Methods: A case-control study was performed including all cases of recurrent stage I, grade 1 endometrioid endometrial cancer at a single institution in a ten-year period. Cases were matched to controls in a 1:2 ratio. Controls were matched by age, BMI, weight and stage. Controls had clinical surveillance lasting at least 6 months beyond the longest time to recurrence of the cases. Molecular testing was performed on archival tumor specimens: microsatellite instability testing with Promega MSI Analysis, POLE mutational status with Sanger sequencing, and mutational status of 67 genes with next-generation sequencing using the ArcherDx VariantPlex Solid Tumor kit. Patient and tumor characteristics and molecular results were compared using chi-square and Fisher's exact tests.
Results: 311 stage I, grade 1 endometrioid endometrial cancers were identified; 15 cases had recurrent disease and available tumor specimens. Cases and controls were similar in median age (57 vs. 59, p=0.53), BMI (33.1 vs. 34.2, p=1.00), weight (83.5 vs. 87.1kg, p=1.00) and stage (IA 86.7% vs. 93.1%, IB 13.3% vs. 6.9%, p=0.60). Recurrence location was vaginal in 60% of cases, pelvic in 20% and abdominal in 20%. Mutations identified at high frequency among cases included PTEN (80%), PIK3CA (67%), CTNNB1 (60%). Both CTNNB1 and MSI-H were present at significantly higher rates in cases than in controls (CTNNB1 60% vs. 27.6%, p=0.04, MSI-H 46.7% vs. 13.8%, p=0.03), while PTEN, PIK3CA, KRAS and TP53 all had equivalent distribution (p values 0.68, 0.34, 0.74 and 0.65 respectively). POLE mutations were found in 0.0% of cases vs. 6.9% of controls (p=0.54). Among specimens demonstrating microsatellite stability (MSS), 87.5% of cases vs. 24.0% of controls had CTNNB1 mutations (p=0.003). CTNNB1 wild type tumors were MSI-H in 83.3% of cases vs. 9.5% of controls (p<0.001).
Conclusions: Compared to controls, CTNNB1 mutation is present at significantly higher rates in recurrent stage I, grade 1 endometrioid endometrial cancers and is found most commonly in MSS tumors. This marker may be useful for prognostic risk stratification and adjuvant therapy decision-making in this otherwise low risk population.

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Abstract #25

Combining methylation markers, genomic instability, and next generation sequencing as a panel for endometrial cancer detection via intravaginal tampon collection

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Objectives: We aimed to develop and evaluate a molecular panel for the early detection of endometrial cancer (EC) from intravaginal tampons by methylation markers, genomic instability, and next generation sequencing (NGS).
Methods: Tampons were collected from women undergoing hysterectomy for EC and women undergoing hysterectomy for benign indications. Extracted tampon DNA underwent the following: 1) low-coverage whole genome sequencing (LC-WGS) using the Illumina HiSeq 2500 according to 51 base-pair single-end sequencing protocol and evaluated for copy number gains and losses (genomic instability) using an in-house bioinformatics pipeline (http://bioinformaticstools.mayo.edu/research/wandy/); 2) pyrosequencing to measure promotor methylation of HOXA9, RASSF1, and CDH13; and 3) NGS using PCR amplification primers followed by Ion Torrent and orthogonal Illumina covering 19 genes commonly found in EC. Sensitivity and specificity for each test and combinations of tests were calculated.
Results: Data from all 3 molecular approaches is presented in Table 1. Sensitivity and specificity for EC via methylation was as follows: 25 benign and 36 EC tampon samples had HOXA9 methylation (42% sensitivity; 100% specificity); 22 benign and 35 EC tampon samples had RASSF1 methylation (40% sensitivity; 100% specificity); 20 benign and 36 EC tampon samples had CDH13 methylation (39% sensitivity;100% specificity). Genomic instability was identified in tampons from 9 (64%) of 14 ECs and 1 (11%) of 9 benign endometrial controls. 18 benign samples and 21 EC samples underwent NGS with mutations detected in 11 (52%) EC samples and 3 (17%) benign samples. When combining the three tests, 11/12 (92%) ECs and 1/7 (14%) controls were positive for either genomic instability, methylation or NGS, resulting in a sensitivity of 92% and specificity of 86%. Interestingly, the benign endometrial control that was positive for genomic instability had an underlying leiomyosarcoma uncovered at hysterectomy.
Conclusions: When combined, genomic instability, methylation, and NGS have a high sensitivity and specificity in detecting EC; however, the combination of genomic instability and methylation provides comparably high sensitivity. Validation of the molecular biomarker combinations and further methylation marker discovery, especially among the rarer EC histologies, are needed to further develop a tampon-based EC detection test.

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Abstract #26

MLH-1 hypermethylation is associated with lower recurrence free survival in patients with endometrial cancer

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Objectives: Approximately 25% of endometrial cancers (EC) are characterized by microsatellite instability due to MLH1 promotor hypermethylation.This study evaluates the prognostic importance of MLH1 hypermethylation among EC patients undergoing universal screening for Lynch Syndrome (LS).
Methods: From August 2012- August 2016, all patients with EC underwent screening for LS using immunohistochemistry (IHC) for mismatch repair (MMR) proteins. Tumors with lack of expression of PMS2 or MLH1 were assessed for MLH1 promotor methylation. Tumors were classified as MMR-I (intact expression of MMR proteins) and MMR- DM (MMR deficient due to MLH1 methylation) Clinical and pathologic factors associated with MMR-DM evaluated using univariate and multivariate analysis. Overall survival (OS) and recurrence free survival (RFS) assessed using cox proportional hazards for patients with at least 2 years of follow up.
Results: Among 720 EC samples evaluated for MMR, 516 (71.6%) were MMR- I, 172 (23.8%) MMR-DM and 32 (4.4%) MMR-DU. Patients with MMR-DM tumors were older (p<0.001) and had a lower BMI (p=0.03) vs. MMR-I patients. MMR-DM tumors were higher grade (grade 2/3,p=<0.001), had positive LVSI (p<0.01), and myometrial invasion >50%(p=0.002). There was no significant difference in stage, adnexal involvement, or cervical stromal invasion between groups. Lymphadenectomy was performed in 316 patients (43.9%), specifically 44.2% of MMR-DM and 41.8% of MMR-I groups. On multivariable analysis, older age (OR 1.03, CI (1.01-1.05), p=0.001), endometrioid histology (OR 5.60, CI (1.71-17.88), p=0.004), and tumor size < 2 cm (OR 0.50 CI (0.31-0.80), p=0.004) were independently associated MMR-DM. Recurrences were observed in 11.2%(19/169) MMR-DM and 5.9% (30/509) of MMR-I patients (p=0.02). Evaluating by FIGO stage, recurrences at early stage (I/II) were seen in 6.6% of MMR-DM (9/137) vs. 2.9% of MMR-I (12/421)

patients (p=0.047). Similarly 22.2% of MMR-DM (6/27) and MMR-I (16/72) groups recurred at advanced stages (III/IV) (p=1.0). Median time to recurrence was 17.5 months for MMR-DM (IQR 9.6,25.29) vs. 22.7 months for MMR-I (IQR 16.6, 29.6). RFS was significantly lower for MMR-DM vs.MMR-I (p=0.01). There was no significant difference in OS between MMR-I and MMR-DM. There was an observed difference in the incidence of locoregional or distant recurrence between MMR-I tumors vs.MMR-DM tumors, with proportionately more distant recurrences in the MMR-I group (30% (9/30) vs. 50% (9/18) locoregional, and 70% (21/30) vs. 50% (9/18) distant recurrences).

Conclusions: ECs with MLH-1 hypermethylation are associated with known adverse prognostic factors including older age, higher grade, LVSI, and myometrial invasion >50%. These tumors have a higher rate of recurrence overall (including those with early stage disease) and a significantly lower RFS versus sporadic EC. MMR-DM status appears to be an important prognostic factor to consider in patient counseling and treatment decision making.

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Abstract #27

The growing burden of endometrial cancer: A major racial disparity affecting hispanic women

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Objectives: Hispanics represent the largest and fastest growing ethnic minority group in the U.S. South Texas has a large Hispanic "minority" population which raises the concern for poorer health outcomes. We sought to compare the age-adjusted incidence rates and annual percent changes (APCs) of endometrial cancer in four geographically distinct Hispanic populations.

Methods: We used data from the U.S. SEER Program and the Texas Cancer Registry to calculate annual age-adjusted endometrial cancer incidence rates and APCs for Hispanics and non-Hispanic whites (NHW) in the U.S., Texas, South Texas, and Bexar County (San Antonio) between 2000 and 2014. APCs were derived using weighted least squares point-estimation; trends were tested for statistical significance using SEER*Stat.

Results: For the time period 2000 to 2014 the age-adjusted endometrial cancer incidence rates per 100,000 for NHW versus Hispanics were 23.9 versus 17.7 for SEER, 17.62 versus16.87 for Texas, 19.0 versus 18.16 for South Texas, and 20.95 versus 21.01 for Bexar County. The APCs for NHW versus Hispanics were 0.8 versus 2.0 for SEER, 0.79 versus 1.79 for Texas, 2.01 versus 2.23 for South Texas, and 2.29 versus 2.39 for Bexar County. The APCs were the highest for the Hispanics under age 50; 2.5 for SEER, 3.5 for Texas, 4.1 for South Texas, and 4.1 for San Antonio. The APCs were lower for Hispanics over age 50; 1.9 for SEER, 1.2 for Texas, 1.5 for South Texas, and1.7 for Bexar County.

Conclusions: Endometrial cancer is typically thought to be a cancer of postmenopausal Caucasian women. However in Texas, particularly in South Texas and Bear County, we found the incidence rates to be equal or higher in Hispanics than NHW. From 2000 to 2014 the incidence of endometrial cancer increased in both Hispanics and NHWs in the 4 populations, but more so in Hispanics. Compared to the SEER population, the incidence of endometrial cancer in Hispanics increased as one moved from Texas as a whole, to South Texas, to Bexar County. The most significant increase in endometrial cancer incidence was seen in the younger Hispanic patients from 2000 to 2010 in all 4 populations. More research needs to be focused on the young Hispanic population to determine unique risk factors and potential interventions.

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Abstract #28

The rate of incidental uterine malignant and premalignant lesions at supracervical hysterectomy for uterovaginal prolapse

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Objectives: To determine the incidence of unexpected malignant or premalignant lesions at time of supracervical hysterectomy (SCH) performed for uterovaginal prolapse (UVP).

Methods: We performed a retrospective cohort study of patients who underwent a SCH with preoperative diagnosis of UVP at a single academic hospital between January 1, 2009 and December 31, 2016. Diagnosis was based on the attending surgeon's primary indication for surgery. Women were excluded if they had another indication. Demographic information and the incidence of unexpected malignant and premalignant lesions was determined.

Results: From 2009- 2016, 7,883 hysterectomies were performed at our institution. Of those, 281 SCH were performed after a preoperative diagnosis of UVP. Twenty-three or 8.2%, had pre-operative uterine sampling within one year prior to the procedure. None of these patients had a malignant or premalignant finding on final pathology. Demographic and surgical data is presented in Table 1. Overall, three SCH patients, or 1.06%, were found to have an unexpected malignant or premalignant findings on final pathology. Two patients were diagnosed with endometrial cancer (both stage 1A, grade 1) and one patient had complex hyperplasia with atypia. One patient underwent subsequent trachelectomy and one patient had close surveillance after opting not to have radiation therapy. Removing patients with benign preoperative sampling, the rate of unexpected findings was 1.16%. There were no demographic characteristics that increased the risk of finding a malignant or premalignant condition on final pathologic diagnosis, which was likely due to the small number of cases.

Conclusions: To our knowledge, this is the first large study examining the risk of underlying malignant and premalignant lesions in women who have a SCH for UVP. Women who are having routine SCH for UVP should be counseled that the rate of incidental uterine malignant and premalignant lesions is approximately 1%.

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Abstract #29

Referral to a weight loss specialist is associated with long-term weight control in endometrial cancer survivors: Long-term follow-up of a prospective cohort study

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Objectives: To prospectively evaluate the long-term effects of medical and surgical weight loss referral of endometrial cancer survivors.

Methods: From December 2013 to May 2015, women ages 18-65 years with complex atypical hyperplasia or stage I-II endometrioid adenocarcinoma and a body mass index (BMI) ≥30kg/m2 were prospectively enrolled at 3 hospitals in an academic health system. Exclusion criteria included non-endometrioid histology, poorly