

The utility of combined mutations and microRNA expression profiling in assessing cancer risk in thyroid nodules

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OBJECTIVE:

- To correlate real-world results of
 - Bethesda (BDC) classification
 - Mutation panel (ThyGENX™)
 - Two-tiered (positive, negative) miRNA classifier (ThyraMIR™)
- To examine the projected real-world absolute risk of cancer of BDC III and BDC IV nodules given mutation panel and miRNA classifier results¹

METHODS:

- 3,472 patients clinically tested by mutation panel and miRNA classifier were reviewed
- Two additional miRNA thresholds, defining a four-tiered approach (Tier 1-4), were determined based on the miRNA score in nodules with known disease status
- Projected absolute risk of cancer at variable cancer probabilities was calculated using Bayes Theorem based on the performance of the mutation panel and miRNA classifier in a previously described study cohort of cytologically indeterminate (BDC III or IV) nodules with surgically confirmed benign or malignant outcomes¹

Table 1. Association between Bethesda categories and individual mutations present in thyroid nodules among entire cohort of patients

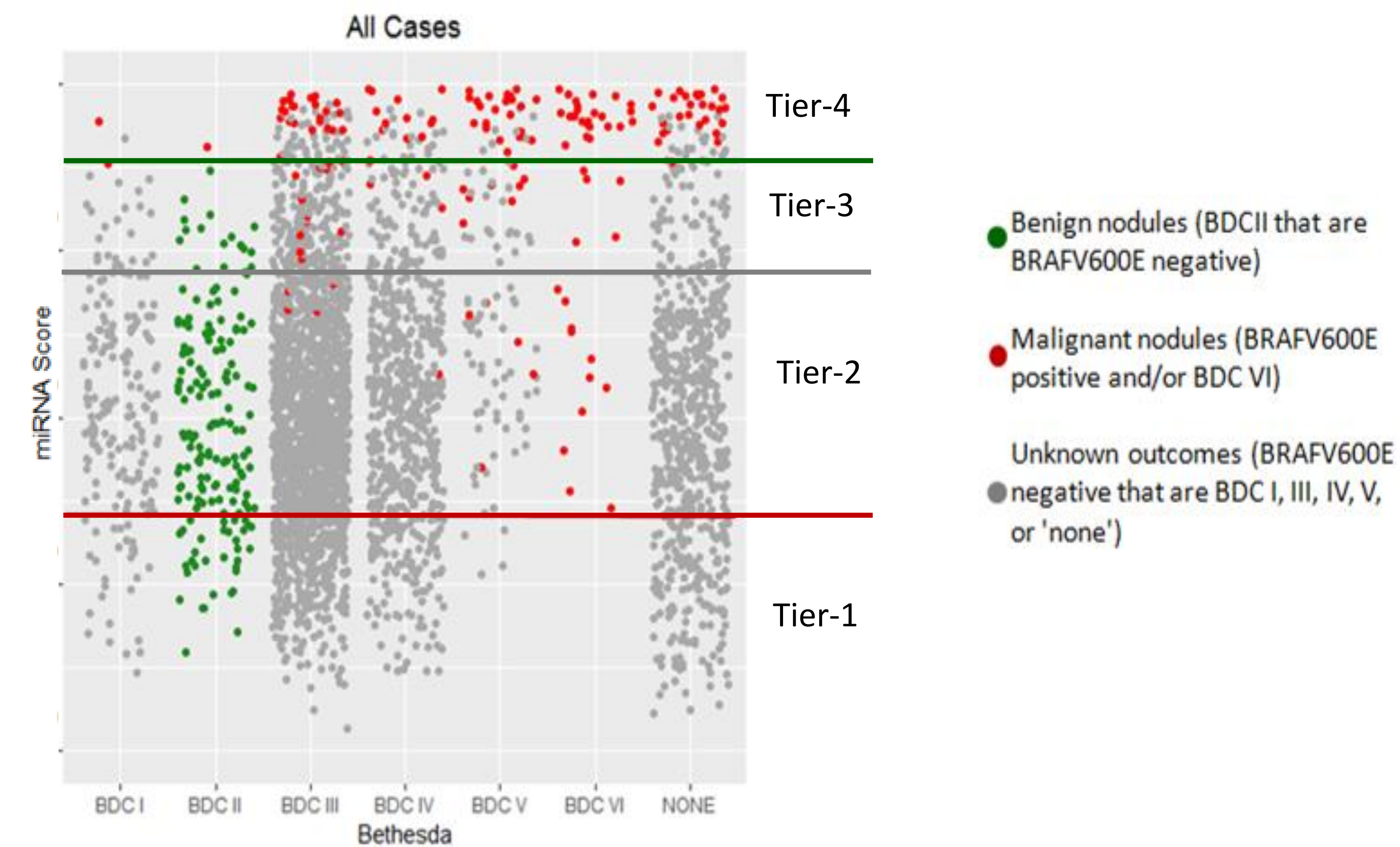
Bethesda Class	n	No Mutation	CCDC6/RET	NCOA4/RET	PAX8/PPARG	PIK3CA	RAS	BRAF X	BRAF (V600E)
NONE	631	86%	-	-	0.2%	-	9%	0.5%	4%
BDC I	188	96%	-	-	-	-	3%	-	1%
BDC II	166	92%	-	-	-	-	8%	-	0.6%
BDC III	1706	80%	0.2%	0.1%	0.8%	0.1%	16%	0.4%	2%
BDC IV	625	78%	0.2%	0.2%	1%	0.2%	16%	1%	3%
BDC V	116	51%	-	-	-	0.9%	17%	0.9%	30%
BDC VI	40	55%	-	-	-	-	3%	-	43%
Total	3472	81%	0.1%	0.1%	0.6%	0.1%	13%	0.5%	4%

BRAF K601E and BRAF A598V ("BRAF X")

- RAS mutation occurred in 8% of BDC II nodules, 16% of BDC III and IV nodules, only 3% of BDC VI nodules
- 43% of BDC VI nodules had BRAF V600E mutation
- 55% of BDC VI nodules lacked any detectable mutational change
- All other mutations occurred infrequently (<1%)

References: 1. Labourier, et al. doi: 10.1210/jc.2015-1158.

Figure 1. miRNA score according to Bethesda classification (BDC) in all thyroid nodules that were benign, malignant or had unknown outcomes independent of mutation panel



- 100% specificity achieved at threshold (green line) above the highest miRNA score clinically observed for benign nodules and above the miRNA threshold previously reported (grey line)¹
- 100% sensitivity achieved at threshold (red line) below the lowest miRNA score clinically observed for malignant nodules and below the miRNA threshold previously reported (grey line)¹
- Four-Tier miRNA approach (Tier 1-4), given three defined thresholds

CONCLUSIONS:

- Mutational change is not sufficient to risk stratify thyroid nodular disease unless accompanied by attention to clinical, imaging and additional molecular findings
- miRNA classification complements cytology and mutation analysis with the capacity to better predict biological aggressiveness
- Results support our previous conclusions¹ regarding the performance of combination mutation panel and miRNA classifier testing in a large cohort of patients tested clinically
- We extend our past results to include a four-tier miRNA approach that further improves sensitivity and specificity for malignancy, which in turn further improves the predictive value of combination mutation panel and miRNA classifier testing
- Importantly, use of the miRNA classifier stratifies cancer risk in patients with RAS mutations and in those who lack all mutations, providing opportunities to personalize patient care

Figure 2. Absolute risk of malignancy in BDC III nodules given mutation panel, the two-tiered miRNA classifier approach¹, and the four-tiered (Tier 1-4) miRNA classifier approach shown in Figure 1

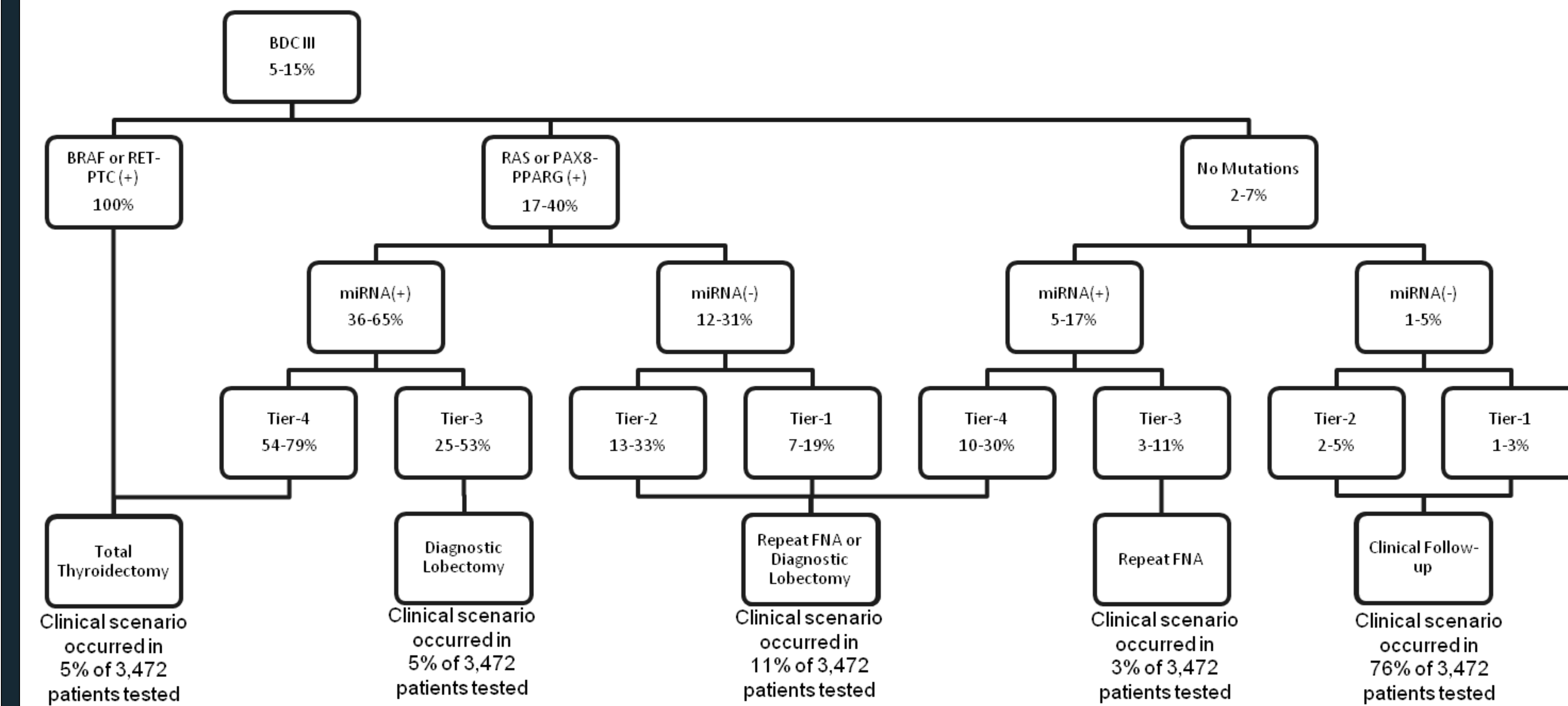


Figure 3. Absolute risk of malignancy in BDC IV given mutation panel, the two-tiered miRNA classifier approach¹, and the four-tiered (Tier 1-4) miRNA classifier approach shown in Figure 1

