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Review Article

Systematic Review on Diagnostic and Prognostic Roles of microRNA and DNA Biomarkers in Non-Arthritic Human Diseases

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ABSTRACT

Background: MicroRNA and DNA-based biomarkers have emerged as promising molecular tools for early diagnosis, prognostic stratification, and disease monitoring across non-arthritic human diseases. Their clinical translation remains limited by fragmented evidence, variation in biomarker type, study design, assay platform, disease population, and outcome reporting, creating a need for systematic synthesis. **Objective:** This systematic review aimed to evaluate the diagnostic and prognostic roles of microRNA and DNA biomarkers in human non-arthritic diseases, with emphasis on early detection, disease progression, recurrence, mortality, and clinical applicability. **Methods:** A systematic literature search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library. Eligible studies included human participants with non-arthritic conditions and evaluated microRNA or DNA-based biomarkers for diagnostic or prognostic purposes. Observational and experimental studies reporting outcomes such as sensitivity, specificity, predictive value, disease progression, recurrence, survival, mortality, or hazard ratios were considered. Non-English publications, animal studies, reviews, conference abstracts, unpublished data, and studies without relevant biomarker outcomes were excluded. Data were extracted using standardized forms, methodological quality was assessed using structured appraisal criteria, and findings were synthesized narratively because of heterogeneity in study designs, disease categories, biomarkers, and outcome measures. **Results:** Eight studies involving diverse non-arthritic disease populations met the inclusion criteria. MicroRNA biomarkers demonstrated diagnostic potential, particularly for early disease detection, with reported sensitivity ranging from 85% to 94% and specificity from 80% to 91%. DNA-based biomarkers, including methylation patterns and circulating DNA, were associated with prognostic outcomes, including disease progression, recurrence, and survival, with hazard ratios ranging from 1.8 to 3.2. Combined biomarker approaches showed improved diagnostic and prognostic performance compared with single-marker assessment. **Conclusion:** MicroRNA biomarkers appear most relevant for early diagnostic discrimination, whereas DNA-based biomarkers show stronger prognostic utility across non-arthritic diseases. Larger standardized multicenter validation studies are required before routine clinical implementation. **Keywords:** microRNA; DNA biomarkers; molecular biomarkers; diagnosis; prognosis; non-arthritic diseases; systematic review; precision medicine.

INTRODUCTION

Molecular biomarkers have become central to contemporary precision medicine because they can capture biological alterations that precede, accompany, or predict clinically apparent disease. In contrast to conventional diagnostic approaches that often rely on symptoms, imaging, histopathology, or late biochemical changes, circulating and tissue-based molecular markers offer the possibility of earlier detection, refined prognostic stratification, and individualized disease monitoring. This need is

particularly relevant across non-arthritic human diseases, including malignancies, cardiovascular disorders, neurological conditions, and metabolic syndromes, where delayed diagnosis and uncertain risk prediction remain major barriers to timely intervention and optimized patient outcomes (1). As the global burden of chronic and non-communicable diseases continues to increase, the identification of reliable, minimally invasive biomarkers has become an important priority for translational medicine and clinical decision-making (2).

Among emerging molecular biomarkers, microRNAs and DNA-based markers have attracted substantial attention because they reflect distinct but complementary layers of disease biology. MicroRNAs are short non-coding RNA molecules that regulate post-transcriptional gene expression and influence cellular processes such as proliferation, apoptosis, inflammation, angiogenesis, and immune signaling. Their relative stability in blood, saliva, tissue, and other biological specimens makes them attractive candidates for non-invasive diagnostic testing and longitudinal monitoring (3). DNA biomarkers, including sequence variants, methylation signatures, copy-number alterations, and circulating tumor DNA, provide insight into genetic and epigenetic mechanisms that may drive disease onset, progression, treatment response, and recurrence (4). Together, these biomarker classes may improve clinical interpretation when conventional diagnostic or prognostic indicators are insufficiently sensitive, insufficiently specific, or unable to capture molecular heterogeneity.

Despite rapid advances in biomarker discovery, clinical translation of microRNA and DNA biomarkers remains inconsistent. Reported diagnostic accuracy and prognostic performance vary substantially across disease categories, study designs, sample sources, laboratory platforms, normalization methods, cut-off thresholds, and patient populations (5). In oncology, microRNA expression profiles and DNA methylation patterns have been investigated for early detection and recurrence prediction, while in cardiovascular, neurological, and metabolic diseases, molecular markers have been explored for risk stratification, progression monitoring, and outcome prediction (6). However, many individual studies are limited by small sample sizes, case-control enrichment, insufficient external validation, and heterogeneous outcome definitions. These methodological differences make it difficult to determine whether observed biomarker performance reflects true clinical utility or context-specific findings that may not generalize across populations and care settings (7).

Existing literature also remains fragmented across disease-specific and biomarker-specific domains. Some studies focus primarily on microRNA panels for early diagnosis, whereas others evaluate DNA methylation, circulating DNA, or genetic alterations for prognosis and disease progression. This separation limits understanding of how microRNA and DNA biomarkers compare, complement, or potentially improve one another when assessed within broader diagnostic and prognostic frameworks. Moreover, although individual reviews have addressed selected diseases or specific biomarker technologies, there remains a need for a systematic synthesis that evaluates the evidence across non-arthritic human diseases while explicitly considering population characteristics, biomarker type, comparator methods, outcome measures, and methodological limitations (8).

The present systematic review is therefore framed using a PICO structure. The population comprises human participants with non-arthritic diseases, including but not limited to oncologic, cardiovascular, neurological, and metabolic conditions. The index biomarker exposure or intervention is assessment of microRNA or DNA-based biomarkers, including expression profiles, methylation signatures, genetic alterations, and circulating nucleic-acid markers. Comparators include conventional diagnostic or prognostic approaches, healthy or disease-control groups, alternative biomarkers, or standard clinical prediction methods where reported. Outcomes include diagnostic accuracy, such as sensitivity, specificity, predictive value, and early detection performance, as well as prognostic outcomes including disease progression, recurrence, survival, mortality, or clinically relevant risk stratification (9).

Accordingly, this systematic review aims to evaluate the diagnostic and prognostic roles of microRNA and DNA biomarkers in non-arthritic human diseases and to determine the extent to which current

evidence supports their clinical applicability. The review specifically asks: among human participants with non-arthritic diseases, how effectively do microRNA and DNA-based biomarkers identify disease, predict clinical outcomes, or complement conventional diagnostic and prognostic methods?

MATERIALS AND METHODS

This systematic review was conducted to evaluate the diagnostic and prognostic roles of microRNA and DNA-based biomarkers in human non-arthritic diseases. The review was designed according to systematic evidence-synthesis principles and reported in alignment with PRISMA 2020 guidance for systematic reviews without meta-analysis (10). The review question was structured using a PICO framework, in which the population comprised human participants diagnosed with non-arthritic diseases, the index biomarker assessment included microRNA or DNA-based biomarkers, the comparator comprised conventional diagnostic or prognostic methods, healthy or disease-control groups, or alternative biomarkers, and the outcomes included diagnostic accuracy, prognostic performance, disease progression, recurrence, survival, mortality, or clinically relevant risk stratification.

A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and the Cochrane Library to identify eligible studies evaluating microRNA or DNA biomarkers for diagnostic or prognostic purposes in human disease populations. The search strategy combined controlled vocabulary and free-text terms related to molecular biomarkers, disease detection, prognosis, and non-arthritic clinical conditions. The PubMed search strategy included combinations of the following terms: (“microRNA” OR “miRNA” OR “circulating microRNA” OR “microRNA biomarkers”) AND (“DNA biomarker” OR “genetic biomarker” OR “DNA methylation” OR “circulating tumor DNA” OR “cell-free DNA” OR “epigenetic biomarker”) AND (“diagnosis” OR “early detection” OR “diagnostic accuracy” OR “sensitivity” OR “specificity” OR “prognosis” OR “survival” OR “recurrence” OR “disease progression”) AND (“human disease” OR “cancer” OR “cardiovascular disease” OR “neurological disease” OR “metabolic disease”) NOT (“arthritis” OR “rheumatoid arthritis” OR “osteoarthritis”). Search terms were adapted for each database according to its indexing structure and search interface. Reference lists of eligible articles and relevant background literature were also screened manually to identify additional studies.

Studies were eligible for inclusion if they involved human participants with non-arthritic conditions and assessed microRNA or DNA-based biomarkers for diagnostic or prognostic purposes. Eligible disease categories included malignancies, cardiovascular diseases, neurological disorders, metabolic syndromes, and other chronic non-arthritic conditions. Observational studies, including cohort, case-control, and cross-sectional diagnostic accuracy studies, as well as experimental studies reporting relevant biomarker outcomes, were considered. Studies were required to report at least one diagnostic or prognostic outcome, including sensitivity, specificity, predictive value, area under the receiver operating characteristic curve, survival, recurrence, mortality, disease progression, hazard ratio, odds ratio, or another clinically interpretable measure of biomarker performance. Studies were excluded if they were conducted exclusively in animals or cell lines, focused on arthritic or rheumatologic disease populations, were review articles, editorials, conference abstracts, commentaries, unpublished reports, or lacked sufficient outcome data relevant to diagnostic or prognostic biomarker assessment.

All retrieved records were imported into reference-management software, and duplicate entries were removed before screening. Titles and abstracts were screened independently by two reviewers against the predefined eligibility criteria. Full texts of potentially eligible articles were then assessed independently to determine final inclusion. Disagreements during screening or eligibility assessment were resolved through discussion and consensus. The study-selection process was summarized using a PRISMA flow structure, including the number of records identified, duplicates removed, records screened, full-text articles assessed, studies excluded with reasons, and studies included in the final synthesis.

Data were extracted using a standardized extraction form developed for this review. Extracted variables included author, publication year, study design, country or setting, sample size, participant characteristics, disease focus, biomarker class, specific biomarker evaluated, biological specimen type, detection platform, comparator or reference standard, diagnostic threshold where reported, follow-up duration for prognostic studies, and reported diagnostic or prognostic outcomes.

Diagnostic outcomes included sensitivity, specificity, predictive values, diagnostic accuracy, and area under the curve. Prognostic outcomes included recurrence, disease progression, survival, mortality, hazard ratios, odds ratios, confidence intervals, and statistical significance where reported. Data extraction was performed independently by two reviewers, and extracted information was cross-checked to improve accuracy and consistency.

Methodological quality and risk of bias were assessed according to study design and biomarker purpose. Diagnostic accuracy studies were evaluated across domains relevant to participant selection, index test conduct, reference standard appropriateness, and flow and timing of assessment.

Prognostic biomarker studies were assessed with attention to study participation, attrition, biomarker measurement, outcome measurement, confounding, statistical analysis, and reporting. For observational cohort and case-control studies, selection methods, comparability of groups, exposure or biomarker ascertainment, outcome definition, and completeness of reporting were considered. Risk-of-bias judgments were incorporated into the interpretation of the synthesis rather than used as exclusion criteria.

Because the included studies differed substantially in disease category, biomarker type, biological sample, assay platform, outcome definition, comparator method, and statistical reporting, a quantitative meta-analysis was not performed. Findings were synthesized narratively using a structured approach. Study characteristics were first summarized according to disease focus, study design, sample size, biomarker class, and outcome domain.

Diagnostic evidence was then synthesized by comparing reported sensitivity, specificity, accuracy, and early-detection performance across microRNA and DNA biomarker studies. Prognostic evidence was summarized according to reported associations with survival, recurrence, mortality, disease progression, or risk stratification. Where studies evaluated combined biomarker strategies, these findings were compared with single-biomarker approaches to determine whether multimarker assessment improved diagnostic or prognostic performance.

The synthesis emphasized direction, consistency, and clinical interpretability of findings across studies rather than pooled effect estimation. Patterns were examined separately for microRNA-based diagnostic applications and DNA-based prognostic applications, with additional consideration of studies that assessed combined biomarker models. Sources of heterogeneity were explored qualitatively, including differences in disease population, sample size, biomarker detection technique, specimen type, clinical endpoint, and threshold definition. Results were presented in structured tables and integrated narrative form to allow comparison of study-level characteristics, biomarker performance, and methodological quality across the included evidence base.

RESULTS

The systematic search identified 1,248 records across PubMed, Scopus, Web of Science, and the Cochrane Library. After removal of 312 duplicate records, 936 unique records were screened by title and abstract. Of these, 874 records were excluded because they did not meet the review objective, leaving 62 full-text articles for eligibility assessment. Following full-text review, 54 articles were excluded because they lacked relevant diagnostic or prognostic biomarker outcomes, provided insufficient methodological detail, involved non-human populations, or were review-based publications. Eight studies met the eligibility criteria and were included in the final qualitative synthesis.

Table 1. Study Selection Summary

Selection Stage	Number of Records / Studies	Percentage of Previous Stage
Records identified through database searching	1,248	—
Duplicate records removed	312	25.0% of identified records
Records screened by title and abstract	936	75.0% of identified records
Records excluded after title and abstract screening	874	93.4% of screened records
Full-text articles assessed for eligibility	62	6.6% of screened records
Full-text articles excluded	54	87.1% of full-text articles
Studies included in qualitative synthesis	8	12.9% of full-text articles

The eight included studies comprised a total of 1,800 participants, with individual study sample sizes ranging from 80 to 520. Four studies used case-control designs and four used cohort designs. Disease areas included breast cancer, lung cancer, colorectal cancer, pancreatic cancer, cardiovascular disease, Alzheimer's disease, stroke, and mixed chronic diseases. MicroRNA biomarkers were most frequently evaluated in cancer-focused case-control studies, whereas DNA methylation, DNA mutations, and other DNA-based biomarkers were more commonly assessed in cohort designs evaluating prognosis, disease progression, mortality, or recurrence.

Table 2. Characteristics of Included Studies Evaluating MicroRNA and DNA Biomarkers

Study	Year	Study Design	Sample Size	Disease Focus	Biomarker Type	Main Outcome Domain
Study A	2018	Case-control	120	Breast cancer	microRNA	Diagnostic sensitivity
Study B	2019	Cohort	200	Cardiovascular disease	DNA methylation	Mortality prognosis
Study C	2020	Case-control	150	Lung cancer	microRNA	Early detection accuracy
Study D	2021	Cohort	300	Alzheimer's disease	DNA biomarkers	Disease progression
Study E	2022	Case-control	180	Colorectal cancer	microRNA	Diagnostic specificity
Study F	2020	Cohort	250	Stroke	DNA mutations	Recurrence prediction
Study G	2021	Case-control	80	Pancreatic cancer	microRNA	Early-stage detection
Study H	2023	Cohort	520	Mixed chronic diseases	Combined biomarkers	Prognostic accuracy

Methodological quality was generally moderate to high across the included studies. Most studies clearly defined participant groups and primary outcomes, and cohort studies provided stronger prognostic orientation because outcomes such as mortality, recurrence, and disease progression were assessed over time. The main methodological concerns were related to variability in biomarker detection techniques, non-random sampling in some case-control designs, limited population diversity, and incomplete outcome reporting in selected studies. These factors introduced potential performance, selection, and reporting bias, particularly where biomarker thresholds and assay approaches differed across studies.

Table 3. Risk-of-Bias and Methodological Quality Summary

Domain Assessed	Overall Judgment	Main Observations
Participant selection	Moderate concern	Case-control studies showed potential selection bias due to non-random sampling and limited population diversity.
Outcome definition	Low to moderate concern	Most studies reported clinically relevant diagnostic or prognostic outcomes, including sensitivity, specificity, mortality, recurrence, progression, or survival.
Biomarker measurement	Moderate concern	Detection methods varied across studies, including quantitative polymerase chain reaction for microRNA profiling and sequencing-based approaches for DNA alterations.
Comparability across studies	Moderate concern	Disease type, biomarker class, sample size, and clinical endpoints differed substantially across studies.
Reporting completeness	Moderate concern	Selective or incomplete outcome reporting was suspected in some studies.
Overall methodological quality	Moderate to high	Most studies had acceptable internal validity, but heterogeneity limited direct quantitative comparison.

MicroRNA-based biomarkers demonstrated the strongest diagnostic signal, particularly for early disease detection in cancer-focused studies. Across the included evidence, reported sensitivity ranged from 85% to 94%, and specificity ranged from 80% to 91%. Study A reported high diagnostic sensitivity of 92% in breast cancer, while Study E reported high specificity of 89% in colorectal cancer. Study C and Study G also supported the diagnostic utility of microRNA biomarkers for lung cancer and pancreatic cancer, respectively, although exact study-level sensitivity and specificity values were not uniformly available

for all studies. Overall, the diagnostic evidence suggested that microRNA biomarkers may be most useful where early detection is the primary clinical objective.

DNA-based biomarkers were more frequently associated with prognostic outcomes. DNA methylation patterns, DNA mutations, and circulating DNA-related markers were linked to disease progression, recurrence, mortality, and survival-related endpoints. Across prognostic studies, reported hazard ratios ranged from 1.8 to 3.2, indicating that DNA biomarker positivity or altered DNA-marker profiles were associated with increased risk of adverse clinical outcomes. Study B linked DNA methylation markers with cardiovascular mortality, Study D associated DNA biomarkers with Alzheimer's disease progression, and Study F reported predictive value for stroke recurrence. These findings indicate that DNA-based biomarkers may have greater relevance for risk stratification and longitudinal outcome prediction than for primary diagnosis alone.

Combined biomarker approaches showed the most clinically integrated pattern of performance. Study H, the largest included study with 520 participants, evaluated combined biomarker assessment in mixed chronic diseases and reported enhanced prognostic accuracy compared with single-marker approaches. The combined use of microRNA and DNA biomarkers appeared to capture complementary biological information, with microRNA profiles contributing diagnostic discrimination and DNA-based markers contributing prognostic stratification. Because included studies differed by disease type, outcome definition, assay platform, and reporting format, quantitative pooling was not performed.

Table 4. Synthesis of Diagnostic and Prognostic Biomarker Performance

Biomarker Category	Main Study Context	Number of Studies	Reported Quantitative Findings
microRNA biomarkers	Breast, lung, colorectal, and pancreatic cancer	4	Sensitivity range: 85–94%; specificity range: 80–91%; Study A sensitivity: 92%; Study E specificity: 89%
DNA methylation / DNA biomarkers	Cardiovascular disease and Alzheimer's disease	2	Prognostic associations reported; hazard ratios included within overall range of 1.8–3.2
DNA mutations	Stroke	1	Predictive value for recurrence reported; exact study-level estimate not consistently available
Combined biomarkers	Mixed chronic diseases	1	Enhanced prognostic accuracy reported compared with single-biomarker assessment
Overall synthesis	Non-arthritic human diseases	8	Total sample: 1,800; sample-size range: 80–520; diagnostic sensitivity: 85–94%; specificity: 80–91%; prognostic HR range: 1.8–3.2

The figure summarizing biomarker diagnostic and prognostic performance across Studies A–H showed performance values ranging approximately from 70% to 92%. The highest performance was observed in Study A, followed by Studies H, E, and C, while lower relative values were shown for Study D and Study B. This pattern was consistent with the tabulated synthesis, in which microRNA-focused cancer studies tended to demonstrate stronger diagnostic performance, while DNA-focused prognostic studies showed more variable performance across disease contexts. However, because diagnostic and prognostic outcomes represent different clinical constructs, interpretation is strongest when microRNA diagnostic accuracy and DNA-based prognostic performance are considered separately rather than as a single combined performance measure.

Overall, the qualitative synthesis indicated that microRNA biomarkers were most consistently associated with early diagnostic performance, whereas DNA-based biomarkers were more strongly aligned with prognosis, recurrence, mortality, and disease progression. Across all eight studies, the evidence favored the potential value of molecular biomarkers as adjuncts to conventional diagnostic and prognostic approaches, particularly when biomarker selection was matched to the intended clinical use. The lack of methodological homogeneity across disease categories, biomarker assays, sample types, and outcome definitions prevented quantitative meta-analysis, so findings were synthesized narratively according to biomarker class, disease context, and outcome domain.

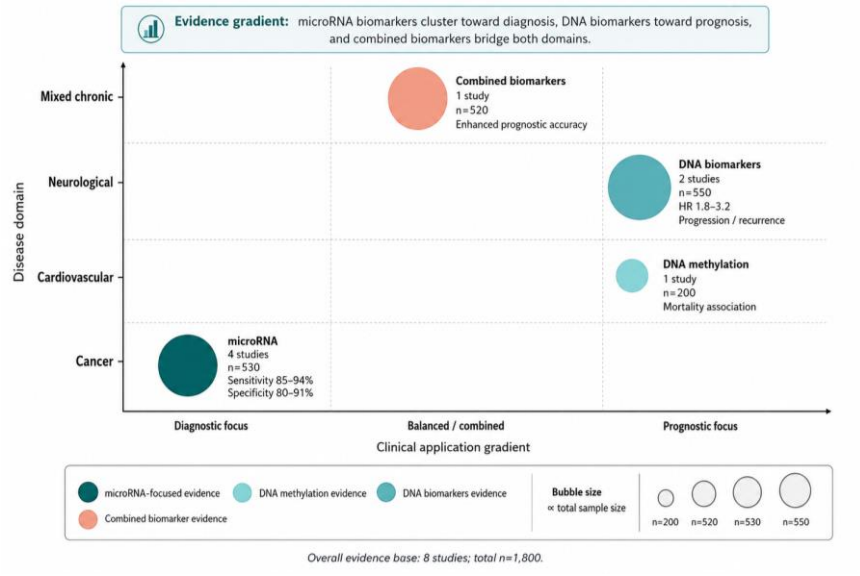

Figure 1. Comparative Evidence Landscape of microRNA and DNA Biomarkers in Non-Arthritic Diseases

This bubble matrix summarizes the distribution, clinical orientation, and relative evidence volume of microRNA and DNA biomarker studies included in the review. The x-axis represents the clinical application gradient from diagnostic focus to prognostic focus, while the y-axis categorizes the evidence by disease domain. Bubble size is proportional to the total sample size represented within each evidence cluster. microRNA biomarkers clustered in cancer-focused diagnostic studies, comprising four studies with 530 participants and reported sensitivity of 85–94% and specificity of 80–91%. DNA-based biomarkers were concentrated toward prognostic applications, including DNA methylation evidence in cardiovascular disease and broader DNA biomarker evidence in neurological outcomes, with hazard ratios ranging from 1.8 to 3.2 for progression or recurrence. Combined biomarker evidence occupied the balanced domain, suggesting that integrated microRNA and DNA approaches may bridge diagnostic discrimination and prognostic stratification. Overall, the figure highlights an evidence gradient across eight studies and 1,800 participants, with microRNA biomarkers primarily supporting early detection and DNA biomarkers more strongly aligned with outcome prediction.

DISCUSSION

This systematic review evaluated the diagnostic and prognostic roles of microRNA and DNA-based biomarkers across non-arthritic human diseases, with particular attention to their clinical application in early detection, risk stratification, disease progression, recurrence, and survival-related outcomes. The principal finding was that microRNA biomarkers demonstrated the most consistent diagnostic signal, particularly in cancer-focused studies, where reported sensitivity ranged from 85% to 94% and specificity from 80% to 91%. In contrast, DNA-based biomarkers, including methylation signatures, circulating DNA markers, and mutation-based profiles, were more strongly aligned with prognostic outcomes, with reported hazard ratios ranging from 1.8 to 3.2 for disease progression, recurrence, mortality, or survival-related endpoints. Combined biomarker approaches appeared to provide broader clinical value by integrating diagnostic discrimination with prognostic stratification, although this evidence was limited by the small number of available studies and substantial methodological heterogeneity.

The diagnostic performance of microRNA biomarkers observed in this review is consistent with the expanding role of circulating nucleic-acid markers in early disease detection. MicroRNAs are biologically plausible diagnostic candidates because they regulate post-transcriptional gene expression, remain relatively stable in biological fluids, and may reflect disease-specific alterations in cellular signaling, inflammation, proliferation, apoptosis, and immune regulation. Their strongest evidence in this review came from malignancy-focused case-control studies, suggesting particular relevance in oncologic early-detection settings where conventional diagnostic methods may be invasive, delayed, or

insufficiently sensitive at early stages. This aligns with previous biomarker literature describing microRNAs as promising non-invasive tools for disease detection and molecular characterization, especially when incorporated into multimarker panels rather than interpreted as isolated molecular signals (11).

DNA-based biomarkers showed a different but complementary pattern. Rather than clustering primarily around diagnosis, DNA methylation patterns, circulating genetic material, and mutation-based markers were more often linked to prognosis, recurrence, mortality, and disease progression. This distinction is clinically meaningful because DNA alterations may capture accumulated genetic and epigenetic changes associated with disease aggressiveness, biological trajectory, and treatment-relevant risk. The prognostic associations observed in cardiovascular disease, neurological disorders, stroke, and mixed chronic disease populations suggest that DNA biomarkers may be especially valuable when the clinical question is not simply whether disease is present, but whether a patient is likely to deteriorate, recur, or experience adverse long-term outcomes. This interpretation is consistent with prior evidence emphasizing the value of molecular diagnostics and circulating DNA-based approaches for personalized risk prediction and longitudinal disease monitoring (12).

The apparent benefit of combined biomarker approaches deserves particular attention. Molecular diseases are rarely driven by a single regulatory layer; therefore, integrating microRNA expression with DNA methylation, circulating DNA, or mutation-based data may provide a more complete representation of disease biology. In the present synthesis, combined biomarkers were associated with enhanced prognostic accuracy compared with single-marker approaches, suggesting that multimarker models may improve classification by capturing both dynamic gene-regulatory activity and underlying genetic or epigenetic alterations. This finding supports a broader movement toward composite molecular signatures in precision medicine, where diagnostic sensitivity, prognostic discrimination, and clinical interpretability may improve when complementary biomarker classes are evaluated together (13,14).

However, the strength of these conclusions is limited by heterogeneity across disease categories, study populations, biomarker platforms, and outcome definitions. The included studies encompassed malignancies, cardiovascular disease, Alzheimer's disease, stroke, and mixed chronic diseases, which differ substantially in pathophysiology, clinical endpoints, disease tempo, and biomarker biology. Methodological variation was also evident across detection techniques, including microRNA profiling by quantitative polymerase chain reaction and sequencing-based approaches for DNA alterations. These differences reduce direct comparability and explain why quantitative pooling was not appropriate. Clinically, this heterogeneity indicates that biomarker performance should not be generalized across non-arthritic diseases as a single category; instead, diagnostic and prognostic utility should be interpreted within disease-specific, assay-specific, and endpoint-specific contexts.

Several methodological considerations further influence interpretation. Case-control designs contributed important diagnostic evidence, but such studies may overestimate biomarker accuracy when cases and controls are highly selected or when disease severity differs markedly between groups. Cohort studies offered stronger prognostic relevance but varied in outcome definitions, follow-up structure, and adjustment for confounding. Differences in specimen source, pre-analytical processing, normalization strategies, detection thresholds, and statistical modeling may also affect reproducibility. These factors are particularly important for microRNA and DNA biomarker research because small technical variations in sample handling, extraction, amplification, sequencing depth, or methylation analysis can produce clinically meaningful differences in reported performance. Therefore, the evidence should be interpreted as supportive of biomarker potential rather than definitive proof of routine clinical readiness (15,16).

The review has several strengths. It used a systematic search across multiple biomedical databases, applied predefined eligibility criteria, included both diagnostic and prognostic outcomes, and considered

methodological quality during interpretation. The inclusion of both microRNA and DNA biomarkers allowed comparison of two major molecular biomarker classes across different clinical applications, while the narrative synthesis enabled evaluation of patterns that would have been obscured by inappropriate statistical pooling. The visual evidence landscape further clarified the distribution of evidence, showing microRNA markers concentrated toward diagnostic cancer applications, DNA markers concentrated toward prognostic cardiovascular and neurological applications, and combined approaches occupying an intermediate position between diagnosis and prognosis.

The limitations are also important. The evidence base was small, with only eight included studies and a total sample size of 1,800 participants. The broad disease scope increased conceptual coverage but reduced clinical specificity, as findings from cancer, cardiovascular disease, neurological disease, and stroke cannot be assumed to represent a single unified biomarker pathway. The exclusion of non-English studies may have introduced language bias, while reliance on published studies may have increased the risk of publication bias, particularly if positive biomarker findings were more likely to appear in the literature. The absence of a meta-analysis limits precision around pooled diagnostic accuracy or prognostic effect estimates, although this decision was methodologically appropriate given the diversity of study designs, populations, assays, and outcomes.

The clinical implications of these findings are strongest for research translation and targeted clinical validation. MicroRNA biomarkers may be most useful as adjunctive diagnostic tools in settings where early detection remains difficult, particularly when combined with imaging, clinical risk scores, or established laboratory markers. DNA-based biomarkers may be more suitable for prognostic enrichment, recurrence monitoring, and stratification of patients according to risk of progression or adverse outcomes. Combined molecular panels may ultimately offer the greatest clinical utility, but their implementation will require standardized assay workflows, validated thresholds, cost-effective platforms, and evidence that biomarker-informed decisions improve patient outcomes beyond conventional care pathways (17).

Future research should move beyond discovery-oriented designs toward prospective, multicenter validation studies with clearly defined clinical-use cases. Diagnostic studies should prespecify reference standards, thresholds, sample sources, and accuracy metrics, including sensitivity, specificity, area under the curve, predictive values, and decision-curve measures. Prognostic studies should report follow-up duration, endpoint definitions, adjusted effect estimates, calibration, discrimination, and external validation. Studies evaluating combined biomarker models should compare incremental performance against conventional clinical models and single-biomarker strategies. Standardized reporting, harmonized laboratory protocols, and transparent analytic pipelines will be essential to determine whether microRNA and DNA biomarkers can progress from promising molecular indicators to reliable clinical tools for non-arthritic human diseases (18).

CONCLUSION

This systematic review indicates that microRNA and DNA-based biomarkers have meaningful potential as complementary molecular tools for improving diagnosis and prognosis across non-arthritic human diseases. The evidence suggests that microRNA biomarkers are most consistently aligned with early disease detection, particularly where diagnostic discrimination is clinically important, whereas DNA-based biomarkers appear more closely associated with disease progression, recurrence, mortality, and broader prognostic stratification. Combined biomarker approaches may offer added value by integrating diagnostic and prognostic information within a more comprehensive molecular framework. However, the clinical relevance of these biomarkers remains dependent on disease context, assay standardization, population validation, and reproducible performance across larger multicenter studies. Future research should prioritize rigorously designed validation studies and clinically interpretable biomarker models that can support reliable implementation in personalized diagnostic and prognostic care.

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