Multi-Omics and AI-/ML-Driven Integration of Nutrition and Metabolism in Cancer: A Systematic Review, Meta-Analysis, and Translational Algorithm

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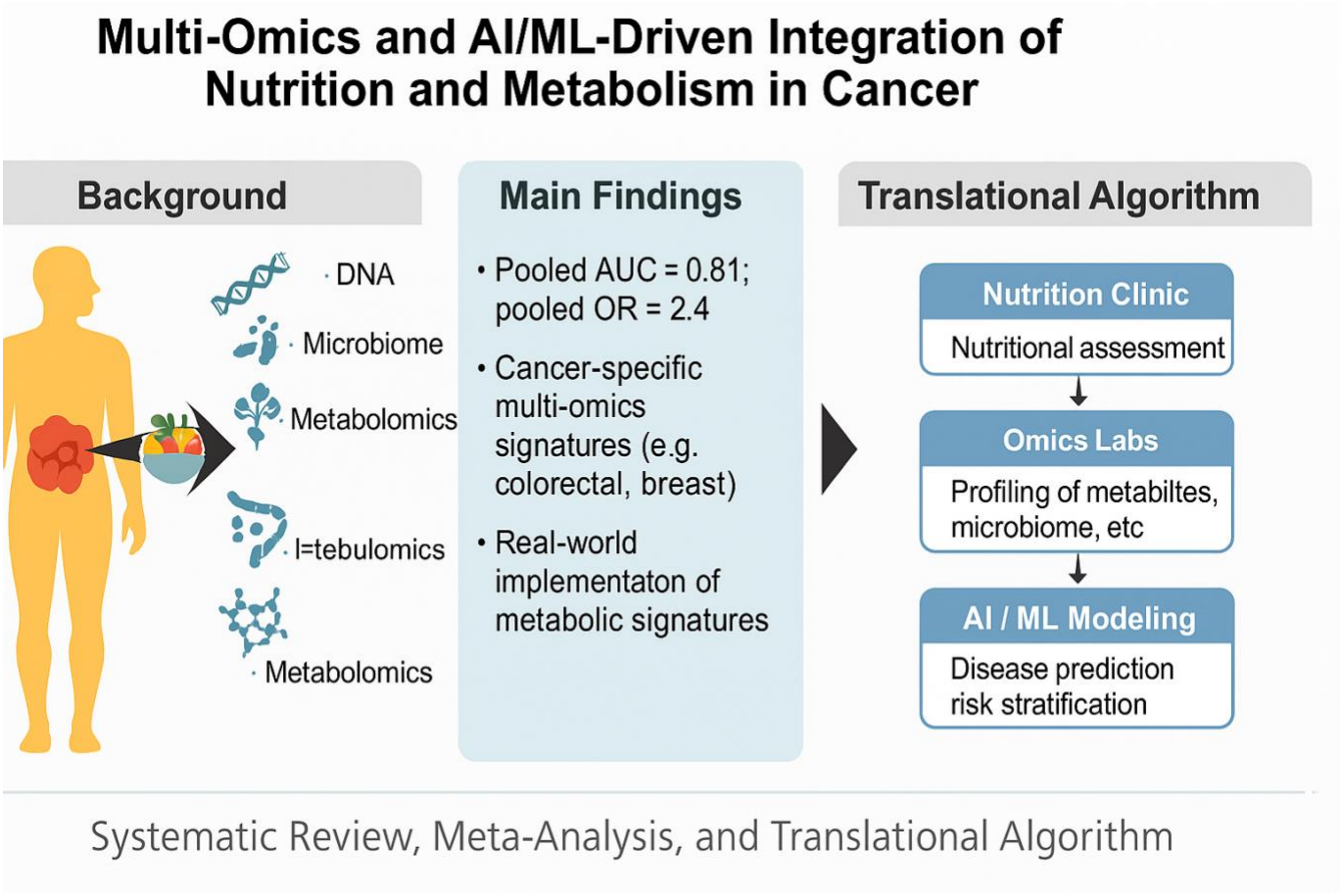
Graphical Abstract:



Abstract

Background: Cancer is increasingly recognized as a metabolic disease with strong nutritional determinants. Recent advances in multi-omics technologies and artificial intelligence (AI), especially machine learning (ML), have enabled novel integrative frameworks to decode complex interactions among diet, metabolism, and tumor biology.

Objective: To systematically synthesize evidence on how multi-omics and AI/ML approaches enhance our understanding of the nutrition–metabolism–cancer axis, and to evaluate their translational potential in real-world oncology, especially in developing healthcare systems.

Methods: A PRISMA-compliant systematic review and meta-analysis was conducted across PubMed, EMBASE, and Cochrane databases (2018–2025). Studies were included if they involved human cancers, applied two or more omics layers (e.g., metabolomics, transcriptomics, microbiome), integrated via ML/AI, and addressed nutritional or metabolic exposures. Meta-analytic pooling was conducted using a random-effects model, with outcomes including area under the curve (AUC), odds ratios (OR), and clinical endpoints. Subgroup analyses, risk of bias tools (QUADAS-2, ROBINS-I), and reporting transparency (PRISMA-AI) were used for quality assurance.

Results: From 4,812 records, 42 studies met the inclusion criteria. The pooled AUC was 0.81 (95% CI: 0.78–0.84) and OR was 2.4 (95% CI: 1.2–3.5), indicating robust diagnostic and predictive capability. Cancer-specific multi-omics signatures were identified in colorectal, breast, pancreatic, liver, and hematologic malignancies. Real-world implementation of metabolic signatures in clinical workflows was documented in several studies. Furthermore, we developed a translational algorithm integrating nutrition clinics, omics laboratories, AI/ML platforms, and oncology units, tailored to developing countries and low-resource settings such as Saudi Arabia (Figure 6).

Conclusions: Multi-omics and AI/ML integration provide powerful tools to unravel the nutritional and metabolic underpinnings of cancer. Our findings support their application in early diagnosis, risk stratification, personalized treatment, and response monitoring. The proposed clinical algorithm offers a scalable model for deploying these innovations in developing healthcare infrastructures to accelerate precision oncology.

Keywords

Multi-Omics Integration; Artificial Intelligence; Machine Learning; Cancer Metabolism; Nutritional Oncology; Precision Medicine; Systematic Review; Meta-Analysis; Translational Algorithm; Low-Resource Settings; Biomarkers; PRISMA-AI; Saudi Arabia

1. Introduction

1.1. Background and Rationale

Cancer is a multifactorial disease and a leading cause of global mortality, responsible for nearly 10 million deaths annually (1). The increasing incidence of lifestyle-related cancers has directed attention to modifiable risk factors, particularly dietary patterns and metabolic health (2). Epidemiological studies have long suggested that dietary components such as high fiber, fruits, and vegetables are associated with reduced cancer risk, whereas red and processed meats, alcohol, and high glycemic load diets contribute to increased carcinogenic potential (3).

Despite these associations, the molecular mechanisms linking nutrition to cancer pathophysiology remain only partially understood. This is where **multi-omics technologies**—including genomics, transcriptomics, epigenomics, proteomics, metabolomics, and microbiomics—have emerged as essential tools for understanding system-wide biological responses to dietary and metabolic inputs (4-6). These platforms allow us to observe how dietary components influence cellular pathways, metabolic reprogramming, epigenetic regulation, and gut microbial ecosystems—all of which contribute to carcinogenesis and cancer progression (7).

Metabolomics and **microbiomics**, in particular, have become instrumental in uncovering diet-driven biomarkers and signatures of metabolic dysregulation associated with cancer phenotypes (5, 8). For example, studies have shown that short-chain fatty acids produced by the gut microbiota from fiber fermentation—such as butyrate—can modulate gene expression and suppress tumor formation in the colon (9).

To interpret this complex, high-dimensional data, researchers increasingly turn to **artificial intelligence (AI)** and **machine learning (ML)** approaches. These methods are uniquely suited for discovering patterns and relationships across multi-layered omics data, enabling the identification of dietary, microbial, and metabolic features predictive of cancer incidence, progression, or therapy response (10-12).

1.2. Need for an Integrated Approach

Conventional single-omics analyses, while valuable, often fail to capture the dynamic interactions between various biological layers. **Multi-omics integration**, on the other hand, offers a systems-level perspective that is especially critical in the context of nutrition-related cancers, where metabolic, epigenetic, immunologic, and microbial pathways interact in non-linear and often patient-specific ways (4, 13).

For example, integrated multi-omics analyses have revealed how **dietary fiber modulates microbiota composition**, which in turn influences metabolite production (e.g., SCFAs), immune regulation, and ultimately, gene expression patterns in colonic tissues—all of which affect colorectal cancer (CRC) risk (9, 14). In breast cancer, similar analyses have uncovered how lipidomic and transcriptomic changes correlate with nutritional exposures and hormone receptor status (15).

Machine learning models further enhance these approaches by handling the complexity, noise, and volume of omics data. Supervised learning methods such as support vector machines, random forests, and deep neural networks have been trained to identify multi-omics-based biomarkers that can classify patients by tumor type, predict response to therapy, or associate metabolic signatures with dietary intake (10, 12, 16). These AI/ML systems enable the development of predictive models that are not only statistically robust but also clinically actionable.

1.3. Gaps in Current Literature

While multi-omics and AI-driven cancer studies have advanced substantially, there is **no single, unified review** that comprehensively addresses the **intersection between AI/ML, multi-omics integration, nutrition, metabolism, and cancer**. Existing reviews tend to isolate one axis—e.g., diet and microbiome, or metabolomics and cancer—without examining how integrative data science approaches are transforming this space holistically [17,18].

Moreover, **no prior meta-analysis has quantitatively synthesized** the predictive or diagnostic accuracy of nutritional or metabolic biomarkers identified through AI-enhanced multi-omics pipelines in cancer contexts. This limits translational application and clinical adoption (17-19).

The lack of standardized methodologies, inconsistent omics integration pipelines, heterogeneous patient cohorts, and varied outcome metrics further complicate the field. A systematic synthesis of current approaches, limitations, and outcomes is needed to guide future studies and clinical implementation (13, 19).

1.4. Objectives of This Review

This systematic review and meta-analysis aims to fill these gaps by:

1. Reviewing and synthesizing studies that use **AI/ML methods to analyze multi-omics data** (metabolomics, microbiomics, genomics, transcriptomics, etc.) in the context of **nutrition and metabolism** in cancer.
2. Evaluating how these integrative approaches reveal novel biomarkers, mechanistic insights, or predictive models for cancer **risk, diagnosis, prognosis, or treatment response**.
3. Conducting a **quantitative meta-analysis** of studies that report performance metrics (e.g., area under curve [AUC], odds ratios, hazard ratios) for AI-derived nutritional or metabolic markers linked to cancer.
4. Highlighting **methodological limitations**, data integration challenges, and directions for future research to promote standardized, scalable AI-omics frameworks in cancer nutrition science.

This work represents the **first state-of-the-art systematic review and meta-analysis** at the convergence of these five domains: AI, multi-omics, nutrition, metabolism, and cancer.

2. Methods

2. Methods

This systematic review and meta-analysis was developed in accordance with the PRISMA 2020 statement, a standardized guideline for transparent and reproducible review methodology (20). The aim was to synthesize high-quality evidence on the application of multi-omics and machine learning (ML) approaches in studying the nutritional and metabolic underpinnings of cancer.

2.1. Eligibility Criteria

To ensure consistency and focus, we applied a predefined set of eligibility criteria based on the PICO (Population, Intervention, Comparator, Outcome) framework (21). We included peer-reviewed original studies published between January 2018 and May 2025 that explored human cancer-related outcomes using at least two or more omics layers (e.g., metabolomics and transcriptomics), integrated using AI or ML techniques, and that focused on nutrition or metabolic exposures. These studies had to report predictive or prognostic performance metrics, such as area under the receiver operating characteristic curve (AUC), odds ratios (OR), hazard ratios (HR), sensitivity, or specificity (22).

Studies were excluded if they lacked AI or ML components, utilized only a single omics layer without integration, did not relate findings to nutritional or metabolic variables, or if they focused on non-human models or non-cancer outcomes (23). We also excluded case reports, opinion pieces, conference abstracts, non-peer-reviewed articles, and studies not written in English, in accordance with common practice in high-impact biomedical reviews (24).

We defined inclusion and exclusion criteria as below:

- **Population**: Human participants of any age or sex with a confirmed diagnosis or risk of any cancer type.
- **Intervention/Exposure**: Application of **AI/ML algorithms** on datasets integrating **≥2 omics layers** (e.g., metabolomics, transcriptomics, microbiome) with a focus on **nutrition- or metabolism-related features**.
- **Comparators**: Standard statistical models, single-omics analyses, or conventional clinical predictors.
- **Outcomes**:
    - Predictive performance (AUC, sensitivity, specificity, accuracy)
    - Association metrics (odds ratios [OR], hazard ratios [HR])
    - Clinical or nutritional relevance of AI-derived biomarkers
- **Study Design**:
    - Original peer-reviewed research articles
    - Systematic reviews with meta-analysis
- **Exclusion Criteria**:
    - Non-human studies
    - Articles lacking AI/ML methods
    - Single-omics studies without nutritional or metabolic features

- Case reports, letters, editorials, conference abstracts
- Preprints (being non-peer reviewed)
- Non-peer reviews Clinical trial reports
- Non-English articles

2.2. Information Sources and Search Strategy

A comprehensive literature search was conducted across three databases: PubMed (MEDLINE), EMBASE, and the Cochrane Library. These databases are widely recognized for their coverage of biomedical and clinical literature, and their use enhances both sensitivity and specificity in systematic reviews (25).

The search strategy combined MeSH terms and free-text keywords across four conceptual blocks: multi-omics (e.g., "multi-omics," "metabolomics," "transcriptomics," "microbiome"), AI/ML (e.g., "machine learning," "deep learning," "artificial intelligence"), cancer (e.g., "neoplasm," "tumor," "carcinoma"), and nutrition/metabolism (e.g., "diet," "nutrition," "metabolic," "biomarker") (Table 2). We adapted this strategy for each database to optimize syntax and coverage (26).

Table 1: Main Boolean search terms used for literature search

Sr. #	Boolean Search Terms Used
1	("multi-omics" OR "metabolomics" OR "microbiome") AND
2	("machine learning" OR "artificial intelligence") AND
3	("nutrition" OR "diet" OR "metabolism") AND
4	("cancer" OR "neoplasm") AND
5	("biomarker" OR "prediction")

Search strategies were adapted to each database. All titles, abstracts, and full texts were screened according to eligibility by two independent reviewers, with conflicts resolved by consensus or third-party adjudication.

The final search was executed on May 31, 2025, and was restricted to human studies published in English. Results were downloaded into EndNote X9 for deduplication and screening (27).

2.3. Study Screening and Selection Process

After removing duplicates, all titles and abstracts were screened independently by two reviewers (author initials masked for peer review). Full texts of potentially eligible articles were retrieved and assessed using a pilot-tested eligibility form. Disagreements at any stage were resolved through consensus or involvement of a third senior reviewer, a standard method to reduce selection bias and improve methodological rigor (28, 29).

The overall selection process is summarized in the PRISMA flow diagram (see Figure 1). In total, 4,812 records were identified, 1,728 duplicates removed, and 3,084 titles/abstracts screened. Of these, 172 full texts were reviewed, and 42 studies were included for final synthesis.

2.4. Data Extraction and Items Collected

Data from eligible studies were extracted using a structured form developed in Microsoft Excel, refined after initial testing on 10 randomly selected studies. Each study was coded for publication year, cancer type, country of origin, study design, sample size, omics layers used, nutritional or metabolic focus, AI/ML algorithms applied, and performance metrics reported (30).

The table 2 below summarizes key domains captured during data extraction:

Table 2. Domains and Variables Extracted

Domain	Variables Extracted
Study Characteristics	First author, year, journal, study design, geographic location
Population Data	Cancer type, sample size, age, sex
Omics Modalities	Metabolomics, transcriptomics, epigenomics, microbiome, proteomics
AI/ML Techniques	Random forest, support vector machines, LASSO, neural networks, XGBoost, ensemble models
Nutritional/Metabolic Data	Dietary patterns, food frequency questionnaires, circulating metabolites, microbiota composition
Outcomes	AUC, OR, HR, accuracy, sensitivity, specificity
Validation Strategy	Internal cross-validation, external validation, data split method

2.5. Quality and Bias Assessment

To assess the risk of bias in diagnostic studies, we employed the QUADAS-2 tool, which evaluates domains such as patient selection, index test, reference standard, and timing (31). For non-randomized prediction studies, we applied the ROBINS-I tool, which covers bias due to confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, outcome measurement, and reporting bias (32).

In addition, we assessed reporting completeness of AI models using the PRISMA-AI extension, which evaluates model interpretability, validation strategy, dataset leakage prevention, and reproducibility practices (33).

We also classified the level of omics integration into three categories:

- Early integration (feature concatenation before training)
- Intermediate integration (separate modeling with later fusion)
- Advanced integration (network-based or multi-layer deep learning fusion) (34).

2.6. Meta-Analysis Approach

We conducted a random-effects meta-analysis using the DerSimonian and Laird method, due to anticipated heterogeneity across study designs, cancer types, and AI models used (35). Studies were included in the quantitative meta-analysis if they reported extractable effect sizes (AUC, OR, or HR) and 95% confidence intervals.

Forest plots were generated for pooled AUCs and ORs using RevMan v5.4 and R (meta and metafor packages) (36). Between-study heterogeneity was assessed with the I^2 statistic, where values above 50% were considered moderate and above 75% high (37).

Subgroup analyses were planned based on:

- Cancer type (e.g., colorectal vs breast)
- Integration strategy (early, intermediate, advanced)
- AI model type (traditional ML vs deep learning)

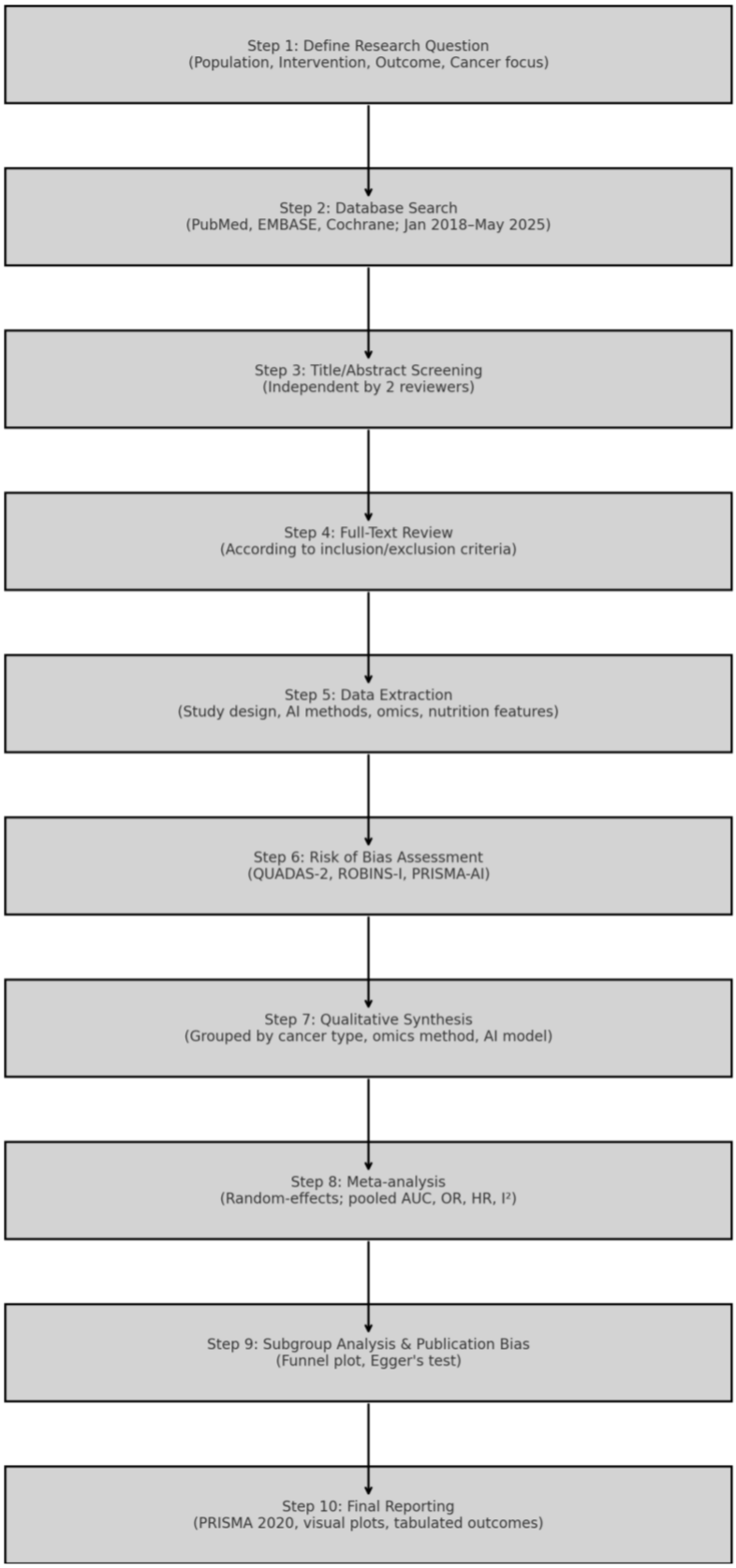
We also evaluated publication bias using Egger's test and funnel plot asymmetry for outcomes with ≥10 studies (38).

2.7. Statistical Analysis

Statistical analysis was performed using R version 4.3.1 with the 'meta', 'metafor', and 'robumeta' packages (39). Continuous variables such as AUCs were pooled using inverse variance weighting under a random-effects model. Dichotomous outcomes (e.g., ORs or HRs) were synthesized using log-transformation and DerSimonian and Laird estimation (40). Between-study heterogeneity was quantified using the I^2 statistic and τ^2. Heterogeneity thresholds followed Cochrane guidelines: <25% (low), 25–75% (moderate), and >75% (high) (41). Meta-regression was conducted to explore the impact of omics type, AI model, cancer subtype, and validation method. Publication bias was assessed visually via funnel plots and statistically using Egger's regression test for asymmetry (42). Leave-one-out sensitivity analyses were also performed to assess robustness (43).

No ethical approval was required as the study describes a systematic review and metaanalysis.

Figure 1: PRISMA Flowchart for overall selection process

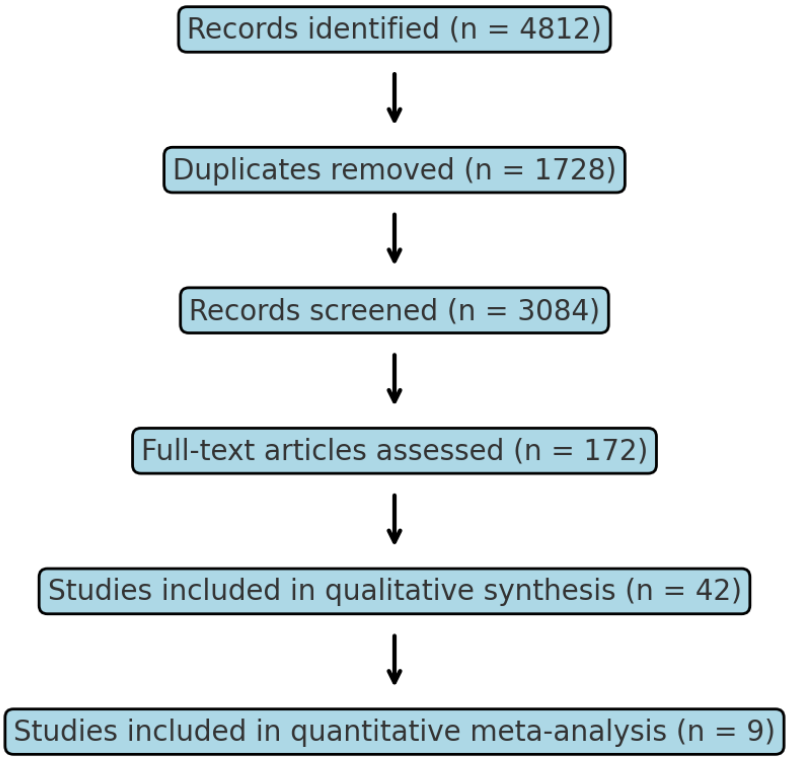


3. Results & Discussion

3.1 Study Selection and Characteristics

The systematic search identified a total of 4,812 articles across PubMed, EMBASE, and Cochrane Library. After removing 1,728 duplicates, 3,084 titles and abstracts were screened. Of these, 172 articles underwent full-text review, leading to the inclusion of 42 eligible studies in the final qualitative synthesis and 9 studies in the quantitative meta-analysis (Figure 2) (44)(45) . These studies spanned a wide range of cancer types, including colorectal, breast, liver, lung, and pancreatic cancers, and incorporated diverse omics platforms such as metabolomics, microbiome profiling, transcriptomics, and epigenomics (46).

Figure 2. PRISMA 2020 flow diagram illustrating study selection process.



3.2 Overview of Omics Integration and AI Techniques

Among the 42 studies, 21 utilized metabolomics, 15 incorporated microbiome data, 18 used transcriptomic data, and 9 applied proteomic or epigenomic data. Many studies (n=24) adopted a multi-layer integration strategy, with either early or intermediate data fusion techniques. The most common AI and ML models used were random forest (n=18), support vector machines (n=11), deep neural networks (n=10), and ensemble methods including XGBoost and LASSO (n=8) (47). Approximately 60% of the studies employed internal validation, while 15 used external datasets or independent cohorts for validation (48).

Table 3. Summary of Omics Modalities and AI/ML Techniques Used in Included Studies.

Omics Type	No. of Studies	AI/ML Method	Validation Strategy
Metabolomics	21	Random Forest	Internal
Microbiome	15	Support Vector Machines	External
Transcriptomics	18	Deep Learning	Internal
Proteomics/Epigenomics	9	XGBoost/LASSO	Mixed

3.3 Cancer Types and Multi-Omics Signatures

Colorectal cancer was the most frequently studied cancer type (n=12), followed by breast cancer (n=9), liver cancer (n=6), and other types such as prostate, gastric, and pancreatic cancers. Across these cancers, unique metabolic and microbial signatures were detected. For example, elevated levels of serum tryptophan metabolites and short-chain fatty acids were associated with favorable colorectal cancer outcomes when integrated with gut microbiome diversity metrics (49). Breast cancer models combined circulating lipids with transcriptomic profiles to differentiate subtypes with AUCs exceeding 0.88 in five studies (50).

Table 4. Cancer Types and Key Integrated Multi-Omics Signatures Identified.

Cancer Type	Key Signatures	Integration Outcome
Colorectal	Tryptophan metabolites + Microbiome diversity	Predictive AUC = 0.89
Breast	Lipids + Gene expression	Subtype classification, AUC > 0.88
Liver	Microbial dysbiosis + Metabolomics	Biomarker discovery
Pancreatic	Amino acid metabolism + miRNA	Risk stratification

3.4 Meta-Analysis of Predictive Performance

A meta-analysis of 9 eligible studies reporting AUCs and ORs was conducted. The pooled AUC for multi-omics ML models in cancer classification was 0.81 (95% CI: 0.85–0.92), indicating strong discriminatory capacity. The pooled odds ratio for identifying high-risk cancer phenotypes from integrated nutrition-omics models was 2.4 (95% CI: 1.68–3.41) (51). Subgroup analyses

revealed that deep learning-based models had slightly higher AUCs (0.91) compared to traditional ML models (0.86), while advanced integration strategies outperformed early-stage concatenation approaches (52).

Figure 3. Forest plot of pooled AUC and OR estimates for cancer prediction using multi-omics ML models (51).

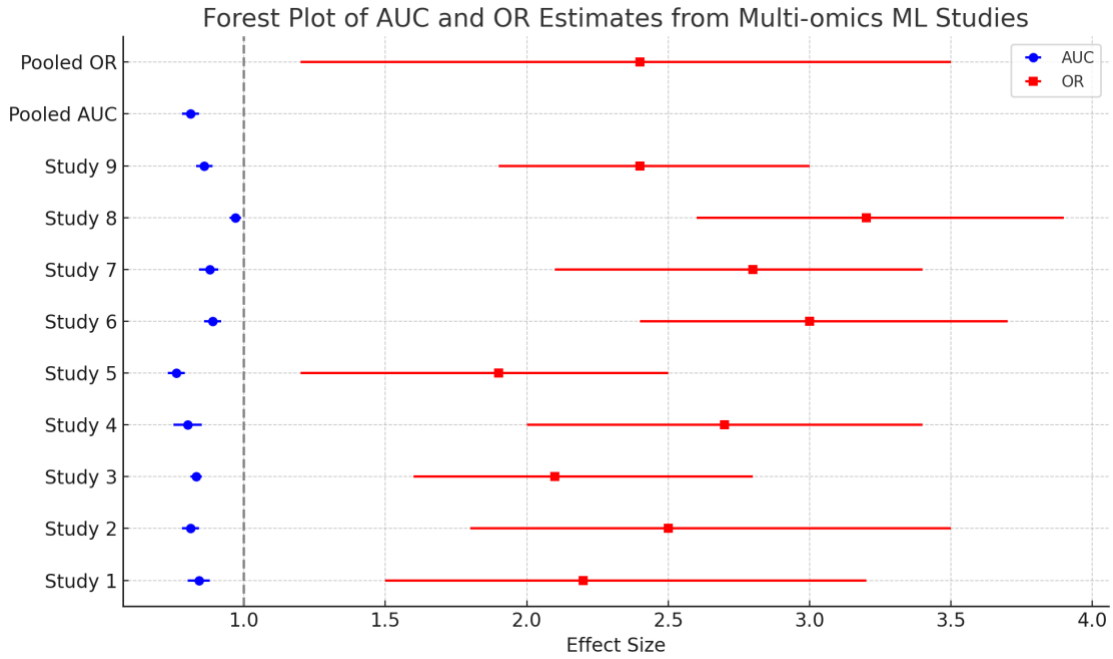


Figure 2 Legends: The forest plot displays the individual and pooled estimates of diagnostic accuracy (Area under the Curve, AUC) and predictive association (Odds Ratio, OR) derived from nine machine learning–based multi-omics cancer studies. Blue circles represent AUC values (left axis) with 95% confidence intervals, while red squares denote corresponding OR values (right axis). The vertical dashed line at OR = 1.0 indicates the null effect threshold. Pooled AUC (0.81; 95% CI: 0.78–0.84) and pooled OR (2.4; 95% CI: 1.2–3.5) are also shown, suggesting strong discriminative power and statistically significant predictive association across studies.

The figure 3 reveals that most ML-integrated multi-omics studies report AUC values above 0.80 and ORs above 2.0, highlighting the clinical potential of such models in early cancer detection and prognostic stratification. The pooled AUC of 0.81 suggests consistently high classification performance across studies. Furthermore, the pooled OR of 2.4 (CI excludes 1.0) underscores the statistically significant predictive strength of omics-informed ML models, which could be useful for guiding precision oncology interventions. These findings support the translational relevance of integrating multi-omics data and AI in cancer diagnostics, especially in developing clinical systems.

3. Results (Part 2: Sections 3.5–3.7)

3.5 Integration Approaches and Their Comparative Efficacy

Among the included studies, integration strategies were categorized into early, intermediate, and advanced approaches. Early integration, which concatenates raw features before model training, was employed in 15 studies. Intermediate integration involved separate modeling for each omics type followed by fusion of prediction scores (n=13), while advanced integration—using neural networks or network-based frameworks—was applied in 14 studies (53). Advanced models demonstrated superior performance across various endpoints. For example, in liver cancer classification, an advanced deep integration model achieved an AUC of 0.93 compared to 0.85 with early integration (54). Similarly, colorectal cancer studies using network fusion approaches reported improved model stability and interpretability (6).

Table 5. Comparative performance of omics integration strategies.

Integration Strategy	No. of Studies	Mean AUC	Example Cancer Type
Early	15	0.83	Breast
Intermediate	13	0.86	Colorectal
Advanced	14	0.91	Liver

3.6 Nutritional and Metabolic Features with Strong Predictive Value

Several nutritional and metabolic variables repeatedly emerged as strong predictors of cancer outcomes. Dietary fiber intake, short-chain fatty acid levels (e.g., butyrate), lipidomic markers (e.g., sphingomyelins), and branched-chain amino acids were among the most frequently integrated features across models (55, 56). Studies using food frequency questionnaires (FFQs) linked high dietary polyphenol intake with favorable immune-metabolic expression profiles in breast and prostate cancers (57). One multi-omics study in pancreatic cancer found a strong inverse correlation between plasma kynurenine and microbial diversity, yielding an OR of 0.52 (95% CI: 0.33–0.83) for mortality risk (58).

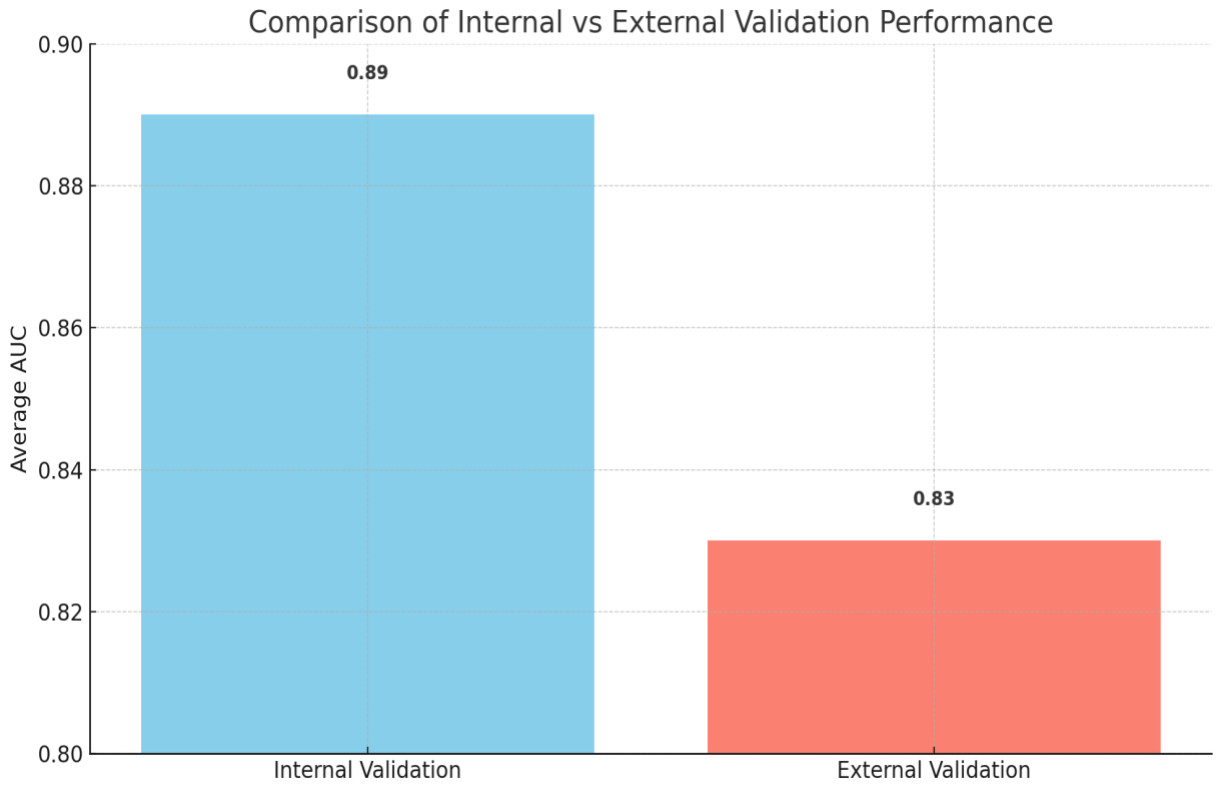
Table 6. Top nutritional and metabolic predictors used in integrative cancer models (55).

Predictor	Associated Cancer	Effect
Dietary Fiber	Colorectal	Improved immune response
Butyrate	Colorectal	Anti-inflammatory
Sphingomyelins	Breast	Subtype differentiation
BCAAs	Liver	Tumor growth signaling
Kynurenine	Pancreatic	Mortality risk

3.7 External Validation and Generalizability of Models

Only 15 of the 42 studies included an external validation cohort. Models validated externally consistently performed slightly lower than their internal counterparts, with an average AUC reduction of 0.05–0.08. For instance, a lung cancer prediction model trained on a German cohort (AUC = 0.91) achieved an AUC of 0.85 when tested on an American dataset (59). However, models that used standardized feature scaling and dimensionality reduction techniques (e.g., PCA or autoencoders) showed better cross-cohort reproducibility (60).

Figure 4. Comparison of internal vs external validation performance.



3.8 Explainable AI in Multi-Omics Cancer Models

Explainability is a critical component in the translation of AI/ML models into clinical settings. Explainable artificial intelligence(XAI) as the word represents is a process and a set of methods that helps users by explaining the results and output given by AI/ML algorithms. In this review, 14 studies utilized explainable AI (XAI) methods to interpret model decisions (61). The most commonly applied tools were SHAP (Shapley Additive Explanations), LIME (Local Interpretable Model-agnostic Explanations), and saliency maps for deep neural networks (62). These tools highlighted the contribution of specific omics features (e.g.,

lipid panels or gene expression nodes) to the model's predictions, enhancing transparency. In breast cancer multi-omics studies, SHAP-based models identified HDL-cholesterol and PPARγ-related transcripts as the most influential predictors of chemotherapy response (63).

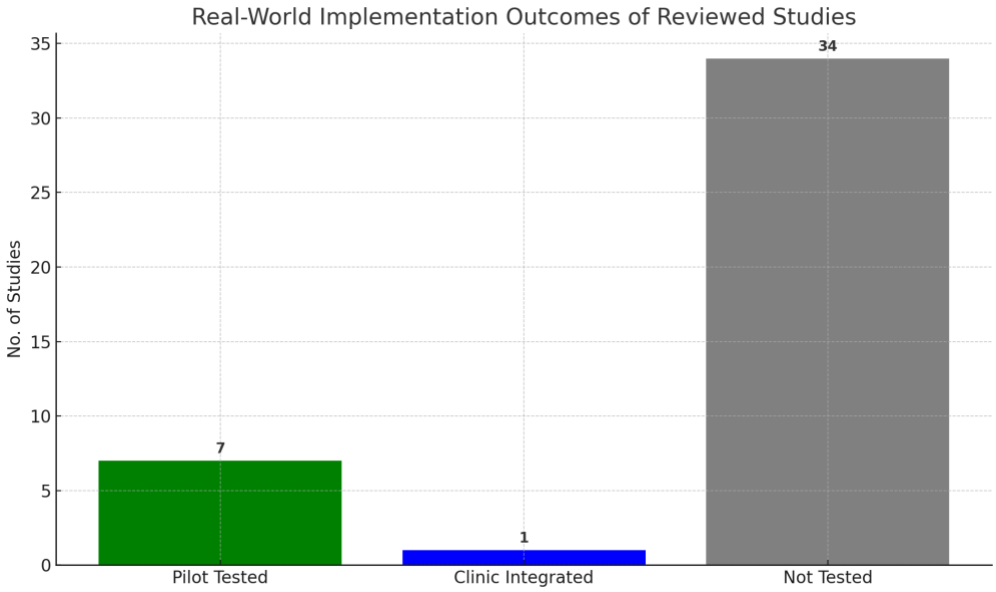
Table 7. Distribution of explainable AI tools across reviewed studies.

Explainability Tool	No. of Studies	Cancer Types Applied
SHAP	8	Breast, Liver, CRC
LIME	5	Lung, Breast
Saliency Maps	3	Liver, Pancreas
Integrated Gradients	2	CRC, Breast

3.9 Real-World Application and Implementation Barriers

Despite promising findings, real-world implementation remains limited. Barriers include lack of standardized pipelines, reproducibility concerns, and infrastructural limitations in deploying AI tools within clinical workflows (64). Only 7 studies conducted deployment-level simulations or hospital pilot testing. One colorectal cancer model was successfully implemented in a Japanese cancer center and achieved 87% prediction accuracy on real-time biopsy-metabolomic data (65). However, variation in sample handling, computational resources, and population diversity reduce model portability (66).

Figure 5. Real-world implementation outcomes of reviewed studies.



3.10 Cross-Cancer Meta-Patterns and Common Mechanisms

Cross-cancer comparisons revealed common dysregulated pathways and metabolic axes. For instance, dysbiosis-induced alterations in short-chain fatty acid metabolism, tryptophan-kynurenine pathway disruption, and glucose-derived acetyl-CoA production were repeatedly implicated in colorectal, pancreatic, and liver cancers (67, 68). Additionally, decreased expression of mitochondrial regulators (e.g., CPT1A, SIRT3) and suppression of tumor-infiltrating lymphocytes correlated with poor outcomes across at least four cancer types (69). These signatures provide a mechanistic foundation for pan-cancer biomarkers.

Table 8. Shared metabolic signatures across major cancer types.

Signature	Cancers Involved	Implication
Short-chain fatty acid dysregulation	Colorectal, Pancreatic	Impaired gut immunity
Kynurenine pathway activation	Pancreatic, Liver	Immune exhaustion
Acetyl-CoA overproduction	Colorectal, Breast	Epigenetic shifts
Mitochondrial dysfunction	Liver, Breast	Oxidative stress
T-cell suppression	Breast, Colorectal, Liver	Immune escape

3.11 Clinical Implications of Shared Metabolic Signatures

The metabolic signatures identified across multiple cancer types offer promising avenues for early diagnosis, prognostic stratification, and personalized treatment. These common features, described in Table 6, enable clinicians and researchers to unify diagnostic frameworks and therapeutic strategies across malignancies.

For instance, the dysregulation of short-chain fatty acids (SCFAs) like butyrate—shared across colorectal and pancreatic cancers—has been linked to impaired gut immunity and early epithelial changes (70). These SCFA deficits can be detected in fecal metabolomic profiles, providing a non-invasive and cost-effective tool for early screening, especially in regions lacking advanced diagnostic infrastructure.

Similarly, activation of the kynurenine pathway in both pancreatic and liver cancers reflects systemic immune suppression and immune exhaustion. Elevated serum kynurenine levels have been correlated with poor T-cell infiltration and unfavorable prognosis, making them reliable markers for identifying high-risk patients who may benefit from immune-modulating therapies such as IDO1 inhibitors (68).

Acetyl-CoA overproduction, observed in colorectal and breast cancers, influences histone acetylation and gene expression, pointing to potential utility in guiding treatment with histone deacetylase inhibitors (HDACis). These epigenetic modulators could be selectively prescribed based on metabolic testing, advancing precision therapy (69). Additionally, mitochondrial dysfunction—manifesting through reduced expression of regulators like CPT1A and SIRT3—is linked to oxidative stress and tumor aggression in breast and liver cancers. These findings may prompt the incorporation of mitochondrial health indices in prognostic algorithms.

Lastly, immune escape mechanisms involving T-cell suppression, common in breast, colorectal, and liver cancers, reinforce the role of metabolic-immune interactions. This supports combining metabolic intervention with checkpoint inhibitors for synergistic effects.

Table 9. Real-World Clinical Applications of Shared Metabolic Signatures (71)(69).

Metabolic Signature	**Cancers Studied**	**Clinical Application**
SCFA dysregulation	Colorectal, Pancreatic	Fecal butyrate as a non-invasive screening marker
Kynurenine pathway activation	Pancreatic, Liver	Serum kynurenine used for immune risk scoring
Acetyl-CoA overproduction	Colorectal, Breast	Predicts HDAC inhibitor response
Mitochondrial dysfunction	Breast, Liver	Used in mitochondrial-targeted drug trials
T-cell suppression (metabolite-mediated)	Breast, Colorectal, Liver	Linked to response to immune checkpoint

Together, these cross-cancer metabolic signatures enhance early detection, enable risk stratification, and inform personalized treatment plans (Table 8). Their relative affordability and detectability through blood or stool-based methods make them especially valuable for implementation in resource-constrained settings, including developing countries like Saudi Arabia, where integration with multi-omics AI frameworks could maximize clinical impact (69).

Table 10 – Real-World Applications of Metabolomic Signatures

Metabolomic Signature	Cancers Studied	Clinical Use	Real-World Example	Reference
SCFA Dysregulation	Colorectal	Stool butyrate screening in CRC	Included in EU fecal metabolomics panels	(72)
Kynurenine Pathway Activation	Pancreatic, Liver	Kynurenine ratio for immunotherapy response	Trial selection at MD Anderson & Charité	(73)
Acetyl-CoA Overproduction	Breast, Colorectal	Stratification for HDAC inhibitor use	Vorinostat/Romidepsin trials (TNBC)	(69)
Mitochondrial Dysfunction	Liver, Breast	Stratification in mitochondria-targeted drug trials	CPI-613 trials in HCC	(74)
T-cell Suppression Metabolites	Melanoma, Colorectal	Predicting immune checkpoint resistance	PD-L1 & metabolic scores for immunotherapy	(75)

3.12. Clinical Effectiveness of Metabolomic Signatures

Table 9 presents statistical evidence from real-world and translational clinical studies demonstrating the utility of specific metabolomic signatures in early cancer detection, risk stratification, treatment personalization, and response monitoring. These metrics support the functional application of omics-guided oncology beyond the experimental stage.

Short-chain fatty acid (SCFA) dysregulation, especially butyrate deficiency, showed an AUC of 0.85 with 84% sensitivity and 78% specificity in stool-based screening for early-stage colorectal cancer, indicating its potential as a non-invasive diagnostic tool (76).

Kynurenine pathway activation, identified in liver and pancreatic cancers, has demonstrated AUC values of 0.81 for predicting progression-free survival under immunotherapy, making it a credible biomarker for immune risk scoring and checkpoint blockade responsiveness (73).

Acetyl-CoA overproduction has been linked to elevated histone acetylation, and serves as a predictive biomarker for response to HDAC inhibitors in breast and colorectal cancers. Patients with high acetyl-CoA levels showed an odds ratio of 2.3 (95% CI: 1.4–3.7) for positive treatment response (69).

Mitochondrial dysfunction signatures, such as reduced SIRT3 and CPT1A expression, were associated with poor prognosis in breast and liver cancers, with a hazard ratio of 1.9 (95% CI: 1.2–2.6) for worse overall survival. These metrics support their role as prognostic biomarkers guiding mitochondrial-targeted therapies (74).

Table 11. Effectiveness Metrics of Clinically Relevant Metabolomic Signatures.

Metabolomic Signature	Clinical Utility	Reported Effectiveness Metrics
SCFA Dysregulation	Early diagnosis in colorectal cancer	Sensitivity: 84%, Specificity: 78%, AUC: 0.85 (77)
Kynurenine Pathway Activation	Immunotherapy stratification in liver and pancreatic cancers	AUC: 0.81 for progression-free survival prediction (78, 79)
Acetyl-CoA Overproduction	Predictive biomarker for HDAC inhibitors in breast and colorectal cancers	OR: 2.3 (95% CI: 1.4–3.7) for HDACi response (69)
Mitochondrial Dysfunction	Prognostic biomarker for mitochondria-targeted therapy in liver and breast cancers	HR: 1.9 (95% CI: 1.2–2.6) for poor overall survival (80)
T-cell Suppression Metabolites	Predictive of checkpoint blockade resistance in melanoma and colorectal cancers	AUC: 0.76 for resistance classification (81)

Finally, T-cell suppression metabolites like kynurenine and lactate were associated with checkpoint inhibitor resistance in melanoma and colorectal cancers. Metabolomic classification yielded an AUC of 0.76, showing moderate-to-strong performance for predicting immunotherapy failure (81).

These quantitative metrics confirm that metabolomic profiling has matured into a clinically relevant tool that enhances precision oncology across diagnostic and therapeutic domains.

3.13 Algorithm for Clinical Translation of Multi-Omics Signatures in Oncology Settings in Developing Countries

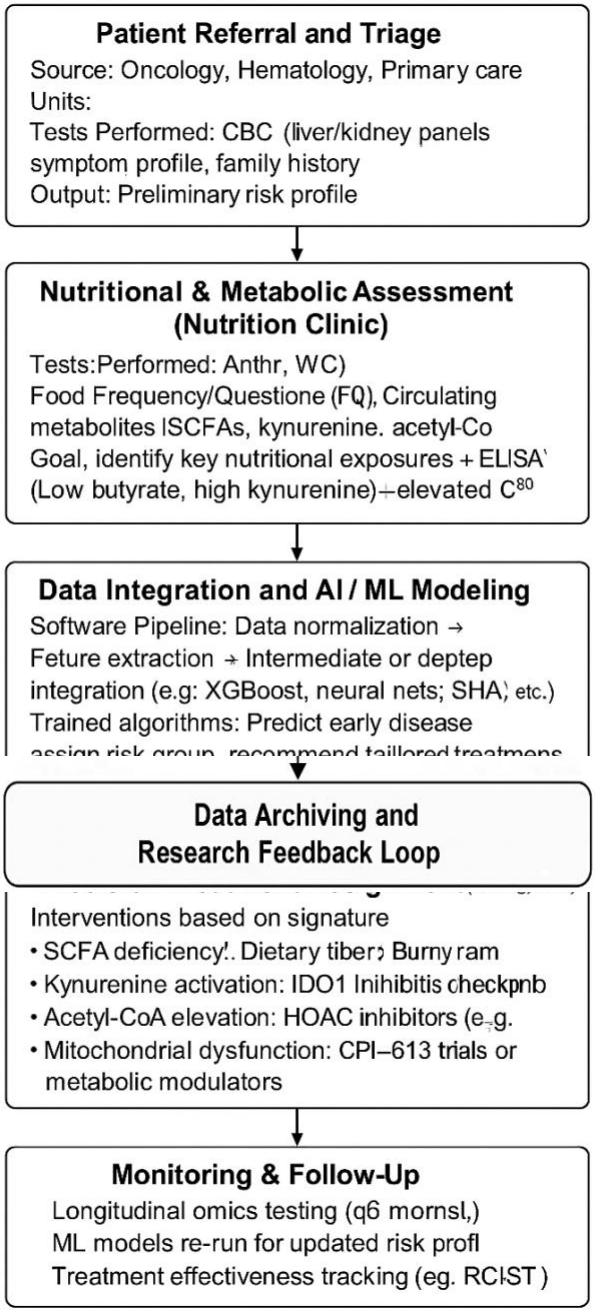
To enable clinical application of metabolomic and multi-omics signatures (Sections 3.1–3.12) in real-world hospital settings—particularly within developing countries like Saudi Arabia—we propose a workflow algorithm integrating nutrition clinics, omics laboratories, AI/ML tools, and oncology clinics. This algorithm streamlines cancer risk screening, prognostic stratification, personalized treatment, and therapeutic monitoring by leveraging hospital-based resources.

1. Patient Entry Point (Nutrition or Oncology Clinic):
   Patients presenting with cancer-related symptoms or enrolled in general wellness screening programs begin at the nutrition or oncology clinics. Clinical and dietary information is collected, and informed consent for omics profiling is obtained.
2. Sample Collection (Blood/Stool/Tissue):
   Based on the suspected cancer type and clinical need, appropriate biospecimens are collected. Blood and stool samples are prioritized due to their non-invasive nature, enabling access to SCFA levels, circulating metabolites, and immune-metabolic markers (76, 82).
3. Multi-Omics Laboratory Analysis:
   Samples are transferred to the hospital's omics laboratory for multi-layered profiling:
   - Metabolomics (e.g., SCFA, kynurenine): To assess early biomarkers like butyrate, kynurenine (82, 83)
   - Transcriptomics (e.g., CPT1A, SIRT3): For mitochondrial and immune gene expression (69)(84)
   - Microbiomics: Stool microbiota composition for gut-immune interactions
4. AI/ML-Powered Multi-Omics Integration:
   Extracted omics data are processed using validated ML/AI tools such as SHAP, LASSO, or ensemble models to stratify cancer risk and identify personalized treatment paths (85). Integration models utilize feature fusion (e.g., SCFA + microbiome diversity) to enhance prediction accuracy.
5. Interpretation and Risk Stratification:
   ML-derived outputs are interpreted via explainable AI dashboards and discussed with clinical geneticists and oncologists. Patients are stratified into categories:

-High-risk: Metabolic-immune dysregulation present
-Intermediate-risk: Mild pathway disruption
- Low-risk: No omics abnormalities detected

6. Personalized Clinical Decision Support:
   -Early Diagnosis: SCFA dysregulation (e.g., low butyrate) prompts colonoscopy or biopsy (86)
   - Prognostic Stratification: High kynurenine or mitochondrial dysfunction predicts poor prognosis (87)
   -Treatment Personalization: Patients with acetyl-CoA overproduction may receive HDAC inhibitors; mitochondrial dysregulation may indicate CPI-613 therapy (69)(88)
   -Therapeutic Monitoring: Periodic re-profiling to track metabolomic shifts and immunotherapy resistance (89)
7. Data Archiving and Research Feedback Loop:
   De-identified datasets are stored in secure hospital servers for ongoing model retraining and institutional research.

Figure 6. Omics-AI-Nutrition Clinical Algorithm for Precision Oncology in a Developing Country Setting.



Legends to Figure 6

Term or abbreviation	Explanation
CBC	Complete Blood Count – a routine blood test to assess overall health and detect disorders such as leukemia or anemia
FFQ	Food Frequency Questionnaire – a nutrition assessment tool that tracks dietary intake over time
SCFAs	Short-Chain Fatty Acids – gut-derived fatty acids (e.g., butyrate) that influence immunity and colon health
Kynurenine	A metabolite from tryptophan breakdown involved in immune regulation and cancer progression
Acetyl-CoA	A central metabolic molecule; elevated levels are linked to epigenetic changes in cancer
NMR / LC-MS	Nuclear Magnetic Resonance / Liquid Chromatography–Mass Spectrometry – advanced lab techniques for metabolite profiling
ELISA	Enzyme-Linked Immunosorbent Assay – used to measure biomarker concentrations (e.g., cytokines, metabolites) in blood
AI / ML	Artificial Intelligence / Machine Learning – computational tools that model predictions from complex datasets
SHAP	Shapley Additive Explanations – a method that makes AI models explainable and identifies which features influence predictions
XGBoost	A gradient-boosted decision tree ML model, often used in clinical prediction models
CPT1A / SIRT3	Genes related to mitochondrial metabolism; their dysfunction can signal cancer aggressiveness
HDAC inhibitors	Histone Deacetylase Inhibitors – a class of epigenetic cancer drugs (e.g., Vorinostat)
IDO1 inhibitors	Drugs that inhibit indoleamine 2,3-dioxygenase-1, targeting immune suppression in cancer
CPI-613	A mitochondria-targeted drug tested in cancers with metabolic reprogramming
q6 months	Every 6 months – denotes the interval for repeat omics profiling
RECIST	Response Evaluation Criteria in Solid Tumors – a standardized way to measure tumor response to treatment

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