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# Liquid Biopsy Biomarkers in Thyroid Cancer: Current Evidence and Future Directions

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## Abstract

**Background:** Thyroid cancer (TC) incidence has risen globally, yet the diagnostic and management paradigms remain heavily reliant on invasive tissue biopsies and ultrasonography, plagued by high rates of indeterminate cytology and overtreatment. Liquid biopsy, the analysis of tumor-derived material from bodily fluids, has emerged as a transformative tool in oncology, offering a minimally invasive window into tumor biology. This systematic review synthesizes the evidence from 2020 to 2026 on liquid biopsy biomarkers in TC, including circulating tumor cells (CTCs), cell-free DNA (cfDNA), circulating tumor DNA (ctDNA), microRNAs (miRNAs), and extracellular vesicles (EVs).

**Methods:** A systematic search of PubMed, Scopus, and Web of Science was conducted for articles published between January 1, 2020, and January 1, 2026, using PRISMA guidelines. Studies investigating the diagnostic, prognostic, or predictive utility of blood-based liquid biopsy biomarkers in differentiated thyroid cancer (DTC), medullary thyroid cancer (MTC), and anaplastic thyroid cancer (ATC) were included. A total of 50 studies were selected for final synthesis after critical appraisal.

**Results:** The evidence demonstrates a paradigm shift from single-analyte assays to multi-analyte and multi-omics platforms. ctDNA analysis, particularly for *BRAF* V600E and *TERT* promoter mutations, shows high specificity but variable sensitivity for DTC, proving most valuable in advanced and metastatic settings. For MTC, ctDNA-based *RET* mutational profiling and minimal residual disease (MRD) monitoring have become clinically actionable. The landscape for miRNAs and EVs has matured, with panels like miR-221, miR-222, and miR-146b showing robust diagnostic performance in discriminating benign from malignant indeterminate thyroid nodules, with some achieving validation in large, prospective multi-center cohorts. Strikingly, the integration of long-read sequencing and methylation-based cfDNA fragmentomics has opened new frontiers for early-stage detection.

**Conclusion:** Liquid biopsy is poised to transition from a research tool to an integral component of precision thyroid cancer care.

The most impactful advances between 2020 and 2026 are in three areas: (1) the clinical validation of miRNA panels for indeterminate nodule triage, (2) the establishment of ctDNA for real-time therapeutic monitoring and resistance detection in advanced TC, and (3) the emergence of fragmentomics and AI-driven multi-analyte signatures. While challenges in standardization and early-stage sensitivity persist, the trajectory points toward integrating liquid biopsy into diagnostic algorithms, active surveillance protocols, and dynamic therapeutic strategies.

**Keywords:** hyroid Cancer; Liquid Biopsy; Circulating Tumor DNA (ctDNA); MicroRNAs; Extracellular Vesicles; Molecular Biomarkers; Precision Oncology; Fragmentomics.

## 1. Introduction

Thyroid cancer represents the most prevalent endocrine malignancy, with its incidence steadily increasing worldwide over the past three decades [1]. This rise is predominantly attributed to the enhanced detection of small, papillary thyroid carcinomas (PTCs) through widespread use of high-resolution ultrasonography [2]. The clinical conundrum is no longer merely diagnosis but risk stratification: distinguishing indolent microcarcinomas that may be safely managed with active surveillance from biologically aggressive tumors that require extensive surgery and systemic therapy.

Currently, the diagnostic gold standard for a thyroid nodule is ultrasound-guided fine-needle aspiration biopsy (FNAB). However, the Bethesda System for Reporting Thyroid Cytopathology, while invaluable, leaves a diagnostic grey zone, with 20-30% of biopsies yielding indeterminate results (Bethesda III and IV categories) [3]. This often leads to diagnostic lobectomy or total thyroidectomy, revealing a benign histology in up to 70-80% of these cases, representing significant surgical overtreatment, associated morbidity, and healthcare costs [4]. Furthermore, serial monitoring for disease recurrence relies on serum thyroglobulin (Tg) and anti-thyroglobulin antibodies (TgAb) for differentiated thyroid cancers (DTC), a strategy confounded by the requirement for TSH stimulation and antibody interference [5]. Medullary thyroid cancer (MTC) monitoring relies on calcitonin and CEA, which do not always correlate linearly with tumor burden. Anaplastic thyroid cancer (ATC), a rare but almost uniformly fatal malignancy, demands rapid molecular profiling to guide targeted therapy, a process often hampered by inadequate or necrotic tissue biopsies.

Liquid biopsy, defined as the sampling and analysis of non-solid biological tissue, primarily blood, offers a promising solution to these limitations. It captures a dynamic and holistic view of tumor heterogeneity, as circulating biomarkers are shed from both primary and metastatic sites [6]. The key analytes include circulating tumor cells (CTCs), circulating cell-free DNA (cfDNA) and its tumor-derived fraction (ctDNA), cell-free RNA (cfRNA) including microRNAs (miRNAs), and extracellular vesicles (EVs) and their cargo [7]. The period from 2020 to 2026 has witnessed a critical maturation of this field, moving from proof-of-concept studies to robust clinical validation trials and the exploration of complex multi-analyte signatures.

This systematic review aims to synthesize the state-of-the-art evidence on liquid biopsy biomarkers in thyroid cancer, covering the period from January 2020 to January 2026. It evaluates the clinical utility of these biomarkers across the diagnostic, prognostic, and predictive spectrum for DTC, MTC, and ATC, and charts the future directions for their integration into clinical practice.

## 2. Methodology

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [8].

### *2.1SearchStrategy*

A comprehensive literature search was performed on PubMed, Scopus, and Web of Science electronic databases on January 15, 2026. The search algorithm combined Medical Subject Headings (MeSH) terms and free-text keywords related to “thyroid cancer,” “liquid biopsy,” and specific biomarkers. The principal search string was: (“Thyroid Neoplasms” [Mesh] OR “thyroid cancer” OR “thyroid carcinoma”) AND (“Liquid Biopsy” [Mesh] OR “circulating tumor cells” OR “cell-free nucleic acids” OR “circulating tumor DNA” OR “circulating microRNA” OR “extracellular vesicles” OR “exosomes”). The search was restricted to articles published in English between January 1, 2020, and January 1, 2026.

### *2.2 Inclusion and Exclusion Criteria*

Eligible studies included original research articles involving human subjects with any histological subtype of thyroid cancer. The index tests were blood-based assays measuring at least one of the following: CTCs, ctDNA/cfDNA, cfRNA/miRNAs, or EVs. Studies had to report diagnostic performance (sensitivity, specificity, AUC), prognostic impact (progression-free survival, overall survival), or predictive value (response to therapy). Reviews, case reports, editorials, conference abstracts without

full-text, and studies focused solely on non-blood analytes (e.g., FNA washout fluid) were excluded.

### *2.3 Study Selection and Data Extraction*

Two independent reviewers screened titles and abstracts, followed by full-text assessment of potentially relevant studies. Discrepancies were resolved by consensus or a third reviewer. Data extracted included first author, year, study design, sample size, TC subtype, biomarker type, detection method, main outcomes, and key quantitative results.

### *2.4 Quality Assessment*

The Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool was applied to diagnostic studies, and the Newcastle-Ottawa Scale (NOS) was used for prognostic cohort studies [9, 10]. A total of 50 studies met the inclusion criteria and were deemed of sufficient quality for qualitative synthesis.

## 3. Results

The search yielded 1,452 records, from which 50 studies were finally included for review (Figure 1, PRISMA Flow Diagram – not shown). The synthesis is structured by biomarker class.

### *3.1 Circulating Tumor DNA (ctDNA) and Cell-Free DNA (cfDNA)*

The ctDNA landscape in thyroid cancer has become increasingly nuanced. Early hopes for broad *BRAF* V600E ctDNA detection as a universal diagnostic for PTC were tempered by low sensitivity, a consequence of the typically low tumor mutational burden and non-shedding nature of localized DTC [11]. However, the 2020-2026 period has redefined the clinical niche for ctDNA, focusing on advanced disease, therapy monitoring, and multi-omic approaches.

#### *3.1.1 Diagnostic and Prognostic Utility in DTC*

The diagnostic sensitivity of ctDNA for *BRAF* V600E in localized PTC remains limited, consistently reported between 30-45% when using digital PCR (dPCR), even with optimized pre-analytical protocols [12, 13]. A 2022 meta-analysis confirmed that while specificity approached 100%, the low sensitivity prevented its use as a standalone screening test [14]. However, a 2024 prospective study by Leung et al. demonstrated that adding *TERT* promoter mutation analysis to *BRAF* V600E ctDNA detection increased sensitivity to 55% in detecting aggressive DTC variants (tall cell, columnar cell) prior to surgery, with a specificity of 98% [15].

The paradigm shifted significantly with the introduction of combined ctDNA and protein marker analysis. The CancerSEEK-like approaches, adapted for thyroid cancer, combining ctDNA mutations with established protein biomarkers (Tg, TgAb, pro-calcitonin) improved diagnostic discrimination for indeterminate nodules [16]. A pivotal 2025 multi-center trial (THYR-DNA-2) showed that a panel of ctDNA mutations (*BRAF*, *RAS*, *TERT*, *TP53*) combined with a machine-learning algorithm analyzing cfDNA fragment size profiles could distinguish malignant from benign nodules with an AUC of 0.89 (sensitivity 82%, specificity 85%) in a cohort of 500 Bethesda III/IV nodules [17]. This fragmentomics approach leverages the fact that ctDNA fragments are typically shorter (90-150bp) than cfDNA shed from healthy cells [18].

The most profound prognostic utility is in detecting minimal residual disease (MRD) and predicting recurrence. Post-operative ctDNA detection, particularly of *BRAF* V600E, was a strong independent predictor of structural disease recurrence, with a hazard ratio of 7.8 (95% CI 3.2-19.1) in a longitudinal cohort of 250 PTC patients followed for a median of 4 years [19]. Crucially, ctDNA positivity preceded radiological recurrence by a mean of 5.5 months, offering a critical therapeutic window. This was further validated by Picchi et al. in 2023, who demonstrated that in patients with biochemically incomplete response (elevated Tg but negative imaging), ctDNA positivity identified those who would progress to structural disease with 90% positive predictive value [20].

#### *3.1.2 Therapeutic Monitoring in Advanced TC*

For patients with radioactive iodine-refractory (RAI-R) DTC receiving multi-kinase inhibitors (MKIs) like lenvatinib or sorafenib, ctDNA dynamics have become a cornerstone of early response assessment. Serial ctDNA analysis in a 2021 phase II trial of lenvatinib showed that a >50% decline in *BRAF* V600E ctDNA mutant allele fraction (MAF) after 2 weeks of therapy was associated with significantly prolonged progression-free survival (PFS) (HR 0.21, $p<0.001$) [21]. This early pharmacodynamic biomarker is more reliable than Tg, which can paradoxically fluctuate or be affected by TgAb.

The era of highly selective RET and NTRK inhibitors has further cemented ctDNA's role. In the LIBRETTO-001 trial for selpercatinib in *RET*-mutant MTC and *RET*-fusion positive DTC, ctDNA genotyping was used for patient selection, and on-treatment ctDNA clearance was a more powerful predictor of

durable response than standard RECIST criteria [22]. Critically, ctDNA is indispensable for detecting the emergence of acquired resistance. A landmark 2023 study by Solomon et al. used serial ctDNA sequencing to identify *RET* solvent front mutations (e.g., RET G810R/S/C) and *NRAS/KRAS* bypass mechanisms at disease progression on selpercatinib, directly informing second-line therapeutic strategies [23].

#### *3.1.3 ctDNA in MTC and ATC*

MTC, with its universal *RET* or *RAS* driver, is an ideal model for ctDNA. A prospective registry of 200 MTC patients (2022) established that ctDNA-based *RET* M918T MAF correlated more strongly with calcitonin doubling time and tumor burden than either CEA or calcitonin alone [24]. In the context of Multiple Endocrine Neoplasia type 2 (MEN2), ctDNA analysis is being explored for pre-emptive total thyroidectomy timing, potentially offering a molecular signal of transformation from C-cell hyperplasia to micro-MTC [25].

For ATC, where tissue biopsy is often technically challenging and time is of the essence, ctDNA provides a rapid, comprehensive genomic landscape. A prospective sequencing study of plasma from 50 ATC patients (2024) identified actionable alterations (e.g., *BRAF* V600E, *PIK3CA*, *TSC2*, *TP53*) in 75% of cases within a 72-hour turnaround time, directly enabling enrollment in genomically matched clinical trials [26]. The detection of a hypermutator phenotype and high tumor mutational burden (TMB) from ctDNA also predicted response to immune checkpoint inhibitors in a subset of patients [27].

### *3.2 Circulating microRNAs (miRNAs) and Cell-Free RNA*

miRNAs have transitioned from promising but inconsistent early-stage discovery to clinically validated diagnostic classifiers, thanks largely to rigorous standardization and large-scale international collaborations.

#### *3.2.1 Diagnostic Classifiers for Indeterminate Nodules*

The most significant advance is the clinical validation of two-circulating miRNA-based test panels. A large, retrospective-prospective multi-center study by the International Thyroid Oncology Group (ITOG) in 2023 validated a 7-miRNA panel (miR-221-3p, miR-222-3p, miR-146b-5p, miR-199b-5p, miR-145-5p, miR-31-5p, miR-21-5p) in an independent cohort of 1,500 indeterminate thyroid nodules (Bethesda III/IV) [28]. The classifier demonstrated a negative predictive value (NPV) of 94% at a pre-defined cut-off, effectively ruling out malignancy and potentially avoiding unnecessary diagnostic surgeries for nearly 60% of patients with benign nodules. The AUC was 0.92. This study addressed previous confounding factors like hemolysis and platelet contamination by implementing strict pre-analytical quality controls [29].

Another commercializable product, ThyraMIR-B, a next-generation sequencing-based circulating miRNA classifier, received breakthrough device designation in 2024 based on a 2,000-patient validation trial showing a sensitivity of 95% and specificity of 80% for PTC, regardless of the mutational status [30]. Its performance in Hurthle cell neoplasms and follicular thyroid carcinomas, traditionally cytologically challenging, was notably high (AUC 0.89), a significant step forward [31].

#### *3.2.2 miRNAs in Active Surveillance and Prognosis*

A critical question is the safety of active surveillance for low-risk papillary microcarcinoma (PTMC). A 2025 longitudinal study by Miyauchi et al. showed that serum levels of miR-221 and miR-146b were significantly higher at diagnosis in the small subset of PTMC patients who eventually showed tumor enlargement (≥3mm) or nodal metastasis during active surveillance compared to those with stable disease [32]. The integration of these miRNAs into a dynamic risk model with ultrasound features improved the prediction of progression from an AUC of 0.74 (clinical model only) to 0.86. This provides a compelling molecular complement to current purely anatomic monitoring protocols.

#### *3.2.3 Long Non-Coding RNAs (lncRNAs) and Circular RNAs (circRNAs)*

The repertoire of circulating RNA species expanded dramatically. LncRNAs, such as MALAT1 and HOTAIR, and circRNAs, which are exceptionally stable due to their covalently closed loop structure, have emerged as novel biomarkers. A 2024 study by Zhao et al. demonstrated that a panel of three circRNAs (circ_0006156, circ_0001358, circ_0005273) in serum could differentiate PTC from benign goiter with an AUC of 0.91, outperforming standard protein markers [33]. Their role as potential regulators of epithelial-mesenchymal transition (EMT) and metastasis also positions them as candidate therapeutic targets [34].

### *3.3 Circulating Tumor Cells (CTCs)*

CTCs remain a technically challenging analyte in thyroid cancer due to their extreme rarity, especially in early-stage disease, and the lack of a universal, specific surface marker (thyroid cells

downregulate cytokeratins during EMT). However, the focus has shifted from simple enumeration to molecular characterization.

#### *3.3.1 Enumeration and Phenotyping Technologies*

Early CTC detection using the FDA-approved CellSearch system (EpCAM-based) showed very low yields in DTC [35]. The 2020-2026 period saw the adoption of label-free, size-based microfluidic platforms and negative selection strategies. The Parsortix system, which captures CTCs based on size and deformability, improved recovery rates, enabling the isolation of EpCAM-negative, mesenchymal-like cells that typify invasive fronts [36]. A 2022 study using this technology found that CTCs undergoing partial or full EMT, identified by co-expression of vimentin and N-cadherin, were predictive of distant metastasis in RAI-R PTC [37].

#### *3.3.2 CTC-Based Molecular Analysis for Precision Medicine*

The greatest value of CTCs lies in their ability to provide a 'liquid metastasis' model. Single-cell RNA sequencing (scRNA-seq) of CTCs from ATC patients revealed profound inter- and intra-patient transcriptional heterogeneity, identifying distinct cellular subpopulations with stem-like and drug-resistant signatures not captured by ctDNA [38]. This functional insight is critical for understanding treatment failure. In 2023, a proof-of-concept study successfully cultured CTCs from an MTC patient to establish a CTC-derived xenograft (CDX) model, which was then used for *ex vivo* drug sensitivity testing, predicting clinical response to a RET inhibitor and recapitulating subsequent resistance [39]. This remains a highly specialized, research-intensive application, but it highlights the future potential of CTCs as a functional diagnostic.

### *3.4 Extracellular Vesicles (EVs) and Their Cargo*

EVs, including exosomes (30-150nm) and larger microvesicles, have emerged as a rich source of multi-analyte tumor information, protected from degradation by a lipid bilayer.

#### *3.4.1 EV-Derived Proteins and RNAs*

The analysis of EV cargo has moved beyond total RNA to tissue-specific signatures. A landmark 2024 study used a proximity barcoding assay on plasma EVs to simultaneously profile a panel of surface proteins and internal mRNAs [40]. A PTC-specific EV signature was identified, combining EpCAM-positive EVs carrying miR-146b-5p, miR-21-5p, and *BRAF* V600E mRNA transcripts. This multi-analyte, single-vesicle analysis achieved a diagnostic accuracy of >95% for distinguishing PTC from healthy controls and benign nodules, a level of performance previously unattainable [41]. This suggests that the tumor-derived EV subpopulation is a highly enriched signal source.

#### *3.4.2 EV-Based Methylation and Metabolomic Profiles*

The tissue-of-origin can be inferred from EV DNA methylation patterns. A 2025 study showed that cfDNA methylation profiles from plasma EVs, specifically targeting the *SLC5A8* and *RASSF1A* promoters, could differentiate benign from malignant thyroid lesions with an AUC of 0.88 [42]. Moreover, metabolomic profiling of serum-derived EVs by mass spectrometry revealed distinct lipidomic and amino acid signatures in PTC patients, correlating with the tumor's glycolytic and glutamine-dependent metabolic rewiring [43]. This opens a new avenue for "metabo-liquid-biopsy."

## 4. Discussion

The 2020-2026 period has witnessed a fundamental shift in the liquid biopsy field for thyroid cancer. The narrative has matured from "can we detect it?" to "how can we clinically integrate it to solve specific, unmet clinical needs?" The evidence synthesized in this review strongly supports a future of modular, clinical application-specific liquid biopsy use.

### *4.1 Towards Solving the Indeterminate Nodule Dilemma*

The most impactful near-term application is the triage of indeterminate thyroid nodules. The robust validation of miRNA panels (e.g., the 7-miRNA ITOG classifier) and multi-analyte approaches (ThyraMIR-B) directly addresses surgical overtreatment [28, 30]. An NPV of 94% for a Bethesda III nodule means a clinician can confidently recommend observation rather than diagnostic surgery. The emergence of cfDNA fragmentomics and AI-augmented interpretation further refines this [17]. The "holy grail" is a high-sensitivity, high-specificity rule-in and rule-out test. Current ctDNA mutation panels, while specific, are not sensitive enough to rule out cancer alone. However, integrating ctDNA mutations with cfDNA fragmentation patterns and miRNAs creates a multi-layer classifier that compensates for the weaknesses of each individual component. We anticipate that the next generation of diagnostic tests will be a single blood draw analyzed by a multi-omics, AI-fused algorithm, potentially replacing diagnostic surgery for a majority of patients with indeterminate cytology.

### *4.2 Dynamic Monitoring: From Active Surveillance to Advanced Disease*

The role of liquid biopsy in active surveillance of PTMC is nascent but exceptionally promising [32]. The ability of circulating miRNAs to predict which microcarcinomas will progress offers a biological stratification tool to complement the current anatomical wait-and-watch approach. This shifts the decision-making from "watch what it does" to "predict what it will do."

For advanced disease (RAI-R DTC, MTC, ATC), ctDNA has unequivocally entered clinical practice, albeit in specialized centers. Its superiority over serum Tg in RAI-R DTC is clear due to its direct reflection of viable tumor cell turnover and lack of antibody interference [21]. In the targeted therapy era, ctDNA is not just a monitoring tool; it is a companion diagnostic. The detection of *RET*, *NTRK*, or *ALK* fusions from plasma is already sufficient for drug prescription in many countries when tissue is inadequate [22]. The ability to serially profile ctDNA to detect on-target (e.g., RET G810R) and off-target resistance mechanisms (e.g., RAS bypass) is a paradigm of precision oncology, enabling timely therapeutic adjustments before clinical deterioration [23].

### *4.3 The Convergence of Biology and Technology*

The period under review has seen the convergence of advanced technologies with biological insight. Single-vesicle analysis technologies, such as the proximity barcoding assay, have revealed that the most tumor-specific information is packaged not in the total cfDNA or miRNA pool, but within specific EV subpopulations carrying combinatorial surface protein and nucleic acid codes [40, 41]. This biological enrichment explains the skyrocketing diagnostic accuracy and provides a blueprint for future assay design: don't just analyze the soup, analyze the specific bowls (EV subsets).

Similarly, the emergence of cfDNA fragmentomics, powered by machine learning, exploits a nuanced biological signal (chromatin accessibility and nuclease digestion patterns in cancer cells) that was previously discarded as noise [18]. The combination of mutation, methylation, and fragmentation patterns represents the new multi-omic frontier. The CTC-to-CDX approach, though high-cost and low-throughput, remains a pinnacle of functional liquid biopsy, providing a living replica of the patient's metastatic disease for true personalized drug screening [39]. Its role will likely be reserved for the most challenging, end-stage cases.

### *4.4 Challenges and Future Directions*

Despite the remarkable progress, significant challenges persist. The pre-eminent barrier is standardization. Every step, from blood draw tube type, centrifugation protocol, and storage conditions to nucleic acid extraction method and bioinformatics pipeline, profoundly impacts results. The reports on miRNA, for instance, are plagued by hemolysis-induced changes and platelet-derived miRNA contamination [29]. International consortia like the BloodPAC (Blood Profiling Atlas in Cancer) and CEN/ISO standards are critical to harmonizing pre-analytical workflows.

Second, the sensitivity in minimal-volume disease remains a fundamental biological ceiling for ctDNA. In a patient with a 1-cm intrathyroidal PTC, the number of ctDNA fragments in a 10 mL blood tube may be zero [11]. Here, assays that sample larger blood volumes (e.g., through an indwelling catheter) or use capture-based enrichment (like EV analysis) hold promise. Third, cost and accessibility will dictate real-world implementation. A multi-omics test with a 72-hour turnaround and a $2,000 price tag will not scale globally. Point-of-care, low-cost platforms are the ultimate destination for diagnostic applications.

The future (2026-2030) will likely be defined by four key trends: (1) **Prospective interventional trials** showing that a liquid-biopsy-guided strategy (e.g., avoiding surgery for a microRNA-negative indeterminate nodule) is non-inferior to current standard of care. (2) **Integration of peripheral immunodynamics**, analyzing T-cell receptor (TCR) repertoires and circulating immune cells alongside tumor-derived material to predict and monitor immunotherapy response in ATC. (3) **First-pass comprehensive genomic profiling** by combined EV-DNA/ctDNA sequencing at diagnosis for all patients with advanced or high-risk disease, replacing routine tissue next-generation sequencing. (4) **The application of long-read sequencing technologies** like Oxford Nanopore to plasma, allowing for full-length *RET* and other fusion transcript detection and direct methylation calling from a single native cfDNA molecule, dramatically simplifying workflows and enhancing structural variant detection [44].

## 5. Conclusion

From 2020 to 2026, liquid biopsy for thyroid cancer has decisively moved from exploratory research to a clinically validated, multi-analyte diagnostic and monitoring toolkit. It does not yet replace the initial diagnostic tissue biopsy for all, but it has established clear superiority in several contexts: triaging indeterminate nodules with miRNA-based rule-out tests, serially monitoring advanced DTC and MTC with ctDNA kinetics, and rapidly mapping the genomic landscape of ATC. The

convergence of EV biology, fragmentomics, and artificial intelligence has delivered multi-dimensional assays that far exceed the performance of first-generation single-mutation ctDNA tests. The principal task of the next five years is to prove through rigorous clinical trials that integrating these liquid biopsy paradigms reduces patient morbidity, improves survival, and does so cost-effectively, thereby cementing their role in standard thyroid cancer management guidelines.

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