

Precision Thyroid Oncology: A Review of Multi-Omics Biomarkers and Spatiotemporal Technologies

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Abstract: Thyroid cancer (TC), the most prevalent endocrine malignancy worldwide, encompasses a broad spectrum of biological behaviors ranging from indolent microcarcinomas to lethal anaplastic variants. Despite advancements in standard care, critical clinical “bottlenecks” persist, including the diagnostic ambiguity of Bethesda III/IV nodules, the rising prevalence of radioiodine-refractory (RAI-R) differentiated TC, and the dismal survival rates of anaplastic thyroid carcinoma (ATC). The rapid evolution of biomarkers has catalyzed a paradigm shift from traditional anatomical-pathological staging to a sophisticated “Molecular Taxonomy” model, providing the cornerstone for precision oncology. This review systematically delineates the multi-dimensional landscape of TC biomarkers, encompassing genomic and transcriptomic drivers (eg, BRAF, RAS, TERT, RET, NTRK), epigenetic regulators (miRNAs, lncRNAs, circRNAs, and DNA methylation), and the proteomic interface. We highlight the transformative role of Liquid Biopsy 2.0-including ctDNA-based minimal residual disease (MRD) detection and exosomal multi-omics-in enabling non-invasive, longitudinal surveillance. Furthermore, we explore how cutting-edge technologies, such as single-cell sequencing and spatial transcriptomics, are deciphering intratumoral heterogeneity and redefining the “functional invasive front”. Clinical translation is addressed through the lens of personalized management: from the use of genomic classifiers (eg, ThyroSeq v3) in preoperative triage to biomarker-guided “de-escalation” or “intensification” of therapy. Finally, we discuss the imperative of addressing ancestry-specific molecular divergence (specifically in Asian cohorts). However, significant challenges remain, including the high cost of multi-omics integration and the lack of standardized protocols for clinical implementation. We conclude by envisioning a future integrated with multimodal AI models, patient-derived organoids (PDOs), and metabolic reprogramming markers, aiming to provide a holistic framework for the “early screening-precise diagnosis-tailored therapy-dynamic monitoring” continuum in thyroid oncology.

Keywords: thyroid cancer, precision oncology, molecular taxonomy, liquid biopsy, tumor microenvironment, spatial transcriptomics, clonal evolution, multi-modal artificial intelligence, radioiodine refractoriness, ancestry-specific medicine

Introduction

Thyroid cancer (TC) remains the most prevalent endocrine malignancy worldwide, accounting for approximately 1.0–1.5% of all systemic cancers.¹ While global incidence rates have entered a “plateau phase”, the clinical challenge has fundamentally shifted from simple detection to a more nuanced balance: mitigating the overdiagnosis of indolent tumors while preventing the undertreatment of aggressive variants.² The 2022 WHO classification (5th Edition) and subsequent 2025 updates have catalyzed a move toward a “hierarchical taxonomic” approach, where biological behavior is increasingly defined by molecular footprints-such as BRAF, RAS, and TERT-rather than morphology alone.³

Despite significant therapeutic advances, three critical “bottlenecks” continue to impede optimal patient outcomes: (1) the diagnostic “gray zone” of Bethesda III/IV indeterminate nodules, which still leads to excessive diagnostic surgeries;⁴

(2) the clinical conundrum of radioiodine-refractory (RAI-R) DTC, driven by the loss of Sodium-Iodide Symporter (NIS) expression;⁵ and (3) the therapeutic resistance in advanced Medullary (MTC) and Anaplastic (ATC) subtypes, often fueled by tumor microenvironment (TME) remodeling and clonal evolution.⁶

The year 2025 marks a definitive transition in precision oncology, moving from traditional “Anatomical Staging” to a “Molecular Risk Stratification” paradigm.⁷ Biomarkers have transcended their role as simple diagnostic aids, becoming integrated into the entire longitudinal care continuum—from AI-powered preoperative assessment and selective targeted therapeutics (eg, RET inhibitors) to the rise of liquid biopsy for minimal residual disease (MRD) monitoring.^{8,9} Alongside these advanced molecular tools, ongoing debates surround complementary and highly accessible clinical biomarkers. For instance, recent retrospective analyses evaluating the association between ABO blood groups, Rhesus (Rh) factors, and PTC risk have yielded conflicting results, underscoring the complexity of identifying universal and easily implementable risk markers.¹⁰

In this review, we systematically evaluate the transformative role of biomarkers in the precision management of thyroid cancer, providing a comprehensive framework from molecular evolution to clinical application (Figure 1).¹¹ The structure of this review is organized as follows: **Classification and Molecular Mechanisms of Thyroid Cancer Biomarkers**

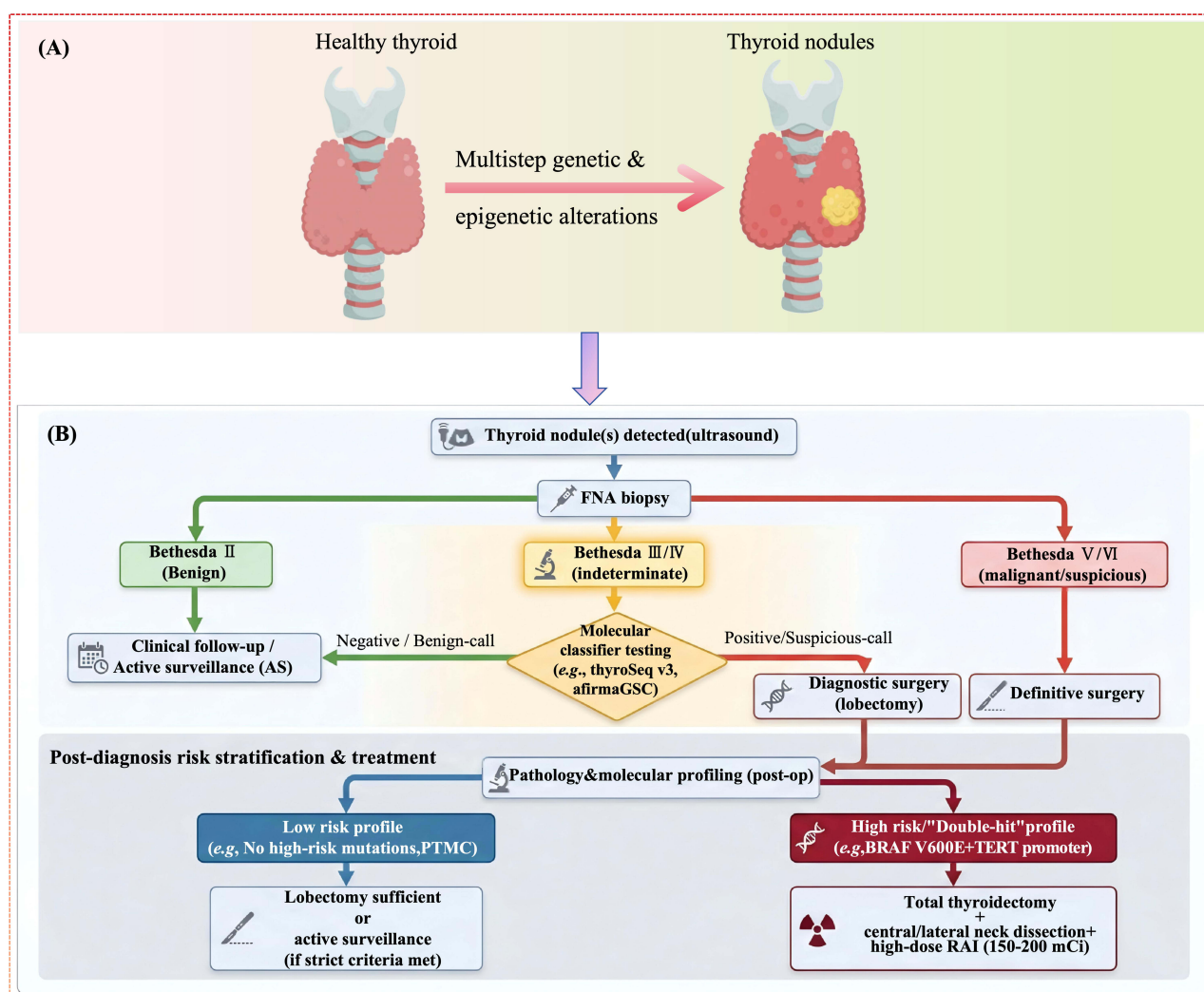


Figure 1 Molecular evolution and precision management framework for thyroid nodules and thyroid cancer. **(A)** Schematic illustration showing the transformation from a healthy thyroid gland to thyroid nodules driven by multistep genetic and epigenetic alterations. **(B)** A precision diagnostic and therapeutic workflow following ultrasound detection and fine-needle aspiration (FNA). The flowchart outlines the triage path based on Bethesda cytological categories (II: Benign; III/IV: Indeterminate; V/VI: Malignant/Suspicious) and molecular classifier testing, leading to risk-adapted surgical interventions and adjuvant treatments.

Abbreviations: AS, Active Surveillance; PTMC, Papillary Thyroid Microcarcinoma; RAI, Radioactive Iodine.

delineates the molecular mechanisms and classification of genomic, epigenetic, and proteomic markers.¹² [Discovery of Novel Biomarkers Driven by Cutting-Edge Technologies](#) explores how cutting-edge technologies, including single-cell sequencing and spatial transcriptomics, are deciphering intratumoral heterogeneity to identify novel diagnostic targets.¹³ Furthermore, [Clinical Translation of Biomarkers: Orchestrating Precision Oncology](#) discusses the clinical translation of these markers in risk stratification and companion diagnostics, particularly in the context of emerging ethnic-specific data and multimodal AI models.¹⁴ Finally, [Challenges and Future Perspectives: Navigating the Next Frontier](#) addresses current challenges in technical standardization and health economics, offering a forward-looking perspective on the future of personalized thyroid oncology.^{15,16}

Classification and Molecular Mechanisms of Thyroid Cancer Biomarkers

Genomic and Transcriptomic Biomarkers: Drivers of Lineage-Specific Oncogenesis

The genomic landscape of TC is characterized by a high degree of lineage specificity, primarily driven by the reciprocal dysregulation of the MAPK and PI3K/AKT/mTOR signaling axes.^{17,18} These genomic alterations do not function in isolation; rather, they dictate the metabolic and phenotypic identity of the tumor.¹⁹ The intricate correlation between these genomic drivers and their respective clinical phenotypes is synthesized in [Table 1](#).

Canonical Drivers of the MAPK and PI3K Pathways

Among the myriad of genetic drivers, the BRAF V600E mutation stands as the prototypical activator of the MAPK pathway in papillary thyroid carcinoma (PTC).²⁰ Beyond its staggering prevalence in Asian cohorts (>80%), recent single-cell transcriptomic analyses (2024) have unveiled that *BRAF*-mutant cells harbor a distinct “dedifferentiation signature”.²¹ This signature is characterized by the profound suppression of the Sodium-Iodide Symporter (NIS/SLC5A5), providing a mechanistic explanation for the intrinsic radioiodine resistance frequently observed in these clinical phenotypes.^{22,23} This divergence is further conceptualized by the distinction between “BRAF-like” and “RAS-like” transcriptomic profiles, where the former is associated with a more severe loss of the Thyroid Differentiation Score (TDS).^{24,25}

While *BRAF* mutations are synonymous with PTC, RAS family mutations (HRAS, KRAS, and NRAS, particularly at codon 61) serve as the fundamental “gatekeepers” of follicular neoplasia.²⁶ Unlike the linear signaling of *BRAF*, *RAS* mutations bifurcate to activate both the MAPK and PI3K pathways, fostering a more indolent but metabolically distinct phenotype.²⁷ However, the oncogenic potential of *RAS* is highly context-dependent; the acquisition of secondary “genetic hits”—such as mutations in *EIF1AX* or *TP53*—is a hallmark of clonal evolution, propelling the transition from indolent follicular tumors toward high-grade differentiated or anaplastic carcinomas (ATC).^{28–30} Complementing these point mutations is the PAX8/PPAR γ rearrangement, which functions as a dominant-negative inhibitor of wild-type PPAR γ .³¹ This fusion represents a unique epigenetic-transcriptomic bridge in follicular thyroid carcinoma (FTC), often correlating with a more favorable metabolic profile than its *RAS*-mutant counterparts ([Figure 2](#)).³²

Table 1 Molecular Landscape and Clinical Significance of Core Driver Mutations in Thyroid Cancer

Biomarker Type	Key Alterations	Target Pathway	Prevalence (Global vs Asian)	Clinical Implication & Prognosis
Point Mutations	<i>BRAF</i> V600E	MAPK	45% (G) vs >80% (A)	Aggressive PTC; loss of NIS expression; RAI refractoriness.
Gene Fusions	<i>TERT</i> Promoter	Telomere	15% (PTC), 70% (ATC)	“Genetic Amplifier”; poor OS; synergistic with <i>BRAF</i> .
	<i>RAS</i> (N/H/K)	MAPK/PI3K	40-50% (FTC)	Early oncogenic event; progression to PDTC/ATC.
	<i>RET/PTC</i>	MAPK	10-20% (PTC)	Radiation-related TC; favorable prognosis in adults.
Co-mutations	<i>NTRK1/2/3</i>	TRK	5-13% (PTC)	Pan-cancer actionable target; responsive to Larotrectinib.
	<i>PAX8/PPARγ</i>	Transcriptional	35% (FTC)	Diagnostic for follicular neoplasm; lower recurrence.
	<i>BRAF</i> + <i>TERT</i>	Synergistic	~10% (G) vs 18% (A)	Extremely high recurrence risk (HR >5.0); surgical escalation.

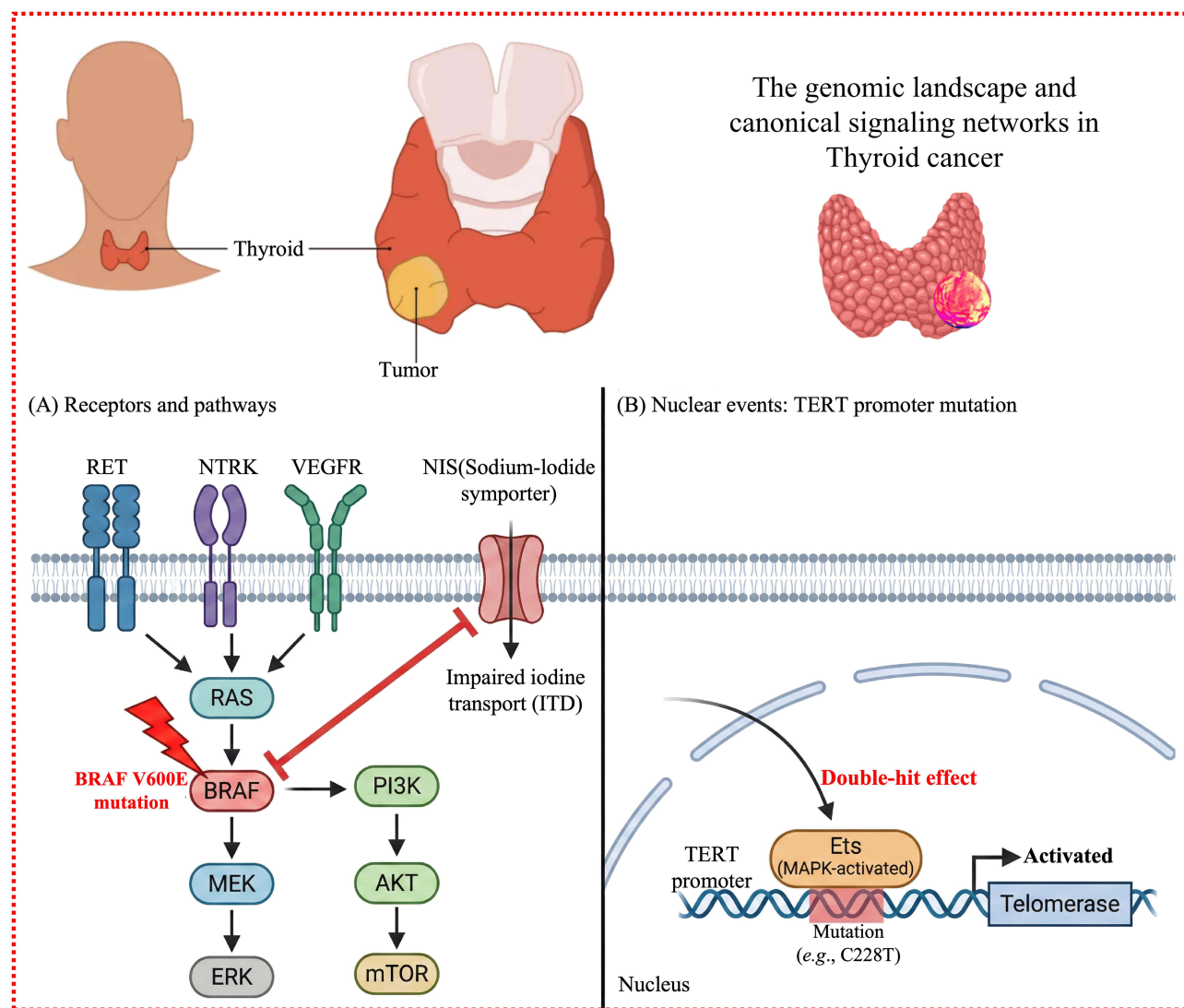


Figure 2 The genomic landscape, signaling networks, and synergistic “Double-Hit” mechanisms in thyroid cancer. (Top Panel) Illustration bridging gross thyroid anatomy with molecular pathogenesis. **(A)** Receptor signaling cascades demonstrating the activation of MAPK (RAS-BRAF-MEK-ERK) and PI3K-AKT-mTOR pathways by tyrosine kinases (RET, NTRK, VEGFR). The red flash highlights the BRAF V600E mutation, which constitutively activates the MAPK pathway and represses the Sodium-Iodide Symporter (NIS), leading to impaired iodine transport (ITD). **(B)** Nuclear events depicting the “Double-Hit” synergy, where MAPK-activated Ets transcription factors bind to mutated *TERT* promoters (eg, C228T) to aberrantly reactivate telomerase.

The Expanding Landscape of Kinase Fusions

The molecular taxonomy of TC has been further refined by the identification of rare but therapeutically actionable gene fusions.³³ Kinase fusions involving *RET*, *NTRK*, and *ALK* are particularly prevalent in pediatric populations and radiation-induced TC.³⁴ While *RET/PTC1* and *RET/PTC3* have long been recognized as classic drivers, the 2025 clinical consensus has shifted toward “agnostic targeting”. This shift is supported by the landmark LIBRETTO-531 trial, which established selective RET inhibitors, such as Selpercatinib, as superior first-line options over multi-kinase inhibitors (MKIs) for *RET*-fusion-positive TC.^{35–37} Similarly, *NTRK* fusions (eg., *ETV6-NTRK3*) have emerged as high-value targets, with Larotrectinib delivering durable objective responses in advanced, treatment-refractory cases.³⁸

TERT Promoter Mutations: The “Master Switch” of Lethality

The most critical evolutionary milestone in TC progression is arguably the acquisition of TERT promoter mutations (C228T/C250T).³⁹ These alterations act as a “master switch” for telomere immortality, but their clinical lethality is largely realized through the “Double-Hit” synergistic model.⁴⁰ In this framework, the co-occurrence of *TERT* with *BRAF*

V600E or *RAS* mutations creates a potent feed-forward loop: MAPK-induced Ets transcription factors bind specifically to the de novo sites created by the *TERT* mutation, drastically upregulating telomerase activity.^{41,42} This synergy represents the most robust genomic predictor of disease-specific mortality (HR>5.0) in differentiated TC, marking the definitive boundary between low-risk disease and terminal malignancy.⁴³

Epigenetic Markers: The Regulatory Dark Matter of Tumor Plasticity

Beyond the hardwired genomic landscape, epigenetic alterations provide a layer of “soft” regulation that fundamentally dictates tumor plasticity and adaptive resistance.⁴⁴ These modifications, encompassing non-coding RNA (ncRNA) networks and DNA methylation, act as dynamic rheostats that modulate gene expression without altering the primary DNA sequence.^{45,46}

Among the vast ncRNA landscape, MicroRNA (miRNA) hubs—specifically miR-221/222 and miR-146b—have emerged as central drivers of tumor microenvironment (TME) remodeling.⁴⁷ miR-146b, in particular, has been shown to modulate TGF- β signaling, thereby facilitating the activation of resident fibroblasts into cancer-associated fibroblasts (CAFs).⁴⁸ This regulatory complexity is further extended by Circular RNAs (circRNAs) and Long non-coding RNAs (lncRNAs).⁴⁹ Notably, recent studies (2024) highlight circBRAF as a highly stable, exosome-encapsulated scaffold.⁵⁰ Unlike linear mRNA transcripts, the unique covalent loop structure of circRNAs confers resistance to exonucleases, positioning them as superior candidates for non-invasive, serum-based diagnostic panels.⁵¹

Parallel to ncRNA regulation, the DNA methylation landscape has transitioned from single-gene analysis to comprehensive Whole-Genome Bisulfite Sequencing (WGBS).⁵² This high-resolution approach has identified “CpG Island Methylator Phenotypes” (CIMP) in anaplastic thyroid carcinoma (ATC), reflecting a state of profound epigenetic reprogramming.⁵³ These signatures are increasingly being translated into clinical practice through commercial panels such as ThyMet (AUC 0.828).^{54,55} By leveraging these epigenetic footprints, clinicians can effectively bypass the morphological limitations of traditional cytology, particularly in Bethesda IV indeterminate nodules where cytological distinction is often impossible.⁵⁶

Proteomic Markers: Refining the Histopathological Interface

While genomic and epigenetic markers offer the “blueprints” and “regulatory logic” of oncogenesis, proteomics reflects the actual functional state of the tumor.⁵⁷ This protein-level information is essential for validating the biological consequences of upstream molecular alterations.⁵⁸

Historically, the triple immunohistochemical (IHC) panel—comprising Galectin-3, CK19, and HBME-1—has remained the gold standard for pathological validation, achieving a combined diagnostic accuracy of 97%.⁵⁹ However, the field is now moving toward Next-Generation Proteomics, characterized by spatial resolution.⁶⁰ Spatial Proteomics (2025) has successfully identified focal clusters of Matrix Metalloproteinase-9 (MMP-9) and VEGF-C at the “invasive front” of the tumor.^{61,62} These findings provide a spatial map of metastatic potential that traditional bulk sequencing frequently obscures, offering a more precise tool for predicting extrathyroidal extension and lymph node involvement.⁶³

Liquid Biopsy: From Static Snapshots to Dynamic Surveillance

The ability to monitor these molecular and proteomic changes non-invasively has led to the emergence of Liquid Biopsy 2.0, shifting the diagnostic paradigm from static tissue snapshots to real-time, dynamic surveillance.⁶⁴

Central to this transition is the detection of Minimal Residual Disease (MRD) via postoperative circulating tumor DNA (ctDNA). By tracking hallmark mutations like *BRAF* or *TERT*, MRD assays can identify biochemical recurrence months before thyroglobulin (Tg) elevation or structural imaging can detect macroscopic lesions.^{65,66} Complementing ctDNA is the analysis of exosomes, which act as “biocontainers” for a cocktail of miRNAs and proteins.⁶⁷ Due to their ability to cross the blood-brain barrier, exosomal multi-omics have become invaluable for monitoring central nervous system metastases in ATC.⁶⁸ Furthermore, the 2024 validation of non-blood-derived biopsies, such as urinary thyroglobulin (uTg) and salivary miR-146b, offers a truly non-invasive, point-of-care screening tool.⁶⁹ These modalities are particularly critical for patients with high thyroglobulin antibody (TgAb) titers, where traditional serum Tg testing is clinically unreliable.⁷⁰

The TME and Immuno-Oncology: Mapping the “Cold-to-Hot” Transition

As liquid biopsy enables the tracking of tumor evolution, it also reveals the critical role of the Tumor Microenvironment (TME) in modulating treatment response.⁷¹ Although thyroid cancer is traditionally viewed as an “immunologically cold” malignancy, advanced subtypes exhibit significant immune infiltration that can be exploited therapeutically.⁷²

In aggressive TC variants, the recruitment of M2-type tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) creates an immunosuppressive “shield” that facilitates immune evasion.⁷³ The high infiltration of CD163+ macrophages is now recognized as a validated marker for progression toward radioiodine (RAI) refractoriness.⁷⁴ To counteract this, Immune Checkpoint Blockade (ICB) strategies are being refined.⁷⁵ The COMBI-AT trial (2024/2025 updates) has revolutionized the treatment of ATC by demonstrating that “Triple Therapy”—combining Dabrafenib and Trametinib with Pembrolizumab—can achieve an Objective Response Rate (ORR) of 56%.⁷⁶ This strategy leverages MAPK inhibition to “prime” the TME, increasing PD-L1 expression and effectively converting an immunologically “cold” environment into a “hot”, T-cell-inflamed state.⁷⁷ Beyond the PD-1/PD-L1 axis, second-generation checkpoints such as TIGIT and LAG-3 are emerging as vital targets for patients who develop resistance to initial ICB therapy, marking the next frontier in personalized immuno-oncology.^{78,79}

Discovery of Novel Biomarkers Driven by Cutting-Edge Technologies

The traditional “bulk-sample” analysis paradigm, which averages molecular signals across millions of cells, inherently masks the critical intratumoral heterogeneity (ITH) that drives treatment failure.⁸⁰ To overcome this limitation, the integration of single-cell resolution, spatial context, and deep-learning-based radiomics has provided a potent “technical engine” for identifying next-generation biomarkers that capture the spatiotemporal complexity of thyroid cancer.^{81,82} The transformative potential of these cutting-edge technologies in identifying next-generation biomarkers is consolidated in Table 2.

Single-Cell Sequencing (scRNA-Seq): Mapping Clonal Evolution and Fitness

Single-cell transcriptomics has fundamentally redefined our understanding of thyroid cancer as a complex, co-evolving cellular ecosystem rather than a monolithic mass of malignant cells.⁸³ By dissecting the transcriptome at the individual cell level, recent scRNA-seq studies (2024/2025) have identified distinct “evolutionary trajectories” within papillary thyroid carcinoma (PTC).⁸⁴ A pivotal discovery in this field is the spatial and functional coexistence of proliferative clones (enriched for BRAF V600E and Ki-67) and migratory clones (characterized by MMP-9 and VIM expression).^{85,86} Crucially, clinical data suggest that post-surgical recurrence is often not driven by the primary proliferative mass, but by the survival of these quiescent migratory clones that effectively evade standard cytotoxic or radioiodine therapies.⁸⁷

Furthermore, the identification of a CD44⁺/CD24[−] stem-like subpopulation, or Cancer Stem Cells (CSCs), has provided a crucial mechanistic link to radioiodine (RAI) refractory phenotypes.^{88,89} These cells undergo a profound metabolic and transcriptomic “re-wiring”—orchestrated by the transcription factors SOX2 and OCT4—which actively

Table 2 Emerging Technologies for Next-Generation Biomarker Discovery

Technology	Data Dimension	Novel Biomarker Identified	Resolution/Value	Future Prospect
scRNA-seq Spatial Transcriptomics Radiomics Liquid Biopsy 2.0 Organoids (PDOs)	Single-cell Transcriptome	CD44+ Stem-like subpopulations	Cellular heterogeneity and Clonal fitness	Predicting RAI resistance and relapse.
	Spatiotemporal RNA	FIF (Functional Invasive Front)	Niche interaction (Tumor-CAF -TAM)	Mapping metastatic potential in situ.
	Voxel-level Imaging	Virtual Biopsy (AI signatures)	Non-invasive phenotype prediction	Reducing FNAB biopsy frequency.
	ctDNA/Exosomes	MRD (Minimal Residual Disease)	Ultra-sensitive kinetic monitoring	Real-time surveillance of clonal evolution.
	Functional 3D Culture	Drug Sensitivity Score (DSS)	Ex vivo clinical “Avatars”	Personalized “Trial-and-Error” screening.

suppresses the expression of the sodium-iodide symporter (SLC5A5/NIS).⁹⁰ Clinical evidence indicates that a CSC density exceeding 5% serves as a potent biomarker for poor prognosis, with 5-year recurrence rates soaring to 52%.⁹¹ Consequently, therapeutic strategies targeting the IL-6/STAT3 signaling axis within this niche are currently being explored to “re-sensitize” these recalcitrant populations to RAI.⁹²

Spatial Transcriptomics: Decoding the “Functional Invasive Front”

While single-cell sequencing provides a high-resolution parts list of the tumor, Spatial Transcriptomics (ST) preserves the vital architectural context, transitioning research from “what cells are present” to “where and how they interact”.⁹³

This spatial lens has led to the redefinition of the tumor margin as a “Functional Invasive Front” (FIF)-a highly active metabolic zone (~100-150 μm wide) where malignant cells engage in dynamic crosstalk with Cancer-Associated Fibroblasts (CAFs) and M2-polarized macrophages.^{94,95} This region is characterized by a “molecular storm” of CCL2, FGF2, and MMP-2, which collectively facilitate stromal degradation and immune evasion.⁹⁶ Emerging data suggest that the molecular density of the FIF is superior to traditional TNM staging in predicting occult lymph node metastasis.⁹⁷ Moreover, ST has unveiled a phenomenon of “molecular mosaicism”, where distinct regions of a single tumor harbor divergent actionable fusions, such as BRAF mutations in the core versus MET or RET rearrangements at the periphery.⁹⁸ This spatial heterogeneity underscores the necessity of moving toward multi-target therapeutic strategies to prevent clonal escape (Figure 3).⁹⁹ Despite these profound insights, the routine clinical application of spatial transcriptomics is currently hindered by significant limitations, including high computational costs, complex bioinformatic pipelines, and the strict requirement for high-quality or fresh tissue samples.

Radiomics and Radio Genomics: The Rise of Virtual Biopsy

Complementing these molecular insights, the fusion of Artificial Intelligence (AI) and medical imaging is enabling a new era of “Virtual Biopsies”, offering non-invasive molecular phenotyping across the entire tumor volume.¹⁰⁰

Deep-learning models, particularly Convolutional Neural Networks (CNNs), can now extract sub-visual texture features-such as heterogeneous internal echoes and irregular microcalcifications-to predict BRAF V600E status with an impressive AUC of 0.89–0.92.¹⁰¹ This capability is significantly reducing the reliance on invasive fine-needle aspiration biopsy (FNAB) in up to 30% of Bethesda II/III cases.¹⁰² Beyond simple diagnosis, radiogenomic signatures allow for high-precision preoperative risk stratification; for instance, the presence of “Radiographic Extrathyroidal Extension” (rETE) combined with CT-based lymph node radiomics achieves an AUC of 0.87 for predicting aggressive behavior.¹⁰³

As we enter the “Multimodal 2.0 Era”, the most advanced models are now integrating Radiomics with cfDNA and clinical proteomics. In the management of RAI-R DTC, these multi-modal fusion models have achieved an AUC of 0.94 in predicting treatment response to tyrosine kinase inhibitors (TKIs) like Lenvatinib.¹⁰⁴ By providing an earlier read on efficacy than traditional RECIST criteria, these models empower clinicians to pivot to second-line therapies months before structural progression becomes apparent, truly embodying the goal of individualized precision oncology.¹⁰⁵ However, it must be acknowledged that AI-driven radiomics and multimodal models still face substantial translational barriers, primarily the lack of large-scale, cross-institutional validation and the need for standardized imaging protocols, which currently restrict their widespread clinical implementation.

Clinical Translation of Biomarkers: Orchestrating Precision Oncology

The clinical utility of thyroid cancer (TC) biomarkers has transcended their role as auxiliary diagnostic aids, evolving into the central pillars that dictate the entire management continuum.^{106,107} By integrating molecular insights into clinical practice, the field has moved toward an “Orchestrated Precision” model, encompassing preoperative classification, intensity-modulated risk stratification, and real-time resistance monitoring.^{108–110}

Preoperative Diagnosis: Resolving the Indeterminate Nodule Paradox

Molecular profiling has fundamentally revolutionized the management of Bethesda III/IV nodules, where traditional morphology often proves inconclusive.¹¹¹ The current diagnostic landscape is dominated by high-precision Next-

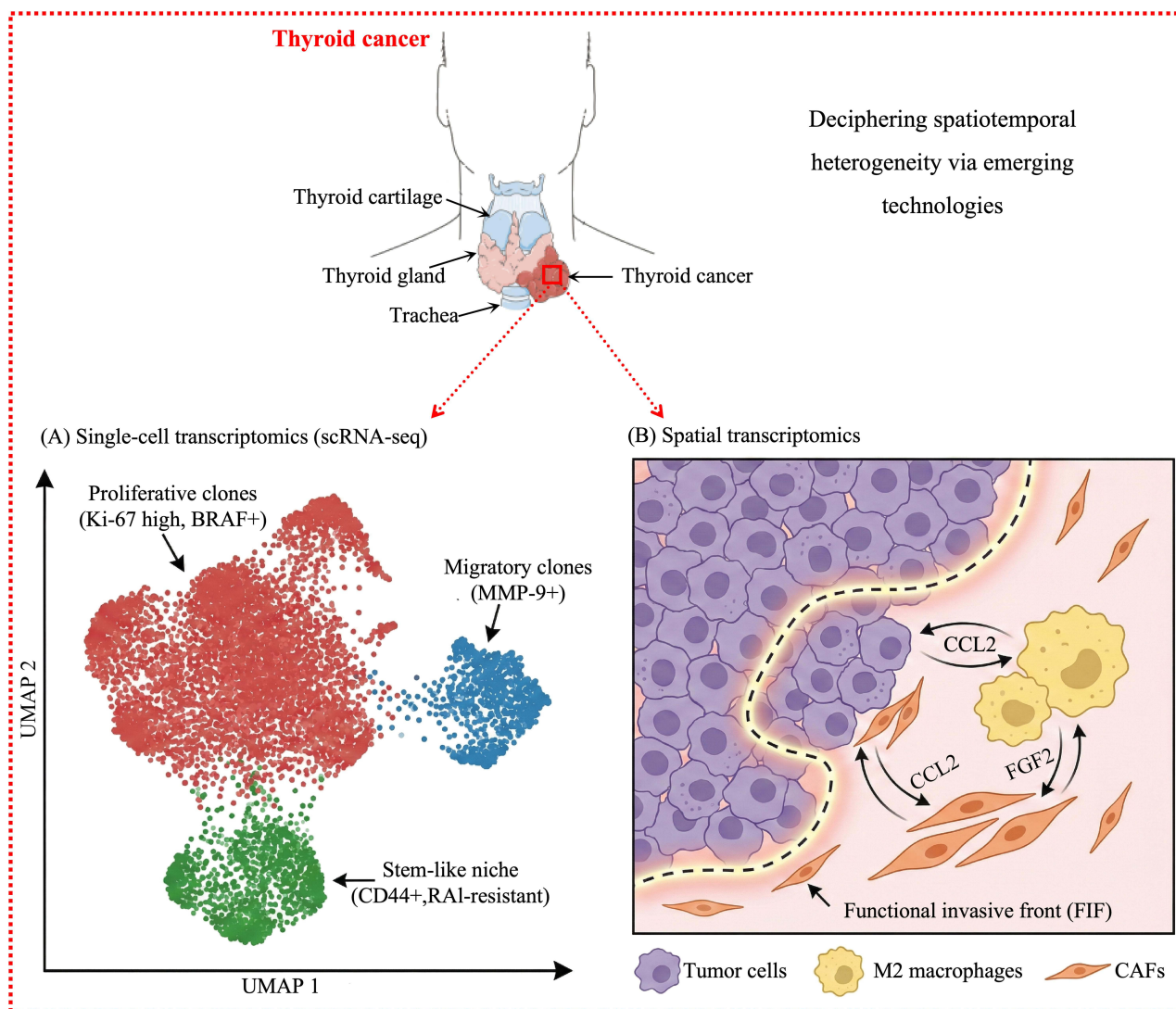


Figure 3 Deciphering intratumoral heterogeneity and the microenvironmental niche via spatiotemporal omics. (Top Panel) Schematic transitioning from gross tumor anatomy to single-cell and spatial resolution. (A) Single-cell transcriptomic (scRNA-seq) UMAP projection displaying three distinct tumor subpopulations: Proliferative clones (Ki-67 high, BRAF+), Migratory clones (MMP-9+), and a Stem-like niche (CD44+, RAI-resistant). (B) Spatial transcriptomics map depicting the functional invasive front (FIF; dashed line). The diagram illustrates the spatial crosstalk between tumor cells, M2-polarized macrophages, and Cancer-Associated Fibroblasts (CAFs) mediated by CCL2 and FGF2 signaling.

Generation Molecular Panels that move beyond single-gene testing.^{112,113} As of the 2025 clinical consensus, the utilization of multi-gene genomic classifiers (GECs), such as ThyroSeq v3 (leveraging DNA/RNA-based NGS) and Afirma GSC (utilizing RNA sequencing and machine learning), has become standard practice.^{114,115} These platforms have achieved a Negative Predictive Value (NPV) exceeding 94%, effectively facilitating a “rule-out” strategy that spares patients with benign molecular signatures from unnecessary diagnostic lobectomies.^{116–118}

Beyond genomic sequencing, the “2.0 Era” of diagnosis is characterized by the synergy of multi-omic data.¹¹⁹ The ThyMet-US model, for instance, integrates DNA methylation signatures with AI-enhanced ultrasonography.^{120,121} This multimodal approach has boosted the specificity for diagnosing Papillary Thyroid Microcarcinoma (PTMC) to twice that of ultrasound alone, achieving an AUC of 0.923.^{122–124} Such integration is critical in mitigating the global crisis of thyroid cancer overdiagnosis while ensuring that aggressive variants are not overlooked during the initial triage.^{125,126} A comparative analysis of the leading commercial genomic classifiers and their diagnostic performance metrics is provided in Table 3. In summary, integrating genomic classifiers and multimodal diagnostic tools into preoperative

Table 3 Comparison of Leading Preoperative Molecular Classifiers for Indeterminate Nodules (Bethesda III/IV)

Product Name	Methodology	Biomarker Targets	Sensitivity/ Specificity	Negative Predictive Value (NPV)	Clinical Utility
ThyroSeq v3	NGS (DNA/RNA)	112 Genes (SNVs, Fusions, CNVs)	94% / 82%	97%	“Rule-out” and “Rule-in” malignant potential.
Afirma GSC	RNA-seq + ML	Whole Transcriptome + Ensembles	91% / 68%	96%	High NPV; reduces unnecessary surgeries.
ThyGeNEXT/ ThyraMIR	NGS + miRNA	Oncogenes + 10 miRNAs	95% / 90%	97%	Combines genomic and epigenetic insights.
ThyMet-US (China)	DNA Methylation	6 Methylation Markers + AI-US	90% / 94%	92%	Optimized for Asian cohorts and PTMC management.

protocols effectively mitigates diagnostic ambiguity, facilitating a safe “rule-out” strategy that significantly reduces unnecessary diagnostic surgeries.

Risk Stratification: Calibrating Treatment Intensity

A cornerstone of precision oncology in TC is the ability to calibrate treatment intensity-achieving “de-escalation” for low-risk cohorts while “intensifying” therapy for those harboring aggressive molecular footprints.^{127,128}

In the context of de-escalation and active surveillance (AS), the absence of *BRAF V600E* and *TERT* promoter mutations has become a mandatory prerequisite for entering AS protocols for PTMC (≤ 1 cm).¹²⁹ For post-surgical differentiated thyroid cancer (DTC), the identification of a “molecular cure” marker-defined by a TSH-stimulated Thyroglobulin (Tg) level <0.1 ng/mL in conjunction with negative *TSHR* mRNA-justifies a significant reduction in long-term follow-up frequency.^{130,131}

Conversely, the identification of the “Double-Hit” genotype (*BRAF* + *TERT* or *RAS* + *TERT*) mandates an immediate escalation in treatment.¹³² These high-risk patients typically require total thyroidectomy supplemented by prophylactic or therapeutic neck dissection.¹³³ Furthermore, in the adjuvant setting, high-activity Radioactive Iodine (RAI) therapy (150–200 mCi) is prioritized.^{134,135} Emerging evidence suggesting NIS (Sodium-Iodide Symporter) downregulation in these genotypes may further prompt the early introduction of re-differentiation agents to restore RAI sensitivity before the disease becomes refractory.^{136,137} In essence, biomarker-guided risk stratification empowers clinicians to precisely calibrate treatment intensity, ensuring safe de-escalation for indolent tumors while justifying aggressive, multimodal interventions for high-risk variants.

Companion Diagnostics: Matching Targets and Navigating Resistance

The era of “one-size-fits-all” multi-kinase inhibitors (MKIs) is rapidly being superseded by biomarker-driven targeted therapy, where companion diagnostics ensure precise drug-patient matching.¹³⁸ The landmark LIBRETTO and ARROW trials have firmly established *RET* fusions and mutations as high-value actionable targets in both MTC and PTC.¹³⁹ Selective inhibitors like Selpercatinib and Pralsetinib have demonstrated superior Objective Response Rates (ORR) and significantly lower toxicity profiles compared to traditional systemic therapies.¹⁴⁰

Despite these promising results, it is crucial to acknowledge that the literature contains conflicting findings regarding the universal efficacy of these targeted agents.¹⁴¹ For instance, real-world data and retrospective analyses have occasionally reported discrepant objective response rates to specific kinase inhibitors when comparing Asian and Western cohorts, or across distinct fusion partners (eg., CCDC6-RET vs NCOA4-RET).¹⁴² These controversial outcomes underscore the complexity of tumor biology and complicate the establishment of universally applicable treatment guidelines.¹⁴³ However, the efficacy of these targeted agents is often limited by the emergence of secondary resistance.¹⁴⁴ A critical frontier in 2025 is the real-time identification of bypass mechanisms, such as MET amplification, which has been implicated in resistance to Lenvatinib.^{145–147} The clinical implementation of MET inhibitors (eg., Capmatinib) as a co-targeting strategy has shown remarkable potential in reversing resistance, achieving tumor shrinkage

Table 4 Targeted Therapies and Companion Biomarkers in Advanced Thyroid Cancer

Therapeutic Target	Targeted Drug	Companion Biomarker	Representative Trial	Clinical Efficacy (ORR/PFS)	Status/Recommendation
RET (Mut/ Fusion)	Selpercatinib	<i>RET</i> Fusion/ Mutation	LIBRETTO-531	ORR: ~80%; HR: 0.28 vs MKIs	FDA approved; First-line for MTC/PTC.
BRAF V600E	Dabrafenib + Trametinib	<i>BRAF</i> V600E	ROAR (ATC)	ORR: 61%; Median OS: 14.5 mo	Standard of care for BRAF+ ATC.
NTRK Fusion	Larotrectinib	<i>NTRK</i> 1/2/3 Fusion	NAVIGATE	ORR: 75%	Agnostic targeting; high durability.
VEGFR (RAI-R)	Lenvatinib	NIS loss (Phenotype)	SELECT	PFS: 18.3 mo vs 3.6 mo	First-line for RAI-R DTC.
PD-I/PD-LI	Pembrolizumab	PD-LI TPS / TMB	KEYNOTE-158	ORR: 22% (ATC)	Combined with TKIs for “Hot” tumors.

of approximately 28% in recent refractory cohorts.^{148,149} These dynamic underscores the necessity of longitudinal molecular monitoring to adapt therapeutic strategies as the tumor’s clonal architecture evolves under selective pressure.^{150,151} The landmark clinical trials and the corresponding companion biomarkers guiding targeted interventions in advanced thyroid cancer are summarized in [Table 4](#).

Postoperative Surveillance: From Static Monitoring to Liquid Biopsy 2.0

The longitudinal management of TC is currently undergoing a fundamental paradigm shift, moving beyond static biochemical monitoring toward high-frequency “molecular snapshots” enabled by next-generation liquid biopsy.^{152,153} This evolution is particularly critical for patients harboring anti-thyroglobulin antibodies (TgAb+), a clinical scenario where conventional protein-based thyroglobulin (Tg) assays often yield technically compromised or unreliable results.¹⁵⁴ In such cohorts, the integration of TSHR mRNA and Calcitonin/CEA doubling times offers a more robust kinetic assessment of the tumor burden, providing clinicians with a clearer window into the disease’s biochemical trajectory.¹⁵⁵

Beyond refining traditional markers, perhaps the most transformative advancement in postoperative care is the integration of the Minimal Residual Disease (MRD) paradigm.¹⁵⁶ By detecting hallmark *BRAF* or *TERT* mutations via circulating cell-free DNA (cfDNA), MRD assays can predict structural recurrence 3–6 months earlier than even the most sensitive high-resolution imaging modalities, such as PET/CT. This early warning system, further bolstered by the analysis of exosomal miR-221/222 and circulating tumor cells (CTCs), facilitates a shift toward “pre-emptive” therapeutic adjustments.^{157–159} By identifying molecular progression before it manifests as macroscopic disease, clinicians can intervene during an optimal window of lower tumor burden, significantly enhancing the prospects for long-term disease control and potentially curative outcomes ([Figure 4](#)).¹⁶⁰

Challenges and Future Perspectives: Navigating the Next Frontier

While the integration of molecular biomarkers has fundamentally reshaped the clinical management of thyroid cancer (TC), several formidable barriers persist that prevent the full realization of “population-specific precision”.¹⁶¹ Transitioning from generalized evidence to tailored oncology requires addressing deep-seated clinical, technical, and socio-economic challenges.¹⁶²

Current Core Challenges: Bridging the Gap Between Theory and Practice

A primary concern in contemporary thyroid oncology is the ancestry-specific molecular divergence.¹⁶³ The genomic architecture of TC exhibits profound ethnic heterogeneity; specifically, Chinese cohorts demonstrate a “hyper-mutation” phenotype within the MAPK pathway.¹⁶⁴ In these populations, the prevalence of the *BRAF* V600E mutation reaches approximately 80%, nearly double the ~45% observed in Western cohorts.^{165,166} More critically, the synergistic *BRAF* +*TERT* co-mutation rate-associated with a 72% five-year recurrence risk in Asians compared to 58% in Westerners-suggests a more aggressive clinical trajectory that necessitates a departure from Western-centric diagnostic thresholds.¹⁶⁷

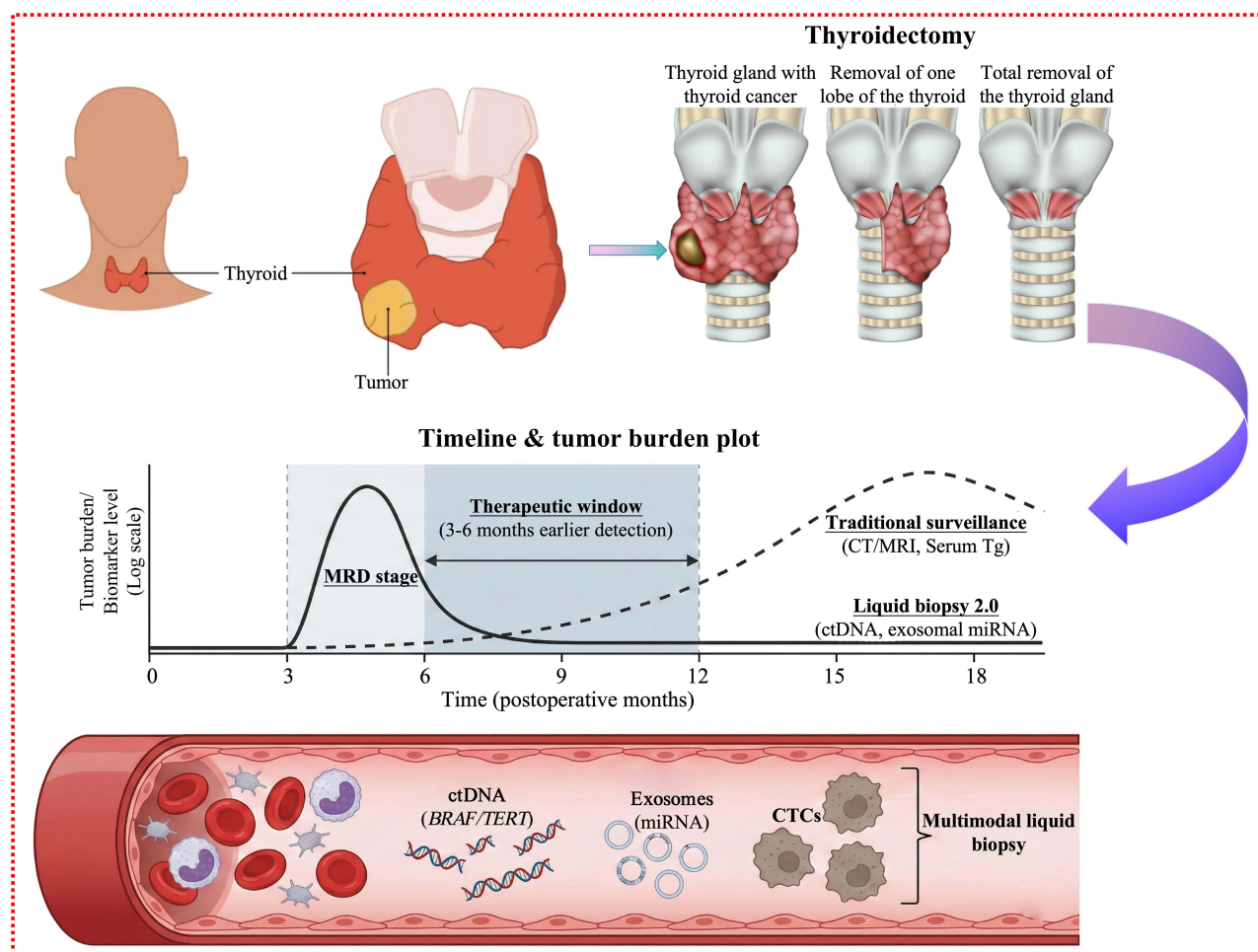


Figure 4 Longitudinal surveillance and the Minimal Residual Disease (MRD) paradigm in thyroid cancer. (Top and Middle Panels) Kinetic trajectory comparing detection thresholds. The dashed line represents traditional surveillance (serum Tg, CT/MRI) detecting macroscopic recurrence. The solid line represents Liquid Biopsy 2.0 (ctDNA, exosomal miRNA) detecting MRD. The shaded area indicates the therapeutic window (3–6 months earlier detection) between molecular relapse and clinical recurrence. (Bottom Panel) Diagram illustrating multimodal liquid biopsy analytes in the bloodstream, including circulating tumor DNA (ctDNA), exosomes, and circulating tumor cells (CTCs). Tg, Thyroglobulin.

Consequently, the reliance on Western-derived genomic classifiers, such as ThyroSeq v3, leads to a notable performance decline, with the positive predictive value (PPV) dropping from 83% to 75% in Chinese clinical settings.^{168,169} This discrepancy highlights the urgent need for ethnicity-calibrated molecular diagnostic panels.¹⁷⁰

Beyond biological diversity, the clinical utility of biomarkers is hampered by methodological standardization and quality control (QC) bottlenecks.¹⁷¹ Significant “technical noise” remains, characterized by sensitivity variances across platforms (*eg.*, Sanger vs NGS vs ARMS-PCR) and up to a 20% discrepancy in circulating cell-free DNA (cfDNA) yields due to non-standardized extraction protocols.¹⁷² Consequently, clinicians often face conflicting diagnostic reports. For instance, discordant variant allele frequency (VAF) readouts between different sequencing platforms (*eg.*, amplicon-based NGS versus hybrid capture-based NGS) frequently result in contradictory clinical interpretations.¹⁷³ A low-abundance mutation identified by one highly sensitive assay may be entirely missed by another, creating a diagnostic dilemma: does a low VAF represent a true oncogenic driver requiring intensified treatment, or merely subclonal “noise”? The absence of Certified Reference Materials (CRMs) for ultra-low frequency mutations precludes the cross-institutional validation required for a global diagnostic consensus.¹⁷⁴

Furthermore, the field faces a dual dilemma: the identification of triage biomarkers for indolent versus invasive micro-PTC, and the inherent spatiotemporal heterogeneity of advanced disease.¹⁷⁵ While overdiagnosis remains a global concern, current markers fail to reliably exclude latent aggressive potential, as evidenced by the 1–2% “false-benign”

rate in Bethesda II categories.¹⁷⁶ Concurrently, the phenomenon of “Clonal Switch”—where a BRAF-positive primary tumor evolves into a RAS-positive metastatic lesion—underscores the limitations of static tissue biopsies and the risks associated with single-site molecular profiling.¹⁷⁷

Future Research Directions: The Convergence of Technology and Biology

To overcome these obstacles, the next generation of TC management is gravitating toward the convergence of multi-modal Artificial Intelligence (AI) and functional biology.¹⁷⁸

Modern AI-driven “Virtual Biopsies” are evolving from simple image-feature extraction to deep-learning fusion models that integrate radiomic textures, digital pathology, and genomic data. State-of-the-art models (2025/2026) have already achieved an AUC of 0.95 in predicting radioiodine refractoriness, providing a non-invasive tool to visualize tumor biology in three dimensions.^{179,180} Complementing this digital revolution is the rise of Patient-Derived Organoids (PDOs) as “clinical avatars”.¹⁸¹ With an 80% concordance rate between ex vivo drug sensitivity and clinical response, PDOs offer a functional precision medicine platform to preemptively identify resistance in medullary (MTC) and anaplastic (ATC) subtypes before disease progression occurs.¹⁸²

Simultaneously, the research focus is expanding to identify novel vulnerabilities through metabolic and epigenetic reprogramming.¹⁸³ Metabolic biomarkers, such as elevated lactate dehydrogenase (LDH) and glutamine dependency (SLC1A5 upregulation), have emerged as prognostic signatures in ATC with an AUC of 0.956.¹⁸⁴ In the realm of immuno-metabolism, the expression of GLUT1 on tumor-associated macrophages (TAMs) has shown promise as a companion diagnostic for immune checkpoint inhibitor (ICI) therapy, linking cellular energetics directly to immune evasion.^{185,186}

Finally, as we strive for global equity, health economics and “value-based” precision medicine must remain at the forefront.¹⁸⁷ A “Tiered Molecular Triage” strategy—utilizing cost-effective ARMS-PCR for initial screening followed by comprehensive NGS for high-risk cohorts—is essential for sustainability.^{188,189} In the Chinese healthcare context, this

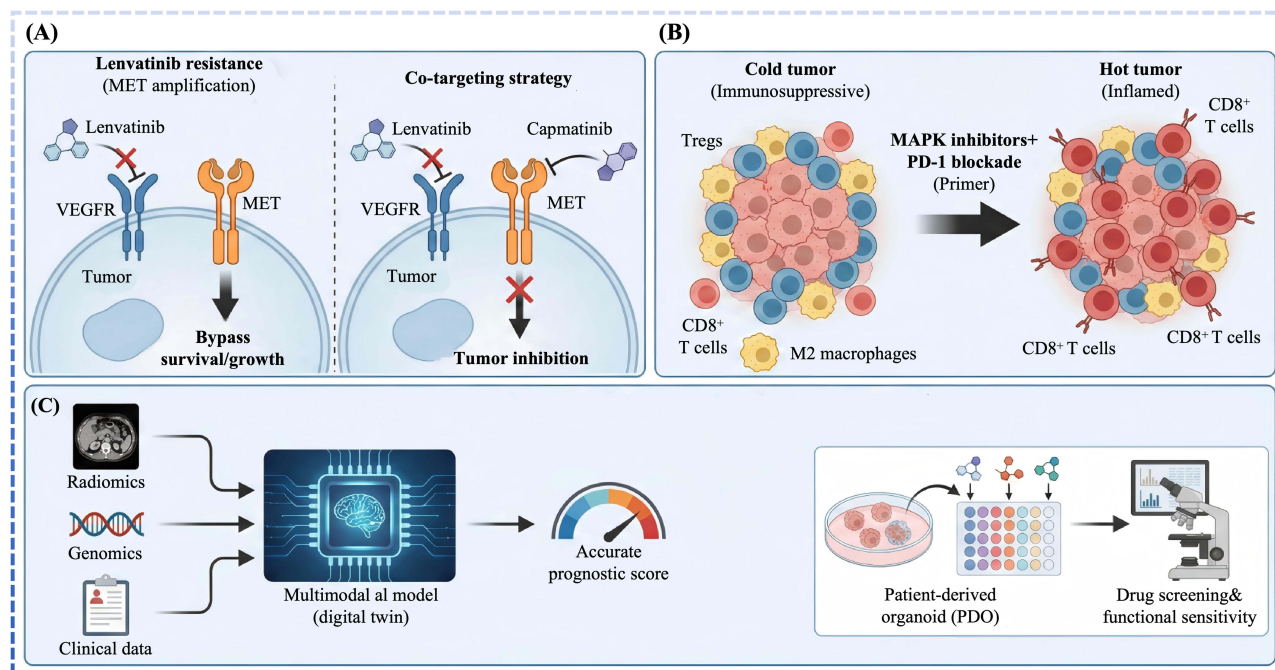


Figure 5 Mechanisms of adaptive resistance and emerging frontiers in precision thyroid oncology. **(A)** Illustration of bypass signaling and co-targeting. The left panel shows Lenvatinib resistance mediated by MET amplification. The right panel demonstrates a co-targeting strategy combining Lenvatinib and Capmatinib to achieve tumor inhibition. **(B)** Immune microenvironment reprogramming. The schematic shows the transition from an immunosuppressive “cold” tumor (rich in Tregs and M2 macrophages) to an inflamed “hot” tumor (infiltrated by CD8⁺ T cells) following combined MAPK inhibition and PD-1 blockade. **(C)** Functional precision medicine workflow integrating radiomics, genomics, and clinical data into a multimodal AI model (digital twin), alongside patient-derived organoids (PDOs) for drug screening and prognostic scoring. Tregs, Regulatory T cells.

approach has been validated as highly cost-effective, with an Incremental Cost-Effectiveness Ratio (ICER) of 28,000 RMB/QALY, far below the WHO-recommended thresholds for sustainable innovation.¹⁹⁰

Conclusion: Toward a Data-Driven Precision Paradigm

The landscape of thyroid oncology is undergoing a historic paradigm shift.¹⁹¹ Traditional management, long anchored in static anatomical-pathological staging, has reached its plateau, often struggling with the dual challenges of overdiagnosis in low-risk nodules and therapeutic failure in advanced, RAI-refractory disease.^{192,193} The integration of multi-dimensional biomarkers has emerged as the “Core Engine” of a new, dynamic, and longitudinal management continuum.¹⁹⁴

From the molecular taxonomy redefined by MAPK/PI3K axes to the epigenetic rheostats and proteomic functional states, biomarkers now resolve the “Indeterminate Nodule” paradox with unprecedented sensitivity.¹⁹⁵ The rise of Liquid Biopsy 2.0 and the characterization of the Tumor Microenvironment (TME) have paved the way for “Cold-to-Hot” immune transitions, shifting the paradigm toward proactive, tumor-informed surveillance.^{195,196} As we look toward the next decade, the technological synergy of single-cell resolution, spatial transcriptomics, and multimodal AI will continue to unmask the clonal evolution of thyroid cancer, providing a definitive spatial map for complex, individualized therapies.^{197,198}

In summary, TC biomarkers have transcended their role as auxiliary tools to become the architects of “Tailored Medicine”.¹⁹⁹ Ultimately, the integration of multimodal AI with non-invasive liquid biopsies represents the most promising direction for routine patient management, offering a scalable solution to reduce overtreatment while precisely tracking minimal residual disease. By harmonizing spatiotemporal biology with ethnicity-specific data and advanced AI, we are entering an era where every patient receives a diagnosis and treatment plan as unique as their own molecular fingerprint, ultimately transforming the prognosis and quality of life for thyroid cancer patients globally (Figure 5).^{200,201}

Acknowledgments

Lei Huang and Xinghua Deng are co-first authors for this study. The authors would like to express their sincere gratitude to Mr. Li Wang from Chongqing Medical and Pharmaceutical College, Chongqing, China for his invaluable contributions to the manuscript; His meticulous efforts ensured the accuracy and reliability of the research findings of the present study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The authors declare that financial support was received for the research, authorship and publication of this article. This work was funded by the Scientific Research and Innovation Team of Chongqing Youth Vocational & Technical College (No. CQY2021CXTDB01), the Science and Technology Research Program of Chongqing Municipal Education Commission (No. KJQN202204107; No. KJQN202402821; No. KJQN202502819), the Technological Innovation Project of Shapingba District, Chongqing (No. 2025016; No. 2025017; No. 2025031), Joint project of Chongqing Health Commission and Science and Technology Bureau (Joint Key Laboratory Open Project) (No. 2026KFXM051), Natural Science Foundation of Chongqing (No. CSTB2025NSCO-GPX1116), 2026 Chongqing Municipal Health Commission Traditional Chinese Medicine Research Project (No. 2026WSJK158), 2024 Scientific research project of Chongqing Medical and Pharmaceutical College (No. ygzrc2024101), 2024 Chongqing Medical and Pharmaceutical College Innovation Research Group Project (No. ygz2024401), Science and Health Joint Medical Research Project of Shapingba District, Chongqing (No. 2024SQKWLHMS051), 2025 Scientific research project of Chongqing Medical and Pharmaceutical College (No. YGZZK2025116), respectively.

Disclosure

The authors declare that they have no competing interests in this work.

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