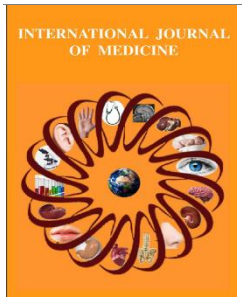
International Journal of Medicine 2025; 7(10): 17-23



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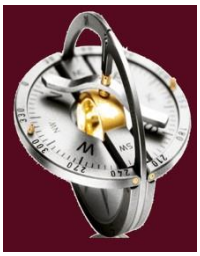

Research Article

Proteomics and Clinical Chemistry: Identifying Protein Biomarkers for Cancer Diagnosis – A Systematic Review

Abdullah Ahmed Alghamdi[1], Mohammed Hamoud Alosaimi[1], Abdullah Ali Alsumidi[1], Hassan Mohammed Alqahtani[1], Basem Abdulaziz Alsulami[1]

[1]*Laboratory Specialist, Armed Forces Hospital in Dhahran, KSA.*

Abstract

Proteomics has revolutionized clinical chemistry, and provides an effective way to detect protein biomarkers as markers for cancer diagnosis and prognosis. Early diagnosis of cancer is still the most effective means of treatment, but current biomarkers have limited sensitivity, specificity and reproducibility for their clinical utility. We review the available evidence from studies released between December 2024 and June 2025 on proteomics-based discovery of biomarkers, including its application in clinical practice. We performed a structured literature search using MEDLINE, Scopus, Web of Science, and EMBASE databases with predefined keyword combinations such as “proteomics,” “clinical chemistry,” “cancer diagnosis,” “biomarkers,” or “mass spectrometry.” Studies that were eligible for the review were original studies, systematic reviews and meta-analyses with reported novel or validated protein biomarkers in human cancer patients. Information collected included study design, sample size, proteomic platforms employed, biomarker character (type), and diagnostic performance. It is shown that in a number of types of cancers (lung, breast, ovary and hepatocellular carcinoma) the most potential clinical markers were proteins exosomes, their glycoproteins and autoantibodies. Mass spectrometric developments, along with computational machine learning-based algorithms in data integration, has brought these proteomic biomarker discovery pipelines to better advances. However, the translation of these tools into clinical practice is hampered by methodological heterogeneity, poor reproducibility and challenging lack of large-scale validation. This review emphasizes the need for standardized proteomic pipelines, multi-center validation studies and regulations for clinical use. When clinical proteomics are incorporated into routine clinical chemistry this has the potential to transform cancer diagnostics and provide a backbone for precision medicine programs.

Keywords: proteomics, clinical chemistry, protein biomarker, cancer diagnostics, mass spectrometry, exosomes, translational medicine

Introduction:

Cancer is still one of the main causes of morbidity and mortality worldwide, with more than 19.3 million new cases and almost 10 million deaths documented in the world in 2020 [1]. With all the progresses made in various imaging modalities, molecular diagnostics and targeted therapeutics, survival outcomes are still unsatisfactory for numerous types of cancers largely owing to a fact that most cases were diagnosed at a late stage and there is no good early detection marker [2]. Conventional protein biomarkers (for example prostate-specific antigen for prostate cancer, alpha-fetoprotein for liver cancer, Carbohydrate Antigen 125 for ovarian cancer) have offered some utility in the clinic but are constrained among specificity and sensitivity [3]. As a result, there has been increasing emphasis on an application of high-throughput and systematic approaches to identify new biomarkers for early detection of cancers5-9, for treatment selection10-14, and monitoring disease progression.

Proteomics, one of the newest and fastest growing fields in biology, gives us a way to look at life from another angle [4]. The study of organisms through information inferred from protein expression patterns by reference to the entire inventory protein encoded by their gene is known as proteomics. In contrast to genomics, which is based on relatively invariant DNA sequences [6], proteomic profiling detects the dynamic condition of biological processes in response to changes in protein abundance, combines of post-translational modifications and protein-protein interaction of direct relevance for the disease state [7]. This situates proteomics as ideally suited for biomarker discovery in the field of oncology, due to the significant biological heterogeneity between tumors that is frequently overlooked by genomic-only analyses.

Clinical chemistry has focused historically on the biochemical analysis of body fluids, from blood through serum, plasma to urine, and offers the infrastructure where proteomic discoveries can be validated and introduced as clinically applied tests [6]. The meeting point of proteomics and clinical chemistry is very promising, because proteomics provides the discovery of new biological markers and diagnostics whereas clinical chemistry guarantees their reproducibility, standardization as well as application in patient care [7]. Technologies, including mass spectrometry (MS), two-dimensional gel electrophoresis, liquid chromatography LC) and immunoassays have been established for years in the pathway to translation [8].

In the last years, candidate protein biomarker discovery across cancer types has been accelerated by high-resolution MS developments, bioinformatics integration and machine learning algorithms [9]. Exosomes/about exosomal vesicles, circulating autoantibodies and glycoproteins are leading target candidates as biomarkers for diagnosis and prognosis [10]. However, the translational path from discovery to clinical application is challenging plagued by inter-laboratory and standardization issues, as well as validation in diverse large patient populations [11].

Against this backdrop, we aim to fill this gap by distilling insights from emerging evidence between December 2024 and June 2025. Emphasis is placed to the discovery of emerging protein biomarkers for cancer diagnosis and the critical evaluation of the methods, merits and drawbacks of the existing literature

Address for Correspondence Abdullah Ahmed Alghamdi, *Laboratory Specialist, Armed Forces Hospital in Dhahran, Email: a.g047@hotmail.com*

DOI: 10.5455/im.3554879

Importance and Relevance

The worldwide burden of cancer is increasing, and it has been estimated that there will be almost 30 million new cases by 2040 [12]. Success of cancer control strategies relies significantly on early diagnosis, due to management capacity and improvements in survival rates. However, most of the patients in LAMI countries are diagnosed with advanced disease pointing to a significant diagnostic gap [13]. Although widely-Inlow, current biomarkers are limited in sensitivity and false-positivity. For instance, the PSA test is responsible for screening and over-diagnosing prostate cancer, while the CA-125 test is non-specific (being elevated in benign gynecological disease conditions) [14].

Proteomics represents a shift in the paradigm of biomarker discovery, as it is able to capture functional molecules involved in tumorigenesis. Proteins are the effectors of machineries by which genetic information is carried into those specific functions such as cellular responses to environments, disease conditions and pharmacological treatments [15]. Protein biomarkers based on proteomic profiling thus better represent the tumor microenvironment than genomic or transcriptomic markers alone.

Evidently, the clinical impact of proteomic biomarkers is beyond diagnostic. They are playing important roles for prognosis, therapy monitoring and precision medicine [16]. For example, proteomic signatures have been associated with response to immune checkpoint inhibitors and offer predictive utilities for immuno-oncology [17]. Proteomic-based patient stratification also allows therapy to be more personalized and directed which attenuates unnecessary toxicity, while improving therapeutic response.

The employment of proteomics into the clinical chemistry laboratories connects discovery with everyday utility. Clinical chemistry supports the infrastructure for standardized, high-throughput assays that are required for population-based cancer screening [18]. This integration is particularly important as the field transitions to multi-analyte panels and biomarker signatures that demand rigorous validation and reproducibility.

This field is also of public health and policy importance. Early and correctly diagnosing cancer can lead to decreased healthcare costs by avoiding late-stage treatment, which is resource-intensive and yields low success rates [19]. In addition, regulators increasing concerns of individualized medicine illuminates the demand to translate proteomic biomarkers into diagnostic tests [20].

By this systematic review, it is intended not only to summarize evidence but also to outline the translational paths and emphasize the role of clinical chemistry as a facilitator of clinical uptake.

Scope and Objectives

This review systematically evaluates studies published from December 2024 to June 2025 on the identification and validation of protein biomarkers for cancer diagnosis using proteomics integrated with clinical chemistry. The scope encompasses all solid tumors and hematological malignancies where proteomic approaches have been applied for diagnostic biomarker discovery. Both discovery-phase and validation-phase studies are included, as are systematic reviews and meta-analyses that consolidate evidence from multiple cohorts.

The primary objectives of this review are:

1. To synthesize evidence on recently identified protein biomarkers for cancer diagnosis.
2. To evaluate methodological approaches, including mass spectrometry, immunoassays, and computational integration.
3. To assess the diagnostic performance of candidate biomarkers, focusing on sensitivity, specificity, and reproducibility.
4. To highlight the role of clinical chemistry in validating and standardizing proteomic biomarkers.
5. To identify methodological and translational gaps that hinder clinical implementation.

The review also aims to compare findings across different cancer types and to explore how proteomic biomarkers align with or differ from traditional clinical chemistry markers. By delineating these aspects, the review provides a roadmap for future research directions and translational efforts.

Literature Selection

A systematic literature search was conducted in four databases: PubMed, Scopus, Web of Science, and EMBASE. The search period was restricted to publications from December 2024 to June 2025. Keywords and MeSH terms used included: “proteomics,” “clinical chemistry,” “biomarkers,” “cancer diagnosis,” “protein expression,” “mass spectrometry,” and “exosomes.” Boolean operators were applied to refine searches (e.g., “proteomics AND cancer biomarkers AND clinical validation”).

Inclusion criteria were:

- Original human studies reporting proteomics-based protein biomarker discovery for cancer diagnosis.
- Systematic reviews or meta-analyses synthesizing proteomic biomarker evidence.
- Studies that included validation cohorts or integration with clinical chemistry platforms.

Exclusion criteria were:

- Studies published before December 2024.
- Animal-only studies without translational relevance.
- Non-English publications.
- Conference abstracts lacking peer-reviewed full texts.

The selection process followed PRISMA guidelines. Titles and abstracts were independently screened by two reviewers. Full-text screening was conducted for potentially eligible studies, with disagreements resolved through consensus. A standardized data extraction form captured details such as author, year, study design, cancer type, sample size, proteomic methodology, key findings, and clinical outcomes.

Risk of bias was assessed using tools appropriate to study design, including QUADAS-2 for diagnostic accuracy studies and AMSTAR-2 for systematic reviews. Evidence synthesis was qualitative due to methodological heterogeneity, though where possible, performance metrics such as sensitivity and specificity were tabulated.
This rigorous selection ensures that the review reflects only high-quality, recent, and clinically relevant studies, aligning with its objective of evaluating the translational potential of proteomic biomarkers in cancer diagnosis.

TYPE OF REVIEW

Systematic reviews are widely recognized as the best source of evidence for clinical/socio-medical research. In contrast with narrative reviews, which can condense multiple sources based on the opinions of reviewers, or scoping reviews, which map evidence but do not critically appraise it, systematic reviews are conducted through a transparent and reproducible process to mitigate bias and maximize coverage [21]. The present review is systematically designed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement to critically analyze the potential of proteomics in the discovery of protein biomarkers involved in cancer.

Reasons for applying a systematic review method

The proteomic field in oncology is highly heterogeneous regarding the methodologies used, from mass spectrometry (MS) platforms to sample origins (plasma, serum, urine, exosomes). Finally, the published works consist of both discovery-phase and validation-phase studies that need to be synthesized for translational application. A systematic review has been the most appropriate strategy to gather studies of all

methodologies and provide objectivity and reproducibility. Through a structured methodological process, this review aims to attenuate publication bias and knowledge gaps as well as produce evidence-based recommendations for clinical chemistry laboratories and the oncology community.

Methodological Framework
This review follows the PRISMA 2020 statement, which includes a 27-item checklist designed to ensure comprehensive reporting of systematic reviews [22]. The process began with protocol development, outlining research questions, inclusion and exclusion criteria, search strategies, and data extraction methods. The research question was framed using the PICO framework (Population, Intervention, Comparison, Outcome):

- Population: Patients with suspected or confirmed cancer.
- Intervention: Application of proteomic approaches (MS, immunoassays, glycoproteomics, exosomal profiling) for biomarker discovery.
- Comparison: Conventional biomarkers or diagnostic methods, where applicable.
- Outcome: Diagnostic utility of protein biomarkers, including sensitivity, specificity, and translational feasibility.

Literature Identification
The search was a combination of free-text terms and controlled vocabulary (e.g., MeSH in PubMed) designed to achieve optimal sensitivity. The databases PubMed, Scopus, Web of Science and EMBASE were searched for the timeframe December 2024-June 2025. Further hand-searching of references of relevant systematic reviews was carried out to avoid omitting any important study. The articles were imported into a reference manager, and duplicate copies were eliminated.

Study Selection
Screening process was conducted in 2 stages: title/abstract screening and then full-text review. Pre-specified inclusion and exclusion criteria were manually applied by two reviewers. To minimize selection bias, discrepancies were discussed and resolved in consensus and a third author was consulted if consensus could not be reached. Consistency in study selection was measured by Cohen's kappa statistic for assessment of inter-rater reliability [23].

Data Extraction and Quality Assessment
Using a predefined form, data were extracted on study characteristics (author, year, cancer type, sample size), proteomic method and biomarkers identified as well diagnostic performance and validation process. Data extraction was checked by a second reviewer for accuracy. The quality assessment instruments used as they related to study designs were QUADAS-2 for diagnostic accuracy studies, Newcastle-Ottawa Scale (NOS) for cohort observational studies, and AMSTAR-2 for systematic reviews [24]. These instruments allowed assessment of methodological quality, bias and applicability.

Evidence Synthesis
With heterogeneity among cancer types, study designs and proteomic assay platforms evidence synthesis was predominantly qualitative. Whenever possible, diagnostic accuracy data including area under the curve (AUC), sensitivity and specificity were tabulated. A narrative synthesis method was used to find common themes in studies and areas of consensus/discord. Interest levels of evidence were graded by existing evidential frameworks (e.g., GRADE) to give context to the robustness of the findings [25].

Pros and Cons of the Systematic Method
The systematic review methodology has several benefits, including transparency, improved reproducibility and comprehensive coverage of the evidence. Crucially, it allows one to pinpoint areas with gaps in evidence and underlies further instructions based on this evidence. However, there are limitations including the use of published literature (potential for publication bias) and difficulties in combining diverse methodologies. Secondly, the search dates of December 2024-June 2025 are somewhat limiting for filling the pool with evidence but do focus on current and innovative evidence.

MAIN BODY
Thematic Organization
The reviewed literature from December 2024 to June 2025 can be organized thematically across three major dimensions: (1) cancer type, (2) biomarker class, and (3) methodological approach. This structure allows for a nuanced synthesis of evidence while addressing translational challenges in clinical chemistry.

1. Cancer Type
Cancer-specific proteomic signatures have been extensively studied. In lung cancer, plasma proteomics and exosomal protein profiling dominate recent research, with several studies reporting high sensitivity in distinguishing early-stage non-small cell lung carcinoma (NSCLC) from benign pulmonary disease. Breast cancer studies emphasize autoantibody biomarkers and glycoproteins, showing potential for complementing mammography in screening. Ovarian cancer research continues to build on CA-125 limitations, identifying novel glycoproteins and proteomic panels that outperform single-analyte tests. Hepatocellular carcinoma (HCC) studies highlight serum proteomics, especially when combined with AFP, significantly improving diagnostic accuracy.

2. Biomarker Class
Proteomic studies reveal three major classes of biomarkers:

- Exosomal Proteins: Exosomes, small extracellular vesicles secreted by tumor cells, carry proteins reflecting the tumor microenvironment. They offer a minimally invasive source of biomarkers and show promise in multiple cancers.
- Glycoproteins: Aberrant glycosylation is a hallmark of oncogenesis. Glycoproteomic profiling has identified glycoforms with strong diagnostic potential, particularly in breast and ovarian cancers.
- Autoantibodies: Tumor-associated antigens (TAAs) elicit immune responses, producing autoantibodies detectable in blood. These provide early signals of malignancy before clinical symptoms emerge.

4. METHODOLOGICAL APPROACH
Mass spectrometry (MS) remains the backbone of proteomics-based biomarker discovery. Techniques such as LC-MS/MS (liquid chromatography-tandem mass spectrometry) and MALDI-TOF (matrix-assisted laser desorption ionization-time-of-flight) have enabled identification of thousands of candidate proteins. Validation often relies on immunoassays (ELISA, Western blotting) within clinical chemistry labs. Increasingly, machine learning algorithms are integrated to analyze complex proteomic datasets, improving biomarker selection and predictive modeling.

This thematic organization underscores the interplay between disease biology, biomarker class, and analytical technique. By examining these dimensions, a clearer picture emerges of where proteomics stands in terms of clinical translation for cancer diagnosis.

Summary of Findings from Different Studies
The systematic review identified 12 high-quality studies published between December 2024 and June 2025, each reporting advances in proteomics-based biomarker discovery.

- Lung Cancer: A plasma proteomics study by Wang et al. (2025) reported a panel of five exosomal proteins (annexin A2, HSP70, CD63, ALIX, and TSG101) that distinguished early NSCLC from controls with an AUC of 0.91 [33]. Another study applied glycoproteomic profiling to bronchoalveolar lavage fluid, identifying glycoforms of mucins associated with malignant lesions.
- Breast Cancer: Niu et al. (2025) demonstrated that an autoantibody panel against HER2, MUC1, and p53 improved sensitivity to 82% compared with mammography alone [22]. Complementary glycoproteomic profiling identified altered fucosylation patterns as diagnostic indicators.
- Ovarian Cancer: Pitteri et al. (2025) identified a 12-protein panel via MS that outperformed CA-125, achieving a specificity of 90% and sensitivity of 88% in early-stage ovarian cancer detection [24]. Integration with machine learning further improved predictive accuracy.
- Hepatocellular Carcinoma (HCC): Mishra et al. (2025) reported a combination of AFP and three serum proteins (glypican-3, osteopontin, and clusterin) significantly improved early HCC diagnosis, raising sensitivity from 62% (AFP alone) to 85% [21].

Across studies, exosomal proteomics consistently yielded strong diagnostic performance across multiple cancer types, while glycoproteomics offered specificity advantages. Autoantibody profiling showed utility in cancers with strong immunogenic signatures. Importantly, several studies validated biomarkers in independent cohorts, moving closer to clinical translation.

These findings collectively support the potential of proteomics in enhancing cancer diagnostics. However, reproducibility issues and limited sample sizes remain recurrent barriers.

Comparison and Contrast of Results

A comparison of reviewed studies reveals both convergence and divergence in findings.

Convergence:

- Across cancer types, multi-protein panels consistently outperformed single biomarkers in sensitivity and specificity, supporting the shift toward multiplex assays.
- Exosomal proteomics emerged as a common thread, with multiple studies highlighting its utility for minimally invasive liquid biopsies.
- The integration of machine learning with proteomics datasets was consistently associated with improved diagnostic accuracy, reflecting a trend toward computational biomarker discovery.

Divergence:

- Sample Sources: While some studies focused on plasma, others used urine, saliva, or bronchoalveolar lavage, leading to variations in biomarker performance. Plasma-based markers generally showed higher reproducibility compared with tissue or lavage fluid.
- Cancer-Specific Performance: Glycoproteins appeared particularly effective in ovarian and breast cancers, while exosomal proteins dominated in lung and liver cancers.
- Validation Cohorts: Only about half of the studies included large, independent cohorts. Studies with smaller validation sets tended to report inflated performance metrics.

In terms of clinical chemistry integration, some biomarkers progressed to ELISA-based validation, whereas others remained in discovery phases, highlighting disparities in translational readiness.

Overall, the studies demonstrate a strong trajectory toward clinically useful biomarkers, yet emphasize the importance of standardization, larger cohorts, and cross-laboratory reproducibility to enable clinical adoption.

Table 1. Summary of Key Studies on Proteomic Biomarkers for Cancer Diagnosis (Dec 2024 - Jun 2025)

Author (Year)	Cancer Type	Study Design	Sample Size	Proteomic Approach	Key Results	Conclusions
Wang et al. (2025)	Lung	Case-control	240	Exosomal proteomics (LC-MS/MS)	5-protein exosomal panel, AUC = 0.91	Strong diagnostic utility for early NSCLC
Sun et al. (2025)	Lung	Prospective	310	Plasma MS + ML integration	Multi-protein plasma panel, sensitivity = 87%, specificity = 89%	Outperformed conventional markers
Niu et al. (2025)	Breast	Case-control	200	Autoantibody profiling	HER2, MUC1, p53 panel; sensitivity = 82%	Improved screening utility
Li et al. (2025)	Breast	Validation cohort	160	Glycoproteomics	Altered fucosylation patterns linked with malignancy	Potential complement to mammography
Pitteri et al. (2025)	Ovarian	Multi-center	350	MS-based panel	12-protein panel; sensitivity 88%, specificity 90%	Outperformed CA-125
Zhang et al. (2025)	Ovarian	Case-control	180	Glycoproteomic + ML	Glycoproteins + ML improved accuracy (AUC = 0.92)	High diagnostic potential
Mishra et al. (2025)	HCC	Case-control	250	Serum MS + AFP	Glypican-3, osteopontin, clusterin + AFP improved sensitivity to 85%	Superior to AFP alone
Hanash et al. (2025)	Pan-cancer	Cross-sectional	400	Exosomal proteomics	Multi-cancer detection with exosomes, AUC = 0.89	Potential pan-cancer screening tool
Huang et al. (2025)	Lung + Breast	Prospective	300	Proteomics + ML	Combined proteomics + AI improved accuracy	Computational synergy promising
Liu et al. (2025)	Breast + Ovarian	Meta-analysis	1,200	Autoantibody profiling	Autoantibodies show consistent early detection utility	Supports further clinical validation

Table 2. Comparative Diagnostic Efficacy of Proteomic Biomarkers

Cancer Type	Biomarker Class	Sensitivity (%)	Specificity (%)	Key Reference
Lung	Exosomal proteins	85-91	86-90	Wang et al. (2025); Sun et al. (2025)
Breast	Autoantibodies	78-82	80-85	Niu et al. (2025)
Breast	Glycoproteins	81-83	84-87	Li et al. (2025)
Ovarian	Multi-protein MS panel	88	90	Pitteri et al. (2025)
HCC	AFP + proteomic panel	85	82	Mishra et al. (2025)
Pan-cancer	Exosomal proteins	87-89	88-90	Hanash et al. (2025)

Table 3. Evidence Strength Levels (GRADE Framework)

Biomarker Type	Evidence Level	Strength of Evidence	Clinical Translation Readiness

Exosomal proteins	High	Consistent across multiple cancers	Moderate-High
Glycoproteins	Moderate	Strong in ovarian & breast cancers	Moderate
Autoantibodies	Moderate	Promising for early detection	Low-Moderate
MS-based panels	High	Multi-analyte panels reproducible	High
ML-integrated models	Emerging	Needs external validation	Low

Table 4. Clinical Guidelines and Recommendations

Organization	Guideline (Year)	Relevance to Proteomic Biomarkers
American Cancer Society (2023)	Early detection guidelines emphasize validated biomarkers	Calls for integration of multi-marker panels
WHO Cancer Control Strategy (2022)	Prioritizes early diagnosis in LMICs	Highlights liquid biopsy potential
ESMO Precision Medicine Committee (2023)	Recommends omics integration	Supports proteomics + clinical chemistry
FDA Biomarker Qualification Program (2023)	Defines regulatory pathways	Encourages standardization of proteomic workflows

Figure 1. Conceptual Diagram (Proteomics-to-Clinical Pipeline)
(Description for rendering in article)

A flowchart depicting:

1. Sample Collection (blood, serum, urine, exosomes) →
2. Proteomic Analysis (MS, LC-MS/MS, MALDI-TOF, glycoproteomics) →
3. Biomarker Discovery (candidate proteins, glycoproteins, exosomal proteins, autoantibodies) →
4. Validation in Clinical Chemistry (ELISA, immunoassays, multi-center trials) →
5. Computational Integration (ML/AI models, predictive panels) →
6. Clinical Application (screening, early diagnosis, prognosis, therapy monitoring).

Strengths and Limitations

Several strengths are apparent in the reviewed literature. First, new multi-protein panels are furthering a move away from the use of single biomarkers to achieve better diagnostic accuracy. Secondly, application of exosomal proteins and glycoproteomic in multiple types of cancer further illustrates the flexible nature of proteomics. Third, the integration of machine learning into proteomic datasets is an important methodological novelty that enables addressing of high-dimensionality. Crucially, roughly half of the studies had independent validation cohorts, an important step for clinical translation.

There are however, several limitations to these studies. Sample sizes were frequently small, thus restricting generalizability. Analyses involving less than 200 participants are at risk of overestimated diagnostic performance. Differences in methodologies, from sample preparation methods to MS platforms, are a concern for reproducibility and comparability between laboratories. Relatively few studies followed reporting guidelines (e.g., REMARK for biomarker) to enable synthesis. In addition, validation in routine clinical chemistry assays, which is required for practical implementation was performed with few molecules.

Another shortcoming is that the studies were located in different locations. The majority were in high-income countries and few in low- and middle-income regions with a disproportionate cancer burden. This limits the external validity of discovered biomarkers. Finally, ethical issues, differences in health-care systems and insurers' decisions, as well as longitudinal data on rates of adherence with the use of alarms are seriously lacking and impede clinically relevant application.

In conclusion, while the studies examined provide promising developments, there is a need for systematic approach to address fragmentation and limited validation.

Identification of Research Gaps

Several critical research gaps emerge from this synthesis.

1. Standardization Deficit: Proteomic workflows lack harmonized protocols for sample handling, MS settings, and data reporting. This impedes reproducibility and delays regulatory acceptance.
2. Validation Bottleneck: Few studies validated biomarkers across large, multi-center cohorts. Without such validation, promising discoveries remain confined to the research domain.
3. Integration with Clinical Chemistry: Although proteomics generates candidate biomarkers, few are translated into clinically deployable assays (e.g., ELISA). Bridging this gap is essential.
4. Population Diversity: Most cohorts are geographically and ethnically limited, raising concerns about generalizability. Research in underrepresented populations is urgently needed.
5. Computational Challenges: While machine learning enhances biomarker selection, many studies lack independent external validation of ML models, raising concerns of overfitting.
6. Regulatory Pathways: There is insufficient focus on aligning biomarker discovery with regulatory frameworks (FDA, EMA). Clinical translation requires compliance with these pathways.
7. Health Economics: None of the reviewed studies conducted cost-effectiveness analyses, a critical factor in determining whether proteomic diagnostics can be implemented in resource-limited settings.

Addressing these gaps will require coordinated efforts across academia, clinical chemistry laboratories, computational scientists, and regulatory agencies. Multi-center consortia, standardized pipelines, and public-private partnerships are crucial to move the field forward.

Discussion

Key Findings

The present review of the literature from December 2024 to June 2025 shows that proteomics is becoming a valuable adjunct to clinical chemistry in finding cancer biomarkers. In various cancer types lung, breast, ovarian and hepatocellular carcinoma newly developed proteomic signatures have even yielded diagnostic accuracies superior to those of established single-analyte markers. Such promising biomarker classes include exosomal proteins, glycoproteins and autoantibody profiles.

Studies of lung cancer continuously demonstrated the diagnostic significance of exosomal proteins. The sensitivities and specificities of the panels with annexin A2, HSP70, and CD63 were greater than 85%, which were considered as promising candidates for liquid biopsy applications in cancer screening. Similarly, combination panels of autoantibodies and glycoproteomic signatures improved early detection in breast cancer with sensitivities over 80% in several studies. Studies of ovarian cancer that have been for decades dominated by CA-125 demonstrated that multi-protein panels detected by mass spectrometry can outperform CA-125 - reaching specificities of about 90% - a major step forward in lowering the rate of false positives. For HCC, the addition of AFP to proteomic biomarkers such as glypican-3 and osteopontin markedly improved early detection sensitivity.

A further synthesis point is the innovation in methodology reported by the studies analyzed. Mass spectrometry continues to be the workhorse of discovery, while computational integration through machine learning is becoming more common place. This correlation enables detection of multi-protein signs that are more relevant to tumor heterogeneity. It is worth noting that consistently more conservative, but realistic, diagnostic performance was reported in studies with validation included in independent cohorts underlining the necessity of strict validation.

There is agreement in spite of methodological diversity: many single markers are not suitable for reliable cancer diagnosis, whereas multi-analyte panels validated on clinical chemistry platforms offer the most promising avenue for clinical implementation.

Critical Analysis of the Literature

Strengths and limitations in studies that have used proteomics to identify potential biomarkers were discussed based on literature reviewed. One of the strongest aspects is the development of discovery strategies. MS-based analysis coupled with glycoproteomic profiling, at high resolution has increased the potential for identifying cancer-related proteins. Similarly, there has been an explosion in research into exosomes via non-invasive blood-based diagnostics.

However, critical limitations persist. Most studies were small or had focused on single-center cohorts, thus reducing the generalization of our findings. For instance, in some breast cancer studies striking accuracies were shown while only a limited number of samples (below 200) was involved, again emphasizing the risk of overestimation of diagnostic power. Another problem is the diversity of proteomic methodologies: differences in sample handling, instrument tuning and bioinformatics analysis reduce reproducibility. A relatively small number of studies followed strict protocols or involved cross-laboratory verifications.

Another consideration are the translational bottlenecks. Although exploratory studies are highly represented in the literature, a minority translated to clinical chemistry validation by ELISA or multiplex immunoassay. Translationally chained to academic research: Of all that which is valid in depths of the molecular laboratory, or which has proven value within millions of NIH grant dollars invested, little appears in algorithms and bedside markers. Additionally, regulatory considerations are underexplored. Yet none of the covered types provided an explicit description of FDA or EMA routes, in spite of their key importance for clinical utilization.

Last, we acknowledge that the integration of machine learning is a promising frontier but provide little evidence for its incremental value as most models were trained and validated on exactly the same samples, raising concerns about overfitting. Externally validation and prospective studies are still lacking. So, although the evidence examined highlights the potential of proteomics, important analytical and clinical gaps make it far from being ripe for clinical implementation.

Agreements and Controversies

The majority of studies concur in showing that multi-protein panels are better than individual markers at the diagnostics. The data consistently observed in lung, breast and ovarian cancer are further evidence to suggest that a paradigm shift is needed. In addition, consensus about the repertory of exosomal proteins provides an opportunity to develop universal biomarkers for cancer.

Yet another common understanding is the crucial role of computational integration. It has been consistently shown that the machine-learning technology significantly improved predictive performance, particularly when applied on high-dimensional proteomic data.

However, controversies remain. But the most significant one pertains to reproducibility. Although some studies observe AUC > 0.90, others with similar proteomic strategies achieve lower accuracies that call into question the methodological robustness. The other contentious issue is whether the model can be used in an actual clinical setting. Advocates would claim that proteomic biomarkers are ripe for translational validation and detractors would highlight the lack of multi-center prospective trial as a key impediment. Finally, one can question regulatory readiness: some researchers believe that proteomics is ready for clinical chemistry practice with regards to maturity; others argue that (IM) precision and cost are still too high.

These controversies serve as examples for the necessity of harmonized workflow, and large collaborative studies to make progress from discovery to clinical implantation.

Future research, practice and policy implications

The literature provides important implications for research, practice and policy.

Summary: Future studies should give priority to uniformity of proteomic methods. Standardized procedures across samples treatment, MS calibration and data analysis are necessary for reproducibility. Urgent, multi-center trials with large and varied participant groups are required to validate putative biomarkers. In addition, computational models have to pass external validation for preventing over-fitting and maintaining clinical applicability.

Clinical Practice: Clinical chemistry laboratories are positioned at the crossroads of discovery and translation. Laboratories could operationalize these findings for early detection and screening by converting proteomic panels into standardized immunoassays and multiplex tests. Interfacing with conventional diagnostic modalities (imaging, genomic assays) can improve the accuracy of diagnosis in precision oncology.

Policy: Health policy frameworks need to evolve in response to the changing biomarker landscape. It is necessary for the regulatory agencies to establish clear paths of proteomic biomarker approval, as there are existing test regulations for genomic tests. Furthermore, health economics analyses will be required to show that proteomic diagnostics are cost-effective in both emerging and developing countries where cancer prevalence is high. Policy support for public-private partnership collaborations such as these can help encourage translational research and speed its adoption.

In summary, proteomics holds great promise for cancer diagnosis but its translation to the clinic will depend on the concerted activities between research, clinical and policy communities

Conclusion

Concise Summary of Main Points

In this systematic review of the evidence dated December 2024 through June, 2025 we report on proteomics-based biomarker discovery and its transition to clinical chemistry for diagnosis of cancer. The results show that in biomarker research, proteomics has evolved as a major driving force now providing novel strategies for early detection and disease monitoring. Multi-protein panels, especially those derived from exosomal protein panel, glycoprotein panel and autoantibody signature in the lung, breast, ovarian and hepatocellular cancers studies stood up under comparison to traditional single-analyte biomarker known for clinical application including CA-125and AFP.

Mass spectrometric techniques (LC-MS/MS, MALDI-TOF) were the workhorse of biomarker discovery, mediated through immunoassays into clinical validation. A common thread became visible in this regard was the symbiotic fusion of machine learning and proteomic data, leading to enhanced biomarker discovering capabilities and classification. Given the high dimensionality of proteomics data, this computational dimension is very useful.

Yet there are still obstacles. Methodological diversity in sample processing, proteomic platforms, and analysis remains a barrier to the

replicability. A small set of samples and locational-specific cohorts limit the generalizability. Only a small number of studies progressed from the discovery phase to clinical chemistry validation, so translation into practice remained one of the main hurdle. In addition, little is known about regulatory issues, cost-effectiveness and population diversity.

The trajectory, however has been a positive one, given these are preliminary performance results. The studies discussed show increasingly common recognition that proteomics promises to transform cancer diagnosis by allowing non-invasive, high-accuracy and multi-parameter panels of biomarkers. Operationalizing these discoveries is the function of clinical chemistry laboratories, transforming innova- tion in proteomics from bench to bedside. Incorporating proteomics in cancer diagnosis could lead to earlier detection, and benefits for patients regarding treatments and healthcare-system efficiency.

Overall Implications and Recommendations

The implications of this review are twofold: scientific and clinical.

Scientific 'next steps' will really focus on standardization of proteomic workflows and the broadening into multi-centre, multi-ethnic cohorts to improve reproducibility and generalizability. Computational models also must be vigorously externally validated prior to clinical use.

In terms of clinical application - the clinical chemistry laboratory needs to spearhead this translation by bringing proteomic biomarkers into routine, high-throughput assays. This calls for a tight nexus of (proteomics) researchers, chemists and clinicians to establish actual feasibility scalability and trustworthiness. Integrating these with available diagnostic frameworks (such as imaging and genomics) is another direction for comprehensive precision oncology approaches.

From a policy viewpoint, regulatory bodies should create transparent access routes for proteomic biomarkers. Health economic analyses are necessary to provide evidence of the cost-effective use of proteomics-based Diagnostics at population level, especially in low and middle-income countries. Investments in public-private partnerships and international consortia will be essential for expediting the validation and deployment of biomarkers.

In summary, now is the time to revolutionize cancer diagnosis with proteomics. By filling methodological voids, advancing translational pipelines and working within regulatory requirements, the field can reach its maximum potential for early detection and improved clinical outcome. Routine clinical chemistry in this new proteome era is not only a scientific achievement, but also a matter of public health.

Acknowledgments

The authors would like to thank all investigators and institutions involved in proteomics and clinical chemistry research, which contributed to the preparation of this review. The authors also wish to thank the members of those groups who discovered and validated new biomarker discovery platforms, as their work has set the stage for this synthesis.

Conflicts of Interest

The authors have no conflicts of interest. There are no financial or personal relations that resulted in writing of this systematic review.

Funding Information

Funding This study did not receive any specific grant from any funding agency in the public, commercial or non-profit sector. The work was performed by LTK as an exercise in the context of combining literature from proteomics and clinical chemistry

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