THU-168

Clinical Validation of the Afirma Genomic Sequencing Parathyroid Classifier

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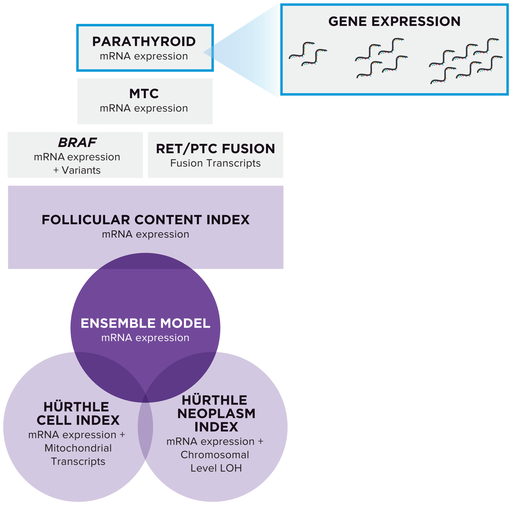
INTRODUCTION

The parathyroid glands are located adjacent to the thyroid and occasionally within it. Enlarged and imbedded parathyroid glands can be mistaken as thyroid nodules or suspicious lymph nodes. On fine needle aspiration biopsy (FNAB) of such lesions, cytology is often indeterminate, failing to identify its parathyroid origin and potentially resulting in an unnecessary thyroid surgery. The Afirma Genomic Sequencing Classifier (GSC) identifies genomically benign thyroid nodules among those with indeterminate FNAB to prevent unnecessary diagnostic surgery using RNA sequencing and machine learning algorithms. Integrated cassettes are used to detect the molecular signatures of specific neoplasms that may further alter patient care, such as unsuspected parathyroid tissue (Figure 1). Here we report the clinical performance of the parathyroid classifier cassette used with the GSC.

FIGURE 1.
Afirma Genomic Sequencing Classifier (GSC) Integrated Workflow



METHODS

Algorithm training was performed with a set of 476 FNAs–6 parathyroid and 470 thyroid FNAs. An additional 97 tissues were used in feature selection, but not model training (Table 1). A support vector machine classifier was developed using 109 differentially expressed genes, including the 5 genes in the Afirma GEC parathyroid cassette (Figure 2).

TABLE 1.
TRAINING COHORTS

1A. Core FNA Training Set (Parathyroid=6, Non-Parathyroid=470)

Parathyroid Cohort

Cohort	Bethesda III	Bethesda IV
ENHANCE Arm1	2	0
Parathyroid	3	1

Non-Parathyroid Cohort

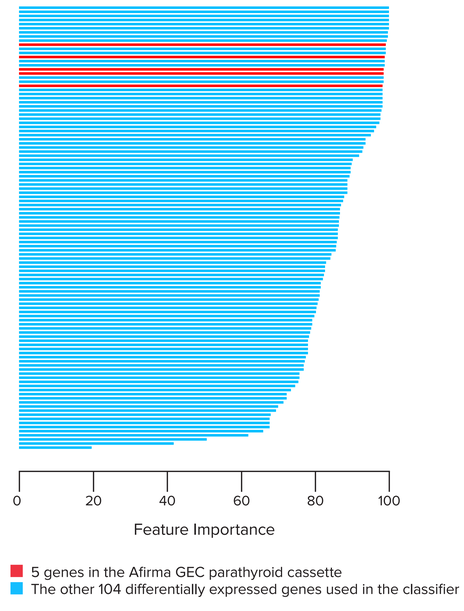
Cohort	Bethesda III	Bethesda IV
ENHANCE Arm1	209	76
ENHANCE Arm2	50	14
Cytol GECB	111	
MTC	5	5

1B. Auxiliary Tissue Training Set (n=97)

Cohort	Parathyroid	Non-Parathyroid
MTC	0	21
Parathyroid	21	0
Hürthle Tissue	0	25
Tissue	0	30

FIGURE 2.
Relative Importance of 109 Parathyroid Classifier Genes

109 genes used in the classifier are sorted by their relative importance where 100% indicates the highest importance. 5 genes that were used in the previous version of the parathyroid cassette are highlighted in red in this figure.



RESULTS

The final locked classifier was blindly validated on an independent test set of 195 FNAs (118 Bethesda III, 77 Bethesda IV). The classifier had 100% sensitivity [4/4 parathyroid correctly called positive; CI 39.8-100%] and 100% specificity [191/191 thyroid correctly called negative; CI 98.1-100%] (Table 2). All positive samples had clinical/surgical confirmation of the parathyroid etiology, while all negative samples were negative on surgical pathology.

TABLE 2.
Independent Validation Performance (n=195)

		Truth Label (n = 195)	
		Parathyroid	Non-Parathyroid
Parathyroid Classifier Result	Positive	4	0
	Negative	0	191

Sensitivity	Specificity
100% (39.8-100%)	100% (98.1-100%)

CONCLUSIONS

Preoperative genomic identification of parathyroid tissue facilitates appropriate management of parathyroid tissue within and adjacent to the thyroid gland. Reporting the result of the Parathyroid Classifier with every GSC test may help avoid inappropriate interventions, costs, and potential complications.[1]

1. Meltzer, C et al. *Otolaryngology–Head and Neck Surgery* 2016.

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