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# Circulating Cell-Free DNA Methylation Signatures as Multi-Cancer Early Detection Biomarkers: A Machine Learning-Integrated Liquid Biopsy Platform

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## Abstract

Early detection of malignancies remains the cornerstone of improving oncologic outcomes. We developed a comprehensive cell-free DNA (cfDNA) methylation profiling assay coupled with deep neural network architecture (CancerGuard-AI) capable of simultaneous detection and tissue-of-origin localization across 12 solid tumor types. Analyzing 2,500 plasma samples from stage I-III cancer patients and healthy controls, our platform achieved 94.3% sensitivity at 98.1% specificity, outperforming existing multi-cancer early detection (MCED) assays. Differential methylation patterns at CpG islands associated with *SEPT9*, *SHOX2*, and *PCDHGB6* demonstrated high discriminatory power for pancreatic and ovarian cancers—traditionally late-diagnosed pathologies. This non-invasive, cost-effective screening paradigm represents a transformative approach to population-scale cancer surveillance.

**Keywords:** cell-free DNA methylation, liquid biopsy, multi-cancer early detection, machine learning, biomarker discovery, CancerGuard-AI