North Carolina Society of Gastroenterology 2024 Annual Meeting

The ABCs of GCTA: A Primer for Gastroenterologists on CRC Risk Assessment

Carol A. Burke, MD, FASGE, FACG, AGAF, FACP
Staff Gastroenterologist, Director Center for Hereditary Polyposis
Departments of Gastroenterology, Hepatology and Nutrition,
and Colorectal Surgery

Cleveland Clinic

Joint Providership

ASGE
American Society for Gastrointestinal Endoscopy

Disclosures:

Research: Freenome, Emtora
Consultant: Sebela, Guardant
Speaker: Ambry

LEARNING POINTS

- Recognize hereditary GI cancer syndromes
- Understand who to refer for genetic testing
- Develop patient surveillance strategies

KNOWLEDGE CHECK

Which of the following patients, with the only cited risk factor, should be referred for genetic testing?

1. Personal history of a colon cancer age 63
2. Personal history of jejunal cancer age 58 and father with rectal cancer age 77
3. Personal history 20 adenomas on 6 colonoscopies over 15 years beginning at age 50

Joint Providership

ASGE
American Society for Gastrointestinal Endoscopy

ANSWER

Which of the following patients, with the only cited risk factor, should be referred for genetic testing?

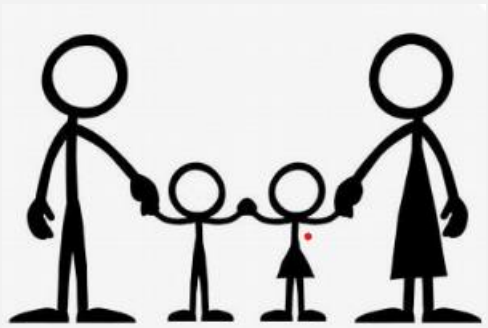
1. Personal history of a colon cancer age 63
2. Personal history of jejunal cancer age 58 and father with rectal cancer age 77
3. Personal history 20 adenomas on 6 colonoscopies over 15 years beginning at age 50

Joint Providership

ASGE
American Society for Gastrointestinal Endoscopy

IMPORTANCE OF IDENTIFYING HEREDITARY CANCER PATIENTS

- 1:279 individuals have Lynch syndrome (LS)
  - LS causes 3-5% of CRC and endometrial cancers
- 1 of 5 patients with CRC < 50 years old have germline pathogenic variant associated with cancer
  - ~50% without typical history associated with the pathogenic variant
- Identifying HRC alters management
  - Patient and at risk family members



HOW WILL YOU KNOW THESE PATIENTS

Office/Endoscopy Suite

- Personal History of Polyps or CRC
- Family History of Polyps or Cancer
- Referrals for Germline Pathogenic Variant

FEATURES OF HEREDITARY CRC SYNDROMES

Syndrome	Lynch Syndrome	Constitutional Mismatch Repair Deficiency (CMMRD)
Genes	MLH1, MSH2, MSH6, PMS2, EPCAM	*MLH1, MSH2, MSH6, PMS2*
Inheritance Pattern	Autosomal *Dominant* *Adult* Onset	Autosomal *Recessive* *Pediatric* Onset
Features	**Cancers** Colorectal Endometrial/Ovarian Gastric/small bowel Pancreatico-biliary Urothelial Brain Sebaceous Carcinoma **Others** Sebaceous Adenoma Colorectal Adenomas Small Bowel Adenomas	Gastro 2017;152:1605–1614

Organ	Estimated penetrance, %	Age at diagnosis, median (range), *y*
Small-bowel adenomas[a]	50	12 (10–20)
Colorectal adenomas[a]	>90	9 (6–15)
Small-bowel cancer	10	28 (11–42)
Colorectal cancer[b]	70	16 (8–48)
Low-grade brain tumors	Unknown	Unknown
High-grade brain tumors[c]	70	9 (2–40)
Lymphoma	20–40	5 (0.4–30)
Leukemia	10–40	8 (2–21)
Endometrial cancer	<10	(19–44)
Urinary tract cancer	<10	(10–22)
Other sites[d]	<10	(1–35)

FEATURES OF HEREDITARY POLYPOSIS SYNDROMES

Syndrome	Gene(s)	Features
Familial Adenomatous Polyposis	*APC*	CRC/duodenal/gastric/thyroid/brain cancer, CR/duodenal/gastric adenomas, osteomas, soft tissue tumors, desmoid tumors, CHRPE
***MYH*-Associated Polyposis**	*MUTYH*	Similar to FAP, usually attenuated features
***NTHL1*- Associated Polyposis**	*NTHL1*	CR/duodenal adenomas (oligopolyposis),meningioma, CRC/endometrial/breast/urothelial/Ca
Polymerase Proofreading Associated Polyposis	*POLE, POLD1*	CR/duodenal adenomas, CRC/endometrial/brain ca
***MSH3*- Associated; *MLH3*-Associated Polyposis**	*MSH3/MLH 3*	CR/duodenal adenomas, CRC/gastric ca, astrocytoma
***AXIN2*- Associated Polyposis**	*AXIN2*	Oligodontia, ectodermal dysplasia, duodenal/CR adenomas, CRC/HCC/breast/lung/prostate ca
Peutz-Jeghers Syndrome	*STK11*	Mucocutaneous pigmentation, hamartomas, breast, GI, pancreatic, and rare GYN/testicular cancers
PTEN Hamartoma Tumor Syndrome	*PTEN*	Intestinal hamartomas, glycogen acanthosis, skin lesions, macrocephaly, CRC/breast/hyroid/renal/endometrial ca
Juvenile Polyposis Syndrome	*BMPR1A, SMAD4*	Intestinal hamartomas, CRC/gastric ca, S*MAD4* –Hereditary Hemorrhagic Telangiectasia

RECOGNIZING HEREDITARY CRC

Personal History

- Early age intestinal and extra-intestinal tumors
- Pathology of tumors
- Number/size of polyps
- Extra-intestinal features

Family History

- 3 generations
- Presence & age of cancers
- Age and cause of death
- Features of Hereditary Ca

WHO TO REFER FOR GENETIC TESTING

INDIVIDUALS RECOMMENDED FOR GENETIC TESTING FOR LYNCH SYNDROME

Personal History

- Tumor with MMR deficiency
- Individual with a LS CA and any of the following:
  - Diagnosis < 50 yo
  - Synchronous or metachronous LS CA independent of age
  - FDR or SDR with LS CA < 50 yo
  - ≥ 2 FDR or SDR with LS CA independent of age
- ≥ 5% risk of MMR gene pathogenic variant based on predictive models

Family History

- ≥ 1 FDR with CRC or EC < 50 yo
- ≥ 1 FDR with CRC or EC and synchronous or metachronous LS CA independent of age
- ≥ 2 FDR or SDR with LS CA including 1 diagnosed < 50 yo
- ≥ 3 FDR or SDR with LS CA independent of age

LS CA: CRC, endometrial, gastric, ovarian, pancreatico-biliary, urothelial, brain, small intestine, and sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas (Muir-Torre syndrome)

NCCN Genetic/Familial High-Risk Assessment: Colorectal. Version 2. 2023

INDIVIDUALS RECOMMENDED FOR HEREDITARY ADENOMATOUS POLYPOSIS

RECOMMEND TESTING

- Family History Known Variant
- ≥ 20 cumulative adenomas
- CHRPE: Congenital hypertrophy of retinal pigment epithelium (multifocal, bilateral)

CONSIDER TESTING

- 10-19 cumulative adenomas
- Desmoid tumor, hepatoblastoma
- Cribiform-morular variant of papillary thyroid Ca
- Unilateral CHRPE
- Individual with Serrated Polyposis and Adenomas

NCCN Genetic/Familial High-Risk Assessment: Colorectal. Version 2. 2023

Approach to Testing
Multigene panel testing (MGPT) vs Single Site

Risk Status	Testing Strategy
Family Pathogenic Variant *Known*	→ Test for Family Variant
	MGPT maybe indicated based on other cancers in family
Family Pathogenic Variant *Unknown*	→ MGPT

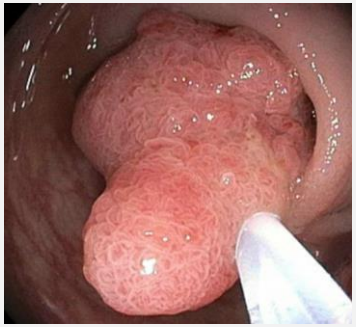
NCCN Genetic/Familial High-Risk Assessment: Colorectal. Version 2. 2023

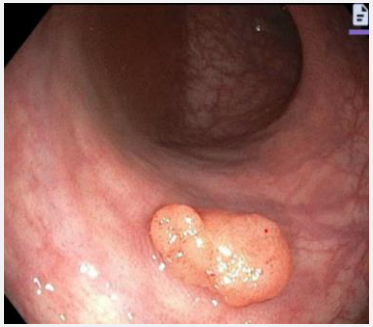
POTENTIAL GERMLINE TESTING OUTCOMES

Pathogenic/Likely Pathogenic	• Variant associated with disease • Follow management recommendations for pathogenic variant detected • Offer cascade testing to at risk relatives
Variant of Uncertain Significance	• Variant not actionable; Inadequate info on impact of variant on disease • Manage patient on personal and family cancer history • Do not test family members for variant
Negative	• Manage patient based upon personal and family cancer history

CASE PRESENTATION: 3/2022

- 48 yo WF (+) MTsDNA
- Colonoscopy: **8 polyps** :
- 1 @ 15 mm rectum
- 3 @ 2- 4 mm transverse
- 2 @ 7-35 mm descending
- 2 @ 2 -5 mm sigmoid





- Pathology: **8 tubular adenomas; 2 TVA with HGD**

CASE PRESENTATION (CONTINUED)

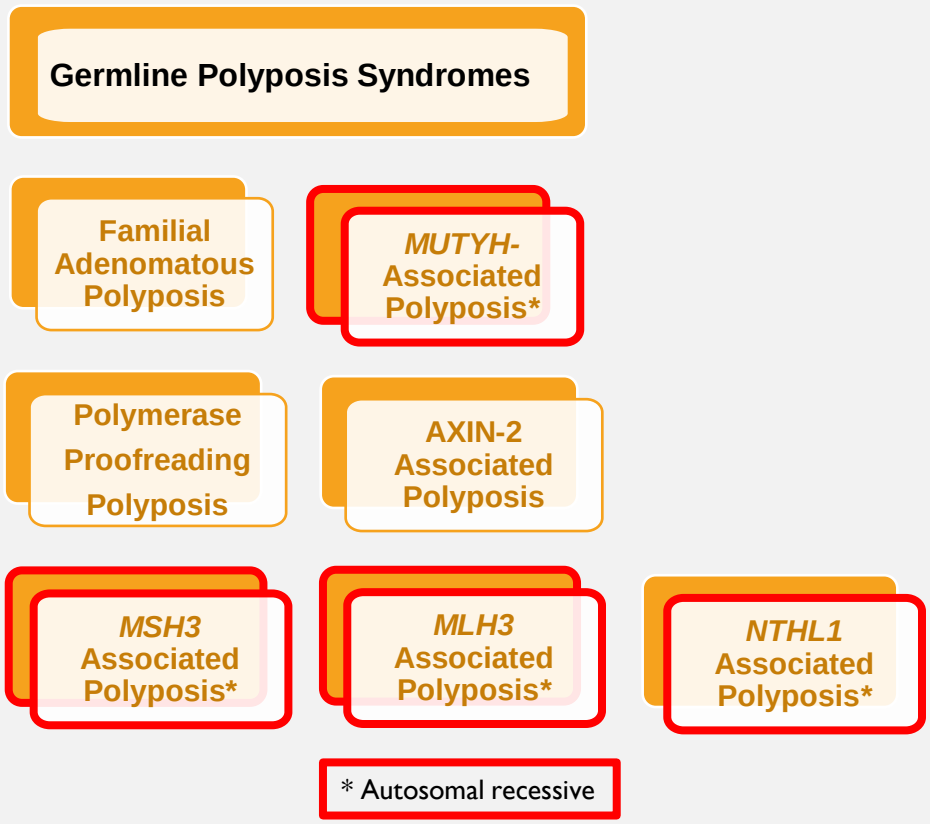
- Healthy, BMI 19.8
- Never smoker, no ETOH; Regular Exerciser
- **Family Cancer History**
- Father – Glioblastoma diagnosed age 64, died 66
- Paternal Grandmother - Thyroid Cancer age 20's
- Paternal Aunt - Cervical Cancer
- Maternal Grandmother- Colon polyps
- Maternal Grandfather- Lung Ca (smoker)
- Maternal half uncle - Bone Ca deceased at 7 y/o
- Maternal uncles (1)- Lung Ca (smoker); (1) Melanoma

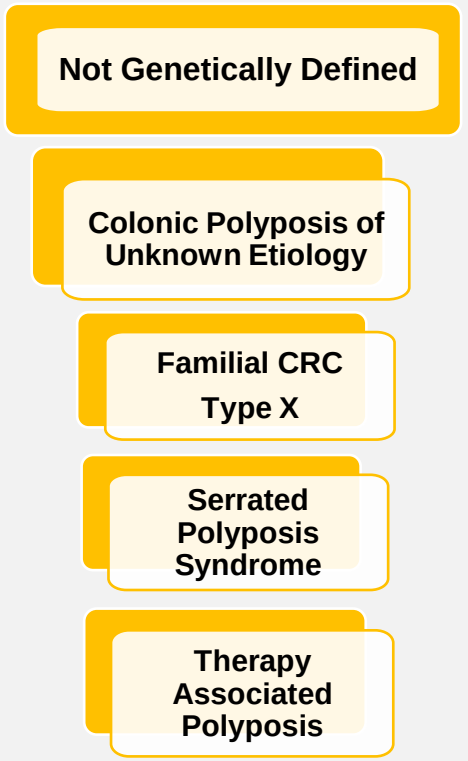
CASE PRESENTATION: 8/2022 REPEAT COLONOSCOPY

5 additional polyps:

- 1 @ 2 mm transverse: **tubular adenoma**
- 2 @ 4-6 mm sigmoid: **tubular adenoma** and an SSP
- 2 @ 2-3 mm rectum: **tubular adenoma** and hyperplastic polyp
- **Colonoscopy Summary:** 11 adenomas including numerous advanced adenomas
- **Other risk:** Father brain Ca age 64; PGM;Thyroid Ca age 20; Paternal aunt: Cervical unknown age; MGM: polyps; maternal aunt: melanoma
- **Thoughts and next steps?**

Causes of Adenomatous Polyps and CRC





CASE MANAGEMENT QUESTION

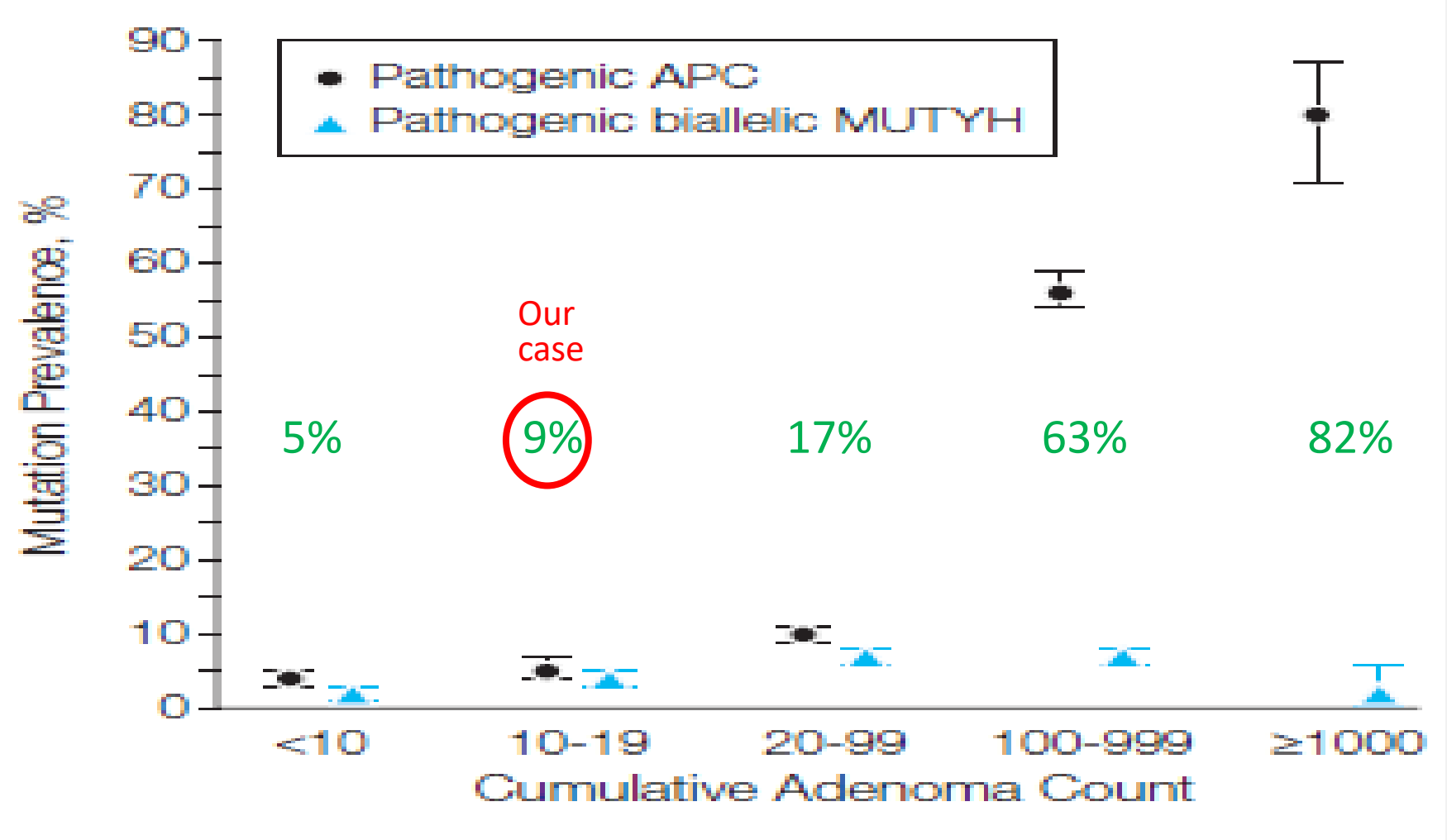
What is best advice for this patient?

1. MGPT testing is indicated

2. Single site testing for an *APC* pathogenic variant is indicated

3. Likelihood of detecting a germline pathogenic variant is 2%

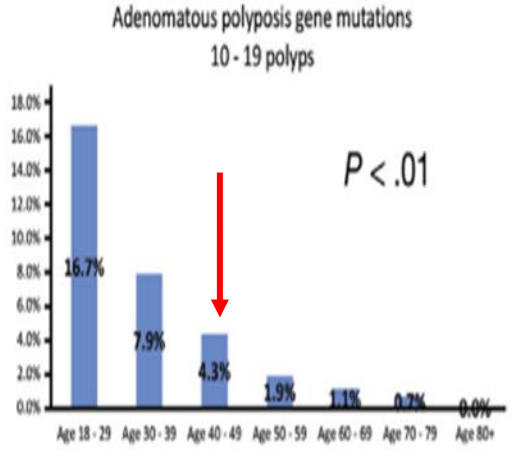
APC AND *MUTYH* TESTING IN ADENOMATOUS POLYPOSIS

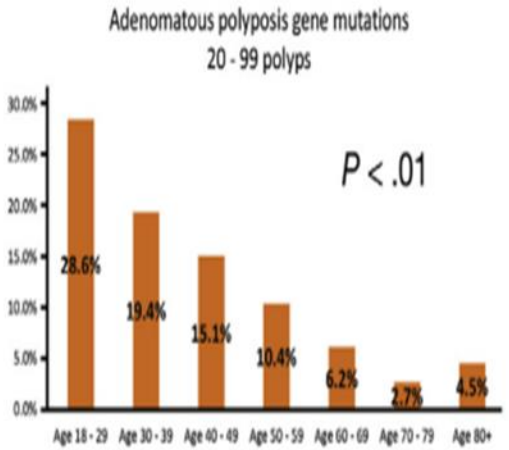


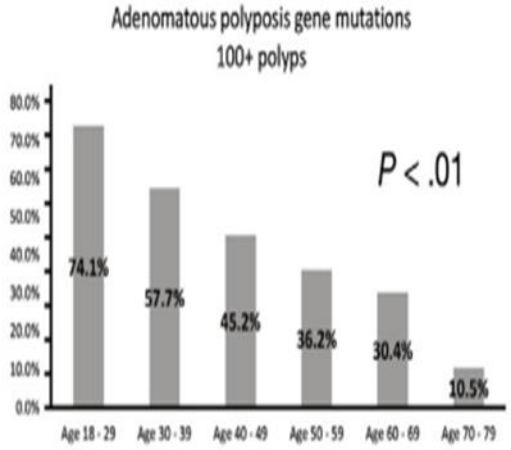
N= 8676
Full sequencing and large rearrangement of *APC*
Targeted sequencing of *MUTYH* (Y179C and G396D)

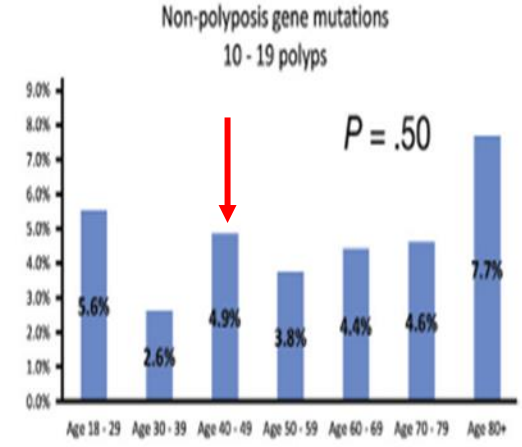
JAMA. 2012;308(5):485-492

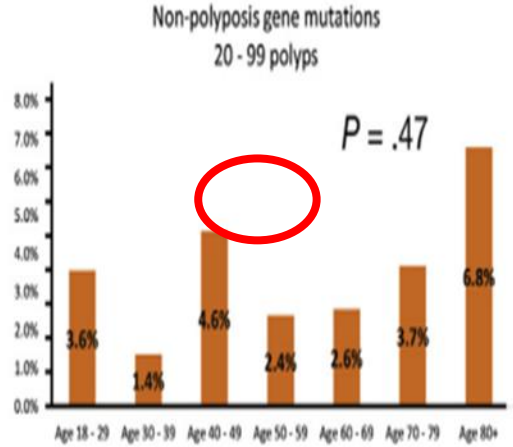
PREVALENCE OF PATHOGENIC VARIANTS IN PATIENTS WITH NUMEROUS COLORECTAL POLYPS

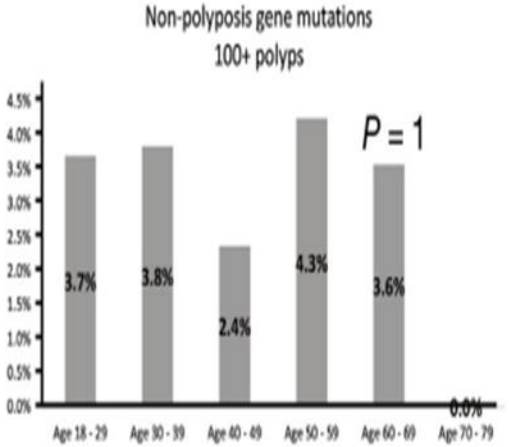












Clin Gastro Hepatol 2019;17:2008–2015

CASE MANAGEMENT QUESTION

What is best advice for this patient?

1. MGPT testing is indicated

2. Single site testing for an *APC* pathogenic variant is indicated

3. Likelihood of detecting a germline pathogenic variant is 2%

CASE PRESENTATION: 10/2022
GERMLINE TESTING: MGPT

GENE	TRANSCRIPT
APC*	NM_000038.5
ATM*	NM_000051.3
AXIN2	NM_004655.3
BAP1	NM_004656.3
BARD1	NM_000465.3
BLM	
BMPR1A	
BRCA1	
BRCA2	
BRIP1	
BUB1B	
CDH1	
CDK4	
CDKN2A (p14ARF	
CDKN2A (p16INK	
CEP57*	
CHEK2	
CTNNA1	NM_001903.3
DDX41	NM_016222.3
DICER1*	NM_177438.2
ENG*	NM_000118.3
EPCAM*	NM_002354.2
FH*	NM_000143.3
FLCN	NM_144997.5
GALNT12	NM_024642.4
GREM1*	NM_013372.6
HOXB13	NM_006361.5
MAX*	NM_002382.4
MBD4	NM_003925.2
MEN1*	NM_130799.2
MET*	NM_001127500.1
MITF	NM_000248.3
MLH1*	NM_000249.3
MLH3*	NM_001040108.1

GENE	TRANSCRIPT
MSH2*	NM_000251.2
MSH3*	NM_002439.4
MSH6*	NM_000179.2
MUTYH	NM_001128425.1
NF1*	NM_000267.3
	.6
	5.3
	5.5
	1.3
	1.3
	0.2
	4.3
	4.4
	5.2
	3.3
	5.4
	3.5
RPS20	NM_001023.3
SDHA*	NM_004168.3
SDHAF2	NM_017841.2
SDHB	NM_003000.2
SDHC*	NM_003001.3
SDHD	NM_003002.3
SMAD4	NM_005359.5
SMARCA4	NM_001128849.1
STK11	NM_000455.4
TMEM127	NM_017849.3
TP53	NM_000546.5
TSC1*	NM_000368.4
TSC2	NM_000548.3
VHL	NM_000551.3

RESULT: NEGATIVE

About this test

This diagnostic test evaluates 64 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

DIAGNOSIS: COLONIC POLYPOSIS OF UNKNOWN ETIOLOGY (CPUE)

- Patient with > 10-20 lifetime cumulative adenomas
- No pathogenic variant on MGPT

10-19 Adenomas	20-100 Adenomas	> 100 Adenomas
• Colonoscopy based on clinical factors • Consider EGD	• Colonoscopy q 1-2 yrs • EGD • Colectomy if not endoscopically controllable	**Manage as FAP** • Colonoscopy • EGD • Thyroid ultrasound • Colectomy if not endoscopically controllable

NCCN Genetic/Familial High Risk Assessment: Colorectal version 2. 2023

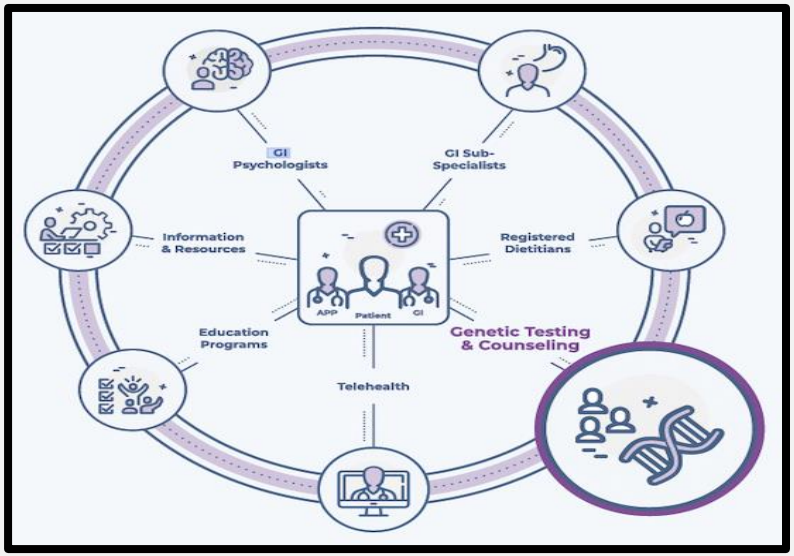
CASE SUMMARY AND RECOMMENDATIONS

Diagnosis: CPUE

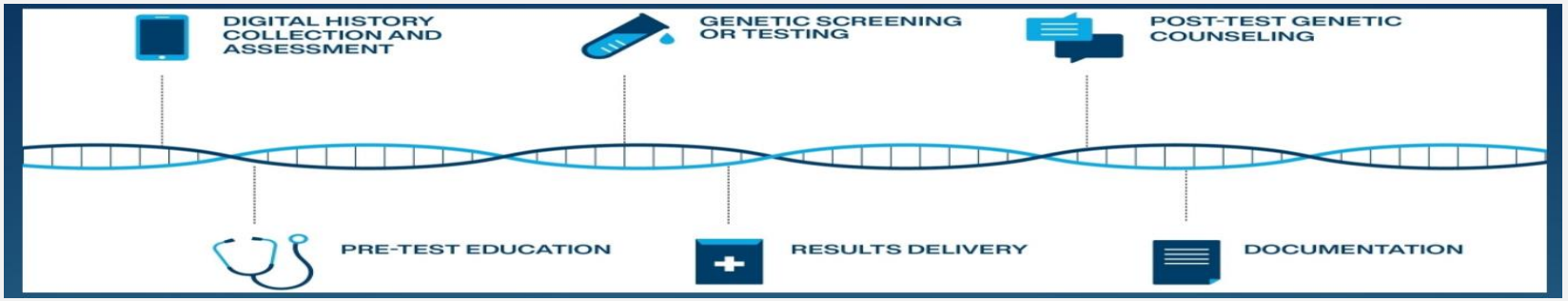
- EGD normal including biopsy of papilla; repeat 5 years
- Colonoscopy in 1 year, then lengthen
- FDR: Baseline colonoscopy age 38 and frequency pending findings

OPTION FOR RISK ASSESSMENT IN YOUR PRACTICE

GI ON DEMAND
GastroGirl™
Gastroenterology's Integrated, Multidisciplinary Care and Support Platform



- Web-based, patient-facing, risk assessment
- Provided prior to GI appointment via text, email or tablet
- Followed by pretest education and counseling via short videos and text
- Post-testing, results digitally sent to patient and provider
- Expedited post-test counseling provided



GI ON DEMAND GENE PANEL AND TEST RESULTS

APC	ATM	AXIN2	BARD1	BMPR1A
BRCA1	BRCA2	BRIP1	CDH1	CDK4
CDKN2A	CHEK2	DICER1	EPCAM	GREM1
HOXB13	MLH1	MLH3	MSH2	MSH3
MSH6	MUTYH	NBN	NF1	NTHL1
PALB2	PMS2	POLD1	POLE	PTEN
RAD51C	RAD51D	RECQL	RPS20	SMAD4
SMARCA4	STK11	TP53		

CRC, polyposis, breast, ovarian, prostate, pancreatic, genes

Number of GI Appts 8/2021-5/2023	Assessment Sent	Assessment Completed	NCCN Criteria Met	Tests Ordered	Tests Completed
31,034	38.6%	61.3%	24.2%	29%	73.4%

GT Result	Positive	Negative	VUS
379 Tested	16.4%	24.3%	59.4%

GI ON DEMAND POSITIVE FINDINGS

- 12 individuals with high-risk cancer susceptibility syndromes
  - Lynch syndrome= 7
  - Hereditary Breast-Ovarian Cancer Syndrome= 4
  - Li Fraumeni Syndrome= 1
- 13 individuals with pathogenic/likely pathogenic variants in moderate risk genes
- 24 individuals were carriers of autosomal recessive disorders that may not affect cancer risk but are important for reproductive counseling

Pambianco D, ACG Vancouver 2023

CONCLUSIONS

- Patients with Hereditary Cancer are not being identified
  - Limited genetic specialists to see patients and order testing
- GI practice risk assessment program found 24% of patients met NCCN criteria for genetic testing
  - Less than 1/3 who met criteria *had testing ordered by provider*
  - Majority of *patients with testing ordered underwent testing*
  - Pathogenic variants found in 16%
- Pathogenic variants found in ~10% of patients with > 10-19 cumulative adenomas
- Use personal + family history + genetic test results for management