**Objective**

Molecular testing of thyroid nodules with indeterminate fine-needle aspiration (FNA) cytology is increasingly used to inform patient management. Recently, a prospective, blinded, multicenter clinical validation study of ThyroSeq v3 Genomic Classifier (GC) was performed, although the experience with the routine utilization of this test has not been reported.

**Methods**

ThyroSeq v3 GC is based on next-generation sequencing of DNA and RNA, testing for >12,000 DNA variants, >120 gene fusions, and multiple copy number alterations (CNA) and gene expression alterations (GEA). We performed data analysis of the first 3,783 consecutive FNA samples with indeterminate cytology tested by ThyroSeq v3 GC from November 1, 2017 to March 1, 2018.

**Results**

During the 4-month period, 3,783 samples were tested including 3,081 (81%) from nodules with Bethesda III-V cytology, 567 (15%) Bethesda IV, and 135 (4%) Bethesda V cytology. Of those, 74 (2%) were canceled due to an insufficient amount of cells, and 125 (3%) were negative but had an inadequate proportion of thyroid cells. Among the remaining 3,584 (95%) fully informative samples, 62% yielded a 'negative' and 38% a 'positive' test result. The latter included 25 (0.7%) samples positive for parathyroid and 5 (0.14%) for medullary thyroid carcinoma markers. Among 1,348 test-positive nodules of follicular thyroid-cell origin, 74 (5.5%) had a high risk molecular profile (TERT or TP53 mutations coexisting with other mutations or alone), 224 (16.6%) BRAF V600E-like mutations/fusions, 730 (54.2%) RAS-like mutations/gene fusions, 192 (14.2%) CNA and 64 (4.7%) GEA.

**Conclusion**

In this large consecutive series of indeterminate cytology nodules, ThyroSeq v3 GC demonstrated:
- 62% (59/97) rate of sample adequacy for testing
- 62% of test-negative cases with expected low residual cancer risk, so that diagnostic surgery may be avoided in most of these patients
- Among test-positive cases, interpretation of genetic findings with assigned cancer probability and risk of recurrence may inform more individualized management of these patients.