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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-01

Research Categories » Moderate penetrance colorectal cancer syndromes

DISTRIBUTION AND CHARACTERIZATION OF GASTROINTESTINAL TUMORS SEEN IN CANCER PATIENTS WITH GERMLINE PATHOGENIC OR LIKELY PATHOGENIC VARIANTS IN *CHEK2*

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BACKGROUND: Germline pathogenic/likely pathogenic variants (PV) in *CHEK2* have been linked to increased risk for gastrointestinal (GI) cancers, with most studies focused on colorectal cancer (CRC). We aimed to characterize GI tumors among *CHEK2* PV carriers.

METHODS: Retrospective review of patients (pts) consented to an IRB-approved matched tumor/normal next-generation sequencing (NGS) protocol from 12/2015 through 1/2020. Pts with GI tumors and underlying *CHEK2* PV were identified. Pts that also had another high-risk GI-associated PV were excluded. Tumors were assessed for loss of heterozygosity (LOH) using the FACETS algorithm. Clinical data were abstracted and correlated using non-parametric tests.

RESULTS: Of 16,172 pan-cancer pts, 30%(4931) had GI tumors: 12%(1971/16,172) CRC, 12%(1880) pancreatic, 1.8%(305) gastric, and 4.8%(775) other. 2%(317) of all pan-cancer pts had underlying germline *CHEK2* PV's. There was a 1.6%(78/4931) *CHEK2* PV prevalence in pts with GI tumors overall [CRC:1.5% (29/1971), pancreatic: 1.5%(28/1880), other: 1.5%(12/775)], compared to 3%(9/305) gastric (p=0.048; gastric vs. non-gastric GI). LOH data was available for 69% (54/78) of tumors. Only 22% (12/54) of tumors demonstrated LOH of the *CHEK2* wildtype allele, which did not differ by tumor type, likely due to sample size [CRC: 26%(6/23), pancreas: 27%(4/15), gastric: 33%(2/6), other: 0%(0/10) p=0.48]. 10% (26/261) of pts with *CHEK2* founders [c.1100delC (5/54), p.I157T (12/124), and p.S428F (9/83)] had CRC, compared to 5% (3/56) with non-founder *CHEK2* PV, though this was not statistically significant (p=0.28). The mean age at CRC diagnosis did not differ between *CHEK2* PV carriers and germline-negative CRC pts (53 vs. 54, respectively; p=0.6).

CONCLUSIONS: *CHEK2* PVs were seen in pts with a wide array of GI tumors, with a slight enrichment in gastric cancer compared to other GI cancers. A limited subset of tumors demonstrated LOH, which did not vary by tumor origin. Larger studies are needed to further refine *CHEK2*-associated GI cancer risks.

Keywords: CHEK2, GI cancer, moderate penetrance

O-02

Case Reports » Case Series on any topic

GERMLINE *MBD4* DEFICIENCY IN PATIENTS WITH COLONIC POLYPOSIS AND ACUTE MYELOID LEUKEMIA (AML)

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BACKGROUND: *MBD4* has recently been associated with recessive predisposition to colorectal polyposis and early-onset acute myeloid leukemia (AML). Loss of the base excision repair function of *MBD4* allows CG to TG mutations to accumulate causing the predisposition. Few cases of *MBD4* deficiency appear in the literature, and prevalence is unknown.

METHODS: Clinical presentation

RESULTS: We present three cases of patients with *MBD4* deficiency from two Ohio centers. Case 1: A 28-year-old female who experienced an unusually long and painful recovery from surgical resection of a recurrent rectal tubulovillous adenoma and was subsequently diagnosed with AML. Germline multigene panel testing revealed biallelic loss-of-function variants in *MBD4*, one truncating and one frameshift. Case 2: A 45-year-old female presenting with bilateral vestibular schwannoma, history of adenomatous polyposis requiring colectomy at age 33, AML at 35, and papillary thyroid cancer. Her brother had colorectal cancer at age 24 in the setting of polyposis, lymphoma, and AML. Germline exome sequencing identified biallelic truncating variants in *MBD4*. Somatic genetic testing of her leukemia, thyroid cancer, a schwannoma, and an adenoma revealed acquired C to T mutations in driver genes consistent with each neoplasm, including biallelic pathogenic *APC* variants in the adenoma. Case 3: A 50-year-old male with history of adenomatous polyposis diagnosed at 29 and AML at age 37. Initial germline multigene panel testing was negative. Expanded panel testing found biallelic variants in *MBD4*, one frameshift and one splice mutation. Our experience suggests that several individuals with this predisposition may remain unidentified. *MBD4* is not routinely interrogated on most multigene cancer predisposition panels, but our cases illustrate that individuals with adenomatous polyposis and early-onset AML, including in the absence of family history, should be evaluated.

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

Keywords: MBD4, Polyposis, Leukemia

O-03
Research Categories » Gastric cancer-related syndromes

YOUNG-ONSET GASTRIC CANCERS ARE OFTEN EARLY GASTRIC CANCERS

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ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

BACKGROUND: The incidence of young-onset gastric cancer (YOGC), defined as GC before 50, is rising. Previous works claimed that YOGC has a worse prognosis than in the elderly. The underlying cause of YOGC remains unclear and the clinicopathological characteristics incompletely understood

METHODS: We conducted a cohort study of patients with YOGC diagnosed from 2015 to 2021. We collected clinical and familial data and performed multi-gene panel testing on all. We evaluated the histological subtype and the presence of H.Pylori (HP) from available samples

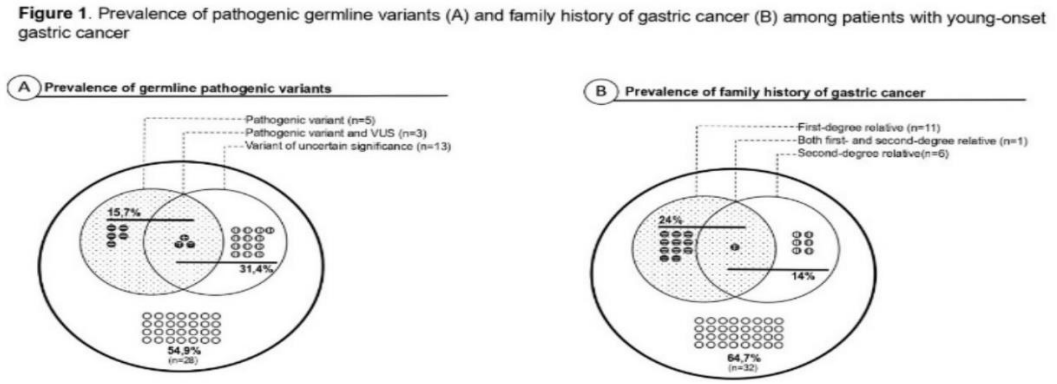
RESULTS: We included 51 patients with YOGC (52.9%M, 47.1%F; median age 42±7.5y). HP status was evaluated on 31 patients (66.6%): 31% had HP, 9.6% eradicated HP. 54.8% were HP-negative and presented with a more advanced stage than HP-positive YOGC (mean stage: III vs I, p<0.05). 27.5% drank alcohol daily (2.5±1.66 units/day), 23.5% sometimes, and 49% never; 25.5% were smokers, 23.5% former smokers (average cigarette consumption: 17,6±12,1/day), and 51% were non-smokers. 13.7% were both drinkers and smokers. 15.8% had a germline pathogenic variant (4 CDH1; 1 EPCAM; 1 PTEN; 2 TP53). 64.7% had no family history of GC, 25.4% reported a first degree relative with GC and 13.7% a second degree relative with GC (F1). 25.4% of YOGC were at the gastric body, 23.5% at the antrum, and 23.5% at the cardia. 66.6% were diffuse-type adenocarcinoma and 19.6% intestinal-type. 23.5% of YOGC were early gastric cancers (EGC), 54.3% had tumor staging of T3 and above. 50% of EGCs had a family history of GC and 16.6% had a germline pathogenic variant (T1).

CONCLUSIONS: YOGC often presents as diffuse-type adenocarcinoma. One in six patients with YOGC has a germline pathogenic variant, suggesting that all patients should receive panel testing at diagnosis. One in four YOGCs presents with early gastric cancer, possibly implying that younger age does not entail worse outcomes.

Keywords: Stomach, early-onset, helicobacter, early gastric cancer

Figure 1

Prevalence of pathogenic germline variants (A) and family history of gastric cancer (B) among patients with young-onset gastric cancer



ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1

Chief presenting complaint of young-onset gastric cancer patients with early-gastric cancer (pT1)

Table 1. Chief presenting complaint of young-onset gastric cancer patients with early-gastric cancer (pT1)

N	T stage	Chief complaint
1	T1	Epigastric pain
2	T1	Unknown
3	T1	Dyspnea, epigastric pain, peptic ulcer-like symptoms
4	T1	Heartburn, epigastric pain
5	T1a	Diarrhea
6	T1a	Family history of young-onset gastric cancer, epigastric pain
7	T1a	Dyspepsia, nausea, epigastric pain
8	T1b	Family history of young-onset gastric cancer, epigastric pain, nausea
9	T1b	Dyspepsia
10	T1b	Iron-deficiency anemia, previous history of rectal desmoid tumor
11	T1b	Hereditary diffuse gastric cancer (HDGC), deceased first-degree relative with HDGC
12	T1b	Family history of young-onset gastric cancer

O-04

Research Categories » Gastric cancer-related syndromes

CTNNA1 GERMLINE VARIANTS ASSOCIATE WITH A DISEASE SPECTRUM EXTENDING BEYOND HEREDITARY DIFFUSE GASTRIC CANCER

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BACKGROUND: *CDH1*-associated Hereditary Diffuse Gastric Cancer (HDGC) predisposes to diffuse gastric cancer (DGC) and/or lobular breast cancer (LBC). *CTNNA1*/αE-catenin germline truncating pathogenic variants cause HDGC and missense variants cause Macular Dystrophy Patterned-2. The full *CTNNA1*-disease spectrum and variant-type associated causality is unknown. Large cohorts and in vivo models are essential to disclose genotype-phenotype associations.
METHODS: Collaboration with ERN-GENTURIS partners, external Institutions and literature search, allowed collecting clinical data on 67 probands and 142 relatives *CTNNA1* germline variant carriers/relatives. We molecularly/clinically classified variants; categorized families according to HDGC-criteria and analyzed genotype-phenotype correlations. We developed a *Drosophila melanogaster* αE-catenin-knockdown model to study *CTNNA1* impairment in different tissues.

RESULTS: Sixty-seven families carried rare *CTNNA1* germline variants, being 32% Pathogenic (PV) and 32% Likely Pathogenic (LPV), all truncating. Early-onset DGC and Breast Cancer of unknown-histotype (BC) were the predominant phenotypes. In PV-carriers, DGC predominated (42%), followed by LBC (5%) and other HDGC non-classical cancer phenotypes, such as Colorectal, Prostate and Thyroid cancer (6%, 5% and 4%, respectively). LPV-carriers developed mainly BC and Melanoma (59% and 7%, respectively). Phenotypes differed significantly between PV- and LPV-families ($p<0.00001$). Most PV- and LPV-related cancers were early-onset. *Drosophila* α-catenin knockdown in wing and eye primordial tissues induced fly lethality, and surviving flies presented aggressive phenotypes and comorbidities. Human wild-type αE-catenin expression in the eye rescued fly survival and organ development, while a human αE-catenin bearing a HDGC-PV failed to rescue both abovementioned parameters.

CONCLUSIONS: Early-onset DGC/LBC are frequent cancers in *CTNNA1* PV-carriers, however, disease spectrum extends beyond HDGC-classical phenotypes. *CTNNA1* LPV-carriers disease spectrum diverges from classical-HDGC. Current data claims for phenotype-driven *CTNNA1*-specific variant classification rules, which can be supported by robust in vivo testing models, as the one we developed. The humanized *Drosophila* model enables functional analysis of *CTNNA1* germline variants in a tissue specific manner.
Acknowledgements: FCT-PhD fellowship(Ref:2020.05773.BD); LEGOH Project(Ref:PTDC/BTM-TEC/6706/2020); ERN-GENTURIS(Project-ID No.739547).

Keywords: CTNNA1, Hereditary Diffuse Gastric Cancer, Germline Variants, Genotype-Phenotype Associations

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-05

Research Categories » Lynch syndrome

DISPARITIES IN THE UPTAKE OF CASCADE GENETIC TESTING AMONG FAMILY MEMBERS OF MUTATION-POSITIVE LYNCH AND HBOC SYNDROME PATIENTS

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BACKGROUND: Cascade testing (CT) involves genetic testing of at-risk biologic family members after the identification of a pathogenic/likely pathogenic variant (P/VLP) in a proband. Studies comparing uptake of CT based on proband race/ethnicity, age, socioeconomic status (SES), and genetic syndrome are limited.

METHODS: A retrospective data analysis was utilized to identify probands with a P/VLP in Lynch syndrome (LS), BRCA1/2, or other HBOC syndrome genes (ATM, CHEK2, PALB2) at a commercial testing laboratory. An individual was considered to have CT if they underwent any type of genetic testing that included analysis of the known familial P/VLP after the proband. The rates of CT based on the proband's age at testing, gene(s) impacted, racial/ethnic group, and SES determined by the median household income of the proband's zip code were studied. SES was controlled for when evaluating the impact of race and ethnicity on CT utilization.

RESULTS: From December 2016 through May 2018, 6237 patients tested positive for a P/VLP in LS or HBOC genes, with 20.36% having at least one family member undergo CT. White probands had the highest rate of CT, even after adjustment for SES (see Table 1). No significant differences in uptake were observed between low, medium, and high-SES groups. The age of the proband impacted the rate of CT, with older probands (40+) being significantly more likely to have relatives undergo CT (see Table 2). Probands carrying a P/VLP in a LS gene had an uptake rate of 23.38%, compared to 20.30% in probands with a P/VLP in BRCA1/2 (p=0.043).

CONCLUSIONS: CT is underutilized, particularly by family members of non-white and young probands. Identifying barriers to CT is necessary to develop outreach alternatives and interventions that will increase the utilization of CT for families of younger probands (<40) and non-white racial/ethnic groups. Future studies will examine how gratis CT affects uptake.

Keywords: cascade testing, Lynch syndrome, HBOC syndrome, BRCA1/2, health disparities

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

Table 1

Table 1. Utilization of Cascade Testing Based on Proband Race/Ethnicity

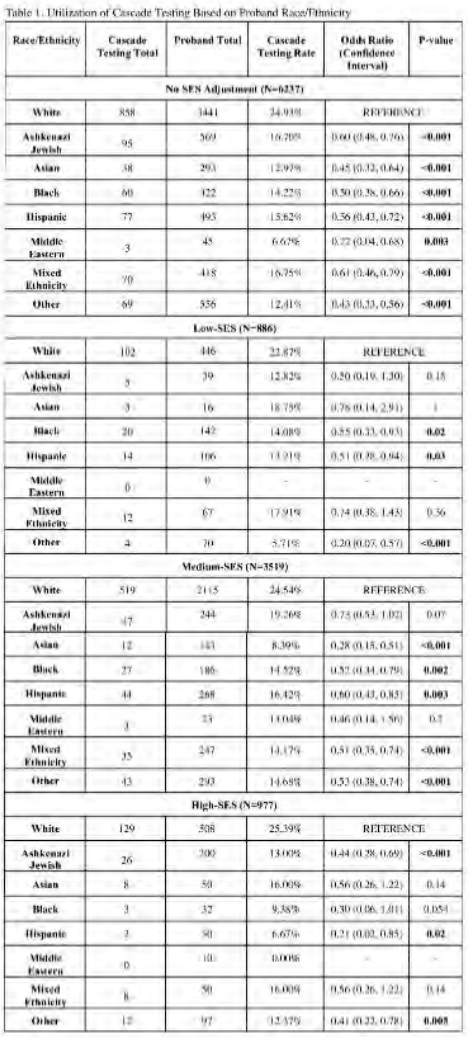

Table 1. Utilization of Cascade Testing Based on Proband Race/Ethnicity

Race/Ethnicity	Cascade Testing Total	Proband Total	Cascade Testing Rate	Odds Ratio (Confidence Interval)	P-value
No SES Adjustment (N=6237)					
White	858	3441	24.93%	REFERENCE	
Ashkenazi Jewish	95	569	16.70%	0.61 (0.48, 0.76)	**<0.001**
Asian	38	293	12.97%	0.45 (0.32, 0.64)	**<0.001**
Black	60	422	14.22%	0.50 (0.38, 0.66)	**<0.001**
Hispanic	77	493	15.62%	0.56 (0.43, 0.72)	**<0.001**
Middle Eastern	3	45	6.67%	0.22 (0.04, 0.68)	**0.003**
Mixed Ethnicity	70	418	16.75%	0.61 (0.46, 0.79)	**<0.001**
Other	69	556	12.41%	0.43 (0.33, 0.56)	**<0.001**
Low-SES (N=886)					
White	102	446	22.87%	REFERENCE	
Ashkenazi Jewish	5	39	12.82%	0.50 (0.19, 1.30)	0.15
Asian	3	16	18.75%	0.76 (0.14, 2.91)	1
Black	20	142	14.08%	0.55 (0.33, 0.93)	**0.02**
Hispanic	14	106	13.21%	0.51 (0.28, 0.94)	**0.03**
Middle Eastern	0	0	-	-	-
Mixed Ethnicity	12	67	17.91%	0.74 (0.38, 1.43)	0.36
Other	4	70	5.71%	0.20 (0.07, 0.57)	**<0.001**
Medium-SES (N=3519)					
White	519	2115	24.54%	REFERENCE	
Ashkenazi Jewish	47	244	19.26%	0.75 (0.53, 1.02)	0.07
Asian	12	143	8.39%	0.28 (0.15, 0.51)	**<0.001**
Black	27	186	14.52%	0.52 (0.34, 0.79)	**0.002**
Hispanic	44	268	16.42%	0.60 (0.43, 0.83)	**0.003**
Middle Eastern	3	23	13.04%	0.46 (0.14, 1.56)	0.2
Mixed Ethnicity	35	247	14.17%	0.51 (0.35, 0.74)	**<0.001**
Other	43	293	14.68%	0.53 (0.38, 0.74)	**<0.001**
High-SES (N=977)					
White	129	508	25.39%	REFERENCE	
Ashkenazi Jewish	26	200	13.00%	0.44 (0.28, 0.69)	**<0.001**
Asian	8	50	16.00%	0.56 (0.26, 1.22)	0.14
Black	3	32	9.38%	0.30 (0.06, 1.01)	0.051
Hispanic	2	30	6.67%	0.21 (0.02, 0.85)	**0.02**
Middle Eastern	0	10	0.00%	-	-
Mixed Ethnicity	8	50	16.00%	0.56 (0.26, 1.22)	0.14
Other	12	97	12.37%	0.41 (0.22, 0.78)	**0.005**

Table 2

Table 2. Utilization of Cascade Testing Based on Proband Age

Table 2. Utilization of Cascade Testing Based on Proband Age

Age	Cascade Testing Total	Proband Total (N=6237)	Cascade Testing Rate	Odds Ratio (Confidence Interval)	P-value
0-19y	0	21	0.00%	-	-
20-39y	194	1318	14.72%	REFERENCE	
40-59y	589	2966	19.86%	1.44 (1.20, 1.71)	**<0.001**
60-79y	458	1791	25.57%	1.99 (1.65, 2.40)	**<0.001**
80y+	29	118	24.58%	1.89 (1.21, 2.95)	**0.005**
Not provided	0	23	0.00%	-	-

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-06

Research Categories » Lynch syndrome

DEVELOPMENT OF AN EHR-INTEGRATED ELECTRONIC TOOL FOR THE IDENTIFICATION OF INDIVIDUALS AT-RISK FOR AN INHERITED CANCER SYNDROME

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BACKGROUND: Three million Americans have hereditary cancer syndromes (HCS) but <20% have been diagnosed. Lack of familiarity with suspicion criteria by health providers plays a critical role in this deficiency. Underdiagnosis is even worse among minorities. In order to assist in the identification of at-risk individuals we created an electronic tool integrated in the EHR.

METHODS: To create the familial cancer registry, NCCN and ACMG genetic testing criteria were translated into distinct rule-based conditional logic statements in the Epic® EHR. Each statement evaluated phenotypic attributes for Lynch Syndrome (LS), Hereditary Breast and Ovarian Cancer Syndrome (HBOC), and other cancer syndromes (eg: paraganglioma). Target populations were identified leveraging structured data from the EHR including personal history, familial history and test results. We created 218 rules that serially evaluate each aspect of an individual criteria, which together roll up into a logic statement of at-risk for these syndromes.

RESULTS: Out of 1.5 M patients with active charts in our health care network, we identified 54,000 (3.6%) who qualified for genetic testing. Of those, 11,424 (21.16%), 48,901 (90.56%), and 1,538 (2.85%) met genetic testing criteria for LS, HBOC, and other cancer syndromes respectively. A total of 2,884 (5.3%) already had an identified mutation, including 491/11,424 (4.3%) with LS, 1,499 (3%) with HBOC. Regarding the LS at-risk group, 4,906 (43%) had either already been evaluated or had a pending consult, while 57% had not been identified for genetic testing. Early onset colorectal or endometrial cancer criteria selected 1,757 patients (15.4%). Family history of early-onset LS-related cancer in 1st/2d degree relatives selected 1,221 patients (10.7%).

CONCLUSIONS: An electronic tool integrated in the EHR allowed us the identification of a high number of individuals qualifying for cancer genetic testing not recognized otherwise. An outreach effort has started to test at-risk individuals not yet evaluated.

Keywords: Lynch Syndrome, BRCA, Inherited Cancer Syndrome

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-07

Research Categories » Other

INHERITED CANCER SUSCEPTIBILITY GENE MUTATIONS AMONG PATIENTS WITH APPENDIX CANCER

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BACKGROUND: Germline mutations in APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, and TP53 genes confer a strong susceptibility to gastrointestinal cancers. As a rare cancer, the evaluation of appendiceal cancer predisposition has been very limited. We assessed the prevalence and spectrum of these mutations in patients with appendiceal cancer to determine the utility of germline genetic testing for those with appendix cancer.

METHODS: Patients with appendiceal cancer unselected for family cancer history who underwent germline genetic testing of 14 cancer susceptibility genes performed by a clinical testing laboratory between 2012 and 2016 were included in this cohort study. Clinical and individual/family histories were obtained from clinician-completed test requisition forms. Multi-gene panel testing was performed by targeted custom capture and sequencing and chromosome rearrangement analysis.

RESULTS: Among the 131 appendix cancer patients in the cohort, a total of 16 deleterious mutations were identified in 15 patients (11.5 percent). Six patients (4.6 percent) had a deleterious mutation observed in MUTYH [5, monoallelic MUTYH; 1, biallelic MUTYH]. Four appendix cancer patients (3.1 percent) had a mutation causing Lynch syndrome [4, MLH1], of which three were older than 50 years of age at appendix cancer diagnosis. Five patients had deleterious mutations in other cancer predisposition genes [1, APC c.3920T>A; 2, CHEK2 c.470T>C; 1, SMAD4 c.263_287dup; 1, TP53 c.524G>A].

CONCLUSIONS: One in every 10 patients with appendix cancer undergoing testing for hereditary cancer predisposition carries an inherited gene mutation associated with cancer susceptibility. Given the high frequency and broad spectrum of germline gene mutations, these data suggest that genetic evaluation might be warranted for all patients diagnosed with this rare malignancy and that a systemic sequencing effort for all patients with appendiceal cancer may identify cancer vulnerabilities to exploit for therapeutic development in a cancer type where clinical trials are very limited.

Keywords: appendix cancer, appendiceal cancer, germline mutations, Lynch syndrome, genetic testing, rare cancer

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Research Categories » Pancreatic cancer-related syndromes

UTILITY OF RNA TESTING IN INDIVIDUALS AT INCREASED RISK FOR HEREDITARY OR FAMILIAL PANCREATIC CANCER

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BACKGROUND: PRECEDE is an international consortium designed to improve pancreatic cancer (PC) survival. Participants are offered DNA and RNA testing of 37 cancer susceptibility genes. We hypothesize that RNA testing will improve the classification of pathogenic variants (PV) in PC susceptibility genes and decrease the variant of uncertain significance (VUS) rate associated with panel testing.

METHODS: The 37 gene DNA/RNA panel was completed for 616 individuals. Results were reviewed to determine the number of variant classifications that were affected by RNA data. Calculations were performed to determine the percent increase in PV detection in PC susceptibility genes.

RESULTS: In total, 167 individuals had a PV or likely pathogenic (VLP) variant identified through testing, 151 of which were in a PC susceptibility gene. Three individuals had PV/VLP variants identified that would have been classified as VUS without RNA data, representing a 2.1% increase in detection of PV/VLP in pancreatic cancer susceptibility genes; additionally, three individuals had a PV identified that would have been classified as VLP without RNA data (see Table 1). One variant was reclassified from VUS to likely benign with RNA data; another 16 variants outside of reporting range were determined to be benign with RNA data.

CONCLUSIONS: In a cohort of individuals with or at risk for hereditary pancreatic cancer, data from RNA testing aided in the classification of splice site, deep intronic, and silent variants. Though underpowered, this study suggests that deep intronic variants could be more common in this cohort (1 in 300 samples) than in all-comers who have RNA testing (1 in 1500 samples). Additionally, the number of typically unreported intronic variants that were determined to be benign through RNA data indicates that RNA analysis may be useful if whole genome testing for cancer susceptibility becomes more commonplace.

Keywords: pancreatic cancer, RNA

Table 1

Variants Identified through 37 Gene DNA/RNA Panel Upgraded to Pathogenic with RNA Data

Table 1: Variants Identified through 37 Gene DNA/RNA Panel* Upgraded to Pathogenic with RNA Data

Gene	Variant	Type of Variant	Classification without RNA	Classification with RNA	Race	Sex	Age	Personal Cancer History	Family History of Cancer
ATM	c.901G>A	Missense at last nucleotide of an exon	VUS	PV	White	Female	66	Melanoma	Breast Colon Pancreatic Melanoma
ATM	c.2839-579_2839-576del	Deep intronic	VUS	VLP	White	Male	64	PDAC	Pancreatic Breast
PALB2	c.2559C>T	Silent	VUS	PV	White	Female	66	PNET	Breast Colon Pancreatic Prostate
ATM	c.5763-1050A>G	Deep intronic	VLP	PV	White	Female	67	None	Pancreatic Melanoma Prostate
BRCA1	c.4357+1G>A	Splice site	VLP	PV	African American	Female	62	Breast	Breast Ovary
BRCA2	c.9117G>A	Silent	VLP	PV	African American	Female	52	None	Breast Prostate

*Genes Tested (bolded genes are pancreatic cancer susceptibility genes): **APC**, **ATM**, AXIN2, BARD1, BMPR1A, **BRCA1**, **BRCA2**, BRIP1, CDH1, CDK4, **CDKN2A**, CHEK2, DICER1, **EPCAM**, GREM1, HOXB13, **MLH1**, **MSH2**, MSH3, **MSH6**, MUTYH, NBN, NF1, NTHL1, **PALB2**, **PMS2**, POLD1, POLE, **PRSS1**, PTEN, RAD51C, RAD51D, RECQL, SMAD4, SMARCA4, **STK11** and **TP53**
Abbreviations
PDAC: pancreatic adenocarcinoma
PNET: pancreatic neuroendocrine tumor
VUS: variant of uncertain significance
PV: pathogenic variant
VLP: likely pathogenic variant

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

O-09

Case Reports » Case Series on any topic

NON-BINARY PATIENT WITH A GERMLINE *CDH1* PATHOGENIC VARIANT: COUNSELING AND CLINICAL CONSIDERATIONS

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BACKGROUND: Despite a growing population of non-binary patients, there is limited research on genetic counseling considerations in gender diverse populations with hereditary cancer predisposition syndromes.

METHODS: We describe a 20-year-old non-binary individual (assigned female at birth) who underwent genetic counseling after identification of a germline *CDH1* pathogenic variant (PV), c.283C>T (p.Gln95*). During contracting, we assessed the patient's preferred pronouns, which they indicated are they/them/theirs. Patient was diagnosed with atypical lobular hyperplasia within fibroadenoma at age 19. Though surgical removal of the mass was not medically indicated, they expressed desire to pursue gender affirming top surgery. They recounted that several healthcare providers were hesitant to perform top surgery, given their young age and fact that risk-reducing bilateral mastectomy (BLM) is not typically considered until age 30 for *CDH1*+ individuals. *CDH1*-associated lobular breast cancer risk, unknown residual risk after top surgery as compared to BLM, and psychological impact of surveillance of gender dysphoric organs were discussed. Despite their young age, we recommended BLM rather than top surgery, as has been recommended for transgender males with *BRCA1/2* PVs. A baseline upper endoscopy identified foci of signet ring cell carcinoma. Therefore, we recommended that the patient pursue gastrectomy prior to mastectomy. Patient underwent robotically assisted total gastrectomy, revealing stage IA diffuse gastric cancer. They plan to pursue gender affirming BLM in the future. Given their strong desire to achieve a masculine chest wall appearance, they will be referred to a plastic surgeon experienced in gender affirming top surgery.

RESULTS: Our case highlights several themes, including the importance of confirming gender identity and pronouns, challenges associated with coordination of care, and lack of non-binary specific medical training. More research and clinical guidance for hereditary cancer risk management of gender diverse individuals is needed across the spectrum of cancer predisposition syndromes.

Keywords: CDH1, Non-Binary, Genetic Counseling

O-10

Research Categories » Lynch syndrome

CO-EVOLUTION OF MISMATCH REPAIR LOSS AND THE IMMUNE RESPONSE IN LYNCH SYNDROME

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BACKGROUND: Complete MMR deficiency (MMR-d) in Lynch syndrome (LS) is gained through loss of the remaining functional allele. It is still disputed whether single MMR-d crypt foci (MMR-dcf) represent cancer-initiating lesions. Furthermore, how immune surveillance responds to MMR-dcf has not been examined. We investigate the earliest interactions between MMR-dcf and the immune microenvironment in the LS bowel to characterise the co-evolution of MMR-d clones and the immune system.

METHODS: We collected tissue from 32 patients with confirmed LS which were classified as normal from a LS colon free of cancer (n=13), normal from a LS colon with a distant cancer (n=6) or adenoma adjacent normal tissue (n=13). Immunohistochemical staining for MMR proteins identified the frequency and location of MMR-dcf. We then performed multiplexed, whole-slide cyclic immunofluorescence (CyCIF) to characterise the immune microenvironment around MMR-dcf to identify T-cells, B-cells, macrophages, neutrophils, and immune checkpoints to reveal the immune landscape of MMR-d patches.

RESULTS: We found significantly higher frequency of morphologically normal MMR-d crypts in adenoma adjacent areas (n=196/5149 crypts, in 6/13 patients) compared to areas not adjacent to adenomas (n=1/3333 crypts, in 1/13 patients, p=0.0384). This suggests that MMR-dcf occur very rarely, or that they are quickly removed by negative selection or immune predation. The higher prevalence of MMR-dcf near polyps indicates they are clonal precursors of the polyp, or they form later due to the immune-suppressed microenvironment surrounding polyps. Our CyCIF analysis of the immune microenvironment revealed that MMR-df have increased infiltration of cytoT cells and decreased numbers of Treg cells.

CONCLUSIONS: We present evidence that MMR-dcf are rare in the LS bowel, however patches of morphologically normal MMR-dcf are more prevalent adjacent to adenomas. These foci evoke a cytotoxic immune response. Future work will use NGS to inform the clonality of MMR-dcf and adjacent polyps, and genetic acquisition of immune evasion in MMR-dcf.

Keywords: Lynch syndrome (LS), mismatch repair (MMR), microsatellite instability (MSI), immune landscape, clonal evolution

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Research Categories » Lynch syndrome

CLINICAL OUTCOMES FOLLOWING TERMINATION OF IMMUNOTHERAPY DUE TO LONG-TERM BENEFIT IN MSI-H COLORECTAL CANCER

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BACKGROUND: Immune checkpoint blockade therapy improves survival in patients (pts) with microsatellite instability-high (MSI-H) advanced colorectal cancer (CRC). Oncologists often discontinue immunotherapy after 2 years of disease control based on prior trial data. Recurrence outcomes following discontinuation of immunotherapy and clinicopathologic features associated with recurrence remain underreported.

METHODS: Records from pts with MSI-H CRC from MD Anderson Cancer Center who received immunotherapy

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between 2015-2022 and stopped after clinical benefit were reviewed. Median survival was estimated according to the Kaplan-Meier method. Associations between the event of recurrence and coexisting mutations, metastatic site, primary tumor sidedness, and prior immunotherapy were measured by Fisher's exact tests.

RESULTS: Thirty-six pts with MSI-H CRC without progression on immunotherapy were reviewed. Of these 28 and 8 received anti-PDL1 antibody alone or in combination with anti-CTLA-4 antibody, respectively. Median exposure to prior immunotherapy was 24 months (range, 5-43). After a median follow-up of 19 months (95% CI, 14-26) after stopping immunotherapy, 30 of 36 pts (83%) remained without disease progression. For the 6 patients with progression after stopping, median time to relapse was 13 months (range, 5-31). Median disease-free survival (DFS) was not reached. The estimated 1-year, 2-year, and 3-year DFS probabilities were 90% (95% CI, 79-100), 79.1% (95% CI, 64-98), and 68% (95% CI, 47-98), respectively. Median overall survival from the time that immunotherapy was stopped was 54 months (95% CI, 47-NA). There were no observed associations between disease recurrence and co-existing mutations, metastatic organ involvement, primary tumor sidedness, or immunotherapy used.

CONCLUSIONS: Most pts with MSI-H advanced CRC who achieve initial clinical benefit and do not progress on immunotherapy do not recur after treatment is stopped. Our data suggest that favorable outcomes do occur following cessation of immunotherapy in this setting even with concomitant prognostically unfavorable clinical features (RAS, BRAFV600E mutations; liver, peritoneal metastases).

Keywords: MSI-H colorectal cancer, immunotherapy

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Research Categories » Lynch syndrome

GENETIC TESTING OUTCOMES IN A PROGRAM OF PAN-CANCER TESTING FOR MISMATCH REPAIR DEFICIENCY

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BACKGROUND: In 2017, the FDA approved Pembrolizumab to treat any mismatch repair deficient (dMMR) tumor. MMR immunohistochemistry (IHC) testing then increased across all tumor types. For the first time, MMR IHC was not performed to screen for Lynch syndrome (LS). We present the outcomes of MMR IHC performed outside of a LS screening program.

METHODS: All MMR IHC reports issued between 2017-2021 at a single academic hospital were reviewed. Colorectal cancers (CRC), endometrial cancers (EC), and non-cancerous lesions were excluded. Completion of genetic counseling and testing was determined through chart review and recorded in RedCap. This protocol was approved by the Mass General Brigham IRB.

RESULTS: Between 2017-2021, MMR IHC was completed in 1939 patients without CRC or EC. Absent or weak staining for at least one MMR protein was detected in 115 (5.9%) cases, and the highest rates of dMMR were seen in sebaceous, brain, small intestinal, gastric, and prostate cancers (Table 1). Ten patients with dMMR tumors were already known to have LS. 49 additional patients completed germline testing. Nine (18%) harbored a pathogenic or likely pathogenic variant (PV/LPV). 4 of these were in the corresponding MMR gene, and the remaining 5 were in

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unrelated genes (Table 2). Overall, the identification rate of LS in this cohort was 0.72%, which is similar to the rate in our previously reported CRC and EC universal screening cohort (1.35%; p=0.07). A diagnosis of LS was most commonly made in patients with brain (18.75%) and small intestinal cancers (10.20%).

CONCLUSIONS: Pan-cancer MMR testing for Pembrolizumab consideration can identify new LS cases at a rate similar to universal CRC and EC screening programs. MMR testing should be prioritized in brain and small intestinal tumors. Multigene panel testing is recommended in patients with dMMR, as unexpected PV/LPVs in non-LS genes were found as frequently as LS gene variants.

Keywords: Pembrolizumab, mismatch repair deficiency, universal Lynch syndrome screening

Table 1
Outcomes of pan-cancer MMR IHC screening

Table 1: Outcomes of pan-cancer MMR IHC screening

Tumor Type	Cases	dMMR	dMMR %	Germline testing[b]	Germline LS[b]	LS Detection Rate %
Brain	16	5	31.25	3	3	18.75
Small Intestine	49	11	22.45	9	5	10.20
Ampullary	40	2	5.00	1	1	2.50
Urothelial[a]	133	12	9.02	4	2	1.50
Gastric	145	25	17.24	10	1	0.69
Prostate	190	26	13.68	16	1	0.53
Pancreatic	635	7	1.10	4	1	0.16
Sebaceous carcinoma	8	3	37.50	1	0	0.00
Peritoneal	10	1	10.00	1	0	0.00
Neuroendocrine	11	1	9.09	0	0	0.00
Sarcoma	11	1	9.09	1	0	0.00
Other	18	0	0.00	0	0	0.00
Ovary/fallopian tube	79	4	5.06	2	0	0.00
Unknown Primary	40	2	5.00	1	0	0.00
Esophageal	159	7	4.40	4	0	0.00
Gallbladder	24	1	4.17	0	0	0.00
Gastroesophageal Junction	53	2	3.77	0	0	0.00
Biliary Tract	103	3	2.91	1	0	0.00
Renal	45	1	2.22	0	0	0.00
Liver	52	1	1.92	1	0	0.00
Appendiceal	49	0	0.00	0	0	0.00
Breast	33	0	0.00	0	0	0.00
Lung	25	0	0.00	0	0	0.00
Melanoma	7	0	0.00	0	0	0.00
Mesothelioma	4	0	0.00	0	0	0.00
TOTAL	**1939**	**115**	**5.93**	**59**	**14**	**0.72**

[a]Urothelial=bladder, renal pelvis, ureter
[b]Includes previously known LS cases
dMMR = mismatch repair deficient
LS= Lynch syndrome
Bold = Lynch syndrome associated cancer type

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Research Categories » Lynch syndrome

EVALUATION OF LYNCH SYNDROME RISK MODELS IN A MULTI-CENTER DIVERSE POPULATION

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BACKGROUND: Lynch syndrome (LS) is the most common cause of hereditary colorectal cancer (CRC) and is caused by pathogenic variants in the mismatch repair (MMR) genes. Statistical prediction models such as MMRpro and PREMM5 are widely used to identify LS carriers. However, these models are trained and validated in mostly white populations, and there remains a gap in understanding their performance in Hispanic populations. The purpose of this study was to evaluate the performance of MMRpro and PREMM5 on a large Hispanic cohort from the Clinical Cancer Genomics Community Research Network (CCGCRN).

METHODS: We validated MMRpro and PREMM5 on 3,490 CCGCRN families, of which 1,122 are Hispanic and 2,062 Non-Hispanic. The two models were evaluated for discrimination using the C-statistic, calibration using the observed to expected ratio (O/E), and overall performance using the Brier score and negative and positive predictive value (NPV/PPV) at the 5% carrier probability threshold.

RESULTS: The C-statistic is 0.90 for both MMRpro (95% CI: 0.88, 0.92) and PREMM5 (95% CI: 0.87, 0.92). When stratified by ethnicity, the C-statistics are 0.96 (95% CI: 0.94, 0.97) and 0.86 (95% CI: 0.83, 0.89) for Hispanics and Non-Hispanics, respectively, in MMRpro, and 0.96 (95% CI: 0.94, 0.97) and 0.84 (95% CI: 0.79, 0.88) in PREMM5. Both models underpredict mutation probabilities, with O/E ratios ranging from 1.79 to 1.96. At a 5% threshold, variations in PPV between Hispanics and Non-Hispanics are observed in both models. We observe less variation and higher values in NPVs in both models.

CONCLUSIONS: Overall, MMRpro and PREMM5 perform well in this cohort in predicting the probability of having a pathogenic variant in an MMR gene, with modest underprediction. While these results offer reassurance for the clinical use of MMRpro and PREMM5 in Hispanic populations, further validation studies in underrepresented racial and ethnic populations are crucial.

Keywords: Prevention, Lynch Syndrome, MMRpro, PREMM5

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Research Categories » Lynch syndrome

REAL-TIME USE OF ARTIFICIAL INTELLIGENCE (CADEYE) IN COLORECTAL CANCER SURVEILLANCE OF PATIENTS WITH LYNCH SYNDROME – A RANDOMIZED PILOT TRIAL

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BACKGROUND: Lynch syndrome (LS), an autosomal dominant disorder caused by pathogenic germline variants in DNA mismatch repair (MMR) genes, represents the most common hereditary colorectal cancer (CRC) syndrome. LS patients are at high risk of CRC despite regular endoscopic surveillance. The present study investigates Artificial intelligence (AI)-assisted colonoscopy (CAD-EYE; Fujifilm, Japan) in comparison to HD white-light endoscopy (HD-WLE) for the first time.

METHODS: Patients ⩾ 18 years, with pathogenic germline variant (MLH1, MHS2, MSH6), and at least one previous colonoscopy (interval 10-36 months) were eligible. Patients were stratified by previous CRC and affected MMR gene with a 1:1 allocation ratio (AI-assisted vs. HD-WLE). When the patient was allocated to the AI group the AI system for polyp detection and characterization (EW10-EC02 CAD-EYE system from Fujifilm Japan) was running during withdrawal, whereas in the control group the AI system was shut off. High-definition technology (ELUXEO 7000 system, EC-760R-V/I colonoscope; Fujifilm, Japan) was used for all examinations.

RESULTS: Between Dec-2021 and Dec-2022, 101 patients were randomised and 96 patients analysed (5 excluded due to insufficient bowel preparation). In the HD-WLE arm, adenomas were detected in 12/46 patients compared to 18/50 in the AI arm (26.1% [95% CI 14.3-41.1] vs. 36.0% [22.9-50.8]; p=0.379). The increased ADR was due to identification of flat adenomas (Paris classification 0-IIb and 0-IIc). By HD-WLE, 4/20 flat adenomas compared to 17/30 in the AI arm (p=0.018) were detected, the number of examinations with detection of flat adenomas was higher in the AI arm (3/46 [6.5%] vs. 10/50 [20%]; p=0.07). The median withdrawal time was not statistically different between HD-WLE and AI (14 vs. 15 min; p=0.170).

CONCLUSIONS: We here present first data suggesting that real-time AI-assisted colonoscopy is a promising approach to optimize endoscopic surveillance, in particular to improve the detection of flat adenomas.

Keywords: Lynch Syndrome, Colonoscopy, Artificial Intelligence, Adenoma Detection Rate

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Endoscopic images of artificial intelligence endoscopy in Lynch Syndrome

Images of a 3 mm flat adenoma with high-definition white light endoscopy (A), with Artificial intelligence assisted detection (B), Linked Colour imaging (C) and Blue Light Imaging with differentiation mode (D).

O-15

Research Categories » Other

MULTIGENE PANEL TESTING YIELDS HIGH RATES OF CLINICALLY ACTIONABLE VARIANTS AMONGST COLORECTAL CANCER PATIENTS

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BACKGROUND: Germline multi-gene panel testing (MGPT) is currently recommended only for a subset of individuals with colorectal cancer (CRC); whether MGPT should be performed in all individuals with CRC remains uncertain. Therefore we aimed to determine the yield and potential clinical impact of MGPT across a large, diverse CRC cohort.

METHODS: Retrospective cohort study of all individuals age >=18 with reported CRC who underwent MGPT of >10 genes at a commercial laboratory between 03/2015-05/2021. All data was prospectively collected through a single commercial laboratory and retrospectively analyzed.

RESULTS: A total of 34,244 individuals with a history of CRC underwent germline MPGT and were included. This cohort was predominantly female(60.7%), white(70.6%), and age 50 or older(68.9%), with 35.5% also reporting a non-colorectal malignancy. Of this cohort, 4,864 (14.2%) carried at least one pathogenic/likely pathogenic germline variant (PGV), with 3,111 (9.1%) having a PGV associated with increased CRC/polyposis risk, and 1,048 (3.1%) having an otherwise clinically actionable PGV (Figure 1). Patients under age 30 had the highest rates of PGVs($p<0.001$), and larger gene panels were not clearly associated with higher yield of clinically actionable PGVs (Figure 2). PGVs were more prevalent in individuals of Ashkenazi Jewish descent($p<0.001$) and Hispanic ethnicity($p<0.001$). Across all ages, panel sizes, and races/ethnicities, the rate of clinically actionable PGVs on MGPT was 7.9% or greater. A variant of

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uncertain significance (VUS) was identified in 13,094 (38.2%). Identification of a VUS was not associated with age(p=0.41), but did associate with panel size(p<0.001). VUS prevalence was lower in individuals of Ashkenazi Jewish descent(p<0.001), but higher in Black, Asian, and Hispanic individuals(p<0.001).

CONCLUSIONS: This is the largest study to date examining MGPT in CRC, demonstrating high rates of clinically actionable variants detected across all age groups, panel sizes, and racial/ethnic groups. This work supports consideration of broadening germline genetic testing criteria for individuals with CRC.

Keywords: Multigene panel testing, colorectal cancer

Figure 1

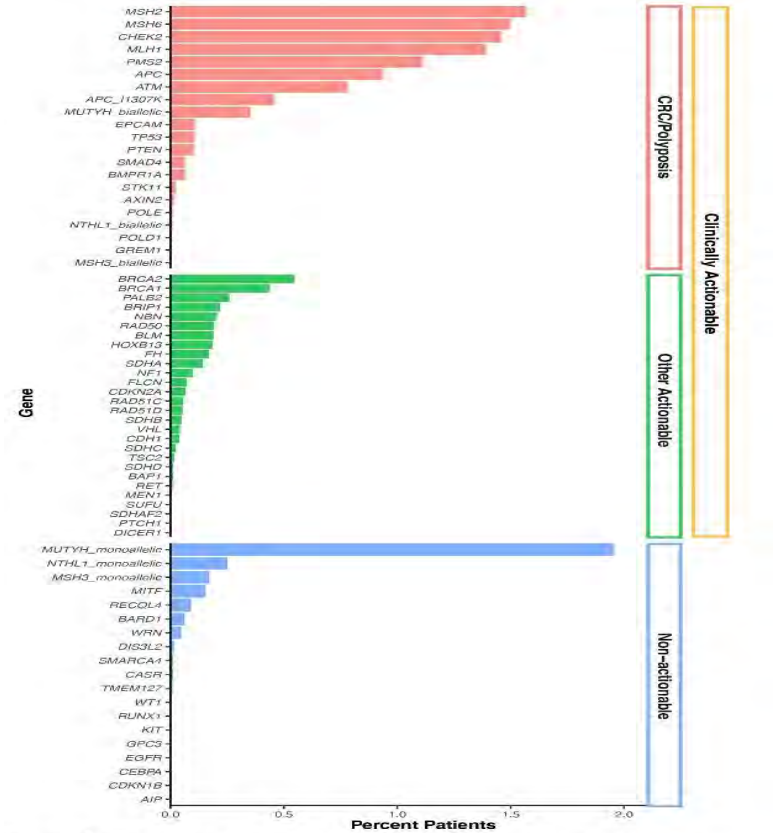

Figure 1. Percent patients with pathogenic or likely pathogenic germline variants by individual gene and clinical relevance. Genes with at least 1 PGV pictured.

Figure 2

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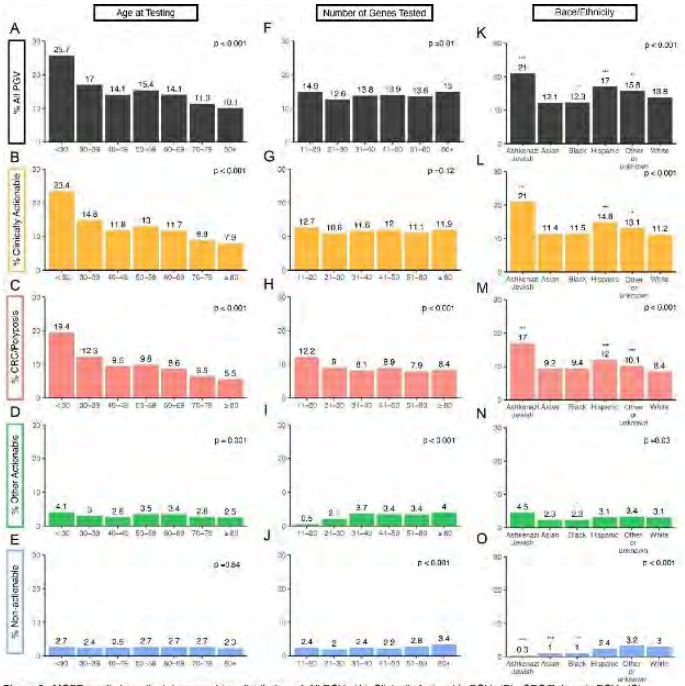

Figure 2. MGPT results by patient demographics: distribution of All PGVs (A), Clinically Actionable PGVs (B), CRC/Polyposis PGVs (C), Other Actionable PGVs (D), Non-actionable PGVs (E) by age; distribution of PGVs (F), Clinically Actionable PGVs (G), CRC/Polyposis PGVs (H), Other Actionable PGVs (I), Non-actionable PGVs (J) by number of genes tested; distribution of PGVs (K), Clinically Actionable PGVs (L), CRC/Polyposis PGVs (M), Other Actionable PGVs (N), Non-actionable PGVs (O) by Race & Ethnicity. Clinically Actionable PGVs include CRC/Polyposis and Other actionable PGVs (I).
*** p <0.001; ** p <0.01, * p<0.05.

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Case Reports » Case Series on any topic

A DEEP DIVE INTO *APC* INTRONS: PAIRED DNA/RNA TESTING IDENTIFIES NOVEL FAP AND AFAP ALLELES IN THE DEEP INTRONIC REGIONS OF *APC*

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BACKGROUND: Pathogenic alleles in APC cause the autosomal dominant syndromes of familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP). FAP and AFAP are characterized by the development of dozens to thousands of adenomatous colon polyps and significantly increased lifetime risks of developing colon cancer. Multigene panel and deletion/duplication testing has been successful in identifying causal mutations in an estimated 85-90% of FAP families and nearly 50% of AFAP families, however, there remains many families with clinical FAP/AFAP diagnoses in which a causal variant is unidentified. Therefore, paired DNA/RNA sequencing can be an important tool to help identify previously undiscovered APC mutations.

METHODS: Paired DNA/RNA sequencing via multigene panel testing at a diagnostic laboratory was used to screen patients for deep intronic variants in APC that result in aberrant RNA splicing. Aberrant RNA transcripts were identified by RNA sequencing and variants were subsequently identified by Sanger sequencing. RT-PCR was performed on patient samples for additional quantification. These alterations were classified according to the ACMG/AMP variant classification guidelines.

ORAL ABSTRACTS AT PRESIDENTIAL SESSIONS

RESULTS: Using paired DNA/RNA sequencing, we identified three novel, deep intronic APC variants, c.730-494C>G, c.933+829G>A, and an as-of-yet unidentified complex intron 14 variant identified by a high expression of r.1744_1958del215. These variants were identified in patients with clinical characteristics consistent with FAP/AFAP and shown to segregate in these families. RNA RT-PCR confirmed the splice impact resulting from these variants, and the combination of evidence lead to clinical classifications of likely pathogenic or pathogenic.

CONCLUSIONS: Paired DNA/RNA testing is able to identify deep intronic variants that have been previously uncharacterized using DNA testing alone and therefore RNA testing is an important tool to characterize the complete spectrum of causal mutations in APC. We hereby confirm that the relevant patient data submitted in this case series is exempt from IRB review.

Keywords: APC, RNA testing, Clinical Classification, FAP, AFAP

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P-01

Case Reports » Case Series on any topic

TRUNCATING VARIANTS IN 5' EXONS OF *APC* ARE ASSOCIATED WITH HIGHLY ATTENUATED PHENOTYPES AND EMPHASIZE THE NEED FOR GENOTYPE-PHENOTYPE CORRELATION.

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BACKGROUND: Loss of function (LoF) alterations at the N-terminus of *APC* are associated with Attenuated Familial Adenomatous Polyposis (AFAP); however, we have identified multiple truncating variants in *APC* coding exons 1 and 2 (CDS1 and 2) in individuals whose polyp burden is below the threshold typically described for AFAP.

METHODS: Retrospective clinical data was curated for individuals in which multigene panel testing for cancer identified alterations predicted to result in premature termination codons (PTCs) in CDS1 and 2 of *APC*. Although AFAP is associated with N- and C- terminal LoF alterations, we observed an unusually attenuated phenotype (0-10 polyps) in multiple patients with these alterations, including p.M1?, p.R24*, p.Q25Rfs*5, p.E46Sfs*4, p.K49*, p.L68Yfs*2, and p.E74*.

RESULTS: Several possibilities could explain this observation, including escape of nonsense mediated decay (NMD), use of an alternate start codon, and/or alternative splicing. To investigate these possibilities, we identified the location of the PTC for each alteration with respect to the N-terminus and in alternative transcripts. While some of these alterations could escape NMD due to their N-terminal location, others that are more distal to the N-terminus are expected to be NMD-prone. Exon skipping due to alternative splicing is also unlikely as all known transcripts for *APC* (NCBI) contain CDS2. CDS1 and 2 encode the oligomerization domain which is required for homodimerization; therefore, it is possible that retention of this domain is critical for pathogenicity.

CONCLUSIONS: Highly attenuated phenotypes observed in individuals with PTCs in CDS1 and 2 of *APC* emphasize a need for robust clinical variant interpretations that are not based solely on assumptions of predicted impact. A thorough understanding of variant effect and genotype-phenotype correlation is critical for reporting accurate classifications and interpretive information to providers.

Keywords: APC, AFAP, N-terminus, LoF, attenuated, alterations

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P-02

Research Categories » Adenomatous polyposis syndromes including FAP

NO NONSENSE: WHEN A PREMATURE TERMINATION IS NOT WHAT IT APPEARS

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BACKGROUND: *APC* exon 9 is subject to naturally occurring alternative splicing leading to an in-frame (IF) transcript. Patients with loss-of-function alterations in the spliced region frequently have attenuated Familial Adenomatous Polyposis (FAP). Three patients in our diagnostic laboratory cohort carrying *APC* c.1042C>T (p.R348*) in exon 9, did

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not report a personal or family history of polyps or colon cancer. This variant has in silico splice predictions suggesting the creation of a weak, novel acceptor site. Patient RNA was analyzed for use of this alternate site.

METHODS: Retrospective review of clinical data and patient RNA was performed on three carriers of this variant who underwent pan-cancer multigene panel testing.
RESULTS: Probands were >50y without a personal or family history of AFAP. One reported a 10-year colonoscopy schedule while the others did not provide colonoscopy information. Both CaptureSeq and RT-PCRSeq analyses consistently revealed the use of a novel cryptic acceptor site leading to incomplete expression of *APC* r.934_1074del141 (p.V312_Q358del). This transcript is predicted to lead to the IF loss of 47 amino acids of unknown function including codon 348 where the nonsense alteration occurs.

CONCLUSIONS: The pool of possibly functional aberrant and naturally expressed IF transcripts exclude the nonsense alteration and may explain the lack of overt AFAP these probands. Based on splicing and clinical data, this variant is classified as a variant of uncertain significance at this laboratory. These cases highlight the importance of considering splicing in the interpretation of every variant type including nonsense and frameshift variants by minimally evaluating in silico splice predictions and ideally by analyzing patient RNA. This can mitigate incorrect a priori classification of variants as pathogenic when they might otherwise have a splicing rescue effect.

We hereby confirm that the relevant patient data submitted in this case series is exempt from IRB review.

Keywords: APC, FAP, AFAP, Polyposis, RNA, alternative splicing

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P-03
Case Reports » Case Series on any topic

AN UNUSUAL CASE OF COLORECTAL POLYPOSIS

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BACKGROUND: Tuberous sclerosis (TS) is an autosomal dominant genetic disorder caused by germline pathogenic variants in *TSC1* or *TSC2*. TS affects a wide range of organs including the brain, heart, skin, eyes, kidney, lung, and liver. Gastrointestinal involvement is rare and mainly presents as hamartomatous polyps restricted to the large bowel. We present the case of a male with colorectal polyposis in the setting of a variant of unknown significance in *TSC2* gene.

METHODS: A 42-year-old male presented with four months of right lower abdominal pain, change in bowel habits, and hematochezia. His family history included a clinical diagnosis of TS in his father, otherwise, negative for familial adenomatosis polyposis and colonic polyposis. An esophagogastroduodenoscopy (EGD) did not demonstrate any gastric, duodenal, or ampullary polyps. Colonoscopy demonstrated a carpeting of diminutive and small polypoid lesions in the rectosigmoid with another twenty-five proximally. Cold snare resection was performed of all lesions proximal to the rectosigmoid and multiple rectosigmoid lesions. Two lesions were adenomatous otherwise the

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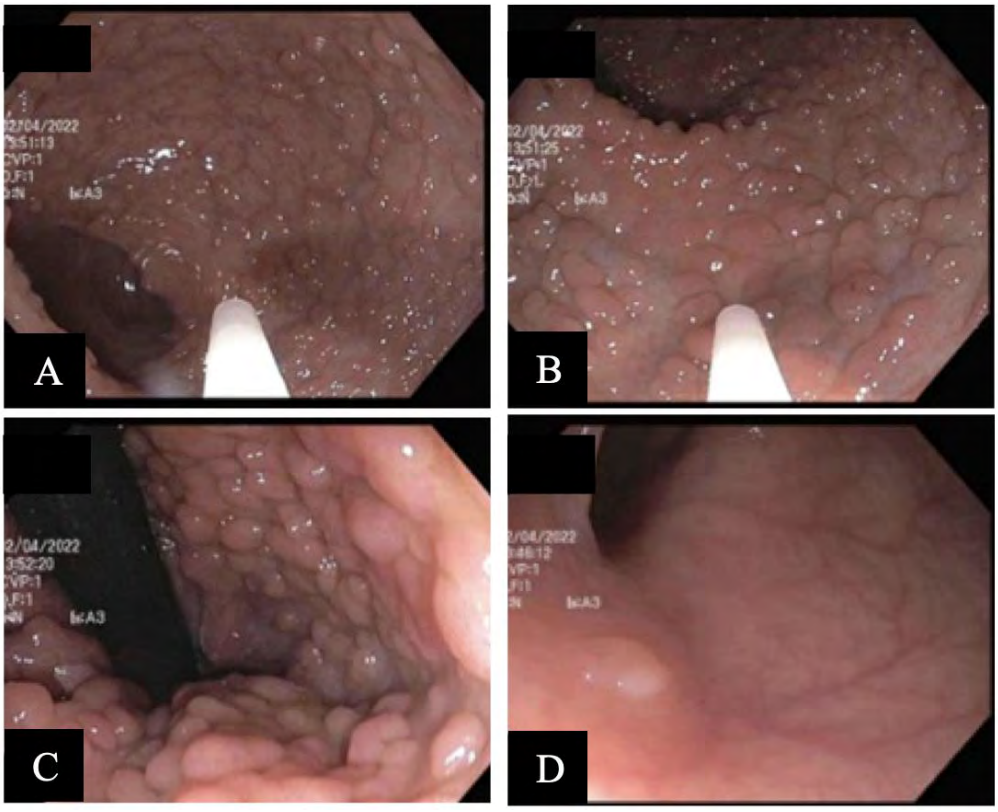
majority were fragments of colonic mucosa with marked prolapse of the muscularis mucosae into the lamina propria consistent with mucosal prolapse type polyps. Given the family history of TS, and his hamartomatous polyposis, multigene panel testing was performed. A variant of unknown significance (p.G1567D) was detected in the *TSC2* gene. The patient had no other clinical manifestations of TS.

RESULTS: Mucosal prolapse type polyposis has been described in TS in one prior case report with genetic testing. The most common findings in the GI tract are hamartomatous polyps and rarely present as polyposis extensively distributed throughout the colorectum. This case highlights the importance of recognizing a colorectal manifestation
of TS.
CONCLUSIONS: I hereby confirm that the consent of the relevant patient has been obtained to submit this.

Keywords: Tuberous Sclerosis, Colorectal Polyposis

Figure 1

A carpeting of mucosal-prolapse polyps in the rectosigmoid colon (Images A, B, C) and scattered mucosal prolapse in the remainder of the colon (Image D).



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MULTI-GENERATIONAL POLYCYSTIC PANCREAS: A CASE REPORT

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BACKGROUND: Isolated polycystic disease of the pancreas (IPDP) is a rare condition with a few cases reported, characterized by numerous cysts in the pancreas without no associated hereditary syndromes, such as Von Hippel-Lindau and polycystic kidney disease. We present the first reported case of IPDP with at least three affected relatives. The etiology for IPDP is currently unknown. Patients with IPDP may present similarly to patients with pancreas cystic lesions (PCLs) – asymptomatic or with abdominal pain, jaundice and/or pancreatitis.

METHODS: The proband was a 59-year-old female who presented with abdominal pain. Magnetic resonance cholangiopancreatography (MRCP) showed innumerable (>100) non-enhancing pancreatic cysts, completely replacing the pancreatic parenchyma and several small hepatic and renal cysts (Figure 1). Her metabolic panel including lipase and CA 19-9 was normal. Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) and microforceps biopsy of three largest cysts was consistent with serous cystadenomas. Germline genetic testing for syndromic hereditary conditions was negative. Gene analysis was not completed; however, the proband does not meet clinical criteria for autosomal dominant polycystic kidney disease. Proband's mother (86-year-old female) and sibling (58-year-old male) both had innumerable pancreatic cysts (Figure 2). The proband's mother had one renal cyst and several hepatic cysts. The proband's sibling had numerous hepatic cysts without renal involvement.

RESULTS: Given the multi-generational nature of the presentation in this family, there is a strong suspicion that this is a hereditary condition. Whole genome sequencing for identification of the underlying genetic variant is currently ongoing. Current management of patients with IPDP is extrapolated from patients with PCLs and includes MRCP with EUS-FNA and microforceps biopsy every 2-3 years to rule out any high-risk cysts.

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

Keywords: Polycystic pancreas disease, Pancreas cystic lesions, Hereditary pancreatic disease, Pancreatic cancer, Hereditary syndromes, genetics

Figure 1

MRCP Scan of Pancreas

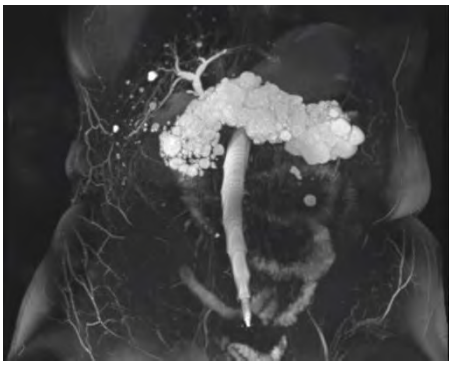

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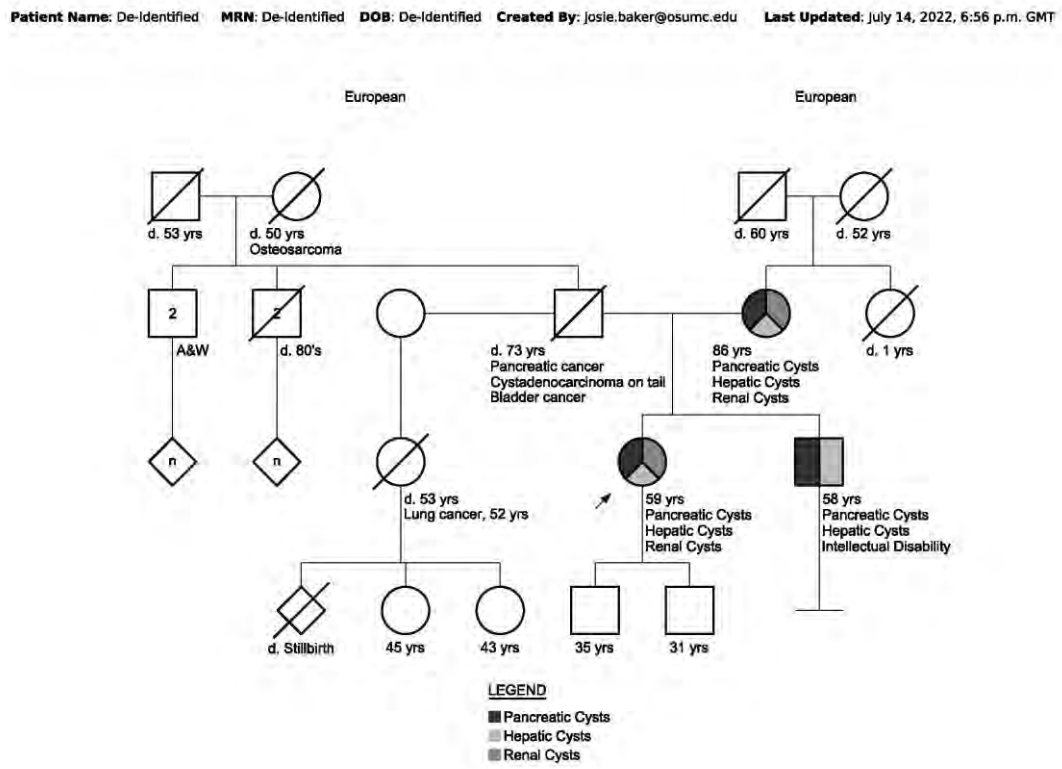
Figure 2
Family Pedigree



P-05
Case Reports » Case Series on any topic

DE NOVO BMPR1A GENE DELETION WITH A DESMOID TUMOR, EARLY ONSET RECTAL CANCER & COLON POLYPS (NO JUVENILE): WHAT'S THE IMPACT OF A DESMOID TUMOR?

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BACKGROUND: *BMPR1A* heterozygous pathogenic findings cause a condition known as Juvenile Polyposis Syndrome (JPS). JPS is characteristically confined to the gastrointestinal (GI) system with an increased risk of GI polyps and cancer(s) (colorectum/gastric/small bowel/pancreas). Polyp burden in JPS can range drastically from 4-5 to 100's throughout one's lifetime. While the hallmark pathology of JPS clinical criteria is juvenile polyps, several cases in the literature have been reported with non-juvenile polyps.

METHODS: The present work reports the case of a 31-year-old *BMPR1A*+ patient, whose prior non-juvenile colon polyps combined with recent extra-colonic tumor are an atypical presentation. Extensive clinical data from the proband and her family was obtained; informed consent and a DNA sample from peripheral blood was taken. Multi-

gene hereditary cancer risk panels(*) were performed in the proband and her parents using next-generation sequencing technology for evaluation.

RESULTS: At 26y, the proband was diagnosed with a rectal cancer presenting as a large fungating bleeding rectal mass with broad base and 12 colon polyps (most adenomatous; none juvenile). The proband's genetic testing revealed a *BMPR1A* full gene deletion; familial testing revealed it to be de novo. At 31y, the proband was diagnosed with a desmoid tumor. Due to the desmoid tumor, prior adenomatous polyps and *BMPR1A*+ results, key discussions were performed.

CONCLUSIONS: *BMPR1A* heterozygotes are characterized by an increased risk of GI polyps and cancer(s). We present an atypical presentation of a de novo *BMPR1A* heterozygote with prior rectal cancer, 12 non-juvenile pathology colon polyps, and recent desmoid tumor. We stress importance of continued dialogue with high-risk patients as unique findings may require evaluation to determine: sporadic vs. evolving clinical spectrum vs. new differential. (*) Testing through Ambry Genetics

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

Keywords: BMPR1A, JPS, Juvenile Polyposis Syndrome, desmoid tumor, adenomatous, juvenile polyps

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P-06

Case Reports » Case Series on any topic

IMMUNOTHERAPY-RESPONSIVE ACINAR CELL PANCREATIC CARCINOMA IN PMS2-RELATED LYNCH SYNDROME

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BACKGROUND: Acinar cell carcinoma (ACC) is a rare pancreatic cancer with at least two prior reports of occurrence in Lynch syndrome (specifically MSH2- and MSH6-related). Here we present a case of immunotherapy-responsive pancreatic ACC in the setting of PMS2-related Lynch syndrome, adding to the growing literature of rare mismatch repair deficient (dMMR) tumors.

METHODS: A 61 year old female was found to have a hepatic mass, biopsy was suggestive of metastatic adenocarcinoma of gastric or hepatobiliary origin. She underwent neoadjuvant chemotherapy (Gemcitabine plus cisplatin) followed by surgery, which found a pancreatic mass, and underwent distal pancreatectomy, splenectomy, and partial hepatectomy. Pathology demonstrated ypT3N0M1 ACC of the pancreatic tail with clear margins. She did not receive adjuvant therapy, and remained in remission for 4 years, please see table for further oncologic history. Tumor-only genetic testing of bony metastasis detected a PMS2 missense variant (c.319C>T (p.R107W)) with conflicting laboratory interpretations, at mutation allele frequency (MAF) of 91%. Microsatellite instability (MSI) of 17.86% was interpreted by the molecular pathologist as MSI-equivocal. Immunohistochemistry (IHC) was performed on same sample and demonstrated proficient MMR. This PMS2 variant was germline confirmed by sequencing of

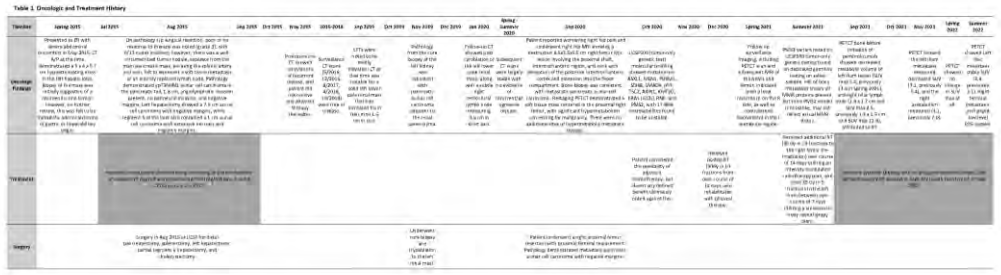
saliva sample. Based on MAF of the PMS2 variant and equivocal MSI, pembrolizumab therapy was initiated. Significant decrease in hypermetabolism in bony metastases was noted two months later on PETCT, with stable disease seen on PETCT nine months later, and patient reported dramatic pain reduction and improved function.

RESULTS: The effectiveness of immunotherapy suggests this pancreatic ACC is likely driven by the germline PMS2 variant. This unusual case highlights the benefits of collaboration between oncology, molecular pathology, and genetics, and that a proportion of pancreatic ACCs are dMMR, including due to PMS2 variants.

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

Keywords: immunotherapy, Lynch syndrome, PMS2, pancreatic acinar cell

Table 1. Oncologic and Treatment History



P-07

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DESMOID FIBROMATOSIS IN A PATIENT WITH GERMLINE CDKN2A MUTATION

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BACKGROUND: Desmoid tumors (DTs), also known as fibromatosis, are locally aggressive, fibroblastic neoplasms within the family of soft tissue sarcomas. Most DTs (85-90%) are sporadic type due to somatic CTNNB1 mutations, while 10-15% of DTs are due to loss-of-function germline variants in the APC gene, as part of Familial Adenomatous Polyposis (FAP). However, there has been rare report of a DT attributed to germline mutations in CDKN2A, the gene implicated in familial atypical multiple mole melanoma – pancreatic cancer syndrome (FAMM-PC). Here we present a second case of a DT in a CDKN2A mutation carrier.

METHODS: A 36-year-old woman with a personal history of >20 dysplastic nevi presented with desmoid fibromatosis of the abdominal wall. She presented with abdominal discomfort and weight loss. Surgical history was remarkable

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for prior appendectomy. Paternal family history was significant for her father who had melanoma and pancreatic cancer (age 50) and her grandmother with melanoma and leukemia (age unknown). Maternal family history was significant for her mother with breast cancer (age 58), an aunt with bilateral breast cancer (age 50 and 55), and an uncle with prostate cancer (age 60). MRI of the abdomen showed a 1.5 x 1.3 cm intramuscular mass of the left rectus abdominis muscle. CT guided biopsy revealed desmoid fibromatosis. Germline genetic testing revealed CDKN2A pathogenic variant (c.149A>G; p.Q50R).

RESULTS: While germline mutations in CDKN2A are commonly associated with melanoma and pancreatic cancer, the present case leads us to contemplate DTs as a potential manifestation of these mutations. The Cdkn2ab locus has been shown to play a critical role in the oncogenicity of the WNT pathway, a well-described common pathway known to contribute to DTs, thus making the association biologically plausible.

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

Keywords: desmoid tumor, fibromatosis, CDKN2A

P-08

Case Reports » Case Series on any topic

IMPORTANCE OF TIMELY GENETICS SERVICES AND CRITICAL EVALUATION OF DIAGNOSIS AND REPORTED FAMILY HISTORY WHEN ASSESSING FOR HEREDITARY CANCER SYNDROMES

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Providence St. Joseph Health

BACKGROUND: Cancer pathology and family history are routinely utilized to assess risk for hereditary cancer syndromes but may be inaccurate. Therefore, critical evaluation is imperative. Additionally, delay in access to genetics services may postpone cancer management.

METHODS: 51-year-old identical female twins A and B presented to our same-day genetics clinic (administered by genetics-assistant with genetic counselor oversight) within 1-business day of diagnosis of ductal carcinoma in-situ (DCIS) and invasive lobular carcinoma, respectively.
Reported family history included: maternal grandmother with neuroblastoma(40s), father with liver/pancreatic cancer(50s), paternal grandfather with lung cancer(70s), paternal grandmother with breast cancer(50s). Both patients underwent comprehensive hereditary cancer testing and were positive for a pathogenic CDH1-gene mutation. As almost all breast cancers associated with CDH1-mutations are lobular, case was discussed with pathology department. E-cadherin testing of Patient-A's tumor was negative and diagnosis was revised to pleiomorphic lobular carcinoma in-situ.
Updated family history discussion revealed limited contact with father and uncertain accuracy of his cancer diagnosis with reported rectal bleeding and hematemesis near end of life.
Their paternal half-sisters', unaffected in their 30s, pursued testing and were positive for the familial CDH1-gene mutation, confirming the paternal origin of this mutation.
Within a month of diagnosis, patients received genetic testing results and revised diagnosis. Patient A and B have since undergone bilateral mastectomies and prophylactic gastrectomies. This case also led to modification of pathology protocols with addition of E-cadherin testing for all DCIS tumors.

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RESULTS: Reported family histories and diagnostic results may be inaccurate and should be carefully interpreted. Suspicion of discordant results should be discussed with the indicated department (ie. pathology) for confirmation of correct diagnosis and continual process improvement. Same-day genetics services provide opportunity for timely genetics results and subsequent follow-up and management.

CONCLUSIONS: I hereby confirm that the consent of the relevant patients has been obtained to submit this "Case-Reports/Case-Series"

Keywords: CDH1, Lobular breast cancer, genetic testing, genetics services, hereditary cancer, HDGC

P-09

Research Categories » Adenomatous polyposis syndromes including FAP

GERMLINE MBD4 PATHOGENIC VARIANTS IN CANCER

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[4]Hereditary Cancer Program, Catalan Institute of Oncology; Oncobell Program, IDIBELL, Hospitalet de Llobregat, Barcelona, Spain; Catalan Institute of Oncology, IDIBGi, Girona, Spain; Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain

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BACKGROUND: Biallelic loss-of-function germline variants in the base excision repair (BER) gene *MBD4* cause a cancer syndrome characterized by increased risk to adenomatous polyposis, colorectal cancer (CRC), acute myeloid leukemia (AML) and uveal melanoma (UVM). To expand the knowledge on this syndrome, we studied *MBD4* in individuals affected with tumors that fit the syndrome's phenotypic spectrum.

METHODS: Germline predicted damaging (population MAF<0.1%, REVEL score >0.5) variants in *MBD4* were interrogated in individuals diagnosed with CRC (n=543), adenomatous polyposis (n=192), UVM (n=88), or with personal/familial history of CRC or polyposis and hematologic malignancies (n=10). Sequencing of *MBD4* coding regions was performed on polyposis patients and patients with personal/familial history of CRC/polyposis and hematologic malignancies. For CRC and UVM patients, *MBD4* information was obtained from TCGA (exome sequencing data). Somatic 2nd hit information, including somatic mutations, copy number alterations and promoter hypermethylation, was obtained from TCGA; tumor mutational burden (TMB) and signatures were calculated with MuSiCa and Signal, respectively.

RESULTS: A homozygous missense variant in *MBD4*, c.181T>C; p.C61R, was identified in a CRC patient. Eight patients were heterozygotes for predicted pathogenic variants in *MBD4*. For all nine patients, tumor molecular features were

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analyzed. The MBD4-associated mutational signature SBS96 and TMBs of 4.6 and 12.3 mut/Mb were detected in the CRC developed by the homozygous patient, and in the UVM of a patient with a germline canonical splice-site variant and somatic *MBD4* loss (2nd hit), respectively.

CONCLUSIONS: Biallelic germline pathogenic variants in *MBD4* are rare among CRC, polyposis and UVM patients. Monoallelic pathogenic *MBD4* variants may also predispose to cancer when a 2nd hit occurs in the target organ. The presence of relatively high TMB and SBS96 may be used for *MBD4* variant interpretation and to elucidate an MBD4-related etiology

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Keywords: Adenomatous polyposis, hereditary colorectal cancer, uveal melanoma, acute myeloid leukemia.

P-10

Research Categories » Adenomatous polyposis syndromes including FAP

BIALLELIC VARIANTS IN *NTHL1* AND *MSH3* IN INDIVIDUALS ASCERTAINED FROM A MULTIGENE PANEL TESTING (MGPT) COHORT: A DESCRIPTIVE ANALYSIS

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BACKGROUND: Autosomal recessive familial polyposis has been reported in association with biallelic pathogenic variants (BPVs) in *NTHL1* and *MSH3*. Current publications for these genes describe a small number of families ascertained from colorectal cancer (CRC) and/or polyposis cohorts. We aim to contribute to the available data and describe features in individuals with *NTHL1* and *MSH3* BPVs identified via multi-gene panel testing (MGPT).

METHODS: A retrospective data review of cases was performed with *NTHL1* and *MSH3* BPVs detected by MGPT (32 to 81 genes) between January 2019 and December 2021. Proband histories were obtained via test requisition forms and clinical documents submitted to our laboratory. Unless otherwise state d, individuals with BPVs do not have co-occurring PVs in other genes.

RESULTS: Ten individuals (6 females, 4 males) were found to have BPVs in *NTHL1*, 9 with a history of polyposis and 4 with a diagnosis of CRC (mean age of diagnosis: 46.75 years). Of the females, 4 had breast cancer (mean age of diagnosis: 50.4 years), 2 of which were bilateral. Three individuals were found to have BPVs in *MSH3*, 2 with a history of polyposis and 1 with a diagnosis of CRC at 44 years. The positive rate for *NTHL1* and *MSH3* BPVs was 0.00513% and 0.00155%, respectively.

CONCLUSIONS: This descriptive analysis adds to the limited literature on individuals with BPVs in *NTHL1* and *MSH3* and supports the hypothesis that BPVs in *NTHL1* and *MSH3* predispose to familial polyposis. In our cohort, 12 of 13 individuals reported a personal history of CRC or polyposis. Our results indicate that BPVs in *NTHL1* and *MSH3* are exceedingly rare and continued study is necessary to determine the full phenotypic spectrum and penetrance of tumors in individuals with BPVs - particularly for the observed breast cancer, which could be a product of a MGPT cancer predisposition cohort.

Keywords: polyposis, hereditary colorectal cancer, genetic testing

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Figure 1

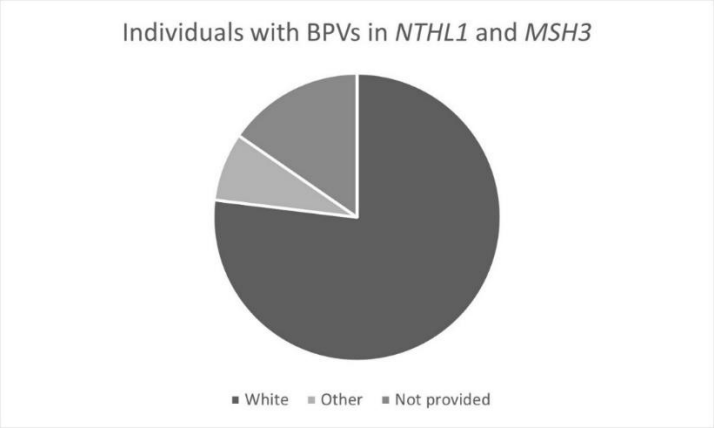

Table 1

Case	Gene	Variants	Sex	Age at testing (in years)	Polyposis?/ # if known	CRC? (age at dx)	Other cancers
1	*NTHL1*	p.Y130* (c.390C>A) p.Q90* (c.268C>T)	F	59	Yes/unknown	No	melanoma, breast, head and neck cancer, SCC
2	*NTHL1*	p.Q90* (c.268C>T p.Q90* (c.268C>T)	F	44	Yes/9	No	bilateral breast, BCC
3	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	50	Yes/10+	No	N/A
4	*NTHL1*	p.Q145* (c.433C>T) p.Q90* (c.268C>T)	F	51	Yes/unknown	Yes/45	N/A
5	*NTHL1*	c.139+1G>A c.139+1G>A	M	73	Yes/40+	Yes/54	N/A
6	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	58	Yes/7+	Yes/56	bilateral breast
7	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	F	37	Not reported	No	breast
8	*NTHL1* *RAD51D*	p.Q90* (c.268C>T) p.Q90* (c.268C>T) p.R232* (c.694C>T)	M	41	Yes/20+	No	N/A
9	*NTHL1*	p.Q90* (c.268C>T) p.Q90* (c.268C>T)	M	77	Yes/17+	No	N/A
10	*NTHL1*	p.Q90* (c.268C>T) c.139+1G>A	M	44	Yes/30+	Yes/32	N/A
11	*MSH3*	c.1660_1661delAT (p.M554Efs*14) c.1660_1661delAT (p.M554Efs*14)	F	50	Yes/unknown	No	breast
12	*MSH3*	c.2807delT (p.F936Sfs*21) c.2807delT (p.F936Sfs*21)	F	44	Not reported	Yes/44	N/A
13	*MSH3*	c.978_984delTTCCCGG (p.F326Lfs*3) c.260_263delAGAA (p.K87Rfs*14)	M	66	Yes/19+	No	N/A

BCC = basal cell carcinoma; SCC = squamous cell carcinoma; s/p = status post; N/A = not applicable

POSTER ABSTRACTS

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Research Categories » Adenomatous polyposis syndromes including FAP

EFFICACY OF WHOLISTIC TURMERIC SUPPLEMENT ON PATIENTS WITH FAMILIAL ADENOMATOUS POLYPOSIS- A RANDOMIZED, DOUBLE BLINDED, PLACEBO-CONTROLLED STUDY

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BACKGROUND: Familial adenomatous polyposis (FAP) is characterized by hundreds of adenomas in the colon. Previous studies had demonstrated that curcumin, a constituent of the spice turmeric can cause regression of polyps. Wholistic turmeric (WT) contains additional bioactive compounds such as turmerones which may also contribute to this effect. We performed a double-blinded randomized controlled trial to assess the efficacy of WT in patients with FAP.

METHODS: Ten FAP patients were randomly assigned to receive either 8 capsules/day of WT, each containing 123.65mg curcuminoids and 26.79mg turmerones, or placebo for 6 months. Colonoscopies were performed at baseline, and after 6 months. Number, size and cumulative polyp burden (combined size of all polyps) were assessed.

RESULTS: No differences were noted between groups in change from baseline polyp number (-10% and -12.8%, p=0.896), mean polyp size (-9.41% and -9.2%, p=0.610) and polyp burden (-23.43% and -33.69%, p=0.886). Stratifying the data according to right (transverse colon to cecum) vs left colon (rectum to descending colon) indicated a decrease in median polyp number (from 5.5 to 1.5, p=0.06) and polyp burden (24.25mm to 11.5mm, p=0.028) in the left colon of patients in the WT group which was not apparent in the placebo group or right colon. Adjusting for baseline polyp characteristics in the left colon we noted the adjusted mean polyp number was lower by 5.39 (p=0.034) and adjusted mean polyp burden was lower by 14.68mm (p=0.059) in the WT group compared to placebo.

CONCLUSIONS: We did not note any beneficial effects of WT on polyp number, size or burden in FAP patients, with a notable exception of left sided polyps which reduced in number and burden. Whether WT can be used to reduce polyp burden of patients with predominantly left sided polyps remains to be seen as further larger prospective trials are required.

Keywords: FAP, chemoprevention, curcumin

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Figure 1

Individual patients' polyp characteristics at baseline and post-treatment

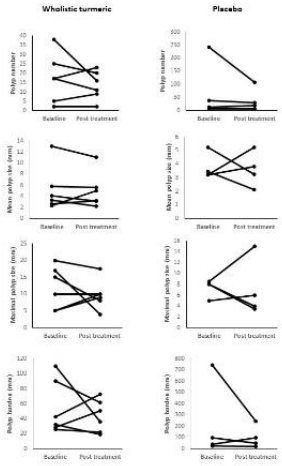
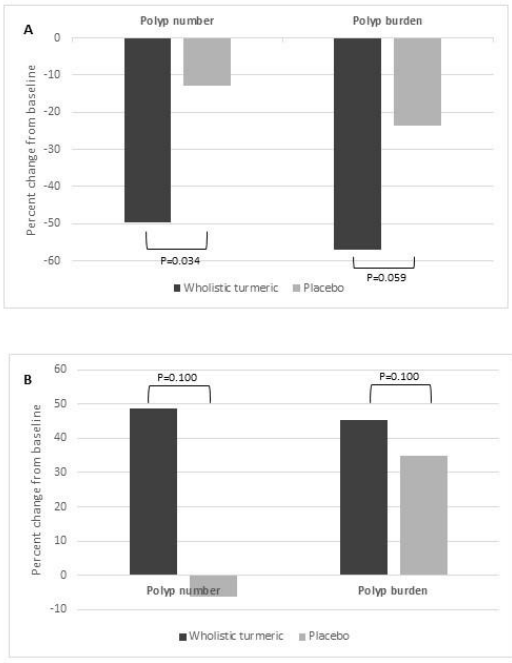


Figure 2

Change (%) in polyp number and burden in the (A) left and (B) right colon for the two groups



POSTER ABSTRACTS

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Research Categories » Adenomatous polyposis syndromes including FAP

IMPROVING RATE OF GENETIC REFERRAL FOR ADENOMATOUS POLYPOSIS

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BACKGROUND: Despite multiple guidelines recommending genetic evaluation of patients with 10 or more lifetime colorectal adenomas, referral rates for genetic counseling and completion of testing are low. Timely referrals would help optimize care for patients and their relatives through appropriately directed measures to reduce cancer-associated morbidity and mortality.

METHODS: We conducted a quality improvement (QI) project aiming to improve the referral rate for genetic counseling by 10% in patients with 10 or more cumulative lifetime adenomas. In phase one, we retrospectively identified target patients by analyzing 500 consecutive patients with colonoscopy performed at our center with at least one adenoma removed endoscopically from October to December 2021. In phase two, starting January 2022, we asked the pathologists that interpret colonoscopy specimens to prospectively identify target patients and insert into the pathology report an intervention statement suggesting referral to genetics. In phase three, we again retrospectively identified patients for January to March 2022 through the same process as in phase one. We analyzed the percentage that had been referred to genetics in both cohorts. Comparisons were done with Fisher's exact test.

RESULTS: A total of 1000 patients were reviewed and 36 met criteria for genetics referral (3.6%). In phase one, 5/20 (25%) were referred for genetic counseling. In phase two, the intervention statement was successfully inserted in 5/16 (31.3%). In phase three, 4/16 (25%) were referred to genetics (p = 1.0). Of those with the intervention statement inserted into the pathology report, 3/5 (60%) received a referral, while only 1/11 (9%) without intervention statement inserted received a referral (p=0.06).

CONCLUSIONS: There was a trend towards a higher referral rate for those with our QI intervention implemented, although we did not achieve our aim of improving the overall referral rate to genetics. Future steps will include strategies to increase the insertion rate of our intervention statement.

Keywords: Adenomatous Polyposis, Quality Improvement, Genetics Referral, Genetic Counseling and Testing

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Research Categories » Counseling, Behavioral Health, Psychosocial, and Survivorship

ACTIONABLE PATHOGENIC GERMLINE VARIANTS DISCOVERED BY PANEL-BASED HEREDITARY CANCER TESTING IN FAMILIES WITH PREVIOUSLY IDENTIFIED PATHOGENIC VARIANTS

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BACKGROUND: Multi-gene hereditary cancer panels (MGHCP) have revolutionized how patients with germline mutations are identified by testing multiple genes at the same time. Despite the availability of panel testing, many patients with a known familial mutation will only undergo single site genetic testing due to limitations in guideline recommendations and insurance coverage. This approach risks a failure to detect additional pathogenic variants and an inappropriate management of cancer risk. In our clinical experience, a subset of patients pursue MGHCP testing despite a known familial mutation. We investigated the patients from our risk assessment clinic with mutations that would be missed from single site testing and determined how medical management may have been changed due to the presence of the newly identified mutation.

METHODS: The Fox Chase Cancer Center Risk Assessment Program (RAP) Registry was queried to identify patients who underwent MGHCP testing who carry more than one mutation. Clinical pedigrees were reviewed on patients and families identified with multiple germline mutations. Screening management guidelines were determined from the most recent NCCN guidelines published at the time the patient tested (Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic and Genetic/Familial High-Risk Assessment: Colorectal). The RAP Registry is an IRB approved protocol (IRB 09-831).

RESULTS: We identified 19 patients since introducing MGHCP testing in 2014 who would have received incomplete genetic risk assessment if they only underwent single site testing. Screening management changed in 55% (11/19) of these patients (Table 1). 37% (7/19) of these patients did not meet NCCN criteria for additional germline testing beyond single site testing.

CONCLUSIONS: Patients undergoing single site cascade testing are at risk of receiving inaccurate risk assessment based on incomplete ascertainment of germline cancer risks and can consider MGHCP testing. Insurance coverage of MGHCP testing may be a barrier for some of these patients.

Keywords: single site testing, hereditary cancer panels

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Table 1

Table 1: Pathogenic variants that would have been missed on single-site testing

Table 1: Pathogenic variants that would have been missed on single-site testing

Patient #	Proband's Relationship to Patient	Patient Sex	Patient Personal History of Cancer	Mutation(s) in Proband	Mutation(s) in Patient	Change in management due to second mutation?	Met NCCN criteria for additional genetic testing?
1	Mother	M	None	*BRCA2* c.1813del	*BRCA2* c.1813del and *NTHL1* c.268C>T	No	No
2	Paternal Cousin	M	None	*MSH6* c.3261dupC	*BRIP1* Exon 8 del	No	No
3	Brother	M	Prostate at age 66	*BRCA1* c.68_69del	*BRCA1* c.68_69del and *APC* I1307K	Yes	Yes
4	Maternal Uncle	F	None	*MSH6* c.3647-1G>A	*MSH6* c.3647-1G>A and *APC* I1307K	No	No
5	Paternal Aunt	F	Breast at age 58	*BRIP1* c.2292_2295 del	*CHEK2* c.1100delC	Yes	No
6	Paternal Aunt	F	None	*BRCA2* c.6486_6489 delACAA	*MUTYH* c.1187G>A	No	Yes
7	Mother	F	None	*BRCA2* 6174delT	*APC* I1307K	Yes	No
8	Mother	F	None	*BRCA1* c.5385insC	*BRCA1* c.5385insC and *CHEK2* I157T	No	Yes
9	Sister	M	None	*APC* c.994C>T and *NTHL1* c.268C>T	*APC* I1307K	Yes	No
10	Mother	M	None	*BRCA2* c.475+1G>T	*CHEK2* I157T	No	Yes
11	Sister	F	Duodenal at age 46	*BRCA2* c.9435_9436 delGT	*MSH2* c.1865C>T	Yes	Yes
12	Daughter	M	Sarcoma at age 57	*MSH6* c.578del	*MSH6* c.578del and *BRCA1* c.5096G>A	Yes	Yes
13	Brother	M	Prostate at age 63	*MSH2* c.942+3A>T	*BRCA2* c.6037A>T	Yes	Yes
14	Father	F	None	*MLH1* c.1731G>A	*BRCA2* c.7007G>C	Yes	Yes
15	Sister	F	Uterine at age 59	*ATM* c.7638_7646 del	*FANCC* c.362_363delTA	No	Yes
16	Father	F	None	*PMS2* Deletion Exons 6-7	*NBN* c.1903A>T	No	No
17	Maternal Aunt	F	None	*BRCA1* c.3867G>T	*BRCA1* c.68_69del	Yes	Yes
18	Granddaughter	F	Breast at age 64 and melanoma at age 67	*BRCA2* c.7558C>T	*MSH6* c.1767del	Yes	Yes
19	Daughter	F	Uterine at age 45, Gastric at age 46, Small bowel at age 52, Colon at 72, Breast at 76, and GIST at 78	*PMS2* c.137G>T	*MSH2* c.942+3A>T	Yes	Yes

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P-14

Research Categories » Counseling, Behavioral Health, Psychosocial, and Survivorship

PATIENT EXPERIENCES MANAGING UNCERTAINTY AND FOLLOWING MANAGEMENT GUIDELINES FOR LYNCH SYNDROME IN A POPULATION SCREENING PROGRAM

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BACKGROUND: The Geisinger MyCode Community Health Initiative (MyCode) is a healthcare-based population biobank that returns actionable genomic results to clinical care. This study explored how individuals identified with Lynch syndrome (LS) via MyCode evaluate and manage uncertainty, engage with clinicians, and follow recommended medical management.

METHODS: Semi-structured interviews were conducted with MyCode patient-participants who had a pathogenic/likely pathogenic variant identified in an LS-associated gene (MLH1, MSH2, MSH6, PMS2). Interviews, which focused on experiences receiving their LS result and navigating subsequent medical management, were thematically analyzed. Chart review was completed to extract LS-related management for each participant. Chart review data were coupled with qualitative data to elucidate the relationship between participant uncertainty management, clinical conversations, and subsequent surveillance.

RESULTS: Seventeen participants completed interviews (8 male, 9 female). Participants described uncertainty about what their LS result meant for their care and managed that uncertainty with primary care providers (PCPs), genetic counselors, and a specialized multidisciplinary LS clinic. Individuals who had no evidence in their electronic health record of discussing their result with a clinician tended to evaluate the LS result as not important to their care and had not completed colonoscopy or other surveillance. In contrast, individuals who managed their initial uncertainty by seeking care with the LS specialty clinic described re-evaluating their uncertainty regarding recommended management and tended to engage in surveillance that closely matches National Comprehensive Cancer Network (NCCN) guidelines. Finally, participants who relied on their PCPs to manage their LS care described feeling more uncertain about management recommendations and tended to have limited surveillance.

CONCLUSIONS: Our findings illuminate how individuals with an LS result from population screening evaluate their risk and manage uncertainty with their clinicians. Findings suggest that access to clinical resources and medical professionals may assist patients in managing uncertainty about LS care, thus facilitating appropriate surveillance.

Keywords: Lynch syndrome, uncertainty, medical management, patient-clinician communication

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P-15

Research Categories » Counseling, Behavioral Health, Psychosocial, and Survivorship

INFLUENCES OF HEALTHY LIFESTYLE ON QUALITY OF LIFE OVER TIME IN PATIENTS WITH COLORECTAL CANCER

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BACKGROUND: Health-related quality of life is an important indicator of treatment outcomes in cancer patients. The impact of postoperative lifestyles on health-related quality of life warrants further study. The purpose of the study was to investigate the influence of physical activity, fiber intake, and sleep quality on changes in quality of life over time in postoperative colorectal cancer patients.

METHODS: This is a longitudinal observational study. A convenient sample of colorectal cancer patients was recruited from a medical center in Taiwan. Data were collected by using structured questionnaires at 1, 3 and 5 months postoperatively. Questionnaires included the Modified International Physical Activity Questionnaire, Fiber

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Intake, Table Study-Quick Food Scan, Pittsburgh Sleep Quality Index, and Functional Assessment of Cancer Therapy: General. Generalized estimating equations were used to analyze trends inhealth-related quality of life over time. Multivariate analyses were conducted to explore predictors of health-related quality of life change over time.

RESULTS: Results showed no significant temporal difference in health-related quality of life. The average values at 1, 3 and 5 months after operation were 101.7 (SD = 18.5) and 98.7 (SD = 20.1), and 99.7 (SD = 18.1), respectively. Results of multivariate analysis results showed that education level, marital status, occupational status, economic status, postoperative adjuvant treatment, smoking habits, drinking habits, fiber intake, physical activity, and sleep quality were significant predictors of health-related quality of life changes.

CONCLUSIONS: Colorectal cancer patients who maintained high levels of physical activity, consumed adequate fiber, and slept well had better health-related quality of life. Appropriate measures are recommended for such patients to increase physical activity and fiber intake, and improve sleep quality, so that patients after colorectal cancer surgery can achieve better health-related quality of life.

Keywords: colorectal cancer, physical activity, fiber intake, sleep, health-related quality of life

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P-16

Research Categories » Delivery of Care and Alternative Models

A STEP TOWARDS PATIENT CENTERED CARE: COMBINED ENDOMETRIAL BIOPSY AND COLONOSCOPY FOR LYNCH SYNDROME

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BACKGROUND: The National Comprehensive Cancer Network recommends individuals with Lynch syndrome undergo endometrial biopsy and colonoscopy every 1-2 years. Endometrial biopsies are performed awake, causing considerable discomfort, whereas most colonoscopies are performed under sedation. Combining these procedures can reduce pain and lower the burden of additional exams. Despite published data, few institutions offer combined screening. Here we present our institution's experience with goals to encourage others to adapt this model.

METHODS: At clinic visits, patients with a uterus were offered combined screening if both procedures were due. Moderate sedation or general anesthesia support were used per individual medical indications. Endometrial biopsy was performed immediately following endoscopic procedures. No positioning stirrups were utilized. Endoscopies were performed by a single gastroenterologist with expertise in hereditary cancers and endometrial biopsies by a nurse practitioner with specialized training.

RESULTS: All patients offered combined screening preferred this versus awake endometrial biopsy. From January 2021 to present, 16 patients, all self-identified as cis-gender females, underwent combined screening. The majority were aged 30 – 49 years (10), with age range of 33 – 71 years. The success rate of obtaining an endometrial sample was 10/16 (62.5%). Endometrial sample could not be obtained due to positioning difficulties (4/6) and cervical

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stenosis (2/6). 2/6 had historical or subsequent failures on dedicated gynecological exam, and 1/6 have had no further attempts for comparison. Pathology results of the endometrial sample were normal in 6/10, and had insufficient sample in 4/10. Colon polyps were found in 4/16 individuals. There were no post-procedural complications. All patients preferred to repeat future endometrial biopsy under sedation.

CONCLUSIONS: Combined screening under sedation is feasible and preferred by patients. We next plan to implement stirrups and improve lighting to increase biopsy success. Further research is needed to study patient satisfaction scores, cost savings, and improvement of patient compliance with endometrial surveillance.

Keywords: NCCN, endometrial biopsy, Lynch syndrome, sedation, combined surveillance, colonoscopy

Table 1. Individuals with Lynch syndrome undergoing combined surveillance (n=16)

Table 1. Individuals with Lynch syndrome undergoing combined surveillance (n=16)

Ethnicity/Race			
Caucasian	8	Other	2
Asian	5	Unknown/Not given	1
Hispanic			
Yes	3	Not given	1
No	12		
Age (years)			
30-39	2	60-69	0
40-49	8	70-79	2
50-59	4		
Gene			
PMS2	9	MLH1	1
MSH6	4	EPCAM	0
MSH2	2		
Endometrial biopsy completed			
Yes	10	No	6
Endometrial biopsy pathology			
Insufficient sample	4	Normal	6
Reason endometrial biopsy not completed			
Anatomical stenosis	2	Positioning	4
Abnormal colonoscopy (polyps found)			
Yes	4	No	12

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P-17

Research Categories » Delivery of Care and Alternative Models

INNOVATIVE APPROACHES TO EXPANDING CANCER GENETIC TESTING IN MICHIGAN (PROJECT MIGHT)

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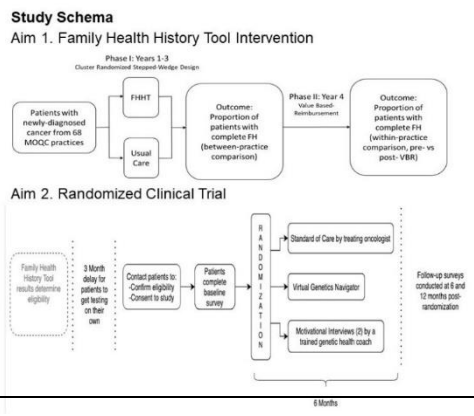
BACKGROUND: Although germline genetic variants are implicated in 5-20% of cancers, only a fraction of people at risk for hereditary cancer syndromes undergo germline genetic testing (GT). GT disparities are created in part by provider-patient communications, leading to incomplete family history collection and referrals to GT. People affected by cancer report limited knowledge regarding availability and understanding of GT. Project MiGHT, an NCI Cancer Moonshot U01 grant, developed digital and counseling interventions to improve identification of individuals with genetic susceptibility to cancer and to increase GT uptake.

METHODS: Aim 1 tests the impact of a patient-facing electronic family health history tool (FHHT) on family history assessment in 69 diverse oncology practices in the Michigan Oncology Quality Consortium (MOQC). Aim 2 employs a 3-arm randomized clinical trial (RCT) to evaluate the impact of two behavioral interventions on GT uptake: (1) a website with tailored messaging and (2) motivational interviewing phone calls, compared to usual care. Participants in Aim 2 include individuals diagnosed with breast, ovarian, endometrial, colorectal, prostate, or pancreatic cancer who meet clinical criteria for but have not undergone GT. We propose to enroll 600 participants (200 per arm) over the next two years.

RESULTS: Completion rates of the FHHT to date ranges from 8-50% and varies by oncology practice. Of the patients who completed the FHHT, approximately 20% met clinical criteria for genetic evaluation. Of these, one-third had completed GT excluding them from the intervention. Practices with existing GT referral processes reported higher rates of GT. Enrollment is ongoing.

CONCLUSIONS: Project MiGHT addresses clinical challenges in implementation and dissemination of genomic medicine by increasing patient knowledge of their risk for hereditary cancer syndromes and decreasing the barriers to GT. This work engages multidisciplinary expertise in developing approaches for delivery of precision oncology care in diverse healthcare settings.

Keywords: genetic testing, community practices, family history, clinical trial



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Research Categories » Delivery of Care and Alternative Models

COMPARING TELEMEDICINE AND IN-PERSON GASTROINTESTINAL CANCER GENETIC APPOINTMENT OUTCOMES DURING THE COVID-19 PANDEMIC

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BACKGROUND: BACKGROUND: The study purpose is to compare outcomes associated with completion of genetic testing between telemedicine and in-person cancer risk assessment appointments during the COVID-19 pandemic.

METHODS: METHODS: Data was collected about patients with scheduled appointments between July 2020 and June 2021 in a gastrointestinal cancer risk evaluation program (GI-CREP) that utilized both telemedicine and in-person visits throughout the COVID-19 pandemic.

RESULTS: RESULTS: A total of 293 patients had a GI-CREP appointment scheduled and completion rates of in-person versus telemedicine appointments were similar. Individuals diagnosed with cancer and those with Medicaid insurance had lower rates of appointment completion. Although telehealth was the preferred visit modality, there were no differences in recommending genetic testing nor in the consent rate for genetic testing between in-person and telemedicine visits. However, of patients who consented for genetic testing, more than three times more patients seen via telemedicine did not complete genetic testing compared to those seen in-person (18.3% versus 5.2%, p=0.008). Furthermore, telemedicine visits had a longer turnaround time for genetic test reporting (32 days versus 13 days, p<0.001).

CONCLUSIONS: Compared to in-person GI-CREP appointments, telemedicine was associated with lower rates of genetic testing completion, and longer turnaround time for results.

Keywords: Gastrointestinal cancer, genetics services, risk assessment, telegenetics, COVID-19

Figure 1

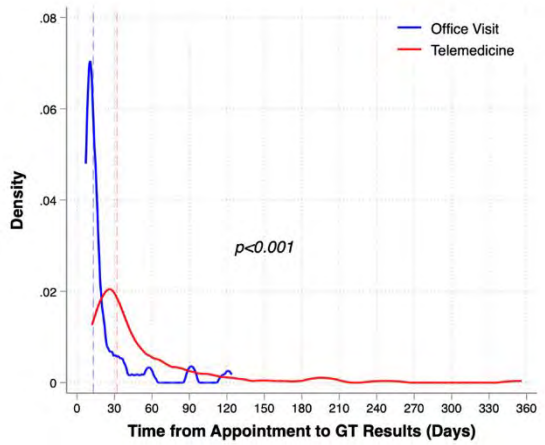

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Table 1

Median Income ($), median (IQR)	82571.5 (66230.5, 106778)	93571 (69305, 104928)	0.51	81519 (64237, 104318)	84632 (68224, 107388)	0.72
Personal History of Cancer						
No	147 (62.3%)	15 (30.0%)	<0.001	62 (69.7%)	85 (57.8%)	0.069
Yes	89 (37.7%)	35 (70.0%)		27 (30.3%)	62 (42.2%)	
Referral Reason						
Personal history of cancer	80 (33.9%)	34 (59.6%)		22 (24.7%)	58 (39.5%)	
Family history of cancer	85 (36.0%)	10 (17.5%)		36 (40.4%)	49 (33.3%)	
Personal history of polyps	47 (19.9%)	2 (3.5%)	<0.001	21 (23.6%)	26 (17.7%)	0.24
Family history of genetic syndrome	17 (7.2%)	2 (3.5%)		7 (7.9%)	10 (6.8%)	
Other	7 (3.0%)	9 (15.8%)		0 (0.0%)	0 (0.0%)	
Visit Type						
In-person	89 (37.7%)	25 (43.9%)	0.39			
Telemedicine	147 (62.3%)	32 (56.1%)				
Genetic Testing Recommended						
No				5 (5.6%)	11 (7.5%)	0.58
Yes				84 (94.4%)	136 (92.5%)	
Consented for Genetic Testing (if recommended)						
No				7 (8.3%)	10 (7.4%)	0.79
Yes				77 (91.7%)	126 (92.6%)	
Genetic Testing Completed (if consented)						
No				4 (5.2%)	23 (18.3%)	0.008
Yes				73 (94.8%)	103 (81.7%)	

Table 1 (cntd)

Table 1: Cohort characteristics by appointment completion status and modality amongst patients scheduled for a GI-CREP appointment.

	Appointment Completion (N = 293)			Type of Appointment Completed (N = 236)		
Factor	**Appointment Completed (N=236)**	**Appointment Not Completed (N=57)**	**p-value**	**In-Person Office Visit (N=89)**	**Telemedicine (N=147)**	**p-value**
Age, median (IQR)	49 (37, 60.5)	54 (44, 65)	0.064	53 (38, 65)	45 (36, 57)	0.013
Sex						
Female	129 (54.7%)	35 (61.4%)	0.36	50 (56.2%)	79 (53.7%)	0.72
Male	107 (45.3%)	22 (38.6%)		39 (43.8%)	68 (46.3%)	
Race						
White	174 (73.7%)	38 (66.7%)		65 (73.0%)	109 (74.1%)	
Black	28 (11.9%)	8 (14.0%)		9 (10.1%)	19 (12.9%)	
Hispanic	9 (3.8%)	0 (0.0%)	0.22	5 (5.6%)	4 (2.7%)	0.75
Asian	11 (4.7%)	4 (7.0%)		5 (5.6%)	6 (4.1%)	
Other	14 (5.9%)	7 (12.3%)		5 (5.6%)	9 (6.1%)	
Marital Status						
Single	83 (35.2%)	22 (38.6%)	0.63	29 (32.6%)	54 (36.7%)	0.52
Married	153 (64.8%)	35 (61.4%)		60 (67.4%)	93 (63.3%)	
Religion						
Christian	115 (48.7%)	27 (47.4%)		45 (50.6%)	70 (47.6%)	
Jewish	29 (12.3%)	5 (8.8%)	0.25	14 (15.7%)	15 (10.2%)	0.24
Muslim	5 (2.1%)	4 (7.0%)		3 (3.4%)	2 (1.4%)	
Other	87 (36.9%)	21 (36.8%)		27 (30.3%)	60 (40.8%)	
Insurance						
Private	173 (73.3%)	29 (50.9%)		60 (67.4%)	113 (76.9%)	
Medicare	45 (19.1%)	15 (26.3%)	<0.001	22 (24.7%)	23 (15.6%)	0.19
Medicaid	17 (7.2%)	9 (15.8%)		6 (6.7%)	11 (7.5%)	
Other/Unknown	1 (0.4%)	4 (7.0%)		1 (1.1%)	0 (0.0%)	
Distance to Center, median (IQR)	19.75 (8.8, 33.95)	21.4 (11.9, 32.7)	0.30	16.3 (7.1, 33.5)	20.4 (9.6, 34.3)	0.50

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Research Categories » Delivery of Care and Alternative Models

IMPLEMENTATION OF A MULTI MODAL BEST PRACTICE BUNDLE TO IMPROVE GENETIC TESTING REFERRAL FOR PANCREATIC CANCER PATIENTS

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BACKGROUND: All patients diagnosed with pancreatic ductal adenocarcinoma (PDAC) should be recommended to complete genetic testing to inform treatment and family risk. The Wilmot Cancer Institute Hereditary Cancer Program led the implementation of a best practice bundle, which included provider education, electronic medical record prompting, automatic referral, and an ordering Smartset in May of 2021. Here we report baseline referral and completion rates prior to implementation, the initial experience with the bundle and recommendations for future adaptations.

METHODS: Medical record data were retrospectively reviewed to evaluate referral rates for all new patients diagnosed with PDAC one year prior to implementation of the bundle. After six months, eligible providers completed a one-on-one remote interview. We present descriptive and summary statistics for the medical record data and thematic summaries of qualitative field notes.

RESULTS: The sample included 138 individuals with PDAC. Of those, 99 were referred for genetic testing (71%), 71.5% of those referred completed testing (50% of the total diagnosed with PDAC), and 15.4% had a pathogenic variant. Data are still pending regarding referral and completion rates after implementation. Five oncology providers participated in interviews. Overall, medical oncology providers were satisfied with the bundle and found the prompting helpful. Feedback was given about the best place for the alert to provide maximal exposure. Adaptations related to the frequency of the alert and ongoing provider engagement and education were discussed.

CONCLUSIONS: Our preliminary data is similar to other documented rates of referral for genetic testing, test completion and pathogenic variant detection. A multi-modal provider-focused best practice bundle is overall acceptable by providers. Evaluation of the impact of the bundle on referral and ways to sustain and provide engagement will be the target of future work. Additionally, given baseline data, other components of the testing process should be targeted to improve testing completion.

Keywords: pancreatic cancer, practice alert, genetic testing

P-21

Research Categories » Delivery of Care and Alternative Models

PERFORMANCE OF INHERET® RISK ASSESSMENT TOOL FOR IDENTIFYING PATHOGENIC GERMLINE VARIANTS AMONG INDIVIDUALS REFERRED FOR CANCER GENETICS EVALUATION

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BACKGROUND: Identification of individuals with inherited susceptibility to cancer offers opportunities for early detection and prevention. The National Comprehensive Cancer Network (NCCN) has guidelines for genetic referral, however these criteria can be challenging to apply. INHERET employs a patient-facing health survey and a risk assessment algorithm to identify individuals meeting NCCN criteria for genetic evaluation. We examined INHERET's performance for identifying individuals with a pathogenic germline variant (PGV) conferring cancer susceptibility.

METHODS: Individuals evaluated at an academic cancer genetics clinic between 8/2021-2/2022 were invited to complete INHERET before their appointment. INHERET reports (met vs. did not meet referral criteria) were compared with outcomes of genetic testing to evaluate the tool's performance.

RESULTS: Seventy individuals completed INHERET and pursued genetic testing; mean age 51.5 years [23-76]; 54.3% female; 35.7% affected with cancer. Forty-one of 70 (58.6%) were flagged by INHERET as meeting NCCN referral guidelines; 20 (28.6%) did not meet criteria, and 9 (12.8%) were classified as "clinician discretion." All 11 individuals with a gastrointestinal cancer were flagged (colorectal n=6, pancreatic n=4, appendiceal n=1). Overall, twelve (17%) had a PGV in a cancer susceptibility gene (ATM n=2, BRCA2 n=1, CDKN2A n=1, CHEK2 n=4, PMS2 n=1, SDHC n=1, SMAD4 n=1, TP53 n=1), of which 6 met criteria per INHERET and 2 were eligible per clinician discretion (CHEK2 low-penetrance variant). Of the remaining 4, 3 were missed due to patient data entry error (failure to indicate a familial PGV) and the fourth (PGV in BRCA2) had no notable cancer history, but was referred due to colorectal adenomas.

CONCLUSIONS: INHERET's NCCN-based algorithm identified individuals meeting criteria for genetic evaluation across multiple hereditary cancer syndromes. Performance of the tool depends on accuracy of patient-entered family history information. Patient education on providing family history may increase the utility of the INHERET tool, especially for those with a familial PGV.

Keywords: Genetic testing, Lynch syndrome, BRCA, HBOC

P-22

Research Categories » Other

ATTITUDES ABOUT SHARING GENETIC TEST RESULTS IN FAMILIES WITH HEREDITARY CANCER SYNDROMES

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BACKGROUND: Genetic testing to identify pathogenic germline variants (PGV) has made it possible to prevent cancers in families affected by hereditary syndromes. This study aimed to identify factors which influence how genetic testing information is shared among relatives.

METHODS: Individuals who underwent genetic evaluation in a genetics clinic between 1998-2021 who tested positive for a PGV in a cancer susceptibility gene were invited to complete an online survey. Subjects were asked their level of comfort with sharing their results. Genetic knowledge was assessed via a 16-item validated measure (KnowGene) and compared by syndrome using a one-way ANOVA.

RESULTS: Out of 1,314 patients invited, 316 completed the survey. The 3 most common syndromes/genetic diagnoses were Lynch Syndrome (LS n=99, 31%), Familial Adenomatous Polyposis (FAP n=33, 10%), and Hereditary

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Breast Ovarian Cancer (HBOC n=30, 9%). In this subgroup of 162 subjects, the majority were female (n=111, 69%) with average age of 53.6 years (range 18-85). Overall, respondents felt very comfortable sharing genetic test results with family members (mean score 9.1 where 1=extremely uncomfortable and 10=extremely comfortable). Genetics knowledge scores were slightly higher among individuals with LS and HBOC (each with mean score 11/16) compared with FAP (mean score 10/16) however this difference was not significant (p-0.24). LS respondents reported the highest rate of uptake of genetic testing among family members (average of 5.5 relatives tested), compared with HBOC (4.2 relatives), with FAP (3.6 relatives); significantly lower compared with HBOC and LS ($p<0.05$).

CONCLUSIONS: In this cohort of individuals, we observed high levels of communication and comfort with sharing genetic testing results. However, uptake of genetic testing among relatives and genetics knowledge scores were slightly lower for individuals with FAP, when compared with LS or HBOC. Since individuals with FAP are often diagnosed as children/adolescents, genetic counseling for adults with FAP may be of benefit.

Keywords: Lynch Syndrome, Cancer genetics, Hereditary Breast Ovarian Cancer, Familial adenomatous polyposis

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Research Categories » Delivery of Care and Alternative Models

ONCOLOGIST KNOWLEDGE OF COST OF GENETIC TESTING

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BACKGROUND: Cost of germline genetic testing (GT) is a major concern for patients. The cost of GT has decreased substantially over the last several years, however, it is not clear to what extent oncologists are knowledgeable about the current cost of testing. The purpose of this study was to investigate oncologists' knowledge of GT costs.

METHODS: We deployed a survey to oncologists who are members of the Michigan Oncology Quality Consortium, a physician-led quality improvement collaborative. The modified Dillman method was used, and responses were collected from December 2020 - May 2021. Responses to the question, "If a patient were to ask you how much it would cost for them to have clinical genetic testing for hereditary cancer syndromes, what would you tell them?" were independently coded by three investigators into one of three categories – correct and helpful, correct and not helpful, or incorrect and not helpful. We investigated associations between the number of years in practice and provider perception of cost as a barrier to GT.

RESULTS: Response rate to the survey was 61.2% (194/317). Only 25% of respondents provided an answer that was both correct and helpful to patients. Nearly 40% of respondents gave an answer that was correct but non-specific and would not help a patient decide about pursuing GT. About 28% of respondents gave an incorrect answer. No associations were found between cost response category and other factors.

CONCLUSIONS: Most oncologists in our statewide sample do not have an accurate understanding of the cost of germline GT. Lack of precise information about GT cost may lead patients to believe that GT is not important or not accessible. Providing incorrect information may prevent patients and their families from pursuing genetic counseling. Improving oncologists' knowledge about the cost of testing may decrease patient barriers to genetic risk assessment.

Keywords: cost, genetic testing

Table 1. Physician response categories and examples

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Physician Response	Count (%)	Example responses
Correct and Helpful	48 (24.7)	"Approximately $250 if out of pocket"
Correct and Not Helpful	76 (39.2)	"Defer to a genetic counselor" "Cost varies based on insurance"
Incorrect and Not Helpful	54 (27.8)	"Several thousand dollars" "I don't know"
Missing	16 (8.2)	--
Total	194	--

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Research Categories » Delivery of Care and Alternative Models

DECREASED TIME FROM DIAGNOSIS TO REFERRAL OF PDAC PATIENTS: A QUALITY IMPROVEMENT EFFORT

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BACKGROUND: Pancreatic ductal adenocarcinoma (PDAC) represents the third leading cause of cancer-related death. Germline mutations are present in up to 10% of cases, having implications for treatment and familial risk. The National Comprehensive Cancer Network guidelines recommend genetic counseling/testing (GC/GT) for all individuals with PDAC. The goals of this quality improvement program were to increase the number of patients referred for GC/GT and decrease time to referral.

METHODS: Tumor registry data were reviewed for PDAC diagnosed in 2019 (baseline), 2020 (implementation) and 2021 (modification). Patient-focused materials were provided to navigation and hepatobiliary teams who were encouraged to discuss the importance of GC/GT at first contact. An electronic survey was incorporated into the navigation distress screening tool to identify eligible and willing patients, with automated email referral for GC/GT and standardized order sets. Review of electronic records was conducted to determine rates of referral, time from diagnosis to referral, appointment completion and testing rates. The project was determined to be exempt by the Ascension St. Vincent IRB.

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RESULTS: Average time from first contact to referral for GC/GT improved from baseline (210 days) in each subsequent year (101 days in 2020, 63 days in 2021) and although the referral rate did not change from baseline to year one, it slightly improved in year two (Figure 1). Of 33 tested over 3 years, 12% had a pathogenic variant (two each BRCA2, CHEK2). Notably, 50% of patients diagnosed with PDAC during this time period are now deceased.

CONCLUSIONS: Although the time from diagnosis to referral decreased, many patients with PDAC were never referred. Patients with PDAC who fail to have GC/GT represent missed opportunities to discover underlying hereditary etiology, impacting their treatment and family members' risk awareness. Additional efforts are needed to improve referral for GC/GT

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Keywords: Pancreatic cancer, hereditary cancer testing, genetic counseling, quality improvement

Figure 1: Quality improvement measures of PDAC patients referred for GC/GT

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Research Categories » Early Onset Colorectal Cancer

THE DIAGNOSTIC YIELD OF COLONOSCOPIC SURVEILLANCE POST EARLY ONSET COLORECTAL CANCER RESECTION

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BACKGROUND: The primary benefit of post-colorectal cancer (CRC) colonoscopic surveillance is to detect and remove premalignant lesions to prevent metachronous CRC. Current guidelines for long-term colonoscopic surveillance post early-age onset CRC (EOCRC) resection are based on limited evidence. The aim of this study was to assess the diagnostic yield of colonoscopic surveillance post-EOCRC resection, and identify risk factors associated with advanced and non-advanced neoplasia.

METHODS: A retrospective cohort study conducted at St Mark's Hospital, London, United Kingdom, for patients

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diagnosed with EOCRC that underwent at least one episode of post-CRC colonoscopic surveillance between 1978 and 2022.

RESULTS: In total, 908 colonoscopic surveillance procedures were performed in 195 patients over 2581.3 person-years of follow-up. The diagnostic yield of metachronous CRC, advanced adenomas and non-advanced adenomas were 1.76%, 3.41% and 22.69% respectively. Sixteen patients(8.21%) developed metachronous CRC and the majority(87.5%) were detected more than 3 years post index EOCRC diagnosis. Risk factors associated with non-advanced neoplasia were male gender (OR, 1.83; 95% CI 1.04 -3.26, P=0.04), family history of CRC in first degree relative (OR, 0.95, 95% CI 0.91-0.99, P=0.004) and Dukes' stage A (OR, 2.77; 95% CI 1.07-7.79, P=0.04). There was no significant difference detected between surveillance episodes in the yield of non-advanced neoplasia and advanced neoplasia(P=0.0707 and P=0.8382 respectively). The prevalence of advanced neoplasia and non-advanced neoplasia for Lynch syndrome were 6.97% and 24.66% respectively, and for EOCRC in which Lynch syndrome is excluded, they were 4.63% and 58.29% respectively. Detection of advanced neoplasia was significantly higher in Lynch syndrome(26.15%) compared to EOCRC where Lynch syndrome is excluded(13.13%) (OR, 2.343; 95% CI, 1.014 to 5.256; P=0.0349).

CONCLUSIONS: During colonoscopic surveillance post-EOCRC resection, the long-term risk of developing metachronous advanced neoplasia remains high in the context of Lynch syndrome but this trend is not as clearly evident when Lynch syndrome has been excluded.

Keywords: Early onset colorectal cancer, EOCRC, Lynch syndrome, Metachronous, Neoplasia; colonoscopic surveillance

Table 1: Number of patients with metachronous CRC, advanced adenomas and non-advanced adenomas detected via long term colonoscopic surveillance post-EOCRC resection based on data were mismatch repair (MMR) status was available.

Table 1: Number of patients with metachronous CRC, advanced adenomas and non-advanced adenomas detected via long term colonoscopic surveillance post-EOCRC resection based on data were mismatch repair (MMR) status was available.

	Lynch syndrome (N=65)	Lynch syndrome excluded (N=99)
CRC	10 (15.38%)	5 (5.05%)
Advanced adenomas	10 (15.38%)	8 (8.08%)
Non advanced adenomas	31 (47.69%)	45 (45.45%)

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Research Categories » Early Onset Colorectal Cancer

EARLY ONSET VS. LATER ONSET COLORECTAL CANCER DIAGNOSIS: ANALYSIS OF GENETIC TESTING OUTCOMES

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BACKGROUND: Amidst the ongoing debate of universal germline testing for colorectal cancer (CRC), we describe genetic testing outcomes in individuals with CRC, specifically comparing early onset CRC (<50y, EO-CRC) to later onset CRC (LO-CRC)

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METHODS: A retrospective chart review was performed for individuals with CRC seen in a cancer genetics clinic between 2017 and 2021. If multiple CRC primaries were present in one individual, the age of diagnosis of the first primary was used. Descriptive statistics and Fisher exact test ($p<0.05$) were calculated.

RESULTS: Our study population included 444 individuals; 207 (46.6%) with EO-CRC and 237 (53.4%) with LO-CRC (Table 1). Genetic testing was not performed for 54 individuals; the remaining 390 patients underwent multi-gene testing. At least one likely pathogenic/pathogenic variant (LPV/PV) was identified in 76/390 (19.5%) individuals undergoing testing, excluding heterozygous results for recessive conditions. Of the six patients with two germline mutations, five occurred in were individuals with EO-CRC (83.3%). The positive-test rate was 20.3% (38 individuals) for EO-CRC and 18.7% (38 individuals) for LO-CRC; this was not significantly different ($p=0.0703$).Genes were categorized as CRC genes (61 LPV/PVs: APC, CHEK2, MLH1, MSH2, MSH6, biallelic MUTYH, PMS2, POLD1, SMAD4, TP53), and non-CRC genes (21 LPV/PVs: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDKN2A, MITF, NF1, PALB2, RAD50, RAD51C, SDHA, SDHAF2, SDHB, VHL) (Table 2). CRC genes accounted for 83.7% of LPV/PV in EO-CRC compared to 64.1% in LO-CRC ($p=0.0478$).

CONCLUSIONS: Although the positive-test rate was similar between EO-CRC and LO-CRC, we observed more CRC-related LPV/PVs with EO-CRC. However, the genetic diversity in each group emphasizes the importance of multi-gene testing. As the evidence for testing all patients with CRC evolves, continued collaboration is necessary among genetic counselors and oncology/GI providers to ensure patients are receiving comprehensive testing and appropriate management recommendations.

Keywords: early onset CRC, genetic testing outcomes

Fig1

Breakdown of 444 individuals with colon and rectal cancer and their genetic testing outcomes

Table 1: Breakdown of 444 Individuals with Colon and Rectal Cancer						
	Early Onset			Later Onset		
	Colon	Rectal	CRC Total	Colon	Rectal	CRC Total
Total	171	36	**207**	202	35	**237**
No Test	14	6	**20**	26	8	**34**
Positive Test	34	4	**38**	35	3	**38**
Negative Test	123	26	**149**	141	24	**165**

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Fig2

Distribution of genes in which likely pathogenic/pathogenic variants were identified in this cohort

Table 2: Distribution of Likely Pathogenic/Pathogenic Variants (n=82)			
	EO-CRC	LO-CRC	Total
CRC Genes			
APC	5	1	6
CHEK2	3	5	8
MLH1	10	4	14
MSH2	7	5	12
MSH6	1	7	8
MUTYH	2 (Biallelic)	0	2
PMS2	4	3	7
POLD1	2	0	2
SMAD4	1	0	1
TP53	1	0	1
Total	**36**	**25**	**61**
Non-CRC Genes			
ATM	1	3	4
BARD1	0	1	1
BRCA1	1	1	2
BRCA2	0	2	2
BRIP1	0	1	1
CDKN2A	0	1	1
MITF	0	1	1
NF1	0	1	1
PALB2	1	0	1
RAD50	1	0	1
RAD51C	0	1	1
SDHA	1	1	2
SDHAF2	1	0	1
SDHB	1	0	1
VHL	0	1	1
Total	**7**	**14**	**21**

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Research Categories » Other

SEEING DOUBLE! PATIENTS WITH COLORECTAL CANCER AND MULTIPLE GERMLINE PATHOGENIC VARIANTS

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BACKGROUND: The increased uptake of multi-gene panel testing (MGPT) for hereditary cancer has led to the identification of patients with multiple pathogenic/likely pathogenic variants (P/LPV). We examined the genetic testing outcomes and clinical presentations in patients with colorectal cancer (CRC), focusing on those with multiple P/LPV.

METHODS: A retrospective chart review was performed for patients with a diagnosis of CRC seen for genetic counseling between 2017 and 2021.

RESULTS: Seventy-six patients with CRC tested positive for at least one P/LPV; over 85% of these patients had MGPT. Six of the 76 (7.9%) had two P/LPV. One patient had MUTYH-Associated Polyposis (MAP) syndrome and was excluded, leaving five patients with double positives for analysis (Table 1 for reference). Of these, three had P/LPV in two CRC genes (MLH1/CHEK2, PMS2/CHEK2, MSH2/PMS2), while two had combinations of CRC and non-CRC genes (CHEK2/CDKN2A, APC/SDHA). The age at first CRC diagnosis ranged from 28-50y; two patients were diagnosed with more than one type of cancer. While all patients reported a family history of cancer, the family histories were not always reflective of the cancer spectrum associated with the patients' P/LPV. Only two patients

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were referred for genetic testing at the time of the CRC diagnosis; none of the patients with multiple cancers were referred for MGPT at time of first cancer diagnosis.

CONCLUSIONS: While this is a small cohort, the majority of the patients with two P/LPV were diagnosed with CRC earlier than the NCCN published average age of diagnosis for the respective genes for patients with only one P/LPV. Since a minority of patients were referred for testing at their initial diagnosis, especially for MGPT, this highlights the benefit of offering MGPT to patients with CRC and emphasizes the need for more studies in patients with multiple P/LPV to ensure comprehensive screening and management.

Keywords: multiple germline variants, hereditary colorectal cancer

Double Positives - Table 1

Table 1

Patient Sex[a], Age at DOS (y)	Genes with P/LPV	Age(s) at CRC Dx (y)	NCCN Average Age CRC Onset[b] (y)	Additional Cancer History (Age Dx, y)	Reported Family History of Cancer
Male, 66	*MLH1* *CHEK2*	28, 66	*MLH1*: 44, *CHEK2*: N/A	Non-melanoma skin cancer (62)	Breast, CRC, Gastric, Renal
Female, 67	*PMS2* *CHEK2*	48	*PMS2*: 61-66, *CHEK2*: N/A	N/A	CRC, Glioblastoma, Liver, Thyroid
Male, 77	*MSH2* *PMS2*	35	*MSH2*: 44, *PMS2*: 61-66	Sebaceous neoplasms (61, 63); Small bowel cancer (69); Prostate cancer (69); Non-melanoma skin cancer (unknown)	CRC, Prostate
Female, 50	*CHEK2* *CDKN2A*[c]	50	*CHEK2*: N/A, *CDKN2A*: N/A	N/A	Multiple myeloma
Male, 47	*APC*[d] *SDHA*	46	*APC*: 39, *SDHA*: N/A	N/A	Breast, CRC, Throat

[a] Sex refers to sex assigned at birth; DOS refers to genetic counseling Date of Service
[b] NCCN Genetic/Familial High-Risk Assessment: Colorectal v1.2022
[c] This *CDKN2* variant is c.146T>C, which has conflicting classifications of pathogenicity among different clinical laboratories
[d] This *APC* pathogenic variant is associated with classic Familial Adenomatous Polyposis (FAP)

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Research Categories » Early Onset Colorectal Cancer

DOWNREGULATION OF MITOCHONDRIAL FUSION MARKERS IS ASSOCIATED WITH HUMAN COLORECTAL CANCER

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BACKGROUND: Dysregulation of mitochondrial dynamics (fusion and fission) has been linked to the initiation and progression of different types of cancer including colorectal cancer. Mitochondrial fusion is mediated by dynamin-like proteins, including mitofusin 1 (MFN1), mitofusin 2 (MFN2), and optic atrophy 1 protein (OPA1). Conversely, mitochondrial fission results in a large number of small fragments, which is mediated mainly by dynamin-related

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protein 1 (DRP1). The present study is an interim analysis of the ongoing project "to study the role of mitochondrial dynamics proteins in colorectal cancer in north Indian patients".

METHODS: The expression level of mitochondrial fusion markers in 22 colorectal cancer patients was studied by RT-qPCR after the preparation of cDNA from both the tumor and normal tissues. The expression level of target genes mfn1 and mfn2 was normalized by endogenous control using β-actin. GraphPad Prism software was used for data compilation. An unpaired t-test was performed for comparison between the two groups. P-value < 0.05 was taken as statistically significant.

RESULTS: There were 16 males (73%) and 6 females in the age range of 28-71 years. Out of these 22 patients, 13 were colon cancer (59%) and 9 rectal cancer patients. In our study both the fusion markers (mfn1 and mfn2) were significantly downregulated in 16 out of 22 patients (73%) with colorectal cancer.

CONCLUSIONS: Our interim analysis suggests that loss of mitochondrial fusion markers mfn1 and mfn2 is associated with the initiation and progression of colorectal cancer in north India. Further study with large sample size is necessary to validate this finding.

Keywords: Colorectal Cancer, mitochondrial dynamics, fusion markers

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P-30

Research Categories » Gastric cancer-related syndromes

KEY FACTORS ASSOCIATED WITH THE DETECTION OF HEREDITARY DIFFUSE GASTRIC CANCER ON ENDOSCOPY IN INDIVIDUALS WITH GERMLINE *CDH1* MUTATIONS

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BACKGROUND: Individuals with germline pathogenic *CDH1* variants have a high risk of hereditary diffuse gastric cancer. Sensitivity of esophagogastroduodenoscopy (EGD) in detecting signet ring cell carcinoma (SRCC) in this population is low. We aimed to identify endoscopic findings and biopsy practices associated with detection of SRCC.

METHODS: This retrospective cohort included individuals with a germline pathogenic/likely pathogenic *CDH1* variant undergoing at least one EGD at Memorial Sloan Kettering Cancer Center (MSKCC) between January 1, 2006 and March 25, 2022. The primary outcome was detection of SRCC on EGD. Findings on gastrectomy were also assessed. The study included periods before and after implementation of the Cambridge protocol for endoscopic surveillance, allowing for assessment of a spectrum of biopsy practices.

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RESULTS: Ninety-eight *CDH1* patients underwent at least one EGD at our institution. SRCC was detected in 20 (20%) individuals on EGD overall, and in 50/58 (86%) of those undergoing gastrectomy (Table 1). Most SRCC foci were detected in the gastric cardia/fundus (EGD: 50%, gastrectomy: 62%) and body/transition zone (EGD: 60%, gastrectomy: 62%; Table 1). Biopsies of gastric pale mucosal areas were associated with detection of SRCC (p<0.01; Table 2). The total number of biopsies taken on EGD was associated with increased detection of SRCC (p=0.01), with 43% detected when 40 or more biopsies were taken (Table 2).

CONCLUSIONS: Targeted biopsies of gastric pale mucosal areas and increasing number of biopsies taken on EGD were associated with detection of SRCC. SRCC foci were mostly detected in the proximal stomach, supporting updated endoscopic surveillance guidelines. Further studies are needed to refine endoscopic protocols to improve SRCC detection in this high-risk population.

Keywords: hereditary diffuse gastric cancer, endoscopy, signet ring cell carcinoma

Table 1

Table 1. Characteristics of individuals with a pathogenic/likely pathogenic *CDH1* variant and at least one endoscopic exam at MSKCC

Characteristics	Individuals with *CDH1* Mutation - Overall Cohort (n=98)
Age (mean)	43.8 (13.8)
Female (%)	68 (69%)
Race/Ethnicity	
Non-Hispanic White	89 (91%)
Black	5 (5%)
Asian	4 (4%)
Unknown	2 (2%)
Family History of Gastric Cancer	
First or Second Degree	70 (72%)
Third degree only	8 (8%)
No Family History	20 (20%)
Personal History of Breast Cancer (in Females, n=68)	
Invasive Lobular Breast Cancer	14 (21%)
Lobular Carcinoma In Situ	9 (13%)
Other Breast Cancer	1 (1%)
None	44 (65%)
Personal History of Other Cancer (Excluding Breast Cancer)	
Colon/Rectal	5 (5%)
Basal Cell Carcinoma	1 (1%)
Melanoma	1 (1%)
Multiple Myeloma	1 (1%)
None	92 (94%)
Type of *CDH1* Variant	
Pathogenic	84 (86%)
Likely Pathogenic	14 (14%)
Median Follow Up (Range) From genetic testing to last EGD or gastrectomy:	7.1 months (0.3-168.0mo)
Total Number of EGD Procedures Overall	178
Total Number of EGDs per Patient	
1	66 (68%)
2	14 (14%)
≥3	18 (18%)
SRCC Detected on EGD	
Initial EGD	13 (13%)
Any EGD	20 (20%)
Location of SRCC Foci on EGD (n=20)	
Cardia/Fundus	10 (50%)
Body/Transition Zone	12 (60%)
Antrum/Pre-pyloric	2 (10%)
Gastrectomy	58 (59%)
SRCC Detected on Gastrectomy	50 (86%)
Location of SRCC Foci (n=50)	
Cardia/Fundus	31(62%)
Body/Transition Zone	31 (62%)
Antrum/Pre-pyloric	8 (16%)
Death	
Metastatic Breast Cancer	2 (2%)
Other Cause	2 (2%)

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Table 2

Table 2. Findings on upper endoscopy and detection of signet ring cell carcinoma (SRCC) on endoscopy in individuals with pathogenic/likely pathogenic variants in *CDH1* with at least one endoscopic exam at MSKCC.

Finding	Total EGDs (n=178)	SRCC Detected (n=20)	P-value
Any Abnormality on EGD	84	11 (13%)	0.46
Targeted Biopsy (n=84)			
Pale Area	13	4 (31%)	**0.01**
Nodular Mucosa	17	0 (0%)	0.34
Erosion/Ulcer	10	1 (10%)	0.99
Polyps	33	0 (0%)	0.52
Erythema	42	2 (5%)	0.49
Additional Histologic Findings (n=176)			
Normal Mucosa	54	6 (11%)	0.99
Gastritis	100	12 (12%)	
Intestinal Metaplasia	21	2 (10%)	
Atypia/Dysplasia	1	0 (0%)	
***Helicobacter pylori* Positive**	5	0 (0%)	0.57
Total Number of Biopsies per EGD (n=174)			
<20	68	5 (7%)	**0.01**
20-29	70	5 (7%)	
30-39	29	6 (21%)	
≥40	7	3 (43%)	

Note: Procedures for which complete pathology reports or records confirming total number of biopsies taken were not available were excluded.

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Research Categories » Gastric cancer-related syndromes

GENERATION OF HUMAN IPSCS FROM HDGC FAMILIES CARRYING THE *CDH1* C.1901C>T PATHOGENIC VARIANT AND WGS ANALYSIS OF CANDIDATE HDGC GENETIC MODIFIERS

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BACKGROUND: Hereditary diffuse gastric cancer (HDGC) caused by *CDH1* germline pathogenic, or likely-pathogenic variants predisposes to early onset diffuse gastric (DGC) and lobular breast cancer (LBC). Intriguingly, disease penetrance is incomplete, and most families display individual phenotype heterogeneity reflecting great variability in clinical behaviour or age of onset. We aim to characterize the genome and transcriptome of mutation carriers to distinguish young-affected carriers from old-healthy carriers in a group of 11 Portuguese families carrying the same *CDH1* c.1901C>T variant, which we demonstrated to be a bona fide pathogenic variant in Northern Portugal. We seek to establish the largest HDGC *CDH1* mutated induced Pluripotent Stem Cell (iPSC) biobank and identify genetic modifiers that either predispose or protect carriers, leading to a more robust predicted risk of disease development.

METHODS: 27 individuals from 11 families sharing a *CDH1*-founder variant were selected for WGS and analyzed with an in-house developed pipeline proved to be feasible in prioritizing true-positive and disease-causing SNVs. Additionally, blood samples for reprogramming using the Sendai virus integration-free method were obtained from 9 individuals: 3 young-affected carriers; 3 old-healthy carriers and 3 non-carriers
RESULTS: Our genome-wide strategy allowed us to identify novel specific SNVs of each carriers' groups (young vs old) that can be candidate genetic modifiers for HDGC. The generated iPSCs are being tested for chromosomal stability, expression of pluripotency markers and differentiated into stomach organoids to explore its distinct transcriptional profiles and validate the candidate modifiers.

CONCLUSIONS: This is a pioneer work that establishes for the first time a new cell model to study HDGC that can be further differentiated towards stomach and breast organoids, the main targets organs of HDGC disease development. Additionally, candidate modifiers will be validated in our 3D cell models and c.1901C>T variant-specific penetrance will be calculated for the families in study.

Keywords: Hereditary Diffuse Gastric Cancer, CDH1, Genetic Modifiers, penetrance, iPSCs, WGS

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Research Categories » Gastric cancer-related syndromes

PAIRING TUMOR TESTING WITH GERMLINE SEQUENCING INCREASES THE NUMBER OF PATHOGENIC GERMLINE VARIANTS IDENTIFIED

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BACKGROUND: Genomic profiling of paired tumor/benign tissue can identify pathogenic germline variants (PGV) responsible for cancer syndromes. Detecting these PGVs may benefit tested patients and their family members through cascade testing (CT), preventing cancer-related deaths. We explored the impact of this tumor profiling on cancer syndrome diagnosis.

METHODS: A protocol was implemented between the Tumor Profiling Lab (TPL) and the Cancer Genetics and Prevention Program (CGPP) at Yale: oncologists and CGPP are notified when a PGV is identified though tumor testing. The notification invites the oncologist to refer the patient to CGPP. Our analysis includes data from 1/2018

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to 12/2021. Primary outcome was PGV identification. Secondary outcomes included number of patients referred to CGPP, seen by CGPP, and advised for CT.

RESULTS: A total of 144 patients (5%) with over twenty cancer types had a PGV; ninety-seven (67.4%) were new diagnoses. Forty-five of the ninety-seven (46.4%) were referred to CGPP. Over half of those referred were seen (26/45, 57.8%), and all those seen were advised for CT.
Of the 144 patients with PGVs, ninety-one (63.2%) were not seen by CGPP. Of these, thirty-nine (42.9%) were advised by their oncologist to undergo CT of family members. There was a statistically significant difference in CT advice for patients who were seen by CGPP compared to those not seen (53 vs 40, p <0.01). Overall, ninety-two of the 144 patients (63.9%) received CT advice either from CGPP or from their oncologist.

CONCLUSIONS: Two-thirds of individuals with PGVs identified by paired tumor/benign tissue analysis had not been previously diagnosed by standard of care approaches. Patients seen by CGPP were more likely to be advised for CT (p <0.01). Ninety-two families were advised for CT, with several hundreds of individuals potentially benefitting from preventive cancer measures.

Keywords: tumor sequencing, cascade testing, germline variant

Figure 1: Baseline Demographics

Baseline Demographics	**N = 144**
Age when tumor testing performed, mean (range)	60.2 (10-90)
Gender, n (%)	
Female	73 (50.7)
Male	71 (49.3)
Race, n (%)	
White	118 (82.0)
Black or African American	11 (7.6)
American Indian or Alaska Native	2 (1.4)
Asian	2 (1.4)
Other/Not Listed, Patient Refused, or Unknown	11 (7.6)
Ethnicity, n (%)	
Hispanic or Latinx	7 (4.9)
Not Hispanic or Latinx	137 (95.1)
Stage when tumor testing performed*, n (%)	
Stage IV	117 (82.4)
Stage I, II, or III *Two patients with unclear staging	25 (17.6)
Known Pathogenic Germline Variant (PGV), n (%)	
Known	47 (32.6)
New	97 (67.4)
Known to CGPP, n (%)	
Known	25 (17.4)
Not Known	119 (82.6)
Referral to CGPP, n (%)	
Referred	49 (34.0)
Not Referred	71 (49.3)
N/A (Known to CGPP)	24 (16.7)
Seen by CGPP, n (%)	
Seen	53 (36.8)
Not Seen	91 (63.2)
Days from referral to visit, median (range)	17 (1-217)
Advised for CT (including seen by CGPP), n (%)	
Advised	92 (63.9)
Not advised	52 (36.1)
Advised for CT (if not seen by CGPP), n (%)	**N = 91**
Advised	39 (42.9)
Not advised	52 (57.1)

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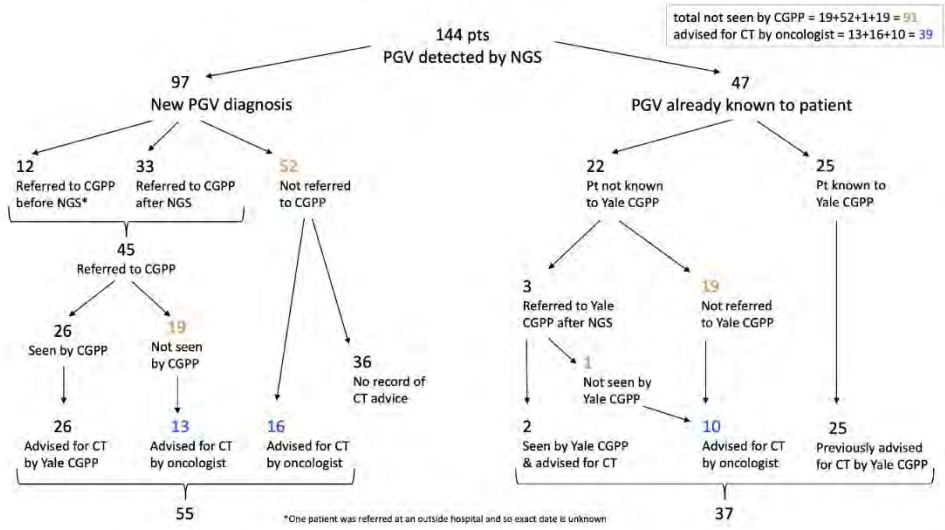
Figure 2: Flow Chart



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Research Categories » Gastric cancer-related syndromes

THE EXPECTATION FOR CONVERSION THERAPY OF STAGE 4 GASTRIC CANCERS

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BACKGROUND: The prognosis of unresectable stage 4 gastric cancer(GC) is very poor, and 5 year-survival late is less than 10 % in the world. Because of advanced recent chemotherapy, and annual immunotherapy, still only a few, but slightly increasing the cases of resettable shifted are getting long-term survival benefit. The reason why GC has poor progression, cancer introducing MDSCs (Myeloid-derived suppressor cell) already build metastatic Niche in the microenvironment. We are measuring that MDSCs for new biomarker. Our department has been challenging such a conversion therapy by minimum invasive (laparoscopic and robotic) surgery for 5 years. Conversation surgery means the mission exchanging for impossible to possible. Recently CONVO-GC-1 trial has been published, recommend to classify 4 categories, the absence (categories 1 and 2) or presence (categories 3 and 4) of macroscopically detectable peritoneal dissemination. We evaluate the results of conversion therapy, in the treatment of GC following these categories. And present our biomarker project of MDSCs for GC.

METHODS: Retrospective analysis of 116 Stage 4 GC cases in Juntendo between 2016 and 2021. Patients who received any therapy and/or surgery were further identified to define the conversion group.

RESULTS: Out of 116 chemotherapy performed for GC in Juntendo, 17 cases underwent conversion therapy(14%). Her2 positive case(n=4) did not get good response, DFS rate, compare with negative cases (category 1=7, category2=4, category3=2). Especially Category2 and 3 treated by DSF had good responses DFS rate, compare with chemotherapy alone. MDSCs results very similar with lung cancer result. This time, we show this conversion cases MDSCs scores.

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CONCLUSIONS: Conversion therapy may offer the possibility of prolonged survival for GC patients, classify CONVO-GC-1 trial.

Keywords: gastric cancer, conversion surgery, MDSCs

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Research Categories » Gastric cancer-related syndromes

PAIRED GENETIC TESTING AT DIAGNOSIS OF ESOPHAGEAL AND/OR GASTRIC CANCER INCREASES ACCESS TO TARGETED THERAPY AND CANCER PREVENTION.

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BACKGROUND: People diagnosed with gastro esophageal cancer (GEC) face a dismal 5-year overall prognosis. Tumor profiling in patients with GEC guides eligibility for targeted therapy that have proven to be highly effective in microsatellite instable (MSI) tumors and reveal the presence of a hereditary cancer syndrome (HCS). Coverage for germline genetic testing is often denied for patients with GEC because guidelines for testing eligibility and multigene panel recommendations are lacking.

METHODS: Patients with GEC are enrolled from our NCI-designated cancer center in Seattle, Washington between January 2021 and December 2022. Patients receive paired tumor profiling and germline genetic testing at GEC diagnosis through the University of Washington's OncoPlex and BROCA panels. Results are used to support authorization of targeted therapy. If a patient is identified to carry a pathogenic variant for a HCS, we offer family testing and a consultation with our dedicated high risk and prevention clinics.

RESULTS: 29 patients consented to receive paired testing. In 2021-2022, 5 patients were diagnosed with esophageal cancer, 23 patients had gastric cancer, and 1 patient had two separate primary cancers with one being an esophageal cancer. This is on par with recent studies suggesting that 15%-20% of patients with upper gastrointestinal cancers have a HCS. 5 patients had an actionable result in which they either had MSI or a germline pathogenic variant in a high penetrant DNA damage response gene that led to change in treatment or follow-up screening and prevention.

CONCLUSIONS: Expanding guidelines for germline genetic testing of patients with GEC will help increase identification of a HCS and eligibility for targeted therapies at diagnosis. Identifying King syndrome and Lynch syndrome will also help guide follow up screening, early detection, and prevention for patients with GEC and their at-risk relatives.

Keywords: gastric cancer, esophageal cancer, paired genetic testing, targeted therapy, screening, prevention

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Research Categories » Lynch syndrome

LYNCH SYNDROME IS ASSOCIATED WITH FECAL AND SALIVARY DYSBIOSIS

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BACKGROUND: The oral and fecal microbiota of Lynch syndrome patients (LSP) may differ from healthy controls (HC).

METHODS: We compared the fecal microbiota of 17 LSP (14 MSH2, 2 MLH1, 1 MSH6) vs 21 HC, and the oral microbiota of 37 LSP (9 MLH1, 23 MSH2, 2 MSH6, 3 PMS2) vs 11 HC. 16 LSPs had CRC, 2 gastric cancer, 1 pancreatic cancer, and 1 neuroendocrine tumor. On average, 9.2 years had elapsed from cancer treatment to microbiota collection. We purified and amplified the V3-V4 region of the 16s rRNA gene and discriminated microbial from human reads with BMTagger. For species/family/order level analysis, reads were mapped to the collection of all available genomes with Kraken2 for exact alignment of k-mers and accurate read classification. Relative abundances were calculated with Pavian. Differential abundance were performed with DESeq2 upon variance-stabilizing transformation.

RESULTS: UMAP analysis could differentiate oral samples from fecal samples at the order, family, and species level. Fecal beta-diversity (but not alpha-diversity) differentiated LSP vs HC. LSPs demonstrated a significant reduction in the abundance of fecal Firmicutes, including 6 bacterial orders, 14 bacterial families and 36 bacterial species. LSPs also showed an increase in fecal Bacteroidetes: these included 15 bacterial orders, 25 bacterial families and 71 bacterial species (Fig1)
Salivary alpha and beta diversity differentiated LSP vs HC. LSPs demonstrated a significant reduction in salivary Proteobacteria (including 3 bacterial orders, 7 bacterial families and 72 bacterial species) and an increase in salivary Firmicutes, with a higher expression of 5 bacterial orders, 8 bacterial families and 36 bacterial species (Fig2).

CONCLUSIONS: LSP demonstrated a significant disruption of both the oral and fecal microbiota. Firmicutes became the dominant salivary phylum over Proteobacteria. The increase in salivary Bacteroidetes lead to a significant decrease in salivary Firmicutes.

Keywords: microbiota, microbiome, firmicutes, proteobacteria, oral, intestinal

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Figure 1

Fecal microbiota composition (Panel A) of Lynch syndrome patients, compared to age-matched and sex-matched healthy controls, and differential abundance (Panel B) in the fecal microbiota in terms of order, family, and species

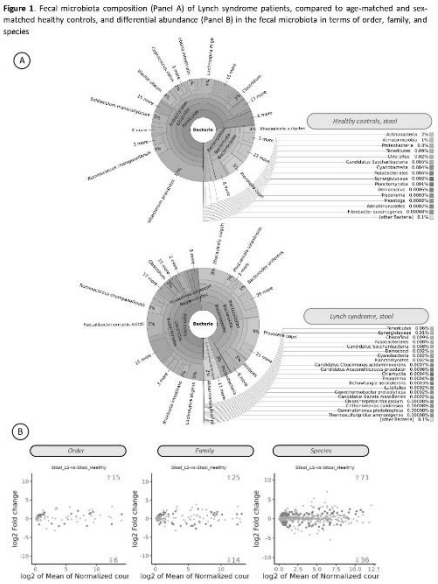
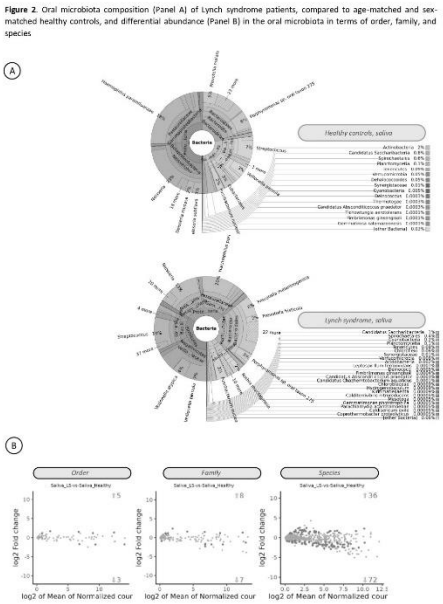


Figure 2

Oral microbiota composition (Panel A) of Lynch syndrome patients, compared to age-matched and sex-matched healthy controls, and differential abundance (Panel B) in the oral microbiota in terms of order, family, and species



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Research Categories » Lynch syndrome

IMPLEMENTING SYSTEMATIZED PATIENT-FACING LYNCH SYNDROME (LS) RISK ASSESSMENT IN ONCOLOGY USING THE ELECTRONIC HEALTH RECORD (EHR) SYSTEM

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BACKGROUND: Lynch syndrome (LS) is the most common inherited cause of colorectal (CRC) and endometrial cancers. Significant provider and institutional level barriers limit LS detection. PREMM5 is a validated tool that uses personal and family cancer history for LS risk assessment and is recommended by national professional societies. We examined the feasibility of using a patient-facing PREMM5 screener embedded in an electronic health record (EHR) system as a means of improving LS identification.

METHODS: The PREMM5 LS screener intake questions were iteratively adapted to be completed by patients rather than healthcare providers. The patient-facing PREMM5 LS screener was embedded in the EHR (Epic) at the Dana-Farber Cancer Institute (DFCI) to enable offsite and onsite completion. All new gastrointestinal (GI) cancer patients seen at DFCI for initial oncology consultation from 6/2020-2/2022 were invited through the EHR portal to complete the screener. PREMM5 scores ⩾2.5% were considered "positive", with genetics referral recommended. Beginning 2/2021, the EHR generated an automated provider-facing alert for positive screens.
RESULTS: 40% (1646/4119) of new GI cancer patients completed the screener. 406/1646 (25%) had a positive PREMM5 screen (mean age 52 years), of whom 66% were male, and 61%, 13% and 10% had CRC, neuroendocrine and pancreas cancer respectively. 95% (387/406) of screen positives completed the PREMM5 screener offsite. 157/406 (39%) received a genetics referral (not including 564 referrals from GI oncology during the study period but outside this workflow), 20 of whom had a pathogenic variant (PV) on germline testing – Figure 1.

CONCLUSIONS: Practice-wide patient-facing EHR-integrated PREMM5 risk assessment is feasible and identified GI oncology patients not referred as part of standard workflows as warranting genetic evaluation, resulting in the identification of numerous actionable germline PVs. EHR-integrated screening has the potential to streamline genetic risk assessment for non-genetics providers. Ongoing refinement and stakeholder engagement are needed to optimize future deployment.

Keywords: PREMM5, LS Screener

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Figure 1_LS risk assessment

FIGURE 1. GERMLINE TESTING RESULTS IN PREMM5 POSITIVE SCREENS N = 89 (%)	
Pathogenic variant	20 (22)
MSH2	2 (9)
PMS2	1 (4)
ATM	2 (9)
CHEK2	1 (4)
TP53	1 (4)
MUTYH biallelic	1 (4)
BRCA1	1 (4)
BRCA2	1 (4)
NTHL1 monoallelic	3 (13)
MUTYH monoallelic	3 (13)
RECQL4 monoallelic	1 (4)
RAD50	2 (9)
BLM	1 (4)
Variant of Uncertain Significance	21 (24)
Negative	48 (54)

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Research Categories » Lynch syndrome

RISK AND PREDICTORS OF GASTRIC AND INTESTINAL CANCER IN PATIENTS WITH LYNCH SYNDROME

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BACKGROUND: The risk of gastric and small intestinal cancer in patients with Lynch syndrome (LS) remains unclear. We sought to evaluate the risk and predictors of gastric and intestinal cancer in patients with LS in a large, diverse population.

METHODS: All patients diagnosed with LS in 1/1/1997-12/31/2020 carrying at least one pathogenic variant (PV)/likely pathogenic variant (LPV) of mismatch repair genes at Kaiser Permanente Northern California (KPNC) were included. We calculated the incidences of gastric and intestinal cancer and the standardized incidence ratios (SIRs) relative to the KPNC general population. Multivariable logistic regression was conducted to identify predictors of both cancers.

RESULTS: Of 1107 patients diagnosed with LS with a median follow-up of 19.3 years (interquartile range 9.4-24.0

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years), 11 had gastric cancer (including 8 with MSH2, 2 MLH1 and 1 PMS2 PV/LPV); 11 had intestinal cancer (including 6 MSH2, 3 MLH1, 1 MSH6 and 1 PMS2 PV/LPV). For gastric cancer, cumulative incidence by age 80 was 8.06 (1.82-20.54) in males and 4.13 (0.53-14.40) in females. SIR was 8.16 (4.07-14.60) overall, 24.36 (10.52-48.00) in MSH2 PV/LPV carriers, and 7.89 (0.96-28.50) in MLH1 PV/LPV carriers. MSH2 PV/LPV (adjusted odds ratio [aOR]) 5.27 [1.03-27.05]) and Helicobacter pylori infection (aOR 5.52 [1.72-17.75]) were independent predictors of gastric cancer. For intestinal cancer, cumulative incidence by age 80 was 7.88 (3.37-14.88) in males and 2.53 (0.25-10.53) in females. SIR was 21.73 (10.42-39.97) overall, 44.24 (14.37-103.25) in MSH2 PV/LPV carriers, and 34.93 (7.20-102.08) in MLH1 PV/LPV carriers. Female sex was associated with lower risk of intestinal cancer (aOR 0.15 [0.04-0.56]).

CONCLUSIONS: Patients with LS had a significantly increased risk of gastric cancer and intestinal cancer. Screening endoscopy should be primarily considered for carriers of MSH2 and MLH1 PV/LPV and those with Helicobacter pylori infection. Risk associated with PMS2 and MSH6 PV/LPV should be further determined.

Keywords: Lynch Syndrome, gastric cancer, intestinal cancer, risk

Table 1

Table 1. Characteristics of patients with Lynch syndrome with vs. without a diagnosis of gastric or intestinal cancer

Table 1. Characteristics of patients with Lynch syndrome with vs. without a diagnosis of gastric or intestinal cancer

Characteristic	Total, n (%)	Patients with gastric cancer, n (%)	Patients with intestinal cancer, n (%)	Patients without gastric or intestinal cancer, n (%)
All	1107 (100.0)	11 (100.0)	11 (100.0)	1085 (100.0)
Median age at gastric or intestinal cancer diagnosis, years (IQR)	N/A	56 (42-63)	57 (50-66)	N/A
Sex				
Female	729 (65.9)	4 (36.4)	2 (18.2)	723 (66.6)
Male	378 (34.1)	7 (63.6)	9 (81.8)	362 (33.4)
Race and ethnicity				
Asian	164 (14.8)	0	0	164 (15.1)
Black	33 (3.0)	1 (9.1)	0	32 (3.0)
Hispanic	173 (15.6)	4 (36.4)	2 (18.2)	167 (15.4)
Non-Hispanic White	661 (59.7)	6 (54.6)	8 (72.7)	647 (59.6)
Other	76 (6.9)	0	1 (9.1)	75 (6.9)
MMR gene				
MLH1	257 (23.2)	2 (18.2)	3 (27.3)	252 (23.2)
MSH2/EPCAM	296 (26.7)	8 (72.7)	6 (54.6)	282 (26.0)
MSH6	241 (21.8)	0	1 (9.1)	240 (22.1)
PMS2	313 (28.3)	1 (9.1)	1 (9.1)	311 (28.7)
Family history of gastric cancer				
First-degree relative				
No	1062 (95.9)	11 (100.0)	N/A	1041 (95.9)
Yes	45 (4.1)	0	N/A	44 (4.1)
Second-degree relative				
No	992 (89.6)	9 (81.8)	N/A	973 (89.7)
Yes	115 (10.4)	2 (18.2)	N/A	112 (10.3)
Personal history of other malignancy				
Colorectal				
No	812 (73.4)	6 (54.6)	6 (54.6)	800 (73.7)
Yes	295 (26.6)	5 (45.4)	5 (45.4)	285 (26.3)
Endometrial				
No	961 (86.8)	8 (72.7)	10 (90.9)	943 (86.9)
Yes	146 (13.2)	3 (27.3)	1 (9.1)	142 (13.1)
Other				
No	904 (81.7)	5 (45.4)	9 (81.8)	890 (82.0)
Yes	203 (18.3)	6 (54.6)	2 (18.2)	195 (18.0)
History of *H. pylori* infection				
Not tested	550 (49.7)	1 (9.1)	4 (36.4)	545 (50.2)
H. pylori negative	432 (39.0)	4 (36.4)	5 (45.5)	423 (39.0)
H. pylori positive	125 (11.3)	6 (54.6)	2 (18.2)	117 (10.8)
Smoking				

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Table 2

Table 2. Predictors of gastric cancer and intestinal cancer in patients with Lynch syndrome

Table 2. Predictors of gastric cancer and intestinal cancer in patients with Lynch syndrome

Variable	Adjusted odds ratio	95% CI
Gastric cancer		
Race/ethnicity		
Racial/ethnical minorities	0.84	0.28-2.51
Non-Hispanic white (ref)	1.0	
Sex		
Female	0.40	0.14-1.18
Male (ref)	1.0	
MMR gene		
MLH1	1.53	0.23-10.30
MSH2	5.27	1.03-27.05
MSH6	0.46	0.02-8.76
PMS2 (ref)	1.0	
Family history of gastric cancer		
Yes	1.39	0.37-5.23
No (ref)	1.0	
H. pylori infection		
Yes	5.52	1.72-17.75
Not tested	0.29	0.05-1.52
No (ref)	1.0	
Intestinal cancer		
Race/ethnicity		
Racial/ethnical minorities	0.56	0.17-1.84
Non-Hispanic White (ref)	1.0	
Sex		
Female	0.15	0.04-0.56
Male (ref)	1.0	
MMR gene		
MLH1	2.44	0.38-15.86
MSH2	3.89	0.69-21.94
MSH6	1.32	0.15-11.90
PMS2 (ref)	1.0	

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Research Categories » Lynch syndrome

INVESTIGATING THE ASSOCIATION BETWEEN LYNCH SYNDROME AND THE PREVALENCE OF AUTOIMMUNE DISORDERS

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POSTER ABSTRACTS

BACKGROUND: Lynch syndrome (LS) is caused by germline pathogenic variants in one of the mismatch repair (MMR) genes. It contributes to a significant portion of MMR deficient tumors, which have high levels of microsatellite instability. The insertion/deletion mutations that accumulate in microsatellites lead to neoantigen production, which triggers immune responses. T-cell responses towards these neoantigens have been observed in the peripheral blood of individuals with LS without tumor development. These data suggest that having a germline MMR pathogenic variant may elicit an immune response, raising the question of whether LS patients are at higher risk for autoimmune disorders. This study aims to assess prevalence of autoimmune disorders in a LS cohort, which has not been previously described.

METHODS: The study included 312 patients diagnosed with LS who are enrolled in our Hereditary Colorectal and Associated Tumor Registry. A retrospective chart review investigated for the presence of 30 autoimmune disorders in these patients. The prevalence of each autoimmune disorder was compared to that of the general population using two-sided exact binomial tests.

RESULTS: Of 312 patients, 35 individuals were identified to have autoimmune disorders, including 10 of 30 autoimmune conditions assessed (see figure 1). Most of the identified autoimmune disorders did not show significant differences in their prevalence compared to the general population. The prevalence of inflammatory bowel disease (IBD), however, was 1.92% in this study compared to 0.48% in the general population (p=0.004237) and rates of up to 1.5% in previously described LS cohorts.

CONCLUSIONS: This study suggests that LS patients may have higher rates of IBD, but do not seem to have significantly higher frequencies of other autoimmune disorders. Future studies should involve larger sample sizes to conduct further statistical analyses on the cancer risks in LS patients with autoimmune disorders and explore potential mechanisms of IBD overrepresentation in LS patients.

Keywords: Lynch syndrome, autoimmune disorders

Table1. Demographic breakdown by various categories: overall vs the presence of autoimmune disorders

Variable	Categories	Registry demographics		Without autoimmune disorders		With autoimmune disorders		X^2	p
		n=312	(%)	n=277	(%)	n=35	(%)		
Sex	Male	109	(27%)	101	(36%)	8	(23%)	2.796	0.094
	Female	203	(73%)	176	(64%)	27	(77%)		
Age*	<50	138	(44%)	125	(45%)	13	(37%)	0.901	0.343
	≥50	174	(56%)	152	(54%)	22	(63%)		
Race	American Indian or Alaska Native	4	(1%)	3	(1%)	1	(3%)		
	Asian	4	(1%)	4	(1%)	0	(0%)		
	Black or African American	7	(3%)	7	(3%)	0	(0%)		
	Hispanic	1	(0%)	1	(0%)	0	(0%)		
	Native Hawaiian or Other Pacific Islander	0	(0%)	0	(0%)	0	(0%)		
	White	294	(94%)	260	(94%)	34	(97%)		
	Other**	2	(1%)	2	(1%)	0	(0%)		
Prior Cancer Hx*	Yes	193	(62%)	173	(62%)	20	(57%)	0.421	0.516
	No	119	(38%)	104	(38%)	15	(43%)		
Mutation Type	MLH1	70	(22%)	65	(23%)	5	(14%)	6.786	0.079
	MSH2/EPCAM	114	(37%)	105	(38%)	9	(26%)		
	MSH6	78	(25%)	65	(23%)	13	(37%)		
	PMS2	50	(16%)	42	(15%)	8	(23%)		

Hx history
*Age and cancer history are based on the time of the enrollment
**Other: mixed racial group

Demographic data is broken down by sex, age, race, prior cancer history, and mutation types. No significant differences were observed between patients with and without autoimmune disorders. This study cohort is predominantly composed of white females.

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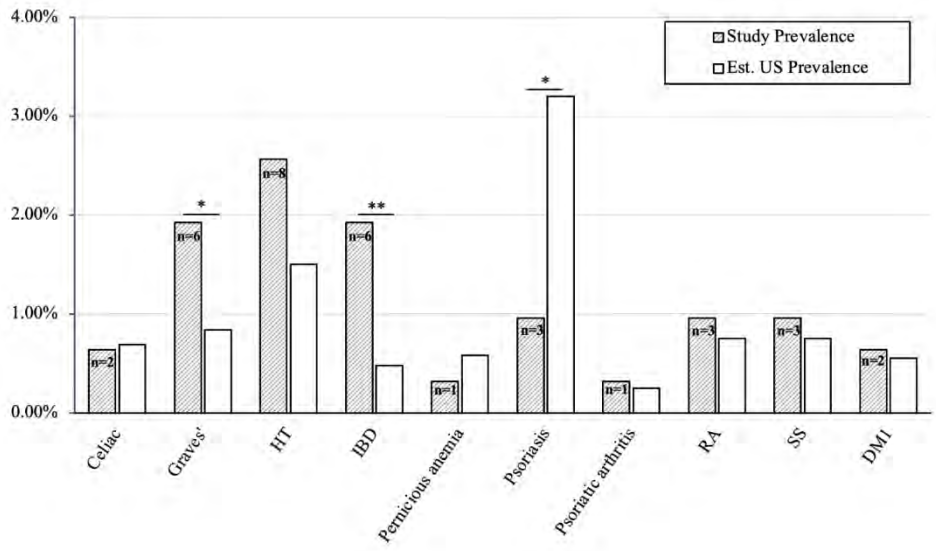
There are more individuals over 50 years old in both groups. The age of enrollment was used for this table. Prior cancer history was also obtained at the time of enrollment. Pathogenic variants in MSH2/EPCAM are most represented in this study cohort.

Figure 1. Prevalence of autoimmune disorders per condition



*The prevalence of each autoimmune disorder in this study was compared to that of the estimated United States general population. Significant differences were obtained for Graves' disease (p=0.04983), IBD (p=0.004237), and psoriasis (p=0.02229). * represents a nominally significant difference (p<0.05) and ** represents a significant difference after Bonferroni correction (p<0.005). HT= Hashimoto's Thyroiditis, IBD= Inflammatory Bowel Disease, RA= Rheumatoid Arthritis, SS= Sjogren's syndrome, DM1= Type1 Diabetes Mellitus. Other 20 autoimmune disorders assessed include addison's disease, ankylosing spondylitism, aplastic anemia, Behcet's disease, chronic inflammatory demyelinating polyneuropathy, cutaneous lupus, eosinophilic granulomatous polyangiitis, giant cell arteritis, granuloma annulare, Guillain-Barre syndrome, Henoch-Schonlein purpura, IgA nephropathy, multiple sclerosis, myasthenia gravis, myositis, pemphigus vulgaris, polyarteritis nodosa, scleroderma, systemic lupus erythematosus, and vasculitis.*

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Research Categories » Lynch syndrome

STAKEHOLDER VIEWS OF THE FUTURE NEEDS TO IMPROVE IMPLEMENTATION OF SCREENING FOR LYNCH SYNDROME

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BACKGROUND: The PCORI SPRINTS (Stakeholders Working Together for Strategic Planning Retreats in Tumor Screening) Project is a collaboration between the Lynch Syndrome Screening Network (LSSN) and AliveAndKickn that aims to identify the current clinical and patient-centered issues, gaps, barriers, and priorities for Lynch syndrome screening programs to improve the identification of individuals with Lynch syndrome.

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METHODS: Two activities were conducted using a deliberative engagement format. The first activity was conducted in conjunction with the Living with Lynch Patient Workshop in Columbus, Ohio from September 10-12, 2021. The second activity was conducted in conjunction with the 2021 Collaborative Group of the Americas on Inherited Gastrointestinal Cancer (CGA-IGC) virtual Meeting November 13-15. A follow up survey including the strategic priorities and a series of actions identified to make progress towards those priorities was sent to all participants. Respondents rated each action step based on its importance and feasibility.

RESULTS: Sixteen individuals (12 patients, 4 caregivers/spouses) participated in the Living with Lynch workshop and 25 clinician/researcher stakeholders participated in the CGA-IGC activity. Five participants (three patients and two clinician/researchers) completed the follow up survey. Three main strategic priority areas were identified across all stakeholder groups: 1) Cascade testing, 2) Facilitating true universal tumor screening/identification, and 3) the creation and use of registries. Additional priorities not under these areas were identified by patient/caregiver stakeholders related to adhering to guidelines and downstream care activities. Activities both important and feasible for each priority area included: encouraging optimized implementation of LS screening programs, education and awareness building about LS, and using registry data to answer priority research questions.

CONCLUSIONS: Engagement of stakeholders is important to ensuring the programs and research priorities promoted by organizations like the LSSN meet the needs and address barriers experienced by individuals with Lynch syndrome and clinician/researchers dedicated to impacting their lives.

Keywords: Lynch syndrome, engagement

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Research Categories » Lynch syndrome

UNDERSTANDING UNIVERSAL LYNCH SYNDROME TUMOR SCREENING PROGRAM IMPLEMENTATION IN HEALTHCARE SYSTEMS – COMPARISON OF SYSTEMS WITH AND WITHOUT PROGRAMS

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BACKGROUND: Variable implementation of Universal tumor screening (UTS) for Lynch syndrome (LS) in health systems is one reason most individuals with LS remain undiagnosed. The IMPULSS study was designed to understand this variability and retrospectively identify core components of implementation and optimization across multiple purposively selected healthcare systems.

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METHODS: Semi-structured interviews guided by the Consolidated Framework for Implementation Research (CFIR) were conducted with 66 organizational stakeholders across 9 healthcare systems. Interviews were coded for CFIR constructs and process diagrams for LS screening were constructed. CFIR constructs were further coded for valence and multi-value coincidence analysis was conducted to identify key difference-makers between systems without UTS programs, non-optimized UTS programs, and optimized UTS programs.

RESULTS: A total of 19 different workflows for LS screening within the 9 health systems were identified. Five elements important for optimally implemented and efficient LS tumor screening programs were determined. The two key ingredients for an optimized LS screening program identified were the presence of a maintenance champion and a positive inner setting. Programs that are not optimally functioning had positive perceptions of relative advantages/evidence, mixed inner setting, and lacked a maintenance champion. Key difference-makers resulting in organizations without programs were negative attitudes, lack of knowledge, and mixed perceptions of relative advantages/evidence for universal tumor screening. This solution explained 17 of 18 analytic units and had the highest consistency (1 out of 1), highest coverage (0.9 out of 1), and second highest fit robustness score (0.82).

CONCLUSIONS: Knowing and targeting health system-specific implementation issues and contextual attributes can help individuals seeking to implement/optimize UTS programs to better address specific issues likely to make a difference in their organization. These results are influencing the development of targeted tools to more effectively facilitate UTS program implementation, maintenance, and optimization to improve the overall identification of individuals with LS.

Keywords: Lynch Syndrome, Tumor Screening, Implementation, Coincidence Analysis

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Research Categories » Lynch syndrome

MSI DETECTION IN CIRCULATING TUMOR DNA IN A HETEROGENOUS COHORT OF ADVANCED CANCER PATIENTS WITH AND WITHOUT UNDERLYING LYNCH SYNDROME

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BACKGROUND: Lynch Syndrome(LS) is a cancer predisposition with high-risk of multiple cancers that characteristically demonstrate microsatellite instability(MSI-H). Analyzing mutations in circulating tumor DNA(ctDNA) has emerged as a method to monitor treatment response. We leveraged MSI loci captured by our ctDNA NGS platform(MSK-ACCESS) to detect MSI in ctDNA of advanced cancer patients. METHODS: Patients were consented to an IRB-approved protocol of tumor/germline NGS assessment(MSK-IMPACT). LS status was determined by presence of a germline mutation in an MMR gene. ctDNA samples were prospectively collected from patients with advanced MSI-H-tumors. Tumor fraction was estimated by average variant allele fraction(VAF) across all genomic sites mutated in tumor. MSI-ctDNA was classified as binary: “MSI-detected”/“MSI-not-detected.” We assessed if MSI-ctDNA detection varied by LS-status, age, gender, tumor-type, and immune checkpoint inhibitor(ICI)use in patients with clinically-active disease as determined by standard clinical imaging.

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RESULTS: 105 samples were collected from 59 patients (30 female) with history of advanced MSI-H tumors, of which 50(85%) had clinically-active disease. MSK-IMPACT tumor-types included 19(38%) colorectal, 7(14%) uterine, 11(22%) gastroesophageal, 3(6%) urothelial, 2(4%) prostate, 1(2%) small bowel, and 7(14%) other. 20(40%) patients had LS. Median age did not differ by LS-status [LS:55.5, non-LS:60(p=0.13)]. Among patients receiving ICI(n=44), 16(36%) had pre-ICI ctDNA collected. MSI-ctDNA was detected in 9(56%) patients pre-ICI but only 4(14%) post-ICI (p=0.003). MSI-ctDNA detection did not vary by LS-status(p=0.2), age(p=0.13), gender(p=0.8), or tumor-type(*p=0.6;GI vs. non-GI*). 15%(9/59) patients were considered NED at initial ctDNA; however, 4 had MSI-detected including an LS-patient with prostate cancer previously treated with ICI with subsequent diagnosis of MSI-H small bowel cancer. Another presumed NED gastroesophageal patient had subsequent disease recurrence.

CONCLUSIONS: MSI-ctDNA detection was impacted by ICI, but not LS-status, age, sex, or tumor-type. MSI-ctDNA may provide increased utility in patients at risk for multiple MSI-H cancers. Additional studies are needed to maximize detection.

Keywords: Lynch Syndrome, MSI, ctDNA

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Research Categories » Lynch syndrome

CHARACTERIZATION OF SARCOMAS IN PATIENTS WITH LYNCH SYNDROME

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BACKGROUND: Lynch syndrome (LS) is a hereditary cancer predisposition syndrome caused by germline pathogenic/likely pathogenic variants (PVs) in the mismatch repair (MMR) genes. While colorectal and endometrial cancers are the most common malignancies observed in the setting of LS, sarcomas have also been reported. We sought to characterize the prevalence of LS in a cohort of patients with sarcoma.

METHODS: Retrospective review of patients consented to an IRB-approved matched tumor/normal next-generation sequencing (NGS) protocol (MSK-IMPACT) was performed to identify patients with soft tissue or bone sarcoma and germline MMR PVs (MLH1, MSH2/EPCAM, MSH6, PMS2), diagnostic of LS. Tumor MMR status was evaluated via immunohistochemical staining (IHC) and/or NGS-based microsatellite instability (MSI) analysis. Clinical records were reviewed, and descriptive statistics were performed.

RESULTS: Among 27,834 cancer patients, 5% (n=1391) had a sarcoma. Of patients with sarcoma, 1.1% (15/1391) had LS, of which 46.6% (7/15) tumors were MMR-deficient via IHC and/or MSI analysis. A PV in the MSH2 gene was identified in 46.6% (7/15) of sarcoma patients. PVs in the MLH1, MSH6, EPCAM and PMS2 were reported in 20% (3/15), 20% (3/15), 6.7% (1/15), 6.7% (1/15) of patients, respectively. IHC was concordant in 83.3% (5/6) of tumors with data available. Loss of heterozygosity (LOH) favoring the mutated germline allele was observed in 67% (6/9) of tumors assessed. Only 13.3% (2/15) of patients had a personal history of a LS-associated malignancy, with 60% (9/15) of these cases meeting genetic testing criteria for LS. None of the patients had a co-occurring PV in known sarcoma predisposition genes, such as TP53.

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CONCLUSIONS: These findings support the role of sarcoma as a rare component tumor in LS. Additional research is needed to better understand the molecular pathogenesis of sarcoma development in LS, and the potential therapeutic utility of LS germline testing for of patients with sarcoma.

Keywords: Sarcoma, Lynch syndrome, mismatch repair

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Research Categories » Lynch syndrome

ESTABLISHING A DEEP MUTATIONAL SCAN FOR FUNCTIONAL CLASSIFICATION OF MSH6 MISSENSE VARIANTS

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BACKGROUND: Lynch Syndrome is a dominantly inherited colorectal and gynecological cancer predisposition syndrome caused by loss-of-function variants in genes encoding DNA mismatch repair (MMR) factors. MSH6 is one of the key MMR factors implicated in Lynch Syndrome, and is notable in particular for its high penetrance for endometrial cancer risk. Actionability of clinical MSH6 testing is limited by the burden of missense variant interpretation as demonstrated by MSH6 missense variants in the NCBI ClinVar database, nearly all of which (2745/2802, 98.0%) are either unclassified (i.e., variants of uncertain significance) or have conflicting interpretations. To improve variant classification, We applied deep mutational scanning (DMS) to systematically generate functional data.

METHODS: We have established a DMS-based platform to systematically test missense variants across MSH6, and here we describe proof-of-principle experiments targeting a 50-residue segment of MSH6 (codons 1054-1103). We generated a saturation mutagenesis library representing all 950 distinct missense variants within this region, and introduced these one at a time into human HAP1 MSH6 knockout cells. These cells are then treated with the nucleotide analog 6-thioguanine, which selects against intact MMR activity, to deplete neutral MSH6 variants and enrich for pathogenic variants, resulting in a loss of function (LoF) score to quantify MMR activity.

RESULTS: Consistent with known functional constraint in this region, 18.8% of missense variants have a deleterious LoF score, especially around the critical p.R1076 residue, and among proline substitutions in regions of secondary structure. The LoF scores of this pilot tile were 100% concordant with known clinical pathogenic (4/4) and benign (5/5) classifications, and are well correlated with effects observed at the equivalent residues in the binding partner and distant paralog MSH2 in a previous DMS study from our group.

CONCLUSIONS: These experiments demonstrate the feasibility of deep mutational scanning of all possible MSH6 missense variants, toward their prospective interpretation.

Keywords: Genetic testing, deep mutational scanning, Lynch Syndrome, variant reclassification

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Research Categories » Lynch syndrome

UNDERUTILIZATION OF A MEDICAL POLICY COVERING UNIVERSAL MSI, IHC, AND GENETIC TESTING IN ALL PATIENTS WITH COLORECTAL CANCER

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BACKGROUND: Universal tumor screening via microsatellite instability (MSI) and/or immunohistochemistry (IHC) of all newly diagnosed colorectal cancers (CRC) is recommended. Professional societies recommend stratifying CRC patients for Lynch syndrome (LS) germline genetic testing (GGT) based on MSI/IHC results or personal/family history characteristics. In 2020, a large national US health plan instituted a medical policy covering GGT for all CRC patients. The study objective was to assess LS testing and treatments for patients diagnosed with CRC under this medical policy.

METHODS: Retrospective analyses were conducted using a longitudinal, real-world asset of de-identified administrative claims data. The study cohort included adults with newly diagnosed CRC (≥2 claims for ICD10 C18.x, C19.x, C20.x, C21.8) from 1/2017-12/2020; the earliest CRC claim was the index diagnosis date. Continuous enrollment in a plan ≥12 months pre-diagnosis and ≥6 months post-diagnosis was required with ≥1 claim for initial antineoplastic systemic therapy (ST) ≤6 months post-diagnosis. Patients were stratified into four cohorts based on receipt of GGT/IHC/MSI before initial ST. Rates of treatment, including immune checkpoint inhibitors (ICI) use, were examined by cohort during the variable follow up period.

RESULTS: Among 9,066 CRC patients, 903 (10%) had both GGT and MSI/IHC, 5,745 (63.4%) had MSI/IHC only, 130 (1.4%) had GGT only, and 2,228 (25.2%) had no testing (Table 1). Significant differences ($p<0.001$) in surgery, radiation, and ICI utilization was observed across all four cohorts (Figure 1).

CONCLUSIONS: Universal MSI/IHC did not occur in >25% of insurance-covered CRC patients. Despite a universal GGT policy for CRC patients, testing was only performed in 11.4% of patients. Underutilization of universally authorized MSI/IHC/GGT highlights the need for systematic implementation of GGT to expand access to precision therapies and improve patient care.

Keywords: colorectal cancer, tumor testing, germline testing

Figure 1

Proportion of patients receiving surgery, radiation, and immune checkpoint inhibitors in each cohort. p<0.05, assessed by Chi-Square test, for comparison between all four cohorts for surgery, radiation, and immune checkpoint inhibitor.

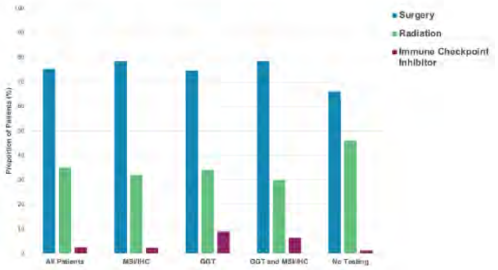

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Table 1

Demographics of colorectal cancer patients by cohort.

	All Cohorts N=9,066	Cohort 1 GGT ✅, MSI/IHC ❌ N=130	Cohort 2 GGT ✅, MSI/IHC ✅ N=903	Cohort 3 GGT ❌, MSI/IHC ❌ N=2,228	Cohort 4 GGT ❌, MSI/IHC ✅ N=5,745
% of total population of 9,066	100	1.4	10.0	25.2	63.4
Age in yrs, mean (SD)^	64.2 (12.7)	55.3 (14.8)	56.2 (14.2)	66.5 (12.0)	64.8 (12.0)
Female, N (%)	4,099 (45.2)	63 (48.4)	441 (48.8)	1,050 (45.9)	2,545 (44.3)
Site of diagnosis^, N (%) **C18 or C19 (colon)** **C20 or C21.8 (rectal)** **Colon and rectal**	 6,094 (67.2) 2,222 (24.5) 750 (8.3)	 83 (63.9) 32 (24.6) 15 (11.5)	 684 (75.8) 146 (16.2) 73 (8.1)	 1,304 (57.0) 806 (35.2) 178 (7.8)	 4,023 (70.0) 1,238 (21.6) 484 (8.4)
Follow-up^, mean (SD), median	22.8 (12.5), 20	22.5 (12.0), 21	21.7 (12.1),19	23.8 (13.3), 21	22.5 (12.3), 20

^p<0.05; assessed by ANOVA (continuous variables) and Chi-square test (proportions)

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Research Categories » Lynch syndrome

STUDY OF AGE-AT-CANCER DIAGNOSIS & COST IN UNIVERSAL SCREENING TO DETECT LYNCH SYNDROME IN THE OVERALL COLORECTAL AND ENDOMETRIAL CANCER POPULATION

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BACKGROUND: Advancing age and genetics are the greatest risk factors for developing colorectal cancer (CRC) and endometrial cancer (EC). Lynch syndrome (LS) is the most common cause of hereditary CRC (hCRC) and hereditary EC (hEC). LS patients carry a germline DNA mismatch repair mutation which predisposes them to develop hCRC and hEC at a much younger age than patients with sporadic CRC and EC. Identifying LS patients is important because cancer screening and early detection save lives. While early age-at-CRC and age-at-EC diagnoses are hallmarks of hCRC and hEC, test-performance-characteristics and cost-effectiveness have not been determined for "Age". To detect LS, universal screening of tumor tissue, using IHC and/or MSI pre-testing, is recommended for all CRC and EC patients regardless of age.

METHODS: For detecting LS, we analyzed “Age” using: i) age-at-LS diagnosis in our cohort (~500 cases) of CRC and EC patients including cases based on our institution’s universal MSI/IHC pre-testing of tumors (~1,200) and subsequent germline testing; ii) age-at-diagnosis of all CRC and EC diagnoses in the US from the SEER cancer registry.

RESULTS: Cost effectiveness analysis based on the ROC curve and costs associated with diagnosis showed that an age-cutoff of <65 is optimal for detecting hCRC and <74 for hEC patients.

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CONCLUSIONS: Pre-testing tumors for LS using these optimal age-cutoffs would be cost-effective and reduce overall costs by 65% while retaining sensitivity of >90%. These findings provide quantitative information that might be considered by clinicians in the use of universal screening at their institutions.

Keywords: Lynch syndrome, Universal screening, cost effectiveness

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Research Categories » Lynch syndrome

DIFFERENCES IN LYNCH SYNDROME COLONOSCOPY SURVEILLANCE BY PATHOGENIC VARIANT

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BACKGROUND: Among patients with Lynch syndrome, there is limited data on differences in endoscopic surveillance by pathogenic variant (MLH1, MSH2, MSH6, & PMS2), and surveillance for colorectal cancer (CRC) with colonoscopy every 1-2 years is recommended for all patients. We aimed to evaluate colonoscopy surveillance outcomes in patients with Lynch syndrome overall and compare findings by variant.

METHODS: We retrospectively reviewed colonoscopy results in patients with Lynch syndrome at our institution. Of 221 patients identified by participation in the Hereditary Gastrointestinal Cancer Registry (HGCR), 101 were included with >1 colonoscopy. Variables and surveillance results from diagnosis to May 2020 were compared by variant. Primary outcomes included development and recurrence of adenoma, CRC, high grade dysplasia (HGD), advanced adenoma (AA), and sessile serrated lesions (SSL). Logistic regressions were evaluated the relationship between pathogenic variants and development or recurrence of adenoma, SSL, and AA/HGD/CRC. A survival analysis evaluated the development of primary outcomes in patients with > 2 colonoscopies.

RESULTS: 327 colonoscopies were reviewed. Baseline characteristics were similar, but patients with MLH1 had more colonoscopies. PMS2 was associated with decreased odds of AA/HGD/CRC development compared to MLH1 (OR.102, CI.013-.507) and adenoma development compared to MSH2 (OR.240, CI.057-.902). Among those with > 2 colonoscopies, there was no significant difference in adenoma or AA/HGD/CRC development, but MSH2 had a lower risk of SSL compared to MLH1 (HR.053, CI.004-.762) and MSH6 (HR.067, CI.005-.861). For recurrence, PMS2 had a lower risk of adenoma recurrence compared to MLH1 (OR=.021, CI.021-.001) and MSH2 (OR.084, CI.006-.726). Similarly, MSH6 (OR.068, CI.004-.652) had a lower risk of adenoma recurrence compared to MLH1.

CONCLUSIONS: Surveillance colonoscopy outcomes, including SSL development, differed based on the pathogenic variant present. These findings suggest the need to further evaluate appropriate surveillance intervals based on variant.

Keywords: Lynch, variant, surveillance

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PREMALIGNANT COLONIC POLYPS AND SECOND PRIMARY MALIGNANCIES IN PATIENTS WITH LYNCH SYNDROME WITH DMMR TUMORS POST IMMUNE CHECKPOINT BLOCKADE (ICB)

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BACKGROUND: Lynch syndrome (LS) is a pan-cancer syndrome characterized by deficient MMR (dMMR) status of associated tumors sensitizing them to immune checkpoint blockade (ICB). The utility of ICB to intercept the oncogenic process in LS pts is being evaluated.

We previously demonstrated the enduring risk of pre-neoplastic polyps and second primary malignancies after ICB exposure in pts with LS. Herein we present updated analysis and mechanistic correlative work. METHODS: METHODS: The Memorial Sloan Kettering LS database was queried for all patients who received ⩾1 cycle of ICB. LS was defined by presence of a germline pathogenic alteration in DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2, EPCAM). Tumor and matched normal DNA next-generation sequencing (NGS) was performed via MSK-IMPACT, (NCT01775072).

RESULTS:138 patients with LS received ICB, predominantly (70.2%, 97/138) for metastatic cancer, 115 patients with a dMMR tumor and 23 with a pMMR tumor. Median duration of follow-up post ICB exposure was 31 months. Excluding 33 pts who remain on ICB or pts who have died, 44.8% (47/105) of pts had ⩾1 colonoscopy post ICB completion. Of these 47 pts, 14 (30%) had ⩾ 1 pre-neoplastic adenomas. Median time to adenoma development was 22 months (95% CI 16.52-27.48) from last colonoscopy and 12 months (95% CI 5.1-18.9 months) from last ICB dose. Ten patients (7.2%) developed a second primary malignancy on or following ICB (median time 21.5 months); 9/10 tumors were dMMR. NGS on pre-ICB and post-ICB tumor samples was available for 5/10 pts.; strikingly ⩽ 1 shared somatic mutation was identified.

CONCLUSIONS: In LS-patients post ICB exposure, the risk of preneoplasia and neoplasia persists. Absence of shared somatic mutations suggests differential mutation-derived neoantigens in post ICB tumors. Immunogenomic evaluation of second primaries after ICB in LS patients is warranted.
Surveillance strategies should be continued for LS patients post ICB.

Keywords: Lynch syndrome, Immune checkpoint blockade, Immune interception

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GYNECOLOGICAL CANCER RISK-MANAGEMENT NEEDS FOR INFORMATION AMONG WOMEN WITH LYNCH SYNDROME

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BACKGROUND: Women with Lynch syndrome (LS) are at an increased lifetime risk of gynecological cancers, and risk-management interventions for these types of cancers are largely low in efficacy. This study aimed to examine the experience of individuals with LS as they weighed decisions about gynecological risk-management options and to identify gaps in their information needs.

METHODS: Participants with pathogenic variants in MMR genes were recruited from a hereditary cancer registry and a gynecological oncology clinic at a cancer centre. Three groups were interviewed: those who had undergone risk-reducing surgery that included hysterectomy and bilateral salpingo-oophorectomy (RRS; n=11, M age = 50 years), those undergoing gynecological cancer screening (CS; n=14, M age = 33 years), and those who had either yet to decide or had not begun screening (NS; n=6, M age = 26 years). Gene mutations included: MLH1 (n=10), MSH2 (n=7), MSH6 (n=8), PMS2 (n=5), and EPCAM (n=1). Participants completed semi-structured telephone interviews. Qualitative thematic analysis was used to examine their experiences and to understand what information would be helpful to these individuals with LS.

RESULTS: Findings revealed a myriad of informational decision-making needs across all three groups. RRS participants reported desiring more information about hormone replacement therapy and managing post-surgical physical changes, and more comprehensive post-surgery engagement with practitioners. CS participants discussed having to self-advocate for screening with their healthcare providers and desired tailored information regarding risk-management, including surgery. NS participants expressed the need for information about cancer risk related to their gene mutation, accuracy of screening tests, and family planning; they also desired more support from healthcare providers around LS. Strategies were recommended by all groups to improve care.

CONCLUSIONS: Individuals with LS need access to greater information about gynecological cancer screening and RRS, coping with psychological and physical impacts of managing LS cancer risk, and self-advocacy strategies.

Keywords: Lynch syndrome, gynecological cancer, risk-management, decision-making, informational needs

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ESTABLISHING COLONOSCOPY ADENOMA DETECTION RATE AS QUALITY METRIC IN LYNCH SYNDROME

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BACKGROUND: In the general population, adenoma detection rate (ADR) is inversely correlated with post-colonoscopy colorectal cancer (PCCRC) and therefore the main quality metric for screening colonoscopy. However, in Lynch Syndrome (LS), such quality metric does not exist. Our aim is to characterize ADR in LS patients to establish ADR as a benchmark and develop a defined threshold to monitor colonoscopy quality in this high-risk group.

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METHODS: This retrospective cohort study included patients with a defined LS gene mutation (MLH1, MSH2, MSH6, PMS2 or EPCAM) from three health systems in the USA. Exclusion criteria included patients with inflammatory bowel disease and patients carrying additional genetic mutations with increased cancer risk. Polyp detection metrics were adenoma, advanced adenoma (AA), and colorectal cancer (CRC) detection rates. Colonoscopy quality metrics were monitored as a function of each surveillance colonoscopy and over years of surveillance.

RESULTS: Of 164 included patients, 114 underwent index colonoscopy and 94 underwent at least 1 surveillance colonoscopy. Genetic data was available for 157 patients: 26.8% MLH1, 31.2% MSH2, 25.4% MSH6, 14.6% PMS2 and 2% EPCAM. Adenoma, AA and CRC detection rate at index colonoscopy were 14.0%, 13.4%, and 15.2% respectively. The adenoma, AA, and CRC detection rate per surveillance colonoscopy were 13.3%, 3.2%, and 0.3% respectively, and per year of surveillance were 9.5%, 2.3%, and 0.2% respectively. Index and surveillance ADR were similar between centers.

CONCLUSIONS: This preliminary data serves as template to correlate ADR per colonoscopy and per year surveillance with PCCRC in LS. ADR at surveillance colonoscopy was comparable to index exam, either due to rapid polyp development in these high-risk individuals, missed polyps at index exam or both. The current sample size is too small to assess ADR and PCCRC correlation. Larger sample size would help better characterize ADR in LS and to ultimately provide recommendations for detection threshold quality metrics.

Keywords: Lynch Syndrome, Quality Metrics, Hereditary Cancer, Adenoma Detection Rate

Fig1

Fig 1. Findings at index and surveillance colonoscopy. Overview of endoscopic findings at index and surveillance colonoscopy over total number of surveillance colonoscopies and years of surveillance based on the included colonoscopies. Subgroup analysis performed on surveillance colonoscopies that were performed within 36 months of the previous colonoscopy. ADR = adenoma detection rate (including tubular adenoma <10mm), AADR = advanced adenoma detection rate (including tubular adenoma >10mm, tubulovillous adenoma, and tubular adenoma with high grade dysplasia).

Findings during colonoscopy	At index colonoscopy	Per surveillance colonoscopy	Only surveillance within 36 months	Per year of surveillance	Only surveillance within 36 months
Normal	65 (57.0%)	314 (80.5%)	278 (82%)	314 (47.1%)	278 (58.6%)
ADR	23 (20.2%)	51 (13.1%)	45 (13.3%)	51 (7.7%)	45 (9.5%)
AADR	22 (19.3%)	16 (4.1%)	11 (3.2%)	16 (2.4%)	11 (2.3%)
Cancer detection rate	25 (21.9%)	5 (1.3%)	1 (0.3%)	5 (0.8%)	1 (0.2%)
Total	114 (100%)	390 (100%)	339 (100%)	666.6 years	474.8 years

Fig2

Fig 2. Distribution of Lynch Syndrome mutations in the cohort.

Mutation	Total
MLH1	42 (26.8%)
MSH2	49 (31.2%)
MSH6	40 (25.4%)
PMS2	23 (14.6%)
EPCAM	3 (2%)
Total	157 (100%)

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THE POTENTIAL BENEFIT OF MMR, MSI AND TMB AS SOC IN THE RMH DIAGNOSTIC PATHWAY CONSIDERING THE INTRODUCTION OF THE NHS NATIONAL GENOMIC TEST DIRECTORY

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BACKGROUND: In 2020 the UK's NHS introduced the National Genomic Test Directory prompting an evaluation of existing diagnostic pathways. The Royal Marsden Hospital (RMH) is a leading cancer hospital, with the Molecular Diagnostic Laboratory designated as the lead genomic cancer testing centre for the North Thames Genomic Laboratory Hub. We propose that integrated NGS testing for mismatch repair (MMR) genes, microsatellite instability (MSI) and tumour mutational burden (TMB) in somatic testing, could, if confirmed in the germline, assist clinicians in the diagnosis of Lynch Syndrome.

METHODS: MMR/MSI/TMB NGS was correlated with available MMR immunohistochemistry (IHC) and MSI NGS was validated with Promega's OnctoMATETM MSI Dx Analysis system.

RESULTS: MSI NGS caller showed good concordance with MSI polymerase chain reaction (PCR) methods at 94.5% (86/91). Good concordance with mismatch repair deficient (MMR-d) IHC at 87.5% (21/24). The TMB caller demonstrated a right shifted normal distribution of the MMR-d IHC set vs MMR proficient IHC set however significant overlap between the two sets made interpretation limited. The TMB caller detected 3 POLE hypermutator cases with >100 mutations/Mb. The TMB scores helped classify 3 previously undescribed POLE variants as likely pathogenic. We found a hit rate of 4.4% (46/1052) of cases suspected of Lynch Syndrome when MMR and MSI NGS is combined, including one known Lynch Syndrome case confirmed by germline testing.

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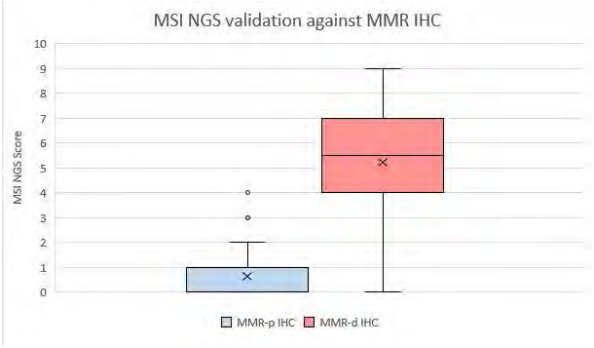
CONCLUSIONS: While promising, further work is required to fully validate the MSI and TMB callers. Moreover, a wider discussion is needed before the implementation of such an extension of scope to the RMH diagnostic pathway. Caution must be exercised when interpreting experimental results in the diagnostic setting. The previously untapped RMH dataset presents a unique opportunity to evaluate MSI, TMB and MMR-d in a variety of cancer types, with unique insights into clinical implementation within one of the world's leading genomics services.

Keywords: Mismatch repair (MMR), Microsatellite instability (MSI), Tumour mutational burden (TMB), Lynch Syndrome (LS), Next-generation sequencing (NGS)

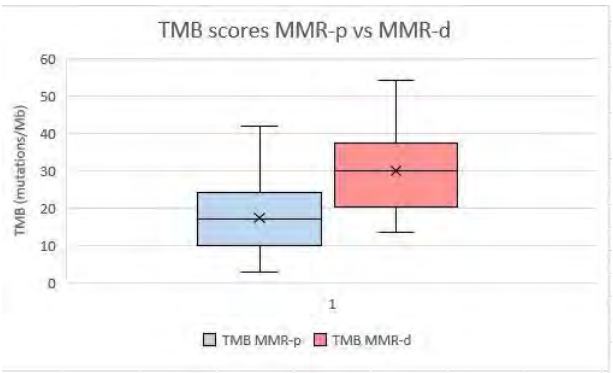
MSI NGS caller MMR-p vs MMR-d Box and whisker



Novel POLE variants TMB scores compared to known pathogenic variants.

Sample. No	Variant 1	VAF	Call	Variant 2	VAF	Call	TMB score (M/Mb)
21/03894	c.857C>G p.(Pro286Arg)	20.2%	Likely path				108.49
21/00626	c.1279_1280delinsAT p.(Ala427Ile)	19.7%	VUS	c.1196C>T p.(Ala399Val)	5.70%	VUS	198
20/12893	c.5725C>T p.(Arg1909Ter)	18.2%	VUS	c.1376C>T p.(Ser459Phe)	21.50%	Likely Path	130.19
21/05402	c.857C>G p.(Pro286Arg)	25.5%	Likely path				141.04
20/16217	c.857C>G p.(Pro286Arg)	16.6%	Likely path				107.14

TMB NGS caller MMR-p vs MMR-d Box and whisker



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MISMATCH REPAIR IMMUNOHISTOCHEMISTRY RESULTS ON NON-COLORECTAL AND NON-ENDOMETRIAL TUMOURS

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BACKGROUND: Universal reflex mismatch repair (MMR) immunohistochemistry (IHC) is becoming standard testing on colorectal (CRC) and endometrial cancers (EC). MMR deficient (MMRD) tumours may prompt germline testing for Lynch syndrome (LS), and consideration of immunotherapy treatments. Expanded tumour testing strategies are outlined to assess MMRD CRC/EC (e.g. somatic biallelic MMR, BRAF V600E, MLH1 promoter methylation). Little is understood about IHC and expanded testing in non-CRC/EC tumours.

METHODS: The Familial GI Cancer Registry (FGICR) at the Zane Cohen Centre follows individuals with LS and/or MMRD tumours. This study examined IHC results in non-CRC/EC LS tumours and expanded tumour results in MMRD non-CRC/EC tumours.

RESULTS: 283 non-CRC/EC MMRD tumours (240 individuals) were identified. 222 were LS-related (179 individuals), 2 had germline PVs impacting MMR (POLE, MLH1 epimutation), 8 biallelic MMR somatic loss, 15 MLH1 methylation, 2 somatic POLE, 1 BRAF V600E, 3 were unresolved after subsequent testing and 30 did not have expanded tumour testing. Table 1 shows expanded test results.
251 LS patients had 318 non-EC/CRC tumours (222 MMRD and 96 MMR proficient (MMRP)). This represents 35 non-CRC/EC sites. 4 IHC intact tumours were found to be MSI-H, but these were counted as MMRP since IHC is often tested in absence of MSI. 70% of non-CRC/EC tumours were MMRD correlating with germline MMR variant. In sites with > 3 tumours, strong correlations with LS was seen in ACC, bile duct, sarcoma, urothelial kidney/ureter and stomach cancers. Low correlation (< 50%) was seen in breast, cervix, non-urothelial kidney, liver, lung, prostate and thyroid cancer. See Table 2 (summary) and Table 3 (by gene).

CONCLUSIONS: Expanded tumour testing can resolve MMRD non-CRC/EC tumours. IHC can show correlation of non-CRC/EC tumours to LS. Low correlation was seen in tumours not typically linked to LS or those at high frequency in the general population.

Keywords: Lynch syndrome, Mismatch repair deficient tumour, Non-colorectal/endometrial cancers

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Table 1: Expanded tumour results in non-CRC/EC MMRD tumours (n=31, 3 unresolved, 28 resolved)

Table 1: Expanded tumour results in non-CRC/EC MMRD tumours (n=31, 3 unresolved, 28 resolved)

Resolved?	Site	Age	IHC	Methylation (Y/N) or *BRAF*	Somatic result	Germline PV
N	Small Bowel	53	MSH2/6		No variants	
N	Small Bowel	35	MSH2/6		*MSH2* PV	
N	Cervix	43	MLH1/PMS2	N	*MLH1* PV	
Y	Ureter	60	MSH2/6		*MSH6* PV + LOH	*POLE*
Y	Sebaceous adenoma	53	MSH2/6		Both *MSH2* and *MSH6* LPV + LOH	
Y	Ovarian (E)	53	MSH2/6		*MSH2* PV + LOH	*RAD51C*
Y	PSU	48	MSH2/6		*MSH2* PV + LOH	
Y	Sebaceous ca	53	MSH2/6		Biallelic *MSH2* PVs	
Y	Ovarian (CC)	55	MSH2/6		Biallelic *MSH2* PVs	
Y	Ovarian (CC/E)	51	MSH2/6		Biallelic *MSH2* PVs	
Y	Lung	44	MLH1/PMS2	N	Biallelic *MLH1* PVs	
Y	Stomach	59	MLH1/PMS2	N	*MLH1* PV + LOH	
Y	Ovarian (E/CC/S)	33	MSH6		*POLE* (hypermutant)	*BRCA1*
Y	Ovarian (CC/E)	44	PMS2		*POLE* (hypermutant)	
Y	Stoma	82	MLH1/PMS2	*BRAF*		*TP53*
Y	Keratoacanthoma	37	MLH1/PMS2	Y		*MLH1* epimutation
Y	Ovarian (E)	46	MLH1/PMS2	Y		
Y	Ovarian (CC/E)	45	MLH1/PMS2	Y		
Y	Small Bowel	50	MLH1/PMS2	Y		
Y	Neuroendocrine	40	MLH1	Y		
Y	Stomach	39	MLH1/PMS2	Y		
Y	Muscle (E)	45	MLH1/PMS2	Y		
Y	Ampulla	72	MLH1/PMS2	Y		
Y	Gastroesophageal	53	MLH1/PMS2	Y		
Y	Stomach	81	MLH1/PMS2	Y		
Y	Stomach	86	MLH1/PMS2	Y		
Y	Gastroesophageal	30	MLH1/PMS2	Y		
Y	Gastroesophageal	55	MLH1/PMS2	Y		
Y	Ovarian – (E)	59	MLH1/PMS2	Y		
Y	Small Bowel	63	MLH1/PMS2	Y		
Y	Small Bowel	66	MLH1/PMS2	Y		

Definition: PSU – primary site unknown, CC – clear cell, E – endometriod, S – serous

Table 2: IHC results in non-CRC/EC tumours from LS patients (n=318 tumours)

Table 2: IHC results in non-CRC/EC tumours from LS patients (n=318 tumours)

Site	MMRD	MMRP	Total	Overall MMRD (%)
Adrenal cortical carcinoma	4	0	4	100
Ampulla	4	1	5	80
Appendix	1	0	1	100
Bile Duct	4	0	4	100
Bladder	20	7	27	74
Brain - GBM	9	2	11	82
Brain - Meningioma	0	1	1	0
Breast	18	36	54	33
Cervix	1	3	4	25
Esophagus	1	0	1	100
Fallopian tube	0	1	1	0
Gallbladder	0	1	1	0
Kidney - urothelial	15	0	15	100
Kidney - other*	0	3	3	0
Liver	3	3	6	50
Liver - NET	0	1	1	0
Lung	2	2	4	50
Lymphoma	0	1	1	0
Multiple myeloma	1	0	1	100
Omentum	1	0	1	100
Ovarian	30	5^	35	86
Panceas	9	1	10	90
Pancreas NET	1	0	1	100
Parathryoid		1	1	0
Pelvis	2	0	2	100
Prostate	11	12^	23	48
Sarcoma	3	0	3	100
Skin (Sebaceous)	22	2	24	92
Skin cancer (non-sebaceous)	6	4	10	60
Small bowel	21	4^^	25	84
Stomach	15	0	15	100
Thyroid	0	4	4	0
Tunica vaginalis	0	1	1	0
Ureter	17	0	17	100
Vaginal	1	0	1	100
Total	222	96	318	70

* kidney – other includes renal cell carcinoma, clear cell carcinoma and chromophobe
^ one of the MMRP tumour was found to be MSI-H.
^^ two of the MMRP tumours were found to be MSI-H.

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Table 3: IHC results in non-CRC/EC tumours from LS patients by MMR gene (n=318 tumours)

Table 3: IHC results in non-CRC/EC tumours from LS patients by MMR gene (n=318 tumours)

	MLH1		MSH2		MSH6		PMS2		EPCAM		
Site	MMRD	MMRP	MMRD	MMRP	MMRD	MMRP	MMRD	MMRP	MMRD	MMRP	Total
ACC	1		3								4
Ampulla	2		2		0	1					5
Appendix	1										1
Bile Duct	4										4
Bladder	5		15	5	0	1	0	1			27
Brain - GBM	3		5	1	1	1					11
Brain - other			0	1							1
Breast	6	5	9	12	2	8	1	11			54
Cervix			1	3							4
Esophagus	1										1
Fallopian tube						1					1
Gallbladder						1					1
Kidney	3		11		1						15
Kidney - other*				1		1		1			3
Liver		1	2		1	1		1			6
Liver - NET		1									1
Lung	1	1	1	1							4
Lymphoma				1							1
Multiple myeloma	1										1
Omentum			1								1
Ovarian	7	1^	12	0	9	2	1	1	1	1	35
Pancreas	1		7	1	1						10
Pancreas NET			1								1
Parathryoid		1									1
Pelvis	1		1								2
Prostate	1	5	8	2^	1	1	1	3	0	1	23
Sarcoma			2		1						3
Skin (Sebaceous)	7	2	14		1						24
Skin cancer - other	4	2	2	1		1					10
Small bowel	4	1^	12	1	4	2^	1	0	0	0	25
Stomach	2		10				3				15
Thyroid	0	2	0	1	0	1	0	0	0	0	4
Tunica vaginalis	0	0	0	0	0	0	0	1	0	0	1
Ureter	2		12		3						17
Vaginal			1								1
Total	57	22	132	31	25	22	7	19	1	2	318

* kidney – other includes renal cell carcinoma, clear cell carcinoma and chromophobe
^ one of the MMRP tumour was found to be MSI-H.

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COLON AND ENDOMETRIAL CANCER DIAGNOSES IN A POPULATION-BASED LYNCH SYNDROME COHORT COMPARED TO MATCHED CONTROLS

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BACKGROUND: Geisinger's MyCode, a healthcare-based population biobank, returns clinically actionable genomic results, including pathogenic/likely pathogenic variants in Lynch syndrome (LS) genes. Cancer risks in individuals identified with LS through population-based genomic screening programs remain unclear, challenging risk management decisions.

METHODS: MyCode participants who received an LS result from 2015-2020 and did not have prior genomic confirmation of LS were eligible for this analysis. Relatedness was determined using exome data; one proband from each family was included. Controls did not have an LS variant and were matched for age (median difference 1.6 years), sex, race, BMI category (normal, overweight, obese), and smoking status. Cases and controls were included if they provided a three-generation, targeted LS pedigree and excluded if they reported a hereditary cancer predisposition in their family or had a non-LS variant in a hereditary colorectal or gynecological cancer gene. Reviewers manually extracted personal and family history data from pedigrees. Pedigrees were reviewed to determine whether they met National Comprehensive Cancer Network (NCCN 1.2021) criteria for LS evaluation.

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McNemar's test was performed to assess differences in probands' rates of cancer and meeting NCCN criteria; Wilcoxon signed rank test was performed to assess cancer rates in relatives.

RESULTS: A total of 169 cases (10 *MLH1*, 7 *MSH2*, 81 *MSH6*, and 71 *PMS2*) and 169 controls were included. Case probands and their relatives had significantly higher rates of colon and endometrial cancers than controls. Cases were more likely to meet NCCN criteria.

CONCLUSIONS: This study provides evidence that individuals with LS identified through population-based screening, and their relatives, have higher colon and endometrial cancer rates than controls. Even so, clinical guidelines would not have identified two-thirds of cases, suggesting that genomic screening provides an effective means to identify at-risk individuals. Further research is required to tailor risk management recommendations to individuals identified via population-based screening.

Keywords: Lynch syndrome, population genomic screening, cancer incidence

Fig1 Case-Control Cancer Rates

	Case (N=169)	Control (N=169)	P-value
Colon cancer rate in probands	13 (7.7%)	2 (2.4%)	0.035[1]
Endometrial cancer rate in probands	12 (11.5%)	0 (0%)	<0.001[1]
Colon cancer rate in first- and second-degree relatives	Mean: 3.1% Median (IQR): 0.0 (0.0, 5.0)	Mean: 0.9% Median (IQR): 0.0 (0.0, 0.0)	<0.001[2]
Endometrial cancer rate in first- and second-degree relatives	Mean: 2.2% Median (IQR): 0.0 (0.0, 0.0)	Mean: 0.5% Median (IQR): 0.0 (0.0, 0.0)	<0.001[2]
Family history meets NCCN criteria for LS evaluation	56 (33.1%)	12 (7.1%)	0.001[1]

[1]McNemar test p-value; [2]Wilcoxon signed rank p-value

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MISMATCH REPAIR DEFICIENCY AND LYNCH SYNDROME IN UNSELECTED GLIOMA PATIENTS

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BACKGROUND: Glioma is part of the Lynch syndrome (LS) cancer spectrum. However the association is poorly documented. Previous observations were likely confounded by constitutional mismatch repair deficiency (CMMRD), while prospective studies only suggest a minor risk increase. We identified MMR-deficient (MMRd) tumors by

performing somatic sequencing and immunohistochemistry (IHC) in a large series of unselected gliomas. We report their characteristics, and the associated germline testing results.

METHODS: Somatic multigene sequencing was carried out on all treatment-naïve adult gliomas at Pitié-Salpêtrière Hospital, Paris between 2017 and 2022. For gliomas with ⩾1 MMR pathogenic variant (PV), MMR IHC was done. Gliomas with ⩾1 MMR PV and protein expression loss were considered MMRd. Eligible patients were then referred to Oncogenetics for germline testing. To obtain complementary age-based MMRd prevalence estimates, MMR IHC was done in a random selection of IDH-wild type glioblastomas.

RESULTS: ⩾1 somatic PV was observed in 9/1552 gliomas (0.6%). Protein expression loss matched the involved gene. Of these nine, five turned out to have a previously-undiagnosed cancer susceptibility syndrome. Four had LS, with germline PV in MSH2 (n=3) and MLH1 (1). One case had PMS2-associated CMMRD. Mean age at glioma diagnosis was 28 (range 19-47). Histology was IDH-wild-type glioblastoma for the five tumors. No case had first-degree family history of a LS-spectrum cancer. One additional case was a known MSH2 PV carrier. The three remaining cases had purely somatic MSH6 PV. In the complementary IHC study, 6.4% of IDH-wild type glioblastomas diagnosed <age 50 had MMR expression loss.

CONCLUSIONS: MMRd should be sought in all IDH-wild type glioblastomas diagnosed under the age of 50, as a substantial proportion seems to be linked to LS.

Keywords: Lynch syndrome, glioma, glioblastoma, mismatch repair, immunohistochemistry, microsatellite instability.

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Research Categories » Lynch syndrome

AN ASSESSMENT OF RACIAL AND GENDER DISPARITIES IN GENETIC COUNSELING OR TESTING FOR PATIENTS WITH MISMATCH REPAIR DEFICIENT TUMORS

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BACKGROUND: Patients with absent mismatch repair protein(s) on immunohistochemistry (IHC) found by universal tumor screening (UTS) have mismatch repair deficiency (dMMR). Those with absence of MLH1 and PMS2 need testing for acquired MLH1 hypermethylation (MHM), done by assessing for BRAF mutation. Patients with dMMR tumors with MHM ruled out when indicated should undergo genetic counseling/testing (GC/T) for Lynch syndrome (LS). Gender and racial disparities have been seen in GC/T in UTS programs. Our goal was to identify gender, racial or ethnic disparities in follow-up GC/T at our institution.

METHODS: Electronic medical records were reviewed for all cases screened with UTS between 1/9/2009- 5/27/2021 noting patient gender, race, ethnicity; MMR IHC results, BRAF mutation or MHM; appointments with genetics and genetic testing uptake.

RESULTS: 3145 patients got UTS with MMR IHC (1538 males,1607 females). 2718 were white, 295 black, 51 Asian, and 33 Hispanic. Race was not available for 48. 205 (6.5 %) had a non-methylated dMMR tumor, without a BRAF

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mutation or MHM (when indicated) indicating need for genetic counseling. There were 113 males (55.1%) and 92 females (44.9%). Of the 202 with known race, 168 were white (83.2%), 23 black (11.4%), 10 Asian (5.0%), and 1 Hispanic (0.5%). Of 205 dMMR patients, 96 (46.8%) saw genetics; rates were similar for men (44.2%) and women (50%). A chi-squared test of independence showed no significant differences in patients seen by genetics according to race or ethnicity with 47.0% (79/168) white, 39.1 % (9/23) black, 70% (7/10) Asian and 100% (1/1) Hispanic (p=0.28). 100% of patients seen by genetics pursued genetic testing.

CONCLUSIONS: While the rate of genetic counseling completion for patients with non-methylated dMMR tumors (46.8%) needs improvement, no significant disparities were seen by gender or race. When seen by genetics, patients were equally likely to pursue germline genetic testing, regardless of race or gender.

Keywords: Lynch Syndrome, Disparities

Table 1

	White	Black	Asian	Hispanic/Latino	Male	Female
Total	2718	295	51	33	1538	1607
***Genetics Indicated**	168/2718 (6.2%)	23 /295 (7.8%)	10/51 (19.6%)	1/33 (3.0%)	113/ 1538 (7.3%)	92/1607 (5.7%)
Seen by genetics	79/168 (47.0%)	9/23 (39.1%)	7/10 (70.0%)	1/1 (100.0%)	50/113 (44.2%)	46/92 (50.0%)
Genetic Testing Uptake	79 (100%)	9 (100%)	7 (100%)	1 (100%)	50 (100%)	46 (100%)

***Genetics indicated = dMMR by IHC and no *MLH1* methylation or *BRAF* mutation when indicated.**

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Research Categories » Lynch syndrome

USING PREMM5 TO DISTINGUISH BETWEEN SPORADIC AND LYNCH-ASSOCIATED MLH1-DEFICIENT COLORECTAL CANCER

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BACKGROUND: Most cases of colorectal cancer (CRC) with microsatellite instability (MSI) and mismatch repair (MMR) deficiency (MMR-D) are sporadic, caused by acquired inactivation of MLH1 via promoter methylation rather than Lynch Syndrome (LS). MLH1 promoter methylation analysis can be used to distinguish between sporadic and LS-associated MLH1-deficient CRC, but such testing is expensive, requires specialized laboratory expertise, and may not be feasible in low-resource settings. We hypothesized that PREMM5 could be an alternative to MLH1 promoter methylation testing to distinguish sporadic versus LS-associated MLH1-deficient CRC.

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METHODS: Data were extracted from a retrospective institutional cohort of 1058 patients with CRC, unselected for age at diagnosis, MSI/MMR status, or family history of cancer, recruited from December 2008 to March 2014, all of whom underwent germline testing with a 25-gene panel (including all LS genes). Tumor were deemed to have abnormal immunohistochemistry for MLH1 (MLH1-deficient) if staining was weak, patchy, or completely absent. Personal/family cancer histories for individuals with MLH1-deficient CRC were assessed using PREMM5, with PREMM5 scores ⩾2.5% indicating a need for germline LS testing.

RESULTS: MSI/MMR results were available on 553/1058 (52.3%) cases of which 70 were abnormal, including 49 that were MLH1-deficient. Of the 49 that were MLH1-deficient, 30 (61.2%) had PREMM5 scores ⩾2.5%, 11 of whom had germline LS pathogenic variant (10 MLH1; 1 PMS2) and 2 had non-LS pathogenic variants (1 ATM, 1 BRCA2). None of the 19 MLH1-deficient CRCs with PREMM5 scores <2.5% harbored a pathogenic germline LS variant. PREMM5 assessment at a score cutoff ⩾2.5% had 100% sensitivity and 100% negative-predictive value for identifying LS among those with MLH1-deficient CRC.

CONCLUSIONS: PREMM5 accurately distinguishes between sporadic and LS-associated MLH1-deficienct CRCs and thus may be an acceptable substitute for MLH1 promoter methylation analysis, particularly in low resource settings. These findings should be validated in larger cohorts.

Keywords: Lynch Syndrome, MLH1-deficient colorectal cancer, PREMM5

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Research Categories » Lynch syndrome

A PATIENT-FACING CLINICAL DECISION SUPPORT TOOL FOR GENETICALLY-GUIDED PERSONALIZED MEDICINE IN LYNCH SYNDROME

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BACKGROUND: Lynch syndrome (LS) is a hereditary cancer susceptibility condition associated with varying levels of cancer risk depending on which of 5 causative genes harbors a pathogenic variant. Lifestyle and medical interventions provide patients with options that can further modify their cancer risk. We developed a patient-facing Clinical Decision Support (CDS) tool that applies Genetically-guided Personalized Medicine (GPM) for individuals with LS.

METHODS: The CDS tool was developed through a patient-focused iterative design process that utilized focus groups and cognitive interviews. The knowledge base used to estimate patient specific risk leverages a rigorously curated literature review. The user interface and risk estimate algorithms were coded using R Shiny. RESULTS: Our CDS tool facilitates GPM by 1) informing patients of their personal cancer risks; 2) educating patients on relevant lifestyle and medical interventions, and the potential impacts of those interventions; 3) improving risk communication between patients and providers, while also addressing providers' resource limitations; and 4)

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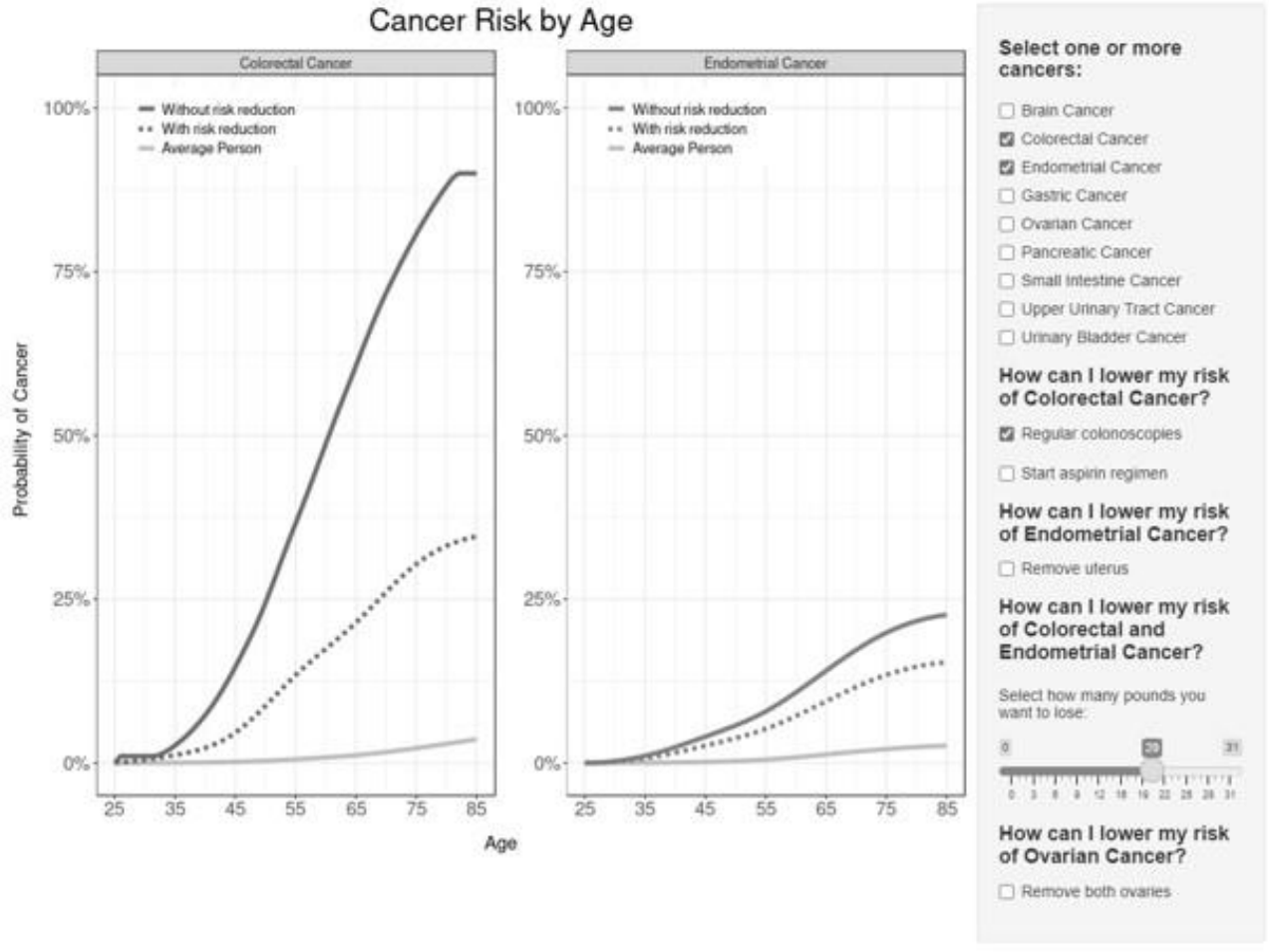
supporting communication among relatives with the goal of increasing cascade testing. The tool is publicly available at https://hereditarycancer.dfci.harvard.edu/mylynch/

CONCLUSIONS: As genetic panel testing becomes more widely-available, GPM will play an increasingly important role in patient care, and CDS tools offer patients and providers tailored information to inform decision making. This CDS tool for GPM benefits patients and families with Lynch syndrome by providing them with more personal cancer risk estimates and available interventions to lower these risks. The tool will improve clinician-patient communication and encourage adoption of risk reducing strategies and cascade testing.

Keywords: Lynch Syndrome, Mismatch Repair (MMR), Clinical Decision Support (CDS) Tool, Genetically-guided Personalized Medicine (GPM), Multi-gene Panel Testing, Cascade Testing

Fig1

User-interface excerpt for a 25-year-old, female LS patient with a MLH1 pathogenic mutation showing colorectal and endometrial cancer risks with intervention effects. Additional cancers and intervention settings may be selected on the right



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Research Categories » Moderate penetrance colorectal cancer syndromes

COLORECTAL NEOPLASIA AND FAMILY HISTORY IN PATIENTS WITH GERMLINE ATM MUTATIONS

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BACKGROUND: Germline heterozygous mutations in ATM are common in the population (0.5-1.0%) and are associated with risk of breast (BC) and pancreatic cancers (PC). The relationship of ATM mutations to CRC risk remains uncertain. Panel testing in CRC patients identified ATM carriers at frequencies similar to the population carrier rate (<50 CRC: 4/450 0.89%; Pearlman JAMAOnc 2017; unselected CRC: 10/1058 0.95%, Yurgelun JCO 2017), while research from our group identified moderate CRC risk for carriers (OR for CRC 1.49, p<0.0001) (Hall CancerPrevRes 2021). ATM is large (350 kDa, 66 exons) with multiple functional domains. We previously identified c.7271T>G as a hotspot for BC (OR 3.76); here we hypothesize a genotype-phenotype association of ATM mutations to CR neoplasia (CR polyps and/or CRC) and explore this in our institutional database.

METHODS: ATM carriers were identified through a dedicated electronic database. Personal (PHx), family (FHx) history and mutation status, were abstracted from clinical pedigrees, a linked research database, and the EMR (FCCC-IRB 09-831).

RESULTS: 37 ATM carriers were identified, w/64.8% (24/37) reporting PHx CRC neoplasia (n=12), FHx of CR neoplasia (n=12) or both (n=6). 5.4% (2/37) had PHx of CRC and 29.7% (11/37) had PHx of CR polyps, while 35.1% (13/37) reported FHx of CRC in an FDR or SDR (46% of these eoCRC), and 24.3% (9/37) reported an FDR or SDR w/CR polyps. 8/24 patients w/PHx or w/FHx CR neoplasia had mutations in the kinase domain (n=3) or the immediately adjacent dimerization domain (n=5) at 3' end of ATM, including a 65F w/sessile serrated polyposis (c.9139C>T) and a family w/eoCRC, BC, and eoPC (c.8266A>T). 3/24 unrelated families reporting CR neoplasia shared the c.7638_7646del mutation.

CONCLUSIONS: 3' ATM mutations localized to the kinase and dimerization domains may differentially predispose to CR polyps and CRC.

Keywords: ATM, colorectal cancer, genotype-phenotype

Figure1

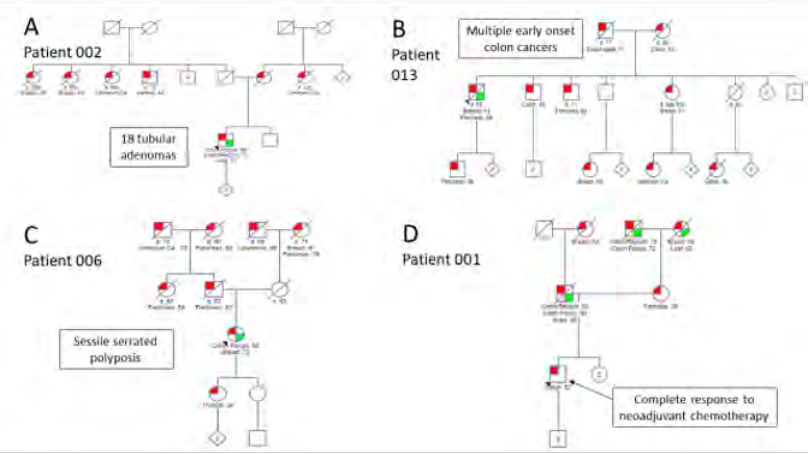

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Table 1

Identifier	Age at diagnosis (age)	Sex	ATM mutation (nucleotide)	ATM mutation (amino acid)	Cancer or polyp family history (age)	Other details
001 (Panel D)	CRC (52)	M	c.138_141del	p.His46Glnfs*9	FDR CRC (60), FDR polyps (60), SDR CRC (72), SDR polyps (72)	Complete response to neoadjuvant chemotherapy
002 (Panel A)	CRC (73), Polyps (65)	M	Exon 5 deletion			Adenomatous polyposis w/ 18 tubular adenomas
003	Polyps (49)	M	c.8814_8824del	p.Met2938Ilefs*14		Pancreatic ca. w/ complete response to chemotherapy
004	Polyps (58)	M	c.2124+1G>A (splice donor)		SDR CRC (45), SDR polyps (45)	TDR CRC (68), TDR CRC (73), TDR polyps (56)
005	Polyps (57)	M	c.7638_7646del	p.Arg2547_Ser2549del	SDR CRC (45)	
006 (Panel C)	Polyps (65)	F	c.9139C>T	p.Arg3047*		Sessile serrated polyposis
007	Polyps (40)	M	c.496+5G>A (Intronic)		FDR CRC (62), FDR polyps (40)	
008	Polyps (65)	M	c.7666_7684del	p.Thr2556Profs*2		
009	Polyps (44)	F	c.2921+1G>A			
010	Polyps (50)	F	c.7638_7646del	p.Arg2547_Ser2549del	FDR polyps (55), FDR polyps (60)	
011	Polyps (58)	M	c.1065+1G>T (splice donor)		FDR CRC (83), FDR polyps (83)	
012	Polyps (54)	F	c.3206del	p.Pro1069Leufs*2		
013 (Panel B)		M	c.8266A>T	p.K2756*	FDR CRC (60), FDR CRC (45), SDR CRC (40)	
014		F	c.2849T>G	p.L950R	FDR polyps (51)	
015		F	c.6679C>T	p.Arg2227Cys	FDR polyps (<50), 2 SDR polyps	
016		F	c.2413C>T	p.Arg805*	FDR CRC (26)	
017		F	c.4591C>T	p.Gln1531*	FDR polyps	
018		F	c.7638_7646del	p.Arg2547_Ser2549del	2 FDR polyps	
019		F	c.7271T>G	p.Val2424Gly	FDR polyps (32)	
020		F	c.7630-2A>C		FDR CRC (58)	
021		F	c.6100C>T	p.Arg2034Ter	FDR CRC (75)	
022		F	c.1027_1030del	p.Glu343Ilefs*2	FDR polyps (71)	TDR CRC (43)
023		F	c.5681_5682delAG	p.Glu1894Alafs*9	SDR CRC (40s)	
024		M	c.1110C>G	p.Tyr370*	SDR CRC (55)	

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Research Categories » Other

KNOWN COLORECTAL CANCER POLYGENIC RISK SCORE IS ASSOCIATED WITH BASELINE SCREENING COLONOSCOPY FINDINGS BUT NOT FOLLOW UP COLONOSCOPY OUTCOMES

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BACKGROUND: Polygenic risk scores (PRS), which calculate genetic risk for colorectal cancer (CRC), may help prioritize individuals for CRC screening. Yet, it remains unknown if these risk-prediction tools are generalizable to other populations, or whether PRS can assess long-term risk after the initial colonoscopy. We investigated an existing PRS to determine associations with baseline and incident advanced neoplasia (AN) in a screening population.

METHODS: The CSP#380 screening colonoscopy cohort includes 10 years of clinical follow-up and a biorepository comprised of selected individuals with baseline advanced neoplasia and matched individuals without neoplasia. A PRS was constructed for each individual from 136 pre-specified CRC-risk single nucleotide polymorphisms, and based on the summed total number of present risk alleles (0-2) weighted by published effect sizes (Huyghe et al. 2019). Multivariate logistic regression was used to evaluate the PRS for associations with AN prevalence at initial screening colonoscopy (n=610), or incident AN in participants with at least one follow-up colonoscopy (n=468). The PRS was analyzed categorically by quartiles and as a continuous variable in stratified analyses.

RESULTS: An increased PRS was associated with higher prevalence of AN at baseline screening colonoscopy (Table 1). In stratified analyses, odd ratios for baseline AN were highest in Europeans and participants aged 65-75+. The PRS was not associated with incident AN during follow-up, including in stratifications by age, race, or baseline colonoscopy findings (Table 2).

CONCLUSIONS: A higher PRS was associated with increased risk for AN at screening colonoscopy. Ongoing work will determine whether this PRS can provide more precise risk stratification across diverse populations to better inform recommendations for CRC screening initiation. However, this PRS did not appear to be associated with risk of AN after the screening colonoscopy. More research is needed to augment current blood-based tools, potentially with genetic information from colonic tissues, to develop individualized follow-up strategies.

Keywords: Colorectal cancer, screening, surveillance, colonoscopy, polygenic risk score

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Table 1

Table 1: Association between Weighted Polygenic Risk Score and Prevalent Advanced Neoplasia Outcomes at Baseline Screening Colonoscopy

	Number of Participants with Baseline Advanced Neoplasia N, (%)	Baseline Advanced Neoplasia Odds Ratio (95% CI)*	p-value
PRS as Categorical Variable in Entire Cohort (n = 610)			
Weighted PRS by Quartile			
1st Quartile (n=128)	19 (14.8%)	ref	ref
2nd Quartile (n=164)	54 (32.9%)	3.2 (1.8-5.9)	<0.001
3rd Quartile (n=156)	46 (29.5%)	2.7 (1.5-5.0)	0.002
4th Quartile (n=162)	52 (32.1%)	3.0 (1.6-5.6)	<0.001
PRS as Continuous Variable in Stratified Analyses			
Race[+]			
European (n=498)	143 (28.7%)	7.8 (2.3-27.0)	0.001
Non-European (n=112)	28 (25.0%)	0.9 (0.1-11.3)	0.93
Age[+]			
Age 50-64 (n=286)	76 (26.6%)	4.1 (0.8-21.1)	0.09
Age 65-75+ (n=324)	95 (29.3%)	6.2 (1.4-28.0)	0.02

* Models adjusted for race (based on genetic ancestry by principal component analysis), sex, and age [at last colonoscopy or first colonoscopy with advanced neoplasia]

[+] Given small ranges, all Polygenic Risk Scores (PRS) were multiplied by 100 for scale to provide more intuitive interpretation of odds ratios for each 1 point increase in PRS.

Table 2

Table 2: Association between Weighted Polygenic Risk Score and Incident Advanced Neoplasia Outcomes during Colonoscopy Follow Up

	Number of Participants with Incident Advanced Neoplasia at First Follow-Up Exam N, (%)	Incident Advanced Neoplasia at First Follow Up Exam (95% CI)* (n = 468)	p-value	Number of Participants with Incident Advanced Neoplasia Ever After Baseline Screening N, (%)	Ever Incident Advanced Neoplasia After Baseline Screening (95% CI)* (n = 468)	p-value
Entire Cohort (n = 610)						
Weighted PRS by Category						
1st Quartile (n=96)	4 (4.2%)	Ref	ref	6 (6.7%)	ref	ref
2nd Quartile (n=129)	7 (5.4%)	1.5 (0.4-5.9)	0.56	18 (14.0%)	2.6 (1.0-7.4)	0.06
3rd Quartile (n=122)	6 (4.9%)	1.3 (0.4-5.3)	0.69	11 (9.0%)	1.6 (0.6-4.8)	0.41
4th Quartile (n=121)	6 (5.0%)	1.3 (0.4-5.3)	0.71	14 (11.6%)	1.8 (0.7-5.5)	0.24
Stratified Analyses						
Race[+]						
European (n=386)	19 (4.9%)	2.5 (0.2-46.5)	0.52	42 (10.9%)	3.2 (0.4-23.3)	0.26
Non-European (n=82)	4 (4.9%)	0.02 (0-9.6)	0.25	7 (8.5%)	0.1 (0-13.7)	0.43
Age[+]						
Age 50-64 (n=228)	7 (3.1%)	2.0 (0.02-15.8)	0.76	13 (5.7%)	1.8 (0.1-48.6)	0.74
Age 65-75+ (n=240)	16 (6.7%)	1.0 (0.1-24.7)	0.98	36 (15.0%)	2.3 (0.3-21.3)	0.44
Baseline Colonoscopy Findings[+]						
No Adenomas/Low-Risk Adenomas (n=296)[&]	8 (2.7%)	0.8 (0.01-42.5)	0.90	12 (4.1%)	0.5 (0.02-12.9)	0.67
3+ Non-advanced Adenomas(n=25)	4 (16.0%)	0.5 (0-50.5)	0.82	4 (16.0%)	0.5 (0-50.5)	0.82
Advanced Neoplasia (n=147)	11 (7.5%)	0.6 (0.01-41.3)	0.84	33 (22.4%)	1.3 (0.1-21.8)	0.86

* Models adjusted for race (based on genetic ancestry by principal component analysis), sex, and age [at last colonoscopy or first colonoscopy with advanced neoplasia]

[+] Given small ranges, all Polygenic Risk Scores (PRS) were multiplied by 100 for scale to provide more intuitive interpretation of odds ratios for each 1 point increase in PRS.

[&] Defined as no adenomas or 1-2 small (<10mm) adenomas at baseline

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Research Categories » Other

PROVIDING MORE ANSWERS FOR PATIENTS WITH SUPPLEMENTAL RNA ANALYSIS OF COLORECTAL CANCER ASSOCIATED GENES

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BACKGROUND: Identification of pathogenic/likely pathogenic (P/LP) germline variants is important to clarify a patient's cancer risk; guide screening, determine risk reducing interventions, and treatment; and inform cascade testing. The introduction of next generation sequencing panels has improved P/LP variant rates while simultaneously increasing variant of uncertain significance (VUS) rates, relative to standard Sanger sequencing. RNA sequencing can help to resolve the clinical significance of variants predicted to alter RNA splicing and identify splice-altering variants in regions outside of the standard reportable range (±20bp of intronic sequence adjacent to the exons) of routine DNA sequencing. The aim of this study was to report the VUS resolution and variant discovery from RNA sequencing performed at a single commercial laboratory.

METHODS: An RNA-sequencing assay was run on whole blood for 63 transcripts from an 84 multi-cancer gene panel. Analysis was limited to 20 genes (APC, AXIN2, BMPR1A, CDH1, CHEK2, EPCAM, GREM1, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, POLD1, POLE, PTEN, SMAD4, STK11, TP53) related to hereditary colorectal cancer (CRC) risk. Data were captured to identify eligible variants reclassified to benign/likely benign (B/LB) or P/LP as well as variants discovered outside of the DNA sequencing range as a result of RNA sequencing.

RESULTS: 16,390 unique samples were run on the DNA/RNA assay. A total of 1,581 patients had eligible variants for RNA analysis. Based on RNA analysis, VUSs were downgraded to B/LB for 677 (4.1%) patients and upgraded to P/LP for 24 (0.1%) patients. Eight (0.05%) patients had deep intronic variants discovered (Table).

CONCLUSIONS: RNA analysis helped to reclassify eligible splice-altering variants in genes associated with hereditary CRC in 4.2%, with the majority being downgraded to B/LB. The rate of variant discovery was very low.

Keywords: germline genetic testing, hereditary colorectal cancer, RNA

Table. Deep intronic variants discovered by RNA analysis

Table. Deep intronic variants discovered by RNA analysis

Gene	Number of Patients	Variant Interpretation
MSH2	1	Variant of uncertain significance
APC	2	Likely pathogenic
APC	1	Variant of uncertain significance
*MSH3**	2	Variant of uncertain significance
POLE	2	Variant of uncertain significance

*monoallelic

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Research Categories » Other

A PRECISION MEDICINE GAP: LIMITED RECOGNITION OF COLORECTAL PATIENTS ELIGIBLE FOR GERMLINE TESTING IN MOLECULAR RESIDUAL DISEASE TESTING SETTING

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BACKGROUND: Germline testing for hereditary colorectal cancer (CRC) has traditionally been offered to patients with strong cancer family histories, whose colon tumors revealed mismatch repair deficiency (dMMR), and/or individuals diagnosed with CRC under age 50. Underdiagnosis of hereditary cancer syndromes is often attributed to the complexity or unawareness of family history or phenotypic criteria.1,2 The National Comprehensive Cancer Network (NCCN) guidelines for CRC were recently updated (v. 1.2022) to consider germline multigene panel testing (MGPT) evaluation for all individuals with CRC.3,4 Our goal was to evaluate documentation of MGPT in CRC patients referred for molecular residual disease (MRD) testing.

METHODS: This retrospective cohort study reviewed clinical data submitted to a commercial laboratory for consecutive CRC patients referred from non-academic medical facilities for MRD testing during a two month study period. Medical diagnoses, treatment history, family history and germline genetic evaluation status were obtained from the test requisition form and pathology reports. Clinical notes were reviewed in 77/80 cases.

RESULTS: Of the 80 patients met criteria for inclusion, 65/80 (81%) had documented MMR testing of their colorectal tumor. Whereas five had abnormal immunohistochemistry, only two (40%) had documented germline results. 19/80 (24%) met NCCN criteria solely based on a personal CRC diagnosis <50 years, but only 1/19 (5.3%) had documented MGPT. Only 5/80 (6%) of all CRC patients had documented MGPT.

CONCLUSIONS: Our real world data from the community oncology precision medicine setting suggests that a majority of CRC patients who received MRD testing and met the prior NCCN criteria for MGPT may not have received evaluation beyond routine MMR status. Process and educational improvements are needed in community health settings to increase access and uptake of germline testing in CRC patients regardless of age at diagnosis or MMR status.

Keywords: genetic testing, hereditary screening, family history, multigene panel testing,

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Research Categories » Pancreatic cancer-related syndromes

BLOOD-BASED BIOMARKER ASSAY RESULTS IN THE CONTEXT OF SUBJECT FAMILY HISTORY, GENETIC HISTORY, CANCER HISTORY & ETHNICITY: PANFAM-1 STUDY RESULTS

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[2]Varied

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BACKGROUND: The PanFAM-1 prospective clinical trial (ClinicalTrials.gov Identifier: NCT03693378) was open from January 2016 thru November 2021 and enrolled subjects at increased risk of developing pancreatic ductal adenocarcinoma (PDAC), including those with pathogenic variants (PGVs) in PDAC susceptibility genes and first-degree relatives (FDRs) of those with Familial Pancreatic Cancer (FPC).

METHODS: Subjects underwent standard of care imaging and planned six-month blood collections for a blood-based biomarker (IMMray PanCan-d) analysis. Here we report IMMray PanCan-d test results in the context of subject family history, genetic history, cancer history, and ethnicity. Categorical variables analyzed using Chi square.

RESULTS: A total of 1,255 patients were enrolled for a median of 23 months (range 12 – 71 months). 3 PDACs were detected during the study period. Subjects with PGVs comprised 41% of samples. Positive results were seen in similar frequency in those with FPC (3.8%) and PGVs (2.6%) (p=0.082). Positive results were seen in samples from subjects with >3 affected FDRs more frequently than others (9% vs 2%, p=0.002). No other individual PGV was associated with more frequent positive or negative results. Samples from subjects with prior invasive melanoma exhibited more positive results compared to those with other prior cancer history (6% vs. 2%) (p=0.004). However, samples from subjects with PGVs in CDKN2A or BRCA2 did not show a corresponding increase in positive test results. Samples from self-described Black/African American subjects were more frequently positive than those from other race or ethnicity (11% vs 3%, p= 0.008).

CONCLUSIONS: IMMray PanCan-d test positivity was associated with a number of different subject attributes in the high-risk surveillance groups studied in PanFAM-1. These associations may suggest additional lines of investigation in this large study cohort.

Keywords: pancreatic cancer, biomarker, pdac, familial pancreatic cancer

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Case Reports » Case Series on any topic

PROFUSE POLYPOSIS DUE TO CONCOMITANT PATHOGENIC VARIANTS IN BMPR1A AND MSH6 – A CASE STUDY

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BACKGROUND: Juvenile polyposis syndrome (JPS) is a hamartomatous polyposis syndrome that causes juvenile polyps in the stomach, small bowel, and colorectum and an increased risk of gastric and colorectal cancer. JPS is caused by pathogenic variants in BMPR1A and SMAD4. Lynch syndrome (LS) is caused by pathogenic variants in MLH1, MSH2, MSH6, PMS2, and EPCAM. Individuals with LS are at an increased risk of developing endometrial, small bowel, pancreatic, urothelial in addition to colon and gastric. While colonoscopy and EGD screening recommendations are similar for JPS and LS, patients with LS also require screening outside of the digestive track. Herein, we report a case of an individual with JPS and LS.

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METHODS: Patient was enrolled in the Jagelman Registy. Cologene TM database and electronic medical record were used to obtain personal and family history, genetic testing, colonoscopy, EGD and operative findings.

RESULTS: Patient is a 64 year old male with a history diabetes and a thoracic aortic aneurysm. Father and brother are deceased from cancer (unknown primary or age). Polyposis diagnosis was at 14 due to symptoms. He underwent multiple colon surgeries, first at age 14, and ultimately underwent an end ileostomy due to multiple polyps including inflammatory juvenile type, tubular adenomas and a large tubulovillous adenoma at age 55. The patient was clinically diagnosed and managed as though he had FAP until presenting to our center at age 60. He then underwent multigene panel testing that revealed a pathogenic variant, c.730C>T (p.Arg244*), in BMPR1A and a variant of uncertain significance (VUS) in MSH6 c.2972C>T (p.Pro991Leu). The patient underwent screening and was found to have duodenal adenoma. At age 63, the MSH6 VUS was reclassified to likely pathogenic.

CONCLUSIONS: Utilization of a multigene panel in this case helped to establish the correct polyposis diagnosis of JPS and LS to warrant screening for additional cancers.

Keywords: Lynch Syndrome, Juvenile polyposis, multigene panel, reclassified

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Research Categories » Adenomatous polyposis syndromes including FAP

EXTRA-COLONIC MANIFESTATIONS OF COLONIC POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE) BY COLONIC ADENOMA COUNT

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BACKGROUND: Colonic polyposis of unknown etiology (CPUE) is defined as having 10 or more cumulative colonic adenomas without a detectable genetic variant. While screening of the upper gastrointestinal tract and thyroid is recommended by guidelines in patients with ⩾100 adenomas, experts support screening on an individualized basis in patients with <100 adenoma despite the lack of supporting evidence. This study aims to define extra-colonic findings of CPUE in a single tertiary center.

METHODS: Cologene TM database was queried for patients with colonic polyposis, defined as cumulative lifetime ⩾ 10 adenomas and negative testing for APC, MYH and/or multigene panel testing. Patients were subdivided into 3 groups based on their colonic polyp count: 10- 19, 20 - 99, and ⩾ 100 adenomas. Age at diagnosis of colonic polyposis, presence of a family history of colorectal cancer, cutaneous findings, osteomas, desmoid tumor, upper endoscopy findings and thyroid ultrasound results if completed were collected.

RESULTS: 151 patients were identified with a median age of 52 (Q25-Q75:40-61).Of the 148 patients with colonic adenoma count, 18 (12.1%) had 10-19 cumulative adenomas, 85 patients (57.4%) had 20-99 adenomas and 45 patients (30.40%) had 100 or more adenomas. Compared to patients with 10-19 and 20-99 adenomas, patients with ⩾100 adenoma were younger at diagnosis (54 vs 55 vs 39 respectively, p=0.002). Proportions of patients with gastric polyps (27.7% vs 23.8% vs 42.2%, p=0.09) and duodenal adenomas (11.1% vs 4.7% vs 13.3%y, p=0.20) were similar among individuals with 10-19, 20-99 and ⩾100 adenomas, respectively. Thyroid nodules, osteoma, desmoid, CHRPE

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and cutaneous manifestations occurred in patients with oligopolyposis (adenoma count 20-99) similarly to patients with ⩾ 100 adenomas of unknown etiology (table).

CONCLUSIONS: Extra-colonic manifestations, particularly upper gastrointestinal polyps are not uncommon in CPUE with less than 100 adenomas. Upper endoscopic surveillance is advisable in these patients.

Keywords: colonic polyposis, adenoma

Table: Demographic data and extra-colonic manifestations in patients with CPUE by colonic adenoma count.

	Cumulative number of colonic adenoma			
	10-19 (n=18)	20-99 (n=85)	≥100 (n=45)	P value
Age(yrs) (Median, IQR)	54±9.2	55±1	39±24.5	0.002*
Male gender (n, %)	14 (77.7%)	46 (56.1%)	26 (57.7%)	0.23
Race • White • Black • Other	 15 (83.3%) 2 (11.1%) 1 (5.5%)	 70 (88.6%) 9 (11.3%) 0 (0.0%)	 39 (88.6%) 4 (9.0%) 1 (2.2%)	0.81**
Multigene panel testing Family history of CRC	5 (14.2%) 9 (50.0%)	20 (57.1%) 43 (50.5%)	10 (28.5%) 17 (40.4%)	0.89 0.54
FDR with CRC	5 (31.2%)	27 (32.5%)	13 (30.9%)	0.98
Extra-colonic manifestations				
Gastric fundic gland polyps	5 (27.7%)	20 (23.8%)	19 (42.2%)	0.09
Duodenal/ampullary adenoma	2 (11.1%)	4 (4.7%)	6 (13.3%)	0.20
Thyroid nodules	0 (0.0%)	6 (7.0%)	2 (4.4%)	0.55***
Thyroid cancer	0 (0.0%)	1 (1.1%)	1 (2.2%)	
Osteoma	0(0.0%)	4 (4.7%)	2 (4.4%)	0.94***
Desmoid tumor	0 (0.0%)	3 (3.5%)	2 (4.4%)	0.79***
CHRPE	0 (0.0%)	2 (2.3%)	2 (4.4%)	0.51***
Cutaneous/subcutaneous findings (sebaceous cysts, lipoma, epidermoid cysts,etc.)	2 (11.1%)	9 (10.5%)	7 (15.5%)	0.70

*Statistically significant difference between adenoma 10-19, 20-99 vs >100, ** comparison between White vs Black + Others, ***comparison between adenoma 20-99 and >100 adenomas..

Mood's Median test was used to compare medians and Fisher's exact method was used to compare proportions among the 3 groups.

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Research Categories » Gastric cancer-related syndromes

DIAGNOSTIC YIELD OF ENDOSCOPIC SCREENING FOR IDENTIFICATION OF SIGNET RING CELL IN CARRIERS OF A PATHOGENIC VARIANT IN CDH1: SINGLE CENTER EXPERIENCE

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BACKGROUND: Pathogenic variants (PV) in CDH1 are associated with hereditary diffuse gastric cancer (HDGC). Recommendations for prophylactic total gastrectomy (PTG) are established for carriers of PV in CDH1. Pre-operative upper endoscopy (EGD) to detect overt cancer or occult signet ring cells (SRC) and annual surveillance endoscopy in individuals deferring PTG is suggested. The yield of EGD detection of SRC varies from 9-60% even in expert hands. A “Bethesda” protocol (targeted biopsy and 4 random biopsies from 22 locations) was compared to Cambridge protocol targeted biopsies of pale patches, other abnormalities, and a > 30 random biopsies in 5 gastric locations. Highly accurate detection of occult, early stage, SRC cancer is necessary for surveillance to be a viable alternative for patients declining PTG. Aim was to describe the diagnostic yield of EGD surveillance in our center for detection of SRC foci in asymptomatic CDH1 carriers using gastrectomy as the gold standard.

METHODS: Carriers of CDH1 PV with ⩾1 EGDs. Demographics, personal and family history of cancer, endoscopic findings, and surgical histology was reviewed. Our EGD biopsy protocol evolved to include targeted biopsy and 7 random biopsies from 4 quadrants in 11 areas under high-definition white light endoscopy. Preoperative detection of SRC was compared with gastrectomy specimens, when available, to calculate the sensitivity of our endoscopy protocol.

RESULTS: 61 PV carriers from 39 families were identified. 12 excluded (symptomatic, presented with cancer). 49 patients with a mean age of 44.7-years, 68% female with 101 EGDs were included [table 1]. 24 (49%) patients underwent gastrectomy 3 without SRC on preoperative biopsy or gastrectomy specimen. Of remaining 21, 16 had SRC detected preoperatively on EGD. Preoperative detection of SRC in the Weiss Center protocol was 81%. [Table 2].

CONCLUSIONS: Our protocol for HDGC surveillance for asymptomatic CDH1 PV patients shows a high yield for preoperative detection of SRC.

Keywords: CDH1, EGD, Gastric Cancer, Gastrectomy, Signet Ring Cell

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Table 1

Demographic Characteristic

Patients	n=49
Age 1st EGD (mean years, range)	44.7 (13.7-73.9)
Age last EGD (mean years, range)	45.8 (13.7-73.9)
Total number of EGDs per patient	
1, n (%)	24 (49%)
2, n (%)	11 (24%)
3, n (%)	11 (18%)
4, n (%)	2 (4%)
5, n (%)	0
6, n (%)	2 (4%)
7, n (%)	0
8, n (%)	1 (2%)
#EGDs performed	n=101
#EGDs / Endoscopist, n (%)	
• Endoscopist 1	83
• Other Endoscopists	18
Endoscopic complications	0
EGD when SRC were detected	
1st EGD	11
2nd EGD	3
3rd EGD	3
4th EGD	1
Number of patients undergoing gastrectomy	24
Sensitivity of Preoperative detection of SRC (one patient underwent 2 EGDs and SRC detected on random biopsy on both exams)	17/21 (81%)

Table 2

Gastrectomy Characteristics

Gastrectomy	n=24	
Indication, n (%)	SRC on Gastrectomy Specimen	No SRC on Gastrectomy Specimen
SCR found on EGD with biopsies pre-operatively	16	0
No SRC found on EGD with biopsies pre-operatively	5	3
Location of SRC on specimen		
Fundus only	3	
Cardia only	2	
Antrum only	2	
Fundus and cardia	2	
Fundus and body	1	
Antrum and fundus	1	
Body, fundus, and cardia	2	
Antrum, body, and fundus	1	
Antrum, fundus, and cardia	1	
Antrum, body, fundus, and cardia	1	
Antrum, body, and cardia	1	
Unknown location	4	
Pathologic stage		
T1aN0M0	21/24	

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Research Categories » Hamartomatous and other polyposis syndromes

A CASE OF DUODENAL ADENOCARCINOMA IN JUVENILE POLYPOSIS OF INFANCY

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BACKGROUND: Juvenile Polyposis of Infancy (JPI) is a rare syndrome caused by deletions in chromosome 10q23 encompassing BMPR1A and PTEN resulting in diffuse intestinal hamartomatous polyposis within the first years of life accompanied by protein-losing enteropathy, diarrhea, anemia, anasarca, and failure to thrive. Many JPI patients die in infancy.

METHODS: We report a patient with JPI with a history of gastrointestinal (GI) bleeding at age 8 months and protein-losing enteropathy at age 3 prompting subtotal colectomy and ileostomy. Other features included penile lentigines, angiolipomas, gingival papillomatous changes, macrocephaly, and extensive GI polyposis. On presentation to our center in 2018 at age 18 the patient was asymptomatic, BMI was 27.3 kg/m2, complete blood count and comprehensive metabolic profile were normal. EGD demonstrated diffuse esophageal glycogenic acanthosis, 25, 2-10mm proximal gastric polyps and innumerable 2-8 mm duodenal polyps (Figure 1). The 10 largest gastric and largest duodenal polyp were resected and confirmed gastric non-dysplastic hamartomas, fundic gland, and hyperplastic polyps and a non-dysplastic duodenal hamartoma. Similar findings were noted on EGDs in 2019 and 2021.

At age 26, 10 months after the last EGD, the patient required hospitalization for melena and hemoglobin of 5.8 g/dL. EGD revealed a bleeding mass in the second portion of the duodenum confirmed to be an invasive moderately-differentiated adenocarcinoma. An open classic pancreaticoduodenectomy was performed. The duodenum, appearing normal from the outside, contained a palpable mass and multiple enlarged, firm lymph nodes were appreciated. Pathology revealed a 2.7cm poorly differentiated pT2N0 duodenal adenocarcinoma arising in extensive hamartomatous polyposis.

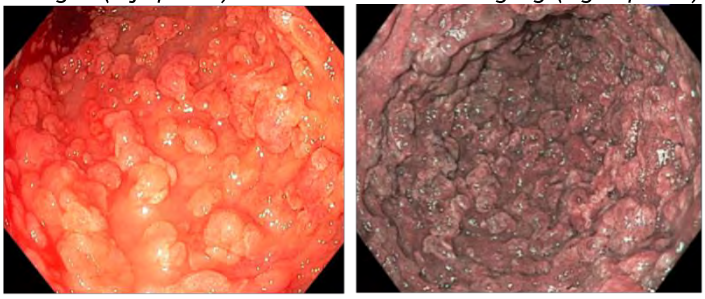
RESULTS: We describe the first reported case of duodenal adenocarcinoma in the setting of severe duodenal hamartomatous polyposis due to JPI. We will continue with aggressive small bowel surveillance with EGD and capsule endoscopy and recommend the use of sirolimus to control the polyp burden.

CONCLUSIONS: Consent obtained to submit this abstract

Keywords: Juvenile polyposis of infancy, duodenal adenocarcinoma

Figure 1

Endoscopic appearance of duodenal polyposis under high-definition white light (left panel) and narrow band imaging (right panel).



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Research Categories » Other

IF YOU BUILD IT THEY WILL COME: DOWNSTREAM BENEFIT TO THE HEALTHCARE SYSTEM FROM A HEREDITARY COLORECTAL CANCER REGISTRY

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BACKGROUND: The Jagelman Cancer Registry (JCR) is a hereditary colorectal cancer registry (HCCR) that was established at the Cleveland Clinic in 1979 with the goal of preventing death from colorectal cancer. Patient's clinical encounters for treatment and surveillance are managed through the registry. This study examines the downstream benefits of a hereditary cancer registry to the healthcare system.

METHODS: A prospective hereditary colorectal cancer database (Cologene™) was used to identify patients enrolled in the JCR during a single 12-month period. Data regarding hereditary syndrome related office visits, procedures, surgeries, imaging, and pathology requisitions during the subsequent 5 years (2015-2020) were abstracted from the database and supplemented with the electronic medical record (EMR).

RESULTS: The JCR enrolled 107 patients in 2015. A total of 87 patients who had a confirmed pathogenic/likely pathogenic variant in a hereditary colorectal susceptibility gene or who met clinical criteria for a hereditary colorectal cancer syndrome were included. There were 55 patients with a polyposis syndrome (FAP 47, MAP 1, JPS 4, PJS 1, Cowden 2) and 32 with Lynch syndrome. A personal history of cancer was present in 14 patients at the time of enrollment in the registry and no patients developed a new cancer during an average of 3.4 years of follow up. There were 20 patients that did not return for follow up after one year, including 3 patient deaths. A total of 2431 billable appointments (average ~ 28 per patient) were completed between 2015 and 2020. There were 1091 office visits, 425 endoscopic procedures, 127 surgeries, and 412 imaging studies. (Table 1)

CONCLUSIONS: Patients enrolled in a HCCR require intense treatment and surveillance, including many diagnostic and therapeutic interventions. Establishing a registry result in significant downstream benefit to the health care system that can outweigh the initial costs for registry creation and maintenance

Keywords: Hereditary Registry, Downstream Benefits, Colorectal Cancer

Table 1

Table 1.

	Encounter Type	n (average per patient)
Office Visits	Gastroenterology	63 (0.7)
	Colorectal Surgery	230 (2.6)
	Other	798 (9.1)
Procedures	Upper Endoscopy	158 (1.8)
	Lower Endoscopy	267 (3.1)
Surgery	Inpatient	73 (0.8)
	Outpatient	54 (0.6)
Pathology	Surgical Pathology	372 (4.3)
Radiology	MRI	38 (0.4)
	CT	235 (2.7)
	X-Ray	139 (1.6)
	Ultrasound	131 (1.5)

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