Post-colonoscopy colorectal cancers in Lynch syndrome

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Lynch syndrome

- **Most common hereditary CRC syndrome:** 3% of all colorectal cancers
- **Cause:**
  - Germline mutations in the MMR genes (*MLH1/MSH2/MSH6/PMS2*) or Epcam
  - Autosomal dominant pattern of inheritance (50% probability of transmission)
- **Phenotype:**
  - High risk for CRC (30-80%) and other extracolonic tumors
  - Tumors display mismatch repair deficiency
- **Prevalence in general population:** UNDERDIAGNOSIS is the main issue!

**Estimated population carrier frequency for MMR genes**

<table>
<thead>
<tr>
<th>Gene</th>
<th>1 in...</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>1,946</td>
<td>1,480-2,564</td>
</tr>
<tr>
<td>MSH2</td>
<td>2,841</td>
<td>2,101-3,846</td>
</tr>
<tr>
<td>MSH6</td>
<td>758</td>
<td>509-1,126</td>
</tr>
<tr>
<td>PMS2</td>
<td>714</td>
<td>480-1,062</td>
</tr>
<tr>
<td>Any MMR gene</td>
<td>279</td>
<td>192-403</td>
</tr>
</tbody>
</table>

Win AK et al. CEBP 2017
CRC prevention: colonoscopy

**Goals of colonoscopy:**
- **Reduce incidence**: early detection + resection (precursors)
- **Reduce mortality**: early detection (precursors + localized CRC)

**Incidence**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrigoni et al. 2004</td>
<td>2 199</td>
<td>5 132</td>
<td>0.26</td>
<td>[0.05, 1.35]</td>
</tr>
<tr>
<td>Jablonska et al. 1995</td>
<td>9 364</td>
<td>146 239</td>
<td>0.02</td>
<td>[0.01, 0.03]</td>
</tr>
<tr>
<td>Jarvinen et al. 2000</td>
<td>6 133</td>
<td>17 119</td>
<td>0.28</td>
<td>[0.11, 0.75]</td>
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<tr>
<td>Stuckless et al. 2012</td>
<td>28 152</td>
<td>116 170</td>
<td>0.11</td>
<td>[0.06, 0.18]</td>
</tr>
<tr>
<td>Stupart et al. 2009</td>
<td>14 129</td>
<td>13 49</td>
<td>0.34</td>
<td>[0.15, 0.78]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>977</strong></td>
<td><strong>709 100.0%</strong></td>
<td><strong>0.13</strong></td>
<td><strong>[0.04, 0.41]</strong></td>
</tr>
</tbody>
</table>

**Mortality**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Events Total</th>
<th>Control Events Total</th>
<th>Weight</th>
<th>Odds ratio M-H, random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrigoni et al. 2004</td>
<td>1 199</td>
<td>1 132</td>
<td>0.66</td>
<td>[0.04, 10.67]</td>
</tr>
<tr>
<td>Jablonska et al. 1995</td>
<td>0 364</td>
<td>84 239</td>
<td>0.00</td>
<td>[0.00, 0.04]</td>
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<tr>
<td>Jarvinen et al. 2000</td>
<td>0 133</td>
<td>9 119</td>
<td>0.04</td>
<td>[0.00, 0.76]</td>
</tr>
<tr>
<td>Stupart et al. 2009</td>
<td>3 129</td>
<td>6 49</td>
<td>0.17</td>
<td>[0.04, 0.71]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>825</strong></td>
<td><strong>539 100.0%</strong></td>
<td><strong>0.06</strong></td>
<td><strong>[0.00, 0.93]</strong></td>
</tr>
</tbody>
</table>

**OR=0.13 (0.04-0.41)**

**OR=0.06 (0.0-0.93)**

Ladabaum et al. Gastro 2015
Incident vs PCCRC

INCIDENT COLORECTAL CANCER (=PCCRC)
All CRC detected under colonoscopy screening/surveillance

INTERVAL CANCER
CRC detected before recommended screening/surveillance interval

PCCRC subcategories

<table>
<thead>
<tr>
<th>Interval type</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected before recommended screening/surveillance interval</td>
<td>Detected at recommended screening/surveillance interval</td>
<td>Detected after recommended screening/surveillance interval</td>
<td>Where no screening/surveillance interval had been recommended</td>
</tr>
</tbody>
</table>

Rutter M. Gastroenterology 2018
Incident CRC under surveillance colonoscopy


35% at age 60

Vasen et al. Gastro 2010

6% after 10 y f-u

Engel et al. Gastro 2018

8.4% after 10 y f-u

At age 70 y-o close to 45%

Moller P et al. Gut 2017

Moller P et al. Gut 2018
Incident CRC under surveillance colonoscopy

Conclusions: The hypothesis that the high incidence of CRC in path_MLH1 carriers was caused by a higher incidence in the Finnish series was not valid. We discuss whether the results were influenced by methodological shortcomings in our study or whether the assumption that a shorter interval between colonoscopies leads to a lower CRC incidence may be wrong. This second possibility is intriguing, because it suggests the dogma that CRC in path_MLH1 carriers develops from polyps that can be detected at colonoscopy and removed to prevent CRC may be erroneous. In view of the excellent 10-year overall survival in the Finnish and non-Finnish series we remain strong advocates of current surveillance practices for those with LS pending studies that will inform new recommendations on the best surveillance interval.

Crypts of a macroscopically normal gut surface. Thus, one may speculate that MMR mutation carriers are capable of producing CRC not only inside an adenoma but also independently of a macroscopically visible adenoma, which in turn may rise cancer-associated mortality, the high frequency of interval cancers in patients under regular colonoscopic surveillance with polypectomy suggests that a significant proportion of colorectal lesions are undetectable by colonoscopy and subsequently manifest as cancer within surveillance intervals.

Engel et al. Gastro 2018
Moller P et al. Gut 2017
Moller P et al. Gut 2018
CRC prevention in Lynch syndrome

Colonoscopy has reached its limits!

Are you doing it right?

Epidemiologist/Geneticist

Gastroenterologist
What do we know about CRC in LS?

- **Adenoma** is the main precursor, with **rapid progression to carcinoma.** Dwell-time 35.2±22.3 months for CRC (Edelstein et al. CGH 2011). >2/3 CRC occur in the proximal colon.

- **Serrated lesions** prevalence is comparable with the general population (Vleugels JLA et al. Gastro Endoscopy 2018), and do not display MMR deficiency.

- **MMR deficiency** is present in around 75% of adenomas from LS patients (Ahadova et al. IJC 2018), more frequently in the advanced ones (MMR has been seen as a non-initiating event that may accelerate progression to cancer).

- **MMR deficient crypt foci** (colonic crypts with lack of protein expression) exist in the apparently normal colon (Kloor M et al. Lancet Oncol 2012): main precursors??

  - Proximal location
  - Non-polypoid appearance: OR= 3.6 95%CI 1.9-6.8 p<0.001
  - Proximal non-polypoid appearance: OR=6.9 95%CI 2.9-16.4 p<0.001
  - Adenomas containing HGD > frequently non-polypoid
  - Overall, features that makes them difficult to identify....
Model of CRC carcinogenesis in LS

Normal mucosa -> Adenoma MMR proficient

ACF MMR deficient

<3 years

Adenoma MMR proficient

Adenoma MMR deficient

Carcinoma

“non-polypoid pathway”

“invisible lesions”

Adapted from Ahadova et al. IJC 2018
Main cause of incident CRC during surveillance? Quality of colonoscopy vs. “invisible pathway”

- **Unclear which factor contribute the most** to the development of incident CRC in LS

  Likely cause of interval CRC in screening colonoscopies

  - Missed lesions
  - Inadequate exam/surveillance
  - Incomplete resection
  - New lesions

  Robertson. Gut 2013
  Le Clerq. Gut 2014

- **Understanding** how LS cancers arise will help to more effectively prevent CRC

- **Most studies focused on incidence of CRC in large cohorts of Lynch syndrome patients under surveillance have not focused on colonoscopy QUALITY**
Quality in colonoscopy: 7 domains

- Detection and resection of lesions is highly variable among endoscopists.
- ADR → inverse correlation with interval cancer INCIDENCE and MORTALITY.

Kaminski et al. Endoscopy 2017
Kahi et al. CGH 2011
Pohl et al. Gastroenterology 2013
Kaminski et al. NEJM 2010
Corley et al. NEJM 2014
Evidence of quality issues in LS surveillance

- **Completeness of colonoscopy**
  - Up to 30% of incident CRC in LS had either incomplete colonoscopy or missing info (Dutch registry)
  - Up to 30% of LS colonoscopies in LS are either incomplete or info is missing (Manchester Familial CRC registry)

- **Bowel preparation**
  - Up to 50% of incident CRC in LS, previous colonoscopy had either missing info or poor prep (Dutch registry)
  - Up to 25% of LS colonoscopies in LS have either poor prep or missing info (Manchester Familial CRC registry; Specialized French Network)

- **Surveillance interval**
  - Up to 40% of LS have inappropriate surveillance (Manchester Familial CRC Registry: 32%; US Cancer Genetic Clinics (Stoffel et al. Am J Gastro 2010): 27%; Specialized French network: 37.6% of patients)
  - PLSD: 69% of incident CRC had an interval between last colonoscopy and CRC >2 years

Based on these data, it is likely that a meaningful proportion of colonoscopies in Lynch syndrome patients have poor quality....

Argillander TE et al. UEGJ 2018; Sanchez et al. DDW 2018
Haanstra JF et al. Int J Colorectal Dis 2013
Perrod et al. Therap Advances in Gastro 2018
M. W. J. van Vuurt van Pinxteren et al. Familial Cancer 2012
Newton et al. Colorectal Disease 2014
Stoffel et al. Am J Gastro 2010
Incidence of CRC in Lynch syndrome healthy carriers under colonoscopy screening (n=538)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cumulative incidence at the age of 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1</td>
<td>13.8% (95%CI:5.9-30.3%)</td>
</tr>
<tr>
<td>MSH2</td>
<td>18.5% (95%CI: 8.8-36.4%)</td>
</tr>
<tr>
<td>MSH6</td>
<td>1% (95%CI: 0.15-7.1%)</td>
</tr>
</tbody>
</table>

Sanchez et al. DDW2018
<table>
<thead>
<tr>
<th></th>
<th>Gene</th>
<th>Gender</th>
<th>CRC Age</th>
<th>TNM</th>
<th>Nº of previous colonoscopies</th>
<th>Age 1st colonoscopy</th>
<th>Follow up (months)</th>
<th>Colonoscopy previous to CRC</th>
<th>Time since previous colonoscopy (months)</th>
<th>Complete</th>
<th>Adequate Bowel Cleansing</th>
<th>Result</th>
<th>Cromo-endoscopy/High definition</th>
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</thead>
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<tr>
<td>1</td>
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<td>Female</td>
<td>41</td>
<td>T1N0MX</td>
<td>1</td>
<td>37</td>
<td>247.46</td>
<td>42</td>
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<td>Yes</td>
<td>Normal</td>
<td>Polyps</td>
<td>No</td>
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<td>Male</td>
<td>44</td>
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<td>20</td>
<td>297.86</td>
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<tr>
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<td>Male</td>
<td>55</td>
<td>T1N0Mx</td>
<td>7</td>
<td>43</td>
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<td>33</td>
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<td>5</td>
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<td>Female</td>
<td>64</td>
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<td>63</td>
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<td>6</td>
<td>MLH1</td>
<td>Female</td>
<td>58</td>
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<td>49</td>
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<td>Yes</td>
<td>Polyps</td>
<td>No</td>
<td>No</td>
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<tr>
<td>7</td>
<td>MSH2</td>
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<td>59</td>
<td>T4N0M0</td>
<td>4</td>
<td>53</td>
<td>83.68</td>
<td>10</td>
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<td>8</td>
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<td>45</td>
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<td>55</td>
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<td>5</td>
<td>49</td>
<td>154.12</td>
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<td>10</td>
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<td>129.02</td>
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<tr>
<td>12</td>
<td>MSH2</td>
<td>Male</td>
<td>48</td>
<td>T3N2Mx</td>
<td>4</td>
<td>42</td>
<td>83.42</td>
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<td>No</td>
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<td>35</td>
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<td>30</td>
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<tr>
<td>14</td>
<td>MLH1</td>
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<td>177.61</td>
<td>42</td>
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<td>Yes</td>
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<td>15</td>
<td>MSH2</td>
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<td>43</td>
<td>Unknown</td>
<td>1</td>
<td>42</td>
<td>31.82</td>
<td>15</td>
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<td>Unknown</td>
<td>2</td>
<td>59</td>
<td>85.42</td>
<td>42</td>
<td>Yes</td>
<td>Yes</td>
<td>Normal</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Quality issues (longer interval, poor bowel prep) were present in 7/17 (41%) incident CRCs; 15/17 (88%) if we include lack of information on the reports.
Appropriate surveillance interval?

- No international consensus on the appropriate interval (1-3 y): *are shorter intervals associated with lower CRC incidence?*

In the Netherlands one of the largest series of HNPCC families (51 families including 394 first-degree relatives, mean follow-up 5 years) participates in a nationwide surveillance programme that is financially supported by the government. An unexpectedly high occurrence of advanced cancers was detected within 3.5 years after a negative screening examination (table). Another

<table>
<thead>
<tr>
<th>Patient*/sex</th>
<th>Age at diagnosis (yr)</th>
<th>Location of tumour</th>
<th>Stage (Dukes)</th>
<th>Previous negative examination</th>
<th>Interval</th>
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</thead>
<tbody>
<tr>
<td>1/M</td>
<td>46</td>
<td>R</td>
<td>C</td>
<td>Colonoscopy</td>
<td>2 yr, 7 mo</td>
</tr>
<tr>
<td>2/F</td>
<td>46</td>
<td>R</td>
<td>B</td>
<td>Colonoscopy</td>
<td>2 yr</td>
</tr>
<tr>
<td>3/F/F</td>
<td>41</td>
<td>R</td>
<td>C</td>
<td>Barium enema</td>
<td>2 yr, 6 mo</td>
</tr>
<tr>
<td>4/M</td>
<td>40</td>
<td>R</td>
<td>B</td>
<td>Colonoscopy</td>
<td>3 yr, 6 mo</td>
</tr>
<tr>
<td>5/F</td>
<td>53</td>
<td>R</td>
<td>B</td>
<td>Colonoscopy</td>
<td>3 yr</td>
</tr>
<tr>
<td>6/F</td>
<td>51</td>
<td>R</td>
<td>C</td>
<td>Colonoscopy</td>
<td>2 yr, 2 mo</td>
</tr>
</tbody>
</table>

Engel C et al. Gastroenterology 2018

16,327 colonoscopic examinations (1984-2015)
- German HNPCC Consortium (n=1,027) → 1 year interval
- Dutch Lynch syndrome Registry (n=806) → 1-2 years interval
- Finnish Lynch syndrome Registry (n=914) → 2-3 years interval

Median of colonoscopy intervals was calculated

COX regression analysis to identify factors associated with CRC risk
Surveillance interval

Engel C et al. Gastroenterology 2018
Surveillance interval

No difference in **TNM stages** (stage IV: 1% Germany, 3% Dutch; 1% Finnish)

**Stage IV** not related with interval since last colonoscopy (overall....not case by case analysis)
Surveillance interval

Male sex
Age >40 y at index colonoscopy
Adenoma at index colonoscopy
MLH1/MSH2 mutation carriers

No difference in **TNM stages** (stage IV: 1% Germany, 3% Dutch; 1% Finnish)

**Stage IV** not related with interval since last colonoscopy (overall....not case by case analysis)
Why interval does not matter?

- Shorter interval leads to slow progression.
- Short interval results in slow progression.

<table>
<thead>
<tr>
<th>Initiation</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>Stage I-III</td>
</tr>
</tbody>
</table>

1 year  | 2 year  | 3 year  |

- Short interval results in slow progression.
Chromoendoscopy in Lynch syndrome

- **Adenoma miss rate** in colonoscopy is 2-26% depending on size (Van Rijn *et al.*, *Am J Gastroenterol* 2006)
- Adenoma miss rate in Lynch syndrome: up to 55% (Stoffel *et al.* *CPR* 2008)

CE is used to **improve detection** and **characterization** of subtle colorectal lesions

Enhance visualization of surface structures and vascular pattern
- Dye-based CE (indigo carmine)
- Virtual: NBI (Olympus), AFE, FICE (Fuji), i-Scan (Pentax), LCI (Fuji), BLI (Fuji)

CE with indigo-carmine increases the detection of lesions (OR of at least 1 neoplastic lesion OR=1.53; 95%CI 1.3-1.8) (Brown *et al.* Cochrane Review).
CE with IC in Lynch syndrome

Non-randomized back-to-back

WLE

CE > WLE
ADR
Number adenomas
Number of flat adenomas
Adenomas proximal colon
Longer procedure

CE

Randomized parallel back-to-back

WLE

CE = WLE (>20min)
ADR
Longer procedure

Hurlstone et al. 2005
Lecomte et al. 2005
Rahmi et al. 2015
Hüneburg et al. 2009

CE with IC in Lynch syndrome

**RCT parallel**

**CE (prox colon)=WLE**

**ADR**

**CE longer procedure**

Haanstra J et al. UEGW2017

**N=123**

**N=118**

**T0**

**WLE**

**CE**

**T1**

**CE=WLE**

**ADR**

**CE longer procedure**

**CE>WLE serrated lesions <5mm**

Rivero et al. UEG 2018

(Wednesday presentation)
Virtual CE in Lynch syndrome

Non-randomized back-to-back

NBI > WLE (SD)
ADR
Number adenomas
Number of flat adenomas

WLE

NBI

Patients with >1 adenoma
Number adenomas
Number of flat adenomas
(regardless of inspection time for i-Scan)

Randomized cross-over back-to-back

Bisschops R et al. Endoscopy 2017
Ramsoekh et al. Gut 2010

Van de Wetering et al. EJG&H 2018

Chromoendoscopy in LS: summary

• Three RCT using chromoendoscopy with IC suggest a very limited clinical benefit in terms of ADR for considerable extra effort, which may not translate into improved cancer prevention.

• Evidence about virtual chromoendoscopy is still limited
Conclusions (I)

- Successful CRC prevention is linked to **Key Performance Indicators (KPI)** in sporadic patients (Bowel prep, cecal intubation, ADR).

- **Quality issues** in colonoscopy surveillance in Lynch syndrome carriers exist and may explain at least in part the cause of incident CRC during surveillance.

- **Optimization** of colonoscopy performance could further **reduce the risk during surveillance**.
  
  ✓ Need for coordinated management (referring physician and endoscopy)
  ✓ Dedicated high-risk clinics or networks are more likely to follow high quality standards in high-risk patients
  ✓ Colonoscopy quality should be at least reach (if not exceed) the KPIs required for sporadic colonoscopy.
  ✓ Colonoscopy performed by high detectors with high-proficiency in the detection and resection of non-polypoid lesions.
  ✓ Chromoendoscopy with IC → as quality of colonoscopy improves.....probably smaller clinical effect at cost of prolonged procedural time
Conclusions (II)

Personalized screening recommendations.....
- **Quality!**
- Gender
- Age
- Previous history of CRC
- MLH1/MSH2 vs MSH6/PMS2
- Previous history of adenomas