Supplementary material: Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: ESGE Guideline

Appendix 1s: Topics and key questions

<table>
<thead>
<tr>
<th>1. Statements regarding Lynch syndrome</th>
<th>Task forces (leads in bold)</th>
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<tr>
<td>What are the quality standards for colonoscopy in Lynch syndrome patients?</td>
<td>Monique van Leerdam/Victorine Roos</td>
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<td>What is the appropriate age to start colonoscopy surveillance in Lynch syndrome patients?</td>
<td>Maria Pellisé</td>
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<td>What is the optimal interval of colonoscopy surveillance in Lynch syndrome patients?</td>
<td>Michal Kaminski/Maria Rupinska</td>
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<td>What is the role of advanced imaging techniques in colonoscopy surveillance in Lynch syndrome patients?</td>
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<td>What is the role of gastric surveillance (including H. Pylori eradication) in Lynch syndrome patients?</td>
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<td>Is there a role for small-bowel surveillance in Lynch syndrome patients?</td>
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<thead>
<tr>
<th>2. Statements regarding familial colorectal cancer</th>
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<tbody>
<tr>
<td>What is the influence of family history on relative and absolute risk of developing CRC?</td>
<td>Rodrigo Jover</td>
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<tr>
<td>Does colonoscopy reduce the CRC incidence and/or mortality in people with family history of CRC?</td>
<td>Monique van Leerdam/Victorine Roos</td>
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<td>What is the optimal time interval for screening colonoscopies in people with family history of CRC?</td>
<td>Evelien Dekker</td>
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<tr>
<td>What is the optimal age to start screening colonoscopy in people with family history of CRC?</td>
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</table>
## Table 1s. Summary table: Starting age for colonoscopy surveillance in Lynch syndrome

<table>
<thead>
<tr>
<th>First Author [Ref in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study sample and mutation distribution</th>
<th>Male/ female ratio</th>
<th>Age</th>
<th>Intervention</th>
<th>Comparision</th>
<th>Follow-up time</th>
<th>Outcomes: cumulative CRC risk</th>
<th>Outcomes: CRC risk by age</th>
<th>Index case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hendriks [51]</td>
<td>2004</td>
<td>Register study</td>
<td>146 MSH6</td>
<td>59/87</td>
<td>NR</td>
<td>NR</td>
<td>MLH1/ MSH2 mutation carriers</td>
<td>NR</td>
<td>Mean CRC risk: MLH1; MSH2; MSH6 At 30 years, men: 4.1% (0.1-7.9); 2.0% (0-4.4); 1.7% (0-5.0) At 50 years, men: 31% (19-41); 39% (28-48); 63% (49-73) At 70 years, men: 65% (39-80); 63% (49-73); 69% (42-83) At 30 years, women: 4.3% (0.9-7.7); 0%; 0% At 50 years, women: 26% (17-34); 30% (18-40); 10% (2.4-17) At 70 years, women: 53% (33-66); 68% (43-82); 30% (12-44)</td>
<td>The mean age at CRC diagnosis males; females: MLH1: 43 years; 43 years. MSH2: 44 years; 44 years. MSH6: 55 (26-84) years; 57 (41-81) years.</td>
<td>Included</td>
</tr>
<tr>
<td>Plaschke [52]</td>
<td>2004</td>
<td>Register study</td>
<td>396 MSH6</td>
<td>NR</td>
<td>NR</td>
<td>Colorectal surveillance every 1-2 years</td>
<td>1579 MLH1/ MSH2 mutation carriers</td>
<td>NR</td>
<td>Frequency CRC: MSH6: 61 MLH1/MSH2: 563</td>
<td>Median age of CRC onset: MSH6: 54 (51-56) years MLH1/MSH2: 44 (43-45) years</td>
<td>Included</td>
</tr>
<tr>
<td>Ramssoekh [14]</td>
<td>2009</td>
<td>Retrospective cohort study</td>
<td>70 MLH1, 67 MSH2, 109 MSH6.</td>
<td>92/154</td>
<td>At the time of mutation analysis: mean 49±16 years</td>
<td>Colorectal surveillance in 194/246 MMR mutation carriers</td>
<td>NA</td>
<td>Mean 7±4 years</td>
<td>At age 70 years males; females: MLH1: 78%; 57% MSH2: 57%; 52% MSH6: 54%; 30%</td>
<td>Median age of CRC onset: males; female: MLH1: 45 (33-63) years; 50 (25-79) years MSH2: 43 (20-51) years; 44 (29-82) years MSH6: 48 (32-84) years; 53 (34-61) years</td>
<td>Included</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Cases</td>
<td>Methods</td>
<td>Findings</td>
<td>Excluded</td>
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<tr>
<td>Vasen [28]</td>
<td>2010</td>
<td>Retrospective cohort study</td>
<td>290 MLH1, 328 MSH2, 127 MSH6.</td>
<td>308/437</td>
<td>Surveillance colonoscopy every 1-2 years</td>
<td>Mean 7.2 (0.4-13.7) years</td>
<td>CRC incidence males and females: &lt;40 years: 11/337 (3.3%) ≥40 years: 22/408 (5.4%)</td>
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<tr>
<td>Edelstein [17]</td>
<td>2011</td>
<td>Retrospective cohort study</td>
<td>30 MLH1, 24 MSH2.</td>
<td>21/33</td>
<td>Colonoscopy surveillance with interval of 1.7 ±1.2 years</td>
<td>Mean 9.3 years</td>
<td>Mean numbers of neoplastic lesions: 20-29 years: 1.3±0.5 30-39 years: 1.8±1.4 40-49 years: 2.2±1.8 50-59 years: 3.5±2.9 60-69 years: 5.3±5.1 70–79 years: 7.6±6.8</td>
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<tr>
<td>Lee [58]</td>
<td>2013</td>
<td>Retrospective cohort study</td>
<td>16 MSH6, 7 PMS2</td>
<td>NR</td>
<td>Mean age at CRC diagnosis: 48.5 (32-70) years in MSH6 and 40.7 (22-57) years in PMS2.</td>
<td>Included</td>
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<tr>
<td>Jenkins [54]</td>
<td>2015</td>
<td>Meta-analysis</td>
<td>508 MLH1 families, 606 MSH2 families.</td>
<td>NR</td>
<td>CRC incidence males; females: 20-29 years: 1.4%; 1.0% 30-39 years: 4.8%; 3.3% 40-49 years: 7.6%; 6.2% 50-59 years: 14.0%; 8.7% 60-69 years: 9.0%; 6.3% 70-79 years: 7.6%; 5.4%</td>
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<tr>
<td>Sanchez [53]</td>
<td>2017</td>
<td>Retrospective study of prospectively observed data</td>
<td>449 MLH1, 371 MSH2, 197 MSH6, 68 PMS2.</td>
<td>478/630</td>
<td>Mean age at inclusion was 45.2±15.</td>
<td>At age 70 years: MLH1: 25.6% (13.2-38.2) MSH2: 22.1% (11.3-35.1) MSH6: 6.3% (0-12.8) PMS2: 25.6% (13.2-38.2)</td>
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<tr>
<td>Ten Broeke [50]</td>
<td>2018</td>
<td>Multicenter, register study</td>
<td>513 PMS2</td>
<td>NR</td>
<td>At age 80 years males; females: PMS2: 13% (7.9-22); 12% (6.7-21%). General population: 6.6%; 4.7%.</td>
<td>Excluded</td>
<td></td>
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<tr>
<td>Lamba [55]</td>
<td>2019</td>
<td>Prospectively maintained national database</td>
<td>98 MLH1, 159 MSH2, 103 MSH6, 21 PMS2.</td>
<td>NR</td>
<td>Colonoscopy surveillance every 1-2 years from age 25</td>
<td>Median 4.43 (1-28) years</td>
<td>Mean age at CRC diagnosis: 54 years, 55.5% female.</td>
<td>Excluded</td>
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<tr>
<td>Moller [15,16]</td>
<td>2017; updated in 2018</td>
<td>Multicentre prospective study</td>
<td>1473 MLH1, 1060 MSH2, 462 MSH6 and 124 PMS2.</td>
<td>885/1057</td>
<td>Colonoscopy surveillance</td>
<td>NA</td>
<td>Mean 7.8 years</td>
<td>MLH1: 46%</td>
<td>MSH2: 35%</td>
<td>MSH6: 49%</td>
<td>PMS2: 10%</td>
</tr>
</tbody>
</table>

Legend. NR, Not reported; CRC, colorectal cancer; MMR, mismatch repair; NA, Not Applicable.
### Table 2s. Summary table: Colonoscopy surveillance intervals in Lynch syndrome

<table>
<thead>
<tr>
<th>First author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study sample and mutation distribution</th>
<th>Male/female per subgroup</th>
<th>Age (mean±SD, or median [range]) per subgroup</th>
<th>Intervention: colonoscopy interval</th>
<th>Comparison</th>
<th>Outcome/ Findings</th>
</tr>
</thead>
</table>
Non-surveillance group: CRC incidence 19 (16 %, P= 0.014). CRC rate mutation positive subjects: 41% (P= 0.02). CRC relates deaths: 9. Overall death rates: 26 subjects (p= 0.03) and 12 in mutation-positive subjects (P=0.05). |
| de Vos tot Nederveen Cappel [27] | 2002                | Retrospective registry based cohort study | 199 LS with proven mutation.  
1. No CRC before index colonoscopy.  
2. After partial or segmental colectomy due to CRC. | NR | NR | Colonoscopy surveillance every 2-3 years.  
1. No CRC before index colonoscopy.  
2. After partial or segmental colectomy due to CRC | The 10-year cumulative risk of developing CRC:  
1. No CRC before index colonoscopy: 10.5 (95 percent confidence interval, 3.8-17.2).  
2. After partial colectomy due to CRC:  
15.7 (95 percent confidence interval, 4.1-27.3) and 3.4 percent after subtotal colectomy.  
12 CRC were detected in proven mutation carriers, 10 of them were early CRC (Dukes A&B). Number of CRCs within 1-2 years from colonoscopy: 4, number of CRCs beyond 2 years from colonoscopy: 8. |
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Number of HNPCC Families</th>
<th>Surveillance Group</th>
<th>Non-Surveillance Group</th>
<th>Age at Inclusion</th>
<th>CRC Diagnosis</th>
<th>Compliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mecklin*</td>
<td>2007</td>
<td>Retrospective registry based cohort study</td>
<td>Cohort (n=420)</td>
<td>NR</td>
<td>Median age at beginning of surveillance: 36.0 (20-74) years.</td>
<td>Colonoscopy surveillance every 2-3 years</td>
<td>NA</td>
<td>The cumulative risk of adenoma by age 60: 68% (95% confidence interval [CI], 50–80%) in men and 48% (95% CI, 29–62%) in women. The estimated cumulative risk up to age 60 years for the development of cancer found as a result of surveillance at an interval of 2–3 years was 35% (95% CI, 16–49%) in men and 22% (95% CI, 7%–34%) in women.</td>
</tr>
<tr>
<td>Stupart [57]</td>
<td>2009</td>
<td>Prospective cohort study</td>
<td>Surveillance group: 129. Non-surveillance group: 49</td>
<td>Surveillance group: 58/71. Non-surveillance group: 26/23</td>
<td>Colonoscopy every 2 years until age 30, annually thereafter.</td>
<td>Non-surveillance</td>
<td>Surveillance group: CRC diagnosis 14/129 (11%). Earlier CRC stage than in the non-surveillance group (P = 0.032). Death from CRC 3/129 (2%). Non-surveillance group: CRC diagnosis 13/49 (27%) (P = 0.019). Death from CRC: 6/49 (12%) (P = 0.021).</td>
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<tr>
<td>Engel [34]</td>
<td>2010</td>
<td>Prospective, multicenter, cohort study</td>
<td>HNPCC families (n=1126): CRC negative (n=402) versus CRC positive (n=724). 1. MUT group: Pathogenic germline mutation in a mismatch repair gene (633 families): 222 MLH1, 337 MSH2, 63 MSH6, 11 not tested. 2. MSI group: Without mutation but with microsatellite instability (296 families). 3. MSS group: Fulfilled Amsterdam criteria without microsatellite instability (117 families).</td>
<td>Total: 558/568</td>
<td>Age at inclusion: 44.0 (37.0–53.9) years.</td>
<td>CRC negative: 1 year interval</td>
<td>CRC positive: 1 year interval</td>
<td>Cumulative age-dependent CRC risk: CRC negative group at 60 years: similar in the MUT and MSI groups (P = .80; 23.0% at the age of 60 years for the 2 groups combined; 95% confidence interval [CI], 14.8%–31.2%), significantly lower in the MSS group (1.8% at the age of 60 years; 95% CI, 0.0%–5.1%; MUT/MSI vs MSS, P = .01). CRC positive group at 60 years: 23.7% (95% CI, 14.5%–32.9%) to develop a metachronous CRC within 20 years after the first CRC.</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Cohort Details</td>
<td>Lynch Syndrome Cohort</td>
<td>Non-Lynch Syndrome Cohort</td>
<td>Mean Age at Start Evaluation</td>
<td>Follow-up Period</td>
<td>CRC Risk</td>
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<tr>
<td>Vasen [28]</td>
<td>2010</td>
<td>Retrospective cohort study</td>
<td>Lynch syndrome cohort (n=745): 290 MLH1, 328 MSH2, 127 MSH6. Non-Lynch syndrome cohort (n=344).</td>
<td>Lynch syndrome cohort: 308/437. Non-Lynch syndrome cohort: 157/187</td>
<td></td>
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<td>1-2 year interval in Lynch syndrome</td>
<td>Cumulative CRC risk: 6% after 10 years of follow-up. CRC: MSH6 1/127, MLH1 19/290, MSH2 13/328 (univariate analysis: HR, 0.74 (95% CI: 0.52–1.04), P = 0.08). In the multivariate analysis, these variables remain borderline.</td>
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<tr>
<td>Stuckless [36]</td>
<td>2012</td>
<td>Retrospective cohort study</td>
<td>Cohort (n=322): Screened: 152 MSH2 Non-screened: 170 MSH2</td>
<td>54/98</td>
<td>Age at screening: Male: 36 years Female: 38 years</td>
<td>1-2 year interval</td>
<td>No screening</td>
<td>Screened versus non-screened group: Males: Interval CRC 41 (27%), median time from last screening 1.7 years. Median age to CRC: 58 years versus 47 years (p&lt;0.01). Median survival: 66 years versus 62 years (p=0.034). Females: Interval CRC 10 (15%), median time from last screening 2.1 years. Median age to CRC: 79 years versus 57 years (p&lt;0.01). Median survival: 80 years versus 63 years (p&lt;0.01).</td>
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<td>Haanstra [24]</td>
<td>2013</td>
<td>Retrospective, multicenter registry study</td>
<td>Cohort: 2,101 registered relatives (about 70% of them being proven carriers). In 29 LS patients (all proven mutation carriers), 31 interval cancers were detected within or at 24 months of previous colonoscopy between 1995 and 2011.</td>
<td>14/17</td>
<td>Age: 52.0 (34.9–73.3) years</td>
<td>Colonoscopy surveillance every 1-2 years starting at the age 20-25.</td>
<td>NA</td>
<td>Of all interval cancers, 77% were at local stage (T1-3N0Mx), 39% had a previous CRC. In 3 patients (9%) with an incomplete previous colonoscopy, CRC was located in the unexamined colon. In 6/9 patients with an adenoma during previous colonoscopy, the cancer was detected in the same colonic segment as the previously removed adenoma. 16/31 interval CRCs had unreported bowel preparation.</td>
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<tr>
<td>Newton [26]</td>
<td>2015</td>
<td>Retrospective, multicenter registry study</td>
<td>Screened population (n=227): 85 MLH1, 119 MSH2, 21 MSH6, 2 PMS2. Unscreened population (n=689).</td>
<td>NR</td>
<td>Colonoscopy at least every 2 years from the age of 25.</td>
<td>Unscreened population.</td>
<td>Cumulative incidence of CRC to the age of 70: Screened population: 25% (95% CI 17–32%) in the surveillance population. Unscreened population: 81% (95% CI 78–84%) (P &lt; 0.0001). Screened population: CRC diagnosis 19 (8.4%) after median surveillance of 4.4 years (8 among patients who had no prior CRC). All CRCs diagnosed within 2 years were early stage (A &amp; B); 2 CRCs were advanced (Dukes C) after 35 and 51</td>
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<tr>
<td>Author</td>
<td>Year</td>
<td>Study Type</td>
<td>Country</td>
<td>MLH1</td>
<td>MSH2</td>
<td>MSH6</td>
<td>PMS2</td>
<td>TASCD1</td>
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<td>Seppala [56]</td>
<td>2017</td>
<td>Prospective cohort</td>
<td>Finnish cohort: 505 MLH1. non-Finnish cohort: 439 MLH1.</td>
<td>Finnish cohort: 246/259. non-Finnish cohort: 184/255.</td>
<td>Age at inclusion: Finnish cohort: 35.2 ± 12.1 non-Finnish cohort: 36.1±11.0</td>
<td>Finnish: 3 year interval</td>
<td>non-Finnish: 1-2 year interval</td>
<td>Finnish cohort: Cumulative CRC incidences at 70 years: 41% for males and 36% for females. Time from last colonoscopy to CRC: 32.7 months. Ten-year overall survival after CRC: 88%. non-Finnish cohort: Cumulative CRC incidence at 70 years: 58% for males and 55% for females (p&gt;0.05). Time from last colonoscopy to CRC: 31.0 months (p&gt;0.05). Ten-year overall survival after CRC: 91% (p&gt;0.05).</td>
</tr>
<tr>
<td>Anyla [31]</td>
<td>2018</td>
<td>Prospective cohort</td>
<td>Cohort (n=121): 43 MLH1, 51 MSH2, 3 MSH6, 1 PMS2, 1 TASCD1, 1 MLH1 + variant MSH2, 21 no mutation found.</td>
<td>71/50</td>
<td>44 (16-70) years</td>
<td>2 year interval</td>
<td>NA</td>
<td>Metachronous CRC: 39 (32.2%) after a median interval of 24 (6-57) months since last colonoscopy. More commonly in MSH2 mutation carriers (58 vs. 35%, p = 0.001).</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Design</td>
<td>Cohort Size</td>
<td>Before Inclusion</td>
<td>After Inclusion</td>
<td>Scientific Data</td>
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<td>Perrod [60]</td>
<td>2018</td>
<td>Prospective cohort study</td>
<td>(n=118): 46 MLH1, MSH2 52, MSH6 18, 2 PMS2. After inclusion (n=144): 56 MLH1, 64 MSH2, 22 MSH6, 2 PMS2</td>
<td>Before inclusion: 38/80 years.</td>
<td>After inclusion: 51±13 years.</td>
<td>Optimized screening program (PRED-IdF) allowing an adjustment of the interval between colonoscopies, depending on bowel preparation, chromoendoscopy achievement and adenoma detection.</td>
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<tr>
<td>Lee [58]</td>
<td>2012 (supplement)</td>
<td>Retrospective cohort study</td>
<td>Cohort (n=64): 43 MLH1 17 MSH2, 4 MSH6.</td>
<td>NR</td>
<td>NR</td>
<td>Postoperative endoscopic surveillance, median interval 12 months.</td>
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<tr>
<td>Lamba [55]</td>
<td>2017 Conference Abstract</td>
<td>Observational study of national database</td>
<td>Cohort (n=381): 98 MLH1, 159 MSH2, 103 MSH6, 21 PMS2.</td>
<td>NR</td>
<td>Mean age at enrollment: 43 years.</td>
<td>Colonoscopy every 1-2 years from the age of 25 years.</td>
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</table>

Legend. HNPCC, Hereditary Non-polyposis Colorectal Cancer; CRC, colorectal cancer; LS, Lynch syndrome; MSI, Microsatellite instable; MSS, Microsatellite stable; ADR, Adenoma detection rate; PDR, polyp detection rate.

Table 3As. Summary table: Advanced imaging techniques in surveillance of Lynch syndrome: dye based chromoendoscopy versus white light and NBI

<table>
<thead>
<tr>
<th>First Author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study sample and mutation distribution</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Hurlstone [45]</td>
<td>2005</td>
<td>Unicenter Back-to-back sequential</td>
<td>MMR (84%) ± Amsterdam II. N=25</td>
<td>Conventional colonoscopy with targeted CE followed by indigo carmine pancolonic CE SD</td>
<td>NA</td>
<td>Number of adenomas: WLE: 11 CE: 32 ADR WLE: 28% ADR CE: 68% P = 0.001</td>
</tr>
<tr>
<td>Lecompte [39]</td>
<td>2005</td>
<td>Unicenter Back-to-back sequential</td>
<td>MMR (50%) ± Amsterdam N=33</td>
<td>Conventional colonoscopy followed by Indigo carmine CE proximal to splenic flexure SD</td>
<td>NA</td>
<td>Number of adenomas in the proximal colon WLE: 3 CE: 11 ADR WLE: 9% ADR CE: 30% P=0.045</td>
</tr>
<tr>
<td>Stoffel [44]</td>
<td>2008</td>
<td>Multicenter, Randomized Two arms Back to back parallel</td>
<td>MMR 85% ± Amsterdam N=54</td>
<td>First pass WLE Second pass: 1. Indigo carmine pancolonic CE 2. At least 20 minutes WLE inspection, SD</td>
<td>First pass WLE Second pass: CE: 10 (4 in arm CE; 6 in ≥20’inspection) Second pass: CE: 3 WLE ≥ 20’inspection: 7 P= 0.77 ADR first pass WLE: 15% ADR second pass CE: 11% ADR second pass WLE ≥20’: 19% P = 0.27</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Setting</td>
<td>Endoscopy</td>
<td>Colonoscope</td>
<td>MMR</td>
<td>WLE/CE</td>
</tr>
<tr>
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<td>-----------</td>
<td>-------------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Hüneburg [40]</td>
<td>2009</td>
<td>Unicenter</td>
<td>Back-to-back</td>
<td>Two arms</td>
<td>MMR 89% ± Amsterdam N=109</td>
<td>WLE follow by Indigo carmine pancelonic CE SD/HD</td>
</tr>
<tr>
<td>Rahmi [41]</td>
<td>2015</td>
<td>Multicenter</td>
<td>Back-to-back</td>
<td>Different endoscopist second pass</td>
<td>MMR 100% N=78</td>
<td>Standard endoscopy followed by Indigo carmine pancelonic CE SD</td>
</tr>
<tr>
<td>Haanstra [61]</td>
<td>2019</td>
<td>Multicenter; randomized; Parallel</td>
<td>MMR 100% N=246</td>
<td>Indigo carmine CE proximal to splenic flexure SD/HD</td>
<td>Conventional WLE SD/HD</td>
<td>ADR Whole colon WLE: 27% CE: 30% (P= 0.56) ADR Proximal colon: WLE 16% CE:24% (P=0.013)</td>
</tr>
<tr>
<td>Rivero- Sánchez [62]</td>
<td>2019</td>
<td>Multicenter; randomized; Parallel</td>
<td>MMR 100% N= 256</td>
<td>WLE HD * High adenoma detectors</td>
<td>Indigo carmine pancelonic CE HD * High adenoma detectors</td>
<td>WLE ADR: 28.1% (95% CI 21.1 – 36.4%) CE ADR: 34.4% (95% CI 26.4 – 43.3%) P= 0.2 (WLE non- inferior to CE)</td>
</tr>
</tbody>
</table>

Legend. NBI, Narrow-band imaging; SD, standard definition; HD, high definition; MMR, mismatch repair; WLE, white-light endoscopy; CE, Chromoendoscopy; ADR, Adenoma Detection rate; n.s, not significant; CI, confidence interval.
**Table 3Bs.** Summary table: Advanced imaging techniques in surveillance of Lynch syndrome: virtual chromoendoscopy vs white light and CE

<table>
<thead>
<tr>
<th>First Author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study sample and mutation distribution</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>East [43]</td>
<td>2005</td>
<td>Unicenter Back-to-back sequential</td>
<td>MMR (13%) ± Amsterdam II. N=62</td>
<td>WLE followed by NBI Exera II proximal to sigmoid colon HD</td>
<td>NA</td>
<td>Number of adenomas: WLE: 25 NBI: 46 ADR WLE: 27% ADR NBI: 42% P=0.004</td>
</tr>
<tr>
<td>Hüneburg [40]</td>
<td>2009</td>
<td>Unicenter Back-to-back Two arms **Polyps were not removed in the first pass</td>
<td>MMR 89% ± Amsterdam N=109</td>
<td>WLE follow by Indigo carmine pancholic CE SD/HD</td>
<td>NBI followed by Indigo carmine pancholic CE SD/HD</td>
<td>Number of adenomas: WLE: 7 CE after WLE: 13 NBI: 11 CE after NBI: 39 ADR WLE: 15% ADR CE: 19% ADR NBI: 14% ADR CE: 35%</td>
</tr>
<tr>
<td>Bisschops [42]</td>
<td>2017</td>
<td>Unicenter, Back-to-back Cross-over</td>
<td>MMR 64% N=61</td>
<td>WLE followed by i-scan HD</td>
<td>i-scan followed by WLE HD</td>
<td>Number of adenomas -First pass WLE: 5 second pass i-scan:8 Miss rate 62% -First pass i-scan 15 Second pass WLE 2 Miss rate 12% (P=0.007) ADR WLE: 19%-&gt;iScan: 16% ADR iScan:30%-&gt;WLE 7% (P=0.098)</td>
</tr>
<tr>
<td>Samaha [63]</td>
<td>2018 Conference Abstract</td>
<td>Multicenter Back-to-back sequential Non-inferiority</td>
<td>MMR (100%) N= 138</td>
<td>First pass: NBI Second pass: Indigo carmine CE HD</td>
<td>NA</td>
<td>Number of adenomas: NBI:39 CE 75 ADR NBI: 20.3% ADR CE: 30.4% (NBI inferior to CE)</td>
</tr>
</tbody>
</table>

Legend. NBI, Narrow-band imaging; HD, high definition; SPS, serrated polyposis syndrome; WLE, white-light endoscopy; CE, Chromoendoscopy; CI, confidence interval
Table 4s. Summary table: Gastric surveillance in Lynch syndrome

<table>
<thead>
<tr>
<th>First Author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Size study sample</th>
<th>Study sample surveillance</th>
<th>Gastroscopy findings</th>
<th>H. Pylori testing</th>
<th>Positivity rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renkonen [70]</td>
<td>2002</td>
<td>Prospective clinical trial</td>
<td>73 MMR positive</td>
<td>NR</td>
<td>1/73</td>
<td>23/73</td>
<td>10/73</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>32 MMR negative</td>
<td>NR</td>
<td>0/32</td>
<td>11/32</td>
<td>6/32</td>
</tr>
<tr>
<td>Soer [68]</td>
<td>2016</td>
<td>Retrospective cohort study</td>
<td>443 MMR mutation carriers</td>
<td>132 patients</td>
<td>35/132</td>
<td>8/35</td>
<td>23/35</td>
</tr>
<tr>
<td>Gallatsatos [69]</td>
<td>2017</td>
<td>Retrospective cohort study</td>
<td>66 mutation-proven Lynch syndrome patients</td>
<td>21 patients</td>
<td>10/21</td>
<td>0/10</td>
<td>0/10</td>
</tr>
</tbody>
</table>

Legend. MMR, mismatch repair; NR, Not reported.
<table>
<thead>
<tr>
<th>First Author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Sample size</th>
<th>Intervention</th>
<th>Findings</th>
<th>Secondary procedures</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saurin [85]</td>
<td>2010</td>
<td>Prospective comparative study</td>
<td>35</td>
<td>VCE vs CT enteroclysis</td>
<td>VCE (31/35): Certain: polyp (n=1), ileal tumor (n=1) Uncertain: polyps (n=4), enlarged irregular folds (n=5). CT enteroclysis 35/35: Certain: - Uncertain: 7 patients (including tumor).</td>
<td>VCE: Polyp: DBE failed, surgical resection (adenoma 10mm and jejunal carcinoma T3N0M0). Uncertain: DBE or duodenoscopy (n=4): 4mm adenoma (n=1). CT enteroclysis: Uncertain: DBE (n=7): DBE failed, surgery (n=1).</td>
<td>Prevalence of small bowel neoplasia 8.6%. CT enteroclysis missed the two adenomas.</td>
</tr>
<tr>
<td>Samaha</td>
<td>2012</td>
<td>Conference Abstract</td>
<td>46</td>
<td>VCE</td>
<td>NR</td>
<td>NR</td>
<td>Prevalence small bowel neoplasia 2%.</td>
</tr>
<tr>
<td>Haanstra [84]</td>
<td>2015</td>
<td>Prospective multicenter trial</td>
<td>200</td>
<td>VCE</td>
<td>Polyps &gt;1cm: n=17. Polyps &lt;1cm (no investigation): n=6.</td>
<td>Gastroduodenoscopy (n=10): TisN0Mx adenocarcinoma (n=1), TVA (n=1), inflammation (n=1), Brunner’s gland (n=2), heterotopic gastric mucosa (n=1), NA (n=4). SBE/ DBE (n=6): lymphoid hyperplasia (n=1), NA (n=5)</td>
<td>Prevalence small bowel neoplasia 1.5%: &gt;50 years within reach of gastroduodenoscope. Follow-up: 7 months after negative VCE, duodenal cancer (T2N0Mx).</td>
</tr>
<tr>
<td>Haanstra [86]</td>
<td>2017</td>
<td>Prospective multicenter trial</td>
<td>155/200</td>
<td>VCE</td>
<td>Polyps &gt;1cm: n=13. Polyps &lt;1cm (no investigation): n=2.</td>
<td>Gastroduodenoscopy (n=5): Brunner’s gland (n=1), swollen normal mucosa (n=1), polyp (normal mucosa) &lt;5mm (n=1), NA (n=2) SBE/ DBE (n=8): polyp (lymphoid hyperplasia) 6-9mm (n=1), polyp (FGP) &lt;5mm (n=1),</td>
<td>No small bowel neoplasia.</td>
</tr>
<tr>
<td>Hammoudi [87]</td>
<td>2019</td>
<td>Retrospective cohort study</td>
<td>154</td>
<td>Upper endoscopy, performed every 3–4 years, in the occasion of a colonoscopy, according to our PRED-IdF guidelines.</td>
<td>≥1 duodenal lesion: 7 (4.5%), median age at diagnosis was 58 years (range: 49–73). Three lesions were invasive adenocarcinomas. MLH1: 2.4% (1 out of 41). MSH2: 7.1% (6 out of 85). OR: 5.17, IC95% (0.8–60.07), p = 0.1307.</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Legend. VCE, Video capsule endoscopy; MR, Magnetic Resonance; CT, Computer tomography; NR, Not reported; TVA, tubulovillous adenoma; NA, Not Applicable; SBE, Single balloon endoscopy; DBE, Double balloon endoscopy; FGP, Fundic gland polyp; NA, Not Applicable.
Table 6s. Family history and risk of developing colorectal cancer: overview of Wong et al. and Roos et al.

<table>
<thead>
<tr>
<th>Family history</th>
<th>First Author, Ref. [91] in Guideline</th>
<th>Year of publication</th>
<th>Number of studies included</th>
<th>Overall risk estimate (95%CI)</th>
<th>First Author, Ref. [95] in Guideline</th>
<th>Year of publication</th>
<th>Number of studies included</th>
<th>Case-control study risk estimate (95%CI)</th>
<th>Number of studies included</th>
<th>Cohort study risk estimate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 FDR</td>
<td>Wong</td>
<td>2018</td>
<td>7</td>
<td>1.82 (1.51-2.18)</td>
<td>Roos</td>
<td>2019</td>
<td>8</td>
<td>1.92 (1.53-2.41)</td>
<td>3</td>
<td>1.37 (0.76-2.46)</td>
</tr>
<tr>
<td>≥1 FDR</td>
<td>Wong</td>
<td>2018</td>
<td>63</td>
<td>1.76 (1.57-1.97)</td>
<td>Roos</td>
<td>2019</td>
<td>41</td>
<td>2.22 (2.00-2.48)</td>
<td>12</td>
<td>1.67 (1.52-1.82)</td>
</tr>
<tr>
<td>≥2 FDR</td>
<td>Wong</td>
<td>2018</td>
<td>9</td>
<td>2.68 (1.92-3.74)</td>
<td>Roos</td>
<td>2019</td>
<td>8</td>
<td>2.81 (1.73-4.55)</td>
<td>3</td>
<td>2.40 (1.76-3.28)</td>
</tr>
<tr>
<td>FDR &lt;50 years</td>
<td>Wong</td>
<td>2018</td>
<td>4</td>
<td>3.55 (1.84-6.83)</td>
<td>Roos</td>
<td>2019</td>
<td>2</td>
<td>3.57 (1.07-11.85)</td>
<td>4</td>
<td>3.26 (2.82-3.77)</td>
</tr>
<tr>
<td>FDR &lt;60 years</td>
<td>Wong</td>
<td>2018</td>
<td>NR</td>
<td>NR</td>
<td>Roos</td>
<td>2019</td>
<td>3</td>
<td>2.40 (2.12-2.73)</td>
<td>4</td>
<td>2.02 (1.59-2.57)</td>
</tr>
</tbody>
</table>

FDR, first-degree relative; CI, confidence interval; NR, Not reported.
Table 7s. Surveillance in familial risk of colorectal cancer: intervals and outcomes

<table>
<thead>
<tr>
<th>First author [Ref. in Guideline]</th>
<th>Year of publication</th>
<th>Study design</th>
<th>Study sample size</th>
<th>Age range</th>
<th>Definition of family history</th>
<th>Method of family history assessment</th>
<th>Lynch syndrome excluded?</th>
<th>Intervention: surveillance interval</th>
<th>Comparison</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dove-Edwin [98]</td>
<td>2005</td>
<td>Prospective, observational cohort study</td>
<td>Group 1 = 197 individuals Group 2 = 536 individuals Group 3 = 391 individuals Group 4 = 554 individuals</td>
<td>20-82 years</td>
<td>Group 1: 1 FDR with CRC &lt;45 yo Group 2: 2 FDR or 1 FDR + 1 SDR Group 3: ≥3 individuals affected over two generations, one a FDR of the other two, but no cases diagnosed &lt;50 yo Group 4: HNPCC</td>
<td>NR</td>
<td>Group 4</td>
<td>Offered from age 25. 5-year intervals or 3-year intervals if an adenoma was diagnosed. Later, individuals in a family with HNPCC were offered colonoscopy every 1-3 years.</td>
<td>NA</td>
<td>Families with moderate risk (group 1-3): Advanced adenoma and CRC under age &lt;45 on initial colonoscopy: 1.1% and 0%. On follow-up colonoscopy (5-year interval) if advanced neoplasia was absent initially (1.7% and 0.1%, respectively). Advanced neoplasia on initial colonoscopy: 12% of advanced neoplasia on follow-up (3-year interval). Multiple adenomas on initial colonoscopy: 41% had an adenoma on follow-up (3-yearly surveillance), but 0% had advanced neoplasia. Incidence of CRC: 80% lower (P = 0.00004) than the expected incidence in the absence of surveillance when the family history was taken into account. Significant reduction in mortality: 81% in moderate-risk</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Study Type</td>
<td>Baseline Characteristics</td>
<td>Surveillance Interval</td>
<td>Exclusion Criteria</td>
<td>Surveillance</td>
<td>Findings</td>
<td></td>
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<tr>
<td>Brenner [100]</td>
<td>2011</td>
<td>Population-based case-control study</td>
<td>FH among first diagnosed CRC cases = 232 (14.1%) FH among controls = 192 (10.4%)</td>
<td>≥30 years</td>
<td>≥1FDR</td>
<td>Standardized interviews or questionnaire to those individuals not willing to participate in a personal interview.</td>
<td>NR</td>
<td>Population-based case-control study FH among first diagnosed CRC cases = 232 (14.1%) FH among controls = 192 (10.4%) Standardized interviews or questionnaire to those individuals not willing to participate in a personal interview.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hennink [102]</td>
<td>2015</td>
<td>Multicenter randomized controlled trial</td>
<td>Patients with &lt;3 adenomatous polyps at baseline: Group A (6 years surveillance) = 262. Group B (3 and 6 years surveillance) = 266.</td>
<td>45-65 years</td>
<td>1 FDR with CRC &lt;50 years 2FDR with CRC at any age</td>
<td>Medical (99%) and pathology (47%) reports. Verified.</td>
<td>Excluded</td>
<td>Group A: 6 year surveillance interval Group B: 3 year surveillance interval Advanced adenomatous polyps at first follow-up: group A (6.9%) versus 3 years in group B (3.5%) (crude OR, 2.0; 95%CI 0.89 to 4.7; P=0.09) (adjusted OR, 2.44; 95%CI 1.03 to 5.78; P=0.044). Advanced adenomatous polyps at the final follow-up at 6 years: group A (6.9%) versus 6 years in group B (3.4%) (crude OR, 2.1; 95%CI 0.89 to 5.0; p=NS) (adjusted OR, 2.61; 95%CI 1.06 to 6.45; P=0.038).</td>
<td></td>
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</tr>
<tr>
<td>Samadder [101]</td>
<td>2017</td>
<td>Cohort study</td>
<td>First negative colonoscopy &amp; Family history = 7,515 First negative colonoscopy &amp; No family history = 138,864</td>
<td>50-80 years</td>
<td>≥1FDR</td>
<td>Linkage between the Utah Population Database and the Utah Cancer Registry. Not ascertainment.</td>
<td>Excluded</td>
<td>Family history: 5 year surveillance interval No family history: 10 year interval Family history: the SIR for CRC overall was significantly reduced up to 5 years (SIR 0.39, 95%CI 0.13–0.64) following a negative colonoscopy, and 5-10 years (SIR 0.74, 95%CI 0.32–1.16). No family history: the SIR for CRC overall was significantly reduced up to 10 years following that index procedure (SIR 0.28, 95% CI: 0.24–0.33).</td>
<td></td>
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</tbody>
</table>
Hatfield [99] 2018 Case-control study 324 individuals (162 screened; 162 unscreened) The median ages of males and females at entry into screening; 44.8 (95% CI 42.2–47.4) vs. 44.5 (41.8–47.2) years. Family members eligible for study were born after 1909, were FDR of incident CRC cases, and presumed to be at 50% a priori risk for a inheriting genetic CRC susceptibility factor. FCCTX families were identified from population-based cohorts where incident cases with CRC were recruited into the Newfoundland Familial Colorectal Cancer Registry between 1999 and 2003, or had been referred to the Provincial Medical Genetics Program. Yes Follow-up colonoscopies at 1–2-year intervals Unscreened control group from the families, matched for age at entry into screening and for sex. INCIDENCE OF CRC: 12% of males developed CRC after 30 years of follow-up, compared to 46% of unscreened males (RR=0.27; 95% CI: 0.10–0.71). Regarding females, 7% had developed CRC after 30 years of follow-up, compared to 49% of unscreened females (RR=0.19; 0.07–0.48). MORTALITY: survival was significantly better in screened compared to unscreened males (RR = 0.38). At 30 years of follow-up, 45.5% of males had died in the screened group compared to 62.8% in the unscreened group. In screened females, mortality at 30 years of follow-up was 7.2%, whereas in unscreened females, it was 60.4% (RR = 0.14).

Legend. FDR, First-degree relative; NR, Not reported; HNPCC, Hereditary Non Polyposis Colorectal Cancer; NA, Not Applicable; CRC, Colorectal cancer; FH, Family history; (a)OR, (adjusted) Odds Ratio; NS, Not significant; CI, confidence interval; SIR, Standardized Incidence Ratio; FCCTX, Familial colorectal cancer type X.
<table>
<thead>
<tr>
<th>First Author [Ref. in Guideline]</th>
<th>Year of Publication</th>
<th>Study</th>
<th>Definition of family history</th>
<th>Method of family history assessment</th>
<th>Lynch syndrome excluded?</th>
<th>Risk: Type of cancer</th>
<th>FH: Type of cancer</th>
<th>Age of person at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fuchs [103]</td>
<td>1994</td>
<td>Prospective cohort study</td>
<td>$\geq 1$ FDR</td>
<td>Questionnaire and medical records and pathology reports.</td>
<td>NR</td>
<td>CRC</td>
<td>CRC</td>
<td>For participants under the age of 45 years who had one or more affected first-degree relatives, the relative risk was 5.37 (95%CI 1.98 to 14.6), and the risk decreased with increasing age (P for trend, &lt; 0.001).</td>
</tr>
<tr>
<td>Hemminki [104]</td>
<td>2001</td>
<td>Prospective cohort study</td>
<td>$\geq 1$ FDR</td>
<td>NR</td>
<td>NR</td>
<td>CRC</td>
<td>CRC</td>
<td>SIR for CRC in offspring by their age: &lt;40 years --&gt; SIR 2.20 (95%CI 1.74-2.70) 40-49 years --&gt; SIR 2.01 (95%CI 1.71-2.33) &gt;50 years --&gt; SIR 1.18 (95%CI 0.99-1.39)</td>
</tr>
<tr>
<td>Andrieu [105]</td>
<td>2003</td>
<td>Case-control study</td>
<td>FDR+SDR</td>
<td>&quot;Only three families (0.4%) fulfilled the Amsterdam criteria of 3 cases of CRC&quot;</td>
<td>CRC</td>
<td>CRC</td>
<td>CRC</td>
<td>Risk of developing CRC: ≤ 50 years: RR 2.07 (95%CI 0.99-3.80) 51-60 years: RR 1.67 (95%CI 0.97-2.68) 61-70 years: RR 1.28 (95%CI 0.85-1.85) &gt; 70 years: RR 1.60 (95%CI 1.19-2.10)</td>
</tr>
<tr>
<td>Johns [106]</td>
<td>2002</td>
<td>Retrospective cohort study</td>
<td>$\geq 1$ FDR</td>
<td>Medical reports</td>
<td>Not excluded, however birth prevalence of mutations is only approximately 1 in 2,800.</td>
<td>CRC</td>
<td>CRC</td>
<td>Cumulative CRC risk in first-degree relatives of CRC cases 30 years --&gt; 0.2 (0.08-0.7) 35 years --&gt; 0.6 (0.3-1.3) 40 years --&gt; 0.6 (0.3-1.3) 45 years --&gt; 1.4 (0.9-2.3) 50 years --&gt; 1.8 (1.2-2.8) 55 years --&gt; 2.8 (2.0-4.0) 60 years --&gt; 3.6 (2.6-4.9) 65 years --&gt; 5.8 (4.4-7.7) 70 years --&gt; 6.9 (5.3-9.0) 75 years --&gt; 8.5 (6.4-11.1)</td>
</tr>
<tr>
<td>Kune [107]</td>
<td>1989</td>
<td>Case-control study</td>
<td>≧1 FDR</td>
<td>Questionnaire</td>
<td>NR</td>
<td>CRC</td>
<td>CRC</td>
<td>When relative risks were estimated by age in 2 groups, a statistically significant association was found between FH of CRC and the respondent's age of less than 50 years (RR l&lt; 50 years = 8.54, 95%CI 1.9-39; RR 50 years or older = 1.87, 95% CI = 1.4-2.8; and p value associated with the difference between the 2 age groups = 0.05</td>
</tr>
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<td>-----</td>
<td>-----------------------------------------------</td>
</tr>
</tbody>
</table>
| Samadder [108] | 2015 | Case-control study | FDR+SDR | NR | Patients with known hereditary cancer syndromes other than FAP (in particular Lynch syndrome) and IBD could not specifically be excluded; however, these conditions account for less than 3% of all CRCs and are therefore unlikely to modify the statistical associations demonstrated. | CRC | CRC | Risk of CRC  
<50 years --> HR 2.28 (95%CI 1.86-2.80)  
≧50 years --> HR 1.81 (95%CI 1.71-1.92) |

Legend. FDR, First-degree relative; NR, Not reported; CRC, Colorectal cancer; CI, confidence interval; SIR, Standardized Incidence Ratio; SDR, Second Degree Relative; RR, Relative Risk; HR, Hazard Ratio.