

# ONCOLOGY: Molecular Biomarkers of Thyroid Cancer

**Sample Type to Test:** Fine needle aspirates; Cytology smears; formalin fixed paraffin embedded tissue (FFPE); peripheral blood/buccal swabs for germline testing

Biomarker	Specific Alterations/ Alternative terms	Indications	Result Interpretation Significance	Assay Techniques
<b>BRAF</b>	Variants in codons 600, 601	Diagnosis: Screening of indeterminate cytology thyroid nodules  Prognosis  Therapy selection/ response prediction	High specificity for papillary thyroid carcinoma  Higher risk of recurrence in PTC  Consideration of BRAF-targeted therapy in metastatic disease not amenable to RAI therapy	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>HRAS</b>	Variants in codons 61, 12, 13	Diagnosis: Screening of indeterminate cytology thyroid nodules	Frequently seen in follicular adenomas, follicular carcinomas, NIFTP, and invasive follicular variant of PTC	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>NRAS</b>	Variants in codons 61, 12, 13	Diagnosis: Screening of indeterminate cytology thyroid nodules	Frequently seen in follicular adenomas, follicular carcinomas, NIFTP, and invasive follicular variant of PTC	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>KRAS</b>	Variants in codons 61, 12, 13	Diagnosis: Screening of indeterminate cytology thyroid nodules	Frequently seen in follicular adenomas, follicular carcinomas, NIFTP, and invasive follicular variant of PTC	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>RET</b>	M918T; A883F; variants in C634, C609, C611, C618, C620, C630; G533C; D631Y; K666E; E768D; L790F; V804L; V804M; S891A; R912P	Diagnosis  Prognosis  Therapy selection/ response prediction  In germline, risk of hereditary MTC	Medullary thyroid carcinoma  Somatic M918T mutation in sporadic MTC associated with aggressive clinical course and poor prognosis  Consideration of targeted RET inhibitors or multikinase inhibitors in MTC patients with unresectable locally advanced or metastatic disease  In MEN2A, MEN2B or familial MTC syndromes	NGS, pyrosequencing, Sanger sequencing, genotyping, PCR-based assays
<b>RET/PTC1 &amp; RET/PTC3 rearrangements</b>	<i>RET/PTC1</i> = fusion of <i>RET</i> with <i>CCDC6</i> <i>RET/PTC3</i> = fusion of <i>RET</i> with <i>NCOA4</i>	Diagnosis: Screening of indeterminate cytology thyroid nodules  Therapy selection/ response prediction	Highly specific for PTC  Consideration of targeted RET inhibitors or multikinase inhibitors	RT-PCR, NGS including RNA-Seq, AMP
<b>NTRK1, NTRK2, NTRK3 rearrangements</b>		Diagnosis: Screening of indeterminate cytology thyroid nodules  Therapy	Highly specific for PTC  Consideration of targeted NTRK inhibitors in patients with advanced or aggressive disease.	RT-PCR, NGS including RNA-Seq, AMP
<b>PAX8/PPARG rearrangement</b>		Diagnosis: Screening of indeterminate cytology thyroid nodules	Primarily seen in follicular carcinomas, but may also been seen at lower frequencies in follicular adenomas and the follicular variant of PTC	RT-PCR, NGS including RNA-Seq, AMP

**Abbreviations:** RAI - radioactive iodine; NIFTP - noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC - papillary thyroid carcinoma; MTC - medullary thyroid carcinoma; NGS – next generation sequencing; RT-PCR – Reverse Transcription PCR, AMP - anchored multiplex PCR

**Where to Test:** Testing should be performed in laboratories that are certified under Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity (molecular pathology) testing.

**References:**

National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Thyroid Carcinoma. Version 2.2017 – May 17, 2017; NCCN.org. accessed 1/18/2018

Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016 Jan;26(1):1-133.

Wells SA Jr, et al. American Thyroid Association Guidelines Task Force on Medullary Thyroid Carcinoma. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid*. 2015 Jun;25(6):567-610.

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