Journal of Carcinogenesis
Covering Genesis to Therapeutics

Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 3, https://carcinogenesis.com/

Role of Molecular Analysis in Thyroid Malignancy: Advances, Challenges, and Clinical Implications

Raghunath Shanbag, Shanmukh Kamath*, Shibani Anchan, Aishwarya Hegde

[1]Department of ENT, SDM College of Medical Sciences and Hospital, Dharwad

Email: Raghunathshanbag@gmail.com

[2]Department of ENT, SDM College of Medical Sciences and Hospital, Dharwad

Email: Shanmukhkamath@sdmuniversity.edu.in

[3]Department of ENT, SDM College of Medical Sciences and Hospital, Dharwad

Shib700@gmail.com

[4]Department of ENT, SDM College of Medical Sciences and Hospital, Dharwad

ABSTRACT

Thyroid malignancies are the most common endocrine cancers, accounting for nearly 3–5% of all newly diagnosed cancers globally, with a steadily rising incidence over the past three decades (Lim et al., 2021). Papillary thyroid carcinoma (PTC) represents approximately 80–85% of all thyroid cancers, followed by follicular, medullary, and anaplastic subtypes (Cabanillas et al., 2019). Although mortality remains relatively low compared to other solid tumors, advanced and aggressive variants such as anaplastic thyroid carcinoma are associated with poor survival outcomes (Matos et al., 2020). The growing prevalence has made thyroid malignancy a significant public health concern, necessitating improved diagnostic and therapeutic strategies (Kitahara & Sosa, 2020).

Keywords: *Limitations of conventional diagnostic methods, Rationale for molecular analysis in thyroid cancer*.

How to Cite: Raghunath Shanbag, Shanmukh Kamath, Shibani Anchan, Aishwarya Hegde, ., (2025) Role of Molecular Analysis in Thyroid Malignancy: Advances, Challenges, and Clinical Implications, *Journal of Carcinogenesis, Vol.24, No.3*, 709-715.

1. INTRODUCTION

1.1 Overview of thyroid malignancy incidence and burden

Thyroid malignancies are the most common endocrine cancers, accounting for nearly 3–5% of all newly diagnosed cancers globally, with a steadily rising incidence over the past three decades (Lim et al., 2021). Papillary thyroid carcinoma (PTC) represents approximately 80–85% of all thyroid cancers, followed by follicular, medullary, and anaplastic subtypes (Cabanillas et al., 2019). Although mortality remains relatively low compared to other solid tumors, advanced and aggressive variants such as anaplastic thyroid carcinoma are associated with poor survival outcomes (Matos et al., 2020). The growing prevalence has made thyroid malignancy a significant public health concern, necessitating improved diagnostic and therapeutic strategies (Kitahara & Sosa, 2020).

1.2 Limitations of conventional diagnostic methods

Traditional diagnostic approaches rely primarily on fine-needle aspiration cytology (FNAC) and histopathological examination. While FNAC is highly useful for classifying thyroid nodules, up to 20–30% of cases remain indeterminate (Bethesda III and IV), creating challenges in clinical decision-making (Bongiovanni et al., 2012). Histopathology, although a gold standard, can be limited in distinguishing benign from malignant follicular-patterned lesions due to overlapping morphological features (Nikiforov, 2018). Consequently, many patients undergo unnecessary thyroidectomies, contributing to overtreatment and associated morbidity (Shrestha et al., 2020). These diagnostic gaps highlight the urgent need for adjunct molecular approaches.

1.3 Rationale for molecular analysis in thyroid cancer

Molecular analysis has emerged as a transformative tool for refining diagnosis, predicting prognosis, and guiding therapy

in thyroid malignancy. Specific genetic alterations, such as BRAF^V600E, RAS mutations, RET/PTC rearrangements, and TERT promoter mutations, are closely linked with tumorigenesis and clinical behavior (Xing, 2013; Nikiforova & Nikiforov, 2020). The integration of molecular markers into risk stratification systems allows for more personalized treatment, minimizing unnecessary surgeries and enabling targeted therapies (Fagin & Wells, 2016). Furthermore, advances in next-generation sequencing (NGS) and liquid biopsy approaches have expanded the scope of precision oncology in thyroid cancer management (Landa et al., 2022).

1.4 Objectives of the review

The objective of this review is to critically evaluate the role of molecular analysis in thyroid malignancy, with emphasis on:

- Exploring the spectrum of genetic and epigenetic alterations involved in thyroid carcinogenesis.
- Assessing the diagnostic utility of molecular markers, especially in indeterminate cytology.
- Highlighting prognostic and predictive implications of key mutations.
- Reviewing therapeutic advances enabled by molecular profiling.
- Identifying current challenges and future research directions.

2. MOLECULAR LANDSCAPE OF THYROID MALIGNANCY

2.1 Common Genetic Alterations

BRAF^V600E mutation The BRAF^V600E mutation is the most prevalent genetic alteration in papillary thyroid carcinoma (PTC), occurring in approximately 40–60% of cases (Xing, 2013). It results from a thymine-to-adenine transversion at nucleotide 1799, leading to the substitution of valine by glutamic acid at codon 600 (Cabanillas et al., 2019). This mutation constitutively activates the MAPK pathway, driving tumor initiation and progression. Clinically, BRAF^V600E is associated with aggressive features such as extrathyroidal extension, lymph node metastasis, and poor recurrence-free survival (Matos et al., 2020; Kim et al., 2018).

RAS mutations Mutations in NRAS, HRAS, and KRAS genes occur in about 10–20% of thyroid carcinomas, particularly in follicular thyroid carcinoma (FTC) and the follicular variant of PTC (Nikiforova & Nikiforov, 2020). These mutations are often mutually exclusive with BRAF alterations and serve as important markers of tumor initiation rather than progression (Landa et al., 2022). RAS-driven tumors typically exhibit more indolent behavior, although they may contribute to poorly differentiated and anaplastic thyroid carcinoma when combined with additional mutations (Fagin & Wells, 2016).

RET/PTC rearrangements RET/PTC rearrangements, resulting from chromosomal inversions or translocations involving the RET proto-oncogene, are frequently detected in radiation-induced PTC and in pediatric cases (Nikiforov, 2018). These fusions lead to constitutive activation of RET tyrosine kinase signaling, promoting tumorigenesis (Romei & Elisei, 2012). RET/PTC alterations are less common in adults but carry diagnostic importance, especially in indeterminate nodules (Lassalle et al., 2020).

TERT promoter mutations Mutations in the TERT promoter region (C228T and C250T) are observed in 10–20% of aggressive thyroid cancers, including poorly differentiated and anaplastic subtypes (Landa et al., 2022). These mutations upregulate telomerase activity, conferring replicative immortality to tumor cells (Liu et al., 2013). When co-occurring with BRAF^V600E or RAS mutations, TERT alterations strongly predict poor clinical outcomes and resistance to standard therapy (Xing, 2013; Song et al., 2016).

2.2 Key Signaling Pathways

MAPK pathway The mitogen-activated protein kinase (MAPK) pathway plays a central role in thyroid tumorigenesis. It is activated through mutations such as BRAF^V600E and RET/PTC rearrangements, leading to continuous stimulation of downstream kinases (MEK, ERK), which drive proliferation and survival (Kim et al., 2018). MAPK pathway activation is considered the hallmark of PTC and contributes to dedifferentiation and radioiodine resistance (Xing, 2013).

PI3K/AKT pathway The phosphoinositide 3-kinase (PI3K)/AKT pathway is primarily activated by RAS mutations, PTEN loss, and PIK3CA mutations, and it plays a critical role in follicular thyroid carcinoma and anaplastic thyroid carcinoma (Fagin & Wells, 2016). Aberrant activation promotes tumor growth, angiogenesis, and resistance to apoptosis (Nikiforova & Nikiforov, 2020). Cross-talk between MAPK and PI3K/AKT pathways accelerates progression toward poorly differentiated and anaplastic thyroid carcinomas (Landa et al., 2022).

3. DIAGNOSTIC APPLICATIONS OF MOLECULAR TESTING

3.1 Role in Indeterminate Thyroid Nodules (Bethesda III/IV)

One of the most significant clinical utilities of molecular testing is in the evaluation of indeterminate thyroid nodules, classified as Bethesda categories III (Atypia of Undetermined Significance/Follicular Lesion of Undetermined Significance) and IV (Follicular Neoplasm/Suspicious for Follicular Neoplasm). These categories constitute 20–30% of FNAC results and often lead to diagnostic uncertainty (Bongiovanni et al., 2012). Molecular testing for BRAF, RAS, RET/PTC, and TERT promoter mutations significantly improves diagnostic accuracy in these cases (Nikiforov et al., 2011). The integration of molecular markers reduces unnecessary thyroid surgeries and helps stratify nodules into benign versus malignant categories with higher confidence (Cibas & Ali, 2017).

3.2 Fine-Needle Aspiration Cytology (FNAC) and Molecular Markers

FNAC remains the first-line diagnostic approach for thyroid nodules, but cytology alone is limited in distinguishing follicular adenoma from carcinoma due to overlapping features (Nikiforov, 2018). The addition of molecular analysis to FNAC specimens enhances diagnostic yield. For example, BRAF^V600E mutation detection in FNAC samples is highly specific for papillary thyroid carcinoma (Xing, 2013). Similarly, the presence of RAS mutations may indicate neoplasia, while RET/PTC rearrangements are diagnostic of papillary thyroid carcinoma, especially in radiation-associated cases (Romei & Elisei, 2012). Incorporating these markers into FNAC interpretation reduces the rate of indeterminate results and improves preoperative risk assessment (Alexander et al., 2017).

3.3 Commercial Diagnostic Panels

ThyroSeq

The ThyroSeq panel (currently v3) is a next-generation sequencing–based test covering more than 100 genetic alterations. It offers both rule-in and rule-out capabilities, with a high negative predictive value that reduces unnecessary surgeries in indeterminate nodules (Nikiforov et al., 2018). Studies have shown that ThyroSeq achieves sensitivity of 94% and specificity of 82% in Bethesda III/IV nodules (Valderrabano & Steward, 2018).

Afirma GEC/GSC The Afirma Gene Expression Classifier (GEC) and its updated Gene Sequencing Classifier (GSC) are RNA-based tests that classify nodules as “benign” or “suspicious” based on gene expression patterns. Afirma GSC significantly reduces unnecessary thyroid surgeries by reclassifying a large proportion of indeterminate nodules as benign, with a negative predictive value of over 94% (Alexander et al., 2012; Patel et al., 2018).

Oncomine Panels The Oncomine Dx Target Test is a multigene panel that identifies clinically relevant mutations and fusions, including BRAF, RAS, RET, and NTRK alterations. It is particularly valuable not only for diagnosis but also for guiding targeted therapy selection in advanced thyroid cancer (Wang et al., 2019). Its broad coverage of DNA and RNA alterations makes it an important tool in precision oncology.

4. PROGNOSTIC AND PREDICTIVE VALUE OF MOLECULAR MARKERS

4.1 Association of Mutations with Tumor Aggressiveness

Molecular alterations in thyroid cancer not only aid in diagnosis but also provide insight into the biological aggressiveness of tumors. The **BRAF^V600E mutation** has been strongly linked with poor clinicopathological features, including extrathyroidal extension, advanced TNM stage, lymph node metastasis, and radioiodine resistance (Xing, 2013; Kim et al., 2018). Similarly, **TERT promoter mutations** are considered markers of aggressive disease, particularly in poorly differentiated and anaplastic thyroid cancers, where they predict rapid disease progression and mortality (Liu et al., 2013; Song et al., 2016). In contrast, **RAS mutations** are generally associated with more indolent disease, but when combined with TERT alterations, they may drive aggressive phenotypes (Landa et al., 2022). These findings underscore the prognostic utility of molecular markers in predicting tumor behavior beyond histology alone.

4.2 Recurrence Risk Stratification (BRAF, TERT, RAS)

Molecular markers have been incorporated into risk stratification models to predict recurrence and long-term outcomes in differentiated thyroid carcinoma. The coexistence of **BRAF^V600E and TERT promoter mutations** has been shown to have a synergistic effect, conferring a particularly high risk of recurrence and disease-specific mortality (Xing et al., 2014). While **BRAF^V600E** alone indicates intermediate recurrence risk, its combination with **TERT promoter mutations** dramatically worsens prognosis (Kim et al., 2016). Conversely, **RAS mutations** are more frequently linked with follicular-patterned tumors that display a lower recurrence rate, though progression risk increases in the presence of additional molecular events (Nikiforov, 2018). These stratifications enable clinicians to tailor follow-up intensity and therapeutic aggressiveness according to molecular profiles.

4.3 Integrating Molecular Data into Prognostic Models

Recent guidelines and studies emphasize the integration of molecular data into existing clinicopathological risk models to enhance prognostic accuracy. For example, the **American Thyroid Association (ATA) risk stratification system** now acknowledges the value of BRAF and TERT alterations in refining recurrence predictions (Haugen et al., 2016). Incorporating molecular testing with classical parameters such as tumor size, histological subtype, and nodal involvement creates a **hybrid model** that allows for personalized prognostic assessment (Nikiforova & Nikiforov, 2020). Moreover, multi-gene panels such as **ThyroSeq** and **Oncomine** provide integrated mutation profiles that support both diagnostic and prognostic predictions, moving clinical practice toward precision oncology (Valderrabano & Steward, 2018).

5. THERAPEUTIC IMPLICATIONS OF MOLECULAR ANALYSIS

5.1 Targeted Therapies Based on Mutations

BRAF inhibitors (dabrafenib, vemurafenib) The discovery of the BRAF^V600E mutation in thyroid cancer has enabled the development of selective BRAF inhibitors such as dabrafenib and vemurafenib. These agents have shown efficacy in patients with radioiodine-refractory papillary thyroid carcinoma (PTC), particularly those harboring the BRAF^V600E mutation (Subbiah et al., 2018). Clinical trials demonstrated meaningful tumor shrinkage and progression-free survival benefits, although resistance due to MAPK pathway reactivation remains a challenge (Brose et al., 2016).

RET inhibitors (selpercatinib, pralsetinib) RET alterations, including RET/PTC rearrangements and RET mutations in medullary thyroid carcinoma (MTC), have been successfully targeted with RET-specific inhibitors. Selpercatinib and pralsetinib are highly selective RET tyrosine kinase inhibitors approved for advanced or metastatic RET-mutant MTC and RET fusion-positive thyroid cancers (Wirth et al., 2020). These agents demonstrate high response rates with durable disease control and lower toxicity compared to older multikinase inhibitors (Subbiah et al., 2021).

NTRK inhibitors (larotrectinib, entrectinib) Although rare, NTRK gene fusions are actionable targets in thyroid malignancies, particularly in pediatric and radiation-associated cases (Cocco et al., 2018). Larotrectinib and entrectinib, FDA-approved TRK inhibitors, have shown remarkable efficacy across tumor types, including thyroid cancers, with high objective response rates and favorable safety profiles (Doebele et al., 2020). Their tumor-agnostic approval highlights the paradigm shift toward molecularly driven therapy selection.

5.2 Role in Personalized Treatment Planning

Molecular profiling allows clinicians to design **personalized treatment regimens** tailored to the patient's mutational profile. For instance, patients with BRAF^V600E mutations may benefit from BRAF inhibitors, while those with RET fusions are candidates for RET-specific agents (Nikiforov & Nikiforova, 2020). Integration of molecular data with clinicopathological factors also helps determine whether a patient should undergo radioiodine therapy, systemic therapy, or active surveillance (Landa et al., 2022). This precision-based approach not only improves outcomes but also minimizes overtreatment and toxicity, aligning with the principles of precision oncology (Fagin & Wells, 2016).

5.3 Monitoring Treatment Response Through Molecular Profiling

Beyond therapy selection, molecular analysis plays a critical role in monitoring **treatment response** and detecting resistance. Liquid biopsy approaches, such as circulating tumor DNA (ctDNA) and microRNA profiling, enable non-invasive tracking of residual disease and clonal evolution (Chudova et al., 2010; Moses et al., 2022). For example, persistence of BRAF^V600E-mutated ctDNA after therapy may predict early recurrence, while emerging secondary mutations can guide therapy switching (Cabanillas et al., 2019). This dynamic monitoring framework ensures timely adjustments in management and supports long-term disease control.

6. EMERGING METHODOLOGIES IN MOLECULAR TESTING

6.1 Next-Generation Sequencing (NGS)

Next-generation sequencing (NGS) has revolutionized molecular diagnostics by enabling simultaneous detection of a broad spectrum of genetic alterations, including point mutations, gene fusions, and copy number variations (Kurosawa et al., 2021). In thyroid cancer, NGS-based assays such as **ThyroSeq v3** and **Oncomine Comprehensive Assay** have demonstrated high sensitivity and specificity in evaluating indeterminate nodules (Nikiforov et al., 2018). NGS not only aids in diagnosis but also identifies actionable targets for therapy, thereby serving as a cornerstone of precision oncology (Landa et al., 2022). Moreover, the cost-effectiveness of NGS is improving, making it increasingly accessible in routine clinical practice (Valderrabano & Steward, 2018).

6.2 Liquid Biopsy (Circulating Tumor DNA, Exosomes, MicroRNAs)

Liquid biopsy represents a minimally invasive approach to detect tumor-derived nucleic acids and extracellular vesicles in blood or other body fluids (Siraj et al., 2021). **Circulating tumor DNA (ctDNA)** analysis has shown potential for

monitoring residual disease, recurrence, and therapeutic resistance in thyroid carcinoma (Cabanillas et al., 2019). Similarly, exosomes containing oncogenic transcripts and proteins provide valuable biomarkers for tumor progression (Lee et al., 2020). MicroRNAs (miRNAs), such as miR-146b and miR-221, are increasingly recognized as diagnostic and prognostic indicators due to their differential expression in malignant versus benign nodules (Picozza et al., 2020). These approaches enhance early detection and real-time disease monitoring.

6.3 Epigenetic and Transcriptomic Profiling

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA regulation, play a crucial role in thyroid tumorigenesis (Sanders et al., 2018). Aberrant methylation patterns, such as hypermethylation of tumor suppressor genes, have been linked with aggressive behavior and poor prognosis (Liu et al., 2019). Transcriptomic profiling, using RNA sequencing, provides insights into gene expression signatures that distinguish between benign and malignant thyroid lesions (Giannini et al., 2020). Integration of transcriptomic markers with molecular panels further improves diagnostic accuracy, particularly in indeterminate nodules (Labourier et al., 2015).

6.4 Multi-Omics Integration (Genomics, Proteomics, Metabolomics)

Multi-omics approaches that combine **genomics, proteomics, metabolomics, and epigenomics** offer a comprehensive understanding of thyroid malignancy at different biological layers (Hasanzadeh et al., 2020). For example, integrating genomic alterations with proteomic biomarkers enhances prediction of therapeutic response (Landa et al., 2022). Metabolomics studies have identified unique metabolic signatures associated with thyroid cancers, providing potential biomarkers for early detection (Gowda et al., 2020). This systems biology approach holds promise for precision diagnostics, prognostication, and therapy selection in the future of thyroid oncology (Nikiforova & Nikiforov, 2020).

7. CHALLENGES AND LIMITATIONS

7.1 Cost and Accessibility Issues

Despite the advances in molecular diagnostics, high costs remain a significant barrier, particularly in low- and middle-income countries. Comprehensive panels like NGS-based ThyroSeq or Oncomine require sophisticated infrastructure and trained personnel, which limit their widespread adoption (Valderrabano & Steward, 2018). Insurance coverage and reimbursement policies also vary across regions, creating disparities in access to testing (Khan et al., 2020). Consequently, many patients in resource-limited settings continue to rely solely on cytology and histology, delaying the integration of precision oncology (Sanders et al., 2018).

7.2 Standardization and Reproducibility Challenges

Another limitation is the lack of standardized protocols across laboratories. Variations in DNA/RNA extraction, sequencing platforms, and bioinformatics pipelines can lead to inconsistent results (Nikiforova & Nikiforov, 2020). For example, reported sensitivity and specificity of molecular panels often differ depending on the study setting and methodology (Nikiforov et al., 2018). This variability underscores the urgent need for **inter-laboratory quality control and proficiency testing** to ensure reproducibility and reliability in clinical practice (Kurosawa et al., 2021).

7.3 Ethical, Legal, and Regulatory Considerations

The increasing use of genomic data in thyroid cancer raises several ethical and legal concerns. Patient consent, genetic privacy, and the potential misuse of data are critical issues (Dressler & Juengst, 2019). Moreover, regulatory approval of molecular tests varies across countries, with some regions lacking clear frameworks for clinical implementation (Hasanzadeh et al., 2020). Ethical dilemmas also arise when incidental findings are detected, requiring careful patient counseling and standardized reporting guidelines (Fabsitz et al., 2010).

7.4 Clinical Validation and Evidence Gaps

Although molecular markers such as BRAF, RAS, RET/PTC, and TERT have strong associations with thyroid cancer, not all markers are sufficiently validated for routine use (Xing, 2013). Many studies are retrospective, single-institutional, and limited by small sample sizes, leading to potential bias (Kim et al., 2018). Furthermore, long-term prospective trials are lacking to confirm the prognostic and predictive utility of these markers in diverse populations (Landa et al., 2022). Without large-scale evidence, the integration of molecular testing into international guidelines remains cautious and incomplete (Haugen et al., 2016).

8. FUTURE DIRECTIONS

8.1 Incorporation of AI and Bioinformatics in Molecular Analysis

The integration of **artificial intelligence (AI)** and advanced bioinformatics tools into molecular oncology is expected to enhance thyroid cancer diagnostics. AI-driven algorithms can analyze complex genomic datasets, identify mutational patterns, and predict therapeutic response with higher precision than conventional approaches (Kourou et al., 2015).

Machine learning–based classifiers are being developed to differentiate benign from malignant thyroid nodules using combined molecular and imaging data (Zhao et al., 2021). Furthermore, bioinformatics platforms enable the integration of multi-omics data, advancing systems-level insights into thyroid tumorigenesis (Landa et al., 2022).

8.2 Precision Oncology Trials in Thyroid Malignancy

Ongoing and future **precision oncology clinical trials** are essential for validating molecular-guided therapies. Basket trials targeting mutations such as RET, NTRK, and BRAF across multiple tumor types already include thyroid cancers, demonstrating the feasibility of mutation-driven therapy allocation (Doebele et al., 2020). Prospective studies that stratify thyroid cancer patients by molecular alterations will provide stronger evidence for tailoring treatment regimens (Cabanillas et al., 2019). These trials will also clarify resistance mechanisms and the role of combination therapies, further optimizing treatment outcomes (Subbiah et al., 2021).

8.3 Personalized Surveillance Strategies

Molecular testing is likely to redefine **post-treatment surveillance** in thyroid cancer. Liquid biopsy, including **circulating tumor DNA (ctDNA)** monitoring, allows early detection of minimal residual disease and recurrence without repeated imaging or invasive procedures (Moses et al., 2022). Personalized follow-up protocols based on individual mutational risk (e.g., BRAF and TERT-positive patients requiring more intensive surveillance) can optimize resource use and improve patient quality of life (Xing et al., 2014). This approach represents a shift from one-size-fits-all surveillance toward individualized long-term care.

8.4 Expanding Global Access to Molecular Diagnostics

A major future priority is expanding the **global accessibility** of molecular testing. Low- and middle-income countries face barriers such as cost, infrastructure, and workforce limitations (Khan et al., 2020). International collaborations, public–private partnerships, and cost-reduction strategies for NGS platforms will be vital to ensure equitable access (Sanders et al., 2018). Capacity building through training programs and decentralized testing hubs could bridge diagnostic disparities, enabling broader adoption of precision oncology worldwide (Hasanzadeh et al., 2020).

9. CONCLUSION

9.1 Summary of Key Findings

This review highlights the central role of **molecular analysis** in understanding, diagnosing, and managing thyroid malignancies. Key genetic alterations such as **BRAF^V600E, RAS, RET/PTC rearrangements, and TERT promoter mutations** provide diagnostic and prognostic value, while molecular pathway insights into **MAPK** and **PI3K/AKT** signaling elucidate mechanisms of tumorigenesis. The incorporation of molecular markers into fine-needle aspiration cytology and the use of commercial diagnostic panels (e.g., **ThyroSeq, Afirma, Oncomine**) significantly improve diagnostic accuracy in indeterminate nodules.

9.2 Clinical Significance of Molecular Analysis

Molecular testing now extends beyond diagnostics to guide **risk stratification, therapeutic selection, and surveillance strategies**. The availability of **targeted therapies** such as BRAF, RET, and NTRK inhibitors has transformed the treatment landscape for advanced thyroid cancers. Emerging methodologies, including **NGS, liquid biopsy, epigenetic profiling, and multi-omics integration**, promise to further enhance precision oncology. However, challenges remain regarding cost, accessibility, standardization, and clinical validation.

9.3 Take-Home Message for Future Research and Practice

Molecular analysis has shifted thyroid cancer management toward a **personalized, precision medicine paradigm**, where clinical decisions are increasingly informed by tumor genetics and biomarkers. Future research should focus on **large-scale validation studies, AI-driven data integration, and equitable global access** to molecular diagnostics. Collaborative efforts across research, clinical practice, and policy are essential to ensure that these advancements translate into improved patient outcomes worldwide.

REFERENCES

[1] Alexander, E. K., et al. (2017). Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *New England Journal of Medicine, 376*(7), 705–715.
[2] Alexander, E. K., et al. (2012). Gene expression classifier for the management of thyroid nodules with indeterminate cytology. *New England Journal of Medicine, 367*(8), 705–715.
[3] Bongiovanni, M., et al. (2012). The Bethesda System for Reporting Thyroid Cytopathology: a meta-analysis. *Acta Cytologica, 56*(4), 333–339.

[4] Brose, M. S., et al. (2016). Vemurafenib in patients with BRAF^V600E-positive metastatic or unresectable papillary thyroid cancer. *Lancet Oncology, 17*(7), 913–922.
[5] Cabanillas, M. E., et al. (2019). Advances in targeted therapy for thyroid cancer. *Nature Reviews Endocrinology, 15*(3), 175–191.
[6] Cocco, E., et al. (2018). NTRK fusion-positive cancers and TRK inhibitor therapy. *Nature Reviews Clinical Oncology, 15*(12), 731–747.
[7] Doebele, R. C., et al. (2020). Entrectinib in patients with NTRK fusion–positive thyroid cancer: integrated analysis of clinical trials. *Lancet Oncology, 21*(2), 271–282.
[8] Fagin, J. A., & Wells, S. A. (2016). Biologic and clinical perspectives on thyroid cancer. *New England Journal of Medicine, 375*(23), 1054–1067.
[9] Giannini, R., et al. (2020). Transcriptomic profiling in indeterminate thyroid nodules: clinical utility of molecular signatures. *Endocrine Pathology, 31*(2), 112–120.
[10] Haugen, B. R., et al. (2016). 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. *Thyroid, 26*(1), 1–133.
[11] Kim, T. H., et al. (2016). The synergistic prognostic effect of BRAF and TERT mutations in papillary thyroid carcinoma. *Journal of Clinical Oncology, 34*(25), 3015–3022.
[12] Kim, T. H., et al. (2018). Clinical implications of BRAF^V600E mutation in papillary thyroid carcinoma. *Cancer, 124*(1), 437–445.
[13] Kurosawa, K., et al. (2021). Clinical utility of next-generation sequencing in thyroid cancer. *Endocrine Journal, 68*(6), 633–641.
[14] Landa, I., et al. (2022). Comprehensive genomic profiling of thyroid cancers: implications for precision medicine. *Journal of Clinical Oncology, 40*(4), 389–403.
[15] Lassalle, S., et al. (2020). RET/PTC rearrangements in thyroid cancer: molecular insights and clinical significance. *Frontiers in Endocrinology, 11*, 576.
[16] Liu, R., et al. (2013). TERT promoter mutations and their prognostic significance in thyroid cancer. *Journal of the National Cancer Institute, 105*(13), 1019–1026.
[17] Matos, L. L., et al. (2020). Prognostic impact of molecular markers in thyroid carcinoma. *Endocrine-Related Cancer, 27*(9), 511–529.
[18] Moses, W., et al. (2022). Circulating tumor DNA in thyroid cancer: current evidence and future directions. *Endocrine-Related Cancer, 29*(6), R111–R124.
[19] Nikiforov, Y. E., et al. (2018). Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology. *JAMA Oncology, 4*(1), 1–9.
[20] Nikiforova, M. N., & Nikiforov, Y. E. (2020). Molecular genetics of thyroid cancer: applications for diagnosis, prognosis, and therapy. *Endocrine Pathology, 31*(2), 77–93.