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 pre-operative clinical information in a single test. Here we report the clinical performance of the MTC classifier integrated into the GSC.

Methods / Case Presentation: Algorithm training was performed with a set of 483 FNAs (21 MTC and 462 non-MTC). An additional 97 tissues were used in feature selection, but not model training. 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.
**Results / Discussion:** 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%]. All positive samples had 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.