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

**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 1.0.0.1

**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 (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 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)**

+ \_\_\_ ≥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 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

**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](#_ENREF_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](#_ENREF_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](#_ENREF_3)

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](#_ENREF_6) *BRAF* K601E is an unusual *BRAF* mutation, which had been reported in follicular variant of papillary thyroid carcinoma and rarely in follicular adenomas.[13](#_ENREF_13),[14](#_ENREF_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](#_ENREF_2),[4](#_ENREF_4),[5](#_ENREF_5),[8](#_ENREF_8),[15](#_ENREF_15),[16](#_ENREF_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](#_ENREF_8),[17](#_ENREF_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](#_ENREF_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](#_ENREF_19),[20](#_ENREF_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](#_ENREF_19),[20](#_ENREF_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](#_ENREF_21), [22](#_ENREF_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](#_ENREF_21),[22](#_ENREF_22)

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

Rearrangements of the *NTRK1* gene occur in <5% of papillary carcinomas.[23](#_ENREF_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](#_ENREF_24) *NTRK3* fusions have been reported in papillary thyroid carcinomas.[25](#_ENREF_25),[26](#_ENREF_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](#_ENREF_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](#_ENREF_28)

**References**

1. Filie AC, Asa SL, Geisinger KR, et al. Utilization of ancillary studies in thyroid fine needle aspirates: a synopsis of the National Cancer Institute Thyroid Fine Needle Aspiration State of the Science Conference. *Diagn Cytopathol*. 2008;36(6):438-441.

2. Nikiforov YE, Steward DL, Robinson-Smith TM, et al. Molecular testing for mutations in improving the fine-needle aspiration diagnosis of thyroid nodules. *J Clin Endocrinol Metab*. 2009;94(6):2092-2098.

3. Alexander EK, Kennedy GC, Baloch ZW, et al. Preoperative diagnosis of benign thyroid nodules with indeterminate cytology. *New Engl J Med.* 2012;367(8):705-715.

4. Nikiforov YE, Ohori NP, Hodak SP, et al. Impact of mutational testing on the diagnosis and management of patients with cytologically indeterminate thyroid nodules: a prospective analysis of 1056 FNA samples. *J Clin Endocrinol Metab*. 2011;96(11):3390-3397.

5. Nikiforov YE, Carty SE, Chiosea SI, et al. Highly accurate diagnosis of cancer in thyroid nodules with follicular neoplasm/suspicious for a follicular neoplasm cytology by ThyroSeq v2 next-generation sequencing assay. *Cancer*. 2014;120(23):3627-3634.

6. Liu X, Qu S, Liu R, et al. TERT promoter mutations and their association with BRAF V600E mutation and aggressive clinicopathological characteristics of thyroid cancer. *J Clin Endocrinol Metab*. 2014;99(6):E1130-E1136.

7. Melo M, da Rocha AG, Vinagre J, et al. TERT promoter mutations are a major indicator of poor outcome in differentiated thyroid carcinomas. *J Clin Endocrinol Metab*. 2014;99(5):E754-E765.

8. Nikiforova MN, Wald AI, Roy S, Durso MB, Nikiforov YE. Targeted next-generation sequencing panel (ThyroSeq) for detection of mutations in thyroid cancer. *J Clin Endocrinol Metab*. 2013;98(11):E1852-E1860.

9. Ricarte-Filho JC, Ryder M, Chitale DA, et al. Mutational profile of advanced primary and metastatic radioactive iodine-refractory thyroid cancers reveals distinct pathogenetic roles for BRAF, PIK3CA, and AKT1. *Cancer Res*. 2009;69(11):4885-4893.

10. Xing M, Liu R, Liu X, et al. BRAF V600E and TERT promoter mutations cooperatively identify the most aggressive papillary thyroid cancer with highest recurrence. *J Clin Oncol*. 2014;32(25):2718-2726.

11. Xing M, Clark D, Guan H, et al. BRAF mutation testing of thyroid fine-needle aspiration biopsy specimens for preoperative risk stratification in papillary thyroid cancer. *J Clin Oncol.* 2009;27(18):2977-2982.

12. The Cancer Genome Atlas Research Network. Integrated genomic characterization of papillary thyroid carcinoma. *Cell*. 2014;159(3):676-690.

13. Park JY, Kim WY, Hwang TS, et al. BRAF and RAS mutations in follicular variants of papillary thyroid carcinoma. *Endocr Pathol*. 2013;24(2):69-76.

14. Chiosea S, Nikiforova M, Zuo H, et al. A novel complex BRAF mutation detected in a solid variant of papillary thyroid carcinoma. *Endocr Pathol*. 2009;20(2):122-126.

15. Gupta N, Dasyam AK, Carty SE, et al. RAS mutations in thyroid FNA specimens are highly predictive of predominantly low-risk follicular-pattern cancers. *J Clin Endocrinol Metab*. 2013;98(5):E914-E922.

16. Boichard A, Croux L, Al Ghuzlan A, et al. Somatic RAS mutations occur in a large proportion of sporadic RET-negative medullary thyroid carcinomas and extend to a previously unidentified exon. *J Clin Endocrinol Metab*. 2012;97(10):E2031-E2035.

17. Dobashi Y, Sugimura H, Sakamoto A, et al. Stepwise participation of p53 gene mutation during dedifferentiation of human thyroid carcinomas. *Diagn Mol Pathol*. 1994;3(1):9-14.

18. Garcia-Rostan G, Camp RL, Herrero A, Carcangiu ML, Rimm DL, Tallini G. Beta-catenin dysregulation in thyroid neoplasms: down-regulation, aberrant nuclear expression, and CTNNB1 exon 3 mutations are markers for aggressive tumor phenotypes and poor prognosis. *Am J Pathol*. 2001;158(3):987-996.

19. de Groot JW, Links TP, Plukker JT, Lips CJ, Hofstra RM. RET as a diagnostic and therapeutic target in sporadic and hereditary endocrine tumors. *Endocrine Rev*. 2006;27(5):535-560.

20. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. *Thyroid*. 2009;19(6):565-612.

21. Kelly LM, Barila G, Liu P, et al. Identification of the transforming STRN-ALK fusion as a potential therapeutic target in the aggressive forms of thyroid cancer. *Proc Nat Acad Sci USA*. 2014;111(11):4233-4238.

22. Demeure MJ, Aziz M, Rosenberg R, Gurley SD, Bussey KJ, Carpten JD. Whole-genome sequencing of an aggressive BRAF wild-type papillary thyroid cancer identified EML4-ALK translocation as a therapeutic target. *World J Surg*. 2014;38(6):1296-1305.

23. Greco A, Miranda C, Pierotti MA. Rearrangements of NTRK1 gene in papillary thyroid carcinoma. *Mol Cell Endocrinol*. 2010;321(1):44-49.

24. Musholt TJ, Musholt PB, Khaladj N, Schulz D, Scheumann GF, Klempnauer J. Prognostic significance of RET and NTRK1 rearrangements in sporadic papillary thyroid carcinoma. *Surgery*. 2000;128(6):984-993.

25. Leeman-Neill RJ, Kelly LM, Liu P, et al. ETV6-NTRK3 is a common chromosomal rearrangement in radiation-associated thyroid cancer. *Cancer*. 2014;120(6):799-807.

26. Ricarte-Filho JC, Li S, Garcia-Rendueles ME, et al. Identification of kinase fusion oncogenes in post-Chernobyl radiation-induced thyroid cancers. *J Clin Invest*. 2013;123:4935-4944.

27. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. *Nat Rev Endocrinol*. 2011(11);7:569-580.

28. Lui WO, Zeng L, Rehrmann V, et al. CREB3L2-PPARgamma fusion mutation identifies a thyroid signaling pathway regulated by intramembrane proteolysis. *Cancer Res*. 2008;68(17):7156-7164.