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Real World Experience with ThyroSeq® V3 Genomic Classifier in Thyroid Nodules with Indeterminate Cytology: Results of Testing of the First 3,783 Consecutive Samples

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OBJECTIVES

Molecular testing of thyroid nodules with indeterminate fine-needle aspiration (FNA) cytology is increasingly used to inform patient management. Recently, a prospective, blinded, multicenter clinical validation study of ThyroSeq v3 Genomic Classifier (GC) was performed, although the experience with the routine utilization of this test has not been reported.

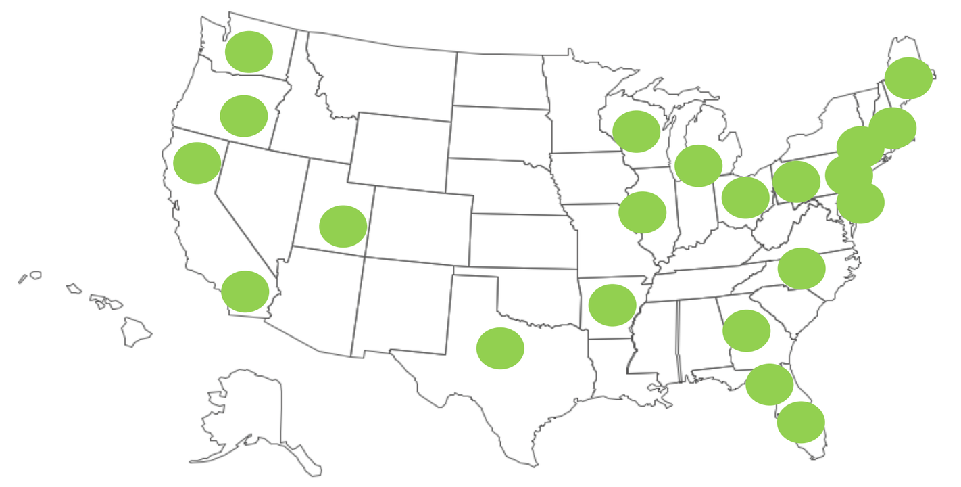
METHODS

ThyroSeq v3 GC is based on next-generation sequencing of DNA and RNA, testing for >12,000 DNA variants, >120 gene fusions, and multiple copy number alterations (CNA) and gene expression alterations (GEA). We performed data analysis of the first 3,783 consecutive FNA samples with indeterminate cytology tested by ThyroSeq v3 GC from November 1, 2017 to March 1, 2018.

RESULTS

During the 4-month period, 3,783 samples were tested including 3,081 (81%) from nodules with Bethesda III, 567 (15%) Bethesda IV, and 135 (4%) Bethesda V cytology. Of those, 74 (2%) were canceled due to an insufficient amount of cells, and 125 (3%) were negative but had an inadequate proportion of thyroid cells. Among the remaining 3,584 (95%) fully informative samples, 62% yielded a 'negative' and 38% a'positive' test result. The latter included 25 (0.7%) samples positive for parathyroid and 5 (0.14%) for medullary thyroid carcinoma markers. Among 1,348 test-positive nodules of follicular thyroid-cell origin, 74 (5.5%) had a high risk molecular profile (TERT or TP53 mutations coexisting with other mutations or alone), 224 (16.6%) BRAF V600E-like mutations/fusions, 730 (54.2%) RAS-like mutations/gene fusions, 192 (14.2%) CNA and 64 (4.7%) GEA.

Sample collection and study design



3,783 consecutive samples

3,081 (81%) Bethesda III-V cytology

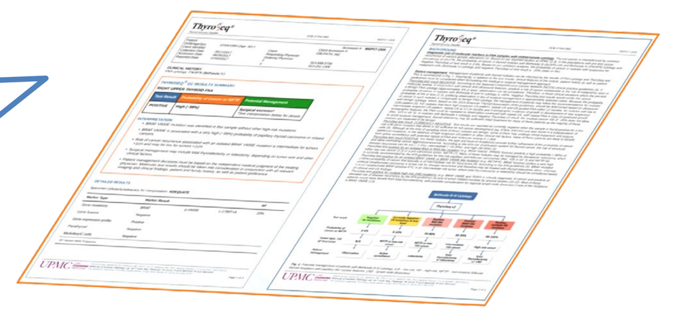
Insufficient
74 (2%) no cells
125 (3%) no thyroid cells

Adequate
3,584 (95%) thyroid cells

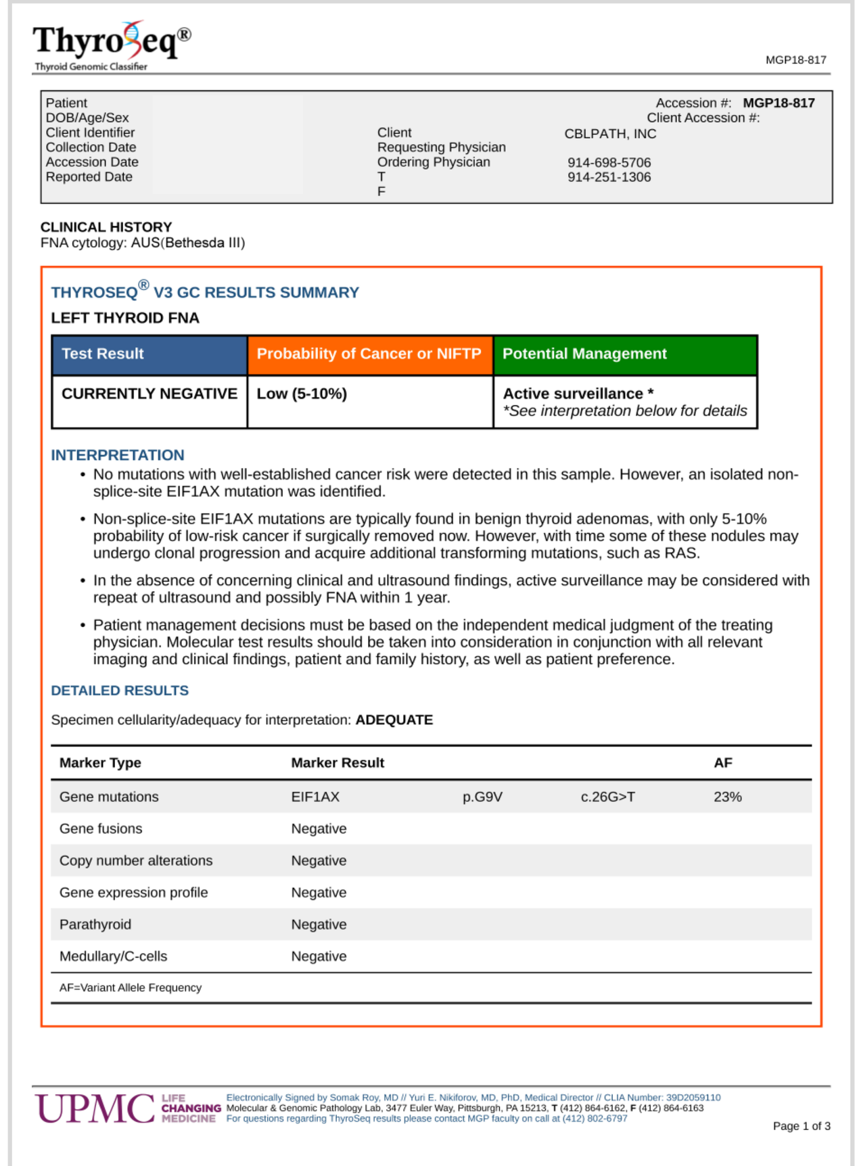
ThyroSeq Generate Sequencing Data
>12,000 DNA variants
>120 RNA fusions
DNA copy number alterations
RNA gene expression alterations

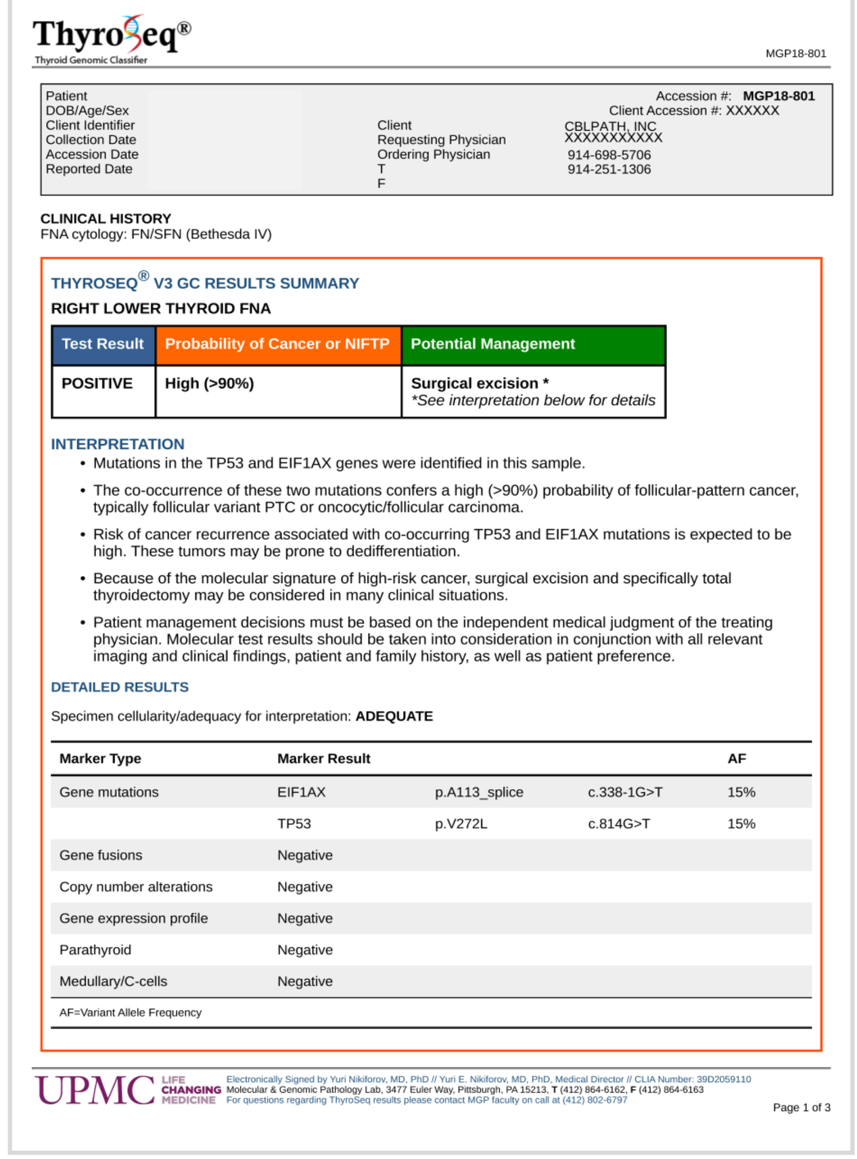
ThyroSeq Interpret Data
Knowledge Database of >3,000 genotyped patient nodules with surgical outcome

ThyroSeq reports provide the assessment of cancer probability and potential management



ThyroSeq Provides Interpretation of Genetic Findings Based on Genomic Classifier and ThyroSeq Knowledge Database





Schematic Representation of the Study Results and Proportion of Samples Tested Negative and Positive by ThyroSeq with Specific Groups of Test-Positive Results

Bethesda III-V cytology

ThyroSeq® GC

62% ThyroSeq Negative

38% ThyroSeq Positive

	1%	5%	20%	6%	2%
	MTC, PH, other non-FTL	Copy number alterations	RAS-like alterations	BRAF-like alterations	High-risk alterations
*Expected probability of Cancer/NIFTP**	100%	59%	62%	100%	100%

Individualized patient management

*Based on prospective multicenter blinded validation study (Steward et al. 2017 ATA abstract)

CONCLUSIONS

In this large consecutive series of indeterminate cytology nodules, ThyroSeq v3 GC demonstrated:

- High (95%) rate of sample adequacy for testing
- 62% of test-negative cases with expected low residual cancer risk, so that diagnostic surgery may be avoided in most of these patients
- Among test-positive cases, interpretation of genetic findings with assigned cancer probability and risk of recurrence may inform more individualized management of these patients.