

ONCOLOGY: Molecular Biomarkers of Thyroid Cancer

Sample Type to Test: Fine needle aspirate; 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
BRAF	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
HRAS	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
NRAS	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
KRAS	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
RET	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
RET/PTC1 & RET/PTC3 rearrangements	RET/PTC1 = fusion of RET with CCDC6 RET/PTC3 = fusion of RET with NCOA4	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, AMP
NTRK1, NTRK2, NTRK3 rearrangements		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, AMP
PAX8/PPARG rearrangement		Diagnosis: Screening of indeterminate cytology thyroid nodules	Primarily seen in follicular carcinomas, but may also be seen at lower frequencies in follicular adenomas and the follicular variant of PTC	RT-PCR, NGS, AMP

Abbreviations: RAI - radioactive iodine; NIFTP - noninvasive follicular thyroid neoplasm with papillary-like nuclear features; PTC - papillary thyroid carcinoma; MTC - medullary thyroid carcinoma; AMP - anchored multiplex PCR

Where to Test: Testing should be performed in the 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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