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Novel Multi-Dimensional Liquid Biopsy Paradigms: Harnessing ctDNA Fragmentomics and AI-Enhanced Detection for Next-Generation Cancer Screening

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ABSTRACT: Liquid biopsy is a disruptive approach to cancer diagnostics, which examines cell-free RNA, extracellular vesicles, circulating tumour DNA, and circulating tumour cells in bodily fluids. In contrast to invasive tissue biopsy, it can monitor tumor dynamics in real time and in a noninvasive manner allowing early detection and signaling the personalized therapy. The enhancement of sensitivity of next generation sequencing, fragmentomics, and integration of multi-omics has allowed a lesser emphasis on allele fractions in detection of mutation, epigenomic, and proteomic changes. Integration with machine learning and AI takes it a step further by examining multi-modal data and stratifying patient risk. Clinical validation, regulatory approvals, marketing authorizations, and FDA Breakthrough Device Designation of multi-cancer early detection (MCED) tests such as the GRAIL Galleri test illustrate the plausibility of early detection, but limitations in cancer detection in early stages persist, coupled with limitations in addressing tumor heterogeneity. Economic models indicate that liquid biopsy lowers costs of treatments at the final stages and increases the quality-adjusted life years, which validates its clinical meaningfulness. However, there are ongoing issues of global access, equity and population specific validation. Vigorous academic-industry collaborations, convergence of international standards and AI-enabled large data platforms will open up new directions. Liquid biopsy is placed as scalable and minimally invasive, thus has the potential of revolutionizing precision oncology in the global arena.

KEYWORDS: Liquid biopsy, Circulating tumor DNA (ctDNA), Fragmentomics, Circulating tumor cells (CTCs), Next-generation sequencing (NGS), Multi-omics integration.

I. INTRODUCTION AND BACKGROUND

1.1. The Early Detection Imperative in Cancer Care

Cancer is one of the health burdens in the world and 20 million and 9.7 million new cases and deaths, respectively, were reported in the year 2022. By 2050 it is estimated that there will be a 77 percent increase to 35 million new cases annually. The earlier it is detected, the better are the chances of survival- stage I breast cancer has a five year survival of 99 percent, where as advanced stages of the disease have a survival bit of 27 percent. Yet, only five of the malignancies are screened by existing programs leaving 71 percent of cancer deaths attributed to non-screened cancer. Late-stage diagnosis increases the cost of healthcare as stage IV accounts to 4-19 times higher than the early stage of illness plunging 37-49 percent of households into catastrophic expenditure not only in medical services, but also the loss of productivity, care giving, and disability [1]. Diagnostics based on tissue have severe disadvantages, even though they are conventional. Pneumothorax (1015%) and hemorrhage (15%) can follow lung biopsies. Turn-aroundtimes of 3.6 days are experienced, with advanced cases often no longer having sufficient samples to access molecular testing. Tumor heterogeneity also restricts accuracy and patient and diagnosis delays stretch to days and months. The barriers delay initiation of treatment, which has the effect of letting the disease progress and deteriorate the prognoses, an aspect that cements the necessity of less invasive options to approach cancerization diagnostics [2].

1.2. Evolution of Liquid Biopsy Technology

The underlying theoretical foundations of liquid biopsy originated in 1869 when Thomas Ashworth observed, in a metastatic cancer patient, what were circulating tumor cells (CTCs), and speculated that CTCs were involved in the process of spreading cancer. In 1948, Mandel and Metais made the discovery of cell-free DNA (cfDNA) in plasma which, however, were only linked to cancer in the 1970s. Extracellular vesicles were identified in the 1960s but confirmed to be cancer biomarkers very recently, in 2017. Liquid biopsy is a term coined by Alix-Panabieres and Pantel

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in 2010, initially as an application to CTCs, but soon applied to ctDNA, following the democratization of next-generation sequencing (NGS) after 2012 [3]. Clinical adoption was made on advantage of the regulatory progress Accelerated In 2013 the CellSearch CTC system was approved to monitor advanced cancers by the FDA. Momentum was gained in 2016 with cobas EGFR Mutation Test v2, the first point-of-care NSCLC ctDNA test. In 2020 FoundationOne Liquid CDx was approved as a comprehensive tumor profiling test. GRAIL Galleri, a test that combines genome-wide methylation and machine learning, implements cancer detection which exceeds 50 cancers. Multi-omics platforms enabled by AI are another example of the role AI will have in expediting and improving the precision of drug development with the 2024 FDA ctDNA guidance [4].

1.3. Conceptual Framework of ctDNA Biology

ctDNA is produced and released by tumor cells via active secretion, as well as, apoptosis and necrosis, and transported via extracellular vesicles. In apoptosis, genomic DNA is chopped into 160180 base pairs in segments that travel as nucleosome-sized particles whereas necrosis has larger and irregular breaks (greater than 10,000 base pairs) because the cell membranes do not have time to reform [5]. Besides, viable tumor cells transfer DNA actively by exosome and microvesicle transfer, facilitating communication in tumor cells. Unique tumor mutations can be identified in cell-free DNA pools at variant allele frequencies as low as 0.01, and ctDNA clearance has a plasma half-life of 15 min to 2.5h, primarily via renal, hepatic, and nuclease mechanisms, which allows nearly real-time assessment of tumor kinetics. This has an important advantage compared to tissue biopsy since ctDNA can reflect treatment response or minimal residual disease within days [6].

Notably, ctDNA is related to the tumor burden. Allele fractions of more than 1 percent normally indicate a tumor volume of more than 10 cm 3, whereas in cases with low tumor burdens early-stage tumors (<1 cm 3), allele fractions of less than 1 may be encountered. The sensitivity of tumor progression to quantitative ctDNA assays is months prior to radiographic evidence and follow-up changes after surgery or systemic therapy. Improvements to progression-free survival can be also foreseen through such measurements. In this way ctDNA is a minimally invasive, repetitive and very informative biomarker which reflects faithfully tumor, response, and disease dynamics making it a wonderful tool in the cancer monitoring and even personalized therapy [7].

II. TECHNICAL FOUNDATIONS AND METHODOLOGICAL ADVANCES

2.1. ctDNA Detection Technologies

The new generation of sequencing (NGS) technology has transformed ctDNA testing to enable the analysis of hundreds to thousands of loci at once. The high-depth hybrid-capture NGS platforms can identify single-nucleotide substitutions, insertion, deletions, copy-number alterations, and structural variant rearrangements as low as 0.1% variant allele fraction of the total sequencing depth, depending on the level reached of 10 000 or greater [8]. The advances in unique molecular identifiers and error-suppression algorithms have further led to the low-frequency false-positive rates being < 1/10 6, allowing reliable low-frequency variant detection.

Targeted amplification, dPCR are an alternative that can provide cost-effective and relatively fast quantification of known mutations. Droplet dPCR partitions the sample into thousands of nanoliter droplets, which makes it possible to sensitively detect mutations with a VAF of 0.01% in hotspot regions of genes like EGFR, KRAS, and PIK3CA. Validation Analytical validation necessitates judging linearity, precision and limit-of-detection across variants as well as in allele frequencies that are normally tested by means of synthetic reference standards and patient-derived cfDNA samples **Table 1**. Clinical-grade reproducibility and accuracy is required by strict proficiency testing and platform-to-platform comparisons [10].

2.2. NOVEL FOCUS: Fragmentomics and Pattern Recognition

The pattern of cfDNA fragments reveals presence of the chromatin structure and DNA/DNA contractivity and form non-random patterns in cancer cases. It has been demonstrated that fragments of ctDNA are depleted in unprotected areas by nucleosomes, thereby resulting in a modal size of ~166 bp, as compared to the broader 167-180 bp found with healthy cfDNA. Smaller fragments (90150 bp) are often associated with cleavage in regions of oncogenes-rich chromatin leading to cancer-specific signatures. Furthermore, the periodicities (10 bp) in ctDNA indicate helical turns of DNA on nucleosomes and can unveil tumour-specific positions of nucleosomes and forecast gene expression [11]. Long-read sequencing gives the additional advantage of being able to reconstruct nucleosome-occupancy maps and open and closed chromatin marks without prior tumor mutation information. Machine learning helps fragmentation

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analysis, by identifying size distributions, terminal motifs, and genomic locations. Random forests, SVM, and CNN models deliver a high accuracy (AUC > 0.95). Combining fragmentation with methylation and nucleotide patterns to generate deep learning classification networks makes early detection of cancer possible at variant allele frequencies as low as 0.1 percent, and opens new applications in using liquid biopsies [12].

2.3. Multi-Omics Integration

The inclusion of genomic alteration and mutational profiling in combination with ctDNA provides broader liquid biopsy use. Larger NGS-based panels such as hybrid-capture and amplicon-based assays can cover hundreds of cancer-relevant genes and scan them to SNV, indel, CNV, and structural variants with allele frequencies as low as 0.1%. The use of unique molecular identifiers in ultra-deep sequencing lowers the error rates and it is possible to accurately quantify rare killing in heterogeneous tumors. Whole genomic profiles are being commercially performed to guide individual treatment of >300 genes in NSCLC, breast and colorectal cancers. Mutational data integrates with fragmentomics to improve the detection of minimal residual disease and predict the risk of relapse compared with mutation-only pipelines [13]. DNA methylation is a significant source of variations, which achieve ideal biomarkers of early prevalence and tissue-of-origin invariation **(Figure 1)**. Similarity, global hypomethylation and hypermethylation of CpG island are detectable using bisulfite sequencing or restriction analysis with a stability of ~99.5% specificity. GRAIL Galleri is among the platforms that utilise methylation at 30,000 loci in order to classify over 50 cancers. When used together with metabolomic and proteomic data, genomic, epigenomic, and proteomic features integrated into the machine learning models achieve the AUC above 0.98, allowing comprehensive precision oncology [14].

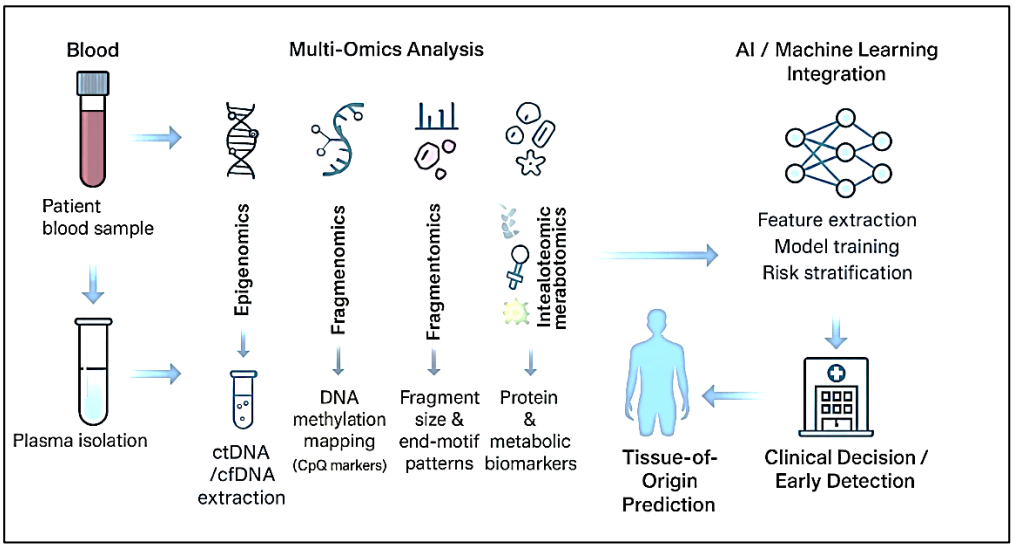

Figure 1: *Schematic overview of a liquid biopsy based multi-omics workflow using patient blood samples. Integrated analysis of ctDNA epigenomics, fragmentomics, proteomics, and metabolomics enables tissue-of-origin prediction. AI/machine learning models support feature extraction, risk stratification, and early clinical decision-making.*

Table 1: Technical Foundations and Methodological Advances in ctDNA-Based Liquid Biopsy

Domain	Methodology/Technology	Key Features	Sensitivity/ Specificity	Clinical/Research Applications	Ref.
ActDNA Detection Technologies	**Hybrid-Capture NGS**	High-depth sequencing (≥10,000x); detects SNVs, indels, CNVs, structural variants	Variant allele fraction (VAF) ≥0.1%	Comprehensive genomic profiling; clinical-grade mutation detection	[16]
	Unique Molecular Identifiers (UMIs) & Error	Error correction reduces false positives to $<10^{-6}$	High analytical validity	Reliable detection of low-frequency variants	[17]

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	Suppression				
	Targeted Amplification (amplicon assays)	Focused regions; cost-effective	Moderate sensitivity	Monitoring known hotspots (e.g., EGFR, KRAS, PIK3CA)	[18]
	Droplet Digital PCR (ddPCR)	Partitioning into nanoliter droplets; mutation quantification	Detects VAF ≥0.01%	MRD monitoring, hotspot mutation detection	[19]
	Validation Requirements	Linearity, precision, LOD testing with reference standards	Platform reproducibility essential	Clinical accreditation, regulatory compliance	[20]
Fragmentomics & Pattern Recognition	**Fragment Size Distribution**	Cancer ctDNA enriched at ~166 bp (mononucleosomal); shorter fragments (90–150 bp) in oncogene loci	Distinguishes tumor vs. healthy cfDNA	Mutation-independent cancer detection	[21]
	Nucleosome Mapping (Paired-End Sequencing)	Oscillation curves reveal nucleosome positioning & chromatin accessibility	Epigenetic landscape profiling	Gene expression inference, tissue-of-origin prediction	[22]
	Fragment End-Motif Analysis	Non-random cleavage patterns; 10 bp periodicity	Tumor-specific fragmentation signatures	Epigenetic profiling without mutation data	[23]
	AI/Machine Learning Models	Random forests, SVM, CNNs; extract fragmentomic features	AUC >0.95	Malignant vs. benign differentiation, MRD, early-stage cancer	[24]
	Unsupervised Clustering	Identifies novel fragmentation subtypes	Enhances heterogeneity analysis	Resistance/relapse prediction	[25]
Multi-Omics Integration	**Genomics (NGS panels)**	100–300+ cancer-related genes; UMIs reduce errors	VAF ≥0.1%	Targeted therapy guidance; relapse prediction	[26]
	Fragmentomics + Mutation Integration	Combines mutation & fragmentation features	Better relapse prediction vs. mutation-only	MRD quantification	[27]
	Epigenomics (DNA Methylation)	CpG hypermethylation (e.g., BRCA1, GSTP1); hypomethylation	Specificity ~99.5%	Tissue-of-origin classification (e.g., Galleri test, >50 cancers)	[28]
	Proteomics	Mass spectrometry, immunoassays (CEA, CA-125, PSA)	Tumor-specific post-translational modifications	Ovarian, pancreatic, prostate cancer biomarker panels	[29]
	Metabolomics	Oncometabolites (e.g., 2-HG in IDH-mutant gliomas); altered amino acid/lipid profiles	Functional tumor activity signatures	Glioma, metabolic reprogramming biomarkers	[30]
	AI-Driven Multi-Omics Models	Integrative ML frameworks combining genomics, epigenomics, proteomics, metabolomics	AUC >0.98 in early-stage cohorts	Multi-cancer early detection (MCED), precision oncology	[32]

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III. CLINICAL APPLICATIONS IN EARLY CANCER DETECTION

3.1. Multi-Cancer Early Detection (MCED) Platforms

GRAIL Galleri test is an early program of MCED technology that includes large-scale multi-cancer profiling of blood cfDNA methylation complemented with machine learning to predict tissue of origin. By using a carefully selected panel of CpGs, it makes use of a supervised classifier that has been trained on tens of thousands of cancer and normal samples with an accuracy of over 93% in a dozen cancer types. The test uses only 10 mL of peripheral blood and includes powerful quality controls, including bisulfite conversion monitoring and methylation normalization. The average days of turn around (10-14 days) is an advantage that makes it applicable in preventive care. Unambiguous molecular barcoding with error-correction coding provides a specificity of 99.5%, which limits undesired positive results when such diagnostic plans are performed in asymptomatic populations and avoids subsequent testing not indicated by the positive test result [33].

CCGA clinical validation data: Sensitivity was shown to be 51.5% at a false-positive rate of 0.7 across >50 cancer types, with sensitivity stage-dependent (16.8% stage I, 90.1% stage IV). The accuracy of predicting tissue of origin was 88 percent with lower-confidence calls. A prospective study conducted in the real-world involving 10,000 symptom-free persons in the age range 50-75 years yielded 45 percent positive predictive value with biopsy-confirmed malignancies in 12 types of tissue, and cancerous diseases in lack of any standard screening method. Crucially, the ability to detect earlier and condense diagnostic intervals by 30 percent using Galleri and PET-CT follow-up highlights the potential of the idea of MCED testing complementing existing screening models as well as supporting population-wide early detection [34].

3.2. Organ-Specific Screening Applications

CRC screening has been improving with the discovery of specific methylation ctDNA markers that allow the possibility of noninvasive, early diagnostics to operate. Plasma cfDNA hypermethylation of gene promoters (SEPT9, NDRG4, BMP3) has demonstrated good diagnostic capacity with sensitivity values of 68-72% and specificity over 80% being FDA approved (Epi proColon assay). These methylation markers are better than the conventional fecal occult blood tests because the markers are with higher patient compliance and much earlier detection of lesions that could turn precancerous. Through integrating these methylation profiles with fragmentomics and mutation analysis, an additional sensitivity was achieved in case of early-stage CRC as well as advanced adenomas [35]. Large studies underway are progressively improving panel-based methylation assays to increase detection without increasing false positive rates, particularly in ethnic mixtures.

Autoantibody detection added to ctDNA screening technology for lung cancer helps to address the issue of low ctDNA shedding: ctDNA is absent in early stages, and detecting autoantibodies can help supplement ctDNA detection. Autoantibodies recognizing the tumor related antigens including p53, CAGE, and GBU4-5, and SOX2 have been found sensitive and specific with 68 percent sensitivity and 90 percent specificity in the detection of early stage non-small cell lung cancer (NSCLC) which complements the low dose CT scans [36]. Combination of autoantibody panels and ct D N A mutation analysis have enhanced diagnostic precision and the decreased false-positive result among high-risk patients. In breast cancer, liquid biopsy enables sensitive longitudinal detection of recurrence through ctDNA measurements, and is predictive of minimal residual disease many months prior to imaging or clinical relapse [37]. Mutations in PIK3CA, ESR1 and TP53 are among those most frequently followed to direct modifications of adjuvant therapy with lead times of 6 12 months. These liquid biopsy applications demonstrate how organ-specific applications will shape the future of precision screening domains based on the tumor biology and risk of the patient, with the potential to improve survival through timely detection and dynamic observation of disease progression [38].

3.3. NOVEL FOCUS: AI-Enhanced Detection Algorithms

CNNs are being adapted to the data used solving liquid biopsy problems in order to detect weak patterns of biomarkers. CNNs take advantage of hierarchical feature extraction and learn cfDNA fragmentation and methylation status and mutational signatures simultaneously. This facilitates the strong separation of tumor-derived DNA to the background cfDNA and allows the identification of variant allele fractions down to 0.01% with AUC >0.95 across a variety of cancers [39]. The SNs can also facilitate the classification of tissue-of-origin and support diagnostics based on specific, particular organs; and contribute to early diagnostics. In addition to CNNs, multi-omics liquid biopsy measurements are being standardized into unified vectors through natural language processing (NLP) to fuse genomic, epigenetic and proteomic signals (**Figure 2**). This enhances diagnostic modelling through improving signal to numbers. In

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combination with electronic health records, NLP algorithms provide context to molecular findings in the context of clinical annotations. In combination with demographic, lifestyle, and other factors, risk stratification models based on gradient boosting and support vector machines provide >90% sensitivity in high-risk groups and can be used to stratify populations to prioritize screening resources [40].

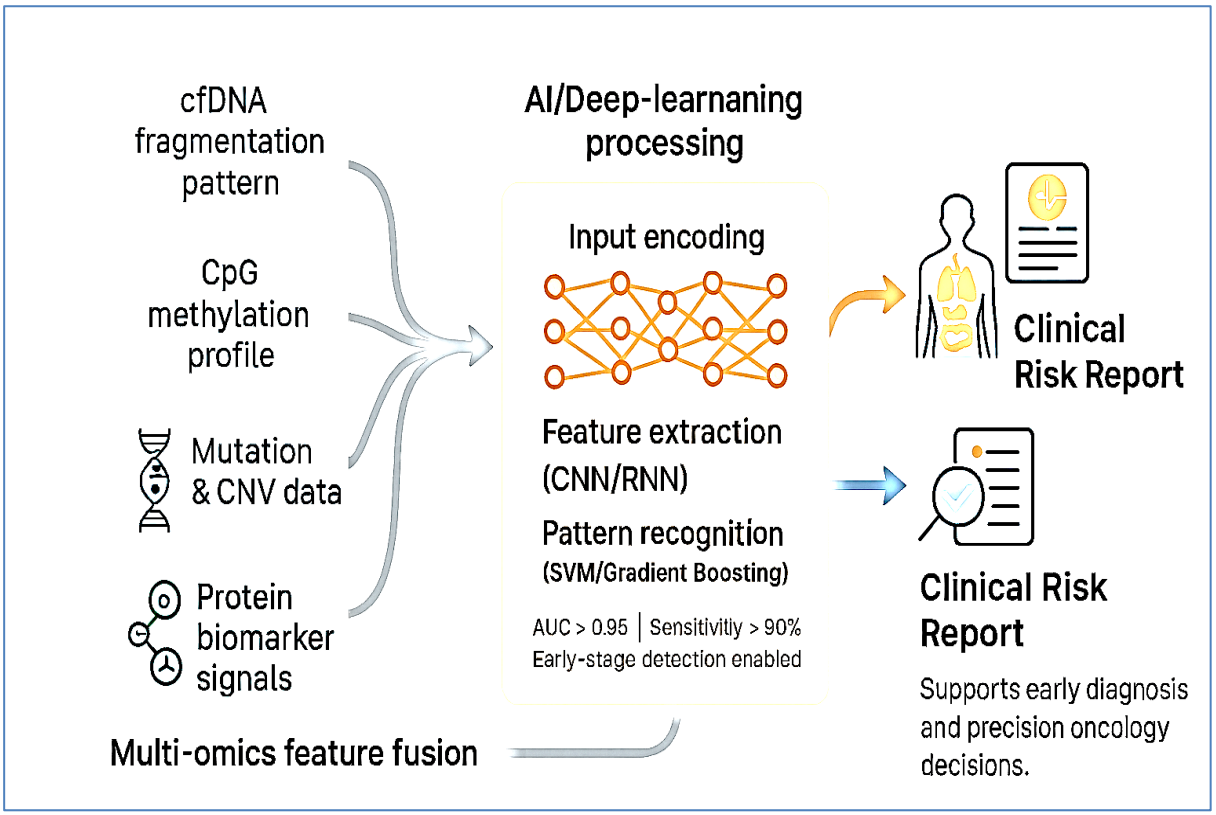

Figure 2: *Multi-omics features including cfDNA fragmentation, CpG methylation, genomic alterations, and protein biomarkers are integrated for analysis. AI/deep-learning models perform feature extraction and pattern recognition to enable high-sensitivity early detection. The workflow generates clinical risk reports supporting early diagnosis and precision oncology decision-making.*

IV. REGULATORY LANDSCAPE AND CLINICAL VALIDATION

4.1. FDA Approval Pathways and Requirements

Setting up of liquid biopsy assays, especially ctDNA-based tests, warrants rigorous analytical and clinical validation as determined by the U.S. FDA. Analytical validation aims at sensitive, specific, and accurate, reproducible and low detection limits on contrived and patient samples. Assays have to be able to reliably identify low-frequency variants and limit false result. Clinical validation links the biomarker measurability with the outcomes like diagnosis, prognosis or the reaction to the treatment based on the prospective trials or the case-control studies within the studies [41]. The FDA focuses on laboratory to laboratory reproducibility, demographic representation and validation in the target patient population. Guidance documents and programs, among them the Breakthrough Device Program have sped the review of high-impact genomic technologies. The Breakthrough Device designation reduces the approval time by providing rolling submissions, and expedited consultations, and is often completed in 6-12 months. Such tests as Foundation One Liquid CDx and Cobas EGFR Mutation Test v2 were some significant tests that followed this pathway. In addition to the U.S., IMDRF and the EU IVDR, regulatory harmonization is created to ensure standardized validation, surveillance, and post-market safety across the globe [42]. Learning across countries, especially with multi-cancer early detection systems, and incorporation of real-world evidence are essential to address the lack of continuity in safety and efficacy and equitable access.

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4.2. Clinical Trial Design and Evidence Generation

Liquid biopsy assay design in a clinical trial may vary according to whether the clinical trial is interventional or non-interventional. Interventional trials make active use of the assay to inform treatment choice or to monitor therapy and thus require prospective, randomized designs to show clinical benefit. Such non-interventional studies commonly use correlations between the assay result and clinical outcome to determine sensitivity, specificity and predictive runts, usually with retrospective studies or longitudinal cohorts. In case of early detection programs, trials initially might consist of non-interventional trials leading into the interventional trials that determine effects on outcomes and mortality [43]. Important criteria in the selection of the endpoints include the biomarkers minimal residual disease detection, lead-time to diagnosis, recurrence rates, and progression-free survival which are frequently used as surrogate endpoints. Mortality reduction has become the ideal endpoint even long-term follow-up is required including large cohorts. As observational evidence increasingly becomes accepted as real-world evidence (RWE), making a difference both in validation and regulatory support, and integration of liquid biopsy into the standard practice, evidence gathered in electronic health records and registries, but also patient-reported data, finds its place alongside trials [44], [45].

V. CLINICAL IMPLEMENTATION AND HEALTHCARE INTEGRATION

5.1. Laboratory Infrastructure and Standardization

Acceptable clinical follow-up of liquid biopsy involves high-quality laboratories that have Problematic QC/trust and proficiency testing. QC measures contain assessment of sample integrity, avoidance of sample contamination as well as regular calibration of NGS platforms and NGS and PCR. Standardized reference materials support proficiency run testing and thereby inter-laboratory reproducibility, CLIA, CAP and ISO 15189 requirements infrastructure supports analytic validity and patient safety. Turnaround is also important: automated assays and streamlined bioinformatics have reduced sample-to-report turnaround to under 10 days with stringent pre analytical controls to minimize nucleic acid degradation [46]. Laboratory workers require specialized training and testing of competencies required to carry out accurate assays and their interpretation. Ongoing training in bioinformatics, the science of assessing clinical applications and the basics of assays enhances quality control. Molecular pathologists, oncologists, and laboratory scientists should collaborate to ensure an effective integration of liquid biopsy into oncology practice and lead to standardization and assurance of providing reliable patient care.

5.2. Clinical Decision-Making Integration

The results of liquid biopsies have become a part of precision oncology, and ctDNA mutations, including but not restricted to EGFR, ALK, BRCA, and PIK3CA, have been proven to have an actionable mutation. Such information can be used to select targeted treatment, enroll patients into biomarker-based clinical trials and help incorporate treatment guidelines like NCCN and ESMO [46]. Dynamic ctDNA profiling identifies resistance mutations in real-time, allowing timely therapies to be changed to provide the best hopes of success. Monitoring intervals are also dependent on cancer type with most monitored at intervals of 4 -12 weeks during the active treatment period and 3 -6 months during surveillance, which would allow detection of minimal residual disease and allows early prediction of relapse. Correlation of ctDNA and imaging and/or tumor markers increases sensitivity and specificity. This should be implemented effectively through counseling and interpretation on patients. There is a need to communicate clearly, the limitation of the assays and possible inaccurate results as well as the context of discoveries [47], [48]. Collaboration of oncologists, pathologists, and genetic counselors helps to provide patient-specific guidance, maintain ethical practice of informed consent, and maintain patient-centered decision-making in precision cancer care.

VI. CONCLUSION

Circulating tumor DNA (ctDNA) sequencing and liquid biopsy is an example of a paradigm-shifting oncology diagnostic and precision medicine modality, due to its minimally invasive nature, high specificity of analysis, and abilities to undergo tumor dynamics and therapeutic response. MCEDs like the Galleri by GRAIL support personalised treatment choice and early diagnosis to improve cancer diagnosis. However, there still exist significant issues, such as insufficient sensitivity of early-stage neoplasms, heterogeneity of tumours, regulatory and reimbursement barriers, and the lack of standardisation. The focus of future work should be on the development of ultrasensitive, multi-omics, and AI-combined assays, based on large multicentric validation studies. The combination of these assays and imaging modalities and standardisation of clinical procedures might support the accuracy of diagnosis. The regulators and policymakers must integrate approval routes, ensure fair access, and approve strategic reimbursement frameworks. The

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cooperation between academic institutions, industry, regulatory agencies, and payers will be invaluable to the full utilization of liquid biopsy in the context of precision oncology on the global scale.

Conflict of Interest
The authors have no conflict of interest

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Data Availability
All the data presented in this manuscript are original and have not been published elsewhere.

Authors' Contributions
The authors confirm contribution to the paper as follows: **BSHW**: Writing the paper; **TS**: Study conception and design; **SH**: Data Collection, **IH**: Writing and reviewing the paper. All authors reviewed the results and approved the final version of the manuscript.

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