2025 CGA-IGC Annual Meeting

The Collaborative Group of the Americas on Inherited Gastrointestinal Cancer

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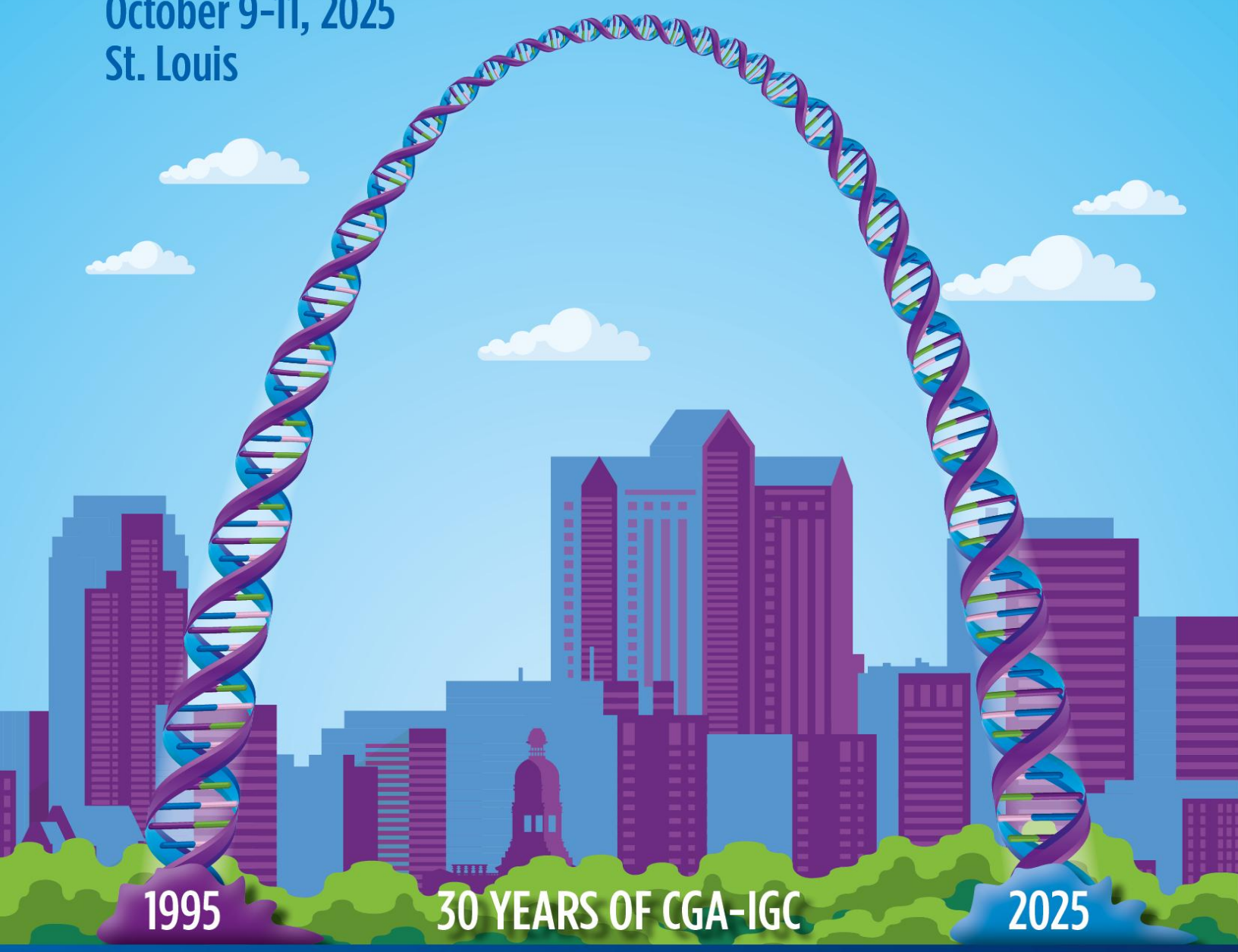
St. Louis



1995 30 YEARS OF CGA-IGC 2025

ABSTRACTS E-BOOK

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ORAL ABSTRACTS IN PRESIDENTIAL SESSIONS

O-001 CANCER PENETRANCE AMONG CTNNA1 LOSS-OF-FUNCTION CARRIERS: INITIAL CANCER RISK ESTIMATES FROM THE CTNNA1 FAMILIAL EXPANSION (CAFÉ) STUDY

General Research - Gastric cancer-related syndromes

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Background and Aim: Loss-of-function variants (LOFVs) in CTNNA1 are associated with hereditary diffuse gastric cancer syndrome (HDGC). The only risk estimate-to-date for CTNNA1 carriers, based on 13 families, showed a nearly 50% lifetime risk for gastric cancer (GC). The CTNNA1 Familial Expansion (CAFÉ) study was initiated in 2021 to better define CTNNA1 cancer penetrance and phenotypes. Herein we present cancer risk estimates from 52 CTNNA1 LOFV families in the CAFÉ study.

Methods / Clinical Presentation / Preliminary Data : CAFE study participants carried a CTNNA1 LOFV, signed informed consent, and completed RedCap questionnaires. The cumulative risk (to age 80) of GC and breast cancer (BC) for carriers was estimated with the genotype restricted likelihood method, accounting for non-genotyped individuals and conditioning on all observed phenotypes and genotypes of probands to obtain unbiased estimates.

Results / Discussion / Project Plan and Timeline: To date, 52 families are enrolled, including 30 unique CTNNA1 LOFVs. CTNNA1 probands were median age of 47y [IQR 38.6-59.4], 79% female, 94% White and 54% had a cancer diagnosis. GC was diagnosed in 10% of probands (aged 20-53y) and 37% had a first (FDR) or second degree relative (SDR) with GC. Breast cancer (BC) was diagnosed in 25% of probands (aged 40-65y), and 69% had a FDR or SDR with BC. Seventeen other cancers were observed with melanoma being most common (6%). Cumulative risk for a CTNNA1 LOFV carrier to develop GC was 10.3%. The cumulative risk for a female CTNNA1 LOFV carrier to develop BC was 49.5%, with no increased male BC risk.

Conclusions / Requirements for Collaboration: Results from the CAFÉ study represent the largest penetrance analysis of CTNNA1 LOFV carriers to date. GC risk to age 80 is 10.3%, which is substantially lower than prior risk estimates, whereas BC risk is 49.5% to age 80. These updated cancer risk estimates will be important for counseling CTNNA1 LOFV carriers and developing risk management strategies.

Keywords: gastric cancer, Hereditary Diffuse Gastric Cancer

O-002 DNA MISMATCH REPAIR DEFICIENCY AND CLINICAL FEATURES OF PROSTATE CANCER AMONG LYNCH SYNDROME PATIENTS

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by germline pathogenic variants (PV) in mismatch repair (MMR) genes. While prostate cancer (PC) is not considered a classic LS-associated malignancy, emerging evidence suggests increased PC risk in this population. This study characterizes the incidence and the clinical and molecular features of PC in men with LS.

Methods / Clinical Presentation / Preliminary Data : A prospectively maintained institutional registry of patients undergoing germline genetic testing was reviewed to identify adult males with LS. Clinical data on PC diagnosis and treatment was obtained from the electronic medical record. Mismatch repair deficiency (dMMR) was assessed by immunohistochemistry (IHC).

Results / Discussion / Project Plan and Timeline: Among 235 adult males with LS, 35 were diagnosed with PC at a median age of 60 years (IQR: 57-69). The cumulative incidence of PC by age 75 was 37% (95%CI: 26-49%). Most tumors were clinically localized; two cases presented with metastatic disease. dMMR was identified in 10/26 (39%) of evaluable tumors, including 9/12 (75%) of MSH2/EPCAM carriers and 10/14 (71%) of NCCN unfavorable intermediate- or high-risk cancers ($p < 0.001$). LS patients with a family history of PC were three times more likely to develop the disease (OR 3.0, $p < 0.001$), compared to those without a family history. This study was limited by the number of cases at one academic medical center.

Conclusions / Requirements for Collaboration: MMR-deficient PC was significantly associated with higher-risk clinical and pathologic features, suggesting that MMR testing should be considered for LS patients with PC to help inform clinical management. Additionally, these data support targeted PC screening among LS patients, particularly those with a family history of PC.

Keywords: Lynch syndrome, Hereditary Prostate Cancer, Mismatch Repair Deficiency

O-003 SPATIALLY RESOLVED TRANSCRIPTOMIC ANALYSIS OF GASTRIC PRECANCERS ARISING IN GERMLINE CDH1 VARIANT CARRIERS

General Research - Gastric cancer-related syndromes

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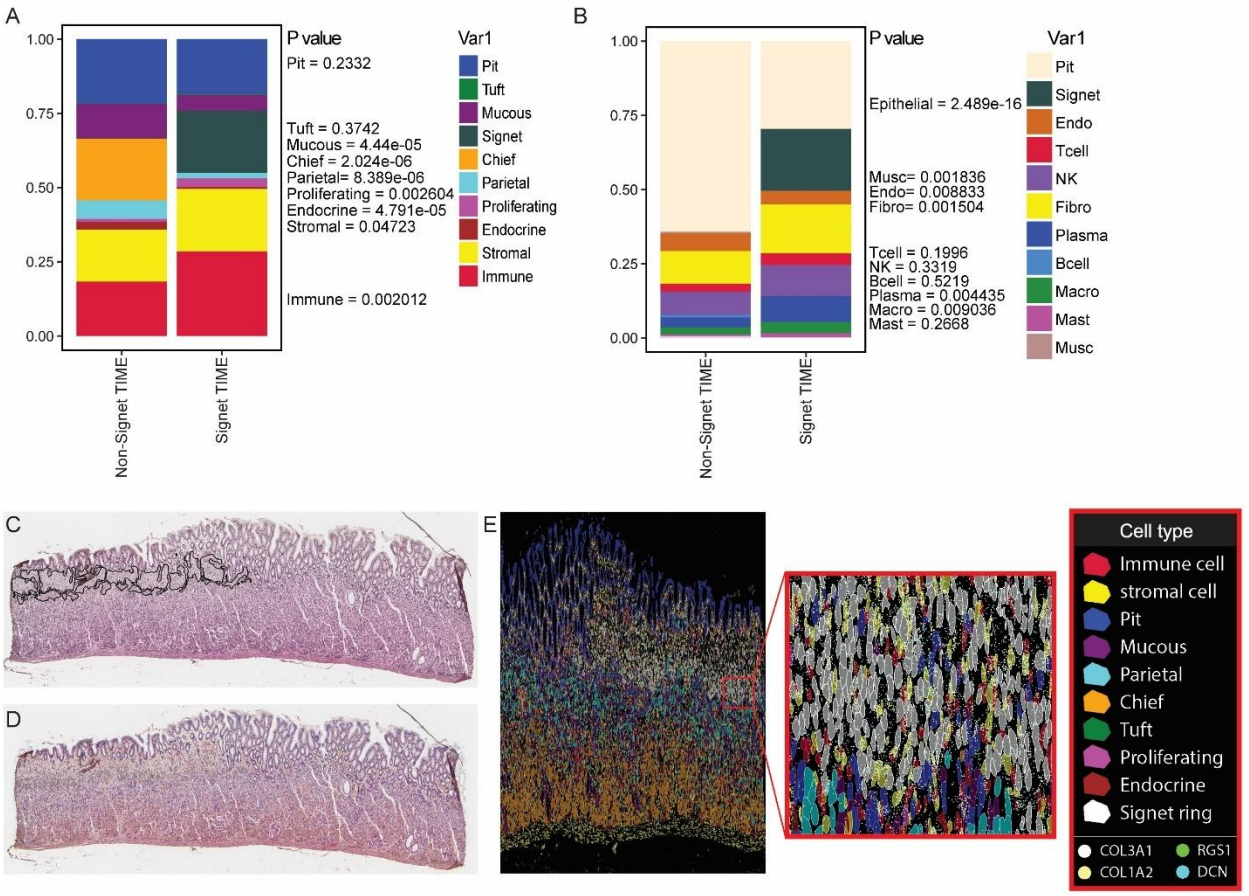
Background and Aim: Occult, intramucosal signet ring cell (SRC) lesions are an expected finding in individuals with germline CDH1 loss-of-function variants, irrespective of age and family history of cancer. SRC lesions exhibit variable progression to advanced gastric cancer, however, the drivers of progression are unknown. We investigated the gastric SRC microenvironment to characterize the precancer microenvironment (PME) and its potential association with tumorigenesis.

Methods / Clinical Presentation / Preliminary Data : We performed spatial transcriptomic analysis of SRC lesions with subcellular resolution (10X Genomics Xenium). Formalin fixed tissue from 12 patients with pathogenic germline CDH1 variants was selected. A custom gastric cancer panel and Xenium Multi-Tissue and Cancer panel were used. We assigned a 50μm perimeter around SRC foci to incorporate the PME and applied a single-cell profiling strategy. Enrichment analyses using KEGG database and gene ontology were performed.

Results / Discussion / Project Plan and Timeline: Sub-cellular spatial transcriptomic analysis demonstrated 32% of genes (218/674) were differentially expressed between SRC lesions and adjacent non-SRC gastric tissue ($p<0.05$, $|\log2FC|\geq1$). Within the SRC PME, we identified differentially expressed genes related to extracellular matrix remodeling and epithelial-to-mesenchymal transition (COL3A1, VIM, CLU) and immune cell infiltration and trafficking (ALDH1A3, RGS1, DCN, CPA3). Moreover, the SRC PME harbored significantly larger immune ($p=0.002$) and stromal ($p=0.047$) compartments compared to non-SRC adjacent gastric tissue. Within the immune compartment of SRC PME, plasma cells ($p=0.004$) and macrophages ($p=0.009$) were more abundant than non-SRC. Enrichment analyses of differentially expressed genes in plasma cells (FAM3D, SCGB2A1, C15orf48) and macrophages (CTSE, FCGR3A, PIGR) in the SRC PME demonstrated upregulation of inflammatory responses to antigenic stimulus and antigen processing, immune receptor activity, and antigen presentation.

Conclusions / Requirements for Collaboration: High-resolution spatial transcriptomic analysis of the SRC precancer microenvironment demonstrates expanded immune and stromal compartments. Within the immune compartment, gene expression indicates a discrete immune response in gastric SRC, which offers potential insight to the variable progression of precancerous SRC among CDH1 variant carriers.

Keywords: hereditary, CDH1, gastric cancer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COL1A2
DCN

O-004 ANALYSIS OF MISSENSE VARIANTS IN RPS20 AND AN ASSOCIATION WITH COLORECTAL CANCER PREDISPOSITION

General Research - Early Onset Colorectal Cancer

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Background and Aim: RPS20 has been posited as a colorectal cancer (CRC) predisposition gene, but only six families have been published in the literature. Four families harbor loss-of-function (LoF) variants, and two harbor missense variants with unknown impact. We studied 36 individuals with LoF variants showing 45-fold odds of CRC relative to a negative multigene panel testing (MGPT) cohort. (wildtype, WT; p=< .001), characterizing CRC risks similar to MLH1. However, data is lacking on the association of RPS20 missense variants with CRC. Here, we assess the CRC prevalence in >500 individuals with RPS20 missense variants.

Methods / Clinical Presentation / Preliminary Data : Retrospective review of individuals undergoing pan-cancer MGPT (17-91 genes) between 01/2019-04/2024 revealed 513 individuals carrying 125 rare, heterozygous missense variants in RPS20. Variants were pooled by computational predictor to select the most likely deleterious variants. Using ICD-10 data, CRC prevalence was compared among RPS20 missense and a WT MGPT cohort ascertained during the same period. Three variants were selected for structural assessment based on past literature and/or clinical history.

Results / Discussion / Project Plan and Timeline: Carriers of 125 unique missense variants in RPS20 showed no significant enrichment of CRC relative to WT (OR 0.94 95% CI [0.6,1.5] p=.91). When stratifying based on computational predictors, variants with the most deleterious predictions showed the greatest prevalence of CRC, but this was not statistically significant (OR 1.85 95% CI [0.7,4.2] p=.15). Structural analyses of previously reported p.Glu33Val and p.Val54Leu variants did not predict significant destabilization, but a clinically suspicious variant (p.Leu24Pro) identified in our cohort is anticipated to moderately decrease structural stability.

Conclusions / Requirements for Collaboration: Initial analyses of pooled RPS20 missense variants did not show a statistical association with CRC; however, combined computational, structural, and clinical data may be utilized to identify rare pathogenic missense variants. Further study of predicted-damaging variants is warranted in larger cohorts, as ours may be underpowered to detect increased odds of CRC.

Keywords: Colorectal Cancer, hereditary cancer, multigene panel testing, familial colon cancer

Table 1: Selected missense variants

Cohort	Ascertainment	Family	Patient	Genotype	BayesDel score (ACMG points)	Alpha-missense score (ACMG points)	SpliceAI	Structural analysis	Sex	Cancer phenotype (age at diagnosis)
Broderick, et al. 2017 PMID: 27713038	Cohort of individuals with CRC meeting Amsterdam I/II criteria	1	1	c.160G>C p.Val54Leu	0.20 (+1)	0.9587 (+2)	<0.1	Inconclusive; stabilizing (-0.5244 kcal/mol)	M	Colon (41)
Djursby, et al. 2020 PMID: 33193653	Families meeting Amsterdam I/II criteria	2	2	c.98A>T p.Glu33Val	0.43 (+3)	0.9987 (+4)	DL 0.03, DG 0.77	Inconclusive; negligibly destabilizing (0.789 kcal/mol)	F	Colon (67, 73)
			3						F	Cecum (37), Rectum (73)
			4						F	Colon (60)
			5						F	Vulva (47)
			6						M	Colon (59)
			7						F	Colon (24)
This cohort	Individuals undergoing MGPT for diverse cancer indications	3	8	c.71T>C p.Leu24Pro	0.49 (+3)	0.9997 (+4)	<0.1	Conclusive; moderately destabilizing (6.033 kcal/mol)	F	Colon (26), Breast (44)
		4	9						F	Rectal (51)

O-005 EVALUATING THE DIAGNOSTIC YIELD OF UPDATED GENETIC TESTING IN INDIVIDUALS WITH IDIOPATHIC ADENOMATOUS POLYPOSIS

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: Advancements in technology expanded and improved genetic testing for adenomatous polyposis syndromes. The National Comprehensive Cancer Network (NCCN) now recommends genetic testing including at least 12 polyposis-associated genes (APC, AXIN2, BMPR1A, GREM1, MSH3, MUTYH, NTHL1, POLE, POLD1, PTEN, SMAD4, and STK11) in individuals with 10 or more cumulative adenomas. Many individuals with idiopathic adenomatous polyposis (IAP) previously underwent limited genetic testing and may benefit from updated testing to identify underlying hereditary polyposis syndromes. In this study, we aim to evaluate the diagnostic yield of updated genetic testing in individuals with IAP and prior uninformative genetic results.

Methods / Clinical Presentation / Preliminary Data : Twenty-one individuals with IAP and uninformative genetic testing prior to routine Next-Generation Sequencing in 2016 were identified (Table 1). It was confirmed that their testing did not include all the 12 current NCCN recommended polyposis-associated genes. These individuals subsequently underwent updated multi-gene panel testing with an average number of genes assessed as 64 (range: 23-91).

Results / Discussion / Project Plan and Timeline: Updated genetic testing identified pathogenic variants (PV) in 6/21 (29%) with four (19%) of the PVs associated with a polyposis phenotype (APC [x2], AXIN2, and biallelic PMS2) and two (10%) were associated with other cancer predisposition syndromes (ATM and RAD51C). Although APC was included in the initial testing for the two patients found to have APC PVs, the previously completed deletion/duplication analysis did not include the 5' UTR.

Conclusions / Requirements for Collaboration: Updated genetic testing in individuals with IAP had a very high yield and identified previously undetected PVs. Thus, it enabled more accurate diagnoses and personalized surveillance recommendations as well as identification of at-risk family members. Given the improved diagnostic yield, it is crucial to update genetic testing for individuals with unexplained polyposis who have previously undergone limited testing, due to small gene lists and/or outdated technology, ensuring alignment with current standards.

Keywords: idiopathic adenomatous polyposis, colonic polyposis of unknown etiology, panel testing, diagnostic yield, APC

Table 1: Demographics for Individuals with IAP and Genetic Testing (GT)

Key: Initial Genetic Testing (GT1), Updated Genetic Testing (GT2), Interval adenoma count represents the number of adenomas that have developed between initial and updated genetic testing.

ID	Age (GT1)	Age (GT2)	Adenoma Count (GT1)	Adenoma Count (GT2)	Interval Adenoma Count	GT1 Genes	GT2 Gene Total	Results Type
1	68	75	20	30	10	*APC, MUTYH* (multisite)	48	**Positive *ATM*** (c.8371_8374del; p.V2791GfsX14)
2	61	66	10	13	3	*APC, MUTYH*	48	Negative
3	53	68	18	94	76	*APC, MUTYH* (multisite)	85	Negative
4	29	45	10	20+	10-19	*APC, MUTYH* (multisite)	46	**Positive biallelic *PMS2*** (c.1A>G); exon 9-10 deletion
5	62	70	19	28	19	*APC, MUTYH* (multisite)	47	Negative
6	27	33	11	14	3	*APC, MUTYH*	62	VUS: *MLH3*
7	74	84	12	85	73	*APC, MUTYH*	47	**Positive *AXIN2*** (c.1594G>T; p.E532*)
8	51	58	18	45	27	*APC, MUTYH*	47	Negative
9	59	71	13	21	8	*APC, MUTYH*	77	VUS: *TSC2*
10	51	60	100+	100+	Total colectomy	*APC, MUTYH, SMAD4, BMPR1A, PTEN, STK11*	49	VUS: *POLD1* (c.3298G>A; p.G1000R)
11	40	49	10	19	9	*APC, MUTYH, STK11*	91	Negative
12	27	33	100+	NA	Total colectomy	*APC, MUTYH*	41	VUS: *ATM* (x2)
13	29	49	100+	NA	Total colectomy	*APC, MUTYH* (multisite)	91	**Positive *APC*** (c.5'UTRdel) VUS: *CRA1, SDHA*
14	36	40	20+	77	50-59	*APC, MUTYH, AXIN2, BMPR1A, GREM1 PTEN, POLE, POLD1, SMAD4, STK11*	23	Negative
15	61	70	15	23	8	*APC, MUTYH*	76	VUS: *ALK*
16	45	66	50+	NA	Total colectomy	*APC* sequencing only	71	**Positive *APC*** (c.5'UTRdel)
17	54	67	10	10	0	*APC, MUTYH* (multisite)	71	Negative
18	61	70	10+	27	10-19	*APC, MUTYH, AXIN2, BMPR1A, GREM1 PTEN, POLE, POLD1, SMAD4, STK11*	90	VUS: *APC* (c.323G>A; p.G108E)
19	53	60	17	17	0	*APC, MUTYH, PTEN, SMAD4, STK11*	71	**Positive *RAD51C*** (c.706-2A>C)
20	62	75	25	32	7	*APC, MUTYH* (multisite)	76	Negative
21	55	65	14	50+	40-49	*APC, MUTYH*	85	Negative

O-006 INTEGRATING GENETIC SOCIAL WORK TO ADDRESS PSYCHOSOCIAL CHALLENGES IN HEREDITARY CANCER CARE

General Research - Counseling, Behavioral Health, Psychosocial, and Survivorship

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Institutions:[1]Weill Cornell Medicine , [2]New York Presbyterian

Background and Aim: Hereditary cancer syndromes (HCS), including Lynch syndrome, present individuals with significant psychosocial burdens that persist even in the absence of a personal cancer diagnosis. Patients often experience anxiety, guilt, and isolation while navigating gynecologic and gastrointestinal surveillance, complex family communication, and decisions about risk-reducing interventions. These challenges, shaped by life stage, identity, and social context, are often overlooked in standard care models. This study aimed to identify the psychosocial needs of individuals with HCS and evaluate the impact of embedding a genetic social worker into a hereditary cancer prevention program.

Methods / Clinical Presentation / Preliminary Data : From July 2023 to April 2025, clinical observations and quality improvement data were collected in a multidisciplinary genetics clinic. A genetic social worker—licensed in mental health and trained in hereditary cancer—delivered tailored psychosocial interventions via video, phone, in-person, or electronic formats. Support was customized across four core domains: psychosocial counseling, care coordination tools, site-specific support groups, and family testing assistance. For patients with Lynch syndrome, interventions also included coordination of gynecologic surveillance (e.g., endometrial biopsy) and colorectal screening support. Patients were surveyed 2–4 weeks post-intervention and asked to retrospectively rate their stress before and after using a 0–10 Numeric Rating Scale.

Results / Discussion / Project Plan and Timeline: Patients reported emotional strain throughout their care journey, particularly during decision-making, risk disclosure, and ongoing surveillance. These stressors reflected highly individualized psychosocial needs that are often invisible to traditional oncology workflows. Among surveyed patients, 65% reported reduced stress, and median scores declined from 6 to 4 (Figure 1). Outcomes showed fewer patients with high stress (>5) and more with low stress (<5) post-intervention (Figure 2). High engagement demonstrated the model's accessibility, demand, and feasibility.

Conclusions / Requirements for Collaboration: Tailored genetic social work interventions address emotional and logistical complexities in hereditary cancer care. This scalable model improves adherence, facilitates family communication, and supports integration of psychosocial care into high-risk prevention settings.

Keywords: psychosocial support, patient support, holistic care, anxiety, Lynch syndrome

Figure 1. Distribution of Stress Scores Before and After Genetic Social Work Intervention

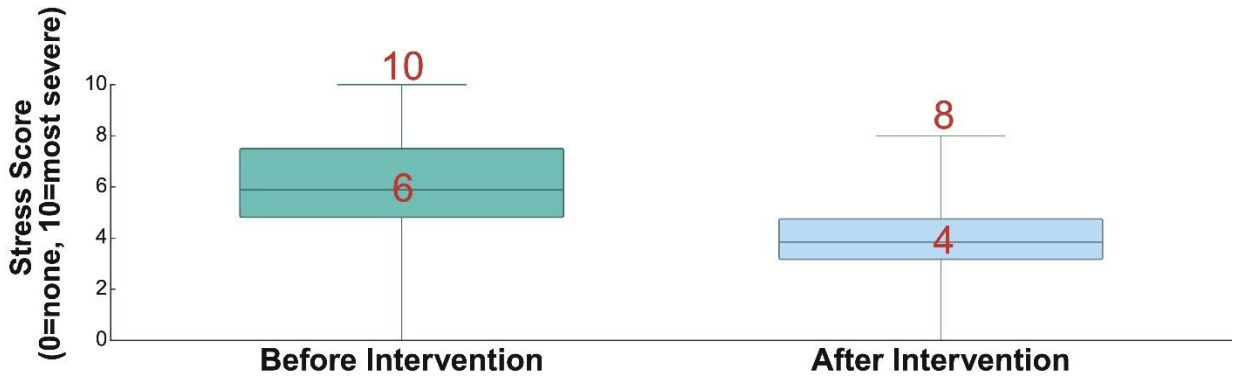

Figure 2. Patient-Reported Stress Outcomes Before and After Intervention

Patient Reported Measure (n=47)	Before Genetic Social Work	After Genetic Social Work
Reported stress	42 (89%)	37 (79%)
Stress ≥ 5	36 (77%)	21 (45%)
Stress < 5	12 (26%)	27 (57%)
Median stress score	6	4

O-007 POST OPERATIVE OUTCOMES OF CDH1 CARRIERS UNDERGOING GASTRECTOMY– RESULTS FORM THE GASTRIC CONSORTIUM

General Research - Gastric cancer-related syndromes

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Institutions:[1]University of Chicago, Section of Gastroenterology, Hepatology and Nutrition, Chicago, Illinois, [2]Department of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, [3]Michigan Medicine Cancer Genetics Clinic, The University of Michigan Ann Arbor, Michigan, [4]Division of Human Genetics, The Ohio State University Wexner Medical Center, Columbus, Ohio, [5]Division of Gastroenterology, Hepatology & Nutrition, The Ohio State University Wexner Medical Center, Columbus, Ohio, [6]Zane Cohen Centre for Digestive Diseases, Sinai Health System, Toronto, Ontario, [7]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, [8]Division of Gastroenterology and Hepatology, The University of Kansas Medical Center and The University of Kansas Cancer Center, Kansas City, Kansas, [9]University of Colorado Anschutz Medical Center, Aurora, Colorado, [10]Department of Clinical Genetics, Cancer Prevention and Control Program, Fox Chase Cancer Center, Philadelphia, Pennsylvania, [11]Department of Medicine and Cancer Center. Yale University. New Haven, Connecticut, [12]Department of Gastroenterology, University of California, San Francisco, California, [13]Division of Digestive and Liver Diseases, Columbia University, New York, New York

Background and Aim: Data on long-term outcomes following total gastrectomy in CDH1 carriers are scarce. Herein the multicenter GASTRIC (Group of investigAtors STriving toward Research In CDH1) Consortium aims to evaluate medical and surgical outcomes in CDH1 carriers undergoing gastrectomy.

Methods / Clinical Presentation / Preliminary Data : CDH1 pathogenic/likely pathogenic variant carriers who underwent gastrectomy were retrospectively identified from 12 academic centers in North America. Outcomes were ascertained from electronic medical records. Association between continuous variables was assessed using Mann-Whitney test, and chi-square/Fisher's exact tests for categorical variables.

Results / Discussion / Project Plan and Timeline: Overall, 391 carriers have been included, of these 197 (50.3%) underwent gastrectomy. Baseline characteristics and outcomes are presented in Table 1. Factors positively associated with decision to undergo gastrectomy were family history of gastric cancer (mean 2.7 relatives vs. 1.4, p=0.001), gastric biopsies positive for signet ring cell carcinoma (35.7% vs. 13.9%, p<0.001) and positive smoking status (31.9% vs. 21.3%, p=0.021). All individuals lost weight after gastrectomy, with maximal median weight loss of 23.8% (IQR 18.6-31.5) which was noted 11.3 months after surgery. New weight equilibrium (of -20.3%, Figure 1) was achieved 36 months after surgery.

Seventy-five individuals (38.1%) developed post-surgical events, mainly anastomotic strictures (16.7%) and leakage (6.6%). Only 53 individuals (26.9%) underwent bone density scans after surgery, of which 20 (37.7%) were found to have osteopenia and 10 (18.8%) with osteoporosis. Median T-score significantly dropped from -0.9 to -1.4 ($p=0.011$). Ninety-six individuals (48.7%) developed nutritional deficiencies during follow-up mainly iron and B12 deficiencies (19.7% each). Greater weight loss was associated with one or more nutritional deficiencies (-28.1% vs. -22.1%, $p<0.001$).

Conclusions / Requirements for Collaboration:: Gastrectomy for CDH1 carriers is associated with significant post-surgical morbidity. These risks should be discussed during the surgical decision-making process and should guide coordinated, multidisciplinary post-operative care planning.

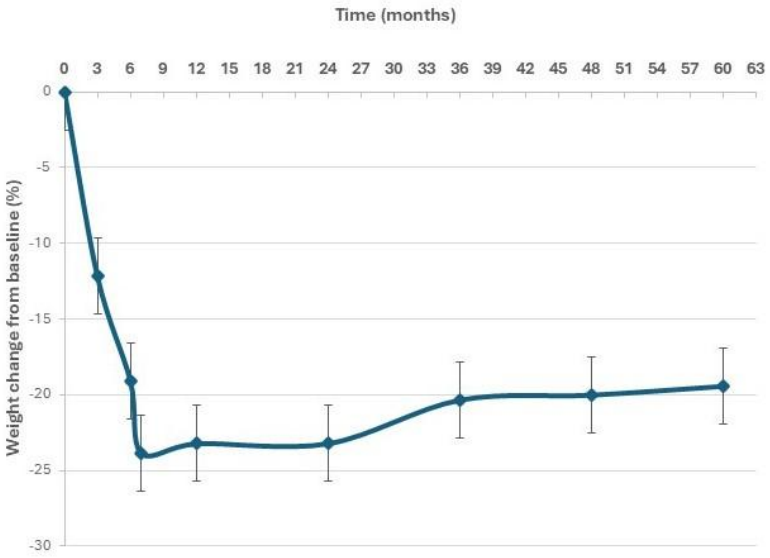
Keywords: Hereditary Diffuse Gastric Cancer, CDH1, surgical outcome

Table 1: Baseline characteristics and outcomes of patients undergoing total gastrectomy

Baseline characteristics (n=197)		
Age at surgery, range	44.4 (14.1-79.9)	
Female (%)	131 (66.5)	
Smoking history (%)	63 (31.9)	
Heavy alcohol use (%)	12 (6.1)	
Race (%)		
White	167 (84.7)	
Black	8 (4.1)	
Asian	10 (5.1)	
Other	12 (6.1)	
Ethnicity – Hispanic (%)	13 (6.6)	
Post surgical early events (≤30 days)	**Number of patients (%)**	**Median time after surgery, days (IQR)**
Leakage	13 (6.6)	5.7 (0-14)
Abscess formation requiring drainage	8 (4.1)	30 (7.5-45)
Wound infection requiring antibiotic	8 (4.1)	15 (1-22.5)
Hemorrhage	4 (2.1)	1.8 (1.3-2.8)
Pneumonia	4 (2.1)	9.4 (6.6-12.2)
Re-intubation	3 (1.5)	2.4 (1.6-3.1)
DVT/PE	1 (0.5)	7.8
Post surgical late events	**Number of patients (%)**	**Median time after surgery, months (IQR)**
1-3 months		
Anastomotic stricture requiring dilatations	33 (16.7)	3 (2-4)
Need for revision surgery	6 (3.1)	1.5 (0.5-14)
Pleural effusion requiring drainage	1 (0.5)	3
>3 months		
Surgical hernia requiring repair	8 (4.1)	34 (22.5-72.5)
Pancreatic complications	4 (2.1)	75.1 (37.7-112.5)
Bowel obstruction	4 (2.1)	59 (36-82)
Severe psychiatric complications	3 (1.5)	45.5 (26.2-64.7)
Death	2 (1)	29.5 (11-38.7)
Other	15 (7.6)	30 (1-30)
Dietary deficiencies and nutritional complications	**Number of patients (%)**	**Median time after surgery, months (IQR)**
Iron deficiency	39 (19.7)	11 (5-30)
Vitamin B12 deficiency	39 (19.7)	7.5 (2-23.2)
Copper deficiency	3 (1.5)	71.5 (36.5-71.5)
Zinc deficiency	16 (8.1)	8 (6-32.5)
Vitamin D deficiency	30 (15.2)	6.5 (3-20.7)
Folic Acid deficiency	2 (1.1)	94 (51-137)
Vitamin A deficiency	5 (2.5)	13 (10-14)
Thiamine deficiency	2 (1.1)	4.5 (3.7-5.2)
Dumping syndrome	25 (12.7)	75 (60-240)

DVT/PE – deep vein thrombosis/pulmonary embolism, IQR – interquartile range

Figure 1: Weight loss trajectory after total gastrectomy



O-008 REAL WORLD ADHERENCE TO COLORECTAL CANCER SCREENING IN PATIENTS WITH MLH1 AND MSH2 LYNCH SYNDROME AT A TERTIARY COMMUNITY CANCER CENTER

General Research - Lynch syndrome

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Institutions: [1]Providence Swedish Cancer Institute, [2]Fred Hutchinson Cancer Center

Background and Aim: Lynch syndrome is a common genetic predisposition that increases up to 10-fold the lifetime risk of colorectal cancers (CRC). Colonoscopy is an effective strategy for early detection and prevention of CRC and is recommended annually for patients 40 years and older with pathogenic variants (PV) in MLH1 and MSH2. We report on the adherence of this population to colonoscopy screening.

Methods / Clinical Presentation / Preliminary Data : CRC screening behavior for patients with a pathogenic variant (PV) diagnosed between 2006 and 2024 at a tertiary community cancer center in Seattle, WA was reviewed. Data collected include age, sex at birth, PV, personal and family cancer history at the time of PV detection, and the number, timing, and findings at colonoscopy post PV detection. Patients were stratified into 3 adherence groups based on the timing and frequency of colonoscopy relative to National Comprehensive Cancer Network guidelines. Screening adherence was calculated as the percentage of observed person-time when a patient received colonoscopy within the recommended timeframe.

Results / Discussion / Project Plan and Timeline: 51 patients with PV in MLH1 (n=22) and MSH2 (n=29) were identified. Median age at PV detection was 41 years (range 21-87), 27 (53%) were diagnosed in association with a new cancer diagnosis, 14 (27%) for known familial PV, and 10 (20%) based on family history. Over time, 20% (n=9) were 100% adherent, 67% (n=31) were partially adherent, and 13% (n=6) were not adherent to colonoscopy. Of the 37 patients who were partially or non-adherent, reasons for non-adherence included: new cancer diagnosis, medical comorbidities, declining or delaying care, and incorrect screening guidance.

Conclusions / Requirements for Collaboration: This dataset summarizes real-world adherence to colonoscopy in patients with MLH1 and MSH2. Overall, 80% of patients were either partially or non-adherent at some point during follow-up. We identified multiple reasons for suboptimal adherence that can inform future institutional interventions to increase adherence to colonoscopy screening.

Keywords: Colorectal Cancer, screen, colonoscopy, screening, Lynch syndrome, adherence

Variable	MLH1 N = 22[1]	MSH2 N = 29[1]
Age at LS Diagnosis (years)	45	45
Sex		
Female	18	21
Male	4	8
Race		
Asian	2	4
Other	0	1
Unknown	2	3
White	18	21
Follow-up Time (years)		
0-5	8	15
6-10	5	5
11-20	9	9
Reason for Genetic Testing		
Cancer Diagnosis	9	15
Family History of Cancer	6	6
Family History of LS	7	8
Site of Cancer Diagnosis		
GI	6	5
Gyn	2	6
Breast	1	2
Other	1	4
N/A	12	12

[1] Mean; n

Variable	Age 25-40[1]	Age >40[1]
Number of Colonoscopies per Patient		
0	0	6
1	3	5
2+	14	13
Colonoscopy Findings		
Benign findings	18	27
Cancer	1	5
No findings	30	28

[1] n

Follow-up Time (years)	0-5 N = 13[1]	6-10 N = 10[1]	11-20 N = 18[1]
Screening Adherence (%)			
Not Adherent (0-25)	2 (15%)	2 (20%)	2 (11%)
Partially Adherent (26-75)	5 (38%)	4 (40%)	10 (56%)
Adherent (76-100)	6 (46%)	4 (40%)	6 (33%)

[1] n (%)

O-009 IDENTIFYING BARRIERS TO HISPANIC/LATINO PARTICIPATION IN CANCER CLINICAL TRIALS: A PILOT STUDY

Diversity/Equity/Inclusion/Justice

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Background and Aim: Cancer is the leading cause of mortality in the US Hispanic/Latino (H/L) community, with colorectal cancer (CRC) accounting for over 10% of cancer-related deaths. Unfortunately, the H/L population faces multiple challenges across the cancer care continuum including inadequate screening, assessment of family cancer history, referral to cancer genetic counseling, when indicated, treatment, and cancer clinical trial (CCT) participation. H/L participation in CCTs is essential to assure that advances arising from CCTs are also applicable to the H/L community. Since H/L underrepresentation in CCTs is a multifaceted phenomenon with barriers at the physician-, healthcare system, and patient-level, we conducted a prospective study aimed at identifying H/L-specific barriers utilizing a Church-based approach.

Methods / Clinical Presentation / Preliminary Data : The "Proyecto Latino Contra Cancer Colorrectal (PeLear CCC)" study was a prospective, culturally and linguistically appropriate, interventional trial (NCT06426927) which utilized a church-based approach to recruit H/L participants. Twenty Spanish-speaking individuals were invited to participate in a semi-structured, one-on-one, qualitative interview aimed at identifying barriers to H/L CCT participation. Interviews were conducted in Spanish, recorded, transcribed, and analyzed using ATLAS.ti.

Results / Discussion / Project Plan and Timeline: Although data analysis is still in progress, barriers to CCT participation identified thus far include language discordance, financial strain/stress associated with participation, lack of preventative care, negative health experiences, potential impact on immigration status/ work and unfamiliarity with the US healthcare system and research process. Facilitators include language concordance, positive health experiences, participant incentives, gained knowledge, and family involvement. Upon completion, the top 2 conceptual themes within each interview section and the top 3 higher-level, holistic themes across the sections will be reported in terms of percentage of participants.

Conclusions / Requirements for Collaboration: Our results will provide essential information for improving the participation of H/L in CCTs including those aimed at understanding the complex nuances of hereditary gastrointestinal cancer predisposition.

Keywords: health disparities, Colorectal Cancer, trials, cancer clinical trials, ethnicity

O-010 WHO'S IN THE DRIVER'S SEAT? ASSESSMENT OF GERMLINE DRIVERS OF EARLY-ONSET ENDOMETRIAL CANCER

General Research - Other

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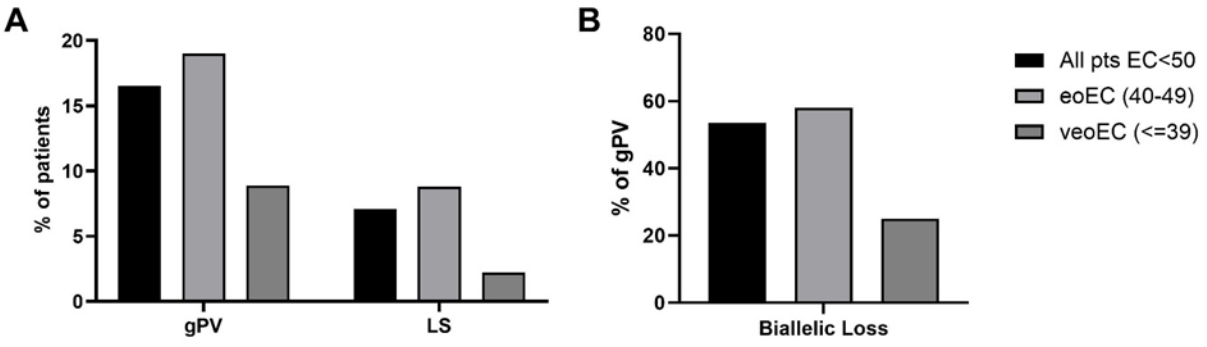
Background and Aim: Endometrial cancer (EC) is occurring in younger patients (pts), and there is a growing awareness of germline drivers of EC. We sought to define germline pathogenic variants (gPV) in pts with EC diagnosed age <50 years.

Methods / Clinical Presentation / Preliminary Data : Pts with EC treated at our institution underwent clinical tumor-normal sequencing from 1/2015-6/2021, inclusive of germline analysis of ≥76 genes. Clinical variables were collected, and pts with early-onset (eo, ages 40-49) and very-early-onset (veo, age ≤39) EC were identified.

Results / Discussion / Project Plan and Timeline: Of 1625 pts, 170 (10.5%) were diagnosed age< 50, including 125 pts with eoEC and 45 pts with veoEC. Of 170 pts, 28 (16.5%) had at least 1 gPV, with 32 unique gPV. gPV were found in 24/125 (19%) pts with eoEC and 4/45 (8.9%) pts with veoEC. Lynch Syndrome (LS) occurred in 12 pts (5 MSH2, 4 MSH6, 3 MLH1), with 11 pts in the eoEC and 1 pt in the veoEC group. The youngest pt with EC at age 31 had an MLH1 gPV. Other gPV were in high-penetrance genes with possible association with EC (1 BRCA1, 1 PALB2) or no known association with EC (4 CHEK2, 2 ATM, 1 RET). 10 gPV were in genes with autosomal recessive inheritance or genes with no known cancer risks in heterozygotes. Biallelic loss was observed in 16/28 tumors (57%) with 15/24 (63%) in the eoEC group and 1/4 (25%) in the veoEC group. Biallelic loss was identified in EC of pts with BRCA1 and PALB2 gPV. 21/28 (75%) pts were the familial proband, and 11/28 (39.3%) pts had family history of cancer, 3 with family history of early-onset EC.

Conclusions / Requirements for Collaboration: gPVs are common in pts with early-onset EC, which may influence timing of risk-reduction interventions. Heterogeneity was observed between eoEC and veoEC groups, suggesting that drivers may be different between these groups.

Keywords: germline, Endometrial, Lynch syndrome


A
20
15
10
5
0
% of patients
gPV
LS
B
80
60
40
20
0
% of gPV
Biallelic Loss
All pts EC<50
eoEC (40-49)
veoEC (<=39)

O-011 SOMATIC AND MOLECULAR ALTERATIONS IN COLORECTAL CANCER BY BIRTH COHORT

General Research - Early Onset Colorectal Cancer

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Background and Aim: Incidence rates of early-onset colorectal cancer (CRC) have risen globally, with younger birth cohorts - born after 1960 - experiencing higher rates. However, whether somatic mutation profiles vary across birth cohorts remains unclear. This study examines differences in the mutational landscape of CRC by birth cohort.

Methods / Clinical Presentation / Preliminary Data : CRC patients who underwent somatic next generation sequencing (NGS) for 154-168 genes in an in-house lab between 2015–2022 were retrospectively identified. Microsatellite instability status was determined by NGS as either microsatellite stable (MSS) or high (MSI-H). Hereditary cancer syndromes or inflammatory bowel disease patients were excluded. Genes were then grouped according to their molecular pathway. Demographic and tumor characteristics were collected. Differences in somatic mutations across birth cohorts were assessed using chi-square/Fisher's exact tests and logistic regression. Confounders adjusted for included CRC stage, location, neoadjuvant chemo/radiotherapy, and age.

Results / Discussion / Project Plan and Timeline: Overall, 369 CRC patients were identified (baseline characteristics presented in Table 1). Twenty (5.4%) had MSI-H hypermutated tumors (>10 mutation/Mb) and were analyzed separate from MSS tumors. Patients with MSI-H tumors had an earlier birth year than MSS patients (median 1946 vs. 1956, $p<0.001$), but this association was not significant after adjusting for confounders ($p=0.99$). Among MSS tumors, median tumor mutational burden (5 mutations/Mb) did not vary by birth cohort ($p=0.68$). Figure 1 illustrates the mutations identified by birth cohort. There was no significant difference in expression of any of the genes across birth cohorts using multiple statistical methods (examples shown in Table 2). Pathway-level analysis showed no significant birth cohort differences as well (Figure 1B).

Conclusions / Requirements for Collaboration: The mutational landscape of CRC was not significantly influenced by birth cohort, suggesting that the observed shifts in CRC incidence across generations are unlikely to be driven by changes in underlying tumor genomics. However, larger studies are needed to validate these findings.

Keywords: early onset colorectal cancer, somatic testing

Table 1: Baseline characteristics of the study cohort

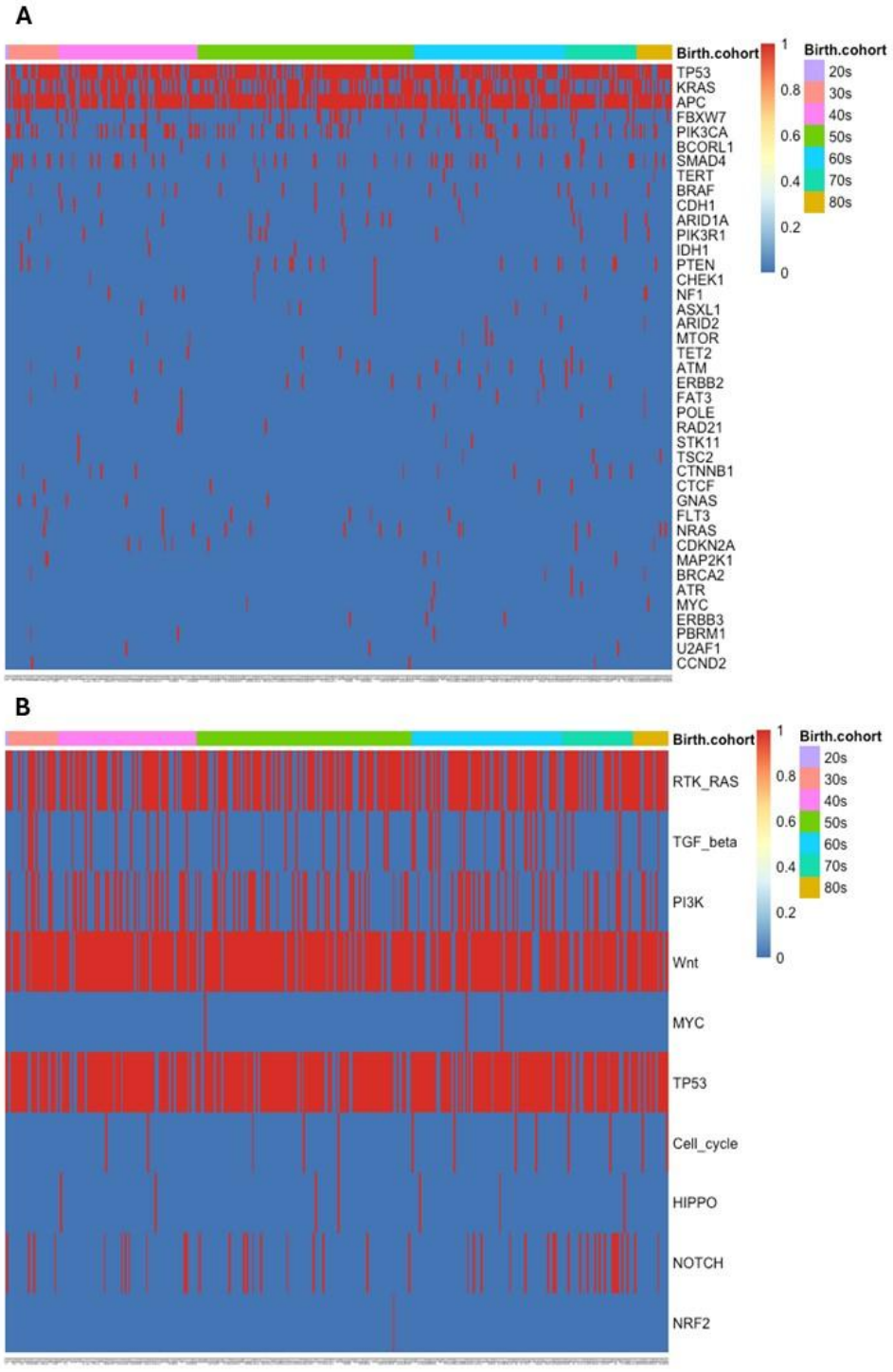
Parameter	All (n=369)
Birth cohort (%)	
1920s	4 (1.1)
1930s	30 (8.1)
1940s	79 (21.4)
1950s	119 (32.2)
1960s	80 (21.6)
1970s	37 (10.1)
1980s	19 (5.1)
1990s	1 (0.2)
Age at time of diagnosis, median (IQR)	62.9 (52.9-70.8)
Sex – male (%)	195 (52.8)
Race (%)	
White	192 (52.1)
Black	151 (40.9)
Asian	8 (2.1)
Other	8 (2.1)
Ethnicity – Hispanic (%)	22 (5.9)
Stage (%)	
I	6 (1.6)
II	43 (11.6)
III	70 (18.9)
IV	250 (67.7)
Location – right sided (cecum to splenic flexure) (%)	128 (34.6)
Received chemo/radiation therapy prior to tumor testing (%)	119 (32.2)
MSI-H (%)	20 (5.4)
TMB, mutations/Mb, median (IQR)	5.4 (4-7)
MSS only	5 (4-7)
MSI-H only	57.7 (49.6-62.7)

MSI-H – microsatellite instability-high, MSS – microsatellite stable, TMB – tumor mutational burden.

Table 2: Odds of identifying a mutation by birth year, based on univariate logistic regression. Shown are the most commonly identified genes in the study

Gene	Odds ratio per year increase	95% CI	p-value
TP53	1.01	0.98-1.03	0.381
KRAS	0.99	0.97-1.01	0.293
APC	1.01	0.98-1.03	0.463
BRAF	1.01	0.96-1.04	0.966
FBXW7	0.99	0.97-1.02	0.767
PIK3CA	0.98	0.96-1.01	0.272
SMAD4	0.99	0.97-1.02	0.758

Figure 1: (A) Mutation spectrum and (B) mutation-pathways spectrum of the microsatellite stable cancers



O-012 AREAS OF UNCERTAINTY IN PANCREATIC CANCER SURVEILLANCE: A SURVEY ACROSS THE INTERNATIONAL PANCREATIC CANCER EARLY DETECTION (PRECEDE) CONSORTIUM

General Research - Pancreatic cancer-related syndromes

Authors: Anjeli Manam[1], Bryson W. Katona[2], Jessica Everett[3], Phil Hart[4], Sigurdis Haraldsdotir[5], Vivek Kaul[6], Kelsey Klute[7], Kasmintan Schrader[8], Daniel Sussman[9]

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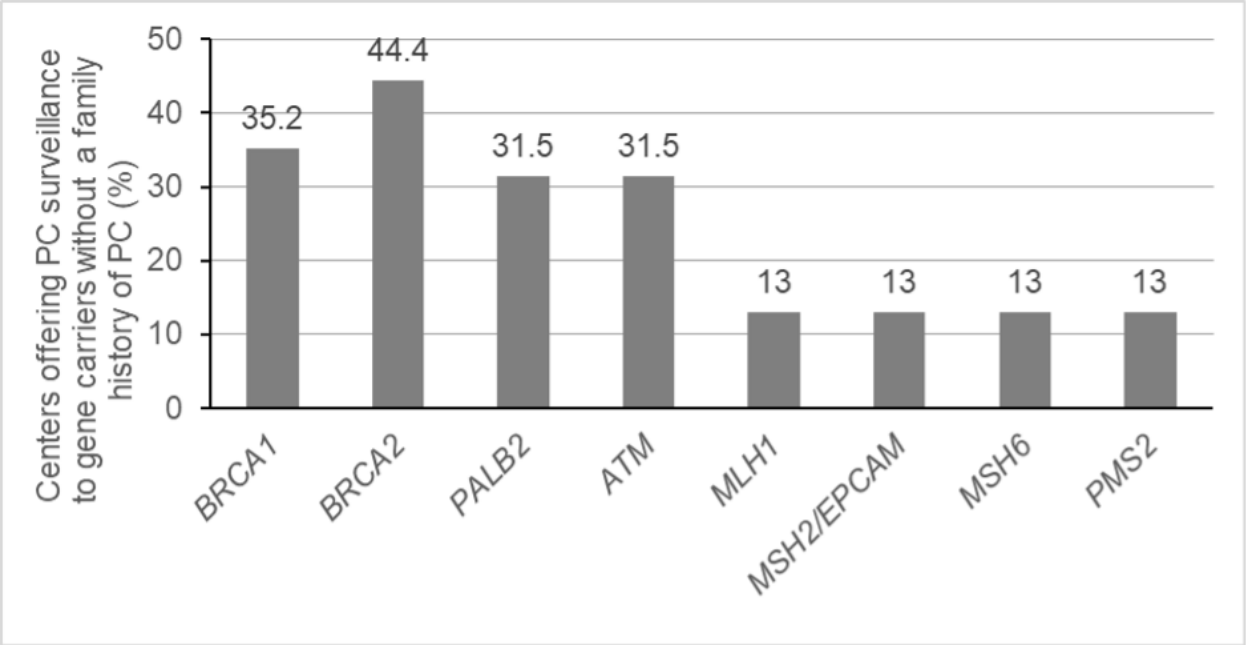
Background and Aim: Pancreatic cancer (PC) surveillance is increasingly recommended for high-risk individuals. Guidelines address eligibility criteria and how surveillance should be performed but are not all concordant, leading to heterogeneity in clinical practice. Areas of substantial discordance include use of family history to determine which gene carriers should undergo surveillance and how surveillance imaging is performed. Herein we compare PC surveillance strategies across centers in the international Pancreatic Cancer Early Detection (PRECEDE) Consortium.

Methods / Clinical Presentation / Preliminary Data : This cross-sectional study utilized a RedCap-based survey administered April-July 2024 to all 57 PRECEDE institutions (37 US-based). The site PI (or designee) completed the survey reflecting PC surveillance practices of their center, with one response per institution. Survey questions were related to surveillance eligibility for BRCA1/2, ATM, PALB2, and Lynch syndrome carriers and imaging approaches.

Results / Discussion / Project Plan and Timeline: Of 57 PRECEDE centers, 54 (95%) completed the survey. For gene carriers, there was substantial heterogeneity amongst centers with respect to whether family history of PC was utilized when assessing eligibility for surveillance (Figure 1). In absence of family history, 44.4% and 35.2% of centers would offer PC surveillance to BRCA2 and BRCA1 carriers, respectively, while 31.5% would offer surveillance to PALB2 and ATM carriers. There was general consensus that surveillance should start at age 50 for men and women across all genes. 64.8% of centers use MRI abdomen as index imaging followed by an alternative modality if index imaging was unremarkable (Table 1). The majority recommend annual surveillance imaging. Common barriers to surveillance included insurance coverage and out-of-pocket costs (42.6%, 18.5% respectively).

Conclusions / Requirements for Collaboration: This is the largest assessment of global PC surveillance practices to date, showing variability in practice patterns. Additional investigations should refine risk stratification for offering PC surveillance to gene carriers without a family history of PC. Future work should address imaging strategies and the impact on patient outcomes and resource utilization.

Keywords: pancreatic cancer, pancreatic cancer early detection, Lynch syndrome, surveillance, cancer prevention



	% (N=54)
Initial (index) imaging surveillance modality	
MRI Abdomen	64.8
EUS	25.9
CT Abdomen	3.7
Other	5.6
Motivations for selecting index surveillance modality	
Higher sensitivity than other modalities	40.7
Cost/Insurance considerations	24.1
Radiation considerations	24.1
Ability to evaluate for certain non-pancreatic cancers during the study	24.1
Anesthesia considerations	22.2
IV contrast considerations	3.7
Other	33.3
Second imaging surveillance modality (after unremarkable index imaging)	
Different than index	64.8
Same as index	35.2
Average time interval between first and second surveillance imaging test (after unremarkable index imaging)	
1 year	74.1
6 months	14.8
It would occur soon after index testing (i.e. patients get both an EUS and MRI upon entering surveillance)	7.4
Other	3.7
Typical longitudinal surveillance modality used after 2 unremarkable imaging studies	
Alternating MRI Abdomen/EUS	66.7
MRI Abdomen only	22.2
EUS only	3.7
CT Abdomen only	3.7
Other	3.7
Average time interval between longitudinal surveillance imaging tests after 2 unremarkable imaging studies	
2 years	3.7
1 year	85.2
6 months	11.1
Other	0.0

O-013 CAUSES OF DEATH AMONG INDIVIDUALS WITH LYNCH SYNDROME (LS) IN THE IMMUNOTHERAPY ERA

General Research - Lynch syndrome

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Institutions: [1]Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA, USA, [2]Dana-Farber Cancer Institute and Harvard T.H. Chan School of Public Health, Boston, MA, USA, [3]Dana-Farber Cancer Institute, Boston, MA, USA

Background and Aim: Individuals with LS predominantly develop MMR-D/MSI-H cancer, for which immunotherapy can be curative, even in the metastatic setting, leading to tissue-agnostic FDA approval for pembrolizumab for any advanced MMR-D/MSI-H cancer in May 2017. The primary aim of this study was to assess the causes of death in individuals with LS in the era of immunotherapy.

Methods / Clinical Presentation / Preliminary Data : We performed retrospective cohort study of individuals with LS seen at a single academic cancer center for oncology/genetics-related care, who died after 05/30/2017. Data cut-off was 12/20/2024. An expert panel adjudicated the cause of death after a detailed review of the electronic medical record (EMR). Data regarding personal cancer history, germline and somatic testing, and treatment were obtained from the EMR.

Results / Discussion / Project Plan and Timeline: Fifty-four individuals with LS were known to have died since May 2017 (52% female; median age at death 64; IQR 51-75), of whom 44 were determined to have died of cancer and/or cancer treatment toxicities/complications [Table 1]. Of these, 19/44 (43%) died of MMR-proficient cancer (5 pancreatic, 4 colorectal cancers), 20/44 (45.5%) died of MMR-D/MSI-H cancer (6 colorectal, 4 pancreatic cancers), and 5/44 (11.4%) died of cancer with unknown/indeterminate MMR/MSI status. Among those with MMR-D cancer, 5/20 (25%) died from treatment-related toxicity; 14/20 (70%) had progression of disease on immunotherapy. Deaths from MMR-proficient cancer were seen among patients with MSH2-, MSH6- and PMS2-associated LS but not MLH1-associated LS.

Conclusions / Requirements for Collaboration: In this single center analysis, MMR proficient cancers - particularly pancreatic and colorectal - were a frequent cause of death amongst individuals with LS. MMR-deficient cancers resistant to immunotherapy and treatment-associated deaths were other significant contributors to mortality. Larger, multi-center studies are warranted to validate these findings.

Keywords: Lynch syndrome, mortality, cause of death, pMMR, dMMR, immunotherapy

Table 1: Cancer-related deaths among individuals with Lynch Syndrome in the era of immunotherapy

	Cancer-related deaths (n=44)	dMMR (n=20)	pMMR (n=19)	indeterminate MMR (n=5)
Male (%)	20 (45.5)	9 (45.0)	9 (47.4)	2 (40.0)
Germline mutation				
MLH1	5 (11.4)	4 (20.0)	0 (0.0)	1 (20.0)
MSH2	12 (27.3)	7 (35.0)	5 (26.3)	0 (0.0)
EPCAM	1 (2.3)	1 (5.0)	0 (0.0)	0 (0.0)
MSH6	15 (34.1)	6 (30.0)	6 (31.6)	3 (60.0)
PMS2	11 (25.0)	2 (10.0)	8 (42.1)	1 (20.0)
Age at terminal cancer diagnosis (median, IQR)	58.48 [46.65, 70.38]	57.43 [43.56, 72.30]	60.12 [50.39, 69.35]	47.58 [46.68, 69.38]
Age at death (median, IQR)	62.55 [49.96, 73.75]	62.55 [48.72, 74.06]	63.20 [52.71, 73.15]	52.85 [49.38, 70.05]
Terminal cancer diagnosis				
Colorectal	11 (25.0)	6 (30.0)	4 (21.1)	1 (20.0)
Pancreatic	10 (22.7)	4 (20.0)	5 (26.3)	1 (20.0)
Glioblastoma	4 (9.1)	3 (15.0)	1 (5.3)	0 (0.0)
Endometrial	3 (6.8)	1 (5.0)	1 (5.3)	1 (20.0)
Breast ductal carcinoma	2 (4.5)	0 (0.0)	1 (5.3)	1 (20.0)
Gastric	2 (4.5)	2 (10.0)	0 (0.0)	0 (0.0)
Ovarian	2 (4.5)	1 (5.0)	1 (5.3)	0 (0.0)
Small bowel adenocarcinoma	2 (4.5)	2 (10.0)	0 (0.0)	0 (0.0)
Urinary tract	2 (4.5)	1 (5.0)	1 (5.3)	0 (0.0)
Cholangiocarcinoma	1 (2.3)	0 (0.0)	0 (0.0)	1 (20.0)
Adenocarcinoma of unknown primary	1 (2.3)	0 (0.0)	1 (5.3)	0 (0.0)
Anal squamous cell	1 (2.3)	0 (0.0)	1 (5.3)	0 (0.0)
Synchronous breast ductal carcinoma and squamous cell lung cancers	1 (2.3)	0 (0.0)	1 (5.3)	0 (0.0)
Papillary Thyroid	1 (2.3)	0 (0.0)	1 (5.3)	0 (0.0)
Vaginal adenocarcinoma (gastric type)	1 (2.3)	0 (0.0)	1 (5.3)	0 (0.0)
Death resulting from toxicity of cancer treatment				
Immunotherapy	2 (4.55)	2 (10)	0 (0.0)	0 (0.0)
Experimental therapy	1 (2.27)	1 (5)	0 (0.0)	0 (0.0)
Infectious complications	1 (2.27)	1 (5)	0 (0.0)	0 (0.0)
Surgical complications	1 (2.27)	1 (5)	0 (0.0)	0 (0.0)

O-014 UNEXPECTEDLY LOW CANCER INCIDENCE ASSOCIATED WITH CDH1 VARIANTS IN A LARGE, UNSELECTED HEALTHCARE POPULATION

General Research - Gastric cancer-related syndromes

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Background and Aim: CDH1 pathogenic/likely pathogenic (P/LP) variants increase the risk for diffuse gastric and lobular breast cancers. Most data on cancer penetrance come from clinically ascertained cohorts, potentially overestimating cancer risks. We evaluated clinical presentation of unselected individuals with CDH1 P/LP variants from a healthcare-based biobank.

Methods / Clinical Presentation / Preliminary Data : MyCode is a biobank of participants consented to health-based research which integrates exome sequencing with electronic health records (EHR) and includes the disclosure of medically actionable results. We assessed available sequences for CDH1 P/LP variants and reviewed the EHRs of adult participants for relevant personal and family cancer histories.

Results / Discussion / Project Plan and Timeline: Among participants with exome sequence data (n=230,072), 41 participants (approximately 1 in 5,612) had a P/LP variant. Figure 1 summarizes details from 40 adult participants (65% female, age range 23-96 years, median age 56.33 years) included in EHR review. Twenty-three (58%) had a personal or family history consistent with CDH1; 3 (7.7%) had gastric cancer (mean diagnosis 64 years), and 2/26 females (7.7%) had invasive lobular breast cancer. Eighteen (45%) had a family history of gastric (9, 22.5%) or breast cancer (9, 22.5%). Five participants were clinically aware of their CDH1 variant. Six participants (15%) met NCCN criteria for genetics evaluation but were not referred for germline testing.

Conclusions / Requirements for Collaboration: Two conclusions about CDH1-associated cancer emerge from examining this unselected population compared to prior data from clinical cohorts: cancer rates in unselected populations may be lower (8% vs. 13.6-42%) and, in the case of gastric cancer, may be diagnosed later. Given 15% of our cohort met NCCN criteria for CDH1 evaluation but were not referred for testing, our data also underscore potential missed opportunities for clinical ascertainment of CDH1 variants in those with suggestive personal or family histories.

Keywords: CDH1, diffuse gastric cancer, lobular breast cancer, hereditary cancer, genomic screening

Figure 1

	Adult MyCode Participants with P/LP *CDH1* Variants (n=40)	Clinically Ascertained Cohorts Based on the Literature[1]
Personal history of gastric cancer	3 (7.5%)	Females: 13.6%–33%[1] Males: 20.5%–42%[1]
Age of gastric cancer diagnosis	Mean 63.6 years Range: 60-70 years	47-49 years[1]
Personal history of lobular breast cancer	2 (7.7% of females)	36.8%–55% females[1]
Age of lobular cancer diagnosis	45 and 69 years	51-54 years[1]
Personal history of non-*CDH1*-related cancers	9 (22.5%) including colorectal (3), pancreatic, endometrial, non-Hodgkin lymphoma, renal, prostate, lung	---
Family history of gastric cancer (specific pathology unknown)	9 (22.5%)	----
Family history of breast cancer (specific pathology unknown)	9 (22.5%)	---
Personal or family history of gastric or breast cancer	23 (57.5%)	---
Prior clinical identification of germline *CDH1* variant	5 (12.5%) 4 referred for germline *CDH1* evaluation based on suggestive family history 1 referred for germline *CDH1* evaluation due to personal history of lobular breast cancer	---
Met NCCN criteria for *CDH1* evaluation, but were not clinically ascertained	6 (15%) 3 participants with suggestive *CDH1* somatic findings 3 patients with family history meeting NCCN criteria for *CDH1* evaluation	---

[1]National Comprehensive Cancer Network. (2024). *Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (Version 3.2024)*. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf.

O-015 BEYOND FAMILIAL ADENOMATOUS POLYPOSIS: GENOTYPE-PHENOTYPE CORRELATIONS DISCERN GERMLINE VERSUS SOMATIC APC WHOLE-GENE DELETIONS AMONG 860,000 TESTS

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: APC whole-gene deletions are typically associated with classic familial adenomatous polyposis (FAP), and rarely attenuated FAP. Whole-gene deletions may also signify larger contiguous gene deletions, often linked to syndromic features if germline. Given APC's location on chromosome 5q22.2, extensive deletions in this region—especially without polyposis—may indicate clonal hematopoiesis, such as 5q deletion-associated myelodysplasia. This study examines the characteristics of APC deletions identified through cancer gene diagnostic testing.

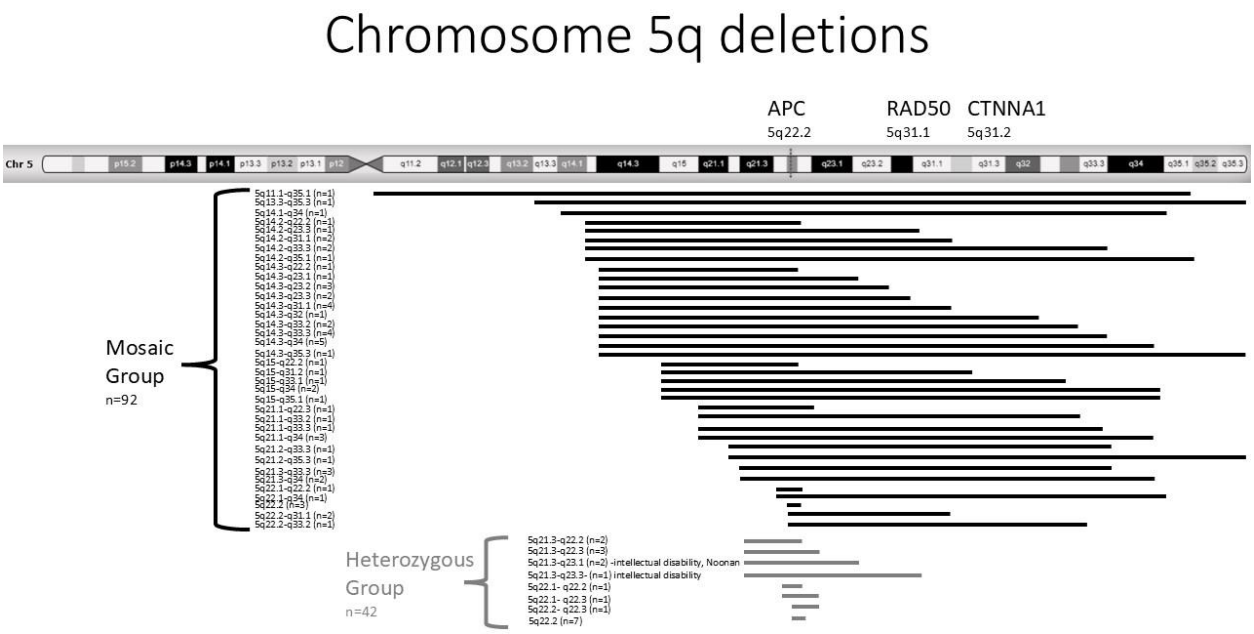
Methods / Clinical Presentation / Preliminary Data : A combination of next generation sequencing, custom array, and/or multiplex ligation-dependent probe amplification (MLPA) was used by Ambry Genetics to detect APC gene deletions. Deletions were classified as heterozygous or mosaic based primarily on deletion extent and correlated with phenotypic characteristics from de-identified, self-reported personal and family histories.

Results / Discussion / Project Plan and Timeline: Between 2016 and 2024, 866,822 APC tests were conducted, revealing 134 APC whole-gene deletions: 42 (31%) heterozygous and 92 (69%) mosaic. The heterozygous group was significantly younger (mean age 37.6) than the mosaic group (mean age 72.5). Colorectal polyp counts (available in 43 individuals) were significantly greater in the heterozygous group (n=23; mean 300; range 3.5-1000) compared to the mosaic group (n=20; mean 4.8; range 1-15). Deletion size was larger (mean 43.9Mb; range: .16-123.1 Mb) and more heterogeneous in the mosaic group and smaller (4.8 Mb; range: .3-23.7 Mb) in the heterozygous group (Figure 1). None of the mosaic cases met FAP criteria or reported syndromic features. Nine mosaic individuals had active hematologic disease or follow-up testing confirming blood-limited deletions.

Conclusions / Requirements for Collaboration: Comprehensive analysis of APC whole-gene deletions, alongside clinical data, suggests two distinct genotype-phenotype correlates: heterozygous deletion indicative of FAP and mosaic deletions suggestive of 5q deletion-associated myelodysplasia. Mosaicism may be constitutional or result from clonal hematopoiesis or hematologic malignancy, which may not be apparent prior to standard germline testing. Interdisciplinary collaboration is essential to elucidate APC gene deletions and guide appropriate care plans.

Keywords: Myelodsplastic syndrome, 5q deletion, whole gene deletion, APC whole gene deletion, clonal hematopoiesis

Chromosome ideogram was generated using the DECIPHER database (https://deciphergenomics.org)



O-016 EFFECT OF GLP-1 RECEPTOR AGONIST USE ON POLYP BURDEN IN FAMILIAL ADENOMATOUS POLYPOSIS: A CASE SERIES

Case reports / Case series

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Background and Aim: Recent studies suggest glucagon like peptide-1 (GLP-1) receptor agonists, such as semaglutide (Ozempic), may modulate inflammatory pathways as well as aid with weight loss, with potential to reduce risk for cancer. We evaluated colorectal polyp burden in patients with Familial Adenomatous Polyposis (FAP) before and after use of GLP-1 receptor agonists.

Methods / Clinical Presentation / Preliminary Data : We used retrospective chart review to identify five patients with confirmed FAP who had been started on GLP-1 receptor agonists for weight loss (n=3) or diabetes (n=2). All five patients were obese (mean BMI 46, range 39-65) and took the GLP-1 for a mean of 15 months (range 1-28 months). Four patients had attenuated FAP with intact colons and one was post-colectomy [Table 1]. Three patients demonstrated stable colorectal polyp burden (+/- 1), one had a reduction in polyp number by 84% (from 32 to 5), and one had an increase in polyp count from 100+ to 200+. The patient with the most significant reduction in colorectal polyp number had been taking the GLP-1 agonist for >2 years and was the only one who experienced weight loss >10kg during the study timeframe (D= -19.5 kg).

Results / Discussion / Project Plan and Timeline:A subset of obese FAP patients may experience reduction in polyp burden after GLP-1 receptor agonist use.

Conclusions / Requirements for Collaboration: Further studies are warranted to validate GLP-1 receptor agonists' efficacy and elucidate potential mechanisms for polyp reduction in FAP which may involve anti-inflammatory effects and/or metabolic modulation in the colonic mucosa.

Keywords: polyposis, polyp, weight, glp-1

Table 1: Patient Characteristics and Outcomes after GLP-1 Therapy

Birth Sex	Age (Years)	FAP Surgery Status	Diabetes (Y/N)	Indication for GLP-1 therapy	Duration of GLP-1 therapy (months)	Pre-GLP-1 # of Polyps	Post-GLP-1 # Polyps	% Change in Polyps	Pre-GLP-1 Weight (kg)
Female	65	Pre-colectomy	N	Weight loss	22	2	3	+50%	123
Female	36	Pre-colectomy	N	Weight loss	10	8	7	-12.5%	196.2
Female	56	Post-colectomy	Y	Diabetes	1	3	2	-33.3%	95.9
Male	51	Pre-colectomy	Y	Diabetes	15	>100	>200	+100%	145.2
Male	61	Pre-colectomy	N	Weight loss	28	32	5	-84.4%	187.8

RAPID TALKS IN PRESIDENTIAL SESSIONS

RT-001 FINANCIAL DISTRESS AMONG YOUNG ADULTS WITH EARLY-ONSET GASTROINTESTINAL CANCERS: A CALL TO ACTION

General Research - Early Onset Colorectal Cancer

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Background and Aim: The incidence of early-onset gastrointestinal cancers (eoGIC, <50 years) is on the rise and the overall cancer burden and its economic impact are expected to grow with it. For young individuals, such financial strain may have long-term consequences for themselves and their families. We hereby report on the socio-economic consequences of eoGIC.

Methods / Clinical Presentation / Preliminary Data : We collected clinical, socio-economic data from patients with early-onset colorectal and esophago-gastric cancers (eoCRC and eoEGC, respectively), all of whom received germline genetic testing. Financial toxicity (FT) was measured through the validated COmprehensive Score for financial Toxicity-Functional Assessment of Chronic Illness Therapy (COST-FACIT). COST-FACIT scores ≥23 were considered as not having FT. Mild FT was defined as COST-FACIT scores between 15-22, moderate as 8-14, and severe as ≤7.

Results / Discussion / Project Plan and Timeline: We enrolled 77 patients with eoGICs (Tab.1), and 14% carried a germline pathogenic variant (7 MMR, 1 BRCA1, 1 BRCA2, 2 MUTYH). 38/77 of these patients (49.4%) reported having suffered from mild-to-severe FT as a result of their diagnosis: 24.7% reported mild FT, 11.7% moderate FT, and 13% severe FT. The development of mild-to-severe FT was not associated with age at diagnosis, biological sex, type of eoGIC, presence of hereditary syndrome, stage at diagnosis, relocation to another region for cancer treatment, year/time since diagnosis. However, one notable finding was that patients who reported mild-to-severe FT were more commonly unemployed at diagnosis (p= 0.025) and referred greater additional expenses for healthcare services not covered by national healthcare system (p=0.029).

Conclusions / Requirements for Collaboration: Within a universal healthcare system, nearly half of patients with eoGIC report mild-to-severe FT. This finding was statistically associated with increased out-of-pocket healthcare expenses and unemployment at diagnosis. These findings highlight socio-economic support mechanisms should be integrated into cancer care to provide more effective and sustainable policy solutions, particularly for this vulnerable population of young patients.

Keywords: early-onset colorectal cancer, early-onset gastric cancer, early-onset esophageal cancer, young adults, financial toxicity

Tab. 1: Epidemiological, clinical and social characteristics of early-onset gastrointestinal cancers stratified by financial toxicity score.
*p value refers to Chi² or Fisher's Exact test; among valid responses

Characteristics	All respondents n.77 n (%)	No financial toxicity (COST score 23-44) n. 39 (50.6%) n (%)	Financial toxicity (COST score 0-22) n. 38 (49.4%) n (%)	p value *
Age at diagnosis				
Mean ± SD (years)	41.3 ± 6.6	41.61 ± 7.48	41.03 ± 5.72	0.704
Gender				
Male	35 (45%)	22 (56.4%)	13 (34.2%)	0.148
Female	42 (55%)	17 (43.6%)	25 (65.8%)	
eoGIC				
eoCRC	59 (76.6%)	26 (66.7%)	33 (86.8%)	0.068
eoEGC	18 (23.4%)	13 (33,3%)	5 (13.2%)	
Germline PV				
Yes	11 (14%)	3 (7.7%)	8 (21%)	0.177
No	66 (86%)	36 (92.3%)	30 (79%)	
Stage				
0-II	48 (62.3%)	24 (61.5%)	24 (63.1%)	1.0
III-IV	29 (37.7%)	15 (38.5%)	14 (36.9%)	
Employment status				
Unemployed	13 (16.9%)	3 (7.7%)	10 (26.3%)	**0.025**
Employed	62 (80.5%)	36 (92.3%)	26 (68.4%)	
Prefer not to answer	2 (2.6%)	0	2 (5.3%)	
Additional expenses for healthcare services not covered by national healthcare system				
No	18 (23.4%)	14 (35.9%)	4 (10.5%)	
< 500 euro	15 (19.5%)	8 (20.5%)	7 (18.4%)	**0.029**
500-1000 euro	16 (20.8%)	8 (20.5%)	8 (21%)	
> 1000 euro	25 (32.5%)	7 (17.9%)	18 (47.4%)	
Prefer not to answer	3 (3.8%)	2 (5.1%)	1 (2.6%)	
Relocation to another region for cancer treatment				
Yes	18 (23%)	9 (23.1%)	9 (23.7%)	
No	56 (73%)	27 (69.2%)	29 (76.3%)	1.0
Prefer not to answer	3 (4%)	3 (7.7%)	0	
Years since diagnosis				
Mean ± SD	6.6 ± 6.2	6.2 ± 5.2	7 ± 6.98	0.569
Time since diagnosis				
< 1 year	3 (3.9%)	1 (2.6%)	2 (5.3%)	0.403
1 year	2 (2.6%)	0	2 (5.3%)	
2 to 4 years	28 (36.4%)	16 (41%)	12 (31.6%)	
5 or more years	43 (55.8%)	21 (53.8%)	22 (57.9%)	
Missing	1(1.3%)	1 (2.6%)	0	

RT-002 GENETIC CANCER PREVENTION CLINIC: CLINICAL OUTCOMES REVIEW

General Research - Delivery of Care and Alternative Models

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Background and Aim: Our high-volume cancer genetics program based in an academic medical center has identified >10,000 pathogenic variants (PVs) in cancer genes. The need for a clinic to coordinate long-term complex care for these individuals was identified. The GI Genetic Cancer Prevention Clinic (GCPC) was recently established for those with known PVs. We aim to analyze the high-risk patient population served by GCPC.

Methods / Clinical Presentation / Preliminary Data : Patients are seen annually by a genetic counselor, physician, and genetic nurse navigator. Current NCCN management guidelines are reviewed and referrals/procedures are coordinated. Data, including demographics, genetic/medical/management compliance history, was collected through retrospective chart review and stored in a REDCap database (STU-2024-0553). Descriptive statistics were calculated.

Results / Discussion / Project Plan and Timeline: From January 2023 through April 2025, 155 unique patient encounters occurred (122 new, 33 follow-up). Patients were mostly female (n=77, 63.1%), White (n=98, 80.3%), and spoke English (n=119, 97.5%). Patients had 132 PVs in 19 genes, most commonly APC (n=28, 21.2%) and PMS2 (n=27, 20.5%). Lynch syndrome genes combined for 68 total PVs (51.5%) (Figure 1). The majority are previvors (no personal cancer history; n=79, 64.8%).New patient encounters resulted in 270 referrals placed for procedures/consultations within the institution (avg: 2.21/patient; Figure 2). The number of referrals per patient ranged from 0 (n=16, 13.1%) to 6 (n=2, 1.6%). Most common referrals were screening colonoscopy (n=69, 56.6%), EGD (n=63, 51.6%) and labs (n=46, 37.7%); which were similar to referrals for follow-ups. For new patients, at least one colonoscopy was performed on 65 patients and >1 neoplastic lesion was detected in 40 patients (61.5%) affecting 25 previvors (62.5%). (Figure 3).

Conclusions / Requirements for Collaboration: GCPC is a desired genetic clinical home that functions in a ‘hub and spoke’ model, which supports associated services in our center. GCPC physicians providing endoscopy services provides value with detected neoplasms in previvors. Future directions include monitoring management compliance rates and downstream revenue.

Keywords: high-risk genetics clinic, endoscopy, cancer genetics

Gene	Number of PV	% of PV
APC	28	21.2%
PMS2	27	20.5%
MSH2	15	11.4%
MLH1	12	9.1%
MSH6	13	9.8%
*MUTYH***	10	7.6%
PTEN	7	5.3%
STK11	5	3.8%
ATM	2	1.5%
*BRCA1**	2	1.5%
CDH1	2	1.5%
SMAD4	2	1.5%
CDKN2A	1	0.8%
*CFTR**	1	0.8%
CTNNA1	1	0.8%
EPCAM	1	0.8%
*HFE**	1	0.8%
*MITF**	1	0.8%
PALB2	1	0.8%
Total	**132**	

Figure 1: Breakdown of pathogenic variants (PV) for 122 patients seen in GCPC. Of note, 12 patients had more than one PV, and two patients were seen for a clinical diagnosis of hereditary polyposis (no PV).

* Non-GI gene included because the patient had another PV that qualified them for GI GCPC.

** Four patients had MUTYH-Associated Polyposis (MAP) accounting for 8 of these PV. The remaining two PV were detected as a single PV in a patient with another PV that qualified them for GI GCPC.

Type of Referral	New Patient Visits: Referrals N (%)	Follow-Up Visits: Referrals N (%)
Screening Colonoscopy	69 (56.6%)	15 (45.5%)
EGD	63 (51.6%)	11 (33.3%)
Labs	46 (37.7%)	11 (33.3%)
Imaging	33 (27.0%)	6 (18.2%)
Derm	18 (14.8%)	3 (9.1%)
PCP	9 (7.4%)	1 (3.0%)
High Risk Gyn Onc Clinic	8 (6.6%)	1 (3.0%)
Other	7 (5.7%)	0 (0.0%)
Digestive Disease	4 (3.3%)	0 (0.0%)
Diagnostic Colonoscopy	3 (2.5%)	0 (0.0%)
Breast Surgical Consult	2 (1.6%)	0 (0.0%)
Neurology	2 (1.6%)	1 (3.0%)
High Risk Breast Clinic	1 (0.8%)	1 (3.0%)
Gyn Onc Surgical Consult	1 (0.8%)	0 (0.0%)
Pancreatic Cancer Prevention Clinic	1 (0.8%)	2 (6.1%)
Endocrine	1 (0.8%)	0 (0.0%)
Support Services	1 (0.8%)	1 (3.0%)
Urology	1 (0.8%)	1 (3.0%)
Total Referrals	**270**	**54**
Referrals per Patient	**2.21**	**1.64**

Figure 2: Referrals for services/orders placed during GCPC by visit type (new patient vs. follow-up).

Number of Procedures	Patients N (%)	Total Number of Neoplastic Lesions				
		0	1-10	11-20	21-100	>100
EGD						
0	64 (52.5%)	-	-	-	-	-
1	54 (44.3%)	35	13	2	2	2
2	3 (2.5%)	-	-	-	1	2
3	1 (0.8%)	-	-	-		1
Colonoscopy						
0	57(46.7%)	-	-	-	-	-
1	58 (47.5%)	23	26	2	4	3
2	5 (4.1%)	2	1	-	-	2
3	2 (1.6%)	-	-	-	1	1
EUS or ERCP						
0	117 (95.9%)	-	-	-	-	-
1	5 (4.1%)	1	3	-	1	-
Capsule Endoscopy						
0	121 (99.2%)	-	-	-	-	-
1	1 (0.8%)	-	1	-	-	-

Figure 3: Endoscopy procedures for 122 patients performed since initial visit in GCPC. Neoplastic lesions include adenomas and polyps of various pathologies.

RT-003 MUTYH-ASSOCIATED POLYPOSIS IN ADOLESCENTS: A CASE SERIES

Case reports / Case series

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Background and Aim: MUTYH-associated polyposis (MAP), caused by biallelic MUTYH pathogenic/likely pathogenic variants, leads to gastrointestinal (GI) polyposis and increased cancer risk in adulthood. Per NCCN, GI surveillance recommendations start at age 25-30. We present four adolescents with MAP and polyps.

Methods / Clinical Presentation / Preliminary Data : Patient 1, a 22-year-old male, underwent colonoscopy at age 16 based on hematochezia and had three large multilobulated (largest piece measuring 3.5 cm) tubular/serrated polyps with dysplasia. A colorectal cancer multi-gene panel (MGP) showed MUTYH c.536A>G; p.Tyr179Cys homozygosity. Twelve 1-3 mm sessile rectosigmoid polyps were subsequently removed, but pathology showed normal tissue. Esophagogastroduodenoscopy (EGD) was not performed. Patient 2 (sister of patient 1) is a 15-year-old female diagnosed with MAP via familial testing. Colonoscopy performed due to early polyp onset in her brother revealed one <2 mm sigmoid colon polyp with focal adenomatous change; EGD showed no polyps. Patient 3, an 18-year-old transgender female, underwent colonoscopy and EGD at age 16 based on GI symptoms and had ten <2 cm colonic tubular adenomas. A colorectal cancer MGP revealed homozygosity for MUTYH c.536A>G; p.Tyr179Cys. Patient 4, a 16-year-old male, underwent EGD at age 15 based on reflux and abdominal pain, which revealed hundreds of fundic gland polyps (FGPs). Colonoscopy was normal. APC genetic testing (including evaluation of promoter 1B) was negative, but a colorectal cancer MGP revealed homozygosity for MUTYH c.1103G>A; p.Gly368Asp.

Results / Discussion / Project Plan and Timeline: This case series demonstrates GI polyps can occur in adolescents with MAP. This includes one adolescent with FGPs, which have been reported in 11% of MAP patients, but we are not aware of another MAP case with FGPs in adolescence.

Conclusions / Requirements for Collaboration: Germline testing via MGP should be considered for adolescents with one or more adenomatous polyps, or with multiple FGPs without a known cause. More data is needed to inform the optimal GI surveillance initiation age in MAP.

Keywords:gastrointestinal, predisposition, polyps, MUTYH-associated polyposis, germline genetic testing, pediatric

RT-004 CIGARETTE SMOKING AND AGE OF PANCREATIC ADENOCARCINOMA DIAGNOSIS FOR HEREDITARY PANCREATIC CANCER PATIENTS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Cigarette smoking is associated with earlier pancreatic adenocarcinoma (PDAC) diagnosis, but there are few studies examining smoking and PDAC onset in high-risk individuals (HRI) who have pathogenic variants (PV) in PDAC susceptibility genes or meet criteria for familial pancreatic cancer (FPC). This study aims to evaluate smoking and age of PDAC diagnosis in HRIs.

Methods / Clinical Presentation / Preliminary Data : Of 3064 patients with histologically confirmed PDAC in our registry, 969 patients underwent genetic testing. 136 had a PV while 833 tested negative, including 114 FPC patients and 719 sporadic patients (Table 1). Analysis of variance and t-tests were used to compare PDAC diagnosis age for PV, FPC, and sporadic patients by smoking history.

Results / Discussion / Project Plan and Timeline: PV patients were diagnosed significantly earlier than sporadic patients among never (65.6 vs 68.5 years, P=0.04, Table 2) and past smokers (65.9 vs 69.9 years, P=0.02). This trend continued for current smokers but was not significant (59.5 vs 62.2 years, P=0.29). Patients who stopped smoking within 20 years of diagnosis were diagnosed earlier than those who stopped more than 20 years ago, an effect most pronounced for PV patients. PV patients were diagnosed significantly earlier than sporadic patients for those who quit within 20 years (58.9 years vs 65.6 years, P=0.05); the trend was not significant for those who quit more than 20 years ago (70.1 vs 72.9 years, P=0.14). Smoking history did not significantly impact diagnosis age for FPC patients compared to sporadic patients.

Conclusions / Requirements for Collaboration: PDAC patients with PVs were diagnosed earlier than sporadic patients, particularly for never and past smokers. PV patients were diagnosed earlier than sporadic patients with recent smoking cessation but not remote cessation. The perceptible effects of past smoking and recent cessation demonstrate a disproportionate danger of smoking for PV patients. Future multicenter studies are warranted to further evaluate these findings.

Keywords: pancreatic cancer, smoking, risk factor

Table 1. Baseline demographics, tumor stage, and smoking history for 969 cases of histologically confirmed pancreatic ductal adenocarcinoma (PDAC) that had undergone genetic testing for PDAC-associated pathogenic variants from the PDAC Gene Environment Risk (PAGER) study

	All patients	Pathogenic variant-associated pancreatic cancer[a]	Familial pancreatic cancer[b]	Sporadic pancreatic cancer	
	N = 969	N = 136	N = 114	N = 719	P
Age at diagnosis, years (SD)	67.6 (10.8)	64.9 (12.5)	69.0 (9.7)	67.9 (10.5)	0.004
Sex, no. (%)					0.23
Female	490 (50.6)	76 (55.9)	62 (54.4)	352 (49.0)	
Male	479 (49.4)	60 (44.1)	52 (45.6)	367 (51.0)	
Race, no. (%)					0.07
Asian	5 (0.5)	1 (0.7)	2 (1.8)	2 (0.3)	
Black	42 (4.3)	5 (3.7)	7 (6.1)	30 (4.2)	
White	921 (95.0)	129 (94.9)	105 (92.1)	687 (95.5)	
Other	1 (0.1)	1 (0.7)	0 (0.0)	0 (0.0)	
Clinical stage at diagnosis, no. (%)					0.76
Local	197 (20.3)	29 (21.3)	25 (21.9)	143 (19.9)	
Regional	381 (39.3)	57 (41.9)	38 (33.3)	286 (39.8)	
Metastatic	277 (28.6)	38 (27.9)	36 (31.6)	203 (28.2)	
Unknown	114 (11.8)	12 (8.8)	15 (13.2)	87 (12.1)	
BMI, kg/m^2 (SD)					
At diagnosis	27.5 (5.6)	27.8 (5.6)	27.2 (5.8)	27.5 (5.6)	0.73
Lifetime usual[c]	30.8 (6.6)	32.1 (6.3)	29.5 (5.7)	30.9 (6.7)	0.11
Lifetime maximum	31.9 (6.7)	31.5 (5.2)	32.0 (7.0)	32.0 (7.0)	0.88
Cigarette smoking, no. (%)					0.60
Never	500 (51.6)	75 (55.1)	64 (56.1)	361 (50.2)	
Past	307 (31.7)	41 (30.1)	35 (30.7)	231 (32.1)	
Current	158 (16.3)	19 (14.0)	15 (13.2)	124 (17.2)	
Unknown	4 (0.4)	1 (0.7)	0 (0.0)	3 (0.4)	
Smoking cessation, no. (%)					0.61
Current smoker	158 (33.7)	19 (31.1)	15 (30.0)	124 (34.6)	
1-20 years prior to diagnosis	113 (24.1)	12 (19.7)	15 (30.0)	86 (24.0)	
>20 years prior to diagnosis	176 (37.5)	26 (42.6)	15 (30.0)	135 (37.7)	
Unknown	22 (4.7)	4 (6.6)	5 (10.0)	13 (3.6)	

N, number; P, p-value; SD, standard deviation; BMI, body mass index

[a]Pathogenic variant frequencies: BRCA2, 41; ATM, 36; BRCA1, 18; PALB2, 10; CDKN2A, 8; TP53, 8; MSH6, 7; PMS2, 4; MSH2, 3; STK11, 1; MLH1, 0; EPCAM, 0; APC, 0

[b]Patients with family history of PDAC in a first-degree relative

[c]Calculated from patient-reported usual weight or if reported usual weight was unavailable, weight at diagnosis plus patient-reported weight loss

Table 2. Smoking history and age at PDAC diagnosis among patients in the PAGER study

	All patients		Pathogenic variant-associated pancreatic cancer			Familial pancreatic cancer			Sporadic pancreatic cancer		
	Age at diagnosis, years (95% CI)	N	Age at diagnosis, years (95% CI)	N	P[a]	Age at diagnosis, years (95% CI)	N	P[b]	Age at diagnosis, years (95% CI)	N	P
Smoking status	P < 0.0001[c]		P = 0.13[c]			P = 0.02[c]			P < 0.0001[c]		
Never smoker	68.1 (67.2, 69.0)	500	65.6 (62.7, 68.5)	75	0.04	69.0 (66.4, 71.5)	64	0.72	68.5 (67.4, 69.5)	361	Ref.
Past smoker	69.6 (68.4, 70.7)	307	65.9 (62.0, 69.8)	41	0.02	71.5 (68.7, 74.3)	35	0.37	69.9 (68.6, 71.2)	231	Ref.
Current smoker	61.9 (60.3, 63.5)	158	59.5 (53.6, 65.4)	19	0.29	63.1 (58.6, 67.5)	15	0.74	62.2 (60.4, 64.0)	124	Ref.
Unknown		4		1			0			3	
Smoking cessation history	P < 0.0001[c]		P = 0.005[c]			P = 0.002[c]			P < 0.0001[c]		
Current smoker	61.9 (60.3, 63.5)	158	59.5 (53.6, 65.4)	19	0.29	63.1 (58.6, 67.5)	15	0.74	62.2 (60.4, 64.0)	124	Ref.
1-20 years prior to diagnosis	65.3 (63.3, 67.3)	113	58.9 (51.2, 66.6)	12	0.05	68.4 (63.7, 73.1)	15	0.35	65.6 (63.3, 68.0)	86	Ref.
>20 years prior to diagnosis	72.5 (71.2, 73.8)	176	70.1 (65.5, 74.6)	26	0.14	73.5 (70.2, 76.8)	15	0.78	72.9 (71.5, 74.3)	135	Ref.
Unknown		22		4			5			13	

PDAC, pancreatic ductal adenocarcinoma; CI, confidence interval; N, number; P, p-value

[a]Comparing age at diagnosis for pathogenic variants patients to sporadic patients by smoking status and cessation history

[b]Comparing age at diagnosis for familial pancreatic cancer patients to sporadic patients by smoking status and cessation history

[c]Comparing age at diagnosis by smoking status and cessation history within each cohort

RT-005 REPEAT GASTRIC BODY AND ANTRUM BIOPSIES IN LYNCH SYNDROME YIELD NEWLY IDENTIFIED GASTRIC INTESTINAL METAPLASIA

General Research - Lynch syndrome

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Background and Aim: Lynch Syndrome (LS) increases risk for gastric cancer. The National Comprehensive Cancer Network (NCCN) recommends upper endoscopic screening in LS including non-targeted biopsies of the gastric body and antrum to detect Helicobacter pylori (HP) and/or gastric intestinal metaplasia (GIM). We previously demonstrated a 5.5% rate of GIM and 3.6% rate of HP in LS, however the utility of repeat gastric biopsies on subsequent upper endoscopies remains uncertain. We aimed to determine the rate of GIM and HP on repeat gastric body and antrum biopsies in LS.

Methods / Clinical Presentation / Preliminary Data : LS individuals who underwent upper endoscopy with non-targeted gastric body and antrum biopsies performed were included. Procedures were performed between September 2018 and October 2024, data was input into REDCap.

Results / Discussion / Project Plan and Timeline: Of 683 individuals with LS, there were 286 (42%) individuals with at least one, 140 (20%) individuals with two or more, and 43 (6%) individuals with three or more upper endoscopies with non-targeted gastric body and antrum biopsies. The overall prevalence of GIM detected with non-targeted body and antrum biopsies was 8%. The rate of HP was 2%. Of individuals without GIM detected on an initial upper endoscopy with non-targeted gastric body and antrum biopsies, 4% had GIM newly identified on their second upper endoscopy, and 1% had GIM newly identified on a subsequent (third or greater) upper endoscopy after having two prior procedures with no GIM. HP was not newly identified on any subsequent upper endoscopies.

Conclusions / Requirements for Collaboration: Current LS guidelines recommend non-targeted biopsies from the gastric body and antrum during upper endoscopy; however, it remains uncertain whether these biopsies should be performed with subsequent upper endoscopies. Amongst a LS cohort undergoing serial upper endoscopies, repeat gastric body and antrum biopsies continued to yield newly identified GIM, providing support for non-targeted gastric body and antrum biopsies being considered on all upper endoscopies performed in LS.

Keywords: Lynch syndrome, gastric cancer, upper endoscopy, gastric intestinal metaplasia, Helicobacter pylori, surveillance, Lynch syndrome, gastric cancer, upper endoscopy, gastric intestinal metaplasia, Helicobacter pylori, surveillance

Gastric body and antrum biopsy findings, No. (%)	First EGD n = 286	Second EGD n = 140	3+ EGDs n=43
Antrum biopsies			
Gastric intestinal metaplasia	15 (5%)	13 (9%)	4 (9%)
New diagnosis of gastric intestinal metaplasia	-	6 (4%)	1 (2%)
Helicobacter pylori	7 (2%)	0	0
Body biopsies			
Gastric intestinal metaplasia	4 (1%)	2 (1%)	1 (2%)
New diagnosis of gastric intestinal metaplasia	-	0	0
Helicobacter pylori	7 (2%)	0	0

Table 1. Upper Endoscopy findings of the LS cohort where non-targeted body and antrum biopsies were performed.

	Characteristics of Those who Underwent EGD without GIM N=263	Characteristics of Those who Underwent EGD with GIM N=23
Female Sex	184 (70%)	12 (52%)
Race		
White	228 (87%)	20 (87%)
Asian	12 (5%)	2 (9%)
Black	10 (4%)	0 (0%)
Other	13 (5%)	1 (4%)
Lynch Syndrome Gene		
EPCAM	6 (2%)	1 (4%)
MLH1	46 (17%)	3 (13%)
MSH2	72 (27%)	7 (30%)
MSH6	68 (26%)	10 (43%)
PMS2	71 (27%)	2 (9%)

Table 2. Characteristics of individuals with LS who underwent EGD with gastric body and antrum biopsies who had GIM compared to those who do not.

RT-006 EVALUATION OF AN EMPLOYER-BASED CANCER BENEFIT PROGRAM FACILITATED BY GENETIC COUNSELORS

General Research - Delivery of Care and Alternative Models

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Institutions:[1]Thermo Fisher Scientific

Background and Aim: Cancer navigation programs have gained traction in response to the complexity and rising costs of the U.S. healthcare system. Increasingly, self-insured employers are seeking third-party cancer services, like navigation programs, to support employees and reduce costs. We have taken a unique approach by developing an employer-based cancer benefit program (CBP) facilitated by genetic counselors. The CBP provides navigation, genetic counseling/testing, and referrals to additional internal benefits. This study aims to evaluate the CBP by measuring enrollment over time, participant satisfaction, and uptake of additional benefits.

Methods / Clinical Presentation / Preliminary Data : Participant eligibility criteria for the CBP included a cancer diagnosis or a cancer-related concern, and enrollment in the company medical plan. All participant data and communications were tracked in a HIPAA secure, internal Customer Relationship Manager-like (CRM) system. Demographic and enrollment data was pulled from system logs and analyzed by business intelligence interactive data visualization software. Participant satisfaction was measured using 10-point Likert scales in a post-service survey form.

Results / Discussion / Project Plan and Timeline: The number of participants enrolled in the CBP has increased steadily since program inception (Fig. 1). Data collected in 2024 shows that participants enroll at various times after diagnosis (Fig. 2), many within the first three months. In addition, participant satisfaction and recommendation scores have remained high over the years (Table 3). Lastly, we observed a 12% increase in enrollment in our medical plan oncology nurse support program and a 7% increase in uptake of an employer-sponsored medical second opinion service compared to norms of companies without a CBP.

Conclusions / Requirements for Collaboration: Individuals with cancer face challenges navigating their diagnoses, including balancing work, making treatment decisions, managing costs, and understanding available employer benefits. Our findings suggest that an employer-based CBP facilitated by genetic counselors has successfully aided employees in these challenges as evidenced by consistent program growth, higher uptake of other cancer-related benefits offerings and high participant satisfaction scores.

Keywords: genetic counseling, patient support, care coordination

Figure 1. CBP Enrollment by year

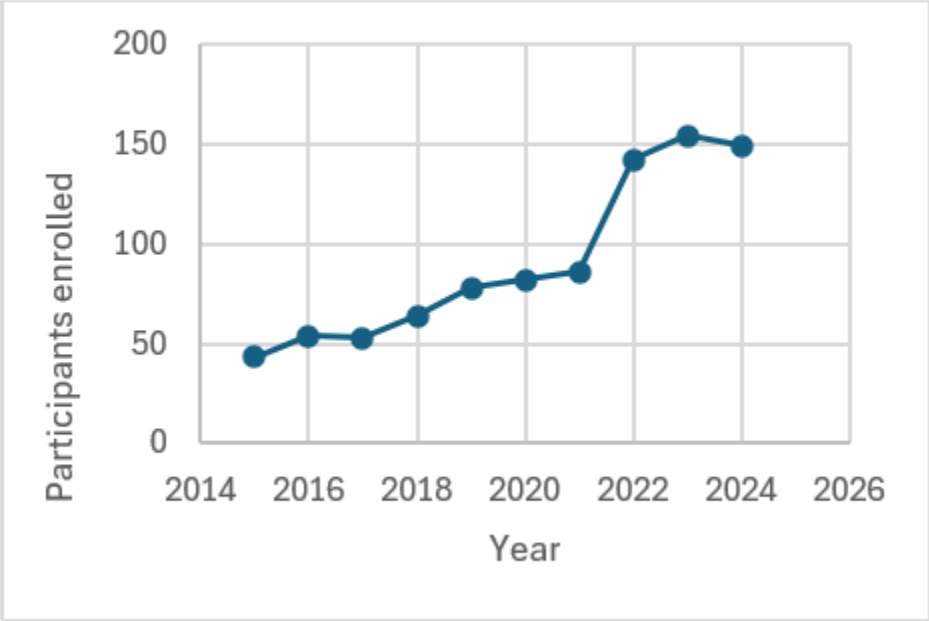

Figure 2. Time since diagnosis at enrollment

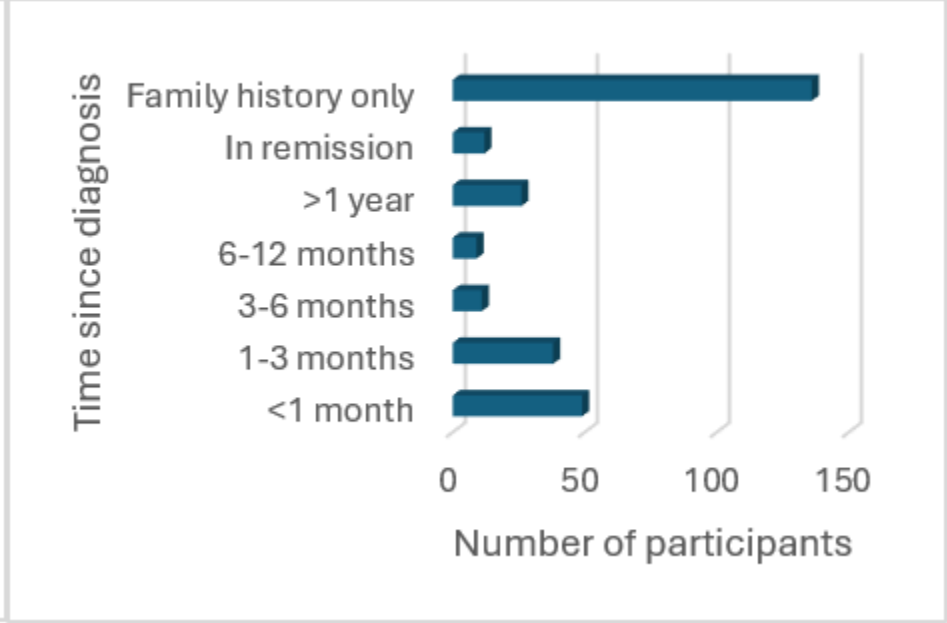

Table 3. Participant satisfaction and recommendation scores

Year	Satisfaction Score	Recommendation score
2024	9.45	9.45
2023	9.83	9.83
2022	9.56	9.56
2021	9.8	9.8

RT-007 ASSESSMENT OF REASONS FOR PANCREATIC CANCER SURVEILLANCE CESSATION OR DEFERRAL AMONGST HIGH-RISK INDIVIDUALS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Individuals with increased familial or genetic risk of developing pancreatic cancer (PC) may be recommended to undergo annual PC surveillance. Whether high-risk individuals (HRIs) participate in PC surveillance and barriers to PC surveillance are not well characterized. This study aims to identify reasons that HRIs cease or defer PC surveillance.

Methods / Clinical Presentation / Preliminary Data: Eligible participants included: (1) those with prior annual PC surveillance with no surveillance in ≥2 years or (2) those getting PC surveillance with a ≥2 year period without surveillance. Participants were interviewed by telephone. Responses were analyzed using content analysis.

Results / Discussion / Project Plan and Timeline: Thirty-one interviews were completed and 27 were analyzed. Sixteen participants had familial PC (51.6%) and 15 had a pathogenic germline variant in either BRCA2 (n=8, 25.8%), PALB2 (n=2, 6.5%), or ATM/BRCA1/CDKN2A/MSH6/STK11 (n=1 each, 3.2%). Interviewees were 80.6% women and 96.8% White with mean age 65.6 years. The following reasons for PC surveillance cessation or deferral were reported: logistical barriers (n=9, 33.3%), other health concerns (n=9, 33.3%), being advised by a different provider to defer or cease surveillance (n=8, 29.7%), difficulty recalling surveillance recommendations (n=6, 22.2%), the COVID-19 pandemic (n = 6, 22.2%), moving out of the service delivery area (n = 5, 18.5%), cost (n = 5, 18.5%), procedure-related concerns (n = 4, 14.8%), and non-medical life events (n = 2, 7.4%).

Conclusions / Requirements for Collaboration: This study demonstrates that the most frequently cited reasons for PC surveillance cessation or deferral were logistical barriers, other health issues precluding surveillance, different PC surveillance recommendations between providers, and patient knowledge/recall of recommended PC surveillance. Providers, including genetic counselors, must be able to address patient concerns about PC surveillance as part of risk assessment. Further research is necessary to understand reasons for PC surveillance cessation or deferral in a broader population of HRIs, as well as the best ways to overcome these challenges.

Keywords: Pancreatic cancer surveillance, Hereditary pancreatic cancer, interview, genetic counseling

RT-008 EXPANDING THE SPECTRUM: EXTRA-COLONIC MALIGNANCIES IN MUTYH-ASSOCIATED POLYPOSIS

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: Studies show extra-colonic (EC) cancer risks associated with MUTYH-associated polyposis (MAP) include duodenal, gastric, ovarian, bladder, and skin cancer, although other controversial EC cancer risks remain including breast, endometrial, and thyroid cancer. Our institution noticed a trend in the diagnosis of cancers such as renal and thyroid cancer in MAP patients. We aimed to evaluate the EC cancer incidence in an MAP patient population.

Methods / Clinical Presentation / Preliminary Data: A hereditary GI cancer registry database was queried to identify patients with biallelic MUTYH pathogenic variants (PV) or patients with polyposis and a family history of biallelic MUTYH PV. Patient demographics, cancer diagnosis, staging, and treatment information were obtained via chart review. Cancer types were classified using the SEER Site Recode ICD-O-3/WHO 2008 classification and excluded basal and squamous cell skin cancers. SEER stat was used to obtain standard incidence ratios (SIR) by cancer type and were adjusted for age and sex.

Results / Discussion / Project Plan and Timeline: Among 86 patients with MAP – 60.5% were diagnosed with a malignancy, 27.9% with an EC malignancy, and 11.6% with >1 EC malignancy. There were 7 cases of thyroid cancer (SIR 37.2, CI 36.8-37.5), all of which were papillary type. There were 5 cases of leukemia (SIR 25.6, CI 25.2-26.0), of which, 3 were chronic lymphocytic and 2 were chronic myeloid type. There were 3 cases of renal cancer (SIR 9.1, CI 8.5-9.8), all of which were clear cell type. There were no significant risk factors for the development of an EC malignancy, although increasing age was a risk factor for the diagnosis of >1 EC malignancy (OR 1.14, CI 1.03-1.32).

Conclusions / Requirements for Collaboration: MAP may be associated with an increased risk of multiple extra-colonic cancers including thyroid cancer, leukemia, and renal cancer. Future studies with a larger cohort are needed to confirm these findings. This study was limited by its retrospective nature and small sample size.

Keywords: Extra-Colonic, mutyh, MUTYH-associated polyposis

Table 1: Patient Demographics

Characteristic	Number of Patients (N=86)
Sex, n (%)	
Male	48 (55.8%)
Female	38 (44.2%)
Race, n (%)	
White	79 (91.9%)
Unknown	4 (4.6%)
Multi-racial	2 (2.3%)
Asian	1 (1.2%)
Ethnicity, n (%)	
Hispanic	2 (2.3%)
Non-Hispanic	82 (95.3%)
Unknown	2 (2.3%)
Age at MAP diagnosis, median (range)	47.5 (23-68)
Age at first cancer diagnosis, median (range)	53 (16-78)
Age at colorectal cancer diagnosis, median (range)	46 (26-62)
Current Age, median (range)	65 (26-92)
Developed malignancy, n (%)	52 (60.5%)
Colorectal malignancy, n (%)	37 (43.0%)
Extra-colonic malignancy, n (%)	24 (27.9%)
≥1 extra-colonic malignancies, n (%)	10 (11.6%)
Family history of cancer, n (%)	66 (76.7%)
First degree relative	22 (25.6%)
Second degree relative	12 (13.9%)
Both	31 (36.0%)
Pathogenic Variant (N=78), n (%)	
Homozygous G396D	9 (11.6%)
Homozygous G382D	8 (10.3%)
Homozygous Y165C	6 (7.7%)
Homozygous R231H	3 (3.8%)
Homozygous Y179C/Y179C	3 (3.8%)
Y179C/G396D	8 (10.3%)
Y165C/G382D	7 (9.0%)
Y165C/other	13 (16.7%)
G396D/other	8 (10.2%)
G382D/other	3 (3.8%)
Y179C/other	3 (3.8%)
Other	7 (9.0%)

Table 2: Frequency of Extra-Colonic Malignancies in MAP Patient Population

Site of Cancer	Gender	n	SIR (95% CI)	Obs %-risk by 75y (95% CI)	Age at diagnosis, median (range)
All extra-colonic malignancies	Both	35	9.6 (6.4 – 12.8)	59.3 (37.9 – 73.3)	55.5 (16 – 80)
Skin		9			
Basal Cell		6			
Squamous Cell		2			
Melanoma	Female	1	8.5 (2.8 – 14.2)	1.1 (0.0 – 3.3)	32
Thyroid	Both	7	37.2 (36.8 – 37.5)	9.6 (2.4 – 16.3)	45 (42 – 59)
Synchronous lesion		5			
Blood		6			
Leukemia	Male	5	25.6 (25.2 – 26.0)	15.9 (0.0 – 31.4)	58 (24 – 72)
Chronic Lymphocytic	Male	3	41.0 (40.7 – 41.3)	5.7 (0.0 – 12.2)	56 (24 – 63)
Chronic Myeloid	Male	2	39.4 (39.1 – 39.7)	4.6 (0.0 – 10.8)	65 (58 – 72)
Lymphoma	Female	1	33.0 (32.7 – 33.4)	1.1 (0.0 – 3.2)	16
Breast	Female	5	1.93 (0.52 – 3.3)	6.0 (0.0 – 12.4)	53 (44 – 78)
Invasive Lobular		2			
Invasive Ductal		1			
DCIS		1			
Unknown		1			
Renal	Male	3	9.1 (8.5 – 9.8)	6.0 (0.0 – 12.6)	53.5 (47 – 60)
Prostate	Male	3	0.7 (-1.6 – 3.0)	6.1 (0.0 – 14.8)	66 (54 – 76)
Bladder	Female	1	3.5 (2.4 – 4.5)	5.0 (0.0 – 14.1)	67
Duodenal	Female	1	36.6 (36.3 – 36.9)	1.5 (0.0 – 4.3)	51
Esophageal	Male	1	7.3 (6.6 – 8.0)	1.8 (0.0 – 5.3)	56
Liver	Male	1	512.3 (512.2 – 512.4)	1.1 (0.0 – 3.4)	22
Lung	Male	1	2.2 (0.9 – 3.5)	1.7 (0.0 – 4.8)	54
Parotid	Male	1	21.3 (20.9 – 21.8)	6.2 (0.0 – 17.4)	69
Testicular	Male	1	16.5 (16.0 – 17.0)	1.3 (0.0 – 3.9)	45
Tongue	Male	1	4.9 (4.1 – 5.8)	8.3 (0.0 – 22.7)	73
Tonsillar	Female	1	128 (127.9 – 128.2)	1.3 (0.0 – 3.9)	46
Uterine	Female	1	1.4 (-0.3 – 3.0)	1.8 (0.0 – 5.3)	56

RT-009 COMPARING AND CONTRASTING LIVED EXPERIENCES OF PATIENTS WITH LYNCH SYNDROME AND POLYPOSIS SYNDROMES

General Research - Lynch syndrome

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Background and Aim: The two most common hereditary colon cancer syndromes are Lynch syndrome (LS) and polyposis syndromes (PS) (e.g., Familial Adenomatous Polyposis, hamartomatous polyposis syndromes). Both syndromes share increased lifetime risks for intestinal and extra-intestinal cancers and require frequent surveillance exams and surgical interventions, yet their life experiences are varied.

Methods / Clinical Presentation / Preliminary Data : Narrative data was collected from 44 semi-structured, in-depth, qualitative interviews with individuals living with Lynch syndrome and polyposis syndromes across the United States. Participants were recruited using maximum variation sampling related to age, gender, sexual identities, geographic location, and self-reported race/ethnicity. Recruitment occurred through cancer genetic clinics at three academic medical centers and community-based recruitment. Interview transcripts were analyzed with a deductive approach based on an adapted framework for living well with chronic illness.

Results / Discussion / Project Plan and Timeline: 21 patients were included in the analysis (14 with LS, 7 with PS). A common theme across both groups was the need to educate themselves and members of their healthcare teams about their diagnoses. Multiple contrasting themes were identified across both groups (Figures 1-3). In general, PS patients identified more negative experiences with family, insurance, and their healthcare team compared to LS patients. They also described more changes to daily life, difficulty coping with current symptoms, and feelings of fear and sadness about their diagnosis, as opposed to LS patients who described a better ability to cope and willingness to seize each day.

Conclusions / Requirements for Collaboration: Patients with LS and PS describe a common issue with lack of knowledge of their healthcare teams about their diagnoses. Differences across the groups exist pertaining to support networks, coping skills, and feelings towards life post-diagnosis with more negative experiences in PS patients. This illustrates a need for different resource allocation across these two groups such as ensuring access to health psychology and social work in GI genetics clinics, particularly for individuals with polyposis syndromes.

Keywords: Lynch syndrome, polyposis

Table 1. Sample characteristics			
Characteristic	**Overall N=21**	**Lynch syndrome (LS) N=14**	**Polyposis syndromes (PS) N=7**
Sex			
Female	12 (57%)	8 (57%)	4 (57%)
Race/ethnicity			
Non-Hispanic White	16 (76%)	12 (86%)	4 (57%)
Non-Hispanic Black	3 (14%)	1 (7%)	2 (29%)
Two or more races	1 (5%)	1 (7%)	--
Did not disclose	1 (5%)	--	1 (14%)
Age at diagnosis			
≤25 years	4 (20%)	3 (21%)	1 (14%)
>25 years	17 (80%)	11	6
Geographic region of residence			
East	7 (33%)	7 (33%)	4 (29%)
Midwest	12 (57%)	12 (57%)	8 (57%)
West	2 (10%)	2 (10%)	2 (14%)

Figure 1. Venn diagram illustrating overlap and differences between identified themes across LS and PS patients

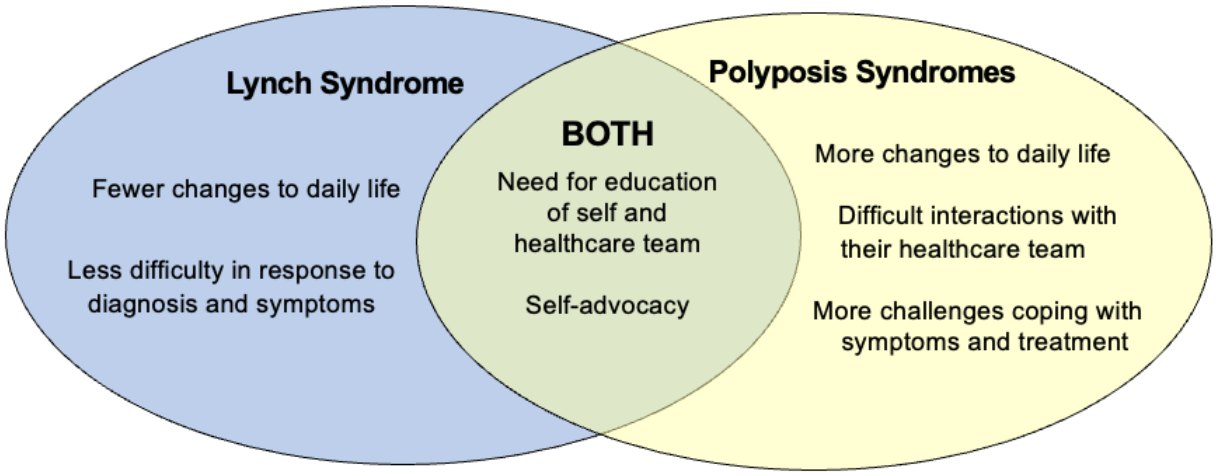


Figure 2. Dendrogram displaying trends in interview themes, clustered by similarity. The two major branches of the tree show that patients with PS more often identified fear and sadness with respect to outlook on life post-diagnosis, as well as difficulties managing their condition. Patients with LS more often identified themes of managing well and acceptance of their diagnosis.

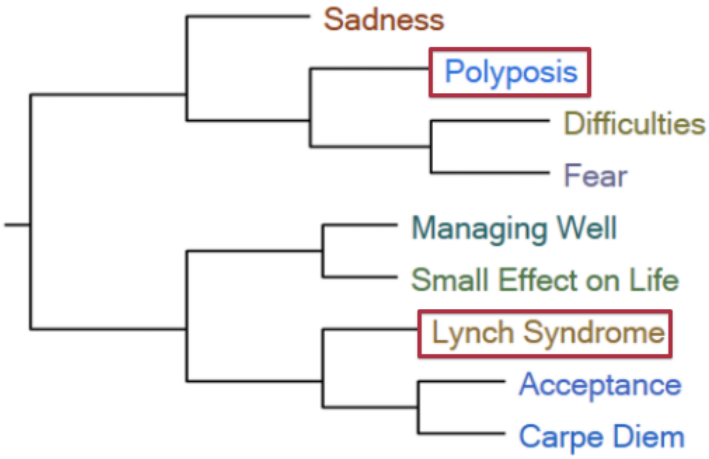
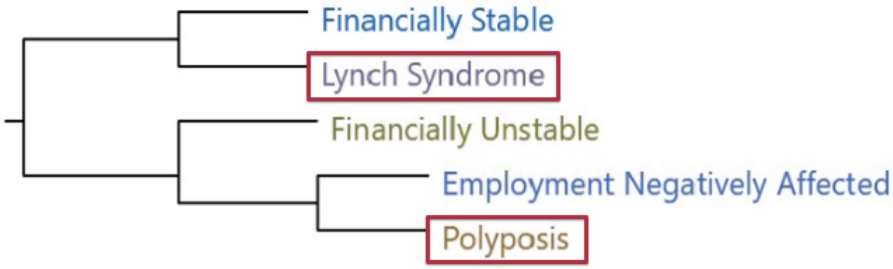


Figure 3. Dendrogram displaying trends in interview themes, clustered by similarity. The two major branches of the tree show patients with LS expressed more financial stability as compared to patients with PS who expressed financial instability associated with negative effects on their employment.



RT-010 THE LONGEST DOCUMENTED FOLLOW-UP OF A LARGE AMPULLARY ADENOMA IN FAP: A 30-YEAR CANCER-FREE CASE

Case reports / Case series

Authors: Youssef Soliman[1]

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Background and Aim: Ampullary adenomas (AA) in patients with familial adenomatous polyposis (FAP) are recognized precursors to carcinoma, yet progression to cancer remains rare. The largest longitudinal study to date reported limited progression over a follow-up of up to 11 years (Singh et al. 2022). Current guidelines recommend surgical resection for advanced adenomas or when endoscopic therapy is not feasible; however, pancreaticoduodenectomy (PD) remains associated with significant morbidity. The need for individualized, risk-adapted decision-making is growing.

Methods / Clinical Presentation / Preliminary Data: We present the longest documented follow-up—30 years—of a large AA in an FAP patient with histologically confirmed cancer-free status. A 63-year-old woman with FAP, diagnosed three decades prior and treated with proctocolectomy, initially deferred surgery for an ampullary lesion due to surgical risks and avoided surveillance due to sedation-related concerns. Upon re-establishing care, she underwent upper endoscopy revealing Spigelman Stage IV polyposis and a >5 cm lobulated ampullary polyp. Despite PET avidity and polyp size, endoscopic ultrasound-guided sampling of mesenteric lymph nodes showed no malignancy. Given multidisciplinary team (MDT) input, she underwent PD. Final pathology confirmed high-grade dysplasia without carcinoma in the ampullary polyp, and six regional lymph nodes were negative for malignancy. The patient recovered well post-operatively.

Results / Discussion / Project Plan and Timeline: This case illustrates an unusually indolent course of a large ampullary adenoma in FAP, challenging conventional assumptions about progression risk. Notably, the patient's only validated risk factor for clinically significant progression (per Singh et al. 2022) was lesion size >1 cm. In light of this, and modern advances in imaging and surveillance, conservative management may be reasonable in select cases absent clear malignant features.

Conclusions / Requirements for Collaboration: This case supports more nuanced surgical decision-making for AA in FAP and highlights the need for prospective studies to refine risk stratification and potentially reduce overtreatment.

Keywords: polyp, FAP, surveillance, whipple, pancreaticoduodenectomy, organ preservation

RT-011 RATE AND ROOT CAUSE ANALYSIS OF POST-COLONOSCOPY COLORECTAL CANCER IN LYNCH SYNDROME: THE POTENTIAL OF THE LINEAGE CONSORTIUM

Collaborative

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Background and Aim: Etiology of post-colonoscopy CRC (PCCRC) in LS is not well characterized. The World Endoscopy Organization (WEO) established definitions of PCCRC in the general population, suggesting root cause analysis (RCA) as a quality measure. We aimed to adapt WEO definitions to characterize PCCRC rates and RCA in LS within the LINEAGE consortium.

Methods / Clinical Presentation / Preliminary Data: Clinical data from individuals with LS with at least one CRC were entered into the LINEAGE database. Individuals with inflammatory bowel disease, and non-adenocarcinoma/unavailable histology were excluded. Per WEO, PCCRC-3y was defined as CRC diagnosed 6-36 months post-colonoscopy. LS-adapted definitions included PCCRC-2y (6-24 months) and PCCRC-1y (6-12 months). Using the WEO framework, RCA classified PCCRCs as 1) missed/rapidly growing lesion after adequate exam, 2) missed/rapidly growing lesion after inadequate exam, 3) detected lesion, not resected, and 4) detected lesion, incompletely resected.

Results / Discussion / Project Plan and Timeline: Of 386 with LS, 46 were diagnosed with 60 discrete CRCs (11 had ≥2 CRCs). Most had PVs MLH1/MSH2/EPCAM (76%), were male (60%), and diagnosed with LS within 6 months of CRC diagnosis (61%). Participant and cancer characteristics are shown in Table 1. Six of the cancers (10%) were PCCRC-3y (three of which were PCCRC-2y, one PCCRC-1y), all diagnosed by colonoscopy. Only one of the PCCRCs was an interval cancer (diagnosed before next recommended surveillance). The PCCRC-1y was missed due to an incomplete exam. 3 cases were missed/rapidly growing lesions with adequate exams, and 2 were detected lesions with possible incomplete resection (Table 2).

Conclusions / Requirements for Collaboration: 10% of CRCs in our cohort were PCCRCs per WEO definition, with majority being missed or rapidly growing lesions in adequate exams diagnosed within 6-24 months post-colonoscopy. The LINEAGE database is well-positioned to describe rates and RCA of PCCRC in LS on a large scale. Joining the consortium and contributing data will inform why CRC occurs despite colonoscopy.

Keywords: Lynch syndrome, Colorectal Cancer, colonoscopy, quality

Table 1. (A) Patient and (B) Cancer Characteristics

(A) Patients	N = 46[1] (%)	(B) Cancers	N = 60[1] (%)
Age at Cancer Diagnosis	46.0 (37.0, 51.0)	**Anatomic Location**	
Male	28 (60.9)	Right Colon[2]	28 (46.7)
Genotype		Left Colon[3]	16 (26.7)
MLH1	15 (32.6)	Rectum[4]	10 (16.7)
MSH2	17 (37.0)	Other/Not documented	6 (10.0)
MSH6	6 (13.0)	**Stage**	
PMS2	5 (10.9)	I	17 (28.3)
EPCAM	3 (6.5)	II	14 (23.3)
Race		III	12 (20.0)
White	39 (84.8)	IV	5 (8.3)
Black	2 (4.3)	Not documented	12 (20.0)
Native American	1 (2.2)	**Grade**	
Asian	1 (2.2)	Well differentiated	8 (13.3)
Other/Unknown	3 (6.5)	Moderately differentiated	25 (41.7)
Hispanic/Latino	6 (13.0)	Poorly differentiated	4 (6.7)
BMI	27.4 (24.4, 30.6)	Not specified	23 (38.3)
Dyslipidemia	11 (23.9)	**Size (cm)**	2.7 (1.9, 6.2)
Diabetes	7 (15.2)	**Microsatellite Testing**	
Former or current tobacco use	23 (50.0)	High	12 (20.0)
Current alcohol use	26 (56.5)	Stable	5 (8.3)
Time from LS diagnosis to CRC		Not available	43 (71.7)
+/- 6 months	28 (60.9)	**Immunohistochemistry***	
LS >6 months before CRC	10 (21.7)	MLH1 absent	10 (38.5)
LS >6 months after CRC	8 (17.4)	MSH2 absent	6 (23.1)
Multiple CRCs	11 (23.9)	MSH6 absent	8 (29.6)
		PMS2 absent	15 (57.7)

[1]Median (IQR); n (%); [2]Cecum, ascending, hepatic flexure, transverse; [3]Splenic flexure, descending, sigmoid; [4]Rectosigmoid, rectum;
BMI: Body Mass Index; CRC: colorectal cancer; MSI: Microsatellite Instability
*Of those where testing was completed/documented

Table 2. Characteristics of Post-Colonoscopy Colorectal Cancer Cases

Age/Sex/Gene	Colonoscopy setting & indication	Colonoscopy Findings	Rec follow-up (months)	Colonoscopy to CRC (months)	How CRC diagnosed	Cancer location	Stage	PCCRC Root Cause Analysis
44/M/*MLH1*	Academic, abnormal imaging	No polyps	<6	7.6	Asymptomatic surveillance	Descending	II	PCCRC-1y missed inadequate
65/M/*MLH1*	Academic, surveillance	<10mm ascending TA, removed en bloc CS	12	23.1	Asymptomatic surveillance	Ascending	II	PCCRC-2y detected, incompletely resected
40/M/*EPCAM*	Academic, surveillance	5mm ascending TA, removed en bloc CS	12	30.6	Asymptomatic surveillance	Ascending	I	PCCRC-3y detected, incompletely resected
78/F/*MSH2*	Academic, surveillance	No polyps	12	33.7	Asymptomatic surveillance	Sigmoid	I	PCCRC-3y Missed/rapid growth, adequate
42/F/*PMS2*	Community, surveillance	No polyps	24	23.6	Asymptomatic surveillance	Transverse	I	PCCRC-2y Missed/rapid growth, adequate
68/M/*MSH2*	Academic, surveillance	No polyps	12	13.5	Asymptomatic surveillance	Anastomosis (Ileocolonic)	IV	PCCRC-2y Missed/rapid growth, adequate

PCCRC: Post-colonoscopy Colorectal Cancer; CS: Cold Snare; PCCRC-1y: 6-12 months post colonoscopy; PCCRC-2y 6-24 months post colonoscopy; PCCRC-3y: 6-36 months post colonoscopy; TA: Tubular adenoma; HGD: High-grade dysplasia

RT-012 CANCER RISK IN INDIVIDUALS WITH HAMARTOMATOUS POLYPOSIS SYNDROMES: A CALL FOR COLLABORATION

Collaborative

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Background and Aim: Peutz-Jeghers syndrome (PJS) and Juvenile polyposis syndrome (JPS) are hamartomatous polyposis syndromes associated with increased gastrointestinal cancer risk. However, polyp and cancer risk estimates for PJS and JPS, especially those without a pathogenic germline variant (PGV) in SMAD4/BMPR1A (mutation-negative JPS), remain limited as these estimates are based on small, older data sets that are likely not reflective of cancer risks in present day practice where affected individuals are followed with aggressive surveillance. Determining accurate cancer risks for hamartomatous polyposis syndromes is crucial for determining appropriate surveillance regimens for this at-risk population.

Methods / Clinical Presentation / Preliminary Data: In our initial cohort of 64 individuals with mutation-negative JPS, there was only one GI cancer identified, indicating that GI cancer risk may not be increased in mutation-negative JPS. Additionally, this cohort demonstrated no upper GI polyps, distinguishing mutation-negative JPS from SMAD4/BMPR1A-associated JPS where upper GI polyps are common.

Results / Discussion / Project Plan and Timeline: This will be a retrospective cohort study involving collaboration between multiple pediatric and adult centers to collect cases of individuals with JPS and PJS along with polyp burden and cancer incidence data. Specifically, we plan to work with other centers to expand on this cohort of individuals with mutation-negative JPS, and collect data on SMAD4/BMPR1A-associated JPS and PJS patients including information on polyp and cancer development. We are aiming to have DUAs completed and data collected by mid-2026.

Conclusions / Requirements for Collaboration: We are actively recruiting pediatric and adult institutions to collaborate on this project who follow at least 10 JPS/PJS patients. Through this collaborative study we aim to create the largest cohort-to-date of individuals with hamartomatous polyposis syndromes. This cohort will allow us to better understand polyp development and cancer risk, which will ultimately be critical to inform surveillance practices in pediatric and adult patients with hamartomatous polyposis.

Keywords: JPS, PJS, Hamartomas

RT-013 PERCEPTIONS OF GASTRIC CANCER RISK AND ATTITUDES TOWARDS ENDOSCOPIC SURVEILLANCE IN PATIENTS WITH CDH1 PATHOGENIC VARIANTS

Collaborative

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Background and Aim: Risk of gastric cancer in individuals with CDH1 pathogenic variants ranges from 10-38% depending on family history. Endoscopic surveillance is a viable approach in select patients, yet limited data exist regarding patient perspectives. Our aims are to describe patient perceptions of gastric cancer risk and attitudes toward endoscopic surveillance. This collaboration will establish factors that influence patient decision-making and inform risk communication strategies.

Methods / Clinical Presentation / Preliminary Data : An electronic survey will assess perceived risk of gastric cancer and attitudes, barriers & facilitators to endoscopic surveillance (Table). We will assess factors in domains 1-4 that are associated perceptions and attitudes. We will present preliminary descriptive data from GASTRIC consortium sites at CGA 2025.

Results / Discussion / Project Plan and Timeline: We will include English-reading adults with CDH1 pathogenic or likely pathogenic variant. We will recruit via: (1) GASTRIC consortium (12 centers); (2) centers independent of consortium; (3) postcard marketing material (Figure) for direct patient recruitment. The postcard will be shared with professional society (CGA, InSiGHT, IGCLC) members, advocacy groups and posted on social media (LinkedIn, BlueSky, etc.).Timeline:July 31: Finalize survey instrumentAugust 1-Aug 22: First round survey distribution (GASTRIC sites with IRB approval & with initial promotion via social media)October 8: Present descriptive results at CGA and solicit more participationOctober-December 2025: Additional site onboarding and data collection February-April 2026: Data analysis, draft CGA 2026 abstract and manuscript

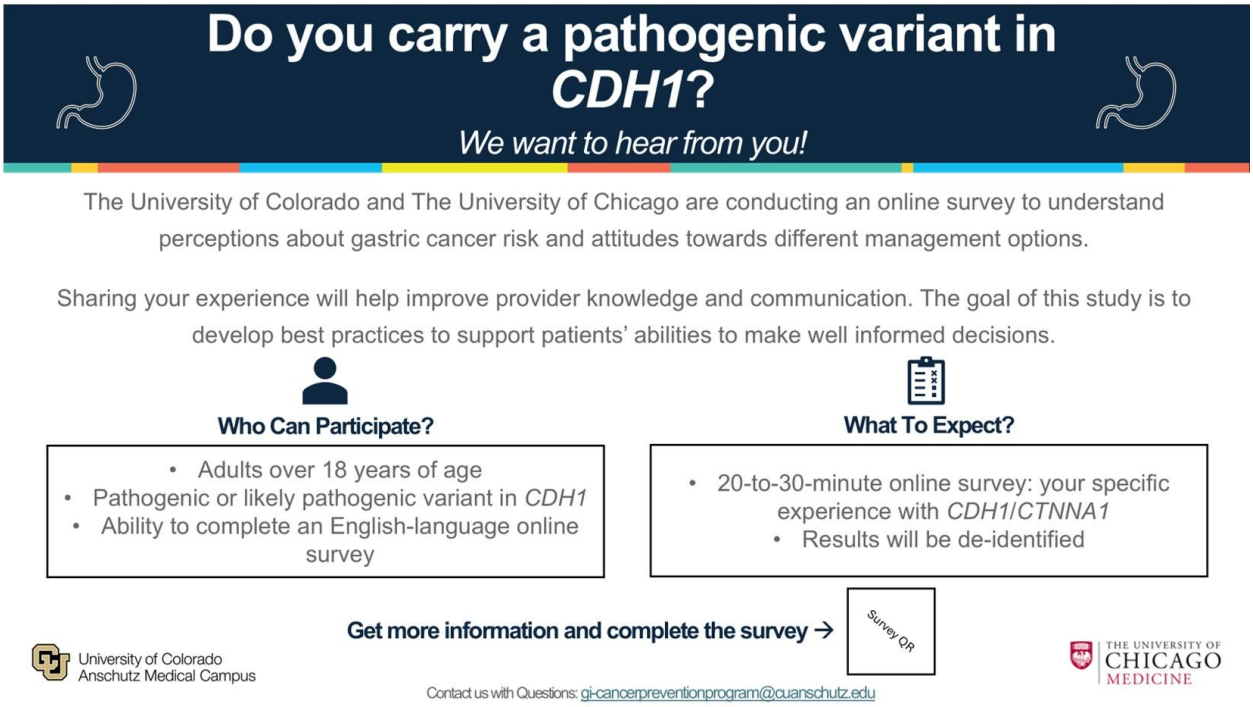
Conclusions / Requirements for Collaboration: There are two options to participate:1. Local submission and regulatory approval (draft protocol provided by study team). This will require sites to gain approval to collect minimum de-identified characteristics (age, sex, race, ethnicity, surgical status) from non-responders so that we can compare differences2. Promote study via postcard distribution to CDH1 patients Note: An investigator from sites that gain regulatory approval and share responder/non-responder demographics will be invited as co-author on all future academic products

Keywords: CDH1, gastric cancer, gastrectomy, upper endoscopy, surveillance

Table. *CDH1* Survey Domains & Elements. The primary outcomes are to assess participant perceptions of gastric cancer risk (domain 5) and attitudes towards surveillance (domain 6). Data collected in domains 1-4 are intended to assess factors that may be associated with risk perception and attitudes towards surveillance.

Domain 1: Demographics
Age, age at time of *CDH1* dx, year of *CDH1* dx, sex, race, ethnicity, urbanicity, geographic region, access to hereditary cancer center, *CDH1* specialist, insurance, highest education, household income, smoking, alcohol, medical comorbidities
Domain 2: Personal history & experience: gastric
Patient ever told they have gastric cancer - If so, how dx (bx vs gastrectomy), whether told invasive vs indolent (T1A) vs unknown If gastrectomy, age, indication, findings - Short term adverse events (AEs) - Long term AEs, quality of life - Decisional affirmation/regret If no gastrectomy - Plans to get gastrectomy - Undergoing surveillance? - If so, short/long term AEs with EGD, quality of life, cost/coverage, travel required - Decisional affirmation/regret
Domain 3: Personal history & experience: breast (if applicable)
Patient ever told they have breast cancer - If so, how dx (bx vs mastectomy) If mastectomy, type, age, indication, findings - Short term adverse events (AEs) - Long term AEs, quality of life - Decisional affirmation/regret If no mastectomy - Plans to get mastectomy - Undergoing surveillance? - If so, quality of life, cost/coverage, travel required - Decisional affirmation/regret
Domain 4: Family history and experience with breast and gastric cancer, surgery and surveillance
Family members die of invasive gastric or breast cancer Family members have short term AEs with gastrectomy or mastectomy Family members with persistent/prolonged AEs, QOL with gastrectomy or mastectomy Family members under EGD surveillance? Family members under breast surveillance?
Domain 5: Perceived lifetime risk of invasive gastric cancer
Sources of information Trust in sources of information Perceived lifetime risk of getting invasive cancer if no surgery done, compared to general population Confidence in this estimation Perceived factors that increase/decrease risk (endoscopy findings, family history, sex, smoking, age, diet, stress, etc.)
Domain 6: Attitudes, Barriers & Facilitators to Endoscopic surveillance
Factors that influence decision-making: risk of getting/dying from invasive cancer, medical risk of surgery/surveillance (including risk of missing cancer on surveillance), impact on quality of life, family outcomes, family advice, anxiety/psychological distress Potential barriers/facilitators: cost, travel, coverage, access to expertise, frequency of testing, invasiveness of testing

Figure. Post-card for Direct Patient Recruitment. This postcard will be (1) shared with professional societies to distribute to their members to share with patients, (2) shared with patient advocacy organizations to share with their members, and (3) posted on social media.



POSTER ABSTRACTS

P-001 APC MUTATION-INDUCED RETARDATION OF TISSUE RENEWAL IS FUNDAMENTAL TO COLON TUMORIGENESIS

General Research - Adenomatous polyposis syndromes including FAP

Authors: Bruce Boman[1]

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Background and Aim: Every tissue-type has a specific rate of renewal that maintains its structural integrity throughout life. Our Aim is to understand how changes in the rate of tissue renewal underlie colon cancer development.

Methods / Clinical Presentation / Preliminary Data: For colon tumorigenesis, we measured kinetic changes that occur in human and murine intestinal crypts having different APC genotypes.

Results / Discussion / Project Plan and Timeline: Quantitative histologic mapping showed that transitions between the different cell phenotypes are progressively delayed along the axis of APC mutant crypts. The extent of this delay was greater in homozygous than in heterozygous APC-mutant crypts. In ApcMin/+ mouse intestine, clearance of BrdU from pre-labeled crypts was significantly slower than in wildtype-Apc mice. Kinetic modeling showed that retarded crypt renewal increases the number of cell divisions required for differentiation which causes incomplete differentiation and progressive expansion of the proliferative cell populations.

Conclusions / Requirements for Collaboration: Thus, our findings reveal that APC mutation-induced retardation of tissue renewal is a key driver mechanism in tumor initiation and development.

Keywords: Colorectal Cancer

P-002 ETIOLOGY OF EARLY-ONSET CRC: THE ESSENTIAL QUESTIONS

General Research - Early Onset Colorectal Cancer

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Background and Aim: A genetic etiology hasn't been discovered yet for early-onset CRC (EOCRC). The current suspect is gut microbiome (E. coli and colibactin genotoxin). However, besides CRC, it doesn't explain the surge in other early-onset cancer-types occurring on a global scale.An essential question is why do somatic APC mutations occur at a relatively young age in EOCRC patients? Indeed, APC mutations are initiating events in both EOCRC and later-onset CRC (LOCRC). Moreover, most other cancer types frequently have inactivated APC due to promoter hypermethylation. However, we didn't find young cancers (age <50) to have increased APC hypermethylation. So, we surmise that something is retarding tissue renewal so that somatic mutations are retained instead of being extruded during tissue turnover. We conjecture that EOCRC involves an essential nutrient required for tissue renewal.

Methods / Clinical Presentation / Preliminary Data: Accordingly, we investigated the seven essential vitamins that require adequate dietary intake. Indeed, these vitamins are essential for tissue homeostasis because germline mutations in their receptors cause birth defects. Furthermore, population-based studies report vitamin A deficiency in pre-school-aged children. Also, vitamin B12 deficiency during pregnancy can cause developmental anomalies. Consequently, young-aged individuals might be prone to any cancer-initiating effects of vitamin A or vitamin B12 deficient diets.

Results / Discussion / Project Plan and Timeline: Our bioinformatics analysis shows a high frequency of somatic mutations (2x-fold) in receptors for vitamin B12 (CUBN), vitamin A (retinol), (STRA6), and retinoic acid (RARG, PPARG) in EOCRCs (<45) vs. LOCRCs. We also found RARG hypermethylation occurs frequently in EOCRCs ($p<0.05$).

Conclusions / Requirements for Collaboration: Two mechanisms may explain how decreased vitamin-based signaling leads to delayed tissue renewal that causes retention of somatic APC mutations in colonic epithelium:1. Reduced retinoid signaling leads to incomplete differentiation.2. Vitamin B12 depletion amplifies WNT signaling. Thus, we hypothesize that aberrant vitamin A (retinol) or vitamin B12 metabolism and APC mutation-induced activation of WNT signaling are co-factors in promoting EOCRC.

Keywords: early-onset colorectal cancer

P-003 SOURCES OF HOPE AMONG PATIENTS LIVING WITH FAP

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: Instillation of hope is the process of actively fostering a belief in the patient that positive change is possible, that their suffering has meaning, and that healing can occur even in the presence of chronic illness or adversity. In the context of chronic hereditary conditions like familial adenomatous polyposis (FAP), instilling hope can mitigate feelings of helplessness and trauma, helping patients reframe their identities, reclaim agency, and envision a meaningful life despite their diagnosis. In this study we present patient-reported data that indicates where hope arises in a life affected by FAP.

Methods / Clinical Presentation / Preliminary Data: A survey of patients with FAP included the open-ended question that asked: “How have you found hope, meaning, positivity or endurance since your diagnosis?”

Results / Discussion / Project Plan and Timeline: 43 patients answered the question. 17 gave a philosophical answer, 9 identified God and prayer, 8 identified family, 6 identified caregivers and 3 said that “others” and “love” gave them hope. We performed qualitative analysis, using 6 categories and 14 subcategories. The responses to be presented reflect a wide spectrum of coping styles and sources of hope. Despite the chronic and traumatic nature of the disease, participants draw strength from relational connections, spiritual faith, stoic endurance, medical reassurance, cognitive reframing, and present-moment living.

Conclusions / Requirements for Collaboration: This qualitative insight underscores the importance of holistic, relational, and trauma-informed care in supporting the mental and emotional well-being of FAP patients. Medical providers who communicate empathy, optimism, and belief in the patient’s capacity to adapt are not offering empty reassurance—they are engaging one of the most powerful, evidence-based healing tools in human medicine. You and your team, when you connect with your patients and engage them in systems of hope, become part of the best most effective treatment.

Keywords: counseling

P-004 RENAL TRACT ULTRASOUND SURVEILLANCE FOR MUTYH-ASSOCIATED POLYPOSIS: INSIGHTS FROM 19 YEARS OF CLINICAL PRACTICE

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: Prior studies indicate extra-colonic manifestations associated with MUTYH-associated polyposis (MAP) may include duodenal adenomas, duodenal cancer, gastric cancer, ovarian cancer, bladder cancer, and skin cancer. Most guidelines recommend upper and lower endoscopy surveillance but are silent on surveillance recommendations outside of the gastrointestinal tract. Our institution identified a trend in the diagnosis of renal cancer in MAP patients and established an ultrasound surveillance protocol for genitourinary tract cancers. This study aims to assess the results of this surveillance protocol, and we hypothesize surveillance with renal tract ultrasound is a feasible option for MAP patients.

Methods / Clinical Presentation / Preliminary Data: A hereditary gastrointestinal cancer registry database was queried to identify patients with biallelic MUTYH pathogenic variants (PV) or patients with polyposis and a family history of biallelic MUTYH PV. MAP patients were included if they had ≥1 evaluation by a provider at our institution. Our institution recommended surveillance ultrasound of the kidneys, ureters, and bladder for MAP patients starting at time of diagnosis and repeated every 5 years. Ultrasound information including total number, mean number per patient, frequency, and results were recorded.

Results / Discussion / Project Plan and Timeline: Among 81 MAP patients, 56 (69.1%) had a renal tract ultrasound, and a total of 125 ultrasounds were completed – 104 (83.2%) surveillance and 21 (16.8%) diagnostic. The median starting age was 53 (24-79). The mean number of ultrasounds per patient was 1.6 (SD 1.4) with a median observation time of 7 (0-37) years from the time of MAP diagnosis. The median time between surveillance ultrasounds was 55 (2-127) months. 2 (1.9%) patients were diagnosed with a malignancy on ultrasound – 1 bladder cancer and 1 renal cancer on ultrasound. Sensitivity and specificity were 100%, respectively.

Conclusions / Requirements for Collaboration: Our data suggests renal tract ultrasound may be an effective surveillance method that can be utilized to identify renal and bladder cancers in MAP patients.

Keywords: MUTYH-associated polyposis, Renal Tract Ultrasound, extra-colonic manifestations

Figure 1: Outcomes of Renal Tract Ultrasound in an MAP Patient Population

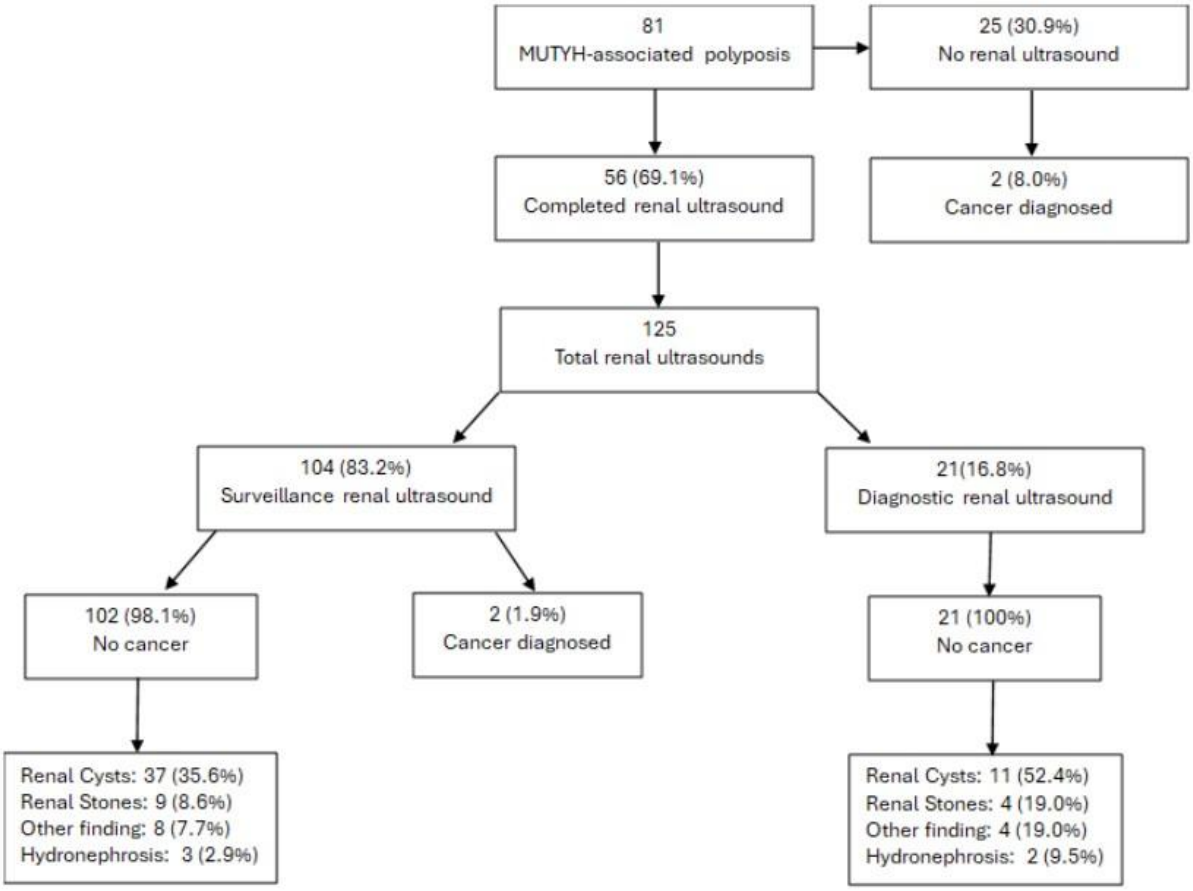

Table 2: Performance Characteristics of Renal Tract Ultrasound Surveillance in an MAP Patient Population

	Cancer Present	No Cancer	Total
Ultrasound Positive	2	0	2
Ultrasound Negative	0	54	54
Total	2	54	56

Metric	Value
Sensitivity	100%
Specificity	100%
Positive Predictive Value (PPV)	100%
Negative Predictive Value (NPV)	100%

Table 1: Renal Tract Ultrasound Characteristics

Characteristic	MAP patients (N=81)
Completed renal tract ultrasound, n (%)	56 (69.1%)
Age at start of surveillance, median (range)	53 (24-79)
Number of renal tract ultrasounds per patient, mean (SD)	1.6 (1.4)
Observation time, years, median (range)	7 (0-37)
Months between renal tract ultrasounds, median (range)	44.5 (2-131)
Diagnosed with renal tract cancer, n (%)	4 (4.9%)
Patient completed ultrasound	2 (2.5%)
Patient did not complete ultrasound	2 (2.5%)
Renal tract cancer type, n (%)	
Bladder cancer	1 (1.2%)
Renal cancer	3 (3.7%)
Age at renal tract cancer diagnosis, median (range)	60 (47-67)
Renal tract cancer stage, n (%)	
Patient completed ultrasound	
Stage 0 (Grade Ta)	1 (1.2%)
Stage 4	1 (1.2%)
Patient did not complete ultrasound	
Stage 1	1 (1.2%)
Stage 4	1 (1.2%)

P-005 AN UPDATE ON APC P.I1307K HOMOZYGOSITY: OBSERVATIONS FROM 74 INDIVIDUALS FROM A LARGE MULTIGENE PANEL TESTING COHORT

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: APC c.3902T>A (I1307K) is a common pathogenic variant (PV) in the Ashkenazi Jewish (AJ) population with frequency nearing 4% (gnomAD V4.1.0). Unlike typical PVs in APC, it is associated with a small (1.7-fold) increased odds of colorectal cancer (CRC) in Ashkenazim. The cancer risk for homozygotes is unknown and published data is based on small samples. This work aims to quantitatively evaluate I1307K homozygotes' cancer risk.

Methods / Clinical Presentation / Preliminary Data: We reviewed clinical/demographic data from a multigene panel (MGPT) tested cohort from May 2012-April 2024. This includes cohorts of comprehensive I1307K homozygotes (n=74), select I1307K heterozygotes (n=344), and MGPT-negative individuals (WT, n=19,810). Individuals with another PV were excluded. Comparisons were made using Fisher's exact test and Mann-Whitney U test.

Results / Discussion / Project Plan and Timeline: The age at testing and age at first cancer in the homozygotes was older relative to WT (61 vs. 52 years, p<.001 and 58.5 vs. 53 years, p=0.006). Although there was no difference between homozygote and WT groups for overall cancer or colon polyps, there was less overall cancer (OR=0.656, p<0.001) and a higher frequency of polyps (OR=1.74, p=0.019) in heterozygotes versus WT. There were no differences in CRC or multiple primary CRC frequencies in homozygotes or heterozygotes relative to WT.

Conclusions / Requirements for Collaboration: Homozygotes did not have a higher odds of CRC versus WT, however, the expected observation that heterozygotes have increased odds of CRC was also not observed in this dataset. This could be due to the small effect size of the association in heterozygotes, bias in recruitment and phenotype reporting in this clinical cohort, the small number of cases available for this study, and/or other confounding factors including not accounting for ethnic genetic background. More sophisticated statistical models, including logistic regressions and power calculations, are planned and may further clarify the risk of CRC in these groups.

Keywords: Colorectal Cancer, I1307K, Homozygous, polyps, Risk

P-006 EARLY EXPERIENCE WITH CLINICAL SOMATIC MOSAIC APC TESTING FOR COLONIC POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

General Research - Adenomatous polyposis syndromes including FAP

Authors: Michelle McSweeny[1], Corinne Zrada[1], Michael Hall[1]

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Background and Aim: ~20% of de novo cases of FAP result from somatic mosaic mutations in APC (1, 2, 3). At FCCC, we offer APC somatic testing of adenomas for patients with > 18 cumulative adenomas (CPUE) and negative germline testing. Currently, there are no established guidelines regarding which patients should undergo this testing, or what type of polyps should be sequenced to assess for mosaicism. Here we describe our early experience with this testing and propose guidance on patient and specimen selection.

Methods / Clinical Presentation / Preliminary Data: We started mosaicism testing in November 2023. To date, five patients met our criteria for and consented to testing. We obtained colonoscopy and pathology records and selected three adenomas from each patient for somatic NGS through our in-house molecular laboratory. Selection of polyps was guided by size and histology, with preference for larger adenomas (preferred > 10 mm) and with high-grade dysplasia (HGD), while also choosing samples from different regions of the colon and from different colonoscopies over time to avoid the chance of duplicate specimens.

Results / Discussion / Project Plan and Timeline: Patient 1 demonstrated a recurring APC mutation in all three adenomas, confirming a diagnosis of somatic mosaic FAP (Figure 1). Patient 2 had a sample failure in two polyps due to insufficient DNA and small polyp size (Table 1). Patients 3 and 4 had no recurring APC mutations, suggesting a low likelihood of mosaic FAP. Patient 5's analysis is currently pending and will be included in the final poster presentation of this abstract.

Conclusions / Requirements for Collaboration: Our early and limited findings suggest that somatic mosaic FAP may be more likely in patients with profuse polyposis that develops at younger ages. We propose considering somatic APC testing for patients with >20 adenomas before age 50, or >30 after age 50. Advanced adenomas are preferred, though polyps >5-9 mm may yield sufficient DNA when larger ones are not available.

Keywords: mosaicism, FAP, somatic, adenomas, APC, CPUE

P-007 RESTORING THE FUNCTION OF THE TUMOR SUPPRESSOR - ADENOMATOUS POLYPOSIS COLI (APC) IN FAMILIAL ADENOMATOUS POLYPOSIS (FAP) PATIENTS

General Research - Adenomatous polyposis syndromes including FAP

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Background and Aim: Colorectal cancer (CRC) is one of the most common and deadly cancers, with early screening significantly improving detection in individuals over 50. Approximately 5–10% of CRC cases are hereditary, with hereditary polyposis colorectal cancer accounting for 3–5%. Familial adenomatous polyposis (FAP), the most common form of HPCC, is primarily caused by germline mutations in the tumor suppressor gene APC. FAP leads to the development of hundreds to thousands of precancerous adenomas and carries a high risk for extracolonic tumors. Without intervention, these adenomas inevitably progress to cancer. Most APC mutations in FAP patients are either nonsense or frameshift mutations, resulting in loss of function. Nonsense mutations in general contribute to around 11% of all pathogenic human mutations, spanning nearly 100 genes, and often cause severe syndromes with no available treatment. This includes diseases such as Rett syndrome, cystic fibrosis, and Duchenne muscular dystrophy. The aim of this study is to explore the therapeutic potential of nonsense mutation suppression by promoting premature termination codon (PTC) readthrough—also known as nonsense suppression—with the ultimate goal of restoring functional protein expression in FAP

Methods / Clinical Presentation / Preliminary Data: Previous studies have employed translational readthrough-inducing drugs (TRIDs) such as aminoglycoside antibiotics, which bind to the ribosome and partially restore full-length protein production.Here, we show that the nontoxic macrolid antibiotics can resore APC expression and function of the APC protein in CRC cell lines, in FAP derived organoids and in FAP patients.

Results / Discussion / Project Plan and Timeline: We provide evidence showing that combinations of different TRIDs and protein translation modifiers can induce restoration of the APC protein, resulting in reduced oncogenic phenotypes

Conclusions / Requirements for Collaboration: The development of safe, effective, and clinically relevant nonsense suppression therapies remains a critical unmet need. The identification and optimization of non-toxic TRIDs—potentially as single agents or in combination—is essential for treating hereditary and sporadic diseases, such as FAP, caused by nonsense mutations.

Keywords: cancer, polyps, APC

P-008 EXPANSION OF A WELL-KNOWN AFAP KINDRED: GASTRIC POLYPOSIS AND CANCER RISK

Case reports / Case series

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Background and Aim: We present a case series through a four-generation pedigree within Kindred 439 (K439) and Kindred 353 (K353), a large, well-documented family with an APC pathogenic variant (PV) {c.426_427delAT; p.Leu143Alafs} and a shared common ancestor (Neklason et al, 2008). Familial Adenomatous Polyposis (FAP), an autosomal dominant hereditary cancer syndrome caused by PV in the APC gene, primarily predisposes to colorectal polyposis and cancer. However, extracolonic manifestations—particularly gastric polyposis and carcinoma—are increasingly recognized, with limited data reported. This case series describes a branch of the large American FAP pedigree K353/K439, where individuals exhibit segregation and presentation of severe gastric polyposis (>100 polyps) and/or gastric cancer.

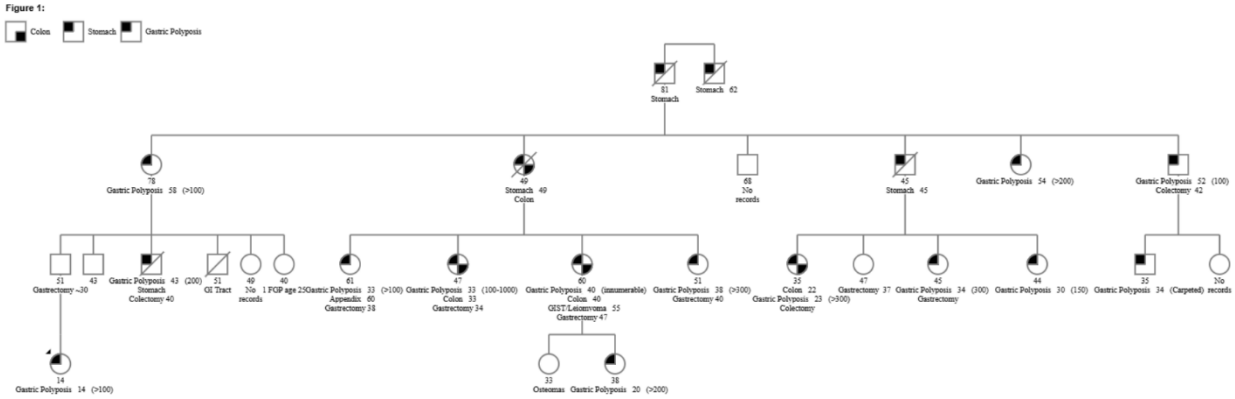
Methods / Clinical Presentation / Preliminary Data: In this family branch of 49 members, 27 (55%) were identified as APC PV carriers through genetic testing, clinical diagnosis, or family reports. Of these, 14 (52%) developed gastric polyposis, with 11 confirmed histologically as fundic gland polyps. The average age at gastric polyposis detection was 34 (range: 14–58). Among those with gastric polyposis, 5 (36%) developed gastric cancer, with the earliest diagnosis at age 42. Only one underwent gastrectomy post-cancer diagnosis. Six other APC-PV family members had prophylactic gastrectomies, averaging age 39. Notably, a 14-year-old showed a stomach “carpeted” with fundic gland polyps despite no detectable colorectal polyposis, underscoring the severity of this gastric phenotype. Her father had a prophylactic gastrectomy in his 30s. See Figure 1 for the full pedigree.

Results / Discussion / Project Plan and Timeline: This case series highlights severe gastric manifestations in a family with an APC PV (c.426_427delAT), raising questions about penetrance, modifier genes, and environmental factors. Ongoing analysis of this branch underscores the need to consider upper endoscopy screening in FAP patients; while prompts reconsideration of cancer mitigation strategies, as six individuals underwent prophylactic gastrectomies outside current standard care.

Conclusions / Requirements for Collaboration: Further research is needed to better evaluate this familial branch's inheritance patterns, modifiers, surveillance and management strategies.

Keywords: gastric polyposis, FAP, gastrectomies, pedigree, prophylactic gastrectomy, gastric cancer, penetrance

Figure 1:


Colon
Stomach
Gastric Polyposis
81
Stomach
Stomach 62
78
Gastric Polyposis 58 (>100)
49
Stomach 49
Colon
68
No
records
45
Stomach 45
Gastric Polyposis 54 (>200)
Gastric Polyposis 52 (100)
Colectomy 42
51
Gastrectomy ~30
43
Gastric Polyposis 43 (200)
Stomach
Colectomy 40
51
GI Tract
49
No 1
records
40
FGP age 25
61
Gastric Polyposis 33 (>100)
Appendix 60
Gastrectomy 38
47
Gastric Polyposis 33 (100-1000)
Colon 33
Gastrectomy 34
60
Gastric Polyposis 40 (innumerable)
Colon 40
GEST/Leiomyoma 55
Gastrectomy 47
51
Gastric Polyposis 38 (>300)
Gastrectomy 40
35
Colon 22
Gastric Polyposis 23
Colectomy
47
Gastrectomy 37
45
Gastric Polyposis 34 (300)
Gastrectomy
44
Gastric Polyposis 30 (150)
35
Gastric Polyposis 34 (Carpeted)
No
records
14
Gastric Polyposis 14 (>100)
33
Osteomas
38
Gastric Polyposis 20 (>200)

P-009 MLH1-LYNCH SYNDROME PRESENTING AS MALE BREAST CANCER (MBC): A RARE CASE REPORT

Case reports / Case series

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Background and Aim: Male breast cancer (MBC) is rare, accounting for <1% of cancers in men. It is primarily associated with pathogenic variants in the BRCA2, PALB2, CHEK2, or PTEN genes. Breast cancer risk associated with Lynch syndrome (LS) remains a controversial topic. We report here a male patient with breast cancer due to an MLH1-LS that was successfully treated with immunotherapy.

Methods / Clinical Presentation / Preliminary Data: A 40-year-old male patient presented with breast cancer. Pre-testing genetic evaluation reveals a familial history of cancer suggestive of LS: pancreatic cancer in the patient's father and colorectal cancer in his brother. Multigene panel genetic testing identified the NM_000249.3(MLH1):c.555_556delAC(p.His186GlnfsTer5) pathogenic variant. Since the patients developed metastasis, tumor profiling was performed to search for therapeutic options. MSI-high, TMB>16, and the genomic signature of LS were identified in the tumor. Since the FDA approved the use of pembrolizumab for patients with MSI-high solid tumors that cannot be surgically removed or have spread, treatment with pembrolizumab was initiated. The patient achieved a complete response to pembrolizumab, with no evidence of disease recurrence at last follow-up.

Results / Discussion / Project Plan and Timeline: The NCCN guideline does not currently include breast cancer screening as a standard recommendation for LS patients. However, a modestly increased risk of breast cancer in LS patients, particularly those with MLH1 or MSH2 mutations, has been suggested. Mismatch repair deficiency (MMRD) was confirmed in the MBC case reported here, leading to the identification of a therapeutic option that resulted in a complete response and disease remission.

Conclusions / Requirements for Collaboration: The case reported here supports that breast cancer, although rare, could be developed as part of the tumor spectrum caused by MLH1-related LS. The immunotherapy treatment could lead to disease remission in these patients if MMRD is confirmed by tumor profiling.

Keywords: Male breast cancer, MLH1, Lynch syndrome, MSI-high solid tumor, Treatment

P-010 GASTRIC ADENOCARCINOMA AND PROXIMAL POLYPOSIS OF THE STOMACH (GAPPS): A CASE REPORT FOR A RARE SYNDROME

Case reports / Case series

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Background and Aim: Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS) is a rare, autosomal dominant syndrome caused by pathogenic variants in promoter 1B of the APC gene. First described in 2012, GAPPS is characterized by numerous polyps and dysplasia confined to the stomach body and fundus. Its prevalence, penetrance, and expressivity remain unclear.

Methods / Clinical Presentation / Preliminary Data: A 63-year-old white Hispanic woman of Cuban ancestry sought evaluation after her 27-year-old daughter was diagnosed with diffuse gastric polyposis and tested positive for a likely pathogenic APC promoter 1B variant (c.-191T>G) and a pathogenic MUTYH variant (c.1187G>A). The patient reported a family history of colon cancer (father at age 75 and paternal uncle in his 50s), early-onset breast cancer (paternal cousin), and stomach cancer (maternal grandmother at 88). Her own endoscopy in 2012 showed benign sessile polyps in the stomach body; by 2024, follow-up endoscopy showed diffuse polyposis in the body and fundus. The patient tested positive for the same variants as her daughter and was referred to surgical oncology for consideration of prophylactic gastrectomy.

Results / Discussion / Project Plan and Timeline: This case emphasizes the potential for GAPPS underdiagnosis even with routine endoscopies, as the patient was self-referred due to her daughter's results in 2024 despite personally having stomach polyps in 2012. It also illustrates how different the age-of-onset can be between family members. For those with GAPPS, current NCCN guidelines recommend annual endoscopy from age 15 and consideration of prophylactic gastrectomy from age 20. However, gastric polyposis is not explicitly included in their referral criteria for germline evaluation.

Conclusions / Requirements for Collaboration: As access to germline testing expands and detection of APC promoter 1B variants improves, increased diagnosis of GAPPS is likely. There is a need for standardized referral and testing criteria, and for increased awareness of GAPPS amongst gastroenterologists and other providers so that patients may be tested and managed in a timely manner.

Keywords: GAPPS, gastric polyposis, APC, APC promoter 1B, gastric cancer

P-011 A PATIENT WITH AN IDENTICAL SOMATIC MLH1 MUTATION IN TWO METACHRONOUS LYNCH-ASSOCIATED TUMORS: A CASE OF SUSPECTED CONSTITUTIONAL MOSAICISM

Case reports / Case series

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Background and Aim: Lynch syndrome (LS) is a hereditary cancer syndrome caused by mutations in DNA mismatch repair (MMR) genes. De novo MMR mutations and constitutional mosaicism in LS are rare. Here we describe a patient with two LS-associated tumors harboring the same somatic MLH1 mutation and negative germline testing.

Methods / Clinical Presentation / Preliminary Data: A 63-year-old woman of Venezuelan ancestry presented with endometrial adenocarcinoma and a history of ovarian cancer at age 53. Immunohistochemistry showed loss of MLH1/PMS2 in both tumors, with no MLH1 promoter methylation. Tumor sequencing in 2024 identified the same pathogenic MLH1 variant (c.493delG) in both tumors, with variant allele frequencies of 67% (ovarian) and 54% (endometrial). Despite the high allele frequencies suggestive of germline origin, germline testing was negative for this MLH1 variant in the patient, her unaffected daughter, and her 24-year-old son with colon cancer. The son's colon tumor retained MMR protein expression. Tumor testing revealed three APC variants (p.I1307K, p.I1307fs, p.L954*), and germline testing confirmed the moderate-risk APC p.I1307K variant, inherited from his unaffected Ashkenazi Jewish father.

Results / Discussion / Project Plan and Timeline: The recurrence of the same MLH1 mutation across two LS tumors in the patient, along with negative blood-based germline testing, raises suspicion for constitutional mosaicism of LS confined to certain tissues arising from the mesoderm. Additional testing on alternative mesoderm-derived tissues may help confirm this. For the patient's son, the germline APC p.I1307K mutation combined with somatic APC variants explains his early-onset colon cancer.

Conclusions / Requirements for Collaboration: This case highlights the importance of performing both tumor and germline testing when evaluating suspected LS. It also illustrates the challenges that arise when test results are inconsistent. In the absence of clear guidelines for managing mosaic LS, patients and their relatives may face either insufficient or overly aggressive surveillance. Depending on the tissues involved, standardized management recommendations may be necessary to guide care in these complex situations.

Keywords: Lynch syndrome, constitutional mosaicism, mosaicism, tumor testing, germline testing

P-012 GERMLINE MLH1 PROMOTER VARIANTS CAN CAUSE LYNCH SYNDROME CANCERS DISPLAYING MLH1 HYPERMETHYLATION WITH OR WITHOUT CONSTITUTIONAL MLH1 METHYLATION.

Case reports / Case series

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Background and Aim: A significant proportion of patients with clinicopathologically suspected Lynch syndrome (LS) remain genetically unexplained after germline multi-gene panel testing (MGPT). Secondary testing for constitutional MLH1 methylation (epimutation) is performed in selected patients with MLH1-deficient tumors. However, MGPTs do not fully interrogate the MLH1 promoter region (only the epimutation-associated c.-27C>A). We continue to screen for constitutional MLH1 methylation and promoter variants in patients presenting with MLH1-deficient cancer <60 years with negative MGPT results and/or tumor MLH1 hypermethylation for alternative causes of LS.

Methods / Clinical Presentation / Preliminary Data: MLH1 promoter was Sanger sequenced and methylation status tested by pyrosequencing and methylation-specific droplet-digital PCR in DNA from blood leukocytes and/or saliva, buccal, tumor and adjacent normal tissues. Allelic expression was measured in RNA by pyrosequencing at coding SNP c.655A>G.

Results / Discussion / Project Plan and Timeline: Proband 1 had no cancer family history but developed MLH1-deficient endometrial cancer at 38 years. Her MGPT was negative, but promoter sequencing revealed the previously reported c.-42C>T variant. Her tumor showed MLH1 hypermethylation and loss-of-heterozygosity of the wildtype allele. Constitutional MLH1 methylation was undetected in various normal tissues. Allelic expression was reduced to 70% in saliva RNA from two unaffected carrier relatives and the mother, who developed multiple adenomas at 56 years. Proband 2 developed colon cancer at 31 years and had a significant family history. Her cousin developed ovarian (endometrioid) cancer at 33 years. Both their MGPTs were negative. Both their tumors displayed MLH1-deficiency, hypermethylation, and loss-of-heterozygosity. We found a promoter microdeletion linked in cis to mosaic (10-36%) constitutional MLH1 methylation and reduced (15%) allelic expression. Extended testing in relatives showed the microdeletion cosegregated with constitutional methylation and cancer.

Conclusions / Requirements for Collaboration: These cases indicate some MLH1 promoter variants cause LS featuring MLH1-hypermethylated tumors. They illustrate firstly, that tumor MLH1 hypermethylation does not necessarily rule out LS, and secondly, the need for comprehensive coverage of the MLH1 promoter region in MGPTs.

Keywords: Lynch syndrome, MLH1, Promoter, Constitutional methylation, Promoter variants

P-013 CASE REPORTS OF THERAPY ASSOCIATED POLYPOSIS IN PEDIATRIC CANCER SURVIVORS

Case reports / Case series

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Background and Aim: Childhood cancer survivors have treatment-related risks that require lifelong monitoring. Pediatric survivorship clinics utilize The Children's Oncology Group (COG) Long Term Follow-up and National Comprehensive Cancer Network (NCCN) Survivorship Guidelines to direct surveillance, including colonoscopy screening. Current recommendations from COG and NCCN suggest colonoscopy every 5 years beginning 5 years after radiation or at age 30 (whichever occurs last) in patients who were exposed to abdomen, pelvis, spine, or total body irradiation (TBI). NCCN recommends that all childhood cancer survivors with a history of chemotherapy (without radiation) start colonoscopy 10 years after chemotherapy or at age 35 (whichever occurs last). Our aim was to review our cancer survivors to determine if there are patients who may require colonoscopies at a younger age.

Methods / Clinical Presentation / Preliminary Data: In this case series, we present three childhood and young adult cancer survivors who developed colon polyps in their late teens or early twenties. All three developed gastrointestinal symptoms including abdominal pain, diarrhea, and hematochezia within 10 years of completing their cancer treatment which prompted earlier than recommended colonoscopies and the discovery of at least one tubular adenoma as well as sessile serrated and pedunculated polyps. None of the three had a family history of colon cancer, and all three had negative germline genetic testing.

Results / Discussion / Project Plan and Timeline: Two of the 3 patients had astrocytoma, and one had relapsed T-cell acute lymphoblastic leukemia. Each was treated with a cyclophosphamide equivalent dose (CED) between 7,112-10,817 mg/m2; one received TBI and spinal boost. Collectively, this suggests that their polyp history can be attributed to therapy associated polyposis, likely associated with alkylating agents.

Conclusions / Requirements for Collaboration: We propose that patients treated with high CED and/or radiation to abdomen/pelvic area may benefit from colonoscopy screening earlier than the published guidelines recommend for detection of precancerous polyps associated with their childhood cancer treatment.

Keywords: cancer, polyposis, therapy associated polyposis

P-015 DISCORDANT GERMLINE RESULTS AND CLINICAL PRESENTATION IMPACTING CLASSIFICATION OF AN STK11 VARIANT

Case reports / Case series

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Background and Aim: Peutz-Jeghers syndrome (PJS) is a hereditary cancer syndrome caused by STK11 germline mutations, characterized by mucocutaneous pigmentation, hamartomatous polyps, and high cancer risks. We describe a family with an STK11 likely pathogenic variant (LPV) yet no clinical features of PJS, and how this impacted variant classification.

Methods / Clinical Presentation / Preliminary Data: A 36-year old unaffected female underwent germline panel testing due to family history of maternal aunt with ovarian cancer. She was identified to have an STK11 LPV described as c.1042del. She had no mucocutaneous pigmentation nor hamartomatous polyps identified via endoscopy or colonoscopy. Familial testing identified the variant in her maternal half-sister, confirming maternal inheritance and their mother as an obligate carrier. Neither had reported PJS features, with absence of hamartomatous polyps confirmed via colonoscopy/pathology reports. Given high penetrance of PJS and discordant familial presentation, variant classification was explored with the performing laboratory, which did not previously have variant segregation or phenotype data. Based on clinical presentation, the variant was downgraded to variant of uncertain significance (VUS).

Results / Discussion / Project Plan and Timeline: The STK11 variant was initially classified as LPV due to predicted nonsense-mediated decay (NMD) based on a 1999 publication describing a downstream variant causing PJS (c.1246A>T). However, NMD has not been confirmed in our proband's STK11 variant or the 1999-reported variant, which are both located at the 3' end of STK11 (exons 8 and 9 of 9 coding exons). PJS has high penetrance with no reported cases of unaffected STK11 carriers and therefore lack of PJS features in this family contributed to downgrade to VUS, having significant implications on management and cascade testing recommendations.

Conclusions / Requirements for Collaboration: Clinical data, including phenotype and variant segregation, should be used to inform variant classification and impact patient care. Clinicians can partner with testing laboratories especially in cases of discordant germline results and clinical presentation.

Keywords: variant classification, STK11, Peutz-Jeghers syndrome

P-016 MICROSATELLITE INSTABILITY HIGH (MSI-H) COLORECTAL CANCER (CRC) ASSOCIATED WITH A GERMLINE PATHOGENIC VARIANT (GPV) IN BRCA1

Case reports / Case series

Authors: Devang Namjoshi[2], Michael J Hall[1], Eric Tetzlaff[1]

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Background and Aim: MSI-H CRC primarily occurs sporadically, w/~20% occurring in pts w/Lynch syndrome/LS due to a gPV in a mismatch repair (MMR)/LS gene. MSI-H CRC is highly responsive to immunotherapy, but management of breakthrough disease remains uncertain.

Methods / Clinical Presentation / Preliminary Data: We present a patient w/MSI-H right-sided CRC and BRCA1 gPV.

Results / Discussion / Project Plan and Timeline: A 52F without personal history presented w/abdominal pain and 10 pound weight loss. CT revealed multiple bulky necrotic abdominal masses, w/biopsy showing mucinous adenocarcinoma, likely colorectal. Colonoscopy confirmed a partially circumferential non-obstructive cecal mass. PET/CT revealed avid R-colon and peritoneal masses (SUV14-15). Initial locally-performed universal LS screening showed equivocal loss of MLH1/absence of PMS2—both BRAF V600E and MLH hypermethylation were negative. Subsequent commercial NGS reported MSI-H w/TMB 36 mut/Mb, and PVs in BRAF V600E(VAF22%), RNF43 G659fs(VAF44%), MSH6 F1088fs(VAF10%) but low LOH (~5%). Pembrolizumab q3 weeks produced marked clinical improvement @1 month and near complete response @9 months. However, @1year CT revealed a new 2 cm splenic hilar node that was PET avid (SUV13), while the treated CRC primary and abdominal masses were not avid. Surgical resection of the splenic node and the R colon was undertaken 1.5 years after diagnosis: final path showed a metastatic splenic node deposit and a R colon with no tumor identified but a single positive pericolonic lymph node (1/22). Germline testing was LS negative but revealed a BRCA1 PV (del exon20-23) that was not identified by previous tumor NGS.

Conclusions / Requirements for Collaboration: This case highlights a rare MSI-H CRC, w/BRAF V600E+ but somatic MLH1 hypermethylation(-), LS(-), and an occult (tumor NGS negative) germline BRCA1 PV. Remarkably, surgery to remove a solitary sanctuary metastasis in the splenic hilum incidentally led to removal of a PET-occult pericolonic node at the primary site, highlighting the potential value of consolidative surgery after immunotherapy even in patients with complete radiographic response.

Keywords: MSI-H, Colorectal Cancer, immunotherapy, brca1

Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
Mismatch Repair Status	**IHC**	**Protein**	**Deficient (Loss)**	**BENEFIT**	**dostarlimab**	**Level 1**
					nivolumab, nivolumab/ipilimumab combination, pembrolizumab	**Level 2**
BRAF	**Seq**	**DNA-Tumor**	**Pathogenic Variant Exon 15 | p.V600E**	**BENEFIT**	**cetuximab + encorafenib**	**Level 2**
				LACK OF BENEFIT	vemurafenib/dabrafenib monotherapy	Level 3
MSI	**Seq**	**DNA-Tumor**	**High**	**BENEFIT**	**nivolumab, nivolumab/ipilimumab combination, pembrolizumab**	**Level 2**
TMB	**Seq**	**DNA-Tumor**	**High, 36 mut/Mb**	**BENEFIT**	**pembrolizumab**	**Level 2**
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 2

Genes Tested with Pathogenic or Likely Pathogenic Alterations

Gene	Method	Analyte	Variant Interpretation	Protein Alteration	Exon	DNA Alteration	Variant Frequency %
APC	Seq	DNA-Tumor	Pathogenic Variant	p.S1465fs	16	c.4393 _4394dupAG	21
ARID1A	Seq	DNA-Tumor	Pathogenic Variant	p.P224fs	1	c.671delC	23
	Seq	DNA-Tumor	Pathogenic Variant	p.P1468fs	18	c.4403delC	22
ATM	Seq	DNA-Tumor	Pathogenic Variant	p.K2811fs	58	c.8432delA	24
AXIN2	Seq	DNA-Tumor	Pathogenic Variant	p.G665fs	8	c.1994delG	22
BRAF	Seq	DNA-Tumor	Pathogenic Variant	p.V600E	15	c.1799T>A	22
CASP8	Seq	DNA-Tumor	Likely Pathogenic Variant	p.P411L	9	c.1232C>T	25
FANCM	Seq	DNA-Tumor	Pathogenic Variant	p.V1336fs	14	c.4005delA	23
KMT2C	Seq	DNA-Tumor	Pathogenic Variant	p.V2707fs	38	c.8119delG	22
KMT2D	Seq	DNA-Tumor	Pathogenic Variant	p.P2968fs	34	c.8903delC	11
	Seq	DNA-Tumor	Pathogenic Variant	p.G1235fs	11	c.3704delG	21
	Seq	DNA-Tumor	Pathogenic Variant	p.R845fs	10	c.2533delC	22
MSH6	Seq	DNA-Tumor	Pathogenic Variant	p.F1088fs	5	c.3261dupC	10
NSD1	Seq	DNA-Tumor	Pathogenic Variant	p.V1486fs	10	c.4455delA	22
RNF43	Seq	DNA-Tumor	Pathogenic Variant	p.G659fs	9	c.1976delG	44
SETD2	Seq	DNA-Tumor	Pathogenic Variant	p.R1407fs	3	c.4219delA	23
STK11	Seq	DNA-Tumor	Pathogenic Variant	p.E57fs	1	c.169delG	30

P-017 MEASURING PREFERENCES FOR DIETARY PREVENTION INTERVENTIONS AMONG PATIENTS (PTS) WITH LYNCH SYNDROME (LS)

General Research - Lynch syndrome

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Background and Aim: LS is characterized by increased lifetime risk of multiple CA types. While intensive screening can lower risk of LS CAs, additional preventive measures could further benefit motivated pts. Our recent study (JCO Precision Oncology 2024) found that pts with LS only modestly uptake ASA/NSAIDs for CA prevention. Here, we examine perceptions of dietary interventions for prevention of LS CAs.

Methods / Clinical Presentation / Preliminary Data: PREVENTLynch participants completed an online survey about screening behaviors and CA prevention preferences. Pts were recruited through the Fox Chase Risk Assessment Program Registry and through online announcements by LS advocacy groups. Pts rated five dietary interventions: resistant starch-RS, vitamin supplements-VS, online nutritional feedback-NF, intermittent fasting-IF, and low inflammatory index diet-LID (0-10, low-to-high) for perceived convenience, side effects concerns, reassurance to reduce CA risk, and research participation interest, benchmarked to annual colonoscopy (CO). Score differences were evaluated by Wilcoxon rank sum.

Results / Discussion / Project Plan and Timeline: Participants (n=280) were diverse by age, state/country (39 states; 15% non-US residents) but predominantly female (84%)/white (92%). VS(1.77), NF(1.94) and RS(2.00) were more convenient than CO(3.40)($p<0.001$). Perceived side effects of ONF(1.81)($p<0.001$) were lowest compared to CO(2.46), especially among US pts (1.73) vs non-US (2.31)($p<0.05$). CO reassurance (8.25) was significantly higher than all proposed interventions (VS 5.04, RS 4.85, ONF 5.72, LID 5.04, all $p<0.001$). Notably, pts w/neoplasia history expressed lowest reassurance from IF(4.73, $p<0.001$), while non-US participants rated VS(3.49 vs 5.28), IF(4.08 vs 5.10) and LID(4.4 vs 5.24)(all $p<0.001$) significantly less favorably than US pts. Research interest was highest for RS(7.31) and NF(7.06) and lowest for IF(6.31). Pts w/neoplasia history had higher interest in research of VS(7.21) than those without (6.60)($p<0.05$).

Conclusions / Requirements for Collaboration: Dietary interventions show promise as low-risk adjuncts to CO surveillance w/favorable acceptability among LS pts. Our findings highlight the value of measuring pt preferences when developing risk-reducing interventions to maximize real-world uptake and downstream effectiveness.

Keywords: Lynch syndrome, dietary, cancer prevention

P-018 CLINICAL AND MOLECULAR CHARACTERISTICS OF YOUNG ADULT PANCREATIC CANCER: A SINGLE-CENTRE REVIEW

General Research - Pancreatic cancer-related syndromes

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Institutions: [1]Saint Vincent Hospital, [2]Fox Chase Cancer Center

Background and Aim: Pancreatic cancer (PC) incidence continues to rise globally. Early-onset PAC (eoPC), defined as PC diagnosed <50 or <55, have distinct pathologic and clinical features which remain poorly characterized. Young adult PC (yaPC) diagnosed under the age of 40 is exceeding rare, representing only <5% of PC. Recent studies have documented a 4% increased incidence of yaPC since the year 2000. Here, we review clinical characteristics of n=10 patients (pts) w/yaPC.

Methods / Clinical Presentation / Preliminary Data: We conducted a retrospective 10-year EHR-based review for pts diagnosed w/yaPAC at Fox Chase Cancer Center (2015-2024). Demographics, medical history, clinical presentation, treatment, germline/somatic genetic results, and outcomes were collected.

Results / Discussion / Project Plan and Timeline: Ten pts met inclusion criteria. Median age at diagnosis of PC was 35 years. 50% were female, and reported race/ethnicity included 40% African American(AA), 40% Caucasian and 20% Hispanic. Family history of malignancy was present 9/10 pts, and 6/10 reported a 1stdegree(n=1), 2nddegree(n=2) or 3rddegree(n=3) relative w/PC. Four women (2 AA, 2 Hispanic) had pseudopapillary neoplasm of the pancreas either in the pancreatic body(n=1) or tail (n=3) –3/4 were cured surgically, 1 died of metastatic disease. 6 pts had pancreatic adenocarcinoma—3/6 were inoperable at diagnosis, while 3 underwent Whipple resection after neoadjuvant chemotherapy; however, 2/3 recurred in the liver. All pts having MMR testing were MSS (7/7). Germline testing was performed in 7/10: one PV in ATM(c.8266A>T) and a VUS in NBN(c.935T>C) were identified. Somatic PVs were identified in 4 pts (TSC1, CHD7, EWSR1-ATF fusion, ATM and SMAD4). Patient with PV in ATM(c.8266A>T) diagnosed 8/2023 has been on a clinical trial of an ATR kinase inhibitor for >1year w/stable disease.

Conclusions / Requirements for Collaboration: yaPC represents a unique subset of PC w/rising incidence and includes both low- and high-grade cancers. Prognosis for yaPC w/adenocarcinoma is poor even for very young pts, though clinical trials of targeted inhibitors show promise.

Keywords: Pancreatic, young adults, early-onset

P-019 MOSAICISM IN SMAD4 - A CASE REPORT

Case reports / Case series

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Background and Aim: A clinical diagnosis of Juvenile Polyposis Syndrome (JPS) is defined by > 5 colonic juvenile polyps, multiple juvenile polyps throughout the gastrointestinal tract, or >1 juvenile polyp with a family history. Pathogenic Variants (PV) in BMPR1A or SMAD4 are found in 50% of individuals with a clinical diagnosis of JPS. Limited case studies on SMAD4 mosaicism exist, and phenotypes vary. We present a case of SMAD4 mosaicism.

Methods / Clinical Presentation / Preliminary Data: Male with 5-year history of rectal bleeding was scoped at age 33. No pertinent family history. Germline pan-cancer panel was negative for PV. Paired polyp-germline testing identified the same SMAD4 exon 5-12 deletion in two polyps and at blood levels consistent with constitutional mosaicism. Gastrointestinal Phenotype: Esophagus and duodenum normal. 6 gastric polyps, 3- 20 mm; pathology hamartomatous. Colon phenotype: 22 polyps found on 3 colonoscopies. Size 2-42 mm; pathology inflammatory, juvenile, hamartomatous. Recurrent epistaxis and an agitated shunt study that is positive, which is possible Hereditary Hemorrhagic Telangiectasia based on Curacao criteria.

Results / Discussion / Project Plan and Timeline: SMAD4 constitutional mosaicism is almost always de novo. Presentation is rare, and phenotype is variable which may lead to delayed diagnosis.

Conclusions / Requirements for Collaboration: In cases with phenotypic JPS, patients may need paired polyp-germline testing to find mosaic mutations that germline testing failed to detect. These results impact clinical management and guide risk assessment for family members. Furthermore, surveillance with specialists is essential in caring for these individuals.

Keywords: Hamartomatous, mosaicism, juvenile polyposis, genetic counseling, somatic testing

P-020 SERRATED POLYPS SEGREGATING IN FAMILY MEMBERS WITH A CO-OCCURRING BRCA1 PATHOGENIC VARIANT AND RNF43 VARIANT OF UNKNOWN SIGNIFICANCE (VUS)

Case reports / Case series

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Background and Aim: BRCA1 and RNF43 are both tumor suppressor genes located on chromosome 17q. Pathogenic variants in RNF43 have been identified as a rare cause of serrated polyposis syndrome (SPS); however, its interactions with other tumor-suppressor genes has been poorly characterized.

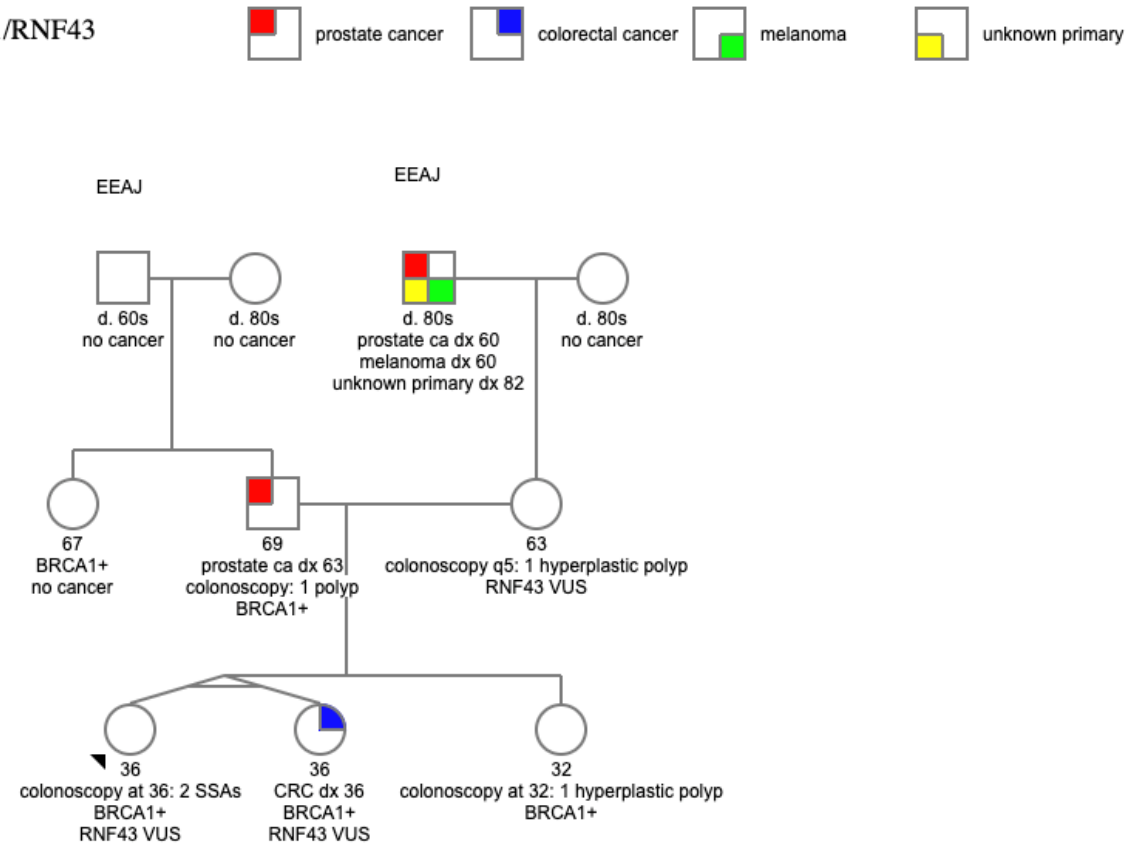
Methods / Clinical Presentation / Preliminary Data: We present a case of a healthy 36-year-old female who presented to the high-risk colorectal cancer clinic one week after a diagnosis of early onset metastatic colorectal cancer in her identical twin sister. Our patient and her sister were found to have a pathogenic BRCA1 variant c.68_69delAG, (p.E23Vfs*17) and an RNF43 VUS c.575C>T (p.P192L). The RNF43 VUS has conflicting classifications of pathogenicity, with some labs classifying it as benign or likely benign. On colonoscopy, the patient was found to have 2 sessile serrated polyps. Family history was unrevealing of other relatives with colorectal cancer. Further segregation testing revealed that the BRCA1 variant was paternally inherited and the RNF43 variant was maternally inherited. The patient's mother has a history of 1 hyperplastic polyp on colonoscopy. Their other sister was found to be BRCA1+ and RNF43-, with 1 hyperplastic polyp on colonoscopy.

Results / Discussion / Project Plan and Timeline: RNF43's nature is still being understood as a possible susceptibility gene for SPS. Further review of the literature yielded a study of a family with familial colorectal cancer type X (FCCTX) in which 4 out of 7 individuals who inherited both a familial pathogenic BRCA1 variant and RNF43 variant developed colorectal cancer. The authors suggest a possible digenic inheritance of BRCA1 and RNF43 resulting in higher risk for colorectal cancers.

Conclusions / Requirements for Collaboration: Segregation of BRCA1 and RNF43 variants in individuals with early-onset colorectal cancer and with sessile serrated polyps suggest a possible increased risk of colorectal cancer when inherited together.

Keywords: serrated polyps, Colorectal Cancer, BRCA

-BRCA1/RNF43


prostate cancer
colorectal cancer
melanoma
unknown primary
EEAJ
EEAJ
d. 60s
no cancer
d. 80s
no cancer
d. 80s
prostate ca dx 60
melanoma dx 60
unknown primary dx 82
d. 80s
no cancer
67
BRCA1+
no cancer
69
prostate ca dx 63
colonoscopy: 1 polyp
BRCA1+
63
colonoscopy q5: 1 hyperplastic polyp
RNF43 VUS
36
colonoscopy at 36: 2 SSAs
BRCA1+
RNF43 VUS
36
CRC dx 36
BRCA1+
RNF43 VUS
32
colonoscopy at 32: 1 hyperplastic polyp
BRCA1+

P-022 LYNCH SYNDROME CAUSED BY PMS2-PMS2CL GENE CONVERSION

Case reports / Case series

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Background and Aim: Lynch syndrome (LS) risks, surveillance, and testing methods differ considerably based on the implicated gene. Most notably, the identification of PMS2-associated LS presents many challenges. High sequence homology between PMS2 and one of its pseudogenes, PMS2CL, creates technical difficulty distinguishing between LS-causing PMS2 and nonfunctional PMS2CL variants. Additionally, while individuals with MLH1 or MSH2 variants may have striking personal/family histories that aid in variant interpretation, families with PMS2 variants often exhibit lower penetrance, later onset of tumor development and an overall more subtle clinical presentation.

Methods / Clinical Presentation / Preliminary Data: Herein, we describe an individual referred for testing in our laboratory for disambiguation of uncertain results obtained from an outside laboratory. Previous testing identified a potential deletion of PMS2 exon 11 but was inconclusive regarding whether this deletion occurred in PMS2 or PMS2CL. Additionally, while the patient had a personal history of sebaceous adenoma, the remaining personal/family clinical history was not overtly suggestive of LS.

Results / Discussion / Project Plan and Timeline: Long-range PCR performed by our lab identified a hybrid allele, in which exons 11-15 of the PMS2 gene were converted to PMS2CL sequence, resulting in a frameshift in exon 11. This variant results in early termination and is expected to undergo nonsense mediated decay, confirming a diagnosis of LS for this individual

Conclusions / Requirements for Collaboration: This case highlights the importance and complexities of testing 3’ exons of PMS2. Accurate determination of the identified variant in PMS2 vs PMS2CL is important for patients and their families to receive correct diagnosis, appropriate follow-up testing and/or surveillance if warranted. Methodologies such as long-range PCR may aid in disambiguation between PMS2- and PMS2CL-associated variants, though routine supplemental testing may increase costs and turnaround time. Cases such as this one highlight the need for more sophisticated, scalable and cost-effective workflows to aid in PMS2 testing.

Keywords: Lynch syndrome, PMS2, PMS2CL, gene conversion

P-023 PAIRED GERMLINE-SOMATIC PROFILING TO DETERMINE DRIVERS OF OVARIAN CANCER IN THE SETTING OF CONCURRENT PMS2 AND RAD51D GERMLINE PATHOGENIC VARIANTS

Case reports / Case series

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Background and Aim: Germline pathogenic variants (gPV) in PMS2 and RAD51D increase the risk of ovarian cancer (OC). Paired germline-somatic profiling may determine germline drivers in cases of concurrent gPV to inform familial risk counseling.

Methods / Clinical Presentation / Preliminary Data: A 55-year-old female was diagnosed with Stage IA ovarian clear cell carcinoma that exhibited retained expression of mismatch repair (MMR) proteins on immunohistochemistry (IHC). Family history was significant for maternal aunt with OC, maternal grandmother with gastric cancer, and father and paternal grandfather with colon cancer. The patient consented to paired germline/somatic sequencing (MSK-IMPACT). The OC tumor was analyzed for 505 genes, including assessment of microsatellite instability (MSI). The patient underwent germline evaluation of 90 genes, which found a PMS2 c.1123C>T (p.Gln375*) gPV, diagnostic of Lynch Syndrome (LS), and a RAD51D c.574C>T (p.Gln192*) gPV. Loss of heterozygosity (LOH) was assessed by the FACETS algorithm which found no LOH for either PMS2 or RAD51D in the OC tumor. Somatic profiling revealed a microsatellite stable (MSS) tumor with 10 mutations. Inferred mutational signatures revealed a dominant APOBEC signature rather than a homologous recombination deficiency (HRD)-related signature. The patient underwent hysterectomy/bilateral salpingo-oophorectomy and chemotherapy. She was counseled to follow LS surveillance, and genetic testing was recommended for her at-risk relatives. She is alive and well seven years after her OC diagnosis.

Results / Discussion / Project Plan and Timeline: PMS2 and RAD51C gPV are associated with increased risk for OC. In the setting of concurrent gPV with overlapping cancer risks, somatic profiling can clarify tumor drivers. This patient's clear cell OC appears to be unrelated to either gPV, which provides valuable insight regarding OC risk for family members who may not share either germline mutation.

Conclusions / Requirements for Collaboration: I hereby confirm that the consent of the relevant patient has been obtained to submit this case report.

Keywords: ovarian cancer, Lynch syndrome, germline, somatic

P-024 CDH1-ASSOCIATED DIFFUSE GASTRIC CANCER BEING TREATED AS GASTROPARESIS: IMPLICATIONS FOR CANCER GENETICS EDUCATION FOR HEALTH CARE PROVIDERS

Case reports / Case series

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Background and Aim: Hereditary Diffuse Gastric Cancer (HDGC) is a rare genetic disorder associated with pathogenic CDH1 variants that increase the risk of gastric and lobular breast cancer. There is a lack of awareness of this genetic syndrome among healthcare providers, which can lead to delayed diagnosis.

Methods / Clinical Presentation / Preliminary Data: Eleven months prior to the diagnosis, a 43-year-old male—with a family history of gastric cancer and a known CDH1 PV among family members (father, sister, and niece)—presented to a local physician with intractable nausea, vomiting, and weight loss of 100 lbs. Workup (CT scan, celiac serologies, and colonoscopy) was unrevealing. An EGD showed excessive retained fluid in the stomach and erythematous gastric mucosa. Biopsies were normal. Gastric emptying study showed 82% retention at 4 hours. Due to non-response to management of presumed gastroparesis, the patient was evaluated by several physicians, but without improvement. At presentation to our institution, CT imaging showed emphysematous gastritis and possible antral luminal narrowing. A PET scan showed mild non-specific uptake. The patient was evaluated by the gastroenterology service, who along with the surgical oncologist, suspected linitis plastica. Genetic testing confirmed CDH1 PV. The patient underwent a total gastrectomy with Roux-en-Y esophagojejunostomy, partial colectomy, and lymph node dissection. A diagnosis of poorly differentiated gastric adenocarcinoma with 19 metastatic lymph nodes was made. Currently, the patient is undergoing chemotherapy and is supported by total parenteral nutrition.

Results / Discussion / Project Plan and Timeline: Our case highlights the lack of awareness about rare genetic syndromes leading to a ~1-year delay in diagnosis, and limitations of endoscopic biopsies. New gastrointestinal symptoms in HDGC should raise suspicion for an infiltrative gastric cancer and lead to a timely referral to a specialist in hereditary cancers.

Conclusions / Requirements for Collaboration: Cancer genetics should become an integral part of the education of physicians and physician extenders so that patients with potential cancer-predisposition can receive appropriate diagnosis and care.

Keywords: Hereditary Diffuse Gastric Cancer, CDH1, E-cadherin, Malignancy, Gastroparesis, surveillance

P-025 DO DIGITAL TOOLS SUPPORT A DIVERSITY OF PATIENT VALUES? A QUALITATIVE STUDY USING THE GENETICS ADVISER

General Research - Counseling, Behavioral Health, Psychosocial, and Survivorship

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Background and Aim: Despite the well-established role of patient values in shared decision-making, there are limited efforts to explore the range of values held by diverse populations and how they inform decision-making for genomic testing. This gap is particularly concerning given the especially value-laden nature of decisions for exome sequencing (ES) and learning incidental findings. We aim to explore the range of values raised when selecting incidental findings from ES and how these are supported by the Genetics Adviser digital health application.

Methods / Clinical Presentation / Preliminary Data: We conducted semi-structured qualitative interviews with participants undergoing ES and receiving incidental findings as part of an RCT. Interviews were analyzed using interpretive description.

Results / Discussion / Project Plan and Timeline: Sixteen participants were interviewed, who were primarily women (11/16) and aged 59 on average (range: 39-76 years). Participants unanimously expressed that their decision to receive all incidental findings available to them from ES preceded use of the Genetics Adviser. Surprisingly, decision-making was not described as a deliberate process for participants and occurred within a 'black box' before even using the Genetics Adviser. This 'black box' describes a complex system of hidden motivational factors involved in decision-making. Three

overarching values emerged from unpacking this ‘black box’, including: a sense of family stewardship, an imperative to accumulate information, and the notion of restoring or maintaining personal agency. Participants valued having Genetics Adviser to confirm their predetermined decision by clarifying, contextualizing, and instilling confidence in their decision.

Conclusions / Requirements for Collaboration: Participants enter decision-making for ES with a predetermined decision guided by three core values that motivate patients’ decision to learn incidental findings: family stewardship, an information imperative, and preserving agency. Interestingly, these values predetermined decision-making for ES, but were clarified, contextualized and reinforced by the Genetics Adviser. These findings challenge the dogma surrounding decision support and genetic counselling in clinical genetics and can inform how digital tools can better support patient values.

Keywords: incidental findings, digital tools, patient values, exome sequencing, decision-making

P-026 BARRIERS TO MEETING PREVIVORS' SUPPORTIVE CARE NEEDS: GENETIC COUNSELORS' EXPERIENCES

General Research - Counseling, Behavioral Health, Psychosocial, and Survivorship

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Background and Aim: Previvors, individuals living with an inherited mutation who have never been diagnosed with cancer, experience a unique set of challenges related to their personal risk and family history of cancer. Research on the experience of previvors has largely focused on BRCA mutation carriers, rather than the growing population of patients who have mutations in genes associated with moderate cancer risk or rare hereditary cancer syndromes. Existing research demonstrates that previvors have supportive care needs (SCNs) that are not being met through standard genetic counseling sessions, psychotherapy, and support groups. For previvors with mutations in genes beyond BRCA, SCNs are even less well understood. Therefore, this study sought to assess genetic counselor (GC) perceptions of previvor SCNs as well as barriers and facilitators to meeting needs.

Methods / Clinical Presentation / Preliminary Data: We performed semi-structured interviews with cancer GCs across the U.S (N=14). Interviews were recorded, transcribed, and interview data were thematically analyzed using interpretive description.

Results / Discussion / Project Plan and Timeline: GCs indicated that outstanding previvor SCNs include concerns over finances, sexual and reproductive health, and psychosocial distress. Participants reported barriers to providing supportive care including limited time to assess needs and lack of access to formal support services for previvors. GCs shared that implementation of dedicated follow-up clinics for previvors have been helpful in addressing the longitudinal SCNs of their patients and that expanded access to social work and psychosocial oncology services would be helpful. GCs described the role that cancer screening guidelines play in enabling patient access to supportive care needs and suggested that developing guidelines for managing the SCNs of previvors may help them advocate for better access to services for their patients.

Conclusions / Requirements for Collaboration: These findings deepen our understanding of the unique SCNs needs of previvors and build on prior work suggesting the need to integrate psychosocial oncology services into the care of previvors.

Keywords: previvor, supportive care, genetic counselor

P-027 PRELIMINARY EVALUATION OF A CANCER GENETIC RISK ASSESSMENT TOOL IN PRIMARY CARE

General Research - Delivery of Care and Alternative Models

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Institutions: [1]Center for Clinical Genetics and Genomics, University of Chicago, Chicago, IL, USA, [2]Section of General Internal Medicine, University of Chicago, Chicago, IL, USA

Background and Aim: One in five adults has a family history suggestive of a familial or hereditary cancer predisposition syndrome but most remain undiagnosed. Cancer risk assessment is challenging especially in primary care due to competing priorities and limited time. As a quality improvement initiative, we developed a short survey tool based on NCCN genetic testing guidelines to easily assess breast-ovarian, prostate and GI cancer syndromes. Our aim was to evaluate initial outcomes from implementation of the tool in primary care.

Methods / Clinical Presentation / Preliminary Data: A 10-item self-administered paper survey tool was developed to assess family history of multiple cancer types based on clinical criteria from guidelines. Participants were also asked their preferences about the tool. A pilot phase was implemented in a Gender-Based Care Clinic from 9/2024 to 4/2025. Answering “yes” to any question prompted referral to genetics services.

Results / Discussion / Project Plan and Timeline: The tool was completed by 36 participants (92% female; 55% Black; median age 47) (Table 1). Of these, 12 (33.3%) participants screened positive (Table 2). Six (16.7%) answered “yes” to more than one question. The most frequent positive responses were family history of early-onset cancer (n=7) and multiple relatives on the same side of the family with breast cancer (n=6). Two (16.7%) have completed a genetic counseling visit to date. The majority (94%) reported they would complete the tool in MyChart before a primary care visit.

Conclusions / Requirements for Collaboration: A third of patients who completed a short risk assessment tool in primary care screened positive. Participants reported positive experiences with the tool. These preliminary results suggest that a short survey tool could facilitate identification of high-risk individuals in primary care. Future directions include inclusion of more male patients, survey automation through MyChart and benchmarking of the survey tool with extensive clinical criteria and genetic test results.

Keywords: Genetics, cancer, risk assessment, primary care

Table 1.

Demographics	N (%)
Gender	
Cisgender Male	0 (0.0)
Cisgender Female	33 (91.7)
Non-binary	1 (2.8)
Transgender Male	1 (2.8)
Transgender Female	1 (2.8)
Age at risk assessment	
Median (IQR)	47.6 (34.6-59.4)
Self-Reported Race/Ethnicity	
Asian/Southeast Asian	3 (8.3)
Ashkenazi Jewish	0 (0.0)
Black/African American	20 (55.6)
Hispanic/Latinx	2 (5.5)
Native American	0 (0.0)
Native Hawaiian/Pacific Islander	1 (2.8)
White	12 (33.3)
Other/Unknown	0 (0.0)
Preferred Language	
English	36 (100)
MyChart status	
Active	36 (100)
Insurance type	
Public	7 (19.4)
Private	29 (80.6)

Table 2. Risk Assessment Tool

Part 1 – Risk Assessment Tool (n=36)	**N (%) "Yes"**
Has anyone in your family had ovarian cancer?	4 (11.1)
Have any men in your family had breast cancer?	2 (5.6)
Has anyone in your family been diagnosed with breast, colorectal, endometrial (uterine) or prostate cancer before age 50?	7 (19.4)
Have 2 or more relatives on the same side of your family been diagnosed with breast cancer?	6 (16.7)
Have 2 or more relatives on the same side of your family been diagnosed with colorectal cancer?	0 (0.0)
Have any of your first-degree relatives (siblings, children, or parents) been diagnosed with pancreatic cancer?	0 (0.0)
Have any men in your family had metastatic (stage 4) prostate cancer?	3 (8.3)
Have you ever tested positive for a gene related to cancer risk before?	0 (0.0)
Has anyone in your family tested positive for a gene related to cancer risk before?	0 (0.0)
Part 2 – Participant experience (n=35)	**N (%)**
Do you feel like you know enough about your family history to answer the questions accurately?	
Yes	27 (77.1)
No	8 (22.9)
Did you feel comfortable answering the questions?	
Yes	35 (100)
No	0 (0.0)
Would you answer these questions if we sent them to you in MyChart before your appointment?	
Yes	33 (94.3)
No	2 (5.7)
When is the best time for us to ask you these questions about your family history?	
Before my visit in MyChart	12 (34.3)
In the waiting room	2 (5.7)
In the exam room	4 (11.4)
No preference	17 (48.6)

P-028 GERMLINE GENETIC TESTING TRENDS FOR PANCREATIC CANCER CARE IN THE COMMUNITY

General Research - Delivery of Care and Alternative Models

Authors: Heather Hannon[1]

Institutions: [1]Bon Secours Cancer Institute

Background and Aim: Literature exploring genetic testing rates for pancreatic ductal adenocarcinoma (PDAC) suggests that uptake remains low despite national guidelines recommending universal germline testing. We aimed to explore germline testing rates and pre-test education trends for PDAC at our community cancer center.

Methods / Clinical Presentation / Preliminary Data: A chart review was performed evaluating patients diagnosed with PDAC who had at least one visit with an oncologist at our community cancer center between January 1, 2024, and December 31, 2024. Variables analyzed included the frequency of germline testing ordered, the frequency of pre-test education and who provided education, and type of germline test ordered.

Results / Discussion / Project Plan and Timeline: Fifty-two patients met criteria, and 50% had germline testing ordered. Most germline testing (85%) was ordered point-of-care by medical oncologists. Among patients for whom testing was ordered by medical oncologists, only 32% had documentation of pre-test education in the chart. Fifteen percent of patients had testing ordered by genetics professionals, and all of these patients had documentation of pre-test education in the chart. The majority of patients received multi-gene panels, while 27% had pancreas cancer-focused panels ordered by the medical oncologist, and 8% had breast cancer-focused panels (which lacked certain PDAC genes) ordered by the medical oncologist. Notably, two patients who received a pancreas-focused panel were later recommended additional testing due to family and personal history.

Conclusions / Requirements for Collaboration: Point-of-care models can enhance genetic testing for PDAC patients in community settings. An assessment of genetic testing trends at our community center indicated that relying on community oncologists to make germline testing decisions may result in PDAC patients failing to receive guideline-recommended genetic care. While not every PDAC patient requires formal pre-test counseling, implementing a systems-wide approach that includes input from genetics professionals can help standardize multi-gene panels and pre-test educational materials, ensuring that the appropriate tests are ordered and patients receive crucial information about the testing process.

Keywords: Pancreatic adenocarcionma,, germline genetic testing, Education, Pre-test, Pre-test

P-029 POPULATION-BASED HEREDITARY CANCER SCREENING IN A GENERAL ENDOSCOPY CLINIC: EVALUATING INTEREST, UPTAKE, AND OUTCOMES

General Research - Delivery of Care and Alternative Models

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Background and Aim: Though healthcare providers utilize criteria from society guidelines to identify patients at risk for hereditary cancer, patients are underreferred. Population-based genetic screening may improve referrals, though its effectiveness is unknown. We aim to evaluate the interest in, uptake, and outcomes of genetic services in a general patient population presenting for endoscopy.

Methods / Clinical Presentation / Preliminary Data: A screening questionnaire developed to highlight personal and/or family history indicative of a hereditary cancer syndrome based on current NCCN guidelines for several cancers was distributed between Feb - Sept 2024 to all patients presenting for endoscopy. High-risk features per NCCN criteria were grouped into broader items and a “yes” response was classified as high-risk. All participants were offered genetics evaluation regardless of their responses. Two-proportion Z-test was used for data analysis.

Results / Discussion / Project Plan and Timeline: 1010 questionnaires were completed: 135 (13.3%) participants expressed interest in a genetics evaluation; 105 (77.8%) were high-risk and 30 (22.2%) were not. High-risk participants were more likely to request further evaluation compared to those who were not ($p=2.17 \times 10^{-10}$). A majority (99/105, 94.3%) of high-risk participants who desired genetic counseling had not been previously tested. Ultimately, 25/135 (18.5%) participants saw a genetic counselor, 12/25 (48.0%) had germline genetic testing, of which 3 (25%) had clinically significant findings. Two met NCCN criteria with actionable results in ATM and NTHL1.

Conclusions / Requirements for Collaboration: Patients presenting for endoscopic procedures are interested in genetic counseling, particularly amongst those considered to be high-risk per NCCN, and population genetic screening through a questionnaire greatly enabled their identification. Interestingly, less than a fifth of high-risk participants who indicated interest in genetic counseling presented for an appointment, highlighting a gap between interest and engagement. Overall, population screening in endoscopy centers may improve identification of at-risk individuals.

Keywords: genetic testing guidelines, genetic counseling, germline genetic testing

P-030 ENDOSCOPIC SURVEILLANCE OUTCOMES IN A GENETIC CANCER PREVENTION CLINIC FOR HIGH-RISK GI PATIENTS

General Research - Delivery of Care and Alternative Models

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Background and Aim: The GI Genetic Cancer Prevention Clinic (GCPC) provides specialized management and follow-up care tailored to an individual's risk based on a pathogenic variant (PV) in a cancer predisposition gene. As part of this care, patients are referred for endoscopies based on current NCCN guidelines. We aim to analyze endoscopic surveillance outcomes for individuals with an identified PV.

Methods / Clinical Presentation / Preliminary Data: Data, including demographics, genetic/medical/management compliance history, was collected through retrospective chart review and stored in a REDCap database (STU-2024-0553) for GCPC patients from January 2023 to April 2025. High-risk lesions are characterized by the number of adenomas, polyp size, and advanced histology in accordance with NCCN guidelines. Descriptive statistics were calculated.

Results / Discussion / Project Plan and Timeline: During the study, 122 patients established care in GCPC. Patients were mostly female (n=77, 63.1%), White (n=98, 80.3%), and spoke English (n=119, 97.5%). Of these patients, 69 (56.5%) were referred for screening colonoscopy and 63 (51.6%) referred for EGD. Most referred patients completed imaging including 65 with >1 colonoscopy and 58 with >1 EGD; additional surveillance included EUS/ERCP (5) and capsule endoscopy (1). Of those who underwent surveillance, 21 patients had at least one high-risk lesion detected (Figure 1). Many of these patients were previvors (n= 14, 66.7%) of which half have an APC PV (n=7, 50.0%). Twelve patients were classified as high-risk based on the number of adenomas, including three previvors with >100. Twelve patients were high-risk based on polyp size. Nine patients were high-risk based on advanced histology including high-grade dysplasia, ampullary adenomas, or tubulovillous adenomas.

Conclusions / Requirements for Collaboration: GCPC allows focused prevention efforts for hereditary cancer conditions. Previvors accounted for the majority of patients with high-risk endoscopy findings, and GCPC allows ease of access to follow up care to maximize cancer prevention. Future directions include long-term outcomes for patients in GCPC with high-risk lesions compared to those outside of a clinical home.

Keywords: high-risk endoscopic findings, genetic risk, high-risk endoscopic findings, genetic risk

Gene with PV	Age at GCPC	Personal Cancer History	High-Risk Category	Summary of High-Risk Lesions		
				Colonoscopy	EGD	ERCP
APC	22	Thyroid, Colon	Adenoma number, polyp size, advanced histology	>100 TAs & TVAs Max size 50 mm	30 duodenal adenomas	-
APC	24	Previvor	Adenoma number, advanced histology	50 TAs	1 ampullary adenoma	Same EGD finding
APC	27	Previvor	Adenoma number, polyp size, advanced histology	>100 TAs Max size 30 mm High grade dysplasia	30 duodenal adenomas 1 ampullary adenoma	-
APC	27	Desmoid Tumor	Adenoma number, advanced histology	25 TAs	1 ampullary adenoma	-
APC	32	Previvor	Adenoma number, polyp size, advanced histology	>100 TAs & TVAs Max size 20 mm	-	-
APC	39	Previvor	Adenoma number	3 TAs	-	-
APC	40	Previvor	Adenoma number	3 TAs	-	-
APC	42	Pancreas	Adenoma number, polyp size	>100 TAs Max size 25 mm	-	-
APC	48	Previvor	Adenoma number	3 TAs	-	-
APC	55	Previvor	Adenoma number	>100 TAs	-	-
APC	67	Kidney, Pancreas, Desmoid Tumor	Polyp size, advanced histology	1 TVA Max size 10 mm	-	-
Biallelic *MUTYH*	56	Previvor	Adenoma number	18 TAs	-	-
MSH2	56	Colon, Ovary	Polyp size, advanced histology	3 TAs & TVAs Max size 20 mm	-	-
MSH2	65	Uterus	Adenoma number	3 TAs	-	-
PJS*	32	Previvor	Polyp size	Max size 50 mm	-	-
PMS2	31	Previvor	Polyp size	Max size 12 mm	-	-
PTEN	43	Previvor	Advanced histology	-	1 ampullary adenoma	-
SMAD4	21	Previvor	Polyp size	Max size 30 mm	-	-
SMAD4	40	Previvor	Polyp size, advanced histology	-	1 ampullary adenoma Max size 20 mm	Same EGD finding
STK11	40	Breast	Polyp size	-	Max size 30 mm**	-
STK11	46	Previvor	Polyp size	Max size 10 mm	-	-

Figure 1: Summary of high-risk lesions detected on endoscopy screenings for patients following their initial GCPC visit. One patient (*) has a clinic diagnosis of Peutz-Jeghers Syndrome (PJS). Another patient (**) had polyps removed using double balloon enteroscopy which were initially detected on capsule endoscopy. Previvors do not have a personal history of cancer. TA: tubular adenoma, TVA: tubulovillous adenoma, EGD: Esophagogastroduodenoscopy, ERCP: endoscopic retrograde cholangiopancreatography.

P-031 REVISITING THE UNKNOWN: UPDATED GENETIC TESTING THROUGH RE-CONTACTING AND RE-REFERRAL OF PATIENTS WITH IDIOPATHIC ADENOMATOUS POLYPOSIS

General Research - Delivery of Care and Alternative Models

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Institutions: [1]The Ohio State University, Department of Internal Medicine, Division of Human Genetics, Columbus, Ohio, USA , [2]The Ohio State University, Department of Internal Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Columbus, OH, USA

Background and Aim: Technological advancements have expanded genetic offerings in polyposis from targeted APC and MUTYH analysis to comprehensive multi-gene panels. The National Comprehensive Cancer Network (NCCN) now recommends evaluation of 12 polyposis-associated genes in individuals with ≥10 cumulative adenomas. Prior to routine use of Next-Generation Sequencing in 2016, individuals with uninformative genetic testing were not assessed for all currently recommended genes. The benefit of re-evaluating individuals with idiopathic adenomatous polyposis (IAP) is unknown, and it is unclear if this approach would be widely acceptable. In this study, we aimed to evaluate the feasibility and uptake of re-contacting and re-referrals for individuals with IAP.

Methods / Clinical Presentation / Preliminary Data: Fifty-seven individuals with IAP and uninformative genetic testing were identified (initial testing from 1995–2015). Of these, 16 had already been re-referred to genetics by clinicians after 2016. Thirty-one individuals were eligible for re-contacting and were notified via mailed letters and follow-up phone calls. The remaining 10 individuals, who were deceased or residing outside of Ohio, were excluded from re-contact efforts.

Results / Discussion / Project Plan and Timeline: Among the 31 re-contacted individuals, seven (23%) completed updated genetic counseling and testing, eight (26%) declined, and 16 (52%) could not be reached (Figure 1). Undeliverable letters, disconnected phone numbers, and lack of response to calls and voicemails hindered recontacting efforts. In contrast, 14/16 (88%) of re-referred individuals underwent updated testing. Notably, 90% (18/20) of all re-referrals were due to a personal history of adenomas, and gastroenterologists initiated 70% (14/20) of re-referrals (Figure 2). All individuals re-referred had developed additional adenomas between their initial and updated testing.

Conclusions / Requirements for Collaboration: Re-referrals had a higher uptake than re-contacting initiatives in promoting updated genetic testing. Barriers to re-contact included outdated patient information and low response rates. Institutions should enhance re-referral systems and educate providers on the benefits of repeat testing to improve access to updated genetic testing for individuals with IAP.

Keywords: idiopathic adenomatous polyposis, Recontacting, re-referrals, colonic polyposis of unknown etiology, APC

Figure 1: Clinical Recontacting Initiative Process

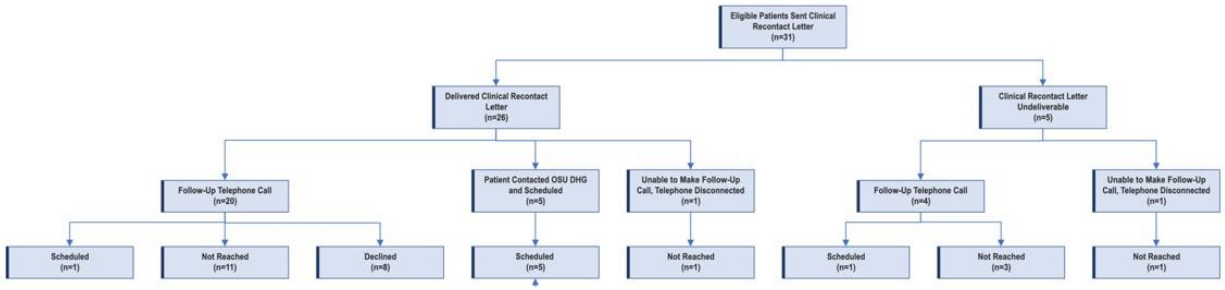
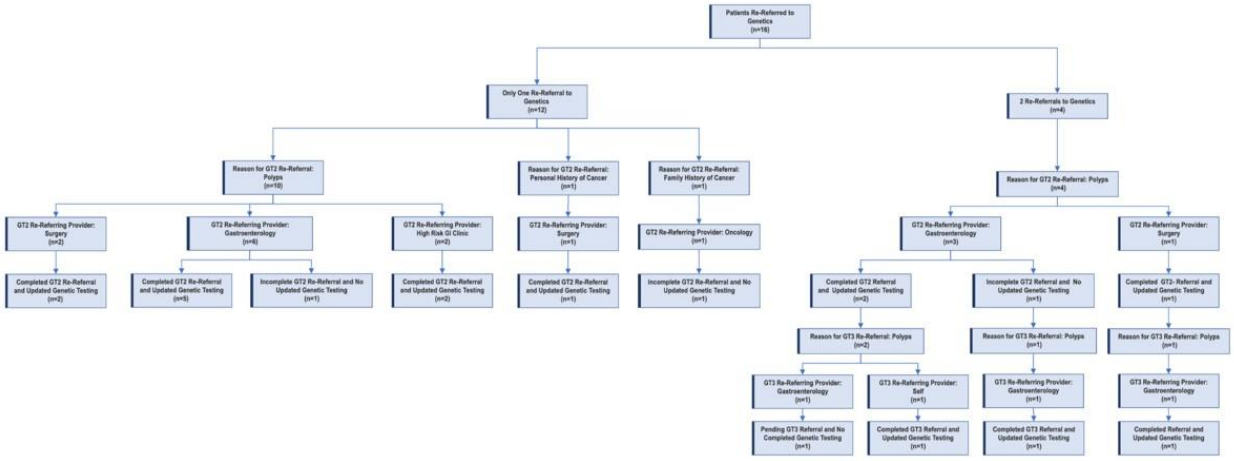


Figure 2: Re-referrals Patterns



P-032 CANCER PREVALENCE IN MSH3 HETEROZYGOTES

General Research - Early Onset Colorectal Cancer

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Institutions: [1]Ambry Genetics

Background and Aim: Biallelic pathogenic and likely pathogenic variants in MSH3 are associated with MSH3-related polyposis and colorectal cancer. However, observations of MSH3 heterozygotes with early-onset colorectal cancers (CRC) and/or polyposis raise questions of possible cancer associations. In prior studies, no increased CRC risk was observed in MSH3 heterozygotes; however, these studies are limited by small sample size or variant annotation that depends on in-silico tools and imputation.

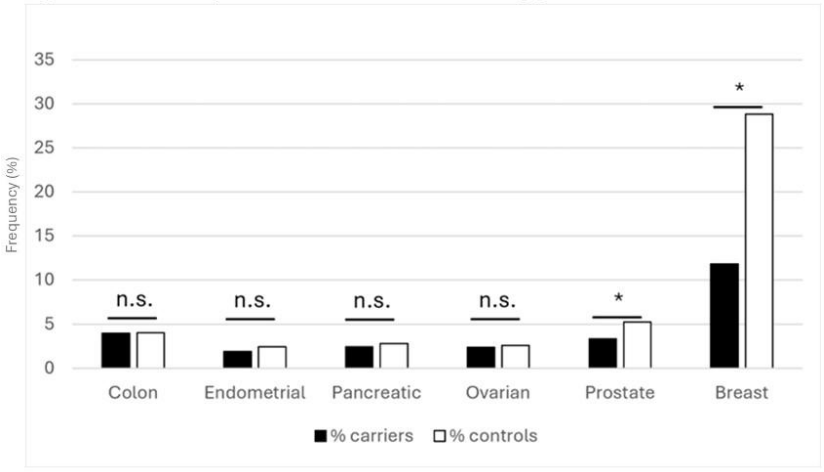
Methods / Clinical Presentation / Preliminary Data: We retrospectively analyzed the prevalence of colorectal and other tumors in confirmed MSH3 heterozygotes (n=1,317) identified from a large pan-cancer multigene panel testing (MGPT, between 2018-2024) cohort. Tumor phenotypes were inferred through ICD-10 codes, validated for high sensitivity and specificity. Using Fisher's exact test, the prevalence of reported tumors in MSH3 heterozygotes were compared to genotypically negative individuals (n=102,858) that had pan-cancer MGPT (70+ genes).

Results / Discussion / Project Plan and Timeline: The prevalence of CRC in MSH3 heterozygotes was 3.95% compared to 4.03% in the negative cohort (OR=0.977, 95% CI 0.725-1.292, p=.94). Additionally, the prevalence of endometrial cancer in MSH3 heterozygotes was 1.90% compared to 2.41% in the negative cohort (OR=0.78, 95% CI 0.503-1.162 p=.27). Additional cancers such as ovarian (2.35% vs 2.57%) and pancreatic (2.43% vs 2.82%), showed no statistically significant difference compared to the control group, with breast (11.85% vs 28.82%) and prostate (3.34% vs 5.22%) showing a statistical negative association.

Conclusions / Requirements for Collaboration: These data show no significant enrichment of colorectal, endometrial, ovarian, or pancreatic cancers in MSH3 heterozygotes compared to a large, similarly ascertained negative MGPT cohort. Breast and pancreatic cancer show a negative association; however, this may reveal test order or other bias rather than a protective effect. Proactive assessment with thorough phenotype curation in larger cohorts is warranted to fully assess MSH3-related disease risks. This study adds to the growing body of evidence showing no cancer predisposition in MSH3 heterozygotes, providing important information for clinical management.

Keywords: Colorectal Cancer, polyposis, MSH3, AUTOSOMAL RECESSIVE INHERITANCE

Figure 1. Cancer prevalence in *MSH3* heterozygotes



*=p<.01; n.s.= not significant

Table 1. Odds of cancers in *MSH3* heterozygotes compared to genotype negative controls

	Heterozygotes N (%) of 1,317	Controls N (%) of 102,858	OR	95%CI	P value
Colon	52 (3.95)	4,152 (4.04)	0.977	0.725 to 1.292	p= .943
Endometrial	25 (1.89)	2,485 (2.42)	0.782	0.503 to 1.162	p= .276
Pancreatic	32 (2.43)	2,905 (2.82)	0.857	0.582 to 1.219	p= .450
Ovarian	31 (2.35)	2,647 (2.57)	0.913	0.616 to 1.305	p= .725
Prostate	44 (3.34)	5,370 (5.22)	0.627	0.453 to 0.849	p= .0017
Breast	156 (11.85)	29,650 (28.83)	0.332	0.279 to 0.393	p < .0001

P-033 UNRAVELING THE GENETIC SUSCEPTIBILITY SPECTRA OF SPORADIC EARLY-ONSET COLORECTAL CANCER ACROSS A RACIALLY/ETHNICALLY DIVERSE PATIENTS IN THE USA

General Research - Early Onset Colorectal Cancer

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Background and Aim: Early-onset colorectal cancer (EOCRC) is a leading cause of death in the young population in the USA. Although genetic susceptibility to cancer is primarily associated with a family history of cancer, in this study, we investigated the role of genetic susceptibility in seemingly sporadic EOCRC patients.

Methods / Clinical Presentation / Preliminary Data: We performed whole-exome sequencing (WES) on genomic DNA extracted from blood leukocytes of twenty-five EOCRC patients receiving treatment at Cedars-Sinai Medical Center (USA). Ancestry informative markers were extracted from WES data. Clinical and sociodemographic data were obtained from medical records.

Results / Discussion / Project Plan and Timeline: The EOCRC cases comprised 9 females and 16 males with an average age at diagnosis of 41.6 years (range 20 to 49), at stages I (n=2), II (n=4), III (n=10), and IV (n=9). Fifteen of the EOCRC cases (60%) carried a total of 32 pathogenic or likely pathogenic variants (PVs or LPVs) across 27 genes. While eight of these genes (APC, BBS10, ERCC6, FANCM, FLG, HFE, MSH4, and NBAS) are recognized as cancer predisposition genes, our study identifies 19 additional genes not previously classified as primary cancer risk genes, accounting for 53.2% (17/32) of the deleterious variants. Genetic ancestry estimation using the Dodecad Globe13 panel was consistent with self-reported ancestry and revealed distinct population groups with significant contributions from Northern European and Mediterranean ancestries, followed by East Asian, African, and Amerindian ancestries.

Conclusions / Requirements for Collaboration: In this racially and ethnically diverse EOCRC case series, inherited predisposition appears to play a substantial role in the development of seemingly “sporadic EOCRC”. Our findings indicate that up to 60% of sporadic EOCRC cases carry PVs or LPVs associated with an increased cancer risk. Therefore, enhanced genetic surveillance for EOCRC cases is essential. Additionally, our study suggests that novel cancer-susceptibility genes may play a role in the development of EOCRC across diverse populations.

Keywords: colorectal cancer, early-onset, genetic susceptibility, ancestry.

P-036 PENETRANCE OF CDH1 PATHOGENIC VARIANTS: A MULTICENTER ANALYSIS FROM THE GASTRIC CONSORTIUM

General Research - Gastric cancer-related syndromes

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Background and Aim: Pathogenic genetic variants (PGV) in CDH1 confer elevated risks for diffuse gastric and lobular breast cancer. However, gastric cancer risk estimates continue to evolve, with the most recent study estimating lifetime risk at approximately 10% (95% CI, 6%-23%). We aimed to evaluate the penetrance of CDH1 pathogenic variants in a large multicenter, clinically ascertained cohort.

Methods / Clinical Presentation / Preliminary Data: CDH1 PGV carriers were retrospectively identified from 12 North American academic centers. Family history of gastric and/or breast cancer were collected from pedigrees. When known, signet ring cell carcinoma foci confined to the mucosa (T1a) were not considered as positive cancer history. Lifetime cumulative risk (by age 80) of gastric and breast cancer were evaluated using Bayesian estimation approach and modified Weibull distribution, adjusting for ascertainment bias.

Results / Discussion / Project Plan and Timeline: Overall, 5141 individuals from 189 families were included, of which 765 (14.9%) have a known CDH1 PGV. Baseline characteristics are presented in Table 1. Seventy-two families (38.1%) had frameshift variants, 31 (16.4%) intronic variants, 30 (15.9%) nonsense, 25 (13.2%) cryptic splice site, 22 (11.6%) large deletions/duplications, 3 (1.6%) missense and one with (0.5%) initiation codon variant. In individuals with a known CDH1 PGV the prevalence of gastric

and female breast cancer was 20.6% (158/765) and 27.9% (124/443), respectively. The cumulative risk of gastric cancer by age 80 was 25.5% (95% CI, 20.5%-30.5%) for males and 28.7% (23.3%-34.3%) for females. The risk of female breast cancer was 38.9% (31.6%-46.7%). Figure 1 illustrates the age-specific cumulative risks of gastric and breast cancers.

Conclusions / Requirements for Collaboration: In this large multicenter cohort, cumulative gastric cancer risk was 25%-29% - marginally above the upper limit reported in the most recent study, yet lower than earlier estimates. Breast cancer risk remained consistent with previous reports. Ongoing work aims to stratify risk by the number of affected first-, second-, and third-degree relatives.

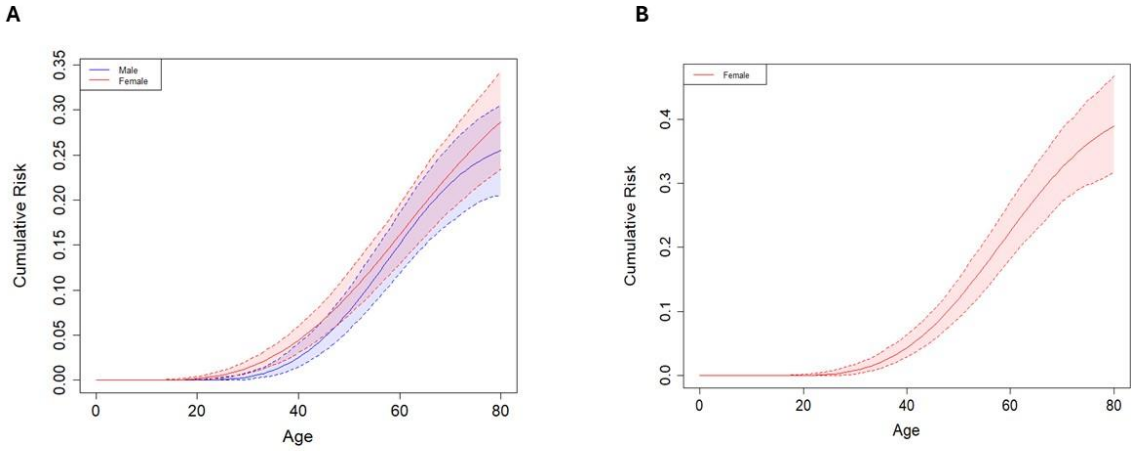
Keywords: CDH1, gastric cancer, breast cancer, penetrance

Table 1: Baseline characteristics of study cohort

Individuals (n=5141)	
Sex – female (%)	2450 (47.6)
Race (%)[a]	
White	163 (86.2)
Black	9 (4.7)
Asian	3 (1.5)
Other	14 (7.4)
Ethnicity (%)[a]	
Hispanic	15 (7.9)
Age at last follow up, mean (+/-SD)	53.1 (+/- 29.5)
Number of gastric cancer cases, mean (%)	329 (6.4)
Confirmed diffuse histology, mean (%)	78 (1.5)
Age at diagnosis of gastric cancer (+/-SD)	51.1 (+/- 13.7)
Number of breast cancer cases, mean (%)	317 (6.2)
Confirmed lobular histology, mean (%)	77 (1.5)
Age at diagnosis of breast cancer(+/-SD)	53.7 (+/- 11.8)
Individuals who underwent genetic testing (%)	1381 (26.8)
Number of positive results (%)	765 (14.8)
Families (n=189)	
Number of individuals per family, mean (+/-SD)	27.2 (+/- 17.4)
Families with ≥3 gastric cancer cases (%)	47 (24.9)
Families with ≥3 breast cancer cases (%)	43 (22.8)

[a]Percentages are based on data from individuals actively followed across multiple study sites

Figure 1: Cumulative lifetime risk of developing (A) gastric and (B) breast cancers



P-037 PREVALENCE OF HELICOBACTER PYLORI EXPOSURE AND RISK FACTORS AMONGST BRCA1 AND BRCA2 CARRIERS

General Research - Gastric cancer-related syndromes

Authors: Kole Buckley[1], Linda Zhu[1], Kevin Dinh[1], Ryan Hausler[2], Ariana Majer[1], Keely Beyries[1], Kara Maxwell[2], Bryson Katona[1]

Institutions: [1]Division of Gastroenterology and Hepatology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, [2]Division of Hematology and Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA

Background and Aim: Recent evidence has demonstrated that BRCA1/2 pathogenic germline variant (PGV) carriers with a Helicobacter pylori (Hp) infection may have up to a 9-fold increased risk of gastric cancer (GC) compared to uninfected carriers, indicating that Hp may be an important risk factor for BRCA1/2-associated GC. Although the prevalence of Hp in western populations is generally low, rates among BRCA1/2 PGV carriers in the U.S. are uncertain. Herein, we assessed Hp IgG levels amongst a broad cohort of U.S. based BRCA1/2 PGV carriers to determine the prevalence of Hp exposure.

Methods / Clinical Presentation / Preliminary Data: 959 BRCA1/2 PGV carrier serum samples were obtained from the University of Pennsylvania Basser Center for BRCA biobank. A commercially available ELISA kit that detects Hp IgG was used to determine Hp IgG positivity. Compared to gastric biopsies which only assesses for active infection, assessment of Hp IgG allows for determination of Hp exposure even after eradication.

Results / Discussion / Project Plan and Timeline: Of the combined 959 BRCA1/2 PGV carriers tested, 168 (17.5%) tested positive for Hp IgG (Figure 1). Individually, 73 (16.9%) BRCA1 and 95 (18.1%) BRCA2 PGV carriers were Hp IgG positive. When comparing patient characteristics, increasing age and non-white race were significantly associated with Hp IgG positivity (Table 1).

Conclusions / Requirements for Collaboration: Herein we present data on a large U.S. based cohort of BRCA1/2 PGV carriers tested for Hp exposure, showing that 17.5% of BRCA1/2 carriers had Hp IgG positivity consistent with active or prior Hp. Given the high rates of Hp exposure as well as the synergistic increase in GC risk amongst BRCA1/2 PGV carriers with Hp, baseline Hp testing should be considered in all BRCA1 and BRCA2 PGV carriers. Future studies are needed to better understand the role of Hp in gastric carcinogenesis in BRCA1/2 PGV carriers as well as whether prior Hp exposure leads to persistently increased GC risk, even after eradication.

Keywords: gastric cancer, BRCA, Helicobacter pylori

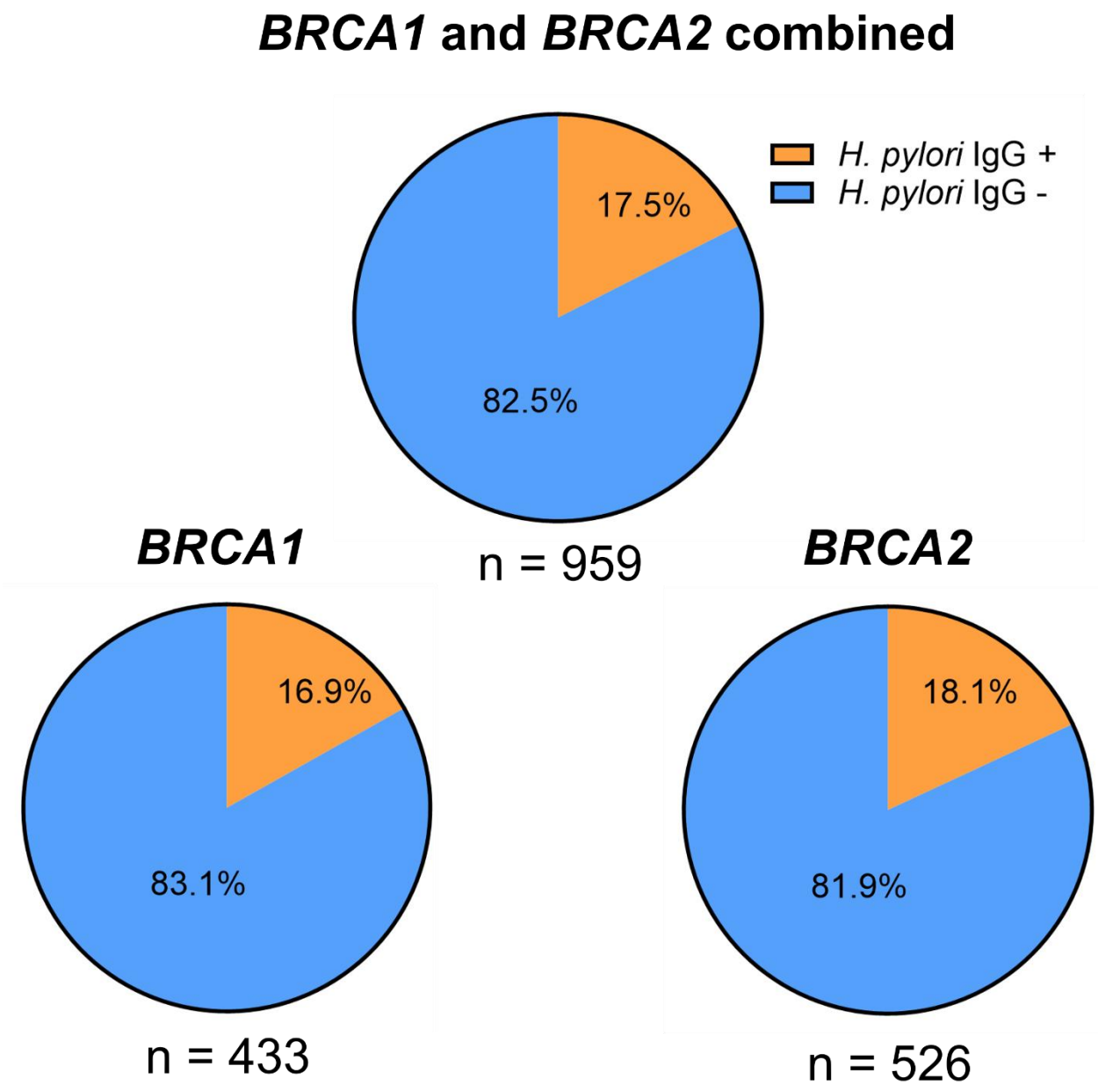

BRCA1 and BRCA2 combined
H. pylori IgG +
H. pylori IgG -
17.5%
82.5%
n = 959
BRCA1
16.9%
83.1%
n = 433
BRCA2
18.1%
81.9%
n = 526

Table 2: Stratification of baseline characteristics by *Hp* IgG status

Characteristic	*H. pylori* IgG positive	*H. pylori* IgG negative	*P*-value	Adjusted *P*-value
Age (years), mean (SD)	56.6 (14.8)	52.7 (14.4)	0.0015	**0.012**
Gender				
Male, *n* (%)	19 (21.1)	90 (78.9)	1	1
Female, *n* (%)	151 (21.5)	703 (78.5)		
Pathogenic germline variant				
BRCA1, *n* (%)	74 (20.6)	360 (79.4)	0.67	1
BRCA2, *n* (%)	96 (22.2)	433 (77.8)		
Race				
White, *n* (%)	138 (18.8)	735 (81.2)	2.49E-06	**2.24E-05**
Other, *n* (%)	32 (64)	50 (36)		
Ashkenazi Jewish ethnicity				
Ashkenazi Jewish, *n* (%)	52 (17.6)	296 (82.4)	0.0874	0.52
Non-Jewish, *n* (%)	105 (24.1)	435 (75.9)		
Alcohol				
Alcohol ever, *n* (%)	99 (19.3)	512 (80.7)	0.02	0.14
Alcohol never, *n* (%)	23 (35.9)	64 (64.1)		
Smoking				
Has smoked, *n* (%)	44 (23.7)	186 (76.3)	0.53	1
Never smoked, *n* (%)	80 (20.8)	385 (79.2)		
Marital Status				
Married, *n* (%)	110 (22.6)	486 (77.4)	0.37	1
Not married, *n* (%)	42 (18.9)	222 (81.1)		
Family history of gastric cancer				
Yes, *n* (%)	13 (26.5)	49 (73.5)	0.49	1
No, *n* (%)	157 (21.2)	738 (78.8)		

P-038 POST-SURGICAL COMPLICATIONS IN PATIENTS WITH COLORECTAL CANCER AND GERMLINE GENETIC TESTING RECEIVING EITHER PARTIAL OR EXTENDED RESECTIONS

General Research - Lynch syndrome

Authors: Mohammad Ali Abbass[1], Sarah Nielsen[2], Daniel Pineda-Alvarez[2], Edward Epslin[2], Emily Russell[2]

Institutions: [1]Memorial Sloan Kettering Cancer Center, [2]Labcrop (Invitae)

Background and Aim: Synchronous and metachronous colorectal (CRC) cancers are indicative of Lynch syndrome (LS) and LS diagnosis can guide surgical decision-making. Previously we confirmed that performing germline genetic testing (GGT) pre-surgery for new CRC diagnoses was more likely to result in extended resections, especially for MLH1/MSH2/EPCAM carriers, whose metachronous CRC risk can be ~50%. We compared real-world post-surgical complication rates in CRC patients receiving partial versus extended resections to augment surgical decision-making.

Methods / Clinical Presentation / Preliminary Data: GGT (Labcorp, formerly Invitae Corp.) and insurance claims (Komodo Healthcare MapTM) data for adults with non-metastatic colon (CC) or rectal (RC) cancer and CRC surgery from 2015-25, ≥6 months of claims pre-CRC diagnosis, ≥30 days of claims post-CRC surgery, and EPCAM/MLH1/MSH2/MSH6/PMS2 GGT. ICD10/CPT/HCPCS codes defined post-surgical complications (Table 1 footnote). Statistical tests compared post-surgical complication rates following partial (partial/segmental colectomy or proctectomy) or extended (total colectomy or total proctocolectomy) resections. Univariable and multivariable regression modeled variables associated with post-surgical complications.

Results / Discussion / Project Plan and Timeline: Of 1942 CRC patients (1871 CC, 71 RC), 15% were LS-positive (15% CC, 10% RC). 1832(94%) had partial (13% LS-positive) and 110(6%) had extended resections (40% LS-positive). A mean(SD) of 1.6 (0.9) post-surgical complications in 618(34%) patients with partial compared to 2.0 (0.8) in 42(38%) with extended resections (p=0.016); RC patients had one additional complication on average post-extended resections (Table 1). Extended resections weren't associated with post-surgical complications in univariable (OR(95% CI): 1.2(0.8-1.8)) or multivariable models (1.2 (0.8-1.8)). Males, Black patients, and patients with Medicaid or Medicare had higher odds of post-surgical complications than females (1.4(1.1-1.7)), White patients (1.4(1.0-2.0)), and patients with commercial insurance (1.8(1.4-2.4)); 1.9(1.4-2.6)) (Tables 1&2).

Conclusions / Requirements for Collaboration: While the extended resection cohort was small, we didn't observe an association between post-surgical complications and extended resection in CRC patients. Demographic factors associated with post-surgical complications should be studied further to identify gaps in quality of care.

Keywords: Lynch syndrome

Table 1. Post-surgical complications by type of cancer and procedure

	Patients with colon cancer				**Patients with rectal cancer**	
	Patients with partial resections		**Patients with extended resections**		**Patients with partial resections**	**Patients with extended resections**
	All (N=1781)	**Lynch positive** (N= 243)	**All** (N= 90)	**Lynch positive** (N= 40)	**All** (N= 51)	**All** (N= 20)
Total N (%) complications	599 (34)	92 (38)	33 (37)	13 (32)	19 (37)	9 (45)
Mean (SD) number of complications	1.6 (0.9)	1.7 (0.8)	1.8 (0.8)	1.8 (0.7)	**1.6 (0.9)**	**2.6 (0.9)**

***post-surgical complications included any of the following within 30 days: small bowel obstruction, acute renal failure, urinary tract infection, surgical site infection, urinary retention, deep vein thrombosis, postoperative MI, splenic injury, postoperative fistula, ureteral injury, adhesions, desmoids, anastomosis leak, diverting ostomy, re-operative surgery, ER visits, intraoperative and postprocedural complications and disorders of digestive system

+statistically significant ($p<0.05$) comparisons in bold; patients with Lynch syndrome and rectal cancer not shown in the table due to small numbers.

Table 2. Post-surgical complications by procedure and demographic factors

Complications N (%)	**All Patients** (N=1,942)	**Partial Resection** (N=1,832)	**Extended Resection** (N=110)	**White patients** (N=1,366)	**Black patients** (N=156)	**Commercial Insurance** (N=1,232)	**Medicare** (N=411)	**Medicaid** (N=265)
Any complications	660 (34.0)	618 (33.7)	42 (38.2)	**448 (32.8)**	**64 (41.0)**	**359 (29.1)**	**178 (43.3)**	**115 (43.4)**
Multiple complications	300 (15.4)	**271 (14.8)**	**29 (26.4)**	**194 (14.2)**	**38 (24.4)**	**159 (12.9)**	**80 (19.5)**	**58 (21.9)**
ER visits	415 (21.4)	390 (21.3)	25 (22.7)	**271 (19.8)**	**46 (29.5)**	**218 (17.7)**	**104 (25.3)**	**89 (33.6)**
Urinary tract infection	146 (7.5)	135 (7.4)	11 (10.0)	99 (7.2)	12 (7.7)	80 (6.5)	38 (9.2)	26 (9.8)
Acute renal failure	114 (5.9)	103 (5.6)	11 (10.0)	80 (5.9)	11 (7.1)	**50 (4.1)**	**47 (11.4)**	16 (6.0)
Small bowel obstruction	76 (3.9)	>71(>3.9)	<5 (<4.5)	**41 (3.0)**	**13 (8.3)**	50 (4.1)	14 (3.4)	12 (4.5)
Anastomosis leak	71 (3.7)	66 (3.6)	5 (4.5)	47 (3.4)	6 (3.8)	36 (2.9)	20 (4.9)	14 (5.3)
Urinary retention	53 (2.7)	48 (2.6)	5 (4.5)	39 (2.9)	<5 (<3.2)	26 (2.1)	19 (4.6)	7 (2.6)
Other complications	151 (7.8)	136 (7.4)	15 (13.6)	107 (7.8)	18 (11.5)	90 (7.3)	34 (8.3)	25 (9.4)

+bold numbers indicate statistically significant ($p<0.05$ after Bonferroni correction for multiple testing) comparisons: partial resection compared to extended resection, White patients compared to Black patients, commercial insurance compared to Medicare, commercial insurance compared to Medicaid

P-040 A FREQUENTLY OCCURRING MSH2 VARIANT IN MIDDLE EASTERN AND NORTH AFRICAN PATIENTS WITH LYNCH SYNDROME: EVIDENCE FOR A POSSIBLE FOUNDER VARIANT

General Research - Lynch syndrome

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Institutions: [1]Nancy and James Grosfeld Cancer Genetics Center, Corewell Health William Beaumont University Hospital, Royal Oak, Michigan, United States of America , [2]Oakland University William Beaumont School of Medicine, Rochester, Michigan, United States of America

Background and Aim: Lynch syndrome (LS) is a common cause of hereditary colon, endometrial, and ovarian cancer. LS is caused by germline pathogenic variants (PVs) in the mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) and EPCAM. Little is known about LS in Middle Eastern and North African (MENA) populations. We describe our institution's experience with a unique MSH2 PV in a cohort of individuals with MENA ancestry.

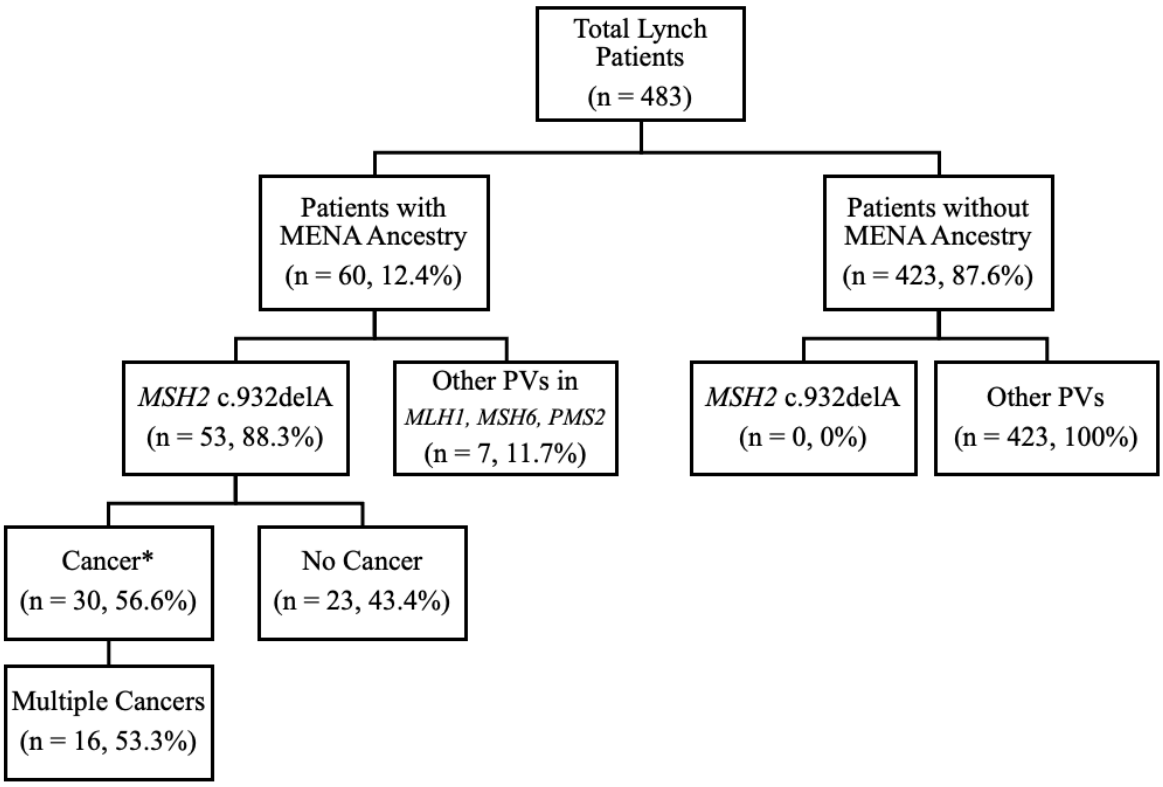
Methods / Clinical Presentation / Preliminary Data: Records of patients with LS and MENA ancestry seen in a high-volume cancer genetics center between January 2008 – March 2024 were analyzed. We reviewed genetic test results, cancer history, family history, and pathology.

Results / Discussion / Project Plan and Timeline: A total of 483 LS patients were identified, of whom 60 (12.4%) had MENA ancestry. Of those, 53 individuals (88.3%) from 22 separate families harbored the same PV in MSH2, c.932delA (p.N311Tfs*20). This variant was only detected in our MENA LS population. Of the 53 individuals with this variant, 30 (56.6%) had at least one cancer diagnosis (17 colon, 12 endometrial, 7 renal/urothelial, 6 ovarian, 4 breast, 7 other) and 23 were unaffected. Of affected individuals, 16 (53.3%) had more than one cancer. The average age of colon cancer onset was 49.6 years, (26-72 y.o.). All 9 colon cancers with available MMR immunohistochemistry showed loss of MSH2/MSH6 protein expression. Amsterdam II criteria were met by 17 families (77.3%). Pancreatic cancer was present in close relatives in 6 families (27.3%). Additionally, 14 families underwent cascade testing (mean: 4 relatives, range: 1-13), identifying 25 "true negative" individuals.

Conclusions / Requirements for Collaboration: This study is the first report of a recurrent MSH2 c.932delA PV in MENA patients with LS. This variant was seen exclusively in our MENA patients, and demonstrated a highly penetrant cancer phenotype. These findings suggest a possible LS founder variant in the MENA population. Further studies are needed to better characterize LS in this population.

Keywords: Lynch syndrome, cascade testing, founder variant, middle eastern/north african, msh2

Figure 1. Lynch Syndrome Patients Seen from January 2008 – March 2024 with Middle Eastern and North African (MENA) Ancestry



*Common cancers included colon, endometrial, renal/urothelial, and ovarian.

P-041 FAMILY COMMUNICATION PREFERENCES IN HEREDITARY CANCER SYNDROMES

General Research - Lynch syndrome

Authors: Kimberly Burke[1], Holly Etchegary[2], Lesa Dawson[4], Brenda J. Wilson[2], Kathleen Hodgkinson[3]

Institutions: [1]Infection Control, Humber River Hospital, North York, ON, Canada, [2]Faculty of Medicine, Community Health and Humanities, Memorial University, Newfoundland, Canada, [3]Faculty of Medicine, Discipline of Genetics, Memorial University, Newfoundland, Canada, [4]Obstetrics and Gynecology, Memorial University, Newfoundland & University of British Columbia, British Colombia, Canada

Background and Aim: Individuals with a family history of hereditary cancer syndromes, such as Hereditary Breast and Ovarian Cancer (HBOC) and Lynch Syndrome (LS), are at an elevated risk of developing multiple cancers. However, studies suggest that up to 50% of at-risk relatives do not attend genetic counselling, limiting their access to risk-reducing strategies. This study investigates family communication preferences to enhance genetic counselling uptake in affected families.

Methods / Clinical Presentation / Preliminary Data: Design: National cross-sectional survey (online) Participants: 119 (58 probands, 50 relatives) Analysis: Descriptive statistics, Mann-Whitney U & Kruskal-Wallis tests

Results / Discussion / Project Plan and Timeline: Demographics:96% of probands and 94% of relatives were femaleMean ages: Probands 56.9 ±16 years; Relatives 48.2 ±11 yearsCommunication Preferences:85% of probands felt responsible to inform family67% preferred healthcare provider assistance72% of relatives wanted info from a provider53% also accepted info from the probandDigital Tools:55% of probands supported secure apps/websitesOnly 29% of relatives preferred digital methodsNo significant effect of receiving a family letter ($p > 0.05$)

Conclusions / Requirements for Collaboration: A mismatch exists between current family-led communication and participants' preferences. A hybrid model that combines healthcare provider outreach with family input may improve genetic counselling uptake and risk awareness.

Keywords: Lynch syndrome, predisposition, hereditary, genetic counseling, cascade testing, cancer

Exploring Family Communication Preferences in Hereditary Cancer Syndromes: A National Survey

Kimbrely Burke[1], Lesa Dawson[2], Kathleen Hodgkinson[3], Brenda Wilson[4], Holly Etchegary[4]

1 Humber River Hospital, North York, ON. Canada
2 Memorial University, NL.& University of Brilischa, BC
3 Discipline of Genetics - Marm University. NL
4 Community Health and Humanities, Memadity, NL

BACGROUND

Hereditary Breast and Ovarian Cancer (HBOC) elevate canncer risk among family members. vst. nearly half of at risk relatives do not access genetic counsciling. Misstidy explorocs communication preferch cez between probands and their relatives to quide better outreach.

OBJECTIVES

- Identify how probands communicate genetic risk to tamily
- Explore how relatives prefer to receive this infor-
- Assess the role of healtncare providers ard digital tools in communicat!

IMPLICATIONS

- Guide practice for genetic counsellors
- Inform public health outreach strategies
- Encourage development of hybrid risk communication models

RESULTS

- **Demographics:**

86% of probands and 94% of relatives were female

Mean ages:
Probands 56.3 ± 16 years
Relatives 48.2 ± 11 years

- **Communication Preferences:**

85% of probands felt responsible to infom lanily

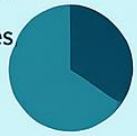
67% prefered healthcare provider assistance

72% of relatives wanted info from am provider

- **Digital Touls:**

55% of probands supported secure apps/websites

Only 29% of relatives prefered digital methods



CONCLUSIQN

A mistmatch exists between current family led communication and participants. preferences.

A hybrid model that combines healthcare provider oufreach with family input may improve genetic counselling uptake and risk awareness.

Family Communication Preferences in Hereditary Cancer Syndromes

Kimberly Burke[1], Lesa Dawson[2], Kathleen Hodgkinson[3], Brenda Wilson[4], Holly Etchegary[4]

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Background

Hereditary Breast and Ovarian Cancer (HBOC) elevate cancer risk among family members. Yet, nearly half of at-risk relatives do not access genetic counselling. This study explores communication preferences between probands and their relatives to guide better outreach.

Objectives

- Identify how probands communicate genetic risk to family
- Explore how relatives prefer to receive this information
- Assess the role of healthcare providers and digital tools in communication

Methods

A national Canadian cross-sectional study was conducted using an online survey that collected responses from 119 participants (58 probands and 50 relatives).

The survey assessed probands' experiences communicating genetic risk to relatives and relatives' preferred methods of receiving this information.

Data were analyzed using descriptive statistics and non-parametric tests.

Results

Demographics:
- 96% of probands and 94% of relatives were female
- Mean ages: Probands 56.9 ± 16 years; Relatives 48.2 ± 11 years

Communication Preferences:
- 85% of probands felt responsible to inform family
- 67% preferred healthcare provider assistance
- 72% of relatives wanted information from a provider
- 53% supported direct communication from the proband

Digital Tools:
- 55% of probands supported secure apps/websites
- Only 29% of relatives preferred digital methods

Implications

- Guide practice for genetic counsellors
- Inform public health outreach strategies
- Encourage development of hybrid risk communication models

Conclusion

A mismatch exists between current family-led communication and participants' preferences. A hybrid model that combines healthcare provider outreach with family input may improve genetic counselling uptake and risk awareness.

P-042 CLINICAL CHARACTERISTICS AND TUMOR PHENOTYPE OF OVARIAN CANCER IN LYNCH SYNDROME

General Research - Lynch syndrome

Authors: Christina Curtin[1], Qin Zhou[1], Cara Waterson[1], Alexia Iasonos[1], Bree Martin[1], Nikita Mehta[1], Ozge Birsoy[1], Yelena Kemel[1], Zsofia Stadler[1], Alicia Latham[1], Amir Momeni Boroujeni[1], Britta Weigelt[1], Ying Liu[1]

Institutions: [1]Memorial Sloan Kettering Cancer Center

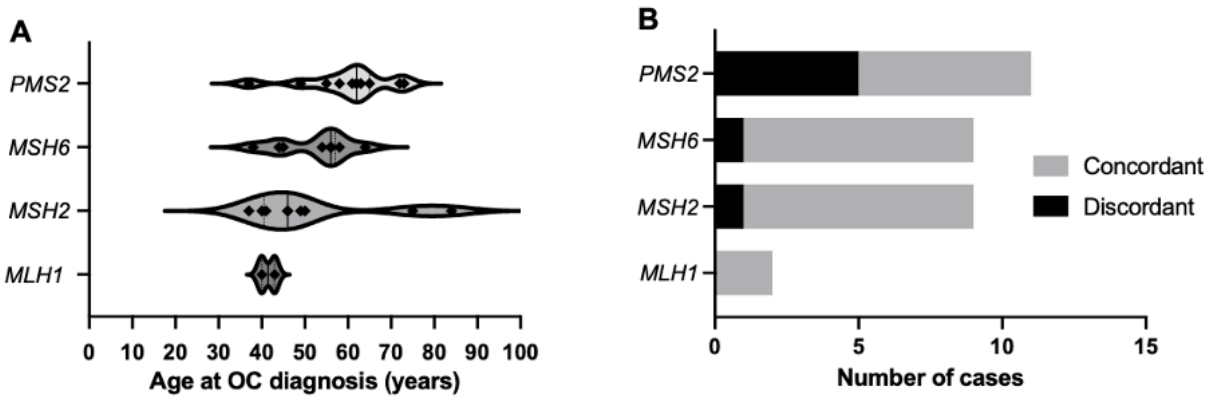
Background and Aim: Lynch Syndrome (LS) is associated with increased risk of ovarian cancer (OC); however, this varies by gene. We sought to characterize clinical features and tumor phenotype of OC in LS.

Methods / Clinical Presentation / Preliminary Data: We identified patients with LS and OC treated at our institution who underwent tumor-normal panel sequencing (MSK-IMPACT) between 3/2016 - 12/2024. Mismatch repair (MMR) and microsatellite instability (MSI) status were determined by immunohistochemistry (IHC) and next generation sequencing (NGS), respectively. Concordant tumors were defined as MMR-deficient or MSI-high.

Results / Discussion / Project Plan and Timeline: Among 31 patients with LS, 11 (35%) PMS2, 9 (29%) MSH6, 9 (29%) MSH2, and 2 (6.5%) MLH1, median age at OC diagnosis was 55 years (range 37 – 84). Fourteen (45%) patients had synchronous endometrial cancer. Median age at OC diagnosis was 62 years in PMS2-associated OC, 56 years in MSH6-associated OC, 46 years in MSH2-associated OC, and 42 years in MLH1-associated OC. Stage III/IV disease was present in 5 (45%) PMS2-associated OCs, 6 (54%) MLH1/MSH2-associated OCs, and 1 (11%) MSH6-associated OC. Eleven (35%) OCs were endometrioid, 8 (26%) high-grade serous OC (HGSOC), 5 (16%) clear cell, and the remaining 7 (23%) were mixed/other histologies. HGSOC comprised 6 (55%) of PMS2-associated OCs but only 1 (11%) MSH6-associated and 1 (9%) MLH1/MSH2-associated OC case. IHC and NGS were performed in 29 (93.5%) and 25 (80.6%) cases, respectively. Concordance and discordance were observed in 24 (77%) and 7 (23%) OCs, respectively, with 100% concordance in MLH1, 89% concordance in MSH2/MSH6, and 55% concordance in PMS2 OC. HGSOC were more likely to be discordant (71%) compared to other histologies (29%; p=0.006).

Conclusions / Requirements for Collaboration: OC age and tumor phenotype varies by LS gene, which has important implications for gene-specific counseling of OC risk. Notably, PMS2-associated OC was later-onset and enriched in HGSOC and MMR discordant tumors.

Keywords: Lynch syndrome, ovarian cancer, next generation sequencing


A
PMS2
MSH6
MSH2
MLH1
0 10 20 30 40 50 60 70 80 90 100
Age at OC diagnosis (years)
B
PMS2
MSH6
MSH2
MLH1
Concordant
Discordant
0 5 10 15
Number of cases

P-043 KNOWLEDGE OF GENETIC RISK IN PARTICIPANTS AT-RISK FOR LYNCH SYNDROME-ASSOCIATED GASTROINTESTINAL CANCERS: KNOWGENE SCORES AT BASELINE AND 12-MONTHS

General Research - Lynch syndrome

Authors: Emerson Delacroix[1 2], John Rice[3], Ken Resnicow[4], Sarah Austin[1], Erika Koeppe[1], Jennifer J. Griggs[1 5], Elena Martinez Stoffel[1 5]

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Background and Aim: Patient understanding of inherited cancer risk is crucial for optimal management of gastrointestinal (GI) cancers, particularly for those with a higher likelihood of Lynch Syndrome due to personal and/or family history. Understanding the extent to which interventions can improve knowledge is a key step in addressing gaps in patient knowledge.

Methods / Clinical Presentation / Preliminary Data: Enrolled participants in a randomized clinical trial with a 6-month educational intervention for persons with a higher likelihood of hereditary cancer syndromes (n=776) completed the KnowGene Scale, a validated measure of genetic risk knowledge, at baseline and after 12 months. Participants were stratified by cancer risk group: personal or family history of Lynch-associated cancers (colorectal, endometrial, and others) versus others. Linear mixed effects regression was used to assess change in mean knowledge scores over time between groups.

Results / Discussion / Project Plan and Timeline: At baseline, participants with Lynch-associated cancer risk history (n=81) had the lowest proportion correct knowledge scores (0.43 [95% CI: 0.36, 0.49]), compared to 0.55 in those with family history only and 0.52–0.50 in other groups. A significant Time × Group interaction was found in the full model ($F(6, 1326) = 4.60$, $p < 0.001$). At 12 months after Baseline (6 months after the educational intervention), the Lynch group showed the largest absolute improvement amongst the groups (+0.09 [0.026, 0.16]) with statistically significant change from baseline at both 6 and 12 months ($p < 0.01$).

Conclusions / Requirements for Collaboration: Participants at higher likelihood for Lynch-associated GI cancers initially had less knowledge about genetic risk but exhibited the most substantial gains following genetics education over the intervention period. These findings highlight the need for tailored educational interventions to address knowledge gaps in populations at high-likelihood for GI cancer and underscore the value of increased understanding of cancer risk and genetic testing uptake.

Keywords: Lynch syndrome, cancer, gastrointestinal, genetic risk, patient education, knowledge, longitudinal study

P-044 ELECTRONIC HEALTH RECORD ANALYSIS OF LYNCH SYNDROME PHENOTYPE IN LARGE INTEGRATED HEALTH SYSTEM

General Research - Lynch syndrome

Authors: Blake Jones[1], Allison DePersia[2], Mark Dunnenberger[2], Christopher Ward[3]

Institutions: [1]Department of Medicine, Division of Gastroenterology and Hepatology, Endeavor Health, Evanston, IL, [2]Mark. R. Neaman Center for Personalized Medicine, Endeavor Health, Evanston, IL, [3]Department of Data Analytics, Endeavor Health, Skokie, IL

Background and Aim: Lynch Syndrome (LS) cancer (ca) penetrance data is primarily derived from patients who completed germline genetic testing (GGT) due to personal or family ca history (traditional GGT). At Endeavor Health, the Neaman Center for Personalized Medicine (PMED) facilitates GGT through a novel population health screening program (population GGT), in addition to traditional GGT. We aimed to characterize LS ca penetrance using structured electronic medical record (EMR) data for the entire cohort as well as by GGT pathway, population or traditional.

Methods / Clinical Presentation / Preliminary Data: Patients with a pathogenic or likely pathogenic variant (PV) in a LS gene from 2018 to present were identified from the electronic data warehouse. Patient demographics, personal and family ca history were abstracted. Descriptive analysis and comparison between testing pathways was performed.

Results / Discussion / Project Plan and Timeline: 273 patients were identified with a PV (29 (10%) MLH1, 36 (13%) MSH2, 90 (33%) MSH6, 120 (44%) PMS2), 110 (40%) traditional and 163 (60%) population. Of traditional GGT, 35 (32%) carried a MLH1/MSH2 PV compared to 30 (18%) population. Demographics, including age, sex, and race, were not significantly different between traditional and population. Overall, 65 (24%) had a personal history of LS ca, 45 (41%) traditional and 20 (12%) population. Family history of LS ca in a first degree relative was noted in 142 (52%) of all LS patients, 84 (76%) traditional and 58 (36%) population. The median number of affected first or second degree relatives per LS patient was 1 in the overall cohort, 3 traditional and 1 population.

Conclusions / Requirements for Collaboration: LS patients identified by population GGT were less likely to carry PVs in high penetrance LS genes MLH1/MSH2, have a personal history of LS ca, or report a family history of LS ca compared to patients identified by traditional GGT. Further evaluation of these patient populations is warranted to inform LS ca penetrance and guide clinical management.

Keywords: Lynch syndrome, germline genetic testing, screening, Hereditary Nonpolyposis Colorec, Colorectal Cancer

P-045 UNIVERSAL TUMOR SCREENING FOR LYNCH SYNDROME AND RATE OF GERMLINE GENETIC TESTING IN JAPANESE COUNTRYSIDE

General Research - Lynch syndrome

Authors: Kenji Fujiyoshi[1], Sudo Tomoya[1], Satoshi Shimamura[1], Fumiki Koga[1], Takahiro Shigaki[1], Naohiro Yoshida[1], Takafumi Ochi[1], Takefumi Yoshida[1], Fumihiko Fujita [1]

Institutions: [1]1. Department of Surgery, Kurume University, Kurume, Fukuoka, Japan

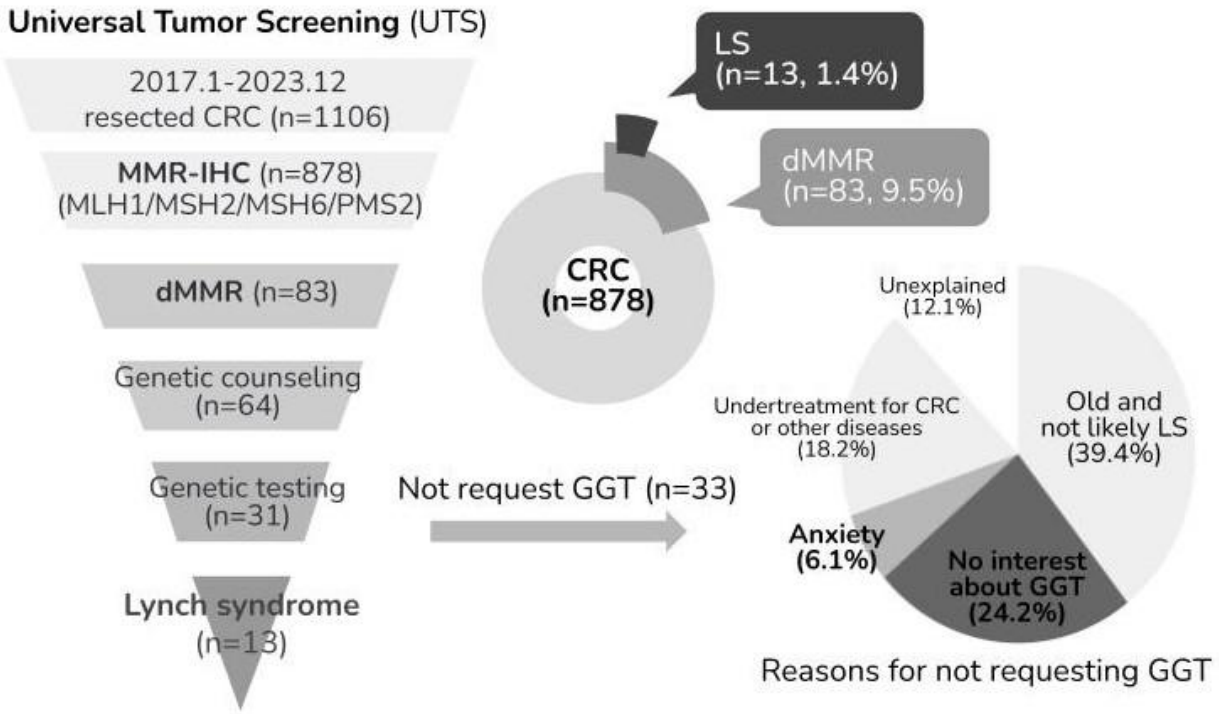
Background and Aim: Lynch syndrome (LS) has been identified as the most prevalent hereditary tumor in colorectal cancer (CRC). Germline genetic testing (GGT) for LS isn't covered by Japanese national insurance. Some patients are reluctant to undergo GGT due to the psychosocial implications and their low interest in genetics.

Methods / Clinical Presentation / Preliminary Data: We have implemented UTS with mismatch-repair protein immunohistochemistry (MMR-IHC) since 2017 at a cancer center hospital in the Japanese countryside. All patients with deficient-MMR (dMMR) CRC received genetic counseling, and GGT was performed at research expense for those who requested it. We examined the current status of UTS, the rate of GGT, and the reasons for not requesting GGT.

Results / Discussion / Project Plan and Timeline: In 1106 primary CRC surgically resected from January 2017 to December 2023, MMR-IHC was performed in 878, and 83 cases showed dMMR (9.5%). Of those, 77% were GGT candidates after excluding MLH1-deficiency and BRAF mutations (n=18), assumed sporadic. All GGT candidates were counseled, and 48% of them underwent GGT. Of 13 LS cases, 11 were MLH1/MSH2/MSH6=3/7/3, and 2 had VUS. The GGT group (n=29) was younger (61 vs. 75 y.o.) and had more cases with MSH2-MSH6 deficiency (44% vs. 19%); 33 had no-GGT. Reasons for not requesting GGT included: 17 cases (39%) of old age and lack of family history indicating a low likelihood of LS, 8 cases (24%) of no interest, 2 cases (6%) of anxiety about GGT, 6 cases (18%) of chemotherapy, other disease, or perioperative death, and 4 cases (12%) of unexplained.

Conclusions / Requirements for Collaboration: Our study demonstrated about 6% of patients did not request GGT due to anxiety, and at least 24% did not want GGT due to lack of interest. To improve the rate of GGT with patients' pay, more interest in medical genetics and meeting patients’ needs may be necessary.

Keywords: Lynch syndrome, germline genetic testing, Colorectal Cancer, universal tumor screening


Universal Tumor Screening (UTS)
2017.1-2023.12
resected CRC (n=1106)
MMR-IHC (n=878)
(MLH1/MSH2/MSH6/PMS2)
dMMR (n=83)
Genetic counseling
(n=64)
Genetic testing
(n=31)
Lynch syndrome
(n=13)
LS
(n=13, 1.4%)
dMMR
(n=83, 9.5%)
CRC
(n=878)
Not request GGT (n=33)
Unexplained
(12.1%)
Undertreatment for CRC
or other diseases
(18.2%)
Old and
not likely LS
(39.4%)
Anxiety
(6.1%)
No interest
about GGT
(24.2%)
Reasons for not requesting GGT

P-046 HEREDITARY CANCER REGISTRY ENROLLMENT IMPROVES SURVEILLANCE UPTAKE IN LYNCH SYNDROME

General Research - Lynch syndrome

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Background and Aim: Timely identification and surveillance of Lynch Syndrome (LS) is critical for cancer prevention, yet genetic testing referral and adherence with guideline-recommended surveillance remains inconsistent. European studies suggest hereditary cancer registry enrollment improves cancer surveillance outcomes; limited US-based data exists. We aim to describe genetic counseling (GC) referral patterns and evaluate the impact of registry enrollment on surveillance adherence and cancer risk for LS patients. We hypothesize universal LS screening facilitates GC referrals by colorectal surgeons and registry enrollment improves cancer surveillance compared to non-enrolled patients.

Methods / Clinical Presentation / Preliminary Data: Patients with mismatch repair-deficient colorectal cancer suspicious for LS (no BRAF V600E mutation or MLH1 promoter hypermethylation) were identified between 2010-2021 by reviewing pathology reports at a tertiary care institution and data collection was supplemented with EMR and institutional hereditary cancer registry review. GC referrals and outcomes were recorded by referring specialty. Among LS patients, surveillance completion, frequency, and cancer development were compared between registry-enrolled and non-enrolled patients. Surveillance ratios were defined as observed over expected surveillance frequency based on institution guidelines.

Results / Discussion / Project Plan and Timeline: Of 223 eligible patients, 185 (82.9%) were referred for GC, 135 (73.0%) completed GC, of which 124 (91.8%) completed genetic testing. Colorectal surgeons made most referrals (56.7%). 72 patients were newly diagnosed with LS, of whom 92.0% were referred to our registry and 61.3% enrolled in the registry. Registry patients were more likely to complete recommended surveillance compared to non-registry enrolled patients: colonoscopy (88.9% vs 66.7%, $p=0.02$), dermatologic exam (77.8% vs 37.0%, $p<0.01$), and gynecologic assessments (91.7% vs 25.0%, $p<0.01$). Median lower endoscopy surveillance ratios were significantly higher among registry patients (0.66 vs 0.22).

Conclusions / Requirements for Collaboration: While genetic testing uptake is high after GC completion, gaps remain in referral patterns. Enrollment in a hereditary cancer registry is associated with significantly improved adherence with LS-related surveillance, suggesting registries play a critical role in cancer prevention efforts.

Keywords: Lynch syndrome, Registry, surveillance, Colorectal Cancer, genetic testing

Table 1: Provider genetic counseling referral practices by specialty

Hospital Location	Colorectal	Oncology	GI	Other	Unknown	p-value
Overall (N=185), n (%)	105 (56.7%)	63 (34.0%)	4 (2.2%)	9 (4.9%)	4 (2.2%)	<0.01
Main Campus (N=94), n (%)	75 (79.8%)	15 (16.0%)	2 (2.1%)	2 (2.1%)	0 (0.0%)	<0.01
Regional Campus (N=91), n (%)	30 (33.0%)	48 (52.7%)	2 (2.2%)	7 (7.7%)	4 (4.4%)	<0.01

Table 2: Lynch Syndrome Patient Demographics

Characteristic	Number of patients (n=72)
Age at diagnosis, median (range)	57 (19-89)
Sex, n (%)	
Male	43 (59.7%)
Female	29 (40.3%)
Race	
White	59 (81.9%)
Black	7 (9.7%)
Multi-racial	3 (4.2%)
Unknown	2 (2.8%)
Asian	1 (1.4%)
Ethnicity	
Hispanic	2 (2.8%)
Non-Hispanic	70 (97.2%)
Pathogenic Variant	
MLH1	15 (20.8%)
MSH2	22 (30.5%)
MSH6	22 (30.5%)
PMS2	12 (16.8%)
Unknown	1 (1.4%)
Referring Provider Hospital Location, n (%)	
Main Campus	44 (61.1%)
Regional Campus	28 (38.9%)
Referred to Registry, n (%)	66 (92.0%)
Contacted by Registry, n (%)	58 (87.9%)
Enrolled in Registry, n (%)	45 (62.5%)
Main Campus	28 (63.6%, 28/44)
Regional Campus	17 (60.7%, 17/28)
History of Gynecologic Cancer prior to LS diagnosis, n (%)	8 (11.1%)
Registry	4 (22.2%, 4/18)
No Registry	4 (36.4%, 4/11)
History of TAH/BSO prior to LS diagnosis, n (%)	15 (20.8%)
Registry	6 (33.3%, 6/18)
No Registry	7 (63.6%, 7/11)

Table 3: Cancer surveillance outcomes based on registry enrollment

Characteristics	Registry (n=45)	No Registry (n=27)	p-value
Follow up time in years, median (range)	6.9 (0.1-15.9)	4.3 (0.1-14.1)	0.03
Completed ≥1 lower endoscopy surveillance after LS diagnosis, n (%)	40 (88.9%)	18 (66.7%)	0.02
Months between lower endoscopy, median (range)	13.0 (5-60)	13.0 (2-59)	0.94
Lower endoscopy surveillance ratio, median (range)	0.66 (0-2.7)	0.22 (0-0.8)	<0.01
Metachronous Advanced Neoplasia, n (%)	6 (13.3%)	6 (22.2%)	0.33
Metachronous CRC diagnosis, n (%)	1 (2.2%)	2 (7.4%)	0.29
Completed EGD, n (%)	37 (82.2%)	19 (70.4%)	0.24
Months between EGDs, median (range)	27.0 (3-65)	24 (11-45)	0.39
EGD surveillance ratio, median (range)	0.9 (0-1.9)	0.4 (0-0.86)	0.07
Gastroduodenal cancer diagnosis, n (%)	0 (0.0%)	1 (3.4%)	0.20
Completed skin cancer surveillance, n (%)	35 (77.8%)	10 (37.0%)	<0.01
Months between skin cancer surveillance, median (range)	13.5 (5-70)	12 (4-40)	0.40
Skin cancer surveillance ratio, median (range)	0.32 (0.0-1.8)	0.00 (0.0-0.57)	<0.01
Skin cancer diagnosis, n (%)	5 (11.1%)	1 (3.7%)	0.27
Proportion of patients with uterus after LS diagnosis, n (%)	12 (66.7%, 12/18)	3 (27.3%)	0.04
Completed Gynecologic Assessment, n (%)	11/12 (91.7%)	1 (25.0%, 1/4)	<0.01
TAH/BSO after LS diagnosis, n (%)	9 (75.0%, 9/12)	1 (25.0%, 1/4)	0.07
Indication			
Risk Reducing	6 (66.6%, 6/9)	1 (100%, 1/1)	
Endometrial Cancer	2 (22.2%, 2/9)	0 (0.0%, 0/1)	
Endometrial Hyperplasia	1 (11.1%, 1/9)	0 (0.0%, 0/1)	
Endometrial Biopsy, n (%)	7 (58.3%, 7/12)	0 (0.0%, 0/4)	0.04
Indication			
Surveillance	4 (57.1%, 4/7)	0 (0.0%, 0/4)	
Diagnostic	3 (42.9%, 3/7)	0 (0.0%, 0/4)	
Surveillance Biopsy Results			
Cancer/Hyperplasia	3 (75.0%, 3/4)	-	
No Cancer/Hyperplasia	1 (25.0%, 1/4)	-	

P-047 STREAMLINED CARE FOR CANADIANS WITH MISMATCH REPAIR DEFICIENT CANCERS THROUGH FULL-SERVICE GENETIC AND EPIGENETIC DNA SEQUENCING

General Research - Lynch syndrome

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Background and Aim: The Genome Canada Genomic Applications Partnership Program (GAPP) funds research implementation projects that address real world opportunities and challenges identified by industry, government, not-for-profits and other "receptors" of genomics knowledge and technologies. GAPP projects are collaborations between academic researchers and receptor organizations, and are co-funded by Genome Canada, receptors and other stakeholders.

Methods / Clinical Presentation / Preliminary Data: In 2021, researchers at the Princess Margaret Cancer Center developed a comprehensive - paired germline/somatic test for mismatch repair (MMR) deficient tumors called "MultiMMR". This panel was demonstrated to detect mutations and copy number alterations within MMR genes as well as promoter/constitutional methylation and microsatellite instability.

Results / Discussion / Project Plan and Timeline: An application to the GAPP grant program was funded for UHN and Dynacare that includes three objectives. 1) Expand the current MultiMMR assay to include expanded hereditary cancer gene panel (MultiMMRv2), 2) Enhance the MultiMMR protocol to enable genome and epigenomic analysis of low quantities of DNA and for cfDNA (cfMultiMMR), 3) Develop and implement a mainstreaming genetic counselling program to streamline testing pathways and support ordering physicians. This test is being validated on a collection of fresh and formalin-fixed tumour tissues, matched normal samples, and cell-free DNA to maximize accessibility to this test.

Conclusions / Requirements for Collaboration: The combination of the MultiMMR test, with an innovative and collaboratively developed mainstreaming program, we hypothesize will provide all downstream testing required to determine causative variants that explain mismatch repair deficient tumors in a fraction of the current turnaround time and for significantly less cost. We predict that more timely diagnosis of carriers of Lynch Syndrome and CMMRD will lead to the identification of at-risk family members resulting in many lives saved yearly.

Keywords: mismatch repair genes, Lynch syndrome, germline genetic testing, Mismatch Repair Deficiency, tumor testing

P-048 POOLED OCCURRENCE OF ADENOMA BY MISMATCH REPAIR SUBTYPE AMONG INDIVIDUALS WITH LYNCH SYNDROME: A SYSTEMATIC REVIEW AND META-ANALYSIS

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) is the most prevalent inherited cause of colorectal cancer (CRC), with screening colonoscopies recommended to begin between ages 20 and 25. Few studies report the occurrence of adenomas categorized by mutation subtype in LS. This study aims to aggregate existing data to this end, by meta-analysis methods.

Methods / Clinical Presentation / Preliminary Data: We conducted a literature search across electronic databases such as PubMed, Embase, MEDLINE, and Web of Science For full-text screening, we selected only those articles that provided longitudinal screening and/or surveillance data on adenoma occurrence by LS mutation subtype for analysis. Standard meta-analysis methods were followed using random-effects models, and I2% statistic was used to study heterogeneity.

Results / Discussion / Project Plan and Timeline: The initial search identified 2,237 studies, with 1,781 undergoing abstract screening. Ultimately, 34 articles were eligible for full-text screening, and 4 provided relevant data for statistical analysis. Two of the studies were prospective and two were retrospective, comprising a total of 1,776 patients included in the meta-analysis. Most participants had either MLH1 (n=755) or MSH2 (n=746) mutations. Over half (55.7%) of the study participants were female and the mean age at baseline colonoscopy was 41.5 years. The pooled occurrence of adenoma in LS individuals with MLH1 mutation was 27.9% (95%CI [12.6 - 51], I2=96%), with MSH2 mutation was 43.8% [33.7-54.5], I2=79%, with MSH6 mutation was 43.9% [35 - 53.1], I2=34% and with PMS2 mutation was 40.6% [26.1 - 56.9], I2-34%. The pooled values are summarized in Table-1. There was not enough data on EPCAM mutation to calculate pooled values.

Conclusions / Requirements for Collaboration: This meta-analysis reports the first ever pooled occurrence of adenomas in individuals with LS. Individuals with MSH6 mutation demonstrated adenoma detection as high as 43.9%, followed by MSH2 mutation at 43.8%. Future research is warranted to ascertain the colonoscopy surveillance interval in individuals with LS.

Keywords: Lynch syndrome, cancer, polyp, adenoma

Table: Pooled occurrence of adenoma by Lynch syndrome mutation subtype

Sub-group of Lynch syndrome patients	Pooled occurrence of adenoma (95% confidence interval)	I2% heterogeneity
MLH1	27.9% (12.6 - 51); 4 studies	96%
MSH2	43.8% (33.7 - 54.5); 4 studies	79%
MSH6	43.9% (35 - 53.1); 3 studies	34%
PMS2	40.6% (26.1 - 56.9); 2 studies	0
EPCAM	not enough studies to pool	-

P-049 LYNCH SYNDROME PATHOGENIC VARIANT PREVALENCE IN A POPULATION BIOBANK: ANALYSIS OF RESULTS FROM THE COLORADO CENTER FOR PERSONALIZED MEDICINE BIOBANK

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) due to pathogenic variants (PV) in MLH1, MSH2, MSH6, PMS2, or EPCAM, is the most common cause of inherited predisposition to colorectal, endometrial, and other LS related cancers. Most descriptions of LS incidence and cancer risks are from cancer-based population registries. We describe the incidence of LS-related PV in our population-based biobank using research data from Whole Exome Sequencing and SNP technology. We also describe how this data compares to a calculated estimate from 2017 of 1 in 279 of the population (MLH1 1/1,946, MSH2 1/2,841, MSH6 1/758, PMS2 1/714).

Methods / Clinical Presentation / Preliminary Data: From September 2015 to June 2024, 94,826 samples were collected and eligible for inclusion into the biobank database. Pathogenic/likely pathogenic variants (PV/LPV) in the four LS-related genes on the ACMG 3.2 secondary findings list (MLH1, MSH2, MSH6, PMS2) were included if classified as PV/LPV by an expert panel or multiple ClinVar submitters and had a minor allele frequency <0.01. Rare or private variants were not identified by our process.

Results / Discussion / Project Plan and Timeline: A total of 225 LS PV/LPV were identified: 33 MLH1(14.7%), 22 MSH2 (9.8%), 85 MSH6 (37.8%), 85 PMS2 (37.8%).

Conclusions / Requirements for Collaboration: In LS cancer-based registries, MLH1 and MSH2 PV are most common (27-41% MLH1, 39-48% MSH2, 13-26% MSH6, 3.8-6.4% PMS2). In our biobank, we identified more PV in MSH6 and PMS2 (37.8%, 37.8%) and fewer in MLH1 and MSH2 (14.7%, 9.8%). This finding aligns with the higher population prevalence of MSH6 and PMS2 PV calculated in 2017, and supports the higher prevalence of Constitutional Mismatch Repair Deficiency (CMMRD) related to biallelic PV in MSH6 or PMS2. Our biobank shows a lower LS PV incidence (1 in 421) than the 2017 estimate (1 in 279). Ongoing population biobank studies will help refine LS incidence, an important goal for future research.

Keywords: Lynch syndrome, biobank, population-based biobank, MLH1, msh2, msh6, PMS2

P-050 UNIQUE CHARACTERISTICS OF LYNCH SYNDROME-ASSOCIATED MISMATCH REPAIR-DEFICIENT COLORECTAL INTRAMUCOSAL CARCINOMA

General Research - Lynch syndrome

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Background and Aim: Colorectal intramucosal carcinoma (IMC) has been increasingly recognized in patients with Lynch syndrome (LS), but its pathologic features have not been studied. This study aims to characterize the clinicopathologic features and immunophenotypes of LS-associated mismatch repair (MMR)-D IMCs.

Methods / Clinical Presentation / Preliminary Data: Pathology database between 2004 – 2024 was searched for colorectal IMC. Pathology material and medical charts were reviewed and immunostains for MMR proteins, CK7, CK20, CDX2, SATB2, and b-catenin performed. Data were compared with student's t test and Fisher Exact test.

Results / Discussion / Project Plan and Timeline: 31 colorectal IMCs were included: 9 LS-associated MMR-D IMCs (study group), 5 sporadic MMR-D IMCs (control group 1), and 17 MMR-P IMCs (control group 2). Patients in study group were 10 years younger, were more likely to have prior malignancies, and had shorter colonoscopy interval when compared to control groups ($p<0.05$) [Table 1]. Most patients present with polyps and location of polyp and size of adenomas were comparable between study and control groups ($p>0.05$). LS-associated MMR-D IMCs were larger, occupied larger area of adenoma, more frequently grew between normal glands, showed medullary and mucinous differentiation ($p<0.05$ for all). Expression of CK7, CDX2, SATB2 were comparable between the study and control groups ($p>0.05$). LS-associated MMR-D IMCs were less likely to express CK20 than the control ($p<0.05$). Three (of 8, 37.5%) LS-associated MMR-D IMCs showed b-catenin nuclear immunoreactivity independently of MMR gene involved, histologic features, or CK20 expression ($p>0.05$ for all) [Table 2].

Conclusions / Requirements for Collaboration: LS patients with MMR-D colorectal IMC were younger, more often had prior malignancies, and shorter colonoscopy interval. LS-associated MMR-D IMCs were larger and more infiltrative despite comparable polyp size and configuration. Most LS-associated MMR-D IMCs lacked CK20 expression and 37.5% had nuclear β-catenin immunoreactivity. The findings support a fast adenoma to carcinoma progression and suggest involvement of APC/Wnt pathway in LS tumorigenesis.

Keywords: beta-catenin, cytokeratin 20, intramucosal adenocarcinoma, Lynch syndrome, medullary carcinoma, mismatch repair deficiency

P-051 UNRAVELING DIFFERENCES IN THE COLONIC MICROBIOME IN MSH6 AND PMS2 LYNCH SYNDROME CARRIERS

General Research - Lynch syndrome

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Background and Aim: Individuals with Lynch syndrome (LS) have up to a 60% lifetime risk for colorectal cancer (CRC). Monitoring microbiome changes may offer a novel CRC screening method, as fluctuations in microbiome stability, or dysbiosis, may indicate preneoplastic lesions or CRC. To utilize the microbiome as a potential screening technique, we must first understand and identify intrinsic differences in microbiome composition across LS. This initial study characterized the colonic microbiome of MSH6 and PMS2 previvors using at-home stool collections.

Methods / Clinical Presentation / Preliminary Data: Participants were consented as part of The Ohio State University Hereditary and High-risk Gastrointestinal Neoplasia Registry and Biorepository and provided a Zymo DNA/RNA Shield Fecal collection tube for at-home collection. DNA isolation (100ng) was completed using the QIAamp FastStool DNA kit (Qiagen) and sent to Novogene for reads-based shotgun metagenome sequencing and bioinformatic analysis. Taxonomic profiling was performed using MetaPhlAn4, and functional read profiling completed using HUMAnN3, including MetaPhlAn, DIAMOND 0.9.36, and UniRef and ChocoPhIAn databases. Statistical significance was set at $p<0.05$.

Results / Discussion / Project Plan and Timeline: Our analyses showed distinct differences in microbial species relative abundance between individuals with MSH6 (N=5) and PMS2 (N=4) pathogenic variants (Figure 1). Individuals with MSH6 had greater species diversity, while PMS2 had a higher abundance of Phocaeicola dorei. Comparing MSH6 and PMS2, the relative abundance of active metabolic pathways were not different, however differences in linear discriminant analysis scores were noted, described in Figure 2. These data show distinct differences in microbiome composition between MSH6 and PMS2. We have sequenced an additional 20 samples; analysis is ongoing.

Conclusions / Requirements for Collaboration: We demonstrated intrinsic differences in microbiome composition in individuals with MSH6 and PMS2 pathogenic variants. Elucidating microbiome differences between LS patients is necessary to exploit changes, or dysbiosis, for CRC detection and provide insight into differential penetrance. This study is a critical step towards the development of a stool-based non-invasive strategy for CRC detection.

Keywords: Lynch syndrome, msh6, PMS2, microbiome, Colorectal Cancer, Hereditary Nonpolyposis Colo, Hereditary Nonpolyposis Colorec

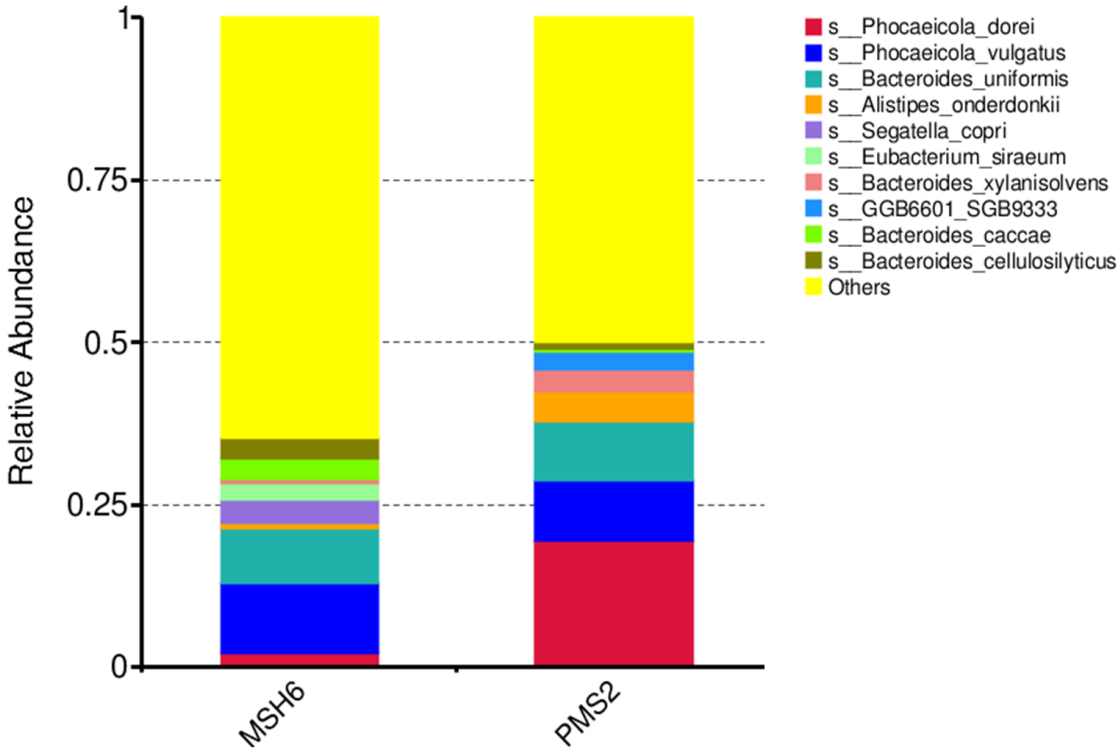

Figure 1. *MSH6* (N=5) and *PMS2* (N=4) relative species abundance. Notable differences in species abundance and type were observed between genes.

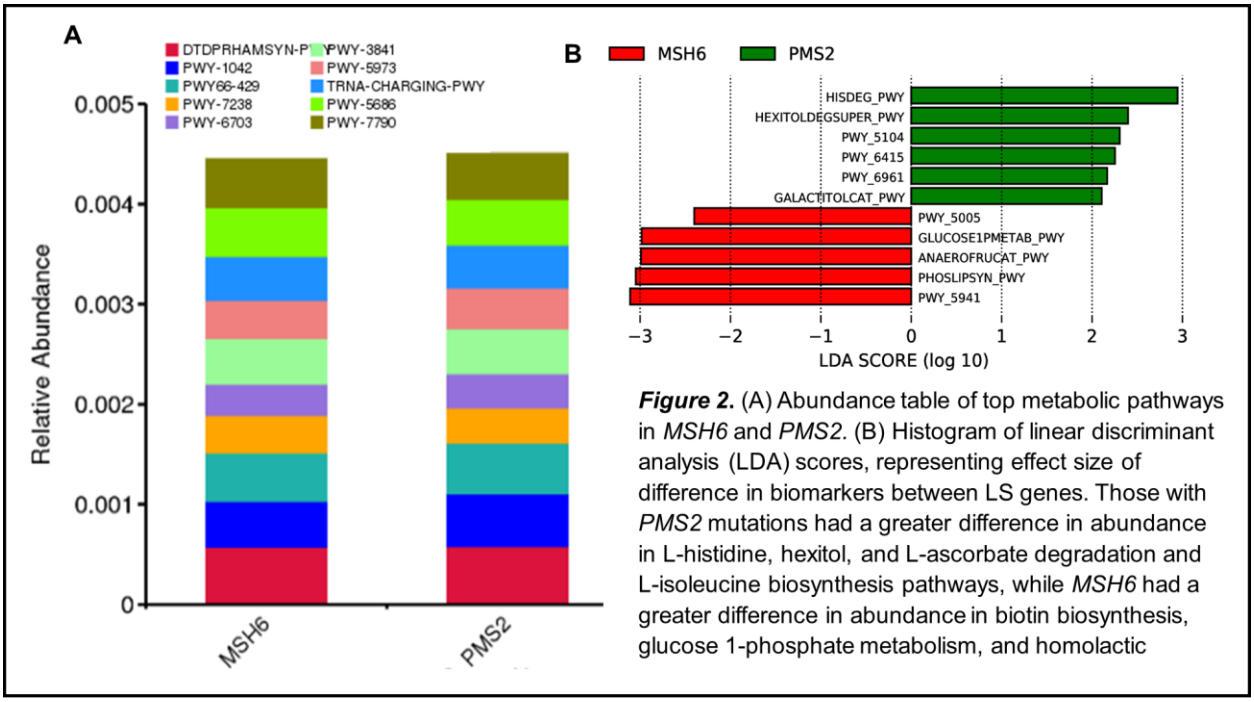

Figure 2. (A) Abundance table of top metabolic pathways in *MSH6* and *PMS2*. (B) Histogram of linear discriminant analysis (LDA) scores, representing effect size of difference in biomarkers between LS genes. Those with *PMS2* mutations had a greater difference in abundance in L-histidine, hexitol, and L-ascorbate degradation and L-isoleucine biosynthesis pathways, while *MSH6* had a greater difference in abundance in biotin biosynthesis, glucose 1-phosphate metabolism, and homolactic

P-052 A RETROSPECTIVE REVIEW OF ASSOCIATED UROTHELIAL MALIGNANCIES WITHIN A LYNCH SYNDROME POPULATION

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) is a familial, autosomal dominant condition with increased predisposition to multiple malignancies including urothelial cancers: upper tract urothelial carcinoma (UTUC) and bladder cancer. While literature on screening these patients for urothelial cancer is limited, a handful of case reports have been published showing surveillance for UTUC is effective in raising detection rate in this population1,2,3. We sought to investigate risk factors for development of urothelial cancers in this patient population to improve early screening and detection, particularly given a lack of clear, standardized guidelines nationally.

Methods / Clinical Presentation / Preliminary Data: We conducted a retrospective review of individuals with LS seen at a multidisciplinary cancer genetics clinic to quantify diagnoses of urothelial cancers (bladder, UTUC). Parameters assessed included personal history of urothelial cancer, family history, smoking history, TNM stage, age at diagnosis, and baseline method of detection (screening vs symptomatic). Fisher's exact test analysis was performed for categorical comparisons.

Results / Discussion / Project Plan and Timeline: Of 700 individuals with LS, 15 (2%) had a history of urothelial cancer. Average age of diagnosis was 63 years (range 40-81). Approximately half (7/15, 47%) had one or more relatives with urothelial cancer. Individuals with MSH2/MSH6 variants showed significantly increased odds (4.4x; $p < 0.05$) of developing urothelial cancer than those with MLH1/PMS2 variants. 6 cancers were detected through screening and 6 were diagnosed based on symptoms; data on detection method were not available for the remaining 3 individuals. Of the symptom-detected patients, 3 (50%) had negative baseline screening before developing urothelial cancer. 6 patients had other urologic primaries including prostate (n=5) and kidney (n=1).

Conclusions / Requirements for Collaboration: Individuals with MSH2/MSH6 pathogenic variants were significantly more likely to develop urothelial cancer, comprising nearly 90% of the cases in this selected cohort. Nearly half of these had a family history of urothelial cancer. More aggressive surveillance of this sub-population may be warranted.

Keywords: Lynch syndrome, Colorectal Cancer, Urologic Cancer, screening

P-053 ADENOMA INCIDENCE TRENDS BY GENOTYPE IN LYNCH SYNDROME: A RETROSPECTIVE COHORT STUDY OF 318 MD ANDERSON CANCER CENTER PATIENTS

General Research - Lynch syndrome

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Background and Aim: Lynch Syndrome (LS), the most common hereditary colorectal cancer (CRC) syndrome, is associated with elevated adenoma and carcinoma risks. While surveillance guidelines broadly account for mismatch repair (MMR) gene-specific risk, colonoscopy intervals remain largely uniform. This study aimed to assess genotype-specific differences in neoplasia incidence to inform more tailored surveillance strategies.

Methods / Clinical Presentation / Preliminary Data: We analyzed 318 LS patients with pathogenic variants in MLH1, MSH2, MSH6, PMS2 or EPCAM each with ≥2 surveillance colonoscopies between 2015–2025 at MD Anderson Cancer Center, Texas, USA. Individuals with prior colorectal surgery, inflammatory bowel disease, incomplete colonoscopy, or sigmoidoscopy-only exams were excluded. Adenoma (tubular, tubulovillous [TVA], SSA) and advanced neoplasia (advanced adenoma or CRC) rates were assessed over three follow-up visits. Statistical comparisons used Kruskal-Wallis and Fisher's exact tests (α=0.05).

Results / Discussion / Project Plan and Timeline: Among 205 patients with follow-up (median age 43.4, median follow-up 1089 days), tubular adenomas (TA) were observed in 58.8%, sessile serrated adenomas (SSA) in 16.2%, and advanced neoplasia (AN) in 7.8%. Five CRCs (2.4%) were identified overall. MSH2/EPCAM carriers (n=79) had the highest neoplasia burden, with TA in 57.0%, SSA in 20.3%, and 3 of 5 CRCs. MLH1 carriers (n=50) had TA in 43.4%, SSA in 2.0%, and 2 CRCs (4.0%). PMS2 (n=37) had the lowest burden (TA 21.6%, SSA 5.4%) and no CRCs. While per-visit incidence trends were not statistically significant, total adenoma count across genotypes differed significantly ($p<0.05$). Additionally, TA and TVA incidence at first follow-up varied significantly by genotype ($p = 0.036$ and 0.037, respectively).

Conclusions / Requirements for Collaboration: These findings reveal significant genotype-specific differences in cumulative adenoma and CRC burden among LS carriers. While MSH2/EPCAM and MLH1 carriers exhibited the highest neoplasia rates, PMS2 carriers demonstrated consistently low lesion and cancer incidence. These results support the need for genotype-based surveillance strategies to reduce unnecessary procedures while preserving cancer prevention.

Keywords: Lynch syndrome, colonoscopy, mismatch repair genes, cancer prevention, adenomas

Table 1: Neoplasia Outcomes by LS Genotype (*n* = patients with ≥1 follow-up)

Genotype	*n* (%)	TA (%)	SSA (%)	AN (%)	CRC (%)
MLH1	50 (24.4)	43.4	2.0	6.0	4.0
MSH2/EPCAM	79 (38.5)	57.0	20.3	5.1	3.8
MSH6	39 (19.0)	38.5	12.8	10.3	0.0
PMS2	37 (18.0)	21.6	5.4	2.7	0.0

P-054 ENDOMETRIOSIS AND ECTOPIC ENDOMETRIAL CANCER IN LYNCH SYNDROME

General Research - Lynch syndrome

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Background and Aim: Endometriosis, the presence of endometrial tissue outside of the uterus, affects an estimated 10% of females of reproductive age. Although the malignant transformation rate is low (~1%), the clinical implications are significant. To our knowledge, there are no data on whether inherited risk for endometrial cancer (EC), such as Lynch syndrome (LS), impacts the risk for endometriosis or ectopic EC. We aimed to identify the prevalence of endometriosis and incidence of ectopic EC in our patients with LS.

Methods / Clinical Presentation / Preliminary Data: Adult females with LS were identified from an institutional genetic testing registry. Surgical history was obtained from the electronic medical record. Patients were identified as having endometriosis only if it was described in a surgical pathology report.

Results / Discussion / Project Plan and Timeline: Among 385 female patients with LS, 252 underwent gynecologic surgery and 180 had pathology reports available for review. Endometriosis was identified in 29% (52/180) of surgical samples. Of those with endometriosis, 27 (51%) were diagnosed with eutopic EC and 2 (4%) developed ectopic EC. One case of ectopic EC encircled the rectosigmoid colon; the second was confined to an ovarian endometrioma. Overall, 85 cases of EC were identified. EC was diagnosed in 56% (29/52) of patients with endometriosis and 44% (56/128) of those without (p=0.1, NS).

Conclusions / Requirements for Collaboration: LS patients in our cohort had a threefold higher prevalence of endometriosis compared to general population estimates. While endometriosis is a known risk factor for EC, there was no statistically significant increase in EC incidence in LS patients with endometriosis. The malignant transformation rate remained low. Although limited by sample size, these data suggest ectopic EC remains a rare but serious risk in patients with LS. Currently, there are no recommendations to screen patients for EC after risk-reducing hysterectomy. Given these data, patients and providers should be aware of the residual risks at extra-uterine endometriosis sites even after hysterectomy.

Keywords: endometriosis, ectopic endometrial cancer, endometri, endometriosis in Lynch syndrome

P-055 A CONSEQUENCE OF UNIVERSAL SEQUENCING OF ENDOMETRIAL CANCER: FINDING HEREDITARY BREAST AND OVARIAN CANCER RISK

General Research - Lynch syndrome

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Background and Aim: As a proof of concept, our institution began a clinical strategy of universal next generation sequencing (NGS) of all patients undergoing hysterectomy for endometrial cancer. This strategy allows for Lynch syndrome screening, tumor classification, and identification of actionable alterations for treatment or clinical trials.

Methods / Clinical Presentation / Preliminary Data: NGS was ordered at the time of evaluating the hysterectomy specimen for pathology. The presence of a somatic pathogenic or likely pathogenic variant (P/LPV) in a gene associated with a hereditary syndrome prompted a referral for germline genetic testing. We investigated the prevalence of somatic P/LPV in BRCA1, BRCA2, and PALB2, as well as rates of referral to clinical genetics services and germline confirmation.

Results / Discussion / Project Plan and Timeline: From January 2020 through April 2024, 54 of 567 (10%) endometrial cancers were found to have a somatic P/LPV in BRCA1, BRCA2, and/or PALB2. 38 of 54 (70%) were referred for genetic counseling/testing, of whom 31 (57%) patients underwent germline genetic testing, and 5 (9%) were confirmed to have a P/LPV in BRCA1 (n=1), BRCA2 (n=3), or PALB2 (n=1). Two patients with BRCA2 had serous endometrial cancer, including one with involvement of the fallopian tube. The patient with BRCA1 had a synchronous high grade serous fallopian tube carcinoma. All three patients with serous histology had personal histories of young onset breast cancer, two of whom had 5 years of exposure to tamoxifen. Three of 5 patients had a family history of breast cancer.

Conclusions / Requirements for Collaboration: In addition to Lynch syndrome, NGS of endometrial cancer may find individuals at risk for other hereditary cancer syndromes, including HBOC, supporting current recommendations to confirm somatic BRCA1/2 and PALB2 P/LPV with germline genetic testing. However, many BRCA1/2 and PALB2 somatic P/LPV are likely passenger variants, associated with hypermutated or ultramutated tumors driven by microsatellite instability or POLE respectively.

Keywords: Endometrial, NGS, Lynch syndrome, HBOC

Table 1: Patients with Somatic BRCA1/2 and/or PALB2

Patient	Histology	TCGA	Somatic Var	VAF%	Germline Var	Age at Dx	Race	Hispanic	Language
No Referral, No Germline									
1	endometrioid	Hypermutated MSI	BRCA2	43		75	White	No	English
2	endometrioid	Hypermutated MSI	BRCA2	47		54	Unknown	Unknown	English
3	endometrioid	Ultramutated POLE	BRCA2	37		45	Other	No	English
4	endometroid	Hypermutated MSI	BRCA2	40		66	Asian	No	English
5	endometrioid	Hypermutated MSI	BRCA1	26		52	White	No	English
6	endometrioid	Hypermutated MSI	BRCA2, PALB2	37, 33		77	White	No	English
7	endometrioid	Ultramutated POLE	BRCA2	31		70	White	No	English
8	endometrioid	MSI low, IHC MMRd	BRCA1	19		56	White	No	English
9	endometrioid	Hypermutated MSI	BRCA1	29		62	Other	Yes	Spanish
10	endometrioid	Hypermutated MSI	BRCA2	14		74	White	No	English
11	endometrioid	Ultramutated POLE	BRCA1	8		55	Other	No	Spanish
12	endometrioid	Ultramutated POLE	BRCA2	40		75	White	No	English
13	endometrioid	Hypermutated MSI	BRCA1	32		51	White	No	English
14	endometrioid	Ultramutated POLE	BRCA2	39		55	White	No	English
15	endometrioid	Ultramutated POLE	BRCA2	14		54	Other	Yes	Spanish
16	endometrioid	Hypermutated MSI	PALB2	23		54	Asian	No	Ilocano
Yes Referral, Not Seen, No Germline									
17	endometrioid	Hypermutated MSI	BRCA2	36		74	Asian	No	English
18	endometrioid	Ultramutated POLE	BRCA1, BRCA2	34, 31		59	White	No	English
19	endometrioid	Ultramutated POLE	PALB2	18		60	White	No	English
20	endometrioid	Copy number low	PALB2	51		67	Black	No	English
Yes Referral, Yes Seen, No Germline									
21	endometrioid	Hypermutated MSI	BRCA2	26		65	White	Yes	English
22	endometrioid	Hypermutated MSI	BRCA2	33		67	Other	Yes	English
23	endometrioid	Ultramutated POLE	PALB2	47		61	White	No	English
No Referral, Yes Germline Negative									
24	endometrioid	Ultramutated POLE	BRCA2	31		54	White	No	English
25	endometrioid	Ultramutated POLE	BRCA2	37		56	White	No	English
26	endometrioid	Hypermutated MSI	BRCA2	39		52	Asian	No	Mandarin
27	endometrioid	Ultramutated POLE	BRCA1	39		53	Asian	No	English
28	serous	Copy number high	BRCA1	41		70	Asian	No	Cantonese
Yes Referral, Not Seen, Yes Germline Negative									
29	endometrioid	Ultramutated POLE	BRCA2	31		60	Asian	No	English
30	endometrioid and serous	Copy number high	BRCA2	35		72	Native American	No	English
Yes Referral, Yes Seen, Yes Germline Negative									
31	endometrioid	Hypermutated MSI	BRCA1	29		59	White	No	English
32	endometrioid	Ultramutated POLE	BRCA2	31		48	White	No	English
33	endometrioid	Ultramutated POLE	BRCA1	13		58	White	No	English
34	endometrioid	Ultramutated POLE	BRCA1	38		64	Asian	No	English
35	endometrioid	Hypermutated MSI	BRCA2	33		51	Other	No	English
36	endometrioid	Hypermutated MSI	BRCA1	29		66	White	No	English
37	endometrioid	Hypermutated MSI	BRCA1, PALB2	15,19		74	White	No	English
38	endometrioid	Copy number high	BRCA2	25		70	White	No	English
39	endometrioid	Ultramutated POLE	BRCA2	35		58	Other	Yes	Spanish
40	endometrioid	Hypermutated MSI	BRCA2, BRCA2	42,13		64	Other	Yes	Spanish
41	serous	Copy number high	BRCA1	14		65	Asian	No	Tagalog
42	endometrioid and serous	Copy number high	BRCA2	14		69	White	No	English
43	endometrioid	Ultramutated POLE	BRCA2	33		59	Other	Yes	Spanish
44	endometrioid	Hypermutated MSI	BRCA2	45		62	Other	Yes	Spanish
45	endometrioid	Hypermutated MSI	PALB2	37		52	Other	No	English
46	endometrioid	Hypermutated MSI	BRCA2, PALB2	48, 26		62	White	No	English
Yes Referral, Yes Seen, Yes Germline Positive									
47	endometrioid	Hypermutated MSI	BRCA2	16	MSH2	46	White	No	English
48	endometrioid	Hypermutated MSI	BRCA2	11	MSH6	55	White	No	English
49	endometrioid	Ultramutated POLE	BRCA2	18	MSH2	59	White	No	English
50	serous	Copy number high	BRCA2	35	BRCA2	52	Asian	No	Mandarin
51	serous	Copy number high	BRCA2	87	BRCA2	68	Other	Yes	Spanish
52	endometrioid	Copy number low	PALB2	47	PALB2	54	White	No	English
53	endometrioid	Copy number low	BRCA2	43	BRCA2	52	Other	Yes	Spanish
Yes Referral, No Seen, Yes Germline Positive									
54	serous	Copy number high	BRCA1	86	BRCA1	58	White	Yes	Spanish

P-056 COLORECTAL CANCER IN LYNCH SYNDROME: MOST CASES DIAGNOSED AT INDEX COLONOSCOPY OR AFTER DELAYED SURVEILLANCE

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) is the most common inherited cause of colorectal cancer (CRC). This study aimed to evaluate the timing of CRC diagnosis in relation to colonoscopy surveillance and LS diagnosis.

Methods / Clinical Presentation / Preliminary Data: We queried our cancer risk registry to identify patients with LS who were also diagnosed with CRC. A retrospective analysis was conducted to review colonoscopy timeline and patient characteristics.

Results / Discussion / Project Plan and Timeline: We identified 36 registry consented patients with a new CRC over the last 10 years. Of 36 patients diagnosed with CRC 29 (81%) were diagnosed with LS after their CRC diagnosis. Among these, 23 (79%) had CRC identified at their first colonoscopy, with 22 presenting symptomatically and only one diagnosed via routine screening. The remaining 6 were diagnosed during a subsequent colonoscopy performed 24–120 months after the prior exam (median: 48 months). Most patients met criteria for genetic testing based on personal or family history, yet were not tested prior to cancer diagnosis. Among the 7 patients with a known LS diagnosis prior to CRC, one was diagnosed on first colonoscopy at age 37, while the remaining 6 were diagnosed during follow-up colonoscopies 13–85 months after their previous exam (median: 51 months). In their prior colonoscopy, all had adequate bowel preparation. Most cancers in this group were Stage 1 (3/7). Only one patient was up to date with surveillance; those overdue typically had more advanced-stage CRC.

Conclusions / Requirements for Collaboration: In this single-center cohort, the majority of CRC cases in LS patients were diagnosed at the time of their initial colonoscopy, typically in the setting of symptoms. CRC in patients already known to have LS was uncommon, and when it did occur, it was generally associated with delays in surveillance. These findings highlight the critical importance of early LS identification and adherence to surveillance guidelines to reduce the burden of CRC.

Keywords: Lynch syndrome, colonoscopy, germline genetic testing, Colorectal Cancer, surveillance, adherence, cancer prevention

P-057 VALIDATION OF A PLASMA BIOMARKER ASSAY FOR FRAMESHIFT MUTATIONS IN LYNCH SYNDROME

General Research - Lynch syndrome

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Background and Aim: We have previously reported the feasibility of detecting frameshift mutations in blood from Lynch Syndrome (LS) patients with tumors and in asymptomatic carriers of variants and further demonstrated that the same biomarker panel was applicable to constitutional mismatch repair deficiency syndrome (CMMRD). This was accomplished by developing a highly sensitive assay using targeted sequencing and a panel of 122 mononucleotide repeat loci. To support future efforts aimed at defining the clinical utility of this panel, we have initiated CLIA validation studies on the assay.

Methods / Clinical Presentation / Preliminary Data: CLIA validation process was established, and SOP has been generated. Samples were procured from various sources with variable storage conditions and processing protocol and sequenced using Illumina NextSeq 2000. Data was analyzed using an Archer Analysis pipeline.

Results / Discussion / Project Plan and Timeline: We have established guidelines for CLIA validation of the assay. The process is ongoing in a CLIA certified lab and is outlined here. The accuracy of the system is being tested using 20 gDNA in a blind fashion with established QC metrics. Precision, comparability, and reproducibility will be tested at different days by different operators to determine the inter-operator variance. The reportable range will be assessed using varying mutational burden associated with LS and positive controls. The reference ranges will also be determined. Analytical specificity/sensitivity including a limit of detection will be assessed. Additional bridging studies will be performed on plasma-derived cell free DNA to complete the validation.

Conclusions / Requirements for Collaboration: The CLIA validated assay can be the basis for technology transfer to other laboratories to define its clinical utility. We will be conducting studies aimed at assessing the potential for early cancer detection, clinical surveillance of disease progression and response to interventions. The biomarker panel may be of particular value in conjunction with vaccine studies targeting frameshift peptides corresponding to loci represented in the panel.

Keywords: Lynch syndrome, CMMRD, Frameshift mutation, Biomarker, CLIA validation

P-058 DEVELOPMENT OF A REGISTRY FOR INDIVIDUALS WITH LYNCH SYNDROME: INFRASTRUCTURE, RECRUITMENT, AND EARLY INSIGHTS

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) – a hereditary cancer syndrome caused by pathogenic germline variants (PGVs) in MLH1, MSH2, MSH6 and PMS2 genes, and EPCAM deletions – causes increased lifetime risk of cancers across multiple organ systems. Longitudinal biospecimen collection correlated with well-annotated clinical data is critical to understanding patient-specific factors that can influence LS cancer risks and ultimately help improve outcomes. The aim of this study is to develop a systematic, serial biospecimen (blood, stool, tissue, urine) bank linked to a clinical data repository to facilitate basic and translational LS-focused research.

Methods / Clinical Presentation / Preliminary Data: The study team and digital health vendor (Vibrent Health) developed the LS Registry portal (www.LSRegistry.org) for electronic consent and modular survey delivery. Prospective participants are offered enrollment at in-person clinical visits/screening procedures, telehealth visits, patient-facing conferences and via mailed outreach. Enrollment is available to both Dana-Farber Cancer Institute (DFCI) and non-DFCI patients. A completed consent activates the administration of baseline surveys and follow-up surveys are released annually from the date of consent. Surveys include demographics, genetic testing, personal and family health history, cancer screening behaviors and diet history using validated measures when available. Participants provide blood and urine specimens at in-person visits with the option of remote phlebotomy.

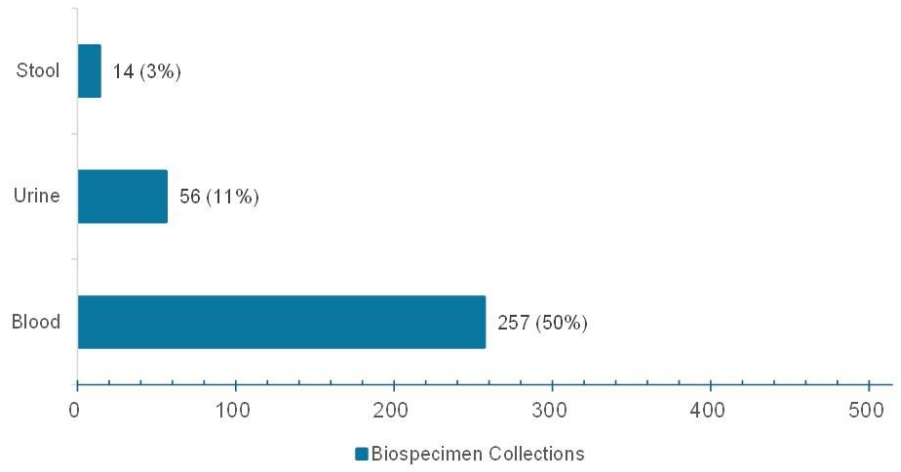
Results / Discussion / Project Plan and Timeline: We have enrolled 523 participants (Table 1): 397 (76%) females, 469 (89%) DFCI patients, average age 53 years; the majority (466, 89%) completed electronic consent. Most participants have MSH6 (153, 29%) and PMS2 (130, 25%) PGVs and 45% (233) have no history of cancer. Baseline survey completion rates range from 35% (diet) to 54% (demographics). Longitudinal survey and biospecimen collection (Figure 1) are ongoing.

Conclusions / Requirements for Collaboration: The modular portal simplified electronic consent, upload of test results, and survey completion with advanced functionality for automated reminders to support participant engagement. Future directions include optimizing survey modules and the deployment of non-English translations.

Keywords: lynch syndrome, recruitment, participant engagement, research biorepository, clinical data collection, data management

TABLE 1. DESCRIPTION OF LYNCH SYNDROME REGISTRY PARTICIPANTS N = 523 (%)	
Female	397 (76)
Age at enrollment in years, mean (SD)	53 (14)
DFCI Participants	469 (90)
Non-DFCI Participants	54 (10)
Race	
American Indian or Alaska Native	1 (0.2)
Asian	17 (3)
Black or African American	5 (1)
White	470 (90)
Unknown or Other	30 (6)
Ethnicity	
Hispanic	10 (2)
Non-Hispanic	467 (89)
Unknown	46 (9)
Pathogenic Germline Variant	
MLH1	99 (19)
MSH2	129 (25)
MSH6	153 (29)
PMS2	130 (25)
EPCAM	12 (2)
Personal history of any cancer	290 (55)
Colorectal	95 (33)
Endometrial	48 (17)
Breast	42 (14)
Ovarian	11 (4)
Prostate	10 (3)
Melanoma	9 (3)
Other	75 (26)

FIGURE 1. BIOSPECIMEN COLLECTIONS*



*Biospecimen collection was initiated over time starting with blood (Aug. 2023), stool (May 2024) and urine (Jan. 2025)

P-059 CLINICAL AND MOLECULAR CHARACTERISTICS OF OVARIAN CANCER IN LYNCH SYNDROME PATIENTS

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) carriers have a higher risk for developing ovarian cancer (OC) than the general population. LS-associated OC (LS-OC) is reported to have a more favorable outcome than sporadic OC. We investigated clinical and molecular characteristics of LS-OC and compared these to sporadic OC.

Methods / Clinical Presentation / Preliminary Data: We queried an institutional data warehouse to identify LS carriers from Brigham and Women's Hospital/Dana Farber Cancer Institute diagnosed with invasive OC between 1984 and 2023 after IRB approval. Clinical data was retrieved from the patients' electronic medical records. Tumor next-generation sequencing data was available for 11 patients with LS-OC, 1,261 patients with high-grade serous OC (HGSOC), and 104 patients with clear cell OC (CCOC) for comparison.

Results / Discussion / Project Plan and Timeline: There were 59 patients identified with LS-OC. The median age of diagnosis was 47 (range 27 - 75 years) compared to 63 in the Non-LS-OC cohort. Most patients identified as White (93%) and non-Hispanic (85%), with pathogenic germline variants in MSH6 (40%), MSH2 (34%), PMS2 (19%), and MLH1 (9%). The most common OC subtypes were endometrioid (26/59, 44%), serous (17/59, 29%) and clear cell (9/59, 15%) and had a poor differentiation (grade 3, 25/59, 43%) Most cancers were diagnosed at an early stage (stage I/II, 36/59, 61%) and had a 5-year survival rate of 72%. LS-OC (n=11) showed a median of 13 mutations (IQR 85) compared to a median of 7 mutations (IQR 5) in 1,897 Non-LS-OC. TP53 mutations were found in 100% of LS HGSOC similar to the 95% of Non-LS HGSOC, and in 67% (2/3) of clear cell LS-OC vs 14% of Non-LS CCOC (15/111).

Conclusions / Requirements for Collaboration: LS-OC is diagnosed earlier, at a younger age, and exhibit a higher mutation burden, suggesting distinct molecular characteristics. These findings emphasize the need to better understand molecular pathogenesis of LS-OC to improve prevention, early detection, and treatment.

Keywords: cancer, Lynch syndrome, hereditary, Ovarian tumor

P-060 EMPOWERING INDIVIDUALS AT RISK FOR LYNCH SYNDROME: USER-DRIVEN DEVELOPMENT OF AN INTERVENTION BOOKLET FOR CASCADE GENETIC SERVICES

General Research - Lynch syndrome

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Background and Aim: Cascade testing for Lynch syndrome remains underutilized, missing opportunities for cancer prevention and treatment. Based on focus group findings, we developed an intervention booklet for at-risk families highlighting implications of family history, testing motivators, steps for genetic testing, and potential costs. To ensure user needs were met, we sought their feedback to guide iterative revisions.

Methods / Clinical Presentation / Preliminary Data: We conducted semi-structured online interviews with recently tested and untested individuals, who evaluated the content, format, and feasibility of the booklet. Two waves of feedback were collected so far (n =13) and critical insights were analyzed.

Results / Discussion / Project Plan and Timeline: Wave 1 participants (7 tested, 1 untested) valued the booklet for addressing questions and providing actionable information, especially the Q&A section with peer stories highlighting top motivators - “lifesaving information,” “personalized medical management,” and “family values.” Participants appreciated the direct yet open-minded tone for informed decision making. They found the inheritance content helpful, though some were confused about risks to extended relatives. Participants were surprised by risks beyond colon cancer and valued understanding gene-specific cancer risks. They resonated with the fear of colonoscopy as a barrier to testing and discussed more emotional barriers. Participants appreciated learning about steps for accessing genetic services and costs, and they requested more screening cost information. Following revisions including adding stories to illustrate fear, anxiety, and guilt in the process, Wave 2 participants (3 tested, 2 untested) mentioned balancing difficult emotions with positivity. Younger participants perceived the family planning content useful. Participants wanted personalized pedigrees to understand their inheritance risks. Among all participants, peer stories were seen as relatable and impactful, though a few found them redundant and suggested tone adjustment. Feedback also led to formatting improvements.

Conclusions / Requirements for Collaboration: User feedback led to iterative improvements in an intervention booklet for cascade testing. We will collect more user feedback from families and healthcare providers.

Keywords: Lynch syndrome, hereditary, genetic counseling, cascade testing, user-centered

P-061 THE LANDSCAPE OF CANCER DIAGNOSES IN PMS2 MUTATION CARRIERS, BY SELF-REPORTED ANCESTRY

General Research - Lynch syndrome

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Background and Aim: PMS2 is a mismatch repair gene associated with Lynch syndrome, and confers an elevated risk for colorectal, endometrial, and possibly other cancers. Estimates of associated cancer risks are nebulous given its low penetrance, especially among diverse populations. Understanding the landscape of cancer diagnoses in diverse populations is important to develop personalized management recommendations for PMS2 mutation carriers.

Methods / Clinical Presentation / Preliminary Data: We performed a retrospective analysis within the Myriad Collaborative Research Registry (MCRR), a registry of de-identified clinical, genetic, and genomic data from 1,277,012 cancer patients tested at Myriad Genetics. We queried the MCRR for patients with PMS2 pathogenic and likely pathogenic variants in cancer patients undergoing germline testing. We then compared the differences in cancer rates between PMS2-positive and PMS2-negative cohorts based on self-reported ancestries.

Results / Discussion / Project Plan and Timeline: PMS2 mutation rates in the White, Black and Asian cohorts were 0.20% (1,502/755,466), 0.08% (91/107,422) and 0.16% (63/38,761), respectively. Colorectal cancer distribution in the PMS2-positive non-Hispanic White, Black, Asian cohorts was higher compared to ancestry-specific PMS2-negative cohorts (White: 4.95-fold; Black: 6.8-fold; Asian: 3.7-fold). Endometrial cancer distributions were higher in the PMS2-positive ancestry-specific cohorts than in the PMS2-negative ancestry-specific cohorts (White: 4.18-fold; Black: 4.48-fold; Asian: 6.41-fold).

Conclusions / Requirements for Collaboration: The distribution of colorectal and endometrial cancers was higher in PMS2 mutation carriers across Non-Hispanic White, Asian, and Black populations. However, the magnitude of difference in cancer distribution for PMS2 mutation carriers varied between the three ancestries. This difference could be explained by multiple factors. For example, the Black and Asian cohorts had fewer patients versus the White cohort. Additionally, social determinants of health may affect the ability of eligible patients to undergo hereditary cancer testing. Multivariate logistic regression is required to determine statistical significance of these differences, but these data emphasize the importance of improved access to genetic testing services in diverse populations.

Keywords: Lynch syndrome, ancestry, PMS2, Endometrial, Colorectal, Race

P-062 EFFICACY OF SMALL BOWEL PROCEDURES AS SCREENING MODALITIES FOR SMALL BOWEL CANCER IN PATIENTS WITH LYNCH SYNDROME

General Research - Lynch syndrome

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Background and Aim: Lynch syndrome (LS) is a hereditary cancer syndrome characterized by an increased risk of colorectal cancer (CRC) and small bowel cancer (SBC)1. The lifetime risk of developing SBC in patients with LS ranges from 0.4-12%, but there are no guidelines regarding SBC screening practices for this population2. In prospective studies, capsule endoscopy appears to be an ineffective small bowel screening method in asymptomatic patients with LS, and enterography has not been investigated for this purpose3. This study aims to examine characteristics of LS patients in our registry who underwent SBC screening, along with trends in SBC screening practices between 2003-2025, to determine efficacy of increased surveillance in this population.

Methods / Clinical Presentation / Preliminary Data: In this single-center retrospective study, 104 patients ≥ age 18 with a diagnosis of LS between 2003-2025 were included. Patients were stratified by if they had either CT enterography, MR enterography, push enteroscopy, or capsule endoscopy at least once and the year they were performed.

Results / Discussion / Project Plan and Timeline: Of 104 patients screened, 31 patients (29.8%) underwent at least one SBP between 2003-2025, with a total of 44 SBPs performed. Of those 31 patients, 1 patient was found to have pathologically confirmed jejunal adenocarcinoma on push enteroscopy, which was performed for diagnostic purposes. Only the MLH1 genotype and personal history of CRC were significantly correlated with SBPs (Table 1). Between 2020-2025, the MSH6 genotype was significantly associated with less SBPs (Table 2). Annual SBC screening trends are shown in Figure 1.

Conclusions / Requirements for Collaboration: This study demonstrates that use of SBPs as a screening modality has increased over the past 5 years at our center, despite having minimal diagnostic yield for SBC. The lack of SBCs detected questions the utility of SBPs as a screening modality in patients with LS. Multi-center prospective data is needed for further investigation, such as part of the LINEAGE Consortium.

Keywords: Lynch syndrome, screening, cancer prevention, small bowel

	Total LS Patients (n=104)	LS Patients Small Bowel Procedures (n=31)	P Value
Male	36 (34.6%)	8 (25.8%)	0.36
Female	68 (65.3%)	23 (74.2%)	0.36
White	91 (87.5%)	28 (90.2%)	0.67
Black	4 (3.8%)	1 (3.2%)	0.87
Other Race	9 (8.7%)	2 (6.5%)	0.69
Personal History of CRC	23 (22.1%)	14 (45.3%)	0.01
Personal History of SBC	4 (38.5%)	1 (3.2%)	0.87
Family History of CRC	85 (81.7%)	27 (87.1%)	0.48
Family History of SBC	4 (3.8%)	0 (0%)	0.27
MLH1	24 (23.1%)	19	0.000061
MSH2	26 (25%)	12	0.14
MSH6	22 (21.2%)	4	0.31
PMS2	21 (20.2%)	4	0.36

SBC Screening with SBPs 2020-2025							
	No SBPs (n=75)	**All SBPs (n=36)**	**CT Enterography (n=11)**	**MR enterography (n=17)**	**Push enteroscopy (n=3)**	**Capsule endoscopy (n=5)**	**P value**
Male	28 (37.3%)	11 (30.6%)	1 (9.1%)	8 (47.1%)	1 (33.3%)	1 (20%)	0.18
Female	47 (62.7%)	25 (69.4%)	10 (90.9%)	9 (52.9%)	2 (66.7%)	4 (80%)	0.18
White	65 (86.7%)	33 (91.7%)	10 (90.9%)	16 (94.1%)	3 (100%)	4 (80%)	0.73
Black	2 (2.6%)	2 (5.6%)	1 (9.1%)	0 (0%)	0 (0%)	1 (20%)	0.33
Other Race	8 (10.7%)	1 (2.7%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0.77
Personal History of CRC	10 (13.3%)	17 (47.2%)	7 (63.6%)	7 (41.2%)	1 (33.3%)	2 (40%)	0.62
Personal History of SBC	1 (1.3%)	4 (11.1%)	1 (9.1%)	2 (11.8%)	1 (33.3%)	0 (0%)	0.54
Family History of CRC	57 (76%)	31 (86.1%)	11 (100%)	14 (82.4%)	3 (100%)	3 (60%)	0.15
Family History of SBC	4 (5.3%)	1 (2.7%)	0 (0%)	1 (5.9%)	0 (0%)	0 (0%)	0.76
MLH1	17 (22.7%)	12 (33.3%)	3 (27.3%)	7 (41.2%)	1 (33.3%)	1 (20%)	0.78
MSH2	15 (20%)	14 (38.9%)	6 (54.5%)	6 (35.2%)	1 (33.3%)	1 (20%)	0.57
MSH6	20 (26.7%)	3 (8.3%)	0 (0%)	1 (5.9%)	0 (0%)	2 (40%)	0.05
PMS2	16 (21.3%)	4 (11.1%)	1 (9.1%)	2 (11.8%)	1 (33.3%)	0 (0%)	0.54
EPCAM	2 (2.7%)	2 (5.6%)	1 (9.1%)	1 (5.9%)	0 (0%)	0 (0%)	0.16

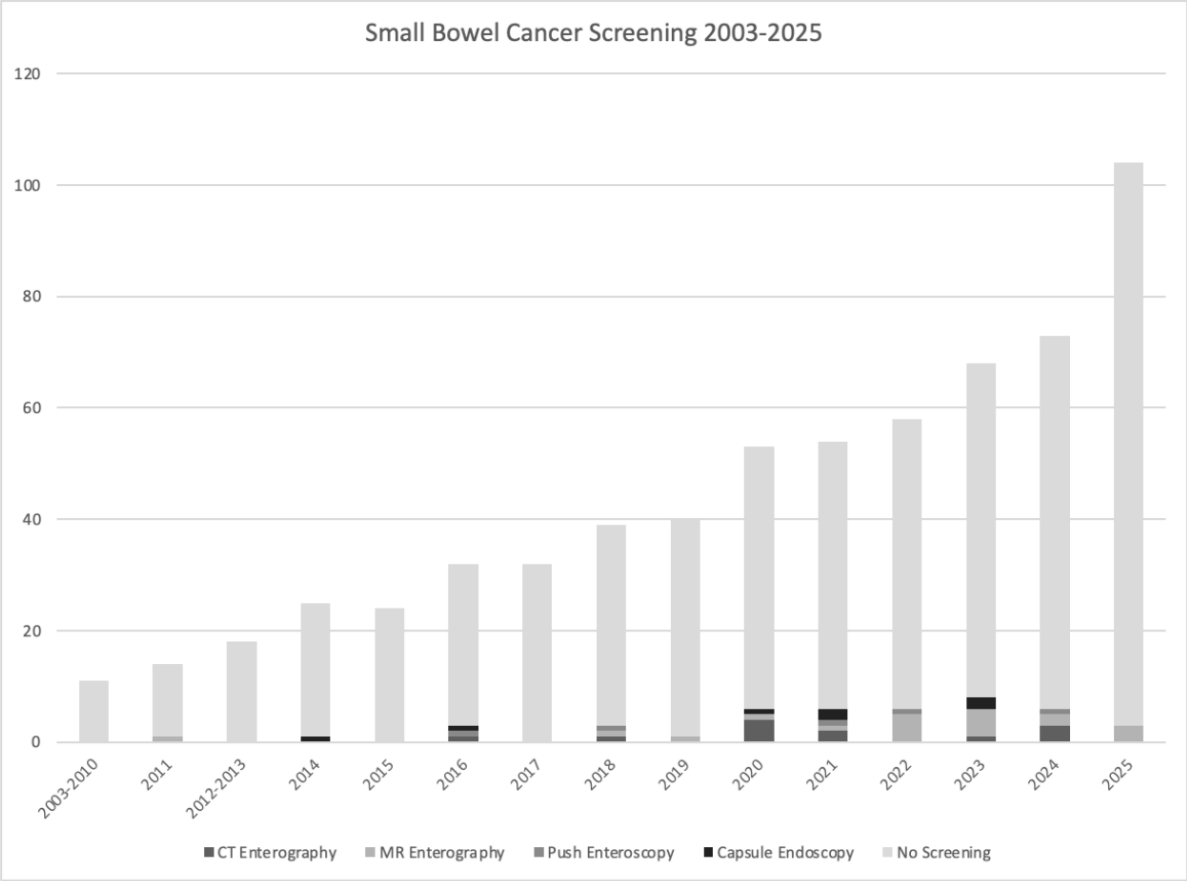

Figure 1: A total of 44 small bowel procedures were performed between 2003-2025, including 12 CT enterographies, 20 MR enterographies, 5 push enteroscopies, and 7 capsule endoscopies. Bars represent cumulative unscreened patients.

P-063 CHARACTERIZATION OF SURVIVAL OUTCOMES FOR DIFFERENTIALLY EXPRESSED FBN1 IN GASTROINTESTINAL CANCERS

General Research - Moderate penetrance genes

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Background and Aim: Collectively, gastrointestinal (GI) cancers account for approximately 26% of all cancer diagnoses and over 35% of all cancer-related deaths worldwide. Differentially expressed FBN1, the gene that leads to Marfan's syndrome, has been shown to promote proliferation and progression of GI tumors.

Methods / Clinical Presentation / Preliminary Data: TCGA COAD, STAD, READ, and ESCA project clinical data and STAR counts for the FBN1 gene were queried. 1,243 patients were separated into high expression (HEG) or low expression (LEG) groups based on median expression levels. Kaplan-Meier survival curves were generated to compare survival between groups based on primary cancer site. These curves were regenerated after regrouping primary sites into colorectal, esophagus, and stomach to achieve higher n values. Univariate Cox Proportional Hazards Models were created for the groups assessing AJCC pathologic stage, M, N, and T, ethnicity, gender, race, primary site, and primary diagnosis.

Results / Discussion / Project Plan and Timeline: Primary colon ($p = 0.00042$), stomach ($p=0.0022$), sigmoid colon ($p=0.015$), and esophagus ($p<0.0001$) cancers had significant Kaplan-Meier curves. After grouping, primary colorectal ($p=0.0005$) and stomach ($p=0.036$) cancers were significant. In univariate Cox analysis, significant factors for HEG were AJCC pathologic Mx (HR 36.2, $p=0.012$) and sigmoid colon (HR 14.6, p-0.039). Significant factors for LEG were White race (HR 0.65, $p=0.033$), ajcc pathologic M1b (HR 12.6, $p=0.013$), N1a (HR 6.56, $p=0.010$), N2 (HR 1.57, $p=0.007$), N3 (HR 1.59, $p=0.079$), and N3b (HR 4.55, $p=0.011$), and esophagus primary site (HR 24.0, $p<0.001$).

Conclusions / Requirements for Collaboration: Differential expression of FBN1 in colon, stomach, sigmoid colon, and esophageal cancer leads to worse survival. High FBN1 expression increases sigmoid colon cancer mortality. Low FBN1 expression may be associated with progression of GI cancer, especially spreading to lymph nodes, and worse outcomes in esophageal cancer. Marfan's syndrome patients may be at increased risk for GI cancers and should be included in future study.

Keywords: gastrointestinal, genetic, FBN1, differentially expressed genes

P-064 REVIEWING ALLEGHENY HEALTH NETWORK'S COLORECTAL ONCOLOGY DEPARTMENT'S REFERRAL RATE TO CANCER GENETICS FOR HEREDITARY COLORECTAL CANCER 2023

General Research - Other

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Background and Aim: Colorectal cancer (CRC) is mostly sporadic, but about 10% are due to hereditary cancer syndromes (HCS). Referral for genetic counseling is essential for patients at risk, as they have different screening, prevention, and treatment guidelines. Previous research shows under-utilization of family history, age of diagnosis, and immunohistochemistry (IHC) in referrals. This study evaluates CRC referral rates for genetic counseling and the rate of positive HCS diagnoses at Allegheny Health Network (AHN).

Methods / Clinical Presentation / Preliminary Data: Data from 451 CRC patients diagnosed at AHN between January 1 and December 31, 2023, were reviewed. Referral practices were assessed based on National Comprehensive Cancer Network (NCCN) guidelines.

Results / Discussion / Project Plan and Timeline: Of the 451 CRC patients, 207 met referral criteria, and 41.5% (86/207) were accurately referred. Patients meeting multiple criteria were 2.66 times more likely to be referred than patients who met one criterion (p-value 2.8 x 10-9), although there was no statistical difference in pathogenic rates (p-value .5202). The least-referred group (3.57%, 1/28) had only a personal history of another HCS-related cancer. Among patients who underwent genetic testing, 24.2% (15/62) had pathogenic/likely pathogenic variants (PV/LPV). Comparing the PV/LPV to the study's CRC population, the PV/LPV rate is 3.33% (15/451).

Conclusions / Requirements for Collaboration: Referral rates were significantly below NCCN recommendations, indicating that improvements in provider referrals are needed. The difference in the number of criteria affecting referral rate suggests that providers may be more aware of a genetic factor when multiple criteria are met. However, because both patient groups have statistically similar pathogenic rates emphasizes that all patients who meet the criteria should be referred. Patients with only a previous history of cancer are the most under-referred group, suggesting that provider knowledge regarding previous cancer history, including non-CRC, is lacking. Lastly, a PV/LPV rate of only 3.33% suggests the majority of HCSs are going undiagnosed in this population.

Keywords: genetic, Colorectal Cancer, hereditary, germline genetic testing, genetic counseling

P-065 COLONOSCOPY FINDINGS AND POLYP PATHOLOGY IN CHEK2 CARRIERS: A SINGLE-CENTER EXPERIENCE

General Research - Other

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Background and Aim: CHEK2 is a moderate-penetrance cancer susceptibility gene implicated in colorectal cancer (CRC) risk. Despite recent guideline shifts recommending average-risk screening for CHEK2 carriers, real-world colonoscopic data remain limited. We conducted a retrospective review to characterize polyp burden, histology, and distribution in CHEK2 pathogenic variant carriers at our institution.

Methods / Clinical Presentation / Preliminary Data: We reviewed data collected from 2011-2024 of individuals with confirmed pathogenic or likely pathogenic CHEK2 variants from our institutional hereditary cancer registry. All available colonoscopy and pathology reports were analyzed. Data included demographics, cancer history, age at colonoscopy, Boston bowel prep score, and polyp features (number, size, morphology, histology, location). Descriptive statistics summarized findings; detection patterns were assessed across successive colonoscopies and stratified by sex and race.

Results / Discussion / Project Plan and Timeline: Among 144 patients with CHEK2 variants, 154 colonoscopies were reviewed. Median age at colonoscopy was 54. Polyps were identified in 51% of patients, most commonly tubular adenomas (28.6%), followed by sessile serrated lesions (10.4%) and hyperplastic polyps (18.3%). Advanced adenomas, defined by villous features, size ≥10 mm, high-grade dysplasia, or cancer, were found in 4.5%. Polyps ≥1 cm were observed in 7.1%, and four colonoscopies had polyps ≥2 cm. CRC was diagnosed in 1.3%. Anatomically, 22.1% had proximal-only polyps, 16.2% distal-only, and 12.3% had polyps in both regions. Detection rates of tubular adenomas and proximal lesions increased with successive colonoscopies. Comparative rates with average-risk screening populations are shown in Figure 1.

Conclusions / Requirements for Collaboration: This single-center cohort of CHEK2 carriers exhibited a moderate polyp burden, with tubular adenomas predominating and low advanced neoplasia and CRC rates. These findings support recent NCCN recommendations to de-intensify CRC screening in this group. However, the presence of proximally located polyps may be useful for endoscopists when conducting average-risk screening and surveillance.

Keywords: genetic, colonoscopy, polyps, chek2, cohort study, high-risk clinic, endoscopy, cancer genetics

Figure 1. Comparison of Colonoscopy findings: CHEK2 Cohort vs. Average-Risk Population

Finding	**Average risk population**	**CHEK2 cohort**
≥1 adenoma	30%[1]	28.6% (44/154)
Advanced adenomas*	5-10%[2]	4.5% (7/154)
Sessile Serrated lesions	5-8%[3]	10.4% (16/154)
CRC prevalence	~1%[4]	1.3% (2/154)

*Advanced Adenomas were classified as having either tubulovillous/villous histology or high-grade dysplasia, an Adenoma ≥ 10mm or confirmed cancer

P-066 UPDATES ON PARENT-OF-ORIGIN DETERMINATION OF PATHOGENIC VARIANTS IN HEREDITARY CANCER GENES WITHOUT PARENTAL DATA IN REAL-WORLD SAMPLES

General Research - Other

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Background and Aim: Assigning the parent-of-origin (PofO) of autosomal variants without parental DNA has long limited both research and clinical practice. Parent-of-Origin-Aware genomic analysis (POAga) overcomes this barrier by integrating chromosome-scale haplotyping with DNA-methylation profiles at imprinted loci, enabling single-sample PofO determination (Akbari, Hanlon et al. Cell Genomics 2023). Blinded testing in retrospective hereditary-cancer cohorts is validating POAga's analytical accuracy, and prospective pilot clinical implementation is informing its utility for variant curation, risk management, and cascade testing in Tier 1 cancer syndromes. Collectively, these efforts are building a real-world catalogue of fully phased, PofO-resolved genomes from individuals carrying pathogenic variants in cancer-susceptibility genes.

Methods / Clinical Presentation / Preliminary Data: Under research-ethics approval, blood samples are being collected from carriers of pathogenic variants in hereditary-cancer genes representing a range of ages, sexes, ethnicities, cancer histories, and known or unknown parental segregation. Strand-seq and long-read whole-genome sequencing are being used to generate haplotypes, phase imprinted-locus methylation, and assign PofO with POAga.

Results / Discussion / Project Plan and Timeline: To date, 250 samples have yielded 255 independent pathogenic variants distributed across 19 genes: BRCA2 (n = 42), BRCA1 (39), MLH1 (27), MSH2 (29), MSH6 (24), SDHD (22), PMS2 (19), PALB2 (14), ATM (13), CDH1 (9), EPCAM (2), SDHAF2 (2), CHEK2 (3), MUTYH (2), TP53 (4), CDKN2A (1), POT1 (1), RAD51D (1), and SDHC (1). PofO was successfully assigned for 221 variants (86.7 %). Concordance with known or reconstructed segregation was 98.6 % (218 / 221). PofO remained unresolved in 34 variants (13.3%), primarily due to polymorphic imprinted methylation or extended runs of homozygosity that impeded phasing.

Conclusions / Requirements for Collaboration: These data support POAga's ability to accurately assign PofO from routine blood samples in hereditary cancer patients. Continued case accrual and method refinement aim to resolve currently unassigned variants, further define real-world performance, and solidify POAga's potential to transform genetic risk assessment, clinical management, and cascade testing.

Keywords: Parent-of-Origin-Aware genomic analysis, long-read sequencing, Strand-seq, methylation, imprinting, phasing, Parent-of-Origin-Aware genomic analysis, long-read sequencing, Strand-seq, methylation, imprinting, phasing

P-067 CASCADE TESTING RATES IN PANCREATIC DUCTAL ADENOCARCINOMA IN A POPULATION-BASED HEREDITARY CANCER PROGRAM

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Universal germline testing (UGT) in pancreatic ductal adenocarcinoma (PDAC) has been recommended since 2018. Once a pathogenic variant (PV) is identified, cascade testing in relatives is essential for delivering the promise of UGT, targeted familial risk assessment and risk reduction strategies. To date, there is limited data on cascade testing in hereditary pancreatic cancer. This study explored rates of cascade testing in a publicly funded, population-based hereditary cancer program in British Columbia, Canada.

Methods / Clinical Presentation / Preliminary Data: Cascade testing rates were measured among 100 sequential unrelated PDAC patients diagnosed between March 2014 and December 2023 with PGVs in genes associated with hereditary pancreatic cancer risk. Testing status for relatives living “in-province” was obtained from the provincial Progeny database and status for relatives “out-of-province” was obtained by chart review of proband self-report and/or medical records.

Results / Discussion / Project Plan and Timeline: Cascade testing occurred in at least one first-degree relative (FDR) in 70% and in at least one second-degree relative (SDR) in 25% of probands. Cascade testing rates were 23.2% among all FDRs (149/641) and 4.2% among all SDRs (60/1434) for an average of 2.09 relatives tested per proband. For 75% of patients, both parents were deceased. Segregation of the PV to one side of the family had been confirmed for 21%. Almost half of patients passed away within 12 months of receiving their genetic test results (n=47).

Conclusions / Requirements for Collaboration: This study provides additional data on cascade testing rates specific to the PDAC population undergoing UGT and underlines the need for new processes to improve timely family communication and to clarify parental segregation once a hereditary cancer risk is identified, particularly given the limited life expectancy of this diagnosis. Further analysis is underway to understand predictors of testing and the impact of new tools in the prospective setting, including clinician facilitated cascade testing and parent-of-origin-aware genomic analysis.

Keywords: cancer prevention, genetic counseling, cascade testing, germline genetic testing, pancreatic cancer

P-068 COMPARISON OF GERMLINE PATHOGENIC VARIANT RATES IN UNAFFECTED INDIVIDUALS WITH SECOND-DEGREE VERSUS FIRST-DEGREE RELATIVES WITH PANCREATIC CANCER

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Individuals diagnosed with pancreatic cancer (PC) have a higher risk of testing positive for a pathogenic variant (PV) in genes associated with PC. In 2018, clinical guidelines recommended germline testing for all individuals with PC and their unaffected first- and second-degree relatives (FDR and SDR). In 2020, guidelines limited testing to only FDR of individuals with PC. This study evaluated the PV rate for individuals unaffected with cancer, with either an FDR or SDR diagnosed with PC, who were referred for hereditary cancer testing.

Methods / Clinical Presentation / Preliminary Data: The study included individuals who had multigene pan-cancer germline testing (25 to 48 genes) between September 2013 and September 2024. Cohorts were separated by whether an FDR or SDR with PC was reported and compared to individuals with a personal history of PC. Individuals with a family history of other cancers or both an FDR and SDR with PC were excluded.

Results / Discussion / Project Plan and Timeline: The FDR and SDR group included 1531 and 2803 individuals, respectively. These were compared to 2153 individuals with PC and no family history of cancer. PV rates were 7.4% in the FDR group and 6.4% in the SDR group, compared to 10.0% for individuals with a PC diagnosis. Excluding monoallelic MUTYH, the highest prevalence of PVs were identified in BRCA2, ATM and PALB2 in the PC cohort; ATM, BRCA2 and CHEK2 in the FDR cohort; and ATM, CHEK2 and APC in the SDR cohort. There was a marked increase in those with a SDR with PC undergoing testing in 2019, followed by a decline, aligning with changes in national guidelines.

Conclusions / Requirements for Collaboration: The PV rate was similar in unaffected individuals with an FDR versus an SDR with PC, providing evidence supporting restoring genetic testing guidelines to include unaffected individuals with a SDR may be appropriate.

Keywords: germline genetic testing, unaffected, pancreatic cancer

P-069 BEYOND BRCA1/2: THE SIGNIFICANT ROLE OF ATM PATHOGENIC VARIANTS IN GENETIC PREDISPOSITION TO PANCREATIC DUCTAL ADENOCARCINOMA IN ISRAELI PATIENTS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: The ATM (Ataxia-Telangiectasia Mutated) gene plays a crucial role in the DNA damage response (DDR). Germline pathogenic variants (PVs) in this gene are associated with increased susceptibility to several cancers, including pancreatic ductal adenocarcinoma (PDAC) and breast cancer. While prior studies have highlighted the prevalence of ATM PVs in familial PDAC and general PDAC cohorts, none has examined this in the Israeli population. Our aim was to determine the prevalence of ATM PVs in an unselected cohort of Israeli PDAC cases.

Methods / Clinical Presentation / Preliminary Data: This study analyzed data from PDAC patients who underwent multigene panel testing (MGPT) at Sheba and Kaplan hospitals in Israel between 2015 and 2024.

Results / Discussion / Project Plan and Timeline: Out of 331 PDAC patients included (59% male; mean age at diagnosis: 63 years; 52% Ashkenazi Jewish descent), seventy germline PVs were identified in 68 individuals across 11 cancer-predisposing genes. Of these, 58 subjects (17.2%) carried mutations in a gene with a known PDAC predisposition (ATM, BRCA1, BRCA2, CDKN2A and MSH6). Additionally, 12 individuals had mutations in genes without established PDAC risk in heterozygous carriers (e.g., APC I1307K variant, BLM, CHEK2, NBN, NSD, NF1). The most commonly mutated genes were BRCA1 and BRCA2, followed by ATM, with ten carriers identified.

Conclusions / Requirements for Collaboration: Overall, 20.5% of PDAC patients carried a PV in a cancer-predisposing gene, and 3.02% carried an ATM PV. These findings align with global studies and represent the largest genetically assessed PDAC cohort in Israel to date. As ATM is a clinically actionable gene with familial implications, it highlights the importance of genetic screening and prevention strategies. While ATM PVs currently lack personalized therapeutic options, ongoing research may reveal future benefits, given ATM's role in the DDR pathway.

Keywords: Pancreatic, ATM, ISRAEL, predisposition, germline genetic testing, multigene panel testing

P-070 RESULTS FROM A SECOND CLINICAL VALIDATION STUDY OF PANCREASURE, A BLOOD-BASED BIOMARKER TEST FOR EARLY-STAGE PANCREATIC CANCER IN HIGH-RISK PATIENTS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Early detection of pancreatic ductal adenocarcinoma (PDAC), has an impact on patient outcomes. Patients with known pathogenic genetic variants (PGV), family history predisposing them to PDAC, or presence of cystic neoplasms should undergo regular surveillance per clinical guidelines. Interval imaging, the current standard of care for these programs, can be costly, burdensome, and often with limited accuracy. We previously conducted a clinical validation (CV) study (CLARITI) where PancreaSure, a serum-based early detection test for PDAC, showed high performance in differentiating early-stage disease versus high-risk control patients. We set out to conduct a second CV study of this test (VERIFI, NCT06947395).

Methods / Clinical Presentation / Preliminary Data: This is a multicenter, case-control, blinded study to investigate the performance of PancreaSure, a blood-based biomarker signature comprising a mathematical summation of ICAM-1, THSB1, CTSD, TIMP1, and CA19-9 values with a predefined cutoff to differentiate Stage I and Stage II PDAC, collected ad hoc, from controls at high-risk due to PGV, family history, or presence of pancreatic cystic neoplasm.

Results / Discussion / Project Plan and Timeline: Serum from 115 Stage I-II PDAC cases and 270 high-risk controls were collected from six US sites (Table 1). PancreaSure sensitivity and specificity was 77% and 88%, respectively. The test had significantly better sensitivity than CA19-9 alone (65%, $p<0.001$). High performance was seen in key sub-populations including patients with diabetes and harboring pancreatic cysts. In a pooled analysis including data from CLARITI, PancreaSure demonstrated 78% sensitivity and 92% specificity in over 1400 patients (317 Stage I and Stage II PDAC cases and 1134 high-risk controls).

Conclusions / Requirements for Collaboration: PancreaSure showed high accuracy in a second multicenter, US-based clinical validation study and in a pooled analysis of existing CV data. These results are additional evidence supporting the robustness of the test's performance and suggests PancreaSure can serve as a tool for early-stage PDAC detection in high-risk patients and in key sub-populations.

Keywords: pancreatic cancer early detection, liquid biopsy, Pancreatic cancer surveillance, pancreatic ductal adenocarcinoma, pancreatic cancer, Biomarker

Table 1. Demographics table of VERIFI study participants

		All Data (N = 386)	Cases (N = 115)	Controls (N = 271)
Age, median (SD) **Range**		67 (8.8) 45 - 88	68 (8.8) 48 - 88	67 (8.7) 45 - 88
Age (Categorical)	< 65	150 (38.9%)	35 (30.4%)	115 (42.4%)
	≥ 65	236 (61.1%)	80 (69.6%)	156 (57.6%)
Gender	Female	209 (54.1%)	56 (48.7%)	153 (56.5%)
	Male	177 (45.9%)	59 (51.3%)	118 (43.5%)
Ethnicity	Hispanic/Latino	20 (5.2%)	6 (5.2%)	14 (5.2%)
	Not Hispanic/Latino	346 (89.6%)	99 (86.1%)	247 (91.1%)
	White	330 (85.5%)	93 (80.9%)	237 (87.5%)
Race	Black/African American	24 (6.2%)	8 (7%)	16 (5.9%)
	Asian	14 (3.6%)	7 (6.1%)	7 (2.6%)
	American Indian/Alaska Native	1 (0.3%)	1 (0.9%)	0 (0%)
***Familial or Genetic Mutation**	Yes	250 (64.8%)	31 (27%)	219 (80.8%)
	No	136 (35.2%)	84 (73%)	52 (19.2%)
Diabetes	Yes	77 (19.9%)	45 (39.1%)	32 (11.8%)
	No	309 (80.1%)	70 (60.9%)	239 (88.2%)
Cystic Lesions	Yes	145 (37.6%)	16 (13.9%)	129 (47.6%)
	No	241 (62.4%)	99 (86.1%)	142 (52.4%)
PDAC Diagnosis	Yes	115 (29.8%)	115 (100%)	0 (0%)
	No	271 (70.2%)	0 (0%)	271 (100%)
Clinical Stage	Stage 1	56 (14.5%)	56 (48.7%)	0 (0%)
	Stage 2	59 (15.3%)	59 (51.3%)	0 (0%)

**Familial: History of first-degree relative/second-degree relative diagnosed with PDAC. Genetic mutation: Carrier of known genetic mutation predisposing PDAC (per NCCN guidelines). PDAC cases were collected ad-hoc. Familial/genetic status of PDAC cases were determined post-hoc. PDAC, pancreatic ductal adenocarcinoma*

P-071 IMPACT OF FAMILY HISTORY OF EARLY-ONSET PANCREATIC CANCER ON AGE OF PANCREATIC DIAGNOSIS IN PATHOGENIC VARIANT CARRIERS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Family history of pancreatic cancer (FHPC) is a risk modifier for individuals with a pathogenic variant (PV) in a moderate penetrance PC susceptibility gene. Most guidelines indicate that surveillance begins at age 50, or 10 years before the earliest age of diagnosis in the family, a rule extrapolated from colon data. We aimed to evaluate the impact of FHPC on age of PC diagnosis (DxAge) and compare detection rates in individuals with FH of early-onset PC ((EoPC), diagnosed <60) using different surveillance initiation timepoints.

Methods / Clinical Presentation / Preliminary Data: Individuals with PC and a PV in ATM, BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6, or PMS2 were identified in the Myriad Collaborative Research Registry. Probands' DxAge and reported FHPC were recorded. T-tests compared DxAge of individuals with and without reported FHPC. For individuals who reported a first-degree (FDR) or second-degree (SDR) relative with EoPC, McNemar's test compared the differences in surveillance detection rates for probands if surveillance had begun at different timepoints.

Results / Discussion / Project Plan and Timeline: Our query identified 1275 individuals with PC and a PV; 220 were excluded because DxAge was unavailable and 18 were excluded because reported FHPC was more distant than SDR, leaving 1037 individuals. At least one FDR/SDR with PC was reported for 235 individuals, while no FHPC was reported for 802 individuals. There was no significant difference in DxAge between individuals with a reported FHPC and those without (Table 1).67 individuals reported a FDR/SDR with EoPC. Table 2 illustrates the differences in surveillance detection rates using different initiation timepoints. Beginning surveillance 10 years before the earliest age of diagnosis in the family would have detected significantly more PC cases than beginning at age 50 (p=0.005).

Conclusions / Requirements for Collaboration: In this cohort, the presence or absence of FHPC alone did not predict DxAge, but accounting for family history of EoPC in surveillance initiation recommendations could be justified.

Keywords: pancreatic cancer, family history, age of diagnosis

Table 1: Average age of PC diagnosis in individuals with and without FH of PC

	No FH	FH					
		FDR/SDR	p-value*	FDR	p-value*	SDR	p-value*
Total cohort n=1037	62.11 (+/-12.14) n=802	63.15 (+/-11.27) n=235	0.239	64.1 (+/-11.28) n=147	0.066	61.58 (+/-11.12) n=88	0.696
HBOC n=910	62.51 (+/-11.90) n=695	63.24 (+/-11.01) n=215	0.423	64.1 (+/-10.89) n=137	0.146	61.72 (+/-11.72) n=78	0.578
ATM n=222							
BRCA1 n=154							
BRCA2 n=461							
PALB2 n=73							
Lynch syndrome n=127	59.53 (+/-13.32) n=107	62.25 (+/-14.04) n=20	0.408	64.00 (+/-16.50) n=10	0.323	60.50 (+/-11.11) n=10	0.825
MLH1 n=11							
MSH2 n=44							
MSH6 n=36							
PMS2 n=36							

Key:
PC: Pancreatic cancer
FH: Family history
HBOC: Hereditary breast and ovarian cancer
FDR/SDR: Individuals who reported at least one affected first-degree or second-degree relative
FDR: Individuals who reported at least one affected first-degree relative
SDR: Individuals who reported any affected first-degree relatives are excluded
*: p-values compare each FH group to the no FH group using t-tests

Table 2: Differences in the number of proband PC diagnoses that could have been detected if surveillance began at different timepoints compared to age of diagnosis in FDR/SDR diagnosed with PC before age 60

Age to Begin Surveillance	Proband diagnoses theoretically detected	p-value*
At age 50	55/67 (82.09%)	
At age of youngest diagnosis in the family	56/67 (83.58%)	0.317
5 years before youngest age of diagnosis in the family	58/67 (86.57%)	0.083
10 years before youngest age of diagnosis in the family	63/67 (94.03%)	0.005

Key:
PC: pancreatic cancer
FDR: first degree relative
SDR: second degree relative
*: p-values compare each proportion to the “at age 50” proportion with McNemar’s test

P-072 SENSITIVITY OF AGE AND FAMILY HISTORY CRITERIA FOR DETERMINING PANCREATIC CANCER (PC) SURVEILLANCE ELIGIBILITY AMONG THOSE WITH HEREDITARY PC RISK

General Research - Pancreatic cancer-related syndromes

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Background and Aim: PC surveillance (PCS) for individuals with pathogenic/likely pathogenic germline variants (PGVs) predisposing to PC is associated with earlier stage at diagnosis and improved survival, compared to historical controls. For those with such PGVs, PCS eligibility has been determined based on family history (FH) of PC and age [Table 1]. For PGV carriers (excluding CDKN2A/STK11), guidelines have required a FH of PC in ≥1 first-/second-degree relatives (FDR/SDR) for PCS eligibility. Limited data have evaluated the sensitivity of these criteria.

Methods / Clinical Presentation / Preliminary Data : We evaluated the sensitivity of age and FH criteria for PCS in the Myriad Collaborative Research Registry (MCRR) and a clinic-based (CB) cohort of PC patients at an oncology clinic at an academic cancer center. Among individuals with PC who had known PGVs found on clinical germline testing, we evaluated which carriers would have been eligible for PCS at the time of PC diagnosis, based on age and FH.

Results / Discussion / Project Plan and Timeline: 10,917 (55.5% female) and 1,523 (49.2% female) PC patients with prior germline testing were evaluated in the MCRR and CB cohorts, respectively (median age at PC diagnosis: 66 years in both cohorts), of whom 928 (8.5%) and 148 (9.7%) harbored PGVs in PC susceptibility genes. Overall, 211/928 (22.7%; MCRR) and 37/148 (25.0%; CB) PGV carriers met both gene-specific PCS criteria [Table 1]. 792/928 (85.3%; MCRR) and 131/148 (88.5%; CB) PGV carriers met gene-specific age criteria for PCS. Among individuals with PGVs in genes requiring FH of PC for PCS, only 196/892 (22.0%; MCRR) and 35/143 (24.5%; CB) fulfilled FH criteria.

Conclusions / Requirements for Collaboration: Most PC patients with PC susceptibility gene PGVs would not have met gene-specific age/FH criteria for PCS. FH of PC has particularly poor sensitivity in identifying PGV carriers who go on to develop PC, demonstrating the need for re-evaluating FH as a criterion for PDAC surveillance eligibility.

Keywords: Hereditary pancreatic cancer, Pancreatic cancer surveillance, Hereditary breast and ovarian cancer syndromes, Lynch syndrome, Pancreatic cancer screening

Table 1

	Met FH criterion of PC in FDR/SDR - n (%)	Met age criterion# - n (%)	Met age and FH criteria - n (%)
MCRR cohort (n=928)			
ATM (n=181)	46 (25.4)	166 (91.7)	43 (23.8)
BRCA1 (n=132)	26 (19.7)	109 (82.6)	24 (18.2)
BRCA2 (n=403)	92 (22.8)	340 (84.4)	80 (19.9)
PALB2 (n=59)	11 (18.6)	48 (81.4)	10 (16.9)
MLH1 (n=11)	4 (36.4)	9 (81.8)	4 (36.4)
MSH2 (n=39)	4 (10.3)	26 (66.7)	3 (7.7)
EPCAM (n=0)	0	0	0
MSH6 (n=32)	4 (12.5)	27 (84.4)	4 (12.5)
STK11 (n=2)	NA	2 (100)	2 (100)
CDKN2A (n=32)	NA	31 (96.9)	31 (96.9)
TP53 (n=24)	4 (16.7)	23 (95.8)	4 (16.7)
Multiple of the above* (n=13)	5 out of 11 (45.5)	11 (84.6)	6 (46.2)
Total:	**196/892 (22.0)**	**792/928 (85.3)**	**211/928 (22.7)**
Clinic cohort (n=148)			
ATM (n=49)	17 (34.7)	44 (89.8)	15 (30.6)
BRCA1 (n=28)	8 (28.6)	26 (92.9)	8 (28.6)
BRCA2 (n=45)	5 (11.1)	38 (84.4)	4 (8.9)
PALB2 (n=13)	3 (23.1)	12 (92.3)	3 (23.1)
MLH1 (n=0)	0	0	0
MSH2 (n=3)	1 (33.3)	3 (100)	1 (33.3)
EPCAM (n=0)	0	0	0
MSH6 (n=1)	0	1 (100)	0
STK11 (n=0)	NA	0	0
CDKN2A (n=4)	NA	4 (100)	4 (100)
TP53 (n=2)	1 (50.0)	2 (100)	1 (50.0)
Multiple of the above* (n=3)	0 out of 2	1 (33.3)	1 (33.3)
Total:	**35/143 (24.5)**	**131/148 (88.5)**	**37/148 (25.0)**

NA: Not applicable

age ≥30 years for *STK11*; age ≥40 years for *CDKN2A*; age ≥50 years for other PC risk genes; or 10 years before the youngest PC in the family

* Multiple genes in the MCRR cohort include *ATM* and *BRCA2* (n=4); *ATM* and *PALB2* (n=3); *ATM* and *BRCA1* (n=1); *ATM* and *CDKN2A* (n=1); *BRCA1* and *BRCA2* (n=2); *BRCA1* and *TP53* (n=1); *BRCA2* and *CDKN2A* (n=1). Multiple genes in the CB cohort include *ATM* and *PALB2* (n=2); *ATM* and *CDKN2A* (n=1).

P-073 COMPARISON OF PANCREATIC FINDINGS ON ABDOMINAL IMAGING FOR HIGH-RISK INDIVIDUALS VERSUS MATCHED AVERAGE-RISK INDIVIDUALS

General Research - Pancreatic cancer-related syndromes

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Background and Aim: Pancreatic cancer screening via MRI/MRCP is recommended for High-Risk Individuals (HRI) with Familial Pancreatic Cancer (FPC) and/or certain pathogenic germline variants (PGVs). Pancreatic cystic lesions (PCLs) are common screening findings. Prior studies suggest PCL prevalence/natural history differences in HRI, but none have compared HRI to average-risk individuals (ARI). Thus, we sought to quantify PCL differences between HRIs and ARI controls.

Methods / Clinical Presentation / Preliminary Data: 317 HRI were age-, sex- and race-matched via random algorithm to 634 ARI undergoing MRI/MRCP between 7/2018-9/2024. Data collected included demographics, genetic/familial factors, and baseline MRI/MRCP outcomes. HRI were classified as FPC or PGV ± PDAC family history. Statistical analysis compared: all HRI versus all ARI; single HRI subgroups vs. matched ARI, and; single HRI subgroups vs. other HRI.

Results / Discussion / Project Plan and Timeline: Overall, HRIs were more likely to have PCLs than ARIs (50.8% vs. 25.7%, $P < 0.001$). FPC HRI were more likely to have PCLs (54.1% vs. 44.4%, $P = 0.049$) and larger average duct diameters (2.5 ± 0.6 mm vs. 2.2 ± 0.44 mm, $P = 0.004$) than PGV carriers. Despite higher prevalence, PCL were smaller in HRI than ARI (7.4 ± 5.7 mm vs. 10.8 ± 12.6 mm; $P = 0.002$). HRI and ARI did not differ regarding worrisome feature incidence (PCL septation and/or thickened wall; duct dilation). No solid lesions were observed.

Conclusions / Requirements for Collaboration: This is the first large study to explore PCL prevalence in HRI versus matched controls with no genetic/familial risks. PCLs are significantly more common in HRIs undergoing MRI/MRCP, compared to matched ARI. All PCLs in HRI were deemed low-risk, with no baseline solid lesions. Future studies should stratify HRI subgroups to determine PDAC predictors (PCL-related, etc.). Future studies should examine the clinical impact of higher prevalence of PCLs in HRIs, and whether this translates to a higher risk of PCL-derived progression or malignancy.

Keywords: cancer, Pancreatic, pancreatic cancer, Pancreatic cancer screening, genetic risk

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