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Review Article

Next-Generation Biomarkers in Cardio-Oncology: Translating Multi-Omics Research into Clinical Practice

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ABSTRACT:

Cardiovascular complications remain a major cause of morbidity and mortality among cancer survivors. While conventional biomarkers such as cardiac troponins and natriuretic peptides have significantly improved the detection of cancer therapy-related cardiovascular toxicity (CTR-CVT), their ability to identify subclinical injury and predict long-term outcomes remains limited. Recent advances in multi-omics technologies, including genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics, have transformed biomarker discovery in cardio-oncology. These next-generation biomarkers provide mechanistic insights into the molecular pathways underlying cardiotoxicity and offer opportunities for personalized risk stratification, early diagnosis, and therapeutic intervention. Emerging molecular signatures, including circulating microRNAs, extracellular vesicles, cell-free DNA, protein panels, metabolic fingerprints, and epigenetic markers, have demonstrated considerable promise for identifying cardiovascular injury before overt functional decline occurs. Integration of multi-omics datasets with artificial intelligence and machine learning approaches further enables the development of predictive models capable of supporting precision cardio-oncology. This review summarizes recent advances in next-generation biomarkers, highlights their clinical applications, discusses current challenges in translation, and explores future directions toward personalized cardiovascular monitoring and management in cancer patients.

KEYWORDS: Cardio-oncology; Multi-omics; Biomarkers; Proteomics; Metabolomics; Transcriptomics; Epigenomics; MicroRNA; Extracellular Vesicles; Precision Medicine; Artificial Intelligence; Cardiotoxicity

INTRODUCTION

The growing population of cancer survivors has led to increasing recognition of cardiovascular disease as a major determinant of long-term outcomes. Advances in chemotherapy, targeted therapies, immune checkpoint inhibitors, and radiation therapy have substantially improved cancer

survival; however, these treatments may induce diverse forms of cardiovascular toxicity. Early identification of susceptible individuals remains a major challenge in cardio-oncology.

Traditional cardiac biomarkers, including cardiac troponins and natriuretic peptides, have improved surveillance strategies but often reflect established myocardial injury rather than preclinical molecular alterations. Recent developments in high-throughput omics technologies provide unprecedented opportunities to identify molecular signatures associated with treatment-related cardiovascular injury before clinical manifestations emerge.

Multi-omics approaches enable comprehensive characterization of biological systems at multiple levels, including genetic predisposition, transcriptional regulation, protein expression, metabolic alterations, and epigenetic modifications. Integration of these datasets may facilitate personalized risk prediction, earlier intervention, and improved clinical outcomes. This review focuses on emerging next-generation biomarkers and their translational potential in modern cardio-oncology.

2.MULTI-OMICS PLATFORMS FOR CARDIOVASCULAR RISK STRATIFICATION IN CANCER PATIENTS

Before overt cardiotoxicity develops, cancer therapies trigger complex molecular alterations across multiple biological pathways. Multi-omics technologies provide a comprehensive framework for identifying susceptible patients and understanding mechanisms of cardiovascular injury.

i. Genomics

Genomic biomarkers identify inherited genetic variants associated with increased susceptibility to anthracycline-induced cardiomyopathy, trastuzumab-related cardiac dysfunction, and radiation-associated cardiovascular disease. Variants in genes involved in oxidative stress regulation, sarcomere structure, mitochondrial function, and drug metabolism have been linked to differential cardiotoxicity risk.

ii. Transcriptomics

Transcriptomic profiling evaluates messenger RNA and non-coding RNA expression patterns associated with myocardial stress and inflammation. Circulating microRNAs have emerged as particularly promising biomarkers because they are stable in blood and reflect ongoing cellular processes.

iii. Proteomics

Proteomic analyses enable large-scale assessment of proteins involved in myocardial injury, fibrosis, inflammation, endothelial dysfunction, and oxidative stress. High-throughput protein panels may identify novel pathways that are not captured by conventional biomarkers.

vi. Metabolomics

Metabolic profiling provides insight into mitochondrial dysfunction, altered energy metabolism, lipid disturbances, and oxidative stress induced by cancer therapies. Metabolomic signatures may serve as highly sensitive indicators of early cardiac injury.

v. Epigenomics and Microbiomics

DNA methylation patterns, histone modifications, and gut microbiome alterations have recently emerged as potential contributors to cardiovascular toxicity. These biomarkers may offer additional layers of biological information for precision risk assessment.

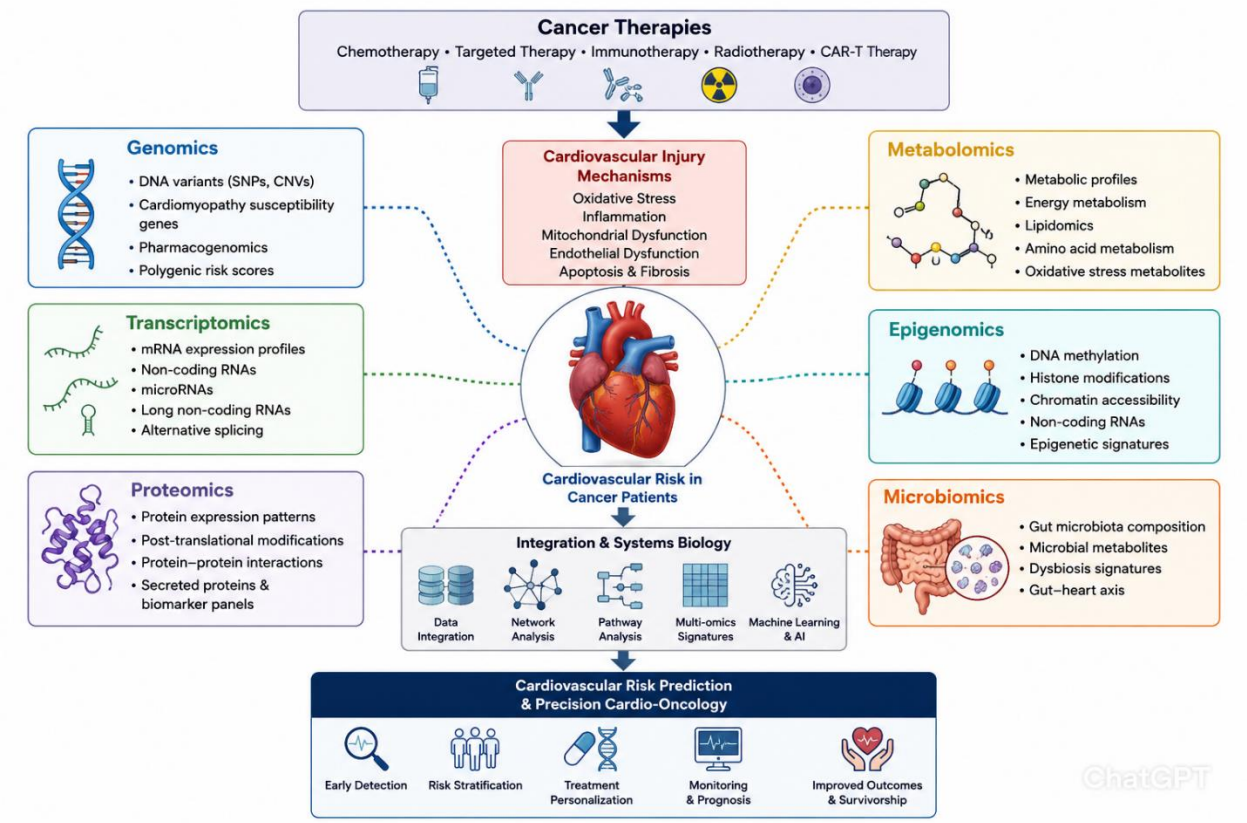

Figure 1. *Schematic overview of multi-omics platforms in cardio-oncology showing integration of genomics, transcriptomics, proteomics, metabolomics, epigenomics, and microbiomics for cardiovascular risk prediction*

3. EMERGING MOLECULAR BIOMARKERS BEYONDCONVENTIONAL CARDIAC MARKERS

While troponins and natriuretic peptides remain clinically valuable, next-generation biomarkers provide mechanistic information that may improve early detection and individualized management.

i. Circulating MicroRNAs

MicroRNAs regulate gene expression and participate in pathways involving apoptosis, fibrosis, inflammation, and angiogenesis. Specific microRNAs, including miR-1, miR-21, miR-34a, miR-126, and miR-208, have been associated with chemotherapy-induced myocardial injury.

ii. Extracellular Vesicles and Exosomes

Extracellular vesicles transport proteins, nucleic acids, lipids, and signaling molecules between cells. Their cargo reflects tissue-specific responses to therapy and may provide highly sensitive indicators of cardiovascular injury.

iii. Cell-Free DNA and Mitochondrial DNA

Cell-free DNA released from damaged cardiomyocytes represents a promising biomarker for detecting subclinical myocardial injury. Elevated circulating mitochondrial DNA may indicate oxidative stress and inflammatory activation.

vi. Novel Protein Biomarkers

Emerging protein biomarkers include:

- Growth Differentiation Factor-15 (GDF-15)
- Soluble ST2
- Galectin-3
- Osteopontin
- Myeloperoxidase
- Heart-type Fatty Acid Binding Protein (H-FABP)

These markers reflect fibrosis, inflammation, oxidative stress, and ventricular remodeling.

V. Metabolic Biomarkers

Metabolic signatures involving amino acids, acylcarnitines, lipid mediators, and oxidative stress metabolites may identify cardiotoxicity before structural abnormalities become evident.

Table 1. Representative Next-Generation Biomarkers in Cardio-Oncology

Biomarker Category	Representative Biomarkers	Biological Significance	Potential Clinical Utility
Genomics	SNPs in RARG, TTN, HER2 pathways	Genetic susceptibility	Risk prediction
Transcriptomics	miR-1, miR-21, miR-34a, miR-208	Gene regulation	Early detection
Proteomics	GDF-15, ST2, Galectin-3	Inflammation and fibrosis	Monitoring progression
Metabolomics	Acylcarnitines, lipid metabolites	Energy metabolism	Subclinical injury detection
Epigenomics	DNA methylation signatures	Gene expression control	Personalized risk assessment
Extracellular Vesicles	Exosomal RNA and proteins	Cell communication	Therapy response monitoring
Cell-Free DNA	cfDNA, mtDNA	Cellular injury	Early myocardial damage

Table Explanation: This table summarizes the principal classes of next-generation biomarkers currently under investigation for precision cardio-oncology applications. Unlike conventional biomarkers, these markers provide mechanistic information and may improve early detection of cardiovascular injury.

4. INTEGRATION OF ARTIFICIAL INTELLIGENCE AND MULTI-OMICS DATA

The complexity of multi-omics datasets requires advanced computational approaches. Machine learning algorithms can identify hidden patterns across genomic, proteomic, metabolomic, and clinical datasets.

Applications include:

- Individualized cardiotoxicity risk prediction
- Early identification of vulnerable patients
- Dynamic monitoring during treatment
- Personalized therapeutic recommendations
- Clinical decision support systems

5. CHALLENGES IN CLINICAL TRANSLATION

Several barriers currently limit implementation of next-generation biomarkers:

- Lack of standardized analytical methods
- Small validation cohorts
- Limited longitudinal studies
- High cost of omics technologies

- Complex bioinformatic requirements
- Regulatory and reimbursement challenges

6. FUTURE PERSPECTIVES AND PRECISION CARDIO-ONCOLOGY

Future research is expected to focus on integrated multi-omics panels rather than single biomarkers. Combining molecular biomarkers with advanced imaging, wearable technologies, and artificial intelligence may enable real-time cardiovascular surveillance.

Large-scale international consortia and prospective clinical trials are likely to accelerate validation efforts. Ultimately, precision cardio-oncology may evolve toward individualized cardiovascular care plans tailored to each patient's molecular risk profile.

CONCLUSION

Next-generation biomarkers derived from genomics, transcriptomics, proteomics, metabolomics, epigenomics, and extracellular vesicle research are reshaping the landscape of cardio-oncology. These biomarkers provide deeper mechanistic insights into cancer therapy-related cardiovascular injury and hold significant promise for early diagnosis, risk stratification, and personalized management. Although several challenges remain regarding standardization, validation, and clinical implementation, ongoing advances in multi-omics technologies and artificial intelligence are expected to facilitate translation into routine practice. The future of cardio-oncology will likely depend on integrated molecular profiling approaches that enable precision cardiovascular care for cancer patients and survivors.

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