The Genomic Landscape of Preoperative FNAs positive for the Afirma GSC Medullary Thyroid Cancer Classifier

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BACKGROUND

The Afirma Genomic Sequencing Classifier (GSC) uses RNA sequencing to assess FNA specimens from cytologically indeterminate thyroid nodules, which are also tested for specific molecular aberrations associated with thyroid cancer via a suite of highly accurate malignancy classifiers (figure 1). The suite can also be applied independently to Bethesda VI nodules. The Afirma Xpression Atlas (XA) (figures 1 and 2) is a RNA sequencing-based add-on test that reports expressed nucleotide variants and fusions across 511 cancer-associated genes (figure 3), when added to Afirma GSC and/or malignancy classifiers.

Medullary thyroid cancer (MTC) is a rare subtype of thyroid cancer that can appear in any Bethesda category. Previously, the Afirma MTC classifier demonstrated 100% sensitivity and specificity among 201 FNA samples that included 21 MTC.1 Herein, we report the prevalence and expression of all variants and fusions among 511 cancer cases. Using RNA sequencing, Afirma Xpression Atlas reports expressed genomic variants and fusions among 511 genes. Therapies targeting some of these alterations are available or under investigation.

METHODS

All Afirma GSC and malignancy classifier tests run in the Veracyte Clinical Laboratory between July 2017 and November 2018. Examination of 22,130 FNAs revealed 77 MTC+ cases. Among consecutive Afirma GSC tests, 28 were Bethesda III/Iv (30% out of 942), 22 ordered FNA tests were done on an additional 4 and 8 MTC cases from Bethesda V and VI nodules, respectively. Examining all MTC cases revealed that 55.8% harbored a variant or fusion (figure 3).

RESULTS

Among consecutive Afirma GSC tests, 28 were Bethesda III/Iv (30% out of 942) and 27 were Bethesda IV (65% out of 942). Provider-ordered Afirma testing was done on an additional 4 and 8 MTC cases from Bethesda V and VI nodules, respectively. Examining all MTC cases revealed that 55.8% harbored a variant or fusion (figure 3).

CONCLUSIONS

In indeterminate FNA samples, the Afirma GSC can help to clarify the risk of MTC. In our cohort of Bethesda III-VI MTC+ FNAs, the Afirma XA identified a variant or fusion in 74.0%. Limitations of this study include the lack of knowledge regarding germline RET status (which should be checked in all patients with an identified RET variant or confirmed MTC) and final pathology on MTC+ samples. Future studies may investigate how the preoperative identification of a known MTC driver mutation in a biopsy sample can inform the pre-operative evaluation, the surgical plan, and the potential role of targeted therapy (figures 1 and 3).

REFERENCE