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2734 17 Avenue SW,
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+15878858911
editorial-office@sciformat.ca

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ARTIFICIAL INTELLIGENCE-ENHANCED LIQUID BIOPSY IN CANCER MONITORING: FROM TREATMENT RESPONSE TO EARLY DETECTION OF DISEASE RECURRENCE

Vanessa Gąsiorowska (Corresponding Author, Email: vanessagasierowska@gmail.com)
Our Lady of Perpetual Help Hospital in Wołomin, 05-200 Wołomin, ul. Gdynska 1/3, Poland
ORCID ID: 0009-0008-2420-627X

Karolina Grodkowska-Szukala
Municipal Hospital in Zabrze, Zabrze, Poland
ORCID ID: 0009-0000-6179-7242

Ewa Jachimczak
University Hospital in Krakow, Poland
ORCID ID: 0009-0009-6899-3460

Natalia Smyczyńska
SZPZLO Warszawa Praga-Północ, Warsaw, Poland
ORCID ID: 0009-0008-8213-3531

Ewa Wojtanowska
Medical University of Lodz, Poland
ORCID ID: 0009-0007-4813-9473

Paulina Jaruga
Regional Specialized Hospital No. 4, Bytom, Poland
ORCID ID: 0009-0009-3178-3785

Julia Paczyna
Regional Specialized Hospital No. 4, Bytom, Poland
ORCID ID: 0009-0006-5485-7167

Julia Kozicka
Medical University of Lodz, Poland
ORCID ID: 0009-0003-8138-6231

Mateusz Michalak
Medical University of Warsaw, Warsaw, Poland
ORCID ID: 0009-0002-5495-4670

Marcin Mazur
Medical University of Lodz, Poland
ORCID ID: 0009-0008-2408-2107

ABSTRACT

Liquid biopsy has emerged as an important minimally invasive technology in contemporary oncology, enabling repeated assessment of tumor-derived molecular information through blood and other biological fluids. Circulating tumor DNA (ctDNA), circulating tumor cells, cell-free DNA methylation patterns, extracellular vesicles, circulating RNA and fragmentomic signatures may provide dynamic information about tumor burden, treatment response, molecular residual disease and cancer recurrence. However, liquid biopsy generates complex, multidimensional datasets in which tumor-derived signals may be extremely small relative to biological and technical background. Artificial intelligence (AI), including machine learning and deep learning, offers a potential computational framework for integrating these heterogeneous signals and generating clinically meaningful predictions.

This review examines the emerging convergence of AI and liquid biopsy, with particular emphasis on longitudinal cancer monitoring rather than cancer detection alone. The available PubMed-indexed literature was reviewed to evaluate the potential role of AI-enhanced liquid biopsy in treatment-response assessment, minimal residual disease detection, prediction of treatment resistance and early identification of disease recurrence. Evidence from colorectal, lung, breast, hepatocellular and other solid tumors is discussed. The review also addresses major translational barriers, including low tumor shedding, clonal hematopoiesis, analytical heterogeneity, external validation, algorithmic bias, interpretability, data privacy, cost and uncertainty regarding clinical actionability. Current evidence indicates that AI can extract complementary biological information from complex circulating biomarker datasets, but prospective validation is still required before widespread implementation. AI-enhanced liquid biopsy may ultimately support a transition from episodic, imaging-centered surveillance toward personalized, dynamic and molecularly informed cancer monitoring.

KEYWORDS

Artificial Intelligence, Liquid Biopsy, Cancer Recurrence, Precision Oncology

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1. Introduction

Cancer diagnosis and treatment have entered an era in which the biological complexity of individual tumors increasingly determines clinical decision-making. Conventional oncology has traditionally relied on tissue pathology, radiological imaging, serum biomarkers and clinical assessment. These approaches remain indispensable; however, each provides only a partial representation of tumor biology. Tissue biopsy can offer detailed histopathological and molecular information but is invasive, may be difficult to repeat, and samples only a limited spatial component of a heterogeneous malignancy. Imaging primarily reflects anatomical changes and may not detect molecular evolution until substantial disease progression has occurred.

Liquid biopsy has emerged as a complementary technology capable of providing tumor-associated molecular information through minimally invasive sampling of blood and other body fluids (Nikanjam et al., 2022; Markou et al., 2022). Circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), circulating tumor cells (CTCs), extracellular vesicles and circulating RNA are among the principal analytes investigated in oncology. The potential clinical applications include molecular profiling, treatment selection, treatment monitoring, detection of molecular residual disease (MRD), identification of resistance mechanisms and prediction of recurrence (Lone et al., 2022; Markou et al., 2022; Nikanjam et al., 2022).

The particular value of liquid biopsy is its potential for longitudinal assessment. Unlike a conventional tissue biopsy, blood sampling can be repeated at multiple time points during treatment and follow-up. Consequently, liquid biopsy may provide a dynamic representation of tumor evolution rather than a single molecular snapshot. Serial ctDNA measurements, for example, can demonstrate changes in tumor-derived molecular signals before conventional radiological progression becomes evident (Bartolomucci et al., 2025; Li et al., 2025).

The clinical relevance of this approach is supported by accumulating evidence across several tumor types. In colorectal cancer, postoperative ctDNA detection has been associated with a substantially increased risk of recurrence and has been investigated as a tool for guiding adjuvant therapy (Chen et al., 2022; Choi et al., 2024; Tie et al., 2016). In breast cancer, systematic evidence indicates that ctDNA positivity during follow-up is associated with significantly worse disease-free and overall survival (Nader-Marta et al., 2024). In lung cancer, ctDNA-based MRD assessment is increasingly investigated as a prognostic marker and potential tool for treatment stratification (Tang et al., 2023; Xia et al., 2023).

Nevertheless, the increasing sophistication of liquid biopsy creates a new analytical problem. Modern assays may simultaneously generate information about thousands of genomic and epigenomic features, including mutations, copy-number changes, methylation patterns, fragment lengths, fragment-end motifs and nucleosomal organization. The tumor-derived signal may represent only a small fraction of the total cfDNA pool. Consequently, distinguishing clinically relevant tumor signals from biological and technical noise can be challenging (Tébar-Martínez et al., 2023; Association for Molecular Pathology & College of American Pathologists, 2024).

Artificial intelligence (AI) may provide an analytical framework capable of addressing this complexity. Machine-learning algorithms can identify nonlinear relationships between molecular variables, whereas deep-learning approaches can process high-dimensional genomic, epigenomic and fragmentomic datasets. Recent studies demonstrate that AI-assisted liquid biopsy can integrate multiple weak signals that may be difficult to interpret using conventional single-biomarker approaches (Tsui et al., 2025; He et al., 2023).

Importantly, the most clinically meaningful application of AI-enhanced liquid biopsy may not be cancer detection alone. A rapidly developing research direction is longitudinal cancer monitoring, in which repeated molecular measurements are used to estimate treatment response, identify MRD, detect emerging resistance and predict recurrence.

This distinction has major implications for oncology. Early detection of cancer is clinically valuable, but after a diagnosis has already been established, clinicians frequently face a different problem: determining whether treatment is working, whether microscopic disease remains after apparently successful therapy, and whether recurrence is likely to develop before it becomes radiologically or clinically apparent.

AI-enhanced liquid biopsy could potentially address these questions by integrating serial molecular data with clinical characteristics, pathology, imaging and treatment history. Instead of providing a single binary result, such systems could generate individualized probabilities of treatment response, disease persistence or future recurrence.

The objective of this review is therefore to critically examine the convergence of AI and liquid biopsy in dynamic cancer monitoring, with particular emphasis on treatment response, MRD, treatment resistance and early detection of recurrence. The review also evaluates the technological, clinical, ethical and social barriers that must be addressed before this approach can be integrated into routine oncology practice.

2. Methodology

This study was conducted as a narrative review of contemporary PubMed-indexed literature concerning liquid biopsy, artificial intelligence and cancer monitoring.

The review was designed to provide a clinically oriented synthesis rather than a formal systematic review or meta-analysis. No quantitative pooled effect estimate was calculated by the authors. The literature was organized thematically according to major clinical applications of AI-enhanced liquid biopsy.

A targeted search of the PubMed/MEDLINE database was performed using combinations of the terms “liquid biopsy,” “circulating tumor DNA,” “cell-free DNA,” “artificial intelligence,” “machine learning,” “deep learning,” “cancer monitoring,” “minimal residual disease,” “treatment response,” “treatment resistance,” “cancer recurrence,” “fragmentomics,” “methylation,” and “multi-omics.” Additional searches combined these terms with colorectal cancer, non-small cell lung cancer, breast cancer, hepatocellular carcinoma and pancreatic cancer.

Priority was given to peer-reviewed studies and reviews indexed in PubMed, with particular attention to publications from 2022 to 2026. Earlier landmark studies were included when they established fundamental evidence regarding ctDNA, MRD or longitudinal tumor monitoring.

Articles were considered relevant if they addressed liquid biopsy technologies, ctDNA/cfDNA analysis, AI or machine-learning analysis of circulating biomarkers, MRD detection, treatment-response monitoring, prediction or detection of treatment resistance, cancer recurrence prediction, or integration of multi-omic

liquid-biopsy data. Studies focusing exclusively on tissue-based AI applications without a liquid-biopsy component were not considered central to this review.

The identified literature was synthesized according to the clinical pathway: baseline molecular assessment → treatment → serial liquid biopsy → AI-based analysis → response assessment → MRD detection → resistance prediction → recurrence surveillance. Particular attention was paid to clinical validity, analytical limitations, external validation, interpretability, standardization and potential implications for patient-centered oncology.

3. Results

Liquid biopsy encompasses the analysis of tumor-associated material circulating in blood or other biological fluids. Current technologies include analysis of ctDNA, cfDNA, CTCs, extracellular vesicles and circulating RNA (Nikanjam et al., 2022; Markou et al., 2022). Among these analytes, ctDNA has become one of the most intensively studied because it can contain tumor-specific genomic and epigenomic information. Depending on the assay, clinically relevant characteristics may include somatic mutations, copy-number alterations, methylation patterns and fragmentomic signatures.

The principal advantage of ctDNA is its potential for repeated measurement. Tumor-derived molecular signals may change rapidly following initiation of treatment, providing a potentially earlier indication of biological response than conventional imaging (Bartolomucci et al., 2025; Li et al., 2025). A trajectory can contain clinically meaningful information even when individual measurements are difficult to interpret. The interpretation of such trajectories becomes increasingly complex when multiple mutations and molecular features are measured simultaneously. This creates a natural role for AI.

4. Major Liquid-Biopsy Biomarkers Relevant to Artificial Intelligence

ctDNA is released into the circulation from tumor cells through apoptosis, necrosis and other biological processes. Its potential clinical applications include molecular genotyping, treatment selection, treatment-response monitoring, MRD detection, recurrence prediction and resistance detection. A recent review emphasized that ctDNA is increasingly being investigated as a dynamic biomarker for treatment monitoring across lung, colorectal and breast cancers (Bartolomucci et al., 2025). Another recent review described ctDNA as a pan-cancer biomarker with both prognostic and predictive potential (Hitchen et al., 2025). However, ctDNA concentration varies substantially according to tumor type, disease stage, tumor burden, anatomical location and biological characteristics.

Cancer-associated DNA methylation abnormalities can provide information about malignant tissue that is not dependent on a single somatic mutation. Methylation-based approaches are attractive for early cancer detection and tissue-of-origin classification. Because methylation data are highly multidimensional, AI is increasingly used to identify combinations of CpG sites or methylation patterns associated with malignancy. The 2026 systematic review and meta-analysis by Filis et al. identified 109 studies evaluating machine learning and cfDNA features for early cancer detection (Filis et al., 2026).

Fragmentomics refers to analysis of physical properties of cfDNA fragments, including fragment length, end motifs, genomic distribution and nucleosomal patterns. Cancer alters chromatin organization and cell-death processes, potentially generating distinctive cfDNA fragmentation profiles (Mathios et al., 2024). Fragmentomics is particularly suited to AI because it produces high-dimensional data.

CTCs are intact malignant cells released into the circulation. Their rarity and heterogeneity make detection challenging, but CTCs may provide information about tumor phenotype, metastatic potential and treatment response. Recent research has demonstrated the feasibility of combining CTC enumeration with machine-learning-based biomarkers for cancer classification (Liu et al., 2026).

Extracellular vesicles and circulating RNA provide additional molecular information. Exosomes may contain DNA, RNA, microRNA and proteins that reflect tumor biology. Circulating RNA signatures may also provide information regarding tumor phenotype. The integration of these analytes with ctDNA could theoretically generate a more complete molecular representation of disease, although analytical complexity and reproducibility remain important challenges.

Table 1. Major liquid-biopsy analytes and their potential role in AI-enhanced cancer monitoring.

Analyte	Principal information	Potential AI application	Main limitation
ctDNA	Tumor-specific genomic alterations	MRD, response, recurrence, resistance	Low abundance
cfDNA methylation	Epigenetic tumor signatures	Classification and tissue-of-origin prediction	Biological heterogeneity
Fragmentomics	Fragment length/end patterns	High-dimensional classification	Complex analysis
CTCs	Intact tumor cells	Enumeration and phenotypic classification	Very low abundance
Extracellular vesicles	DNA/RNA/protein cargo	Multi-omic prediction	Isolation variability
Circulating RNA	miRNA and other RNA signatures	Prognosis and treatment prediction	Reproducibility
Multi-omics	Combined molecular information	Integrated AI prediction	Data harmonization

5. Artificial Intelligence as an Analytical Layer

AI should not be considered a replacement for liquid biopsy technology. Rather, it can be conceptualized as an analytical layer between biological measurement and clinical decision-making.

The basic workflow is: biological sample → molecular assay → high-dimensional data → AI analysis → clinical prediction → clinical decision. Machine-learning approaches include random forests, support-vector machines, gradient boosting, neural networks and ensemble models. Deep learning can process particularly complex data structures and may be useful when multiple molecular modalities are integrated.

A recent systematic review and meta-analysis found high pooled diagnostic performance for AI-enhanced liquid biopsy, although substantial between-study heterogeneity was observed (Sisca et al., 2026). This finding is encouraging but requires careful interpretation. A high AUROC in a retrospective dataset does not demonstrate clinical utility. The critical question is whether an AI prediction changes patient management in a way that improves outcomes.

6. AI and Treatment-Response Monitoring

Conventional assessment of treatment response is frequently based on imaging. Imaging remains essential, but molecular changes may precede anatomical changes. Serial ctDNA analysis has therefore attracted substantial interest as an early dynamic biomarker. A 2025 review summarized evidence that ctDNA may inform treatment selection, monitor response and identify resistance across several solid tumors (Bartolomucci et al., 2025).

In metastatic colorectal cancer, sequential ctDNA analysis has been associated with treatment response and survival outcomes [7,21]. The potential contribution of AI is to transform repeated measurements into an individualized trajectory. Instead of ctDNA positive/negative, a model may consider baseline level, rate of decline, mutation-specific kinetics, clinical characteristics, treatment and imaging.

ctDNA clearance is one of the most investigated molecular-response concepts. In metastatic colorectal cancer, patients demonstrating ctDNA normalization during systemic therapy have shown more favorable outcomes than those with persistent molecular disease (Choi et al., 2024). Similar concepts are being investigated in patients receiving immunotherapy. A 2025 systematic review and meta-analysis found that ctDNA clearance during neoadjuvant immune-checkpoint inhibitor therapy was associated with pathological complete response, although specificity was limited and heterogeneity was substantial (Valenza et al., 2025).

A biomarker can therefore be biologically informative without yet being sufficiently validated to determine treatment. AI may improve prediction by incorporating additional variables, but it cannot compensate for inadequate clinical validation.

7. Minimal Residual Disease

MRD is one of the most important potential applications of liquid biopsy. Following apparently curative treatment, imaging may show no evidence of disease even though microscopic tumor cells remain. The detection of ctDNA after surgery may provide molecular evidence of residual disease.

The landmark study by Tie et al. demonstrated that postoperative ctDNA detection in stage II colorectal cancer was strongly associated with recurrence (Tie et al., 2016). Subsequent studies and meta-analyses have confirmed the prognostic significance of postoperative ctDNA in colorectal cancer (Chen et al., 2022).

The DYNAMIC randomized trial demonstrated that ctDNA-guided management could reduce chemotherapy use in selected patients with stage II colon cancer without compromising recurrence-free survival within the predefined study framework (Tie et al., 2022). More recent evidence has extended ctDNA-guided treatment research to stage III disease. The DYNAMIC-III trial confirmed the strong prognostic value of ctDNA but also demonstrated that simply escalating chemotherapy in ctDNA-positive patients does not necessarily improve outcomes (Reinert et al., 2025).

This distinction is crucial. AI may identify patients at high risk, but risk prediction is not equivalent to therapeutic benefit.

8. AI-Based Prediction of Cancer Recurrence

Cancer recurrence is perhaps the most clinically attractive target for AI-enhanced liquid biopsy. After curative-intent treatment, conventional surveillance is generally scheduled according to population-level guidelines. Patients with different biological risks may nevertheless receive similar follow-up schedules. Liquid biopsy introduces the possibility of risk-adapted surveillance.

The patient could undergo serial blood sampling, with AI continuously updating recurrence risk. A conceptual model is: tumor characteristics + treatment + postoperative ctDNA + serial ctDNA kinetics + imaging + clinical variables → individualized recurrence probability.

Evidence in colorectal cancer demonstrates that postoperative ctDNA positivity is associated with substantially increased recurrence risk (Chen et al., 2022). In breast cancer, systematic evidence demonstrates strong associations between ctDNA detection and worse disease-free and overall survival (Nader-Marta et al., 2024).

AI may further refine risk prediction by incorporating molecular dynamics rather than relying on a single measurement. The clinical challenge is to determine whether earlier molecular detection leads to an intervention that improves outcomes.

9. Treatment Resistance

Tumors evolve under therapeutic pressure. The emergence of resistant clones can sometimes be detected molecularly before radiological progression. Liquid biopsy is particularly attractive because it can be repeated without obtaining new tissue.

Serial ctDNA profiling can reveal emerging alterations associated with resistance. Dynamic ctDNA assessment in KRAS G12C-mutated tumors demonstrated that early changes in circulating mutant DNA were associated with response and progression-free survival during targeted therapy (Choi et al., 2024).

A recent review of liquid biopsy in cancer drug resistance emphasized its potential for real-time monitoring of tumor evolution and treatment resistance and highlighted integration with AI and big-data technologies as a future direction (Liquid biopsy in cancer drug resistance, 2026). AI could theoretically identify patterns of molecular evolution more complex than a single resistance mutation.

However, treatment decisions should not be based solely on a predicted resistance state until prospective clinical validation demonstrates that intervention based on that information improves outcomes.

10. Tumor-Specific Applications

Colorectal cancer currently represents one of the strongest clinical environments for ctDNA-guided monitoring. Applications include postoperative MRD, recurrence prediction, adjuvant treatment selection, monitoring metastatic disease, treatment-response assessment and detection of emerging resistance (Chen et al., 2022; Choi et al., 2024; Tie et al., 2016, 2022; Reinert et al., 2025).

NSCLC presents a particularly interesting application because of its molecular heterogeneity and rapid therapeutic evolution. ctDNA-based MRD assessment has demonstrated prognostic significance in patients

receiving curative-intent treatment (Tang et al., 2023; Xia et al., 2023). A recent review describes the integration of AI with ctDNA in NSCLC for mutation detection, MRD prediction and earlier relapse detection (Wang et al., 2026).

Breast cancer is another major field for ctDNA-guided surveillance. The 2024 meta-analysis by Nader-Marta et al. demonstrated that ctDNA detection was associated with substantially increased risks of recurrence and death (Nader-Marta et al., 2024). AI could potentially combine ctDNA status with receptor status, tumor grade, pathological response, genomic characteristics and treatment regimen.

Hepatocellular carcinoma is also relevant because ctDNA, methylation and other circulating biomarkers are being investigated for diagnosis, prognosis and monitoring. Interpretation is challenging because underlying liver disease can affect circulating molecular signals.

Pancreatic cancer represents a major unmet clinical need. The combination of liquid biopsy and AI is attractive, but evidence remains less mature than in colorectal cancer or lung cancer. Small sample sizes, case-control designs and insufficient external validation remain major concerns.

11. Multi-Omics and Deep Learning

The future of liquid biopsy is unlikely to depend on a single biomarker. Genomic alterations, DNA methylation, fragmentomics, circulating RNA, proteins and extracellular vesicles may each capture different aspects of tumor biology.

An integrative approach may therefore outperform a single-modality strategy. AI is particularly relevant because multi-omics datasets rapidly become too complex for conventional statistical approaches. Recent work emphasizes the clinical development of MRD and multi-cancer early detection using liquid-biopsy multiomics with AI (Shibuki et al., 2026).

Deep learning applied to cfDNA fragmentomic information may eventually allow inference of tumor phenotypic information traditionally obtained from tissue. Such approaches are promising but remain experimental and require independent clinical validation.

12. Clinical Advantages of AI-Enhanced Liquid Biopsy

Potential advantages include minimally invasive longitudinal monitoring, dynamic assessment, integration of heterogeneous data, early identification of molecular change, individualized risk prediction, potential treatment adaptation and, in selected contexts, reduction of unnecessary interventions.

These advantages support the concept of liquid biopsy as a component of precision oncology rather than merely an alternative diagnostic test.

13. Limitations

Low tumor shedding is a fundamental limitation. Not all tumors release sufficient DNA into circulation, and low ctDNA concentration can produce false-negative results.

Clonal hematopoiesis can generate mutations in blood cells that may be mistaken for tumor-derived mutations, particularly in mutation-based assays.

Analytical variability is another important issue. Different laboratories use different sample-processing protocols, sequencing platforms, variant-calling algorithms and thresholds.

False-positive and false-negative results can lead to unnecessary procedures or false reassurance. Many AI studies are also based on small retrospective datasets, creating a risk of overfitting.

External validation is essential because models developed in one population may perform poorly in another. Differences in ethnicity, age, cancer prevalence, disease stage, treatment patterns and sequencing platforms may affect model performance.

Interpretability is also important. Clinicians may be reluctant to make treatment decisions based on a model that produces a risk score without explaining the main contributing factors.

14. Standardization and Clinical Validation

Standardization is one of the most important prerequisites for clinical translation. Consensus recommendations concerning cfDNA assay validation emphasize sample collection, plasma processing, cfDNA extraction, sequencing methodology, analytical sensitivity, variant classification, bioinformatics and reporting (Association for Molecular Pathology & College of American Pathologists, 2024).

The AI layer introduces additional requirements, including model architecture, training and validation datasets, external validation, calibration, missing-data handling, feature selection and threshold selection.

Future studies should report sensitivity, specificity, positive and negative predictive values, calibration and decision-curve analysis in addition to AUROC. Clinical utility must be demonstrated prospectively.

15. Ethical and Social Implications

The implementation of AI-enhanced liquid biopsy raises issues beyond laboratory medicine. A molecular result indicating increased recurrence risk can have substantial psychological consequences, particularly when molecular recurrence precedes conventional imaging.

Liquid biopsy can generate highly sensitive molecular information. When these data are combined with electronic health records and AI systems, data governance and cybersecurity become essential.

Algorithmic bias is another concern. AI systems trained predominantly on specific populations may perform differently in other demographic groups. Training datasets should therefore include diverse patient populations.

Advanced sequencing and AI infrastructure may initially be available primarily in high-resource healthcare systems. This creates a potential risk that technological innovation may increase healthcare inequality.

AI should support rather than replace the clinician. Treatment decisions based on an algorithm must remain embedded within clinical judgment and multidisciplinary decision-making.

16. From Biomarker to Clinical Decision-Support System

The ultimate objective should not be development of increasingly accurate diagnostic algorithms. The objective should be clinically useful decision-support systems.

A diagnostic model asks whether a molecular signal is compatible with cancer. A monitoring system asks what the patient's probability of treatment response, residual disease, resistance or recurrence is, and what should be done about it.

A future system could integrate liquid biopsy, imaging, pathology, electronic health records, treatment history, clinical characteristics and longitudinal AI analysis. The output could be an individualized risk profile.

Table 2. Potential clinical applications of AI-enhanced liquid biopsy.

Clinical question	Liquid-biopsy input	AI function	Potential clinical implication
Is treatment effective?	Serial ctDNA	Trajectory analysis	Early response assessment
Does MRD remain?	ctDNA	Risk classification	Adjuvant treatment stratification
Is resistance developing?	Serial genomic alterations	Pattern recognition	Earlier confirmatory testing
Is recurrence likely?	Serial ctDNA + clinical variables	Risk prediction	Personalized surveillance
Is imaging necessary?	Molecular trajectory	Risk stratification	Targeted imaging
Can multiple biomarkers be integrated?	Multi-omic data	Multimodal learning	Personalized decision support

Importantly, the 2026 ASCO guideline states that ctDNA results should be used when they can support an evidence-based clinical action; negative, inconclusive or clinically discordant results may require tissue-based confirmation, and concentration-based ctDNA measures should not be used as surrogate measures of disease (Lockwood et al., 2026). This guidance reinforces the principle that molecular information must be interpreted within clinical context.

17. Future Perspectives

Future models should incorporate time rather than analyzing isolated samples. Time-series models may be particularly appropriate for serial ctDNA measurements.

Multi-omic liquid biopsy may increase sensitivity by integrating genomic, methylomic, fragmentomic and transcriptomic information.

Explainable AI may facilitate physician acceptance by providing understandable information regarding the variables contributing to predictions.

Federated learning may allow institutions to collaborate on AI development without transferring all patient-level data to a centralized database.

The next generation of systems may combine liquid biopsy, radiology, digital pathology, clinical records, genomics and patient-reported outcomes.

The most important research priority is prospective interventional validation. Future trials should compare AI-guided management with standard care and measure overall survival, disease-free survival, quality of life, treatment toxicity, healthcare utilization and cost-effectiveness.

18. Discussion

The evidence reviewed in this article demonstrates that liquid biopsy and artificial intelligence are converging at a particularly important point in the evolution of precision oncology.

Liquid biopsy provides repeated access to tumor-associated molecular information, while AI provides computational tools for integrating increasingly complex data. The combination is potentially most valuable in longitudinal monitoring.

The traditional oncology pathway is relatively episodic: diagnosis → treatment → scheduled imaging → clinical assessment → treatment decision. AI-enhanced liquid biopsy could support a more dynamic pathway: diagnosis → molecular characterization → treatment → serial liquid biopsy → AI analysis → updated risk estimate → targeted clinical assessment → treatment adaptation.

The strongest current clinical evidence concerns the prognostic value of ctDNA. Studies in colorectal cancer, breast cancer and lung cancer demonstrate associations between molecular positivity and adverse outcomes (Chen et al., 2022; Nader-Marta et al., 2024; Tang et al., 2023; Xia et al., 2023; Tie et al., 2016). The next step is to determine whether AI can improve upon these established biomarkers.

Recent evidence suggests that AI can extract additional information from complex datasets (Filis et al., 2026; Sisca et al., 2026; Wang et al., 2026; Shibuki et al., 2026). However, many studies remain retrospective, the biological signal is not uniform across cancers, and an accurate prediction may not have an established therapeutic consequence.

The DYNAMIC-III trial is particularly informative. It demonstrates that ctDNA can strongly stratify prognosis, but intensifying conventional chemotherapy solely because ctDNA is positive did not improve recurrence-free survival (Reinert et al., 2025). This finding emphasizes the distinction between prediction and intervention.

Future studies should therefore ask not only whether AI can predict recurrence, but whether it can predict recurrence sufficiently early and accurately to enable an intervention that improves outcomes.

Overall, the literature supports a cautious but optimistic interpretation. Liquid biopsy is already clinically relevant in selected contexts, while AI is increasingly capable of extracting information from complex molecular data. The convergence of these technologies could make oncology surveillance more dynamic and individualized. However, the field should resist equating computational novelty with clinical readiness. The central question is not whether an algorithm can recognize a molecular pattern, but whether that pattern can be measured reliably, interpreted correctly, communicated responsibly, and translated into an action that improves patient outcomes.

The strongest future evidence will come from prospective studies with predefined clinical actions. Such trials should specify the assay, sampling schedule, AI model, decision thresholds, confirmatory procedures, and treatment pathways before outcome data are analyzed. Endpoints should include not only sensitivity, specificity, AUROC, and lead time, but also recurrence-free survival, overall survival, quality of life, unnecessary imaging, invasive procedures, treatment exposure, patient-reported anxiety, and healthcare costs. Randomized designs will be particularly important when the model is intended to change treatment rather than simply provide additional prognostic information.

A further priority is integration with existing clinical workflows. An AI system that requires clinicians to leave the electronic health record, manually upload molecular results, and interpret a separate dashboard is less likely to achieve routine adoption. Ideally, validated molecular risk information would be presented alongside pathology, imaging, treatment history, and laboratory results, with clear documentation of the evidence supporting the prediction. The system should also distinguish between automated alerts, recommendations for confirmatory testing, and actual treatment decisions. This separation can reduce the risk that clinicians perceive an algorithmic prediction as an autonomous prescription.

The regulatory environment is likely to evolve alongside the technology. AI models that influence diagnosis, prognosis, or treatment may require continuous performance monitoring because both laboratory assays and clinical practice change over time. Model drift can occur when sequencing platforms are updated, treatment patterns change, new variants become clinically relevant, or patient populations shift. A clinically deployed system should therefore include mechanisms for version control, recalibration, auditability, and post-deployment surveillance. These requirements are particularly important for longitudinal systems that may be used repeatedly throughout a patient's cancer journey.

From a health-system perspective, AI-enhanced liquid biopsy could potentially reduce the frequency of unnecessary imaging or invasive procedures, but it could also increase testing and downstream investigations. A high-sensitivity model may identify many low-probability molecular signals that trigger repeat blood tests, imaging, biopsies, or specialist consultations. Economic evaluation should therefore consider the complete diagnostic pathway rather than the price of the blood test alone. Cost-effectiveness will depend on assay cost, testing frequency, downstream procedures, treatment changes, patient outcomes, and healthcare-system capacity.

The social implications of molecular surveillance are substantial. A patient who receives a molecular result indicating elevated recurrence risk may experience anxiety even when imaging remains negative. Conversely, repeated negative results can provide reassurance but may also create false confidence if the assay has limited sensitivity in a particular tumor type. Communication of AI-generated risk estimates therefore requires careful attention to uncertainty. Clinicians should explain whether the result is prognostic, predictive, or investigational; what the assay can and cannot detect; and what action, if any, follows from the result. Patient-centered implementation should be considered alongside analytical validation.

Equity and generalizability should also be treated as technical requirements. Cancer incidence, tumor biology, treatment access, screening practices, and laboratory infrastructure vary across populations. If training datasets disproportionately represent patients from major academic centers or particular demographic groups, performance may not transfer to community hospitals or underrepresented populations. International validation is particularly relevant for a technology intended for broad oncology use. Models should be assessed for calibration and error patterns across age groups, sex, ancestry, socioeconomic context, tumor stage, and healthcare settings, while avoiding inappropriate use of sensitive attributes as shortcuts for biological prediction.

The integration of multi-omics data creates both an opportunity and a methodological challenge. Genomic variants, methylation patterns, fragment size distributions, circulating RNA, proteins, extracellular vesicles, and clinical variables may contain complementary information. An AI system can potentially learn interactions among these domains that are difficult to identify with conventional statistical models. Yet adding more variables does not automatically improve clinical performance. Multi-omic models can become vulnerable to overfitting, missing data, batch effects, and differences in assay availability. The most useful future systems may therefore be modular, allowing models to operate reliably with a core set of validated measurements while incorporating additional modalities when they are available.

Interpretability has a practical role in this setting. Clinicians are accustomed to integrating pathology, imaging, laboratory results, and clinical history, and they may reasonably question an algorithm that produces a high-risk score without an understandable rationale. Explainable AI methods such as feature attribution, SHAP values, partial dependence, or clinically interpretable nomograms may help reveal whether a prediction is driven by plausible biological features. However, interpretability should not be confused with correctness. A model can provide a convincing explanation for an incorrect prediction. Explainability therefore complements, rather than replaces, external validation and prospective evaluation.

The challenge of false-negative results is equally important. A negative ctDNA test does not necessarily exclude residual disease because tumor shedding varies by tumor type, anatomical site, disease burden, vascularity, and biological phenotype. Low-volume disease may remain below the analytical detection threshold. Consequently, an AI model should not convert a negative molecular result into an unconditional

statement that recurrence is absent. Instead, the model should estimate risk while explicitly accounting for assay sensitivity and the clinical context. This is particularly important in settings such as brain metastases, low-shedding tumors, and tumors with limited circulating burden.

Clonal hematopoiesis further complicates interpretation of mutation-based liquid biopsy. Age-related or therapy-related hematopoietic clones can release DNA carrying somatic alterations that resemble tumor-derived variants. Without appropriate controls or matched leukocyte sequencing, an AI system may learn associations that are biologically misleading. This is a reminder that computational sophistication cannot compensate for inadequate biological annotation. The most robust pipelines will likely combine algorithmic filtering with orthogonal laboratory information, including matched white-blood-cell DNA, tumor tissue when available, and longitudinal confirmation of suspicious variants.

Data quality is another central determinant of model reliability. Liquid-biopsy datasets are particularly vulnerable to preanalytical variation because blood collection tubes, processing time, centrifugation, storage conditions, DNA extraction, sequencing depth, error suppression, and bioinformatic pipelines can all influence the final signal. If a machine-learning model learns laboratory-specific artifacts instead of tumor biology, apparent performance may collapse when it is transferred to another institution. This problem is especially relevant to multicenter studies and to AI models that integrate fragmentomics or other subtle features. Standardized protocols and detailed reporting of preanalytical and analytical variables should therefore be considered part of the model itself rather than peripheral laboratory information.

The DYNAMIC experience in colorectal cancer illustrates why this distinction matters. ctDNA-guided management has demonstrated that molecular risk can be incorporated into treatment selection and can reduce unnecessary chemotherapy in selected patients. At the same time, later trials and broader clinical experience emphasize that the direction of a ctDNA result does not always translate into a simple treatment rule. The appropriate response to molecular positivity may differ according to tumor stage, treatment context, assay design, and available therapies. AI could eventually personalize these interpretations by combining molecular kinetics with clinicopathological and imaging information, but such systems should be evaluated as clinical strategies rather than merely as prediction algorithms.

The evidence base also demonstrates a recurring difference between prognostic and predictive biomarkers. Prognostic information estimates the natural risk of an outcome, whereas predictive information indicates whether a patient is likely to benefit from a particular intervention. A positive postoperative ctDNA result can be strongly prognostic for recurrence, but it does not by itself establish that escalation of therapy will improve outcome. This distinction has direct implications for AI development. A model trained to predict recurrence should not automatically be presented as a model that recommends treatment. Clinical decision-support systems require an additional layer of evidence demonstrating that acting on the model improves outcomes compared with standard care.

Treatment-response monitoring provides a related example. A rapid fall in ctDNA may indicate a favorable molecular response, whereas persistent or rising ctDNA may identify patients at higher risk of treatment failure. Nevertheless, the biological interpretation varies according to tumor type, treatment mechanism, disease burden, and assay sensitivity. Targeted therapy can produce rapid molecular changes that differ from the kinetics observed with immunotherapy, chemotherapy, or radiotherapy. In addition, treatment-induced tumor-cell death may transiently increase circulating nucleic acids. AI models that incorporate treatment class, timing of blood collection, baseline tumor burden, molecular subtype, and imaging may therefore outperform models that interpret ctDNA concentration in isolation.

The concept of molecular lead time deserves particular attention. The ability of ctDNA to identify recurrence before radiological progression is one of the principal reasons why liquid biopsy is attractive for surveillance. However, an earlier molecular signal is not automatically equivalent to a clinically meaningful benefit. If no effective intervention can alter the natural history of molecular relapse, detecting recurrence earlier may increase the duration of uncertainty without improving survival. Conversely, if early detection allows a curative local intervention or a more effective systemic therapy, molecular lead time could become highly valuable. AI may help distinguish clinically meaningful molecular trajectories from transient or low-level signals, but this hypothesis requires prospective intervention trials rather than retrospective association studies.

Another important issue is the longitudinal nature of cancer monitoring. Most conventional machine-learning studies treat each blood sample as an independent observation, although the biological question is inherently temporal. A postoperative ctDNA result is interpreted differently when it is persistently positive, newly positive, declining, or repeatedly negative. Similarly, a molecular alteration detected during systemic

therapy may represent transient tumor injury, clonal selection, technical noise, or the emergence of a resistant population depending on the preceding measurements. AI methods that explicitly model trajectories, rates of change, and relationships between sequential observations may therefore provide more clinically relevant information than models based on a single time point. Time-series methods, recurrent architectures, survival models with time-varying covariates, and dynamic Bayesian approaches are promising directions, but they require datasets in which sampling schedules and treatment changes are accurately recorded.

The clinical meaning of an AI-enhanced liquid-biopsy result depends on more than diagnostic accuracy. A model can achieve a high area under the receiver operating characteristic curve while still failing to improve patient outcomes if its predictions are poorly calibrated, are generated too late to influence care, or do not identify an actionable intervention. This distinction is particularly important in oncology, where surveillance and treatment decisions are made under conditions of uncertainty. A recurrence-risk estimate has value when it changes the timing or intensity of confirmatory testing, enables a clinically useful intervention, or reduces unnecessary procedures without compromising safety. Therefore, the most important endpoint for future AI-liquid-biopsy studies should increasingly move from model discrimination toward clinical utility.

19. Proposed Framework for Clinical Translation

A staged implementation framework is proposed: (1) analytical validation of the liquid-biopsy assay; (2) algorithmic development and internal validation; (3) external multicenter validation; (4) prospective observational validation; (5) clinical-utility trials evaluating management changes; (6) outcome trials demonstrating patient benefit; and (7) health-system implementation evaluating cost, workflow, equity and scalability.

This framework may prevent premature adoption of technologically impressive but clinically insufficiently validated systems.

20. Conclusions

Artificial intelligence-enhanced liquid biopsy represents a rapidly developing technology with the potential to transform cancer monitoring. Liquid biopsy provides a minimally invasive method for repeated molecular assessment, while AI can integrate high-dimensional genomic, epigenomic, fragmentomic and clinical data.

The strongest emerging applications include treatment-response monitoring, minimal residual disease detection, treatment-resistance prediction and recurrence prediction. Current evidence supports the prognostic and predictive value of ctDNA in several solid tumors and demonstrates that AI can improve interpretation of complex circulating biomarker datasets.

Nevertheless, technological sophistication alone is insufficient. Clinical translation requires standardized assays, high-quality datasets, external validation, interpretable models, prospective clinical trials, evidence of clinical utility, appropriate data governance and attention to healthcare equity.

The future of oncology may move from periodic, imaging-centered surveillance toward continuous or serial molecular monitoring supported by artificial intelligence. The ultimate measure of success, however, will not be algorithmic accuracy. It will be whether AI-enhanced liquid biopsy enables clinicians to make better decisions and whether those decisions lead to better outcomes for patients with cancer.

Finally, implementation should remain patient-centered. Molecular surveillance can potentially reduce uncertainty by identifying meaningful biological change earlier, but it can also create new forms of uncertainty when results are borderline, discordant with imaging, or not linked to an available intervention. Patients should be informed about the purpose and limitations of testing, the possibility of false-positive and false-negative results, and the implications of an AI-generated risk estimate. When these principles are respected, AI-enhanced liquid biopsy may contribute to a future oncology model that is more longitudinal, adaptive, and biologically informed while preserving clinician oversight and patient autonomy.

AI-enhanced liquid biopsy should therefore be developed as a clinical decision-support technology rather than as an autonomous diagnostic authority. The reliability of the final output depends on the entire chain from blood collection and molecular assay design to data preprocessing, model training, validation, calibration, interpretation, and clinical action. Failures at any point in this chain can undermine an otherwise sophisticated system. Standardization, transparent reporting, external validation, and prospective trials are consequently essential components of technological development.

The most promising near-term applications are likely to be those in which the biological question is clearly defined and the consequence of the result can be specified in advance. These include postoperative MRD assessment, early treatment-response monitoring, identification of molecular resistance, and recurrence-risk stratification in cancers where ctDNA has already demonstrated clinical validity. Broader applications such as multi-cancer early detection remain highly promising but require particularly strong prospective evidence because the prevalence of disease in screening populations is low and false-positive results can have substantial consequences.

In practical terms, the emerging model of oncology surveillance is not a replacement of imaging, pathology, or clinical examination, but a more continuous information architecture in which molecular measurements can be interpreted between conventional clinical encounters. Serial liquid biopsy can provide an additional temporal layer, while AI can synthesize molecular trajectories with treatment exposure, imaging, and patient characteristics. The resulting system could help clinicians determine when a molecular change is sufficiently credible to justify repeat testing, targeted imaging, biopsy, treatment reassessment, or closer surveillance.

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