Colorectal Cancer Screening / Surveillance

Impact of Positive Family History

43. Schweizerische Koloproktologie-Tagung

27. Januar 2024

Kaspar Truninger

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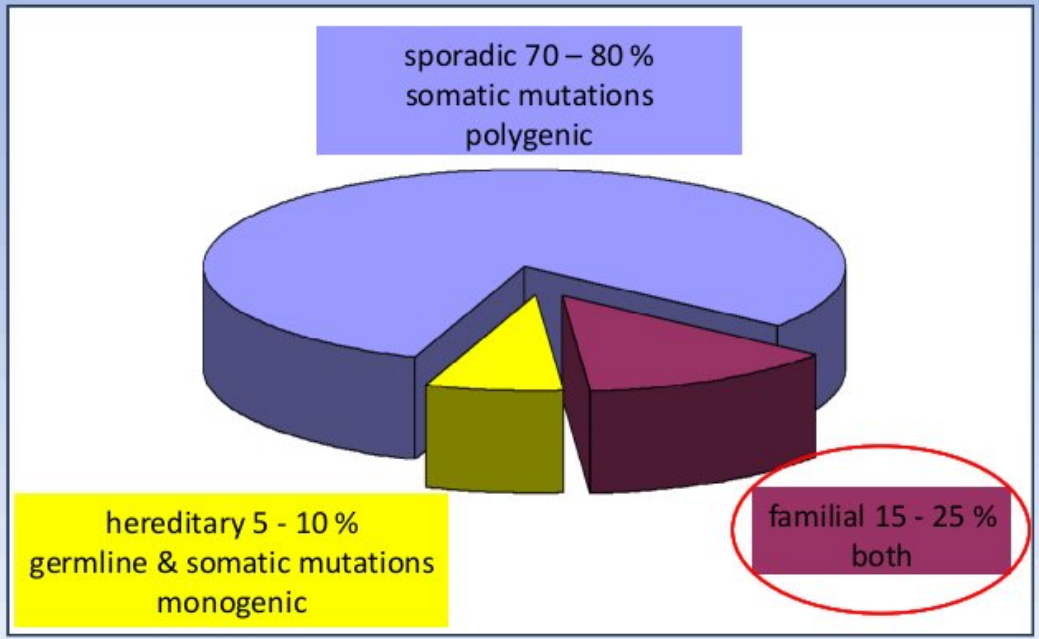
Gastroenterologie
Oberaargau

USZ Universitäts Spital Zürich

Colorectal Cancer Burden



The New England
Journal of Medicine

Volume 331 DECEMBER 22, 1994 Number 25

A PROSPECTIVE STUDY OF FAMILY HISTORY AND THE RISK OF COLORECTAL CANCER

CHARLES S. FUCHS, M.D., EDWARD L. GIOVANNUCCI, M.D., GRAHAM A. COLDITZ, M.B., B.S., DAVID J. HUNTER, M.B., B.S., FRANK E. SPEIZER, M.D., AND WALTER C. WILLETT, M.D.

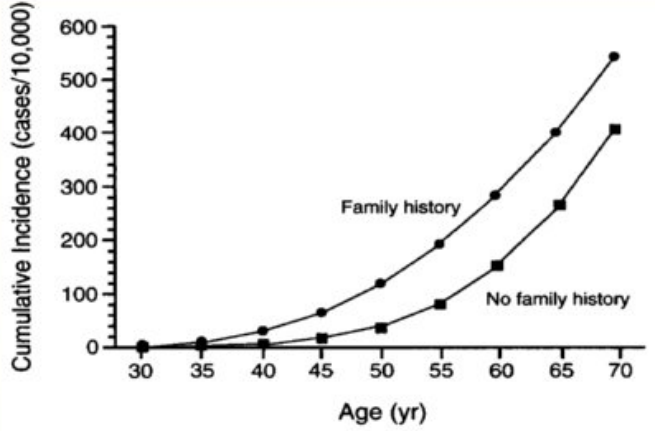


Figure 1. Cumulative Incidence of Colorectal Cancer According to Age and the Presence or Absence of a Family History of the Disease.

Table 2. Risk of Colorectal Cancer among Study Participants According to the Presence or Absence of a Family History of the Disease.*

PARTICIPANTS	NO. OF CASES	PERSON-YEARS OF FOLLOW-UP	AGE-ADJUSTED RR (95% CI)	MULTIVARIATE RR (95% CI)
Men				
No family history	127	161,716	1.0	1.0
Family history	21	14,377	1.64 (1.04–2.58)	1.60 (1.01–2.55)
Women				
No family history	263	607,577	1.0	1.0
Family history	52	56,359	1.77 (1.32–2.37)	1.76 (1.31–2.38)
Total				
No family history	390	769,293	1.0	1.0
Family history	73	70,736	1.72 (1.34–2.19)	1.72 (1.33–2.20)

Clinical Gastroenterology and Hepatology 2019;17:2657–2667

SYSTEMATIC REVIEWS AND META-ANALYSES

Siddharth Singh, Section Editor

Effects of Family History on Relative and Absolute Risks for Colorectal Cancer: A Systematic Review and Meta-Analysis

Victorine H. Roos,[*,a] Carolina Mangas-Sanjuan,[‡,a] Mar Rodriguez-Girondo,[§] Lucia Medina-Prado,[‡] Ewout W. Steyerberg,[§] Patrick M. M. Bossuyt,[‖] Evelien Dekker,[*] Rodrigo Jover,[‡,b] and Monique E. van Leerdam[¶,#,b]

Relative CRC Risk associated with having FDR with CRC

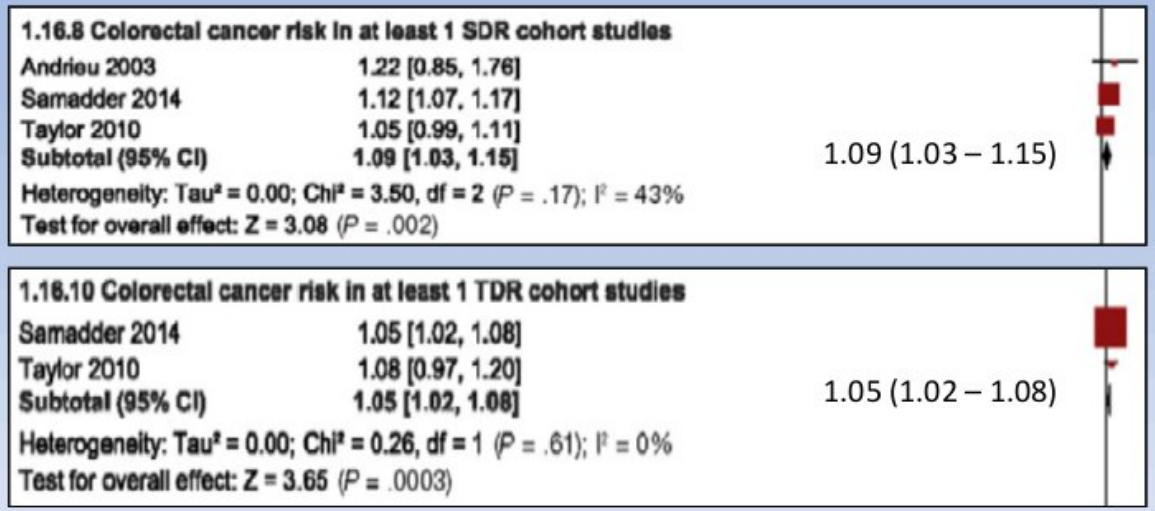
CRC risk 1 FDR cohort studies (3)	1.37 (0.76 – 2.46)
CRC risk at least 1 FDR cohort studies (12)	1.67 (1.52 – 1.82)
CRC risk at least 2 FDR cohort studies (3)	2.40 (1.76 – 3.28)

Impact of Age at CRC Diagnosis on FH-related CRC Risk

CRC risk having at least 1 FDR < 50 yrs cohort studies (4)	3.26 (2.82 – 3.77)
CRC risk having at least 1 FDR > 50 yrs cohort studies (3)	1.83 (1.55 – 2.16)
CRC risk having at least 1 FDR < 60 yrs cohort studies (4)	2.02 (1.59 – 2.57)
CRC risk having at least 1 FDR > 60 yrs cohort studies (4)	1.60 (1.35 – 1.90)

VH Roos et al. 2019

Relative CRC Risk associated with having ≥ 1 SDR/TDR with CRC

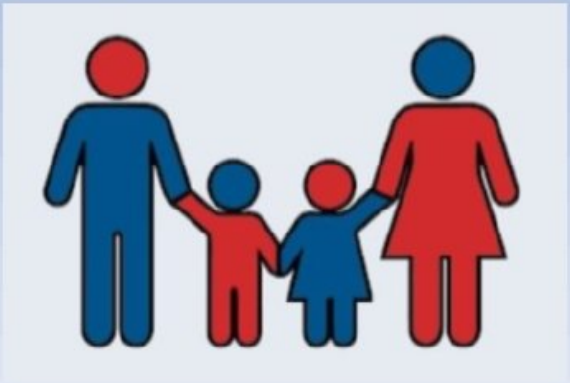


VH Roos et al. 2019

Familial Colorectal Cancer

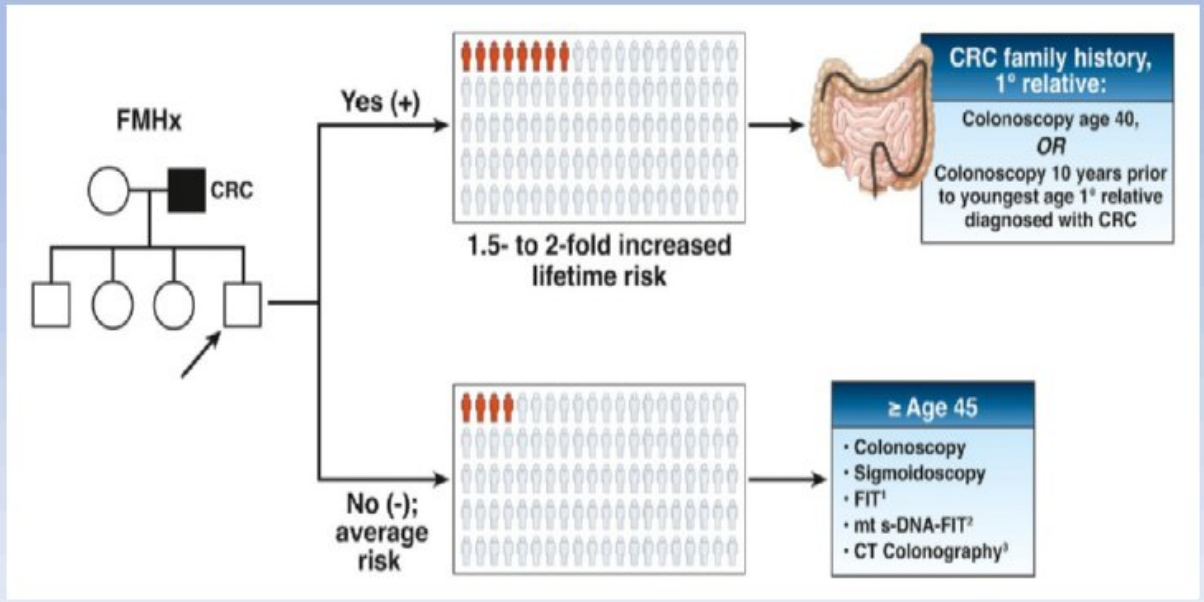
You are at increased risk if.....

.....you have a parent, sister or brother who had colorectal cancer



→ intensified screening

Familial CRC: AGA Screening Recommendations



intensified screening → differentiated approach

RB Issaka et al. 2023

Familial CRC: Screening Recommendations

Society	Definition	Modality	Age to start	Frequency
ESGE 2019	1 FDR age < 50 2 FDR any age	Colonoscopy	40	Colonoscopy 5 yrs
US-MSTF 2017	1 FDR age < 60 2 FDR any age 1 FDR age ≥ 60	Colonoscopy Any Modality	40* 40	Colonoscopy 5 yrs** as per average risk
CAG 2018	1 FDR any age 2 FDR any age	Colonoscopy Colonoscopy	40-50* 40*	Colonoscopy 5-10 yrs Colonoscopy 5 yrs
BSG 2020	1 FDR age < 50 2 FDR any age	Colonoscopy	55	FIT every 2 yrs
CC Austr 2017	1 FDR age < 55 2 FDR any age 1 FDR & ≥ 2 SDR any age	FIT Colonoscopy	40-50 50	2 years Colonoscopy 5 yrs

* or 10 years before the youngest affected relative ** if no advanced neoplasia till age 60, longer intervalls can be discussed

Familial CRC: Screening Recommendations

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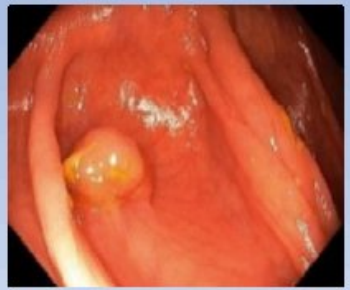
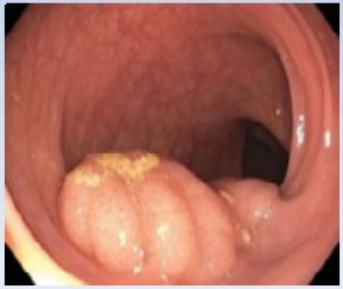
CRC Risk for Relatives of Patients with Polyps

adenomatous polyps (AP)

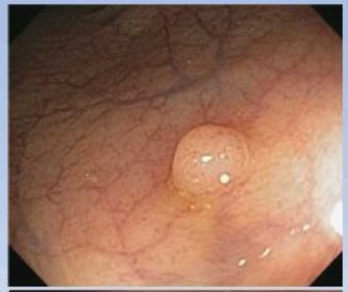


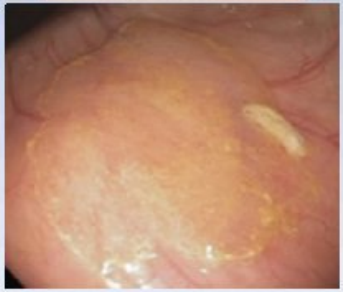


nonadvanced

advanced

serrated polyps (SP)





Relative CRC Risk for Relatives of Patients with any AP

	Cases		Controls				
Relationship	Affected	Unaffected	Affected	Unaffected	RR	95% CI	*P*
FDR	5530	8173	4251	8737	1.33	1.26-1.40	<.001
SDR	4222	7433	3901	7941	1.15	1.09-1.20	<.001
TDR[a]	12,740	20,827	12,402	22,277	1.09	1.06-1.12	<.001

TMF Tuohy et al. 2014

Relative CRC Risk for Relatives of Patients with Advanced AP

	CRC in Relatives of Probands Diagnosed With AAs						
	Cases		Controls				
Relationship	Affected	Unaffected	Affected	Unaffected	RR	95% CI	*P*
FDR	143	22,089	93	22,799	1.68	1.29-2.18	<.001
SDR	83	39,315	103	41,830	0.85	0.63-1.13	.265
TDR[a]	227	50,589	253	52,656	0.94	0.79-1.13	.528

TMF Tuohy et al. 2014

Relative CRC Risk for Relatives of FDR with Polyp-Subtype

Polyp types in FDRs	≥70 years	60-69 years	50-59 years	<50 years	P_{trend}
Hyperplastic polyps					
No. of cases (%)	503 (0.7)	572 (0.8)	427 (0.6)	165 (0.2)	
No. of controls (%)	1,975 (0.6)	2,132 (0.6)	1,445 (0.4)	562 (0.2)	
OR (95% CI)*	1.12 (1.01-1.25)	1.22 (1.11-1.35)	1.37 (1.22-1.53)	1.36 (1.13-1.63)	<.0001
Sessile serrated polyps					
No. of cases (%)	43 (0.1)	47 (0.1)	28 (0.0)	5 (0.0)	
No. of controls (%)	164 (0.0)	157 (0.0)	85 (0.0)	31 (0.0)	
OR (95% CI)*	1.06 (0.75-1.51)	1.39 (0.98-1.96)	1.68 (1.08-2.61)	0.80 (0.30-2.16)	0.02
Tubular adenomas					
No. of cases (%)	1,047 (1.5)	791 (1.2)	422 (0.6)	198 (0.3)	
No. of controls (%)	3,591 (1.1)	2,388 (0.7)	1,361 (0.4)	443 (0.1)	
OR (95% CI)*	1.24 (1.16-1.34)	1.51 (1.39-1.65)	1.40 (1.24-1.57)	1.94 (1.62-2.32)	<.0001
Tubulovillous adenomas					
No. of cases (%)	908 (1.3)	537 (0.8)	313 (0.5)	98 (0.1)	
No. of controls (%)	2,894 (0.9)	1,500 (0.4)	844 (0.3)	199 (0.1)	
OR (95% CI)*	1.32 (1.22-1.43)	1.50 (1.35-1.66)	1.58 (1.38-1.82)	2.22 (1.71-2.87)	<.0001
Villous adenomas					
No. of cases (%)	136 (0.2)	65 (0.1)	33 (0.0)	18 (0.0)	
No. of controls (%)	437 (0.1)	153 (0.0)	77 (0.0)	30 (0.0)	
OR (95% CI)*	1.18 (0.96-1.44)	1.69 (1.24-2.30)	1.84 (1.20-2.81)	2.06 (1.09-3.91)	<.0001

M Song et al. 2021

Relative CRC Risk by Number of FDR with Polyps

Polyp types in FDRs	Cases (n=68 060)	Controls (n=333 753)	Multivariable adjusted odds ratio (95% CI)*	Multivariable+family history of CRC adjusted odds ratio (95% CI)†
Any polyps				
No of FDRs with any polyps:				
0	62 318 (91.6)	314 893 (94.3)	1 (Ref)	1 (Ref)
1	5220 (7.7)	17 627 (5.3)	1.58 (1.53 to 1.63)	1.38 (1.33 to 1.43)
≥2	522 (0.8)	1233 (0.4)	2.27 (2.03 to 2.53)	1.70 (1.52 to 1.90)
P for trend	–	–	<0.001	<0.001

M Song et al. 2021

Familial Sporadic Colorectal Polyps: Screening Recommendations

No statement: ESGE, BSG, CC Australia etc.

Society	Definition	Modality	Age to start	Surveillance
US-MSTF	1 FDR aAP / aSP age < 60 2 FDR aAP / aSP any age	Colonoscopy	40*	every 5 yrs**
	1 FDR aAP / aSP age ≥ 60	any modality	40	as per average risk

* or 10 years before the youngest affected relative ** if no advanced neoplasia till age 60, longer intervall to be discussed

aAP / a SP: documented histology of advanced polyp !!

Envoi
SPECIALIST PATHOLOGISTS
inside insights

Update No.5 - 2019 Dr C Rosty

Updated WHO classification – colorectal serrated neoplasms

WHO classification of colorectal serrated lesions and polyps

Definition: Colorectal serrated lesions and polyps are characterised by serrated architecture of the epithelium.

Classification:

- Hyperplastic polyp (microvesicular and goblet cell rich subtype) (HP)
- Sessile serrated lesion (SSL)
- Sessile serrated lesion with dysplasia
- Traditional serrated adenoma (TSA)
- Unclassified serrated adenoma

Serrated Polyposis Syndrome

Criterion 1:

At least 5 serrated lesions/polyps proximal to the rectum

- all being ≥ 5 mm in size
- with ≥ 2 being ≥ 10 mm in size

Criterion 2:

More than 20 serrated lesions/polyps of any size distributed throughout the large bowel

- with ≥ 5 being proximal to the rectum

SP polyp count is cumulative over multiple colonoscopies

Relative CRC Risk for Relatives of Patients with SPS

First-degree relatives					Second-degree relatives				
Median age (min–max)	O	E	SIR (95% CI)	*P*	Median age (min–max)	O	E	SIR (95% CI)	*P*
55 (25–83)	54	10.47	5.16 (3.70–7.30)	<0.001	66 (34–85)	48	34.78	1.38 (1.01–1.91)	0.04

AK Win et al. 2012

Relative CRC Risk for Relatives of Patients with SPS

	Risk in patients with SPS			Risk in FDRs of SPS			Risk in SDRs of SPS			Risk in TDRs of SPS		
	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*	RR	95% CI	*P*
CRC	10.68	1.15–98.8	0.04	5.54	1.98–15.5	0.001	0.65	0.21–1.99	0.45	0.47	0.12–1.86	0.28

P Kanth et al. 2022

Surveillance for Relatives of Patients with SPS

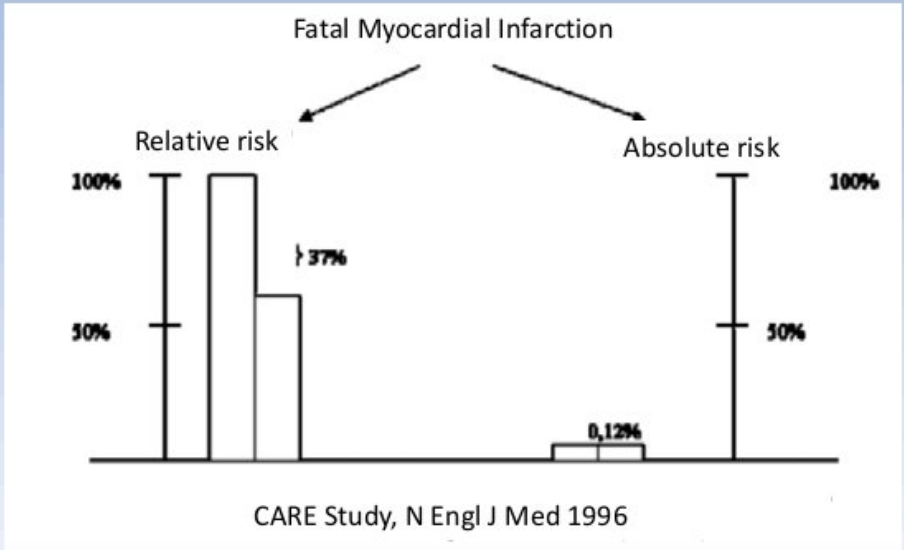
Society	Definition	Modality	Age to start	Surveillance
BSG 2020	FDR	Colonoscopy	40*	every 5 years
CC Australia	FDR	Colonoscopy	40*	every 5 years
ESGE 2019	FDR	Colonoscopy	45	every 5 years

* or 10 years earlier than index case

Relative / Absolute Disease Risk

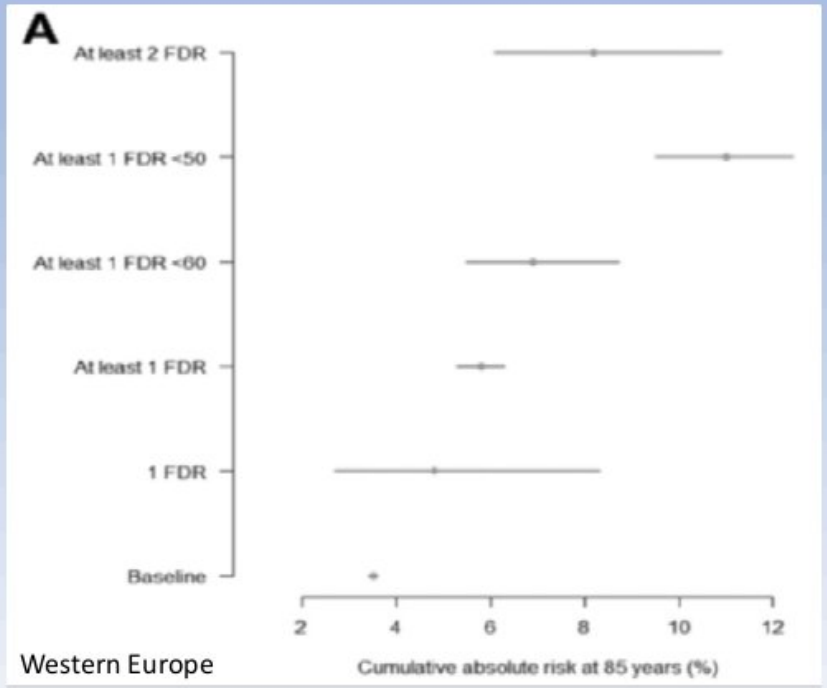
wonder drug reduces fatal heart attack risk in 5 years by 37 %

wonder drug reduces fatal heart attacks in 5 yrs from 1.8 % to 1.2 % (0.12% / yr)



CARE Study, N Engl J Med 1996

Cumulative Absolute CRC Risk at Age 85 for Relatives of Pts. with CRC



8.2 % (6.1-10.9)

11 % (9.5-12.4)

6.9 % (5.5-8.7)

5.8 % (5.3-6.3)

4.8 % (2.7-8.3)

3.5 %

VH Roos et al. 2019

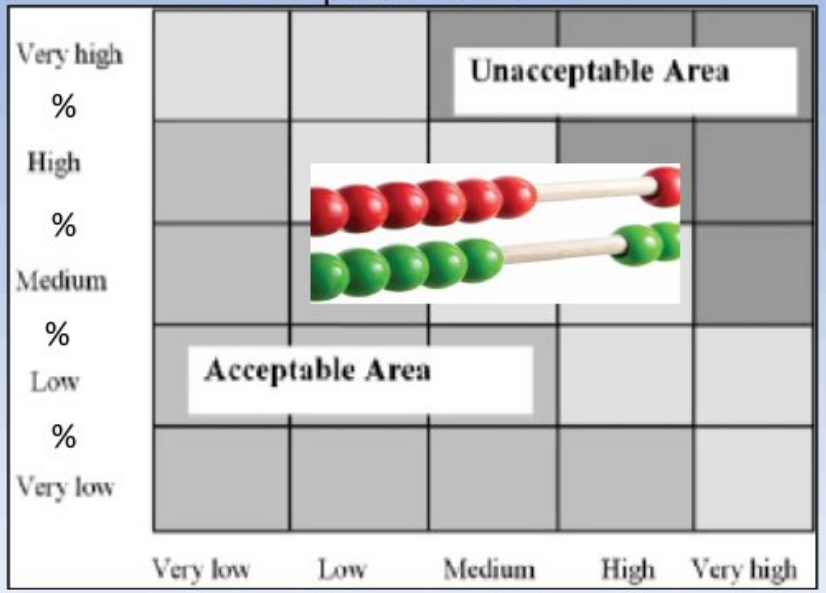
Cumulative Absolute CRC Risk at Age 70 for Relatives of Pts. with SPS

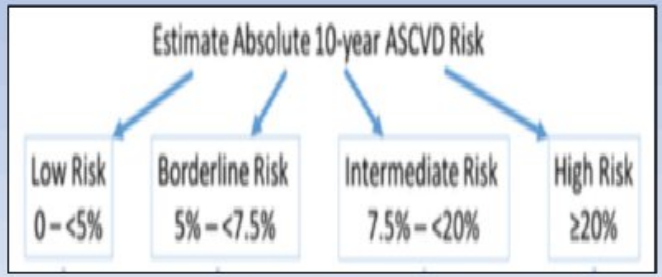
	Cumulative risk % (95% confidence interval)		
	Combined	**First-degree relatives**	**Second-degree relatives**
Male	7.01 (5.49 9.02)	15.34 (11.26 20.99)	4.36 (3.21 5.98)
Female	5.23(4.10–6.76)	11.60 (8.46–16.01)	3.24 (2.38–4.46)

AK Win et al. 2022

Threshold for Intensivied CRC Screening /Surveillance

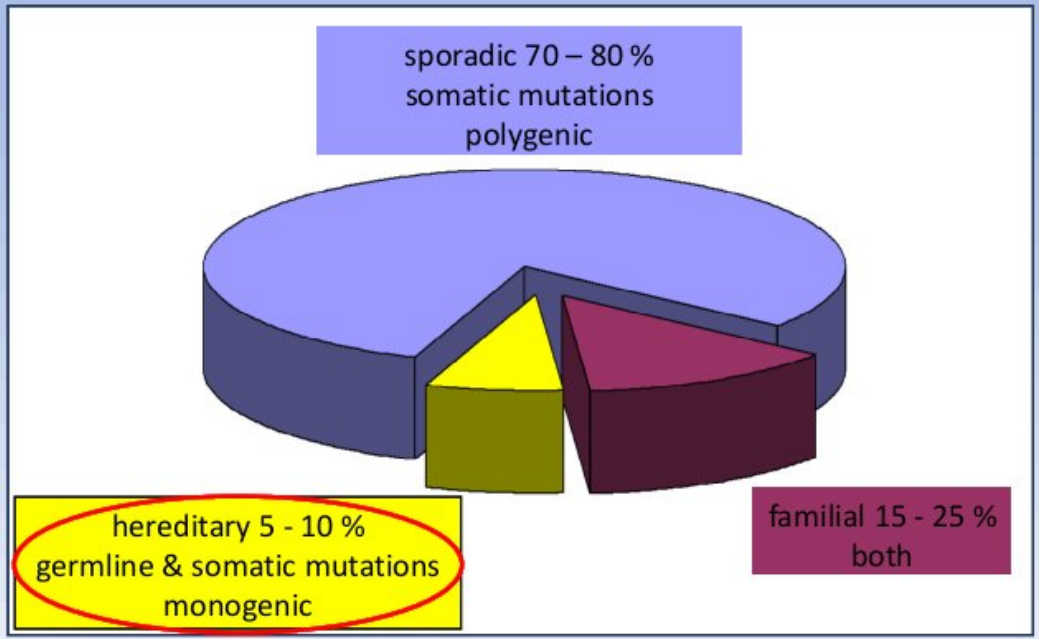
acceptable risk level?



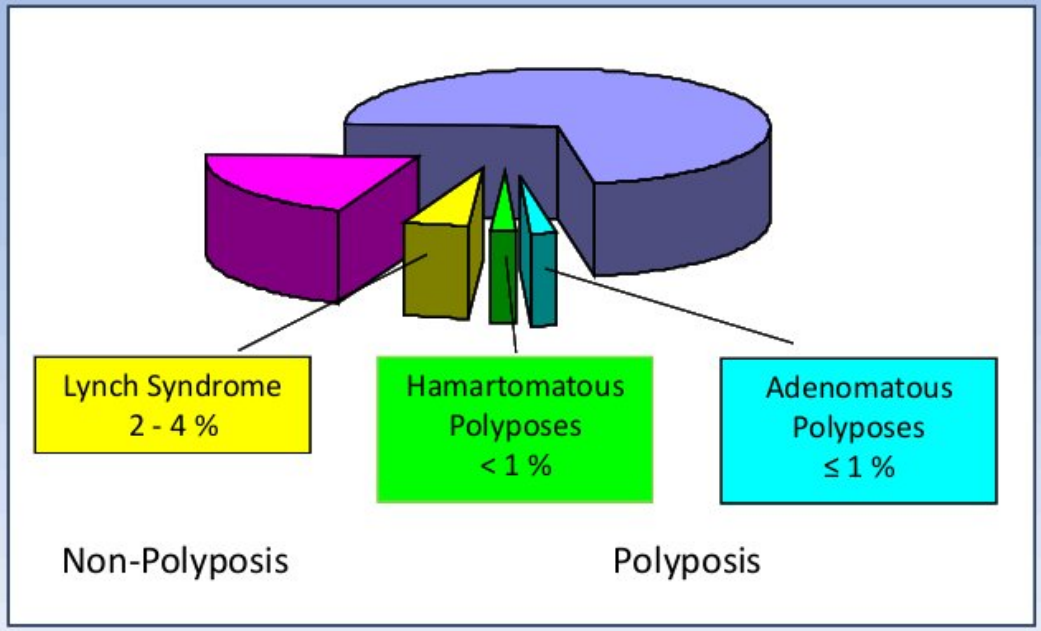


DM Lloyd-Jones et al. AHA / ACC 2019

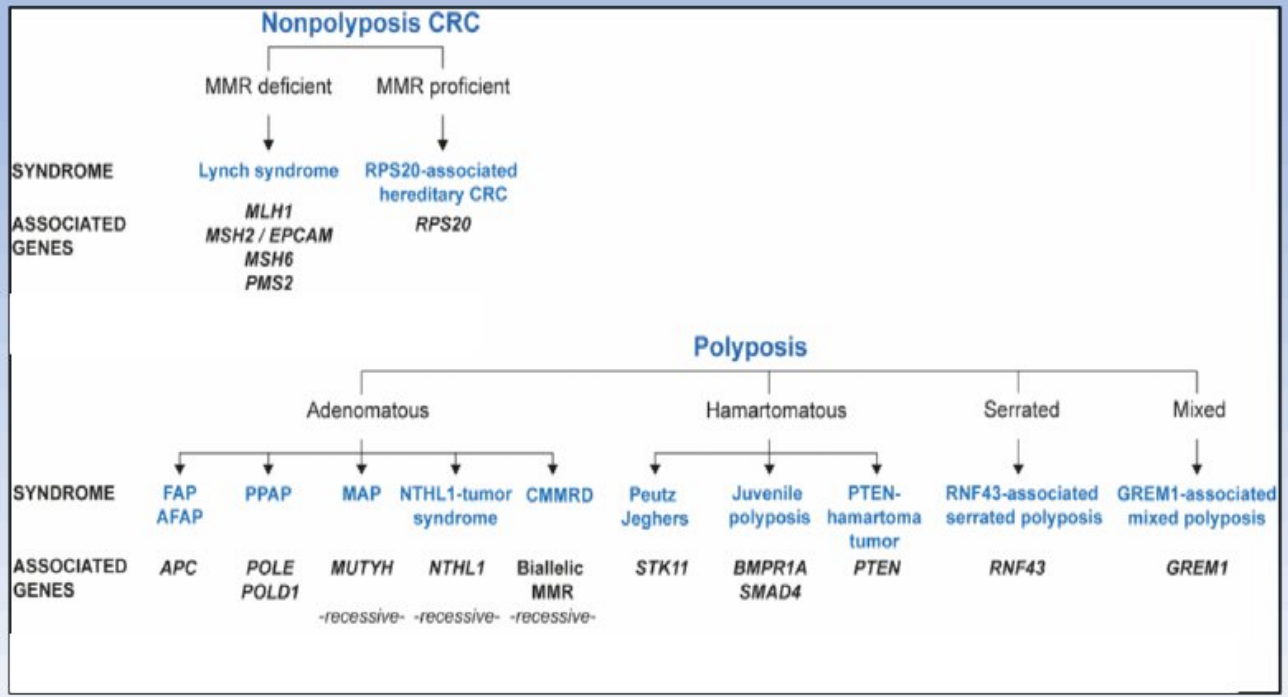
Hereditary Colorectal Cancer Burden



Hereditary Polyposis and Non-polyposis Syndromes



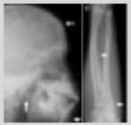
Hereditary CRC Syndromes, Phenotypes, Causal Genes

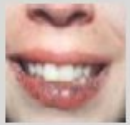


MD Alvarez et al. 2021

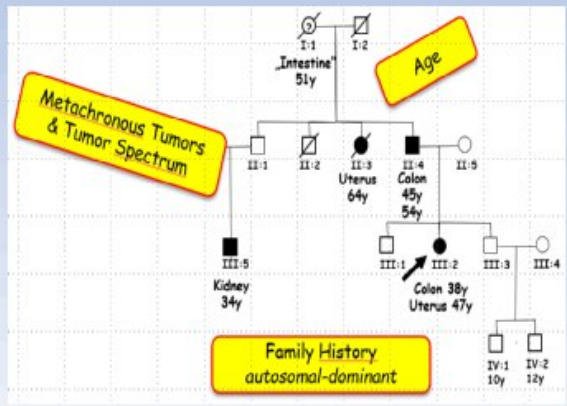
Clinical Suspicion of Inherited Tumor Predisposition

- Cancer before age 50
- Syn- / metachronous cancers
- Rare / specific tumor types

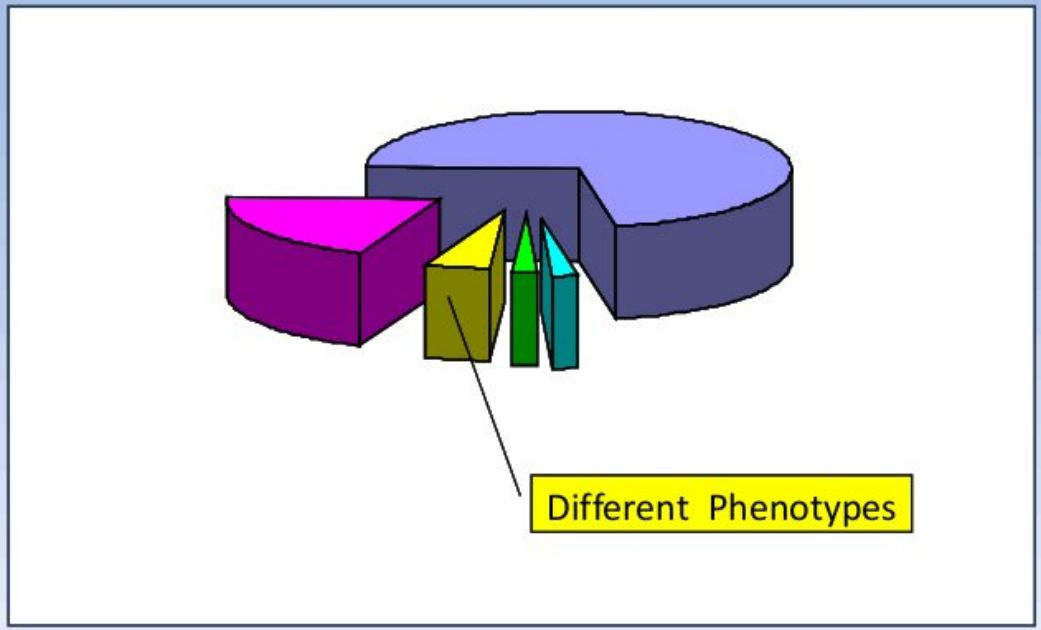




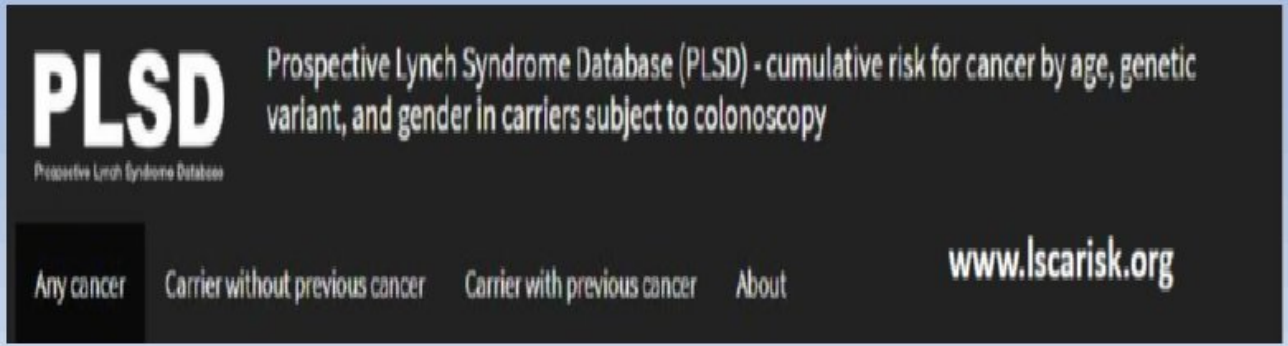
- Cumulative > 10 AP at age 60, > 20 AP at age 70
- Positive family history



Lynch Syndrome

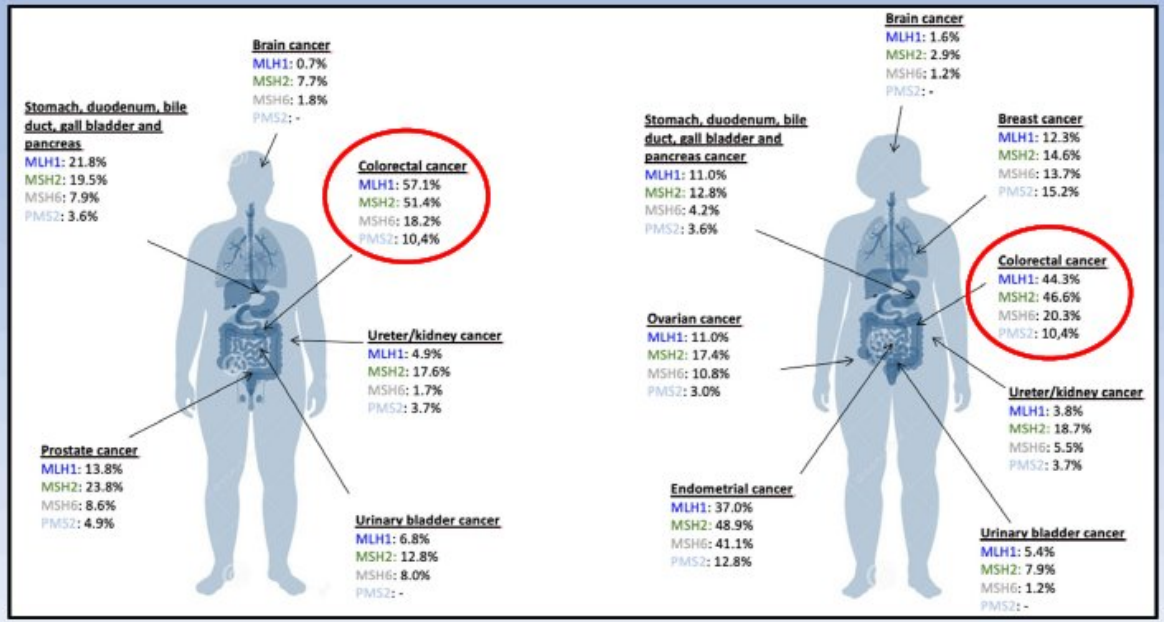


Big Data in Lynch Syndrom



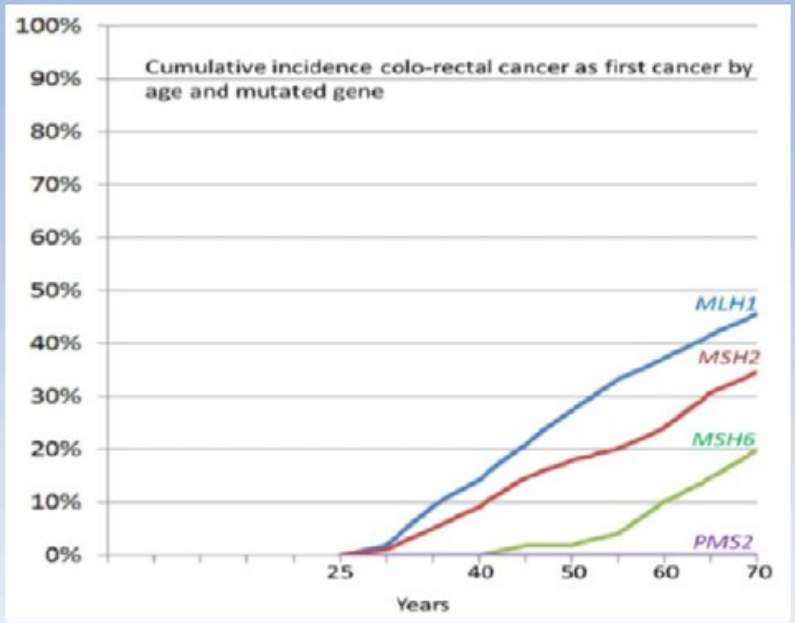
established 2012

Cumulative Cancer Risk at Age 75 related to Gene and Gender



J Llach et al. 2022

Cumulative CRC Risk at Age 70 by Gene

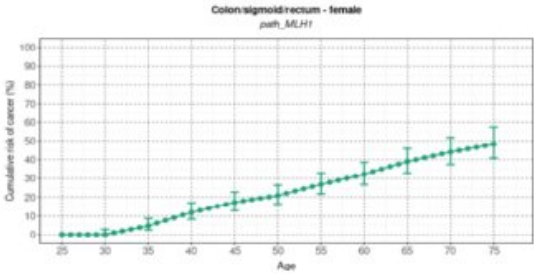


P Moller et al. 2017

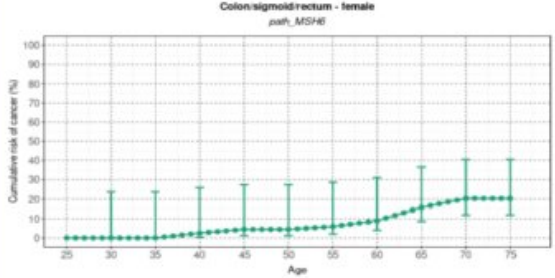
PLSD
Prospective Lynch Syndrome Database

Prospective Lynch Syndrome Database (PLSD) - cumulative risk for cancer by age, genetic variant, and gender in carriers subject to colonoscopy

Any cancer | Carrier without previous cancer | Carrier with previous cancer | About



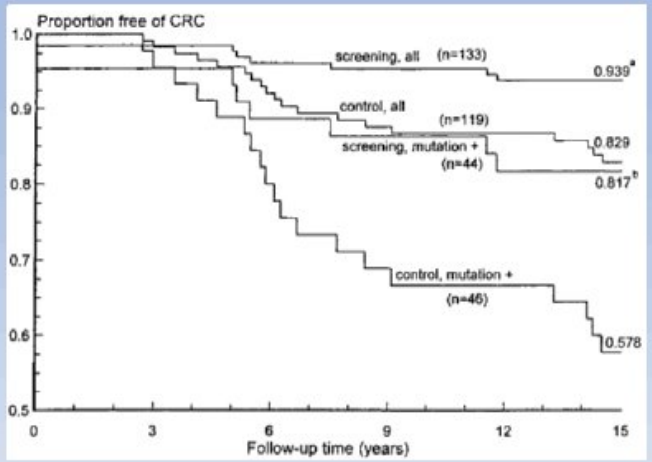
Age	Risk (%)	95% Confidence interval
25	0.00	[0 - 0]
40	11.80	[8.2 - 16.9]
50	20.60	[16.2 - 26.4]
60	32.20	[26.7 - 38.6]
70	44.10	[37.4 - 51.8]
75	48.30	[40.9 - 57.4]



Age	Risk (%)	95% Confidence interval
25	0.00	[0 - 0]
40	2.50	[0.4 - 25.9]
50	4.40	[1.2 - 27.4]
60	8.90	[3.9 - 31]
70	20.30	[11.8 - 40.5]
75	20.30	[11.8 - 40.5]

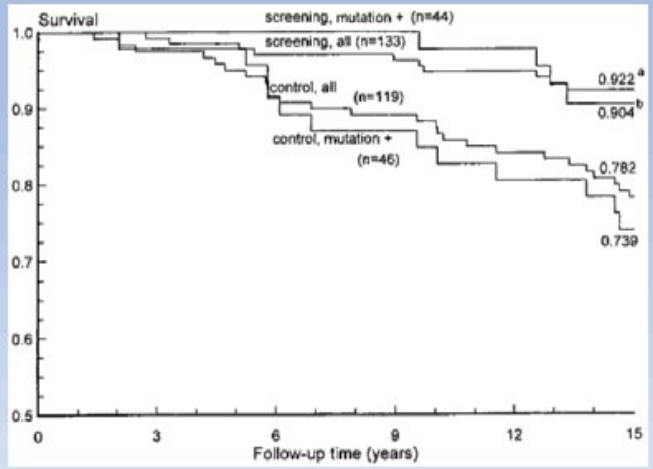
cumulative risk for cancer by age, genetic variant, and gender

Screening for CRC in Families with HNPCC



incidence

screen vs.no screen: 62 % risk reduction



mortality

screen vs.no screen: 66 % risk reduction

HJ Järvinen et al. 2000

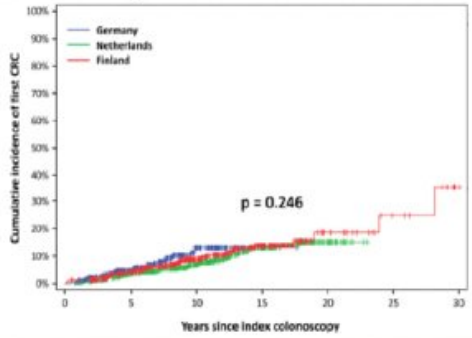
Different Colonoscopic LS Surveillance Policies

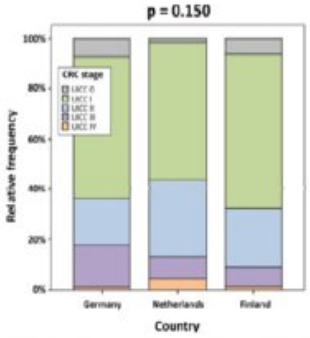
Recommended colonoscopy intervals in Lynch syndrome

Germany	The Netherlands	Finland
1-yearly	1-2-yearly	2-3-yearly

Outcome in 2747 patients

No reduction of CRC risk or tumor stage with shorter intervals



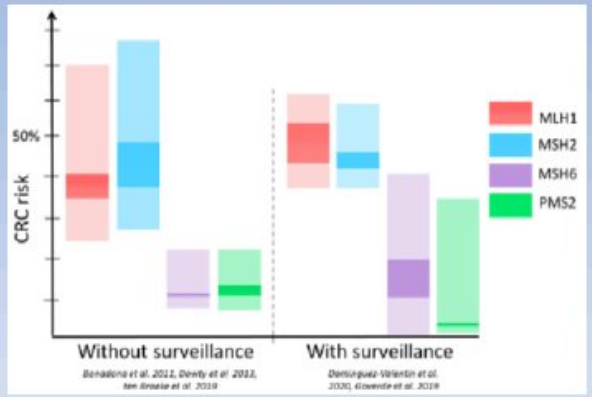


C Engel et al. 2018

Effect of Surveillance on CRC Risk

TABLE 1 CRC risk under surveillance in LS variant carriers independent of the affected MMR gene

Study	Setting	Colonoscopy interval (years)	Observation time	CRC incidence
Jarvinen et al [41]	Prospective	3	15 years	18%
De vos tot Nederveen Cappel et al [44]	Retrospective	2 to 3	10 years	10.5% (95% CI: 3.8-17.2)
Mecklin et al [42]	Prospective	2 to 3	Age 60	Men: 35% (95% CI: 16%-49%) Women: 22% (95% CI: 7%-34%)
Järvinen et al [45]	Prospective	2 to 3	11.5 years	12.4%
Stupart et al [46]	Prospective	1 to 2	5 years	11%
Engel et al [47]	Prospective	1 to 2	Age 60	23% (95% CI: 14.8%-31.2%)
Vasen et al [48]	Retrospective	1 to 2	10 years	6% (95% CI: 2.7%-8.7%)
Newton et al [49]	Retrospective	2	Age 70	25% (95% CI: 17-32%)
Engel et al [54]	Prospective	1 to 3	10 years	8.4% (95% CI: 7.1%-10.2%)



message to MMR mutation carriers
surveillance colonoscopy cannot always prevent crc, but detect it early

A Ahadova et al. 2020

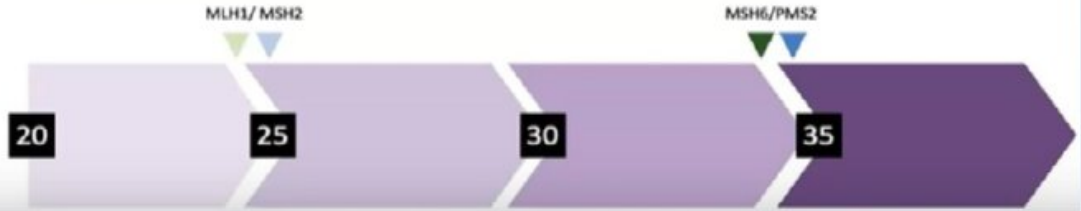
CRC Survival in LS with Colonoscopy Surveillance

Parameter	5-year survival (%)	95% CI (%)	10-year survival (%)	95% CI (%)
Interval				
Less than 1.5 years	89	[43–98]	89	[43–98]
1.5 to 2.5 years	95	[83–99]	90	[75–96]
2.5 to 3.5 years	94	[77–98]	90	[72–97]
Over 3.5 years	92	[57 99]	92	[57 99]
Stage[a]				
I	98	[84–99.7]	93	[79–98]
II	97	[80–99.6]	94	[78–98]
III	82	[55–94]	82	[55–94]

M Dominguez et al. 2020

TIME TO BEGIN COLORECTAL CANCER SURVEILLANCE

Societies supporting starting at 25 years for *MLH1/MSH2* and 35 for *MSH6/PMS2*	Societies supporting starting at 25 years for *MLH1/MSH2* and 35 for *MSH6/PMS2*, with reservations	Societies supporting 20-25 years for all LS carriers	Societies not providing a direct recommendation on the age to start
ESGE	ASCRF ("consider")	USMSTF	Manchester
BSG		ASCRF	JSMO
ACPGBI		ACG	NICE
UKCGG			SGO
EHTG			
ESCP			
ESMO			
NCCN			



G Cavestro, EHTG 2023

INTERVALS OF COLORECTAL CANCER SURVEILLANCE

Societies supporting surveillance every 1 year	Societies supporting surveillance every 1-2 years	Societies supporting surveillance every 2 years	Societies supporting surveillance every 2-3 years	Societies supporting surveillance every 5 years
ASCRF (*consider, and "after segmental colectomy"*)	USMSTF	ESGE	EHTG (*MLH1, MSH2, MSH6*)	EHTG (*PMS2*)
ACG (*conditional*)	ASCRF	BSG	ESCP (*MLH1, MSH2, MSH6*)	ESCP (*PMS2*)
	ESMO	ACPGBI		
	ACG	UKCGG		
	JSCCR	EHTG ("after segmental colectomy")		
	ESDO	ESCP ("after segmental colectomy")		
	NCCN			

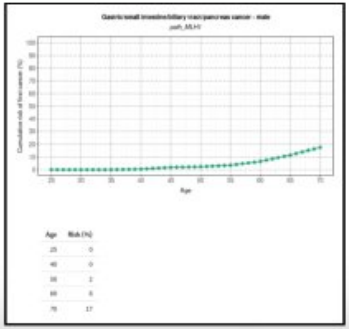
G Cavestro, EHTG 2023

USE OF CHROMOENDOSCOPY

Societies supporting it	Societies supporting it with reservations	Societies not supporting it	Societies without a statement
ESDO	ESGE (*"Suggests"*)	BSG	JSMO
ESMO	EHTG	ACPGBI	Manchester
		UKCGG	NICE
		ESCP	USMSTF
		NCCN	ASCRF
			ACG
			JSCCR
			SGO

Gastric Cancer Surveillance

Societies supporting it	Societies supporting it with reservations	Societies against it	Societies without a statement
USMSTF ("consider")	ESMO (high-risk areas and family history)	ESGE	JSMO
ASCRF ("consider")	JSCCR (before CRC surgery and high-risk areas)	BSG	Manchester
ACG ("consider")		ACPGBI	NICE
ESDO		UKCGG	NICE
NCCN			SGO
			EHTG
			ESCP



AGE TO START GASTRIC CANCER SURVEILLANCE

Societies supporting starting at 30-35 years	Societies supporting starting before 30 years, with reservations	Societies against it	Societies without a statement
USMSTF	ESDO	ESGE	EHTG
ESMO	NCCN	BSG	ESCP
JSCCR		ACPGBI	Manchester
		UKCGG	NICE
			ACG
			SGO
			JSMO

INTERVALS OF GASTRIC CANCER SURVEILLANCE

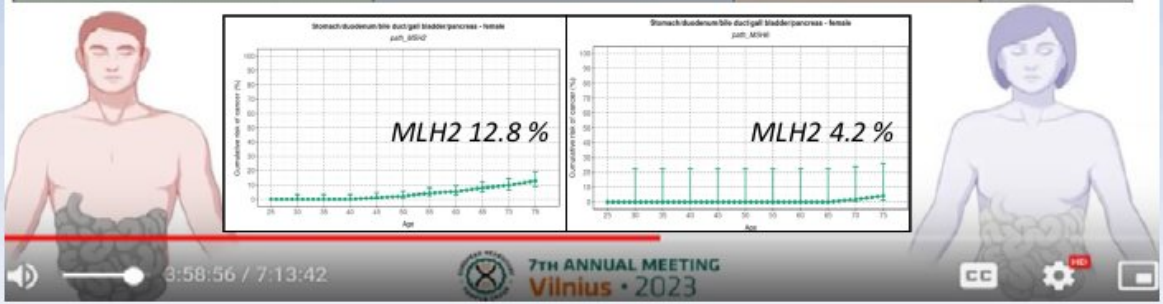
Societies supporting intervals of 1-3 years	Societies supporting intervals of 2-3 years	Societies supporting EGDS at every colonoscopy session	Societies against it	Societies without a statement
ESMO	USMSTF	ESDO	ESGE	EHTG
JSCCR	ASCRF		BSG	ESCP
	NCCN		ACPGBI	Manchester
			UKCGG	NICE
				ACG
				SGO
				JSMO

H.PYLORI TESTING AND ERADICATION

Societies supporting it	Societies supporting it with reservations	Societies against it	Societies without a statement
BSG	ESGE (non invasive)		JSMO
ACPGBI	USMSTF ("treatment" only)		EHTG
UKCGG			ESCP
ESMO ("consider")			Manchester
ACG ("consider")			NICE
JSCCR ("consider")			SGO
ESDO			ASCRF
NCCN			

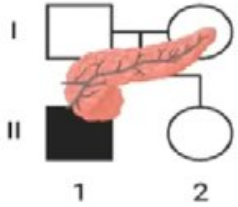
SMALL BOWEL CANCER SURVEILLANCE

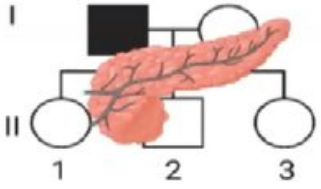
Societies supporting it	Societies supporting it with reservations	Societies against it	Societies without a statement
	NCCN	ESGE	JSCCR
		BSG	SGO
		ACPGBI	ESDO
		UKCGG	JSMO
		USMSTF	EHTG
		ASCRF	Manchester
		ESMO	NICE
		ACG	ESCP



PANCREATIC CANCER SURVEILLANCE

Societies supporting routine pancreatic surveillance	Societies supporting pancreatic surveillance in families with at least one FDR affected	Societies against routine pancreatic surveillance	Societies without a statement
	ESMO ("consider")	BSG	ESGE
	ACG	ACPGBI	JSMO
	JSCCR (at the time of CRC surgery)	UKCGG	ESGE
	ESDO ("consider")	USMSTF	Manchester
	NCCN (at least one FDR/SDR, but not for *PMS2*)		NICE
			ASCRF
			SGO
			EHTG
			ESCP

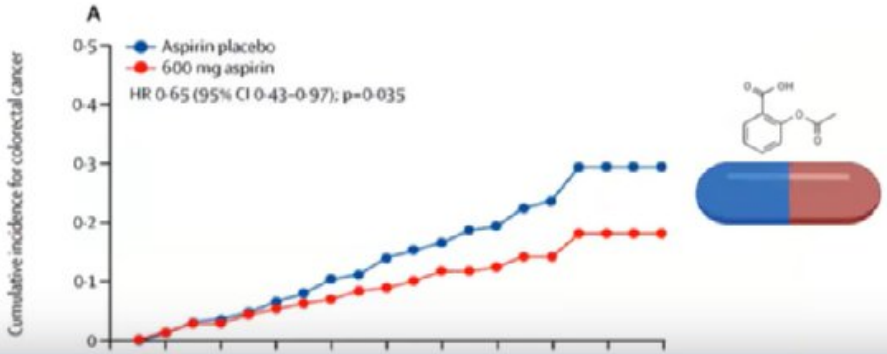




7TH ANNUAL MEETING
Vilnius · 2023

MEDICAL INTERVENTION
Aspirin

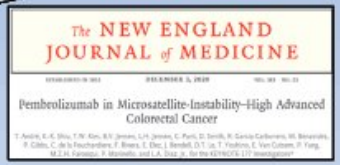
Societies supporting it	Societies partially supporting it	Societies not supporting it	Societies without a statement
EHTG, ESCP	BSG, ACPGBI, UKCGG	NICE	**ESGE**
Manchester	USMSTF	ACG	
NCCN	ASCRF	JSCCR	
	ESMO		

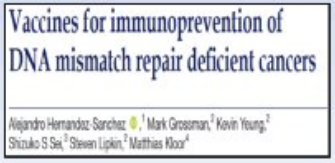


CRC screening /surveillance for Relatives with a Positive Family History für Colorectal Neoplasia

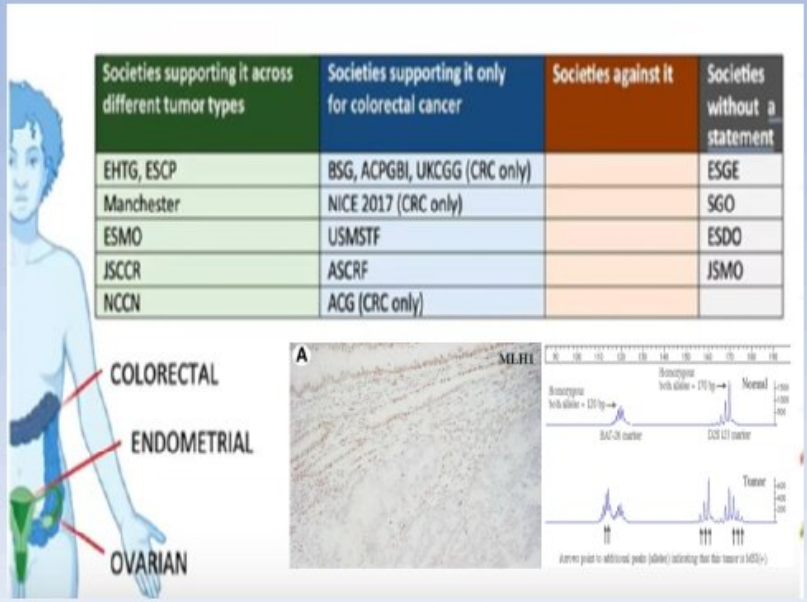
unified guidelines?

Universal Tumor Testing for Mismatch Repair Deficiency





Societies supporting it across different tumor types	Societies supporting it only for colorectal cancer	Societies against it	Societies without a statement
EHTG, ESCP	BSG, ACPGBI, UKCGG (CRC only)		ESGE
Manchester	NICE 2017 (CRC only)		SGO
ESMO	USMSTF		ESDO
JSCCR	ASCRF		JSMO
NCCN	ACG (CRC only)		



IHC Staining

MSI Testing

Lynch-like Syndrome (LLS)

- Mismatch repair deficient, but no pathogenic mutation in MMR genes
- No V600E mutation in *BRAF*
- No methylation in *MLH1* promoter

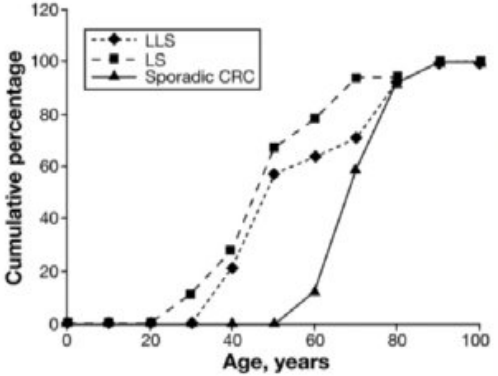


Figure 1. Cumulative age of onset of CRC in first-degree relatives of patients with LS, LLS, and sporadic CRC.

Table 3. SIRs Between Families With LLS and Families With LS/Sporadic CRC

	LS (n = 80)		*P*	LLS (n = 177)		*P*	Sporadic CRC (n = 845)	
	No. of tumors	SIR (95% CI)	value[a]	No. of tumors	SIR (95% CI)	value[b]	No. of tumors	SIR (95% CI)
CRC	18	6.04 (3.58–9.54)	<.001	14	2.12 (1.16–3.56)	<.001	15	0.48 (0.27–0.79)
Non-CRC LSRC	6	2.81 (1.03–6.12)	.09	8	1.69 (0.73–3.34)	.5	27	1.20 (0.79–1.74)
Total	24	4.69 (3.00–6.98)	<.001	22	1.94 (1.22–2.94)	<.001	42	0.78 (0.56–1.05)

[a]Comparing the SIR of the LS and LLS groups.
[b]Comparing the SIR of the LLS and sporadic CRC groups.

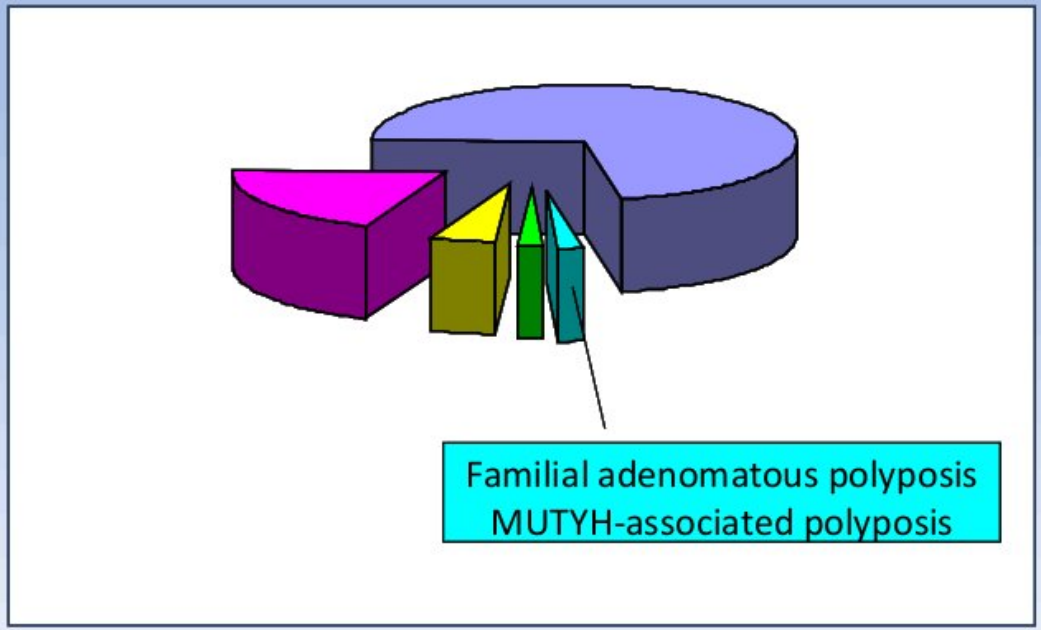
CRC screening with colonoscopy every 3 years
(at least in pts with EOCRC or strong FH for LS-related cancers

Rodriguez-Soler et al. 2013

Familial Colorectal Cancer Type X (FCCTX)

- Amsterdam criteria fulfilled
- No pathogenic mutation in MMR genes >> Mismatch repair proficient
- Compared to LS
  - Lower CRC risk, slower progression of adenoma-carcinoma sequence
  - Later age of onset compared to LS
  - Predominantly distal location (sigmoid, rectum)
  - Lower risk for extracolonic tumors compared to LS
  - Lower frequency of poor differentiation, lymphocytic infiltration, mucin production
- ASGE: colonoscopy every 3-5 years, starting 10 years before the age at diagnosis of the youngest affected relative

Hereditary Adenomatous Polyposis Syndromes



Hereditary Adenomatous Polyposis Syndromes

TABLE 2. Cancer risks and genes associated with hereditary polyposis syndromes

Syndrome	Gene	Inheritance pattern	Lifetime cancer risks	Percentage
Familial adenomatous polyposis	*APC*	Autosomal dominant	Colorectum	Nearly 100
			Duodenum/ampulla	4-12
			Stomach	1
			Pancreas	2
			Thyroid	1-2
			Liver (hepatoblastoma)	1-2
			Central nervous system (medulloblastoma)	<1
Attenuated FAP	*APC*	Autosomal dominant	Colorectum	70
			Duodenum/ampulla	4-12
			Thyroid	1-2
MUTYH-associated polyposis	*MUTYH*	Autosomal recessive	Colorectum	80
			Duodenum	4
			Stomach	1

J Yang et al. 2020

Hereditary Adenomatous Polyposis Syndromes

Polyp subtype	Polyposis syndrome	Gene	Germline mutation found	Incidence	Clinical criteria	CRC risk
Adenomatous	Familial adenomatous polyposis (FAP)	*APC*	70%–90%	1 in 10000	Classic: > 100 adenomas in colon/rectum at age 25	100%
					Attenuated: < 100 adenomas in colon/rectum at age 25	69%
	MUTYH-associated polyposis (MAP)	*MUTYH*	16%–40%	1–4 in 10000	20–100 adenomas in colon/rectum	19%–43%

ME v Leerdam et al. 2019

Endoscopic Surveillance Adenomatous Polyposis Syndromes ASGE

Condition	Screening examination	Starting age at screening	Surveillance interval	Quality of evidence
FAP	Sigmoidoscopy or colonoscopy Colonoscopy when polyps are found	10-12 y	1-2 y	⊕⊕⊕○
Attenuated FAP	Colonoscopy	18-20 y	1-2 y	⊕⊕○○
MUTYH- associated polyposis	Colonoscopy	18-20 y	1-2 y	⊕⊕○○
MUTYH heterozygote + first-degree relative with CRC	Colonoscopy	40 y, or before 10 y age of first-degree relative's age of CRC diagnosis	5 y	⊕○○○
MUTYH heterozygote without family history of CRC	Unknown	Unknown	Unknown	–
After total colectomy with IPAA	Pouch endoscopy	1 y after surgery	1-2 y 6 mo if advanced adenoma including HGD	⊕○○○
After subtotal colectomy and ileorectal anastomosis	Sigmoidoscopy	6 mo after surgery	6 mo to 1 y	⊕○○○

J Yang et al. 2020

Endoscopic Surveillance Adenomatous Polyposis Syndromes ESGE

Polyposis syndrome	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	12–14 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps >5 mm
MUTYH-associated polyposis	18 years	Every 1–2 years	Pre- and post-colectomy: remove all polyps >5 mm

Hereditary Polyposis Syndromes

Polyp subtype	Polyposis syndrome	Gene	Germline mutation found	Incidence	Clinical criteria	CRC risk
Adenomatous	Familial adenomatous polyposis (FAP)	*APC*	70 % – 90 %	1 in 10 000	Classic: > 100 adenomas in colon/rectum at age 25	100 %
					Attenuated: < 100 adenomas in colon/rectum at age 25	69 %
	MUTYH-associated polyposis (MAP)	*MUTYH*	16 % – 40 %	1 – 4 in 10 000	20 – 100 adenomas in colon/rectum	19 % – 43 %
Hamartomatous	Peutz–Jeghers syndrome (PJS)	*STK11/LKB1*	80 % – 94 %	1 in 250 000	**1** ≥ 2 histologically confirmed Peutz–Jeghers polyps **2** any number of Peutz–Jeghers polyps in an individual with a positive family history of PJS **3** presence of characteristic mucocutaneous pigmentations in an individual with a positive family history of PJS **4** any number of Peutz–Jeghers polyps in an individual with characteristic mucocutaneous pigmentation	15 % – 57 %
	Juvenile polyposis syndrome (JPS)	*SMAD4, BMPR1A*	40 % – 60 %	1 – 1.6 in 100 000	**1** ≥ 5 juvenile polyps are present in the colon/rectum or in other parts of the gastrointestinal tract **2** any number of juvenile polyps in a patient with one or more relatives affected with JPS	39 % – 68 %
Serrated	Serrated polyposis syndrome (SPS)	No germline mutation identified	NA	31 – 80 in 10 000 in FIT screening 42 in 10 000 in colonoscopy screening	**1** ≥ 5 serrated polyps proximal to the sigmoid with ≥ 2 being > 10 mm **2** > 20 serrated polyps of any size distributed throughout the colon	15 % – 30 %

ME v Leerdam et al. 2019

Endoscopic Surveillance Polyposis Syndromes ESGE

Polyposis syndrome	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	12 – 14 years	Every 1 – 2 years	Pre- and post-colectomy: remove all polyps > 5 mm
MUTYH-associated polyposis	18 years	Every 1 – 2 years	Pre- and post-colectomy: remove all polyps > 5 mm
Peutz–Jeghers syndrome	Baseline: 8 years Routine: 18 years	Baseline: if polyps found, every 1 – 3 years Routine: every 1 – 3 years	Elective polypectomy
Juvenile polyposis syndrome	12 – 15 years	Every 1 – 3 years	Elective polypectomy for polyps > 10 mm
Serrated polyposis syndrome	NA	1 year: after ≥ 1 advanced polyp or ≥ 5 non-advanced clinically relevant polyps 2 years: after no advanced polyps or < 5 non-advanced clinically relevant polyps	Clearing/surveillance phase: remove all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia

ME v Leerdam et al. 2019

Endoscopic Surveillance Hereditary Polyposis Syndromes ESGE

Polyposis syndrome	Modality	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	Esophagogastroduodenoscopy	25 years	According to Spigelman score, adjusted for appearance of the ampulla	Non-ampullary adenomas: considerer endoscopic resection of adenomas ≥ 10 mm Ampullary adenomas: consider discussing endoscopic treatment in a multidisciplinary setting for adenomas ≥ 10 mm, showing excessive growth, or with suspicion of invasive growth
MUTYH-associated polyposis	Esophagogastroduodenoscopy	35 years	According to Spigelman score, adjusted for appearance of the ampulla	Non-ampullary adenomas: considerer endoscopic resection of adenomas ≥ 10 mm Ampullary adenomas: consider discussing endoscopic treatment in a multidisciplinary setting for adenomas ≥ 10 mm, showing excessive growth, or with suspicion of invasive growth
Peutz–Jeghers syndrome	Esophagogastroduodenoscopy	Baseline: 8 years Routine: 18 years	Baseline: if polyps found, every 1 – 3 years Routine: every 1 – 3 years	Elective polypectomy
	MRI studies or video capsule enteroscopy	8 years	Every 1 – 3 years	Elective polypectomy for polyps > 15 – 20 mm, preferably using device-assisted enteroscopy
Juvenile polyposis syndrome: *SMAD4* mutation carriers	Esophagogastroduodenoscopy	18 years	Every 1 – 3 years	Gastric management should be discussed in a multidisciplinary setting
Juvenile polyposis syndrome: *BMPR1A* mutation carriers	Esophagogastroduodenoscopy	25 years	Every 1 – 3 years	Gastric management should be discussed in a multidisciplinary setting
Serrated polyposis syndrome	NA	NA	NA	NA

ME v Leerdam et al. 2019

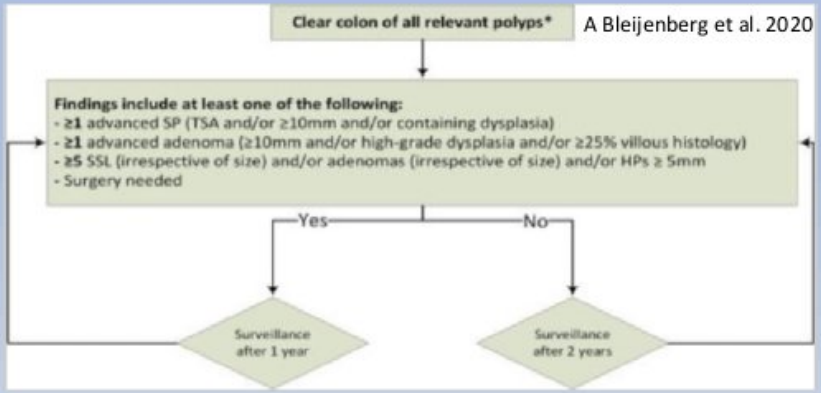
Endoscopic Surveillance of FAP and MAP: ESGE / BSG / ASGE

Risk of cancer and recommendations for endoscopic surveillance.

	FAP	MAP
Germline mutation	*APC*	*MUTYH*
Risk of cancer		
Colorectum	100%	80–90%
Duodenum	5–10%	1%
Stomach	1%	2%[A]
Endoscopic surveillance frequency		
Colonoscopy (pre-colectomy)	1 to 3-yearly from age 10–14	1 to 3-yearly from age 18–20
Pouchoscopy/sigmoidoscopy (post-colectomy)	½ to 3-yearly	½ to 3-yearly
Gastroduodenoscopy	½ to 5-yearly from age 20–25	½ to 5-yearly from age 30–35
Endoscopic polypectomy indications		
Colorectum/ileal pouch	Adenomas > 5 mm	Adenomas > 5 mm
Duodenum	Duodenal or ampullary adenomas ≥10 mm	Duodenal or ampullary adenomas ≥10 mm
Stomach	Adenomas > 5 mm	Adenomas > 5 mm

AS Aelvoet et al. 2022

Personalized Surveillance in SPS



		Age to start	Surveillance intervall	Treatment indication
ESGE M v Leerdam et al. 2019	Serrated polyposis syndrome	NA	1 year: after ≥ 1 advanced polyp or ≥ 5 non-advanced clinically relevant polyps 2 years: after no advanced polyps or < 5 non-advanced clinically relevant polyps	Clearing/surveillance phase: remove all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia

BSG	Serrated polyposis syndrome	Affected individuals (WHO 2019)	Colonoscopy	From age of diagnosis	1–2 yearly until age 75 years
		FDRs of affected individuals	Colonoscopy	40 (or 10 years earlier than the index case)	5 yearly until age 75 years