10500 Oral Abstract Session

Sensitivity of age and family history (FH) criteria for determining pancreatic cancer (PC) surveillance (PCS) eligibility among individuals with hereditary PC risk.

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Background: PCS for individuals with pathogenic/likely pathogenic germline variants (PGVs) predisposing to PC is associated with earlier stage at diagnosis (dx) and improved survival, compared to historical controls. For those with such PGVs, PCS eligibility is determined based on FH of PC and age (age ≥30 years for those with *STK11* PGVs; age ≥40 for *CDKN2A*; age ≥50 for other PC risk genes [Table 1]; or 10 years before the youngest PC in the family). For PGV carriers (apart from *CDKN2A/STK11*), guidelines have required a FH of PC in ≥1 first-/second-degree relatives (FDR/SDR) for PCS eligibility. Limited data have evaluated the sensitivity of these criteria in determining which high-risk individuals benefit from PCS. **Methods:** We evaluated the sensitivity of age and FH criteria for PCS in the Myriad Collaborative Research Registry (MCRR). Individuals who were diagnosed with PC and underwent germline genetic testing were included. To determine the number of PGV carriers who would have been eligible for PCS at the time of their PC dx, FH of cancer and personal cancer history were ascertained from data contained in MCRR at the time of germline testing. **Results:** Among 11,248 PC patients who underwent germline testing, 55.5% were female and 59.2% were non-Hispanic White/European. The mean age at PC dx was 64.6 years. PGVs predisposing to PC were detected in 969 (8.6%) individuals [Table 1], of whom 224 (23.1%) met gene-specific PCS criteria. Of the 969, 829 (85.6%) met gene-specific *age criteria* for PCS. Of the 931 individuals with PGVs in genes requiring FH, only 208 (22.2%) fulfilled *FH criteria* for PCS. **Conclusions:** Most individuals with PC who harbor PGVs in PC susceptibility genes would not have met gene-specific age/FH criteria for PCS. FH of PC has particularly poor sensitivity in identifying PGV carriers who go on to develop PC, supporting recent removal of this criterion from NCCN guidelines for *BRCA2/ATM*. Validation in a clinic-based cohort is ongoing. These data suggest that FH of PC should not be used to determine which PGV carriers are eligible for PCS. Research Sponsor: Betsy Rowe and Family.

Gene (n)	Met FH criterion of PC in FDR/SDR - n (%)	Met age# criterion - n (%)	Met age and FH criteria (%)
***ATM* (186)**	47 (25.3)	170 (91.4)	44 (23.7)
***BRCA1* (137)**	28 (20.4)	114 (83.2)	26 (19.0)
***BRCA2* (428)**	101 (23.6)	363 (84.8)	88 (20.6)
***PALB2* (61)**	11 (18.0)	50 (82.0)	10 (16.4)
***MLH1* (11) /**	4 (36.4) /	9 (81.8) /	4 (36.4) /
***MSH2* (40) /**	4 (10.0) /	27 (67.5) /	3 (7.5) /
***MSH6* (32)**	4 (12.5)	27 (84.4)	4 (12.5)
***TP53** (25)**	4 (16.0)	23 (92.0)	4 (16.0)
***CDKN2A* (34) /**	NA	33 (97.1) /	33 (97.1) /
***STK11* (2)**		2/2 (100)	2/2 (100)
> 1 PGV (13)	5/11 (45.5)	11/13 (84.6)	6/13 (46.2)

NA: Not applicable.
#Age ≥30 years for *STK11*; age ≥40 for *CDKN2A*; age ≥50 for other PC risk genes; or 10 years before the youngest PC in the family.
*Ancillary testing to confirm germline status vs clonal hematopoiesis/mosaicism is not available.

10501 Oral Abstract Session

A prospective study of whole-body MRI (WBMRI) as part of a multimodality screening program for individuals with Li-Fraumeni syndrome (LFS).

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Background: Individuals with LFS are at risk for developing cancer in multiple organs and therefore require a multimodal cancer screening program. We assessed the performance of annual WBMRI in early cancer detection for individuals with LFS. **Methods:** Individuals with a germline pathogenic or likely pathogenic variant in the *TP53* gene (defined as LFS) and without cancer diagnosed or treated in the preceding 6 months were eligible to undergo annual non-contrast WBMRI. Clinical findings on WBMRI, follow-up studies, and biopsies were prospectively assessed. Cancer incidence during the study period and up to 18 months after WBMRI was evaluated. **Results:** 162 eligible participants (pts) with LFS (127 adult, 35 pediatric) underwent a total of 477 WBMRIs; 119 (73%) underwent 3 or more. Median age at enrollment was 37 years; 75% of pts were female. Classic or Chompret diagnostic criteria for LFS were met for 66% (84/127) of adult and 77% (27/35) of pediatric pts. Follow-up studies for findings on WBMRI were pursued for 61.4% (78/127) of adult and 34.3% (12/35) of pediatric pts. Biopsies were performed without complication in 18% (29/162) of pts with 39.5% of 38 biopsies confirming a cancer diagnosis. The percentage of pts requiring follow-up studies or biopsies decreased with consecutive WBMRIs (Table 1). During the study period, 37 cancers were diagnosed in 33 pts (27 adults, 6 children); 26 of these pts were alive at the time of data cut off. Fifteen of 37 cancers (40.5%) were asymptomatic cancers diagnosed by WBMRI; 86% (13/15) of these (in 12 patients) were localized and treated with curative intent, including 3 lung cancers and 4 pelvic/abdominal sarcomas. Ten of these 12 pts remain alive at the time of last follow-up. The 22 cancers not diagnosed on WBMRI included five sarcomas, and one each of adrenocortical, lung, thyroid and renal cell carcinoma as well as cancers not likely to be detected on WBMRI (4 breast/chest wall, 3 endoluminal, 3 hematologic, and 3 metastatic recurrences). **Conclusions:** Annual WBMRI contributes substantially to detection of asymptomatic localized cancers among individuals with LFS but interval cancers remain common. Our study highlights limitations of WBMRI and the need for further research to enhance early detection and interception of cancer in LFS. Research Sponsor: Li-Fraumeni Syndrome Association (LFSA); The Cantor Foundation; National Cancer Institute; P30 CA008748 (PI: Vickers); Breast Cancer Research Foundation.

Sequence of WB-MRI scans and timing of follow-up studies, biopsies, and cancer diagnoses.

WB-MRI scan number	# pts evaluated	# pts with follow-up studies n (%)	# pts with biopsies n (%)	# pts dx with ca by WBMRI n (%)	# ca dx based on WBMRI n	# pts with interval ca dx n (%)	# interval ca dx by other means or symptoms (not detected on WBMRI) n
1	162	60 (37.0)	20 (12.3)	6 (3.7)	7	8 (4.9)	8
2	143	38 (26.6)	12 (8.4)	6 (4.2)	6	7 (4.9)	9
3	119	21 (17.6)	3 (2.5)	0 (0)	0	3 (2.5)	3
4	33	5 (15.2)	1 (3.0)	1 (3.0)	1	2 (6.1)	2
5	11	1 (9.1)	0 (0)	1 (9.1)	1	0 (0)	0
6	5	1 (20)	0 (0)	0 (0)	0	0 (0)	0
7	3	1 (33.3)	0 (0)	0 (0)	0	0 (0)	0

pts: participants, ca: cancer, dx: diagnosed.

10502 Oral Abstract Session

The eREACH study: A randomized study of an eHEALTH delivery alternative for cancer genetic testing for hereditary predisposition in patients with metastatic cancers.

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Background: With FDA approval of targeted therapies in patients with germline *BRCA1/2*-related advanced cancers there is a need to evaluate efficient and effective delivery models for germline cancer genetic testing. **Methods:** eREACH is a 4 arm non-inferiority study where traditional standard-of-care pre-test (visit 1) and post-test (visit 2) counseling delivered by a genetic counselor (GC) are replaced with a patient-centered eHealth (digital) intervention in patients with advanced or metastatic cancer. GC visits were offered by telehealth in the home. Arms include: A (GC/GC), B (GC/digital), C (digital/GC) and D (digital/digital). Those assigned to a digital visit could request a visit with a GC if preferred. Surveys were completed at baseline (T0), after visit 1 (T1), visit 2 (T2) and 6 months (T3). Primary non-inferiority outcomes are change in knowledge and anxiety (T0-T1, T0-T2). Secondary outcomes include uptake of testing, depression, cancer specific distress, responses to testing and satisfaction. We used an intention-to-treat approach (ITT) and as-treated approach (secondary). We used ANOVAs and chi-squared tests for hypothesis testing. For non-inferiority testing, we had additional rules based on the magnitude and sign of effects. **Results:** 229 participants were recruited from 14 states through Penn Medicine, community sites and social media, with 56-60 per arm.- Participants were 35-91 YO (mean 67 YO),and37% were male, 17% were non-white and 43% had less than a college education. 70% were from academic sites, 21% from community sites and 9% from social media. Cancer types were: 52% breast, 26% prostate, 18% pancreatic, and 5% ovary. 173 (76%) of patients completed testing (12% had a positive result, 12% had a VUS). In our primary ITT analyses, we met the non-inferiority threshold for all primary and secondary outcomes except for knowledge (T0-T2) and uptake of testing. Increases in knowledge (T0-T2) were greater in Arms A-C as compared to Arm D, although differences were small (averages +2.03-2.54 v +1.23). Uptake of visit 1 was lower in the digital arms (A: 94.7%, B: 92.7% v. C: 76.7%, D: 82.5%), although uptake of testing after visit 1 met non-inferiority. 20% assigned to Arm C and 11% assigned to Arm D requested a GC. As-treated non-inferiority analyses were similar to the ITT results. **Conclusions:** Offering patient-centered digital delivery models with one digital visit and one visit with a genetic counselor is non-inferior to two visits with a genetic counselor for patients with metastatic cancer. Reminders, outreach or completion of digital platforms in clinic could address differences in uptake. The fully digital model may be associated with small differences in knowledge gain, although the clinical significance may be small., and longitudinal data could help inform the appropriateness of the fully digital model.
Research Sponsor: None.

10503 Oral Abstract Session

Feasibility of Pap-derived ctDNA for detection of sporadic and Lynch-associated endometrial cancer.

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Background: Patients (pts) with Lynch Syndrome (LS) have high risk of endometrial cancer (EC) and are recommended risk-reducing hysterectomy (RR-Hys/BSO) due to lack of effective screening. As plasma-derived circulating tumor DNA (plasma-ctDNA) lacks adequate sensitivity in EC, we sought to evaluate Pap-derived ctDNA (Pap-ctDNA) as a novel, non-invasive assay for EC detection. **Methods:** Plasma-ctDNA and Pap-ctDNA were obtained from pts with EC undergoing surgery or LS undergoing RR-Hys/BSO under an IRB-approved protocol. Paired tumor/normal sequencing of ECs was compared to genomic findings from plasma-ctDNA and Pap-ctDNA. Somatic variants in plasma and Pap samples were genotyped using matched tumor tissue, with average allele frequency (VAF) calculated. Tumors were assessed for MSI and/or MMRD via MSISensor or IHC. In LS pts, pathology for precursor lesions was assessed. **Results:** 19 pts (16 EC, 3 LS) underwent prospective collection of 42 samples (20 plasma, 22 Pap). 56% of ECs were low-grade endometrioid and 81% early-stage (I/II) (Table). 12.5% of ECs were MMRD due to MLH1 hypermethylation. Median yield of Pap-ctDNA was higher than plasma-ctDNA (91ng vs. 19.5ng; p=0.0004). 94% of ECs had mutations covered within target regions of both assays, with mutations detected in 93% of Pap-ctDNA, but only 33% of plasma-ctDNA. In pts with mutations detected in both assays, median VAF was higher in Pap-ctDNA vs. plasma-ctDNA in all 5 cases (Table; p=0.012). Among the 13 pts with early-stage EC, 92% of Pap-ctDNA vs 23% of plasma-ctDNA were positive. Of 3 LS pts, one had a focus of MMRD atypical hyperplasia concordant with germline MMR mutation; plasma and Pap-ctDNA were negative. **Conclusions:** Pap-ctDNA from EC pts results in higher ctDNA yield than plasma-based testing. Tumor mutations were detected in >90% of Pap-ctDNA even in early-stage EC, versus only 23% of plasma-ctDNA samples. Pap-ctDNA for early-detection of EC is feasible and is a promising tool for average and high-risk individuals with potential applicability in other neoplasms. Research Sponsor: Society of Memorial Sloan Kettering Cancer Center.

EC characteristics.

ID	Histology	Stage	MSS/ MMRD	Plasma ctDNA yield (ng)	Pap ctDNA Yield (ng)	Avg VAF mutations-Plasma	Avg VAF mutations-Pap
1	G2 Endometrioid	IA	MSS	19.49	36.83	-	-
2	G1 Endometrioid	IA	MSS	57.27	144.97	-	0.00014
3	G1 Endometrioid	IA	MSS	44.3	179.2	-	0.006
4	Carcinosarcoma	IIIC	MSS	23.78	28.21	0.0062	0.279
5	Serous	IV	MSS	38.45	17.03	0.0046	0.403
6	G1 Endometrioid	IA	MSS	13.76	21.38	-	0.004
7	Mesonephric-like	II	MSS	21.34	31.3	-	0.123
8	G2 Endometrioid	IA	MMRD- MLH1 hypermeth	10.67	185.5	0.0092	0.119
9	G1 Endometrioid	IA	MSS	23.92	27.35	-	0.049
10	Serous	IA	MSS	15.61	110	-	0.277
11	G2 Endometrioid	IA	MMRD-MLH1 hypermeth	8.44	222.65	-	0.066
12	Carcinosarcoma	IA	MSS	14.54	104.19	-	0.433
13	Mixed endometrioid, serous	IVB	MSS	22.96	102.85	-	0.166
14	G2 Endometrioid	IA	MSS	7.46	145.68	0.0007	0.125
15	G2 Endometrioid	IA	MSS	19.45	141.34	-	0.156
16	Serous	IB	MSS	19.38	79.2	0.0005	0.473

Gene-specific outcomes in patients with Lynch syndrome treated by immune checkpoint blockade for advanced cancer.

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Background: Lynch syndrome (LS), caused by germline pathogenic variants (gPVs) in DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*), is characterized by microsatellite instability (MSI)/mismatch repair deficiency (MMRd) of associated tumors. The impact of the underlying gPV on the prognosis of LS patients with advanced cancer receiving ICB has not been elucidated. **Methods:** Consecutive cancer-affected LS pts consented to tumor-normal DNA sequencing via MSK-IMPACT (NCT01775072), from 01/2014-01/2024 with advanced solid tumors and receiving ≥1 ICB dose were identified. In cases of multiple cancers, only the first one was considered. MSI and MMRd was assessed via NGS-derived MSISensor score or IHC staining, respectively. Radiological response rates and survival were assessed. **Results:** Among 186 LS patients, 132 had an ICB treated advanced tumor with the following prevalence of gPV: *MSH2* 41% (N=54), *MLH1* 28% (N=37), *PMS2* 17% (N=23), and *MSH6* 14% (N=18). The most represented tumor types were colorectal (35%, N=46), urothelial (14%, N=18), pancreatic/biliary (13%, N=17), upper gastro-intestinal (11%, N=15), endometrial (11%, N=15). Objective response rate was 58%, including 35% with radiological complete response (CR) with higher CR rates in g*MLH1* and g*MSH2* patients (Table). Median follow-up was 53 months [range:0.3-116.3]. Median overall survival (mOS) / Progression free survival (mPFS) were significantly prolonged in *non-gPMS2* patients vs. g*PMS2* patients (Table). MMR IHC was available for 107 (80%) tumors identifying 88% (n=94) as MMRd and 12% (n=13) as MMRp tumors. 69% (9/13) of MMRp tumors were in *PMS2* patients with 8 being both MMRp and MSS suggesting a sporadic origin rather than LS-related cancer. Stratifying by MMRd and MSI status, mOS was similar in patients with MMRd/MSI and MMRd/MSS tumors (109 months vs not reached (NR); HR=0.86; 95%CI [0.35-2.13]), but significantly diminished in in pts with MMRp as compared to MMRd tumors (20 vs 109 months, HR=0.27; 95%CI [0.77-0.96]). In g*PMS2* patients with MMRd tumors, median OS was 27.7 months. **Conclusions:** ICB treatment results in high CR rates in LS patients. The shorter mOS amongst LS patients with *gPMS2* compared to other LS genes is partially explained by the higher prevalence of sporadic MMRp tumors. Even in the context of an MMRd tumor, patients with g*PMS2* have worse outcomes than LS patients with other gPVs. Research Sponsor: MSKCC; T32-CA009512; U.S. National Institutes of Health; P30 CA008748; Swim Across America; Servier Foundation; Cycle for survival; Romeo Milio Lynch Syndrome Foundation; Nuovo Soldati; Tournut SNFGE; Ligue contre le Cancer; Philippe Foundation.

Treatment	Total	Complete Response % (n)	Objective Response Rate % (n)	Disease Control rate % (n)	mPFS (months)	mOS (months)
MSH2	54	46% (25)	65% (35)	89% (48)	45	109
MLH1	37	41% (15)	65% (24)	81% (30)	50	NR
PMS2	23	9% (2)	30% (7)	74% (17)	11	20
MSH6	18	22% (4)	61% (11)	78% (14)	109	NR
MLH1/ MSH2/ MSH6	109	40% (44)	64% (70)	84% (92)	52	109
Non-PMS2 vs PMS2	-	OR=7.1 95%CI [1.7-31.6] P=0.003	OR=4.1 95%CI [1.5-10.3] P=0.005	OR=1.9 95%CI [0.64-5.6] P=0.24	HR=0.21 95%CI [0.13-0.35]. P<0.0001	HR=0.19 95%CI [0.10-0.35] P=0.0005

10505 Oral Abstract Session

Phase Ib study of a plasmid DNA–based immunotherapy encoding the hTERT, PSMA, and WT1 (INO-5401) +/- IL12 (INO-9012) followed by electroporation in cancer patients and healthy individuals with *BRCA1/2* mutations.

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Background: Pathogenic variants in *BRCA1/2* increase the risk of breast, ovarian, pancreatic and prostate cancer. Non-surgical risk-reduction strategies are needed. We evaluated an immunological approach for cancer interception via a DNA plasmid vaccine. INO-5401 is a recombinant plasmid-derived DNA based immunotherapy encoding 3 tumor-associated antigens: human telomerase reverse transcriptase (hTERT), prostate specific membrane antigen (PSMA), and Wilms Tumor-1 (WT1). INO-9012 is a DNA plasmid encoding IL-12 deployed as an immune adjuvant. Previous studies have shown that INO-5401 in combination with INO-9012 administered via intramuscular (IM) injection followed by electroporation (EP) with CELLECTRA is both immunogenic and tolerable in cancer patients and may lead to efficacy. **Methods:** The primary objective of NCT04367675 is to evaluate the safety of INO-5401 +/- INO-9012 followed by EP in individuals with *BRCA1/2*. Cohort A included adults with prior localized cancer, no evidence of disease (N = 16); Cohort B, healthy individuals with no prior cancer (goal N = 28). Eligibility: ECOG performance status 0-1, normal ECG, and adequate bone marrow, hepatic, and renal function. Treatment: INO-5401 9 mg IM followed by EP (Arm 1) and INO-5401 9 mg in combination with INO-9012 1 mg IM. followed by EP (Arm 2) on Day 1, and weeks 4, 8, 12. Subjects are assessed at the time of therapy, 2 weeks after each therapy and then every 16 weeks for 2 years. Secondary endpoints (not reported here) include evaluation of immune response. **Results:** 42 of 44 planned subjects are enrolled and have received >1 vaccine (N = 24 *BRCA2*; N = 15 *BRCA1*, N = 3 *BRCA1* and *BRCA2*). All doses will be administered by June 2025 and safety data during administration will be complete. In Cohort A, 17 women, 1 man were treated (median age of 52 [range 39-75]). In Cohort B (healthy individuals), 14 women, 12 men were treated (median age of 48 [range 31-69]). 148 doses have been given. One patient received only 1 vaccine due to treatment-related Grade 1 hematoma. Treatment-related AEs were seen in 95% of subjects, largely grade 1 injection site reactions. AEs seen in > 25% are as below. Grade 3 AEs were seen in 6 (15%), including urticaria (N = 1), vasovagal reaction (N = 1), and hypertension (N = 4), none of which were treatment-related. **Conclusions:** Administration ofa recombinant plasmid-derived DNA based immunotherapy encoding hTERT, PSMA and WT1, +/- IL12, followed by electroporation is feasible and safe in individuals with *BRCA1/2*, including healthy individuals with no prior cancer. The most common AEs are injection site reactions, all of which were Grade 1/2. Clinical trial information: NCT04367675. Research Sponsor: Inovio Pharmaceuticals.

CTCAE Term	Grade 1	Grade 2	Frequency
Pain	N=26	N=3	72.5% (N=29)
Bruising	N=26	N=0	65.0% (N=26)
Swelling	N=19	N=0	47.5% (N=19)
Redness	N=14	N=0	35.0% (N=14)
Injection Site Reaction	N=11	N=2	32.5% (N=13)

10506 Oral Abstract Session

Menopausal hormone therapy after a diagnosis of breast cancer in women with a *BRCA* pathogenic variant and risk of death.

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Background: Use of menopausal hormone therapy (MHT) is contraindicated for women with a personal history of breast cancer. This topic is of importance among women with a pathogenic or likely pathogenic variant (mutation) in *BRCA1* or *BRCA2* given their tendency to develop early onset disease as well as the recommendation to undergo oophorectomy prior to natural menopause. **Methods:** We conducted a prospective analysis of MHT use following breast cancer in *BRCA* carriers and the risk of death. The study included *BRCA* carriers with a diagnosis of breast cancer, no history of another cancer, no prior MHT use, and who were enrolled in a longitudinal study. Women who initiated MHT after their diagnosis were matched to women who did not use MHT on year of birth, age of diagnosis, and treatments received – resulting in 183 matched pairs. We followed women from the date of first MHT use in the exposed and the matched date in the unexposed. Cox proportional hazards was used to estimate the hazard ratio (HR) and 95% confidence intervals (CI) for the risk of death associated with MHT use. **Results:** Among the 183 MHT users, 53 (29%) used a local MHT and 130 (71%) used a systemic MHT. After 6.0 years of follow-up (range 0.01-22.7); there were 9 (4.9%) deaths in the MHT group vs. 22 deaths (12%) in the no MHT group ($P = 0.01$). The corresponding number of breast cancer deaths were 6 (3.3%) vs. 16 (8.7%) ($P = 0.03$). The HR for all-cause mortality was 0.31 (95%CI 0.14-0.69; $P = 0.004$) and for breast cancer-specific mortality was 0.27 (95%CI 0.10-0.70; $P = 0.007$). The corresponding risk estimates for all-cause death by invasiveness were 0.25 (95%CI 0.11-0.61; $P = 0.002$) and 0.54 (95%CI 0.07-4.02; $P = 0.54$) for invasive disease and DCIS, respectively. All-cause mortality with use of systemic MHT was 0.27 (95%CI 0.11-0.67; $P = 0.005$) and was 0.19 (95%CI 0.03-1.45; $P = 0.11$) for local MHT. Compared to never HRT use, the HR for E-alone was 0.35 (0.12-1.02; $P = 0.05$) and was 0.58 (95%CI 0.08-4.29; $P = 0.59$) for E+P. Subgroup analyses by formulation, gene mutation and tumour pathology are on-going. **Conclusions:** Although based on small strata, the preliminary findings are suggestive of no increased risk of death with MHT use after *BRCA*-breast cancer and may offer an opportunity to improve quality of life in this unique population. Replication in larger datasets are needed. Research Sponsor: Breast Cancer Canada.

10507 Oral Abstract Session

Glucagon-like peptide-1 receptor agonists and incidence of obesity-related cancer in adults with diabetes: A target-trial emulation study.

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Background: Obesity is a major risk factor for cancer development. However, whether glucagon-like peptide-1 receptor agonists (GLP-1RAs), a class of diabetes medication which causes weight loss, reduce cancer incidence is unknown. This study investigated whether GLP-1RAs reduce the risk of obesity-related cancer in adults with diabetes and obesity compared to dipeptidyl peptidase-4 inhibitors (DPP-4is), a weight-neutral class of diabetes medication. **Methods:** 85,015 adult patients from 43 U.S. health systems with a body mass index ≥ 30 kg/m2 and a diagnosis of diabetes, who newly initiated a GLP-1RA or DPP-4i between 2013 and 2023 were included. Patients prescribed GLP-1RAs (mean age, 56.8 years) were matched 1:1 on propensity score for GLP-1RA prescription and prescription year with patients prescribed DPP-4is (mean age, 56.8 years). Obesity-related cancer incidence was compared between groups. **Results:** Over a mean follow-up of 3.9 years, there was a lower risk of obesity-related cancers (adjusted HR, 0.93; 95% CI, 0.88-0.98; P=0.005) and all-cause death (adjusted HR, 0.92; 95% CI 0.87-0.97; P=0.001) associated with GLP-1RA use versus DPP-4i use. Assessments of cancer subtypes showed protective associations between GLP-1RA use and colon and rectal cancers. **Conclusions:** GLP-1RAs were associated with a lower risk of obesity-related cancer compared with DPP-4is in a large, real-world cohort of patients with diabetes and obesity. Future studies should prospectively assess the role of GLP-1RAs in cancer prevention. Research Sponsor: National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; R01 DK115534 to MEG; National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; K24 HL155861 to MEG; National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health; K01 DK121825 to JS.

Adjusted hazard ratios of incidence of composite obesity-related cancer and all-cause death in propensity-matched patients prescribed GLP-1RAs versus DPP-4is (n=85,015 pairs).

Outcome	Sex	Events/$N_{at\ risk}$ (GLP-1RA)	Events/$N_{at\ risk}$ (DPP-4i)	HR (GLP-1RA/ DPP-4i)	P	$P_{interaction}$
Obesity-related cancer (composite)	Overall	2,501/85,015 (2.9%)	2,671/85,015 (3.1%)	0.93; 95% CI, 0.88-0.98	0.005	NA
Obesity-related cancer (composite)	Female	1,754/44,762 (3.9%)	1,898/45,182 (4.2%)	0.92; 95% CI, 0.86-0.98	0.01	0.63
Obesity-related cancer (composite)	Male	747/40,253 (1.9%)	773/39,833 (1.9%)	0.95; 95% CI, 0.86-1.05	0.29	0.63
All-cause death	Overall	2,783/85,015 (3.3%)	2,961/85,015 (3.5%)	0.92; 95% CI, 0.87-0.97	0.001	NA
All-cause death	Female	1,219/44,762 (2.7%)	1,514/45,182 (3.4%)	0.80; 95% CI, 0.74-0.86	<0.001	<0.001
All-cause death	Male	1,564/40,253 (3.9%)	1,447/39,833 (3.6%)	1.04, 95% CI, 0.96-1.11	0.34	<0.001

Adjusted hazards ratios calculated using Cox regression represent ratios of the incidence of composite obesity-related cancer and all-cause death in matched pairs of patients prescribed GLP-1RA versus DPP-4i over average follow-up durations of 3.8 years (GLP-1RA) and 3.9 years (DPP-4i). Results of sex-stratified and sex interaction analyses are also displayed. The threshold for statistical significance is $P<0.05$.

10508 Oral Abstract Session

Association of glucagon-like peptide 1 receptor agonists with cancer risk in obesity adults with and without diabetes: A target trial emulation study.

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Background: The use of glucagon-like peptide 1 receptor agonists (GLP-1RAs) has substantially expended given their remarkable benefits in managing obesity. Yet, their impact on long-term cancer risk remains unclear, with existing real-world evidence being limited and yielding conflicting results. **Methods:** This retrospective cohort study followed a target trial emulation design using 2014–2024 OneFlorida+ electronic health records (EHR) data. Adults (≥18 years) eligible for anti-obesity medications (AOMs) and without a cancer history were included. We compared GLP-RA users vs. non-users, with 1:1 propensity score matching applied to balance baseline factors between the two groups. The primary outcomes include the incidence of 16 obesity-associated cancers (liver, thyroid, pancreatic, bladder, colorectal, lung, kidney, breast, endometrial, meningioma, esophageal adenocarcinoma, gallbladder, upper stomach, ovarian, multiple myeloma, and prostate), assessed over a follow-up period of up to 10 years. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), and cumulative incidences were estimated using Kaplan-Meier analyses. **Results:** After matching, 43,317 GLP-1RA users were compared with 43,315 non-users. The incidence rates of the 16 cancers were 20.5 versus 23.6 per 1,000 person-years, respectively, indicating a significantly lower overall cancer risk among GLP-1RA users (HR, 0.83 [95% CI, 0.76–0.91]) compared to non-users. In particular, GLP-1RA use was associated with a reduced risk of endometrial cancer (HR, 0.75 [95% CI, 0.57–0.99]), ovarian cancer (HR, 0.53 [95% CI, 0.29–0.96]), meningioma (HR, 0.69 [95% CI, 0.48–0.97]), and esophageal adenocarcinoma (HR, 0.34 [95% CI, 0.12–0.94]). However, GLP-1RA users showed a trend toward an increased risk of kidney cancer (HR, 1.38 [95% CI, 0.99–1.93]), particularly among the younger adults (≤65 years) and overweight patients (BMI 27–29.9). **Conclusions:** In this large cohort of real-world obesity population with and without diabetes, GLP-1RA use was associated with an overall reduction in obesity-related cancer risk, as well as lower risks of several specific cancers. However, a potential elevated risk of kidney cancer, especially in younger or moderately obese individuals, highlights the need for targeted surveillance and longer-term follow-up to clarify the underlying mechanisms and clinical implications of these findings. Research Sponsor: None.

10509 Clinical Science Symposium

Association between type of BRCA1/2 pathogenic/likely pathogenic variants and outcome in young patients with breast cancer: Results from an international cohort study.

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Background: Pathogenic/likely pathogenic variants (P/LPVs) in the *BRCA1 or BRCA2* genes significantly increase the risk of developing breast cancer (BC) and other malignancies, with distinct clinicopathologic features depending on the gene involved. However, the clinical implications of the type of P/LPVs within *BRCA1* or *BRCA2* genes remain to be elucidated. **Methods:** The BRCA BCY Collaboration (NCT03673306) is an international, multicenter, hospital-based, retrospective cohort study that included *BRCA* carriers diagnosed with invasive BC at the age of ≤40 years between January 2000 and December 2020. In this analysis, only patients with detailed available information on P/LPVs in the BRCA genes were included. Clinicopathologic features and survival outcomes (disease-free survival [DFS] and overall survival [OS]) were investigated according to P/LPV types (insertion-deletion mutations [INDEL] *vs* single nucleotide variants [SNV] *vs* copy number variations [CNV]; truncating *vs* non-truncating P/LPVs; frameshift *vs* nonsense *vs* splicing *vs* missense P/LPVs). **Results:** Out of 5660 patients from 109 centers worldwide, 3294 were eligible for the present analysis (2080 *BRCA1* and 1214 *BRCA2*). Overall, 61.3% of patients carried INDEL, 32.7% SNV and 6.0% CNV; 76.5% of patients exhibited truncating P/LPVs and 8.4% non-truncating P/LPVs (15.1% not classifiable). Frameshift mutations were the most common (60.3%), followed by nonsense (21.2%), splicing (9.6%), and missense (8.4%) P/LPVs. In both *BRCA1* and *BRCA2* carriers, no statistically significant differences in baseline clinicopathologic variables and P/LPV types were observed except for fewer patients with nodal involvement among CNV of BRCA2. Median follow-up was 7.9 (IQR 4.5-12.9) years. No association between the type of P/LPV in both *BRCA1* and *BRCA2* carriers and DFS was observed, except for better DFS in patients with missense variants of *BRCA2* gene. Compared to patients with non-truncating variants, patients with truncating variants in *BRCA1* had a shorter OS (HR 2.00; 95%CI 1.17-3.41). Albeit not statistically significant, a numerically worse OS was observed among *BRCA2* patients with truncating P/LPVs (HR 6.27 95% CI 0.86-45.87). In *BRCA1* carriers, compared to patients with frameshift P/LPVs, those with missense variants were associated with better OS (HR 0.48 95%CI 0.28-0.84 for missense). In *BRCA2* carriers, similar results were observed. **Conclusions:** In this global cohort of young BRCA carriers with BC, truncating P/LPVs were associated with poorer prognosis, and missense P/LPVs with improved prognosis. This study advances our understanding of the influence of specific types of *BRCA1/2* P/LPVs on BC characteristics and outcomes, potentially suggesting more personalized prevention strategies and treatment approaches. Clinical trial information: NCT03673306. Research Sponsor: None.

10510 Clinical Science Symposium

Germline pathogenic variants in cancer predisposition genes and overall survival of women with breast cancer.

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Background: The impact of germline pathogenic or likely pathogenic variants (PVs) in cancer predisposition genes on overall survival (OS) after breast cancer diagnosis is not well defined. In particular, unbiased OS estimates from population-based studies accounting for clinical subtypes of breast cancer (based on ER, PR, and HER2 status) and for genes other than *BRCA1/2* are lacking. **Methods:** The study included 25,168 prospectively followed women with locoregional invasive breast cancer within the population-based CARRIERS study. Germline sequencing using a custom multigene amplicon-based panel was performed to identify PVs. OS was compared between germline PV carriers in *ATM, BRCA1, BRCA2, CHEK2* and *PALB2* and non-carriers (negative for germline PVs in 13 known breast cancer predisposition genes) for each clinical subtype of breast cancer from the time of breast cancer diagnosis to death or last follow up in a multivariable Cox proportional hazard regression analysis adjusting for age at diagnosis, race/ethnicity, histology, TNM stage, type of surgery, use of adjuvant radiation, chemotherapy and endocrine agents. **Results:** Among 25,168 women with breast cancer, germline PVs in one of the five breast cancer predisposition genes were detected in 5.8% of the women [*ATM*: 0.8%, *BRCA1*: 1.3%, *BRCA2:* 1.6%, *CHEK2*: 1.5%, and *PALB2*: 0.6%]. Among women with ER+ breast cancer, compared to non-carriers, a significantly worse OS was noted for *BRCA1* (Hazard Ratio (HR): 1.8, 95% Confidence Interval (CI): 1.1 – 3.0, p=0.02) and *BRCA2* (HR: 1.8, 95%CI: 1.4 – 2.4, p<0.001), but not for *ATM* (HR: 1.2, 95%CI: 0.8 – 1.7, p=0.40) or *CHEK2* (HR:1.0, 95%CI: 0.8 – 1.3, p=1.0) PV carriers. Worse OS was noted in *PALB2* PV carriers with ER+ breast cancer (HR:1.5, 95%CI: 0.9 – 2.2, p=0.09), although it did not reach statistical significance. Similar HR estimates for OS as with ER+ breast cancer were observed in women with ER+/HER2- breast cancer for *BRCA1*, *BRCA2* and *PALB2* PV carriers, but only *BRCA2* results were statistically significant. Among women with ER-negative breast cancer, compared to non-carriers, a significant difference in OS was not observed for PV carriers in *ATM* (HR:0.8, 95%CI: 0.4 – 1.8, p=0.63), *BRCA1* (HR:1.2, 95%CI: 0.8 – 1.7, p=0.35), *BRCA2* (HR: 0.8, 95%CI: 0.5 – 1.2, p=0.29), *CHEK2* (HR: 0.7, 95%CI: 0.3 – 1.4), or *PALB2* (HR: 0.9, 95%CI: 0.5 -1.7, p=0.78). **Conclusions:** The suggestive differences in OS by ER status of the tumor in *BRCA1* and *BRCA2* PV carriers warrant further investigation of underlying tumor biology and assessment of endocrine sensitivity of breast cancer in germline PV carriers. Research Sponsor: None.

10511 Clinical Science Symposium

Cancer risk of pathogenic germline variants among 164,774 adult cancers.

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Background: Pathogenic germline variants (PGV) in cancer-predisposition genes influence the development of many cancer types but our understanding of cancer risks in PGV carriers remains underexplored. This study aims to further characterize the spectrum of cancers associated with PGVs and factors contributing to the development of multiple primary cancers among PGV carriers. **Methods:** A case-control analysis of 61,453 cancer cases and 366,709 controls in the UK Biobank (UKBB) was performed to test for the associations between risks of 43 solid tumor types and PGVs in 237 cancer predisposition genes. We evaluated each association according to the ClinGen Gene-Disease Validity framework and categorized those with moderate or less evidence as novel. An independent validation cohort of 103,321 cases 340,786 controls from All of Us, Mass General Brigham Biobank, TCGA, Memorial Sloan Kettering IMPACT, and a case-control study of ovarian cancer was used to replicate novel associations. **Results:** We identified 51 novel associations between solid tumor development and PGVs in the UKBB. Out of these, 32 were also significantly associated ($p<0.05$) in our validation cohorts (Table 1). Among PGV carriers in the UKBB, 16% had one primary malignancy and 2% had two or more. Across most PGV carriers, we observed higher risks of multiple primary cancers compared to single primary cancers. Using cox proportional hazards models, we found that PGV carriers with a personal history of cancer showed a higher hazard ratio of second cancer compared to healthy controls, particularly among those diagnosed with the first cancer earlier in life. The association between PGVs and second cancer remained significant in case-only analysis limited to cancer survivors and adjusted for primary tumor type suggesting this was not explained by shared risk factors. **Conclusions:** These findings expand our understanding of spectrum of cancer risks associated with predisposition genes and highlight that PGV carriers are at high risk of developing multiple primary cancers. In addition to family history, personal history of cancer should be considered for tailored cancer screening in genetically predisposed individuals. Research Sponsor: None.

Novel associations between PGV genes and selected cancers. Shown are the odds ratio estimates from the meta-analysis of replication cohorts.

Cancer	Genes Odds ratio (95% CI)				
Breast	*BAP1* 4.68 (2.13-10.25)	*BRIP1* 1.63 (1.18-2.26)	*LZTR1* 2.01 (1.56-2.6)		
Colorectal	*ATM* 1.43 (1.07-1.93)	*BARD1* 2.33 (1.28-4.26)	*BRCA1* 1.69 (1.2-2.37)	*BRCA2* 1.69 (1.27-2.25)	*FLCN* 2.6 (1.17-5.74)
Melanoma	*BLM* 1.68 (1.05-2.71)	*BRCA1* 2.15 (1.29-3.58)			
Lung	*BRCA2* 3.16 (2.36-4.23)	*NBN* 1.94 (1.07-3.53)			
Endometrial	*BRCA1* 8.05 (4.83-13.4)	*BRCA2* 2.32 (1.19-4.54)	*MSH3* 2.25 (1.07-4.72)		
Urinary	*ATM* 1.71 (1.21-2.44)				
Renal	*MITF p.E318K* 1.85 (1.16-2.97)	*WRN* 2.71 (1.39-5.29)			
Head and neck	*CDKN2A* 6.22 (3.31-11.7)	*FANCM* 2.2 (1.38-3.52)			
Ovary	*DDX41* 4.56 (1.56-13.36)	*PALB2* 3.33 (1.98-5.61)			

10512 Rapid Oral Abstract Session

Interactions between polygenic variants and clinical factors as predictors of breast cancer risk in the UK Biobank.

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Background: Polygenic risk scores (PRSs) combine information from single-nucleotide polymorphisms (SNPs) across the genome to explain substantial genetic breast cancer (BC) susceptibility. Previous studies have demonstrated that a multiple-ancestry PRS (MA-385) based on 56 ancestry-informative and 329 BC-associated SNPs is accurate for diverse populations and ranks among the most important known factors affecting the risk of BC development. However, medical guidelines call for more evidence before endorsing the clinical use of PRS, including studies to evaluate possible interactions of SNPs with environmental and hormonal risk factors. Here, we use longitudinal outcomes from the UK Biobank (UKB) to explore interactions of MA-385 and the five most informative individual BC-associated SNPs with the widely used Tyrer-Cuzick (TC) risk model and individual TC risk factors. **Methods:** The study cohort included 197,509 female UKB participants with no history of cancer at the time of study enrollment. We used Cox proportional hazards models to test associations of MA-385, individual BC SNPs, TC, and individual TC risk factors with BC outcomes. Effect modification of MA-385 and individual SNPs by clinical risk factors was evaluated by including interaction terms in the models. All models were adjusted for age at UKB enrollment and 10 principal components. Hazard ratios (HRs) and 95% confidence intervals (CIs) are reported per standard deviation, and significance tests were performed using two-sided p-values based on likelihood-ratio test statistics. **Results:** After a median follow-up of 11.8 years, 7,419 (3.8%) participants were diagnosed with BC.In a model including both MA-385 and TC, MA-385 was a significantly better predictor of BC development (HR = 1.56; 95% CI 1.53-1.60, $p = 3.2 \times 10^{-329}$) over the TC model (HR = 1.21; 95% CI 1.18-1.23; $p = 5.4 \times 10^{-69}$). We found no evidence of interaction between MA-385 and TC ($p = 0.31$), nor between individual SNPs and TC. After Bonferroni adjustment for multiple testing (102 tests), we found no evidence of interaction between MA-385 or individual SNPs with clinical TC factors. The strongest evidence for interaction was found between a BC SNP on chromosome 2 (rs13387042) and age at UKB enrollment (unadjusted $p = 0.002$; Bonferroni adjusted $p = 0.23$). **Conclusions:** In a longitudinal analysis of UKB, MA-385 was a highly significant predictor of BC risk and substantially improved prediction over TC. In contrast, interactions of MA-385, and individual BC SNPs, with TC and individual clinical factors in the TC model were not statistically significant. Clinical TC factors have minimal, if any, impact on the strength of the association between MA-385 and BC. These results may help to alleviate concerns expressed in guidelines that SNPs interact with environmental or hormonal risk factors. Research Sponsor: Myriad Genetics.

10513 Rapid Oral Abstract Session

Association of an ancestry-specific variant near the *ESR1* gene with cancer risk and breast density in women of self-reported Hispanic ancestry.

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Background: A single-nucleotide polymorphism (SNP), rs140068132, located in the 6q25 region near the *ESR1* gene, is common in self-reported Hispanic women but rare or absent in other populations. Previous studies have shown that rs140068132 is associated with a significantly reduced risk of breast cancer (BC) and may be particularly protective against triple-negative BC (TNBC). Further research suggests that rs140068132 may be linked to lower breast density. However, existing studies have been small, yielding imprecise estimates, and potential associations with cancers beyond BC remain unknown. **Methods:** We examined associations of rs140068132 with BC, TNBC, ovarian cancer (OC), endometrial cancer (EC), and BI-RADS breast density in a consecutive cohort of self-reported Hispanic women referred for hereditary cancer testing with a multigene panel. Cancer associations of rs140068132 were estimated as odds ratios (ORs), with 95% confidence intervals (CIs), from multivariable logistic regression models adjusted for personal/family cancer history, genetic ancestry, and age. We used Fisher's Exact Test to determine whether homozygous rs140068132 carriers had lower BI-RADS breast density than heterozygous or non-carriers. P-values are reported as two-sided. **Results:** Among 55,463 Hispanic women, 9,304 (16.8%) were affected by BC, 998 (1.8%) by TNBC, 1,520 (2.7%) by OC, and 1,616 (2.9%) by EC. 2,053 women were unaffected and had breast density assessment. 9,665 (17.4%) women were heterozygous for rs140068132, and 629 (1.1%) were homozygous. Consistent with previous studies, we found a highly significant protective effect per allele of rs140068132 for overall BC (OR 0.64; 95% CI 0.60-0.69; $p = 6.1 \times 10^{-37}$) and TNBC (OR 0.53; 95% CI 0.44-0.64; $p = 7.4 \times 10^{-11}$). This finding translates to an overall BC risk reduction of 1.6-fold for heterozygous and 2.4-fold for homozygous carriers compared to non-carriers. TNBC risk was reduced by 1.9-fold for heterozygous and 3.6-fold for homozygous carriers compared to non-carriers. Homozygous rs140068132 carriers were more than 3 times less likely to have high (heterogeneously or extremely dense) breast density compared to heterozygous or non-carriers (OR 3.30; 95% CI 1.22-10.35; $p = 0.0095$). rs140068132 was not associated with risk of OC (OR 0.98; 95% CI 0.86-1.11; $p = 0.77$) or EC (OR 1.08; 95% CI 0.96-1.21; $p = 0.23$). **Conclusions:** We present findings from the largest study to date on cancer risks associated with rs140068132. Our research indicates that rs140068132 does not substantially affect the risk of OC or EC. We confirmed previous reports of significantly reduced risk of BC, particularly TNBC, among carriers of rs140068132, and we provided precise estimates of the ORs per allele. These findings have important implications for genetic risk assessment and may guide personalized BC prevention and treatment strategies. Research Sponsor: Myriad Genetics.

10514 Rapid Oral Abstract Session

Association between allostatic load and breast radiomic features among diverse women undergoing screening mammography.

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Background: Allostatic load (AL), an indicator of chronic physiologic stress, is associated with increased breast cancer incidence and all-cause mortality in patients diagnosed with breast cancer. Mammographic density (MD) is a well-established breast cancer risk factor. We developed a deep learning, specifically convolutional neural network (CNN)-based, mammographic evaluation, which is a more accurate predictor of breast cancer risk than MD, particularly among Black and Hispanic women. We evaluated the relationship between AL and CNN risk score in a cohort of racially/ethnically diverse women undergoing breast cancer screening. **Methods:** We conducted a retrospective cohort study of women aged 35-74 years, without a personal history of breast cancer, with available clinical data to calculate AL score and mammograms for CNN analysis (output = risk score from 0-1), who underwent screening mammography at Columbia University Irving Medical Center (CUIMC) in New York, NY from 2014-2018. We extracted data on demographics, MD (BIRADS A-D), laboratory values, vital signs, and body mass index (BMI) from the electronic health record (EHR). We calculated AL score using biometrics from 4 physiologic systems: cardiovascular (heart rate, systolic and diastolic blood pressure), metabolic (BMI, blood glucose, albumin, alkaline phosphatase), renal (creatinine, blood urea nitrogen), and immune (white blood cell count). AL scores ranged from 0 to 10, and patients received one point for each lab value out of the reference range. High AL was defined as an AL score above the median for the overall cohort. Multivariable logistic regression analyses were conducted to evaluate the association between high AL and demographic factors, breast cancer risk factors, and CNN risk score. **Results:** Among 9,798 evaluable women, mean age was 57.0 (standard deviation [SD], 9.5), including 24.7% non-Hispanic White, 9.6% non-Hispanic Black, 36.1% Hispanic, and 4.0% Asian women. Median AL score was 3. In multivariable analyses, high AL was associated with older age (odds ratio [OR]=1.03, 95% confidence interval [CI]=1.02-1.03). Compared to non-Hispanic White women, Black and Hispanic women had increased odds of having high AL (OR= 2.62, 95% CI = 2.23-3.08 and OR = 2.12, 95% CI =1.90-2.37, respectively). MD was inversely associated with high AL, and there was no significant association between CNN risk score and AL. **Conclusions:** In this cohort of diverse women undergoing screening mammography, we observed a significant association between high AL and older age and Black and Hispanic race/ethnicity. However, MD was inversely associated with high AL, likely due to higher BMI, and CNN risk score was not associated with AL. Future studies should evaluate the association between novel breast radiomic features and genetic and hormonal biomarkers of breast cancer risk. Research Sponsor: National Cancer Institute; R01CA293927; National Cancer Institute; P30CA013696; National Center for Advancing Translational Sciences; KL2TR001874; Susan G. Komen Foundation; Susan G. Komen Career Catalyst Research Award.

10515 Rapid Oral Abstract Session

Disparities in cancer screening and preventive care access among LGBTQ+ populations: A cross-sectional analysis.

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Background: The incidence and outcomes of certain health conditions, particularly cancers, can vary significantly across different sexual orientation groups, often influenced by disparities in healthcare access and preventive service utilization. Previous research indicates that sexual minorities may face barriers to appropriate healthcare, increasing the importance of understanding how these disparities manifest in preventive health behaviors, such as cancer screenings. This study aims to identify these differences in preventive care among different sexual orientation groups. **Methods:** The study utilized the Behavioral Risk Factor Surveillance System (BRFSS), an annual nationwide survey collecting health-related data from approximately 400,000 U.S. adults, as the primary data source. The data was cleaned for missing cases. The study population included respondents who completed the optional Sexual Orientation and Gender Identity (SOGI) module, while excluding those with missing data on key variables such as sexual orientation, gender identity, and cancer screening. Descriptive statistics were generated from the database to characterize the study population and examine distributions across different demographic and health behavior variables. Statistical analyses were performed to assess associations between sexual orientation and various cancer screening behaviors. **Results:** The final analysis included 278,519 cases, with demographic characteristics presented in Table. Disparities in educational attainment were observed across sexual orientation groups, with straight individuals representing the largest group across all education levels. A significant association was found between sexual orientation and mammogram screening (p=0.001; Fisher's Exact Test), with higher screening rates among straight respondents (851 yes vs. 144 no) compared to gay, bisexual, and other groups. No significant associations were found for cervical cancer screening (p=0.818) or sigmoidoscopy utilization (p=0.818). Mammogram screening varies by sexual orientation, while other preventive practices show uniform utilization across groups. **Conclusions:** The findings highlight significant disparities in mammogram screening among LGBTQ+ individuals, with no such gaps in cervical cancer screening or sigmoidoscopy. These results call for targeted interventions to enhance mammogram uptake in LGBTQ+ communities. Research Sponsor: None.

Distribution of sexual orientation groups among different races.

Race/Ethnicity	Gay	Straight (Not Gay)	Bisexual	Something Else	Total
White only, Non-Hispanic	4026	191801	6340	3020	205187
Black only, Non-Hispanic	358	19582	571	358	20869
Other race only, Non-Hispanic	337	15483	530	394	16744
Multiracial, Non-Hispanic	175	5978	458	204	6815
Hispanic	604	22044	1028	829	24505
Don't know/Not sure/Refused	78	4054	98	169	4399
Total	5578	258942	9025	4974	278519

10516 Rapid Oral Abstract Session

Risk patterns for second primary malignancies among human papillomavirus (HPV)–associated first primary cancer survivors in the United States.

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Background: Previous studies have shown an increased risk of second primary malignancies (SPMs) among human papillomavirus (HPV)-associated first primary cancer (FPC) survivors; however, this has not been comprehensively examined by cancer site and patient's sex. We utilized a large population-based database to examine disparities in SPM risk by site of HPV-associated first and second cancers. **Methods:** From 17 United States population-based Surveillance, Epidemiology and End Results (SEER) program cancer registry areas, we identified 124,802 ≥12-month survivors of HPV-associated invasive FPCs (including oropharynx, anus, vulva, vagina, cervix and penis) diagnosed between 2000-2021. Standardized incidence ratios (SIRs) and accompanying 95% confidence intervals (CIs) quantified SPM risk by cancer site compared with the general population. Excess SPM risks were calculated based on SIRs and excess absolute risks (EARs) per 10,000 person-years at risk (PYR). **Results:** Overall, we observed 13,431 SPMs after HPV-associated FPCs representing a 1.6-fold significantly increased risk (95% Confidence Interval [CI] = 1.61-1.67) compared to the general population and an excess of 68 cases per 10,000 PYR. All index HPV-associated FPCs showed statistically significant increased SPM risk compared to the general population. SIRs varied significantly by FPC site with female survivors of vulvar, oropharyngeal and vaginal cancers resulting in higher SPM risk (SIR_{vulva}= 2.46; CI = 2.33-2.58; EAR = 166, $SIR_{oropharynx-female}$= 2.02; CI = 1.90-2.14; EAR = 121 and SIR_{vagina}= 1.81; CI = 1.56-2.08; EAR = 96) compared to other sites ($p < 0.001$). Analyses by patient's sex revealed significantly increased SPM risk among female survivors of oropharyngeal cancer compared to the males ($SIR_{oropharynx-male}$= 1.66; CI = 1.61-1.70; $p < 0.01$) but not after anal cancer ($p > 0.05$). Results from SPM site specific analyses revealed significantly higher SIRs for second solid cancers compared to hematological malignancies ($SIR_{solidSPM}$= 1.69; CI = 1.66-1.72; $SIR_{hematSPM}$= 1.03; CI = 0.96-1.11; $p < 0.001$). Among the solid SPMs, the risk of developing a HPV-associated SPM was significantly higher than that of developing a non-HPV-associated SPM ($SIR_{HPV-SPM}$= 8.89; CI = 8.59-9.21 versus $SIR_{non-HPV-SPM}$= 1.33; CI = 1.30-1.35; p-heterogeneity < 0.001); and the difference was more pronounced in females than the males. Strikingly increased SIRs were observed for penile (SIR = 17.61), vulvar (SIR = 27.83) and vaginal (SIR = 32.09) SPMs. **Conclusions:** Using a large-scale population-based data, we observed remarkable similarity in SPM risk by FPC site suggesting a potential role of shared HPV-associated etiology between the two malignancies. SPMs have emerged as an important challenge for cancer survivors, therefore, further research to understand drivers of the observed patterns is warranted. Research Sponsor: None.

10517 Rapid Oral Abstract Session

The development and validation of a simulation model–based calculation engine to support individualized physical activity prescriptions for breast cancer survivors.

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Background: Current cancer physical activity guidelines recommend clinicians offer individualized 'physical activity prescriptions' to cancer survivors. However, there are limited data to support individualized physical activity prescriptions for breast cancer survivors in clinical settings. We aimed to develop a simulation model-based 'calculation engine' for a clinical decision tool that could generate individualized breast cancer outcomes associated with physical activity considering the individual characteristics of breast cancer survivors. **Methods:** We adapted an established and validated simulation model developed within the Cancer Intervention and Surveillance Modeling Network (CISNET) to estimate breast cancer-specific mortality, all-cause mortality, and life-years gained with post-treatment physical activity for women aged 50-75 years at diagnosis with stage I-III breast cancer. Model inputs were derived from clinical trials, cohort studies, national survey, and registry data. Breast outcomes were generated for 41,472 unique subgroups based on all possible combinations of age, hormone status, HER2 status, stage, tumor size, grade, body mass index, surgery, and treatment. External validation was conducted using an independent data source. We summarized 10-year breast cancer and all-cause mortality rates for varying combinations of weekly aerobic (e.g., 2.5-5.0 hours/week) and muscle-strengthening (e.g., ≥2 days/week) activity. **Results:** Overall, the 10-year breast cancer-specific and all-cause survival rates for stages I-III were 89.1% and 83.2%. These results varied by individual characteristics and physical activity levels. For example, in a 65-69-year-old-woman diagnosed with stage I, hormone receptor-positive, HER2-negative breast cancer, and a body mass index of ≥30kg/m2, the 10-year breast cancer-specific and all-cause survival rates for 0-0.5 hours/week of physical activity were 87.1% and 80.1%, respectively. If the woman was to increase aerobic activity to 0.5-2.5 hours/week, 10-year breast cancer survival increased to 88.5%, and all-cause survival increased to 81.1%. Meeting physical activity guidelines (i.e., 2.5-5.0 hours/week of moderate-intensity aerobic activity; and ≥2-days/week of muscle strengthening activity) was associated with increases in 10-year breast cancer and all-cause survival rates to 93.0% and 82.9%, respectively. The model closely replicated observed rates in independent data. **Conclusions:** These data provide a calculation engine for a clinical decision tool to support individualized physical activity prescriptions and discussions for breast cancer survivors. Research Sponsor: U.S. National Institutes of Health.

10518 Rapid Oral Abstract Session

Dietary polyphenols and the risk of prostate cancer in the prospective Southern Community Cohort Study.

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Background: In the US, prostate cancer incidence is highest among underrepresented and underserved populations, including Black and low-income populations. Polyphenols, common in plant-based foods, are biologically active compounds previously associated with decreased risk of prostate cancer. Objectives: We examined intake of total polyphenols, classes, and subclasses with risk of prostate cancer in the Southern Community Cohort Study (SCCS), a large prospective cohort study established in 2002-2009 to study the causes of racial and income cancer disparities in 12 southern states. **Methods:** Polyphenol intakes (mg/day) derived from food frequency questionnaires were grouped into quintiles. Prostate cancer diagnosis was obtained from state cancer registries and death records. Cox proportional hazard models were used to estimate hazard ratios and 95% confidence intervals to determine associations between polyphenol intakes and prostate cancer risk. Analyses included 29,325 participants, including 1,145 incident prostate cancer cases. **Results:** Higher total polyphenol intake was associated with a modestly decreased risk of prostate cancer compared to the lowest intake except in the highest quintile. 8 subclasses of polyphenols derived primarily from tea, fruit juices, and red wine were associated with a statistically significant decreased risk of prostate cancer comparing the highest to lowest quintiles (e.g. HR 0.58; 0.47-0.72, $p_{trend} < 0.001$ for flavanols). Most associations were similar between Black and White individuals, but flavonoids (HR 0.42; 0.28-0.63, p = 0.0005) and hydroxybenzoic acids (HR 0.45; 0.30-0.67, p = 0.0001) were statistically significant only among White participants. In stratified analyses by smoking status and household income, only flavones were associated with a statistically decreased risk of prostate cancer, specifically among current smokers and participants with an income < $15000. **Conclusions:** Polyphenol intakes were associated with decreased prostate cancer risk among both Black and White participants. Further studies should evaluate whether polyphenol intake is associated with decreased risk for later stages of prostate cancers. Research Sponsor: Meharry Vanderbilt Tennessee Cancer Partnership; 54CA163072; National Cancer Institute; U01CA202979.

10519 Rapid Oral Abstract Session

Escalating impact of alcohol-related cancer mortality in the US: A call for action.

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Background: Alcohol consumption is known to be a significant risk factor for cancer. This year, the US Surgeon General recommended adding cancer risk warning labels to alcoholic beverages, emphasizing the need for increased awareness. However, data on its impact on individual cancer mortality remains limited. This study aims to evaluate trends in alcohol-associated cancer mortality in the US utilizing Global Burden of Disease (GBD) database. **Methods:** We utilized data from the GBD to analyze absolute and proportional Age-Standardized Mortality Rates (ASMR) attributable to heavy alcohol use—defined as consumption exceeding the theoretical minimum risk exposure level—in the US from 1990 to 2021. We evaluated ASMR for all cancers combined, followed by specific cancers, including esophageal, liver, laryngeal, breast, colorectal, lip-oral cavity, nasopharyngeal, and other (oro/hypo) pharyngeal. Results were reported per 100,000 population and stratified by gender, state, and age groups (20–54, 55+). Estimated Annual Percentage Change (EAPC) was calculated using JoinPoint regression analysis. **Results:** Alcohol-associated cancer deaths in the U.S. doubled from 1990 (11,896) to 2021 (23,207). The 55+ age group showed a significantly higher ASMR than the 20-54 age group (Table 1). Proportional alcohol-associated ASMR increased for all cancers and individual cancers across both age groups and genders, except for liver cancer in 55+ age group. In 2021, for 55+ age, liver cancer had the highest alcohol-associated proportional ASMR in males (38.5%), followed by nasopharyngeal cancer (31.8%), while in females, nasopharyngeal (18.9%) and oro/hypopharyngeal cancers (18.4%) ranked highest. In 20-54 age, lip-oral cavity cancer had the highest alcohol-associated proportional ASMR for both genders (m:41.8%; f: 26.9%). In 2021, the District of Columbia had the highest alcohol-associated all-cancer ASMR (m:10.0; f:3.6) followed by Texas (7.5) for males and New Hampshire for females (2.9). In contrast, Utah had the lowest (m:3.5; f:1.4). On evaluating trends, a constant increase was observed in alcohol-associated ASMR for 55+ age group for males (EAPC 0.5, 2008-2021) and females (EAPC 1.1, 2006-2021). **Conclusions:** Alcohol-associated cancer mortality has significantly increased in the U.S. over the past three decades, with a disproportionate burden observed in males and individuals aged 55 and older. Our findings highlight the critical need for targeted prevention efforts, public health policies, and increased awareness to address the rising impact of alcohol consumption on cancer-related mortality across different demographic groups and regions. Research Sponsor: None.

Alcohol associated-all cancer ASMR.

Age (n=Absolute, %= Proportional)	Male - 1990	Male - 2021	Female - 1990	Female -2021
Overall	5.7 (0.03%)	6.2 (0.04%)	2.6 (0.02%)	2.2 (0.02%)
20-54	2.2 (4.3%)	2.4 (6.8%)	1.8 (3.3%)	1.4 (3.6%)
55+	27.3 (2.4%)	31.7 (4.3%)	10.7 (1.5%)	10.4 (1.9%)

Association between wildfire-dominated $PM_{2.5}$ exposure and non-small cell lung cancer survival in California.

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Background: Wildfire emissions include hazardous constituents, including fine particulate matter ≤2.5 μm in diameter ($PM_{2.5}$). $PM_{2.5}$ exposure is associated with increased risk of lung cancer. However, the impact of wildfire-dominated $PM_{2.5}$ exposure on survival after non-small cell lung cancer (NSCLC) diagnosis is unknown. **Methods:** We identified all patients diagnosed with NSCLC in the California Cancer Registry between 2017-2020. Daily $PM_{2.5}$ was estimated over the same period by random forest regression fusing official air quality monitoring, satellite observations, meteorological modeling, predictive smoke modeling, and low-cost sensors, producing a consensus estimate of $PM_{2.5}$ over a 1-square kilometer grid across California. We quantified $PM_{2.5}$ exposure by averaging daily $PM_{2.5}$ in the 12 months after NSCLC diagnosis based on home address at time of diagnosis. Adjusted cox-proportional hazards regression was used to estimate the hazard ratio (HR) for cancer-related death associated with $PM_{2.5}$ exposure following NSCLC diagnosis overall and stratified by smoking status and stage at diagnosis. We adjusted for patient demographics, comorbidity, body mass index, rural residence, and COVID-19 time-period. **Results:** Among 18,585 patients with NSCLC, the mean age was 70.4 years (standard deviation [SD] 10.5) and the mean $PM_{2.5}$ concentration was 9.8 $\mu g/m^3$ (SD 2.0). Higher mean daily $PM_{2.5}$ in the 12 months after NSCLC diagnosis was associated with 20% increased hazard of cancer-related death (Table). There was a 55% increase in hazard of cancer-related death associated with $PM_{2.5}$ among patients with stage IV disease and no prior smoking use (Table). Notably, patients with Stage IV disease with former or current tobacco use who received immunotherapy had improved cancer-specific survival with more days of high $PM_{2.5}$ concentration (i.e., days with $PM_{2.5}$ ≥55 $\mu g/m^3$), HR=0.79, 95% confidence interval 0.66-0.94. **Conclusions:** In this large population-based NSCLC cohort, wildfire-dominated $PM_{2.5}$ exposure after diagnosis was independently associated with increased risk of cancer-related death. The improved survival among patients with Stage IV disease with a smoking history treated with immunotherapy warrants additional investigation. As the size and frequency of wildfires increases, our findings have important public health and clinical implications for patients with NSCLC. Research Sponsor: National Cancer Institute; 5K12CA138464; National Cancer Institute; P30CA093373; California Department of Public Health; Centers for Disease Control and Prevention's (CDC) National Program of Cancer Registries; 1NU58DP007156.

Hazard ratio (HR) for cancer-related death associated with $PM_{2.5}$ concentration after NSCLC diagnosis.

	Number of Patients	Number of Cancer-Related Deaths	Cancer-Related Death HR (95% confidence interval)
Total cohort	18,585	6,097	1.20 (1.05-1.37)
No prior tobacco use	5,059	1,565	1.36 (1.04-1.78)
Former or current tobacco use	13,526	4,532	1.17 (1.01-1.36)
Stage IV, no prior tobacco use	2,198	1,079	1.55 (1.12-2.16)
Stage IV, former or current tobacco use	3,783	2,097	1.09 (0.87-1.36)

10521 Poster Session

Large-scale clinical validation of a blood-based, multi-cancer, early detection test across different sample types, platforms, and populations.

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Background: Many established cancer screening or diagnostic methods often face challenges in low- and middle-income countries due to high cost, complexity, and reliance on extensive medical infrastructure. OncoSeek, a multi-cancer early detection (MCED) test developed with a panel of protein tumor markers (PTMs), is both affordable (reagent cost ~$20) and accessible, requiring only a blood draw. We evaluated its performance of multi-cancer detection and diagnosis in large-scale clinical studies. **Methods:** 15,122 participants (3,029 cancer vs 12,093 non-cancer) were divided into one training and six validation cohorts according to the different sites in three countries (Brazil, China, and United States). One tube of blood (plasma or serum) from each participant was collected and quantified using a panel of 7 PTMs (AFP, CA125, CA15-3, CA19-9, CA72-4, CEA, and CYFRA 21-1) through four common immunoassay platforms (Roche, Abbott, Luminex, and ELISA) in both retrospective and prospective settings. OncoSeek, utilizing artificial intelligence (AI) algorithm, was developed to differentiate cancer cases from non-cancer cases based on 7 PTM concentrations and clinical information including age and sex. It also predicted the potential affected tissue of origin (TOO). Furthermore, the fifth validation cohort, comprising 1849 patients (1031 cancer vs 818 non-cancer), was leveraged to broaden OncoSeek's application for cancer diagnosis. This cohort specifically targeted symptomatic patients, requiring further confirmation through biopsy or surgery. **Results:** The conventional clinical method, using a single threshold for each PTM, lead to accumulate the false positive rate with the growing number of PTMs. However, OncoSeek, empowered by AI, significantly reduced the false positive rate, elevating specificity from 54.3% to 93.0% and achieving an overall sensitivity of 51.7% in the training cohort. Performance remained robust (58.4% sensitivity and 92.0% specificity) across all seven cohorts, with area under the curve (AUC) values ranging from 0.744 to 0.912. The overall accuracy of TOO prediction was 65.4%. In the fifth cohort with symptomatic patients, OncoSeek achieved a 0.845 AUC for cancer diagnosis at 73.1% sensitivity and 90.6% specificity. **Conclusions:** OncoSeek significantly outperforms the conventional clinical method, showcasing its robust performance across various races, sample types, and platforms. The extensive retrospective assessment of OncoSeek in a symptomatic population demonstrates the feasibility of this MECD test in aiding clinicians for decision-making. Its accuracy of TOO facilitates the diagnostic workup. Research Sponsor: None.

10522 Poster Session

Multi-cancer risk prediction in asymptomatic adults using urinary glycosaminoglycan profiling.

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Background: Current screening guidelines are based on established risk factors such as age and tobacco use. Currently, no biomarker is routinely used to predict cancer risk. We investigated urinary glycosaminoglycan profiles - aggregated in a "GAGome score" - for multi-cancer risk prediction. **Methods:** In this population-based case-cohort study, we included adults from the Lifelines Cohort Study, Netherlands presumed healthy at baseline. All cases who self-reported any-type cancer or died by the 5-year study visit were confirmed in the Dutch Cancer Registry and matched 1:5 to randomly selected controls. We developed a multivariable Cox proportional hazard regression to estimate the hazard ratio (HR) for incident cancer given the GAGome score and adjusted for established risk factors. Model improvement was assessed using the likelihood ratio test. Then, we used 5-year risk predictions to stratify subjects in four groups: "Low" (<0.15%), "High" (>2%), and "Very high" (>8.5%) risk, or "Intermediate" if otherwise (reference group). Using sampling weights, we estimated the 5-year observed risk in each group, as well as the potentially screen-detectable rate and false positive rate across population and cancer subsets. **Results:** We included 5436 adults (median age = 49 years, 58% females) of whom 827 were diagnosed with incident cancer within 5 years. A standard deviation increase in the GAGome score had an HR = 1.66 (95% CI: 1.62–1.70) for incident cancer – ranging 1.27 for endometrial cancer to 3.4 for cancer of unknown primary - explaining 36% of the variance ($p < 0.0001$). The observed 5-year risk for "Low", "Intermediate", "High", and "Very high GAGome risk" were 0.18%, 2.3%, 7.6%, and 32%, respectively. A "High GAGome risk" or higher prediction would detect 54% of incident cancers (including 54% of in situ carcinomas) with a 17% false positive rate. **Conclusions:** Implementing urine GAGomes as a strategy for risk-stratified targeted screening could pave the way for personalized surveillance approaches and potentially identify a broader range of adults with increased risk of cancer that are not being captured by current screening programs. Research Sponsor: Elypta AB.

10523 Poster Session

The effect of metformin exposure on colorectal cancer incidence according to tumor sidedness.

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Background: Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality. Tumor sidedness influences treatment decisions due to differences in tumor biology and response to therapies. Metformin, a widely used anti-diabetic medication, has been suggested to reduce CRC risk. This study aims to evaluate the relationship between metformin exposure and CRC risk based on tumor-sidedness. **Methods:** A nested case-control study was conducted using the Veterans Administration (VA) database (1999–2020). CRC cases were identified and classified by tumor sidedness. Controls were selected via incidence-density sampling and matched on age, sex, index date, and first VA encounter. Exposure of interest was cumulative metformin use prior to the index-date. Conditional logistic regression was used to estimate adjusted odds-ratios (ORs) and 95% confidence intervals (CIs), adjusted for race, BMI, smoking, aspirin, statins, and other anti-diabetic medications. **Results:** The study included 31,078 patients treated with metformin and 310,621 matched controls. Metformin exposure did not influence the incidence of right-sided CRC with an adjusted OR of 1.03 (95%CI 0.92 – 1.16) and 0.96 (95%CI 0.83 – 1.12) with metformin exposure of 1-3 years and 3-5 years, respectively. In contrast, in patients with left-sided CRC metformin use was associated with a decrease in CRC incidence, with an adjusted OR of 0.90 (95%CI 0.82 – 0.98) and 0.87 (95%CI 0.77 – 0.98) with metformin exposure of 1-3 years and 3-5 years, respectively. **Conclusions:** Metformin was associated with a decrease in the incidence of left-sided CRC incidence. These results suggest the influence of tumor sidedness, not only on treatment effect, but on prevention strategies as well. Research Sponsor: None.

10524 Poster Session

Development and validation of a model to predict future breast cancer risk after ER-positive and HER2-negative breast cancer.

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Background: Request for bilateral mastectomy after a unilateral breast cancer (BC) diagnosis is increasing. In many cases the benefit of bilateral mastectomy is likely to be small and offset by substantial risks of morbidity, financial toxicity and overburdening of healthcare systems. It is difficult to accurately determine personal risk of developing a future BC. Existing risk prediction models only predict risk for contralateral BC. Australian consumers identified an unmet need for a model that estimates risk of developing BC in any residual breast tissue (ipsi- or contra-laterally); to help women diagnosed with unilateral BC make informed decisions about bilateral mastectomy. **Methods:** Data from 1,162 female BC cases participating in two Australian cohort studies were used to develop a model to predict risk of BC for women who developed a 1st invasive ER positive, HER2 negative BC after cohort entry or within 2 years prior to cohort entry. Women with a germline pathogenic variant in a BC predisposition gene, and those who received neoadjuvant systemic therapy were excluded. 187 (88 ipsilateral, 96 contralateral, 3 unknown laterality) BC events (161 invasive and 26 DCIS) occurred over a median follow-up of 13.8 years. Flexible parametric survival analysis was used, with time since diagnosis as the time scale, and death due to any cause considered as a competing event. Potential predictors of future BC risk were investigated, including age at 1st BC, age at 1st birth, parity, breastfeeding duration, menopausal hormone therapy use, BMI, number of 1st-degree relatives with BC, BC polygenic risk score (PRS-313), contralateral mammographic density, surgery (breast conservation vs unilateral mastectomy), tumor grade and size, number of positive axillary nodes, associated LCIS, and use of adjuvant chemotherapy or radiation. Retained in the final risk prediction algorithm (all $P < 0.05$) were age at diagnosis of 1st BC, surgery type, radiation therapy, family history, and PRS-313. For external validation of the model, data from 3,136 cases (eligibility criteria as per the training set) with 181 subsequent BC events participating in the international Breast Cancer Association Consortium were used. Calibration and a time-dependent area under the curve (AUC) at 10 years were assessed to determine model performance. Sensitivity analysis excluding PRS-313 was also performed (as it is usually not available in clinical practice). **Results:** Discriminatory ability at 10 years was AUC = 0.66 (95% CI 0.62-0.70) or 0.65 (95% CI 0.61-0.69) if PRS-313 was excluded. The model was well calibrated; expected (176 cases) to observed (181 cases) ratio = 0.97 (95% CI 0.84-1.13). **Conclusions:** This model provides valid estimates of 10-year BC risk after a 1st ER-positive HER2-negative BC and may be useful in collaborative decision-making between patients and their surgeons when considering bilateral mastectomy. Research Sponsor: National Breast Cancer Foundation (Australia); IIRS-20-029; National Health and Medical Research Council (Australia); 1195294.

10525 Poster Session

Colonoscopy quality indicators for colorectal cancer precursors: Sessile serrated lesion and adenoma detection rates from a large clinical study of a blood-based test for CRC screening.

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Background: Colorectal cancer (CRC) is the second leading cause of cancer-related deaths globally. Colonoscopy can reduce mortality by removing precancerous lesions or detecting cancer at an earlier, more treatable stage, with the adenoma detection rate (ADR) as the standard colonoscopy quality indicator. In 2024, the sessile serrated lesion detection rate (SSLDR) was introduced as a new multisociety colonoscopy quality indicator. Both quality indicators have associated performance targets, primarily based on benchmarking to colonoscopy registry data. Serrated lesions, which are precursors to 10-30% of CRC, are often missed due to their flat appearance, indistinct borders, and proximal locations. Published SSLDR data is limited, and to our knowledge, this is the first analysis of SSLDRs and ADRs in a large prospective, multicenter clinical study in an average-risk population. **Methods:** PREEMPT CRC, a clinical validation study of a blood-based test for CRC screening in adults aged 45-85, included 200 diverse U.S. sites. Based on thorough medical review of colonoscopy and pathology reports, SSLDRs and ADRs were calculated across 27,010 subjects that completed screening colonoscopy in the clinical validation. SSLDR and ADR were defined as the percentage of colonoscopies in which at least one SSL or adenoma was detected, respectively. Results were stratified by age and sex, and compared to established performance targets from colonoscopy quality guidelines. **Results:** The overall SSLDR in PREEMPT CRC was 7.2%, surpassing the newly recommended performance target of $\geq 6\%$. The overall ADR was 34.9%, aligning with the latest target of 35% overall (40% in males, 30% in females). The ADR increased significantly with age, from 26.9% in the 45-49 age group to 40.8% in the 75+ age group ($p < 0.001$). In contrast, the SSLDR remained consistent across age groups, with the 45-49 year age group (7.1%) similar to the overall SSLDR (7.2%) ($p = 0.789$). The ADR demonstrated a clear sex-dependence (41.9% in males, 29.4% in females, $p < 0.001$), while the SSLDR did not (7.4% in males, 7.1% in females, $p = 0.433$). **Conclusions:** The overall SSLDR and ADR in PREEMPT CRC were consistent with the updated colonoscopy quality guidelines, with the SSLDR exceeding the target, suggesting that the target could be updated from 6% to 7%. Our results underscore the age- and sex-independent risk of serrated lesions. Notably, even the SSLDR in the 45-49 year age group (7.1%, 6.2%-8.0%) exceeded the 6% performance target. Given the relatively high ADR of 26.9% observed among 45 to 49-year-olds, and the age-independence of the SSLDR, our findings highlight the importance of advocating for early CRC screening, especially in younger populations where screening adherence is generally poor. Clinical trial information: NCT04369053. Research Sponsor: None.

10526 Poster Session

Machine learning for cancer risk stratification: A bi-directional approach to screening.

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Background: Cancer screening programs are often limited by high costs, invasiveness, and potential false results. Machine learning (ML) applied to routine medical data could enable risk-stratified screening approaches. We developed ML models to predict 10-year cancer risk using data from routine periodic health examinations, aiming to identify both high and low-risk populations. **Methods:** We analyzed data from individuals who underwent routine health examinations at Rambam Medical Center (2002-2021), matched with the Israeli National Cancer Registry. After quality control, including removal of cases with previous tumors, we excluded cancers diagnosed less than 183 days after the visit to avoid prevalent cases. Using data from the initial visit only, we developed two XGBoost models for 10-year cancer risk: Model 1 (baseline) using only age and gender, and Model 2 incorporating 53 features including demographics, lifestyle factors (smoking, alcohol, physical activity), laboratory results (26 parameters including complete blood count, biochemistry, and lipids), medication categories (9 groups including statins, antihypertensives, antidiabetics), and medical history (7 disease categories). Models were trained on 75% of the data with cross-validation and evaluated on a 25% hold-out set. **Results:** Our cohort included 27,901 individuals (61% male, mean age 47±10 years), with 1,960 future incidents of cancer diagnosed at median follow-up of 8 years. Most common malignancies were prostate (21%), breast (19%), skin (15%), and colorectal (12%) cancers. For model development, we reduced the dataset to include only individuals with 10-year follow-up or cancer event within the 10-year window (N = 16,859, cancer cases = 1,268). Model 2 significantly outperformed Model 1 (AUC 0.799 vs 0.706, $p < 0.0001$) and demonstrated remarkable risk stratification. Against a population baseline risk of 7.3%, Model 2 identified: 1) a low-risk group (bottom 50%) with only 1.9% 10-year cancer risk; 2) an high risk group (90-99th percentile) with 25.1% risk (3.5-fold increase); and 3) a very high-risk group (top 1%) with 74.4% risk (10-fold increase). In comparison, the highest-risk group in Model 1 (top 1%) achieved only 20.0% risk. The most important predictive features were age, monocyte count, albumin, total bilirubin, and LDL cholesterol. **Conclusions:** ML analysis of routine health examination data can effectively stratify cancer risk, identifying both very low and exceptionally high-risk groups. This bi-directional stratification could enable more efficient screening strategies: reduce screening intervals or invasiveness in the large low-risk population, while intensifying screening in high-risk groups. Future studies should evaluate and validate these findings in different populations and study whether this approach can improve the efficiency and cost-effectiveness of cancer screening programs. Research Sponsor: ICRF - Israel Cancer Research Fund.

10527 Poster Session

Efficacy and toxicity of low-doses versus standard-dose enzalutamide in advanced prostate cancer: A real-world study with implications for cancer prevention/ interception.

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Background: Prostate cancer (PCa) is the most frequent cancer in males in the US and EU. Enzalutamide is effective in biochemically recurrent and advanced PCa but is associated with considerable adverse events (AEs) at standard doses (160 mg/day). In the ENACT trial, enzalutamide monotherapy reduced the risk of PCa progression compared to active surveillance (AS) in patients with intermediate/low-risk, but AEs were frequent (eg, 55% fatigue). Preliminary case reports suggest that low/intermediate doses (≤80 mg/day) retain efficacy while reducing toxicity. This study evaluates the efficacy and safety of low/intermediate dose vs standard-dose enzalutamide in advanced PCa in a real-world Italian cohort. **Methods:** This single-center, retrospective observational study included 140 assessable metastatic PCa patients treated with enzalutamide for castration resistant (80%) or sensitive (20%) PCa between August 1, 2014 and December 31, 2023. Patients were categorized based on the total dose (actual vs predicted) taken: low (L, ≤50%, n = 11), intermediate (I, > 50% and ≤80%, n = 16), and high (H, > 80%, n = 113). The primary endpoint was the 12 month progression-free survival (PFS) by restricted mean survival time to account for violation of proportional hazards assumption. Secondary endpoints included PSA response (decline ≥50% at 3 months), overall survival (OS) at 36 months and worsening of AEs of special interest (fatigue, neurological disorders, hypertension). PFS and OS were adjusted for ECOG performance status at baseline. **Results:** The three dose groups were not different at baseline on PSA, BMI, Gleason Score, age and castration resistance. The choice of L dose treatment at baseline was due to clinical judgment in 82% of cases (PS > 0 or age > 80), whereas the I dose was due to toxicity reduction after initial high dose in 63%. The median follow-up time was 13.6 months [IQR, 7.2 – 23.1]. There were no significant differences in PFS at 12 months on H vs I dose (10.4 vs 11.4 mo, $p = 0.09$) and H vs L dose (10.4 vs 9.2 mo, $p = 0.37$). There was no difference among dose groups in PSA response (70% vs 75% vs 60% on H, I, L, respectively). The use of I or L doses showed no evidence of adverse effects on OS at 36 months. The rate of fatigue worsening on H vs I vs L dose was 61.1%, 63.0% and 27.3% ($p = 0.03$ for H vs L). Worsening of neurological disorders and hypertension was 19.5%, 18.8% and 0% and 18.6%, 18.8% and 9.1% on H vs I vs L, respectively. **Conclusions:** In our real-life observational cohort, low/intermediate doses of enzalutamide show comparable efficacy relative to high dose while improving tolerability, indicating the need for further search of the optimal dose of this expensive drug. Moreover, our findings prompt a study of low-intermediate dose enzalutamide in the prevention/interception setting in patients with low/intermediate risk prostate cancer under AS. Research Sponsor: None.

10528 Poster Session

Growing burden of cancer and high body mass index in the United States from 1990-2021: A benchmarking cross-state analysis.

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Background: Cancer (CA) remains a major public health challenge and is the second leading cause of death and disability in the United States. Among the various modifiable risk factors, a high body mass index (h-BMI) significantly contributes to the burden of non-communicable diseases, including CA. **Methods:** This study is the first to estimate deaths and disability attributable to h-BMI for 12 different CA types across the USA, disaggregated by age, sex, year, and location, using the standardized Global Burden of Disease Study 2021 methodology from 1990–2021. **Results:** From 1990-2021, the annual percentage change (APC) in age-standardized mortality rates (ASMR) due to CA attributable to h-BMI increased by 0.22%, disability-adjusted life years rates (ASDALR) by 0.19%, and years lived with disability rates (ASYLDR) by 0.78%. Among all CA, the highest increase in APC for ASMR was observed for liver CA at 3.81%, followed by pancreatic CA at 2.66%, uterine CA at 1.16%, thyroid CA at 0.84%, multiple myeloma at 0.50%, and kidney CA at 0.35%. Conversely, APC decreased for leukemia by 0.16%, ovarian CA by 0.37%, non-Hodgkin lymphoma by 0.44%, and gall bladder and biliary tract CA by 0.45%, as well as for colon and rectum CA by 0.49%, and breast CA by 0.85%. Among states, Mississippi observed the highest increase in APC for ASMR at 1.21%, followed by Oklahoma at 1.39%, West Virginia at 1.20%, and New Mexico at 1.19%. In terms of ASYLDR, the largest increases were seen in New Mexico at 1.83%, California at 1.77%, Mississippi at 1.74%, West Virginia at 1.60%, and Tennessee at 1.47%. Age-wise, individuals aged 20-54 recorded 3,833 deaths (95% uncertainty interval: 1,727-5,876), while those 55 and older recorded 43,371 deaths (16,854-71,488) in 2021. Similarly, DALYs for ages 20-54 were 173,448 (82,011-258,288), and for those 55 and older were 930,410 (366,885-1,528,824). In terms of gender, males observed higher increases in ASMR and ASDALR compared to females, with 0.58% vs 0.06% and 0.46% vs 0.05%, respectively, while females saw higher increases in ASYLDR at 1.02% compared to 0.86% from 1990-2021. **Conclusions:** Deaths due to CA attributable to h-BMI accounted for 14.95% of all CA attributable risk factors in 2021. Notably, liver, pancreatic, and uterine CA have shown the most significant rises in ASMR, highlighting an urgent need for targeted public health strategies and research to address these alarming trends. Conversely, decreases in APC for CA like leukemia, ovarian, and breast CA suggest that some progress is being made, possibly attributed to advancements in treatments and early detection programs. Age and gender analyses further illuminate the disproportionate burden of CA on older adults and males, though females exhibit a higher increase in YLDs. Research Sponsor: None.

10529 Poster Session

Sex-based disparities in HPV-related cancer outcomes: Insights into social determinants of health.

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Background: Human papillomavirus (HPV) is the most common sexually transmitted infection and a leading cause of several cancers. Research suggests that males are more likely to be infected with HPV compared with females and, as a result, have a higher incidence of HPV-related cancers, attributable to multiple social determinants of health (SDoH) factors. This study was to examine these sex-based disparities, with a focus on SDoH. **Methods:** The US nationally representative sample of HPV related cancer adults were analyzed from the 2011-2023 National Health and Nutrition Examination Survey (NHANES). Participants who reported having diagnosis of HPV-related cancers were included in our study. Descriptive analyses were performed, and weighted logistic regression models were used to examine associations between HPV-related cancers(Oropharyngeal Cancer, Esophageal Cancer, Prostate Cancer, Cervical Cancer, Anal Cancer, and Uterine Cancer) and key SDoH variables, including HPV vaccination, mental health issue, education level, smoking, poverty level, and health insurance coverage. Analyses were stratified by sex and adjusted for survey weights. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). **Results:** A total of 692 participants (equating to 22,115,631) with HPV-related cancer were identified from NHANSE 2011-2023, with 60.3% males and 39.7% females. Compared with females, the prevalence of HPV-related cancer was significantly higher among males (34% vs. 20%). Notably, none of the males with HPV-related cancer had received HPV vaccination. Men aged 65 years and older had more than 16 times greater odds of having HPV-related cancers compared to those under 65. In contrast, older women were only 1.5 times more likely to report HPV-related cancers, highlighting a striking disparity between older males and females. Males without a high school degree have significantly lower odds of HPV-related cancer (OR: 0.38, 95% CI: 0.27–0.56). This may be attributed to a lack of HPV awareness and knowledge among males, leading to underreporting. Furthermore, non-Hispanic Black (NHB) males (OR: 1.92, 95% CI: 1.43–2.57) had greater odds of HPV-related cancer compared to non-Hispanic White (NHW) males. In comparison, NHW females had higher odds of HPV-related cancers compared with other racial and ethnic groups. These findings highlight the distinct SDoH risk factors contributing to HPV-related cancers across males and females, resulting in disparities in HPV-related cancer outcomes. **Conclusions:** These findings underscore the disparities faced by males regarding HPV-related cancer. Addressing these inequities requires targeted interventions focusing on men who are particularly vulnerable to HPV-related cancers, including increasing vaccination rates and reducing behavioral risks for males. Research Sponsor: None.

10530 Poster Session

Do health care providers offer advice to adolescents about nicotine-containing product use?

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Background: Use of tobacco and other nicotine-containing products is a major preventable cause of cancer. Most individuals initiate nicotine product use during adolescence. Advice from health care providers is important to decrease nicotine product initiation and encourage cessation among individuals using these products. It is unclear how frequently providers offer this advice to adolescent patients. We analyzed national survey data to better understand provider interactions with adolescents about nicotine product use. **Methods:** We analyzed data from 16,120 U.S. middle- and high-school students (weighted to represent a population of 21,836,206) who saw a health care provider (doctor, dentist, or nurse) in the past 12 months and had non-missing data on nicotine product use, family affluence level, and receipt of provider advice regarding nicotine product use from the 2021 National Youth Tobacco Survey (NYTS), a school-based, self-administered survey. Nicotine product use was determined from responses to 13 NYTS questions on use of tobacco or nicotine-containing products; those who indicated use of any products in the past 30 days were classified as "current users". Receipt of advice was assessed from 3 questions on advice to not use cigarettes, e-cigarettes, or other nicotine-containing products during health care provider visits. Family affluence was based on 4 questions on family vacations, cars, computers, and bedrooms. Multivariable logistic regression analyses examined associations of receipt of advice with sociodemographic characteristics separately for current and non-current users, controlling for whether providers asked about nicotine product use adjusting for the complex survey design of the NYTS. **Results:** Of the sample, 1262 (weighted 7.9%) currently used nicotine products. Current users were significantly ($p < 0.05$) more likely to be older, female, and non-Hispanic White (vs. non-Hispanic Asian or Hispanic); 51.3% of current users vs. 44.0% of non-current users received health care provider advice. Among current users, older students were less likely to receive advice (odds ratio [OR] 0.85 per year of age, 95% confidence interval [CI] 0.77-0.93) while males (vs. females) were more likely to receive advice (OR 2.51, 95% CI 1.64-3.86). Among non-current users, older students were less likely to receive advice (OR 0.91, 95% CI 0.89-0.94). Males vs. females (OR 1.54, 95% CI 1.42-1.68); non-Hispanic Blacks vs. non-Hispanic Whites (OR 1.18, 95% CI 1.03-1.36); and those from highly affluent families (OR 1.20, 95% CI 1.06-1.36) were more likely to receive advice. **Conclusions:** Only half of adolescents received nicotine product use advice from health care providers. Those more likely to use nicotine products (older, female, non-Hispanic White students) were less likely to receive advice. Increased provider advice targeting at-risk populations may help decrease adolescent nicotine product use. Research Sponsor: None.

10531 Poster Session

Awareness, knowledge, and attitudes toward breast cancer polygenic risk scores for precision prevention in a multiethnic cohort of high-risk women.

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Background: Polygenic risk scores (PRS) have been shown to improve the risk assessment of breast cancer. Though commercially available in the US, PRS testing remains controversial clinically. Recent qualitative research suggests that PRS is understood and accepted by women. However, quantitative research on PRS awareness, knowledge, and attitudes in the US population is scarce. **Methods:** Between July-September 2024, we surveyed high-risk women without breast cancer enrolled in the Chicago Multiethnic Epidemiologic Breast Cancer Cohort and Cancer Prone Registry. PRS awareness was assessed by asking whether participants had ever read/heard about PRS prior to the survey and discussed PRS with a provider. PRS knowledge was measured using an 11-item "true/false" assessment. The total score ranges from 0-11, with higher scores indicating better knowledge. Participants were also asked to what extent they agreed that PRS testing should be offered to the general population and a routine part of breast cancer risk assessment; and how likely receiving a PRS influences their behaviors toward risk management, using a 4-point Likert scale. We performed linear regression, controlling for demographic and socioeconomic factors. **Results:** Of 828 women (mean age 56.8 years), 69.5% identified as White, 20.8% as Black, and 9.7% as Other. Overall, 18.5% and 13.2% had ever read/heard about PRS and discussed it with a provider, respectively. Further, 32.9% reported having learned about PRS from a genetic counselor, followed by 23.1% from their own research/reading, 11.2% from a primary care provider, and 6.3% from an oncologist. There were no significant racial/ethnic differences in PRS awareness (Black 13.0%, Other 19.2%, White 20.7%; $p = .082$) and discussion (Black 11.8%, Other 11.3%, White 14.1%; $p = .874$). The overall mean score on PRS knowledge was 9.7 (SD 1.4). Black (β −0.47, *se* 0.14; $p = .001$) or Other (β −0.50, *se* 0.17; $p = .003$) women were less likely than White women to score higher on PRS knowledge. Higher education (p-trend $< .001$) and income (p-trend = .002) levels were highly associated with increased knowledge scores. 95.4% and 96.2% agreed or strongly agreed that PRS testing should be offered to the general population and a routine part of breast cancer risk assessment, respectively; 93.9% reported receiving a PRS likely or very likely influences their behaviors toward risk management. Attitudes toward PRS were also high across racial/ethnic and socioeconomic groups. **Conclusions:** In this diverse cohort of women, PRS awareness and discussion were low, and there were notable gaps in PRS knowledge. Our findings underscore the need to improve patient-provider communication of breast cancer risk and address gaps in PRS knowledge/health literacy when implementing genetic testing including PRS to increase the uptake of risk-stratified, personalized breast cancer screening. Research Sponsor: National Institute on Aging; T32AG000243; Susan G. Komen Breast Cancer Foundation; TREND21675016; Breast Cancer Research Foundation; BCRF-23-071; National Cancer Institute; R01CA228198; National Cancer Institute; P20CA233307; Susan G. Komen Breast Cancer Foundation; SAC210203.

10532 Poster Session

Evaluating the impact of long-term glucocorticoid use on cancer risk in patients with rheumatologic diseases: A retrospective cohort study.

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Background: Long-term glucocorticoid (GC) therapy is widely used in the management of rheumatologic diseases, but its immunosuppressive effects have raised concerns about a potential increased risk of cancer. The association between long-term steroid use in patients with rheumatologic diseases and the development of cancer remains unclear. This study aims to evaluate cancer prevalence in patients with rheumatologic conditions who are on long-term steroids compared to those who are not. **Methods:** A retrospective cohort study was conducted involving 35,272 patients with rheumatologic diseases between 2011 and 2024. Patients with rheumatoid diseases were categorized into two groups: those receiving long-term GC therapy (≥30 days; n=5521) and those not on GC therapy (n= 29,751). Cancer prevalence was assessed in both groups as well as their subgroups based on sex, and age. Prevalence rates and odds ratios (OR) were calculated to determine the association between steroid use and cancer. **Results:** Cancer prevalence was significantly higher among GC users (34.2%) compared to non-GC users (20.8%). The odds ratio for cancer in GC users was 1.97 (95% CI: 1.95–2.02), indicating 97% increased odds of cancer for GC users. Stratified by sex, female GC users had a cancer prevalence of 32.6%, compared to 19.9% in non-GC users, with an odds ratio of 1.96 (95% CI: 1.48–2.59), suggesting a nearly two-fold increase in cancer risk. In male patients, cancer prevalence in GC users was 38.2%, compared to 23.4% in non-GC users, with an odds ratio of 2.02 (95% CI: 1.72–2.41), indicating a 102% increase in cancer risk. In those aged over 18 years, cancer prevalence in GC users was 34.5%, compared to 21.3% in non-GC users, with an odds ratio of 1.94 (95% CI: 1.75–2.14), suggesting a significantly higher cancer risk for those on long-term steroid therapy. **Conclusions:** Long-term steroid use in patients with rheumatologic diseases is associated with a higher prevalence of cancer. This association was observed across both sexes and age groups. The substantial cancer risk observed in patients without a personal history of cancer underscores the need for cautious GC prescribing and regular cancer screening. Further investigations should focus on additional factors, including race and comorbidities, to better understand the modulating factors behind this association and refine clinical decision-making.
Research Sponsor: None.

10533 Poster Session

The Selfie study: Cervical precancer detection using novel human papillomavirus biomarkers.

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Background: Human papillomavirus (HPV) causes the majority of cervical cancers worldwide. Dual stain cytology can detect HPV oncogenic activity through biomarkers p16/Ki-67 in cervical samples. Dual stain is an acceptable triage strategy for HPV-positive results from clinician-collected samples, reducing the number of low-risk individuals sent for colposcopy or treatment. However, the ability of dual stain to triage self-collected vaginal specimen is poorly understood. The Selfie Study is an observational study to assess the diagnostic accuracy of different biomarkers for cervical precancer on self-collected samples. Here, we evaluated dual stain cytology in clinician and self-collected specimens for detection of cervical precancer. **Methods:** Individuals with a cervix ages 25-69 years undergoing cervical cancer screening, colposcopy, or treatment at George Washington University (GWU) and Sarasota Memorial Hospital (SMH) were included in this study (August 2020-August 2024). Participants were instructed to perform self-collection prior to clinician-collection during the clinic visit. Demographics and clinical outcomes of dual stain on paired cervicovaginal samples and presence of cervical intraepithelial neoplasia 2 or worse (CIN2+) were recorded and assessed using descriptive statistics. Differences in sensitivity and specificity of dual stain to detect CIN2+ between the two collection methods were assessed using McNemar's test. **Results:** A total of 548 participants enrolled in Selfie. Paired dual stain results were available for 411 participants (411/548, 75%), of which 24 participants were CIN2+ (24/411, 5.8%). Missing results were due to inadequate/absent staining for one or both collection methods. Dual stain was positive in 63 clinician-collected samples (63/411, 15.3%) and in 39 (39/411, 9.5%) self-collected samples. Overall percent agreement between collection methods was 89.3% (367/411). Percent positive agreement was 39.7% (29/73). Dual stain was 83.3% (20/24) sensitive to detect CIN2+ in clinician-collected samples and 45.8% (11/24) sensitive in self-collected samples (83.3% versus 45.8%, p = 0.003). **Conclusions:** Dual stain on self-collected samples had significantly lower sensitivity for detection of CIN2+ compared to clinician-collected samples. Additional research is needed to evaluate whether the performance is more comparable for CIN3+ endpoints. Our study highlights the challenges of conducting triage assays from self-collected specimens. Clinical trial information: NCT04423679. Research Sponsor: U.S. National Institutes of Health.

10534 Poster Session

Analyzing trends in multimorbidity-related mortality among patients with cancer and myocardial infarction: A decadal analysis.

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Background: Multimorbidity, defined as the coexistence of two or more chronic conditions, poses major challenges to healthcare systems globally. Cancer and myocardial infarction (MI) are leading causes of mortality, yet their combined impact remains underexplored. This study investigates trends in multimorbidity-related mortality among U.S. patients with cancer and MI over two decades, aiming to identify patterns and correlations to guide healthcare interventions and policies. **Methods:** Data were extracted from the Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database from 1999 to 2020. Death certificates were analyzed for adults aged 25 years and older, with cancer and MI deaths identified using ICD-10 codes (I20 and C00–C97). Variables such as age, sex, race/ethnicity, geographical region, urban-rural classification, and location of death were extracted. Crude and age-adjusted mortality rates (AAMR) per 100,000 population were calculated and Join point regression analysis was employed to assess mortality trends and annual percent changes (APC). Statistical significance was defined at $p < 0.05$. **Results:** A total of 200,884 deaths were analyzed, with 59.9% occurring in medical facilities, followed by deaths at home (25.09%), nursing homes (12.85%), and hospice facilities (2.10%). The overall AAMR declined significantly from 6.83 in 1999 to 3.33 in 2020.Males consistently had higher mortality, with AAMR dropping from 10.85 to 4.79, compared to females (4.30 to 2.22). The highest mortality was observed in individuals aged 85 and above (CMR: 41.42). Mortality trends declined across all age groups until stabilization in recent years. Racial disparities persisted, with NH Black/African Americans experiencing higher mortality rates (8.91 in 1999 to 3.92 in 2020). Geographic analysis showed the highest mortality rates in the Midwest and Northeast regions. Metropolitan and non-metropolitan areas showed declining mortality trends until 2015, followed by stabilization or slight increases in recent years. **Conclusions:** A significant decline in multimorbidity-related mortality has been observed in patients with cancer and MI over the past two decades, with notable disparities across gender, age, race, and geography. Targeted healthcare strategies are essential to address the specific needs of high-risk populations and ensure equitable access to healthcare resources. Research Sponsor: None.

10535 Poster Session

Can we determine the mechanism behind cancer risk reduction with glucagon-like peptide-1 receptor agonists (GLP-1RAs)?

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Background: Growing evidence suggests that GLP-1RAs may reduce cancer risk in patients with type 2 diabetes (T2D). Most studies have focused on obesity-related cancers (ORCs), with weight loss proposed as a key mechanism. Additional potential mechanisms include the anti-inflammatory effects of GLP-1RAs on various pathways. We evaluated the impact of GLP-1RAs on weight loss and ORC incidence, as well as their effects on lung cancer, which is considered a non-ORC. **Methods:** We utilized the TriNetX database to analyze patients with T2D prescribed a single GLP-1RA from 2010 to 2021. Patients with prior cancer diagnoses were excluded. Semaglutide, dulaglutide, and liraglutide were individually compared to exenatide due to their greater weight loss potential. Propensity score matching (1:1) was used to adjust for demographics, comorbidities, HbA1c, BMI, and medications. Patients were followed for 3 and 5 years, and Cox proportional hazards analyses assessed the risk of 13 ORCs and lung cancer. **Results:** We identified 726,846 patients prescribed GLP-1RAs and conducted multiple comparisons, which were well-matched across analyses. Among the agents, semaglutide demonstrated the greatest weight-loss effect, while exenatide had the least. However, the differences in weight loss did not translate to significant changes in the risk of ORCs. The hazard ratios for semaglutide were 1.11 (95% CI: 0.95–1.29) at 3 years and 1.08 (95% CI: 0.95–1.24) at 5 years. For liraglutide, the hazard ratios were 1.02 (95% CI: 0.88–1.19) at 3 years and 1.05 (95% CI: 0.93–1.20) at 5 years. Dulaglutide had hazard ratios of 1.03 (95% CI: 0.89–1.20) at 3 years and 1.01 (95% CI: 0.89–1.14) at 5 years. None of these differences were statistically significant compared to exenatide. Similarly, no significant differences were observed in the risk for lung cancer. For semaglutide, the hazard ratios were 0.88 (95% CI: 0.59–1.30) at 3 years and 0.88 (95% CI: 0.62–1.25) at 5 years. Liraglutide had hazard ratios of 0.91 (95% CI: 0.62–1.34) at 3 years and 0.90 (95% CI: 0.65–1.24) at 5 years, and dulaglutide had hazard ratios of 1.02 (95% CI: 0.71–1.49) at 3 years and 1.10 (95% CI: 0.81–1.49) at 5 years. These findings indicate no significant differences in cancer risks, whether for obesity-related cancers or non-ORC, lung cancer, among the four GLP-1RAs. **Conclusions:** All four GLP-1RAs demonstrated similar cancer risks for obesity-related cancers despite differences in weight loss among the agents. Similarly, no differences were observed in the risk of non-obesity-related cancer, specifically lung cancer. This suggests that weight loss does not clearly explain a link between GLP-1RAs and reduced cancer risk, as the results were consistent for both obesity-related and non-obesity-related cancers. Research Sponsor: None.

10536 Poster Session

Estimation of population attributable fractions based on integrated global cancer incidence data, 1990-2021.

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Background: The global cancer burden is increasing, yet emerging risk factors for cancer incidence have not been comprehensively summarized in terms of the population attributable fraction (PAF) from a global perspective. **Methods:** We first searched and screened cancer risk factors from 435,977 studies in the Embase, PubMed, and Cochrane databases. Cancer risk effect sizes, such as RR (relative risk), HR (hazard ratio), and IRR (incidence rate ratio) values, were then obtained from meta-analyses. We further estimated population attributable fractions (PAFs) for each risk factor, cancer type, gender, SDI (Socio-demographic Index), modifiability, and trends from 1990 to 2021, using 94 pre-defined risk factors and 39 cancer types. These risk factors include lifestyle factors, environmental exposures, occupational risks, metabolic factors, comorbidities, and family or cancer history. **Results:** A total of 811 cancer risk effect sizes were obtained covering 75 countries or regions, including 18,084 cancer RR/HR/IRR values. In 2021, 64.1% (56.7% - 71.4%) of global cancer incidences were attributable to the evaluated risk factors, with modifiable risk factors accounting for 57.6%. Among the evaluated cancers, the proportion of incidence cases attributed to risk factors exceeded 50% in 26 types of cancer, with the leading cancers being cervical cancer (97.1%), Kaposi's sarcoma (91.2%), vaginal cancer (87.0%), lung cancer (84.6%), and laryngeal cancer (83.2%). In terms of individual risk factors, tobacco use (17.9%), infection (16.1%), and overweight or obesity (10.2%) contributed the highest PAFs, followed by family and genetic history (6.9%), alcohol consumption (5.7%), cardiovascular diseases (5.0%). The high SDI region shows a higher PAF (68.2% [61.5%–75.0%]) compared to the non-high SDI region (59.6% [52.2%–67.0%]). From 1990 to 2021, the global cancer incidences attributable to risk factors increased from 61.8% to 64.1%. Overweight or obesity, neurological and psychological disorders, and dietary factors were the top three leading increasing risk factors. **Conclusions:** The global cancer burden is significantly influenced by a wide range of modifiable and non-modifiable risk factors, with over 64% of cancer incidence in 2021 attributable to these factors. The rising trends in overweight or obesity, neurological and psychological disorders, and diabetes factors between 1990 and 2021 highlight the urgent need for targeted interventions to address these rapidly growing risks and reduction of the cancer burden. Research Sponsor: Shanghai Xiaohe Medical Laboratory Co., Ltd.

10537 Poster Session

Development and clinical validation of a cell-free DNA methylation sequencing test for multi-cancer early detection.

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Background: Achieving robust early-stage sensitivity in multi-cancer early detection (MCED) poses challenges, relying on large cohorts of early-stage samples and reliable prediction frameworks. Particularly for gastrointestinal cancers (GICs) with poor compliance of screening, early-stage sensitivity in MCED remains insufficient. Moreover, accurate tumor localization is crucial for choosing subsequent diagnostic procedures but remains suboptimal. We evaluate the performance of Genie-seq within the ProFuture study (NCT05874648), focusing on its capacity to detect five high-mortality cancers: lung, colorectal, liver, stomach, and esophageal cancers. **Methods:** The ProFuture study is a prospective multicenter case-control study that initially enrolled 3,515 participants. Following evaluations and a minimum of a half-year follow-up, 3,036 participants remained analyzable. Participants were divided into training (920 cancer; 629 non-cancer), validation (300 cancer; 215 non-cancer), and independent validation (605 cancer; 367 non-cancer) sets. Plasma cfDNA underwent a 1000X target enzymatic methyl sequencing assay (Genie-seq) targeting cancer-specific methylation patterns identified from 2,420 tumor and plasma samples. The assay normalizes abnormal fragment reads within blocks to minimize interference, using a maximization model to select sensitive and robust features. A gradient-boosted tree model was developed to integrate these features for cancer prediction, utilizing a one-vs-rest strategy to determine the tissue-of-origin (TOO). **Results:** Specificity remained consistently high across all phases: 99.0% (95% CI: 97.7-99.6%) in training, 99.1% (96.7-99.9%) in validation, and 99.2% (97.6-99.8%) in independent validation. Sensitivity was 68.6% (65.5-71.6%) in training, 71.0% (65.5-76.1%) in validation and 69.6% (65.8-73.2%) in independent validation. In independent validation set, stages I-III (account for 85.5% of cases) sensitivity reached 65.8% (61.5-69.9%) for all cancer types and 72.1% (66.9-76.9%) for three GICs. The TOO classifier assigned the origin in all screen-positive cases, achieving an accuracy of 87.4% (83.9-90.4%) in independent validation, including reducing misclassification from lung to esophageal cancer due to squamous similarity to 4.5%. **Conclusions:** This MCED test accurately identified signals from five tumor types especially in the early stages. Precise TOO localization minimizes the healthcare burden of subsequent diagnoses. The consistency of performance from training to clinical validation underscores the robustness of feature selection strategy, mitigating the risk of overfitting. Notably, this study demonstrated exceptional sensitive detection of early-stage GICs, indicating the potential efficacy of Genie-seq in MCED within the ongoing interventional Prosight study (NCT06790355). Clinical trial information: NCT05874648. Research Sponsor: None.

10538 Poster Session

Utilizing cancer community outreach and engagement to explain impact of age, income, residence, knowledge, and survivorship on cancer fatalism in urban and rural/marginalized areas.

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Background: Nigeria has the highest cancer burden in sub-Saharan Africa, with 124,815 incidences and 78,899 deaths. Popular fatalistic beliefs such as *"cancer is a death sentence"* and *"cancer is not my portion"* exist in this population, which potentially affects cancer prevention, early detection and increases poor treatment outcomes. Yet, factors responsible for these fatalistic cancer beliefs remain largely unknown. This study utilized cancer community outreach and engagement (COE) to understand cancer health disparities among Nigerians. Specifically, we assessed the association of age, income, residence, cancer knowledge, screening, survivorship, and current health on cancer fatalism (i.e., the view that cancer is a death sentence) in Nigeria. **Methods:** A cross-sectional study was used to collect data from participants (n = 1457, 18-68 years old), in two COE events and two marginalized communities. Participants completed questionnaires via self-assessment. Multiple linear regression was used to analyze the data. **Results:** Our findings showed that individuals who had not previously participated in cancer COE events reported higher cancer fatalism ($\beta = 1.21$, $p < 0.001$) compared to those who had previously participated. More cancer knowledge was related to lower cancer fatalism among participants ($\beta = -0.21$, $p = 0.002$). Participants who reported lower monthly income ($\beta = 1.05$, $p = 0.002$) and those who reported mid-low monthly income ($\beta = 1.28$, $p < 0.001$) had higher cancer fatalism. Participants aged 30-49 ($\beta = 0.46$, $p = 0.049$), residing in rural communities ($\beta = 0.62$, $p = 0.006$), and those who were married ($\beta = 0.51$, $p = 0.029$) reported higher cancer fatalism. **Conclusions:** Our study showed that participating in cancer COE events may lower cancer fatalism. The global cancer control communities, donor agencies, and Nigeria's National Institute on Cancer Research and Treatment need to encourage more COE events as a crucial strategy for early detection and closing the cancer disparity gaps. There is a need for more cancer awareness and policy advocacy on cancer in this population. Research Sponsor: None.

10539 Poster Session

Machine learning–informed navigation of patients in persistent poverty zip codes to improve colorectal cancer screening: A prospective controlled study.

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Background: Colorectal cancer (CRC) screening remains suboptimal, particularly in racially diverse and low-income populations. Machine learning (ML) algorithms trained on routine electronic health record (EHR) data may accurately predict CRC risk. Further, patient navigation programs can address screening barriers such as lack of transportation access and low health literacy around colonoscopy preparation. We tested the impact of an intervention combining ML-based risk stratification and an evidence-based CRC screening navigation program on CRC screening rates and outcomes. **Methods:** This prospective nonrandomized controlled study (NCT05383976) was conducted at a large academic health system, enrolling adults over 50 years of age and at average-risk of CRC. All adults resided in Persistent Poverty zip codes (defined by the US Census Bureau) in the Philadelphia metro area, were attributed to a primary care physician (PCP), and had a colonoscopy order that had not been completed within the past 6 months. We adapted a validated ML algorithm that was previously trained on 22 variables – including age, sex, and longitudinal complete blood counts – to predict CRC risk. Patients enrolled in the intervention arm were prioritized by the ML algorithm for a structured navigation program, including risk-targeted phone-based education, appointment facilitation, transportation support, and mailed FIT tests. A concurrent control cohort received navigation but was not prioritized by the ML algorithm. Adjusted logistic regression models assessed the intervention's impact on the co-primary outcomes of (1) CRC screening completion (colonoscopy or FIT), and (2) positive screening result, defined as precancerous adenoma (sessile serrated, inflammatory, villous, malignant) and/or positive FIT. **Results:** 382 patients were enrolled (199 intervention, 183 control). Among intervention patients, 71.4% were reached via phone and 66.4% scheduled screening, with 26.2% and 17.6% completing colonoscopy and FIT, respectively (see Table). Screening completion was similar for intervention vs. control (46.2% vs. 43.2%; adjusted OR 1.02, 95% CI 0.67-1.56, p=0.93). For intervention vs. control, precancerous adenoma detection was 8.5% vs. 5.2% (aOR 2.43, 95% CI 0.48–12.3, p=0.57) and tubular adenoma detection was 35.6% vs. 25.0%. **Conclusions:** ML-informed navigation was feasible, did not increase screening engagement, and marginally increased rates of precancerous and tubular adenoma detection. Refinements in ML risk stratification and enhanced navigator outreach may maximize impact. Clinical trial information: NCT05383976. Research Sponsor: National Cancer Institute.

Navigator services provided in intervention group.

Number of telephone calls to outreach	
1	81 (40.7%)
2	34 (17.1%)
3+	27 (13.5%)
Prep letter sent	11 (7.7%)
Prep kit sent	24 (16.9%)
Colonoscopy/FIT education	27 (19.0%)
Transportation arrangement	8 (5.6%)

Clinical and radiological characteristics of intermediate and high-risk cases in the Brazilian early lung cancer screening trial (BRELT3): Insights into Lung-RADS categories 3 and 4 and biopsy decision-making factors.

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Background: Lung cancer is the leading cause of cancer death worldwide, and low-dose computed tomography (LDCT) effectively reduces mortality through early detection. BRELT1 and BRELT2, from the Propulmão initiative, highlighted the feasibility of lung cancer screening (LCS) programs in Brazil. This report examines demographic and radiological characteristics of patients with Lung-RADS (LR) 3 and 4 nodules in BRELT3, a mobile LDCT-based LCS initiative, and factors influencing biopsy indication. **Methods:** This prospective cohort study included current or former smokers (cessation ≤15 years), with a smoking history of ≥20 pack-years, aged 50–80 years. Those with LDCT classified as LR 3 or 4 were analyzed, and clinical and tomographic data were collected. The Brock malignancy probability model (PMB, 10% threshold) was applied retrospectively to assess its association with biopsy indication. Statistical methods included logistic regression, t-test, Mann-Whitney, chi-square, and Fisher's exact test. Ethical Committee approval was obtained (SENAI-CIMATEC / Santa Izabel Hospital; n° 67431523.6.0000.9287 / 67431523.6.3001.5520). **Results:** Among 2018 screened patients, 223 (11.1%) had findings for lung cancer risk, Of these, 44.4% classified as LR3 and 55.6% as LR4. Median age was 64 years, with 87.4% self-identified as Black, 63.2% as current smokers, and 75.8% reported no family history of lung cancer. Nodules were predominantly single (82.5%) and solid (77.1%), with a mean size of 13.12 mm. LR3 nodules were smaller (9.53 mm) and exhibited lower PMB (7.43%) compared to LR 4 (15.99 mm; PMB: 18.93%). Biopsy was indicated for 45 participants (98% LR4). Nodules requiring biopsy were larger (22.97 vs 10.63 mm) and had higher PMB (26.44 vs 10.64%). Predictors for biopsy included irregular or spiculated contours (OR 5.83; $p < 0.05$), LR4B/4X vs.4A classification (OR 5.00; $p < 0.05$), PMB > 10% (OR 5.36; $p < 0.05$) and nodule size (OR 1.10; $p < 0.05$). Of the 45 nodules indicated for biopsy, 24 underwent the procedure, and 5 progressed to surgery. **Conclusions:** Mobile LDCT-based screening programs showed potential in identifying high-risk nodules among underserved populations. Factors influencing biopsy decisions included nodule size, irregular or spiculated contours, LR 4B/4X classification, and PMB > 10%. Integrating PMB into LCS may improve diagnostic accuracy and biopsy decision-making, enhancing early lung cancer detection. Research Sponsor: Bristol-Myers Squibb Foundation; Boehringer Ingelheim Brazil; Diagnósticos da América S.A. (DASA); AstraZeneca Brazil; Lung Ambition Alliance; Ethicon Brazil; Panther Brazil.

Association between nodules' characteristics and biopsy indication.

Characteristic (n = 45)	OR (CI 95%; p-value)*
Irregular or spiculated contours	5.83 (2.86 - 11.88; $p < 0.05$)
Lung-RADS 4B/4X vs.4A	5.00 (1.61 - 15.54; $p < 0.05$)
PMB - %	1.05 (1.03 - 1.07; $p < 0.05$)
Nodule size - mm	1.10 (1.06 - 1.13; $p < 0.05$)

*Univariate logistic regression. OR = Odds Ratio; CI = Confidence Interval.

10541 Poster Session

Cost-effectiveness analysis of population-based screening for 6-gene panel testing for hereditary breast and ovarian cancer.

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Background: Genetic testing for hereditary breast and ovarian cancer (HBOC) has relied on clinical and family history criteria. This approach, has been shown to overlook a significant number of mutation carriers who could benefit from preventative measures. Increasing evidence supports genetic testing in an unselected population, which facilitates the identification of more carriers and allows for the implementation of risk reduction strategies. The aim of this study is to evaluate the cost-effectiveness of utilising an expanded gene-panel in an unselected female population. **Methods:** A Microsoft Excel-based simulation model of a hypothetical cohort of unselected and previously untested 30 years old women was devised to assess three strategies. Strategy 1: genetic testing of unselected women for mutations of a 6-gene panel *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CHEK2* and *TP53*, Strategy 2: screening to individuals fulfilling family history (FH) criteria for HBOC testing and Strategy 3: no genetic screening. New Generation sequencing (NGS) using TrueSight hereditary cancer panel from Illumina was used as testing platform. The analysis includes quality adjusted life year (QALY) as a health outcome. The incremental cost-effectives ratio (ICER) is calculated using health-care costs and QALYs per treatment strategy, illustrating the additional cost in relation to the additional health benefit (QALYs) associated with the 6 gene-panel strategy compared to the FH-based strategy. One-way sensitivity analyses expressed as ICER, evaluates the uncertainty and the impact of specific parameters on the results. **Results:** A cohort of100 000 unselected women was simulated through the model over 80 cycles as well as women meeting criteria for HBOC investigation. The mutation carriers detected were 1307 and 191 for the unselected population group and FH respectively. As direct effect, 339 risk reducing surgeries (mastectomy or/and salpingo-oophorectomy) were performed in the strategy 1 compared with 50 in the strategy 2. The probabilistic analysis shows that if the willingness to pay is €100.000 per QALY, the unselected population-based testing has 75% probability of being cost-effective. **Conclusions:** Population-based screening with a six-gene panel has 75% probability to be cost-effective if the willingness to pay is over €100 000. This strategy reduces the number of (HBOC) cases and cancer specific mortality which strengthens the benefits of this screening strategy in cancer prevention. Research Sponsor: None.

Outcomes.

Outcomes	Scenario Population-based	FH-based	Difference
Life years	2 713 534	2 713 369	165
QALY	2 147 507	2 147 312	196
Cost per life years gained (€)			98 079
ICER (cost per QALY gained) (€)			82 642
Costs (€)			
Screening	13 311 720	163 417	13 148 304
Risk reducing Surgery	4 557 420	666 608	3 890 812
Surveillance	45 330 899	43 413 884	1 917 015
Cancer	180 119 575	182 884 672	-2 765 098
Total Cost	243 319 615	227 128 581	16 191 034

10542 Poster Session

The potential of multi-cancer early detection screening in reducing cancer incidence and mortality in high-risk groups: A modeling study.

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Background: Emerging liquid biopsy multi-cancer early detection (MCED) tests have the potential to revolutionize early cancer detection. Using a simulation model, we estimated their impact on cancer incidence and mortality in high-risk groups. **Methods:** We developed Simulation Model for MCED(SiMCED), a microsimulation model of 14 solid tumor cancer types. MCED test sensitivities were derived from the ASCEND-2 case-control study. Using a 10-year horizon, we simulated the life course of 100,000 adults aged 50-84 years, representing the US general population. In addition, we simulated screening in three high-risk groups: smokers (former and current), heavy alcohol users, and individuals with a family history of cancer in ≥1 first-degree relatives (FDRs). Cancer diagnosis could arise from usual care or annual MCED screening. After a cancer diagnosis, individuals followed SEER survival curves to determine the time and cause of death (cancer- or non-cancer-related). **Results:** The table presents overall 10-year reductions in stage IV cancer incidence and mortality per 100,000. Among smokers, MCED screening had the greatest impact (in absolute reduction terms) on lung cancer, which accounted for more than 50% of late-stage incidence. Compared to usual care only, MCED screening reduced stage IV lung cancer incidence by 43% (2,028 vs 1,146) and cancer mortality by 16% (2,589 vs 2,247). Among heavy alcohol users, MCED screening had the greatest impact on lung, colorectal, and head and neck cancer. The stage IV incidence reduction in these three cancer types were, respectively, 44% (805 vs 454), 57% (286 vs 122), and 33% (398 vs 265). The cancer mortality reduction in these three cancer types were, respectively, 14% (1,014 vs 876), 33% (371 vs 248), and 16% (265 vs 223). In the familial cancer cohort, MCED screening had the greatest impact on lung, colorectal, and pancreatic cancer. The stage IV incidence reduction in these three cancer types were, respectively, 44% (821 vs 461), 57% (257 vs 111), and 58% (233 vs 98). The cancer mortality reduction in these three cancer types were, respectively, 14% (1,030 vs 888), 33% (328 vs 220), and 14% (326 vs 279). **Conclusions:** MCED screening demonstrates potential to reduce late-stage cancer incidence and mortality in both the general population and high-risk groups. These findings highlight the value of MCED tests in advancing early detection and improving cancer outcomes. Research Sponsor: Exact Sciences Corporation.

Cohort	Usual care: Stage IV cancer incidence	Usual care + MCED: Stage IV cancer incidence	Reduction: Stage IV cancer incidence	Usual care: Cancer mortality	Usual care + MCED: Cancer mortality	Reduction: Cancer mortality
General population	2,117	1,229	888 (42%)	2,612	2,149	463 (18%)
Smokers	3,523	2,034	1,489 (42%)	4,392	3,691	701 (16%)
Heavy alcohol users	2,619	1,548	1,071 (41%)	3,099	2,552	547 (18%)
Family history of cancer in ≥1 FDRs	2,365	1,360	1,005 (42%)	2,899	2,374	525 (18%)

10543 Poster Session

One-year impact of a large-scale pilot multimodal personalized early cancer detection and prevention program for individuals at high risk of cancers.

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Background: The Interception program (IP) is a unique initiative aiming to assess the value of a dedicated personalized care pathway for individuals at high risk (HR) of different cancers. IP includes identification of HR individuals in primary care, a One-Day-Clinic (ODC) (including individual care and workshops aimed at information, education, awareness; informed prevention decisions on an evidence-based shared personalized early detection and prevention plan), implementing and monitoring this plan with community professionals and MyInterception digital follow-up. **Methods:** This prospective, cohort study analysed data from participants who entered IP between Jan 2021 and May 2023. Eligible participants were adults at high risk of breast ($>$ 2.5% at 5 yrs), lung ($>$ 1.6% at 5 yrs), prostate, pancreatic cancer, or Lynch syndrome. Data cut-off was June 2024. Primary endpoint was the 1-yr adherence rate to planned screening and risk-reduction measures (RRM), (the latter defined by full smoking cessation for smokers, or $>$1 point improvement of WCRF score for others (or stable if was $>$5 out of 7). Secondary endpoints were awareness of risk, screening and prevention measures, and cancer incidence. We assessed factors associated with 1-yr adherence to screening and RRM. **Results:** 719 participants were eligible for the present assessment, median age 50 (range 21-81), 80% female. 83% tertiary education, 38% active smokers, at HR of breast (360), lung (281), other (78) cancers. Median baseline WCRF score was 4 (range 0.5-7), 65% had a score $<$ 5. At 1 yr, global adherence to both screening and RMM was 57%. Adherence to screening measures was between 82 and 100% overall. The 1-yr median WCRF score (N = 290) was 4.5 (range 1.25–7) (p = $<$ 7.8e-07 vs baseline), 41% had improved ($>$ = 1 point) their score while 7.4% had remained stable $>$5. However, only 18% smokers succeeded in fully quitting smoking. The crude incidence of new cancer cases was 1.5%. We found major improvements in perceived knowledge and in the accuracy of self-estimated cancer risk scores 8 days after the ODC (p = $<$ 2.2 e-16). In the multivariable logistic regression analysis, increasing age was associated with higher odds of global adherence (OR = 1.02 per year, 95% CI [1.001, 1.046], p = 0.03). Male sex was associated with a trend toward increased adherence (OR = 1.7, 95% CI [0.97, 3.15], p = 0.06). Smokers had significantly lower odds of adherence compared to other risk categories (OR = 0.17, 95% CI [0.09, 0.3], p $<$ 0.0001). Among smokers, male sex was significantly associated with higher odds of adherence compared to female sex (OR = 2, 95% CI [1.1, 3.6], p = 0.01). **Conclusions:** IP demonstrated promising results in promoting cancer risk reduction and achieving satisfactory adherence to screening among HR individuals. However, challenges remain, particularly in enhancing adherence to RRM and reaching less educated populations. Research Sponsor: Odyssea, Fondation Philanthropia,; Fondation Gustave Roussy, Banque des Territoires; France 2030 Tiers Lieux Numériques en santé.

10544 Poster Session

Clinical impact of integrating polygenic risk scores with breast cancer risk assessment models: Results from the prospective multisite GENRE-2 clinical trial.

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Background: Incorporation of Polygenic Risk Scores (PRS) can refine traditional breast cancer risk assessment models to provide precise estimates of breast cancer risk. However, the impact of such an integrated model on clinical decision-making related to breast cancer surveillance and preventive strategies is not fully understood. **Methods:** The GENRE-2 is a prospective single-arm multisite clinical trial (NCT04474834) incorporating PRS into standard breast cancer risk assessment models to determine the impact of PRS on clinical decisions on breast cancer prevention and surveillance. Women at high risk of breast cancer due to NCI-BCRAT 5-year risk of $\geq$ 3%, or IBIS (Tyrer-Cuzik) 10-year breast cancer risk of $\geq$5%, biopsy-proven high-risk breast lesion, or a pathogenic variant (PV) in *ATM*, *BRCA1*, *BRCA2*, *CHEK2* or *PALB2*, were enrolled from five sites in the United States. All women were invited to complete surveys on their breast surveillance and cancer prevention decisions based on pre-PRS standard risk models and post-PRS risk estimation, and further annual surveys are planned for 10 years. **Results:** Among 902 women enrolled in the study, 605 (median age: 52 years) received PRS results and completed a survey to date. Of those who received PRS results,195 (32.2%) were PV carriers. Among non-carriers, the median 10-year and lifetime pre-PRS IBIS-based risk was 10.0% and 28.7%, respectively. Among PV carriers, the CanRisk-based 10-year and lifetime pre-PRS risk estimates were 6.3% and 25.2% for *ATM*, 22.3% and 77.6% for *BRCA1*, 18.5% and 77.7% for *BRCA2*, 7.1% and 25.7% for *CHEK2*, and 16.8% and 38.0% for *PALB2* PV carriers, respectively. After the incorporation of PRS, the lifetime risk of breast cancer increased by at least 10% in 31% of non-carriers and 7.7% of PV carriers and decreased by at least 10% in 10.7% of non-carriers and 7.7% of PV carriers. The proportion of non-carriers with lifetime risk $<$ 20% or $>$ 40% changed from 17.3% and 22.0%, respectively, in the pre-PRS evaluation to 24.4% and 32.9%, in the post-PRS evaluation. A higher lifetime post-PRS score was associated with intent to take preventive action (surgery or endocrine agents). In non-carriers, the proportion of women with a lifetime risk $<$ 20% with intent to take preventive action was 11%, compared to 36.8% of those with a lifetime risk $>$ 40% ($p < 0.001$). Similarly, in PV carriers, the proportion of women with lifetime risk $<$ 20% with intent to take preventive action was 20.8% compared to 41.1% of those with lifetime risk $>$ 40% ($p = 0.015$). **Conclusions:** The GENRE-2 trial demonstrates that the incorporation of PRS into breast cancer risk assessment models in high-risk women is feasible and leads to clinically meaningful changes in breast cancer risk estimates and decision-making regarding preventive strategies. Evaluation of the implementation of breast cancer risk management strategies in study participants is ongoing and will be reported. Clinical trial information: NCT04474834. Research Sponsor: J. Christopher and Anne N. Reyes Foundation.

10545 Poster Session

Genetic predictors of 16,000 multi-omic traits and associations with breast cancer survival outcomes in the Pathways Study.

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Background: Polygenic scores (PGS) enable the computation of a genetic predictor for any trait where a well-developed algorithm is available. This is appealing when such trait is not directly measured in the study population for association testing. Based on a large prospective breast cancer cohort, we calculated and investigated the prognostic value of >16,000 PGS of multi-omic traits, including plasma proteomics, plasma metabolomics, and whole-blood transcriptomics. **Methods:** The Pathways Study is a prospective cohort study of women with breast cancer who were enrolled soon after diagnosis in 2006-2013 at Kaiser Permanente Northern California, with ongoing follow-up. Using genome-wide genotypes from 3,995 study participants, we calculated 16,020 multi-omic PGS from the INTERVAL study (https://www.omicspred.org/). We analyzed three outcomes: overall survival (OS), breast cancer specific survival (BCSS), and disease-free survival (DFS), with a median (range) follow-up time of 10.5 (0.2-14.2) years. We derived hazard ratios (HRs) and 95% confidence intervals (CIs) for one standard deviation (sd) increment in PGS from multivariable hazards models in the total study population, among those self-reported as non-Hispanic White (NHW), and by tumor estrogen receptor (ER) status in NHW women, with multiple testing corrected by a false discovery rate (FDR) of q<0.10. **Results:** The median age at diagnosis was 60 (23.6-94.8) years, with the majority of the study population (68%) self-identifying as NHW. Most women had ER+ tumors (83.4%), diagnosis at stages I and II (89%), and 13.3% had HER2+ tumors. The majority (60%) had lumpectomy and adjuvant therapy (44.3% radiotherapy, 47.0% chemotherapy, 74.6% hormonal therapy). Four PGS-survival outcome tests reached statistical significance with an FDR q<0.10, notably all between gene expression PGS and OS, including OPGS013029 for *TINCR* in NHW patients, and OPGS011920 for *TTLL7*, OPGS009036 for *RNF4*, and OPGS011365 for *GGT7* in NHW ER- patients (Table). None of the PGS for proteomic or metabolomic traits reached this level of significance after controlling for multi-testing. **Conclusions:** By leveraging a large catalog of PGS of multi-omic molecular traits, we identified PGS for whole-blood RNA expression for four genes in significant associations with overall survival. Pending on validation in future studies, these genes may have prognostic value for breast cancer. Research Sponsor: None.

PGS of multi-omics traits and associations with OS in the pathways study.

Study population (race, ER status)	PGS	Outcome	Multi-omic trait	HR (95%CI) per sd increment of PGS	p	FDR q
NHW	OPGS013029	OS	RNA_TINCR	0.82 (0.76, 0.89)	3.01E-06	0.05
NHW ER-	OPGS011920	OS	RNA_TTLL7	1.40 (1.22, 1.60)	8.45E-07	0.01
NHW ER-	OPGS009036	OS	RNA_RNF4	1.54 (1.28, 1.85)	4.07E-06	0.03
NHW ER-	OPGS011365	OS	RNA_GGT7	1.54 (1.27, 1.88)	1.60E-05	0.09

10546 Poster Session

Impact of 2021 United States cancer screening guideline changes on racial and ethnic differences in patient-reported adherence to age-appropriate colorectal cancer screening.

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Background: In 2021, the US Preventive Services Task Force and the US Multi-Society Task Force on Colorectal Cancer updated screening guidelines to recommend that average-risk colorectal cancer (CRC) screening should begin at age 45. We used nationally representative survey data to assess CRC screening among patients across racial/ethnic groups ages 45-49 and 50+ before and after the 2021 guideline changes. **Methods:** 2019-2023 biannual data from the National Health Interview Survey (NHIS) was used to select individuals aged ≥45 years old who responded regarding receipt of appropriate CRC screening. Patients with prior history of CRC or missing data were excluded. Survey-adjusted percentages were used to characterize differences in CRC screening adherence by racial/ethnic group. Multivariable logistic regression models adjusting for age, gender, year, marital status, and geography generated adjusted odds ratios (aORs) with 95% CI to examine associations of race/ethnicity and CRC screening adherence. **Results:** 188,620 patients met inclusion criteria. Overall, patients aged ≥50 had similar CRC screening prevalence before and after guideline changes (58% vs. 61% pre- and post-change) while patients aged 45-49 years had a 10% increase in appropriate screening (21% vs 31% pre- and post-change); largest screening increase was in Non-Hispanic Black (13.92% increase) and Non-Hispanic Asian patients (12.76%) while smallest increase was noted in Hispanic patients (7.05% increase). Prior to guideline changes, among patients 45-49 years old, Asian patients (aOR: 0.45 95%CI: 0.24-0.86) were less likely to report cancer screening compared to non-Hispanic White patients. After guideline changes, among patients 45-49 years old, patients identifying as Asian (aOR: 0.56 95% CI 0.34-0.92) and Hispanic (aOR: 0.62 95% CI 0.41-0.94) were less likely to report age-appropriate cancer screening compared to non-Hispanic White patients, while there was no difference for non-Hispanic Black patients (aOR: 1.31 95% CI 0.91-1.89). Year-age interaction was significant ($p < 0.001$), while year-race interaction was not significant. **Conclusions:** Our study highlights that while patient-reported adherence to CRC screening increased among patients 45-49 years old after updated screening guidelines, screening disparities were observed among Asian and Hispanic patients. Guidelines had a distinct impact on pts aged 45-49 in relation to pts ≥50 who were not impacted by the changes. The time-race interaction was not significant, suggesting no evidence of improvement in the degree of disparity. Patient reported CRC screening rates after guideline changes among pts 45-49 is lagging compared to pts ≥50; further work is needed to implement the updated guideline recommendations and improve screening adherence. Research Sponsor: None.

10547 Poster Session

Bariatric surgery and risk of gastrointestinal and hormone-sensitive cancers in patients with metabolic-associated steatotic liver disease and obesity: A multi-center matched cohort study.

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Background: Metabolic-associated steatotic liver disease (MASLD) is strongly associated with an increased risk of hormone-sensitive and gastrointestinal (GI) malignancies due to obesity-related pro-inflammatory states and altered hormone metabolism. Bariatric surgery (BS) has shown promise in ameliorating MASLD and obesity-related comorbidities; however, data on its potential to reduce cancer risk in this population remain scarce. Hence, we aimed to assess the impact of BS on the risk of hormone-sensitive and GI cancers in patients with MASLD and obesity using a multicenter, matched cohort design. **Methods:** We conducted a retrospective cohort study utilizing the TriNetX. Patients who underwent BS (including Roux-en-Y Gastric Bypass and Sleeve Gastrectomy) were included in the BS cohort and matched controls who are standard of care without a history of BS. We performed 1:1 propensity score matching (PSM) to reduce confounder factors, including demographics, comorbidities, BMI, nicotine dependence, and family history of malignancy. A 1-year lag time was applied to minimize protopathic bias. Cox proportional hazard analysis was performed to calculate hazard ratios (HR) for overall cancer risk, hormone-sensitive cancers (endometrial, breast, prostate, kidney, and ovarian), and GI cancers (colon, rectal, pancreatic, biliary, and hepatocellular). **Results:** A total of 9848 patients with MASLD underwent BS, while 183837 MASLD patients had no history of BS. After PSM, 9791 patients were included in each cohort. The mean follow-up was 4.8 years for BS and 5.1 years for controls. BS was associated with a significantly lower overall cancer risk (HR: 0.72 (0.65-0.80)). Among hormone-sensitive cancers, BS patients demonstrated reduced risks of endometrial (HR 0.50) and breast cancer (HR 0.62), with no significant differences for prostate, ovarian, lung, or thyroid cancer. A lower risk of kidney cancer was noted (HR 0.91). For GI malignancies, BS patients had a reduced risk of HCC (HR 0.32), malignant neoplasms of the cholangiocarcinoma (HR 0.29), pancreatic cancer (HR 0.18), and colon cancer (HR 0.53). No differences were observed for esophageal or gastric cancers. **Conclusions:** In this large multicenter analysis, BS was associated with a significantly lower risk of hormone-sensitive and GI cancers in patients with MASLD and obesity. These findings suggest that weight loss and improved metabolic profiles following surgery may mitigate the pro-inflammatory and pro-neoplastic effects of obesity and MASLD. Further research is needed to explore BS's underlying mechanisms and long-term cancer prevention benefits. Research Sponsor: None.

10548 Poster Session

Escalating burden and trend of cancer attributable to smoking in Southeast Asia, east Asia and Oceania from 1990-2021: A benchmarking systematic analysis.

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Background: Cancer (CA) is a leading cause of death and disability in Southeast Asia (SEA), East Asia (EA), and Oceania. Among the various risk factors, smoking is notably the most preventable. Its strong association with various CA types underscores the urgent need for effective tobacco control measures as a cornerstone of CA prevention strategies. **Methods:** This study utilized the standardized methodology of the Global Burden of Disease Study 2021 to estimate deaths, disability-adjusted life years (DALYs), and years lived with disability (YLDs) attributable to smoking for 16 types of CA in SEA, EA and Oceania, stratified by age, sex, year, and location from 1990-2021. The results are presented in absolute counts and age-standardized rate. **Results:** The annual percentage change (APC) in the total number of deaths due to CA attributable to smoking increased by +2.64%, DALYs by +2.16%, and YLDs by +3.57% from 1990-2021. Regionally, the highest increase in APC was observed in EA, with deaths at +2.67% and DALYs at +2.14%. For age-standardized mortality rates (ASMR), highest increases in APC were observed in Indonesia (+0.81%), Kiribati (+0.02%), Marshall Islands (+0.56%), and Niue (+0.16%), while declines were observed in most other regions. By cancer type, the highest increases in APC in deaths were observed due to kidney CA (+4.43%), pancreatic CA (+3.54%), tracheal, bronchus, and lung CA (+3.45%), lip and oral cavity CA (+3.29%), and prostate CA (+3.23%). Moderate increases were observed due to colon and rectum CA (+2.87%), leukemia (+2.76%), bladder CA (+2.13%), liver CA (+1.81%), breast CA (+1.76%), larynx CA (+1.59%), esophageal CA (+1.50%), other pharynx CA (+1.35%), stomach CA (+0.83%), and cervical CA (+0.62%). Nasopharynx CA was the only type to show a slight decline (-0.03%). By age, an APC of +0.90% was observed in deaths among individuals aged 20-54 years and +2.97% among those aged 55+ years. By gender, APC for deaths were +2.69% in males and +2.18% in females, DALYs were +2.19% in males and +1.80% in females, and YLDs were +3.63% in males and +3.04% in females. **Conclusions:** Deaths due to CA attributable to Smoking accounted for 60.31% of all attributable risk factors in 2021. The observed increases in the APC in deaths, DALYs, and YLDs due to smoking-attributable cancers highlight a significant and growing public health burden, particularly in EA and among males and older age groups. These trends emphasize the need for strengthened tobacco control policies, early CA detection programs, and targeted public health interventions to address regional and demographic disparities. For clinicians, these findings underscore the importance of prioritizing smoking cessation counseling, routine CA screenings, and personalized treatment strategies to mitigate the impact of smoking-related CA. Research Sponsor: None.

10549 Poster Session

Global burden and trend of pancreatic cancer in high-income countries: A 30-year analysis of disease dynamics.

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Background: Pancreatic cancer (PC) has a disproportionately high impact in high-income countries (HIC), where it ranks as the 3rd leading cause of cancer-related deaths, compared to 6th globally. **Methods:** This study is the first ever systematic analysis estimating the incidence, prevalence, mortality, disability, and associated risk factors of PC across the HIC and its territories from 1990-2021. Using a standardized approach, this analysis examines data by age, sex, year, and location, using insights from the Global Burden of Disease Study 2021. The results are presented in absolute count and age-standardized rate (per 100,000). **Results:** From 1990-2021, the total prevalence counts increased from 89,475 (95% UI: 85,159–92,609) to 214,254 (95% UI: 192,172–227,351), while deaths rose from 105,828 (95% UI: 99,853–109,660) to 216,444 (95% UI: 193,299–230,784). Concurrently, disability-adjusted life years (DALYs) increased from 2.3 million (95% UI: 2.2–2.3) to 4.1 million (95% UI: 3.8–4.3). Western Europe exhibited the highest regional burden throughout the study period. Nationally, Denmark demonstrated the highest annual percentage change (APC) in the age-standardized incidence rate (ASIR) at 1.34%, followed by France (1.18%), Switzerland (0.85%), Germany (0.82%), and the United States (0.33%). Similarly, the highest APC in the age-standardized mortality rate (ASMR) was observed in Denmark (1.25%), followed by Switzerland (0.78%), France (0.73%), and the United States (0.20%). In 2021, the age group 70–74 years recorded the highest incidence (36,968; 95% UI: 34,001–38,744), mortality (34,990; 95% UI: 32,218–36,771), and DALYs (703,300; 95% UI: 646,488–738,141). Gender-specific analyses revealed that females exhibited a greater burden increase, with APCs of 0.52% in ASIR and 0.30% in ASMR, compared to 0.28% and 0.10%, respectively, in males. Notably, the age-standardized DALY rate (ASDALR) increased by 0.20% in females but decreased by 0.05% in males. **Conclusions:** Deaths due to PC accounted for 7.77% of all cancer related casualties in 2021 in HIC. The concentration of disease burden in older populations (70–74 years) and the greater increase observed in females compared to males highlight critical demographic and gender-specific disparities. Furthermore, the increase in DALYs, even in regions with stabilizing or declining mortality, calls for enhanced strategies to address long-term disability and improve quality of life. Research Sponsor: None.

Annual percentage of change in pancreatic cancer from 1990-2021 in high income region, age-standardized rate (per 100,000).

High Income Region	AAPC (%), 1990-2021, ASIR	AAPC (%), 1990-2021, ASMR	AAPC (%), 1990-2021, ASDALR
Australasia	0.38	0.15	0.01
High-income Asia Pacific	0.42	0.22	-0.01
High-income North America	0.29	0.14	0.04
Southern Latin America	-0.08	-0.14	-0.18
Western Europe	0.46	0.27	0.14

10550 Poster Session

Evaluation of a plasma cell-free DNA methylation-based multi-cancer detection test.

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Background: Blood-based multi-cancer detection (MCD) tests hold promise for early cancer detection. MCD tests should demonstrate high specificity, clinically meaningful sensitivity, and provide information to guide clinical diagnostic evaluation. **Methods:** We developed an MCD test that leverages a next-generation sequencing epigenomics hybrid capture assay (Shield) to measure DNA methylation in regions differentially methylated across solid tumor cancers. We then implemented a two-step classification algorithm. First, a regression model (multi-cancer classifier) was trained to distinguish cancer from non-cancer samples at 98% target specificity. Next, a cancer signal of origin (CSO) model was trained to categorize 10 solid tumors (Table 1) in samples predicted to be cancer. The test was evaluated in a blinded case-control cohort of plasma samples (3mL; Streck) from adults with treatment naïve cancer, or who were self-reported cancer free with 1 year of follow-up (NCT05334069). **Results:** Final evaluable dataset was 962 participants (excludes 31 (3.1%) that failed quality control). Median age was 62 years (range: 40-78). 55% were female. Self-reported race was 81% White. Observed specificity was 98.6% (436/442). Sensitivity for the 10 cancer types included in the CSO model was 59.7% (224/375) and was 55.7% (263/472) overall when incorporating 4 solid tumor types not included in the CSO model. Primary or secondary CSO prediction was 92% accurate for the cancer types included (Table 1). **Conclusions:** In this cohort, this MCD test shows 59.7% sensitivity, 98.6% specificity, and 92% primary or secondary CSO accuracy for the cancer types included. Integrating an MCD test with an FDA approved blood-based CRC screening test may increase the MCD clinical value in the intended use population, which should be studied further. A version of this MCD test is being studied in a prospective, interventional study evaluating MCD testing feasibility. Research Sponsor: None.

Overall and per cancer sensitivity and CSO accuracy results.

	Overall Sensitivity %	Sensitivity Stage I/II, %	Sensitivity Stage III/IV, %	Primary or Secondary CSO Accuracy, %
All Samples, 472	**56%**	**31%**	**81%**	-
Cancers included in CSO caller, 375	**60%**	**35%**	**84%**	**92%**
Bladder, 13	62%	44%	100%	75%
Breast, 86	45%	17%	88%	97%
Colorectal, 41	83%	53%	100%	91%
Esophageal-Stomach, 25	96%	100%	95%	96%
Hepatocellular, 16	94%	100%	92%	67%
Lung, 57	67%	41%	93%	97%
Ovarian, 20	70%	80%	67%	100%
Pancreas, 59	68%	50%	96%	93%
Prostate, 59	21%	3%	41%	92%
Cancers not included in CSO caller, 97	**40%**	**18%**	**65%**	
Endometrial, 29	38%	12%	75%	
Head & Neck, 15	80%	100%	63%	
Kidney, 44	34%	0%	71%	
Melanoma, 9	11%	0%	20%	

10551 Poster Session

Incidence of viral and non-viral etiologies of hepatocellular carcinoma (HCC) in the US over time by race and ethnicity.

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Background: HCC has an incidence of 5–6 cases per person-yr in the US, with varying rates among different racial and ethnic groups. While viral HCC accounts for ~50% of all HCC cases in North America, recently, a shift from viral to non-viral HCC was observed in the US. Here, we investigate the incidence of viral and non-viral HCC over time across different racial and ethnic groups in the US. **Methods:** This is a cross-sectional study using data from the TARGET-HCC registry, a longitudinal observational cohort study enrolling adult patients (pts) with newly diagnosed HCC across 43 academic and community centers in the US. Pts were enrolled from 1 Jan 2017 to 30 Sep 2023, and consented to share medical records 36 mo retrospectively and prospectively for up to 60 mo. **Results:** Among 2,924 enrolled pts, etiology was available for 2,139 (73%). Median (IQR) age was 64 (59, 68) yr and 77% were male. At HCC diagnosis, 66% of pts had BCLC stage 0/A, 16% BCLC B, 13% BCLC C, and 6% BCLC D; 69% of pts had Child-Pugh class A, 26% class B, and 5% class C. 1,727 (81%) pts had underlying cirrhosis. 1,484 (72%) pts were White, 414 (20%) Black/African American (Black/AA), 86 (4%) Asian/Native Hawaiian or Pacific Islander (Asian/NH/PI), and 68 (3%) American Indian/Alaskan Native. 1,786 (87%) pts were of non-Hispanic ethnicity and 257 (13%) of Hispanic ethnicity. The incidence of viral and non-viral HCC over time by race and ethnicity is shown in the Table. In the overall population, although the incidence of viral HCC decreased over time, it remained higher than that of non-viral HCC across all periods. The proportion of pts diagnosed with viral vs non-viral HCC was 75% vs 59% in 2014–2016, 69% vs 55% in 2017–2019, and 65% vs 57% in 2020–2023. **Conclusions:** Despite variations in the number of pts enrolled in each period, there is an overall trend of decreasing incidence of viral HCC over time across all racial groups. The incidence of viral HCC has declined among non-Hispanics but increased among Hispanics. Nevertheless, non-viral liver disease remains the most common cause of HCC in Hispanics. Research Sponsor: AbbVie Inc.; n/a.

	2014–2016			2017–2019			2020–2023		
Race (R)/Ethnicity (E)[a]	Total, N	Viral, n (%)	Non-Viral, n (%)	Total, N	Viral, n (%)	Non-Viral, n (%)	Total, N	Viral, n (%)	Non-Viral, n (%)
Overall, N=2138[b]	545	411 (75)	324 (59)	1441	994 (69)	793 (55)	152	99 (65)	87 (57)
R: White	371	253 (68)	241 (65)	1003	631 (63)	608 (61)	110	66 (60)	71 (65)
R: Black/AA	114	111 (97)	53 (46)	268	243 (91)	97 (36)	32	29 (91)	9 (28)
R: Asian/NH/PI	25	23 (92)	9 (36)	61	46 (75)	26 (43)	0	0	0
R: American Indian/Alaska Native	12	9 (75)	5 (42)	55	37 (67)	32 (58)	1	0	1 (100)
E: Non-Hispanic	454	352 (78)	263 (58)	1210	842 (70)	658 (54)	121	78 (64)	66 (55)
E: Hispanic	62	35 (56)	43 (69)	174	107 (61)	109 (63)	21	14 (67)	16 (76)

The percentage may add to more than 100 because pts have mixed etiologies.
[a]Etiology for 7 pts of "Other" ethnicities: 2 viral in 2014–2016; 4 viral and 3 non-viral in 2017–2020.
[b]1 pt diagnosed ≤2013 not included.

10552 Poster Session

Early-onset (EO) cancer trends in Brazil: A comprehensive analysis of hospital-based cancer registry data (2000–2019).

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Background: The rising incidence of early-onset (EO) cancers (< 45 years) since the 1990s presents a global public health challenge. In Brazil, Hospital-Based Cancer Registries (HCR) provide essential data for understanding cancer epidemiology, encompassing diagnosis, treatment, and outcomes. This study analyzes temporal trends in EO cancer incidence rates (IR) and clinical data in Brazil from 2000 to 2019. **Methods:** A retrospective cohort study was conducted using data from the Brazilian HCR system (SIS-RHC). Individuals aged 19–44 years, diagnosed with malignant neoplasms (ICD-10) and treated within Brazil's oncology network, were included. Temporal trends in cancer incidence (2000–2019) were evaluated using the Mann-Kendall test, and bivariate analyses explored associations between demographic and clinical variables. **Results:** A total of 701,115 individuals were included (mean age: 35 years, SD: 6.62); the cohort was predominantly female (71.9%), non-white (54%), with basic education (49%), and residing in the southeast region (44%). Family history of cancer was reported by 47%, alcohol use by 28%, and smoking by 29%. The Unified Health System (SUS) referred to 79% of cases. Breast (21%) and cervical (21%) cancers were the most prevalent malignancies, followed by non-melanoma skin cancers (8.8%) and thyroid cancer (7.3%). Colon cancer ranked seventh (2.8%). Most cases were diagnosed at localized stages (51.7%), with 28.3% regional and 19.8% metastatic. Localized diagnoses increased significantly over time. Sex differences were observed across age groups and cancer stages ($p < 0.001$). Annual cancer cases rose significantly from 93,714 cases (2000 to 2004) to 222,301 cases (2015 to 2019) ($p < 0.001$). Incidence rates (IR) increased with age and over time, rising from 5.65 (ages 19–24) and 46.80 (ages 40–44) in 2000 to 12.28 and 77.11 in 2019. Peaks in IR were observed in 2014 and 2016, reaching 17.41 (ages 19–24) and 111.42 (ages 40–44). Overall, reported cases increased by 219% during the study period. **Conclusions:** The incidence of EO cancers in Brazil rose by 219% between 2000 and 2019, with breast cancer as the leading malignancy. These findings emphasize the growing cancer burden among younger populations and the need for enhanced cancer registries to guide targeted EO interventions. Future population-based studies are critical to validate and expand upon these results. Research Sponsor: Fundação de Amparo à Pesquisa e Inovação do Espírito Santo (FAPES); 155/2021.

10553 Poster Session

Evaluation of a polygenic risk score for breast cancer in Chinese women: A three-stage case-control study of 13,715 subjects.

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Background: Polygenic risk score (PRS) is a valuable tool for predicting the risk of breast cancer (BC). However, limited studies have been conducted in Chinese women. This study aimed to develop and validate a PRS which could be used to identify individuals with high risk of breast cancer. The associations between the PRS and patients' clinicopathological characteristics or survival outcomes were also evaluated. **Methods:** The PRS was developed based on findings from genome-wide association studies (GWAS) and validated in four independent cohorts with a three-stage design. A total of 7,056 patients and 6,659 controls were enrolled from Fujian Medical University Union Hospital (FJMUUH) and Shanghai Breast Cancer Genetics Study (SBCGS). Five approaches were utilized to calculate the PRS, including repeated logistic regression (RLR), logistic ridge regression (LRR), artificial neural network (ANN), random forest (RF) and support vector machine (SVM). Logistic regression analyses were performed to assess the association between established PRS and clinicopathological characteristics. The correlation between PRS and patients' survival outcomes was evaluated by cox regression models. **Results:** The LRR-based PRS was indicated to have the best predictive accuracy among five approaches (AUC = 0.601, OR per 1 SD increase = 1.39, Table 1). Women in the top 5% and 80-95% percentiles of PRS had a 1.43-fold and a 1.34-fold elevated risk of developing breast cancer compared with those at average risk (PRS in 40-60th percentiles). The predictive performance of PRS for patients with HER-2 positive tumors was demonstrated to be higher than that of HER-2 negative tumors (AUC = 0.612 vs 0.585, OR = 1.47 vs 1.35). It was also identified that the PRS was not correlated with age at diagnosis nor tumor characteristics. In survival analyses, an increase in PRS was associated with unfavorable disease-free survival (DFS) for ER negative patients (HR = 1.48, 95% CI = 1.08-2.03, p= 0.016). However, this association diminished after adjusting for clinicopathological characteristics. Regarding overall survival (OS), we observed significant correlations between increased PRS and overall survival (adjusted HR = 1.35, 95% CI = 1.05-1.75, p= 0.021), especially among ER negative patients (adjusted HR = 1.57, 95% CI = 1.07-2.30, p= 0.021) in the multivariate model. **Conclusions:** The PRS could provide additional information for Chinese women at high risk of breast cancer and holds significant value for BC screening. An increase in PRS also indicates an unfavorable prognosis and could play a crucial role in the clinical management of breast cancer patients at the time of diagnosis. Research Sponsor: None.

10554 Poster Session

Trends in cancer incidence in Singapore over the last two decades.

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Background: Singapore has witnessed a significant rise in cancer incidence over recent decades. The most rapid increase in age-specific incidence of cancer was observed among younger age group in recent years. Gaining insight into the factors driving this trend is essential for developing prevention strategies. **Methods:** This population-based study analysed 268,189 cancer cases diagnosed between 2000 and 2021 from the Singapore Cancer Registry via the TRUST platform (https://trustplatform.sg/). Cases diagnosed in 2020 and 2021 were subsequently excluded from the trend analysis due to potential COVID-19 effects. We first examined the temporal trend of age-standardized incidence rate and estimated average annual percentage changes (AAPC) using Joinpoint regression analysis. Decomposition analysis was performed to assess the increase in cancer cases attributable to changes in population age structure, population size, and cancer risk due to epidemiological factors. We conducted an Age-Period-Cohort analysis to estimate the net drift, local drift, and the cohort- and period-specific incidence rate ratio (IRR). These analyses were repeated for the four most common cancers in Singapore: breast, colorectal, lung and prostate cancer. **Results:** Over the 22-year period, the number of cancer cases nearly doubled for both men and women. The age-standardized incidence rate rose from 200.77 per 100,000 to 246.43 per 100,000 for women and remained stable at 235.30 per 100,000 for men. The AAPC was 0.92% (0.73%-1.15%) for women and 0.13% (-0.01%- 0.30%) for men, and was the largest for female breast and prostate cancer. Decomposition analysis showed that aging population was the primary driver for an overall increase in cancer cases, whereas change in cancer risk had the highest impact for breast cancer, prostate cancer and lung cancer in men. The Age-Period-Cohort analysis revealed significant period and birth cohort effects with a net drift of 1.17% (0.90% - 1.43%) for women and 0.78% (0.54% - 1.05%) for men. For breast cancer, both birth cohort and period effects showed an increasing trend [IRRcohort1990vs1950 = 1.47 (0.98-2.22), IRRperiod2015vs2000 = 1.24 (1.17-1.31)]. A similar trend was observed for prostate cancer [IRRcohort1970vs1935 = 3.42(1.83-6.38), IRRperiod2015vs2000 = 1.74(1.59-1.92)]. In contrast, a decreasing trend was noted for lung cancer in men [IRRcohort1970vs1945= 0.65(0.48-0.87), IRRperiod2015vs2000 = 0.76 (0.70-0.82)]. **Conclusions:** The rising cancer incidence in Singapore is multifactorial, with demographic factors, particularly an ageing population, playing a significant role. Our analysis revealed important temporal patterns and a notable rise in cancer risk for breast and prostate cancers, likely influenced by shifts in environmental and lifestyle factors, and cancer screening. These insights should be used to inform and guide future public health policies aimed at addressing modifiable risk factors. Research Sponsor: Singapore Translational Cancer Consortium.

10555 Poster Session

Racial differences in the association between agent orange exposure and the progression of monoclonal gammopathy of undetermined significance to multiple myeloma in US Veterans.

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Background: Agent Orange (AO), an herbicide used during the Vietnam War Era (1/9/1962-5/7/1975), is implicated in myelomagenesis due to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). TCDD has a long half-life (3.2 years) and many occupations (e.g. pest control, agricultural, etc) are exposed. Work from our group (Liu L, et al., *JHO* 2024) demonstrated that AO exposure during the high TCDD period of 1/9/1962-11/30/1965 was associated with increased risk of monoclonal gammopathy of undetermined significance (MGUS) to myeloma (MM) progression. Given the higher incidence of MM in Black patients, we assessed whether there are racial differences in this association. **Methods:** We identified patients diagnosed with MGUS from 10/1/1999-12/31/2021 in the Veterans Health Administration. a published natural language processing-based algorithm was used to confirm diagnoses of MGUS and MM. We excluded: progression<1y, non-IgG/IgA subtype, race other than Black or White due to low numbers, no service during 1/9/1962-5/7/1975, and birth years outside of 1924-1953 so that the groups with and without exposures both have the same birth year range. Patients were stratified by race (Black or White). AO exposure was stratified by three TCDD levels: high (1/9/1962–11/30/1965), medium (12/1/1965–12/31/1970), or low (1/1/1971–5/7/1975). The association between AO exposure levels and progression were estimated using multivariable Fine-Gray subdistribution hazard model with death as a competing event and presented by multivariable-adjusted hazard ratio (aHR). The covariates included age, sex, body mass index (BMI), monoclonal protein (M-protein) level, MGUS subtype, and Charlson Comorbidity Index (CCI). **Results:** We identified 3,960 Black patients (AO exposed: n=865 [21.8%]) and 6,887 White patients (AO exposed: n=1,986 [28.8%]) with MGUS. Compared to no exposure: Black patients had aHR 1.03 (95% CI 0.51-2.06) for high, aHR 0.88 (95% CI 0.65-1.17) for medium, and aHR 0.3 (0.08-1.18) for low exposure, and White patients had aHR 1.80 (95% CI 1.14-2.83) for high, aHR 1.18 (95% CI 0.95-1.46) for medium, and aHR 1.17 (95% CI 0.66-2.05) for low exposure. **Conclusions:** White patients had an 80% increased risk of progression with AO exposure during the high TCDD period. No association was observed in Black patients. Research Sponsor: National Cancer Institute; R01 CA253475; National Cancer Institute; CA265735.

Multivariable analysis of the association between AO exposure and risk of progression to MM by race.

Variable	Black (N=3,960) aHR (95% CI)	P-value	White (N=6,887) aHR (95% CI)	P-value
AO Exposure				
No exposure	**ref.**		**ref.**	
Low TCDD Level	0.30 (0.08-1.18)	0.08	1.17 (0.66-2.05)	0.59
Medium TCDD Level	0.88 (0.65-1.17)	0.37	1.18 (0.95-1.46)	0.14
High TCDD Level	1.03 (0.51-2.06)	0.94	1.80 (1.14-2.83)	0.01

The covariates included age, sex, MGUS subtype, BMI, m-protein, and CCI at MGUS diagnosis.

10556 Poster Session

Lung cancer combined with interstitial lung disease: Controversial role of preexisting hypertension and emphysema observed in a fully followed 20-year patient cohort.

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Background: The coexistence of interstitial lung diseases (ILD) and lung cancer (LC) presents a clinical challenge. ILD, including idiopathic pulmonary fibrosis (IPF) and non-IPF entities, is associated with an elevated risk of LC. However, the clinical features, treatment patterns, and survival outcomes of ILD-LC, especially IPF-LC, remain underexplored. We aimed to comprehensively evaluate survival outcomes and risk factors for mortality of ILD-LC patients based on a real-world long-term clinical cohort. **Methods:** A total of 1,341 eligible patients for this study were drawn from the Epidemiology and Genetics of Lung Cancer research program database (Mayo Clinic) including 96 IPF-LC, 111 Non-IPF ILD-LC, 99 ILD-only, and 1,035 propensity-matched LC-only patients (Controls). Data were collected on demographics, comorbidities, tumor features, treatment, and patient outcomes. Survival analyses used Kaplan-Meier methods; risk factors were assessed via Cox Proportional Hazards models. All comparisons reported below were statistically significant with p-values$\leq$0.001 unless specified. **Results:** Among the 20,470 primary LC patients who were diagnosed from 1997 through 2016 and followed to 2021, 207 (1.0%) had ILD-LC, of which 96 (46.4%) had IPF. Comparing to Controls, ILD-LC patients were 4 years older at the time of LC diagnosis, 63.8% (vs. 52.8%) male, had a higher rate of former smokers (60.4% vs. 47.3%), a lower proportion of adenocarcinoma (37.7% vs. 57.5%), and a higher proportion of squamous cell (28.0% vs. 20.3%) and small cell carcinoma (13.5% vs. 8.4%). Although no significant differences in either LC stage or grade, ILD-LC patients had a significantly higher mortality rate (90.3% vs. 78.8%), particularly among IPF-LC patients (97.9% vs. 83.8%). ILD-LC patients were less likely to undergo surgery or receiving pharmacological treatments (73.9% vs. 93.5%). The median 5-year overall survival rate (OS, months) were 49.5 for Controls, 35.2 for Non-IPF ILD-LC patients, and 15.9 for IPF-LC patients. Analysis of six most common comorbidities revealed that pulmonary hypertension was associated with worse OS in ILD-LC patients compared to those without it (11.9% vs. 20.1%, $P < 0.05$); however unexpectedly, hypertension in ILD-LC patients was associated with better OS (21.3% vs. 14.4%) and emphysema in IPF-LC patients with better OS (7.9% vs. 3.4%, $P < 0.05$) when compared to those without the two comorbidities, respectively. **Conclusions:** This study highlights the poorer survival outcomes in ILD-LC patients, particularly IPF-LC patients, emphasizing the need for further investigation into optimized therapies and comorbidity management. Our findings also call for attention to two unexpected associations of hypertension and emphysema, warranting in-depth research on the possible biological and physiological mechanisms. Research Sponsor: U.S. National Institutes of Health; R03 CA77118, R01 CA80127, R01 CA84354; National Institute on Aging; R01 AG034676, R01 AG052425; Mayo Clinic Foundation.

10557 Poster Session

GLP-1 receptor agonists and breast cancer risk in type 2 diabetes.

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Background: Type 2 diabetes mellitus (T2DM) is associated with an increased risk of breast cancer. Glucagon-like peptide 1 receptor agonists (GLP-1RAs), which improve glucose metabolism and promote weight loss, are widely used to treat T2DM. However, the trophic activity of GLP-1RAs is concerning. In diabetic patients, GLP-1 receptors are highly expressed in breast cancer tissues and their activation can lead to breast cancer cell proliferation. Combining GLP-1RAs and dipeptidyl-peptidase IV inhibitors (DPP4i), which also enhance GLP-1 pathway, was associated with more cases of breast cancer in the FDA Adverse Event Reporting system. We investigated the relationship of GLP-1RAs with breast cancer in T2DM patients using Epic Cosmos, a HIPPA law-compliant dataset with longitudinal records of 289 million de-identified patients. **Methods:** A retrospective cohort study was performed on patients with T2DM but without breast cancer. Patients treated with GLP1-1RAs between 1/1/2010 and 12/31/2020 were compared to those treated with metformin, sodium-glucose cotransporter-2 inhibitor (SGLT2i), sulfonylurea (SU), DPP4i, thiazolidinediones (TZD) or insulin. The incidence of breast cancer was tracked from 1/1/2021 to 12/12/2024. Subgroup analysis was conducted on White patients, African American patients, and five subgroups with different BMI ranges. Risk ratio (RR) and 95% confidence interval (CI) were calculated via RStudio (version 2024.09.1). **Results:** Patients with T2DM and treated with GLP-1RAs had a higher incidence of breast cancer compared to patients treated with each of the other antidiabetics (Table). Results of subgroup analysis were consistent with the overall effect; except that in the obese subgroups, GLP-1RA exposure was not associated with breast cancer compared with DPP4i. Weight and age were not significantly different between each pair of cohorts. **Conclusions:** GLP-1RAs was associated with an increased incidence of breast cancer compared to other antidiabetic regimens in patients with T2DM in a long-term observation. Acting on identical pathway, GLP-1RAs may show a blunt effect versus DPP4i in obese patients. The study is empowered by an enormous sample size in Epic Cosmos. Future improvements include stratifying exposure levels and stringently matching confounders. Research Sponsor: None.

GLP-1RAs cohorts	Non-GLP-1RAs cohorts	GLP-1RAs cohorts cancer cases (%)	Non-GLP-1RAs cohorts cancer cases (%)	RR (95% CI)
(-) Metformin (N=209090)	(+) Metformin (N=4989038)	1406 (0.67%)	25037 (0.50%)	1.34 (1.27-1.41)
(-) SGLT2i (N=639303)	(+) SGLT2i (N=826786)	4014 (0.63%)	4380 (0.53%)	1.19 (1.14-1.24)
(-)SU (N=497603)	(+) SU (N=2465377)	3109 (0.63%)	11271 (0.46%)	1.37 (1.31-1.42)
(-)DPP4i (N=716984)	(+) DPP4i (N=1123264)	4220 (0.59%)	5966 (0.53%)	1.11 (1.07-1.15)
(-)TZD (N=838249)	(+) TZD (N=464680)	5212 (0.62%)	2141 (0.46%)	1.35 (1.28-1.42)
(-) Insulin (N=467130)	(+) Insulin (N=2757742)	2921 (0.63%)	9895 (0.36%)	1.74 (1.67-1.82)

Unmasking the link between sleep apnea and lung cancer risk: A retrospective propensity-matched cohort study.

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Background: Obstructive sleep apnea (OSA) is a prevalent disorder characterized by intermittent hypoxia, systemic inflammation, hypercapnia, and oxidative stress. These factors pose a risk for carcinogenesis and potential tumor formation. The association between OSA and lung cancer remains unclear. This study evaluates the impact of OSA on lung cancer incidence using a large-scale retrospective cohort analysis. **Methods:** A comparative outcomes analysis was conducted using the TriNetX database. Data were extracted from the Johns Hopkins Medicine healthcare organization. Two cohorts were defined: patients with OSA (Cohort 1, n = 124,100) and those without OSA (Cohort 2, n = 2,330,110). Propensity score matching (PSM) was employed to balance baseline characteristics, including age, gender, race, and comorbid conditions, resulting in 62,750 in each cohort. The primary outcome was lung cancer incidence (ICD-10: C34), with risk difference (RD), risk ratio (RR), and odds ratio (OR) calculated to compare the cohorts. Statistical significance was set at $p < 0.05$. **Results:** Before propensity score matching, the OSA cohort had a higher mean age (60.8 $\pm$ 16.6 vs. 51.8 $\pm$ 20.3 years) and a higher prevalence of comorbid conditions such as obesity, hypertension, and diabetes compared to the non-OSA cohort (all $p < 0.001$). After PSM, demographic and clinical characteristics were well-balanced between cohorts. In the matched analysis, the incidence of lung cancer was slightly higher in the OSA cohort at 0.8% (n = 530) compared to 0.7% (n = 440) in the non-OSA cohort. The RD was 0.1% (95% CI: 0.0%-0.2%, p = 0.004 via T-Test), and the RR was 1.205 (95% CI: 1.062-1.366). The OR for lung cancer in OSA patients relative to non-OSA patients was 1.206 (95% CI: 1.063-1.369). Kaplan-Meier survival analysis showed a modestly reduced time to lung cancer diagnosis in the OSA cohort, although the difference was not clinically significant. **Conclusions:** This study reveals a statistically significant association between OSA and lung cancer risk. Subsequent studies are needed to investigate the degree of clinical significance between OSA and lung cancer. OSA patients may benefit from screening and/or early intervention strategies. Additionally, further research is needed to elucidate the potential mechanism and pathogenesis of lung cancer formation in OSA patients. Research Sponsor: None.

Lung cancer incidence and associated risk estimates in patients with and without OSA.

Cohort	Lung cancer incidence	RD	RR	OR
OSA (n=62,750)	0.8% (n=530)	0.1% (95% CI: 0.0%-0.2%, p = 0.004	1.205 (95% CI: 1.062-1.366)	1.206 (95% CI: 1.063-1.369)
Non-OSA (n=62,750)	0.7% (n=440)			

10559 Poster Session

Exposure to Di-2-ethylhexyl phthalate and hormone receptor-positive breast cancer incidence.

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Background: Phthalates are ubiquitous environmental endocrine disruptors. As the predominant phthalate, di-2-ethylhexyl phthalate (DEHP) has been considered possibly carcinogenic to humans but large-scale longitudinal evidence is needed to further clarify its carcinogenicity. Up to date, no study have examined the in-situ DEHP exposure in breast cancer, in comparison with normal breast tissue or benign breast tumor.The present study aims to examine the association between DEHP exposure and incidence of hormone receptor-positive breast cancer (HR+BC) , both in a large cohort and in a group of patients whose in-situ DEHP exposure was analyzed. **Methods:** In 116,885 women of UK Biobank cohort, diagnosis of HR+BC was ascertained using general practitioner prescription records and information from National Health Service Cancer Registry and National Death Index. Baseline and yearly-average level of external DEHP exposure via water were estimated for each individual by linking chemical monitoring record of European Environment Agency with home address of the participants by Kriging interpolation model. We used Cox proportional hazards regression to estimate the association between DEHP exposure by water and risk of breast cancer. Furthermore, in-situ internal exposure level of DEHP in tumor tissue and normal breast tissue in 67 Chinese women with HR+BC or benign tumors was quantified using high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS), then binary Logistic regression was used to explore whether the in-situ DEHP level was higher in HR+BC compared to benign tumor or normal breast tissues. **Results:** In the UKB cohort women, during a median of 13.5 years follow up, the fourth quartile of baseline DEHP was associated with 1.20 fold risk of HR+BC (95% CI, 1.1 to1.4, $P < 0.001$). As for yearly-average exposure, each quartile of DEHP was positively associated with higher risk of HR+BC (HR, 1.12; 95% CI, 1.1 to 1.17, $P_{trend} < 0.001$). The fourth quartile of yearly-average DEHP was associated with 1.52 fold risk of HR+BC (95% CI, 1.31 to 1.78, $P < 0.001$). No significant association was found between DEHP exposure and hormone receptor-negative breast cancer ($P = 0.294$). In the Chinese women, the overall detection rate of DEHP (detected in any tissue type) in HR+BC women was significantly higher than in women with benign tumors (96.2% V.S. 7.1%, $P < 0.001$), and the detection rate of DEHP in breast cancer tissues was higher than in benign tumor tissue (55.7% V.S. 4.5%, $P < 0.001$). Logistic regression showed that breast cancer tissue was associated with a higher risk of DEHP contamination compared with benign tumor tissue (OR,11.77; 95% CI, 1.20 to 115.25, $P = 0.034$). **Conclusions:** Real-world level of DEHP exposure was associated with higher risk of HR+BC. The results may be crucial for effective and precise prevention of breast cancer. Research Sponsor: Chongqing Science and Technology Commission; 2024NSCQ-KJFZMSX0314; Daping hospital; ZXAIYB014.

10560 Poster Session

Burden and trend of breast cancer attributable to high red meat consumption in the United States from 1990-2021: An insight from the Global Burden of Disease study 2021.

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Background: Breast Cancer (BC) 4th most common cause of cancer in the United States (USA). In the USA, dietary factors, particularly high red meat consumption, have been implicated in the increased risk of breast cancer among women. Studies suggest that red meat intake is associated with a higher incidence of breast cancer, possibly due to carcinogens formed during cooking at high temperatures. **Methods:** We estimated incidence, deaths and disability-adjusted life years (DALYs), Years lived with disability (YLDs) due to BC attributable to diet high in red meat by age, year, location across the USA from 1990-2021 using global burden of disease study 2021. **Results:** The total percentage change (TPC) in deaths increased by 9% (range: -59% to 54%), while DALYs rose by 1% (range: -47% to 51%) from 1990 to 2021. At the sub-national level, the highest TPC in deaths was observed in Nevada, with a 148% increase, followed by Utah (80%), Alaska (69%), and Arizona (68%) over the same period. In contrast, the District of Columbia experienced the largest decrease, with a 39% reduction in deaths. Age-wise, the highest number of deaths in 2021 occurred in the 70–74-year age group, with 968 cases, while the 60–64-year age group recorded the highest number of DALYs at 26,627. Among individuals aged 55 years and older, there were 6,253 deaths (range: -2,860 to 13,435), while those aged 20–54 years recorded 1,056 deaths (range: 400 to 2,267). Regarding DALYs, the 20–54-year age group accounted for 52,503 (range: -19,790 to 114,305), and the 55+ age group contributed 142,073 (range: -70,770 to 303,577) in 2021. **Conclusions:** The results underscore the importance of widespread education campaigns promoting healthier dietary patterns, policy interventions to encourage reduced red meat consumption, and targeted prevention strategies for at-risk populations. Clinically, these findings emphasize the critical role of healthcare providers in integrating dietary risk assessments and personalized nutritional counseling into routine care. By addressing this modifiable risk factor, both public health initiatives and clinical practices can work synergistically to reduce the burden of BC, improve patient outcomes, and advance preventive care strategies. Research Sponsor: None.

10561 Poster Session

Recent trends in cancer distribution and survival outcomes among adolescent and young adult patients: A national data analysis.

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Background: Cancer distribution varies significantly among adolescents and young adults (AYAs) aged 15 to 39. Understanding these trends is essential for developing strategies to enhance early detection and improve survival outcomes. This study analyzes national data to assess time-bound changes in new cases and survival outcomes within the AYA population. **Methods:** A retrospective cohort study was performed using the National Cancer Database to analyze AYA patients diagnosed with the 20 most common cancer types by mortality from 2004 to 2021. Patients with confirmed malignant neoplasms, ≥6 months of follow-up, and known survival status were included. Descriptive statistical methods were used to evaluate demographic characteristics, while survival outcomes were analyzed using Kaplan-Meier estimates and multivariable Cox proportional hazard models. Linear regression models were used to analyze changes in new cases over time for each cancer group. **Results:** A total of 637,460 AYA cancer patients were included in the analysis. The median age was 33 years (IQR: 27-37). Most were female (61.5%) and White (79.6%). Breast cancer was the most common malignancy (21.3%), followed by central nervous system (CNS) tumors (11.6%), melanoma (9.3%), testicular cancer (8.5%) and colorectal cancer (CRC, 6.9%). Between 2004 and 2021, CRC, leukemia, liver, pancreatic, renal, stomach, and uterine cancers showed significant increases in new cases ($P< 0.001$), with CRC having the highest increase (annual rate change [β]:1.7, $P< 0.001$). Bladder, Hodgkin lymphoma (HL), melanoma, cervical and lung cancer significantly decreased ($P< 0.001$), with melanoma showing the largest decline (β: -1.83, $P< 0.001$). Breast, CNS, and ovarian cancers showed no significant trends. Among AYA cancer patients, the survival rate at 3 and 6 years were 89.2% and 83.9%, respectively. The overall survival rate at 12 years was 78.1%, with the highest survival rates observed in testicular cancer (93.1%), HL (91.4%) and melanoma (90.8%), and the lowest in liver (38.6%) and stomach cancer (41.3%). AYA cancer patients aged 35–39 (HR: 1.28, 95% CI:1.25-1.30, $P< 0.001$), Black (HR: 1.47, 95% CI: 1.45-1.5, $P< 0.001$), and Hispanic individuals (HR: 1.03, 95% CI: 1.01-1.05, $P= 0.003$) had worse survival outcomes. **Conclusions:** Our findings indicate that the proportion of AYAs diagnosed with certain cancers, such as colorectal, liver, renal and stomach cancers, has significantly increased over the past two decades. Prioritizing early detection and tailored treatment strategies are crucial to addressing this growing challenge. Further research is needed to understand the underlying factors contributing to these trends. Research Sponsor: None.

Annual rate changes in cancer distribution.

Cancer group	β	P
↑Trends		
CRC	1.7	<0.001
Renal	0.63	<0.001
Uterus	0.53	<0.001
↓Trends		
Melanoma	-1.83	<0.001
HL	-0.84	<0.001
Cervical	-0.66	<0.001

Epidemiology of *MET* gene mRNA expression in metastatic colorectal cancer: Analyses of a real-world clinicogenomic database.

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Background: The *MET* proto-oncogene encodes the c-Met protein and is associated with promotion of tumor growth, angiogenesis, metastasis, and drug resistance. Our objective was to describe the prevalence of increased corresponding to c-Met protein expression and its associations with demographic and clinical characteristics among patients with metastatic colorectal cancer (mCRC) in a US-based clinicogenomic database. **Methods:** We conducted a retrospective cohort study of patients diagnosed with mCRC between 2014 and 2023 using the ConcertAI Patient360 electronic health record database with linkage to Caris Life Sciences genomic data. Patients were followed from first-line therapy (index time) until death or end of study follow up (Jan 2024). A 5-fold cross-validated and cross-cohort tested machine learning classifier trained on c-Met protein immunohistochemistry (IHC) labels (defined as 3+, ≥10% staining) was applied to derive prevalence of increased MET gene mRNA expression from whole transcriptome sequencing. Prevalence rate ratios (RR) with 95% confidence intervals (CI) were calculated using modified Poisson regression. **Results:** From an overall cohort of 1,020 patients with mCRC with a median age of 63 at metastatic diagnosis, 46% were female and 70% were non-Hispanic White, 20% non-Hispanic Black, 1% non-Hispanic Asian, and 5% Hispanic. At mCRC diagnosis, 81% had an ECOG performance status of 0-1 and 71% were diagnosed with de novo metastatic disease. The overall prevalence of increased MET gene mRNA expression corresponding to 3+, ≥10% c-Met IHC staining in the cohort was 35% (95% CI 32-38) and most samples (84%) were collected prior to treatment initiation. Patients with and without increased expression at this cutoff were broadly similar with respect to demographic and clinical characteristics. However, trends suggested that patients with increased expression had greater representation of individuals that were ages ≥75 years, non-Hispanic Black, had body mass index (BMI) <18.5 kg/m2, ECOG of ≥2, colon as primary tumor site and were microsatellite stable. **Conclusions:** Increased MET gene mRNA expression was observed among 35% of patients with mCRC in our cohort and was correlated with older age, low BMI at metastatic diagnosis, non-Hispanic Black race/ethnicity, poor performance status, colon as primary site, and microsatellite stable tumors. Research Sponsor: AbbVie.

		Prevalence	RR (95% CI)			Prevalence	RR (95% CI)
Age, years	<45	32%	REF	Race/ ethnicity	NH White	35%	REF
	45-54	34%	1.06 (0.75, 1.50)		NH Black	40%	1.12 (0.92, 1.36)
	55-64	33%	1.03 (0.73, 1.46)	ECOG	0	34%	REF
	65-74	35%	1.07 (0.77, 1.50)		1	35%	1.03 (0.85, 1.24)
	≥75	42%	1.30 (0.93, 1.83)		≥2	44%	1.29 (1.00, 1.68)
BMI (kg/ m^2)	<18.5	53%	1.47 (1.03, 2.10)	Primary site	Rectum	29%	REF
	18.5-24.9	36%	REF		Colon	37%	1.29 (1.03, 1.62)
	25.0-29.9	35%	0.96 (0.78, 1.19)	MSS/MSI	MSI-H	28%	REF
	≥30.0	34%	0.94 (0.77, 1.16)		MSS	36%	1.28 (0.84, 1.96)

10563 Poster Session

Decoding tumour bacterial ecosystems: Topological data analysis of bacterial association with immunogenicity.

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Background: The tumour microbiome is increasingly recognised as a key contributor to cancer progression and clinical outcomes, as highlighted in recent iterations of the Hallmarks of Cancer. Translating microbial signatures into actionable insights is hampered by a reliance on dimensionality reduction and a limited capacity to dissect non-linear relationships, leading to incomplete and inconsistent findings. Topological Data Analysis (TDA) is an unsupervised machine learning method that overcomes these limitations by preserving the complexity of high-dimensional data. Here, we applied TDA to characterise tumoural bacterial ecosystems across cancer types. **Methods:** Analysis was conducted using BioCorteX's knowledge graph and proprietary engines v20250124_015926. The dataset constituted of 551 sequenced primary tumour microbiome samples from six cancer types, as well as associated host age and gender. TDA Mapper was used to generate network graphs of the bacterial data, combined with an enrichment algorithm to analyse host metadata. Clusters in the TDA network represent samples with overlapping microbiome features. **Results:** The resultant network graph shows clear clustering of tumour bacteria along cancer types, suggesting distinct signatures of tumoural bacteria for each cancer. Notably, TNCB and melanoma cluster in the same area, while ovarian, colorectal, and glioblastoma cluster together in a different area of the graph. NSCLC clusters separately to both of the other two major clusters. Host age and gender do not significantly interact with the bacterial signatures or the cancer types. **Conclusions:** This strengthens the notion of highly cancer-specific tumoural bacteria, while also highlighting the similarities observed across cancer types. Notably, the 2 main clusters could suggest a bacterial association with immunogenicity: TNBC and melanoma tumours are both immune-responsive, while ovarian, colorectal, and glioblastoma tumours are generally not. Previous studies have suggested a major role of tumoural bacteria in immune responses, and this study suggests that tumoural bacteria can distinguish cancer immunogenicity. Further, it demonstrates the potential of TDA to extract novel insights from large, high-dimensional datasets, surpassing traditional approaches. Capturing non-linear associations is crucial for understanding complex host-bacteria interactions, paving the way for more precise characterisation of cancer-specific microbial signatures, with implications for oncology and therapeutic development. Research Sponsor: BioCorteX Inc.

10564 Poster Session

Environmental PFAS exposure as an understudied social determinant of health for endometrial cancer disparities: A geospatial study in Florida.

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Background: Endometrial cancer (EC) is the most common gynecological malignancy in the U.S. Although overall survival rate for EC in the US is 81%, non-Hispanic Black (NHB) women die from EC at higher rates than non-Hispanic White (NHW) women. Currently, population-based research on social determinants of health associated with EC disparities is limited. PFAS exposure has been linked to increased risk for EC, but the potential impacts of environmental PFAS exposure on EC disparities are largely understudied. This research examined how EC incidence rates and mortality odds by census tracts vary with respect to proximity to industrial PFAS facilities as well as drinking water PFAS contamination in Florida. **Methods:** Florida cancer registry data from 2011 to 2020 was used to calculate age-adjusted incidence rates and mortality odds (number of mortalities divided by number of cases diagnosed) of both Type I and Type II EC by race/ethnicity for all census tracts in Florida. Data on the locations of industrial facilities handling PFAS as well as ZIP codes with public drinking water tested positive for PFAS were obtained from US EPA. A geographic information system was used to calculate indicators of proximity to PFAS facilities within 5 km of a census tract. Statistical tests including two-way ANOVA and two-sample t-test were used to compare mean incidence rates and mortality odds for three levels of PFAS proximity and drinking water PFAS status. **Results:** A total of 11,796 cases (8,931 in NHW, 1,821 in Hispanics, and 1,044 in NHB) of Type I EC and 9,715 cases (6,088 in NHWs, 1,450 in Hispanics, and 2,177 in NHB) of Type II EC were diagnosed and geocoded to 3,095 census tracts in Florida from 2011 to 2020. ANOVA showed that higher proximity to PFAS facilities is associated with higher rates of poverty as well as higher likelihood of drinking water PFAS contamination. Census tracts with higher proximity to PFAS show higher age-adjusted incidence and mortality odds for both Types I and II EC in NHW. NHB living in areas with higher PFAS proximity show higher mortality odds, while no statistically significant associations were found for Hispanic. T-tests showed that positive drinking water PFAS status is associated with higher aged-adjusted incidence and mortality odds for Type I EC in NHW as well as higher type II EC mortality odds in NHB and Hispanic. **Conclusions:** Results of this study demonstrate environmental PFAS exposure as a critical yet underexplored social determinant of health for EC epidemiology. Further research is needed to unearth the effect mechanism and to firmly establish PFAS exposure as a risk factor for EC disparities in the population. Such efforts can help develop public health policies to protect vulnerable populations from PFAS exposure and subsequent EC development as well as to accelerate the regulation process for environmental PFAS contamination. Research Sponsor: None.

10565 Poster Session

Nationwide analysis and trend of liver cancer mortality attributable to drug use in United States from 1991 to 2021.

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Background: Liver cancer attributable to drug use represents an escalating public health concern in the United States (US). This study analyzes mortality, and related metrics for liver cancer attributed to drug use from 1991 to 2021, focusing on national and state-level trends and examining gender disparities and geographic variations with projections of Age-standardized mortality rates (ASMR) extending to 2040. **Methods:** The Global Burden of Disease (GBD) 2021 database was used to extract age-standardized mortality rate (ASMR) and disability-adjusted life years (DALY) for liver cancer mortality attributable to drug use in the United States from 1991 to 2021. Mortality data were stratified by gender, year, and region. Joinpoint regression analysis was performed to further evaluate trends and Annual Percent Change (APC) was calculated. Time series regression was used to calculate projected ASMR in 2040. **Results:** From 1991 - 2021, the ASMR for liver cancer attributable to drug use in the U.S. increased nearly threefold, from 0.54 per 100,000 (95% CI: 0.44–0.65) to 1.60 per 100,000 (APC:6.51%, 95% CI: 1.35–1.84). The DALY rate rose significantly from 15.22 per 100,000 to 39.36 per 100,000, highlighting the growing burden. Gender analysis revealed higher ASMRs in males, increasing from 0.74 to 2.12 per 100,000, compared to 0.38 to 1.14 per 100,000 in females, with APC of 6.25% and 6.55%, respectively. A state-level analysis of ASMR in 2021 showed the highest ASMR in California (2.27), followed by the District of Columbia (2.11), and Michigan (1.93). Meanwhile, Nebraska (0.73) had the lowest ASMR in 2021, followed by Iowa (0.91) and New York (1.15). The highest annual percent change (APC) was 11.47% in Nebraska, while the lowest was 3.58% in the District of Columbia. The Joinpoint regression analysis identifies five distinct periods of varying Annual Percent Changes (APC) in liver cancer mortality attributable to drug use. From 1991 to 2001, there was a sharp increase in mortality (APC = 5.75%), followed by slow growth between 2001-2007 (APC = 2.86%). However, from 2007-2010, there was a reacceleration (APC = 4.63%). Between 2010 - 2016, the growth rate decreased further (APC = 2.67%), after which 2016 - 2021, mortality rates stabilized (APC = 0.58%). The forecasted national ASMR for 2040 is estimated to be approximately 2.38 per 100,000. **Conclusions:** This study underscores a substantial rise in liver cancer mortality attributable to drug use in the United States from 1991 to 2021, with notable gender and geographic disparities. Projected increases in ASMR, coupled with observed trend shifts, emphasize the urgent need for targeted prevention and intervention strategies to mitigate the growing burden of drug use-related liver cancer. Research Sponsor: None.

10567 Poster Session

Germline pathogenic variants in *BRCA1-, BRCA2-*, and *PALB2-* genes among Ethiopian young women and men diagnosed with breast cancer.

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Background: Breast cancer incidence is rapidly increasing in low-and-middle-income countries (LMICs), where access to care is limited and survival outcome is poor. Young women and men are overrepresented among breast cancer (BC) patients diagnosed in LMICs in Sub-Saharan Africa (SSA), for reasons not yet fully understood. As hereditary cancer is more common in young women and men with BC, genetic factors may play a significant role. Even though carriers of germline pathogenic variants (PV) in the genes *BRCA1*, *BRCA2*, and *PALB2* have a very high risk of BC, studies of PV in these genes are very limited in SSA. In order to increase knowledge, this study investigated the prevalence of PV in high-risk BC susceptibility genes in young women and men diagnosed with BC in Ethiopia. **Methods:** This is a descriptive cross-sectional study. One-hundred young women (age 18-39) and men (all ages) diagnosed with invasive BC were included from Departments of Oncology and Surgery at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. Potential participants were given oral and written information by a trained physician, and those consenting were included in the study. Basic patient- and tumor characteristic as well as information about family history was collected. DNA was extracted from blood samples, before shipment to BRCAlab, Lund University, Sweden for genetic analysis of genes *BRCA1*, *BRCA2* and *PALB2*, using a gene panel and next generation sequencing on an Illumina platform. **Results:** Genetic analysis results were available for 89 study patients. There was a high proportion (21.3%) of PV in tested genes. In total, 19 PV were found in *BRCA1* (n = 7), *BRCA2* (n = 8) and *PALB2* (n = 4). One of the PV was in a male. There were five individuals with an identical PV in *BRCA1* (c.4524G > A, NM_007294.3), three individuals with identical PV in *BRCA2* (c.5159C > A, NM_000059.3), and two individuals with identical PV in *PALB2* (c.1216delG, NM_024675.4). Two novel PV not previously reported in literature were found, *BRCA1* c.5278-864_5332+621del, NM_007294.3 and *PALB2* c.1169_1170del, NM_024675.4. **Conclusions:** This study demonstrates that germline PV in *BRCA1*, *BRCA2* and *PALB2* are common among young women and men diagnosed with BC in Ethiopia, with over 1 out of 5 patients carrying a PV. Genetic predisposition appears to play an important role in the tumor genesis in the studied group. Multiple patients carried identical PV, which could indicate that the detected PV are founder variants. Since the majority of the patients in Ethiopia are young, and male BC seem more prevalent compared to in western countries, efforts directed to these groups and development of services for genetic testing and follow-up programs for carriers of PV should be further emphasized. This approach has the potential to reduce BC incidence, morbidity and mortality through increased awareness, risk-reducing procedures and earlier cancer detection. Research Sponsor: Swedish Research Council.

10568 Poster Session

Discrepancies between germline and somatic laboratories in the reporting of germline cancer predisposition variants.

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Background: Individuals with a cancer diagnosis may not qualify for germline testing to identify cancer predisposition variants due to restrictive testing guidelines. However, many have somatic Next Generation Sequencing (NGS) to guide treatment. Somatic NGS may offer a less restrictive approach to identify germline variant carriers. However, the rate of germline variant reporting via somatic NGS is unclear. We investigated what percentage of known germline variants were reported by matched somatic testing laboratories. **Methods:** Cancer patients seen at Rutgers Cancer Institute who had a positive germline report between 1/1/18 and 1/31/23 and at least one matched somatic NGS report on file were eligible for the study. We compared each germline-somatic report pair to analyze if the pathogenic/ likely pathogenic (P/LP) germline variant was reported by the somatic NGS laboratory. We also assessed factors impacting germline variant reporting. **Results:** A total of 65 cases were included. Of matched somatic reports, 52.9% reported the corresponding germline variant, while 47.1% of germline variants were not reported by the matched somatic laboratory. The most frequent reasons germline variants were not reported included: (1) the gene was not included on the somatic NGS panel (60%), (2) the germline variant was filtered out of reporting by the somatic NGS laboratory as a suspected incidental germline finding of limited treatment relevance (10%), (3) the variant was intronic (7.5%), and (4) the variant was a copy number variant (7.5%). Less common reasons germline variants were not reported included differences in variant interpretation, limited coverage in the region containing the variant, and suspected mosaicism and/or clonal hematopoiesis. **Conclusions:** Almost 50% of germline variants in this cohort were not reported by the corresponding somatic laboratory. So, our findings suggest that clinical providers cannot rely on somatic NGS for germline variant reporting. We also expanded on reasons certain germline variants were not reported by somatic laboratories beyond reasons previously reported. In our cohort, the second most common reason germline variants were not reported was because the variant was detected and then intentionally filtered out of reporting. In these cases, the somatic lab interpreted the variant as an incidental finding of probable germline origin with limited treatment relevance. This highlights the different goals of germline vs somatic testing labs and how these varying goals impact what is reported to ordering clinicians. We hope our findings will contribute to the growing literature surrounding the overlap between germline and somatic testing methodologies and assist clinicians in their interpretation of genomic results. Research Sponsor: None.

10569 Poster Session

Implementation of pan-cancer universal germline testing in an ethnically diverse and rural community oncology practice.

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Background: Universal germline genetic testing (GGT) is increasingly utilized in precision cancer care. There is limited data on this approach in patients (pts) from historically underrepresented and underserved populations receiving care at community practices. Herein, we present an interim analysis of ~500 unselected pts who underwent standard of care GGT at a rural community oncology practice. **Methods:** The UNITY (UNIversal germline Testing in the communitY) trial (NCT05416710) is a prospective, observational study of pts with newly or previously diagnosed cancer from July 1, 2022-August 1, 2024 (censor date). GGT was performed largely via an 80+ gene panel and insurance-billed. Patient demographic and clinical features were collected by clinicians. NCCN criteria for the pt's primary cancer at the time of GGT determined if the pt was in-criteria (IC) or out-of-criteria (OOC). Differences among groups were determined by two-tailed Fisher's exact, one-way ANOVA and Tukey's HSD tests with significance set at $p < 0.05$. **Results:** 462 pts had complete data: 73% were female; most common cancers: breast (54%), colorectal (14.5%), lung (9%), head & neck (6%), prostate (4%); mean age at diagnosis and testing: 63.2 and 67.6; 21% stage IV/metastatic; 66% Non-Hispanic white, 30% Black/African-American; 17% > 1 cancer diagnosis; 77% family history of cancer; 48% met NCCN criteria; 61% commercial insurance; 27% annual income < $25,000. 47 pathogenic germline variants (PGV) were identified in 41 pts (8.9%). 12 pts (3%) carried a single PGV in a gene associated with autosomal recessive cancer risk (e.g. *MUTYH*) and were excluded from further analyses, resulting in 6.3% (29/462) pts with a PGV. There was no significant difference in the rate of PGVs in IC vs. OOC pts (5.9% vs. 6.7%, $p = 0.85$). 16/29 (55%) pts with PGVs were OOC, with *CHEK2, ATM, BRCA2* being the most frequently mutated genes. Additionally, the majority of PGVs were potentially clinically actionable (25/29, 86%) and most (14/25, 56%) were OOC. 190 (41%) pts had a variant of uncertain significance (VUS) in the absence of a PGV, with Black/African-American pts having significantly higher rates of VUS-only findings compared to non-Hispanic White pts (50% vs. 36%, $p = 0.04$). Conversely, PGV rate showed the opposite pattern (0.7% Black/African-American; 8.5% non-Hispanic White, $p = 0.01$). **Conclusions:** Universal GGT in this diverse cohort identified PGVs in nearly 1 in 15 pts, most of which were potentially clinically actionable, but > 50% would have been missed by NCCN criteria. As Black pts had significantly lower odds of carrying a PGV and higher odds of a VUS result, broader GGT testing criteria would help mitigate racial disparities by increasing the number of (diverse) individuals tested resulting in better representation of genetic variation. Clinical trial information: NCT05416710. Research Sponsor: Labcorp Genetics (formerly Invitae Corp.).

Preventative intervention uptake among women with breast cancer and pathogenic germline variants.

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Background: Risk-reducing (RR) interventions in patients (pts) with pathogenic germline variants (PGV) in breast cancer (BC) risk genes include RR mastectomy (RRM), RR salpingo-oophorectomy (RRSO) and pancreatic cancer surveillance (endoscopic ultrasound [EUS] and/or MR cholangiopancreatography [MRCP]). Gene-specific intervention uptake was stratified by family history (FHx) of cancer in 1903 BC pts with PGV in high/moderate BC risk genes (*ATM, BARD1, BRCA1/2, CDH1, CHEK2, NF1, PALB2, PTEN, RAD51C/D, SK11, TP53*). **Methods:** Germline genetic testing (GGT) and insurance claims data were analyzed female DCIS/BC pts diagnosed 2015-24, GGT <120 days after diagnosis and ≥1 year of claims pre/post-GGT (uptake measured within 1 year of GGT). Inclusion/exclusion criteria followed prior work (PMID 32027353). Following NCCN (Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic and Prostate v2.2025) guidelines, PGV were in genes in the following categories: 1) gene-specific criteria (GSC): eligible for intervention +/- FHx; 2) gene and FHx-specific criteria (GFHxSC): consider (RRM, RSSO) or eligible (EUS/MRCP) for intervention if pt has relevant FHx or 3) Other: no specific intervention eligibility. Multivariable logistic regression models compared odds of intervention uptake for pts stratified by the categories above and by relevant cancer FHx (RRM: breast, RRSO: ovarian, EUS/MRCP: pancreatic). **Results:** 1903 pts with BC had ≥ 1 PGV. Clinico-demographics included were: 70% White, 74% BC FHx, 16% ovarian FHx, 35% pancreatic FHx, and mean (range) age at GGT, 50 (21-90). RRM had the highest uptake (56% overall, 75% in those with GSC PGV). RRSO uptake: 23% overall, 37% in pts with GSC PGV. EUS/MRCP uptake was 9% in pts with GSC PGV or GFHxSC PGV (+) FHx. Pts with GSC PGV (+) FHx had 5x higher odds of RRM vs. pts with GFHxSC PGV (-) FHx. Compared to pts with Other PGV (-) FHx, pts with GSC PGV (+) FHx had 18x higher odds of RRSO and 6x higher odds of MRCP/EUS (Table). **Conclusions:** In this retrospective analysis, intervention uptake generally followed NCCN guidelines, with uptake consistently higher in pts with PGV in GSC genes and positive FHx. Other factors in the shared decision-making process should be studied to identify gaps in quality of care. Research Sponsor: None.

Association of model variables with intervention uptake.

	RRM OR (CI)	RRSO OR (CI)	MRCP/EUS OR (CI)
PGV/FHx	ref: GFHxSC PGV (-) FHx	ref: Other PGV (-) FHx	
GSC PGV (+) FHx	5 (3-8)	18 (11-30)	6 (3-13)
GSC PGV (-) FHx	3 (2-6)	16 (10-24)	3 (1-6)
GFHxSC PGV (+) FHx	NS	7 (2-22)	6 (2-13)
GFHxSC (-) FHx	NA	3 (2-5)	NS
Other PGV (+) FHx	NA	NS	NS
Age	NS	1.5 (1-2)	1.2 (1.0-1.4)
Ethnicity (ref: White)	Hispanic: 2 (1-5)	Ashkenazi Jewish: 0.2 (0-0.7) Asian: 0.4 (0.2-0.9)	Multiracial: 2 (1-4)
Lymph node disease	1.6 (1-2)	0.7 (0.5-1)	NS

OR, odds ratio; CI, 95% confidence interval; NS, not significant (p≥0.05); NA, not applicable; other variables not shown: insurance, DCIS, age2, days from diagnosis to GGT.

10571 Poster Session

Better together: Synergy of germline and somatic testing in HRR pathway-driven cancers.

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Background: Germline and somatic pathogenic variants inform eligibility for poly (ADP-ribose) polymerase inhibitors (PARPi) in breast, ovarian, prostate and pancreatic (BOPP) cancers. The role of BRCA1/BRCA2 in BOPP cancers is well-established, but the significance of other homologous recombination repair (HRR) genes is evolving. Integrating germline and somatic data provides a comprehensive understanding of oncogenesis and informs therapeutic decisions and risk assessment. For example, patients with "two hits" (germline and somatic alteration in the same HRR gene) often exhibit exceptional responses to PARPi. **Methods:** Patients with BOPP cancers receiving standard of care germline genetic testing (GGT) (Labcorp Genetics, formerly Invitae) and comprehensive genomic profiling (CGP) (Omniseq Insight, Labcorp) between 2021-2024 were analyzed. CGP data was queried to determine if the germline pathogenic variant (PGV) 1) was detected in the tumor, 2) had suggestive loss-of-heterozygosity (LOH) with a variant allele fraction (VAF) of $\geq$ 0.6, 3) had a second hit in the same gene, or 4) had somatic mutation(s) in other HRR gene(s). These were compared between BRCA1/BRCA2 and other HRR PGVs using Fisher's exact test with significance set at $<$0.05. **Results:** 607 patients with BOPP cancers underwent GGT and CGP; 57 (9.4%) had $\geq$ 1 PGV in an HRR gene. The PGV+ cohort was 51% White; mean age at GGT was 62 years (26-88). Breast cancer was the most common cancer (27), followed by ovarian (15), pancreatic (12) and prostate (4); 20 (35%) patients had a BRCA1/BRCA2 PGV and 37 (65%) patients had other HRR PGV, primarily CHEK2, ATM, PALB2 (Table). Most (88%) PGV were detected by CGP, with 100% of BRCA2 PGV identified. However, 8 (12%) of PGV+ patients would have been missed by CGP testing alone. VAF $\geq$ 0.6 and/or 2nd hits in the same gene were significantly more likely in those with BRCA1/2 PGV vs. other HRR. Rates of additional mutations in other HRR genes were not significantly different (p$>$0.05) between the groups (Table). **Conclusions:** BRCA1/2 PGV were frequently identified as suspected drivers of BOPP cancers compared to other HRR genes. However, one-third of patients with other HRR variants exhibited features suggestive of driving cancer pathogenesis. These findings may qualify indicated patients for targeted therapies or trials and highlight the synergistic value of combined germline and somatic testing.
Research Sponsor: None.

Tumor characteristics of patients with HRR PGV.

Genes	Total PGV+ patients	N (%) PGV detected by CGP	N (%) VAF ≥ 0.6	N (%) 2nd hit, same gene	N (%) VAF ≥ 0.6 OR 2nd hit	N (%) 2nd mutation, different HRR gene
BRCA1/2	20	17 (85)	**12 (71)**[a]	2 (12)	**14 (82)**[b]	6 (35)
BRCA1	11	8 (73)	7 (88)	0 (0)	7 (88)	2 (25)
BRCA2	9	9 (100)	5 (56)	2 (22)	7 (78)	4 (44)
Other HRR[c]	37	33 (89)	**9 (27)**[a]	4 (12)	**11 (33)**[b]	9 (27)

[a]p=0.011; [b]p=0.005; [c]*CHEK2* (14), *ATM* (7), *PALB2* (5), *BRIP1* (2), *RAD51C* (2); *BARD1*, *BLM, FANCA, FANCA/CHEK2, FANCM, NBN, RAD50* (1 each).

10572 Poster Session

Polygenic risk score for breast cancer in the Thai population: Addressing genetic disparities in underrepresented populations.

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Background: Effective breast cancer prevention and management require accurate risk prediction tools. Polygenic risk scores (PRS) have shown promise but are often less effective in non-European populations due to differences in genetic architecture. This study evaluates PRS performance and adaptation for breast cancer in the Thai population, addressing disparities in underrepresented groups. **Methods:** We retrospectively analyzed breast cancer cases from the Genomics Thailand project at Siriraj Hospital and general population controls from the National Health Examination Survey (NHES) in Thailand. Whole-genome sequencing was performed for cases, and genotyping with imputation was done for controls using the TOPMed r2 reference panel. Clinical data were extracted from electronic medical records. PRS were constructed using SBayesRC, incorporating variants from publicly available genome-wide association study (GWAS) summary statistics and variant functional annotations. Logistic regression and area under the receiver operating characteristic curve (AUC) analyses were conducted using R. **Results:** The discovery cohort included 975 cases and 1,502 controls, with 230 cases and 265 controls in the validation cohort. Of the 330 previously reported GWAS loci, only 231 lead variants were identified in our dataset. We further analyzed variants near these lead variants within the 330 loci, identifying nominal associations with breast cancer for 329 loci ($p<0.05$). Four PRS models were tested: (1) 231 variants, (2) ~7 million functional variants based on European (EUR) data, (3) East Asian (EAS) models, and (4) combined EUR and EAS models. The EUR-based model (AUC 0.66) outperformed the 231-variant model (AUC 0.59) and the population-specific EAS model (AUC 0.58) at $p<0.05$. The combined EUR and EAS models showed no significant improvement over the EUR model alone (AUC 0.66 for both, $p=0.69$). Individuals in the highest PRS risk group (above the 90^{th} percentile) had an odds ratio (OR) of 3.34 for breast cancer compared to the rest of the population (95% confidence interval: 2.54–4.42, $p<0.05$). Among 249 patients with pathology data, PRS was not associated with tumor size, estrogen receptor status, or nodal metastasis. **Conclusions:** In the Thai population, PRS derived from large-scale European GWAS provided the highest prediction accuracy for breast cancer risk. The limited transferability of a top-variant PRS (e.g., 330-variant model) underscores the challenge posed by variant availability in this population. Validation in prospective studies is essential to optimize PRS utility and address disparities in genetic risk prediction. Research Sponsor: None.

10573 Poster Session

Histopathologic and demographic features of non-small cell lung cancer in patients with *BRCA* pathogenic germline variants.

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Background: Patients with pathogenic germline variants (PGVs) in *BRCA1* and *BRCA2* (*BRCA1/2*) have a known increased risk of breast, pancreatic, and prostate cancers. Limited data also suggest a potential increase in lung cancer risk. It is not known if the features of non-small cell lung cancer (NSCLC) in individuals with *BRCA1/2* PGVs differ from those in PGV negative patients. **Methods:** Patients with *BRCA1/2* PGVs were identified using a single-institution registry of PGV patients. Using electronic health records, NSCLC cases were identified via ICD codes. Demographic and histopathologic data were manually abstracted. A PGV negative cohort was derived from NSCLC patient cases detailed in the Penn Medicine Cancer Registry. Categorical variables were compared between the *BRCA1/2* PGV and PGV negative groups using Pearson's chi-squared test. Continuous variables were compared using the Wilcoxon rank-sum test. **Results:** 25 NSCLC patients with PGVs (10 *BRCA1* and 15 *BRCA2*), and 623 PGV negative NSCLC patients were identified. Median age at diagnosis was similar (68, IQR=14 vs 67, IQR=13 years for *BRCA1/2* PGV and PGV negative patients, respectively); sex (64% vs 51% female) and race (80% vs 74% White) were also similar between groups. Never smokers comprised a significantly larger proportion of the *BRCA1/2* PGV cohort (44%) than the PGV negative cohort (16%; $p<0.01$). Stage at diagnosis was similar between groups, with the majority diagnosed with stage I or II disease (56% in *BRCA1/2* PGV vs 66% in PGV negative patients). Histologic findings were also similar, with the most common being adenocarcinoma and squamous cell (68% and 20% in *BRCA1/2* PGV vs 71% and 19% in PGV negative patients, respectively). All 14 BRCA1/2 PGV patients with stage I-II disease received curative intent local therapy; there were 3 recurrences within 5 years. Among 11 *BRCA1/2* PGV patients with advanced stage III-IV disease, 6 had actionable genetic alterations, most commonly in EGFR (3/11). PD-L1 status in these patients was evenly distributed, 3 <1%, 5 1-49%, and 3 >50% expression. **Conclusions:** The histopathologic and demographic features of NSCLC including age and stage at diagnosis and distribution of histology were largely similar for *BRCA1/2* PGV patients and PGV negative patients. However, never smokers represented a significantly larger proportion of the *BRCA1/2* PGV cohort. The presence of actionable genetic alterations and PD-L1 expression in BRCA1/2 PGV patients with NSCLC was comparable to those reported in the general NSCLC population. Research Sponsor: None.

Features of NSCLC in patients with *BRCA1/2* PGVs compared to PGV negative patient.

	BRCA1/2 PGV (N=25)	PGV Negative (N=623)	*p*-value
Median age of onset, years, ± IQR	68±14	67±13	0.68
Female Sex	16 (64%)	319 (51%)	0.21
Never Smoker	11 (44%)	99 (16%)	<0.01
Stage I or II at diagnosis	14 (56%)	370/561 (66%)	0.20
Histology			
Adenocarcinoma	17 (68%)	445 (71%)	0.71
Squamous cell	5 (20%)	120 (19%)	0.92

10574 Poster Session

Profiling DNA damage response in ATM/BRCA2 carriers to inform hereditary cancer risk.

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Background: Approximately 10% of cancers stem from inherited germline pathogenic variants (gPV), predominantly in DNA repair genes including *ATM* and *BRCA1* or *BRCA2*. Identification of a gPV in high-risk families can guide management, however the clinical implications of variants of uncertain significance (VUS) identified by genetic testing remain unclear. Our aim is to develop a DNA damage response (DDR) activity profile of high-risk populations with/without cancer with *ATM or BRCA2* gPV to assist in determining the relevance of *ATM or BRCA2* gPV/VUS. **Methods:** We profiled several key proteins that play a role in DDR using a Luminex-based Multianalyte immunoassay (hereafter referred to as DDR xMAP) in peripheral blood monocytes (PBMCs) derived from whole blood. The standardized DDR xMAP assay was first applied to PBMC specimens from sporadic colorectal cancer (CRC, n = 95) patients and cancer-free age-matched controls (n = 47) at baseline. The DDR xMAP was used to profile seven DDR proteins, phosphorylated Chk1^{S345}, Chk2^{T68}, γH2AX^{S139}, p53^{S15} and total ATR, MDM2, p21. Univariate classification and regression tree analysis was used to identify statistically significant cut points in DDR analyte levels. We then measured the DDR analyte levels in individuals with *BRCA2* gPVs with (n = 11) and without a diagnosis of cancer (n = 11) as well as in cancer-free non-carrier controls (n = 15) at baseline. We compared these values using the two-sided Mann-Whitney test and the Benjamini-Hochberg false discovery rate method to account for multiple markers. **Results:** Using the initial set of CRC cases and healthy controls, we identified statistically significant cut points in multiple DDR analyte levels including total ATR ($>$ 81.8), Chk1^{S345} ($>$ 28.0) and γH2AX^{S139} ($>$ 51.3) that can individually distinguish between CRC cases and cancer-free controls ($P < 0.001$). Next, in preliminary analysis of patients with *BRCA2* gPV with and without cancer had increased levels of all DDR analytes ($P < 0.05$) compared to non-carrier cancer-free controls, except for γH2AX^{S139}. Levels of proteins involved in replication stress response, ATR and downstream Chk1^{S345}, were elevated. Total MDM2 levels, negative regulator of p53, were highly elevated in *BRCA2* gPV carriers. There was not a significant difference between DDR analytes for those with *BRCA2* gPV with and without cancer. **Conclusions:** Profiling key DDR markers can significantly distinguish between CRC patients and cancer-free controls. DDR analytes are significantly increased in PBMC specimens from individuals with *BRCA2* gPV (with or without a diagnosis of cancer) compared to non-carrier cancer-free controls. Ongoing research in high-risk groups will establish cut points for this assay, improving our understanding of DDR activity in individuals with *ATM/BRCA2* gPV and clarifying the clinical significance of gPV/VUS. Research Sponsor: National Cancer Institute; U.S. Department of Defense; W81XWH-18–1-0148; National Institute of Health/National Cancer Institute; 1UH2CA271230-01; Fox Chase Cancer Center.

10575 Poster Session

Age-related germline landscape of endometrial cancer: Focus on early-onset cases.

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Background: Endometrial cancer (EC) has traditionally been associated with older age; however, recent trends indicate more cases in younger women. There is also a growing appreciation for germline drivers of EC, and these may be enriched in younger patients (pts). Given this, we sought to define germline pathogenic variants (gPV) in pts with EC by age. **Methods:** Pts with EC treated at our institution who underwent clinical tumor-normal sequencing from 12/2024-6/2021, inclusive of germline analysis of ≥76 genes, were identified. Clinical variables including age at diagnosis were collected. Logistic regression models evaluated associations between age at EC diagnosis and presence of gPV, biallelic loss, and Lynch syndrome (LS). Age categories were defined as early-onset (EC<50 years) and later-onset (EC ≥70 years) and were compared to those diagnosed ages 50-69 years. Appropriate statistical analysis had been performed. **Results:** Among 1625 pts with EC, median age at diagnosis was 63 (range 24-96) years. We observed differences in gPV rate across age groups, with 28/170 (16%) in early-onset EC, 152/1066 (14%) in EC diagnosed 50-69 years, and 36/389 (9%) in later-onset EC (p=0.016). Biallelic loss also exhibited differences by age groups with enrichment in early-onset EC (8.2% vs. 4.5% vs. 2.1% respectively, p=0.004). LS was enriched in early-onset EC, with 6.5% of patients diagnosed age <50 years having LS. Age was associated with gPV in univariate and multivariable (MV) logistic models, even after adjusting for ancestry and molecular subtype. Compared to those with EC diagnosed 50-69 years, early-onset EC was more likely to be exhibit biallelic loss (OR 3.34 95% CI 1.44-7.35) and be associated with LS (HR 3.49 95% CI 1.63-7.01) in MV models. In contrast, later-onset EC was less likely to be associated with gPV (OR 0.56 95% CI 0.37-0.83) and biallelic loss (OR 0.37 95% CI 0.15-0.82) in MV models. Among early-onset EC, 14/28 (50%) gPV were high penetrance and 14/28 (50%) exhibited biallelic loss. For late-onset EC, only 5/36 (14%) gPV had high penetrance with 8/36 (22%) showing biallelic loss. While the most common high-penetrant gPVs were *MSH2* (n=5), *MSH6* (n=3), and *MLH1*(*n*=3) for the early-onset cohort, the later-onset cohort had gPV in *BRCA2* (n=3), *BRCA1* (n=1), and *PALB2* (n=1). Among the 39 pts with LS and EC, the youngest pt (*MLH1* gPV) was diagnosed at 31 years, and the oldest pt (*PMS2* gPV) was diagnosed at 69 years. Heterogeneity was observed in the early-onset EC cohort. Rates of gPV were 8.9% and 19%, biallelic loss was 0% and 11%, and LS was 2.2% and 8% in those diagnosed <40 years and 40-49 years respectively, suggesting potentially different drivers of very early-onset EC. **Conclusions:** Rates of gPV, biallelic loss and LS differ across age groups for EC, with higher rates of highly penetrant genes that drive tumorigenesis enriched in younger pts. However, very early-onset EC may have different drivers and necessitates more research. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health; P30 CA008748.

10576 Poster Session

Leveraging high variant allele frequencies (VAF) of DNA damage repair (DDR) mutations (muts) in liquid biopsy (LBx) as a surrogate for germline testing: Implications for precision medicine.

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Background: LBx based next-generation sequencing (NGS) provides a minimally invasive means to detect true DDR muts as well as DDR muts that represent clonal hematopoiesis of indeterminate potential (CHIP), and in certain cases identifying high VAF DDR muts of suspected germline origin. Herein, we aim to address the knowledge gap in interpreting these findings to guide germline testing. **Methods:** We retrospectively collected data on patients (pts) with cancer who underwent LBx with FoundationOneLiquid CDx (311 gene panel) from 2022-2024 and tissue biopsy (TBx) based NGS using either Caris Life Sciences or FoundationOne CDx. A panel of 22 muts directly involved in the DDR pathway were designated as DDR muts. Findings from LBx and TBx were reported using descriptive statistics. Best objective clinical responses were evaluated using RECIST v1.1. **Results:** The study cohort consisted of 637 pts tested using LBx, with the majority being male (62.6%; n=399) and white (81%; n=517). On LBx, 203 pts (31.8%; n=203/637) were identified to have one or more DDR muts. Paired testing with LBx and Tbx was available for 221 pts of which 28 pts (12.6%) had 'true CHIP' (identified on LBx but not on TBx), all contributed by ATM and CHEK2 (50% each; n=14/28). Of pts who had paired LBx and TBx (n=221), 24 pts (10.8%) had the same DDR mut on both, suggesting likely somatic origin (True DDRs), the most common being ATM (25%; n=6/24), PALB2 (12.5%; n=3/24) and CDK12 (12.5%; n=3/24). Using a linear mixed-effects model to account for patient- and gene-level variability in VAF, true DDRs had a significantly ($p < 0.001$) higher VAF (median: 46.8, IQR: 49.6, n = 26) compared to true CHIP DDRs (median: 0.24, IQR: 0.29, n = 31). LBx revealed potential germline implications based on high VAF in 7.9% pts (n=50/637) of which 45 pts had DDR muts. Genetic referrals were initiated in 48% (n=24/50) with subsequent confirmatory germline testing done for 66.6% (n=16/24), all confirming germline muts (table 1). Notably, for the 52% (n=26/50) without genetic referrals, 73% (n=19/26) lacked documentation of a referral discussion. Out of the 50 pts with muts likely of germline origin, 19 were enrolled in phase-1 clinical trials, with 6 receiving matched therapies targeting DDR muts (PARP and ATR inhibitors). Of these, 1 had a partial response (CHEK2) and 3 had stable disease (1-MUTYH, 2-PALB2). **Conclusions:** LBx can be used as a potential surrogate indicator of likely germline muts as evidenced by high VAFs. Our findings underscore the need for improved interpretation of LBx reports to guide timely genetic referrals and confirmatory germline testing. Research Sponsor: None.

Gene	Median VAF (IQR)
BAP1 (n=1)	52.4% (52.4-52.4)
MUTYH (n=2)	51.3% (50.7–51.9)
CHEK2 (n=2)	51.0% (50–52)
ATM (n=2)	50.2% (49.8–50.6)
BRCA2 (n=4)	50.0% (48.5–52.2)
PALB2 (n=2)	48.4% (46.7–50.2)
MSH6 (n=1)	46.6% (46.6-46.6)

10577 Poster Session

Estimated prevalence of pathogenic variants in patients with breast, colon, and/or endometrial cancer who do not meet guidelines for genetic testing.

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Background: Patients with cancer who carry pathogenic variants (PVs) in hereditary cancer genes often have improved outcomes when their treatment is guided by their germline genetics. Identifying germline PVs also allows cascade testing of family members to pursue cancer prevention interventions. Guidelines recommend genetic testing for patients with female breast (BC), colorectal (CRC), or endometrial cancer (EC) who meet specific criteria, including early age at diagnosis and/or family history (FH). However, many patients with cancer who do not meet these guidelines may unknowingly carry PVs and may, therefore, receive suboptimal care. **Methods:** Multivariable logistic regression models were constructed to analyze trends in the prevalence of PVs based on age and FH in a consecutive cohort of patients referred for hereditary cancer testing (MyRisk, Myriad Genetics). We report model-based prevalence estimates for patients without FH diagnosed with BC, CRC, or EC at various ages. Prevalence is summarized overall for 25-48 hereditary cancer genes and for genes most frequently implicated in each cancer type. **Results:** Estimates of prevalence of PVs among patients with BC and CRC decreased substantially with age of diagnosis (Table 1). For patients with BC/CRC (respectively) without FH, overall prevalence estimates were 13.0%/11.8% among those diagnosed at age 30, 6.9%/7.1% at age 50 and 2.5%/3.2% at age 80. Among BC patients, PVs were most frequently identified in the *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, and *PALB2* genes. Among CRC patients, PVs were most prevalent in the Lynch syndrome genes *MLH1*, *MSH2*, *MSH6*, *PMS2*. Prevalence was not significantly associated with age at EC diagnosis. Women with no FH had overall prevalence estimates of 7.5% if diagnosed with EC at age 30, 7.3% at age 50 and 7.1% at age 80 (Table 1). PVs were most common in the aforementioned Lynch syndrome genes. **Conclusions:** These results support existing literature that a substantial fraction of patients who do not meet guidelines for genetic testing may carry PVs, including a high prevalence of PVs among EC patients without FH, regardless of age at diagnosis. Elimination of age-based restrictions on genetic testing could improve the survival of cancer patients and their family members. Research Sponsor: Myriad Genetics.

Estimated prevalence (%) according to age of diagnosis among patients with no family history of cancer.

Age at dx	30	40	50	60	70	80
BC	13.0%	9.5%	6.9%	5.0%	3.5%	2.5%
CRC	11.8%	9.2%	7.1%	5.5%	4.2%	3.2%
EC	7.5%	7.4%	7.3%	7.2%	7.2%	7.1%
BC[a]	12.3%	8.3%	5.6%	3.7%	2.4%	1.6%
CRC[b]	7.3%	5.1%	3.5%	2.4%	1.7%	1.1%
EC[b]	4.4%	4.3%	4.3%	4.2%	4.1%	4.1%

BC=breast cancer; CRC=colorectal cancer; dx=diagnosis; EC=endometrial cancer.
[a]*BRCA1, BRCA2, CHEK2, ATM, or PALB2.*
[b]*MLH1, MSH2, MSH6, or PMS2.*

10578 Poster Session

Performance of previously described polygenic risk scores for prostate cancer in a population with mixed ancestry.

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Background: It is unclear whether polygenic risk scores (PRS) for prostate cancer (PrCa), developed using data from European populations, are applicable to individuals of mixed ancestry, such as the Brazilian population. We are conducting a case-control study to evaluate the performance of existing PrCa PRSs in Brazilian people. **Methods:** We prospectively included unselected PrCa patients (pt). The control group consisted of 347 elderly community men from Sao Paulo city (SABE cohort) included from 2000 to 2010, with whole genome sequencing (WGS 30x depth) data previously reported in the ABRAOM study. Men who developed cancer in the follow-up were excluded. The mean age at admission to the study was 72 years. DNA was extracted from blood samples for performing WGS at 15x depth (PrCa pt), using Illumina technology. VCF quality filtering and pre-processing were performed according to best practices of GATK, BCFtools and Plink. Ancestry composition was calculated using ancestry-informative markers derived from global populations. AUCs were calculated using the results from the total PRS value obtained with PGSCalc for cases and controls, without filters. We calculated PRS scores for 11 different PRSs for PrCa, described in 7 studies, derived from people with different ancestries and available in The Polygenic Score (PGS) Catalog or the literature (BARCODE1). **Results:** A total of 588 PrCa patients were included. The median age at diagnosis was 64.6 years. Most patients were diagnosed with clinical stages II (32.8%) and III (43.1%), and ISUP grades 2 (40.2%) and 3 (22.9%). Twenty PrCa pt, who were carriers of pathogenic or likely pathogenic germline variants on high and moderate penetrance prostate cancer predisposition genes, were excluded. The mean ancestry genetic composition for PrCa pt was 61.4% European and 24.6% African. We calculated the AUC for the Brazilian cohort (BZL) for 11 PRSs available in PGS Catalog. 1) PGS000030 - Schumacher et al. 2018; 147 SNPs - AUC BZL: 0.666; 2) PGS000751 - Du et al. 2019; 178 SNPs - AUC BZL: 0.694; 3) PGS000662 - Conti et al. 2021, 269 SNPs - AUC BZL: 0.705; 4) PGS002796, PGS002797, PGS002798, PGS002799 - Shi Z, et al. 2022; 232, 67, 128, 138 SNPs - AUC BZL, respectively: 0.684; 0.663; 0.670; 0.627; 5) PGS002240, PGS002241 - Mars et al. 2022; 1,092,093 (AUC BZL: -) and 6,497,734 SNP (AUC BZL: -) PRS for risk prediction of common diseases. 6) PGS003460 - Chen F et al. 2023; 278 SNPs - AUC BZL: 0.702; 7) Barcode1 - 130 SNPs - AUC BZL:0.674. **Conclusions:** We used WGS 15x to improve SNP capture associated with population genetic differences. PRS 269 (Conti et al., 2021) and PRS 278 (Chen F et al. 2023) yielded the best results, suggesting that a multiancestry-derived PRS may be applicable to the admixed Brazilian population. We continue including participants to confirm these results. Research Sponsor: None.

10579 Poster Session

Frequency and spectrum of BRCA pathogenic/likely pathogenic variants in the Hispanic population of south Florida: A retrospective analysis.

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Background: The genetic landscape of hereditary breast and ovarian cancer in diverse populations remains underexplored, particularly within Hispanic/Latino communities. While *BRCA1* and *BRCA2* pathogenic and likely pathogenic (P/LP) variants are well-studied in some ethnic groups, data on Hispanic populations with varied ancestries is limited. South Florida's unique demographic, characterized by a large Hispanic population with ancestries from the Caribbean, Central, and South America, provides an opportunity to examine the prevalence and spectrum of *BRCA1* and *BRCA2* variants in this group. **Methods:** Data was extracted from Progeny and Cerner PowerChart and de-identified in MS Excel. The cohort consists of individuals who underwent germline genetic testing (ranging from single site to multigene panels) at Miami Cancer Institute's Clinical Genetics clinic from 01/01/2017 to 07/08/2022 with a personal/family history of breast and/or ovarian cancer. The sample was categorized by self-reported race, ethnicity, and ancestry, with a focus on White, Black, and Hispanic/Latino categories. We compared *BRCA1* and *BRCA2* P/LP variants across race/ethnicity. **Results:** A total of 3,784 cases were reviewed, predominantly female (97.6%), with 73.6% (n = 2786) affected by breast cancer. The median age was 54 years (range: 20-92). Most of the population identified as Hispanic/Latino (65%, n = 2,460), with Cuban ancestry reported most frequently on both maternal (38.4%) and paternal (37.3%) sides. The prevalence of *BRCA1* and *BRCA2* P/LP variants in Hispanic/Latino individuals was 5.1% (126 of 2460), with the majority having a BRCA2 variant (n = 86; 68.2%). Variants of uncertain significance were observed in 3.4% of the Hispanic population. The most frequent P/LP variants in *BRCA1* included c.211A > G (n = 5, 12.5%) and c.3331_3334delCAAG (n = 3, 7.5%). In *BRCA2*, common P/LP variants were c.771_775del (n = 8, 9.3%), c.2808_2811del (n = 6, 7%), c.5799_5802del and c.9235delG (each n = 5, 5.8%), and c.5073dupA (n = 4; 4.6%). **Conclusions:** This cohort revealed a variety of unique P/LP variants in *BRCA1* (n = 31) and *BRCA2* (n = 56), reflecting the genetic diversity in this population. Other cancer susceptibility gene P/LP variants were noted but were not the focus of the study. Notably, *BRCA2* c.771_775del (n = 8), an established Icelandic founder variant not reported to be recurrent in Hispanics, was only observed in those of Cuban/Spaniard ancestry in this cohort. Other variants, such as c.9235delG and c.5073dupA in *BRCA2*, were identified in Nicaraguan and Cuban populations for the first time. The study also highlighted common founder and recurrent variants in European, Caribbean, Central, and South American populations. South Florida's Hispanic population, including individuals from underrepresented regions, offers a rich and unique dataset of *BRCA1* and *BRCA2* P/LP variants. Research Sponsor: None.

10580 Poster Session

Mainstreaming the diagnosis of Lynch syndrome (LS) in colorectal cancer (CRC) patients: The ItaLynch study.

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Background: International guidelines recommend universal screening for LS through somatic DNA mismatch repair deficiency (dMMR) testing in CRC. However, LS remains largely underdiagnosed, often due to inconsistent referrals from oncologists to genetic counseling and germline testing. We report preliminary results of the ItaLynch study, proposing a mainstream, oncologist-led diagnostic pathway for LS. **Methods:** ItaLynch is a prospective, observational, multicenter, multidisciplinary Italian study on pts with dMMR CRC. It started in May 2021, and is ongoing in 23 high-volume centers. The ItaLynch diagnostic pathway is based on three key steps. The first step is universal screening through dMMR testing by immunohistochemistry (IHC) in all CRC pts. The second step consists of reflex testing and a Lynch alert: MLH1-deficient (dMLH1) pts undergo reflex testing for $BRAF^{V600E}$ and, if wild-type, for MLH1 promoter methylation. A Lynch alert is added to the pathology report of all dMMR CRC pts. The alert is positive for pts with a high risk of LS as per reflex testing results or loss of non-MLH1 proteins; it is negative for pts not likely to have a hereditary predisposition (i.e. $BRAF^{V600E}$ mut or *MLH1* promoter hypermethylated dMLH1). The third and most innovative step is the oncologist-led mainstreaming germline testing for pts with a positive Lynch alert. Carriers of a germline pathogenic variant (PV) as well as those who have non-informative test results but are clinically suspicious are then referred to post-test genetic counselling. **Results:** Up to Dec. 19 2024, we enrolled 1,146 pts with dMMR CRC. Among the 937 pts eligible for the current analysis, 714 (76%) were dMLH1, and 223 (24%) displayed loss of non-MLH1 proteins. Reflex testing was carried out in 653 (91%) of the dMLH1 pts and 271 (41%) were *BRAF* wt. Of these, 219 (80%) subsequently underwent *MLH1* promoter methylation testing, and 98 (45%) were not hypermethylated. Of these, 60 (61%) underwent oncologist-led germline genetic testing, and 11 (18%) were carriers of an LS-associated PV. Among the 223 cases with loss of non-MLH1 proteins, 157 (70%) underwent genetic testing, and 86 (55%) were diagnosed with LS. At the time of writing, the overall proportion of LS cases is 10% (97/937 pts with data available for the current analysis). These 97 LS cases represent 45% of the 217 pts who were flagged with a positive Lynch alert and underwent oncologist-led genetic testing (60 of which with dMLH1 and 157 with non-MLH1 loss). **Conclusions:** Overall, our large cohort is representative of the population of pts with dMMR CRC. Our novel diagnostic algorithm, through the implementation of the Lynch Alert flagging system that identifies dMMR CRC pts with a high likelihood of LS and of an oncologist-led germline genetic testing, obtained a high diagnostic yield. Further analyses are ongoing on the entire cohort to evaluate the feasibility of the proposed diagnostic pathway. Research Sponsor: None.

10581 Poster Session

Identification of germline hereditary cancer syndrome variants and associated cancers in a healthcare biobank population.

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Background: Identification of pathogenic/likely pathogenic variants (P/LPV) in hereditary cancer syndrome (HCS) genes enables surveillance and prevention. Population genomic screening can complement traditional ascertainment of at-risk individuals based on personal or family history. But lack of data on cancer risks in unselected individuals with a HCS P/LPV challenges clinical decision making in these cohorts. We summarize a biobank's population screening for HCS variants and a case-control assessment of reported relevant cancers. **Methods:** MyCode is a health system biobank with >357,000 patients consented to research leveraging exome and electronic health record (EHR) data and to the receipt of medically relevant P/LPV. Available exomes were evaluated for P/LPV in 27 HCS genes based on predicted molecular consequence and ClinVar status. Clinically confirmed P/LPV were disclosed to eligible patients (cases). Patients' prior knowledge of their result was determined using EHR data and patient report. Relevant cancer diagnoses were extracted from the EHR using validated methods in cases and variant-negative controls (n=169,099) with available EHR data. Associations between P/LPV and relevant cancers were assessed using a Firth logistic regression in 9 genes with >30 cases. Ages of diagnoses were compared using Wilcoxon rank sum test. **Results:** 183,822 patients' exomes have been evaluated; 2,035 P/LPV in 27 HCS have been disclosed to 2,027 patients. 80% (n=1,625) of patients were previously unaware of their result. Increased odds and earlier ages of diagnosis for a subset of relevant cancers were observed in patients with P/LPV (Table). **Conclusions:** HCS P/LPV were disclosed to 1.1% of biobank patients, most of whom were unaware of their result. P/LPV were associated with a higher odds and earlier age of diagnosis of some relevant cancers compared to controls, indicating that genomic screening facilitates ascertainment of at-risk individuals. To guide clinical recommendations, research on cumulative cancer risks in broader populations will be needed. Research Sponsor: Geisinger; Goldsmith Foundation; Regeneron Genetics Center.

Associations (OR and 95% CI) between P/LPV and relevant cancers.

Gene	Breast	Ovarian	Pancreatic	Prostate	Colorectal	Endometrial	Thyroid (Medullary)	Renal
APC **n=61**					15.8 (6.5-33.5)*,a			
BRCA1 **n=308**	13.4 (9.6-18.5)*,a	28.6 (18.5-42.8)*,a	2.4 (0.5-6.7)	1.5 (0.8-2.6)				
BRCA2 **n=599**	6.0 (4.6-7.7)*,a	7.6 (4.6-11.9)*	2.1 (0.7-4.7)	2.4 (1.6-3.5)*				
PALB2 **n=133**	2.5 (1.2-4.7)*	2.5 (0.3-9.2)	6.0 (1.2-17.3)*	2.7 (1.0-6.4)*				
MLH1 **n=48**		2.2 (0.02-15.5)	3.4 (0.02-24.2)	0.5 (0.03-4.1)	59.6 (31.0-111.8)*,a	26.5 (11.6-56.3)*,a		
MSH6 **n=212**		0.6 (0.01-4.3)	2.1 (0.2-7.6)	1.7 (0.8-3.2)	5.2 (2.8-8.8)*,a	14.0 (8.3-22.5)*,a		
PMS2 **n=194**		1.9 (0.2-7.0)	0.7 (0.01-5.1)	1.0 (0.4-2.3)a	4.7 (2.4-8.2)*	4.3 (1.8-8.5)*		
RET **n=105**							2690.6 (1593.8-4580.1)*	
SDHB **n=45**								11.4 (3.1-30.5)*

*denotes significant OR α = 0.05, [a]age of diagnosis significantly lower in cases.

10582 Poster Session

Clinical characteristics of young-onset breast cancer and the role of germline pathogenic variants.

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Background: Breast cancer is the most common cancer in young women, with an increasing incidence over the past two decades. This study aims to evaluate the characteristics of young-onset breast cancers among patients aged ≤50 and compare tumor characteristics by germline mutation carrier status. **Methods:** Patients with breast cancer diagnosis ≤50 years old and evaluated across the Mayo Clinic enterprise between 2000 and 2024 were identified through the prospective Mayo Clinic Breast Cancer Study and the institutional tumor registry. Demographics, tumor characteristics, and clinical outcomes were obtained and described using summary statistics. Germline pathogenic or likely pathogenic variant (PV) carrier status for 5 established breast cancer predisposition genes (BRCA1, BRCA2, ATM, CHEK2 and PALB2) was available in a subset of unselected patients who consented to participation in sequencing studies at Mayo Clinic. Clinical characteristics were compared between PV carriers in each gene and non-carriers utilizing Chi-square test. All tests were two-sided and p-value less than 0.05 was considered statistically significant. **Results:** Among 8,462 patients (8435 women, 27 men) with breast cancer diagnosis at age ≤50 in the study, the median age of diagnosis of breast cancer was 44 years (range 18 – 49). At diagnosis, 84% had invasive disease, 43% of the tumors were high-grade, 15.8% had triple-negative breast cancer (TNBC), more than two-thirds (67.5%) presented with stage I or II breast cancer, and 3.7% had bilateral breast cancer. Among the 2,527 patients who consented to germline sequencing, 10.1% were found to be carriers of PVs; these included BRCA1 (3.3%), BRCA2 (2.7%), CHEK2 (2.3%), ATM (1.3%), and PALB2 (0.6%). Compared to non-carriers, a significant enrichment ($p<0.05$) of invasive breast cancer (92.6% vs. 83.3%) and high grade tumors (61.7% vs. 31.4%) were noted in BRCA1 PV carriers, and of bilateral breast cancer (13.4% vs. 3.8%) and high grade tumors (46.4% vs. 31.4%) in BRCA2 PV carriers. After exclusion of in-situ disease, proportion of TNBC was observed to be significantly higher in BRCA1 (61.3%), BRCA2 (15.5%) and PALB2 (30.7%) PV carriers compared to non-carriers (11.2%), whereas >90% of ATM or CHEK2 PV carriers had ER+ breast cancer and none had TNBC. A significant difference in stage at presentation was not observed by germline PV carrier status. **Conclusions:** The high frequency (>10%) of PVs in young-onset breast cancer underscores the importance for genetic testing in this population. The observed differences in breast cancer phenotypes based on germline PV carrier status among young-women may have significant implications for clinical outcomes and needs to be further explored. Research Sponsor: None.

10583 Poster Session

NuGenA (Nurse Led Genetic Counselling and Awareness): A proof-of-concept to implementation of genetic counseling for HBOC in LMICs.

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Background: Poor access to genetic testing and counselling represents a major gap in cancer care in resource-restricted-settings. Our pilot work in Eastern India (2017-2019) demonstrated improved uptake of BRCA genetic testing (89% vs.55%) in ovarian cancer (OC) after training one nurse specialist in genetic counselling. We introduced NuGenA program in 2020 to scale-up this effort as proof-of-concept. **Methods:** Ethical approvals were obtained (KolGo/CTRI/2021/06/034308/HMSC). A nurse-led structured training program combining lectures/modules/live-demonstration-workshops/role-playing using offline and virtual learning methods were administered to sensitize/train all tiers of nurses including train-the-trainers in genetic counselling. A comprehensive NuGenA questionnaire including demographic, family history, CAM, pre/post-test counselling satisfaction-regret scale, QOL and willingness-to-pay (WTP) for genetic testing was administered by trained nurses. Physician and nursing interviews were conducted at 1 year to assess barriers/challenges/success of program. KolGoTrg EASE (Ethical/Acceptable/Affordable/Sustainable/Scalable/Effective/Early-diagnosis-and-treatment of barriers) matrix was used to measure key performance indicators and impact of implementation. **Results:** Through 40 sessions/workshops, 126 nurses were trained across India (8 centres, 34 nurses), Nepal (10 centres,30 nurses), Bangladesh (2 centres,60 nurses) and Africa (2 centres,2 nurses) with significant improvement in post training KAP scores. 7 genetic clinic/set-ups were created. 270 OC patients and 458 family members were counselled by nurses. 159 OC patients had BRCA testing, 48 (30%) being positive. Until now, out of 235 at-risk family members identified, 90 were counselled and 12 tested for BRCA (6 positive);2 opted for risk-reducing surgery. Unique barriers/challenges were identified including cost of BRCA test, provider hesitancy, social stigma, requiring customised solutions. WTP for genetic testing using CoPay model was accepted by 99/158 (62%). Another 100 community-nurses were sensitized through NuGenA camps/sessions approved by government/health authorities resulting in conduct of >150 COBRA (cervix/oral/ovary/breast-cancer awareness) sessions and patient-public-engagement initiatives. NuGenA modules are being included in national/international nursing curriculums. A World Ovarian Cancer Coalition charter-champion award and adoption by IGCS training sites exemplify global recognition/outreach. **Conclusions:** Nurse-led model proved scalable and impactful in resource-restricted settings, facilitating transformative changes in provider/patient-public engagement, attitude and practice towards genetic testing. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2022IIG-7593471658; DST-UKIERI; DST/INT/UK/P-134/2016; OVARCOME, USA; MEDGENOME LABS LIMITED, INDIA; Kolkata Gynecological Oncology Trials and Translational Research Group.

10584 Poster Session

Concordance of somatic whole exome sequencing and germline genotyping of DPYD to screen for DPD deficiency.

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Background: Fluoropyrimidines are amongst the most commonly used chemotherapeutic agents in the treatment of gastrointestinal and breast malignancies. Fluoropyrimidines carry a risk of severe adverse events in the 2-3 % of the population with DPD deficiency caused by decreased function variants of DPYD. As a result, pre-treatment testing to identify patients with decreased function variants including DPYD genotyping is critical. However, pre-treatment DPYD genotyping is not yet broadly used in the United States. We hypothesized that our in-house somatic exome DHCancerSeq assay could serve as an effective tool to screen for DPD deficiency. **Methods:** We identified patients in our health system with somatic whole exome sequencing who had clinical DPYD genotyping using either a limited real time PCR assay (including the *2A, *13, and c.2846A > T alleles) or a dedicated NGS-based PGx panel covering all known clinically relevant mutations in DPYD. HapB3 screening on the somatic whole exome was performed using only the coding sequence variant (c.1236G > A), not the causative deep intronic variant (c.1129-5923C > G), given the known high linkage disequilibrium amongst these variants. We then evaluated concordance of somatic whole exome sequencing and targeted germline genotyping. **Results:** A total of 115 patients had DPYD genotyping results from both somatic and germline testing and were eligible for evaluation of concordance (48 germline PCR tests and 67 NGS based). There was complete (100%) concordance of genotypes across germline and somatic assays, with genotypes of DPYD *1/*1 (106/106 samples), *1/*2A (3/3), *1/*13 (2/2) and *1/HapB3 (4/4). **Conclusions:** There was 100% concordance of somatic whole exome sequencing with traditional germline testing for DPYD deficiency. While germline testing remains the standard of care given the nuances of somatic copy number changes, our results suggest that somatic whole exome sequencing is a viable and efficient screening tool for DPD deficiency. Research Sponsor: None.

10585 Poster Session

Clinical features and occurrence of other cancers in patients with chronic lymphocytic leukemia and their families with *POT1* tumor predisposition syndrome.

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Background: *Protection of telomere 1 (POT1)* tumor predisposition syndrome (POT1-TPD) is a hereditary leukemia predisposition syndrome that is identified in up to 5% of patients with chronic lymphocytic leukemia (CLL) and is characterized by a predisposition to other cancers such as gliomas, melanomas, angiosarcomas, and cardiac myxomas. Herein, we report clinical features and cancer diagnoses of the largest cohort of patients with CLL and members of families with POT1-TPD published to date. **Methods:** Patients and family members with pathogenic or likely pathogenic germline *POT1* variants evaluated in the Hereditary Hematologic Malignancy Clinic (HHMC) at MD Anderson Cancer Center were included. Individuals with a variant of uncertain significance (VUS) in the *POT1* gene were also included if found to have telomeres >90th percentile of age predicted length. **Results:** A total of 24 individuals in 17 families were identified. At the time of referral, 11 (46%) had a diagnosis of CLL, and 1 (4%) had monoclonal B-cell lymphocytosis (MBL). The remaining 12 individuals had no history CLL or MBL and were referred based on family history; however, 4 were found to have MBL at the time of referral (4/12, 17%). Among the 24 individuals, additional malignancies included: 6 melanoma, 3 hematologic cancers (1 CML, 2 NHL), and 1 papillary thyroid cancer. Among the 17 families, we documented a high reported prevalence of melanoma (8/17, 47%), CLL (6/17, 25%), glioblastoma (3/17, 18%) and sarcoma (2/17, 12%). Details of the *POT1* variants were available for 16 families. Variants were classified as pathogenic in 7 (44%), likely pathogenic in 7 (44%), and as VUS in 2 (19%). Additional pathogenic germline variants in *CHEK2*,*BRCA2*, and *MITF* were observed in 3 (19%) families, respectively. Five families had telomere length testing performed (31%), and lymphocyte telomere lengths were above the 99th percentile in 60% and above the 90thpercentile in 100%. The patients with CLL (n=11) had a median age at diagnosis of 55 years (range 29-68). 82% of patients had diploid karyotype, 64% had del13q by FISH, and 60% had mutated IGHV. Of the 7 patients with NGS testing performed, additional somatic mutations were present in 6 (86%) and *NOTCH1* was the most common (43%). Five patients (45%) have received treatment for CLL with a median time to treatment of 4.5 years from diagnosis (95% CI 4.3, 4.6). Median overall survival of all patients was 13.8 years (95% CI 9.4, 18.3). **Conclusions:** This analysis provides insights into familial patterns of malignancy and the natural history of CLL in individuals with POT1-TPD. Patients with germline POT1 variants appear to develop CLL and MBL at an early age. Evaluation from a genetic counselor and augmented cancer screening due to the high risk of solid tumors and other hematological malignancies is paramount. Research Sponsor: None.

Incidence of concurrent pathogenic variants in *BRCA1* breast cancer patients.

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Background: Over the years, advancements in genetic testing have led to an expansion in the number of detectable mutations. This progress has enabled the identification of patients with pathogenic genetic variants, allowing for the implementation of tailored cancer screening strategies. For patients with breast cancer or high risk of breast cancer, there are advocates for comprehensive expanded genetic testing panels while others prefer to only perform selective testing for genes associated with breast cancer. The goal of this study was to determine how often patients with *BRCA1* pathogenic variants have additional mutations picked up on panel tests and whether they are clinically significant. **Methods:** We used the Myriad Collaborative Research Registry to access de-identified information on breast cancer patients with *BRCA1* variants. We looked at the data collected from individuals that were tested for mutations in 26 or more genes. We identified the most commonly mutated genes that are found in patients with *BRCA1* mutations. For this study, the term deleterious is equivalent to pathogenic/likely pathogenic. **Results:** Among breast cancer patients who underwent expanded panel testing for at least 26 genes, 10,250 individuals were identified to carry deleterious mutations. Of these, 400 patients had deleterious mutations in two or more genes. Within this subgroup, 184 individuals had deleterious *BRCA1* mutations along with at least one additional pathogenic mutation. Table 1 lists the most frequently mutated additional genes in patients with *BRCA1* mutations in our dataset. The most common pathogenic mutations that co-occur with *BRCA1* mutations were found in *MUTYH* (31.5%), *CHEK2* (12.5%), *BRCA2* (12.5%), and *ATM* (11.4%). One patient had deleterious mutations in *BRCA1* and two additional genes (*MUTYH* and *BRIP1*). **Conclusions:** Our data underscores the importance of evaluating patients for additional gene mutations. Extensive evidence demonstrates that certain pathogenic genes increase the risk of specific cancers. Restricting genetic testing to a targeted panel of breast cancer-associated genes may overlook other pathogenic genes that could predispose these individuals to additional malignancies. For instance, identifying pathogenic mutations in *PMS2*, in addition to *BRCA1*, could lead to meaningful alterations in clinical management. Further research is essential to investigate the clinical significance of co-occurring genetic variants, particularly those involving *BRCA1* and other high-risk genes. Research Sponsor: None.

Most commonly identified concurrent pathogenic genes in *BRCA1* breast cancer.

Concurrent pathogenic gene	Count
MUTYH	58 (31.5%)
CHEK2	23 (12.5%)
BRCA2	23 (12.5%)
ATM	21 (11.4%)
BRIP1	16 (8.7%)
PALB2	8 (4.3%)
PMS2	8 (4.3%)
NTHL1	6 (3.3%)
BARD1	4 (2.2%)

Genes in bold are known to be associated with breast cancer.

10587 Poster Session

Exploring the prevalence of germline mutations in young-onset biliary tract cancer (BTC).

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Background: The American Society of Clinical Oncology (ASCO) and NCCN recommend germline testing for patients (pts) with biliary tract cancers (BTC), particularly those diagnosed at a young age. Prior studies estimate that approximately 15% of pts with BTC harbor pathogenic germline alterations. Germline testing can identify hereditary cancer syndromes, guide targeted therapy, and inform family counseling. This study aimed to further characterize and describe the prevalence of pathogenic germline variants (PGVs) in patients with young-onset BTC (YO-BTC). **Methods:** We conducted a retrospective review of medical records for pts diagnosed with YO-BTC (ages 18–55) across all Mayo Clinic tri-sites from January 2014 to October 2024. Data collected included results from germline DNA sequencing, tumor genetic testing, demographics, history of other malignancies, and family history of cancer. The primary outcome was the identification of pathogenic germline mutations associated with cancer predisposition. **Results:** Among 239 pts with YO-BTC, the median age at diagnosis was 43 years (range 19–55), with 62% female and 65.2% identifying as white. Clinical germline testing (e.g., Invitae, Ambry, Myriad) was performed in 123 pts (51.5%), revealing PGVs in 15 pts (12.1%), variants of uncertain significance (VUS) in 30 pts (24.3%), and likely benign variants in 4 pts (3.2%). Among those with PGVs, DNA repair mutations were the most common findings (10/15), including ATM (4), CHEK2 (2), BRCA2 (2), BAP1 (1), and PALB2 (1). One pt had a Lynch syndrome-associated mutation (MSH6), and four had mutations in other cancer-related genes (MUTYH, HOXB13, RMRP, and PIK3CA). Tumor genomic profiling (via CARIS, TEMPUS, or FoundationOne) was performed in 9 pts with PGVs, detecting the variant in 4 (44%), while liquid biopsy (Guardant) identified the PGV in 4 of 6 cases (66.6%).The majority of PGV carriers had advanced BTC (14/15), with intrahepatic cholangiocarcinoma being the most prevalent (11/15), while 4 had extrahepatic cholangiocarcinoma. Additionally, most PGV carriers had a first- or second-degree relative with a prior history of malignancy (14/15), and 3 pts had a second malignancy. Of the 15 pts with PGVs, 4 had BTC associated with primary sclerosing cholangitis. **Conclusions:** In this large institutional series of YO-BTC, PGVs were identified in 12.1% of pts, demonstrating a significant yield from germline testing in this population. Notably, tissue and liquid biopsies demonstrated different detection rates for PGVs, underscoring the variability in PGVs reporting across platforms. Germline testing through CLIA-approved methods should remain the standard of care. DNA repair pathway mutations, particularly ATM, CHEK2, and BRCA2, were the most frequently identified PGVs, highlighting their role in the pathogenesis of YO-BTC and their potential to guide treatment decisions. Research Sponsor: None.

10588 Poster Session

Limited versus expanded multigene germline genetic testing among adolescents and young adults (AYA) with breast cancer.

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Background: In low- and middle-income countries, like ours, breast cancer is diagnosed mostly in younger women. With a median age of 50-52 years, breast cancer is diagnosed at least 10 years younger than in Western societies. Though most breast cancer cases are sporadic, 5-10% of cases are hereditary and mostly related to *BRCA1* or *BRCA2* variants. However, the widespread use of genetic testing, mutations other than BRCA1/2 are currently detected, the clinical importance of which is questionable. In this paper, we aim to study the prevalence and pattern of pathogenic/likely pathogenic (P/LP) variants among adolescents and young adults (AYA). **Methods:** Blood samples of patients with breast cancer diagnosed at age 39 years or younger were obtained for DNA extraction and sequencing. Mutations were classified as benign/likely benign (non-carrier), P/LP (carrier), and variant of uncertain significance (VUS). At the initial phases of testing, patients were tested for only *BRCA1* and *BRCA2* (n = 415), then *PALB2* was added (n = 145). With availability and affordability of germline genetic testing, 267 patients were tested utilizing an 84-gene panel before we settled on a 21-gene panel (n = 897). Testing was done at reference referral labs. All patients were counselled by a genetic counsellor before and after testing. **Results:** During the study period, a total of 1,724 patients with breast cancer diagnosed at age 18-39 had germline genetic testing and were included in the analysis. Majority (n = 1,530, 88.8%) were Jordanian, while the rest were non-Jordanian Arab. Median (range) age was 35 (15-39) years, and except for 6 patients, all were female. Among the whole group, 262 (15.2%) had pathogenic or likely pathogenic (P/LP) variants and were mostly *BRCA2* (n = 121, 46.2%) and *BRCA1* (n = 76, 29.0%). Other variants include *TP53* (n = 15, 5.7%), *ATM* (n = 12, 4.6%), *CHEK2* (n = 11, 4.2 %) and *PALB2* (n = 8, 3.1%). Rate of P/LP variants was significantly higher among patients younger than 30 years (23.6%) compared to a rate of 13.8% among older ones aged 30-39 years, p = 0.0001. Rates of P/LP variants were higher in patients tested with the 84-multigene panel (17.9%) compared to those who were tested with the 21-MGP (15.5%) or BRCA1/2 with or without *PALB2* (13.6%). VUS rates were significantly higher with expanded gene testing; 54.7% with 84-gene, 22.5% with 21-gene and less than 10% with limited gene testing, $p < 0.0001$. Limiting testing to *BRCA1, BRCA2, PALB2, CHEK2, TP53* and *ATM* would include 92.7% (n = 243) of all P/L variants. The remaining 19 (7.3%) are variants of low penetrance. **Conclusions:** The rate of P/LP variants in AYA patients, particularly those under 30 years, with breast cancer is higher than what has been previously observed in older patients. Expanding genetic testing beyond *BRCA1, BRCA2, PALB2, CHEK2, ATM*, and *TP53* in this age group leads to a lower yield and a significantly higher proportion of VUS. Research Sponsor: None.

10589 Poster Session

Sequential EHR interventions to increase genetic testing for breast and ovarian cancer predisposition across diverse patient populations in gynecology practices at Penn Medicine.

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Background: Genetic testing (GT) identifies individuals who may benefit from increased surveillance and risk reduction strategies. GT is under-utilized, especially in those without a personal history of cancer and in minority populations. **Methods:** We identified a patient cohort meeting NCCN criteria for genetic testing utilizing electronic health record (EHR) phenotyping in 2 diverse gynecological practices. NCCN criteria included individuals with a personal history of ovarian cancer, early-onset (<50) breast cancer diagnosed before 2021, or a family history (FH) of ovarian cancer or male breast cancer. Participants with prior genetics visits were excluded. Patient nudges and provider messaging strategies were introduced to boost genetic counseling consultation. Nudges included patient portal messaging (PP) followed by texts using the Way To Health platform (WH) in those that did not respond to PP. For non-responders to patient directed nudges, genetic counseling consult orders were placed using Epic's Pend & Send tool and sent to their gynecologist. Endpoints included the open rate for PP, response rate for the WH text, and the number of genetic counseling appointments completed. Differences between the clinics were calculated by Chi Square. **Results:** Of 1055 patients identified and who received a PP message regarding genetic counseling, 81% had a FH of ovarian cancer. Characteristics of the patient populations differed across clinics: Clinic D (n=505): 71.3% Black, 18% White and 67% < 45 years. Clinic R (n=550):10% Black, 83.5% White and 63% > 60 years.79% opened PP and 22.1% replied to PP, more in Clinic R (26.7% vs 17.0%, p<0.001). Patient engagement by PP or WH was 59.8% (631/1055), more in Clinic R (67.1% vs 51.9%, p<0.001). Of those that connected by patient nudges, 62.8% (396/631) declined additional follow-up (more in Clinic R, 41.5% then Clinic D, 33.3%, p=0.014), either due to incorrect family history in EHR, prior genetic testing, or, in the majority of cases, because they were not interested (296/631) (46.9%). Provider nudges added little to patient nudges with regard to GT uptake. 25% (266/1055) scheduled and 14.9% (157/1055) of the cohort completed GT appointments with no difference between the two (Clinic D 13.9% vs Clinic R 15.8%, p=NS). **Conclusions:** Patient directed nudges led to engagement of nearly 60% of patients in two diverse gynecology practices. 25% of individuals scheduled and 14.9% completed appointments, with continued follow-up. Although engagement in PP and WH differed between the two clinics, the number of visits did not. An EHR-based approach to identifying patients and encouraging genetic testing is a relatively low effort, scalable strategy to increase reach and encourage engagement in genetic counseling. However, a majority of patients either did not respond or did not wish to be tested. Clinical trial information: NCT05721326. Research Sponsor: National Cancer Institute; P50 CA244690; Basser Center for BRCA.

10590 Poster Session

Clinical utility of germline genetic testing in diverse cancer types.

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Background: Germline genetic testing (GGT) is often recommended for cancer patients with an estimated ≥10% risk of carrying a clinically actionable pathogenic germline variant (PGV). Clinical utility of GGT is understudied for many cancer types, making assessing risk challenging. Herein we describe interim results from a GGT study of diverse cancer types. **Methods:** The PROACTIVE (Profile And Cancer gene Testing for IndiVidual Evaluation) Study is an ongoing institute-wide study at Dana-Farber Cancer Institute through which participants may opt-in to blood- or saliva-based clinical GGT of 133-156 genes, with results returned. Participants were identified by their clinical program, mainly consisting of those who did not meet clinical criteria for GGT based on having cancers that are considered low-risk for hereditary cancer predisposition syndromes. Clinically actionable PGV were defined as those that conferred potential eligibility for clinical management guidelines, targeted therapies and/or clinical trials. **Results:** Between 03/15/2019 and 11/30/2024, 1569 participants completed GGT. PGV were identified in 437/1569 (27.9%) participants, however 285 (18.2%) had PGV associated only with autosomal recessive cancer risk or low penetrance. Clinically actionable PGV were identified in 152/1569 (9.7%) participants and made up one-third (152/437) of PGV results. Clinically actionable PGV were identified most frequently in *ATM*, *CHEK2*, *APC*, *BRCA2*, and *TP53*, with the highest rates in gastric, central nervous system (CNS), and thyroid cancer (Table). High risk PGV were identified in 67/1569 (4.3%) participants, and were most frequent in the gastric, thyroid, and CNS cohorts (Table). Only 47/1569 (3.0%) participants had a PGV that was concordant with their cancer type. **Conclusions:** GGT identified clinically actionable findings in nearly 1 in 10 participants, most of whom were considered low-risk for hereditary cancer predisposition based on their personal cancer types. Most clinically actionable results were secondary findings unrelated to the presenting cancer type, but still impact cascade testing and screening for second primary cancers. This demonstrates the clinical utility of offering universal pan-cancer GGT to a broader range of cancer patients. Research Sponsor: None.

Largest cohorts by cancer type.

Cancer Type^	N	Any PGV (%)	Clinically Actionable PGV (%)	High Risk PGV (%)	PGV Concordance with Cancer Type (%)
Lung	409	130 (32)	41 (10)	16 (4)	8 (2)
Sarcoma*	229	59 (26)	19 (8)	9 (4)	6 (3)
Endometrial (normal IHC)	206	52 (25)	13 (6)	6 (3)	5 (2)
CNS*	125	37 (30)	15 (12)	6 (5)	3 (2)
Renal*	121	27 (22)	8 (7)	5 (4)	2 (2)
Bladder	77	13 (17)	5 (7)	2 (3)	0 (0)
Thyroid*	56	14 (25)	6 (11)	4 (7)	2 (4)
Cholangiocarcinoma	53	10 (19)	4 (8)	2 (4)	0 (0)
Gastric	40	13 (33)	7 (18)	3 (8)	1 (3)

*Includes adult and pediatric participants.
^Additional enrolled cancer types with fewer participants (N) include: melanoma, mesothelioma, multiple myeloma, therapy-associated polyposis, tongue, colon, breast.

10591 Poster Session

Clinical significance of germline CFTR mutations in pancreatic cancer.

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Background: Pancreatic ductal adenocarcinoma (PDAC) remains a malignancy with high cancer-related mortality. The majority of PDAC is sporadic, but approximately 10% are implicated by germline mutations. We recently reported that CFTR was one of the most mutated germline genes occurring in 11.9% of 1203 patients with PDAC. However, the clinical implications of germline CFTR mutations remain unknown. This study sought to evaluate the differences in clinical outcomes in PDAC patients with and without germline CFTR mutations. **Methods:** Eligible patients were ≥18 years who consented for BioBank specimen collection and Invitae genetic testing (n = 66). Patients were separated into two groups: patients with a known CFTR mutation (pathogenic variant or variant of uncertain significance (VUS)) (n = 35), and an age- and stage-matched cohort with no known CFTR mutation (n = 31). Subgroups were further stratified by stage at diagnosis: Stage I-III (early stage) vs Stage IV. Survival analysis was performed using Kaplan-Meier method and log-rank testing. A P-value < 0.05 was considered significant. Multiple linear regression was performed to investigate any associations between clinical variables (age at diagnosis, pathogenic variant vs VUS, history of smoking, alcohol use, pancreatitis) and survival. **Results:** A total of 35 patients with germline CFTR mutations and 31 age- and stage-matched patients were analyzed. Across all stages, the CFTR group had a median OS of 868 days vs 462 days (95% CI 1.014-3.48, P = 0.0390) in the non-mutated group. There was no difference in median OS between CFTR-mutant and non-mutant groups when stratified by early stage (I-III) disease: 929 days vs 765 days (95% CI 0.5950-2.478, P = 0.8543), respectively. Notably, CFTR mutated patients with stage IV disease derived greater OS benefit compared to the non-mutated group (572 days vs 182 days, 95% CI 1.025-9.639, P = 0.0140). Within the pathogenic (n = 25) and VUS (n = 10) subgroups of the germline CFTR mutant group, there was no difference in survival between those with pathogenic variants vs VUS (868 days vs 535 days, 95% CI 0.5233-5.031, P = 0.3573). Within the CFTR group, there was no difference in outcomes when analyzing for exposure to risk factors including smokers and non-smokers (868 days vs 572 days, 95% CI 0.2290-1.897, P = 0.5137), history of pancreatitis and no pancreatitis (929 vs 868 days (95% CI 0.3719-3.080, P = 0.5877), and alcohol use (chronic and social) and no alcohol use (939 days vs 622 days, 95% CI 0.5245-4.345, P = 0.0612). Multiple linear regression did not show any significant associations between pre-specified clinical variables and survival. **Conclusions:** This study suggests there is an association between germline CFTR mutation and improved survival in patients with advanced PDAC. CFTR may be a potential prognostic biomarker, which underscores the need for further studies focusing on the implications of CFTR mutations and PDAC. Research Sponsor: None.

10592 Poster Session

Germline genetic testing for hereditary cancer syndromes among newly diagnosed patients with solid tumors: A report of 10,000 patients from the Jordanian Exploratory Cancer Genetics study.

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Background: Hereditary factors play a key role in the risk of developing several cancers. Identification of germline cancer predisposing genes can have important implications for cancer screening, risk-reduction, risk-reducing interventions, and treatment decisions. **Methods:** In this study, patients with various cancers diagnosed and treated at King Hussein Cancer Center (KHCC) between January 2014 and December 2024 who had germline genetic testing (GGT) were retrospectively reviewed. Most patients were tested as per the National Comprehensive Cancer Network (NCCN) guidelines for GGT, while 3,319 patients were tested as part of a study for universal testing of all newly diagnosed cancer patients. Genetic testing was performed at reference commercial laboratories, or at academic centers. **Results:** The study involved 9,872 patients, the mean age at diagnosis was 49.7 (range: 18-90) years. Breast cancer was the most prevalent cancer type, comprising 67.3% of all cases, followed by colorectal cancer at 11.5%. Pathogenic/likely pathogenic (P/LP) variants were detected in 1,007 (10.2%) of the patients, while variants of uncertain significance (VUS) accounted for 33.6% of all genetic test results, highlighting the challenges of expanded panel testing. The most frequently identified pathogenic genes were BRCA1 and BRCA2, with 197 (2.0%) and 333 (3.4%) P/LP variants detected, respectively. Other notable genes included CHEK2 (n=28), PALB2 (n=38) and TP53 (n=47). Breast and colorectal cancers showed the highest number of pathogenic variant detections, with breast cancer accounting for 66.3% of all P/LP cases. Among less common cancers, ovarian cancer demonstrated a relatively high pathogenic variant rate (21.9%) despite its lower overall prevalence. Testing eligibility played a significant role in outcomes, with the majority of patients undergoing guideline-based testing (60%) and 26% undergoing universal testing. Expanded testing panels increased the detection of VUS significantly but did not improve pathogenic variant detection rates compared to guideline-based testing ($p<0.001$). There was also a significant association between cancer type and genetic testing results ($p<0.001$), underscoring the importance of cancer-specific testing strategies. **Conclusions:** These findings highlight the high prevalence of pathogenic variants in breast and colorectal cancers, the clinical relevance of BRCA1/2 and other high-risk genes, and the trade-offs of expanded genetic testing panels in balancing broader detection capabilities with interpretive challenges due to increased VUS rates. This emphasizes the need for targeted genetic counseling and strategic use of comprehensive testing panels for optimal clinical impact. Research Sponsor: None.

10593 Poster Session

Results of a program addressing multi-level barriers to completion of hereditary cancer genetic testing (GT) among underserved and minority individuals in Texas.

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Background: 5-10% of breast and colorectal cancers are hereditary, but uptake of GT among eligible individuals remains low. Our previous study showed that only 10 % of the 150 underserved and minority women deemed eligible for GT based on our validated Cancer Genetic Risk Assessment (CGRA) completed GT. Based on lessons learned, we implemented a multi-level program including: 1) genetic services education; 2) one-stop CGRA screening, scoring, and GT, 3) financial navigation, 4) telegenetics, and evaluated its impact. **Methods:** This prospective 12-months two-part program was implemented in Harris County, Texas, in 2023-2024. The primary outcome was GT completion. Both participants and providers received education about hereditary cancers. In the first part of the program, women who presented for mammography screening at clinics in underserved communities filled out the CGRA. In the second part, participants who identified as Black filled out the CGRA during events organized by trusted community organizations. The CGRA was scored and, if warranted, a saliva-based GT kit was offered during the visit or mailed later. Our study coordinator assisted with all financial paperwork. When a pathogenic variant (PV) or variant of uncertain significance (VUS) was found, participants received telegenetic counseling; others were notified of negative results. Socio-demographic characteristics and genetic services participation were analyzed via descriptive statistics and standard tests of association. Program implementation was assessed via in-depth interviews with a purposeful sample of participants and providers, which were audio-recorded, transcribed, double-coded, and analyzed via thematic analysis. **Results:** In the first part of the program, out of 870 women who presented for mammography screening and were approached, 590 (87%) agreed to be screened via CGRA (median age 52), including 537 (91.0%) who identified as Hispanic, 427 (72.4%) with preferred language Spanish. Median annual salary was 19,200. 99 (16.8%) were eligible for GT and 54 (54.5%) completed it, with 35 (64.8%) negative, 14 (25.9%) VUS, 5 (9.2%) PV in MUTYH , NF1, CHEK2, MSH3. In the second part of the program, out of 4,192 people who attended 20 community events, 390 (9.3%) individuals were screened via the CGRA (median age 54); all identified as Black. Median annual salary was 65,000. 187 (47.9%) were eligible for GT and 97 (51.8%) completed it, with 74.2% (72) testing negative, 22.7% (22) VUS, 3.09% (3) PV in RAD51C, CHEK2, BRCA1. GT completion was not associated with race, ethnicity, or salary ($p > 0.05$). Based on interviews with 56 participants and 16 providers, main GT facilitators included program convenience, while main barriers included cost and fear of results. **Conclusions:** Our program was successful in improving GT completion among underserved and minority participants. Clinical trial information: NCT05649072, NCT05694559. Research Sponsor: Susan G. Komen; CH22GCT001; The Community Outreach and Engagement Fund for Underserved Texans (COEFUT) sponsored by the Quasi Endowment Committee (QEC); RCTS number: 2022-00060886-Y1.

10594 Poster Session

Germline genetic testing among patients with pancreatic cancer (PC): A Pancreatic Cancer Action Network (PanCAN) patient survey.

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Background: Universal germline genetic testing for PC is endorsed by multiple professional organizations like the National Comprehensive Cancer Network (NCCN), yet implementation remains limited. We sought to investigate practices related to germline testing in PC and identify potential causes of under-testing through a large patient survey. **Methods:** We used the PanCAN patient registry to administer this HIPAA-compliant survey electronically to patients and caregivers. Logistic regression was used to determine the association between patient-reported demographic and clinical characteristics and the odds of undergoing germline genetic testing. A multivariate model was built to include all characteristics that were significant on univariate analysis. The association between receipt of genetic counseling and cascade germline genetic testing among first degree relatives (FDR) of patients with germline mutations was assessed via a chi-square test. **Results:** A total of 1,046 patients with PC were included, of which, 724 (69.2%) reported undergoing germline genetic testing. On multivariate analysis, race ($p = 0.01$), insurance type ($p < 0.01$), stage ($p < 0.01$), and treatment facility type ($p < 0.01$) were significantly associated with the odds of undergoing germline genetic testing after PC diagnosis. Black patients (compared to White) [OR = 0.42 (95% CI 0.23-0.78)], uninsured patients (compared to Medicare) [OR = 0.11 (95% CI 0.03-0.44)], patients insured through Veterans Health Administration (compared to Medicare) [OR = 0.26 (95% CI 0.08-0.92)] and patients receiving care at large [OR = 0.62 (95% CI 0.46-0.84)] and small community practices (compared to academic/teaching hospitals) [OR = 0.51 (95% CI 0.29-0.88)] were at significantly decreased odds of undergoing germline genetic testing. Patients with stage IV (compared to stage I) [OR = 2.23 (95% CI 1.46-3.40), stage II/III PC (compared to stage I) [OR = 1.58 (95% CI 1.11-2.23)] and those with private insurance (compared to Medicare) [OR = 1.51 (95% CI 1.11-2.05)] were at significantly increased odds of undergoing germline genetic testing. Of 724, 167 (23.2%) patients reported testing positive for germline mutations. Only 103 of 167 (61.7%) of these patients reported cascade testing among FDR. Patients undergoing genetic counselling had higher rates of cascade germline genetic testing among FDR (67.7% v 38.2%, $p < 0.01$). **Conclusions:** This is one of the largest patient-reported surveys from recent times suggesting sub-optimal implementation of guideline-based germline genetic testing in PC. This study highlights key inequities in testing based on race, insurance and practice setting. Our findings also underscore the critical role of genetic counselling in facilitating cascade testing among FDR of patients with PC and germline genetic mutations. Research Sponsor: None.

10595 Poster Session

Concordance of parent-of-origin predictions for hereditary cancer variants using proband-only analysis.

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Background: Determining the parental origin of germline variants is a critical gap in clinical genetics, essential for risk management, variant classification, and cascade genetic testing. Traditional methods rely on testing family members, which can be time-consuming and impractical when relatives are unavailable, deceased, or unwilling to participate. Parent-of-Origin-Aware Genomic Analysis (POAga) offers a transformative solution by enabling accurate assignment of any autosomal variant to either parent with 99% accuracy using only a blood sample from the proband. This method integrates methylation and sequence data from Oxford Nanopore long-read sequencing with chromosome-length haplotypes generated from Strand-seq, leveraging the accurate phasing of imprinted differentially methylated regions (iDMRs) that occur on each autosome to infer the parent of origin (PofO) of variants across the genome. This study aims to validate POAga across multiple hereditary cancer syndromes, including high-penetrance conditions such as hereditary breast and ovarian cancer (HBOC) and Lynch syndrome, as well as rarer syndromes with PofO effects and other genes associated with breast and gastrointestinal malignancies. **Methods:** Blood samples from carriers of pathogenic variants in *ATM*, *BRCA1*, *BRCA2*, *CDH1*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *PALB2*, *SDHD*, *SDHAF2* and *TP53* with known parental segregation, are currently being ascertained and undergoing whole-genome analysis to determine the analytic validity of POAga. These samples span diverse demographics, including variations in age, sex, ethnicity, and cancer status. PofO predictions are made according to previously described methods (Akbari V, Hanlon VCT, *et al*. Cell Genom. 2022 Dec 21;3(1):100233) under an REB-approved protocol. **Results:** To date, 188 individuals carrying 189 pathogenic variants with known parental segregation have been analyzed. The distribution of variants includes *BRCA2* (n=31), *MLH1* (n=23), *MSH2* (n=22), *BRCA1* (n=22), *SDHD* (n=21), *MSH6* (n=20), *PALB2* (n=14), *PMS2* (n=13), *ATM* (n=9), *CDH1* (n=9), *SDHAF2* (n=2), *EPCAM* (n=2) and *TP53* (n=1). PofO assignment was successful for 172 of 189 (91%) variants. Only one sample with an *MLH1* variant was misassigned, while all other cases demonstrated concordance between the predicted and known parental origin (188 of 189, 99.5% accuracy). **Conclusions:** These results support the ability of POAga to accurately infer the parental origin of pathogenic variants in diverse hereditary cancer syndromes using only blood sample from the proband. Ongoing validation will further assess its feasibility in real-world clinical settings and refine its clinical translation. POAga represents a powerful advancement in hereditary cancer genetics, with the potential transform how we conduct genetic cancer risk assessments for patients and families. Research Sponsor: BC Cancer Foundation; Canadian Institutes of Health Research; Genome Canada Genomic Applications Partnership Program; University of British Columbia; Canadian Foundation for Innovation; Canada Research Chairs Program; BC Cancer.

10596 Poster Session

Clinical decision support system based on artificial intelligence and the patient's subjective intention treatment model: A randomized controlled clinical trial.

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Background: To achieve intelligent diagnosis and treatment of tumors through the application of artificial intelligence and to meet the needs of areas lacking medical resources, a new treatment model based on the patient's subjective intention (PSI) was proposed, and a clinical decision support system (CDSS) called Doctors In Hands (DIH) was designed. Here, we report the DIH trial with the PSI treatment model to evaluate its efficiency. **Methods:** In this randomized controlled open-label trial (ChiCTR2400094469), patients from the departments of oncology, internal medicine, and surgery signed informed consent forms and were randomly divided into the clinician group, the CDSS plus clinician group and the CDSS group. The PSI treatment model was applied in the CDSS group. The primary endpoint was the sensitivity of alternative diagnoses and treatment options. The secondary endpoints were patient satisfaction and the specificity of alternative diagnoses and treatment options in different departments and groups. A multimodal large model based on the novel PSI treatment model was used as the intelligent platform for diagnosis and treatment data analysis and human–computer interaction. **Results:** A total of 120 patients and 9 doctors were enrolled and randomly divided into three groups. In the clinician group, the sensitivity and specificity of diagnosis were 0.82 and 0.76, the Youden index was 0.58. In the CDSS group, the sensitivity and specificity were 0.85 and 0.80, the Youden index was 0.65. For the CDSS plus clinician group, the sensitivity and specificity were 0.90 and 0.87, the Youden index was 0.77. Subgroup analysis of patients according to treatment strategy revealed that the satisfaction of patients in the PSI-based CDSS group was significantly greater than that of patients in the clinician group (92% vs. 86%, $P < 0.01$), but there was no significant difference between the CDSS group and the CDSS plus clinician group (92% vs. 93%, $P = 0.37$). Subgroup analysis of the PSI-based CDSS group according to diagnostic strategy revealed that the diagnostic accuracy for patients from the department of oncology was significantly greater than that for patients from the department of internal medicine (0.88 vs. 0.81, $P < 0.05$) but was not significantly different from that for patients from the department of surgery (0.88 vs. 0.87, $P = 0.14$). **Conclusions:** DIH has good performance in the diagnosis of tumors and development of treatment plans. In the PSI model, patients can make independent choices regarding disease treatment plans according to the objective clinical or basic research evidence provided by DIH to reduce the duration of consultation and save medical resources. The clinical significance of this trial is that the CDSS can promote the sharing of medical resources and improve the efficiency and quality of clinical work in areas lacking medical institutions. Clinical trial information: ChiCTR2400094469. Research Sponsor: None.

10598 Poster Session

Impact of incretin mimetic therapy on weight change in patients with cancer: A pan-cancer analysis from a single institutional cohort.

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Background: An elevated body mass index (BMI) is a frequent comorbidity in patients with cancer. Chemotherapy can exacerbate metabolic dysfunction and weight gain, further complicating cancer management. Glucagon-like peptide-1 receptor agonists (GLP-1RA) are indicated for the treatment of diabetes (DM) and obesity, promoting weight loss through mechanisms such as insulin secretion, delayed gastric emptying, and reduced appetite. However, their effect after a cancer diagnosis, particularly during chemotherapy, remains underexplored. **Methods:** This was a single-institution retrospective study evaluating cancer patients prescribed GLP-1 receptor agonists (GLP-1RA). Patient demographics, cancer type (solid vs. hematologic), and treatment details were extracted from the medical records. The overlap between GLP-1RA therapy and chemotherapy administration was recorded. Changes in BMI were analyzed using descriptive statistics, including percentiles and median values. A one-sample t-test assessed the overall significance of BMI changes, while subgroup analyses using Welch two-sample t-tests evaluated the impact of chemotherapy, sex, and cancer type on BMI reduction. R software was used to perform statistical analyses. **Results:** Between 2015 and 2024, 339 cancer patients were treated with GLP-1RAs, mainly semaglutide (48%) and liraglutide (28%). DM was the primary indication in 92% patients (Table 1). The median age at initiation was 60.8 years (range: 19.0–88.2), for a median duration of 11.8 months (range: 2.6–94.1). Median BMI decreased from 32.5 kg/m^2 (range: 18.9–58.9) pre-treatment to 31.5 kg/m^2 (range: 16.6–60.2) on/post-treatment, with a median change of -1.0 kg/m^2 (95%CI: -1.64, -1.01) and a median percentage reduction of -3.71% (95%CI: -4.59%, -2.83%). Subgroup analyses showed significant BMI reductions in patients receiving chemotherapy (median: -4.18%, 95%CI: -6.38%, -2.82%) and those not receiving chemotherapy (median: -2.32%, 95%CI: -4.32%, -2.31%), with no significant difference between the groups (95%CI: -0.22, 1.28). Additionally, BMI reductions were consistent across sex (95%CI: -0.91, 0.36) and cancer type (solid vs. hematologic, 95%CI: -0.77, 0.64). **Conclusions:** GLP-1RA use resulted in weight loss in cancer patients independent of chemotherapy exposure, sex, or cancer type. Although the degree of weight loss was modest, findings were consistent with GLP1-RA treatment dosed for a diabetes indication. These findings support the need for clinical trials evaluating incretin mimetics for weight management and their potential impact on cancer-specific outcomes. Research Sponsor: None.

Patient demographics.

Variable:	# of Patients (*n*):	%:
Sex: F / M	180 / 156	54 / 46
White	171	61
Black	56	20
Asian	20	7
Other Race or Unknown	34	12
Solid Tumor	249	74
Hematological Cancer	87	26
Chemotherapy During GLP-1RA	103	30
GLP-1RA Use for DM Indication	313	92

10599 Poster Session

Assessing the association between cycles of fertility treatments with gonadotropins and cancer risk.

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Background: Fertility treatments such as in vitro fertilization (IVF) and controlled ovarian hyperstimulation relies on exogenous hormones known as gonadotropins that directly stimulate ovarian activity. Concerns have arisen regarding the increased risk of hormone-sensitive cancer development due to repeated hormonal stimulation. The literature regarding this risk is ambiguous. We aimed to assess the association between the number of fertility treatments with gonadotropins (FT-GT) cycles and cancer risk in a large national HMO database. **Methods:** The Clalit Health Services database was analyzed between 2003-2013 to identify females who underwent FT-GT along with matched controls by age, ethnicity and socioeconomic status. FT-GT cycles were identified through the use of gonadotropins. Controls were matched 4:1 with untreated females. Patients were grouped based on number of FT-GT cycles being 1–4, 5–7, or ≥8. Cancer risk analysis focused on breast, colon, thyroid, stomach and pancreas, as well as any detectable cancer. We performed a separate sub-analysis of women who received ≥10 FT-GT cycles. **Results:** A total of 178, 637 patients were analyzed- 39,068 received FT-GT; 24,716 underwent 1–4 cycles; 7,774 underwent 5–7 cycles; and 6,578 received ≥8 cycles. For the separate sub-analysis, 3,949 women received ≥ 10 cycles. The median follow-up was 12.6 years. The risk of breast cancer increased with the number of FT-GT cycles, with the highest risk observed in patients receiving ≥8 cycles (HR = 1.67, 95% CI: 1.22-2.27), followed by 5-7 cycles (HR = 1.42, 95% CI: 1.07-1.89), and 1-4 cycles (HR = 1.34, 95% CI: 1.15-1.56), when adjusting for hypothyroidism. When analyzing the ≥ 10 cycle sub-group, the hazard ratio for breast cancer reaches 1.79 (95% CI: 1.19-2.70). There was no correlation between FT-GT cycle number and colon, stomach or pancreatic cancer, or any other detected cancer. **Conclusions:** It appears that females receiving FT-GT are at a higher risk for breast cancer from the first cycle. The risk of breast cancer increases with the number of FT-GT cycles. None of the other cancers analyzed showed any significant cancer risk associated with FT-GT. Research Sponsor: None.

10600 Poster Session

Decoding oncology terminology: Using large language models for patient education.

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Background: Large language models (LLMs), such as OpenAI's ChatGPT-4, are designed to process natural language and generate responses to text-based prompts. While these models have shown promise in addressing clinical and patient-related inquiries, they lack integration with dedicated medical knowledge databases, leading to potential inaccuracies. Meanwhile, healthcare professionals and models explicitly trained in medical texts frequently rely on specialized terminology, which can create significant barriers to clear and patient-friendly communication. This study aims to utilize LLMs to translate complex medical terminology into easy-to-understand explanations, focusing on hematology and oncology fields where communicating medical concepts to the public is particularly challenging. Our objective is to develop a solution that ensures explanations are both accurate and accessible, bridging the gap between technical medical knowledge and patient comprehension. **Methods:** We curated a dataset of cancer-related terms and their explanations from two sources: the National Cancer Institute (NCI) Dictionary, which provides detailed medical definitions, and simplified explanations based on National Comprehensive Cancer Network (NCCN) guidelines for patients. Using Meta's LLaMA 7 B-based chat model, we implemented retrieval-augmented generation (RAG) to enable the model to access the NCI Dictionary as needed. To fine-tune the model to generate patient-friendly explanations, we applied LoRA-based supervised fine-tuning (SFT). The model was evaluated on a holdout set of terms. Readability was measured using the Flesch Reading Ease Score (FRES) and Dale-Chall Readability Formula (DCRF). Improvements in accessibility were quantified through a two-sample t-test, comparing the mean readability scores of the model's outputs against the baseline. **Results:** The fine-tuned model demonstrated significant improvements in both accessibility and readability, achieving a 5% and 4% increase in the FRES (baseline: 69.25; output: 72.60, $P < 0.01$) and DCRF (baseline: 9.50; output: 9.15, $P < 0.01$), respectively. Preliminary results also indicate the model's capability to translate entire paragraphs of dense medical text into patient-friendly explanations. Expert validation on a larger scale is currently underway, further solidifying the model's potential to revolutionize patient communication in oncology. This innovative approach sets a new standard for leveraging advanced language models in healthcare education. **Conclusions:** We successfully trained a LLM specifically designed to simplify complex oncology medical terms into patient-friendly language. By serving as a reliable tool for delivering precise and accessible medical information, it holds the potential to reduce the workload of healthcare providers and enhance patient understanding in clinical settings. Research Sponsor: None.

10601 Poster Session

Recruitment strategies and enrollment for a virtually supervised exercise intervention for Hispanic/Latinx breast cancer survivors.

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Background: Hispanic and/or Latinx cancer survivors remain underrepresented in clinical trials, particularly in exercise oncology and energy balance research, with less than 1% of exercise oncology trials focused on this population. The purpose of this analysis was to describe recruitment strategies and enrollment rates among Hispanic and/or Latinx breast cancer survivors screened for and enrolled in an exercise intervention. **Methods:** The ROSA Trial was a culturally tailored, virtually supervised exercise intervention designed to mitigate metabolic dysregulation in sedentary, overweight/obese Hispanic and/or Latinx breast cancer survivors. Trial recruitment strategies at the Dana-Farber Cancer Institute (DFCI) involved screening pre-determined electronic medical records of breast cancer patient lists for the DFCI Boston location, direct referral from the DFCI Merrimack Valley satellite which is comprised of $>$ 70% Hispanic patient population, recruitment letter mail outs the Massachusetts Department of Public Health (MDPH) cancer registry, American Cancer Society (ACS) Making Strides for Breast Cancer Boston events (2022-23), and media outlets. Descriptive statistics were used to determine frequency of recruitment strategies used and screening variables. **Results:** Trial recruitment occurred from September 2021-August 2024. The majority of women screened were identified at the DFCI Boston location (70%) followed by the MDPH (23%), DFCI Merrimack Valley (5%), and ACS events (2%). Out of 710 women screened, 396 were ineligible. Main reasons for ineligibility included did not identify as Hispanic/Latinx (n = 78; 19.7%), not sedentary (n = 60; 15.2%), and lived out of country/state (n = 56; 14.1%). Of the 314 women deemed eligible, 240 declined participation, with primary reasons including no communication response (i.e., never responded to voicemails or emails; n = 84; 35%), not interested (n = 46; 19.2%), and no time/scheduling issues (n = 42; 17.5%). There were 74 women who consented for the trial from the 314 deemed eligible, resulting in a 23.6% success rate. A total of 64 women were successfully randomized with 10 women unable to proceed to randomization due to no time (n = 4) or did not provide a specific reason/stopped responding to study staff (n = 6). Randomized participants were 55.47 $\pm$ 9.5 years old, overweight or obese (BMI = 30.33$\pm$ 5.6), postmenopausal (71%), diagnosed primarily with stage I (37.1%) or stage II (37.1%) breast cancer. **Conclusions:** Multiple recruitment strategies with specific attention to consistent points of contact are necessary to recruit Hispanic and/or Latinx breast cancer survivors in the Greater Boston area. Unique situations such as residency out of the country is important to consider in the planning of future trials among said population. Clinical trial information: NCT04717050. Research Sponsor: American Cancer Society.

10602 Poster Session

Women's breast cancer mortality trends: The impact of lifestyle factors from the 2021 Global Burden of Disease (GBD) study.

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Background: Breast cancer (BC) remains a leading cause of death among women globally. Understanding the role of modifiable risk factors is critical for designing targeted prevention strategies. The 2021 GBD study offers a comprehensive analysis of global health, quantifying the impact of diseases and risk factors on morbidity and mortality worldwide. This study provides an updated risk factor analysis in relation to women's BC mortality over the past three decades. **Methods:** Data from the study were used to examine trends in BC mortality in the United States from 1990 to 2021, stratified by age group representing younger pre-menopausal (ages 20-54) and older post-menopausal women (ages ≥55), associated with five key risk factors: tobacco use, red meat consumption, alcohol consumption, high body mass index (BMI), and high fasting plasma glucose (FPG). Age-standardized mortality rates (ASMR) were calculated for each factor, and differences between age groups were analyzed. All rates were reported per 100,000 population. Joinpoint regression analysis was conducted to evaluate trends. **Results:** In 2021, a high red meat diet (consuming >70 g/day of red meat), was the leading risk factor for BC-ASMR overall (2.3), both in older (11.4) and younger (1.4) women, contributing 14% to ASMR across all age groups. Older women had significantly higher ASMR for all risk factors (Table 1). From 1990 to 2021, tobacco-associated BC-ASMR exhibited the greatest decline, with a global reduction of 55.06%, more pronounced in younger (58.39%) than older (46.58%) women. Alcohol-related mortality also decreased significantly, more evident in younger (37.69%) than older (13.09%) women. While the absolute increase in risk factor-associated ASMR was observed with high FPG (+4.4%), a proportional ASMR increase was observed for all three metabolism-related risk factors, including high FPG (+75%), high BMI (+32%), and alcohol use (+14%). High FPG was associated with increased BC-ASMR in both age groups, while younger women experienced a significant rise due to high BMI (+689%). **Conclusions:** These findings highlight the impact of modifiable risk factors on BC mortality. There is a notable reduction in tobacco and alcohol-related deaths, particularly among younger women, likely due to public health campaigns and smoking cessation programs. Moreover, the rising prevalence of alcohol intake in older women, the growing impact of metabolic-related morbidity in younger women, and the hormonal changes amplifying BMI-related risks in post-menopausal women, stress the need for targeted health interventions that could markedly reduce the burden of BC mortality globally. Research Sponsor: None.

Risk factors	Overall trend (1990-2021)	Ages 20-54	Ages ≥55
Tobacco	1.4→0.6	1.1→0.5	5.2→2.8
Alcohol use	1.4→1	1.3→0.8	4.6→4
High FPG	1.1→1.1	0.36→0.39	5.7→6.2
High BMI	2→1.6	0.02→0.1	12.5→10.4
Diet high in red meat	3.9→2.3	2.3→1.4	17.4→1.5

10603 Poster Session

Are indulgent lifestyle practices the driving determinants behind the rising cancer rates in young adult men?

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Background: This study aims to determine trends and incidences of cancers associated with social behaviors including tobacco use, excess body fat, alcohol consumption, insufficient physical activity, and human papillomavirus infection among male adults in the U.S. over a 20 year study period. **Methods:** Cancer incidence was extracted from the United States Cancer Statistics Public Use Database (USCS). Tobacco associated cancers were defined as: oropharyngeal, esophageal, stomach, colorectal, liver, pancreas, larynx, lung, kidney, bladder, and acute myeloid leukemia cancers. Obesity associated cancers were defined as: colorectal, liver, kidney, and thyroid cancers. Alcohol associated cancers were defined as: oropharyngeal, esophageal, colorectal, liver, and larynx cancers. Physical-inactivity associated cancers were defined as colorectal cancers. HPV associated cancers were defined as: oropharyngeal, penile, and anorectal cancers. SEER*Stat 8.4.1.2 and Joinpoint regression program 5.0.2 were employed to calculate estimated and actual incidence rates per 100,000 women. **Results:** Based on USCS data, the 2021 incidence of tobacco, obesity, alcohol, physical-inactivity, and HPV associated cancers for males was 217.4, 111.9, 80.9, 27.2, and 9.5 per 100,000, respectively. Moreover, besides HPV associated cancers which had an average annual percent change (AAPC) from 2001-2021 of 0.9% ($p<0.001$) among males, physical-inactivity, alcohol, tobacco and obesity associated cancers decreased at -2.63% ($p<0.001$), -1.29% ($p<0.001$), -1.28% ($p<0.001$), and -0.41% ($p<0.001$), respectively. Evaluating cancer trends among young adult males, physical-inactivity, obesity, alcohol, and tobacco associated cancers have been increasing for males aged 20-49, each with the sharpest rise among those aged 20-24 at 4.15% ($p=0.037$), 3.43% ($p<0.001$), 2.09% ($p<0.001$), and 1.22% ($p<0.001$), respectively. In contrast, incidence for these cancers has been decreasing among all older age groups of men (≥50). Among 20-24 year old males in 2021, the incidence of tobacco, obesity, alcohol, and physical-inactivity associated cancers was 6.46, 4.8, 2.13, and 1.16 per 100,000 men, respectively. Lastly, HPV associated cancers decreased among all males younger than 55 and increased for older male age groups (≥55) - particularly for the 65-69 age group (AAPC: 2.17%, $p<0.001$). **Conclusions:** Of cancer-related sociobehavioral lifestyle risk factors, young men were most impacted by cancers associated with tobacco use. However, younger males observed the highest annual increases in cancer incidence for these modifiable risk factors, particularly in physical-inactivity in obesity and physical-inactivity associated and obesity associated cancers. Further research is warranted to investigate whether diet, physical inactivity, alcohol, tobacco, or HPV among younger adults play a larger role in these trends. Research Sponsor: None.

10604 Poster Session

Skewed offspring distribution of *TP53* pathogenic variants in Israeli Li-Fraumeni syndrome families.

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Background: Li-Fraumeni Syndrome (LFS) [OMIM #151623] is an autosomal dominant cancer predisposition syndrome caused primarily by germline pathogenic (PV) or likely pathogenic variants (LPV) in the TP53 gene. Classical autosomal dominant (AD) inheritance predicts a 50% risk of inheritance for offspring of TP53 PV/LPV carriers. However, clinical observations in Israeli LFS families suggest a higher-than-expected prevalence of TP53 PV/LPV carriers among offspring. This study aims to further investigate this phenomenon. **Methods:** Relevant clinical data from 36 LFS families followed at Sheba Medical Center's high-risk clinic (2015–2024) were reviewed under an IRB-approved protocol. Twenty families met inclusion criteria after excluding those with incomplete clinical data or carriers without offspring. Detailed pedigree analyses were conducted to determine the carrier status of all offspring of confirmed and obligate TP53 mutation carriers. Probable carriers were defined as individuals who fulfilled two criteria: (1) a diagnosis of an LFS-associated malignancy, and (2) being a first-degree relative of a confirmed carrier. Deceased parents with LFS-associated malignancies, whose partners had normal TP53 sequencing and whose offspring tested positive for TP53 PV/LPV, were also considered obligate carriers. A t-test was used to compare the observed proportion of TP53 PV/LPV carriers among offspring with the expected 50% inheritance rate for AD conditions. **Results:** A total of 174 individuals met the study criteria and were either genotyped for the family-specific TP53 PV/LPV or assigned obligatory or probable carrier status. Of these, 115 (66.1%) were identified as TP53 PV/LPV carriers, either through genotyping (n= 87), obligatory (n= 13) or probable carrier designation (n= 15). This observed proportion was significantly higher than the expected 50% based on AD inheritance ($p<0.0001$). Out of the TP53 PV/LPV carriers, 67 (58.3%) individuals were healthy at the time of genotyping, and 62 (53.9%) were male. **Conclusions:** Our findings reveal a significant skewing of TP53 variant inheritance in Israeli LFS families, with a higher-than-expected prevalence of carriers among offspring. To our knowledge, this phenomenon has not been previously reported in LFS. A potential mechanism for this skewing may involve TP53's role in cell cycle regulation and apoptosis. Reduced TP53 protein levels could confer a selective advantage during early embryonic development by enhancing cell proliferation, potentially improving embryonic survival and implantation success. If corroborated in larger and ethnically diverse LFS cohorts, this finding could have implications for genetic counseling, particularly in reproductive decision-making for LFS families. Further research is needed to validate these findings and explore the underlying biological mechanisms driving this skewing. Research Sponsor: None.

10605 Poster Session

Long-term safety of belzutifan in von Hippel-Lindau syndrome: A single-center experience.

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Background: Belzutifan has improved control in Von Hippel-Lindau (VHL) syndrome, reducing the need for interventions. However, its long-term safety and side effect burden remain incompletely understood. This study evaluates long-term safety, tolerability and the impact of dose modifications in VHL patients (pts) treated with belzutifan. **Methods:** A single-center retrospective study of VHL pts ≥ 18 years treated with belzutifan at Vanderbilt (Nov 2018 - Dec 2024). Demographic and clinical data were collected. The primary endpoint was treatment discontinuation. Secondary endpoints included incidence of adverse events (AEs) (any-grade and grade ≥ 3 per CTCAE 5.0), dose reductions, time to dose reduction, treatment interruptions, subsequent procedures, and treatment failure (defined as radiological progression per RECIST 1.1 or physician assessment) while on treatment. Follow-up duration was defined as the time from the belzutifan initiation to last follow-up or discontinuation. **Results:** Twenty-five pts were identified, with a median age of 42 years, 64% female and 88% white, with a baseline hemoglobin of 13.7 (range: 11.0 – 19.0). As of January 2025, the median follow-up was 32.5 months (mo) (range: 2.5 – 75). Most common VHL-associated neoplasms included CNS hemangioblastomas (88%), renal cell carcinoma (72%), and pNET (32%). All pts started belzutifan at 120 mg. AEs occurred in 92% of pts (detailed in Table 1). Anemia was observed in 64% of pts (no grade ≥ 3), with a median onset of 3.4 mo (range: 1.1 – 17.7). Treatment interruptions were required by 68% of pts. At the last follow-up, 32% remained on 120 mg, 52% were on 80 mg, and 16% discontinued. The median time to discontinuation was 33 mo (range: 24.5 – 34); due to symptomatic anemia (1 pt), grade 3 hypoxia (1pt), disease progression (1pt) and a non-related death (1pt). Dose reductions were needed by 60% of pts, primarily due to anemia, with a median time to dose reduction of 6.8 mo (range: 1 – 17). Among the 15 pts with dose reductions, none experienced treatment failure during a median follow-up of 21.3 mo (range: 1 – 31), although one pt had persistent grade 3 hypoxia. No pts required transfusions and 8% received erythropoietin stimulating agents. Before belzutifan, 92% of pts had undergone procedures related to VHL manifestations. Following treatment initiation, 8% required additional procedures. **Conclusions:** These findings provide long-term safety data on belzutifan in VHL. While AE were common, dose reductions were effective in maintaining tolerability without compromising disease control. Research Sponsor: None.

Adverse events in at least 5% of the safety population (25 pts).

	Any-grade	Grade ≥ 3	Leading to dose reduction	Leading to discontinuation
Fatigue	20 (80)	1 (4)	4 (16)	0
Anemia	16 (64)	0	9 (36)	1 (4)
Nausea	8 (32)	0	2 (8)	0
Dizziness	8 (32)	0	0	0
Headache	7 (28)	0	1 (4)	0
Hypoxia	2 (8)	1 (4)	1 (4)	1 (4)
AST or ALT elevation	2 (8)	0	1 (4)	0
Cognitive impairment	2 (8)	0	0	0
Pericardial Effusion	2 (8)	1 (4)	2 (8)	0

LBA10606 **Poster Session**

The Genetic Information and Family Testing (GIFT) trial.

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10607 Poster Session

Breast cancer post-ovarian cancer in germline non-BRCA homologous recombination (HR) gene pathogenic variant carriers.

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Background: Ovarian cancer (OC) is characterized by deficiencies in homologous recombination (HR). Although germline and somatic *BRCA1/2* pathogenic variants (PVs) play a critical role in HR and OC, germline PVs in other genes associated with HR, such as *RAD51C, RAD51D, BRIP1*, and *PALB2*, have also been linked to an increased risk of OC development. Most of these genes are also associated with increased risk of certain types of breast cancer (BC). However, little is known about risks of secondary BC after OC in this germline non-BRCA HR population. **Methods:** We identified patients with OC treated at a single institution undergoing tumor-normal sequencing (MSK-IMPACT) from 07/01/2015 to 12/31/2020. Germline assessment of ≥76 genes was performed, including HR genes *ATM*, *BARD1*, *BRIP1*, *FANCA*, *FANCC*, *NBN*, *PALB2*, *RAD50*, *RAD51B*, *RAD51C*, and *RAD51D*. Biallelic inactivation was assessed within tumors at the germline variant locus using the FACETS (fraction and allele-specific copy number estimates from tumor sequencing) algorithm. In this study, genes with high rates of biallelic inactivation (≥60%) were included based on role in OC tumorigenesis. Thus, we focused on patients with *BRIP1*, *PALB2*, and *RAD51B/C/D* PVs and further extracted clinical data including secondary BC screening patterns and rates. **Results:** Of the 882 patients with OC and germline assessment, 56 (6%) had germline PV in non-BRCA HR genes, and 35 (4%) patients had germline PV in *BRIP1* (n = 13), *PALB2* (n = 4), *RAD51B* (n = 4), *RAD51C* (n = 4), or *RAD51D* (n = 10). With a median follow-up after OC diagnosis of 55.82 months, no metachronous BC diagnosis occurred in these 35 patients. Among this cohort, 23 (66%) patients received PARP inhibitor therapy for OC, and 17 (49%) patients died from OC. Three patients (9%) were diagnosed with BC before OC diagnosis (germline *PALB2*, *RAD51B,* and *RAD51D* PV carriers). All 3 patients were BC disease-free at the time of data cutoff, and 2 died of their OC. Twenty-five patients (71%) underwent BC screening during OC treatment/follow-up with annual mammography, and 4 (16%) underwent additional annual magnetic resonance imaging. Only two patients were more intensively followed due to abnormal breast findings that were resolved during the follow-up. No patients underwent risk-reducing breast surgery. Interestingly, 30 patients (86%) had a family history of cancer: 12 (40%) with breast cancer, 6 (20%) with ovarian cancer, 8 (27%) with both breast and ovarian cancer, and 4 (13 %) with other cancers. **Conclusions:** BC incidence after OC diagnosis and treatment in non-BRCA HR germline PV carriers remains low, probably due to the poor prognosis of OC and the potential preventive effects of PARP inhibitor treatments on BC development. Further prospective studies are needed to address this question. Research Sponsor: MSK Cancer Center Support Grant by the NIH/NCI (P30 CA008748); International Mobility Grants IDIBGI 2023; SEOM Visiting Fellowship for short-term visits to reference centers 2024.

10608 Poster Session

Codon 167 missense mutations in von Hippel-Lindau syndrome: Genotype-phenotype correlations in a population-based study.

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Background: Von Hippel-Lindau (VHL) disease is caused by germline mutations of the *VHL* gene, resulting in multicentric and multiorgan tumors. Codon 167 is most commonly affected by pathogenic missense mutations (MMs). The objective of this study is to elucidate the clinical features of individuals with germline pathogenic MMs at codon 167 of *VHL*. **Methods:** 674 patients from 282 unrelated families were enrolled. Their clinical features and prognosis were reviewed. **Results:** 86 patients from 41 unrelated families were identified with codon 167 MMs, indicating codon 167 MMs account for the largest number of patients and families. Codon 167 MMs were associated with a significantly higher risk of pheochromocytoma (HR=7.384, 95%CI 4.496-12.126, P<0.001), lower risks of central nervous system hemangioblastoma/CHB (HR=0.568, 95%CI 0.412-0.781, P=0.001) and renal cell carcinoma/RCC (HR=0.693, 95%CI 0.483-0.993, P=0.046). And codon 167 MMs correlated with better overall survival (HR=0.408, 95%CI 0.210-0.790, P=0.008) and CHB-specific survival (HR=0.201, 95%CI 0.062-0.645, P=0.007) compared with other mutations. The most dominant types of codon 167 MMs are c.499C>T p.Arg167Trp (45.3%) and c.500G>A p.Arg167Gln (48.8%). Multivariate Cox regression analyses discover that the mutation type was not an independent factor for VHL-associated tumors. **Conclusions:** In the VHL disease population, codon 167 MMs account for more than 10% of patients and unrelated families. Individuals with codon 167 MMs had unique clinical features and should be described as a separate subtype of VHL syndrome. The results of this study were important for genetic counseling and clinical decision-making. Research Sponsor: Peking University First Hospital; 2023SF40.

Cox regression analyses of age-related tumor risks between codon 167 MMs, oMMs and TR.

Tumor	Variables	Univariate analysis			Multivariate analysis		
		HR	95%CI	P value	HR	95%CI	P value
Overall	**Sex** (Male vs. Female)	0.974	0.829-1.144	0.744	0.971	0.827-1.141	0.772
	Mutational type			0.510			0.505
	Codon 167 MMs	0.928	0.724-1.188	0.552	0.928	0.724-1.189	0.556
	oMMs	0.905	0.762-1.076	0.258	0.905	0.761-1.075	0.254
	TR	**Reference**			**Reference**		
CHB	**Sex** (Male vs. Female)	1.157	0.956-1.401	0.135	1.149	0.949-1.391	0.154
	Mutational type			**0.001**			**0.001**
	Codon 167 MMs	0.566	0.411-0.778	**<0.001**	0.568	0.412-0.781	**0.001**
	oMMs	0.772	0.631-0.946	**0.013**	0.774	0.632-0.947	**0.013**
	TR	**Reference**			**Reference**		
RA	**Sex** (Male vs. Female)	1.160	0.823-1.634	0.397	1.170	0.831-1.649	0.368
	Mutational type			**0.010**			**0.010**
	Codon 167 MMs	0.651	0.381-1.113	0.117	0.653	0.382-1.117	0.120
	oMMs	0.571	0.390-0.836	**0.004**	0.569	0.388-0.833	**0.004**
	TR	**Reference**			**Reference**		
RCC	**Sex** (Male vs. Female)	1.070	0.858-1.335	0.547	1.069	0.857-1.334	0.552
	Mutational type			0.092			0.092
	Codon 167 MMs	0.693	0.483-0.993	**0.046**	0.693	0.483-0.993	**0.046**
	oMMs	0.848	0.670-1.071	0.167	0.848	0.671-1.072	0.167
	TR	**Reference**			**Reference**		
PCT	**Sex** (Male vs. Female)	0.792	0.637-0.985	**0.036**	0.789	0.634-0.981	**0.033**
	Mutational type			0.356			0.330
	Codon 167 MMs	0.772	0.542-1.099	0.151	0.765	0.537-1.089	0.136
	oMMs	0.945	0.748-1.195	0.638	0.947	0.749-1.196	0.646
	TR	**Reference**			**Reference**		
PHEO	**Sex** (Male vs. Female)	1.145	0.788-1.663	0.478	1.153	0.793-1.676	0.455
	Mutational type			**<0.001**			**<0.001**
	Codon 167 MMs	7.374	4.491-12.110	**<0.001**	7.384	4.496-12.126	**<0.001**
	oMMs	2.603	1.592-4.257	**<0.001**	2.597	1.588-4.247	**<0.001**
	TR	**Reference**			**Reference**		

10609 Poster Session

Clinical characteristics and cancer spectrum among breast cancer patients with TP53 germline mutation from a single institution.

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Background: Li-Fraumeni syndrome (LFS), due to germline TP53 mutations, is associated with elevated risks of multiple cancers including early onset breast cancer (BC). Due to multi-disciplinary cancer screening and treatment access, The UT MD Anderson Cancer Center (MDACC) follows a large cohort of individuals diagnosed with LFS. We aimed to describe women with BC diagnosed with LFS and the spectrum of their additional cancer history before and after BC. **Methods:** Patients with BC and LFS were identified from a prospective BC database between 2001-2024. Patients with a pathogenic variant in TP53, and in two cases a variant of uncertain significance with special clinical consideration for LFS-management, were included for review. We evaluated the cancer histories and described the breast cancer characteristics of these women. We identified the incidence of secondary cancers post radiation therapy and secondary leukemia in patients who received alkylating agents given known secondary malignancy risks with such exposures. Summary statistics were generated for the population along with statistical methods for associations between factors of interest including, Chi-squared test and Fisher's exact test. **Results:** Ninety-six women were identified with a history of BC and clinically followed for a diagnosis of LFS. A total of 127 breast tumors diagnosed among 96 women with mean age 35.8 (range 20-69 years). Of these, 68 patients had one primary BC, 26 had two BCs, one had three BCs, and one had four BCs. Individuals ranged from having a diagnosis of 1 to 7 individual cancers; 54 individuals had BC as well as at least one other type of cancer besides BC. Among individuals with more than one cancer, excluding individuals with only BCs, BC was the first cancer diagnosis in 67% (36/54). Other than BC, the other most common cancers were 40 sarcomas, 14 leukemia/other hematologic malignancy, 9 thyroid cancers, 7 brain cancers, and 29 other cancers. Fifty-six percent (54/96) of women received radiation treatment with 14 (26%) individuals developing a subsequent radiation-induced malignancy (RIM). Fourteen percent developed a hematologic malignancy following anthracycline exposure (8/56). **Conclusions:** This study describes the LFS population followed in a high-risk, multi-disciplinary clinic to further understand the spectrum of cancers among women with BC. Our study found that 29% of patients have at least a second BC. More than half of the patients also had a non-BC primary and, in the majority, BC was their first cancer. We also found a high rate of RIM as well as high rate of hematologic malignancies. Understanding multiple cancer histories in LFS could lead to better screening for other cancers. Summarizing the natural history of cancer frequency helps clinicians better predict when genetic testing may be warranted and aim to increase early detection of subsequent cancers. Research Sponsor: None.

10610 Poster Session

Characterization of hereditary tumor risk in individuals with SDHA germline variants.

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Background: Paragangliomas (PGLs) are rare neuroendocrine tumors with a high degree of heritability; up to 30% of individuals diagnosed with a PGL are estimated to have a germline pathogenic variant (GPV) related to hereditary PGL risk. GPVs in the *SDHA* gene have been associated with a PGL and gastrointestinal stromal tumor (GIST) risk lower than that of other hereditary PGL predisposition genes (van der Tuin *et al.* 2018). However, data about penetrance, tumor characteristics, and other aspects of *SDHA* carriers is limited. Further characterization of *SDHA* GPV is important to better understand tumor risks and develop *SDHA*-specific screening recommendations. **Methods:** Participants were identified from the Family Cancer Assessment Clinic at the University of Utah Huntsman Cancer Institute and had an *SDHA* pathogenic/likely pathogenic variant. Cancer diagnoses and diagnostic modalities were confirmed by medical records. **Results:** Out of 93 identified *SDHA*+ individuals, 14 (15%) had a personal history of an *SDHA*-associated tumor (10 PGL and 4 GIST). None of these individuals also had a known family history of an *SDHA*-associated tumor. Average age at diagnosis was 37 (range = 17-69) with two diagnoses under age 18. There were no cases of multiple PGL/GIST in a single individual. Head and neck PGLs were the most common *SDHA*-associated tumor (7/14, 50%). They appeared to have lower malignancy risk (0/7, 0%) compared to extra-adrenal PGL (3/3, 100%) and GIST diagnoses (3/4, 75%). Secreting PGLs were rare (1/10, 10%). SDHB immunohistochemistry staining was completed for 8/14 PGL/GIST and was deficient in 5/8 (63%). Fifty-four (58%) *SDHA*+ individuals were seen by HCI's hereditary paraganglioma clinic and 39 (42%) had undergone some type of high-risk PGL screening as of January 2025. The most common reasons for not undergoing screening or being seen by the clinic included age <10 years old or >70 (8/93), deceased status (4/93), and current active cancer treatment (16/93). Fifty-eight of 93 (63%) *SDHA* variants were an incidental finding or a known familial variant without a family history of PGL/GIST. Zero (0/79) asymptomatic individuals have had a documented PGL/GIST diagnosis after *SDHA*+ genetic testing. **Conclusions:** As work continues to develop gene-specific hereditary PGL screening recommendations, our analysis adds to the body of research affirming lower penetrance of *SDHA* variants compared to other hereditary PGL genes. Additionally, the lack of individuals with a personal and family history of *SDHA*-associated tumors or with multiple tumors indicates that a more nuanced approach to screening recommendations in this patient population is likely warranted. However, the younger age of onset and increased malignancy risk seen in the affected individuals in our study compared to sporadic PGL indicates that in certain contexts, such as in an individual diagnosed with a PGL/GIST, an *SDHA* GPV could impact surgical and treatment decisions. Research Sponsor: None.

10611 Poster Session

Famitinib for familial adenomatous polyposis-associated aggressive desmoid tumors: 32-month follow-up from a single-center exploratory study.

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Background: Desmoid tumors (DTs) associated with familial adenomatous polyposis (FAP) are rare, locally aggressive soft-tissue tumors with high recurrence rates and poor prognosis. Famitinib, an orally administered multi-targeted tyrosine kinase inhibitor targeting VEGFR-2, PDGFR, c-KIT, and FGFR, has shown promising efficacy in a prospective, single-arm study for these patients (pts). This report presents updated efficacy and safety data from a 32-month follow-up. **Methods:** Pts with FAP carrying germline APC mutations and pathologically confirmed DTs that progressed within 6 months according to RECIST v1.1 criteria were enrolled. Famitinib was administered at 20 mg once daily in 3-week cycles. The primary endpoint was the objective response rate (ORR). Secondary endpoints included disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** Between November 2021 and March 2023, 12 eligible pts were enrolled, with a median age of 35.5 years (range: 25-53). Of these, 41.7% (5/12) were male. Intra-abdominal (IA) DTs were present in 83.3% (10/12) of pts, while 2 pts had extra-abdominal (EA) DTs. Eight pts presented with stage III-IV DTs characterized by rapid progression and severe symptoms. As of January 20, 2025, the median follow-up duration was 32.2 months (21.8-37.9). Seven pts achieved partial response (PR), and five achieved stable disease (SD), with a median time to response of 7.1 months (4.1-11.7). The confirmed ORR was 50%, with a DCR of 100%. Among pts with IA DTs, the confirmed ORR was 60.0% (6/10). One patient who achieved PR withdrew from the study after being diagnosed with duodenal cancer. The 6-month and 1-year PFS rates were 100% and 91.7%, respectively, while the 1-year OS rate was 100%. At 2 years, the PFS and OS rates were 54.5% and 72.7%, respectively. The median PFS and OS were not reached. Treatment-emergent adverse events (TEAEs) occurred in all pts (100%). The most common TEAEs (all grades) included COVID-19 (91.7%), leukopenia (83.3%), hypertension (83.3%), neutropenia (83.3%), proteinuria (66.7%), and elevated bilirubin levels (50%). Grade 3 TEAEs occurred in six pts, including neutropenia (41.7%), leukopenia (25%), hypertension (16.7%), hand-foot syndrome (8.3%), intestinal obstruction (8.3%), and abdominal hemorrhage (8.3%). One patient experienced a grade 4 adverse event (intestinal perforation), declined surgical intervention, and passed away three months later. All male pts tolerated the 20 mg dose, while 5 female pts (71.4%) reduced to 15 mg. **Conclusions:** Famitinib demonstrated sustained clinical efficacy and meaningful survival benefits in pts with FAP-associated aggressive DTs after a median follow-up of 32 months. Given the unique characteristics, careful monitoring for intestinal perforation and the risk of second primary tumors is crucial during treatment. Clinical trial information: ChiCTR2100051307. Research Sponsor: None.

10612 Poster Session

A phase 2 study of lanreotide as a therapy for pheochromocytomas (PCs) and paragangliomas (PGs).

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Background: PCs arise from adrenomedullary chromaffin cells, while PGs are derived from extra-adrenal chromaffin cells of the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis, or the parasympathetic ganglia located along the glossopharyngeal and vagal nerves in the neck and base of skull. Although considered neuroendocrine tumors [NETs] by many, their rarity and often difficult management has meant they're never included in clinical trials of NETs. And while they express somatostatin receptors [SSTRs] comparable to other NETs haven't been managed with SSTR-antagonists. **Methods:** Conducted clinical trial to assess efficacy/toxicity of Somatuline Depot / Lanreotide Autogel every 4 weeks in patients with advanced/metastatic PC/PG. Evidence of recent disease progression while either not receiving any therapy or receiving a therapy deemed ineffective was required. Treatment planned for 52 weeks with option to continue for additional 52 weeks. Endpoints included OS, PFS and response according to RECIST. Additionally given rarity of these cancers, estimates of tumor growth rates were planned to allow comparisons to data in NETs enrolled in CLARINET. **Results:** Eighteen patients median age 42 years enrolled including 11 females and 7 males of whom 13 were white, 2 black, 3 other. 14/18 had an SDHx mutation. Prior therapies included surgery, RT, chemotherapy, and PRRT. Lanreotide was well tolerated with 68%G1, 26%G2, 6.5%G3 and $<$ 1%G4 adverse events (AEs) and no unexpected toxicities. No patient discontinued treatment for AEs. Blood pressure control uneventful. Ten patients completed two years of lanreotide, three ongoing, two discontinued at one year due to burden of traveling for participation and three had PD. RECIST response at one year was 15 SD, and 3 PD. One additional patient had PD at the two-year assessment. Serum chromogranin was elevated in only 4/18 and was not helpful in assessing response. With a median follow up of 40 months, median PFS exceeds 2 years with only three deaths to date 14, 18 and 52 months after enrollment. Rates of tumor growth and regression could be assessed in 16/18 patients. Growth was not detected in 5/16 but estimable in 11/16 with a median growth rate of 0.00067/day [tumor doubling time, 1034 days] compared to rate of 0.00046 for 83 patients treated with lanreotide in CLARINET. **Conclusions:** These data demonstrate efficacy for lanreotide in the treatment of PC/PG comparable to that previously found in NETs with prolonged disease stability the primary outcome. Given emerging data with PC and PG reports limited efficacy for Lutathera with meaningful toxicity, these data with lanreotide achieving a longer median PFS support a management strategy for PC/PG similar to that employed with NETs. Begin with a SSTR antagonist, extract its benefit and delay Lutathera administration until meaningful, consistent disease progression is documented. Clinical trial information: NCT03946527. Research Sponsor: Ipsen Biopharmaceuticals.

10613 Poster Session

Genetics and family history in a diverse cohort of females with early-onset breast cancer.

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Background: Genetic testing for breast cancer susceptibility genes is a crucial component of clinical care for patients with early-onset breast cancer (EOBC) diagnosed < age 50 with implications for treatment and surgical decision-making, future surveillance, and cascade genetic testing for family. Limited data exist regarding prevalence of pathogenic/likely pathogenic variants (P/LPV) and patterns of family history (FH) of cancer across diverse patient populations and merit further research given the rise in EOBC rates. This study examines a cohort of EOBC patients from a cancer genetics program at a comprehensive cancer center to derive insights into the genetic and FH spectrum for a diverse cohort of patients with EOBC in hopes of informing clinical care and public awareness strategies. **Methods:** A retrospective analysis of women seen in the Smilow Cancer Genetics and Prevention program at Yale-New Haven Hospital from 2015-2023 was conducted. Women diagnosed with EOBC who underwent germline genetic testing were included. Data on demographics, age at diagnosis, genetic test results, and FH of breast, ovarian, pancreatic, and prostate cancer in $1^{st}/2^{nd}/3^{rd}$ degree relatives was obtained from the electronic medical record and Progeny family history software using manual and automated querying and natural language processing. The dataset was assessed for frequency of P/LPVs in cancer predisposition genes, variants of uncertain significance (VUS), and FH of cancer. Fisher's exact test was used to assess the association between categorical variables, and ANOVA to assess the difference in continuous variables among groups. **Results:** 1676 women with available race and ethnicity data were analyzed. Patients identified as White (83.3%), Black (11.5%), Asian (5.3%). 5% of all patients identified as Latinx. Mean age at diagnosis was 42.4 years (SD 5.48 years). P/LPVs were identified in 15.1% and VUS in 22.6%. The most common genes with P/LPVs were *ATM* (4.8%), *BRCA2* (4.1%), *CHEK2* (4.1%), and *BRCA1* (3.0%). Rates of Ashkenazi Jewish ancestry were higher for Whites (7.5%) compared to Blacks (1.0%) and Asians (1.0%) ($p<0.001$). Family history of breast cancer was higher among Black (80.2%) and White patients (80.9%) than Asians (53.4%) ($p<0.001$), as was history of prostate cancer (Black, 29.7%; White, 29%; Asian, 11.4%, $p=0.017$). P/LPV rates were highest among Whites (15.8%), followed by Blacks (11.5%) and Asians (10.2%) while VUS rates were highest for Asians (34.1%) and Blacks (28.6%) than Whites (21.0%) ($p<0.001$). **Conclusions:** Our results from a diverse EOBC population underscore the higher rates of P/LPVs among White patients while non-White populations have higher rates of VUS. Given the rise in EOBC rates, greater genetic insights as well as additional factors impacting EOBC risk need to be identified and studied particularly across diverse racial/ethnic populations. Research Sponsor: None.

10614 Poster Session

Post-mastectomy surveillance: A patient-reported survey of 110 women with Li-Fraumeni syndrome.

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Background: Li-Fraumeni syndrome (LFS) is a highly penetrant autosomal dominant hereditary disorder associated with young onset breast cancer (BC). Therapeutic mastectomy is preferred to enable avoidance of radiation at BC diagnosis (dx), and bilateral mastectomy (BM) for risk reduction as a preventive strategy. After a BM, current guidelines do not recommend post-mastectomy breast screening beyond clinical breast examination (CBE) for LFS carriers. During a patient-focused discussion at the 6th Li-Fraumeni Syndrome Association (LFSA) Symposium in 2022, women expressed concern about not being offered imaging after the surgery. We therefore conducted a survey study to investigate BC screening practices and new breast events following BM in women with LFS. **Methods:** Recruitment was performed through electronic invitation sent to members of the LFSA. Respondents 18 years or older who self-identified as having an LFS dx and a personal history of BM, were invited to answer a survey about their cancer history, breast screening, breast surgery and breast events after mastectomy. Post-BM BC event was defined as the first BC event after BM. Questionnaires were administered from August 13th to September 3rd, 2024. Bivariate associations between BC history and clinical characteristics were assessed using Fisher's exact test for nominal categorical variables and two-sample Wilcoxon tests for continuous variables. **Results:** Among 148 respondents, 110 were eligible; 30 (27.3%) had BM for risk reduction and 80 (72.7%) for BC treatment (60 unilateral BC and 20 for bilateral BC). Median age at first mastectomy was 35.5 years (IQR 28.2,43.0). Most patients (n=82; 74.5%) underwent breast reconstruction with implants only. Periodic CBE performed by a health provider was reported by 70 respondents (63.6%). Patients with BC prior to mastectomies received more clinical surveillance (71.2% vs 43.3%, $p<0.01$). Follow-up imaging with any modality in regular intervals was reported by 52 respondents (47.3%), and there were no differences between groups regarding BC history and imaging modalities used for surveillance. At a median follow-up of 6 years (IQR 3.0-9.8), a total of 10 post-BM BC events (10/110, 9%) were reported, 50% were identified due to symptoms. Among patients who were receiving imaging surveillance (n=52), only 1 BC event was identified through breast MRI screening. was not significantly associated with a new BC event after BM (p=0.28). All BC events in patients with a BC prior to mastectomies were in the ipsilateral breast of the first BC. Patients with a prior BC had a longer follow-up (7.0 vs 3.0 years, p=0.003). **Conclusions:** Breast cancer events after mastectomies in this cohort were identified by symptoms rather than surveillance. Further studies are needed to distinguish these subsequent BC events as recurrences or new primaries, and to confirm the clinical value of breast imaging in this setting. Research Sponsor: None.

10615 Poster Session

Clinicopathologic and allele-specific analysis of germline *ATM* alterations in a pan-cancer cohort.

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Background: *ATM* is a tumor suppressor gene involved in DNA repair and telomere maintenance. *ATM* biallelic pathogenic or likely pathogenic germline variants (gPV) are associated with ataxia-telangiectasia syndrome. Monoallelic ATM gPV are associated with increased cancer risk; however, their contribution to carcinogenesis has not been elucidated. We sought to characterize the genomic landscape of gPV *ATM*-associated cancers in a pan-cancer cohort. **Methods:** *ATM* alterations (germline and somatic) were identified in patients (Pts) with a solid tumor diagnosis sequenced with MSK-IMPACT, an FDA-approved, tumor-normal paired targeted NGS. Genetic-imputed ancestry clinicopathologic characteristics and FACETS estimated allele-specific copy number profiles were evaluated. Samples with purity <0.2 or with undetermined copy number profiles were excluded. HRD score was evaluated using FACETS profiles. Both somatic and germline sequencing data were analyzed within protocol NCT01775072. **Results:** Among 40,136 Pts with cancer who underwent germline testing, 1.1% (n=442) harbored an *ATM* gPV, inclusive of 2 Pts with biallelic *ATM* gPVs. The most frequent mutations were: R2547_S2549del (n=17), K2756* (n=14) and V1268* (n=11). Among these, R2547_S2549del and K2756* were identified exclusively in Pts with European ancestry, while E343Ifs*2 (n= 9/10) and c.1065+1G>T (n= 6/7) were most prevalent in Pts with Ashkenazi Jewish (AJ) ancestry. Concomitant gPVs in other genes were observed in 10% (n=47), with the most frequent ones being *APC* (I1307K), *MUTYH*, *BRCA2*, *CHEK2*, and *BRCA1*. 63,270 out of 86,039 tumor samples had usable FACETS profiles. *ATM* somatic allele-specific information was available for 67% (297/442) of Pts. 62% (197/317) of tumor samples from Pts with monoallelic *ATM* gPVs exhibited somatic biallelic (Bi) *ATM* inactivation, while 38% (120/317) retained monoallelic (Mono) ATM status. The underlying mechanism of Bi-ATM inactivation was loss of heterozygosity in 75% (149/197) and additional somatic *ATM* mutations in 25% (48/197). Samples from Pts with tumors known to be associated with ATM gPVs (Breast, Pancreatic and Prostate cancers) had significant enrichment in Bi-ATM inactivation compared to tumors without strong association with ATM gPVs (88% Vs 58%; $p<0.01$). Although samples with Bi-*ATM* had higher overall HRD-scores compared to Mono-*ATM* (median = 34 Vs 20; $p<0.01$), no significant enrichment in HRD-High phenotype was seen in Bi-*ATM* (23 Vs 18; $p=0.49$). **Conclusions:** Evaluation of a pan-cancer Pt population with *ATM* gPVs demonstrated a high prevalence of biallelic somatic inactivation. Most Pts with *ATM* gPVs who had malignancies implicated in *ATM*-associated cancer risk, had biallelic somatic inactivation in their tumors suggestive of their contribution to tumorigenesis. While biallelic ATM inactivation is associated with higher genomic instability, no enrichment in HRD phenotype was observed. Research Sponsor: National Cancer Institute/National Institutes of Health Cancer Center Support grant to Memorial Sloan Kettering Cancer Center; (P30 CA008748).

10616 Poster Session

Cancer genetics evaluation among individuals at risk for Lynch syndrome across all qualifying indications.

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Background: < 20% of individuals suspicious for Lynch syndrome (LS) and other inherited cancer syndromes undergo genetic testing in the US. Undiagnosed individuals will not benefit from enhanced screening and prophylactic interventions. Thus, to dramatically increase the identification of at-risk individuals and respective indications, we set up the At-Risk Cancer Genetic Syndrome Identification Registry (ACAGEN-ID). **Methods:** NCCN/ACMG criteria for genetic testing were translated into three distinct rule-based conditional logic statements in the EHR. A total of 218 rules that serially evaluate each aspect of individual criteria and roll into a logic statement of "at-risk" for inherited cancer syndromes. The rules assess personal history (PH) and/or family history (FH) of cancers, determine age at onset, and categorize family relationships. Patient's genetic evaluation status, sociodemographic, and clinical data were extracted. Descriptive statistics used for summary. Pearson chi-square used for comparison of categorical variables. **Results:** Out of 1.34 million individuals in Yale New Haven Health System, ARCAGEN-ID identified 5,190 at risk individuals for LS. Of those, 3,581 (69%) had not been previously evaluated. Accuracy was assessed through a manual review of 130 randomly selected individuals among the identified, which showed appropriate identification in 129 cases. Among the already evaluated, 509/1609 (31.6%) had a pathogenic variant (PV): 124 (24.6%) MSH2, 112 (22.2%) MSH6, 55 (10.9%) MLH1, 118 (23.4%) PMS2, 3 (0.6%) EPCAM, 141(28%) other PV. Newly identified individuals through ARCAGEN-ID more often had only a PH of cancer (39.99% vs 21.01%) or only FH of cancer (41.02% vs 38.41%), and less often both, PH and FH (18.99% vs 40.58%) ($p < 0.01$). The great majority of individuals with only qualifying FH or PH had not been identified before (80.90% and 70.39% respectively), while half (51.01%) with both, PH and FH, had already been identified. Having an early onset (EO) LS-associated cancer was the most common reason for prior identification (22.30%), though EO endometrial cancer (EC) (107/1135, 9.42%) was much less recognized than EO Colorectal Cancer (CRC) (284/775, 36.64%, $p < 0.01$). The highest missed identification before ARCAGEN-ID implementation was individuals with ≥2 LS-related cancers: 69.85% (190/272); FH of EO-CRC: 66.67% (298/449); ≥3 FH of CRC. Even 29.73% (121/407) of individuals with FH of diagnosed LS had been missed. 263/385 (68.31%) Patients with Non-EC/CRC related LS cancers were not evaluated. **Conclusions:** Current practice misses most individuals at-risk for LS across all qualifying indications.A system that can leverage currently existing information in the EHR can dramatically improve the identification without any other added resources. An automated outreach pilot project is underway to assess feasibility and outcomes. Research Sponsor: None.

10617 Poster Session

Familial lung cancer: A thirteen-year prospective analysis of participants with germline EGFR T790M pathologic variant.

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Background: Lung cancer in never-smokers is the eighth leading cause of cancer-related mortality in the United States. Familial lung cancer, a rare syndrome associated with germline *EGFR* pathologic variants (PV) such as T790M (accounting for 0.3-0.9% of lung adenocarcinomas), is a recently identified cause of non-tobacco-related lung cancer. Data on this population is limited. We describe a 13-year prospective analysis, the longest thus far to study the natural history. **Methods:** From2011 to 2024, 19 participants enrolled in a National Cancer Institute study of *EGFR* germline PV (NCT01306045).Eligibility included: (1) lung cancer diagnosis (invasive or pre-invasive) with two affected family members, (2) first-degree relative of someone with a germline *EGFR* PV, (3) T790M detected in lung cancer tumor before tyrosine kinase inhibitor, (4) significant family history of lung cancer, or (5) *EGFR* germline PV detected externally. Participants with germline *EGFR* PV were followed prospectively. Germline *EGFR* PV carriers completed risk-based screening computed tomography. Germline *EGFR* PV participants with lung cancer were followed while completing guideline-directed treatment and surveillance. Lung nodules were examined using standard radiologic assessment. **Results:** Of 19 enrolled participants, seven (37%) had germline *EGFR* T790M. Demographics of *EGFR* germline T790M versus not include mean age at enrollment (46, 56), gender (female 4, 9), white/African American/Asian race (6/1/0, 10/0/2), and current/former/never smoker (0/6/1, 0/4/7). Of the seven participants with *EGFR* T790M, three (43%) had lung adenocarcinoma diagnosed on average at age 63 (range, 53-80), two as stage I and one as stage IV. The other four (57%) did not have lung cancer during the study period. At diagnosis with germline *EGFR* T790M (average age 31, range 26-36), all four participants without cancer had multiple bilateral pulmonary nodules and/ or ground glass opacities (GGO) which, over 6-10 years, remained stable to slightly larger, with increased numbers. One germline *EGFR* T790M participant developed multiple primary lung adenocarcinomas (invasive, minimally invasive, in situ) over 26 months and metastasis 14 months later. One primary started with ground glass components and became solid and larger over 26 months. The two participants with stage IV lung adenocarcinoma survived 15 and 67 months. **Conclusions:** Our study confirms that germline *EGFR* T790M carriers present as early as the third decade of life with multiple bilateral GGOs that can remain dormant for years before exhibiting malignant behavior. Long-term surveillance imaging is necessary, and volumetric changes can potentially be automatically quantified using artificial tools. However, further studies are needed to define a risk-based schedule and examine the role of prophylactic therapy, such as osimertinib. Clinical trial information: NCT01306045. Research Sponsor: None.

10618 Poster Session

Mammography results in male *BRCA* carriers.

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Background: Patients assigned male at birth (AMAB) with pathogenic germline variants (PGVs) in *BRCA1* or *BRCA2* (*BRCA+*) have a 1-10% lifetime risk of developing breast cancer (BC). NCCN guidelines currently recommend that male *BRCA1/2* carriers consider annual mammograms. However, there is minimal data on the mammography among male *BRCA1/2* carriers. **Methods:** We identified a cohort of 489 *BRCA+* male patients with male gender identity from the electronic health record (EHR) at Penn Medicine who had no prior BC diagnosis. Charts were reviewed to determine indication for and results of mammography episodes between 2008-2024. A mammography episode was defined as all breast imaging studies obtained for a specific reason, i.e. asymptomatic screening or for symptoms within six months. An independent cohort of 1808 *BRCA* negative AMAB patients with male gender identity and no prior BC diagnosis from the Penn Medicine EHR was analyzed for the true positive rate of BI-RADS 4/5 findings. **Results:** Of 489 *BRCA+* individuals, 85 (17%) patients completed at least one mammography episode and 46 (9%) had at least one subsequent mammography episode during the study period. Of 85 *BRCA+* patients, 71% had *BRCA2* PGVs. Of 404 patients who did not complete a mammogram, 270 were at least 50 years old at the time of data abstraction. Of these 270 patients, 50% had no discussion of mammograms in their charts, 8% of patients had a physician ordered mammogram that was not completed by the patient, and 42% had a shared decision-making discussion between the physician and patient indicating a decision against mammography. The first observed and subsequent mammography episodes were ordered for asymptomatic screening in 65% and 83% of 85 *BRCA+* individuals, respectively. In *BRCA*neg individuals, 92% of mammography episodes were for symptoms. Nine (11%) and one (2%) *BRCA+* individuals were diagnosed with BC after the first observed or subsequent mammography episode, respectively. No breast cancers were identified on mammography episodes among asymptomatic patients. Combining all mammography data, the true positive rate of BI-RADS 4 mammograms was significantly higher in *BRCA+* vs *BRCA*neg individuals (71% vs 11%, p=0.0007); whereas the true positive rate of BI-RADS 5 mammograms was similar in *BRCA+* vs *BRCA*-neg individuals (100% vs 82%, p=0.54). Hormone receptor status and clinical stage of identified BC were similar between *BRCA+* and *BRCA*neg individuals. **Conclusions:** The majority of male *BRCA1/2* carriers in our cohort did not complete mammography. All BC diagnosed in *BRCA+* individuals were identified on mammography episodes obtained for symptoms. The true positive rate of a BI-RADS 4 mammogram was significantly higher in *BRCA+* compared to *BRCA*neg individuals. Additional data is needed regarding whether mammography identifies asymptomatic BC in male *BRCA1/2* carriers and whether mammograms improve clinical outcomes. Research Sponsor: None.

10619 Poster Session

The evolution of breast cancer genetic testing: Comparative outcomes of NCCN, ASCO, and universal guidelines in 6,000+ patients.

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Background: Germline genetic testing for breast cancer has significantly advanced over the past decade. At King Hussein Cancer Center, 6,336 breast cancer patients underwent genetic testing between 2012 and 2024, transitioning from limited BRCA1/2/PALB2 panels to comprehensive 20-gene and 84-gene panels. Eligibility criteria evolved from strict criteria for testing to broader NCCN and ASCO guidelines by 2024. Universal genetic testing was implemented for all breast cancer cases between April 2021 and September 2022. ASCO guidelines have simpler eligibility criteria, whereas NCCN guidelines are more complex and regularly updated. **Methods:** This study analyzed genetic testing trends, categorized results by panel type, and compared detection rates of pathogenic/likely pathogenic (P/LP) variants and variants of uncertain significance (VUS). Detection rates were assessed using Chi-square tests, and linear regression calculated annual changes in positive rates. Outcomes were compared between guideline-based (ASCO/NCCN) and universal testing. **Results:** Of 6,336 patients, 1,731 (27.3%) underwent testing with the 84-gene panel, 3,759 (59.3%) with the 20-gene panel, and 846 (13.4%) with limited testing. Testing volumes increased from 248 cases between 2012-2017 to ~1,000 annually after 2021. Overall, 686 (10.8%) patients had P/LP variants, with higher rates in patients under 30 years (24.4%) and triple-negative breast cancer (20.6%). Among 5490 patients tested with multigene panels, P/LP detection rates were similar: 10.5% (306/2917) for NCCN, 9.4% (87/924) for ASCO, and 9.1% (150/1649) for Universal; p-value was 0.276. No significant difference in P/LP rates was observed between the 84-gene panel 9.2% (160/1,731), and the 20-gene panel 10.2% (383/3,759, p=0.297), but the VUS rate was significantly higher in the 84-gene panel (66.2% vs. 26.2%; p<0.001). **Conclusions:** Expanded panels (84-gene) did not improve detection of P/LP but significantly increased VUS rates. Universal testing did not lower P/LP detection rates compared to guideline-based testing, and no significant difference was observed between ASCO and NCCN guidelines. ASCO guidelines, offering simpler eligibility criteria, or even universal testing, may be more practical compared to the periodically updated NCCN guidelines and should improve compliance and referral rates. Research Sponsor: None.

Genetic testing.

Genetic testing		Number 6,336	P/LP	p-value	VUS	p-value
Limited test (BRCA1/2, PALB2)		846	143.0 (16.9%)		73.0 (8.6%)	
Multigene panel (5490)	84-gene panel	1,731	160/1731 (9.2%)	0.297	1146/1731 (66.2%)	<0.001^
	20-gene panel	3,759	383/3759 (10.2%)		986/3759 (26.2%)	
Guidelines*	Universal testing	1649	150 (9.1%)	0.276	1131 (68.6%)	<0.001^
	NCCN Guideline	2917	306 (10.5%)		784 (26.9%)	
	ASCO Guidelines	924	87 (9.4%)		217 (23.5%)	

*Excluding patients with limited genetic testing.
^Pearson's chi-squared test.

10620 Poster Session

Rurality and screening colonoscopy participation in patients with Lynch syndrome.

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Background: Lynch Syndrome (LS) is a hereditary condition that increases risk for colorectal and other primary cancers. LS arises from pathogenic variants (PVs) in *MLH1*, *MSH2*, *MSH6*, and *PMS2*. Gene-specific prevention and surveillance strategies exist, and screening colonoscopy reduces overall mortality. Several barriers to screening colonoscopy are known, however the impact of rurality is not well characterized. **Methods:** We enumerated a cohort of LS patients residing in Vermont or upstate New York who were seen by the Cancer Genetics Program at the University of Vermont, and for whom regular screening colonoscopies were recommended based on current PV- and age-based NCCN guidelines. We reviewed electronic medical records and abstracted patient characteristics and colonoscopy procedures performed between 2021-2024, capturing most recent practices while avoiding the impact of COVID-19 restrictions. We defined screening compliance as having >1 colonoscopy in the 3-year period, concordant with the minimum expected number of procedures over this time period for all PV groups. We assigned rurality status (metropolitan/micropolitan vs. small town/rural) based on residential ZIP code using Rural-Urban Commuting Area codes. We fit log-binomial and proportional odds regression models to estimate the impact of rurality and recency of a genetics focused clinic visits on colonoscopy adherence and on the number of colonoscopies received, adjusting for age, sex, and PVs. **Results:** We enrolled 201 LS patients for whom annual, bi- or triennial colonoscopies were recommended. Median age at baseline was 60 years (range: 28-98), 131 (65%) were female, and 58 (29%) resided in a small town/rural setting. Compared with metropolitan/micropolitan, small town/rural residence was associated with a lower probability of having ≥1 screening colonoscopy in the 3-year follow-up period (43% vs. 64%; RR=0.67, 95% CI: 0.49, 0.92). This association did not change substantially upon adjustment for age, sex, and pathogenic variants. Small town/rural residence was also associated with undergoing fewer colonoscopies in the 3-year period (cumulative OR=0.46, 95% CI: 0.25, 0.84). Furthermore, recency of Cancer Genetics Program clinic visit was associated with a higher probability of receiving at least one colonoscopy, independent of rurality (*e.g.*, RR for last visit ≤3 years ago, compared with last visit >10 years ago = 1.8, 95% CI: 1.1, 2.8). **Conclusions:** In a cohort of patients with LS, residing in a rural area was associated with a reduced probability of compliance with screening colonoscopy. Resources should be invested in studies aimed at understanding and ameliorating the mechanisms underlying this association. Shorter time since last clinic visit in the genetics program was associated with a higher likelihood of having a screening colonoscopy, suggesting the importance of genetics longitudinal follow-up for hereditary cancer patients. Research Sponsor: None.

10621 Poster Session

Retrospective review of hereditary leiomyomatosis and renal cell cancer at a single institution.

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Background: Hereditary Leiomyomatosis and Renal Cell Carcinoma (HLRCC) is an autosomal dominant syndrome caused by loss-of-function mutations in the Fumarate Hydratase (*FH*) gene. HLRCC poses an elevated risk for skin leiomyomas, uterine fibroids, pheochromocytomas, paragangliomas, and renal cell cancer (RCC), particularly FH-deficient RCC and potentially clear cell RCC. It is recommended that patients with personal and/or family history of a single skin leiomyoma, multiple FH-deficient (by immunohistochemistry (IHC)) uterine fibroids, pheochromocytoma, paraganglioma, or FH-deficient RCC be tested for, among other genes, germline *FH* mutations, with yearly surveillance with abdominal imaging being the recommendation if positive. To better describe this patient population, we present our experience with high-volume referrals for HLRCC testing at a single institution. **Methods:** We performed retrospective chart review (2017-present) of all patients referred for HLRCC testing at the Hereditary Renal Cell Carcinoma & VHL Disease Clinic and the Hemangioblastoma Center at the Massachusetts General Cancer Center. The study was approved by the Massachusetts General Brigham IRB. **Results:** We herein describe the largest, to our knowledge, series of HLRCC patients (67) at a single institution. While the majority (30, 45%) of cases were referred due to an incidental genetic finding either on prenatal screening or through a comprehensive multi-cancer gene panel sent for hereditary cancer screening, 31% (21) of patients were referred after being found to have an HLRCC-related lesion. Of this subset, the most common first HLRCC-related lesion was a uterine fibroid that was FH-deficient by IHC (13), followed by an equal number of skin leiomyomas (4) and RCCs (4). Importantly, we calculate the rate of patients later confirmed to have an HLRCC diagnosis (pathogenic variant by genetic sequencing) based on referral reason: patients referred for uterine fibroids deficient in FH by IHC, 59.1% (13 of 21); patients referred for RCC either with loss of FH by IHC or papillary RCC, 80% (4 of 5); patients referred with cutaneous leiomyomas deficient in FH by IHC, 66.7% (4 of 6); and patients with family members with known diagnosis of HLRCC, 83.3% (15 of 18). Mutations in positive HLRCC cases either caused premature termination by nonsense or frameshift (18, 26.9%), point mutations by missense (22, 32.8%), or had an AAA duplication at c.1431_1433, causing a lysine duplication at amino acid residue 477 of the fumarate hydratase protein (20, 22.9%), the last of which has ongoing discussion of true association with HLRCC. One patient was indeed seen to have papillary RCC with this mutation, supporting the association of c.1431_1433dupAAA with HLRCC. **Conclusions:** In sum, we describe populations characteristics, common reasons for referral, and likelihood of genetic testing confirmation for patients with concern for HLRCC. Research Sponsor: None.

10622 Poster Session

Characteristics and outcome of breast cancers diagnosed in patients with germline ATM mutations.

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Background: The purpose of this study is to investigate clinicopathologic characteristics of invasive breast cancers diagnosed in individuals carrying germline mutations in ATM. Individuals with germline pathogenic variants (PV) in ATM have an elevated lifetime risk of breast cancer (17-52%). Clinical characteristics and outcomes of breast cancer amongst patients with ATM PV are not well described. Our aim was to describe a cohort and clinical outcome of patients with breast cancer and ATM PVs. **Methods:** Patients receiving care at MD Anderson Cancer Center with at least one invasive breast cancer diagnosis and who underwent germline testing and were found to have a germline ATM PV were included in the study. Individuals with co-occurring germline mutations in BRCA2 and CHEK2 were excluded. Germline positive and tested negative patients were identified using our prospective Breast Cancer and Clinical Cancer Genetics research database. **Results:** 86 patients with ATM PV were identified. Overall ER positivity was 94.19%. 72.09% were ER+/HER2- and 22.09% were ER+/HER2+. HER2+/ER- and TNBC occurred at lower rates in this cohort (2.33% each). When compared to ATM PV negative, patients with ATM PVs were more likely to have ER+ tumors (HR 1.26). Most individuals with ATM PVs were diagnosed with Stage I (40.7%) or II (34.9%) disease. However, they were more likely to be diagnosed at Stage IV than the control cohort (10.47% vs 1.99%, HR 5.25). Amongst patients receiving neoadjuvant chemotherapy, the pathologic Complete Response (pCR) rate in the ATM positive cohort was 15.63% (5/32), compared to 46.09% in the control group. Locoregional recurrence rates were similar in the ATM and control cohorts (8.14% and 5.85%), but those with germline ATM PVs were more likely to have distant recurrence (23.26% vs 10.96%, HR 2.12).Individuals with germline ATM PVs were also more likely to be diagnosed with a second or third invasive breast cancer than those in the control group (9.3% vs 2.79%, HR 3.33). Overall survival was not significantly different between the two cohorts. In addition to invasive breast cancers, we collected data on secondary malignancies and found that in the ATM PV cohort, 34.88% were diagnosed with at least one additional invasive cancer, including breast, gynecologic, colorectal, pancreatic, melanoma, and other tumor types. **Conclusions:** Patients with hereditary ATM PVs diagnosed with breast cancer have distinct characteristics and outcomes. In our cohort patients with ATM PVs had a higher risk of distant metastasis suggesting a more aggressive disease course that may require tailored treatment strategies. In addition, they also have an increased risk of developing second and third primary breast cancers, therefore risk reducing mastectomy should be considered. Finally, because of increased risk of non-breast malignancies, screening for potential new malignancies is warranted in this patient population.
Research Sponsor: None.

TPS10623 Poster Session

A process evaluation trial of a telehealth service intervention to support uptake of breast cancer prevention medications.

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Background: Breast cancer prevention medications (BCPrevMeds), such as tamoxifen and anastrozole, halve breast cancer (BC) risk. Our prior research has shown that only 2% of Australian women who know they are at increased risk of BC have ever used BCPrevMeds, and that this evidence-implementation gap is driven by lack of awareness of BCPrevMeds by patients and their primary care physicians (PCPs). In addition, few PCPs report feeling confident to discuss BCPrevMeds, most would not initiate prescribing, but 98% would provide ongoing prescriptions if initiated by a specialist. The Preventing Cancer with Medications (PCMed) Specialist Telehealth Service intervention was developed, based on the Knowledge to Action Implementation Framework, to respond to these findings. The PCMed intervention delivers personalised information to patients to facilitate their informed decision-making, initiates BCPrevMeds prescriptions, and supports PCPs to manage patients during their treatment course. **Methods:** A mixed methods process evaluation trial is evaluating the effectiveness, adoption, acceptability, feasibility, fidelity, and cost of the PCMed intervention. Women aged 20-70 years with no history of invasive BC or DCIS are eligible if they have a remaining lifetime BC risk $>$ 20% or 10-year risk of $>$ 5%. The intervention includes 1 to 2 telehealth sessions with a medical oncologist or nurse practitioner in which patients receive tailored education about the BCPrevMeds relevant to them, a personalised discussion of the absolute risk reduction they could achieve with BCPrevMeds and tailored discussion of other benefits and side-effects of BCPrevMeds applicable to them. Those who desire BCPrevMeds receive a prescription and are reviewed in 8 to 10 weeks to manage any side-effects. Care is then transferred to the PCP who receives educational information and detailed instructions to continue management. A telephone hotline is available for clinicians and patients to address any concerns relating to side effects during the treatment course. Effectiveness of the PCMed Service intervention will be determined by comparing uptake of BCPrevMeds before and after the intervention, using a chi-square, Fisher's exact test, and/or mixed effects regression (as appropriate based on the number of uptake events). Secondary outcomes include adoption of the intervention (the proportion of eligible women who attend the PCMed Service), acceptability for patients and referring clinicians (survey and semi-structured interviews based on the Theoretical Framework of Acceptability), feasibility and fidelity (adherence to the planned intervention processes), and cost (using a micro-costing approach). Currently 33 of a planned 63 participants have been recruited - sample size is based on 80% power to detect a change in uptake from 2% to 20%. Clinical Trial Information: ISRCTN 15718519. Clinical trial information: 15718519. Research Sponsor: Tour de Cure; RSP-307-2024; National Health and Medical Research Council (Australia); 1195294.

TPS10625 Poster Session

A phase II biomarker RCT in women at high risk for breast cancer: Low dose tamoxifen and lifestyle changes for breast cancer prevention (TOLERANT study).

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Background: Breast cancer (BC) prevention in high-risk women is crucial. Tamoxifen, despite its efficacy, has limited use due to its side effects. Low-dose tamoxifen (LDT) has shown much better balance between BC risk reduction and adverse effects. Additionally, lifestyle interventions (LI) like intermittent caloric restriction (ICR) and physical activity may further reduce BC risk by modulating factors such as mammographic density (MD) and sex hormone-binding globulin (SHBG) levels, which we showed is correlated with reduced breast cancer risk. This study evaluates whether LDT increases circulating SHBG more effectively than LI with or without ICR after six months. **Methods:** The TOLERANT study is a randomized, four-arm, phase II trial involving 200 high-risk women recruited from four Italian hospitals. Participants will be randomly assigned to one of four intervention arms: (1) LDT, (2) LDT + ICR, (3) LI with step counter, (4) LI with step counter + ICR. Interventions will last six months, and participants' adherence will be monitored through visits, telephone calls and diaries. Eligible women are aged 18-70 with a high risk for BC due to genetic predisposition or a history of intraepithelial neoplasia. Key exclusion criteria include history of invasive BC, BMI <18.5, and certain medical conditions. LDT involves 10 mg tamoxifen every other day. ICR follows a "5:2 diet" model, with five days of normal intake and two days at 25% of regular caloric intake. LI includes personalized advice and step counters targeting 10,000 steps per day. Primary outcome is the change in SHBG levels. Secondary outcomes include changes in metabolic and inflammatory markers, QoL, body composition, microbiome diversity, and MD. Blood and stool samples will be collected at baseline (B), three (3M), and six months (6M) to analyze biomarkers. Body composition will be assessed using bioelectrical impedance analysis, at B, 3M and 6M and MD will be measured in a subset of participants using digital mammography. As of January 20, 2025, a total of 43 participants have been enrolled, including 18 with DCIS and 25 high-risk women. The study, which has received approval from relevant ethics committees, will provide insights into the effectiveness of LDT and LI in reducing BC risk among high-risk women. The results could inform personalized prevention strategies, balancing efficacy with QoL. Trial registration: EuCT number:2023-503994-39-00; Clinical trials.gov NCT06033092 Funding: This work is funded by European Union – Next Generation EU – PNRR M6C2 – Investimento 2.1 Valorizzazione e potenziamento della ricerca biomedica del SSN – Project Code: PNRR-MAD-2022-12376567 - PI Bernardo Bonanni. Co-PI Sara Gandini. The funders had no role in study design, data collection and analysis, or abstract preparation. Reference*: Guerrieri-Gonzaga A et al. PLoS One. 2024 doi journal.pone.0309511. Clinical trial information: NCT06033092. Research Sponsor: European Union – Next Generation EU – PNRR M6C2.

TPS10626 Poster Session

The Hercules study: A prospective real-world evaluation of screening whole-body MRI (sWB-MRI) for multi-cancer detection and general preventive healthcare.

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Background: Cancer remains a leading cause of mortality, with major gaps in early detection contributing to later-stage diagnoses and poorer outcomes. While single cancer screening methods are effective for specific populations, they leave most cancers undiagnosed such that only 14% of cancers are detected through screening. Multi-cancer detection technologies, such as screening whole-body MRI (sWB-MRI), address this gap by enabling simultaneous systemic cancer risk stratification. Advances in sWB-MRI protocols, including whole-body diffusion-weighted imaging, improve tumor detection without the use of ionizing radiation or contrast agents. This positions sWB-MRI as a non-invasive, radiation-free tool for preventive care suitable for longitudinal monitoring. The need for prospective studies using standardized image acquisition and reporting frameworks, larger cohorts, and long-term follow-up data motivated this study. **Methods:** The Hercules Project is a prospective real-world data study evaluating the predictive accuracy and utility of sWB-MRI for detecting cancer and other clinically significant diagnoses (CSD). Radiological scoring frameworks used include: ONCO-RADS: A validated 5-point scale stratifying cancer risk, from no oncological relevance (ONCO-1) to highly suspicious (ONCO-5). CSD Framework: A novel 5-point scale categorizing pathologies (not limited to cancer) from no clinical relevance (CSD-1) to findings requiring expedited follow-up (CSD-5). Radiologists assign ONCO-RADS and CSD scores during scan interpretation, applied to structured reports by body region and organ system. These frameworks support sensitivity, specificity, PPV and NPV analyses by type of diagnosis. Follow-up at 12–18 months compares findings with diagnostic confirmation and clinical outcomes, enabling analysis of diagnostic pathways and long-term patient impact. Participants are enrolled via one of two arms: Pragmatic: Self-funded participants paying participation-fees reflecting typical U.S. out-of-pocket costs for sWB-MRI. Health Equity: Subsidized access (10–50% of cohort) reduces financial barriers for underserved populations, with sliding-scale subsidies (50–100%) based on socioeconomic factors. Endpoints: Primary endpoints include diagnostic accuracy (sensitivity, specificity, ROC AUC, PPV, NPV), time-to-diagnosis, stage at detection, healthcare utilization (e.g. TCOC), and cost-effectiveness (e.g., QALY). Exploratory endpoints assess the impact of socioeconomic and biological factors on disparities, and the utility of sWB-MRI enabled multi-dimensional diagnostics structured by ONCO-RADS and CSD frameworks. Trial Info: The study is active at a research-dedicated MRI center in Boston, with IRB approval for multi-center expansion to 20 locations. Clinical trial information: NCT06212479. Research Sponsor: None.

TPS10627 Poster Session

HERA-TEST: A novel precision oncology tool using breast milk for early detection of postpartum breast cancer.

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Background: The incidence of breast cancer (BC) in women under the age of 45 has risen in recent decades, partly due to delayed childbearing. More specifically, postpartum breast cancer (PPBC), defined as BC diagnosed within 10 years of childbirth, accounts for 5 to 7% of these cases and it is recognized as a distinct clinical and molecular entity. PPBC is associated with increased aggressiveness, a higher risk of metastasis, and worse survival outcomes. Previous research has identified observed distinct signature gene expression associated with DNA repair and cell proliferation pathways, as well as T-cell immunity. However, the key molecular drivers of PPBC remain unclear. Currently, invasive procedures such as breast biopsy or ductal lavage are the primary methods to access tumour biomarkers. In this regard, breast milk represents a promising, unique and accessible source of biomarkers —including exfoliated epithelial cells and miRNAs— that directly reflects the breast microenvironment and could provide valuable insights into early molecular changes associated with cancer development. Ultimately, it holds significant potential for identify biomarkers in breast milk for early identification of women at high risk of developing PPBC. **Methods:** This study aims to recruit 2,000 lactating women, requiring a large-scale awareness campaign and collaboration with eight Andalusian hospitals to facilitate donor recruitment and sample collection. To date, breast milk samples (10–30 mL from each breast) have been collected from 3,000 women, exceeding initial recruitment goals. Samples are preserved in two formats: whole milk stored at -80°C and fractionated components (cells, serum, and lipids). This initiative has led to the establishment of the world's largest breast milk biobank. Simultaneously, dried breast milk samples are being collected parallel to the fresh milk. Additionally, comprehensive clinical, gynaecological and lactation-related data are collected via participant questionnaire, including family history of BC, breastfeeding duration, number of births, weaning patterns, prior breast conditions, and medication history. A multi-omics analysis—including genomic, epigenomic, proteomic, and viromic profiling—will be conducted to identify molecular differences between women who develop PPBC and those who do not. Integrating these findings with clinical and epidemiological data to enhance the understanding of PPBC pathogenesis and improve early detection strategies. Upon identification of robust predictive biomarkers, efforts will focus on adapting the test for use with dried milk samples, facilitating large-scale implementation. This approach aims to address critical gaps in current screening methods for young women, with the ultimate goals of enhancing clinical outcomes, reducing healthcare costs, and advancing precision medicine. Research Sponsor: Instituto de Salud Carlos III; Sociedad Andaluza de Oncología Médica (SAOM).

TPS10628 **Poster Session**

Acolbifene vs tamoxifen for breast cancer prevention in premenopausal women at high risk for breast cancer.

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Background: The TAM01 trial of low dose (5 mg) tamoxifen (LDTAM) vs placebo was associated with significant improvement in risk for breast cancer in postmenopausal women with a hazard ratio of 0.30 along with a favorable side effect profile. Risk reduction in premenopausal women was less clear, with a non-significant hazard ratio of 0.73. Tamoxifen in premenopausal women can induce substantial increases in systemic estradiol and in preclinical studies upregulate endocrine resistance gene *AGR2*. Both phenomena may impact LDTAM efficacy in premenopausal women. A pilot study (NCT00853996) of 20 mg/d of the SERM acolbifene in premenopausal women was associated with reduction in mammographic density, benign breast tissue Ki-67, and estrogen response gene expression (Fabian et al; Cancer Prev Res 2015) with no increase in *AGR2* or vasomotor symptoms. Further studies of LDTAM and acolbifene in premenopausal women are warranted assessing change in imaging and benign breast tissue risk biomarkers with change in systemic hormones, ovarian reserve, and drug metabolites. **Methods:** NCT05941520 is a randomized, double-blind Phase II trial performed as part of the University of Michigan Early Phase Clinical Cancer Prevention (ClinCaP) Consortium part of the Cancer Prevention Clinical Trials Network (CP-CTNet) comparing 6 months of tamoxifen 5 mg and acolbifene 20 mg. Eligible participants are premenopausal women ≥35 without prior invasive breast cancer, but with ≥ 2-fold increased risk for the disease. The primary endpoint is difference in change in levels of *AGR2* mRNA between the two arms. Secondary endpoints are within-arm change in an endocrine response gene index (ERGI), mammographic density, and MENQOL. Exploratory endpoints include within-arm change in benign breast Ki-67, ER, PR and AGR2 protein, association of baseline Anti-Mullerian Hormone (a measure of ovarian reserve) with 6-month serum estradiol and change in tissue estrogen responsive gene expression and *AGR2*. Based on the preliminary data, mean log base2 (fold change, FC) of *AGR2* in the acolbifene arm is assumed to be -1, which is tantamount to a 50% reduction. The estimated SD of the log2(FC) is 2.25. Assuming a log2(FC) of +0.6 in the low dose tamoxifen arm (50% increase), and the same SD as in the acolbifene arm, 36 evaluable subjects per arm are required to detect, with 80% power at an alpha = 0.03 (two-sided), a difference in FC of this magnitude between the two arms. Secondary endpoints are assessed via paired samples t-test or Wilcoxon signed-rank test. Target enrollment in this 4-site trial is 80 over 2.5 years. The protocol opened for accrual at the University of Kansas Medical Center in October 2024 and as of January 2025 is pending activation at the other sites. Clinical trial information: NCT05941520. Research Sponsor: National Cancer Institute.