

## Background

A new paradigm is emerging for genetic testing of patients with carcinoma of the uterus (UC). With next-generation sequencing (NGS), clinicians can choose to test only a limited number of genes such as the five Lynch syndrome (LS) genes involved in mismatch repair and *PTEN*, or a more comprehensive panel of cancer genes. The clinical utility of genes such as the LS genes and *PTEN* is established. NCCN guidelines, however, indicate that additional genes not typically associated with UC are also actionable for prevention of other malignancies. We report data on the diagnostic yield in UC patients using a comprehensive multigene panel of 80+ genes, and the implications for clinical management.

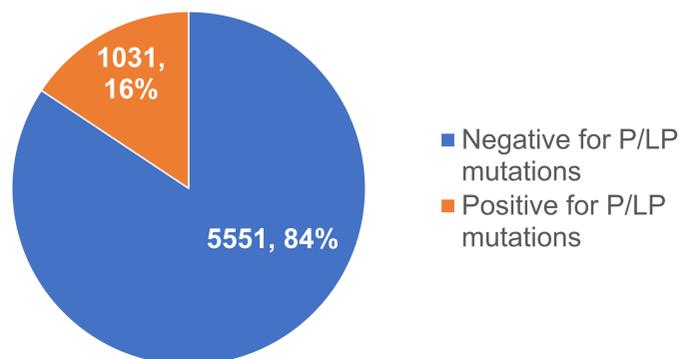
## Methods

We studied 6,582 consecutive patients with UC who were referred for testing at Invitae. Genomic DNA variants were identified using an NGS-based hereditary cancer panel of up to 83 genes; panel size was determined by the ordering clinician. Patients' medical histories were obtained from test forms and were de-identified for this analysis.

## Results

A Pathogenic or Likely Pathogenic (P/LP) variant was identified in 1,031 (15%) patients (Figure 1).

### Positive Rate in Uterine Carcinoma patients referred for Germline Genetic testing

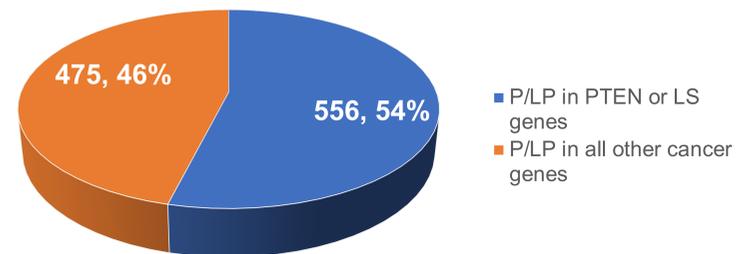


**Figure 1.** Positive rate of cancer gene mutations in patients referred for genetic testing. P/LP – pathogenic/likely pathogenic,

Of the mutation carriers, 54% had a P/LP variant in *PTEN* or the LS genes, while 39% had a P/LP variant in other cancer-risk genes, including *ATM*, *BRIP1*, *CHEK2*, *PALB2*, *PTEN*, *TP53* and others (excluding *MUTYH* heterozygotes; Figure 2).

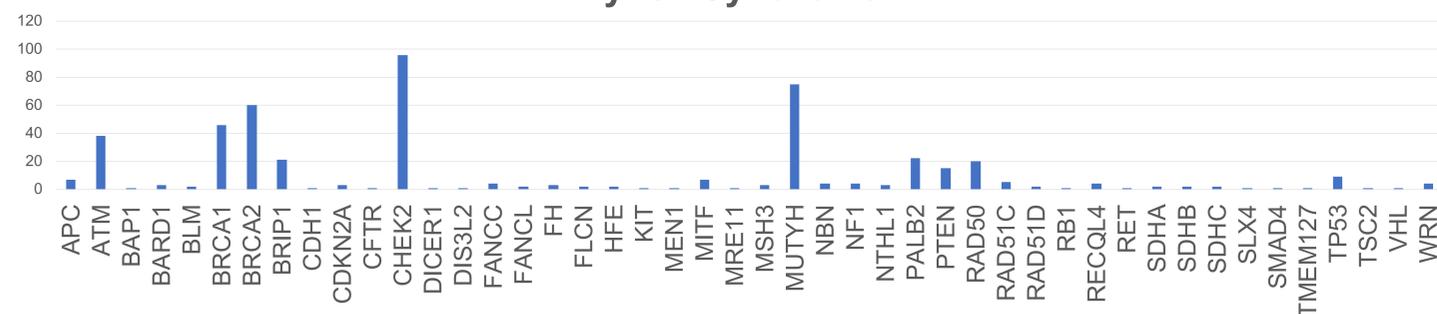
## Results (cont.)

### Rate of *PTEN* & Lynch Syndrome mutations



**Figure 2.** Fraction of uterine carcinoma patients with P/LP mutations in *PTEN* or the Lynch Syndrome (LS) genes (i.e. *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), and those with P/LP mutations in other known cancer genes (e.g. *APC*, *BRCA1*, *BRCA2*, *TP53*, etc.).

### Mutations in patients with Uterine Carcinoma in genes beyond Lynch Syndrome



**Figure 3.** Distribution of P/LP mutations in known, non-Lynch Syndrome cancer genes.

The clinical utility of these germline P/LP variants includes 32% with clinical trial eligibility, 52% with eligibility for FDA approved therapies, >90% with management recommendations based on NCCN guidelines, and cascade testing of at risk family members (Table 1).

Germline result-based intervention	% of positive patients eligible
Clinical trial eligibility (e.g. NCT02286687)	336 patients (32%)
FDA-approved therapy	544 patients (52%)
Clinical trial or FDA-approved therapy	880 patients (85%)
Established management recommendations (including surveillance and cascade testing of relatives)	953 patients (>90%)

**Table 1.** Clinical utility of germline mutations observed in patients with uterine carcinoma, including clinical treatment trials, FDA approved precision therapy and published management guidelines.

## Conclusions

- Multi-gene panel testing identified P/LP variants in genes with published management recommendations that would have been missed by a targeted UC gene panel.
- Over 80% of patients with P/LP germline variants were potentially eligible for precision therapeutic intervention based in part on their germline test results.
- These data highlight the benefit of comprehensive gene panels for the evaluation of UC and the impact these results can have on cancer intervention, surveillance and family variant cascade testing protocols.