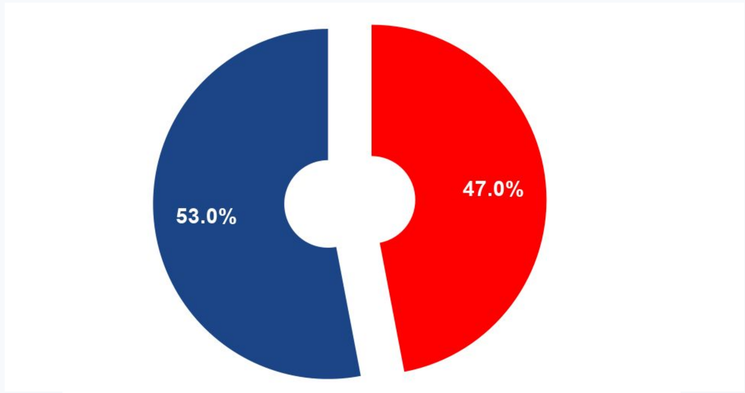
Biomarker Thresholds

MetS risk thresholds were identified across three key biomarkers, offering reference values for patient stratification and clinical screening.

Biomarker	Threshold	MetS Prevalence
SAD	>25 cm	69.3%
SHBG	<30 nmol/L	65.7%
HbA1c	≥6.5%	79%

Simulated Klotho Modulation

Digital-twin modeling simulated counterfactual Klotho perturbation by factors of 0.5, 1.5, 2, 2.5, and 3 within a range of 300 to 1,000 pg/mL. The cohort stratified into two groups:



~53%

Likely Responders

Patients whose predicted MetS risk was inversely impacted under simulated Klotho modulation

~47%

Non-Responders

Patients whose predicted MetS risk was unchanged or moved in-line with simulated Klotho modulation

CONCLUSIONS

1. Interpretable AI enables transparent, patient-level MetS risk profiling from real-world data, overcoming limitations of single biomarkers.
2. Klotho acts as a negative correlate and contextual modifier of MetS risk rather than a dominant predictor.
3. Simulation-based stratification identifies likely responders to Klotho modulation, supporting patient enrichment and hypothesis generation for precision trial design.