Actionable Germline Findings in Endometrial Cancer from a Large Multigene Panel Tested Cohort

Adela Rodríguez Hernandez MD, Magan Trottier, MS, MSc, Miki Horiguchi, PhD, Carolyn Horton, MS, Linda M. Polfus PhD, Brittany L. Bychkovsky MD, MSc, Judy E. Garber, MD, Jessica D. St. Laurent, MD, Huma Q. Rana, MD, MPH

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. We assessed the prevalence of potentially actionable germline PVs in EC and their clinicopathologic associations.

Methods: This retrospective cohort included 3,844 EC patients (pts) who underwent pan-cancer germline multigene panel testing at a single diagnostic laboratory (2018–2025). Pts < 18 years, with mosaic results, or unclear pathology were excluded. Clinical and pathologic variables were compared between pts with and without PVs using appropriate statistical methods, including multivariable logistic regression.

Results: The final cohort comprised 3,693 females; 46.6% were non-Hispanic White and 8.3% African American. Median age at testing was 62 years and median age at diagnosis was 57 years. Overall, 20.8% (n = 804) harbored a PV in a high- or moderate-penetrance gene. Among 852 PVs identified, 46.9% occurred in DNA damage response (DDR) genes, 37.0% in LS genes, and 16.1% in other genes. The most frequent DDR PVs were *BRCA2* (12.6%), *CHEK2* (9.2%), *BRCA1* (8.0%), *ATM* (7.5%), *PALB2* (3.1%). *PTEN* accounted for 3.2% of the PV. PV carriers were younger at testing (60 vs 62 years; p = 0.014) and diagnosis (54 vs 57 years; p < 0.001), more often African American (12.4% vs 7.2%; p < 0.001), and had higher rates of colorectal cancer (7.7% vs 3.4%; p < 0.001) and multiple primary cancers (41.7% vs 36.8%; p = 0.012). In multivariable analysis, younger age at EC diagnosis (OR 0.99; p = 0.028) and personal history of colorectal cancer (OR 1.84; p < 0.001) remained independently associated with PV status. Histologic subtype distribution differed between LS and DDR groups (p < 0.001); endometrioid tumors were more frequent in LS (26.6% vs 22.7%), whereas serous carcinoma (7.3% vs 1.1%) and carcinosarcoma (4.2% vs 1.8%) were more frequent in DDR.

Among pts with available immunohistochemical (IHC) data (n = 810), 51.2% (n = 415) showed mismatch repair protein loss. Of these, 96 (23.1%) had PVs in LS genes, 13 (3.1%) in DDR genes, and 9 (2.2%) in other genes; 297 (71.6%) had no germline PV. Notably, among 161 pts with MLH1/PMS2 loss and confirmed *MLH1* promoter methylation, 25 (15.5%) still harbored PVs; 4 (2.5%) in LS genes, 16 (9.9%) in DDR genes and 5 (3.1%) in other genes.

Conclusions: Germline PVs were identified in over 20% of EC cases, extending beyond LS or Cowden syndrome. The presence of PVs in *MLH1*-methylated tumors—traditionally considered sporadic—is a critical finding that challenges current tumor-only triage. These results support universal multigene germline testing in EC. A complementary case–control analysis including cancer-free controls and an independent validation cohort will be presented.