Afirma®
GENOMIC SEQUENCING CLASSIFIER

Clinical Validation of the Afirma Genomic Sequencing Classifier for Medullary Thyroid Cancer

Presented at the
87th Annual Meeting of the American Thyroid Association

October 18-22
Victoria, BC, Canada

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Clinical Validation of the Afirma Genomic Sequencing Classifier for Medullary Thyroid Cancer

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INTRODUCTION

Cytopathological evaluation of thyroid fine-needle aspiration biopsy (FNAB) specimens can fail to raise preoperative suspicion of medullary thyroid cancer (MTC), missing more than one-half of these uncommon, yet aggressive malignancies. Serum calcitonin screening for MTC in thyroid nodule patients is controversial because this has a high false-positive rate. The Afirma Genomic Sequencing Classifier (GSC) identifies, by using RNA sequencing and machine learning algorithms, genomically benign thyroid nodules among those with indeterminate FNAB to prevent unnecessary diagnostic surgery. Additional cassettes are used to detect the molecular signatures of specific neoplasms that further alter patient care. An MTC classifier cassette is included in the GSC to provide additional preoperative clinical information in a single test. Here we report the clinical performance of the MTC classifier integrated into the GSC.

METHODS

Algorithm training was performed with a set of 483 FNAs (21 MTC and 462 non-MTC) [Table 1A].

TABLE 1A.

Non-MTC Cohort	Bethesda III	Bethesda IV
ENHANCE Arm1	208	75
ENHANCE Arm2	50	14
Cytol GECB	111	
Parathyroid	3	1

MTC Cohort	Bethesda III	Bethesda IV	Bethesda V	Bethesda VI
ENHANCE Arm1	2	1	0	0
MTC*	3	5	6	4

An additional 97 tissues were used in feature selection, but not model training (Table 1B).

TABLE 1B.

Cohort	Non-MTC	MTC
MTC*	0	21
Parathyroid	21	0
Hurthle Tissue	25	0
Tissue	30	0

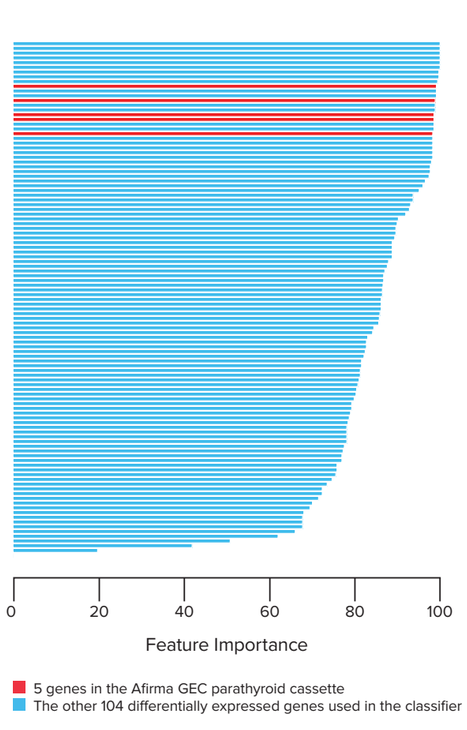
*All MTC samples had clinical/surgical confirmation of MTC.

A support vector machine (SVM) classifier was developed using 108 differentially expressed genes, which includes the five genes in the Afirma GEC medullary thyroid cassette (Figure 1).

FIGURE 1:

Feature Selection

108 differentially expressed 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 MTC cassette are highlighted in red in this figure.



RESULTS

The final classifier was blindly tested on 211 independent FNAs, which included 21 MTC and 190 non-MTC from benign and malignant neoplasms. The classifier had 100% sensitivity [21/21 MTC FNAs correctly called positive; CI = 83.9-100%] and 100% specificity [190/190 non-MTC FNAs correctly called negative; CI = 98.1- 100%] (Table 2). All positive samples had clinical/surgical confirmation of MTC, while all negative samples were negative for MTC on surgical pathology.

TABLE 2:

Validation Results

		Truth Label*	
		MTC	Non-MTC
MTC Classifier	Positive	21	0
	Negative	0	190

Sensitivity	Specificity
100% (83.9-100%)	100% (98.1-100%)

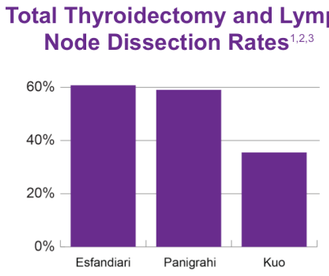
*All positive samples have clinical/surgical confirmation of MTC, while all negative samples were negative for MTC on surgical pathology.

CONCLUSIONS

The accurate preoperative genomic identification of MTC usually alters patient care by solidifying the need for timely, more thorough surgery, and necessitating MTC specific preoperative evaluations, including screening for concomitant pheochromocytoma and primary hyperparathyroidism (Figure 2).

FIGURE 2:

Surgery Rates for Patients with MTC



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Veracyte speakers honoraria: KP, PL, MS; Veracyte consultant: PL, RG, PS, VL; Veracyte institutional research support: PL, MS; Veracyte equity owner: RK, JK, JH, SW, NB, JB, SK,UI, DW, TT