# B-19

## Classifying and Grading Archived Gastrointestinal Neuroendocrine Tumors Through microRNA Sequencing

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**BACKGROUND:** Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) are clinically diverse neoplasms that are challenging to classify and grade. microRNAs (miRNAs) are small RNA molecules that are excellent biomarkers due to their abundance, cell-type- and disease stage-specificity, and stability in fresh and archived clinical samples. Due to their diagnostic utility in most cancers, we hypothesized that miRNAs are also valuable classificatory markers in GEP-NETs.

**METHODS:** Using quantitative barcoded small RNA sequencing and state-of-the-art sequence annotation, we generated comprehensive miRNA expression profiles from archived pancreatic, ileal, appendiceal, and rectal neuroendocrine tumors. Following data preprocessing, we randomly assigned sample profiles to discovery (80%) and validation (20%) sets prior to data mining using machine-learning techniques.

**RESULTS:** High expression analyses indicated that miR-375 was the most abundant individual miRNA and miRNA cistron in all GEP-NETs. Leveraging prior knowledge that GEP-NET behavior is influenced by embryonic derivation, we developed a dual-layer hierarchical classifier for differentiating GEP-NET types. In the first layer, our classifier discriminated midgut (ileal, appendiceal) from non-midgut (rectal, pancreatic) NETs based on miR-615 and -92b expression. In the second layer, our classifier discriminated ileal from appendiceal NETs

based on miR-125b, -192, and -149 expression, and rectal from pancreatic NETs based on miR-429 and -487b expression. Our classifier achieved accuracies of 98.5% and 94.4% in discovery and validation sets, respectively. We also provide provisional evidence that low- and intermediate-grade pancreatic NETs can be discriminated based on miR-328 expression.

**CONCLUSION:** GEP-NETs can be reliably classified and potentially graded using miRNA markers, complementing morphological and immunohistochemistry-based diagnostic approaches. We have extended the current study to include NETs from many different anatomic sites.