

Allostatic load as a mediator of exposomic risk pathways to early-onset cancer: A cross-cohort validation study.

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Background: Early-onset cancer (EoC, defined as any solid tumor diagnosed ≤ 50 years age) incidence has increased 79% globally since 1990. Traditional risk models focus on isolated exposures or specific rare genetic variants and have limited utility for EoC, as high-penetrance mutations account for $<10\text{--}20\%$ of cases depending on tumor type. Allostatic load (AL) – the cumulative physiological burden of chronic stress across neuroendocrine, immune, and metabolic systems – may represent a pan-EoC mechanism linking environmental exposures to EoC carcinogenesis. **Methods:** We analyzed 13,745 adults aged ≤ 50 years (2,749 EoC cases) across two population-based cohorts: UK Biobank (UKB; $n=5,100$) and NIH All of Us Research Program (AoU; $n=8,645$). AL was constructed by summing standardized indicators for 8–11 baseline biomarkers representing cardiovascular (blood pressure), metabolic (HbA1c, glucose, cholesterol, BMI), and immune (CRP, WBC, albumin) domains. An exposome score was derived via bifactor analysis of 61 (UKB) and 11 (AoU) baseline exposures spanning diet, lifestyle, neighborhood, and psychosocial factors. Propensity score matching controlled for age, sex, race/ethnicity, and socioeconomic indicators. Mediation analysis estimated indirect effects of exposome on EoC operating through AL. **Results:** Mean age was 43.0 years in UKB and 39.8 years in AoU; 72.5–76.5% were female. For each SD increase in baseline AL, there was 11–18% increased odds of subsequent EoC (AoU OR: 1.18 [95%CI 1.12–1.24]; UKB OR: 1.11 [1.04–1.18]). Exposome score was significantly associated with AL (AoU $\beta=0.09$; UKB $\beta=0.08$; both $p<0.001$). Mediation analyses revealed significant indirect effects in both cohorts, with non-significant direct effects (Table). For exposome-related cancers, AL mediated 8.7–15.4% of exposomic risk. **Conclusions:** This is the first multinational population-level study to demonstrate that AL mediates environmental risk pathways to EoC, supporting the hypothesis that cumulative environmental burden promotes carcinogenesis through physiological stress pathways. AL represents a potentially modifiable target for EoC risk stratification. Future research integrating polygenic risk and longitudinal exposome assessments may refine mechanistic understanding and enable precision prevention approaches for this growing public health challenge. Research Sponsor: U.S. National Institutes of Health; 5K08CA263541.

Mediation of exposome-EoC association via AL				
Cohort	Cancer Group	Indirect Effect* (p)	Direct Effect# (p)	Proportion Mediated (p)
AoU	All	0.005 (<0.001)	−0.012 (0.14)	—
AoU	Exposome-Related	0.001 (<0.001)	0.007 (0.06)	15.4% (0.02)
UKB	All	0.002 (<0.001)	−0.005 (0.63)	—
UKB	Exposome-Related	0.001 (0.01)	0.008 (0.17)	8.7% (0.14)

* β of exposome-EoC effect operating through AL.
β of exposome-EoC effect independent of AL.
Exposome-related cancers: colorectal, lung, liver, bladder, upper GI.

Predicting multi-cancer risk from EHR data using multi-agent LLMs.

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Background: Accurate multi-cancer risk prediction is essential for optimizing screening strategies and yet remains challenging due to heterogeneous and longitudinal electronic health record (EHR) data. Large language models (LLMs) offer a unified framework for multi-cancer risk assessment without disease-specific model training, but single-agent LLMs struggle to reason effectively over long patient histories. **Methods:** We developed a multi-agent system (MAS) composed of chained LLM agents with episodic memory to synthesize longitudinal EHR data into comprehensive cancer risk profiles. The system generates 1-year cancer risk scores (1–10) for individual cancer types. Using Truveta Data, we identified cases for 9 cancer types with clinically recognized precursor signs using clinician-curated diagnostic codes. For each cancer type, 500 cases were randomly sampled and matched 1:1 with controls by 10-year age group and sex. All structured EHR data (conditions, laboratory results, observations, medications, and procedures) up to 1 year before diagnosis or index date were included. Performance was evaluated across cancer types; lung cancer was used as a benchmark cohort for comparison with traditional machine learning (ML) models and a single-agent LLM baseline. **Results:** The MAS demonstrated heterogeneous but clinically meaningful discrimination across cancer types (AUROC range: 0.64 to 0.80), with liver cancer performing the best and colorectal cancer the worst. In the lung cancer cohort, performance (AUROC=0.79) was comparable to that of trained ML models (AUROC: XGBoost 0.82, logistic regression 0.73, k-nearest neighbors 0.58). Beyond risk prediction, the system generated concise patient summaries and interpretable rationales that supported downstream analyses, including cancer real-world evidence generation and exploratory knowledge discovery. Compared with a single-agent LLM, the MAS showed improved temporal coherence and clinical reasoning. **Conclusions:** A multi-agent LLM system can leverage longitudinal EHR data to estimate short-term multi-cancer risk within a unified framework, without cancer-specific model training. These findings support the potential role of LLM-based systems as scalable tools to inform risk stratification and screening strategies in real-world clinical populations. Research Sponsor: Truveta.

The MAS's performance.									
	Lung	Ovarian	Liver	Pancreatic	Colorectal	Multiple Myeloma	Lymphoma	Gastric	Bladder
AUROC	0.79	0.68	0.80	0.66 [0.62,	0.64 [0.61,	0.70 [0.67,	0.69 [0.66,	0.69	0.71
[95% CI]	[0.77, 0.82]	[0.65, 0.71]	[0.77, 0.83]	0.69]	0.68]	0.73]	0.72]	[0.66, 0.72]	[0.68, 0.74]

Beyond hematologic malignancies: Clonal hematopoiesis of indeterminate potential and the risk of solid tumors in the UK biobank.

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition characterized by somatic mutations in hematopoietic stem cells. While CHIP is associated with hematologic malignancies, its relationship with solid tumors remains incompletely characterized. We conducted a comprehensive analysis of CHIP and cancer risk in a large population-based cohort. **Methods:** We analyzed 409,150 UK Biobank participants with whole exome sequencing, including 13,709 (3.4%) with CHIP. CHIP was defined as somatic mutations in myeloid driver genes at variant allele frequency (VAF) $\geq 2\%$. Incident cancers were ascertained through registry linkage over median 15.5-year follow-up. We performed propensity score-matched Cox regression adjusting for age, sex, ethnicity, smoking, BMI, diabetes, chronic kidney disease, and family history. Gene-specific, VAF-stratified, and multi-hit analyses were conducted. **Results:** Among 77,695 incident cancers, CHIP was associated with increased risk of any cancer (HR 1.22, 95% CI 1.18–1.27), including both hematologic and solid tumors. Associations were strongest for myeloid neoplasms (HR 10.49, 95% CI 8.64–12.74), including AML (HR 11.09), MDS (HR 9.75), and MPN (HR 8.03). For solid tumors, significant associations were observed for lung cancer (HR 1.50, 95% CI 1.31–1.73), particularly adenocarcinoma (HR 1.79, 95% CI 1.48–2.16), and esophageal cancer (HR 1.52, 95% CI 1.13–2.03). Notably, esophageal squamous cell carcinoma showed particularly elevated risk (HR 2.28, 95% CI 1.37–3.81). VAF-stratified analyses revealed dose-response for esophageal cancer: large clones (defined as VAF $\geq 20\%$) conferred HR 2.23 (95% CI 1.32–3.75) and very large clones (defined as VAF $\geq 30\%$) HR 2.72 (95% CI 1.39–5.30). Multi-hit CHIP (≥ 2 mutations) was associated with HR 3.35 (95% CI 1.46–7.71) for esophageal cancer and HR 4.07 (95% CI 1.79–9.21) for esophageal adenocarcinoma. Gene-specific analyses showed TET2 mutations increased esophageal adenocarcinoma risk (HR 2.46, 95% CI 1.21–5.03). Results remained consistent in 5-year landmark analyses. **Conclusions:** CHIP is associated with significantly increased risk of both hematologic and select solid malignancies. We identify esophageal cancer, particularly squamous cell carcinoma, as a novel CHIP-associated malignancy with clear dose-response by clone burden. These findings warrant external validation and, if confirmed, suggest CHIP features may help refine risk stratification strategies for selected solid tumors. Research Sponsor: None.

Effect of type and location of *BRCA2* deleterious variant on prognosis and survival in metastatic prostate cancer: A longitudinal, international, cohort study from hormone-sensitive to castration-resistant settings.

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Background: Emerging evidence suggests that *BRCA*-altered prostate cancer (PC) is not a unique molecular subtype. However, the prognostic and therapeutic relevance of specific pathogenic/likely pathogenic variant (PV) in metastatic PC (mPC) remains poorly defined. We investigated the impact of *BRCA2* PV type and position on clinical outcomes across different metastatic settings. **Methods:** This international, hospital-based cohort study (Jan 2020–Apr 2025) included mPC patients (pts) across 29 centers who underwent germline, somatic, and/or ctDNA *BRCA* testing. Analysis included three settings: 1) mHSPC (ADT+docetaxel vs. ADT+ARPi); 2) mCRPC (ARPi vs. taxanes); 3) mCRPC treated with PARP inhibitors (PARPi). Outcomes [Time on Treatment (ToT); Overall Survival (OS)] were analyzed by PV type (frameshift, missense, nonsense, splicing; indels, SNV, CNV) and position: 1) Functional Domains (FDs) (RAD51-BD [AA 900–2000] vs. DBD [AA 2459–3190] vs. Others); 2) The recently identified Prostate Cancer Cluster Regions (PCCR) (c.756–c.1000 and 3' of c.7914 vs. Others). **Results:** Of 2,119 pts included, 401 harbored Homologous Recombination Repair PVs. In the cohort of 1,411 mHSPC pts, *BRCA2*-mutated ($n = 201$) showed significantly shorter OS vs. wild-type (mOS 63 vs 76 months; HR 1.2, $p = 0.02$), regardless of first-line therapy. Contrary to previous reports, *BRCA2*-mutated mHSPC pts had superior ToT from ADT+ARPi vs. ADT+docetaxel (55 vs 15 mos; HR 3.5, $p < 0.001$). Within the *BRCA2* subgroup, PV location was highly prognostic for OS. In mHSPC, PCCR-outside variants (c.756–c.1000/3' of c.7914) and non-FD variants (RAD51-BD/DBD-outside) were associated with shorter OS (PCCR: 57 vs 97 mos, HR 4.0, $p = 0.006$; FD: 47 vs 88 mos, HR 3.0, $p < 0.001$). Similar prognostic impacts were confirmed in 684 mCRPC pts (PCCR: 78.0 vs 38.0 mos, HR 3.3, $p = 0.01$; FD: 64.0 vs 34.0 mos, HR 2.7; $p = 0.009$). Among 201 pts treated with olaparib, those with RAD51-BD PVs achieved significantly longer ToT (20.0 vs 7.0 mos; $p = 0.01$) and longer OS. Furthermore, frameshift deletions were associated with shorter OS compared to other PV types (15.9 vs 26.0 mos; $p = 0.04$). **Conclusions:** This is the largest longitudinal study to demonstrate that *BRCA2* PV type and location are critical determinants of survival and treatment response in mPC. Our findings identify a "high-risk" molecular subgroup (PCCR and RAD51-BD/DBD-outside and frameshift deletions) with significantly poorer outcomes. These results provide a rationale for refined risk-stratification and personalized treatment selection, including early PARPi integration, in *BRCA2*-mutated patients. Research Sponsor: None.

Association between the rs72725854(A>T) allele and prostate cancer in males of African ancestry in a US population-based database.

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Background: Black males have a 70% excess incidence of and two-fold higher mortality from prostate cancer (PCa) compared to White males in the US. The rs72725854(A>T) variant ('T' allele) is a common African ancestry-specific variant that is associated with PCa in large case-control studies in the US and Africa. We measured the association between the 'T' allele and PCa in a unique US population-based cohort. **Methods:** We conducted a retrospective time-to-event cohort study using the *All of Us* database (Duke IRB Pro00117610). We included males of African ancestry who met the following criteria: 1) were at least 35 years old at *All of Us* enrollment; 2) had undergone whole genome sequencing; 3) had linked electronic health record (EHR) data; 4) had no Systemized Nomenclature of Medicine – Clinical Terms (SNOMED-CT) diagnosis of PCa prior to *All of Us* enrollment. PCa diagnoses were ascertained by the following EHR-based phenotyping algorithm: two PCa SNOMED-CT diagnosis codes plus evidence of PCa treatment with radical prostatectomy, radiotherapy or androgen deprivation therapy. The date of PCa diagnosis was defined as the latter of second diagnosis code date or first treatment date. Individuals were censored at last visit in the EHR if they did not meet the primary endpoint of PCa diagnosis. The association between each additional 'T' allele and time from *All of Us* enrollment to PCa diagnosis was measured using Cox regression methods, adjusting for the top 5 genetic principal components, age, and rare pathogenic variants (RPVs) in PCa predisposition genes (*ATM*, *BRCA1/2*, *HOXB13* X285K African-ancestry variant, and *PALB2*). Included RPVs had pathogenic/likely pathogenic designation in ClinVar with at least two stars. **Results:** Our study included 18,846 male participants of African ancestry, with 2,349 (12.5%) and 90 (0.5%) being heterozygous and homozygous for the 'T' allele, respectively. Median age at enrollment was 56.0 years (interquartile range 48.5 – 62.3). There were 91 cases of PCa during a median follow-up of 25.6 months (interquartile range 3.0 – 45.9). For each additional 'T' allele, there was a 3.4-fold increased hazard of PCa (HR 3.38; 95% CI 2.31 – 4.95; $p = 3.92 \times 10^{-10}$). Age (HR 1.09; 95% CI 1.06 – 1.11; $p = 2.74 \times 10^{-15}$) and RPVs in *ATM* (HR 7.54; 95% CI 1.84 – 30.90; $p = 5.03 \times 10^{-3}$) were also significantly associated with increased PCa diagnosis. *BRCA2* RPVs (HR 4.94; 95% CI 0.68 – 35.68; $p = 0.112$) and *HOXB13* X285K (HR 2.61; 95% CI 0.36 – 19.02; $p = 0.343$) were associated with PCa, but did not meet statistical significance. There were no *BRCA1* or *PALB2* RPVs among participants with PCa. **Conclusions:** In a large, US population-based study, we confirmed an association between the common rs72725854(A>T) variant and PCa diagnosis. This variant has a per-allele effect on PCa risk that is similar in magnitude to RPVs in PCa predisposition genes, and should be considered for inclusion in PCa genetic testing panels. Research Sponsor: None.

Prospective prostate cancer screening in germline pathogenic variant carriers: The PATROL study.

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Background: Germline pathogenic variants (gPV) in prostate cancer (PCa) risk genes are associated with aggressive disease, but optimal screening thresholds for this population are unclear. We report early results from the Prostate Cancer Screening for People at Genetic Risk for Aggressive Disease (PATROL) study. **Methods:** PATROL is a multicenter, prospective study enrolling participants ≥ 40 years with a gPV in at least one of 13 PCa risk genes. Biopsy is recommended using age-specific prostate-specific antigen (PSA) thresholds: > 1.0 ng/mL ($< 50y$), > 1.5 ($50-59y$), > 2.0 ($\geq 60y$). Prostate multiparametric MRI is encouraged at baseline and within 1 year of biopsy. Clinically significant PCa (csPCa) was defined as Grade Group (GG) ≥ 2 (NCT04472338). **Results:** As of 12/1/2025, 436 participants were enrolled; 69% carried *BRCA1/2* gPVs (*BRCA2* 46%, *BRCA1* 22%), 12% carried mismatch repair gene variants, and gPVs in other genes were each $\leq 7\%$. Overall, 106 participants underwent 119 on-study biopsies (median age 61 [IQR 53–68]) with a median PSA 2.3 ng/mL [IQR 1.3–3.9]. GG1 disease was detected in 21/119 (18%) biopsies and csPCa in 21/119 (18%) biopsies. Among csPCa, the median PSA was 3.2 ng/mL (IQR 2.2–4.1), and 76% (16/21) had a PIRADS 4–5 lesion. Fifteen (71%) and 14 (67%) of GG1 and csPCa, respectively, were identified in participants with *BRCA1/2* gPVs. In multivariable logistic regression adjusting for age, PSA, and genetic status, PI-RADS 4–5 was associated with csPCa (OR 12.2, 95% CI 3.3–45.4). Of the 17 men with GG1 PCa, 11 (65%) elected active surveillance. Of the 11 men on surveillance, median follow up time was 19 months, with one (9%) upgraded to GG ≥ 2 and who underwent definitive treatment. In total, 25 participants underwent definitive treatment; 18 with initial diagnosis of csPCa, six GG1 who elected for definitive treatment and one enrollee with GG1 upgraded to GG ≥ 2 . Of the 25 patients who elected definitive treatment, 88% (22/25) of underwent surgery, two underwent radiation, and one underwent focal therapy. Of surgery patients, there were no postoperative complications. At a median follow-up time of 16 months, all currently have undetectable PSA, and one patient required salvage radiation therapy. **Conclusions:** Age-specific PSA-driven biopsy in gPV carriers yielded ~20% csPCa detection, with two-thirds occurring at PSA < 4 ng/mL (common biopsy threshold). MRI (PI-RADS 4–5) strongly predicted csPCa and may improve inherited-risk screening algorithms. With limited follow-up, surveillance of low-risk PCa among gPV carriers appears to be feasible, and definitive treatment of gPV carriers found with csPCa is effective. Clinical trial information: NCT04472338. Research Sponsor: Bassett Center for BRCA; Canary Foundation; CureBRCA; Pacific NW Prostate Cancer SPORC; Department of Defense Prostate Cancer Research Program.

Association of GLP-1 agonists with breast cancer incidence in women.

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Background: Excess weight is a key modifiable risk factor for breast cancer. Glucagon-like peptide-1 receptor agonists (GLP-1) promote weight loss and improve markers of metabolic health. However, the effect of GLP-1 on breast cancer risk among women eligible for breast cancer screening remains unclear. **Methods:** We conducted a retrospective, time-dependent cohort study from January 1, 2022, to June 30, 2025, using electronic health records. We identified 217,025 unique patients who underwent breast imaging, restricting the sample to women aged 45 to 80 years with a BMI greater than 25 and a documented imaging outcome (n=94,827; median age 61). The primary outcome was breast cancer detection. GLP-1 use was defined as a first prescription prior to the exam date and assessed in relation to race, ethnicity, age, and type 2 diabetes. To address potential confounding between these covariates and GLP-1 exposure, we performed one-to-one, case-control matching using propensity scores based on age, race, ethnicity, highest BMI, breast density, and type 2 diabetes diagnosis. **Results:** Among 94,827 women, 2,314 (2.4%) were diagnosed with breast cancer during the study period, while 92,513 (97.6%) were not. Of the total, 15,107 (15.9%) had GLP-1 exposure, and 79,720 (84.1%) did not. Among those exposed to GLP-1, 249 (1.65%) developed breast cancer, while 14,858 (98.4%) did not. Among women without exposure to GLP-1, there were 2065 (2.6%) women with breast cancer and 77,655 (97.4%) of women without breast cancer. GLP-1 exposure was associated with a lower incidence of breast cancer (OR 0.630 (0.552, 0.720); p<0.0001). In the matched logistic regression analysis (30,214 observations; 581 cancer cases), GLP-1 exposure prior to the exam date was associated with a lower incidence of breast cancer (OR 0.746, 95% CI: 0.632–0.880; p<0.0005). **Conclusions:** In this large observational study of women undergoing breast imaging at a major academic center, GLP-1 treatment was associated with a significantly lower incidence of breast cancer after accounting for age, race, ethnicity, BMI, breast density, and type 2 diabetes status. These findings support the need for prospective trials investigating incretin medications for breast cancer prevention. Research Sponsor: Pennsylvania Breast Cancer Coalition.

Matched case-control contingency table for GLP-1 exposure prior to exam date and breast cancer.			
		No cancer	Total
GLP-1	249 (1.65%)	14858 (98.35%)	15107
No GLP-1	332 (2.20%)	14775 (97.80%)	15107
Total	581 (1.92%)	29633 (98.08%)	30214

Primary prevention of acute leukemias in high-risk patients: The therapeutic promise of GLP-1 receptor agonists.

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Background: Despite advances in understanding leukemogenesis, no validated primary prevention strategies exist. Obesity is a dose-dependent risk factor for leukemia. Emerging data implicate epigenetic regulators, specifically the histone methyltransferase GLP (EHMT1), as a driver of leukemic survival; its inhibition induces cell death in CLL and promotes differentiation in AML. We present the first real-world analysis evaluating GLP-1 receptor agonists (GLP-1RA) for the primary prevention of leukemia in high-risk populations. **Methods:** Using the TriNetX global research network (150 million patients across 108 healthcare organizations), we identified adults at elevated leukemia risk based on ≥ 1 factor (prior chemo/radiation, MDS, MPN, family history, genetic syndromes, tobacco use, or BMI ≥ 30). Patients with ≥ 2 months of GLP-1RA use were propensity-matched 1:1 to non-users by demographics, comorbidities, and prior chemotherapy. The primary endpoint was the incidence of ALL, AML, CLL, or CML; secondary endpoints were adverse events related to GLP-1RA. Individuals with pre-existing leukemia were excluded. Cox proportional hazards models and sensitivity analyses were used to assess associations. Sensitivity and subgroup analysis confirmed robustness. **Results:** Of 426,670 high-risk individuals, 213,335 were matched to each cohort; standardized mean differences were < 0.1 for all covariates. Across > 1.2 million person-years of follow-up, GLP-1RA use was associated with a 63% risk reduction in incident AML (47/213,300 vs 75/213,261; HR 0.37, 95% CI 0.26–0.53; $p < 0.001$) and a 50% reduction in ALL (42/213,304 vs 53/213,277; HR 0.50, 95% CI 0.33–0.75; $p = 0.001$). The protective effect for AML remained significant when restricted to patients with prior chemotherapy exposure and was independent of baseline BMI. No significant reductions were observed for CML or CLL. While GI adverse events were higher in the GLP-1RA cohort, the protective signal was consistent across age and ethnic subgroups. **Conclusions:** This is the first large-scale study to demonstrate a significant reduction in incident AML and ALL using GLP-1 receptor agonists in high-risk patients. By linking clinical metabolic intervention to the EHMT1 epigenetic pathway, these findings provide a novel, scalable pharmacologic strategy for the primary prevention of acute leukemias, potentially transforming the management of high-risk and obese populations. Research Sponsor: None.

Comparative analysis of tirzepatide versus metformin and insulin in type 2 diabetes patients across the 13 most common cancers.

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Background: Emerging glucose-lowering therapies may influence cancer risk in patients with type 2 diabetes mellitus (T2DM). While several GLP-1 receptor agonists have been evaluated, data on tirzepatide, a dual GLP-1/GIP agonist with established cardiometabolic benefits, remain limited. We assessed the comparative risk of incident cancers and all-cause mortality among T2DM patients treated with tirzepatide versus metformin or insulin. **Methods:** We conducted a retrospective cohort study using TriNetX, a U.S.-based federated electronic health record network. Adults with T2DM initiating tirzepatide, metformin, or insulin between February 28, 2020 and February 28, 2025, without prior cancer, were included. Propensity score matching (1:1, greedy nearest-neighbor) balanced demographics, BMI, HbA1c, diabetes duration, and comorbidities. Cox proportional hazards models estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the 13 most common incident cancers and all-cause mortality. **Results:** After 1:1 propensity score matching, baseline demographic, metabolic, diabetes-related, psychosocial, and medication characteristics were well balanced between groups, with minimal residual differences across age, sex, race/ethnicity, HbA1c, obesity severity, diabetes complications, and concomitant glucose-lowering therapies. In the tirzepatide versus insulin comparison, tirzepatide use was associated with significantly lower risks of multiple solid and hematologic malignancies, including lung, pancreatic, liver, colorectal, kidney, and endometrial cancers, as well as non-Hodgkin lymphoma (all log-rank $p < 0.01$), with no significant differences observed for prostate, thyroid, melanoma, bladder cancer, or leukemia. In the tirzepatide versus metformin comparison, tirzepatide was associated with significantly lower risks of lung cancer (HR 0.086, 95% CI 0.020–0.373; $p < 0.001$), pancreatic cancer (HR 0.124, 95% CI 0.015–1.039; $p = 0.022$), and breast cancer (HR 0.462, 95% CI 0.254–0.840; $p = 0.009$), while risks of other malignancies were not significantly different between groups. Across both matched cohorts, tirzepatide was consistently associated with markedly lower all-cause mortality compared with insulin and metformin, with absolute risk reductions of 4.8% and 0.6%, respectively (both $p < 0.001$). **Conclusions:** Among patients with type 2 diabetes, tirzepatide was associated with consistently lower all-cause mortality and reduced incidence of multiple cancers compared with insulin and metformin in a large, propensity-matched real-world analysis. These findings highlight tirzepatide as a glucose-lowering therapy with a potentially favorable oncologic risk profile, warranting prospective validation and mechanistic investigation. Research Sponsor: None.

Safety and performance results from PATHFINDER 2, a registrational study of a multi-cancer early detection (MCED) test in an intended-use population.

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The full, final text of this abstract will be available at meetings.asco.org on the day of presentation and in the online supplement to the June 10, 2026, issue of the *Journal of Clinical Oncology*.

A randomized non-inferiority trial of an eHealth delivery alternative for cancer genetic testing for hereditary cancer (eREACH2).

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Background: Germline cancer genetic testing is a standard evidence-based practice, with established risk reduction and cancer screening guidelines for genetic carriers. Yet, many at-risk patients do not have access to genetic services due in part to a workforce shortage of genetic counselors (GC). The randomized non-inferiority eREACH1 study found that digital delivery of pre-test or post-test counseling (e.g. a 1-visit model) was non-inferior 2-visits with a GC and reduced GC time per patient in patients with metastatic cancer. Outcomes with digital alternatives in the broader population of patients with and without cancer who meet criteria for genetic testing is unknown. **Methods:** eREACH2 is a randomized 4-arm non-inferiority trial where traditional pre-test (visit 1) and post-test (visit 2) counseling delivered by a GC are replaced with a patient-centered eHealth (digital) intervention in patients with and without cancer who meet national guidelines for germline genetic testing. 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. All participants have a designated GC directing their care, even if they complete a digital visit. Surveys were completed at baseline (T0), after visit 1 (T1), visit 2 (T2) and 6 months (T3). The primary outcomes are non-inferiority in uptake of genetic services and change in genetic knowledge and general anxiety from T0-T2. Secondary outcomes included uptake of testing (89-92% across arms) and additional cognitive, affective and behavioral outcomes. We used modified non-inferiority ANOVAs and modified equivalency chi-squared tests for hypothesis testing using an intention-to-treat (ITT) and confirmatory per-protocol analyses. **Results:** 773 participants were recruited from across the US with 49.8% from rural areas and 188-198 per arm. Participants were 20-87 YO (mean 51 YO), 13% were male, 12% were non-white, 29% had less than a college education, and 33% had a personal history of cancer. 584 (76%) patients completed testing (14% had a positive result, 16% had a VUS). In our primary ITT analyses, we met the non-inferiority threshold for uptake of genetic services and all short-term (T0-T2) primary and secondary cognitive and affective outcomes. 3% assigned to digital visit 1 and 9% assigned to digital visit 2 requested a GC. Per-protocol analyses were similar to the ITT results. **Conclusions:** In this large randomized, nationally recruiting trial of representative patients with and without cancer who are candidates for cancer genetic testing, offering patient-centered digital delivery models is non-inferior to two visits with a GC. This patient-centered digital intervention is an evidence-based alternative delivery model to improve access to and efficiency of cancer genetic testing. Clinical trial information: NCT05427240. Research Sponsor: National Cancer Institute; U01CA243702.

Impact of population-based testing for pathogenic variants in breast cancer genes on screening recommendations in the WISDOM study.

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Background: The relative contributions of pathogenic variants (PV) in breast cancer (BC) genes, polygenic risk scores (PRS), and clinical risk factors to inform risk-stratified screening have not been well-studied on the population level. The WISDOM Study, a study of risk-based screening, used panel-based testing for PVs in 9 BC genes and the Breast Cancer Surveillance Consortium risk model modified by PRS (BCSC-PRS) to generate screening recommendations for > 30,000 participants undergoing risk-based screening. Women with PVs in high-penetrance genes were assigned q6 month screening (alternating MRI and mammogram). Those with PVs in moderate-penetrance genes were assigned q6 screening or yearly mammogram depending on family history. To determine the impact of PV detection on screening assignments, we examined the concordance between screening strategies informed by PV status vs. BCSC-PRS only. **Methods:** We analyzed participants with high-penetrance (*BRCA1*, *BRCA2*, *TP53*, *PALB2*, *STK11*, *CDH1*), moderate-penetrance (*CHEK2*, *ATM*), or *CHEK2* low-penetrance (*I157T*, *S428T*) PVs. We performed cross-tabulations of hypothetical (based on BCSC-PRS only) vs. actual (which considers PV) screening recommendation. To generate hypothetical screening recommendations, we calculated individual BCSC-PRS 5-year risk and applied the trial's risk-based screening algorithm as if there were no PV. We considered initial (Year 1) screening recommendations to reflect that PV testing occurred at time of enrollment. We stratified analyses by PV category and age. **Results:** Our analysis included 714 women with a PV, of which 32% were high-penetrance, 39% were moderate-penetrance, and 29% were *CHEK2* low-penetrance. Median age was 53 (IQR 45–62) years and 86% self-reported as non-Hispanic White. We found little overlap between screening recommendations based on PV status vs. BCSC-PRS. In women with a high-penetrance PV, 1.3% (3/234) would have received a q6 screening recommendation based on BCSC-PRS. In women with a moderate-penetrance PV, 33% (92/278) were assigned to q6 screening, of whom 6.5% (6/92) would have received the same assignment under BCSC-PRS. Additionally, 65% (182/278) were assigned to yearly mammogram, of whom 2.2% (4/182) would have received the same assignment under BCSC-PRS. In women with PVs aged 40–49, 67% (187/280) would have been recommended no screening until age 50 based on BCSC-PRS. In women with PVs aged 50–74, 90% (390/432) would have been recommended biennial screening. **Conclusions:** Most women with PVs in BC genes would not have otherwise been recommended for enhanced screening based on clinical and PRS risk. Our results highlight the importance of testing for PVs as a cornerstone of risk-based screening on the population level. Future studies will examine opportunities for risk reduction as we integrate genetic and non-genetic risk factors. Clinical trial information: NCT02620852. Research Sponsor: PCORI; PCS-1402-10749; National Cancer Institute; R01CA237533; Breast Cancer Research Foundation; SPEC-18-006, SPEC-22-018, SPEC-24-026; Robert Wood Johnson Foundation; 71864; Safe-way Foundation.

Real-world evaluation of germline pathogenic variants (PVs) in cancer-predisposition genes among unselected South Asian women with breast or ovarian cancer.

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Background: Prior reports of high frequency of *BRCA1* and *BRCA2* (*BRCA1/2*) PVs among South Asian women from Bangladesh, India, Nepal, and Pakistan with breast or ovarian cancer require validation in large prospective unselected cohorts. **Methods:** Individual-level anonymized patient data from two prospective cohorts were pooled to evaluate the prevalence of germline PVs among South Asian women: the South Asian Regional Alliance for Hereditary Cancers (SARAH Consortium) in Bangladesh, Nepal, and Pakistan, and the previously reported Nurse-led Genetic Counseling and Awareness (NuGenA) expansion cohort in India. Both studies enrolled consecutive cases of histologically confirmed newly diagnosed breast or epithelial ovarian cancer irrespective of age at diagnosis or family history. In both studies, participants completed questionnaires on personal and family history (first-, second- or third-degree) and provided blood for germline genetic testing after written consent. PVs in cancer predisposition genes including *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* were identified as part of the studies utilizing a multigene panel and the results were returned to ordering clinicians. The data cutoff date for this analysis was November 30, 2025. **Results:** The analysis included 1,711 South Asian women with breast (n=1,210) or ovarian (n=501) cancer. A family history of breast or ovarian cancer was noted in 177 (10.3%). Among breast cancers, 94% were invasive, 84% were ductal, 35% were triple-negative and over two-thirds presented with nodal involvement. Germline PVs across 13 predisposition genes were observed in 17.7% of breast and 35.9% of ovarian cancers. Notably, *BRCA1/2* PVs accounted for most of these PV (13.6% of breast and 28.3% of ovarian cancer cases) with PVs in all genes except *BRCA1/2* under 1%. The frequency of *BRCA1/2* PVs was 24.4% in triple-negative breast cancer and 8.0% in ER+/HER2-. *BRCA1/2* PV carriers were diagnosed with breast cancer at a younger age than non-carriers (Median age: 42 vs 46 years, $P<0.001$), with no age difference observed in ovarian cancer (50 vs. 51 years, $P=0.79$). Notably, among the 306 *BRCA1/2* PV carriers identified, 229 (74.2%) did not report a family history of breast or ovarian cancer. **Conclusions:** We confirm a high prevalence of *BRCA1/2* PVs among unselected South Asian women with either breast or ovarian cancer. The observations of younger age at cancer diagnosis, and low rates of family history support the need for population-specific germline genetic testing and risk management strategies in South Asia. Research Sponsor: Conquer Cancer, the ASCO Foundation; Mayo Clinic Breast Cancer Specialized Programs of Research Excellence (SPORE); Mayo Clinic Ovarian Cancer Specialized Program of Research Excellence (SPORE); MedGenome Labs.

Fine-scaled genomic ancestry clusters to reveal population-specific cancer enrichments in the All of Us Research Program.

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Background: Specific populations exhibit known enrichments for certain cancers, such as breast cancer (BC) in Ashkenazi Jewish individuals. However, identification typically relies on self-reported race or broad continental genomic labels, which can obscure risks in understudied or admixed U.S. populations. **Methods:** Using All of Us (AOU) v8 (n=415k), participants with electronic health records (EHR) and whole-genome sequencing (WGS) were grouped into clusters based on genomic segments identical by descent. Clusters were labeled using genomic and anthropological references. We curated clinical data to remove duplicate or mislabeled entries (e.g., misidentifying metastatic lesions as primary tumors). Enrichment was determined via logistic regression, adjusting for age, sex, BMI, socioeconomic status, smoking, and recruitment site, with correction for multiple hypothesis testing using Benjamini-Hochberg. **Results:** A total of 245k individuals with EHR and quality-controlled WGS were assigned to 58 clusters; 41876 individuals were identified with at least one primary cancer diagnosis, spanning 19 broad types. A non-comprehensive selection of model results are presented in Table 1. These include previously established risks, such as BC enrichment in Ashkenazi-Jewish populations and prostate cancer in African Americans compared to Non-Jewish Europeans (NJE). Other, more novel findings include significant BC enrichment in admixed Hawaiians and colorectal cancer (CRC) in Puerto Rican and Dominican groups (not observed in the African American cluster). While individuals of Mexican ancestry showed lower lung cancer enrichment, this was not consistent in other admixed Hispanic populations, such as Colombians. **Conclusions:** Fine-scaled genomic clustering identifies cancer risks with higher precision than race-based or broad ancestral statistics. This methodology facilitates the identification of globally rare, potentially pathogenic variants that are enriched within specific subpopulations. These results underscore the necessity of granular ancestry data in understanding the genetic architecture of complex diseases like cancer. Research Sponsor: None.

Cancer	Population	Population Case N (%)	NJE Case N (%)	Odds Ratio (95% CI)	q-val
BC ¹	Ashkenazi Jewish	915 (10.6%)	6.9%	1.33 (1.23-1.44)	<0.001
Prostate ²	African American	852 (5.4%)	8.0%	1.51 (1.38-1.65)	<0.001
BC ¹	Hawaiian	<20* (9.4%)	6.9%	2.64 (1.39-5.03)	0.040
CRC	Puerto Rican	89 (1.5%)	1.5%	1.54 (1.24-1.93)	0.003
CRC	Dominican	81 (1.4%)	1.5%	1.85 (1.32-2.61)	0.008
CRC	African American	491 (1.2%)	1.5%	1.16 (1.04-1.30)	0.06
Lung	Mexican	95 (0.4%)	1.1%	0.66 (0.53-0.82)	0.005
Lung	Colombian	<20* (0.7%)	1.1%	0.92 (0.33-2.54)	0.97

1: Percentages only include female participants.

2: Percentages only include male participants.

*: Counts of less than 20 are hidden to comply with AoU reporting requirements.

Low-dose tamoxifen for pre-cancer and early disease: A pooled analysis by menopausal status.

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Background: Adjuvant endocrine prevention reduces the risk of subsequent breast cancer events after ductal carcinoma in situ (DCIS) and precursor lesions, but the toxicity of standard-dose tamoxifen or aromatase inhibitors limits its use. Low-dose tamoxifen (Babytam) has demonstrated a favorable balance of efficacy and tolerability. Whether the magnitude and pattern of benefit vary by menopausal status remains undefined. We performed a pooled analysis of three studies to evaluate Babytam according to menopausal status and type of breast cancer event. **Methods:** Individual patient data from two randomized trials (Trial 007, JCO 2009; 27:3749; Trial Tam-01, JCO 2023; 41:3116) and one observational study (Int J Cancer 2016; 139:2127) were pooled. Babytam was administered at 5 mg/day (RCTs) or 10 mg every other day (observational). The primary endpoint was recurrence of any breast cancer event, defined as ipsilateral recurrence or new ipsilateral breast cancer, contralateral breast cancer (CBC), distant metastases, or death. Competing risk models were applied for CBC. Multivariable Cox proportional hazards models with study-level random effects were used. Analyses were stratified by menopausal status. **Results:** A total of 1,772 women were included, 1,568 with DCIS, 101 with ADH, 81 with LCIS, and 21 with pT1a. Babytam significantly reduced overall breast cancer events, with differential effects by menopausal status and event type (table). Reduction in any breast cancer event was driven by a marked decrease in ipsilateral events among postmenopausal women, whereas the preventive effect on CBC was confined to premenopausal women. Few distant metastases or deaths occurred. **Conclusions:** In this pooled analysis, Babytam significantly reduced breast cancer events following in situ and microinvasive disease, confirming and extending the preventive efficacy observed in TAM-01. Menopausal status was a key modifier of benefit, with ipsilateral risk reduction predominating in postmenopausal women and CBC prevention in premenopausal women. These findings underscore the biological heterogeneity of early breast neoplasia and support Babytam as a risk-adapted, de-escalated endocrine prevention strategy that enables individualized decision-making balancing efficacy, toxicity, and patient characteristics. Clinical trial information: NCT06982313. Research Sponsor: Breast Cancer Research Foundation Award; Grant No. PPI-23-002.

Effect of low-dose tamoxifen (babytam) on overall recurrence and contralateral breast cancer by menopausal status.

Population	Menopausal status	Babytam events/N	Control events/N	HR (95% CI)	p-value
ER+	Overall	152/678	192/629	0.68 (0.55-0.84)	<0.001
	Pre	109/366	98/269	0.83 (0.63-1.09)	0.17
	Post	40/292	91/354	0.52 (0.36-0.76)	<0.001
ER-	Overall	7/19	57/225	1.20 (0.54-2.65)	0.65
Considering CBC only					
All patients	Overall	39/812	68/960	0.66 (0.44-1.00)	0.05
	Pre	22/457	40/387	0.46 (0.27-0.77)	0.003
	Post	16/335	27/560	1.04 (0.55-1.96)	0.89
ER+	Overall	35/678	51/629	0.65 (0.42-0.99)	0.046

Clinical impact of *MSH3* loss-of-function alterations in patients treated with immune checkpoint blockade across cancer types.

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Background: *MSH3* is an alternate mismatch repair protein specialized in the recognition of larger indels through its interaction with *MSH2* within the MutS β complex. While monoallelic germline *MSH3* variants are not associated with cancer susceptibility, the impact of *MSH3* loss-of-function (LOF) alteration has not been systematically assessed for immune checkpoint blockade (ICB) sensitivity. **Methods:** Tumors with *MSH3* loss-of-function alterations were identified by next-generation sequencing in the MSKCC IMPACT cohort (discovery cohort). Overall survival (OS) from diagnosis and from ICB initiation was compared between *MSH3*-altered and wild-type (WT) tumors using 2:1 propensity score matching, adjusting for age, sex, disease stage, and tumor type. Tumors harboring pathogenic *POLE* or *POLD1* mutations were excluded. An independent pan-cancer cohort (Caris) was used for validation. **Results:** Among 65,570 profiled tumors, 767 patients (1.2%) carried *MSH3* LOF alterations, including 46 (6.0%) germline variants. *MSH3* LOF tumors were MMR-deficient (MMRd) in 71.2% of cases, MMR-proficient (MMRp)/microsatellite instable (MSI) in 2.6% and MMRp/ microsatellite stable (MSS) in 26.2%. In MMRd tumors, *MSH3*-LOF occurred mainly in colorectal (64%), endometrial (20%), and esophagogastric cancers (12%), whereas in MMRp tumors it was most frequent in lung (17.4%), colorectal (12.5%), breast (10.3%), and esophagogastric cancers (4.9%). In MMRd tumors, patients with *MSH3* LOF tumors experienced significantly prolonged OS compared with *MSH3* WT tumors after ICB (mOS NR vs 85.2 months (mo), $p = 0.008$), attributed to the fact that they were all MSI while discordant cases (MMRd/MSS) were observed only in the absence of *MSH3* LOF. To further assess the impact of *MSH3* LOF on immunogenicity independent of classical MSI, we performed specific analysis in MMRp/MSS tumors. While these tumors remained mostly TMB low (median TMB 7 Mut/Mb vs 5 Mut/Mb, $p = 0.14$) with a modest but significant increase in MSI score (1.01 vs 0.42, $p = 0.013$), *MSH3* LOF patients had significantly improved OS following ICB compared with propensity matched WT controls (median OS 33.7 [95% CI 18.4–NR] vs 20.4 mo [95% CI 12.5–24.5]; $p = 0.015$). In particular, germline and somatic *MSH3* altered tumors were associated with similar benefit (median OS 33.7 [95% CI 14.4–NR] and 31.1 mo [95% CI 17.3–NR], respectively). No survival difference was observed among patients who did not receive ICB ($p = 0.91$). Predictive value of *MSH3* LOF for improved OS after ICB was independently validated in the Caris cohort. **Conclusions:** Somatic and germline *MSH3* LOF alterations define a unique subset of cancers with enhanced sensitivity to ICB, in particular in MMRp/MSS tumors, where *MSH3* deficiency may drive immunogenicity through mechanisms distinct from classic MSI. These data support *MSH3* LOF as a potential predictive biomarker for immunotherapy benefit. Research Sponsor: None.

Intralesional PD-1 blockade for oral cancer prevention: First-in-class phase 1 trial.

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Background: Oral premalignant lesions affect 5% of the global population with transformation rates of 1–8% in mild-moderate dysplasia and up to 36% in severe dysplasia. Current management via surgical excision yields 30–40% recurrence despite negative margins, with cumulative functional morbidity. We hypothesized intralesional delivery would achieve immune remodeling while eliminating systemic exposure. **Methods:** We conducted a phase 1, open-label, dose-escalation trial of intralesional nivolumab in patients with histologically confirmed oral epithelial dysplasia (NCT05327270). Twenty-nine patients received 10 mg or 20 mg intralesional nivolumab every three weeks for four cycles. Primary endpoints were safety and tolerability; secondary endpoints included lesion response, progression to carcinoma, pharmacokinetics, spatial immune profiling, and, uniquely for this population, prospective patient-reported outcomes (PROs). **Results:** No dose-limiting toxicities occurred; 94% of adverse events were grade 1–2 with no systemic immune-related toxicities. Plasma nivolumab concentrations remained 10-fold below IV dosing without accumulation. Lesion area decreased 60% across cohorts with 41% histologic downgrading. Twelve-month cancer-free survival was 75.8%; all progression events were detected early and surgically salvageable. We performed the first prospective longitudinal analysis of PROs in oral premalignancy. High study completion (86%) and adherence rates, despite significant travel burden, coupled with stable or improved quality-of-life scores (specifically pain and swallowing), indicate that repeated intralesional injections are a feasible, non-toxic approach associated with no functional adversity. Unlike surgical standards that degrade function, this strategy preserved patient quality-of-life. Mechanistic analyses using spatial transcriptomics and multiplexed immunofluorescence revealed immune activation exclusively in treated lesions: increased CD4+ and CD8+ T cell infiltration, enriched CCR7+ activated dendritic cells, elevated CD103+ tissue-resident CD8+ T cells, and formation of higher-order immune assemblies. Untreated non-index lesions from the same patients showed no immune changes, definitively demonstrating anatomically restricted immune activation. PBMC profiling confirmed absence of systemic immune response. **Conclusions:** This first-in-class trial demonstrates intralesional PD-1 blockade safely reprograms premalignant tissue immunity without systemic toxicity, establishing lesion-directed checkpoint inhibition as a viable cancer interception strategy. These findings have established the foundation for a randomized, placebo-controlled Phase 2 trial currently enrolling at MD Anderson Cancer Center (NCT06561087) and support broader applicability to accessible other epithelial precancers including cervical and anal. Clinical trial information: NCT05327270. Research Sponsor: CPRIT; RP210176.

Global development and validation of the Lung Cancer Prevention Score (LCPS): A quantitative framework linking policy strength, incidence, and outcomes across 40 countries.

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Background: Lung cancer is the leading cause of cancer worldwide. Despite advances in tobacco control, national prevention efforts remain fragmented. We developed and validated the Lung Cancer Prevention Score (LCPS), a 0–100 composite linking prevention policy strength with real-world outcomes for global benchmarking and equity tracking. **Methods:** Two LCPS models were created. Policy LCPS quantified 12 weighted domains: smoke-free laws, TAPS bans, $\geq 50\%$ pictorial warnings, $\geq 75\%$ excise tax, plain packaging, legal-age limits, e-cigarette control, LDCT screening, asbestos ban, radon plan, clean-cooking access, and occupational carcinogen controls. Data-Driven LCPS combined age-standardized incidence (ASIR), mortality (ASMR), mortality-to-incidence ratio (MIR), smoking prevalence, GDP, health expenditure, and HDI (normalized 0–1; higher = stronger prevention). Data from GLOBOCAN 2022, WHO GTCR 2023, World Bank, and UNDP HDR 2023 covered 40 countries (G20 + 20 others). Analyses included correlation, regression (adjusted for GDP, HDI), Bland–Altman agreement, and ROC AUC for $\text{MIR} \leq 0.60$. **Results:** Among 32 complete datasets, Policy and Data-Driven LCPS correlated moderately ($r = 0.31$; 95% CI -0.04 – 0.60). Discrimination of favorable outcomes ($\text{MIR} \leq 0.60$) showed AUC 0.68 vs 0.77. High-policy countries (≥ 75) had lower smoking (17%) and MIR (0.45) than those < 60 (27%, 0.65; $p < 0.001$). Policy LCPS inversely correlated with ASIR ($r = -0.42$; $p = 0.004$); Data-Driven LCPS showed a stronger link ($r = -0.55$; $p < 0.001$). Each 10-point LCPS-D increase predicted 2.4 fewer cases per 100 000 ($\beta = -0.24 \pm 0.07$; $p = 0.002$). Results were consistent across income tiers. **Conclusions:** LCPS provides a validated, reproducible framework connecting prevention policy to measurable cancer burden. Data-Driven LCPS reflected performance most accurately, while Policy LCPS defined actionable tiers linked to lower smoking, incidence, and MIR. LCPS serves as a quantitative global benchmark for policy evaluation. Research Sponsor: None.

Policy-driven lung cancer prevention score (LCPS-P) and data-driven lung cancer prevention score (LCPS-D): Domains and scoring weights.

Component	Type	Wt	Rule / Effect
Smoke-free law	P	1	Yes = 1
TAPS ban	P	1	Yes = 1; Partial = 0.5
Pictorial $\geq 50\%$	P	1	Yes = 1
Excise $\geq 75\%$	P	1	Yes = 1
Plain pack	P	0.5	Yes = 1
Legal age	P	0.5	18–19 = 0.5; $\geq 21 = 1$
E-cig reg	P	0.5	Full/Prescr = 1; None = 0
LDCT screen	P	2	Nat = 1; Reg = 0.5
Asbestos ban	P	1	Yes = 1
Radon plan	P	1	Yes = 1
Clean-cook $> 90\%$	P	1	Yes = 1
Occ carcinogen ctrl	P	1.5	Yes = 1
ASIR	D	1	Lower = better (1-scaled ASIR)
ASMR	D	1	Lower = better (1-scaled ASMR)
MIR	D	1	Lower = better (1-scaled MIR)
Smoking prev	D	1	Lower = better
GDP	D	0.5	Higher = better
Health exp	D	0.75	Higher = better
HDI	D	0.5	Higher = better
Scoring	—	—	Policy LCPS = $\sum (\text{weight} \times \text{value}) / 12 \times 100$; Data LCPS = $\sum (\text{weighted norm}) / \sum \text{weights} \times 100$

Family cancer history and perceived value of multi-cancer early detection tests in a national U.S. sample.

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Background: Family history of cancer has a strong influence on individuals' perceived cancer risk and has been shown to be a key determinant of cancer prevention behaviors. As novel precision-screening technologies such as Multi-Cancer Early Detection (MCED) blood tests emerge, understanding how familial cancer experience shapes public awareness and openness to adoption is essential for equitable implementation. **Methods:** We analyzed data from a nationally representative survey (Health Information National Trends Survey 7), of U.S. adults aged ≥ 18 years ($N = 5,789$). Weighted analyses accounted for complex survey design and population structure. The prevalence of awareness and perceived value of MCED tests among individuals with a family history of cancer, as well as population characteristics, including socio-demographics, family history of cancer, and cancer-related beliefs were estimated. Weighted multivariable logistic regression models evaluated associations between family history and two primary outcomes: awareness and perceived acceptability of MCED adjusting for sociodemographic factors, personal cancer beliefs, and perceived cancer risk. **Results:** Of the overall study sample, 74.3% reported a family history of cancer. The sample was 50.6% female, 63.3% Non-Hispanic White, 10.9% Black, 16.1% Hispanic, and 4.9% Asian. In total, 17.3% reported prior awareness of MCED tests and 74.2% perceived MCED as valuable. After adjustment, family history of cancer was not associated with MCED awareness ($OR = 0.94$; 95% CI = 0.66–1.34; $p = 0.71$). However, family history was significantly associated with higher acceptability of MCED testing ($OR = 1.50$; 95% CI = 1.15–1.96; $p = 0.004$). **Conclusions:** Adults with a family history of cancer are more willing to adopt Multi-Cancer Early Detection blood tests even without prior awareness. In this study, family history was not associated with MCED awareness but was significantly associated with higher perceived value and acceptability. This contrast suggests that receptivity to MCED may be driven more by perceived risk in the form of prior family history than by knowledge alone. Increasing general awareness may therefore be insufficient to promote broad uptake, highlighting the need to consider differences in risk perception when designing communication strategies as MCED moves toward clinical integration. Research Sponsor: None.

GLP-1 receptor agonists for primary prevention of breast cancer in high-risk women: A real-world analysis of efficacy and safety.

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Background: Therapeutic options for breast cancer (BC) prevention for high-risk women remain limited, and not all eligible patients opt for endocrine therapy due to concerns related to adverse events (AEs). GLP1RAs are widely used for obesity and type 2 diabetes mellitus; their role in BC primary prevention (PP) in high-risk women with obesity has not been evaluated.

Methods: Using the TriNetX Global Network (150 million patients, 108 organizations), we analyzed de-identified records of high-risk women aged 18–90 years with a BMI ≥ 30 who had health care encounters between January 1, 2000, and January 1, 2025, identified via ICD-10 codes. High risk was defined as at least one of the following: genetic predisposition to BC, family history of BC, atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, or dense breasts. Patients were grouped as having GLP1-RA use or no GLP-1RA use. Patients with a prior history of BC or use of endocrine therapy were excluded. GLP-1RA users were propensity score-matched 1:1 with non-users based on demographics, comorbidities, social determinants of health, lifestyle factors, BMI, HbA1c, and prior breast imaging. Incident BC served as the primary endpoint, with key AEs as secondary measures. Kaplan–Meier analysis and Cox proportional hazards models were utilized to assess outcomes, which were further validated through subgroup and sensitivity analyses. **Results:** Among 80,480 high-risk women with a BMI ≥ 30 , 46,581 were assigned to each cohort. Baseline demographics were balanced between cohorts (mean age: 46 years, 70% White, 21% Black). Median follow-up was 2,790 vs 2,630 days for GLP-1RA users and non-users, respectively. BC incidence was 2.95% in GLP-1RA users (1,164/39,495 cases) vs 3.01% in non-users (1,200/39,057 cases) (3.27 vs. 3.57 cases per 1,000 person-years; HR 0.844; 95% CI, 0.779–0.915). GLP-1RA users exhibited an increased risk of endometrial cancer (HR 1.273; 95% CI, 1.088–1.491) and osteoporosis (HR 1.124; 95% CI, 1.054–1.199). No significant association was observed for venous thromboembolism. Gastro-intestinal AEs were significantly higher in the GLP-1RA cohort. **Conclusions:** GLP-1RA use was associated with a modest reduction in BC incidence among high-risk women with obesity in this real-world study. Prospective randomized trials are needed to validate these associations. Research Sponsor: None.

A SEER-based Joinpoint analysis investigating the effect of shared decision-making on prostate cancer stage at diagnosis.

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Background: Prostate cancer screening recommendations in the United States have evolved over the last two decades. The U.S. Preventive Services Task Force (USPSTF) recommended against routine prostate-specific antigen (PSA) screening for men ≥ 75 in 2008 and for all men in 2012 (Grade D), followed by a transition to shared decision-making for men ages 55–69 in 2018 (Grade C). These changes have raised concern for later-stage presentation. Few analyses have leveraged national data through 2022 to evaluate whether the 2018 guideline modification has affected stage-specific incidence. **Methods:** We queried the Surveillance, Epidemiology, and End Results (SEER) Program for malignant prostate cancer cases diagnosed from 2000–2022 using the SEER 17 Registries Research Data (November 2024 submission), which provides population-based incidence coverage for approximately 26% of the United States. Cases were limited to men aged ≥ 55 at diagnosis. Age-adjusted incidence rates (per 100,000; 2000 U.S. standard population) were extracted separately for localized and distant Prostate malignancies (Summary Stage 2000+) using SEER*Stat incidence rate sessions. Annual rates and standard errors were exported for analysis. Joinpoint regression (Joinpoint v5.4.0) was used to estimate Annual Percent Change (APC) for each trend segment, with model selection determined by the Bayesian Information Criterion and weighting by standard error. Up to four joinpoints were permitted, and the software automatically selected the optimal number. Average Annual Percent Change (AAPC) was calculated to summarize overall trends. **Results:** Localized prostate cancer incidence declined significantly from 2004–2022 (APC = -3.12% ; $p < .05$). Distant prostate cancer incidence decreased from 2000–2010 (APC = -0.95% ; $p < .05$), followed by a significant increase from 2010–2022 (APC = $+6.04\%$; $p < .05$). Joinpoint analysis identified a statistically significant inflection point near 2010 that temporally follows USPSTF recommendations discouraging routine PSA screening. No additional joinpoint or attenuation in distant-stage incidence was observed following the 2018 guideline revision. **Conclusions:** Using up-to-date national registry data through 2022, our analysis corroborates prior work demonstrating rising distant-stage prostate cancer incidence following guideline changes that reduced PSA screening. The absence of a joinpoint following the 2018 revision suggests that the shift to shared decision-making has not yet reversed or slowed this trend. Research Sponsor: None.

Glucagon-like peptide-1 receptor agonist for primary prevention of hepatocellular carcinoma in high-risk patients: A real-world analysis across metabolic, viral, alcoholic, and hereditary liver disease.

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Background: Hepatocellular carcinoma (HCC) is a leading cause of cancer mortality. While antiviral and metabolic therapies have reduced incidence, scalable pharmacologic strategies for primary prevention (PP) remain a critical unmet need. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have demonstrated preclinical antitumor activity and the potential to mitigate hepatic lipotoxicity while promoting metabolic reprogramming to stabilize cirrhosis. However, while chemoprevention signals are observed in metabolic dysfunction-associated steatotic liver disease (MASLD) and type 2 diabetes, the efficacy of GLP-1RAs for PP across diverse liver disease etiologies remains underexplored. To address this gap, we conducted a global, multicenter analysis on the efficacy and safety of GLP-1RAs for the PP of HCC in a pan-etiology high-risk cohort. **Methods:** A retrospective cohort study was conducted using the TriNetX database (150M patients across 108 health organizations). Adults 18–90 years at elevated HCC risk with ≥ 1 risk factor (chronic viral hepatitis, cirrhosis, MASLD, alcohol use disorder, or hereditary liver disorders) were identified. Cohort A (≥ 3 months of GLP-1RA) was propensity score-matched 1:1 with Cohort B (non-users) on demographics, HbA1c, BMI, and MELD-Na scores. The primary endpoint was incident HCC, and secondary endpoints were incidence of gastrointestinal (GI) side effects. We employed a 3-month lag period to mitigate immortal time bias. Time-to-event outcomes were assessed via Kaplan-Meier analysis and Cox proportional hazards models. Sensitivity & subgroup analyses were performed to confirm robustness across non-metabolic etiologies. **Results:** After matching, 592,718 patients were analyzed (296,359 per cohort). Median follow-up was 2,450 days for GLP-1RA users vs 2,114 days for non-users. GLP-1RA use was associated with a 73% reduction in incident HCC (140/296,345 events vs 432/296,198) [HR 0.271 (0.224–0.328)], (NNT=1,015). Notably, the protective effect was most pronounced in non-diabetics [HR 0.179 (0.140–0.229)] and lean patients (BMI < 29) [HR 0.161 (0.103–0.252)]. Risk reductions were sustained across all etiologies, including alcohol liver disease (HR 0.379), cirrhosis (HR 0.456), chronic viral hepatitis (HR 0.477), and MASLD (HR 0.605). GLP-1RA use was associated with a significant increase in GI adverse events. **Conclusions:** GLP-1RA use was associated with a 73% reduction in incident HCC, consistent across subgroups. The enhanced benefit in non-diabetic and lean cohorts suggests a direct anti-neoplastic mechanism independent of weight loss or glycemic control. The NNT of 1,015 highlights the substantial public health impact of GLP-1RA therapy in preventing a high-mortality malignancy. These findings warrant prospective validation. Research Sponsor: None.

Integrating multi-cancer early detection into cancer screening programs in the United States: A cost-effectiveness modeling study.

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Background: In 2021, standard-of-care (SoC) screening for breast, cervical, colorectal, lung, and prostate cancers in the United States cost \$43.2 billion to detect 197,773 cancers, with colonoscopy—used as a primary colorectal screening modality—accounting for \$23.7 billion, the largest share of expenditures (54.9%). Multi-cancer early detection (MCED) blood tests could complement SoC single-cancer early detection (SCED) screening but may substantially increase overall costs if implemented without concurrent redesign of screening pathways.

Methods: A static decision model used 2021 U.S. SoC screening volumes and costs, 2020 Census data, cancer-specific incidence in high- and low-risk groups, and published SCED and MCED performance to simulate 75.6 million unique screened individuals after adjusting for overlap across programs. We evaluated (1) SoC alone, (2) SoC plus either a low-cost two-step MCED assay (OncoSeek followed by SeekInCare; “OncoSeek Duet”, \$143/person) or a higher-priced cfDNA methylation-based MCED test (Galleri, \$949/person), and (3) a budget-neutral strategy replacing primary colonoscopy with FIT, designated as SCED 2.0, with savings reinvested to fund OncoSeek Duet for all screened individuals. **Results:** SoC alone detected 197,773 cancers (262 per 100,000) with a PPV of 0.7% at a total cost of \$43.2 billion, or \$218,276 per cancer detected. Adding OncoSeek Duet increased detections to 398,586 (527 per 100,000; 2.0-fold), PPV to 43.3% (61.9-fold increase) and total cost to \$54.0 billion (25.0% increase), reducing cost per cancer to \$135,429, while expanding detection to 9 additional cancer types beyond the 5 SoC targets. Adding Galleri yielded 572,223 cancers (757 per 100,000; PPV of 60.7%) at \$114.9 billion total cost (2.7-fold increase) and \$200,823 per cancer, improving yield but with markedly higher budget impact than OncoSeek Duet. SCED 2.0 cut costs to \$20.0 billion (2.2-fold decrease), reduced cost per cancer to \$106,876, saved \$23.1 billion, and yielded 187,509 detections (5.2% decrease). Reinvesting these savings to provide OncoSeek Duet for all restored and expanded detection to 391,022 cancers (2.1-fold increase), maintained a high PPV of 42.9%, incurred \$78,899 per cancer and produced a \$12.3 billion surplus without increasing overall screening expenditure. **Conclusions:** In this U.S. modeling analysis, integrating MCED into SoC screening substantially increased cancers detected and lowered cost per cancer, particularly when using lower-cost OncoSeek Duet. Optimizing high-cost SCED components, such as colonoscopy, can fully finance population-wide MCED while preserving or improving efficiency, supporting a value-based, budget-neutral path for MCED implementation in national screening programs. Research Sponsor: None.

Time-restricted eating and metformin (TEAM) in invasive breast cancer or DCIS: A randomized, phase IIb, window-of-opportunity presurgical trial.

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Background: Preclinical studies indicate that metformin administered during fasting synergizes with feeding–fasting cycles to suppress tumor growth through activation of the PP2A–GSK3 β –MCL1 pathway. The TEAM trial evaluated the feasibility, safety, biological, metabolic, and clinical effects of a short-term metabolic intervention combining prolonged nightly fasting and metformin in operable hormone receptor–positive breast cancer. **Methods:** TEAM is a randomized, phase IIb, presurgical window-of-opportunity trial. Women with hormone receptor–positive operable invasive breast cancer or DCIS were randomized 1:1 to either ≥ 16 -hour nightly fasting plus metformin 750 mg bid and nutritional counseling (experimental [exp] arm) or to healthy WCRF lifestyle recommendations (control arm). Both groups wore a Continuous Glucose Monitor (CGM) per protocol data downloads. Treatment duration was 4–6 weeks before surgery. The primary endpoint is the absolute change in centrally assessed Ki67 between biopsy and surgery in invasive disease or DCIS. A co-primary endpoint was the difference in post-treatment Ki67 in cancer-adjacent DCIS. Analyses were intention-to-treat. **Results:** A total of 120 patients were randomized and completed the study (mean $\pm$ SD, 32 $\pm$ 8.6 days). As of December 31, 2025, 105 were evaluable for paired Ki67 analysis due to tissue availability. Since the complete results will be presented at the meeting, current data are descriptive with no inferential statistics and p-values, as per DSMB recommendation. Median baseline Ki67 was 15% in both arms. Median absolute Ki67 change was –3 percentage points (IQR –7 to 1) in the exp arm versus –2 (IQR –4 to 4) in the control arm. The median absolute change in invasive disease was –3 (–7 to 2) versus –1 (–3 to 4), and Ki67 reduction $\geq 3\%$ occurred in 53% versus 32%, in the exp and control arm, respectively. Post-treatment Ki67 in cancer-adjacent DCIS was 3.5 (2–8.5) vs 4 (2–7). There were 3 pathological CR in the exp arm and 0 in the control arm during the presurgical window. Median weight decreased by 1.75 kg in the exp arm relative to the control arm. Mean tumor 18F-FDG PET SUV decreased by 22% versus 4% in a subgroup of 25 patients with tumors ≥ 15 mm. Reductions were observed in glucose, HOMA-IR, leptin, C-peptide, insulin and IGF-I. Changes in CIP2A and MCL1 were observed in patients with Ki67 reduction. Median adherence to ≥ 16 -hour fasting was 100% (97.4–100); overall metformin adherence was 95% (85%–99%). No dose-limiting toxicities or grade ≥ 3 hypoglycemia occurred. **Conclusions:** These preliminary results show that short-term metabolic intervention was feasible, safe, highly compliant, and very inexpensive, and was associated with favorable antiproliferative and metabolic changes that warrant further investigation in breast cancer prevention and treatment. Full results will be presented at the meeting. Clinical trial information: NCT05023967. Research Sponsor: Division of Cancer Prevention, National Cancer Institute; Grant #: UG1CA242609; Italian Ministry of Health; (Grant #: RF-2019-12370733).

Cost-effective colorectal cancer screening in the United States: Comparative analyses of four molecular tests.

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Background: Colorectal cancer (CRC) screening in the United States is costly, largely driven by expensive colonoscopy procedures. In 2021, 22.3 million screening tests were performed, costing \$27.5 billion; colonoscopy alone accounted for 9.2 million tests and \$23.7 billion in expenditure (54.8% of the \$43.2 billion spent on five major cancers). This study compared available molecular tests to identify an approach that balances performance and cost as a primary alternative to colonoscopy. **Methods:** Four molecular tests were evaluated: two FDA-approved stool-based (fecal immunochemical tests [FIT] and multitarget stool DNA test [Cologuard]) and two blood-based (the FDA-approved cfDNA-based Shield and the multiomics-based SimpleScreen). Performance data came from published literature and clinical trials (NCT04136002, NCT01397747, NCT04369053). Cost analyses used 2021 U.S. screening volumes: FIT, Cologuard, and colonoscopy costs were based on 2021 fee schedules, Shield pricing on Medicare rates; SimpleScreen was excluded due to cost unavailability. **Results:** For CRC, Cologuard had the highest sensitivity (92.3%) but lower specificity (84.4%), whereas FIT showed lower sensitivity (73.8%) but the highest specificity (93.4%). Shield and SimpleScreen showed intermediate sensitivities (83.1%, 79.2%) and specificities (89.2%, 91.1%). For advanced precancerous lesions, blood-based tests showed minimal detection power, with post-test probabilities (equal to PPV) close to pre-test prevalence (Shield 17.4% vs 14.3%; SimpleScreen 13.5% vs 9.5%; post/pre ratios 1.2 and 1.5). In contrast, stool-based tests modestly increased post-test probabilities: Cologuard 20.7% vs 7.6%, post/pre ratios 4.0; and FIT 27.6% vs 7.6%, post/pre ratios 4.4, indicating preventive potential and supporting their use as alternatives to colonoscopy. Cost analysis further identified FIT as the most cost-effective alternative, with the lowest per-case cost of \$57, compared to \$651 for Cologuard, \$2,571 for colonoscopy, and \$1,495 for Shield. Replacing colonoscopy with FIT for the 9.2 million current colonoscopy screenings in 2021 would reduce CRC screening expenditures from \$27.5 billion to \$4.3 billion (84.2% reduction). Comparatively, Cologuard lower costs to \$9.8 billion (64.3% reduction) and Shield to \$17.6 billion (36.0% reduction). Nationally, the overall cost for the five major cancers was reduced to \$20.0 billion, resulting in a saving of \$23.2 billion, which could be reallocated to future multi-cancer screening programs to expand population coverage. **Conclusions:** FIT provides the best balance of performance, preventive potential, and cost-effectiveness. By reducing colonoscopy demand and national screening costs while maintaining adequate detection, it supports sustainable population-wide screening and warrants consideration in guidelines and reimbursement policies. Research Sponsor: None.

Using digital screening to increase early identification of hereditary breast and ovarian cancer syndrome: A multicenter cluster-randomized trial.

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Background: Early identification of hereditary breast and ovarian cancer syndrome (HBOCS) in primary gynecological care is essential for timely referral to specialized counseling and risk-adapted prevention. Yet, identification mostly occurs after disease onset, thereby thwarting preventive efforts. To facilitate early identification of healthy HBOCS carriers along the HBOCS care pathway in Germany, we developed a modular cross-sectoral digital care platform (dVP_FAM). This study compared the impact of dVP_FAM with standard care on increasing the proportion of healthy individuals with HBOCS. This project was funded by the Innovation Fund of the German Federal Joint Committee. **Methods:** We conducted a two-arm, cluster-randomized trial including 42 primary gynecological centers (20 intervention, 22 control) in Germany. In the intervention centers, patients filled out a digital HBOCS screening questionnaire based on the inclusion criteria of the German Consortium HBOC. Results were reviewed and validated by primary care gynecologists, who then decided whether to initiate referral to a specialized HBOC center via the digital platform. Control centers followed usual care. A mixed-effects logistic regression model with random intercepts was used to account for clustering at the study center level. Odds ratios (ORs) and 95% confidence intervals were estimated. **Results:** In the intervention centers, 5,534 individuals completed digital screening; 1,116 (20.2%) met inclusion criteria (IC+), and 507 (9.2%) were uncertain about family history. Of these 1,623 individuals, 664 requested an appointment at an HBOC center. A total of 467 individuals (intervention group (IG): n = 329, mean age = 45.6 (SD 12.3), 99.4% female; control group (CG): n = 138, mean age = 46.2 (SD 13.5), 99.3% female) met the primary endpoint. Among IG, 282 participants (85.7%; [83.3%, 88.6%]) were healthy at the initial counseling at the HBOC center compared with 110 participants (79.7%; [73.5%, 84.7%]) in the CG. After adjusting for center effects, the observed odds of healthy counselees were lower in the CG than in the IG (OR = 0.67; 95% CI, 0.28–1.59; p = 0.368). **Conclusions:** The IG showed a higher proportion of healthy individuals at risk for HBOCS. Although not significant, this trend may suggest that supporting primary care physicians with a digital screening platform facilitates early identification of HBOCS within cross-sectoral care pathways. Clinical trial information: DRKS00030371. Research Sponsor: German Federal Joint Committee; 01NVF20002.

Incorporating CA19-9 testing in a prospective study of pancreatic cancer surveillance (PCS) among high-risk individuals (HRIs).

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Background: For individuals at an increased risk of pancreatic cancer (PC), imaging-based PCS is recommended. However, despite PCS among such individuals, when PC is diagnosed, it is found at an advanced stage in over 25% of individuals. Blood-based biomarkers of PC, such as carbohydrate antigen 19-9 (CA19-9) and HbA1c, can be abnormal prior to radiographic findings among individuals with PC. However, it is unknown whether prospective assessment of these biomarkers would allow for earlier detection or interval PC of PC among HRIs undergoing PCS.

Methods: We conducted a single-institution (Dana-Farber Cancer Institute) prospective study of HRIs undergoing imaging-based PCS with annual MRCP and/or EUS (NCT06122896). All participants signed informed consent; the institutional IRB approved the study. CA19-9 was measured at baseline and every 6 months. Individuals with normal imaging but abnormal CA19-9 value underwent additional imaging, and short-interval repeat CA19-9 measurement. Personalized, genotype-adjusted, CA19-9 reference ranges were calculated based on fucosyltransferase (FUT) enzymes FUT3 and FUT2 variant analysis. Herein, we report outcomes from baseline PCS assessment. We measured the specificity of unadjusted and adjusted CA19-9.

Results: 231 HRIs (mean age 62, 71% female, 47% with a previous history of cancer) underwent baseline PCS. 105 HRI (46%) had a pathogenic germline variant (PGV) predisposing to PC and met 2023 NCCN eligibility criteria for PCS surveillance, 77 (33%) HRI had a family history of PC without a predisposing PGV; 49 HRI (21%) had other indications for PCS. 153 (66%) HRIs underwent baseline PCS with MRCP [Table]; the remainder underwent an EUS. No HRIs were diagnosed with PC on baseline imaging. 98 (42%) HRI had pancreatic cyst(s) detected on baseline imaging. All abnormal CA19-9 tests (unadjusted = 5, genotype-adjusted = 1) were considered false positives as additional imaging did not reveal additional pancreatic pathology. The specificity of unadjusted and genotype-adjusted CA19-9 was 97.8% (95% CI: 95.0-99.3) and 99.5% (95% CI 97.3-100). Two individuals with concern for a focal lesion on EUS underwent immediate workup with imaging (n=1) and biopsy (n=1), both with reassuring findings. One individual was found to have a paraganglioma. **Conclusions:** Baseline unadjusted CA19-9 testing led to unnecessary follow-up studies in 2% of HRI undergoing imaging-based PCS. Genotype-adjusted CA19-9 may have superior specificity compared to unadjusted CA19-9. Longitudinal biomarker assessment, including serial CA19-9 and HbA1c, is ongoing. Clinical trial information: NCT06122896. Research Sponsor: The Hale Family Centre for Pancreatic Cancer Research.

Characteristic	n (%)
Baseline imaging	231 (100)
MRCP	153 (66)
EUS	78 (34)
Individuals with cystic lesion(s) detected	98 (42)
Individuals with cyst(s) > 1cm	21 (9)
MPD > 4mm	2 (0.9)
Elevated unadjusted CA19-9 (> 35 U/mL)	5/229 (2.2)
Elevated genotype-adjusted CA19-9	1/205 (0.5)

MPD: main pancreatic duct.

Correlates of patient enrollment in a population-based randomized controlled trial of cascade genetic testing in families with hereditary cancer susceptibility.

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Background: Clinical trials that enroll patients through virtual approaches are growing but there is little information about the impact on access. The Genetic Information and Family Testing (GIFT) study was a population-based cluster RCT that evaluated an online platform that delivered cancer genetic education and home germline testing to families with hereditary cancer susceptibility. We examined correlates of patient enrollment to address potential barriers to trial access. **Methods:** We identified a random sample of adult patients with any cancer type diagnosed in Georgia or California in 2018-19 who linked to a pathogenic variant (PV) in a cancer susceptibility gene through a SEER-based data infrastructure. We initiated a mailed survey four years after diagnosis. We invited all respondents who recalled a PV on testing to enroll online in GIFT. Enrolled patients could invite their first- and second-degree relatives to enroll through the online platform. The primary endpoint was the proportion of relatives who received testing through the platform. We examined clinical and sociodemographic correlates of patient enrollment. **Results:** 4,300 patients were selected and 2,285 completed the survey (53.1%); 2,006 of 2,285 respondents were eligible and invited to GIFT (87.8) and 412 enrolled (20.5). The Table shows clinical and sociodemographic correlates of patient enrollment for the 1,994 with complete data. There were no substantial differences in enrollment by PV grouping, cancer type, sex, or race/ethnic groups. Enrollment was lower in older patients, those with lower education levels, and those living in census tracts with higher poverty levels. **Conclusions:** GIFT successfully enrolled a diverse patient population through a virtual approach. Moderate sociodemographic gradients observed in GIFT motivate strategies to ensure access to clinical trials that use virtual approaches to patient enrollment. Trial Registration: NCT05552664 at clinicaltrials.gov. Research Sponsor: U.S. National Institutes of Health; U01CA254822; American Cancer Society; RSG-20-025-01.

	Patients Enrolled		
	n	%	p
Gene Type with PV			0.601
BRCA1/2 or other breast cancer-related	1,650	22	
Lynch Syndrome or other gastrointestinal (GI)-related	225	23	
Cancer type			0.702
GI	145	20	
Ovary/uterine	86	23	
Female breast	1,234	22	
Prostate	72	24	
Other	407	19	
Sex			0.594
Male	222	20	
Female	1,722	22	
Age			<.001
<45	501	27	
45-64	1,025	22	
65+	414	15	
Education			<.001
HS or less	311	12	
Some college	531	22	
College graduate	527	25	
Graduate degree	499	26	
Race/Ethnicity			0.379
Non-Hispanic White	1,270	22	
Black	180	25	
Asian	164	19	
Hispanic	345	19	
Census Tract Poverty			0.204
>19%	145	19	
10-19%	401	19	
<10%	1,398	23	

Clinical characteristics and risk factors of individuals ineligible for lung cancer screening at a tertiary care center.

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Background: Lung cancer screening (LCS) reduces mortality, yet many individuals with lung cancer do not meet the 2021 USPSTF eligibility criteria. We compared clinical characteristics and risk factors in individuals with lung cancer who were ineligible and eligible for LCS. **Methods:** We conducted a retrospective study of individuals with a new or prior diagnosis of lung cancer at Indiana University Health from April 1, 2025 – December 4, 2025. We recruited individuals during their clinic visits and used electronic medical records and a patient-completed survey to obtain demographic information, smoking history, and lung cancer risk factors at diagnosis (high-risk lung disease/occupation, first-degree family history of lung cancer, autoimmune disease, prior chest-wall radiation). Individuals were stratified using the 2021 USPSTF criteria. Continuous and categorical variables were compared with T-tests and χ^2 /Fisher's exact tests. Logistic regression models were used for multivariate analysis. **Results:** 242 individuals were evaluated and 128 (53%) were ineligible for LCS. The median age was 63 among ineligible individuals, 56% were female, 70% were white, and 25% were black (64, 55%, 80%, and 17% respectively among LCS eligible). These individuals were more likely to have adenocarcinoma (80% vs. 56%, $p<0.001$) and present with stage IV disease compared to those eligible for LCS [51% vs. 26%, adjusted OR 2.13 (95% CI, 1.01 – 4.57), $p=0.048$]. Of note, 24 individuals (19%) were <50 or >80 years old and 46 (36%) were never-smokers; however, tobacco exposure was common (64% ever-smokers, 21% used other tobacco products, 56% secondhand exposure). Most of these individuals had high-risk lung disease (61%), Table. Multivariate analysis adjusting for smoking revealed no association between LCS eligibility and secondhand exposure or high-risk occupation, $p=0.340$ and 0.275 . Interestingly, 1/3 of individuals in both cohorts had a first-degree relative with lung cancer. **Conclusions:** Most individuals with lung cancer in our cohort were ineligible for LCS using the 2021 USPSTF criteria and were more likely to present with metastatic disease. Many had significant tobacco exposure and other risk factors similar to those eligible for LCS. Our findings suggest the current LCS criteria exclude a large at-risk population and should be re-evaluated to account for risk factors beyond age and pack-years. Research Sponsor: Indiana University School of Medicine.

Risk Factor	Ineligible n=128 (%)	Eligible n=114 (%)	p
Ever-smokers (≥ 100 cigarettes)	82 (64.1)	114 (100)	<0.001
Use of Other Tobacco Product	27 (21.1)	47 (41.2)	<0.001
High-Risk Lung Disease (e.g., COPD)	78 (60.9)	95 (83.3)	<0.001
Secondhand Smoking	71 (55.5)	79 (69.3)	0.340*
High-Risk Occupation (e.g., firefighting)	47 (36.7)	58 (50.9)	0.275*
1 st Degree Family History	42 (32.8)	40 (35.1)	0.343
Autoimmune Disease	12 (9.4)	10 (8.8)	1.000
Chest Wall Radiation	11 (8.6)	11 (9.6)	0.951

*Adjusted for smoking.

Disparities in cancer screening across disease sites for transgender and gender-diverse patients.

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Background: Over 2 million Americans identify as transgender, nonbinary, or gender-diverse (TGD) and limited data exist on cancer screening in this population. This study examines uptake rates of recommended breast, cervical, colorectal, and prostate cancer screening in TGD persons and reports factors predictive of screening uptake. **Methods:** A cross-sectional single-institution cohort study was conducted at a tertiary referral center with a specialized LGBTQIA+ Inclusion Health Clinic (IHC). Adult patients self-identifying as TGD with a health-care encounter from January 2023-May 2025 were identified in our Clinical Research Data Warehouse. Demographic, clinical, and screening data for breast, cervical, colorectal, and prostate cancers were collected. The American Cancer Society, National Comprehensive Cancer Network, and UCSF transgender breast cancer screening guidelines were used as standards for screening indications. Multivariable logistic regression was conducted to evaluate factors predictive of guideline-concordant screening uptake. **Results:** We identified 2,478 TGD patients (821 transgender men (TGM), 789 transgender women (TGW), and 868 gender-diverse (GD) patients). Median age was 28 years (range 18-86) and 62% were treated at the IHC. Most patients were White (78.3%) and non-Hispanic (91.1%). Sixty-four percent of patients used private health insurance, 26.2% used government insurance, and 9.2% were uninsured. Average duration of gender-affirming hormone therapy was 4.0 years (IQR 2.0, 6.0), and 31% of patients had received gender-affirming surgery. Fifty-two percent of patients had some family cancer history at any disease site. Rates of guideline-concordant cancer screening uptake are presented in Table 1. On multivariate analyses, GD gender identity (OR 2.55, 95% CI 1.68-3.88, $p<0.001$), age (OR 1.05, 95% CI 1.02-1.08, $p<0.001$), and treatment at the IHC (OR 2.24, 95% CI 1.50-3.40, $p<0.001$) were predictors of cervical cancer screening uptake. No significant predictors were identified of screening uptake for other disease sites. **Conclusions:** Gender-specific medical care is valuable for promoting guideline-concordant cancer screening uptake. Even in a specialized care center, we found poor rates of recommended cancer screening uptake in TGD patients, demonstrating opportunities to improve uptake of gender-specific cancer screening. Research Sponsor: None.

Rates of guideline-concordant cancer screening uptake by disease site and gender identity.					
Disease Site	Overall (n=2,478)	TGW (n=789)	TGM (n=821)	GD (n=868)	p-value
Breast	49.2%	40.8%	38.5%	60.0%	0.12
Cervical	41.3%	NA	31.5%	51.2%	<0.001
Colorectal	43.4%	41.7%	31.0%	51.4%	0.3
Prostate	20.7%	19.6%	NA	26.3%	0.7

Development and validation of a multidimensional cfDNA assay for cancer detection and tissue-of-origin prediction.

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Background: Early detection remains a major unmet need in oncology, and multi-cancer early detection assays that analyze circulating cell-free DNA features have shown promise for detecting multiple cancers with high specificity and tissue-of-origin prediction. Here, we leverage whole-genome sequencing (WGS) to extract multiple cfDNA features (genomic, fragmentomic, and estimated methylation) from a single assay to enable multi-cancer early detection and tissue-of-origin (TOO) localization. **Methods:** Plasma samples were collected in a multicenter, prospective case-control study. From $5\times$ low-pass WGS data, multiple cfDNA feature sets were extracted, including fragmentomic, genomic, and inferred epigenetic features. Machine learning models were trained for cancer detection (healthy vs. cancer) and tissue-of-origin (TOO) classification. The training set included 3,577 healthy and 3,578 cancer participants, and the independent validation set included 2,384 healthy and 2,386 cancer participants. Cancer cases spanned 56 cancer types, grouped into 21 cancer classes. **Results:** Age and sex are evenly distributed across healthy and cancer samples in both the training and validation datasets (Table 1). At 99% specificity, cancer detection sensitivity increased with stage and was consistent between training and validation cohorts: Stage I: 70.66% vs 70.89%, Stage II: 80.41% vs 80.27%, Stage III: 89.89% vs 88.58%, and Stage IV: 92.23% vs 91.76%. Across tumor types, sensitivity at 99% specificity varied substantially, ranging from 57.43% (Thyroid tumor) and 63.87% (Kidney cancer) to 95.96% (Lymphoma) and 99.07% (Liver/Biliary cancer). Tissue-of-origin prediction achieved high accuracy in machine-learning predicted cancer-positive samples (Top-1/Top-2: 0.75/0.89 in training; 0.75/0.88 in validation). **Conclusions:** We developed a cost-efficient blood test (CanScan Pro) using multidimensional cfDNA features from low-pass WGS and machine learning that detects cancers at 99% specificity, with sensitivity increasing by stage and similar performance in training and validation cohorts. The model predicts tissue of origin with high accuracy, which may help guide downstream diagnostic evaluation following a positive result and thereby enhance real-world clinical utility. Research Sponsor: None.

Patient characteristics.

	Train		Valid	
	Healthy (N=3577)	Cancer (N=3578)	Healthy (N=2384)	Cancer (N=2386)
Age				
Mean (SD)	57.8 (6.46)	57.7 (14.74)	58.1 (6.63)	57.2 (15.00)
Median [Min, Max]	57.0 [45.0, 76.0]	60.0 [11.0, 91.0]	57.0 [45.0, 76.0]	59.0 [11.0, 92.0]
Sex				
F	2018 (56.4%)	1655 (46.3%)	1355 (56.8%)	1101 (46.1%)
M	1559 (43.6%)	1923 (53.7%)	1029 (43.2%)	1285 (53.9%)
Stage TNM				
-	3577 (100%)	0 (0%)	2384 (100%)	0 (0%)
I	0 (0%)	1060 (29.6%)	0 (0%)	718 (30.1%)
II	0 (0%)	883 (24.7%)	0 (0%)	588 (24.6%)
III	0 (0%)	811 (22.7%)	0 (0%)	534 (22.4%)
IV	0 (0%)	824 (23.0%)	0 (0%)	546 (22.9%)

Implementation of a multi-cancer early detection (MCEd) test in a private practice: Adoption, performance, and repeat-testing patterns.

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Background: Century City Medical Management (CCMM), a network of private primary care practices, implemented MCEd testing as part of their cancer screening program. The MCEd test detects a cancer signal in cell-free DNA isolated from peripheral blood and predicts the cancer signal origin (CSO). We describe CCMM's MCEd testing workflow and real-world performance.

Methods: MCEd testing is discussed with all CCMM patients as part of routine care, and shared decision-making guides test utilization. Pts with a positive MCEd test result (cancer signal detected) are directed to pursue targeted diagnostic evaluation. This analysis reports on data from 1,949 pts who had 2,922 MCEd tests, with results returned between 11/29/21 and 11/24/25. Diagnostic evaluations and clinical outcomes were collected through a Quality Assurance Program via follow-up with ordering providers. All data were deidentified in accordance with HIPAA using the Expert Determination method. The cancer signal detection rate (CSDR) was defined as the proportion of positive MCEd tests among all tests administered during the first screening round. Among pts with diagnosed cancers and data available, CSO accuracy (top-two predictions) and median time to diagnosis were calculated. Results of MCEd retesting after an inconclusive workup and the frequency of annual MCEd screening were evaluated. **Results:** At the first MCEd test (N = 1,949), median age was 63y (IQR: 55-71), 47.5% were female, and the CSDR was 1.03% (95% CI, 0.63-1.58%; 20/1,949). Across all screening rounds, 24 pts had a positive MCEd result; 16/24 had ≥ 12 mo follow-up at data cutoff. Among these 16, 3 had an active cancer at testing. Of the 13 pts with ≥ 12 mo follow-up and no active cancer at testing, 7 were subsequently diagnosed with cancer. CSO accuracy was 100% (7/7). None of the diagnosed cancers had USPSTF A/B-recommended screening. 1 diagnosis (symptomatic pt) occurred before MCEd results were returned; median time from test results to diagnosis of the other 6 was 62 days (IQR: 30.5-143). 5 pts with an initial positive test but negative CSO-directed workup had an MCEd retest and ≥ 12 -mo follow-up. Among these, 4 pts with a negative retest remained cancer-free through the end of follow-up, and 1 with a positive retest was diagnosed with a cancer matching the initial and retest CSO. Among 996 pts tested with >15 mo of follow-up, 686 (69.6%) received ≥ 2 MCEd screening tests. The most common interval between consecutive tests was annual (9-15mo), with $<10\%$ exceeding an 18-mo interval. **Conclusions:** MCEd testing in a real-world population achieved test performance, CSO accuracy, and diagnostic resolution timelines consistent with prior studies, with high annual screening uptake and clinical utilization of repeat testing after inconclusive CSO-directed workups. The findings support feasible and scalable implementation of MCEd testing in primary care. Research Sponsor: GRAIL, Inc.

Generalizable cancer detection from ultra-low-pass whole-genome sequencing of cell-free DNA using a sequentially fine-tuned transformer framework.

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Background: Ultra-low-pass whole-genome sequencing (ULP-WGS) of cell-free DNA (cfDNA) provides a cost-effective approach for cancer screening, yet its clinical translation is constrained by extreme data sparsity and poor model generalizability, particularly in low-tumor fraction (TF) settings. **Methods:** We developed Fragmentia-AI WGS, a mutation-independent framework that leverages a transformer-based multiple-instance learning architecture with sequential fine-tuning across TF strata to extract latent cancer-associated signals from ULP-WGS data ($\sim 0.02\times$ coverage, $\sim 128k$ reads). Model performance and generalizability were evaluated across multiple independent cohorts, including a pan-cancer test cohort across 17 cancer types, a public online cohort sequenced on a different platform, and an analytical variability assessment cohort comprising samples processed under heterogeneous technical and pre-analytical conditions. Clinical relevance was further examined by associating prediction scores with progression-free survival (PFS) in patients with advanced non-small cell lung cancer receiving immunotherapy. **Results:** Sequential fine-tuning across all TF strata substantially improved performance in low-TF samples compared with high-TF-only training, yielding a 35.6% relative increase in AUC in the low-TF subgroup (from 0.652 to 0.884 in the validation cohort). In the independent test cohort, the model achieved an overall AUC of 0.930 (95% CI: 0.924 – 0.936), with consistently strong performance across TF levels (high TF: 0.984; medium TF: 0.958; low TF: 0.910) and across cancer types. External validation in the public cohort demonstrated robust cross-platform and cross-population generalizability (AUC: 0.929; sensitivity: 0.78; specificity: 0.92). Prediction scores remained stable across heterogeneous experimental conditions, supporting robustness to technical and pre-analytical variability. Notably, lower model prediction scores were independently associated with prolonged PFS (hazard ratio: 0.49, 95% CI: 0.31 – 0.77; $p = 0.002$) after adjusting for sex, age, clinical stage, and histologic subtype. **Conclusions:** Fragmentia-AI WGS enables robust and generalizable cancer detection as well as clinically meaningful risk stratification from ultra-sparse cfDNA sequencing, underscoring its potential for scalable and cost-effective liquid biopsy applications. Research Sponsor: None.

Beyond detection: Five-year screening behaviors and patient-reported perceptions in DETECT-A participants.

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Background: Multi-cancer early detection (MCED) blood testing may improve early cancer detection. The impact of MCED testing on anxiety and standard of care (SoC) cancer screening adherence is not fully understood. Detecting cancers Earlier Through Elective mutation-based blood Collection and Testing (DETECT-A) enrolled 10,006 women aged 65 to 75 years from the Geisinger Health System (GHS) with no previous history of cancer and assessed a single instance of MCED (CancerSEEK) testing in 9,911 subjects. Herein, we report cancer survey results, and SoC screening adherence over a 5-year follow-up period (5YFU). **Methods:** Medical record review and participant surveys administered at prespecified intervals, including approximately 5 years after enrollment, were used to assess patient experience, anxiety, and commitment to SoC screening. Decision regret/participation was assessed using a 5-item, 5-point agreement scale; perceived impact on anxiety, depression, and intention to adhere to SoC screening were assessed using 3-option directional responses (more/less/no change), with a 'prefer not to answer' option. Observed SoC screening adherence was assessed through August 2024. SoC screening eligibility (U.S. Preventive Services Taskforce criteria) and adherence data were available for DETECT-A subjects. Changes in adherence over time were assessed using a mixed effects model. **Results:** 8,114 subjects completed all survey questions. 97.3% expressed no participation regret; 94.8% noted a willingness to participate again. Most participants reported no changes in anxiety (89.4%) or depression (96.6%) levels since enrollment. 98.7% reported an equal or greater likelihood of adhering to SoC screening. SoC screening adherence was assessed for a subset of DETECT-A subjects who had at least one month of active GHS patient status (Breast and CRC) and were also eligible for screening (Lung, Breast, CRC). DETECT-A subject SoC adherence was high at consent (Lung: 28.0%, Breast: 88.4%, CRC: 73.9%) and remained high at one year (Lung: 38.5%, CRC: 82.3%) or two-year (Breast: 87.7%) follow-up post consent. Adherence remained high throughout the follow-up period. **Conclusions:** DETECT-A subjects were satisfied with study participation and reported little change in anxiety and depression. Reported commitment to SoC screening adherence was high and observed adherence to recommended screening modalities was maintained over the follow-up period. In a controlled setting of a prospective clinical trial, MCED testing did not contribute to anxiety or depression and did not interfere with adherence to SoC screening. Research Sponsor: Exact Sciences Corporation.

Evaluation of a novel blood-based lung cancer screening test in elevated-risk subjects.

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Background: Less than 20% of individuals recommended for lung cancer (LC) screening are screened each year by low dose computed tomography (LDCT), highlighting the need for a more acceptable screening modality. Tumor-associated extracellular vesicles and particles (EVPs) are highly abundant in blood and carry surface biomarkers from their tumor cell of origin, providing a readily measurable analyte class for blood-based screening tests. Test sensitivity may be improved by EVP abundance; specificity by simultaneous measurement of multiple co-localized cancer-related markers on a vesicle surface. We report performance of an EVP-based LC Screening Test in plasma samples from elevated risk participants in the National Lung Screening Trial (NLST). **Methods:** The LC Test (biomarkers and classifier) was locked following a training study, after which we validated consistent assay performance in an independent cohort. Here we evaluated the LC Screening Test in a blinded case-control study nested within the ACRIN Biomarker Arm of the NLST. The study included all available incident LC cases for which subject-matched blood samples were available from the year of diagnosis (T) and the year prior (T-1) (n = 48 cases; 96 samples). Controls were age-matched NLST subjects who had no LC detected before or within the trial follow up period (n = 60). LC Test results were determined blinded to case-control status, with unblinding by ECOG-ACRIN. LC Test sensitivity was calculated at a threshold pertaining to 90% specificity, superior to 87% reported specificity for LDCT in NLST (Lung RADS v1.1). LDCT positivity was based on Lung RADS v1.1 interpretation. **Results:** Across two screening encounters (T and T-1), 34.4% sensitivity, similar across stages, was observed for the blood-based LC Screening Test, compared to 39.5% sensitivity for LDCT, p = 0.53 McNemar test, indicating no significant difference in observed sensitivity between LDCT and the blood test. Complementarity in detection was observed between LDCT vs blood-test detected cases across all histologies. A mean 42% increase was observed in LC Screening Test scores from T-1 to T, indicating signal increase may provide additional sensitivity. **Conclusions:** The blood-based LC Screening Test exhibits similar performance to LDCT in detecting preclinical lung cancer in high-risk individuals and detects some LCs not found by LDCT. The data supports further evaluation of the LC Test for LC screening. Research Sponsor: Mercy BioAnalytics.

Histology	Dx Modality	Total Detected	Detected by One Test	Detected by Both	Detected by Neither
Adenocarcinoma	LDCT	37% (17/46)	24% (11/46)	13% (6/46)	44% (20/46)
Adenocarcinoma	Blood Test	33% (15/46)	20% (9/46)	13% (6/46)	44% (20/46)
Squamous	LDCT	42% (10/24)	29% (7/24)	13% (3/24)	50% (12/24)
Squamous	Blood Test	21% (5/24)	8% (2/24)	13% (3/24)	50% (12/24)
Small Cell	LDCT	43% (6/14)	14% (2/14)	29% (4/14)	36% (5/14)
Small Cell	Blood Test	50% (7/14)	21% (3/14)	29% (4/14)	36% (5/14)
Other	LDCT	42% (5/12)	50% (6/12)	17% (2/12)	25% (3/12)
Other	Blood Test	25% (3/12)	33% (4/12)	17% (2/12)	25% (3/12)

Next-generation multi-cancer early detection (MCED) assay: Independent blinded validation of a locked serum multi-omics NMR test with stage I sensitivity.

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Background: Blood-based MCED assays could complement existing screening, but many approaches show reduced sensitivity in early-stage disease. Wholomics developed a serum multi-omics MCED assay integrating metabolomic, lipidomic, and proteomic features quantified by proprietary NMR-based technology, designed to capture systemic biology associated with early tumor development. We report independent, blinded validation of a locked MCED assay developed on multi-center data; across training and validation, the program included >1,400 individuals and >13 cancer types. The full assay pipeline was locked before application to the independent validation cohort. **Methods:** Model development leveraged prior multi-center data (N = 1,211) from five European centers (669 cancers, 65% were stage 0-II; 442 controls plus precancerous/benign cohorts). We evaluated an independent validation cohort (N = 216) with 116 cancers (50% were stage 0-II [stage I n = 40; stage II n = 16]; cancers included colon, rectal, pancreatic, cervical, uterine, bladder, breast, gastric, renal, ovarian) and 100 controls with screening-relevant conditions (e.g., dyslipidemia, prediabetes, benign prostatic hyperplasia, osteoarthritis, etc.). Samples were analyzed with fully prespecified locked assay pipeline (proprietary NMR profiling according to SOP with predefined QC, data preprocessing, biomarker feature set, machine-learning model, and decision threshold) and applied to blinded outcome labels. Primary endpoints were specificity and sensitivity (overall, stage I, stage III-IV). 95% CIs for sensitivity and specificity were calculated using the Wilson score method; AUC 95% CIs were calculated using DeLong's method. **Results:** The locked MCED assay achieved specificity of 99.0% (99/100; 95% CI 94.6–99.8; false-positive rate 1.0%) and overall sensitivity of 93.1% (108/116; 95% CI 87.0–96.5). Stage I sensitivity was 95.0% (38/40; 95% CI 83.5–98.6), Stage III-IV sensitivity remained high in advanced stages at 93.1% (54/58; 95% CI 83.6–97.3). AUC was 0.991 (95% CI 0.979–1). High overall sensitivity was observed across multiple tumor types, including pancreas, stomach, kidney, colon (each 100% overall) and rectum (92.3% overall). **Conclusions:** In an independent blinded validation, a locked serum multi-omics NMR-based MCED approach demonstrated high specificity and high sensitivity, including strong stage I performance, across multiple solid tumors in a screening-relevant case-control setting. These findings support clinical utility for shifting detection toward earlier, more treatable stages and warrant prospective studies to confirm real-world performance and downstream impact. Research Sponsor: Wholomics GmbH.

Precision risk stratification for lung cancer in COPD: Evidence from the All of Us Program.

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Background: Chronic obstructive pulmonary disease (COPD) is a well-established independent risk factor for lung cancer, yet determinants of cancer susceptibility within this high-risk population remain incompletely characterized. Identifying clinical and genomic predictors is essential to improve risk stratification, early detection, and precision prevention strategies. **Methods:** We conducted an age-matched case-control study using de-identified data from the *All of Us* Research Program to evaluate sociodemographic characteristics, comorbidities, and genetic variants associated with lung cancer risk among adults with COPD. Baseline characteristics were summarized using descriptive statistics. Multivariable logistic regression was used to estimate adjusted odds ratios (AORs) controlling for relevant confounders. Genome-wide association studies (GWAS) were performed with rigorous quality control, population stratification adjustment, and correction for multiple testing. **Results:** Among 633,540 participants, 26,570 (4.2%) had COPD, including 2,044 (7.7%) with lung cancer. The mean age was 67.5 ± 11.4 years; 43.4% were male. In multivariable analysis, Asian ancestry was associated with increased lung cancer risk (AOR 2.25, 95% CI 1.55–3.26). Age 66–95 years conferred a 29% higher risk, and family history of lung cancer increased risk by 34% (95% CI 1.15–1.57). Hypothyroidism (AOR 1.58, 95% CI 1.27–1.97) and hyperlipidemia (AOR 1.32, 95% CI 1.04–1.68) were independently associated with lung cancer. GWAS identified 19 variants significantly associated with lung cancer risk, including rs539223166, rs551676206, rs922466204, rs144626313, rs147989022, and rs74502961. **Conclusions:** Distinct clinical and genetic factors contribute to lung cancer susceptibility among individuals with COPD. Integrating these determinants may enhance risk prediction and inform targeted surveillance strategies. Research Sponsor: None.

Impact of AI-based risk stratification integrating routine laboratory data with age on screening volume and multi-cancer early detection yield.

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Background: Early cancer detection improves survival, yet population-wide screening remains costly and logistically challenging. Traditional cancer risk models, such as lifestyle-based assessments and polygenic risk scores, offer limited predictive performance. Routine laboratory tests (complete blood count, urinalysis, and biochemical panels) are performed in primary care and may harbor latent cancer signals. We developed an AI-based cancer risk assessment (CRA) model using routine laboratory data to enrich cancer cases and improve the cost-effectiveness of downstream multi-cancer early detection (MCED) testing. **Methods:** Routine laboratory data from 7,672 individuals (1,245 cancer; 6,427 non-cancer) across two hospitals were retrospectively collected and used to develop a random forest based CRA model incorporating 56 selected routine laboratory features. Among them, 5,392 (70.3%) also underwent OncoSeek test, a validated MCED assay based on seven protein tumor markers (e.g., AFP, CEA). OncoSeek screening performance was estimated under two enrichment strategies: (1) age-based enrichment (≥ 50 years), and (2) risk-stratified enrichment using a joint CRA-age model. A two-dimensional CRA-age risk landscape was used to estimate cancer incidence across strata. Strata with a modeled cancer incidence $\geq 0.57\%$, corresponding to the overall cancer incidence among Chinese adults (GLOBOCAN 2017), were classified as high risk. Performance metrics from both strategies were applied to simulate OncoSeek screening outcomes in a hypothetical cohort of 1,000,000 adults aged ≥ 20 years. **Results:** In the simulated cohort with an overall cancer incidence of 0.57%, direct OncoSeek screening detected 2,450 cancers with a PPV of 5.6%. Age-based screening (≥ 50 years) required screening 536,206 individuals (-46.4%), increased cancer incidence to 0.92%, and detected 2,327 cancers. In contrast, CRA-age risk-stratified screening reduced the screened population to 178,660 individuals (-82.1%), enriched cancer incidence to 2.69%, and detected 2,402 cancers. Compared with age-based screening, CRA-age stratification improved PPV from 7.6% to 15.9%, reduced false positives by 55.2% and lowered the cost per cancer detected from \$18,436 to \$5,950 (-67.7%), while preserving overall cancer detection. **Conclusions:** AI-based CRA-age risk stratification enables efficient population-level cancer screening by restricting downstream MCED testing to a high-risk subset comprising approximately one-fifth of the population, while preserving overall cancer detection. This strategy substantially improves PPV, reduces false positives, and lowers the cost per cancer detected. These findings support a risk-stratified MCED screening paradigm as a scalable and economically sustainable alternative to population-wide or age-based population screening. Research Sponsor: None.

Machine learning–optimized multi-biomarker panel for discriminating lung cancer from LDCT-positive benign pulmonary nodules.

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Background: Accurate discrimination between lung cancer and benign pulmonary nodules remains a critical challenge in lung cancer screening, particularly among individuals with positive findings on low-dose computed tomography (LDCT). Blood-based biomarkers with proven biological relevance may improve risk stratification when integrated with advanced analytical approaches. Serum carcinoembryonic antigen (CEA), serum amyloid A (SAA), and osteopontin (OPN) are biomarkers reflecting tumor burden, host inflammatory response, and tumor microenvironmental activity, respectively. The discriminatory performance of these three biomarkers between healthy individuals and lung cancer patients has previously been validated in a cohort exceeding 2,000 subjects (ASCO 2025, Abstract #489322). Building on this foundation, the present study evaluates whether algorithmic integration of these biomarkers can improve discrimination of lung cancer within the clinically challenging population of LDCT-positive pulmonary nodules. **Methods:** Serum CEA, SAA, and OPN levels were quantified by ELISA in patients with histologically confirmed lung cancer and individuals with LDCT-positive benign pulmonary nodules. To enhance discrimination within this high-risk cohort, machine learning–based modeling was applied. Multiple analytical methods were evaluated, and a Random Forest classifier was selected to capture inter-marker correlations and non-linear biological relationships. The dataset was divided into independent training and validation cohorts. Diagnostic performance was assessed using sensitivity, specificity, and area under the receiver operating characteristic curve (AUC). **Results:** In the LDCT-positive pulmonary nodule population, the machine learning–optimized three-biomarker panel demonstrated strong discriminatory performance. In the validation cohort, the model achieved an AUC of 0.879, with a sensitivity of 88.8% and a specificity of 83.3% for differentiating lung cancer from benign nodules. The algorithm consistently outperformed individual biomarkers and linear models, including in early-stage lung cancer. **Conclusions:** Application of machine learning to a biologically complementary three-protein biomarker panel significantly enhances discrimination of lung cancer within LDCT-positive high-risk pulmonary nodule populations. These findings support the clinical utility of this non-invasive approach as an adjunct to LDCT, addressing a key diagnostic gap in lung cancer screening and management. Research Sponsor: None.

Association of high postoperative physical activity with ctDNA MRD positivity and recurrence-free survival across solid tumors: The SCRUM-MONSTAR LIFELOG study.

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Background: Physical activity is associated with improved survival across multiple cancer types, yet its relationship with molecular residual disease (MRD) detected by circulating tumor DNA (ctDNA) remains unclear. We examined whether objectively measured physical activity correlates with postoperative ctDNA status. **Methods:** The LIFELOG study, ancillary to MONSTAR-SCREEN-3, enrolled patients who underwent curative surgery for solid tumors. Participants wore a wrist-based device targeting 1 month during the early postoperative period. Accelerometer and photoplethysmography data were processed to derive metrics including mean acceleration, moderate-to-vigorous physical activity (MVPA) percentage, longest MVPA bout, and high-intensity heart rate zone percentage. K-means clustering (k=3) classified patients into activity phenotypes. ctDNA was assessed serially using an ultra-sensitive whole-genome sequencing-based MRD assay (Myriad Genetics). ctDNA positivity at 1 and 3 months postoperatively were compared between activity phenotypes, with overlap weighting used to adjust for potential confounders. **Results:** Of 127 enrolled patients, 4 were excluded due to no device data, leaving 123 for analysis. Adequate wear time (≥ 10 hours/day on ≥ 3 days/week) was achieved in 113 patients (91.9%). Cancer types included colorectal (n=29), urothelial (n=24), hepatocellular (n=13), gastric (n=11), renal (n=11), and others (n=35). Median age was 70.1 years; 57.7% were male; 46.3% had stage III-IV disease. Clustering identified three phenotypes: Cluster 1 (high activity; n=10), Cluster 2 (moderate; n=53), and Cluster 3 (low; n=60). Activity metrics differed across clusters (any $P < 0.001$). Cluster 3 had significantly inferior recurrence-free survival compared with Clusters 1+2 (hazard ratio 4.01; 95% confidence interval, 1.10-14.6; $P = 0.035$). Postoperative ctDNA positivity was significantly higher in Cluster 3 compared with Clusters 1+2 at both 1 month (32.5% vs 6.4%; $P = 0.002$) and 3 months (30.0% vs 2.4%; $P < 0.001$). At 3 months, this difference persisted after adjustment for age, sex, adjuvant chemotherapy, stage, and cancer type ($P = 0.003$). Among 80 patients with evaluable ctDNA data at both 1 and 3 months, of 15 patients who were ctDNA-positive at 1 month; conversion to ctDNA-negative at 3 months was observed in 66.7% in Clusters 1+2 versus 16.7% in Cluster 3 ($P = 0.15$). Of 65 patients who were ctDNA-negative at 1 month; conversion to ctDNA-positive at 3 months was observed in 0% in Clusters 1+2 versus 7.7% in Cluster 3 ($P = 0.16$). **Conclusions:** Lower objectively measured physical activity was associated with higher postoperative ctDNA positivity rates and inferior recurrence-free survival. These findings warrant validation in larger cohorts and investigation of exercise-based interventions in postoperative cancer care. Research Sponsor: Japan Agency for Medical Research and Development (AMED); JP25ck0106950h0002; National Cancer Center Research and Development Fund; 2024-A-05.

The PROFOUND study: A large-scale prospective multicenter case-control trial of a multi-cancer early detection (MCED) test in China.

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Background: Early cancer detection reduces morbidity and mortality, but current recommended screening in China misses many lethal cancers. Emerging liquid biopsy-based MCED tests have the potential to increase the number of screen-detected cancers when added to recommended screening. In this study, we evaluate the performance of a MCED test tailored to 16 cancer types covering 85% of China's total cancer incidence, including malignancies without recommended screening tests in the large-scale, prospective, multicenter case-control PROFOUND study. **Methods:** A total of 10,541 participants from over 50 sites nationwide were enrolled, with the cohort comprised by a training set (7,487 participants: 4,448 cancer, 3,039 non-cancer) and a test set (3,054 participants: 1,740 cancer, 1,314 non-cancer). It included 16 major cancer types encompassing diverse pathological subtypes, with stage I-III cases accounting for 83.31% of all cancer samples. All cancer cases were confirmed via pathological diagnosis. Blood samples underwent targeted methylation profiling and were analyzed with the Genie-ADLA AI algorithm to train, validate and independently verify the MCED assay, as well as assess its clinical performance (sensitivity, specificity, tissue-of-origin [TOO] prediction accuracy). **Results:** In the validation set, specificity was 99.03% (95% CI: 98.27%–99.51%), overall sensitivity was 70.63% (95% CI: 67.23%–71.67%) and sensitivity for stage I–III cancers was 66.03% (95% CI: 63.53%–68.46%). The overall TOO prediction accuracy reached 85.21% (95% CI: 83.05%–87.20%). For the five highest-mortality cancers (liver, colorectal, esophageal, gastric and lung cancer), sensitivities were 87.85%, 90.48%, 83.78%, 72.85% and 69.54% respectively. Sensitivities of lung adenocarcinoma and non-adenocarcinoma were 48.75% and 92.96%, respectively. Among them, non-adenocarcinoma is more likely to be missed in recommended screening tests. For cancers without recommended screening (pancreatic, ovarian, gallbladder cancer, lymphoma), sensitivities reached 64.75%, 87.88%, 100% and 74.72%, respectively. **Conclusions:** Powered by the Genie-ADLA AI algorithm, the PROFOUND study's MCED assay demonstrated robust performance including high sensitivity, specificity and TOO prediction accuracy for 16 cancer types (including cancers do not have recommended screening). It may serve as a complementary tool to augment recommended screening and revolutionize early cancer detection paradigms. A prospective interventional clinical study covering 16 cancer types will be launched to further validate MCED's clinical effectiveness. Clinical trial information: NCT06217900. Research Sponsor: Shanghai Xiaohu Medical Laboratory Co. Ltd.

Prospective evaluation of the psychological impact of multicancer early detection (MCED) blood testing: A smartphone-based patient-reported outcomes study.

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Background: Earlier detection may reduce cancer mortality by reducing the number of cancers diagnosed at advanced stages. Prospective data evaluating the emotional impact of MCED testing are limited, particularly when paired with digital engagement tools. Smartphone-based applications offer an opportunity to monitor patient-reported distress in real time and provide scalable support throughout the testing journey. The Falcon registry is a large prospective study evaluating the Exact Sciences MCED test in clinically cancer-free individuals that included evaluation of patient reported outcomes (PRO) using digital tools. **Methods:** Falcon (NCT06589310) is a multi-site registry enrolling up to 25,000 participants, 50-80 years of age. Participants receive the MCED test annually for 3 years and complete PRO measures, including the Generalized Anxiety Disorder-7 (GAD-7) assessment. The assessment is administered via the myBSWHealth digital platform at baseline (T₀), ≤ 14 days of receiving test results (T₁), and at approximately 6 months (T₂). Reminders encouraged timely survey completion, and adaptive content was delivered based on distress scores. GAD-7 scores are categorized for clinical interpretation of anxiety: 0-4 minimal, 5-9 mild, 10-14 moderate, 15-21 severe. Clinically meaningful changes ($\pm > 4$) in anxiety severity at T₀-T₁ and T₀-T₂ were assessed. **Results:** 8,977/9,204 (97.5%) enrolled participants from 08/2024-01/2026 across the Baylor Scott & White Health System have an activated MyBSWHealth account. 4125 had the potential for 6-month follow-up at data analysis; 2729 (66.1%) completed ≥ 1 GAD-7 and 2161 (52.4%) had a T₀ score. Most participants (94.9%) had minimal to mild anxiety at T₀; however, a subset of participants (5.1%) demonstrated moderate to severe anxiety prior to testing. Overall, GAD-7 scores stayed within the minimal anxiety range over time with medians (interquartile ranges) of 1.00 (4.00), 0.00 (3.00) and 1.00 (4.00) at T₀, T₁ and T₂, respectively. Among the 1219 participants who completed the GAD-7 at both T₀ and T₁, 86% had no clinically meaningful change in anxiety severity, 7% had a decrease, and 6% had an increase. Among the 989 participants who completed the GAD-7 at both T₀ and T₂, 85% had no change, 7% had a decrease, and 8% had an increase. **Conclusions:** Digital assessment of anxiety during MCED blood testing gives real-time data on the effects of cancer screening in an average risk population. Despite concerns about the potential for population-based cancer screening to increase anxiety, our preliminary findings suggest low levels of anxiety that remain stable in the majority of participants who completed follow-up assessments after receiving an MCED test result. Additional data for anxiety and distress using the Post-Traumatic Stress Disorder (PTSD) Checklist for DSM-5 (PCL-5) will be presented. Clinical trial information: NCT06589310. Research Sponsor: Exact Sciences Corporation.

Performance of a cfDNA methylation–based MCED test in patients with clinicoradiologic suspicion of cancer.

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Background: Radiographic findings concerning for malignancy frequently prompt extensive diagnostic evaluations that fail to yield a definitive diagnosis, resulting in delayed treatment, persistent uncertainty, and unnecessary interventions. Multi-cancer early detection (MCED) tests based on circulating cell-free DNA (cfDNA) methylation have demonstrated high specificity in asymptomatic screening populations; however, performance in individuals with clinical suspicion of malignancy remains unclear. We compared the performance of a cfDNA methylation–based MCED test in asymptomatic participants and in participants with imaging–based suspicion of malignancy. **Methods:** Adults aged 45–79 years enrolled in CORE-HH (NCT05435066) were evaluated in (1) a case–control cohort ($n = 4,137$) comprising asymptomatic participants who reported no history of cancer ($n = 2,523$) and newly diagnosed cancer participants ($n = 1,614$); and (2) a prospective cohort ($n = 209$) of individuals with imaging–based suspicion of malignancy undergoing clinical evaluation (cancer confirmed, $n = 155$; no cancer, $n = 54$). Cancer types included lung, breast, colorectal, prostate, pancreatic/hepatobiliary, head and neck, gynecologic, and hematologic malignancies. Samples were analyzed using a cfDNA methylation–based MCED test incorporating an AI/ML model, at a pre-specified specificity of 98.5%. Test performance was compared between cohorts among non-cancer participants and among early-stage (stage I–II) and late-stage (stage III–IV) cancer cases using Fisher’s exact test (two-sided). **Results:** Among non-cancer participants ($n = 2,577$), empirical specificity was 98.1% (53/54) in the clinical suspicion cohort and 98.5% (2,485/2,523) in the asymptomatic case–control cohort (OR, 1.23; 95% CI, 0.03–7.6; $p = 0.56$). Overall sensitivity was 54.8% (85/155) in the clinical suspicion cohort and 53.9% (870/1,614) in newly diagnosed cancer cases from the case–control cohort (OR, 1.04; 95% CI, 0.74–1.47; $p = 0.87$). Stage I–II sensitivity was 27.7% (18/65) vs 28.7% (204/711) ($p = 1.00$), and stage III–IV sensitivity was 82.9% (58/70) vs 81.5% (573/703) ($p = 0.87$), for the clinical suspicion and case–control cohorts, respectively. Overall cancer stage distribution was similar between cohorts ($p = 0.89$). **Conclusions:** At the prespecified 98.5% specificity threshold, the cfDNA methylation–based MCED test demonstrated comparable specificity and sensitivity in prospectively enrolled participants undergoing evaluation for imaging–based suspicion of malignancy and in a case–control cohort of newly diagnosed cancer cases versus asymptomatic controls. Recognizing the tendency of case–control designs to overestimate test performance, these results describe MCED test performance in a cohort with clinical suspicion of malignancy, extending characterization beyond asymptomatic screening populations. Clinical trial information: NCT05435066. Research Sponsor: None.

A phase II open-label, single-arm study to evaluate the efficacy of pembrolizumab for leukoplakia.

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Background: Oral leukoplakia and erythroleukoplakia represent high-risk premalignant lesions of the oral cavity, with malignant transformation to head and neck squamous cell carcinoma reported in up to 36% of cases. Therapies are limited, with surgical resection remaining the standard of care despite high recurrence rates. Immune checkpoint inhibitors (ICIs) have emerged as a potential preventive strategy. We evaluated whether the efficacy of the PD-1 inhibitor pembrolizumab may serve as a preventive strategy to reduce progression to invasive carcinoma in patients (pts) with these premalignant lesions. **Methods:** This non-randomized, open-label, multi-center phase II clinical trial enrolled pts between June 2019 and December 2025. Eligible pts had oral leukoplakia, erythroleukoplakia, or proliferative verrucous leukoplakia with moderate dysplasia, severe dysplasia, or carcinoma in situ. Patients with previously treated squamous cell carcinoma (SCC) were included. Pts received pembrolizumab 200 mg intravenously every 3 weeks for 6 months. The primary endpoint was clinical response at 6 months, defined as the proportion of patients achieving a complete response (CR) or partial response (PR). CR was defined as complete lesion resolution on visual inspection sustained for ≥ 4 weeks. PR was defined as a $\geq 50\%$ reduction in the product of the two largest perpendicular dimensions of a single lesion or the sum of all measurable lesions. The secondary objectives included clinical response rate at 9 and 12 months, and toxicity. **Results:** Sixteen pts received at least one dose of pembrolizumab. The median age was 63.5 years (range, 33–82), and 44% were female. Three patients had previously treated SCC. Baseline pathology demonstrated moderate dysplasia in 31% and severe or high-grade dysplasia in 69% of patients. At 6 months, the clinical response rate was 44% (7/16; 95% CI, 23–67%), including CR in 19% (3/16) and PR in 25% (4/16) of pts. Progressive disease occurred in 38% (6/16) of patients. Clinical response rates were 31% at 9 months (5/16) and 19% at 12 months (3/16). Median follow-up was 9 months. Treatment-related adverse events (TRAE) occurred in 69% of pts, most commonly fatigue (31%), mucositis/oral discomfort (31%), hypothyroidism (25%), and gastrointestinal immune-related events, including diarrhea or colitis (25%). Grade ≥ 3 treatment-related adverse events occurred in 19%, with no grade 4–5 events or treatment-related deaths. One pt discontinued due to TRAE. **Conclusions:** These findings suggest that PD-1 blockade may represent a feasible preventive approach for high-risk oral premalignant lesions and warrants further investigation as a preventive option. Biomarker evaluation of pre-treatment and on-treatment biopsies are ongoing to inform predictors of response. Clinical trial information: NCT03603223. Research Sponsor: Merck.

Risk prediction models for familial breast cancer: A Cochrane systematic review and meta-analysis.

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Background: Women with a family history of breast cancer (BC) have an increased risk of developing the disease. Several BC risk prediction models are used in clinical practice to estimate future BC risk, however, their comparative performance in women with a family history of BC is uncertain. The aim of this study was to systematically identify, describe, and critically appraise BC risk prediction models developed or validated in women with a family history of BC, and to synthesize their performance in predicting BC occurrence in this population. **Methods:** We searched MEDLINE, Embase, CINAHL, and ISI Web of Science up to February 2022, with a targeted MEDLINE update to 19 December 2024. We included studies that developed or externally validated BC risk prediction models in women with a family history of BC, provided family history was included as a predictor. Data were extracted using the CHARMS checklist, and risk of bias was assessed using PROBAST. Where data from more than three validation studies were available, random-effects meta-analyses of calibration (observed/expected [O/E] ratios) and discrimination (c-statistic) were conducted. **Results:** Forty-five studies were included. Twelve models were externally validated in the target population; four were validated more than three times and included in meta-analyses. Reporting quality was variable, and most studies had high or unclear risk of bias. The Gail (BCRAT) model was well calibrated (pooled O/E 1.06, 95% CI 0.91–1.25) but showed modest discrimination (c-statistic 0.61, 95% CI 0.57–0.66). BOADICEA was also well calibrated (O/E 0.98, 95% CI 0.90–1.17) with modest discrimination (c-statistic 0.65, 95% CI 0.58–0.71). Tyrer-Cuzick (IBIS) overpredicted risk (O/E 0.86, 95% CI 0.74–0.98), while BRCAPRO underpredicted risk (O/E 1.44, 95% CI 1.25–1.62). Discriminatory accuracy was similar across Tyrer-Cuzick v8, BOADICEA, and BRCAPRO, with pooled c-statistics of 0.64 (0.58 to 0.71), 0.65 (0.58 to 0.71), 0.64 (0.54 to 0.73) respectively and slightly higher than Gail (pooled c-statistic 0.61 (0.57 to 0.66)). **Conclusions:** In women with a family history of BC, Gail and BOADICEA are well calibrated, while Tyrer-Cuzick overpredicts and BRCAPRO underpredicts risk. No model demonstrated clearly superior discrimination. Considering both calibration and discrimination, BOADICEA may be useful for clinical risk assessment in this population, although conclusions are limited by study heterogeneity, small numbers of validation studies in the target population, and high or unclear risk of bias. Improved model performance and reporting are needed. This abstract is based on a post-peer review version of a Cochrane Review. Upon acceptance, the final version is expected to be published in the Cochrane Database of Systematic Reviews (www.thecochranelibrary.com). Research Sponsor: Health Research Board.

Evaluating the impact of the 2021 USPSTF age expansion (50–54 years) on racial disparities in early-stage lung cancer diagnosis.

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Background: In 2021, the USPSTF updated its guidelines to address known racial disparities in lung cancer outcomes. By lowering the screening age to 50 and reducing the pack-year threshold, one of the goals was to better identify Black individuals, who historically develop cancer at younger ages and with lower smoking intensity than their White counterparts. However, despite this expanded eligibility, screening uptake among the newly eligible 50–54 years cohort remains low. Our study evaluates whether these policy changes have translated into a tangible 'stage shift' toward earlier detection among the newly eligible age group and assesses if these benefits are being realized equitably across racial groups. **Methods:** We conducted a retrospective cohort study using SEER November 2024 sub data (21 Registries) for non-small cell lung cancer (NSCLC) cases. We compared the Pre-Guideline (2016–2019) period to the Post-Guideline (2022) period, excluding initial COVID-19 and transition years (2020–2021). A Difference-in-Differences (DiD) approach compared the newly eligible Target Group (50–54 years) against a Control Group (45–49 years) to control for secular staging trends. The primary outcome was the percentage of localized disease at diagnosis, stratified by race. **Results:** In the newly eligible 50–54 cohort, White patients demonstrated a robust stage shift, with localized disease increasing from 23.2% to 28.7% ($p<0.001$). Conversely, Black patients in the target age group experienced a decline in localized detection from 20.1% to 17.5%, with a concurrent rise in distant-stage diagnoses. Notably, Black patients in the younger control group (45–49) showed improved early detection (+3.3%), suggesting the disparity was specific to the guideline implementation in the target cohort. The DiD interaction was significant ($p<0.05$), confirming racially distinct outcomes. Hispanic patients saw a case volume surge without a significant rise in localized disease (22.3% to 22.6%). **Conclusions:** Initial data following the 2021 USPSTF expansion suggests an early stage shift for White patients aged 50–54, while a similar trend was not observed among Black patients in this first year of implementation. This divergence may reflect a temporary implementation lag, variability in provider adoption, or early access delays rather than a definitive failure of the policy. Continued longitudinal surveillance is required to determine whether this gap represents a transient uptake issue or a persistent disparity necessitating targeted structural interventions. Research Sponsor: None.

Impact of age expansion on early detection (% localized disease).				
Group	Race	Pre-Guideline (2016-19)	Post-Guideline (2022)	Net Change
Target (50-54 years)	White	23.22%	28.65%	+5.43%
	Black	20.14%	17.53%	-2.61%
	Hispanic	22.33%	22.58%	+0.25%
Control (45-49 years)	White	21.20%	22.44%	+1.24%
	Black	17.79%	21.09%	+3.30%

Evaluation of a novel blood-based lung nodule triage test in elevated-risk subjects.

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Background: In the National Lung Screening Trial (NLST), 4,354 (6%) of LDCT scans were positive with Lung RADS scores of 3 or 4A, and 162 lung cancers (LCs) were diagnosed within one year of the associated scan. Despite the elevated risk of malignancy, referral for immediate diagnostic (Dx) workup is not recommended; as a result, diagnosis is delayed by an average of 106 days compared with subjects assigned a Lung-RADS 4B or 4X score, who are referred for immediate Dx workup. This delay highlights the need for methods to further risk stratify these subjects and enable more timely evaluation. Tumor-associated extracellular vesicles and particles (EVPs) are highly abundant in blood and carry surface biomarkers from their tumor cell of origin, providing a readily measurable analyte class. We report performance of an EVP-based Lung Nodule Triage Test in detecting LC as a function of Lung RADS score in plasma samples from NLST subjects. **Methods:** The Triage Test (biomarkers and classifier) was locked following a training study. Here we evaluated the Triage Test in a blinded case-control study nested within the ACRIN Biomarker Arm of the NLST. The study included LC cases diagnosed within 24 months of blood draw (n = 51 cases; 99 samples), including longitudinal samples from 48 subjects. Controls were age-matched NLST subjects who had no LC detected before or within the trial follow up period with Lung RADS v1.1 scores of 1 or 2 (n = 60). Triage Test results were determined blinded to case-control status, with unblinding done by ECOG-ACRIN. A static threshold set to 90% specificity was applied to Triage Test scores. **Results:** Among the 99 samples with a diagnosis of LC within 24 months of blood draw, the Triage Test exhibited 34% sensitivity for detection of LC. The Triage Test exhibited 43% sensitivity in samples associated with LDCT-positive screen results not recommended for immediate Dx workup. The projected positive predictive value (PPV) for the Triage Test applied as a reflex test for individuals with Lung RADS 3 and 4A is 13.8% (95% CI: 5.7% - 30.5%, bootstrapping test sensitivity and specificity). **Conclusions:** The blood-based Lung Nodule Triage Test exhibits clinically meaningful performance for detection of LC among subjects with LDCT Lung RADS 3 and 4A scores. The data supports further evaluation of the Triage Test for reflex testing of indeterminate lung nodules. Research Sponsor: Mercy BioAnalytics.

	Lung RADS Score	1	2	3	4A	4B/X	3+4A	Total
NLST LDCT Arm	# LDCT Screens	39,840	28,674	2,282	2,072	1,898	4,354	74,766
NLST LDCT Arm	# LC Dx Within 12M of Screen	26	100	32	130	428	162	716
NLST LDCT Arm	LC Prevalence	0.07%	0.3%	1.4%	6.3%	22.6%	3.7%	1.0%
NLST LDCT Arm	Avg. Days to Dx vs Lung RADS 4B/X	93	101	128	84	n/a	106	n/a
Present Study	# Cases	23	37	5	9	25	14	99
Modeled Implications of Reflex Testing	Triage Test Sensitivity	30% (7/23)	32% (12/37)	60% (3/5)	33% (3/9)	36% (9/25)	43% (6/14)	34% (34/99)
Modeled Implications of Reflex Testing	# True Positive Workups	8	32	19	43	154	69	246
Modeled Implications of Reflex Testing	# False Positive Workups	3984	2867	228	207	n/a	435	7287
Modeled Implications of Reflex Testing	PPV	0.2%	1.1%	7.8%	17.3%	n/a	13.8%	3.3%

GLP-1 therapy and hormone receptor–positive breast cancer risk and survival: A real-world analysis.

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Background: Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are increasingly used for weight management and cardiometabolic risk (CMR) reduction, yet their association with breast cancer (BC) incidence and survival in non-diabetic women with elevated BMI remains unclear. We evaluated the relationship between GLP-1 RA exposure and incident BC, as well as overall survival (OS), in a large real-world (RW) cohort of women without laboratory-defined diabetes. **Methods:** We conducted a retrospective cohort study using the TriNetX US Collaborative Network including female patients (pts) with BMI 25–35 kg/m². Age <50 vs ≥50 years served as proxies for pre- and postmenopausal status, with a ≥50 sensitivity analysis to assess age/menopause confounding. Pts with HbA1c ≥6.5% or prior BC were excluded. Cohorts were propensity score matched (PSM) on age at index, BMI, metformin and statin exposure, BRCA mutation status, hormonal contraceptive use, parity, breastfeeding history, and smoking status. The primary endpoint was incident HR+/HER2– BC, summarized as incidence proportion and risk reduction estimates; secondary analyses evaluated HR+/HER2+, HR–/HER2+, and triple-negative breast cancer (TNBC). OS was evaluated using Kaplan–Meier and Cox regression. **Results:** After PSM, 148,709 pts were included (mean age 45.8 ± 9.54 years in both cohorts). Over a median 36-month follow-up, incident HR+/HER2– BC was lower with GLP-1 RA vs controls (0.29% vs 0.33%), with an absolute difference –0.04% (95% CI –0.081 to –0.001%; P=0.046) and RR 0.88 (95% CI 0.77–0.99). OS was improved with GLP-1 RA vs controls (HR 0.75, 95% CI 0.65–0.86; P<0.0001). No difference in BC incidence was found for HR+/HER2+ (RR 0.98, 95% CI 0.86–1.12) or HR– subtypes, including HR–/HER2+ BC (RR 0.83, 95% CI 0.55–1.23) and TNBC (RR 0.68, 95% CI 0.41–1.12). Findings for HR+/HER2– were consistent across menopausal strata (Table). In the postmenopausal cohort (n=91,577; mean age 63.3 ± 6.88 vs 62.4 ± 6.52 years), GLP-1 RA exposure was also associated with lower incidence of HR+/HER2– BC (RR 0.93, 95% CI 0.86–0.99) and improved OS (HR 0.87, 95% CI 0.81–0.94; P=0.0003). **Conclusions:** In a large non-diabetic cohort of women with BMI 25–35 kg/m² and no prior BC, GLP-1 RA exposure was associated with a modest reduction in incident HR+/HER2– BC and improved OS. Despite limited follow-up and age-based menopausal proxies, these findings provide RW evidence supporting prospective validation with standardized exposure definitions and longer follow-up. Future studies should clarify whether GLP-1 RAs confer direct antitumor effects or indirect benefits mediated through weight loss and CMR reduction and identify pts most likely to derive BC risk and survival benefit. Research Sponsor: None.

GLP-1 RA and HR+/HER2– BC outcomes.		
	RR (Breast Cancer Incidence)	HR (Overall Survival)
Age <50	0.88 (0.77–0.99)	0.75 (0.65–0.86)
Age ≥50	0.93 (0.86–0.99)	0.87 (0.81–0.94)

Evaluation of intervention strategies to improve follow-up after FIT/FOBT tests: A systematic review and meta-analysis.

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Background: Colorectal cancer (CRC) is the third most common cancer worldwide, with the majority of patients diagnosed at advanced stages. Early detection through screenings has been shown to improve morbidity and mortality. However, follow-up after Fecal Immunochemical Test (FIT) / Fecal Occult Blood Test (FOBT) screenings remains low, with 30%–61% compliance to colonoscopy screening and 28–49% compliance to repeat FIT/FOBT surveillance. Our study aims to evaluate 1) interventions targeting colonoscopy completion post-positive FIT/FOBT and improving adherence to follow-up after negative FIT/FOBT, and 2) the rate of colonoscopy completion post-positive FIT/FOBT and the rate of repeat FIT/FOBT adherence after a negative result. **Methods:** We searched MEDLINE, Embase, and Cochrane from inception to December 20, 2025, to identify cohort studies or randomized controlled trials (RCTs) comparing interventions to improve follow-up colonoscopy after positive FIT/FOBT and repeat FIT/FOBT after negative FIT/FOBT. We computed risk ratios (RR) with accompanying 95% confidence Intervals (CIs) for each study and pooled the results using a random-effects meta-analysis. **Results:** Twenty-seven studies involving 30,974 patients were included. 19 studies (11,905 patients) evaluated interventions to improve colonoscopy completion after a positive FIT/FOBT. Patient-level interventions (RR 1.30, 95% CI 1.17–1.44, n=13) and system-level interventions (RR 1.45, 95% CI 1.20–1.77, n=6) significantly increased colonoscopy completion. Patient navigation (RR 1.28, 95% CI 1.15–1.41), patient reminders (RR 1.32, 95% CI 1.04–1.67), and provider reminders (RR 1.45, 95% CI 1.16–1.83) were effective. Patient reminders via messaging (RR 1.55, 95% CI 1.31–1.83) were more effective than calling (RR 1.10, 95% CI 0.91–1.33, p=0.0083). Follow-up colonoscopy increased from 45.8% in controls to 65.9% after interventions. 8 studies (19,069 patients) assessed repeat FIT/FOBT adherence after a negative result. Patient navigation (RR 1.89, 95% CI 1.36–2.63) and patient reminders (RR 1.31, 95% CI 1.01–1.71) significantly improved adherence, increasing rates from 46.0% in controls to 66.5% after interventions. Based on our findings, we developed a protocol to improve colonoscopy completion post-positive FIT/FOBT and adherence to follow-up after negative FIT/FOBT. **Conclusions:** Patient-level and system-level interventions improve adherence to follow-up colonoscopy post FIT/FOBT. Patient navigation and patient reminders increase completion of follow-up colonoscopy and adherence to follow-up FIT/FOBT. Healthcare systems should adopt patient-level and system-level interventions to enhance compliance with follow-up after initial FIT/FOBT testing. Research Sponsor: None.

Contemporary trends in early-stage non-small cell lung cancer diagnosis and disparities, 2018–2022.

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Background: Early detection of non-small cell lung cancer (NSCLC) improves survival. We evaluated stage trends in adults aged 50-80 with NSCLC in SEER 2018-2022 after the 2021 screening expansion and the COVID-19 pandemic. **Methods:** We included 112,183 SEER cases aged 50-80 with primary NSCLC from 2018-2022. Histology was classified as adenocarcinoma, squamous, large cell or other/unknown. Stage at diagnosis was categorized as early (0-II) versus late (III-IV). Early-stage proportions were calculated by year, sex, race, age, income quartile, rurality and histology. Trends were tested using the Cochran–Armitage test. Multivariable logistic regression evaluated associations with early-stage diagnosis. To adjust for changing eligibility, NHIS 2018-2022 data were used to estimate screening-eligible shares by age-sex-race strata and standardize stage distributions. **Results:** Among 112,183 patients (median age 69; 56% male), 39,023 (34.9%) were early stage. Early-stage diagnoses increased modestly from 34.4% in 2018 to 35.6% in 2022, with a dip to 33.8% in 2020 (Table 1). Women had higher early-stage rates (~38%) than men (~32%), and White patients had higher rates (~37%) than Black or American Indian/Alaska Native patients (~29%). Logistic regression showed male sex (OR 0.78) and non-adenocarcinoma histology (ORs 0.16-0.25) were associated with lower odds of early detection; income quartile and rurality were not significant. Eligibility-standardized analyses produced similar trends, suggesting limited impact of the 2021 screening expansion to date. **Conclusions:** Between 2018 and 2022, early-stage NSCLC detection in SEER improved only slightly. Sex and racial disparities persisted. Enhanced outreach, particularly to men and racial/ethnic minorities, and broader low-dose computed tomography implementation are needed to accelerate stage migration. Research Sponsor: None.

Early-stage NSCLC diagnoses by year (ages 50–80).

Year	Total cases	Early-stage cases	Early-stage proportion*
2018	23,482	8,069	34.36%
2019	24,061	8,427	35.02%
2020	20,633	6,965	33.76%
2021	22,099	7,772	35.17%
2022	21,908	7,790	35.56%

*The Cochran–Armitage test indicated a statistically significant upward trend ($p < 0.05$), but the absolute increase was modest.

Oncoseek 2.0: An updated blood-based assay for multi-cancer early detection.

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Background: Early identification of cancer remains essential for improving survival and reducing downstream treatment costs, yet effective and scalable multi-cancer screening strategies are still limited. OncoSeek is a previously validated, AI-based multi-cancer early detection (MCED) assay integrating protein tumor markers (PTMs) with clinical data, demonstrating 58.4% sensitivity, 92.0% specificity, and 70.6% tissue-of-origin accuracy in > 15,000 participants. To improve detection of specific cancer types and expand cancer-type coverage, we developed OncoSeek 2.0 by incorporating three additional PTMs and evaluated its performance in validation cohort. **Methods:** OncoSeek 2.0 retained the original machine-learning framework of OncoSeek 1.0, with expanded PTM inputs (ProGRP, SCCA, and tPSA). Performance was evaluated in a retrospective validation cohort comprising 1,267 cancer and 355 non-cancer individuals. Overall performance, including cancer-type-specific sensitivity, was assessed and compared with OncoSeek 1.0. **Results:** OncoSeek 2.0 incorporated three additional PTMs (ProGRP, SCCA, and tPSA) to enhance cancer-type-specific detection. ProGRP levels were significantly elevated in small cell lung cancer compared with other cancers and healthy controls; SCCA concentrations were higher in squamous cell carcinomas (esophageal, cervical, and lung) than in non-squamous cancers and controls; and tPSA was selectively increased in prostate cancer (all $P < 0.0001$). Compared with OncoSeek 1.0, OncoSeek 2.0 achieved a higher AUC (0.917 vs 0.860) and improved sensitivity from 65.3% to 77.6% at 90.1% specificity across 15 pre-specified cancer types collectively accounting for 76.5% of global cancer mortality. Sensitivity gains were notable in lung (75.1% → 84.3%), prostate (58.8% → 88.2%), cervical (55.6% → 65.6%), and esophageal (39.6% → 62.4%) cancers. When stratified by tumor stage, OncoSeek 2.0 achieved sensitivities of 54.2% for stage I, 71.7% for stage II, 79.8% for stage III, and 88.4% for stage IV, consistently outperforming OncoSeek 1.0, which achieved sensitivities of 30.2%, 53.8%, 62.3%, and 85.7% for stages I through IV, respectively. **Conclusions:** By integrating three additional cancer-type-specific PTMs, OncoSeek 2.0 substantially improves sensitivity while maintaining high specificity and low reagent cost (~\$30 per test). The upgraded assay enhances detection across multiple tumor types and disease stages, with particularly pronounced gains in lung, prostate, cervical, and esophageal cancers. These results support OncoSeek 2.0 as a scalable and clinically actionable MCED approach for population-level early detection, particularly for cancers lacking USPSTF-recommended screening and in low- and middle-income countries. Research Sponsor: None.

A Korea–USA multicenter study of duodenal pancreatic fluid–derived exosomal CES1 and MAN2A1 as pancreas-proximal biomarkers for early pancreatic cancer detection.

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Background: Small pancreatic lesions often yield limited tissue via endoscopic ultrasound (EUS)-guided biopsy, and serum CA19-9 provides poor discrimination in high-risk settings. Duodenal pancreatic fluid (DPF), obtained during routine endoscopy/EUS, is a pancreas-proximal, low-noise biofluid that may enrich tumor-derived exosomal signals. We evaluated whether DPF exosomal proteins complement serum CA19-9 to discriminate PDAC from controls. **Methods:** DPF was collected during upper endoscopy/EUS with or without secretin. DPF-derived exosomes ($n = 26$) were profiled by LC-MS/MS, and CES1/MAN2A1 were prioritized by stage-pattern clustering. Candidates were quantified by ELISA in a Korea–USA multicenter cohort ($n = 123$, prespecified to detect a target AUC of 0.94; 63 PDAC, 60 controls; 4 Korean sites and 1 US site, combined with serum CA19-9 using a locked stacked ensemble model with LightGBM meta-learner trained only on out-of-fold predictions). High-risk controls included IPMN and chronic pancreatitis. Orthogonal validation used pancreatic juice from surgery or ERCP (PDAC $n = 20$; chronic pancreatitis $n = 20$). The primary endpoint was AUC for PDAC versus controls, compared with CA19-9 alone and in the CA19-9–normal subgroup; performance was also assessed in early-stage PDAC versus high-risk controls. 95% confidence intervals (CIs) were estimated by cross-validated resampling. **Results:** LC-MS/MS identified 2,460 proteins; 130 were differentially expressed (> 2 -fold, $p < 0.05$). ELISA confirmed higher exosomal CES1 and MAN2A1 in PDAC versus controls ($p < 0.001$). The multi-marker model achieved an AUC of 0.995 (95% CI 0.982–1.000), a sensitivity of 98.33% (95% CI 0.931–1.000), and a specificity of 100% (95% CI 0.925–1.000), outperforming CA19-9 alone (AUC 0.63). In patients with CA19-9 in the normal range (< 37 U/mL), the model maintained high discrimination (AUC 0.931, 95% CI 0.746–1.000) with 100% sensitivity. For early-stage PDAC (stage I–II, $n = 23$) versus high-risk controls ($n = 20$, including IPMN), AUC was 0.976 (95% CI 0.924–1.000). In orthogonal validation, CES1/MAN2A1 in pancreatic juice were elevated in PDAC patients ($p < 0.001$) but not in matched serum, supporting pancreas-proximal enrichment. Decision curve analysis showed a higher net benefit than CA19-9 across clinically relevant thresholds. **Conclusions:** A DPF exosome–derived CES1/MAN2A1 signature integrated with CA19-9 using a locked ensemble model showed high diagnostic discrimination and supportive biological plausibility across a Korea–USA multicenter cohort. These results suggest a pancreas-proximal exosomal biomarker that addresses a critical gap in early detection of pancreatic cancer. Clinical trial information: NCT07030348. Research Sponsor: the Ministry of Health & Welfare, Republic of Korea; RS-2024-00435385; the Korean government (MSIT).

Clinical outcomes and cumulative cost of preventive surveillance versus treatment in Li–Fraumeni syndrome: Results from the European PREVENTABLE project.

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Background: Li–Fraumeni syndrome (LFS), caused by *TP53* pathogenic variants, is one of the most severe hereditary cancer predisposition syndromes, characterized by very early cancer onset, broad tumor spectrum, and a high lifetime risk of multiple cancers. At the European level, no large-scale health economics study has compared LFS proactive cancer preventive management including intensive multiorgan surveillance and early cancer detection, with treatment approaches initiated after the first tumor occurs in individuals at high cancer risk. To address this gap, and within the European PREVENTABLE project, we evaluated healthcare pathways and cumulative costs of proactive prevention versus treatment in LFS European families. **Methods:** We retrospectively collected clinical data from 866 individuals from seven European countries (ERN GENTURIS centers), including 505 *TP53* gene carriers (27% of whom were children) and 361 non-carrier family members. Based on multidisciplinary expertise, we developed a structured LFS care matrix, mapping patient clinical trajectories and clinical procedures across diagnosis, risk reduction strategies, surveillance and treatments. Costs were estimated using standardized French hospital tariffs, and data were collected via a GDPR-compliant digital tool interface developed by the PREVENTABLE consortium. **Results:** From 866 individuals, 155 were *TP53* carriers without a prior cancer diagnosis at the time of genetic testing, defining the preventive arm. During follow-up (median 75 months; range 6–267), 20 individuals developed one or more cancers. The mean prevention cost per patient was €6,046.8 (range €451–€71,854.76). Among the 273 patients with a history of cancer prior to genetic testing, 109 had early-stage disease and 164 had advanced-stage disease (median follow-up 83 months; range 2–468). The mean treatment cost per patient was €53,906 (range €385.50–€440,760.93). Overall cumulative costs were €937,258 for prevention and €15,103,188 for treatment, including €5,245,915 for early-stage cancers and €9,857,273 for advanced-stage cancers. Preventive mastectomy was performed in 24% of women in either prevention or treatment groups. **Conclusions:** This first European cumulative cost analysis demonstrates that treatment costs for LFS far exceed prevention costs (9-fold), providing strong economic evidence in favor of early genetic diagnosis and preventive surveillance. These findings support public health decision-making and the harmonization of care pathways within the framework of precision medicine in Europe. Preventable is funded by the European Union (EU) under Grant no 101095483. Research Sponsor: European Union; 101095483.

Prenatal hormonal imprinting reflected by anogenital distance and risk of breast cancer: A case-control study of 839 women.

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Background: Anogenital distance (AGD) is a sexually dimorphic, stable anthropometric marker set during fetal development and widely used as a proxy of prenatal androgen/estrogen balance. We hypothesized that AGD is associated with the risk of developing breast cancer (BC), a hormone-dependent disease. **Methods:** We conducted a prospective case-control study in Murcia (Spain) including 422 incident BC cases and 417 controls (2022-2024). Two AGD measures were obtained by trained examiners: ano-clitoral (AGDAC, "long") and ano-fourchette (AGDAF, "short"). Models were adjusted for age and BMI; quintile-based logistic regressions assessed non-linear associations. Stratified analyses were performed by menopausal status. Molecular subtype and Oncotype Recurrence Score (RS) (n=81 luminal tumors) were explored. **Results:** Compared with controls, BC cases showed longer AGDAC (mean 85.0 vs 81.2 mm; $p<0.01$) and shorter AGDAF (28.6 vs 29.8 mm; $p=0.02$). Across AGDAC quintiles, we observed an inverse risk gradient: lowest quintile vs highest, aOR 0.34 (95% CI 0.22-0.54; $p<0.001$). The association was stronger in premenopausal women (Q1 vs Q5 aOR 0.31; 95% CI 0.16-0.59; $p=0.001$). AGD was not associated with tumor subtype (luminal A/B, HER2+, triple-negative) nor with genomic risk ($RS>25$ vs ≤ 25). **Conclusions:** AGD, especially AGDAC, emerges as a non-invasive, inexpensive clinical marker of BC susceptibility, independent of molecular subtype and genomic risk. Findings suggest prenatal endocrine programming may prime lifetime BC risk, with a pronounced effect in hormonally active (premenopausal) women. If validated, AGD could enhance risk stratification and early detection pathways in population screening and prevention clinics. Research Sponsor: None.

Odds ratio (OR) for cases of breast cancer controls according to quintiles of AGD measures, taking the fifth quintile as a reference.

Breast cancer (n=422) vs. controls (n=417)						
AGD in quintiles (Median for each quintile)	Cases	Controls	Odds Ratio ^a (95%CI)	P- trend	Odds Ratio ^b (95%CI)	P- trend
AGD_{AF}						
5 th (38.0 mm)	80	89	1.0 (reference)		1.0 (reference)	
4 th (32.1 mm)	75	93	0.90 (0.58-1.4)		0.95 (0.61-1.5)	
3 rd (28.5 mm)	84	80	1.2 (0.76-1.8)		1.5 (0.95-2.3)	
2 nd (25.3 mm)	87	80	1.2 (0.76-1.8)		1.5 (0.95-2.3)	
1 st (21.4 mm)	96	75	1.4 (0.93-2.2)	0.26	1.9 (1.3-3.1)	0.01
AGD_{AC}						
5 th (99.0 mm)	114	54	1.0 (reference)		1.0 (reference)	
4 th (88.4 mm)	79	88	0.43 (0.27-0.66)		0.40 (0.26-0.63)	
3 rd (82.6 mm)	82	87	0.45 (0.29-0.60)		0.42 (0.27-0.66)	
2 nd (77.0 mm)	75	92	0.39 (0.25-0.60)		0.37 (0.23-0.58)	
1 st (69.3 mm)	72	96	0.36 (0.23-0.55)	<0.001	0.34 (0.22-0.54)	<0.001

^aUnadjusted OR.

^bOR adjusted by age and BMI.

^cOR adjusted by. AGDAF: Anogenital distance from the upper verge of the anus to the posterior fourchette
AGDAC: Anogenital distance from the upper verge of the anus to the anterior clitoral surface.

K-ACCELERATE: A multi-center prospective trial to evaluate the utility of a ctDNA-based assay for accelerating multi-cancer diagnosis among high-risk symptomatic participants.

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Background: In low- and middle-income countries, most cancers are diagnosed after symptom onset, where non-specific symptoms complicate referral and delay diagnosis. We previously developed SPOT-MAS, a multi-cancer early detection test integrating epigenetic, genetic, and fragmentomic features of circulating tumor DNA (ctDNA). Here, we report results from K-ACCELERATE (NCT06391749), a prospective multi-center study evaluating SPOT-MAS as a diagnostic aid in symptomatic individuals. **Methods:** Adults (≥ 18 years) with symptoms suggestive of colorectal, gastric, breast, liver, or lung cancer were recruited across 13 hospitals in Vietnam from July 2024. All participants underwent SPOT-MAS testing alongside standard-of-care diagnostics and were followed for up to 12 months. Primary endpoints included sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and tissue-of-origin (TOO) accuracy, using imaging and/or biopsy as the reference standard, analyzed overall and by symptomatic pathway. **Results:** Of 972 eligible participants, 862 achieved diagnostic resolution and completed follow-up, including 130 cancer cases and 732 non-cancer cases. Overall sensitivity and specificity of SPOT-MAS were 65.4% (95% CI: 56.9–73.0) and 92.1% (95% CI: 89.9–93.8), respectively. Pathway-specific sensitivity was 58.7% for breast cancer, 62.1% for lung cancer, 64.3% for gastrointestinal cancers, 80.0% for liver cancer, and 100% for multiple-pathway presentations. Among confirmed cancer cases, ctDNA-based tissue-of-origin prediction achieved 82.4% accuracy. Incorporation of ctDNA testing into clinical triage increased PPV from 15.1% to 59.4%, representing a nearly four-fold improvement over symptom-based assessment, while maintaining a high NPV of 93.7%. **Conclusions:** This study provides clinical evidence supporting the feasibility of SPOT-MAS as a non-invasive adjunct diagnostic tool for individuals presenting with cancer-related symptoms in low-resource settings. These findings lay the foundation for future prospective interventional studies to evaluate the clinical impact of ctDNA-guided diagnostic pathways in high-risk symptomatic populations. Clinical trial information: NCT06391749. Research Sponsor: None.

Association of clonal hematopoiesis driven by mosaic chromosomal alterations with epigenetic age in the PLCO trial.

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Background: Mosaic chromosomal alterations (mCAs) are age-associated clonal events detectable in peripheral blood and have been linked to hematologic malignancy risk and adverse clinical outcomes. Whether mCAs are associated with accelerated biological aging, as measured by DNA methylation-based epigenetic clocks, remains poorly understood. **Methods:** We analyzed peripheral blood DNA methylation data generated using the Illumina EPIC array from 482 participants in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. mCAs were identified from SNP array data and classified by subtype, including autosomal copy-neutral loss of heterozygosity (CN-LOH), gains, losses, and loss of the sex chromosome. Epigenetic age was estimated using six established DNA methylation clocks: Hannum, Horvath pan-tissue/skin and blood, PhenoAge, GrimAge & DunedinPACE. Associations between mCA presence, mCA subtype, clonal burden, and epigenetic age acceleration were evaluated using multivariable linear regression models adjusted for age, sex, smoking status, body mass index, and genetic ancestry. **Results:** Among 482 participants, 261 were mCA-free and 221 had at least one detectable mCA. Individuals with any detectable mCA exhibited higher epigenetic age acceleration than mCA-free individuals across multiple clocks, with the most consistent effect sizes across mCA subtypes observed for GrimAge. Although age acceleration was directionally higher among individuals with mCAs across all non-rate-based clocks, statistically significant differences were observed only for the Hannum, PhenoAge, and GrimAge clocks. For GrimAge, estimated effects for mCA-positive individuals were uniformly positive, except for gain-only events, with effect sizes ranging from 1.2 to 1.9 years of age acceleration. Age acceleration increased with clonal burden: participants with multiple mCAs ($n = 51$) exhibited greater age acceleration than those with a single mCA ($n = 170$), particularly for GrimAge and PhenoAge. Higher cellular fraction was also associated with increased age acceleration, with significant associations observed for GrimAge ($\beta = 2.97$, 95% CI 0.82–5.12, $p = 0.007$) and Hannum ($\beta = 4.25$, 95% CI 1.14–7.37, $p = 0.008$) clocks. **Conclusions:** Mosaic chromosomal alterations, particularly CN-LOH and higher clonal burden states, are associated with accelerated biological aging in peripheral blood leukocytes. Epigenetic age acceleration was most consistently observed using GrimAge, a mortality- and healthspan-associated clock, with more variable and less consistent associations observed for chronological age-trained and rate-based clocks. These findings suggest that epigenetic age acceleration may represent a clinically relevant feature of clonal hematopoiesis, warranting further investigation in aging populations. Funded by NCI Contract No. 75N91019D00024. Research Sponsor: National Cancer Institute.

Use of multiplex digital profiling of DNA methylation heterogeneity to enable sensitive early detection of non–small cell lung cancer from low-volume liquid biopsies.

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Background: Early detection of non–small cell lung cancer (NSCLC) within liquid biopsies remains limited by the extremely low abundance and heterogeneous nature of circulating tumor DNA (ctDNA) in plasma, particularly in patients with indeterminate pulmonary nodules. DNA methylation is an attractive early biomarker; however, conventional PCR- and sequencing-based assays have limited ability to sensitively and cost-effectively assess heterogeneous epiallelic methylation patterns at low variant fractions. We developed a digital microfluidic platform that enables multiplex, single-molecule profiling of DNA methylation heterogeneity to improve early NSCLC detection. **Methods:** We applied REM-DREAMing (Ratiometric-Encoded Multiplex Discrimination of Rare EpiAlleles by Melt), a digital high-resolution melt (dHRM) platform combining nanowell-based digital PCR with ratiometrically encoded, methylation-agnostic probes. Following bisulfite conversion, cfDNA was digitized into >40,000 nanoliter wells, enabling copy-by-copy assessment of methylation density across a five-gene biomarker panel previously associated with NSCLC. Analytical sensitivity and multiplex performance were compared against quantitative methylation-specific PCR (qMSP) and digital MSP (dMSP). Clinical feasibility was evaluated in plasma from patients with CT-detected indeterminate pulmonary nodules. **Results:** REM-DREAMing resolved heterogeneous methylation patterns at single-molecule resolution and detected methylated epialleles at fractions as low as 0.00005% in a high background of unmethylated DNA. In a cohort of 48 low-volume plasma samples, incorporating intermolecular methylation density distributions significantly improved classifier performance relative to binary methylation calls. The five-gene panel achieved 93% sensitivity at 90% specificity for early-stage NSCLC, with an AUC of 0.96. Compared with qMSP and dMSP, REM-DREAMing demonstrated superior sensitivity, multiplex scalability, and discrimination of partially methylated epialleles. **Conclusions:** Multiplex digital profiling of DNA methylation heterogeneity enables sensitive, low-cost detection of early-stage NSCLC from limited plasma input. By capturing epigenetic heterogeneity at the single-molecule level, this platform improves diagnostic performance in clinically challenging early detection settings and provides a scalable foundation for expanded biomarker panels. Research Sponsor: National Institutes of Health.

Analytical and clinical performance comparison.

Method	Heterogeneous Methylation Detection	Detectable Copy Number	Analytical Specificity	NSCLC AUC
qMSP	No	10	~0.01%	0.78–0.82
dMSP	No	1	~0.005%	0.85
Bulk MS-HRM	Yes	10	~0.1%	0.80
REM-DREAMing	Yes (single-molecule)	1	0.00005%	0.96

Development of an oncology generative AI foundation model trained on more than a million longitudinal patient journeys across the United States.

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Background: Incidence of cancer diagnoses continues to increase, while the average cost of cancer screening, such as mammogram or colonoscopy, remains high, ranging from hundreds to over a thousand dollars. This study explores the potential of building an oncology foundation model based on Generative Pre-trained Transformers (GPT) to predict future outcomes for patients. We assess the prediction accuracy and feasibility of leveraging the foundation model to inform when screening should be prioritized, thereby reducing the associated burden of unnecessary procedures. **Methods:** The advancement of generative AI offers the opportunity to model the progression of human disease over time. In this study, we extended the GPT architecture and pre-trained it with a subset of Truveta Data containing the electronic health record (EHR) from the journeys of 1.4 million de-identified patients diagnosed with 4 types of cancer (lung, breast, colorectal, prostate). Each sequence of the patient journey—including demographics (age, gender), conditions, lab results (represented by SNOMED-CT and LOINC codes), and the corresponding event time—was tokenized before passing through the GPT model for training. For validation, 1000 patients were randomly sampled from our test data, in which each type of cancer diagnosis constituted 19%–30% of the samples. We used the model to generate synthetic future patient journeys for the selected patients and compared the predicted outcomes with the actual cancer diagnoses within one year. **Results:** The model achieved sensitivities above 78%, with positive predictive values (PPV) between 66% and 90%. More importantly, it demonstrated high specificities above 91%, with corresponding negative predictive values (NPV) above 90%. **Conclusions:** The high specificities and NPV indicate the feasibility of applying generative foundation model pre-trained with EHR data to predict negative cancer outcomes with high accuracy. Since the percentage of screening tests leading to positive cancer diagnosis is relatively low, the projected negative predictive outcomes offer valuable signals for clinicians, which they can use to complement their expert assessment to avoid unnecessary screening and subsequently reduce the burden of screening costs. Research Sponsor: Truveta.

Performance of the foundation model on cancer outcome prediction.

	Lung	Breast	Colorectal	Prostate
Positive predictive value (PPV)	72.77%	90.11%	65.78%	88.88%
Sensitivity	80.28%	79.00%	78.13%	78.26%
Negative predictive value (NPV)	91.87%	96.29%	90.35%	96.27%
Specificity	94.50%	91.45%	94.56%	92.07%

Clinical impact of GLP-1 receptor agonist use on lung cancer incidence in high-risk patients: A real-world analysis.

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Background: Lung cancer (LC) is the leading cause of cancer-related mortality in the United States. Lifetime risk is ~7% in the general population but substantially higher among high-risk groups with tobacco use, environmental exposures, or family/genetic predisposition. Despite screening recommendations for select high-risk populations, no pharmacologic prevention is established. Emerging evidence suggests that Glucagon-like peptide-1 receptor agonists (GLP-1RA) may influence cancer risk through antiproliferative, anti-inflammatory, and immunomodulatory effects, but data on LC remain limited. This study evaluated the association between GLP-1RA use and LC incidence in high-risk patients. **Methods:** This multicenter retrospective study used de-identified electronic health data from TriNetX, a global federated research network. Adults ≥ 18 with high-risk features of tobacco use, environmental or occupational exposure, chronic lung disease, personal/family cancer history, or radiation were included. Participants were stratified by GLP-1RA use. Propensity score matching (1:1) adjusted for demographics, comorbidities, and medications. The primary endpoint was LC incidence. Participants with LC before the study entry were excluded. Multivariate logistic regression and Cox models assessed associations; results reported as hazard ratios (HRs) with 95% confidence intervals (CIs). **Results:** Before matching, 2,715,963 participants were identified. After matching, 68,374 were analyzed (34,187 per cohort) with similar demographics (mean age 58, 54% female, 46% male; 75% White, 17% Black, 1.5% Asian). Median follow-up was 2,324 days. LC incidence was 2% (688/33,784) in the GLP-1RA cohort vs 2.4% (797/33,369) in controls, yielding an absolute risk reduction of 0.4% and a number needed to treat (NNT) of 250. GLP-1RA use was associated with a 31% reduction in LC incidence [HR 0.687 (0.621–0.761)]. **Conclusions:** In this large retrospective cohort of high-risk individuals, GLP-1RA use was associated with lower LC incidence compared with matched controls. Despite modest absolute risk reduction, relative risk reduction and favorable number needed to treat suggest potential population-level impact in a disease with limited preventive options. Findings are biologically plausible given the anti-inflammatory, metabolic, and immunomodulatory effects of GLP-1RAs. While causal inference is limited by observational design, this study supports further prospective investigation of GLP-1RAs as a pharmacologic strategy for LC prevention in high-risk populations. Research Sponsor: None.

Multimodal risk phenotyping of early-onset colorectal cancer.

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Background: Early-onset colorectal cancer (EOCRC) is rising rapidly, yet its risk profile is incompletely defined. Prior studies have largely focused on isolated metabolic or lifestyle factors and have rarely integrated broader sociodemographic context or objective functional measures. We performed multimodal phenotyping to characterize integrated clinical, behavioral, cardiometabolic, and wearable-derived profiles among individuals with EOCRC compared with average-onset CRC (AOCRC). **Methods:** Adults with CRC in the NIH All of Us Controlled Tier Dataset v8 were identified (≥ 2 EHR diagnosis codes ≥ 3 months apart). The primary exposure was age at diagnosis, defined as EOCRC (< 50 years) vs AOCRC (≥ 50 years). Covariates included sociodemographic factors (sex, race/ethnicity, education, employment, health insurance, household income, marital status, neighborhood deprivation). Outcomes included health behaviors (smoking, alcohol use), anthropometrics (BMI, waist circumference), cardiometabolic conditions (dyslipidemia, metabolic syndrome, diabetes, hypertension), laboratory measures (lipids), and wearable-derived (Fitbit) activity, sleep, and heart rate, anchored to the most recent pre-diagnosis timestamp. **Results:** Among 3,915 CRC participants, 710 (18.1%) had EOCRC. The cohort was predominantly male (54.5%), White (64.4%), unemployed (68.6%), with annual income $< \$50k$ (45.5%), and married (53.6%). Participants with EOCRC were less often female (38.7% vs 47.0%) and White (52.7% vs 67.0%) (both $p < 0.001$). EOCRC was associated with higher obesity (42.0% vs 37.0%), higher LDL (101 vs 86 mg/dL), and lower HDL (51 vs 54 mg/dL) (all $p < 0.001$). Alcohol use (60.6% vs 50.5%, $p < 0.001$) and heavy drinking (22.0% vs 16.1%, $p = 0.003$) were more common among participants with EOCRC. In the wearable sub-cohort, EOCRC participants had higher heart rate (76.8 vs 73.8 bpm, $p = 0.03$) and lower sedentary time (773 vs 894 min/day, $p = 0.016$) with no significant differences in sleep metrics or heart rate variability. Female sex was associated with lower odds of EOCRC (OR 0.45, 95% CI 0.25–0.83; $p = 0.01$), while Hispanic ethnicity was associated with higher odds (OR 4.04, 95% CI 1.51–10.86; $p = 0.006$). **Conclusions:** EOCRC is characterized by higher obesity, dyslipidemia, and alcohol use, as well as differences in wearable-derived physiologic and behavioral profiles. Integrating real-world clinical data with digital biomarkers offers a scalable framework for refined risk stratification and precision prevention in EOCRC. Research Sponsor: None.

Multivariable logistic regression examining sociodemographic predictors for EOCRC.		
Variable	OR (95% CI)	P value
Sex		
Male	Ref	
Female	0.45 (0.25–0.83)	0.010
Race/ethnicity		
White	Ref	
Black	2.43 (0.99–5.97)	0.052
Hispanic	4.04 (1.51–10.86)	0.006
Employment		
Unemployed	Ref	
Employed	3.38 (1.87–6.10)	<0.001

Evidence of clonal stability in a 5-year longitudinal prospective cohort of cancer survivors with serial NGS analysis.

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Background: Hematopoietic stem and progenitor cells with preleukemic mutations (mutⁿs), collectively termed clonal hematopoiesis (CHIP) serve as the cellular origin of myeloid neoplasms (MN). While risk of MN development varies, its natural history and transformation potential remain poorly defined. We present findings from our ongoing 10-year CHIP protocol using serial NGS to monitor clonal evolution and MN in cancer survivors. **Methods:** Retrospective analysis of 210 prospective pts from March 2020 to June 2024. Mutⁿs were classified CHIP+ if they had a variant allele frequency (VAF) $\geq 2\%$ (or $\geq 1\%$ for *IDH1*, *IDH2*, and *JAK2*). Clonal evolution was evaluated by annual VAF changes adjusted for age-related increases (e.g. *DNMT3A* increases by $\sim 2\%/yr$ based on published data). Mutⁿs were classified as slow ($\leq 5\%/yr$: *DNMT3A*, *TET2*, *ASXL1*), intermediate ($5-10\%/yr$: *TP53*, *PPM1D*, *IDH1/2*, *KRAS*, *NRAS*, *SF3B1*), or fast-growing ($> 10\%/yr$: *JAK2*, *SRSF2*). BPearson's Chi-squared, Fisher's exact, and Wilcoxon rank-sum tests were used. **Results:** Of 210 pts, 42 (20%) had at least one CHIP+ mutⁿ. Median age was higher in CHIP+ vs. CHIP- pts (66 vs. 59 years, $p < 0.001$). CHIP+ was not significantly associated with sex, race, family history, smoking, alcohol use, prior cancer types (e.g., breast, head and neck) or treatment (chemo, radiation, surgery). Of 487 samples, 56 had detectable somatic mutⁿs. The most frequent mutⁿ were *DNMT3A* ($n = 27$), *PPM1D* ($n = 10$), and *TET2* ($n = 9$). By expected growth kinetics, 37 (66%) mutⁿ were slow-growing, 12 (21.4%) intermediate, 2 (3.5%) fast-growing, and 4 (7.14%) of unknown kinetic category. Beyond VAF-kinetics-based progression, 12 pts developed new mutⁿ in subsequent years - *DNMT3A* ($n = 8$), *PPM1D* ($n = 2$). Some later became undetectable, suggesting transient clones. In total, 12 pts (1 by VAF kinetics, 11 by new mutⁿ acquisition) clonally progressed over 5 years of this study (5.7%). 6 pts regressed by year 2, with gene mutⁿ VAFs becoming undetectable. These included mutⁿ in *PPM1D* ($n = 2$), *CBL* ($n = 2$), *TP53* ($n = 1$), and *DNMT3A* ($n = 1$). Three more pts regressed in year 3, and 1 in year 4. In all, 10 pts showed regression over 5 years (17.8%). Notably, 5 of 10 had received interventions for cardiac comorbidities. Overall, $\sim 94\%$ pts had clonal stability/regression. Slow-growing mutⁿs - *DNMT3A* and *TET2* had median rates of 0.83% and 2.11%, (historical rates $\leq 5\%$). Intermediate mutⁿs like *TP53* and *PPM1D* had median rates of 1.64% and -0.625% , below the expected 5-10% annual rise. *JAK2*, a fast-growing mutⁿ, also showed a lower rate of 0.19%. **Conclusions:** Despite being a high-risk population due to prior solid malignancy and exposure to chemo/radiation, most pts in our five-year longitudinal study showed clonal stability. Even among those who progressed, VAF kinetics remained stable post-detection. CHIP's inflammatory link to cardiovascular disease suggests preventive cardiology may impact clonal behavior. Research Sponsor: None.

Mammography utilization and male breast cancer in BRCA1/2 carriers.

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Background: Males with pathogenic germline variants in *BRCA1/2* (BRCA+) have a 1-10% lifetime risk of developing breast cancer (MBC). NCCN guidelines recommend that BRCA+ males consider annual mammograms. We have prior shown low rates of mammography uptake in an academic cohort from Penn Medicine (PM). We sought to validate these findings about mammography in a national veteran (VA) cohort and to investigate the clinical characteristics of BRCA+ compared to nonBRCA+ MBC. **Methods:** We performed a retrospective analysis of 327 BRCA+ male veterans with no prior history of MBC. The electronic health record was reviewed to determine indication for and results of mammography episodes. A mammography episode was defined as all breast imaging studies obtained for asymptomatic screening or for symptoms within six months. The first mammogram episode identified was referred to as the “initial” mammogram and all other mammography episodes were “subsequent”. To determine BI-RADS PPV, data for 85 PM and 68 VA BRCA+ males were combined and compared to 1819 nonBRCA+ males. To determine clinical characteristics of MBC, data for 30 PM and 18 VA BRCA+ MBC were combined and compared to 104 PM and 122 VA nonBRCA+ MBC. **Results:** Sixty-eight (20%) of VA BRCA+ males underwent an initial mammogram, 57% of which were ordered for screening. Among patients ≥ 50 without mammography, 31% of individuals had no discussion documented and 66% had a shared decision-making discussion against screening with an ordering provider. BI-RADS 4 and 5 findings occurred in six and five mammograms, respectively. MBC was diagnosed in 13% (9/68) after initial and 13% (3/23) after subsequent mammography pooled VA and PM data showed that 95% (21/22) of MBC diagnoses in BRCA+ males were after a symptom-prompted mammogram. BI-RADS 4 PPV was higher in BRCA+ compared to non-BRCA+ men (75% vs 5%, $p < 0.0001$), and BI-RADS 5 PPV was similar (100% vs 67%, $p = 0.0661$). In an expanded cohort of 48 BRCA+ MBC compared to 226 nonBRCA+ MBC, median (IQR) age of diagnosis was 66 (56-73) vs 66 (59-74) ($p = 0.52$). The majority of BRCA+ and nonBRCA+ MBC were ER+Her2- (85% and 90%, respectively, $p = 0.70$). Among those with Oncotype testing, 93% BRCA+ BC had intermediate or high-risk recurrence scores compared to 50% of non-BRCA+ ($p = 0.002$). However, BRCA+ and nonBRCA+ male patients had similar rates of node positivity (40% vs 41%, $p = 0.87$) and progression to metastatic disease (19% vs 16%, $p = 0.67$). **Conclusions:** Analysis of a Veteran cohort of BRCA+ males confirms low rates of mammography as we prior reported in an academic cohort. Counseling and SDM were inconsistently documented, highlighting gaps in guideline implementation. Both BRCA+ and nonBRCA+ MBC were nearly always diagnosed based on symptoms. Both BRCA+ and nonBRCA+ MBC were often node-positive and nearly 20% progressed to metastatic disease. These characteristics suggest the need for prospective evaluation of mammography in high-risk males to reduce rates of advanced disease. Research Sponsor: Bassett Center for BRCA; VA ORD; 1101CX002710; VA ORD; 1101CX002710.

Refining breast cancer risk stratification for selection of women at intermediate to high risk for supplemental MRI screening using artificial intelligence.

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Background: Supplemental MRI screening for women at increased breast cancer risk can detect additional cancers that are occult on mammography. However, its adoption is limited by restricted availability and high false-positive rates. Improved risk stratification is therefore needed to optimize the use of supplemental MRI screening. This study aimed to evaluate the feasibility of a mammography-based artificial intelligence (AI) system for stratifying women at intermediate to high risk for supplemental MRI screening. **Methods:** This retrospective study included consecutive women who underwent abbreviated breast MRI following negative mammography between January 2020 and December 2024. The study cohort comprised women at intermediate to high breast cancer risk, including those with known genetic predisposition, personal history of breast cancer, prior benign or high-risk breast biopsy, or family history of breast cancer. A commercially available AI system was applied to all mammograms, generating both exam-level and breast-level scores representing the likelihood of a malignancy on a scale of 0 to 100. MRI outcomes, false-positive examinations, cancer detection, and positive predictive value (PPV) were evaluated. Univariate analyses were performed to explore associations between breast density and AI-based selection results. **Results:** In 1,588 women (median age, 51 years; range, 24–87), 1,804 screening mammograms and MRI examinations were performed. Of these examinations, 220 resulted in recall, yielding 24 mammographically occult breast cancers (12 ductal carcinoma in situ and 12 invasive cancers) diagnosed within one year and 166 false-positive examinations. The AI system achieved an area under the curve (AUC) of 0.694 (95% CI, 0.499–0.888) in women without a personal history of breast cancer and 0.611 (95% CI, 0.430–0.792) in women with a personal history of breast cancer. Using AI-based selection, 239 of 1,588 women (14.9%) were selected for supplemental MRI, resulting in an 81% reduction in false-positive examinations (31 vs 166) and an improvement in PPV to 20.5% (8 of 39). 6 of 8 detected cancers (75%) were invasive. Breast density was not associated with the AI-based selection strategy. **Conclusions:** Mammography-based AI substantially reduced false-positive supplemental MRI examinations while preferentially selecting women at higher risk for invasive breast cancers, without compromising cancer detection. These findings suggest that AI can refine risk stratification and optimize selection of women to improve the efficiency of supplemental MRI screening. Research Sponsor: National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT); RS-2025-00515472.

Real-world experiences with a multi-cancer detection (MCD) blood test.

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Background: Multi-cancer detection (MCD) blood tests hold promise to screen for multiple cancers simultaneously. MCD tests have been assessed in case-control and prospective studies but have not yet been shown to improve cancer outcomes. Mass General Brigham (MGB) offers a commercially available, non-FDA-approved methylation-based MCD test (Galleri; GRAIL) through our Early Detection & Diagnostics Program. Here, we report our initial experience. **Methods:** In this retrospective, observational study, data were collected from all patients (pts) who underwent MCD testing or were evaluated for a prior positive MCD test at our clinic between May 2023 and December 2024. Pts obtained the test through: 1) self-payment after shared decision making, or 2) an early access demonstration project with GRAIL, Point32Health (insurance company), and MGB whereby pts ≥ 50 y with specific insurance products and an MGB primary care physician were invited to receive a cost-free test if they met ≥ 1 of 4 criteria: personal history of cancer, 1st-degree family history of cancer, elevated BMI, or any smoking history in the past 10 years. All pts tested at MGB underwent pre-test consultation with a medical oncologist or nurse practitioner to review the benefits and limitations of testing. Result management was coordinated by our team. Longitudinal outcomes were abstracted from electronic health records. **Results:** 742 pts had MCD testing (125 [17%] self-pay, 617 [83%] demonstration project). Median (med) age was 59 (IQR 55-63); most were White (92%) and up to date on USPSTF-recommended cancer screening (82%). Med follow up (FU) was 469 days (IQR 462-478); 580 (78%) had > 12 months FU. Four pts received a "cancer signal detected" result (+MCD): 2/742 tested at MGB (0.3%) and 2 who presented to workup +MCD tested elsewhere; 2 were true positives (TP), 2 false positives. In total, 16 pts (2.2%) were diagnosed (dx) with cancer during FU; 2/16 (13%) after +MCD, and 14/16 after negative MCD, with med time from MCD to diagnosis 199 days (IQR 92-464). The two TP tests corresponded to stage I breast cancer and stage III follicular lymphoma. The most common cancers dx were prostate (n = 5, with two stage III-IV dx at 128 and 142 days) and breast (n = 4, all mammogram-detected stage I). Other advanced cancers included stage III cholangiocarcinoma and stage IV adenocarcinoma unknown primary (dx at 515 and 475 days, respectively). **Conclusions:** In this real-world cohort, MCD test positivity was rare, and multiple cancers were dx within 18 months of a negative MCD, including some advanced cases. In particular, prostate cancer was dx in multiple pts after negative MCD, consistent with prior reports of limited MCD sensitivity for prostate cancer. Our cohort may be biased by the requirement to either self-pay or carry a specific insurance product. Larger studies with longer FU are needed to better define the added utility of MCD tests to standard cancer screening. Research Sponsor: None.

Spatial organization of immune surveillance by germline mutation status in the Breast Cancer Family Registry.

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Background: Germline pathogenic variants (gPVs) are associated with increased immune infiltration in resulting tumors; we previously reported increased CD4⁺ and CD8⁺ T-cells in gPV-associated tumors using single-cell spatial profiling. Here, we report the spatial features, including cell-cell co-localization, underlying these immune differences. **Methods:** We analyzed CosMx 6K single-molecule RNA transcriptomics in 222 samples from 144 women in the population-based Northern California Breast Cancer Family Registry. Across 1,083,345 cells and 6,583 genes, multicellular niches were identified by clustering cells based on spatial proximity and cell-type identity using a k-nearest neighbors approach, with the number of niches selected by elbow analysis. Niche proportions were compared between gPV-associated and wild-type tumors using linear models. Linear mixed-effects models were used to identify niche-specific enrichment of cell-type densities and pairwise cell-cell colocalization relative to all other niches. P-values were corrected using Benjamini-Hochberg. **Results:** Of 144 participants, 31 (22%) carried at least one gPV, including BRCA1 (n = 12), BRCA2 (n = 8), PALB2 (n = 3), FANCM (n = 3), ATM (n = 2), and CHEK2, RAD50, and TP53 (n = 1 each). We identified eight cell niches, two of which were enriched in gPV-associated tumors, including within ER/HER2 subtypes: niche 2 (10% of cells in gPV tumors vs 3.7% in non-gPV tumors; Wilcoxon FDR = 0.01) and niche 5 (17% vs 9.4%; FDR = 0.03). Niche 2 and niche 5 proportions were uncorrelated across tumors ($r = -0.13$, FDR = 0.14). Compared with other niches, niche 2 had higher proportions of immature B cells (FDR = 0.006), CD8⁺ T cells (FDR = 0.03), dendritic cells (FDR < 0.001), and macrophages (FDR < 0.001), with no specific cell-cell colocalization pattern. Niche 5 had higher proportions of CD4⁺ T cells (FDR < 0.001), myoepithelial cells (FDR < 0.001), and macrophage-derived stem cells (FDR < 0.001); niche 5 demonstrated increased colocalization across 95 cell-type pairs at FDR < 0.1, including cancer cells with macrophage-derived stem cells and pericytes with natural killer cells (FDR = 0.01 each). Comparing BRCA1 to BRCA2 gPV carriers, niche 2 was more prevalent in BRCA1 tumors (16% vs < 1% in BRCA2; $p = 0.01$); no significant difference was observed for niche 5. **Conclusions:** In this population-based cohort, gPV-associated breast cancers exhibited distinct spatial immune niches. Niche 2, especially enriched in BRCA1 gPV tumors, appears to reflect an inflamed immune environment, whereas niche 5 may represent a more spatially organized stromal-adaptive immune niche characterized by CD4⁺ T-cell enrichment and extensive non-random cell-cell interactions. These findings demonstrate that inherited cancer risk is associated with reproducible immune spatial architectures, with implications for immune-based prevention and interception strategies. Research Sponsor: None.

Quantifying the macroeconomic burden of tobacco-attributable cancers in 2023: Global disparities in value-of-lost-welfare (VLW) in 189 countries.

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Background: Tobacco use is the leading preventable cause of cancer globally, yet the macro-economic welfare losses attributable to tobacco-related cancers remain incompletely quantified. We estimated the global economic burden of tobacco-attributable cancers in 2023 using a standardized value-of-lost-welfare (VLW) framework. **Methods:** Country-level disability-adjusted life years (DALYs) attributable to tobacco for all cancers were obtained from the Global Burden of Disease (GBD) 2023 framework. Gross domestic product (GDP; purchasing power parity, current international dollars) and population data were sourced from the World Bank. VLW was calculated as tobacco-attributable cancer DALYs multiplied by country-specific GDP per capita (PPP). Outcomes included total VLW, per-capita VLW, and VLW as a percentage of national GDP. **Results:** In 2023, tobacco-attributable cancers resulted in 48.44 million DALYs globally (95% UI: 41.06–57.06 million), corresponding to a global value of lost welfare (VLW) of USD 1.61 trillion. The largest absolute economic welfare losses were observed in China (USD 415.3 billion), India (USD 262.8 billion), and the United States (USD 219.4 billion), followed by Japan (USD 96.1 billion) and Brazil (USD 63.7 billion). Together, these five countries accounted for 65.9% of the global VLW attributable to tobacco-related cancers. When normalized to national economic output, the highest VLW-to-GDP ratios were observed in India (1.12%), China (0.69%), Egypt (0.61%), Bangladesh (0.58%), and Pakistan (0.52%), indicating substantial macroeconomic vulnerability in several low- and middle-income countries. By cancer type, tracheal, bronchus, and lung cancer accounted for 24.6 million DALYs, corresponding to a VLW of USD 0.82 trillion, followed by esophageal cancer (6.1 million DALYs; USD 0.21 trillion), stomach cancer (5.4 million DALYs; USD 0.18 trillion), liver cancer (4.9 million DALYs; USD 0.16 trillion), and oral cavity cancer (3.2 million DALYs; USD 0.11 trillion). Collectively, these five cancer types accounted for 91.4% of total tobacco-attributable cancer VLW worldwide. **Conclusions:** In 2023 alone, tobacco-attributable cancers resulted in nearly 50 million DALYs and over \$1.6 trillion in lost economic welfare worldwide, highlighting tobacco use as a dominant driver of both health loss and macroeconomic harm. Research Sponsor: None.

Regional distribution of disability-adjusted life years (DALYs) and economic welfare loss (VLW) attributable to tobacco-related cancers in 2023.

Region	DALYs (millions)	VLW (USD trillion)	VLW/GDP (%)
High-income	11.6	0.75	1.81
Central Europe, Eastern Europe, and Central Asia	4.58	0.17	1.27
Southeast Asia, East Asia, and Oceania	22.87	0.53	1.14
North Africa and Middle East	2.27	0.05	0.57
Latin America and Caribbean	1.72	0.03	0.29
South Asia	4.33	0.04	0.22
Sub-Saharan Africa	0.98	0.00	0.12

Effect of breast density reporting on supplemental MRI and ultrasound use.

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Background: Mammography has lower sensitivity in women with dense breasts due to masking, as both dense tissue and tumor tissue appears white. Supplemental breast imaging, such as MRI or ultrasound, can increase cancer detection among women with dense breasts, but its use is limited by screening capacity, cost, and potential overdiagnosis. The purpose of this study is to understand the impact of changing breast density on supplemental screening use in a longitudinal cohort of women undergoing screening mammography. **Methods:** Participants are from the Boston Mammography Cohort Study (BMCS), a cohort of women undergoing routine screening mammography within the Mass General Brigham health system in Boston, MA enrolled from 2008–2016, with follow up collected through 2022. Participants completed a questionnaire at enrollment which provided demographic, reproductive, lifestyle and behavioral factors. Electronic medical record review provided dates and results of all breast imaging received within the health system. We performed a longitudinal analysis using generalized estimating equations to evaluate the association between breast density and supplemental MRI and/or ultrasound. Women with a history of breast cancer and those without at least one mammogram with reported BIRADS breast density were excluded from the analysis. **Results:** Of the 2,696 women enrolled in BMCS, 87 were excluded for breast cancer prior to enrollment and 16 were excluded for lack of reported BIRADS breast density, leaving 2,593 in the analytic cohort. Of these women, 37.6% were aged 40–49 at the time of enrollment, 71.5% were non-Hispanic white, 46.5% had a body mass index (BMI) of 18.5–24.9, 51.9% were postmenopausal, and 78.0% had no first-degree relatives with breast cancer. Overall, 1.5% (n = 40) were diagnosed with breast cancer, 3.5% (n = 98) received a breast MRI, and 25.8% (n = 669) received a breast ultrasound. In unadjusted analyses, increased breast density was associated with higher rates of supplemental imaging. Compared with women who never had dense breasts, those who always had dense breasts had higher use of MRI (RR 3.7, $p < 0.001$), while ultrasound use was higher among women who sometimes (RR 1.5, $p = 0.0002$) and always (RR 1.7, $p < 0.0001$) had dense breasts. After adjusting for age, race, BMI, menopausal status, family history, and mammogram results, the association between breast density and supplemental imaging was attenuated. Women who sometimes had dense breasts remained more likely to undergo ultrasound and any supplemental imaging compared with women who never had dense breasts, but the associations were smaller and did not reach significant statistical significance. Abnormal mammogram results were the strongest predictor across all models. **Conclusions:** These findings suggest that breast density alone may be insufficient to guide supplemental screening guidelines and support more targeted, risk-informed approaches. Research Sponsor: None.

Circulating cadherin-17 (CA17) in blood as a diagnostic biomarker for gastric cancer.

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Background: The asymptomatic onset of gastric cancer (GC) frequently leads to delayed diagnosis resulting in poor survival. Conventional biomarkers (CA72-4, CEA) lack sensitivity, while emerging cfDNA methods remain costly and complex for routine screening. Our proprietary antigen, Cadherin-17 (CDH17), is selectively overexpressed in gastrointestinal (GI) malignancies. We developed a fully automated, high-throughput Chemiluminescence Immunoassay (CLIA) using proprietary antibodies to monitor the blood circulating levels of CA17 – the soluble form of Cadherin-17 protein in liquid biopsies. CA17 screening offers a complementary minimal invasive diagnostic method that identifies high-risk GC individuals for follow up endoscopy evaluations. **Methods:** A CLIA assay was designed to quantify circulating CA17 protein levels in human serum. The assay was established on the iShine i1910 automated platform, which integrates magnetic microparticle and acridinium ester labelling to generate luminescent signals. Four proprietary monoclonal anti-CA17 antibody clones were evaluated in various capture and detection pair combinations to identify the optimal antibody pairing for assay performance. Serum samples from 114 non-cancer individuals and 113 patients with histologically confirmed gastric cancer were analysed. Assay and biomarker performance was assessed by receiver operating characteristic (ROC) curve analysis to determine assay sensitivity and specificity. **Results:** Four capture/detection antibody pairings were evaluated. The clone 1–clone 2 combination demonstrated superior detection accuracy, yielding an AUC of 0.959 (90.3% sensitivity, 91.4% specificity). This optimal pairing revealed a highly significant difference in CA17 levels between the non-cancer and GC groups (Mann-Whitney test,), confirming its ability to reliably distinguish high-risk individuals. In contrast, the clone 1–clone 3, clone 5–clone 1, and clone 1–clone 4 combinations exhibited inferior performance, with AUCs of 0.784, 0.705, and 0.680, respectively. **Conclusions:** The CA17 CLIA assay demonstrates high sensitivity and specificity for GC detection. As a minimally invasive blood-based test, it enables early identification of high-risk individuals for subsequent confirmatory endoscopy. This cost-effective blood test has the potential to allow screening of GC at the early stages and will significantly impact on patient survival. Research Sponsor: None.

Transdermal drug delivery to the normal and the radiated breast: Determinants of individual variation in skin permeation.

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Background: Primary prevention of breast cancer with oral drugs causes systemic effects which are unacceptable to 85% of high-risk women. Transdermal delivery through breast skin can minimize systemic exposure, but individual variation of permeation, the effects of breast radiation, or increased dose have not been studied. We report a prospective single-arm trial addressing these aspects, using 4-hydroxytamoxifen (4-OHT) an active metabolite of oral tamoxifen. **Methods:** Women with unilateral breast cancer treated with breast conservation and radiotherapy applied 4-OHT gel to both breasts for 4 ± 1 weeks. In Cohort 1 (2 mg/breast/day) we evaluated inter-individual variation of 4-OHT skin permeation in the non-radiated breast based on demographic and skin characteristics. In Cohort 2 (4 mg/breast/day) we evaluated the effect of increased dose. All participants underwent bilateral post-intervention dermal punch and core needle breast biopsy. Drug concentration in tissue and plasma was measured using liquid chromatography-mass spectroscopy. Multivariable linear regression was used to examine the predictors of drug concentration in tissue and plasma. Stepwise model selection was conducted using AIC criteria, with multicollinearity assessed via variance inflation factor (VIF). **Results:** Of 156 consented women, 120 completed intervention and were evaluable for the primary endpoint (breast tissue drug concentration). On multivariable analysis, breast tissue 4-OHT concentration increased with age and White race. Drug concentration was equivalent in the radiated and the non-radiated breasts and was two-fold higher in Cohort 2 (4 mg/breast/day) compared to Cohort 1 (2 mg/breast/day), ($p = 0.001$). Plasma drug concentrations were low in both cohorts; 0.27ng/mL in Cohort 1 and 0.15ng/mL in Cohort 2, ($p = < 0.001$). **Conclusions:** Transdermal delivery of breast cancer prevention drugs is a viable strategy, with higher dose achieving proportional increase in tissue concentration, without increased leakage into the circulation. Further work should pursue formulations of highly active drug metabolites with excellent permeation. Clinical trial information: NCT04009044. Research Sponsor: National Institutes of Health (NIH)/National Cancer Institute (NCI).

Embedding germline genetic testing into African oncology care: Early results from the Genetic Cancer Families (GenCAF) program.

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Background: Breast cancer outcomes in sub-Saharan Africa are marked by early onset, advanced stage at diagnosis, and high mortality. Although prior studies demonstrate a high burden of inherited cancer susceptibility variants in African populations, access to ancestry-informed genetic counseling and testing remains limited due to infrastructure constraints and poor integration into routine oncology care. The GenCAF program was developed to translate prior genomic evidence from Nigeria into a scalable, clinically embedded cancer genomics implementation model in African settings. **Methods:** Consecutive breast cancer patients were prospectively enrolled and offered genetic counseling and testing regardless of age or family history. Germline testing was performed using the Color Hereditary Cancer Test (Color Health Inc). Counseling and result disclosure were delivered by locally trained oncology nurses or breast health specialists using a structured protocol. Clinical and tumor characteristics were correlated with genetic findings. The program was designed for scalability across English- and French-speaking sites. **Results:** Among 263 participants, 235 unrelated index breast cancer cases underwent germline testing. Overall, 43.0% (101/235) had a reportable germline finding, including 21.7% (51/235) with pathogenic or likely pathogenic (P/LP) variants and 21.3% (50/235) with variants of uncertain significance (VUS). Among genes present in $\geq 5\%$ of cases with variant calls, VUS were most frequent in *APC*, *ATM*, *PALB2*, *PMS2*, and *BRCA2*, with several moderate-penetrance DNA repair genes exhibiting disproportionately high VUS burden, representing key candidates for future reclassification as African-ancestry reference data and gene-environment context expand. P/LP variants were most common in *BRCA1* ($n = 22$), *BRCA2* ($n = 13$), *ATM* ($n = 4$), and *PALB2* ($n = 4$). P/LP carriers tended to be diagnosed before age 30 (13.7% vs 7.6%) and were more frequently diagnosed with advanced-stage disease (stage III–IV, 30.6%). Mean age did not differ overall; however, *BRCA1* P/LP carriers had an earlier onset (mean age 40.1 years). **Conclusions:** These findings support integrating germline cancer genetics into routine breast cancer care in Africa through a scalable, nurse-led counseling model. The substantial VUS burden underscores the need for ancestry-informed interpretation and future reclassification efforts incorporating population-specific and environmental data. Planned implementation of point-of-care next-generation and long-read sequencing will further strengthen local diagnostic capacity and enable sustainable, locally driven precision prevention and oncology through risk-informed care. Research Sponsor: Breast Cancer Research Foundation; Susan G. Komen; U.S. National Institutes of Health; R01MD013452.

Age Group (yrs)	P/LP (%)	VUS (%)
<30	13.7	7.6
30–39	15.7	23.9
40–49	23.5	23.4
50–59	27.5	26.6
≥ 60	15.6	19.0

Missed by the guidelines: A meta-analysis of USPSTF lung cancer screening ineligibility among patients diagnosed with lung cancer.

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Background: Lung cancer (LC) screening utilizes low-dose CT recommended by the US Preventive Services Task Force (USPSTF) based on age and smoking history. However, the proportion of patients who develop LC but are ineligible for screening at diagnosis remains unclear. We performed a meta-analysis to quantify the burden of LCs missed under USPSTF 2013 and 2021 criteria and identify key reasons for ineligibility. **Methods:** We systematically searched PubMed, Embase, and Scopus to identify studies reporting USPSTF screening eligibility among adults diagnosed with primary LC who ever smoked. Data were pooled using random-effects models. Primary outcomes included pooled proportions (PP) of LC cases ineligible for USPSTF screening using 2013 and 2021 criteria. Secondary analyses evaluated reasons for ineligibility, including age, smoking pack-years (yrs), and quit-yrs. Statistical significance is defined as $p < 0.05$. Heterogeneity was assessed using the I^2 statistic. **Results:** Eight studies comprising 12,487 LC cases utilized the USPSTF 2013 criteria. The PP of screening-ineligible cases was 57.6% (95% CI, 48.94%–66.2%; $I^2=97.3\%$). Under USPSTF 2021 criteria, 11 studies including 20,313 cases were analyzed, yielding a pooled ineligible proportion of 40.9% (95% CI, 31.9%–50.5%; $I^2=98.8\%$). In reason-specific analyses, insufficient smoking exposure (pack-yrs) was the primary cause of ineligibility using both criteria, accounting for 68.2% (2013) and 59.3% (2021) of ineligible cases. Age-based exclusions declined from 34.7% under USPSTF 2013 to 31.8% under USPSTF 2021. Quit-year restrictions contributed to ineligibility under both criteria (25.8% in 2013; 49.6% in 2021), reflecting a greater proportional contribution among remaining ineligible cases under the 2021 criteria. Categories of ineligibility were not mutually exclusive. **Conclusions:** More than half of LCs were ineligible for screening under USPSTF 2013 criteria, and over 40% remain ineligible under current guidelines. Smoking pack-year thresholds remain the primary reason for ineligibility to screen and thereby miss a cancer diagnosis. These findings highlight limitations of current criteria and support the development of alternative risk-based screening strategies. Research Sponsor: None.

Lung cancer screening ineligibility under USPSTF 2013 and 2021 criteria.

	Pooled Proportion (95% CI)	I^2 (%)
USPSTF 2013 Criteria Overall Ineligibility	57.6% (48.4-66.2)	97
Age-based exclusion (<55 or >80 yrs)	34.7% (28.2-41.8)	70
Insufficient pack-yrs (<30)	68.2% (54.6-79.2)	93
Quit-year exclusion (>15 yrs)	25.8% (10.8-49.8)	97
USPSTF 2021 Criteria Overall Ineligibility	40.9% (31.9-50.5)	98
Age-based exclusion (<50 or >80)	31.8% (18.4-49.0)	96
Insufficient pack-yrs (<20)	59.3% (45.6-71.6)	89
Quit-year exclusion (>15 yrs)	49.6% (37.1-62.0)	94

Reproducible modulation of tissue Ki-67 across lung and prostate cancer interception trials.

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Background: The clinical utility of cancer interception is limited by the lack of validated surrogate endpoints that capture early biological response before histopathologic progression. While morphologic changes often require prolonged follow-up, Ki-67, a nuclear marker of cellular proliferation, provides a dynamic, tissue-based measure of epithelial proliferative activity. However, its reproducibility across high-risk tissue contexts remains debated. We evaluated the consistency of tissue Ki-67 modulation across two independent randomized trials in high-risk lung and prostate epithelia. **Methods:** We analyzed data from two prospective, randomized, placebo-controlled phase II cancer interception trials that prespecified tissue Ki-67 as an endpoint. In the lung cohort (NCT03232138; n=98), high-risk smokers with bronchial dysplasia were randomized to oral sulforaphane (200 μ mol/day) or placebo for 6 months. In the prostate cohort (CAPFISH-3; n=58), patients with low-grade prostate cancer on active surveillance were randomized to long-chain omega-3 fatty acids (3 g/day) or placebo for 12 months. Paired tissue biopsies were obtained at baseline and study completion. Ki-67 expression was quantified by immunohistochemistry with central pathology review. **Results:** Baseline Ki-67 indices were comparable between intervention and placebo arms in both cohorts. Following the intervention, a statistically significant divergence in tissue proliferative activity was observed. In the lung cohort, sulforaphane treatment was associated with a 20% reduction in bronchial epithelial Ki-67, whereas the placebo arm demonstrated a 65% increase (P=0.014). In the prostate cohort, omega-3 supplementation resulted in a 15% reduction in intratumoral Ki-67, compared with a 24% increase in the control arm (P=0.043). Sub-analysis by staining intensity demonstrated preferential suppression among high-intensity (3+) Ki-67-positive cells, including a 44% reduction in the lung intervention arm. Ki-67 modulation correlated with baseline proliferative activity but not with baseline histopathologic features. No significant changes in histopathologic grade or dysplasia scores were observed. **Conclusions:** Tissue Ki-67 demonstrates consistent, reproducible modulation across randomized lung and prostate interception trials, preceding detectable morphologic change. These findings support Ki-67 as a practical early biologic endpoint for phase II cancer interception studies. Research Sponsor: None.

Tissue Ki-67 modulation across randomized cancer interception trials.

Cohort (n)	Intervention	Ki-67 change (Tx)	Ki-67 change (Pbo)	P value
Lung (98)	Sulforaphane	-20%	+65%	0.014
Prostate (58)	Omega-3	-15%	+24%	0.043

Abbreviations: Tx, treatment; Pbo, placebo.

Elevated red blood cell distribution width-to-albumin ratio and incident cancer risk: A prospective cohort study.

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Background: Cancer remains a leading cause of global morbidity and mortality, underscoring the need for accessible biomarkers for early detection and risk stratification. The red blood cell distribution width-to-albumin ratio (RAR) is an emerging composite index integrating markers of erythropoietic stress and nutritional status/hepatic dysfunction, often dysregulated in malignancy and systemic inflammation. Elevated RAR correlates with worse outcomes in patients with sepsis and various cancers; however, its association with incident cancer risk in large prospective cohorts remains uncharacterized. **Methods:** Using UK Biobank data, we conducted a prospective cohort study with 5:1 propensity score matching, yielding an analytic cohort of 112,107 participants (18,916 with elevated RAR, 93,191 with normal RAR). Elevated RAR was defined as > 95th percentile (> 3.48 % dL/g) among cancer-free participants at baseline. Matching balanced groups by age, sex, ethnicity, socioeconomic status, BMI, smoking, alcohol use, diabetes, chronic kidney disease, and family history of cancer. Adjusted Cox proportional hazards regression was utilized to assess associations between elevated RAR and incident cancer. We also performed a 2-year landmark analysis to evaluate reverse causation. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. **Results:** During median follow-up of 15.4 years (1.55 million person-years), 21,307 incident cancers occurred. Elevated RAR was significantly associated with 23% increased overall cancer risk (HR 1.23; 95% CI 1.18–1.27). Cancer-specific analyses revealed strongest associations for hematologic malignancies (HR 1.91; 95% CI 1.70–2.14), including acute myeloid leukemia (HR 2.22; 95% CI 1.37–3.60) and chronic myeloid leukemia (HR 2.78; 95% CI 1.23–6.31). Significant associations were also observed for gastric (HR 2.12; 95% CI 1.57–2.86), liver (HR 1.90; 95% CI 1.38–2.62), lung (HR 1.45; 95% CI 1.27–1.66), and colon cancer (HR 1.48; 95% CI 1.28–1.72). No significant association was observed for breast (HR 1.06; 95% CI 0.96–1.17) or prostate cancer (HR 0.94; 95% CI 0.84–1.05). A 2-year landmark analysis showed that the association with overall cancer risk remained robust (HR 1.19; 95% CI 1.15–1.24). **Conclusions:** Elevated RAR is independently associated with increased incident cancer risk, particularly for hematologic, gastrointestinal, and lung cancers. These associations persisted in 2 year landmark analyses, supporting a potential prospective relationship and motivates further evaluation of RAR, a readily calculable index from routinely obtained laboratory values, in cancer risk models. Research Sponsor: None.

Pancreatic cancer incidence and survival in lean and obese adults with type 2 diabetes: A propensity matched analysis.

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Background: Type 2 diabetes mellitus (T2DM) and excess adiposity are independent risk factors for pancreatic cancer. Pancreatic cancer risk within T2DM across body-mass index (BMI) strata is heterogeneous in real-world cohorts and lean T2DM individuals may represent a distinct high risk phenotype. We compared pancreatic cancer incidence and post-diagnosis survival across BMI strata. **Methods:** We performed a retrospective comparative outcomes analysis using the TriNetX network. Adults with T2DM (HbA1c $\geq 6.5\%$) were categorized as obese (BMI ≥ 30 kg/m²) or lean (BMI < 25 kg/m²). The lean cohort additionally excluded any patient with prior BMI of > 25 kg/m² to control for cancer associated weight loss. The index event was first T2DM diagnosis, and outcomes were evaluated after a 365-day window. Patients with pancreatic cancer prior to the outcome window were excluded. Propensity score matching was done using the following parameters: age, sex, smoking status, pancreatitis, pancreatic cysts, chronic kidney disease, gallstones, family history of pancreatic cancer, and HbA1c. Outcomes assessed were incident pancreatic cancer over 10 years and all-cause mortality among patients with pancreatic cancer and T2DM. **Results:** Total number of patients in the obese group was 1,759,075 with mean age of 57 ± 13.4 years and in the lean cohort were 205,193 with a mean age of 61.8 ± 16.6 years. After propensity score matching, there were 204,086 patients in each group. Mean HbA1c levels were $7.4 \pm 1.8\%$ in the obese group and $7.9 \pm 2.2\%$ in the lean BMI group. The incidence of pancreatic cancer was 0.16% (n = 335) in obese patients as compared to 0.23% in lean (n = 478) patients with a risk difference of 0.07% (p < 0.001). Obesity was associated with lower pancreatic cancer risk (RR 0.692, 95% CI 0.603–0.797; p < 0.001). In the subgroup analysis of patients diagnosed with pancreatic cancer, obese patients had longer median survival (1,109 vs 651 days) with HR 0.853 (95% CI 0.793 – 0.918; p < 0.001). **Conclusions:** Lean adults with T2DM had a higher incidence of pancreatic cancer and worse post-diagnosis survival than obese patients. These results identify lean T2DM as a distinct high-risk phenotype and demonstrate that pancreatic cancer risk within T2DM is heterogeneous and not solely attributable to excess adiposity. Further investigation is needed to elucidate the biological mechanisms underlying this association and its implications for clinical risk assessment. Research Sponsor: None.

Pancreatic cancer incidence and associated risk estimates among obese and lean adults with type 2 diabetes mellitus.

Cohort	Pancreatic cancer incidence	RD	RR
Obese T2DM (n = 204,086)	0.16% (n = 335)	0.07% (95% CI: 0.04 - 0.10), p < 0.001	1.44 (95% CI: 1.25 - 1.66)
Lean T2DM (n = 204,086)	0.23% (n = 478)		

Abbreviations: CI, confidence interval; RD, risk difference; RR, relative risk; T2DM, type 2 diabetes mellitus.

Diagnostic accuracy of blood-based cfDNA fragmentomic assays for lung cancer detection: A meta-analysis of clinically validated cohorts.

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Background: Early detection of lung cancer remains limited by suboptimal sensitivity and specificity of current screening and diagnostic strategies. Blood-based cell-free DNA (cfDNA) fragmentomic assays that leverage genome-wide fragmentation patterns have emerged as a promising noninvasive approach for lung cancer detection. However, reported diagnostic performance varies across studies and clinical settings. A meta-analysis was conducted to evaluate the pooled diagnostic accuracy of cfDNA fragmentomic assays in clinically validated cohorts. **Methods:** We systematically searched PubMed, Cochrane Library, and Scopus for studies evaluating blood-based cfDNA fragmentomic assays for lung cancer detection. Eligible studies were required to be lung cancer-specific, use fragmentomics-based features derived from plasma cfDNA, include an independent validation or test cohort, and report extractable binary diagnostic accuracy data. Training-only studies, multi-omic assays, and studies lacking sensitivity and specificity at a prespecified threshold were excluded. Sensitivity and specificity were jointly pooled using a bivariate random-effects model based on 2×2 contingency tables, accounting for threshold effects and between-study heterogeneity. **Results:** Five studies with independent validation cohorts comprising 725 lung cancer cases and 435 non-cancer controls were included, spanning screening-eligible populations, LDCT-positive pulmonary nodules, early-stage disease, and mixed-risk cohorts. Using a bivariate random-effects model, pooled sensitivity was 87.5% (95% CI, 77.4%–93.4%) and pooled specificity was 85.7% (95% CI, 63.6%–95.4%), corresponding to a pooled positive likelihood ratio of 6.14 (95% CI, 2.34–19.26) and negative likelihood ratio of 0.146 (95% CI, 0.074–0.295), and diagnostic odds ratio of approximately 42. Moderate inter-study heterogeneity was observed ($I^2=62\%$), largely attributable to differences in clinical setting, disease spectrum, and control composition; however, diagnostic performance remained directionally consistent across cohorts. The summary receiver operating characteristic curve demonstrated excellent overall discrimination (AUC 0.92). **Conclusions:** Across clinically validated cohorts, blood-based cfDNA fragmentomic assays demonstrated strong discriminative performance for lung cancer detection. Despite heterogeneity across study populations and clinical use cases, pooled sensitivity and specificity were robust, supporting the potential role of cfDNA fragmentomics as a noninvasive adjunct to existing screening and diagnostic strategies. Research Sponsor: None.

Diagnostic performance of cfDNA fragmentomic assays for lung cancer detection.		
Measure	Estimate	95% CI
Sensitivity	87.5%	77.4–93.4
Specificity	85.7%	63.6–95.4
LR+	6.14	2.34–19.26
LR–	0.15	0.07–0.30
AUC	0.92	–

Enterprise-wide implementation of multicancer detection testing across a large academic health system.

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Background: Multicancer detection (MCD) testing using cell-free DNA methylation patterns is a novel blood-based approach to cancer screening. In 2022, Mayo Clinic implemented offering MCD testing into routine clinical practice. Prior real-world reports have been limited to single-site experiences. We evaluated enterprise-wide implementation of MCD testing across all three Mayo Clinic sites using the Mayo Clinic Platform. **Methods:** We performed a retrospective analysis of de-identified clinical data from Mayo Clinic Platform Discover, including GRAIL Galleri tests performed at Mayo Clinic sites in Rochester, MN; Scottsdale, AZ; and Jacksonville, FL. This activity did not require IRB review per 45 CFR 46.102. Demographics, test results, cancer diagnoses, and prior cancer history were extracted using a privacy-preserving protocol, with data de-identified by expert determination. ICD-10 diagnostic codes were used to identify subsequent cancer diagnoses. **Results:** A total of 8,201 Galleri tests were performed in 7,300 patients; some patients underwent repeat testing. Fifty-seven tests (0.7%) were positive. Among MCD-positive patients, cancer diagnostic codes were identified in 32 patients, yielding a positive predictive value (PPV) of 58.7%. The most common cancers identified were oropharyngeal (34.4%), lymphoid and hematopoietic (34.4%), and gastrointestinal malignancies (18.8%). Among 8,144 MCD-negative tests (99.3% of all testing performed), 423 patients (5.2%) subsequently received a cancer diagnostic code, yielding a negative predictive value of 92.5%. The most commonly identified cancers in this group were male genital organs (36.6%), urinary tract (10.6%), and thyroid or other endocrine glands (7.3%). Overall, 10.1% of patients had a prior cancer history, which was more common in MCD-positive than MCD-negative patients (22.6% vs 10.0%). Patients with positive tests were older (mean age 68.4 vs 61.5 years) and more often male (67% vs 62%). Race distribution was similar. **Conclusions:** Enterprise-wide implementation of MCD testing across diverse clinical settings is feasible within routine workflows. Over half of positive tests were associated with cancer diagnostic codes, supporting the clinical promise of MCD testing. Limitations include incomplete capture of externally diagnosed cancers and lack of cancer signal-of-origin data. The Mayo Clinic Platform enables scalable, secure analytics to support future cancer interception strategies. Research Sponsor: None.

Structural disparities in early-onset colorectal cancer mortality: A national county-level analysis.

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Background: Early-onset colorectal cancer (CRC) incidence and mortality are rising, with significant disparities by geography and socioeconomic status. We examined county-level disparities in early-onset CRC mortality (ages < 55) across the United States to identify modifiable factors associated with mortality rates. **Methods:** We analyzed age-adjusted CRC mortality rates from CDC WONDER. Predictors included rurality (Rural–Urban Continuum Codes 2023: non-metro vs metro), socioeconomic factors (median income, % uninsured, % poverty from County Health Rankings 2025), demographic composition (% non-Hispanic Black, % Hispanic), health behaviors (current smoking, obesity, routine checkup from PLACES 2025), and healthcare access (gastroenterologist, primary care physician, and hospital counts from AHRF 2024–2025). Multivariable linear regression assessed associations between predictors and mortality, with continuous variables standardized to z-scores. Counties with missing or unreliable mortality data were excluded ($p < 0.05$ for significance). **Results:** The final sample included 672 counties. Mean mortality was 4.26 per 100,000 (range 1.7–11.9). Non-metro counties comprised 12.2% ($n = 82$). The model explained 54.8% of variance in mortality ($F = 66.5$, $p < 0.001$). Current smoking was the strongest predictor ($\beta = 0.54$ per SD, 95% CI: 0.38–0.70, $p < 0.001$), indicating a one-SD increase in smoking prevalence corresponded to a 0.54 per 100,000 higher mortality rate. Non-metro counties had 0.80 more deaths per 100,000 than metro counties (95% CI: 0.56–1.05), a 19% increase relative to the mean. Poverty ($\beta = 0.21$ per SD, $p = 0.011$), uninsured rates ($\beta = 0.20$ per SD, $p < 0.001$), and % Black ($\beta = 0.21$ per SD, $p < 0.001$) were also significant. Higher Hispanic population was associated with lower mortality ($\beta = -0.20$ per SD, $p = 0.001$). Healthcare provider variables (gastroenterologist count, primary care count, hospital count) were not significantly associated ($p \geq 0.051$). **Conclusions:** Geographic, socioeconomic, and health behavior factors accounted for 54.8% of variation in early-onset CRC mortality, with smoking showing the strongest association. Non-metro counties and areas with higher poverty, uninsured rates, and smoking prevalence had higher mortality, though these relationships are not causal. Remaining unexplained variance suggests roles for screening uptake, stage at diagnosis, treatment quality, and genetic susceptibility. Findings identify high-risk counties and highlight the need for future causal analyses to clarify pathways underlying disparities and support targeted interventions. Research Sponsor: None.

Quantifying the macroeconomic burden of cancer: Global disparities in value-of-lost-welfare (VLW).

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Background: Cancer (CA) remains a leading global driver of disability and premature death, yet its full macroeconomic toll is rarely quantified. In this study, we estimated the global economic welfare loss attributable to all cancers in 2023 across 183 countries using a standardized Value of Lost Welfare (VLW) framework. **Methods:** We obtained country-level disability-adjusted life years (DALYs) for CA from the Global Burden of Disease Study 2023. Corresponding GDP (PPP, current international dollars) and population data were sourced from the World Bank. We calculated VLW by multiplying DALYs by a fixed monetary value of USD 14,403.29 per DALY, yielding estimates of total VLW, per-capita VLW, and VLW/GDP (%). CA-specific estimates were derived using cause-wise DALY distributions across global and regional levels. **Results:** In 2023, CA caused 268.9 million DALYs globally, resulting in a global VLW of USD 3.87 trillion—equivalent to 2.12% of global GDP, with an average per-capita economic loss of 522 billion. The largest absolute economic losses were reported in China (915.5 billion), India (458.7 billion), and the United States, followed by Japan (126.7 billion) and Brazil (108.6 billion). When adjusted for national GDP, the highest VLW-to-GDP ratios were observed in Zimbabwe (4.24%), Cambodia (4.00%), Mongolia (3.45%), India (3.09%), and Egypt (1.63%), reflecting intense economic vulnerability. Across SDI strata, high-SDI countries bore the greatest economic burden, incurring a VLW of 1.80 trillion, followed by high-middle SDI (808.7 billion), low SDI (568.0 billion), low-middle SDI (406.5 billion), and middle SDI (384.9 billion). While absolute losses were highest in high-SDI settings, VLW/GDP ratios were notably elevated in low- and low-middle SDI regions, signaling disproportionate economic strain in resource-limited contexts. By CA type, lung CA led the global burden with 672 billion in welfare losses, followed by colorectal CA (377 billion), breast CA (355 billion), stomach CA (324 billion), and esophageal CA (202 billion). **Conclusions:** The global macroeconomic cost of CA surpassed USD 3.6 trillion in 2023, with marked disparities across countries and regions. High-burden nations such as China, India, and the U.S. faced the steepest absolute losses, while several low-income countries suffered disproportionately high economic strain relative to GDP. The concentration of losses in five major CA types signals an urgent need for enhanced global investments in CA prevention, early detection, and control. Research Sponsor: None.

Regional cancer burden and economic losses in 2023.			
Region	DALYs (Millions)	VLW (\$ Billion)	VLW/GDP (%)
Sub-Saharan Africa	28.82	415.14	6.64
South Asia	43.72	629.68	3.48
Southeast Asia, East Asia & Oceania	89.19	1284.6	2.76
North Africa & Middle East	14.34	206.6	2.50
Latin America & Caribbean	18.39	264.91	2.36
Central/Eastern Europe & Central Asia	20.89	300.85	2.20
High Income	60.37	869.53	1.25

Multimodal profiling of STIC lesions to identify precursor states with genomic features of high grade serous ovarian cancer.

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Background: High-grade serous ovarian cancer (HGSC) is a lethal gynecologic malignancy characterized by near-universal *TP53* inactivation, chromosomal instability (CIN), and frequent whole-genome doubling. Because population screening is ineffective, risk-reducing salpingo-oophorectomy (RRSO) remains the only proven risk-reduction strategy. Nonetheless, some individuals develop primary peritoneal carcinoma (PPC), and identification of serous tubal intraepithelial carcinoma (STIC) at RRSO is associated with > 30-fold higher PPC risk. We sought to define the molecular steps required for HGSC initiation and identify features of high-risk STIC. **Methods:** We assembled a 201-patient cohort spanning stages of HGSC development, including normal fallopian tube epithelium, p53 signatures, STIC, and early- and advanced-stage HGSC. All specimens underwent multiplex immunofluorescence (mpIF). Forty-five samples from 36 patients were profiled using Visium HD spatial transcriptomics (> 20 million 8- μ m bins). We analyzed epithelial state transitions using unsupervised clustering and trajectory inference. Copy-number variation (CNV) was inferred using spatial inferCNV; CNV calls were validated with matched formalin-fixed paraffin-embedded (FFPE) single-cell whole-genome sequencing. **Results:** mpIF demonstrated lesion-to-lesion variability in cyclic GMP-AMP synthase (cGAS) staining within STIC, consistent with evolving tolerance to CIN before invasion. Spatial transcriptomic clustering identified distinct, reproducible STIC epithelial programs that mapped to histologic features. STIC programs were enriched for NF- κ B and TGF- β signaling and lacked evidence of the JAK/STAT activation observed in advanced HGSC. CNV inference showed that normal fallopian tube and p53 signature lesions were chromosomally stable, whereas STIC displayed broad, genome-wide alterations resembling advanced HGSC, including losses encompassing *TP53*, *BRCA1*, and *BRCA2* and amplifications of *MYC* and *CCNE1*. In a germline *BRCA2* carrier, we identified polyclonal STIC with distinct CNV profiles; trajectory analysis suggested early CNV changes within an expanded secretory population, followed by loss of chromosome 17 (*TP53*), loss of chromosome 13 (*BRCA2*), and subsequent oncogene amplifications (e.g., *MYC*). As lesions became invasive, spatial CNV profiling revealed neighborhoods of clonally related invasive cells with distinct microenvironments, including differences in fibroblast states and vascularization. **Conclusions:** A multimodal atlas of fallopian tube transformation supports a model in which *TP53* loss precedes *BRCA1/2* inactivation and indicates that STIC is genomically similar to advanced HGSC. These findings provide a framework to study early HGSC evolution, stratify STIC risk after RRSO, and inform early-interception strategies. Research Sponsor: Ovarian Cancer Research Alliance; MIG-2023-1-1012; Conquer Cancer Research; U.S. National Institutes of Health; CA281928-01.

Texture and color enhancement imaging (TXI) for polyp detection in colorectal neoplasia screening: A meta-analysis of randomized controlled trials.

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Background: Colonoscopy remains the gold standard for preventing colorectal cancer; however, variable adenoma detection rates (ADR) among endoscopists highlight the need for improved visualization technologies. Texture and Color Enhancement Imaging (TXI) is a novel image-enhanced endoscopy modality designed to optimize the visibility of mucosal lesions by enhancing surface texture and brightness. This meta-analysis evaluates the efficacy of TXI compared to standard high-definition white-light imaging (HD-WLI) in the detection of colorectal neoplasia, specifically assessing whether enhanced visualization translates to higher detection rates of adenomas and polyps in a randomized controlled setting. **Methods:** We conducted a systematic review and meta-analysis of prospective randomized controlled trials (RCTs) published between 2023 and 2025. The analysis included adult patients undergoing colonoscopy for screening, surveillance, or diagnostic indications where TXI was compared to HD-WLI during the withdrawal phase. Primary outcomes included ADR, polyp detection rate (PDR), and adenomas per colonoscopy (APC). Secondary outcomes included polyps per colonoscopy (PPC) and flat lesion detection. Statistical analysis was performed using a random-effects model (DerSimonian-Laird method). Risk ratios (RR) and mean differences (MD) with 95% confidence intervals (CI) were calculated, with heterogeneity assessed via I^2 statistics. **Results:** The analysis pooled data from four RCTs comprising 2,308 patients. The chief finding was a statistically significant 25.5% increase in the Polyp Detection Rate (PDR) with TXI compared to WLI (pooled RR = 1.255; 95% CI: 1.050–1.498; $p < 0.05$). Regarding the Adenoma Detection Rate (ADR), TXI showed a positive trend with a 22% relative increase (pooled RR = 1.220; 95% CI: 0.981–1.519); however, this did not reach statistical significance ($p > 0.05$). Analysis of Adenomas per Colonoscopy (APC) showed no significant difference (MD = 0.153; $p > 0.05$). Substantial heterogeneity was observed across outcomes ($I^2 > 60\%$), suggesting variability in endoscopist experience or study populations. **Conclusions:** Texture and Color Enhancement Imaging demonstrates clear superiority over white-light imaging for overall polyp detection, establishing it as a promising tool for identifying colorectal neoplasia. While TXI significantly improved PDR, the improvement in ADR showed a strong positive trend that did not reach statistical significance, likely due to high between-study heterogeneity. These findings suggest that TXI enhances lesion visibility, particularly for general polyps, but further large-scale RCTs are necessary to definitively establish its impact on adenoma detection and long-term interval cancer prevention. Research Sponsor: None.

GLP-1 receptor agonist therapy and cancer risk and mortality in patients with moderate CKD: A national matched cohort study of 58,000 patients.

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Background: Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have been associated with reduced mortality in patients with Type 2 Diabetes Mellitus (T2DM) and may lower cancer risk. However, the impact of GLP-1 RAs on cancer incidence and mortality in patients with chronic kidney disease (CKD) remains understudied. Thus, in this study we evaluated whether GLP-1 RA use modifies cancer risk and mortality in a contemporary national cohort of patients with moderate CKD. **Methods:** We performed a retrospective cohort study using the TriNetX Research Network, identifying adults aged 18–90 years with T2DM and newly diagnosed stage-3 CKD between January 2015 and February 2025. Patients with prior malignant neoplasms or end-stage renal disease were excluded. Exposure was defined as a prescription for a GLP-1 RA within 90 days before CKD diagnosis; controls had no documented GLP-1 RA use. Outcomes were evaluated beginning 90 days after the index CKD diagnosis to reduce reverse-causation and immortal-time bias. Our primary outcome was any malignant neoplasm. Our secondary outcomes were site-specific malignant neoplasms (colorectal, lung, liver, kidney, pancreatic, breast, and prostate) as well as all-cause mortality. We performed 1:1 propensity score matching balancing demographics, comorbidities, laboratory values (hemoglobin A1c and estimated glomerular filtration rate), and cardiometabolic medications. After matching, we calculated absolute risks, risk differences, hazard ratios, risk ratios, and 95% confidence intervals. Statistical significance was defined as $p < 0.05$. **Results:** After matching, 28,948 patients remained in each group. GLP-1 RA use was associated with significantly lower all-cause mortality (8.6% vs 15.0%; HR 0.57; 95% CI, 0.546–0.599; $p < 0.001$). Overall malignant neoplasm incidence was significantly lower with GLP-1 RA use (7.0% vs 7.7%; RR 0.90; $p < 0.001$). Among site-specific malignancies, the GLP-1 RA group demonstrated lower incidence of lung cancer (0.5% vs 0.8%; RR 0.56; $p < 0.001$), colorectal cancer (0.5% vs 0.7%; RR 0.74; $p = 0.006$), and liver cancer (0.3% vs 0.4%; RR 0.63; $p = 0.001$). Pancreatic cancer (0.2% vs 0.3%; RR 0.89; $p = 0.46$), kidney cancer (0.5% vs 0.6%; RR 0.98; $p = 0.87$), prostate cancer (1.1% vs 1.0%; RR 1.08; $p = 0.32$), and breast cancer (0.7% vs 0.7%; RR 1.11; $p = 0.30$) did not differ significantly based on GLP-1 RA receipt. **Conclusions:** In patients with T2DM and stage-3 CKD, GLP-1 RA therapy was associated with substantially lower mortality and reduced incidence of several major malignancies, particularly lung, colorectal, and hepatocellular cancers. These findings highlight a potential role for GLP-1-mediated metabolic modulation in cancer prevention among high-risk populations. Prospective studies are warranted to clarify mechanisms and confirm these observations. Research Sponsor: None.

Non-random patterns of multiple primary malignancies in the era of cancer survival.

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Background: Improved cancer therapies have increased survival, placing survivors at risk for subsequent primary cancers, yet the epidemiology of multiple primary cancers (MPC) is poorly defined. **Methods:** Using the VA Cancer Registry (2003–2023), we quantified MPC frequency, classified cancers by SEER ICD-O-3 codes and histology, and analyzed incidence and expected versus observed occurrence. **Results:** Among 822,564 veterans with cancer, 11.1% (n=91,279) developed ≥ 2 primary cancers. The frequencies of patients with 2, 3, 4, or ≥ 5 MPC were 81715 (9.9%), 8655 (1.1%), 800 (0.1%), and 109 (0.01%), with similar relative risks across successive cancers. Interestingly, the median age at first cancer was similar across groups (67.3 years for 1 cancer; 66.6, 65.8, and 65 years for 2, 3 and 4 cancers). In contrast, intervals between successive cancers progressively shortened (2.7 years – 2 cancers; 2.5 and 1.8 years – 3 cancers; 2.2, 1.9, and 1.4 years – 4 cancers), suggesting prior cancer influences the risk of subsequent cancer. The 7 most common first and subsequent cancers were prostate, bladder, lung, colon, melanoma, kidney, and oral cavity cancers. We identified three etiologic patterns underlying MPC. First, exposure-related cancers, clustered as expected, lung cancer was the most common 2nd and 3rd cancer after bladder (n=1850 and 231) and oral cavity (n=1581 and 148) cancers, suggesting a relationship to smoking. Second, genetically predisposed cancers did not cluster, likely reflecting the older population. Third, therapy-related cancers increased, with acute myeloid leukemia (AML)/acute lymphoblastic leukemia (ALL) standard rates rising from 0.02/0.003 (1st) to 39.01/3.19 (AML) and 5.04/0.03 (ALL) as 2nd and 3rd primary cancers. Interestingly, the frequency of prostate cancer and chronic lymphocytic leukemia (CLL) declined with increasing cancer order, consistent with earlier detection through established screening practices, and in contrast, lung cancer and multiple myeloma (MM) frequency increased as subsequent cancers, suggesting more complex etiologies, including aging-related risk. **Conclusions:** In this large VA registry analysis, over 11% of cancer survivors developed MPC with consistent patterns of occurrence, shortening inter-cancer intervals, and non-random clustering by exposure-, therapy-, and disease-specific factors. These findings underscore the need for risk-adapted surveillance and long-term survivorship strategies that account for shared etiologies and treatment-related risks rather than assuming stochastic occurrence. Research Sponsor: None.

Frequency of a cancer as MPC.		1 st primary	2 nd primary	3 rd primary	4 th primary
Pts with 2 cancers	Prostate	29.4%	14.1%		
	CLL	2.3%	1.1%		
	Lung	7.8%	20%		
	MM	1.1%	1.7%		
Pts with 3 cancers	Prostate	28.1%	15.6%	9.3%	
	CLL	2.8%	2.2%	1%	
	Lung	5.4%	11.7%	20.6%	
	MM	0.8%	1.5%	2%	
Pts with 4 cancers	Prostate	26%	14.8%	12.1%	7.3%
	CLL	2.4%	1.8%	1.9%	1.4%
	Lung	5.4%	8.4%	13.9%	22.9%
	MM	1%	1.1%	1.8%	2.1%

Differential risk patterns of secondary breast cancer in medullary versus papillary thyroid carcinoma survivors: A SEER-based analysis.

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Background: Prior studies suggest that thyroid cancer (TC) survivors may have an elevated risk of secondary malignancies. However, whether this risk differs by TC histology, specifically with breast cancer (BC), remains unclear. We aimed to investigate the association between TC subtype—papillary thyroid carcinoma (PTC) versus medullary thyroid carcinoma (MTC)—and subsequent BC risk, adjusting for demographic factors. **Methods:** We conducted a retrospective cohort study using the SEER (2000–2022), including adults with a primary, microscopically confirmed PTC or MTC. Subsequent BC occurrence was defined as a binary outcome (yes/no). Multivariable logistic regression was used to estimate adjusted odds ratios (aORs) for MTC versus PTC, controlling for age (<50 vs ≥50 years), sex, and race. Stratified analyses by age and race were also performed. Stata 15 was used for statistical analyses. **Results:** 14,840 patients (14,563 PTC, 277 MTC) were included. MTC patients were older (mean 59.08±12.66 vs 56.16±12.98 years, $p<0.001$) and had a higher proportion of males (44.4% vs 29.4%, $p<0.001$). The overall incidence of secondary BC was lower in MTC patients (7.6% vs 22.5%, $p<0.001$). In unadjusted logistic regression, MTC was associated with significantly lower BC risk (OR=0.28, 95% CI: 0.18–0.44, $p<0.001$). After adjustment, MTC remained significantly protective (aOR=0.34, 95% CI: 0.22–0.55, $p<0.001$). Stratified analyses demonstrated consistent findings across age groups (<50: aOR=0.10, 95% CI: 0.03–0.42; ≥50: aOR=0.34, 95% CI: 0.21–0.54), as well as white and Hispanic patients. **Conclusions:** Survivors of MTC have a substantially lower risk of developing secondary BC compared to PTC survivors. This association persists after adjustment for age, sex, and race, and is consistent across age and most racial subgroups. However, different BC types were not assessed due to limited number of BC patients among MTC survivors, and the small MTC sample size and potential survival differences between groups may affect the results. These findings highlight a possible effect of TC subtype on BC risk, suggesting the potential influence of underlying biological or genetic mechanisms. Research Sponsor: None.

Baseline demographic characteristics of patients with papillary and medullary thyroid carcinoma.

Characteristic	Papillary Thyroid Carcinoma (PTC) (N=14,563)	Medullary Thyroid Carcinoma (MTC) (N=277)	P-value
Age at Diagnosis			0.0002*
Mean ± SD, years	56.16 ± 12.98	59.08 ± 12.66	
Median, years	57	61	
Sex, n (%)			<0.001†
Female	10,288 (70.6)	154 (55.6)	
Male	4,275 (29.4)	123 (44.4)	
Race, n (%)			0.015†
White	10,263 (70.5)	197 (71.1)	
Black	921 (6.3)	15 (5.4)	
American Indian	77 (0.5)	1 (0.4)	
Asian	1,379 (9.5)	13 (4.7)	
Hispanic	1,903 (13.1)	50 (18.1)	

SD: Standard Deviation.

*P-value from two-sample t-test (equal variances assumed).

†P-value from chi-square test for the overall distribution across categories.

Association of prior SARS-CoV-2 infection with advanced cancer presentation in newly diagnosed solid tumors: A real-world data analysis.

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Background: Emerging evidence suggests that the impact of SARS-CoV-2 infection may extend beyond acute respiratory illness, with potential implications for cancer biology. Recent proteomic analyses and reviews have highlighted several ways in which SARS-CoV-2 might interact with host pathways relevant to oncogenesis, tumor progression, and cellular plasticity. Taken together, these findings support a plausible biological rationale that COVID-19 infection may influence the clinical behavior or progression of solid tumors, potentially leading to diagnosis at later stages or the emergence of more aggressive phenotypes. In this study, we use real-world data from the TriNetX US Collaborative network to test the hypothesis that patients with solid tumors who have had COVID-19 are more likely to present with advanced-stage disease compared to those without a history of SARS-CoV-2 infection. **Methods:** We conducted a retrospective cohort study of adults (≥ 18 years) with newly diagnosed solid tumors, including breast, lung, colorectal, and prostate cancers, between January 1, 2021, and December 1, 2025. Patients were categorized based on documented SARS-CoV-2 infection prior to cancer diagnosis (COVID-positive vs COVID-negative), defined using ICD-10 codes and laboratory-confirmed PCR or antigen testing. Patients with any prior cancer diagnosis were excluded. The primary outcome was aggressive presentation, defined as AJCC Stage IV, M1 classification, or ICD-10 codes C77–C79 within 90 days of diagnosis. To reduce confounding, 1:1 propensity score matching was performed based on age, sex, race, ethnicity, cancer type, and comorbidities, including obesity, chronic lung disease, chronic kidney disease, diabetes, and hypertension. **Results:** After 1:1 propensity score matching, 201,131 patients were included in each cohort. Aggressive cancer presentation occurred in 16.8% of COVID-positive patients compared with 15.1% of COVID-negative patients. COVID-positive patients had a higher risk of aggressive disease presentation, corresponding to an absolute risk increase of 1.73% (95% CI, 1.50–1.96) and a relative risk of 1.11 (95% CI, 1.10–1.13). The odds of aggressive presentation were also higher among COVID-positive patients (OR, 1.14; 95% CI, 1.12–1.16; $p < 0.0001$). **Conclusions:** Prior COVID-19 infection was associated with a higher likelihood of advanced and metastatic cancer presentation at diagnosis, even after adjustment for demographic factors and comorbidities. These findings highlight the potential long-term oncologic impact of the COVID-19 pandemic and warrant further investigation. Research Sponsor: None.

Distinct immunogenomic features of cancers arising in solid organ transplant recipients.

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Background: Solid organ transplantation recipients (SOTRs) are at increased risk of cancer due to long-term immunosuppressive therapy to prevent organ rejection. However, the immunogenomic characteristics of cancers arising in SOTRs remain poorly defined, limiting evidence-based treatment decisions, particularly regarding immunotherapy. **Methods:** Next-generation sequencing (NGS) of tumor tissue for DNA (592-gene panel/whole exome) and RNA (whole transcriptome) was carried out at Caris Life Sciences for SOTRs (n=1,024) and individuals without a transplant matched by age, sex, and cancer type (10:1 ratio, n=10,240). Immune cell infiltration in the tumor microenvironment (TME) was estimated by quanTIseq. Interferon-gamma (IFN- γ) signaling was assessed by a 10-gene transcriptomic signature. Tumor mutational burden (TMB) was assessed by NGS. Microsatellite instability (MSI) was assessed by immunohistochemistry (IHC) and NGS, and PD-L1 expression by IHC. Among SOTRs treated with immunotherapy, overall survival was assessed from insurance claims and calculated from treatment initiation to last contact. **Results:** The median age at sample collection was 65 years, with kidney recipients comprising the majority of SOTR cases (59.6%). Non-small cell lung cancer (NSCLC) was the most common malignancy (18.5%), followed by colorectal cancer (CRC, 10.5%). For all tumors combined, SOTRs exhibited significantly reduced adaptive immune cell infiltration in the TME, including CD8⁺ T-cells (SOTR vs non-SOTR median: 0.11% vs 0.23%), regulatory T-cells (1.60% vs 2.10%) and B-cells (3.69% vs 3.91%); no significant differences were observed in innate immune cell fractions except for myeloid dendritic cells (0.64% vs 0.79%). While IFN- γ signatures were similar among all SOTRs and non-SOTRs, SOTRs had significantly lower IFN- γ for NSCLC and cutaneous squamous cell carcinoma (cSCC). Median TMB was significantly higher in SOTRs than non-SOTRs for NSCLC, colorectal cancer (CRC), pancreatic cancer, cSCC, melanoma, and esophageal cancer. MSI was more common in SOTRs overall (4.9% vs 1.9%; $p < 0.0001$) and for CRC (15.8% vs. 6.8%; $p < 0.0001$). PD-L1 positivity was less common in SOTRs than non-SOTRs (12.4% vs 18.6%; $p = 0.021$). Finally, among SOTRs treated with immunotherapy, those with high TMB (≥ 10 mutations/Mb) tended to have better survival than those with low TMB (hazard ratio 0.79, 95%CI 0.47-1.34, $p = 0.374$). **Conclusions:** Despite higher prevalence of tumors with high TMB and MSI for select cancer types, SOTRs had lower adaptive immune infiltration and IFN- γ signaling within the TME, likely reflecting the immunosuppressive anti-rejection treatment. Our findings highlight distinct immunogenomic features of transplant-associated cancers and provide biologic rationale for further study of immunotherapy strategies in carefully selected SOTRs. Research Sponsor: None.

PCSK9 inhibitors and association with lower risk of metastasis.

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates degradation of membrane proteins including the low-density lipoprotein (LDL) receptor and major histocompatibility complex class I (MHC-I) independently. Beyond lipid metabolism, preclinical studies have shown that PCSK9 inhibition reduces metastasis in animal models, suggesting potential to suppress tumor cell proliferation, migration, and immune evasion. However, population-level evidence across malignancies is limited. We evaluated whether PCSK9 inhibitor (PCSK9i) use is associated with risk of cancer metastasis in a large real-world cohort. **Methods:** In this new-user, active-comparator cohort study using the TriNetX U.S. Collaborative Network (≈ 134 million patients), eligible patients were adults who initiated PCSK9i or statins alone for hyperlipidemia between 01/01/2015 and 01/01/2025 and subsequently received a cancer diagnosis. Index date was first prescription of PCSK9i or statin, with follow-up period continued until occurrence of study outcomes. To reduce reverse causation and early detection bias from intensified workup around drug initiation, patients with any cancer diagnosis within 6 months after index were excluded. 1:1 propensity score matching (PSM) balanced pre-index demographics, ASCVD and liver comorbidities, cancer screening procedures (low-dose chest CT, Pap smear, colonoscopy), BMI, and LDL. Primary outcome was time to any metastatic cancer (ICD-10 C77–C79); secondary outcomes were site-specific metastases (liver, lung, bone, brain, lymph node, adrenal gland). Cox proportional hazards models estimated hazard ratios (HRs) with 95% CIs. **Results:** Among 1,149,843 adults newly prescribed PCSK9i or statin (mean age 61.7 years, SD 10.6), median follow-up was 2,926 days. After 1:1 PSM, 8,674 patients remained in each cohort with balanced baseline characteristics (all standardized mean differences < 0.1). Metastatic cancer was diagnosed in 435 PCSK9i patients versus 741 statin patients. The overall hazard of metastasis did not differ significantly (HR 0.96, 95% CI 0.85–1.08). In site-specific analyses, PCSK9i use was associated with lower hazards of liver metastasis (HR 0.64, 95% CI 0.50–0.85) and lung metastasis (HR 0.78, 95% CI 0.65–0.94); hazards for lymph node, brain, adrenal, and bone metastases were similar between groups. Sensitivity analyses accounting for competing risk of death showed consistent directionality. **Conclusions:** In this nationwide cohort study, overall metastatic risk was similar between PCSK9i and statin-only users, but PCSK9i use was associated with lower hazards of liver and lung metastases. Further mechanistic and prospective investigation are warranted to elucidate the role of PCSK9 inhibition in tumor progression and metastasis. Research Sponsor: None.

The effects of the COVID-19 pandemic on cancer incidence and cancer-specific mortality.

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Background: The 2020 COVID-19 pandemic had a significant impact on cancer screening rates and cancer-related outcomes. The purpose of our study was to determine how the pandemic has affected cancer incidence, incidence by Surveillance, Epidemiology and End Results (SEER) stage, and cancer-specific mortality for the most common cancers in incidence and cancer-specific mortality. **Methods:** The data for our population-based cohort study was accessed by permission from the SEER dataset. We aggregated data for incidence and cancer-specific mortality regarding the leading ten cancers in incidence and cancer-specific mortality, plus cervical cancer, between January 1, 2017 and December 31, 2022 and further divided this time period into two 36-month pre-pandemic and post-pandemic groups. Demographic variables were collected for stratified analyses. Poisson regression models were used to estimate incidence and mortality rates for each cancer type, incorporating the natural logarithm of the total population as an offset term to account for differences in population size. **Results:** Nine of eleven cancers showed significantly higher IRRs (incidence rate ratios) for distant SEER stages during the 36-month post-pandemic period. Most importantly, several cancers with established screening modalities had significantly increased IRRs for distant SEER stage of disease including prostate cancer (IRR 1.175, 95% CI: 1.155-1.195, $p < 0.001$), breast cancer (IRR 1.060, 95% CI: 1.040-1.080, $p < 0.001$), and colorectal cancer (IRR 1.034, 95% CI: 1.020-1.048, $p < 0.001$). Cancer-specific mortality showed significantly increased post-pandemic mortality rate ratios (MRRs) for pancreatic cancer (MRR 1.049, 95% CI: 1.041-1.056, $p < 0.001$), prostate cancer (MRR 1.042, 95% CI: 1.032-1.051, $p < 0.001$), and liver cancer (MRR 1.026, 95% CI: 1.016-1.036, $p < 0.001$). Lung cancer (MRR 0.931, 95% CI: 0.927-0.935, $p < 0.001$), Non-Hodgkin's Lymphoma (MRR 0.972, 95% CI: 0.961-0.983, $p < 0.001$) and breast cancer (MRR 0.989, 95% CI: 0.981-0.996, $p = 0.004$) all had significantly lower cancer-specific mortality in our post-pandemic period. **Conclusions:** In this large population-based cohort, we observed a shift towards more distant SEER stage cancer diagnoses in the post-pandemic period. The increase in advanced-stage diseases reflects a higher burden of disease and is particularly concerning for cancers with proven screening benefit. These findings suggest persistent downstream effects of disruptions in routine healthcare and cancer screening which have added to the public health crisis of the COVID-19 pandemic. Research Sponsor: None.

Association of SGLT2 inhibitors and GLP-1 receptor agonists or DPP-4 inhibitors with incident cancer in patients with type 2 diabetes.

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) exert potential anti-tumor effects. Emerging data suggest SGLT2i are associated with reduced cancer incidence in type 2 diabetes (T2D), while incretin-based therapies show mixed results varying by cancer type. Among patients with T2D, we tested that hypothesis that use of SGLT2i, as compared to GLP-1 receptor agonists (GLP-1RA), and dipeptidyl peptidase-4 inhibitors (DPP-4i), would be associated with lower risk of overall and individual cancer types. **Methods:** Matched cohort study using MarketScan US claims database (2016–2022). T2D patients with ≥ 1 metformin prescription and >90 days enrollment before 2nd line therapy initiation were included. SGLT2i users were matched with up to 5 users of other therapies by age, sex, enrollment, and 2nd line therapy initiation dates. ICD codes were used to identify cancer. Cox models adjusted for demographics, comorbidities, and medications. **Results:** Among 365,494 matched patients (mean $\pm$ SD age 54.2 $\pm$ 10.0 years, 48.5% female), 5,422 incident cancers occurred over median 1.43 (maximum 6.75) years follow-up. Cohort included 133,210 SGLT2i users (empagliflozin 55%, dapagliflozin 32%, canagliflozin 12%) and 232,284 comparators (GLP-1RA 60.4%, DPP-4i 39.6%). SGLT2i users showed modestly lower composite cancer risk versus other therapy users [Hazard ratio (HR) 0.94, 95% CI 0.89–0.99]. Compared with DPP-4i use, SGLT2i use demonstrated 10% lower cancer risk (HR 0.90, 95% CI 0.85–0.97), but showed no significant difference versus GLP-1RA use (HR 0.97, 95% CI 0.91–1.04). Analyses by cancer type revealed no significant differences in HR for breast (0.92, 0.84–1.04), prostate (0.96, 0.84–1.08), colorectal (0.96, 0.82–1.12), lung (0.95, 0.78–1.16), pancreatic (1.04, 0.84–1.28), hepatocellular (1.01, 0.76–1.33), renal cell (0.92, 0.76–1.11), endometrial (1.01, 0.79–1.29), or thyroid cancers (0.84, 0.66–1.06). Cancer risk was comparable across individual SGLT2i ($p>0.05$). **Conclusions:** SGLT2i demonstrated a 10% reduction in overall cancer risk versus DPP-4i and comparable efficacy to GLP-1RA, reinforcing SGLT2i's potential oncologic benefits. No associations were observed with individual cancer types, though interpretation is nuanced due to poor precision and short follow-up. Comparable risk among individual SGLT2i suggest a class-wide effect. Future prospective studies with extended follow up are needed to validate these associations and clarify whether SGLT2i offer meaningful cancer risk reduction beyond their established cardiometabolic benefits. Research Sponsor: None.

Hazard ratios (95% CI) for incident cancer, MarketScan databases, 2016-2022.		
	N (events / total)	HR (95% CI)
SGLT2i vs. DPP-4i		
SGLT2i	1,559 / 93,494	0.90 (0.85 - 0.97)
DPP-4i	1,749 / 93,494	Ref
SGLT2i vs. GLP-1RA		
SGLT2i	1,699 / 123,955	0.97 (0.91 - 1.04)
GLP-1RA	1,757 / 123,955	Ref

Predictors of EGFR-mutant primary lung adenocarcinoma.

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Background: The proportion of lung cancer cases in individuals who have never smoked (INS) is increasing. Most of these cases are adenocarcinoma (AC) harboring Epidermal Growth Factor Receptor (EGFR) mutations. As predictors of AC and mutational status (EGFR positive [EGFRp] vs EGFR negative [EGFRn]) are incompletely elucidated, we sought to identify demographic, clinical, and imaging predictors of EGFRp AC. **Methods:** Data were obtained from Weill Cornell's Lung Cancer Database, integrating EGFR mutation status derived from genomic testing, validated natural language processing of unstructured clinical data, and individual and area-level predictors from a large New York City health system. We included patients with early stage, surgically resected primary lung AC, allowing for uniform, robust pathologic and genomic characterization. Lesions were identified on computed tomography (CT) prior to diagnosis. The primary outcome was EGFR positivity. LASSO-penalized logistic regression with 10-fold cross-validation was used to identify key predictors in high-dimensional, correlated data. Model performance was evaluated using cross-validated AUC and classification accuracy. **Results:** Among 1145 adults with primary lung AC (312 subsolid nodules [SSNs] and 833 solid nodules; mean age 69.9 [SD, 9.6]), 58.1% were female and 75.4% had a history of smoking. EGFRp ACs (vs EGFRn) were more likely to present as SSNs (39.3% vs 21.7%, $p < 0.001$) and occur in women (63.6% vs 55.7%, $p = 0.013$), Asian patients (32.7% vs 8.4%, $p < 0.001$), and INS (44.9% vs 15.3%, $p < 0.001$). Those with EGFRp AC were less likely to meet USPSTF lung cancer screening (LCS) criteria (12.5% vs 36.0%, $p < 0.001$) and had lower prevalence of chronic obstructive pulmonary disease, other pulmonary disease, and weight loss at presentation; $p < 0.05$. LASSO-selected predictors of EGFR positivity included SSN density and >1 SSN on CT, former smoking status, family history of LC, and higher exposure to ambient air pollutants (PM_{2.5}, NO₂, O₃). The model demonstrated good discrimination (AUC 0.77, 0.77-0.78). In the SSN subgroup, new LASSO-selected features positively associated with EGFR positivity included right middle lobe location and lobulated margins on CT and SO₂ exposure. Cystic morphology, reticulation, and a new or growing solid component on CT were inversely associated with EGFR positivity. **Conclusions:** In a robust genomically linked and clinically, radiologically, and environmentally enriched dataset, we identified distinct demographic characteristics (female sex, Asian race, family history of LC), CT features (SSN density, multiplicity, lobulated margins), and environmental exposures (PM_{2.5}, NO₂, O₃, SO₂) that may predict EGFR positivity. Moreover, three-fold fewer adults with EGFRp AC met USPSTF LCS criteria. These findings support integrating imaging and non-tobacco risk factors to inform lung AC risk stratification, genomic testing, and more inclusive screening strategies. Research Sponsor: Weill Cornell Medicine Meyer Cancer Center.

Association of sociodemographic, environmental, and health factors with early-onset cancer in a diverse urban cohort.

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Background: Early onset cancer (EOC; diagnosed before age 50) is rising globally, yet its drivers are incompletely understood, especially in diverse community-based populations. We examined sociodemographic, environmental, and health factors associated with EOC in the community-based Chicago Multiethnic Prevention And Surveillance Study (COMPASS) cohort spanning 72 Chicago neighborhoods. **Methods:** This nested case-control study within COMPASS matched EOC cases to controls without cancer 1:2 by age and sex. Standardized mean differences (SMD) compared sample characteristics. Conditional logistic regressions evaluated EOC associations with odds ratios (OR) and 95% confidence intervals (CI), adjusted for race/ethnicity. Meaningful imbalance was defined as $SMD > 0.2$ and statistical significance as $p < 0.05$. **Results:** Among 13,309 COMPASS participants, 265 EOC cases were matched to 530 controls. While the full sample was well balanced by sex (51.4% male), cases were predominantly female (72.8%) and non-Hispanic Black (72.3%). Breast (28.3%) and cervical (16.2%) cancers were most reported. A greater proportion of cases identified as unemployed/disabled but were also college educated and with incomes $\geq \$35,000$ ($SMD = 0.382, 0.326, 0.267$). Parental cancer history was more common in cases ($SMD = 0.504$). No imbalances were observed in neighborhood-level characteristics, including area deprivation index, particulate matter concentration, and healthcare access strain. Cases reported more recent mammography and prostate-specific antigen screening ($SMD = 0.385, 0.407$) but not pap smears ($SMD = 0.195$). Cigarette use did not differ ($SMD = 0.141$). Cases had higher prevalence of type 2 diabetes (T2D), anxiety, and depression ($SMD = 0.216, 0.302, 0.242$), and lower prevalence of allergies ($SMD = 0.229$). EOC was associated with parental cancer history ($OR = 3.62, CI = 2.31-5.67, p < 0.001$), T2D ($OR = 1.65, CI = 1.02-2.69, p = 0.043$), and anxiety ($OR = 2, CI = 1.24-3.23, p = 0.005$), but not sociodemographic or neighborhood factors. **Conclusions:** In this diverse cohort, EOC was associated with multiple factors, including family cancer history, breast/prostate screening, and select health comorbidities. No associations were observed with reported neighborhood-level environmental metrics, current tobacco use, or cervical cancer screening. Our results highlight challenges in measuring sociodemographic and environmental contributors to EOC. Our results align with existing hypotheses on cancer development: familial risk, the potentially protective role of allergies, and T2D-related cancer risk. While causality cannot be inferred, the observed EOC-screening and EOC-anxiety associations warrant further investigation with longitudinal, multilevel research to better define EOC drivers and inform EOC prevention and detection strategies. Research Sponsor: None.

Racial differences in clinical, genomic, and survival outcomes in colorectal cancer.

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Background: Racial differences influence colorectal cancer incidence, biology, and survival, but the clinical and genomic drivers remain unclear. This study evaluates race-based variation in clinical features, metastatic patterns, and key mutations in a large real-world cohort to improve risk stratification and promote equitable treatment. **Methods:** Clinical and genomic data were obtained from MSK-CHORD via cBioPortal, including patients identified as Asian, White, or Black. Variables were analysed in RStudio. Group differences were assessed using chi-square, Fisher's exact tests, or Kruskal–Wallis. Survival was analysed with Kaplan–Meier and Cox models. Significance was set at $p < 0.05$. **Results:** Among 5,168 colorectal cancer patients (White 83.9%, Asian 8.8%, Black 7.4%), several clinical and genomic features varied. Age differed significantly ($p < 0.001$), with Asians and Blacks diagnosed younger (median 58 y vs. 61 y) than Whites. Gender distribution was similar ($p = 0.303$). MSI-instability varied ($p = 0.0321$), lowest in Asians (7.7%) and Blacks (8.3%), and highest in Whites (11.9%). Right-sided tumours differed ($p < 0.001$), being least common in Asians (23.7%) and most common in Blacks (40.8%). Stage at diagnosis was similar ($p = 0.0961$). TMB differed modestly ($p = 0.042$): 5.87 in Asians vs. 6.05 in Black and White patients. FGA showed similarly small variation ($p = 0.046$): 0.17 in Asians, 0.16 in Blacks, and 0.15 in Whites. Liver metastases varied by race ($p < 0.001$): Asians 52%, Blacks 66%, Whites 56%. Reproductive organ involvement differed ($p = 0.012$): Asians 25%, Blacks 27%, Whites 20%; all other metastatic sites showed no differences ($p > 0.05$). Overall survival varied significantly ($p < 0.001$), highest in Asians (71.6 months) and Whites (54.3 months) and lowest in Blacks (32.3 months); Asians had similar mortality risk to Whites (HR 0.94), whereas Blacks had higher risk (HR 1.44). Genomic variation was notable: KRAS ($p = 1.6 \times 10^{-7}$) was highest in Blacks (56.8%), TP53 ($p < 0.001$) was highest in Asians (81.5%), and BRAF ($p = 0.0046$) was lowest in Blacks (7.1%), with no other genes differing. **Conclusions:** Racial differences were evident across outcomes. Black patients had the highest KRAS mutations and worst survival; Asians had the highest TP53 rates and best survival; Whites had the most MSI-H tumours. Other clinical features were similar. These patterns suggest biologic differences relevant to risk and treatment. Research Sponsor: None.

Progestin-only implant and breast cancer risk in adolescents and premenopausal women: A systematic review and meta-analysis.

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Background: Progestin-only long-acting reversible contraception via subdermal etonogestrel implants (Implanon/Nexplanon) is widely used. However, the breast cancer (BC) risk signal potentially attributable to implant exposure remains under-characterized, limiting evidence-based, shared contraceptive counseling. **Methods:** We systematically searched PubMed/MEDLINE, Embase, and the Cochrane Library and screened reference lists for observational cohort and case-control studies comparing etonogestrel/progestin-only implant exposure versus non-use in adolescents and reproductive-aged/premenopausal women (as defined by each study) without prior BC. Studies restricted to hereditary breast cancer predisposition cohorts (BRCA1/2 pathogenic variant carriers) were excluded. The primary endpoint was incident BC (invasive with/without in situ). Maximally adjusted estimates were extracted and harmonized to odds ratios (ORs). Risk of bias was assessed using ROBINS-E. Pooled estimates were generated using inverse-variance random-effects meta-analysis. Heterogeneity was quantified with I2 and Tau2. **Results:** Five studies met inclusion criteria, including three nationwide cohort studies from Denmark/Sweden and two nested case-control studies from the UK and Australia. Across cohort studies, implant exposure contributed 1,659,309 person-years of follow-up with 510 incident BC events. The largest case-control dataset included 67,470 BC cases. Study-specific adjusted ORs ranged from 0.93 to 1.24. In pooled analysis, implant exposure was associated with an increased risk of incident BC (OR 1.23. 95% CI 1.19–1.27, P < 0.0001), with no between-study heterogeneity (I2 = 0%, Tau2 = 0). **Conclusions:** In large, contemporary population-based observational studies excluding hereditary breast cancer predisposition cohorts, use of etonogestrel/progestin-only subdermal implants is consistently associated with a modestly increased risk of incident breast cancer (~23%) compared with non-use. While the absolute risk increase is likely small in younger women, the consistent signal across study designs supports its relevance for individualized risk-benefit discussions and shared contraceptive counseling in routine clinical practice. Research Sponsor: None.

Study (Year)	Design / Country	Population	Implant Type	Odds Ratio (95% CI)
Mørch et al. (2017)	Nationwide cohort, Denmark	Women 15-49 y	Progestin-only	0.93 (0.48-1.80)
Fitzpatrick et al. (2023)	Case-control, UK	Women 16-39 y	Progestin-only	1.22 (0.93-1.60)
Hadizadeh et al. (2025)	Register-based cohort, Sweden	Women 13-49 y	Etonogestrel	1.22 (1.11-1.35)
Hultstrand et al. (2022)	Nationwide cohort, Sweden	Women 15-34 y	Etonogestrel	1.22 (0.98-1.52)
Tuesley et al. (2025)	Case-control, Australia	Women 20-55 y	Etonogestrel	1.24 (1.17-1.32)

Endocrine therapy non-adherence and recurrence risk in patients with breast cancer and major depressive disorder.

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Background: We evaluated whether non-adherence to oral endocrine therapy explains the increased hazard of recurrence among women with major depressive disorder (MDD) and estrogen receptor-positive breast cancer. **Methods:** We established a retrospective cohort of veteran women (age ≥ 18 years), with and without MDD, diagnosed with early-stage invasive estrogen receptor-positive breast cancer between 2010–2019 within the United States Veterans Affairs Healthcare System with follow-up through 2022. We assessed adherence to oral endocrine therapy among continuous users (no treatment gaps ≥ 6 months) over two-years ($N = 2,722$) and five-years ($N = 1,666$). Adherence was measured using the proportion of medication days covered and evaluated across thresholds from $\geq 20\%$ –100%. We used multivariable competing-risks regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the statistical interaction between MDD and endocrine therapy adherence on breast cancer recurrence, adjusting for sociodemographic, clinical, and prognostic factors. **Results:** The hazard of breast cancer recurrence significantly differed between adherent and non-adherent women with MDD beginning at adherence thresholds of $\geq 60\%$ over two-years and $\geq 40\%$ over five-years. At these minimal adherence thresholds, breast cancer recurrence was higher for women with MDD who were non-adherent to endocrine therapy over two-years (HR = 1.65; 95% CI = 1.02–2.62) and five-years (HR = 2.10; 95% CI = 1.16–3.79) compared with adherent women without MDD. In contrast, women with MDD who remained adherent over two-years (HR = 1.21; 95% CI = 0.91–1.64) and five-years (HR = 1.38; 95% CI = 0.85–2.22) had hazards of breast cancer recurrence comparable to those of adherent women without MDD. **Conclusions:** Our findings identify endocrine therapy adherence as a potentially modifiable clinical factor to reduce breast cancer recurrence among women with MDD and estrogen receptor-positive disease. Research Sponsor: Department of Medical Affairs; National Cancer Institute; The Breast Cancer Research Foundation.

Hair relaxer use and breast cancer risk by tumor molecular subtypes.

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Background: Women of West African ancestry, including US populations, are disproportionately diagnosed with aggressive breast cancers including triple negative tumors. Previously, hair relaxer use has been associated with increased breast cancer risk in the Ghana Breast Health study (GBHS), with former users at an over 2-fold increased risk compared to never users. We aimed to determine if relaxer use risk associations differed by tumor molecular subtypes suggesting possible biological mechanisms of carcinogenesis. **Methods:** The GBHS is a population-based case-control study conducted 2013–2015 in Accra and Kumasi, with 1,071 pathologically confirmed invasive breast cancer cases (87% had available estrogen receptor (ER) status) and 2,106 matched controls, aged 18–74 years. Molecular subtypes were defined using St Gallen's criteria using molecular marker data for ER, progesterone receptor, human epidermal growth factor receptor-2 (HER2), and grade (G). Molecular tumor subtypes defined as: Lum A (ER/PR+, HER2- and G1/G2, N = 260), Lum B- (ER/PR+, HER2- and G3, N = 468), Lum B+ (ER/PR+, HER2+ and G1/G2, N = 195), HER2-Enriched (ER-, PR- and HER2+, N = 59), Triple-Negative (ER, PR, and HER2-, N = 129). We imputed missing data using chained equations. Polytomous logistic regression models were used to estimate odds ratios (ORs) with 95% confidence intervals (CIs) for associations of relaxer use with breast cancer subtypes. Models were adjusted for matching factors (age, hospital site), and potential confounders: education, parity, age at first birth, and median breastfeeding months per child. Results were combined across imputed datasets. Heterogeneity (p-het) in breast cancer risk by tumor molecular subtypes using polytomous logistic regression case-only models. **Results:** Relaxer use was common (ever-use of relaxers 96% of cases and 94% of controls). Compared to never users, increased risk for former users compared to never users was observed across subtypes. While magnitudes of risk differed ($OR_{LumA} = 2.59$, 95% CI [1.01–6.60], $OR_{LumB+} = 2.69$, 95% CI [0.47–15.47], $OR_{LumB-} = 1.74$, 95% CI [0.33–6.93], $OR_{HER2-Enriched} = 3.66$, 95% CI [0.75–17.98], $OR_{Triple-Negative} = 1.21$, 95% CI [0.37–4.00]), there was no statistical evidence of etiologic heterogeneity by subtype (p-het = 0.59). Similarly, other measures of relaxer use (duration, age at first use, lye or non-lye) did not show any evidence of heterogeneity. **Conclusions:** In this population with a high proportion of aggressive tumor subtypes, breast cancer risk associated with relaxer use did not support etiologic heterogeneity by molecular subtype, however, power was limited. These findings suggest that relaxer exposure is unlikely to explain subtype-specific breast cancer risk patterns. Future investigations should pool studies for improved power, evaluate other molecular tumor characteristics and relaxer products' formulations to clarify carcinogenic mechanisms to reduce risk. Research Sponsor: Intramural Research Program of the National Institutes of Health.

Prevalence of oral and genital HPV-45 and non-vaccine-targeted HPV-35 among U.S. adults.

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Background: High-risk human papillomavirus (HPV) types 35 and 45 are oncogenic non-16/18 subtypes that contribute measurably to HPV-attributable genital and oropharyngeal cancers. Unlike HPV-45, HPV-35 is not targeted by the current 9-valent vaccine. Although high prevalence of these subtypes has been reported in some global sub-populations, data on their prevalence and distribution in the U.S. adult population remains limited. **Methods:** We conducted a cross-sectional analysis of adults aged 18-64 years from the National Health and Nutrition Examination Survey (NHANES) cycles 2013-2016. HPV was detected via self-collected oral rinse specimens, vaginal swabs, and penile swabs. HPV vaccination history and sexual behaviors were self-reported. We estimated survey-weighted type-specific HPV prevalence and used survey-weighted Poisson regression to calculate adjusted prevalence ratios (aPRs), accounting for age, sex, race/ethnicity, vaccination status, and number of lifetime sexual partners. **Results:** Oral HPV prevalence was low overall, with HPV-16 remaining the most frequently detected type (0.87%). Genital HPV showed a broader distribution of oncogenic types. Among men, penile HPV-35 (1.93%, 95% CI 1.27-2.60%) and HPV-45 (1.94%, 95% CI 1.37-2.50%) were less prevalent than HPV-16 (3.97%, 95% CI 3.13-4.80%) and slightly more prevalent than HPV-18 (1.71%, 95% CI 1.20-2.22%), though confidence intervals overlapped. Among women, vaginal HPV-35 (1.40%, 95% CI 0.95-1.85%) and HPV-45 (1.71%, 95% CI 1.21-2.21%) were also less common than HPV-16 (2.95%, 95% CI 2.14-3.77%) and comparable to HPV-18 (1.26%, 95% CI 0.88-1.65%), again with overlapping confidence intervals. While there were extremely low rates of dual oral-genital infections, males exhibited slightly higher, though non-significant, dual infection prevalences for HPV-35 (0.03% vs. 0%), HPV-45 (0.21% vs 0.07%), and HPV-16 (0.17% vs. 0.11%) compared to females. Non-Hispanic Black participants had a significantly higher genital prevalence of both HPV-35 (aPR 2.75, 95% CI 1.71-4.42) and HPV-45 (aPR 2.08, 95% CI 1.13-3.85) compared with Non-Hispanic White participants. Prevalence was higher among males than females for both types, although these differences did not reach statistical significance. **Conclusions:** In this nationally representative sample of U.S. adults, we found that HPV-35, a high-risk type not included in the current 9-valent vaccine, showed genital prevalence comparable to vaccine-covered types and marked racial disparities. These findings highlight the importance of continued HPV surveillance and targeted prevention strategies. Additionally, future studies should investigate these subtypes in HPV-associated malignancies. Research Sponsor: None.

Genome-wide association and Mendelian randomization analyses of body mass index and breast cancer risk in women of African ancestry.

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Background: The relationship between adiposity and breast cancer risk is complex and incompletely understood, particularly among women of African ancestry. We investigated the association between genetically predicted and excess body mass index (BMI) and breast cancer risk in the African Ancestry Breast Cancer Genetic Consortium (AABCG) using complementary genetic and epidemiologic approaches. **Methods:** We conducted a genome-wide association study (GWAS) of BMI in AABCG. Independent BMI-associated variants were then used as instrumental variables in one-sample Mendelian randomization (MR) analyses, using two-stage residual inclusion with logistic regression to estimate the causal effect of BMI on breast cancer risk. To explore the joint influence of genetic and non-genetic contributions to BMI, we constructed a BMI polygenic risk score and defined the BMI polygenic-measured gap (BMI-PGM) as the difference between the percentile of observed BMI and the percentile of genetically predicted BMI. BMI-PGM was categorized into three groups based on quartile distribution: discordantly low ($\leq 25^{\text{th}}$ percentile), concordant ($25^{\text{th}}-75^{\text{th}}$ percentile), and discordantly high ($\geq 75^{\text{th}}$ percentile). The association between BMI-PGM and breast cancer risk was evaluated. **Results:** We identified thirteen loci that were associated with BMI at the genome-wide significance level. Of these, seven loci had not been reported in prior GWAS of BMI. In the MR analyses ($n = 31,522$), genetically predicted BMI was inversely associated with overall breast cancer risk: odds ratio (OR) = 0.92 per 5 kg/m² increase, 95% confidence interval (CI) 0.86–0.99, $p = 0.028$. In stratified analyses, there was a stronger inverse relationship observed for estrogen receptor (ER) negative compared with ER positive breast cancer. Inverse associations with similar effect sizes were observed in analyses stratified by menopausal status. Compared with women whose observed BMI was discordantly low relative to their genetically predicted BMI, those with concordant BMI had a modestly increased risk of breast cancer (OR = 1.08, 95% CI 1.02–1.14, $p = 0.0074$), while women with discordantly high BMI had a 12% higher risk of breast cancer (OR = 1.12, 95% CI 1.05–1.19, $p = 0.00049$). **Conclusions:** Genetically predicted higher BMI was associated with lower breast cancer risk, whereas BMI in excess of genetic predisposition was associated with increased risk. These opposing associations highlight a distinction between genetically mediated body size versus excess weight that likely reflects adverse metabolic processes. Together, these results underscore the roles of both genetic susceptibility and modifiable influences on adiposity in breast cancer etiology and highlight the importance of maintaining a healthy weight to reduce breast cancer risk, despite variability in genetic predisposition to adiposity across the population. Research Sponsor: Conquer Cancer, the ASCO Foundation; 2025YIA-4865769673; National Cancer Institute; K12CA139160.

Genetic correlation and causal associations between metabolic traits and lung cancer risk.

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Background: Lung cancer is the leading cause of cancer-related mortality worldwide. We evaluated whether associations between metabolic traits and lung cancer risk reflect shared genetic susceptibility or causal effects of metabolic dysregulation. **Methods:** GWAS summary statistics from European-ancestry participants were obtained for lung cancer (TRICL-ILCCO; $n = 29,266$ cases, $56,450$ controls), body mass index (BMI; GIANT; $n = 681,275$), blood lipids, triglycerides (TG), high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL), from the Global Lipids Genetics Consortium (GLGC; $n = 1,320,016$), and type 2 diabetes (T2D; T2DGGI; $n = 242,283$ cases, $1,569,734$, controls). Genome-wide genetic correlations were estimated using LD score regression. Two-sample Mendelian randomization analyses were conducted with lung cancer as the outcome using inverse-variance weighted models, with weighted median, MR-Egger, and weighted mode sensitivity analyses. Heterogeneity and pleiotropy were assessed using Cochran's Q, MR-Egger intercept, and MR-PRESSO. **Results:** Lung cancer demonstrated significant positive genetic correlations (r_g) with BMI ($r_g = 0.16$, $P = 1.0 \times 10^{-4}$), TG ($r_g = 0.14$, $P = 3.0 \times 10^{-4}$), and T2D ($r_g = 0.09$, $P = 0.017$), and a significant inverse correlation with HDL ($r_g = -0.14$, $P = 2.4 \times 10^{-5}$). No significant genetic correlation was observed for LDL. In MR analyses, genetically predicted BMI was associated with increased lung cancer risk (475 SNPs; IVW $\beta = 0.23$, SE = 0.05 , $P = 2.0 \times 10^{-6}$; OR = 1.26, 95% CI 1.14–1.38), and remained statistically significant after outlier correction ($\beta = 0.21$, $P = 7.2 \times 10^{-6}$), with no evidence of distortion. In contrast, no supporting evidence of causal associations between lung cancer risk and genetically predicted HDL, TG, LDL, or T2D liability across primary and sensitivity estimators (all $P > 0.05$). Cochran's Q tests indicated heterogeneity across genetic instruments; however, MR-Egger intercept tests did not provide evidence of directional horizontal pleiotropy. **Conclusions:** These findings suggest that metabolic health, particularly obesity, may play a clinically meaningful role in lung cancer risk assessment. Considering obesity alongside established smoking-related determinants may enhance lung cancer prevention efforts. Research Sponsor: American Cancer Society; RSG-22-079-01; National Cancer Institute/U.S. National Institutes of Health; P30CA134274.

Lung cancer incidence and PM_{2.5}: Evaluating the association with varying spatial scales and durations of exposure estimates.

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Background: Particulate matter with a diameter of 2.5 μm or less (PM_{2.5}) is classified as an IARC group 1 carcinogen based on decades of research. However, little is known about how the association between PM_{2.5} and lung cancer incidence is impacted by varying spatial and temporal methods of estimating exposure. **Methods:** We performed a nested case-control analysis using the Department of Veterans Affairs (VA) Clinical Data Warehouse. Patients were eligible for inclusion if they had a recorded date of birth, smoking data, and quarterly location data for 40 or more quarters between 2009 and 2021. Cases were required to have at least 10 years of location data prior to diagnosis; diagnoses and diagnosis dates were identified using the VA Central Cancer Registry. Controls were matched in a 4:1 ratio on age (by birth quarter), smoking status (self-reported, defined as “Smoker” vs. “Never Smoker”), and the specific calendar quarters contributing to the PM_{2.5} average. Modeled daily PM_{2.5} estimates at a spatial resolution of 1 km² for the entire contiguous United States (US) were aggregated to quarterly estimates at three US Census geography levels (block group, census tract, and county). After case-control matching, we evaluated the impact of different spatial and temporal measures of PM_{2.5} exposure on the association between PM_{2.5} and lung cancer incidence. Specifically, we evaluated estimates at the block group, census tract, and county level with both 5-year and 10-year averages. Associations were evaluated using conditional logistic regression; model fit was assessed using the Akaike Information Criterion (AIC). **Results:** Approximately 4.7 million veterans met our inclusion criteria. Of these, 8451 veterans developed incident lung cancer at least 10 years after the observation period began; 33,150 matched controls were selected. All models showed a statistically significant increase in the risk of lung cancer with increasing PM_{2.5} exposure, with odds ratios (ORs) ranging from 1.06 (95% CI 1.04-1.09) to 1.13 (95% CI 1.10-1.17) and p-values < 0.001 for all models. In both the 5-year and 10-year analyses, models with larger spatial units (county > census tract > block group) had higher ORs and superior model fit by AIC. All models with 10-year averages had higher ORs and lower AIC values compared to models with 5-year averages. **Conclusions:** Our findings add to the considerable body of research that demonstrates an epidemiologic association between PM_{2.5} and lung cancer incidence. Furthermore, our results demonstrate that this association is robust to various methods of estimating patient PM_{2.5} exposure. Finally, these data suggest that using county-level PM_{2.5} estimates and an estimate duration of at least 10 years may be preferable to finer spatial scales and shorter estimate durations in future studies. Research Sponsor: None.

Quantifying equol-producing and beta-glucuronidating gut bacteria in breast cancer using 16S rDNA sequencing methods.

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Background: Gut bacteria with hormone-modulating potential may influence breast cancer (BC) risk: Equol-producing bacteria convert dietary isoflavones into equol, a phytoestrogen that binds estrogen receptors, while beta-glucosidating bacteria affect glycosides of dietary phytoestrogens, and beta-glucuronidating bacteria regulate the deconjugation and reabsorption of endogenous estrogens. We aimed to investigate whether gut bacterial species that have the potential to affect phytoestrogens or endogenous estrogens can be detected using 16S rDNA sequencing methods, and to what extent this detection may be influenced by the choice of 16S hypervariable region targeted for sequencing. **Methods:** DNA extracted from stool samples of women with BC (n = 112) and healthy controls (n = 171) was subjected to PCR amplification and high-throughput sequencing of the V1-V3 and V3-V4 16S rRNA hypervariable regions, commonly used regions in microbiome research. Data was processed using QIIME, and taxonomy assignment was performed with the SILVA database to the species level. Relative abundance and detection of taxa in cases vs controls were evaluated using Wilcoxon and McNemar's tests in R. Taxa were classified as equol-producing based on Setchell and Clerici (2010) or beta-glucuronidating and beta-glucosidating based on Dabek et al (2008). **Results:** The relative abundance of equol-producing bacteria was significantly higher in the BC group vs controls in the V1-V3 (p = 0.0007); V3-V4 (p = 0.0089) regions, and when both regions were summed (p = 0.0011). *Adlercreutzia equolifaciens* was detected 29.6% more often in a presence/absence analysis of the V1-V3 region (V1-V3 presence: 93.0%, V3-V4 presence: 63.4%, p < 0.001), while *Fingoldia magna* was detected 21.1% more often in the V3-V4 region (V1-V3 presence: 18.0%, V3-V4 presence: 39.1%, p < 0.001). The relative abundance of beta-glucuronidating and beta-glucosidating bacteria was significantly higher in the BC group vs controls in the V1-V3 region (p = 0.0094) and when both regions were summed (p = 0.0254), and approached significance in the V3-V4 region (p = 0.0534). Presence of *Bifidobacterium adolescentis* was detected 21.8% more often in the V1-V3 region (V1-V3 presence: 21.8%, V3-V4 presence: 0.00%, p < 0.001), and *Roseburia inulinivorans* was detected 21.1% more often in the V3-V4 region (V1-V3 presence: 63.0%, V3-V4 presence: 83.1%, p < 0.001). **Conclusions:** Equol-producing and beta-glucuronidating and beta-glucosidating bacteria appear enriched at the species-level analysis in BC subjects, but detection of specific organisms is sensitive to the 16S region sequenced. Accurate identification of hormone-modulating taxa requires both the V1-V3 and V3-V4 regions, as either alone is insufficient to capture the full range of taxa. Additional analyses with absolute quantification such as qPCR are needed to validate the results. Research Sponsor: University of Illinois Chicago; U.S. National Institutes of Health.

Early lessons from the implementation of a pan-African clinico-genomic cancer platform: The African Cancer Atlas.

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Background: Limited representation of African populations in cancer genomics constrains the clinical applicability of precision oncology. We describe the establishment and early outcomes of The African Cancer Atlas (TACA), a multi-site platform integrating genomics, harmonized clinical data, and community engagement for adult breast cancer research across Africa. **Methods:** TACA, led by Yemaachi Biotech, has so far been implemented across five countries (Ghana, Nigeria, Côte d'Ivoire, Kenya, and Seychelles). In early 2025, foundational activities included institutional review board (IRB) approvals, execution of memoranda of understanding and material transfer agreements, site activation, and structured engagement with clinicians, patient advocates, and community stakeholders through Yemaachi's African Cancer Network to support trust-building and study uptake. Participant recruitment began in July 2025. Breast cancer patients were enrolled following IRB approval, with informed consent supported by site-based education on genomics research. Clinical data were captured in UVOSYO-Yemaachi's clinical database. Peripheral blood was collected at recruitment, and formalin-fixed paraffin-embedded (FFPE) tumor tissue was obtained subsequently and shipped to our central laboratory in Accra. Blood and tissue underwent DNA extraction and quantitative and qualitative quality control (QC) prior to sequencing. **Results:** To date, 236 participants have been recruited across the five TACA sites. Blood-derived DNA demonstrated acceptable quality for downstream sequencing, whereas FFPE tumor tissue quality varied substantially, leading to exclusion of cases that failed QC. Among enrolled participants, 97.9% were female, with a mean age of 50.8 years (SD 13.1). A total of 26.7% reported a family history of cancer, with participants in Seychelles having the most significant family history of 87% ($p < 0.001$). Triple-negative breast cancer accounted for 38.1% of tumors overall, ranging from 21.1% in Kenya to 68.1% in Nigeria. Significant between-country variation was observed for triple-negative breast cancer ($p < 0.001$) and hormone receptor status (all $p < 0.001$). Key implementation challenges included prolonged IRB approval timelines related to limited familiarity with cancer genomics, cross-border biospecimen transport constraints necessitating in-country DNA extraction in some settings, and variability in FFPE tissue quality impacting sequencing yield. **Conclusions:** TACA demonstrates the feasibility of coordinated multi-country recruitment and clinical data harmonization for adult cancer genomics in Africa, while highlighting critical regulatory, logistical, and biospecimen quality barriers. Research Sponsor: None.

Variants of uncertain significance and contralateral risk-reducing mastectomy in early-stage breast cancer across safety-net and private hospital settings.

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Background: Germline genetic testing informs surgical decisions in early-stage breast cancer. Guidelines recommend considering contralateral risk-reducing mastectomy (RRM) for patients with pathogenic or likely pathogenic variants in high-risk genes, but not for those with variants of uncertain significance (VUS). Despite this, VUS results may still affect surgical decisions. This study examines the impact of VUS on surgical decision-making across two university-affiliated settings: a safety-net hospital and a private hospital. **Methods:** We retrospectively reviewed patients with early-stage invasive breast cancer treated between 2012 and 2022 who underwent germline testing before surgery at both a safety-net and a private hospital. Patients with VUS were compared with genetically negative controls. Logistic regression was used to identify factors associated with RRM. **Results:** The cohort included 86 safety-net VUS patients, 115 safety-net controls, 102 private VUS patients, and 97 private controls. Table 1 highlights demographic differences between the hospitals. RRM was performed in 28 safety-net VUS patients (32.6%), 20 safety-net controls (17.4%), 37 private VUS patients (36.3%), and 45 private controls (46.4%). Stepwise regression analysis of the full cohort showed that treatment at the private hospital was independently associated with higher rates of RRM compared with the safety-net hospital, regardless of VUS status (OR 4.52, 95% CI 2.10 – 9.75, $p < 0.001$). Additional factors associated with higher RRM rates included higher tumor stage, higher tumor grade, and younger age at diagnosis. In hospital-specific analyses, VUS status did not influence RRM decisions at the private hospital. However, at the safety-net hospital, patients with VUS were more likely to undergo RRM than those with negative genetic testing (OR 2.38, 95% CI 1.09 – 5.21, $p = 0.031$). **Conclusions:** Surgical decision-making for RRM is influenced by multiple clinical and institutional factors. While VUS status did not affect surgical decisions at the private hospital, it was associated with increased RRM rates at the safety-net hospital. This finding suggests that differences in counseling practices and patient perceptions of genetic risk may exist within the safety-net setting, where patients may face more uncertainty about access to future care. Further studies are needed to better characterize these disparities and promote guideline-concordant care. Research Sponsor: None.

Patient demographics by hospital.				
		Safety-Net (n = 201)	Private (n = 199)	p-value
Race/Ethnicity	Non-Hispanic White	8 (4.0%)	116 (58.3%)	< 0.001
	Non-Hispanic Black	41 (20.4%)	39 (19.6%)	
	Hispanic	141 (70.1%)	12 (6.0%)	
	Other	11 (5.5%)	32 (16.1%)	
Language Spoken	English	72 (35.8%)	199 (100%)	< 0.001
	Non-English	129 (64.2%)	0 (0%)	
Insurance	Insured	62 (30.8%)	196 (98.5%)	< 0.001
	Uninsured	139 (69.2%)	3 (1.5%)	

A pilot study of a digital, patient-directed consent process for MSK-IMPACT tumor-normal genetic testing in gynecologic cancer.

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Background: Although germline and somatic genetic testing is increasingly recommended for many cancers including gynecologic cancers, uptake remains low. Barriers include consenting processes that are time consuming for patients and providers. We sought to test uptake and acceptability of a digital, self-directed genetic testing consent process. **Methods:** We developed a digital, self-guided consenting process for MSK-IMPACT tumor-normal targeted sequencing called “read and sign” (R&S) that included an educational video and information about genetic testing along with a direct digital consent. We performed a pilot study in gynecologic surgery (GYNS) and medical oncology (GMO) clinics to evaluate the uptake of genetic testing and other metrics including time to consent, clinic time saved, and patient satisfaction. Briefly, adults with gynecologic cancers eligible for MSK-IMPACT were sent R&S consent via electronic health record. Research staff followed up with patients at 2, 7, and 14 days. If patients did not consent after 14 days, the clinical team was notified to follow-up. This study was approved under IRBs 12-245 and X25-012. **Results:** Between 10/6/2025 and 12/31/2025, we identified 173 patients (122 GYNS and 51 GMO) eligible for MSK-IMPACT and offered them R&S consent. This represented 8% of total MSK-IMPACT consents across the institution during this time. Median age was 61 years. 106 (61%) patients identified as White, 27 (16%) as Asian, 17 (10%) as Black, and 24 (14%) as Hispanic. Most common cancer types were endometrial (n=75, 43%) and ovarian (n=39, 23%). In GYNS, 102/122 (84%) patients consented with R&S, and 59 (58%) consented on the same day the R&S consent was sent. On average, 8 minutes of in-person clinic time per patient was saved using R&S, but 35 (29%) patients had 0 time saved, and 7 (7%) consents were later completed in-person after initial incomplete R&S attempt. One patient who completed the R&S consent later withdrew consent. In GMO, 50/51 (98%) patients consented via R&S, with 38 (76%) consented on the same day. On average, 14 minutes of clinic time per patient was saved, and 4 (8%) patients ultimately required in-person consent. Average time to consent was 3.3 days in GYNS and 1.7 days in GMO. Among 11 patients who completed surveys, 10 (91%) were very/somewhat satisfied with R&S. More in-depth surveys and semi-structured interviews with a subset of patients and staff are ongoing, and data will be forthcoming. **Conclusions:** A digital, self-guided consent for MSK-IMPACT genetic testing was feasible and acceptable with some differences in workflow between surgical and medical oncology clinics. The R&S consent process empowers patient decision-making and should be scaled to other cancer types. Research Sponsor: U.S. National Institutes of Health.

Germline testing in Asian American and Pacific Islander women with breast cancer.

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Background: Per the American Cancer Society, the overall breast cancer incidence rate rose 1% per year from 2012 to 2021, while it increased 2.7% per year for Asian American and Pacific Islander (AAPI) women. Cases increased by 50% for AAPI women under age 50, on par with White women. This study was conducted to examine rates and results of germline genetic testing in AAPI women with breast cancer. **Methods:** In this retrospective analysis, AAPI women with breast cancer were identified from a non-consecutive dataset of patients undergoing multi-gene panel testing (MGPT) at a national clinical diagnostic laboratory. Descriptive statistics were performed and differences in variant frequencies between groups were assessed using two-proportion z-tests. **Results:** From January 2016 through April 2025, 3.8% of women who underwent germline genetic testing reported AAPI ancestry (50,043/1,320,261). AAPI women made up 4.1% of all women with breast cancer who underwent MGPT. Comparatively, the most recent U.S. Census data from 2024 showed 7.0% of the population self-identified as AAPI women. The median age of AAPI women who underwent germline testing was 54 years and the most frequent pathogenic/likely pathogenic (P/LP) variants in order were BRCA2, BRCA1, ATM, PALB2, TP53, and CHEK2 (56.0% of P/LP variants). Most AAPI women (79%) resided in large metropolitan areas, and more than half (53%) had private insurance. AAPI women with breast cancer had lower rates of P/LP variants compared with White women (6.8% vs. 9.2%; $p < 0.0001$) and all non-AAPI women tested (6.8% vs 8.9%; $p < 0.0001$). Among women ≤ 50 years, P/LP rates remained lower in AAPI compared with White women (7.9% vs 10.7%; $p < 0.0001$) and all non-AAPI women (7.9% vs 10.5%; $p < 0.0001$). Younger AAPI women exhibited higher P/LP rates than older AAPI women (11.2% < 40 vs 6.24% > 40), consistent with age-associated trends across ethnicities (14.0% all non-AAPI < 40 vs 8.45% all non-AAPI > 40). **Conclusions:** In this study cohort, AAPI women with breast cancer make up a smaller than expected proportion of all tested women with breast cancer, despite similar breast cancer incidence rates as White women. AAPI women with breast cancer who had genetic testing tended to reside in large metropolitan areas and have private insurance. These factors and others should be considered when thinking about how to broaden access to genetic testing and counseling in the future, especially in younger AAPI women who have comparably higher rates of P/LP variants. Research Sponsor: None.

Impact of germline *BRCA* pathogenic or likely pathogenic variants on fertility potential and reproductive outcomes in young women with breast cancer: A systematic review and meta-analysis.

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Background: In young women with a diagnosis of breast cancer (BC), the impact of germline *BRCA* (*gBRCA*) pathogenic or likely pathogenic variants (PVs) on their reproductive reserve and fertility outcomes remains uncertain. This systematic review and meta-analysis assessed the influence of harboring *gBRCA* PVs on ovarian reserve, efficacy of fertility preservation (FP) techniques, and pregnancies after BC diagnosis. **Methods:** A systematic PubMed/MEDLINE search was conducted with no date restrictions up to June 30th, 2025 (CRD420251114990). Eligible studies included retrospective and prospective case-control or cohort studies and clinical trials, comparing at least one of the following outcomes between *gBRCA* carriers vs. non-carriers: ovarian reserve parameters [i.e., anti-Müllerian hormone (AMH) levels or antral follicle count (AFC)] at BC diagnosis (objective 1); efficacy of FP techniques (i.e., number of total and mature retrieved oocytes, and cryopreserved oocytes before chemotherapy) (objective 2); likelihood of conceiving after treatments (objective 3). Pooled mean differences and risk ratios (RRs) with 95% confidence intervals (CI) were calculated using a random-effects model. **Results:** Out of 5,325 screened records, 18 studies met the inclusion criteria and were included in the final analysis (2,631 patients, of whom 737 *gBRCA* carriers). Mean age of patients at BC diagnosis was 32.6 years for *gBRCA* carriers and 33.1 years for non-carriers. Among 12 studies (n=1,529 patients) reporting on objective 1, *gBRCA* carriers (n=399) showed significantly lower AMH levels compared with non-carriers, with a mean difference of -0.5 (95% CI -0.8; -0.2) ng/mL, and a numerically lower AFC count (-0.8; 95% CI -2.3; +0.8). Among the 11 studies (n=1,027 patients) addressing objective 2, *gBRCA* carriers (n=318) had a lower median number of total oocytes (-1.8; 95% CI -3.3; -0.3), retrieved mature oocytes (-1.6; 95% CI -2.8; -0.3), and numerically lower cryopreserved oocytes (-1.1; 95% CI -2.7; +0.6). Subgroup analyses showed that reductions in ovarian reserve and FP outcomes were mainly driven by *BRCA1* carriers (n=184), whereas reproductive outcomes in *BRCA2* carriers (n=125) were comparable to those of non-carriers. Regarding objective 3, only one study (n=75 patients) reported the likelihood of conceiving after BC using assisted reproductive technologies (ART) and showed no differences between *gBRCA* carriers (n=20) and non-carriers (RR 0.28; 95% CI 0.04; 2.04). **Conclusions:** Young patients with BC harboring *gBRCA* PVs showed reduced AMH levels and lower FP efficacy, while no differences were observed in pregnancy rates after BC through ART, although evidence remains limited. Prospective studies are needed to optimize oncofertility counselling young *gBRCA* carriers. Research Sponsor: None.

Longitudinal follow-up after identification of variants of uncertain significance in highly penetrant cancer predisposition genes.

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Background: ASCO and the NCCN recommend that patients with variants of uncertain significance (VUS) in hereditary cancer predisposition genes undergo periodic variant reassessment, since reclassification of VUS as pathogenic or likely pathogenic (P/LP) may alter clinical management. However, the extent to which such longitudinal follow-up occurs in practice has not been studied. **Methods:** Data were retrospectively reviewed from patients who underwent germline genetic testing for cancer-related indications from 2015-2025 at an adult genetics clinic in an academic-affiliated, safety-net healthcare system. Analyses were restricted to patients found to have VUS (without P/LP variants) in any of 23 highly-penetrant cancer predisposition (HPCP) genes based on the NCCN guidelines for genetic/familial high-risk assessment: *APC*, *ATM*, *BMPR1A*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CDKN2A*, *CHEK2*, *EPCAM*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *MUTYH* (biallelic), *PALB2*, *PMS2*, *PTEN*, *RAD51C*, *RAD51D*, *SMAD4*, *STK11*, and *TP53*. The primary outcome of interest was the percent of patients who adhered to clinician recommendations for follow-up after VUS disclosure, excluding those for whom insufficient time had elapsed to assess follow-up status. Chi-square tests were used to assess if follow-up rates differed among patients with VUS that were considered “clinically concordant” (personal history of a tumor consistent with the gene’s neoplastic spectrum), “possibly concordant” (history of a relevant neoplasm in a 1st/2nd degree relative but not the patient), or “likely incidental” (no relevant personal or family cancer history). **Results:** Of 2028 tested patients, 25% (n = 501) were found to have one or more cancer-related VUS (without P/LP variants), including 308 with VUS in HPCP genes. At the time of initial result disclosure, 11% of these patients were discharged from further follow-up, while the remaining 89% were advised to return for variant reassessment, typically within 2 years. Adherence to these recommendations was low overall, with only 38% returning for any post-disclosure follow-up. Rates of follow-up were similar among patients with VUS classified as clinically concordant (40%), possibly concordant (34%), or likely incidental (45%); p = 0.47. **Conclusions:** Despite clear clinician guidance to return for variant reassessment, most patients with VUS in highly-penetrant genes did not engage in recommended follow-up, even in the presence of a clinically compatible personal and/or family cancer history. Alternative approaches to longitudinal VUS management – such as automated recontact and/or direct-to-patient notification of variant reclassifications – should be explored to mitigate the risk of loss to follow-up in this population. Research Sponsor: None.

Intensity of chemotherapy regimens for patients with Lynch syndrome and colorectal cancer.

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Background: Lynch syndrome (LS), associated with inherited pathogenic variants (PVs) in *MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM*, is the most common inherited colorectal cancer (CRC) syndrome. Nearly all LS-associated CRCs are mismatch repair-deficient and microsatellite instability-high (dMMR/MSI-H), a phenotype associated with low recurrence risk and limited benefit from single-agent chemotherapy. Guidelines recommend no adjuvant chemotherapy for most dMMR/MSI-H stage II CRC. A fluoropyrimidine + oxaliplatin is recommended for all dMMR/MSI-H stage III CRC. **Methods:** We linked SEER registry records from Georgia and Los Angeles to germline genetic testing results from 4 labs. We included patients with resected stage II or III CRC diagnosed 2013–19 who linked to genetic test results. Chemotherapy details were extracted from SEER text fields completed by registrars. Regimens were classified as 1) No adjuvant chemotherapy; 2) Less intensive (5-FU or capecitabine); 3) More intensive (5-FU or capecitabine + oxaliplatin). We examined associations between genetic testing results and intensity of adjuvant chemotherapy. Covariates included age, sex, race, ethnicity, rurality. **Results:** Among 2770 patients, 1176 had stage II and 1594 had stage III CRC; 271 had a LS gene PV. The table shows results of multivariable analysis stratified by stage. Adjuvant chemotherapy intensity did not vary between patients with LS versus negative genetic test results. Older age was associated with receipt of no or less intensive chemotherapy in stage II and III CRC. Hispanic patients with Stage III CRC were more likely to receive no chemotherapy compared to non-Hispanic White patients. **Conclusions:** In this population-based cohort of CRC patients from two states, adjuvant chemotherapy regimen intensity did not vary with germline genetic test results. These findings suggest that patients with LS and stage II CRC are being overtreated. Clinicians may require education about optimizing CRC therapy for patients with LS. Research Sponsor: National Cancer Institute; R37 CA251464.

	Stage II No Chemo (OR, 95% CI)	Stage II Less Intensive (OR, 95% CI)	Stage III No Chemo (OR, 95% CI)	Stage III Less Intensive (OR, 95% CI)
Genetic Test Result				
Negative (Ref)				
Lynch PV	1.39 (0.86-2.24)	0.60 (0.29-1.26)	0.94 (0.42-2.11)	1.06 (0.50-2.26)
Other PV	0.80 (0.39-1.65)	1.03 (0.42-2.54)	0.58 (0.23-1.41)	1.29 (0.67-2.51)
VUS only	0.89 (0.61-1.30)	0.57 (0.35-0.94)	0.99 (0.65-1.50)	0.81 (0.53-1.25)
Age (years)	1.05 (1.04-1.07)	1.02 (1.00-1.03)	1.07 (1.05-1.08)	1.05 (1.03-1.06)
Female (vs. male)	0.96 (0.68-1.29)	0.89 (0.59-1.34)	1.00 (0.69-1.46)	1.15 (0.80-1.64)
Race/Ethnicity				
Non-Hispanic White (ref)				
Asian	0.75 (0.42-1.32)	1.21 (0.60-2.43)	1.24 (0.60-2.57)	1.22 (0.67-2.24)
Black	1.11 (0.67-1.84)	1.06 (0.56-1.98)	1.30 (0.75-2.25)	0.93 (0.52-1.66)
Hispanic	1.05 (0.66-1.67)	0.60 (0.30-1.18)	1.71 (1.02-2.87)	1.31 (0.77-2.24)
Rural (vs. urban)	1.14 (0.64-2.02)	1.31 (0.63-2.75)	1.08 (0.57-2.03)	1.26 (0.69-2.28)

Clinical implementation of an online family cascade genetic testing platform: The Preventive Risk Outreach and Cascade Testing (PROACT) initiative.

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Background: Cascade genetic testing of relatives in families with hereditary cancer susceptibility is an essential strategy to reduce the burden of cancer through targeted risk reduction. However, current testing rates for eligible relatives are low. A promising strategy is to directly engage relatives of affected patients through an online referral service that delivers genetic risk education and the option for home genetic testing to relatives. In the recent GIFT randomized clinical trial, we evaluated an online cascade testing platform for relatives of cancer patients identified through SEER registries. Here, we asked whether a clinical genetic counseling encounter could extend the reach of this approach. **Methods:** We implemented a pilot project at the Stanford Clinical Cancer Genetics Program that deployed an online hereditary cancer education and germline testing platform for first- and second-degree relatives of patients with a pathogenic or likely pathogenic variant (PV/LPV) in a cancer susceptibility gene. Eligible patients had a germline PV/LPV identified within the past year, spoke English, and had at least one adult first- or second-degree relative in the United States or Canada who had not, to the patient's knowledge, been tested for the PV/LPV. The virtual family referral service was offered to all eligible patients seen over a six-month period. Primary endpoints were the proportions of eligible relatives in the family who 1) were invited by the enrolled patient through the platform; and 2) ordered testing through the platform (processed by Color Health Inc). Here we report preliminary results from the initial project period; we will report results from the six-month project at time of presentation. **Results:** Between October 14, 2025 and January 20, 2026, 58 patients with germline PV/LPVs were offered the online tool and 23 patients (40%) enrolled. For these 23 patients, genetic counselors presumptively identified 191 relatives eligible for testing (70 first-degree and 121 second-degree). Patients invited 113 relatives (59%) of whom 57 (50%) accessed the tool and 50 confirmed their eligibility (no prior testing). Among confirmed eligible relatives who accessed the tool, 33 (66%) ordered testing, representing 17% (33/191) of all presumptively eligible relatives. **Conclusions:** Preliminary results from this clinic-based initiative to deliver cascade genetic testing through an online platform show promise. The findings suggest that an online platform can amplify the clinical genetics encounter and increase cascade testing of relatives in families with hereditary cancer susceptibility. Digital approaches to cascade testing may be particularly impactful for reaching relatives with limited access to care, where traditional cascade testing pathways are challenging. A multi-site clinical trial is planned through the PROACT Initiative. Research Sponsor: Bright Pink.

Initial findings from the PROMISE Registry, a US decentralized, prospective prostate cancer genetic registry.

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Background: The role for genetic testing (GT) for prostate cancer (PCa) patients (pts) has expanded to find pts with germline pathogenic variants (PV) for therapeutic opportunities given FDA-approvals for PARP inhibitors in metastatic PCa as well as understanding familial cancer risk and opportunities for tailored screening and risk reduction. The PROMISE Registry (NCT04995198) was set up as a genetic registry to partner with PCa pts for rapid access to a new standard of care given insurance coverage and clinical implementation were initially major barriers. A second goal is to characterize disease features and treatment outcomes to inform management and provide updates about novel therapeutic clinical trials, both of which remain important to rare genetic variant carriers. **Methods:** PROMISE is a US decentralized prospective PCa genetic registry initiated in 2021 with initial phase to enroll and provide clinical-grade germline genetic testing (30 gene cancer-specific panel) to 5,000 PCa pts to identify ~500 PCa pts with variants of interest (pathogenic variants, PV, and variants of uncertain significance, VUS) in DNA repair genes for long-term clinical follow-up of 15 years (LTFU). Here, we report the initial phase testing results and identification of the LTFU cohort. Study design and enrollment strategy have been reported separately. **Results:** Between 2021-2026, 7,275 pts with any stage PCa across 50 US states self-consented to PROMISE, of which 5,674 (78%) of pts completed genetic testing, indicating feasibility of patient-directed, decentralized enrollment. We have identified 495 (8.7%) pts for LTFU. Baseline data is reported for n=367 (Table 1, will be updated at time of presentation). The most frequently observed PV/LPV variants being in *CHEK2* (25%), *BRCA2* (23%), *ATM* (12%), and *BRCA1* (4.6%). At the time of PCa diagnosis, the majority of LTFU pts had non-metastatic disease, with 47% of pts with Gleason>7, median PSA of 5 ng/mL, and median time from diagnosis to PROMISE GT of 25 months. **Conclusions:** PROMISE is a nationwide decentralized PCa genetic registry that has completed initial goal to recruit 5,000 PCa pts to offer germline genetic testing and recruit a cohort of 500 for LTFU. Data about diagnosis characteristics are reported, and analysis of ongoing disease course, treatment response/outcomes and overall survival is being collected. Clinical trial information: NCT04995198. Research Sponsor: Advancing Cancer Treatment, Inc.; U.S. Department of Defense; W81XWH-18-2-0060, W81XWH-17-2-0043; NIH Pacific Northwest Prostate Cancer SPORE; CA097186.

Long-term follow-up participant demographics.

Characteristic	Overall, N = 367
Age at Diagnosis (yrs)	63 (57, 69)
Race	N = 361 (6, nr)
Asian, American Indian or Alaska Native, Multiracial, Other	22 (6.0%)
Black or African American	22 (6.0%)
White	317 (86%)
Disease State at Diagnosis	N = 348 (19, nr)
Metastatic	46 (13%)
Non-metastatic	302 (87%)
Time from Diagnosis to PROMISE GT (months)	25 (4, 82)
Gleason Score	N = 280 (87, nr)
≤7	148 (53%)
>7	132 (47%)
PSA At Diagnosis (ng/mL)	5 (0, 10) (88, nr)

Subjects with baseline data entered. nr=not reported.

Median (Q1, Q3); n (%).

Actionable germline findings in endometrial cancer from a large multigene panel tested cohort.

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Background: Although most endometrial cancers (EC) are sporadic, 2–6% arise in the setting of Lynch syndrome (LS) or Cowden syndrome. The prevalence and clinical correlates of other germline pathogenic/likely pathogenic variants (PVs) remain incompletely characterized. We assessed the prevalence of potentially actionable germline PVs in EC and their clinicopathologic associations. **Methods:** This retrospective cohort included 3,844 EC patients (pts) who underwent pan-cancer germline multigene panel testing at a single diagnostic laboratory (2018–2025). Pts < 18 years, with mosaic results, or unclear pathology were excluded. Clinical and pathologic variables were compared between pts with and without PVs using appropriate statistical methods, including multivariable logistic regression. **Results:** The final cohort comprised 3,693 females; 46.6% were non-Hispanic White and 8.3% African American. Median age at testing was 62 years and median age at diagnosis was 57 years. Overall, 20.8% (n = 804) harbored a PV in a high- or moderate-penetrance gene. Among 852 PVs identified, 46.9% occurred in DNA damage response (DDR) genes, 37.0% in LS genes, and 16.1% in other genes. The most frequent DDR PVs were *BRCA2* (12.6%), *CHEK2* (9.2%), *BRCA1* (8.0%), *ATM* (7.5%), *PALB2* (3.1%). *PTEN* accounted for 3.2% of the PV. PV carriers were younger at testing (60 vs 62 years; p = 0.014) and diagnosis (54 vs 57 years; p < 0.001), more often African American (12.4% vs 7.2%; p < 0.001), and had higher rates of colorectal cancer (7.7% vs 3.4%; p < 0.001) and multiple primary cancers (41.7% vs 36.8%; p = 0.012). In multivariable analysis, younger age at EC diagnosis (OR 0.99; p = 0.028) and personal history of colorectal cancer (OR 1.84; p < 0.001) remained independently associated with PV status. Histologic subtype distribution differed between LS and DDR groups (p < 0.001); endometrioid tumors were more frequent in LS (26.6% vs 22.7%), whereas serous carcinoma (7.3% vs 1.1%) and carcinosarcoma (4.2% vs 1.8%) were more frequent in DDR. Among pts with available immunohistochemical (IHC) data (n = 810), 51.2% (n = 415) showed mismatch repair protein loss. Of these, 96 (23.1%) had PVs in LS genes, 13 (3.1%) in DDR genes, and 9 (2.2%) in other genes; 297 (71.6%) had no germline PV. Notably, among 161 pts with *MLH1*/*PMS2* loss and confirmed *MLH1* promoter methylation, 25 (15.5%) still harbored PVs; 4 (2.5%) in LS genes, 16 (9.9%) in DDR genes and 5 (3.1%) in other genes. **Conclusions:** Germline PVs were identified in over 20% of EC cases, extending beyond LS or Cowden syndrome. The presence of PVs in *MLH1*-methylated tumors—traditionally considered sporadic—is a critical finding that challenges current tumor-only triage. These results support universal multigene germline testing in EC. A complementary case-control analysis including cancer-free controls and an independent validation cohort will be presented. Research Sponsor: PROACTIVE study supported by DFCI.

Expanded germline genetic testing of patients with hematologic malignancies to identify high proportion with hereditary cancer predisposition.

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Background: Identifying hereditary cancer predisposition in patients with hematologic malignancies is critical for their clinical management, surveillance, donor selection, family, and reproductive counseling. However, genetic testing for patients with hematologic malignancies has been limited, largely due to the difficulty of obtaining suitable DNA samples for germline analysis. Heme Germline-MSK-IMPACT is a clinically validated assay for germline testing using nail or saliva DNA, depending on the patient's cancer type, in a non-invasive, rapid, and high-throughput manner, with the matched tumor analysis supporting results interpretation.

Methods: Genetic testing was performed on 1300 consecutive patients with a clinical diagnosis or suspicion of a hematologic malignancy on Heme Germline-MSK-IMPACT, targeting 82 hereditary cancer predisposition genes. All individuals receiving somatic testing via paired tumor-normal sequencing on MSK-IMPACT-Heme as part of their clinical care were eligible to consent for germline analysis.

Results: Germline pathogenic or likely pathogenic variants (gPVs) in hereditary cancer predisposition genes were identified in 16.7% (217/1300) of patients, with 5.8% (76/1300) having high penetrance autosomal dominant gene variants. gPVs known to be associated with hematologic malignancies were detected in *DDX41* (n = 14), *POT1* (n = 3), *RUNX1* (n = 2), *ETV6* (n = 1), *TP53* (n = 1). Additionally, four patients had biallelic variants in genes causing autosomal recessive disorders that confer increased risk for hematologic malignancies (*FANCA* (n = 2), *ATM*, *MSH6*). Other high-risk cancer predisposition genes with gPVs identified in multiple patients were *BRCA2* (n = 16), *BRCA1* (n = 15), *MSH6* (n = 4), *RTEL1* (n = 4), *CDKN2A* (n = 3), and *PALB2* (n = 3). Moderate penetrance gPVs were detected in 6.2% (81/1300) of patients in genes such as *CHEK2* (n = 36), *ATM* (n = 24), and *LZTR1* (n = 8).

Twenty-four (1.8%) patients had two or more gPVs identified. **Conclusions:** Germline testing in a broad cohort of individuals with hematologic malignancies detected hereditary cancer predisposition in a substantial proportion of the patients. This ratio is comparable to the rate of cancer predisposition variants identified in patients with solid tumors in recent studies. Matched tumor data analysis is ongoing to uncover second hits and correlations for improving our understanding of the hereditary contribution to hematologic malignancies. Research Sponsor: National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center; P30 CA008748; Marie-Josée and Henry R. Kravis Center for Molecular Oncology, the Precision, Interception and Prevention Program; Robert and Kate Niehaus Center for Inherited Cancer Genomics; V Foundation.

Prevalence of microsatellite stable Lynch syndrome and universal germline testing: A pan-cancer analysis of 246,694 patients.

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Background: Lynch Syndrome (LS) is an inherited cancer syndrome that confers up to a 60% lifetime risk of colorectal (CRC), endometrial (EC), or other cancers, and up to a 40% risk of a second primary cancer. The current standard-of-care includes LS screening upon the diagnosis of CRC or EC (especially in patients < 50 years old or with a strong family history) via immunohistochemistry for mismatch repair (MMR) protein deficiencies or microsatellite instability (MSI) testing algorithms; germline genetic testing is subsequently performed in MMR-deficient cases for confirmation. To assess the concordance between MSI status and LS, we evaluated the proportion of patients with pathogenic or likely pathogenic germline variants in a LS gene (LS-PGVs) who had microsatellite stable (MSS) tumors. **Methods:** We analyzed a pan-cancer cohort (n = 246,694) of patients who underwent personalized ctDNA testing (Signatera, Natera, Inc.), which involved whole exome sequencing (WES) of tumor and matched normal samples. MSI status was assessed in the tumor WES data by the MSISensor2 algorithm (MSI-H was defined as score ≥ 6.5). Germline single-nucleotide variants and short insertions/deletions from germline WES were identified and annotated with Variant Effect Predictor (v.105). The pathogenicity of variants in LS genes (*EPCAM*, *MSH2*, *MSH6*, *MLH1*, and *PMS2*) was determined using classifications available in the ClinVar database. **Results:** The pan-cancer cohort largely consisted of patients with CRC (n = 107,907; 44% of cohort), breast (n = 55,330; 22%), and other cancer types (each $\leq 4\%$ of cohort) including EC (n = 5519; 2%). MSI status was determined in 84% (207,536/246,694) of the cohort, of whom 93% (193,110/207,536) had MSS tumors. LS-PGVs were identified in 1% (2418/207536) of the MSI-scored pan-cancer cohort. Among all pan-cancer patients with LS-PGVs, 36% (862/2418) had MSS tumors. Most patients with *EPCAM* PGVs (91%; 32/35) had MSS tumors. Conversely, only 17% (101/588) of patients with *MLH1* PGVs had MSS tumors. We next assessed concordance between LS-PGVs and MSI status in CRC and EC. Among CRC patients with an MSI score (n = 97,309), 12% (11,752/97,309) had MSI-H and 88% (85,554/97,309) had MSS tumors. Further, LS-PGVs were identified in 2% (1,759/97,309), of whom 25% (437/1,759) had MSS tumors. In EC patients with MSI scores (n = 4,625), 20% (926/4625) had MSI-H and 80% (3699/4625) had MSS tumors. Of these, LS-PGVs were identified in 2% (86/4625) among whom 44% (38/86) had MSS tumors. **Conclusions:** LS-PGV yield was 2% for both CRC and EC, and a substantial proportion of these patients had MSS tumors (CRC: 25%; EC: 44%). Given the high risk for secondary cancers associated with LS and the implications for cascade testing, these findings strengthen the existing recommendation for considering broader germline screening of all EC and CRC patients for LS. Research Sponsor: None.

Spectrum of germline pathogenic and novel BRCA1 and BRCA2 gene mutations in a cohort of 1780 breast and ovarian carcinoma patients from east India.

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Background: Advances in our understanding of the molecular basis of cancer have pushed us in a new era of personalized medicine in oncology. The adoption of personalized medicine in Breast cancer (BC) and Ovarian cancer (OC) care holds significant promise. Homologous recombination repair (HRR) process aids in the restoration of halted replication forks during DNA replication. Where, an effective HRR depends on the normal functioning of oncoproteins, BRCA1 and BRCA2 playing crucial roles. **Methods:** Germline Next Generation Sequencing based BRCA1 & BRCA2 gene panel on ion torrent technology was employed in 1780 diagnosed BC and OC patients for genetic-molecular evaluation. Bioinformatics pipelining and data analysis was performed as per Ion Reporter pre-designed stringent workflows for germline variant screening. Variants were called as per ACMG guidelines and framework. **Results:** A total of 993 (55.8%) BC, 673 (37.8%) OC and 114 (6.4%) patients with co-existing BC & OC participated in the study. Out of which, 232 (13%) patients were found to harbour a clinically significant BRCA1 or BRCA2 gene variant. Predominantly, BRCA1 was the most mutated gene (68%; n = 158), followed by BRCA2 (32%; n = 74) across cohort. 48.2% of BRCA variants were noted in BC while 41.7% in OC and 10.1% in co-existing BC & OC patients respectively. Majority of the pathogenic variants (55.4%) were detected in high-grade tumors with mean age of 45.2 years. Exon-10 (33.3%) of BRCA1 and exon-11 (47.2%) of BRCA2 genes were the most mutated regions detected. Additionally, findings revealed 21 (9.1%) novel (14 in BRCA1 and 07 in BRCA2 genes) variants across BRCA genes not reported previously in ClinVar (NCBI) or BIC (Breast Information Core) databases. BRCA1 gene, exon-02, c.68_69del (185delAG) was the most pre-dominant (10.3%) variant in the patient cohort. **Conclusions:** India has emerged as the global cancer capital with BC being the most incidental cancer in women. Investigating the BRCA1, BRCA2 gene status in the current patient cohort has enabled the identification of not only the recurring hotspot pathogenic variants but also novel variants, as per the NCCN guidelines with actionable targets. Among BC, elevated and alarming frequency of TNBC patients (37.5%) was noted. The study findings provide a wide spectrum of BRCA gene variants specific to East-Indian patients with novel gene mutations pertaining to Indian population. These findings support the development of targeted therapeutic strategies by enabling the alignment of individual patients with treatments most likely to confer clinical benefit. Such precision oncology approaches may improve therapeutic efficacy, minimize treatment related toxicity, and ultimately enhance quality of life among cancer patients. **Keywords:** Breast & Ovarian cancer; BRCA1; BRCA2; NGS; Precision therapeutics. **Research Sponsor:** None.

Association of thymic epithelial tumors (TETs) with Lynch syndrome (LS) per germline genetic testing and molecular tumor analysis.

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Background: LS is a hereditary cancer syndrome that increases risk for gastrointestinal, gynecologic, genitourinary, and other cancers, and is typically characterized by microsatellite instability (MSI-H), mismatch repair–deficiency (MMR-D), and high tumor mutational burden (TMB). TETs, including thymomas and thymic carcinomas, are rare neoplasms not known to be associated with LS and usually show low TMB and microsatellite–stable (MSS) biology. We sought to describe the clinical, pathologic, and molecular characteristics of TETs diagnosed in individuals with LS seen at our institution. **Methods:** We conducted a retrospective, single-institution study to identify TETs among individuals with LS. We queried all LS patients seen in the DFCI Cancer Genetics and Prevention program from 1990 (n = 1,386) and identified those with a TET. We also reviewed TET cases that had paired tumor–germline sequencing between July 2023 and September 2025 (n = 12) to identify additional cases with LS pathogenic germline variants (PGVs). Clinical and molecular data, including MMR immunohistochemistry (IHC), and tumor and germline sequencing reports, were abstracted from the medical record. **Results:** Of the 1,398 cases reviewed, 4 females were identified with TETs (1 thymoma and 3 thymic carcinomas) diagnosed at a median age of 54.0 years (range 23–70 years), all with a confirmed PGV in an MMR gene [Table 1]. All four cases had tumor characteristics consistent with MMR-D. Two TETs were MMR-D by IHC, and one TET had biallelic *MLH1* variants on somatic testing, so MMR-D is inferred. Three TET cases were MSI-H by next generation sequencing, and one was MSS, despite being MMR-D by IHC. Three cases had high TMB and one did not have TMB assessment. One patient received neoadjuvant chemotherapy for two cycles, with the addition of pembrolizumab after discovering the tumor’s MSI-H status; this patient had a pathological complete response at surgery. One patient received neoadjuvant chemotherapy, surgery, and adjuvant proton beam radiation; another received neoadjuvant chemoradiotherapy followed by surgery. The fourth underwent resection and plans adjuvant therapy. All four are alive at a median of 34.8 months post-surgery (range 3.6–60.7 months). **Conclusions:** Our data show that TETs in patients with LS frequently demonstrate molecular biology (MMR-D, MSI-H, TMB-H) like other classic LS-associated cancers, suggesting that these may be rare manifestations of LS. Further clarifying the link between LS and TETs may have important implications for treatments. Research Sponsor: None.

Age at diagnosis	Sex	Histologic subgroup	TMB (mut/Mb)	Microsatellite status	MMR status	PGV
53	F	Thymoma	30.4	MSI-H	MMR-D	MLH1 c.1116+2T>G
70	F	Thymic squamous cell carcinoma	18.25	MSI-H	NA	MSH6 5'UTR_EX6del
23	F	Poorly differentiated carcinoma, favor thymic origin	14.48	MSI-H	MMR-D	MSH2 c.1906G>C
55	F	Thymic carcinoma	NA	MSS	MMR-D	PMS2 c.2137C>T

Population-based analysis of cancer disparities and social determinants of health in hereditary cancer syndrome carriers: A Healthy Nevada Project study.

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Background: Hereditary cancer syndromes account for approximately 5–10% of all cancers, the most common being Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS). Despite the availability of genetic testing that can reduce cancer morbidity and mortality in carriers, significant disparities exist across various socioeconomic and racial groups. **Methods:** This retrospective cohort study analyzed participants from the Healthy Nevada Project (HNP) who underwent genetic testing for hereditary cancer syndromes. A study protocol was developed by the research committee prior to implementation. Participants were classified as positive or negative for HBOC syndrome (BRCA1/2 pathogenic variants) and Lynch syndrome (mismatch repair gene pathogenic variants). Race, age and ethnicity were categorized along with census tract-level social determinants of health (SDOH) measures including median household income and percent rural population. Descriptive statistics characterized the cohort by demographic and clinical variables. Associations between SDOH and cancer outcomes including diagnosis and age at diagnosis, were assessed using chi-square and logistic regression analysis to test for significance. Multivariable logistic regression models were constructed to assess independent associations between SDOH factors and cancer outcomes, adjusting for confounding variables. **Results:** A total of 47,737 patients were identified using the HNP database. Genetic testing occurred after cancer diagnosis in 99.6% of participants with cancer (2,542/2,552). Delays differed significantly across racial groups ($p < 0.001$). There were no significant bivariate nor multivariate associations between HBOC and gender ($p = 0.63; 0.61$), race ($p = 0.52; 0.70$), Ethnicity ($p = 0.36; 0.67$), income ($p = 0.75; 0.88$) or rurality ($p = 0.52; 0.63$). In multivariable logistic regression, younger age at testing was independently associated with genetic test positivity (OR 0.993 per year; 95% CI 0.988–0.999; $p = 0.014$). **Conclusions:** Population-based studies examining the intersection of hereditary cancer syndromes and SDOH remain limited, particularly in diverse cohorts that reflect real-world demographics. The absence of differences in pathogenic variant prevalence across sociodemographic groups suggests that population-based genetic screening may mitigate traditional disparities in genetic yield. However, observed differences in age at testing indicate persistent inequities in timing of access, which may influence early cancer detection. In fact, delayed post-diagnosis genetic evaluation is common across all SDOH groups in this cohort. Understanding these relationships is essential for developing equitable cancer prevention and control strategies that address both genetic predisposition and the social context in which carriers live. Research Sponsor: None.

Evidence supporting *RPS20* as a colorectal cancer susceptibility gene from a case-control MGPT study.

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Background: Ribosomal protein S20 (*RPS20*) is increasingly included in colorectal cancer (CRC) germline multigene panel testing (MGPT) and clinical management guidelines, despite limited evidence of gene-disease association. Germline loss-of-function (LOF) variants in *RPS20* have been observed in a small number of individuals with CRC, without tumor loss-of-heterozygosity, and have typically been classified as variants of uncertain significance (VUS). We conducted a case/control study of individuals heterozygous for *RPS20* LOF variants to evaluate the CRC and colorectal polyp risk compared to controls and cases of established CRC susceptibility genes. **Methods:** Cases and controls underwent MGPT at Invitae (now part of Labcorp) from May 2018–May 2025. Cases included individuals with a single LOF variant in *RPS20* who had no identified pathogenic variants (PV) in other hereditary cancer genes and no VUS in established CRC risk genes; controls consisted of individuals with no PV or VUS identified. To reduce ascertainment bias, cases and controls were identified from requisitioned (clinician-ordered, reported) and unrequisitioned (run on MGPT backbone but unreported) data, under WCG protocol 1167406. Ninety controls were randomly sampled and age/sex matched to cases. CRC/polyp diagnoses were determined by clinician-reported ICD10 codes and keywords and compared between cases and controls utilizing Fisher's exact tests. To compare risk estimates with a well-defined hereditary CRC syndrome, odds of CRC/polyps in cases with *RPS20* LOF variants and in cases with mismatch repair gene PVs (*MLH1*, *MSH2*, *MSH6*, *PMS2*), both compared to controls, were estimated with multivariable logistic regression that included sex, age, requisition status, family history of cancer, and race/ethnicity. **Results:** Twenty-seven heterozygous *RPS20* LOF cases were identified (median age at testing 48 years [IQR 35–37]). CRC prevalence was significantly higher in *RPS20* LOF cases (63.0%) compared with controls (11.1%, $p < 0.001$), while polyp prevalence did not differ (7.4% vs. 10.0%, $p = 1$). In multivariable analysis, *RPS20* LOF variants were associated with increased odds of CRC compared with controls (odds ratio [OR] 18.0; 95% confidence interval [CI], 5.2–62.1), comparable to odds observed for MMR gene PGV cases (OR 9.5; 95% CI, 6.6–13.7). **Conclusions:** Heterozygous *RPS20* LOF variants identified through MGPT are associated with substantially increased CRC risk. By incorporating age- and sex-matched controls and unrequisitioned testing data, this study reduces ascertainment bias and supports *RPS20* as a CRC susceptibility gene. Larger studies are needed to inform clinical management. Research Sponsor: None.

Multivariable logistic regression, *RPS20* LOF cases compared to controls.

Cancer/ polyps	OR	CI	p-value
CRC	18.0	5.2 - 62.1	<0.001
Colon polyps	0.8	0.2 - 3.0	0.719
CRC/polyps	10.2	3.5 - 29.5	<0.001
Other Cancer	2.5	0.9 - 6.6	0.114

Feasibility of a novel oncologist-led diagnostic algorithm for Lynch syndrome in colorectal cancer patients: The ItaLynch study.

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Background: International guidelines recommend universal Lynch syndrome (LS) screening in colorectal cancer (CRC) using tumor mismatch repair deficiency (dMMR) testing. However, LS remains underdiagnosed worldwide, largely due to inconsistent referral for genetic counseling and germline testing. We report the final feasibility results of a novel, mainstreamed, oncologist-led diagnostic algorithm for LS. **Methods:** ItaLynch is a prospective, observational, multicenter Italian study on patients with dMMR CRC (May 2021–Dec 2025; 23 high-volume centers). The pathway includes: (1) universal dMMR screening by immunohistochemistry (IHC) in all CRC; (2) reflex testing and “Lynch alert”: MLH1-deficient (dMLH1) tumors undergo BRAFV600E testing and, if wild-type, MLH1 promoter methylation; a Lynch alert is added to all dMMR pathology reports (positive for high LS risk based on reflex testing or non-MLH1 loss; negative for BRAFV600E-mutated or MLH1-hypermethylated cases); (3) oncologist-led mainstream germline testing for patients with positive alert, followed by post-test genetic counseling for carriers of pathogenic variants (PV) or clinically suspicious cases. **Results:** Up to Dec. 31 2025, we enrolled 1,482 pts with dMMR CRC. Overall, 1,316 were eligible for analysis (14 not eligible; 152 not yet filled out). Excluding 104 cases with incomplete data, 1,212 patients were evaluable from somatic to germline testing. Overall, 1033 (85%) completed the ItaLynch diagnostic pathway, demonstrating the strong feasibility of this algorithm. Of patients with IHC data, 975 (78%) were dMLH1 and 281 (22%) had non-MLH1 loss. BRAF testing was performed in 904/975 (93%) dMLH1 cases; 386/904 (43%) were BRAFwt. MLH1 methylation testing was done in 329/386 (86%); 146/329 (44%) were not hypermethylated. Germline testing was performed in 108/146 (74%), identifying 21 LS-associated PV (19%). Among non-MLH1 loss, 232/281 (83%) underwent germline testing and 115 (50%) were diagnosed with LS. Overall, germline testing was performed in 361/1,033 adherent patients (35%), identifying 143 PV (40% of tests) and 24 VUS; PV prevalence was 14% (143/1,033). Mainstreaming reduced genetic pre-test counseling visits by 54% (196/361 avoided) and, compared with universal germline testing, avoided 672/1,033 tests (65%). Post-test counseling uptake was 83% among PV carriers. Median turnaround time from somatic to germline diagnosis was 217 days for dMLH1 and 73 days for non-MLH1. Among non-adherent patients, 67 underwent germline testing (14 PV, 3 VUS). In the full cohort, 157 PV were identified (MLH1 37, MSH2 57, MSH6 43, PMS2 20). **Conclusions:** This oncologist-led, mainstreamed diagnostic pathway for LS is feasible and optimized use of healthcare resources. Analyses of pathway deviations (15%), cost-effectiveness, and clinical/translational outcomes are ongoing. Research Sponsor: None.

A randomized controlled trial of a multilingual digital genetic cancer risk assessment tool in a diverse patient population.

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Background: Most individuals with hereditary cancer risk remain unidentified, particularly racial, ethnic, and linguistic minorities and those publicly insured. Patient-facing digital tools may improve personal/family history collection and genetic cancer risk assessment (GCRA). In this randomized controlled trial (RCT), we evaluated a multilingual digital GCRA tool in a diverse, predominantly publicly insured population. **Methods:** An IRB-approved RCT (NCT05562778) was conducted among new patients at four urban academic gynecology clinics. Eligible patients (≥ 18 years old, English-, Spanish-, Cantonese-, or Mandarin-speaking, no prior cancer genetic testing (GT)) were randomized to a digital GCRA tool versus usual care. The digital tool collected patient history and generated National Comprehensive Cancer Network (NCCN)-based GT eligibility reports for providers. Usual care relied on clinician assessment of personal/family history. The primary outcome was clinician identification of high-risk patients and recommendation for GT. **Results:** From 10/2023 to 10/2025, 210 patients enrolled in the study; 104 (50%) were randomized to GCRA via digital tool and 106 (50%) via clinician interview. Eighty (38%) patients self-identified as Hispanic, 39 (19%) non-Hispanic White, 40 (19%) non-Hispanic Black, and 51 (24%) Asian; 159 (76%) were English-speaking, 40 (19%) Spanish-speaking, and 11 (5%) Mandarin/Cantonese-speaking. Most were publicly insured (133, 63%), (Table 1). In the intervention arm, 99 (95%) completed the digital tool. Among all patients, 36 (17%) were identified as meeting NCCN criteria for high risk of hereditary cancer and thus eligible for GT (intervention: 14; control: 22). Use of the digital GCRA tool was associated with a higher likelihood of high-risk patients being identified and recommended GT (13 [93%] vs. 3 [14%]; $P = < 0.001$). Digital tool completion and high-risk identification did not differ by race, ethnicity, or language. **Conclusions:** In a diverse, predominantly publicly insured population, a multilingual digital GCRA tool increased identification and recommended GT for those at elevated risk for hereditary cancer. Integrating such tools may improve detection of at-risk individuals and reduce disparities in genetic service utilization. Clinical trial information: NCT05562778. Research Sponsor: Weill Cornell Medicine: Research Assistance for Primary Parents; Weill Cornell Medicine: Ritu Banga Healthcare Disparities Research; Weill Cornell Medicine: Meyer Cancer Center.

Participant characteristics.			
Characteristic	Total	Control	Intervention
Age in years (median, (IQR))	45.5 (34-59)	46.5 (34-58)	43.4 (33.5-59)
Race and Ethnicity (N (%))			
Hispanic	80 (38%)	40 (38%)	40 (38%)
Non-Hispanic White	39 (19%)	20 (19%)	19 (18%)
Non-Hispanic Black	40 (19%)	21 (20%)	19 (18%)
Asian	51 (24%)	25 (24%)	26 (25%)
Primary Insurance (N (%))			
Public	133 (63%)	64 (60%)	69 (66%)
Private	46 (22%)	26 (25%)	20 (19%)
No Coverage/Other	31 (15%)	16 (15%)	15 (14%)

IQR: interquartile range. Public: Medicaid, Medicare, or other government insurance. Private: employment-based or directly purchased.

Age-stratified evaluation of subsequent primary malignancy risk in patients with primary Lynch syndrome–spectrum cancers.

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Background: Lynch syndrome spectrum cancers (LSSC) include several of the most common cancers in both men and women. Patients with LS are advised to undergo intensive cancer screening and genetic evaluation. However, most at-risk individuals are not assessed by a cancer geneticist, especially those in middle or older age, despite these cancers often appearing late in life. This study evaluates the incidence and timing of LS-related and non-LS-related subsequent primary malignancy (SPMs) in patients diagnosed with LSSCs. **Methods:** We used SEER data (1992–2021) to identify patients with LSSC — colorectal (CRC), endometrial (EC), gastric, Bladder/GU tract (GUC), Small bowel, ovarian, pancreatic, sebaceous, and brain (BC) by using histology and site code. Demographics, survival data, and SPMs details were extracted. Patient were stratified by age < 40 years, 40–60 years, and > 60 years. We calculated the mortality-related competitive risk-adjusted cumulative incidence (CI) of SPMs at 5 and 10 years for both LSSCs and all cancers. Median follow up were calculated by reverse KM method. We calculated the time to the development of 1st SPM after the index cancer diagnosis. Proportions were compared using chi-square test. **Results:** We identified 774955 patients with LSSC (50.4% Female, mean age 66.2 (SD 13.3) with a median follow-up of 149 months. 74331 (9.6%) patients developed a subsequent malignancy, with 30666 (41.3%) of all SPM had at least 1 LSSC. In < 40 year, 40–60-year, and > 60 years groups, 4.5%, 8.1%, and 10.5 % of total patients with LSSCs had a SPM of which 68.2%, and 43.3%, and 39.9 % patient had at least 1 LSSCs ($p < 0.001$). Median time to cancers and adjusted CI is given in the table. There was significant difference in distribution of primary (p -value < 0.01) and subsequent (p -value < 0.01) LSSC. CRC was the most common primary LSSC across age group, with Brain, and EC, and GU Cancers were the 2nd most common cancer in < 40, 40–60, and > 60-year age group respectively representing 19.3%, 16.7%, and 22.9% cancers of respective LSSCs. Among SPM, CRC was the most common across all age group (42.8% of LSS SPM) whereas EC was 2nd most common LSS SPM in < 40 years, and GU cancers in both 40–60 (35%), and > 60 (31.8%) years group. **Conclusions:** For LSSC patient, likelihood of developing SPM increased with longer survival, and older patients demonstrated the highest SPM burden for both LSSC and non-LSSCs. These findings suggest that cancer genetics evaluation and robust LS-directed surveillance should be extended beyond younger populations, as older patients remain at significant risk for LS-related SPMs. Research Sponsor: None.

Age group	18-40 Years	41-60 Years	>60 Years
Median follow up (months)	131	141	155
Median time to any SPM	40	52	28
Median time to subsequent LSSC	22	28	22
	Any SPM		
5-year CI %	2.8	4.7	7.8
10-year CI %	3.7	7.1	10.6
	Subsequent LSSC		
5-year CI %	2.3	2.4	3.3
10-year CI %	2.8	3.2	4.3

Prevalence, tumor characteristics, and clinical impact of *LZTR1* pathogenic variants in a large, pan-cancer cohort.

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Background: Heterozygous germline pathogenic/likely pathogenic (P/LP) loss-of-function (LOF) variants in *LZTR1* are associated with hereditary schwannomatosis. To date, the prevalence and penetrance remain poorly defined, and there are currently no well-established surveillance guidelines for individuals with incidental *LZTR1* P/LP variants. We sought to describe the prevalence of *LZTR1* P/LP variants in a large pan-cancer cohort, characterize the tumor genomic profile of patients with these variants, and report the clinical utility of surveillance imaging in asymptomatic carriers diagnosed incidentally. **Methods:** Patients with germline P/LP variants in *LZTR1* were identified from pan-cancer patients who prospectively enrolled in an institutional review board-approved protocol of matched tumor-normal DNA sequencing (MSK-IMPACT). Clinical and tumor characteristics of *LZTR1* carriers were collected from electronic medical records. **Results:** Among 50,537 patients who underwent germline genetic testing via MSK-IMPACT, 157 (0.31%) were found to harbor a heterozygous germline P/LP variant in *LZTR1*. Eight patients presented with a schwannoma diagnosis at the time of genetic testing with an additional three reporting a prior history of schwannoma, for a total of 11 (7.01%) meeting criteria for *LZTR1*-associated schwannomatosis. In the remaining 146 (93%) of patients, the germline *LZTR1* P/LP variant was an incidental finding. The most common cancer types in those identified incidentally included prostate (23), breast (22), colorectal (21), sarcoma (14), and uterine (9). Of the 6 schwannomas with tumor data available, all exhibited a second somatic mutation in the *NF2* gene, and 5 displayed loss of heterozygosity of the *LZTR1* locus in the tumor favoring the mutant allele. LOH data was available for 117 non-schwannoma tumors. Of these, 33 (28.2%) were found to have LOH favoring the mutant *LZTR1* allele. Of patients diagnosed incidentally, 29 underwent MRI of the brain and total spine after detection of the *LZTR1* P/LP variant for schwannoma screening. An additional 104 patients underwent whole body imaging (PET/CT or CT chest, abdomen, and pelvis) for cancer surveillance. All patients were asymptomatic and did not have clinical evidence of schwannomatosis on history or physical exam. Of these 133 asymptomatic *LZTR1* carriers, no (0%) schwannomas were identified. **Conclusions:** The prevalence of *LZTR1* P/LP variants was 0.3% in an unselected pan-cancer population with < 10% meeting criteria for *LZTR1*-associated schwannomatosis, suggesting low penetrance. Imaging performed after variant detection did not identify previously unrecognized disease, suggesting limited clinical utility of routine surveillance in asymptomatic carriers without supportive clinical features. These findings support a more selective, risk-informed approach to management of incidental *LZTR1* variants. Research Sponsor: None.

Diabetes risk reduction diet and mortality outcomes following breast cancer diagnosis in Black women.

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Background: Black women continue to experience a ~40% higher breast cancer mortality rate than White women. Type II diabetes (T2D) management-related factors have received increasing attention as contributors to this disparity. Emerging evidence, largely derived from studies conducted among White women, suggests that adherence to the diabetes risk reduction diet (DRRD) may be associated with improved breast cancer outcomes. Despite Black women having more than twice the risk of developing T2D compared with White women, no studies to date have examined the association between the DRRD and mortality among Black breast cancer survivors. **Methods:** We conducted a cohort analysis of 1,732 Black breast cancer survivors from the Women's Circle of Health Follow-Up Study. Participants' prediagnostic intake of DRRD components was calculated from validated food frequency questionnaires that included: cereal fiber, coffee, nuts, whole fruits, polyunsaturated/saturated fat ratio, glycemic index, trans fats, sugar-sweetened beverages, and red/processed meat. Consumption levels for each component were scored 1-5, summed to form a DRRD adherence score (higher scores signify greater adherence), and further categorized into tertiles. Death outcomes and causes were ascertained via linkage to the New Jersey State Cancer Registry. Associations with mortality were evaluated using multivariable-adjusted Cox proportional hazards regression models. **Results:** After a median of 10.8 years of follow-up since diagnosis, 422 total deaths (213 breast cancer-related) were identified. The mean DRRD score was 26 (std 5.5). In the multivariable-adjusted model, women with higher scores had a 34% lower risk of breast cancer-specific mortality (top vs. bottom tertile HR = 0.66; 95% CI = 0.46-0.93; p = 0.02) and a 23% lower risk of overall mortality (HR = 0.77; 95% CI = 0.59-1.00; p = 0.05). The associations were consistent across diabetes and menopausal status, and also across household income subgroups. However, the risk reduction appeared more pronounced among women with early-stage disease (HR = 0.54; 95% CI = 0.34-0.88), luminal tumor subtypes (HR = 0.49; 95% CI = 0.28-0.87), those with a BMI ≥ 30 kg/m² (HR = 0.55; 95% CI = 0.34-0.88), and those in the lower half of the neighborhood socioeconomic status distribution (HR = 0.57; 95% CI = 0.35-0.93), compared with their respective counterparts. **Conclusions:** This study represents the first and largest investigation of DRRD adherence and breast cancer outcomes among Black women. Our findings suggest that greater DRRD adherence may offer a protective effect on both breast cancer-specific and overall mortality in Black women, a population facing the highest breast cancer mortality in the US. More broadly, these results, together with prior evidence, suggest that adhering to dietary patterns consistent with T2D prevention may be important for both White and Black breast cancer survivors. Research Sponsor: National Cancer Institute; R01CA185623; National Cancer Institute; P30CA072720-5929; National Cancer Institute; R01CA100598; National Cancer Institute; R00CA267557; Muriel Genfan Endowed Scholarship Fund; National Cancer Institute; 75N91021D00009; National Program of Cancer Registries (NPCR); NU58DP007117.

Leisure-time physical activity among US cancer survivors, 2020-2024.

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Background: Physical activity (PA) after a cancer diagnosis reduces treatment-related side effects and improves quality of life and cancer outcomes. Historical data show that most cancer survivors do not meet recommended levels of aerobic and strength training PA. However, the recent pattern of PA in people with cancer remained unexamined. **Methods:** This pooled cross-sectional study analyzed data from the 2020, 2022, and 2024 National Health Interview Survey to examine the prevalence and predictors of meeting PA guidelines among US cancer survivors vs. non-cancer adults. The analytic sample included adults aged ≥ 18 years with available cancer history. Data were collected on frequency and duration of aerobic and strength training PA. Age-adjusted prevalence of meeting aerobic (≥ 150 minutes per week of moderate-intensity activity or ≥ 75 minutes per week of vigorous-intensity activity) and strength training (≥ 2 days per week) PA guidelines were estimated across sociodemographic and health characteristics among cancer survivors and non-cancer adults. Multivariable logistic regression models were fitted to identify factors associated with meeting PA guidelines among cancer survivors. **Results:** The final sample included 8,974 cancer survivors (Mean age: 65.7 [SE: 0.21]; 57.3% female) and 79,036 non-cancer adults (Mean age: 46.6 [SE: 0.11]; 51.1% female). After age-adjustment, 44.5% of cancer survivors met guidelines for aerobic exercise (95% CI: 41.8-47.3), 28.9% for strength training (26.3-31.6), and 22.2% for both (19.8-24.7%), significantly lower than the non-cancer group (48.3%, 32.5%, and 26.0%; all $p < 0.01$). Patterns of lower prevalence were consistent across aerobic, strength training, and combined guidelines. Among cancer survivors, age-adjusted prevalence of meeting PA guidelines was significantly lower among those who were female, non-Hispanic Black or Hispanic, had lower levels of education or income, lived alone, were unemployed, had BMI ≥ 25 , or were current smokers (all $p < 0.05$). Survivors of gynecological and lung cancers had significantly lower age-adjusted prevalence of meeting both aerobic and strength training guidelines, while gastrointestinal cancer survivors had lower prevalence of meeting strength training guidelines only (all $p < 0.01$). After adjustment for all covariates, not meeting PA guidelines in cancer survivors remained significantly associated with older age, female, lower education level, BMI ≥ 25 , current smoking, and presence of cardiovascular disease or diabetes (all $p < 0.05$). **Conclusions:** During 2020 and 2024, fewer than 1 in 4 cancer survivors met both aerobic and strength training PA guidelines. These findings underscore a critical need to integrate PA interventions into standard oncology survivorship care, with particular attention to addressing socioeconomic barriers and tailoring programs for survivors with comorbidities and high-risk cancer types. Research Sponsor: National Cancer Institute; 5T32CA057711-32.

Alcohol-related hospitalizations among patients with cancer in the United States: Trends and associated risk factors.

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Background: Alcohol consumption is associated with an increased risk of developing multiple cancers and has been linked to higher cancer-related mortality. Alcohol dependence and harmful alcohol use may also compromise oncologic care and worsen the clinical course. However, little is known about the prevalence and outcomes of alcohol-related hospitalizations among patients with cancer. **Methods:** We analyzed trends and risk factors of alcohol-related hospitalizations among adults with cancer using the National Inpatient Sample database for the years 2016–2021. Alcohol-related admissions were identified using ICD-10 codes for intoxication, withdrawal, alcohol-induced mood and psychotic disorders, and other alcohol-induced disorders. Prevalence estimates were adjusted using discharge-level weights to represent national data. Linear and multivariate logistic regression were used to assess trends in alcohol-related admissions and associations with sociodemographic and clinical characteristics. **Results:** Among 12,027,846 non-elective hospitalizations for patients with cancer, 15,205 (0.13%) were alcohol related. From 2016 to 2021, we observed an average increase of 185 admissions per year (from 2130 to 3200, $P = 0.009$). After adjusting for all non-elective hospitalizations in cancer patients, the linear time trend in alcohol-related admissions increased by an average of 0.008% per year ($P < 0.001$). When stratified by diagnosis type, alcohol withdrawal was the leading cause of alcohol-related admissions (69.4%), followed by alcohol intoxication (22.2%). Factors associated with alcohol-related admissions included male sex, younger age, white race, rural residence, housing instability, opioid use disorder, mood and psychotic disorders (Table 1). **Conclusions:** Alcohol-related hospitalizations are rare among patients with cancer but have shown a significant upward trend in recent years. The factors linked to alcohol-related admissions in this population mirror known risk factors for harmful alcohol use among non-cancer patients. Further research is needed to improve alcohol use disorder screening, prevention, and management strategies for patients with cancer, particularly in high-risk populations. Research Sponsor: None.

Multivariable predictors of alcohol-related hospitalizations in cancer patients.

Characteristics	Alcohol-related hospitalization Odds Ratio (95% CI)
Sex	
Female	1 (reference)
Male	3.18 (2.90-3.47)
Age category, years	
18-29	1.72 (1.18-2.53)
30-49	5.96 (5.11-6.94)
50-69	4.25 (3.78-4.79)
>70	1 (reference)
Race/ethnicity	
White	1 (reference)
Black	0.57 (0.51-0.66)
Hispanic	0.51 (0.43-0.60)
Asian	0.15 (0.10-0.26)
Other	0.67 (0.56-0.81)
Hospital location	
Urban	1 (reference)
Rural	1.29 (1.11-1.50)
Housing instability	5.84 (5.00-6.84)
Opioid use disorder	2.37 (2.01-2.81)
Depressive disorder	3.51 (3.23-3.82)
Psychotic disorder	1.27 (1.01-1.61)

Association of proton pump inhibitor use with cancer-specific mortality in a nationally representative U.S. cohort (NHANES, 1999–2018).

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Background: Proton pump inhibitors (PPIs) are widely used and often continued beyond recommended durations. Evidence linking chronic PPI use to adverse cancer outcomes and mortality is mixed. Potential mechanisms include hypergastrinemia, altered gastric mucosa, and microbiome changes that may influence tumor behavior and treatment response. We assessed the association between baseline PPI use and cancer-specific mortality in a nationally representative U.S. cohort. **Methods:** Ten NHANES cycles (1999–2018) linked to the NHANES Linked Mortality Files (1999–2018) were pooled. Adults ≥ 18 years who were mortality-eligible and had examination follow-up time (PERMTH_EXM) were included. A formal written protocol was not developed; the analysis plan (study objective, exposure, endpoint, covariates, and primary models) was prespecified through discussion with the study team prior to final analyses. Baseline PPI exposure was defined from the 30-day prescription medication inventory (container-verified when available). A curated text algorithm identified PPIs using generic/brand/OTC names and fixed-dose combinations. Cancer death was defined as leading cause of death = malignant neoplasm; non-cancer deaths were censored (cause-specific hazard). Survey-weighted Cox models incorporated strata/PSU and pooled MEC weights (WTMEC2YR/10). Models used complete-case covariates per model. **Results:** Among 56,253 adults (1,850 cancer deaths), baseline PPI use was associated with higher cancer-specific mortality in unadjusted analysis and remained elevated after sequential adjustment (Table). **Conclusions:** PPI use was associated with higher cancer-specific mortality in a nationally representative U.S. cohort. These findings support careful review of PPI indication and duration and reinforce deprescribing when PPIs are not clearly indicated. Residual confounding remains possible, warranting studies using designs that better address this bias. Research Sponsor: None.

Sequentially adjusted survey-weighted Cox models estimating the cause-specific hazard of cancer death associated with PPI use (NHANES 1999–2018).

Model	N	Events	HR (CI)
Model 0: Unadjusted	56253	1850	2.63 (2.21 - 3.12)
Model 1: +Age +Sex	56253	1850	1.36 (1.14 - 1.62)
Model 2: +Race +PIR	51140	1695	1.40 (1.17 - 1.68)
Model 3: +Diabetes +Hypertension +HLD	51140	1695	1.40 (1.18 - 1.67)
Model 4: +log(cotinine)+log(metals)	9538	407	1.45 (1.10 - 1.91)

PIR = Poverty Income Ratio.

HLD = Hyperlipidemia.

Metals = lead, cadmium, mercury.

HRs represent cause-specific hazards for cancer death; non-cancer deaths were treated as censoring events.

The impact of high body-mass index on cancer mortality in the United States: An emerging public health challenge.

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Background: Obesity prevalence has increased markedly in the United States, yet the contribution of high body-mass index (BMI) to age-standardized mortality rates (ASMR) across cancer types, sex, and age groups over three decades remains poorly defined. We evaluated temporal trends in BMI-associated ASMR to identify cancers and populations most affected and inform prevention and equity-focused strategies. **Methods:** Using Global Burden of Disease (GBD) 2023 data, we extracted U.S. mortality estimates attributable to high BMI for neoplasms overall and selected cancer types from 1990–2023. BMI-associated ASMRs were compared by cancer type and sex, alongside age-specific rates for adults aged 20–54 years and all-age estimates. Age-standardized rates were used to distinguish changes in risk from demographic aging, while age-specific analyses assessed early-onset burden. **Results:** Between 1990–2023, BMI-attributable cancer mortality among adults aged 20–54 years increased by 44% (1.79 to 2.58), indicating a shift in the population-level burden toward earlier life. Overall BMI-attributable ASMR increased from 7.28 to 7.87, while all-age mortality increased from 9.15 to 14.15. Among evaluated cancers, liver, pancreatic, and uterine cancers demonstrated the largest increases in BMI-attributable ASMR. Liver cancer ASMR increased from 0.29 to 1.02 (~250%), pancreatic cancer from 0.13 to 0.40 (~200%), and uterine cancer from 1.02 to 1.74 (~70%). Early-onset BMI-attributable mortality also increased for liver (0.11 to 0.33), pancreatic (0.04 to 0.12), and colon cancer (0.53 to 0.90). Male predominance was observed for liver, pancreatic, kidney, and colon cancers, whereas uterine cancer accounted for the highest BMI-attributable burden among women. Marked geographic heterogeneity was observed, with the highest-to-lowest state BMI-attributable ASMR ratio of approximately 2.36 in 1990 (District of Columbia vs Hawaii) and 1.75 in 2023 (West Virginia vs Hawaii), indicating persistent but shifting geographic disparities. These patterns suggest amplification of existing cancer inequities at the population level over time. **Conclusions:** High BMI represents an increasingly important population-level contributor to cancer mortality burden in the U.S., with rising BMI-attributable ASMRs for metabolically associated malignancies and emerging early-onset burden. These findings underscore the importance of obesity prevention and metabolic risk reduction earlier in life as potential strategies to mitigate future cancer mortality and reduce inequities. Research Sponsor: None.

BMI-associated cancer mortality rates by age group and sex, United States, 1990–2023.			
Age group / Metric	Sex	1990	2023
20-54	Both	1.79	2.58
	Female	1.67	2.62
	Male	1.91	2.54
All ages	Both	9.15	14.15
	Female	11.41	16.44
	Male	6.77	11.82
Age-standardized	Both	7.28	7.87
	Female	8.00	8.43
	Male	6.29	7.20

Oxybutynin for vasomotor symptoms across cancer-related and menopause-associated settings: A systematic review and meta-analysis of randomised control trials and observational studies.

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Background: Vasomotor symptoms, including hot flashes, are a frequent and debilitating adverse effect among postmenopausal women and patients receiving cancer-directed hormonal therapies, particularly endocrine therapy in breast cancer and androgen deprivation therapy in prostate cancer. Hormone-based therapies are often contraindicated in cancer populations, underscoring the need for effective non-hormonal treatment strategies. Oxybutynin, an anticholinergic agent approved for overactive bladder, has emerged as a potential non-hormonal therapy for vasomotor symptoms; however, the magnitude of benefit and tolerability across randomized studies in diverse clinical populations has not been comprehensively quantified. **Methods:** A systematic search of PubMed, Embase, Cochrane CENTRAL, and clinical trial registries was performed to identify randomized controlled trials evaluating oxybutynin for vasomotor symptoms in postmenopausal women and cancer populations, including patients receiving endocrine therapy and androgen deprivation therapy. Outcomes included change in hot flash composite score (frequency $\times$ severity), change in hot flash frequency, and discontinuation due to adverse effects. **Results:** 5 studies were identified, including four randomized controlled trials and one observational cohort (409 randomized participants). Oxybutynin was associated with a significant improvement in hot flash composite score compared with control (mean difference 8.81, 95% confidence interval 6.51–11.10; $p < 0.00001$; $I^2 = 54\%$). Subgroup analyses demonstrated greater improvement with higher doses (5 mg twice daily) compared with lower doses (2.5 mg twice daily), although both dose ranges were superior to control. Hot flash frequency was significantly reduced with oxybutynin (mean difference 3.88 episodes per day, 95% confidence interval 2.96–4.80; $p < 0.00001$; $I^2 = 42\%$), with larger reductions observed with higher-dose regimens. Treatment discontinuation due to adverse effects was more frequent with oxybutynin (odds ratio 2.90, 95% confidence interval 1.19–7.10; $p = 0.02$; $I^2 = 0\%$), consistent with a dose-related increase in anticholinergic adverse effects, most commonly dry mouth. **Conclusions:** Across studies in women and men with cancer-related and menopause-associated vasomotor symptoms, oxybutynin was associated with clinically meaningful reductions in symptom frequency and severity, with evidence of a dose-response relationship and a trade-off with increased anticholinergic adverse effects. These findings inform the role of oxybutynin as a non-hormonal therapeutic option in populations in whom hormonal therapies are limited or contraindicated. Research Sponsor: None.

CAMPERR: A multicenter, prospective, observational study to evaluate a cfDNA-based genome-wide methylation enrichment assay for multicancer early detection (MCED), identification of molecular residual disease, and relapse prognostication.

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Background: Despite advances in cancer treatment, a lack of established population-level cancer screening strategies for early detection across cancer types contributes to cancer-related mortality. Emerging MCED liquid biopsy tests represent a screening approach with potential to enable detection of multiple malignancies at earlier stages in the disease process. We previously showed that an initial classifier based on a genome-wide methylome enrichment platform detected 12 cancer types, including early-stage, low-shedding tumors (Park et al. AACR 2023. Abs 1030). However, clinical performance of the platform has not been evaluated prospectively. Thus, the CAMPERR study (NCT05366881) was designed to train and validate a cell-free methylated DNA immunoprecipitation and high throughput sequencing (cfMeDIP-seq)-based test for detection and differentiation of 20 pre-selected cancer types, representing 93% of annual cancer incidence and 88% of annual cancer deaths. Longitudinal follow-up for a subset of participants with lung cancer will enable training and validation for MRD-based recurrence prognostication. **Methods:** This case-control study is enrolling participants with 20 different pre-specified cancer types (n=2400) and those without known cancer (n=3900). Eligible participants are ≥ 40 years of age and not receiving treatment for cancer at the time of enrollment or taking any demethylating/hypomethylating agents. Cases include individuals with newly diagnosed (≤ 120 days), untreated cancer or recurrence of a cancer originally diagnosed > 5 years ago. Cancers of interest are stage I-IV bladder, brain, breast, cervical, colorectal, endometrial, esophageal, gastric, head and neck, hepatobiliary, leukemia, lung, lymphoma, multiple myeloma, ovarian, pancreatic, prostate, renal, sarcoma, and thyroid. Participants with stage I-III lung cancer will have clinical follow-up and blood draws after completion of first-line treatment, every 3 mo for the first year thereafter, and every 6 mo for an additional 2 years. Eligible control participants have not been diagnosed with invasive cancer in the last 5 years and will have clinical follow-up ≥ 12 mo from enrollment to evaluate cancer status. Liquid biopsy results will not be returned to clinicians or participants. The primary objective is cancer detection. Secondary objectives include detection of specific cancer types, identification of the tissue of origin, and prognostication of clinical outcomes (eg, recurrence-free survival, overall survival). CAMPERR is currently enrolling at 15 sites. As of December 3, 2025, 2108 of 2400 cancer cases have been enrolled, including prostate (n=225), lung (n=216), colorectal (n=211), breast (n=193), and pancreatic (n=192); controls are fully enrolled. Clinical trial information: NCT05366881. Research Sponsor: Adela, Inc.

Cancer recognition and assessment through non-invasive evaluation (CRANE): A prospective clinical validation study of a multi-biomarker class multi-cancer early detection (MCED) test in Japan.

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Background: Japan has established screening programs for gastric, colorectal, lung, cervical, and breast cancers. Blood-based multi-cancer early detection (MCED) tests utilize the measurement of shared tumor-derived biomarkers (ctDNA, proteins) and machine learning to simultaneously detect several cancer types. By complementing current cancer screening, MCED testing has the potential to detect a wide range of cancers at earlier stages and expand existing screening efforts. CRANE is a prospectively collected, case-control study of Exact Sciences' MCED test (Cancerguard) to assess the overall sensitivity and specificity of the MCED test in a Japanese population. The secondary objective is to evaluate test performance across cancer types and stages. **Methods:** The study will include Japanese participants aged 45-84 years. Participants must provide written informed consent prior to providing a peripheral blood sample. A cancer cohort of approximately 1,000 participants with newly diagnosed confirmed cancer will be included in the study. Cancer cases will be recruited to obtain a diverse representation of cancer types and stages while also considering prevalence rates by cancer type. Emphasis will be placed on the 16 cancers with the highest incidence in Japan: lung, gastric, prostate, colorectal, breast, liver, pancreatic, bladder/renal pelvis, non-Hodgkin lymphoma, esophageal, kidney, uterine, cervical, ovarian, biliary tract, and head and neck. Approximately 1,000 non-cancer control participants will be included in the study, corresponding to the age and gender distribution from current population estimates reported by the Statistics Bureau of Japan. These participants will have no known cancer at enrollment, with status confirmed based on up-to-date routine cancer screening consistent with Japanese national cancer screening programs and subsequently through a 12-month follow-up after enrollment. Participants are enrolled at clinical sites in Japan, including cancer screening centers affiliated with the Japan Cancer Society. Whole blood will be collected at study sites in LBGard tubes, shipped to a local laboratory, processed to isolate the plasma and buffy coat, and then frozen. The frozen plasma and buffy coat samples will be shipped to the Exact Sciences clinical laboratory (Madison, WI, USA) for analysis. Approximately 300 non-cancer control samples and ~50 cancer case samples will undergo interim testing to assess test logistics and preliminary performance. No protocol modifications or enrollment pauses will occur based on interim testing results. Final testing will occur once all participants have been enrolled. The study duration is expected to be approximately 24 months. This study is funded by Exact Sciences Corporation. Clinical trial information: UMIN000059407. Research Sponsor: Exact Sciences Corporation.

BRCA-P: Can denosumab reduce breast cancer risk in *BRCA1* mutation carriers?

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Background: The likely ‘cell-of-origin’ that leads to breast cancer in *BRCA1* mutation carriers is a progenitor cell that is highly proliferative and prone to DNA damage. This progenitor cell expresses RANK ligand receptor [RANK] and is hyper-responsive to progesterone through paracrine signaling mediated by RANK ligand [RANKL]. Notably, high tissue expression of RANKL has recently been found in mechanosensitive (stiff) breast tissue and is associated with increased breast density, a recognized breast cancer risk factor. **Methods:** The BRCA-P trial is a randomized, double-blinded, placebo-controlled multi-centre international phase 3 trial evaluating the RANKL inhibitor denosumab as a possible breast cancer risk-reducing agent (EudraCT 2017-002505-35; NCT04711109). The safety profile of denosumab is generally well understood, as it is currently approved for the treatment of osteoporosis, bone metastases and giant cell tumor of bone. The study is led by the ABCSG (Austria), in collaboration with individual country sponsors in seven participating countries. Eligible participants include women age 25–55 years who carry a *BRCA1* pathogenic variant, are unaffected by breast or ovarian cancer, and are not pregnant or currently trying to become pregnant. Participants must also have not undergone prophylactic bilateral mastectomy or be currently taking a chemopreventive agent such as tamoxifen. They are randomised 1:1 to receive either denosumab 120 mg or placebo subcutaneously every 6 months for 5 years. The study primary objective is to evaluate the reduction in the risk of any breast cancer (invasive or DCIS). The safety profile and tolerability of denosumab in this setting will be also studied. Secondary and exploratory objectives include reduction in risk of ovarian, fallopian tube and other cancers, reduction in mammographic breast density, reduction in clinical fractures, effects on bone health and bone turnover markers and quality of life. BRCA-P completed its recruitment phase in December 2024, with 364 participants randomised globally. This investigator-initiated study is supported by Amgen. Clinical trial information: NCT04711109. Research Sponsor: U.S. Department of Defense.

Lung cancer screening for early detection of suspicious lung nodules in Latin America (LUCAS-LATAM).

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Background: Lung cancer (LC) remains the leading cause of cancer-related death in the Latin American (LATAM) region, accounting for 1 in 10 cancer deaths, attributable to late stage diagnosis in above 85%. Clinical utility of low-dose CT (LDCT) in early detection of LC has been established. However, these trials primarily focus on smokers, excluding non-smokers, who account for over one-third of LC globally. Recent studies document a need to expand screening criteria. Prevalence of light smokers and non-smokers among LC patients in LATAM is high (35% of patients being non-smokers). Geographic and socio-economic barriers hinder early detection of LC. Despite effectiveness, access to LDCT is limited in LATAM. Artificial intelligence (AI) based algorithms have demonstrated improved accuracy in predicting the risk of LC among patients with an incidental pulmonary nodule (IPN) detected on chest radiographs. Qure.ai has developed a model (qXR) that generates a lung nodule malignancy score (LNMS) based on the nodule's characteristics in a chest X-ray (CXR): low risk or high risk. **Methods:** Prospective study to assess LC screening with LDCT in LATAM and prospectively evaluate qXR in CXR at the initial visit correlating with the finding of the initial LDCT in patients with other high risk criteria to develop LC. 2000 patients will be recruited in 4 LATAM countries (Mexico 700 pts, Costa Rica 300 pts, Colombia 500 pts, Argentina 500 pts) Inclusion criteria include patients ≥ 50 years of age with one of the following: a. exposure to wood smoke (at least 100 hours/year), b. family history of LC in a first degree relative, c. COPD and/or emphysema, d. smokers with tobacco index of 10 y or more. Exclusion criteria: a. LC diagnosis or other type of cancer 5 years prior to screening, b. loss of 10% of baseline weight 6 months before, c. ineligible for LDCT, d. life expectancy ≤ 5 years, and e. previous history of pulmonary nodules. The primary objective of the study is the utility of LDCT-based LC screening in identifying suspicious lung nodules in smokers and non-smokers across LATAM, with secondary objectives including: 1- Utility of qXR-LNMS of CXR for LC risk assessment to exclude low risk patients from LDCT screening, 2- Utility of LDCT-based LC screening in subjects with various risk profiles in LATAM, 3- Prevalence of lung nodules in the study population, 4- Mortality rate in the subjects diagnosed with an anomaly in the LDCT (with or without LC diagnosis). Study design: Visit 1: CXR by qXR and LDCT1 Visit 2: LDCT2 : (12/24 months as applicable ± 2 weeks)(interval of LDCT2 is determined by the findings of the Visit 1) Low risk by qXR and Lung RADS 1 or 2: repeat in 24 months Low risk by qXR and Lung RADS 3, high risk by qXR and Lung RADS 1, 2, 3: repeat in 12 months Telephonic follow-up visits (at 6 month interval post LDCT2 for 2 years) Any Lung RADS 0, 4A, 4B, 4X or S will be assessed in a thoracic oncology multidisciplinary team. Research Sponsor: Astra Zeneca.

SOLAR: A post-approval study evaluating longitudinal performance of a blood-based test for screening individuals at average risk for colorectal cancer (CRC).

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Background: CRC is a leading cause of cancer-related mortality; CRC screening has been shown to reduce mortality through detection of early-stage disease, yet adherence to recommended screening remains suboptimal. Shield is a methylation partitioning cell-free DNA (mp-cfDNA) blood-based test indicated for CRC screening in average-risk adults age 45 years or older. This test achieved 83% sensitivity for CRC and 90% specificity for advanced neoplasia in a prospective, observational study that enrolled over 20,000 patients (ECLIPSE), and became the first blood-based screening test approved by the FDA as a primary CRC screening option in July 2024. SOLAR is an FDA-mandated, post-approval study to evaluate longitudinal performance of the blood-based mp-cfDNA test in the intended use population. **Methods:** SOLAR (NCT06880055) is an observational, prospective study supplemented with real-world data to evaluate the mp-cfDNA test following a second round of CRC screening. Patients will receive an initial mp-cfDNA test (Shield, Guardant Health, Palo Alto, CA) at baseline (T₀). Deidentified healthcare claims data will be collected to assess overall health and any development of disease at 1 and 2 years following the baseline test (T₁ and T₂, respectively). Patients with a negative screening result at T₀ will receive a screening colonoscopy alongside a blood draw approximately 3 years after baseline screening (T₃). Patients with a positive result at T₀ will be recommended to receive diagnostic colonoscopy. Individuals aged 45-81 years at average-risk for CRC are eligible for the trial. Individuals who have a personal/family history of CRC or are at high risk for CRC are excluded. Those with a positive result from any of the following CRC screening tests are also excluded: fecal occult blood test or fecal immunochemical test within the last 12 months, multi-target stool DNA test within the last 36 months, mp-cfDNA test within the last 36 months, or another CRC screening method within the last six months. Primary outcome is the performance of the mp-cfDNA test at T₃, including sensitivity for CRC or advanced adenoma detection and specificity for advanced neoplasia detection. Enrollment began July 2025. There are currently 29 active study sites across the US. Clinical trial information: NCT06880055. Research Sponsor: Guardant Health.