Introduction/Background MLH1 promoter hypermethylation is common in sporadic microsatellite unstable endometrial cancer but data on MLH1 promoter hypermethylated endometrial cancer (MLH1-PM EC) is sparse. We aimed to identify the clinical and molecular characteristics of MLH1-PM EC.

Methodology Descriptive analysis of 246 tumours from patients treated between September 2007 to June 2022.Mismatch repair proteins (MMR) were tested by immunohistochemistry (IHC). Tumour specimens were sequenced using the Royal Marsden RMH200Solid panel which includes 233 genes and evaluates microsatellite instability (MSI) and tumour mutational burden (TMB). Droplet Digital PCR (ddPCR) was used for DNA methylation analysis in each case. Patients' characteristics were recorded from our electronic records.

Results MLH1-PM was identified in 71/246 tumours (28.9%): 61 were MMRd and 10 MMR proficient by IHC. The most common protein loss was MLH1/PM2 in 57/61 cases (93.5%). Isolated loss of MSH6 was present in 3 cases and both MSH2/MSH6 loss in 1 case. MLH1-PM tumours were MSI high in 47/71 (66.2%) of cases with a mean TMB of 30.96 mut/mb (12.21–193.93) and MSS in 24/71 (33.8%) of cases with a mean TMB of 48.65 mut/mb (0–231.91). The predominant histological subtype was endometrioid (n=64). Most tumours were stage I or II at diagnosis (n=55). Mean age at diagnosis was 65 years (32–90) and mean body mass index (BMI) was 31.64 (17.3–53.9). 14/71 (19.7%) patients presented with relapsed disease after initial diagnosis: loco–regionar, 14/71 (19.7%) patients presented with relapsed disease after initial diagnosis: loco–regionar, 9/71 (12.5%) patients presented with isolated disease after initial diagnosis: loco–regionar.

Conclusion MLH1-PM EC is found in 30% of unselected EC patients and harbors genomic alterations that may have potential prognostic and therapeutic implications. Further studies are needed to develop appropriate treatment strategies.

Disclosures Dr. Alexandra Taylor: MSD.
Dr. Angela George: Astra Zeneca, GSK, Roche, Merck.