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 pathway via a next-generation sequencing (MSK-IMPACT) were identified (N=11,975) from 2015-5-2019. The medical record of pts with likely pathogenic/likely germline (LP/LG) 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/LG variants in a cancer predisposition genes including 777 (6.5%) in genes with potentially targetable therapeutic implications. 416 BRCA2, 543 MLH1, 394 LS (67.4% of microsatellite-high LS cases), 417 PALB2, 368.8% RAD51C/DI and 19.3% ATM. Of those with advanced disease (n=554), 45.3% received targeted treatment (Table) including 50.9% BRCA2/2, 58.3% LS (67.4% of microsatellite-high LS cases), 41.7% PALB2, 36.8% RAD51C/DI and 19.3% ATM. Carriers of patients receiving a poly (ADP-ribose) polymerase inhibitor (PARP-i) in the setting of a BRCA2/2 mutation, 55.1% had breast or ovarian cancer. However, 44.8% had other tumors, including: intestine, prostate, bile duct, gastric, whereas the drug was given in a research setting. Among PALB2 pts receiving PARP-i, 53.8% (18/33) had breast or pancreatic 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 Cancer Genomics.

Gene(s) with potential targetable therapy Drug Class % of advanced cancer patients receiving therapy
BRCA1, BRCA2 PARP-I 50.9% (165/324)
Lynch syndrome (MLH1, MSH2, MSH6, PMS2, EPCAM) Checkpoint inhibitors 58.3% (42/72) (irrespective of MS)
RAD51C/D RAD51D 36.8% (19/52)
PTEN Tyrosine kinase inhibitor 60% (5/8)
TSC Hedgehog-signaling inhibitors 6.2% (1/16)
ATM ALK kinase inhibitor 0% (0/2)
ERBB2 EGFR inhibitor 100% (1/1)
MET MET kinase inhibitor 0% (0/1)

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 (> = 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 > 70 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 pts sequenced, 4341 (58%) had >2 cancers (Table). Of those, 2794 (2,4%) had > 4 cancers. Cancer pairs where SIR of 2nd cancer was higher than expected included: colon-colon, prostate-pancreas, lung-lung, breast-breast, prostate-lung, breast-lung and breast-prostate in men & lung-breast, breast-prostate, thyroid prostate in women. 1580 (36%) pts had germline (324/21% had 160) pathogenic/likely pathogenic (PLPV) variants. Of these, 124 (0.64%), 66250%) pts had high, moderate penetrance. vs. the remainder had low penetrance, recessive or vs. of uncertainty. Of pts with high penetrance, 132 (84%) had at least one tumor type concordant with germline findings. Conclusions: 18% of pts in this cohort had MPC. This was a significant excess over expected incidence in some cancer combinations. Of pts with germline testing, 21% had a PLPV, with most (66%) being high or moderate penetrance. Assessment for loss of heterozygosity in tumor & germline sequence of the full MPC cohort is ongoing. Research Sponsor: Robert and Katie Neubauer Center for Inherited Cancer Genomics.

Observed (O) BC Expected (E) BC Observed (O) BC Expected (E) BC
Race/Ethnicity N % N %
NHW 80,260 6133 6408.6 0.96 (0.93-0.98)
Asian American 5980 373 471.8 1.05 (0.95-1.17)
Hispanic 2386 115 153.2 0.75 (0.62-0.90)
Asian/Pacific Islander 1097 68 89.4 1.00 (0.84-1.16)
Native American 305 22 20.9 1.05 (0.66-1.59)
Other 929 53 66.5 0.80 (0.60-1.04)
TOTAL 91,893 6836 7199.5 0.99 (0.93-0.97)

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Comprehensive breast cancer (BC) risk assessment for CHEK2 carriers incorporating a polygenic risk score (PRS) and the Tyrer-Cuzick (TC) model.

Methods: 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.

Results: We detected significant correlation of CHEK2 status with FH (ρ = 4.1 × 10^{-17}) and of PRS with FH among CHEK2 carriers (ρ = 1.7 × 10^{-10}). For these factors, joint effects were co-estimated using the FS method. In an independent cohort, 24%, 0% and 0% of CHEK2 carriers were categorized as 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-variant panel. Model development was based on analysis of CHEK2 PV carriers (N = 4,331) and women negative for CHEK2 PV carriers (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 who were tested from July 2019 and not included in model development. Results: We detected significant correlation of CHEK2 status with FH (ρ = 4.1 × 10^{-17}) and of PRS with FH among CHEK2 carriers (ρ = 1.7 × 10^{-10}). For these factors, joint effects were co-estimated using the FS method. In an independent cohort, 24%, 1%, and 0% of CHEK2 carriers were categorized as low (< 20%), moderate (20%-50%) and high (> 50%) remaining lifetime risk based on the combined model.

Conclusions: CHEK2, PRS and TC are all predictive for FH among CHEK2 carriers. The primary outcome was cancer risk 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 (88%) of CC carriers (ρ = 1.7 × 10^{-10}). For these factors, joint effects were co-estimated using the FS method. In an independent cohort, 24%, 1% and 0% of CHEK2 carriers were categorized as low (< 20%), moderate (20%-50%) and high (> 50%) remaining lifetime risk based on the combined model.

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Background: With the expansion of mutigene panel testing for cancer susceptibility, increasing numbers of patients are identified with pathogenic/likely pathogenic variants (PALPV) 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 77,198 participants (5366; 93% 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, RAD51C, RAD51D, BRIP1, 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 PV, 11.4% reported ooph (50% under age 50 when known), did as 132% (of 228) with CHEK2 VUS, 8.8% (of 261) with ATM PV (66.7% under age 50), and 8.3% (of 387) with ATM VUS. In the 184 women with PALB2 PV, 14.1% reported ooph (35.3% under age 50) as did 11.6% (of 198) with PALB2 VUS. Of those who reported ooph to PROMPT, 4.7% reported “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. Complete HPV vaccination coverage for females aged 18-26 at 53% and males aged 16-17 at 43% in the Northeast, and mean cost for each vaccination type and brand was with Point-of-Service (POS) and Cervarix at $106, and the highest was with POS and Gardasil at $120 (-6% from 2017), $165 (-3%) and $220 (+5%) for Cervarix (n=151), Gardasil (n=151), and Gardasil (n=151) respectively. Vaccination coverage increased; for females ages 13-15 by 6% and 16-17 by 15%. In 2018, by region, the highest coverage was in the South west at 55% and the lowest in the Mid west at 45%. Vaccination coverage by year, sex, and age is summarized by vaccine brand and health plan type.

Complete HPV 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 13-17 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 59 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) or ≥3 doses (age 16-45) within 12 months and receipt of 2 doses (age 9-15 years) or 3 doses (age 16-45 years) within 12 months and complete vaccination coverage was 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 vaccination type and brand was with Point-of-Service (POS) and Cervarix at $106, and the highest was with POS and Gardasil at $120 (-6% from 2017), $165 (-3%) and $220 (+5%) for Cervarix (n=151), Gardasil (n=151), and Gardasil (n=151) respectively. Vaccination coverage increased; for females ages 13-15 by 6% and 16-17 by 15%. In 2018, by region, the highest coverage was in the South west at 55% and the lowest in the Mid west at 45%. Vaccination coverage by year, sex, and age is summarized by vaccine brand and health plan type.

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
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 hypothesized that oncologic therapy selects for acquired mutations in the blood (clonal hematopoiesis; CH) particularly those in the DNA damage response pathway (DDR) including ATM, 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 1.9-8.5, 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 CH further, we performed a retrospective review 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 and radiation or 232 were untreated or received targeted therapies. The growth rate of DDR CH was significantly higher among those who were exposed to PARPi (+1% 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.

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; therefore, confirmatory germline testing is required. In this quality improvement (QI) initiative, we evaluated the proportion of referrals to genetic counseling for patients with potentially heritable germline alterations on NGS reports, thus confirming actionable PVs. Methods: We generated a list of high-risk mutations (HRMs) that merit genetic 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. Positive HRMs, 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. Malignancies included breast (49%), gastrointestinal (42%), lung (17.8%), genitourinary/renal (12%), and other (9.2%). 75 (16.1%) patients had at least one actionable alteration, including 19 (4.9%) patients with mutations in BRCA2 that were subsequently referred to GC. 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.
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 drug therapy. Tumor NGS also reveals potential 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 (PT). 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 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 (GOOC) 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 (37%) were confirmed to have a germline mutation. Of the 115 Pts that did not meet 2020NG/FA, 47 (41%) underwent GCT and 19 (17%) 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 can enhance the identification of germline mutation carriers and navigate them to appropriate GCT. Ongoing work will clarify data on cascade testing. We are currently developing automated workflows for GCT. Research Sponsor: None.

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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: Vinnet 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 (CXR-LC). However, PTs vary in their ability to identify suspicious CXR-LC findings. We have developed a deep learning model based on chest radiographs from the Prostate, Lung, Colorectal & Ovarian (PLCO) trial and validated the model externally in the National Lung Screening Trial (NLST).

Methods: We developed a deep learning model to identify smokers with a high risk of developing incident lung cancer within 3.3% per year. We used 41,856 persons aged 55-74 from the PLCO trial to develop and test the model. 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=11,285, all CMS eligible, 12-year follow-up), and externally in the National Lung Screening Trial (NLST, n=11,285, all CMS eligible, 12-year follow-up).

Results: In the PLCO dataset, the deep learning model had an AUC of 0.88 for incident lung cancer (N=5,493). The final model was tested in held-out smokers from PLCO (N = 5,493), yielding 95% CI: 0.85-0.90. In the NLST dataset, the deep learning model had an AUC of 0.85 for incident lung cancer (N=11,285), yielding 95% CI: 0.82-0.88.

Conclusions: The deep learning model, validated in the PLCO and NLST datasets, is a potential tool to identify high-risk smokers for lung cancer screening. Based on the encouraging results, a multicenter validation study and a clinical trial are planned.

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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, the penetrance in the general population is largely unknown, and 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 conducted a systematic literature review and identified a total of 473 studies regarding eleven genes: ATM, BARD1, CDH1, CHEK2, NBN, NF1, PALB2, PTEN, RECAL, STK11, and TP53.

Methods: We included studies that assessed penetrance by estimating the risk of developing cancer in a specific or general population, or by comparing penetrance across different populations.

Results: A total of 49 penetrance studies were identified, with a median of nine studies per gene (range: 4-16). The case-control study was the dominant study type, followed by population studies and genetic linkage studies. The most common report format was a table or figure showing the risk estimates for each gene.

Conclusions: The penetrance of cancer susceptibility genes varies widely across different studies and populations. Future research should focus on improving the accuracy and reliability of penetrance estimates for these genes. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

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Visit abstracts.asco.org for the the most up-to-date abstract information, including the full list of authors and disclosures.
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 (mPC) be offered testing. This has implications for treatment choices and position, it is recommended that all men with metastatic prostate cancer.

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, FANC, 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 BRCA1, 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 98% (7/7) found doing 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 accurate genetic testing for men with mPC.

Research Sponsor: Cancer Institute NSW, Sydney Catalyst, University of Sydney, Australian Prostate Cancer Research Centre, NSW.

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 bioinformatic analysis of commonly amplified and methylated 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 215 women evaluated 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 endometroid histology (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 of 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.
Characterization of clonal hematopoiesis of indeterminate potential mutations from germline whole exome sequencing data. First Author: Hsin-Ta Wu, Naten, 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 Signaterra 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 1.04 (~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 42%, 1.94%, and 1.38%, respectively. Other genes containing CHIP mutations included PDGFRα, NRAS, KMT2A, EZH2, GATA2, GNAS, CEBPA, ETV6, HRAS, DNMT3A, TET2, and MLH1, MSH2, MSH6, EPCAM. Recent studies suggest limited extra-colonics cancers among germline PMS2 mutation carriers. First Author: Alicia Latham, Memorial Sloan Kettering Cancer Center, New York, NY

Prevalence and clinical characterization of MMR-D/MSI extra-colonic cancers and an extra-colonic germline mutation carrier. First Author: Leigh Boehmer, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Prevalence and clinical characterization of MMR-D/MSI extra-colonic cancers and an extra-colonic germline mutation carrier. First Author: Leigh Boehmer, Memorial Sloan Kettering Cancer Center, New York, NY

Performance of polygenic risk scores for cancer prediction in an academic biobank. First Author: Hariharan 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 various types 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 SNPs to improve disease risk and the usefulness of a cancer biomarker in a community cohort of women with breast cancer who met guidelines. Given this disconnect, ACCC part-nered with Natera, Inc., San Carlos, CA for the most up-to-date abstract information, including the full list of authors and disclosures.
studies are needed to further characterize pancreatic cancer risks in patients 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 novel 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.L359P [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 reporter system. Functional characterization was further validated by protein co-immunoprecipitation and RAD51 recruitment assay. Results: PALB2 L24F [c.72G>C] and p.L359P [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.P121V [c.3636C>T], p.P1101R [c.3303C>G], and p.E1018D [c.3054G>A]), when compared to the wild-type PALB2. The p.L24F and p.L359P 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 personal 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 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 CHEK2, 2 in NBN, and 1 in PALB2). 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 of breast and/or ovarian cancer, and more likely to have a significant family history of breast and/or ovarian cancer. 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.
Five year trelozolet versus placebo in BRCA1/2 germline mutations carriers: Final results of LEBER, a double-blind randomized phase III breast cancer prevention trial. 

First Author: Claire-Pascal, 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: LEBER is a randomized, double-blind, placebo-controlled phase III trial evaluating 5-year treatment with trelozolet 2.5 mg/dL (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 end-point 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) at 1 year (360). 270 pts were randomized in 5 groups 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 arms. 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 L and P arms (92% vs 91%, HR 0.83; 95%CI: 0.63-2.03; 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 0.43-3.9), gBRCA1 versus gBRCA2 and presence of BRCA1 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 trelozolet versus placebo in women with gBRCA1/2 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.
A single-institution and commercial laboratory database analysis of BRIP1-associated cancer risks
First Author: Kristen Daniell, Fox Chase Cancer Center, Philadelphia, PA

Background: BRIP1/FANCJ participates in DNA repair and replication via interactions with BRCA1 and possibly MLH1. Previous studies have reported that pathogenic variants (PVs) 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 (HC) has identified BRIP1 PVs 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 PVs 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; 25% were BRIP1 PV). Multivariate 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, 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 PVs were also identified among several patients with striking PHX and negative panel testing: BC <40 (N=3), bilateral BC (N=4), TNBC (N=1), 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% (1.6/879,864,740) 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 CRC. Findings did not support associations of BRIP1 with CRC, melanoma, endometrial, or pancreatic cancer. Conclusions: BRIP1 PVs can be identified in patients with diverse CA histories. These results confirm studies showing that BRIP1 PVs 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.

<table>
<thead>
<tr>
<th>Variant</th>
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<tr>
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Notable VUS

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<td>Mel</td>
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All breast cancers were in women.

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 testing. 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 CA 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 (KnowMed 2.0) 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, the EMR template, 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 03/01/19 – 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%) referred appts and testing (57/113 pts) did not have a return visit. Referrals in non-CA pts also increased by 127; 604 (2018) vs 264 (2018) suggesting a halo effect. Analyses suggest the program to be economically viable, with a financial growth rate of 127%. EMR templates embedded with the NCCN guidelines for reflex referrals can appropriately increase the utilization of genetic services. Breast genetics screening and resultant appointment rates increased significantly in 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.

Return of results after somatic tumor mutation profiling in advanced cancer: Potential impact on care.
First Author: Michael 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 enthusiasm for Molecular Tumor Profiling (MTP) therapies. Two cohorts (G1 and G2) comprising 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 EOCG 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 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 MICRA, IES and HADs were not impacted by type of result. Interactions between gender and age, parental status, cultural diversity and result were non-significant for all psychological outcomes. 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 distressing patients. Research Sponsor: National Health and Medical Research Council of Australia grant.

G1: Actionable, Tx via Oncologist (N=152)
G2: Actionable, Tx via Oncologist (N=208)
G3: Non-Actionable (N=210)

Return of results after somatic tumor mutation profiling in advanced cancer: Potential impact on care.
First Author: Anna Bergamaschi, Bluestar Genomics, San Diego, CA
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. Mihliroon, University of Michigan, Ann Arbor, MI

Background: Minority populations experience inequities of access to cancer genetics care. 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, >70% of high-risk patients remain unidentified. We evaluated the impact InheRET on patients with a prior history of cancer. Methods: A retrospective cohort study of patients with a prior history of the Comprehensive Cancer Network (CNC) Guideline-compliant referrals for cancer genetic counseling. Patients: Patients from 3 clinics were consented online to use InheRET before genomic testing. Review of patient history questionnaire. Results: 628 patients were consented over a year, 955 (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, age 50.1 yrs) compared to those with advanced degrees (n=139, age 45.4 yrs); and patients age 70+ experienced increased difficulties. Among primary care patients (n=35), 43 established patients were newly identified as meeting CNC 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. Turn-around-times to receive the patient 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 using InheRET while the majority complete the health history questionnaire. It is a feasible tool to 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 manner, complete and encompasses more family members than with paper forms. Turn-around-times to receive the patient 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 using InheRET while the majority complete the health history questionnaire. It is a feasible tool to complete this health history tool more frequently and in greater detail than by paper forms.

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1544 Poster Session (Board #36), Fri, 8:00 AM-11:00 AM
Outcome of patients with breast cancer and a germline BRCA4 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 breast cancer patients with recurrent breast cancer who have undergone testing at 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 DFS 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 these patients needs to be taken into consideration when pre- ventive 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
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 (UVMMC) 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 chi2 test. Results: 342 patients underwent genomic testing at UVMMC over the study period, with a median age of 61. Common tumor types include: CNS (19%), NSCLC (17%), ovarian (8%), sarcoma (8%), and endo- minal (7%). Potential germline mutations were most common prior tumor history. 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. Conclusions: 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. Genomic testing can reveal hereditary cancer syndromes, often with tumors not previously evaluated; tumor screening in patients with potential 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 germline BRCA1, PALB2, and Lynch mutations. In this cohort, only 17 of 71 patients who had genetic testing were subsequently referred to a genetics clinic. One of the objectives 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.

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Germline alterations other than BRCA in triple negative breast cancer (TNBC) patients who underwent neoadjuvant therapy (NAT) on a prospective clinical trial. First Author: Divya 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 mutations 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 (ARTMIST: NAT: 02276431). 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 variant 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 level of p<0.05. Results: Germline results and pCR were available for 152 patients. Median age was 55 years (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 mutations. Conclusions: Breast cancer related germline mutations other than BRCA in TNBC are less common compared to 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.

Cancer Prevention, Risk Reduction, and Genetics

Ancestry-specific gene expression profiles in TNBC tumors. First Author: Wendy Marie Dean-Colomb, Louisiana 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 their 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 (SSR) groups: African American (AA, n = 42) and European American (EA, n = 33). Using best practices established by TCGA, we assembled 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 (adj 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 SSR. Using an extended TNBC subtypes and altered functional oncologic pathways are evidence that biological underpinnings in TNBC tumors 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 precise disease management. Research Sponsor: Susan Q. Kom. 

Oncogenes of Lynch syndrome (LS) patients treated with immune checkpoint inhibitors (ICI). First Author: Shabana Bar, 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 responses 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, 194 had cancer and 22 received ICIs. Among the patients analyzed, the mean age at diagnosis of 1st cancer was 51 years. 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 PO, 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 event) and have not had relapse. One responder progressed after 18 cycles of therapy. The DCR was 71% at 12 months follow up. Median progression free 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 ICI. Our data supports LS associated tumors with survival. In conclusion LS patients with PO and 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.

Pathologic 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 well described. Methods: Patients identified with a PV in likely or confirmed 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, treatment and clinicopathologic features were collected. 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=23). Nearly all (98.5%) were women, with 2 male BC in ATM carrier. 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 (2A, 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. 3.1% were diagnosed with BC 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.

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A noninvasive multi-analyte approach for lung cancer screening of patients with pulmonary nodules. First Author: Hong Zheng, Department of Thoracic Surgery, 7-Municipal 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 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 integrated multi-analyte-based approach of multi-analytic molecular and clinical profiles greatly out-performs any single-analyte profiling. Conclusions: Multi-analyte algorithm-based approach can be utilized to assist in lung cancer screening for patients with pulmonary nodules. It has demonstrated a high accuracy through independent validation, and has outperformed any single-analyte testing in our study. Research Sponsor: None.

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Background: Medical 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-care 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.

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

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

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. Conclusions: Using a pre-specified mutation scoring system, we found that cfDNA methylation 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 methyleome profiling, we first applied a machine learning approach to classify each cancer type versus healthy controls in the training cohort (HCC: n = 63; CRC independent validation: n = 109; CRC validation: n = 104; CRC external validation: n = 58; PC: n = 97; healthy individuals: n = 841). 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, of which 10% were independent 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 = 89.5%), 89.5% (specificity = 95.8%), and 76.7% (specificity = 91.7%) for HCC, CRC, and PC, respectively. Using a parallel methyleome matrix derived 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 with an improving trend of cancer types. Conclusions: A novel liquid biopsy test that underwents methyleome 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.
Evaluation of a mobile cervical cancer screening program in São Luís, Maranhão, Brazil: Impact and challenges. First Author: Rachael 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 Luís, 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 characteristics: 47.3% completed high school education; 37.8% were housewives; 16.1% were unemployed; 56.3% were married; 99.8% 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 difficulties to scheduling; 23.3% time constraints, 11.2% being ashamed, and 10.4% financial restrains. There were 65 (6.9%) abnormal results (LSIL in 17%, HsIL in 0.7%, and in situ adenocarcinoma in 1 case), for whom future 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 facilitated the access to Pap tests, their results and recommendations. Although Pap test was easily available, the non-organized process of invitation, follow-up, and then referral of positive cases for further investigation, as offered by the Brazilian public health services, limit screening efficacy and CC control. Research Sponsor: None.

Epigenetic control of breast cancer susceptibility. First Author: Natascia Marini, 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 MethyCap 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 refGene GRCh38.p12 using STAR v2.2.0, and downsampled for differential 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-scores to identify differentially methylated pathways. Analysis was performed using IPA v06_01. Results: We identified 1355 CpGs that were differentially methylated between high- and average-risk breast tissues (ΔZ > 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 (log2 FC = -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 3MPR1B. Two hypomethylated/ upregulated long non-coding RNAs were also identified in high-risk breast tissues. 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 for mechanistic research and could potentially be utilized for early detection and 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 Pitaluga Quality of Life Fund.

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 hysterec- tomy 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 a nationwide sample of women undergoing bilateral salpingo-oophorectomy or 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. Results: 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 hysterec- tomies 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 42% 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 per- sistent 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 na- tional societies. Future studies evaluating the overall efficacy and long-term complications of OS are needed to support its continued widespread use. Research Sponsor: None.

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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 (HR 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 chemotherapy or surgical excision with future cancer risk. Among the 587 patients without a history of breast cancer, 103 patients in the surgery group and 111 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, was safe in selected women with ADH and was associated with a lower risk of subsequent breast cancer compared to surgical excision. Screening guidelines.

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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 ages 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, weighted by Geisinger Health Plan (GHP), and completed both screening 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 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 (χ²(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 pre-enrollment period. Subsequent to enrollment, 10 did 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, was safe in selected women with ADH and was associated with a lower risk of subsequent breast cancer compared to surgical excision. Screening guidelines.

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Projection of 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 changes to project change in cancer incidence and death rates 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 inci- dences 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 cancer in 2040 in the US will be breast (319,100 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 4th 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 prostate (45,000 deaths in 2040) and liver & intrahepatic bile duct (38,000 deaths in 2040) cancer surpassing colorectal cancer (38,000 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 future diagnoses and deaths, particularly in colorectal, thyroid, lung, breast cancers, 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 health funding allocations, healthcare planning, and health policy efforts. Research Sponsor: None.

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Background: Malignancies associated with DPP4 inhibitors and GLP1 receptor agonists:

<table>
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<tr>
<th>Cancer</th>
<th>DPP4i (OR 95% CI)</th>
<th>GLP1Ra (OR 95% CI)</th>
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<td>All cancer</td>
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<td>0.14 (0.12-0.16)</td>
</tr>
</tbody>
</table>

Conclusions: DPP4i and GLP1Ra users were not associated with increased cancer risk overall. However, they were associated with increased or decreased risk of specific cancer types. 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 (FFQ data was labeled for water energy and urinary nitrogen for protein intake) (n=544). Subsequently, regression equations incorporating participant characteristics were developed acknowledging differential reporting dietary intake using biomarkers (doubly labeled water for energy and urinary nitrogen for protein intake). 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 between 1993-1998, 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 were less likely to have breast cancers, 7,634,460 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 different types of cancer. When adjusted for sex, age, smoking status, alcohol abuse history, hemoglobin A1C (9.0% vs < 9.0%) and BMI (< 30 vs 30-kg/m²) around initiation of anti-diabetic agents, the aOR was 1.01 (95%CI: 0.94-1.08) for DPP4i and 1.06 (95%CI: 0.93-1.20) for GLP1Ra compared 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.

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-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 ~600 kcal/day and ~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 alcohol, energy, fat, and 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 1.6 years later, median intakes 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. BrCa-related 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.
Metabolic syndrome, metabolic comorbidity 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 who were followed for at least 10 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 frequent matching on age, sex, and geographic location. 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 comorbidity 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, 95% CI 1.04-1.22), 18% (OR: 1.18, 95% CI 1.07-1.31), and 40% (OR: 1.40, 95% CI 1.22-1.61) higher risk of early-onset CRC (P trend <0.001), respectively. These associations were driven by proximal CRC (OR for 1 vs 0 metabolic condition: 1.10, 95% CI 1.00-1.22; for 2 vs 1: 1.33, 95% CI 1.07-1.61) and distal colon cancer, OR ≥2 vs 0: 1.25, 95% CI 1.03-1.53, but not rectal cancer (OR=2 vs 0: 1.07, 95% CI 0.92-1.24). Conclusions: Metabolic syndrome and metabolic comorbidity 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.

The incidence of colorectal cancer in young patients in the United States: Who, what, when and why? First Author: Hanyu Chen, 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, time trends, and outcomes 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 were reported, using annual percent change (APC) were performed using SEER*Stat and adjusted incidence at 45.26 per 100,000 patients. Younger patients were 35.22 in 2014, with an APC of -3.24. Although over 35% cases were diagnosed at high stage, 25.8% compared to only 18.4% in older patients. Of 1,886,441 individuals, the overall age-adjusted incidence of CRC decreased from 52.59 (per 100,000) in 2001 to 40.81 (per 100,000) in 2014 (Ptrend <0.0001). The disparity of CRC was more prominent in patients with CML and widened after introduction of modern therapy and 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 (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 disparity of cumulative incidence between counties was especially small in counties with comparatively 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-year 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 disparity of outcome between counties was less pronounced with relatively small change 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 differences were 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], 1.039-1.041); male (HR, 1.011; 95% CI, 1.001-1.021); race, White (HR, 1.049; 95% CI, 1.039-1.060); ethnicity, Asian (HR, 1.019; 95% CI, 1.009-1.029); Hispanic (HR, 1.011; 95% CI, 0.999-1.025); 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.

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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 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 HBOC 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-gepanel test, and 201 had post-test counseling. Germline mutation (n=317) was identified in 39.7% of our screened and tested population. Currently 1 in 400 patients screened in our ACC. Clinical trial information: UMCIRB 19-001052. Research Sponsor: Pfizer and consider broader gene panels as newer mutations become linked to HBOC.

Methods:

The CONTEST (HBOC Risk Management: Provision of Genomic Information for Community Hospitals) study is a choice study of pretest video-based genetic education (VBGE) or in-person Genetic Counseling (GC). Alternate GC strategies need to be developed to accommodate high demand for genetic counseling (GC). A novel testing and prevention model for community hospitals (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 testing: A patient-choice study. First it was offered at the appointment. Consenting patients provided a saliva sample same day in clinic for the CLIA-certified Color Genomics 30-gene cancer gene panel.

Conclusions: As the CONTEST project continues, we aim to enhance access 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 mutation (4%). We hope to expand use of testing from parks with higher involvement and 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. The CONTEST project is a first step in expanding 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.

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

<table>
<thead>
<tr>
<th>Criteria</th>
<th># of pts meeting criteria</th>
<th>Total pts with data for criteria</th>
<th>% of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RegionalAny T, NL, MO</td>
<td>1178</td>
<td>2.4%</td>
<td></td>
</tr>
<tr>
<td>2 Metastatic Any T, Any N, M1</td>
<td>1763</td>
<td>4.6%</td>
<td></td>
</tr>
<tr>
<td>3 High risk: T3 or T4</td>
<td>1081</td>
<td>25.2%</td>
<td></td>
</tr>
<tr>
<td>4 High risk: PSA at diagnosis = 20ng/mL</td>
<td>1929</td>
<td>45.4%</td>
<td></td>
</tr>
<tr>
<td>5 High risk: PSA at diagnosis &gt;20ng/mL</td>
<td>1929</td>
<td>45.4%</td>
<td></td>
</tr>
<tr>
<td>6 Very high risk: Gleason primary 5</td>
<td>1589</td>
<td>6.9%</td>
<td></td>
</tr>
<tr>
<td>7 Very high risk: Gleason 5/5</td>
<td>1492</td>
<td>21.1%</td>
<td></td>
</tr>
<tr>
<td>8 Ashkenazi Jewish</td>
<td>1773</td>
<td>10.6%</td>
<td></td>
</tr>
<tr>
<td>9 ≥3 cancers on same side of family</td>
<td>2113</td>
<td>5.3%</td>
<td></td>
</tr>
<tr>
<td>10 Intraductal/ductal histology</td>
<td>2122</td>
<td>0.9%</td>
<td></td>
</tr>
</tbody>
</table>

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.

Background: Germline testing (GT) for prostate cancer (PCA) is rapidly increasing with higher demand for genetic counseling (GC). Alternate GC strategies need to be developed to accommodate high demand for genetic counseling (GC). 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 (Connor 1993), and satisfaction (DeMarco 2004). Understanding of personal preference and patient-reported outcomes from the evaluation of the PCA cohort was identified from the Penn Medicine Biobank via ICD 9/10. 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 (4.2019). Results: 893/127 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. Results: We report a novel finding of a large population of pts with high Gleason score, high risk, and 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 large 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 counseling for a large cohort.

Research Sponsor: Penn Medicine Bassett Center Grant.

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 these 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 population 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 11/2016-12/2020 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: Patients were offered to providers, and results were discussed by email and phone with a genetic counselor. UPC and/or LVLP was measured and compared to previously reported data from the retrospectively tested UW TAN cohort. t-test was performed. Results: 84% (190/ 226) of approached patients underwent mPC GC. Mean age of consent was 80 (25-88) completed GT. 6.6% (12/182) of men were found to carry LP/LVLP in DNA repair genes. 3 in BRCA2, 2 in BRCA1, 4 in ATM, and 3 in CHEK2. Overall, 6.6% rate of LP/LVLP in DNA repair genes was comparable to the 8.8% previously reported in the UW TAN cohort (p = 0.695). Conclusions: Dedicated clinic-based strategies to offer and provide genetic counseling and services for patients with mPC provided a feasible and reliable procedure and services for patients with mPC. Further studies are needed to validate results and 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 (Pou, Sokolova, and Cheng, unpublished observations). Introduction of LP/LVLP in the PUG-VA PC Clinic 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.

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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 for Lynch syndrome; BRCAPRO for BRCA1/2). With the emergence of multiplex 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 develop 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, FMS2, 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 excellent ability to predict pathogenic variants in high penetrance genes at 90% sensitivity (90% 23.9% 10.6% 96.0% 9.4 0.67) and 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.


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 hematopoiesis.

Methods: Using the University of Chicago’s institutional NGS capability, we performed an Next generation sequencing (NGS) gene panel retesting of families with 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 in 8 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.

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 photorecurrence. 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). 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 in 8 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.

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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, MSH2, 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-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 significant 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 4.65 for patients with a pathogenic genetic mutation; 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). The effect was not present for patients with pathogenic mutations or VUS.

Conclusions: A pathogenic result does not impact QoL scales immediately post 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 or uncertain risk of ovarian cancer.

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

Comparison of genomic instability variants 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, gene panel to myChoice HRD.

Methods: Mutation screening for a set of 11 genes in the HR pathway (BRCA1, BRCA2, MSH2, MRE11A-1, NBN, PALB2, RAD51C, RAD51D, BARD1, BRCAP1, CHEK2, MSH6) 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, MSH2, 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-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 significant 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 4.65 for patients with a pathogenic genetic mutation; 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). The effect was not present for patients with pathogenic mutations or VUS.

Conclusions: A pathogenic result does not impact QoL scales immediately post or post GT or 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 or uncertain risk of ovarian cancer.

Poster Session (Board #78), 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 sites for patients within 1 year from 2014 to 2019, pts were identified by ICD-10 codes Z15.01, Z15.02, Z15.09, Z15.89, C50.919, C99.8, and C54.1. Pts with mutations 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, 9. 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).

Conclusions: Pts undergoing GT at our institution tended to be referred to a GC, with a pathologist, or a genetic counselor (66% vs 34%). While the overall rate of referral to a GO was 22%, for patients with increased or uncertain risk of OC, referral to a GO was associated with increased 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 undergoing GT by a GC, vs 57% of pts associated with a GS, are referred 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.

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-Sylvestre 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 34%) in safety net hospitals, including ours. To improve adherence, we used the myChoice HRD test to offer germline genetic counseling (GC) to women with epithelial ovarian cancer between 4/1/2018 and 12/31/2019. We hypothesized that increased uptake of risk reducing surgery (RRS) would have been missed by %LOH or the 11-gene panel in these two cohorts.

Conclusions: 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., Salt Lake City, UT

<table>
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<table>
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<th>11-gene panel</th>
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*Could not be calculated because positive results by the 11-gene panel were not continuous
Background: We report our large cohort of pediatric cancer patients undergoing prospective germline and somatic testing. Our dataset is a significant addition to the 1,573 children reported to date who have undergone germline and somatic 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% (20/254) with sarcomas, and 12% (13/105) with other solid tumors. The most frequent mutations were in RB1 (n = 26) 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, RAD51 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 discordant 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.

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 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 < 0.001. 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 a highly penetrant 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 of screening, counseling and other preventive strategies. Research Sponsor: U.S. National Institutes of Health.
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 neoplasms, were analyzed. Eligibility was per NCCN criteria and cancer survivors needing 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 menstrual 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 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 3,411 participants was analyzed. 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 detected in 10 subjects (2.2%) and other cancers were detected 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 predictive values occurred in 15 (9.9%), lung cancer was diagnosed in 1 (0.7%), and other cancers were diagnosed in 3 subjects (1.9%). Non-adequate subjects were excluded from 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 Ewing King Biomedical Research.