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RESEARCH ARTICLE

Artificial Intelligence, ctDNA, and Biomarker-Driven Precision Oncology: Emerging Molecular Strategies for Cancer Diagnosis and Therapeutic Response Prediction

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ABSTRACT

Precision oncology has emerged as a transformative paradigm in cancer diagnosis and therapeutic decision-making through the integration of molecular diagnostics, genomic profiling, artificial intelligence (AI), and translational medicine. Conventional oncology approaches based primarily on histopathological classification frequently fail to address the extensive intertumoral and intratumoral heterogeneity that contributes to therapeutic resistance, metastatic progression, and variable clinical outcomes. Recent advances in next-generation sequencing (NGS), circulating tumor DNA (ctDNA)-based liquid biopsy technologies, transcriptomics, multi-omics integration, and AI-assisted computational oncology have significantly improved biomarker discovery, molecular surveillance, therapeutic response prediction, and personalized treatment strategies. Machine learning and deep learning algorithms are increasingly utilized for tumor classification, digital pathology, radiomics, survival prediction, biomarker-guided therapeutic optimization, and recurrence monitoring. ctDNA-based liquid biopsy platforms further provide minimally invasive approaches for longitudinal tumor profiling, minimal residual disease (MRD) detection, clonal evolution analysis, and real-time therapeutic response monitoring. Molecular biomarkers including EGFR mutations, HER2 amplification, KRAS mutations, microsatellite instability (MSI), tumor mutational burden (TMB), and angiogenic signaling markers are increasingly incorporated into precision therapeutic frameworks. Additionally, AI-assisted integration of genomics, transcriptomics, proteomics, epigenomics, and metabolomics has accelerated translational precision medicine. Despite substantial advances, major challenges remain, including biomarker standardization, AI interpretability limitations, sequencing costs, data heterogeneity, and clinical implementation barriers. This review discusses recent advances in AI-assisted precision oncology, molecular biomarker systems, ctDNA technologies, therapeutic resistance mechanisms, translational oncology, and emerging multi-omics frameworks. The review also highlights future directions involving AI-assisted molecular surveillance, computational oncology platforms, and personalized cancer therapeutics.

KEYWORDS

Precision oncology, artificial intelligence, ctDNA, liquid biopsy, molecular biomarkers, translational medicine, computational oncology, therapeutic resistance, personalized medicine

ARTICLE INFORMATION

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1. Introduction

Cancer remains one of the leading causes of morbidity and mortality worldwide despite substantial advances in molecular therapeutics and diagnostic technologies [1]. According to recent epidemiological analyses, cancer-related mortality continues to increase because of population aging, environmental exposure, lifestyle-associated risk factors, and persistent therapeutic resistance mechanisms [2]. Traditional oncology approaches based primarily on histopathological tumor classification and anatomical localization frequently fail to account for the genomic, transcriptomic, and epigenetic complexity underlying tumor heterogeneity.

Tumor heterogeneity represents a major hallmark of cancer biology and contributes significantly to metastatic dissemination, immune evasion, therapeutic resistance, and disease recurrence [3]. Intratumoral heterogeneity results from genomic instability, clonal evolution, epigenetic remodeling, and tumor microenvironment adaptation, ultimately leading to substantial variability in therapeutic responsiveness among patients with similar histopathological diagnoses.

Precision oncology has therefore emerged as a transformative approach integrating molecular diagnostics, biomarker-guided therapeutics, genomic profiling, computational biology, and translational medicine to personalize cancer management strategies [4]. Recent advances in high-throughput sequencing technologies including whole-genome sequencing, transcriptomics, singlecell sequencing, and circulating tumor DNA (ctDNA)-based liquid biopsy systems have significantly improved tumor molecular characterization and biomarker discovery.

Artificial intelligence (AI) has rapidly become one of the most important technologies in modern oncology because of its capacity to analyze multidimensional biomedical datasets generated from genomics, radiology, pathology, transcriptomics, proteomics, and electronic health records [5]. Machine learning and deep learning algorithms can identify molecular signatures associated with tumor progression, therapeutic responsiveness, recurrence risk, and survival outcomes with greater efficiency than conventional statistical approaches.

Recent developments in ctDNA-based liquid biopsy technologies have further revolutionized molecular oncology by enabling minimally invasive longitudinal monitoring of tumor-derived genetic material [6]. ctDNA analysis facilitates minimal residual disease (MRD) monitoring, early recurrence detection, clonal evolution analysis, and real-time therapeutic response assessment. These advances have substantially expanded the role of biomarker-guided translational oncology and personalized medicine.

This review discusses recent advances in molecular biomarker systems, AI-assisted precision oncology, therapeutic resistance mechanisms, ctDNA technologies, translational multi-omics integration, and emerging computational oncology frameworks involved in modern cancer management. Figure 1 illustrates the overall workflow of AI-assisted precision oncology, highlighting the integration of tumor molecular profiling, ctDNA-based liquid biopsy, artificial intelligence, biomarker identification, therapeutic decision-making, and longitudinal disease monitoring.

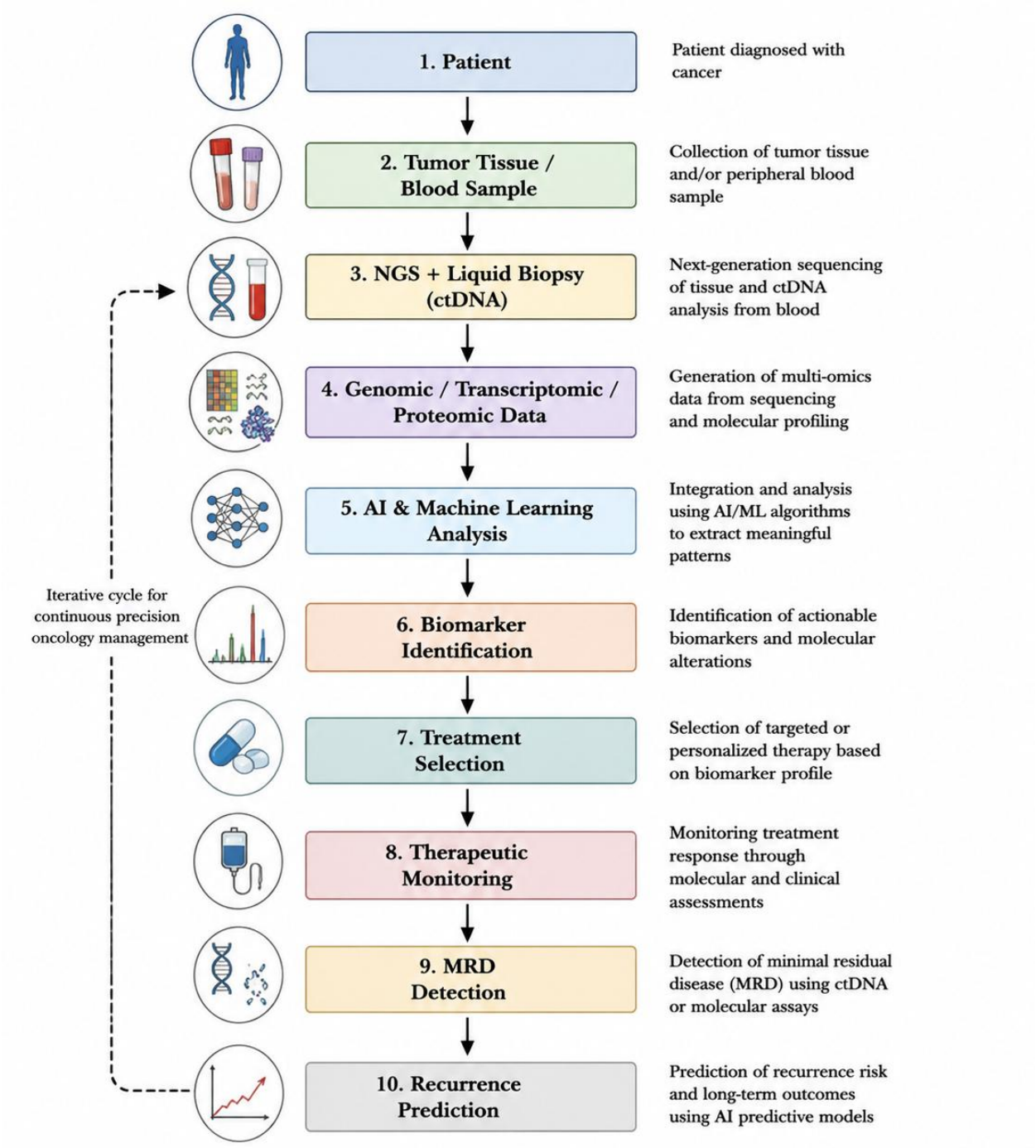


Figure 1. *Workflow of AI-assisted precision oncology integrating multi-omics data and ctDNA-based liquid biopsy for biomarker-driven cancer diagnosis, therapeutic selection, treatment monitoring, minimal residual disease (MRD) detection, and recurrence prediction. Molecular information obtained from tumor tissue and peripheral blood is analyzed using artificial intelligence and machine learning algorithms to identify clinically actionable biomarkers that guide personalized therapeutic decision-making and longitudinal disease surveillance.*

2. Molecular Biomarkers in Precision Oncology

2.1 Overview of Molecular Biomarkers

Molecular biomarkers are measurable biological indicators associated with physiological or pathological processes and are increasingly utilized in cancer diagnosis, prognosis, therapeutic response prediction, disease surveillance, and personalized

therapeutic planning [7]. Biomarkers may include genomic mutations, transcriptomic signatures, epigenetic alterations, proteomic expression patterns, metabolic signatures, and circulating tumor-derived molecules reflective of tumor biology.

Precision oncology relies heavily on biomarker-guided therapeutic systems because tumors with similar histopathological features frequently demonstrate markedly different genomic and transcriptomic profiles associated with variable therapeutic responsiveness.

2.2 Genomic Biomarkers

Genomic biomarkers represent some of the most clinically actionable molecular indicators in oncology. Somatic mutations, copy number alterations, chromosomal rearrangements, and oncogenic pathway dysregulation significantly influence tumor progression and therapeutic susceptibility.

Important genomic biomarkers include:

- EGFR mutations in non-small cell lung cancer,
- HER2 amplification in breast cancer,
- KRAS mutations in colorectal and pancreatic cancers,
- BRAF V600E mutations in melanoma,
- ALK rearrangements,
- and TP53 alterations across multiple malignancies [8] [25].

These biomarkers are increasingly incorporated into targeted therapeutic frameworks and companion diagnostic systems. The major clinically actionable molecular biomarkers, their associated cancer types, and corresponding therapeutic applications are summarized in Table 1.

Table 1. *Major Molecular Biomarkers Used in Precision Oncology*

Biomarker	Associated Cancer Type	Clinical Application
EGFR	Non-small cell lung cancer (NSCLC)	EGFR-targeted tyrosine kinase inhibitors
HER2	Breast cancer	HER2-targeted therapy (e.g., trastuzumab)
KRAS	Colorectal and pancreatic cancers	Predicts resistance to anti-EGFR therapy
BRAF V600E	Melanoma	BRAF-targeted inhibitors
ALK	Non-small cell lung cancer (NSCLC)	ALK-targeted inhibitors
MSI	Multiple cancers	Selection for immune checkpoint inhibitor therapy
TMB	Multiple cancers	Predictive biomarker for immunotherapy response
TP53	Multiple malignancies	Prognostic biomarker and disease monitoring

2.3 Transcriptomic Biomarkers and Gene-Expression Signatures

Transcriptomic profiling has become increasingly important in precision oncology because gene-expression signatures can identify molecular pathways associated with tumor aggressiveness, recurrence risk, and therapeutic responsiveness [9]. AI-assisted gene-expression profiling systems are now utilized to stratify patients according to molecular subtype and treatment sensitivity.

Commercially available transcriptomic assays including Oncotype DX, PAM50, MammaPrint, and Decipher have significantly improved therapeutic planning and recurrence prediction in several malignancies.

Recent AI-assisted meta-analytical studies have further highlighted the role of transcriptomic biomarkers in predicting therapeutic responsiveness and improving precision oncology frameworks [10].

2.4 Tumor Mutational Burden and Microsatellite Instability

Tumor mutational burden (TMB) reflects the total number of somatic mutations within a tumor genome and has emerged as an important predictive biomarker for immunotherapy responsiveness [11]. Tumors with elevated TMB frequently generate increased neoantigen loads that improve immune recognition.

Microsatellite instability (MSI), resulting from mismatch repair deficiency, similarly predicts responsiveness to immune checkpoint blockade therapies. MSI-high tumors demonstrate enhanced responses to PD-1 inhibitors across multiple malignancies.

2.5 Angiogenic Biomarkers and Tumor Microenvironment Remodeling

Angiogenesis plays a critical role in tumor progression, metastatic dissemination, and therapeutic resistance. Vascular endothelial growth factor (VEGF) signaling pathways regulate tumor vascularization and remain major therapeutic targets in oncology.

Important angiogenic biomarkers include:

- VEGF-A,
- VEGFR-1,
- VEGFR-2,
- platelet-derived growth factor (PDGF),
- angiopoietins,
- and hypoxia-inducible factor-1α (HIF-1α) [12].

Dysregulation of angiogenic signaling contributes to tumor hypoxia, metastatic progression, immune suppression, and resistance against anti-angiogenic therapies.

3. Artificial Intelligence in Precision Oncology

3.1 Machine Learning and Deep Learning in Oncology

Artificial intelligence has transformed computational oncology through the development of predictive models capable of analyzing multidimensional biomedical datasets [13]. Machine learning methodologies commonly utilized in oncology include:

- supervised learning,
- unsupervised clustering,
- reinforcement learning,
- deep neural networks,
- convolutional neural networks (CNNs),
- recurrent neural networks (RNNs),
- and natural language processing (NLP).

Deep learning models demonstrate strong performance in tumor classification, genomic interpretation, radiological imaging analysis, and digital pathology.

3.2 AI in Digital Pathology

Digital pathology systems integrated with AI increasingly support automated histopathological interpretation. CNN-based computational models can identify tumor morphology, mitotic activity, immune infiltration, necrosis, and molecular subtype characteristics with high diagnostic accuracy [14].

AI-assisted pathology systems may substantially reduce observer variability and improve diagnostic reproducibility in clinical oncology.

3.3 Radiomics and Radiogenomics

Radiomics involves extraction of quantitative imaging features from radiological datasets including CT, MRI, and PET imaging. AI-assisted radiomic analysis enables identification of imaging biomarkers associated with tumor aggressiveness, metastatic potential, and therapeutic responsiveness [15].

Radiogenomics further integrates imaging characteristics with genomic and transcriptomic data to facilitate non-invasive molecular characterization of tumors and improve personalized therapeutic planning.

3.4 AI-Assisted Predictive Oncology Systems

AI-driven predictive oncology systems analyze genomic, transcriptomic, proteomic, imaging, and clinical datasets to predict therapeutic responsiveness and survival outcomes [16]. Machine learning algorithms can identify molecular signatures associated with chemotherapy sensitivity, immunotherapy responsiveness, targeted therapy resistance, and recurrence risk.

AI-assisted oncology surveillance systems have also improved population-level cancer analytics and epidemiological monitoring. Recent computational oncology platforms analyzing cancer incidence and mortality trends have highlighted disparities in cancer screening accessibility and therapeutic outcomes across diverse populations [17].

4. Therapeutic Resistance Mechanisms in Precision Oncology

Therapeutic resistance remains one of the major causes of treatment failure and disease recurrence in oncology [18]. Resistance mechanisms involve genomic instability, pathway redundancy, epithelial-mesenchymal transition (EMT), cancer stem cell activation, immune evasion, and tumor microenvironment remodeling.

Anti-angiogenic therapies targeting VEGF signaling pathways frequently demonstrate substantial initial efficacy but eventually encounter adaptive resistance mechanisms involving:

- fibroblast growth factor (FGF) signaling,
- PDGF-mediated vascular remodeling,
- HGF/c-MET activation,
- HIF-1α signaling,
- and recruitment of pro-angiogenic inflammatory cells [19] [27].

Tumor hypoxia further promotes genomic instability, metastatic dissemination, and cancer stem cell survival. EMT-associated transcription factors including Snail, Twist, and ZEB1 contribute to invasive phenotypes and therapeutic resistance.

Recent translational oncology studies integrating AI-assisted molecular profiling with ctDNA-based longitudinal surveillance may improve prediction of resistance evolution and facilitate personalized therapeutic adaptation [20] [26].

5. ctDNA and Liquid Biopsy Technologies

5.1 Biology of ctDNA

Circulating tumor DNA consists of fragmented tumor-derived nucleic acids released into circulation through apoptosis, necrosis, and active cellular secretion [21]. ctDNA fragments contain tumor-specific mutations, methylation patterns, chromosomal rearrangements, and genomic alterations reflective of evolving tumor biology.

Because ctDNA reflects real-time tumor dynamics, liquid biopsy technologies have become increasingly important in precision oncology.

5.2 ctDNA Detection Technologies

Major ctDNA analytical technologies include:

- digital droplet PCR (ddPCR),
- BEAMing,
- targeted NGS,
- ultra-deep sequencing,
- methylation-based assays,
- and fragmentomics-based analysis [22] [28].

These approaches demonstrate high analytical sensitivity for detecting low-frequency tumor variants and minimal residual disease.

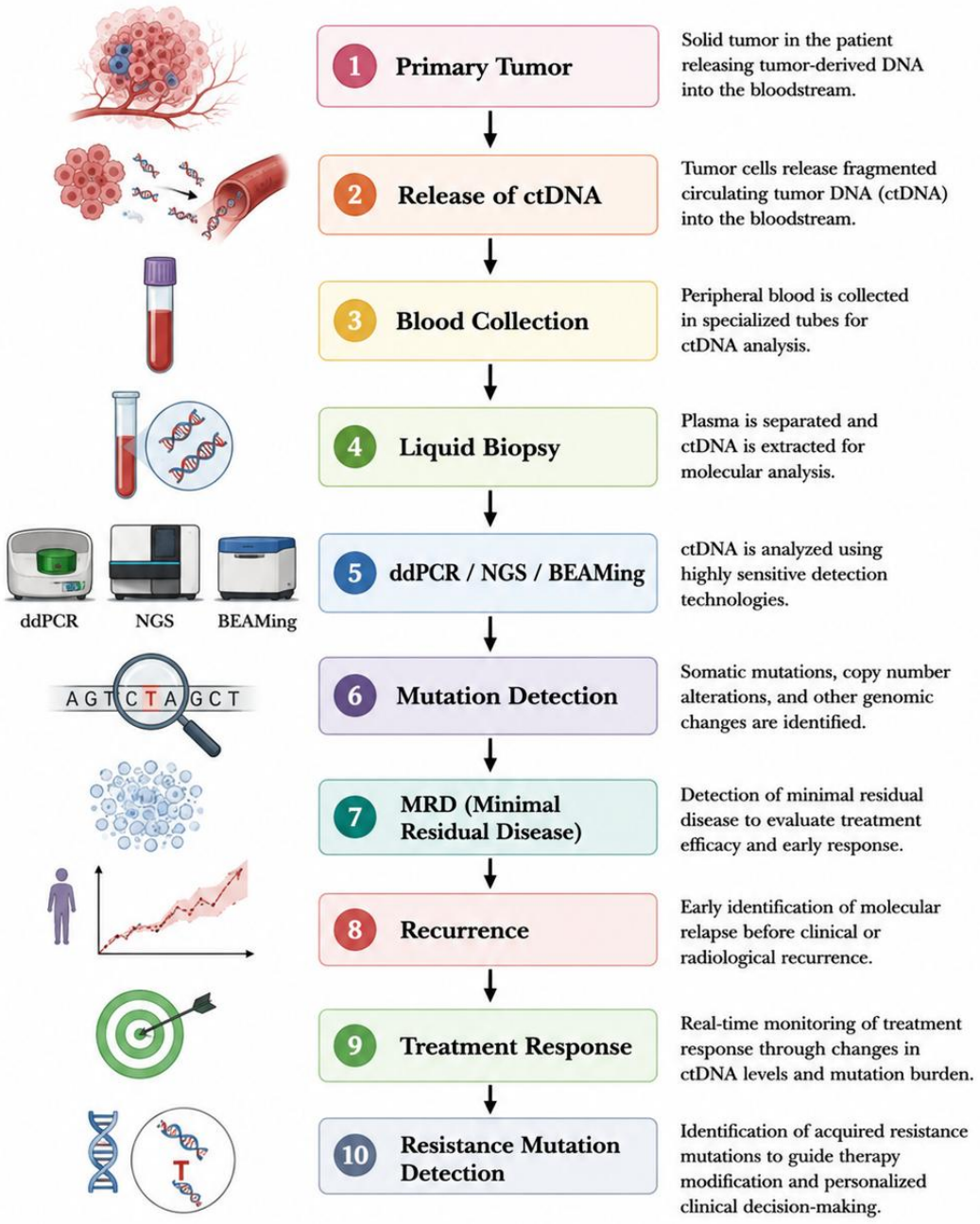
5.3 Clinical Applications of ctDNA

Clinical applications of ctDNA-based liquid biopsy systems include:

- minimal residual disease monitoring,
- early recurrence detection,
- therapeutic response assessment,
- clonal evolution analysis,
- longitudinal molecular surveillance,
- and resistance mutation detection [23].

The integration of AI-assisted analytics with ctDNA profiling may significantly improve predictive oncology systems and personalized surveillance strategies. Figure 2 illustrates the complete workflow of ctDNA-based liquid biopsy, from tumor-derived DNA release through molecular analysis to mutation detection, minimal residual disease (MRD) monitoring, recurrence prediction, treatment response assessment, and resistance mutation identification.

Figure 2. *Clinical workflow of ctDNA-based liquid biopsy in precision oncology. Tumor-derived circulating tumor DNA (ctDNA) released into the bloodstream is collected through peripheral blood sampling and analyzed using highly sensitive molecular technologies, including digital droplet PCR (ddPCR), next-generation sequencing (NGS), and BEAMing. The resulting molecular information supports mutation detection, minimal residual disease (MRD) monitoring, recurrence prediction, treatment response assessment, and identification of acquired resistance mutations, enabling personalized cancer management.*



6. Multi-Omics Integration in Precision Oncology

Modern precision oncology increasingly utilizes multi-omics integration frameworks combining:

- genomics,
- transcriptomics,
- proteomics,
- metabolomics,
- epigenomics,
- and single-cell sequencing technologies [24] [29].

AI-assisted integration of multi-omics datasets improves biomarker discovery, pathway analysis, tumor subtype characterization, and therapeutic response prediction. Single-cell sequencing technologies further improve understanding of intratumoral heterogeneity and clonal evolution.

7. Translational Oncology and Clinical Applications

Translational oncology aims to bridge laboratory discoveries with clinical cancer management. Biomarker-guided oncology systems are increasingly incorporated into:

- companion diagnostics,
- immunotherapy stratification,
- targeted therapy selection,
- ctDNA-guided therapeutic monitoring,
- and personalized surveillance systems.

FDA-approved biomarker-guided therapies now exist for EGFR-mutated lung cancer, HER2-positive breast cancer, BRAF-mutant melanoma, and MSI-high tumors [25].

AI-assisted clinical decision-support systems integrating genomics, pathology, radiology, and ctDNA analytics may significantly improve therapeutic optimization and precision healthcare implementation.

8. Challenges and Limitations

Despite major advances, several limitations remain in AI-assisted precision oncology:

- biomarker standardization limitations,
- AI interpretability challenges,
- sequencing cost barriers,
- data heterogeneity,
- limited multicenter validation,
- ethical concerns regarding patient data privacy,
- and regulatory implementation challenges.

Large international validation studies and explainable AI frameworks remain necessary for widespread clinical implementation.

9. Future Perspectives

Future precision oncology systems will likely integrate:

- AI-assisted ctDNA surveillance,
- wearable biosensor systems,
- real-time molecular monitoring,

- multi-omics predictive analytics,
- automated therapeutic recommendation systems,
- and personalized computational oncology platforms.

Advances in computational biology, molecular diagnostics, and translational medicine may significantly improve cancer detection, therapeutic response prediction, and long-term patient management.

10. Conclusion

Artificial intelligence, ctDNA technologies, molecular biomarkers, and translational multi-omics systems are transforming modern precision oncology. AI-assisted computational oncology improves therapeutic response prediction, biomarker discovery, and personalized treatment optimization, while ctDNA-based liquid biopsy systems provide minimally invasive approaches for longitudinal molecular surveillance and minimal residual disease monitoring.

The continued integration of AI-driven analytics with biomarker-guided molecular diagnostics may substantially improve future precision medicine frameworks, therapeutic personalization, and translational oncology outcomes.

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