Caring for the CRC Patient with a Hereditary Syndrome: Surveillance of Other Organs & Surgical Decision Making

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Disclosures

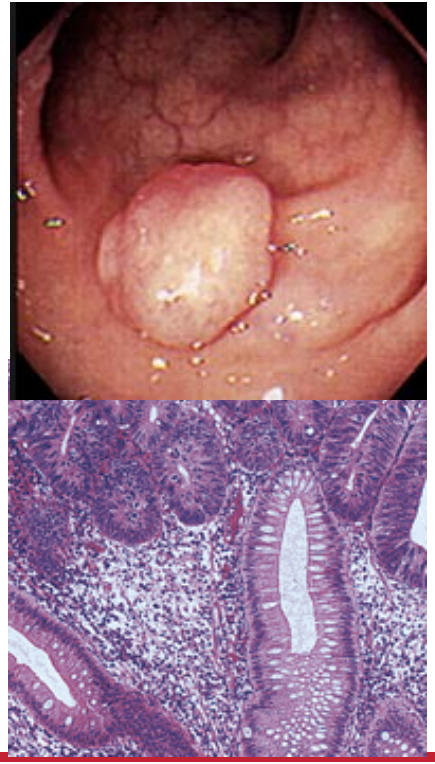
- No disclosures

Learning Objectives

Describe	screening recommendations for colonic and extra-colonic cancers for adenomatous polyposis syndromes
Compare and contrast	surgical options and indications for patients with hereditary CRC syndromes
Explain	the role of genetic testing in surgical decision making for patients with polyposis syndromes

Adenomatous Polyps & Colorectal Cancer

- Present on colonoscopy in 23-58% of adults
- May have multiple adenomatous polyps
- Most patients with multiple polyps do **not** have a genetic syndrome
- 20-30% CRC patients have a family history of CRC/polyps



Gastrointestinal Pathology: An Atlas and Text, 2008.

Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis	Lynch Syndrome	Familial Colorectal Cancer Type X
MYH-Associated Polyposis	Newly described syndromes	No clear syndrome

Clinical Case

- 51F with synchronous transverse and descending colon cancers
- PMHx: endometrial cancer
- Fam Hx: Father with rectal cancer ~70; brother died of brain tumor in childhood; paternal grandmother ?cancer
- Colonoscopy: 2 cancers; 2 tubular adenomas

Clinical Considerations

- Cancer treatment
- Extent of surgery
- Diagnosing a possible syndrome
- Screening & Surveillance of other organs
- Screening & Surveillance for at-risk family members
- Psychosocial and QoL impact

Lynch Syndrome

- 2-5% of CRC cases are related to LS
  - 8-17% of CRC cases under age 50
- Defect in mismatch repair genes
  - ***MLH1, MSH2, MSH6, PMS2***
  - Less common: *MSH3*
- 1 in 370 individuals in the US carries a pathogenic mutation in a MMR gene
- Multiple polyps
- Early age of onset CRC: mean 45 years
- Accelerated adenoma to carcinoma sequence

Hampel H et al. Cancer Prev Res, 2011.
Bartenson R et al. NEJM, 2006. .
Hampel H et al. JCO, 2008.
Kravochuck SE, Gut, 2014.

Risk of CRC in Lynch Syndrome Patients

	MLH1		MSH2		MSH6		PMS2
Age	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Both*
30	4.5	0	2.6	1.9	0	0	0
50	33.6	20.8	18.1	16.9	6.3	4.4	0
75	57.1	48.3	51.4	46.6	18.2	20.3	10.4

Dominguez-Valentin M. Genet Med. 2020.

Non-Colonic Malignancies in Lynch Syndrome

- Gynecologic
- Small bowel
- Gastric
- Hepatobiliary and pancreatic
- Urologic
- Breast and prostate
- Brain
- Skin

Risk of All Cancers in Lynch Syndrome

	MLH1	MSH2	MSH6	PMS2
Colon	46-61%	33-52%	10-44%	8.7-20%
Endometrial	34-54%	21-57%	18-49%	13-26%
Ovarian	4-20%	8-38%	1-13%	-
Renal pelvis/ureter **Bladder**	0.2-5% 2-7%	2.2-28% 4.4-12.8%	0.7-5.5% 1-8.2%	-
Small Bowel	0.4-11%	1.1-10%	1-4%	-
Pancreas	6.2%	0.5-1.6%	1.4-1.6%	-
Biliary	1.9-3.7%	0.02-1.7%	0.2-<1%	-

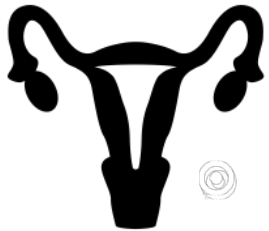
Clinical Features of LS-associated CRC

- Early-age of onset
- Predominance of R sided CRC
- Rapid progression of adenoma to carcinoma sequence
- Improved oncologic outcomes
- Decreased response to 5-FU based chemotherapy
- Response to immunotherapy

Popat S et al. JCO, 2005.
Des Guetz G et al. Eur J Cancer, 2009.

Gynecologic Malignancies in Lynch Syndrome: Endometrial & Ovarian

- Higher risk in *MSH2* & *MSH6*
- Endometrial cancer
  - Lifetime risk:
    - 18-60% (*MLH1);* 20-60% (*MSH2);* 16-70% (*MSH6);* 13-24% *(PMS2)*
  - Mean age at diagnosis: 46-54 years
- Ovarian cancer
  - 7-24% lifetime risk
  - Mean age at diagnosis: 43-50 years
- Screening
  - Annual pelvic exam & endometrial biopsy
  - Initiate by age 30-35
  - Role of TVUS and CA-125 less clear
- Prevention
  - Prophylactic TAH/BSO by age 40
  - Offer TAH/BSO at time of colectomy



Giardiello et al. *Dis Colon Rectum.* 2014
Barrow E et al. *Clin Genetics.* 2009.
Vasen HF et al. *J Clin Oncol*. 2001.
Schmeler KM et al. *NEJM*. 2006.

Small Bowel Cancer in Lynch Syndrome

- Higher risk in *MSH2 & MSH6*
- Lifetime risk: 0.6-7%
- Median age: 39—53 years
- Tumors evenly distributed throughout small bowel
- No routine screening

Vasen et al. *Gut.* 2013
Schulmann K et al. *Gastroenterol.* 2005

Gastric Cancer in Lynch Syndrome

- Rate of gastric cancer in Lynch Syndrome patients: 1.6%
- Lifetime risk 5-13%
- Median age at diagnosis: 49-55 years
- Risk highest in *MSH2*
- Screening
  - EGD + gastric antrum biopsy starting at age 30
  - Surveillance q2-4 years

Capelle LG et al. *Gastroenterology*. 2010.

Hepatobiliary & Pancreatic Cancer in Lynch Syndrome

- Lifetime risk of biliary cancer: .02-4%
- Median age at diagnosis: 54-57 years
- Lifetime risk of pancreatic cancer: 0.4-4%
- Median age at diagnosis: 63-65 years
- No recommended screening
  - May be detectable on ultrasound or with LFTs

Vasen HF et al. *J Med Genetics.* 2007
Syngal S et al. *Am J Gastroenterol*. 2015.

Urologic Cancer in Lynch Syndrome

- Urothelial cell carcinoma
- Individuals with *MSH2-MSH6* mutations
  - 0.4-20% lifetime risk
  - 20x risk of general population
- Median age: 56 years
- Screening: annual urinalysis/cytology starting age 30-35
  - Other options: cystoscopy, CT urogram
- Questionable increased risk of bladder cancer

Joost et al. *Urology.* 2015
Huang et al. *Bladder Cancer.* 2018

Breast and Prostate Cancer in Lynch Syndrome

- Prostate cancer relative risk = 3.67
- Debatable increased risk for breast cancer
- Screening
  - Routine screening per guidelines
  - No evidence of early onset or higher stage at diagnosis

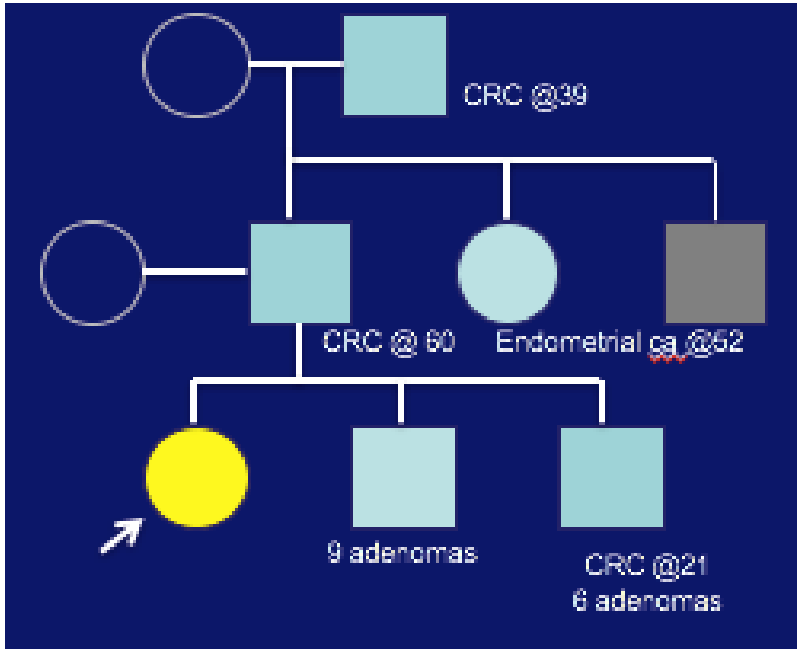
Haraldsdottir et al. *Genet Med.* 2014

Surveillance for Non-Colonic Malignancies

Organ System	Surveillance Test	Frequency
Skin	Skin Exam	Annually
Gynecologic	Endometrial Biopsy ?TVUS, CA-125	Annually
Small bowel	Capsule endoscopy	No recommendation
Stomach	EGD	1-3 years
Hepatobiliary/Pancreas	?Ultrasound	No recommendation
Urologic	Urinalysis/Cytology	Annually
Breast cancer	Mammogram	Per general population guidelines

Family History: Amsterdam II Criteria

- At least **3** relatives
- At least **2** generations are affected
- At least **1** relative was diagnosed at 50 years of age or earlier
- **1** is a first-degree relative of the other two



Utility of Amsterdam Criteria

- Sensitivity 40-80%
- Specificity: 50%
- Positive Predictive Value: 75%

Southey M et al. JCO, 2005.
Lynch HT et al. NEJM, 2003.

Impact of Pre-Operative Testing on Surgical Management of Lynch Syndrome

Extent of colorectal surgery

- Consider STC at time of initial surgery

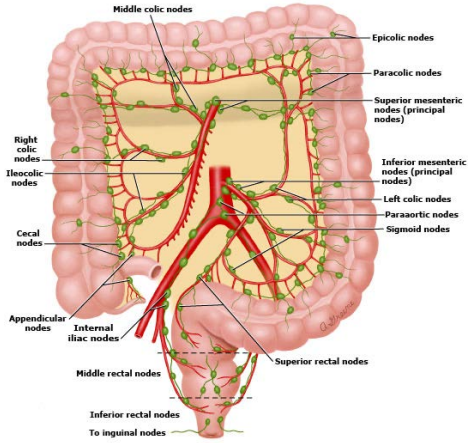
Consideration for other procedures

- Consider prophylactic TAH/BSO in women beyond childbearing age

Appropriate screening for other malignancies

- Colonoscopy recommended at 1-2 year intervals beginning at approximately age 25 for patients with LS

Benefits for at-risk family members



Guillem JG et al. JCO, 2006.
Nataranjan N et al. DCR, 2010.
Lindor N et al. JAMA, 2006.
Boilensen AEB et al. Acta Obstetrica, 2008.

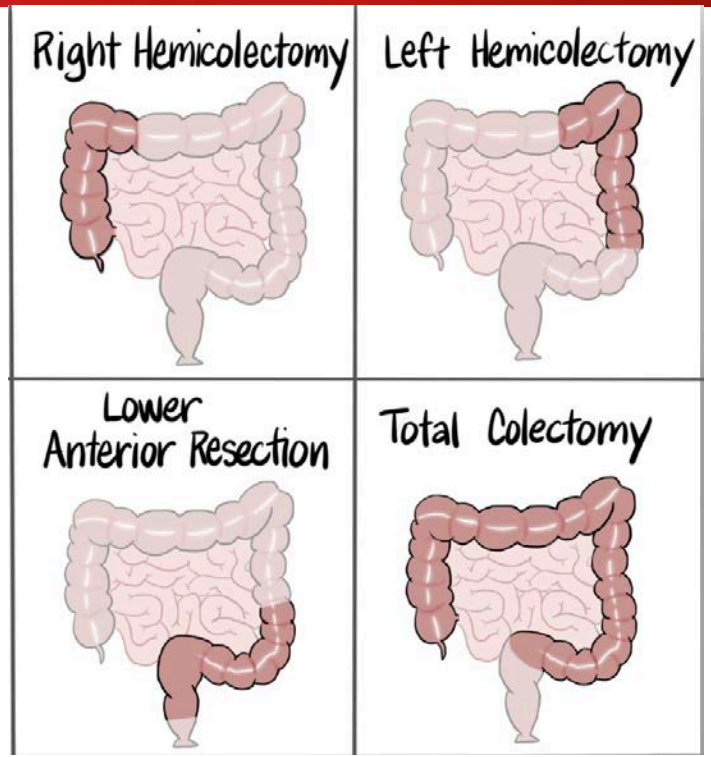
Prophylactic TAH/BSO during Colectomy for Lynch Syndrome

- Factors to consider:
  - Age
  - Family History
  - Genotype
  - Childbearing history & preferences

Risk of Endometrial Cancer	
General Population	1.67%
MLH1	32.5%
MSH2	44.6%

Schmeler KM. NEJM, 2006.
Lindor NM. JAMA, 2006.
Stoffel E. Gastroenterology, 2009.

Extent of Colectomy for Lynch Syndrome



	Segmental Resection	Total Abdominal Colectomy
Metachronous Adenoma	33%	11%
Metachronous Carcinoma	22-25%	0-8%

Kalady M. Ann Surgery, 2010.
Parry S. Gut, 2010.

Immunotherapy for MMR-d CRC

PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer

Andrea Cercek, M.D., Melissa Lumish, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.A., Jinru Shia, M.D., Michelle Lamendola-Essel, D.H.Sc., Imane H. El Dika, M.D., Neil Segal, M.D., Marina Shcherba, M.D., Ryan Sugarman, M.D., Ph.D., Zsofia Stadler, M.D., Rona Yaeger, M.D., et al.

- 12 patients with stage II-III MMR-d rectal cancer
- Treated with PD-1 inhibitor x6 months
- 100% clinical complete response
- Sustained at 12 months

Current Guidelines for Surgical Management of Lynch Syndrome

1. After diagnosis of CRC, total abdominal colectomy is preferred
2. But, segmental resection should be considered because of functional outcomes
3. Annual colonoscopy should be performed after segmental resection
4. In the setting of LS, rectal cancer should be treated with standard of care protocols and the decision for concomitant colectomy is individualized
5. TAH/BSO should be offered to women who have finished childbearing who are undergoing surgery for CRC

Herzig DO et al. DCR 2017.

Lynch Syndrome – Bottom Line

- Patients are at risk for a variety of cancers
- Close surveillance is required
- Ideal to test at-risk family members
- Multi-disciplinary coordination leads to better outcomes

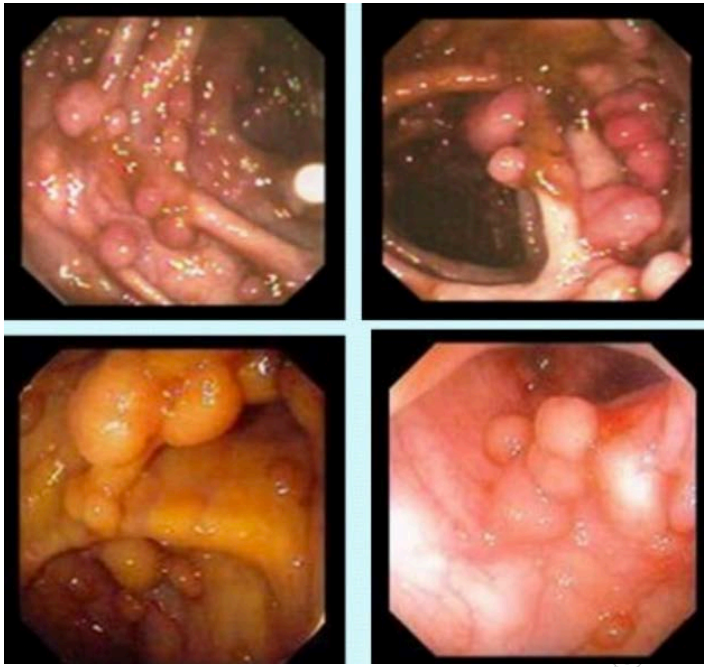
FAP Genetic Mutation

- Autosomal dominant
- Mutation: Adenomatous polyposis coli (APC) gene
  - Chromosome 5q21
- Tumor suppressor gene
- 25% of patients are de-novo mutations
- Anyone with >10-20 lifetime adenomas should have genetic testing

Syngal S, Gastroentrol 2015.
Gupta S, J Natl Comp Canc Netww, 2017.

Clinical Case

- 23 year old female with anemia x 3 years; weight loss x20lbs
- Father died of CRC in 30s; paternal grandmother CRC in 60s
- Exam:
  - Rectal mass 1.5cm above anal verge
- EGD: Duodenal polyps
- Colonoscopy: diffuse polyposis from just above dentate through R colon
- MRI: T3N1
- CT no metastatic disease, no other abnormalities
- CEA 1.2



Clinical Issues

- Diagnosing a possible syndrome
- Rectal cancer treatment
- Screening & Surveillance of other organs
- Screening & Surveillance for at-risk family members
- Psychosocial and QoL impact
- Fertility

FAP Phenotype

- Classical: Hundreds to thousands of adenomatous polyps
- Median age for adenoma development: 17 years
- Median age for CRC: 40 years
- Untreated median age for death: 44 years

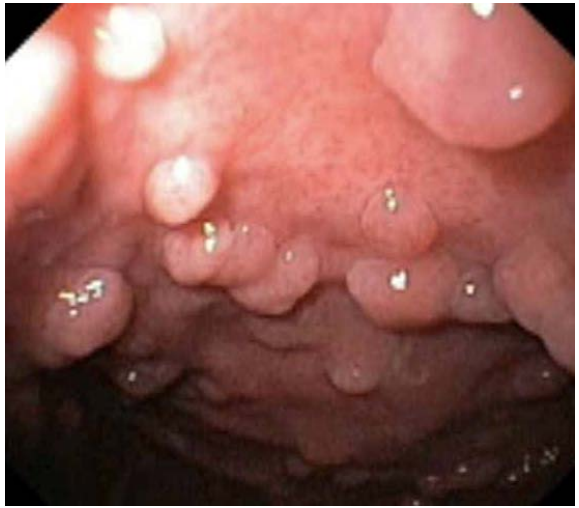
Classifying FAP by Phenotype

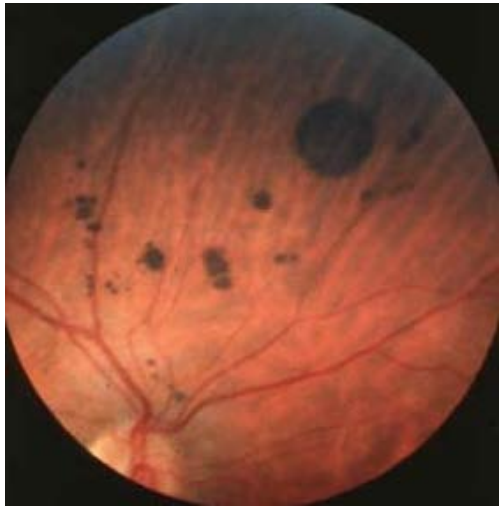
Phenotype	Codon	Estimated no. polyps	Age of onset
Attenuated	1-57 312-412 1596-2843	<100	Fourth and fifth decades
Intermediate	158-311 413-1249 1465-1595	Hundreds	Second and third decades
Severe/profuse	1250-1464	Thousands	First and second decades

Nieuwenhuis MH. Dis Colon Rectum, 2009

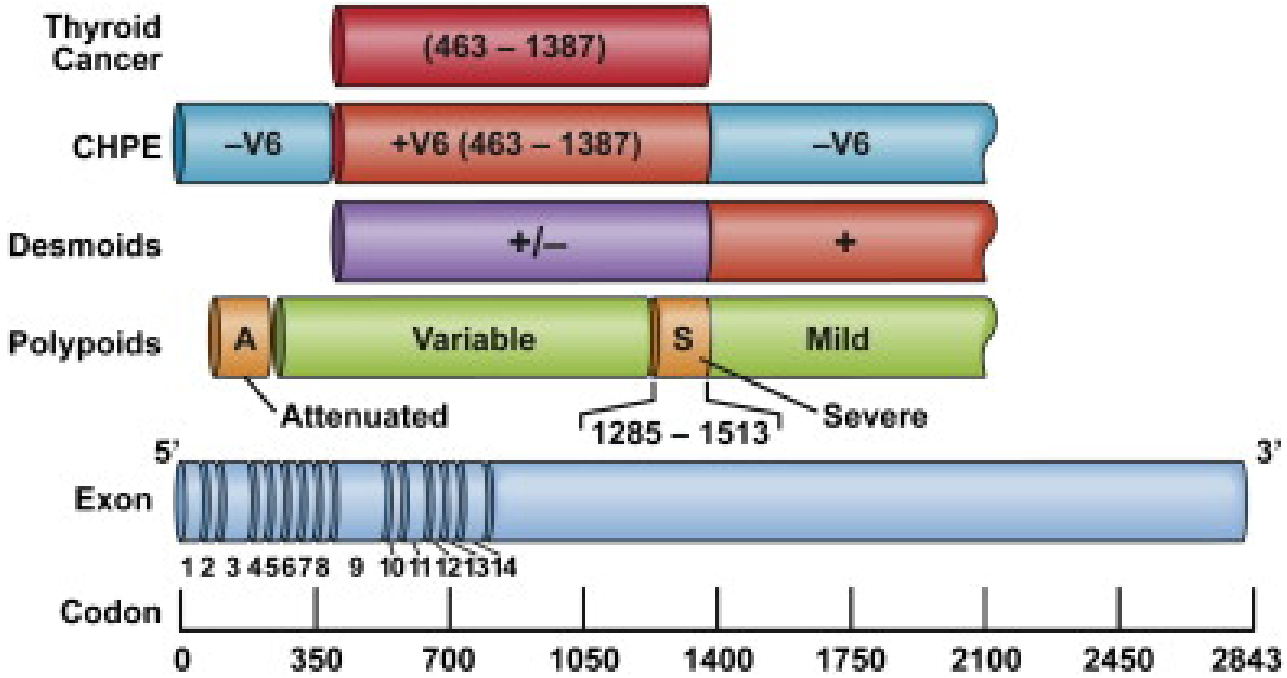
Familial Adenomatous Polyposis

- Benign lesions:
  - Fundic gland polyps
  - CHRPE
  - Osteomas/fibromas
  - Desmoid tumors
  - Adrenal tumors
- Other cancers
  - Periampullary tumors
  - Gastric Cancer
  - Brain (Medulloma)
  - Thyroid cancer
  - Hepatoblastoma





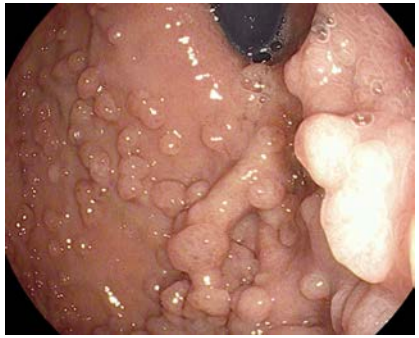
Genotype-Phenotype Correlations in FAP



Church et al. *Surg Oncol Clin N Am.* 2009

Gastric & Duodenal Lesions in FAP

- Fundic gland polyps



- Gastric Cancer
  - Lifetime risk <1%
  - ↑risk with carpeting, >20mm polyps, polypoid mounds, adenomas
- Duodenal adenomas & cancer
  - 50% periampullary
  - Lifetime risk duodenal cancer 3-5%
  - Risk of duodenal polyps ~90%
  - Mean age 45-52 years
- Screening: EGD starting at age 25-30 years
  - Surveillance interval based on findings (Spigelman staging of polyps)
    - Size, number, histology, dysplasia

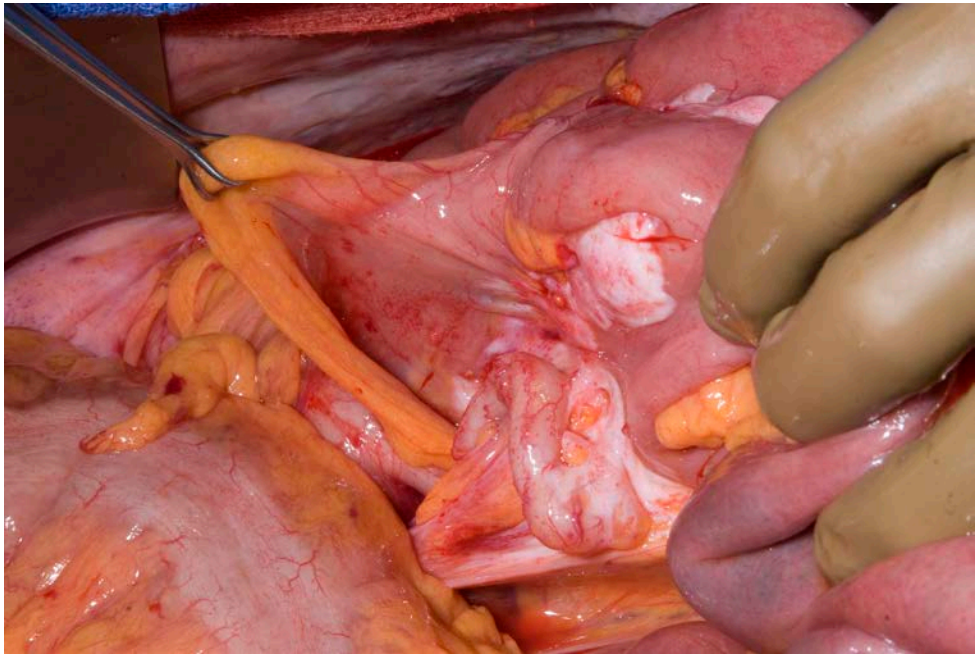
Gastric & Duodenal Lesions in FAP

- Fundic gland polyps
- Gastric Cancer
  - Lifetime risk <1%
  - ↑risk with carpeting, >20mm polyps, polypoid mounds, adenomas
- Duodenal adenomas & cancer
  - 50% periampullary
  - Lifetime risk duodenal cancer 3-5%
  - Mean age 45-52 years
- Screening: EGD starting at age 25-30 years
  - Side viewing scope
  - Surveillance based on findings (Spigelman staging of polyps)

Syngal S et al. *Am J Gastroenterol.* 2015.
Leone PJ. *Gastrointest Endosc.* 2019
Galiatsatos P et al. . *Am J Gastroenterol.* 2006.

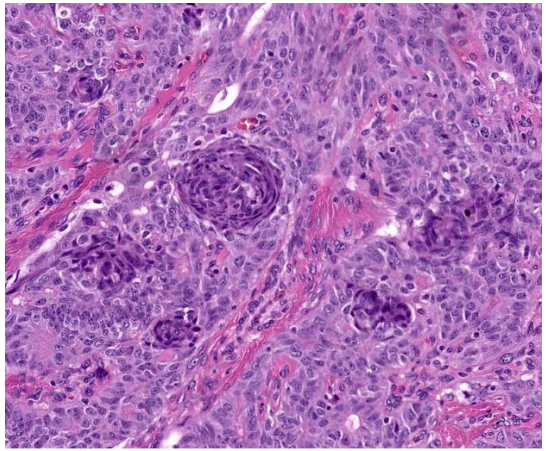
Desmoid Tumors in FAP patients

- 1 in 6 FAP patients develop desmoids after surgery
- Risk factors
  - Surgical trauma (major)
  - Female gender
  - Family history of desmoids
  - Mutation at 3’ end APC gene
- Type of surgery (TAC vs RPC) – no influence
- Young nulliparous women should undergo laparoscopic procedures



Thyroid Cancer in FAP patients

- Incidence 1-12% in registry studies
- Lifetime risk ~12%
- Mean age: 28 years
- Typically papillary cancer
  - Cribiform morular variant associated with FAP
- Screening: Thyroid ultrasound
  - High frequency of benign findings on ultrasound



Truta et al. *Fam Cancer.* 2003
Jarrar et al. *Annals Surg.* 2011
Herraiz et al. *Clin Gastroenterol Hepatol.* 2007
Steinhagen et al. *Clin Colorectal Cancer.* 2012

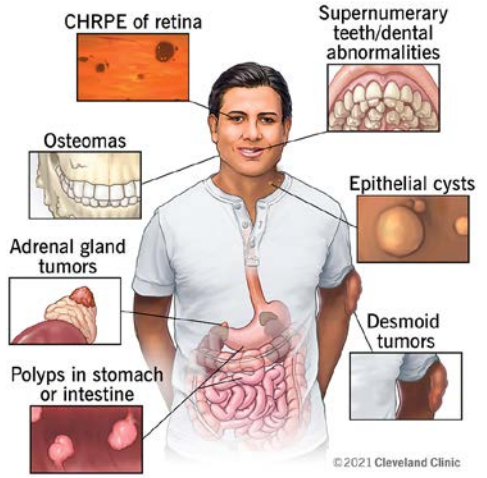
Hepatoblastoma in FAP

- Incidence: 1.6%
- Male predominance
- Occurs early in life
- Screening: Ultrasound and αFP every 3-6 months starting at 6 months up to age 5-10 years
- Complicated decision because it requires genetic testing very early in life to determine if child is at-risk

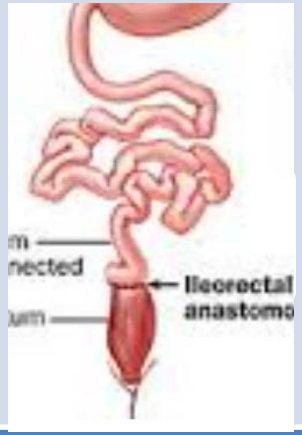
Giardello FM. *Gutt.* 1996.

Surveillance for Non-Colonic Malignancies in FAP

Organ System	Surveillance Test	Frequency
Stomach/ duodenum	EGD	At least every 3 years
Thyroid	Ultrasound	Annually
Liver (hepatoblastoma) *controversial	Ultrasound and alpha-fetoprotein	Every 6 months until 5-10 years of age
Adrenal	Ultrasound	Not recommended

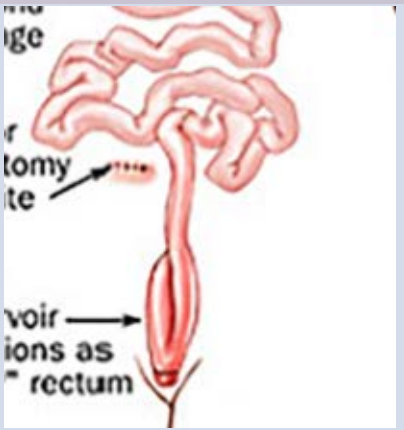


Surgical Options for FAP patients



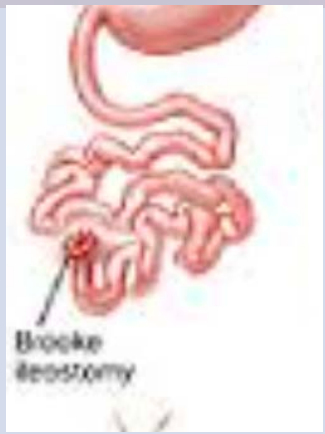
Total Abdominal Colectomy with IRA

- <30 polyps, able to clear endoscopically
- Surveillance and cancer risk



Proctocolectomy with ileal pouch-anal anastomosis (IPAA)

- Surveillance and cancer risk



Total proctocolectomy with permanent ileostomy

University Hospitals

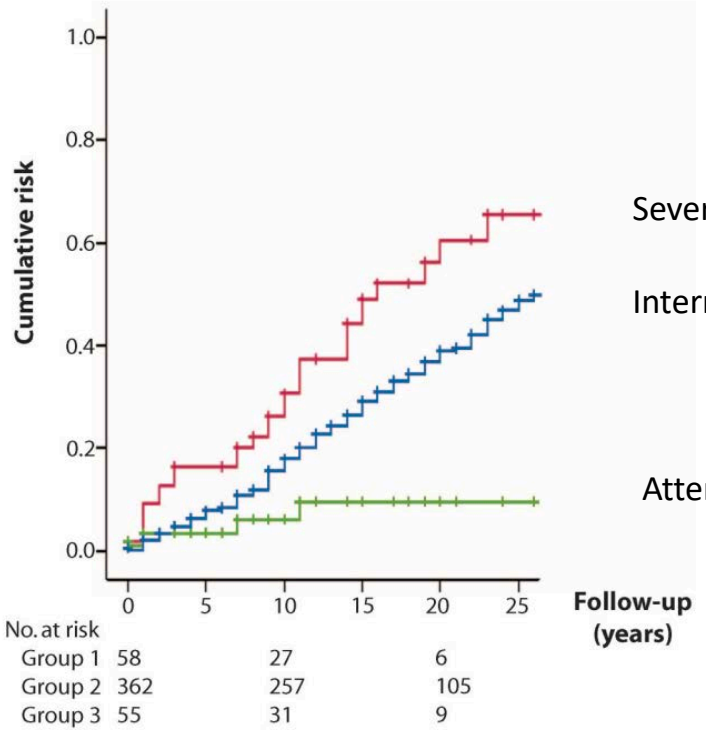
Larson D. Dis Colon Rectum, 2008.
Larson D. Ann Surg, 2006.

UH RISES
Research in Surgical Outcomes and Effectiveness

Comparing Surgical Options for FAP Patients

	IRA	IPAA
Operative Time	★	
Pelvic Dissection Sexual/Urinary functional outcomes	★	
Minimizing Future Cancer Risk		★
Surveillance		★
Bowel Function Seepage/Leakage Frequency of BMs	★	
Fertility/Fecundity	★	

Risk of Proctectomy after IRA: Genotype



Severe phenotype

Intermediate phenotype

Attenuated phenotype

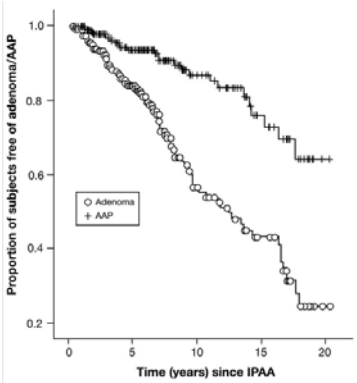
Risk of Proctectomy After IRA: Phenotype

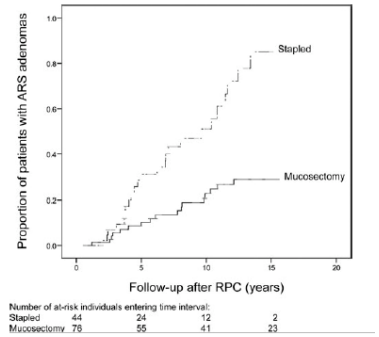
Rectal Polyps	Colon Polyps	Number of Patients	% Requiring Proctectomy
<20	<1000	95	**0**
<20	>1000	17	**13%**
>20	<1000	32	**15%**
>20	>1000	33	**56%**

Church JM. Dis Colon Rectum, 2001

Neoplasms in IPAA Pouch

- Cumulative risk of developing an adenoma in the pouch at 10 years: 42%
- Cumulative risk of developing a carcinoma in the pouch at 10 years: 0.5- 1%
- Most carcinomas develop at anastomosis or rectal cuff
- Management options:
  - Endoscopic polypectomy
  - Transanal excision
- May require pouch excision





University Hospitals

Friederich P. Clin Gastroenterol Hepatol, 2008.
Odzemir Y. Dis Col Rectum, 2013.
Van Roon A, Ann Surg, 2011.

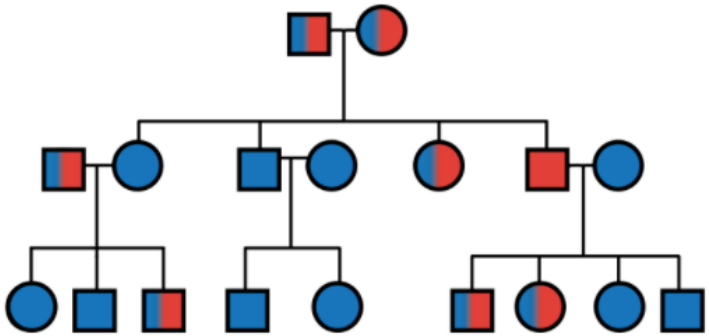
UH RISES Research in Surgical Outcomes and Effectiveness

MYH-Associated Polyposis

- Autosomal recessive gene
  - Carrier frequency in N America ~2%
- Variable penetrance
- Prevalence of 26-50% in patients with 10-100 adenomatous polyps; 7-29% in patients with 100-1000 polyps
- CRC between 4th and 7th decade
- Extracolonic tumor spectrum not well defined

Genetic Testing for MAP

- CRC diagnosed <40 years of age
- >10 adenomatous polyps in the absence of APC mutation
- Family history of CRC consistent with **autosomal recessive** pattern of inheritance, with or without polyps



Hegde M et al, Genet Med, 2014

Risk of CRC in *MYH*-Mutation Carriers

- Carrier frequency:
  - 2% in British/North American populations
  - 1.7-2.3% of CRC patients
- Odds-ratio CRC: 1.15-2.0

Balaguer F et al. Clin Gastroenterol Hepatol. 2007.
Win AK et al. Fam Cancer. 2010.
Croitoru ME et al. J Nat Can Institute. 2004
Cleary SP et al. Gastroenterol. 2009.

Extracolonic Manifestations in MAP Patients

- **Gastroduodenal lesions**
  - Duodenal adenomas and hyperplastic polyps
  - Gastric adenomas
  - Gastric fundic gland polyps
  - **Duodenal adenoma/cancer**

- **Extraintestinal tumor sites**
  - Duodenum
  - Breast
  - Endometrial
  - **Ovarian**
  - **Bladder**
  - Thyroid
  - **Skin** (sebaceous adenoma, epidermoid cyst, etc)
  - Lipomas

Vogt et al. *Gastroenterol.* 2009
Win AK et al. *Int J Cancer,* 2016.

Management of MAP

Annual colonoscopy *if* adenomas can be cleared

Timing and extent of surgery depends on ability to clear poyps, rectal burden, presence of malignancy

Upper endoscopy beginning @ age 30

Lack of data to support any one approach – expert consensus

Non-Adenomatous Polyposis Syndromes

- Peutz-Jeghers Syndrome (PJS)
- Juvenile Polyposis Syndrome (JPS)
- *PTEN* Syndromes
  - Cowden Syndrome
  - Bannayan-Riley-Ruvalcaba Syndromes
- Serrated Polyposis Syndrome
- Hereditary Mixed Polyposis Syndrome

Who Should Get Genetic Evaluation?

- Anyone with a family member with + genetic syndrome
- Early age of onset (<45 years)
- Clinical criteria for non-adenomatous polyposis syndromes

Lynch Syndrome

- dMMR tumor
- Personal/family history of LS associated tumor at age <50
- 2+ family members with LS associated tumors (any age)

Polyposis Syndromes

- >20 adenomas (lifetime); consider if 10-19 polyps
- Family history of polyposis syndrome
- Bilateral CHRPE
- Cribiform morular variant thyroid cancer
- Desmoid, hepatoblastoma, unilateral CHRPE

Registries for Hereditary Cancer Syndromes

- Structured program to identify, track, follow at-risk patients
- Coordination of care
- Access to experts
- Tracking/data

Registries Improve Outcomes

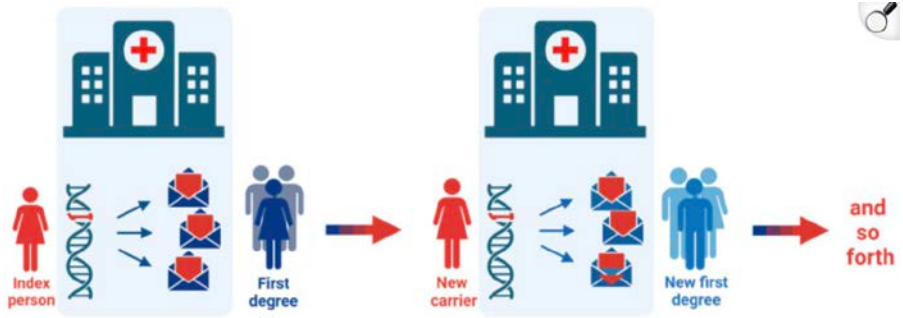
- Earlier detection of cancer
- Improved mortality
- Adherence to screening
- Cascade of testing for at-risk family members
- Psychosocial benefits
- Access to clinical trials
- Data for research to improve outcomes
- Cost effective for hospital systems

Improved Mortality for Patients in Registries

- Dutch LS Registry: 146 families/2788 individuals
  - ↓ 70% in standardized mortality ratio
- Enrollment → surveillance leads to ↓50% risk of CRC
- NHS study: registries improve identification of LS patients and subsequent cancer risks
- Registries ↑ uptake of prophylactic colectomy in FAP and ↓ risk of CRC/mortality

de Jong AE et al, Gastroenterology. 2006.
Jarvinen H et al, Gastroenterology, 2006.
McRonald, FE et al, Eur J Human Gen, 2024.
Belchetz LA, DCR 1996
Bulow, S, Gut. 2003.

Impact of Registries on Family Members



- Danish Registry: Improved testing in at risk-family members via outreach (7.3 additional individuals tested; 54% uptake)

Conclusions

- Early onset CRC patients need genetic evaluation
- Diagnosis of hereditary CRC syndromes impacts surveillance
  - Multi-disciplinary care essential
- Surgical recommendations vary with CRC syndromes
- Test patients and then at risk family members

Thank you