FAMILIAL GI CANCER SYNDROMES
LYNCH SYNDROME

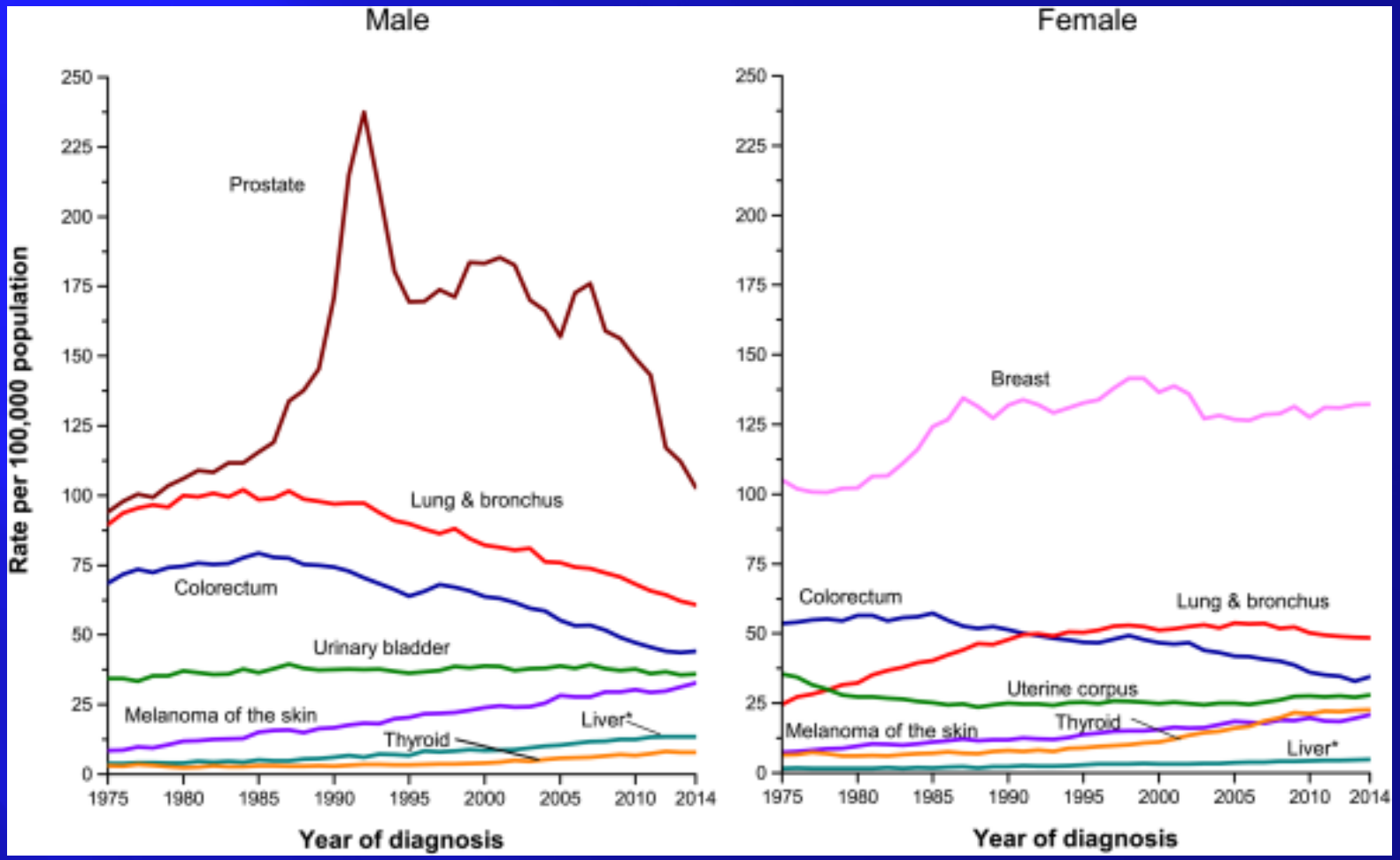
Patrick Brady, MD
Professor of Medicine
USF College of medicine

Colorectal Cancer

- Colorectal cancer (CRC) is a major American health problem that ranks as the second leading cause of cancer death after lung cancer.
- The lifetime probability of developing CRC is 4.5% (1/22) in males and 4.2% (1/24) in females.
- In 2018 141,250 new cases and 50,630 deaths are expected.
- 5 year survival is 65% which is increased since 1985 due to earlier detection and more effective therapy.

CA: A Journal for Clinicians. 2018; 68: 7-30.

Incidence of Colorectal Carcinoma



CA: A Journal for Clinicians. 2018; 68: 7-30.

CRC Etiology

- The cause of CRC is multifactorial with environmental factors and inheritance playing a role.
- Approximately 70-80% of CRC seems to be sporadic disease with no evidence of an inherited disorder.
- In 20-30% an inherited component might be causative.

Hereditary Causes of Colon Cancer

Syndrome	Inheritance	Precursor Lesion
Lynch	Autosomal Dominant	Adenoma
Familial Polyposis	Autosomal Dominant	Adenoma
Attenuated FAP	Autosomal Dominant	Adenoma
MYHAP	Autosomal Recessive	Adenoma
Serrated Adenoma Syndrome	Unknown	Sessile Serrated Adenoma
Hamartomatous Polyposis Peutz-Jagher Syndrome Familial Juvenile Polyposis Familial Hyperplastic Polyposis	Usually Autosomal Dominant	Hamartoma

Lynch Syndrome (LS)

- Lynch syndrome (LS) was first described by Henry Lynch in in 1966. It is an autosomal dominant condition which is the most common cause of inherited CRC.
- It accounts for 3% of CRC and 2% of endometrial cancer. Approximately 1,000,000 individuals in US have LS.
- Germline mutation of genes (MLH1, MSH2, MSH6, PMS2) in the DNA mismatch repair pathway are the cause of LS.
- Genetic testing can confirm the diagnosis, justify surveillance by risk stratification, aid in surgical planning and chemoprevention, and help in decisions regarding family and career planning.

Lynch HT, et al. Arch Intern Med 1966; 117:206-12.
Fishel R, et al. Cell 1993; 75: 1027-38.

EPCAM Gene Mutations

- EPCAM gene is located just upstream of the MSH2 gene.
- Deletions in the terminal codon of EPCAM result in silencing of the MSH2 gene and produces a phenotype similar to LS.
- In families where the deletion is isolated to the stop codon of EPCAM, a colon only phenotype occurs.
- If the deletion also includes critical portions of the MSH2 promotor, a full LS phenotype occurs.

Lynch HT, et al. Am J Gastroenterol 2011; 106: 1829-36.

Microsatellite Instability

- A phenomenon manifested by mutations in simple repetitive sequences (microsatellites) found in tumor DNA but not in the DNA of adjacent normal tissue.
- Microsatellite instability (MSI) is caused by MMR gene mutations.
- MSI is found in most (>90%) of colon malignancies in LS and in 12% of sporadic colon cancers.
- MSI is graded as high (> 30% of markers are unstable), low or stable. Most LS CRCs are MSI high.

Aaltonen LA, et al. Science 1993; 260: 812-816.

Gene Specific Cumulative Risk of Colorectal Cancer by Age 70

Gene Mutation	Risk %	Mean Age at Diagnosis
Sporadic Colon Cancer	4.5	69
MLH1/MSH2 Male Female	 27-**74** 22-**61**	 27-46
MSH6 Male Female	 22 10	 54-63
PMS2 Male Female	 20 15	 47-66

Gastrointest Endosc 2014; 80: 97-2017.

Cancer Incidence Depends on Mutation

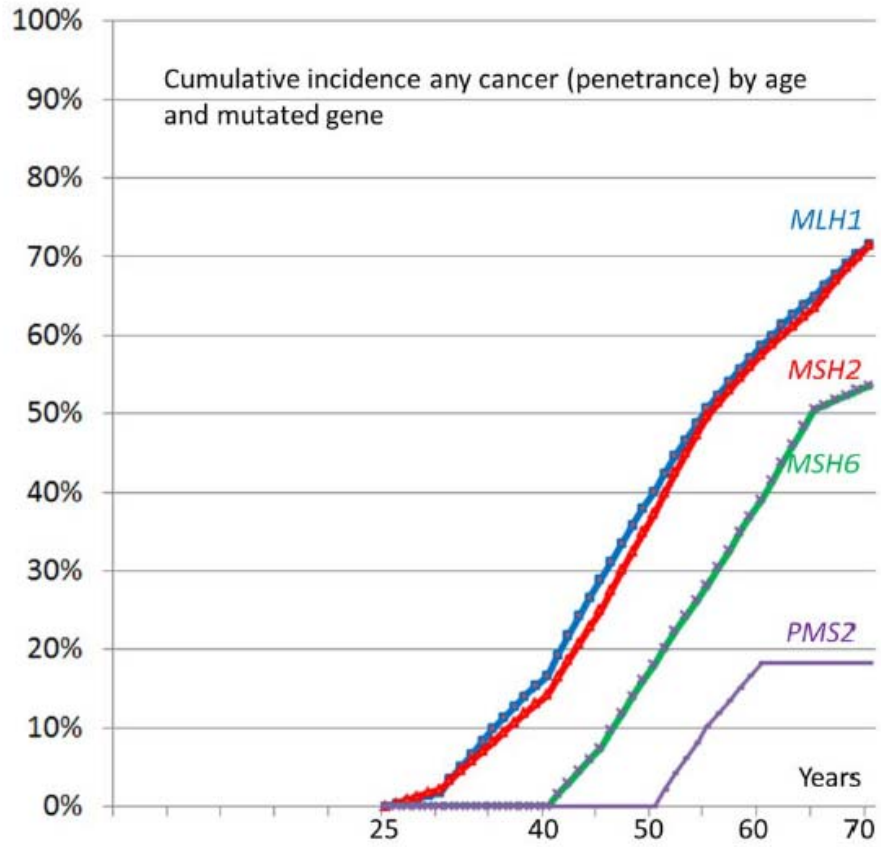
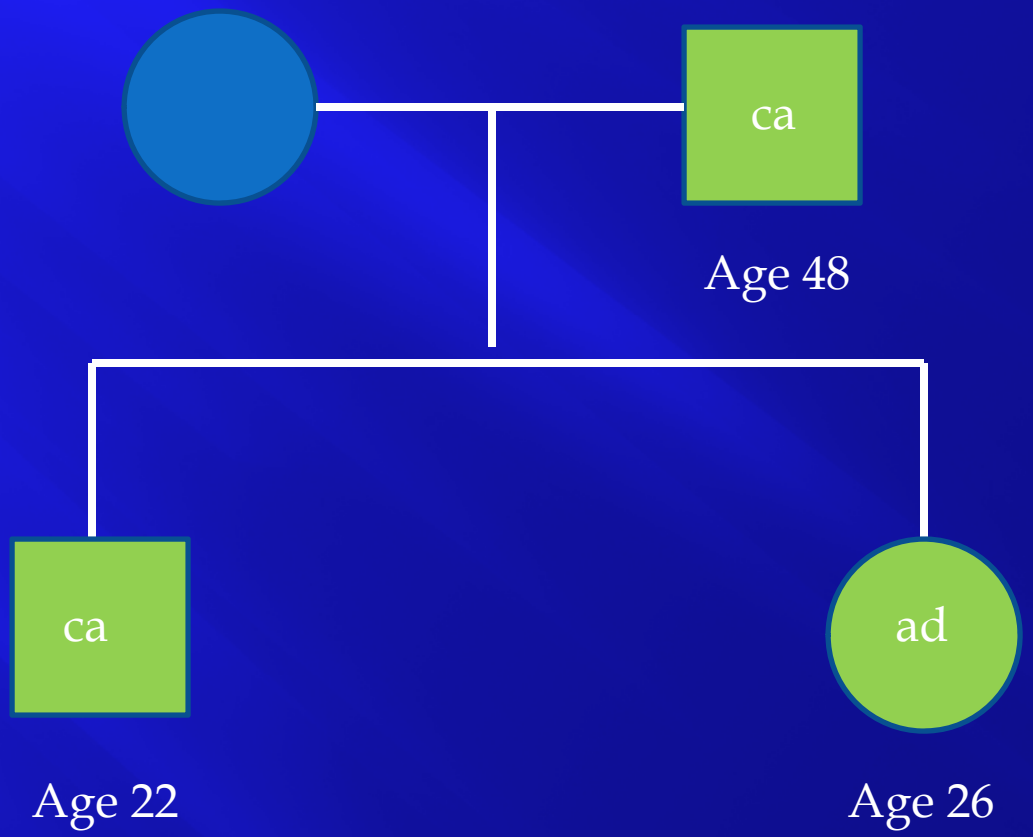


Figure 1 Calculated cumulative incidences by age and mutated gene for any cancer.

Møller P, et al. Gut 2017;**66**:464–472.

LS Family



LS –Associated Tumors

- These include CRC, endometrium, stomach, pancreas, ovary, ureter, renal pelvis, biliary tract, brain (gliomas), small bowel, sebaceous glands, and ketratoacantomas.
- Endometrial cancer is the second most common LS associated malignancy.It occurs in approximately 54% of women with MLH1 and MSH2 mutations , **71% in MSH6**, and 15% in PMS2.

Clinical Features

- Colorectal cancers arise primarily on the right side of the colon (60-80%).
- The precursor lesion is a discrete adenoma which may be flat. Usually develop <3 adenomas. These frequently have advanced features such as a villous component or high grade dysplasia.
- The adenoma-carcinoma sequence is more rapid in LS with polyp to cancer dwell times estimated to be 35 months.
- Mean age at diagnosis of CRC is 44-61 years.
- There is a high rate of metachronous CRC; 16% at ten years, 41% at 20 years.

LS Variants

- Muir-Torre Syndrome is a rare variant of LS with skin sebaceous gland neoplasmas(adenomas and carcinomas), and neoplasms of the hair follicles, keratoacanthomas. MSH2 mutations most common in this group.
- Constitutional mismatch repair deficiency syndrome occurs in patients and families with biallelic mutations of the MMR genes. These patients develop café au lait spots early in childhood or in teenage years.

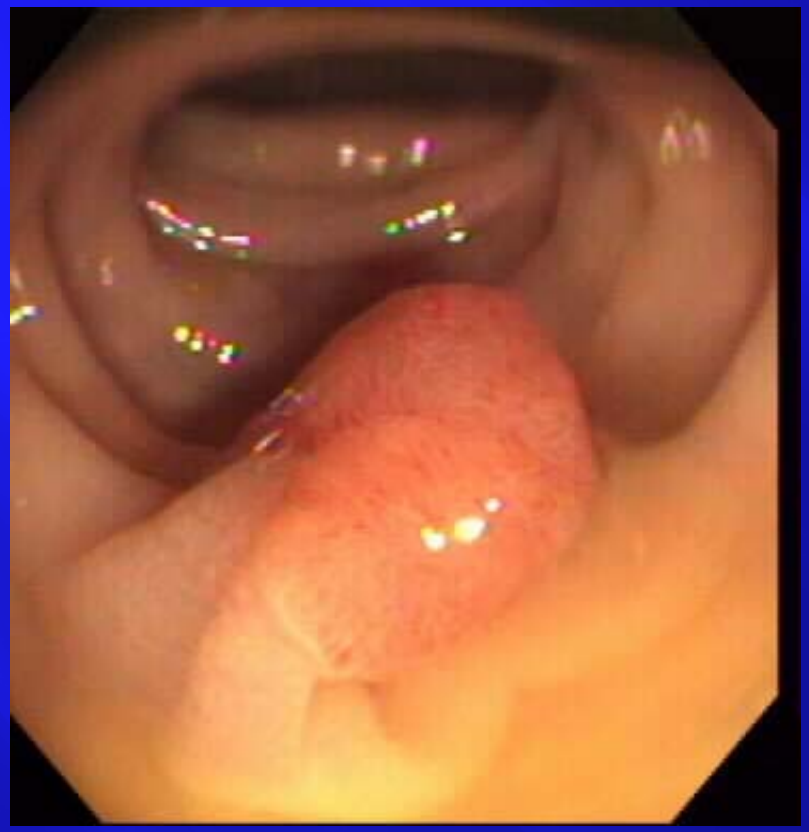
Survival After First Cancer in LS

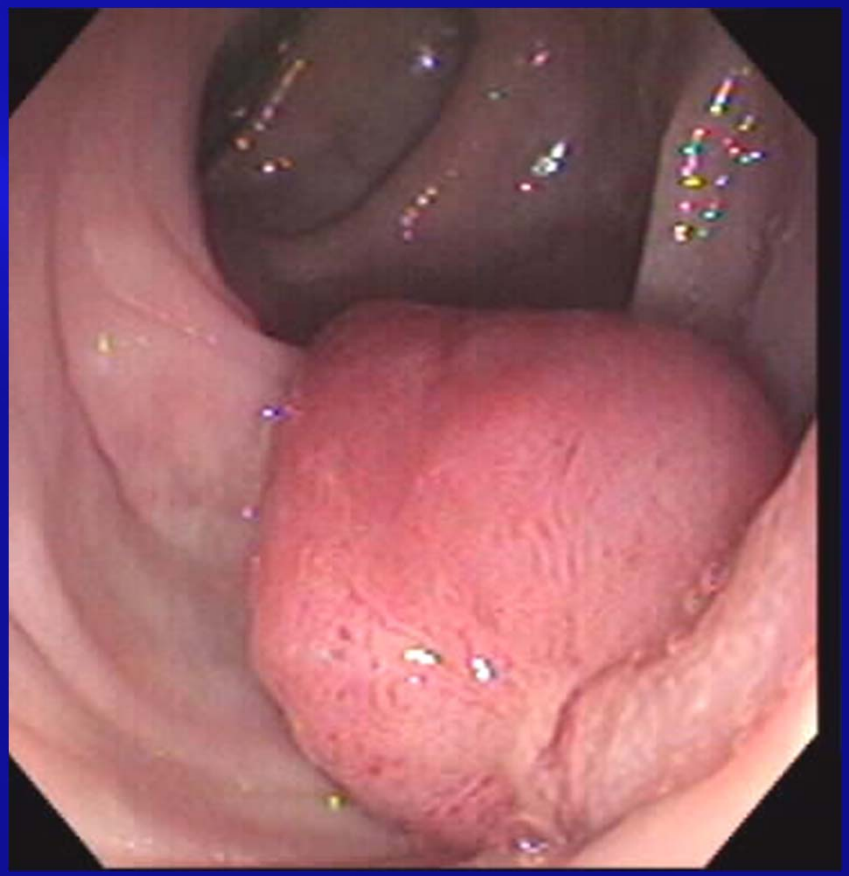
Table 7 5-year and 10-year crude survival after first cancer diagnosed by cancer type in Lynch syndrome (LS) patients without prior or prevalent cancer at first colonoscopy

Group	Number cases	5-year survival (95% CI)	10-year survival (95% CI)
Any cancer	301	90% (86 to 93)	87% (83 to 91)
Colorectal cancer	140	94% (90 to 98)	91% (84 to 95)
Endometrial cancer	71	98% (88 to 99.8)	98% (88 to 99.8)
Ovarian cancer	19	88% (60 to 97)	89% (60 to 97)
Upper GI cancer	24	58% (36 to 75)	53% (31 to 71)
Urinary tract cancer	17	82% (51 to 93)	73% (42 to 89)

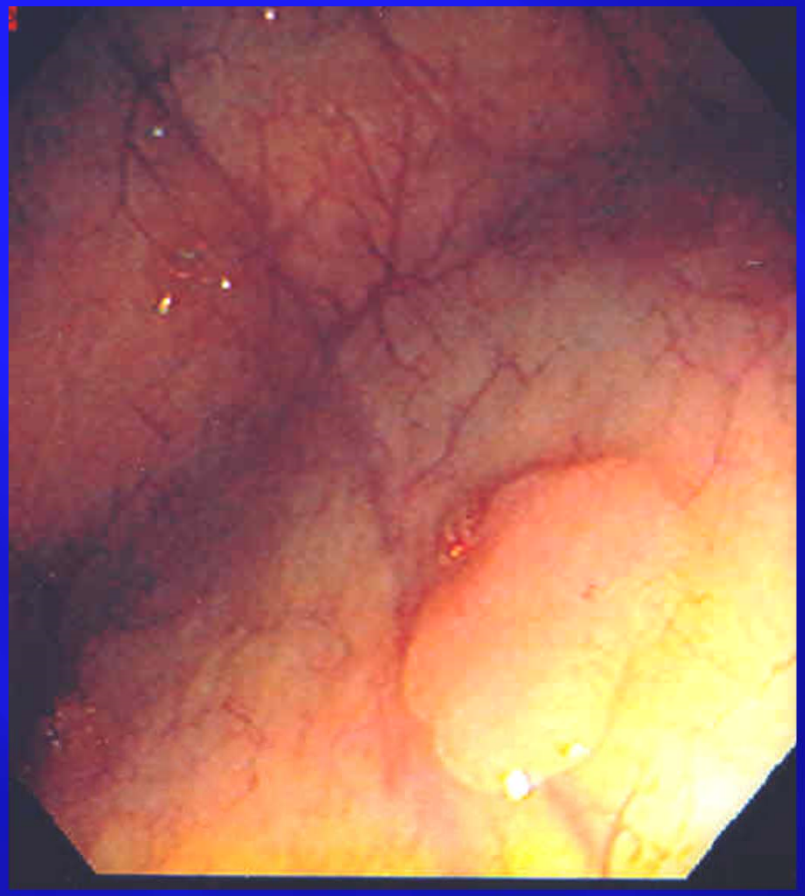
Møller P, et al. Gut 2017;**66**:464–472.

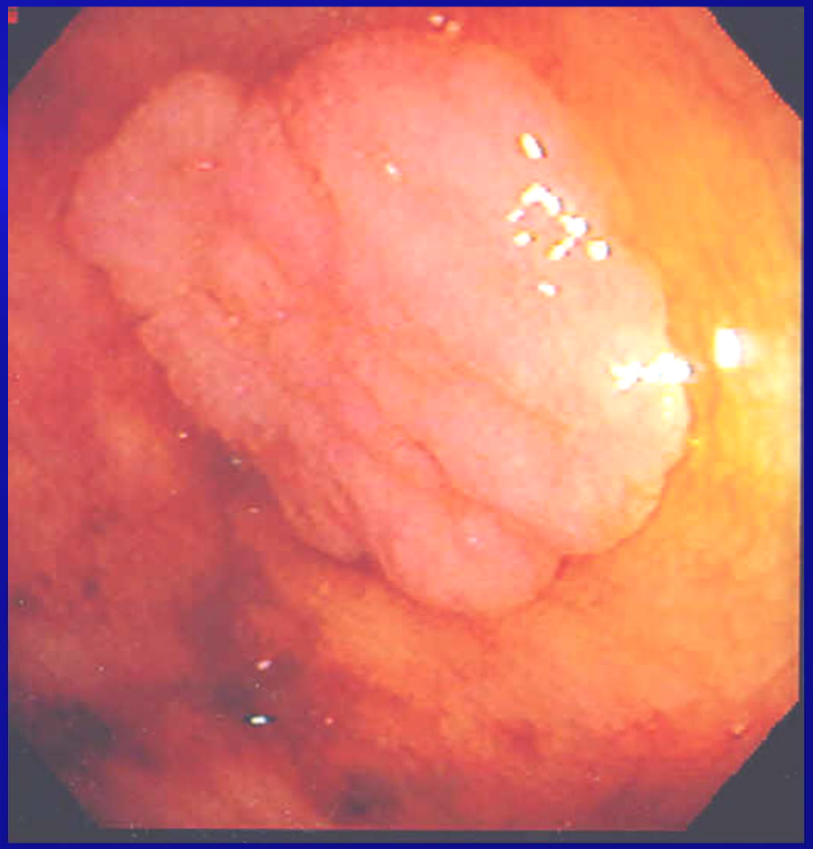
Adenomatous Polyps





Flat Adenomas





Histopathology of LS CRC

- More frequently poorly differentiated.
- Can have signet cell histology.
- Abundant extracellular mucin is present.
- There is tumor and peritumoral lymphocyte infiltration (Crohn's like pattern).
- LS patients have improved survival stage for stage copared with sporadic CRC.

Identification of LS

- Clinical Criteria
  - Amsterdam Criteria
  - Bethsda Criteria
- Computational Models
- Tumor Testing
  - Molecular testing of tumor for MSI
  - Immunohistochemical testing
- Genetic Testing
  - Germline testing of individuals for mutations in MLH1, MSH2, MSH6, PMS2, and EPCAM genes.
- Universal Testing

Amsterdam II Criteria*

- 3 or more family members with LS-related cancers, one of whom must be a first degree relative of the other two.
- 2 consecutive affected generations.
- One of more HNPCC-related cancers diagnosed < 50 years.
- FAP has been excluded.
- Sensitivit yof 22% and Specificity of 98%.

*Must meet all criteria to diagnose LS.

Vasen HFA, et al. Gastroenterol 1999; 116: 1453-56.

Familial CRC Type X
FCRCTX

- FCRCTX refers to patients or families that meet the Amsterdam criteria, but when tumors are tested , lack the MSI characteristic of LS.
- The age at diagnosis of CRC in these families is slightly older than LS families.
- The lifetime risk of CRC is lower than in LS. The standardized incidence ratio is for CRC is 2.3 for FCRCTX, and 6.1 for LS.
- FCRCTX families do not have an increased risk of extracolonic cancers.

Revised Bethesda Guidelines*

- CRC diagnosed before age 50.
- 2 LS cancers in one person (can be two colon cancers).
- CRC with MSI histology.
- CRC or LS associated tumors diagnosed before age 50 in at least one first degree relative.
- CRC or LS associated tumor diagnosed at any age in 2 first or second degree relatives.
- Sensitivity 82%, specificity 77%.

*Must meet one criteria to be tested for MSI.

Umar A. J Natl Cancer Inst2004; 96: 261-8.

CRC Risk Assessment Tool

1. 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, ovaries, small intestine, urinary tract, pancreas, or brain
2. Have you had any of the following conditions diagnosed before age 50?
   - -Colon or rectal cancer
   - -Colon or rectal polyps
3. Do you have three or more relatives with a history of colon or rectal cancer (This includes parents, brothers and sisters, children, grandparents, aunts, uncles and cousins)?

Yes to any question refer for additional testing or genetic evaluation.

Kastrinos F, et al. Am J Gastroenterol; 2009; 104: 1508-18.

Computational Models

- MMRpredict model. 69% sensitivity, 90% specificity. Available online at: hnpccpredict.hgu.mrc.ac.uk/.
- MMRpro model. Uses molecular testing results if available. 89 % sensitivity, 85% specificity. Available online at: www.4utsouthwestern.edu/breasthealth/cagene/.
- PREMM[1,2,6,] model. Sensitivity 90%, specificity 67%. Available online at: premm.dfci.harvard.edu.

Screening in Community Setting PREMM1,2,6

- Investigated the feasibility of systematic risk assessment for LS in a community GI practice.
- PREMM1,2,6 adapted for self administration by patients.
- 6 month study of 3134 individuals presenting for office visits or endoscopy.
- Genetic counseling and mutational analysis offered to all patients with scores >5% or greater.
- 174 patients had scores > 5% and 6 patients had positive genetic testing for LS.

Luba DG. Clin Gastroenterol Hepatol 2018; 16:49-58.

Tumor Testing

- Testing of tumor tissue can be done on formalin fixed tissue from surgical resection specimens or biopsies from CRC and large adenomas, or endometrial cancer. Labs in the US save specimens for at least 7 years.
- Microsatellite instability testing using PCR based molecular testing of CRC tissue for MSI is estimated to be 89% sensitive and 90% specific.
- Immunohistochemistry testing (IHC) of tumor tissue for lack of expression of MMR gene proteins has a sensitivity of 83% and specifivity of 89% for LS.

Molecular Testing for MSI
Single Gate Population BasedSamples

Author	Year	Sensitivity %	Specificity %
Poynter	2008	100 (93.9, 100.0)	61.1 (57.0, 65.1)
Barnetson	2006	66.7 (47.2, 82.7)	92.5, 89.1, 95.2)
Southey	2005	72.2 (46.5, 90.3)	87.8 (73.8, 95.9)

Since MSI is a triage test with an aim of maximizing individuals with LS who eventually receive a correct diagnosis, it appears preferable to maximize sensitivity.

Coelho H. BMC Cancer 2017; 17: 836-849.

IHC Testing and BRAF Mutation

- Loss of MLH1 protein on IHC tumor testing may be secondary to a somatic mutation in the BRAF gene leading to hypermethylation of the MLH1 promotor.
- The use of BRAF testing when MLHI expression is lost can help distinguish sporadic cancers from germline mutation in LS.

Universal Testing

- Approximately 28%of LS patients are missed with the most liberal clinical criteria, revised Bethesda guidelines.
- This lead to the suggestion of universal testing of all newly diagnosed CRC in patients < 70. IHC testing appears to be the most cost-effective and sensitive approach.*
- Patients with positive testing are referred for counseling and genetic testing.
- In the future, germline testing rather than tumor evaluation might be the most cost effective universal testing approach.

*Ladabaum U. Ann Intern Med 2011; 155: 69-79.

Cost Effectiveness of Universal Testing

- Design: Markov model that incorporated risk for colorectal, endometrial, and ovarian cancers.
- Target: All persons with newly diagnosed colorectal cancer and their relatives.
- Screening for the Lynch syndrome with IHC followed by BRAF mutation testing up to age 70 years cost $44,000 per life year gained.
- The benefit accrued primarily to relatives with a mutation associated with LS, particularly women, whose life expectancy increased 4 years with hysterectomy and salpingo-oophorectomy and adherence to CRC screening recommendations.

Organizations Recommending Universal Testing

1. Evaluation of Genomic Application in Practice and Prevention (CDC)
2. Healthy People 2020
3. National Comprehensive Cancer Network (NCCN)
4. US Multi-Society Task Force on Colorectal Cancer

Genetic Testing

- Germline testing of individuals for a deleterious mutation in MLH1, MSH2, MSH6, PMS2 or EPCAM genes.
- Confirms the diagnosis of LS in a patient or family.
- It can determine the status of at risk family members in pedigrees where the mutation has been found.
- It can direct the management of affected and unaffected individuals.

Genetic Testing Strategy

Clinical and Family Status	Recommended Testing
Clinically affected member-family mutation known	Site specific germline mutation testing.
Clinically affected member-family mutation not known	MSI testing of tumor. If positive, germline testing for MMR/EPCAM mutations.
Unaffected (at risk) member-family mutation known	Mutation specific germline testing.
Unaffected (at risk) member-family mutation unknown	Find affected family member to test. Once the mutation is determined, test the at risk person for that mutation.

Genetic Counseling

- Pre and post-test genetic counseling is recommended due to the clinical, psychological, financial, and ethical issues raised by the testing process.
- Counseling includes the taking of a personal and family medical history, education about the disorder, exploration of psychosocial issues, informed consent, disclosure of cost and risk of genetic discrimination, disclosure of test results, and follow up.
- Barriers to genetic testing include cost (can exceed $4800), and concern about discrimination.
- Federal legislation, Genetic Information Nondiscrimination Act of 2008, eliminated a positive gene test as a health insurance pre-existing condition, or factor for employment in most instances.

Screening for CRC in LS

- There is strong evidence supporting the use of screening in patients at risk for or affected with LS.
- Persons at risk for LS who underwent colonoscopic surveillance had 65% (p=0.003) fewer deaths from CRC compared with those who refused surveillance.*
- In a study of colonoscopy surveillance of members of LS families, there was a 72% decrease in mortality from CRC in those undergoing screening.**
- In several studies, more frequent colonoscopy (every 2 years or <) was associated with earlier stage CRC at diagnosis, and a lower incidence of CRC.

*Jarvinen HJ. J Clin Oncol2009; 27: 4793-7.

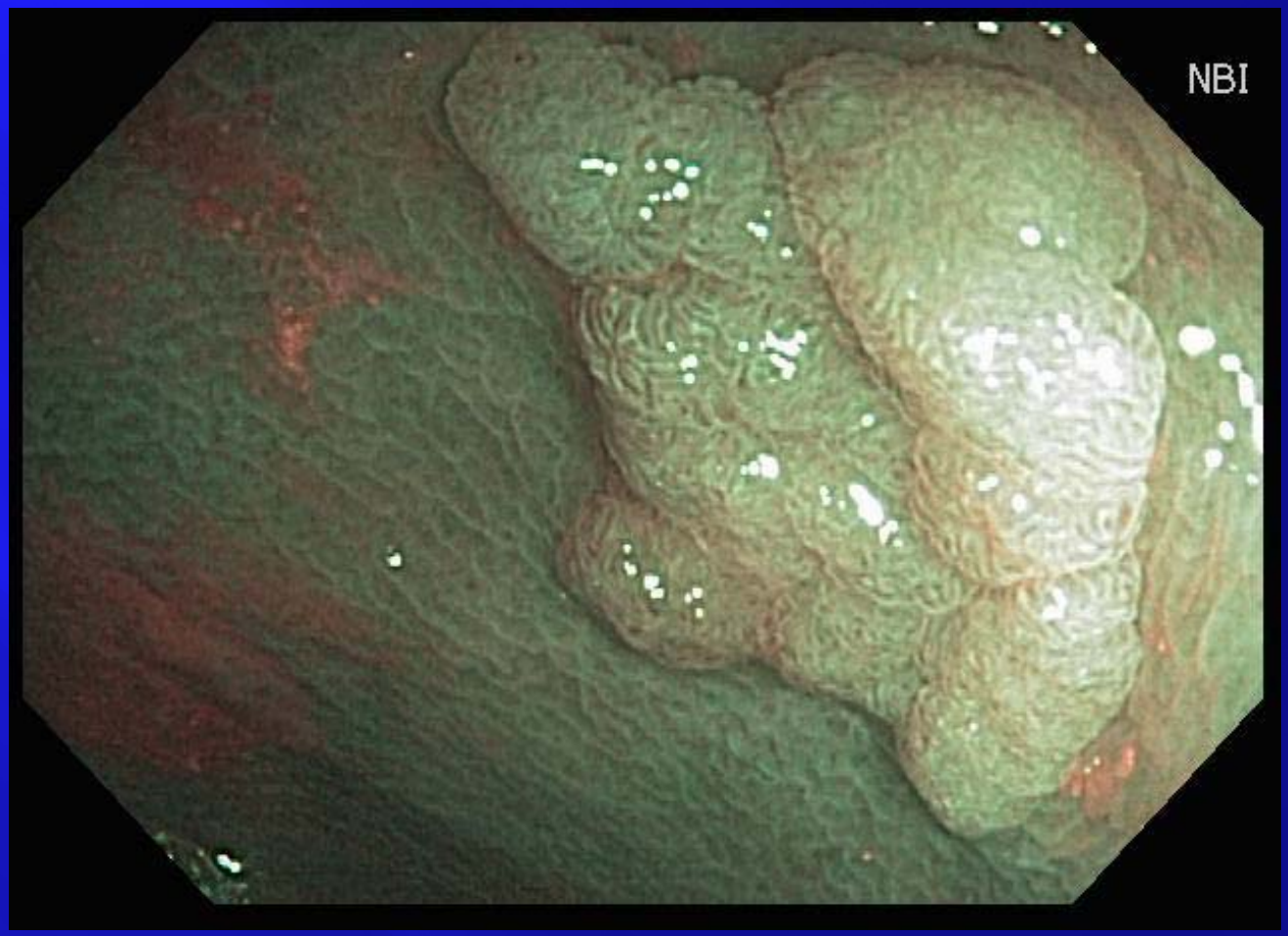
**Dove-Edwin I. BMJ; 2005; 331: 1047.

CRC Screening in LS Guideline

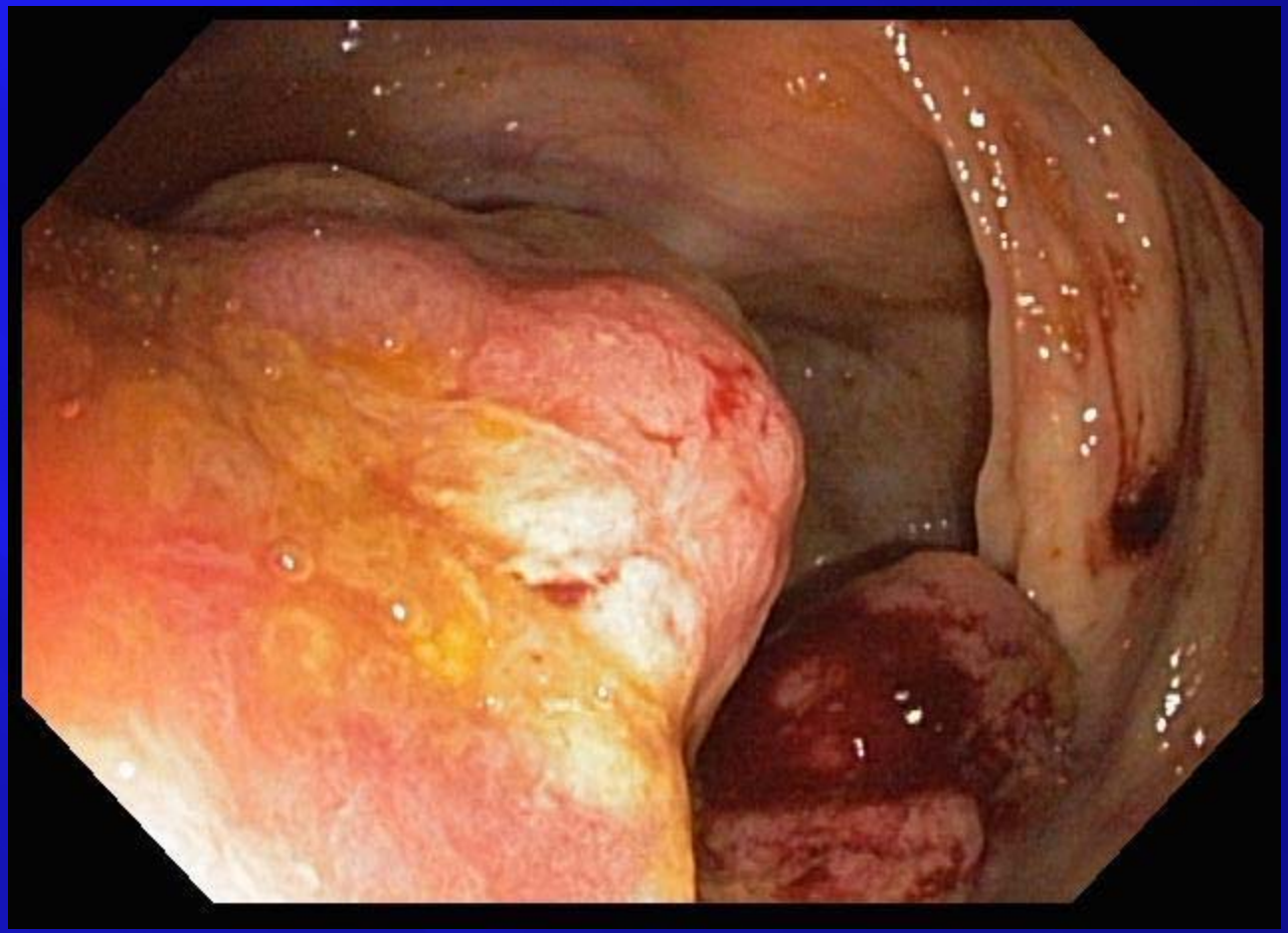
- Screening for CRC by colonoscopy is recommended in persons at risk for (first degree relatives of those affected) and those affected with LS every 1-2 year, beginning between the ages of 20-25 years or 2-5 years before the youngest age of diagnosis of CRC in the family if diagnosed before age 25.
- In surveillance of MMR germline mutation positive patients, yearly colonoscopy should be considered.

Consensus statement by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc, Am J Gastroenterol 2014.

Cecal Adenoma



Interim Carcinoma in LS



Screening for Endometrial Cancer (EC)

- Second most common cancer in LS with lifetime risk of 21-60%.
- Endometrial sampling is useful in identifying some asymptomatic cancers, and those with premalignant endometrial lesions.*
- Transvaginal ultrasound has poor sensitivity and specificity for the diagnosis of EC in this population.

Stuckless S, et al. Clin Genet 2013; 83: 359-64.

EC Screening in LS Guideline

- Screening for EC should be offered to women at risk for or affected with LS by pelvic examination and endometrial sampling annually starting at age 30-35 years.

Consensus statement by the US Multi-Society Task Force on Colorectal Cancer.

Ovarian Cancer

- Estimates of the cumulative risk of ovarian cancer in LS ranges from 0.3 to 20%.
- No studies of the effectiveness of ovarian cancer screening for women in LS families are available.
- Based on expert opinion, screening for ovarian cancer should be offered to women at risk for or affected with LS by transvaginal ultrsound annually beginning at are 30-35 years.

Consensus statement by the US Multi-Society Task Force on Colorectal Cancer.

Prophylactic Hysterectomy and Oophorectomy

- A US retrospective study of 315 LS women showed no cancers in the surgery group compared with a 35% and a 5.5% rate of uterine and ovarian cancer in the non-surgical group.*
- A modeling study evaluating screening and surgical strategies concluded that annual screening starting at age 30, followed by prophylactic surgery at age 40 was the most effective gyn cancer prevention strategy.**
- The Multi-Society Task Force guidelines recommends hysterectomy and bilateral salpingo-oophorectomy be offered to women with LS who have finished childbearing or at age 40.

*Schmeler KM. NEJM 2006; 354: 261-9.
**Kwon JS. Cancer 2008; 113: 326-35

Screening for Other LS Cancers

- Screening for gastric cancer by EGD should be considered at age 30-35 and every 2-3 years thereafter.
- Screening for cancer of the urinary tract should be considered annually starting at age 30-35 years.
- Screening not recommended for small intestinal cancer, pancreatic cancer, prostate and breast cancer (beyond what is recommended for the general population.

Consensus statement by the US Multi-Society Task Force on Colorectal Cancer

Treatment of CRC in LS

- The risk of metachronus cancer after partial colectomy is high (16-19% at 10 years).
- The risk is reduced if subtotal or total colectomy and ileorectal anastomosis is performed (0-3.4%).
- Colectomy with ileorectal anastomosis is the primary treatment for colon carcinoma in LS.
- If the rectum is involved, total proctocolectomy and ileal pouch-anal anastomosis is recommended.

Win AK. Ann Surg Oncol 2013; 20: 1829-36.

Colorectal/Adenoma/Carcinoma Prevention Program 2 (CAPP2)

- CAPP2 reported on long term follow up (55.7 months) of LS randomized to 600 mg of aspirin daily (427) or placebo (434).
- The time to first CRC hazard ratio was 0.41 in the aspirin group (CI 0.19-0.86; P=0.02).
- Analysis of all LS cancers revealed a protective effect of aspirin. HR =0.65 (CI 0.42-1.00; P=0.05).
- There was no difference in adverse events between the ASA and placebo groups.

Burn J. Lancet 2011; 378: 2081-7.

Chemoprevention

- There is growing evidence that aspirin is beneficial in preventing cancer in LS patients.
- Treatment of an individual patient with ASA is an option after discussion of patient risks, benefits and uncertainties of treatment .

Summary

- LS is the most common cause of hereditary CRC.
- It is due to germline mutations in the MMR genes.
- MSI is the hallmark of LS tumors and can be detected with molecular testing or IHC on formalin fixed tissue.
- Genetic testing for MMR germline mutations confirms the diagnosis.
- Colonoscopic screening has been shown to reduce the incidence of colon cancers, and to diagnose cancers at an earlier stage and is recommended every 1-2 years beginning at age 20-25.