Results: Of the NC cases, 544 women (39%) were less than age 60 and 281 (52%) of them had IHC testing. The IHC results were abnormal in 52 cases (10%) and 18 (3%) had no methylation of MLH1 promoter, suggestive of Lynch Syndrome. In SC, 279 of the 646 women (43%) were under age 60 and 242 (87%) had IHC testing with 54 (19%) abnormal results and 15 (5%) abnormal after methylation testing. There were 855 cases in women older than age 60 in NC and 95(11%) had IHC testing, 23 (3%) were abnormal and 3 (<1%) abnormal after methylation testing. There were 367 cases in women older than age 60 in SC, and 300 (82%) had IHC testing with 96 (26%) abnormal results and 8(2%) abnormal after methylation testing. A genetics referral was placed for 118 (22%) women in NC and 45 (16%) women in SC underage 60, and 88 (10%) women in NC and 40 (10%) in SC over age 60. As a result of abnormal IHC testing, Lynch syndrome was diagnosed in 15(1%) women in NC and 10(1.5%) in SC. There were 6 (1%) cases in NC and 4 (1%) cases in SC for women under age 60, and no cases in NC and 2(<1%) cases in SC for women over age 60. For women referred to genetics for reasons other than abnormal IHC, LS was detected in women under 60 in 5 (1%) and 3 (1%) of cases and for women over 60 LS was detected in 4(<1%) and 1(<1%) of cases in NC and SC, respectively. When comparing detection of LSin the two regions., there were no significant differences in rates of overall detection (p=0.36) nor were there differences in detection in women less than 60 (p=0.65) or over 60 (p=0.44).
Conclusions: Although universal IHC screening of EC would be expected to identify more cases of LS than age based IHC screening, there was not a difference in the detection of lynch syndrome in EC in two regions of a large California health care system with these different policies.

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Abstract #32

Universal immunohistochemistry testing in endometrial cancer tumors maximizes Lynch Syndrome identification among affected individuals

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Objectives: Universal colorectal cancer (CC) screening for Lynch syndrome (LS) via mismatch repair proteins (MRP) immunohistochemistry (IHC) testing has become commonplace. Although endometrial cancer (EC) has been proven to be the sentinel malignancy in many women diagnosed with LS, universal screening of EC has not been widely adopted. We report our experience with the detection of Lynch syndrome comparing universal screening for both EC and CC in a large non-profit health plan.
Methods: We instituted universal CC screening in April 2014, and added universal EC screening in November 2015. All tumors are screened via IHC for presence of the four MRP, reflex methylation testing of MLH1 is employed where indicated. We tabulated all abnormal IHC and subsequent somatic and germline testing results to assess the frequency of detected LS cases amongst females with EC or CC, and males with CC based on age at diagnosis. Statistical analysis was performed using Pearson's Chi-square, and relative-risk.
Results: We performed IHC on 6164 tumors in 5804 patients (EC=1421, female CC= 2157, male CC= 2406). Abnormal IHC results were found in 982 (15.9%) tumors (347 EC, 383 female CC, 251 male CC), occurring more frequently in the EC cohort (24.4% vs 17.8% vs 10.4%, p<0.001). Mismatch repair (MMR) pathogenic/likely pathogenic gene mutations were identified in 114 patients (2%). Of the germline mutations, 35/114 (30.7%) were in patients >60 (EC 21%, female CC 27%, male CC 36%). We observed a slightly higher but not statistically significant detection of LS among women with EC than CC (2.9% vs. 2.5% vs. 2.6%, p=.80). In women ≤60 at the time of cancer diagnosis the relative risk of LS in those with EC (4.56, 95% CI 2.54-8.42) was equivalent to those with CC (7.17, 95% CI 4.49-11.44). The relative risk of LS among women with either EC or CC was higher than among male CC patients (2.90, 95% CI 1.97-4.50).
Conclusions: Our universal IHC testing results show that a larger proportion of EC tumors yield abnormal results than CC tumors. In our experience MMR gene mutations were more frequently detected among women screened via EC than CC. Routine screening in all age groups improves detection in patients who might otherwise be excluded from guideline-based approaches. Adding EC to the universal screening program identified Lynch in 25% of patients that might have otherwise been missed. Our experience confirms that universal EC screening for MRP offers the optimal management approach to identify patients with Lynch syndrome and inform future screening, detection and prevention efforts for themselves and their at-risk relatives.

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Abstract #33

Patterns of risk reducing surgery in germline homologous recombination deficiency/non-BRCA mutation carriers

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Objectives: To describe clinicopathologic characteristics of women with germline HRD/non-BRCA (gHRD/non-BRCA) mutations to those with BRCA mutations who choose to have risk reducing surgery (RRSO).
Methods: Women with pathogenic germline mutations associated with ovarian cancer who had risk reducing surgery were identified in a women's cancer program at a single institution from 1/2000- 6/2017 in a IRB approved study. All patients were asymptomatic with normal physical exams, CA 125 values and imaging prior to RRSO. Demographics and clinico-pathologic characteristics were extracted from the medical records. Continuous variables were analyzed using Mann-Whitney U tests and categorical variables were analyzed with Student's T-tests.
Results: 14 gHRD/non-BRCA (APC, ATM, BARD1, BRIP1, CHEK2, MUTYH, PALB2, PMS2, and RAD51C) and 259 BRCA1/2 mutation carriers were identified. There was no difference between gHRD/non-BRCA versus BRCA mutation carriers in age at genetic testing (47 v. 45 years, p=.27) and age at RRSO (48 v. 46 years, p=.50). Time between diagnosis and RRSO between the two groups was statistically significant (343 v. 169 days, p=.05). A family history of breast or ovarian cancer, and a personal history of breast cancer, was common in both cohorts. GHRD/non-BRCA mutation carriers more frequently had documented official genetic counseling (64% v. 31%, p=.03). Occult carcinoma, STIC, or dysplasia were only seen among BRCA mutation carriers (5%). Two gHRD/non-BRCA patients had interval salpingectomies compared to 11 BRCA mutation carriers. GHRD/non-BRCA mutation carrier were less likely to have prophylactic mastectomies (21% v. 65%, p=.01) but just as likely to have concomitant hysterectomy as BRCA mutation carriers.
Conclusions: Germline HRD/non-BRCA mutation carriers have more genetic counseling compared to women with germline BRCA mutations. Despite similar family and personal history of breast cancer, they are less likely to have prophylactic mastectomies than BRCA mutation carriers. No gHRD/non-BRCA mutation carriers had occult cancer at RRSO despite longer interval between testing and

RRSO. Further study of cancer risks associated with gHRD/non-BRCA mutations is necessary to guide recommendations for risk-reducing surgery.

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Abstract #34

Exploratory analysis of somatic BRCA mutations in endometrial cancer and its clinical implications

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Objectives: Germline BRCA mutations in ovarian cancer patients are associated with improved response to chemotherapy and survival. With the increased use of molecular profiling, many women with endometrial cancer (EC) have been found to harbor somatic BRCA mutations, the significance of which is unknown. The goal of this study is to evaluate the prognostic and predictive features of somatic BRCA mutations (sBRCA+) in EC.

Methods: An IRB-approved, retrospective review of patients with molecularly profiled, EC from 3 academic institutions between 2010 – 2017 was performed. Summary statistics were used to describe demographic and clinical characteristics. Analysis included a comparison of response and survival following treatment with platinum-based chemotherapy among sBRCA+ and somatic BRCA wild-type (sBRCAwt) patients.

Results: Of the 109 patients included, 12.8% were sBRCA+ (Table). Of these, the median age was 47.5 yrs and 62% were endometrioid. This was not statistically different from the 95 sBRCAwt patients, of which the median age was 50 yrs and 66% were endometrioid (all $p>0.05$). sBRCA+ pts were more likely to have microsatellite instability-high (MSI-H) tumors than sBRCAwt (50% vs 17%, $p=0.01$). Of the 45 patients with complete chemotherapy data available, the median progression-free survival (PFS) was 26 mo. There was no difference in the distribution of sBRCA+ patients above and below the median PFS (23% vs 18%, $p=0.69$). The median overall survival (OS) for the 108 pts with evaluable data was 30.4 mo. There was no statistical difference in the distribution of sBRCA+ patients above and below the median PFS (19% vs 8%, $p=0.11$). Of the 14 sBRCA+ patients, 4 had germline mutation testing and all 4 were negative.

Conclusions: Among EC patients, somatic BRCA mutations are relatively uncommon. sBRCA+ patients are more likely to have MSI-H tumors, but no other clinical factors were associated with these mutations. While there appears to be a trend towards improved OS among sBRCA+ patients, this was not statistically significant, likely due to the small numbers in our cohort. Data collection continues with recruitment of additional sites to improve the power of this study.

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Abstract #35

Pilot early detection trial of longitudinal combined biomarker assessment for ovarian cancer risk among BRCA affected women

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Objectives: Screening for ovarian cancer with CA-125 using a set cut off for normal values has inadequate sensitivity for clinical use. A risk of ovarian cancer algorithm which systematically interprets longitudinal changes in CA-125 values to detect the first significant rise above a woman's baseline has shown promise. The objective of this pilot early detection study was to assess personalized risk using an expanded longitudinal algorithm that detects the first significant rise above a woman's baseline in either CA-125 or HE4.

Methods: BRCA1/2 affected women who had chosen to defer prophylactic oophorectomy were recruited to participate in a prospective early detection trial. Patients self-allocated into two groups: 1. standard of care surveillance according to NCCN recommendations and 2. combined biomarker surveillance using CA-125 and HE4 assayed every 4 months. Biomarkers were evaluated using the Risk of Ovarian Cancer Algorithm (ROCA) which calculates the probability of having a change-point in the biomarker, used as a surrogate for having undetected ovarian or fallopian tube cancer. ROCA risk scores were calculated for the individual markers as well as for the combination. Risk estimates were categorized as normal, intermediate, and elevated. Post-test follow up for elevations in any individual risk score (CA-125, HE4 or combination) was trans-vaginal sonography (TVS) for intermediate risk, and TVS and review by gynecologic oncologist for elevated risk.

Results: 149 BRCA 1 and 2 affected women enrolled in the ROCA biomarker arm of the screening study and 409 blood draws over 1.4 years provided 409 time points for analysis. Abnormal individual risk scores were identified in 95 (23%) of 409 time points; 68 (16.7%) were intermediate and 27 had elevated risk scores (6.7%). Retrospective analyses of the combination CA125/HE4 ROCA score showed that 50 time points (12.2%) had a rise over time in one or both markers with an elevated combined risk score. One stage IIA fallopian tube cancer with serous tubal intra-epithelial cancer (STIC) was identified from the study group at patient-initiated risk reducing salpingo-oophorectomy (RRSO). Nonetheless, in that case the combined ROCA and the individual HE4 ROCA reported elevated risks.

Conclusions: Combination biomarker risk scoring is feasible, and this preliminary evaluation appears to show improved specificity compared with individual risk scoring, reducing the number of false positives by about one-half. Further evaluation, particularly to clarify potential confounders, is needed before firm judgments can be made about mitigating the clinical imprecision of CA 125 testing when using this novel testing method.

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Poster Presentations

Poster #1

Predictive factors of genetic referral for advanced, epithelial ovarian cancer patients at a Single-Institution Cancer Center

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Objectives: Given 15-20% of invasive epithelial ovarian cancer (EOC) cases are attributed to genetic mutations, the Society for Gynecologic Oncology (SGO), National Comprehensive Cancer Network (NCCN)