Paired DNA/RNA genetic testing to uncover a cryptic *PTEN* pathogenic variant (PV) associated with diffuse colonic ganglioneuromatosis

Dong Kim, Michelle McSweeny, Demitrios Dedousis, Yana Chertock, Marcy Richardson, Michael J Hall

BACKGROUND
Phosphatase and tensin homolog (PTEN) hamartoma tumor syndrome (PTHS) is a family of related genetic disorders including Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba Syndrome (BRRS), adult Lhermitte-Duclos disease and Proteus syndrome (PS). Germline PTEN PVs remain unidentified in many individuals and families, including 40% of individuals with a clinical diagnosis of BRRS, 80% with PS, and 15% with classic CS. While it's conceivable that non-PTEN PVs underlie these cases, standard DNA testing may also miss clinically relevant PTEN PVs detectable by comprehensive testing including RNA analyses.

METHODS
A 64 year-old woman with history of breast cancer (age 42 and 53) and prior thyroidectomy for multiple thyroid nodules and papillary thyroid cancer was referred for genetic counseling following abnormal screening colonoscopy which showed extensive ganglioneuromatosis in the colon and rectum. No hamartomas were identified. EGD was normal. She denied past personal or family history of gastrointestinal (GI) abnormalities. On physical exam, she was macrocephalic (59.5 cm), and had tongue papules, facial lesions (possibly trichilemmomas), and acrochordons in the axillae bilaterally.

RESULTS
DNA and RNA testing via the Ambry CancerNext-Expanded Panel with RNAInsight was offered. Initial germline molecular analysis was negative, but RNA testing identified a deep intronic PV at c.209+2047A>G. This variant results in alternative splicing of the PTEN protein product. This result has led to an ongoing retrospective collaborative study of prevalence of deep intronic variants in the PTEN gene detected by RNA analysis and their association with GI-associated and non-GI manifestations of germline PV in the PTEN gene including CS and BRRS. Preliminary results will be presented at CGA-IGC 2024.

CONCLUSIONS
Intronic PTEN PVs missed by DNA sequencing but detectable by RNA analysis explain a currently uncertain portion of negative results in patients manifesting phenotypic features of and/or meeting clinical criteria for CS and other PTEN-associated disorders.