



## THYROID CANCER

### An evaluation of the molecular marker tests for thyroid cancer

#### BACKGROUND

Thyroid nodules are very common, occurring in up to 50% of the population. The main concern about a thyroid nodule is whether it is a cancer. Fortunately, ~95% of thyroid nodules are benign (non-cancer). Thyroid biopsy is the best test outside of surgery in determining whether thyroid nodule is cancerous or not. However, 15-20% of thyroid biopsies are indeterminate, meaning a diagnosis between cancer and benign cannot be made by simply looking at the cells. In the most recent cytology classification system, indeterminate biopsies fall into Bethesda category III (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS) and Bethesda category IV (follicular or hurthle cell lesion). In the past, most of the patients with indeterminate thyroid biopsies were referred to surgery, resulting in a lot of surgeries for benign disease.

Measuring molecular markers, which are gene mutations that are seen in cancer, allows the identification of indeterminate biopsies as benign and, thus, to avoid surgery.

There are 3 such companies offering measurement of molecular markers in thyroid biopsy specimens:

- Thyroseq™ — a gene sequencing test that evaluates 5 classes of genetic alterations in 112 genes,
- Afirma GEC or GSC™ — a gene-expression classifier that identifies biopsies as “benign” or “suspicious,” and
- mir-THYtype™ — an mRNA-based classifier test.

These 3 papers report the performance of these assays in evaluating Bethesda III and IV indeterminate biopsies.

#### SUMMARY OF THE STUDIES

##### Thyroseq™

Steward DL et al Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. *JAMA Oncol.* Epub 2018 Nov 8. PMID: 30419129.

This study was performed across 10 institutions (9 in the United States and 1 in Singapore) from January 2015 to December 2016. Patients who underwent biopsies of thyroid nodules that were indeterminate and who subsequently underwent surgery were included. A total of 256 subjects with 286 indeterminate nodules were included in the analysis. Of these biopsies, 59% of nodules had a negative Thyroseq v3 result (i.e., no high-risk mutations). Five (3%) samples were reported as negative that turned out to be low-risk cancers. Thyroseq v3 identified 13 of 34 (38%) of benign Hürthle-cell adenomas as positive for cancer, but correctly identified 10 of 10 Hürthle-cell cancers.

##### Afirma™

Harrell RM et al 2018 Statistical comparison of Afirma GSC and Afirma GEC outcomes in a community endocrine surgical practice: early findings. *Endocr Pract.* E-pub 2018 Nov 1. PMID: 30383497.

This study reviewed nodules tested with the original Afirma GEC (collected January 2011 to June 2017) or the Afirma GSC (collected August 2017 to June 2018). A total of 481 GEC-tested nodules were compared to 139 GSC-tested nodules. Benign results were obtained in 85 of 139 (61.2%) in the GSC group and 200 of 481 (41.6%) in the GEC group, resulting in a concomitant decrease in surgery. The largest increase in identifying benign results was in those with Hurtle cell cytology, as 17.3% of GEC-tested nodules were reported as benign as compared to 64.7% of GSC-tested samples. The percentage of suspicious nodules using Afirma that were proved to be cancer was 120 of 209 (57.4%) in the GEC group and 28 of 37 (75.7%) in the GSC group.

##### mir-THYtype™

Santos MTD et al 2018 Molecular classification of thyroid nodules with indeterminate cytology: development and validation of a highly sensitive and specific new miRNA-based classifier test using fine-needle aspiration smear slides. *Thyroid.* Epub 2018 Nov 22. PMID: 30319072.





## THYROID CANCER, continued

An analysis was performed to identify patients with thyroid nodules who underwent thyroid biopsy between January 2013 and July 2017 that resulted in indeterminate cytology (Bethesda classes III to V) and who underwent total or partial thyroidectomy. Overall, the mir-THYpe test was able to correctly classify 153 of 173 samples. Of the 76 cancer samples, 70 were correctly classified while 83 of the 97 benign samples were correctly classified.

### WHAT ARE THE IMPLICATIONS OF THESE STUDIES?

These 3 molecular marker tests use different techniques

to evaluate indeterminate biopsy sample and all perform well to identify benign nodules which do not have to proceed to surgery. Two of these tests are currently being used commercially (Thyroseq™ and Afirma GSC™) while the mir-THYtype™ is a new test that does not require a separate biopsy sample for analysis. These tests are a major step forward in the analysis of thyroid nodules and present a much great opportunity to decrease the number of surgeries done for benign thyroid nodules.

— Alan P. Farwell, MD, FACE

### ATA THYROID BROCHURE LINKS

Fine Needle Aspiration Biopsy of Thyroid Nodules: <https://www.thyroid.org/fna-thyroid-nodules/>

Thyroid Cancer (Papillary and Follicular): <https://www.thyroid.org/thyroid-cancer/>

Thyroid Nodules: <https://www.thyroid.org/thyroid-nodules/>

### ABBREVIATIONS & DEFINITIONS

**Thyroid biopsy:** a simple procedure that is done in the doctor's office to determine if a thyroid nodule is benign (non-cancerous) or cancer. The doctor uses a very thin needle to withdraw cells from the thyroid nodule. Patients usually return home or to work after the biopsy without any ill effects.

**Indeterminate thyroid biopsy:** this happens a few atypical cells are seen but not enough to be abnormal (atypia of unknown significance (AUS) or follicular lesion of unknown significance (FLUS) – Bethesda category III) or when the diagnosis is a follicular or hurthle cell lesion (Bethesda category IV). Follicular and hurthle cells are normal cells found in the thyroid. Current analysis of thyroid biopsy results cannot differentiate between follicular or hurthle cell cancer from noncancerous adenomas. This occurs in 15-20% of biopsies and often results in the need for surgery to remove the nodule.

**Molecular markers:** genes and microRNAs that are expressed in benign or cancerous cells. Molecular markers can be used in thyroid biopsy specimens to either to diagnose cancer or to determine that the nodule is benign. The two most common molecular marker tests are the Afirma GSC™ and Thyroseq™.

**Genes:** a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

**Mutation:** A permanent change in one of the genes.

**microRNA:** a short RNA molecule that has specific actions within a cell to affect the expression of certain genes.

