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Supplement 1: Evidence GRADE Tables

GRADE Table 1: Studies of FHCC

Author, year	Country	Study population	Design	Findings	Comments
Jacobs (2018)[36]	USA	Stratified risk by age, gene	Prospective study of average risk patients on a surveillance programme	FH was significantly associated with metachronous adenomas (OR = 1.14; 95% CI = 1.01–1.29), however larger studies are needed to confirm possible but statistically non-significant findings related to metachronous AAs 1.15 (0.96–1.37)	Not powered to detect differences in AA prevalence
Plath (2017)[37]	Germany	191 people with a FDR with CRC. Not stratified by degree of FH. Aged 40-54 years	A cross-sectional study in general practice.	86 (45%) underwent a colonoscopy during study period. No CRC was found, but 16.3% had any adenoma, and 7.0% had AA. The utilization of colonoscopies among participants increased up to 82% after counselling by general practitioners.	

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Quintero (2016)[38]	Spain	214 FDR aged 25-75 years, of people with CRC. FHCC stratified by age (1x FDR above or below 60 years), and 2x FDRs any age.	Cross-sectional analysis included data from 8,498 individuals undergoing their first lifetime screening colonoscopy between 2006 and 2012 at six Spanish tertiary hospitals, 3,015 were defined as asymptomatic FDR of patients with CRC and 3,038 as asymptomatic with average-risk for CRC.	Compared to an average-risk group, advanced neoplasia were more prevalent in individuals with 2x FDR with CRC (odds ratio [OR] 1.90; 95% confidence interval [CI] 1.36–2.66, p < 0.001), but not in those with 1x FDR with CRC diagnosed at ≥60 y (OR 1.03; 95% CI 0.83–1.27, p = 0.77) and <60 y (OR 1.19; 95% CI 0.90–1.58, p = 0.20). After the age of 50 y, men developed advanced neoplasia over two times more frequently than women and advanced neoplasia appeared at least ten y earlier. Fewer colonoscopies by 2-fold were required to detect one advanced neoplasia in men than in women.	
Weigl (2016)[39]	Germany	4313 patients with a first diagnosis of CRC (cases) and 3,153 controls recruited from 2003 to 2014 were included. A	Population based case-control study	A FHCC was associated with a 41% increase in risk of CRC (OR: 1.41, 95% CI 1.22-1.63) after adjustment for sex and age. Participants with a history of colonoscopies had a lower CRC risk compared with persons	Colonoscopy may mitigate CRC risk in people with a FH

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		total of 582 cases (13.5%) and 321 (10.2%) controls reported a history of CRC in a first-degree relative		without previous colonoscopies and without FH (OR: 0.25, 95% CI, 0.22–0.28 for persons without FH and OR 0.45, 95% CI, 0.36–0.56 for persons with FH).	
Hennink (2015)[33]	Netherlands	508 people with 1x FDR CRC diagnosed age <50 years or two affected FDRs Study Population: aged 45-65 years	RCT FACTS (Familial CRC Surveillance) study. Patients with 0-2 adenomas at baseline were randomly assigned to one of two groups: group A (colonoscopy at 6 years) or group B (colonoscopy at 3 and 6 years). The primary outcome measure was advanced adenomatous polyps (AAs).	Intention-to-treat analysis showed no significant difference in the proportion of patients with AAs at the first follow-up examination at 6 years in group A (6.9%) versus 3 years in group B (3.5%).	Only AAs at baseline was a significant predictor for the presence of AAs at first follow-up (OR 5.2 (1.6 to 16.87)).
Forsberg (2015)[32]	Sweden	1203 FHCC	Observational longitudinal study.	8% incidence of AAs. The risk of future AAs was only associated with the prevalence of	The risk of future advanced lesions was

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		Stratified FDR any age at diagnosis of CRC, FDR <50 years, 2 FDRs any age, or only SDR and TDR	1203 index colonoscopies, and 594 surveillance procedures following index colonoscopy	advanced lesions at the screening colonoscopy on 1209 patients with a FHCC (multivariate analysis OR 5.22: 9%% CI 2.3-9.94).	only associated with the prevalence of advanced lesions at the screening colonoscopy
Forsberg (2015)[40]	Sweden	1397 FHCC, plus 745 controls without a FH who took part in a population-based colonoscopy study. Stratified 1x FDR <50 years, or 2x FDRs/SDR/TDRs, or 3x FDRs/SDRs/TDRs all of whom underwent a single index screening colonoscopy only	Observational case-control study	In LS, 30% of the individuals had adenomas and 10% AAs. The corresponding figures for AAs in the other risk groups were 14–24% (High moderate) and 4–7% (Low moderate), compared with 10% and 3% in the control group. The relative risk of having adenomas and AAs was, compared to controls, significantly higher for all risk groups except the group with the lowest risk. Age was a strong predictor for adenomas and AAs in both risk individuals and controls.	Age was a strong predictor for adenomas and advanced adenomas in both risk individuals and controls.

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Ng (2013)[41]	Hong Kong	374 siblings of patients with AAs (not CRC), with a mean age of 58 years	Blinded, cross-sectional case-control study	The prevalence of advanced neoplasms was 7.5% among siblings of patients 2.9% among controls.	Controls were people whose relatives did not have adenomas thus may have been a truly low risk group.
Mesher (2013)[26]	Multicentre International	1585 people with a high familial risk of CRC	Data from six European centres. Families were classified as FCC type X if they fulfilled the original Amsterdam criteria (AC) and late onset (LOFCC) if they fulfilled the AC apart from not having a cancer aged under 50.	1585 individuals (median age 47.3, 44% male) from 530 FCC families (349 FCC type X) underwent a total of 4,992 colonoscopies with 7,904 patient-years of follow-up. Both FCC type X and LOFCC have a high prevalence of CRCs and on follow-up develop high-risk adenomas (including multiple adenomas) from age 30-40 years, but infrequent interval cancers.	No difference between FCC-X and LOFCC cohorts. The prevalence of AAs was >11.5% in people from the age of 40 years
Morois (2014) [20]	France	Large cohort study	92,078 women of the E3N prospective cohort, 692 CRCs were diagnosed after a	In women with no prior colonoscopy, those with FHCC had a 80% higher CRC risk than those without FHCC. In women with previous colonoscopy, CRC risk was similar	Colonoscopy may mitigate CRC risk in people with a FH

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			median follow-up of 15.4 years.	in women with and without FHCC (p for interaction = 0.04).	
Newton (2013)[15]	United Kingdom	Patients who had at least one CRC were categorized as follows: moderate risk (n = 383), LS (n = 528) and average (population) risk (n = 409).	A retrospective longitudinal study of the Regional Familial CRC Registry	The 1-KM (Kaplan-Meier estimate) in moderate-risk patients was 2.7%, 6.3% and 23.5% at 5, 10 and 20 years, respectively. In average (population)-risk patients, the 1-KM was 1.3%, 3.1% and 7.0% at 5, 10 and 20 years, and the cumulative incidence function was 0.3%, 0.6% and 2.4% at the same time points, respectively.	The authors conclusion was that this this justifies proactive lifelong surveillance in those CRC with moderate familial risk of CRC. However it is not clear that colonoscopic surveillance effectively mitigates this risk.
Tsai (2012)[30]	USA	4,967 patients were divided into 643 with and 4,324 without a FHCC aged 40-89 years. Stratified by 1x FDR, or	A large, prospective study of an unselected population in San Diego, California to assess the impact of a FHCC on the	Of the 643 patients with a FH, 38 (5.9%) had advanced neoplasia, one of which was cancer. Of the 4,324 patients without a FH, 211 (4.9%) had advanced neoplasia including seven cancers. The relative risk for	

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		1x FDR aged <60 years, or 2x FDRs	prevalence of advanced neoplasia on screening colonoscopy	finding advanced neoplasia in patients with a single affected FDR was 1.21 (95% CI, 0.87–1.69; P = 0.31).	
Wilschutt (2010)[19]	na	FHCC, not stratified	Meta-analysis	Adenoma prevalence was significantly higher in individuals with a FH than in those without (OR 1.7, 95% CI 1.4–3.5),	
Puente (2011)[42]	Spain	263 people with FH CRC aged 25-75 years. Not stratified by degree of FH	Observational Study	AAs or cancer was identified in 21.3% of 263 patients with a FHCC	in this study they did not actively exclude LS was not actively excluded.
Armelao (2011)[43]	Italy		Observational Study	AA incidence of 11% in patients aged 45-75 years with an unselected FHCC.	
Meulen-de Jong (2011)[23]	Netherlands	456 people with FHCC aged 45-65 years. Stratified by 1FDR age <50 years, or 2 FDRs any age	Observational Study	Adenomas were detected in 85 (18.6%) and adenomas with advanced pathology in 37 subjects (8.1%)	
Wark (2009)[25]	USA	345 people. Stratified by 1 or 2 FDRs with	Health Professionals Follow-Up Study (HPFS):	A FHCC was similarly associated with advanced and non-advanced adenomas	

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			an ongoing prospective study among 51,529 male US health professionals who responded to a mailed questionnaire in 1986 when they were between 40 and 75 years old	[multivariable odds ratio (OR) (95% confidence interval): advanced versus adenoma-free: 1.67 (1.47–1.91), non-advanced versus adenoma-free: 1.70 (1.49–1.94)],	
Stormorken (2007)[44]	Norway	343 people with 3 FDRs	Observational Study.	8 of 343 (2.1%) had either AAs or cancer in 3 years of mean follow-up	
Pezzoli (2007)[45]	Italy	In 5 years, 776 subjects were interviewed and 733 (94.4%) agreed to an endoscopic examination (M/F:375/401; mean age 55 years): 562 colonoscopies were performed.	Observational Study.	8% of patients had either AAs or cancer.	

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Regula (2006)[46]	Poland	10443 people aged 40-66 years. Stratified Age 40-49 with any FH, or age 50-66 stratified by 1 FDR<60, 1 FDR >60 or 2 FDRs any age	A cross-sectional analysis of the data from a large colonoscopy-based screening program that included 50,148 participants who were 40 to 66 years of age.	FH is an independent predictor of CRC risk. 10.0 to 15.6% of the participants (depending on their age) had a FHCC	
Dove-Edwin (2006)[35]	United Kingdom	197 people from AC families	Microsatellite instability tested in all families. 29 families were classified as LS and 68 as non-LS.	AAs occurred in 7 of 91 (7.7%) LS individuals and 15 of 197 (7.6%) FCC-X individuals, adjusted relative risk 1.15 (95% CI: 0.6–2.3). There were no cancers in the FCC-X group vs 4.4% CRC in Lynch patients, indicating lower risk of CRC in FCC-X despite equivalent AA risk.	A FH of microsatellite stable tumours was associated with significantly lower prevalence of advanced neoplasia in AC families
Dove-Edwin (2005)[31]	United Kingdom	1678 people with a FHCC. Stratified by one FDR <45 years, 2 FDRs, 3	A highly stringent surveillance programme with 1678 individuals	AAs and cancer were most common in families with hereditary non-polyposis CRC (on initial colonoscopy 5.7% and 0.9%, respectively). In the families with moderate	Patient registration and adherence of surveillance

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		FDRs but none < 50 years, or AC	from HNPCC and moderate risk families.	risk, these findings were particularly uncommon under age 45 (1.1% and 0%) and on follow-up colonoscopy if AAs were absent initially (1.7% and 0.1%). The incidence of CRC was substantially lower-80% in families with moderate risk (P = 0.00004), and 43% in families with HNPCC (P = 0.06)-than the expected incidence in the absence of surveillance when the FH was taken into account.	programmes mitigates CRC risk
Bradshaw (2003)[29]	United Kingdom	176 people with a FHCC. Stratified by 'moderate risk' or Amsterdam criteria	Observational study.	Only 5 of 104 patients in the moderate risk group (1-2 FDRs) had adenomas, with only 1 AA. Of these 2 were under 50 years. Median age of individuals who underwent colonoscopy in both increased risk groups was 43 years.	There was a low adenoma detection rate which may reflect the historical nature of this and other older study.
Clark (2003)[47]	United Kingdom	186 people with a FHCC. Stratified by one FDR <45 years or 2 FDRs any	Observational study.	10% of 238 individuals in a moderate risk group had either cancer or adenomas.	

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		age using contemporary BSG guidelines			
Dowling (2000)[27]	Australia	232 people with a FHCC. Stratified by one FDR <45 years or multiple relatives	Observational study.	In 232 patients, 4 AAs and 2 cancers (2.5%) were identified, with only 1 AA before age 50 years. The adenoma detection rate (ADR) was 14% overall.	

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GRADE Table 2. Adenoma detection with dye-based chromoendoscopy in LS surveillance

Study	Timeframe	Type	n	HD	WT WLE	WT CLE	ADR WLE	ADR CLE	MAP WLE	MAP CLE
Lecomte 2005[82]	2001-2003	Tandem, sequential	33	No	n/a	17	15%	n/a	0.69	1.25
Huneburg 2009 [91]	2005-2007	Tandem, sequential	47	No	7.6	18.0	15%	28%*	0.53	0.98
Stoffel 2008 [83]	Pre-2008	Tandem, Randomised 2nd exam	52	No	25.3	29.8	n/a	n/a	0.5	0.4
Rahmi 2015 [85]	2008-2009	Tandem, sequential	78	No	10.0	21.5	23%	41%	0.3	0.7
Haanstra 2019 [86]	2008-	Parallel group RCT	246	50%	12	18	27%	33%		
Rivero Sanchez 2018 [87]	2016-2017	Parallel group RCT	256	Yes	13.5	18.4	28%	34%	1.0	0.86

WT, withdrawal time; ADR, adenoma detection rate; MAP, mean adenomas per patient; *WLE and NBI series combined

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GRADE Table 3. Adenoma detection with virtual chromoendoscopy in LS surveillance

Study	Timeframe	Type	n	HD	WT WLE	WT VCE	ADR WLE	ADR VCE	MAP WLE	MAP VCE
East 2008 [84]	2006	NBI, Tandem right colon, sequential	62	Yes	6.3	7.0	27%	42%	0.40	0.74
Bisschops 2017 [98]	2010-2012	I-SCAN, Tandem, randomised	61	Yes	8.1	8.9	13%	23%	0.11*	0.37*

*WLE or I-SCAN only, not in addition as in NBI study

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GRADE table 4: What is the appropriate colonoscopy surveillance interval for patients for LS?

Author, year	Country	Study population	Design	Findings	Comments
Moller, 2018 [111]	Multicentre International	3119 LS patients Affected and unaffected by cancer 1473 MLH1 (13,846y) 1060 MSH2 (7492y) 462 MSH6 (2613y) 124 PMS2 (524y)	Prospective observational multicentre study, which estimated cancer incidence and survival in LS patients up to age 75 for 24,475 observation years Stratifies risk by age, gene	Cumulative incidences at 75y for CRC were 46% (MLH1), 43% (MSH2), and 15% (MSH6). CRC was not observed in PMS2 carriers. Most CRC affected the colon rather than sigmoid/rectum 5-year and 10 year survival for colon cancer was 96% and 75% respectively 5-year and 10 year survival for recto-sigmoid cancer was 75% and 70% respectively	Low number of *PMS2* observation years Wide CIs of the observed point estimates
Moller, 2017 [112]	Multicentre International	1942 LS patients without previous cancer	Prospective observational multicentre study, which estimated cancer incidence	151 patients developed CRC	Cumulative incidences for first cancers

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		944 *MLH1*, 616 *MSH2*, 305 *MSH6*, 77 *PMS2*	and survival in LS patients receiving colonoscopic surveillance for 13,782 observation years Stratifies risk by age, gene, and gender	CRC cumulative incidences (first cancer) at 70y by gene were 46% (MLH1), 35% (MSH2), 20% (*MSH6*) and 0% (PMS2) 5 year and 10-year survival after 1st CRC was 94% and 91% respectively Median time since last colonoscopy in 145 CRC was 31.8 months, median 27 months (range 7-123 months)	Low number of *PMS2*/*MSH6* observation years
Moller, 2017 [110]	Multicentre International	1273 LS patients with previous cancer diagnoses 944 MLH1, 616 MSH2, 305 MSH6, 77 PMS2	Prospective observational multicentre study, which estimated incidence of subsequent cancers and survival in LS patients with prior cancer diagnosis for 7753 observation years Stratifies risk by age, gene,	Cumulative incidences of subsequent CRC were 46% (MLH1), 48% (MSH2), and 23% (MSH6) Time since last colonoscopy to CRC was available for 133/141 patients in whom first cancer was CRC; 60 (46%) of CRCs were diagnosed within 2y and 102 (78%) within 3y	Did not have details of previous CRC treatment for previously affected patients No detail about adenomas removed

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				10-year CRC survival was 91%, and for MLH1 (91%), MSH2 (92%), and MSH6 (100%)	Low number of PMS2 mutation carriers
Author, year	**Country**	**Study population**	**Design**	**Findings**	**Comments**
Engel, 2018 [114]	Germany, NL, Finland	2747 LS patients from 3 LS registries; German HNPCC Consortium (n= 1027), Dutch LS registry (n= 806), & Finnish LS Registry (n=914). MMR carriers: 407 MLH1, 986 MSH2, 354 MSH6	Prospective observational study, which collected data from 16,327 colonoscopic examinations (1984 -2015) of 2747 LS patients from three countries with different surveillance policies annually (Germany), 1-2 yearly (NL), and 2-3yearly (Finland) 23,309 person-yrs observation time Cohort 1: pts unaffected with CRC before start	At index colonoscopy; 10.2% prevalent adenomas and 2.3% prevalent CRC ADR was 15.6% in cohort 1 and 14.1% in cohort 2; no significant difference in ADR between the 3 countries (p=0.996 for cohort 1 and p=0.411 for cohort 2) No significant differences in UICC stages of incident CRC were observed between countries (p=0.150) or by time interval since last colonoscopy (p=0.240) After 10 years follow-up, cumulative CRC incidence was 8.4% for first CRC and 14.1% for metachronous ; no significant difference	KPI data for colonoscopies nor available Incident cancers defined as screened detected and symptomatic cancers (therefore includes interval cancers) National protocol interval length could have been modified based on risk factors

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			Cohort 2: pts already treated for CRC	in cumulative CRC incidence seen between countries in cohort 1 (p=0.246) and 2 (p=0.432) 21% of Germany patients longer intervals (>1.5y) and 13% of Dutch (>2.5%), and 9% of Finnish patients had shorter intervals (<1.5yrs)	Did not include PMS2/EPCAM 2 MLH1 founder mutations (79% of Finnish group were MLH1 mutation carriers)
ten Broeke, 2018 [115]	International multi-centre	284 PMS2 families (211 European, 19 Ohio , and 54 from CCFR), with 1,904 first- and 2,974 second degree relatives; 513 confirmed carriers	Retrospective cancer risk study, which used modified segregation analysis for estimation of HR and age-specific cumulative risks (penetrance) Includes population-based patients	Cumulative CRC risk (up to 80y) was ~13% (95% CI, 7.9-22%) for male carriers and 12% (95% CI, 6.7-21%) for females (general population 6.6% and 4.7% respectively) Mean age at CRC diagnosis was 59.4 (14.7 SD) for FDR and 62.7 (3.0 SD) for SDR	Largest PMS2 dataset Unconfirmed cancer diagnoses used in analysis – retrospective analysis Potential genetic and environmental modifiers

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Author, year	**Country**	**Study population**	**Design**	**Findings**	**Comments**
Newton, 2015 [106]	UK	227 LS mutation carriers or obligates (85 MLH1, 119 MSH2, 21 MSH6, 2 PSM2)	Retrospective longitudinal study investigating screening compliance in LS mutation carriers on a regional familial CRC registry under and not under screening	439 colonoscopies assessed for timeliness, of which 68% compliant (interval <27 months) 313/339 colonoscopies were complete (92.3%), 26/339 (7.7%) did not reach the caecum Bowel prep poor in 36/340 (9.6%) Cumulative incidence of CRC (up to 70y) was 25% (95% CI 17-32%) in surveillance grp vs 81% (95% CI 78-84%) in grp not screened (p<0.0001)	

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Haanstra, 2013 [68]	NL	2,384 proven and obligate mutation carriers	Retrospective analysis of data from the Dutch LS Registry and 2 large hospitals in NL examining the characteristics of patients with interval cancers and the features of such cancers (MLH1 32%, MSH2 41%, MSH6 23%, PMS2 2%, EPCAM 2%)	31 interval cancers in 29 patients (median age 52 (range 35-73), all MLH1 and MSH2 carriers Median interval since last surveillance colonoscopy was 17 (range 2-24) months. Most diagnosed between 1 and 2y after previous examination In 5 patients (16%) complete colon examination was not achieved during previous colonoscopy; in 3/5 of these patients (60%), CRC was found in the part of colon not reached previously In patients without previous surgery for CRC, 84% was proximally located; 77% of interval cancers were local stage (T1-3N0Mx)	

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				In 16/31 colonoscopy reports, the quality of bowel preparation was not reported.	
Author, year	**Country**	**Study population**	**Design**	**Findings**	**Comments**
de Vos tot Nederveen, 2002 [107]	NL	857 at-risk individuals from 114 families with HNPCC or MMR mutations	Observational study comparing the stage of screen-detected CRC with more frequent (2 years and less) and less frequent colonoscopy (>2y)	Interval 2y or <2y: Dukes' A (n = 4), B (n = 11), and C (n=1) Interval >2y: Dukes' A (n = 3), B (n = 10), and C (n = 6) Earlier tumour stage observed in those with more frequent colonoscopy (2y or less) vs less frequent colonoscopy – 93.8% vs. 68.4%	

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Vasen, 2010 [113]	NL	745 at-risk individuals from 205 LS pedigrees (with MLH1, MSH2, MSH6)	Retrospective cohort study investigating the rate of interval cancers with screening. Colonoscopy 1-2y Mean follow-up: 7.2y	Thirty-three interval cancers; (83% local stage); ranging from 34 to 71y, 4 cases <40; higher in carriers older than 40y Higher risk of interval cancer in MLH1 and MSH2 mutation carriers, compared to MSH6 carriers (1/127) 6% risk of interval cancer over 10y	
Rijcken, 2002 [118]	NL	100 HNPCC adenomas (from 46 AC+/LS mutation carriers) and 152 sporadic adenomas (from control group)	Retrospective analysis comparing the characteristics of 100 HNPCC adenomas with 152 sporadic adenomas	HNPCC adenomas more likely to be proximally located (50% vs. 26%; p=0.018), and smaller than sporadic adenomas All proximal HNPCC ≥5mm were highly dysplastic vs. 17% of the larger sporadic polyps (p<0.001) – and often more highly dysplastic than larger distal HNPCC adenomas (p<0.001)	

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GRADE Table 5: Studies: Constitutive mutations in early onset colorectal cancer (EOCRC)

Study	lation	Type/Limitations	Age of CRC	Testing	Results Tumour testing	Results germline testing
Pearlman 2017 [166]	450 EOCRC cases	Prospective study Good study No age stratification into decades	<50 years	IHC/MSI on tumour block n=450 25 cancer susceptibility gene panel on germline DNA n=450	48 (10.7%) dMMR tumour 3 *MLH1* hypermethylation 402 (89.3%) pMMR	37 LS, 2 MAP, 7 somatic MMR mutations, 1 constitutional hypermethylation 9 (2%) high penetrance CRC genes 13 (3%) other high/mod penetrance cancer predisposing gene 10 (2.5%) low penetrance CRC genes 145 patients (32%) VUS
Mork 2015 [167]	193 EOCRC	Retrospective study Good study but germline testing variable. No age	<35 years	IHC/MSI tumour n=173 Phenotype directed germline testing n=21	45 (26%) dMMR tumour	23 (51%) MMR mutation 21 (100%) pathogenic mutation in *APC, MUTYH* (biallelic), MMR genes (biallelic), TP53

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		stratificatio n				
Stoffel 2018 [168]	315 EOCRC	Retrospecti ve study Some missing data. Numbers in paper do not add up, so difficult to assess what was tested.	<50 years	IHC/MSI tumour n=146 Germline testing n= 430 (?)	38 (12%) dMMR tumour 126 (40%) pMMR tumour 151 (48%) MMR status tumour UK	17 (41%) MMR gene mutation 5(4%) high penetrance CRC gene mutation 14 (9%) high penetrance CRC gene mutation 79 (18%) high penetrance CRC gene mutations

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GRADE Table 6: Studies of patients with Multiple colorectal adenomas

Study	Population	Total Number	10-19 Adenomas	20-99 Adenomas	Gene Panel	Yield/Comments
Stanich 2019 [166]	US patients with >10 polyps	3789	1342	1657	*APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53, GREM1, POLD1, POLE*	7.6% of those with 10-19 adenomas and 13.7% in those with 20-99 adenomas
Grover 2012 [188]	MCRA	7225	970	3253	*APC, MUTYH*	9% 10-9 adenomas and 17% 20-99 adenomas
Nielsen 2007 [193]	10-99 adenomas in	146	na	na	*APC, MUTYH*	12.30%
Li 2017 [194]	Chinese MCRA	96	na	na	*APC, MUTYH*	57% had a pathogenic mutation identified versus only 2% in those without this personal or FH
Cheng 2015 [190]	Cases of 5-100 adenomas without *APC* or *MUTYH* mutations	178	na	na	Low penetrance SNPs rs6983267, rs10795668, rs3802842	3% of cases of 5-100 adenomas without APC or MUTYH mutations

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Ngeow 2014 [195]	5-29 polyps, at least one a hamartoma or serrated lesion	421	na	na	*ENG, PTEN, STK11*, *BMPR1A* and *SMAD4*	10.80%
Spier 2016 [192]	At least 20 synchronous or 40 metachronous adenomas no *MUTYH* or *APC* mutations	20	na	na	*APC* mosaicism	25%
Spier 2015 [189]	At least 20 synchronous or 40 metachronous adenomas no *MUTYH* or *APC* mutations	144	na	na	DNA polymerase gene pathogenic variants	1.30%

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