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Systematic Review on the Clinical Utility of Biomarkers in Early Diagnosis and Prognosis of Human Diseases

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ABSTRACT

Background: Biomarkers may improve early diagnosis and prognostic stratification across human diseases, but translation into clinical practice remains inconsistent. Objective: To systematically evaluate evidence on diagnostic and prognostic utility and clinical readiness of biomarkers across diverse disease domains. Methods: A systematic review of systematic reviews and meta-analyses was conducted using PubMed, Scopus, and Google Scholar. Ten eligible reviews (2008–2024) were included after predefined screening. Data were synthesized narratively due to heterogeneity in diseases, biomarker platforms, matrices, and validation stages. Results: Biomarker clinical utility demonstrated marked heterogeneity driven by validation maturity and biological context. Alzheimer's disease CSF biomarkers (T-tau, P-tau, Aβ42, NFL) showed the strongest readiness for clinical implementation, supported by large meta-analytic evidence (15,699 patients and 13,018 controls) with robust disease–control separation (e.g., CSF T-tau ratio 2.54; P-tau ratio 1.88; Aβ42 ratio 0.56; all p<0.0001). Promising candidates in other domains remained in early validation or discovery phases, including pancreatic cancer microRNA panels with sensitivity and specificity exceeding 90%, uterine disease metabolomics models with AUC up to 0.99, and acute kidney injury biomarkers such as cystatin C, KIM-1, IL-18, and NGAL. Endometriosis peripheral biomarkers demonstrated persistent validation failure despite extensive candidate identification. Conclusion: Biomarkers are clinically implementable only in select contexts, while most candidates require external validation, assay standardization, and demonstration of incremental value over existing clinical pathways before routine adoption.

Keywords

Biomarkers; Early diagnosis; Prognosis; Validation; Standardization; Clinical readiness; Precision medicine.

INTRODUCTION

Delayed diagnosis and inaccurate prognostic stratification remain persistent barriers to optimal clinical decision-making across major disease domains, contributing to preventable morbidity, late-stage presentation, and inefficient allocation of healthcare resources (1). Conventional diagnostic pathways often rely on symptom onset, imaging changes, or non-specific laboratory markers, which may emerge only after substantial disease progression. This diagnostic latency is especially consequential in conditions with long preclinical phases (e.g., neurodegenerative disease), rapidly progressive biology (e.g., pancreatic cancer), or overlapping symptom profiles with benign states (e.g., endometriosis), where early-stage detection and precise risk assessment could meaningfully change outcomes (2).

Biomarkers—measurable biological characteristics reflecting normal processes, pathogenic processes, or responses to therapeutic interventions—have been positioned as central enablers of earlier diagnosis, prognostic forecasting, and personalization of care (3). Advances in proteomics, genomics, transcriptomics, and metabolomics have accelerated biomarker discovery, resulting in thousands of candidate markers reported across the literature. However, translation into routine clinical practice has been slow and inconsistent. While some biomarkers have achieved widespread adoption and guideline endorsement, most remain confined to exploratory research contexts due to limited validation, inconsistent assay performance, lack of standardized cut-offs, and insufficient demonstration of incremental value over established diagnostic or prognostic approaches (4).

The apparent variability in biomarker "success" across diseases raises an important interpretive challenge: poor clinical uptake may reflect not the intrinsic inadequacy of biomarkers as a concept, but differences in disease pathophysiology, biological signal stability, and validation maturity. Biomarkers measured in anatomically proximate fluids (e.g., cerebrospinal fluid in neurodegenerative disease) may capture disease-specific molecular changes more directly than peripheral blood, where signals may be diluted or confounded by systemic inflammation and comorbidities (5). Likewise, early-phase studies, particularly case–control discovery designs with small sample sizes, may report exaggerated performance due to overfitting and spectrum bias, with performance declining substantially upon external validation (6).

Although numerous disease-specific systematic reviews have evaluated candidate biomarkers, there remains a relative lack of integrative evidence syntheses that assess biomarker clinical utility across diverse disease domains using a consistent translational lens—specifically focusing on validation maturity, technical standardization, and clinical readiness rather than comparing biomarker classes in isolation (7). Addressing this gap is essential for clinicians, researchers, and policymakers seeking to distinguish biomarkers that are ready for implementation from those requiring coordinated validation programs and standardized analytic pipelines. Therefore, this systematic review aimed to evaluate the clinical utility of

biomarkers for early diagnosis and prognosis across major human diseases by synthesizing evidence from systematic reviews and meta-analyses. The primary outcomes were diagnostic performance indicators (e.g., sensitivity, specificity, AUC, effect sizes) and validation readiness for clinical implementation, while secondary outcomes included prognostic associations, risk stratification utility, and reported barriers to implementation (8).

MATERIALS AND METHODS

This study was designed as a systematic review of systematic reviews and meta-analyses evaluating the clinical utility of biomarkers for early diagnosis and prognosis across human diseases. The review methodology followed a structured and predefined approach to enhance transparency and reproducibility. The review focused on biomarker applications relevant to clinical decision-making, including early detection, differential diagnosis, prognostic stratification, monitoring, and treatment response prediction.

A structured literature search was conducted in major biomedical databases including PubMed, Scopus, and Google Scholar, using combinations of keywords and Boolean operators related to biomarkers ("biomarker", "protein biomarker", "genetic biomarker", "metabolomic*", "microRNA"), early diagnosis ("early diagnosis", "screening", "detection"), prognosis ("prognosis", "survival", "risk stratification", "outcome"), and disease categories ("Alzheimer*", "cancer", "pancreatic", "oral cancer", "hepatocellular carcinoma", "endometriosis", "acute kidney injury", "cardiac amyloidosis", "osteoporosis", "mesothelioma"). Searches were restricted to English-language publications involving human evidence synthesis. Reference lists of included reviews were also screened to identify additional eligible studies. The final search yield was screened and filtered using predefined criteria, resulting in a final inclusion of 10 reviews.*

Studies were eligible if they met all of the following criteria: (i) systematic reviews or meta-analyses, (ii) focused on human biomarkers used for early diagnosis and/or prognosis, (iii) reported performance metrics such as sensitivity, specificity, AUC, effect size ratios, or prognostic associations (e.g., hazard ratios), and (iv) clearly described the disease domain and biomarker measurement matrix (blood, serum/plasma, urine, cerebrospinal fluid, tissue, or other biological fluids). Exclusion criteria included narrative reviews without systematic methodology, editorials and commentaries, animal or in vitro studies, case reports, and reviews lacking extractable diagnostic or prognostic performance indicators.

Screening was conducted in two stages, beginning with title and abstract screening, followed by full-text evaluation to confirm eligibility. Data extraction was performed using a standardized framework capturing: year of publication, disease domain, biomarker class (proteomic, genomic/transcriptomic, metabolomic, multi-omics), biological matrix, clinical application (early diagnosis, prognosis, monitoring, treatment response), number of included primary studies and participants when reported, diagnostic performance measures (sensitivity, specificity, AUC, effect sizes), prognostic performance measures (hazard ratios, survival associations), quality/risk-of-bias tools used within the included reviews, and authors' conclusions on validation maturity and clinical readiness.

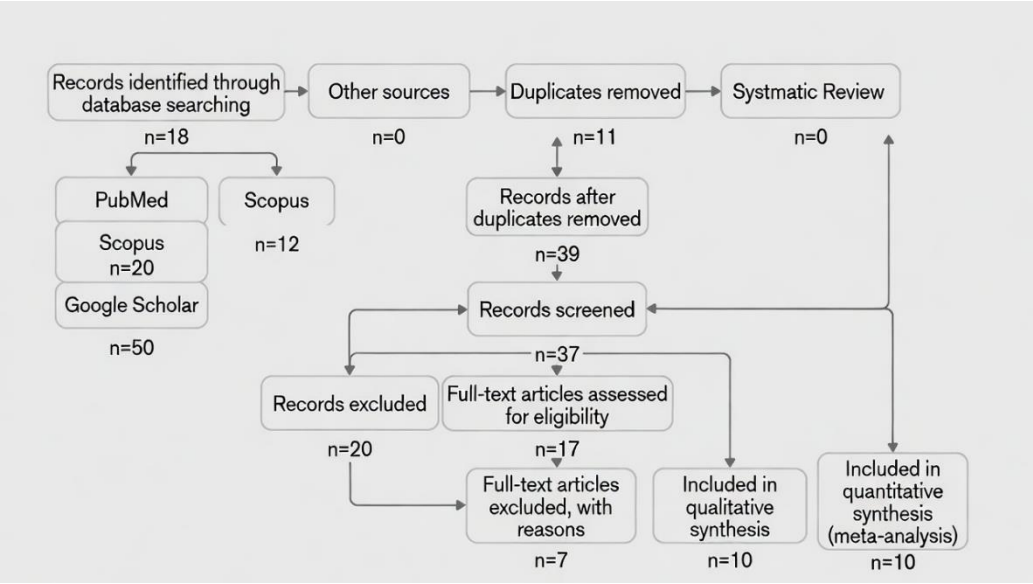

Figure 1 PRISMA Flowchart

Given the high heterogeneity across disease domains, assay technologies, and validation stages, a quantitative meta-analysis across all included reviews was not performed. Instead, evidence was synthesized narratively with structured comparative tables. Biomarker readiness was interpreted using a validation-maturity framework emphasizing: consistency across studies, external validation, assay standardization, availability of cut-offs/reference ranges, and evidence of incremental value over existing clinical pathways. As this study synthesized published literature, formal ethical approval was not required. Transparency was supported by explicit tabulation of included sources and extraction domains.

RESULTS

A total of 10 systematic reviews/meta-analyses published between 2008 and 2024 were included, spanning neurodegenerative disease, oncology, renal injury, cardiac amyloidosis, osteoporosis, and gynecologic conditions.

Table 1. Characteristics of Included Systematic Reviews and Meta-Analyses (n = 10)

First Author (Year)	Disease Area	Biomarker Platform	Matrix	Review Type	Primary Clinical Application
Olsson (2016)	Alzheimer's disease	Proteomic	CSF and blood	Systematic review + meta-analysis	Early diagnosis; differential diagnosis
Senaratne (2023)	Pancreatic cancer	Genomic (microRNAs)	Blood/serum/plasma	Systematic review	Early diagnosis; prognosis; differential diagnosis
Tokarz (2020)	Uterine diseases	Metabolomic	Plasma/serum/urine + local fluids	Systematic review	Early diagnosis; prognosis
Coca (2008)	Acute kidney injury	Proteomic	Serum + urine	Systematic review	Early diagnosis; risk stratification
May (2010)	Endometriosis	Peripheral biomarkers	Serum/plasma/urine	Systematic review	Early diagnosis; monitoring
Schillebeeckx (2021)	Malignant pleural mesothelioma	Proteomic	Serum/plasma	Systematic review + meta-analysis	Early diagnosis
Fernández-Olavarría (2016)	Oral cancer	Proteomic	Serum	Systematic review	Early diagnosis; prognosis
Sohel (2024)	Hepatocellular carcinoma	Multi-omics	Not specified	Systematic review	Diagnosis; prognosis; treatment response
Albulushi (2024)	Cardiac amyloidosis	Proteomic	Blood/serum	Systematic review + meta-analysis	Early diagnosis; prognosis
Raposa (2024)	Osteoporosis	Proteomic	Blood/urine	Systematic review	Diagnosis; prognosis; risk stratification

Table 2. Quantitative Diagnostic/Discriminatory Performance Reported in Included Reviews

Disease Area	Biomarker(s) / Model	Reported Performance	Interpretation
Alzheimer's disease	CSF T-tau	Ratio 2.54 (95% CI 2.44–2.64), p<0.0001	Strong case–control separation; clinically implementable in specialized settings
Alzheimer's disease	CSF P-tau	Ratio 1.88 (95% CI 1.79–1.97), p<0.0001	Robust diagnostic signal; validation maturity high
Alzheimer's disease	CSF Aβ42	Ratio 0.56 (95% CI 0.55–0.58), p<0.0001	Strong inverse separation consistent with disease biology
Alzheimer's disease	CSF NFL	Ratio 2.35 (95% CI 1.90–2.91), p<0.0001	Strong discriminatory performance; supports diagnostic aid and stratification
Alzheimer's disease	Plasma T-tau	Ratio 1.95 (95% CI 1.12–3.38), p=0.02	Modest performance vs CSF; peripheral matrix limitations
Pancreatic cancer	miR-196a + miR-196b	Sensitivity and specificity >90%	Promising for early detection; requires large external validation and prospective testing
Uterine diseases (endometriosis)	Metabolomics model	AUC 0.99 (discovery cohorts)	Likely overfitting risk; external validation rarely performed
Cervical cancer	Metabolomics model	Sensitivity 93%, specificity 91%, AUC 0.97	High discriminatory performance; discovery-phase dominance limits clinical readiness
Endometrial cancer	Metabolomics model	AUC 0.84 (diagnosis); AUC 0.94–0.97 (survival stratification models)	Diagnostic moderate; prognostic modeling promising but early-phase
Hepatocellular carcinoma	AFP and novel markers	Diagnostic accuracy ~70–90%	Moderate performance; heterogeneity and underlying liver disease confounding likely
AKI	Serum cystatin C; urine NGAL, IL-18, KIM-1	Reported as strong-performing markers (varies by purpose)	Requires large prospective validation; incremental value over creatinine essential
Oral cancer	EGFR + Cyclin D1 panel	Highest combined diagnostic performance (qualitative)	Panel performance appears stronger than single markers; quantitative pooling limited

Table 3. Clinical Readiness Assessment by Disease Domain (Validation Maturity)

Disease Domain	Readiness Category	Evidence Summary	Major Barriers to Implementation
Alzheimer's disease (CSF T-tau/P-tau/Aβ42/NFL)	Clinically implementable (specialized settings)	Very large meta-analytic evidence; strong discrimination	Assay harmonization, laboratory cut-off variability, clinical certification and standardization
Cardiac amyloidosis (NT-proBNP, troponins)	Clinically useful as adjuncts	Established markers supported; used with imaging	Correlation variability with imaging; workflow integration; standardization for novel markers
Acute kidney injury (cystatin C, KIM-1, IL-18, NGAL)	Late validation / not yet routine	Promising; quality generally good	Need large multicenter validation; incremental prognostic value over creatinine; cost and assay variability
Pancreatic cancer (microRNA panels ± CA19-9)	Early validation / promising	High sensitivity/specificity in reported models	Prospective validation; population heterogeneity; assay standardization; high-risk screening context needed
Uterine disease metabolomics	Discovery phase (high apparent performance)	AUC values up to 0.99	Overfitting risk; small cohorts; limited external validation; reporting gaps; assay standardization
Hepatocellular carcinoma biomarkers	Early-to-mid validation	Diagnostic accuracy 70–90%; prognostic associations reported	Tumor heterogeneity; cirrhosis confounding; cut-off standardization; validation in diverse cohorts
Oral cancer biomarkers	Early-to-mid validation	Multiple candidates; panel approaches promising	Variable quality; heterogeneous outcomes; limited standardization and longitudinal validation
Malignant pleural mesothelioma	Validation incomplete / inconsistent evidence	Contradictory findings; no validated early detection test	Need early-stage cohorts, standardized panels, and external validation
Endometriosis peripheral biomarkers	Validation failure	>100 candidates; none clinically useful	Disease heterogeneity; weak peripheral signal; inconsistent methodology; biology may limit peripheral biomarker approach
Osteoporosis biomarkers	Adjunctive / interpret cautiously	Biological variability significant; measurement improved	High biological variability; unclear clinical thresholds; cost; external confounding

Proteomic biomarkers were evaluated in most reviews, commonly using blood-based matrices, while urine-based biomarkers were prominent in acute kidney injury and some gynecologic contexts. Only Alzheimer's disease evaluations prominently included cerebrospinal fluid (CSF) biomarkers. Across included reviews, biomarker utility showed substantial heterogeneity, which aligned more strongly with validation maturity and biological context than with biomarker class alone.

The included evidence base comprised 10 systematic reviews/meta-analyses published between 2008 and 2024 across heterogeneous disease domains, with oncology-related indications representing the largest subgroup and proteomic biomarkers evaluated most frequently, typically in blood-based matrices (Table 1). Only Alzheimer's disease evidence synthesis incorporated anatomically proximate CSF sampling in a major way, while endometriosis and cancer biomarker assessments predominantly relied on peripheral blood or urine. Across reviews, clinical applications clustered around early diagnosis and differential diagnosis, with fewer studies reporting robust prognostic endpoints or longitudinal treatment-

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response validation. Notably, several included reviews explicitly highlighted early-phase discovery dominance, limited external validation, and inconsistent reporting, indicating that most biomarker fields remain translationally immature despite extensive candidate identification.

Quantitative performance data were most mature and interpretable in Alzheimer's disease, where meta-analysis across large populations demonstrated strong discrimination between patients and controls using core CSF biomarkers (Table 2). In the Alzheimer's disease meta-analysis, CSF T-tau showed a ratio of 2.54 (95% CI 2.44–2.64; p<0.0001), CSF P-tau a ratio of 1.88 (95% CI 1.79–1.97; p<0.0001), and CSF Aβ42 an inverse ratio of 0.56 (95% CI 0.55–0.58; p<0.0001), reflecting a robust and biologically coherent diagnostic signal. CSF NFL also demonstrated strong separation (ratio 2.35; 95% CI 1.90–2.91; p<0.0001). In contrast, plasma T-tau showed weaker discriminatory capability (ratio 1.95; 95% CI 1.12–3.38; p=0.02), reinforcing that peripheral matrix sampling often yields reduced signal-to-noise compared with CSF. Outside neurodegeneration, pancreatic cancer microRNA panels achieved sensitivity and specificity exceeding 90% in reported models, especially when combined with CA19-9, while metabolomics models for uterine diseases demonstrated extremely high discriminatory performance with AUC up to 0.99 for endometriosis and AUC 0.97 with 93% sensitivity and 91% specificity for cervical cancer. However, these results were frequently derived from discovery-phase case–control cohorts and were rarely externally validated, indicating that apparent performance may overestimate real-world clinical utility.

Clinical readiness grading demonstrated a clear gradient in translational maturity across disease domains (Table 3). Alzheimer's disease CSF biomarkers (T-tau, P-tau, Aβ42, NFL) were the only biomarkers categorized as clinically implementable in specialized settings based on large-scale consistent evidence, although assay harmonization and laboratory cut-off variability remain major barriers. Cardiac amyloidosis markers such as NT-proBNP and troponins were considered clinically useful adjuncts but still require improved integration with imaging and standardized interpretation. In acute kidney injury, cystatin C, KIM-1, IL-18, and NGAL were consistently identified as promising markers, but the field remains at a late validation stage, requiring large prospective multicenter studies and demonstration of incremental value over serum creatinine-based pathways. Endometriosis exhibited the most striking validation failure, with over 100 candidate peripheral biomarkers identified across decades yet none achieving clinical utility, suggesting that disease heterogeneity and weak peripheral signal may represent fundamental obstacles for blood-based biomarker strategies. Collectively, these findings indicate that biomarker translation is primarily limited by validation rigor, standardization, and clinical integration rather than an inherent inability of biomarkers to detect disease, with success most likely when stable disease-specific molecules are measured in biologically proximate matrices and validated through large-scale standardized programs.

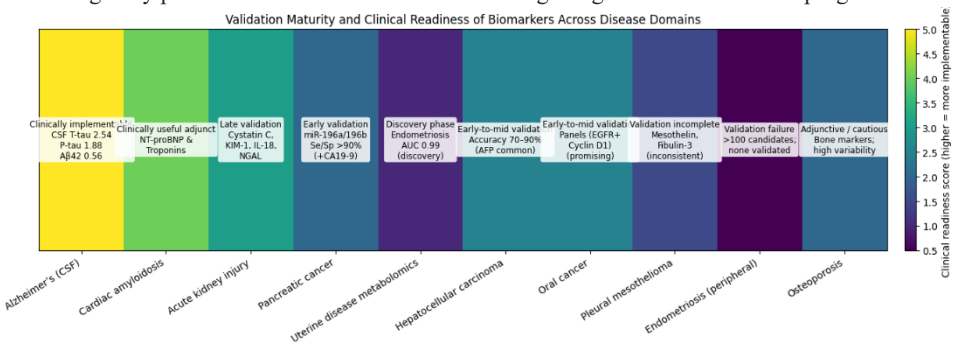

Figure 2 Integrated readiness heatmap demonstrates that biomarker translation

This integrated readiness heatmap demonstrates that biomarker translation is highly disease-dependent and primarily driven by validation maturity and biological context rather than biomarker class alone. Alzheimer's disease CSF biomarkers (T-tau ratio 2.54, P-tau ratio 1.88, Aβ42 ratio 0.56; all p<0.0001) represent the highest level of readiness with robust case–control separation in large meta-analytic evidence, whereas uterine disease metabolomics shows extremely high discovery-phase discrimination (endometriosis AUC 0.99) but remains constrained by limited external validation and overfitting risk. Pancreatic cancer microRNA panels demonstrate promising early validation performance with sensitivity and specificity exceeding 90% in reported models, especially when combined with CA19-9, but require prospective verification. Acute kidney injury biomarkers (cystatin C, KIM-1, IL-18, NGAL) cluster in late validation because incremental benefit over serum creatinine and multicenter generalizability remain insufficiently proven. Endometriosis peripheral biomarkers are mapped as a validation failure despite identification of >100 candidates over 25 years, reinforcing that heterogeneous diseases measured through peripheral matrices may lack a stable, disease-specific circulating signal required for clinically useful biomarkers.

DISCUSSION

This systematic review of systematic reviews/meta-analyses demonstrates that biomarker clinical utility for early diagnosis and prognosis varies substantially across disease domains and reflects validation maturity, biological signal stability, and matrix proximity more than biomarker platform alone (9–11). Among included evidence syntheses, Alzheimer's disease biomarkers showed the strongest readiness for clinical implementation. The large meta-analysis covering 15,699 patients and 13,018 controls reported robust discriminatory separation between Alzheimer's disease and controls for core CSF biomarkers, including T-tau ratio 2.54 (95% CI 2.44–2.64; p<0.0001), P-tau ratio 1.88 (95% CI 1.79–1.97; p<0.0001), and Aβ42 ratio 0.56 (95% CI 0.55–0.58; p<0.0001), with similarly strong performance for CSF NFL (ratio 2.35; p<0.0001) (9). The observed superiority of CSF compared with plasma (plasma T-tau ratio 1.95; p=0.02) supports the translational principle that biomarkers measured in anatomically proximate matrices provide higher signal-to-noise and more reliable clinical discrimination when pathology is localized and molecular targets are stable (9,12). Nevertheless, even this mature domain remains limited by assay heterogeneity and variable laboratory cut-offs, indicating that high performance does not automatically translate into universal clinical adoption without harmonized assay calibration and clinically certified platforms (9).

In cardiac amyloidosis, established biomarkers such as NT-proBNP and troponins were consistently represented as clinically useful adjuncts for early detection and prognosis, but interpretation remains dependent on integration with imaging and clinical phenotyping, where variability in correlations may complicate clinical decision-making (10). A similar pattern emerges in acute kidney injury, where biomarkers such as cystatin C,

KIM-1, IL-18, and NGAL are repeatedly identified as promising for early detection, differential diagnosis, and risk stratification, yet routine implementation is limited by the need for large multicenter validation, heterogeneity in AKI etiologies, and uncertainty regarding incremental value beyond creatinine-based algorithms and clinical risk models (13). In these settings, biomarker success appears constrained not by absence of biological signal but by incomplete demonstration that biomarker-informed pathways improve outcomes, reduce delays, or change management compared with established clinical approaches (13).

Oncology biomarker evidence showed intermediate translational maturity and notable heterogeneity by tumor biology, clinical stage, and assay platform (11,14,15). In pancreatic cancer, circulating microRNA panels achieved high reported diagnostic performance (sensitivity and specificity >90% for miR-196a/196b combinations), with additional gains when combined with CA19-9 (14). While this suggests potential for high-risk screening or diagnostic augmentation, the broader implementation question remains whether these panels maintain performance in real-world populations with confounding benign pancreatic and hepatobiliary disease, and whether standardized assays and cut-offs can be established across laboratories and ethnic populations (14). Hepatocellular carcinoma biomarkers demonstrated moderate diagnostic accuracy (approximately 70–90%, with AFP frequently studied), with prognostic associations reported but often without harmonized effect measures across studies, reflecting confounding by cirrhosis and chronic liver disease and the need for standardized validation pipelines (11). For oral cancer, multiple serum biomarker candidates were reported, with panel approaches (e.g., EGFR and Cyclin D1) appearing more informative than single markers; however, heterogeneity in study design and limited longitudinal validation restrict firm conclusions on clinical readiness (15). Malignant pleural mesothelioma represents a case where extensive biomarker research has not yet yielded a validated early detection test; contradictory findings and incomplete validation highlight the need for standardized multi-marker panels, inclusion of early-stage cases, and external validation as prerequisites for clinical translation (16).

Gynecologic conditions illustrated the most divergent translational pathways. Metabolomics models for uterine diseases showed extremely high discriminatory performance in discovery settings, including endometriosis AUC 0.99 and cervical cancer AUC 0.97 with 93% sensitivity and 91% specificity, and endometrial cancer models demonstrating AUC 0.84 for diagnosis with prognostic stratification models reaching AUC 0.94–0.97 (17). However, the metabolomics field remains predominantly discovery-driven, with small cohorts, limited external validation, and frequent reporting gaps in sample processing and statistical methodology, creating high risk of overfitting and limited generalizability. In stark contrast, endometriosis peripheral biomarker research demonstrates a long-standing validation failure, with over 100 candidate biomarkers proposed across decades and no single marker or panel achieving reliable clinical utility, suggesting that disease heterogeneity and weak peripheral signal may impose fundamental limitations on blood-based diagnostic biomarkers for this condition (18).

Collectively, these findings support a translational hierarchy for biomarker implementation: discovery must be followed by internal replication, external validation across diverse cohorts, assay harmonization and cut-off standardization, evaluation of incremental value over clinical pathways, and assessment of workflow feasibility and cost-effectiveness. The readiness gradient shown in the integrated figure reinforces that only a subset of biomarker domains have progressed through these steps. Future research should prioritize prospective multicenter cohort validation, standardized assay platforms, and clear demonstration that biomarker-informed decisions improve clinically meaningful outcomes rather than merely increasing statistical discrimination in case–control designs. In resource-limited contexts, implementation studies should also evaluate affordability, turnaround time, and integration with existing diagnostic workflows to ensure equity in biomarker-enabled precision medicine.

CONCLUSION

This systematic review of systematic reviews/meta-analyses demonstrates that biomarker clinical utility for early diagnosis and prognosis is currently robust only in select disease contexts, with the strongest evidence supporting Alzheimer's disease CSF biomarkers (T-tau, P-tau, Aβ42, NFL) as clinically implementable in specialized settings, while most cancer, kidney, cardiac, osteoporosis, and gynecologic biomarker candidates remain in discovery or early validation phases requiring external validation, assay harmonization, and standardized cut-offs before routine clinical adoption. The consistent pattern across disease domains indicates that biomarker success depends on stable disease-specific biology, anatomically proximate measurement matrices, and rigorous validation pipelines, and future research should prioritize prospective multicenter validation and demonstration of incremental value over established clinical diagnostic and prognostic pathways to enable reliable translation into patient care.

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