International Journal of General Medicine

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

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

Lei Huang[1,*], Xinghua Deng[2,*], Zhenjun Xi[3], Xiaofang Huan[2], Jingxin Mao[3], Xiaobing Li[3]

[1]General Education School, Chongqing Youth Vocational & Technical College, Chongqing, 400712, People's Republic of China; [2]Science and Education Department, People's Hospital of Shizhu Tujia Autonomous County, Chongqing, 409199, People's Republic of China; [3]Science and Technology Industry Development Center, Chongqing Medical and Pharmaceutical College, Chongqing, 401331, People's Republic of China

*These authors have contributed equally to this work

Correspondence: Jingxin Mao; Xiaobing Li, Science and Technology Industry Development Center, Chongqing Medical and Pharmaceutical College, 82 University Town Middle Road, Shapingba, Chongqing, 401331, People's Republic of China, Email 2230040@cqmpc.edu.cn; xiaobing.li@cqmpc.edu.cn

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]

https://doi.org/10.2147/IJGM.S602509
Received: 10 February 2026
Accepted: 1 May 2026
Published: 18 May 2026

(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

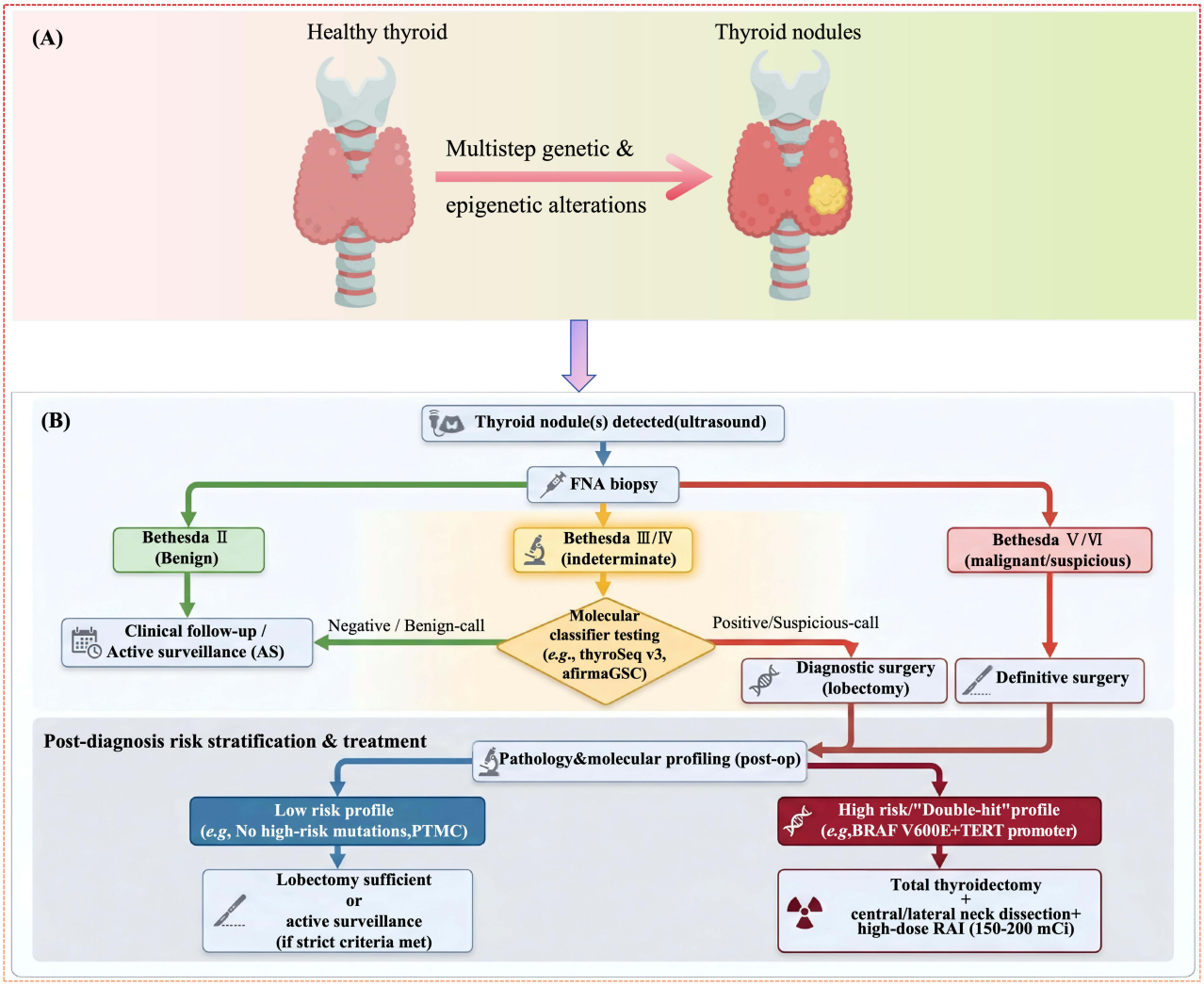

Figure 1 Molecular evolution and precision management framework for thyroid nodules and thyroid cancer. (**A**) Schematic illustration showing the transformation from a healthy thyroid gland to thyroid nodules driven by multistep genetic and epigenetic alterations. (**B**) A precision diagnostic and 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.

https://doi.org/10.2147/IJGM.S602509

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/PPARγ rearrangement, which functions as a dominant-negative inhibitor of wild-type PPARγ.[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	*BRAF* V600E	MAPK	45% (G) vs >80% (A)	Aggressive PTC; loss of NIS expression; RAI refractoriness.
	TERT Promoter	Telomere	15% (PTC), 70% (ATC)	"Genetic Amplifier"; poor OS; synergistic with BRAF.
	RAS (N/H/K)	MAPK/PI3K	40-50% (FTC)	Early oncogenic event; progression to PDTC/ATC.
Gene Fusions	*RET/PTC*	MAPK	10-20% (PTC)	Radiation-related TC; favorable prognosis in adults.
	NTRK1/2/3	TRK	5-13% (PTC)	Pan-cancer actionable target; responsive to Larotrectinib.
	PAX8/PPARγ	Transcriptional	35% (FTC)	Diagnostic for follicular neoplasm; lower recurrence.
Co-mutations	*BRAF + TERT*	Synergistic	~10% (G) vs 18% (A)	Extremely high recurrence risk (HR >5.0); surgical escalation.

https://doi.org/10.2147/IJGM.S602509

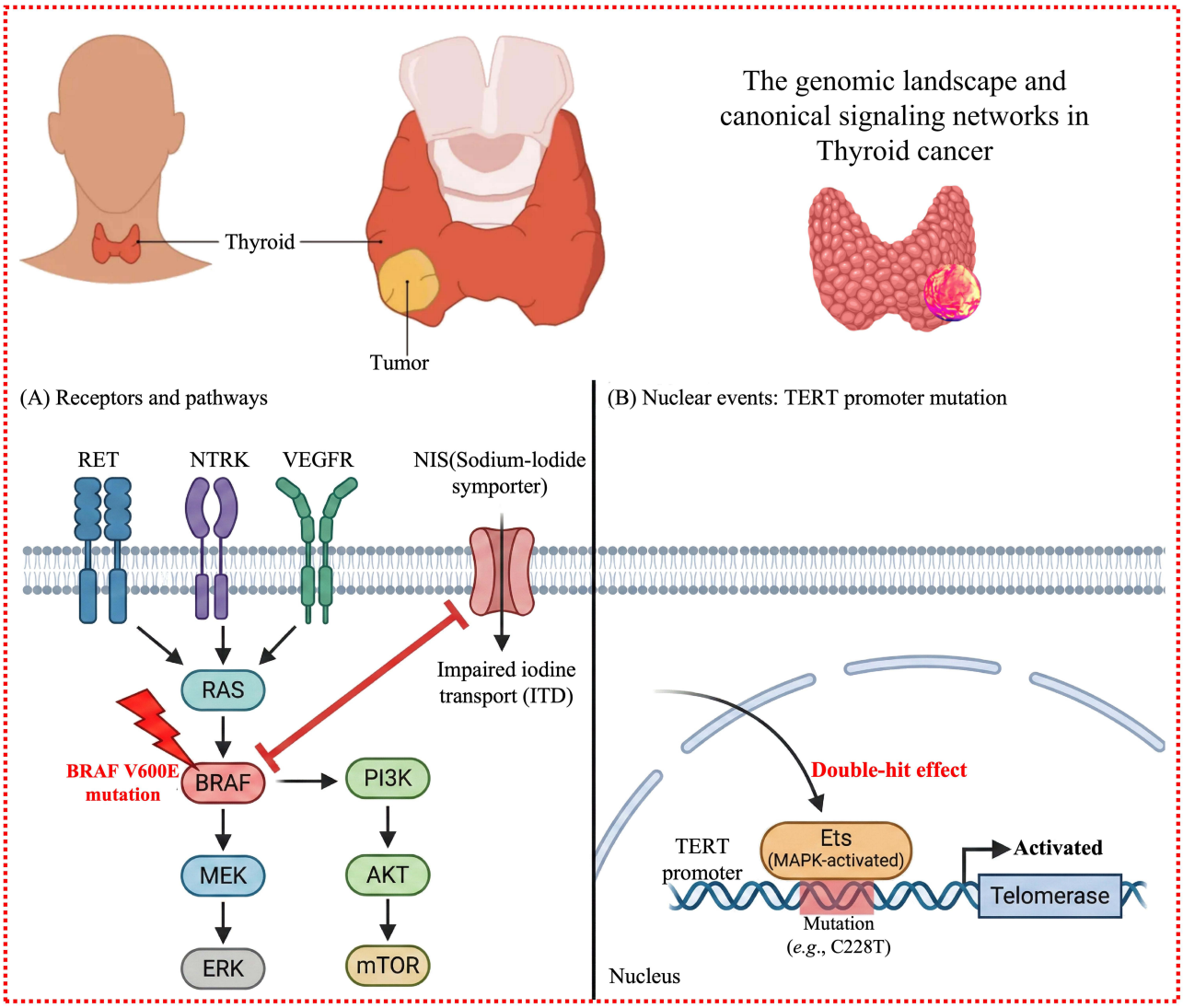

Figure 2 The genomic landscape, signaling networks, and synergistic "Double-Hit" mechanisms in thyroid cancer. (Top Panel) Illustration bridging gross thyroid anatomy with molecular pathogenesis. (**A**) Receptor signaling cascades demonstrating the activation of MAPK (RAS-BRAF-MEK-ERK) and PI3K-AKT-mTOR 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	Single-cell Transcriptome	CD44+ Stem-like subpopulations	Cellular heterogeneity and Clonal fitness	Predicting RAI resistance and relapse.
Spatial Transcriptomics	Spatiotemporal RNA	FIF (Functional Invasive Front)	Niche interaction (Tumor-CAF -TAM)	Mapping metastatic potential in situ.
Radiomics	Voxel-level Imaging	Virtual Biopsy (AI signatures)	Non-invasive phenotype prediction	Reducing FNAB biopsy frequency.
Liquid Biopsy 2.0	ctDNA/Exosomes	MRD (Minimal Residual Disease)	Ultra-sensitive kinetic monitoring	Real-time surveillance of clonal evolution.
Organoids (PDOs)	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-

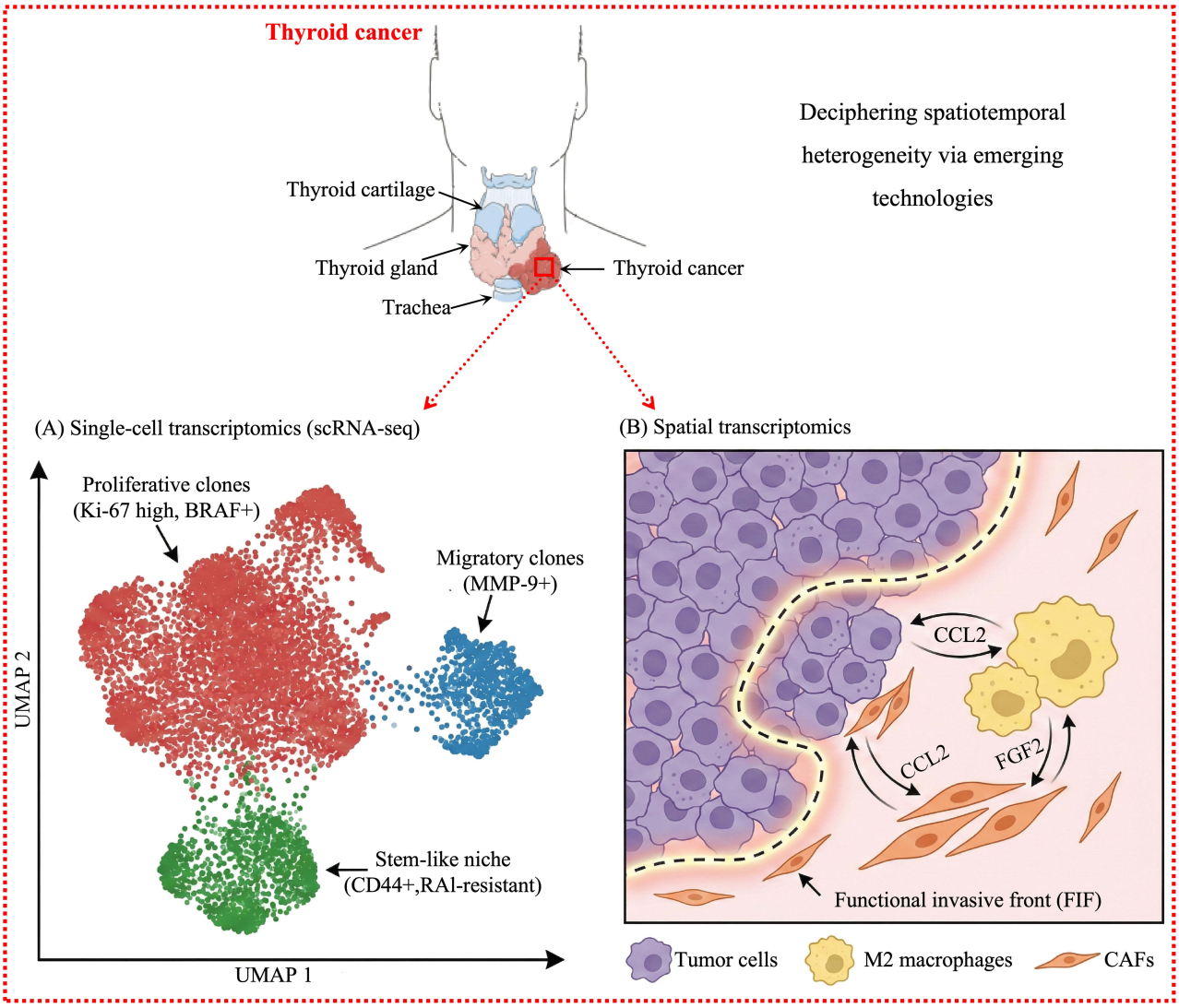

Figure 3 Deciphering intratumoral heterogeneity and the microenvironmental niche via spatiotemporal omics. (Top Panel) Schematic transitioning from gross tumor anatomy to single-cell and spatial resolution. (**A**) Single-cell transcriptomic (scRNA-seq) UMAP projection displaying three distinct tumor 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	*RET* Fusion/ Mutation	LIBRETTO-531	ORR: ~80%; HR: 0.28 vs MKIs	FDA approved; First-line for MTC/PTC.
BRAF V600E	Dabrafenib + Trametinib	*BRAF* V600E	ROAR (ATC)	ORR: 61%; Median OS: 14.5 mo	Standard of care for BRAF+ ATC.
NTRK Fusion	Larotrectinib	*NTRK* 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-1/PD-L1	Pembrolizumab	PD-L1 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]

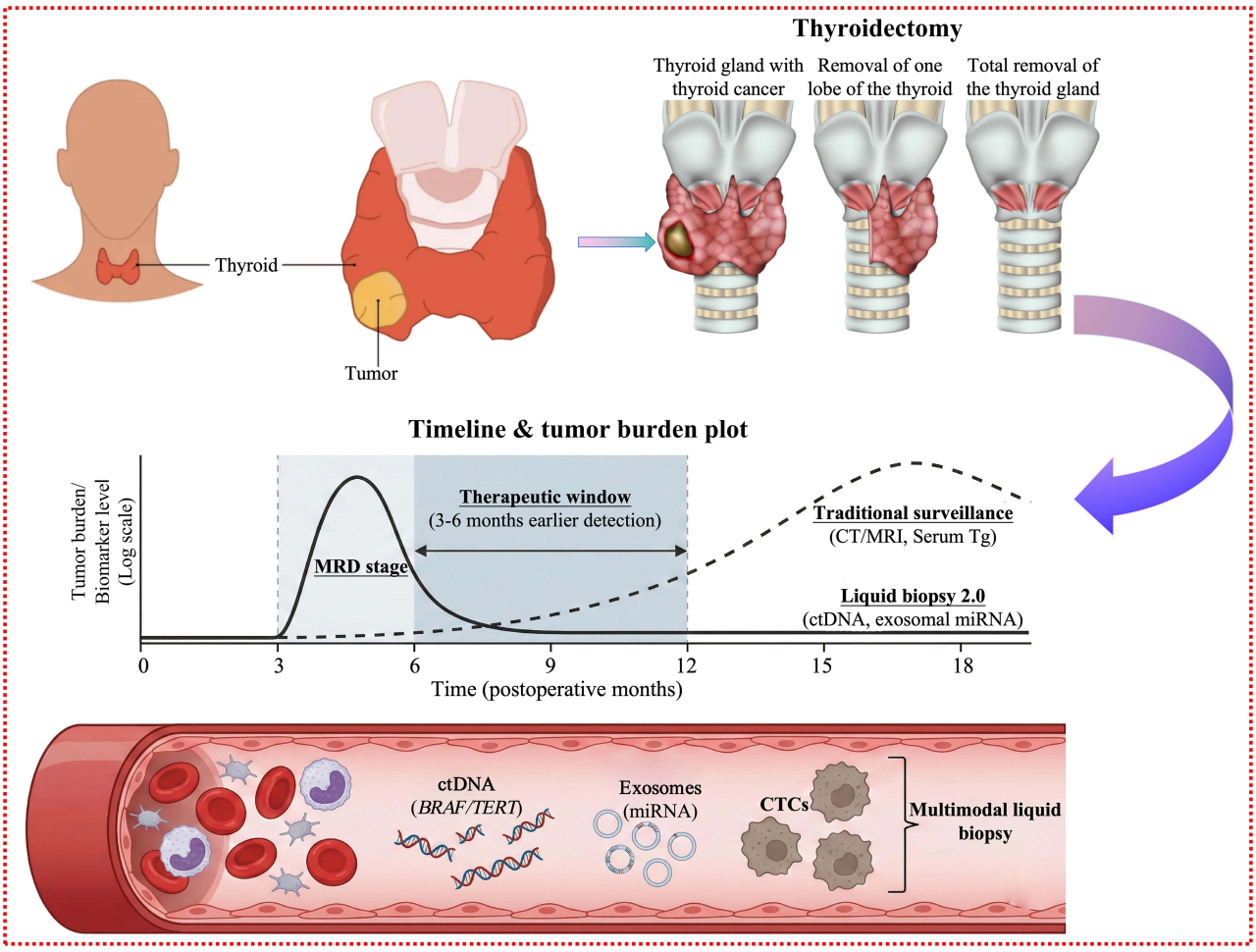

Figure 4 Longitudinal surveillance and the Minimal Residual Disease (MRD) paradigm in thyroid cancer. (Top and Middle Panels) Kinetic trajectory comparing detection thresholds. The dashed line represents traditional surveillance (serum Tg, CT/MRI) detecting macroscopic recurrence. The solid line represents 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"

https://doi.org/10.2147/IJGM.S602509

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

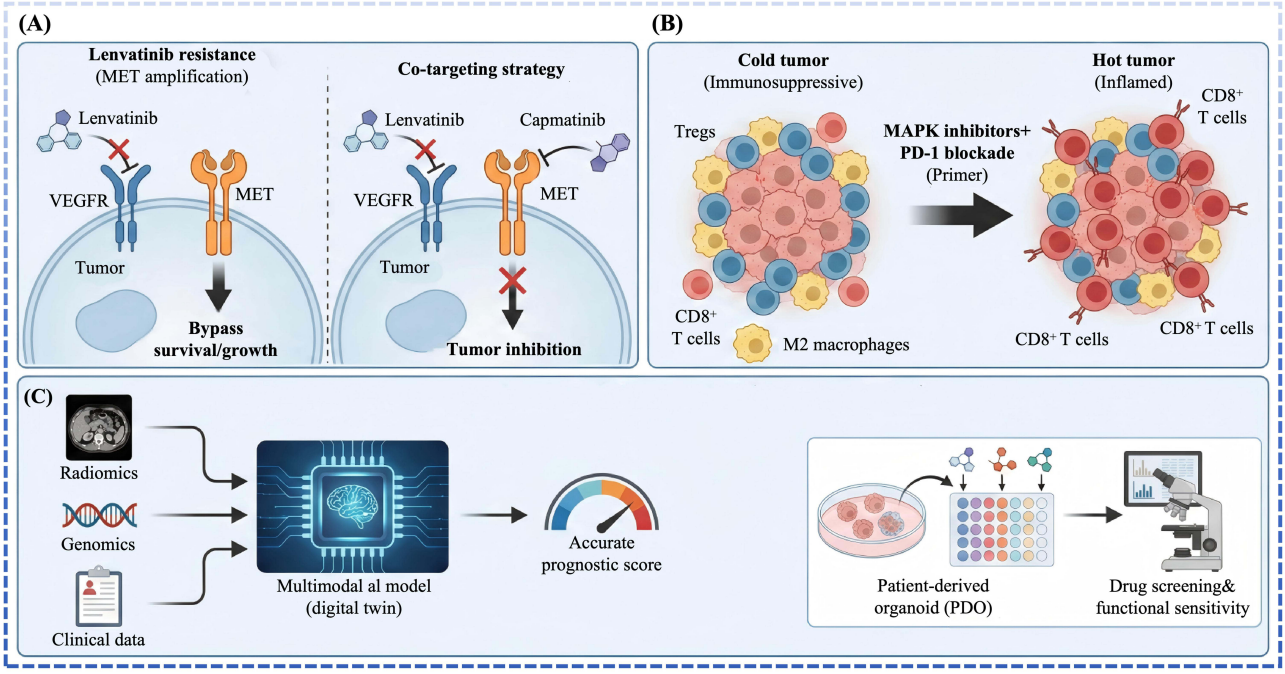

Figure 5 Mechanisms of adaptive resistance and emerging frontiers in precision thyroid oncology. (**A**) Illustration of bypass signaling and co-targeting. The left panel shows Lenvatinib resistance mediated by MET amplification. The right panel demonstrates a co-targeting strategy combining Lenvatinib 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.

References

1. Bae YJ, Schaab M, Kratzsch J. Calcitonin as biomarker for the medullary thyroid carcinoma. *Recent Results Cancer Res*. 2025;223:155–182. doi:10.1007/978-3-031-80396-3_610.1007/978-3-031-80396-3_6
2. Bagheri-Yarmand R, Grubbs EG, Hofmann MC. Thyroid C-cell biology and oncogenic transformation. *Recent Results Cancer Res*. 2025;223:51–91. doi:10.1007/978-3-031-80396-3_310.1007/978-3-031-80396-3_3
3. Bai Z, Li L, Guan T, et al. Clinical prognosis and bioinformatic analysis of primary thyroid lymphoma. *Medicine*. 2021;100(6):e24598. doi:10.1097/md.000000000002459810.1097/md.0000000000024598
4. Baloch Z, Gubbiotti MA, Canberk S, et al. Oncocytic tumors in the thyroid: a tri-focal review - integrated cytopathological, pathological, and molecular perspectives. *Acta Cytol*. 2025;69(5):424–440. doi:10.1159/00054473910.1159/000544739
5. Banerjee S, Nahar U, Dahiya D, et al. Role of cytotoxic T cells and PD-1 immune checkpoint pathway in papillary thyroid carcinoma. *Front Endocrinol*. 2022;13:931647. doi:10.3389/fendo.2022.93164710.3389/fendo.2022.931647
6. Bansal R, Saxena U. Integrative analysis of potential biomarkers involved in the progression of papillary thyroid cancer. *Appl Biochem Biotechnol*. 2023;195(5):2917–2932. doi:10.1007/s12010-022-04244-510.1007/s12010-022-04244-5
7. Baptista PF, Fonseca LCM, Carvalho AFC, et al. Brain metastasis from calcitonin-negative medullary thyroid carcinoma. *Ann Endocrinol*. 2022;83(4):258–260. doi:10.1016/j.ando.2022.04.01510.1016/j.ando.2022.04.015
8. Barwal TS, Sharma U, Rana MK, et al. A diagnostic and prognostic value of blood-based circulating long non-coding RNAs in thyroid, pancreatic and ovarian cancer. *Crit Rev Oncol Hematol*. 2022;171:103598. doi:10.1016/j.critrevonc.2022.10359810.1016/j.critrevonc.2022.103598
9. Bathe OF, Stretch C. Prognostic biomarkers for papillary thyroid cancer: reducing overtreatment, improving clinical efficiency, and enhancing patient experience. *Technol Cancer Res Treat*. 2025;24:15330338251361633. doi:10.1177/15330338251361633 10.1177/15330338251361633
10. Aydoğdu YF, Büyükkasap Ç, Göbüt H, et al. ABO blood group and Rhesus factor as potential markers in papillary thyroid cancer: a retrospective comparative analysis (2015–2023). *Langenbecks Arch Surg*. 2025;411(1):25. doi:10.1007/s00423-025-03920-4
11. Bespalov A, Barchuk A, Auvinen A, et al. Cancer screening simulation models: a state of the art review. *BMC Med Inform Decis Mak*. 2021;21(1):359. doi:10.1186/s12911-021-01713-5
12. Bielak C, Arya A, Savill S. Circulating microRNA as potential diagnostic and prognostic biomarkers of well-differentiated thyroid cancer: a review article. *Cancer Biomark*. 2023;36(3):193–205. doi:10.3233/cbm-21050410.3233/cbm-210504
13. Božović A, Mandušić V, Todorović L, et al. Estrogen receptor beta: the promising biomarker and potential target in metastases. *Int J Mol Sci*. 2021;22(4). doi:10.3390/ijms2204165610.3390/ijms22041656
14. Çağlar Çil Ö, Metin ÖK, Çayır A. Evaluation of mitochondrial copy number in thyroid disorders. *Arch Med Res*. 2022;53(7):711–717. doi:10.1016/j.arcmed.2022.10.00310.1016/j.arcmed.2022.10.003
15. Cameselle-Teijeiro JM, Sobrinho-Simões M. Histopathology of C cells and medullary thyroid carcinoma. *Recent Results Cancer Res*. 2025;223:9–50. doi:10.1007/978-3-031-80396-3_210.1007/978-3-031-80396-3_2
16. Cao J, He X, Li X, et al. The potential association of peripheral inflammatory biomarkers in patients with papillary thyroid cancer before radioiodine therapy to clinical outcomes. *Front Endocrinol*. 2023;14:1253394. doi:10.3389/fendo.2023.125339410.3389/fendo.2023.1253394
17. Cao Z, Zhang Z, Liu R, et al. Serum linkage-specific sialylation changes are potential biomarkers for monitoring and predicting the recurrence of papillary thyroid cancer following thyroidectomy. *Front Endocrinol*. 2022;13:858325. doi:10.3389/fendo.2022.85832510.3389/fendo.2022.858325
18. Capitoli G, Alviano AM, Monza N, et al. Biomarker identification through spatial proteomics for the characterization of indeterminate thyroid nodules. *Endocrine*. 2025;90(2):800–809. doi:10.1007/s12020-025-04383-910.1007/s12020-025-04383-9
19. Carnazza M, Quaranto D, DeSouza N, et al. The current understanding of the molecular pathogenesis of papillary thyroid cancer. *Int J Mol Sci*. 2025;26(10). doi:10.3390/ijms2610464610.3390/ijms26104646
20. Chen L, Li Z, Li X, et al. Evaluating the influence of anti-PD-1 immunotherapy combined with IMRT on thyroid dysfunction in nasopharyngeal carcinoma. *Front Immunol*. 2024;15:1495946. doi:10.3389/fimmu.2024.149594610.3389/fimmu.2024.1495946
21. Abdalla AS, Rahman M, Khan SA. Promising therapeutic targets for recurrent/metastatic anaplastic thyroid cancer. *Curr Treat Options Oncol*. 2024;25(7):869–884. doi:10.1007/s11864-024-01219-y10.1007/s11864-024-01219-y
22. Chen Y, Pan G, Wu F, et al. Ferroptosis in thyroid cancer: potential mechanisms, effective therapeutic targets and predictive biomarker. *Biomed Pharmacother*. 2024;177:116971. doi:10.1016/j.biopha.2024.11697110.1016/j.biopha.2024.116971
23. Chuang YC, Kuo YJ, Hang JF. Intranodal thyroid inclusions revisited: a morphological analysis and application of BRAF VE1 immunohistochemistry. *Histopathology*. 2025;86(6):878–890. doi:10.1111/his.1539410.1111/his.15394
24. Clavel Rolland N, Graslin F, Schorsch F, et al. Investigating the mechanisms of action of thyroid disruptors: a multimodal approach that integrates in vitro and metabolomic analysis. *Toxicol In Vitro*. 2024;100:105911. doi:10.1016/j.tiv.2024.10591110.1016/j.tiv.2024.105911
25. De Leo A, Ruscelli M, Maloberti T, et al. Molecular pathology of endocrine gland tumors: genetic alterations and clinicopathologic relevance. *Virchows Arch*. 2024;484(2):289–319. doi:10.1007/s00428-023-03713-410.1007/s00428-023-03713-4
26. De Lima EU, Dos Santos FF, Da Silva IC, et al. Reduced expression of FOXE1 in differentiated thyroid cancer, the contribution of CPG methylation, and their clinical relevance. *Front Endocrinol*. 2024;15:1454349. doi:10.3389/fendo.2024.145434910.3389/fendo.2024.1454349
27. Delcorte O, Craps J, Mahibullah S, et al. Two miRNAs enriched in plasma extracellular vesicles are potential biomarkers for thyroid cancer. *Endocr Relat Cancer*. 2022;29(7):389–401. doi:10.1530/erc-21-034310.1530/erc-21-0343
28. Dhuli K, Medori MC, Donato K, et al. Omics sciences and precision medicine in thyroid cancer. *Clin Ter*. 2023;174(Suppl 2(6):11–20. doi:10.7417/ct.2023.246710.7417/ct.2023.2467

29. Dos Santos Valsecchi VA, Betoni FR, Ward LS, et al. Clinical and molecular impact of concurrent thyroid autoimmune disease and thyroid cancer: from the bench to bedside. *Rev Endocr Metab Disord*. 2024;25(1):5–17. doi:10.1007/s11154-023-09846-w10.1007/s11154-023-09846-w
30. Du Y, Liu P, Zhang W, et al. Serum thyroglobulin as a biomarker of iodine excess and thyroid disease occurrence in adults. *J Trace Elem Med Biol*. 2023;78:127172. doi:10.1016/j.jtemb.2023.12717210.1016/j.jtemb.2023.127172
31. Eichhorn J, Nelson N, Raichandani S, et al. Prostate-specific membrane antigen PET/CT detection of prostate cancer metastasis to thyroid and cricoid cartilages. *Clin Nucl Med*. 2024;49(5):481–483. doi:10.1097/rlu.0000000000005111 0.1097/rlu.0000000000005111
32. Farooqi SJ, Zhao Z, Öjlert ÅK, et al. Serum cytokines as a biomarker for immune checkpoint inhibitor toxicity in patients with pleural mesothelioma. *Front Immunol*. 2024;15:1480183. doi:10.3389/fimmu.2024.148018310.3389/fimmu.2024.1480183
33. Feng JL, Zheng WJ, Xu L, et al. Identification of potential LncRNAs as papillary thyroid carcinoma biomarkers based on integrated bioinformatics analysis using TCGA and RNA sequencing data. *Sci Rep*. 2023;13(1):4350. doi:10.1038/s41598-023-30086-010.1038/s41598-023-30086-0
34. Ferreira RR, Carvalho RV, Coelho LL, et al. Current understanding of human polymorphism in selenoprotein genes: a review of its significance as a risk biomarker. *Int J Mol Sci*. 2024;25(3). doi:10.3390/ijms2503140210.3390/ijms25031402
35. Frye CC, Tennant L, Yeager A, et al. Overexpression of human DNA polymerase theta is a biomarker of aggressive and DNA repair-deficient papillary thyroid cancers. *Surgery*. 2024;176(5):1380–1387. doi:10.1016/j.surg.2024.05.00610.1016/j.surg.2024.05.006
36. Gambardella C, Mongardini FM, Paolicelli M, et al. Role of inflammatory biomarkers (NLR, LMR, PLR) in the prognostication of malignancy in indeterminate thyroid nodules. *Int J Mol Sci*. 2023;24(7). doi:10.3390/ijms2407646610.3390/ijms24076466
37. Gao X, Zhang R, He Y, et al. EphB3 protein is a potential ancillary diagnostic biomarker for thyroid cancers. *Ann Diagn Pathol*. 2024;69:152262. doi:10.1016/j.anndiagpath.2023.15226210.1016/j.anndiagpath.2023.152262
38. Giovanella L, Ceriani L, Garo ML. Is thyroglobulin a reliable biomarker of differentiated thyroid cancer in patients treated by lobectomy? A systematic review and meta-analysis. *Clin Chem Lab Med*. 2022;60(7):1091–1100. doi:10.1515/cclm-2022-015410.1515/cclm-2022-0154
39. Gong W, Zheng E, Liu M, et al. Risk factors and outcomes of thyroid immune-related adverse events following PD-1/PD-L1 inhibitors treatment in a large tertiary Chinese center. *BMC Endocr Disord*. 2025;25(1):171. doi:10.1186/s12902-025-01986-110.1186/s12902-025-01986-1
40. Grätz C, Changoer P, Chiang DM, et al. Extracellular vesicle-associated transcriptomic and proteomic biomarkers show in vitro potential for vandetanib treatment monitoring in anaplastic thyroid cancer. *Sci Rep*. 2025;15(1):32464. doi:10.1038/s41598-025-18319-w10.1038/s41598-025-18319-w
41. Gulwani D, Upadhyay P, Goel R, et al. Unfolding of imminent bio-signatures in the prognosis of thyroid cancer; the emergence of estrogen related receptor gamma (ERRγ) as a Hurricane. *Asian Pac J Cancer Prev*. 2023;24(2):375–387. doi:10.31557/apjcp.2023.24.2.37510.31557/apjcp.2023.24.2.375
42. Guo K, Qian K, Shi Y, et al. LncRNA-MIAT promotes thyroid cancer progression and function as ceRNA to target EZH2 by sponging miR-150-5p. *Cell Death Dis*. 2021;12(12):1097. doi:10.1038/s41419-021-04386-010.1038/s41419-021-04386-0
43. Guo M, Sun Y, Wei Y, et al. Advances in targeted therapy and biomarker research in thyroid cancer. *Front Endocrinol*. 2024;15:1372553. doi:10.3389/fendo.2024.137255310.3389/fendo.2024.1372553
44. Hamidi S, Dadu R, Iyer PC, et al. Circulating tumor DNA as a biomarker for disease surveillance in anaplastic thyroid cancer. *JCO Precis Oncol*. 2025;9:e2500067. doi:10.1200/po-25-0006710.1200/po-25-00067
45. He Y, Zhao L, Tang X, et al. Prognostic implications of synaptophysin, CD56, thyroid transcription factor-1, and Ki-67 in pulmonary high-grade neuroendocrine carcinomas. *Ann Diagn Pathol*. 2024;68:152239. doi:10.1016/j.anndiagpath.2023.15223910.1016/j.anndiagpath.2023.152239
46. Higgins KE, Sadow PM, Johnson DN, et al. Columnar cell thyroid carcinoma: a heterogeneous entity demonstrating overlap between papillary thyroid carcinoma and follicular neoplasms. *Head Neck Pathol*. 2024;18(1):39. doi:10.1007/s12105-024-01645-210.1007/s12105-024-01645-2
47. Hong K, Cen K, Chen Q, et al. Identification and validation of a novel senescence-related biomarker for thyroid cancer to predict the prognosis and immunotherapy. *Front Immunol*. 2023;14:1128390. doi:10.3389/fimmu.2023.112839010.3389/fimmu.2023.1128390
48. Hong S, Lin B, Xu M, et al. Cell-free DNA methylation biomarker for the diagnosis of papillary thyroid carcinoma. *EBioMedicine*. 2023;90:104497. doi:10.1016/j.ebiom.2023.10449710.1016/j.ebiom.2023.104497
49. Horesh A, Pollack R, Nechushtan H, et al. Tumor PD-L1 expression and molecular profiling are not associated with immune checkpoint inhibitor-induced thyroid dysfunction in advanced NSCLC patients. *Pathol Oncol Res*. 2023;29:1610951. doi:10.3389/pore.2023.161095110.3389/pore.2023.1610951
50. Hu G, Niu W, Ge J, et al. Identification of thyroid cancer biomarkers using WGCNA and machine learning. *Eur J Med Res*. 2025;30(1):244. doi:10.1186/s40001-025-02466-x10.1186/s40001-025-02466-x
51. Huang H, Yin Y, Mao Y, et al. FABP3 methylation as a novel biomarker for the differentiation and classification of benign and malignant thyroid nodules. *Front Endocrinol*. 2025;16:1630001. doi:10.3389/fendo.2025.163000110.3389/fendo.2025.1630001
52. Huang Y, Liu S, Wen Y. Hyalinizing trabecular tumor of the thyroid: a comprehensive review of clinicopathological features, diagnostic dilemmas, and emerging molecular insights. *Ann Diagn Pathol*. 2026;80:152539. doi:10.1016/j.anndiagpath.2025.15253910.1016/j.anndiagpath.2025.152539
53. Huang Y, Xie Z, Li X, et al. Development and validation of a ferroptosis-related prognostic model for the prediction of progression-free survival and immune microenvironment in patients with papillary thyroid carcinoma. *Int Immunopharmacol*. 2021;101(Pt A):108156. doi:10.1016/j.intimp.2021.10815610.1016/j.intimp.2021.108156
54. Iacobas DA, Iacobas S. Papillary thyroid cancer remodels the genetic information processing pathways. *Genes*. 2024;15(5). doi:10.3390/genes1505062110.3390/genes15050621
55. Ibrahim DR, El-Kholany SH, Ghattas MH, et al. Circulating MiRNAs in thyroid cancer: prognostic promise of miR-155 and limitations of miR-429. *Mol Biol Rep*. 2025;53(1):147. doi:10.1007/s11033-025-11249-w10.1007/s11033-025-11249-w
56. Iwama S, Kobayashi T, Arima H. Management, biomarkers and prognosis in people developing endocrinopathies associated with immune checkpoint inhibitors. *Nat Rev Endocrinol*. 2025;21(5):289–300. doi:10.1038/s41574-024-01077-610.1038/s41574-024-01077-6
57. Jiang H, He Y, Lan X, et al. Identification and validation of potential common biomarkers for papillary thyroid carcinoma and Hashimoto's thyroiditis through bioinformatics analysis and machine learning. *Sci Rep*. 2024;14(1):15578. doi:10.1038/s41598-024-66162-210.1038/s41598-024-66162-2

58. Jin M, Kim M, Jeon MJ, et al. Inflammatory biomarkers predict outcomes of patients with radioactive iodine refractory thyroid cancer treated with sorafenib. *Endocrine*. 2023;81(2):298–305. doi:10.1007/s12020-023-03348-010.1007/s12020-023-03348-0
59. Kaur M, Chatterjee D, Aggarwal P, et al. Primary leiomyosarcoma of the thyroid gland. *Indian J Pathol Microbiol*. 2022;65(1):142–144. doi:10.4103/ijpm.Ijpm_1380_2010.4103/ijpm.Ijpm_1380_20
60. Kilicarslan S, Hiz-Cicekliyurt MM. Identification of potential biomarkers of papillary thyroid carcinoma. *Endocrine*. 2025;87(2):758–771. doi:10.1007/s12020-024-04068-910.1007/s12020-024-04068-9
61. Kim CA, Kim M, Jin M, et al. Prognostic roles of inflammatory biomarkers in radioiodine-refractory thyroid cancer treated with lenvatinib. *Endocrinol Metab*. 2024;39(2):334–343. doi:10.3803/EnM.2023.185410.3803/EnM.2023.1854
62. Kim HI, Kim WG, Kim M, et al. Biomarker role of thyroid irAE and PD-L1 positivity in predicting PD-1 blockade efficacy in patients with non-small cell lung cancer. *Cancer Immunol Immunother*. 2024;73(12):260. doi:10.1007/s00262-024-03852-w10.1007/s00262-024-03852-w
63. Kobayashi T, Iwama S, Arima H. Clinical characteristics and potential biomarkers of thyroid and pituitary immune-related adverse events. *Endocr J*. 2024;71(1):23–29. doi:10.1507/endocrj.EJ23-052410.1507/endocrj.EJ23-0524
64. Kori M, Temiz K, Gov E. Network medicine approaches for identification of novel prognostic systems biomarkers and drug candidates for papillary thyroid carcinoma. *J Cell Mol Med*. 2023;27(24):4171–4180. doi:10.1111/jcmm.1800210.1111/jcmm.18002
65. Kotani A, Tatara Y, Sakamoto R, et al. Relationship between amino acid transporter activity and radioactive iodine therapy efficacy in differentiated thyroid cancer. *Oncol Rep*. 2025;54(6). doi:10.3892/or.2025.899310.3892/or.2025.8993
66. Kotwal A, Simpson R, Whiteman N, et al. Relaxin-2 is a novel biomarker for differentiated thyroid carcinoma in humans. *Biochem Pharmacol*. 2024;225:116323. doi:10.1016/j.bcp.2024.11632310.1016/j.bcp.2024.116323
67. Kudelka MR, Lasanajak Y, Smith DF, et al. Serum glycomic profile as a predictive biomarker of recurrence in patients with differentiated thyroid cancer. *Cancer Med*. 2023;12(6):6768–6777. doi:10.1002/cam4.546510.1002/cam4.5465
68. Kurohama H, Matsuda K, Kishino M, et al. Comprehensive analysis for detecting radiation-specific molecules expressed during radiation-induced rat thyroid carcinogenesis. *J Radiat Res*. 2021;62(Supplement_1):i78–i87. doi:10.1093/jrr/rraa13910.1093/jrr/rraa139
69. Larsson M, Rudqvist NP, Spetz J, et al. Age-related long-term response in rat thyroid tissue and plasma after internal low dose exposure to (131) I. *Sci Rep*. 2022;12(1):2107. doi:10.1038/s41598-022-06071-410.1038/s41598-022-06071-4
70. Lazure P, Sireci A, Subbiah V, et al. Challenges in diagnosis and biomarker testing for RET-altered lung and thyroid cancer care: an international mixed-method study. *BMC Med Educ*. 2023;23(1):410. doi:10.1186/s12909-023-04396-w10.1186/s12909-023-04396-w
71. Lei Q, Wang Y, Li J, et al. Increased SEMA6B expression as a potential prognostic and immune cell infiltration biomarker in thyroid cancer patients. *Aging*. 2023;15(9):3572–3585. doi:10.18632/aging.20469110.18632/aging.204691
72. Li B, Cai Z, Zhang Y, et al. Biomarkers associated with papillary thyroid carcinoma and Hashimoto's thyroiditis: bioinformatic analysis and experimental validation. *Int Immunopharmacol*. 2024;143(Pt 3):113532. doi:10.1016/j.intimp.2024.11353210.1016/j.intimp.2024.113532
73. Li C, Dong X, Yuan Q, et al. Identification of novel characteristic biomarkers and immune infiltration profile for the anaplastic thyroid cancer via machine learning algorithms. *J Endocrinol Invest*. 2023;46(8):1633–1650. doi:10.1007/s40618-023-02022-610.1007/s40618-023-02022-6
74. Li G, Wang H, Zhong J, et al. Circulating small extracellular vesicle-based miRNA classifier for follicular thyroid carcinoma: a diagnostic study. *Br J Cancer*. 2024;130(6):925–933. doi:10.1038/s41416-024-02575-010.1038/s41416-024-02575-0
75. Li J, Yin Y, Huang H, et al. RUNX1 methylation as a cancer biomarker in differentiating papillary thyroid cancer from benign thyroid nodules. *Epigenomics*. 2023;15(23):1257–1272. doi:10.2217/epi-2023-033810.2217/epi-2023-0338
76. Abooshahab R, Zarkesh M, Hedayati M. Metabolomics fingerprinting of thyroid malignancies: a GC/MS-based approach for subtype classification and biomarker discovery. *BMC Cancer*. 2025;25(1):1586. doi:10.1186/s12885-025-15073-010.1186/s12885-025-15073-0
77. Li L, Zhang L, Jiang W, et al. Mitochondrial proteome defined molecular pathological characteristics of oncocytic thyroid tumors. *Endocr Pathol*. 2024;35(4):442–452. doi:10.1007/s12022-024-09834-z10.1007/s12022-024-09834-z
78. Li S, Li S, Lin M, et al. Interleukin-17 and vascular endothelial growth factor: new biomarkers for the diagnosis of papillary thyroid carcinoma in patients with Hashimoto's thyroiditis. *J Int Med Res*. 2022;50(1):3000605211067121. doi:10.1177/0300060521106712110.1177/03000605211067121
79. Li Z, Zhao Y, Huang P, et al. Pan-cancer analysis of the immunological and oncogenic roles of ATAD2 with verification in papillary thyroid carcinoma. *Sci Rep*. 2024;14(1):22263. doi:10.1038/s41598-024-73274-210.1038/s41598-024-73274-2
80. Lin Y, Gan F, He X, et al. Identification of ferroptosis-associated long noncoding RNA prognostic model and tumor immune microenvironment in thyroid cancer. *J Immunol Res*. 2022;2022:5893998. doi:10.1155/2022/589399810.1155/2022/5893998
81. Liu C, Pan Y, Li Q, et al. Bioinformatics analysis identified shared differentially expressed genes as potential biomarkers for Hashimoto's thyroiditis-related papillary thyroid cancer. *Int J Med Sci*. 2021;18(15):3478–3487. doi:10.7150/ijms.6340210.7150/ijms.63402
82. Liu J, Chen M, Li S, et al. Biomarkers in the early stage of PD-1 inhibitor treatment have shown superior predictive capabilities for immune-related thyroid dysfunction. *Front Immunol*. 2024;15:1458488. doi:10.3389/fimmu.2024.145848810.3389/fimmu.2024.1458488
83. Liu JF, Zou B, Xiang C, et al. Comprehensive bioinformatics analysis unveils THEMIS2 as a carcinogenic indicator related to immune infiltration and prognosis of thyroid cancer. *Sci Rep*. 2024;14(1):8156. doi:10.1038/s41598-024-58943-610.1038/s41598-024-58943-6
84. Abooshahab R, Zarkesh M, Sameni M, et al. Expression of TSPAN1 and its link to thyroid nodules: one step forward on the path to thyroid tumorigenesis biomarkers. *BMC Cancer*. 2024;24(1):1414. doi:10.1186/s12885-024-13176-810.1186/s12885-024-13176-8
85. Liu Q, Ye J, Liu B, et al. Elevated cancer-associated hyaluronan correlates with diagnosis and lymph node metastasis of papillary thyroid cancer. *Lab Invest*. 2024;104(8):102104. doi:10.1016/j.labinv.2024.10210410.1016/j.labinv.2024.102104
86. Liu R, Lv X, Wang H, et al. Targeting syndecan-2 inhibits papillary thyroid cancer invasiveness and de-differentiation. *BMC Endocr Disord*. 2025;25(1):242. doi:10.1186/s12902-025-02055-310.1186/s12902-025-02055-3
87. Liu T, Zhang D, Ouyang W, et al. Identification and functional characterization of hub genes CLTA, EDIL3, HAPLN1, and HIP1 as diagnostic biomarkers and therapeutic targets in thyroid cancer and Hashimoto's thyroiditis. *Clin Exp Med*. 2025;25(1):162. doi:10.1007/s10238-025-01689-w10.1007/s10238-025-01689-w
88. Liu Y, Wang J, Hu X, et al. Radioiodine therapy in advanced differentiated thyroid cancer: resistance and overcoming strategy. *Drug Resist Updat*. 2023;68:100939. doi:10.1016/j.drup.2023.10093910.1016/j.drup.2023.100939
89. LoCastro E, Paudyal R, Konar AS, et al. A quantitative multiparametric MRI analysis platform for estimation of robust imaging biomarkers in clinical oncology. *Tomography*. 2023;9(6):2052–2066. doi:10.3390/tomography906016110.3390/tomography9060161

90. Loganathan T, Doss CGP. Biomarker identification of medullary thyroid carcinoma from gene expression profiles considering without-treatment and with-treatment studies-A bioinformatics approach. *Adv Protein Chem Struct Biol*. 2024;142:367–396. doi:10.1016/bs.apcsb.2023.12.01110.1016/bs.apcsb.2023.12.011
91. Long X, Zhang Z, Li Y, et al. ScRNA-seq reveals novel immune-suppressive T cells and investigates CMV-TCR-T cells cytotoxicity against GBM. *J Immunother Cancer*. 2024;12(4). doi:10.1136/jitc-2024-00896710.1136/jitc-2024-008967
92. Lopes NMD, Lens HHM, da Silva Brito WA, et al. Role of papillary thyroid carcinoma patients with Hashimoto thyroiditis: evaluation of oxidative stress and inflammatory markers. *Clin Transl Oncol*. 2022;24(12):2366–2378. doi:10.1007/s12094-022-02891-y10.1007/s12094-022-02891-y
93. Lu DN, Zhang WC, Lin YZ, et al. Single-cell and bulk RNA sequencing reveal heterogeneity and diagnostic markers in papillary thyroid carcinoma lymph-node metastasis. *J Endocrinol Invest*. 2024;47(6):1513–1530. doi:10.1007/s40618-023-02262-610.1007/s40618-023-02262-6
94. Luo JH, Zhang XX, Sun WH. F12 as a reliable diagnostic and prognostic biomarker associated with immune infiltration in papillary thyroid cancer. *Aging*. 2022;14(8):3687–3704. doi:10.18632/aging.20403710.18632/aging.204037
95. Ma Z, Song P, Ji D, et al. Thyroid hormones as biomarkers of lung cancer: a retrospective study. *Ann Med*. 2023;55(1):2196088. doi:10.1080/07853890.2023.219608810.1080/07853890.2023.2196088
96. MacDonald WW, Wakely PE, Argyris PP. On vascular lesions of the thyroid gland with emphasis on intrathyroidal hemangioma: clinico-pathologic characterization of two cases and review of the literature. *Head Neck Pathol*. 2024;18(1):108. doi:10.1007/s12105-024-01722-610.1007/s12105-024-01722-6
97. Machens A, Dralle H. Multiple endocrine neoplasia type 2: towards a risk-based approach integrating molecular and biomarker results. *Curr Opin Oncol*. 2024;36(1):1–12. doi:10.1097/cco.000000000000100910.1097/cco.0000000000001009
98. Macvanin MT, Gluvic ZM, Zaric BL, et al. New biomarkers: prospect for diagnosis and monitoring of thyroid disease. *Front Endocrinol*. 2023;14:1218320. doi:10.3389/fendo.2023.121832010.3389/fendo.2023.1218320
99. Maloberti T, Repaci A, Poppi L, et al. Exploring the role of TERT in thyroid Cancer: a systematic review. *Crit Rev Oncol Hematol*. 2025;213:104792. doi:10.1016/j.critrevonc.2025.10479210.1016/j.critrevonc.2025.104792
100. Marzocchi C, Capezzone M, Sagnella A, et al. Pregnancy-associated plasma protein A mRNA expression as a marker for differentiated thyroid cancer: results from a "surgical" and a "cytological" series. *J Endocrinol Invest*. 2022;45(2):369–378. doi:10.1007/s40618-021-01655-9
101. Alkaya M, Bayram A, Yaşar M, et al. Lipocalin-2 expression in papillary thyroid carcinoma and its association with clinicopathological characteristics. *Eur Arch Otorhinolaryngol*. 2025;282(1):451–456. doi:10.1007/s00405-024-08954-w
102. Aneed IK, Luaibi NM, Abdulqader SN. Investigating the clinical significance of immune and thyroid biomarkers in women with breast cancer and Hashimoto's thyroiditis. *Reprod Biol*. 2025;25(2):101011. doi:10.1016/j.repbio.2025.101011
103. Matei M, Matei S-C, Dumitru CS, et al. Preoperative expression profiles of miR-146a and miR-221 as potential biomarkers for differentiating benign from malignant thyroid nodules. *Int J Mol Sci*. 2025;26(15):7564. doi:10.3390/ijms26157564
104. Mathur P, Rana C, Agarwal S, et al. Thyroid gland metastasis: a diagnostically challenging entity. *J Cancer Res Ther*. 2025;21(7):1318–1326. doi:10.4103/jcrt.jcrt_291_24
105. Meirovitz A, Nisman B, Allweis TM, et al. Thyroid hormones and morphological features of primary breast cancer. *Anticancer Res*. 2022;42(1):253–261. doi:10.21873/anticanres.15480
106. Yu S-I, Chang Y-K, Sheu M-L, et al. Thyroiditis and thyroid cancer: bioinformatics analysis of gene expression data. *In Vivo*. 2024;38(5):2205–2213. doi:10.21873/invivo.13684
107. Yuan M, Zheng X, Zheng S, et al. Exosomal PKM2: a noninvasive diagnostic marker linking macrophage metabolic reprogramming to gastric cancer pathogenesis. *Cancer Sci*. 2025;116(6):1537–1549. doi:10.1111/cas.70056
108. Zhang L, Yu S, Hong S, et al. Comprehensive analysis of BTNL9 as a prognostic biomarker correlated with immune infiltrations in thyroid cancer. *BMC Med Genomics*. 2023;16(1):234. doi:10.1186/s12920-023-01676-8
109. Zhang M, Zhao J, Dong H, et al. DNA methylation-specific analysis of G protein-coupled receptor-related genes in pan-cancer. *Genes*. 2022;13(7). doi:10.3390/genes1307121310.3390/genes13071213
110. Zhang Q, Cao Z, Wang Y, et al. Proteomic analysis of tissue proteins related to lateral lymph node metastasis in papillary thyroid microcarcinoma. *J Proteome Res*. 2025;24(1):256–267. doi:10.1021/acs.jproteome.4c00737
111. Xu K, Wu X. Recent development on nanomaterial-based biosensors for identifying thyroid tumor biomarkers. *Biotechnol Appl Biochem*. 2024;71(6):1329–1338. doi:10.1002/bab.2632
112. Xu M, Cheng A, Yu L, et al. AHNAK2 is a biomarker and a potential therapeutic target of adenocarcinomas. *Acta Biochim Biophys Sin*. 2022;54(11):1708–1719. doi:10.3724/abbs.2022112
113. Xu X, Sun T, Jing J. TMPRSS4 is a novel biomarker and correlated with immune infiltration in thyroid carcinoma. *BMC Endocr Disord*. 2022;22(1):280. doi:10.1186/s12902-022-01203-310.1186/s12902-022-01203-3
114. Yaeger R, McKean MA, Haq R, et al. A next-generation BRAF inhibitor overcomes resistance to BRAF inhibition in patients with BRAF-mutant cancers using pharmacokinetics-informed dose escalation. *Cancer Discov*. 2024;14(9):1599–1611. doi:10.1158/2159-8290.Cd-24-002410.1158/2159-8290.Cd-24-0024
115. Yang R, Yang N, Yin P, et al. PCDH8 is a novel prognostic biomarker in thyroid cancer and promotes cell proliferation and viability. *Funct Integr Genomics*. 2024;24(2):35. doi:10.1007/s10142-024-01312-310.1007/s10142-024-01312-3
116. Zhang QY, Wang Y, Zhang Q, et al. Construction of thyroid cancer classification and iodine metabolism related diagnostic model using thyroid differentiation score and bioinformation. *Medicine*. 2024;103(36):e39464. doi:10.1097/md.000000000003946410.1097/md.0000000000039464
117. Zhang R, Wang Z, Wang H, et al. CTHRC1 is associated with BRAF(V600E) mutation and correlates with prognosis, immune cell infiltration, and drug resistance in colon cancer, thyroid cancer, and melanoma. *Biomol Biomed*. 2024;25(1):42–61. doi:10.17305/bb.2024.1039710.17305/bb.2024.10397
118. Zhang S, Ma M, Li J, et al. A pyroglutamate aminopeptidase 1 responsive fluorescence imaging probe for real-time rapid differentiation between thyroiditis and thyroid cancer. *Anal Chem*. 2024;96(15):5897–5905. doi:10.1021/acs.analchem.3c0587210.1021/acs.analchem.3c05872
119. Yao Y, Xu P, Ying T, et al. Integrative analysis of DNA methylation and gene expression identified follicular thyroid cancer-specific diagnostic biomarkers. *Front Endocrinol*. 2021;12:736068. doi:10.3389/fendo.2021.73606810.3389/fendo.2021.736068

120. Ye G, Zhang X, Li M, et al. Integrated analysis of circulating and tissue proteomes reveals that fibronectin 1 is a potential biomarker in papillary thyroid cancer. *BMC Cancer*. 2023;23(1):412. doi:10.1186/s12885-023-10839-w10.1186/s12885-023-10839-w
121. Ye H, Sun X, Ding Q, et al. The emerging roles of circRNAs in papillary thyroid carcinoma: molecular mechanisms and biomarker potential. *Protein Pept Lett*. 2023;30(9):709–718. doi:10.2174/0929866530666230804104057
122. Zhang X, Luo B, Sun M, et al. Research progress of DNA methylation in the diagnosis and treatment of thyroid carcinoma. *Int Immunopharmacol*. 2025;152:114426. doi:10.1016/j.intimp.2025.11442610.1016/j.intimp.2025.114426
123. Zhang X, Meng X, Wang P, et al. Bioinformatics analysis for the identification of Sprouty-related EVH1 domain-containing protein 3 expression and its clinical significance in thyroid carcinoma. *Sci Rep*. 2024;14(1):4549. doi:10.1038/s41598-024-55187-210.1038/s41598-024-55187-2
124. Zhang Y, Li X, Wang J, et al. Exploring salivary iodine concentration as a biomarker for iodine status and thyroid nodules in females from different water iodine areas: a cross-sectional study. *Am J Clin Nutr*. 2024;120(1):162–169. doi:10.1016/j.ajcnut.2024.04.02310.1016/j.ajcnut.2024.04.023
125. Zhang Y, Zhang Q, Zheng Y, et al. Soluble DPP4 can act as a diagnostic biomarker in Hashimoto's thyroiditis with thyroid papillary carcinoma. *J Cancer Res Ther*. 2023;19(4):1048–1054. doi:10.4103/jcrt.jcrt_919_2310.4103/jcrt.jcrt_919_23
126. Zhao S, Zhang P, Niu S, et al. Targeting nucleotide metabolic pathways in colorectal cancer by integrating scRNA-seq, spatial transcriptome, and bulk RNA-seq data. *Funct Integr Genomics*. 2024;24(2):72. doi:10.1007/s10142-024-01356-510.1007/s10142-024-01356-5
127. Wenter V, Albert NL, Ahmaddy F, et al. The diagnostic challenge of coexistent sarcoidosis and thyroid cancer - a retrospective study. *BMC Cancer*. 2021;21(1):139. doi:10.1186/s12885-020-07745-w10.1186/s12885-020-07745-w
128. Wesselingh R, Broadley J, Buzzard K, et al. Electroclinical biomarkers of autoimmune encephalitis. *Epilepsy Behav*. 2022;128:108571. doi:10.1016/j.yebeh.2022.10857110.1016/j.yebeh.2022.108571
129. Wijewardene A, Clifton-Bligh RJ, Wang B, et al. Evaluating the prognostic potential of circulating cell-free DNA in advanced thyroid cancer. *Endocr Relat Cancer*. 2025;32(2). doi:10.1530/erc-24-022710.1530/erc-24-0227
130. Wu SC, Chi SY, Rau CS, et al. Identification of circulating biomarkers for differentiating patients with papillary thyroid cancers from benign thyroid tumors. *J Endocrinol Invest*. 2021;44(11):2375–2386. doi:10.1007/s40618-021-01543-210.1007/s40618-021-01543-2
131. Wu X, Wang S, Wang C, et al. Bioinformatics analysis identifies coagulation factor II receptor as a potential biomarker in stomach adenocarcinoma. *Sci Rep*. 2024;14(1):2468. doi:10.1038/s41598-024-52397-610.1038/s41598-024-52397-6
132. Xiao H, Liang J, Liu S, et al. Proteomics and organoid culture reveal the underlying pathogenesis of Hashimoto's thyroiditis. *Front Immunol*. 2021;12:784975. doi:10.3389/fimmu.2021.78497510.3389/fimmu.2021.784975
133. Xie Z, Li X, He Y, et al. Analysis of the prognostic value and potential molecular mechanisms of TREM-1 overexpression in papillary thyroid cancer via bioinformatics methods. *Front Endocrinol*. 2021;12:646793. doi:10.3389/fendo.2021.64679310.3389/fendo.2021.646793
134. Zhao YX, Ma LB, Yang Z, et al. TET1 is a diagnostic and prognostic biomarker associated with immune infiltration in papillary thyroid cancer. *Biochem Genet*. 2024;62(2):718–740. doi:10.1007/s10528-023-10442-510.1007/s10528-023-10442-5
135. Zhou F, He Z, Lu Z, et al. Solitary fibrous tumor of the thyroid: a case report and literature review. *Asian J Surg*. 2024;47(1):689–690. doi:10.1016/j.asjsur.2023.09.15910.1016/j.asjsur.2023.09.159
136. Xu B, Baine MK, Jungbluth A, et al. Detection of SEZ6, a therapeutic target, in medullary thyroid carcinoma. *J Clin Endocrinol Metab*. 2025;110(7):2041–2046. doi:10.1210/clinem/dgae67210.1210/clinem/dgae672
137. Xu H, Zhang Y, Wu H, et al. High diagnostic accuracy of epigenetic imprinting biomarkers in thyroid nodules. *J Clin Oncol*. 2023;41(6):1296–1306. doi:10.1200/jco.22.0023210.1200/jco.22.00232
138. Wang J, Ma Y, Lin H, et al. Predictive biomarkers for immune-related adverse events in cancer patients treated with immune-checkpoint inhibitors. *BMC Immunol*. 2024;25(1):8. doi:10.1186/s12865-024-00599-y10.1186/s12865-024-00599-y
139. Wang JR, Zafereo ME, Cabanillas ME, et al. The association between thyroid differentiation score and survival outcomes in papillary thyroid carcinoma. *J Clin Endocrinol Metab*. 2025;110(2):356–363. doi:10.1210/clinem/dgae53210.1210/clinem/dgae532
140. Wang Y, Wang J, Wang C, et al. DIO3OS as a potential biomarker of papillary thyroid cancer. *Pathol Res Pract*. 2022;229:153695. doi:10.1016/j.prp.2021.15369510.1016/j.prp.2021.153695
141. Wang Y, Zhang Y, Li Y, et al. Elevated PDE4C level serves as a candidate diagnostic biomarker and correlates with poor survival in thyroid carcinoma. *Sci Rep*. 2024;14(1):6813. doi:10.1038/s41598-024-57533-w10.1038/s41598-024-57533-w
142. Wang Y, Zhou S, Wang D, et al. Complement C4-A and plasminogen as potential biomarkers for prediction of papillary thyroid carcinoma. *Front Endocrinol*. 2021;12:737638. doi:10.3389/fendo.2021.73763810.3389/fendo.2021.737638
143. Wang Y, Zou J, Li Y, et al. Serological biomarkers predict immune-related adverse events and clinical benefit in patients with advanced gastrointestinal cancers. *Front Immunol*. 2022;13:987568. doi:10.3389/fimmu.2022.98756810.3389/fimmu.2022.987568
144. Wang Z, Li X, Liu S, et al. ITGA10 can be used as a potential diagnostic and prognostic biomarker of thyroid cancer. *Asian J Surg*. 2024;47(6):2958–2960. doi:10.1016/j.asjsur.2024.02.11910.1016/j.asjsur.2024.02.119
145. Zhou J, Song X, Li Y, et al. Dynamic changes of serum miR-105-3p expression and prognostic value evaluation of postoperative thyroid cancer. *Acta Biochim Pol*. 2023;70(4):997–1003. doi:10.18388/abp.2018_639810.18388/abp.2018_6398
146. Zhou J, Song X, Li Y, et al. Dynamic changes of serum miR-105-3p expression and prognostic value evaluation of postoperative thyroid cancer. *Cell Mol Biol*. 2023;69(12):118–123. doi:10.14715/cmb/2023.69.12.1910.14715/cmb/2023.69.12.19
147. Zhou M, Lv W, Han P, et al. Plasma extrachromosomal circular DNA as a potential diagnostic biomarker for nodular thyroid disease. *Clin Transl Med*. 2024;14(6):e1740. doi:10.1002/ctm2.174010.1002/ctm2.1740
148. Wei J, Wang X, Jiao K. Orthodenticle homeobox OTX1 promotes papillary thyroid carcinoma progression and is a potential prognostic biomarker. *Genet Res*. 2023;2023:5513812. doi:10.1155/2023/551381210.1155/2023/5513812
149. Wen Y, Yi X, Shi J, et al. Diagnostic value of thyroid-related serological indicators and pan-immune-inflammation value for differentiated thyroid carcinoma. *Front Immunol*. 2025;16:1662638. doi:10.3389/fimmu.2025.166263810.3389/fimmu.2025.1662638
150. Zhu N, Cai L, Qian L. Upregulation of GZMK, TREM2, and OR4D10 as prognostic biomarkers in thyroid cancer: a pan-cancer and TCGA data analysis. *Int J Mol Sci*. 2025;26(8). doi:10.3390/ijms2608388710.3390/ijms26083887
151. Zhu X, Li X, Cui H, et al. Synaptotagmin-like 5 is a potential biomarker and correlates with immune infiltrates in thyroid carcinoma. *J Mol Histol*. 2025;56(5):300. doi:10.1007/s10735-025-10593-210.1007/s10735-025-10593-2

152. Treviño-Juarez AS, Gonzalez-Gonzalez JG, Rodriguez-Gutierrez R, et al. Integrative bioinformatic analysis identifies differentially expressed gene targets as potential biomarkers for anaplastic thyroid cancer. *J Egypt Natl Canc Inst*. 2025;37(1):16. doi:10.1186/s43046-025-00282-210.1186/s43046-025-00282-2
153. Turk AT. Molecular pathology of thyroid follicular epithelial cell-derived neoplasia: an update. *Arch Pathol Lab Med*. 2025;150(1):50–57. doi:10.5858/arpa.2025-0258-RA10.5858/arpa.2025-0258-RA
154. Tywanek E, Michalak A, Świrska J, et al. Autoimmunity, new potential biomarkers and the thyroid gland-the perspective of Hashimoto's thyroiditis and its treatment. *Int J Mol Sci*. 2024;25(9). doi:10.3390/ijms2509470310.3390/ijms25094703
155. Valderrabano P, Eszlinger M, Stewardson P, et al. Clinical value of molecular markers as diagnostic and prognostic tools to guide treatment of thyroid cancer. *Clin Endocrinol*. 2023;98(6):753–762. doi:10.1111/cen.1488210.1111/cen.14882
156. Vasquez ND, Hompanera TS, Chao-Crecente M. Immunohistochemical study protocol in thyroid pathology. *Methods Mol Biol*. 2025;2876:221–239. doi:10.1007/978-1-0716-4252-8_1510.1007/978-1-0716-4252-8_15
157. Wan B, Deng P, Dai W, et al. Association between programmed cell death ligand 1 expression and thyroid cancer: a meta-analysis. *Medicine*. 2021;100(14):e25315. doi:10.1097/md.00000000000025310.1097/md.0000000000025315
158. Wang C, Gu Y, Men X, et al. TAP test image dynamic tracking study after thyroid cancer surgery and after radiotherapy and chemotherapy. *Comput Math Methods Med*. 2021;2021:8072126. doi:10.1155/2021/807212610.1155/2021/8072126
159. Wang CC, Lu DD, Shen MH, et al. Clinical value of Cyclin D1 and P21 in the differential diagnosis of papillary thyroid carcinoma. *Diagn Pathol*. 2023;18(1):123. doi:10.1186/s13000-023-01410-z10.1186/s13000-023-01410-z
160. Wang J, Li Z. TREM2 is a prognostic biomarker and correlated with an immunosuppressive microenvironment in thyroid cancer. *Dis Markers*. 2022;2022:1807386. doi:10.1155/2022/180738610.1155/2022/1807386
161. Samardzic VS, Macvanin MT, Zafirovic SS, et al. Nitric oxide, thyroglobulin, and calcitonin: unraveling the nature of thyroid nodules. *Front Endocrinol*. 2023;14:1241223. doi:10.3389/fendo.2023.124122310.3389/fendo.2023.1241223
162. Santoro F, Linari A, Maletta F, et al. Solitary fibrous tumor of the thyroid: report of three cases with a focus on cytological features and histological clues for malignancy. *Virchows Arch*. 2023;483(2):245–250. doi:10.1007/s00428-023-03542-510.1007/s00428-023-03542-5
163. Sayar I, Gurbuzel M. Potentially important markers in thyroid neoplasia: claudin-1 and MMP-7. *Niger J Clin Pract*. 2023;26(4):412–416. doi:10.4103/njcp.njcp_440_2210.4103/njcp.njcp_440_22
164. Seipel AH, Mechahougui H, Mach N, et al. Primary extra-osseous Ewing sarcoma of the thyroid: a case report and review of the literature. *Head Neck Pathol*. 2022;16(2):581–586. doi:10.1007/s12105-021-01365-x10.1007/s12105-021-01365-x
165. Shakiba E, Boroomand S, Kia SK, et al. MicroRNAs in thyroid cancer with focus on medullary thyroid carcinoma: potential therapeutic targets and diagnostic/prognostic markers and web based tools. *Oncol Res*. 2024;32(6):1011–1019. doi:10.32604/or.2024.04923510.32604/or.2024.049235
166. Shen B, Zhang Y, Tie Y. Fatty acid metabolism influences the immune microenvironment in papillary thyroid cancer and identifies SCD as a novel biomarker. *Front Endocrinol*. 2025;16:1534393. doi:10.3389/fendo.2025.153439310.3389/fendo.2025.1534393
167. Singh Ospina N, Brito JP. Novel assessment of epigenetic imprinting biomarkers for the diagnosis of thyroid nodules. *Nat Rev Clin Oncol*. 2023;20(3):139–140. doi:10.1038/s41571-022-00720-310.1038/s41571-022-00720-3
168. Song P, Chen T, Gu P, et al. RXRG as a novel biomarker and its correlation with immune infiltration in thyroid carcinoma. *Vivo*. 2025;39(4):2013–2034. doi:10.21873/invivo.1399810.21873/invivo.13998
169. Sönmez G, Ünlütürk U. A systematic review of emerging RNA markers in thyroid fine needle aspiration cytology samples: advancements and challenges. *Endocrine*. 2025;89(2):365–379. doi:10.1007/s12020-025-04266-z10.1007/s12020-025-04266-z
170. Studeny T, Kratzer W, Schmidberger J, et al. Analysis of vascularization in thyroid gland nodes with superb microvascular imaging (SMI) and CD34 expression histology: a pilot study. *BMC Med Imaging*. 2021;21(1):159. doi:10.1186/s12880-021-00690-510.1186/s12880-021-00690-5
171. Suh YY, Hwang YJ, Bae JM, et al. Thyroid carcinoma with NSD3::NUTM1 fusion and secondary TERT promoter mutation: a case report and literature review. *Int J Surg Pathol*. 2025;33(3):725–730. doi:10.1177/1066896924127196610.1177/10668969241271966
172. Sun Y, Hu W, Huang J, et al. Predictive value of LncRNA LINC01184 in papillary thyroid cancer development and prognosis and its regulatory effect on cellular processes. *Endocr Res*. 2025;50(3):148–156. doi:10.1080/07435800.2025.249527410.1080/07435800.2025.2495274
173. Sun Z, Feng D, Jiang L, et al. Integrated proteomic and metabolomic analysis of plasma reveals regulatory pathways and key elements in thyroid cancer. *Mol Omics*. 2023;19(10):800–809. doi:10.1039/d3mo00142c10.1039/d3mo00142c
174. Surman M, Wilczak M, Jankowska U, et al. Shotgun proteomics of thyroid carcinoma exosomes - Insight into the role of exosomal proteins in carcinogenesis and thyroid homeostasis. *Biochim Biophys Acta Gen Subj*. 2024;1868(9):130672. doi:10.1016/j.bbagen.2024.13067210.1016/j.bbagen.2024.130672
175. Tan HL, Qin ZE, Duan SL, et al. Association of thyroid autoantibodies with aggressive characteristics of papillary thyroid cancer: a case-control study. *World J Surg Oncol*. 2024;22(1):224. doi:10.1186/s12957-024-03501-710.1186/s12957-024-03501-7
176. Tanoglu EG, Kilinc Z, Adiguzel S, et al. The role of exosomal long non-coding RNAs in head, neck and thyroid cancers. *Med Oncol*. 2025;43(2):78. doi:10.1007/s12032-025-03203-410.1007/s12032-025-03203-4
177. Todorović L, Stanojević B. VHL tumor suppressor as a novel potential candidate biomarker in papillary thyroid carcinoma. *Biomol Biomed*. 2023;23(1):26–36. doi:10.17305/bjbms.2022.785010.17305/bjbms.2022.7850
178. Park J, An S, Bae JS, et al. Overweight as a biomarker for concomitant thyroid cancer in patients with Graves' disease. *Front Endocrinol*. 2024;15:1382124. doi:10.3389/fendo.2024.138212410.3389/fendo.2024.1382124
179. Aparnna JN, Ayyanar P, Sable MN, et al. Warthin-like Papillary Thyroid Carcinoma: a Case Report and Review of the Literature. *Int J Surg Pathol*. 2025;33(4):956–963. doi:10.1177/1066896924129189510.1177/10668969241291895
180. Arcovito G, Franchi A. Thyroid angiosarcoma: a comprehensive review. *Semin Diagn Pathol*. 2026;43(1):150979. doi:10.1016/j.semdp.2025.15097910.1016/j.semdp.2025.150979
181. Peng X, Zhao H, Ye L, et al. Biomarker identification and risk prediction model development for differentiated thyroid carcinoma lung metastasis based on primary lesion proteomics. *Clin Cancer Res*. 2024;30(14):3059–3072. doi:10.1158/1078-0432.Ccr-23-380610.1158/1078-0432.Ccr-23-3806
182. Prasad PA, Raju K. Diagnostic utility of CK19 and galectin-3 in differentiating papillary thyroid carcinoma from nonneoplastic lesions of thyroid. *J Cancer Res Ther*. 2022;18(3):644–649. doi:10.4103/jcrt.jcrt_563_2110.4103/jcrt.jcrt_563_21

183. Quan T, Cockburn J, Dhesy-Thind S, et al. The significance of thyroid hormone receptors in breast cancer: a hypothesis-generating narrative review. *Curr Oncol*. 2024;31(5):2364–2375. doi:10.3390/curroncol3105017610.3390/curroncol31050176
184. Razavi SA, Kalari M, Haghzad T, et al. Exploring the potential of myo-inositol in thyroid disease management: focus on thyroid cancer diagnosis and therapy. *Front Endocrinol*. 2024;15:1418956. doi:10.3389/fendo.2024.141895610.3389/fendo.2024.1418956
185. Razavi SA, Khorsand B, Salehipour P, et al. Metabolite signature of human malignant thyroid tissue: a systematic review and meta-analysis. *Cancer Med*. 2024;13(8):e7184. doi:10.1002/cam4.718410.1002/cam4.7184
186. Ren X, Shu J, Wang J, et al. Machine learning reveals salivary glycopatterns as potential biomarkers for the diagnosis and prognosis of papillary thyroid cancer. *Int J Biol Macromol*. 2022;215:280–289. doi:10.1016/j.ijbiomac.2022.05.19410.1016/j.ijbiomac.2022.05.194
187. Rodríguez-Rodero S, Morales-Sánchez P, Tejedor JR, et al. Classification of follicular-patterned thyroid lesions using a minimal set of epigenetic biomarkers. *Eur J Endocrinol*. 2022;187(3):335–347. doi:10.1530/eje-22-001210.1530/eje-22-0012
188. Ruz-Caracuel I, Rosell A, Geryková L, et al. Multi-center assessment of DLL3 expression by immunohistochemistry in medullary thyroid carcinoma. *Endocr Pathol*. 2025;36(1):49. doi:10.1007/s12022-025-09894-910.1007/s12022-025-09894-9
189. Ryška A, Capdevila J, Dettmer MS, et al. Molecular predictive biomarker testing in advanced thyroid cancer - a European consensus. *Eur Thyroid J*. 2025;14(4). doi:10.1530/etj-25-002410.1530/etj-25-0024
190. Sahu A, Shahin M, Jain P, et al. Cribriform morular thyroid carcinoma: a rare case and associated uncommon features. *Int J Surg Pathol*. 2024;32(5):1009–1016. doi:10.1177/1066896923120657210.1177/10668969231206572
191. Mete O, Boucher A, Schrader KA, et al. Consensus statement: recommendations on actionable biomarker testing for thyroid cancer management. *Endocr Pathol*. 2024;35(4):293–308. doi:10.1007/s12022-024-09836-x10.1007/s12022-024-09836-x
192. Mneimneh WS, Asa SL. Divergent lineage markers in anaplastic thyroid carcinoma. *Am J Surg Pathol*. 2024;48(2):230–237. doi:10.1097/pas.0000000000021531 0.1097/pas.0000000000002153
193. Möller K, Gulzar T, Lennartz M, et al. TTF-1 is a highly sensitive but not fully specific marker for pulmonary and thyroidal cancer: a tissue microarray study evaluating more than 17,000 tumors from 152 different tumor entities. *Virchows Arch*. 2024;485(5):815–828. doi:10.1007/s00428-024-03926-110.1007/s00428-024-03926-1
194. Mondin A, Bertazza L, Barollo S, et al. Validation of miRNAs as diagnostic and prognostic biomarkers, and possible therapeutic targets in medullary thyroid cancers. *Front Endocrinol*. 2023;14:1151583. doi:10.3389/fendo.2023.115158310.3389/fendo.2023.1151583
195. Muñoz I, Solórzano M, Fuentes I, et al. Noninvasive follicular thyroid neoplasia with papillary-like nuclear characteristics (NIFTP): Clinico-Pathological Analysis in a Chilean Centre. *Clin Endocrinol*. 2025;103(6):888–894. doi:10.1111/cen.7002610.1111/cen.70026
196. Nappi A, Miro C, Cicatiello AG, et al. The thyroid hormone activating enzyme, DIO2, is a potential pan-cancer biomarker and immunotherapy target. *J Endocrinol Invest*. 2025;48(5):1149–1172. doi:10.1007/s40618-024-02526-910.1007/s40618-024-02526-9
197. Neto LPM, Dos Santos L, Carvalho L, et al. Integrating Raman spectroscopy and RT-qPCR for enhanced diagnosis of thyroid lesions: a comparative study of biochemical and molecular markers. *J Pharm Biomed Anal*. 2025;261:116844. doi:10.1016/j.jpba.2025.11684410.1016/j.jpba.2025.116844
198. Nkosi D, Crowe WE, Altman BJ, et al. SATB2 is an emergent biomarker of anaplastic thyroid carcinoma: a series with comprehensive biomarker and molecular studies. *Endocr Pathol*. 2024;35(4):432–441. doi:10.1007/s12022-024-09833-010.1007/s12022-024-09833-0
199. Ntotsikas K, Lazarioti S, Daraki V, et al. Thyroglobulin as a rapid and cost-effective biomarker for diagnosis of thyroid carcinoma brain metastasis: a case report of a patient with metastatic hurthle cell thyroid carcinoma. *Am J Case Rep*. 2023;24:e939025. doi:10.12659/ajcr.93902510.12659/ajcr.939025
200. Pakkanen E, Kalfert D, Ahtiainen M, et al. PD-L1 and PD-1 expression in thyroid follicular epithelial dysplasia: hashimoto thyroiditis related atypia and potential papillary carcinoma precursor. *Apmis*. 2022;130(5):276–283. doi:10.1111/apm.1321810.1111/apm.13218
201. Pan J, Fu B, Huang S, et al. Downregulated granzyme M expression: implications for the immune system and prognosis of thyroid cancer. *Gene*. 2025;961:149494. doi:10.1016/j.gene.2025.14949410.1016/j.gene.2025.149494