



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

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## **CAP Thyroid Carcinoma Biomarker Template Revision History**

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### **Version Code**

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

**Version:** ThyroidBiomarkers 1.0.0.1

### **Summary of Changes**

Minor typographical and data element naming changes.

## Biomarker Reporting Template

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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 (explain): \_\_\_\_\_

##### + Adequacy of Resected Specimens or Cell Blocks for Testing (Note A)

- +  Adequate
  - + Estimated tumor cellularity (area used for testing): \_\_\_\_\_%
- +  Suboptimal (explain): \_\_\_\_\_

*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 ( $\beta$ -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 Testing Method(s) (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 Testing Method(s)**

- +  Direct (Sanger) sequencing
- +  Next-generation (high-throughput) sequencing
- +  Other (specify): \_\_\_\_\_

**+ NRAS, HRAS, KRAS, AKT1, TP53, and PIK3CA Mutational Analysis Testing Method(s)(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 Testing Method(s)**

- + \_\_\_ 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 Testing Method(s)**

- + \_\_\_ 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 Testing Method(s)**

- + \_\_\_ In situ hybridization
- + \_\_\_ Reverse transcriptase polymerase chain reaction (RT-PCR)
- + \_\_\_ Immunohistochemistry
  - + Clone (specify): \_\_\_\_\_
- + \_\_\_ Next-generation (high-throughput) sequencing

**+ CTNNB1 Mutational Analysis Testing Method(s)**

- + \_\_\_ Direct (Sanger) sequencing
- + \_\_\_ Next-generation (high-throughput) sequencing
- + \_\_\_ Immunohistochemistry
  - + Clone (specify): \_\_\_\_\_

**+ Sensitivity/Limit of Mutation Detection (Note A)**

- + \_\_\_  $\geq 20\%$
- + \_\_\_  $\geq 10\%$
- + \_\_\_  $\geq 5\%$
- + \_\_\_ Other (specify): \_\_\_\_\_%

**+ Other Methods Used (if applicable)**

- + Specify method: \_\_\_\_\_

**+ COMMENT(S)**


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*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 May 25, 2016).*

*All reported gene sequence variations should be identified following the recommendations of the Human Genome Variation Society (<http://varnomen.hgvs.org>; accessed May 25, 2016).*

## Explanatory Notes

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### 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.<sup>1</sup> 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).<sup>2</sup>

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).<sup>3-5</sup>

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.<sup>6-12</sup> *BRAF* K601E is an unusual *BRAF* mutation, which had been reported in follicular variant of papillary thyroid carcinoma and rarely in follicular adenomas.<sup>13,14</sup>

### 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*).<sup>2,4,5,8,15,16</sup>

### 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.<sup>8,17</sup>

### 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  $\beta$ -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.<sup>18</sup>

### 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.<sup>19,20</sup>

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.<sup>19,20</sup>

### 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.<sup>21,22</sup> In advanced papillary thyroid carcinomas and in dedifferentiated thyroid tumors, the presence of an *ALK* fusion may represent a therapeutic target for crizotinib.<sup>21,22</sup>

### H. *NTRK1* and *NTRK3* Mutational Analysis

Rearrangements of the *NTRK1* gene occur in <5% of papillary carcinomas.<sup>23</sup> Different fusion 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.<sup>24</sup> *NTRK3* fusions have been reported in papillary thyroid carcinomas.<sup>25,26</sup> In vitro studies showed that *ETV6/NTRK3* aberrantly activates phosphatidylinositol 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.<sup>27</sup> 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.<sup>28</sup>

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