Clinical management of polyposis and non-polyposis syndromes

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High-Risk Colorectal Cancer Clinics

- Focused on colorectal cancer
- Decentralized (network)
- Population-based approach (active)
- Hereditary and familial forms, and premalignant lesions
- Treatment and follow-up integrated

Balaguer et al. Med Clin (Barc) 2008
High-Risk Colorectal Cancer Clinics

Referral center
- Management based on genetic testing
- Complex therapeutic procedures

Community-based center
- Management based on family history
- Basic therapeutic procedures

Primary care physician
- Identification of individuals at risk

Balaguer et al. Med Clin (Barc) 2008
Barcelona’s CRC Screening Program

- **Target population**: asymptomatic, average-risk population (men and women 50-69 years-old) → 450,000 individuals
- **Screening approach**: biennial FIT
- **Work-up examinations**: colonoscopy (CT-colonography)
- **Health providers**: hospital-based, primary care physicians, community pharmacies
EPICOLON Consortium

EPICOLON 1 (2000-2001)
- 1978 CRC patients (level 1)
- 1222 CRC patients (level 2)

EPICOLON 2 (2006-2007)
- 895 CRC patients
- 904 healthy controls

EPICOLON 3 (ongoing)

- H. Arnau de Vilanova (Lleida)
- H. Gral. Vic
- H. Mar (Barcelona)
- H. Clínic (Barcelona)
- H. Esperit Sant (Sta. Coloma Gramenet)
- H. Germans Trias i Pujol (Badalona)
- H. Alt Penedès (Vilafranca del P.)
- Institut Dexeus (Barcelona)
- H. Mútua de Terrassa
- H. Gral. Granollers
- H. Gral. Alacant
- H. La Fe (València)
- H. 12 octubre (Madrid)
- H. Gral. Guadalajara
- H. Cristal Piñor (Ourense)
- H. Meixoeiro (Vigo)
- H. Reina Sofía (Córdoba)
- H. Virgen del Rocío (Sevilla)
- H. Univ. Canarias (Tenerife)
COLONPREV Study

Average-risk population

Randomization 1:1

Information + invitation ± reminding letters

Appointment: Local Screening Office (questionnaire, post-randomization consent)

Group I: Biennial FIT (n= 27,749)

Group II: Colonoscopy (n= 27,749)

Colorectal cancer: epidemiology

- Sporadic: 69%
- Polyposis syndromes: 26%
- Lynch syndrome: 1%
- MYH-associated CRC: 1%
- IBD: 1%
- Familial CRC: 1%

Castells et al. Gastroenterology 2009
Polyposis and non-polyposis colorectal syndromes

POLYPOSIS

Adenomas
- >100: CLASSICAL FAP
  - APC
  - MUTYH
  - POLE
  - POLD1
- 20-100: ATENUATED FAP
  - STK11

Hamartomas
- >20 or >5 prox.: PEUTZ-JEGHERS
  - SMAD4
  - BMPR1A
- ?: JUVENILE POLYPOSIS
  - PTEN
- ?: COWDEN SYNDROME
  - PTEN

Serrated polyps
- ?: SERRATED POLYPOSIS

NON-POLYPOSIS

MMR REPAIR DEFICIENCY?
- YES: LYNCH SYNDROME
  - MLH1
  - MSH2
  - MSH6
  - PMS2
  - EpCAM
- No: FAMILIAL CRC TYPE X
  - ?
  - MUTYH

FAMILIAL CRC TYPE X

MMR REPAIR DEFICIENCY?
- Yes: LYNCH SYNDROME
  - MLH1
  - MSH2
  - MSH6
  - PMS2
  - EpCAM
- No: FAMILIAL CRC TYPE X
  - ?
  - MUTYH
Colorectal cancer: pathogenesis

- Chromosomal instability
- CpG island methylator phenotype
- Microsatellite instability

Castells et al. Gastroenterology 2009
Colorectal cancer: pathogenesis

- Syndromic (hereditary) forms
  - Suppressor pathway
    - Familial adenomatous polyposis
  - Mutator pathway
    - Lynch syndrome
  - Methylator pathway
    - Serrated polyposis

- Sporadic forms
  - CRC-MSS
  - CRC-MSI
  - CRC-CIMP
Familial adenomatous polyposis (FAP)

- Autosomal dominant disorder
- One in 15,000 live births
- More than 100 polyps
- Diffuse distribution
- Onset: 15-20 year-old
- Extracolonic manifestations: upper GI adenomas, congenital hypertrophy of the retinal pigment epithelium, osteomas, and dental anomalies (Gardner syndrome), brain tumor (Turcot syndrome)
- Germline APC gene mutations
- Overall CRC risk ~100% by age 40-50
FAP: screening

Identified mutation

- Positive
  - Colonoscopy yearly
    - Polyposis
      - Proctocolectomy / total colectomy
    - Upper endoscopy
    - Abdominal CT
    - Ortopantomomography

- Negative
  - Exclusion
FAP: genotype-phenotype correlation

Attenuated FAP (5’ UTR)

Hipertrophy of the retinal pigment epithelium (542-1309)

Advanced FAP (1285, 1465)

Extracolonic manifestations (1465, 1546, 2621)

Upper GI adenomas (1051-1600)

Domains
- Armadillo repeat
- β-catenin binding (15-aa repeat)
- β-catenin downregulation (20-aa repeat)
- Microtubule binding
- EB1/RP1 binding

Exons
- 1 3 5 7 9 1113 15
- 2 4 6 8 101214

Codons
- 1 400 800 1200 1600 2000 2400 2800

Extra-adenomatous manifestations (1465, 1546, 2621)

Upper GI adenomas (1051-1600)
Surgical treatment in FAP patients

- Total colectomy with ileorectal anastomosis
  - Codon 0 - 200
  - Codon >1500
  - Mild familial phenotype and no rectal polyps
  - Attenuated FAP

- Proctocolectomy with ileoanal anastomosis
  - Codon 200 - 1500
  - Severe familial phenotype
  - Diffuse disease
Medical treatment in FAP patients

A Randomized, Double-Blind, Placebo-Controlled Trial of the Effects of Rofecoxib, a Selective Cyclooxygenase-2 Inhibitor, on Rectal Polyps in Familial Adenomatous Polyposis

ClinicalTrials.gov Id: NCT01483144
Serrated polyposis
(hyperplastic polyposis syndrome)

Definition (WHO 2010)
- ≥5 proximal serrated polyps (at least, 2 polyps ≥10 mm), or
- ≥20 serrated polyps (any size, any location), or
- any serrated polyp in a person with one FDR with serrated polyposis

- 1 in 3000 (0.03%) individuals in sigmoidoscopy-based screening (Lockett et al. Gut 2001)
- 1 in 1818 (0.06%) individuals in colonoscopy-based screening (Orlowska et al. Gut 2012)
- 8 in 2355 (0.34%) individuals after a positive FIT (Moreira et al. Gut 2013)
- 5 in 755 (0.66%) individuals after a positive gFOBT (Biswas et al. Gut 2013)
Serrated polyposis and CRC risk

- Endoscopic surveillance in 77 patients with serrated polyposis
- Multicenter observational study, 1982-2008
- 27 (35%) patients developed CRC (22 at baseline examination)

Cumulative risk: 7% at 5 years

Boparai et al. Gut 2010
Sessile serrated pathway

Morphologic changes

Normal mucosa
\[\rightarrow\]
ACF
\[\rightarrow\]
MVHP
\[\rightarrow\]
SSA
\[\rightarrow\]
SSA-HGD
\[\rightarrow\]
CRC

Molecular changes

BRAF mutation
\[\rightarrow\]
Apoptosis inhibition
\[\rightarrow\]
p16, IGFBP7, others? methylation
\[\rightarrow\]
Neoplastic progression through CIMP-H

MLH1 methylation

MCC / APC methylation and/or p53, 18q LOH...

MSI-H tumors
\[\rightarrow\]
MSS tumors

- Proximal tumors
- Mutated BRAF
- CIMP-H
- MSI-H (MSS)
- MLH1 loss

Goel and Balaguer. Curr CRC Rep 2011
## Detection rate of proximal serrated polyps per endoscopist

<table>
<thead>
<tr>
<th>Comparison (vs endoscopist 1)</th>
<th>Odds ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopist 2</td>
<td>0.50 (0.29–0.85)</td>
<td>.0114</td>
</tr>
<tr>
<td>Endoscopist 3</td>
<td>0.31 (0.21–0.44)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Endoscopist 4</td>
<td>0.57 (0.31–1.05)</td>
<td>.0701</td>
</tr>
<tr>
<td>Endoscopist 5</td>
<td>0.67 (0.48–0.94)</td>
<td>.0198</td>
</tr>
<tr>
<td>Endoscopist 6</td>
<td>0.40 (0.21–0.78)</td>
<td>.0066</td>
</tr>
<tr>
<td>Endoscopist 7</td>
<td>0.59 (0.45–0.79)</td>
<td>.0003</td>
</tr>
<tr>
<td>Endoscopist 8</td>
<td>0.66 (0.30–1.46)</td>
<td>.3055</td>
</tr>
<tr>
<td>Endoscopist 9</td>
<td>0.65 (0.47–0.91)</td>
<td>.0111</td>
</tr>
<tr>
<td>Endoscopist 10</td>
<td>0.16 (0.09–0.29)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Endoscopist 11</td>
<td>0.05 (0.01–0.37)</td>
<td>.0033</td>
</tr>
<tr>
<td>Endoscopist 12</td>
<td>0.11 (0.03–0.46)</td>
<td>.0025</td>
</tr>
<tr>
<td>Endoscopist 13</td>
<td>0.57 (0.40–0.82)</td>
<td>.0021</td>
</tr>
<tr>
<td>Endoscopist 14</td>
<td>0.19 (0.11–0.35)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Endoscopist 15</td>
<td>0.50 (0.29–0.85)</td>
<td>.0114</td>
</tr>
</tbody>
</table>

CI, confidence interval.

Endoscopic appearance of serrated lesions

- Frequently flat or sessile
- Covered by mucus
- Overlooked during colonoscopy: missed lesions → interval CRC
  - Right sided
  - Microsatellite instability (MSI)
  - CIMP-H

![Endoscopic images of serrated lesions](image-url)
Missed lesions at baseline colonoscopy (median (IQR))

<table>
<thead>
<tr>
<th>Lesion Type</th>
<th>White-light (n=30)</th>
<th>Chromoendoscopy (n=41)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All polyps</td>
<td>3 (1 - 9)</td>
<td>6 (2-11)</td>
<td>0.048</td>
</tr>
<tr>
<td>Serrated lesions</td>
<td>1 (0 - 5)</td>
<td>3 (1 - 9)</td>
<td>0.046</td>
</tr>
<tr>
<td>Proximal serrated lesions</td>
<td>0 (0 - 2)</td>
<td>2 (1 - 6)</td>
<td>0.015</td>
</tr>
<tr>
<td>Adenomas</td>
<td>1 (0 - 2)</td>
<td>1 (0 - 3)</td>
<td>0.610</td>
</tr>
</tbody>
</table>

Image enhancement techniques in SPS

Patients from FIT-based population screening (n=3444)

At least 1 proximal serrated lesion ≥5 mm (n=196)

Reassessment colonoscopy (11.9 ± 1.7 months) (n=71)

SPS diagnosis (n=11)

SPS diagnosis (n=20)

Rivero et al. (submitted)
Endoscopic submucosal dissection
Serrated polyposis and CRC risk

- CRC prevalence: 47/310 (15%)
- CRC diagnosis:
  - 35 (74.5%) at SPS diagnosis
  - 4 (8.5%) incidentally
  - 8 (17%) before SPS diagnosis
- Cumulative CRC risk: 1.8% at 5 years

Variables associated with CRC in patients with SPS

<table>
<thead>
<tr>
<th>Variables</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of proximal SSA/P</td>
<td>1.05</td>
<td>1.01-1.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Number of proximal SL with HGD</td>
<td>2.14</td>
<td>1.01-4.60</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Carballal et al. Gut 2015
Exome sequencing SPS project

- Up to 15% of patients with SPS have family history of CRC and/or SPS → predisposition genes still unknown

- Exome sequencing in families with aggregation for SPS
  - ≥ 2 patients exome sequenced per family
  - Germline and matched tumor/serrated polyp exome sequencing in some patients (candidate tumor suppressor genes)
Mutational screening of the exonuclease domain in \textit{POLE} and \textit{POLD1} (150 patients with multiple adenoma and early-onset CRC)

- Two variants being further analyzed → functional studies performed in yeast (in progress)
Patients with newly diagnosed non-polyposis CRC

- **IHC for MMR proteins**
  - **Retained expression**
    - No inherited MMR defect
    - Amsterdam criteria +
      - Familial colorectal cancer type X
  - **Loss of MSH2 / MSH6 / PMS2**
    - Germline mutation analysis of MSH2 / MSH6 / EPCAM / PMS2
      - If CRC diagnosed ≤50 years-old
    - Consider MUTYH genetic testing
    - Lynch-like syndrome
  - **Loss of MLH1**
    - Somatic BRAF V600E mutation or MLH1 promoter methylation analyses
      - BRAF wild-type / no MLH1 hypermethylation
        - Germline MLH1 mutation analysis
          - Mutation
            - No mutation
          - No mutation
            - Sporadic MSI tumor
        - BRAF mutated / MLH1 hypermethylation
          - Lynch syndrome
          - Mutation
            - No mutation

Balaguer et al. Colorectal Cancer 2013
Lynch syndrome

- Autosomal dominant disorder
- Early onset CRC: <45 years of age
- Location in proximal colon
- Histology: undifferentiated, signet-ring cell type
- Multiple CRC (synchronous, metachronous)
- Multiple neoplasms (endometrial, gastric, small bowel, renal, ovarian, and skin)
- **Amsterdam criteria**: 3 relatives with CRC and/or HNPCC-associated neoplasia, 2 successive generations, and 1 diagnosed before age 50
Cumulative risk of colorectal cancer in MMR gene mutation carriers

Kempers et al. Lancet Oncol 2011
Lynch syndrome screening

Probability of overall survival

- Screening, mutation + (n=44)
- Screening, all (n=133)
- Control, all (n=119)
- Control, mutation + (n=46)

\[ p = 0.003 \text{ (all)} \]

\[ p = 0.05 \text{ (mutation +)} \]

Järvinen et al. Gastroenterology 2000
Lynch syndrome: pathogenesis

MSH2, MLH1, MSH6, PMS2 (germline mutation)

Normal mucosa → Second hit

Microsatellite instability

Loss of protein expression

TGF-β-RII, BAX, IGFIIR

Carcinoma
Performance of MSI vs. IHC screening for the identification of Lynch syndrome

Piñol et al. JAMA 2005
Identification of Lynch syndrome

- **Clinical criteria:**
  - Amsterdam criteria
  - Amsterdam II criteria
  - Bethesda guidelines
  - Revised Bethesda guidelines
  - Jerusalem recommendations

- **Pathological scores:**
  - MsPath model

- **Mathematical algorithms:**
  - Leiden
  - PREMM\textsubscript{1,2,6}
  - MMRpredict
  - MMRpro
Moreira et al. JAMA 2012
## Diagnostic yield of strategies for Lynch syndrome identification

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Bethesda</th>
<th>Jerusalem</th>
<th>Selective*</th>
<th>Universal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.96%</td>
<td>2.12%</td>
<td>2.23%</td>
<td>2.90%</td>
</tr>
</tbody>
</table>

*Selective strategy: tumor MMR testing of CRC patients diagnosed ≤70 years-old, and in older patients fulfilling the Bethesda guidelines*

---

Moreira et al. JAMA 2012
Strategies for the identification of Lynch syndrome

Tumor MMR testing

Germline MMR gene analysis

*Selective strategy: tumor MMR testing of CRC patients diagnosed ≤70 years-old, and in older patients fulfilling the Bethesda guidelines

Moreira et al. JAMA 2012
CRC multiplicity in Lynch syndrome

Synchronous colorectal cancer

- MLH1: 7.40%
- MSH2: 6.70%
- General population: 2.40%

Metachronous colorectal cancer (annual rate)

- MLH1: 2.10%
- MSH2: 1.70%
- General population: 0.33%

*p = 0.016*

*p = 0.041*

Metachronous CRC in Lynch syndrome

Kaplan-Meier failure estimate

Cumulative risk of metachronous CRC (%)

Analysis time (year)

Parry et al. Gut 2011
Chromoendoscopy in Lynch syndrome

Polyps found on 1\textsuperscript{st} (standard) and 2\textsuperscript{nd} (intensive inspection vs. chromoendoscopy) colonoscopies

<table>
<thead>
<tr>
<th>1\textsuperscript{st} colonoscopies (standard)</th>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><img src="image1.png" alt="Diagram 1" /></td>
<td><img src="image2.png" alt="Diagram 2" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2\textsuperscript{nd} colonoscopies (intensive inspection vs. chromoendoscopy)</th>
<th>Intensive Inspection Arm 2nd Colonoscopy</th>
<th>Chromoendoscopy Arm 2nd Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Diagram 3" /></td>
<td><img src="image4.png" alt="Diagram 4" /></td>
<td></td>
</tr>
</tbody>
</table>

Chromoendoscopy in Lynch syndrome

Number of adenomas per subject and procedure time for 1st and 2nd colonoscopies by randomization arm

Arm 1: intensive inspection

Arm 2: chromoendoscopy

High-magnification chromoendoscopy in HNPCC: a “back-to-back” study

<table>
<thead>
<tr>
<th></th>
<th>Phase 1 Colonoscopy</th>
<th></th>
<th>Phase 2 Colonoscopy</th>
<th></th>
<th>p *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
<td>Median</td>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>All lesions</td>
<td>0</td>
<td>0–4</td>
<td>2</td>
<td>0–8</td>
<td>0.017</td>
</tr>
<tr>
<td>Adenomas</td>
<td>0</td>
<td>0–3</td>
<td>1</td>
<td>0–4</td>
<td>0.001</td>
</tr>
<tr>
<td>Adenomas with HGD</td>
<td>0</td>
<td>0–1</td>
<td>0</td>
<td>0–2</td>
<td>ns</td>
</tr>
<tr>
<td>Flat adenomas</td>
<td>0</td>
<td>0–1</td>
<td>1</td>
<td>0–2</td>
<td>0.004</td>
</tr>
<tr>
<td>Flat adenomas with HGD</td>
<td>0</td>
<td>0–1</td>
<td>0</td>
<td>0–2</td>
<td>ns</td>
</tr>
</tbody>
</table>

Hurlstone et al. Am J Gastroenterol 2005
Segmental vs. total colectomy in Lynch syndrome: a decision model

Maeda et al. J Clin Oncol 2010
Rectal cancer in Lynch syndrome

- 2/3 of CRC occur in the proximal colon
- 1/3 in the distal colon and rectum

Neoadjuvant therapy may be induce MSH6 loss and, therefore, material obtained before treatment should be prioritized (You et al. 16th Annual Meeting CGA-ICC, Boston, 2012)

**Surgical approach** ➔ **individualized**
- Abdominoperineal resection
- Segmental resection with anastomosis (i.e. low anterior proctectomy)
- Proctocolectomy with ileal pouch anal anastomosis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LAR (proctectomy)</th>
<th>Proctocolectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncologic</td>
<td>=</td>
<td>=</td>
</tr>
<tr>
<td>Morbidity</td>
<td>✓✓</td>
<td>✓</td>
</tr>
<tr>
<td>Function</td>
<td>✓✓</td>
<td>✓ (diarrhea)</td>
</tr>
<tr>
<td>Metachronous CRC</td>
<td>17%-50%</td>
<td>✓✓✓</td>
</tr>
</tbody>
</table>
Lifetime risk of extracolonic tumors

Koornstra et al. Lancet Oncol 2009
Cumulative risk of endometrial cancer in MMR gene mutation carriers

Incidence of endometrial cancer in Lynch syndrome: prophylactic hysterectomy

Schmeler et al. NEJM 2006
Phenotype comparison of *MLH1* and *MSH2* mutation carriers

Stoffel *et al*. Cancer Epidemiol Biomarkers Prev 2008

![Bar chart showing phenotype comparison of MLH1 and MSH2 mutation carriers.](chart.png)

- **CRC**
  - MLH1: 79%
  - MSH2: 69%
  - *p*=0.08

- **Endometrial**
  - MLH1: 20%
  - MSH2: 27%
  - *p*=0.33

- **Others**
  - MLH1: 9%
  - MSH2: 24%
  - *p*=0.001
Gastric cancer in Lynch syndrome

Cumulative incidence by gender

Cumulative incidence for MMR mutation carriers

Capelle et al. Gastroenterology 2010
# Surveillance for extracolonic malignancies in Lynch syndrome

**Generally recommended**<sup>48,49</sup>

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Beginning age (years)</th>
<th>Interval (years)</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endometrial and ovarian cancer</td>
<td>30–35</td>
<td>1</td>
<td>Transvaginal ultrasound, intrauterine sampling, gynaecological examination</td>
</tr>
<tr>
<td>Upper urinary-tract cancer*</td>
<td>25–35</td>
<td>1–2</td>
<td>Urinanalysis and cytology</td>
</tr>
<tr>
<td>Stomach cancer†</td>
<td>30–35</td>
<td>1–2</td>
<td>Gastroduodenoscopy</td>
</tr>
</tbody>
</table>

**Generally not recommended but can be considered for individual cases or families**

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin cancer</td>
<td>Dermatological inspection</td>
</tr>
<tr>
<td>Small-bowel cancer</td>
<td>Capsule endoscopy</td>
</tr>
<tr>
<td>Pancreaticobiliary tumours</td>
<td>Endoscopic ultrasound</td>
</tr>
</tbody>
</table>

*Some recommend limiting surveillance to families with more than one case of urinary-tract cancer,<sup>49</sup> others do not propose any restrictions.<sup>15,48</sup> †Recommended in families with more than one case of stomach cancer or in populations with a high incidence.<sup>49</sup>

Koornstra et al. Lancet Oncol 2009
Pancreatic cancer in Lynch syndrome

Kastrinos et al. JAMA 2009
Surveillance in familial pancreatic cancer
Lesions identified by EUS or CT (n = 14)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2N1</td>
<td>IPMN (CIS)</td>
<td>IPMN</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td>IPMN (microinvasive?)</td>
<td>IPMN vs PanIN</td>
<td>IPMN</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td></td>
<td>IPMN</td>
<td>IPMN</td>
<td>Accessory spleen</td>
</tr>
<tr>
<td></td>
<td>IPMN</td>
<td>IPMN</td>
<td>Pancreatic abscess and focal pancreatitis</td>
</tr>
<tr>
<td></td>
<td>IPMN</td>
<td></td>
<td>Mild focal pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Focal fibrosis and atrophy</td>
</tr>
</tbody>
</table>

Lesions unidentified by EUS or CT (n = 13)

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic carcinoma and hepatic metastases</td>
<td>PanIN 1–3</td>
<td>PanIN 1–2</td>
<td>PanIN 1</td>
</tr>
<tr>
<td></td>
<td>PanIN 1–3</td>
<td>PanIN 1–2</td>
<td>Serous cystadenoma</td>
</tr>
<tr>
<td></td>
<td>PanIN 1–2</td>
<td>PanIN 1–2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PanIN 1–2</td>
<td>PanIN 1A–1B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PanIN 1A</td>
<td>and 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PanIN 1–2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients with newly diagnosed non-polyposis CRC

IHQ for MMR proteins

Loss of MSH2 / MSH6 / PMS2
- Retained expression
  - No inherited MMR defect
    - Amsterdam criteria +
      - Familial colorectal cancer Type X
    - If CRC diagnosed ≤50 years-old
      - Consider MUTYH genetic testing
- Loss of MLH1
  - Somatic BRAF V600E mutation or MLH1 promoter methylation analyses
    - BRAF wild-type / no MLH1 hypermethylation
      - Germline MLH1 mutation analysis
        - No mutation
        - Mutation
          - Lynch-like syndrome
          - Lynch syndrome
        - Mutation
          - No mutation
        - No mutation
          - Sporadic MSI tumor

Balaguer et al. Colorectal Cancer 2013
# Lynch-like syndrome

Standardized incidence ratios (SIR)\(^1\) for cancer

<table>
<thead>
<tr>
<th></th>
<th>Lynch syndrome (n=80)</th>
<th>p value</th>
<th>Lynch-like syndrome (n=177)</th>
<th>p value</th>
<th>Sporadic CRC (n=845)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>6.04 (3.58-9.54)</td>
<td>&lt;0.001</td>
<td>2.12 (1.16-3.56)</td>
<td>&lt;0.001</td>
<td>0.48 (0.27-0.79)</td>
</tr>
<tr>
<td>Non-CRC LS-related cancer(^2)</td>
<td>2.81 (1.03-6.12)</td>
<td>0.09</td>
<td>1.69 (0.73-3.34)</td>
<td></td>
<td>1.20 (0.79-1.74)</td>
</tr>
</tbody>
</table>

\(^1\)SIR for cancer were calculated as the ratio of the observed to expected number of cases in first-degree relatives diagnosed in the families at the time of inclusion.

\(^2\)Non-CRC Lynch syndrome-related cancers: endometrium, ovaries, upper urinary tract, stomach, small intestine, and hepatobiliary system.

---

Rodríguez-Soler et al. Gastroenterology 2013
Lynch-like syndrome

Cumulative age of onset of CRC in first-degree relatives of patients with Lynch syndrome (LS), Lynch-like syndrome (LLS), and sporadic CRC

Rodríguez-Soler et al. Gastroenterology 2013
Lynch-like syndrome

Differences in the appearance of new cases of cancer during follow-up

Rodríguez-Soler et al. Gastroenterology 2013
### Lynch-like syndrome

#### Somatic events in unexplained MLH1- and MSH2-deficient CRC and endometrial cancer

<table>
<thead>
<tr>
<th></th>
<th>MLH1-deficient tumors (n=18)</th>
<th>MSH2-deficient tumors (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any somatic event</td>
<td>17 (94%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Loss of heterozygosity (LOH)</td>
<td>8 (44%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td><strong>Two pathogenic hits</strong></td>
<td><strong>8 (44%)</strong></td>
<td><strong>5 (71%)</strong></td>
</tr>
<tr>
<td>Combination of VUS and either</td>
<td>3 (17%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>a pathogenic mutation or LOH</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mensenkamp & Vogelaar *et al.* *Gastroenterology* 2014
Prevalence of somatic *MLH1* promoter hypermethylation in Lynch syndrome

Moreira *et al*. Cancer 2015
Familial colorectal cancer type X

Amsterdam criteria
- At least 3 relatives with CRC
- One should be first degree relative of other 2
- At least 2 successive generations affected
- At least 1 CRC diagnosed before age 50
- Familial adenomatous polyposis excluded
- Diagnosis confirmed by histology

MSI analysis
IHC (MHS2, MLH1, MSH6, PMS2)

Altered IHC, MSI
Lynh syndrome

Normal IHC, MSS
Familial CRC type X

Lindor et al. JAMA 2005
## Familial colorectal cancer type X

<table>
<thead>
<tr>
<th>Lynch syndrome</th>
<th>Familial CRC type X</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Amsterdam criteria, ( % (n) )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amsterdam I</td>
<td>90 (9)</td>
<td>53 (8)</td>
</tr>
<tr>
<td>Amsterdam II</td>
<td>10 (1)</td>
<td>47 (7)</td>
</tr>
<tr>
<td>Colon cancer, ( %^* )</td>
<td>31.5</td>
<td>17.9</td>
</tr>
<tr>
<td>Endometrial cancer, ( %^* )</td>
<td>5.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Age colon cancer( ^\dagger )</td>
<td>53.8 ± 5.4</td>
<td>60.2 ± 7.9</td>
</tr>
<tr>
<td>Age endometrial cancer( ^\dagger )</td>
<td>52.4 ± 5.1</td>
<td>51.36 ± 13.4</td>
</tr>
</tbody>
</table>

*Percentage of family members affected with colorectal or endometrial cancer in the family, including the proband, corrected for family size.

\( ^\dagger \)Age (mean ± SD) at diagnosis of all family members affected with colorectal or endometrial cancer in the family.
Methylation of *long interspersed nucleotide element-1* (LINE-1) as surrogate marker for global methylation.

<table>
<thead>
<tr>
<th></th>
<th>Mean % <em>LINE-1</em> methylation</th>
<th>Mean rank</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSS HNPCC</td>
<td>60.08 (21)</td>
<td>56.05</td>
<td></td>
</tr>
<tr>
<td>Lynch syndrome</td>
<td>66.29 (20)</td>
<td>94.80</td>
<td>.015</td>
</tr>
<tr>
<td>MSI sporadic</td>
<td>67.27 (45)</td>
<td>105.41</td>
<td>.001</td>
</tr>
<tr>
<td>MSS sporadic</td>
<td>65.13 (90)</td>
<td>86.22</td>
<td>.009</td>
</tr>
</tbody>
</table>

Goel *et al.* Gastroenterology 2010
Familial CRC type X: exome sequencing

Selection criteria:
- No alterations in APC, MUTYH and MMR genes
- 3 or more relatives affected
- At least 2 consecutive generations affected
- At least one CRC case diagnosed before the age of 60

Exome sequencing of germline DNA of 42 patients with familial CRC MSS (29 family clusters) from high-risk CRC clinics (H. Clínica Barcelona, Trinidad Caldés-San Carlos Madrid, Luis Bujanda-Donosti, Joaquín Cubiella-Ourense, EPICOLON)
Familial CRC type X: exome sequencing

28 VARIANTS CONFIRMED BY SANGER SEQUENCING

Segregation analysis in additional affected family members (CRC and AA)

17 variants with correct segregation
2 variants with correct CRC but not AA segregation
9 variants with incorrect CRC segregation

FAM3 (I129, H432)

BMP4

FAM3 (I129, H432)

SMARCA4
c.295C>T (p.R99W)

<table>
<thead>
<tr>
<th>NAME</th>
<th>MUTATION</th>
<th>SEG CRC and AA</th>
<th>LOH</th>
<th>FUNCTION</th>
<th>OMIM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDKN1B</td>
<td>c.195G&gt;T (p.Q65H)</td>
<td>Y 4/4</td>
<td>Y</td>
<td>DNA damage response, induction of apoptosis, negative regulation of cell proliferation</td>
<td>600778 multiple endocrine neoplasia, hereditary prostate cancer</td>
</tr>
<tr>
<td>XRCC4</td>
<td>c.497_498delTG (p.V166Efs*3)</td>
<td>Y 2/2</td>
<td>Y</td>
<td>DNA ligation involved in DNA repair, double-strand break repair</td>
<td>194363 peripheral B-cell lymphoma</td>
</tr>
<tr>
<td>EPHX1</td>
<td>c.293G&gt;A (p.R98Q)</td>
<td>Y 2/2</td>
<td>Y</td>
<td>metabolism of xenobiotics by cytochrome P450</td>
<td>132810 lymphoproliferative disorder</td>
</tr>
<tr>
<td>NFKBIZ</td>
<td>c.2153_2154dupAT (p.<em>719Ifs</em>10)</td>
<td>Y 4/4</td>
<td>N</td>
<td>TNF-alpha/NF-kB signaling pathway</td>
<td>608004</td>
</tr>
<tr>
<td>SMARCA4</td>
<td>c.295C&gt;T (p.R99W)</td>
<td>Y 3/3</td>
<td>N</td>
<td>regulation of cell growth, regulation of mitotic cell cycle, chromatin remodeling</td>
<td>603254 rhabdoid tumor predisposition syndrome, SCCOHT(S)</td>
</tr>
<tr>
<td>BARD1</td>
<td>c.1811-2A&gt;G</td>
<td>Y 2/2</td>
<td>N</td>
<td>DNA repair, apoptosis, cell cycle arrest</td>
<td>601593 breast cancer susceptibility</td>
</tr>
<tr>
<td>BRCA2</td>
<td>c.7759C&gt;T (p.L2587F)</td>
<td>Y 2/2</td>
<td>N</td>
<td>double-strand break repair, DNA damage checkpoint</td>
<td>600185 familial breast and ovarian cancer susceptibility, pancreatic cancer susceptibility, Fanconi anemia</td>
</tr>
</tbody>
</table>
Colorectal cancer: epidemiology

- Sporadic: 69%
- Polyposis syndromes: 27%
- Lynch syndrome: 2%
- IBD: 1%
- Familial CRC: 1%

Piñol et al. Eur J Gastroent Hepatol 2004
Incidence of CRC according to their family history

Fuchs et al. NEJM 1994
Incidence of CRC in relatives of patients with CRC

Age at diagnosis of proband

- control
- > 55 years
- 45-54 years
- < 45 years

Cumulative incidence (%) vs. Age of relatives (years)

Colorectal cancer family risk

FDR: 1\textsuperscript{st} degree relative
SDR: 2\textsuperscript{nd} degree relative
TDR: 3\textsuperscript{rd} degree relative

Castells et al. Gastroenterology 2009
Familial CRC screening

1st degree

Number of affected relatives

≥ 2

Colonoscopy / 5 years (beginning: 40 year-old or 10 years earlier)

< 60 year-old

Colonoscopy / 5 years (beginning: 40 year-old or 10 years earlier)

≥ 60 year-old

FOBT / 1-2 years and/or sigmoidoscopy / 5 years, or colonoscopy / 10 years (beginning: 40 year-old)

Affected relative

1

Age at diagnosis
<table>
<thead>
<tr>
<th>SNP</th>
<th>Region</th>
<th>Gene</th>
<th>cases/controls</th>
<th>OR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs6983267</td>
<td>8q24.21</td>
<td>MYC</td>
<td>8,264/6,206</td>
<td>1.21 (1.15-1.27)</td>
</tr>
<tr>
<td>rs4939827</td>
<td>18q21.1</td>
<td>SMAD7</td>
<td>8,413/6,949</td>
<td>1.18 (1.12-1.23)</td>
</tr>
<tr>
<td>rs16892766</td>
<td>8q23.3</td>
<td>EIF3H</td>
<td>18,831/18,540</td>
<td>1.25 (1.19-1.32)</td>
</tr>
<tr>
<td>rs3802842</td>
<td>11q23.1</td>
<td>?</td>
<td>14,500/13,294</td>
<td>1.12 (1.07-1.17)</td>
</tr>
<tr>
<td>rs4779584</td>
<td>15q13.3</td>
<td>GREM1</td>
<td>7,922/6,741</td>
<td>1.26 (1.19-1.34)</td>
</tr>
<tr>
<td>rs10795668</td>
<td>10p14</td>
<td>?</td>
<td>18,831/18,540</td>
<td>1.12 (1.10-1.16)</td>
</tr>
<tr>
<td>rs4444235</td>
<td>18q21.1</td>
<td>BMP4</td>
<td>20,288/20,971</td>
<td>1.11 (1.08-1.15)</td>
</tr>
<tr>
<td>rs9929218</td>
<td>16q22.1</td>
<td>CDH1</td>
<td>20,288/20,971</td>
<td>1.10 (1.06-1.12)</td>
</tr>
<tr>
<td>rs10411210</td>
<td>19q13</td>
<td>RHNCP2</td>
<td>20,288/20,971</td>
<td>1.15 (1.10-1.20)</td>
</tr>
<tr>
<td>rs961253</td>
<td>20p12.3</td>
<td>BMP2</td>
<td>20,288/20,971</td>
<td>1.12 (1.08-1.16)</td>
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<tr>
<td>rs6691170</td>
<td>1q41</td>
<td>DUSP10</td>
<td>18,185/20,197</td>
<td>1.06 (1.03-1.09)</td>
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<tr>
<td>rs10936599</td>
<td>3q26.2</td>
<td>TERC</td>
<td>18,185/20,197</td>
<td>0.93 (0.91-0.96)</td>
</tr>
<tr>
<td>rs11169552</td>
<td>12q13.3</td>
<td>?</td>
<td>18,185/20,197</td>
<td>0.92 (0.90-0.95)</td>
</tr>
<tr>
<td>rs4925386</td>
<td>20q13.33</td>
<td>LAMAS</td>
<td>18,185/20,197</td>
<td>0.93 (0.91-0.95)</td>
</tr>
<tr>
<td>rs1957636</td>
<td>14q22.2</td>
<td>BMP4</td>
<td>24,910/26,275</td>
<td>1.08 (1.05-1.11)</td>
</tr>
<tr>
<td>rs4813802</td>
<td>20p12.3</td>
<td>BMP2</td>
<td>24,910/26,275</td>
<td>1.09 (1.06-1.12)</td>
</tr>
<tr>
<td>rs2736100</td>
<td>5p15.33</td>
<td>TERT</td>
<td>16,039/16,430</td>
<td>1.07 (1.04-1.10)</td>
</tr>
<tr>
<td>rs1323111</td>
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<td>CDKN1A</td>
<td>21,096/16,430</td>
<td>1.16 (1.10-1.22)</td>
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<tr>
<td>rs3824999</td>
<td>11q34</td>
<td>POLD3</td>
<td>21,096/16,430</td>
<td>1.16 (1.10-1.22)</td>
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<td>rs5934683</td>
<td>5q31.1</td>
<td>SHROOM2</td>
<td>21,096/16,430</td>
<td>1.07 (1.04-1.10)</td>
</tr>
<tr>
<td>rs1208929</td>
<td>13p33</td>
<td>SLCSA9</td>
<td>2,317/2,447</td>
<td>0.86 (0.78-0.95)</td>
</tr>
<tr>
<td>rs11987193</td>
<td>8p12</td>
<td>DUSP4</td>
<td>2,317/2,447</td>
<td>0.78 (0.70-0.87)</td>
</tr>
<tr>
<td>rs10774214</td>
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<td>CCND2</td>
<td>11,870/14,190</td>
<td>1.04 (1.00-1.09)</td>
</tr>
<tr>
<td>rs6471614</td>
<td>5q31.1</td>
<td>PITX1</td>
<td>11,870/14,190</td>
<td>1.07 (1.02-1.11)</td>
</tr>
<tr>
<td>rs2423279</td>
<td>20p12.3</td>
<td>HAQ1</td>
<td>11,870/14,190</td>
<td>1.07 (1.03-1.12)</td>
</tr>
<tr>
<td>rs11903757</td>
<td>12p13.32</td>
<td>CCND2</td>
<td>15,752/21,771</td>
<td>1.16 (1.10-1.22)</td>
</tr>
<tr>
<td>rs6471614</td>
<td>5q31.1</td>
<td>PITX1</td>
<td>15,752/21,771</td>
<td>1.07 (1.02-1.11)</td>
</tr>
<tr>
<td>rs10911251</td>
<td>14q25.3</td>
<td>LAMC1</td>
<td>15,752/21,771</td>
<td>1.06 (1.03-1.15)</td>
</tr>
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<td>rs3217810</td>
<td>12p13.32</td>
<td>CCND2</td>
<td>13,654/16,022</td>
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<td>rs3217901</td>
<td>12p13.32</td>
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<td>15,752/21,771</td>
<td>1.16 (1.10-1.22)</td>
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<tr>
<td>rs59336</td>
<td>12q24.21</td>
<td>TBX3</td>
<td>15,752/21,771</td>
<td>1.06 (1.03-1.13)</td>
</tr>
<tr>
<td>rs704017</td>
<td>10q22.3</td>
<td>ZMIZ1-AS1</td>
<td>14,963/31,945</td>
<td>1.10 (1.06-1.13)</td>
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<tr>
<td>rs11196172</td>
<td>10q25.2</td>
<td>TCF7L2</td>
<td>14,963/31,945</td>
<td>1.14 (1.10-1.18)</td>
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<tr>
<td>rs174537</td>
<td>11q12.2</td>
<td>MYRF</td>
<td>14,963/31,945</td>
<td>1.16 (1.12-1.19)</td>
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<tr>
<td>rs4246215</td>
<td>11q12.2</td>
<td>FEN1</td>
<td>14,963/31,945</td>
<td>1.15 (1.12-1.19)</td>
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<tr>
<td>rs174550</td>
<td>11q12.2</td>
<td>FADS1</td>
<td>14,963/31,945</td>
<td>1.15 (1.12-1.19)</td>
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<td>rs1535</td>
<td>11q12.2</td>
<td>FADS2</td>
<td>14,963/31,945</td>
<td>1.15 (1.12-1.19)</td>
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<tr>
<td>rs10849432</td>
<td>12p13.31</td>
<td>CD9</td>
<td>14,963/31,945</td>
<td>1.14 (1.09-1.18)</td>
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<tr>
<td>rs12603526</td>
<td>17p13.3</td>
<td>NXXN</td>
<td>14,963/31,945</td>
<td>1.10 (1.06-1.14)</td>
</tr>
<tr>
<td>rs1800469</td>
<td>19q13.2</td>
<td>TGFB1</td>
<td>14,963/31,945</td>
<td>1.09 (1.06-1.12)</td>
</tr>
<tr>
<td>rs2247114</td>
<td>19q13.2</td>
<td>B9D2</td>
<td>14,963/31,945</td>
<td>1.09 (1.06-1.12)</td>
</tr>
<tr>
<td>rs1035209</td>
<td>10q24.2</td>
<td>ABCC2/MRP2</td>
<td>4,037/15,937</td>
<td>1.12 (1.08-1.16)</td>
</tr>
</tbody>
</table>

41 variants for CRC genetic susceptibility in 37 loci

- Common, low-penetrance CRC genetic components
- ~10% of the estimated genetic susceptibility

Houlston et al. Nat Genet 2008
Tenesa et al. Nat Rev Genet 2009
Houlston et al. Nat Genet 2010
Tomlinson et al. PLoS Genet 2011
Kinnersley et al. Br J Cancer 2012
Fernández-Rozadilla et al. BMC Genomics 2013
Jia et al. Nat Genet. 2013
Peters et al. Gastroenterology 2013
Zhang et al. Nat Genet 2014
Whiffin et al. Hum Mol Genet 2014
Cumulative impact of 10 common genetic variants on colorectal cancer risk

Dunlop et al. Gut 2012
## Genotype – phenotype correlation of susceptibility variants in CRC patients

<table>
<thead>
<tr>
<th>SNP</th>
<th>Chromosomal region</th>
<th>Gene</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs16892766</td>
<td>8q23.3</td>
<td>EIF3H</td>
<td>Tomlinson et al.</td>
</tr>
<tr>
<td>rs10795668</td>
<td>10p14</td>
<td></td>
<td>Tomlinson et al.</td>
</tr>
<tr>
<td>rs3802842</td>
<td>11q23.1</td>
<td></td>
<td>Tenesa et al. Pittman et al.</td>
</tr>
<tr>
<td>rs4779584</td>
<td>15q13.3</td>
<td>CRAC1 (HMPS)</td>
<td>Jaeger et al.</td>
</tr>
<tr>
<td>rs4939827</td>
<td>18q21.1</td>
<td>SMAD7</td>
<td>Broderick et al. Tenesa et al.</td>
</tr>
<tr>
<td>rs4444235</td>
<td>14q22.2</td>
<td>BMP4</td>
<td>Tomlinson et al.</td>
</tr>
<tr>
<td>rs9929218</td>
<td>16q22.1</td>
<td>CDH1</td>
<td>Tomlinson et al.</td>
</tr>
<tr>
<td>rs10411210</td>
<td>19q13</td>
<td>RHPN2</td>
<td>Tomlinson et al.</td>
</tr>
<tr>
<td>rs961253</td>
<td>20p12.3</td>
<td></td>
<td>Tomlinson et al.</td>
</tr>
</tbody>
</table>

Abulí et al. Gastroenterology 2010
Genotype – phenotype correlation of susceptibility variants in CRC patients

Abulí et al. Gastroenterology 2010

TNM stage

Personal history of colorectal adenomas

Family history of CRC

1.48 (1.15-1.90)

1.39 (1.11-1.72)

2.04 (1.35-3.03)
Acknowledgements

EPICOLON Consortium

COLONPREV Investigators

EPICOLON Consortium
Clinical management of polyposis and non-polyposis syndromes

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Suspected Lynch syndrome

Germline analysis: 25-gene, NGS panel

- 1260 participants
  - 100% personal Hx LS-associated cancer
  - 74% family Hx LS-associated cancer
  - 88% fulfilled NCCN criteria for LS testing

- Lynch mutation only (N = 111) 61%
- Both Lynch and non-Lynch mutation (N = 3) 2%
- Non-Lynch mutation only (N = 68) 37%

- LS mutation: 114 patients (9.0%)
- Non-LS mutation: 71 patients (5.6%)
  - High-penetrance genes: 24 (1.9%)
  - VUS: 479 patients (38.0%)

Yurgelun et al. Gastroenterology 2015