Short Call Oral 6

Thyroid Nodules & Goiter Saturday Oral Clinical 9:05 AM

Development and Validation of Classifiers to Enhance the Afirma Genomic Sequencing Classifier Performance Among Hürthle Cell Specimens

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Introduction: Most Hürthle cell dominant Bethesda III+IV thyroid nodules undergo diagnostic surgery, yet most are histologically benign. The Gene Expression Classifier (GEC) provided these samples a high NPV, but most were GEC suspicious. To maintain a high NPV while providing more benign results, we built two dedicated classifiers to work with the core Genomic Sequencing Classifier (GSC), which uses RNA sequencing and machine learning algorithms to identify benign nodules preoperatively with overall 91.1% sensitivity and an improved 68.3% specificity.

Methods: A Hürthle cell classifier was developed using 1,408 nuclear and mitochondrial genes to differentiate Hürthle cytology specimens (H+) from non-Hürthle specimens (H-). A

separate Hürthle neoplasm classifier was developed using 2,041 genes and a chromosome-level loss-of-heterozygosity statistic built from 189,731 genomic variants to differentiate Hürthle neoplastic specimens (N+) from non-neoplastic Hürthle specimens (N-), only among H+ specimens. H+N+ and all H- specimens are subject to the canonical GSC cutoff, while an adjusted threshold is used only for H+N- specimens. We applied this process in a blinded fashion to the prospective, multicenter, and blinded Bethesda III+IV samples that originally validated the GEC, of which 191 had sufficient remaining RNA.

Results: 1 MTC, 3 BRAF V600E+ PTC, and 1 with inadequate follicular cell content were identified by upstream classifiers, leaving 186 specimens for GSC core classifier testing, of which 37 (20%) resulted H+; among these, 16 were classified as Hürthle non-neoplastic (N-). Among these H+N- specimens, 9 (56%) had canonical benign GSC scores and would result GSC benign by either threshold. However, the Hürthle-adjusted threshold rescued the other 44% to a benign result. Among the 26 Hürthle cell adenomas and carcinomas, the final GSC sensitivity for malignancy identification was 88.9%, and the specificity to identify benign lesions was 58.8%, a 47% absolute improvement of specificity above the previous GEC.

Conclusion: The improved overall GSC specificity results from improvements among both Hürthle and non-Hürthle Bethesda III+IV specimens. GSC testing of both Hürthle and non-Hürthle nodules may safely reduce unnecessary diagnostic surgery.