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Risk of Structural Disease Recurrence Reclassification of Differentiated Thyroid Cancer from 2015 to 2025 American Thyroid Association (ATA) Guidelines

JANE ZWEIBACH,[1] CATHERINE EKLADIOS,[1] KARA KONO,[1] PATRICIA TRAN,[1] TAYLOR B. CAVAZOS,[2] MOHAMMED ALSHALALFA,[2] JOSHUA P. KLOPPER,[2] AMY S. CHANG,[1]

1. Scripps Clinic Medical Group, Division of Diabetes & Endocrinology, La Jolla, CA. 2. Veracyte, Inc., South San Francisco, CA.

CONTACT: EUGENIA.ZWEIBACH@HOAG.ORG

INTRODUCTION

- The 2025 American Thyroid Association (ATA) Thyroid Cancer guidelines subdivided the 2015 intermediate risk of recurrence group into low-intermediate (L-I) and intermediate-high (I-H) groups and incorporated histologic specific categories.
- Thyroid cancers in a 2015 risk category may be assigned to a different 2025 category based on these changes.
- The Afirma Genomic Sequencing Classifier (GSC) utilizes whole-transcriptome-derived RNA sequencing as the test platform providing a wealth of mRNA data for every sample analyzed.

AIM

The aim of this study was to evaluate demographic and genomic differences in cancers recategorized from 2015 to 2025 ATA risk of structural recurrence categories.

METHODS

- A retrospective, single-center study of thyroid cancer cases that underwent Afirma Genomic Sequencing Classifier testing as part of routine clinical care.
- Each case was assigned 2015 and 2025 ATA risk of recurrence labels.
- Cases that shifted categories were compared with those that remained stable.
  - Most shifts were from the 2015 ATA low risk category; therefore, it was used as the reference for demographic and molecular differences.
  - ATA 2025 I-H and high samples were combined for analysis.
- Expressed molecular variants and fusions and differences in Afirma Genomic Resource for Intelligent Discovery (GRID) data were evaluated.
- Statistical analyses utilized the Mann-Whitney U Test for three pairwise group comparisons across 35 GRID signature pathways: 2015/2025 ATA low vs. 2025 L-I, 2015/2025 ATA low vs. 2025 I-H, and 2025 I-L vs. 2025 I-H. Fisher's exact test was used to assess differences in categorical demographic variables, while the Kruskal-Wallis test was used for continuous variables.

RESULTS

- Seventy-two cases were classified using ATA 2025 criteria: 26 low, 19 L-I, 16 I-H, and 11 high (Table 1):
  - Of the 3 cancers that were 2015 ATA high risk, all 3 remained high risk by 2025 classification (Figure 1).
  - Of 45 ATA 2015 low risk cancers, only 25 remained low risk in 2025, while 15 shifted to L-I, 3 to I-H, and 2 to high risk (Figure 1).
- Average tumor size increased across 2025 risk strata (p=NS, Table 2):
  - Low (1.7 cm) to L-I (2.05 cm) to I-H/high (3.02 cm).
  - No significant differences were seen in age, sex, or Bethesda category between groups.
- There were no significant differences in the proportion of expressed variants and fusions (by Afirma Xpression Atlas (XA)) between cancers that remained low risk from 2015->2025 and those that were reclassified to a higher risk category in 2025 (Table 3).
- Analysis of Afirma GRID molecular hallmarks of cancer showed a trend for linear decreases in Immunomodulatory signature signaling and Apical surface hallmark while there was a linear increase in Angiogenesis hallmark signaling from 2025 ATA low to ATA I-H/high groups (p = 0.1, Figure 2).

TABLE 1

ATA Risk of recurrence categories: Correlation of 2015 to 2025 categorization

		2025 ATA Risk				
		Low	Low-Intermediate	Intermediate-High	High	Totals
2015 ATA Risk	Low	25	15	3	2	**45**
	Intermediate	0	3	10	5	**18**
	High	0	0	0	3	**3**
	Totals	**25**	**18**	**13**	**10**	

FIGURE 1

Sankey diagram illustrating shifts in ATA risk classification between the 2015 and 2025 Guidelines

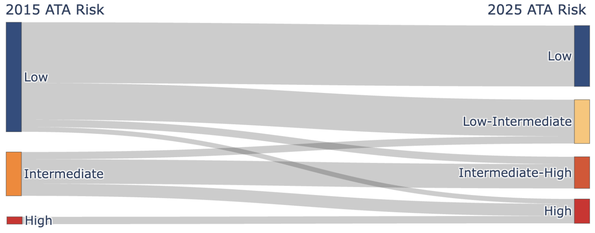


TABLE 2

Demographics – no significant differences were seen across groups

Demographics		Low in 2015 & 2025	Low-intermediate in 2025	Intermediate-High / High in 2025
N		25	15	5
Nodule Size	Mean [Q1, Q3]	1.70 [1.20, 2.00]	2.05 [1.05, 3.05]	3.02 [2.15, 3.58]
Age at surgery	<55	16 (64.0%)	7 (46.7%)	4 (80%)
	>55	9 (36.0%)	8 (53.3%)	1 (20%)
Sex	Female	17 (68.0%)	11 (73.3%)	4 (80%)
	Male	8 (32.0%)	4 (26.7%)	1 (20%)
Bethesda classification	III/IV	16 (64.0%)	14 (93.3%)	4 (80%)
	V/VI	9 (36.0%)	1 (6.7%)	1 (20%)

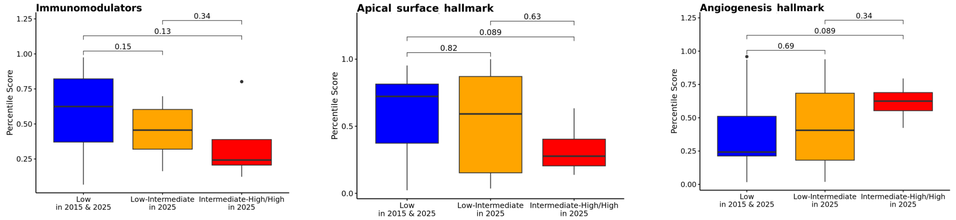
TABLE 3

Proportion of Afirma Xpression Atlas (XA) variants and fusions by ATA risk category — no significant differences were seen across groups

XA result	Low in 2015 & 2025 (N=25)	Low-Intermediate in 2025 (N=15)	Intermediate-High / High in 2025 (N=5)
Any XA variant	12 (48%)	5 (33%)	2 (40%)
BRAF:p.V600E	6 (40%)	2 (13%)	1
KRAS:p.Q61R	0	1	0
SPOP:p.P94R	0	1	0
NRAS	4 (16%)	1	1
HRAS	2 (8%)	0	0
Any XA fusion	3 (12%)	0	1
ALK::EML4	0	0	1
ALK::TG	1	0	0
CCDC6::RET	1	0	0
ETV6::NTRK3	1	0	0

FIGURE 2

Afirma GRID molecular hallmarks across ATA risk categories



CONCLUSIONS

- When reassessed using the 2025 ATA criteria, a substantial proportion of cases originally classified as low risk in 2015 were reassigned to higher risk categories.
  - This shift was not explained by differences in commonly expressed variants or gene fusions, suggesting genomic signals identified by GRID may inform a molecular basis for reclassification.
- These findings provide biologic support for the 2025 ATA risk classification by showing that their refined clinical categories likely correspond to underlying genomic differences.
  - Our results suggest that the 2025 ATA criteria, although developed from clinicopathologic data, may reflect distinct molecular profiles that were previously unrecognized.
- Larger, multi-institutional studies are warranted to increase sample size and power to validate these observations and define their prognostic utility.