

# Cytopathology & Histopathology

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## Large independent prospective study to evaluate the performance of ThyroSeq V.2 multigene next-generation sequencing panel analysis on cancer diagnosis in thyroid nodules with indeterminate cytology

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**Context:** Fine-Needle Aspiration Biopsy (FNAB) is important in predicting thyroid malignancy. However 10-35% of FNAB are indeterminate and these nodules are usually surgically removed for diagnosis. Commercial molecular testing may improve the diagnostic accuracy of FNAB and reduce the number of operations but have limited independent validation in clinical practice.

**Objective:** To evaluate the performance of ThyroSeq V.2 to predict malignancy in 745 sequential FNABs with a Bethesda III, IV and V classification.

**Design:** Prospective observational study.

**Setting:** Academic Medical Center.

**Results:** 745 thyroid nodule FNAB's were evaluated. 235 nodules with an indeterminate cytology (Bethesda III-IV-V; ITN), underwent ThyroSeq V.2 analysis. Gene mutations, fusions and overexpression were detected in 84 patients (36%), of whom 45 (54%) had a thyroidectomy with 31 (69%) thyroid cancers and 14 benign nodules (31%). The most frequent genetic alterations detected by ThyroSeq V.2 in excised nodules were NRAS (p.Q61R,c.182A>G) mutation in benign nodules, follicular variant of papillary cancers and follicular cancers (40%, 31% and 29%, respectively), BRAF (p.V600E,c.1799 T>A) mutation in the papillary thyroid cancers (43%), and calcitonin gene expression in the medullary cancers (100%). Of the 136 patients with indeterminate FNAB and negative molecular analysis, 21 had surgery (15%); of which 20 were benign (95%) and 1 was an encapsulated follicular variant of thyroid cancer (5%). ThyroSeq V.2 test of indeterminate nodules had a sensitivity of 97% (confidence interval (CI) 84-100%), specificity of 59% (CI 41-75%), PPV of 69% (53-82%), NPV of 95% (CI 76-100%), an overall accuracy of 77% (CI 65-87%) with a prevalence of disease of 49% (CI 36-61%).

**Conclusions:** ThyroSeq V.2 provides a highly sensitive method to detect thyroid malignancy in ITN nodules but the specificity was lower than expected compared to initial studies as a result of the detection of an array of mutations in benign lesions.

### Biography

Sandra Cerda is board certified in Anatomic and Clinical Pathology and in Cytopathology by the American Board of Pathology. She has obtained her Medical School degree from Universidad de Alcalá de Henares in Madrid, Spain and completed her Residency and Fellowship training at Boston University School of Medicine. She is the Director of Cytopathology at Boston Medical Center. Her research interests are based in thyroid pathology, cytopathology and colorectal malignancy and inflammatory bowel disease.

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