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Liquid Gold: Leveraging AI Algorithms to Decode Circulating Tumour DNA (CTDNA) for Multi-Cancer Early Detection (MCED)

Yash Srivastav[1*], Anoop Yadav[1], Mohd Danish[1], Mohd Atif Shah[1], Alok Yadav [1], Vivek Singh[1], Shivani Singh[1]

[1]D.K.R.R Pharmacy College, Amberpur, Sitapur (Uttar Pradesh), India

***Corresponding Email: yashsrv.108@gmail.com**

Abstract:

Liquid biopsy using circulating tumor DNA (ctDNA) is gaining momentum as a powerful non-invasive tool for multi-cancer early detection (MCED) and precision medicine. The current paper highlights the role of artificial intelligence (AI), encompassing machine learning and deep learning techniques, in refining the analytical process of ctDNA to facilitate early cancer detection, diagnosis, prediction of the tissue of origin, and individualized disease management. Clinical trials in humans for various cancers, such as lung, colorectal, pancreatic, breast, and ovarian cancer, illustrate the ability of AI-enhanced ctDNA technology to detect even minute molecular changes in terms of mutations, epigenetic patterns, fragmentation features, and chromosome anomalies with higher sensitivity and specificity. In addition, the review highlights the biological relevance of ctDNA, the clinical utility of AI-based MCED systems, and the benefits of non-invasive testing, continuous surveillance, and detection of multiple cancers through a single blood sample. However, significant drawbacks, including low ctDNA concentration in early-stage tumors, false positives and negatives, non-standardization, ethical issues, and expensive technology, are substantial impediments to clinical adoption. Nonetheless, AI-powered ctDNA diagnostics hold immense promise for revolutionizing cancer screening in the future.

Keywords: Circulating Tumor DNA (ctDNA), Artificial Intelligence, Multi-Cancer Early Detection (MCED), Liquid Biopsy, Machine Learning, Precision Oncology, Cancer Diagnostics, Deep Learning.

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1. INTRODUCTION

Cancer is still one of the major causes of death around the world; there is no doubt that it is a heavy burden placed upon healthcare services worldwide, despite numerous technological developments made in diagnostics and treatment of the condition. It should be said that cancer diagnosis at its earliest stages can significantly improve survival rate [1]. Unfortunately, some existing methods, such as tissue biopsies, radiology, and detection of tumor markers in blood, have certain limitations, such as their invasiveness, late diagnosis, low sensitivity to early-stage tumors, and insufficient reflection of tumor heterogeneity. Recently, circulating tumor DNA (ctDNA), which is a part of cell-free DNA, secreted by tumors and found in the patient's bloodstream, has gained popularity among other noninvasive diagnostics methods.

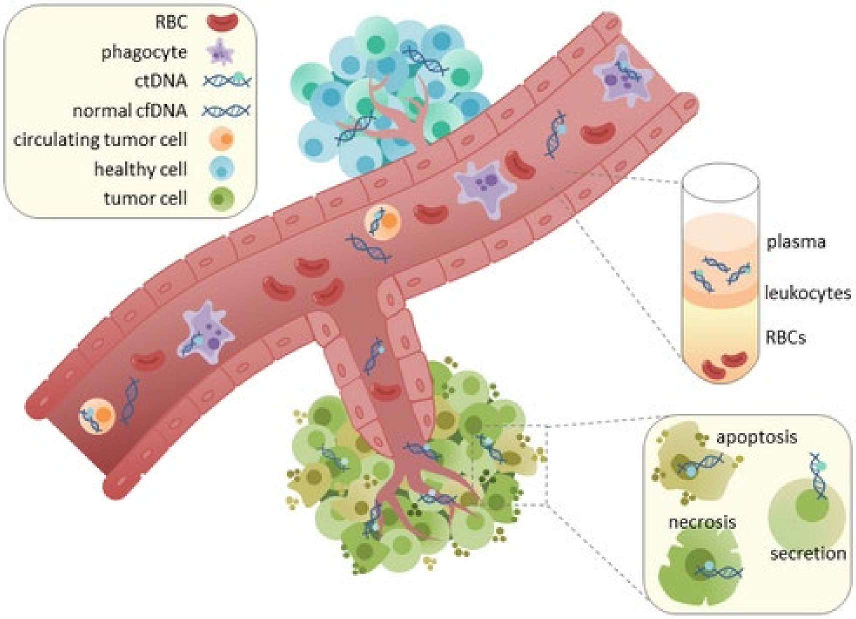

Figure 1: Circulating Tumor DNA [2]

The fusion of artificial intelligence (AI) with liquid biopsy technology utilizing ctDNA has radically changed MCED research. AI technologies, such as machine learning and deep learning algorithms, can perform analysis of complicated genome data sets with enhanced performance parameters, including sensitivity, specificity, and prediction capabilities. It has been proven by various studies on patients that the application of AI for the analysis of ctDNA can help detect multiple types of cancer at once using only one blood sample collected from the patient [3]. Therefore, AI-enhanced ctDNA testing has been acknowledged as an innovative breakthrough in the field of oncology capable of revolutionizing cancer screening practices and saving human lives around the world.

1.1 Background Information and Context

Cancer is among the leading causes of mortality around the world, with millions of people being diagnosed every year. Cancer detection can help improve the survival rate and the outcome of the condition. However, traditional diagnostic methods like tissue biopsy, imaging, and biomarker tests can be invasive, fail to detect early signs, or lack sensitivity, which hampers treatment efforts. The emergence of circulating tumor DNA (ctDNA), a type of cell-free DNA that enters the bloodstream from tumors, is now seen as a reliable biomarker for noninvasive detection of cancer. CtDNA has several molecular features of cancer, such as specific mutations, methylation patterns, fragmentation patterns, and chromosomal abnormalities, that could help diagnose the cancerous conditions [4]. Multi-cancer early detection (MCED) methods have revolutionized cancer diagnostics, allowing the identification of several different cancer types using ctDNA through a single blood test. Artificial intelligence (AI) has been used in ctDNA detection, with improvements in diagnostic and prediction power of machine learning and deep learning models applied to humans.

1.2 Objectives of the Review

The primary objective of this review is to critically examine:

- To examine the role of artificial intelligence algorithms in improving circulating tumor DNA (ctDNA)-based multi-cancer early detection (MCED) systems.
- To evaluate human clinical studies related to AI-assisted ctDNA diagnostics for cancers such as lung, colorectal, pancreatic, breast, and ovarian cancer.
- To analyze the biological significance and diagnostic potential of ctDNA biomarkers in noninvasive cancer detection and precision oncology.
- To assess the major advantages, challenges, strengths, and limitations associated with AI-driven ctDNA-based MCED technologies.
- To explore future clinical applications, translational opportunities, and research directions for AI-assisted ctDNA diagnostics in personalized cancer screening and monitoring.

1.3 Importance of the Topic

The convergence of AI with liquid biopsy techniques based on ctDNA is one of the key innovations in contemporary oncology and precision medicine. AI-enabled ctDNA diagnosis provides a non-invasive, highly sensitive, and possibly affordable method for diagnosing cancer at an early stage, even those cancers where no efficient screening tests are available yet. Early detection of tumors improves patients' prognoses, increases the efficacy of treatment, and extends survival rates. Moreover, AI-enabled ctDNA analysis contributes to individualized therapy planning, continuous tumor monitoring, and large-scale cancer screening programs [5]. Considering the global increase in cancer cases, the creation of reliable and affordable AI-based MCED systems is becoming more relevant than ever.

2. HUMAN CLINICAL STUDIES AND DIAGNOSTIC POTENTIAL OF AI-DRIVEN CTDNA

AI-driven ctDNA technology can be seen as an innovative non-invasive method for MCED that involves the use of blood samples in detecting tumor-associated molecular alterations. There are a number of studies that indicate the efficacy of AI in improving the diagnosis and prognosis of cancers, including lung, colon, pancreatic, breast, and ovarian cancers [6].

2.1 Biological Basis of Circulating Tumor DNA

The tumor circulating DNA derives from cancer cells that undergo programmed cell death by apoptosis or necrosis or secretion in the microenvironment. ctDNA molecules tend to be smaller compared to DNA molecules shed by normal cells and are found in combination with DNA shed by healthy cells. The amount of ctDNA present in the circulation is determined by the size and activity of the tumor.

Clinical studies conducted on human subjects indicate that there are several molecular changes associated with cancer in ctDNA, which include:

- Single-nucleotide polymorphisms (SNVs)

- Copy number polymorphisms (CNVs)
- DNA methylation alterations
- Chromosomal instability
- Fragmentation signatures
- Microsatellite instability

In the early stages, the amount of ctDNA released by the cancer is negligible; thus, detection is extremely difficult. Modern sequencing tools, coupled with artificial intelligence-based computer analytics, have greatly enhanced the ability to detect these scarce tumor markers against a vast background of normal DNA sequences [7].

2.2 Multi-Cancer Early Detection (MCED): Concept and Clinical Significance

The term MCED is used to describe the diagnosis of different forms of cancer simultaneously within one test system. Traditional screening for cancers is usually restricted to certain types of cancer, including breast, cervical, colorectal, and prostate cancer [8]. Some cancers are hard to screen, making their early detection difficult and contributing to bad outcomes.

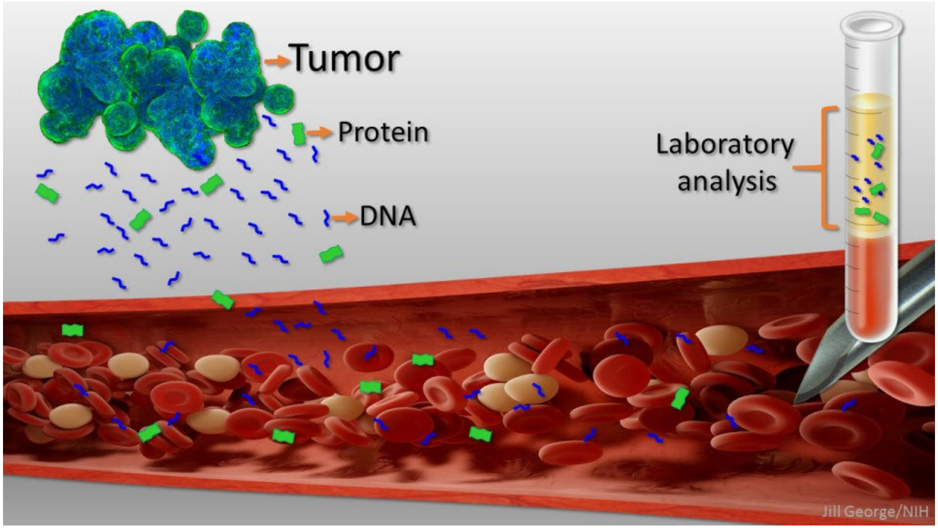

Figure 2: Multi-cancer Early Detection (MCED) [9]

There are many benefits associated with ctDNA based MCED tests:

- Non-invasive test using blood samples
- Multiple cancer detection at one time
- Early diagnosis before symptoms arise
- Less pain to patients
- Increased accessibility to population screenings

Human clinical trials have demonstrated that MCED can detect various cancers through promising levels of accuracy. The use of AI is vital when analyzing data produced from MCED tests.

2.3 Human Clinical Studies and Major Findings

Several large-scale human clinical studies have evaluated AI-assisted ctDNA-based MCED systems [10].

- **Study on Methylation-Based MCED Platforms:** Clinical studies using large samples of asymptomatic human patients demonstrated that methylation-based assays for MCED combined with machine learning provided both high specificity and moderate-to-high sensitivity in diagnosing many types of cancer.
- **Studies in Lung Cancer:** Clinical studies in human patients having lung cancer have shown that the AI-based ctDNA analysis provides improved sensitivity compared to conventional serological markers of lung cancer at an early stage. In addition, combination of ctDNA mutations with deep learning-based DNA methylation analyses further improved diagnosis [11].
- **Colorectal Cancer Screening Using AI-based Techniques:** Several human-based clinical studies have shown that AI-based ctDNA methylation analysis provided high levels of accuracy in screening of colorectal cancer. AI models used effectively discriminated patients having early-stage colorectal cancer and patients suffering from high-risk adenomas.
- **AI-based Clinical Studies on Pancreatic Cancer:** Advanced diagnosis of pancreatic cancer due to absence of efficient screening strategies is a serious issue. The clinical studies based on human patients demonstrated that AI-assisted ctDNA analysis enhanced detection of pancreatic ductal adenocarcinoma through identifying molecular patterns.
- **Breast and Ovarian Cancer Diagnosis:** AI-Based Human Studies: Clinical studies conducted on patients having breast and ovarian cancer showed that ctDNA analysis assisted by machine learning algorithms provided improved sensitivity in early-stage cancer identification.

2.4 Strengths and Weaknesses of AI-Assisted ctDNA-Based Multi-Cancer Early Detection (MCED)

Strengths

- **Noninvasive Diagnostic Approach:** Among the many benefits of MCED based on ctDNA is the non-invasive nature of the process compared to the traditional method of taking a biopsy from the body tissues.
- **Cancer Early Detection Capacity:** With the aid of artificial intelligence, ctDNA testing allows for detection of changes at a molecular level related to cancer at an early stage even before physical manifestations of the disease occur. This greatly improves chances for early action, thus improving survival rates in cancer patients [12].
- **Multi-cancer Testing:** Another advantage of using MCED technology is the ability to test for various types of cancer in one blood test. This is much better than the current practice of conducting organ-specific tests, which may be limited to certain cancer types that do not have standardized tests like ovarian and pancreatic cancers.

Weaknesses

- **Low ctDNA Concentration in Early-Stage Cancer:** One of the key issues with using ctDNA for MCED is the rarity of ctDNA in early-stage cancers. Separating rare ctDNA from an overwhelming amount of cfDNA in the blood is difficult and could result in false-negative findings.

- **Misinterpretation of Benign Findings:** AI might occasionally interpret benign changes at the molecular level as being linked to cancer, producing a false-positive result. Conversely, low ctDNA content could lead to false negatives due to an inability to detect ctDNA reliably [13].
- **Inadequate Standardization:** At present, there is a lack of standardization of blood sampling techniques, sequencing machines, bioinformatics workflows, and AI models used.

3. ADVANTAGES AND CHALLENGES OF AI-ASSISTED CTDNA-BASED MULTI-CANCER EARLY DETECTION

The use of AI in ctDNA diagnostic techniques is one of the most effective ways of detecting cancers early in their development stages [14]. The benefits of this technology include high sensitivity, specificity, earlier detection, real-time monitoring, and personalization of treatment for patients with different types of cancers. With the help of machine learning and deep learning algorithms, AI helps detect multiple cancers with just one sample of blood [15].

3.1 Advantages of AI-Driven ctDNA Diagnostics

The use of artificial intelligence-enabled circulating tumor DNA (ctDNA) tests presents some key benefits for MCED [15]. The application of AI technology alongside liquid biopsies has made it easier to detect sophisticated changes within the molecules of tumors, thus making the diagnosis more effective and applicable.

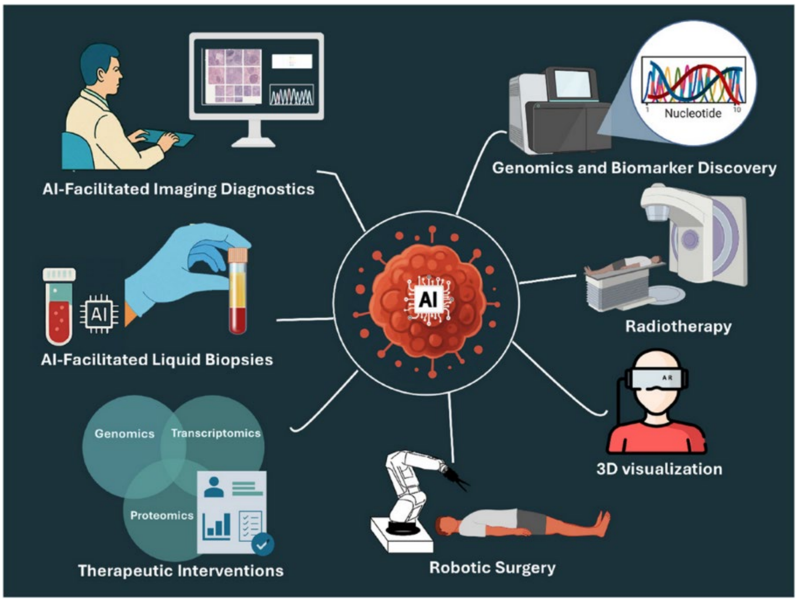

Figure 3: AI-Driven ctDNA Diagnostics Treatment [16]

- **High Sensitivity and Specificity:** Another one of the key benefits of using AI-based ctDNA analysis methods is that they provide high sensitivity and specificity in detecting cancerous cells. Using machine and deep learning models and analyzing big datasets related to genome and epigenome of the patient, AI technologies can detect the cancer-related patterns of mutations, which otherwise cannot be recognized by traditional statistical methods [17]. The simultaneous analysis of mutation profile, methylation signature, fragmentation pattern, and CNV enables increasing the accuracy of diagnosis and minimizing the number of misdiagnosed cases.

- **Non-Invasive Testing:** The traditional biopsy methods involve surgical interventions that are relatively invasive and cause pain, discomfort, complications, and some restrictions. Unlike traditional biopsies, liquid biopsy involves drawing a tiny blood sample from the patient, which does not create any discomfort. Liquid biopsy is non-invasive and minimally invasive method, which increases its acceptability and provides opportunities for repeated testing.
- **Early Detection Potential:** Early detection is one of the crucial variables that influence cancer outcomes. AI-assisted analysis of ctDNA facilitates the recognition of tumor-related molecular changes before any clinical or radiographic manifestations have occurred. Modern AI models have the potential to recognize very minute amounts of ctDNA present during the early stages of tumor formation, thus increasing the probability of recognizing cancers while they are still potentially curable. It is especially relevant when discussing extremely aggressive forms of cancer like pancreatic, ovarian, and lung cancers, which have poor prognosis due to late diagnosis [18].
- **Continuous Real-Time Monitoring of Disease Progression:** Continuous and real-time monitoring is another important strength of ctDNA tests. Regular sampling and analysis of liquid biopsies give an opportunity to estimate the effectiveness of therapy, to assess the presence of residual disease, tumor evolution, and cancer recurrence without conducting multiple invasive procedures on the patient. AI technologies can help analyze the collected data sets in a very short time frame.
- **Personalized Oncology and Precision Medicine:** The use of artificial intelligence (AI) for ctDNA analysis is highly beneficial for developing personalized oncology. Molecular data derived from ctDNA can be used for developing personalized treatments by considering specific features of a particular cancer of a patient. AI algorithms help to recognize certain mutations, predict therapeutic effectiveness, and differentiate among various subtypes of a tumor. Personalized screening and treatment can enhance treatment results without causing any harm to patients [19].
- **Multiple Cancers Early Detection:** Traditional cancer screening techniques are mainly associated with detecting cancers in single organs only. AI-supported MCED technologies allow multiple cancers detection at one time using a small amount of blood taken once. Multiple cancers early detection using one test is an important step for cancer prevention, as current screening programs are often ineffective for many types of tumors.

3.2 Challenges and Limitations

Even with these tremendous improvements in the development of AI-driven ctDNA diagnostic methods, there are still many scientific, technical, medical, and even ethical obstacles that make it difficult for these diagnostic methods to be widely adopted in medicine [20].

- **Low ctDNA Abundance in Early-Stage Cancers:** One of the main difficulties associated with using ctDNA for diagnostics is the fact that early-stage tumors contain only minute quantities of ctDNA. At the beginning of tumor development, cancerous cells secrete only small amounts of DNA into the bloodstream, which makes its detection particularly challenging. The high presence of background cell-free DNA from healthy organs makes this task even more complicated. However, while AI algorithms increase accuracy, negative findings could appear despite the presence of ctDNA at concentrations lower than the limit of detection.

- **Heterogeneous Datasets and Lack of Generalizability:** When developing an AI algorithm, it is important to remember that datasets used to train human clinical AI models are quite heterogeneous and might include different patient groups, various types of cancers, sequencing platforms, sample preparation procedures, etc. Heterogeneity can lead to inconsistencies in model performance and lack of generalizability to a wider population.
- **False Positives and Biological Confounders:** False positives have emerged as a major challenge with ctDNA-based diagnosis of tumors. The aging-related clonal hematopoiesis, inflammation, and other benign mutations might result in the detection of mutations that look like those caused by cancers. Artificial intelligence algorithms could sometimes mistake such signals to be indicative of malignancy, leading to unnecessary testing, patient distress, and extra healthcare expenses [21].
- **Standardization Absence:** To date, little has been done about standardizing blood collection protocols, storage conditions, sequencing techniques, bioinformatics workflows, and validation schemes for AI applications. Variations in the process used in laboratories can affect the outcome of the study. This lack of standardized protocol means that there are no consistent guidelines for clinical practice yet.
- **Ethical, Legal, and Regulatory Concerns:** Several concerns arise with regard to AI-powered genomic diagnostics regarding patient privacy, data security, consent, and lack of algorithmic transparency. Genetic material analyzed during ctDNA diagnostics is particularly sensitive, and its mishandling can result in privacy issues or misappropriation. Furthermore, many existing AI diagnostic tools operate on a “black box principle” implying that the reasoning process behind their operation remains unclear. This may decrease physician confidence as well as hinder accountability.
- **High Costs and Technological Requirements:** State-of-the-art sequencing, computational technology, and AI-based algorithms used for analysis necessitate substantial expenditure and sophisticated technological solutions. High costs can prevent widespread application of MCED in underdeveloped healthcare systems and poor countries. Besides, implementation demands specialists possessing appropriate training and knowledge [22].

4. CLINICAL TRANSLATION AND FUTURE PERSPECTIVES OF AI-DRIVEN CTDNA-BASED MCED

AI-enhanced circulating tumor DNA (ctDNA) technology for clinical use is among the recent developments in precision oncology and preventive medicine. MCED platforms are gaining attention for implementation into population-based screening programs based on their ability to detect several cancers with non-invasive testing of blood samples. It was clinically confirmed through human clinical trials that AI in combination with ctDNA analyses improves diagnostic accuracy and increases chances of tissue origin identification. This technology can lead to earlier treatment and, consequently, better patient survival rates [23].

Among the areas with promising prospects in this context, multimodal markers analysis should be highlighted. They can include not only ctDNA mutations but also epigenetics, fragmentomics, proteomics, transcriptomics, and imaging data from clinical trials. Artificial intelligence will become especially helpful in developing predictive models based on such multidimensional data sets. Multimodal methods might be useful in detecting cancers at very early stages when the concentration of ctDNA in the bloodstream is low [24].

A further area that could benefit greatly from AI technologies relates to personalized cancer screening [26]. The use of AI systems could facilitate individualized assessment of the risk of developing cancer through analyzing predispositions based on one's genome and other characteristics, such as age, lifestyle choices, environmental influences, and molecular markers [27].

Applications of ctDNA analysis enabled by AI technologies also include real-time monitoring and longitudinal surveillance. Liquid biopsy monitoring on a regular basis might allow for timely detection of minimal residual disease, recurrence, drug resistance, and progression of the condition. All of these applications are likely to have positive impacts on patients' treatment [28].

Even though much progress has been made, several hurdles need to be overcome prior to implementing AI-based ctDNA analysis in practice on a larger scale [29]. The necessity of standardizing sample collecting procedures, DNA sequencing methods, data processing algorithms, and the validation of the technology cannot be ignored. Furthermore, other factors must be considered, such as regulatory approvals, cost-effectiveness, physician education, and more [30].

Table 1: Summary of Literature on AI, Liquid Biopsy, and Biomarkers in Cancer Detection and Precision Oncology [31]

Author(s) & Year	Study Focus	Methodology/Approach	Key Findings
Sahoo et al. (2025) **[32]**	Role of artificial intelligence in cancer epigenomics for pan-cancer detection and precision medicine	Review of AI integration with epigenetic datasets and biomarker analysis	Reported that machine learning and deep learning improved cancer diagnosis, classification, and prognosis prediction through enhanced identification of epigenetic biomarkers such as DNA methylation and histone modifications. The study emphasized improved early cancer detection and personalized therapeutic strategies.

Simancas-Racines et al. (2025) [33]	Liquid biopsy and multi-omic biomarkers in breast cancer detection and monitoring	Review of circulating tumor DNA, circulating tumor cells, extracellular vesicles, and transcriptomic biomarkers	Found that liquid biopsy technologies enabled minimally invasive and real-time monitoring of tumor progression and treatment response. The integration of multi-omic biomarkers improved diagnostic precision, therapy guidance, and recurrence monitoring in breast cancer patients.
Tan et al. (2024) [34]	Translation of epigenetics in cell-free DNA liquid biopsy technology and precision oncology	Review of epigenetic alterations and sequencing-based liquid biopsy approaches	Demonstrated that cell-free DNA liquid biopsy supported non-invasive cancer screening, tumor profiling, and treatment monitoring. The study highlighted that advances in sequencing technologies and bioinformatics improved the sensitivity and specificity of epigenetic biomarker detection.
Tenchov et al. (2024) [35]	Recent advancements in biomarkers for early cancer detection, especially pancreatic and liver cancers	Comprehensive review of genetic, proteomic, metabolomic, and circulating biomarkers	Reported that emerging biomarker technologies improved early cancer screening accuracy and enabled timely clinical intervention. The study highlighted the importance of liquid biopsy, AI-assisted biomarker analysis, and multi-omic integration in personalized cancer management.
Tenchov et al. (2024) [36]	Translational challenges and future opportunities in biomarker-based cancer diagnostics	Analytical review of clinical implementation barriers and future directions	Identified major challenges including clinical validation, standardization, cost-effectiveness, and large-scale implementation of biomarker technologies. The study concluded that interdisciplinary collaboration

			and advanced computational approaches were essential for improving the clinical utility of cancer diagnostics.

Future research using human samples would benefit from the use of multicenter and prospective trials among varied populations in order to assess the clinical value of AI-aided ctDNA-based MCED diagnostic tools. In addition, the development of AI models that are clear and understandable would be crucial for building physician trust. In summary, there is significant promise in the future of AI in ctDNA-based diagnosis.

5. DISCUSSION

In summary, this review shows that the utilization of AI-aided ctDNA methods has played a crucial role in improving MCED through accurate diagnosis, early identification of cancers, and personalized disease monitoring [37]. Although there are issues of limited ctDNA availability, erroneous results, and absence of standardization, AI-enabled ctDNA tests have promising prospects in precision medicine and cancer screening in the future.

5.1 Interpretation and Analysis of the Findings

The results of this review show how the incorporation of artificial intelligence (AI) technology with ctDNA-based liquid biopsy approaches has made great strides in the development of MCED. Clinical trials in humans show how AI-enabled ctDNA tests can enhance diagnosis by increasing sensitivity, specificity, prediction of the tissue of origin, and real-time disease detection in conditions like lung, colorectal, pancreatic, breast, and ovarian cancers [38]. Machine learning and deep learning techniques have proven to be quite successful at analyzing complicated genetic and methylation data, which helps in detecting any cancer-related molecular changes. Detecting multiple cancers from a single blood test is a huge improvement in precision oncology.

5.2 Implications and Significance

Clinical significance of AI-assisted ctDNA diagnostics is immense in the field of contemporary oncology and preventive medicine. Early diagnosis of cancer significantly increases the chances of successful treatment and prolonging patients' lives, and the use of AI-powered MCED systems can help to eliminate many problems connected with traditional organ-specific screening. It enables minimally-invasive, highly-sensitive, and personalized approach to the diagnosis and therapy, which will be especially important in the era of growing incidence of cancer around the world [39]. Moreover, using the combination of multiple biomarkers, including methylation markers, fragmentation profiles, mutations, and clinical data can significantly increase the accuracy and utility of such approach in diagnosing various kinds of cancer.

5.3 Research Gaps and Future Directions

Although there are several achievements that are promising, some limitations and areas for further research need to be considered. Firstly, the low ctDNA concentration in early-stage cancer patients remains a problem regarding detection sensitivity, and false negatives and positives might occur during the diagnosis. Moreover, non-standardized sample processing, sequencing techniques, bioinformatic tools, and artificial intelligence algorithms limit results' reproducibility in future investigations. In addition, ethical issues associated with genomic privacy, patient data protection, algorithmic bias, and access to healthcare must be considered in the analysis [40]. Human studies should address performing multicenter prospective studies in different populations to prove the clinical utility of AI-supported ctDNA MCED systems in the future.

6. CONCLUSION

The current study illustrates that the application of AI technology in ctDNA-based liquid biopsy has become an innovative tool for MCED and personalized oncology. Studies on human participants confirm that AI-aided ctDNA profiling leads to an increase in sensitivity and specificity rates, tissue-of-origin determination, early detection of cancer, and personalized treatment plans for various cancers such as lung, colorectal, pancreatic, breast, and ovarian cancer. Machine learning and deep learning approaches allow researchers to analyze complicated genomic, epigenomic, and methylation data, making liquid biopsy tools more effective and valuable in clinical practice. Despite the promising progress in the development of AI-aided ctDNA-based MCED systems, issues like low ctDNA concentration at early stages of cancer, errors in test results, lack of standardization, ethical problems, and high expenses hinder widespread adoption of such tests. However, the integration of AI with liquid biopsy techniques shows great promise for further improvement of cancer screening methods and saving lives from oncological diseases.

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