Digestive Diseases of the Caribbean '22
Novel Insights in the Management of Gastrointestinal and Liver Diseases
Honoring Women's Leadership in Gastroenterology and Hepatology
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Diagnosis and Management of Hereditary Polyposis

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Disclosures

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- Member: US Multi-Society Task Force on Colorectal Cancer, National Comprehensive Cancer Network Guideline on Genetic/Familial High-Risk Assessment: Colorectal

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Learning objectives

- *Categorize* hereditary polyposis syndromes by colon polyp histology
- *Recognize* diagnostic features of the most common hereditary adenomatous syndromes
- *Understand* recommended management strategies for individuals/families with hereditary adenomatous polyposis

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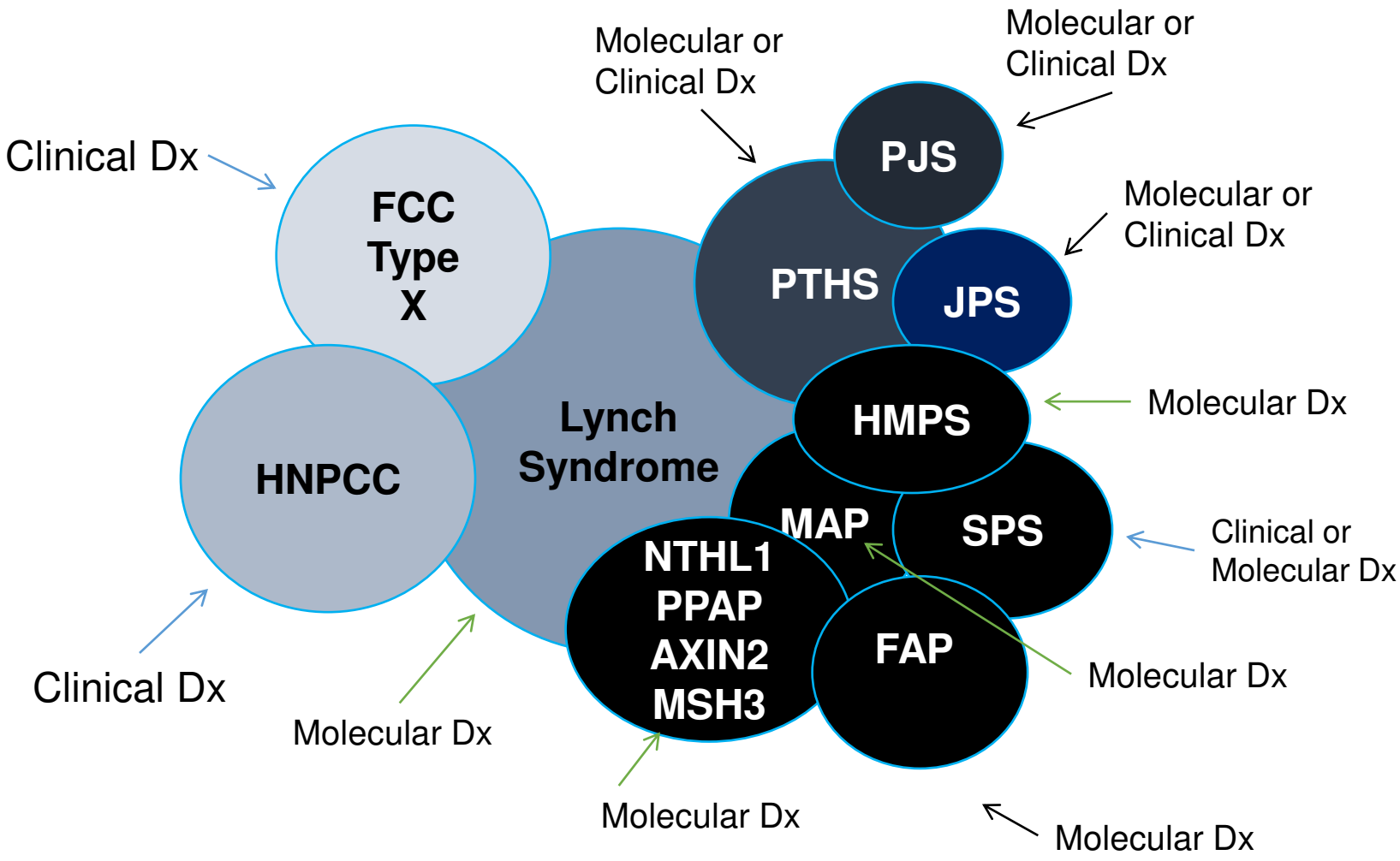
Hereditary Polyposis Syndromes

Syndrome	Gene(s)	Features (all include CRC)
Familial Adenomatous Polyposis	*APC*	Colorectal/duodenal adenomas/Ca, gastric polyposis/Ca, thyroid cancer, osteomas, soft tissue tumors, adrenal adenomas, desmoids
***MYH*-associated polyposis**	*MUTYH*	Similar to FAP with attenuated features
***NTHL1*- associated polyposis**	*NTHL1*	Colorectal/duodenal adenomas; breast/endometrial/urothelial cancer; meningioma
Polymerase proofreading associated polyposis	*POLE, POLD1*	Colorectal adenomas; endometrial/ovary/brain cancer
***MSH3*-associated polyposis** ***MLH3*-associated polyposis**	*MSH3* *MLH3*	Colorectal/duodenal adenomas; gastric cancer;early-onset astrocytoma Colorectal adenomas; breast ca
***AXIN2*- Associated Polyposis**	*AXIN2*	Oligodontia, ectodermal dysplasia, duodenal/CR adenomas, CRC/HCC/breast/lung/prostate ca
Constitutional Mismatch Repair Deficiency (CMMRD)	*MLH1,MSH2, MSH6. PMS2*	Colorectal/duodenal adenomas/Ca, brain tumors, hematologic malignancies, café au lait spots
Peutz-Jeghers Syndrome	*STK11*	Mucocutaneous pigmentation, GI hamartomas; rare GYN/testicular cancers breast/pancreatic/gastric/SB/uterine ca
***PTEN* Hamartoma Tumor Syndrome**	*PTEN*	Intestinal hamartomas, glycogen acanthosis, skin lesions, macrocephaly, breast/thyroid/renal/endometrial ca
Juvenile Polyposis Syndrome	*BMPR1A, SMAD4*	Gastric/colorectal hamartomas, gastric cancer, S*MAD4* –HHT overlap

Syndromic and Phenotypic Overlap



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Causes of Adenomatous Polyps and CRC

Germline Polyposis Syndromes

- Familial Adenomatous Polyposis
- *MUTYH*-Associated Polyposis*
- Polymerase Proofreading Polyposis
- AXIN-2 Associated Polyposis
- *MSH3* Associated Polyposis*
- *MLH3* Associated Polyposis*
- *NTHL1* Associated Polyposis*

Germline DNA Mismatch Repair Deficiency Syndromes

- Constitutional MMR Deficiency (CMMRD)*

Not Genetically Defined/Environmental

- Colonic Polyposis of Unknown Etiology
- Familial CRC Type X
- Serrated Polyposis Syndrome
- Therapy Associated Polyposis

* Autosomal recessive

Hereditary Polyposis Syndromes

- Hereditary adenomatous polyposis syndromes are cancer predisposition syndromes, CRC and other organs
- Entry points into your practice
  - At time of colonoscopy
  - Office visit
    - Personal or family cancer or polyp history
    - Referred for positive result on multi gene panel test

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Recognizing Hereditary Polyposis and Colorectal Cancer Syndromes

Personal History

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

Family Cancer History

- Gather in 3 generations
- Occurrence and age of cancer or polyps
- Age and cause of death
- Presence of features within spectrum of hereditary polyposis

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Hereditary CRC Syndrome Screener

	YES	NO
• Do you have a **first-degree relative** (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50?		
Colon or rectal cancer	☐	☐
Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain	☐	☐
• Have **you** had any of the following conditions diagnosed before age 50?		
Colon or rectal cancer	☐	☐
Colon or rectal polyps	☐	☐
• Do you have three or more relatives with a history of colon or rectal cancer? (this includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins)	☐	☐

Identified 77 % of high-risk individuals and 95 % of LS mutation carriers

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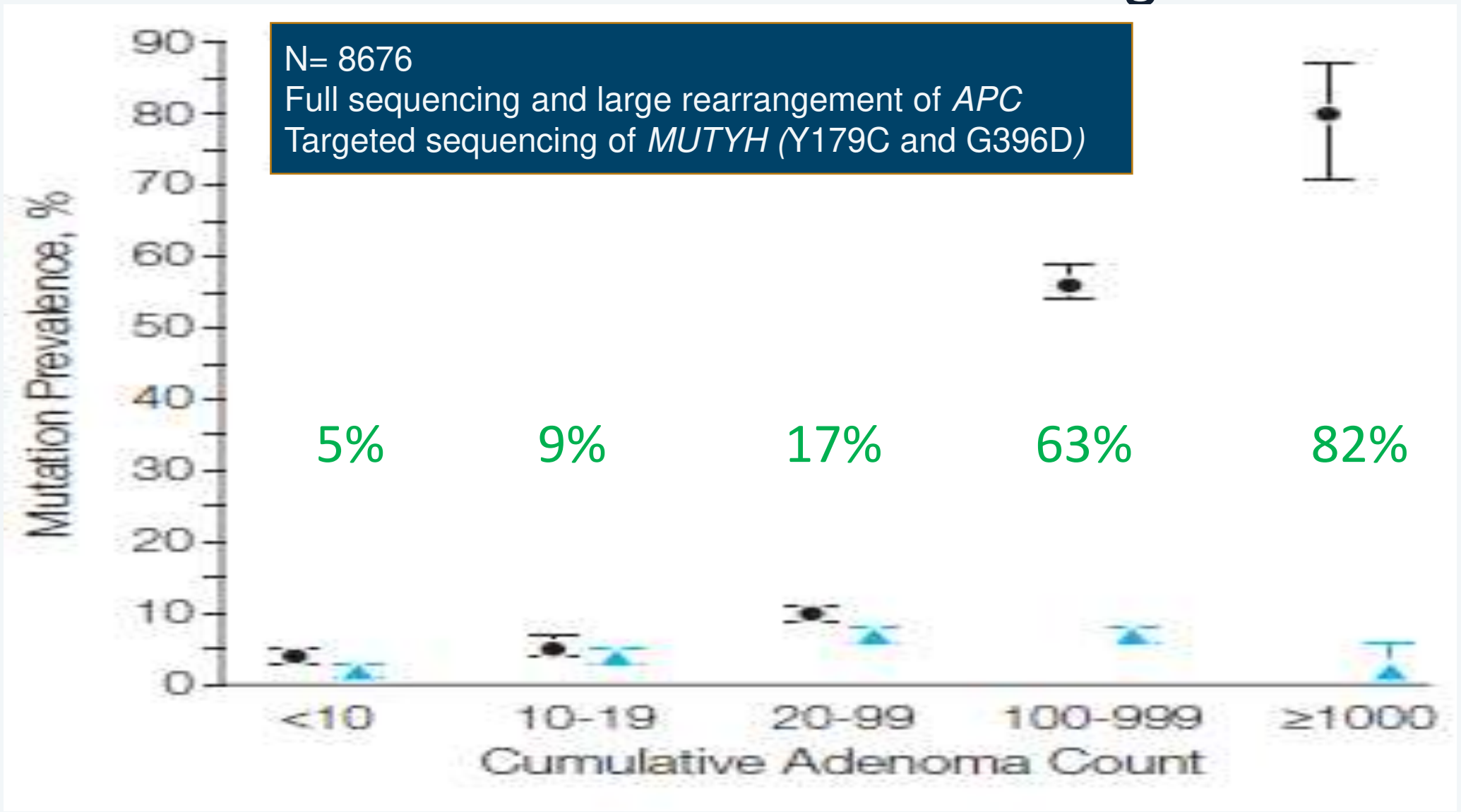
Kastrinos F, et al . Am J Gastroenterol 2009; 104:1508 – 1518;

Prevalence of Germline Pathogenic Variants in *APC* and 2 common *MUTYH* genes



Grover S, et al. JAMA. 2012;308(5):485-492

Germline Multi-Gene Panel Testing in CRC

N=450
< 50 yo

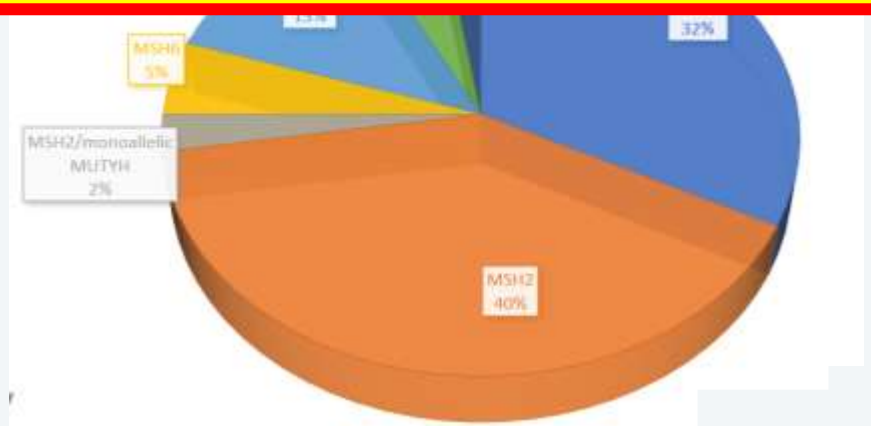
Tumor Testing for MMR Status

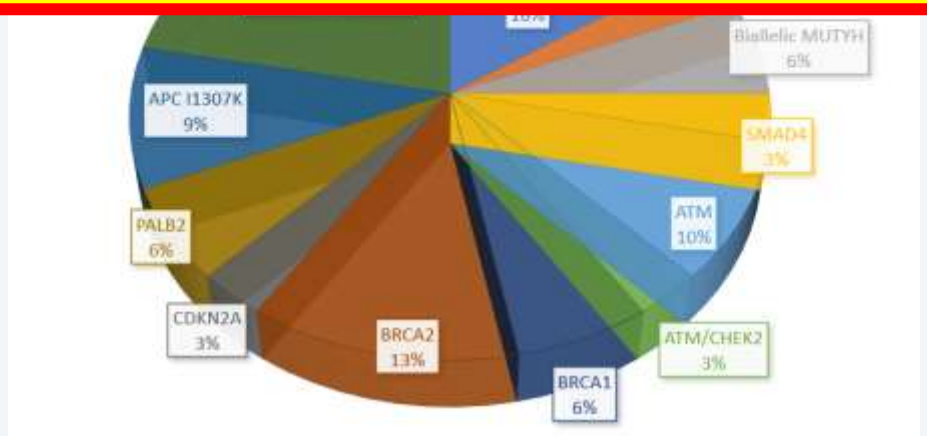
MMR deficient
N=48 (11%)

MMR proficient
N=402 (89%)

APC, ATM, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDK4, CDKN2A, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, SMAD4, STK11, TP53

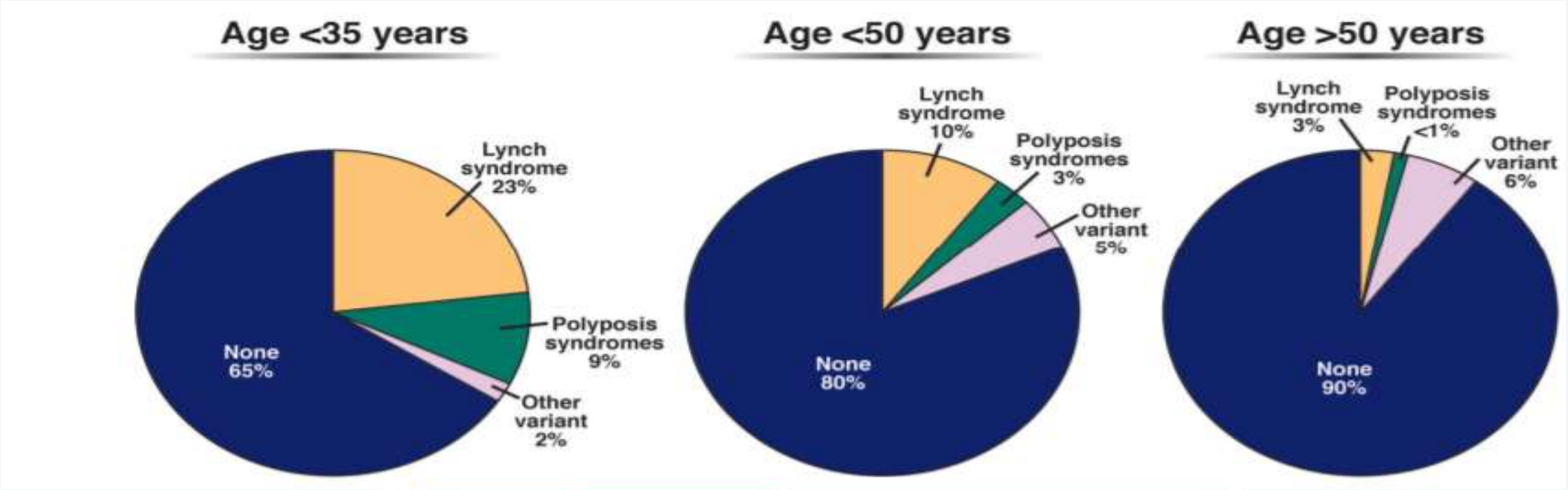
In both cohorts, 33% patients with pathogenic variant did not meet genetic testing criteria for the gene(s) in which they had a mutation.





Pearlman R, et al JAMA Oncol. 2017;3(4):464-471

Prevalence of Germline Pathogenic Variants in CRC by Age



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	*APC*	*BRCA1*	*CHEK2*
MSH2	*MUTYH*	*BRCA2*	*ATM*
MSH6	*SMAD4*	*TP53*	*NBN*
PMS2	*BMPR1A*	*PALB2*	*BARD1*
	PTEN	*CDKN2A*	*BRIP1*
	POLE		

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Stoffel, Gastroenterology. 2020; 158(2): 341–353

Indications for Polyposis Genetic Testing

Family History	Personal History	
Recommend Testing		**Consider Testing**
Known germline pathogenic variant	≥ 20 cumulative adenomas	10-19 cumulative adenomas
	≥ 2 hamartomas	Desmoid tumor
Meets clinical criteria for polyposis syndrome and no germline testing done in affected relatives	Multi-focal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)	Cribiform-morula variant of papillary thyroid cancer
		Hepatoblastoma
		Unilateral CHRPE
		Meets WHO Criteria for Serrated Polyposis Syndrome with some adenomas

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Adapted from NCCN guidelines V1.2021 Genetic Familial High-Risk Assessment: Colorectal

Recommendations for Multi-Gene Panel Testing for Hereditary CRC

- CRC diagnosed < 50 yrs
- Multiple Lynch syndrome* cancers
- CRC and ≥ 1 FDR with CRC or endometrial cancer
- $PREMM_5$ score ≥ 2.5% or MMRpro, or MMR predict score ≥ 5%
- MMR deficient CRC not due to MLH1 promoter methylation
- Patients meeting other genetic testing criteria
- ≥ 10 cumulative colorectal adenomas
- ≥ 3 cumulative GI hamartomatous polyps

*CRC, endometrial, urothelial, small bowel, gastric, pancreatic/biliary tract, sebaceous carcinoma, glioblastoma

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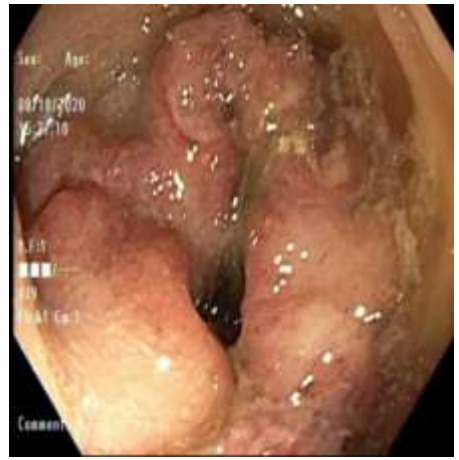
Heald B, et al. Familial Cancer (2020) 19:223–239

Case 1. August 1 2020 Virtual Visit

- 43 yr old male: change in BMs, rectal bleeding
- January started saw palmetto for urinary symptoms and it helped resolve those symptoms but bowel habits started to change
  - Frequent, bloody, tenesmus, nausea, no weight loss or systemic features
  - Past Medical History: nephrolithiasis
  - Family History: no IBD, CRC or other cancers, brother 60 had “polyps”
- Height 6’2” weight 290
- Labs CBC, CMP, Sed rate, CRP, stool infectious panel: normal
- Colonoscopy: 6, 6-25 mm polyps and ……



Case 1.

- Pathology:
  1. Colon, ascending, transverse, and descending, polyps: Tubular and tubulovillous adenomas
  2. Colon, sigmoid, tumor, biopsy: Invasive adenocarcinoma, moderately differentiated

  MMR Status Report - Immunohistochemistry staining for mismatch repair proteins: Normal

  MLH1, PMS2, MSH2, and MSH6 proteins expressed in cancer nuclei. Mismatch repair (MMR) status: Proficient (microsatellite stable)
- Low Anterior Resection and colo-colic anastomosis
  - Adenocarcinoma invades pericolonic adipose tissue; surgical margins negative.
  - - Perineural and lymphovascular space invasion noted, including extramural venous invasion.
  - - Metastatic adenocarcinoma in two lymph nodes (2/28).
  - Approximately 4, 2-4 mm polyps noted in the specimen, Tubular adenomas, Hyperplastic polyps.

Differential Diagnosis and Next steps?

Recommendations for Multi Gene Panel Testing

- CRC diagnosed < 50 yrs
- Multiple Lynch syndrome* cancers
- CRC and ≥ 1 FDR with CRC or endometrial cancer
- $PREMM_5$ score ≥ 2.5% or MMRpro, or MMR predict score ≥ 5%
- MMR deficient CRC not due to MLH1 promoter methylation
- Patients meeting other genetic testing criteria
- ≥ 10 cumulative colorectal adenomas
- ≥ 3 cumulative GI hamartomatous polyps

Case 1. Next Steps

- Genetic counseling, multi gene panel testing

Two Pathogenic variants identified in MUTYH. MUTYH is associated with autosomal recessive MUTYH-associated polyposis.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
MUTYH	c.1187G>A (p.Gly396Asp)	heterozygous	PATHOGENIC
MUTYH	c.536A>G (p.Tyr179Cys)	heterozygous	PATHOGENIC

About this test

This diagnostic test evaluates 47 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.

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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 information on impact of germline 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

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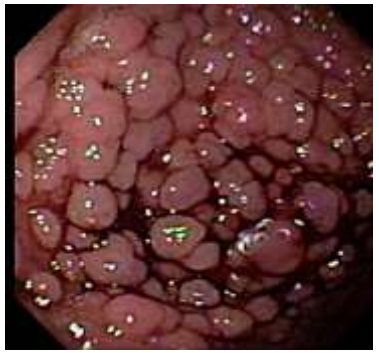
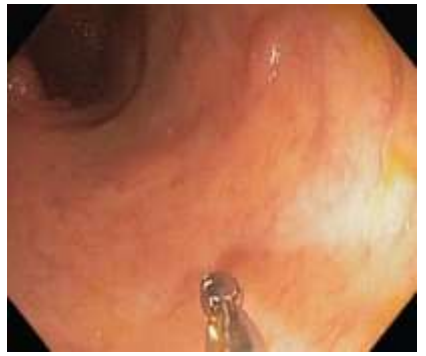
Case 1. Management of patient and family

- Endoscopic surveillance of remaining colorectum and UGI tract
- Offer at risk relatives testing of family *MUTYH* pathogenic variant
  - Follow MAP management recommendations for bi-allelic PV carriers
  - For mono-allelic PV carriers with first degree relative with CRC:
    - Colonoscopy every 5 years beginning age 40 or 10 years prior to age of first degree relative with CRC, whichever is earlier



Adenomatous Polyposis Syndromes



Familial Adenomatous Polyposis (FAP)

- Autosomal Dominant
- Pop prevalence: 1:10,000 individuals
- Due to PV in *APC* gene
  - Tumor suppressor gene
  - 30% cases are de novo
- Risk of CRC: 60-90%
  - Based on polyposis burden
- Risk of extra-colonic tumors

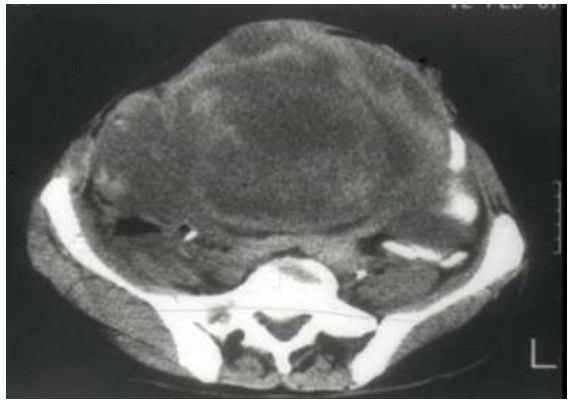
MUTYH Associated Polyposis (MAP)

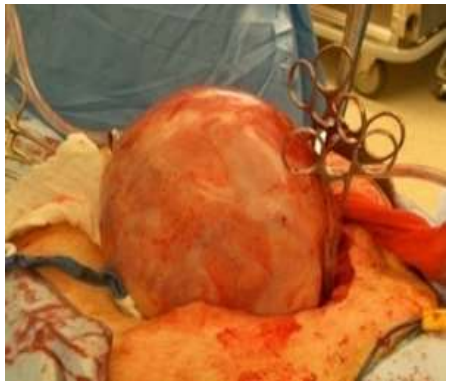
- Autosomal recessive
- Pop prevalence: 1-2% mono-allelic carriers of PV in *MUTYH*
- Due to bi-allelic PV in *MUTYH gene*
  - Base excision repair gene
- Risk of CRC: 50% @ 48 yrs
  - Attenuated colorectal polyposis
- Spectrum of extra-colonic tumors similar to FAP but milder and less prevalent

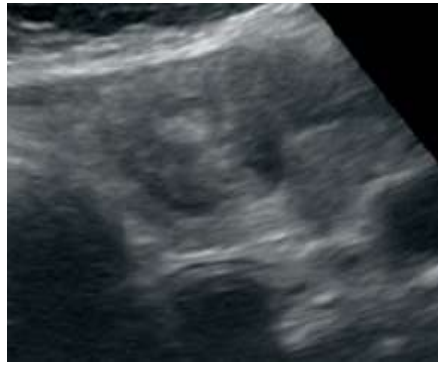
Features of FAP (MAP)

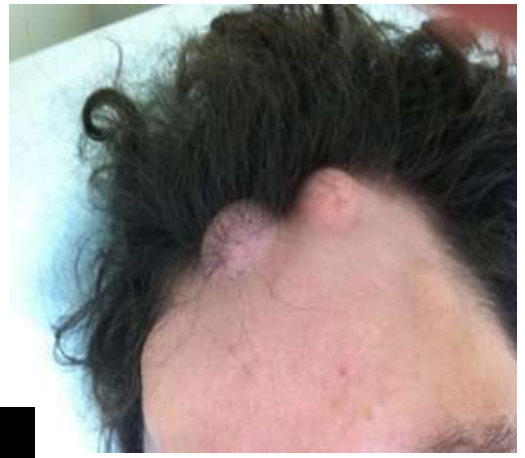
- CRC and polyposis
- Gastric polyposis and cancer
- Duodenal polyposis and cancer
- Desmoid tumors (15%)
- Thyroid carcinoma (2-17%)
- Adrenal adenoma (7-13%)
- Osteomas (50-90%)
- Supernumerary teeth (11-27%)
- CHRPE (70-80%)
- Soft tissue tumors (50%)
  - Lipoma, fibroma, sebaceous cysts

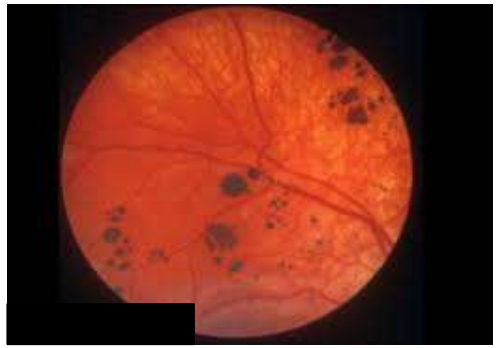
Hepatoblastoma (<2%)











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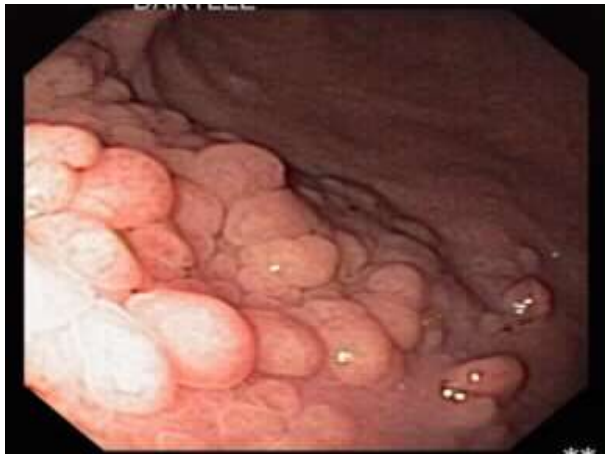
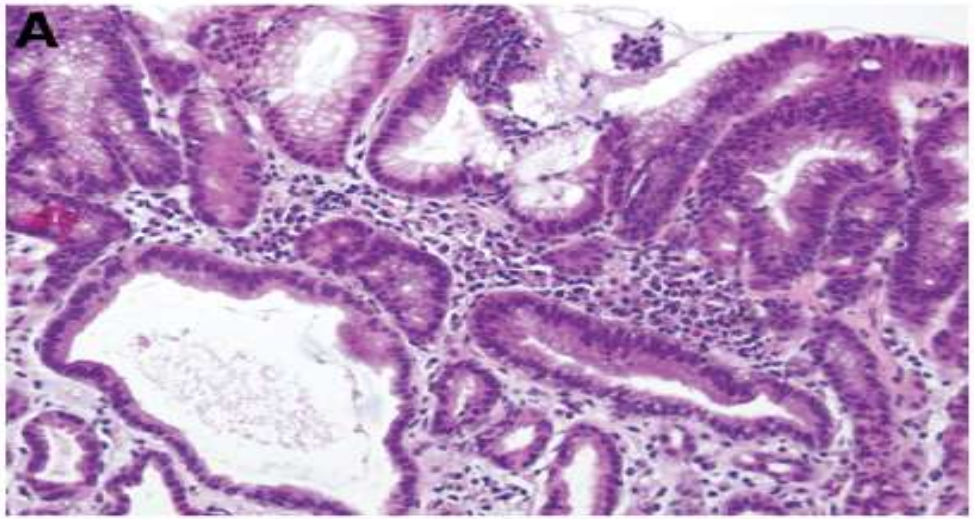
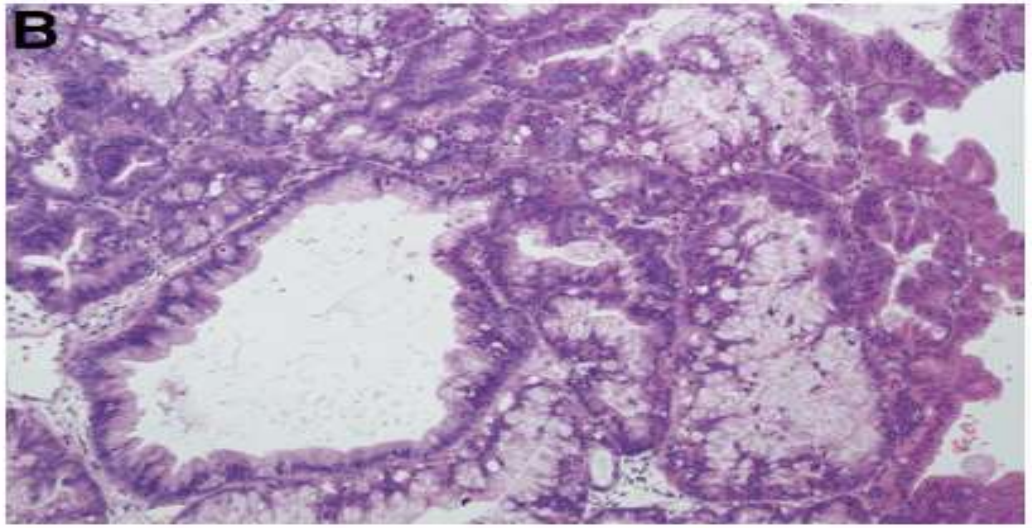
Gastric features of FAP/MAP

- Fundic gland polyposis
  - Prevalence: 88%
  - 50% with low grade foveolar dysplasia
  - 3% HGD







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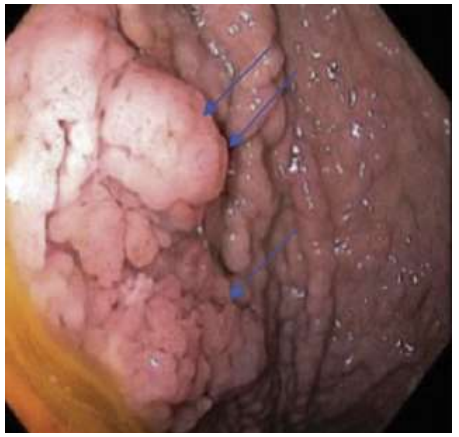
Bianchi L,, et al. Clin Gastro Hep 2007;6:180

Gastric Cancer in FAP

- 767 patients with ≥ 1 EGD between 2001-2016
- 1 case between 1979 and 2006
- 9 cases diagnosed between 2012- 2016
- Mean age 57 years (35-75 yrs)
- Prevalence: 1.3%; Standardized incidence ratio of 140
- All in proximal stomach, unifocal
- 60% Stage IV and died of disease within months



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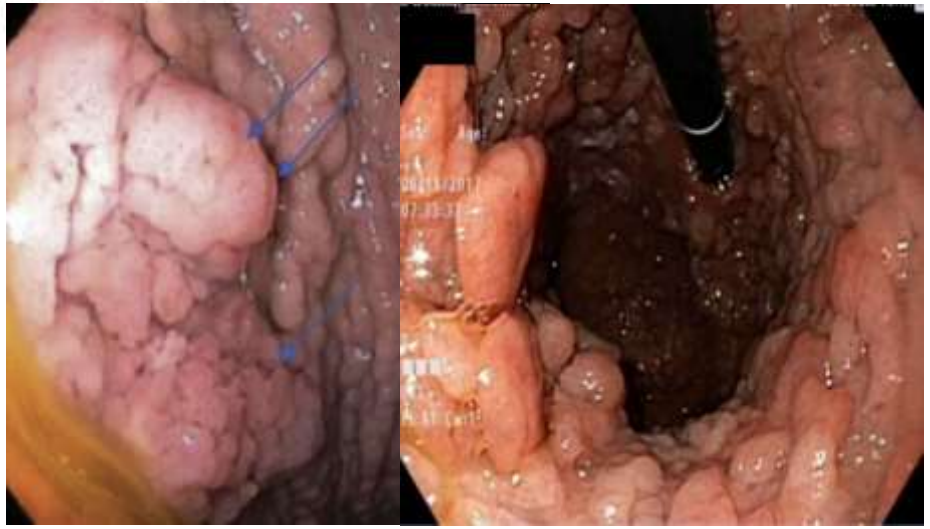
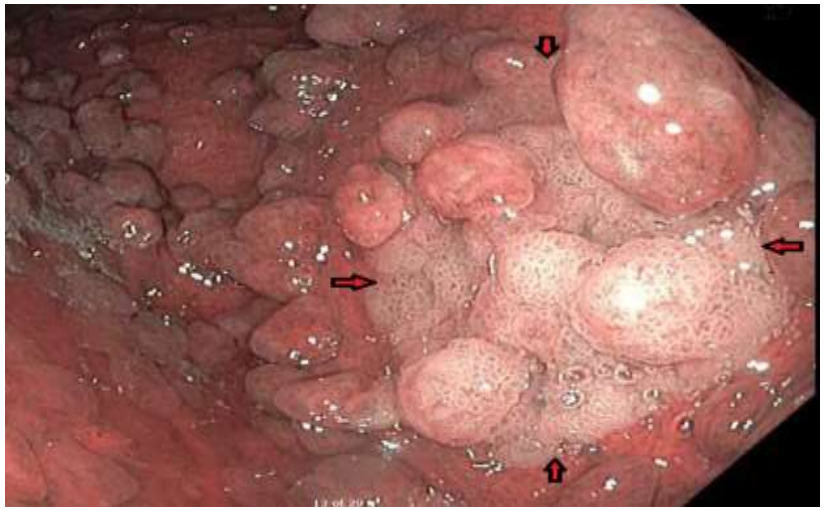
Mankaney G, Familial Ca 2017:16:371

Endo-Pathologic Features of Gastric Cancer Risk





Das Kunnathu N, GIE 2018;88(3):569-570

Table 1. Comparison of Gastric Endoscopic Findings

	FAP Patients with WMP N = 14	FAP Controls N = 70
Carpeting of proximal polyposis	100%	26%
Polypoid mounds	29%	0%
Solitary polyps ≥ 1 cm	57%	16%

Table 2. Comparison of Gastric Histologic Findings

	FAP Patients with WMP N=14		FAP Controls N=70
Feature	Pathology of WMP	Pathology outside WMP	
Fundic Gland Polyp - No Dysplasia	2 (14.2%)	12 (85.7%)	49 (70%)
Fundic Gland Polyp - Low Grade Dysplasia	13 (92.8%)	14 (100%)	38 (54.2%)
Fundic Gland Polyp - High Grade Dysplasia	3 (21.4%)	4 (28.5%)	5 (7.1%)
Tubular Adenoma	4 (28.5%)	4 (28.5%)	5 (7.1%)
Pyloric Gland Adenoma	2 (14.2%)	3 (21.4%)	3 (4.3%)
Adenocarcinoma	0	2 (14.2%)	0

Endoscopic Findings in Proximal Polyposis

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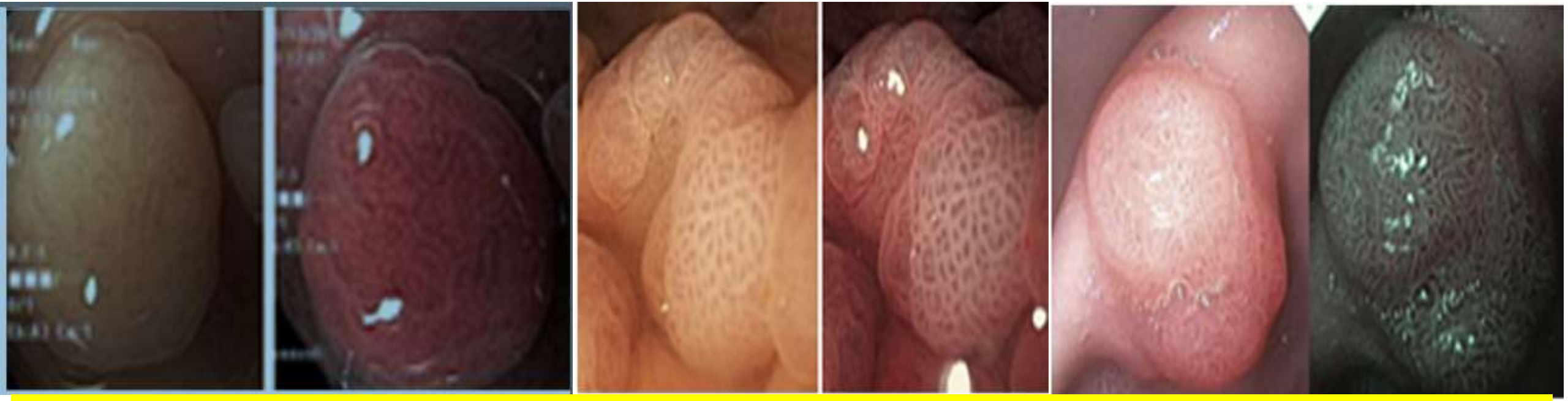
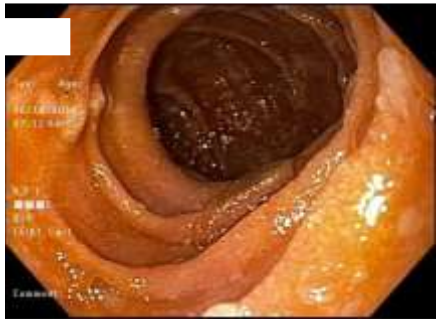


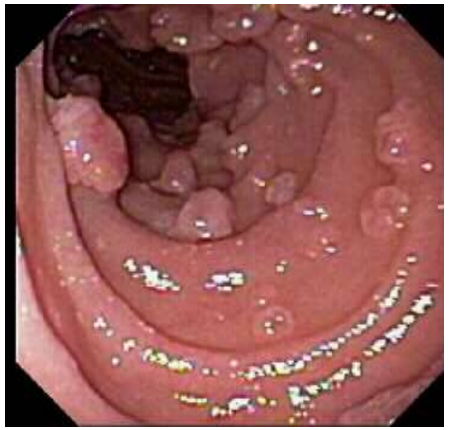
FGP PGA TA

- Consensus criteria were developed based on 128 low-risk and 22 high-risk polyps
- Using the surface morphology criteria, 5 endoscopists distinguished high- from low-risk polyps with sensitivity and specificity of 79% each.
- The k coefficient was .45

Mankaney G, Gastrointest Endosc. 2020 Sep;92(3):755-762

Duodenal features of FAP





- Duodenal adenomas
  - Prevalence: 100%
- Adenomatous papilla[1]
  - 54% if papilla appears normal
  - 89% if papilla appears abnormal
- Periampullary/Duodenal cancer
  - Prevalence: 2-36%[2]
  - Cancer risk greatest in Stage VI duodenal polyposis
    - Nearly half of patients with duodenal cancer did not have Stage IV duodenal polyposis[3]

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[1]Burke C, GIE 1999;49:358 [2]Groves C Gut 2002;50:636 [3]Thiruvengadam S, Gastrointest Endosc. 2019 Feb;89(2):345-354

Staging of Duodenal Polyposis

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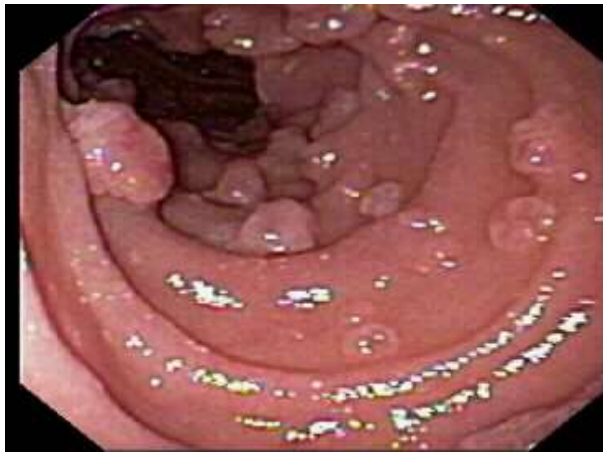
	1 point	2 points	3 points
No. of polyps	1-4	5-20	>20
Polyp size (mm)	1-4	5-10	>10
Histology	Tubular	TVA	Villous
Dysplasia	Mild	Moderate	Severe



Spigelman AD. Lancet 1989;2: 783

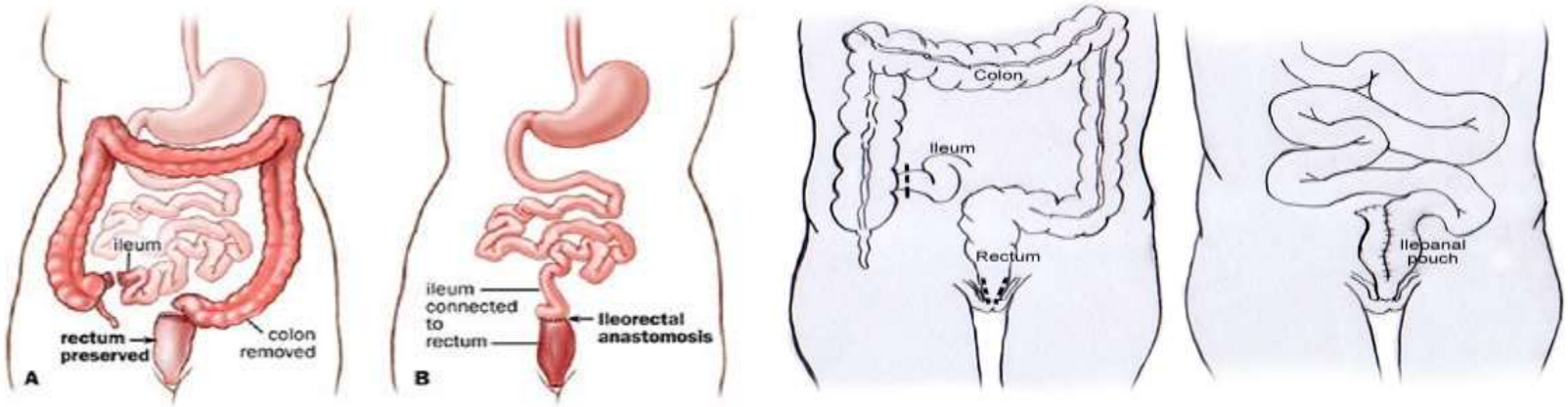
Stage	Points	10 yr Cumulative Cancer Risk	Surveillance: EGD with Evaluation of Papilla FAP: 20-25 yrs MAP: 30-35 yrs
0	0	0%	4 yrs
I	1-4	0%	2-3 yrs
II	5-6	2.3%	1-3 yrs
III	7-8	2.4%	6-12 mos
IV	9-12	36%	Consider Duodenectomy; Expert EGD Q 3-6 months

Groves C Gut 2002;50:636

NCCN : genetic familial high risk assessement Colorectal 2020

FAP/MAP Polyposis Surgery

- Required if symptoms, advanced adenomas or excess or progressive polyp burden
- Need to know rectal polyp burden and desmoid risk
- Operations
  - Total colectomy and ileorectal anastomosis (IRA)
  - Proctocolectomy and ileal pouch anal anastomosis



This picture shows a colectomy with ileorectal anastomosis.

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Surveillance of FAP/MAP

Phenotype	Procedure	Age (yrs)	Interval (yrs)
Classic FAP	Colonoscopy preferred Over FS	10-15	1 year
aFAP/MAP	Colonoscopy	18-20/25-30	1-2 yrs
Surgical Consult		When polyps detected	
Post operative	FS or pouchoscopy	NA	6-12 months
Thyroid	Thyroid Ultrasound	Late teens	2-5 yrs if normal

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NCCN guidelines Genetic/Familial High Risk Assessment Colorectal. 2021
Feng X, et al Thyroid. 2015;Mar;25(3):325-32. PMID: 25585202
Monachese M, et al. Fam Cancer 2019 Jan;18(1):75-82

Colonic Polyposis of Unknown Etiology

Cumulative History of >10-20 adenomas and Negative Multi-Gene panel testing

Phenotype (based on cumulative lifetime adenomas)	Management/Surveillance
Personal history of ≥100 adenomas	Manage as FAP (See FAP-1)
Personal history of 20–<100 adenomas: Adenoma burden that cannot be managed endoscopically	• Surgical evaluation and counseling if appropriate • Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) and repeat following duodenal surveillance guidelines on page FAP-B.
Personal history of 20–<100 adenomas: Adenoma burden manageable by colonoscopy and polypectomy	• High-quality colonoscopy and polypectomy every 1–2 years ▸ At minimum, clearing of all polyps (≥2 mm) is recommended. Repeat at short interval if residual polyps are present. • Consider baseline upper endoscopy (including complete visualization of the ampulla of Vater[d]) and repeat following duodenal surveillance guidelines on page FAP-B. • Surgical evaluation may be considered if polyps not manageable or based on patient preference
Personal or family history of 10–19 adenomas	• Manage based on clinical judgment. Frequency of surveillance may be modified based on factors such as age at which patient met cumulative adenoma threshold or total number of adenomas at most recent colonoscopy, with more frequent surveillance favored for younger age at meeting threshold or higher adenoma burden at last colonoscopy. See NCCN Guidelines for Colorectal Cancer Screening
Family history of ≥100 adenomas in a first-degree relative[b,c] AND meets one of the following criteria: 1) Family member tested, with no pathogenic variant identified; OR 2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified	• High-quality colonoscopy every 12 mo beginning at age 10–15 y. In some families, based on clinical judgement, initiating colonoscopy beginning in late teens, then every 2 y may be appropriate. ▸ If no adenomas, then can lengthen interval to every 2 y. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment. ▸ If ≥100 adenomas found, manage based on Classical FAP Treatment and Surveillance: Personal History (See FAP-1) or ▸ If <100 adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (See AFAP-1)
Family history of 20–<100 adenomas in a first-degree relative[b,c] AND meets one of the following criteria: 1) Family member tested, with no pathogenic variant identified; OR 2) Family member not tested and the unaffected individual with family history has been tested, with no pathogenic variant identified	• High-quality colonoscopy beginning in late teens, then every 2 y. Initial initiation age and frequency of colonoscopy may be modified based on clinical judgment. If multiple surveillance exams without adenomas on follow-up, may lengthen interval further based on clinical judgment. ▸ If adenomas found, manage based on AFAP Treatment and Surveillance: Personal History, Adenoma/Polyp Burden (See AFAP-1)

NCCN guidelines Genetic/Familial High Risk Assessment Colorectal. 2021

Conclusions

- Hereditary adenomatous polyposis syndromed are not rare
  - ≥ 10% in individuals with 10-19 lifetime cumulative adenomas
- FAP and MAP are the most common hereditary adenomatous syndromes
  - Gastroenterologist are key in management of these syndromes
- Germline testing indicated
  - > 10-20 cumulative lifetime adenomas
  - If known PV in family
  - Test affected patient first, then family members when PV detected
  - If no affected relative consider germline testing in at risk individual
- Multi-gene panel testing
  - Consider where more than one syndrome possible
  - Broadening the clinical phenotype of CRC
    - At least 30% of patients with germline PV did not meet classic criteria for that syndrome