# 10611:*Actionable Germline Findings in Endometrial Cancer from a Large Multigene Panel Tested Cohort*

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## Background

- Although most endometrial cancers (EC) are sporadic, **2–6% arise in the setting of Lynch syndrome (LS) or Cowden syndrome.** The prevalence and clinical correlates of other germline pathogenic/likely pathogenic variants (PVs) remain **incompletely characterized.**

**Objectives:**

- To evaluate the prevalence of potentially actionable PVs in a large cohort of patients with endometrial cancer undergoing Multigene Panel Testing (MGPT), including both established and emerging cancer predisposition genes.
- To evaluate the relationship between PVs and clinicopathologic features, compare their prevalences with that in an age- and ethnicity-matched cancer-free control population, and clarify their role in EC susceptibility and the clinical utility of MGPT.

## Methods

**STUDY DESIGN & COHORT**

Retrospective cohort of **3,612 EC patients** who underwent pan-cancer germline multigene panel testing at a single diagnostic laboratory (2018–2025).

**EXCLUSIONS**

- <18 years
- Mosaic results
- Genetic testing before 2018
- Unknown tested genes
- Unclear origin

**POSITIVE GROUP (PVs/LPVs)**

Pathogenic/likely pathogenic variants, excluding:

VS.

**NEGATIVE GROUP (VUS + carriers + negative results)**

**Excluded from positive group (carriers):**

- Low-penetrance / risk-modifying variants:
  - *APC* I1307K
  - *CHEK2* (I157T, S428F, T476M)
  - Selected *FH* variants
- Variants in *CASR, CFTR, CPA1, CTRC, PRSS1, SPINK1*
- Monoallelic carriers in recessive genes (*BLM, FANCC, MRE11A, MSH3, MUTYH, NBN, NTHL1, RAD50, RECQL, XRCC2*)
- *EPCAM* (due to genes tested included in the control group)

**CASE/CONTROL ANALYSIS**

CASES (n = 3,612) — CONTROLS (n = 3,612)

Matched 1:1 by age, sex and ethnicity

For each of the 35 genes:
- Prevalence (%)

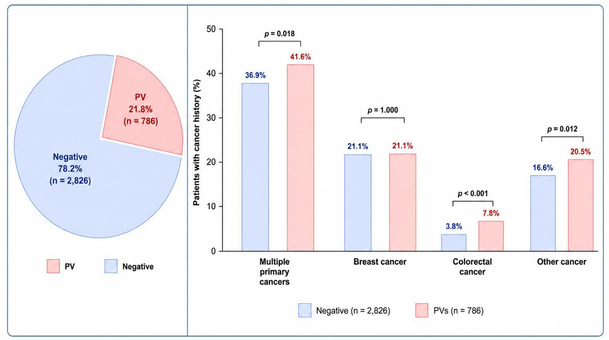
Groups compared using Fisher's exact test

**STATISTICAL ANALYSIS**

Clinical and pathologic variables compared between patients with and without PVs using appropriate statistical methods.

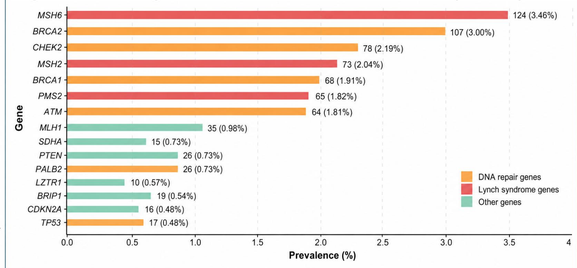
## Results/Graphs/Data

**Figure 1. Cancer History by germline status in the EC cohort**




- Patients with PVs were **younger at germline testing** compared with the negative group (median 60 vs. 63 years; P = 0.015).
- **PV carriers** underwent testing with **smaller gene panels** than the negative group (median 53.5 vs. 71 genes tested; P = 0.002).
- Significant differences in **ethnicity distribution** were observed between groups (P < 0.001), with a **higher proportion of African American/Black individuals among PV carriers.**

**Figure 2. Prevalence of PVs in cancer predisposition genes among PV carriers in the EC cohort (n=786)**




***Note.*** Genes with 10 or fewer PV carriers (n, %): *RET* (7, 0.36%), *POT1* (6, 0.31%), *RAD51D* (8, 0.23%), *CTNNA1* (4, 0.21%), *BARD1* (7, 0.20%), *SMARCA4* (6, 0.19%), *HOXB13* (4, 0.12%), *TMEM127* (2, 0.10%), *SDHD* (2, 0.10%), *SDHB* (2, 0.10%), *SDHAF2* (2, 0.10%), *FLCN* (2, 0.09%), *RAD51C* (2, 0.06%), *NF1* (2, 0.06%), *MUTYH* (2, 0.06%), *DICER1* (2, 0.06%), *CDH1* (2, 0.06%), *TSC2* (1, 0.05%), *VHL* (1, 0.04%), *EPCAM* (0, 0.00%).

- Patients with PVs had a younger **age at primary cancer diagnosis** compared with the negative group **(median 56 vs. 52 years; P < 0.001).**
- Patients with PVs also had a **younger age at EC diagnosis** compared with the negative group (median 58 vs. 54 years; **; P < 0.001).**

**Figure 3. Prevalence and distribution of PVs according to IHC status (A) and *MLH1* promoter methylation (B)**

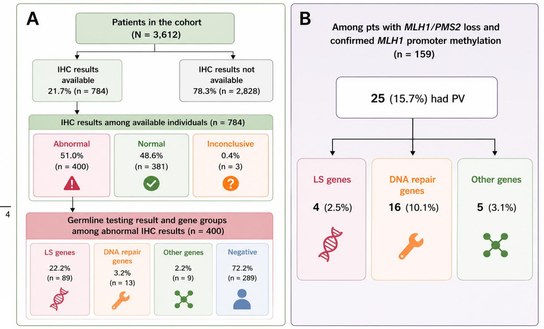



**Figure 4. Case–control analysis of PVs in 35 cancer predisposition genes showing statistically significant genes only)**

| Gene | Cases (N = 3,612) N (%) | Cases Proportion (%) | Cases p value | Cases OR (95% CI) | Controls (N = 3,612) N (%) | Controls Proportion (%) | Controls p value | Controls OR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| *any35genes* | 786 (21.76%) | 21.76% | <0.001 | 2.95 (2.56–3.41) | 311 (8.61%) | 8.61% | <0.001 | 2.95 (2.56–3.41) |
| *BRCA1* | 68 (1.91%) | 1.91% | <0.001 | 2.11 (1.37–3.31) | 33 (0.91%) | 0.91% | <0.001 | 2.11 (1.37–3.31) |
| *BRCA2* | 107 (3.00%) | 3.00% | <0.001 | 2.63 (1.82–3.86) | 42 (1.16%) | 1.16% | <0.001 | 2.63 (1.82–3.86) |
| *CHEK2* | 78 (2.19%) | 2.19% | 0.001 | 1.91 (1.29–2.85) | 42 (1.16%) | 1.16% | 0.001 | 1.91 (1.29–2.85) |
| *CTNNA1* | 4 (0.21%) | 0.21% | 0.022 | Inf (1.05–Inf) | 0 (0.00%) | 0.00% | 0.022 | Inf (1.05–Inf) |
| *MLH1* | 35 (0.98%) | 0.98% | <0.001 | 7.12 (2.77–23.30) | 5 (0.14%) | 0.14% | <0.001 | 7.12 (2.77–23.30) |
| *MSH2* | 73 (2.04%) | 2.04% | <0.001 | 18.76 (7.01–70.66) | 4 (0.11%) | 0.11% | <0.001 | 18.76 (7.01–70.66) |
| *MSH6* | 124 (3.46%) | 3.46% | <0.001 | 14.36 (7.31–32.18) | 9 (0.25%) | 0.25% | <0.001 | 14.36 (7.31–32.18) |
| *MITF* | 20 (1.01%) | 1.01% | 0.024 | 2.16 (1.07–4.41) | 17 (0.47%) | 0.47% | 0.024 | 2.16 (1.07–4.41) |
| *PMS2* | 65 (1.82%) | 1.82% | <0.001 | 4.75 (2.63–9.18) | 14 (0.39%) | 0.39% | <0.001 | 4.75 (2.63–9.18) |
| *PTEN* | 26 (0.73%) | 0.73% | <0.001 | Inf (6.67–Inf) | 0 (0.00%) | 0.00% | <0.001 | Inf (6.67–Inf) |
| *SDHA* | 15 (0.73%) | 0.73% | 0.001 | 4.44 (1.62–13.98) | 6 (0.17%) | 0.17% | 0.001 | 4.44 (1.62–13.98) |
| *SMARCA4* | 6 (0.19%) | 0.19% | 0.011 | Inf (1.32–Inf) | 0 (0.00%) | 0.00% | 0.011 | Inf (1.32–Inf) |
| *TP53* | 17 (0.48%) | 0.48% | <0.001 | Inf (4.19–Inf) | 0 (0.00%) | 0.00% | <0.001 | Inf (4.19–Inf) |

0% 5% 10% 15% 20% 25%

Proportion of subjects (%)

Proportion of subjects (%)

Only genes statistically significant between cases and controls are shown (p,0.05).
CI: confidence interval; OR: odds ratio; Inf: infinite

- The strongest association was in patients with **uterine + colorectal cancer (OR 5.40)**, followed by those with **uterine + breast cancer (OR 4.14).**
- Patients with multiple **primary tumors overall (OR 3.49) and uterine cancer only (OR 2.66)** also remained enriched versus controls.

## Conclusions

- **The overall PV detection rate in patients with EC was remarkably high at 21.8%.**
- **A younger age at germline testing, first cancer diagnosis, and EC diagnosis was significantly associated with presence of a PV.**
- **PVs were identified in 15.7% of individuals with MLH1/PMS2-deficient and *MLH1* promoter methylation-positive EC.**
- **A marked enrichment of PVs in cases (primarily involving mismatch repair and certain DNA repair genes) indicates a strong genetic contribution to EC risk.**

## Future directions

- **Validate findings in an independent clinical cohort.**
- **Investigate and functionally characterize novel signals in newly implicated genes.**
- **Universal genetic testing strategies in EC patients should be considered.**
- **Tailor gene-specific clinical recommendations and risk management.**

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