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BIOMARKERS DISCOVERY IN TYPE 2 DIABETES MELLITUS: FROM OMICS TECHNOLOGIES TO CLINICAL PRACTICE

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Abstract:

Background: *Type 2 diabetes mellitus (T2DM) is caused by complex pathophysiological processes including progressive insulin resistance, pancreatic β-cell dysfunction, chronic systemic inflammation and altered interorgan metabolic communication1. The ability of common clinical markers such as fasting plasma glucose and glycated hemoglobin (HbA1c) to identify early subclinical alterations or discriminate between disease subphenotypes1 is limited.*

Objective: *To review current literature of multi-omic biomarker discovery in T2DM with focus on predictive discrimination, mechanistic contribution across omic layers, and translational, regulatory and clinical implementation barriers2.*

Data Sources: *Comprehensive synthesis of studies indexed in PubMed, MEDLINE, Scopus and Web of Science evaluating genomics, epigenomics, transcriptomics, proteomics, metabolomics, microbiomics and machine-learning-driven multi-omics integration2.*

Review Methods: *A state-of-the-art structured review of human prospective cohorts, case-cohort designs, clinical trial evaluations, assay standardization and regulatory qualification pathways2.*

Key Findings: *Among individual omic layers, plasma proteomics showed the highest discriminative performance for prediction of incident T2DM5. Targeted proteomic panels (e.g., 15 proteins) improve the C-index of established clinical models by 0.022–0.0235. Metabolomic signatures, including branched-chain amino acids (isoleucine, leucine, valine) and aromatic amino acids (phenylalanine, tyrosine), may reflect metabolic dysregulation >10 years prior to clinical onset4. Epigenetic methylation probes at TXNIP, ABCG1, and PDK4 capture cumulative metabolic memory 2 Integrating full multi-omic profiles yields modest predictive improvements (+0.006 to +0.05 C-index increment) over targeted proteomic-clinical models due to biological signal redundancy 5*

Conclusion: *Multi-omic biomarker profiling improves T2DM risk prediction and subphenotyping. For clinical translation, standardized analytical workflows, cross-population validation in diverse cohorts, cost-utility optimization, and formal regulatory qualification2 are required.*

Keywords: *Diabetes Mellitus, Type 2 Biomarkers Proteomics Metabolomics Precision Medicine Multi-omics*

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INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is a metabolic disorder that affects multiple systems. It is characterized by peripheral insulin resistance, progressive deterioration of pancreatic β-cell function, ectopic lipid deposition, chronic low-grade systemic inflammation, and altered interorgan communication1. Conventional clinical diagnostic metrics like fasting plasma glucose, 2 h oral glucose tolerance testing and glycated hemoglobin (HbA1c) are effective for identifying overt hyperglycemia but provide limited information on subclinical metabolic dysregulation1. Significant β-cell mass loss and compensatory hyperinsulinemia are observed years before reaching diagnostic glycemic thresholds1, narrowing the therapeutic window for early, disease-modifying interventions.High-throughput omics profiling (genomics, epigenomics, transcriptomics, proteomics, metabolomics and microbiomics) enables deep molecular phenotyping across multiple biological strata2. Although several candidate signatures associated with incident T2DM and microvascular/macrovascular complications have been identified in exploratory studies, clinical implementation has been limited2. There are significant barriers to routine clinical adoption including inconsistent predictive performance across validation cohorts, unstandardized pre-analytical sample preparation, limited cross-ethnic portability and no health economic assessments2.

This state-of-the-art review evaluates multi-omic biomarker discovery in T2DM, assessing the relative predictive discrimination of individual and integrated omic layers, detailing underlying physiological mechanisms and examining regulatory science requirements for clinical translation2. This manuscript integrates longitudinal population cohorts, tissue-specific multi-omic investigations and standard ML models to offer an analytical framework for the translation of molecular biomarkers into standardized clinical practice2. Omics Domains in Type 2 Diabetes Mellitus Biomarker Discovery Genomics and Polygenic Risk Scoring

Genome-wide association studies (GWAS) have identified over 500 genetic loci associated with T2DM susceptibility, enabling the creation of polygenic risk scores (PRS)5. While PRS captures the inherited background risk over the lifespan of an individual, its ability to predict medium-term incident T2DM in isolation is less than established clinical risk scores such as the Cambridge Diabetes Risk Score (CDRS) or clinical models including baseline HbA1c5. In unselected prospective population cohorts, addition of a T2D-PRS to clinical prediction models yields marginal improvements in risk discrimination, with increases in C-index of +0.001 to +0.0066.

The predictive performance of genetic risk scoring differs markedly across glycemic sub strata5. For example, in normoglycaemic individuals (baseline HbA1c < 42 mmol/mol [6.0%]), the addition of a T2D-PRS to clinical risk models results in a separate performance gain of a C-index increase of 0.06 (from baseline clinical models to an overall C-index of 0.83)5. However, individuals in the top quartile of polygenic burden within normoglycaemic cohorts have an absolute 20-year incidence rate of T2DM that is roughly half that seen in individuals with baseline prediabetes5. This divergence highlights a key epidemiological limitation of inherited risk scoring: genetic variants are a static susceptibility determined at conception but do not reflect dynamic physiological exposures, biological aging, environmental changes or metabolic adaptation1. Epigenomics and DNA Methylation Signatures

Epigenome-wide association studies (EWAS) look at DNA methylation patterns, mostly at cytosine-phosphate-guanine (CpG) dinucleotide sites, providing a biological link between inherited genetic susceptibility and environmental factors1. Prospective population cohorts EWAS analyzes identified 106 differentially methylated probes (DMPs) and 62 differentially methylated regions (DMRs) associated with fasting plasma glucose and long-term HbA1c trajectories2. Differentially methylated key gene targets were thioredoxin-interacting protein (TXNIP), ATP-binding cassette sub-family G member 1 (ABCG1), pyruvate dehydrogenase kinase 4 (PDK4) and arrestin domain-containing 4 (ARRDC4)2. TXNIP promoter hypermethylation decreases gene expression, impairs thioredoxin activity, increases cellular reactive oxygen species (ROS), and increases β-cell apoptosis2 mechanistically. By contrast, altered methylation of ABCG1 suppresses reverse cholesterol transport in peripheral macrophages, thereby accelerating low-grade metabolic inflammation in visceral adipose tissue2. Epigenetic methylation patterns are markers of metabolic memory, and they reflect cumulative glycemic exposure and chronic tissue stress more reliably than do transient glucose fluctuations1.Transcriptomics and Network Analysis of Regulation

Transcriptomic profiling of metabolic tissues such as pancreatic islets, liver, skeletal muscle and visceral adipose reveals active gene regulatory networks that control glucose and lipid homeostasis 1. Integrated liver transcriptomics and proteomics analyzes identified cytidylate kinase 1 (CMPK1) for concordant

expression changes and direct link to hepatic gluconeogenesis and steatosis2. Multi-omic integration in human pancreatic islets identified single nucleotide polymorphisms (rs1516938) and principal islet proteins, including sacsin (SACS), thioredoxin-interacting protein (TXNIP), opioid receptor delta 1 (OPRD1), ras homolog family member T1 (RHOT1), and anoctamin 1 (ANO1), that regulate glucose-stimulated insulin secretion and mitochondrial membrane dynamics3Systems biology studies integrating genomic, epigenomic and transcriptomic data show significant pathway enrichment in immune cell activation and cellular glucose uptake networks2. We identified master regulators including interferon regulatory factor 7 (IRF7), cluster of differentiation 74 (CD74) and major histocompatibility complex Class II (HLA) genes2 by using network centrality metrics. These observations indicate that tissue-specific immune cell infiltration and antigen presentation in adipose and hepatic tissues precede systemic insulin resistance.1 However, transcriptomic signatures of circulating blood have a high intra-individual variability due to circadian rhythms, acute stress and concurrent pharmacotherapy, and thus require strict normalization protocols prior to clinical use1. Proteomics and Circulating Risk Signatures

Among the individual omic domains, plasma proteomics consistently yields the best predictive discrimination for incident T2DM5. Circulating protein signatures have been identified predicting diabetes onset up to 15 years prior to clinical diagnosis5 using high-throughput profiling platforms, either multiplex aptamer-based assays or proximity extension assays.

In the prospective EPIC-Norfolk case-cohort study (N=1,105; 10,792 person-years of follow-up) and the UK Biobank validation cohort (N=42,840), sparse proteomic panels of 10–15 circulating proteins yielded independent C-indices of 0.82–0.88 in the absence of clinical measurements5. Adding a focused panel of 15 proteins to usual clinical risk calculators (for example, the Cambridge Diabetes Risk Score that includes baseline HbA1c) raised the C-index from 0.862 to 0.884 (ΔC-index = +0.022, $p < 0.001$) for a constant net reclassification index (NRI) of 42.0%6. Key changed proteins belong to various biological pathways such as complement cascade activation, proteolysis, lipid-protein assembly, coagulation, and vascular endothelial injury2.Metabolomics, Small-molecule metabolites

Liquid chromatography-tandem mass spectrometry (LC-MS) and nuclear magnetic resonance (NMR) spectroscopy metabolomic profiling captures real-time gene-environment interactions in biochemistry perturbations11. Evidence from the Framingham Offspring Study (N=2,422 followed for 12 years) showed that circulating concentrations of branched-chain amino acids (BCAAs: isoleucine, leucine, valine) and aromatic amino acids (phenylalanine, tyrosine) are independent predictors of future T2DM. Those with BCAA levels in the top quartile had more than five times the risk of developing diabetes as those with BCAA concentrations in the lowest quartile, independent of baseline BMI, fasting plasma glucose and fasting insulin levels4. From a mechanistic perspective, elevated circulating BCAAs impair mitochondrial oxidation pathways in skeletal muscle and liver, resulting in the accumulation of toxic acylcarnitine intermediates15. These intermediates overstimulate mammalian target of rapamycin complex 1 (mTORC1), leading to inhibitory serine phosphorylation of insulin receptor substrate 1 (IRS-1) and impaired downstream phosphoinositide 3-kinase (PI3K)/Akt signaling15. Prior to the development of T2DM, metabolomic disturbances include changes in ratios of C3 and C5 acylcarnitines, depletion of lysophosphatidylcholine species and increased short chain fatty acids4.

Microbiomics and the Gut-Liver Axis

The intestinal microbiome influences host metabolic homeostasis by converting dietary substrates into bioactive metabolites1. Metagenomic analysis showed that prediabetes and T2DM were linked to lower levels of butyrate-producing anaerobic bacteria, including Roseburia intestinalis and Faecalibacterium prausnitzii1. The reduction of short-chain fatty acids (SCFAs), particularly butyrate and propionate, leads to reduced activation of free fatty acid receptors 2 and 3 (FFAR2/FFAR3) on enteroendocrine L-cells19. This downregulation leads to reduced secretion of glucagon-like peptide-1 (GLP-1), impaired glucose-stimulated insulin release and increased hepatic gluconeogenesis1.

Predictive Performance, Integration of Multi-Omics and Machine Learning

The combination of multiple omic layers by advanced machine learning architectures such as Random Forest classifiers, gradient boosting algorithms and deep neural networks can allow for non-linear feature selection across complex datasets2. A Random Forest model combining circulating microRNAs, mRNAs and plasma proteins in the Qatar Biobank cohort (N=962) discriminated T2DM patients from healthy controls with an area under the receiver operating characteristic curve (AUC) of 0.83, F1 score of 0.78 and overall accuracy of 0.767. Model interpretation with SHAP (SHapley Additive exPlanations) revealed

a regulatory axis of protective microRNA-29c (miR-29c) and risk-promoting prominin-1 (PROM1), and markers of vascular complications such as angiopoietin-2 (ANGPT2, fold change=1.64, p=0.0038) and placenta growth factor (PlGF, fold change=0.66, p=0.037)7.

In an integrative multi-omic study of 3,451 participants, Mendelian randomization and causal mediation analysis were used to prioritize 20 causal candidate biomarkers and 190 signaling pathways2. Collecting duct lectin 11 (COLEC11) was identified as a causal mediator of glycemic deterioration and inclusion of this finding into multi-omic prediction models improved predictive AUC by 27.5% over baseline clinical parameters2.

Large population cohort comparative assessments suggest a key epidemiological pattern: multi-omic models perform better than baseline clinical risk scores but the relative improvement from integrating multiple omic layers is reduced compared to optimized targeted proteomic panels5. In the UK Biobank dataset, adding 15 plasma proteins to the clinical Cambridge Diabetes Risk Score increased the C-index (+0.0226). However, adding 11 metabolites and a T2D-PRS to this proteomic-clinical model improved the C-index by only +0.007 (to 0.891)6. This marginal small improvement is biologically co-linear and functionally redundant to a considerable degree between circulating small molecules, plasma proteins and background polygenic susceptibility5.

Table 1 summarizes landmark prospective multi-omic studies for T2DM prediction. Table 2 Comparative evaluation of individual omic layers.

Study Cohort & Reference	Study Design & Sample Size	Omic Domains Analyzed	Key Biomarker Findings	Predictive Discrimination (C-Index / AUC)
EPIC-Norfolk Case-Cohort [cite: 5, 13]	Prospective case-cohort (N=1,105; 375 incident T2D cases)	PRS, Proteomics, Metabolomics	Top 10 plasma proteins achieved best single-layer performance without clinical data.	Clinical model: 0.82; Clinical + Top 10 Multi-omic: 0.87 (ΔC=0.05, p=0.045).
UK Biobank Prospective Cohort [cite: 6, 10]	Prospective population cohort (N=42,840; 1,090 incident cases)	PRS, Proteomics (15 proteins), Metabolomics (11 metabolites)	Proteomics contributed the primary predictive gain; full multi-omics added minimal incremental value.	Clinical CDRS: 0.862; CDRS + Proteomics: 0.884 (ΔC=0.022); Full Multi-omics: 0.891 (ΔC=0.007 vs proteomic).
Qatar Biobank Cohort [cite: 7, 20]	Case-control & cross-sectional (N=962; 434 T2D, 36 Retinopathy)	MicroRNA, mRNA, Proteomics	Identified miR-29c-PROM1 regulatory axis; ANGPT2 (FC=1.64) and PlGF (FC=0.66) marked vascular injury.	Random Forest ML classifier: AUC 0.83, F1 score 0.78, Accuracy 0.76.
Framingham Offspring Study [cite: 4, 11]	Prospective nested case-control (N=2,422; 12-year follow-up)	Targeted LC-MS Metabolomics	BCAAs (Isoleucine, Leucine, Valine) and aromatic AAs presage incident T2DM.	Top quartile BCAA combination conferred >5-fold increased risk of future T2DM.

Korean EWAS Cohort [cite: 2]	Prospective epidemiology cohort	Epigenomics (DNA Methylation)	Identified 106 DMPs and 62 DMRs linked to FPG and HbA1c (*TXNIP*, *ABCG1*, *PDK4*).	Epigenetic methylation scores correlated with long-term glycemic deterioration.

Omic Domain	**Primary Biomarker Targets**	**Dominant Pathophysiological Mechanisms**	**Predictive Strengths**	**Key Translational Barriers**
Genomics	Polygenic Risk Scores (PRS), risk SNPs	Inherited β-cell secretory defects, adiposity distribution	Static across lifespan; enables early risk stratification in normoglycaemic cohorts	Poor cross-ethnic portability; marginal incremental risk discrimination over clinical metrics
Epigenomics	*TXNIP*, *ABCG1*, *PDK4*, *ARRDC4* methylation	Oxidative stress, macrophage inflammation, metabolic memory	Captures chronic, cumulative environmental and lifestyle exposures	Tissue-specific patterns; sensitivity to pre-analytical sample handling
Transcriptomics	*CMPK1*, *IRF7*, *CD74*, *SACS*, *RHOT1*	Immune-adipose crosstalk, hepatic gluconeogenesis, islet mitochondrial dysfunction	Deep insight into active cellular responses and regulatory drivers	High intra-individual temporal volatility; standard RNA stability challenges
Proteomics	ANGPT2, PlGF, COLEC11, inflammatory panels	Endothelial injury, systemic low-grade inflammation, complement activation	Strongest single-layer predictor; stable circulating targets	High assay cost; batch variation across aptamer vs antibody platforms
Metabolomics	BCAAs (Iso, Leu, Val), Phenylalanine, Tyrosine	Mitochondrial acylcarnitine overload, mTORC1 activation, IRS-1 inhibition	Real-time biochemical readout; sensitive to direct dietary/microbiome shifts	Complex mass spectrometry alignment; postprandial measurement variability

Translational Medicine, Regulatory Science and Clinical Trial Methodology

Translating multi-omic signatures into certified clinical diagnostics requires adherence to regulatory science frameworks, analytical validation and clinical trial paradigms2. Regulatory agencies such as the U.S. Food and Drug Administration (FDA) through the Biomarker Qualification Program (BQP) and the European Medicines Agency (EMA) have strict criteria for analytical validity, clinical validity and clinical utility8.Analytical validity is demonstrated by precision, accuracy, linearity, lower limit of detection, sample matrix stability and inter-laboratory reproducibility2. High-throughput untargeted

platforms (e.g., SomaScan, Olink, or untargeted LC-MS) are often prone to batch effects, signal drift and matrix interference, requiring translation to targeted multiplex assays (e.g., multiple reaction monitoring mass spectrometry [MRM-MS] or automated immunoassay panels) suitable for CLIA-certified clinical laboratories2.

A crucial step in regulatory qualification involves establishing the Context of Use (COU)8 for the biomarker. The COU defines a specific clinical use, such as enrichment of patient selection in Phase II/III clinical trials, stratification of prediabetes subphenotypes, or as a surrogate endpoint2. Multi-omic software algorithms intended for use as In Vitro Diagnostics (IVD) or Software as a Medical Device (SaMD) must adhere to quality management systems (ISO 13485) and risk management protocols8 from a product life-cycle perspective.

Evidence of clinical utility is provided by prospective randomized controlled trials (RCTs) or pragmatic clinical trials showing that biomarker-driven management results in improved patient outcomes compared with standard clinical care2. Moreover, health technology assessment (HTA) bodies need health economic assessments to show that multi-omic testing offers a favorable Incremental Cost-Effectiveness Ratio (ICER) per quality-adjusted life year (QALY) gained compared with standard HbA1c screening6.

Table 3: Translational and Regulatory Omics Biomarker Development Pipeline.

Translational Stage	Methodological & Regulatory Requirements	Primary Technical Challenges	Key Regulatory & Clinical Milestones
1. Exploratory Discovery	Untargeted multi-omic profiling; false discovery rate (FDR) control; pilot cohort validation	High assay noise; batch effects; biological sample degradation	Identification of candidate molecular signatures
2. Analytical Validation	Calibration curves; spike-recovery testing; CV < 10–15%; inter-laboratory ring trials	Matrix interference; platform drift; multiplex assay cross-reactivity	Compliance with ISO 15189 / CLIA analytical standards
3. Clinical Validation	Evaluation in independent, prospective, multi-ethnic prospective cohorts	Population heterogeneity; outcome misclassification	Statistical proof of discrimination (C-index gain, NRI)
4. Regulatory Qualification	Submission to FDA Biomarker Qualification Program / EMA Qualification Advice	Proof of Context of Use (COU); demonstrating superiority over standard metrics	Formal FDA Context of Use (COU) approval
5. Health Technology Assessment	Cost-effectiveness analysis (ICER per QALY gained); pragmatic outcome trials	Demonstrating health economic value over standard HbA1c testing	Coverage and reimbursement approval (CMS / NICE)

DISCUSSIONS:

The investigation of multi-omic biomarkers has transformed the evaluation of T2DM risk from static glycemic metrics to dynamic molecular profiling.1 Circulating proteins and small molecule metabolites consistently give the strongest predictive signal for incident disease, reflecting early subclinical changes in mitochondrial oxidation, endothelial integrity and low grade systemic inflammation2.

A key insight from large prospective cohorts is that

whereas multi-omic integration outperforms traditional clinical risk tools, the incremental benefit of broad untargeted omic layers decreases compared to targeted proteomic panels5. In the UK Biobank cohort, addition of 15 plasma proteins to the clinical Cambridge Diabetes Risk Score increased C-index by +0.022, vs. +0.0076 for addition of 11 metabolites and a polygenic risk score. This result shows significant biological co-linearity as downstream plasma proteins integrate upstream genetic predisposition and metabolic stress5. There are several unanswered questions before broad clinical implementation can happen2. First, how can diagnostic developers reconcile the broad scope of untargeted multi-omics with the lower cost and operational simplicity needed for clinical laboratory adoption?6 Second, how do we integrate dynamic molecular markers (metabolomics, proteomics) with static inherited metrics (PRS) to create actionable dynamic risk scores?1

Multi-omic profiling provides a well-established framework for patient enrichment in clinical trials for drug developers and regulators2. Clinical trial participants can be stratified by BCAA overload or specific endothelial inflammatory markers (ANGPT2, PlGF), allowing targeted recruitment of high-risk subphenotypes and increasing statistical power and reducing sample sizes7.

Future Outlook

Future multi-omic biomarker research should move from broad exploratory discovery to clinical implementation science, targeted panel refinement, and pragmatic trial evaluations2. The development of lean, targeted panels—combining 10 to 15 key plasma proteins (e.g., ANGPT2, COLEC11) with targeted metabolite ratios (e.g., BCAAs) and clinical risk metrics—represents the most realistic route to clinical deployment2. Sparse targeted assays reduce test costs, simplify pre-analytical workflows and are easily integrated into automated clinical laboratory platforms6. Furthermore, the integration of single-cell multi-omics, spatial transcriptomics and causal inference methods (such as Mendelian randomization) will help elucidate the mechanisms connecting circulating biomarkers to specific organ pathologies2. Embedding predictive machine learning algorithms into electronic health record (EHR) platforms will allow for automated real-time risk stratification and actionable recommendations for precision diabetes prevention3.

Research Gaps

Pre-Analytical Workflow Harmonization: Absence of standardized pre-analytical sample collection, processing protocols and bioinformatic normalization algorithms across mass spectrometry and proteomic platforms2.Longitudinal Dynamic Profiling: Over-reliance on single baseline biospecimen sampling, ignoring intra-individual temporal dynamics, circadian changes and long-term metabolic trajectories1.Interventional Outcome Evidence: No prospective randomized controlled trials (RCTs) have shown that biomarker-guided preventive interventions improve long-term clinical outcomes compared to standard clinical care2. Health Economic Evaluations: No rigorous cost-effectiveness analyzes have been conducted to evaluate Incremental Cost-Effectiveness Ratios (ICER) per quality-adjusted life year (QALY) gained for multi-omic panels compared to standard HbA1c screening2.

Clinical Implications

1. Subphenotyping prediabetes: Distinguishing hepatic insulin resistance (prominent in impaired fasting glucose) from peripheral muscle resistance (prominent in impaired glucose tolerance) by BCAA and epigenetic signatures for individualized pharmacologic and lifestyle interventions.Vascular Complication Risk Stratification: Circulating biomarkers (ANGPT2, PlGF, miR-29c) to identify diabetic patients at high risk for retinopathy and cardiovascular complications before overt end-organ damage7. Precision Drug Selection: Specific anti-diabetic therapies (e.g., SGLT2 inhibitors, GLP-1 receptor agonists, metformin) to individual multi-omic disease subphenotypes to maximize therapeutic response9

Limitations of the Current Evidence

Ancestral cohort bias: Large-scale prospective biobanks (e.g., UK Biobank, EPIC-Norfolk) are largely composed of people of European ancestry, leading to reduced validity of genetic and epigenetic markers across heterogeneous world populations.

Observational Study Dominance: The majority of the published evidence comes from prospective observational cohorts, with a paucity of evidence from interventional clinical trial paradigms2.High assay costs and operational complexity: Broad untargeted omic profiling is still too expensive to be deployed in routine healthcare, and requires specialized equipment and bioinformatic infrastructure2.

CONCLUSION:

Multi-omics technologies have expanded our understanding of the pathogenesis of Type 2 Diabetes Mellitus. Plasma proteins, branched-chain amino acids and DNA methylation probes identify subclinical metabolic decompensation years before diagnostic hyperglycemia is present.2. Plasma proteomics

provides the best single-layer predictive discrimination for incident T2DM but full multi-omic profiling results in modest incremental performance gains due to biological signal overlap5. Data Availability StatementSuccessful clinical translation will require analytical standardization, cross-validation in diverse multi-ethnic cohorts, formal health economic evaluation and regulatory qualification2.

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