Comparison of clinical features in *PTEN* positive patients ascertained by single-gene testing versus hereditary cancer multi-gene panel testing

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PTEN hamartoma tumor syndrome (PHTS)/Cowden syndrome (CS) is a phenotypically diverse but well-described clinical condition. Historically, *PTEN* analysis has been performed in patients with clinical histories suggestive of CS/PHTS. However, with hereditary cancer multi-gene panel testing, *PTEN* analysis is being performed in patients with clinical histories suspicious for a hereditary cancer predisposition syndrome, but not specific to CS/PHTS. We sought to describe differences in clinical histories of patients found through *PTEN* single-gene versus multi-gene testing to harbor a pathogenic or likely pathogenic *PTEN* alteration, and to explore possible reasons for these differences.

Molecular results for 32,093 patients who had *PTEN* sequencing and deletion/duplication analyses at our diagnostic laboratory were reviewed. Overall, 173 patients (0.5%) were positive for a pathogenic or likely pathogenic alteration ("*PTEN* positives"), with 113 (65%) ascertained by single-gene testing (N=2,632) and 60 (35%) by multi-gene testing (N=29,461). Retrospective test requisition review was performed to identify patients meeting CS/PHTS diagnostic or clinical testing criteria (NCCN Guidelines Version 2.2014; GeneReviews® [Updated 2014 Jan 23]) and to define clinical features in these patients.

Significantly more *PTEN* positives were identified in the single-gene cohort (4%) than in the multi-gene cohort (0.2%) (2-sample test for equality of proportions, $p<0.001$). Clinical history was provided for 160 *PTEN* positives, of which 72 patients (45%) met criteria. Nearly two-thirds (64%) of the *PTEN* positives ascertained by single-gene testing met criteria, compared with 12% of those ascertained by multi-gene testing ($p<0.001$).

As expected, the most frequently reported features in the 160 patients with clinical history available were macrocephaly, breast cancer, and gastrointestinal (GI) hamartomas, present in 45%, 43%, and 13% of patients, respectively. Macrocephaly and GI hamartomas were both reported in significantly more single-gene patients than multi-gene patients ($p<0.001$). Breast cancer was reported in significantly more multi-gene than single-gene patients ($p<0.001$). Furthermore, breast cancer was the sole CS/PHTS feature reported in 16% of patients and was the sole feature in significantly more multi-gene than single-gene patients (36% vs. 5%, $p<0.001$). Autism was reported in 4% of patients, accounting for 4% of single-gene and 2% of multi-gene patients.

These findings reveal significant differences in clinical features reported in patients undergoing single-gene testing for *PTEN* versus those undergoing hereditary cancer multi-gene testing. Patients undergoing multi-gene testing due to cancer history may not be evaluated for some features of CS/PHTS, such as macrocephaly and autism. It is surprising that GI hamartomas were only reported in 3% of multi-gene patients, as this feature would likely be assessed in a cancer genetics evaluation. Similarly, patients undergoing single-gene testing for autism and macrocephaly may not be evaluated for cancer family history. Clarifying these clinical histories may reveal additional patients meeting CS/PHTS criteria.

These findings also suggest that breast cancer alone warrants a targeted clinical exam for CS/PHTS, including an accurate head circumference measurement. Furthermore, of the 88 patients with clinical history provided but not meeting CS/PHTS criteria, 1 in 5 (20%) reported no CS/PHTS-specific features. Based on clinical histories provided and current diagnostic and clinical testing criteria, over half

(51%) of our *PTEN* positive cohort would have been missed. Our findings support the need for more comprehensive exam of patients presenting with any single feature suggestive of CS/PHTS, including breast cancer. Further investigation is needed to determine whether differences between patients ascertained by single-gene versus multi-gene testing simply reflect incomplete histories obtained by the clinician, incomplete information provided to the lab, or if differences reflect limitations in current CS/PHTS diagnostic and clinical testing criteria.