1500 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Targeted therapy based on germline analysis of tumor-normal sequencing (MSK-IMPACT) in a pan-cancer population. *First Author: Zsofia Kinga Stadler, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor mutational profiling for identification of somatic alterations for targeted treatment is increasingly being performed in advanced cancer patients (pts). We sought to assess the clinical utility of germline mutation profiling for targeted therapeutic interventions in a pan-cancer patient population. **Methods:** All pts who had germline genetic testing through a prospective protocol via a next-generation sequencing panel (MSK-IMPACT) were identified (N=11,975) from 2015-5/2019. The medical record of pts with likely pathogenic/pathogenic germline (LP/P) alterations in genes with known therapeutic targets were reviewed to identify germline-targeted treatment either in a clinical or research setting. **Results:** We identified 2,043 (17.1%) pts who harbored LP/P variants in a cancer predisposition genes including 777 (6.5%) in genes with potentially targetable therapeutic implications: 416 *BRCA1/2,* 149 DNA mismatch repair genes (Lynch syndrome, LS), 122 *ATM*, 45 *PALB2*, 26 *RAD51C/D*, 7 *RET*, 4 *TSC*, 3 *PTCH1*, 2 *ALK*, 1 *EGFR*, 1 *MET* and 1 *KIT*. Of those with advanced disease (n=554), 45.3% received targeted therapeutic treatment (Table) including 50.9% BRCA1/2, 58.3% LS (67.4% of microsatellite-high LS cases), 41.7% *PALB2*, 36.8% RAD51C/D and 19.3% *ATM* carriers. Of patients receiving a poly (ADP-ribose) polymerase inhibitor (PARP-I) in the setting of a *BRCA1/2* mutation, 55.1% had breast or ovarian cancer; however, 44.8% had other tumors, including pancreas, prostate, bile duct, gastric, wherein the drug was given in a research setting. Among *PALB2* pts receiving PARP-Is, 53.3% (8/15) had breast or pancreas cancer; 46.7% had cancer of the prostate, ovary or unknown primary. **Conclusions:** In our pan-cancer analysis, 6.5% of pts harbored a targetable germline variant highlighting the importance of germline analysis in advanced cancer pts for selection of both FDA-approved treatments and clinical trial participation with germline-targeted therapeutics. Research Sponsor: Internal MSK Funding.

Gene(s) with potential targetable therapy	Drug Class	% of advanced cancer patients receiving targeted therapy
BRCA1, BRCA2	PARP-I	50.9% (165/324)
Lynch syndrome (*MLH1, MSH2, MSH6, PMS2, EPCAM*)	Checkpoint-inhibitors	58.3% (42/72) (irrespective of MSI) 67.4% (29/43) (MSI-High)
ATM	PARP-I	19.3% (17/88)
PALB2	PARP-I	41.7% (15/36)
RAD51C, RAD51D	PARP-I	36.8% (7/19)
RET	Tyrosine kinase inhibitor	60% (3/5)
TSC	mTOR inhibitor	0% (0/3)
PTCH1	Hedgehog-signaling inhibitor	33.3% (1/3)
ALK	ALK kinase inhibitor	0% (0/2)
EGFR	EGFR inhibitor	100% (1/1)
MET	MET kinase inhibitor	0% (0/1)

1501 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Tumor/normal genomic profiling in patients with metastatic solid tumors identifies pathogenic germline variants of therapeutic importance. *First Author: Erin Frances Cobain, University of Michigan, Ann Arbor, MI*

Background: Tumor molecular profiling via next-generation sequencing (NGS) is routinely utilized to direct patients toward clinical trials of targeted therapeutics. NGS testing of paired tumor/normal samples identifies incidental pathogenic germline variants (PGVs), having potential implications for patients and their families. **Methods:** From 2011-2018, 1,015 patients with metastatic, refractory solid tumors underwent targeted (1700 genes) exome and transcriptome sequencing of matched tumor/normal samples through the Michigan Oncology Sequencing program. Identified PGVs that conferred increased cancer risk or were associated with certain autosomal recessive conditions were reported to the treating oncologist. Chart reviews were conducted every 3 months to assess whether PGV identification impacted treatment decision making. **Results:** 169 PGVs were identified in 160 unique patients (15.8% of cohort). 69 PGVs (41%) harbored a clear somatic second hit event in the tumor. PGVs associated with defects in double-strand DNA repair (*BRCA1, BRCA2, ATM, PALB2, BRIP1)* or DNA mismatch repair (*MLH1, MSH2 and PMS2*) were identified in 49 patients (5% of cohort, 31% of patients with PGVs), 37 of which had not previously been identified. 14 PGVs in DNA double-strand repair and 7 PGVs in DNA mismatch repair were identified in cancer types not commonly associated with hereditary breast ovarian cancer or Lynch syndromes, including cancers of unknown primary origin and sarcomas. 7 patients received a PARP inhibitor (PARPi), 3 patients received an immune checkpoint inhibitor (ICI) and 1 patient received both PARPi and ICI therapy on the basis of a PGV in DNA repair. 6 patients achieved clinical benefit, defined as time on treatment $\geq$ 6 months. A patient with cancer of unknown primary origin and PGV in MSH2 achieved exceptional response to ICI therapy, with complete response ongoing and lasting 23 months. **Conclusions:** Targeted NGS of matched tumor/normal samples identified PGVs in about 1 in every 6 patients with metastatic solid tumors. Approximately 40% of PGVs are associated with a somatic second hit in the tumor, supporting their role in tumor pathogenesis. Unexpected PGVs with therapeutic implications are identified in patients with diverse cancer types, providing opportunities to use targeted therapies with potential for significant clinical benefit. Given this finding, testing for PGVs in DNA repair genes should be considered in all patients with metastatic solid tumor malignancies. Research Sponsor: U.S. National Institutes of Health, Other Foundation, University of Michigan Rogel Cancer Center.

1502 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Characterization of patients with multiple primary tumors. *First Author: Karen Anne Cadoo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: 17% of patients (pts) with a cancer diagnosis in the U.S. have a prior malignancy. We sought to characterize pts with multiple (≥2) primary cancers (MPC) & identify potential drivers of cancer risk to guide management. **Methods:** Pts prospectively consented (1/2013-2/2019) to tumor-normal sequencing via custom targeted NGS panel. A subset consented to testing of >76 germline cancer predisposition genes. IARC 2004 rules for defining MPC were applied.Age adjusted gender specific standardized incidence ratios (SIR) for cancer event combinations occurring in at least 5pt were calculated using R statistical package. **Results:** Of 24417 pts sequenced, 4341 had MPC (18%). (Table) 3465 (80%) had 2, 4% had >4 cancers. Cancer pairs where SIR of 2nd cancer was higher than expected included: colon-colon, prostate-pancreas, bladder-prostate in men & lung-lung, breast-pancreas, thyroid-pancreas in women. 1580 (36%) pts had germline testing; 324 (21%) had 361 pathogenic/likely pathogenic (P/LP) variants (vts). Of these, 157 (48%), 66(20%), pts had high, moderate penetrance vts. The remainder had low penetrance, recessive or vts of uncertain utility. Of pts with high penetrance vt, 132 (84%) had at least one tumor type concordant with germline findings. **Conclusions:** 18% of pts in this cohort had MPC. There was a significant excess over expected incidence in some cancer combinations. Of pts with germline testing, 21% had a P/LP vt, with most (69%) being high or moderate penetrance. Assessment for loss of heterozygosity in tumor & germline sequencing of the full MPC cohort is ongoing. Research Sponsor: Robert and Kate Niehaus Center for Inherited Cancer Genomics.

N=4341		N (%)	
Male (M)		1917 (44)	
Female (F)		2424 (56)	
Ever smoker		2230 (51)	
Caucasian		3697 (91)	
Ashkenazi Jewish		919 (21)	
# primary cancers:			
2		3465 (80)	
3		684 (16)	
>4		192 (4)	
Median age at first diagnosis (range)		58 (0-89)	
<18 yrs		11 (2%)	
BMI median (range)			
M		27(16-47)	
F		25 (15-54)	
M	SIR Confidence Interval	F	SIR CI
Cancer 1-Cancer 2	(CI)	Cancer 1-Cancer 2	
Colon-colon	**8 3.9-12.5**	Lung-lung	**13 10.8-15.4**
Prostate-pancreas	**7 5.7-9.4**	Breast-pancreas	**10 7.7-12.6**
Bladder-prostate	**7 5.4-8.4**	Thyroid-pancreas	**9 1.9-18.1**
Lung-Lung	**6 4.5-7.7**	Colon-colon	**7 3.2-12.2**
Colon-pancreas	6 1.2-11.3	Colon-lung	**7 4.3-9.8**
Bladder-lung	**5 3.7-7.2**	Thyroid-lung	**6 3.2-9.3**
Colon-bladder	4 1.1-6.6	Colon-thyroid	5 1.1-10.6
Prostate-bladder	**4 2.7-4.4**	Breast-breast	**5 4.8-5.8**
Prostate-thyroid	3 1.4-5.5	Breast-lung	**5 4.2-5.7**
Colon-Lung	**3 1.6-5.0**	Thyroid-breast	**5 3.1-6.6**
Colon-prostate	**3 1.9-4.3**	Bladder-lung	**5 2.0-7.7**
Prostate-lung	2 2.4-3.5	Breast-thyroid	**3 1.7-3.6**
Thyroid-prostate	2 1.1-3.4	Breast-colon	**2 1.5-3.1**

Bold=second tumor SIR observed>expected

1503 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Performance of the IBIS/Tyrer-Cuzick (TC) Model by race/ethnicity in the Women's Health Initiative. *First Author: Allison W. Kurian, Stanford School of Medicine, Stanford, CA*

Background: The TC model, a breast cancer (BC) risk assessment tool based on family cancer history, reproductive and lifestyle factors is used to guide BC screening and prevention. TC was developed and validated largely in non-Hispanic White (NHW) women. We evaluated the calibration and discrimination of TC version 7.02 among racially/ethnically diverse post-menopausal women enrolled in the Women's Health Initiative (WHI) clinical trials or observational study. **Methods:** WHI enrolled post-menopausal women from 1993-1998 and followed them prospectively for BC incidence. We included women aged ≤80 years at enrollment with no prior BC or mastectomy and with data required for TC, including weight, height, ages at menarche, first birth and menopause, menopausal hormone therapy use and family history of breast or ovarian cancer in first or second-degree relatives. Calibration was assessed by the ratio of observed BC cases to the number expected by TC (O/E), with expected cases calculated as the sum of cumulative hazards. We tested for differential discrimination by race/ethnicity (NHW, African American, Hispanic, Asian/Pacific Islander, Native American, other) using Cox regression. Time to BC was modeled using age, race/ethnicity, TC estimate (transformed by log of relative lifetime risk), and a term for interaction between race/ethnicity and TC estimate. **Results:** During the follow-up period (median 18.9 years, maximum 23.4 years), 6,836 new BC cases were diagnosed among 91,893 women. TC was well-calibrated overall (O/E 0.95) in NHW and African Americans, but over-estimated risk for Hispanics (O/E 0.75, Table). Results suggested good calibration for Asian/Pacific Islanders and Native Americans, but sample sizes were small. Discrimination did not differ significantly by race/ethnicity (two-sided p-value for interaction = 0.33). **Conclusions:** TC provided similar risk discrimination among post-menopausal women of different racial/ethnic groups over nearly 20 years of follow-up; however, it overestimated risk for Hispanics. Future studies in diverse populations are warranted, with need for a more accurate breast cancer risk assessment tool for Hispanics. Research Sponsor: Myriad Genetics, U.S. National Institutes of Health.

Race/Ethnicity	N	Observed (O) BC cases	Expected (E) BC cases	Calibration (O/E Ratio) (95% CI)
NHW	80,260	6133	6408.6	0.96 (0.93-0.98)
African American	5903	373	411.0	0.91 (0.82-1.00)
Hispanic	2368	115	153.2	0.75 (0.62-0.90)
Asian/Pacific Islander	2131	140	139.2	1.01 (0.85-1.19)
Native American	305	22	20.9	1.05 (0.66-1.59)
Other	926	53	66.5	0.80 (0.60-1.04)
TOTAL	91,893	6836	7199.5	0.95 (0.93-0.97)

1504 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Comprehensive breast cancer (BC) risk assessment for CHEK2 carriers incorporating a polygenic risk score (PRS) and the Tyrer-Cuzick (TC) model. *First Author: Shannon Gallagher, Myriad Genetics, Inc., Salt Lake City, UT*

Background: Women with pathogenic variants in the moderate penetrance *CHEK2* gene have on average an estimated > 20% lifetime risk for breast cancer, thereby meeting an established threshold for more aggressive screening, including consideration of breast magnetic resonance imaging (MRI). However, we previously showed that *CHEK2* penetrance is modified by an 86-SNP PRS. *CHEK2* risk is further modified by family history (FH) and other TC model variables. Here, we describe development of a comprehensive risk prediction model for women of European ancestry to more precisely estimate risk by incorporating *CHEK2*, PRS and TC V7.02. The number of *CHEK2* carriers with low (< 20%), moderate (20%-50%) and high (> 50%) remaining lifetime risk based on the combined model was examined in an independent study cohort. **Methods:** This IRB-approved study included de-identified clinical records from 358,471 women of European ancestry who were tested clinically for hereditary cancer risk with a multi-gene panel. Model development was based on analysis of *CHEK2* PV carriers (*N*= 4,331) and women negative for BC gene PV (*N* =353,681) who were tested between September 2013 and July 2019. Risk estimates incorporating *CHEK2*, PRS and TC were calculated using a fixed-stratified (FS) method that accounts for correlations between risk factors in a manner equivalent to multivariable co-estimation. Risk stratification was assessed in an independent cohort of *CHEK2* carriers (*N*= 459) who were tested after July 2019 and not included in model development. **Results:** We detected significant correlation of *CHEK2* status with FH ($p = 4.1 \times 10^{-17}$) and of PRS with FH among *CHEK2* carriers ($p = 1.7 \times 10^{-5}$). For these factors, joint effects were co-estimated using the FS method. In an independent cohort, 24.0% of *CHEK2* carriers were categorized as low risk (< 20%), and 62.6% were categorized as moderate risk (20-50%). For 13.4% of *CHEK2* carriers, risk estimation incorporating PRS and TC generated BC risks of greater than 50%, consistent with genes recognized as highly penetrant. **Conclusions:** In *CHEK2* PV carriers, comprehensive risk assessment could inform individualized decision-making and may lead to improved targeting of screening and prevention strategies. Research Sponsor: Myriad Genetics.

1505 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

BARCODE 1: A pilot study investigating the use of genetic profiling to identify men in the general population with the highest risk of prostate cancer to invite for targeted screening. *First Author: Ros A. Eeles, Institute of Cancer Research and The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Genetic profiling could be used to target population screening for prostate cancer (PrCa). Approximately 170 single nucleotide polymorphisms (SNPs) have been identified that associate with PrCa development. Although these confer a low to moderate risk of PrCa, the risk is cumulative with increasing number of risk alleles. BARCODE1 is the first study to prospectively investigate the use of a genetic profile in PrCa screening in the UK general population. **Methods:** A custom Eurek Genomics (EG) SNP assay was developed. Healthy males aged 55-69 were invited to participate via their General Practitioners (GPs). Saliva samples were collected via mailed collection kits. After DNA extraction, genotyping was conducted using the EG assay and a polygenic risk score (PRS) was calculated for each participant. The PRS was calculated using the sum of the weighted alleles for 130 risk loci. Men in the top 10% of the genetic risk profile were invited for prostate MRI and biopsy at the Royal Marsden Hospital (RMH) in London. **Results:** Invitation letters were sent to 1434 men; overall uptake was 26% (range 13%-47%). 87% of responders were eligible for study entry. DNA was extracted from 303 samples and genotyped. Data were available for 285 men following QC. Mean PRS was 10.33 with a standard deviation of 0.64; twenty-five participants with a PRS above the 90^{th} centile were identified for screening with MRI and prostate biopsy. Of these men (after exclusions due to medical comorbidity/invitations declined) 9 out of 20 had an abnormal MRI (45%) and 18 men underwent biopsy with 7 diagnoses of PrCa (38.8%). All cancers were low-risk with a mean PSA of 1.8 and were managed with Active Surveillance (AS). There were two adverse events following biopsy, both simple lower urinary tract infections managed with oral antibiotics. Average duration of follow-up is 4.5 months (range 1-11). **Conclusions:** Successful completion of recruitment has shown this community study to be feasible, with an average uptake of 26%. Approximately 70 GP sites have been identified to allow a transition to the full BARCODE-1 study which will recruit 5000 men. The use of genetic profiles to guide PrCa screening is attractive; it requires a one-off test utilising germline DNA which can be assessed for risk loci which are constant, unlike PSA which fluctuates. The results of the BARCODE1 study will be important in defining the role of genetic profiling in targeted PrCa population screening. Research Sponsor: European research council.

1506 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Results from MAGENTA: A national randomized four-arm noninferiority trial evaluating pre- and post-test genetic counseling during online testing for breast and ovarian cancer genetic risk. *First Author: Elizabeth M. Swisher, University of Washington School of Medicine, Seattle, WA*

Background: Hereditary breast and ovarian cancer (HBOC) is preventable when genetic risk is identified. We aimed to test whether pre and/or post-test genetic counseling is needed to optimally deliver online accessible genetic testing. **Methods:** MAGENTA (Making GENetic Testing Accessible) is a four-arm non-inferiority trial evaluating electronic genetic education and results delivery alone or combined with pre-test only, or post-test only telephone genetic counseling compared to mandatory pre- and post-test counseling (control arm) in women at risk of HBOC (NCT02993068). Regardless of assigned arm, all subjects with a pathogenic mutation received post-test telephone counseling. All subjects were enrolled electronically as part of either a family history cohort (FHC) or a cascade cohort (CC, known familial mutation). The primary outcome was cancer risk distress at 3 months and the trial was powered for the FHC. Secondary outcomes included completion of testing (i.e., received results), anxiety, depression, quality of life, and decisional regret, all measured by standardized scales. **Results:** Enrollment is complete and a total of 3,822 participants were randomized, 3,111 in FHC and 711 in CC. Participants were enrolled from all 50 states, but most were white/non-Hispanic (88%). Among participants that completed genetic testing, 173 (7.2%) had a mutation in a breast or ovarian cancer gene, with 114 (5.7%) of FHC and 59 (14.2%) of CC. In the primary intention-to-treat analysis of FHC, each of the three experimental arms was non-inferior to the control arm for distress at 3 months ($p < 0.025/3 = 0.0083$). In the CC, no and pre-test only counseling were also non-inferior ($p < 0.025/3 = 0.0083$). Distress was lowest in the arm with neither pre nor post-test counseling. Overall, 318 (18%) participants had very high distress at three month follow-up, and this rate was not significantly different across arms. Anxiety, depression and decisional regret did not have statistically significant differences across arms at follow-up. Test completion was highest in the no counseling arm (86.4%) and lowest in the control arm (60.6%). **Conclusions:** Electronic genetic education and results release without genetic counseling was non-inferior with regard to patient distress and was associated with higher test completion and lower distress. These results support use of a genetic testing paradigm providing individualized genetic counseling only for patients with positive test results. Clinical trial information: NCT02993068. Research Sponsor: Stand up to Cancer.

1507 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

A randomized controlled trial of video-education or in-person genetic counseling for men with prostate cancer (ProGen). *First Author: Huma Q. Rana, Medical Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Approximately 10% of men with advanced prostate cancer (PC) have pathogenic/likely pathogenic variants (PV) in cancer susceptibility genes and their identification may lead to targeted therapy. Genetic testing (GT) can also guide cancer surveillance and prevention for family members. While GT is recommended for men with potentially lethal PC, traditional testing models are strained, and access limited. The ProGen study examined a novel pretest model aimed at providing access to GT while promoting informed consent. **Methods:** Inclusion criteria were: potentially lethal PC (metastatic, localized with Gleason score ≥8, rising/persistent PSA after local therapy), diagnosis age ≤ 55 years, prior malignancy, family history suggestive of a PV and/or at oncologist's discretion. Consented subjects from 3 sites were randomized 3:1 to video education (VE) or in-person genetic counseling (GC). Subjects who consented to GT had 67 genes analyzed (Ambry, USA) with results disclosed by telephone by a genetic counselor. Outcomes included GT uptake, PV prevalence, and survey measures of satisfaction, distress, genetics knowledge, family communication, and impact on cancer care (obtained at the time of intervention, and at 1, 4, and 12 months after result disclosure). Two-sided Fischer exact tests were used for between-arm comparisons. **Results:** Over a 2-year period: 662 subjects were randomized, VE or GC were completed by 604 subjects (VE: 93.1%, GC: 88.8%) of whom 596 subjects (VE:98.9%, GC:97.9%) consented to GT. To date, 591 subjects have completed GT (VE: 99.3%, GC: 98.6%). At the time of intervention, most subjects agreed or strongly agreed that their assigned arm was useful (VE: 95%, GC: 88%). Differences were not statistically significant. Notably, 84 PV were identified in 78 subjects (13.2%), with *BRCA1/2* PV accounting for 32% of subjects with a positive result (*BRCA2*:21, *BRCA1*:4). **Conclusions:** In this randomized trial, both novel VE and traditional GC yielded high GT uptake without significant differences in outcome measures of acceptability and satisfaction. VE enabled access to critical GT results while maintaining the core tenants of informed consent. PV were found in 13.2% of subjects, 32% of whom had *BRCA1/2* PV. Analysis of collected survey data to inform strengths and limitations of VE as compared with pretest GC will be presented. Clinical trial information: NCT03328091. Research Sponsor: 2018 Medical Oncology Department Award.

1508 Oral Abstract Session, Fri, 8:00 AM-11:00 AM

Uptake of oophorectomy in women with findings on multigene panel testing: Results from the Prospective Registry of Multiplex Testing (PROMPT). *First Author: Susan M. Domchek, University of Pennsylvania, Philadelphia, PA*

Background: With the expansion of multigene panel testing for cancer susceptibility, increasing numbers of patients are identified with pathogenic/likely pathogenic variants (P/LP V) in genes which do not have a clearly actionable increased risk of ovarian cancer (OC) (lifetime risk of OC >5%). However, there is concern that patients and/or providers may ascribe OC risk to such genetic findings with the potential for unnecessary oophorectomy (ooph). **Methods:** The Prospective Registry of Multiplex Testing (PROMPT) is an online registry for individuals with a genetic alteration detected on multiplex panel testing for cancer susceptibility. Participants self-enroll and complete baseline and annual follow-up questionnaires. PROMPT has enrolled 7388 participants (6936; 93.9% women) since September 2014. **Results:** 1566 women in the PROMPT registry reported ooph, the indications for which were reported as either cancer treatment (n=481, 30.7%) or benign disease (n=432, 27.6%). An additional 186 (12.8%) reported PV in genes associated with lifetime OC risk >5% (*BRCA1, BRCA2, RAD51C, RAD51D, BRIP*, or Lynch syndrome genes). The remaining 467 did not have guideline based indications for ooph due to OC risk and are described further here. 92 (19.7%) had a variant of uncertain significance (VUS) in genes associated with OC, 241 (51.6%) had a personal history of breast cancer (BC) and no VUS in OC genes, and 119 (25.5%) had no personal history of BC and no VUS in OC genes. The majority of women had no family history (FH) of OC in first or second degree relatives (Table). Most ooph occurred prior to age 50. Of the 405 women with *CHEK2* P/LP, 11.4% reported ooph (59% under age 50 when age known), as did 13.2% (of 228) with *CHEK2* VUS, 8.8% (of 261) with *ATM* P/LP (66.7% under age 50), and 8.3% (of 387) with *ATM* VUS. In addition, of the 184 women with *PALB2* P/LP, 14.1% reported ooph (35.3% under age 50) as did 11.6% (of 198) with *PALB2* VUS. Of those who reported provider discussions, 47.2% stated "my provider recommended this" (including >60% in the OC gene VUS group) and an additional 25.2% stated "my provider presented this as an option, but not a requirement". In those with no FH of OC, 45.8% stated that their provider recommended ooph. **Conclusions:** 10-15% of women with PV/VUS in genes not associated with a high risk of OC reported ooph without a clear indication. Research Sponsor: Komen, Breast Cancer Research Foundation.

Underwent ooph	No reported FH OC	Ooph <50
VUS in gene associated with OC N=92	68.1%	51.5%
Personal history BC (no OC VUS) N=241	85.0%	58.7%
No BC, no OC VUS N=119	56.2%	73.0%

1510 Poster Discussion Session; Displayed in Poster Session (Board #2), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Vitamin D supplements and marine omega-3 fatty acids and development of advanced cancer. *First Author: Paulette Chandler, Brigham and Women's Hospital/Harvard Medical School, Boston, MA*

Background: Epidemiologic data suggest that vitamin D supplementation may reduce cancer mortality. We tested whether vitamin D and/or omega-3 supplementation reduces the incidence of advanced stage cancer at diagnosis or lethal cancer, and whether body mass index (BMI) modifies these associations. **Methods:** The VITamin D and OmegA-3 TriaL (VITAL) is a randomized, placebo-controlled, 2x2 factorial trial of vitamin D3 (cholecalciferol, 2000 IU/day) and marine omega-3 fatty acids (1 g/day) that enrolled men aged ≥50 years and women aged ≥55 years free of cancer and cardiovascular disease at baseline. For this particular analysis, the primary outcome is a composite of metastatic and fatal invasive total cancer. Secondary analyses included examination of BMI (<25, 25-<30, and >= 30 kg/m^2) as effect modifiers of the observed associations. **Results:** VITAL randomized 25,871 participants, among whom 1,617 were diagnosed with invasive cancer over a median 5.3 year intervention period. No significant differences by treatment arm (vitamin D vs placebo: hazard ratio [HR]=0.96; 95% confidence interval, 0.88-1.06; p=0.47; omega-3 vs placebo; HR 1.03 [0.93-1.13]; p=0.56) were observed. However, a significant reduction in advanced cancers (metastatic or fatal) was found for those randomized to vitamin D, compared to placebo (226 assigned to vitamin D and 274 to placebo; HR 0.83 [0.69-0.99]; p=0.036). There was no difference by omega-3 assignment (246 assigned to omega-3 and 254 to placebo: HR 0.97 [0.81-1.15], p=0.72). When stratified by BMI, there was a significant reduction for the vitamin D arm in incident metastatic or fatal cancer among those with normal BMI (BMI<25: HR 0.62 [0.45-0.86], but not among those who were overweight or obese (BMI 25-<30: HR 0.89 [0.68-1.17]; BMI >=30: HR 1.05 [0.74-1.49]); p for interaction by BMI =0.03. There was no effect modification by BMI noted for the omega 3 arm. **Conclusions:** In a randomized clinical trial, supplementation with vitamin D, but not omega-3s, reduced incidence of advanced (metastatic or fatal) cancer in the overall cohort, with strongest risk reduction in normal weight individuals. Further research is needed to understand these findings. Clinical trial information: NCT01169259. Research Sponsor: U.S. National Institutes of Health.

1511 Poster Discussion Session; Displayed in Poster Session (Board #3), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Complete human papillomavirus vaccination coverage over a 13-year period in a large population of privately insured U.S. patients. *First Author: Yull Edwin Arriaga, University of Texas Southwestern Medical Center, Dallas, TX*

Background: In the US, Human Papillomavirus (HPV) vaccination coverage is low, particularly in adolescents aged 13-15 years with respect to the Healthy People 2020 goal of 80%. There has been variability in the definition of measuring vaccination coverage in published studies. We examined complete HPV vaccination coverage in a population of privately insured individuals in the US. **Methods:** This retrospective study used IBM MarketScan Commercial Database, years 2006 to 2018. Inclusion criteria were ages 9 to 45 years and continuous enrollment from age 9 years or from 2006. Complete HPV vaccination coverage was defined as receipt of 2 doses (age 9-15 years) or 3 doses (age 16-45 years) within 12 months and stratified by year, demographics, and US region. Mean vaccination costs per dose were summarized by vaccine brand and health plan type. **Results:** The table summarizes complete HPV vaccination coverage by selected age groups for 2006 (n=12,221,938), 2010 (n=4,692,633), 2014 (n=2,808,132), and 2018 (n=1,662,148). From 2017 to 2018, the percentage of members who received HPV vaccine increased; for females ages 13-15 by 1% and 16-17 by 5% while for males ages 13-15 by 6% and 16-17 by 15%. In 2018, by region, the highest coverage was in females aged 18-26 at 53% and males aged 16-17 at 43% in the Northeast, and mean cost for each brand was $120 (-6% from 2017), $165 (-3%) and $220 (+5%) for Cervarix (n=151), Gardasil (n=8,201) and Gardasil 9 (n=139,356), respectively. The rate of utilization of Gardasil 9 increased from 33% (2015) to 94% (2018) of all vaccines. The lowest mean HPV vaccine cost by health plan type and brand was with Point-of-Service (POS) and Cervarix at $106, and the highest was with POS with Capitation and Gardasil 9 at $243. **Conclusions:** In a commercially insured US population, complete HPV vaccination coverage was lower than the Healthy People 2020 goal, but increased over time. Coverage varied according to health plan type and by region. In 2018, Gardasil 9 had the highest mean cost but was the most utilized vaccine, which may be related to broader coverage of HPV types. This study was limited by the transient nature of member enrollment and complexity of measuring complete vaccination coverage. These results should inform policy makers and practicing clinicians about the gap in vaccination coverage. Research Sponsor: IBM Watson Health.

Complete HPV vaccination coverage by year, sex, and age.

		Vaccination Coverage (%) by Year			
Sex	**Age (years)**	**2006**	**2010**	**2014**	**2018**
Female	11-12	0	13	20	19
	13-15	0	26	32	37
	16-17	0	27	37	43
	18-26	0	19	34	41
Male	11-12	0	0	14	16
	13-15	0	0	20	32
	16-17	0	0	13	33
	18-26	0	0	4	18

1512 Poster Discussion Session; Displayed in Poster Session (Board #4), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Smoking cessation (SC) and lung cancer (LC) outcomes: A survival benefit for recent-quitters? A pooled analysis of 34,649 International Lung Cancer Consortium (ILCCO) patients. *First Author: Aline Fusco Fares, Princess Margaret Hospital, Toronto, ON, Canada*

Background: Tobacco smoking profoundly impacts LC risk; however, data are limited as to what extent SC prior to diagnosis impacts LC overall survival (OS) and lung cancer specific survival (LCSS). LC screening offers a possible teachable moment, but there is uncertainty of SC benefits after a lifetime of smoking. We use the ILCCO database to answer if SC prior to LC dx is associated with better OS and LCSS, considering time since smoking cessation (TSSC). **Methods:** Using individual data, analysis was performed on 17 ILCCO studies with available TSSC to estimate survival using univariable analysis and models of stage-adjusted and cumulative smoking-adjusted multivariable analysis. Adjusted Hazard Ratios (aHR) from Cox models, cubic spline smooth curves and Kaplan-Meier curves were created. Sensitivity analysis was performed for TSSC and LCSS on 13 studies. **Results:** Of 34649 patients, 14322 (41%) were current smokers 14273 (41%) ex-smokers and 6054 (18%) never smokers at diagnosis. We confirmed that ex-smokers (aHR 0.88 CI 0.86-0.91) and never smokers (aHR 0.76 CI 0.73-0.8) improved OS compared to current smokers. Amongst ex-smokers, < 2y TSSC (aHR 0.88 CI 0.82-0.94), 2-5y TSSC (aHR 0.83 CI 0.77-0.90) and > 5y TSSC (aHR 0.8 CI 0.76-0.84) had improved OS compared to CS. Sensitivity analysis showed a trend towards improved LCSS survival for < 2y TSSC (aHR 0.95 CI 0.86-1.05) and 2-5y TSSC (aHR 0.93 CI 0.83-1.04), whereas > 5y TSSC significantly improved LCSS by 15% (aHR 0.85 CI 0.78-0.92). To mimic the LC screening participants, in analysis of > 30 pack-years individuals, associations were strikingly strong: < 2y TSSC had improved OS by 14% (aHR 0.86 CI 0.80-0.93); 2-5y TSSC by 17% (aHR 0.83 CI 0.76-0.90); and > 5 TSSC by 22% (aHR 0.78 CI 0.74-0.83), compared to current smokers; for < 30 packs-years, a trend towards better OS was observed for < 2y TSSC (aHR 0.95 CI 0.92-1.02) and 2-5y TSSC (aHR 0.86 CI 0.74-1.01), whereas > 5y TSSC improved OS by 23% (aHR 0.77 CI 0.72-0.82). **Conclusions:** Among ex-smokers, the risk of overall death was reduced by 12% on < 2y TSSC, 17% on 2-5y TSSC and 20% > 5y TSSC, whereas for LCSS, the benefit was significant only for > 5y TSCC, compared to current smokers at time of diagnosis. Here we demonstrate that convincing screening participants to quit smoking at any point of their trajectory, even just prior to dx such as < 2y TSSC, improved OS, and LCSS benefit was present beyond 5y of quitting. These relationships are independent of pack-years, age, across all stages and other prognostic variables. Research Sponsor: ILCCO studies: including multiple supporters (Alan Brown Chair in Molecular Genomics, NCI grants, the Intramural Research Program of the Center for Cancer Research, Mayo Foundation, etc).

1513 Poster Discussion Session; Displayed in Poster Session (Board #5), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

The impact of poly ADP ribose polymerase (PARP) inhibitors on clonal hematopoiesis. *First Author: Kelly L Bolton, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Poly (ADP-ribose) polymerase (PARP) inhibitors are an important new class of anti-cancer therapies. Therapy-related myeloid neoplasia (tMN) has been reported following PARPi therapy, and is associated with adverse outcomes. Further insight is required into the risk of tMN conferred by PARPi therapy, independent of germline genetic background and prior therapy. We have shown that oncologic therapy selects for acquired mutations in the blood (clonal hematopoiesis; CH) particularly those in the DNA damage response pathway (DDR) including *PPM1D*, *TP53* and *CHEK2* and that CH confers an increased risk of tMN. We hypothesized that characterization of the relationship between CH and PARPi therapy provides insight into its potential for leukemogenesis and may offer opportunities for tMN prevention. **Methods:** We assessed for CH in the blood of 10,156 cancer patients, including 54 who received PARPi therapy, 5942 who received another systematic therapy or radiation therapy and 4160 untreated prior to blood draw. **Results:** Patients exposed to PARPi therapy were more likely to have CH (33%) compared to those exposed to other systemic therapies or radiation (18%) or untreated patients (16%). This was particularly pronounced for DDR CH; 25% of PARPi treated patients had DDR CH compared to 2% of untreated patients. In a multivariable model accounting for demographics, exposure to chemotherapeutic agents, radiation therapy and germline *BRCA* mutation status, exposure to PARPi conferred an increased risk of DDR CH (OR = 3.6, 95% CI 1.5-8.5, p = 0.004). This effect was attenuated after accounting for cumulative exposure to therapy (OR = 2.8, 95% CI 0.97-8.2, p = 0.06) suggesting a multifactorial contribution to the enrichment of CH following PARPi therapy. To characterize this further we performed a prospective collection of patients with CH over a median follow-up time of 58 months. During the follow-up period, 17 patients received PARPi, 360 received cytotoxic therapies or radiation and 232 were untreated or received targeted therapies. The growth rate of DDR CH was significantly higher among those who were exposed to PARPi (median, +2.8% increase in VAF per year) compared to untreated patients (+0.08% per year, p = 0.02) and those exposed to other cytotoxic therapies (+1% per year, p = 0.04). **Conclusions:** Taken together our data suggests that PARPi therapy promotes the expansion of DDR CH. Future studies should examine the potential of CH to identify individuals at high risk of tMN following PARPi therapy and to develop therapies aimed to prevent tMN in patients with CH. Research Sponsor: Internal Funds.

1514 Poster Discussion Session; Displayed in Poster Session (Board #6), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Clinical conundrums: Developing a strategy for discerning TP53-associated chip and coherent clinical care. *First Author: Jeffrey N. Weitzel, City of Hope, Duarte, CA*

Background: Germline *TP53* mutations are associated with Li-Fraumeni syndrome (LFS). However, approximately 20% of commercial laboratory multigene panel test (MGPT)-detected pathogenic *TP53* variants represent aberrant clonal expansion (ACE), rather than a germline finding, and are often detected in individuals that lack classic features of LFS. Clonal hematopoiesis (CH) is a form of ACE, and in the absence of an abnormal hemogram is termed Clonal hematopoiesis of indeterminate potential (CHIP). CHIP is often associated with a pathogenic variant (PV) in hematopoietic pathway gene(s) at a variant allele frequency (VAF) less than expected for a heterozygous germline finding. The prevalence increases with age and exposure to chemotherapy. The presence of a skewed VAF is usually noted in a comment on a genetic test result, however, clinicians without genetic training often lack understanding of the comment and need strategies to discern the difference between germline findings, CHIP, and post-zygotic mosaicism. Our studies illuminate possible strategies for discernment for clinicians. **Methods:** Among 113 cases with MGPT-detected *TP53* PVs, enrolled in the Clinical Cancer Genomics Community Research Network registry, we obtained additional tissues, family history and complete blood count (CBC) reports on 42 cases. DNA extracted from formalin fixed paraffin embedded (FFPE) tumor/normal tissues, blood, saliva, eyebrow plucks, was analyzed using a previously validated custom myeloid and CH gene (n = 79) amplicon-based QIAseq panel. PVs with VAF $>$ 2% were included in analyses. **Results:** Germline status was confirmed for 6 cases (one with a CH PV), post-zygotic mosaicism was supported for 5 cases and 2 were indeterminant. 12 had results supporting ACE/CH, with additional CH-associated PV(s) identified in 5/12 (41%); n = 2 of each *TET2*, *ATM*, *TP53*; and increasing VAF over time for the driver *TP53* PV was noted in 2. Of these 2 one was identified to have a hematopoietic malignancy identified through analysis of the CBCs and bone marrow biopsy in parallel with the increasing VAF. Additional results are pending for 7 cases. **Conclusions:** With the use of our multi-tissue NGS strategy, serial sampling of suspected ACE/CH cases, family history and CBC analyses we were able to discern the status of most *TP53* genetic findings. This work has direct translational impact, refining risk estimation and improving the clinical care of patients with *TP53* PVs, while avoiding unnecessary LFS-related care and enabling appropriate care for those with ACE. Research Sponsor: U.S. National Institutes of Health.

1515 Poster Discussion Session; Displayed in Poster Session (Board #7), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Genetic counseling referrals after next generation sequencing testing. *First Author: Rafael Gonzalez, Duke University Health System, Durham, NC*

Background: Next generation sequencing (NGS) testing of tumor tissue or blood is performed to identify 'actionable' mutations that might guide patient care. NGS testing might incidentally identify germline mutations associated with cancer syndromes. No distinction is made between germline and somatic alterations on NGS reports, thus confirmatory germline testing is required. In this quality improvement (QI) initiative, we evaluated the frequency of referrals to genetic counseling (GC) for patients with potentially heritable germline mutations identified through NGS testing. **Methods:** We generated a list of high-risk mutations (HRMs) which merit GC referral based on NCCN guidelines. NGS test results for 3,400 consecutive patients with solid tumor malignancies were reviewed by the molecular tumor board from 1/2014-9/2019 and were screened for pathogenic HRMs. Basic demographic, oncologic, and GC data were retrospectively abstracted for each patient. The outcomes of interest were the frequency of HRMs identified through NGS testing, the proportion of patients subsequently referred to GC, and the proportion of patients ultimately diagnosed with a hereditary cancer syndrome. **Results:** 472 individual patients (14%) had NGS testing with one or more HRM identified; 465 patients were evaluable which corresponded to 519 HRMs that were included in the analysis (Table). Malignancies included were gastrointestinal 199 (42.8%), lung 83 (17.8%), genitourinary/renal 56 (12.0%), breast 49 (10.5%), gynecologic 35 (7.5%), and other 43 (9.2%). 75 (16.1%) patients had germline testing prior to NGS testing. Of those patients without prior germline genetic testing, 62 (15.9%) were referred to GC, and 19 (4.9%) patients were diagnosed with a hereditary cancer syndrome. **Conclusions:** Tumor NGS testing identifies HRMs that may represent an undiagnosed heritable germline mutation. Providers ordering NGS tests should review results for HRMs, refer to GC when appropriate, and offer confirmatory germline testing for patients and their families. Research Sponsor: None.

HRM	Frequency, N	Referred to GC, n (%)	+ Hereditary germline mutation, n (%)
MLH1	10	2 (20.0)	1 (10.0)
MSH2	18	1 (5.6)	4 (22.2)
MSH6	18	6 (33.3)	3 (16.7)
PMS2	12	3 (25.0)	4 (33.3)
SMAD4	149	12 (8.1)	3 (2.0)
BMPR1A	1	1 (100)	0 (0)
BARD1	5	0 (0)	0 (0)
BRCA1	54	9 (16.7)	15 (27.8)
BRCA2	75	27 (36.0)	19 (25.3)
BRIP1	12	3 (25.0)	3 (25.0)
PALB2	18	3 (16.7)	1 (5.6)
RAD51C	4	0 (0)	0 (0)
NBN	8	1 (12.5)	0 (0)
ATM	108	13 (12.0)	4 (3.7)
CHEK2	27	4 (14.8)	4 (14.8)

1516 Poster Discussion Session; Displayed in Poster Session (Board #8), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

The prevalence of germline mutations among patients with solid tumors with genomic alterations identified on tumor testing: Results from a tertiary care academic center molecular tumor board. *First Author: Catherine Watson, Duke University, Durham, NC*

Background: The proportion of germline versus somatic mutations identified on genomic tumor testing of solid malignancies is not well characterized. We compared somatic and germline testing results in patients with breast, ovarian, pancreatic or prostate cancer with a genomic alteration identified on tumor testing. **Methods:** Retrospective chart review was performed using a tertiary care academic center's database of somatic tumor testing results obtained via FoundationOne and Guardant testing. Patients with breast, ovarian, pancreatic or prostate cancer who had a genomic alteration identified on tumor testing, including pathogenic and VUS variants, in *BRCA1*or *BRCA2*,*CHEK2*, *ATM*, *BRIP1*, *RAD51-C*,*RAD51D*, *PALB2*and *CDH1*and who had also received germline testing were identified. Analysis was performed to assess prevalence of germline results. The association between mutant allele fraction (MAF) and germline mutation status was also assessed. **Results:** Results: 124 patients with breast, ovarian, pancreatic or prostate cancer were identified who had a genomic alteration of interest also tested for via germline testing. 54 (32.5%) of tumor mutations were also identified on germline testing. Proportion of genomic results that were germline was wide, ranging from 0-85.7% depending on the gene and variant classification (Table). Germline mutations were present in 36.4% of breast, 25% of ovarian, 53.3% of pancreatic, and 20.9% of prostate cancer patients who had a tumor alteration present. Alterations that were found to be concordant in both somatic and germline testing had an average MAF of 0.54, and alterations identified on somatic testing only had an average MAF of 0.30. **Conclusions:** Our findings suggest that approximately one-third of genomic alterations on tumor testing will be of germline origin. However, concordance rates may be gene and variant dependent. Higher MAF may be associated with germline alteration status, but further evaluation is needed. Thus, while information provided by genomic tumor testing may be suggestive of a correlating germline mutation, no single alteration type or MAF value is reliably predictive. Research Sponsor: None.

Concordance between somatic and germline alterations.

Gene	Total N	Somatic and Germline (%)
BRCA1	29	10 (34.5)
BRCA2	62	20 (32.3)
RAD51C	2	0 (0)
BRIP1	6	2 (33.3)
PALB2	9	7 (77.8)
BARD1	8	2 (25)
ATM	32	6 (18.8)
CHEK2	7	6 (85.7)
CDH1	11	1 (9.1)

1517 Poster Discussion Session; Displayed in Poster Session (Board #9), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

The impact of tumor NGS testing on hereditary cancer risk assessment and population management in an integrated community health care system. *First Author: Sachdev P. Thomas, Kaiser Permanente, Dept of Medical Oncology, Vallejo, CA*

Background: Next-generation sequencing (NGS) for tumor molecular profiling is used in Oncology to identify 'actionable alterations' for clinical trials or on/ off-label therapy. Tumor NGS can also reveal potentially heritable germline mutations. The frequency of such incidental germline mutations has been estimated to be 4-15%. The 2015 ASCO Statement supports communication of medically relevant incidental germline findings from somatic mutation profiling to patients (PTS). The impact of tumor NGS testing on hereditary cancer risk assessment programs in the context of a wider population management strategy is unknown. We sought to evaluate this within our Kaiser Permanente Northern California (KPNC) population with ready access to tumor NGS and an ongoing hereditary cancer risk assessment program. **Methods:** Kaiser Permanente Northern California (KPNC) is part of a large, integrated health care system. NGS at KPNC is performed in collaboration with STRATA Oncology, a precision oncology partnership. All NGS results are reviewed by a multidisciplinary KPNC Genomic Oncology Committee (GOC)which also includes genetic counselors and pathologists. We examined all NGS reports between November 2017 through December 2019 to determine the types of cancers tested, number with a possible germline mutation and number referred for genetic counseling and testing (GCT). **Results:** 4,825 PTS with advanced cancer underwent STRATA NGS testing. A total of 207 PTS (4.3%) were identified as potential germline mutation carriers, all 207 were recommended for GCT referral. Of these, 92 (45.0%) separately met 2020 NCCN Criteria for Genetic/Familial High-Risk Assessment (2020NG/FA), prior to tumor NGS; 115 (53.6%) did not and 3 (1.4%) had insufficient information. The cancers most frequently meeting NCCN criteria were pancreatic, breast and colon. Of the 92 PTS who met 2020NG/FA, 60 (65%) underwent GCT and 34 (57%) were confirmed to have a germline mutation. Of the 115 PTS that did not meet 2020NG/FA, 47 (41%) underwent GCT and 19 (40%) were confirmed to have a germline mutation. Overall germline mutations were confirmed in 16.5% of patients who did not meet 2020NG/FA and 37% who did. **Conclusions:** In our community-based integrated healthcare system, systematic review of next-generation sequencing results by an expert GOC led to more robust identification of germline mutation carriers and navigated them to appropriate GCT. Ongoing work will clarify data on cascade testing. We are currently developing automated workflows for GCT. Research Sponsor: None.

1518 Poster Discussion Session; Displayed in Poster Session (Board #10), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Expanding the diagnostic yield of germline genetic testing in cancer patients using deep learning. *First Author: Saud H Aldubayan, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: Germline genetic analysis is an essential tool for implementing precision cancer prevention and treatment. However, only a small fraction of cancer patients, even those with features suggestive of a cancer-predisposition syndrome, have detectable pathogenic germline events, which may in part reflect incomplete pathogenic variant detection by current gold-standard methods. Here, we leveraged deep learning approaches to expand the diagnostic utility of genetic analysis in cancer patients. **Methods:** Systematic analysis of the detection rate of pathogenic cancer-predisposition variants using the standard clinical variant detection method and a deep learning approach in germline whole-exome sequencing data of 2367 cancer patients (n = 1072 prostate cancer, 1295 melanoma). **Results:** Of 1072 prostate cancer patients, deep learning variant detection identified 16 additional prostate cancer patients with clinically actionable pathogenic cancer-predisposition variants that went undetected by the gold-standard method (198 vs. 182), yielding higher sensitivity (94.7% vs. 87.1%), specificity (64.0% vs. 36.0%), positive predictive value (95.7% vs. 91.9%), and negative predictive value (59.3% vs. 25.0%). Similarly, germline genetic analysis of 1295 melanoma patients showed that, compared with the standard method, deep learning detected 19 additional patients with validated pathogenic variants (93 vs. 74) with fewer false-positive calls (78 vs. 135) leading to a higher diagnostic yield. Collectively, deep learning identified one additional patient with a pathogenic cancer-risk variant, that went undetected by the standard method, for every 52 to 67 cancer patients undergoing germline analysis. Superior performance of deep learning, for detecting putative loss-of-function variants, was also seen across 5197 clinically relevant Mendelian genes in these cohorts. **Conclusions:** The gold-standard germline variant detection method, universally used in clinical and research settings, has significant limitations for identifying clinically relevant pathogenic disease-causing variants. We determined that deep learning approaches have a clinically significant increase in the diagnostic yield across commonly examined Mendelian gene sets. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

1519 Poster Discussion Session; Displayed in Poster Session (Board #11), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Deep learning to identify high-risk smokers for lung cancer screening from chest radiographs. *First Author: Vineet Raghu, Cardiovascular Imaging Research Center (CIRC), Department of Radiology, Massachusetts General Hospital & Harvard Medical School, Boston, MA*

Background: Appearance on chest radiography may inform selection of high-risk smokers for lung cancer screening CT, beyond Centers for Medicare & Medicaid Services (CMS) eligibility criteria. **Methods:** A convolutional neural network (CXR-LC) predicting 12-year incident lung cancer from the chest radiograph image, age, sex, and smoking status (current/former) was developed in 41,856 persons aged 55-74 from the Prostate, Lung, Colorectal & Ovarian trial (PLCO). The final model was tested in held-out smokers from PLCO (n=5,615, 37.9% CMS eligible, 12-year follow-up), and externally in the National Lung Screening Trial (NLST, n=5,493, all CMS eligible, 6-year follow-up). Sensitivity was compared at a fixed screening population size defined by CMS eligibility. Ordinal CXR-LC risk score (low/indeterminate/high/very high) was based on development dataset 12-year probability thresholds (<2%/2-<3.3%/3.3-<8%/≥8%). Results are provided in test datasets only. **Results:** In the PLCO test dataset, CXR-LC was more sensitive than CMS eligibility at a fixed screening population size (74.9% vs. 63.8%, p=0.01) and missed 30.8% fewer lung cancers. CXR-LC risk groups were associated with incident lung cancer in PLCO test dataset smokers (very high vs. low CXR-LC risk: 12.4 vs 1.1 lung cancers/1,000 person-years) with external testing in NLST (all CMS eligible: 12.7 vs 2.3) (Table). This association was robust to adjustment for radiologist findings and the PLCOm2012 risk score. **Conclusions:** CXR-LC identified smokers at high risk of incident lung cancer, beyond CMS eligibility. Research Sponsor: U.S. National Institutes of Health.

Incident lung cancer within CXR-LC risk strata by test dataset.

	PLCO (N = 5,615)				NLST (N = 5,493)			
CXR-LC risk score	12-year lung cancer incidence (%)	per 1,000 person-years (95% CI)	Adj HR* (95% CI)	p	6-year lung cancer incidence (%)	per 1,000 person-years (95% CI)	Adj HR* (95% CI)	p
Low	30 / 2541 (1.2%)	1.1 (0.8,1.6)	Ref		17/1279 (1.3%)	2.3 (1.4,3.7)	Ref	
Indeterminate	22 / 948 (2.3 %)	2.2 (1.4,3.3)	1.8 (1.0,3.1)	0.04	17/871 (2.0%)	3.4 (2.1,5.5)	1.3 (0.7,2.6)	0.41
High	82 / 1497 (5.5%)	5.3 (4.3,6.6)	4.0 (2.6,6.1)	<0.001	115/2509 (4.6%)	8.1 (6.8,9.8)	3.0 (1.8,5.1)	<0.001
Very High	73 / 629 (11.6%)	12.4 (9.8,15.6)	7.5 (4.8,11.9)	<0.001	57/834 (6.8%)	12.7 (9.8,16.4)	3.9 (2.2,6.9)	<0.001
Total	207 / 5615 (3.7%)	3.5 (3.1,4.0)			206/5493 (3.8%)	6.6 (5.8,7.6)		

*adjusted for PLCOm2012 score and radiologist findings Abbreviations: Adj HR, Adjusted Hazard Ratio; CI, confidence interval

1520 Poster Discussion Session; Displayed in Poster Session (Board #12), Fri, 8:00 AM-11:00 AM, Discussed in Poster Discussion Session, Fri, 8:00 AM-11:00 AM

Comparing and assessing the reported penetrance of cancer susceptibility genes for breast cancer. *First Author: Kanhua Yin, Massachusetts General Hospital, Boston, MA*

Background: It is critical for oncologists to be aware of unbiased and interpretable cancer risks (i.e., penetrance) in carriers with germline pathogenic variants in cancer susceptibility genes. However, relevant literature is large and varies significantly in study design, patient ascertainment, and types of risk estimates reported. This heterogeneity can cause inconsistent conclusions between studies and create barriers for clinicians to understand and apply them in practice. To further understand the current literature, we assessed penetrance studies associated with non-BRCA breast cancer susceptibility genes based on study design and ascertainment adjustment. **Methods:** We used a validated natural language processing-based abstract classifier to identify all penetrance studies regarding eleven genes: ATM, BARD1, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, RECQL, STK11, and TP53. Relevant studies were then manually annotated as "with ascertainment adjustment" if a study was based on: (1) a general population; (2) a pedigree analysis or a family-based study with appropriate ascertainment adjustment; or (3) a hospital-based study or a panel testing analysis with well-matched cases and controls. **Results:** A total of 49 penetrance studies were identified, with a median of nine studies for each gene (range: 4-16). The case-control study was the dominant study type, accounting for over 80% in five genes, 50% in two genes, and 18% to 43% in the other four genes. The proportion of studies with ascertainment adjustment was generally low (mean: 33%) and varied widely between different genes (7% to 80%). Contradictory breast cancer risks (no increased risk vs. significantly increased risk) were found in eight genes (73%) (Table). The most common ascertainment bias identified was a case-control study with cases (patients) who had a strong family history but using general population controls. **Conclusions:** Ascertainment bias is common in penetrance studies, but few studies adjust for it appropriately. Clinicians should be aware of this issue, and new methods are warranted to select unbiased risk estimates, synthesize them, and provide the accurate general-population penetrance. Research Sponsor: None.

As an example: Reported penetrance of NF1 for breast cancer.

First author	Study design	Risk type	Risk estimates (95%CI)	Statistical significance
Wang X	Cohort	SIR	5.2 (2.4-9.8)	Yes
Sharif S	Cohort	SIR	3.5 (1.9-5.9)	Yes
Uusitalo E	Cohort	SIR	3.04 (2.06-4.31)	Yes
Walker L	Cohort	SIR	1.87 (0.61-4.37)	No
Madanikia SA	Cohort	SIR	1.71 (0.54-4.12)	No
Couch FJ	Case-control	OR	0.94 (0.55-1.62)	No

1521 Poster Session (Board #13), Fri, 8:00 AM-11:00 AM

Evaluation of a mainstream model of genetic testing for men with prostate cancer. *First Author: Tahlia Scheinberg, Chris O'Brien Lifehouse, Camperdown, Australia*

Background: In order to identify the ~12% with inherited cancer predisposition, it is recommended that all men with metastatic prostate cancer (mPC) be offered testing. This has implications for treatment choices and cancer prevention in family. Limited geneticists/genetic counsellors globally present a major barrier to testing. We tested a potential solution, mainstreaming, where testing is performed by the patient's oncologist. **Methods:** Men with mPC at three Australian sites were offered germline genetic testing at their medical oncology appointment. Panel testing (*ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *EPCAM*, *FANCA*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2*, *RAD51D* and *TP53*) was performed on saliva/blood (Invitae). Primary outcomes were clinician and patient acceptability (modified Royal Marsden Satisfaction Questionnaires). Secondary outcomes included mutation rates and cost-effectiveness. A sample size of 44 provided 90% power, with a one-sided alpha of 5%, to distinguish a proportion of men happy with mainstreaming of 80% vs. 60% or less. Allowing for 25% drop-out, we aimed to recruit 60 men. **Results:** Of 66 men offered testing from April to November 2019, 63 (95%) accepted. Four pathogenic variants were identified (2 *BRCA2*, 1 *NBN*, 1 *MSH6*). 48 patients and eight clinicians completed questionnaires. Acceptability was high. All (48/48) patients were happy to have been tested, and 45/48 (94%) were happy to have been tested at their oncology appointment. All were happy to receive their results from their oncologist. All clinicians were satisfied mainstreaming and 88% (7/8) felt confident doing so. Mainstreaming was cost-effective, requiring 87% fewer genetic consultations than traditional genetic counselling. **Conclusions:** This study shows that mainstreaming of men with mPC is feasible, resource efficient and acceptable to both clinicians and patients. Widespread implementation as a new standard of care would facilitate timely access to genetic testing for men with mPC. Research Sponsor: Cancer Institute NSW, Sydney Catalyst, University of Sydney, Australian Prostate Cancer Research Centre, NSW.

1522 Poster Session (Board #14), Fri, 8:00 AM-11:00 AM

Discovery of a core-panel of markers for a blood-assay for cancer detection utilizing cfDNA methylation changes. *First Author: Lasika Seneviratne, SCORA/LA Cancer Network, Los Angeles, CA*

Background: Cancer screening is limited to several cancers despite improved outcome A screening test should be acceptable, safe, and relatively inexpensive[1] Tumors shed cfDNA to the blood where abundant tumor-specific methylation changes can be detected [1]https://www.who.int/cancer/detection/variouscancer/en/. **Methods:** This is a prospective, multicenter, observational study under two protocols NCT04264767, NCT04264754. Plasma was collected from 1,255 subjects: 586 treatment-naïve cancer patients and 639 controls, in 21 sites and biobanks. Training set I (211 cases/99 controls) was used to select the 6 final markers for the core panel, training set II (200 controls) was used to lock the algorithm, and set the threshold to a score yielding specificity of 95%. The validation set (342 cases/310 controls) was performed utilizing the pre-specified algorithm and threshold. Plasma was separated from a single EDTA tube within 4 hours of blood draw. EpiCheck's reagents and methylation-sensitive enzymes (Nucleix, Israel) were used for DNA extraction, digestion, and amplification in real-time PCR (ABI 7500 Fast Dx, Applied Biosystems). **Results:** Age was comparable but sex and smoking history were different (more women in cases, more smokers in controls). In the validation cohort twelve cancer types were included, with prominent representation of major cancer types (19% Breast, 14% colorectal and 21% lung) and stages I&II (56%). Specificity and sensitivity were maintained high at 94% and 62%. Highest sensitivity was demonstrated in GI cancers (77% colorectal, 83% esophageal, 100% gastric) and non-solid malignancies (83%). Sensitivity in early stage cancers (stages I, II & IIIA) was 51%, led by Sarcoma (83%) esophageal (76%) and colorectal (61%). **Conclusions:** This 6-marker blood-based methylation assay is a promising initial component in a future cancer screening test, generating significant signal in early cancers and utilizing simple and inexpensive PCR technology. Clinical trial information: NCT04264767, NCT04264754. Research Sponsor: Nucleix.

	Training I (cases)	Training I (controls)	Training II (controls)	Validation (cases)	Validation (Controls)
N	211	99	200	342	310
Sex, M/F	91/118	84/15	149/51	134/208	217/93
Age, median (range)	64 (25-93)	54 (45-81)	60 (45-84)	63 (25-91)	61 (43-83)
Smoking history (current /former/never/ unk)	25/11/68/107	27/72/0/0	62/134/4/0	69/48/70/155	85/207/17/1
Specificity %		96	95		94
Sensitivity %	60			62	
Sensitivity by stage – solid tumors % (I/II/III/IV)	27/ 57/ 74/ 77			41/ 60/ 67/ 86	
Sensitivity early stages (I, II, IIIa)/ late stages (IIIB, IIIC, IV) %	51/ 79			52/82	
Sensitivity non-solid tumors %	69			82	

1523 Poster Session (Board #15), Fri, 8:00 AM-11:00 AM

Comprehensive molecular assessment of mismatch repair deficiency in Lynch-associated ovarian cancers using next-generation sequencing (NGS) panel. *First Author: Rachel Soyoun Kim, University of Toronto, Toronto, ON, Canada*

Background: Abnormalities in mismatch repair (MMR) gene may be the result of pathogenic germline (Lynch syndrome) and somatic mutations as well as epigenetic events. Abnormalities in MMR have been described in non-serous/non-mucinous ovarian cancer (OC) but few studies have examined the causes of these MMR defects (MMRd). To address this, we have completed targeted mutational and methylation sequencing on MMRd OC cases. **Methods:** Women with newly diagnosed non-serous/mucinous OC (N = 215) were prospectively recruited from three cancer centers in Ontario, Canada between 2015-18. Tumors were reflexively assessed for MMR protein expression by immunohistochemistry. Tumor DNA was extracted from macrodissected MMRd cases and MMR-intact (MMRi) controls following pathology review. Matched tumor-normal samples were run on a custom NGS panel to identify germline and somatic mutations, copy number variants, rearrangements and promoter methylation in MMR and associated genes. **Results:** Of the 215 women enrolled in our study, 185 (86%) had OC alone and 30 (14%) had synchronous OC and endometrial cancer. Twenty-eight (13%) cases were MMRd, 11 of which were synchronous. The MMRd cohort had median age of 52.5 years, with mostly stage I (N = 14; 50%), grade 1 or 2 disease (N = 18; 64%) with endometrioid histotype (N = 18; 64%). One patient had recurrence after median follow-up of 33.6 months (13.2-93.6). There was no significant difference in overall/progression-free survival between the MMRd and MMRi patients. Using the NGS panel, Lynch syndrome (LS) was detected in 39% of MMRd cases (11/28; 7 OC and 4 synchronous): 7 *MSH6*, 2 *MLH1*, 1 *PMS2*, and 1 *MSH2*. Clinical germline sequencing was performed on all cases and verified panel findings. An explanation for the observed MMR phenotype was available for 18/20 deficient cases, including 9/10 $MLH1^{-}/PMS2^{-}$ (7 somatic methylation, 1 bi-allelic somatic deletion, 1 germline mutation), 0/1 $PMS2^{-}$, 6/7 $MSH6^{-}$ (6 germline mutations) and 2/2 $MSH2^{-}/MSH6^{-}$ (1 germline mutation, 1 bi-allelic somatic mutation). Concordance between clinical and research panel sequencing results was 90%. None of the germline mutations were missed by the panel. **Conclusions:** Use of our custom NGS panel allows for the streamlined assessment of hereditary and somatic causes of MMR deficiency in OC and may be an attractive screening strategy for LS in this population. Research Sponsor: Canadian Cancer Society Research Institute Prevention Grant.

1524 Poster Session (Board #16), Fri, 8:00 AM-11:00 AM

Genotype and phenotype correlation of common cancer predisposition syndromes in sarcoma cases. *First Author: Milita Zaheed, Garvan Institute of Medical Research, Darlinghurst, NSW, Australia*

Background: Sarcomas are rare heterogenous cancers affecting a predominantly younger population. The most recognised autosomal dominant contributor being pathogenic *TP53* variants associated with Li Fraumeni Syndrome (LFS). When referred, patient eligibility for germline *TP53* testing is assessed using classic or Chompret LFS criteria. Other heritable cancer syndromes which can be associated with sarcoma (breast/ovarian, colorectal) are more commonly considered in clinical practice. In some centres germline testing is offered to only those who meet established clinical criteria. Heritable cancer predisposition has several implications including therapy and clinical risk management. Here we report the concordance between clinical criteria and genotypes in sarcoma families. **Methods:** We included 1,664 sarcoma probands from the International Sarcoma Kindred Study. Eligibility for genetic testing was assessed using internationally accepted clinical criteria for recognised cancer syndromes. Whole genome sequencing was performed on peripheral blood DNA and variants in the ACMG cancer gene list were classified as pathogenic or likely pathogenic using established bioinformatics pipelines. **Results:** The median age of sarcoma diagnosis in 1664 probands (798 males, 866 Females) was 48 years (range 1-93). The median age of first cancer diagnosis was 46.5 years (0-93) with 291 probands having multiple primary cancers. Of 1504 informative pedigrees, 243 (16%) met criteria for testing; 207 (14%) *TP53*; 19 (1%) *BRCA1/2*; 2 (<1%) colorectal cancer (CRC) genes and 15 (1%) familial melanoma. Of 12 *TP53* PVs identified, 9 met *TP53* testing criteria. Of 13 PVs identified in HR genes (7 *BRCA2*, 4 *PALB2* and 2 *BRCA1*) only 1 (*PALB2*) met *BRCA1/2* testing criteria and 2 met Chompret criteria. Both *BRCA1* cases were male with a 1st degree relative with ovarian cancer. In CRC genes (1 *APC*, 2 *MSH2*, 4 *MSH6*, 1 *PMS2*), none met CRC testing criteria but 4 met Chompret criteria. No *CDKN2A* PVs were identified in melanoma families. **Conclusions:** In probands with sarcoma, clinical criteria for eligibility for testing for common non-LFS heritable syndromes perform poorly. This should be considered when making decisions regarding germline testing. Research Sponsor: Rainbows for Kate Foundation, Australian National Health and Medical Research Council.

1525 Poster Session (Board #17), Fri, 8:00 AM-11:00 AM

Characterization of clonal hematopoiesis of indeterminate potential mutations from germline whole exome sequencing data. *First Author: Hsin-Ta Wu, Natera, Inc., San Carlos, CA*

Background: Clonal hematopoiesis of Indeterminate Potential (CHIP) is an age-related phenomenon where somatic mutations accumulate in cells of the blood or bone marrow. It is a source of biological noise that causes false-positives in ctDNA analysis and is present in up to 20% of individuals over the age of 70. The presence of CHIP has been linked to an increased risk of hematologic cancers and cardiovascular disease. The Signatera assay filters CHIP mutations through tumor tissue and germline sequencing thereby reducing false-positive results and focuses on tumor-specific mutations for each patient. **Methods:** Whole exome sequencing data (average depth ~250x) analyzed from patients' buffy coat (n = 159) was used to characterize CHIP mutations. Variant calling was performed using Freebayes variant caller with allele frequency threshold between 1% and 10%. Following which variant annotation and selection was performed based on the top 54 genes that are most implicated in myeloid disorders. The selected variants were further screened based on the reported variants in the literature and/or the Catalog of Somatic Mutations in Cancer (COSMIC). **Results:** The analysis revealed an average of 0.14 (0-2) CHIP mutations per patient with an average variant allele frequency of 3.49% (1%-8.5%). The most common CHIP mutations were observed in *DNMT3A*, (n = 17), *TET2* (n = 7) and *TP53* (n = 7) genes. The percentage of patients with at least 1 mutation found in *DNMT3A, TET2,* and *TP53* were 4.2%, 1.94%, and 1.38%, respectively. Other genes containing CHIP mutation included *CEBPA, ETV6, HRAS, PDGFRA, NRAS, KMT2A, EZH2, GATA2, GNAS* at a frequency below 1%. CHIP mutations were not observed in patients younger than 40 years, but they increased in frequency with every decade of life thereafter. The incidence of CHIP increased from 0.04 for the 40-50 yrs age group to 0.18 for individuals older than 60. Further analysis of associations between incidence of CHIP and cancer type, prior exposure to chemotherapy as well as longitudinal evolution of CHIP mutations during cytotoxic treatment are underway and will be presented. **Conclusions:** CHIP, a common finding in the elderly population is an important factor to consider in ctDNA analysis and most frequently involves *DNMT3A, TET2,* and *TP53* genes. The frequency of CHIP can be impacted by a number of other factors such as cytotoxic chemo- or radiotherapy. Research Sponsor: Natera, Inc.

1526 Poster Session (Board #18), Fri, 8:00 AM-11:00 AM

BRCA testing concordance with national guidelines for patients with breast cancer in community cancer programs. *First Author: Leigh Boehmer, Association of Community Cancer Centers, Rockville, MD*

Background: Current National Comprehensive Cancer Network guidelines for genetic/familial high-risk assessment state that testing for highly penetrant breast/ovarian cancer genes is clinically indicated for women with early onset ($\leq$ 45 years) or metastatic HER-2 negative breast cancer. A recent Association of Community Cancer Centers (ACCC) survey (N = 95) showed that $>$ 80% of respondents reported $\leq$ 50% testing rate of patients with breast cancer who met guidelines. Given this disconnect, ACCC partnered with 15 community cancer programs to assess practice gaps and support interventions to improve access to genetic counseling (GC)/testing. **Methods:** Pre-intervention data from 9/15 partner programs for women diagnosed with stages 0-III breast cancer between 01/01/2017 and 06/30/2019 was collected. De-identified variables included: family history documentation, GC appointment/test results, and timing of results relative to treatment decisions. **Results:** There were 2691 women with stages 0-III breast cancer. Forty-eight percent (1284/2691) had a documented high-risk family history, 57% (729/1284) of whom had a GC appointment. This was a significantly higher rate of GC compared to the 23% (181/778) of women with no family history and 6% (35/629) of women with no documentation of family history ($p < 0.0001$). Patients $\leq$ 45 years old attended a GC appointment 72% (199/278) of the time and 49% (135/278) had genetic test results, with 84% (113/135) receiving results before surgery. For women with test results available before surgery, 37% (119/322) had breast conserving surgery, compared to 60% (144/240) with test results disclosed post-operatively ($p < 0.0001$). **Conclusions:** Genetic testing is underutilized in a community cohort of women with breast cancer. Further analysis is needed to understand the impact genetic test results have on surgical decisions. Opportunities exist to improve current rates of appropriate GC/testing. ACCC will share results of quality improvement projects to illuminate which strategies hold promise in reducing the hereditary breast cancer GC/testing practice gap. Research Sponsor: Pfizer, Inc.

1527 Poster Session (Board #19), Fri, 8:00 AM-11:00 AM

Prevalence and clinical characterization of MMR-D/MSI extra-colonic cancers among germline PMS2 mutation carriers. *First Author: Alicia Latham, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *PMS2*-associated Lynch syndrome (LS) may have a more modest phenotype than that associated with other mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, EPCAM*). Recent studies suggest limited extra-colonic cancers, and modified risk-reducing measures can be provided. Understanding the spectrum of risk is of critical importance as some LS-associated cancers do not have effective screening, requiring risk-reducing surgery (endometrial, ovarian). As MMR-deficiency (MMRD)/ microsatellite instability (MSI) is associated with LS pan-cancer, we sought to characterize *PMS2*-associated malignancies according to MMR/MSI status. **Methods:** Review of cancer patients (pts) consented to an IRB-approved protocol of tumor/germline next-generation sequencing (NGS) identified 43 germline heterozygous *PMS2* mutation carriers. Tumors were evaluated for MSI via MSIsensor and/or corresponding MMR protein expression via immunohistochemical staining (IHC). Clinical variables were correlated with MMR/MSI status, comparing via Chi-square or standard T-test. **Results:** There were $>$ 10 tumor types; 69.8% (30/43) were extra-colonic cancers (endometrial (n = 4), ovarian (n = 6), small bowel (n = 3), urothelial (n = 2), pancreas (n = 3), prostate (n = 3), breast (n = 3), brain (n = 3), biliary (n = 1), spindle cell sarcoma (n = 1), and hepatoblastoma (n = 1)). 46.5% (20/43) of tumors were MMRD/MSI. 61.5% (8/13) of colorectal cancers (CRC) were MMRD/MSI, compared to 40% (12/30) of extra-colonic tumors. All endometrial and small bowel cancers were MMRD/MSI. Of 6 ovarian cancers, 3 were clear-cell, 1 endometrioid, and 2 high-grade serous (HGS). The only MMRD/MSI ovary tumor was HGS. 73.9% (17/23) of pts with MMRP/MSS tumors had recurrent/metastatic disease vs 30% (6/20) of pts with MMRD/MSI tumors (p= 0.004). Mean age at diagnosis did not differ significantly between MMRP/MSS and MMRD/MSI groups (49 vs. 57, respectively, p= 0.146). 11.6% (5/43) of pts had a prior cancer, with only one patient having prior CRC. Pts with extra-colonic tumors were less likely to meet clinical pt and family history LS testing criteria than those with CRC (63.3% (19/30) vs. 7.7% (1/13); $p<$ 0.001). **Conclusions:** While *PMS2*-related LS may have a more modest clinical phenotype, in this single-institution study, 60% (12/20) of patients with MMRD/MSI tumors presented with extra-colonic cancers. We caution counseling pts with *PMS2*-associated LS about reduced extra-colonic risk until more complete information about penetrance, spectrum, and age distribution of cancer is available. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

1528 Poster Session (Board #20), Fri, 8:00 AM-11:00 AM

Performance of polygenic risk scores for cancer prediction in an academic biobank. *First Author: Heena Desai, University of Pennsylvania Perelman School of Medicine, Philadelphia*

Background: The discovery of rare genetic variants associated with cancer have a tremendous impact on reducing cancer morbidity and mortality when identified; however, rare variants are found in less than 5% of cancer patients. Genome wide association studies (GWAS) have identified hundreds of common genetic variants significantly associated with a number of cancers, but the clinical utility of individual variants or a polygenic risk score (PRS) derived from multiple variants is still unclear. **Methods:** We tested the ability of polygenic risk score (PRS) models developed from genome-wide significant variants to differentiate cases versus controls in the Penn Medicine Biobank. Cases for 15 different cancers and cancer-free controls were identified using electronic health record billing codes for 11,524 European American and 5,994 African American individuals from the Penn Medicine Biobank. **Results:** The discriminatory ability of the 15 PRS models to distinguish their respective cancer cases versus controls ranged from 0.68-0.79 in European Americans and 0.74-0.93 in African Americans. Seven of the 15 cancer PRS trended towards an association with their cancer at a $p<0.05$ (Table), and PRS for prostate, thyroid and melanoma were significantly associated with their cancers at a bonferroni corrected $p<0.003$ with OR 1.3-1.6 in European Americans. **Conclusions:** Our data demonstrate that common variants with significant associations from GWAS studies can distinguish cancer cases versus controls for some cancers in an unselected biobank population. Given the small effects, future studies are needed to determine how best to incorporate PRS with other risk factors in the precision prediction of cancer risk. Research Sponsor: U.S. National Institutes of Health.

Association of Cancer PRS with associated cancers in an institutional biobank.

Cancer*	EUR Case / Control	AUC-EUR	OR (95% CI) - EUR	p	AFR Case	AUC - AFR	OR (95% CI) - AFR	p
Prostate	396 / 2937	0.757	1.580 (1.405 -1.779)	**2.87E-14**	213 / 943	0.838	1.282 (1.077 - 1.532)	**5.61E-03**
Thyroid	119 / 4699	0.686	1.480 (1.233 - 1.778)	**2.69E-05**	64 / 3125	0.748	1.284 (0.996 - 1.657)	**5.37E-02**
Melanoma	262 / 4699	0.720	1.287 (1.135 - 1.457)	**7.62E-05**	10 / 3125	0.797	0.795 (0.407 - 1.503)	**4.90E-01**
CRC	162 / 4699	0.728	1.246 (1.061 - 1.464)	**7.47E-03**	85 / 3125	0.780	1.244 (0.999 - 1.553)	**5.24E-02**
Lung	199 / 4699	0.681	1.158 (1.011 - 1.317)	**2.93E-02**	115 / 3125	0.841	1.112 (0.927 - 1.307)	**2.23E-01**
Breast	238 / 1762	0.700	1.160 (1.005 - 1.338)	**4.18E-02**	190 / 2182	0.777	1.223 (1.043 - 1.437)	**1.35E-02**
Glioma	38 / 4699	0.716	1.149 (0.830 - 1.592)	**4.03E-01**	16 / 3125	0.762	1.871 (1.777 - 3.002)	**8.51E-03**

1529 Poster Session (Board #21), Fri, 8:00 AM-11:00 AM

ATM mutation carriers and family history of pancreatic cancer. *First Author: Jeannie Klavanian, Beaumont Hospital, Royal Oak, MI*

Background: Multigene panel testing (MGT) is commonly utilized in patients with a personal or family history of cancer. One of the more common gene mutations identified is in the *ATM* gene, associated with a moderately increased risk of breast and other cancers. There are reports of an association with pancreatic cancer, however the exact risks are unclear. The aim of this study is to describe the family history of pancreatic cancer in a cohort of *ATM* mutation carriers, and to evaluate possible genotype/phenotype correlation. **Methods:** Patients who underwent MGT, between '13 and '19, and tested positive for a pathogenic/likely pathogenic *ATM* mutation were included in this study. Family history, with a focus on pancreatic cancer, and genetic testing results were analyzed. **Results:** A total of 114 patients were identified to carry an *ATM* mutation. Twenty-two (19.3%) individuals had a family history of pancreatic cancer in a close relative, and of those, 13 (11.4%) had an affected first degree relative, and 11 (9.6%) had an affected second degree relative. Among the families with pancreatic cancer, 20 close relatives had a personal history of pancreatic cancer, with the youngest diagnosed at age 40, the oldest diagnosed at age 91, and a mean age of diagnosis of 66.5 years. Thirteen unique variants were identified: 4 splice site, 3 missense, 3 frameshift, 1 nonsense, and 1 silent. Two families had the known high-penetrance *ATM* mutation, c.7271T > C (p.V2424G). **Conclusions:** This study describes the association of pancreatic cancer in individuals found to carry pathogenic *ATM* mutations. A significant proportion (19.3%) of patients had a family history of pancreatic cancer in a close relative, diagnosed as young as age 40. The mean age of diagnosis was slightly younger than the average age in the general population (age 70). As pancreatic cancer screening continues to improve, this information will be an important component to help guide cancer risk assessment and future screening recommendations for *ATM* mutation carriers. Additional larger studies are needed to further characterize pancreatic cancer risks in patients with ATM gene mutations. Research Sponsor: None.

1531 Poster Session (Board #23), Fri, 8:00 AM-11:00 AM

Functional analysis of patient-derived PALB2 missense variants of uncertain significance. *First Author: Shijie Wu, Department of Breast Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: Inherited *PALB2* pathogenic variants are associated with an increased lifetime risk for breast cancer development. However, the interpretation of numerous *PALB2* missense variants of uncertain significance (VUS) identified in germline genetic testing remains a challenge. Here, we assessed the impact of breast cancer patient-derived VUS on PALB2 function and identified pathogenic *PALB2* missense variants that may increase cancer risk. **Methods:** A total of seven potentially pathogenic *PALB2* VUS identified in 2,279 breast cancer patients were selected for functional analysis. All these selected VUS were assessed by SIFT, Align-GVGD, and PolyPhen2 *in silico* and were predicted to be deleterious by at least two *in silico* algorithms. The p.L35P [c.104T > C] variant was also included, for which pathogenicity has been recently confirmed. The effects of the VUS on the homologous recombination (HR) activity of PALB2 were tested by U2OS/DR-GFP reporting system. Functional characterization was further validated by protein co-immunoprecipitation and RAD51 recruitment assay. **Results:** *PALB2* variants p.L24F [c.72G > C] and p.L35P [c.104T > C] showed the most significant disruption to the HR activity of PALB2 relative to the wild-type condition, retaining only 52.2% ($p = 0.0013$) and 8.5% ($p < 0.0001$) of HR activity respectively. Moderate but statistically significant HR deficiency was observed for four other variants (p.P405A [c.1213C > G], p.T1012I [c.3035C > T], p.E1018D [c.3054G > C], and p.T1099M [c.3296C > T]). We found no statistical differences for the p.K628N [c.1884G > T] and p.R663C [c.1987C > T] in the HR activity compared to wild-type PALB2. The p.L24F and p.L35P variants compromised the BRCA1-PALB2 interaction and reduced RAD51 foci formation in response to DNA damage. **Conclusions:** We have identified a novel patient-derived pathogenic *PALB2* missense variant, p.L24F [c.72G > C], that compromises PALB2-mediated HR activity. We suggest the integration of the identified pathogenic variants into breast cancer genetic counseling and individualized treatment regimens for better clinical outcomes. Research Sponsor: the Key Program of the Natural Science Foundation of Zhejiang Province (LZ16H160002), the Zhejiang Provincial Program for the Cultivation of High-level Innovative Health Talents.

1532 Poster Session (Board #24), Fri, 8:00 AM-11:00 AM

Cancer risk management and family communication of genetic test results among women with inherited breast cancer genes. *First Author: Tuya Pal, Vanderbilt University Med Center, Nashville, TN*

Background: Identification of inherited breast cancer may guide care, with benefits amplified through family testing. **Methods:** Females with a pathogenic/likely pathogenic (P/LP) variant in *BRCA1/2, PALB2, CHEK2,* and/or *ATM* were surveyed about cancer risk management, family communication of genetic test results, and family testing. Comparisons were made across genes. **Results:** The 235 participants with P/LP variants (186 *BRCA1/2*, 28 *PALB2*, 15 *CHEK2*, and 6 *ATM*) had a median age of 54 and 61% had a prior breast cancer diagnosis. For women with P/LP variants in *BRCA1/2*, *PALB2*, and *ATM/CHEK2*, bilateral mastectomy rates were 79%, 61%, and 52%, respectively; and risk-reducing oophorectomy rates were 89%, 30%, and 37%, respectively. All women with *PALB2* and *ATM/CHEK2* P/LP variants with a bilateral mastectomy had a personal or family history of breast cancer; however, only 27% of those with a risk-reducing oophorectomy had a family history of ovarian cancer. Family communication of genetic test results and family testing rates were higher for those with P/LP variants in *BRCA1/2* compared to others. **Conclusions:** Bilateral mastectomy and risk-reducing oophorectomy were relatively common among women with *PALB2* and *ATM/CHEK2* P/LP variants in our study, suggesting overtreatment through risk-reducing surgery. Furthermore, strategies to improve family communication of genetic test results and family testing are needed to amplify testing benefits. Research Sponsor: U.S. National Institutes of Health, Institutional Funding.

1533 Poster Session (Board #25), Fri, 8:00 AM-11:00 AM

Urgent cancer genetic counseling and testing for young, premenopausal women with breast cancer (BC): Impact on surgical decision-making for contralateral risk-reducing mastectomy. *First Author: Phuong L. Mai, UPMC Magee-Womens Hospital, Pittsburgh, PA*

Background: In women newly diagnosed with unilateral breast cancer (BC), contralateral risk-reducing mastectomy (CRRM) to decrease risk for additional primary BC is an appropriate option for some individuals, such as those with significantly increased risk due to a pathogenic variant (PV) in a breast cancer predisposition gene. Genetic testing at the time of BC diagnosis for young women has become more available and could aid in the decision-making process. We evaluated the trends for CRRM in a cohort of women diagnosed with BC at age ≤45 years who were seen in a multidisciplinary clinic where genetic counseling and testing is offered to each patient. **Methods:** A single institution, prospectively maintained database of patients seen in a BC multidisciplinary clinic between November 2014 and June 2019 was reviewed. Patients were included if they had non-metastatic, unilateral BC diagnosed ≤45 years of age, and underwent genetic testing at the time of BC diagnosis. Associations between surgical treatment (lumpectomy, mastectomy, or mastectomy with CRRM) and age at diagnosis, BC stage, family history, and genetic testing results were evaluated. **Results:** 184 patients were included in the analysis. The prevalence of a PV in a breast cancer predisposition gene was 15.8% (29/184; 1 in *ATM*, 12 in *BRCA1*, 8 in *BRCA2*, 5 in CH*EK2*, 2 in *NBN*, and 1 in *NF1*). 69% of the PV were in *BRCA1* and *BRCA2*. 126 (68.4%) tested negative, and 29 (15.8%) had a variant of uncertain significance (VUS) in various genes. Overall, 63 patients (34.2%) elected to have CRRM. Of the 29 patients with a PV, 24 (82.8%) had CRRM. Women who chose CRRM were younger, more likely to test positive for a PV in a breast cancer predisposition gene, and more likely to have a significant family history of breast and/or ovarian cancer. Among the 155 patients who tested negative or had a VUS, there was no statistically significant association between CRRM and age ($p = 0.58$), test result (negative vs. VUS. $p = 0.12$), or family history ($p = 0.32$). **Conclusions:** For young women with BC seen in a multidisciplinary clinic, a younger age, significant family history, and positive genetic testing result were found to be associated with the decision to undergo CRRM. Among those without a genetic predisposition, having a VUS result was not associated with choosing CRRM. Incorporation of genetic services in the initial evaluation of young patients newly diagnosed with BC could add relevant information in surgical decision making and promote risk-appropriate management. Research Sponsor: None.

1534 Poster Session (Board #26), Fri, 8:00 AM-11:00 AM

Five year letrozole versus placebo in *BRCA1/2* germline mutations carriers: Final results of LIBER, a double-blind randomized phase III breast cancer prevention trial. *First Author: Pascal Pujol, Centre Hospitalier Universitaire, Montpellier, Montpellier, France*

Background: Women with germline *BRCA1/2* (gBRCA1/2) mutations have a 70% lifetime risk of breast cancer (BC). Medical prevention by aromatase inhibitors is effective in high-risk patients (pts), including those with familial risk. However, hormone prevention has not been specifically addressed in women (wn) carrying gBRCA1/2 mutations. **Methods:** LIBER is a randomized, double-blind, placebo-controlled phase III trial evaluating 5-year treatment with letrozole 2.5 mg/day (L) versus placebo (P) on decreasing BC incidence in post-menopausal women with gBRCA1/2 mutations (NCT00673335). Eligible wn were aged 40-70 and could have had unilateral BC $>$ 5 years ago. Randomization was stratified on mutation (*BRCA1/BRCA2*), bilateral oophorectomy and history of prior BC. Primary endpoint was 5-year invasive BC-free survival (BC-FS) in wn with or without previous BC. Main secondary endpoints were safety and quality of life (menopause rating scale, SF36). 270 pts were required to observe 37 events to show a gain in 5-year invasive BC-FS from 80% to 92% (HR=0.35) with 1-sided α=0.05 and 90% power. **Results:** 170 wn were randomized from 02/2008 to 02/2013; 86 and 84 were assigned to the P and L arm. Median age was 55 years (range 40-70). Pt characteristics were well balanced; 59% and 41% carried gBRCA1 and gBRCA2 mutations. In P and L arms, 47% and 43% had prior BC, 43% and 42% stopped treatment prematurely, 37 and 23 serious adverse events occurred, and during active treatment, 8 and 10 wn had grade 3/4 toxicity. Median follow-up was 72.7 months. Five-year BC-FS did not significantly differ between the P and L arms (92% vs 91%, HR 0.83; 95%CI: 0.3-2.3, p=0.73) in the overall population, nor in the subgroups of wn with and without previous BC (74% vs 91%; HR 0.43; 95% CI: 0.1-1.3; 90% vs 86%; HR 1.29; 95% CI 0.4-3.9), gBRCA1 versus gBRCA2 or hormone receptor-positive BC. Letrozole had no effect on quality of life. The two groups did not significantly differ in bone density, which decreased over time in the overall population. **Conclusions:** In this prospective preventive trial, BC-FS was not significantly decreased by letrozole versus placebo in women with *BRCA1/2* mutations. However, the study was underpowered (170 of 270 pts expected). Despite no differences in safety and quality of life, drop-out rate was high in both P and L arms. Clinical trial information: NCT00673335. Research Sponsor: institut national du cancer, programme hospitalier de recherche clinique, unicancer, Pharmaceutical/Biotech Company.

1535 Poster Session (Board #27), Fri, 8:00 AM-11:00 AM

Evaluating the association between clonal hematopoiesis and germline pathogenic and likely pathogenic variants in cancer predisposition genes. *First Author: Elizabeth Anne Comen, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clonal hematopoiesis (CH) is most commonly associated with mutations in genes with a known or putative role in leukemia and with an increased risk for hematologic malignancies. Nearly 50% of primary breast cancers contain leukocytes with CH mutations and CH mutations can be found in breast cancer (BC) tumor infiltrating leukocytes years prior to the development of secondary leukemia. It is currently not known whether CH is more prevalent among BC patients with both germline pathogenic variants and likely pathogenic variants (collectively referred to as PV) in cancer predisposition genes. Here we evaluated the relationship of CH to PV in 546 BC patients (pts). **Methods:** 546 BC pts underwent targeted capture sequencing of tumor and peripheral blood (PB) samples using MSK-IMPACT. Sequencing results from PB were used for identifying PV affecting up to 89 cancer predisposition genes and somatic mutations in 15 genes commonly associated with CH using previously validated methods. All pts consented via an IRB-approved protocol. **Results:** The majority (82.3%) of pts had non-metastatic disease. 59.7% of the 546 pts received chemotherapy and 42.7% received radiation. Of the 546 pts, 90 patients had germline PV in a cancer predisposition gene for a total of 98 germline PV identified (8 patients had 2 germline PV). Mutations in *DNMT3A* followed by *TET2* were the most common CH mutations identified. *CHEK2* PV were statistically significantly associated with CH in a multivariate analysis after controlling for age, prior chemotherapy and radiation therapy (OR: 3.94, CI: 1.51-10.26, p-value $\leq$0.005). Age by decade was significantly associated with the presence of CH in that model (OR: 1.93, CI: 1.53-2.42, p value $\leq$0.001). Of the 8 patients with *CHEK2* germline PV and CH, the most common mutated CH genes were *DNMT3A* (4 pts), followed by *TET2* (2 pts), although our sample size is too small to test for significant enrichment for any specific CH gene, type of CH mutation, or trinucleotide context. Further, CH was not associated with germline PV in other cancer predisposition genes. **Conclusions:** Our findings provide evidence of an association between *CHEK2* germline PV with CH in BC pts, which will be further tested in an expanded cohort. If this association is confirmed, it might have theoretical and practical implications, including cancer prevention strategies. Research Sponsor: None.

1536 Poster Session (Board #28), Fri, 8:00 AM-11:00 AM

Genome Wide Association Study (GWAS) of cognitive impairment after blood or marrow transplantation (BMT) for hematologic malignancy. *First Author: Noha Sharafeldin, University of Alabama at Birmingham, Birmingham, AL*

Background: Cognitive impairment is prevalent in hematologic malignancy patients treated with BMT (autologous: 18.7%; allogeneic: 35.7%; Sharafeldin JCO; 2018). Given the inter-individual variability in risk of cognitive impairment in this population, we investigated the role of genetic susceptibility using a genome-wide single nucleotide polymorphism (SNP) array platform to identify novel genetic associations. **Methods:** *Discovery:* Cognitive function was assessed objectively in 239 adult BMT recipients at pre-specified timepoints: pre-BMT and at 6 mo, 1y, 2y, and 3y post-BMT. A global deficit score (GDS - a summary score of 14 standardized neuropsychological tests) was computed for each patient; a higher score indicated greater cognitive impairment. SNPs passing standard quality control filters ($>$ 1.4M) were used for analysis. Linear mixed effects models used GDS as the outcome, adjusted for age, sex, BMT type, baseline cognitive reserve, and the first four principal components. We used additive, codominant, and genotype models and an adjusted genome-wide significance threshold of 1.25×10^{-8}. Replication: An independent cohort of 544 BMT survivors (192 cases with self-endorsed cognitive problems and 352 controls without) was used for replication. **Results:** *Discovery:* Median age at BMT was 51.3y; primary diagnoses: 47% leukemia, 32% lymphoma, 21% multiple myeloma; 57% males; 69% non-Hispanic whites: 50% allogeneic BMT, median GDS score = 0.22 (range 0-2). Forty-four SNPs were significantly associated with increased GDS (additive model: 3 SNPs; codominant model: 20 SNPs; genotype model: 21 SNPs). Estimates ranged from increase in GDS score by 0.28 points for each additional copy of risk allele, $p = 1.07 \times 10^{-8}$ to increase in GDS score by 1.82 points for two copies of risk allele, $p = 2.3 \times 10^{-11}$. *Replication:* Median age at BMT was 44y; primary diagnoses: 32% leukemia, 49% lymphoma, 19% multiple myeloma; 54% males; 80% non-Hispanic whites: 34% allogeneic BMT. Three SNPs were successfully replicated: rs116334183 resides within *lncRNA-SEMA6D-2*, which facilitates neuronal migration; rs13286152 86kb downstream of *TLE-1*, which promotes neuronal survival; and rs12486041 0.36Mb downstream from *lncRNA-SPTSSB-1*, which regulates sphingolipid production in neuronal axons and 0.36Mb upstream from *TOMM22P6* linked to neural repair. **Conclusions:** In this first GWAS of cognitive impairment post-BMT, we identify 3 SNPs with plausible links to genes implicated in neuronal integrity. Functional studies are currently underway. Research Sponsor: Leukemia and Lymphoma Society (62771-11, Bhatia).

1537 Poster Session (Board #29), Fri, 8:00 AM-11:00 AM

Heterozygous germline ATM mutations in breast cancer: A single academic center experience. *First Author: Anish S Konde, Oakland University William Beaumont Hospital - Rose Cancer Center, Royal Oak, MI*

Background: Heterozygous germline *ATM* mutation carriers have an increased risk of developing breast, pancreas, and other cancers. The clinical and pathologic characteristics of *ATM*-associated breast cancers have not been well defined. **Methods:** Patients who underwent multigene panel testing (MGPT) between 2013-2019 and identified to harbor *ATM* mutations were included in the study. We evaluated demographics, pathology, and surgical management of our *ATM* mutation carriers with breast cancer. **Results:** At total of 319 individuals were identified to have variants in *ATM*, of which 114 were pathogenic/likely pathogenic. The majority of patients were female (82%) and Caucasian (88%). A total of 56 patients (49%) had a personal cancer diagnosis, the most common of which was breast cancer (n = 39). Nine individuals had more than one primary malignancy. The mean age at breast cancer diagnosis was 52, with a range of 25-82. The majority of patients had invasive ductal carcinoma (74%), grade 2 or 3 (90%), and ER and /or PR positive (87%). Of those with known HER2 status, 24% were positive. Thirty-nine percent of patients were lymph node positive, and 42% had lymphovascular invasion. The most common stage at diagnosis was 2 (53%). Of the 39 mutation carriers with breast cancer, 16 (42%) received radiation therapy, and 16 underwent bilateral mastectomy. Of 114 *ATM* positive patients, there were 55 distinct variants. Sixteen (14%) individuals had a mutation in additional cancer predisposition genes. One variant, c.5015delG, was identified in ten patients in a large, consanguineous Iraqi family with an extensive history of pancreatic and other cancers. Eight individuals were identified to have the known high-penetrance variant, c.7271T $>$ G. **Conclusions:** Our study describes the clinical and pathological characteristics of *ATM* mutations carriers with breast cancer. The majority of patients had intermediate to high grade disease, hormone receptor positive, with a suggestion of a higher rate of HER2 positivity and lymph node involvement. Additional studies are needed to elucidate the unique characteristics of *ATM*-associated breast cancer, which may have implications for personalized management. Research Sponsor: None.

1538 Poster Session (Board #30), Fri, 8:00 AM-11:00 AM

A single-institution and commercial laboratory database analysis of BRIP1-associated cancer risks. *First Author: Kristen Danielle Whitaker, Fox Chase Cancer Center, Philadelphia, PA*

Background: *BRIP1/FANCJ* participates in DNA replication and repair via interactions with *BRCA1* and possibly *MLH1*. Previous studies have reported that pathogenic variants (PV) in *BRIP1* are associated with an ~2-fold increase in risk for ovarian cancer (OC) and triple-negative breast cancer (TNBC). Although multigene panel testing for hereditary cancer (CA) has identified *BRIP1* PV and uncertain variants (VUS) in patients with diverse CAs including breast (BC), colorectal (CRC) and melanoma (Mel), association with these CA types has not been established. **Methods:** We examined *BRIP1* risks in two independent populations: Fox Chase Cancer Center (FCCC) and Myriad Genetics (MGL). At FCCC, pedigrees of *BRIP1* PV (*N*= 10) and VUS families (*N*= 47) were reviewed. The MGL population included patients referred for testing by multigene panel (9/2013-12/2019) (*N*= 586,740). Multivariable logistic regression analysis estimated *BRIP1* CA risks as odds ratios (ORs) and 95% confidence intervals (CIs). Models were adjusted for age, sex, ancestry, personal CA history (PHX), and family CA history. **Results:** In the FCCC cohort, *BRIP1* PV carriers (*N*= 12) reported PHX of early-onset (< 50) BC, CRC, and bladder CA. *BRIP1* VUS were also identified among several patients with striking PHX and negative panel testing: BC < 40 (*N*= 3), bilateral BC (*N*= 4), TNBC (*N*= 2), CRC < 40 (*N*= 3), and a patient with 3 CAs < 40 (CRC, BC, and Mel). All FCCC families with a *BRIP1* PV and select VUS families (*N*= 6) are seen in the Table. In the MGL population, 0.3% (1,678/586,740) carried a *BRIP1* PV. Logistic regression analyses found that female *BRIP1* PV carriers have significantly increased risk for OC (OR 2.40, 95% CI 1.93-2.98) and TNBC (OR 1.93, 95% CI 1.52-2.46). Data were insufficient for testing risk of bladder or prostate CA. Findings did not support associations of *BRIP1* with CRC, melanoma, endometrial, pancreatic or gastric CA. **Conclusions:** *BRIP1* PV and VUS may be identified in patients with diverse CA histories. These results confirm studies showing that *BRIP1* PV are associated with an ~2-fold increased risk of OC and TNBC, but do not support increased risks of CRC, melanoma or endometrial CA in *BRIP1* PV carriers. Research Sponsor: Myriad Genetic Laboratories, Inc.

FCCC *BRIP1* families.

	Variant	Carrier	1st Degree Relatives
PV	R798X (*N*= 5)	BC 40	OC 50
		BC 44	CRC 86, Prostate 77
		BC 77	Pancreas 71
		Mel 78	BC 66
		--	
	T997Rfs	BC 55	
	K998E	BC 34, Bladder 37	
	S624X	--	BC 45
	R439X	--	Prostate 70
	K703Ifs	--	CRC 40
Notable VUS	G569R	CRC 36, Mel 37, BC 38	CRC 60
	I902M	CRC 28	
	I482V (*N*= 4)	Bilat BC 43/54 (1 TNBC)	TNBC 48
		Bilat BC 49/63 (1 TNBC)	BC 50, BC 67
		--	Bladder 80
		CRC 60	

All breast cancers were in women

1539 Poster Session (Board #31), Fri, 8:00 AM-11:00 AM

Effect of detection of epigenomic changes in plasma-derived cell-free DNA on multicancer classification. *First Author: Anna Bergamaschi, Bluestar Genomics, San Diego, CA*

Background: Epigenomic changes in DNA methylation patterns are more precisely delineated by active demethylation events as marked by 5-hydroxymethylation (5hmC) of cytosine residues. 5hmC appears to be dynamically modulated in tumor tissues and can be employed as a cancer biomarker. Strategies which interrogate 5hmC genome-wide patterns in a liquid biopsy context may provide efficient and precise technology for early cancer screening and detection. In this study we identified genome-wide 5hmC changes in plasma based circulating free DNA (cfDNA) from breast, colorectal, lung, pancreatic and prostate cancer patients versus non-cancer individuals. **Methods:** cfDNA was isolated from plasma, enriched for the 5hmC fraction using novel click-chemistry protocol for labelling followed by sequencing and alignment to a reference genome to construct features sets of 5hmC patterns. Regularized classification models were constructed to classify cancer samples apart from non-cancer. **Results:** > 500 non-cancer individuals and > 500 cancer patients across five cancer types (breast, colorectal, lung, pancreas and prostate) were included in this study. About 60% of the cancer samples were early stage disease (I or II). The ability to classify non-cancer versus cancer patients was evaluated by 5-fold cross validation of our trained prediction models. Our models were able to classify all breast cancer with a test auROC of 0.86 while prediction model classification for ER negative samples had an auROC of 0.92. Colorectal performance auROC was 0.9; lung auROC = 0.92, pancreatic auROC = 0.97 and prostate auROC = 0.91. Overall sensitivity range, when allowing 2% false positive, was between 85% and 52%. Further using 5hmC signal in blood we were able to identify several signaling pathways specifically relevant to the biology of the cancers investigated. **Conclusions:** These findings further demonstrate that 5hmC changes in cfDNA enable non-invasive detection of breast, colorectal, lung pancreatic, and prostate cancers. Further, 5hmC signals enabled the identification of a suite of cancer signaling pathways differentially enriched in cancers versus non-cancers. These data suggest that dynamic changes in tumor cell methylation, detectable through 5-hydroxymethylation, are contained in the circulating blood and signal active disease biology. Research Sponsor: None.

1540 Poster Session (Board #32), Fri, 8:00 AM-11:00 AM

First year outcomes of an initiative to increase *BRCA* testing among NCCN guideline-eligible breast cancer patients within a large community OCM practice. *First Author: David Michael Waterhouse, OHC (Oncology Hematology Care)/US Oncology Network, Cincinnati, OH*

Background: Pathogenic variants in *BRCA1/BRCA2* can affect a breast CA pts care: preventative interventions, surgical decisions, medical treatments, screening, and family counseling. National data suggests significant non-adherence to NCCN testing guidelines, with only 1/3 of eligible pts referred for genetic services. In 2018, OHC (Cincinnati) launched an APP-centric genetics program. Specially trained APPs carry out genetic counseling and order NCCN-compliant testing. Early data suggested a significant deficit in physician-driven referrals. From 1/01/18 - 07/31/18, 138 new breast pts were estimated to be NCCN guideline-eligible. Only 28 (20%) pts received genetic services. **Methods:** In 2019, the OHC genetics team implemented a standardized screening process for every new breast CA pt. An EMR template (iKnowMed G2) that included NCCN guidelines was created for initial breast CA consultation and Oncology Care Model (OCM) treatment planning. All pts, not just OCM pts, are subject to OCM treatment planning. This automated screening method ensured all breast CA pts were screened, drastically increasing compliance. Through integration of genetics screening into the templates, pts meeting NCCN criteria for testing are reflexively referred for genetic counseling. With USON/McKesson, integrated data fields were developed in the EMR to automate data collection. **Results:** From 01/01/19 – 12/31/19, 717 new breast CA pts were seen at OHC. 676/717 (94%) were screened. Of those screened, 279 new breast CA pts met NCCN criteria for *BRCA* testing. 140 (50%) eligible new pts had appts with the genetics team. Another 50 (18%) had confirmed testing outside of OHC. 57 (20%) refused appts and/or testing. 32 (11%) did not have appts, representing screen fails. Referrals in non-breast CA pts also increased by 127%; 604 (2019) vs 264 (2018) suggesting a halo effect. Analyses suggest the program to be economically viable, with a financial growth rate of 127%. **Conclusions:** EMR templates embedded with the NCCN guidelines for reflex genetics referral can appropriately increase the utilization of genetic services. Breast genetics screening and resultant appt/testing rates increased significantly 2019 vs 2018. Success in BRCA testing in breast CA will lead to expansion to other cancers and genes. Implementation of structured EMR genetics data fields can automate data collection and measure compliance. Integration of genetics screening into universal OCM treatment planning is feasible, economically viable and scalable. Research Sponsor: Pfizer/ACCC.

1541 Poster Session (Board #33), Fri, 8:00 AM-11:00 AM

Return of results after somatic tumor mutation profiling in advanced cancer: Psychological impacts. *First Author: Phyllis Butow, The Chris O'Brien Lifehouse, Camperdown, Australia*

Background: Somatic tumor mutation profiling (STMP) is entering clinical practice. We aimed to investigate psychological impacts of receiving results. **Methods:** Eligible participants had: advanced solid cancers of any histological type; accessible tissue for STMP; and enrolled in the Molecular Screening and Therapeutics (MoST) Program. 1074 participants (91%) completed a baseline assessment prior to STMP (T0), of whom 570 (47%) received results and completed a post-result assessment (T1) of impact of genetic results (MICRA), anxiety and depression (HADS), cancer-specific anxiety (IES), and satisfaction with decision to have STMP. Linear regression models controlling for age, gender, parental status, cultural diversity, education and ECOG status explored associations between result received and psychological outcomes. **Results:** 360 participants received an actionable result and were recommended personalised treatment: 152 via a MoST sub-study (G1) and 208 via their treating oncologist (G2). 210 received a non-actionable result (G3). At T1, G3 were significantly more distressed and less positive about their result (MICRA subscales) and less satisfied with their decision to have STMP than both G1 and G2; G2 was less positive than G1. IES and HADs were not impacted by type of result. Interactions between gender and age, and result were non-significant for all psychological outcomes. Perceived self-efficacy in coping with results (p=0.015) and knowledge (p=0.04) at T0 was significantly correlated with satisfaction with decision at T1; self efficacy (T0) was also correlated with MICRA total (T1) (p=0.006). **Conclusions:** Pathway to treatment receipt is less important to advanced cancer patients than actionability. Patients' self-efficacy to cope with results prior to testing can identify patients vulnerable to distress post-receipt of STMP results who should be offered psychological counseling. Ensuring good knowledge of STMP at consent may avoid decisional regret. Research Sponsor: National Health and Medical Research Council of Australia grant.

	G1: Actionable, Tx via MoST (N=152)	G2: Actionable, Tx via oncologist (N=208)	G3: Non-actionable (N=210)	t statistic	p-value
MICRA, Distress	6.44 (7.0)	6.08 (7.0)	7.95 (6.7)	1.47	p=0.049[1vs3]
Mean (SD)				1.77	p=0.009[2vs3]
MICRA,	4.77 (3.8)	5.92 (4.6)	8.69 (4.4)	3.99	p<0.001[1vs3]
Positive experience				2.83	p<0.001[2vs3]
Mean (SD)				1.16	p=0.014[1vs2]
MICRA, Total	25.75 (16.1)	25.89 (15.6)	32.07 (14.3)	5.92	p<0.001[1vs3]
				5.50	
Total				5.92	p<.001[2vs3]
Mean (SD)				5.50	
Satisfaction with decision	26.75 (4.2	26.03 (5.0)	25.36 (4.4)	1.31	p=0.009[1vs3]
Mean (SD)					

* All other comparisons were non-significant.

1542 Poster Session (Board #34), Fri, 8:00 AM-11:00 AM

Test of an online tool to facilitate NCCN guideline-compliant access to cancer genetics care. *First Author: Kara J. Milliron, University of Michigan, Ann Arbor, MI*

Background: Minority populations experience inequities of access to cancer genetics. We developed and tested an online family history collection and interpretation tool, InheRET, to determine acceptability, validity and utility.Patients are mostly unable to recall accurate family history in clinic and providers have little time to collect the 3-generation pedigree. Thus, ~90% of high risk patients remain unidentified. We evaluated the impact InheRET has on facilitating National Comprehensive Cancer Network (NCCN) Guideline-compliant referrals for cancer genetic counseling. **Methods:** Patients from 3 clinics were consented online to participate. A user experience survey for patients and providers followed the health history questionnaire. **Results:** 628 patients were consented over a year, 555 (>88%) completed the tool. 439 (79%) completed the post-questionnaire user experience. Review of Inheret's recommendations by a genetic counselor found 100% accuracy. Ease of Use: 84-87% of patients reported tool was easy to use. Understandability: 92-97% of patients reported tool was easy to understand. No significant differences were reported between those with high school (n=28, avg age 50.1 yrs) compared to those with advanced degrees (n=139, avg age 45.4 yrs); patients age 70+ experienced increased difficulties. Among primary care patients (n=135), 43 established patients were newly identified as meeting NCCN referral criteria. Healthcare providers found InheRET useful, did not require extra clinical time, and all wish to continue to use it. The patient provided data were more complete and encompassed more family members than with paper forms. Turnaround-times to receive the patient's information were decreased from 4-6 weeks to ~ 72 hours. A patient scheduling backlog of 400 patients was cleared using InheRET. Previously, 40% of cancer genetics patients were lost to follow up, due to not completing their intake forms. This number was reduced to 6.5%. **Conclusions:** Patients find InheRET to be easy to use and understand and they complete this health history tool more frequently and in greater detail than by paper forms. InheRET provides accurate results, verified by in person interviews, in a timely fashion, saving clinical time, possibly enabling increase in earned clinical revenues (under analysis), and improving patient care overall. Importantly, the 43 primary care patients identified to be at increased risk were already established patients, who had not been previously identified as such by their healthcare providers as being at increased risk. Research Sponsor: U.S. National Institutes of Health, Private investors.

1543 Poster Session (Board #35), Fri, 8:00 AM-11:00 AM

Potential germline findings identified during somatic tumor testing: Room for improvement. *First Author: Sundas Khan, University of Vermont Medical Center, Burlington, VT*

Background: Genomic testing, useful for treatment planning and identification of patients for clinical trials, may indicate the presence of a germline mutation. We sought to evaluate the incidence of potentially actionable germline mutations detected via genomic testing and determined rates of germline testing among patients with potential germline mutations. **Methods:** This was a retrospective review of patients undergoing genomic testing at The University of Vermont Cancer Center (UVMCC) between 03/02-11/19. Testing was reviewed for mutations in 60 genes associated with hereditary cancer and recognized as clinically actionable by the American College of Medical Genetics. Records were reviewed for clinical follow-up. Positive (pathogenic or likely pathogenic) genomic test results were evaluated with descriptive analyses. Proportions with 95% confidence intervals are presented and comparisons made using a χ^2 test. **Results:** 342 patients underwent genomic testing at UVMCC over the study period, with a median age of 61. Common tumor types include: CNS (19%), NSCLCA (17%), ovarian (8%), and sarcoma (7%). 59% (203/342) had a mutation in $\geq$ 1 gene associated with hereditary cancer. Most common tumor types with potential germline mutations include: NSCLCA (25%), CNS (18%), ovarian (8%), sarcoma (8%), and endometrial (7%). Potential germline mutations were most commonly identified in TP53, CDKN2A, PTEN, and RB1 (each with mutations in >6% of patients). 58 patients in the cohort have undergone germline testing, of which 19% were positive for germline mutations. Of patients with mutations in the highly penetrant BRCA, PALB2, and Lynch genes, 71% were positive for germline mutations. Young age ($<$ 50) did not enrich for germline mutations ($p > 0.05$). Only 18% (36/203) of patients with potential germline results were referred for genetic counseling. **Conclusions:** Genomic testing can reveal hereditary cancer syndromes. While the majority of patients with tumor mutations in genes associated with hereditary cancer will not have germline mutations, genetic testing is the only way to confirm this. 19% of patients who underwent genetic testing in this cohort had a pathogenic germline mutation. This was enriched to 71% when considering genes rarely mutated in tumors (BRCA, PALB2, and Lynch genes). Only 17% of this cohort underwent genetic testing, representing a significant missed opportunity given the implications of these findings for both patients and families. Patients and their providers should be aware of the potential for germline findings when genomic testing is performed. Research Sponsor: None.

1544 Poster Session (Board #36), Fri, 8:00 AM-11:00 AM

Outcome of patients with breast cancer and a germline *BRCA* mutation in a prospective cohort. *First Author: Banu Arun, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are limited large prospective single institution studies on outcome of breast cancer in patients with germline *BRCA1* and *BRCA2* mutation. The primary aim of this study was to determine the effect of a germline *BRCA1* or *BRCA2* mutation on recurrence-free survival (RFS) and overall survival (OS) in patients with breast cancer. **Methods:** This is a prospective cohort study of patients with invasive breast cancer recruited from the UT MD Anderson Cancer Center Breast Medical Oncology and Clinical Cancer Genetics Center. For the purpose of this analysis, newly diagnosed breast cancer patients who have had germline *BRCA1* and *BRCA2* testing within 12 months were included. Clinical and pathological data, and data regarding outcomes were collected in this prospective cohort. The Kaplan-Meier method and corresponding log-rank test were used to estimate OS and RFS and to compare survival by mutation status. **Results:** Between 1996 and 2015, 3026 patients were recruited. Median age at diagnosis was 45 (19-87) years. A germline *BRCA* mutation was detected in 361 (11.9%) patients (207 with *BRCA1*, 154 with *BRCA2*). After a median follow-up time of 5.3 (0.04-20.7) years, 437 (14.4%) patients recurred and 340 (11.2%) were deceased. At median follow-up time 5 years, 79.3% of *BRCA1*, 91.4% of *BRCA2* and 89.6% of *BRCA* negative patients were disease free; this difference was significant ($p = 0.0001$). Difference in OS between *BRCA1/2*-positive and *BRCA*-negative patients was also significant ($p = 0.0001$), with 81.2% of *BRCA1*, 93.4% of *BRCA2* and 90% of *BRCA* negative patients being alive at 5 years. Amongst 600 patients with triple negative breast cancer (TNBC) patients, DFS and OS were not significantly different between the 3 groups. Of those patients diagnosed under 40 years (n = 937), RFS and OS was significantly different between 3 groups at 5 years (0.001 for RFS and OS); 75% *BRCA1*, 92% *BRCA2* and 86% *BRCA* negative patients were disease free and 77% *BRCA1*, 94% *BRCA2* and 88% *BRCA* negative patients were alive. **Conclusions:** Patients with *BRCA1* or *BRCA2* mutations have different survival outcomes. The prognosis of the first cancer needs to be taken into consideration when deciding for preventive surgeries to prevent second primary breast cancers in these patients. Furthermore, for *BRCA1* mutation carriers more effective therapy strategies need to be evaluated to improve outcome. Research Sponsor: None.

1545 Poster Session (Board #37), Fri, 8:00 AM-11:00 AM

Tumor detection rates in screening carriers with *SDHx*-related hereditary paraganglioma-pheochromocytoma syndrome based on prior tumor history. *First Author: Samantha Greenberg, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Patients with germline pathogenic variants (PVs) in the *SDHx* genes have increased risk for paragangliomas/pheochromocytomas (PGL/PCC), renal cell carcinomas, and gastrointestinal stromal tumors. Expert recommendation suggests individuals with *SDHx* PVs undergo biennial whole-body imaging and annual biochemical testing. This study aimed to evaluate tumor detection rate using standard biochemical and imaging protocols for individuals with *SDHx* PVs, particularly in those with and without *SDHx*-related tumor history, and in those with biochemical testing data. **Methods:** A retrospective longitudinal observational study at the Universities of Michigan, Pennsylvania, and Utah Huntsman Cancer Institute was conducted from the start of each center's screening program through March 1, 2018. Individuals with *SDHx* PVs had clinical imaging with whole body MRI/CT and biochemical testing per expert recommendation. *SDHx*-related tumors identified during clinical screening were measured. **Results:** A total of 263 individuals with *SDHx* PVs completed 491 screens. Individuals with *SDHB* PVs were the most prevalent (n = 188, 71.5%). The average number of screens per subject was 1.87 (range 1-7). A majority (n = 194, 73.7%) of individuals did not have a prior history of PGL/PCC. Overall, *SDHx*-related tumors were detected in 17.1% (n = 45) of the cohort. Of the 46 scans that identified an *SDHx*-related tumor, 85% of them (n = 39) were baseline scans. *SDHx*-related tumors were identified in 18.6% (n = 36/194) of individuals that did not have a prior history of PGL/PCC, whereas they were identified in 13.0% (n = 9/69) of individuals that did have a prior history of PGL/PCC ($p = 0.39$). Biochemical testing was available for 70% (n = 343) of imaging screens, of which 18% (n = 61) had positive biochemistry. Of those with positive biochemistry, 19 tumors were identified on imaging (6%). Sixteen tumors were identified on imaging with negative biochemistry (5%) with a sensitivity of 54% and a specificity of 94%. Utilizing a cut-off of two times the upper limit of normal, 9.91% (n = 34) biochemical tests were positive, and 15 (44.12%) had an *SDHx*-related tumor on corresponding imaging. **Conclusions:** Current *SDHx* screening protocols are effective at identifying *SDHx*-related tumors. Tumors were detected in subjects with a prior history of PGL/PCC and those with no prior history. This suggests lifelong screening is important for all *SDHx* carriers. Imaging is a crucial piece of *SDHx* screening given biochemical testing's sensitivity and specificity. Research Sponsor: None.

1546 Poster Session (Board #38), Fri, 8:00 AM-11:00 AM

Germline alterations other than *BRCA* in triple negative breast cancer (TNBC) patients who underwent neoadjuvant therapy (NAT) on a prospective clinical trial. *First Author: Banu Arun, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Previous studies have related germline *BRCA* mutations to pathologic complete response (pCR) in TNBC cohorts. However, prospective data is lacking on the frequency of non-*BRCA* germline mutations and pCR in TNBC patients who received neoadjuvant therapy (NAT). The aim of this study was to describe germline alterations in comparison with pCR in a prospective cohort of TNBC receiving NAT. **Methods:** Pre-NAT blood was drawn from patients enrolled in a clinical trial of genomically tailored NAT (ARTEMIS: NCT: 02276443, per eligibility patients had to have negative clinical *BRCA* tetsing). Germline DNA was extracted and sequenced on a HiSeq4000 sequencer (Illumina, coverage 60X). Reads were aligned to human reference hg19. Variants were filtered against public databases of normal cohorts: esp6500, 1000 genome, ExAC with a frequency cutoff at 1% in any ethnicity. Two integrative scores were used to evaluate the deleteriousness of the missense variants and the variants predicted to be damaging by both scores were included in the analyses. A 105 pan-cancer susceptibility gene panel was selected based on literature data and commercially available gene panels. NAT included anthracycline and taxane based chemotherapy +/- targeted therapy based on tumor genomic expression. Univariate logistic regression models were used to fit pCR for individual mutations, excluding genes mutated in fewer than three patients. All statistical analyses were performed using R version 3.6.1. with a significance of p=0.05. **Results:** Germline results and pCR were available for 152 patients. Median age was 55 yrs (range: 24-77). 7.9% were stage (st) I, 65.8% st II, 26.3% st III. 55 pts (36%) had pan-cancer associated germline mutations, whereas 33 (21%) had a breast-cancer associated mutation. Greater than 1% mutations were seen in seventeen genes (Table). There was no significant difference in pCR rate after NAT among pts with different germline mutations versus without mutation. **Conclusions:** Breast cancer related germline mutations other than *BRCA* in TNBC are relatively common supporting at least a breast panel (not only *BRCA1/2*) testing. Treatment implications of different germline mutations and their impact on pCR is ongoing on an extended series. Research Sponsor: None.

Gene	% pos	Gene	% pos	Gene	% pos
APC	2.6	*MSH2*	2	*SDHA*	2
BRIP1	1.3	*MSH6*	1.3	*BRCA1*	1.3
ERBB2	1.3	*MUTHY*	2.6	*TSC2*	4
MITF	1.3	*NTHL1*	1.3	*WT1*	1.3
MLH3	3.3	*PMS1*	2	*XRCC3*	1.3
PHB	1.3	*PMS2*	2		

1547 Poster Session (Board #39), Fri, 8:00 AM-11:00 AM

Ancestry-specific gene expression profiles in TNBC tumors. *First Author: Windy Marie Dean-Colomb, Lousiana State University School of Medicine, New Orleans, LA*

Background: Due to persistent disparities in breast cancer mortality, there has been a renewed focus on investigating tumor biology. Deeper exploration has exposed distinctions in tumor biology based upon self-reported race and ancestry. The disparities associated with Triple Negative Breast Cancer (TNBC) across the modern African Diaspora suggests that there is a genetic ancestry connection between its aggressive tumor biology and clinical outcomes. Understanding this connection could hold the key to improving clinical outcomes in this group. **Methods:** We investigated 75 TNBC primary tumors using Self-Reported Race (SRR) groups: African American (AA, n = 42) and European American (EA, n = 33). Using best practices established by TCGA, we analyzed bulk RNA sequencing to measure changes in genome-wide expression levels. We next quantified global ancestry in a novel manner using RNAseq variants using 1000 Genomes as the reference data. We then identified African and European ancestry-associated genes using a logistic regression (adjusted FDR $p < 0.05$) between quantified ancestry and gene expression levels. **Results:** We identified > 150 genes associated with quantified African ancestry. We also found using quantified ancestry was a more robust method to screen for differentially expressed genes than SRR. Using an updated TNBC subtyping method, we noted higher incidences of Basal-like 2 tumors in AAs. Pathway analyses indicated several canonical cancer pathways; including, TP53, NFKB1 and AKT, have altered functionality in patients of African descent. For example, TP53-associated genes were activated in TNBC tumors of AA versus EA. This upregulation, rather than loss of function, is suggestive of polymorphic and/or ancestry-specific expression regulation, likely driven by population-private genetic variants. Lastly, we used TCGA data to validate a subset of African ancestry-specific genes that were upregulated in AA patients in our cohort. Specifically, PIM3, ZBTB22 and PPP2R4 each retained significant upregulation, in our cohort, but also TNBC tumors from TCGA (p = 0.0018, 0.023 and 0.022, respectively). **Conclusions:** Our study has uncovered ancestry-specific gene expression profiles in TNBC tumors. The distinct distribution of TNBC subtypes and altered functional oncologic pathways are evidence that biological underpinnings in TNBC can be driven by shared genetic ancestry. These findings emphasize the need to investigate patient populations of various ancestral origins in order to fully appreciate the molecular diversity in tumor biology for precision of disease management. Research Sponsor: Susan G Komen.

1548 Poster Session (Board #40), Fri, 8:00 AM-11:00 AM

Outcomes of Lynch syndrome (LS) patients treated with immune checkpoint inhibitors (ICI). *First Author: Shahla Bari, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: LS is caused by a germline mutation in one of several DNA mismatch repair (MMR) genes: MLH1, MSH2, MSH6 or PMS2 (d-MMR). A minority of LS patients have MMR proficient tumors (p-MMR). ICI therapy has dramatically changed outcome of d-MMR (majority of LS patients. However, data about response to ICI in LS patients, irrespective of their tumor MMR status is scarce. The aim of this study was to evaluate outcomes of ICI therapy in all LS associated Cancer. **Methods:** This was a retrospective analysis of LS associated cancers treated with one of the 6 ICIs at our center. We also looked at age, sex, microsatellite status, response and survival. **Results:** Out of 262 LS patients analyzed, 194 had cancer and 22 received ICIs. Among the patients analyzed, the mean age at diagnosis of 1st cancer was 51 yrs. There were 10 females (47%). 10 patients had colorectal (45%), 3 urothelial (14%), 2 renal cell, 2 cholangiocarcinoma and one each of esophageal, ovarian, uterine, glioblastoma multiforme and pancreatic cancer. One patient died from progressive disease after receiving a single dose and was not included in the analysis. 17 patients (80%) received Pembrolizumab, 11 patients were microsatellite unstable (MSI), 3 were microsatellite stable (MSS) while 7 were unknown. 2 patients achieved complete response (CR) (10%), 1 patient had partial response (PR) (5%), 13 had stable disease (62%) while 5 had progressive disease (23%) leading to a disease control rate (DCR) of 76%. Of the 3 known MSS Lynch syndrome patients, 2 did not respond while the 3rd continues to respond at 9 months of therapy. Of the 5 patients who had PD, 2 were MSS, 2 unknown and 1 MSI. Among the 16 patients who responded, 15 of 16 (94%) had sustained response and have not experienced disease progression or relapse. 3 of these patients have been off therapy (1 due to immune related adverse evet) and have had no relapse. One responder progressed after 18 cycles of therapy. The DCR was 71% at 12 months as well as 48 months of follow up. Median progression survival has not been reached. Similarly, median overall survival has not been reached. **Conclusions:** Our study is the one of the largest reported analysis of LS associated cancer patients treated with ICIs and included LS patients with both MSI and MSS tumors. Though small, our data suggests robust DCR and prolonged responses in Lynch associated MSS tumors treated with ICI. This encouraging response in MSS tumors along with higher response rates in LS associated cancers as compared to non-LS MSI tumors, suggests that there may be additional drivers of response to ICI in LS patients leading to superior responses. Research Sponsor: None.

1549 Poster Session (Board #41), Fri, 8:00 AM-11:00 AM

Clinicopathologic features of invasive breast cancer (BC) diagnosed in carriers of germline *PALB2*, *CHEK2* and *ATM* pathogenic variants. *First Author: Danika Scott, Stanford University School of Medicine, Stanford, CA*

Background: While germline pathogenic variants (PVs) in *BRCA1/2* account for a large proportion of hereditary breast cancer (BC), PVs in *PALB2*, *CHEK2* and *ATM* are increasingly detected. However, the phenotype and clinical features of invasive BC with these PVs have not been fully described. **Methods:** We identified patients with a PV or likely PV in *PALB2*, *CHEK2* or *ATM* tested clinically at Stanford between 2014 - 2019 who provided informed consent to be included in a prospective cancer genetics registry. Data on baseline demographics, genetic testing history, and clinicopathologic features of diagnosed BC were collected. For patients with a subsequent diagnosis of metastatic BC, we calculated disease-free interval (DFI). **Results:** 130 patients met inclusion criteria for analysis: *ATM* (N=39), *CHEK2* (N=58), *PALB2* (N=33). Nearly all (98.5%) were women, with 2 male BC in *ATM* carriers. Non-Hispanic White ethnicity was most common in *ATM* (64.1%, 95% CI 48.4%-77.3%) and *CHEK2* carriers (69.0%, 95% CI 56.1%-79.4%), but comprised only 39.4% (95% CI 24.7%-56.4%) in *PALB2* carriers. Asian/Pacific Islander (24.2%, 95% CI 12.6%-41.3%) and Hispanic (30.3%, 95% CI 17.3%-47.5%) ethnicities were enriched among *PALB2* mutation carriers. In total, 97.7% learned of their PV status only after a preceding diagnosis of BC and 43.1% were diagnosed with BC at age ≤ 45. Data regarding invasive BC subtypes, incidence of subsequent primary BC, and metastatic recurrence are listed below in the table. Additional data on stage, grade and sites of metastatic spread will be presented. **Conclusions:** We observed clinically important differences in the spectrum of BC subtypes among carriers of *ATM*, *CHEK2* and *PALB2* PVs, in addition to racial/ethnic differences with Asian/Pacific Islander and Hispanic ethnicity enriched among carriers of *PALB2* PVs. Research Sponsor: BRCA Foundation.

	% ATM (N=39)	95% CI	% CHEK2 (N=58)	95% CI	% PALB2 (N=33)	95% CI
Invasive BC Subtype ER and/or PR positive, HER2-negative	71.8%	56.1%-83.6%	86.2%	74.8%-93.1%	60.6%	43.7%-75.4%
Any HER2-positive	25.6%	14.4%-41.2%	13.8%	6.9%-25.2%	3%	<0.01%-16.7%
TNBC	2.6%	<0.01%-14.3%	0.0%	0.0%-7.4%	36.4%	22.1%-53.4%
Diagnosed with Subsequent Primary BC	12.8%	5.1%-27.2%	19%	10.8%-31.0%	21.2%	10.4%-38.1%
Diagnosed with Metastatic BC	5.1%	0.5%-17.8%	17.2%	9.4%-29.1%	24.2%	12.6%-41.3%
Percent Relapse-Free ≥ 5 years	0%	0.0%-48.9%	50%	23.7%-76.3%	12.5%	0.11%-49.2%
Median DFI (years)	4.3		6.4		1.7	

1550 Poster Session (Board #42), Fri, 8:00 AM-11:00 AM

A noninvasive multi-analytic approach for lung cancer screening of patients with pulmonary nodules. *First Author: Hong Zheng, Department of Thoracic Surgery, Xinqiao Hospital, Chongqing, China*

Background: Low-dose computed tomography (LDCT) is an effective approach for lung cancer screening of high-risk patients with pulmonary nodules, however with varying false positive rates depending on the somewhat subjective judgement of the practice professional. Artificial intelligence derived from machine learning of comprehensive patient profiles, including multi-omics and clinical data, has the potential to provide more objective assessment of patient's risk in order to aid clinician's decision making. We have developed a multi-analyte algorithm-based assay (MAAA) that incorporates ctDNA mutation, ctDNA methylation, and protein biomarker profiles evaluated through non-invasive blood-based testing, as well as patient's clinical information, to improve the diagnostic efficacy of lung cancer. **Methods:** 98 high-risk patients with pulmonary nodules were enrolled in two independent cohorts (68 for training/testing and 30 for independent validation). The malignancy of the pulmonary nodules were established through pathology of surgical-removed nodules. Prior to surgery, each patient was also subject to cell-free DNA-based sequencing for DNA mutation and DNA methylation profiling, as well as serum protein biomarker profiling. On the training/testing patient cohort, machine-learning-based predictive models were first built for malignancy status prediction based on each type of molecular or clinical features. A final ensemble model was then constructed to incorporate the measurements based on molecular and clinical markers to provide the ultimate recommendation on the malignancy of the pulmonary nodule. The performance of each individual model and the final ensemble model was benchmarked on the training/testing cohort, and also validated on the independent validation cohort. **Results:** On the 30-patient independent validation cohort, individual prediction models based on clinical information, protein marker, ctDNA mutation, and ctDNA methylation profiles achieved predictive AUC of 0.59, 0.48, 0.71, and 0.84, respectively. The final ensemble model achieved predictive AUC of 0.86, which has strongly indicated that an integrative, algorithm-based approach of multi-analytic molecular and clinical profiles greatly outperforms any single-analytic profiling. **Conclusions:** Multi-analyte algorithm-based approach can be utilized to assist in lung cancer screening for patients with pulmonary nodules. It has demostrated a high accuracy through independent validation, and has outperformed any single-analyte testing in our study. Research Sponsor: None.

1551 Poster Session (Board #43), Fri, 8:00 AM-11:00 AM

Green tea extract to prevent colorectal adenomas in men and women: Results of the MIRACLE trial. *First Author: Thomas Jens Ettrich, Ulm University, Department of Internal Medicine I, Ulm, Germany*

Background: Prevention of colorectal adenomas (CA) can reduce colorectal cancers (CRC). Epidemiological and experimental data suggest that the green tea catechin epigallocatechingallate has an antineoplastic effect in the large bowel. MIRACLE is the largest trial so far to examine the effect of three-year daily intake of green tea extract (GTE) on the incidence of metachronous CA in a Caucasian population. **Methods:** Prospective, parallel group, double-blinded, placebo-controlled, randomized multicenter trial (40 German centers, recruitment 11/2011-6/2015). Patients (n = 1001, age 50-80y), polypectomy ≤ 6 months and tolerating GTE well (one-month run-in) were randomized to receive decaffeinated GTE standardized to EGCG (150 mg bid, capsules) or placebo (P) for 3 years. Primary endpoint: Incidence of metachronous CA at the 3-year follow-up colonoscopy. Secondary endpoints: Occurrence, number, localization, size, histological subtype of CA, frequency of CRC, biomarker and safety. Strata: study center, low-dose aspirin (≤100 mg/d). **Results:** Clinical parameters were well balanced. CA incidence at the 3-year follow-up colonoscopy was analyzed in the modified ITT set (modITT; n = 309 patients (GTE), n = 323 (placebo), timely follow up colonoscopy) and the per protocol set (PP, modITT set without major protocol violations). Incidence of CA was 55.7 % (P) and 51.1% (GTE), (modITT, adj. RR 0.905, one sided, p = 0.081), respectively 54.3 % (P) and 48.3% (GTE) (PP, adj. RR 0.883, one sided, p = 0.058). These differences did not reach statistical significance. In the preplanned exploratory analysis regarding gender incidence of CA in females was 47.9% (P) and 47.6% (GTE) in the modITT-set (adj. RR 0.989; 95%-CI: 0.753,1.299; p = 0.935), respectively 45.4% (P) and 46.9% (GTE) in the PP-set (adj. RR 1.014; 95%-CI: 0.748, 1.373; p = 0.930). In contrast, in the male population incidence of CA in the follow-up colonoscopy was 60.4% (P) and 52.9% (GTE) in the modITT-set (adj. RR 0.846; 95% CI 0.717, 0.999); p = 0.048), respectively 59.1% (P) and 49.1% (GTE) in the PP-set (RR 0.803, 95% CI: 0.666, 0.969; p = 0.022). Thus, GTE intake was associated with a significant, 12.4 relative and 7.5% absolute reduction of metachronous CA in the male modITT population. There were no differences with respect to safety between the groups. **Conclusions:** GTE reduced the incidence of metachronous CA. However, a significant effect was only observed in the in the male population whereas there was no effect in the female population. Clinical trial information: NCT 01360320. Research Sponsor: German Cancer Aid Foundation (Stiftung Deutsche Krebshilfe).

1552 Poster Session (Board #44), Fri, 8:00 AM-11:00 AM

Non-invasive detection of urothelial carcinoma (UC) by cost-effective low-coverage whole genome sequencing from urine exfoliated cells DNA. *First Author: Shuxiong Zeng, Changhai Hospital, Navy Medical University, Shanghai, China*

Background: Urothelial carcinoma (UC) is a malignancy with frequent chromosomal aberrations. The FISH assays were more sensitive as compared to cytology tests. Here we investigated cost-effective whole genome sequencing technology, which is able to detect all chromosomal aberrations for UC diagnoses. **Methods:** UC patients and control group are prospectively recruited in trial NCT03998371. First-morning-voided urine were freshly collected before TURBT or cystectomy. Urine Exfoliated Cells DNA was analyzed by illumina HiSeq X10, followed by genotyping by bioinformatics workflow UCAD. **Results:** 195 individuals were prospectively recruited. 121 UC patients and 67 non-tumor diseases were included in this study. 7 other malignancies as confirmed by pathological testing were excluded. Frequent chromosome copy number changes were found in cancer patients as compared non-tumor controls, including chromosome 3 gain, 17 gain, 7 gain and 9p loss used in FISH assays were found. In addition to that, chr9q loss, 8q gain, 5q loss, 17p loss, 11p loss, 1q gain, 8p loss, 10q loss, 6q loss, 4q loss and 11q loss were also frequent in cancer patients (AUC > 0.65). Metacentric chromosomes showed better AUC compared to acrocentric and telocentric chromosomes (P = 1.7e-03). A novel diagnosis model UCAD was built by incorporating all the chromosomal changes. The model reached performance of AUC = 0.933. At the optimal cutoff |Z| > = 3.16, the sensitivity, specificity and accuracy were 84.7%, 97.9% and 89.0% respectively. The prediction positivity was found correlated with urine microscopy visible epithelial cells (P = 0.00069), tumor invasiveness (Ta/Tis vs the other, P = 0.0048) and tumor grade (P = 0.0030), but not microscopy RBC/WBC findings, urine culture findings, smoke and drinking history. The UCAD model outperformed cytology tests by predicting all 16-cytology positive and 12 cytology negative tumors with comparable specificity. The model found 75.0% more tumors. And UCAD identified more upper urinary tract cancer (P = 0.012) and smaller tumors (< 3cm, P = 5.9e-04). The adding of cytology to UCAD did not improve diagnosing sensitivity and specificity. UCAD reproduce the diagnoses among morning - void urine, morning, afternoon urine samples with correlation coefficient $R^2 > 0.98$. All the urine samples showed high concordances with matched tumor samples ($R^2 > 0.85$). **Conclusions:** UCAD could be a high specific, robust UC diagnoses method with improved sensitivity as compared to cytology tests. Clinical trial information: NCT03998371. Research Sponsor: None.

1553 Poster Session (Board #45), Fri, 8:00 AM-11:00 AM

Relationship between *CYP2D6* genotype, tamoxifen metabolites, and adverse events, tumor biomarkers and breast cancer recurrence in a low-dose phase III trial in noninvasive disease. *First Author: Andrea De Censi, Division of Medical Oncology, E.O. Galliera Hospital, Genoa, Italy*

Background: Low dose tamoxifen (T, 5 mg/d) given for 3 years halved recurrence in 500 women with non-invasive disease (DeCensi et al. JCO 2019). Retrospective studies with 20 mg/d have shown an association between low levels of endoxifen (9-16 nM) or Z-4OHtam (3.26 nM) and recurrence, but recent prospective studies have not confirmed these findings. We measured *CYP2D6* genotype and 8 metabolite levels to determine their associations with adverse events, tumor biomarkers (IGF-I, SHBG, C-reactive protein, CRP) and breast cancer recurrence. **Methods:** CYP2D6 genotyping was performed in the T arm (n = 183) as previously described (Johansson H et al. BCRT 2016). T and metabolites were measured at 1 (n = 169) and 3 y (n = 152) as previously described (Helland T et al. BCR 2017). We tested linear relationships between metabolite levels and biomarkers, adjusting for age, BMI, treatment compliance and baseline biomarker levels. Cumulative incidence of recurrence according to endoxifen levels was calculated by the Cox model. **Results:** Endoxifen concentrations were associated to CYP2D6 metabolizer status (p < 0.001). Median (IQR) endoxifen levels were 8.4 (5.2-11.3) and 8.8 (5.8-11.5) at 1 and 3 y, with only 42% and 47% of subjects reaching 9 nM. Median endoxifen levels were related to pill count (5.5, 7.1 and 9.0 nM/L for medication possession rate < 83.3%, 83.4-99.9%, 100%, respectively). There was no difference in metabolite levels and menopausal symptoms. There was an inverse relationship between endoxifen and endometrial thickness at 3 y (p = 0.04), and between endoxifen or tamoxifen levels and IGF-I levels at 3 y (p = 0.001). T levels were positively associated with SHBG levels in postmenopausal women (p-interaction = 0.04). Endoxifen, T and 4OHtam decreased CRP, with a greater effect in premenopausal women (p-interaction = 0.02). An increase in CRP after 3 years was associated with a HR of 4.37 (95% CI, 1.14-16.73, P = 0.03) of recurrence compared to women with no increase of CRP. Median (IQR) endoxifen levels at year 1 were 8.4 (5.3-11.4) in patients who recurred vs 7.5 (5.1-10.2) in those who did not recur (p = 0.6), although this comparison was underpowered. **Conclusions:** T levels themselves may contribute to clinical activity by decreasing IGF-I and increasing SHBG. Elevated CRP is a predictive factor for recurrence which is down-regulated by T and metabolites. Endoxifen is below 9 nM in the majority of subjects treated with 5 mg/day, although this threshold was obtained in studies up to 20 years. Clinical trial information: NCT01357772. Research Sponsor: Italian Ministry of Health, Italian Association for Cancer Research (AIRC).

1554 Poster Session (Board #46), Fri, 8:00 AM-11:00 AM

Mammography adherence among medically underserved women undergoing cancer genetic risk assessment. *First Author: Candice Schwartz, University of Illinois at Chicago College of Medicine, Division of Medical Oncology, Chicago, IL*

Background: Medically underserved women bear a disproportionate burden of breast cancer (BC) mortality. Early detection is vital for reducing BC deaths. Cancer genetic risk assessment (CGRA) provides an opportunity to identify women at highest risk so that risk-adapted screening can be implemented. The effect of CGRA on mammography adherence among underserved women is unknown. **Methods:** We conducted a study to test the feasibility of performing cancer genetic risk assessment (CGRA) as part of standard primary healthcare at two Federally Qualified Health Centers in Chicago, IL. Racial/ethnically diverse women age 25-69 without a personal history of BC underwent CGRA at the time of an annual well-visit and received the result from their PCP. Medical record review provided data on mammography adherence. Demographic data and measures of perceived BC risk, BC cultural beliefs, fatalism, and BC worry were collected with an enrollment survey. McNemar's test compared the rate of adherence to screening mammography before and after implementation of CGRA, defined as completing a screening mammogram within 18 months prior to or following CGRA, resp., among women eligible for screening (age $>$ 40 at study enrollment). Logistic regression models tested for associations between mammography adherence and demographic characteristics/health beliefs. **Results:** Data was available for 90 participants with increased BC risk (IR) who were eligible for screening and 98 eligible, average risk (AR) participants (in total, 61% black and 37% Latina). Overall, adherence improved from 38% at baseline to 49% following CGRA ($p = 0.03$). Adherence increased from 35% to 51% among IR participants ($p = 0.04$), and from 40% to 47% among AR participants ($p = 0.39$). Data on predictors of adherence will be presented. **Conclusions:** Implementing CGRA as a standard component of primary healthcare improved adherence to screening mammography among racial/ethnically diverse underserved women. The effect was seen primarily in those with increased risk. This intervention could be used to improve uptake of mammography in the subgroup of underserved women who benefit the most from screening. Research Sponsor: None.

1555 Poster Session (Board #47), Fri, 8:00 AM-11:00 AM

A sensitive and quantitative multimodal blood test for the detection of colorectal adenomas and cancer: Correlation with size and number of polyps. *First Author: Shai Friedland, Stanford University Medical Center Gastroenterology and Hepatology, Stanford, CA*

Background: Colonoscopic polypectomy is the primary reason for declining colorectal cancer incidence and mortality. Epidemiological evidence has ordered the timing and risk of pre-cancerous adenomas, localized and invasive cancer along a 7-10 year continuum. The increased size and number of index polyps are correlated with an increased probability of progression to cancer and informs surveillance colonoscopies. **Methods:** A single-center, IRB-approved, prospective, blinded study was conducted at the VA Palo Alto Health Care System. Results for 354 patients with no prior diagnosis of CRC who were scheduled for colonoscopy are presented. Indications for colonoscopy were 86% asymptomatic and 14% with symptoms or positive-FIT. Patients had blood drawn immediately prior to colonoscopy. The test analyzes three biomarkers: circulating gastrointestinal epithelial cells (CEC), validated somatic mutations, and methylation (SEPTIN9) of cell-free DNA and uses incident risk to calculate a CMx Score, scaled from 0 to 100. Multivariate regression methods were used to assess the degree of association between the pre-defined CMx Scores and polyp sizes and number, adjusting for both DNA mutation and DNA methylation status. **Results:** There is a significant association between CMx Scores and polyp size (F value = 5.80, p-value = 0.017). DNA mutation (F value = 1.29, p-value = 0.263) and methylation status (F value = 0.34, p-value = 0.560) were non-significant. Similarly, there is a significant association between CMx Scores and number of polyps (F value = 23.71, p-value $<$ 0.0001). Again, DNA mutation (F value = 1.57, p-value = 0.210) and methylation status (F value = 1.34, p-value = 0.248) were non-significant. These results suggest that CMx Scores, which incorporate CEC, are providing predictive information of polyp sizes and number above and beyond DNA mutation and methylation status alone. **Conclusions:** A novel non-invasive multimodal blood-based assay that analyzes cell-free DNA for somatic mutations and methylation, CEC and integrates SEER incidence risk is significantly associated with polyp size and number. The opportunity to track progression and potentially inform colonoscopy interval is notable. Research Sponsor: CellMax Life.

Disease Category	Subject	Sensitivity (%)	Mean Index Polyp Size (mm)	Mean Polyp Number	Mean CMx Score
Colorectal Cancer	11	100	38.3	4.0	71.3
Advanced Adenomas	53	75.5	17.6	5.2	49.9
Non-advanced Adenomas	178	48.3	5.1	3.1	35.6
Non-Neoplastic Findings	33	9.1	4.4	1.8	20.0
Negative Colonoscopy	79	**Specificity** (%) 89.9	-	0	18.1

1556 Poster Session (Board #48), Fri, 8:00 AM-11:00 AM

3,3'-Diindolylmethane (DIM): A nutritional intervention and its impact on breast density in healthy BRCA carriers compared to non-treated carriers—A prospective clinical trial. *First Author: Rinat Yerushalmi, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel*

Background: Women who carry the *BRCA* mutation are at high lifetime risk of breast cancer, but there is no consensus regarding an effective and safe chemoprevention strategy. A large body of evidence suggests that 3,3-diindolylmethane (DIM), a dimer of indole-3-carbinol (I3C) found in cruciferous vegetables, can potentially prevent carcinogenesis and tumor development. The primary aim of this prospective study was to investigate the effect of DIM supplementation on breast density, a recognized predictive factor of breast-cancer risk. **Methods:** Participants were 23 healthy female *BRCA* carriers (median age 47 years; 78% postmenopausal) who were treated with oral DIM 100 mgx1/d for one year. The amount of fibroglandular tissue (FGT) and background parenchymal enhancement (BPE) on magnetic resonance imaging (MRI) performed before and after the intervention were scored by two independent expert radiologists using the Breast Imaging and Reporting Data System (BI-RADS). Each woman in the cohort was matched by age (within 3 years) and menopausal status to a woman attending the clinic who was not participating in the study and who underwent breast MRI in parallel year. **Results:** A decrease in the average score for FGT amount from 2.8 ± 0.8 at onset to $2.65 \pm 0.842.8$ after one year ($p = 0.031$), with no significant change in BPE ($p = 0.429$). A group of DIM-untreated age- and menopausal-status-matched clinic patients did not show a significant change in FGT amount ($p = 0.33$) or BPE ($p = 0.814$) in a parallel year. Mean estradiol level decreased from 159 to 102 pmol/L ($p = 0.01$), and mean testosterone level, from 0.42 to 0.31 pmol/L ($p = 0.007$). Side effects were grade 1. **Conclusions:** One year's supplementation with DIM 100 mgX1/d in *BRCA* carriers was associated with a significant decline in FGT amount on MRI. Larger randomized studies are warranted to corroborate these findings. Clinical trial information: NCT02197000. Research Sponsor: Israel Cancer Association.

1557 Poster Session (Board #49), Fri, 8:00 AM-11:00 AM

Development of a novel liquid biopsy test to diagnose and locate gastrointestinal cancers. *First Author: Yuying Wang, BGI Genomics, Shenzhen, China*

Background: Cancers of the gastrointestinal (GI) system, including esophagus, stomach, pancreas, gallbladder, liver, bile duct, colon, and rectum are estimated to account for 38% of all cancer incidences and nearly 46% of cancer-related deaths in China. We conducted a multi-center study to evaluate the feasibility of using genetic and epigenetic abnormalities in plasma cfDNA to diagnose and locate GI cancers. **Methods:** We performed parallel genetic and epigenetic profiling of plasma cfDNA from hepatocellular carcinoma (HCC), colorectal cancer (CRC) and pancreatic cancer (PC) patients as well as age-matched healthy individuals by ultra-deep sequencing targeting cancer driver genes, and by targeted bisulfite sequencing covering genome-wide CpG islands, shelves, and shores. **Results:** Using a pre-specified mutation scoring system, we found that cfDNA mutation profiling achieved a sensitivity of 59.6%, 67.2%, and 46.8% for detecting HCC (n = 322), CRC (n = 244) and PC (n = 141) respectively, with a specificity of 95% in healthy controls (n = 207). For 901 plasma cfDNA samples that underwent methylome profiling, we first applied a machine learning approach to classify each cancer type versus healthy controls in the training cohort (HCC: n = 125; CRC: n = 105; PC: n = 97; healthy individuals: n = 84). Random Forest models with 10-fold cross validation achieved an AUC of 0.96 ± 0.04,0.89 ± 0.06, 0.91 ± 0.07 for HCC, CRC, and PC, respectively. Further analyses were performed on the validation cohort, including 172 HCC patients, 162 CRC patients, 60 PC patients, and an independent cohort of healthy individuals (HCC validation: n = 63; HCC independent validation: n = 109; CRC validation: n = 104; CRC external validation: n = 58; PC validation: n = 60; healthy controls: n = 96). The trained model achieved a sensitivity of 83.1% (specificity = 95.8%), 89.5% (specificity = 95.8%), and 76.7% (specificity = 91.7%) for HCC, CRC, and PC, respectively. Using regional methylation markers from diagnostic models for individual cancer types, we built a tissue-of-origin classification model, which achieved a cross-validation accuracy of 83.3% in the training cohort and an accuracy of 80.1% in the validation cohort in assigning correct cancer types. **Conclusions:** Plasma cfDNA methylome profiling identified effective biomarkers for the detection and tissue-of-origin determination of GI cancers, and outperformed mutation-based detection approach. Therefore, a liquid biopsy test capable of detecting and locating GI cancers is feasible and may serve as a valuable tool for early detection and intervention. Research Sponsor: BGI Genomics.

1558 Poster Session (Board #50), Fri, 8:00 AM-11:00 AM

Evaluation of a mobile cervical cancer screening program in São Luis, Maranhão, Brazil: Impact and challenges. *First Author: Rachel Jorge Dino Cossetti Leal, Hospital do Câncer Aldenora Bello, São Luís, Brazil*

Background: Cervical cancer (CC) still represents a public health priority in Brazil, with estimated incidence of 15,43 cases per 100.000 women. CC is the most frequent cause of cancer and cancer-related mortality in women in the state of Maranhão. The Brazilian national screening program recommends cervical cytology (Pap test) every 3 years in women 25-64 years old. Although of public access, the screening program continues to be non-organized. This was a real-life CC screening intervention through a mobile screening unit (MSU) in communities of São Luis, Maranhão. **Methods:** Prospective, intervention-based, analytic study, from April to August, 2018. Women in the assisted communities were offered Pap tests. Tests were collected and results were retrieved within 4 weeks along with further screening recommendations. Quality control and monitoring of the test were done. A structured questionnaire was applied. **Results:** 960 tests were collected and 545 women answered the questionnaire. Median age: 43 (34 – 52), with 88.2% of women within the target age. Socioeconomic charachteristics: 47.3% completed high school education; 37.8% were housewives, 16.1% were unemployed; 56.3% were married; 59.8% had a monthly family-income up to 1 minimum wage ($ 250,00). Previous Pap tests and difficulties: 94.1% had at least one previous test; 78,2% had a test within the past 3 years; 48.4% referred to dificculties to scheduling, 23.3% time constraints, 11.2% being ashamed, and 10.4% financial restrains. There were 65 (6.9%) abnormal results (LSIL in 3%, HSIL in 0.7%, and in situ adenocarcinoma in 1 case), for whom further investigation was recommended. Follow-up was possible in 31 of these cases. More than 50% were still awaiting for additional screening tests at time of contact (>6 month interval). **Conclusions:** MSU strategy faccilitated the access to Pap tests, their results and recommendations. Although Pap test was easily available, the non-organized process of invitation, follow-up and referal of positive cases for further investigation, as offered by the Brazilian public health services, limit screening efficacy and CC control. Research Sponsor: None.

1559 Poster Session (Board #51), Fri, 8:00 AM-11:00 AM

Evaluation of circulating miRNAs for earlier cancer detection through machine-learning expression profiling. *First Author: Jason Chia-Hsun Hsieh, Chang Gung Memorial Hospital, Guashan Township, Taoyuan County, Taiwan*

Background: Earlier cancer diagnosis leads to higher patient survival rate and reduces financial burdens for patients and their families. Over the past five years, liquid biopsy has demonstrated tremendous promise in the early detection of tumor presence. In addition to circulating tumor cells and circulating tumor DNAs, extracellular microRNAs (miRNAs) have also been shown to be promising diagnostic biomarkers. Through machine-learning profiling, we sought to determine whether or not we could use individuals' miRNA expression to distinguish between healthy subjects and cancer patients. **Methods:** Blood samples were collected from healthy donors and from patients of various cancer types. Plasma samples were purified within two hours of sample collection, followed by miRNA extraction. After performing reverse transcription of miRNAs into cDNAs, expression analysis of miRNAs was done using a novel multi-gene, amplification-based detection system that simultaneously analyzes over 160 miRNAs. For subsequent data processing, miRNAs without amplification signals across all profiles were first removed, resulting in 135 miRNAs. These 135 resulting miRNAs were then used as features in Support Vector Machine (SVM) to build OncoSweep classifier, a proprietary prediction algorithm for classification of the samples. Ten-fold cross validation was used to evaluate the performance of OncoSweep. **Results:** 344 healthy donor samples and 417 cancer patient samples were collected for the study. The prediction algorithm, OncoSweep, was derived based on the miRNA expression patterns of the healthy and the patient samples. The algorithm scored an overall accuracy for cancer prediction of 86.47%, with a sensitivity of 91.4%, a specificity of 85%, a PPV of 85% and an NPV of 88.5%. **Conclusions:** Utilizing machine-learning method of analyzing circulating miRNA expression profiles, the derived algorithm OncoSweep shows significant promise in cancer prediction. Validation is currently being performed in a larger study. We believe circulating miRNAs, through stringent sample processing and machine-learning methodology, are powerful biomarkers for earlier cancer detection. Research Sponsor: Quark Biosciences, Inc.

1560 Poster Session (Board #52), Fri, 8:00 AM-11:00 AM

Epigenetic control of breast cancer susceptibility. *First Author: Natascia Marino, Indiana University School of Medicine, Indianapolis, IN*

Background: Epigenetic mechanisms such as DNA methylation are important regulators of gene expression and are frequently dysregulated early in breast carcinogenesis. The relationship between DNA methylation aberrations in normal breast tissue and breast cancer risk remains unclear. **Methods:** Disease-free breast tissue cores donated by 71 high-risk (Tyrer-Cuzick lifetime risk ≥20%) and 79 average-risk women were obtained from the Komen Tissue Bank and processed for whole methylome (Diagenode's MethylCap Library and single-end 75-bp sequencing on Illumina Nextseq) and whole transcriptome (Illumina Nextseq) profiling. Reads from RNA-seq data were aligned to the human genome reference, GRCh38.p12 using STAR v.2.5.2b and tested for differential gene expression using DESeq2 ver. 1.24.0. For DNA methylation data, difference of variation in deduplicated read coverage among 250-bp fixed sized bins spanning CpG islands between high- and average-risk libraries was computed as z-ratios to identify differentially methylated regions. Pathway analysis was performed using IPA v06_01. **Results:** We identified 1355 CpGs that were differentially methylated between high- and average-risk breast tissues ($\Delta Z > 0.5$, FDR < 0.05). Hypomethylated CpGs were overrepresented in high-risk tissue and were found predominantly (68%) in non-coding regions. Hypermethylated CpG sites were found equally in the gene body and non-coding regions. Transcriptomic analysis identified 112 differentially expressed genes (fold change≥2, FDR < 0.05), involved in chemokines signaling, metabolism and estrogen biosynthesis. Among those, FAM83A (logfc = 2.3, FDR = 0.004) was previously described as epigenetically dysregulated in multiple cancers and transforms breast epithelial cell *in vitro*. Methylation-expression correlations revealed 11 epigenetically regulated genes including cellular transformation-associated BMPR1B. Two hypomethylated/upregulated long non-coding RNAs were also identified in high-risk breasts. **Conclusions:** This is the first gene expression/DNA methylation analysis of normal breasts from women at either high or average risk of breast cancer. Our discovery of epigenetically regulated genes associated with breast cancer risk provides an opportunity to mechanistically dissect breast cancer susceptibility and risk-associated molecular alterations. Unlike the current focus of identifying germline mutations or single nucleotide polymorphisms responsible for higher risk, our studies reveal an epigenetic mechanism, which is not discernable through simple genomic sequencing. Research Sponsor: Breast Cancer Research Foundation, Catherine Peachy Fund.

1561 Poster Session (Board #53), Fri, 8:00 AM-11:00 AM

Adoption of opportunistic salpingectomy for ovarian cancer prevention: Results from a nationwide sample of privately insured women. *First Author: Pritesh S Karia, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

Background: Recent evidence indicates that the Fallopian tube is the site of origin for many high-grade serous ovarian cancers, particularly in *BRCA* carriers. This has led to the emergence of opportunistic salpingectomy (OS) as a novel ovarian cancer prevention strategy. Despite limited data, some national societies now recommend OS for ovarian cancer prevention during benign hysterectomy or in place of tubal ligation for sterilization in average-risk women. We assessed patient characteristics associated with increased likelihood of OS and national trends in OS adoption before and after release of recommendations. **Methods:** Data from MarketScan were used to identify women who underwent hysterectomy, tubal ligation, and OS from 2010-2017. Rates of OS were compared and interrupted time series analysis with segmented Poisson regression was used to examine immediate and persistent changes in OS rates before and after recommendations. Rates were calculated quarterly and models were adjusted for age and seasonality. **Results:** A total of 309,574 tubal ligations, 13,574 OS for sterilization, 293,000 hysterectomies, 22,798 hysterectomies with OS were included. Quarterly rates of OS for sterilization and hysterectomy with OS were 3.13 and 4.82 per 100,000 women, respectively. About 92% of OS for sterilization and 56% of hysterectomy with OS were performed in women < 45 years. The most common indication for hysterectomy with OS was uterine fibroids (46%). About 8% of OS for sterilization and 10% of hysterectomy with OS were performed in women with a family history of breast or ovarian cancer. After adjusting for age and seasonality, there was a 250% immediate increase (RR: 3.50; 95% CI: 2.59-4.72) followed by a 14% (RR: 1.14; 95% CI: 1.10-1.18) persistent increase in the quarterly rate of OS for sterilization after versus before recommendation release. There was a 109% immediate increase (RR: 2.09; 95% CI: 1.15-3.81) in the quarterly rate of hysterectomy with OS after versus before recommendation release. No persistent change in the rate of hysterectomy with OS was observed. Significant declines in hysterectomy and tubal ligation rates were observed and these declines were temporally associated with the release of recommendations. **Conclusions:** OS for ovarian cancer prevention has rapidly diffused into clinical practice with the speed of adoption bolstered by recommendations from national societies. Future studies evaluating the overall efficacy and long-term complications of OS are needed to support its continued widespread use. Research Sponsor: None.

1562 Poster Session (Board #54), Fri, 8:00 AM-11:00 AM

Breast cancer events in women with atypical ductal hyperplasia who do not undergo surgical excision. *First Author: Lyndsey Jo Kilgore, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Atypical ductal hyperplasia (ADH) found on core needle biopsy is associated with an upgrade to carcinoma in 10-30% of women, thus surgical excision remains the standard of care. We sought to review the incidence of breast cancer in women with ADH managed by either observation or surgical excision over a 15 year period. **Methods:** Our prospectively maintained registry was reviewed to identify patients with ADH diagnosed by core needle biopsy between 1/2004 and 10/2018. Observed patients were deemed low risk for upgrade after multidisciplinary review confirmed adequate sampling, limited atypia and concordance between imaging and histology. Surgical patients were excluded if upstaged to carcinoma following excision. Patients with $<$ 1 year follow-up were excluded. Subsequent breast cancer was classified as ipsilateral or contralateral to the previous ADH and was further classified as index site if the new cancer was identified in the same quadrant as prior ADH. Multivariate logistic regression models were used to assess potential predictors of subsequent breast cancer events. **Results:** Four hundred and seventy-eight women with 483 ADH lesions met criteria; 305 were observed and 173 underwent excision. Median follow-up was 5.2 years, range 1.1-15.3. At the time of ADH diagnosis, 91 women had a personal history of breast cancer. Age $<$ 50 was the only statistically significant difference between the groups (24.6% vs. 33.3%, p = 0.04). Race, receipt of chemoprevention, prior breast cancer history and median follow-up were not significant between the groups. Prior history of breast cancer was associated with subsequent breast cancer risk in multivariate analysis (OR 2.25, 95% CI 1.04-4.87, p = 0.04). After excluding patients with a history of breast cancer, multivariate analysis demonstrated no association of age, race, use of chemoprevention or surgical excision with future cancer risk. Among the 387 patients without a prior breast cancer history, 21 patients developed a subsequent cancer; 10 in the surgical group and 11 in the observed group (7.3% vs. 4.4% respectively, p = 0.2). Two cancers were identified at the index site in the surgery group (2/137, 1.5%) and three in those observed (3/250, 1.2%). **Conclusions:** Observation, rather than surgical excision, is safe in selected women that have a core biopsy diagnosis of ADH. Index site failures are rare and are superseded by cancer risk elsewhere in the breast. National screening and diagnosis recommendations should consider recommending observation for this select group of patients with ADH. Research Sponsor: None.

1563 Poster Session (Board #55), Fri, 8:00 AM-11:00 AM

Mammography utilization among women with a negative circulating tumor DNA-based early cancer detection test. *First Author: Claire Jones, Geisinger Health System, Danville, PA*

Background: Blood-based tests may enable minimally invasive detection of multiple cancer types. One such test, CancerSEEK, employs ctDNA and protein biomarkers for this purpose. Test performance has been evaluated in women without a history of cancer in an ongoing prospective study called DETECT-A. The introduction of such blood tests holds promise, and their future utility lies in augmenting, not displacing, standard-of-care (SOC) cancer screening. One important safety concern is that a negative test result could provide false reassurance that discourages adherence to SOC cancer screening. To investigate this possibility, we studied delivery of mammography to DETECT-A participants before and after receipt of a negative CancerSEEK result. **Methods:** DETECT-A screened 10,000 women aged 65-75 using CancerSEEK. Participants completed a survey about cancer screening at enrollment and at one-year post-enrollment. We analyzed only those participants who had received a negative CancerSEEK result, were insured by Geisinger Health Plan (GHP), and had completed both surveys. GHP claims data were used to identify mammograms performed within one year prior-to and post-enrollment. Overall utilization was determined by combining claims and survey data at enrollment and one-year post-enrollment. In addition to comparing SOC screening rates pre- versus post-testing, we evaluated the impact of primary care physician (PCP) type (Geisinger versus any other institution), as screening reminder mechanisms differ between institutions. **Results:** Of the 2,241 participants who met analysis criteria, 73.6% (n = 1,650) had a mammogram in the year before enrollment while a significantly great number (79.3%, n = 1,777) did so during the one-year follow-up ($\chi^2(1) = 59.05$, $p < 0.001$). At enrollment, there were 591 participants who had not had a mammogram completed in the previous year, but 404 (68.4%) of them did have a mammogram during the one-year follow-up. The rate of change in mammography utilization did not differ between those who had a Geisinger versus a non-Geisinger PCP ($\chi^2(2) = 1.83$, p = 0.40). **Conclusions:** Participants in a study using a novel blood test for earlier cancer detection had a significantly higher rate of annual mammography after study enrollment and testing. These results indicate that introduction of a minimally invasive ctDNA and protein biomarker-based cancer screening test may engender greater, not lesser, utilization of SOC cancer screening. Further study is required to understand the root causes of increased utilization in this context. Research Sponsor: Marcus Foundation.

1565 Poster Session (Board #57), Fri, 8:00 AM-11:00 AM

Mediation of black/white disparities in triple negative breast cancer by socioeconomic position, reproductive factors and diabetes in the Nurses' Health Study Cohorts I & II. *First Author: Lydia Marcus, University of Wisconsin Milwaukee, Milwaukee, WI*

Background: The higher rates of triple negative (TN) breast cancer (BC) observed among black compared to white women may be attributable to social and reproductive factors, as well as biological conditions like diabetes mellitus type 2. We examine the extent to which the black/white race disparity in TNBC is transmitted through these factors. **Methods:** Data are from the Nurses' Health Study I and II prospective cohorts and include non-Hispanic (nH) black (n = 97) and nH white (n = 8,876) women aged 25-55 years at enrollment with invasive BC diagnoses. Participant characteristics are self-reported or drawn from medical records. We estimated average controlled direct associations (ACDA) using logistic regression with model-based standardization to evaluate the age/body mass index (BMI)-adjusted prevalence difference for TN versus luminal A/B type BC by race, and performed a series of ACDA (with comparison of rescaled coefficients (RC)) controlling for diabetes, mean family income before diagnosis (cont.), husband's education ($<$ college, college, graduate school), parental ownership of participant's childhood home (yes/no), age at menarche (cont.), age at first birth (cont.), parity (integer), and breastfeeding (BF) (parous/never BF, parous/ever BF). **Results:** Compared to nH whites, nh black women had higher prevalence of TNBC (24.5% v. 45.4%; $p < 0.01$), higher prevalence of diabetes (5.5% v. 11.3%; p = 0.01), lower prevalence of BF (59.2% v. 46.6%; p = 0.02), higher mean BMI (26.1 v. 29.9; $p < 0.01$), and lower mean family income ($17,304 v. 15,750; $p < 0.01$). BMI, age, and menopause were positively associated with prevalence of diabetes. In the age/BMI adjusted model, nH black women were 20%-points more likely than nH whites to have TNBC (95% Confidence Interval (CI): 0.11, 0.29). This disparity was reduced to 18.1% after also adjusting for BF (95% CI: 0.09, 0.28), to 13.7% after additionally adjusting for socioeconomic indicators (95% CI: 0.02, 0.25), and to 13.3% after adjusting for all potential mediators (95% CI: 0.01, 0.26). Based on the method of RC, socioeconomic indicators accounted for the largest fraction of mediated effects and BF accounted for most of main effect attenuation associated with reproductive factors; diabetes accounted for negligible effect. **Conclusions:** Our findings support the hypothesis that observed racial differences in TNBC diagnoses may be at least partially mediated by differences in socioeconomic position and reproductive patterns, namely breastfeeding. Research Sponsor: University of Wisconsin.

1566 Poster Session (Board #58), Fri, 8:00 AM-11:00 AM

Projection of cancer incidence and death to 2040 in the US: Impact of cancer screening and a changing demographic. *First Author: Lola Rahib, Cancer Commons, Los Altos, CA*

Background: Coping with the current and future burden of cancer requires an in-depth understanding of cancer incidence and death trends. As of 2020, breast, lung, prostate, and colorectal cancer are the most incident cancers, while lung, colorectal, pancreas, and breast cancer result in the most deaths. Here we integrate observed cancer statistics and trends with observed and estimated US demographic data to project cancer incidences and deaths to the year 2040. **Methods:** Demographic cancer-specific delay-adjusted incidence and death rates from the Surveillance, Epidemiology, and End Results Program (2014-2016) were combined with US Census Bureau population growth projections (2016) and average annual percentage changes in incidence (2011-2015) and death (2012-2016) rates to project cancer incidences and deaths through the year 2040. We examined the 10 most incident and deadly cancers as of 2020. We utilized Joinpoint analysis to examine changes in incidence and death rates over time relative to changes in screening guidelines. **Results:** We predict the most incident cancers in 2040 in the US will be breast (322,000 diagnoses in 2040) and lung (182,000 diagnoses in 2040) cancer. Continuing decades long observed incident rate trends we predict that melanoma (173,000 diagnoses in 2040) will become the 3rd most common cancer while prostate cancer (63,000 diagnoses in 2040) will become the 5th most common cancer after colorectal cancer (139,000 diagnoses in 2040). Lung cancer (61,000 deaths in 2040) is predicted to continue to be the leading cause of cancer related death, with pancreas (45,000 deaths in 2040) and liver & intrahepatic bile duct (38,000 deaths in 2040) cancer surpassing colorectal cancer (34,000 deaths in 2040) to become the second and third most common causes of cancer related death, respectively. Breast cancer deaths (29,000 in 2040) are predicted to continue to decrease and become the fifth most common cause of cancer death. Joinpoint analysis of incidence and death rates supports a significant past, present, and future impact of cancer screening programs on the number of cancer diagnoses and deaths, particularly for prostate, thyroid, melanoma incidences, and lung cancer deaths. **Conclusions:** We demonstrate marked changes in the predicted landscape of cancer incidence and deaths by 2040. Our analysis reveals an influence of cancer screening programs on the number of cancer diagnoses and deaths in future years. These projections are important to guide future research funding allocations, healthcare planning, and health policy efforts. Research Sponsor: None.

1567 Poster Session (Board #59), Fri, 8:00 AM-11:00 AM

Malignancies associated with DPP4 inhibitors and GLP1 receptor agonists: Data from a large real-world database. *First Author: Jiasheng Wang, Met-MetroHealth Medical Center, Cleveland, OH*

Background: DPP44 inhibitors (DPP4i) and GLP1 receptor agonists (GLP1Ra) control type 2 diabetes (T2DM) by promoting GLP-1 pathway; its activation can lead to dysplasia or tumor inhibition based on tissue types. Moreover, DPP4 can act as a tumor suppressor or activator. Few studies have looked at the risk of DPP4i and GLP1Ra on various types of cancer. **Methods:** We inquired an aggregated electronic health record database, Explorys (IBM, NY). Patients (Pts) diagnosed with T2DM from 1/05 to 6/19 were included and followed for 5 years after starting DPP4i, GLP1Ra, or metformin. Odds ratio (OR) were calculated after 6mo of lag time. **Results:** We identified 344,550, 112,000, and 1,245,930 pts in the DPP4i, GLP1Ra, and metformin group, respectively. The three groups were well balanced except pts in the GLP1Ra group had higher BMI. Within 5 years, 24,260 pts (9.5%) in DPP4i, 5,580 (8.7%) in GLP1Ra, and 57,490 (9.3%) in metformin group developed any types of cancer. When adjusted for sex, age, smoking status, alcohol abuse history, hemoglobin A1C ($\leq$9.0% vs $>$ 9.0%) and BMI ($<$ 30 vs $\geq$30 kg/m^2) around initiation of antidiabetic agents, the aOR was 1.01 (95%CI .94-1.08) for DPP4i and 1.06 (95%CI .93-1.20) for GLP1Ra, comparing with the metformin group. For specific cancer types, DPP4i users were associated with significantly higher risk of bladder, kidney, liver cancer and melanoma; while the risk of breast, lung and prostate cancer were reduced. GLP1Ra users were associated with higher risk of thyroid cancer; while the risk of bladder, colon, lung, and prostate cancer were reduced. **Conclusions:** DPP4i and GLP1Ra were not associated with increased cancer risk overall. However, they were associated with increased or decreased risk of specific cancer types. Research Sponsor: None.

	DPP4i		GLP1Ra	
Cancer	**OR (95% CI)**	**P value**	**OR (95% CI)**	**P value**
Bladder	1.18 (1.09-1.29)	$<$ .01	.69 (.58-.83)	$<$ .01
Brain	1.00 (.84-1.19)	.98	1.10 (.82-1.47)	.54
Breast	.90 (.85-.94)	$<$ .01	.99 (.91-1.07)	.75
Colon	.97 (.91-1.04)	.38	.73 (.64-.83)	$<$ .01
Esophagus	.86 (.73-1.00)	.06	1.02 (.78-1.32)	.91
Kidney	1.13 (1.04-1.23)	$<$ .01	1.13 (.98-1.31)	.09
Liver	1.14 (1.02-1.26)	.02	.91 (.75-1.11)	.37
Lung	.91 (.86-.97)	$<$ .01	.60 (.53-.68)	$<$ .01
Lymphoma	.98 (.91-1.05)	.51	.92 (.81-1.05)	.21
Melanoma	1.12 (1.04-1.21)	$<$ .01	.98 (.85-1.12)	.75
Ovary	.91 (.78-1.06)	.23	.82 (.61-1.09)	.17
Pancreatic	.94 (.86-1.04)	.23	.84 (.70-1.00)	.05
Prostate	.87 (.82-.91)	$<$ .01	.65 (.59-.82)	$<$ .01
Stomach	1.03 (.88-1.21)	.70	.74 (.54-1.03)	.07
Thyroid	.89 (.79-1.01)	.08	1.39 (1.16-1.68)	$<$ .01
All cancer	**1.01 (.94-1.08)**	**.84**	**1.06 (.93-1.20)**	**.40**

1568 Poster Session (Board #60), Fri, 8:00 AM-11:00 AM

A comparison of patients' and physicians' expectations regarding precision oncology tests. *First Author: Navdeep Dehar, University Of Calgary, Calgary, AB, Canada*

Background: With the increasing number and frequency of biomarker and genetic tests that are offered to patients with cancer, it is important to ensure that they fully understand the implications of these tests. In this survey study, we aimed to compare the attitudes and expectations of patients and cancer physicians about the role of biomarker and genetic testing in clinical decision-making. **Methods:** Two separate, complimentary, self-administered questionnaires for cancer patients and their physicians, respectively, were collected in Calgary, Alberta, Canada. Survey responses from patients were subsequently matched with those of their corresponding oncologists to form patient–oncologist dyads. We determined the concordance rates between responses of patients and those of their oncologists. **Results:** A total of 113 patients and 15 physicians participated in the study from July to September 2019. Patients demonstrated good understanding of general cancer biology (79%) and diagnostic processes (91%) associated with precision oncology. About 70% patients were willing to undergo minor procedures, and participate in research involving biomarker or genetic testing; however, this was over-estimated by their physicians in 82% of cases. Many patients felt that their tumor should be tested to guide treatment (70%) and were not bothered by potential delays in treatment due to testing (23%). These views from patients were largely shared by their oncologists (concordance 64%). While only 28% patients thought that they had enough knowledge to make informed decisions, majority (68%) said that they needed more information. Importantly, knowledge and expectations regarding the applications of biomarker or genetic test results on actual diagnosis and prognosis were grossly discrepant between patients and their oncologists (concordance 26% and 36%, respectively). **Conclusions:** Patients and cancer physicians tend to be aware of the advances in precision oncology and are willing to participate in biomarker and genetic testing and research. However, they do not consistently agree about the roles and applications of these tests, which may result in misplaced expectations. Strategies to improve education and communication are needed to align these expectations and improve the quality of clinical decision-making. Research Sponsor: None.

1569 Poster Session (Board #61), Fri, 8:00 AM-11:00 AM

Protein intake and breast cancer incidence and mortality. *First Author: Kathy Pan, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA*

Background: Associations between dietary protein intake and breast cancer are unclear, in part due to limitations of dietary self-report. Women's Health Initiative (WHI) investigators compared the accuracy of food frequency questionnaire (FFQ) data on energy and protein intake with objective measures of dietary intake using biomarkers (doubly labeled water for energy and urinary nitrogen for protein [n=544]). Subsequently, regression equations incorporating participant characteristics were developed acknowledging differential reporting dietary data errors based on participant characteristics (Neuhouser Am J Epidemiol). FFQ findings were then used to determine biomarker- adjusted animal vs vegetable protein ratios. **Methods:** We examined associations of energy and protein intake with breast cancer incidence and mortality in Women's Health Initiative (WHI) participants 50-79 years of age at entry between1993-1998, with breast cancers verified by medical record review and survival enhanced by serial National Death Index (NDI) searches through 2016. Associations between sources of protein intake (animal versus vegetable) quintiles and breast cancer incidence and mortality were estimated using multivariable Cox proportional hazards regression. **Results:** With 100,024 eligible participants, after 14 years follow-up, women with higher total protein intake had greater body mass index, were more likely White, menopausal hormone therapy users with higher total energy intake and fat intake. With 6,340 incident breast cancers, 764 deaths from breast cancer and 2,059 deaths after breast cancer, higher vegetable protein intake was associated with significantly lower breast cancer incidence (P for linear trend = 0.01) while higher animal protein intake was associated with significantly higher breast cancer incidence (P for linear trend = 0.03). Higher vegetable protein intake was also associated with significantly lower risk of death after breast cancer (P $<$0.001) but not with lower risk of deaths from breast cancer (breast cancer followed by death attributed to breast cancer). Animal protein intake was not associated with deaths from breast cancer or deaths after breast cancer. **Conclusions:** Based on findings from biomarker-calibrated determination of protein intake by source, higher vegetable protein intake was associated with significantly lower risk of breast cancer incidence and of death after breast cancer while higher animal protein intake was associated with significantly higher risk of breast cancer incidence, but not mortality. Research Sponsor: U.S. National Institutes of Health.

1570 Poster Session (Board #62), Fri, 8:00 AM-11:00 AM

Dietary advanced glycation end products (AGEs) and breast cancer mortality in the women's health initiative (WHI). *First Author: Lindsay Leuthen Peterson, Washington University in St. Louis, St. Louis, MO*

Background: Breast cancer (BrCa) is the second leading cause of cancer death and constitutes about 14% of total cancer deaths among US women. Advanced glycation end-products (AGEs) are implicated in chronic diseases including cancer and cardiovascular diseases (CVD). AGEs are naturally found in animal products and processed foods, and preparing food at high temperatures increases AGE formation. Our goal was to assess the association between post-diagnosis dietary N$^{\varepsilon}$-carboxymethyl-lysine (CML)-AGE intake, a common measure of AGE, and mortality from all-causes, BrCa and CVD among participants with invasive BrCa in the Women's Health Initiative (WHI). **Methods:** The WHI enrolled postmenopausal women aged 50 to 79 years from 1993-1998 into randomized controlled trials and a prospective observational study to examine causes of morbidity and mortality. In this analysis, we included 2,073 women diagnosed with invasive BrCa during follow-up who completed a food frequency questionnaire (FFQ) after diagnosis, had energy intakes between $\geq$600 kcal/day and $\leq$5000 kcal/day, and had CML-AGE intake data available. Women were followed from BrCa diagnosis until death or censoring through March 2018. Cox proportional hazards regression models estimated the hazard ratios (HR) and 95% CIs of mortality risk from all-causes, BrCa and CVD by tertiles of dietary CML-AGE intake with adjustment for age, income, race/ethnicity, study arm, time from diagnosis to FFQ completion, education, physical activity, smoking, BMI, ER/PR status, diagnosis stage, postmenopausal hormone use, intake of energy, alcohol, fat, red and processed meats. **Results:** After a median 15.1 years of follow-up, 642 deaths were reported including 198 BrCa-specific and 129 CVD-specific deaths. The average time from BrCa diagnosis to FFQ completion was 1.5 years. Compared to the lowest tertile of CML-AGE intake, there was an increased risk in the highest tertile for all-cause mortality (HR: 1.51, 95% CI: 1.17-1.94), BrCa (HR: 1.86, 95% CI: 1.19-2.91) and CVD (HR: 2.14, 95% CI: 1.19-3.84) mortality. **Conclusions:** Higher dietary AGE intake after BrCa diagnosis in postmenopausal women was associated with increased risk of mortality from all-causes, BrCa and CVD. Exposure to AGEs could be modified through dietary counseling and evaluated in relation to reduced mortality risk after BrCa diagnosis. Research Sponsor: Susan G. Komen, Other Foundation.

1571 Poster Session (Board #63), Fri, 8:00 AM-11:00 AM

Metabolic syndrome, metabolic comorbid conditions, and risk of early-onset colorectal cancer. *First Author: Hanyu Chen, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO*

Background: The etiology and contributors to the rising incidence of early-onset colorectal cancer (CRC diagnosed under age 50), driven largely by distal and rectal cancer, remain largely unknown. Metabolic syndrome is associated with higher risk of CRC diagnosed at older ages; however, its association with early-onset CRC remains unclear. **Methods:** We conducted a nested case-control study among participants aged 18-50 years with ≥2 years of enrollment and prescription drug coverage in the IBM MarketScan Commercial Databases (2006-2015). Incident CRC cases were identified using ICD-9-CM diagnosis codes. Controls without any cancer were identified using frequency matching on age, sex, geographical region, and duration of insurance enrollment. Metabolic syndrome was defined using either ICD-9-CM diagnosis codes or the presence of at least 3 of the following: obesity, hypertension, hyperlipidemia, and hyperglycemia/type 2 diabetes. In addition to ICD-9-CM codes, hypertension, hyperlipidemia, and hyperglycemia/type 2 diabetes were also defined based on regular use of medications. Multivariable logistic regressions were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs). **Results:** A total of 4,673 early-onset CRC and 40,832 controls were included. Metabolic syndrome was associated with increased risk of early-onset CRC (OR: 1.33, 95% CI 1.16-1.52), after adjusting for a range of potential confounders. The number of metabolic comorbid conditions was positively associated with risk of early-onset CRC in a dose-response fashion. Compared to individuals without any conditions, individuals with 1, 2, ≥3 metabolic conditions had a 13% (OR: 1.13, CI 1.04-1.22), 18% (OR: 1.18, CI 1.07-1.31), and 40% (OR: 1.40, CI 1.22-1.61) higher risk of early-onset CRC (P_{trend}<0.001), respectively. These associations were driven by proximal (OR for ≥2 vs 0 metabolic comorbid conditions: 1.40, CI 1.15-1.69) and distal colon cancer, OR ≥2 vs 0: 1.25, CI 1.03-1.53), but not rectal cancer (OR≥2 vs 0: 1.07, CI 0.92-1.24). **Conclusions:** Metabolic syndrome and metabolic comorbid conditions were associated with increased risk of early-onset CRC, largely driven by proximal and distal colon cancer. Metabolic dysregulations may contribute to the rising incidence of early-onset CRC. Research Sponsor: U.S. National Institutes of Health.

1572 Poster Session (Board #64), Fri, 8:00 AM-11:00 AM

Is there a genomic fingerprint of Radon (Rn)-induced lung cancer (LC)? Comparison of genomic alterations in LC specimens from high and low Rn zones. *First Author: Hina Khan, Rhode Island Hospital-The Warren Alpert Medical School of Brown University, Providence, RI*

Background: Rn-222 is a radioactive gas found in rocks and soil. It emits alpha particles that cause dsDNA breaks and increase potential for carcinogenesis. Rn is the 2nd leading cause of LC in the US after smoking. EPA estimates >15,000 deaths/yr (9% of LC deaths) from Rn. We hypothesize that the impact of Rn exposure may be reflected in LC gene mutation (mut) profiles. **Methods:** Using commercial NGS assays, we retrospectively analyzed genomic DNA alterations in FFPE specimens from 159 LC patients (pts) from the Lifespan Cancer Institute in Rhode Island (2014- 2019), followed by validation in a larger cohort of 5,532 pts using Caris platform. Based on EPA Rn maps, we identified counties with high indoor Rn levels (>4 pci/L; HR), and compared gene mut patterns with those from low Rn zones (<4 pci/L; LR). Based on pt's zip code of residence, we categorized them to HR and LR. In the validation cohort, p values adjusted for multiple comparison (q) of < .05 were considered significant. **Results:** In the pilot cohort, 35 pts (22%) were in HR and 124 (78%) in LR zones. Adenocarcinoma histology was most frequent (73%) and smoking prevalence was high (75%) in both groups. Most prevalent alterations were *TP53, KRAS* and *CDKN2A* muts. In the HR, we noted more frequent recurrent muts in 2 DNA repair genes (DDR): *ATM* (11 vs 1%, p= .00086) and *CHEK2* (6 vs 0%, p= .047) when compared to LR group. When classified into major pathways implicated in lung carcinogenesis, higher frequency of mutations were seen in DDR in HR zones vs. LR (29 vs 13%, p= .038). In the validation cohort, 1,433 (26%) pts were in HR and 4099 (74%) in LR zones. Among the DDR genes, *ATM* muts in HR group tended to be more frequent (4.7 vs 3.4% in LR, p= .03) as well as *PALB2* (0.9 vs 0.4%, p= .02) while no difference seen in *CHEK2*. Other genes with significantly higher prevalence in HR were *TP53, SMARCA4 and NFE2L2* (q< .05); while *KMT2D, KEAP1, CDKN2A, MET, NF2, DNMT3A, CCND1 and FAS* show a trend (p< .05). *EGFR* muts were significantly more frequent in LR zones (8.4 vs 14.6%, q= .001). Similar to the pilot cohort, DDR pathway alterations trend to be higher in HR zones (14 vs 12%, p= .05). Using a high TMB cut-off >10, tumors from HR zones had significantly higher TMB when compared to LR zones (56 vs 48%, q= .0005). **Conclusions:** To our knowledge, this is the first attempt to elucidate the pathobiology of Rn induced LC using gene mut analyses. Our observations suggest that LC associated with higher Rn exposure may have disabled DNA repair pathways and higher TMB. Assuming uniform tobacco smoke exposure, higher Rn was not associated with EGFR mut. Research Sponsor: institutional finances.

1573 Poster Session (Board #65), Fri, 8:00 AM-11:00 AM

The increasing incidence of colorectal cancer in younger patients in the United States: Who, what, when, and where? *First Author: Mary Kathryn Abel, UCSF School of Medicine and Department of Surgery, San Francisco, CA*

Background: Prior studies have shown an increase in the rate of colorectal cancer (CRC) in young individuals in the United States. However, few studies have evaluated the health disparities that exist in this population, particularly using large, national cohorts. We examined differences in age, race, stage, region, and tumor location in younger and older patients with CRC. **Methods:** Data were extracted from the United States Cancer Statistics (USCS) for individuals diagnosed between 2001 and 2014. CRC incidence data among individuals < 50 years old were compared to those > 50 years old. Age-specific and age-adjusted incidences and trend analyses reported as annual percent change (APC) were performed using SEER*Stat and Joinpoint regression. **Results:** Of 1,886,441 individuals, the overall age-adjusted incidence of CRC decreased from 52.59 (per 100,000) in 2001 to 35.22 in 2014, with an APC of -3.24. Although over 35% cases were diagnosed in the Southern United States, the Northeast had the highest age-adjusted incidence at 45.26 per 100,000 patients. Younger patients were diagnosed with distant disease at 25.8% compared to only 18.4% in older patients. Younger patients were also more likely to have sigmoid or rectal cancers compared to older patients (64.3% vs. 45.7%). Of the 170,244 individuals < 50 years, 90,855 (53.4%) were men and 79,389 (46.6%) were women. The age-specific incidence in this younger cohort increased from 5.63 to 6.48 between 2001-2014, with an APC of +1.24 in 2001-2008 compared to +2.55 in 2012-2014. The incidence of CRC in patients aged 0-29, 30-39, and 40-49 years was 0.41 (per 100,000), 6.08, and 21.09, respectively. Black individuals < 50 years had the highest age-specific incidence of CRC (7.16 per 100,000) compared to Asian (6.43), White (6.07), or Hispanic (4.76) individuals. **Conclusions:** Our data suggests that CRC is increasing in young patients, particularly for those between 40-49 years and Black individuals. In our younger cohort, CRC was more commonly found in the sigmoid colon and rectum compared to older patients. Further research is warranted to direct resources towards improved colonoscopy or sigmoidoscopy screening for younger patients at risk. Research Sponsor: None.

1574 Poster Session (Board #66), Fri, 8:00 AM-11:00 AM

Geographic disparity of outcome in patients with cancer over decades: The surveillance, epidemiology, and end results. *First Author: Kenichi Sakurai, Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Improvements in prevention, early detection and therapy of cancer have decreased cancer related mortality yet health disparities continue to exist. We investigated the impact of such disparities in cancer survival. **Methods:** In the Surveillance, Epidemiology, and End Results, we identified 784,341 patients with cancer from 1990 to 2016 in Georgia; 68,493 in 1990-1999, 371,353 in 2000-2009, and 322,932 in 2010-2016. We assessed overall survival (OS) of patients with all cancers, chronic myeloid leukemia (CML), and lung cancer given the dramatic improvement in patient outcomes in CML since 2000 compared to the consistently poor outcome in lung cancer. We assessed distance from each county to the one National Cancer Institute-designated cancer center (NCI-CC) in Georgia. **Results:** The 5-year OS of patients with any cancer was 55% with median OS 80 months; the 5-y OS of each county ranged from 33% to 82% (interquartile range[IQR], 51%-65%)(P < 0.001). The improvement of OS was minimal over decades: 5-year OS was 52%, 55%, and 55% in 1990-1999, 2000-2009, and 2010-2016, respectively; the median was 69 months, 80 months, not reached, respectively (P < 0.001). In patients with lung cancer and CML, the 5-year OS was 15% and 52% with the median of 9 months and 67 months, respectively. The geographic difference between counties was relatively small and constant over time in patients with lung cancer, represented by the width in the range and IQR: range 5%-17%, IQR 9%-13%, median 13% in 1990-1999; range 2%-24%, IQR 10%-14%, median 14% in 2000-2009; and range 4%-24%, IQR 12%-17%, median 17% in 2010-2016. However, the geographic difference was more prominent in patients with CML and widened after introduction of modern therapy: range 20%-42%, IQR 26%-34%, median 32% in 1990-1999; range 14%-83%, IQR 38%-64%, median 53% in 2000-2009; and range 14%-80%, IQR 40%-57%, median 57% in 2010-2016. Multivariate Cox regression showed age (hazard ratio[HR],1.040;95% confidence interval[CI],1.039-1.040;P < 0.001), median county income (HR,0.919; 95% CI,0.916-0.921;P < 0.001), African American (HR,1.021;95% CI,1.210-1.227;P < 0.001), and distance to NCI-CC (each 100 kilometers) (HR,1.021;95% CI,1.017-1.025;P < 0.001) as predictive factors. **Conclusions:** The disparity of cancer care exists between geographic locations. The geographic difference of survival seems more prominent when highly effective therapies are available. Research Sponsor: None.

1575 Poster Session (Board #67), Fri, 8:00 AM-11:00 AM

Population genetic screening for hereditary breast and ovarian cancer in at-risk patients: A novel testing and prevention model for community hospitals reveals high mutation rates rurally. *First Author: Charles Hendrix Shelton, Vidant Health, Nags Head, NC*

Background: Genetic testing for at risk non-cancer patients continues to increase (Guo F, et al Cancer 2020). We identified a high risk of familial breast and ovarian cancer in rural eastern North Carolina, and created a systematic approach for genetic screening, counseling and testing. **Methods:** A family history questionnaire was designed to assess for the risk for hereditary breast and ovarian cancer (HBOC) using NCCN guidelines, and used at key intake points within the unaffected population to determine eligibility for genetic testing. First it was offered at the time of all mammograms. Second, we offered it in the primary gynecology care setting to capture younger patients not participating in screening mammography. Patients meeting HBOC criteria were sent a letter and two phone calls to schedule genetic counseling. Analysis via descriptive statistics. **Results:** 3000 rural women screened using our systematic approach to genetic risk assessment. 22.4% (673/3000) of female patients met NCCN criteria for HBOC panel testing. All offered consultation and counseling. With a backlog to see patients due to higher than expected accrual, 217 patients have completed pre-test genetic counseling, 201 completed local 19-gene panel test, and 201 had post-test counseling. Germline mutations (=>1) that predict for genetic susceptibility to cancer(s) occur in 7.8% of our screened and tested population. Currently 1 in 400 patients screened in our unaffected population carry a BRCA mutation, and 1 in 200 carry some pathogenic mutation that increases risk for HBOC. **Conclusions:** This rural model of screening and prevention of at risk patients for HBOC is successful at detecting pathogenic mutations in unaffected patients before they are diagnosed with cancer. Interestingly, the rate of positivity in the unaffected population (meeting criteria) is as high as the known breast cancer population rate of germline mutations (5-10%), validating the use of testing guidelines with our model. Discovering this susceptibility before a cancer diagnosis resulted in appropriate high risk management with prevention and risk reduction strategies. We plan to expand this model to the male screening population in 2021, and streamline genetic assessment and testing for the larger population at risk by engaging more rural primary care clinics over time to increase testing compliance. We also plan to consider broader gene panels as newer mutations become linked to HBOC. Clinical trial information: UMCIRB 19-001052. Research Sponsor: Pfizer and ACCC.

1576 Poster Session (Board #68), Fri, 8:00 AM-11:00 AM

Burden of genetic testing in an academic biobank by pathological and family history-based criteria in prostate cancer (PCa). *First Author: James Ding, University of Pennsylvania, Philadelphia, PA*

Background: Approximately 5% of localized PCa and 12% of metastatic PCa are associated with germline mutations in DNA repair genes. The National Comprehensive Cancer Network (NCCN) issued genetic testing guidelines to identify PCa patients (pts) likely to harbor a germline DNA repair mutation. The overall burden of this guideline-based, resource-intensive genetic testing is unknown. Using supervised phenotype-genotype information extraction algorithms, we determined the projected genetic testing burden at a single institution adhering to NCCN PCa genetic testing guidelines. **Methods:** A PCa cohort of 2127 pts was identified from the Penn Medicine BioBank via ICD 9/10 codes. Phenotypic data were extracted from the Penn Medicine Cancer Registry and electronic health record systems via natural language processing and manual chart review. Pts were classified based on 9 germline genetic testing criteria outlined in the NCCN PCa guidelines (Version 4.2019). **Results:** 895/2127 pts met at least 1 of the 9 NCCN genetic testing criteria, corresponding to a 42.1% overall genetic testing burden. 35.2% qualified for testing via high-risk localized PCa and 6.4% qualified via metastatic disease. Of the pts with localized PCa (n=2014), 15.1% qualified for genetic testing via high Gleason score, 5.1% via high-risk family history, 3.7% via PSA>20ng/mL, 8.7% via Ashkenazi Jewish descent, and 0.8% via intraductal/ductal histology. **Conclusions:** In this single-center PCa cohort, germline genetic testing was NCCN-guideline recommended for a larger proportion of pts than would otherwise be expected based on previously published reports. Future studies are needed to validate the sensitivity and specificity of these criteria for identifying germline mutations. Our study also highlights a need for novel methods to improve the efficiency of genetic testing for a large cohort. Research Sponsor: Penn Medicine Basser Center Grant.

Number of pts in a biobank meeting individual genetic testing criteria.

	Criteria[1]	# of pts meeting criteria	Total pts with data for criteria	% of pts
1	Regional: Any T, N1, M0	28	1178	2.4%
2	Metastatic: Any T, Any N, M1	113	1763	6.4%
3	High risk: T3 or T4	380	1081	35.2%
4	High risk: Gleason score 8-10	361	1929	18.7%
5	High risk: PSA at diagnosis >20ng/mL	109	1589	6.9%
6	Very high risk: Gleason primary 5	40	1928	2.1%
7	Ashkenazi Jewish	187	1773	10.6%
8	≥3 cancers on same side of family	111	2113	5.3%
9	Intraductal/ductal histology	20	2127	0.9%

[1] Not included due to lack of data: Brother, father, or multiple family members with PCa (not clinically localized grade 1) diagnosed <60 years old or who died from PCa

1577 Poster Session (Board #69), Fri, 8:00 AM-11:00 AM

Video vs. in-person genetic counseling for men considering germline prostate cancer testing: A patient-choice study. *First Author: Veda N. Giri, Departments of Medical Oncology, Cancer Biology, and Urology, Cancer Risk Assessment and Clinical Cancer Genetics Program, Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: Germline testing (GT) for prostate cancer (PCA) is rapidly increasing with higher demand for genetic counseling (GC). Alternate GC strategies need to be studied to address pretest informed consent. Here we conducted a patient-choice study of pretest video-based genetic education (VBGE) or in-person GC (IPGC) and assessed men's preference and patient-reported outcomes from the first cohort of the Evaluation and Management for Prostate Oncology, Wellness, and Risk (EMPOWER) study. **Methods:** Eligibility for EMPOWER includes any male with PCA or at-risk for PCA based on family history or African American race. Men may choose pretest IPGC or VBGE. All receive results by a genetic professional. Demographics and PCA features were collected at baseline. The following outcomes and scales were assessed: baseline anxiety (GAD-7 scale), change in cancer genetics knowledge from baseline (Giri 2019), decisional conflict for GT (O'Connor 1993), and satisfaction (DeMarco 2004). Understanding of personal GT results was assessed after disclosure (Giri 2019). Descriptive statistics summarized results with counts and percentages for categorical variables and mean and standard deviation for continuous variables. Data were compared with Fisher's exact, Chi-squared, or Wilcoxon two-sample tests, as appropriate. Mean change in cancer genetics knowledge was compared with t-tests. Significance level was set a priori at 0.05. All analyses were performed with SAS 9.4 (Cary, NC). **Results:** At the time of this analysis, 94 men were enrolled. Characteristics of the cohort were: White (88.3%), bachelor's degree (67%), PCA diagnosis (93%), mean age of consent 59 years (IPGC) and 61 years (VBGE), Gleason > = 8 (32%), and > = T3 (31%). The majority preferred VBGE (77%) vs. IPGC (23%). Men who opted for IPGC had lower educational levels (< = high school/GED) (18% IPGC vs 7% VBGE) and reported higher baseline anxiety (45% IPGC vs. 24% VBGE). Cancer genetics knowledge improved significantly with IPGC vs. VBGE (+2.5 vs +0.8; $p < 0.01$). No differences were observed in decisional conflict, satisfaction, or understanding of personal GT results between IPGC vs. VBGE. Both groups had high rates of GT uptake (IPGC 91%, VBGE 93%). Pathogenic mutations were identified in 15% in IPGC group and 10.4% in VBGE group. **Conclusions:** A substantial proportion of men opted for VBGE, and results suggest that VBGE is comparable to IPGC for men considering PCA GT. IPGC may be more suitable for men with lower knowledge of cancer genetics and greater levels or anxiety. Further study is warranted. Research Sponsor: TIPS Pilot Funds, Sidney Kimmel Cancer Center, Thomas Jefferson University.

1578 Poster Session (Board #70), Fri, 8:00 AM-11:00 AM

Implementation of systematic germline genetic testing (GT) for metastatic prostate cancer (mPC) patients at the Puget Sound VA prostate oncology clinic. *First Author: Alexandra Sokolova, University of Washington, Seattle, WA*

Background: There is increasing clinical relevance for GT in patients with mPC to evaluate the 2-fold possibilities of molecularly targeted therapies and implications for relatives. NCCN guidelines recommend GT for subsets of men, including those with mPC. While exciting, there are new logistical challenges around workflows for delivering GT services. We sought to address these challenges through a prospective pilot study designed to systematically deliver GT to all men with mPC receiving care at the Puget Sound VA prostate cancer (PUG-VA PC) Clinic. Our hypothesis was that systematic universal GT for men with mPC would identify similar prevalence rates of germline pathogenic/likely pathogenic variants (P/LPV) among veterans compared to previously reported cohorts. **Methods:** We conducted an IRB-approved, prospective trial testing feasibility of a systematic workflow to identify all veterans with mPC seen at PUG-VA PC Clinic between 11/2016-1/2020 to discuss and offer GT. A research coordinator pre-screened each clinic schedule to identify patients with mPC, notified the oncologist to discuss pretest education and GT with the patient at the appointment. Consenting patients provided a saliva sample same day in clinic for the CLIA-certified Color Genomics 30-gene cancer gene panel. Results were issued to patients and providers, and results were discussed by email and phone with a genetic counselor. Uptake of GT and prevalence of P/LPV was measured and compared to previously reported data from the retrospectively tested UW TAN cohort. χ^2-test was performed. **Results:** 84% (190/227) of approached veterans with mPC consented and 80% (182/227) completed GT. 6.6% (12/182) of men were found to carry P/LPV in DNA repair genes: 3 in *BRCA2,* 2 in *BRCA1*, 4 in *ATM,* and 3 in *CHEK2*. Overall, 6.6% rate of P/LPV in DNA repair genes was comparable to the 8.8% previously reported in the UW TAN cohort ($p = 0.69$). **Conclusions:** Dedicated clinic-based strategies to offer and provide GT and services for veterans with mPC is feasible and results in high GT consent and uptake, especially with direct oncologist involvement. Proportion of consenting to proceed with GT was nearly identical to a referral-based specialty Prostate Cancer Genetics Clinic (Pouv, Sokolova, and Cheng, unpublished). The proportion of P/LPV in the PUG-VA PC population was comparable to a geographically similar retrospective cohort. Updated data, including detailed demographics and GT results, will be reported at final presentation. Research Sponsor: U.S. National Institutes of Health, Prostate Cancer Foundation.

1579 Poster Session (Board #71), Fri, 8:00 AM-11:00 AM

Development and validation of the PREMMplus clinical prediction model for multigene hereditary cancer risk assessment. *First Author: Matthew B. Yurgelun, Dana-Farber Cancer Institute, Boston, MA*

Background: Current clinical prediction models provide syndrome-specific numeric estimates of an individual's likelihood of having a specific hereditary cancer syndrome (e.g., $PREMM_5$ for Lynch syndrome; BRCAPRO for *BRCA1/2*). With the emergence of multigene panel testing (MGPT), there is a need to evaluate individuals' risk of carrying a pathogenic variant in a diverse array of cancer susceptibility genes in parallel. This study's aim was to develop and validate the PREMMplus clinical prediction model for multigene cancer risk assessment. **Methods:** PREMMplus was developed in a cohort of 7296 individuals who had undergone germline MGPT at a single center. Logistic regression models were used to examine candidate predictive variables – including age, sex, ethnicity, and personal/family history of cancer – to provide a numeric estimate of an individual's likelihood of carrying a pathogenic/likely pathogenic germline variant in one of 18 cancer susceptibility genes (11 high- [*APC*, *BRCA1/2*, *CDH1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, biallelic *MUTYH*, *PMS2*, and *TP53*] and 7 moderate-penetrance [*ATM*, *CDKN2A*, *CHEK2*, *PALB2*, *PTEN*, *RAD51C*, and *RAD51D*]). Model performance was validated in an independent dataset of 14845 individuals who had undergone MGPT at a commercial laboratory. **Results:** Using clinical characteristics, including personal/family history of 18 cancers plus colorectal adenoma burden, PREMMplus demonstrated an excellent ability to predict pathogenic variants in high penetrance genes at 90% sensitivity. PREMMplus had acceptable performance with the addition of 7 moderate penetrance genes. PREMMplus was well-calibrated and demonstrated comparable performance in the external validation dataset. **Conclusions:** PREMMplus is the first validated risk assessment model to quantify an individual's likelihood of carrying pathogenic variants in a wide diversity of cancer risk genes, and can be used to select individuals who should undergo MGPT. As expected, PREMMplus's discriminatory capacity was reduced with the inclusion of moderate penetrance cancer risk genes. Research Sponsor: U.S. National Institutes of Health.

Cohort	Outcome	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	# Needed To Test to Detect 1 Carrier	AUC (95% CI)
Development	11 high penetrance genes	90%	34.8%	7.4%	98.4%	13.5	0.74 (0.71-0.77)
Development	18 high/ moderate penetrance genes	90%	23.9%	10.6%	96.0%	9.4	0.67 (0.65-0.69)
Validation	11 high penetrance genes	90%	22.8%	5.5%	97.9%	18.3	0.69 (0.66-0.71)
Validation	18 high/ moderate penetrance genes	90%	17.8%	9.8%	94.8%	10.2	0.62 (0.60-0.64)

1580 Poster Session (Board #72), Fri, 8:00 AM-11:00 AM

Hereditary leiomyomatosis and renal cell cancer syndrome (HLRCC): Genotype and phenotype characteristics in a cohort of 197 patients. *First Author: Ana Beatriz Sanchez-Heras, Cancer Genetic Counseling Unit. Hospital General Universitario de Elche, Elche, Spain*

Background: HLRCC is a hereditary condition with autosomal dominant inheritance due to germline mutations in the fumarate-hydratase gene (*FH*). It is characterized by skin leiomyomas (SLM) in 48-84% of individuals, uterine leiomyomas (ULM) in 30-72%, renal cysts (RCy) and renal cell cancer (RCC) in 15-34%. We aimed to describe the genetics, the clinical features and the potential genotype-phenotype associations in the largest cohort of *FH* mutation carriers from Spain. **Methods:** We performed a multicenter, observational, retrospective study of individuals with genetic or clinical diagnosis of HLRCC. We collected clinical information from medical records. We analyzed genetic variants and looked for genotype-phenotype associations. Statistical analyses were performed by IBM-SPSS Statistics-v.22. **Results:** We included 197 individuals (113 women, 84 men), 74 index cases and 123 relatives. Twenty-seven different variants were detected, 26 pathogenic (12 missense, 5 frameshift, 4 large-deletions, 3 splice-site and 2 nonsense) and 1 variant of unknown significance (missense). Of 182 patients with full skin examination, 64.8% presented SLM (median age 36 years; range 8-85). ULM were diagnosed in 90.3% of 103 women with gynecologic exam (median age 30 years; range 17- 55). Hysterectomy was performed in 62.9% (median age 34 years; range 21-54). Of 153 patients with radiological records, 37.3 % presented RCy. Nineteen patients (10.9%) presented RCC, 11 males and 8 females (median age 37 years; range 10-67). The histological diagnoses were: 14 papillary, of which 10 were type 2; 3 clear cell carcinoma and 2 unclassified carcinoma. Six tumors had stage I, 2 stage II, 3 stage III, 4 stage IV, and 4 not available. The median overall survival among patients at stages 3-4 was 2.9 years [1.3-4.5]. Patients with missense pathogenic variants showed higher risk of developing SLM ($p = 0.043$) and ULM ($p = 0.002$) than those with loss of function variants. **Conclusions:** In our cohort, the frequency of RCC (10.9%) is lower than that published in cohorts of similar sample size. The most frequent histology was the papillary type-2; however, other histological patterns do not exclude HLRCC. Individuals with missense pathogenic variants show higher incidence of SLM and ULM. Research Sponsor: None.

1581 Poster Session (Board #73), Fri, 8:00 AM-11:00 AM

Using sequential next-generation sequencing assays to identify germline cancer predisposition variants. *First Author: Ira Lignugaris Kraft, University of Chicago, Chicago, IL*

Background: Next-generation sequencing (NGS) increasingly guides clinical care in hematological malignancies by identifying DNA mutations that change dynamically over time. Clinical samples contain variable numbers of malignant and non-malignant cells. So, careful interpretation is required to determine if a particular variant is somatic, germline, or clonal hematopoietic in origin. **Methods:** The University of Chicago uses a targeted NGS assay of ~1200 genes, reporting 150 as a clinical test. We aimed to identify individuals with hereditary predisposition by detecting persistent variants on sequential assays regardless of disease state. **Results:** 943 NGS assays from July 2017 – Feb. 2020 on 711 patients [ages 1 mo – 95 yrs, median 65 yrs] were included. 2,320 variants in 33 genes were identified with 144 patients having the same variant identified on more than one assay. Single nucleotide variants (SNVs) with variant allele frequency (VAF) ≥ 0.3 were prioritized. The first candidate gene identified with potential germline SNVs was *CSF3R*. 28 unique SNVs in *CSF3R* were found, 14 were confirmed as germline, 6 somatic, and 8 were unconfirmed due to lack of available tissue. At least 2 confirmed germline *CSF3R* variants were likely deleterious based on functional testing. Sequential SNVs were quantified using the coefficient of variation, characterizing each by change in VAF over time. Using a worst-case-scenario analysis, in which unconfirmed variants were not counted as germline, a computer algorithm was designed to identify potential germline variants (specificity 0.89, PPV 0.75). Via an iterative method, the algorithm compares new assays to a pool of previously reported tests, flagging patients with potential germline mutations so that biopsies may be studied in the lab, records reviewed, and referrals placed to genetic counselors. To date, 61 patients with 89 likely germline variants have been identified. Known hereditary hematological malignancy genes, such as *ATM, ASXL1*, *CHEK2*, *DDX41*, *TSC1*, and *RUNX1,* had the most variants identified. Limitations include the challenge in distinguishing variants that do not change over time, reliance on a targeted NGS panel, and normalizing VAF data prior to analysis. **Conclusions:** These data highlight the utility of NGS of bone marrow and peripheral blood samples to identify patients suspected of having germline DNA variants. In addition to identifying known predisposition syndromes, one may discover new inherited cancer syndromes and help guide clinical practice in real time. Research Sponsor: None.

1582 Poster Session (Board #74), Fri, 8:00 AM-11:00 AM

Value of multigene panel retesting of families with *BRCA1/2* mutation-negative hereditary breast and ovarian cancer (HBOC). *First Author: Ekaterina Meshoulam Nikolaeva, Mutua Terrassa, Terrassa, Spain*

Background: Despite the use of clinical eligibility criteria and mutation predictive models, a great proportion of families are negative for germline mutations in *BRCA1/2* genes. Traditionally, risk assessment of inconclusive results included the recommendation of high-risk surveillance protocol, the update of incident cancer cases in the family and the consideration of additional testing to rule out the possibility of phenocopy. More recently, next generation sequencing multigene panels have become a standard practice in cancer genetics clinics worldwide. We addressed the value of multigene panel retesting of *BRCA1/2* negative HBOC families in our institution. **Methods:** After genetic counseling session and informed consent, a total of 137 individuals (119 probands and 18 extra cancer-affected relatives) from distinct *BRCA1/2* negative families were retested using a panel containing 11 breast and ovarian cancer susceptibility genes (*BRCA1/2, PALB2, ATM, CHEK2, PTEN, TP53, STK11, BRIP1, RAD51C, RAD51D*). **Results:** According to the BOADICEA model, the remaining probability of mutation in *BRCA1/2* or *PALB2 genes* in our cohort was 5.5% (0.1-61). The reasons for considering retesting were the addition of any incident cancer diagnosis in 33 cases (24%), a prior study with a low sensitivity screening technique (dHPLC) in 6 families (5%) and the expansion of the study to other putative breast and ovarian susceptibility genes in 98 families (71%). Overall, 3 pathogenic (2 *BRCA2*, 1 *CHEK2*) and 8 likely pathogenic variants (1 *BRCA2*, 4 *CHEK2* and 3 *ATM*) were found. The prevalence was 8%. The detection rate among 19 families with a $> 10\%$ remaining probability of mutation in *BRCA1/2* and *PALB2* genes was 26%. The 3 clinically significant variants in *BRCA2* were detected in 2 families and 1 updated cancer family history (BOADICEA remaining probability of 59, 61 and 12%, respectively). Cascade testing was subsequently done in 15 relatives resulting 8 in mutation carriers and 9 true negatives. **Conclusions:** Our results support the value of updating cancer incident cases and considering expanded panels in selected families. Research Sponsor: None.

1584 Poster Session (Board #76), Fri, 8:00 AM-11:00 AM

Effect of genetic testing results on patient-reported quality of life among patients undergoing panel testing for newly diagnosed ovarian cancer. *First Author: Sarah S. Lee, New York University School of Medicine, New York, NY*

Background: This study compared patient-reported stress, anxiety, and depression between newly diagnosed ovarian cancer patients with pathogenic genetic testing results versus patients with non-informative results (i.e., variants of uncertain significance (VUS) or negative). **Methods:** Patients underwent genetic testing (GT) via a facilitated referral pathway (Frey et al, Gynecol Oncol 2020) through which they were referred for genetic counseling and GT by their gynecologic oncologist within six weeks of diagnosis from 10/2015 to 5/2019. English-speaking patients completed three quality of life (QoL) instruments: Impact of Events Scale (IOES), State-Trait Anxiety Questionnaire (STAI), Hospital Anxiety and Depression Scale (HADS) immediately pre-and post-GT and 6 months post GT. Two-way mixed ANOVA was performed to analyze effect of GT results on QoL over time with significance $p < 0.05$. **Results:** One hundred ten patients were enrolled in the pathway and 83 (76%) patients underwent GT. Among these, 15 (18%) had potentially actionable pathogenic mutations (*BRCA1*-8, *BRCA2*-4, *MSH2-2*, *MRE11A*-1); 26 (31%) had VUS results; 3 (4%) had both a pathogenic mutation and a VUS result; and 42 (51%) had negative results. Sixty patients (72%) completed QoL assessments pre and post GT, and 37 (44%) patients at 6-9 months post GT. For all patients, GT results did not affect QoL scales across our time points. By mean scores across all-comers, patients demonstrated mild stress at each time point and clinically significant anxiety immediate post-GT. All patients had a statistically significance decrease in HADS depression scores over time from pre-GT to 6 months post-GT (mean score 4.98 vs 2.97, $p = 0.020$). Patients with VUS had lower HADS mean anxiety scores across time (3.62) compared to patients with pathogenic (7.44) or negative mutations (6.83, $p = 0.029$). For patients without mutations, there was a significant decrease in clinically significant anxiety by STAI-state score at 6 months ($p = 0.002$) and a decrease in borderline anxiety by HADS scores at 6 months ($p = 0.005$). This effect was not present for patients with pathogenic mutations or VUS. **Conclusions:** A pathogenic result does not impact QoL scales immediately pre or post GT or at 6 months post GT, though patients with negative mutations were more likely to show a decrease in anxiety over time. Patients should be recommended GT at time of diagnosis of ovarian cancer without concern of increased stress, anxiety, or depression based on GT results. Research Sponsor: NYU Langone Health, Pharmaceutical/Biotech Company.

1585 Poster Session (Board #77), Fri, 8:00 AM-11:00 AM

Genetic testing and referral patterns of non-*BRCA* mutation carriers at increased or uncertain risk of ovarian cancer. *First Author: Sarah S. Lee, New York University School of Medicine, New York, NY*

Background: While the management of *BRCA1/2* is clear, management of non-BRCA mutations with increased risk or uncertain risk of ovarian cancer (OC) is not well established. Previously, we reported that referral to a gynecologic oncologist (GO) resulted in a 30-fold increased uptake of risk reducing surgery (RRS). We aimed to identify trends in genetic testing (GT) and referral to a GO of patients (pts) with such mutations. **Methods:** In this retrospective cohort study at 3 satellite sites within 1 institution from 2014 to 2018, pts were identified by ICD-10 codes Z15.01, Z15.02, Z15.09, Z15.89, C50.919, Q99.8, and C54.1. Pts with mutations with increased risk of OC (*MLH1, MSH2/6, PMS2, EPCAM* (LS genes), *RAD51C/D, BRIP1, STK11)* and uncertain risk of OC (*PALB2, ATM, BARD1, NBN)* were included; *BRCA1/2* and variants of uncertain significance were excluded. Outcomes of interest were patterns of GT and referral to a GO. Chi square and logistic regression were used with $p < 0.05$. **Results:** Of 20,000 pts with above ICD-10 codes, 240 pts had genes of interest. Mutations in increased risk of OC included: LS genes, 131; *BRIP1*, 14; *RAD51D*, 8; *RAD51C*, 5; *STK11*, 1. Mutations associated with uncertain risk of OC were: *ATM,* 43; *PALB2*, 23; *NBN*, 10; *BARD1,* 5. Pts with known mutations prior establishing care at our institution (N = 69) were less likely to be referred to a GO (22% vs 78%, $p = 0.015$). Pts with LS genes were more likely to be referred to a GO (52% vs. 25%, $p < 0.001$), to be tested by a GC (52% vs 25%, $p < 0.001$), and to be tested for family history (FH) of known mutation (69% vs 30%, $p < 0.001$). Provider performing GT included: genetic counselor (GC), 66 (28%); medical oncologist, 44 (18%); general obstetrician-gynecologist, 44 (18%); breast surgeon, 6 (3%), and primary care provider, 5 (2%). Of 66 pts tested by a GC, 46 (70%) were referred to GO, vs 48/105 (45%) pts who underwent GT by non-GC ($p = 0.001$). Reasons for GT among pts were: FH of cancer, 113 (47%); personal history of cancer, 56 (23%); known FH of a mutation, 49 (20%); and unknown indication, 22 (9%). When controlling for age, parity, race, insurance, GT provider, and reasons for GT, mutations with increased risk of OC were associated with referral to a GO (OR 3.55, 95% CI 1.88-6.72), along with pts who were tested by a GC (OR 2.65, 95% CI 1.27-5.51). **Conclusions:** Only ~30% of pts underwent GT by a GC, which was associated with increased referral to a GO. LS genes are better known and were associated with higher uptake of GO referral. Education of OC risks of these newer mutations among providers performing GT may increase referral to a GO and uptake of RRS. Research Sponsor: None.

1586 Poster Session (Board #78), Fri, 8:00 AM-11:00 AM

Comparison of genomic instability test scores used for predicting PARP activity in ovarian cancer. *First Author: Kirsten M Timms, Myriad Genetic Laboratories, Inc., Salt Lake City, UT*

Background: Clinical trials have explored the utility of various genomic instability (GI) scores or gene panels to assess deficiencies in the homologous recombination (HR) DNA repair pathway and support PARP inhibitor use in ovarian cancer; however, these methods of assessing homologous recombination deficiency (HRD) may not be equivalent. The myChoice HRD test is the only analytically and clinically validated, FDA-approved HRD test that includes *BRCA1/2* mutation status and three measures of GI. We compared the proportion of patients identified as candidates for PARP inhibitor use by two measures of HRD [percent loss of heterozygosity (%LOH), 11-gene panel] to myChoice HRD. **Methods:** Whole-genome SNP analysis was used to reconstruct ovarian tumor genomic profiles to calculate the myChoice HRD score and %LOH in 2 cohorts (clinical laboratory cohort, N = 3,278; SCOTROC4 trial, N = 248). Mutation screening for a set of 11 genes in the HR pathway (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *MRE11A*, *NBN*, *PALB2*, *RAD51C*, *RAD51D*) was performed for a subset of tumors from the SCOTROC trial (n = 187). Samples were considered positive if the myChoice HRD score was above the threshold (threshold scores of 42 and 33 were assessed), %LOH above the threshold (16%), or a pathogenic variant in one of the 11 HR genes. The correlation between positive results from %LOH and the 11-gene panel were compared to myChoice HRD. Percent positive agreement (PPA) was the proportion of positive test results from myChoice HRD that were also positive by %LOH or the 11-gene panel. **Results:** The table shows the correlation and PPA between myChoice HRD, %LOH, and the 11-gene panel. Overall, 19%-61% of patients identified as positive by myChoice HRD would have been missed by %LOH or the 11-gene panel in these two cohorts. **Conclusions:** These data show that HRD tests used in published and ongoing clinical trials are not equivalent, and they should not be considered interchangeable in predicting PARP inhibitor response in clinical practice. Research Sponsor: Myriad Genetic Laboratories, Inc.

	%LOH	11-gene panel
Clinical testing dataset		
Correlation	0.845	-
PPA – myChoice HRD ≥42	67.7%	-
PPA – myChoice HRD ≥33	53.5%	-
SCOTROC4 cohort		
Correlation	0.89	n/a*
PPA – myChoice HRD ≥42	80.88%	53.06%
PPA – myChoice HRD ≥33	60.61%	38.57%

*Could not be calculated because positive results by the 11-gene panel were not continuous

1588 Poster Session (Board #80), Fri, 8:00 AM-11:00 AM

Effects of initiating in-office germline testing in safety net clinic patients with epithelial ovarian cancer. *First Author: Scott Jordan, University of Miami-Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Germline genetic mutations occur in approximately 25% of women with epithelial ovarian cancers. Recent advances in frontline maintenance therapy for patients with hereditary breast and ovarian cancer syndrome make timely germline testing critical. Adherence to genetic testing remains low (approximately 30% nationally), including at our safety net hospital where germline testing by a genetic counselor was performed in only 38% of patients. After initiating in-office genetic testing, our aim was to compare current patients with historical controls to determine whether this intervention shortened the time to testing and results. **Methods:** IRB approval was obtained. Patients seen for a diagnosis of epithelial ovarian cancer between 4/1/2018 and 12/31/2019 were identified. Patients with only one visit or those who received testing elsewhere were excluded. Patient and visit data were abstracted for each visit during the study period. Comparison was made between patients treated before (control cohort) and after in-office testing was initiated (intervention cohort) on 5/21/2019. Categorical variables were compared using Chi Squared and Fisher's Exact test. Mann Whitney U test was used to compare time from first clinic visit to the date of genetic testing and to the reporting of test results in the chart. All tests were two-sided and significance was set at $p = 0.05$. **Results:** 74 patients were identified and 504 clinic visits were analyzed. 57 (77%) patients were White Hispanic, 15 (20.3%) were Black, and 2 (2.7%) were White non-Hispanic. 56 (75.7%) underwent germline testing. Overall median time to testing from the first clinic visit was 21.2 weeks, and median time to reporting of results was 37 weeks. Though there was no significant difference in testing rate between the cohorts, the time to the date of genetic testing in the intervention group was approximately one-third as long as in the control group (9.6 vs 32.1 weeks, $p < 0.001$). Among the 52 patients with reported genetic results, results were recorded in a clinic note at 4.1 weeks from first visit in the intervention group, compared with 28.8 weeks in the control group ($p < 0.001$). In the intervention group, during clinic visits without genetics performed to date, testing was performed at that visit 25% of the time. **Conclusions:** By initiating in-office testing, time to testing and receipt of results were meaningfully shortened. Removing delays to test results will greatly improve the ability of our patients to receive potentially life-saving maintenance therapy following front line treatment. Research Sponsor: None.

1589 Poster Session (Board #81), Fri, 8:00 AM-11:00 AM

Prospective agnostic germline testing in pediatric cancer patients. *First Author: Elise Fiala, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: We report our large cohort of pediatric cancer patients undergoing prospective agnostic germline sequencing. Our dataset is a significant addition to the 1,573 children reported to date who have undergone agnostic germline sequencing in previous large sequencing studies, each with ascertainment bias. **Methods:** 676 patients with pediatric solid tumors underwent matched tumor-normal targeted DNA sequencing from July 2015 to February 2020. At least 76 genes associated with cancer predisposition were analyzed in the germline, and variants were classified per American College of Medical Genetics guidelines. Pathogenic and likely pathogenic (P/LP) variants were reported to patients/families, who were offered genetic counseling and cascade testing with screening recommendations and referral to a surveillance clinic as appropriate. **Results:** One or more P/LP variants were found in 17% (115/676) of individuals when including low, moderate and high penetrance mutations in recessive and dominant genes, or 12% (81/676) when including moderate and high penetrance mutations in dominant genes. P/LP variants were detected in 40% (21/53) of patients with retinoblastomas, 8% (13/161) with neuroblastomas/ganglioneuroblastomas, 13% (14/112) with brain/spinal tumors, 8% (20/245) with sarcomas, and 12% (13/105) with other solid tumors. The most frequent mutations were in *RB1* (n = 28) and *TP53* (n = 8) in patients with associated tumors. Of patients with moderate/high penetrance mutations, 30% (24/81) had unexpected tumor types, with potential therapeutic relevance in 58% (14/24) including *BRCA1* n = 2, *BRCA2* n = 3, *RAD51D* n = 1, *ATM* n = 1 *MLH1* n = 1, *MSH2* n = 1, *MSH6* n = 1, *PMS2* n = 3, and *SUFU* n = 1. Two patients received immunotherapy based on their germline finding. **Conclusions:** P/LP germline variants are frequently present in patients with pediatric cancer. We are contributing significantly to the cohort size of agnostic sequencing in pediatric cancers. Our experience is similar to other studies with a ~12% detection rate of moderate and high penetrance mutations. Moderate/high penetrance mutations were concordant with the patient's cancer history in 70% of cases, higher than previously reported, likely due to an enrichment of retinoblastoma. While many mutations are identified in patients with associated tumor types, a large proportion of mutations are unexpected based on the patient's history. Clinical actionability of these findings may include screening, risk reduction, family planning, and increasingly targeted therapies. Research Sponsor: Marie-Josee and Henry R. Kravis Center for Molecular Oncology, the Neihaus Center for Inherited Cancer Genomics, the Crawford fund, and the Corning fund.

1590 Poster Session (Board #82), Fri, 8:00 AM-11:00 AM

Streamlining the genetics pipeline to increase testing for patients at risk for hereditary prostate cancer. *First Author: Barry Tong, UCSF, San Francisco, CA*

Background: Metastatic prostate Cancer (mPCa) is increasingly recognized as a heritable disease and germline genetic testing has increasingly become a part of standard of care. At the University of California at San Francisco (UCSF) Genitourinary (GU) Medical Oncology clinic, approximately 850 new patients with mPCa are seen annually. A feasibility pilot Genetic Testing Station (GTS) was developed to expand access to genetic testing among this high-risk population. GTS is facilitated by Genetic Counselor Assistants (GCA) under the supervision of genetic counselors. **Methods:** This is a feasibility pilot of a GTS model among patients with mPCa. In this model, all patients with mPCa are offered a same day GTS visit with a GCA. At the GTS, the patient receives pre-test education via videos developed by genetic counselors. The patient provides informed consent, a family history, and a saliva sample for Invitae's 87-gene panel. All positive results trigger a genetic counselor visit while non-positive results either receive a letter or a genetic counselor visit (in person or via telehealth). To evaluate the model, testing frequency and laboratory turnaround time (TAT) was assessed before and after the pilot. **Results:** In the first four months of the GTS pilot (10/14/2019 – 02/10/2020), 94 patients were referred and received genetic testing. Eight germline positives were identified (BRCA2, CHEK2, HOXB13 MSH6, RECQL4). The average TAT was 8 days. 9.3% of patients were found to have pathogenic mutations through the prostate GTS which is comparable to previously published rates of germline mutations in metastatic prostate cancer patients. In a 4-month time frame the prior to the intervention (10/01/2018-1/31/2019), 26 genetic testing orders were placed. The average laboratory TAT in this prior process was 17 days. Rates of positive germline mutations in the prior model was 8.6%. **Conclusions:** The GTS is a feasible method to increase access to germline genetic testing among a high-risk population. It may reduce barriers to testing and facilitate real-time discussion of treatment and prevention strategies with patients and family members. As a result, we will continue to operate the GTS. This model provides a framework for scaling access for and cascade testing in other high-risk patient groups. Research Sponsor: None.

1591 Poster Session (Board #83), Fri, 8:00 AM-11:00 AM

Diagnostic yield of germline genetic testing following tumor testing in prostate cancer patients. *First Author: Kingshuk Das, Invitae, San Francisco, CA*

Background: NCCN guidelines recommend germline testing for patients with localized or advanced prostate cancer meeting family history or clinical/pathologic criteria. However, the guidelines for somatic molecular analysis generally consider advanced disease only, primarily to inform therapy. As the analytical and clinical specifications of both testing modalities differ accordingly, we examined the results of germline testing following prior somatic testing. **Methods:** We reviewed somatic and germline variants in an otherwise unselected consecutive series of patients who: (a) had a current or previous diagnosis of prostate cancer; (b) had undergone tumor sequencing; and (c) were referred for germline testing. Indications for germline testing included: potential germline origin of somatic test result, treatment or surgical planning, personal or family history, and patient concern. **Results:** 208 patients met study criteria of whom 81 (39%) harbored a pathogenic germline variant (PGV) in a cancer predisposition gene. Certain genes were more likely to harbor germline variants, and 98% (81) of PGVs were potentially actionable (Table). 9.6% of PGVs were not reported by somatic testing, reflecting analytical limitations of the somatic testing. Of note, 11 patients (14%) had PGVs identified after diagnosis of a subsequent primary malignancy. **Conclusions:** The high PGV rate of 39% was unexpected, given reported rates of 11.8% in patients with metastatic prostate cancer and 6% in high-risk localized disease (NCCN)--even considering potential clinician ascertainment bias. This finding, the potential clinical utility of 98% of PGVs identified, the significant proportion unreported by somatic testing, and the fraction of patients diagnosed with a PGV after a subsequent malignancy all suggest that germline testing is an underutilized tool in the care of prostate cancer patients and their families. Research Sponsor: None.

Germline and somatic findings.

Gene	#Findings Total	#Germline (%Total)	NCCN	Utility
BRCA1/2	142	52 (37)	Yes	M,T,C
ATM	19	10 (53)	Yes	M,C
MSH6,PMS2	16	4 (25)	Yes	M,T,C
CHEK2	13	5 (38)	Yes	M,C
PALB2	7	3 (43)	Yes	M,C
NBN	5	3 (60)	No	C
BRIP1	4	2 (50)	No	M,C
CDKN2A	5	1 (20)	No	M
Others	3	3 (100)	No	Varies
	214	83		

NCCN: NCCN recommended prostate cancer germline panel constituent. Utility: Germline findings associated with management guidelines (M), approved therapy (T), clinical trial eligibility (C). Other genes: CFTR, MITF, RAD51C. Genes without germline findings not shown.

1592 Poster Session (Board #84), Fri, 8:00 AM-11:00 AM

Cancer risk and overall survival in APC I1307K carriers. *First Author: Stephen B. Gruber, City of Hope National Medical Center, Duarte, CA*

Background: The germline variant *APC* I1307K is one of the most commonly identified pathogenic variants on germline genetic testing panels. The purpose of the Molecular Epidemiology of Colorectal Cancer study was to quantify the risk of colorectal cancer among carriers, characterize the clinical, pathologic, and molecular features of colorectal cancers arising in patients with *APC* I1307K, and to describe the overall and disease-specific survival of carriers with colorectal cancer. Here, the final results of the Molecular Epidemiology of Colorectal Cancer Study are reported with respect to *APC* I1307K. **Methods:** We consented 6,006 incident, pathologically confirmed cases of colorectal adenocarcinoma and 5,023 age, sex, and ethnicity matched controls without colorectal cancer between March 31, 1998 and July 1, 2017 within a geographically defined area of Northern Israel. Comprehensive, in-person epidemiologic interviews were conducted for cases and controls, with uniform histopathologic review, detailed molecular analysis, medical record review and clinical follow-up for up to 21 years. **Results:** The demographic and clinical features of incident colorectal cancer cases matched the population distribution of colorectal cancer in Israel. *APC* I1307K was identified in 429 (7.1%) of cases and 201 (4.0%) of controls. The estimated relative risk of colorectal cancer among carriers was 1.89 (95% confidence interval, 1.59 - 2.24), $p < 0.0001$. The prevalence and odds ratios differed by ethnic group. Homozygous carriers were at especially high risk, with an odds ratio of 3.90 (95% confidence interval 1.11–13.71). *APC* I1307K carriers were significantly less likely to have microsatellite instable tumors ($p = 0.04$). Overall survival of *APC* I1307K carriers was not significantly different than survival of non-carriers, after adjustment for age, stage, sex, ethnicity, and microsatellite instability. **Conclusions:** *APC* I1307K is an actionable germline mutation that confers meaningful lifetime risk of colorectal cancer in heterozygous and homozygous carriers. *APC* I1307K is not an independent prognostic factor for overall survival or disease specific survival and is not associated with the MSI phenotype. Cumulative lifetime risk estimates inform genetic counseling and provide data for policies regarding the timing and frequency of screening and other preventive strategies. Research Sponsor: U.S. National Institutes of Health.

1593 Poster Session (Board #85), Fri, 8:00 AM-11:00 AM

Relative and absolute risk of second primary neoplasms of the central nervous system. *First Author: Elisa Liu, NYU School of Medicine, New York, NY*

Background: Cranial radiation is known to increase the relative risk for developing a second primary neoplasm, but existing analyses do not take into account differential survival or follow-up. The absolute risk, or true incidence, of developing a second primary neoplasm in the central nervous system (CNS) is not well characterized. **Methods:** Patients diagnosed with cancer from between 1976 and 2016 were sampled using the Surveillance, Epidemiology, and End Results (SEER) Program. Relative risks were estimated using standardized incidence ratios (SIRs) and absolute risks were estimated using cumulative incidence (CI) functions with death as a competing risk. Among CNS primaries, comparison groups were matched by age, sex, year of diagnosis, primary histology, and lesion location. **Results:** Over 3.8 million patient records, including 13,167 second primary CNS tumors, were extracted from SEER. The relative risk of developing a second primary CNS neoplasm is elevated in all patients diagnosed with a CNS primary cancer (SIR = 9.6), but higher in those who received radiation (SIR = 13.1) or chemotherapy (SIR = 12.6). The absolute risk of developing a second primary CNS neoplasm at 25-years is highest in CNS and endocrine cancers (CI 1.0% and 0.50%, respectively). Among long-term ($>$ 10-year) survivors of CNS primaries, the 25-year CI of a second primary CNS neoplasm was 4.4%. Cranial radiation increased the incidence of second primary tumors in pediatric patients (25-year CI 4.8% vs 1.2%, p = 0.007), but not adults (25-year CI 5.1% vs 4.9%, p = 0.85). Chemotherapy did not increase CI in either pediatric (25-year CI 7.0% vs 5.4%, p = 0.87) or adult (25-year CI 3.6% vs 5.8%, p = 0.11) populations. Meningiomas (39.3% vs 22.0%, p = 1e-6) and glioblastomas (21.1% vs 14.6%, p = 0.03) represent a greater proportion of the second primary CNS tumors in those who received cranial irradiation. **Conclusions:** The risk of developing a second primary CNS neoplasm is elevated in patients with a prior CNS cancer. Cranial irradiation increased the CI of second primary tumors in pediatric patients but did not affect adult patients. The association between radiation therapy and risk for subsequent cancers may be limited to the pediatric population. Research Sponsor: None.

1594 Poster Session (Board #86), Fri, 8:00 AM-11:00 AM

Results of a prospective phase II national study: Prophylactic radical fimbriectomy (NCT01608074), in women with a documented high risk of breast/ovarian cancer—Final pathological results and outcomes. *First Author: Eric Leblanc, Centre Oscar Lambret, Lille, France*

Background: Risk-reducing salpingo-oophorectomy (RRSO) is the gold standard in surgical prophylaxis of pelvic high-grade serous carcinoma (HGSC) for women at risk of breast/ovarian cancer. Due to significant adverse effects of early oophorectomy, 20-30% of women delay or deny performing this operation. Recent data highlight the fallopian origin of most pelvic HGSC, especially its fimbrial part. Thus, we suggested a new two-step risk-reducing procedure: the radical fimbriectomy (RF) with delayed oophorectomy (DO) (Leblanc et al Gyn Oncol 2011), leading to the current RF/DO Phase 2 study. We present the definitive results on primary and secondary objectives of this trial. **Methods:** *BRCA1/2* carriers or any women with a documented familial risk of breast/ovarian cancer were first counseled to perform a classical laparoscopic RRSO. If they denied, they were offered to enter the RF/DO study. All specimens were submitted to the SEE-FIM pathological protocol. Pathological data along with all intra- and 30-day and beyond post-operative adverse events were prospectively recorded. Follow-up consisted in an annual clinical breast and gynecological examination, with tumor markers and hormonal status assessment. Primary endpoint was the rate of pelvic serous carcinoma. Secondary endpoints were procedure morbidity, rates of tubal abnormalities, breast cancer, secondary oophorectomy. **Results:** From January 2012 to October 2014, 121 RF were performed: 120 by laparoscopy, 1 laparotomy (concurrent myomectomy). An occult neoplasia was found in 3 cases with 1 invasive HGSC. Intraoperative complications were two grade1 bleedings without transfusion with no grade $\geq$3 early post-operative or delayed complication. With a median follow-up of 5.3 years (0.2 -7.6), no patient developed any pelvic HGSC, 21 patients developed a breast cancer (3 de novo, 18 recurrences/contralateral.). 1 cancer-free *BRCA1*-mutated lady delivered safe twins, after an uneventful post-RF pregnancy obtained with assisted reproductive technology (ART). Overall, 29 women underwent DO (by choice: 12 or menopause: 17) resulting in grade 3b complication in 1 case, but no pathological abnormality. **Conclusions:** RF/DO appears as a safe, well tolerated and effective procedure in terms of occult neoplasia detection. A successful pregnancy with ART was possible after radical fimbriectomy. Longer follow-up and larger cohort are necessary to confirm its efficacy in terms of ovarian cancer prophylaxis. Clinical trial information: NCT01608074. Research Sponsor: PHRC 2011.

1595 Poster Session (Board #87), Fri, 8:00 AM-11:00 AM

Outcomes of lung cancer screening among cancer survivors: An NCCN institution experience. *First Author: Bradley Maller, University of South Florida, Morsani College of Medicine, Tampa, FL*

Background: In 2013, the USPTF recommended low-dose CT (LDCT) screening for individuals at high risk of lung cancer based on data from the National Lung Screening Trial. However, the trial excluded participants with cancer diagnosis $<$ 5 years except for non-melanoma skin cancer, making it unclear whether the data will be generalizable to cancer survivors. This population, while at increased risk of secondary lung cancer, may be prone to false positive results due to anatomic defects or recurrent cancers. Our NCCN institution serves a large number of cancer survivors. We evaluated the outcomes of LDCT screening and the adherence to annual screening among cancer survivors, compared with individuals without cancer history (IWC). **Methods:** Prospectively maintained database of LDCT screening participants was analyzed. Eligibility was per NCCN criteria and cancer survivors needing regular chest CT were not offered LDCT. Participants were asked to complete a self-administered questionnaire on risk factors. Positive result was defined as Lung-RADS $\geq$3, corresponding to nodule $\geq$6 mm. Adherence to LDCT screening was defined as having T1 screening, excluding those $<$ 18 months from T0 at time of analysis. Predicted risk of lung cancer was calculated per PLCOm2012 model. **Results:** To date, 454 subjects have undergone LDCT screening. Positive results occurred in 60 subjects (13.2%) at T0; lung cancer was diagnosed in 10 subjects (2.2%); and other cancers were diagnosed in 5 subjects (1.1%). There were 152 cancer survivors, including survivors of breast (52), prostate (26), bladder or kidney (19), lung (14), and head and neck cancer (13). The median time from cancer treatment to LDCT screening was 6 years (range 0-55). Cancer survivors were older than IWC: median age 67.4 vs. 63.5 years ($p<$ 0.001) and more likely to be active smokers: 37.5% vs. 29.5%, ($p=$ 0.09). The median predicted risk of lung cancer at 6 year was 5.5% vs. 3.2%, ($p=$ 0.15). No significant difference in the screening outcomes was found between groups. Among cancer survivors (N = 152), positive screening occurred in 15 (9.9%); lung cancer was diagnosed in 1 (0.7%); and other cancers were diagnosed in 3 subjects (1.9%). Non-adherence to LDCT screening occurred in 31 out of 152 cancer survivors (20.4%), compared with 81 out of 262 (30.9%) IWC, ($p=$ 0.02). **Conclusions:** About one-third of LDCT screenings at this NCCN institution occurred among cancer survivors. We found no evidence of increased false positive results. However, a higher rate of adherence to annual screening was observed among cancer survivors than IWC. Research Sponsor: James Esther King Biomedical Research.

TPS1597 Poster Session (Board #89), Fri, 8:00 AM-11:00 AM

ECOG-ACRIN tomosynthesis mammographic imaging screening trial (EA1151). *First Author: Etta Pisano, Beth Israel Deaconess Medical Center, Boston, MA*

Background: This randomized trial is intended to determine whether tomosynthesis (TM) should replace the current standard for breast cancer (BC) screening, digital mammography (DM). It is hypothesized that the population of women assigned TM screening for 3-5 rounds will have fewer advanced cancers than the population assigned to DM screening. **Methods:** 164,946 women, ages 45 to 74 years who present for screening mammography and consent to participate will be enrolled across 150 sites in the US, Canada and abroad. Women will be randomized to TM or DM. The frequency and number of screening examinations over a five year period will vary based on menopausal status and whether they have specific risk factors, including - hormone use, family history of BC, deleterious genes, prior benign breast biopsy with diagnosis of LCIS or atypia any kind, or dense breasts. Blood and buccal cells will be collected from as many enrolled women as are willing to provide the samples. All breast biopsies during the trial will undergo gene expression analysis for the PAM50 and other progression pathways (PAM50-plus). All subjects enrolled will be followed long term for at least eight years. The primary endpoint is the proportion of participants who have an advanced breast cancer diagnosed at any time within 4.5 years of randomization in to the trial. Secondary endpoints include measures of diagnostic and predictive performance; rates of recall, biopsy, and interval cancers, prevalence of breast cancer subtypes, and tumor subtype based on PAM50-plus analysis. As of January 17th 2020, there are 104 sites open and 21,452 women enrolled in the trial. The DSMC last reviewed the trial in June 2019 and suggested that the trial continue as planned. Clinical trial information: NCT03233191. Research Sponsor: U.S. National Institutes of Health.