The Majority of Non-Diagnostic (Insufficient) Thyroid Nodule Cytology Samples Can Effectively Undergo Molecular (Combined Mutational and MicroRNA Classifier) Analysis Using a Needle Aspiration Approach

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BACKGROUND

- Non-diagnostic cytology (NDC) (Bethesda I) occur in 5-20% of thyroid nodule fine needle aspirates (FNAs)[1], often resulting in repeat FNAs and increasing healthcare costs.
- The NDC topic tends to be overlooked but is potentially addressable by molecular analysis.

AIM

- To determine if mutational change testing and microRNA (miR) classifier testing can improve diagnostic yield of FNA samples that are NDC (Bethesda I).
- To understand the overall true non-diagnostic rate of mutational change testing and miR classifier testing.

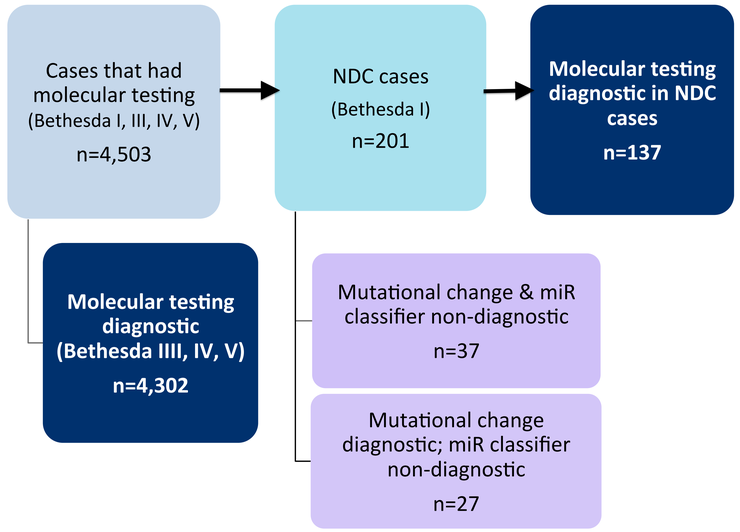
METHODS

- We reviewed 4,503 consecutive thyroid nodule needle aspirates submitted for combined NGS- mutation (ThyGenX) and miR expression (ThyraMIR) classifier analysis correlated with cytology diagnosis.

Table 1: Panels for NGS mutational change and microRNA expression classifier

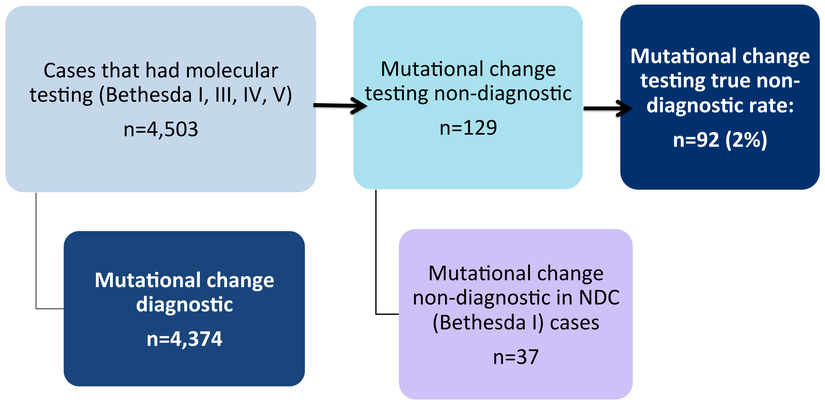
Next Generation Sequencing Mutational Change Panel	
BRAF	BRAF_V600E, BRAF_K601E, BRAF_A598V
HRAS	HRAS_G12V, HRAS_G13R, HRAS_Q61K, HRAS_Q61L, HRAS_Q61R
NRAS	NRAS_G12D, NRAS_G13R, NRAS_Q61R, NRAS_Q61K, NRAS_Q61P
KRAS	KRAS_G12D, KRAS_G12V, KRAS_G13D, KRAS_Q61R
PIK3CA	PIK3CA_E542K, PIK3CA_H1047L, PIK3CA_H1047R
RNA Fusion Transcripts	RET-PTC1
	RET-PTC3
	PAX8-PPARɣ
MicroRNA (MiR) classifier panel	
Down-regulated	miR-204-5p, miR-139-5p, miR-29b-1-5p, miR-155-5p, miR-138-1-3p
Up-regulated	miR-375, miR-551-b-3p, miR-146b-5p, miR-31-5p, miR-222-3p

Figure 1: Schematics of thyroid nodule FNAs that underwent molecular testing, including those with Non-diagnostic cytology (NDC) results (NDC, Bethesda I)



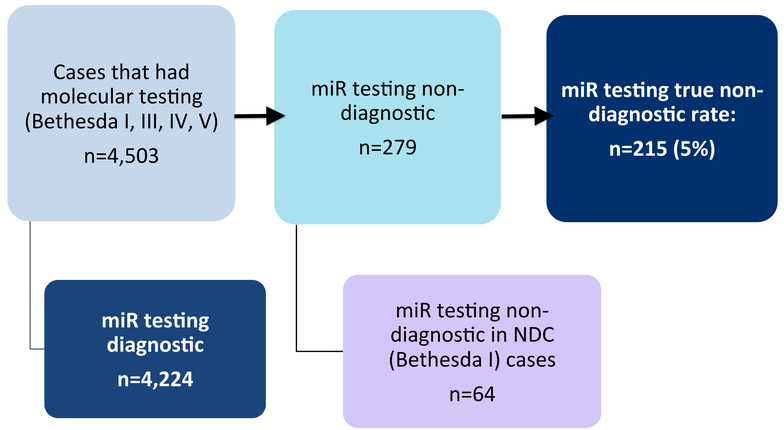
- 4,302/4,503 (96%) of all FNAs were diagnostic by molecular testing.
- 201/4,503 (5%) FNAs were non-diagnostic by cytology (NDC, Bethesda class I).
- 137/201 (68%) NDC cases (Bethesda I) had diagnostic molecular testing.
- The remaining 64/201 NDC cases (32%) failed miR testing with 37 (18.4%) also failing mutational change testing.

Figure 2: Schematic diagram of Rate of non-diagnostic NGS mutational change test results



- 4,374/4,503 (97%) cases had diagnostic mutational change test results.
- Only 129/4,503 cases had non-diagnostic mutational change test results.
- When NDC (Bethesda I) cases were excluded, the true non-diagnostic rate of mutational change testing was only 2%.

Figure 3: Schematic diagram for the rate of non-diagnostic miR test results



- 4,224/4,503 (94%) cases had diagnostic miR testing
- 279/ 4,503 (6.2%) cases failed miR testing
- When NDC (Bethesda I) cases were excluded, the true non-diagnostic rate of miR testing was only 5%.

CONCLUSIONS

- Combined mutational change and miRNA classifier molecular testing of thyroid nodules has very high diagnostic yield, similar to that observed for cytology (95%).
- Such molecular testing can provide diagnostic information for cases (68%) where cytology results are insufficient or non-diagnostic (NDC, Bethesda I).
- The ability of molecular testing to increase the diagnostic yield of an FNA specimen can help to avoid repeat FNA procedures.

REFERENCES

1. Alexander EK et al. J Clin Endocrinol Metab. 2002 Nov;87(11):4924-7