Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

Hereditary GI Cancer Syndromes – Application to GI Practices

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Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

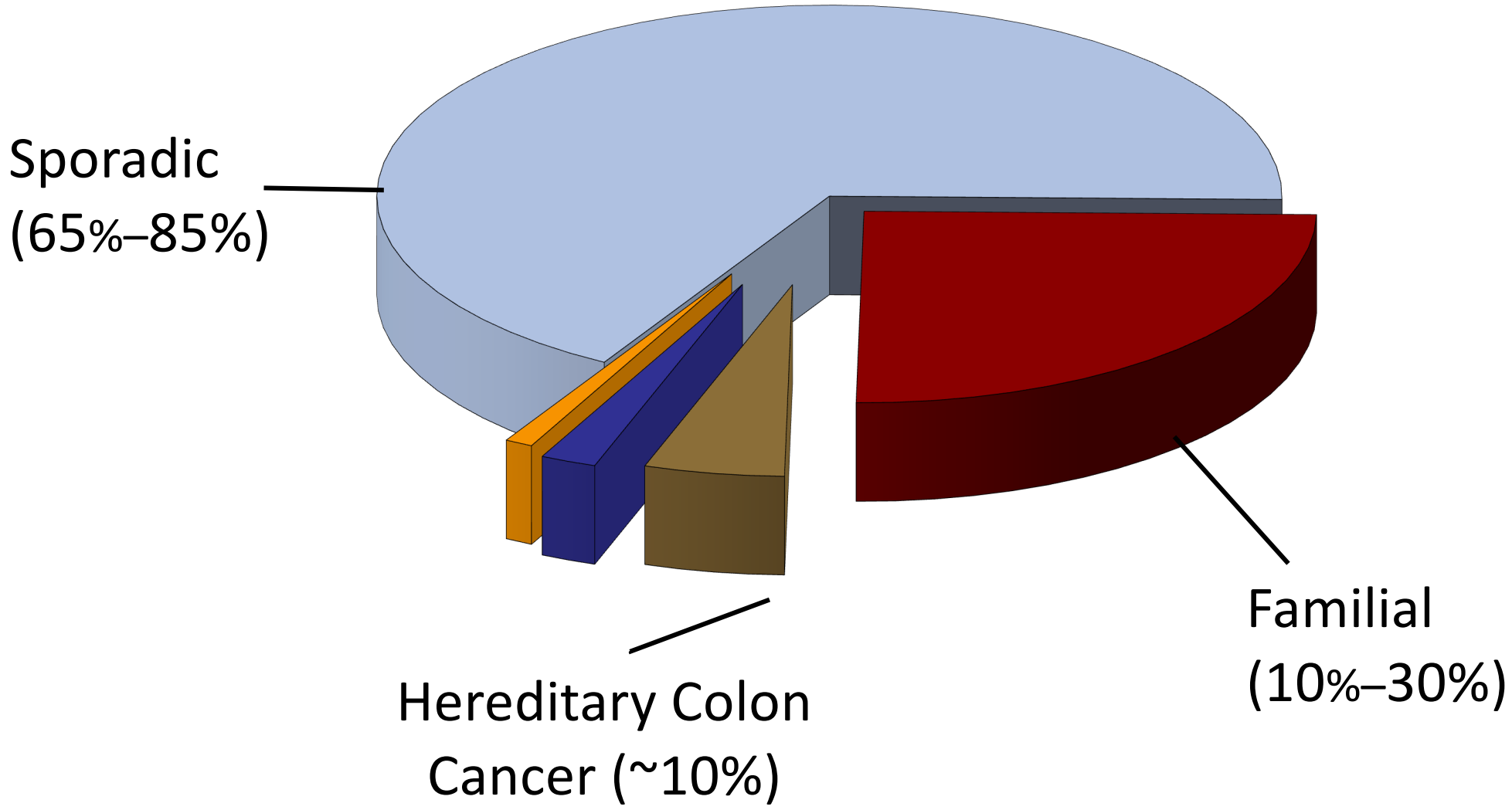
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

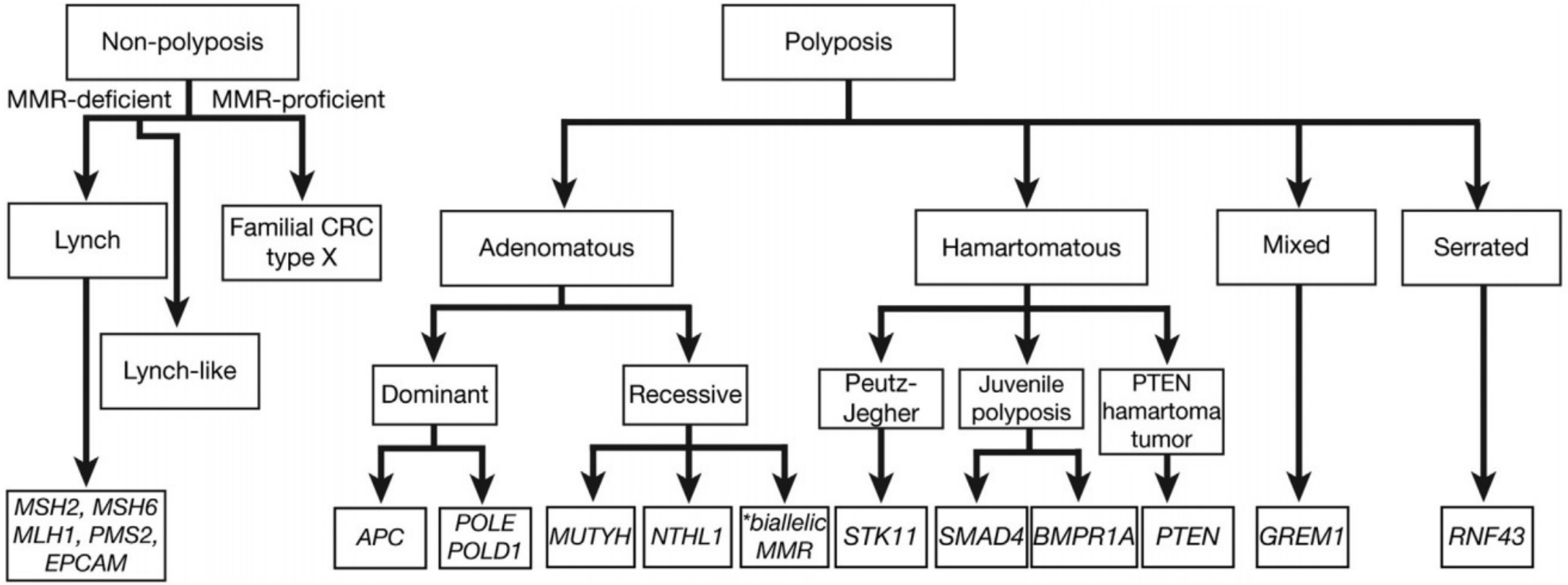
- *Health disparities*
- *Screening barriers*

Colorectal Cancer Risk Groups



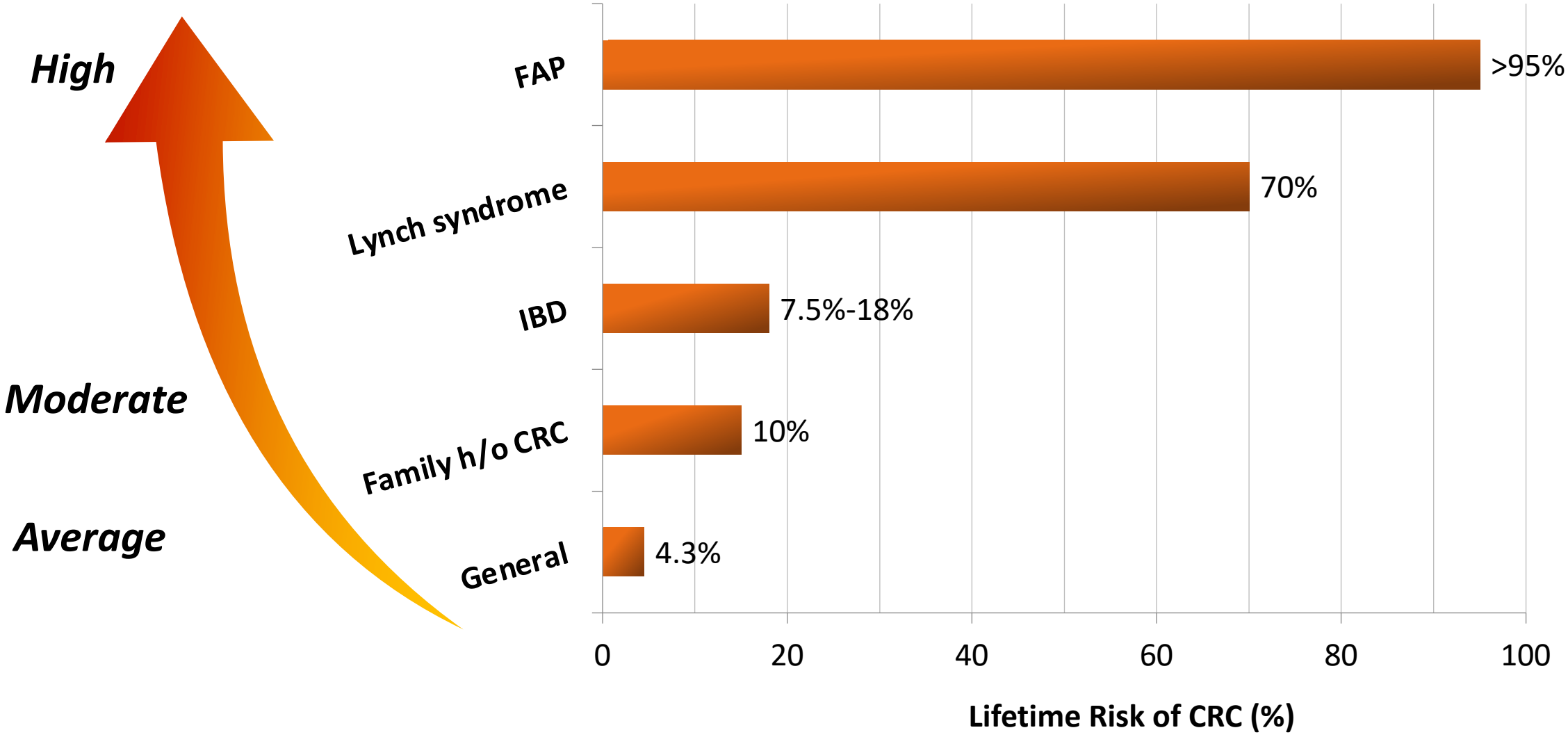
Adapted from Burt RW. Colon cancer screening. Gastroenterology. 2000 Sep 1;119(3):837-53.
Yurgelun MB, Cancer Susceptibility Gene Mutations in Individuals With Colorectal Cancer. J Clin Oncol. 2017 Apr 1;35(10):1086-1095

Hereditary Colorectal Cancer Syndromes



Valle L, *Clinical Gastroenterology and Hepatology* 2017 15809-819

Lifetime Risk of Colorectal Cancer



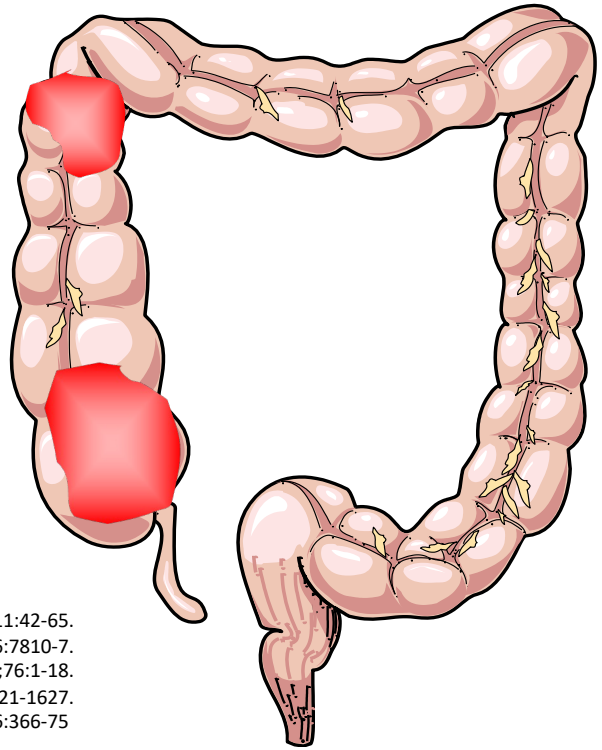
Hereditary Colorectal Cancer Syndromes

Syndrome	**Gene(s)**	**Features**
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Colon cancer, endometrial cancer, ovarian cancer,
Familial Adenomatous Polyposis (FAP)	*APC*	Adenomas, colon cancer, thyroid cancer, osteomas and soft tissue tumors, desmoid tumors
MYH-associated polyposis (MAP)	*MUTYH*	Adenomas, colon cancer, thyroid cancer
Peutz-Jeghers syndrome	*STK11*	Mucocutaneous melanin spots, hamartomas, breast, GI, pancreatic, and rare gynecologic cancers
Cowden syndrome	*PTEN*	Hamartomas, dermatologic lesions, macrocephaly, breast, thyroid, and endometrial cancers
Juvenile polyposis syndrome	*BMPR1A, SMAD4*	Hamartomas, colon cancer, some with *SMAD4* have HHT
Serrated polyposis syndrome	*RNF43*	Serrated polyps

Lynch Syndrome

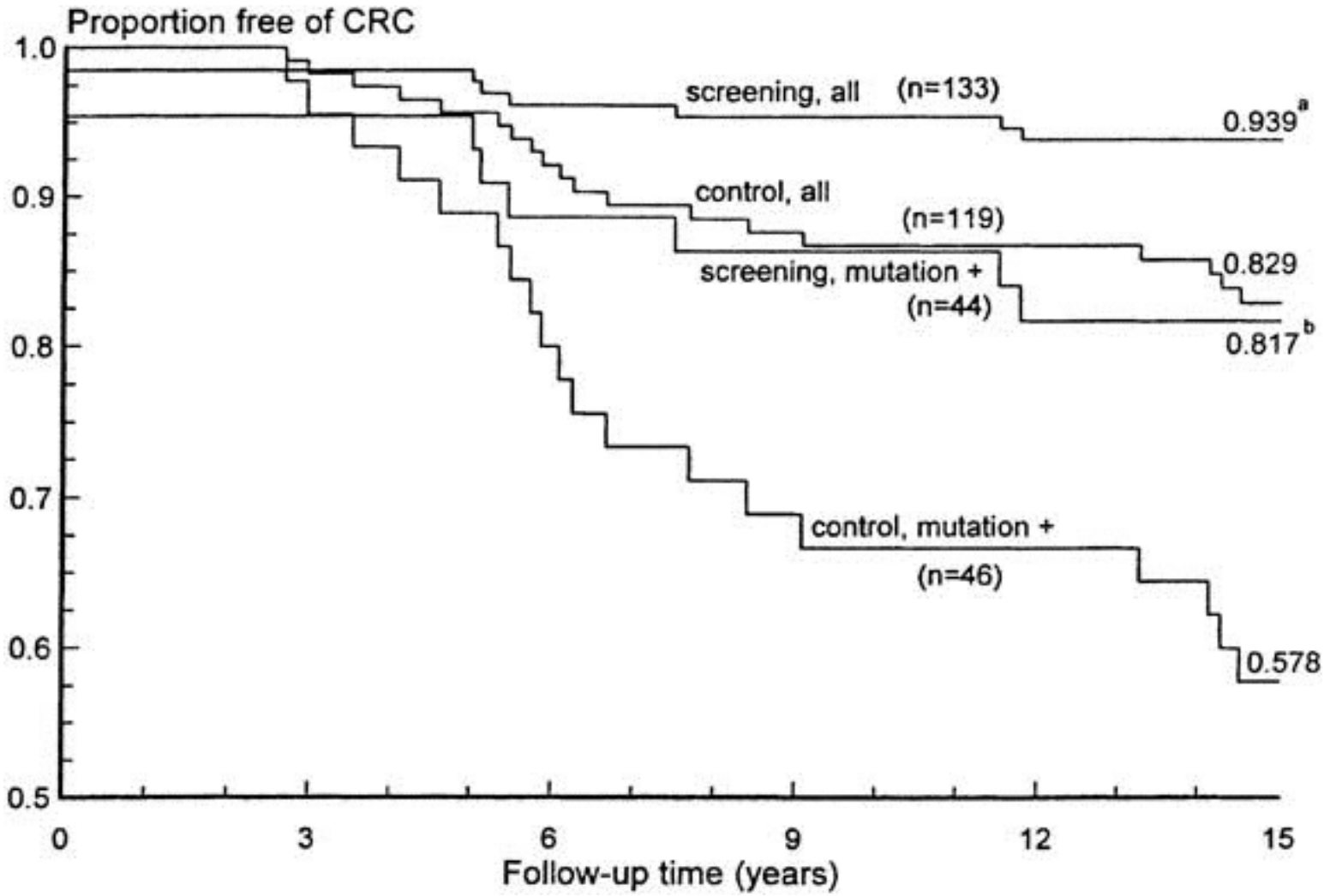
- Most common hereditary CRC cancer syndrome
  - 3% of all CRCs
  - Estimate prevalence of 1 in 279 in the general population
  - High penetrance (>-70% lifetime risk of any Lynch associated cancer)
  - Extracolonic cancer: uterus, ovary, stomach, urothelial, pancreas, and others
  - Accelerated progression to CRC
- Defined by germline mutation in one of the DNA mismatch repair (MMR) genes
  - *MLH1*, *MSH2, MSH6, PMS2,* or *EPCAM*

Family "G", circa 1913: Warthin A. *Arch Int Med* 1913; 12: 546-55



PalomakiGE, et al. Genet Med2009;11:42-65.
HampelH, et al. Cancer Res2006;66:7810-7.
Lynch HT, et al. ClinGenet2009;76:1-18.
Stoffel E, et al. Gastroenterology2009;137:1621-1627.
Win AK, et al. Cancer EpidemiolBiomarkersPrev2017;26:366-75

Colonoscopy reduces mortality in Lynch syndrome



Jarvinen HJ et al. *Gastroenterology* 2000 118:829-834

Colorectal cancer risk in Lynch syndrome

Cancer Site	Population Risk[1]	Lynch syndrome	
		Risk[2]	Average Age at Diagnosis
***MLH1* Cancer Risks**			
Colorectal	4.2%	46%-61%	44 years
***MSH2* and *EPCAM* Cancer Risks**			
Colorectal	4.2%	33%-52%	44 years
***MSH6* Cancer Risks**			
Colorectal	4.2%	10%-44%	42-69 years
***PMS2* Cancer Risks**			
Colorectal	4.2%	8.7%-20%	61-66 years

[1]National Cancer Institute. SEER Cancer Statistics Review 1975-2017

[2] NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020

Lynch Syndrome Surveillance

***MLH1, MSH2*, and *EPCAM* carriers**		
Site	**Screening Procedure and Interval**	**Initiation Age (Y)**
Colorectal	Colonoscopy every 1-2 years	20-25 years*

* Or 2-5 years prior to the earliest colon cancer if diagnosed before age 20

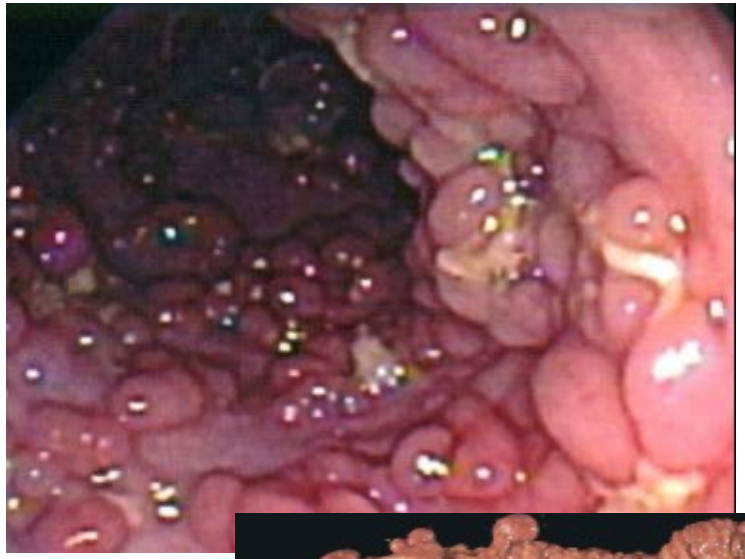
***MSH6* and *PMS2* carriers**		
Site	**Screening Procedure and Interval**	**Initiation Age (Y)**
Colorectal	Colonoscopy every 1-2 years	30-35 years**

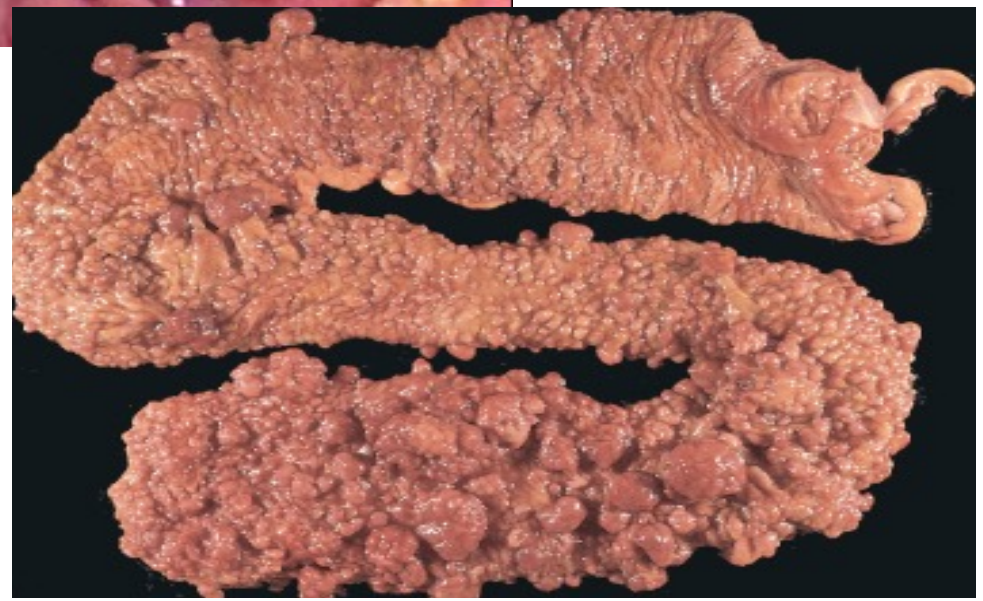
** Or 2-5 years prior to the earliest colon cancer if diagnosed before age 30

[1]NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020
[2]ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

Familial Adenomatous Polyposis (FAP)

- Autosomal dominant syndrome caused by germline mutations in the *APC* gene
- 100s-1000s colorectal adenomas
- Approximately 15% of affected patients develop adenomas by age 10 and 75% by age 20
- <u>Highest lifetime risk of developing colon cancer >95%</u>





Variations of Adenomatous Polyposis

"Classic" FAP

- Majority of cases due to germline *APC* mutations
- 100s-1000s colorectal adenomas
- Risk of cancer is >90% without surgery
- Risk of extracolonic tumors: Upper GI, desmoid, osteoma, thyroid[r]

Attenuated FAP (AFAP)

- Minority have germline *APC* mutations
- 20-100 lifetime adenomas
- Later onset of CRC
- Similar risk of extracolonic manifestations

MUTYH Polyposis (MAP)

- Autosomal Recessive
- Germline mutations in the *MUTYH* gene
- "attenuated" phenotype of 20-100 adenomas
- Extracolonic manifestations less common

FAP Colorectal Cancer Surveillance

Site	Screening Procedure and Interval[1,2]	Initiation Age (Y)
Classic FAP		
Colorectal	Colonoscopy (preferred) for flex sigmoidoscopy every 1 year	10-15 years
Attenuated FAP		
Colorectal	Colonoscopy every 1-2 years	Late Teens
MUTYH Polyposis		
Colorectal	Colonoscopy every 1-2 years	25-30 years (or earlier based on family history)
When adenoma burden is significant, refer for colectomy or proctocolectomy		
Retained Rectum	**Sigmoidoscopy every 6-12 months**	
Ileal Pouch	**Endoscopic evaluation every 1-3 years depending on polyp burden**	

[1]NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020

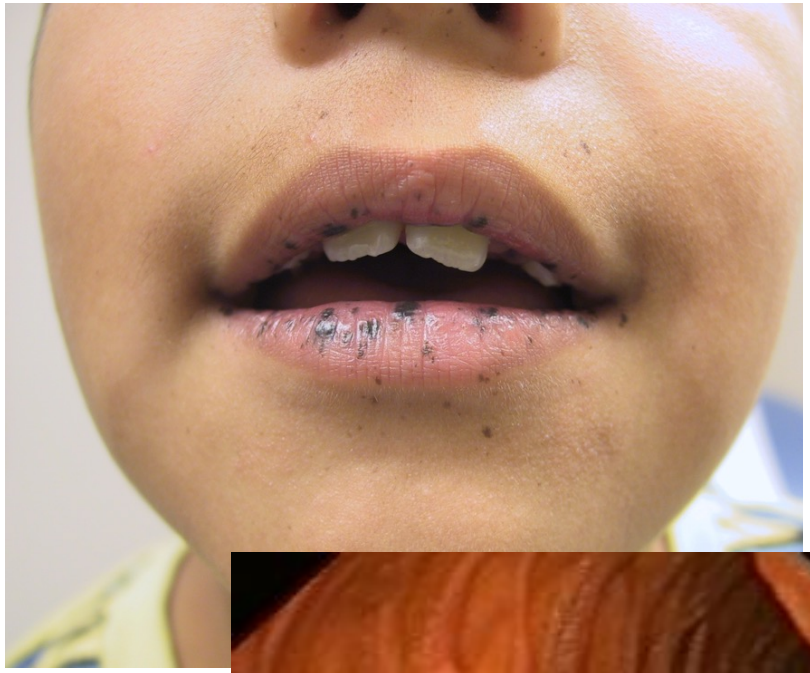
[2]ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

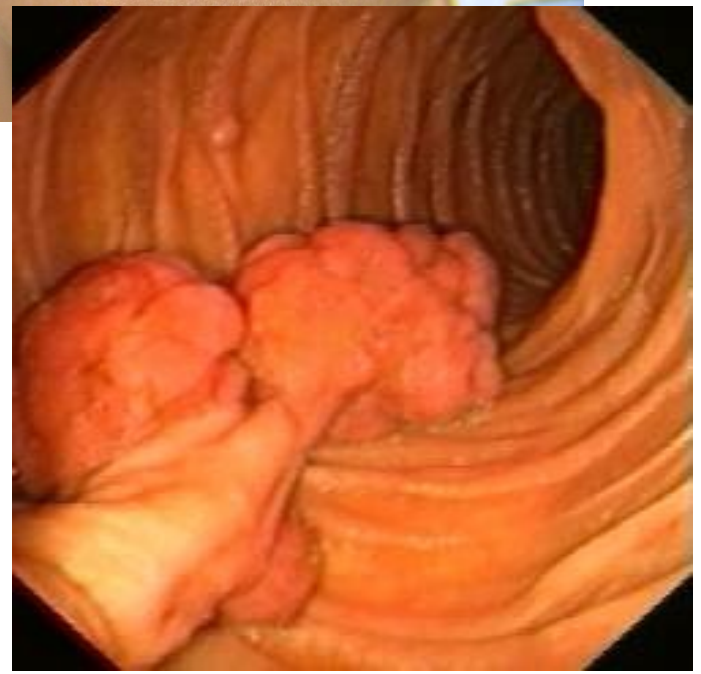
Hamartomatous Polyposis Syndromes

- These are a group of rare, autosomal dominant hereditary disorders associated with increased risk of benign and malignant intestinal and extra-intestinal tumors including colon cancer
- Peutz-Jeghers syndrome
- Juvenile polyposis syndrome
- Cowden syndrome

Peutz Jeghers Syndrome (PJS)

- Mucocutaneous pigmentation (~95%)
  - Perioral region, digits, genital area
- Clinical criteria
- Pathogenic germline variants in the *STK11* gene
- Risk of intussusception is 50%-68% by age 18
  - Various guidelines recommend initiating EGD, colonoscopy, and small bowel visualization starting between ages 8-10 years with repeat surveillance every 2-3 years if polyps are found.
  - If no polyps found on baseline examination, resume at age 18.





Diagnostic Clinical Criteria for PJS

The clinical diagnosis of PJS can be made when an individual meets two or more of the following features:

- ≥2 histologically confirmed Peutz-Jeghers Polyps
- Any number of Peutz-Jeghers polyps in an individual with family history of PJS in a first degree relative
- Characteristic mucocutaneous pigmentation in a person with a family history of PJS
- Any number of PJ polyps in a person with the characteristic mucocutaneous pigmentation of PJS

Colorectal cancer surveillance for PJS

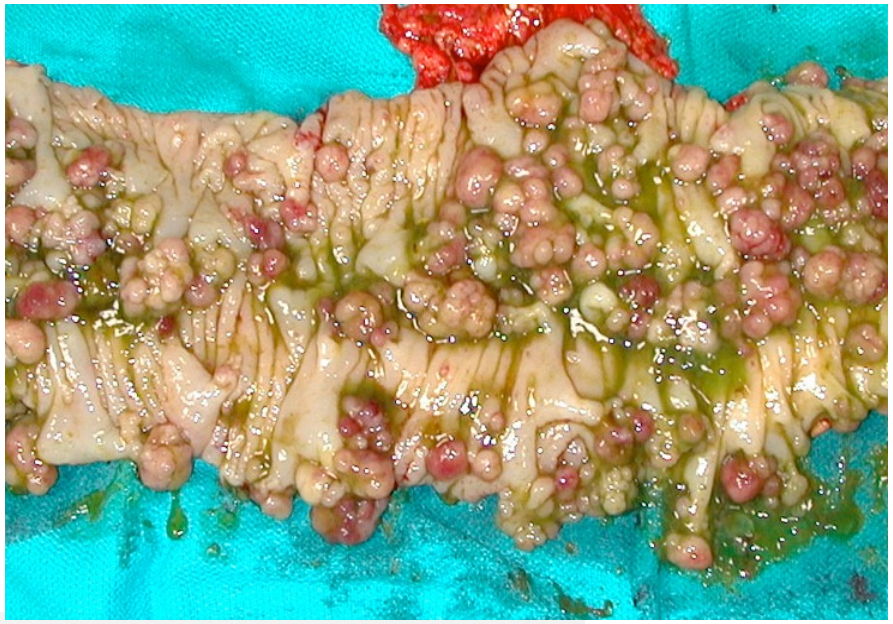
Site	Population Risk[1]	Lifetime Risk[2]	Screening Procedure and Interval[2,3]	Initiation Age (Y)
Colorectal	4.3%	40%	Colonoscopy every 2-3 years*	18 years

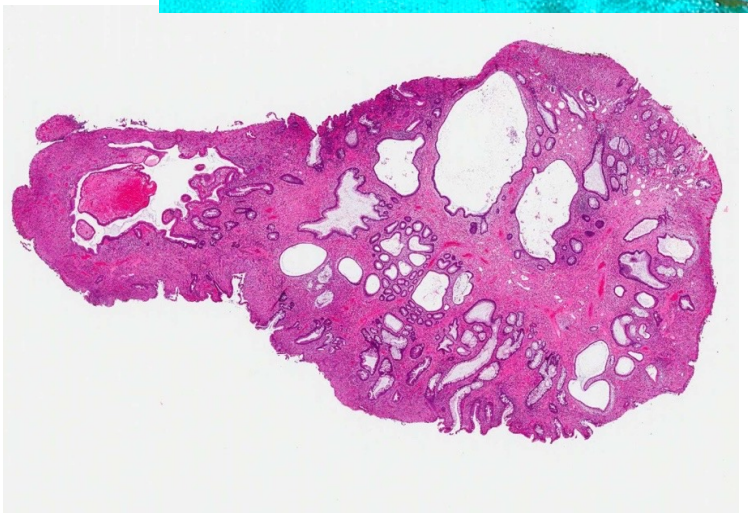
* EGD and small bowel surveillance resumes at age 18 as well

[1]National Cancer Institute. SEER Cancer Statistics Review 1975-2017
[2] NCCN Genetic/Familial High-Risk Assessment: Colorectal V1. 2020
[3]ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

Juvenile Polyposis Syndrome (JPS)

- Multiple juvenile polyps founds in the colon, stomach, and small intestine.
- Solitary juvenile polyps are not syndromic
- Clinical criteria
- Pathogenic germline variants in the *SMAD4* or *BMPR1A* gene





Diagnostic Clinical Criteria for JPS

- The clinical diagnosis of JPS is made when a person has any one of the following:
  - Five or more juvenile polyps of the colon or rectum.
  - Any number of juvenile polyps in parts of the gastrointestinal tract other than the colon.
  - Any number of juvenile polyps and one or more FDRs with JPS.

Colorectal Cancer surveillance for JPS

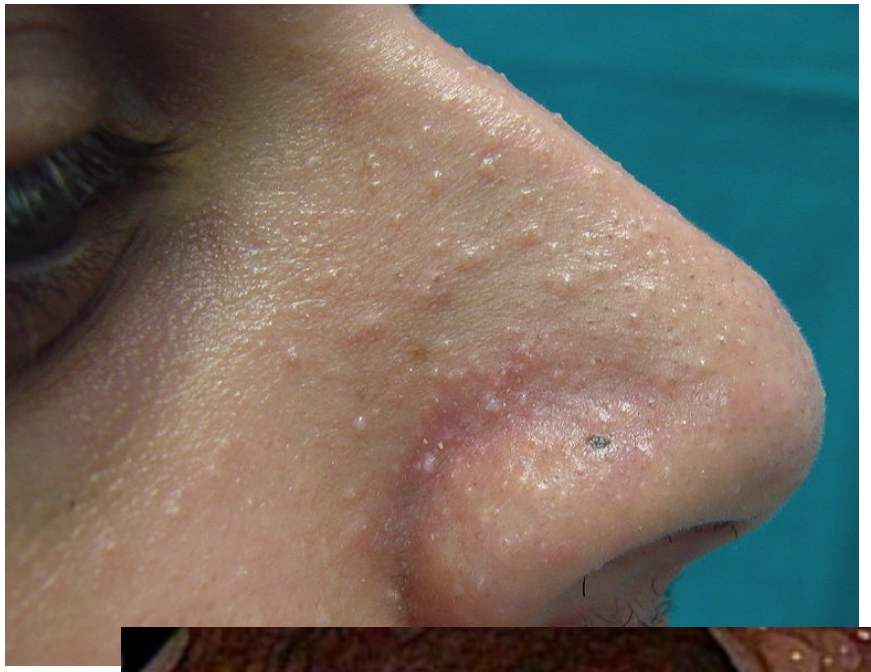
Site	Population Risk[1]	Lifetime Risk[2]	Screening Procedure and Interval[2,3]	Initiation Age (Y)
Colorectal	4.3%	39%	Colonoscopy every 1-3 years	12-15years*

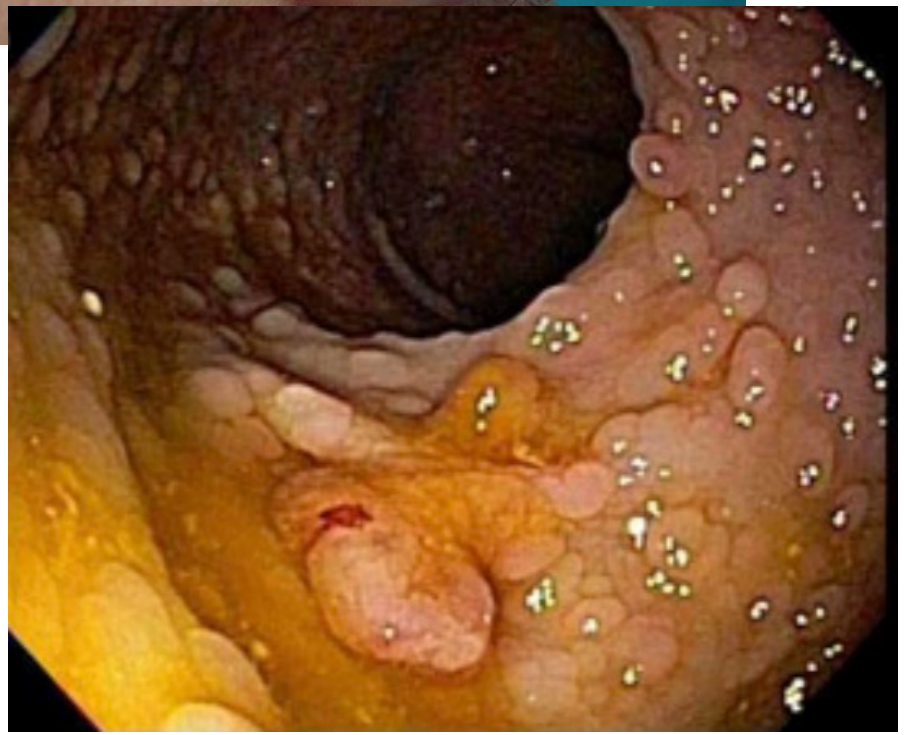
*Colonoscopy can begin earlier that age 12 if there are symptoms, especially rectal bleeding

[1]National Cancer Institute. SEER Cancer Statistics Review 1975-2017
[2] NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020
[3]ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

Cowden syndrome

- Part of a spectrum of PTEN-hamartoma syndrome
- Pathogenic germline variants in the *PTEN* gene
- Diagnostic Criteria:
  - Hamartomas of the skin and gastrointestinal tract
  - Macrocephaly
  - Increased risk of benign and malignant lesions of the breast, thyroid, and uterus
- Gastrointestinal polyps are frequently found- hyperplastic polyps, inflammatory polyps, ganglioneuromas, adenomas





Colorectal cancer surveillance in Cowden syndrome

Site	Population Risk[1]	Lifetime Risk[2]	Screening Procedure and Interval[2]	Initiation Age (Y)
Colorectal	4.3%	9-18%	Colonoscopy every 5 years	35 years

[1]National Cancer Institute. SEER Cancer Statistics Review 1975-2017

[2] NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V1. 2020

Serrated polyposis syndrome (SPS)

World Health Organization (WHO) Criteria Serrated Polyposis Syndrome

1) ≥ 5 serrated lesions proximal to the rectum of which (≥2 must be ≥ 1 cm in size)

2) > 20 serrated polyp lesions through the colon, with ≥ 5 being proximal to the rectum

Dekker et al. WHO Classification of Tumours, Gastroenterology, 2020; 158:1520-1423

Serrated polyposis syndrome (SPS)

- Cumulative risk of colorectal cancer estimated to be 7%-35%
- SPS is commonly grouped with the hereditary polyposis
  - Does not appear to be inherited in a simple Mendelian fashion
- Germline truncating variants in the *RNF43* gene have been reported in several SPS patients
  - although these reported *RNF43* variants do not account for majority of people with SPS.

Colorectal cancer surveillance for SPS

Cancer Site	Population Risk[1]	Sessile Serrated Polyposis Syndrome	
		CRC Risk[2]	Average Age at Diagnosis
Colorectal	4.3%	7-35%	35 years

Site	Screening Procedure and Interval[2,3]	Initiation Age (Y)
Colorectal	Colonoscopy with polypectomy until all polyps ≥5mm are removed Then, every 1-3 years depending on remaining polyp burden	Insufficient data*

*First degree relatives of SPS patients are encouraged to 1) begin colonoscopy at age 40 or 2)at same age as youngest diagnosis of serrated polyposis in the family or 3) 10 years earlier than the earliest diagnosis of CRC in the family due to serrated polyposis.

[1]National Cancer Institute. SEER Cancer Statistics Review 1975-2017
[2]NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020
[3]ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

Who Should Have Genetic Counseling and Testing

- Known pathogenic germline variant in a mismatch repair or polyposis gene in family
- Personal history of ≥ 10 cumulative adenomas
- ≥ 2 lifetime hamartomous polyps
- ≥ 5 serrated polyps/lesion proximal to the rectum
- Personal or family history of colorectal, endometrial, or other Lynch syndrome associated cancer

NCCN Genetic/Familial High-Risk Assessment:Colorectal V1. 2020
ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes 2015

Thank You