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Further Defining the Polyposis Phenotype Associated with *PTEN* Mutations

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BACKGROUND

- *PTEN* hamartoma tumor syndrome (PHTS) is associated with an increased risk for malignancies of the breast, thyroid, and endometrium. More recently renal cell carcinoma and melanoma have also been associated with the disease.
- Colonic polyposis, particularly hamartomatous polyps and ganglioneuromas, is a known feature of *PTEN* carriers. The extent of polyposis in these individuals and related colon cancer risk is poorly described.
- Recent literature suggests that *PTEN* carriers may have a more diverse colonic polyp presentation. [1, 2]

TABLE 1: POLYPOSIS CONDITIONS, CURRENT KNOWLEDGE

Syndrome/Gene(s)	Inheritance[1]	Polyp Type(s)	Cancers & Characteristics
Familial adenomatous polyposis (FAP), *APC*	AD	Adenoma	Colorectal, duodenal, pancreatic, thyroid, liver, CNS
MUTYH-associated polyposis (MAP)	AR	Adenoma	Colorectal, breast
Peutz-Jeghers syndrome, *STK11*	AD	Peutz-Jeghers type	Small bowel, colorectal, breast, ovarian, pancreatic, hyperpigmentation
Juvenile polyposis, *SMAD4* & *BMPR1A*	AD	Juvenile type	Colorectal, stomach, pancreatic, possible hereditary hemorrhagic telangiectasia
PTEN-hamartoma tumor syndrome (Cowden syndrome)	AD	Hamartoma, ganglioneuroma	Breast, thyroid, uterine, colorectal, kidney, cutaneous lesions, macrocephaly, Lhermitte-Duclos disease

[1]AD, autosomal dominant; AR, autosomal recessive

METHODS

- We sought to define the polyp spectrum amongst *PTEN* mutation carriers identified by multi-gene panels.
- Over 14,000 results of five multi-gene panels (BRCAplus, BreastNext, ColoNext, OvaNext, and CancerNext) that include full gene sequencing and gross deletion/duplication analyses of *PTEN* that resulted between March 2012 and March 2014 were reviewed.
- Clinical histories provided by ordering clinicians were reviewed, and clinicians were contacted to confirm history. *Note: Family history of polyposis was not assessed.*

TABLE 2: *PTEN* POSITIVE POLYP HISTORY

Age of 1st Polyp Diagnosis[1]	Polyp Type and Number[1]	Additional Polyp Information
45	Adenoma (7)	Inflammatory (2), Hyperplastic (4), Lipoma (1)
47	Adenoma (20-99)	Hamartoma (20-99)
49	Unk (>100)	n/a
52	Adenoma (20-99)	n/a
58	Hamartoma (10-19)	n/a
66	Adenoma (>100)	n/a
Unk	Adenoma (2-5)	'Mucosal' (Up to 50)
Unk	Unk (20-99)	n/a
Unk	Unk (few)	n/a
Unk	Adenoma (Unk)	n/a
Unk	Unk (2)	n/a

[1] Unk, unknown/unreported information

SUMMARY OF *PTEN* POSITIVE CASES

Twenty-three *PTEN* positive cases were identified in this cohort.

- 11/23 (47.8%) had a reported personal history of colon polyps of varying type and quantity (Table 2).
- Three of these patients met classic or attenuated FAP criteria by having >20 adenomatous polyps; 3 others had >20 polyps of an unspecified type.
- 10/11 patients were female.

The 23 *PTEN* positives were identified on five different multi-gene panels (Figure 1).

- BRCAplus (6 genes): 6/23 mutations (26.1%)
- BreastNext (16-18 genes): 5/23 mutations (21.7%)
- CancerNext (24-28 genes): 5/23 mutations (21.7%)
- ColoNext (14 genes): 5/23 mutations (21.7%)
- OvaNext (19-23 genes): 2/23 mutations (8.7%)

FIGURE 1: PERCENT OF *PTEN* POSITIVES DETECTED ON EACH PANEL (N=23)

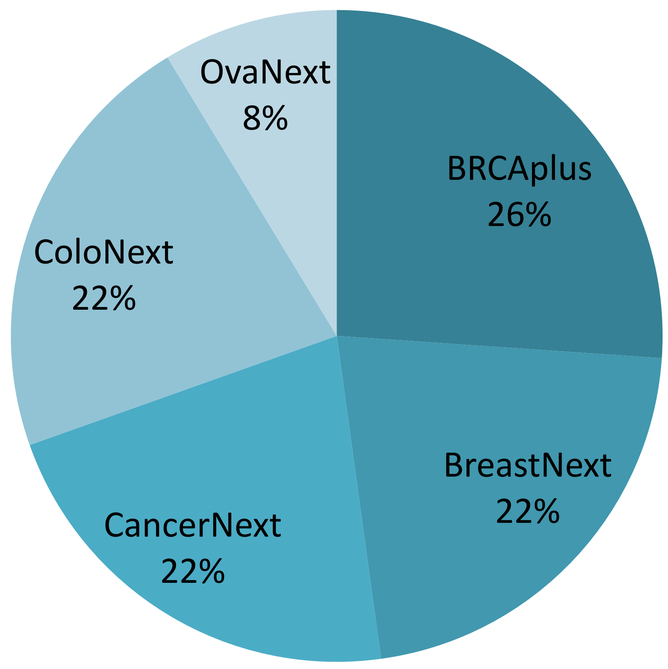
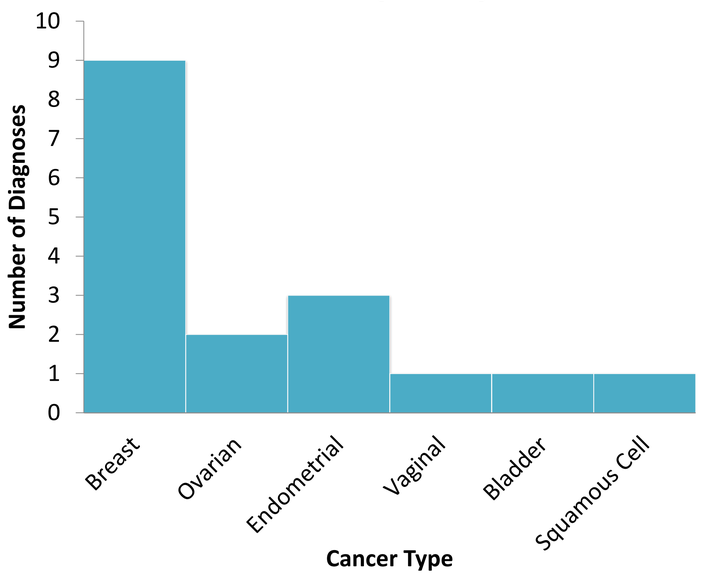


FIGURE 2: CANCER HISTORIES OF *PTEN*-POSITIVE PATIENTS WITH REPORTED POLYPS (N=11)[1]



[1]One individual had no cancer history, while 6 had multiple malignancies.

ADDITIONAL RESULTS

- 2/11 *PTEN* positive cases with polyposis had additional findings on the multi-gene panel.
  - One *APC* VUS
    - Proband cancer history: Breast & uterine cancer
    - Proband polyp history: 20-99 polyps
  - One *PMS2* VUS
    - Proband cancer history: Vaginal cancer
    - Proband polyp history: 100+ polyps
- Polyp history was likely not the main indication for panel testing:
  - All females in the cohort had a personal history of breast or gynecologic cancers (10/10 females in the cohort).
  - Polyp history could be underreported due to patient recall bias, inability to access medical records, and lack of prior colonoscopy.
- This data shows that ***PTEN* mutations may be more commonly associated with a mixed polyposis phenotype** than previously appreciated, supporting previous reports.[1,2]

TAKE-HOME POINTS

- With the advent of multi-gene panel testing, *PTEN* mutations have been identified in patients with non-hamartomatous polyp histologies, widening the spectrum of gastrointestinal disease burden in these patients.
- Our findings suggest that *PTEN* mutations should be part of the differential diagnosis for individuals with adenomatous and mixed polyposis and support the use of multi-gene panel testing in patients with colonic polyposis.
- Additional studies focused on polyp histologies of *PTEN* mutation carriers would help further delineate the gastrointestinal disease burden in these individuals.

REFERENCES

1. Heald et al., Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. *Gastroenterology.* 2010;139:1927–33.
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