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O-001

General Research » Lynch Syndrom

THE IMMUNE PROFILE OF LYNCH SYNDROME-ASSOCIATED COLORECTAL ADENOMAS PINPOINTS THE MAIN DETERMINANTS OF IMMUNE ACTIVATION

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BACKGROUND:Colorectal cancers in Lynch syndrome (LS) carriers, characterized by microsatellite instability (MSI) and pronounced immune infiltration, can develop via three pathways: progression from mismatch repair-proficient (MMRp) or MMR-deficient (MMRd) adenomas and MMRd crypt foci. We recently reported changes in the immune environment in normal mucosa and carcinomas from LS carriers. Here, we analyzed the LS adenoma immune phenotype and its relation to clinicopathological features with particular focus on its dependence on MMRd/MSI.

METHODS:Gene expression profiling was performed using the Nanostring nCounter technology covering 770 immune-relevant genes. In addition, T cell subtype infiltration was quantified by immunohistochemistry in 153 adenomas from 69 LS carriers. Correlation with clinicopathological parameters such as adenoma size, localization, histopathology, and MMR deficiency status was analyzed.

RESULTS:LS adenomas displayed MMRd/MSI in 72% of lesions, with the lowest proportion in *MSH6* carriers. CD3-positive and CD8-positive T cell densities were significantly lower in MMRp lesions compared to MMRd/MSI counterparts, and in rectal compared to colonic adenomas. Adenomas showed significantly lower CD8-positive and significantly higher FOXP3-positive T cell densities than normal mucosa. Gene expression profiling showed significant differences in immune cell composition between adenomas and normal mucosa. Compared to carcinomas, adenomas showed significantly fewer FOXP3-positive T cells.

CONCLUSIONS:Immune profiling of LS adenomas demonstrates that evidence for an immunosuppressive microenvironment is detectable in most LS adenomas. Significantly different immune profiles between MMRd/MSI and MMRp adenomas indicate that MMRd plays an important role in shaping the local immune environment of emerging adenomas, likely as a result of the MSI-induced neoantigen load.

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Keywords: Lynch syndrome, immune phenotype, adenomas

O-002

General Research » Counseling, Behavioral Health, Psychosocial and Survivorship

WHO FALLS BETWEEN THE CRACKS? GEOGRAPHIC ANALYSIS AND FACTORS ASSOCIATED WITH GENETIC TESTING COMPLETION IN COLORECTAL CANCER PATIENTS

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BACKGROUND:Genetic testing is essential to guide treatment and preventative measures in patients with colorectal cancer. Current genetic testing rates remain suboptimal and may be influenced by geographic factors and the genetic consultation setting. We evaluated the geographic location and genetic consultation setting of colorectal cancer patients seen by a genetic counselor.

METHODS:We performed a retrospective review of patients diagnosed with colorectal cancer who were seen by a genetic counselor from 2016 to 2021 at a single institution in the Deep South. Testing was offered to all patients. Key variables of interest included patient demographics, county of residence, area level social vulnerability index (SVI), and the clinic where genetic counseling was performed. The primary outcome was completion of multigene panel germline testing.

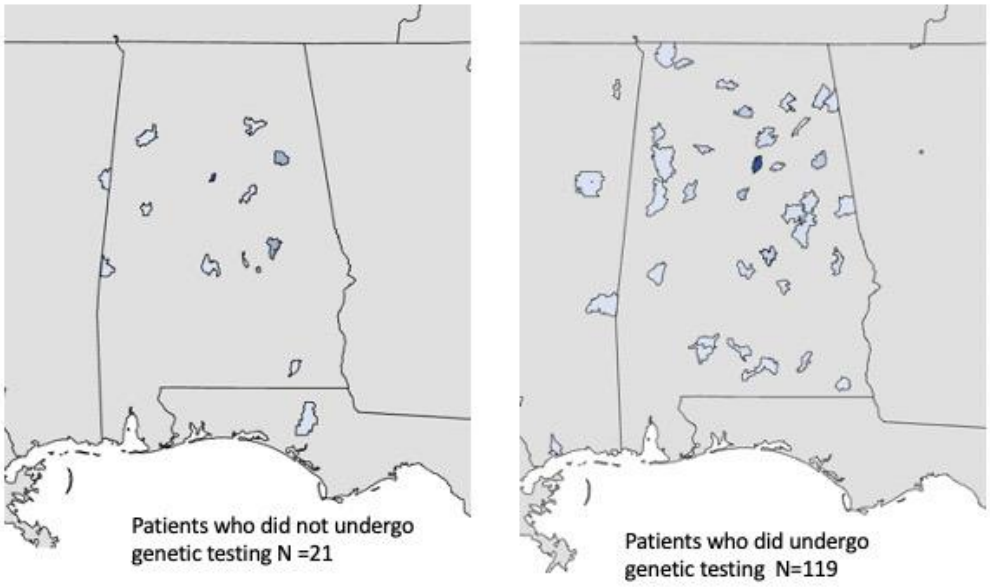
RESULTS:Among 142 patients with colorectal cancer seen by a genetic counselor, the median age was 53 years, 54.9% were female, and 19.0% were Black race. Patients originated from 47 counties across Alabama, Mississippi, and Florida; 27.7% of patients were local (Jefferson County). Genetic testing was completed in 85.2% (N=121). Of those that did not undergo testing, the majority were not local (81% not from Jefferson County) and 24% were from rural counties (Figure). On bivariate analysis, patients who did not complete testing had higher social vulnerability (SVI 0.600) compared to patients who completed testing (SVI 0.504; p=0.04). Patients who had genetic counseling in the genetics clinic were more likely to complete genetic testing (95.8%) compared to patients who were seen over telehealth (82.9%) or in a surgery clinic (63.3%; p<0.01).

CONCLUSIONS:Colorectal cancer patients who did not complete genetic testing after genetic consultation were frequently from non-local areas, and genetic consultation in the genetics clinic was associated with the highest rates of test completion. Better mechanisms to achieve genetic testing for remote colorectal cancer patients are needed.

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Keywords: genetic counseling, geographic analysis, colorectal cancer, genetic testing

Map of Geographic Differences in Genetic Testing



Map of Geographic Differences in Genetic Testing

O-003

Diversity/Equity/Inclusion/Justice » no sub topic

RACIAL DISPARITIES IN TUMOR MICROBIOME IN YOUNG-ONSET AND AVERAGE-ONSET COLORECTAL CANCER

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

BACKGROUND:Young-onset colorectal cancer (yoCRC) is rising alarmingly, with a disproportionate incidence in Black patients as compared to White. We and others have previously shown differences in tumor microbiomes between yoCRC and average-onset colorectal cancer (aoCRC), but it is unknown if these differences contribute to racial disparities. We therefore analyzed racial differences in the intra-tumoral microbiome of CRC in young adults (<50 years).

METHODS:We analyzed 277 samples of CRC patients identified as either non-Hispanic Black or non-Hispanic White, who underwent resection between 2000-2020. Fresh frozen specimens from the primary tumor with paired adjacent nonmalignant tissue were analyzed. The 16s rRNA gene was amplified and sequenced using V4 region primers. Using DADA2, the quality filtered 16S rRNA amplicon reads were clustered and annotated as amplicon sequence variants (ASVs). The abundance count matrix was analyzed for alpha and beta diversity and differential abundance analysis (DAA) using Phyloseq package. Statistical tests included analysis of variance (ANOVA), permutational multivariate analysis (PERMANOVA), linear regression and Wilcoxon test. DAA and correlation analysis were controlled for false discovery rate using Benjamini Hochberg correction.

RESULTS:Differential abundance analysis highlighted key differences in the microbiome composition of Black and White patients with yoCRC. Amongst Black patients, the most prevalent taxa were *Limosilactobacillus, Bacillus, Staphylococcus, Listeria* and *Akkermansia*, whereas amongst White patients the most prevalent taxa were *Enterococcus* and *Escherichia-Shigella* (Table). Microbial profiles were also significantly different between Black patients with yoCRC and aoCRC and between White patients with yoCRC and aoCRC. At ASV level, the microbiome of Black yoCRC is more similar (R2 =0.87) to Black aoCRC, in comparison to white yoCRC (R2=0.57).

CONCLUSIONS:We found significant differences between the intra-tumoral microbiome of yoCRC in the United States by race. Future epidemiologic studies and public health interventions need to account for these differences to reduce risk of yoCRC across various US populations.

Keywords: Young-Onset Colorectal Cancer, Tumor Microbiome, Racial Disparities

Table 1. Most prevalent taxa in Black and White population

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Taxa	Race	p-value	Mean difference between proportion %
Limosilactobacillus	Black	0.007	0.114
Bacillus	Black	0.032	0.100
Staphylococcus	Black	0.001	0.092
Enterococcus	White	0.001	0.043
Escherichia-Shigella	White	0.001	0.012

Table 1. Most prevalent taxa in Black and White population

O-004

General Research » Lynch Syndrome

GENETIC ETIOLOGY OF CONSTITUTIONAL *MLH1* PROMOTER HYPERMETHYLATION: SIXTEEN-YEAR EXPERIENCE FROM A SINGLE DIAGNOSTIC LABORATORY

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BACKGROUND:Constitutional *MLH1* promoter hypermethylation (CMPH) is an infrequent cause of Lynch syndrome with approximately 140 individuals across 100 families described in the literature to date. Most cases are caused by sporadic, primary epimutations without known Mendelian inheritance. A handful of cases, however, arise via secondary epimutation as a result of a germline variant in the promoter of *MLH1*. Our laboratory has performed clinical CMPH testing for sixteen years. Herein, we describe the etiology and phenotype of CMPH within our patient cohort.
METHODS:A retrospective data review was conducted for 390 individuals who underwent CMPH testing at Mayo Clinic Laboratory from 2008-2023. Sanger sequencing of the MLH1 promoter region (GRCh37 chr3:37,034,372-

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

37,035,294) was performed on positive cases.
RESULTS:CMPH was identified in 16% (62/390) individuals, including 60 individuals with Lynch spectrum tumors and 2 asymptomatic individuals with a family history of CMPH. All individuals with CMPH had characteristics consistent with Lynch syndrome: cancer onset ≤50 years of age (71%, 44/62), loss of MLH1 expression (100%, 53/53), tumor hypermethylation (100%, 51/51), WT BRAF (100%, 32/32), and MSI-H (100%, 26/26), additional details described in table 1. CMPH was observed in eleven individuals across five families, consistent with autosomal dominant transmission, suggesting a strong genetic contribution in these families. *MLH1* promoter sequencing identified rare genetic variants in 21% (9/43) of CMPH cases tested, three of which are novel (Table 2).
CONCLUSIONS:*MLH1* sequence variants account for a significant portion of the etiology in individuals with CMPH, highlighting the importance of performing genetic testing that includes the *MLH1* promoter region. The phenotype of individuals with CMPH is consistent with typical *MLH1* Lynch syndrome and may include an increased risk for multiple primaries, highlighting the need of CMPH testing in individuals who meet Lynch syndrome criteria.

Keywords: Constitutional hypermethylation, MLH1 promoter methylation, Epimutation, Lynch syndrome

Table1

Table 1 Characteristics of CMPH testing cohort

		Positive (n=62)	Negative (n=328)
Age	when testing performed, mean, stdev (range)	46.5,12.4 (28-88)	57.8, 15.8 (7-92)
	of first Lynch primary*, mean, stdev (range)	42.1, 11.1 (24-66)	56.9, 14.7 (7-92)
Sex	male, n (%)	28 (23%)	96 (77%)
	female, n (%)	34 (13%)	232 (87%)
Indication	Personal history Lynch tumor, n (%)	55 (16%)	282 (84%)
	Personal history Lynch tumor and family history CMPH, n (%)	5 (71%)	2 (29%)
	Family history CMPH, n (%)	2 (4%)	44 (96%)
Tumor(s)†	Colorectal	53	171
	Endometrial	12	135
	Other Lynch tumor‡	4	24
	Non-Lynch tumor	12	32
# of Lynch primaries	1, n (%)	39 (14%)	242 (86%)
	2, n (%)	15 (29%)	37 (71%)
	3+, n (%)	6 (55%)	5 (45%)

*If age of diagnosis was not provided, age of testing was used
†Each primary was counted, sum will not equal n
‡Other Lynch tumors includes: ovarian/fallopian tube, urothelial, small bowel, pancreas, gastric, and sebaceous primaries

Table2

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 2 Rare *MLH1* variants identified in CMPH cases

Variant	# of cases	gnomAD v3.1.2, alleles (Popmax filtering AF)	Reference
c.-334C>T	1	0/152270 (absent)	This study
c.-256delC	1	0/152186 (absent)	This study
c.-59_-52del	2	0/152282 (absent)	[1]
c.-42C>T	1	15/152252 (0.0001017)	[2,3]
c.[-27C>A;85G>T]	1	0/152228 (absent)	[3-6]
c.-27C>A †	1	0/152272 (absent)	This study
c.27G>A p.(Arg9=)	1	0/152252 (absent)	[3,7]
c.116+106G>A	1	0/152228 (absent)	[7]

†c.85G>T was NOT detected

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O-005

General Research » Pancreatic cancer-related syndromes

OUTCOMES OF THE IMMRAY PANCAN-D™ TEST IN HIGH-RISK INDIVIDUALS UNDERGOING PANCREATIC SURVEILLANCE: PRAGMATIC DATA AND LESSONS LEARNED

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BACKGROUND:An effective blood-based test for pancreatic cancer (PC) surveillance in high-risk individuals has remained elusive. The IMMray PanCan-d is a newly available blood-based test for early detection of PC, however real-world outcomes of this test have not been reported.

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METHODS:We performed a blinded “spike-in” study of 100 individuals who had a IMMray PanCan-d test, including 94 high-risk individuals enrolled in a PC surveillance program with an upcoming EUS scheduled, and 6 individuals with a known diagnosis of PC. All specimens were processed following the commercial laboratory’s standardized operating procedure. For positive predictive value/negative predictive value (PPV/NPV) calculations, disease prevalence was set as 2%.

RESULTS:Cohort characteristics included a median age of 63 [IQR 55-70], 57% female, 96% non-Hispanic White, 57% had PGV in a PC risk gene (BRCA2 most commonly – 18%), 83% with a family history of PC, and 46% with a prior history of cancer (Table 1). Amongst IMMray PanCan-d test results from the 94 individuals undergoing PC surveillance, there was 1 Positive (1%), 7 Borderlines (7%), 73 Negatives (78%), and 13 Tests-Not-Performed due to low CA19-9 expression (14%). Amongst these individuals there were two sub-cm PNETs, 8 IPMNs 1cm or larger, and a sub-cm mass with indeterminate cytology that requires close follow-up, with all of these individuals having Negative IMMray PanCan-d tests. Of the 6 PCs that were spiked in, 4 (67%) yielded a Positive test and 2 (33%) yielded a Negative test. If borderline tests are considered negative test results, the PPV and NPV are 52% and 99% respectively, whereas if borderline tests are considered positive test results, the PPV and NPV are 12% and 99% respectively.

CONCLUSIONS:In real-world practice the IMMray PanCan-d has a robust NPV, however PPV is dramatically influenced by whether Borderline results are characterized as a positive or negative result.

Keywords: Pancreatic cancer surveillance, EUS

Table 1

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1: Characteristics and test results amongst the cohort who underwent IMMray PanCan-d testing

	Total cohort (N = 100)	High-risk individuals without PC (N = 94)	Individuals with PC (N = 6)
Age, median [IQR]	63 [55, 70]	62.5 [55, 70]	68 [58.3, 69.5]
Female sex	57 (57%)	52 (55%)	5 (83%)
White race	98 (98%)	92 (98%)	6 (100%)
PGV in PC risk gene	43 (43%)	41 (44%)	2 (33%)
BRCA1	8	7	1
BRCA2	18	18	0
CDKN2A	7	6	1
ATM	9	9	0
PALB2	4	4	0
STK11	1	1	0
Lynch	8	8	0
>= 1 PGV	2	2	0
Family history of PC	83 (83%)	80 (85%)	3 (50%)
Personal history of non-PC cancer	46 (46%)	43 (46%)	3 (50%)
IMMray PanCan-d test results			
Positive	5 (5%)	1 (1%)	4 (67%)
Borderline	7 (7%)	7 (7%)	0
Negative	75 (75%)	73 (78%)	2 (33%)
Test-Not-Performed	13 (13%)	13 (14%)	0

O-006

Collaborative » no sub topic

DETERMINANTS OF SIGNET RING CELL CARCINOMA IN HEREDITARY DIFFUSE GASTRIC CANCER

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BACKGROUND:Hereditary diffuse gastric cancer (HDGC) poses challenges in management as signet ring cell carcinoma (SRCC) can be indolent and confined to the mucosa (T1a) for years or have a more invasive phenotype. There are no known factors associated with invasive disease, and, therefore, guidelines recommend prophylactic total gastrectomy (PTG) for most patients. The aims of this study are to determine clinical, endoscopic and histologic features associated with either identification of SRCC foci on endoscopy and/or with invasive disease in HDGC patients.
METHODS:Patients with CDH1 pathogenic variants were identified from an academic registry. Clinical, endoscopic, and histological data were collected and compared between individuals with and without SRCC found on endoscopy, and between individuals with localized disease (stage T1a or no cancer) and those with invasive disease (>T1a) found on PTG specimens.
RESULTS:Forty-seven patients were included. Table 1 compares clinical, endoscopic and histological features between patients with and without SRCC found on endoscopy and between invasive and non-invasive disease found on PTG. No clinical or endoscopic features (shown in Figure 1) were associated with SRCC foci or with invasiveness, though a trend towards male sex and older age was noted in the invasive group. Histologically,

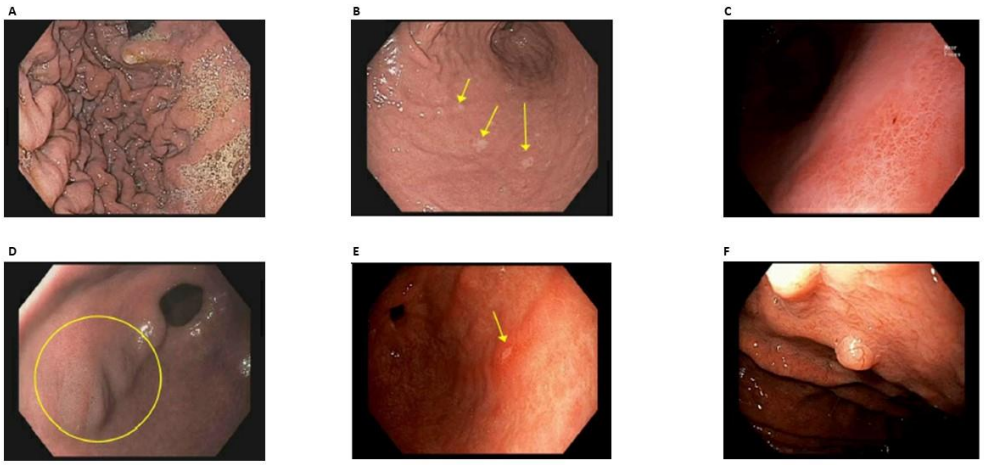
ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

intestinal metaplasia (IM) on biopsies was associated with finding SRCC foci on endoscopy. SRCC found on first endoscopy and IM were associated with invasive disease.
CONCLUSIONS:IM and SRCC on first endoscopy were associated with invasive disease. Older age and smoking might increase risk of invasive disease, but power was limited due to small sample size. Larger, multicenter studies are needed. Currently, 8 US centers have initiated a collaborative retrospective consortium to validate predictors of invasive disease to better risk stratify HDGC patients for surgery or endoscopic surveillance. Additional centers are invited to join and will be provided access to the consortium's REDCap database.

Keywords: Hereditary diffuse gastric cancer, Signet ring cell carcinoma, endoscopic surveillance

Figure 1

Figure 1: Endoscopic features in *CDH1* carriers



A, thickened fundic folds; B, pale mucosal spots (arrows); C, mild erythema (near focus); D, nodularity (circle); E, erosion (arrow); F, polyps

Table 1

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1: Clinical, endoscopic and histologic features in *CDH1+* patients with and without SRCC found on endoscopy and between invasive (>T1a) and non-invasive disease found on surgical specimens

	Endoscopy cohort (n=47)			Surgical cohort (N=20)		
	SRCC on biopsy (n=8)	No SRCC on biopsy (n=39)	p-value	Invasive disease (n=2)	Non-invasive disease (n=18)	p-value
Age at diagnosis (mean +/- SD)	46.1 (+/- 23.0)	45.31 (+/- 13.8)	0.749	61.3 (+/- 1.01)	41.3 (+/- 13.8)	0.063
Male (%)	4 (50)	14 (35.9)	0.692	2 (100)	5 (27.8)	0.111
HDGC clinical criteria met (%)	5 (62.5)	31 (79.5)	0.367	0.367	15 (83.3)	1
# *CDH1+* family members (mean +/- SD)	3.3 (+/- 1.7)	3.7 (+/- 2.4)	0.835	4	3.6 (+/- 2.6)	0.674
# family members with GC (mean +/- SD)	1.75 (+/- 0.5)	1.56 (+/- 1.6)	0.682	3	2.7 (+/- 1.6)	0.589
# SRCC foci on PTG (mean +/- SD)	-	-	-	11	15.5 +/- 17.6	0.941
Smoking (%)	4 (50)	9 (23.1)	0.196	2 (100)	4 (22.2)	0.079
Alcohol use (%)	4 (50)	27 (69.2)	0.209	1 (50)	12 (66.7)	1
# biopsies taken at endoscopy (mean +/- SD)	60.3 (+/- 27.1)	49.8 (+/- 28.3)	0.321	-	-	-
Endoscopic findings (%)						
Thickened mucosal folds	1 (12.5)	1 (2.5)	0.296	1 (50)	0	0.118
Pale spots	2 (25)	12 (30.7)	1	1 (50)	0	0.118
Erythema	4 (50)	16 (41.1)	0.684	2 (100)	7 (38.9)	0.471
Friability	1 (12.5)	0	0.159	1 (50)	0	0.118
Nodularity	1 (12.5)	4 (10.2)	1	1 (50)	1 (5.5)	0.228
Polyp	2 (25)	14 (35.9)	1	0	5 (27.8)	1
Erosions/Ulceration	0	11 (28.2)	0.165	0	7 (38.9)	0.485
Histologic findings (%)						
Intestinal Metaplasia	**3 (37.5)**	**1 (2.5)**	**0.013**	**2 (100)**	**0**	**0.006**
Gastritis	3 (37.5)	24 (61.5)	0.246	2 (100)	10 (55.5)	0.509
Fundic gland polyps	2 (25)	9 (23.1)	1	1 (50)	4 (22.2)	0.468
H. pylori	0	4 (10.2)	0.452	0	2 (11.1)	1
SRCC						
Found on 1st endoscopy	-	-	-	**2 (100)**	**2 (11.1)**	**0.035**
Found on subsequent endoscopy	-	-	-	0	1 (5.5)	1
Multiple foci (>1)	-	-	-	2 (100)	1 (5.5)	0.4

GC – gastric cancer; HDGC – hereditary diffuse gastric cancer; PTG – prophylactic total gastrectomy; SRCC – signet ring cell carcinoma

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O-007

General Research » Other

GERMLINE PATHOGENIC VARIANT PREVALENCE AMONG LATIN AMERICAN AND US HISPANIC INDIVIDUALS WITH GASTROINTESTINAL CANCER OR POLYPS UNDERGOING TESTING

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BACKGROUND:To report on pathogenic germline variants (PGVs) detected among individuals with personal/family history suggestive of a hereditary gastrointestinal (GI) cancer syndrome undergoing multigene panel testing (MGPT) from Latin America and compare them with clinician-reported Hispanic individuals from the United States (US).

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

METHODS:Probands with a personal history of a GI cancer/polyps who underwent clinician-ordered 80+ gene MGPT were grouped according to the ordering clinician's location: US Hispanic (group A), Central America (B), and South America (C). Carriers of a PGV in a gene with autosomal recessive inheritance were excluded from positive rates.

RESULTS:The cohort consisted of 9,915 individuals. PGV rates ranged from 14.9-21.8% (Table). PGV rates were higher in groups B and C compared to A overall, in individuals <50 years, and in those with colorectal cancer or polyps (Table). Rates of variants of uncertain significance were similar between the groups (36.6-39.2%). PGVs in genes associated with Lynch syndrome were the most common finding and identified at higher rates in groups B (8.6%) and C (7.1%) compared to A (4.6%, $p<0.0001$). Group B had higher PGV rates in CDKN2A (2.6%) than C (0.3%, $p<0.0001$) and A (1.1%, $p=0.0063$). Biallelic MUTYH PGVs were observed at a higher rate in group C (1.2%) than A (0.7%, $p=0.0292$). Across all groups, PGVs in other genes were most frequent in APC (1.7-2.4%), ATM (1.3-1.8%), BRCA2 (0.7-1.8%), CHEK2 (0.8-1.1%), and BRCA1 (0.6-1.0%).

CONCLUSIONS:This study highlights the importance of MGPT in Latin American individuals with a personal history of GI cancer/polyps, who can benefit from medical management changes including precision therapies, cancer surveillance and risk-reduction strategies, and cascade testing.

Keywords: colorectal cancer, hereditary gastrointestinal cancer, Latin American, Lynch syndrome, multigene panel testing

Table Latin Am MGPT abstract

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table. Positive rates on multigene panel testing among US Hispanics, individuals from Central America and South America stratified by age at testing and cancer history

	Group A (US Hispanic) N (%)	Group B (Central America^) N (%)	Group C (South America†) N (%)	p value (total cohort) A vs B B vs C A vs C	p value (positive) A vs B B vs C A vs C
Overall **Total cohort** **Positive**	7664 1141 (14.9)	547 119 (21.8)	1704 342 (20.1)		**<0.0001** 0.3945 **<0.0001**
<50* **Total cohort** **Positive**	2922 (38.1) 530 (18.1)	241 (44.1) 74 (30.7)	740 (43.4) 185 (25.0)	**<0.0001** 0.8045 **0.0063**	**<0.0001** 0.0923 **<0.0001**
Colorectal ca **Total cohort** **Positive**	4563 (59.5) 698 (15.3)	287 (52.5) 81 (28.2)	1016 (59.6) 243 (23.9)	**0.0014** **0.0033** 0.9565	**<0.0001** 0.1421 **<0.0001**
Pancreatic ca **Total cohort** **Positive**	1717 (22.4) 240 (14.0)	222 (40.6) 30 (13.5)	448 (26.3) 69 (15.4)	**<0.0001** **<0.0001** **0.0007**	0.9181 0.5641 0.4485
Gastric ca **Total cohort** **Positive**	933 (12.2) 128 (13.7)	39 (7.1) 8 (20.5)	181 (10.6) 21 (11.6)	**0.0003** **0.0163** 0.0753	0.2375 0.1881 0.4768
Colon polyps **Total cohort** **Positive**	1692 (22.1) 313 (18.5)	60 (11.0) 20 (33.3)	295 (17.3) 76 (25.8)	**<0.0001** **0.0003** **<0.0001**	**0.0068** 0.2643 **0.0053**

Abbreviation: ca, cancer
*<50 years at time of testing; ^Bermuda, Bahamas, Costa Rica, Grenada, Guatemala, Honduras, Jamaica, Mexico, Panama, El Salvador; †Argentina, Brazil, Chile, Colombia, Ecuador, Peru, Paraguay, Uruguay, Venezuela

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O-008

General Research » Delivery of Care and Alternative Models

USE OF DIGITAL HEALTH TOOLS WITH POINT-OF-CARE TESTING IMPROVES ACCESS TO GERMLINE GENETIC TESTING WITHIN A GASTROINTESTINAL CANCER CLINIC

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

BACKGROUND:Germline cancer genetic testing could impact the treatment and screening of cancers for patients and their family members; however, many patients who qualify do not get offered such testing. Individually, digital health tools (DHTs) and point-of-care (POC) genetic testing have improved cancer genetic testing access, yet little research has explored the ability of these tools to improve genetic testing access in colorectal cancer clinics. We aimed to assess whether DHT facilitated POC genetic testing improves identification of patients for genetic evaluation and genetic testing uptake in a multidisciplinary gastrointestinal cancer clinic.

METHODS:Before and after study design. Outcomes included the proportion of patients identified for genetic evaluation and consented to genetic testing. In the before group, patients were identified for genetic evaluation by physicians and referred to a genetic counseling clinic to access testing. In the after group, identification and consenting were supported by DHTs, which were administered by genetic counseling assistants, and genetic testing was ordered without referral to a genetic counseling clinic (POC). Data was collected via chart review.

RESULTS:Patients were female (51.8%) with an average age of 61.1 (SD=12.2), white (58.8%) or African-American (39.2%), and non-hispanic/latino (98.0%). In the before group, 6/24 (25%) patients were identified by their care team for genetic evaluation compared to 17/32 (53.1%) patients who were identified by the DHT in the after group (p = 0.03). DHT completion rate was 59.3% (19/32). In the before group, 0/24 (0%) patients consented for genetic testing compared to 8/32 (25%) in the after group (p= 0.02).

CONCLUSIONS:The use of DHTs and a POC genetic testing model improves access to genetic testing within a multidisciplinary gastrointestinal cancer clinic.

Keywords: genetics; colorectal cancer; point-of-care; digital-health-tools

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O-009

General Research » Lynch Syndrome

PATHOGENIC GERMLINE VARIANTS AND LYNCH SYNDROME IN PATIENTS WITH ENDOMETRIAL CANCER ACROSS DIVERSE ANCESTRIES

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

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BACKGROUND:Racial disparities exist in endometrial cancer (EC), with worse outcomes in Black/African American (AA) compared with Non-Hispanic (NH)-White patients. The contribution of ancestry-based variations in germline pathogenic variants (gPVs), particularly Lynch Syndrome (LS), is unknown. We characterized the spectrum of gPVs/LS and genetic counseling in patients with EC by ancestry.

METHODS:Germline assessment of ≥76 cancer predisposition genes was performed in patients with EC undergoing tumor-normal MSK-IMPACT sequencing from 1/1/15-6/30/21. Self-reported race/ethnicity and Ashkenazi Jewish (AJ) ancestry data were used to classify patients into groups. Genetic ancestry was inferred from MSK-IMPACT. Rates of gPV/LS and genetic counseling were compared by ancestry.

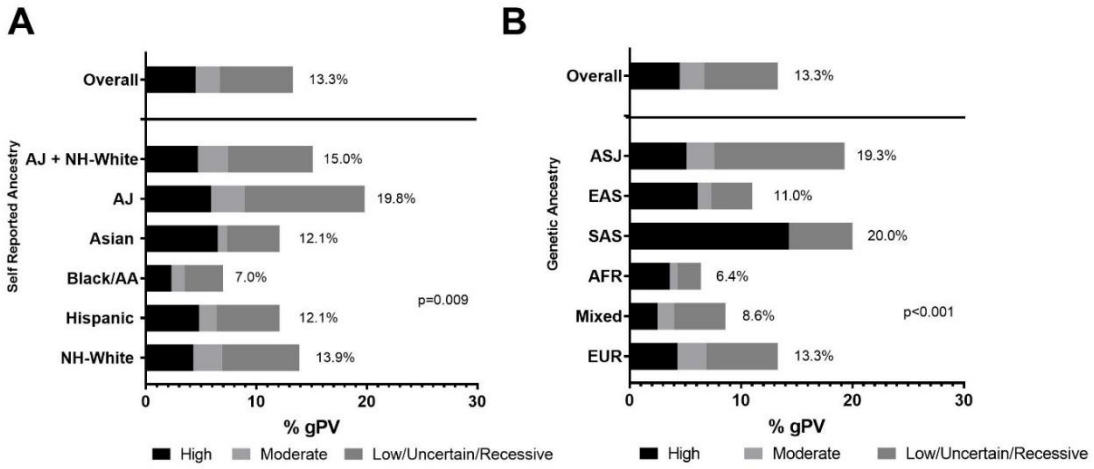
RESULTS:Among 1,625 patients with EC, 216 (13%) had gPV; 39 (2.4%) had LS. Rates of gPV varied by self-reported ancestry (AJ, 40/202 [20%]; Asian, 15/124 [12%]; Black/AA 12/171 [7.0%]; Hispanic, 15/124 [12%]; NH-White, 129/927 [14%]; missing, 77; p=0.009], with similar findings by inferred genetic ancestry (p<0.001). We observed a lower likelihood of gPVs in patients of Black/AA (OR, 0.44; 95% CI: 0.22-0.81) and genetic African (AFR) ancestry (OR, 0.42; 95% CI: 0.18-0.85) and a higher likelihood in patients of AJ genetic ancestry (OR, 1.62; 95% CI; 1.11-2.34) compared with patients of NH-White/European ancestry, even after adjustment for age and molecular subtype. We found low rates of microsatellite instability-high (MSI-H) and enrichment of aggressive copy number-high (CN-H) tumors in Black/AA and AFR patients. Although rates of LS were low overall for Black/AA (1.8%) and AFR (2.9%) patients, this increased when adjusted for MSI-H tumors, Black/AA (8%) and AFR (16%). Among those with newly identified gPVs (n=114), 102 (89%) were seen for genetic counseling, with the lowest rates among Black/AA (75%) and AFR patients (67%).

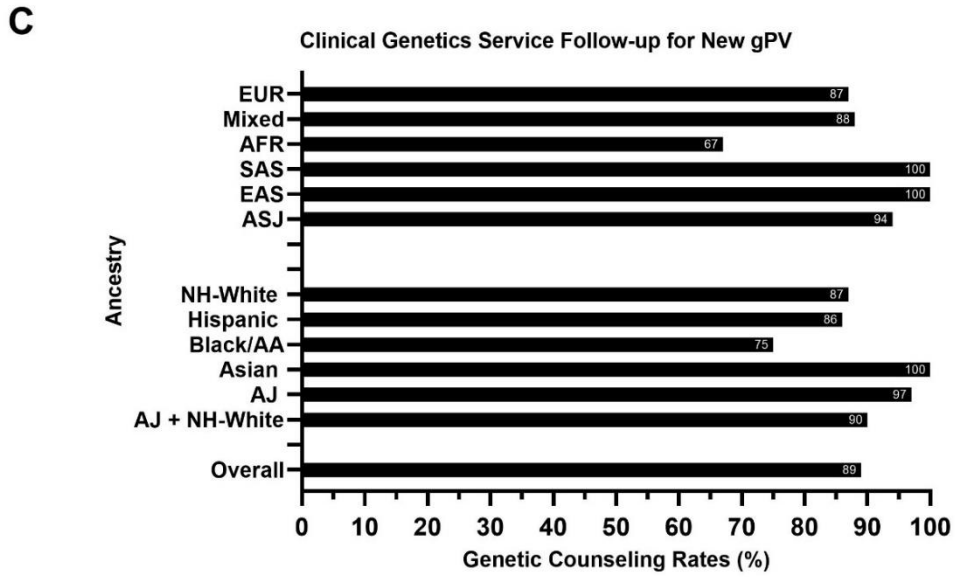
CONCLUSIONS:Rates of gPV, particularly LS, and genetic counseling varied by ancestry, with the lowest rates among Black/AA and AFR patients, potentially contributing to disparities in EC outcomes.

Keywords: endometrial cancer, lynch syndrome, race, ethnicity, ancestry, genetic testing

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Figure 1_Prevalence of Germline Pathogenic Variants and Subsequent Genetic Counseling by Ancestry, Self-Reported and Genetic

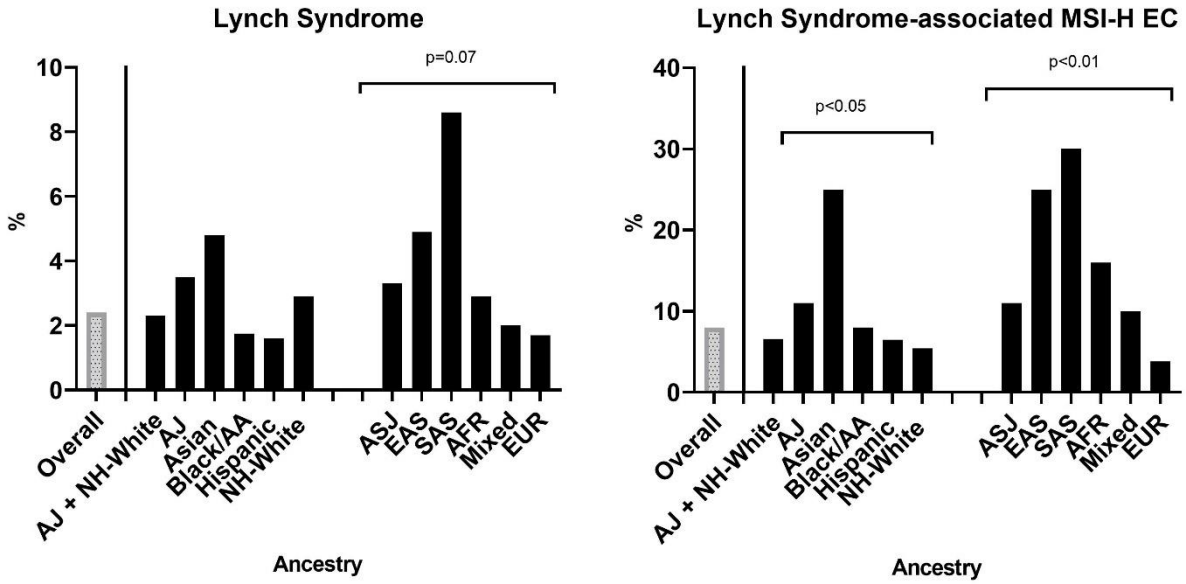




The figure depicts the prevalence of gPVs overall and by self-reported (A) and genetic (B) ancestry, stratified by gene penetrance (high, moderate, low/uncertain/recessive), and rates of subsequent genetic counseling for patients with newly identified gPVs by ancestry, genetic and self-reported (C). Not depicted are 5 patients of NAM genetic ancestry, of whom 2/5 (20%) had 1 high and 1 low/uncertain/recessive gPV. gPV – germline pathogenic variant, AFR – African, EUR – European, EAS – East Asian, NAM – Native American, SAS – South Asian, ASJ – genetic Ashkenazi Jewish, AA – African American, NH – Non-Hispanic, AJ – self-reported Ashkenazi Jewish

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Figure 2_Rates of Lynch Syndrome by Ancestry, Overall and within MSI-H Tumors



The figure depicts rates of Lynch Syndrome overall (A) as well as the proportion driving MSI-H tumors (B) by self-reported and genetic ancestry. Not depicted are 5 patients of NAM genetic ancestry, among whom 1 patient had a BRCA2 gPV. gPV – germline pathogenic variant, AA – African American, AFR – African, EUR – European, EAS – East Asian, NAM – Native American, SAS – South Asian, ASJ – genetic Ashkenazi Jewish, NH – Non-Hispanic, AJ – self-reported Ashkenazi Jewish, MSI-H – microsatellite instability-high,

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O-010

General Research » Moderate penetrance genes

PGT-M FOR HEREDITARY CANCER CONDITIONS - A 12-YEAR TESTING EXPERIENCE AT A SINGLE REFERENCE LABORATORY

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BACKGROUND:Utilization of preimplantation genetic testing (PGT) for monogenic conditions (PGT-M) for

hereditary cancer has evolved.

METHODS:Retrospective analysis of PGT-M for hereditary cancer conditions with concurrent PGT for aneuploidy (PGT-A) performed between 2010-2021 at a laboratory.

RESULTS:PGT-M for hereditary cancer was performed for 501 patients (avg. maternal age 34 years) in 791 in vitro fertilization (IVF) PGT-M cycles: 609/791 (77%) cases had at least one euploid and unaffected embryo; 1604/5690 embryos (28%) were euploid/unaffected.
Eighteen cancer genes were tested in 2010-2015 (T1), with BRCA1, BRCA2, NF1, APC, and TP53 the most common. Forty-five cancer genes were tested in 2016-2021 (T2), with BRCA1, BRCA2, NF1, MSH2, and MLH1 the most common. While genes currently considered to have mild cancer risk (ATM, BARD1, CHEK2, and NBN) were not tested during T1, 14 patients had PGT-M for these genes during T2.
Medical/family history was obtained for 442/501 (88%) patients: 282 (64%) had family history of cancer only, 96 (21%) had personal/family history, 40 (9%) had personal history only, and 24 (5%) had no personal or family history. There was no significant difference in these distributions between T1 and T2.
Thirty-six patients (33 female and 3 male) were referred for IVF with PGT-M after fertility preservation. Of these, 26 patients (72%) had at least one unaffected and euploid embryo on their initial cycle (avg. maternal age 34).

CONCLUSIONS:PGT-M for a wide range of hereditary cancer genes has increased over the past decade. While the most common indications include high risk cancer genes, low/moderate risk cancer genes are also increasingly being referred for testing. This data shows that most patients who undergo PGT-M for a hereditary cancer gene will have at least one unaffected and euploid embryo to transfer. Furthermore, patients pursuing fertility preservation most often have an embryo available for transfer.

Keywords: hereditary cancer testing, genetic testing,

O-011

General Research » Hamartomatous and other polyposis syndromes

CHARACTERIZING GASTROINTESTINAL CLINICOPATHOLOGICAL FEATURES IN CHILDREN WITH *PTEN* HAMARTOMA TUMOR SYNDROME: A BI-INSTITUTIONAL STUDY

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

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BACKGROUND:Gastrointestinal (GI) polyposis is one of the most penetrant features in adults with *PTEN* hamartoma tumor syndrome (PHTS), with affected individuals also having a 17% lifetime risk of colorectal cancer. However, GI phenotypes in children with PHTS are poorly characterized. Thus, we sought to characterize the GI manifestations in children with PHTS and to investigate genotype-phenotype associations.

METHODS:We performed a bi-institutional retrospective chart review of prospectively accrued children with PHTS. Wilcoxon Rank-Sum, Chi-squared, Fisher's exact tests, and multivariable regression were utilized to explore associations between variables.

RESULTS:In this series, 80 patients (60% males) with confirmed *PTEN* variants were included with a median age at consent of 9 years (range 1-21 years). Common GI manifestations included constipation in 41 (51%), feeding issues in 31 (39%), and polyps in 22 (28%). Eosinophilic gastrointestinal disorders (EGIDs) were observed in 5 (6%). Celiac disease, Crohn's disease, and protein losing enteropathy were observed once each. Majority of patients had multiple polyps of mixed histological types. The most common types of polyps observed were fundic gland polyps (7/14, 50%), inflammatory polyps (7/13, 54%), and juvenile polyps (8/15, 53%) in the stomach, small intestine, and colon respectively. EGIDs were observed exclusively in patients without ASD (P = 0.024) and upper GI polyps were associated with decrease odds of ASD (OR, 0.26; P = 0.039). Large *PTEN* deletions/duplications (P = 0.009) and nonsense variants (P = 0.047) were associated with polyps.

CONCLUSIONS:Constipation and feeding issues are common in children with PHTS. Importantly, polyps, comprising of mixed histology, are more prevalent in children with PHTS than previously described. Children without ASD may be predisposed to upper GI polyps and EGIDs. Endoscopic evaluation should continue to be performed in symptomatic children with PHTS, with consideration of closer follow-up in those without ASD.

Keywords: PTEN hamartoma tumor syndrome; autism spectrum disorder; gastrointestinal polyps; eosinophilic gastrointestinal disorders

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Figure 1

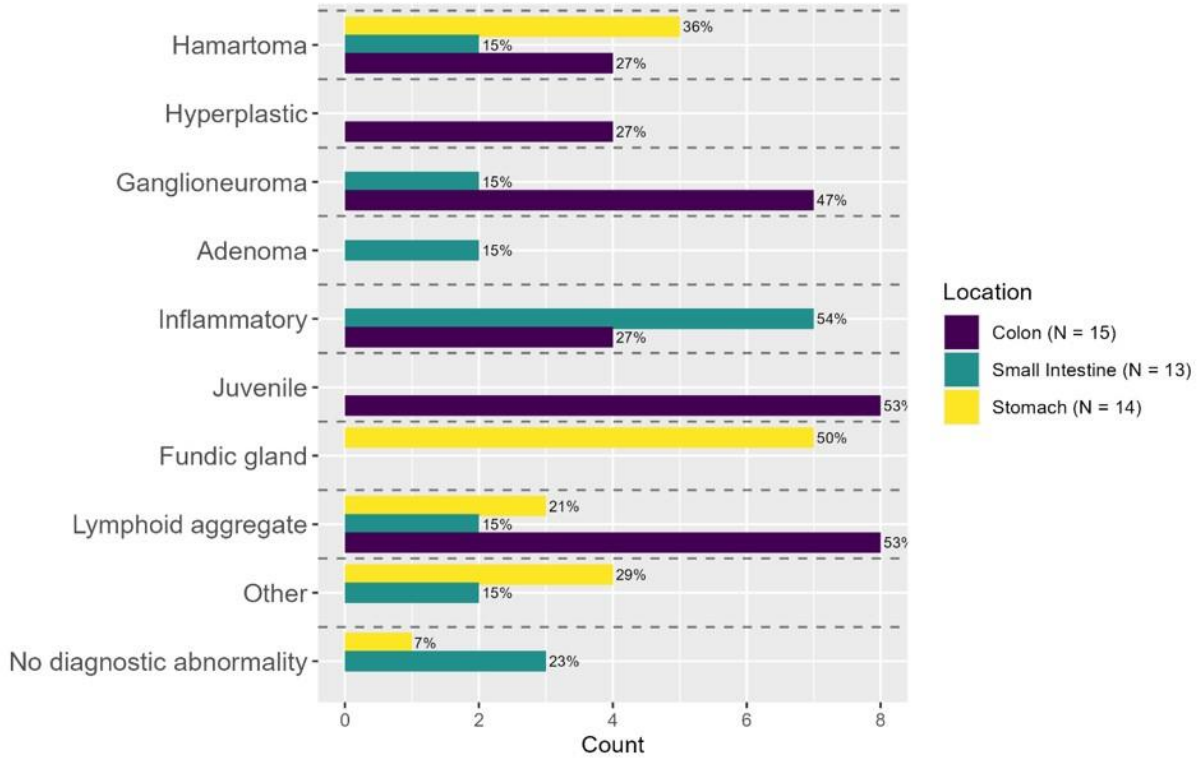

Figure 1. Upper and Lower GI Polyp Histology in Children with PHTS. The grouped bar graph depicts the count (%) for each polyp histology grouped by location, with stomach represented in yellow, small intestine in green, and colon in purple. Note: Hamartomatous, hyperplastic, inflammatory, and juvenile polyps in the stomach were all classified as hamartomatous polyps due to being histologically indistinguishable.

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1

Table 1. PHTS-associated Gastrointestinal Manifestations

Phenotypes	Overall, N = 80[1]	ASD, N = 41[1]	No ASD, N = 39[1]	p-value[2]
# of GI findings per patient	2.00 (1.00, 3.00)	1.00 (1.00, 2.00)	2.00 (0.50, 3.50)	0.5
Symptoms				
Constipation	41 (51%)	24 (59%)	17 (44%)	0.2
Feeding Issues	31 (39%)	16 (39%)	15 (38%)	>0.9
GERD	15 (19%)	7 (17%)	8 (21%)	0.7
Hematochezia	14 (18%)	6 (15%)	8 (21%)	0.5
Confirmed Diagnosis[3]				
Polyps	22 (28%)	8 (20%)	14 (36%)	0.10
UGI polyps	16 (20%)	4 (10%)	12 (28%)	0.074
LGI polyps	15 (19%)	7 (17%)	8 (21%)	0.7
Esophagitis	9 (11%)	4 (9.8%)	5 (13%)	0.7
Gastritis	6 (7.5%)	2 (4.9%)	4 (10%)	0.4
Duodenitis	6 (7.5%)	1 (2.4%)	5 (13%)	0.10
EGIDs	5 (6.2%)	0 (0%)	5 (13%)	0.024
Dysmotility	4 (5.0%)	1 (2.4%)	3 (7.7%)	0.4
Mesenteric lesions	4 (5.0%)	2 (4.9%)	2 (5.1%)	>0.9
Glycogenic acanthosis	2 (7%)	2 (18%)	0 (0%)	0.5
Fatty liver	2 (2.5%)	2 (4.9%)	0 (0%)	0.5
Intussusception	2 (2.5%)	0 (0%)	2 (5.1%)	0.2
Celiac disease	1 (1.3%)	0 (0%)	1 (2.6%)	0.5
Colitis	1 (1.3%)	0 (0%)	1 (2.6%)	0.5
Protein losing enteropathy	1 (1.3%)	0 (0%)	1 (2.6%)	0.5

[1]Median (IQR); n (%)
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
EGIDs, eosinophilic gastrointestinal disorders; GERD, gastrointestinal reflux disease; UGI, upper GI; LGI, lower GI.
[3]Diagnoses that have been verified through clinical, histopathological, imaging or laboratory evaluations

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-012

General Research » Pancreatic cancer-related syndromes

YIELD OF GENETIC TESTING IN PATIENTS WITH A FAMILY HISTORY OF PANCREATIC CANCER IN A PUBLICLY FUNDED HEREDITARY CANCER PROGRAM

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BACKGROUND:Germline pathogenic variants (PVs) are found in up to 15% of individuals with pancreatic ductal adenocarcinoma (PDAC) and National Comprehensive Cancer Network Guidelines (NCCN) have recommended genetic testing in all patients since 2019. Current guidelines extend the germline testing recommendation to individuals with a first degree relative with PDAC, though the frequency and spectrum of PVs have not been well described in this group.
The aim of this pilot was to asses the PV detection rate and impact of the expanded criteria in a publicly funded hereditary cancer program (HCP)..

METHODS:Patients were individuals referred to the HCP; the Progeny database was used to identify all pedigrees that contained both 1) an individual who had panel genetic testing in 2022 and 2) an individual who had pancreatic cancer. Family cancer history and personal medical history were obtained through chart review. Testing was primarily a 76 gene hereditary cancer panel through Ambry Genetics.

RESULTS:Final study population included 221 patients who had >1 first degree relative (n=104) or >1 second-degree relative (n=117) with pancreatic cancer (Figure 1). Self-reported ancestry was Non-European in 22.3% (Table 1). The overall PV rate in the index group was 12.7% (20/157) and PVs in PC-susceptibility genes accounted for the majority. Patients with a personal history of a HBOC/Lynch or other syndrome related cancer

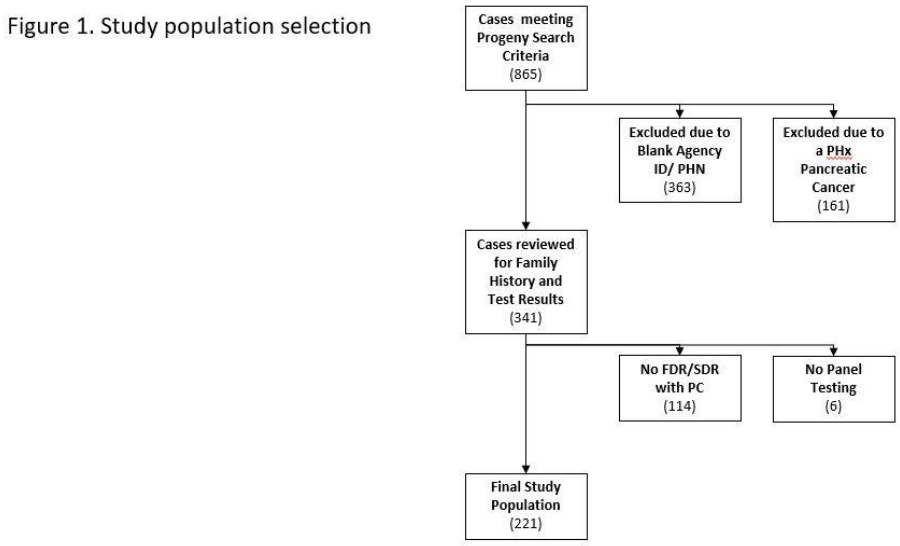
ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

had a significantly higher rate of PVs (17/104= 16.3%) compared to those without (3/53=5.7%, PALB2, MSH2 and CFTR). The rate of actionable pancreatic cancer susceptibility PVs in patients without a personal history of syndrome-related cancers but with a family history of pancreatic cancer was 3.8%.

CONCLUSIONS:As germline genetic testing guidelines contemplate testing in individuals with ≥5% likelihood of carrying a pathogenic/likely pathogenic variant, real world data suggest that testing of first and second degree relatives of patients with PDAC may meet this bar.

Keywords: pancreatic cancer, genetic testing, index testing, pathogenic variant

Figure 1. Study Population Selection



Flow chart showing study population selection

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1. Characteristics of study population

Table 1. Characteristics of Study Population (n=221)

	N	%
Ancestry Reported* • Any European Ancestry • No European Ancestry	 161 36	 81.7 22.3
Personal history of any Cancer	139	62.9
No Personal history of any Cancer	82	37.1
PC in FDR	104	47.1
PC in SDR	117	52.9
FPC kindred	31	14
Index testing	**157**	**71**
Carrier testing	64	29
PV rate overall	48	21.7
PC susceptibility gene PV rate overall PV Gene list:	35	15.8
• ATM	9	
• BRCA2	9	
• PALB2	6	
• BRCA1	3	
• TP53	3	
• CDKN2A	2	
• MSH2	1	
• MSH6	1	
• BRCA1/BRCA2	1	
PV rate in index tests**	20	12.7
PC susceptibility gene PV rate in index tests** PV Gene list:	15	9.6
• ATM	4	
• BRCA2	4	
• PALB2	2	
• BRCA1	2	
• CDKN2A	1	
• MSH2	1	
• MSH6	1	

**n= 197; ethnicity not reported in 24 cases*
***n=157 index tested cohort*
FDR= first degree relative
SDR= second degree relative
PV= pathogenic variant
PC= pancreatic cancer

Table showing characteristics of study population (n=221)

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-013

General Research » Lynch Syndrome

"SHOULD I LET THEM KNOW I HAVE THIS?": EXPERIENCES WITH GENETIC DISCRIMINATION AMONGST PATIENTS WITH HEREDITARY CANCER SYNDROMES

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[8]BC Cancer, Vancouver, Canada; Co-Principal Investigator
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[10]St. Michael's Hospital, Toronto, Canada; University of Toronto, Toronto, Canada; Co-Principal Investigator

BACKGROUND:Hereditary cancer syndromes (HCS) represent approximately 10% of cancer patients. Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (LS) are the most prevalent HCS. Patients are genetically predisposed to developing cancer and require complex care. In addition to medical burdens, many patients are concerned about stigmatization based on their HCS diagnosis; this study aims to describe experiences with genetic discrimination that patients may face.

METHODS:Semi-structured qualitative interviews were conducted with HCS patients residing in Ontario, British Columbia and Newfoundland & Labrador, Canada. All interviewees had a confirmed molecular diagnosis of HBOC or LS. Interpretive description was used to analyze the data.

RESULTS:Across Ontario (n=26), British Columbia (n=23) and Newfoundland & Labrador (n=24), 73 patients with HBOC (n=39) and LS (n=34) were interviewed. Overarchingly, patients worried about whether sharing their HCS genetic diagnosis with others may lead to being judged, stigmatized or discriminated against. Obtaining insurance coverage was of particular concern; patients discussed experiences of being denied coverage, receiving lesser coverage or paying higher fees upon disclosing their HCS status. Patients noted that insurance companies had roundabout ways of soliciting family health and genetic testing history without explicitly asking if an individual was positive for a cancer-associated gene. Beyond the insurance space, patients were also wary of genetic discrimination by employers, family and friends upon sharing their HCS diagnosis. For example, patients did not want employers to question their job performance nor did they want family members to comment on their

appearance after being branded as “sick.” Lastly, many patients were unaware of the Genetic Non-Discrimination Act and expressed interest in learning more about the Act.

CONCLUSIONS:Genetic discrimination is a concern for many HCS patients, especially in terms of insurance coverage impacts. Despite non-discrimination legislation, patients remain uncertain of their rights and wary about sharing their diagnosis with others.

Keywords: genetic discrimination, hereditary cancer syndromes, lynch syndrome, insurance, health policy

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O-014

General Research » Lynch Syndrome

LYNCH SYNDROME (LS) PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) HAVE SIGNIFICANTLY HIGHER INTESTINAL NEOPLASIA RISK THAN LS PATIENTS WITHOUT IBD

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BACKGROUND:Inflammatory bowel disease (IBD) and Lynch syndrome (LS) are both risk factors for colorectal cancer (CRC). Prior research of cancer risk in comorbid IBD and LS has been limited (Table 1), thus it is unclear if these patients have compounded risk due to mucosal inflammation in the setting of mismatch repair deficiency, or require more intensive surveillance. We assessed the prevalence of CRC and EoCRC in LS patients with IBD versus LS alone.

METHODS:We performed a retrospective study of the national Epic Cosmos data set, which includes 205 academic and community centers in the United States using the Epic electronic health record. Cosmos allows aggregate data abstraction based on diagnostic and billing codes. We included those with a billing or encounter diagnosis of LS from 2020 to 2023. We compared baseline characteristics, comorbidities, sociodemographic data, family history, and neoplasia rates in those with LS+IBD vs LS alone using Chi-square tests.

RESULTS:Of 25,873 patients with LS, 567 (2.2%) had comorbid IBD. Patients with LS and IBD were more likely to have a family history of any cancer and a family history of CRC compared to those with only LS (Table 2).

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Compared to LS patients without IBD, LS patients with IBD had a significantly higher prevalence of CRC (12.9% vs 7.7%, p<0.00001), EoCRC (5.1% vs 3.0%, p=0.004), small bowel cancer (2.8% vs 1.2%, p=0.0007), and colorectal polyps (41.6% vs 29.3%, p<0.0001). There was no significant difference in gynecologic or gastric cancer.

CONCLUSIONS:There is a significantly higher prevalence of CRC, EoCRC, small bowel cancer, and colorectal polyps among those with LS and IBD vs LS alone. Future work should focus on potential unique risk factors for neoplasia among LS patients with IBD that may identify a subset of patients who warrant more intensive colorectal surveillance or other risk modifying interventions.

Keywords: Inflammatory Bowel Disease, Lynch syndrome, Epic Cosmos, Colorectal Cancer, Colorectal Polyps, Early Onset Colorectal Cancer

Table 1

Table 1: Existing literature on CRC risk in Lynch Syndrome patients with Inflammatory Bowel Disease (IBD)

Publication	Setting	Overall LS cohort (n)	CRC in LS + IBD (n, %)	CRC in LS Only (n, %)	p-value
Aronson et al. 2010 Hered Cancer Clin Pract	Canada, 1 center 1980-2010	329	1/5 (20%)		
McNamara et al. 2016 Int J Colorectal Dis	Canada, 1 center 1980-2015	12	4/12 (33.3%)		
Derikx et al. 2017 Clin Gastro & Hep	Netherlands, 2 centers 1998-2014	1,046	4/15 (26.7%)	311/1,031 (30.2%)	0.205
Barberio et al. 2022 J Crohn's Colitis	Europe, 13 centers 2022	16	8/16 (50%)		
Faisal et al 2022 World J Clin Oncol	US, 1 center 1979-2019	50	4/7 (57.1%)	23/43 (53.5%)	0.86
Braun & Yen et al 2023 CGA Annual Mtg	US, 205 centers 2020-2023	25,873	73/567 (12.9%)	1,957/25,306 (7.7%)	<0.00001

Existing literature on CRC risk in Lynch Syndrome patients with Inflammatory Bowel Disease (IBD)

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Table 2

Table 2: Characteristics, family history and neoplasia outcomes in Lynch syndrome patients with and without comorbid Inflammatory Bowel Disease (IBD)

	Lynch with IBD (n = 567)	Lynch without IBD (n = 25306)	p
Sex			**0.004**
Female	372 (65.6%)	18010 (71.2%)	
Male	195 (34.4%)	7292 (28.8%)	
Age Group			0.281
18-29 years old	34 (6.0%)	1501 (5.9%)	
30-39	63 (11.1%)	3493 (13.8%)	
40-49	113 (19.9%)	4609 (18.2%)	
50-64	186 (32.8%)	8507 (33.6%)	
65-74	118 (20.8%)	4787 (18.9%)	
75 or older	47 (8.3%)	1876 (7.4%)	
Unknown/Unavailable	6 (1.1%)	147 (0.6%)	
BMI			**0.029**
<18.5	12 (2.1%)	406 (1.6%)	
18.5-24.9	137 (24.2%)	5314 (21.0%)	
25.0-29.9	164 (28.9%)	6012 (23.8%)	
30.0+	164 (28.9%)	7044 (27.8%)	
Unknown/Unavailable	131 (23.1%)	6863 (27.1%)	
Race/Ethnicity			0.088
White	507 (89.4%)	21976 (86.8%)	
Black	33 (5.8%)	1425 (5.6%)	
Asian	15 (2.6%)	763 (3.0%)	
LatinX	22 (3.9%)	2129 (8.4%)	
Other/Unknown	33 (5.8%)	1419 (5.6%)	
Aspirin use	82 (14.5%)	2656 (10.5%)	**0.002**
Active or former smoking	241 (42.5%)	8920 (35.2%)	**0.0003**
Primary Sclerosing Cholangitis	6 (1.1%)	7 (0.0%)	**<0.00001**
Family history			
Any Cancer	306 (54.0%)	12323 (48.7%)	**0.013**
Colorectal cancer	297 (52.4%)	11772 (46.5%)	**0.005**
Endometrial/Uterine Cancer	65 (11.5%)	2821 (11.1%)	0.813
Ovarian Cancer	74 (13.1%)	3028 (12.0%)	0.431
Personal history of neoplasia			
Colorectal adenocarcinoma	73 (12.9%)	1957 (7.7%)	**<0.00001**
Early onset (< age 50) colorectal adenocarcinoma	29 (5.1%)	760 (3.0%)	**0.004**
Colorectal polyp(s)	236 (41.6%)	7412 (29.3%)	**<0.00001**
Gynecological cancer	92 (16.2%)	3629 (14.3%)	0.206
Early onset (< age 50) gynecological cancer	30 (5.3%)	1001 (4.0%)	0.108
Gastric cancer	11 (1.9%)	286 (1.1%)	0.073
Small intestinal cancer	16 (2.8%)	309 (1.2%)	**0.0007**

Characteristics, family history and neoplasia outcomes in Lynch syndrome patients with and without comorbid Inflammatory Bowel Disease (IBD)

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-015
General Research » Lynch Syndrome

ADENOMA PREVALENCE AND INCIDENCE IN LYNCH SYNDROME DO NOT DIFFER BETWEEN GENES

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BACKGROUND:Colorectal adenoma is the main colorectal cancer (CRC) precursor lesion in Lynch syndrome (LS). Previous evidence suggested a lower incidence of adenomas in MLH1 carriers; however, this topic remains poorly studied. We aimed at describing adenoma prevalence and incidence in LS.

METHODS:Multicenter retrospective study including LS carriers under colonoscopy surveillance without a previous CRC. Firstly, we described the age of the first adenoma and advanced adenoma (AA). Then, the adenoma and AA detection rate (ADR and AADR), defined as the prevalence at first colonoscopy. Finally, we described the 10-year-cumulative-incidence for adenomas and AA by gene. We performed cox regression analysis adjusted by gender and age at first colonoscopy

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

RESULTS:We included 1,072 LS carriers, 63% (676) women, 31.9% (342) MLH1; 35.1% (376) MSH2; 24.3%(261) MSH6 and 8.7%(93) PMS2 carriers. Overall, 40.6%(435) and 11% (118) of LS carriers presented at least one adenoma and AA, respectively, without differences between genes (p>0.05). The median age of first adenoma and AA detection was 47(IQR 40-57) and 49 years (IQR 41.8-58), respectively. Adjusted analysis showed that PMS2 carriers developed adenomas at an older age (p 0.046)(Figure 1). The ADR and AADR were 18.8% and 7.2%, respectively, increasing progressively with age(Figure 1). We did not observe differences in neither ADR nor AADR between genes [MLH1 18.1% and 2.9%;MSH2 18.9% and 8.3%;MSH6 20.7% and 6.5%;PMS2 16.1% and 5.4%, p>0.05]. The 10-year-cumulative-incidence of adenomas and AA per gene were: MLH1 62.4% and 19.3%; MSH2 58.7% and 23.9%, MSH6 64% and 20.4% and PMS2 63.1% and 19% (Figure 2). No differences in adenoma incidence were found between genes (p=0.108). However, MLH1/MSH2 carriers showed higher incidence of AA (p=0.022).

CONCLUSIONS:Overall, prevalence and incidence of adenomas in LS do not differ between genes. However, PMS2 carriers develop adenomas at an older age and MLH1/MSH2 carriers present a higher incidence of AA.

Keywords: Adenomas, Lynch syndrome, colonoscopy

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

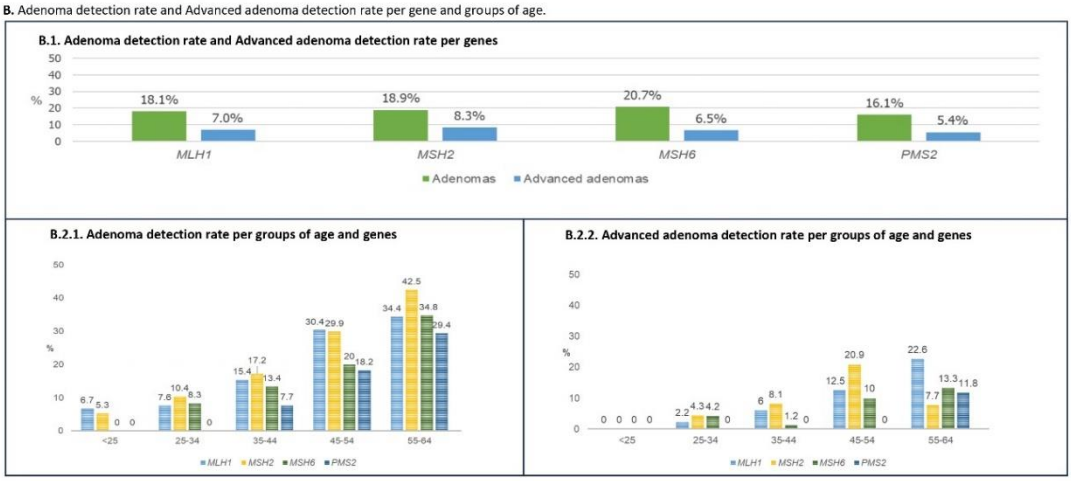
Figure 1

Figure 1. Prevalence, age of first adenoma and advanced adenoma and adenoma detection rate

A. Prevalence and age of first adenoma and advanced adenoma per gene and gender.

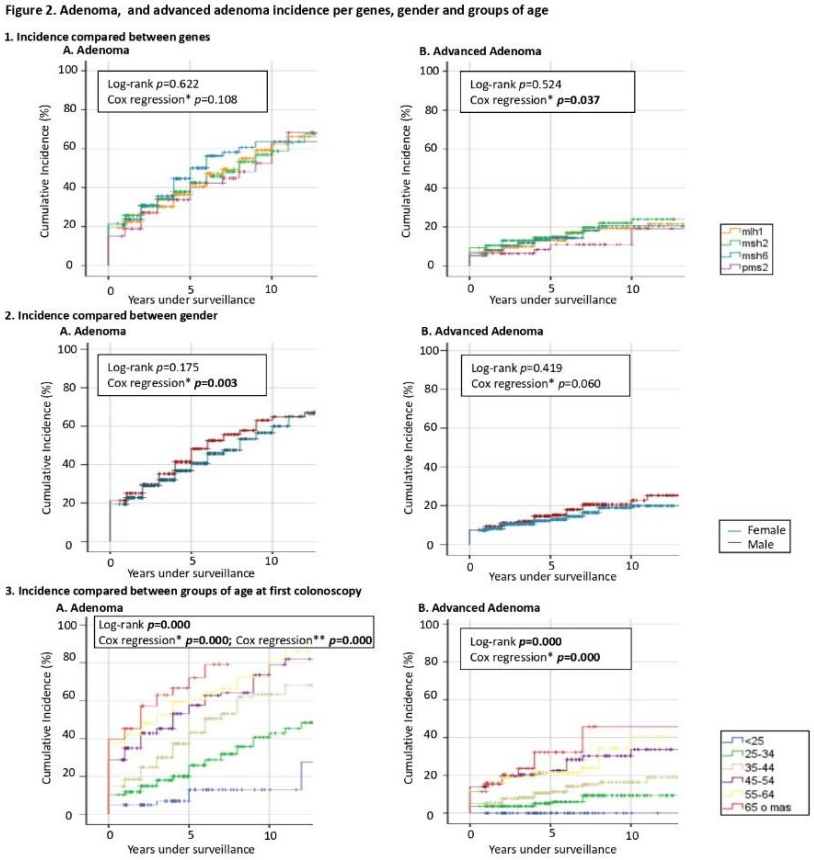
	Total	Genes				*Univariate analysis*	*Multivariate analysis* adjusted by gender and age at first colonoscopy						
		MLH1 (N=342)	***MSH2*** (N=376)	***MSH6*** (N=261)	***PMS2*** (N=93)	All genes	*MLH1 vs all other genes*	*MSH2 vs all other genes*	*MSH6 vs all other genes*	*PMS2 vs all other genes*	*MLH1vs MSH2*	*MSH6 vs PMS2*	*MLH1-MSH2 vs MSH6-PMS2*
Age first colonoscopy	40 (31.25-51)	39 (31-46)	38 (30-48.75)	44 (36-55.5)	46 (36-55)	**.000**	**.000**	**.000**	**.000**	**.001**	.757	.970	**.000**
Females (%)	676 (63.1%)	243 (71.1%)	223 (59.3%)	154 (59%)	56 (60.2%)	**.003**	**.000**	.153	**.018**	**.001**	**.001**	.836	**.006**
Adenomas													
No. (%)	435 (40.6%)	140 (40.9%)	148 (39.4%)	108 (41.4%)	39 (41.9%)	.942	.135	.730	.128	.486	.488	.924	.067
Age of first adenoma	47 (40-57)	47 (40-56)	45 (37-53.8)	53 (42.3-62)	53 (46-65)	**.000**	.469	.170	.620	**.046**	.222	.066	.462
Advanced adenomas (AA)													
No. (%)	118 (11%)	39 (11.4%)	42 (11.2%)	29 (11.1%)	8 (8.6%)	.893	.252	.480	.303	.194	.774	.498	.075
Age of first AA	49 (41.8-58)	47 (39-56)	46.5 (39.5-50.3)	57 (48-62.5)	65 (45-70.5)	**.000**	.261	.091	.971	.218	.117	.324	.536

B. Adenoma detection rate and Advanced adenoma detection rate per gene and groups of age.



ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Figure 2



O-016

Collaborative » no sub topic

HLA TYPE AS A POSSIBLE MODULATOR OF CANCER RISK IN LYNCH SYNDROME: FIRST DATA FROM THE INDICATE NETWORK

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

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BACKGROUND:Lynch syndrome (LS) carriers have a broad lifetime cancer risk range (30-80%). More precise, individual risk estimations for LS carriers would be of high clinical value, allowing tailored cancer prevention and surveillance. Due to the high immunogenicity of LS cancers and a crucial role of the human leukocyte antigen (HLA) repertoire of an individual in determining antigen presentation to the immune system, we hypothesized that a LS carrier's HLA genotype may influence the likelihood of progression from pre-cancerous lesions into cancer.

METHODS:We established a network, INDICATE, to explore the role of HLA type as a possible cancer risk modifier in LS. Clinical information, genomic and tumor DNA has been collected from Germany, Finland, the Netherlands, UK, Hungary. HLA type has been determined using next-generation sequencing including HLA-A, HLA-B and HLA-C gene loci for HLA class I as well as HLA-DRB1, HLA-DQB1 and HLA-DPB1 for HLA class II.

RESULTS:So far, genomic DNA has been collected from 758 LS carriers. Among 635 individuals with cancer history available, 45% of patients have no cancer history, 55% have been previously diagnosed with cancer. The HLA type of the first 619 LS patients has been successfully determined. The most common alleles were HLA-A*02:01 (allele frequency 28.8%) and HLA-B*07:02 (14.1%) for HLA-A and HLA-B, respectively. In a first analysis, a similar distribution of the supertypes HLA-A02, HLA-A03, HLA-B15 and HLA-B07 was observed among patients with and without cancer history. However, in this interim sample set, a potential association between the number of previous tumors and HLA supertype was observed for HLA-A02 and HLA-B58 ($p<0.05$).

CONCLUSIONS: A person's HLA type could be a cancer risk modifier in LS. If validated with continuous INDICATE enrollment, HLA type may have implications for risk-adapted surveillance and the design of next-generation personalized cancer-preventive vaccines.

Keywords: cancer risk modifiers, immunology, HLA type, Lynch syndrome

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-017

General Research » Delivery of Care and Alternative Models

EXPLORING STAKEHOLDERS' PERSPECTIVES ON IMPLEMENTING UNIVERSAL GERMLINE TESTING FOR COLORECTAL CANCER: FINDINGS FROM A CLINICAL PRACTICE SURVEY

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BACKGROUND:New guidelines recommend considering germline genetic testing for all colorectal cancer (CRC) patients. However, there is a lack of data on stakeholders' perspectives on the advantages and barriers of implementing universal germline testing (UGT). This study assessed the perspectives of members of the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC) regarding the implementation of UGT for CRC patients, including readiness, logistics, and barriers.

METHODS:A cross-sectional survey was sent to 317 active members of CGA-IGC. The survey included sections on demographics, clinical practice specialty, established institutional practices for testing, and questions pertaining

to support of and barriers to implementing UGT for CRC patients.

RESULTS:Eighty CGA-IGC members (25%) participated, including 42 genetic counselors (53%) and 14 gastroenterologists (18%). Forty-seven (59%) reported an academic medical center as their primary work setting, and most participants (55%) had over 10 years of clinical practice. While the majority of participants (73%) supported UGT, 65% indicated changes in practice would be required before adopting UGT and 39% indicated these changes would be challenging to implement. There was support for both genetics and non-genetics providers to order genetic testing, and a majority (57%) supported a standardized multigene panel rather than a customized gene panel. Key barriers to UGT implementation included limited genetics knowledge among non-genetics providers, time-consuming processes for obtaining consent, ordering tests, disclosing results, and lack of insurance coverage.

CONCLUSIONS:This study demonstrates wide support among hereditary gastrointestinal cancer experts for implementation of UGT for CRC patients. However, alternative service delivery models utilizing non-genetics providers should be considered to address the logistical barriers to UGT implementation, particularly the growing demand for genetic testing

Keywords: universal germline testing, colorectal cancer

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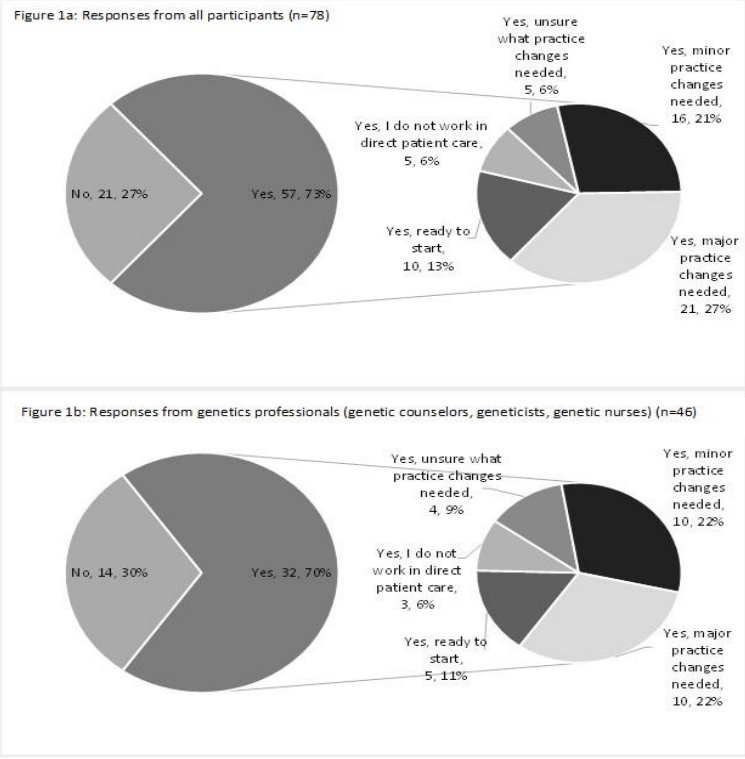
UGT for CRC_Fig1

Figure 1: Support of UGT for all CRC patients.



CRC= colorectal cancer; UGT = universal germline testing

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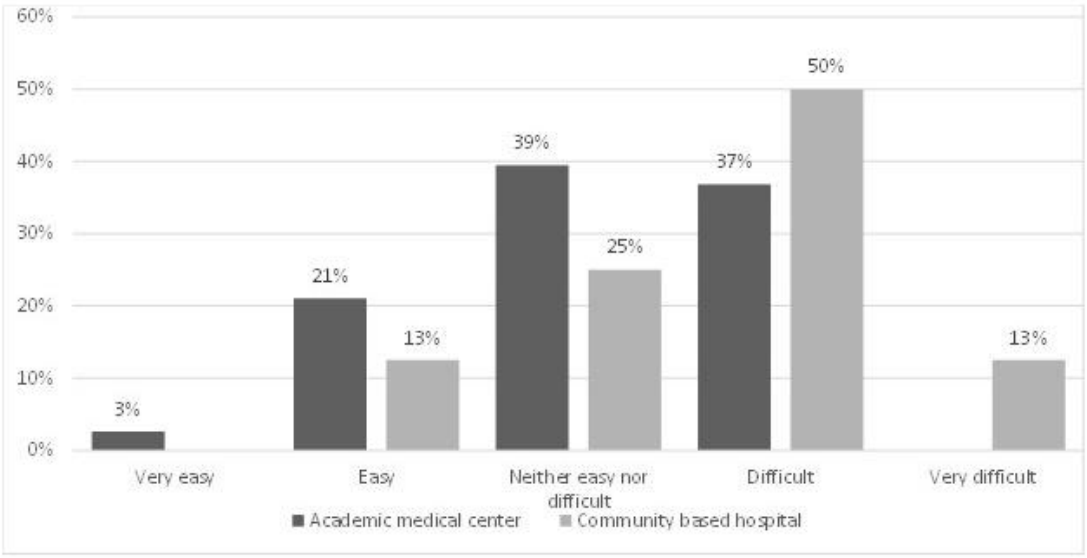
UGT for CRC_Fig2

Figure 2: Ability of respondent's institution to implement UGT for all CRC patients. Data separated by primary work setting: academic medical center (n=38) or community-based hospital (n=16)



CRC= colorectal cancer; UGT = universal germline testing

O-018

Case Report/Case Series » no sub topic

OUTCOMES OF PATIENTS WITH LYNCH SYNDROME UNDERGOING RESTORATIVE PROCTOCOLECTOMY WITH ILEAL POUCH-ANAL ANASTOMOSIS

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BACKGROUND:Rectal cancer patients with Lynch syndrome are at increased risk of developing metachronous colon cancer following segmental resection. The aim of this study was to investigate oncological outcomes and

quality of life of patients with Lynch syndrome who have undergone IPAA.

METHODS:We retrospectively analyzed our hereditary colorectal cancer registry and pelvic pouch registry and identified patients who underwent IPAA in Lynch syndrome.

RESULTS:Between 1999 and 2020, 25 patients underwent IPAA in the setting of Lynch syndrome (21) or HNPCC (4) (40% female, median age 49 (IQR 36 – 55) years). Pathogenic variants were identified in MLH1 in 6 (30%), in MSH2 in 14 (70%), and in MSH6 in 2 (10%) patients. Ten (40%) patients had a history of colorectal cancer and segmental colectomy prior to IPAA. Indication for IPAA was cancer in 22 (88%) cases, of which 3 multisite; dysplasia in 2 (8%); and poor function of prior ileorectal anastomosis in one (4%). Two patients underwent neoadjuvant chemoradiation prior to IPAA. Final pathology was adenocarcinoma in 19 (76%) cases, dysplasia in 2 (8%) cases, and no residual cancer in 4 (16%) cases. Four patients (16%) received adjuvant chemotherapy. After a median follow up of 8 (4 – 9) years, 2 (8%) deaths occurred, one (4%) cancer-related. Two (8%) developed a metachronous cancer (one jejunal, one in a long rectal cuff), one had a local recurrence at the IPAA, and one a distal recurrence. Pouch failure occurred in 2 (8%) cases, due to metachronous lesion at the rectal cuff and pouch volvulus. One patient had a redo pouch due to recurrence at the IPAA. At 5 years, overall survival was 95%, disease free survival was 85%, and pouch survival was 91%.

CONCLUSIONS:In select patients with Lynch syndrome, restorative proctocolectomy with IPAA is associated with excellent long term oncological and pouch outcomes.

Keywords: lynch syndrome, hereditary non-polyposis colorectal cancer; ileal pouch anal anastomosis

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O-019

General Research » Adenomatous polyposis syndromes including FAP

DUODENAL DISEASE IN MUTYH-ASSOCIATED POLYPOSIS: UPDATED FINDINGS FROM AN INTERNATIONAL PROSPECTIVE STUDY

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

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BACKGROUND:The characteristics and progression of duodenal disease in MUTYH-associated polyposis (MAP) are poorly understood. Our study aims to better define its natural history and to inform future upper gastrointestinal (GI) surveillance recommendations.

METHODS:Demographic, genotype and endoscopic surveillance findings have been collated from 650 genetically confirmed MAP patients. Median and range are reported for non-parametric data, and Mann-Whitney U tests performed. Kaplan-Meier analysis and multiple pairwise comparisons of survival curves between genotypes were conducted.

RESULTS:91/650 (14%) of MAP patients had one or more duodenal adenoma at index endoscopy at a median age of 53 years (range; 22-81): this was Spigelman stage I in 61.5%, stage II in 27.5%, stage III in 8.8% and stage IV in 2.2% of patients.
416 patients had follow-up endoscopies (3361 follow up years). Of the patients who had no adenomas at initial endoscopy, 24.2% (83/343), developed adenomas (median follow up 10.4 years, range 7 months to 29.2 years). Spigelman staging progressed in 15.1% of patients (n=63). For a further 11.3% disease progressed but was subsequently down staged by their last endoscopy. Disease progression was mainly attributed to increased adenoma size (39.7%) or villous morphology (29.4%).
Thirty adenomas had high grade dysplasia (HGD): of these, 43.3% (n=13) were <10mm in size, and the smallest adenoma with HGD was 4mm in size. Spigelman stage IV disease was uncommon (n=12, 1.8%, at a median age of 58 years). Five patients (0.8%) developed duodenal cancer, all apparently in the absence of prior Stage IV

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

disease. Y179C and E480* homozygotes were more likely to develop polyps, and at a significantly earlier age than subjects with other common genotypes.

CONCLUSIONS:Current guidelines for surveillance and management of MAP duodenal disease (that were devised for FAP), should be revisited, to better reflect the natural history of MAP.

Keywords: Duodenal Disease, MUTYH-associated polyposis, Spigelman Stage

POSTER ABSTRACTS

POSTER ABSTRACTS

P-001

Case Report/Case Series » no sub topic

"SPLICING IT ALL TOGETHER": DISCOVERY OF A NOVEL LIKELY PATHOGENIC *CDH1* VARIANT USING RNA ANALYSIS

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BACKGROUND:Hereditary Diffuse Gastric Cancer (HDGC) syndrome increases the risk of diffuse gastric cancer (DGC) and lobular breast cancer (LBC), often caused by truncating variants in the *CDH1* gene. Non-truncating variants are generally classified as variants of uncertain significance (VUS). Herein we describe the identification of a novel likely pathogenic *CDH1* variant through use of RNA analysis.

METHODS:A 41-year-old man presented for consultation following a DGC diagnosis. Previous multi-gene panel testing identified a *CDH1* VUS called c.944A>G (p.Asn315Ser). Family history was notable for early-onset breast cancer in his mother (subtype unknown) and early-onset thyroid cancers in siblings, but no known gastric cancer (Figure 1).

The c.944A>G (p.Asn315Ser) variant is predicted to cause an amino acid change from asparagine to serine, which are both neutral and polar. This germline variant was not previously reported in publicly available databases or in the literature, but was reported somatically in two LBCs. The laboratory indicated that this variant was of interest for RNA analysis due to possible creation of a donor splice site.

Paired DNA and RNA analysis detected an abnormal transcript, r.945_1009del, which arises from use of a novel donor site predicted by *in silico* tools and is expected to cause a frameshift and nonsense-mediated decay (p.Asn315Lysfs*13) (Figure 2). Using the patient's clinical and RNA data, the variant was classified as likely pathogenic.

RESULTS:To our knowledge, this is the first reported case of this *CDH1* variant in an individual with DGC. This case illustrates the importance of including RNA analysis upfront when possible, as it may provide a clinically actionable result for a patient and family. Follow up of suspicious VUS identified by DNA analysis with RNA should be discussed with the laboratory.
CONCLUSIONS:We confirm consent of the relevant patient was obtained to submit this Case Report abstract.

Keywords: CDH1, RNA, variant of uncertain significance, variant reclassification

P-002

General Research » Lynch Syndrome

POSTER ABSTRACTS

CANCER RISKS ASSOCIATED WITH GERMLINE PATHOGENIC VARIANTS IN THE *MLH1, MSH2, MSH6, PMS2*, AND *EPCAM* GENES

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BACKGROUND:Lynch syndrome (LS) is caused by germline pathogenic variants (PVs) in the mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or the *EPCAM* gene. LS is associated with high risks of various cancers, notably cancers of the colon, uterus, and stomach, but gene-specific estimates of risk have been limited, especially for the lower penetrance genes *MSH6* and *PMS2*.

METHODS:We examined clinical and genetic records from a consecutive cohort of 899,886 patients referred for hereditary cancer testing between September 2013 and February 2022. Cancer associations of each LS gene were estimated as odds ratios (ORs), with 95% confidence intervals (CIs), from multivariable logistic regression models adjusted for personal and family cancer history, age, ancestry, and sex. P-values are based on Wald statistics and are reported as two-sided.

RESULTS:LS PVs were detected in 1% (8,237/899,866) of the study population. The highest number of PVs were observed in *PMS2* (N=2,959), followed by *MSH6* (N=2,306), *MSH2* (N=1,697), *MLH1* (N=1,267) and *EPCAM* (N=31). PVs in all genes were significantly associated with colorectal cancer, with ORs ranging from 22-fold for *MLH1* to 3-fold for *PMS2* (Table 1). PVs in *EPCAM* were too rare for evaluation of cancers other than colorectal cancer. PVs in *MLH1, MSH2, MSH6*, and *PMS2* were significantly associated with uterine cancer, with ORs ranging from 15-fold for *MSH2* to 4-fold for *PMS2*. *MLH1* and *MSH2* PV carriers had 6- and 4-fold increased risks of gastric cancer, respectively. PVs in *MSH2* and *MSH6* showed statistically significant but modest (<3-fold) associations with ovarian cancer.

CONCLUSIONS:We confirmed a higher prevalence of *PMS2* and *MSH6* compared to *MSH2* and *MLH1* among LS PV carriers. Our data support different gene-specific cancer risks and reduced penetrance of *PMS2* and *MSH6*, where current literature is limited. These results may inform gene-specific cancer risk counseling for LS PV carriers.

Keywords: Hereditary Cancer Testing, MSH6, PMS2, Germline Pathogenic Variants, Lynch

Table 1

POSTER ABSTRACTS

Table 1: Gene-specific cancer associations for Lynch syndrome genes.

Cancer	Gene	OR (95% CI)	P-Value
Colorectal	*MLH1*	22.20 (19.04-25.88)	$<10^{-400}$
	MSH2/ EPCAM	12.55 (10.95-14.40) 11.76 (4.33-31.96)	1.60×10^{-286} 1.30×10^{-06}
	MSH6	4.77 (4.14-5.49)	2.40×10^{-104}
	PMS2	3.10 (2.68-3.59)	1.50×10^{-51}
Uterine	*MLH1*	10.76 (8.62-13.44)	9.30×10^{-98}
	MSH2	15.17 (12.94-17.79)	1.40×10^{-245}
	MSH6	10.99 (9.69-12.45)	4.00×10^{-307}
	PMS2	3.67 (3.12-4.31)	2.40×10^{-56}
Gastric	*MLH1*	5.93 (3.33-10.55)	1.40×10^{-09}
	MSH2	3.66 (1.95-6.86)	5.40×10^{-05}
	MSH6	0.74 (0.23-2.37)	0.61
	PMS2	0.23 (0.03-1.64)	0.14
Ovarian	*MLH1*	1.47 (0.98-2.22)	0.063
	MSH2	2.58 (2.01-3.32)	1.20×10^{-13}
	MSH6	1.63 (1.32-2.01)	6.60×10^{-06}
	PMS2	0.95 (0.75-1.22)	0.71

Gene-specific cancer associations for Lynch syndrome genes.

P-003

Case Report/Case Series » no sub topic

POSTER ABSTRACTS

COMBINED GERMLINE AND MOSAIC SDHA MUTATION IS ASSOCIATED WITH A MULTICANCER SYNDROME INCLUDING NEUROBLASTOMA, RENAL CANCER, AND MULTIFOCAL GIST

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BACKGROUND:We report a 39-year-old man who developed neuroblastoma, renal cell cancer, and multifocal gastrointestinal stromal tumor (GIST) in the stomach over the last 3 decades attributable to SDHA.

METHODS:He had no family history of cancer and no other symptoms or signs of a phakomatosis. Immunohistochemistry (IHC) on his GIST demonstrated succinate dehydrogenase (SDH)- deficiency, with strong c-KIT and DOG-1 expression.

RESULTS:Tumor profiling testing to guide tyrosine kinase inhibitor choice revealed no oncogenic KIT/PDGFRA somatic alteration but two loss of function pathogenic variants in SDHA. Germline genetic testing confirmed one of the two SDHA variants was constitutional. The GIST, neuroblastoma, and renal carcinoma each had second SDHA alterations, providing a unifying genetic diagnosis for patient and his family. Strikingly, the GIST and neuroblastoma and shared the same second somatic SDHA variant, and were not otherwise clonally related tumors, supporting segmental mosaicism of a second SDHA variant.

CONCLUSIONS:To our knowledge this is the first report of a cancer syndrome caused by the combination of a germline and second allele mosaic mutation. Our report provides a basis for studies of mosaicism in patients with autosomal dominant germline cancer predisposition who have an unusually severe or unusual cancer spectrum.

Keywords: multifocal GIST, SDHB deficient, tumor profiling, hereditary cancer syndrome

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P-004

General Research » Delivery of Care and Alternative Models

IMPROVING IDENTIFICATION OF PATIENTS AT AN INCREASED RISK OF CANCER WITHIN A LARGE HEALTHCARE SYSTEM: PEARLS FROM OUR HEREDITARY CANCER WORKING GROUP

POSTER ABSTRACTS

Marianne E Dubard Gault[1], Mercy Y Laurino[2]
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[2]Mercy Y Laurino

BACKGROUND:There is an urgent need to integrate genetic information in the electronic health record (EHR) as detecting a hereditary cancer syndrome (HCS) unlocks access to life-saving targeted therapies and guides cancer screening, risk reduction, early detection, and prevention. Implementing solutions to triage patients meeting National Comprehensive Cancer Network (NCCN) guidelines as well as flag and track patients with a HCS would help ensure delivery of precision medicine for everyone.

METHODS:We received a subaward from the Washington State Department of Health's Screening and Genetics Unit to develop a best practice guideline and protocol for systematic identification of patients meeting NCCN genetic testing guidelines. We formed a hereditary cancer working group (HCWG) by inviting stakeholders across our institution including subject matter experts, frontline staff, procedure and imaging teams, tribal liaison, contracting and payor relations, compliance, information analysts, and ethicist. We met for eleven months to discover current practices, strengths, gaps, and barriers. We also ran a pilot project to review charts of patients who met NCCN guidelines and record whether they were referred to genetics and reason for lack of referral.

RESULTS:Here we outline the overall approach, process, and resources leveraged by our HCWG's to develop best practice guideline. From our pilot, 55.2% (137/248) patients with breast cancer and 55.2% (48/87) patients with colorectal cancer had a referral to genetics in the EHR. For 18.9% (21/111) of patients with breast cancer and 48.7% (19/39) of patients with colorectal cancer who had no referrals placed, there was no documentation as to why the referral was missing.

CONCLUSIONS:Improving identification of patients with a HCS requires a multiprong approach that includes establishing an institutional steering committee, embedding ordering and reporting of genetic tests in one place in the EHR, creating clinical support decision tools, and developing institution-wide in-service training.

Keywords: EHR integration, genetic testing, hereditary cancer syndrome, precision medicine

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P-005

Case Report/Case Series » no sub topic

THYMOMA IN AN INDIVIDUAL WITH MLH1-RELATED LYNCH SYNDROME

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BACKGROUND:Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer. Individuals with LS also have increased risk for endometrial, ovarian, gastric, and urinary tract cancers, among a growing

list of other cancers. Thymoma is a rare cancer with only 1.5/1,000,000 people diagnosed in the United States. To date, there have been few cases of thymoma in LS patients reported in the literature. The following case presentation supports an association between a thymoma and a germline, likely pathogenic, MLH1 variant.

METHODS:We present a 55-year-old female diagnosed with a stage III (pT3N1bM0) transverse colon adenocarcinoma with loss of MLH1/PMS2 at age 47. Her family history met Amsterdam II criteria for LS, and she had genetic testing which revealed a likely pathogenic variant in MLH1: c.116+2T>G. She underwent prophylactic total abdominal hysterectomy and bilateral salpingoophorectomy following her LS diagnosis. She did well for many years until, at age 53, she presented with shortness of breath and chest pain, and was found to have a large pericardial mass. CT-guided biopsy revealed a thymoma. She was treated with first-line carboplatin/etoposide, surgical debulking, and proton beam radiation and is currently in clinical remission.

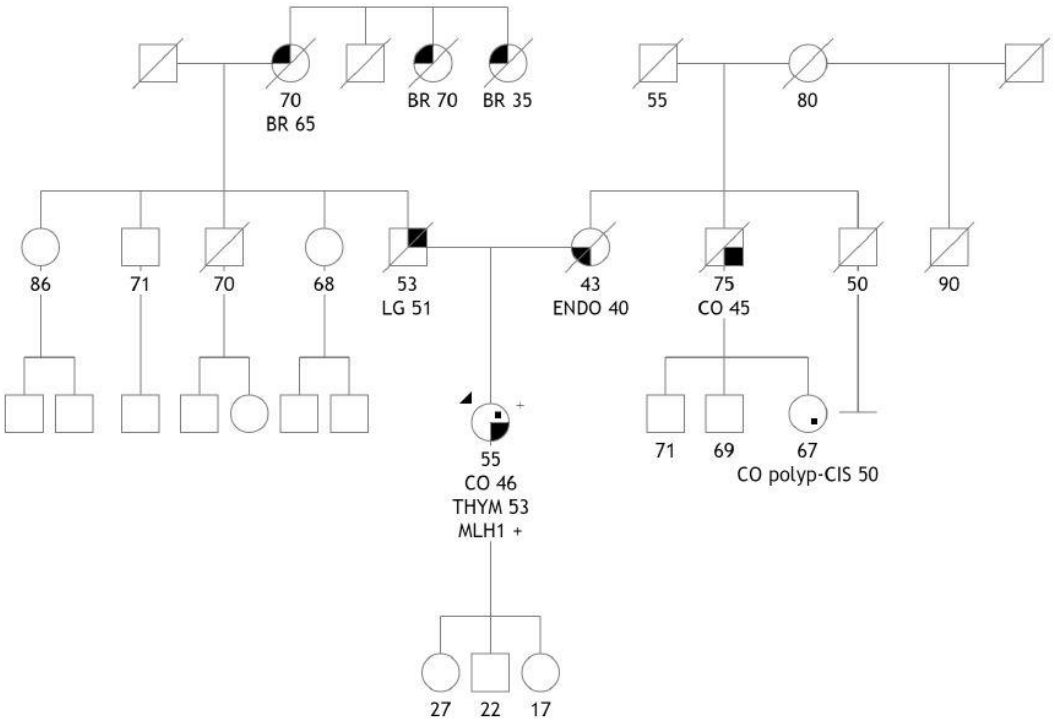
RESULTS:Microsatellite instability analyses and next generation sequencing were performed to characterize the thymoma. The tumor proved to be microsatellite unstable (MSI-H) with a MLH1 c.116+2T>G mutation at a variant allele frequency felt to be consistent with biallelic loss of mismatch repair function. Additionally, the tumor mutational burden was 30.4. These results suggest the thymoma in this patient is related to the detected, germline MLH1 variant.

CONCLUSIONS:We propose a possible association between thymoma and LS, particularly in MLH1 carriers. While thymomas and thymic cancers are rare, and there are no established screening protocols for at-risk individuals, it is important to explore the association with LS, given implications for patients and their families.

Keywords: Lynch Syndrome, MLH1, Thymoma

Figure 1

POSTER ABSTRACTS



Pedigree of a family with a germline, likely pathogenic, MLH1 variant and one case of a thymoma

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P-006

Case Report/Case Series » no sub topic

ELUCIDATING THE ROLE OF A RARE MLH1 VARIANT IN A FAMILY WITH A PREDOMINANCE OF PROSTATE CANCER

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POSTER ABSTRACTS

BACKGROUND:Lynch syndrome (LS) increases risk for multiple cancer types including colorectal, endometrial, gastric, ovarian, urinary tract, among others. Recently, LS has been associated with prostate cancer, a common cancer in males. Approximately 20-30% of LS variants are missense changes; however, missense changes are challenging to interpret, in part to their rarity. We present a family with a prostate cancer-dominant pedigree and a germline, missense variant in MLH1.

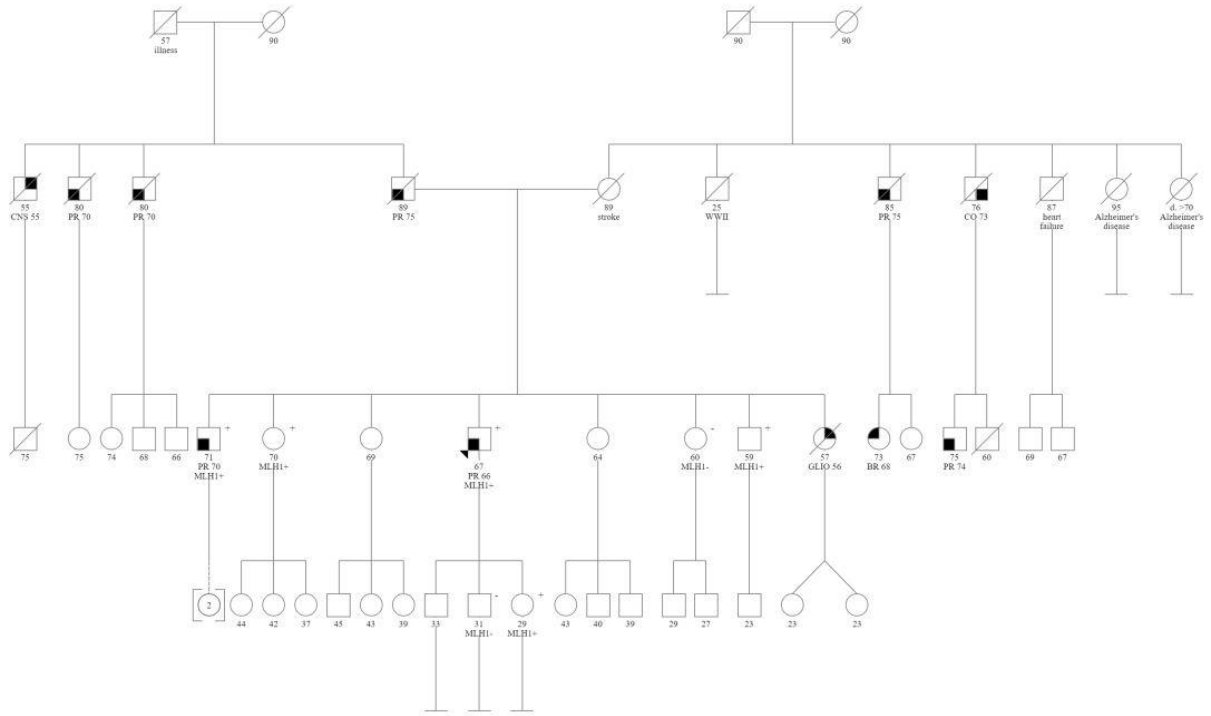
METHODS:Two brothers diagnosed with prostate cancer at ages 67 and 70, had germline genetic testing which revealed a likely pathogenic MLH1 variant: c.1706C>T (p.A569V). The laboratory has seen this variant in two individuals whose colorectal tumors had loss of MLH1/PMS2 on immunohistochemistry (IHC). One of these individuals reported a family history of LS-related cancers. The other's tumor was microsatellite unstable (MSI-H) with a second MLH1 variant. Other laboratories classify this variant as uncertain significance. Interestingly, the brothers' family history doesn't meet Amsterdam II criteria for LS. However, their family has a predominance of prostate cancer (Figure 1). Therefore, IHC and MSI analyses, and somatic genomic profiling, were performed on the prostate cancers to clarify their etiology.

RESULTS:LS-associated tumors commonly exhibit loss of MMR protein(s) on IHC and are MSI-H. Our investigations revealed that both brothers' tumors were MMR proficient and microsatellite stable. Further, somatic testing didn't reveal an additional MLH1 mutation. These results suggest that the brothers' cancers are unlikely to be associated with the detected MLH1 variant. However, the family will continue to be followed for Lynch syndrome.
CONCLUSIONS:We propose that this specific MLH1 variant may be low-penetrance, given the family's relative lack of LS-associated malignancies. Moreover, the tumor analyses performed don't suggest an etiologic link between the MLH1 variant and the prostate cancers in this family; however, data from other families with this variant will address this question more definitively.

Keywords: MLH1, Lynch syndrome, Prostate Cancer, Immunohistochemistry (IHC), Microsatellite Instability (MSI) Analysis, Somatic Testing

Figure 1

POSTER ABSTRACTS



Pedigree of family with rare MLH1 germline variant: c.1706C>T (p.A569V)

P-007

Case Report/Case Series » no sub topic

CASE SERIES: CLINICAL OUTCOMES AFTER SECOND-LINE IMMUNE CHECKPOINT INHIBITOR THERAPY FOR PATIENTS WITH A MISMATCH REPAIR DEFICIENT TUMOR

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BACKGROUND:2-3% of solid tumors are mismatch repair deficient (MMRd) as a result of either sporadic or germline genetic alterations and immune checkpoint inhibitors (ICI) are important treatment options for these patients. However, little is known about the efficacy of continued ICI therapy after initial progression. We describe clinical outcomes for three patients with MMRd tumors from a single center who received multiple lines of ICI therapy.

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METHODS:EMR search identified patients with a MMRd tumor diagnosed between 2012-2022 who received multiple lines of ICI.

Patient 1 had transitional cell carcinoma at age 59 with MSH2/MSH6 loss. She had a complete response (CR) with atezolizumab but eventually relapsed. She was rechallenged with pembrolizumab and again achieved a CR. Germline analysis identified a MSH2 pathogenic variant (PV).

Patient 2 had metastatic gastro-esophageal adenocarcinoma at age 45 with MLH1/PMS2 loss and tumor MLH1-promotor hypermethylation. He had a CR to pembrolizumab for 2.5 years, and at progression was started on ipilimumab/nivolumab with four months of stable disease.

Patient 3 had gastric adenocarcinoma at age 71 with MLH1/PMS2 and MSH6 loss with tumor MLH1-promotor hypermethylation. Tumor/germline analysis identified biallelic somatic MSH6 PVs. He had partial response on pembrolizumab for 14 months, and was subsequently started on ipilimumab/nivolumab, but developed tumor progression after one month.

RESULTS:Clinical benefit to multiple lines of ICI therapy was seen for two out of three patients, including one patient with a germline MSH2 PV. This suggests that ICI rechallenge can be an effective clinical strategy, although more data and improvement in clinical biomarkers are needed to understand which patients may respond. One key question is whether sporadic versus germline mismatch repair tumors should be managed differently.

CONCLUSIONS:I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this Case Reports / Case Series abstract

Keywords: mismatch repair deficiency, immunotherapy, immune checkpoint inhibitors

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P-008

General Research » Lynch Syndrome

RECONTACTING PATIENTS WITH UNEXPLAINED MISMATCH REPAIR DEFICIENCY: LESSONS FROM A PAN-CANCER COHORT

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POSTER ABSTRACTS

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BACKGROUND:Since Lynch syndrome (LS)-associated tumors typically demonstrate mismatch repair deficiency (dMMR), universal tumor screening (UTS) via immunohistochemical staining can help identify patients with LS. Previous studies have documented underlying etiologies of dMMR colorectal and endometrial tumors, but little is understood about other tumor types and the practical considerations of UTS including patient attrition. Patients with a dMMR tumor whose germline testing is negative or uninformative have unexplained mismatch repair deficiency (UMMRD). In this study, we depict the etiologies of pan-cancer dMMR tumors, including endometrial, gastrointestinal, pancreatic, prostate, sebaceous and ovarian, and describe the UMMRD population's current knowledge and desire to pursue additional testing to determine the etiology of their dMMR tumor.

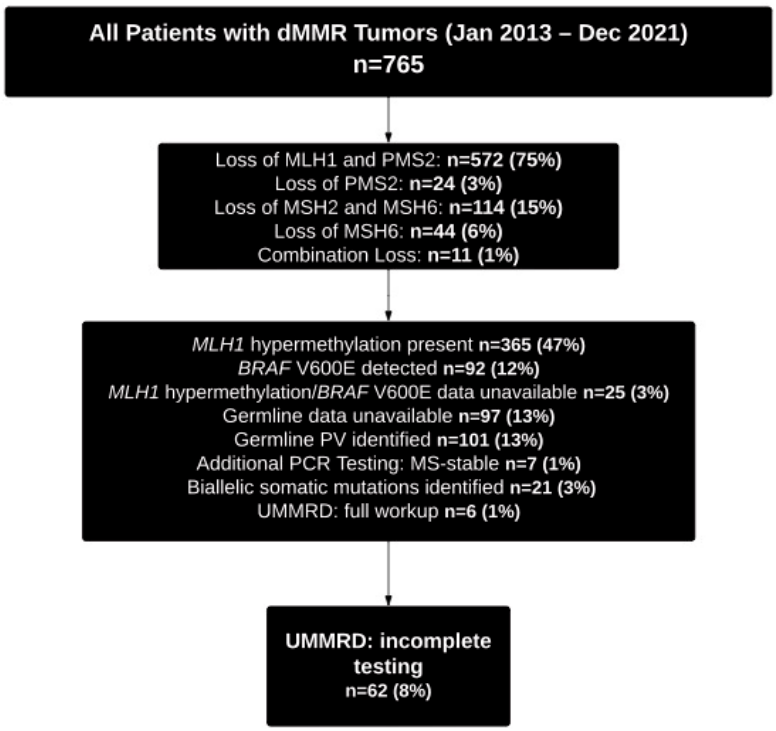
METHODS:A retrospective chart review was performed to describe tumor type and etiology for 765 patients with dMMR tumors identified at a single center between 2013 – 2021. A survey was sent to 29 eligible patients with UMMRD to assess experiences, attitudes and beliefs about their personal cancer history and genetic testing.

RESULTS:Across 14 unique tumor types, we identified 101 (12.5%), 21 (2.7%) and 68 (8.9%) cases of LS, biallelic somatic mutations and UMMRD, respectively. The most prevalent reason for patient attrition within the algorithm was the unavailability of germline data. 7/29 (24.1%) participants responded. Respondents expressed interest in a follow-up genetic counseling visit. Motivations for pursuing testing include determining personal recurrence risk and risk to relatives, identifying a cause for their cancer and surveillance management.
CONCLUSIONS:This study describes the pan-cancer experience of a UTS program at a university medical center, highlighting the limitations of the current testing algorithm. Patients with UMMRD are generally interested in additional testing to resolve the uncertainty of their diagnosis. Adopting a first tier paired tumor-germline testing approach can limit patient attrition, improve etiology confirmation, satisfy patients' motivations, and clarify proband and relative screening recommendations.

Keywords: Lynch, dMMR, Screening, Paired

Fig1

POSTER ABSTRACTS



Landscape of patients with dMMR tumors identified by Stanford Pathology between January 2013 – December 2021

Fig2

Tumor Type	Frequency (Total: 765)	Proportion (%)
Endometrial	364	47.6
Colorectal	258	33.7
Gastric	47	6.1
Esophageal / GEJ	20	2.6
Pancreas	16	2.1
Sebaceous	16	2.1
Ovary	12	1.6
Biliary Tract	9	1.2
Small Bowel	9	1.2
Unknown	8	1.0
Urothelial	2	0.3
Adrenal	1	0.1
Hepatocellular Carcinoma	1	0.1
Prostate	1	0.1
Sarcoma	1	0.1

Frequency of dMMR tumors identified by Stanford Pathology between January 2013 – December 2021

P-009

POSTER ABSTRACTS

Case Report/Case Series » no sub topic

A NOVEL MISSENSE VARIANT IN *CDH1* CAUSES HEREDITARY DIFFUSE GASTRIC AND LOBULAR BREAST CANCER SYNDROME INDEPENDENTLY OF SPLICING

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BACKGROUND:Pathogenic variants (PVs) in *CDH1* cause hereditary diffuse gastric and lobular breast cancer syndrome (DGLBC). Most *CDH1* PVs described in DGLBC families are expected to cause protein truncation or nonsense mediated decay. Currently, the only consensus missense *CDH1* PVs associated with DGLBC disrupt splicing. The absence of non-spliceogenic missense *CDH1* PVs suggests that missense changes are generally tolerated; however, rare undiscovered missense PVs may exist. Herein we present clinical, structural, and RNA evidence supporting the *CDH1* p.G212V c.635G>T as a likely PV, whose mechanism of pathogenicity is through the impact of the missense change rather than splicing.

METHODS:Retrospective review of clinical and RNA data, when available, was performed for six carriers of this variant and used with structural analysis and literature review for classification.

RESULTS:Families with *CDH1* p.G212V c.635G>T fulfilled guidelines for *CDH1* testing. The variant segregated with disease, with a total of six carriers between two families. Cancer histories included DGC (ages 25-57) and LBC (age 80). RNA studies did not identify any abnormal splicing in the *CDH1* gene. However, structural analysis indicated that the variant is expected to destabilize the structure. A close-match variant, p.G212E, is reported as disease causing in the literature.

CONCLUSIONS:The clinical, structural, and hot-spot data, support the *CDH1* p.G212V c.635G>T as likely pathogenic (PS4, PM2_supporting, PP1_supporting, PM1_supporting, PM5). However, it is important to note that this variant would not reach a likely pathogenic classification using the *CDH1* variant curation expert panel guidelines, in part because many of the codes used to evaluate missense changes are not currently recommended due to the absence of missense PVs available to evaluate their use. It is expected that the emergence of variants such as this will help to refine these guidelines.
I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this abstract.

Keywords: CDH1, missense, HDGC, LBC, DGLBC, variant classification

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P-010

General Research » Pancreatic cancer-related syndromes

ATM AND PALB2 VARIANT CURATION GUIDELINES PROGRESS UPDATE: CLINGEN HEREDITARY BREAST, OVARIAN, AND PANCREATIC CANCER VARIANT CURATION EXPERT PANEL

POSTER ABSTRACTS

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BACKGROUND:Variant classification for hereditary breast, ovarian, and pancreatic cancer (HBOP) genes is complicated by multifactorial etiology of cancer and incomplete penetrance, causing lack of consensus in variant classification. To address discrepancies, the ClinGen Hereditary Breast, Ovarian and Pancreatic Variant Curation Expert Panel (HBOP VCEP) is developing gene-specific modifications of the ACMG/AMP sequence variant classification guidelines (ACMG/AMP SVI), starting with ATM and PALB2.

METHODS:The HBOP VCEP focuses on variant interpretation guidance for HBOP genes (ATM, PALB2, CHEK2, RAD51C, RAD51D, BRIP1, and BARD1). HBOP VCEP members meet monthly to review if ACMG/AMP SVI criterion should be adopted, modified, or omitted for each gene. Next, pilot variants are evaluated using the agreed upon gene-specific guidelines. The ClinGen Sequence Variant Interpretation Group provides feedback and approves final rules.

RESULTS:To adjust ACMG/AMP ATM and PALB2 variant classification rules, 4/28 original ACMG/AMP codes were accepted, whereas 7/28 were modified with gene specifications. A further 5/28 and 4/28 codes were clarified with disease specifications and 12/28 and 13/28 codes were omitted for ATM and PALB2, respectively. A pilot classification of 33 ATM variants classified 12 pathogenic (P), 4 likely pathogenic (LP), 6 variant of uncertain significance (VUS), 2 likely benign (LB), and 9 benign (B) variants. Prior to this review, 11/33 variants had conflicting or uncertain classifications in ClinVar (2 Conflicting LP/VUS; 4 Conflicting B/LB/VUS; 5 VUS). In addition, 40 PALB2 variants were classified, 14 P, 6 LP, 12 VUS, 3 LB, and 5 B, and 13/40 variants had conflicting or uncertain classifications in ClinVar (3 Conflicting LP/VUS; 3 Conflicting B/LB/VUS; 7 VUS).

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CONCLUSIONS:Standards for variant evaluation for ATM and PALB2 were developed to provide guidance on variant classification and clarify discrepant variant classifications. Resolution of uncertain and discrepant classifications is crucial for maximizing diagnostic yield and appropriately managing cancer surveillance and treatment.

Keywords: ATM, PALB2, ClinGen

P-011

Case Report/Case Series » no sub topic

COMPLEX GERMLINE GENETIC TESTING REPORTS REQUIRE MULTIDISCIPLINARY EVALUATION

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BACKGROUND:We discuss an abnormal genetic test result that if taken at face value could have caused medical errors. Our aim is to educate health care professionals about the benefits of utilizing multidiciplinacy tumor boards (MTB).

METHODS:A 65-year-old female with no significant family history of cancer (Figure 1) was suspected to have familial adenomatous polyposis (FAP). At age 46, the patient was diagnosed with breast cancer. Testing for BRCA1/BRCA2 mutations was unrevealing. At age 59, she was diagnosed with colon cancer. At age 65, she underwent updated MGPT that showed complete deletion of APC, RAD50, and CTNNA1. The commercial testing laboratory's report stated, "Positive result. Deletions encompassing the entire APC gene have been reported in the literature in individuals with FAP" that led the ordering physician to conclude that the patient had FAP. Also, the APC variant c.3920T>A (p.Ile1307Lys) was found at ~20% allelic fraction. A colonoscopy showed one 5 mm tubular adenoma. Lack of significant polyp burden led the gastroenterologist to involve the MTB that recommended chromosome microarray analysis (CMA) and tissue testing. CMA confirmed the deletions, all on the 5q chromosome. All tissues (colon, stomach and uterus) expressed the wild type sequence and the c.3920T>A variant; both at ~50% allelic fractions ruling out germline APC 5q gene deletion

POSTER ABSTRACTS

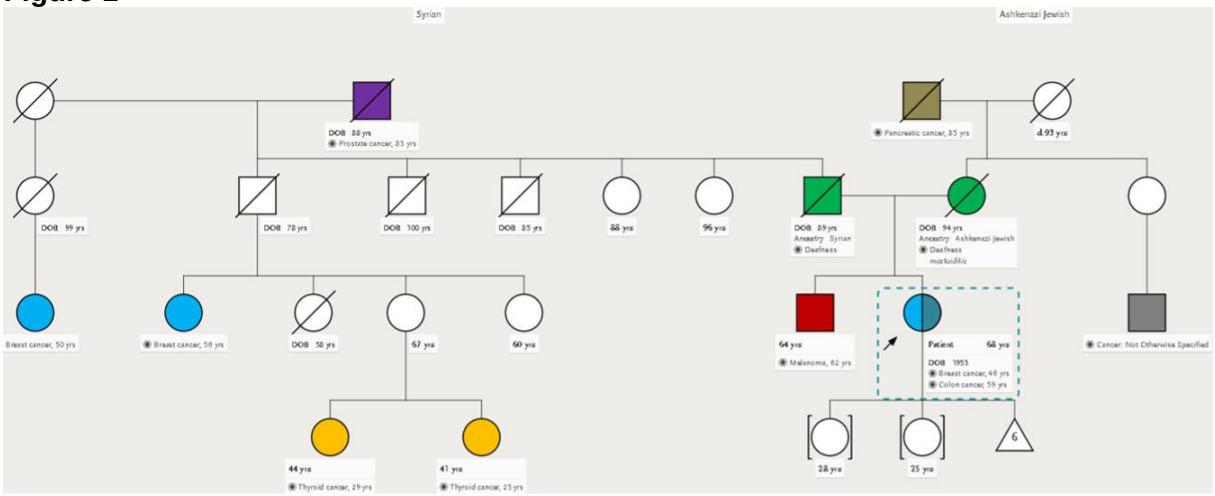
(Figure 2). Thus, the patient did not have FAP but had clonal hematopoiesis of indeterminate potential (CHIP).

RESULTS:Although CHIP causing MGPT mis-interpretation is well-known, 5q deletion raising suspicion of FAP due to APC gene loss has not been described.

CONCLUSIONS:Non-genetics professionals should partner with the MTB to correctly interpret complex genetic testing results for clinical care. Also, tissue-based analysis should be considered to clarify complex pathogenic variants. I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this case report

Keywords: Familial adenomatous polyposis; clonal hematopoiesis of indeterminate potential; multidiciplinacy tumor boards

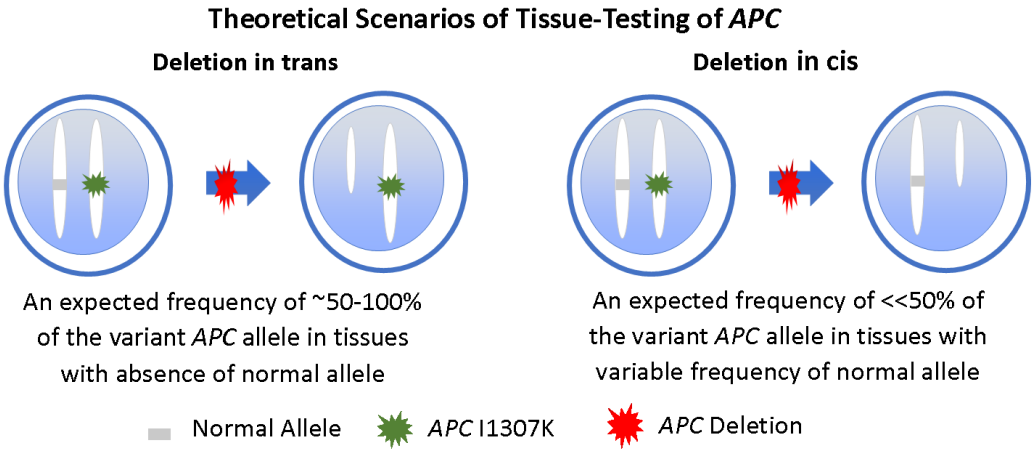
Figure 1



Pedigree chart

Figure 2

POSTER ABSTRACTS



Theoretical scenarios of tissue-based testing based on the results of blood-based genetic testing. The presence of the variant allele guided the interpretation of the results of tissue-based testing and allowed us to establish there was no APC gene loss in tissues.

P-012

Case Report/Case Series » no sub topic

A NOVEL INSERTION/DELETION IN *APC* PROMOTOR 1B IS ASSOCIATED WITH BOTH STOMACH AND COLON POLYPOSIS

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BACKGROUND:Pathogenic variants in APC gene promoter 1B are associated with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). Here, we present a multi-clinic and laboratory identification of a previously undescribed APC promoter 1B insertion/deletion, which appears to cause an autosomal dominant GAPPS presentation as well as colon polyposis. This case series elucidates the potential spectrum of cancer

risks for individuals affected by this and similar APC promotor 1B variants.

METHODS:The family proband is a female of unspecified white ancestry. She was diagnosed with gastric polyposis and adenocarcinoma at age 39 and had a curative gastrectomy. She is now 60 with a reported cumulative history of between 50 to 100 colon adenomas. Multi-gene panel testing in 2022 identified an insertion/deletion within APC promoter 1B: APC c.-192_-191delATinsTAGCAAGGG (NM_001127511).

RESULTS:Across four generations, ages of gastric cancer presentation in the family range from 39-60's, with prophylactic gastrectomies at ages 11 and 13 in the proband's daughter and nephew. Six of the 12 affected relatives have undergone gastrectomy; four had colectomies due to colon polyposis. The youngest known carrier in the family is a 10-year-old female, and the oldest living presumed carrier is the proband's brother, 66.
CONCLUSIONS:This novel indel is suggestive of a joint GAPPS and FAP presentation in a previously unreported large kindred. Although the mechanism for this mixed phenotype is unclear, it suggests there may be previously uncharacterized genotype-phenotype correlations for APC promoter 1B variants. Patients with this and similar APC variants should therefore be evaluated for both stomach and colon polyps for cancer risk management until clearer risk estimates are available. We hereby confirm that the consent of the relevant patient(s) has been obtained to submit this Case Reports / Case Series abstract.

Keywords: APC, FAP, GAPPS, risk-reducing surgery, gastrectomy, colectomy

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P-013

Case Report/Case Series » no sub topic

UTILITY OF SOMATIC TUMOR PROFILING IN DIFFERENTIATING BETWEEN GERMLINE *MSH6*-DRIVEN SYNCHRONOUS TUMORS & CLONALLY RELATED *POLE* ULTRAMUTATED TUMORS

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BACKGROUND:Tumors driven by mutations in the *POLE* exonuclease domain demonstrate an ultramutated phenotype that may affect mismatch repair (MMR) genes, leading to loss of proteins on immunohistochemistry (IHC). Somatic tumor profiling can clarify the significance of suspicious germline variants of uncertain significance (VUS) in MMR genes associated with these tumors.

METHODS:We describe a 48-year-old female initially diagnosed with synchronous grade 1 endometrioid adenocarcinoma of the uterus and bilateral ovaries. Although IHC for MMR proteins was retained in the uterine

and right ovarian tumor, staining for MSH6 was inconclusive in the left ovary. She underwent germline multigene panel testing, which identified a *BRCA2* VUS [c.8016A>G (p.Ile2672Met)] and *MSH6* VUS [c.3800T>C (p.Met1267Thr)]. On somatic testing, the uterine tumor was microsatellite stable (MSS) via MSISensor and exhibited an ultramutated phenotype, with a tumor mutation burden (TMB) of 195.3 mt/Mb associated with a *POLE* hotspot mutation in the exonuclease domain [c.1231G>C (p.V411L)]. To reconcile discordant results, additional somatic profiling was performed of the right and left ovaries, which were both MSS and had the same somatic *POLE* hotspot mutation identified in the uterine tumor. Several somatic *MSH6* mutations were identified in all three specimens and were likely passenger events.

RESULTS:These findings suggest that the patient's tumors, initially thought to be synchronous primaries in the setting of a suspicious *MSH6* VUS, were in fact clonally related ultramutated but MSS tumors driven by a *POLE* exonuclease domain mutation.

CONCLUSIONS:This case highlights how tumor analysis can help to differentiate between synchronous vs. clonally related tumors and resolve suspicious germline VUSs, allowing for more accurate cancer risk assessment in patients and family members.

I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this Case Reports / Case Series abstract.

Keywords: POLE ultramutated, mismatch repair, synchronous tumors, clonally related

Table 1

Table 1: Somatic Landscape of Uterine and Bilateral Ovarian Tumors

	Right Ovary	Left Ovary	Uterus
IHC Pattern	MMR Retained	MSH6 Inconclusive	MMR Retained
MSISensor Score	0.3 (MSS)	0.11 (MSS)	0.39 (MSS)
TMB (mt/Mb)	145.8	109.6	195.3
POLE Variants	*POLE* c.1231G>C (p.V411L)^	*POLE* c.1231G>C (p.V411L)^	*POLE* c.1231G>C (p.V411L)^ *POLE* c.455A>G (p.Y152C) *POLE* c.5794C>T (p.R1932C)
MSH6 Variants	*MSH6* c.1002G>T (p.K334N) *MSH6* c.1102G>T (p.E368*) *MSH6* c.2950A>C (p.N984H) *MSH6* c.3465delG (p.M1156Wfs*28)	*MSH6* c.1102G>T (p.E368*) *MSH6* c.3465delG (p.M1156Wfs*28)	*MSH6* c.1102G>T (p.E368*) *MSH6* c.2882G>T (p.R961I) *MSH6* c.3465delG (p.M1156Wfs*28)

Abbreviations: MMR – mismatch repair, IHC – immunohistochemistry, TMB – tumor mutational burden, MSS – microsatellite stable

^*POLE* hotspot mutation

Somatic Landscape of Uterine and Bilateral Ovarian Tumors

POSTER ABSTRACTS

P-014

Case Report/Case Series » no sub topic

CO-OCCURRING MOSAIC POLE AND APC MUTATIONS IN A PATIENT WITH POLYPOSIS AND METACHRONOUS COLORECTAL CANCERS

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BACKGROUND:Patients with early-onset colorectal polyposis and cancer without identified pathogenic germline variants present clinical conundrums. Optimal management of these patients is uncertain. Our aim is to describe a rare genetic basis for adenomatous polyposis and metachronous colorectal cancers in a young adult.

METHODS:At age 19, a male presented with rectal bleeding and was found to have adenomatous polyps and a mismatch repair proficient (pMMR), stage 2b sigmoid adenocarcinoma treated with total colectomy and ileorectal anastomosis. At age 23, on surveillance examination, a rectal cancer was found at the anastomotic site treated with proctectomy with ileoanal anastomosis and adjuvant chemotherapy. Family history was negative for colorectal polyposis or cancers (Figure 1). Initial germline sequencing of 32 genes and additional germline testing of 77 genes including RNA analysis were negative. Subsequent somatic testing of both cancers, an adenoma, and normal colon tissue was performed.

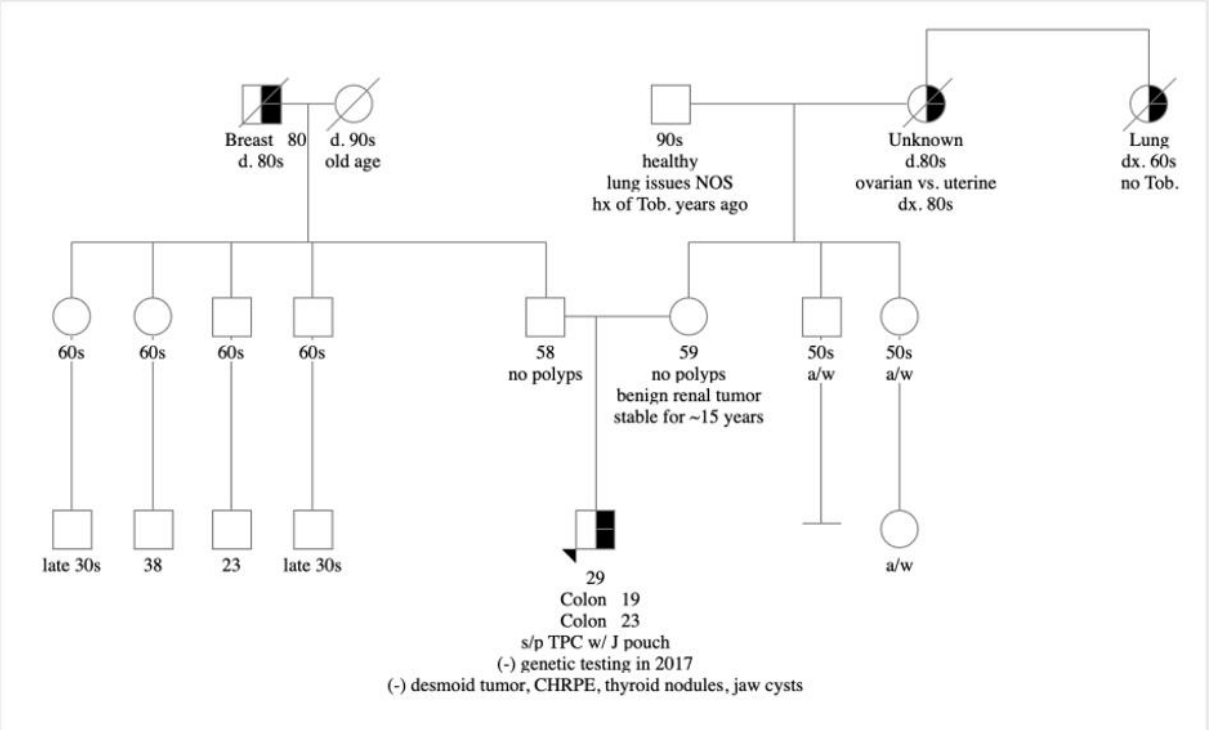
RESULTS:Both cancers and the adenoma shared pathogenic POLE (p.P286R) and APC (p.R1114*) mutations (Table 1). Neither mutation was present in the non-neoplastic colon tissue or saliva sample. The tumor mutation burden for both tumors was very high, consistent with pMMR POLE ultramutator phenotype. The three neoplasms were otherwise not clonally related. The findings are consistent with a segment of colon harboring co-occurring mosaic POLE and APC mutations.

CONCLUSIONS:To our knowledge, this is the first reported case of co-occurring APC and POLE segmental mosaic mutations resulting in colorectal polyposis and metachronous cancers. Given that both cancers had high tumor mutation burden attributable to POLE, immunotherapy would be a possible therapeutic option if needed in the future. This case demonstrates the value of somatic testing to explain unresolved polyposis and cancer cases. We hereby confirm that the consent of the relevant patient has been obtained to submit this Case Report abstract.

Keywords: APC, FAP, POLE, polyposis, colorectal cancer, mosaicism

POSTER ABSTRACTS

Pedigree



Summary of somatic testing on various samples

Sample	*POLE* p.P286R	*APC* p.R1114*	Other
Normal tissue – distal anastomosis	Negative, 0% VAF (variant allele fraction)	Negative, 0% VAF	
Saliva	Negative, 0% VAF	Negative, 0% VAF	
2013 Rectosigmoid Polyp	32% VAF	30% VAF	*MTOR, PIK3CA, APC* & other mutations unique to this sample
2013 Sigmoid tumor	25% VAF	27% VAF	Three unique *APC* & other mutations, Microsatellite stable, TMB – 62 mutations per Mb
2017 Rectal tumor	37% VAF	33% VAF	Unique *PIK3CA*, four *APC* & other mutations. MSI-borderline high, TMB – 77 mutations per Mb

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P-015

Case Report/Case Series » no sub topic

DIGENIC INHERITED PANCREATIC CANCER RISK: A CASE REPORT

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BACKGROUND:All individuals with a personal history of exocrine pancreatic cancer meet NCCN Clinical Practice Guidelines for genetic testing as these results can greatly impact treatment and surveillance. Pursuing genetic testing in a timely matter is crucial as most patients present with advanced disease and have limited survival. Genetic testing helps to develop the most effective treatment plan and provide valuable information on potential screening for family members.

METHODS:The 49 y.o. woman presented with a newly diagnosed pancreatic cancer with liver metastases. Family history was significant for breast cancer in her mother, prostate cancer in her paternal grandfather, and lymphoma in her son. Following pre-test counseling genetic testing was ordered for a comprehensive multi-gene panel (55 genes).

POSTER ABSTRACTS

RESULTS:The proband was identified to carry digenic pathogenic variants (PV) associated with an increased pancreatic cancer risk. One PV was in BRCA2, c.3847_3848delGT and the other PV was in ATM, c.6807G>A. The inheritance of these PVs is unknown, but the proband's mother is scheduled to undergo testing. Due to the BRCA2 PV this patient qualified for treatment with novel molecularly targeted therapy. Shortly after receiving her genetic test results the patient developed COVID and passed away two weeks later due to thrombotic complications, prior to the start of her cancer treatment. Her surviving family members, including a young adult daughter and teenage son, plan on pursuing testing.

CONCLUSIONS:We report a unique case of a patient with newly diagnosed metastatic pancreatic cancer found to carry two significant PVs associated with her diagnosis. This result had potential to impact treatment with novel molecularly targeted therapy. This case emphasizes the importance of multi-gene panel testing and point of care testing for all patients with pancreatic cancer. I hereby confirm that the consent of the relevant patient has been obtained to submit this Case Report abstract.

Keywords: Genetic testing, Pancreatic cancer, Cancer risk reduction, BRCA2, ATM, Pancreas cancer management

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P-016

Case Report/Case Series » no sub topic

A FANCC INTRONIC VARIANT OF UNCERTAIN SIGNIFICANCE IN A CHILD WITH METASTATIC PANCREATIC ADENOCARCINOMA

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BACKGROUND:Pancreatic ductal adenocarcinoma (PDAC) has been reported to have a germline genetic association in about 5.5% of isolated cases, and 10-13% of familial or hereditary cohorts. Studies are linking new germline variants to PDAC annually, with numerous VUS in candidate genes being reported.

METHODS:A 9-year-old boy presented with a 3-week history of abdominal pain, weight loss, vomiting and diarrhea. He then developed jaundice and pruritis. Physical exam and developmental assessment were normal. Imaging revealed an obstructive abnormality in the head of the pancreas with extra- and intrahepatic dilation of the bile ducts and a 1 cm lesion in the liver. Biopsy of the liver lesion revealed metastatic PDAC. Extensive pathology review demonstrated atypical epithelial proliferation forming mucin-producing irregular and anastomosing glands. The tumor was microsatellite stable with a tumor mutation burden of 3.4 Mutations/Mb. The child is currently receiving chemotherapy. The child's family history is significant for cancer in both maternal and paternal relatives; however, no other relative has had PDAC. Germline evaluation was

conducted with a 29-gene pancreatic cancer panel and revealed a c.345+6A>T variant of uncertain significance (VUS) in the FANCC gene. This VUS affects a nucleotide in the consensus splice site in intron 4.

RESULTS:Pancreatic adenocarcinoma is essentially unheard of in children under 10 years old. In adults, PDAC has been associated with a variety of cancer predisposition genes and the National Comprehensive Cancer Network (NCCN) has issued surveillance guidelines for adults carrying germline variants in TP53, BRCA1/2, ATM, PALB2, CDKN2A, among others. Emerging data has identified germline FANCC variants in patients with PDAC. Further studies of FANCC variants of uncertain significance are necessary for variant reclassification and to allow review of current screening guidelines in adults.

CONCLUSIONS:I hereby confirm that the consent of the parents of the child to publish this case report has been obtained.

Keywords: pancreatic adenocarcinoma, pediatric, germline, genetic, FANCC

P-017

Case Report/Case Series » no sub topic

TYLOSIS: NOT A NEW SYNDROME BUT AN UNDERRECOGNIZED ESOPHAGEAL CANCER PREDISPOSITION SYNDROME

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BACKGROUND:Tylosis is a rare autosomal dominant syndrome caused by pathogenic variants (PVs) in the RHBDF2 gene. It is characterized by a high risk for squamous cell carcinoma (SCC) of the esophagus and hyperkeratosis of the palms and soles of feet. The true incidence of esophageal SCC is unknown but is estimated to be around 27% when evaluating multiple cohorts, although one group estimates it as high as 95% by age 65. The American Society of Gastrointestinal Endoscopy recommends endoscopic surveillance every 1-3 years starting at age 30. We aim to raise awareness of this rare genetic syndrome.

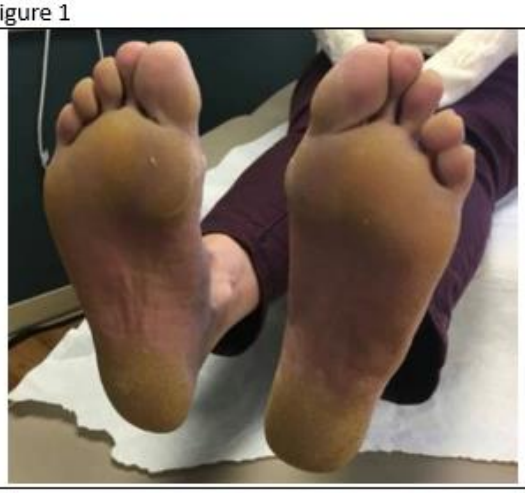
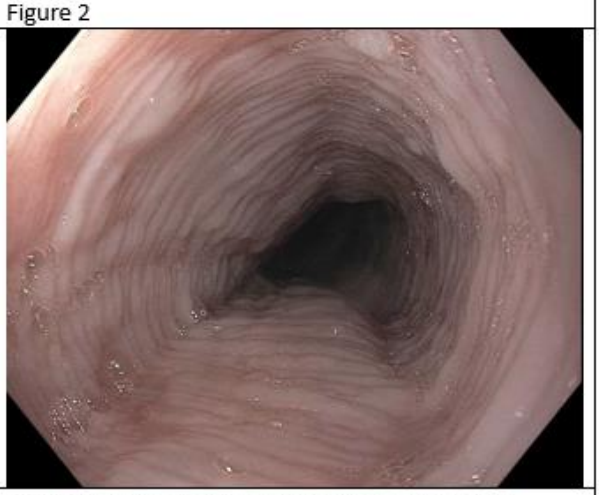
METHODS:A 64-year-old female presented with a diagnosis of tylosis based on the presence of hyperkeratosis of the palms and soles (Figure 1) and family history of esophageal SCC. Research genetic testing identified a PV in RHBDF2 (c.557T>C, p.Ile186Thr) which was confirmed at a clinical diagnostic laboratory. To date, we have confirmed the familial RHBDF2 PV for four additional relatives; none of which

have a history of esophageal cancer (current ages: 64, 55, 42, and 33). Endoscopic surveillance is ongoing for the proband and her 42-year-old daughter. Endoscopic findings include circumferential folds and texture changes of the esophageal mucosa (Figure 2). Histological findings were consistent with tylosis in both: squamous mucosa with increased glycogen and/or focal parakeratosis with one having epidermoid metaplasia/esophageal leukoplakia in the distal esophagus.

RESULTS:The clinical data available supports the suggestion of a lower SCC incidence than historically described. Endoscopic surveillance has successfully identified potential precursors to SCC and supports regular endoscopic screening in the management of tylosis.
CONCLUSIONS:Albeit rare, clinicians working in the hereditary gastrointestinal field need to be aware of tylosis. Genetic testing is available at clinical diagnostic laboratories and should be considered for individuals with a personal or family history of hyperkeratosis and SCC esophageal cancer.

Keywords: Tylosis, hyperkeratosis, squamous cell carcinoma, esophageal cancer, RHBDF2

Figure 1 & Figure 2

Figure 1	Figure 2
	
hyperkeratosis of the soles of feet	circumferential folds and texture changes of the esophageal mucosa

P-018

Case Report/Case Series » no sub topic

SOFT TISSUE TUMORS IN FAP – NOT ALL THAT MEETS THE EYE ARE DESMOIDS

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POSTER ABSTRACTS

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BACKGROUND:Schwannomas are mesenchymal tumors located in peripheral nerves or central nervous system most commonly in the head, neck, mediastinum, or nerve plexuses. They are associated with pathogenic variants (PV) in NF1, NF2, SMARCB1, and LZTR1 and have been rarely reported in familial adenomatous polyposis (FAP).
We report 2 cases of schwannoma in FAP, one occurring in a rare pelvic retrorectal (Pelvic-RR) location.

METHODS:Case 1: 19-year-old female with a history of hepatoblastoma at age 2, treated with partial hepatectomy and chemotherapy developed hematochezia and weight loss. On colonoscopy >800 adenomas were detected. A commercial 84 gene panel (including SMARCB1, NF1, NF2) was performed, detecting APC PV c.3183_3187del. A total proctocolectomy-ileoanal pouch (TPC-IPAA) was aborted after a 9 cm Pelvic-RR presumed desmoid tumor was found and the patient was referred to our center. TPC-IPAA with resection of Pelvic-RR mass was performed. Pathology of the Pelvic-RR mass was consistent with schwannoma. Additional genetic testing did not detect a PV in LZTR1.
Case 2: 46-year-old male with a family history of FAP and desmoids was diagnosed with FAP at age 16, underwent colectomy with IRA at age 20 (>100 polyps). Single site APC testing at age 38 confirmed a PV in APC 453del. Schwannoma was diagnosed age 33 on heel pain evaluation and then found in the neck, back and sciatic nerve. All were surgically removed. Commercial schwannoma panel testing at age 42 confirmed a likely PV, LZTR1 c.2304delG.

RESULTS:The incidence of schwannoma is 0.44/100,000 per year. They are rare in FAP and uncommon to occur spontaneously in the Pelvic-RR location. Not all FAP soft tissue tumors should be attributed to desmoid disease. Additional genetic testing (SMARCB1, NF1, NF2, LZTR1) should be offered if presentation warrants.

CONCLUSIONS:I hereby confirm that consent on the relevant patient(s) has been obtained to submit this case series abstract.

Keywords: Schwannomas, Desmoid, Familial Adenomatous Polyposis (FAP)

POSTER ABSTRACTS

P-019

Case Report/Case Series » no sub topic

MIXED HIGH GRADE OVARIAN CANCER WITH FOCAL LOSS OF MLH1/PMS2 AND GERMLINE *BRCA2* PATHOGENIC VARIANT: INTEGRATION OF GERMLINE AND SOMATIC SEQUENCING

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BACKGROUND:Germline pathogenic variants (gPV) in *BRCA1/2* are associated with high-grade serous ovarian cancer (OC), a homologous recombination-deficient (HRD) phenotype that benefits from PARP inhibitors. In contrast, gPV in the mismatch repair (MMR) genes are associated with endometriosis-associated endometrioid or clear cell OC that exhibit an MMR-deficient phenotype that may benefit from immune checkpoint blockade.

METHODS:A 66-year-old female of Ashkenazi Jewish ancestry was seen due to a diagnosis of Stage II mixed high-grade serous and endometrioid OC, which exhibited subclonal loss of MLH1/PMS2 expression in the endometrioid component. Her family history was significant for a mother with pancreatic cancer at age 70 and a maternal grandmother with breast cancer at age 40. Paired tumor-normal sequencing via MSK-IMPACT identified the *BRCA2* c.5946delT (p.Ser1982Argfs*22) gPV but no gPV or uncertain variants in the MMR genes. In addition, the endometrioid component was microsatellite stable (MSS) and did not harbor somatic mutations affecting the MMR genes; *MLH1* promoter hypermethylation was also not detected. By contrast, there was biallelic inactivation of *BRCA2* within the tumor with loss of the wildtype allele, associated with an HRD mutational signature.

RESULTS:These findings suggest that the patient's OC was likely driven by the *BRCA2* gPV with subclonal loss of MLH1/PMS2 expression as a passenger event. The patient has finished 6 cycles of platinum-based chemotherapy. Based on these findings, she has been recommended PARP inhibitor maintenance therapy. She has also undergone genetic counseling with a plan for cascade testing of at-risk relatives.
CONCLUSIONS:Paired tumor-normal sequencing allows integration of molecular and histologic data to better define tumor phenotypes and germline drivers with implications for both treatment and familial risk assessment.

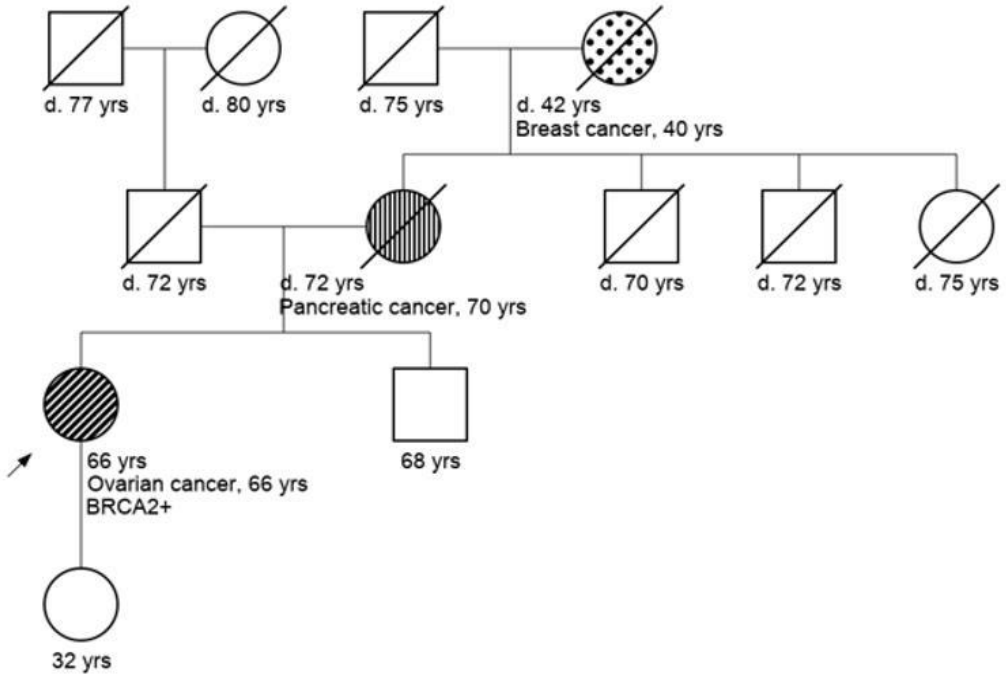
I hereby confirm that the consent of the relevant patient(s) has been obtained to submit this Case Reports / Case Series abstract.

POSTER ABSTRACTS

Keywords: ovarian cancer, BRCA1/2, mismatch repair deficiency, tumor-normal genetic testing

Figure 1

Figure 1: Pedigree



Pedigree

P-020

Case Report/Case Series » no sub topic

A NON-EXONUCLEASE DOMAIN GERMLINE POLE VARIANT IDENTIFIED IN A PATIENT WITH EARLY-ONSET COLORECTAL CANCER

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POSTER ABSTRACTS

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BACKGROUND:Germline *POLE* pathogenic variants (PV) cause polymerase proofreading-associated polyposis (PPAP), characterized by predisposition to colorectal adenomas and carcinomas. While most *POLE* PVs are missense variants found in the exonuclease domain (ED), there is limited evidence to support the pathogenicity of non-ED variants.

METHODS:A 49-year-old Hispanic male presented with a 5cm obstructive sigmoid mass, confirmed to be poorly differentiated invasive adenocarcinoma (T3N1). His maternal grandfather had colon cancer in his 40s and a maternal aunt had an unknown number of colon polyps in her 50s. The patient was enrolled in the ENLACE study, a NCI-Moonshot-funded study of participant engagement in genomic characterization among Hispanic colorectal cancer patients. A germline variant of unknown significance (VUS) in the *POLE* gene, c.2770C>T (p.Arg924Cys), was identified. Somatic testing revealed a high tumor mutational burden (TMB) of 56 mut/Mb and microsatellite instability-high (MSI-H).

RESULTS:PVs in *POLE* are typically found in the ED and are characterized by ultra-high TMB (≥100 mut/Mb), with microsatellite stability (MSS), but can also be drivers of mismatch repair (MMR) deficiency. Non-ED *POLE* variants have been reported as high TMB (10-100 mut/Mb), MSI-H, with some cases explained by *MLH1* hypermethylation or double somatic MMR gene mutations. However, a prior study showed a non-ED *POLE* variant, without ultra-high TMB, that altered function and responded well to immunotherapy (Dong et al., 2022).

CONCLUSIONS:This patient's early-onset diagnosis, family history, MSI-H, and high TMB could suggest *POLE* c.2770C>T pathogenicity. However, until further evidence is obtained, the patient has been counseled as having uninformative germline testing. The patient may benefit from immunotherapy given his high TMB and MSI-H tumor. More studies are needed to understand the role of non-ED *POLE* variants and their association with hereditary colorectal cancer.

I hereby confirm that the consent of the relevant patient has been obtained to submit this Case Reports/Case Series abstract.

Keywords: POLE, non-exonuclease domain, early-onset colorectal cancer

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P-021

Case Report/Case Series » no sub topic

BONE MARROW CHANGES DETECTED ON PERIPHERAL BLOOD MULTI-GENE PANEL TESTING IN A PATIENT WITH COLON CANCER PRIOR TO AML DIAGNOSIS

POSTER ABSTRACTS

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BACKGROUND:Multi-gene panel testing (MGPT) has risks of incidental findings including detection of circulating tumor DNA or hematologic malignancy. The frequency of these incidental results and their management remains unknown.

METHODS:We present a case where MGPT results detected bone marrow changes months prior acute myeloid leukemia (AML) diagnosis. A male with a history of B-cell lymphoma at 61y, in complete remission after Adriamycin-based chemotherapy, was diagnosed with stage 1 sigmoid adenocarcinoma at 64y. Multiple malignancies were noted in family members, including a sister with young-onset colorectal cancer and polyposis (Figure 1). Her MGPT identified a MUTYH pathogenic variant c.536A>G in trans with a MUTYH variant of uncertain significance c.1073_1075delinsACA. MGPT was ordered on the patient's peripheral blood. Two attempts at deletion/duplication analysis failed and only sequencing results were reported. The patient was identified to have the same MUTYH variants as his sister in 46-58% of sequencing reads and a TP53 pathogenic variant c.376-2A>G in 74-84% of sequencing reads. The patient's MGPT results and non-specific symptoms of weakness and malaise raised concerns for potential hematologic malignancy, lymphoma recurrence, or unidentified metastatic malignancy. The patient had unremarkable chest/abdomen/pelvis CT and CBC six weeks after MGPT. Three months after MGPT, while awaiting further work-up, the patient presented with severe leukocytosis and AML was diagnosed. Bone marrow analysis revealed a complex karyotype and the TP53 pathogenic variant c.376-2A>G at 96% variant allele frequency. It is undetermined if the TP53 pathogenic variant was germline.

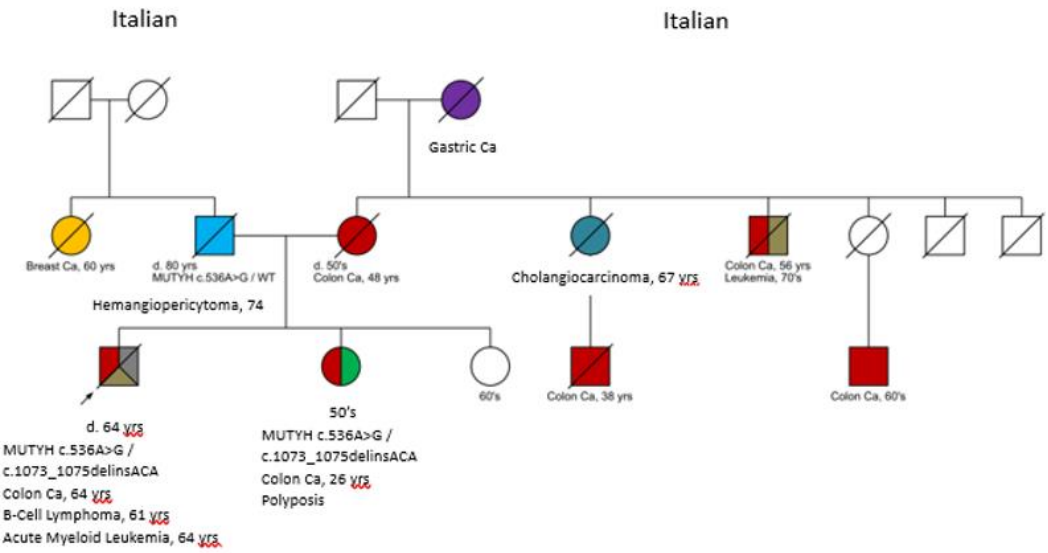
RESULTS:Our case demonstrates the identification of bone marrow changes on MPGT prior to hematologic malignancy clinical presentation. Individuals with failure of deletion/duplication analysis that have variants with higher-than-expected percentage of sequencing reads on MGPT should be considered for hematologic malignancy evaluation.

CONCLUSIONS:I hereby confirm that the consent of the relevant patient has been obtained to submit this Case Report Abstract.

POSTER ABSTRACTS

Keywords: Incidental findings, TP53, AML

Figure 1



3-generation pedigree

P-022

Collaborative » no sub topic

MRD ASSAY EVALUATES RECURRENCE AND RESPONSE VIA A TUMOR INFORMED ASSESSMENT: MARIA-COLORECTAL OBSERVATIONAL TRIAL

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BACKGROUND:Detectable ctDNA in patients with solid tumors has been associated with disease prognosis pre-treatment, assessing response to therapy in the form of minimal residual disease (MRD), and monitoring for recurrence after curative intent treatment. Studies have shown that pretreatment levels of ctDNA, using an individual's cancer profile in conjunction with the patient's germline DNA for high sensitivity MRD detection,are a potential early indicator of disease recurrence after surgery, that ctDNA clearance may be an early predictor of favorable outcomes and has been shown to correlate with pathologic complete response (Forde et al. N Engl J Med. 2022, PMID:35403841), and that this approach has high sensitivity for detecting recurrence for patients in advance of the current standard of care (Abbosh et al. Cancer Res (2020) 80 (16_Supplement): CT023).

METHODS:This is a multi-site, prospective, observational trial in the United States of 200 patients with early stage colorectal cancer undergoing curative intent treatment, using a patient-specific bespoke MRD assay for ctDNA analysis. ctDNA will be analyzed with an NGS-based tumor-informed MRD assay that identifies somatic mutations from DNA obtained from the patient's tumor tissue, subtracts germline variants via NGS-based analysis of the patient's germline DNA, and detects a selected set of between 18-50 tumor-specific ctDNA in their blood. All primary tumor specimens will undergo full exome sequencing using the Personalized Cancer Monitoring (PCM) assay. Impact of results of this CLIA-approved MRD assay on clinical decision making will be captured.

RESULTS:The primary objective is to assess the ability of MRD to predict post-treatment recurrence. Further objectives are to correlate MRD status with pathologic complete response, determine the lead time to detection of recurrence compared to standard of care, and the association of MRD status with overall survival.

CONCLUSIONS:Active enrollment started in March, 2022. Support: Invitae. Clinical trial information: NCT05219734.

Keywords: colorectal cancer, minimal residual disease, MRD, liquid biopsy, trials in progress, collaboration

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P-023

General Research » Other

CLINICIAN REPORTED OUTCOMES OF UNIVERSAL GERMLINE GENETIC TESTING IN COLORECTAL CANCER PATIENTS IN AN ARAB POPULATION

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POSTER ABSTRACTS

BACKGROUND:Little is known about how often identification of a pathogenic germline variant (PGV) is used to inform treatment and management decision-making, particularly in understudied populations. This study was designed to collect clinician reported outcomes (CROs) from unselected colorectal cancer (CRC) pts who underwent germline genetic testing (GGT).

METHODS:The Jordanian Exploratory Cancer Genetics Study was a prospective study of newly diagnosed cancer pts. Pts were classified as in (IC) or out of (OOC) National Comprehensive Cancer Network v1.2020 GGT criteria. Pts underwent an 84-gene panel test with CRO case report forms completed >2 months post-GGT. Analyses were limited to CRC pts. Descriptive statistics and Fisher's exact test were employed.

RESULTS:492 Arabic CRC pts with a mean age at diagnosis of 56.0 (SD 13.0) years were tested; 48.6% met NCCN GGT criteria. PGVs were identified in 95 (19.3%) pts (Table) and were most frequently identified in: APC I1307K (7.4%), Lynch syndrome genes (5.2%), and biallelic MUTYH (1.4%). Among PGV positive pts with informative responses, 3/92 (3.3%) had changes to treatment, and 79/85 (92.9%) had changes to surveillance/follow up recommendations based on GGT results, 25 (31.6%) of whom were OOC. Genetic counseling and/or GGT (GC/GGT) was recommended for relatives of 42/46 (91.3%) positive pts. No changes to treatment or management were made for pts with negative or uncertain results.

CONCLUSIONS:Nearly 1 in 5 Jordanian CRC pts had a PGV identified, with a higher percentage of APC I1307K and biallelic MUTYH observed than in other ethnic cohorts. While a minority of pts had changes to treatment as a result of testing, the majority did have changes to surveillance/follow up. Clinicians appropriately did not escalate treatment or management for pts with negative or uncertain results.

Keywords: hereditary cancer, hereditary colorectal cancer, MUTYH-associated polyposis, universal germline genetic testing

Abdel Razeq JoECG CRC study table

Table. Outcome of GGT in CRC pts

	Overall (n=492)	IC (n=239)	OOC (n=253)
Results	Number (%)		
Positive	95 (19.3)	61* (25.5)	34* (13.4)
Carrier	13 (2.6)	7 (2.9)	2 (2.4)
Negative	124 (25.2)	45# (18.8)	79# (31.2)
Uncertain	260 (52.9)	126 (52.7)	134 (55.0)

*#p<0.05

POSTER ABSTRACTS

P-024

Collaborative » no sub topic

DEMETRA STUDY: PROPOSAL FOR AN INTERNATIONAL MULTICENTER CASE-CONTROL STUDY ON ENDOGENOUS AND EXOGENOUS RISK FACTORS IN EARLY-ONSET COLORECTAL CANCER

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BACKGROUND:Dietary, lifestyle and anthropometric risk factors are still poorly understood in eoCRC patients, despite its established rising incidence.

METHODS:To compare the associations of specific dietary and lifestyle factors (smoking habit, alcohol intake, physical activity) and anthropometric factors between eoCRC patients and healthy age- and sex-matched controls in countries with increasing versus stable or decreasing early-onset colorectal cancer (eoCRC) incidence.
To evaluate the consistency of associations across cohorts in pairwise comparisons.
To assess whether associations differ among specific population subgroups (e.g., sex, ethnicity, smoking habits, BMI, physical activity, family history of CRC).

RESULTS:The online platform is divided into two separate sections: one completed by cases/controls, concerning the semi-quantitative food frequency questionnaire (SQFFQ), lifestyle habits and anthropometric data; one completed by doctors, concerning clinical data.
The SQFFQ approach will ask to report usual frequency of consumption of each food and drink, referred to the two years before eoCRC onset. Information collected will concern types, amount and frequency of consumption of food and drinks, types of seasoning, and methods of cooking. A computer-administered instrument will allow the respondent to select the food consumed and the appropriate portion size from photographs on a screen reducing the burden of coding. All cases and healthy controls will also provide a set of clinical covariates as part of the online platform.

CONCLUSIONS:We aim to compare using the same SQFFQ, the associations of specific dietary and lifestyle factors (smoking habit, alcohol intake, physical activity) and anthropometric factors between eoCRC patients and healthy age- and sex-matched controls in countries with increasing versus stable or decreasing early-onset colorectal cancer (eoCRC) incidence.

Keywords: Collaborative international case-control study proposal, early onset colorectal cancer, endogenous and exogenous risk factors, semi-quantitative food frequency questionnaire.

POSTER ABSTRACTS

P-025

General Research » Delivery of Care and Alternative Models

A MULTIDISCIPLINARY MODEL FOR EARLY-ONSET COLORECTAL CANCER. FROM DIAGNOSIS TO TRANSLATIONAL RESEARCH

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BACKGROUND:The incidence of early-onset colorectal cancer (eoCRC), is increasing globally. Patients with eoCRC are often managed according to clinical practices that are not specific for this age group. eoCRC patients have distinct needs and their disease could has peculiar features that differ from CRC after the age of 50.

METHODS:The team includes gastroenterologists, genetists, abdominal surgeons, gynecologists, urologists, medical oncologists, pathologists, fertility specialists, clinical psychologists and biologists for translational research.
All eoCRC patients are offered multi-gene panel germline genetic testing and genetic counseling. When immediate surgery is indicated, our genetic unit provides uniquely fast genetic results (within 20 days).
Standard segmental resections are offered to eoCRC. Extended surgery is only considered for individuals with a pathogenic variants. Combined surgery with colorectal resection and prophylactic hysterectomy with or without bilateral oophorectomy is considered.
Referral to a reproductive medicine specialist before treatment and/or infertility information is provided. For females seeking pregnancy, but at risk of radiotherapy-induced premature ovarian failure, ovarian transposition is offered.
Oncological treatments and supportive care of eoCRC is personalized based on the patient's needs and expectations
A biobanking of biological speciments from the patients (buffy coat, serum, plasma and tissue speciments from normal tissue and cancer) is collected from each patient for translational research to discover novel mechanisms governing eoCRC and develop innovative therapies

RESULTS:Design a fast-track approach to offer "straight-to-test" clinical evaluation if alarming symptoms are present
Construct a well-established and regular scheme from the bedside to the bench and backwards
Reproduce a quick turn-around strategy to offer genetic test results before the commencement of treatments
Examine the risks of infertility and summarize possible fertility preservation options.

POSTER ABSTRACTS

CONCLUSIONS:A multidisciplinary approach would provide optimal care to eoCRC patients. A transational research staff in the context of the multidisciplinary group can brings translational research from the bench to the bedside.

Keywords: Early onset colorectal cancer management, multidisciplinary group

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P-026

General Research » Gastric cancer-related syndromes

RISK FACTORS AND CLINICAL CHARACTERISTICS OF YOUNG-ONSET GASTRIC CANCER VS. LATE-ONSET GASTRIC CANCER: A CASE-CASE STUDY

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BACKGROUND:Young-onset gastric cancer (YOGC), a GC before 50y, accounts for 5% GC and 3% are part of a hereditary syndrome. Its incidence is rising, presents at an advanced stage at diagnosis, with a poor differentiation and a worse prognosis than in the elderly (late-onsetGC, loGC). YOGC risk factors and characteristics remain unclear. Therefore, we compared YOGCs with loGCs in terms of clinicopathological characteristics and risk factors.

METHODS:We conducted a retrospective case-case study of patients with YOGC and loGC diagnosed from 2015 to December 2022 at IRCCS San Raffaele Hospital (Milan, Italy). We collected clinical data, tumor characteristics (including Helicobacter Pylori status, HP), family history of cancers, smoking, alcohol, BMI. We performed multi-gene panel testing on all YOGC.

POSTER ABSTRACTS

RESULTS:54YOGC (53.7%M,46.3%F; median age at diagnosis 45y) and 217loGCs (61.8%M,38.2%F; median age at diagnosis 72y) were enrolled. 18.5%YOGCs carried a germline pathogenic variant (3CDH1; 2TP53; 2MMR; 1ATM; 1PTEN; 1MUTYH). Having a second-degree relative (SDR) with GC was associated with YOGC (p=0.016). No significant differences were observed for BMI (p=0.083) and HP status (p=0.913); YOGCs reported significantly more actual drinking (52.8%YOGC vs 27.8%loGC, p=0.04) and smoking habits (24.5%YOGC vs 10.4%loGC, p=0.017)(Tab.1).
While YOGCs were mainly at the cardia (31.5%YOGC vs 2.3%loGC, p<0.001), loGCs were mostly at the antrum (40.6%loGC vs 20.4%YOGC, p=0.007). 50%YOGCs were diffuse-type adenocarcinoma (vs 30.4%loGC, p=0.01), while 55.8% loGCs were intestinal-type (vs 16.7%YOGCs, p<0.001). TNM and stage at diagnosis didn't differed significantly, even if 34.9% YOGCs were early-gastric cancers (vs 21.7%loGCs)(Tab.2).

CONCLUSIONS:YOGCs often carry germline pathogenic variants, suggesting that patients with YOGC should receive genetic testing at diagnosis. A SDR with GC, alcohol and smoking could be YOGC's risk factors. YOGC more often presents at cardia and as diffuse-type adenocarcinoma. 34.9%YOGC presents with early-gastric cancer even if not statistically significant (p=0,07), possibly implying that younger age does not entail worse outcomes.

Keywords: Young-onset gastric cancer, risk factors, lifestyle, germline variants

Tables

Table 1. Clinical data and risk factors

		YOGC (54)	loGC (217)	p
Gender (%)	M	29 (53.7%)	134 (61.8%)	0.282
	F	25 (46.3%)	83 (38.2%)	
Age at diagnosis (median [IQR])		45 [39.25, 47.75]	72 [65.00, 77.00]	/
FDR with GC (%)		7 (13.2%)	17 (16.2%)	0,815
SDR with GC (%)		**9 (17%)**	**5 (4.8%)**	**0.016***
Germline PVs (%)		**10 (18.5%)**	/	
BMI (median [IQR])		22 [20.00, 26.50]	24 [22.00, 27.00]	0.083
Drinking (%)	No	**25 (47.2%)**	**65 (72.2%)**	**0.004***
	Yes	**28 (52.8%)**	**25 (27.8%)**	
Smoking (%)	No	**26 (49.1%)**	**78 (47.6%)**	**0.017***
	Former	**14 (26.4%)**	**69 (42.1%)**	
	Smoker	**13 (24.5%)**	**17 (10.4%)**	
HP status (%)	No	17 (54.8%)	42 (59.2%)	0,913
	Eradicated	6 (19.4%)	11 (15.5%)	
	HP +	8 (25.8%)	18 (25.4%)	

Table 2. TNM and Stage at diagnosis

		YOGC (54)	loGC (217)	p
T (%)	1	**15 (34.9%)**	**47 (21.7%)**	0,313
	2	4 (9.3)	22 (10.1)	
	3	16 (37.2)	90 (41.5)	
	4	8 (18.6)	58 (26.7)	
N (%)	0	16 (39.0)	97 (44.7)	0,457
	1	5 (12.2)	26 (12.0)	
	2	9 (22.0)	27 (12.4)	
	3	11 (26.8)	67 (30.9)	
M (%)	0	36 (83.7)	198 (91.2)	0,161
	1	7 (16.3)	19 (8.8)	
stage (%)	1	15 (28.3)	55 (25.3)	0,053
	2	4 (7.5)	51 (23.5)	
	3	8 (15.1)	28 (12.9)	
	4	26 (49.1)	83 (38.2)	

Table 1. Clinical data and risk factors Table 2. TNM and stage at diagnosis

POSTER ABSTRACTS

P-027

Collaborative » no sub topic

FIFTEEN YEAR SEARCH FOR CAUSATIVE APC MUTATION IN A FIVE GENERATION FAMILY REVEALS NONCODING 5'UTR VARIANT IN APC PROMOTER WITH FUNCTIONAL CONSEQUENCE

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BACKGROUND:Germline mutations in the APC gene result in familial adenomatous polyposis which, if untreated, escalates into colon cancer. Genetic markers linked with APC segregated with adenomatous polyposis in the presenting family. APC coding exons and splice junctions failed to reveal pathogenic variants. Additional sequencing of the promoter regions identified a 5' untranslated region (UTR) point mutation, APC c.-40G>A (GRCh37 chr5:112043375), creating a potential out-of-frame ATG start codon. This was confirmed in three affected family branches descending from 1870's. We hypothesize that the false translational start codon squelches translation initiation from the downstream canonical start codon and creates an out-of-frame protein.

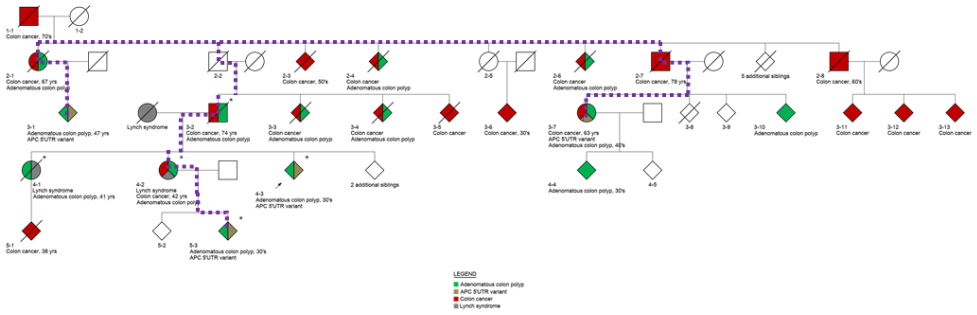
METHODS:PreTIS tool was used to calculate translational initiation confidence in 5'UTR mRNA sequences. A luciferase-based reporter consisting of the entire 5'UTR and first 81 bases of APC (NM_001127511.3) was constructed to look at APC RNA and protein expression. Four constructs were created: 1) WT APC canonical start codon in frame with luciferase and mutation absent; 2) MUT APC canonical start codon in frame with luciferase and mutation present; 3) MUT-IF mutation present and in-frame with luciferase; 4) WT-out-of-frame mutation absent but luciferase in frame with respect to mutation.

RESULTS:The APC c.-40G>A mutation was predicted to create a novel start codon with the highest confidence value of 1.0. Using the WT construct as a baseline, we observed a 7.74[5.46, 10.59] and 1.30[0.93, 1.76] fold decrease in luciferase activity with the MUT and MUT-IF constructs respectively supporting the hypothesis that the false start codon squelches translation initiation from the canonical start codon. Luciferase activity from the MUT-IF construct shows that the alternate start site can be utilized.
CONCLUSIONS:The results of this study provide functional and computational evidence towards classification of APC c.-40G>A. It underlines the importance of clinical labs screening non-coding regions, such as the 5'UTR, which can harbor pathogenic sequence variants.

Keywords: APC, familial polyposis, 5' UTR, mutation, sequencing, luciferase reporter

French Canadian family with familial adenomatous polyposis

POSTER ABSTRACTS



Transmission of the APC 5'UTR mutation is indicated by heavy purple dashes. Original linkage is indicated by asterisk. Lynch syndrome (from mother) is in grey, whereas FAP is from the father. Adenomatous polyps are indicated as green and colon cancer as red with age (if known).

P-028

Collaborative » no sub topic

THE UC SAN DIEGO HEREDITARY/HIGH RISK GI NEOPLASIA REGISTRY: PILOT LYNCH SYNDROME RESULTS

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BACKGROUND:Characteristics and outcomes of individuals at high risk for GI neoplasia are incompletely understood. Registries that concentrate patients with familial GI cancer provide important data to learn from and to improve care. Our aim was to establish the UCSD Hereditary/High Risk GI Neoplasia registry, starting with a focus on Lynch syndrome (LS).

POSTER ABSTRACTS

METHODS:In partnership with the Lynch syndrome INtegrative Epidemiology And GEnetics (LINEAGE) Consortium, we adapted a REDCap hereditary registry previously created at Kansas University Medical Center. We report pilot implementation results for individuals with LS at UCSD 1995- 2023. Descriptive statistics for demographic information, colorectal cancer (CRC) history, and yield of surveillance colonoscopy were summarized.

RESULTS:With minimal adaptation over 2 months, we implemented the database. We included 187 individuals with LS: median age at first visit 53 years; 69.0% female; 12.8% Asian; 3.7% Black; 16.6% Hispanic, and 63.6% non-Hispanic white; with 23.0% MLH1, 33.7% MSH2/EpCAM, 19.8% MSH6, and 23.5% PMS2 pathogenic variant (PV) carriers (Table 1). CRC was present prior to LS diagnosis for 9.7%, simultaneous to LS diagnosis for 14.4%, and after LS diagnosis for 5.3% across all PVs, with significant variation by PV (Table 2). Median and youngest ages for CRC per PV ranging from a low of 43 and 23 for MLH1 to a high of 63 and 38 for PMS2 carriers (Table 2). 167 patients received >=1 colonoscopy: cumulative proportion with CRC and any adenoma were 28.2 and 59.0% for MLH1, 21.3 and 60.7% for MSH2, 20.0 and 60.0% for MSH6, and 5.4 and 51.4%% for PMS2 PV carriers, respectively.

CONCLUSIONS:At UCSD, we leveraged a previously established database to create a registry of racial/ethnically diverse LS PV carriers, with outcomes varying by PV. Pooling our results with LINEAGE will allow for better understanding of LS outcomes and surveillance strategies.

Keywords: Lynch Syndrome, Hereditary Colon Cancer, Registry, Surveillance Outcomes

Table 1

Table 1. UC San Diego Lynch Syndrome Registry: Demographic Information						
	Total	MLH1	MSH2/EpCAM	MSH6	PMS2	p-value
Number, n (%)	187	43 (23.0%)	63 (33.7%)	37 (19.8%)	44 (23.5%)	
Median Age (IQR)	53.0 (43.3,64.9)	50 (38.7, 59.2)	50 (42.2,64.9)	55.3 (46.2,65.3)	56.2 (44.4,66.5)	0.13
Sex at birth, n (%)						0.25
Male	58 (31.0%)	8 (18.6%)	21 (33.3%)	13 (35.1%)	16 (36.4%)	
Female	129 (69.0%)	35 (81.4%)	42 (66.7%)	24 (64.9%)	28 (63.6%)	
Race/Ethnicity, n (%)						0.66
Asian	24 (12.8%)	7 (16.2%)	8 (12.7%)	4 (10.8%)	5 (11.3%)	
Black	7 (3.7%)	2 (4.7%)	2 (3.2%)	3 (8.1%)	0	
Hispanic	31 (16.6%)	7 (16.3%)	11 (17.5%)	8 (21.6%)	5 (11.4%)	
Non-Hispanic White	119 (63.6%)	25 (58.1%)	39 (61.9%)	21 (56.8%)	34 (77.3%)	
Unknown/other	6 (3.3%)	2 (4.7)	3 (4.7%)	1 (2.7%)	0	
Median BMI[1] (IQR)	26.0 (23.0,31.0)	25.0 (22.0,29.0)	24.0 (22.8,32.0)	28.0 (24.0,32.0)	26.0 (22.0,29.0)	0.09
Tobacco smoking[1], n (%)						0.65
Nonsmoker	135 (72.2%)	29 (67.4%)	47 (74.6%)	30 (81.1%)	29 (65.9%)	
Current	8 (4.3%)	4 (9.3%)	3 (4.8%)	0	1 (2.3%)	
Former	38 (20.3%)	9 (21.0%)	11 (17.5%)	6 (16.2%)	12 (27.3%)	
Unknown/other	6 (3.2%)	1 (2.3%)	2 (3.1%)	1 (2.7%)	2 (4.5%)	
Aspirin, n (%)						0.63
Yes	61 (32.6%)	14 (32.6%)	22 (34.9%)	12 (32.4%)	16 (36.4%)	
No	121 (64.7%)	29 (67.4%)	41 (65.1%)	25 (67.6%)	26 (59.1%)	
Unknown	2 (2.7%)	0	0	0	2 (4.5%)	
[1]BMI, smoking, and aspirin use abstracted at time of first UCSD visit						

UC San Diego Lynch Syndrome Registry: Demographic Information

Table 2

POSTER ABSTRACTS

Table 2. UC San Diego Lynch Syndrome Registry: CRC Events and Cumulative Yield of Colorectal Neoplasia Surveillance						
	Total	MLH1	MSH2	MSH6	PMS2	p-value
CRC Events						
n	187	43	63	37	44	
History of CRC[1], n (%)	55 (29.4%)	19 (44.2%)	22 (34.9%)	9 (24.3%)	5 (11.4%)	**<0.01**
Detected prior to LS diagnosis	18 (9.7%)	7 (16.3%)	10 (15.9%)	1 (2.7%)	0	
Detected at time of LS diagnosis	27 (14.4%)	7 (16.3%)	8 (12.7%)	7 (18.9%)	5 (11.4%)	
Detected after LS diagnosis	10 (5.3%)	5 (11.6%)	4 (6.3%)	1 (2.7%)	0	
Median age of CRC diagnosis (IQR), years	47.0 (38.0,54.0)	42.0 (35.0,50.0)	43.5 (38.0,53.0)	51.0 (46.0,62.5)	63.0 (48.5,74.5)	**0.01**
Youngest Age of CRC diagnosis observed, years		23	28	33	48	
Colonoscopy surveillance outcomes among patients with ≥1 surveillance exam						
Number	167	39	61	30	37	
Any Adenoma, n (%)	97 (58.1%)	23 (59.0%)	37 (60.7%)	18 (60.0%)	19 (51.4%)	0.66
Any NAA, n (%)	53 (31.7%)	13 (33.3%)	21 (34.4%)	11 (36.7%)	8 (21.6%)	
Any AA, n (%)	44 (26.4%)	10 (25.7%)	16 (26.2%)	7 (23.3%)	11 (29.8%)	
CRC, n (%)[2]	32 (19.2%)	11 (28.2%)	13 (21.3%)	6 (20.0%)	2 (5.4%)	0.08

[1]Cumulative data includes neoplasia detected at baseline colonoscopy plus subsequent follow up
[2]Includes CRC diagnosed at first (baseline) surveillance exam or at subsequent follow up colonoscopy

UC San Diego Lynch Syndrome Registry: CRC Events and Cumulative Yield of Colorectal Neoplasia Surveillance

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P-029

Collaborative » no sub topic

EVALUATING COLONOSCOPY SCREENING INTERVALS IN PATIENTS WITH LYNCH SYNDROME: EXTENDING RESULTS FROM A LARGE CANADIAN REGISTRY

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BACKGROUND:Lynch Syndrome (LS) screening guidelines originally recommended colonoscopy every 1 to 2 years, beginning between the ages of 20-25 years. Recent studies have questioned the benefits of these short screening intervals in preventing colorectal cancer (CRC). Our goal is to determine how colonoscopy screening intervals impact CRC in patients with LS.

METHODS:We analyzed the demographics, screening practices and outcomes of patients with LS identified through the clinic based Familial Gastrointestinal Cancer Registry at the Zane Cohen Centre, Sinai Health System, Toronto.

POSTER ABSTRACTS

RESULTS:Using a total of 429 patients with LS, we found a positive trend between shorter screening intervals and the number of adenomas detected during colonoscopy surveillance. In turn, any new adenoma detected at screening decreased 10-year CRC incidence by 11.3%. The recommended colonoscopy screening interval of 1-2 year is efficient at detecting adenomas and reducing CRC risk. Yet, the observation that 53.4% of LS patients never had an adenoma warrants further investigation about a possible adenoma-free pathway. The goal of this presentation will be to seek collaboration to pursue this research in different directions including: 1) extending the recruitment of LS patients to other study sites; 2) Evaluate colonoscopy screening intervals on colorectal cancer incidence and maybe on cancer-specific mortality among carriers of pathogenic variants for each MMR gene separately; 3) Better incorporate information on colonoscopy quality; 4) Evaluate the impact of colonoscopy screening interval by colon sites (e.g., distal vs. proximal site).

CONCLUSIONS:This research will try to better understand how colonoscopy screening intervals impact CRC risk and also why some LS patients seem to escape the adenoma-related pathway.

Keywords: Lynch Syndrome; Colonoscopy; Screening Intervals; Adenomas; Colorectal Cancer.

P-030

Collaborative » no sub topic

LYNCH SYNDROME INTEGRATIVE EPIDEMIOLOGY AND GENETICS (LINEAGE) CONSORTIUM

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POSTER ABSTRACTS

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BACKGROUND:Data on Lynch syndrome (LS) genotype-specific cancer risks and risk modifiers are limited in the Americas. The aim of the Lynch syndrome INtegrative Epidemiology And GEnetics (LINEAGE) Consortium is to provide intellectual and infrastructure support for standardized, high-quality data collection to elucidate risk and risk modifiers of prevalent and incident cancer in LS. LINEAGE will be a platform to lead future epidemiologic, mechanistic, and intervention studies in LS.

METHODS:Since June 2022, a working group has met regularly to formulate an organizational structure, roles/expectations, and study design/infrastructure.

RESULTS:The organizational structure is presented in Figure 1. A charter outlining roles/assurances/expectations, data hosting/coordination, and administrative tasks has been drafted. Study design is shown in Figure 2; hybrid retrospective/prospective cohort study of adults with a LS-associated gene variant. We will build a centrally hosted REDCap database, adapted from an existing hereditary cancer registry, for electronic health record (EHR) abstraction, patient and endoscopist surveys. Future initiatives include biospecimen acquisition and banking. Participating sites will contribute baseline data and annual updates for the duration of participation. Additional consortium policies are in development.

CONCLUSIONS:Establishing a LS collaborative consortium of the Americas will help to understand the natural history of LS and enable the development of optimal evidence-based cancer prevention strategies. We invite interested sites to join the LINEAGE consortium. We will provide an onboarding toolkit that will include a draft protocol, consent form, data use agreement and data dictionary. These documents can be adapted to existing registries/databases and site-specific regulatory requirements. In the short term, we expect to contribute to the scientific understanding of cancer risk and risk modifiers of prevalent and incident neoplasia in LS. The long-term goal of LINEAGE is to be a sustainable, high-quality, prospective consortium to collaboratively improve the lives and longevity of those with LS in the Americas.

Keywords: Lc: LINEAGE Council Member; Lynch Syndrome, Epidemiology, Colorectal neoplasia

Figure 1

POSTER ABSTRACTS

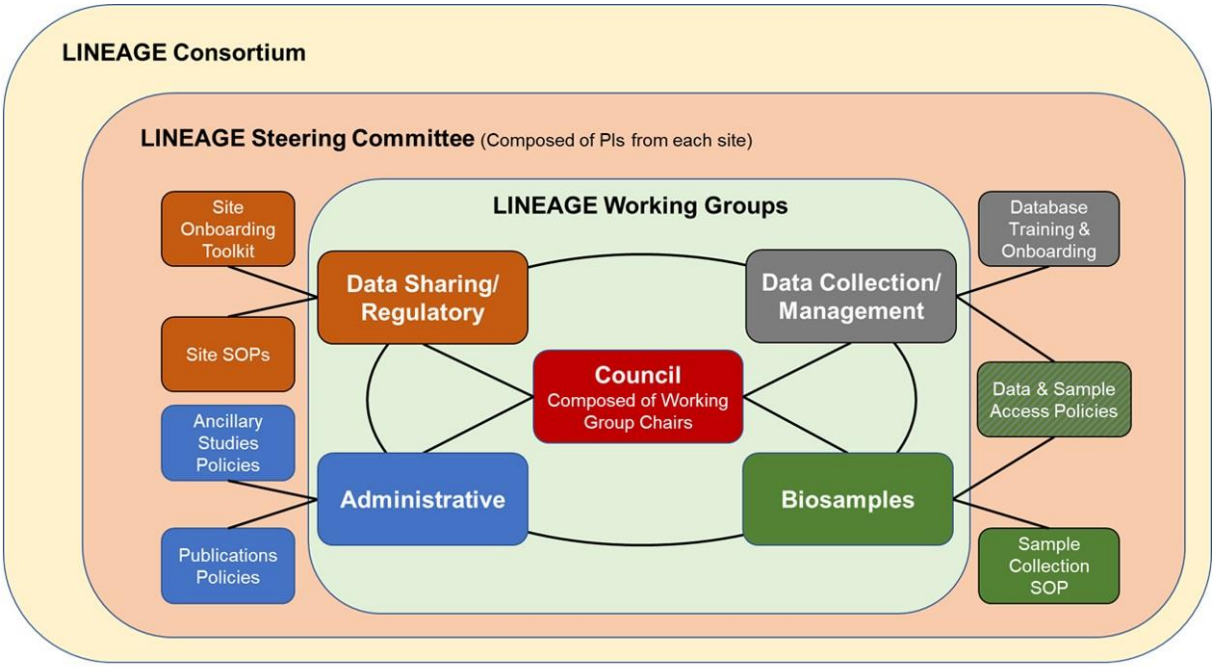

Figure 1. LINEAGE Consortium Structure. The LINEAGE Consortium Steering Committee is composed of a PI from each participating site. The Working Groups include members of the Steering Committee and are chaired by Council members. The Working Groups are responsible for drafting documents and proposals for review and vote by the entire Steering Committee.

Figure 2

POSTER ABSTRACTS

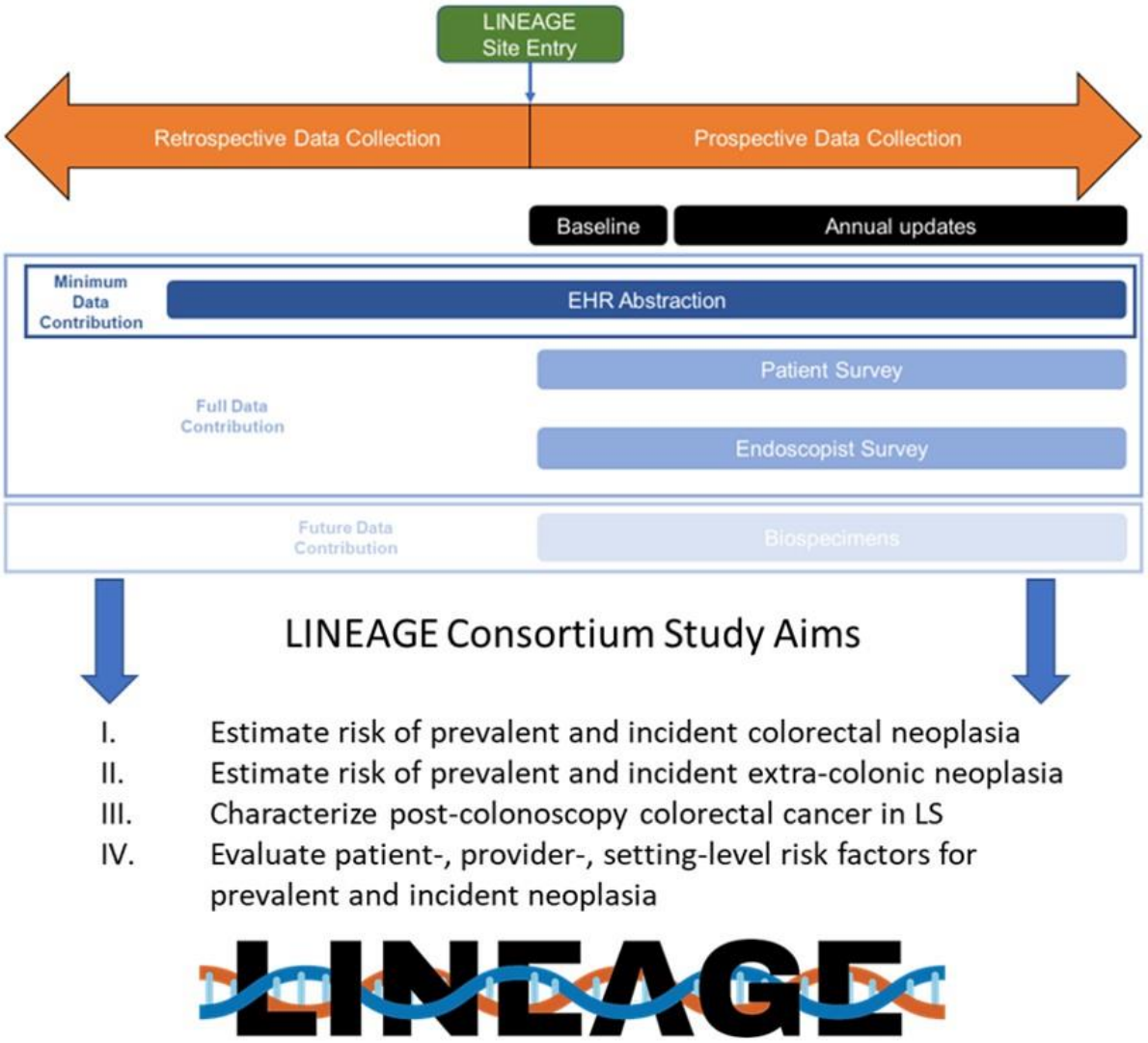

Figure 2. LINEAGE Study Design & Aims. Data abstracted from the EHR will include demographics, health history, genetic testing, and neoplasia outcomes. Patient surveys will collect diet/ lifestyle/medication data not available in the EHR and will verify key exposures (endoscopies) and outcomes (cancer) if performed/diagnosed outside of site EHR. A provider survey will also be completed to collect demographics, training, specialty, practice setting, and annual procedure volume from endoscopists who complete procedures on study participants to assess endoscopist-related quality measures.

POSTER ABSTRACTS

Diversity/Equity/Inclusion/Justice » no sub topic

THE CHALLENGE OF VARIANT CLASSIFICATION IN YOUNG PATIENTS SUSPECTED OF GASTRIC CANCER-RELATED SYNDROMES IN BRAZIL

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BACKGROUND:In Brazil, gastric cancer (GC) ranks as the third most common type of cancer among men and the fifth among women. According to the Brazilian National Cancer Institute, its prevalence varies across different regions. In the Northern and Northeastern regions, GC is the second most frequent cancer among men. Although the incidence of GC has shown a decline, the mortality rate remains alarmingly high.

METHODS:In this study, we present the results of variant calling from whole exome sequencing conducted on 13 young patients (under 40 years of age) from the Northeast region of Brazil whose genetic testing was negative. To analyze the variants, we employed the variant viewer ViVa, a robust tool for variant calling at both germline and somatic levels. Then, we manually classified the variants using a decision tree algorithm for the classification of VUS. This algorithm leveraged the predictive power of 15 different classification models. Furthermore, we classified the variants based on their impact on metabolic pathways associated with DNA replication, DNA repair, cancer hallmarks, tumor suppressor genes, and the CDH1 pathway.

RESULTS:The mean age at diagnosis was 34 years (ranging from 14 to 39 years), and 80% of them had a family history of GC. The diagnoses included 7 gastric, 1 gastroesophageal junction, 4 diffuse-type gastric, and 1 colon adenocarcinoma. Pathogenic variants were identified in the genes KCNJ11, MAP3K6, RET, GBE1, and ABCB6. However, as per clinical guidelines, these genes are not actionable, and therefore no genetic counseling or intervention was offered based on these findings.

CONCLUSIONS:These results underscore the significance of studying underrepresented populations, where genetic variants may be lacking in public databases. By focusing on these populations, we can gain valuable insights into the genetic landscape of GC-related syndromes and develop more comprehensive strategies for diagnosis, prevention, and treatment.

Keywords: Gastric Cancer Syndromes, Variant Calling, Decision Tree, Underrepresented Population

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P-033

Diversity/Equity/Inclusion/Justice » no sub topic

POSTER ABSTRACTS

FREQUENCY OF MISMATCH REPAIR TUMOR DEFICIENCY AND LYNCH SYNDROME IN DIVERSE COLORECTAL CANCER PATIENTS AT A SAFETY-NET MEDICAL CENTER

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BACKGROUND:15% of colorectal cancers (CRC) are mismatch repair deficient (dMMR) and 3-5% of CRC is linked to Lynch syndrome (LS). Most MMR and LS data come from non-Hispanic White patients. We assessed MMR testing/deficiency and genetics outcomes in a diverse population diagnosed with CRC at a safety-net hospital, LAGMC.

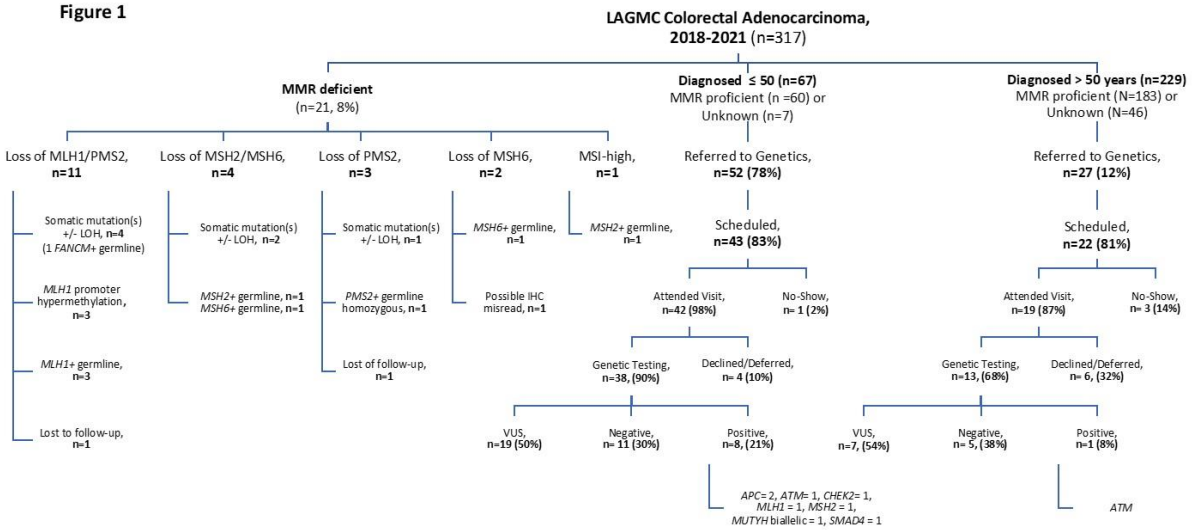
METHODS:We conducted a retrospective review of CRC patients documented by the cancer registrar from January 1, 2019-December 31, 2021. We compared rates and outcomes of MMR testing, genetics referral, scheduling, and attendance for patients with dMMR tumors and those with proficient MMR/untested tumors diagnosed before or after age 50.
RESULTS:Across 317 patients, the average age at diagnosis was 57; 59% male; 71% Hispanic, 28% non-Hispanic White, 14% Asian, 5% Black, 2% other. See Figure 1 for details, but in summary, of the 264 (83%) patients with MMR tumor testing, 8% (21) were dMMR; attributed to somatic events in 53%, germline pathogenic variants in 42%, and IHC misclassification in 1 (5%). 78% of patients diagnosed age ≤50 and 12% >50 were referred to genetics. 82% were scheduled, 94% attended their visit. The decline/deferral rate for genetic testing was higher in patients diagnosed >50 (32% vs. 10%). Among counseled patients, 84% underwent germline testing: 51% ≥ 1 VUS, 31% negative, 18% positive. Across the cohort, 21% underwent germline testing, 2.8% had LS and 2.8% had other cancer predisposition conditions.

CONCLUSIONS:LS diagnoses rate, in this population, was as expected but the rate of CRC dMMR tumors was lower with paired tumor-germline allowing for the resolution of most cases. Genetics referrals, appointment attendance and uptake of germline testing were high, supporting the feasibility of integrated genetic counseling in safety-net settings. Further investigation is needed to understand gaps in MMR tumor testing and referral practices for patients age ≤50 and the clinical impact of genetic testing.

Keywords: Colorectal cancer, Lynch syndrome, minority, Hispanic, Latino, genetic testing

POSTER ABSTRACTS

LAGMC Colorectal Adenocarcinoma (2018-2021)



Flowchart of colorectal adenocarcinoma workup at LAGMC

P-034

General Research » Adenomatous polyposis syndromes including FAP

IS ENDOSCOPIC COLORECTAL SURVEILLANCE SAFE IN *MUTYH*-ASSOCIATED POLYPOSIS?

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BACKGROUND:There is limited data on the safety of endoscopic surveillance in patients with *MUTYH*-Associated Polyposis (MAP). We hypothesized that endoscopic management of polyposis and close surveillance by experts is safe and can help in avoiding or deferring prophylactic colectomy without an

increased risk of death from cancer.

METHODS:MAP patients were identified through our inherited colorectal cancer registry. We included all patients with confirmed bi-allelic *MUTYH* pathogenic variants (PVs) who have more than one colonoscopy documented at our institution over at least 2 years, including patients with and without prior segmental colectomy, but excluded patients with prior extended colectomy. The primary outcome assessed was the development of cancer while under surveillance. Secondary outcome of interest was the need for surgery while under surveillance.

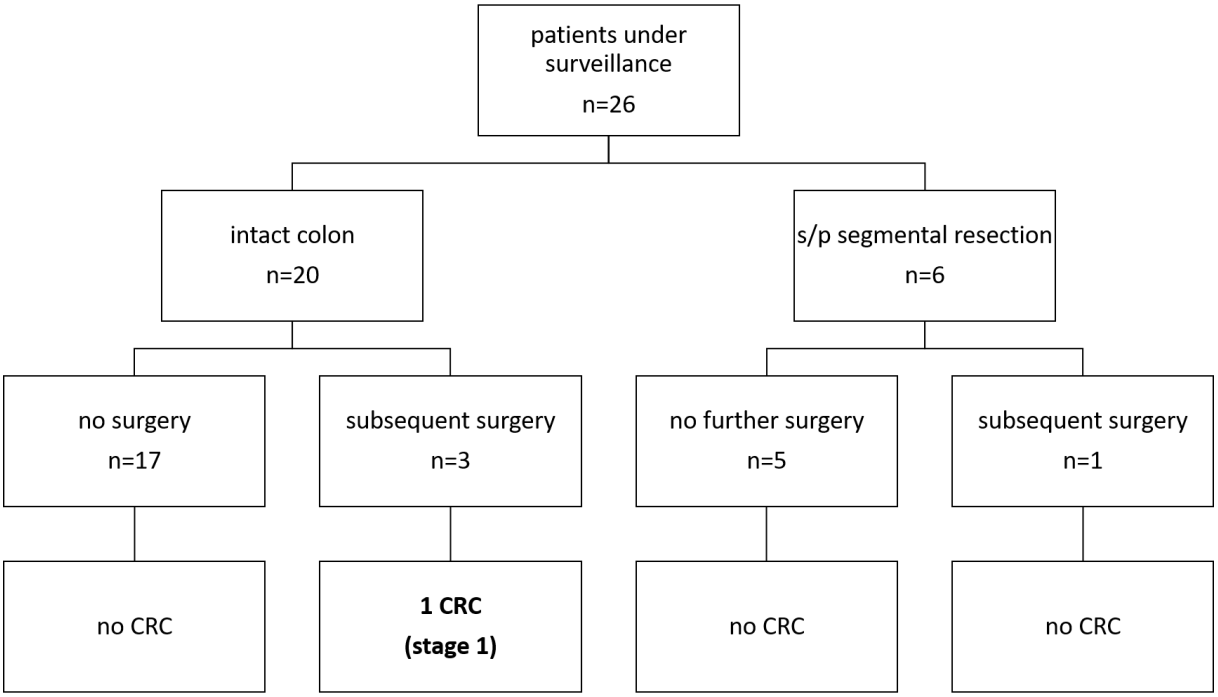
RESULTS:68 patients enrolled in our registry were identified with bi-allelic *MUTYH* PVs. We excluded 42 patients who were not undergoing surveillance at our institution or who had undergone a prior extended colectomy. A total of 26 patients underwent colonoscopic surveillance at our institution following their diagnosis of MAP. The median interval between colonoscopies was 12.4 months (IQR 10.7-14.6). The median follow up was 8.9 years (IQR=6.5-11.7) with a median of 8 (IQR=6-14) colonoscopies per patient. 1 (4%) patient was diagnosed with colorectal cancer while under surveillance. The cancer was stage 1 at resection, and the patient remained cancer free at 8 years after resection. In total 4/26 (15%) patients underwent colectomy while under surveillance. One surgery was for a colonic interposition after esophagectomy, and three were for endoscopically unmanageable polyps.

CONCLUSIONS:The vast majority of MAP patients undergoing expert colonoscopic surveillance did not develop cancer although approximately 12% will required colectomy for polyposis. For patients without cancer, or after previous segmental resection, careful endoscopic surveillance with polyp clearance is a reasonable alternative to colectomy.

Keywords: {MUTYH}, Polyposis, MAP, surveillance, cancer, colectomy

Surveillance Outcomes

POSTER ABSTRACTS



Overview of patients and outcomes while under surveillance

P-035

General Research » Adenomatous polyposis syndromes including FAP

RISK OF PROCTECTOMY AFTER ILEORECTAL ANASTOMOSIS IN FAMILIAL ADENOMATOUS POLYPOSIS IN THE MODERN ERA

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BACKGROUND:Prophylactic surgery for familial adenomatous polyposis (FAP) has evolved over several decades. Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) provides an alternative to total abdominal colectomy with ileorectal anastomosis (TAC/IRA). We have previously shown the rate of proctectomy and rectal cancer after TAC/IRA in the “pre-pouch” era was 32% and 13%, respectively. However, outcomes after TAC/IRA in the "modern era" are not determined.

POSTER ABSTRACTS

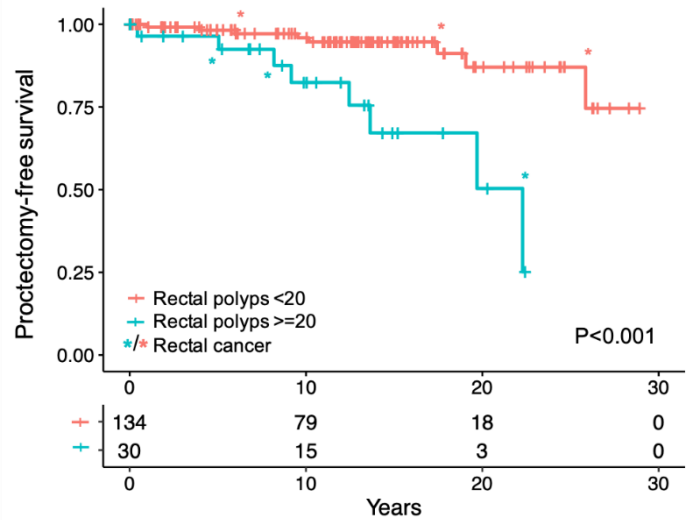
METHODS:Patients with FAP who underwent TAC/IRA from 1993-2020 were identified in an IRB-approved Inherited Colorectal Cancer Registry. Data on demographics, APC pathogenic variants and extra-colonic manifestations were abstracted. Number of rectal polyps present at the time of TAC/IRA was recorded. The primary outcome was rate of proctectomy and secondary outcome was rectal cancer incidence.

RESULTS:197 patients with median age of 24 years (range 10-67) were included. Median follow-up after TAC/IRA was 13 years (IQR 6-17). 16 patients (8%) underwent proctectomy. Indications included rectal cancer in 6 (3%) (2 Stage I and 4 Stage III); polyps with high grade dysplasia in 4 (2%); progressive polyp burden in 3 (1.5%), defecatory dysfunction in 2 (1%); and anastomotic leak in 1 (0.5%). Among 30 patients (18%) with ≥ 20 rectal polyps at the time of TAC/IRA, 8 patients (26%) underwent proctectomy and 3 patients developed rectal cancer (10%). Among 134 patients (82%) with < 20 polyps, 8 patients (6%) underwent proctectomy and 3 patients developed rectal cancer (2%). Number of rectal polyps at the time of TAC/IRA was associated with the likelihood of proctectomy (OR 1.1, P<0.001) but not incident rectal cancer (P=0.3).

CONCLUSIONS:Patients with FAP selected for TAC/IRA by rectal polyp number have low rates of proctectomy and rectal cancer compared to historical controls. With appropriate selection criteria and surveillance, TAC/IRA remains an important and safe treatment option for patients with FAP.

Keywords: Familial adenomatous polyposis, ileorectal anastomosis, rectal preservation, proctectomy, rectal cancer

Time to Proctectomy



Kaplan-Meier analysis comparing time to proctectomy based on rectal polyp number at the time of index colectomy.

P-036

General Research » Adenomatous polyposis syndromes including FAP

POSTER ABSTRACTS

KRAS-G12C AS A BIOMARKER FOR IDENTIFYING *MUTYH*-ASSOCIATED POLYPOSIS PATIENTS

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BACKGROUND: *MUTYH*-associated polyposis (MAP) is an underdiagnosed recessive syndrome that predisposes individuals to colorectal cancer (CRC). It exhibits a remarkable variable phenotype with patients presenting from none to hundreds of adenomatous polyps. Biallelic loss of *MUTYH* causes a specific pattern of somatic mutations, often leading to the presence of *KRAS*-G12C and *PIK3CA*-Q546K mutations in CRC. Despite previous studies suggested the use of KRAS-G12C as a marker for identifying MAP patients, widespread adoption of reflective *MUTYH* germline testing in these patients has not occurred.

METHODS:This study aims to investigate the utility of the detection of *KRAS*-G12C in two scenarios: to identify carriers of germline pathogenic variants (GPVs) in *MUTYH* gene and to classify germline variants of uncertain clinical significance (VUS) in *MUTYH*. We screened a cohort of 98 *KRAS*-G12C CRC patients for the 5 most frequent *MUTYH* GPVs in the Brazilian population using amplicon target sequencing. For identified monoallelic carriers, we performed full *MUTYH* sequencing. Additionally, we are evaluating the frequency of detection of *KRAS*-G12C and *PIK3CA*-Q546K mutations in adenomas and CRC tissues from 21 MAP patients and 3 patients with *MUTYH* VUS.

RESULTS:Among the 98 patients with *KRAS*-G12C, 12 (12.2%) had at least one GPV in MUTYH. Out of these, 8 were MAP (biallelic carriers) and 4 were monoallelic carriers. The MAP detection rate in patients under 60 years old was 15% (7/47). GPVs were associated with an earlier age of CRC onset ($p<0.02$) and the presence of polyps ($p=0.05$). Regarding the second aim, we identified *KRAS*-G12C in a suspected MAP patient with the *MUTYH* VUS p.Pro273Arg.

CONCLUSIONS:In summary, the high detection rate of GPVs in *MUTYH* among CRC patients with *KRAS*-G12C indicates that the presence of this mutation should be considered a biomarker for guiding the diagnosis of MAP, enabling appropriate follow up, surveillance and preventive measures for affected individuals.

Keywords: MUTYH-associated polyposis, KRAS-G12C, PIK3CA-Q546K

P-037

POSTER ABSTRACTS

General Research » Lynch Syndrome

RECLASSIFICATION OF A LOSS OF FUNCTION VARIANT FROM THE *PMS2* GENE TO THE *PMS2CL* PSEUDOGENE IN BRAZILIAN PATIENTS

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BACKGROUND:*PMS2*, a Lynch Syndrome gene, presents challenges in genetic testing due to the existence of multiple pseudogenes, including *PMS2CL*, which shares high homology with the 3' end of *PMS2*. A previous study reported a misclassification of the c.2182_2184delACTinsG loss of function (LoF) variant from the *PMS2CL* pseudogene as *PMS2*. This study aims to describe a series of cases harboring a rare LoF variant in the *PMS2CL* pseudogene that has been incorrectly identified as a pathogenic variant in *PMS2*, with different nomenclatures.

METHODS:We reviewed data from 647 patients who underwent genetic testing using multigene panels at A.C.Camargo Cancer Center. The analysis utilized Sophia Genetics software to identify NM_000535.5(*PMS2*):c.2182_2184delACTinsG or c.2186_2187delTC variants. Sanger sequencing of *PMS2* transcript, obtained with a nested PCR of peripheral blood RNA, was performed.

RESULTS:Among the 647 individuals, 1.8% (12) carried the c.2182_2184delACTinsG variant, with variant allele frequencies ranging from 15 to 34%. The variant was called by two nomenclatures: V1: c.2186_2187delTC (rs587779335) and V2: c.2182_2184delinsG (rs1554294508). By visually inspecting the alignments, we confirmed that both nomenclatures represented the same variant, with V2 being the recommended HGVS nomenclature. Through *PMS2* transcript analysis, we determined that neither V1 or V2 are present in the *PMS2* gene. Genomic databases (ExAC and gnomAD) report an incidence of 2.5% - 5.3% of this variant in the African population. Currently, V1 is classified as "uncertain significance" and V2 as “conflicting” in ClinVar, with several laboratories classifying them as “pathogenic”.

CONCLUSIONS:We identified a frequent African *PMS2CL* LoF variant in the Brazilian population that is misclassified as a *PMS2* variant. It is likely that V1/V2 have been erroneously assigned to *PMS2* in several manuscripts and by clinical laboratories. Considering the limitations of short-read NGS differentiating between certain regions of *PMS2* and *PMS2CL*, the use of complementary methodologies is imperative to provide an accurate diagnosis.

Keywords: Lynch Syndrome, PMS2, PMS2CL, pseudogene

POSTER ABSTRACTS

P-038

General Research » Adenomatous polyposis syndromes including FAP

UPPER ENDOSCOPIC FINDINGS IN MUTY-H MONO-ALLELIC AND BI-ALLELIC COLORECTAL POLYPOSIS CASES

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BACKGROUND:MUTYH associated polyposis (MAP) is often an attenuated colorectal polyposis and is associated with upper gastrointestinal (UGI) neoplasia. As little literature exists we assessed esophagogastroduodenoscopy (EGD) findings in polyposis cases in carriers of mono-allelic and bi-allelic MUTYH pathogenic variants.

METHODS:All patients seen at our center between 2005 and 2021 with colonic polyposis (≥10 colorectal tubular adenomas) and carriers of either a mono-allelic or bi-allelic MUTYH pathogenic variant and with ≥1 EGD were included. Demographic, genetic testing results, and endoscopic findings were obtained. The most advanced EGD findings are reported.
RESULTS:66 patients were included (57 bi-allelic, 9 mono-allelic), diagnosed at a mean age of 52.5 ± 11.3 years. 78% of mono-allelic polyposis patients underwent multi-gene panel testing versus 30% of bi-allelic patients. Barrett's esophagus, esophageal cancer, gastric adenomas, ampullary adenomas, and duodenal cancer were only detected in the bi-allelic group. Duodenal adenomas were reported in 29.8% and 33.3% of bi-allelic and mono- allelic carriers, respectively, with a higher proportion of Spigelman stage I polyposis in the bi-allelic group (58.9% versus 0%). Visualization of the ampulla was reported in 42 (73.7%) and 5 (55.6%) and biopsied in 37 (88.1%) and 5 (100%) of bi-allelic and mono-allelic carriers respectively. Ampullary adenomas were only detected in bi-allelic patients (18.9%) with pathology showing tubular adenoma in 71.4% (5/7)

tubulovillous adenoma in 14% (1), and villous adenoma in 14%.

CONCLUSIONS:3.5% of bi-allelic MAP patients undergoing EGD had UGI cancer; gastric and ampullary adenomas were found only in this group. Nearly 1/3 of our small cohort of mono-allelic MUTYH pathogenic variant carriers had duodenal polyposis and at higher stage than the MAP patients. Comparing EGD features in mono-allelic MUTYH polyposis patients and colonic polyposis-of-unknown etiology is recommended to assess the impact of MUTYH heterozygosity on duodenal polyposis phenotype.

Keywords: MUTYH, polyposis, Esophagogastroduodenoscopy, screening

Table 1: Demographics and Most Advanced Endoscopic Findings

N(%)/ Mean ± SD	Total	Bi-allelic	Mono-allelic
Patients with Upper Endoscopy (EGD)	66 (89.2%)	57 (89.1%)	9 (90.0%)
Age at *MUTYH* diagnosis (years)	52.5 ± 11.3	52.9 ± 11.4	50.5 ± 11.6
Age at first EGD (years)	52.8 ± 11.4	53.3 ± 11.1	49.3 ± 13.6
Male sex	37 (56.1%)	32 (56.1%)	5 (55.6%)
White race	55 (96.5%)	64 (97.0%)	9 (100%)
Multigene panel testing (MGPT)	24 (36.4%)	17 (29.8%)	7 (77.8%)
Highest number of colorectal polyps in 1 colonoscopy			
• <10	13 (19.7%)	10 (17.5%)	3 (33.3%)
• 10-20	19 (28.8%)	16 (28.1%)	3 (33.3%)
• 21-50	12 (18.2%)	12 (21.1%)	0 (0.0%)
• 51-100	8 (12.1%)	6 (10.5%)	2 (22.2%)
• >100	14 (21.2%)	13 (22.8%)	1 (11.1%)
Mean number of EGDs	3.6 ± 2.2	3.5 ± 1.9	4.2 ± 3.5
2 commonest *MUTYH* variants found	**Y165C:** 30 (25%) **G382D:** 24 (20%)	**Y165C:** 28 (25.2%) **G382D:** 24 (21.6%)	**G396D:** 4 (44.4%) **Y165C:** 2 (22.2%)
Esophageal and Duodenal Cancer	2 (3.0%)	2 (3.5%)	0 (0%)
Esophageal findings			
Barrett's esophagus	6 (9.1%)	6 (10.5%)	0 (0%)
Gastric findings			
Gastric polyps	34 (51.5%)	32 (56.1%)	2 (22.2%)
Highest Polyp Number in 1 EGD			
• 1-9	19 (55.9%)	17 (53.1%)	2 (100%)
• 10-30	14 (41.1%)	14 (43.8%)	0 (0%)
• >50	1 (3.0%)	1 (3.1%)	0 (0%)
Largest Polyp Size			
• 1-5 mm	27 (81.8%)	25 (80.6%)	2 (100%)
• 6-9mm	4 (12.1%)	4 (12.9%)	0 (0%)
• >9mm	2 (6.1%)	2 (6.5%)	0 (0%)
Polyp Histology			
• Fundic gland polyp	25 (37.9%)	24 (42.1%)	1 (11.1%)
• Gastric adenoma	3 (4.5%)	3 (5.2%)	0 (0%)

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Table 2: Most Advanced Duodenal and Ampullary findings

N(%)/ Mean ± SD	Total	Bi-allelic	Mono-allelic
Duodenal findings			
Duodenal Adenomas (Tubular/Tubulovillous Pathology)	20 (30.3%)	17 (29.8%)	3 (33.3%)
Largest Adenoma Size			
• 1-5 mm	11 (55%)	10 (58.9%)	1 (33.3%)
• 6-9mm	1 (5%)	1 (5.9%)	0 (0%)
• >9mm	8 (40%)	6 (35.2%)	2 (67.7%)
Highest Spigelman Stage			
• Stage I	10 (50%)	10 (58.9%)	0 (0%)
• Stage II	5 (25%)	3 (17.6%)	2 (66.7%)
• Stage III	4 (20%)	3 (17.6%)	1 (33.3%)
• Stage IV	1 (5%)	1 (5.9%)	0 (0%)
Ampullary findings			
Ampulla visualized	47 (71.2%)	42 (73.7%)	5 (55.6%)
Ampulla biopsied	42 (89.4%)	37 (88.1%)	5 (100%)
Adenoma Detected	7 (16.7%)	7 (18.9%)	0 (0%)
• **Tubular** • **Tubullovillous/Villous**		5/7 (71.4%) 2/7 (28.6%)	

P-039

General Research » Adenomatous polyposis syndromes including FAP

PREVALENCE OF COLORECTAL AND NON-COLORECTAL NEOPLASIA IN POLYPOSIS PATIENTS WITH COLONIC POLYPOSIS OF UNKNOWN ETIOLOGY AND MUTYH PATHOGENIC VARIANTS

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POSTER ABSTRACTS

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BACKGROUND:Carriers of bi-allelic MUTYH pathogenic variants (PV) have an increased colorectal (CRC) and non-colorectal neoplasia risk. However, these risks in polyposis patients with mono-allelic MUTYH PV or colonic polyposis of unknown etiology (CPUE) are not well defined. Understanding neoplasia risk in these patients may help inform patients tailor management.
METHODS:All patients diagnosed with colonic polyposis (> 10 cumulative lifetime adenomas) with either mono-allelic or bi-allelic MUTYH PV or CPUE seen in our high-risk center between 2003-2022 were included. Demographics, personal and family cancer history, and duodenal findings were compared between CPUE by colonic adenoma count, mono-allelic MUTYH, and bi-allelic MUTYH PV carriers.

RESULTS:224 polyposis patients were included: 150 with CPUE, 10 mono-allelic MUTYH PV carriers and 64 bi-allelic MUTYH PV carriers (Table 1). Patient characteristics are in table 1. In CPUE, CRC occurred in 20%, 22.8%, and 27.5% of patients with 10-19 adenomas, 20-99 adenomas, and ≥100 adenomas, respectively. CRC occurred in 50% and 32.8% of mono-allelic and bi-allelic MUTYH PV carriers, respectively (Table 2). In CPUE non-colorectal cancers were diagnosed in 5% of patients with 10-19 adenomas, 22.8% with 20-99 adenomas, and 23.5% with ≥100 adenomas while it occurred in 30% in the mono-allelic MUTYH group and 31.3% in the bi-allelic MUTYH group (Table 2). Duodenal adenomas were noted in 33.3%, 10.1%, and 38% of CPUE patients (10-19, 20-99 and ≥ 100 adenomas, respectively) and in 33.3% and 29.8 % of monoallelic and biallelic MUTYH PV carriers respectively.

CONCLUSIONS:Within limitations of a hereditary CRC registry and a small cohort of mono-allelic MUTYH carriers with polyposis, CRC was enriched versus CPUE and MAP and non-colorectal cancer risk was similar to bi-allelic MUTYH. No obvious increase in duodenal polyposis was noted in mono-allelic MUTYH PV carriers. Larger collaborative studies quantifying impact of MUTYH PV heterozygosity on neoplasia in polyposis patients needed.

Keywords: MUTYH, polyposis, cancer, Colonic polyposis of unknown etiology, colorectal cancer

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Table 1: Characteristics of CPUE and MUTYH PV carriers

	CPUE 10-19 polyps	CPUE 20-99 polyps	CPUE ≥100 polyps	Mono-allelic *MUTYH*	Bi-allelic *MUTYH*
Number of patients	20	79	51	10	64
Age at Diagnosis (years)	50.8 ± 15.7	52.4 ± 14.0	41.7 ± 15.1	50.8 ± 11.0	52.3 ± 11.4
Male	13 (65%)	44 (55.7%)	29 (56.9%)	6 (60%)	35 (54.7%)
White Race	16 (80.0%)	71 (89.9%)	43 (86.0%)	10 (100%)	61 (95.3%)
Ever smoked	11 (55%)	54 (69.2%)	24 (48.0%)	3 (30%)	28 (43.8%)
Alcohol use	16 (80%)	48 (61.5%)	33 (66.0%)	4 (40%)	31 (48.4%)
Multigene Panel Testing	8 (40.0%)	28 (35.4%)	20 (39.2%)	8 (80%)	19 (29.7%)
Family history of Colorectal cancer	12 (60%)	41 (51.9%)	22 (45.8%)	5 (50%)	31 (48.4%)
Colorectal surgery	5 (25%)	29 (36.7%)	39 (76.5%)	6 (60%)	35 (54.7%)
Underwent EGD	12 (60%)	69 (87.3%)	47 (92.2%)	9 (90.0%)	57 (89.1%)
Duodenal adenomas	4 (33.3%)	7 (10.1%)	18 (38.3%)	3 (33.3%)	17 (29.8%)
Highest Spigelman stage					
1	1 (25%)	3 (42.9%)	6 (33.3%)	0 (0%)	10 (58.8%)
2	0 (0%)	0 (0%)	4 (22.2%)	2 (67.7%)	3 (17.6%)
3	3 (75%)	1 (14.3%)	6 (33.3%)	1 (33.3%)	3 (17.6%)
4	0 (0%)	1 (14.3%)	1 (5.6%)	0 (0%)	1 (6.0%)
Stage not available	0 (0%)	2 (28.5%)	1 (5.6%)	0 (0%)	0 (0%)

POSTER ABSTRACTS

Table 2: Colorectal and non-colorectal malignancies among polyposis patients with CPUE and MUTYH PV

	CPUE 10-19 polyps	CPUE 20-99 polyps	CPUE ≥100 polyps	Mono-allelic *MUTYH*	Bi-allelic *MUTYH*
Colorectal cancer	4 (20%)	18 (22.8%)	14 (27.5%)	5 (50.0%)	21 (32.8%)
Non-colorectal cancer	1 (5%)	18 (22.8%)	12 (23.5%)	3 (30.0%)	20 (31.3%)
Non-colorectal cancers by type (N)	Prostate (1)	Skin (10) Lung (4) Bladder (4) Breast (3) Uterus (2) Bone (1) Kidney (1) Lymphoma (1) Prostate (1)	Skin (3) Prostate (3) Breast (2) Lymphoma (2) Testicle (1) Pancreas (1)	Skin (2) Breast (1) Thyroid (1)	Thyroid (8) Skin (5) Breast (4) Prostate (2) Bladder (1) Brain (1) Esophagus (1) Kidney (1) Leukemia (1)

P-040

General Research » Adenomatous polyposis syndromes including FAP]

RENAL AND THYROID ULTRASOUND SURVEILLANCE IN POLYPOSIS PATIENTS WITH MONOALLELIC AND BIALLELIC MUTYH PATHOGENIC VARIANTS

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POSTER ABSTRACTS

BACKGROUND:MUTYH associated polyposis (MAP) is characterized by attenuated polyposis and colorectal and extracolonic malignancy risk including thyroid and urothelial. Data supporting renal/bladder (RUS) and thyroid ultrasound (TUS) surveillance are limited. We describe RUS and TUS findings in monoallelic and biallelic MUTYH polyposis patients undergoing surveillance in our registry.

METHODS:Asymptomatic monoallelic and biallelic MUTYH polyposis patients undergoing ≥1 RUS or TUS between 2007-2021 were included. US findings were reviewed and the most advanced findings described.

RESULTS:64 patients underwent TUS (8 monoallelic, 56 biallelic) and 57 patients RUS (8 monoallelic, 49 biallelic) at a median starting age of 53.4 (46.01–61.78) and 53.3 years (47.10–60.55), respectively. The median number of TUS and RUS per patient was 2 (1–5) and 1 (0–2) and the median surveillance period was 3.1 (0–7.1) and 4.78 years (0–7.57), respectively.
Among monoallelic carriers, TUS was normal in 2 patients (25%), documented nodules in 5 (62.5%; 4 ≥1 cm) and cancer in 1 (12.5%). TUS in biallelic carriers was normal in 17 (30.3%), showed nodules in 33 (58.9%, including 16 ≥1 cm), and cancer in 6 (10.7%) (Figure 1). RUS in monoallelic carriers was normal in 7 (87.5%) and demonstrated a simple cyst in 1 patient. RUS in biallelic patients was normal in 33 (67.3%), showed simple cysts in 14 (28.6%), and cancer in 2 (4.1%; kidney and bladder) (Figure 2).

CONCLUSIONS:In our polyposis surveillance program, thyroid cancer was detected in over 10% of monoallelic and biallelic MUTYH carriers. Urologic malignancy was detected in 4% of biallelic MUTYH carriers. Our data demonstrates a high detection of asymptomatic thyroid cancer on TUS appearing beneficial in both MUTYH groups with polyposis. RUS value is questionable in monoallelic carriers but shows ability to detect asymptomatic renal and bladder cancers in biallelic MUTYH carriers.

Keywords: MUTYH, polyposis, screening, thyroid, renal

Figure 1. Thyroid ultrasound findings stratified by monoallelic and biallelic MUTYH pathogenic variant group.

POSTER ABSTRACTS

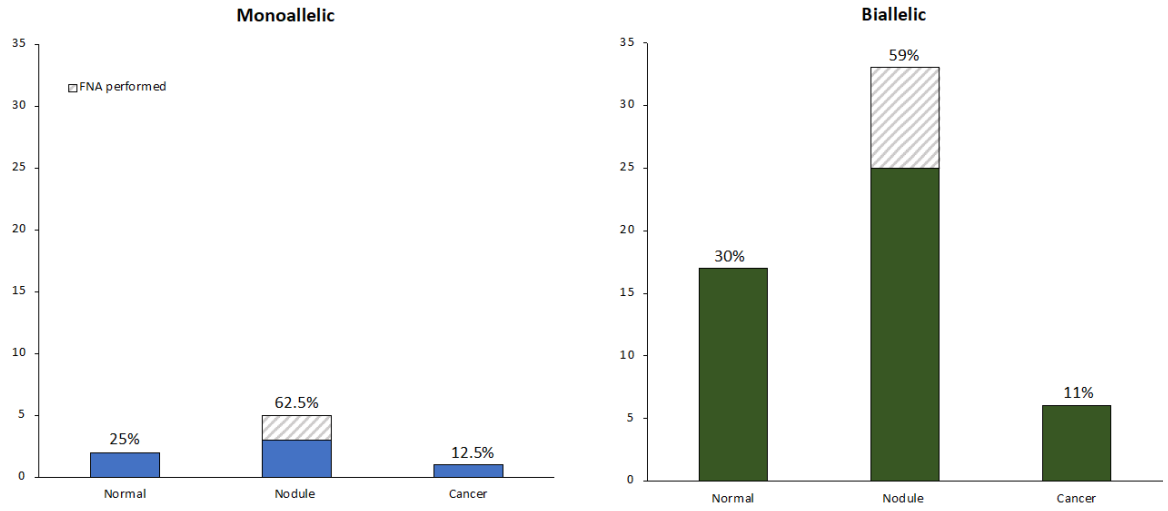
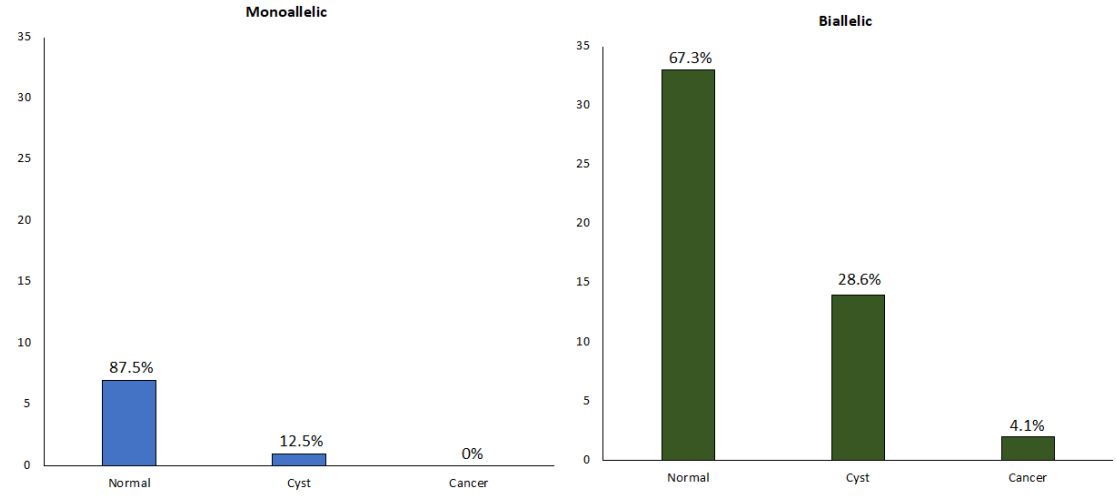


Figure 2. Renal/Bladder ultrasound findings stratified by monoallelic and biallelic MUTYH pathogenic variant group



POSTER ABSTRACTS

P-041

General Research » Adenomatous polyposis syndromes including FAP

HISTORICAL FOLLOW UP AND CANCER RISK IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS AT A SINGLE TERTIARY CARE CENTER

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BACKGROUND:Familial Adenomatous Polyposis (FAP) is a rare genetic syndrome with sparse data on long-term follow up, particularly relating to upper GI tract disease. We present data on follow up of this population at our institution for a period of >30 years.

METHODS:Retrospective data abstraction was performed from electronic health records of FAP patients who underwent gastroenterology evaluation at Mayo Clinic Rochester from 1988-2021. Statistical analysis was done using SPSS, with Chi-square analysis.

RESULTS:498 patients with FAP seen at our institution were included. 252 (50.6%) completed genetic testing to confirm diagnosis, 66 (13.3%) had negative genetic testing but clinical FAP and 180 (36.1%) had clinical FAP but never completed genetic testing. 22 (4.4%) were classified as attenuated FAP. Active tobacco use was present in 92 (19.1%), with 185 (38.5%) having some tobacco use history, obesity in 139 (29.8%) and history of daily alcohol intake in 41 (9.2%). Of these factors, only tobacco use was associated with development of malignancy, both in those with any FAP related cancer (p=0.03) and colon cancer (p=0.01). Upper GI surveillance was commonly completed at our institution (371 (74.5%)) with number of EGDs ranging from 1-39 (mean=6). Desmoid tumors developed in 109 (21.9%). Colon cancer was the most common malignancy, in 86 (17.3%). Other known FAP related cancers were far less common (thyroid cancer 6.2%, duodenal cancer 1.6% and gastric cancer 1.2%). Some degree of colectomy was completed in most (435, 87.3%). Ileal pouch anal anastomosis was most frequent (220, 50.6%) with ileorectal anastomosis (95, 21.8%) next most common.

CONCLUSIONS:This data offers extensive long term follow up of FAP patients. As expected, colon cancer was common in our population, but other FAP cancers were fortunately less so. Tobacco use was associated with increased overall cancer and colon cancer risk in our population, thus strong recommendation of avoidance.

Keywords: FAP, cancer

POSTER ABSTRACTS

Table 1: Association of FAP cancers with modifiable risk factors

Table 1: Association of FAP cancers with modifiable risk factors

Risk factor	Any FAP related cancer	P-value	Colon cancer	P-value	Thyroid cancer	P-value	Gastric cancer	P-value	Duodenal cancer	P-value
Tobacco (Any history of use)		**0.03**		**0.01**		0.9		0.7		0.9
Yes	55/185 (29.7%)		42/185 (22.7%)		12/185 (6.5%)		2/185 (1.1%)		2/185 (1.1%)	
No	62/296 (20.9%)		41/296 (13.9%)		19/296 (6.4%)		3/296 (1.0%)		5/296 (1.7%)	
Alcohol (Daily use)		0.2		0.06		0.4		-		-
Yes	7/41 (17.1%)		6/41 (14.6%)		1/41 (2.4%)		0/41 (0.0%)		0/41 (0.0%)	
No	105/406 (25.9%)		74/406 (18.2%)		29/406 (7.1%)		4/406 (1.0%)		7/406 (1.7%)	
Obesity (BMI>30.0)		0.3		0.6		0.6		0.8		0.7
Yes	38/139 (27.3%)		26/139 (18.7%)		10/139 (7.2%)		1/139 (0.7%)		2/139 (1.4%)	
No	75/327 (22.9%)		55/327 (16.8%)		19/327 (5.8%)		5/327 (1.5%)		5/327 (1.5%)	

P-042

General Research » Adenomatous polyposis syndromes including FAP

PREDICTORS OF DUODENAL HIGH-GRADE DYSPLASIA IN PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS

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BACKGROUND:Patients with Familial Adenomatous Polyposis (FAP) commonly develop multiple duodenal polyps. Polyps with high-grade dysplasia (HGD) may require management with radical surgery to decrease risk of progression to cancer. We aimed to study the association of various demographic and endoscopic features of duodenal polyps with risk of developing HGD in FAP patients.

POSTER ABSTRACTS

METHODS:Data was collected retrospectively from electronic health records of 371 patients with FAP who underwent surveillance EGDs between 1989-2023 at our institution. Statistical analysis was done using SPSS, with Chi-square and Fischer's exact test.

RESULTS:HGD was detected in 21 patients (5.7%), with 6 patients (28.6%) having HGD at first endoscopy. The papilla was the most common location of initial HGD (47.6%). On first endoscopy at our institution, there was papillary adenomatous involvement in 104 (28.0%). On first endoscopy, papillary adenomatous involvement ($p=0.002$) and Spigelman score of ≥7 ($p<0.001$) were associated with development of HGD. There was trend towards association of HGD with age at first endoscopy, more common in those >50 years old ($p=0.06$). HGD was also, unsurprisingly, associated with development of duodenal cancer ($p<0.001$). Time from FAP diagnosis to first endoscopy was longer in patients with HGD (median 14.6 years vs 3.2 years). The use of chemopreventative agents (NSAIDs) was not associated with higher or lower rate of HGD ($p=0.9$). Furthermore, no significant association was found between lifestyle factors (tobacco use, alcohol consumption, BMI) and HGD.

CONCLUSIONS:We analyzed demographic and endoscopic findings in FAP patients for association with duodenal HGD. The Spigelman classification does not include papillary involvement for risk stratification. We demonstrated that papillary adenomatous involvement is associated with developing HGD anywhere in the duodenum. Thus, we suggest changes to Spigelman classification are needed for appropriate risk stratification, as closer follow up in some patients could reduce the rates of HGD and eventually duodenal cancer.

Keywords: FAP, papilla, duodenal polyp

Table1. Association of high-grade dysplasia with demographic and endoscopic variables.

POSTER ABSTRACTS

Clinical characteristics	Without HGD n=350 (%)	With HGD n= 21 (%)	P-value
Age at first endoscopy Mean ± SD Median Range	 46.81 ± 16.87 45.58 (8.95-87.22)	 61.59 ± 13.06 61.44 (35.06-80.89)	**<0.001**
Sex- Male Female	 171 (48.9%) 179 (51.1%)	 10 (47.6%) 11 (52.4%)	0.91
Age at first endoscopy >50 years No Yes	 263 (75.4%) 86 (24.6%)	 12 (57.1%) 9 (42.9%)	0.06
BMI ≥25 No Yes	 122 (34.86%) 203 (58%)	 10 (47.62%) 10 (47.62%)	0.27
History of smoking No Yes	 207 (59.14%) 129 (36.85%)	 15 (71.42%) 6 (28.57%)	0.37
Papilla involved at first endoscopy No Yes	 258 (73.71%) 92 (26.28%)	 9 (42.85%) 12 (57.14%)	**0.002**
Spigelman score ≥7 at first endoscopy No Yes	 307 (87.7%) 43 (12.3%)	 10 (47.6%) 11 (52.4%)	**<0.001**
History of duodenal cancer No Yes	 347 (99.1%) 3 (0.9%)	 17 (81%) 4 (19%)	**<0.001**
History of gastric cancer No Yes	 347(99.14%) 3(0.08%)	 20 (95.23%) 1 (4.76%)	0.19
History of colon cancer No Yes	 291 (83.14%) 59 (16.85%)	 17 (80.95%) 4 (19.04%)	0.80
Chemoprevention used No Yes	 227 (64.86%) 123 (35.14%)	 14 (66.67%) 7 (33.33%)	0.87
History of colectomy No Yes	 33 (9.4%) 316 (90.28%)	 1 (4.76%) 20 (95.23%)	0.47
History of thyroid cancer No Yes	 327 (93.42%) 22 (6.28%)	 18 (85.71%) 3 (14.28%)	0.16

P-043

General Research » Adenomatous polyposis syndromes including FAP

POSTER ABSTRACTS

DUODENAL POLYP SURVEILLANCE IN FAMILIAL ADENOMATOUS POLYPOSIS: LONG-TERM FOLLOW UP AT A SINGLE TERTIARY CARE CENTER

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BACKGROUND:The Spigelman classification aims to stratify patients with Familial Adenomatous Polyposis (FAP) enabling selection of appropriate follow up timing for EGD with goal of reducing risk of duodenal cancer. Our primary objective was to evaluate progression of duodenal polyps on serial EGDs.

METHODS:Data was collected retrospectively from 2547 EGD reports of 371 patients with FAP who underwent surveillance at our institution from 1989-2023. Statistical analysis was done using SPSS with Chi-square tests.

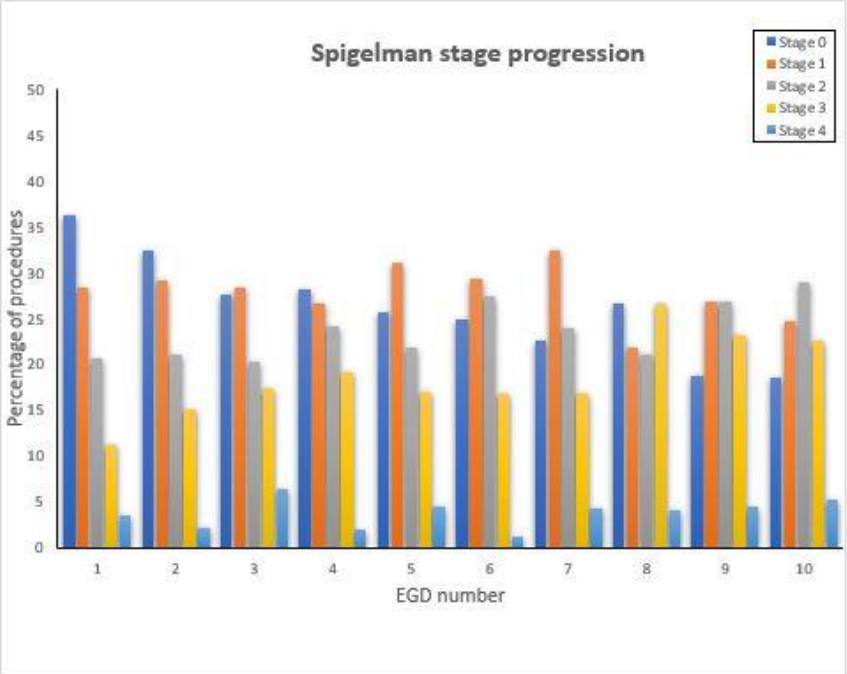
RESULTS:Number of EGDs for each patient ranged from 1-39 (median=6). Median age at last EGD was 46.9. Initial EGD at our center was normal in 129 patients (34.8%), decreasing to 85 (32.5%) and 65 (27.5%) by second and third endoscopy. In following longitudinally, there was significantly higher proportion of patients in Spigelman stage 3-4 in third ($p=0.005$), eighth ($p<0.001$), ninth ($p=0.002$) and tenth ($p=0.002$) endoscopy. It was common to have >20 duodenal polyps (44.5%) and polyps were >10 mm in 17.9% of procedures. Papilla was involved in 32.9% of procedures. In 41.0% biopsy was completed, and polypectomy completed in 19.0%. Polypectomy was done in piecemeal fashion in 113 (23.2%) and whole polypectomy in 374 (76.8%) procedures. For polypectomy, cold snare was used in 47.7%, hot snare in 20.6% and biopsy forceps in 19.3%. Histologically, polyps were predominantly tubular adenoma (66.5%) and tubulovillous adenoma (20.3%), with small proportion normal duodenal mucosa (8.6%). Low grade dysplasia was common (85.9%), with high grade dysplasia (HGD) in 1.7%, and no dysplasia in 12.4%. Duodenal cancer was found in 5 (1.3%) patients. Complications occurred following 66 (2.6%) procedures (pancreatitis (48.5%), bleeding (28.8%), perforation (10.6%)).

CONCLUSIONS:We present extensive data on endoscopic follow up of duodenal polyps in FAP patients. Despite frequent polypectomy and biopsies, there is low risk of complications. Low prevalence of HGD and cancer suggests effectiveness of EGD surveillance in FAP patients.

Keywords: FAP, duodenal polyp

POSTER ABSTRACTS

Spigelman Stage Progression



P-044

General Research » Adenomatous polyposis syndromes including FAP

CURRENT PRACTICE PATTERNS IN PEDIATRIC GASTROENTEROLOGY FOR CHILDREN WITH HEREDITARY POLYPOSIS SYNDROMES

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BACKGROUND:Data on care of pediatric patients with hereditary polyposis syndromes (HPS) including Familial Adenomatous Polyposis (FAP), Juvenile Polyposis Syndrome (JPS), and Peutz-Jeghers Syndrome (PJS) is limited. We aim to describe the current practice patterns for HPS by pediatric GI providers.

POSTER ABSTRACTS

METHODS:An anonymous survey was distributed via the international Pediatric GI Bulletin Board listserv to pediatric gastroenterology providers. The survey was based on available guideline recommendations.

RESULTS:132 pediatric gastroenterologists, 13 fellows, and 1 nurse practitioner (70% USA, 6.7% Canada, 15% Europe) started and 89 completed the survey. 62% identified the ESPGHAN position statements on HPS as most influential to their care recommendations. 41% utilized ACG guidelines, 18% NCCN guidelines and 37% used a combination of guidelines. 56% practiced in free standing children's hospitals and 58% reported access to a geneticist or genetic counselor with expertise in HPS.
76% manage FAP (61% with1-5 patients). Genetic testing was recommended by 34% at birth or first presentation, 32.3% at 10-12 years and 29% deferred to a genetic counselor. 83% recommended initial colonoscopy at 10-12 years with 67% performing EGD with initial colonoscopy in an asymptomatic patient. Cold snare was used by 53% for colorectal polypectomy. 37% felt comfortable performing an ampullary biopsy, 29% report having performed ampullary biopsy. Detection of high-grade dysplasia (79%) was the most important factor for surgical referral and 31% referred to surgery for <50 polyps.
75% manage JPS with majority (53%) managing 1-3 patients. For *SMAD4* carriers, 76% refer for hereditary hemorrhagic telangiectasia screening.
56% manage PJS with majority (67%) managing 1-3 patients. 55% recommend small bowel surveillance by age 8 with capsule endoscopy as preferred initial method (64%).

CONCLUSIONS:Most pediatric gastroenterologists manage few HPS patients. Significant heterogeneity and deviation from guidelines exists. Further expert guidance and increased continuing medical education is recommended given the rarity and potential for complications.

Keywords: Children, Hereditary Polyposis Syndromes, Survey

POSTER ABSTRACTS

Table 1a

Table 1. Selected GI Survey Responses. Statistics presented as Median [P25, P75], N (column %).		Total (N=149)	
Familial Adenomatous Polyposis (FAP)		**N**	**Statistics**
Do you currently manage any patients with a diagnosis of FAP?	Yes	130	99 (76%)
	No		31 (24%)
In an asymptomatic patient with FAP, at what age do you recommend the initial colonoscopy?		129	
	Earliest age available		8 (6.2%)
	10 years		65 (50%)
	12 years		43 (33%)
	14 years		9 (7.0%)
	Do not recommend		1 (0.78%)
	Other		3 (2.3%)
The top three factors when deciding on referral to surgery for colectomy evaluation (ranked order):		115	
	Factor 1: High Grade Dysplasia		91 (79%)
	Factor 2: Number of polyps		47 (41%)
	Factor 3: Age of Patient		31 (27%)
When referring a patient to a surgeon, is the surgeon located at:	Home Institution	115	105 (91%)
	Outside Institution		8 (7%)
	None of the above		2 (1.7%)
What type of surgeon do you most often refer to?	Pediatric Surgeon	116	95 (82%)
	Adult Colorectal Surgeon		21 (18%)
	Adult General Surgeon		0
To the best of your knowledge, what percentage of your patients with FAP who require surgery have?		106	
	IPAA (Pouch)		73 [0,100]
	Ileorectal Anastomosis (IRA)		1 [0,25]
	Completion proctectomy with end ileostomy		0 [0.0]
Do you perform routine screening for hepatoblastoma?	Yes	106	66 (62%)
	No		40 (38%)
Juvenile Polyposis Syndrome (JPS)		**N**	**Statistics**
Do you currently manage any patients with a diagnosis of JPS?	Yes	101	76 (75%)
	No		25 (25%)
In a patient with suspected JPS, which of the following genes do you recommend evaluating for a mutation? *Check all that apply.*		100	
	SMAD4		89 (89%)
	BMPR1A		63 (63%)
	PTEN		67 (67%)
	ENG		18 (18%)
	Other		10 (10%)

Selected GI Survey Responses

Table 1b

If a patient has SMAD4 mutation, do you perform vascular screening or refer them for screening for Hereditary Hemorrhagic Telangiectasia (HHT)?	Yes	100	76 (76%)		
	No		24 (24%)		
In an asymptomatic patient with JPS, at what age do you recommend the initial colonoscopy? Upper Endoscopy (EGD)?			Colon	EGD	
	Earliest Age Available/EGD with initial Colonoscopy	100	40 (40%)	75 (75%)	
	12 years		43 (43%)	8 (8%)	
	15 years		11 (11%)	6 (6%)	
	18 years		4 (4%)	3 (3%)	
	Other/25 years, Gene Mutation Dependent, Do not recommend		2 (2%)	14 (14%)	
Peutz-Jeghers Syndrome (PJS)		**N**	**Statistics**		
Do you currently manage any patients with a diagnosis of PJS?	Yes	96	54 (56%)		
	No		42 (44%)		
In an asymptomatic patient with PJS, at what age do you recommend the initial colonoscopy (Colon)? Upper Endoscopy (EGD)? Small Intestine (SI)?		94	Colon	EGD	SI
	8 years		59 (63%)	55 (59%)	51 (55%)
	10 years		13 (14%)	13 (14%)	18 (19%)
	12 years		13 (14%)	11 (12%)	14 (15%)
	18 years		1 (1.1%)	5 (5.3%)	3 (3.2%)
	Other		8 (8.5%)	10 (11%)	7 (7.5%)
When considering your preferred method for initial surveillance of the small intestine, please rank the following factors from most (1) to least preferred (4).		92			
	Most Preferred: Video Capsule Endoscopy		59 (64%)		
	2nd Preferred: MRE		22 (24%)		
	3rd Preferred: CTE		2(2.2%)		
	Least Preferred: Deep Enteroscopy		9(9.8%)		

Selected GI Survey Responses

POSTER ABSTRACTS

P-045

General Research » Adenomatous polyposis syndromes including FAP

UTILITY OF PAIRED TISSUE AND GERMLINE TESTING IN IDENTIFYING POLYPOSIS PATIENTS WITH MOSAIC APC MUTATIONS

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BACKGROUND:Familial Adenomatous Polyposis (FAP) is caused by germline pathogenic variants (PV) in APC, however, mosaic variants at low allele fraction may not be detected through traditional methods. APC testing on polyp tissue has identified mosaic PVs in some unexplained polyposis patients. This abstract summarizes the Zane Cohen Centre for Digestive Diseases' (ZCC) experience with this testing.

METHODS:APC germline and tissue results were reviewed and chart review was completed for polyposis patients at the ZCC who had APC testing on tissue at the University of Washington (UW), with prior inconclusive germline APC testing at an Ontario lab. Paired DNA from blood and 2 adenomas was tested.

RESULTS:Twenty-three patients had paired germline and adenoma testing for APC. Eight (35%) had mosaic FAP with the same APC PV identified in 2 adenomas, and 50% of these patients were also found to have low allele fraction in the germline. Recurrent APC mutations were not detected in the other 15 cases (65%). See Table 1.

Of the 8 cases with mosaic FAP, average age of pathology-documented first adenoma was 42, with all being < age 60, and 4 (50%) <40. The number of adenomas ranged from 29-161. Only 1 person had <20 adenomas, diagnosed at age 28, while most had >30 or "multiple". Four of the 8 (50%) had additional polyp types.

In the unresolved group, average age of onset was 50, with 4 > age 60 and 4 (27%) < 40. The number of adenomas was 21-66, with only 2 having >50 adenomas. Eight (53%) had up to 21 polyps of additional types.

CONCLUSIONS:More than 1/3 of this cohort had mosaic APC mutations, providing a genetic explanation for people with multiple adenomas. Sample size is small, and further research is needed for determining paired tissue-germline testing criteria.

Keywords: FAP, Polyposis, APC, Mosaic, Somatic, Paired testing

POSTER ABSTRACTS

Table 1

Table 1: Somatic APC Results - Age of first adenoma and number or pathology-confirmed adenomas

Resolved	Mosaic - Adenomas	Mosaic - Germline	Onset Age	# Adenomas
Y	Y	N	51	6*
Y	Y	N	29	29
Y	Y	N	56	50*
Y	Y	N	28	18
Y	Y	Y	39	55
Y	Y	Y	53	33
Y	Y	Y	27	161
Y	Y	Y	53	44*
N			64	32
N			64	48
N			44	32*
N			34	21
N			54	46
N			73	24* (no MR)
N			25	66
N			45	35
N			59	31
N			52	60*
N			58	30
N			50	37
N			38	10 + 30 unkn
N			65	29
N			27	10

* = "multiple" polyps

Somatic APC Results - Age of first adenoma and number or pathology-confirmed adenomas

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P-047

General Research » Counseling, Behavioral Health, Psychosocial and Survivorship

"I WORRY I DON'T HAVE CONTROL": THE PSYCHOSOCIAL IMPACTS OF LIVING WITH A HEREDITARY CANCER SYNDROME

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POSTER ABSTRACTS

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BACKGROUND:Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (LS) are common hereditary cancer syndromes (HCS) where patients are genetically susceptible to developing cancers in their lifetime. Continuous screening and monitoring may impact patient's lives. Evidence describing psychosocial and lifestyle impacts following a HCS diagnosis is limited; this study aims to describe these impacts.

METHODS:Semi-structured qualitative interviews were conducted with diagnosed HBOC or LS patients across 3 Canadian provinces with varying HCS health systems. Interpretive description was used for analysis.
RESULTS:Qualitative interviews were conducted with 73 patients (51 females, 21 males, 1 gender-diverse individual; age ranges 25-80 yrs.) diagnosed with HBOC (n= 39) or LS (n= 34). Cancer worry, the fear of oneself or one's family members developing cancer, was a common concern for patients, rooted in a loss of control: "I worry I don't have control". Resulting from increased cancer risk, patients described heightened symptom monitoring and concerns that unlikely symptoms (e.g. cold symptoms) were cancer-related. Many parents expressed carrier guilt over possibly passing on their HCS to future generations. To cope with cancer worry, patients described shifting their outlook to focus on the positive aspects of their diagnosis. To take control of their cancer, patients noted changes to their lifestyle, such as improving diet, exercise, and social activities. Additionally, some patients sought prophylactic surgeries to reduce their cancer risk, though they noted subsequent psychosocial and lifestyle impacts, such as challenges with body image and delaying family planning. Other strategies to gain control included joining patient groups, seeking professional therapy, or discussing their HCS journey with friends and family with similar lived experiences.
CONCLUSIONS:HCS diagnosis has extensive psychosocial and lifestyle implications. This research highlights the need to provide multidisciplinary support to patients and families living with HCS beyond the point of diagnosis.

Keywords: hereditary cancer syndromes, health policy, psychosocial, lynch syndrome, genetic testing, health care

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P-049

General Research » Delivery of Care and Alternative Models

THE LYNCH SYNDROME CENTER AT DANA-FARBER CANCER INSTITUTE: ADVANCING CLINICAL CARE AND RESEARCH FOR LYNCH SYNDROME PATIENTS

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POSTER ABSTRACTS

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BACKGROUND:Lynch syndrome(LS) is present in 1:279 individuals and can predispose LS carriers to develop multiple different cancers. Recognizing the need for specialized care for LS carriers, the Lynch Syndrome Center(LSC) was established at Dana-Farber Cancer Institute(DFCI) with the aim to provide personalized and comprehensive clinical care for individuals and families affected by LS and to advance research in cancer prevention and early detection.

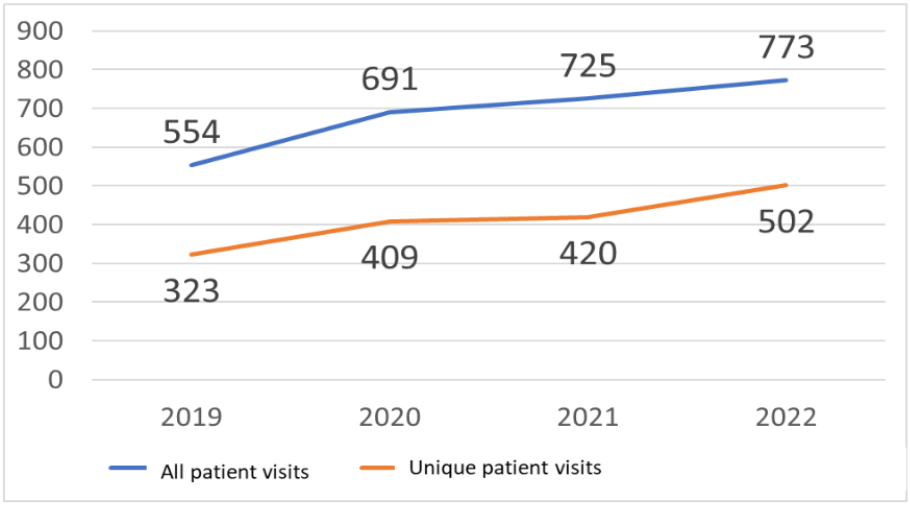
METHODS:The LSC was established in March 2019. LS carriers undergo initial evaluation with genetic counselors and specialized physicians with provider follow-up every 6-12 months to ensure ongoing up-to-date care and monitoring. As of April 2022, all patients receive personalized care plans that provide individualized cancer screening recommendations. Care plans are shared with both LS carriers and their healthcare providers to communicate management recommendations for patients receiving care at DFCI and elsewhere. A dedicated program manager facilitates all aspects of LSC programs and practices.
RESULTS:Between 2019-2022, 1049 patients have been seen at the LSC(Figure 1) from 29 states and 5 countries outside the United States. 470 care plans have been created. The LSC also supports an annual conference(LYNKED IN) to disseminate updates and share new research, empowering LS carriers and their families with knowledge about LS while also fostering a supportive community. To advance research in LS cancer prevention and early detection, the LS Patient Registry and Biobank was recently established to collect longitudinal clinical and lifestyle data(including diet and exercise) and biological specimens(blood, urine, stool and tissue samples) for LSC patients.
CONCLUSIONS:The number and geographic diversity of individuals with LS seeking care at the LSC reflects a need among the LS patient community for multidisciplinary LS-directed care. The LSC at DFCI serves as a clinical model for a dedicated center that provides comprehensive and personalized clinical care, research, and patient support for LS carriers.

Keywords: Lynch syndrome, care model

Figure 1

POSTER ABSTRACTS

Figure 1: Lynch syndrome center patient visits by year



Lynch syndrome center patient visits by year

P-050

General Research » Lynch Syndrome

EVALUATION OF PREMM5 AND PREMMPLUS RISK ASSESSMENT MODELS TO IDENTIFY LYNCH SYNDROME

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BACKGROUND:Multiple clinical hereditary cancer risk models have been developed both for single syndrome and pan-cancer syndrome assessment. To evaluate scenario-specific clinical utility, we compared performance characteristics of Lynch syndrome(LS)-specific model (PREMM5) and multigene cancer risk assessment model (PREMMplus) in identifying LS carriers from two large cohorts derived from a commercial

laboratory(CL) and cancer genetics clinic(CGC).

METHODS:We analyzed data on consecutive patients undergoing germline testing through CL(n=14,849) and CGC(n= 8,691) and restricted study cohorts to patients with a personal and/or family history of LS-associated cancer (n=12,020 for CL;n=6,232 for CGC). Probability risk assessment for LS was calculated using PREMM5 and PREMMplus models. Sensitivity, specificity, positive predictive value(PPV), negative predictive value(NPV) and number needed to test(NNT) were obtained using cut off model score of ≥2.5%. Overall ability to discriminate LS carriers from non-carriers was measured by area under the receiver operating characteristic curve(ROC-AUC). The same approach was performed for a subset of patients with a personal history of LS-associated cancer(n=7,249 for CL;n=3,118 for CGC)

RESULTS:LS was present in 223/12020(1.9%) and 158/6232(2.5%) of CL and CGC cohorts respectively. In both cohorts, PREMM5 had superior discriminatory capacity compared to PREMMplus, but PREMMplus had significantly higher sensitivity for identifying individuals with LS(Table 1). Performance characteristics for PREMM5 and PREMMplus were similar for all patients versus just those with a personal history of LS-associated cancer.

CONCLUSIONS:PREMM5 and PREMMplus both demonstrated high NPV(> 98%) in assessing for LS across all patient cohorts. PREMM5 has a superior discriminatory capacity among LS carriers(ROC-AUCs>0.82) compared to PREMMplus, reflecting differences in development goals: PREMM5 was developed to identify those with mutations in any of five LS genes, while PREMMplus was developed to identify carriers of mutations in any of 19 genes (including LS). Model choice should reflect the patient population and implementation goals.

Keywords: PREMM5, PREMMplus, Lynch syndrome, risk assessment

Table 1

Table 1 Performance characteristics of PREMMplus and PREMM5 in the two cohorts

Cohort	Model	SE (%)	SP (%)	PPV (%)	NPV (%)	NNT	ROC-AUC (95% CI)
CL Cohort	PREMMplus	89.2	21.7	2.1	99.1	47	0.713 (0.674-0.751)
	PREMM5	63.7	82.1	6.3	99.2	16	0.808 (0.773-0.842)
CGC Cohort	PREMMplus	90.5	22.7	3.0	98.9	34	0.684 (0.637-0.730)
	PREMM5	60.8	86.3	10.3	98.8	10	0.795 (0.753-0.837)
CL-LS Affected	PREMMplus	86.7	28.6	2.8	98.9	36	0.724 (0.680-0.769)
	PREMM5	70.5	79.6	7.5	99.1	13	0.825 (0.786-0.864)
CGC-LS Affected	PREMMplus	90.7	31.8	3.2	99.3	32	0.722 (0.656-0.788)
	PREMM5	69.3	83.8	9.5	99.1	11	0.828 (0.770-0.886)

Performance characteristics of PREMMplus and PREMM5 in the two cohorts

POSTER ABSTRACTS

P-051

General Research » Delivery of Care and Alternative Models

IMPROVING FAMILY HISTORY DOCUMENTATION AT THE TIME OF COLONOSCOPY TO INCREASE APPROPRIATE GENETIC CANCER SCREENING REFERRALS

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BACKGROUND:Family histories at the time of colonoscopy allows gastroenterologists to identify patients who would benefit from genetic screening. In practice, obtaining and applying this information to patient recommendations is observed to be inconsistent. After obtaining baseline rate of family history documentation and compliance with appropriate hereditary cancer clinic referrals, we implemented an intervention to improve these rates.

METHODS:We implemented a family history questionnaire including institutional criteria for hereditary cancer clinic referral for all screening and surveillance colonoscopies and updated our colonoscopy procedure report template. Endoscopy reports were retrospectively reviewed for these patients between ages 18-89 from March 2022 to September 2022. Data collected included demographics, family history documentation, and determination of criteria fulfillment for referral to hereditary cancer clinic. The data was stratified into two groups: physicians with designated focus in hereditary colon cancer and remainder of gastroenterology faculty.

RESULTS:806 consecutive colonoscopy reports were reviewed. 275 procedures were performed by the hereditary focus group and 531 by the general group. Family history documentation improved in both the hereditary focus group (93.0% vs 78.1%, p<0.00001) and general group (80% vs 68.3%, p<0.00001). In the hereditary focus group, 6.2% (n=17) of patients met criteria for referral to the hereditary cancer clinic, 5.9% (n=1) were not referred despite meeting institutional criteria, compared with 41.2% (p=0.015) prior to intervention. In the general group, 3.0% (n=16) of patients met criteria for referral, and 37.5% (n=6) were not referred, compared with 61.9% (p=0.141) prior to intervention.

CONCLUSIONS:At our institution, our interventions to improve family history documentation and awareness of institutional criteria for hereditary cancer clinic referral improved the rates of documentation in both groups. Rate of referral improved in the hereditary group the general group is trending towards improvement. Area for improvement exist in both groups and ongoing education and process improvements can further increase these rates.

POSTER ABSTRACTS

Keywords: Family history, documentation, hereditary cancer, referral

P-052

General Research » Delivery of Care and Alternative Models

GENETIC COUNSELING OUTCOMES FROM MEDICAL ONCOLOGIST INITIATED GERMLINE GENETIC TESTING FOR PATIENTS WITH PANCREATIC DUCTAL ADENOCARCINOMA

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BACKGROUND:Pancreatic ductal adenocarcinoma (PDAC) is an aggressive cancer often diagnosed at later stages with a high mortality rate. Germline genetic testing (GGT) for the BRCA1 and BRCA2 genes is recommended for all patients with PDAC to assess eligibility for PARP inhibitors. As PDAC frequently has accelerated disease progression, patients with PDAC should undergo expedited GGT for treatment planning. However, wait times for genetic counseling and testing may delay patients from receiving this information promptly. Our institution piloted a program in which medical oncologists ordered GGT for patients with PDAC and offered the option to be referred to genetic counseling. We investigated the rate of referral and uptake of genetic counseling for this population.

METHODS:Results of GGT from commercial laboratories that were ordered between December 2019 and April 2023 by medical oncologists at Fox Chase Cancer Center for patients with PDAC were reviewed. Electronic medical records and the internal genetics database were utilized to identify patients who were referred and underwent genetic counseling.

RESULTS:From December 2019 to April 2023, 135 patients with PDAC underwent GGT ordered by their medical oncologist. Multigene panels ranged from 13-91 genes. 29 pathogenic variants (PVs) were identified in 23/135 (17%) patients tested (Figure 1).
25/135 (19%) patients were referred for genetic counseling and 10/135 (7%) patients underwent genetic counseling (Figure 2). Half (4/8) of patients carrying high/moderate penetrance PVs underwent genetic counseling while 1/16 (6%) of patients carrying low penetrance/recessive PVs underwent genetic counseling. 5/112 (5%) of patients with no PV pursued genetic counseling.

CONCLUSIONS:Medical oncologist initiated GGT is an option for obtaining expedited GGT for patients with PDAC. Referrals and uptake for posttest genetic counseling for patients with moderate/high risk pathogenic variants were high while referrals and uptake for genetic counseling were low in patients with no PVs or

patients with low penetrance/recessive risk PVs.

Keywords: Pancreatic adenocarcinoma, Germline, Genetic Counseling

Fig1

Figure 1. Pathogenic variants identified in medical oncologist initiated germline genetic testing

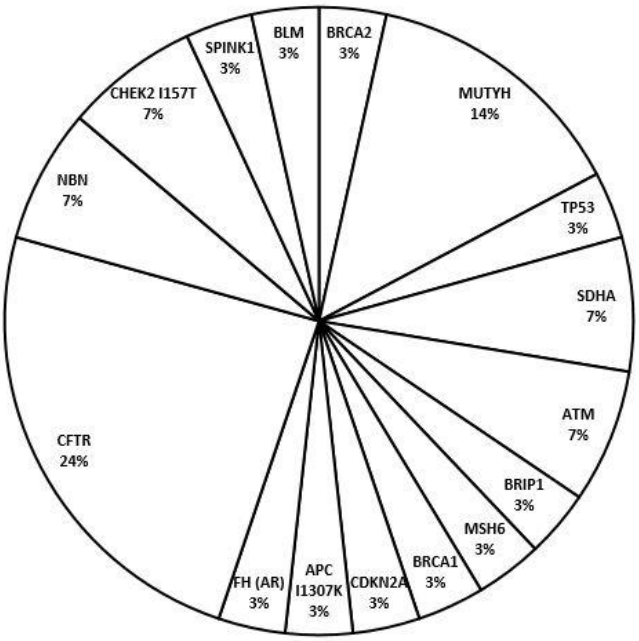
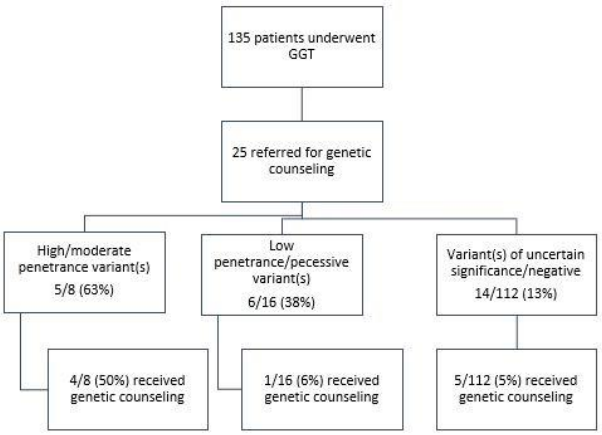


Fig2

Figure 2. Patients referred for posttest genetic counseling and uptake of genetic counseling



P-053

General Research » Delivery of Care and Alternative Models

PREFERENCES FOR COMMUNICATION OF GERMLINE AND SOMATIC GENETIC TEST RESULTS AMONG A COHORT OF HISPANIC COLORECTAL CANCER PATIENTS

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BACKGROUND:The ENLACE study is an NCI Moonshot-funded study of participant engagement in genomic characterization among Hispanic colorectal cancer patients. We report communication preferences for receiving germline and somatic results among the first 100 participants.

METHODS:Colorectal cancer patients were recruited from oncology clinics at the USC Norris Cancer Hospital (34%) or LA General Medical Center, a safety-net hospital (66%). Germline and somatic testing were explained with a pre-test information sheet and study-developed video in English and Spanish. Investigator-developed questions were used to query communication preference for return of results, allowing participants to select multiple providers and express reasons for their preferences. These open-ended responses were categorized.

RESULTS:Participants had a median age of 53 (range 24-87), and were 51% male, 47% with less than high school education, 64% Spanish-preferring, and 73% born outside USA. When asked provider preference for

return of germline results, 81% selected “cancer doctor,” 27% selected “genetic counselor,” 14% selected “primary care or other doctor,” and 13% selected “study personnel.” Similarly, 81% preferred somatic results from “cancer doctor,” 23% from “genetic counselor,” 12% from “primary care or other doctor,” and 8% from “study personnel.” Reasons stated for preferring communication from their cancer doctor include the strong relationship, familiarity, and confidence in their provider, and the doctor’s knowledge level and responsibility for the patient. Those selecting genetic counselor did so because of their expertise in genetics, skill in explaining results, and potential for spending more time explaining results.

CONCLUSIONS:Most participants expressed a preference for return of results from their oncologist, followed by a genetic counselor. Our results also suggest a demand for somatic genetic counseling, which is only partially within the scope of genetic counselors. Further studies exploring these preferences are needed, including how oncology and genetics providers can meet the informational needs of patients.

Keywords: equity, Hispanic, communication, counseling, germline, somatic

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P-054

General Research » Delivery of Care and Alternative Models

FRAGMENTED SYSTEMS OF CARE: AN OVERVIEW OF CANADIAN HEALTH SYSTEM CARE MODELS FOR HEREDITARY CANCER SYNDROMES

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BACKGROUND:Hereditary cancer syndromes (HCS) are one of the most prevalent inherited diseases. Patients with a confirmed genetic diagnosis of a HCS may require lifelong screening and follow up. However, there is limited data on the accessibility and coordination of HCS care across different health jurisdictions in Canada. The purpose of this study is to compare the systems of HCS care in 3 provinces in Canada.

METHODS:Expert leads of provincial HCS care programs in British Columbia (BC), Ontario (ON), and Newfoundland & Labrador (NL) were consulted to provide detailed information about various care systems dimensions.

POSTER ABSTRACTS

RESULTS:Access to and coordination of HCS care across all 3 provinces is fragmented. First, there are inconsistencies in genetic testing referral criteria and management recommendations for carriers. This means that some family members across the country have access to HCS medical services while others do not. Accessing genetic testing is further impaired by the varied and strict eligibility criteria for testing across the provinces. Secondly, all provinces face a genetics workforce shortage, and long wait times for families to access publicly funded testing. Thirdly, provincially-organized screening and surveillance programs only exist for some organs in BC, ON, and NL. The lack of organized screening programs leaves at risk individuals and their family physicians to navigate the system of care alone. This results in inequities in medical outcomes, further exacerbated for underserved populations and rural communities. Lastly, the genetic testing offerings across the 3 provinces vary. Differences in gene panels means that at risk individuals living in different jurisdictions will have inconsistent genetic diagnoses.

CONCLUSIONS:A fragmented and uncoordinated HCS care system may result in socioeconomic and health implications for HCS families. Further investigation is needed to better examine these impacts to inform evidence-based practice for a more coordinated and patient-centered health care system.

Keywords: hereditary cancer syndromes, lynch syndrome, healthcare systems, genetic testing, policy research, care pathway

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P-055

General Research » Delivery of Care and Alternative Models

SPREAD THE WORD: SINGLE-INSTITUTION EXPERIENCE NOTIFYING PATIENTS OF UPDATED NCCN SCREENING GUIDELINES

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BACKGROUND:Guidelines for cancer screening and risk reduction in individuals with hereditary cancer predisposition syndromes are frequently updated based on new data. Attempts to disseminate these updates to relevant patients and their providers have been challenging. Historical approaches, such as encouraging patients to stay in touch with their genetics provider, likely served to worsen healthcare disparities. Our comprehensive cancer center set out to create a standardized process for identifying and proactively notifying relevant patients seen at our institution of updated guidelines. We piloted this process after recent NCCN updates lowered the recommended age for breast cancer screening in individuals with pathogenic and likely pathogenic variants in ATM and CHEK2.

METHODS:Patients seen in our genetics and high-risk surveillance clinics with pathogenic and likely pathogenic variants in CHEK2 and ATM were identified using internal data collected via pedigree software. Deceased patients and patients with low penetrance CHEK2 variants (I157T, Ser428Phe, and T476M) were excluded. Eligible patients of all ages and genders were notified of updated NCCN guidelines via a direct

message in the electronic medical record (EMR) or a mailed letter. All notifications were visible to other providers within the EMR.

RESULTS:Notifications went out to 354 patients. Direct messages were sent to 296 patients and viewed by 77% within 30 days. The remainder of patients, those without the ability to message within the EMR (58 patients) and those who did not view their EMR message, were mailed a letter. Feedback from patients was positive and many responded with messages of thanks. A total of twenty-six (7%) patients reached out with questions about screening resources, family testing, etc.

CONCLUSIONS:We successfully piloted a standardized process to identify and proactively notify relevant patients seen at our institution of updated NCCN guidelines for cancer screening and risk reduction.

Keywords: Notify, NCCN, EMR, Genetics, Update

P-056

General Research » Delivery of Care and Alternative Models

EXAMINING THE VALUE OF GENETIC COUNSELOR INVOLVEMENT IN IDENTIFICATION OF COLORECTAL CANCER PATIENTS THAT QUALIFY FOR GENETIC TESTING

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BACKGROUND:Though hereditary cancer guidelines set forth criteria to determine which newly diagnosed cancer patients may benefit from a genetic evaluation, not all qualifying referrals are captured. We aimed to determine whether genetic counselor review of all new colorectal adenocarcinoma (CRC) cases would identify missed genetic counseling referrals.

METHODS:We performed a retrospective chart review of patients diagnosed with a new primary CRC at Virginia Mason Medical Center, Seattle WA, between January 2021 and October 2021, and identified patients who met at least one of the 2021 NCCN (National Comprehensive Care Network) guideline criteria for hereditary colorectal, breast, ovarian, prostate, or pancreatic cancer genetic testing. We report the number of patients that (1) met criteria and were referred, (2) completed an appointment, and (3) completed genetic

testing. In addition, we report numbers as well as reasons for missed referrals.

RESULTS:124 patients were diagnosed with a CRC, of which 48 (38.7%) qualified for a genetics evaluation. Of the 48 who qualified for a genetics evaluation, 28 (58.3%) were referred for genetic counseling, 24 (50%) had a pre-test counseling appointment, and 21 (43.8%) pursued genetic testing. Of the 21 who opted for genetic testing, 11 (52.4%) were found to have a germline pathogenic variant. Of the 20 (41.66%) who were not referred, the most commonly missed indications were: colorectal polyposis - 3/5 (60%); personal or family history of multiple Lynch syndrome-associated cancers - 2/4 (50%) and 5/8 (62.5%), respectively; early-onset CRC with intact mismatch repair status - 5/11 (45%); and personal and/or family history suggestive of a non-CRC hereditary syndrome - 5/8 (62.5%).

CONCLUSIONS:We demonstrate that involvement of GCs at the time of CRC cancer diagnosis identifies patients appropriate for genetic counseling that would have otherwise been missed.

Keywords: genetic counseling; genetics referrals; hereditary colorectal cancer

Table 1 - Missed Referral Breakdown

Table 1

Criteria	Not referred	Total number in cohort (N=124)
Lynch syndrome • Personal • Family history	 2 5	 4 8
Early-onset CRC (intact MMR on tumor testing)	5	11
Personal and/or family history suggestive of non-CRC syndrome	5	8
Polyposis syndrome	3	5

POSTER ABSTRACTS

P-057

General Research » Early Onset Colorectal Cancer

FAMILIAL CANCER HISTORY AND COMPLETION OF GENETIC TESTING IN YOUNG ONSET COLORECTAL CANCER

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BACKGROUND:Universal germline testing is recommended for patients with early-onset colorectal cancer to inform surveillance, treatment, and cascade testing. Whether familial cancer history influences genetic testing completion in young patients is unclear. We evaluated familial cancer history in young adult colorectal cancer patients and hypothesized that strong family history of Lynch-associated cancers would be associated with higher testing completion.

METHODS:We performed a review of patients with colorectal cancer age ≤50 years diagnosed between 2014 and 2021 who received the entirety of their cancer care at a single institution in the Deep South. Family history of cancer and history of Lynch-associated cancers were abstracted from chart review. The primary outcome was completion of germline multigene panel testing.

RESULTS:Of the 100 included patients, 37% were seen by a genetic counselor and 31% completed genetic testing. There were no differences in age, race, sex, marital or insurance status by testing status ($p>0.05$). Among this population, family history of any cancer was present in 68%, history of cancer in first-degree relative (FDR) was observed in 43%, and second-degree relative (SDR) in 42%. Family history of Lynch-associated cancers was observed in 50%, and family history of colorectal cancer was observed in 28%. Genetic testing completion rates were significantly higher for patients who had family history of any cancer, FDR with cancer, SDR with cancer, or family history of Lynch-associated cancer ($p <0.05$; Table 1). There was no difference in genetic testing rates in patients by family history of colorectal cancer alone ($p >0.05$).

CONCLUSIONS:Less than one third of patients with early-onset colorectal cancer completed genetic testing. However, patients with a family history of any cancer or Lynch-associated cancers were more likely to complete genetic testing. Interventions to improve genetic testing completion in patients lacking family history are needed.

Keywords: colorectal cancer, genetic testing

POSTER ABSTRACTS

Table 1. Genetic testing status by familial cancer history

Table 1. ***Genetic testing status by familial cancer history***

	Genetic testing completion		
	No (N=69)	Yes (N=31)	P-Value
Family history of any cancer			**<0.001**
No family history	90.6%	9.4%	
1-2 relatives with cancer	66.6%	33.3%	
≥3 relatives with cancer	40.0%	60.0%	
First-degree relative with cancer history			**0.004**
No family history	80.7%	19.3%	
≥1 relative with cancer	53.5%	46.5%	
Second-degree relative with cancer history			**0.029**
No family history	77.9%	22.4%	
≥1 relative with cancer	57.1%	42.9%	
Family history of Lynch-associated cancer			**0.005**
No family history	84.0%	16.0%	
1-2 relatives with cancer	55.0%	45.0%	
≥3 relatives with cancer	50.0%	50.0%	

Table demonstrating genetic testing status by familial cancer history

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P-058

General Research » Early Onset Colorectal Cancer

ACCEPTABILITY AND USABILITY OF A DIGITAL CARE NAVIGATOR FOR PRETEST GENETIC EDUCATION IN EARLY ONSET COLORECTAL CANCER

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BACKGROUND:National guidelines recommend germline testing for all patients with early onset colorectal cancer (EOCRC). The Nest digital care navigator is a software platform that provides patients personalized genetic information to assist patients in making informed health decisions about genetic testing. We developed a pretest genetic education intervention (Nest-CRC) to facilitate timely uptake of genetic testing among English and Spanish-speaking EOCRC patients. We evaluated the acceptability and usability of Nest-CRC among

POSTER ABSTRACTS

EOCRC patients and providers using a mixed method approach.

METHODS:English and Spanish-speaking EOCRC patients (n=19) and providers (n=6) completed surveys about their experiences and perspectives on genetic services (Fig 1) and using Nest-CRC (e.g., interest in genetic testing and decision support). Following the Learner Verification approach, we conducted semi-structured interviews with participants and assessed the self-efficacy, attraction, comprehension, cultural acceptability, and usability of Nest-CRC.

RESULTS:Quantitative and qualitative results indicated good acceptability and usability of Nest-CRC. Most participants (92%-100%) agreed that all 5 education modules were easy to understand and helpful (Fig 2). About half had not had genetic testing (n=9); of those participants, 78% (n=7) were interested in genetic testing and 22% (n=2) were not sure after completing Nest CRC. Overall, participants reported high decisional support from Nest-CRC (M=3.9/4). In interviews, participants reported that they felt Nest-CRC provides enough information to decide whether to have genetic testing. They also found Nest-CRC attractive in design, easy to comprehend and use, and acceptable to individuals from varied backgrounds. Participants made specific recommendations about how to improve Nest-CRC including adding a voice-over option, more visual elements, and more information about insurance coverage and potential genetic discrimination.

CONCLUSIONS:Nest-CRC will be refined based on participant's recommendations and re-evaluated. Pilot testing revealed Nest-CRC to be a promising strategy to facilitate pretest genetic education and promote genetic testing among EOCRC patients.

Keywords: early onset colorectal cancer, pretest genetic education, genetic testing, digital care navigator, eHealth

POSTER ABSTRACTS

Fig1

Table 1. Participants' demographic and clinical characteristics

EOCRC Patients (n=19)	**n; %**
Age *(Median; range)*	*43; 27-51*
Spanish-preferring	4; 21%
Female	10; 53%
African American/Black	4; 21%
Hispanic ethnicity	6; 32%
Some college or more	10; 53%
Employed	11; 58%
Stage 4 cancer	7; 37%
Active cancer treatment	9; 47%
History of genetic counseling	8; 42%
History of genetic testing	10; 53%
Providers (n=6)	**n; %**
Age *(Median; range)*	*39; 31-46*
Spanish-preferring	1; 17%
Female	3; 50%
White	6; 100%
Hispanic ethnicity	1; 17%
Physician (MD)	4; 67%
Board Certified Genetic Counselors	2; 33%
Years working with CRC patients *(Median; range)*	*11; 2-13*
Communicate with patients about genetic risk 50% of the time or more	6; 100%

POSTER ABSTRACTS

Fig2

Table 2. Participants' evaluation of Nest-CRC content by module

	Patients (n=19)			Providers (n=6)		
Modules	Strongly Agree/ Agree (n; %)	Neither (n; %)	Disagree/ Strongly disagree (n; %)	Strongly Agree/ Agree (n; %)	Neither (n; %)	Disagree/ Strongly Disagree (n; %)
1. Hereditary colorectal cancer						
Easy to understand	19; 100%	0; 0%	0; 0%	5; 83%	1; 17%	0; 0%
Helpful	19; 100%	0; 0%	0; 0%	4; 67%	2; 33%	0; 0%
2. Genetic testing						
Easy to understand	19; 100%	0; 0%	0; 0%	5; 83%	1; 17%	0; 0%
Helpful	19; 100%	0; 0%	0; 0%	6; 100%	0; 0%	0; 0%
3. Benefits and risks						
Easy to understand	18; 95%	1; 5%	0; 0%	6; 100%	0; 0%	0; 0%
Helpful	19; 100%	0; 0%	0; 0%	5; 83%	1; 17%	0; 0%
4. Care recommendations						
Easy to understand	19; 100%	0; 0%	0; 0%	5; 83%	1; 17%	0; 0%
Helpful	18; 95%	1; 5%	0; 0%	6; 100%	0; 0%	0; 0%
5. Family members implications						
Easy to understand	19; 100%	0; 0%	0; 0%	6; 100%	0; 0%	0; 0%
Helpful	19; 100%	0; 0%	0; 0%	6; 100%	0; 0%	0; 0%

P-060

General Research » Gastric cancer-related syndromes

ENDOSCOPIC SURVEILLANCE IN PATIENTS WITH PATHOGENIC VARIANTS IN CDH1 OR CTNNA1 – A REAL WORLD SCENARIO

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POSTER ABSTRACTS

BACKGROUND:Heterozygous pathogenic germline variants in CDH1 or CTNNA1 cause hereditary tumor syndromes associated with a high risk for diffuse gastric cancer (DGC). Carriers of a pathogenic germline variant (PGV) often show multiple foci of gastric signet ring cell carcinoma (SRCC) and are offered prophylactic total gastrectomy (PTG), especially if there is a positive family history for DGC.

METHODS:Individuals with a PGV in CDH1 or CTNNA1 were evaluated at eight centers from the German Consortium for Familial Intestinal Cancer from 2008 through April 2023.

RESULTS:We identified 117 carriers of a CDH1 PGV and 4 carriers of a CTNNA1 PGV (73 female (60%)). A family history of gastric cancer was apparent in 93/121 patients (77%; 1st degree relative in 77/93; 2nd degree 69/93).
A total number of 177 endoscopic examinations was conducted (range 1-7). In 34/121 (28%) patients (age range 14-53 years), DGC was detected during endoscopy by either targeted (20/34 (59%) patients) and/or multiple random biopsies (15/34 (44%) patients; number of biopsies taken median 31 [range: 2-100). A total number of 14/121 (12%) patients presented with metastatic disease (age range 16-62 years). Omitting random biopsies in our cohort would have led to an under-diagnosis rate of 41%.
Gastrectomy was performed in 29/121 (24%) patients after endoscopic diagnosis of DGC. A PTG was done in 53/121 (44%) patients without prior endoscopic detection of SRCC. Here, a SRCC was detected in 31/53 (59%) patients, including multifocal SRCCs in 23/31 (74%) patients (number of cancer foci 1-15). All SRCCs were confined to the mucosa (pT1a).

CONCLUSIONS:More than two third of the individuals with pathogenic germline variants in CDH1 or CTNNA1 had histopathologic evidence of DGC in endoscopy and/or gastrectomy specimens. In our cohort, we observed no incident tumors (>pT1a) if no macroscopic cancer was apparent at initial endoscopy.

Keywords: CDH1; CTNNA1; HDGC; hereditary diffuse gastric cancer; gastric cancer; random biopsies

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P-061

General Research » Lynch Syndrome

PUSH-ENTEROSCOPY IN LYNCH SYNDROME

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POSTER ABSTRACTS

BACKGROUND:Lynch syndrome (LS) includes a variety of extracolonic malignancies such as gastric (life-time risk 13%) or small bowel cancer (life-time risk 8%). Up to 47% of small-bowel cancers occur in the duodenum and up to 33% in the jejunum, which is missed by current screening modality.

METHODS:Patients with a proven pathogenic variant were included in a surveillance program at our National Center of Hereditary Tumor Syndromes, where all patients are followed prospectively after signing an informed consent. We assessed endoscopic findings using standard esophagogastroduodenoscopy (EGD) compared to push enteroscopy using a pediatric colonoscope at our center. We implemented the routine use of push enteroscopy in August 2022.

RESULTS:Between April 2013 and July 2022, a total number of 445 EGDs were done in 187 patients (range 1-7; 108 (58%) female; 48 years; 66 MLH1 (35.5%); 86 MSH2 (46%); 25 MSH6 (13%); 9 PMS2 (5%); 1 Epcam (0.05%)).
Between August 2023 and April 2023, a total number of 103 EGDs were done in 103 patients (54 (52%) female; 48 years; 38 MLH1 (37%); 46 MSH2 (45%); 11 MSH6 (11%); 4 PMS2 (4%); 1 Epcam (1%); 3 MLH1 and MSH2 (3%)).
Using standard EGD, we detected intestinal metaplasia in 49 (11%) patients, in one patient (MLH1) with dysplasia. Neoplastic and preneoplastic lesions included gastric cancer (5; 1%), gastric adenomas (7; 1.6%), duodenal cancer (1%) and duodenal adenomas (8; 1.8%).
Using push- enteroscopy, we detected intestinal metaplasia in 23 (22%) patients, in one patient (MLH1) with dysplasia. No neoplastic lesions were detected. Additionally, the use of push enteroscopy enabled us to detect three jejunal adenomas (two advanced adenomas).

CONCLUSIONS:This prospective endoscopic study shows that surveillance of the upper GI tract identifies clinically relevant results in a large proportion of LS patients. The use of push enteroscopy does not hamper endoscopic detection of relevant lesions.

Keywords: Lynch syndrome; gastric cancer; duodenal cancer; small bowel cancer; push enteroscopy

POSTER ABSTRACTS

Table 1

	Esophagogastroduodenoscopy (n=445)	Push-Enteroscopy (n=103)
Barrett esophagus	23 (5%) 3 with high-grade dysplasia	4 (4%)
Gastric cancer	5	0
Gastric adenoma	7 (mean size 19 mm)	0
Intestinal metaplasia	49 (11%)	23 (22%)
Helicobacter pylori	21 (5%)	4 (4%)
Duodenal cancer	3 duodenal 2 ampullary	0
Duodenal adenoma	8 (mean size 8 mm)	1 (6 mm)
Jejunal adenoma	0	3 (6, 12 and 15 mm) (2 LGIEN, 1 HGIEN)

Results of endoscopic surveillance using either esophagogastroduodenoscopy or push-enteroscopy

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P-062

General Research » Gastric cancer-related syndromes

ASSESSING SENSITIVITY OF GENETIC TESTING CRITERIA FOR HEREDITARY DIFFUSE GASTRIC CANCER IN MULTIPLE COHORTS

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BACKGROUND:Hereditary diffuse gastric cancer is an autosomal-dominant syndrome most often caused by pathogenic variants in CDH1. The International Gastric Cancer Linkage Consortium (IGCLC) developed clinical criteria for genetic testing and updated them most recently in 2020. Our group previously showed these criteria to have poor sensitivity and proposed our own simpler and more sensitive Yale criteria. The European Reference Network on Genetic Tumour Risk Syndromes (ERN GENTURIS) subsequently proposed expanding the IGCLC criteria and showed its “lobular breast cancer-expanded” criteria to be more sensitive than the IGCLC criteria in a European cohort of CDH1 mutation carriers. The purpose of this study was to compare performance of the ERN GENTURIS criteria with the IGCLC’s and our Yale criteria in an American cohort of CDH1 mutation carriers.

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METHODS:Medical histories of 112 CDH1 mutation carriers, identified predominantly by multigene panel testing, and their 649 family members were reviewed. The percentage of subjects fulfilling the IGCLC criteria, our Yale criteria, and the ERN GENTURIS criteria were calculated.

RESULTS:As previously reported, in our cohort, our Yale criteria had a sensitivity of 87% for CDH1 pathogenic variants, compared with 19% for the IGCLC criteria. The ERN GENTURIS criteria captured 25 families missed by the IGCLC criteria, bringing its overall sensitivity to 41%.

CONCLUSIONS:In our American cohort, the ERN GENTURIS criteria performed better than the IGCLC criteria, but far worse than in the European cohort used to develop them (sensitivity 94%). In contrast, our Yale criteria performed well in both cohorts (sensitivity 87% in our dataset and 95% in the European dataset). More significantly, our criteria do not rely heavily on pathology information from family members (as it is rarely available) and take into consideration recommendations generated by other cancer genetics guidelines, addressing important practical issues encountered in cancer genetics clinics.

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

Table 1

	ERN GENTURIS cohort	Yale/Ambry cohort
Families with pathogenic variants	176	112
Gastric cancer without known histology among probands	7%	37%
Breast cancer without known histology among probands	81%	13%
Gastric cancer without known histology among family members	61%	94%
Breast cancer without known histology among family members	91%	92%
Sensitivity of IGCLC criteria	84%	19%
Sensitivity of Yale criteria	95%	87%
Sensitivity of ERN GENTURIS criteria	94%	41%

Table 1: Comparison of ERN GENTURIS and Yale/Ambry cohorts showing the number of families with *CDH1* pathogenic variants, percent of gastric and breast cancers among probands and relatives without known histology, and sensitivity of different genetic testing criteria. Data in the ERN GENTURIS column reproduced from Garcia-Pelaez et al. Lancet Oncol. 2023 Jan;24(1):91-106.

Comparison of ERN GENTURIS and Yale/Ambry cohorts showing the number of families with CDH1 pathogenic variants, percent of gastric and breast cancers among probands and relatives without known histology, and sensitivity of different genetic testing criteria. Data in the ERN GENTURIS column reproduced from Garcia-Pelaez et al. Lancet Oncol. 2023 Jan;24(1):91-106.

POSTER ABSTRACTS

P-063

General Research » Gastric cancer-related syndromes

ENDOSCOPIC SURVEILLANCE ALLOWS PREDICTION OF BURDEN OF EARLY SIGNET RING CELL CARCINOMA IN HEREDITARY DIFFUSE GASTRIC CANCER SYNDROME

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BACKGROUND:Hereditary diffuse gastric cancer (HDGC) syndrome is commonly linked to *CDH1* germline pathogenic variants (PV) and carries a high lifetime risk of diffuse gastric cancer (DGC). Definitive treatment remains prophylactic total gastrectomy (PTG). However, endoscopic surveillance can be offered to inform decision-making around surgery, although the optimal time for treatment escalation remains unclear. This study aims to establish whether histopathological assessment of endoscopic biopsies can predict burden of early signet ring cell (SRC) carcinoma on PTG specimens.

METHODS:We performed a retrospective review of prospectively collected data on endoscopic and surgical histopathologic results from *CDH1* PV carriers who underwent PTG at Addenbrooke's Hospital between January 2006 and May 2023. Targeted and systematic Cambridge protocol biopsies were performed. Patients with confirmed DGC (stage 2 or higher) at baseline endoscopy were excluded. Pearson correlation was performed to assess the relationship between number of SRC foci on endoscopy and surgical specimens.

RESULTS:46 patients underwent PTG with median of 3 pre-operative surveillance endoscopies over 22 months. The final stage was pT1aN0M0 in 41 patients and pT0N0M0 in 5 patients. The number of SRC foci on PTG specimens ranged from 0 to 273. There was a strong correlation between number of SRC foci on gastrectomy specimens and from targeted and random biopsies when evaluated separately and together for the last 2 and all endoscopies (Table 1). The strongest correlation was seen with the total number of SRC foci on random biopsies for the last 2 endoscopies (r= 0.738, p-value<0.001). Random biopsies outperformed targeted biopsies in the prediction of early SRC burden.

CONCLUSIONS:Endoscopic surveillance with systematic targeted and random biopsies by expert endoscopists within a dedicated specialist service provides useful information to estimate the burden of early SRCC. Low number of SRC foci at last two endoscopies indicate scarce gastric neoplastic involvement.

Keywords: Hereditary diffuse gastric cancer, CDH1 germline mutation, signet ring cell foci

Table 1

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Table 1: Correlation between Endoscopic and Histopathological Assessment of Prophylactic Total Gastrectomy Specimens

Number of patients	Endoscopy	Comparison	Pearson correlation coefficient (r)	p-value
46	Last endoscopy	Targeted biopsies vs gastrectomy	0.167	0.267
		Random biopsies vs gastrectomy	0.214	0.154
		Targeted and random biopsies vs gastrectomy	0.227	0.129
17	Last 2 endoscopies (for patients with ≥2 OGDs)	Targeted biopsies vs gastrectomy	**0.533**	**0.028****
		Random biopsies vs gastrectomy	**0.738**	**<0.001*****
		Targeted and random biopsies vs gastrectomy	**0.706**	**0.002****
46	All endoscopies	Targeted biopsies vs gastrectomy	**0.487**	**<0.001*****
		Random biopsies vs gastrectomy	**0.606**	**<0.001*****
		Targeted and random biopsies vs gastrectomy	**0.656**	**<0.001*****

Correlation between Endoscopic and Histopathological Assessment of Prophylactic Total Gastrectomy Specimens

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P-064

General Research » Gastric cancer-related syndromes

CLINICAL CHARACTERIZATION OF PATIENTS WITH GERMLINE *CTNNA1* AND *CDH1* MUTATIONS

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BACKGROUND:Pathogenic and likely pathogenic variants (PV/LPVs) in *CDH1* give rise to Hereditary Diffuse Gastric Cancer (HDGC). More recently, *CTNNA1* germline PV/LPVs have been identified in families meeting HGDC criteria, however *CTNNA1*-associated disease penetrance remains unclear. Here we review the clinical features of probands with *CTNNA1* and *CDH1* PV/LPVs identified as part of hereditary cancer panel testing through a single commercial laboratory.

METHODS:We performed a retrospective data analysis to identify PV/LPV carriers in *CTNNA1* and *CDH1*. Single-site testing was excluded from analysis. Clinical information was obtained from test request forms completed by healthcare providers at the time of testing.

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RESULTS:Heterozygous PV/LPVs in *CTNNA1* and *CDH1* were identified in 49 and 549 individuals, respectively. Of these individuals, one *CTNNA1* carrier (2.0%) and 33 (6.0%) *CDH1* carriers reported a personal history of gastric cancer. 1/43 (2.3%) female *CTNNA1* carriers and 99/496 (20.0%) female *CDH1* carriers reported a personal history of lobular breast cancer. 24/49 (49.0%) *CTNNA1* carriers and 308/549 (56.1%) *CDH1* carriers reported a personal history of any cancer. Family history of gastric cancer was noted in 8/50 (16.0%) *CTNNA1* carriers and 181/563 (32.1%) *CDH1* carriers. Co-occurring PV/LPVs were noted in 5 *CTNNA1* cases and 36 *CDH1* cases (excluding carriers of recessive conditions and the *APC* I1307K low-penetrance variant). No co-occurring *CDH1* and *CTNNA1* PV/LPVs were identified.

CONCLUSIONS:While gastric cancer and lobular breast cancer were noted in the clinical history of 2 separate *CTNNA1* carriers, our cohort reported a lower incidence of these cancers in *CTNNA1* carriers as compared to *CDH1*. Our data suggest *CTNNA1* may be a lower penetrance gene within an HGDC-spectrum, however additional research is necessary to elucidate cancer risk.

Keywords: Hereditary Diffuse Gastric Cancer, CTNNA1, CDH1, Gastric Cancer

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P-065

General Research » Lynch Syndrome

ONE OF THESE IS NOT LIKE THE OTHERS: A DESCRIPTIVE STUDY OF THE ATTENUATED PHENOTYPE OF PMS2

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BACKGROUND:PMS2 pathogenic germline variants (PGVs) have the lowest penetrance and highest population prevalence of the Lynch syndrome (LS)-associated genes. We hypothesized that patients (pts) with PMS2 PGVs have a less-striking colorectal cancer phenotype than other LS pts and are more likely to be cancer-free or have non-PMS2 associated cancers. This descriptive study compared the phenotypes of PMS2 carriers to other LS pts.

METHODS:Pts undergoing germline genetic testing at a commercial laboratory were queried for those with a single PGV in MLH1, MSH2, EPCAM, MSH6, or PMS2. Demographics and cancer and family history data were clinician-reported. PMS2 carriers were compared to MSH6 and MLH1/MSH2/EPCAM, with descriptive statistics, unpaired two-samples t tests, and Chi-square tests.

RESULTS:The PMS2 cohort was older at testing (mean 55.1±16.0y) than MLH1/MSH2/EPCAM (48.7±15.7y) but had less family history of cancer (84.9%) and colorectal cancer gene panels ordered (4.6%) than MSH6 (86.8%, 5.6%, respectively) and MLH1/MSH2/EPCAM (86.6%, 10.6%). The PMS2 cohort had lower rates of any, colorectal, gastric, uterine, and multiple cancers than MSH6 (any, colorectal, uterine, multiple) and

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MLH1/MSH2/EPCAM (any, colorectal, gastric, uterine, multiple). There was more breast, prostate, and pancreatic cancer among the PMS2 cohort than the MSH6 (breast only) and MLH1/MSH2/EPCAM (breast, prostate, pancreatic) carriers. Comparisons above met our $p<0.05$ significance criteria (Table).

CONCLUSIONS:Pts with PMS2 PGVs were older at the time of testing and had lower rates of any and LS-related cancers than other LS-carriers. There were more observations of breast, prostate, and pancreatic cancer in the PMS2 cohort; however, this study did not evaluate if these rates are comparable to pts with PGVs in non-LS genes. These data can aid in counseling and management of PMS2 carriers.

Keywords: hereditary colorectal cancer, Lynch syndrome, mismatch repair syndrome, PMS2

Table CGA 2023 Heald

Table. Personal history of cancer

Cancer history (n, % of total N)	***PMS2* cohort (N=5,189)**	***MSH6* cohort (N=5,182)**	***P* Value (*PMS2* and *MSH6*)**	***MLH1/MSH2/ EPCAM* cohort (N=7,340)**	***P* Value (*PMS2* and *MLH1/MSH2/ EPCAM*)**
None/ Unknown	2,200 (42.4%)	1,891 (36.5%)	**8.6×10^{-10}**	2,425 (33.0%)	**$<2.2 \times 10^{-16}$**
Colorectal	1,141 (22.0%)	1,571 (30.3%)	**$<2.2 \times 10^{-16}$**	3,436 (46.8%)	**$<2.2 \times 10^{-16}$**
Breast	1,039 (20.0%)	761 (14.7%)	**8.6×10^{-13}**	576 (7.8%)	**$<2.2 \times 10^{-16}$**
Uterine	464 (8.9%)	1,062 (20.5%)	**$<2.2 \times 10^{-16}$**	917 (12.5%)	**4.9×10^{-10}**
Ovarian	187 (3.6%)	213 (4.1%)	0.198	252 (3.4%)	0.644
Gastric	47 (0.9%)	45 (0.9%)	0.922	139 (1.9%)	**9.4×10^{-6}**
Pancreatic	117 (2.2%)	106 (2.0%)	0.505	112 (1.5%)	**0.003**
Prostate	182 (3.5%)	170 (3.3%)	0.559	197 (2.7%)	**0.009**
Polyps	243 (4.7%)	375 (7.2%)	**5.0×10^{-8}**	548 (7.5%)	**3.6×10^{-10}**
Multiple	650 (12.5%)	1,114 (21.5%)	**$<2.2 \times 10^{-16}$**	1,329 (18.1%)	**$<2.2 \times 10^{-16}$**
Other	204 (3.9%)	186 (3.6%)	0.388	263 (3.6%)	0.334

POSTER ABSTRACTS

P-066

General Research » Other

YIELD OF INTEGRATED DNA AND RNA ANALYSIS OF HEREDITARY CANCER ASSOCIATED GENES BASED ON GASTROINTESTINAL CANCER/POLYP DIAGNOSIS

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BACKGROUND:Prior data from our company showed that RNA sequencing impacted variant interpretation (VI) for 6.3% of 20,317 patients undergoing multi-cancer gene panel testing. The intronic variant discovery rate was 0.2%. Here we report the resolution of potential splicing variants (PSVs) and the discovery of intronic variants using RNA sequencing stratified by patients' reported cancer history.

METHODS:RNA sequencing was performed on up to 63 genes from a 47- or 84-gene multi-cancer panel. RNA data were used as functional evidence to aid in reclassification of PSVs to benign/likely benign (B/LB) or pathogenic/likely pathogenic (P/LP). Aberrant splicing was also used to discover variants outside of the reportable DNA range (all coding exons ±20bp of flanking intronic sequence). Cancer history was determined by clinician-reported data on the test requisition form. Data were stratified by: no cancer reported, any type of cancer, colon polyps, or any gastrointestinal (GI), colorectal, or pancreatic cancer. Descriptive statistics and Chi-square with Yates' correction were utilized; significance was set at $p<0.05$.

RESULTS:The cohort consisted of 61,388 patients. Any type of cancer was reported in 18,103 (29.5%), including 5,259 (8.6%) with any GI, 2,393 (3.9%) with colorectal, and 1,054 (1.7%) with pancreatic cancer and 1,947 (3.2%) polyps. There were no differences in impact of RNA sequencing for VI (2.2-2.5% of patients), or discovery (0.1-0.3% of patients) based on phenotype (Table).

CONCLUSIONS:In this study, the impact of RNA sequencing on VI was 2.4%, with the majority of variants of uncertain significance being downgraded to B/LB. The effect of RNA sequencing did not differ based on the patient's reported cancer/polyp history.

Keywords: hereditary gastrointestinal cancer, multigene panel testing, RNA sequencing

Table. Heald et al RNA abstract

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Table. Impact of RNA sequencing on potential splicing variants stratified by reported cancer and polyp history.

Phenotype	% of pts RNA impacted PSV interpretation	% of pts RNA downgraded PSV to B/LB variant	% of pts RNA upgraded PSV to P/LP variant	% of pts with variant* discovered outside of DNA reportable range†
None	2.3	2.0	0.3	0.1
Any	2.3	2.0	0.3	0.2
Any GI cancer	2.2	1.9	0.3	0.1
Colorectal cancer	2.5	2.2	0.3	0.1
Pancreatic cancer	2.4	1.9	0.5	0.3
Colon polyps	2.3	2.0	0.3	0.2

Abbreviations: B/LB, benign or likely benign; GI, gastrointestinal; P/LP, pathogenic or likely pathogenic; PSV, potential splicing variant; pts, patients
*includes benign or likely benign, uncertain, and pathogenic or likely pathogenic variants; †all coding exons ±20bp of flanking intronic sequence

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P-068

General Research » Lynch Syndrome

SURVEILLANCE OF FRAMESHIFT NEOANTIGEN-SPECIFIC T CELLS DURING COLORECTAL TUMOR DEVELOPMENT IN PATIENTS WITH LYNCH SYNDROME

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BACKGROUND:T cell surveillance throughout mismatch repair deficient (MMRd) colon cancer development in Lynch syndrome (LS) is evidenced by i) increased mutation load in MMRd non-neoplastic tissue in LS carriers and ii) a significant correlation between increased T cell infiltration in normal epithelium of LS patients and delayed onset of colorectal cancer. Our group and others previously demonstrated that unrepaired insertion/deletion (indel) mutations in microsatellites caused by loss of MMR protein expression generate

frameshift (fs)-neoantigen peptides that are highly conserved among high microsatellite instability (MSI-H) colon, endometrial, and gastric cancers.

METHODS:We aimed to i) measure fs-neoantigen expression in normal, premalignant, and tumor tissue from patients with LS-associated and sporadic MMRd colon cancer and ii) assess the frequency of fs-specific T cells circulating in peripheral blood and infiltrating MMRd colon lesions. Peripheral blood was collected at the time of colonoscopy to isolate peripheral blood mononuclear cells (PBMCs). Bulk RNA and whole-exome sequencing were performed on normal, adenoma, and carcinoma. Leveraging an in vitro neoantigen-specific T cell expansion and stimulation assay developed by our team for patient PBMCs and tumor infiltrating lymphocytes (TILs), immunogenicity of nine shared fs-peptides in patient peripheral blood was assessed.

RESULTS:We detected fs-neoantigen expression in LS patients throughout MMRd carcinogenesis (normal, adenoma and MMRd carcinoma). In vitro neoantigen-specific T cell expansion and stimulation assays of LS patients with and without adenomas on colonoscopy revealed detectable fs-specific T cells in circulation. We also demonstrated that fs-specific T cells are present in the primary tumor, draining lymph nodes, and metastases of LS patients with colorectal cancer by TCR sequencing.

CONCLUSIONS:We believe this effort will inform target selection for fs-neoantigen-based vaccination to prevent LS-associated tumor development. However, breakthrough tumor growth in the presence of these fs-specific T cell clones suggests suboptimal T cell surveillance in some patients.

Keywords: Lynch syndrome, neoantigens, vaccine, mismatch repair deficient

Figure 1

POSTER ABSTRACTS

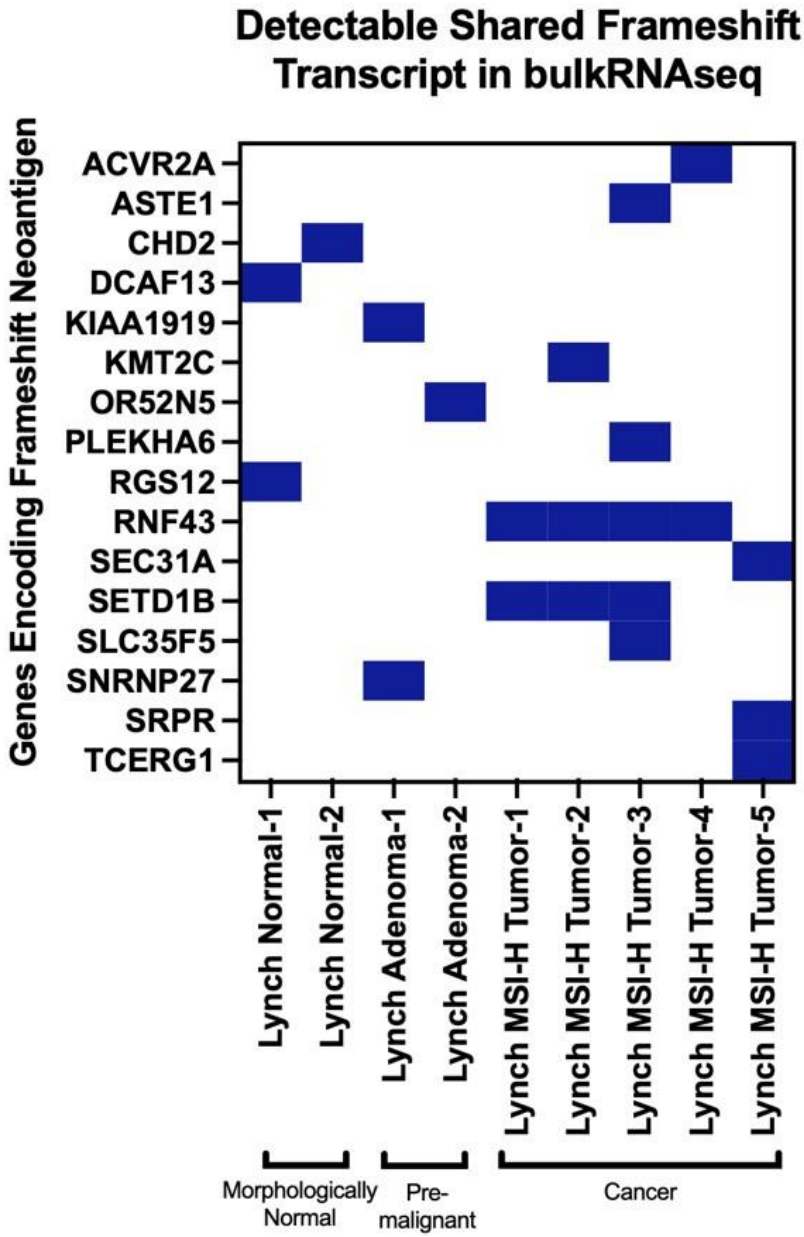

Figure 1. Assessment of fs-neoantigen expression at different stages of tumor development for MMRd CRC using bulk RNA sequencing (Illumina Stranded Total RNA Library) from normal, precancerous (adenoma), and colon tumor tissue from Lynch syndrome patients. Analysis targeted immunogenic indel mutations in genes frequently mutated in microsatellite unstable (MSI-H) tumors shown previously by our group (PMID: 33259803)

P-069

POSTER ABSTRACTS

General Research » Lynch Syndrome

APPLICATION OF DEEP MUTATIONAL SCANNING DATA FOR MLH1 VARIANT INTERPRETATION

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BACKGROUND:Pathogenic germline variants in the DNA mismatch repair (MMR) pathway cause Lynch Syndrome (LS), a hereditary cancer predisposition syndrome affecting more than 1 in every 300 individuals worldwide. Effectiveness of LS genetic counseling is limited by the prevalence of variants of uncertain significance (VUS), which comprise the majority of missense variants identified by clinical genetic testing. METHODS:We have established deep mutational scanning (DMS) as a scalable means for functional testing to support accurate variant interpretation in LS (Jia et al, AJHG, 2021; Scott et al, Genome Biol, 2022), which we now apply to MLH1. We overlaid the results of an MLH1 DMS on clinical databases comprising >15,000 individuals with MMR gene variants from a clinical genetic testing laboratory. To determine their applicability to patients, we first applied these results to MLH1 germline missense variants previously classified as Pathogenic (N= 23) or Benign (N= 27). Additionally, this cohort also included 590 VUS missense variants in MLH1.

RESULTS:All previously classified variants which exhibited normal function in this screen had a benign classification, excluding one variant (c.1517T>C; p.V506A) for which the measured effect was intermediate. Conversely, most variants with abnormal function in our DMS data were previously classified as pathogenic or likely pathogenic, such that this function map provides strong evidence under the OddsPath framework (ClinGen Sequence Variant Interpretation Working Group, Tavtigian et al, Genet Med 2018). Moreover, a majority (78%) of VUS scored in the normal range, consistent with incidentally discovered, benign rare variants unrelated to individual cancer history. By contrast, 12.4% of the clinical missense VUSs exhibited loss of function at the protein level and 5% were predicted to disrupt splicing: reclassification using the functional evidence for these 80 VUSs is ongoing.

CONCLUSIONS:Saturation-scale functional testing via DMS can provide badly needed functional evidence to improve the actionability of genetic testing.

Keywords: Bioinformatics, cancer genetics, variant classification

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P-070

General Research » Lynch Syndrome

POSTER ABSTRACTS

GENETIC REFERRAL PATTERN BY GASTROENTEROLOGY PROVIDERS FOR NEWLY DIAGNOSED COLORECTAL CANCER

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BACKGROUND:Only 6% of patients with newly diagnosed colorectal cancer (CRC) received germline genetic testing to evaluate for CRC susceptible syndromes, with oncologists or colorectal surgeons traditionally ordering genetic testing. We sought to evaluate gastroenterologists' practice patterns for newly diagnosed CRC after endoscopy.

METHODS:Retrospective cohort of consecutive adults with a newly diagnosed CRC by GI between 1/2020-6/2020 at a single academic medical center. Interval time to referral/encounter to subspecialty care, ordered/completed evaluation, and therapy was calculated from baseline, defined as date of CRC diagnosis to date of event.

RESULTS:Among 92 patients with CRC, 56% were non-Hispanic white, 51% were male, with median age of 61 years. Only 35% of these patients were referred to genetic testing. The referral group were younger (median age 50 vs 70 years, p<0.001) and had CRC family history (44% vs 20%, p=0.02) with >2 relatives (43% vs 0%, p=0.01). Compared to the non-referral group, referred patients had shorter interval between diagnosis and referral/encounter with colorectal surgery and oncology (Figure). Among 45% of patients that met National Comprehensive Cancer Network (NCCN) 2020 family history criteria for Lynch syndrome (n=41), only two-thirds were referred for genetic testing, with the majority referred by oncology (78%) followed by GI (11%) and colorectal surgery (7%). 39% had metastatic CRC and only 31% of these were referred for genetic testing. Of the 32 patients who underwent genetic testing, one patient (4%) was diagnosed with Lynch syndrome.

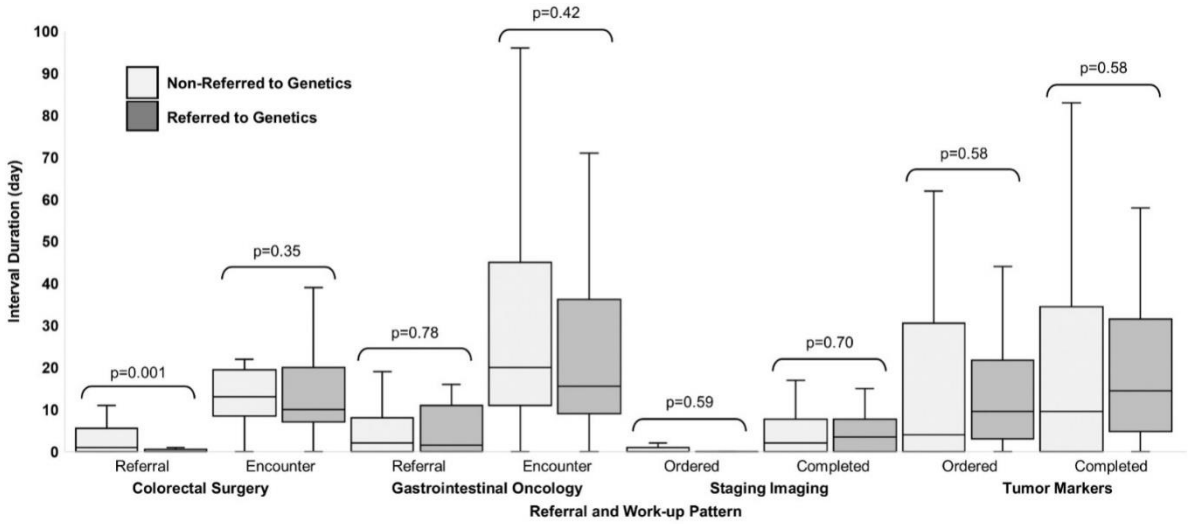
CONCLUSIONS:Two-thirds of CRC patients meeting NCCN 2020 family history criteria for Lynch syndrome were referred for genetic testing, with 11% referred by GI. Despite their role in CRC diagnosis, GI providers rarely initiate the genetic counseling/testing process. Updated NCCN guidelines recommend universal germline testing for CRC, highlighting the urgent need for increased awareness and practice pattern changes among GI providers to improve guideline adherence and outcomes.

Keywords: Lynch Syndrome, Colorectal Cancer, Genetic Testing

Figure

POSTER ABSTRACTS

Figure. Interval duration (days) between colorectal cancer diagnosis and referral to subspecialties, imaging, and lab evaluation according to genetic referral status



P-071

General Research » Lynch Syndrome

IMMUNE EVASION IS MORE FREQUENT IN LYNCH SYNDROME COLORECTAL CANCERS DIAGNOSED AT FIRST COLONOSCOPY THAN IN THOSE DETECTED DURING REGULAR SURVEILLANCE

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BACKGROUND:Despite regular colonoscopy, Lynch syndrome (LS) carriers can develop colorectal cancer. Mechanisms contributing to colorectal cancer development under colonoscopy surveillance (incident cancers) are only partially understood. Previous studies demonstrated that incident cancers differ in their clinical parameters and mutational profile from cancers detected at first colonoscopy examination (prevalent cancers). However, it has been unclear whether incident and prevalent cancers can be distinguished on the basis of their immunological characteristics and whether the development of immune evasion mechanisms could play a role in incident cancer formation.

METHODS:We analyzed incident and prevalent LS colorectal cancers for the presence of *Beta-2-microglobulin* (*B2M*) mutations/B2M expression loss, the most common molecular pathway of immune evasion in LS colorectal cancer, leading to abrogation of HLA class I-mediated antigen expression. We characterized

the immune infiltration profile of incident and prevalent cancers by quantifying distinct T cell subtypes in incident and prevalent cancers from Lynch syndrome carriers.

RESULTS:Eighty-one incident and 57 prevalent colorectal cancers (total n=138) from LS carriers were analyzed in this study. A significantly lower proportion of *B2M*-mutant lesions was identified in incident compared to prevalent cancers (7/81 (8.6%) vs 13/57 (22.8%), p=0.0268). The analysis of T cell densities and correlation with *B2M* mutation status is currently ongoing and the data will be presented at the conference. Four patients in our cohort presented with a prevalent cancer and a subsequent incident cancer. The *B2M* mutations status was consistent between the prevalent and incident cancer pairs in all 4 patients.

CONCLUSIONS:Our study reveals distinct contribution of immune evasion mechanisms to incident and prevalent cancer development. The results suggest intact antigen presentation during the formation of incident cancers, underlining the clinical potential of immune-stimulatory interventions, such as vaccines, to enhance immune recognition and potentially lead to elimination of incident lesions.

Keywords: Lynch syndrome, incident colorectal cancer, surveillance, antigen presentation, immune evasion

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P-072

General Research » Lynch Syndrome

HOW DO PATIENTS WITH HEREDITARY CANCER SYNDROMES NAVIGATE THE HEALTHCARE SYSTEM? A QUALITATIVE COMPARATIVE STUDY ACROSS CANADA

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[9]Patient Partner

BACKGROUND:Hereditary cancer syndromes (HCS) account for 5-10% of all cancers. HCSs such as hereditary breast and ovarian cancer syndrome (HBOC) or Lynch syndrome (LS) can increase one's lifetime risk of cancer and patients may require lifelong follow-up care with a wide range of specialists. However, after

receiving an HCS diagnosis, patients are often left to navigate a complex system of care with variable screening and surveillance programs across provinces. This study aims to understand the care experiences and needs of HCS patients across Canada to inform clinical practice.

METHODS:HCS patients who received a positive genetic test result for HBOC or LS were purposely sampled from clinics in Ontario (ON), Newfoundland and Labrador (NL), and British Columbia (BC), reflecting variation across genetic services and screening programs. Interpretive description was used to analyze the data. RESULTS:Qualitative interviews were conducted with 73 patients (51 females, 21 males, 1 gender-diverse; age range 25-80 yrs) diagnosed with HBOC (n= 39) or LS (n= 34). Several key themes emerged including navigation, advocacy, and access. Patients expressed difficulties in navigating recommended follow-up care and often mentioned a lack of knowledge from their healthcare professionals. Several patients highlighted the need for adequate communication about screening practices following risk-reducing surgeries. Patients often had to self-advocate for referrals and screening appointments. Access to genetic services, specialists and eligibility for screening programs were described as sometimes limited for HCS patients, especially for those with no previous cancer diagnosis.

CONCLUSIONS:This is the first study to compare HCS patients' experiences with care across Canada. HCS patients face numerous healthcare challenges including receiving adequate guidance from healthcare professionals, informational supports, and access to screening. Identifying the needs and challenges for patients with HCS can optimize care experiences and ultimately improve patient outcomes.

Keywords: hereditary cancer syndromes, qualitative, health systems, Lynch, access, health policy

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P-073

General Research » Lynch Syndrome

IMPORTANCE OF ACCURATE *EPCAM* DELETION CHARACTERIZATION TO PREVENT MISDIAGNOSIS OF LYNCH SYNDROME

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BACKGROUND:Gross deletions involving the 3' end of *EPCAM* cause Lynch syndrome (LS). Prior to the introduction of NGS, *EPCAM* deletion screening was typically performed by one MLPA kit throughout the country, in which the 5'-most probe resides in exon 3. Therefore, it can be unclear whether some deletions

encompass the full gene. However, full *EPCAM* deletions may not be disease-causing so accurate differentiation of deletion size has significant clinical implications.

METHODS:We reviewed cases with a gross deletion of *EPCAM* identified at a single laboratory from 2011-2021 to determine how many had a known or possible full *EPCAM* deletion detected via MLPA or microarray. Amsterdam criteria II (AC) and revised Bethesda criteria (BC) were assessed in families with full and partial deletions. Data presented herein are exempt from IRB review.

RESULTS:A total of 349 cases were identified that included an *EPCAM* deletion, 246 of which also included *MSH2*. Isolated *EPCAM* deletions were identified in 103 individuals from 65 unique families. In most families (72.3%; 47/65), MLPA indicated a partial *EPCAM* deletion based on retention of the exon 3 probe. In 9 additional families (13.9% of 65), 5'UTR coverage from a microarray was available and identified a full *EPCAM* deletion. Deletion size could not be determined in 9 remaining families (13.9%). Therefore, a quarter (27.7%) of families with *EPCAM* deletions identified at our laboratory have a known or possible full gene deletion. No families with a known full gene deletion met AC and 1 met BC while 44.7% (n=21) and 89.3% (n=42) of those with a partial deletion met AC or BC, respectively.

CONCLUSIONS:This study identifies a need for re-evaluation of a subset of individuals with *EPCAM* deletions and supports findings that full *EPCAM* deletions are not pathogenic. Accurate characterization of *EPCAM* deletions is critical to prevent misdiagnosis of LS.

Keywords: Lynch syndrome, MLPA, EPCAM, Diagnostic testing, Misdiagnosis, Colorectal cancer

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P-074

General Research » Lynch Syndrome

OUTCOMES OF TUMOR-BASED UNIVERSAL SCREENING FOR LYNCH SYNDROME IN PATIENTS WITH COLORECTAL CANCER IN A LARGE, DIVERSE, COMMUNITY-BASED U.S. POPULATION

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BACKGROUND:Although current professional guidelines recommend screening all colorectal cancers (CRCs) for Lynch syndrome (LS) using tumor-based immunohistochemistry (IHC) or microsatellite instability testing, real-world data on the outcomes of universal screening remain limited. We investigated the outcomes of a universal screening program for LS using reflex tumor MMR IHC in a large, diverse, community-based U.S. population.

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METHODS:All members of Kaiser Permanente Northern California (KPNC) diagnosed with CRC between 2011-2020 were included. Data of MMR IHC, BRAF V600E mutation, MLH1 promoter methylation, and germline analysis were collected from the KPNC's electronic database. We measured the screening rate among CRC patients and the outcomes of LS screening over 10 years.

RESULTS:Among 11,996 patients diagnosed with CRC between 2011-2020, 8,744 were screened for Lynch syndrome using MMR IHC of CRC tumors. The percentages of CRCs with normal MMR IHC, MLH1/PMS2 deficiency, MSH2/MSH6 deficiency, MLH1 deficiency only, MSH2 deficiency only, MSH6 deficiency only, and PMS2 deficiency only were 84.3%, 11.1%, 0.8%, 0.1%, 0.3%, 0.4%, and 0.9%, respectively. The percentage of CRC tumors screened increased from 22.2% in 2011 to 92.0% in 2020 for all CRCs and from 23.0% in 2011 to 93.3% in 2020 for invasive CRCs. The rate of germline testing increased from 2.4% in 2011 to 20.9% in 2020 for all CRCs. One-hundred and eighty-eight patients (2.2%) were diagnosed with Lynch syndrome by germline analysis. Seventy-nine (0.9%), 1062 (12.1%) and 701 (8.0%) were diagnosed with variant of uncertain significance, Lynch-like syndrome, and sporadic CRC with MLH1 deficiency, respectively.

CONCLUSIONS:In a large, diverse, community-based U.S. population, implementation of tumor-based universal screening for LS using MMR IHC resulted in a substantial increase in the screening rate of over 10 years. Further studies are needed to assess factors that affected the uptake of MMR IHC and germline testing among eligible patients.

Keywords: Lynch syndrome, colorectal cancer, screening, mismatch repair

Figure 1

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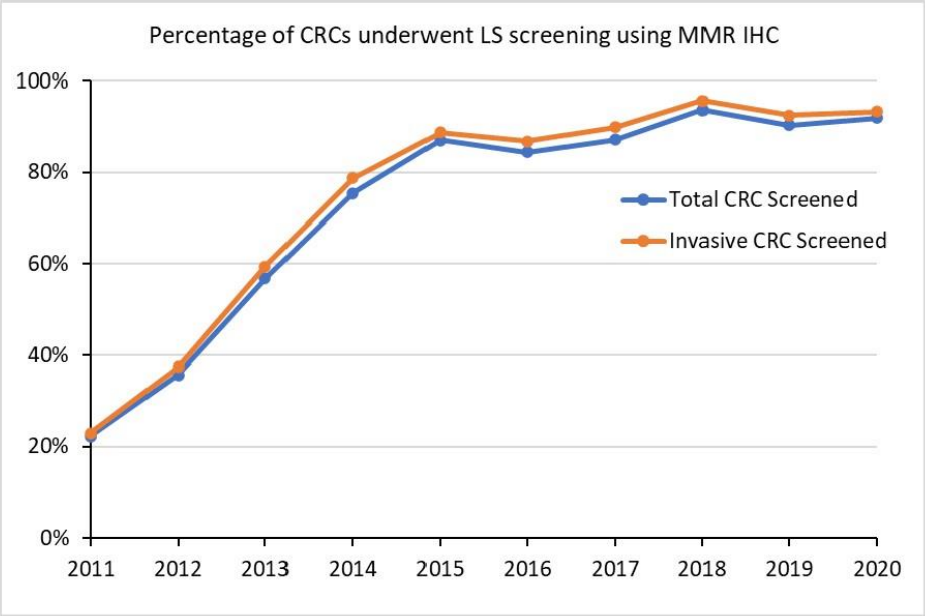
Figure 1. Percentages of CRC tumors screened for LS using MMR IHC at KPNC in 2011-2020



Abbreviations: CRC, colorectal cancer; MMR, mismatch repair; IHC, immunohistochemistry; KPNC, Kaiser Permanente Northern California

Percentages of CRC tumors screened for LS using MMR IHC at KPNC in 2011-2020

Table 1

POSTER ABSTRACTS

Table 1. Characteristics of CRC patients who underwent LS screening using reflex tumor MMR IHC at KPNC in 2011-2020

Characteristic	Normal MMR IHC N (Row %)	MLH1 and PMS2 deficient N (Row %)	MSH2 and MSH6 deficient N (Row %)	MLH1 deficient only N (Row %)	MSH2 deficient only N (Row %)	MSH6 deficient only N (Row %)	PMS2 deficient only N (Row %)	Atypical N (Row %)	Other N (Row %)	Total Screened N (Col %)
Median age at CRC diagnosis (IQR), years	63.4 (53.1 - 2.7)	74.9 (66.3 - 83.2)	60.2 (50.5 - 69.6)	67.8 (56.2 - 70.8)	58.9 (48.5 - 68.7)	61.2 (52.0 - 69.7)	62.8 (50.9 - 74.1)	74.4 (64.5 - 83.6)	67.9 (59.6 - 77.1)	64.7 (54.0 - 74.5)
Age at CRC diagnosis, years										
<= 50	1438 (91.2)	59 (3.7)	21 (1.3)	0 (0.0)	8 (0.5)	7 (0.4)	19 (1.2)	5 (0.3)	20 (1.3)	1577 (18.0)
51-60	1774 (91.5)	87 (4.5)	20 (1.0)	2 (0.1)	5 (0.3)	10 (0.5)	15 (0.8)	0 (0.0)	26 (1.3)	1939 (22.2)
61-70	2031 (86.4)	208 (8.8)	19 (0.8)	2 (0.1)	4 (0.2)	13 (0.6)	19 (0.8)	5 (0.2)	50 (2.1)	2351 (26.9)
71-80	1309 (77.4)	297 (17.6)	10 (0.6)	1 (0.1)	5 (0.3)	3 (0.2)	11 (0.7)	7 (0.4)	48 (2.8)	1691 (19.3)
> 80	816 (68.8)	319 (26.9)	4 (0.3)	0 (0.0)	0 (0.0)	3 (0.3)	11 (0.9)	7 (0.6)	26 (2.2)	1186 (13.6)
Sex										
Female	3373 (80.0)	650 (15.4)	31 (0.7)	3 (0.1)	14 (0.3)	17 (0.4)	39 (0.9)	15 (0.4)	76 (1.8)	4218 (48.2)
Male	3995 (88.3)	319 (7.0)	43 (1.0)	2 (0.0)	8 (0.2)	19 (0.4)	36 (0.8)	9 (0.2)	94 (2.1)	4525 (51.7)
Race and Ethnicity										
Asian	1270 (89.4)	88 (6.2)	13 (0.9)	2 (0.1)	4 (0.3)	9 (0.6)	9 (0.6)	6 (0.4)	19 (1.3)	1420 (16.2)
Black	547 (86.4)	54 (8.5)	3 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	3 (0.5)	4 (0.6)	20 (3.2)	633 (7.2)
Hispanic	1205 (87.7)	111 (8.1)	15 (1.1)	1 (0.1)	3 (0.2)	3 (0.2)	15 (1.1)	0 (0.0)	21 (1.5)	1374 (15.7)
Non-Hispanic White	4313 (81.7)	714 (13.5)	43 (0.8)	2 (0.0)	13 (0.2)	24 (0.5)	48 (0.9)	14 (0.3)	109 (2.1)	5280 (60.4)
Other	33 (89.2)	3 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	37 (0.4)
CRC tumor stage										
Localized	2787 (81.3)	458 (13.4)	32 (0.9)	2 (0.1)	9 (0.3)	13 (0.4)	31 (0.9)	11 (0.3)	84 (2.5)	3427 (39.2)
Regional	3453 (84.3)	464 (11.3)	36 (0.9)	3 (0.1)	9 (0.2)	19 (0.5)	39 (1.0)	12 (0.3)	62 (1.5)	4097 (46.9)
Distant	1023 (93.9)	33 (3.0)	3 (0.3)	0 (0.0)	2 (0.2)	2 (0.2)	5 (0.5)	1 (0.1)	21 (1.9)	1090 (12.5)
Unknown	37 (78.7)	6 (12.8)	1 (2.1)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	47 (0.5)
CRC tumor location										
Proximal to rectum	4965 (79.5)	946 (15.1)	61 (1.0)	5 (0.1)	18 (0.3)	28 (0.4)	68 (1.1)	22 (0.4)	134 (2.1)	6247 (71.4)
Rectum	2403 (96.2)	24 (1.0)	13 (0.5)	0 (0.0)	4 (0.2)	8 (0.3)	7 (0.3)	2 (0.1)	36 (1.4)	2497 (28.6)
Total	7368 (84.3)	970 (11.1)	74 (0.8)	5 (0.1)	22 (0.3)	36 (0.4)	75 (0.9)	24 (0.3)	170 (1.9)	8744 (100)

Abbreviations: CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; IHC, immunohistochemistry; KPNC, Kaiser Permanente Northern California; IQR, interquartile range

Characteristics of CRC patients who underwent LS screening using reflex tumor MMR IHC at KPNC in 2011-2020

Table 2

Table 2. Main outcomes of universal screening of CRC for LS using MMR IHC at KPNC in 2011-2020

Characteristics	Lynch Syndrome, N (Row %)	Variant of uncertain significance, N (Row %)	Lynch-like, N (Row %)	MLH1 deficient sporadic CRC, N (Row %)	Total Screened N (Col %)
Median age at CRC diagnosis (IQR), years	56.3 (46.8 - 64.7)	50.3 (44.4 - 58.5)	50.4 (43.9 - 56.9)	76.5 (68.4 - 83.6)	64.7 (54.0 - 74.5)
Age at CRC Diagnosis, years					
≤ 50	67 (4.2)	43 (2.7)	588 (37.3)	24 (1.5)	1577 (18.0)
51-60	50 (2.6)	18 (0.9)	253 (13.0)	45 (2.3)	1939 (22.2)
61-70	50 (2.1)	7 (0.3)	120 (5.1)	152 (6.5)	2351 (26.9)
71-80	17 (1.0)	10 (0.6)	79 (4.7)	231 (13.7)	1691 (19.3)
> 80	4 (0.3)	1 (0.1)	22 (1.9)	249 (21.0)	1186 (13.6)
Sex					
Female	88 (2.1)	39 (0.9)	557 (13.2)	500 (11.9)	4218 (48.2)
Male	100 (2.2)	40 (0.9)	505 (11.2)	200 (4.4)	4525 (51.7)
Race and Ethnicity					
Asian	37 (2.6)	26 (1.8)	186 (13.1)	51 (3.6)	1420 (16.2)
Black	10 (1.6)	7 (1.1)	59 (9.3)	38 (6.0)	633 (7.2)
Hispanic	37 (2.7)	17 (1.2)	225 (16.4)	79 (5.7)	1374 (15.7)
Non-Hispanic White	104 (2.0)	28 (0.5)	588 (11.1)	530 (10.0)	5280 (60.4)
Other	0 (0)	1 (2.7)	4 (10.8)	3 (8.1)	37 (0.4)
CRC tumor stage					
Localized	87 (2.5)	21 (0.6)	305 (8.9)	333 (9.7)	3427 (39.2)
Regional	79 (1.9)	45 (1.1)	553 (13.5)	335 (8.2)	4097 (46.9)
Distant	15 (1.4)	12 (1.1)	182 (16.7)	24 (2.2)	1090 (12.5)
Unknown	1 (2.1)	0 (0)	2 (4.3)	4 (8.5)	47 (0.5)
CRC tumor location					
Proximal to rectum	171 (2.7)	59 (0.9)	690 (11.0)	691 (11.1)	6247 (71.4)
Rectum	17 (0.7)	20 (0.8)	372 (14.9)	10 (0.4)	2497 (28.6)
Total	188 (2.2)	79 (0.9)	1062 (12.1)	701 (8.0)	8744 (100.0)

Abbreviations: CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; IHC, immunohistochemistry; KPNC, Kaiser Permanente Northern California; IQR, interquartile range

Main outcomes of universal screening of CRC for LS using MMR IHC at KPNC in 2011-2020

POSTER ABSTRACTS

P-075

General Research » Lynch Syndrome

IMPACT OF COVID-19 ON UNIVERSAL TUMOR SCREENING, REFERRAL RATES, AND ATTENDANCE TO CANCER GENETIC COUNSELING AT A SAFETY NET-UNIVERSITY HOSPITAL

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BACKGROUND:Currently, many healthcare systems rely on: (1) universal tumor screening (UTS) of every newly diagnosed colorectal cancer (CRC) with immunohistochemistry (IHC) for Lynch Syndrome genes and/or microsatellite instability (MSI) testing and (2) family/personal history to identify individuals at risk for hereditary CRC suitable for cancer genetic counseling (CGC). Despite its relative low cost, uptake with UTS remains a challenge. Given the impact of COVID-19 on healthcare access and delivery, we explored its effect on several steps of the UTS process in a safety net-University Hospital to identify areas of vulnerability and opportunities for improvement.

METHODS:Using billing records, patients undergoing primary CRC resection were identified and three subgroups created based on surgery date relative to the pandemic (pre-, during- and post-). Two independent reviewers extracted medical record data regarding: performance of UTS; referrals to CGC based on mismatch repair deficiency (dMMR) (absent IHC/MSI-High) and/or age<50 years at diagnosis; attendance to CGC and reasons for not attending CGC.

RESULTS:Between 2018-2022, 361 patients (mean age=61.3 years) underwent resection of a primary CRC. During the pre-, during- and post- COVID-19 time-period, 91%, 92% and 97% of cases were screened with at least MMR IHC, respectively. (Tables 1&2) Of the patients eligible for referral to CGC in each time-period, 62%, 79% and 67% had a referral submitted, but 35%, 37% and 33% did not attend CGC, with the most common reason noted being inability to reach the patient for scheduling.

CONCLUSIONS:Although the COVID-19 pandemic did not significantly impact certain components of an established UTS process (UTS testing and CGC referral/attendance rates) at a safety net-University Hospital, the average referral and attendance rates to CGC were less than optimal throughout. Therefore, further research on barriers preventing physicians from referring and patients from attending CGC should be intensified.

Keywords: Universal Tumor Screening, UTS, Genetic Counseling, Referral, Colorectal Cancer, COVID-19

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Table 1

	Pre-COVID-19 (2018/2019) (n=157)	During-COVID-19 (2020/2021) (n=149)	Post-COVID-19 (2022) (n=55)
MMR IHC & MSI	71% (n=111/157)	66% (n=98/149)	71% (n=39/55)
MMR IHC no MSI b/c ITS	15% (n=23/157)	7% (n=10/149)	4% (n=2/55)
MMR IHC no MSI	5% (n=8/157)	19% (n=28/149)	22% (n=12/55)
Neither MMR IHC nor MSI	9% (n=15/157)	8% (n=13/149)	3% (n=2/55)
[1]Eligible for CGC referral	24% (n=37/157)	23% (n=34/149)	16% (n=9/55)
Referred to CGC	62% (n=23/37)	79% (n=27/34)	67% (n=6/9)
Attended CGC	65% (n=15/23)	63% (n=17/27)	67% (n=4/6)
Did not attend CGC	35% (n=8/23) • 50% (n=4/8) could not be reached. • 38% (n=3/8) were tested outside. • 12% (n=1/8) referral expired.	37% (n=10/27) • 50% (n=5/10) could not be reached. • 40% (n=4/10) unwilling • 10% (n=1/10) no results in the chart	33% (n=2/6) • 50% (n=1/2) could not be reached. • 50% (n=1/2) were tested outside

Table 1: Trends of Universal Tumor Screening, Referral Rates and Attendance to Cancer Genetic Counseling appointments pre-, during- and post-COVID-19. MMR: Mismatch Repair; IHC: immunohistochemistry; MSI: Microsatellite Instability; ITS: Insufficient tumor slide; CGC: Cancer Genetic Counseling

[1]Eligibility for referral to CGC based on: (1) mismatch repair deficiency (dMMR) (i.e., absent IHC/MSI-High) and (2) age<50 years at the time of diagnosis.

Table 2

	Pre-COVID-19 (2018/2019) (n=157)	During-COVID-19 (2020/2021) (n=149)	Post-COVID-19 (2022) (n=55)
No MMR IHC	9% (n=15/157)	8% (n=13/149)	3% (n=2/55)
pMMR IHC	86% (n=134/157)	77% (n=114/149)	84% (n=46/55)
dMMR IHC	5% (n=8/157) - 25% (n=2/8) MSH2 - 13% (n=1/8) MSH2&MSH6 - 62% (n=5/8) MLH1&PMS2 • 60% (n=3/5) MLH1 promoter hypermethylation positive. • 40% (n=2/5) MLH1 promoter hypermethylation negative.	15% (n=22/149) - 5% (n=1/22) MSH6 - 45% (n=10/22) MLH1&PMS2 • 40% (n=4/10) MLH1 promoter hypermethylation positive. • 30% (n=3/10) MLH1 promoter hypermethylation negative. • 30% (n=3/10) MLH1 promoter hypermethylation not tested. -18% (n=4/22) MLH1(weak)&PMS2 • 75% (n=3/4) MLH1 promoter hypermethylation positive • 25% (n=1/4) MLH1 promoter hypermethylation not tested. - 18% (n=4/22) MSH2&MSH6 - 9% (n=2/22) PMS2 - 5% (n=1/22) MSH2	13% (n=7/55) - 61% (n=5/7) MLH1&PMS2 • 5/5 MLH1 promoter hypermethylation positive. - 29% (n=2/7) MSH6
Suspicious	- 63% (n=5/8)	- 86% (n=19/22)	- 29% (n=2/7)
Sporadic	- 37% (n=3/8)	- 14% (n=3/22)	- 61% (n=5/7)

Table 2: MMR IHC status of primary Colorectal Cancers resected pre-, during- and post-COVID-19. IHC: Immunohistochemistry; pMMR: Mismatch repair proficient; dMMR: Mismatch repair deficient.

POSTER ABSTRACTS

General Research » Lynch Syndrome

A SINGLE CENTER EXPERIENCE WITH LYNCH SYNDROME COLORECTAL CANCER INTERCEPTION

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BACKGROUND:Reports from large multicenter studies show approximately a 0.8% rate of colorectal cancer (CRC) per year for Lynch syndrome (LS) patients having lower endoscopy. The endoscopies in these studies are heterogenous with standard and high-definition procedures performed by many different physicians using various techniques. We report a single center experience with a more standardized approach to LS lower endoscopy.

METHODS:We reviewed the records of LS patients having lower endoscopy. All patients had pathogenic or likely pathogenic variants (PV) in *MSH2*, *MSH6*, *MLH1*, *PMS2* or *EPCAM*. High-definition endoscopes were used for all procedures and >95% of procedures were completed by the same physician using the same chromoendoscopy technique.

RESULTS:Ninety-eight patients with Lynch syndrome had 402 lower endoscopies (382 colonoscopies and also 20 flexible sigmoidoscopies for patients status post subtotal colectomy). No patient was diagnosed with CRC and no patient had surgery for a large colon polyp. Total patient years under surveillance was 272. Median age of first colonoscopy was 51 years old with a median of three colonoscopies per patient. The median time from first colonoscopy to last colonoscopy was 34 months. Years of follow up by LS gene with a PV were *MSH2* 103 years, *MLH1* 85 years, *MSH6* 54 years, and *PMS2* 30 years. The adenoma detection rate was highest for *MSH2* LS (35%), followed by *PMS2* (26%), and *MLH1/MSH6* (both 25%). The mean colonoscopy procedure time was 38 minutes (25% percentile – 28 min, 75% percentile - 48 min). Ninety percent of procedures had excellent bowel preparation (Boston bowel prep score = 9).

CONCLUSIONS:CRC is not common in LS patients having high-resolution lower chromoendoscopy with good bowel preparation, and long procedure times by a single physician. For meaningful comparison to larger multicenter datasets, more years under surveillance are needed.

Keywords: Colonoscopy, Lynch syndrome, colorectal cancer, chromoendoscopy

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P-077

General Research » Lynch Syndrome

POSTER ABSTRACTS

HEALTHCARE UTILIZATION AMONG INDIVIDUALS DIAGNOSED WITH LYNCH SYNDROME THROUGH A UNIVERSAL GERMLINE GENETIC TESTING PROGRAM

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BACKGROUND:Most individuals with Lynch syndrome (LS) are unaware of their diagnosis. Criteria-based testing will not close this knowledge gap as it fails to identify ~50% of mutation carriers. Universal germline testing (GT) in oncology may identify more mutation carriers and advance cancer control. However, the clinical utility of universal germline testing is unknown.

METHODS:The enterprise-wide City of Hope INSPIRE study offers opt-in GT for cancer susceptibility (155 genes) and other actionable disorders (34 genes) to all patients at our institution. We used an informatics approach followed by medical record abstraction to evaluate healthcare utilization for patients found to have LS. We queried codified data elements in our electronic data warehouse before and after GT (post testing interval: 1-33 months). We binned care as possibly related to LS based on NCCN guidelines.

RESULTS:Among 16,883 consented patients, 13,946 (82.6%) had GT, and 108 (0.77%) had LS. Forty-eight (44%) were previously known to have LS. The LS patient demographic distribution was: white (n=73, 67%), Asian (n=17, 16%), other (n=18, 17%), Hispanic (n=29; 27%); female (n=73, 67%); the mean age was 55yrs. Eighty-seven percent (n=94) had cancer, including 61% (n = 57) with a LS-associated cancer (colorectal 32%, endometrial 15%, bladder/urinary tract 6%, prostate 6%, ovarian 5%, and esophageal/stomach 4%), and 39% (n = 37) had a cancer not associated with LS. Sixty percent of all LS patients had procedures and/or therapy possibly related to their LS diagnosis. Among new LS patients utilization of colonoscopy, EGD, MRCP, and TVUS increased after testing. Seventeen (18%) cancer patients with Lynch syndrome received immunotherapy.

CONCLUSIONS:We found high levels of relevant healthcare utilization for individuals diagnosed with LS in the context of universal GT. Codified EHR queries were not sufficient alone to fully capture care and assess the clinical utility of system-wide genetic care delivery interventions.

Keywords: Lynch syndrome, universal germline testing

P-078

POSTER ABSTRACTS

General Research » Lynch Syndrome

AN INVESTIGATION OF THE ASSOCIATION BETWEEN USE OF COMMONLY PRESCRIBED MEDICATIONS AND CANCER RISK AMONG INDIVIDUALS WITH LYNCH SYNDROME

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BACKGROUND:Lynch syndrome (LS) is one of the most common heritable conditions, with a prevalence of 1 in 279. Individuals with LS have an 80% lifetime risk of cancer and earlier cancer onset. The CAPP2 study recently demonstrated the utility of chemoprevention among individuals with LS, showing reduced long-term cancer incidence among those randomized to aspirin. Though promising, studies evaluating the potential of other commonly used medications in preventing or reducing cancer incidence in the LS population are limited. Therefore, we conducted a retrospective cohort study of individuals with LS, investigating the association between commonly prescribed medications and LS-associated cancer risk.

METHODS:In this study, we performed a retrospective chart review of individuals with Lynch syndrome, extracting medication use history (exposure) and cancer diagnoses (outcome). Participants were identified by ICD-10 and/or chart free text. The medications of interest are proton pump inhibitors (PPIs), statins, anti-diabetic drugs, and GLP1-R agonists. ‘Users’ had at least two prescriptions in the same drug category on different days and drug use must have occurred prior to cancer incidence or end of study. The outcomes of interest are LS-associated cancers (e.g., gastric, colorectal, gallbladder, pancreatic, etc). Additional covariates were extracted for use in multivariable logistic regression modeling.

RESULTS:Though this study is ongoing, we expect that use of PPIs, statins, and anti-diabetic drugs will demonstrate overall cancer preventive benefit for individuals with LS, consistent with our previous work in the general population. In addition, we expect that use of GLP1-R agonists will be associated with reduced risk of gastrointestinal cancers. Lastly, we expect that these relationships will be modified by LS mutation.

CONCLUSIONS:We anticipate that several commonly prescribed medications will demonstrate cancer preventive benefit for individuals with LS. The individual- and population-level burden of cancer in LS emphasizes the importance and significance of identifying scalable prevention mechanisms.

Keywords: Lynch syndrome, cancer prevention, chemoprevention, medication use

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P-079

General Research » Lynch Syndrome

UNIVERSAL TESTING OF ENDOMETRIAL CANCER: REACHING AN UNDER-SERVED POPULATION

POSTER ABSTRACTS

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BACKGROUND:Up to 12% of women with endometrial cancer (EC) will have Lynch syndrome (LS) or double somatic MMR pathogenic variants (dSMMR). Identifying these women is paramount to reducing future cancer burden for them and their family members. Tumor-based immunohistochemistry (IHC) by pathology provides the ability to detect EC that may be due to Lynch syndrome or dSMMR, however at-risk individuals are not always identified or referred for genetic counselling/testing. A pilot program was performed to offer comprehensive testing of all newly diagnosed EC in the province of Saskatchewan.

METHODS:All women in Saskatchewan with a newly diagnosed EC had mismatch repair (MMR) IHC analysis performed on their EC tumour. Tumours demonstrating deficient MMR (dMMR) for MLH1 underwent somatic MLH1 methylation analysis. dMMR tumours without MLH1 methylation and all tumours demonstrating MSH2, MSH6 or PMS2 deficiency underwent paired somatic/germline MMR testing. Methylated MLH1 tumors and proficient MMR (pMMR) tumors underwent a 30 gene hereditary germline panel.

RESULTS:47 patients were included. 23 tumors demonstrated dMMR IHC pattern, 10 of which included MLH1 deficiency. All MLH1 deficient tumors demonstrated MLH1 methylation. Of the remaining dMMR patients (n=13) 7 patients were found to have Lynch syndrome and 6 patients had dSMMR. 34 pMMR and MLH1 methylated patients underwent the germline panel. Of these 24 patients had negative results, 8 had variants of uncertain significance and 2 had pathogenic variants, one in MUTYH and one in ATM.

CONCLUSIONS:EC tumors demonstrating MSH2, MSH6 or PMS2 IHC deficiency benefit from first-line germline/somatic MMR testing.

Keywords: Lynch, Somatic, MMR

P-080

General Research » Lynch Syndrome

OPTIMIZING SURVEILLANCE STRATEGIES FOR GASTRIC CANCER IN LYNCH SYNDROME: A COST-EFFECTIVENESS ANALYSIS

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BACKGROUND:Lynch syndrome (LS) is caused by germline pathogenic variants (PV) in MLH1, MSH2/EPCAM, MSH6, PMS2. Gastric cancer risk in LS is up to 11%, varying by PV. It is the first LS spectrum cancer in 39% patients. Most LS gastric cancer have a precancerous (Correa) cascade amenable to

endoscopic intervention. Guidelines recommend upper endoscopy (EGD) every 2-4 years starting age 30-40, performed at time of colonoscopy. We present a comparative effectiveness study of EGD surveillance for gastric cancer in LS by PV.

METHODS:We developed a decision-analytic model comparing no surveillance (NSV) versus EGD surveillance, starting at age 35. Individuals received EGD only for symptomatic cancer (NSV) or EGD at 2, 3, and 4-year intervals (Q2SV, Q3SV, Q4SV, respectively) alongside colonoscopy (Figure 1). Model was calibrated to lifetime incidence of gastric cancer by grouping PV into high (MLH1/MSH2, 7.4%), intermediate (MSH6, 5.3%), and low/population risk (PMS2, 0.9%). Quality-of-life utilities, costs and complication rates were derived from literature. Standard 3% discounting was applied over a 65-year time horizon. Outcomes were reported as incremental cost effectiveness ratios (ICERs). Willingness-to-pay (WTP) threshold was set a priori at an ICER of $100,000 per quality-adjusted life-year (QALY).

RESULTS:Q4SV was cost-effective for high (MLH1/MSH2) and intermediate-risk (MSH6) individuals, with ICER of $47,171 and $72,536/QALY, respectively (Table 1). Q2SV and Q3SV was not cost-effective for high and intermediate-risk individuals. For low-risk individuals (PMS2), no strategy was cost-effective. Surveillance strategies showed 49-63% reduction of gastric cancer-related death compared to NSV.

CONCLUSIONS:Our modeling analysis shows that EGD surveillance every 4 years for carriers of MLH1, MSH2 and MSH6 appears to be cost-effective for gastric cancer prevention. For PMS2 carriers, surveillance was not cost-effective. Better understanding of risk of gastric and small bowel cancer in LS (including Helicobacter pylori, specific PV, family history) is needed to improve risk stratification in practice.

Keywords: Lynch Syndrome, Gastric cancer, Cost-effectiveness, Upper endoscopy

POSTER ABSTRACTS

Figure1

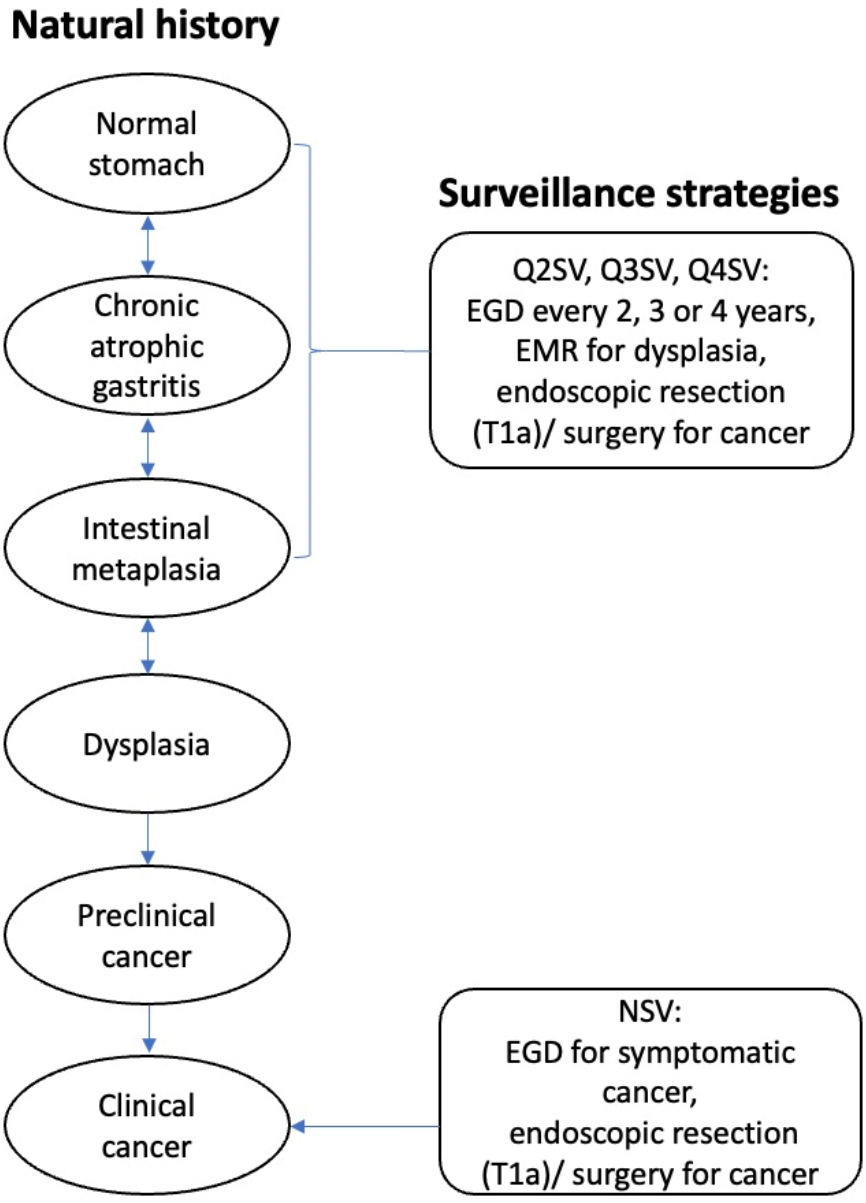

Figure 1. Schematic of strategies for Lynch Syndrome cohort Q2SV, Q3SV, Q4SV: endoscopic surveillance every 2, 3, or 4 years, respectively. If gastric dysplasia, endoscopic resection followed by endoscopic surveillance per current guidelines for gastric dysplasia. NSV: endoscopy for symptomatic cancer only. In all strategies, early cancer (T1a) had endoscopic resection; more advanced cancers had surgery.

Table 1

POSTER ABSTRACTS

	Primary Outcomes					Secondary Outcomes		
Surveillance strategy, in order of cost effectiveness	Cumulative cost, $USD	Incremental cost, $ USD	Effectiveness, QALY	Incremental effectiveness, QALY	ICER, $USD/QALY	Number of EGDs, per patient	Lifetime incident cancer, per 1,000	Cancer deaths, per 1,000
High risk								
NSV	5,940		21.36			0.07	74	69
Q4SV	14,517	8,577	21.54	0.18	47,171	10.5	43	34
Q3SV	16,633	2,116	21.55	0.0079	268,942	13.7	42	33
Q2SV	20,796	4,163	21.56	0.0078	533,870	20.3	40	32
Intermediate risk								
NSV	4,540		21.45			0.05	52	49
Q4SV	13,613	9,073	21.57	0.13	72,536	10.6	33	26
Q3SV	15,754	2,141	21.58	0.005	431,547	13.9	32	25
Q2SV	19,955	4,201	21.58	0.0049	862,306	20.5	31	25
Low risk								
NSV	509		21.81			0.009	9	8
Q4SV	8,931	8,420	21.82	0.017	487,041	11.3	4	3
Q3SV	11,171	2,241	21.83	0.001	2,343,947	14.8	4	3
Q2SV	15,600	4,429	21.83	0.0009	4,779,609	21.9	4	3

$USD, US dollars; QALY, quality adjusted life years * ICER may not add up to due to rounding

Table 1. Analysis of the incremental cost-effectiveness ratio (ICER) of endoscopic screening strategies starting at age 35 years for gastric cancer in Lynch Syndrome

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P-081

General Research » Lynch Syndrome

COLORECTAL CANCER RISK FACTORS IN LYNCH SYNDROME: *MSH2*, ADVANCED ADENOMAS AND ADENOMAS MULTIPLICITY

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POSTER ABSTRACTS

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BACKGROUND:Post-colonoscopy colorectal cancer (PCCRC) remains an important issue in CRC prevention in Lynch syndrome (LS). Besides a colonoscopy interval of >3-years, no other risk factors for PCCRC have been established. We aim at describing PCCRC risk factors in LS during surveillance.

METHODS:Multicenter retrospective study including LS carriers under colonoscopy surveillance. We describe PCCRC risk factors in LS carriers without CRC (healthy carriers, HC). We then analyzed their influence in PCCRC 10-year cumulative incidence by cox regression analysis. Finally, we compared PCCRC 10-year incidence between HC and patients with CRC prior to initiating surveillance.

RESULTS:We included 893 LS HC and 308 patients with previous CRC. In HC, we identified as independent risk factors for PCCRC: *MSH2* carriers (OR=1.86,95%CI:1.01-3.39; p=0.043) and the presence of advanced adenomas (OR=2.37,95%CI:1.22-4.6; p=.011), especially at first colonoscopy (OR=3.11, 95%CI:1.44-6.73; p=0.004) or in >1 colonoscopy (OR=5.25,95%CI:1.94-14.15, p=0.001) (Figure 1A). Performing all colonoscopies in less than 3-year-intervals protected from PCCRC (OR=0.416, 95%CI:0.22-0.78, p=0.007). We then compared the 10-year-cumulative-PCCRC-incidence observing a higher PCCRC risk in *MSH2* carriers(OR=2.1,95%CI:1.17-3.74; p=0.013), LS with advanced adenomas at first colonoscopy (OR=2.55, 95%CI:1.25-5.23; p=0.010) and those with more than one colonoscopy with advanced adenomas(OR=2.62, 95%CI:1.09-6.29; p=0.031) (Figure 1B). We then compared the PCCRC risk in HC vs patients with previous CRC (Figure 2). The latest were older at first colonoscopy (p<0.001), with a higher proportion of male gender (p<0.001), different gene distribution (p<0.005) and different remanent colon length. The PCCRC 10-years-cumulative-incidence was: 7.9% (95%CI:10.84-4.96) and 13.5% (95%CI:8.4-15.6), respectively. However, the Cox-analysis adjusted by gender, gene, age at first colonoscopy, remanent colon length and quality indicators did not found significant differences (p>0.05).

CONCLUSIONS:Being an *MSH2* carrier and presenting advanced adenomas during surveillance double the risk of PCCRC in LS. Interestingly, a previous CRC does not increase the PCCR risk. This information should help personalizing surveillance in LS.

Keywords: Lynch syndrome, risk factors, colorectal surveillance, adenomas

POSTER ABSTRACTS

Figure 1. Post-colonoscopy colorectal cancer risk factors

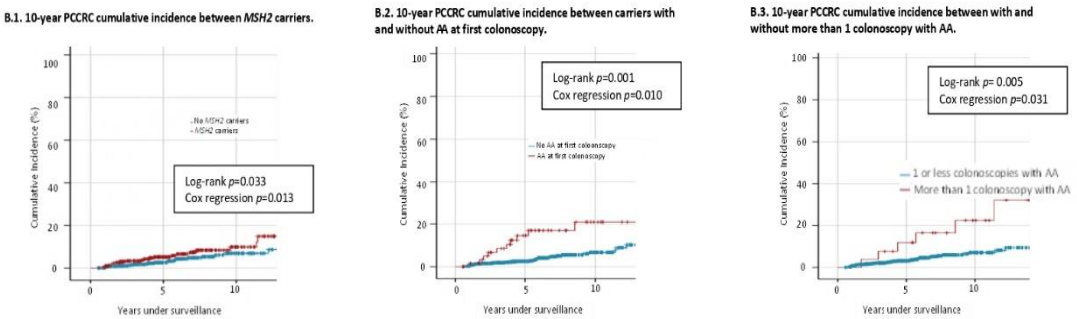
Figure 1. Post-colonoscopy colorectal cancer risk factors

A. Post-colonoscopy colorectal cancer risk factors, logistic regression.

	No incident CRC	Incident CRC	Total	P Value		Multivariate analysis
N (%)	845	48	893			
Females (%)	537 (63.6%)	32 (66.7%)	569 (63.7%)	.758		
MLH1	268 (31.7%)	17 (35.4%)	285 (31.9%)	.634	.035	
MSH2	292 (34.6%)	24 (50%)	316 (35.4%)	**.042**		**.043 [1.86 (1.019-3.394)]***
MSH6	206 (24.4%)	6 (12.5%)	212 (23.7%)	.079		
PMS2	79 (9.3%)	1 (2.1%)	80 (9%)	.115		
Age first colonoscopy	41 (32-51)	44.5 (37-52.75)	41 (32-51)	**.047**		.158*
< 25	61 (7.2%)	1 (2.1%)	62 (6.9%)	.245		
25-34	205 (24.3%)	9 (18.8%)	214 (24%)	.487		
35-44	265 (31.4%)	14 (29.2%)	279 (31.2%)	.873		
45-54	157 (18.6%)	14 (29.2%)	171 (19.1%)	.088		
55-64	107 (12.7%)	7 (14.6%)	114 (12.8%)	.658		
>65	50 (5.9%)	3 (6.3%)	53 (5.9%)	.759		
N Adenoma	384 (45.4%)	26 (54.2%)	410 (45.9%)	.297		
Adenoma at first colonoscopy	162 (19.2%)	15 (31.3%)	177 (19.8%)	.060		
Age first adenoma	47 (41-57)	46.5 (40.75-57.5)	47 (40.75-57)	.087		
More than 1 colonoscopy with adenomas	181 (21.4%)	10 (20.8%)	191 (21.4%)	1		
N Advanced adenoma (AA)	120 (14.2%)	15 (31.3%)	135 (15.1%)	**.003**		**.011 [2.37 (1.22-4.6)]***
Advanced adenoma at first colonoscopy	56 (6.6%)	10 (20.8%)	66 (7.4%)	**.002**		**.004 [3.114 (1.44-6.734)****
Age first advanced adenoma	50 (42-58)	45.5 (36.5-62)	49 (42-57)	.927		
More than 1 colonoscopy with AA	20 (2.4%)	6 (12.5%)	26 (2.9%)	**.002**		**.001 [5.244 (1.943-14.154)]****
Colonoscopy quality indicators						
All complete	765 (90.5%)	38 (79.2%)	803 (89.9%)	**.022**		.254*
All adequate bowel prep (ABP)	426 (50.4%)	21 (43.8%)	447 (50.1%)	.378		
All less than 3 years interval	673 (79.6%)	29 (60.4%)	702 (78.6%)	**.003**		**.007 [.416 (.221-.785)]***

*Multivariate analysis adjusted by MSH2, age at first colonoscopy, all colonoscopies complete, all colonoscopies in less than 3 years interval and an advanced adenoma at any colonoscopy; ** Multivariate analysis adjusted by *MSH2*, age at first colonoscopy, all colonoscopies complete, all colonoscopies in less than 3 years interval and advanced adenoma at first colonoscopy; *** Multivariate analysis adjusted by *MSH2*, age at first colonoscopy, all colonoscopies complete, all colonoscopies in less than 3 years interval and more than 1 colonoscopy with AA

B. 10-year cumulative post-colonoscopy colorectal cancer risk factors by log-rank and Cox regression (adjusted by age at first colonoscopy, less than 3-year intervals and advanced adenomas (AA) at firstcolonoscopy or AA in more than 1 colonoscopy).



A. Post-colonoscopy colorectal cancer risk factors (logistic regression). B. 10-year cumulative post-colonoscopy colorectal cancer risk factors by log-rank and Cox regression.

POSTER ABSTRACTS

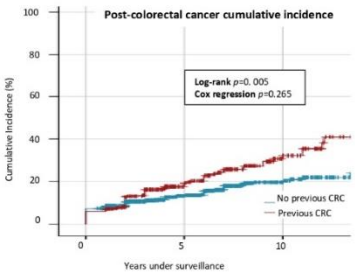
Figure 2. Comparison between healthy carriers and patients with a previous colorectal cancer

Figure 2. Comparison between healthy carriers and patients with a previous colorectal cancer

A. Cohort description and comparison between healthy carriers and patients with a previous colorectal cancer.

	Total	CRC before first colonoscopy	No CRC before first colonoscopy	Univariate analysis		Multivariate analysis
N (%)	1201	308	893			
Females (%)	708 (59%)	139 (45.1%)	569 (63.7%)	.000		.000 [.337 (.250-.454)]
MLH1	435 (36.2%)	150 (48.7%)	285 (31.9%)	.000	.000	.000 [1.97 (1.4-2.75)]
MSH2	415 (34.6%)	99 (32.1%)	316 (35.4%)	.331		
MSH6	256 (21.3%)	44 (14.3%)	212 (23.7%)	.000		.001 [.491 (.32-.76)]
PMS2	95 (7.9%)	15 (4.9%)	80 (9%)	.020		.011 [.43 (.23-.83)]
Age first colonoscopy	43 (35-53.5)	51 (43-59)	41 (32-52)	.000		.000 [1.07 (1.06-1.09)]
N of colonoscopies	3 (2-6)	3 (1-6)	3 (2-6)	.617		
Length of follow-up (y)	5.45 (3.05-8.46)	5.95 (3.41-9.32)	5.34 (2.96-8.15)	.095		
Time between colonoscopies	12.6 (11.78-17.98)	12.59 (12.09-15.92)	13 (12.13-20.85)	.051		
Polyps	761 (63.4%)	553 (61.9%)	208 (67.5%)	.086		
Adenomas	565 (47%)	410 (45.9%)	155 (50.3%)	.186		
Advanced adenomas (AA)	209 (17.4%)	135 (15.1%)	74 (24%)	.001		.667
AA >10 mm	135 (11.2%)	90 (10.1%)	45 (14.6%)	.036		
HGD	60 (5%)	43 (4.8%)	17 (5.5%)	.649		
Villous	53 (4.4%)	36 (4%)	17 (5.5%)	.264		
AA HGD	111 (9.2%)	73 (8.2%)	38 (12.3%)	.039		
<10 mm	61 (5.1%)	37 (4.1%)	24 (7.8%)	.016		
Villous	46 (3.8%)	30 (3.4%)	16 (5.2%)	.168		
AA Villous	107 (8.9%)	68 (7.6%)	39 (12.7%)	.010		
<10 mm	57 (4.7%)	35 (3.9%)	22 (7.1%)	.029		
Non-advanced adenomas (<10mm LGD)	481 (40%)	360 (40.3%)	121 (39.3%)	.787		
Serrated lesions	380 (31.6%)	283 (31.7%)	97 (31.5%)	1		
Hyperplastic polyps	313 (26.1%)	237 (26.5%)	76 (24.7%)	.548		
Sessile Serrated lesions	63 (5.2%)	51 (5.7%)	12 (3.9%)	.239		
Incident CRC	83 (6.9%)	35 (11.4%)	48 (5.4%)	.001		.032 [1.32 (1.05-2.86)]

B. Post-colonoscopy colorectal cancer cumulative incidence compared between healthy carriers and patients with a previous colorectal cancer.



A. Cohort description and comparison between healthy carriers and patients with a previous colorectal cancer. B. Post-colonoscopy colorectal cancer cumulative incidence between healthy carriers and patients with a previous colorectal cancer.

P-082

General Research » Lynch Syndrome

CLINICAL PRESENTATION OF PATIENTS WITH PMS2-LYNCH SYNDROME AT TWO MICHIGAN MEDICAL CENTERS

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BACKGROUND:Although PMS2 pathogenic/likely pathogenic (P/LP) variants are the most prevalent subtype of Lynch syndrome, it is challenging to identify at-risk individuals due to the variable phenotype, resulting in discrepancies across management guidelines. European guidelines recommend screening for colorectal

cancer (CRC), while US-based guidelines recommend surveillance for gastrointestinal and endometrial cancers. We describe the presentation of PMS2-Lynch syndrome (PMS2-LS) among 199 patients across two Michigan medical centers.

METHODS:Retrospective chart review was completed for individuals with PMS2-LS at the Nancy and James Grosfeld Cancer Genetics Center and the University of Michigan Cancer Genetics Clinic (2002-2023).

RESULTS:In total, 199 patients had a PMS2 P/LP variant (65 unique). Ninety-two patients (46.2%) had a personal history of cancer. Sixty-four (32.2%) had LS-related cancer. Twenty-six patients (13.1%) had multiple malignancies, including one patient with six primaries.

The most common malignancy was CRC (16.6%). The mean age at diagnosis was 58.1 years (range 28-78 years), including one with synchronous CRC tumors at age 63. Two patients had metachronous CRCs (range 39-78 years). Other LS-cancers were endometrial (8.5%), prostate (3.0%), pancreatic (3.0%), ovarian (1.5%), bladder/bile duct (1.5%), small bowel (1.5%), and glioblastoma (0.5%). The mean age of diagnosis of endometrial cancer was 56.8 years (range 40-72 years), prostate was 60.3 years (51-76), pancreatic was 66.2 years (51-89), ovarian was 56.5 years (49-64), bladder/bile duct was 57.8 years (57-59), small bowel was 52 years (44-57), and glioblastoma was 52 years.

Other malignancies included sarcoma, hematologic, and cancers of the breast, kidney, esophagus, lung, skin, and thyroid. To note, individuals were ascertained based on personal and/or family history of cancer, prompting the referral to a cancer genetics program.

CONCLUSIONS:PMS2-LS presents within a diverse clinical phenotype. Our shared experience demonstrates patients with PMS2-LS may develop early onset and interval cancers, supporting the recommendation for surveillance with upper/lower endoscopy.

Keywords: Lynch syndrome, PMS2

P-083

General Research » Lynch Syndrome

ATTITUDES TOWARDS PREVENTION OPTIONS IN LYNCH SYNDROME (LS): COMPARING FRAMESHIFT PEPTIDE VACCINATION (FSPVAX), COLONOSCOPY (COLO), AND ASPIRIN (ASA)

POSTER ABSTRACTS

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BACKGROUND:LS is among the most common cancer (CA) syndromes affecting 1:280 individuals and portends high lifetime CA risk. Clinical trials are currently evaluating whether FSPVAX could reduce LS CA risk. FSPVAX enhance immune response to diverse FSP neoantigens in MSI-H tumors and have shown promising results in an MSH2-mutant mouse model and metastatic MSI-H CRC. However, low uptake of ASA chemoprevention in LS patients and negative public attitudes towards vaccination could undermine this novel therapy. Here, we benchmark attitudes towards FSPVAX for CA prevention against colonoscopy and aspirin chemoprevention.

METHODS:The PREVENTLynch survey (IRB 20-8014) was distributed electronically to 1) participants in the Fox Chase Cancer Center (FCCC) Risk Registry and 2) members of a Facebook “LS Support Group” operated by Lynch Syndrome International. LS patients were invited to complete the one-time survey after providing informed consent, and received a gift card incentive upon completion. Demographic/personal/familial CA history were collected. Attitudes were measured on 9-point scales indicating low vs high agreement with belief statements: e.g. “Colonoscopy is a convenient way to lower my risk of LS-related CA.

RESULTS:Overall 296 participants at FCCC, nationally, and internationally completed the survey. Median age was 52.6 years [23-78], 84% female, and 95% White. Affected genes included MLH1 (20.3%), MSH2/EPCAM (35.5%), MSH6 (28.7%), and PMS2 (15.5%). Use of ASA or NSAID chemoprevention was uncommon (32.1% and 5.1% respectively). Compared to COLO, FSPVAX was viewed as more convenient, but side effect concerns were higher, and perceptions of efficacy were lower (all $p<0.001$). Compared to ASA chemoprevention, FSPVAX was less convenient and fostered greater concerns about side effects, but was seen as having higher efficacy (all $p<0.001$).

CONCLUSIONS:Like with ASA chemoprevention, concerns about side effects and efficacy may attenuate FSPVAX trial participation and uptake by patients with LS.

Keywords: Lynch Syndrome, FSPVAX, colonoscopy, aspirin

P-084

General Research » Lynch Syndrome

POLYPOSIS IN PATIENTS WITH LYNCH SYNDROME

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POSTER ABSTRACTS

BACKGROUND:NCCN guidelines recommend patients with ≥10 lifetime adenomas undergo risk assessment and consideration of genetic testing for polyposis syndromes. Lynch Syndrome (LS) is typically not included in the differential diagnosis for polyposis syndromes. Anecdotally, we observed several LS patients with a polyposis phenotype. This study aimed to determine number of lifetime adenomas in the LS patients in our hereditary GI tumor registry, and to evaluate differences in demographic and clinical factors between those with ≥10 and those with <10 lifetime adenomas.

METHODS:We retrospectively reviewed medical records from the LS patients enrolled in our registry since 2005 (N=257) for colorectal cancer diagnoses, colonoscopy outcomes, and other clinical factors. We compared groups of interest using Fisher's exact test and Wilcoxon-Mann-Whitney test.

RESULTS:Based on available records, 11 (4.3%) patients had ≥10 adenomas; 246 had <10 (range: 0-9). One of the 11 patients with ≥10 adenomas had polyposis phenotype prior to LS diagnosis. Number of colonoscopies and follow-up time were significantly higher in the ≥10 group. For assessment of differences, we limited our cohort to those with ≥6 lifetime colonoscopies since this was the minimum in the ≥10 group (N=92). Table 1 shows characteristics of the total cohort alongside those with ≥6 colonoscopies stratified by adenoma number status. No significant differences in the evaluated characteristics were observed between those with ≥10 adenomas and those with <10 adenomas. Interestingly, MSH6 and MSH2 were the most commonly affected genes in the ≥10 group, both 45.5%; compared to 24.7% and 35.8%, respectively, in the <10 group. This is consistent with what has been reported recently by Stanich et al. (MSH6: 57.1% vs. 32.2%; MSH2: 28.6% vs. 26.0%).

CONCLUSIONS:Polyposis occurs in LS; possibly, in particular among those with MSH6 pathogenic variants. LS should be included as a differential for attenuated polyposis.

Keywords: Lynch Syndrome, Polyposis

Fig1.Pg1

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Table 1. Characteristics of the study population

	Total Cohort		6 or More Colonoscopies		
N(%)	N=257		<10 Lifetime Adenomas (N= 81)	≥10 Lifetime Adenomas (N=11)	*p*-value*
Sex					0.33
Male	89 (34.6%)		25 (30.9%)	5 (45.5%)	
Female	168 (65.4%)		56 (69.1%)	6 (54.5%)	
Race					0.70
White	245 (95.3%)		73 (90.1%)	10 (90.9%)	
Black	7 (2.7%)		5 (6.2%)	1 (9.1%)	
Hispanic	1 (0.4%)		1 (1.2%)	0 (0.0%)	
Asian	3 (1.2%)		1 (1.2%)	0 (0.0%)	
Native American	1 (0.4%)		1 (1.2%)	0 (0.0%)	
Medication use					
Aspirin Use (yes)	50 (19.5%)		18 (22.2%)	3 (27.3%)	0.71
Statin Use (yes)	32 (12.5%)		7 (8.6%)	2 (18.2%)	0.29
NSAID Use (yes)	43 (16.7%)		11 (13.6%)	2 (18.2%)	0.65
Affected Gene					0.28
EPCAM	2 (0.8%)		1 (1.2%)	0 (0.0%)	
MLH1	51 (19.8%)		18 (22.2%)	0 (0.0%)	
MSH2	90 (35.0%)		29 (35.8%)	5 (45.5%)	
MSH6	64 (24.9%)		20 (24.7%)	5 (45.5%)	
PMS2	50 (19.5%)		13 (16.1%)	1 (9.1%)	
Current Smoker	40 (15.6%)		9 (11.3%)	1 (9.1%)	1.00
Diagnosis of Colorectal Cancer (CRC), yrs	88 (34.2%)		43 (53.1%)	5 (45.5%)	0.75

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Fig1.Pg2

Age at CRC Diagnosis in yrs, mean (range)	49.6 (24-87)		48.6 (24-70)	52.6 (35-80)	0.80
Colectomy					1.00
Partial	50 (19.5%)		25 (30.9%)	3 (27.3%)	
Sub-Total/Total	28 (10.9%)		12 (14.8%)	1 (9.1%)	
First-Degree Relative with CRC, yrs	134 (52.1%)		45 (55.6%)	7 (63.6%)	0.75
Second-Degree Relative with CRC, yrs	148 (58.0%)		47 (58.8%)	6 (54.6%)	1.00
Time Followed in yrs, mean (range)	6.8 (0-36)		12.2 (4-36)	13.1 (5-26)	0.23
Age at First Colonoscopy in yrs, mean (range)	45.5 (19-87)		47.1 (20-72)	48.9 (26-74)	0.91
Age at First Polyp in yrs, mean (range)	49.2 (22-87)		49.7 (22-70)	50.7 (27-80)	0.87
Number of Colonoscopies, mean (range)	4.7 (1-23)		8.1 (6-16)	11.2 (6-23)	0.01
Number of Adenomas, mean (range)	2.4 (0-44)		2.7 (0-9)	18.7 (10-44)	<0.0001

* *P*-value for ≥10 *vs.* <10, Fisher's exact test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables.

P-085

General Research » Lynch Syndrome

INFREQUENT ASPIRIN USE AMONG LYNCH SYNDROME PATIENTS IN A NATIONALLY REPRESENTATIVE DATABASE IN THE UNITED STATES

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POSTER ABSTRACTS

BACKGROUND:High-dose aspirin decreases colorectal cancer (CRC) risk in Lynch syndrome (LS) based data published in 2011 and 2020. From 2012-2015, the NCCN stated that there was insufficient data to make a recommendation. From 2016-2019, the NCCN stated that the optimal dose/duration is uncertain. In 2020, NCCN said the decision should be individualized. From 2021-present, the NCCN recommends all LS patients at risk of CRC should consider daily aspirin. Given the evolving guidelines in the US, we aimed to measure aspirin use in LS over time and characteristics associated with use.

METHODS:We performed a retrospective study of the national Epic Cosmos dataset, which includes 205 centers in the US who use Epic. Cosmos allows aggregate data abstraction based on diagnostic and billing codes. We included those with a billing/encounter diagnosis of LS from 1/1/2011 to 5/6/2023. We compared baseline characteristics, comorbidities, sociodemographic data, family history, and neoplasia rates in LS patients taking aspirin vs not using Chi-square tests.

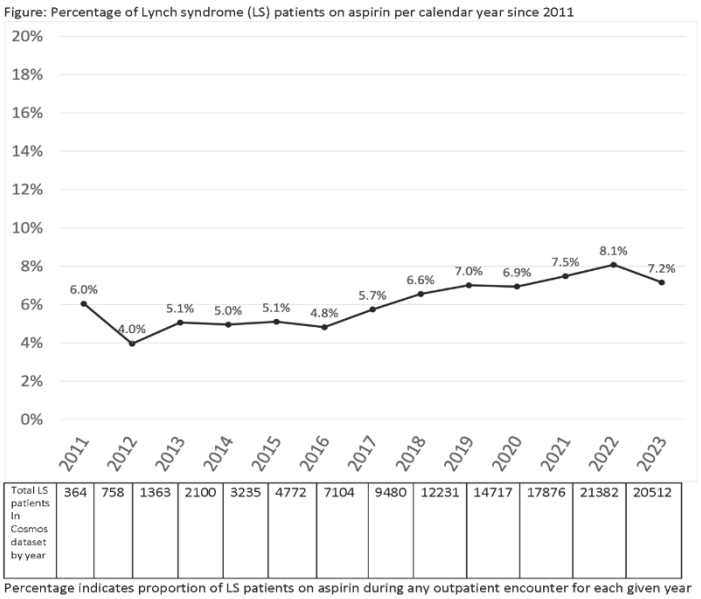
RESULTS:Of 28,526 unique LS patients, 3768 (13.2%) were on aspirin during at least one encounter between 2011-2023. Of those on aspirin, 74.3% were prescribed aspirin and 37.4% reported over-the-counter aspirin use. Patients on aspirin were more likely to be smokers, > age 65, residing in the Midwest or Northeast, morbidly obese, have a history of cardiovascular disease, colon polyps, or a personal or family history of any cancer or CRC (Table). Aspirin use during at least one encounter by year for all LS patients increased from 4.0% in 2012 to 8.1% in 2022 (Figure).

CONCLUSIONS:Although Aspirin use has doubled in LS patients from 2012-2023, overall usage still remains low and presents a CRC prevention opportunity for LS patients in the US. Future work will be needed to examine patient-, provider- and system-level predictors of Aspirin use to target interventions to improve use.

Keywords: Aspirin, Lynch syndrome, Colorectal Cancer, Epic Cosmos

POSTER ABSTRACTS

Figure



Percentage of Lynch syndrome (LS) patients on aspirin per calendar year since 2011

POSTER ABSTRACTS

Table

Table: Characteristics, comorbid diagnoses and family history of cancer among Lynch syndrome patients on and not on aspirin

	On Aspirin (n= 3768)	Not on aspirin (n = 24758)	p-value
Sex			
Female	2422 (64.3%)	17771 (71.8%)	**<0.00001**
Male	1346 (35.7%)	6983 (28.2%)	
Age Group			**<0.00001**
18-29 years old	80 (2.1%)	1570 (6.3%)	
30-39	244 (6.5%)	3634 (14.7%)	
40-49	378 (10.0%)	4787 (19.3%)	
50-64	1238 (32.9%)	8359 (33.8%)	
65-74	1143 (30.3%)	4281 (17.3%)	
75-84	550 (14.6%)	1634 (6.6%)	
85+	131 (3.5%)	329 (1.3%)	
Unknown/Unavailable	4 (0.1%)	164 (0.7%)	
BMI			**<0.00001**
<18.5	221 (5.9%)	416 (1.7%)	
18.5-24.9	1541 (40.9%)	5871 (23.7%)	
25.0-29.9	2207 (58.6%)	6080 (24.6%)	
30.0+	2332 (61.9%)	6842 (27.6%)	
Unknown	14 (0.4%)	5765 (23.3%)	
Active or former smoking	1651 (43.8%)	8485 (34.3%)	**<0.00001**
Race/Ethnicity			**<0.00001**
White	3344 (88.7%)	21434 (86.6%)	
Black	253 (6.7%)	1373 (5.5%)	
Asian	90 (2.4%)	739 (3.0%)	
American Indian	26 (0.7%)	142 (0.6%)	
Other/Unknown	225 (6.0%)	2139 (8.6%)	
LatinX	172 (4.6%)	1394 (5.6%)	
Region of Residence			**<0.00001**
Midwest	1455 (38.6%)	7938 (32.1%)	
Northeast	1108 (29.4%)	6638 (26.8%)	
South	803 (21.3%)	6831 (27.6%)	
West	394 (10.5%)	3289 (13.3%)	
Unknown Census Region	8 (0.2%)	62 (0.3%)	
Community Type			0.079
Rural or Small town	873 (23.2%)	6143 (24.8%)	
Urban (Micropolitan or Metropolitan)	2875 (76.3%)	18468 (74.6%)	
Other	20 (0.5%)	147 (0.6%)	
Social Vulnerability Index			**0.039**
75% or more	811 (21.5%)	4871 (19.7%)	
50-75%	876 (23.2%)	5917 (23.9%)	
25-50%	1028 (27.3%)	6703 (27.1%)	
<25%	1029 (27.3%)	7050 (28.5%)	
Unknown	24 (0.6%)	217 (0.9%)	
Comorbid diagnoses			
Morbid obesity	727 (19.3%)	2552 (10.3%)	**<0.00001**
Coronary Artery Disease	1100 (29.2%)	1587 (6.4%)	**<0.00001**
Ischemic Stroke	325 (8.6%)	290 (1.2%)	**<0.00001**
Any cancer	2670 (70.9%)	13528 (54.6%)	**<0.00001**
Colorectal adenocarcinoma	537 (14.3%)	2366 (9.6%)	**<0.00001**
Benign neoplasm of colon	1860 (49.4%)	8408 (34.0%)	**<0.00001**
Family history of cancer			
Any cancer	2156 (57.2%)	11818 (47.7%)	**< .00001**
Colorectal cancer	1766 (46.9%)	11124 (44.9%)	**0.026**

Characteristics, comorbid diagnoses and family history of cancer among Lynch syndrome patients on and not on aspirin

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General Research » Lynch Syndrome

COLONOSCOPY FINDINGS AND COMPLICATIONS IN A MULTI-INSTITUTIONAL COHORT OF GERIATRIC PATIENTS WITH LYNCH SYNDROME UNDERGOING SURVEILLANCE

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BACKGROUND:In the general population, colorectal cancer (CRC) screening is selectively recommended between ages 76-85 and not recommended over age 85 given unclear benefit in the elderly. There is no guidance on appropriate age to stop surveillance in Lynch syndrome (LS). We investigated the yield and colonoscopy complications in geriatric LS patients.

METHODS:Colon surveillance procedures were reviewed among a multi-institutional cohort of >75-year-old LS patients. A modified previously-validated geriatric frailty index (mMSK-FI) was assigned, with higher scores indicating greater frailty. Complications were assessed 30 days post-procedure and grouped into categories (cardiovascular, pulmonary, neurologic, hematologic, urinary/renal). Clinicopathologic variables were reported and compared using non-parametric tests at the patient and procedure levels.

RESULTS:39 LS patients had in-house colon surveillance >75 years [*MLH1*: 7, *MSH2/EPCAM*: 15, *MSH6*: 9, (PMS2: 8]. 15 (38%) had previous CRC. Patients underwent a median of 2 colon procedures (range 1-7) comprising 113 procedures. Among the 113 pooled procedures, there were 52 (46%) with neoplastic lesions, including 22 (19%) with high-risk adenomas (HRAs) and 7 (6%) with CRCs. Most CRCs were found in *MLH1/MSH2* PV-carriers [6 (86%) vs 1 (14%)]. Among patients with CRC, 6 (86%) underwent further treatment. There were 4 (3.5%) post-procedure complications (Table 1). A significant complication was a CVA 4 days post-procedure in a *PMS2* PV-carrier after having anti-coagulation held for procedure. Median mMSK-FI score was 1 (range 0-4) overall versus 2.5 (range 2-4) among patients with complications. Notably, one *MLH1* PV-carrier with previous CRC was diagnosed with interval metastatic CRC 2 years after normal colonoscopy at 83.

CONCLUSIONS:Our multi-institutional analysis of colonoscopy performed in geriatric LS patients suggests a high rate of colonic neoplasia, but also multiple procedural complications. LS gene penetrance and utilization of a geriatric frailty index may help with individualized decision-making, albeit larger comparative datasets are needed for risk-stratification.

Keywords: Lynch syndrome, colonoscopy, surveillance, outcomes

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Table 1

Table 1. Details on Patients > Age 75 with Post-Procedural Complications

Pt ID	Pt age	MMR gene	Prior CRC history (y/n)	mMSK-FI score	Comorbidities	Complication Group	Complication Details	Procedure Findings
OSU005	79	*PMS2*	N	4	DM, CHF, HTN, HLD/CAD	Neurologic	CVA 4 days post-procedure after AC held	LRA
MSK089	83	*MSH2*	N	2	HTN, HLD/CAD	Urinary/renal	Urinary retention/AKI	NONE
MSK089	85	*MSH2*	N	2	HTN, HLD/CAD	Hematologic	VTE after AC held	HRA
PENN260	80	*MSH2*	Y	3	COPD, HTN, CVA	Hematologic	Post-polypectomy bleed	CRC

Abbreviations: DM – diabetes mellitus; CHF – congestive heart failure; HTN – hypertension; HLD – hyperlipidemia; CAD – coronary artery disease; CVA – cerebral vascular accident; AC – anti-coagulation; AKI – acute kidney injury; VTE – venous thromboembolism; LRA – low risk adenomas; HRA - high risk adenomas; CRC – colorectal cancer

Table 1. Details on Patients > Age 75 with Post-Procedural Complications

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COLORECTAL CANCER MISMATCH REPAIR IMMUNOHISTOCHEMISTRY IN PATIENTS IDENTIFIED WITH LYNCH SYNDROME VIA GENOMIC SCREENING

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BACKGROUND:Lynch syndrome (LS) is increasingly identified through population-level genomic screening, yet cancer presentation among this group is not well understood. We assessed colorectal cancer (CRC) mismatch repair immunohistochemistry (MMR IHC) status and age at diagnosis of individuals identified with

LS via genomic screening.

METHODS:Geisinger's MyCode Genomic Screening and Counseling program, a health system- based genomic sequencing effort, identified and returned pathogenic or likely pathogenic (P/LP) variants in MLH1, MSH2, MSH6, or PMS2 to 402 participants. Electronic health record data were extracted, including CRC, age at diagnosis, MMR IHC, and genetic test results.

RESULTS:Twenty-five (6%) participants had CRC and no prior clinical LS germline testing. Most genomic screening results (n=23) were received a median of four years (range 0.4-32.7 years) after CRC diagnosis. Of 11 (44%) with CRC who had MMR IHC performed, five (45%) were MMR-proficient; all had germline PMS2 (n=3) or MSH6 (n=2) P/LP variants. Six (55%) were MMR-deficient in concordance with their genomic result. In terms of age at diagnosis, one (20%) MMR-proficient CRC and three (50%) MMR-deficient CRCs were diagnosed before age 50. Of participants without MMR IHC (n=14), most were diagnosed prior to 2009 (n=10, 71%) when MMR IHC was routinely implemented at Geisinger or after 2009 but prior to routine assessment and tracking of IHC performance (n=1). The remaining had inadequate tissue to perform IHC (n=2) or were diagnosed at another institution (n=1). Half of participants without MMR IHC (n=7) were diagnosed before age 50.

CONCLUSIONS:Genomic screening identified patients who, based on MMR IHC, met criteria for LS germline testing but had not had prior evaluation and patients who did not screen positive for LS based on MMR-proficient CRC. Population genomic and tumor screening are complementary methods for LS identification. LS diagnosis is key to understanding cancer risks, offering appropriate surveillance, and assessing familial risk.

Keywords: Lynch syndrome, colorectal cancer, genomic screening, mismatch repair

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P-088

General Research » Lynch Syndrome

DECISION-MAKING OUTCOMES FOR MANAGING GYNECOLOGIC CANCER RISK IN LYNCH SYNDROME

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BACKGROUND:Standardized guidelines for the management of gynecologic cancer risk are lacking for patients with Lynch syndrome. Little is known about decision-making surrounding risk management.

METHODS:Medical records were analyzed among Lynch patients who underwent genetic counseling and were followed by gynecologic oncologists in a high-risk clinic at a university medical center from 2013-2023.

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Eligible patients had no prior gynecologic cancer and an intact uterus and/or ovaries.

RESULTS:The 32 women had a median age of 36 (range 20-60). Race/ethnicity was 21/32 (66%) White, non-Hispanic, 5/32 (16%) White, Hispanic, 3/32 (9%) Asian, and 3/32 (9%) Other/Mixed; 30/32 (94%) were English-speaking. Nine patients (28%) had a prior non-gynecologic cancer diagnosis, including 5 with colorectal cancer. Lynch-associated pathogenic variants included MLH1 (10), MSH2 (9), MSH6 (2), and PMS2 (11). Among the 32 women, 9 (28%) underwent surgery, 13 (41%) delayed surgery, 8 (25%) had not decided, 1 (3%) declined surgery, and surgery was not recommended for 1 (3%). Among the 9 who had surgery, 8/32 (25%) completed hysterectomy and bilateral salpingo-oophorectomy and 1 completed hysterectomy only; 4 had benign gynecologic diagnoses, 4 solely desired risk-reduction, and 1 was identified to have Stage 1 endometrial cancer after workup for abnormal bleeding. Reported reasons to delay surgery included desire for fertility (n=5), avoidance of premature menopause (n=4), and personal timing (n=4). Among 23 patients not undergoing surgery yet, 13 (57%) began/continued use of oral contraceptives or intrauterine devices; 10 (43%) received transvaginal ultrasounds, 8 (35%) underwent endometrial biopsy, and 5 (22%) received CA-125. Five (22%) had screening and 3 (13%) had endometrial biopsies only after experiencing abnormal symptoms.

CONCLUSIONS:Gynecologic cancer risk management varied among a population of patients with Lynch syndrome due to individual medical history and personal preferences. High risk gynecologic oncology clinics provide important clinical services, allowing for early cancer detection and personalized risk management.

Keywords: Lynch syndrome, ovarian cancer, uterine cancer, surveillance, risk-reducing surgery

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P-089

General Research » Lynch Syndrome

FREQUENCY AND DETERMINANTS OF MISSED COLONOSCOPY SURVEILLANCE IN LYNCH SYNDROME PATIENTS IN A SCREENING PROGRAM WITHOUT A PROCEDURAL RECALL SYSTEM

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POSTER ABSTRACTS

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BACKGROUND:Societal guidelines recommend Lynch Syndrome (LS) patients undergo colonoscopy surveillance within 24-months. Missed colonoscopy surveillance (MCS) can be attributed to multiple patient or provider causes. We sought to identify the rate and reasons why MCS occurs in LS patients at a tertiary care center.

METHODS:Adult LS patients were identified through The University of Arizona Cancer Registry Genetics Database in which mutations in MSH1, MLH1, PMS2, MSH6 and EPCAM were included. Patients had at least 1 colonoscopy by any of the 11 colonoscopists at Banner University Medical Center. MCS was defined as surveillance interval >24-months. Compliant was defined as intervals ≤24-months. Reasons for MCS was attributed to illness concerns (acute/chronic comorbidity), colonoscopist recommendation of >24-months interval between cases, or patient scheduling failure. Patient scheduling failure refers to MCS that occurred without acute illness/comorbidity or inappropriate colonoscopist recommendation, thus a patient's failure to comply. Primary endpoints included MCS rate and reasons. Secondary endpoints investigated factors correlated with MCS. Groups were compared with Fisher exact test with P-value ≤ 0.05 defining significance.

RESULTS:104 patients were identified 44 of which underwent surveillance from 2012-2023 with mean: 62 months ±37.6. MCS occurred in 24 (54%) patients. Overall, 28/144 colonoscopies (19.4%) had an interval longer than 24-months. Patient scheduling failures accounted for 71.4% (N=20, P=0.01) of MCS while illness concerns 17.9% (N=5) and colonoscopist recommendations 10.7% (N=3) were less frequent. MCS patients had longer surveillance intervals (Mean: 22.25± 10.92 months, P= 0.0001) and total surveillance (Mean: 71.79± 36.84 months, P= 0.08). There was no demographic difference between compliant and MCS patients.

CONCLUSIONS:In an environment with no active recall program, the most common reason for MCS was patient scheduling failure. 5 out of 7 cancers diagnosed were in the missed colonoscopy group. Therefore, effort will be focused on improving patient scheduling rather than provider education intervention

Keywords: Lynch Syndrome, Colorectal Cancer

POSTER ABSTRACTS

Table 1a

Table 1a) *Comparison of those patients who underwent surveillance colonoscopy exclusively with colonoscopy intervals less than or equal to 24 months.*

	Missed Surveillance Patients N=24	Compliant Patients N=20	P-value
Mean age, y	57.26±15.78	55.05±14.27	NS
Female sex	12 (50%)	13 (65%)	
Family history of CRC	18	17	
Proband	7	6	
Prior Cancer History	15	15	
LS Related Surgery History	14	16	
Aspirin	3	2	
Tobacco	12	11	
Gene affected			
MLH1	7	2	0.15
MSH2	5	5	
MSH6	8	9	
PMS2	7	3	
Entire Time Surveilled (Months)			
Mean, SD	71.79± 36.84	51.73± 36.6	0.08
Median	76.35	37.58	
Time in between Colonoscopy (Months)			
Mean, SD	22.25± 10.92	15.64± 7.02	0.0001
Median	18.84	13.46	
Colonoscopy Outcomes			
Total number of surveillance Colonoscopies	91	75	
Colonoscopies with adenomatous polyps	15	15	
Colonoscopies with advanced features	3	3	
Colonoscopies diagnosing cancer	5	2	
Payor			
Private	71	55	0.58
Medicare	10	12	
Medicaid	10	8	

Comparison of those patients who underwent surveillance colonoscopy exclusively with colonoscopy intervals less than or equal to 24 months.

POSTER ABSTRACTS

Table 1b

Table 1b) *Characteristics of surveillance colonoscopies that were late (>24 months) or missed surveillance versus those that were compliant (within 24 months)*

	Missed Surveillance	Compliant Surveillance	P- Value
Total number of Surveillance colonoscopy	28 (19.4%)	116 (80.6%)	
Rationale of Missed Surveillance			
Patient scheduling failure	20 (71.4%)		0.01
Colonoscopist recommendations	3 (10.7%)		
Acute Illness	5 (17.9%)		
Payor change	3	3	0.08
Prior Missed Surveillance	5	9	
Advanced Features	1	5	
Cancer Diagnosis	1	6	
Payor			
Private	20	87	0.80
Medicare	5	16	
Medicaid	3	13	

Characteristics of surveillance colonoscopies that were late (>24 months) or missed surveillance versus those that were compliant (within 24 months)

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POSTER ABSTRACTS

COLONOSCOPY SCREENING ADHERENCE AND RISK-REDUCING HYSTERECTOMY UPTAKE AMONG LYNCH SYNDROME PATIENTS IN A SPECIALIZED, HIGH-RISK CLINIC

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BACKGROUND:NCCN guidelines recommend that Lynch Syndrome (LS) patients undergo colonoscopy surveillance every 1-2 years and women consider risk-reducing hysterectomy/bilateral salpingo-oophorectomy (RR-Hys) once child-bearing is complete. Prior studies have reported 73%-88% rates of colonoscopy adherence, which fall to 64% in those without colorectal cancer (CRC) history. Lower rates of RR-Hys uptake have been reported. Herein we describe adherence among LS patients seen in a specialized, genetic high-risk program at a tertiary cancer center (MSK-CATCH).

METHODS:We reviewed records of LS patients enrolled in MSK-CATCH from 12/2018-12/2022. Only patients with P/LP variants (PVs) in the MMR genes were included. Patients were considered adherent to surveillance if colonoscopy was completed within two years of 12/31/22. Clinical variables were correlated and compared using non-parametric tests.

RESULTS:A total of 100 LS patients were identified (MLH1: 31, MSH2/EPCAM: 22, MSH6: 30, PMS2: 17) Median age was 44.5 (range 20-81) and the cohort was predominantly female (83%). Most (83%) patients had no CRC history. Of CRC-affected patients (n=17), most had MLH1/MSH2/EPCAM PVs compared to MSH6/PMS2 [12 (71%) vs. 5 (29%), respectively; p=0.18]. There was a 95% colonoscopy adherence rate with no difference between CRC-affected and CRC-unaffected patients [15/17 (88%) vs. 80/83 (96%), respectively; p=0.16]. There were 21 female patients greater than or equal to 50 without prior endometrial cancer (EC) or ovarian cancer (OC). 19 (90%) underwent RR-Hys, of which 12 (63%) had surgery at our institution. Among such patients, median age at RR-Hys was 52. While there were no ECs or OCs detected at time of RR-Hys, 4 (33%) patients had a pre-cursor lesion requiring no further treatment.

CONCLUSIONS:In this cohort of predominantly female LS patients without prior CRC or EC followed in MSK-CATCH, colonoscopy adherence and RR-Hys uptake were higher than previously reported. Long-term, longitudinal data is needed to evaluate persistence of these effects.

Keywords: Lynch Syndrome, colonoscopy adherence, risk-reducing hysterectomy

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POSTER ABSTRACTS

General Research » Lynch Syndrome

REVEALING THE HIDDEN COSTS: EXPLORING THE FINANCIAL TOXICITY OF HEREDITARY CANCER SYNDROMES

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BACKGROUND:While Financial toxicity is widely reported in cancer, limited research exists on the financial toxicity in hereditary cancer syndromes (HCS) which amounts to 10% of cases. This study explores the financial toxicity in two prevalent HCS: Hereditary Breast and Ovarian Cancer Syndrome (HBOC) and Lynch Syndrome (LS).

METHODS:Patients across 3 provinces in Canada with a confirmed molecular diagnosis of HBOC or LS were invited to participate in semi-structured qualitative interviews. Interpretive description was used to analyze the data.

RESULTS:Qualitative interviews were conducted with 73 patients (51 female, 21 male, 1 gender-divers; age range 25-80yrs) diagnosed with HBOC (n= 39) or LS (n= 34). For many patients, accessing treatment and routine screenings within their province posed financial hardship, including travel costs and lost wages. Some patients incurred high travel expenses for accessing specialized equipment or healthcare professionals in other provinces (e.g., larger MRI machines). Other financial impacts of HSC included expenses for fertility preservation procedures, reconstructive surgeries, and psychotherapy. Concerns about unidentified financial prospects in the future weighed heavily on the minds of many participants. The possibility of being unable to return to their jobs due to health limitations, choosing a different career path, or the potential financial impact of their passing created financial uncertainty and strain. Participants often relied on their families to help cope with financial challenges. This involved sharing the costs, alternate living arrangements, family members accompanying them to medical appointments, and seeking assistance with childcare. The role of health advocates and supportive employers emerged as crucial factors in mitigating financial burdens.

CONCLUSIONS:Findings revealed novel insights about financial toxicity in HCS in Canada, emphasizing access challenges, ongoing expenses, shared family costs, and financial future uncertainties. Solutions are needed to address these financial burdens.

Keywords: financial burden, hereditary cancer syndromes, lynch syndrome, health policy, genetic testing, patient-partners

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General Research » Lynch Syndrome

COST-EFFECTIVENESS OF UNIVERSAL GERMLINE VS SEQUENTIAL SCREENING FOR LYNCH SYNDROME IN PATIENTS WITH INCIDENT COLORECTAL CANCER IN THE UNITED STATES

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BACKGROUND:Germline testing (GT) for all patients with CRC is not fully endorsed and most guidelines recommend prescreening through tumor testing for Lynch syndrome (LS). Prior studies found universal GT to be cost-ineffective. Nevertheless, none of them considered the real-world diagnostic attrition that occurs through the traditionally endorsed sequential process. We sought to fill this gap by examining the cost-effectiveness of universal GT versus three sequential tumor screening strategies in the context of prospectively adjudicated real-world patient tumor screening attrition.

METHODS:We built a lifetime cohort simulation with nested Markovs of CRC probands under three sequential strategies: i) immunohistochemistry (IHC)->GT (base-case); ii) IHC+MLH1 methylation->GT; iii) IHC+BRAF V600E->GT, versus the fourth strategy: universal GT. SEER data and the Prospective Lynch Syndrome Database informed transition probabilities, with adjustment for age-, gender-, cancer-specific mortality and incidence (colorectal, endometrial, ovarian). Costs were assessed and effectiveness was calculated in quality-adjusted life-years (QALY). Cascade testing with a median of 1 identified LS-positive relative was accounted for. Primary outcome was the incremental cost-effectiveness ratio (ICER) in USD/QALY, at a willingness-to-pay (WTP) threshold of $100,000/QALY, in addition to prespecified deterministic and probabilistic sensitivity analyses to explicitly evaluate uncertainty.

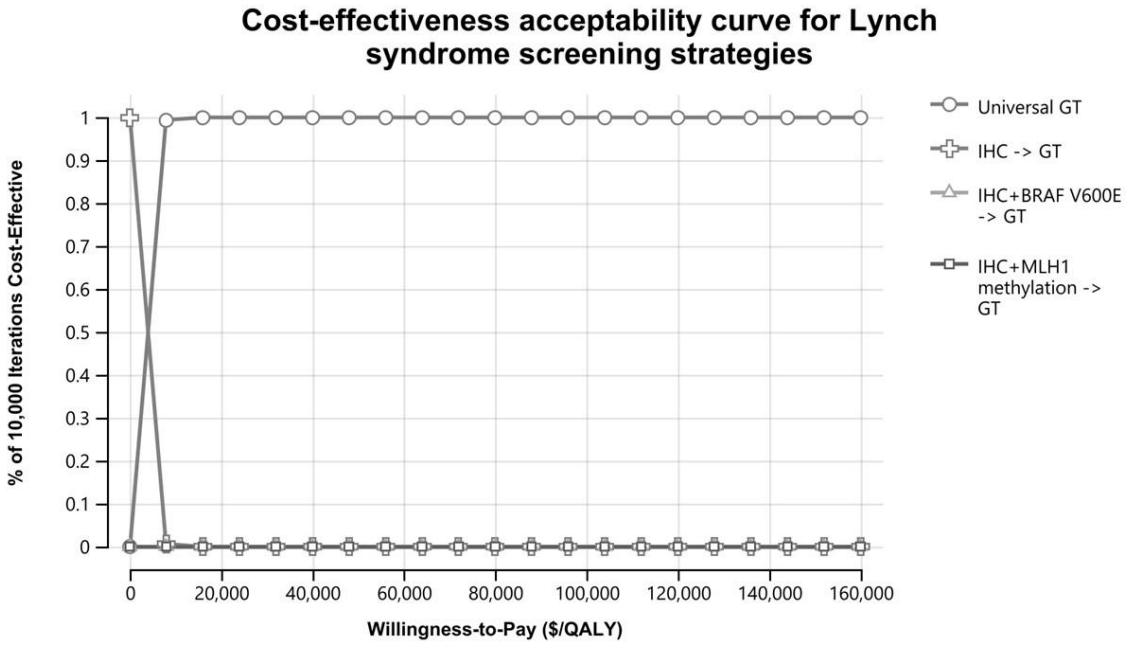
RESULTS:The four strategies accrued 13.05, 13.04, 13.04, and 13.52 QALYs at costs of $100,656, 101,560, 101,787, and $102,245, respectively, with diagnosis identification rates of 25.4%, 24.6%, 24.3% relative to GT. The ICER for universal germline testing, the cost-effective strategy in 100% of 10,000 simulations, was $3,400/QALY [95% credible interval $2,400-7,600/QALY]. Model results were sensitive to the number of identified LS-positive relatives.

CONCLUSIONS:Upfront universal GT is the cost-effective strategy in a real-world US context at a conventional WTP and correctly identifies more patients with LS. Even if sequential tumor screening could increase to 100%, upfront GT remains cost-effective.

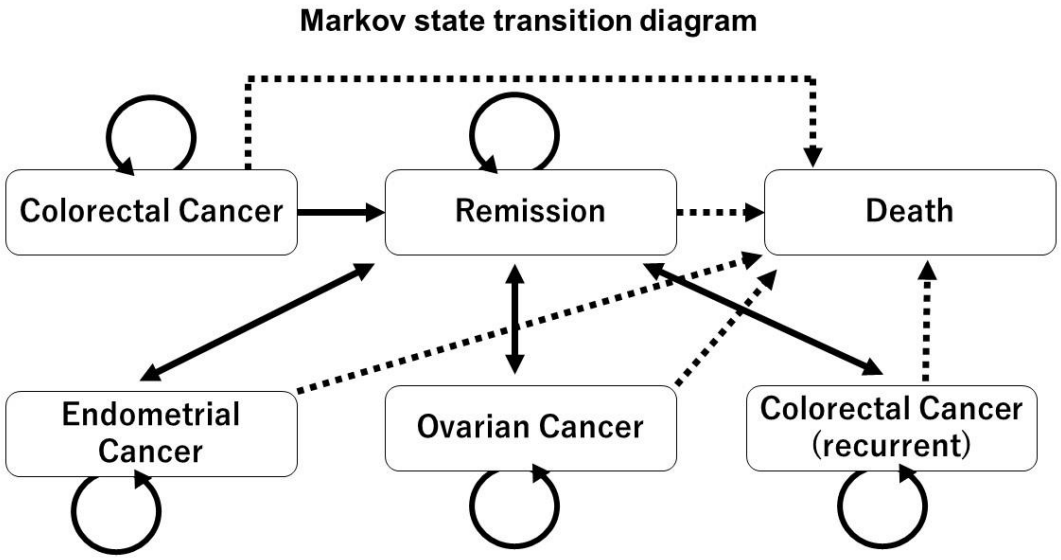
Keywords: cost-effectiveness, hereditary colorectal cancer, decision science, cancer genetics

Cost-effectiveness acceptability curve for Lynch syndrome screening strategies

POSTER ABSTRACTS



Markov state transition diagram



P-093

POSTER ABSTRACTS

General Research » Moderate penetrance genes

COLORECTAL NEOPLASIA IN CHEK2 PATHOGENIC VARIANT CARRIERS

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BACKGROUND:Germline pathogenic variants in CHEK2 are frequently detected by multigene panel testing and associated with an increased risk of colorectal cancer. National guidelines currently recommend colorectal cancer surveillance beginning at an earlier age and at more frequent intervals than average-risk population. The polyp phenotype in CHEK2 carriers is unknown.

\METHODS:This is a single-institution retrospective review of colonoscopies in CHEK2 pathogenic variant individuals. Individuals ≥ 18 years of age who had at least one colonoscopy report in the medical records were included. Advanced neoplasia was defined as the presence of villous features, dysplasia in a serrated lesion, lesions >=1cm, or >=3 lesions.

RESULTS:The twenty-four patients included had a mean age of 53.5 years at index colonoscopy. Fourteen patients had more than one colonoscopy with a median of 2 colonoscopies/individual (range: 2-5) over a median 5.5 years (range:1-12). Of the 45 colonoscopy examinations performed, all were complete examinations to the cecum. Prep quality was reported excellent, good, or adequate in 40/45 (88.9%), fair in 2/45 (4.4%), and poor/inadequate in 3/45 (6.7%). On index colonoscopy, 9/24 (37.5%) had polyps, 3/24 (12.5%) were adenomatous polyps and 3/24 (12.5%) were sessile serrated, of which 3/24 (12.5%) had advanced feature polyps. Out of the lesions biopsied/resected, pathology included adenomatous (10/20, 50%), sessile serrated (6/20, 30%), hyperplastic (3/20, 15%), and adenocarcinoma (1/20, 5%) on index colonoscopy. Median number of polyps on index colonoscopy was 0 (range: 0-5), 5/24 individuals had polyps <1cm, 2/24 1-2cm, and 2/24 >2cm respectively. Over surveillance, 12/22 (54.5%) had polyps, including 1/22 (4.5%) with adenomatous and 6/22 (27.3%) with advanced neoplasia.

CONCLUSIONS:A high prevalence of neoplasia on index colonoscopy as well as over surveillance was found in a small cohort of patients with a pathogenic variant in CHEK2. Further exploration includes analysis of a larger, and more diverse population across multiple regions.

Keywords: CHEK2, moderate penetrance, colon polyps

P-095

General Research » Other

MACHINE LEARNING MODELS IMPACT IN REDUCING VARIANTS OF UNCERTAIN SIGNIFICANCE IN INDIVIDUALS UNDERGOING GENETIC TESTING FOR GASTROINTESTINAL CANCERS

POSTER ABSTRACTS

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BACKGROUND:The classification of missense variants is challenging due to limited evidence. Consequently, many remain categorized as variants of uncertain significance (VUS). VUS are at the core of healthcare disparities, as individuals from racial, ethnic and ancestral (REA) populations underrepresented in large genomic databases and medical literature receive VUS more often. To generate definitive genetic results more equitably across REA groups, we sought to develop gene-specific machine learning (ML) models and evaluate their utility in genetic testing for gastrointestinal and any cancers.

METHODS:From 1/1/2022-5/22/2023, gene-specific ML algorithms (including existing models such as SpliceAI and lab-developed models that leveraged large datasets including gnomAD, AlphaFold protein structures, and others, to model variant effects) were validated and integrated at Invitae. Evidence from these ML models were incorporated into Sherloc, a semi-quantitative variant interpretation framework based on ACMG/AMP guidelines. Only evidence that met a negative or positive predictive value >80% was incorporated during variant interpretation. At least 1 validated model was available for 158 genes during the study period. VUS reduction was calculated, stratified by REA groups.

RESULTS:Of 187,767 (32% from an underrepresented REA group) US based individuals who underwent multigene panel testing for cancer, ~87,400 (47%) had ML evidence applied to ≥1 variant. Models contributed to definitive classification of ≥1 benign/likely benign variant in ~38,500 (21%) individuals and ≥1 pathogenic/likely pathogenic variant in ~1200 (0.6%) individuals. Across any, colorectal, gastric and pancreatic cancer history, a higher percentage of Black (23-30%), Asian (27-34%), and Hispanic (21-32%) individuals had a definitive classification that was dependent on ML evidence compared to White (14-23%, Table).

CONCLUSIONS:Among individuals who had ≥1 variant with ML evidence applied, >20% resulted in a definitive variant classification. ML modeling has demonstrated utility during clinical variant interpretation for cancer, particularly in underrepresented populations.

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General Research » Other

POTENTIALLY ACTIONABLE GERMLINE VARIANTS RATES IN HOMOLOGOUS RECOMBINATION REPAIR GENES IN A LARGE INTERNATIONAL COHORT OUTSIDE OF THE UNITED STATES

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POSTER ABSTRACTS

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BACKGROUND:Identification of pathogenic germline variants (PGVs) in homologous recombination repair (HRR) genes among patients (pts) with breast (BC), ovarian (OC), pancreatic (PaC), and prostate cancer (PrC) is critical to determine potential eligibility for targeted therapies such as PARP inhibitors (PARPi). It is important to evaluate the frequency of PGVs across different regions of the World to help inform the counseling of pts.

METHODS:A retrospective analysis of BC, OC, PaC, and/or PrC pts undergoing GGT through a single laboratory was conducted. Location of the ordering provider determined the assigned region: Asia-Pacific (APAC), Latin America (LATAM), Middle East and African (MEA), and United Kingdom and Europe (UKEU). Analyses were limited to pts tested for PARPi-eligible HRR genes. Descriptive statistics and Chi square with Yates correction were utilized.

RESULTS:The cohort consisted of 40,539 pts with an average age at testing of 51 years. The median number of genes tested ranged from 14-85 (Table). BRCA1 and BRCA2 were the most frequent genes with PGVs (3,358 pts, 8%). LATAM BC pts had significantly higher rates of BRCA1/2 PGVs (10%) than the other 3 regions ($p<0.0007$). OC BRCA1/2 rates were high, and statistically similar, across regions (15-17%, $p>0.08$). Rates of BRCA1/2 and PALB2 in PaC pts did not differ between regions (4-7%, $p>0.08$), nor did rates of BRCA1/2, CHEK2, ATM, and PALB2 in PrC pts (7-11%, $p>0.16$) (Table). In sum, 3,434 pts (9% of those tested for the eligible genes) had PGVs in the above PARPi-eligible HRR genes. A notable limitation is that pts were ascertained by cancer type but information on other PARPi eligibility was not available.

CONCLUSIONS:1 in 12 pts were found to carry PARPi-eligible PGVs across the 4 cancer types and regions analyzed. Knowledge of these PGVs can help inform public health policies, current and future treatment strategies, and identify at-risk family members.

Keywords: homologous recombination repair, international, PARP inhibitor, precision medicine

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Table Nielsen international HRR abstract

Table: Pts with PARPi-eligible PGVs by Region and Cancer Type

Region	Median # of genes tested				Pts tested for PARPi-eligible genes				% pts with PARPi-eligible PGVs*			
	BC	OC	PaC	PrC	BC	OC	PaC	PrC	BC	OC	PaC	PrC
APAC	48	49	50	50	7257	1622	568	533	9	15	4	7
LATAM	84	84	85	85	12202	1319	818	547	10	17	5	8
MEA	85	85	85	85	10410	1135	732	880	7	15	4	7
UKEU	14	48	30	19	2961	174	137	107	7	17	7	10

*BC and OC=*BRCA1/2*; PaC=*BRCA1/2*, *PALB2*; PrC=*ATM, BRCA1/2, CHEK2, PALB2*

P-099

General Research » Other

PARTNERING WITH PATIENTS TO EXPLORE THE PSYCHOSOCIAL AND SOCIOECONOMIC IMPACTS OF HEREDITARY CANCER SYNDROMES

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BACKGROUND:Patient oriented research aims to improve patient outcomes and the quality of research by focusing on patient-identified priorities and engaging patients as partners. Methods for meaningful patient engagement and the role of patient partners in genomics health research are not well described. The aim of this study is to describe the engagement of patient partners in a grant exploring the socioeconomic impacts of

hereditary cancer syndromes (HCS).

METHODS:Six patient partners from 3 provinces with a hereditary breast and ovarian cancer syndrome or Lynch syndrome were recruited. Regular meetings among study staff and patient partners provide consistent communication and co-development opportunities.

RESULTS:Patient partners were invited to engage across all phases of the study: reviewing the grant application, co-developing the study design and materials, and assisting with recruitment, data analysis, and knowledge dissemination. Offering choice in level of involvement is best practice for patient engagement and allows them flexibility around their contributions. Patient partners meet quarterly with the study team, with email communication in between, to provide feedback on study design and materials. Opportunities to review study material on their own time allows for equitable involvement when attending meetings is not always feasible. As this study involves qualitative interviews and data collection about sensitive topics, patient partners' lived experiences have informed study materials. To date, patient partners provided feedback on the qualitative portion of the study. Feedback on early iterations of the interview guide revealed a bias towards negative language about the impact of HCS. Partners reminded the team that there were positive impacts as well and cautioned about the use of exclusively negative language.

CONCLUSIONS:Patient partners provide important insights on the study population and methods. Their role reflects true research co-development. Ultimately, our aim is to build a rigorous patient-oriented research program in hereditary cancers, informed by patient voices.

Keywords: Hereditary cancer syndrome, patient partners, co-designing research, Lynch syndrome

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P-100

General Research » Other

A COMPREHENSIVE ANALYSIS OF THE GENOMIC PROFILE OF POLE/POLD1 MUTATIONS IN METASTATIC COLORECTAL CANCER (CRC)

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POSTER ABSTRACTS

BACKGROUND:Pathogenic mutations in POLE/POLD1 lead to decreased fidelity of DNA replication, resulting in a high tumor mutational burden(TMB-H ≥10 Mt/Mb) independent of deficient mismatch repair(dMMR) and high microsatellite instability(MSI-H); thereby, POLE/POLD1 mutations were reported as potential biomarker for response to immunotherapy treatment. The genomic landscape of POLE/POLD1 mutations in colorectal cancer (CRC) remains unclear. Here, we report the characteristics of POLE/POLD1 mutations in a large real-world cohort of primary metastatic CRC.

METHODS:De-identified records of CRC patients profiled with Tempus xT assay (DNA-seq of 595-648 genes at 500x). Immunological markers analyzed included TMB, MSI, and dMMR. MSI-H was determined through assessment of 239 loci, while dMMR was determined by immunohistochemistry.
RESULTS:Among 9,136 patients with mCRC, 3% (n= 217) harbored somatic POLE/POLD1 mutations (n= 203 POLE, 14 POLD1). No significant differences in the median TMB between the mutant versus (vs.) the wild type (WT) (5 vs. 4 mutations/megabase). However, POLE/POLD1 mutant tumors had a higher frequency of TMB-H (22% vs. 9.9%, p< 0.001), while MSI-H was lower compared to WT tumors (1.8% vs. 6.1%, p=0.018). Among the POLE/POLD1 mutant cohort, copy number loss was the most common genetic variation (59% POLE, 5% POLD1) followed by short variant mutation and copy number amplification. Interestingly, all the 39 tumors (18%) with short variant mutations had TMB-H phenotype, with Pro286Arg, Val411Leu and Ser297Phe being the common amino acid changes. POLE/POLD1 mutant tumors exhibited a higher co-mutation frequency than WT tumors. The most common genetic co-mutations in the mutant group were APC, ALK, LRP1B, RET and NTRK3 (p<0.001). A higher load of co-mutations was noticed in TMB-H vs. TMB-low POLE/POLD 1 mutant subgroups, mainly APC, LRP1B, KMT2C, PIK3CA, BRCA1/2 and PTEN (p<0.05).
CONCLUSIONS:Our findings provide insights on the prevalence, genetic characteristics and co-mutations associated with POLE/POLD1 mutant CRC. Our study highlights the need for further research to understand the clinical significance and implications of POLE/POLD1 mutations in CRC.

Keywords: Immunotherapy, Colorectal Cancer, Mutations, Biomarkers, Tumor Burden/genetics

POLE/POLD1 Mutations and comutations

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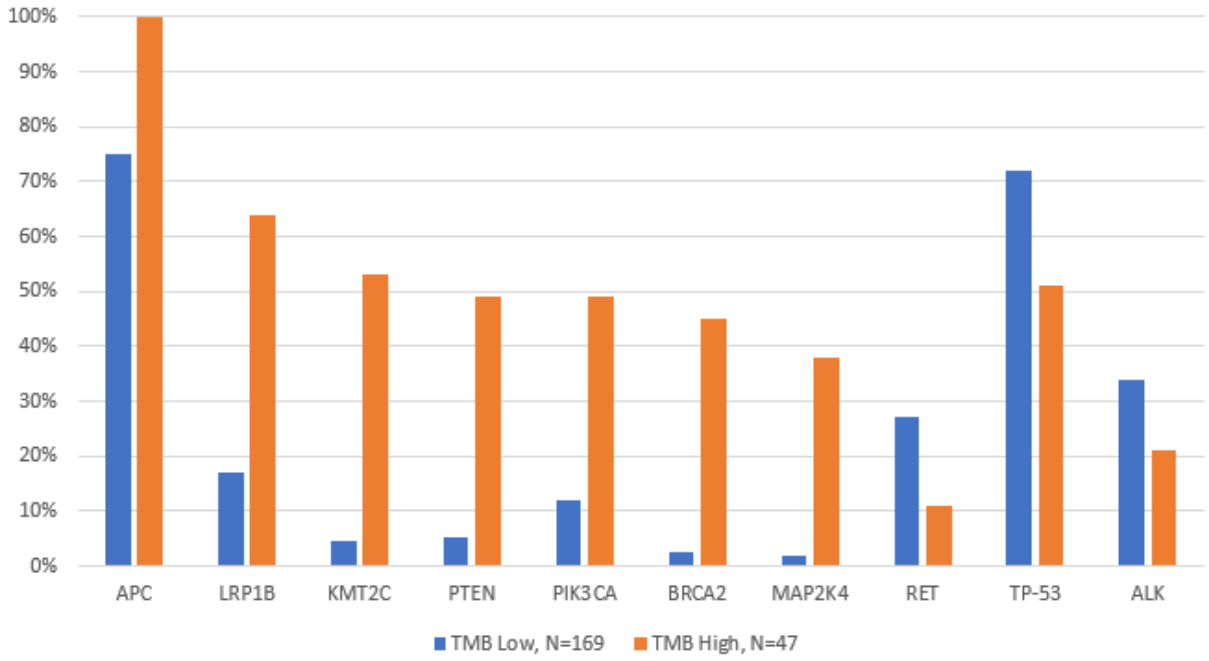
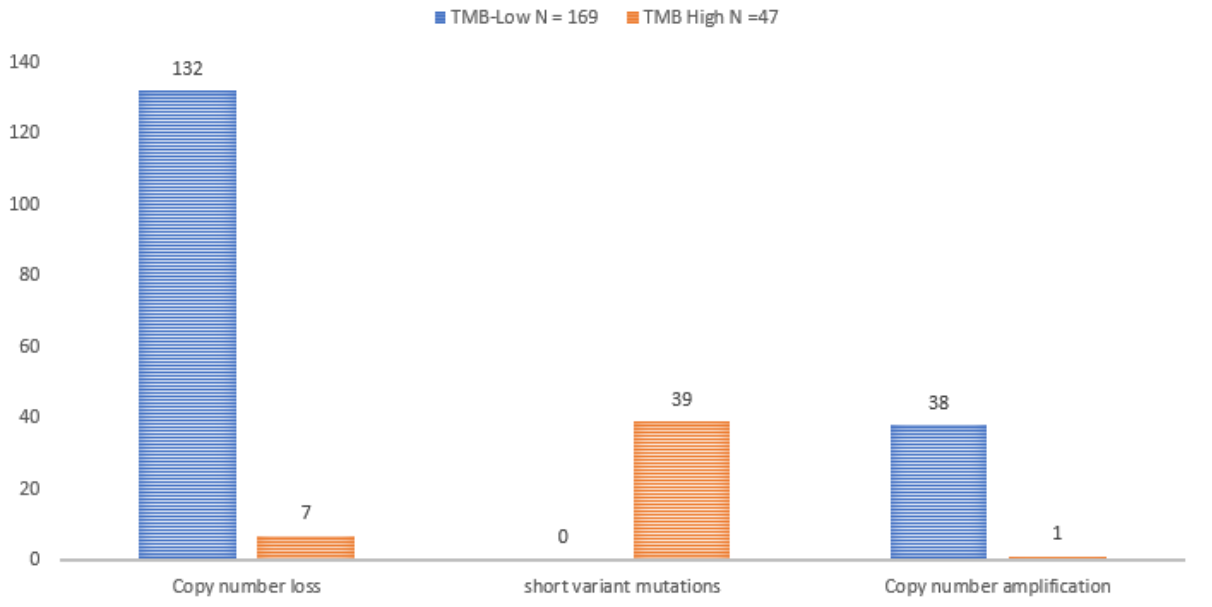


A higher load of co-mutations in TMB-H vs. TMB-low POLE/POLD1 mutant subgroups, mainly APC, LRP1B, KMT2C, PIK3CA, BRCA2, MAP2K4 and PTEN (p<0.05), While TP-53, ALK and RET were most frequently noticed among the TMB-Low subgroup.

POLE/POLD1 Mutations and Genetic Alterations



Copy number loss was the most common genetic variation in the TMB-Low POLE/POLD1 mutant subgroup Vs. Short variant alterations in the TMB-H subgroup.

POSTER ABSTRACTS

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General Research » Pancreatic cancer-related syndromes

FREQUENCY OF REFERRAL OF PATIENTS DIAGNOSED WITH PANCREATIC CANCER FOR CANCER GENETIC COUNSELING AND TESTING AT A SINGLE ACADEMIC MEDICAL CENTER

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BACKGROUND:In 2019, the National Comprehensive Cancer Network recommended universal germline genetic testing for all patients diagnosed with pancreatic adenocarcinoma (PDAC) to guide treatment and familial cancer risk assessment. National rates of referral and completion are reported to be suboptimal. Understanding actual referral and testing patterns can help guide clinical and research innovation. We are conducting a mixed-method study to understand low uptake in universal germline testing in patients with PDAC. Here we present the quantitative findings of referral and completion of genetic testing in PDAC; qualitative findings will be presented at a later date.

METHODS:Data were extracted retrospectively from the electronic medical record and the institution's cancer registry. All adult patients with PDAC treated from May 31st, 2019, through August 31st, 2022 were included. Descriptive statistics summarized the study population and rates of referral, testing, and testing results.

RESULTS:The mean (SD) age of N=338 patients was 73.05 (10.25). Most were White (90.5%), non-Hispanic (51.2%), and female (51.2%). Prior to evaluation at our institution, 11.8% (40) patients had already completed genetic testing. Among the remaining 298 patients, 55.7% (166) were referred for genetic testing, of which 64.5% completed genetic testing. In total, 145 (42.8%) of the 338 patients treated for PDAC completed genetic testing. In those who completed testing, 6.2% (21) were found to have a pathogenic variant, 8.6% (29) had a variant of uncertain significance. Details on pathogenic variants found included: CHEK2 (4) ATM (6) BRCA2 (3) BRCA1 (2) APC (2) CKDN2A (1) HOXB13 (1) BLM (1) and NTHL1 (1).

CONCLUSIONS:Referral and completion are consistent with national averages and require intervention to improve both the referral and the actual completion of testing. Further qualitative data collection will provide insight into the context and process driving these patterns to identify areas for tailored intervention.

Keywords: pancreatic ductal adenocarcinoma, genetic testing, implementation science

Figure

POSTER ABSTRACTS

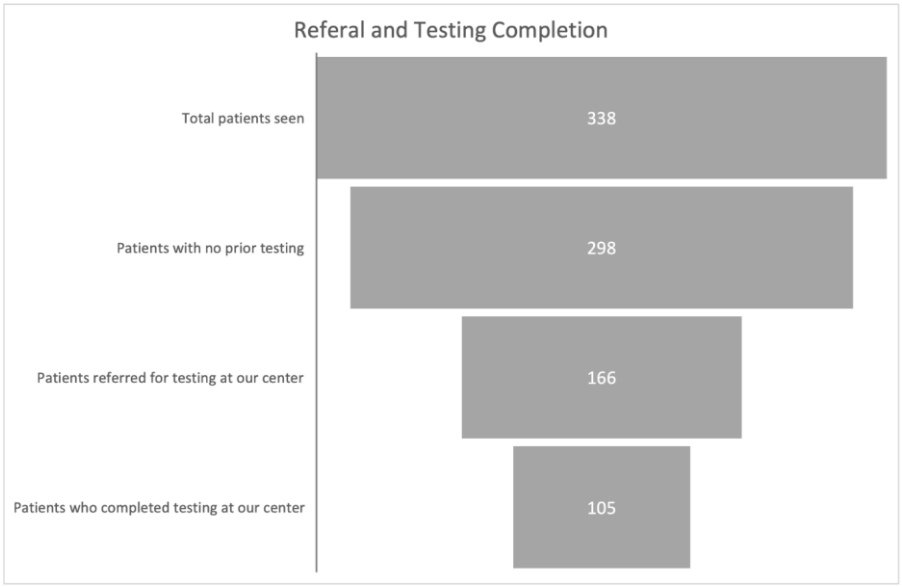
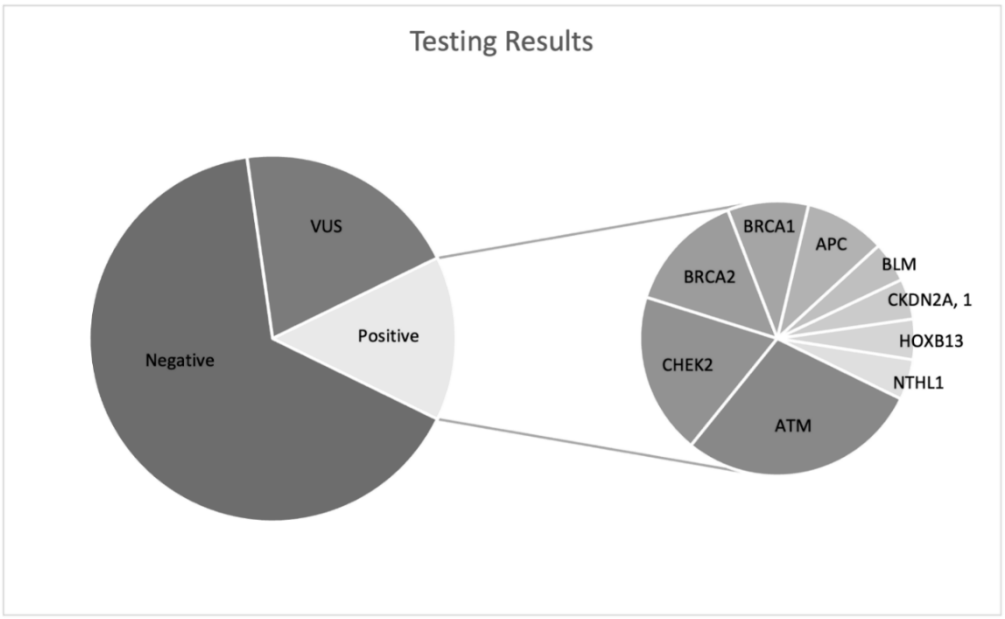


Figure 2



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POSTER ABSTRACTS

General Research » Delivery of Care and Alternative Models

PATIENT-FACING EDUCATIONAL AND RELATIONAL AGENT "PERLA" FOR CANCER GENETIC TESTING

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BACKGROUND:The volume of patients who meet national criteria for germline genetic testing based on a cancer diagnosis is rapidly growing. Traditional pre- and post-test genetic counseling approaches may not be sufficient to meet the growing need. Patients cared for in settings with limited or no genetic services, including low-literacy, non-English speaking, and rural communities already face disparities in access. As such, innovative strategies to optimize genetic counseling approaches are needed. Relational Agents (RAs) are an effective means of automating health education and counseling, as well as overcoming literacy barriers in the use of information technologies. RAs, animated computer characters simulate face-to-face conversation between a patient and a provider using verbal and nonverbal conversational behavior.

METHODS:Here we will describe an ongoing trial to develop and evaluate an English and Spanish RA to communicate personalized pre-test genetic education to a cohort of cancer patients who meet established cancer-based genetic testing criteria across two diverse clinical settings. We hypothesize that the use of an RA will increase the proportion of patients who receive genetic test results within 90 days of initiating cancer care, compared to usual care. Aim 1 is to develop an English- and Spanish-language RA using a patient-driven approach. Aim 2 is to conduct a multisite randomized controlled trial of the RA to deliver pre-test education versus usual care in English- and Spanish-speaking patients to compare the proportion in each arm who receive genetic test results in 90 days. Aim 3 is to understand the implementation.

RESULTS:Preliminary study enrollment, participation, and findings to date will be shared. Barriers and facilitators to study implementation will be discussed.

CONCLUSIONS:If successful, this would be a novel, effective, and scalable means of providing genetics education that could ultimately lead to increased access for patient populations who are traditionally underserved in genetics.

Keywords: genetic testing; relational agent; randomized control trial; implementation science

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POSTER ABSTRACTS

General Research » Pancreatic cancer-related syndromes

PREVALENCE AND PENETRANCE OF SPINK1 PATHOGENIC VARIANTS: A BURDEN TO PATIENTS AND PROVIDERS

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BACKGROUND:SPINK1 is associated with hereditary chronic pancreatitis. N34S (c.101A>G; p.Asn34Ser), a common SPINK1 variant, is reported to be present in 1-2% of the general population. Most studies exploring SPINK1 were conducted in populations affected by pancreatitis and pancreatic cancer. There is a paucity of data regarding the penetrance of pancreatitis among individuals with SPINK1 variants in an unselected population.

METHODS:Results of patients undergoing germline multigene panel testing (MGPT) through the INSPIRE study at City of Hope from 7/1/2020 – 6/12/2023 were reviewed. Medical record abstraction was performed for patients with variants identified in SPINK1 to assess for personal or family history of pancreatitis or pancreatic cancer and other risk factors.

RESULTS:14,254 individuals have undergone MGPT. 208 unique patients had heterozygous variants identified in SPINK1 (1.5%). The majority (203; 97.6%) had the N34S increased risk allele. Eight patients had a personal history of pancreatitis (8/208; 3.8%), of which all had the N34S variant and one had a family history of pancreatitis in a first-cousin. Only 3 (1.4%) could be considered chronic (2) or severe (1 necrotizing pancreatitis in a patient with a 54 pack-year smoking history) and potentially associated with the SPINK1 variant. Among the 5 patients with isolated episodes of acute pancreatitis; 3 were associated with a concomitant pancreatic cancer diagnosis (1 PDAC, 1 PNET, and 1 solid pseudopapillary carcinoma), 1 was associated with cholelithiasis, and 1 was associated with widely disseminated metastases. Among unaffected patients, 7 reported a family history of pancreatitis; 5 of which were first-degree relatives.

CONCLUSIONS:SPINK1 variants are common in the general population and rarely associated with chronic pancreatitis. We recommend that individuals found to have an incidental SPINK1 variant on MGPT receive counseling on lifestyle modifications but do not undergo evaluation or surveillance for pancreatitis unless there is suggestive personal or family history of pancreatitis.

Keywords: Hereditary, chronic pancreatitis, SPINK1

POSTER ABSTRACTS

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General Research » Pancreatic cancer-related syndromes

RISK PERCEPTION AND SURVEILLANCE PRACTICES IN INDIVIDUALS AT INCREASED RISK FOR PANCREATIC DUCTAL ADENOCARCINOMA

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BACKGROUND:Surveillance uptake and adherence for at-risk individuals of pancreatic ductal adenocarcinoma (PDAC) may depend on the perception of PDAC risk and cancer worry. We aimed to determine PDAC risk perception in high-risk individuals and to assess factors associated with PDAC surveillance practices.

METHODS:A questionnaire was sent electronically to individuals with a PDAC-associated pathogenic genetic variant (PGV) and/or first- or second-degree relatives with PDAC. PDAC risk perception, cancer worry, and surveillance uptake were surveyed, and factors associated with increased risk perception and surveillance assessed. Five-year PDAC risk was calculated using PancPRO risk assessment model and correlation with subjective risk assessment was assessed.

RESULTS:Overall, 279/816 (34%) completed the survey. Median perceived PDAC risk was 2-fold (interquartile range 1-4) above respondents' estimates of general population risk. Table 1 summarizes respondents' perceived risk by demographics, personal & family history and general PDAC knowledge. Factors associated with higher perceived risk included non-Hispanic white race, higher education level, affected first degree relative, and a personal cancer history or presence of PGV. Using the PancPRO model, there was no correlation between perceived PDAC risk and 5-year calculated PDAC risk (r=0.003, p=0.96). Older age (OR 1.04, p=0.01), having a first-degree relative with PDAC (OR 3.03, p=0.01), speaking with a medical provider about PDAC cancer risk (OR 2.3, p<0.001) and being aware that surveillance modalities exist (OR 8.3, p=0.008) were significant predictors of undergoing PDAC surveillance. Cancer worry had a very weak correlation across PDAC risk estimates (r=0.16, p=0.013, Figure 1).

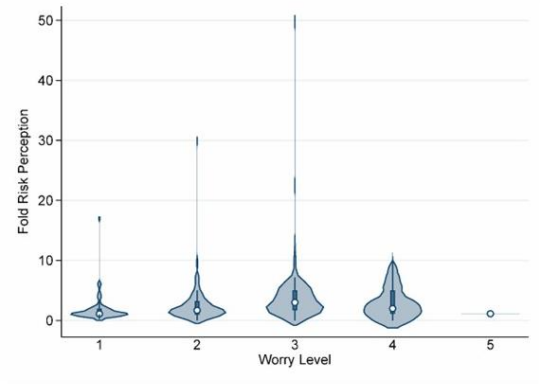
CONCLUSIONS:Individuals at-risk for PDAC do not report accurate perception of their risks. This presents an opportunity for counseling of at-risk patients in order to individualize management and improve surveillance uptake for eligible individuals.

Keywords: pancreatic cancer, risk perception, pancreatic surveillance

POSTER ABSTRACTS

Figure 1

Figure 1. Correlation between risk perception and respondents' cancer worry



1- never, 2- seldom, 3- sometimes, 4- often, 5- all the time
Fold-risk: Respondent's perceived personal PDAC risk divided by perceived general population risk

Table 1

Table 1: PDAC risk perception by demographics, practices and beliefs.

		n (%)	Median perceived PDAC risk fold-change* (IQR)	p-value
Demographic factors				
Age	<50	91 (40.4)	2.0 (1.1 – 5.0)	0.149
	≥50	134 (59.5)	1.9 (1.0 – 3.0)	
Sex	Male	53 (23.2)	2.0 (1.0 – 3.9)	0.973
	Female	175 (76.7)	2.0 (1.1 – 4.0)	
Race	White	205 (91.1)	2.0 (1.1 – 4.0)	0.012
	Black	13 (5.7)	1.0 (1.0 – 1.4)	
	Asian	5 (2.2)	1.1 (1.0 – 4.2)	
	Mixed	2 (0.9)	1.6 (1.1 – 2.0)	
Highest Education level	High school or less	30 (13.1)	1.1 (1.0 – 2.0)	0.004
	Undergrad	76 (33.3)	1.9 (1.0 – 3.2)	
	Post-grad	122 (53.5)	2.0 (1.2 – 5.0)	
Pathogenic genetic variant	Yes	187 (86.5)	2.0 (1.1 – 4.0)	0.008
	No	29 (13.4)	1.1 (1.0 – 2.0)	
Personal cancer history	Yes	105 (45.4)	1.7 (1.0 – 3.0)	0.024
	No	126 (54.5)	2.0 (1.2 – 5.0)	
FDR with PDAC	Yes	58 (25.1)	2.1 (1.4 – 5.0)	0.017
	No	173 (74.9)	1.8 (1.0 – 3.6)	
Practices & Beliefs				
Discussed cancer risk with provider	Yes	145 (62.7)	2.6 (1.5-5)	<0.001
	No	86 (37.2)	1.1 (1-2)	
Thinks PDAC is usually found early	True	63 (27.5)	1.5 (1-3)	0.042
	False	166 (72.4)	2 (1.1-4.4)	
Thinks PDAC can be asymptomatic	True	216 (94.3)	2 (1.1-4)	0.01
	False	13 (5.6)	1.2 (0.6-1.7)	
Knows screening for PDAC exists	True	176 (77.5)	2 (1.1-2.4)	0.06
	False	51 (22.4)	1.7 (1-2.4)	

Fold-risk: Respondent's perceived personal PDAC risk divided by perceived general population risk; FDR – first degree relative; PDAC – pancreatic ductal adenocarcinoma

POSTER ABSTRACTS

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General Research » Pancreatic cancer-related syndromes

PREVALENCE OF FAMILIAL PANCREATIC CANCER AND INHERITED CANCER SYNDROMES IN PANCREATIC CANCER PATIENTS IN ICELAND 2000-2021

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BACKGROUND:Approximately 5-10% of pancreatic ducal adenocarcinoma (PDAC) are familial, defined as ≥2 first-degree relatives or ≥3 relatives with PDAC on the same side of the family. Furthermore, around 10% of PDAC is caused by inherited cancer syndromes. The aim of this study was to identify the prevalence of familial pancreatic cancer from 2010 to 2021 and hereditary cancer syndromes in PDAC patients in Iceland from 2000 to 2021.

METHODS:This retrospective population-based study included all exocrine PDAC cases diagnosed 2000-2021 per the Icelandic Cancer Registry. Information about patients' family histories was obtained from PedigreeAssistant, based on a genealogical database linked to the Icelandic Cancer Registry. Results from genetic testing were retrieved from the medical chart. Data was analysed in Excel and Rstudio. The study was approved by the Institutional Review Board.

RESULTS:A total of 774 patients were diagnosed with PDAC in 2000-2021. Between 2010-2021, 482 patients were diagnosed of whom 84 (17.4%) fulfilled familial pancreatic cancer criteria. Around 20% of patients with familial pancreatic cancer underwent genetic testing, of whom 23.5% had a pathogenic or likely pathogenic germline variant. During 2000-2021, 76 (9.8%) patients underwent genetic testing, of whom 15 (19.7%) had a pathogenic or likely pathogenic germline variant. Pathogenic variants in BRCA2 were most frequent, found in six patients, followed by pathogenic variants in ATM, BRCA1, and BRIP1.

CONCLUSIONS:The prevalence of familial pancreatic cancer in Iceland was 17% which is higher than expected. In previous studies, information about patients' family histories was frequently based on memory but, in this study, recall bias was prevented by using a genealogical database linked with the Icelandic Cancer Registry. Only 10% of patients underwent genetic testing during the 22-year period, and of those tested, the prevalence of pathogenic variants was 20% which could be due to selection bias.

Keywords: Familial pancreatic cancer, hereditary cancer syndromes, genetic testing