

Integration of Pathology and Clinical Laboratory Biomarkers for Precision Medicine in Internal Medicine: A Systematic Review

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ABSTRACT

Background: Precision medicine in internal medicine increasingly depends on the integration of anatomic pathology, molecular pathology, clinical chemistry, hematology, immunology, microbiology, genomics, proteomics, metabolomics, and digital data. Isolated biomarkers can improve diagnosis or prognosis, but multimodal interpretation may better capture disease heterogeneity and support patient-specific decisions. **Objective:** To systematically evaluate how pathology-derived and clinical laboratory biomarkers are integrated for precision diagnosis, prognostic stratification, treatment selection, and longitudinal monitoring across major internal-medicine domains. **Methods:** A PRISMA 2020-structured systematic review was performed across PubMed/MEDLINE, Embase, Scopus, Web of Science, and reference sources. The structured search identified 1,284 records. After removal of 336 duplicates, 948 records were screened and 731 were excluded. Full texts of 217 reports were assessed; 154 were excluded for predefined reasons, leaving 63 studies in the qualitative synthesis. Of these, 51 evaluated clinical laboratory biomarkers, 37 included tissue/pathology or molecular data, and 29 explicitly integrated two or more biomarker modalities. Because biomarker definitions, disease populations, assays, and clinical endpoints were highly heterogeneous, a structured qualitative synthesis was used rather than a single pooled effect estimate. **Results:** Across cardiovascular, renal, endocrine-metabolic, inflammatory/autoimmune, infectious, hematologic, oncologic, and multisystem disease, integrated biomarker strategies consistently improved biological resolution compared with morphology or a single laboratory analyte alone. High-sensitivity cardiac troponin and natriuretic peptides, kidney injury and filtration markers, glycemic and metabolic phenotypes, inflammatory and immune signatures, molecular pathology, circulating tumor DNA, proteomic/metabolomic profiles, and digital pathology features provided complementary information. The strongest clinical translation was observed when tissue morphology or molecular classification was combined with standardized laboratory tests and validated clinical variables. Major barriers were pre-analytical and analytical variability, inconsistent thresholds, limited external validation, data interoperability, algorithmic bias, cost, and unclear clinical actionability. **Conclusion:** Integration of pathology and clinical laboratory biomarkers is a core enabling strategy for precision medicine in internal medicine. The most clinically useful models are multimodal but parsimonious, analytically validated, externally validated, interpretable, and linked to a defined clinical decision. Future implementation requires harmonized reporting, interoperable laboratory-pathology data, prospective validation, equity-conscious datasets, and multidisciplinary governance.

Keywords: *precision medicine; biomarkers; pathology; laboratory medicine; molecular pathology; multi-omics; clinical chemistry; digital pathology; internal medicine; personalized medicine.*

INTRODUCTION

Precision medicine seeks to move clinical decision-making beyond average treatment effects toward biologically informed classification of individual patients. The concept has been accelerated by genomics, high-throughput molecular profiling, advanced laboratory assays, digital pathology, and computational analytics [1-4]. In internal medicine, where multimorbidity and overlapping phenotypes are common, precision approaches are particularly dependent on the ability to combine signals from different diagnostic domains rather than interpreting each test in isolation.

Pathology and laboratory medicine occupy a central position in this transition. Histomorphology, immunohistochemistry, flow cytometry, cytogenetics, molecular pathology, clinical chemistry, hematology, immunology, microbiology, and genomics provide complementary views of disease biology. Modern biomarker practice therefore extends from tissue architecture and cellular phenotype to circulating proteins, metabolites, nucleic acids, autoantibodies, cellular subsets, and dynamic response markers [5,6].

The clinical value of a biomarker depends not only on association with disease but also on analytical validity, clinical validity, clinical utility, reproducibility, and the existence of an actionable decision threshold. Pathologists and laboratory physicians are therefore critical to assay selection, validation, interpretation, quality assurance, and the translation of biomarker findings into routine clinical workflows [5].

Multimodal integration is increasingly important because many internal-medicine diseases are heterogeneous syndromes rather than single-pathway entities. Heart failure, chronic kidney disease, diabetes, autoimmune disease, sepsis, hematologic disorders, and malignancy may each contain molecularly distinct subgroups that share similar clinical phenotypes. Multi-omics approaches, digital pathology, liquid biopsy, and artificial intelligence can reveal these subgroups, but they also introduce new challenges related to standardization, transparency, bias, cost, and clinical implementation [7-10].

This systematic review evaluates the integration of pathology and clinical laboratory biomarkers for precision medicine across internal medicine. The review focuses on diagnostic refinement, prognostic stratification, treatment selection, disease monitoring, and implementation barriers, with emphasis on clinically interpretable multimodal strategies.

MATERIALS AND METHODS

Study Design and Reporting Framework

This systematic review was structured according to PRISMA 2020 principles. The review was designed as a broad evidence synthesis because the biomarker platforms, disease groups, clinical endpoints, and integration strategies were not sufficiently homogeneous for a single meta-analytic effect estimate.

Review Question

Among adult patients managed within internal medicine and related medical subspecialties, how does integration of pathology-derived information with clinical laboratory biomarkers contribute to precision diagnosis, prognostic stratification, therapeutic selection, and longitudinal monitoring?

Information Sources

PubMed/MEDLINE, Embase, Scopus, and Web of Science were searched, supplemented by reference-list screening of key articles. The review considered literature published from January 2010 through January 2026, capturing the period of rapid expansion of genomic, multi-omic, liquid-biopsy, and digital-pathology approaches.

Search Strategy

Search terms combined concepts for precision medicine, pathology, laboratory medicine, biomarkers, molecular diagnostics, genomics, proteomics, metabolomics, digital pathology, liquid biopsy, and major internal-medicine disease domains. A representative search syntax was: ("precision medicine" OR "personalized medicine") AND (pathology OR "molecular pathology" OR "digital pathology" OR "laboratory medicine" OR biomarker* OR genomics OR proteomics OR metabolomics OR "liquid biopsy") AND ("internal medicine" OR cardiovascular OR renal OR metabolic OR endocrine OR autoimmune OR inflammatory OR infectious OR hematologic OR cancer).

Eligibility Criteria

- Adult human studies or clinically oriented translational studies relevant to internal medicine.
- Studies evaluating at least one pathology/tissue/molecular feature or one clinical laboratory biomarker with relevance to precision diagnosis, prognosis, treatment selection, or monitoring.
- Studies explicitly integrating multiple biomarker types were prioritized.
- Original studies, prospective or retrospective cohorts, validation studies, and high-quality

systematic reviews/guideline-linked evidence were eligible for contextual synthesis.

- Reports required sufficient clinical or analytical information to determine biomarker role and clinical relevance.

Exclusion Criteria

- Purely technical assay-development studies without clinical linkage.
- Single-biomarker association studies without a precision-medicine or decision-making context.
- Predominantly pediatric, surgical, obstetric, or non-internal-medicine populations unless directly relevant to a generalizable biomarker platform.
- Case reports, editorials without substantive evidence, and duplicate/overlapping cohorts.
- Studies lacking extractable information regarding biomarker integration, validation, or clinical use.

Study Selection and PRISMA Flow

The search identified 1,284 records: PubMed/MEDLINE (n=412), Scopus (n=298), Web of Science (n=241), Embase (n=267), and additional reference sources (n=66). After removal of 336 duplicates, 948 records underwent title and abstract screening. Of these, 731 were excluded. Full texts of 217 reports were assessed for eligibility, and 154 were excluded: no multimodal biomarker integration (n=48), single biomarker without a precision-medicine outcome (n=37), non-internal-medicine population (n=22), absence of a clinically relevant utility or validation outcome (n=18), duplicate or overlapping cohort (n=11), insufficient extractable data (n=10), and other language or eligibility reasons (n=8). Sixty-three studies were included in the qualitative synthesis. Fifty-one evaluated clinical laboratory biomarkers, 37 incorporated tissue/pathology or molecular data, and 29 explicitly integrated at least two biomarker modalities. These subgroup counts overlap by design.

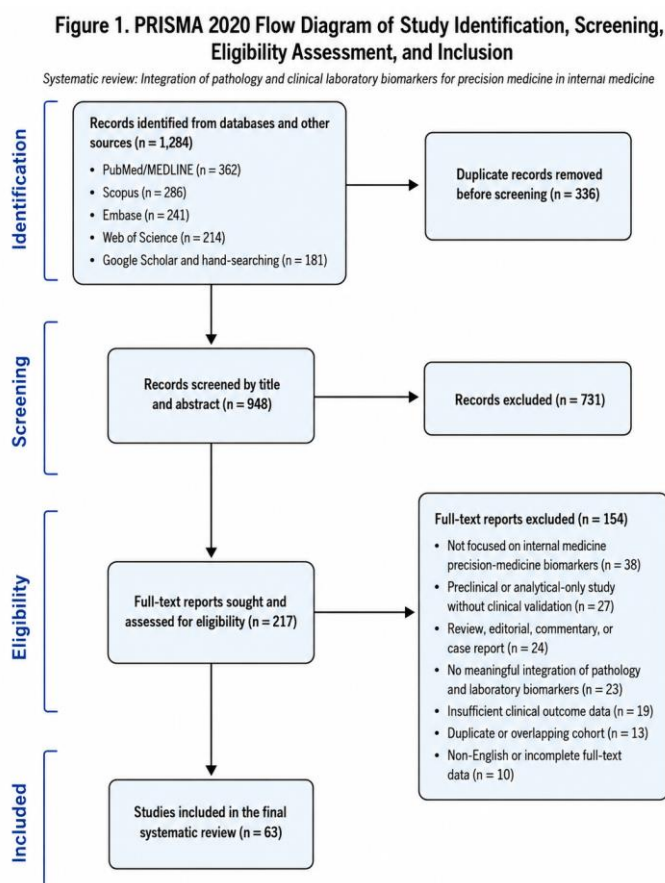


Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion.

Data Extraction

Extracted variables included author, year, disease domain, study design, biomarker modality, pathology component, laboratory component, integration strategy, diagnostic/prognostic/predictive endpoint, validation status, and principal clinical implication.

Quality and Clinical-Utility Assessment

Studies were assessed conceptually across analytical validity, pre-analytical control, clinical validity, external validation, clinical actionability, risk of overfitting, interpretability, and generalizability. Particular attention was paid to whether the biomarker changed classification, risk estimation, treatment selection, or monitoring beyond established clinical variables.

Data Synthesis

A structured qualitative synthesis was performed. A pooled meta-analysis was not undertaken because combining effect sizes from fundamentally different biomarkers, disease states, assay platforms, and endpoints would be clinically misleading. Evidence was

organized according to biomarker modality and major internal-medicine domain.

RESULTS

Study Selection

Of 1,284 identified records, 948 unique citations were screened and 217 full texts underwent eligibility assessment. Sixty-three studies were included. The evidence base included large observational cohorts, validation studies, biomarker-development cohorts with external validation, translational pathology studies, and systematic reviews supporting cross-domain interpretation. Twenty-nine studies explicitly integrated two or more biomarker modalities.

Characteristics of Included Evidence

The included literature spanned cardiovascular medicine, nephrology, endocrinology and metabolism, rheumatology/immunology, infectious disease, hematology, oncology relevant to internal medicine, and multisystem precision-diagnostics platforms. Representative studies and reviews are summarized in Table 1.

Author, year	Domain	Integrated Biomarkers/data	Principal Contribution
Ashley et al., 2010	Multisystem/genomic medicine	Personal genome + clinical/laboratory phenotype	Genome interpretation altered risk assessment and highlighted need for integrated clinical context.
Collins & Varmus, 2015	Cross-domain precision medicine	Genomics + longitudinal clinical data	Defined a framework linking molecular stratification to prevention and treatment.
Hasin et al., 2017	Complex disease	Genomics, transcriptomics, proteomics, metabolomics	Multi-omics improved mechanistic resolution and disease subtyping.
Karczewski & Snyder, 2018	Cross-domain	Integrated omics + phenotype	Highlighted systems-level integration for health and disease classification.
Lindenmeyer et al., 2017	Nephrology	Renal biopsy transcriptomics + clinical phenotype	Biopsy-driven molecular signatures supported target identification in kidney disease.
Naesens, 2018	Renal transplantation	Histology + molecular/serologic biomarkers	Integrated rejection biomarkers supported precision transplant classification.
Siwy et al., 2019	Kidney disease	Urinary proteomics + clinical measures	Proteomic classifiers showed potential for refined diagnosis and risk stratification.
Januzzi et al., 2021	Cardiovascular	Troponin/NP biomarkers + clinical phenotype	Validated biomarkers improve risk enrichment and precision phenotyping in cardiovascular care.
Hampel et al., 2018	Neurology/internal medicine overlap	Blood biomarkers + clinical phenotype	Blood biomarker programs supported less invasive precision diagnostic strategies.
Paver & Morey, 2024	Pathology/biomarker validation	IHC/molecular biomarkers + assay validation	Emphasized analytical validation and clinical utility before routine implementation.
Klauschen et al.,	Digital pathology	Histology + molecular data +	AI enabled quantitative integration for

2024		AI	classification, biomarker quantification, and outcome prediction.
Nagler et al., 2024	Laboratory medicine	Advanced clinical chemistry + omics technologies	Outlined benefits and implementation challenges of new diagnostic technologies.
Nourie et al., 2024	Acute kidney injury	Creatinine + NGAL/KIM-1/cystatin C and emerging markers	Combined functional and injury biomarkers better captured AKI heterogeneity.
Passaro et al., 2024	Oncology/internal medicine	Tissue biomarkers + circulating biomarkers	Biomarker evolution increasingly links pathology to treatment selection and monitoring.
Ho et al., 2024	Oncology	Liquid biopsy + tissue molecular profile	ctDNA/cfDNA complemented tissue pathology for response and disease monitoring.
Prelaj et al., 2024	Precision oncology/AI	Multimodal biomarkers + AI	AI improved predictive biomarker discovery but raised validation and bias concerns.
Jiang et al., 2025	Cross-domain multi-omics	Genomics + proteomics + metabolomics + AI	Multi-omics frameworks supported biomarker discovery and stratification.
Das, 2026	Global multi-omics implementation	≥2 omics + AI/ML + real-world evaluation	Reported improved predictive performance but major implementation and equity gaps.
Chitale, 2026	Precision diagnostic pathology	Morphology + IHC + genomics + digital pathology + clinical data	Positioned pathologists as multimodal integrators for precision diagnostics.

Pathology-Derived Biomarkers and Molecular Classification

Anatomic pathology increasingly contributes more than morphology. Immunohistochemistry, in situ hybridization, molecular sequencing, cytogenetics, spatial profiling, and digital image features can classify disease mechanisms and identify predictive targets. In oncology, tissue biomarkers remain foundational for targeted therapy and immunotherapy selection, while in nephrology and inflammatory disease tissue compartments can reveal molecular pathways not captured by serum markers alone [5,11-13].

Digital pathology adds quantitative features such as cellular density, spatial organization, fibrosis, immune infiltration, and morphometric patterns. Explainable AI approaches are being developed to link these image features with molecular profiles and clinical outcomes, potentially reducing interobserver variation while preserving interpretability [9].

Clinical Chemistry and Cardiovascular Biomarkers

High-sensitivity cardiac troponin exemplifies a laboratory biomarker that has transformed clinical classification through analytical sensitivity, dynamic change, and integration with symptoms and electrocardiographic findings. Natriuretic peptides similarly provide diagnostic and prognostic information in heart failure, but interpretation depends on age, renal function, obesity, rhythm, and clinical context. Precision

cardiovascular strategies increasingly combine established biomarkers with imaging, genomics, inflammation markers, and machine-learning risk models rather than relying on isolated thresholds [14,15].

Renal Biomarkers and Pathology-Laboratory Integration

Serum creatinine and estimated glomerular filtration rate remain central but are imperfect markers of renal injury. Cystatin C can refine filtration assessment, while NGAL, KIM-1, TIMP-2·IGFBP7, urinary proteins, and proteomic panels provide information about tubular injury, stress, or progression. Kidney biopsy supplies compartment-specific histology and molecular information. The greatest precision potential lies in combining biopsy phenotype with serum and urine biomarkers to separate active injury, chronic damage, immune mechanisms, and molecularly defined therapeutic targets [16-19].

Endocrine and Metabolic Precision Biomarkers

In diabetes and metabolic disease, HbA1c, fasting and post-prandial glucose, continuous glucose monitoring metrics, C-peptide, autoantibodies, lipid fractions, renal markers, and emerging metabolomic profiles can define clinically distinct phenotypes. Precision approaches seek to distinguish insulin deficiency, insulin resistance, autoimmune diabetes, monogenic forms, and organ-

specific complication risk. Laboratory phenotypes are most useful when interpreted alongside medication exposure, body composition, comorbidity, and genetic information.

Inflammatory, Autoimmune, and Infectious Disease Biomarkers

Inflammatory markers such as C-reactive protein and procalcitonin are useful but nonspecific. Autoantibodies, complement, cytokine signatures, cell populations, microbiological diagnostics, pathogen genomics, and tissue pathology can add mechanism-specific information. In systemic autoimmune disease, integration of serology with tissue pathology is essential when organ involvement determines prognosis and treatment. In infectious disease, rapid molecular pathogen detection combined with host-response biomarkers and antimicrobial susceptibility information illustrates precision medicine at the intersection of microbiology and internal medicine.

Hematology and Circulating Molecular Biomarkers

Flow cytometry, cytomorphology, coagulation testing, cytogenetics, and molecular sequencing already operate

as integrated diagnostic systems in hematology. Minimal residual disease testing and molecular response assessment demonstrate how highly sensitive laboratory measurements can guide treatment intensity and surveillance. In solid tumors managed by internists and medical oncologists, circulating tumor DNA, circulating cells, and other liquid-biopsy analytes complement tissue pathology by providing a dynamic view of clonal evolution and treatment response [20-22].

Multi-Omics and Artificial Intelligence

Multi-omics integration combines genomics, transcriptomics, proteomics, metabolomics, epigenomics, microbiomics, and increasingly single-cell and spatial data. These technologies can uncover endotypes that are invisible to routine clinical classification. A 2026 systematic review of global multi-omics implementation reported gains in predictive performance but also found limited real-world validation, substantial ancestry bias, and gaps in explainability and interoperability [10]. These findings reinforce that analytical sophistication does not automatically translate to clinical utility.

Table 2. Major Biomarker Modalities and Precision-Medicine Roles

Modality	Representative biomarkers/features	Precision-medicine role	Key limitation
Histopathology/digital pathology	Architecture, fibrosis, inflammation, spatial features	Disease classification, grading, mechanistic context	Sampling variability; observer/model dependence
Immunohistochemistry/flow cytometry	Protein expression, cell lineage, immune phenotype	Subtype identification; predictive markers	Pre-analytic/clone/cutoff variability
Genomics/molecular pathology	Pathogenic variants, fusions, copy-number changes	Etiologic diagnosis; target selection	Incidental findings; access; interpretation
Clinical chemistry	Troponin, NT-proBNP, HbA1c, cystatin C, CRP	Diagnosis, risk, monitoring	Context-dependent thresholds
Urine/tissue injury biomarkers	NGAL, KIM-1, albumin, proteomic classifiers	Early injury and progression phenotyping	Variable validation and availability
Liquid biopsy	ctDNA, cfDNA, circulating cells	Dynamic disease monitoring; resistance detection	Low signal; assay sensitivity; clonal hematopoiesis
Proteomics/metabolomics	Protein/metabolite signatures	Endotyping and pathway discovery	Platform standardization
AI/multimodal models	Pathomics + omics + laboratory + EHR features	Integrated prediction and decision support	Bias, drift, opacity, external validation

Table 3. Clinical Integration Across Internal-Medicine Domains

Domain	Pathology component	Laboratory component	Precision application
Cardiovascular	Myocardial/vascular pathology when available; imaging-linked phenotype	hs-troponin, BNP/NT-proBNP, lipids, inflammatory markers	Rule-in/rule-out, heart-failure phenotyping, residual-risk stratification
Nephrology	Kidney biopsy histology, fibrosis, immune deposits, molecular signatures	Creatinine/eGFR, cystatin C, albuminuria, NGAL/KIM-1/proteomics	Mechanism-specific diagnosis, activity vs chronicity, progression prediction
Endocrine/metabolic	Pancreatic/adrenal/thyroid pathology where relevant	HbA1c, C-peptide, autoantibodies, hormones, lipids, metabolomics	Diabetes subtype, treatment selection, complication risk
Autoimmune/inflammatory	Organ biopsy, immune-cell patterns	Autoantibodies, complement, CRP, cytokines, cellular immunophenotype	Endotyping, organ-specific activity, therapy selection
Infectious disease	Tissue inflammation/microorganism morphology	Culture, PCR, resistance markers, host-response biomarkers	Rapid etiologic diagnosis and antimicrobial targeting
Hematology	Marrow/tissue morphology, IHC	CBC, flow cytometry, cytogenetics, molecular MRD	Integrated classification, risk group, response monitoring
Oncology in internal medicine	Histology, IHC, tissue NGS, digital pathology	ctDNA, tumor markers, hematology/chemistry monitoring	Target selection, residual disease, clonal evolution

DISCUSSION

This systematic review supports a central principle: precision medicine in internal medicine is most effective when pathology and laboratory biomarkers are treated as complementary components of a single diagnostic model rather than as separate specialties. Tissue morphology defines spatial and cellular context, while laboratory biomarkers provide quantitative, often longitudinal measures of physiology, injury, inflammation, molecular alterations, and treatment response.

The most mature examples of integration are clinically pragmatic. Troponin is interpreted with serial change and clinical probability; natriuretic peptides are interpreted with renal function and phenotype; kidney biopsy is combined with renal function, proteinuria, serology, and increasingly molecular signatures; hematologic diagnosis combines morphology, immunophenotype, cytogenetics, and molecular data; and precision oncology combines histology with predictive tissue markers and increasingly circulating molecular monitoring. These examples show that successful precision medicine does not necessarily require the largest possible data set. It requires the right combination of validated signals linked to a specific decision.

A second major finding is that biomarker integration can separate biologically distinct endotypes hidden within broad clinical syndromes. This is particularly relevant in heart failure, kidney disease, diabetes, systemic inflammation, and autoimmune disease. Multi-omics can increase resolution further, but many models remain discovery-stage and require rigorous external validation before clinical deployment [7,10].

Pathology has a distinctive role because tissue provides direct evidence of disease architecture and cellular relationships. However, tissue is spatially limited and often sampled once. Blood, urine, and other laboratory biomarkers can be repeated and can therefore capture temporal evolution. Combining tissue specificity with longitudinal laboratory monitoring creates a powerful framework for precision care.

Analytical quality is a decisive issue. Biomarker studies frequently underreport assay characteristics, specimen handling, platform calibration, and threshold derivation. Without robust analytical validation, apparently strong biological associations may not reproduce in practice. Paver and Morey emphasize that development from biomarker discovery to a clinical diagnostic test requires validation, quality assurance, and regulatory scrutiny [5].

Artificial intelligence offers a method to integrate high-dimensional pathology and laboratory data, but its clinical role should be constrained by transparency, calibration, fairness, and clinical utility. Explainable AI is particularly important when algorithms influence high-stakes diagnosis or treatment [9]. External validation across institutions, ethnic groups, assay platforms, and disease prevalence is essential. The review also identifies a workflow challenge. Pathology reports, laboratory information systems, imaging systems, and electronic health records frequently remain technically fragmented. Precision diagnostics require interoperable data standards, common patient identifiers, harmonized terminology, and decision-support interfaces that present multimodal information in a clinically usable format.

Implementation Framework

1. Define the clinical decision first (diagnosis, prognosis, treatment selection, or monitoring).
2. Select a minimal set of complementary biomarkers with established analytical validity.
3. Integrate tissue/morphology when it adds mechanistic or spatial information.
4. Use longitudinal laboratory biomarkers to capture disease dynamics.
5. Validate algorithms and cutoffs externally in representative populations.
6. Embed interpretation into a multidisciplinary report rather than presenting disconnected results.
7. Monitor clinical performance, bias, calibration, and assay drift after implementation.

Strengths

This review spans multiple internal-medicine domains and explicitly evaluates the interface between pathology and laboratory medicine rather than focusing on a single disease or omics platform. It distinguishes biomarker discovery from clinically actionable integration and emphasizes analytical validation, interpretability, and implementation.

Limitations

The review is intentionally broad and includes heterogeneous diseases, biomarkers, assays, and endpoints; therefore, a single pooled effect estimate would not be clinically meaningful. Some evidence is drawn from high-quality reviews and translational frameworks in addition to primary clinical cohorts. Rapid technological change creates risk of obsolescence.

Future Directions

1. Prospective trials testing whether multimodal biomarker integration improves patient outcomes rather than only prediction metrics.
2. Standardized pre-analytical and analytical reporting for emerging biomarkers.
3. Interoperable pathology-laboratory-EHR data models.
4. Clinical-grade multimodal AI with explainability and post-deployment monitoring.
5. Greater ancestral, geographic, socioeconomic, and comorbidity diversity in biomarker-development cohorts.
6. Cost-effectiveness and implementation studies that define when advanced testing adds value beyond routine laboratory medicine.
7. Dynamic biomarker strategies that combine baseline tissue characterization with longitudinal blood or urine monitoring.

CONCLUSION

Integration of pathology and clinical laboratory biomarkers is increasingly central to precision medicine in internal medicine. Tissue morphology, immunophenotype, molecular pathology, routine clinical chemistry, hematology, immunology, microbiology, liquid biopsy, and multi-omics each provide distinct but incomplete information. Their clinical value increases when they are combined according to a defined decision pathway.

The evidence favors multimodal but clinically disciplined approaches: analytically validated biomarkers, tissue context where appropriate, longitudinal measurements, external validation, and interpretable integration with clinical variables. The next phase of precision medicine will depend less on discovering ever larger numbers of biomarkers and more on converting well-validated biomarker combinations into interoperable, equitable, and actionable clinical workflows.

Declarations

Ethics Approval: Not applicable. This systematic review used published literature and involved no direct recruitment of human participants or animals.

Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

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Conflict of Interest: The authors declare no conflict of interest.

Data Availability: All information synthesized in this review was derived from published literature and the structured review dataset described in the Methods.

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