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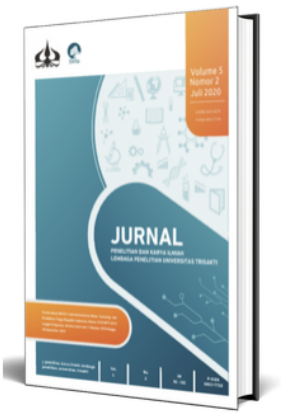

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EPIGENETIC BIOMARKERS in CHRONIC DISEASE: EMERGING APPLICATIONS in DIAGNOSIS, PROGNOSIS, and PRECISION MEDICINE

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ABSTRACT

Epigenetic biomarkers have emerged as promising tools for understanding chronic disease pathogenesis and improving clinical management. Unlike static genetic variants, epigenetic modifications are dynamic and may reflect cumulative environmental exposures, ageing, and disease progression. This review summarizes current evidence on major epigenetic biomarkers, including DNA methylation, histone modifications, and non-coding RNAs, with emphasis on their roles in cancer, cardiovascular disease, respiratory disorders, neurodegeneration, and metabolic disease. Their applications in early diagnosis, prognosis, treatment monitoring, and precision medicine are discussed. Recent advances in high-throughput sequencing, liquid biopsy, multi-omics integration, and artificial intelligence have accelerated biomarker discovery and translational potential. Despite ongoing challenges related to tissue specificity, standardization, and clinical validation, epigenetic biomarkers are expected to play an increasingly important role in personalized healthcare.

ABSTRAK

Biomarker epigenetik telah muncul sebagai alat yang menjanjikan untuk memahami patogenesis penyakit kronis dan meningkatkan manajemen klinis. Tidak seperti varian genetik statis, modifikasi epigenetik bersifat dinamis dan dapat mencerminkan paparan lingkungan kumulatif, penuaan, dan perkembangan penyakit. Tinjauan ini merangkum bukti terkini tentang biomarker epigenetik utama, termasuk metilasi DNA, modifikasi histon, dan RNA non-coding, dengan penekanan pada peran mereka dalam kanker, penyakit kardiovaskular, gangguan pernapasan, neurodegenerasi, dan penyakit metabolik. Aplikasi mereka dalam diagnosis dini, prognosis, pemantauan pengobatan, dan pengobatan presisi dibahas. Kemajuan terbaru dalam pengurutan berkecepatan tinggi, biopsi cair, integrasi multi-omik, dan kecerdasan buatan telah mempercepat penemuan biomarker dan potensi translasionalnya. Terlepas dari tantangan yang masih ada terkait dengan spesifisitas jaringan, standardisasi, dan

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- biomarker epigenetik,
- modifikasi histone,
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- pengobatan presisi,
- RNA non-koding

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validasi klinis, biomarker epigenetik diharapkan memainkan peran yang semakin penting dalam perawatan kesehatan yang dipersonalisasi.

1. INTRODUCTION

Epigenetic regulation refers to heritable changes in gene expression that occur without alterations in the underlying DNA sequence. These modifications include DNA methylation, histone modification, chromatin remodeling, and regulation by non-coding RNAs. Unlike static genetic variants, epigenetic signatures are dynamic and can change over time in response to ageing, disease processes, therapeutic interventions, and environmental exposure (Benčik et al., 2025; Wu et al., 2024).

In recent years, epigenetic biomarkers have emerged as an important focus in biomedical research because they provide information that bridges molecular mechanisms and clinical outcomes. Whereas traditional biomarkers often reflect late-stage pathological changes, epigenetic biomarkers may capture earlier molecular disturbances before overt disease manifestation. Their ability to reflect both intrinsic biological processes and cumulative external exposures makes them particularly valuable in chronic disease research (Wisman et al., 2024; Zhang et al., 2024).

Chronic diseases such as cancer, cardiovascular disease, chronic respiratory disorders, neurodegenerative disease, and metabolic disorders remain leading causes of morbidity and mortality worldwide. These conditions often develop gradually over many years through complex interactions between genetic susceptibility, environmental exposure, lifestyle, and ageing. Conventional biomarkers are often limited by low sensitivity in early disease stages, poor predictive value, or inability to capture dynamic biological changes over time (Batis et al., 2021; Zhao et al., 2025).

Epigenetic biomarkers offer distinct advantages because many are detectable in minimally invasive biological samples, including blood, plasma, saliva, and circulating cell-free DNA. DNA methylation signatures can remain stable enough for clinical analysis while still reflecting disease-associated changes. Similarly, circulating microRNAs and other non-coding RNAs have demonstrated substantial potential as diagnostic and prognostic biomarkers across multiple chronic diseases (Afrifa-Yamoah et al., 2024; García-Giménez et al., 2017).

The development of high-throughput sequencing technologies, methylation arrays, digital PCR, and integrated multi-omics approaches has accelerated the identification of clinically relevant epigenetic biomarkers. These technologies have improved sensitivity, reproducibility, and large-scale profiling capacity. In parallel, machine learning approaches are increasingly used to identify predictive

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biomarker panels and integrate complex epigenetic datasets with clinical outcomes (Lee, 2023; Luo et al., 2024).

In addition to diagnosis, epigenetic biomarkers may contribute to prognosis, therapeutic stratification, disease monitoring, and assessment of environmental exposure. Because epigenetic patterns can reflect cumulative biological ageing and exposure history, they may also provide insights into disease susceptibility before clinical onset (England-Mason, 2025; Kim and Kim, 2026).

This review summarizes major classes of epigenetic biomarkers, their relevance across major chronic diseases, and their emerging applications in diagnosis, prognosis, and precision medicine. Particular emphasis is placed on DNA methylation biomarkers, histone-based markers, and non-coding RNA signatures that are increasingly investigated for clinical translation (Kronfol et al., 2018; Skinner, 2024).

2. MAJOR CLASSES OF EPIGENETICS BIOMARKERS

DNA methylation biomarkers. DNA methylation remains the most extensively investigated epigenetic biomarker in human disease. This mechanism involves addition of a methyl group to cytosine residues, particularly within CpG islands, often resulting in transcriptional repression. Altered methylation patterns may arise during ageing, environmental exposure, inflammation, and chronic disease progression (Jang et al., 2017; Liu et al., 2023; Willmer et al., 2025).

Because methylation patterns are relatively stable and measurable in blood, plasma, and archived tissues, they are highly attractive for biomarker development. Aberrant promoter hypermethylation of tumor suppressor genes and global hypomethylation are among the best characterized epigenetic alterations in cancer. In non-malignant disease, methylation changes in inflammatory, oxidative stress, and metabolic genes have also been identified (Ibrahim et al., 2023; Williams et al., 2025).

Smoking-associated methylation of the AHRR locus remains one of the most replicated examples of exposure-related methylation. Likewise, age-related methylation signatures have enabled development of epigenetic clocks that estimate biological ageing and age-associated disease risk (Grieshober et al., 2020; Pośpiech et al., 2024).

Circulating cell-free DNA methylation analysis has further expanded the translational potential of DNA methylation biomarkers. Cell-free DNA can be analyzed from plasma and provides a minimally

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invasive approach for disease detection, risk stratification, and longitudinal monitoring (Rafiei et al., 2025; Wang et al., 2024).

Histone modification biomarkers. Histone modifications influence chromatin accessibility and transcriptional regulation through acetylation, methylation, phosphorylation, ubiquitination, and related processes. Histone-based biomarkers remain less frequently used clinically than DNA methylation because of technical limitations, but they provide valuable mechanistic insights (Kolady and Wang, 2025; Qi et al., 2025).

Specific histone acetylation and methylation signatures have been associated with chronic inflammatory states, tumor progression, neurodegeneration, and cardiovascular disease. Histone marks may also reflect treatment response and epigenetic drug activity (Liu et al., 2023; Qi et al., 2025).

Measurement often requires specialized laboratory approaches, including chromatin immunoprecipitation followed by sequencing. Although technically demanding, advances in profiling technologies may improve clinical utility in the future (Nakato and Sakata, 2021; Oba and Nakato, 2025).

Non-coding RNA. Non-coding RNAs constitute one of the fastest growing biomarker fields. These molecules include microRNAs, long non-coding RNAs, and circular RNAs. They regulate gene expression through post-transcriptional mechanisms and chromatin-associated regulatory processes (Barbi et al., 2025; Yang et al., 2025).

Circulating microRNAs are detectable in serum, plasma, saliva, urine, and extracellular vesicles. Their relative stability in body fluids supports minimally invasive liquid biopsy applications. Numerous disease-specific microRNA profiles have been identified in cancer, cardiovascular disease, respiratory disorders, and metabolic disease (Takizawa et al., 2022; Yaghoubi et al., 2026).

Long non-coding RNAs are increasingly recognized for tissue-specific regulation and disease stratification. Circular RNAs, because of their structural stability, may also represent highly promising biomarkers (Carbone et al., 2026; Liu et al., 2021).

Integrated biomarker panels

Single epigenetic markers often provide limited predictive power. Consequently, recent studies increasingly combine multiple epigenetic layers into integrated biomarker panels. These may include DNA methylation signatures, circulating microRNAs, and transcriptomic profiles (Chilimoniuk et al., 2025; Zhou et al., 2025).

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Integrated panels may improve diagnostic sensitivity and specificity while better capturing disease heterogeneity. Such approaches are increasingly supported by artificial intelligence and machine learning algorithms capable of identifying predictive molecular patterns in large-scale datasets (Chilimoniuk et al., 2025; Zhou et al., 2025).

EPIGENETIC BIOMARKERS IN CHRONIC DISEASES

Cancer. Epigenetic biomarkers are among the most extensively studied molecular markers in oncology. Aberrant promoter hypermethylation of tumor suppressor genes, global DNA hypomethylation, histone dysregulation, and altered non-coding RNA profiles are common hallmarks of malignant transformation (Zhou et al., 2026; Zhu et al., 2026).

Promoter methylation of genes such as BRCA1, MGMT, RASSF1A, and CDKN2A has been reported in multiple solid tumors and hematologic malignancies. These alterations may contribute to early carcinogenesis by silencing tumor suppressor pathways, impairing DNA repair, and facilitating genomic instability (Blanc-Durand et al., 2023; Malpeli et al., 2019).

Circulating tumor-derived methylated DNA has emerged as a promising liquid biopsy tool for early detection, disease monitoring, and recurrence surveillance. In addition, circulating microRNAs, including miR-21 and miR-155, are increasingly investigated as biomarkers of prognosis and treatment response (da Silva et al., 2025; Simancas-Racines et al., 2025).

The integration of epigenetic signatures into oncology may improve risk stratification and support personalized therapeutic decisions, particularly in cancers characterized by marked molecular heterogeneity (Sadida et al., 2024; Simancas-Racines et al., 2025).

Cardiovascular disease. Epigenetic alterations play important roles in endothelial dysfunction, inflammation, vascular remodeling, and atherosclerotic progression. DNA methylation changes in inflammatory genes, oxidative stress regulators, and vascular signaling pathways have been associated with cardiovascular disease risk (Tang et al., 2021; Zhu et al., 2025).

Methylation changes involving inflammatory mediators, endothelial nitric oxide pathways, and lipid metabolism genes have been reported in coronary artery disease, hypertension, and heart failure. These alterations may precede clinical symptoms and provide opportunities for early detection (Shi et al., 2022; Willmer et al., 2025).

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Circulating microRNAs such as miR-126, miR-208, and miR-499 have been associated with myocardial injury, vascular dysfunction, and prognosis after acute cardiovascular events. Combined epigenetic panels may improve predictive performance beyond conventional biomarkers (Li et al., 2022; Yildiz et al., 2025).

Respiratory disease. Epigenetic biomarkers are increasingly studied in chronic respiratory disorders including COPD, asthma, and interstitial lung disease. Environmental exposures such as smoking and air pollution strongly influence respiratory epigenetic signatures (Benincasa et al., 2021; Ritzmann et al., 2025).

Methylation of the AHRR locus remains one of the most widely validated exposure-associated biomarkers. Altered methylation patterns in inflammatory genes and oxidative stress regulators have also been associated with impaired lung function and disease progression (Pośpiech et al., 2024; Skov-Jeppesen et al., 2023).

Circulating microRNAs have demonstrated potential as indicators of airway inflammation, tissue remodeling, and treatment response. Because respiratory disease often reflects cumulative environmental exposure, epigenetic biomarkers may provide unique exposure-related information (Chaiwangyen et al., 2025; Mirra et al., 2022).

Neurodegenerative disease. Neurodegenerative diseases involve complex interactions between ageing, inflammation, oxidative stress, and neuronal dysfunction. Epigenetic dysregulation is increasingly recognized in Alzheimer's disease, Parkinson's disease, and related conditions (Qasim et al., 2025; Singh et al., 2025).

Altered methylation of genes involved in amyloid processing, synaptic function, mitochondrial homeostasis, and neuroinflammation has been identified. Histone acetylation changes may influence memory formation and neuronal survival (Basavarajappa and Subbanna, 2024; Ma et al., 2023).

Circulating and cerebrospinal fluid microRNAs have shown promise as minimally invasive biomarkers for early detection, disease progression, and therapeutic monitoring. Epigenetic signatures may improve stratification of neurodegenerative disease subtypes (Kuo et al., 2026; Pal and Mandal, 2025).

Metabolic disease. Metabolic disorders such as obesity, insulin resistance, and type 2 diabetes are strongly influenced by epigenetic regulation. Altered methylation of genes involved in insulin

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signaling, adipogenesis, inflammation, and mitochondrial metabolism has been reported (Chaudhry and Sif, 2026; Sandovici et al., 2025).

Several studies have demonstrated methylation changes preceding overt diabetes diagnosis, suggesting potential value in risk prediction. These changes may reflect early metabolic stress and environmental influences including diet and physical inactivity (Kiełbowski et al., 2025; Raciti et al., 2021).

Circulating non-coding RNAs are increasingly investigated as biomarkers of glycemic control, insulin resistance, and treatment response. Epigenetic markers may also improve understanding of long-term metabolic memory and complications (Amine et al., 2025; Tanwar et al., 2021).

3. CLINICAL APPLICATIONS

Diagnostic biomarkers. Epigenetic biomarkers offer significant opportunities for early disease detection, particularly in conditions that develop silently over long periods. Because epigenetic alterations may occur before overt clinical manifestations, they may improve identification of individuals at high risk (García-Giménez et al., 2017; Villa and Stoccoro, 2022).

DNA methylation assays using blood-based or plasma-derived samples are increasingly investigated for screening applications. Liquid biopsy approaches based on circulating methylated DNA and non-coding RNA signatures may enable minimally invasive detection of cancer and chronic systemic diseases (Li et al., 2024; Robaczyńska et al., 2026).

In addition, epigenetic biomarkers may support population-based risk assessment, especially when combined with environmental exposure history, age, and clinical variables (Cote et al., 2017).

Prognostic biomarkers. Specific epigenetic signatures may provide important prognostic information regarding disease progression, severity, and survival. In oncology, promoter methylation of tumor suppressor genes and circulating miRNA profiles are increasingly investigated as predictors of recurrence and treatment outcomes (Parikh and Shah, 2024; Zhu et al., 2026).

In chronic inflammatory and cardiovascular disorders, epigenetic profiles may indicate progression risk, vascular events, and organ dysfunction. Biomarker panels integrating multiple epigenetic signals may improve predictive performance compared with single markers (Młynarska et al., 2026).

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Monitoring and therapeutic response. Epigenetic biomarkers may also support longitudinal monitoring during treatment. Because epigenetic patterns can change dynamically during disease progression and therapeutic intervention, repeated assessment may provide information on treatment response (Kuo et al., 2026; Willmer et al., 2025).

Monitoring of circulating methylated DNA and RNA signatures may assist in detecting residual disease, recurrence, or therapeutic resistance. Such approaches may be particularly useful in oncology and chronic inflammatory conditions (Saha et al., 2025; Xia et al., 2023).

Personalized medicine. Epigenetic biomarkers may contribute to personalized medicine by improving patient stratification and therapeutic targeting. Individual epigenetic profiles can reflect environmental exposure, biological ageing, and disease-specific molecular pathways.

These characteristics support precision prevention, early intervention, and tailored therapeutic decision-making (Edvardsson and Heenkenda, 2025; Guo et al., 2025; Kronfol et al., 2018).

EMERGING TECHNOLOGIES

Recent technological advances have substantially accelerated epigenetic biomarker discovery. Next-generation sequencing, methylation arrays, digital PCR, and high-throughput RNA profiling have improved sensitivity and scalability (Isaic et al., 2025; Yang et al., 2025).

Single-cell sequencing technologies now allow characterization of cell-type specific epigenetic signatures. This is particularly important in heterogeneous diseases such as cancer and inflammatory disorders (Lyu et al., 2025; Wen and Tang, 2018).

Integrated multi-omics approaches combining methylation, transcriptomics, proteomics, and metabolomics provide more comprehensive disease profiling (Luo et al., 2024; Sibilio et al., 2025).

Machine learning and artificial intelligence models are increasingly used to identify predictive biomarker panels, integrate complex datasets, and support clinical decision systems (Benabbou et al., 2026; Borat and Chowdhury, 2026).

CHALLENGES

Despite significant progress, important challenges remain in the clinical implementation of epigenetic biomarkers.

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A major limitation is tissue specificity. Epigenetic signatures may vary substantially across tissues, cell types, and disease stages. Biomarkers detected in peripheral blood may not fully represent target organ changes (Fallet et al., 2023; García-Giménez et al., 2017).

Inter-individual variability related to age, smoking, medication use, diet, and environmental exposure may also influence epigenetic profiles. This complicates interpretation and validation across populations (Colloca et al., 2026).

Technical issues remain significant, including assay standardization, batch effects, reproducibility, and analytical variability. Cross-platform consistency remains an important barrier to routine clinical adoption (Yu et al., 2024).

Longitudinal validation studies, standardized protocols, and diverse population cohorts are required to improve reproducibility and clinical applicability.

FUTURE DIRECTIONS

Future research should focus on integrating environmental exposure data, longitudinal biomarker assessment, and multi-omics analysis. Such approaches may improve understanding of disease susceptibility and progression.

Epigenetic clocks, liquid biopsy, and AI-assisted biomarker discovery are expected to play increasingly important roles in precision medicine.

Additional priorities include development of clinically validated biomarker panels, standardization of analytical workflows, and expansion of studies in underrepresented populations.

The integration of epigenetic biomarkers into preventive medicine and population health research may also improve early intervention strategies.

4. CONCLUSION

Epigenetic biomarkers provide an important bridge between molecular mechanisms and clinical translation. DNA methylation, histone modifications, and non-coding RNAs collectively offer valuable opportunities for disease diagnosis, prognosis, and treatment monitoring.

Growing evidence supports their relevance across cancer, cardiovascular disease, respiratory disorders, neurodegeneration, and metabolic disease. Their ability to capture dynamic biological

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changes and environmental influences makes them uniquely informative compared with conventional biomarkers.

Advances in high-throughput technologies, multi-omics integration, and artificial intelligence are expected to accelerate clinical implementation. Continued validation, standardization, and translational research remain essential to realize the full potential of epigenetic biomarkers in precision medicine.

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Hari K

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Epigenetic Biomarkers in Chronic Disease: Emerging Applications in Diagnosis, Prognosis, and Precision Medicine

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ABSTRACT

Epigenetic biomarkers have emerged as promising tools for understanding chronic disease pathogenesis and improving clinical management. Unlike static genetic variants, epigenetic modifications are dynamic and may reflect cumulative environmental exposures, ageing, and disease progression. This review summarizes current evidence on major epigenetic biomarkers, including DNA methylation, histone modifications, and non-coding RNAs, with emphasis on their roles in cancer, cardiovascular disease, respiratory disorders, neurodegeneration, and metabolic disease. Their applications in early diagnosis, prognosis, treatment monitoring, and precision medicine are discussed. Recent advances in high-throughput sequencing, liquid biopsy, multi-omics integration, and artificial intelligence have accelerated biomarker discovery and translational potential. Despite ongoing challenges related to tissue specificity, standardization, and clinical validation, epigenetic biomarkers are expected to play an increasingly important role in personalized healthcare.

Keywords: DNA methylation; epigenetics biomarkers; histone modification; non-coding RNA; precision medicine.

ABSTRAK

Biomarker epigenetik telah muncul sebagai alat yang menjanjikan untuk memahami patogenesis penyakit kronis dan meningkatkan manajemen klinis. Tidak seperti varian genetik statis, modifikasi epigenetik bersifat dinamis dan dapat mencerminkan paparan lingkungan kumulatif, penuaan, dan perkembangan penyakit. Tinjauan ini merangkum bukti terkini tentang biomarker epigenetik utama, termasuk metilasi DNA, modifikasi histon, dan RNA non-coding, dengan penekanan pada peran mereka dalam kanker, penyakit kardiovaskular, gangguan pernapasan, neurodegenerasi, dan penyakit metabolik. Aplikasi mereka dalam diagnosis dini, prognosis, pemantauan pengobatan, dan pengobatan presisi dibahas. Kemajuan terbaru dalam pengurutan berkecepatan tinggi, biopsi cair, integrasi multi-omik, dan kecerdasan buatan telah mempercepat penemuan biomarker dan potensi translasionalnya. Terlepas dari tantangan yang masih ada terkait dengan spesifisitas jaringan, standardisasi, dan validasi klinis, biomarker epigenetik diharapkan memainkan peran yang semakin penting dalam perawatan kesehatan yang dipersonalisasi.

Kata kunci: biomarker epigenetic; modifikasi histone; methylase DNA; pengobatan presisi; RNA non-coding.

INTRODUCTION

Epigenetic regulation refers to heritable changes in gene expression that occur without alterations in the underlying DNA sequence. These modifications include DNA methylation, histone modification, chromatin remodeling, and regulation by non-coding RNAs. Unlike static genetic variants, epigenetic signatures are dynamic and can change over time in response to ageing, disease processes, therapeutic interventions, and environmental exposure (Benčik et al., 2025; Wu et al., 2024).

In recent years, epigenetic biomarkers have emerged as an important focus in biomedical research because they provide information that bridges molecular mechanisms and clinical outcomes. Whereas traditional biomarkers often reflect late-stage pathological changes, epigenetic biomarkers may capture earlier molecular disturbances before overt disease manifestation. Their ability to reflect both intrinsic biological processes and cumulative external exposures makes them particularly valuable in chronic disease research (Wisman et al., 2024; Zhang et al., 2024).

Chronic diseases such as cancer, cardiovascular disease, chronic respiratory disorders, neurodegenerative disease, and metabolic disorders remain leading causes of morbidity and mortality worldwide. These conditions often develop gradually over many years through complex interactions between genetic susceptibility, environmental exposure, lifestyle, and ageing. Conventional biomarkers are often limited by low sensitivity in early disease stages, poor predictive value, or inability to capture dynamic biological changes over time (Batis et al., 2021; Zhao et al., 2025).

Epigenetic biomarkers offer distinct advantages because many are detectable in minimally invasive biological samples, including blood, plasma, saliva, and circulating cell-free DNA. DNA methylation signatures can remain stable enough for clinical analysis while still reflecting disease-associated changes. Similarly, circulating microRNAs and other non-coding RNAs have demonstrated substantial potential as diagnostic and prognostic biomarkers across multiple chronic diseases (Afrifa-Yamoah et al., 2024; García-Giménez et al., 2017).

The development of high-throughput sequencing technologies, methylation arrays, digital PCR, and integrated multi-omics approaches has accelerated the identification of clinically relevant epigenetic biomarkers. These technologies have improved sensitivity, reproducibility, and large-scale profiling capacity. In parallel, machine learning approaches are increasingly used to identify predictive biomarker panels and integrate complex epigenetic datasets with clinical outcomes (Lee, 2023; Luo et al., 2024).

In addition to diagnosis, epigenetic biomarkers may contribute to prognosis, therapeutic stratification, disease monitoring, and assessment of environmental exposure. Because epigenetic patterns can reflect cumulative biological ageing and exposure history, they may also provide insights into disease susceptibility before clinical onset (England-Mason, 2025; Kim and Kim, 2026).

This review summarizes major classes of epigenetic biomarkers, their relevance across major chronic diseases, and their emerging applications in diagnosis, prognosis, and precision medicine. Particular emphasis is placed on DNA methylation biomarkers, histone-based markers, and non-coding RNA signatures that are increasingly investigated for clinical translation (Kronfol et al., 2018; Skinner, 2024).

MAJOR CLASSES OF EPIGENETICS BIOMARKERS

DNA methylation biomarkers

DNA methylation remains the most extensively investigated epigenetic biomarker in human disease. This mechanism involves addition of a methyl group to cytosine residues, particularly within CpG islands, often resulting in transcriptional repression. Altered methylation patterns may arise during ageing, environmental exposure, inflammation, and chronic disease progression (Jang et al., 2017; Liu et al., 2023; Willmer et al., 2025).

Because methylation patterns are relatively stable and measurable in blood, plasma, and archived tissues, they are highly attractive for biomarker development. Aberrant promoter hypermethylation of tumor suppressor genes and global hypomethylation are among the best characterized epigenetic alterations in cancer. In non-malignant disease, methylation changes in inflammatory, oxidative stress, and metabolic genes have also been identified (Ibrahim et al., 2023; Williams et al., 2025).

Smoking-associated methylation of the AHRR locus remains one of the most replicated examples of exposure-related methylation. Likewise, age-related methylation signatures have enabled development of epigenetic clocks that estimate biological ageing and age-associated disease risk (Grieshober et al., 2020; Pośpiech et al., 2024).

Circulating cell-free DNA methylation analysis has further expanded the translational potential of DNA methylation biomarkers. Cell-free DNA can be analyzed from plasma and provides a minimally invasive approach for disease detection, risk stratification, and longitudinal monitoring (Rafiei et al., 2025; Wang et al., 2024).

Histone modification biomarkers

Histone modifications influence chromatin accessibility and transcriptional regulation through acetylation, methylation, phosphorylation, ubiquitination, and related processes. Histone-based biomarkers remain less frequently used clinically than DNA methylation because of technical limitations, but they provide valuable mechanistic insights (Kolady and Wang, 2025; Qi et al., 2025).

Specific histone acetylation and methylation signatures have been associated with chronic inflammatory states, tumor progression, neurodegeneration, and cardiovascular disease. Histone marks may also reflect treatment response and epigenetic drug activity (Liu et al., 2023; Qi et al., 2025).

Measurement often requires specialized laboratory approaches, including chromatin immunoprecipitation followed by sequencing. Although technically demanding, advances in profiling technologies may improve clinical utility in the future (Nakato and Sakata, 2021; Oba and Nakato, 2025).

Non-coding RNA

Non-coding RNAs constitute one of the fastest growing biomarker fields. These molecules include microRNAs, long non-coding RNAs, and circular RNAs. They regulate gene expression through

post-transcriptional mechanisms and chromatin-associated regulatory processes (Barbi et al., 2025; Yang et al., 2025).

Circulating microRNAs are detectable in serum, plasma, saliva, urine, and extracellular vesicles. Their relative stability in body fluids supports minimally invasive liquid biopsy applications. Numerous disease-specific microRNA profiles have been identified in cancer, cardiovascular disease, respiratory disorders, and metabolic disease (Takizawa et al., 2022; Yaghoubi et al., 2026).

Long non-coding RNAs are increasingly recognized for tissue-specific regulation and disease stratification. Circular RNAs, because of their structural stability, may also represent highly promising biomarkers (Carbone et al., 2026; Liu et al., 2021).

Integrated biomarker panels

Single epigenetic markers often provide limited predictive power. Consequently, recent studies increasingly combine multiple epigenetic layers into integrated biomarker panels. These may include DNA methylation signatures, circulating microRNAs, and transcriptomic profiles (Chilimoniuk et al., 2025; Zhou et al., 2025).

Integrated panels may improve diagnostic sensitivity and specificity while better capturing disease heterogeneity. Such approaches are increasingly supported by artificial intelligence and machine learning algorithms capable of identifying predictive molecular patterns in large-scale datasets (Chilimoniuk et al., 2025; Zhou et al., 2025).

EPIGENETIC BIOMARKERS IN CHRONIC DISEASES

Cancer

Epigenetic biomarkers are among the most extensively studied molecular markers in oncology. Aberrant promoter hypermethylation of tumor suppressor genes, global DNA hypomethylation, histone dysregulation, and altered non-coding RNA profiles are common hallmarks of malignant transformation (Zhou et al., 2026; Zhu et al., 2026).

Promoter methylation of genes such as BRCA1, MGMT, RASSF1A, and CDKN2A has been reported in multiple solid tumors and hematologic malignancies. These alterations may contribute to early carcinogenesis by silencing tumor suppressor pathways, impairing DNA repair, and facilitating genomic instability (Blanc-Durand et al., 2023; Malpeli et al., 2019).

Circulating tumor-derived methylated DNA has emerged as a promising liquid biopsy tool for early detection, disease monitoring, and recurrence surveillance. In addition, circulating microRNAs, including miR-21 and miR-155, are increasingly investigated as biomarkers of prognosis and treatment response (da Silva et al., 2025; Simancas-Racines et al., 2025).

The integration of epigenetic signatures into oncology may improve risk stratification and support personalized therapeutic decisions, particularly in cancers characterized by marked molecular heterogeneity (Sadida et al., 2024; Simancas-Racines et al., 2025).

Cardiovascular disease

Epigenetic alterations play important roles in endothelial dysfunction, inflammation, vascular remodeling, and atherosclerotic progression. DNA methylation changes in inflammatory genes, oxidative stress regulators, and vascular signaling pathways have been associated with cardiovascular disease risk (Tang et al., 2021; Zhu et al., 2025).

Methylation changes involving inflammatory mediators, endothelial nitric oxide pathways, and lipid metabolism genes have been reported in coronary artery disease, hypertension, and heart failure. These alterations may precede clinical symptoms and provide opportunities for early detection (Shi et al., 2022; Willmer et al., 2025).

Circulating microRNAs such as miR-126, miR-208, and miR-499 have been associated with myocardial injury, vascular dysfunction, and prognosis after acute cardiovascular events. Combined epigenetic panels may improve predictive performance beyond conventional biomarkers (Li et al., 2022; Yildiz et al., 2025).

Respiratory disease

Epigenetic biomarkers are increasingly studied in chronic respiratory disorders including COPD, asthma, and interstitial lung disease. Environmental exposures such as smoking and air pollution strongly influence respiratory epigenetic signatures (Benincasa et al., 2021; Ritzmann et al., 2025).

Methylation of the AHRR locus remains one of the most widely validated exposure-associated biomarkers. Altered methylation patterns in inflammatory genes and oxidative stress regulators have also been associated with impaired lung function and disease progression (Pośpiech et al., 2024; Skov-Jeppesen et al., 2023).

Circulating microRNAs have demonstrated potential as indicators of airway inflammation, tissue remodeling, and treatment response. Because respiratory disease often reflects cumulative environmental exposure, epigenetic biomarkers may provide unique exposure-related information (Chaiwangyen et al., 2025; Mirra et al., 2022).

Neurodegenerative disease

Neurodegenerative diseases involve complex interactions between ageing, inflammation, oxidative stress, and neuronal dysfunction. Epigenetic dysregulation is increasingly recognized in Alzheimer's disease, Parkinson's disease, and related conditions (Qasim et al., 2025; Singh et al., 2025).

Altered methylation of genes involved in amyloid processing, synaptic function, mitochondrial homeostasis, and neuroinflammation has been identified. Histone acetylation changes may influence memory formation and neuronal survival (Basavarajappa and Subbanna, 2024; Ma et al., 2023).

Circulating and cerebrospinal fluid microRNAs have shown promise as minimally invasive biomarkers for early detection, disease progression, and therapeutic monitoring. Epigenetic signatures may improve stratification of neurodegenerative disease subtypes (Kuo et al., 2026; Pal and Mandal, 2025).

Metabolic disease

Metabolic disorders such as obesity, insulin resistance, and type 2 diabetes are strongly influenced by epigenetic regulation. Altered methylation of genes involved in insulin signaling, adipogenesis, inflammation, and mitochondrial metabolism has been reported (Chaudhry and Sif, 2026; Sandovici et al., 2025).

Several studies have demonstrated methylation changes preceding overt diabetes diagnosis, suggesting potential value in risk prediction. These changes may reflect early metabolic stress and environmental influences including diet and physical inactivity (Kiełbowski et al., 2025; Raciti et al., 2021).

Circulating non-coding RNAs are increasingly investigated as biomarkers of glycemic control, insulin resistance, and treatment response. Epigenetic markers may also improve understanding of long-term metabolic memory and complications (Amine et al., 2025; Tanwar et al., 2021).

CLINICAL APPLICATIONS

Diagnostic biomarkers

Epigenetic biomarkers offer significant opportunities for early disease detection, particularly in conditions that develop silently over long periods. Because epigenetic alterations may occur before overt clinical manifestations, they may improve identification of individuals at high risk (García-Giménez et al., 2017; Villa and Stoccoro, 2022).

DNA methylation assays using blood-based or plasma-derived samples are increasingly investigated for screening applications. Liquid biopsy approaches based on circulating methylated DNA and non-coding RNA signatures may enable minimally invasive detection of cancer and chronic systemic diseases (Li et al., 2024; Robaczyńska et al., 2026).

In addition, epigenetic biomarkers may support population-based risk assessment, especially when combined with environmental exposure history, age, and clinical variables (Cote et al., 2017).

Prognostic biomarkers

Specific epigenetic signatures may provide important prognostic information regarding disease progression, severity, and survival. In oncology, promoter methylation of tumor suppressor genes and circulating miRNA profiles are increasingly investigated as predictors of recurrence and treatment outcomes (Parikh and Shah, 2024; Zhu et al., 2026).

In chronic inflammatory and cardiovascular disorders, epigenetic profiles may indicate progression risk, vascular events, and organ dysfunction. Biomarker panels integrating multiple epigenetic signals may improve predictive performance compared with single markers (Młynarska et al., 2026).

Monitoring and therapeutic response

Epigenetic biomarkers may also support longitudinal monitoring during treatment. Because epigenetic patterns can change dynamically during disease progression and therapeutic intervention, repeated assessment may provide information on treatment response (Kuo et al., 2026; Willmer et al., 2025).

Monitoring of circulating methylated DNA and RNA signatures may assist in detecting residual disease, recurrence, or therapeutic resistance. Such approaches may be particularly useful in oncology and chronic inflammatory conditions (Saha et al., 2025; Xia et al., 2023).

Personalized medicine

Epigenetic biomarkers may contribute to personalized medicine by improving patient stratification and therapeutic targeting. Individual epigenetic profiles can reflect environmental exposure, biological ageing, and disease-specific molecular pathways.

These characteristics support precision prevention, early intervention, and tailored therapeutic decision-making (Edvardsson and Heenkenda, 2025; Guo et al., 2025; Kronfol et al., 2018).

EMERGING TECHNOLOGIES

Recent technological advances have substantially accelerated epigenetic biomarker discovery. Next-generation sequencing, methylation arrays, digital PCR, and high-throughput RNA profiling have improved sensitivity and scalability (Isaic et al., 2025; Yang et al., 2025).

Single-cell sequencing technologies now allow characterization of cell-type specific epigenetic signatures. This is particularly important in heterogeneous diseases such as cancer and inflammatory disorders (Lyu et al., 2025; Wen and Tang, 2018).

11 Integrated multi-omics approaches combining methylation, transcriptomics, proteomics, and metabolomics provide more comprehensive disease profiling (Luo et al., 2024; Sibilio et al., 2025).

Machine learning and artificial intelligence models are increasingly used to identify predictive biomarker panels, integrate complex datasets, and support clinical decision systems (Benabbou et al., 2026; Borat and Chowdhury, 2026).

CHALLENGES

Despite significant progress, important challenges remain in the clinical implementation of epigenetic biomarkers.

A major limitation is tissue specificity. Epigenetic signatures may vary substantially across tissues, cell types, and disease stages. Biomarkers detected in peripheral blood may not fully represent target organ changes (Fallet et al., 2023; García-Giménez et al., 2017).

Inter-individual variability related to age, smoking, medication use, diet, and environmental exposure may also influence epigenetic profiles. This complicates interpretation and validation across populations (Colloca et al., 2026).

Technical issues remain significant, including assay standardization, batch effects, reproducibility, and analytical variability. Cross-platform consistency remains an important barrier to routine clinical adoption (Yu et al., 2024).

Longitudinal validation studies, standardized protocols, and diverse population cohorts are required to improve reproducibility and clinical applicability.

FUTURE DIRECTIONS

Future research should focus on integrating environmental exposure data, longitudinal biomarker assessment, and multi-omics analysis. Such approaches may improve understanding of disease susceptibility and progression.

Epigenetic clocks, liquid biopsy, and AI-assisted biomarker discovery are expected to play increasingly important roles in precision medicine.

Additional priorities include development of clinically validated biomarker panels, standardization of analytical workflows, and expansion of studies in underrepresented populations.

The integration of epigenetic biomarkers into preventive medicine and population health research may also improve early intervention strategies.

CONCLUSION

Epigenetic biomarkers provide an important bridge between molecular mechanisms and clinical translation. DNA methylation, histone modifications, and non-coding RNAs collectively offer valuable opportunities for disease diagnosis, prognosis, and treatment monitoring.

Growing evidence supports their relevance across cancer, cardiovascular disease, respiratory disorders, neurodegeneration, and metabolic disease. Their ability to capture dynamic biological changes and environmental influences makes them uniquely informative compared with conventional biomarkers.

Advances in high-throughput technologies, multi-omics integration, and artificial intelligence are expected to accelerate clinical implementation. Continued validation, standardization, and translational research remain essential to realize the full potential of epigenetic biomarkers in precision medicine.

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