COLLEGE of AMERICAN PATHOLOGISTS

Template for Reporting Results of Biomarker Testing of Specimens From Patients With Thyroid Carcinoma

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The College of American Pathologists offers these templates to assist pathologists in providing clinically useful and relevant information when reporting results of biomarker testing. The College regards the reporting elements in the templates as important elements of the biomarker test report, but the manner in which these elements are reported is at the discretion of each specific pathologist, taking into account clinician preferences, institutional policies, and individual practice.

The College developed these templates as educational tools to assist pathologists in the useful reporting of relevant information. It did not issue them for use in litigation, reimbursement, or other contexts. Nevertheless, the College recognizes that the templates might be used by hospitals, attorneys, payers, and others. The College cautions that use of the templates other than for their intended educational purpose may involve additional considerations that are beyond the scope of this document.

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CAP Thyroid Carcinoma Biomarker Template Revision History

Version Code
The definition of version control and an explanation of version codes can be found at www.cap.org (search: cancer protocol terms).

Version: ThyroidBiomarkers 1.0.0.0

Summary of Changes
This is a new template.

Thyroid Carcinoma Biomarker Reporting Template

Template web posting date: August 2015

Completion of the template is the responsibility of the laboratory performing the biomarker testing and/or providing the interpretation. When both testing and interpretation are performed elsewhere (eg, a reference laboratory), synoptic reporting of the results by the laboratory submitting the tissue for testing is also encouraged to ensure that all information is included in the patient's medical record and thus readily available to the treating clinical team.

THYROID

Select a single response unless otherwise indicated.

Note: *Use of this template is optional.*

+ SPECIMEN ADEQUACY

+ Adequacy Assessment of Thyroid Fine-Needle Aspirates (Note A)
+ ___ Adequate
+ ___ Inadequate
+ ___ Suboptimal (specify reason): _____

+ Adequacy of Resected Specimens or Cell Blocks for Testing (Note A)
+ ___ Adequate
    + Estimated tumor cellularity (area used for testing): _____%
+ ___ Suboptimal (specify reason): _____

Note: If "Adequate" not selected, please refer to original laboratory report for explanation.

+ RESULTS

+ *BRAF* Mutational Analysis (Note B)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.V600E, c.1799T>A
    + ___ p.K601E, c.1801A>G
    + ___ Other *BRAF* mutation (specify): _____
        + Indicate mutant allele frequency: _____%
+ ___ Cannot be determined (explain): _____

+ *TERT* Mutational Analysis (Note B)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ c.1-124 (C228T)
    + ___ c.1-146 (C250T)
    + ___ Other *TERT* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *NRAS* Mutational Analysis (Note C)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.Q61R, c.182A>G
    + ___ p.Q61K, c.181C>A
    + ___ Other *NRAS* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *HRAS* Mutational Analysis (Note C)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.Q61R, c.182A>G
    + ___ p.G12V, c.35G>T
    + ___ Other *HRAS* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *KRAS* Mutational Analysis (Note C)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.G12D, c.35G>A
    + ___ Other *KRAS* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *AKT1* Mutational Analysis (Note D)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.E17K, c.49G>A
    + ___ Other *AKT1* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *TP53* Mutational Analysis (Note D)
+ ___ No mutation detected
+ ___ Mutation identified (specify): _____
+ ___ Cannot be determined (explain): _____

+ *PIK3CA* Mutational Analysis (Note D)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.H1047R, c.3140A>G
    + ___ Other *PIK3CA* mutation (specify): _____
+ ___ Cannot be determined (explain): _____

+ *CTNNB1 (β-catenin)* Mutational Analysis (Note E)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.S33A, c.97T>G
    + ___ Other *CTNNB1* mutation (specify): _____
+ ___ Cannot be determined

+ *RET* Mutational Analysis (Note F)
+ ___ No mutation detected
+ ___ Mutation identified
    + ___ p.M918T, c.2753T>C
    + ___ Other *RET* mutation (specify): _____
+ ___ Mutation type:
    + ___ Germline (inherited)
    + ___ Somatic (sporadic)
    + ___ Unknown
+ ___ Cannot be determined (explain): _____

+*ALK* Rearrangement (Note G)
+ ___ No rearrangement detected
+ ___ Rearrangement identified
    + ___ *STRN/ALK*
    + ___ *EML4/ALK*
    + ___ Other *ALK* rearrangement (specify): _____
+ ___ Cannot be determined (explain): _____

+*NTRK1* Rearrangement (Note H)
+ ___ No rearrangement detected
+ ___ Rearrangement identified
    + ___ *NTRK1/TPM3*
    + ___ *NTRK1/TFG*
    + ___ Other *NTRK1* rearrangement (specify): _____
+ ___ Cannot be determined (explain): _____

+*NTRK3* Rearrangement (Note H)
+ ___ No rearrangement detected
+ ___ Rearrangement identified
    + ___ *NTRK3/ETV6*
    + ___ Other *NTRK3* rearrangement (specify): _____
+ ___ Cannot be determined (explain): _____

+ *RET* Rearrangement (Note F)
+ ___ No rearrangement detected
+ ___ Rearrangement identified
    + ___ *RET/PTC1*
    + ___ *RET/PTC3*
    + ___ Other *RET* rearrangement (specify): _____
+ ___ Cannot be determined (explain): _____

+ *PPAR gamma* Rearrangement (Note I)
+ ___ No rearrangement detected
+ ___ Rearrangement identified
    + ___ *PAX8/PPAR gamma*
    + ___ *CREB3L2/PPAR gamma*
    + ___ Other *PPAR gamma* rearrangement (specify): _____
+ ___ Cannot be determined (explain): _____

+ Other Markers Tested (if applicable)
+ ___ Specify marker: _____
+ ___ Specify results: _____

+ METHODS

+ Dissection Method(s) (select all that apply)
+ ___ Laser capture microdissection
    + Specify test name[#]: _____
+ ___ Manual under microscopic observation
    + Specify test name[#]: _____
+ ___ Manual without microscopic observation
    + Specify test name[#]: _____
+ ___ Cored from block
    + Specify test name[#]: _____
+ ___ Whole tissue section (no tumor enrichment procedure employed)
    + Specify test name[#]: _____

[#] *If more than 1 dissection method used, please specify which test was associated with each selected dissection method.*

+ *BRAF* Mutational Analysis (select all that apply)
+ ___ Direct (Sanger) sequencing
+ ___ High-resolution melting analysis
+ ___ Next-generation (high-throughput) sequencing
+ ___ Immunohistochemistry
    + ___ VE1 clone
    + ___ Other (specify): _____
+ ___ Other (specify): _____

+ *TERT* Mutational Analysis
+ ___ Direct (Sanger) sequencing
+ ___ Next-generation (high-throughput) sequencing
+ ___ Other (specify): _____

+ *NRAS, HRAS, KRAS, AKT1, TP53,* and *PIK3CA* Mutational Analysis (select all that apply)
+ ___ Direct (Sanger) sequencing
+ ___ High-resolution melting analysis
+ ___ Next-generation (high-throughput) sequencing
+ ___ Immunohistochemistry
    + ___ Clone (specify): _____
+ ___ Other (specify): _____

+ *NRAS* Codons Assessed (select all that apply)
+ ___ Codon 12
+ ___ Codon 13
+ ___ Codon 61
+ ___ Other (specify): _____

+ *HRAS* Codons Assessed (select all that apply)
+ ___ Codon 12
+ ___ Codon 13
+ ___ Codon 61
+ ___ Other (specify): _____

+ *KRAS* Codons Assessed (select all that apply)
+ ___ Codon 12
+ ___ Codon 13
+ ___ Codon 61
+ ___ Other (specify): _____

+ *ALK* Rearrangement
+ ___ In situ hybridization
+ ___ Reverse transcriptase polymerase chain reaction (RT-PCR)
+ ___ Immunohistochemistry
    + ___ *ALK* 5A4 clone
    + ___ *ALK* D5F3 clone
    + ___ Other (specify): _____
+ ___ Next-generation (high-throughput) sequencing

+ *PPAR gamma* Rearrangement
+ ___ In situ hybridization
+ ___ Reverse transcriptase polymerase chain reaction (RT-PCR)
+ ___ Immunohistochemistry
    + ___ Clone (specify): _____
+ ___ Next-generation (high-throughput) sequencing

+ *RET/PTC1*, *RET/PTC3*, *NTRK1,* and *NTRK3* Rearrangement
+ ___ In situ hybridization
+ ___ Reverse transcriptase polymerase chain reaction (RT-PCR)
+ ___ Immunohistochemistry
    + ___ Clone (specify): _____
+ ___ Next-generation (high-throughput) sequencing

+ *CTNNB1* Mutational Analysis
+ ___ Direct (Sanger) sequencing
+ ___ Next-generation (high-throughput) sequencing
+ ___ Immunohistochemistry
    + ___ Clone (specify): _____

+ Sensitivity/Limit of Mutation Detection (Note A)
+ ___ ≥20%
+ ___ ≥10%
+ ___ ≥5%
+ ___ Other (specify): _____%

+ Other Methods Used (if applicable)
+ ___ Specify method: _____

+ COMMENT(S)
_____
_____

Note: Fixative type, time to fixation (cold ischemia time), and time of fixation should be reported if applicable in this template or in the original pathology report.

Gene names should follow recommendations of The Human Genome Organisation (HUGO) Nomenclature Committee (http://hugo-international.org; accessed February 10, 2015).

All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (http://www.hgvs.org; accessed February 10, 2015).

Explanatory Notes

A. Specimen Adequacy
The collection of material for molecular studies should not affect the morphologic cytologic assessment. For fine-needle aspirates (FNA), at the time of the FNA procedure, a small portion of the (residual) aspirated material may be collected into nucleic acids preservative. The material may represent a part of the first needle pass or a separate pass dedicated for the molecular analysis.[1] The storage and transportation conditions (time, temperature) have to be specified by laboratories.

The *quantity* of isolated nucleic acids is the total amount of extracted nucleic acids. The minimal acceptable amount of nucleic acids will depend on the methodology and should be determined by laboratories. The *quality* of DNA and RNA can be assessed by amplification of housekeeping genes (eg, *GAPDH, PGK1)*. The trouble-shooting procedure for suboptimal specimens should be specified (eg, increasing and decreasing the amount of nucleic acid template).[2]

The proportion of follicular thyroid epithelial cells in an FNA sample can be assessed by comparing the expression of the housekeeping gene and a gene known to be expressed predominantly in thyroid follicular cells (eg, keratin 7, thyroid transcription factor 1 [NK2 homeobox 1]), genes expressed in mimics of thyroid nodule (eg, parathyroid hormone), or genes expressed in medullary thyroid carcinoma (ie, calcitonin).[3-5]

The sensitivity of mutation detection and the method used to establish sensitivity should be established by the laboratory for each methodology (eg, serial dilutions of the positive controls in normal blood/lymphocytes or normal formalin-fixed paraffin-embedded tissue).

Resection specimens may be inadequate due to improper fixation, decalcification, low tumor content, or small tumor size.

B. *BRAF* Mutational Analysis
The presence of *BRAF* V600E mutation in a fine-needle aspirate is indicative of about 99% risk of cancer in the sampled thyroid nodule. When identified alone, *BRAF* V600E mutation may merely reflect the conventional morphology or tall cell variant of papillary thyroid carcinoma. The combination of *BRAF* V600E mutation with *TERT, AKT1, PIK3CA*, or *TP53* mutations predicts a more aggressive tumor behavior.[6-12] *BRAF* K601E is an unusual *BRAF* mutation, which had been reported in follicular variant of papillary thyroid carcinoma and rarely in follicular adenomas.[13,14]

***C. RAS* Mutational Analysis**
The finding of *RAS* mutation in a fine-needle aspirate is associated with an about 80% risk of cancer in a given nodule. The most common types of cancer with *RAS* mutations are the encapsulated follicular variant of papillary carcinoma and follicular carcinoma. The remaining *RAS*-positive thyroid nodules are usually diagnosed as follicular adenomas. Sporadic medullary thyroid carcinomas with wild type *RET* genes may harbor *RAS* mutations (*HRAS* or *KRAS*).[2,4,5,8,15,16]

D. *PIK3CA, AKT1*, and *TP53* Mutational Analysis
PIK3CA, AKT1, and *TP53* mutations are usually found in advanced thyroid cancer with propensity for dedifferentiation and distant metastasis.[8,17]

E. *CTNNB1* Mutational Analysis
The presence of *CTNNB1* mutation in a given thyroid nodule is expected to confer a >90% risk of cancer. Point mutations in exon 3 of *CTNNB1* stabilize the protein by making it insensitive for adenomatous polyposis coli (APC)-induced degradation, leading to the accumulation of β-catenin in the nucleus. In thyroid tumors, mutations in exon 3 of *CTNNB1* were also reported in poorly

differentiated and anaplastic carcinomas, but not in well-differentiated carcinomas or benign thyroid nodules.[18]

F. *RET* Mutational Analysis
The presence of *RET* rearrangements in thyroid fine-needle aspirate is associated with >95% risk of cancer, most frequently classic papillary thyroid carcinoma. Mutations of the *RET* gene are typically present in sporadic and familial forms of medullary thyroid carcinoma. Among sporadic medullary carcinomas, RET p.M918T mutation accounts for more than 75% of all somatic *RET* mutations found in medullary carcinomas.[19,20]

Laboratories should disclose whether the test was performed on tissue type (tumor versus normal tissue) that allows distinguishing between germline (inherited) and sporadic (acquired) mutation. Nevertheless, the distinction between sporadic and germline mutation can be reliably made only by testing a nontumorous specimen, preferably patient blood. Clinical management of patients based on the presence of specific *RET* mutations has been defined.[19,20]

G. *ALK* Mutational Analysis
The identification of *ALK* fusions (*STRN/ALK* or *EML4/ALK)* in a thyroid FNA is associated with a very high risk of thyroid cancer. *ALK* fusions were identified in ~1.5% of papillary thyroid carcinomas and in 4% to 9% of dedifferentiated thyroid cancers.[21, 22] In advanced papillary thyroid carcinomas and in dedifferentiated thyroid tumors, the presence of an *ALK* fusion may represent a therapeutic target for crizotinib.[21,22]

H. *NTRK1* and *NTRK3* Mutational Analysis
Rearrangements of the *NTRK1* gene occur in <5% of papillary carcinomas.[23] Different fusions partners of *NTRK1* have been described including *TPM3* and *TPR* genes. Some studies reported that *NTRK1* fusion-positive papillary thyroid carcinomas may have more aggressive biological behavior and higher rate of local recurrence.[24] *NTRK3* fusions have been reported in papillary thyroid carcinomas.[25,26] In vitro studies showed that *ETV6/NTRK3* aberrantly activates phosphatidylinositide 3-kinase signaling pathway. A phase 1a/1b clinical trial of the oral TRK Inhibitor LOXO-101 is available.

I. *PPARG* Mutational Analysis
The presence of rearrangements involving the *PPARG* gene, *PAX8/PPARG* and less frequently *CREB3L2/PPARG,* correlate with ~95% risk of cancer, most frequently follicular variant of papillary carcinoma, followed in frequency by follicular carcinoma. Rare cases of follicular adenoma carrying *PPARG* rearrangements have been reported.[27] Most of thyroid cancers positive for *PPARG* rearrangements are low-grade tumors, whereas 5% to 10% of those tumors have aggressive behavior. Of note, *PPARG* fusions can be exploited as a therapeutic target for advanced thyroid cancer. The presence of *PAX8/PPARG* or *CREB3L2/PPARG* rearrangement in thyroid fine-needle aspirates correlated with >95% risk of cancer, most frequently follicular variant of papillary carcinoma or follicular carcinoma.[28]

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