10TH ANNUAL
ENDOSCOPY SKILLS DAY FOR PRACTICING ENDOSCOPISTS AND THEIR TEAMS
Education for Excellence in Endoscopy
JANUARY 17 - 19, 2020
The Rimrock Resort Hotel, Banff, Alberta

ASEP

Lynch Syndrome Update for 2020

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— HENRY MARSHALL TORY, FOUNDING PRESIDENT, 1908

Objectives

- After this session, the learner will have a better understanding of Lynch Syndrome in regards to:
  - Genetics and epidemiology
  - Clinical criteria and surveillance guidelines
  - Testing for extracolonic cancers
  - Endoscopic strategies

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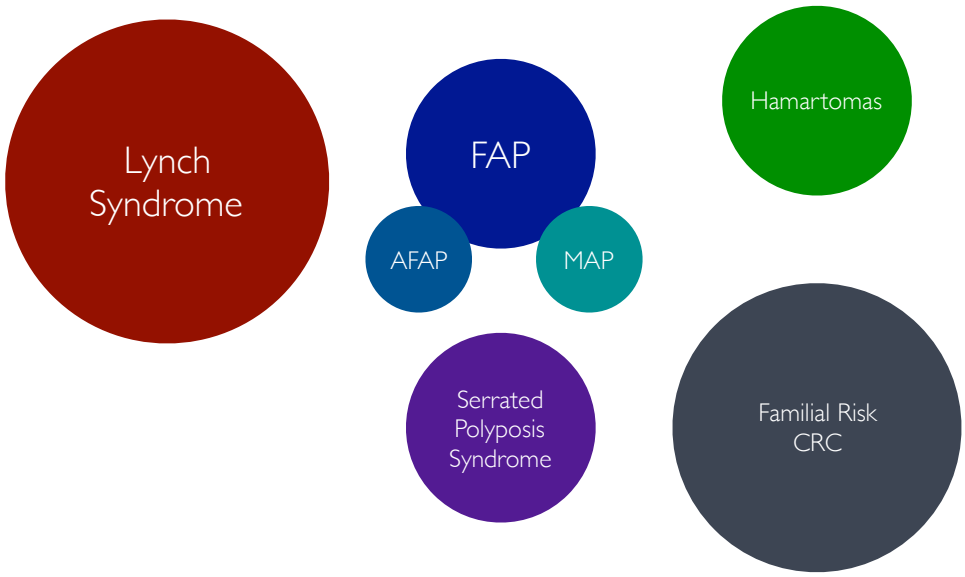
Familial/Genetic Colorectal cancers



Questions to ask

- Does my patient fit the clinical criteria for this syndrome?
- What genetic tests (if any) are available?
- What extracolonic cancers do I have to watch for?
- Can I increase lesion detection during colonoscopy?

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Lynch syndrome Genetics & Epidemiology

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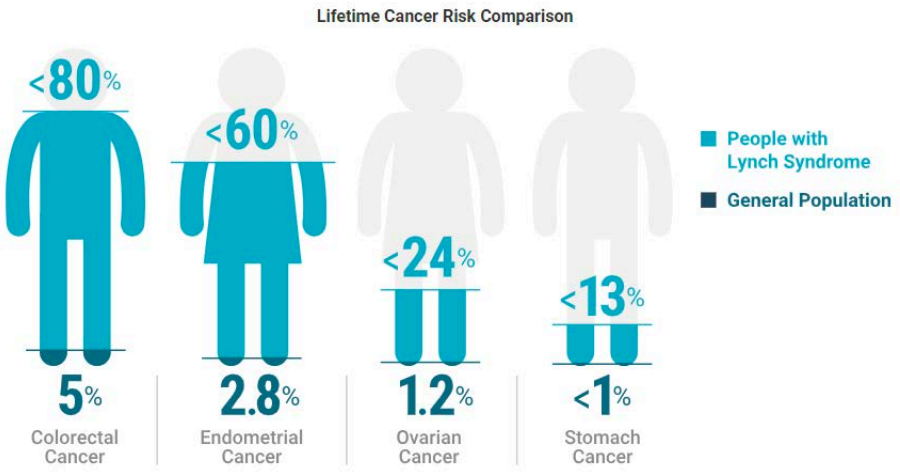
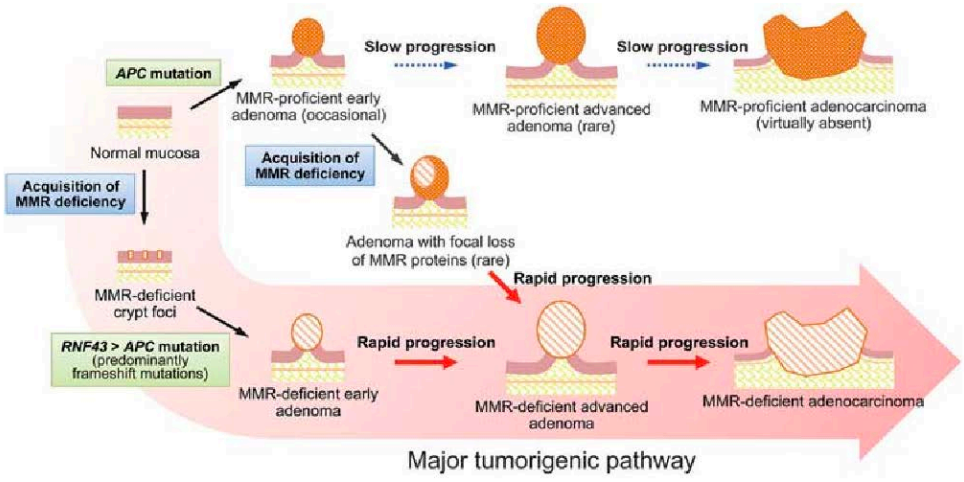
Lynch Risk of Cancer



Lynch Syndrome

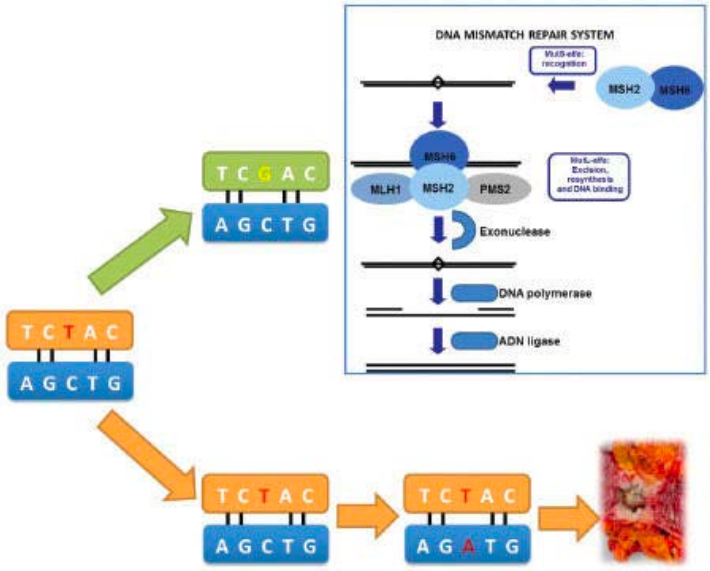
- Aka Hereditary Nonpolyposis Colon Cancer (HNPCC)
- Autosomal dominant
- Most common genetic colorectal cancer
  - 5% of all colon cancers
- Caused by germline mutations that inactivate DNA mismatch repair genes
- Lynch Syndrome can affect organs other than colon
  - Uterine; stomach; pancreas; kidney; small bowel; ovary; skin

Lynch Syndrome Associated Tumorigenesis

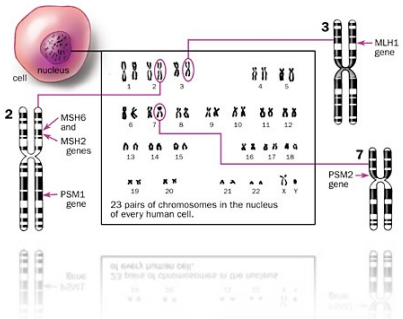


Sekine et al., Modern Pathology 30, 1144-1151(2017)

What is Mismatch repair?



Lynch syndrome genetics & CRC Risk



MLH1
37%

MSH2
41%

MSH6
13%

PMS2
9%

Cumulative Risk of CRC

Syndrome	Gene	Risk	Average age of diagnosis (years)
Sporadic cancer		4.8%	69
Lynch syndrome	*MLH1/MSH2*	M: 27–74% F: 22–61%	27–60
	MSH6	M: 22–69% F: 10–30% M/F: 12%	50–63
	PMS2	M: 20% F: 15%	47–66

Highest
MLH1
MSH2

Intermediate
MSH6

Lowest
PMS2

Syngal et al., Am J Gastroenterol 2015; 110:223–262

Lynch Syndrome - when to suspect

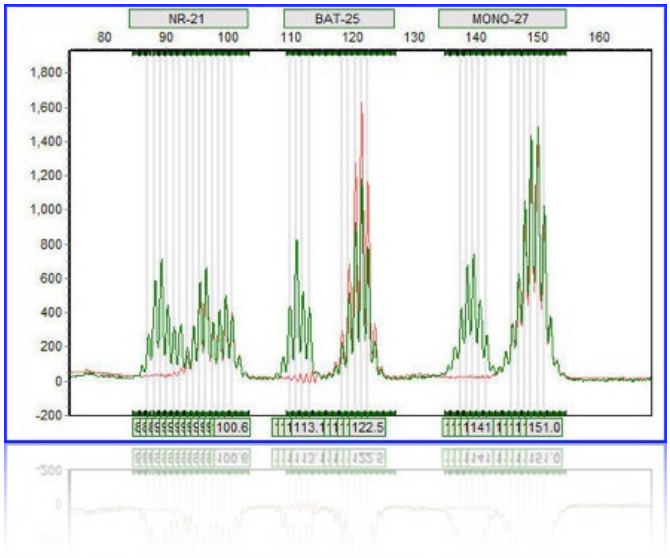
Affected Individuals
(Lynch Associated Cancer)

<50 years
MSI of tumour
Reflex (IHC)

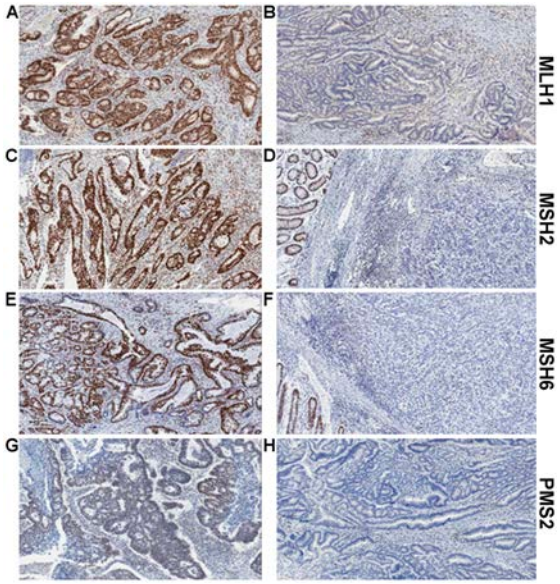
Unaffected Individuals

Amsterdam/Bethesda
Family member with mutation

Microsatellite Instability



Immunohistochemistry (Reflex)



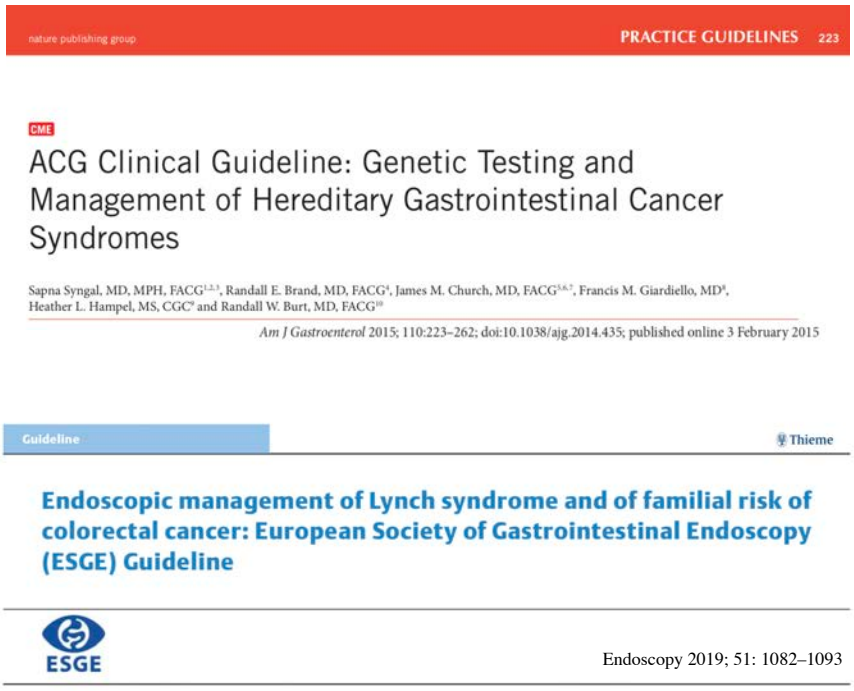
Richman, S."Deficient mismatch repair: Read all about it (Review)". International Journal of Oncology 47, no. 4 (2015): 1189-1202. https://doi.org/10.3892/ijo.2015.3119

Diagnosis by Criteria

- Criterion diagnosis (Amsterdam) 3-2-1:
  - 3 relatives with CRC
  - 2 Successive generations
  - 1 Younger than age 50

- Bethesda
  - CRC or Lynch related cancer
  - 3-2-1
  - Synchronous or metachronous CRC and Lynch related cancer
  - MSI on histology in <50

Surveillance Guidelines



nature publishing group PRACTICE GUIDELINES 223

CME

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG[1,2,3], Randall E. Brand, MD, FACG[4], James M. Church, MD, FACG[5,6,7], Francis M. Giardiello, MD[8], Heather L. Hampel, MS, CGC[9] and Randall W. Burt, MD, FACG[10]

Am J Gastroenterol 2015; 110:223–262; doi:10.1038/ajg.2014.435; published online 3 February 2015

Guideline Thieme

Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

ESGE

Endoscopy 2019; 51: 1082–1093

ACG Guidelines

nature publishing group PRACTICE GUIDELINES 223

CME

ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

Sapna Syngal, MD, MPH, FACG[1,2,3], Randall E. Brand, MD, FACG[4], James M. Church, MD, FACG[5,6,7], Francis M. Giardiello, MD[8], Heather L. Hampel, MS, CGC[9] and Randall W. Burt, MD, FACG[10]

Am J Gastroenterol 2015; 110:223–262; doi:10.1038/ajg.2014.435; published online 3 February 2015

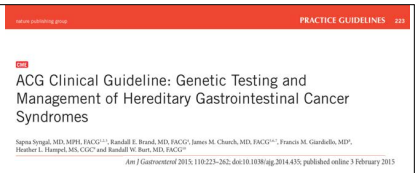
Colonoscopy
Q2yrs
Age 20-25

EGD
Q3-5yrs
Age 30-35

Uterine
Biopsy or US
Age 30-35
Hysterectomy
Age 40-45

Genetic Testing

ACG Guidelines: 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, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain
2. Have you had any of the following conditions diagnosed before age 50 years?
   - Colon or rectal cancer or polyps
3. Do you have three or more relatives with a history of colon or rectal cancer?

If yes to any, comprehensive Family History

Kastrinos F, Allen JI, Stockwell DH *et al*. Development and validation of a colon cancer risk assessment tool for patients undergoing colonoscopy. Am J Gastroenterol 2009;104:1508–18.

ESGE Guidelines

Colonoscopy Q2yrs

MLH1 & MSH2 Age 25

MSH6 & PMS2 Age 35

EGD

Not recommended

Small Bowel

Not recommended

Lynch Extracolonic Cancers

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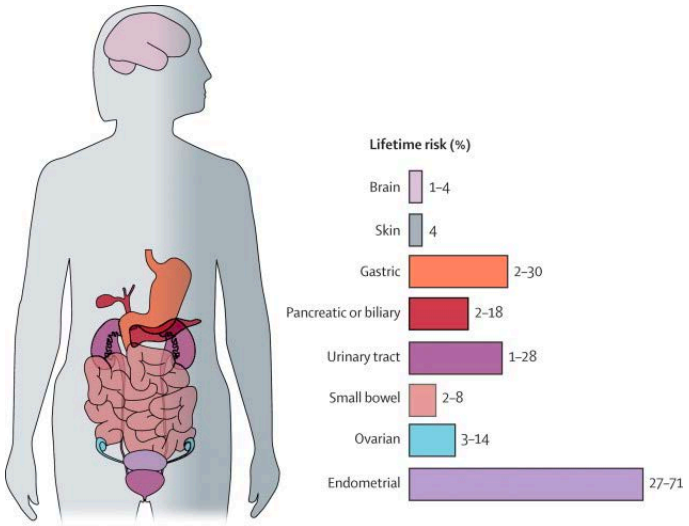
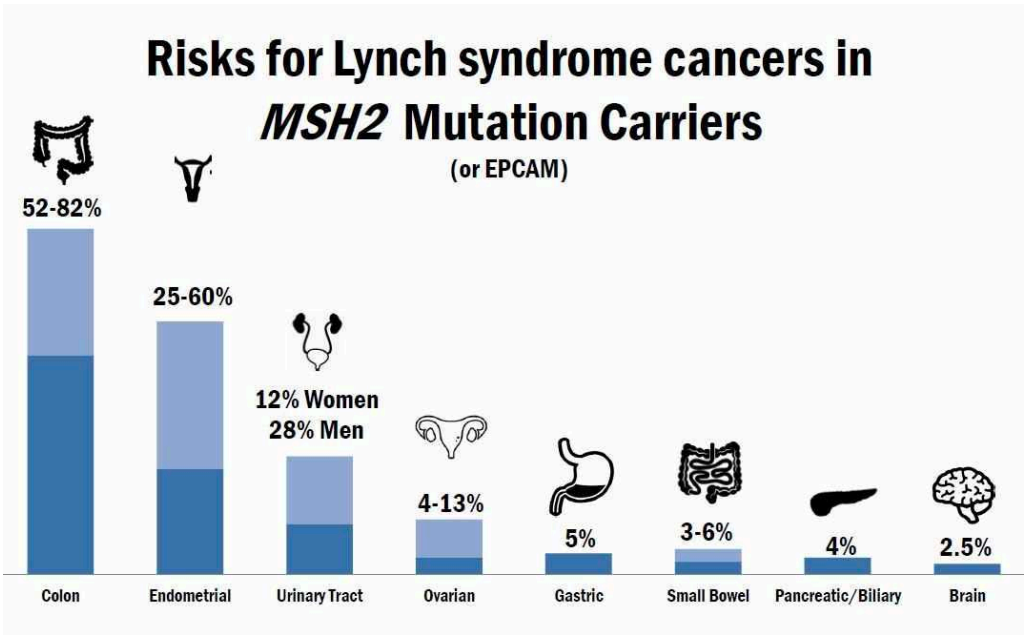
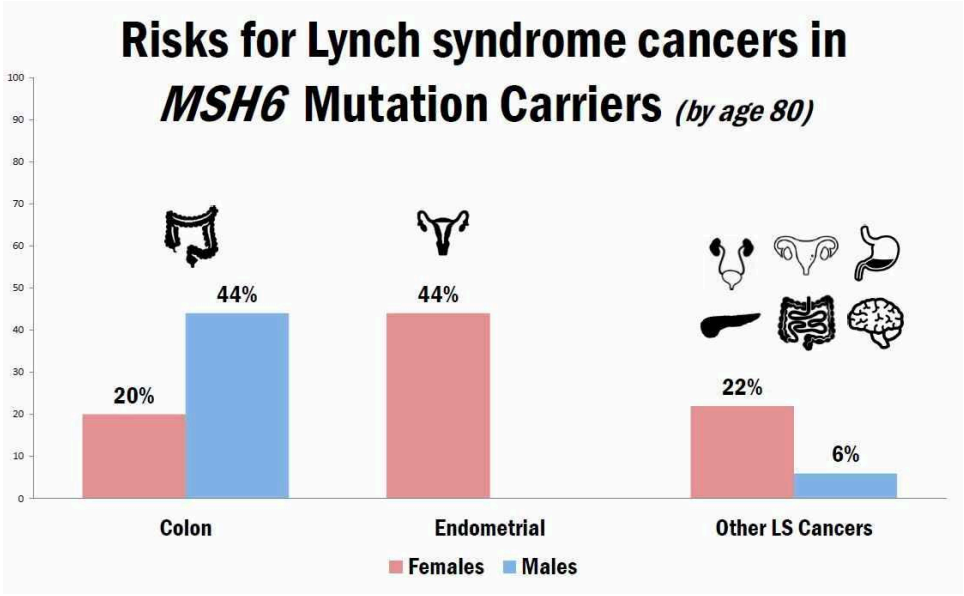
Extra colonic involvement




Risks for Lynch syndrome cancers in
MSH2 Mutation Carriers
(or EPCAM)
52-82%
25-60%
12% Women
28% Men
4-13%
5%
3-6%
4%
2.5%
Colon
Endometrial
Urinary Tract
Ovarian
Gastric
Small Bowel
Pancreatic/Biliary
Brain


Risks for Lynch syndrome cancers in
MSH6 Mutation Carriers (by age 80)
100
90
80
70
60
50
40
30
20
10
0
20%
44%
44%
22%
6%
Colon
Endometrial
Other LS Cancers
Females
Males

Edmonton Genetics surveillance

- Endometrial
  - Annual biopsy, aspirate, CA 125
  - Consider hysterectomy
- Ovarian
  - Annual transvaginal ultrasound
- Small bowel
  - ? VCE
- Kidney
  - Annual Urinalysis and urine cytology
- Skin
  - Survey annually
- EGD
  - Q1-3 years

Lynch Syndrome Endoscopic Strategies

Can we improve surveillance colonoscopy?

- Surveillance in units that follow quality metrics
  - Dedicated Units
- High Definition Endoscopes
- Chromoendoscopy

Chromoendoscopy for Lynch?

ORIGINAL ARTICLE: Clinical Endoscopy

Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial

Jasmijn F. Haanstra, MD,[1,6] Evelien Dekker, MD, PhD,[2] Annemieke Cats, MD, PhD,[3] Fokko M. Nagengast, MD, PhD,[4] James C. Hardwick, MD, PhD,[5] Steven A. Vanhoutvin, MD, PhD,[3] Wouter H. de Vos tot Nederveen Cappel, MD, PhD,[6] Hans F. Vasen, MD, PhD,[5,7] Jan H. Kleibeuker, MD, PhD,[1] Jan J. Koornstra, MD, PhD[1]

Groningen, Amsterdam, Nijmegen, Leiden, Zwolle, the Netherlands

624 GASTROINTESTINAL ENDOSCOPY Volume 90, No. 4 : 2019

TABLE 2. Characteristics of the baseline colonoscopy procedure

	White-light endoscopy (n = 116)	Chromoendoscopy (n = 115)
Total procedure time (minutes), median (IQR)	22 (17-30)	31 (24-42)
Withdrawal time (minutes), median (IQR)	12 (9-16)	19 (15-24)
High-definition scope used, n (%)*	50/111 (45)	57/110 (52)
Bowel preparation, n (%)		
Good	92 (79)	82 (71)
Fair	24 (21)	33 (29)
Adverse event rate	1/116	1/115

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TABLE 3. Endoscopic detection rates at baseline colonoscopy

	White-light endoscopy (n = 116), n (%)	Chromoendoscopy (n = 115), n (%)	*P* value
Patients with polyp(s)	59 (51)	64 (56)	.46
Patients with neoplasia	31 (27)	35 (30)	.56
Patients with advanced neoplasia	7 (6)	5 (4)	.43
Patients with proximal polyps	32 (28)	54 (47)	.003
Patients with proximal neoplasia	19 (16)	28 (24)	.13

TABLE 5. Characteristics of the 2-year colonoscopy procedure

	White-light endoscopy group (n = 92)	Chromoendoscopy group (n = 94)
Total procedure time (minutes), median (IQR)	29 (20-40)	29 (21-38)
Withdrawal time (minutes), median (IQR)	17 (13-24)	19 (13-24)
High-definition scope used, n (%)*	59/91 (65)	62/88 (70)
Bowel preparation, n (%)		
Good	66 (72)	73 (78)
Fair	26 (28)	21 (22)
Adverse event rate	1/92	0/94

Summary

- In regards to Lynch syndrome:

- Caused by germline mutation in MMR gene
- Different MMR gene mutations carry different risks of cancer
  - MLH1 > MSH2 > MSH6 >PMS2
- Diagnosis by tissue MSI/IHC
- Diagnosis in family by Amsterdam/Bethesda criteria
- Surveillance colonoscopy every 2 years - age differs by gene
- Extracolonic surveillance controversial
- Use of chromoendoscopy controversial