



Universiteit
Leiden
The Netherlands

Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline

Leerdam, M.E. van; Roos, V.H.; Hooft, J.E. van; Dekker, E.; Jover, R.; Kaminskis, M.F.; ... ; Ricciardiello, L.

Citation

Leerdam, M. E. van, Roos, V. H., Hooft, J. E. van, Dekker, E., Jover, R., Kaminskis, M. F., ... Ricciardiello, L. (2019). Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy*, 51(9), 877-895. doi:10.1055/a-0965-0605

Version: Not Applicable (or Unknown)
License: [Leiden University Non-exclusive license](#)
Downloaded from: <https://hdl.handle.net/1887/120058>

Note: To cite this publication please use the final published version (if applicable).

Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) Guideline



Authors

Monique E. van Leerdam^{1,2}, Victorine H. Roos³, Jeanin E. van Hooft³, Evelien Dekker³, Rodrigo Jover⁴, Michal F. Kaminski^{5,6,7}, Andrew Latchford^{8,9}, Helmut Neumann¹⁰, Maria Pellisé^{11,12}, Jean-Christophe Saurin¹³, Pieter J. Tanis¹⁴, Anja Wagner¹⁵, Francesc Balaguer^{11,12}, Luigi Ricciardiello¹⁶

Institutions

- 1 Department of Gastroenterology and Hepatology, Netherlands Cancer Institute, Amsterdam, The Netherlands
- 2 Department of Gastroenterology and Hepatology, Leiden University Medical Center and Foundation for the Detection of Hereditary Tumours, Leiden, The Netherlands
- 3 Department of Gastroenterology and Hepatology, Amsterdam University Medical Centers, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
- 4 Department of Gastroenterology, Hospital General Universitario de Alicante, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL), Alicante, Spain
- 5 Cancer Prevention, The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
- 6 Gastroenterology, Hepatology and Clinical Oncology, Medical Centre for Postgraduate Education, Warsaw, Poland
- 7 Department of Health Management and Health Economics, University of Oslo, Oslo, Norway
- 8 Polyposis Registry, St. Mark's Hospital, Harrow, United Kingdom
- 9 Department of Surgery and Cancer, Imperial College London, London, United Kingdom
- 10 Department of Medicine I, University Medical Center Mainz, Mainz, Germany
- 11 Gastroenterology Department, Hospital Clínic de Barcelona, Barcelona, Spain
- 12 Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomediques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain
- 13 Gastroenterology and Endoscopy Unit, Hospices Civils de Lyon, Hôpital E. Herriot, Lyon, France

- 14 Department of Surgery, Amsterdam University Medical Centers, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
- 15 Department of Clinical Genetics, Erasmus Medical Center, Rotterdam, The Netherlands
- 16 Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

Bibliography

DOI <https://doi.org/10.1055/a-0965-0605>

Published online: 23.7.2019 | Endoscopy 2019; 51: 877–895

© Georg Thieme Verlag KG Stuttgart · New York

ISSN 0013-726X

Corresponding author

Monique E. van Leerdam, MD PhD, Department of Gastroenterology and Hepatology, Netherlands Cancer Institute, Plesmanlaan 121, 1066CX, Amsterdam, The Netherlands
m.v.leerdam@nki.nl



Appendix 1s
Online content viewable at:

<https://doi.org/10.1055/a-0965-0605>

MAIN RECOMMENDATIONS

ESGE recommends that individuals with hereditary gastrointestinal polyposis syndromes should be surveilled in dedicated units that provide monitoring of compliance and endoscopic performance measures.

Strong recommendation, moderate quality of evidence, level of agreement 90%.

ESGE recommends performing esophagogastroduodenoscopy, small-bowel examination, and/or colonoscopy earlier than the planned surveillance procedure if a patient is symptomatic.

Strong recommendation, low quality of evidence, level of agreement 100%.

PUBLICATION INFORMATION

This Guideline is an official statement of the European Society of Gastrointestinal Endoscopy (ESGE). The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was adopted to define the strength of recommendations and the quality of evidence.

Introduction

Colorectal cancer (CRC) is the fourth most incident cancer and is the second commonest cause of cancer-related death in Europe [1]. While the majority of CRC is sporadic, twin studies have shown that up to 35% of CRC cases have a familial component [2]. Approximately 2%–5% of CRC cases are genetically determined by mutations in the adenomatous polyposis coli (*APC*), *MUTYH*, DNA mismatch repair, or other predisposing genes [3].

Although hereditary CRC syndromes are rare, it is of great importance that clinicians recognize these syndromes so they can make appropriate management decisions for both the patient and their family members who may also be at risk. Because all patients with polyposis syndrome are at high risk of developing gastrointestinal (GI) malignancies, endoscopic surveillance and interventions are required to prevent the development of cancer or to detect cancer at an early stage. Currently, there is uncertainty about the surveillance intervals and optimal endoscopic management, and guidelines regarding polyposis syndromes are limited. Therefore, the aim of this evidence-based and consensus guideline, commissioned by the European Society of Gastrointestinal Endoscopy (ESGE), is to provide clinicians with a comprehensive overview of the management options regarding endoscopic surveillance and interventions for the most important polyposis syndromes, namely familial adenomatous polyposis (FAP), *MUTYH*-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and serrated polyposis syndrome (SPS) (overview shown in ► **Table 1** [4–28]).

There are several other polyposis-associated genes, including *PTEN*, *GREM1*, *POLE/POLD1*, and biallelic *NTHL1*, that will not be discussed in this guideline because of their low prevalence. A second guideline will focus on the endoscopic management of familial and hereditary non-polyposis syndromes.

Methods

The ESGE commissioned this guideline (chair J.v.H.) and appointed a guideline leader (M.v.L.), who invited the listed authors to participate in the project development. The key questions were prepared by the coordinating team (M.v.L. and V.R.) and were then approved by the other members. The coordinating team formed task force subgroups, each with its own leader, and divided the key topics among these task forces (**Appendix 1 s**; see online-only Supplementary Material).

ABBREVIATIONS

ACG	American College of Gastroenterology
AFAP	attenuated familial adenomatous polyposis
APC	adenomatous polyposis coli
CRC	colorectal cancer
DBE	double-balloon enteroscopy
EGD	esophagogastroduodenoscopy
EMR	endoscopic mucosal resection
ESGE	European Society of Gastrointestinal Endoscopy
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EUS	endoscopic ultrasonography
FAP	familial adenomatous polyposis
GI	gastrointestinal
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HD	high definition
HHT	hereditary hemorrhagic telangiectasia
IDUS	intraductal ultrasound
JPS	juvenile polyposis syndrome
MAP	<i>MUTYH</i> -associated polyposis
MRI-E	magnetic resonance imaging enteroclysis/enterography
NBI	narrow-band imaging
OR	odds ratio
PJS	Peutz-Jeghers syndrome
RCT	randomized controlled trial
RR	relative risk
SPS	serrated polyposis syndrome
VCE	video capsule endoscopy
WLE	white-light endoscopy

The process of developing the guideline included telephone conferences, meetings, and online and face-to-face discussions among the guideline committee members from July 2018 to June 2019. Searches were performed in MEDLINE, Embase, and Cochrane. Articles were selected through title and abstract screening, followed by full-text screening. The results of the search were presented to all members of the guideline committee and statements were created by consensus. Evidence levels and recommendation strengths were assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [29]. Further details on the methodology of ESGE guideline development have been reported elsewhere [30].

In May 2019, a draft prepared by M.v.L. and V.R. was sent to all group members. After the agreement of all group members had been obtained, the manuscript was reviewed by a member of the ESGE governing board and an external reviewer, and was sent for further comments to the ESGE national societies and individual members. After this, it was submitted to *Endoscopy* for publication.

► **Table 1** Overview of polyposis syndromes.

Polyp sub-type	Polyposis syndrome	Gene	Germline mutation found	Incidence	Clinical criteria	CRC risk	References
Adenomatous	Familial adenomatous polyposis (FAP)	APC	70%–90%	1 in 10 000	Classic: > 100 adenomas in colon/rectum at age 25	100%	[4, 5, 23, 24]
					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%	[6, 25, 26]
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%	[7–9, 27, 28]
	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%	[10–13]
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%	[14–22]

FIT, fecal immunochemical test; NA, not applicable.

This guideline was issued in 2019 and will be considered for update in 2024. Any interim updates will be noted on the ESGE website: <http://www.esge.com/esge-guidelines.html>.

As literature on polyposis syndromes is limited, a Delphi procedure was organized within the guideline committee, consisting of two rounds, in order to gain consensus [31]. All guideline committee members, except for the research fellow, were asked to complete the online Delphi questionnaire in isolation, and responses were anonymized to prevent participants from influencing each other [32]. In each round, all the guideline committee members were first asked to rate all the statements with their level of agreement using a seven-point Likert scale: “Very strongly agree,” “Strongly agree,” “Agree,” “Neither agree nor disagree,” “Disagree,” “Strongly disagree,” or “Very strongly disagree” [33]. If the statement was not their area of expertise, participants had the option to opt out. Secondly, participants were asked if the statement was clear and had the opportunity to write down their suggestions for improvement. After the first round of Delphi voting, all statements were dis-

cussed and adjusted if necessary during a face-to-face meeting. Consensus was reached when ≥ 80% of the guideline committee members had voted either “Very strongly agree,” “Strongly agree,” or “Agree” during the second round of the Delphi procedure.

1 General recommendations for patients with a polyposis syndrome

RECOMMENDATION

ESGE recommends that individuals with hereditary gastrointestinal polyposis syndromes should be surveilled in dedicated units that provide monitoring of compliance and endoscopic performance measures.

Strong recommendation, moderate quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends performing esophagogastroduodenoscopy, small-bowel examination, and/or colonoscopy earlier than the planned surveillance procedure if a patient is symptomatic.

Strong recommendation, low quality of evidence, level of agreement 100%.

Management of patients with polyposis syndrome is challenging. Strict follow-up of these patients with high quality endoscopy and polypectomy is essential. It has been proven that provision of healthcare services is more effective when delivered in an organized and coordinated system [34].

Data from the Danish polyposis registry showed a significantly lower CRC risk in call-up cases compared with probands who were not under surveillance. The tracing and follow-up program increased life expectancy by 17.0 years [35]. For these reasons, polyposis patients should be followed in dedicated units (national registries, genetic counseling centers, or high risk cancer centers) where endoscopic surveillance recommendations are monitored and audited, in order to improve adherence and provide the highest quality of care.

Surveillance intervals are provided in this guideline, but for patients with specific complaints, such as anemia, rectal blood loss, or abdominal pain, endoscopic interventions should be performed when indicated and not postponed to the next surveillance examination.

► **Table 2** and ► **Table 3** provide a summary of all of the statements, including starting age and interval of endoscopic surveillance

2 Familial adenomatous polyposis and *MUTYH*-associated polyposis

2.1 Background

FAP is caused by an autosomal dominant mutation in the *APC* gene [36] (► **Table 1**). The disease is characterized by the development of up to 100–1000 adenomas throughout the colon and rectum, and is also associated with extracolonic manifestations [4]. When the disease is left untreated, the cumulative risk of developing CRC is 100% at a median age of 35–45 years [4]. Attenuated FAP (AFAP; arbitrarily defined as <100 adenomas) is associated with a later onset of CRC and the absolute risk is thought to be lower than in those with a classical phenotype (>100 adenomas) [5]. Duodenal adenomatosis is the most frequent extracolonic manifestation in FAP, and there are no robust data demonstrating that those with AFAP have a different duodenal phenotype to those with classical FAP. Approximately 10%–30% of the patients with (attenuated) polyposis phenotype will remain without a detectable mutation. In these patients we suggest they be treated according to their clinical diagnosis.

There is no clear cutoff for referring an individual with a history of colorectal adenomatous polyps for genetic testing. The guideline of the American College of Gastroenterology advises referral for individuals with a history of 10 adenomatous polyps [37]. The Dutch guideline uses 10 or more colorectal adenomatous polyps in patients aged under 60 and 20 or more in those aged under 70 as a cutoff for referral [38].

The other main adenomatous polyposis syndrome is MAP, which is caused by a biallelic mutation in the *MUTYH* gene. Although there is significant phenotypic overlap with FAP, MAP is often associated with a lower number of colorectal polyps and a later age of onset, although significant phenotypic variation is observed [39,40]. The lifetime risk for CRC in MAP patients ranges from 19% to 43% [6].

► **Table 2** Summary table of colonoscopy surveillance statements.

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
<i>MUTYH</i> -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

NA, not applicable.

► **Table 3** Summary table of gastric and small-bowel surveillance statements.

Polyposis syndrome	Modality	Starting age	Surveillance interval	Treatment indication
(Attenuated) familial adenomatous polyposis	Esophagogastro-duodenoscopy	25 years	According to Spigelman score, adjusted for appearance of the ampulla	Non-ampullary adenomas: consider 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
<i>MUTYH</i> -associated polyposis	Esophagogastro-duodenoscopy	35 years	According to Spigelman score, adjusted for appearance of the ampulla	Non-ampullary adenomas: consider 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	Esophagogastro-duodenoscopy	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: <i>SMAD4</i> mutation carriers	Esophagogastro-duodenoscopy	18 years	Every 1–3 years	Gastric management should be discussed in a multidisciplinary setting
Juvenile polyposis syndrome: <i>BMPR1A</i> mutation carriers	Esophagogastro-duodenoscopy	25 years	Every 1–3 years	Gastric management should be discussed in a multidisciplinary setting
Serrated polyposis syndrome	NA	NA	NA	NA

MRI, magnetic resonance imaging; NA, not applicable.

2.2 Colonoscopy surveillance

RECOMMENDATION

ESGE recommends that colonoscopy surveillance in asymptomatic individuals with familial adenomatous polyposis should start at the age of 12–14 years. Strong recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends that colonoscopy surveillance of individuals with familial adenomatous polyposis with an intact colon should be performed every 1–2 years depending on the polyp burden. Strong recommendation, low quality of evidence, level of agreement 90%.

Compared with sporadic cancers, FAP is characterized by extremely early and multifocal carcinogenesis. However, the adenoma–carcinoma sequence is not accelerated, with adenomas taking up to 15 years to become malignant. Studies in patients with known *APC* mutation or clinical polyposis have shown that the median age of polyp development is 12–17 years [41–45]. In addition, the CRC rate below the age of 20 years is very low, approximately 1.3% [46].

Data also indicate that the *APC* mutation site may affect the severity of disease and cancer development. However, there is a wide spectrum of colorectal polyp burden in FAP and AFAP and care needs to be personalized [5]. Therefore, we recommend starting colonoscopy surveillance at age 12–14 years.

Active endoscopic surveillance is associated with a subsequent reduction of CRC incidence and mortality, mostly due to timely early surgical intervention. Studies showed that 47%–69% of symptomatic FAP patients were diagnosed with CRC, as opposed to 2%–4% of relatives with FAP in whom CRC was found during screening [47,48].

RECOMMENDATION

ESGE recommends that colonoscopy surveillance should start at the age of 18 years in asymptomatic individuals with *MUTYH*-associated polyposis.

Strong recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends that colonoscopy surveillance of individuals with *MUTYH*-associated polyposis with intact colons should be performed every 1–2 years depending on the polyp burden.

Strong recommendation, low quality of evidence, level of agreement 90%.

In 16%–40% of the individuals with 20–100 adenomas in whom FAP was excluded, a *MUTYH* mutation was found [37]. Furthermore, biallelic *MUTYH* mutations are found in 7.5% to 12.5% of patients with >100 adenomas in whom a disease-causing *APC* mutation is not found [6]. Nieuwenhuis et al. demonstrated that colorectal polyposis was diagnosed at a mean age of 44.8 years in 254 biallelic *MUTYH* mutation carriers, while CRC was diagnosed in 58% of these individuals at an average age of 48.5 years [49]. Furthermore, these patients had an 11% risk of developing metachronous CRC within 5 years after surgery, suggesting that biallelic *MUTYH* mutation carriers may have accelerated carcinogenesis.

Patients with a monoallelic *MUTYH* mutation do not develop adenomatous polyposis. They do however seem to have a slightly elevated risk of developing CRC compared with the general population, although this is not sufficient to warrant enhanced surveillance. The management of these individuals should be the same as for those in the general population [50, 51].

2.3 Management of colorectal neoplasia in patients with an intact colon

RECOMMENDATION

ESGE suggests that endoscopic management of colorectal adenomas alone is not recommended in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis. It may be considered in individuals who have an attenuated phenotype, provided that high quality surveillance and robust recall systems are in place.

Weak recommendation, low quality of evidence, level of agreement 60%.

RECOMMENDATION

ESGE suggests that, in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis who are not in need of immediate colectomy and are manageable by endoscopy, all polyps >5 mm be removed.

Weak recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE suggests that the timing and type of surgery in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis should be discussed in a multidisciplinary setting, thereby taking into account the sex (fertility), polyp burden, extensiveness of rectal involvement, personal and family history of desmoid disease, and mutation site in the context of social, personal, and educational factors.

Weak recommendation, low quality of evidence, level of agreement 90%.

There are no data indicating that endoscopic polypectomy alone is an appropriate management strategy for patients with FAP. (Laparoscopic) prophylactic surgery is considered the standard of care. Most studies reveal a very narrow window between the diagnosis of colonic polyposis and surgery [43, 45]. However, postponing surgery might be considered based on overall polyp burden, in particular in those with an attenuated phenotype. Some patients with mild polyposis may even be managed endoscopically.

Furthermore, colectomy with ileorectal anastomosis instead of proctocolectomy with ileo-pouch anal anastomosis can be considered if the polyp burden in the rectum is relatively limited (usually <20 adenomas). The choice of surgery should take into account a personal or family history of desmoid disease or a germline mutation predisposing to desmoids [52]. In addition, prophylactic surgery should be personalized based on patient preference and after a thorough discussion of the implications for quality of life and fertility.

Chemoprevention has been proposed as a potential strategy to reduce polyp burden. Until now, no single chemoprevention drug has an approved indication for the management of FAP or MAP [53]. Therefore, endoscopic management and, if necessary, subsequent prophylactic surgery remain the standard of care.

2.4 Surveillance and management of colorectal neoplasia after (procto)colectomy

RECOMMENDATION

ESGE recommends endoscopic surveillance of the rectum or pouch every 1–2 years in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis depending on the polyp burden.

Strong recommendation, low quality of evidence, level of agreement 90 %.

RECOMMENDATION

ESGE recommends endoscopic removal of all polyps >5 mm during surveillance of the rectum or pouch in patients with familial adenomatous polyposis/*MUTYH*-associated polyposis.

Strong recommendation, low quality of evidence, level of agreement 100 %.

RECOMMENDATION

ESGE recommends all polyps be endoscopically removed at the anal transitional zone (rectal cuff) after proctocolectomy and ileo-pouch anal anastomosis.

Strong recommendation, low quality of evidence, level of agreement 89 %.

In FAP patients with total colectomy and ileorectal anastomosis, the incidence of cancer development in the rectal remnant is the biggest concern [54]. The cumulative risk of rectal cancer varies from 11 % to 24 % [55–57], while the cumulative risk of dying from rectal cancer is between 9 % and 12.5 % [55, 58]. Four independent predictors of progressive rectal disease have been described: rectal polyp count exceeding 20 or colonic polyp count of 500 or more prior to colectomy, *APC* mutation at codons 1250–1450, and age less than 25 years at the time of surgery [57].

In FAP patients with proctocolectomy and ileo-pouch anal anastomosis, the incidence of cancer in the pouch is lower than that in the rectal cuff [59]. In a systematic review including 92 pouch-related cancers, 23 cancers (25 %) developed in the pouch and 69 (75 %) in the anal transitional zone [60]. In a large series of 206 patients with FAP who underwent proctocolectomy with ileo-pouch anal anastomosis, the risk of developing adenomas in the pouch was 22 % in the mucosectomy with handsewn anastomosis group, while 51 % developed adenomas in the rectal remnant and/or pouch after stapled ileo-pouch anal anastomosis (median follow-up 10.3 years) [61]. Other studies have shown that mucosectomy handsewn anastomosis is associated with a lower risk of adenomas [59, 62]. Retroflexion in the rectum should always be performed to adequately explore the anal transitional zone.

Evidence on how to manage polyps in the rectal remnant or pouch, and the appropriate interval between endoscopies is scarce. Some experts have shown that, even in severe cases of rectal polyposis, polyp burden in the rectal remnant can be effectively reduced by cold snare polypectomies and endoscopic submucosal resections [63, 64]. One study recommends the use of argon plasma coagulation, but without evidence of its effect on cancer prevention [65].

2.5 Duodenal surveillance and management

RECOMMENDATION

ESGE recommends that individuals with familial adenomatous polyposis start endoscopic duodenal surveillance at the age of 25 years.

Strong recommendation, low quality of evidence, level of agreement 100 %.

RECOMMENDATION

ESGE recommends thorough inspection and description of the duodenum and ampullary site at every surveillance esophagogastroduodenoscopy in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis. The duodenal surveillance interval should be determined on the basis of polyp characteristics.

Strong recommendation, low quality of evidence, level of agreement 100 %.

RECOMMENDATION

ESGE suggests considering endoscopic resection of non-ampullary duodenal adenomas ≥ 10 mm in patients with familial adenomatous polyposis/*MUTYH*-associated polyposis.

Weak recommendation, low quality of evidence, level of agreement 90 %.

RECOMMENDATION

ESGE suggests duodenal polyps and the ampulla should be biopsied only if they are not amenable to endoscopic removal, either because they are too large or because there is a suspicion of invasive growth.

Weak recommendation, low quality of evidence, level of agreement 89 %.

Individuals with FAP are also at high risk for developing duodenal adenomas. In 30 %–92 % of FAP patients, duodenal adenomas are detected, with a lifetime risk approaching 100 % [66–70]. However, only a minority of patients develop duodenal cancer, with a cumulative risk ranging from 4 % to 10 % by

the age of 60 [66,69–73]. The median age at duodenal cancer diagnosis varied from 52 to 67 years [67, 69,74–76]. Regular duodenal surveillance and prophylactic surgery has resulted in a significantly improved prognosis in FAP patients [74].

During esophagogastroduodenoscopy (EGD), the severity of duodenal polyposis is assessed using the Spigelman classification system (► **Table 4**). Scores for the number, size, histology, and grade of dysplasia of the duodenal adenomas result in a Spigelman stage varying from I to IV [77]. Several risk factors for developing duodenal cancer are acknowledged: age; Spigelman stage IV at first endoscopy; duodenal polyps ≥ 10 mm or containing high grade dysplasia; and ampullary adenomas with high grade dysplasia, a (tubulo)villous component, or high grade dysplasia [67,70,74–76]. To obtain all components of the Spigelman score, pathology results are needed; however, routine biopsies of duodenal polyps may interfere with optical diagnosis and future endoscopic resection because of fibrosis. Therefore, taking routine biopsies is currently not recommended. If endoscopic removal is not necessary because the adenomas are small and there is no suspicion of invasive growth, the Spigelman stage should be determined based on previous pathology reports or optical diagnosis to determine the severity of duodenal polyposis and the surveillance interval. The site of the ampulla in particular should be evaluated and reported accurately, as this is a location of preference for adenoma and cancer development [78].

► **Table 4** Spigelman Score, adapted from Spigelman et al. [77].
a Points awarded in the calculation of Spigelman score.

Findings at duodenoscopy	1 point	2 points	3 points
Number of adenomas	1–4	5–20	>20
Size, mm	1–4	5–10	>10
Histology*	Tubular	Tubulovillous	Villous
Dysplasia*	Low grade	NA	High grade

* Based on pathology obtained for complete endoscopic removal of duodenal polyps or prior pathology results.

► **Table 4** Spigelman Score, adapted from Spigelman et al. [77]. b Recommended surveillance interval on the basis of the Spigelman score.

Spigelman score	Spigelman stage	Surveillance interval*
0 points	0	5 years
1–4 points	I	5 years
5–6 points	II	3 years
7–8 points	III	1 year
9–12 points	IV	6 months, consider (endoscopic or surgical) treatment

* Additional adjustment based on inspection of the ampullary region.

The surveillance interval should be based both on the Spigelman stage and on separate judgment of the ampulla, with surveillance adapted to the shortest interval. For a normal ampulla, a surveillance interval of 5 years seems safe; for adenomatous changes in an ampulla <10 mm, a surveillance interval of 3 years; and for an ampulla ≥ 10 mm, a surveillance interval of 1 year is proposed. Cap-assisted endoscopy has been shown to effectively visualize the ampulla in 95% of FAP patients, avoiding the need for additional side-viewing endoscopy and causing less burden for the patient [79]. The indications for biopsy need to be carefully considered and biopsies should not be taken routinely as biopsies of the ampulla may result in pancreatitis.

Nine widely varying, small single-center studies, including 6–35 patients, described the effect of endoscopic removal of non-ampullary duodenal adenomas in FAP patients [80–88]. The most frequently reported complications were (intraprocedural) bleeding and mild post-procedural abdominal pain [81–83,88]. During follow-up, ranging from 18 months to 9.9 years, one case of duodenal cancer was observed in a patient who had refused endoscopic surveillance after suffering a severe post-polypectomy bleed [80, 81,84,87,88]. Recurrence rates at the resection scar of non-ampullary duodenal adenomas varied widely from 22% to 100% [84, 85,87,88].

In one study, 35 FAP patients with Spigelman stage IV duodenal polyposis were treated with argon plasma coagulation for small and flat adenomas and endoscopic mucosal resection (EMR) for sessile and flat adenomas over 10 mm [86]. In this study, Spigelman scores decreased in 95% of the patients. Furthermore, a modeling analysis revealed a 60% decrease in mean Spigelman score after 150 months [86]. However, Balmforth et al. showed that downstaging of Spigelman IV patients resulted in an increased rate of duodenal disease progression compared with the patients with primary disease progression [89]. Surveillance interval after duodenal polypectomy needs to be determined by the expert endoscopist. There is a lack of data and a need to better understand the biology of duodenal and ampullary adenomas and cancer in order to develop a new system to stratify cancer risk.

RECOMMENDATION

ESGE recommends starting endoscopic duodenal surveillance in individuals with *MUTYH*-associated polyposis at 35 years of age.

Strong recommendation, low quality of evidence, level of agreement 90%.

In MAP, the prevalence of duodenal adenomas is lower than in individuals with FAP, with 17%–34% at a median age of 50 years [90,91]. Only 6% of these patients with MAP developed ampullary disease [90]. Because duodenal polyposis occurs later in life and with a slower progression than in individuals with FAP, duodenal surveillance may commence at a higher age. Walton et al. showed that only 8 of 92 MAP patients (9%) underwent an endoscopic intervention, starting at 38 years [90]. In this series, two duodenal cancers were diagnosed in

patients with MAP over the age of 60 years who were not undergoing surveillance [90]. Duodenal cancers in MAP patients can often occur without significant duodenal polyp burden [90, 92].

RECOMMENDATION

ESGE suggests treatment for individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis who have ampullary adenomas ≥ 10 mm showing excessive growth or suspicion of invasive growth should be discussed in a multidisciplinary setting.
Weak recommendations, low quality of evidence, level of agreement 100%.

Duodenal polyps in FAP and MAP often occur in the region of the ampulla [78]. To prevent ampullary cancer, endoscopic ampullectomy can be performed in individuals with adenomatous changes of the ampulla. However, ampullectomy is associated with severe complications, therefore benefits and harms should be weighed in an experienced multidisciplinary setting. The effect of endoscopic ampullectomy has been evaluated in three small observational studies, including 8–28 FAP patients [93–95]. In these series, complication rates such as pancreatitis (19%–20%), bleeding (4%–13%), and abdominal pain (8%) were high [93, 94]. Recurrence at the site of ampullectomy occurred in 0–67% of the cases after a follow-up ranging from 53 to 85 months with no evidence of ampullary cancer [93–95]. In one study of 15 FAP patients, two (13%) required surgery after multiple repeated endoscopic resections [93].

Finally, if endoscopic ampullectomy is indicated but not possible in an expert center, the patient should be referred for surgical intervention.

RECOMMENDATION

ESGE suggests that endoscopic ultrasonography should not be routinely performed in the pretherapeutic evaluation of ampullary adenomas in individuals with familial adenomatous polyposis/*MUTYH*-associated polyposis. It may be considered for assessment of large or suspicious ampullas to help exclude invasive growth.
Weak recommendation, low quality of evidence, level of agreement 89%.

In the literature, endoscopic ultrasonography (EUS) for the pretherapeutic staging of ampullary tumors has focused mainly on advanced ampullary cancers. One study focusing on ampullary adenomas in 38 FAP patients showed no EUS utility, with no information on duct involvement [93]. A comparison of preoperative staging of ampullary tumors showed comparable accuracy of EUS and intraductal ultrasound (IDUS), with an accuracy of 63% (EUS) and 78% (IDUS), in particular for advanced stages [96]. On the other hand, over-staging at EUS/IDUS occurred in 25%–40% of cases of benign adenoma or early cancers [96–98]. Therefore, EUS and IDUS present limitations in

the pretherapeutic evaluation of ampullary tumors, with over-staging of early and even benign lesions.

RECOMMENDATION

ESGE recommends performing thorough gastric assessment at the time of duodenal surveillance. If gastric adenomas are suspected, endoscopic resection is recommended, or surgical resection if endoscopically unresectable.
Strong recommendation, moderate quality of evidence, level of agreement 100%.

In patients with FAP, fundic gland polyps are reported in 20%–88% [99, 100]. Fundic gland polyps are thought to have little tendency for malignant transformation. On the other hand, gastric adenomas are considered to have a premalignant potential, given that 8%–14% of gastric adenomas harbor high grade dysplasia [101, 102]. Historically, the risk of developing gastric cancer among Western FAP patients was not found to be higher than the general population [102–104]. However, two recent series from Western countries, described 17 cases of gastric cancer, with a median age at diagnosis between 50 and 60 years [102, 103]. In both series, the proximal cancers were associated with carpeting fundic gland polyposis, which can make identification of the premalignant adenoma extremely difficult. These findings suggest that identification and resection of gastric adenomas are important to prevent the development of gastric cancer, but currently there are no data as to whether or not this is effective.

RECOMMENDATION

ESGE recommends that prophylactic duodenectomy in familial adenomatous polyposis/*MUTYH*-associated polyposis should be reserved for those patients with the most advanced disease, which cannot be endoscopically managed.
Strong recommendation, low quality of evidence, level of agreement 100%.

Two retrospective studies reported that 4%–6% of the FAP patients had been surgically treated for duodenal polyposis, describing mortality rates after pancreas-preserving duodenectomy ranging from 5% to 33% [105, 106]. The in-hospital morbidity was 49%, without differences between patients with benign adenomatosis and cancer [106]. After duodenectomy, adenomas occurred in 78% of the FAP patients in the neo-duodenum after a mean of 46 months, indicating the need for endoscopic surveillance in these patients [107]. Therefore, it is crucial that the neo-duodenum is accessible for endoscopic surveillance.

3 Peutz–Jeghers syndrome

3.1 Background

PJS is characterized by the development of hamartomatous polyps [3]. PJS is diagnosed using clinical criteria (► **Table 1**) or by a pathogenic germline mutation in the serine threonine kinase 11 tumor suppressor gene (*STK11/LKB1* gene), which is found in 80%–94% of PJS patients [7]. Individuals with perioral or buccal pigmentation and/or two or more GI hamartomatous polyp(s) or a family history of PJS should be referred for genetic testing [37].

The predominant clinical feature of PJS is GI polyposis, most often found in the small bowel (60%–90%), where they may cause bleeding, anemia, and intussusception [108, 109]. The cumulative risk of GI cancers (excluding pancreatic cancer) has been reported to be around 33% at the age of 60, increasing to 57% at the age of 70 years [8]. However, data are often historical, retrospective, and subject to bias that probably overestimates the cancer risk.

Surveillance of the GI tract in PJS patients has two purposes: (i) to detect GI polyps that may cause complications (bleeding, anemia, intussusception) and should be removed (in particular small-bowel polyp-related complications are the predominant clinical problem) [110, 111]; (ii) to detect cancer (mainly occurring in adults) at an early stage [9].

3.2 Esophagogastroduodenoscopy and colonoscopy surveillance

RECOMMENDATION

ESGE recommends a baseline esophagogastroduodenoscopy and colonoscopy at the age of 8 years in asymptomatic individuals with Peutz–Jeghers syndrome. Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends starting routine esophagogastroduodenoscopy and colonoscopy surveillance at the age of 18 if the baseline endoscopy is negative. Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends an interval of 1–3 years based on phenotype for esophagogastroduodenoscopy and colonoscopy. Strong recommendation, low quality of evidence, level of agreement 100%.

Most studies about cancer risk in PJS patients are single-center cohort studies and rather small, which may overestimate the cancer risk because of ascertainment bias. Giardiello et al. performed a systematic review including 210 PJS patients from six studies and reported a cumulative risk of gastric cancer of 29% at 15–64 years of age, with a relative risk (RR) of 213 (95% confidence interval [CI] 96–368) compared with the general population [112]. The average age of gastric cancer diagnosis was 30–40 years [9, 113]. The cumulative risk of colon cancer was 39% at 15–64 years of age, with an RR of 84 (95% CI 47–137) [113–115].

There are no prospective studies evaluating the effect of surveillance strategies for gastric cancer, duodenal cancer, or CRC. Furthermore, there is no evidence regarding the type and frequency of surveillance and starting/stopping age. Hamartomas are predominantly found in the small bowel and colon and only seldomly give rise to complications in the esophagus or stomach. Latchford et al. evaluated 28 PJS patients who had undergone one or more surveillance endoscopies by the age of 18 [111]. In 17 patients a significant gastroduodenal or colonic polyp was found, including 20 gastroduodenal polyps over 10 mm [111]. In this series, no PJS patients were observed to develop GI cancer. Furthermore, dysplasia or atypia was very rarely observed.

3.3 Small–bowel surveillance

RECOMMENDATION

ESGE recommends small-bowel surveillance from the age of 8 years in asymptomatic individuals with Peutz–Jeghers syndrome. Strong recommendation, moderate quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends an interval of 1–3 years based on phenotype for small-bowel surveillance. Strong recommendation, moderate quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends either MRI studies or video capsule enteroscopy for small-bowel surveillance. Strong recommendation, moderate quality of evidence, level of agreement 89%.

Symptoms related to small-bowel polyps are frequent and intussusception is seen by the age of 10 in 33% and by the age of 20 in 50% of PJS patients [110]. The cumulative risk of small-bowel cancer was 13%, with an RR of 520 (95%CI 220–1306) [113]. The average age of diagnosis of small-bowel cancer was 37–42 years [9, 113]. However, it is difficult to interpret these data because of the small studies, which may overestimate cancer risk due to ascertainment bias, and misinterpretation of pseudoinvasion as cancer.

Currently, magnetic resonance imaging enteroclysis/enterography (MRI-E) and video capsule endoscopy (VCE) are the most used imaging modalities for detection of polyps in the small bowel [109, 116–119]. There are four studies that have compared MRI-E and VCE, including a total of 47 patients with PJS [118–121]. Gupta et al. [118] did not find a significant difference between the two modalities for the detection of clinically relevant polyps (>10mm), as opposed to Urquhart et al. [119], who showed superiority for VCE over MRI-E. Both modalities do miss clinically relevant polyps (>15–20mm or smaller polyps that do give rise to symptoms). Based on the current literature, both VCE and MRI-E are reasonable options for small-bowel surveillance.

3.4 Management of small-bowel polyps

RECOMMENDATION

ESGE recommends that elective polypectomy should be performed for small-bowel polyps >15–20mm to prevent intussusception. In a symptomatic patient, smaller polyps causing obstructive symptoms should be removed.

Strong recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends device-assisted enteroscopy for the removal of polyps. Based on phenotype, intraoperative enteroscopy could be considered.

Strong recommendation, moderate quality of evidence, level of agreement 89%.

In a cohort study including 110 PJS patients, 69% developed at least one intussusception at a median age of 16 years [110]. The intussusception occurred in the small bowel in 95% of the cases. Based on the histology of 37 cases, intussusception occurred owing to polyps with a median diameter of 35mm (15–60mm). In almost all publications, the indication for balloon endoscopy is set at polyps over 10–15mm on VCE or MRI-E, although some studies used a threshold of 20mm [109]. Several studies have shown that polypectomy of relevant small-bowel polyps can prevent the need for emergency surgery [108, 122, 123].

Balloon-assisted enteroscopy facilitates polypectomy in almost all patients with clinically relevant polyps [109]. Single-balloon and double-balloon enteroscopy (DBE) have been shown to be effective for the removal of polyps up to 60mm [124] and 100mm [125], respectively. Prior abdominal surgery is not a contraindication for balloon enteroscopy. For individuals with too many small-bowel polyps, or large or high risk polyps, laparoscopically-assisted DBE or intraoperative enteroscopy can be performed [123].

The effect on cancer reduction is not known. Only one T2N0 adenocarcinoma in the jejunum has been detailed in the DBE literature, which has reported more than 3000 polypectomies [109, 111, 126].

4 Juvenile polyposis syndrome

4.1 Background

The diagnosis of JPS is based on clinical criteria [10] (► **Table 1**). Individuals with five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract should undergo genetic testing [37]. A germline mutation in *SMAD4* or *BMPR1A* is identified in around 40%–60% of those with a clinical diagnosis. Germline mutations in these genes result in two relatively different phenotypes [127]. *SMAD4* mutation carriers present with colonic and gastric involvement, in combination with hereditary hemorrhagic telangiectasia (HHT), whereas *BMPR1A* mutation carriers mostly develop a colonic phenotype [11, 12]. JPS is associated with an increased GI cancer risk varying from 39% to 68% [10, 13].

4.2 Colonoscopy surveillance

RECOMMENDATION

ESGE recommends that colonoscopy screening in asymptomatic individuals with juvenile polyposis syndrome starts at the age of 12–15 years.

Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends an interval of 1–3 years based on phenotype for routine colonoscopy surveillance in individuals with juvenile polyposis.

Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends that colorectal polyps >10mm should be removed in individuals with juvenile polyposis syndrome to prevent complications and the development of colorectal cancer.

Strong recommendation, low quality of evidence, level of agreement 90%.

Almost all patients with *SMAD4* and *BMPR1A* germline mutations present with colonic hamartomas, with a wide range of disease expression from a few polyps to over 100 polyps [128–130]. Very young patients with symptomatic polyposis have been reported (4–12 years) [129, 130]. In the largest published series of 84 cases fulfilling the clinical criteria for JPS, from the Johns Hopkins' hospital, 8 of the 84 patients (9.5%) developed CRC between the ages of 30 and 58 years, with a lifetime calculated risk of 37% [13]. In another retrospective series from Baltimore, the frequency of colectomy was 49% [128]. Besides classical cases, a much more severe phenotype has been described in patients harboring a microdeletion in chromosome 10 that involves both the *BMPR1A* and *PTEN* genes [131].

4.3 Esophagogastroduodenoscopy surveillance

RECOMMENDATION

ESGE recommends that esophagogastroduodenoscopy surveillance should start at the age of 18 years in asymptomatic individuals with a *SMAD4* mutation. Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE suggests that esophagogastroduodenoscopy surveillance should start at the age of 25 years in asymptomatic individuals with a *BMPR1A* mutation. Weak recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends an interval of 1–3 years depending on phenotype for esophagogastroduodenoscopy surveillance in individuals with juvenile polyposis syndrome. Strong recommendation, low quality of evidence, level of agreement 90%.

RECOMMENDATION

ESGE recommends gastric management (polypectomy, surgery, surveillance) be discussed in expert multidisciplinary teams as no clear algorithm can be proposed based on the available data. Strong recommendation, low quality of evidence, level of agreement 100%.

The lifetime risks of extracolonic cancers, including stomach, pancreas, and small intestine, are difficult to quantify owing to a lack of good quality data. Risks that have been reported vary from 20% to 60% [132]. However, these are likely to be influenced by overestimation of risk due to ascertainment bias.

Gastric cancer has not been reported among patients below the age of 35 years [128]. However, the majority of *SMAD4* mutation carriers develop gastric hamartomas at an early age, which may progress into a severe diffuse hamartomatous gastritis mimicking Menetrier disease in adulthood [127, 128, 130, 133]. On the other hand, based on limited data, *BMPR1A* carriers do not seem to present with gastric involvement [127, 129].

4.4 Small-bowel surveillance

RECOMMENDATION

ESGE does not recommend small-bowel surveillance in asymptomatic individuals with juvenile polyposis syndrome. Strong recommendation, low quality of evidence, level of agreement 100%.

Small-bowel involvement in JPS is rare and, if present, predominantly located in the duodenum [127, 128, 130]. Wain et al. found a prevalence of 29% for duodenal polyps in *SMAD4* mutation carriers [130]. Involvement of the distal duodenum in JPS is not described [134, 135]. In addition, no cases of jejunal or ileal carcinoma have been reported. Therefore, EGD seems to be sufficient for small-bowel surveillance in JPS patients. Finally, the association of *SMAD4* mutation with HHT suggests that, in expert centers, management of iron deficiency anemia unexplained by EGD and colonoscopy could be an indication for small-bowel evaluation with VCE. In patients with evidence of HHT, screening for vascular lesions in other organs should be performed.

5 Serrated polyposis syndrome

5.1 Background

SPS has emerged as the most frequent form of polyposis, with an estimated prevalence of up to 1:111 (0.9%) of individuals in fecal occult blood test-based screening cohorts and up to 1:238 (0.42%) in primary screening cohorts [14–17]. SPS is often grouped with the hereditary polyposis syndromes although no underlying gene defect has been identified yet. SPS is diagnosed using clinical criteria defined by the World Health Organization criteria, recently revised (► **Table 1**) [18, 136].

The prevalence of CRC in patients with SPS has been estimated to range between 15% and 30% and there is an increased risk for CRC prior to or at the time of SPS diagnosis and treatment [14, 19–22]. In one prospective and three retrospective cohorts, the cumulative 5-year incidence of CRC under endoscopic surveillance ranged between 0 and 7.0% [14, 19, 20, 137].

5.2 Colonoscopy surveillance and management of neoplasia

RECOMMENDATION

ESGE recommends endoscopic removal of all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia in individuals with serrated polyposis syndrome before and after entering surveillance.

Strong recommendation, low quality of evidence, level of agreement 100%.

RECOMMENDATION

ESGE recommends a surveillance interval of 1 year following a colonoscopy with ≥ 1 advanced polyp¹ or ≥ 5 non-advanced clinically relevant polyps².

Strong recommendation, low quality of evidence, level of agreement 80%.

RECOMMENDATION

ESGE recommends a surveillance interval of 2 years in patients with no advanced polyps¹ or < 5 non-advanced clinically relevant polyps².

Strong recommendation, low quality of evidence, level of agreement 100%.

In SPS patients, successful endoscopic treatment at diagnosis (the so-called “clearing phase”) can be achieved in the majority of patients [14, 20, 138]. However, clearing in some cases requires commitment, time, and expertise to perform a large number of polypectomies in one or more procedures [138]. Accordingly, these patients should be managed in dedicated units with expert endoscopists in order to prevent unnecessary surgery. Studies with expert endoscopists have shown that EMR of large serrated lesions is easy, safe, and has a lower recurrence rate than for adenomas [139].

The risk of developing CRC during endoscopic surveillance following diagnosis and clearing of the initial polyp burden seems to be low. Based on two large retrospective cohort studies, the cumulative incidence during surveillance varied from 0 to 3.1% after 3–5 years [14, 20]. The median interval between surveillance colonoscopies in these cohort studies varied between 12 and 19 months [14, 19–22, 138, 140]. Although the CRC risk during surveillance is low, one retrospective and one prospective cohort study reported that the incidence of advanced neoplasia during surveillance is as high as 34%–42% after 3 years of surveillance [19, 22].

¹ Advanced polyps: (tubulo)villous adenomas, adenomas with high grade dysplasia, adenomas ≥ 10 mm in diameter, traditional serrated adenomas, serrated lesions with dysplasia, serrated lesions ≥ 10 mm in diameter.

² Non-advanced clinically relevant polyps: any adenoma or serrated polyp that does not meet the criteria for an “advanced polyp,” with the exception of hyperplastic polyps < 5 mm in diameter (which can be left in situ).

In a recent study, 271 SPS patients were prospectively followed during a median of 3.6 years of surveillance using a personalized surveillance protocol [141]. Patients were surveilled at intervals of either 1 or 2 years, depending on their most recent polyp burden and the risk of metachronous advanced neoplasia. SPS patients were recommended a surveillance interval of 1 year if: one or more advanced serrated lesions or adenomas had been removed; if cumulatively ≥ 5 relevant polyps (sessile serrated lesions [irrespective of size], adenomas [irrespective of size], and/or hyperplastic polyps > 5 mm) had been removed; or if surgery was needed during the last surveillance/clearing phase. In all other cases, a 2-year surveillance interval was recommended. The cumulative CRC and advanced neoplasia incidences after 5 years were 1.3% and 44%, respectively. In the majority of patients, a 2-year interval was recommended. Following the 2-year protocol, the incidence of advanced neoplasia during the next colonoscopy was 16%, compared with 24% following the shortened 1-year interval (odds ratio [OR] 0.57, 95%CI 0.31–1.07). This evidence suggests that surveillance is safe, less demanding than the clearing phase, and that surveillance can be extended to 2 years in a large proportion of patients. During surveillance all polyps ≥ 5 mm and all polyps of any size with optical suspicion of dysplasia should be removed.

5.3 Advanced imaging in colonoscopy surveillance

RECOMMENDATION

ESGE recommends the use of high definition systems in the endoscopic surveillance of individuals with serrated polyposis syndrome.

Strong recommendation, moderate quality of evidence, level of agreement 89%.

Tandem colonoscopy studies have demonstrated that around 30% of serrated lesions are missed during conventional colonoscopy, and this is especially relevant in high risk conditions such as SPS [142]. The usefulness of virtual chromoendoscopy (narrow-band imaging [NBI]) in SPS surveillance has been assessed in two randomized crossover studies [143, 144]. The first single-center study included 22 patients and showed lower polyp miss rates with high definition (HD)-NBI compared with HD white-light endoscopy (HD-WLE; OR 0.21; 95%CI 0.09–0.45) [143]. However, in the second multicenter study, comparison of the overall polyp miss rates of HD-WLE and NBI showed no significant difference ($P=0.065$) [144].

Recently, a multicenter randomized controlled trial (RCT) evaluated the usefulness of conventional chromoendoscopy with indigo carmine for the detection of colonic polyps in SPS [145]. This study demonstrated a significantly higher additional polyp detection rate in the HD chromoendoscopy group (0.39; 95%CI 0.35–0.44) than in the HD-WLE group (0.22; 95%CI 0.18–0.27; $P<0.001$). HD chromoendoscopy detected more serrated lesions (40% vs. 24%; $P=0.001$), serrated lesions proximal to the sigmoid colon (40% vs. 21%; $P=0.001$), and serrated lesions > 5 mm proximal to the sigmoid colon (37% vs. 18%; $P=0.013$) than HD-WLE. Therefore, based on this single RCT the

use of conventional chromoendoscopy improves polyp detection and could be considered in the surveillance of SPS patients. However, its routine use must be balanced against practical considerations.

Finally, a recent RCT evaluated the usefulness of Endocuff-assisted colonoscopy in the surveillance of SPS [146]. In this study, with 123 SPS patients included, no statistical differences were found between Endocuff-assisted colonoscopy and HD-WLE colonoscopy for the detection of overall polyps, serrated lesions, sessile serrated lesions, and adenomas.

5.4 Screening of first-degree relatives

RECOMMENDATION

ESGE recommends that, for first-degree relatives of individuals with serrated polyposis syndrome, colorectal cancer screening by colonoscopy should be offered from the age of 45 years.

Strong recommendation, moderate quality of evidence, level of agreement 80 %.

RECOMMENDATION

ESGE recommends that, for first-degree relatives of individuals with serrated polyposis syndrome, colorectal cancer screening by colonoscopy should be offered every 5 years. If polyps are found, surveillance should be based on polyp characterization.

Strong recommendation, low quality of evidence, level of agreement 90 %.

Most SPS cases seem non-familial. However, the presence of the disease in family members has been described in previous reports [137, 147, 148]. Moreover, various studies have described an increased incidence of CRC in relatives of patients with SPS. Boparai et al. investigated the risk of CRC in 347 first-degree relatives of 57 patients with SPS; they established an absolute risk of CRC of 8 % and an RR of 5.4 (95%CI 3.7–7.8) [149]. Two other studies reported an absolute risk of CRC of 12 %–15 % in first-degree relatives [150, 151]. The age at diagnosis of CRC in relatives ranged from 55 to 62 years in these studies [148–150]. During follow-up of these first-degree relatives of patients with SPS, retrospective studies [148, 152, 153] found a high risk of CRC and advanced polyps. Hazewinkel et al. prospectively investigated the yield of screening colonoscopy in 77 first-degree relatives of patients with SPS in whom no CRC was found, with significant polyps being present in 43 % of patients [154].

Discussion

The management of patients with polyposis syndromes is challenging. The various types of polyposis syndrome have variable risks for a large spectrum of cancers. In addition, the phenotype may differ among individuals having a specific germline mutation, and even within/between family members carrying the same mutation. Furthermore, in a proportion of patients with clinical polyposis, no germline mutation can be identified. This guideline gives a framework on how these patients should be endoscopically managed according to the current literature and expert opinion (► **Table 2** and ► **Table 3**).

The ESGE aligns with the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) guidelines on polyposis syndromes in children and young adults [155–157]. The ESPGHAN guideline differs from this guideline with regard to the colonoscopy interval for FAP patients with intact colon, with this being 1–3 yearly in the ESPGHAN guideline and 1–2 yearly in our guideline [156]. We have chosen to align the FAP and MAP surveillance intervals to make it less confusing for endoscopists. Again, the interval should mainly be based on phenotype and the endoscopist may lengthen the surveillance interval based on adenoma characteristics (number, size, and degree of dysplasia). The main difference with the American College of Gastroenterology (ACG) guideline is the proposed endoscopic management for gastric and duodenal adenomas in (A)FAP and MAP patients [37]. In contrast with the ACG guideline, the ESGE guideline does not recommend random sampling of fundic gland polyps during EGD surveillance. Furthermore, the ESGE advises endoscopic polypectomy of duodenal adenomas of ≥ 10 mm.

Disclaimer

The legal disclaimer for ESGE Guidelines [30] applies to the current Guideline.

Acknowledgments

The authors gratefully acknowledge Prof. Vasen and Prof. Hassan for their valuable comments on the manuscript.

Furthermore, we would like to thank Arne Bleijenberg, Ariadna Sanchez, Sabela Carballal, Gerhard Jung, Aleksandar Gavric, Dr. Dora Colussi, Dr. Chiara Pierantoni, and Faridi van Etten-Jamaludin for their assistance regarding the systematic searches and literature review.

Lastly, we would like to acknowledge Claire Guy for arranging the Delphi procedure and Pauline Roucheteau and Francoise Heidenreich for organizing all the meetings and telephone conferences for the guideline.

Competing interests

E. Dekker was an advisory board chair for Cancer Prevention Pharmaceuticals (2019) and is a co-editor for *Endoscopy*. M. F. Kaminski has received speaker's, teaching, and consultancy fees from Olympus (2017 to present) and speaker's and teaching fees, and a loan of equipment from Fujifilm (2019). H. Neuman has provided consultancy services to Fujifilm and Pentax (2012 to present). M. Pellisé has received consultancy fees from Norgine Iberia (2019), speaker's fees from Casen Recordati (2017–2019), Olympus (2017), and Jansen (2018), and is a co-editor for *Endoscopy*; her department has received an equipment loan from Fujifilm (2017 to present) and a research donation from Fujifilm (2019). J. E. van Hooft has received lecture fees from Medtronic (2014–2015) and Cook Medical (2019), and consultancy fees from Boston Scientific (2014–2017); her department has received research grants from Cook Medical (2014–2018) and Abbott (2014–2017).

F. Balaguer, R. Jover, A. Latchford, L. Ricciardiello, V. H. Roos, J.-C. Saurin, P. J. Tanis, M. E. van Leerdam, A. Wagner have no competing interests.

References

- [1] Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; 68: 394–424
- [2] Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. *NEJM* 2000; 343: 78–85
- [3] Jaspersion KW, Tuohy TM, Neklason DW et al. Hereditary and familial colon cancer. *Gastroenterology* 2010; 138: 2044–2058
- [4] Bussey HJR. Familial polyposis coli: family studies, histopathology, differential diagnosis, and results of treatment. Baltimore: Johns Hopkins University Press; 1975
- [5] Burt RW, Leppert MF, Slattery ML et al. Genetic testing and phenotype in a large kindred with attenuated familial adenomatous polyposis. *Gastroenterology* 2004; 127: 444–451
- [6] Nielsen M, Morreau H, Vasen HF et al. MUTYH-associated polyposis (MAP). *Crit Rev Oncol Hematol* 2011; 79: 1–16
- [7] Utsunomiya J, Gocho H, Miyanaga T et al. Peutz-Jeghers syndrome: its natural course and management. *Johns Hopkins Med J* 1975; 136: 71–82
- [8] Hearle N, Schumacher V, Menko FH et al. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006; 12: 3209–3215
- [9] van Lier MG, Wagner A, Mathus-Vliegen EM et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. *Am J Gastroenterol* 2010; 105: 1258–1264; author reply 1265
- [10] Jass JR, Williams CB, Bussey HJ et al. Juvenile polyposis – a precancerous condition. *Histopathology* 1988; 13: 619–630
- [11] Burt RW, Bishop DT, Lynch HT et al. Risk and surveillance of individuals with heritable factors for colorectal cancer. WHO Collaborating Centre for the Prevention of Colorectal Cancer. *Bull World Health Organ* 1990; 68: 655–665
- [12] Chevrel JP, Amouroux J, Gueraud JP. [3 cases of familial juvenile polyposis]. *Chirurgie* 1975; 101: 708–721
- [13] Brosens LA, van Hattem A, Hyland LM et al. Risk of colorectal cancer in juvenile polyposis. *Gut* 2007; 56: 965–967
- [14] JE IJ, Rana SA, Atkinson NS et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. *Gut* 2017; 66: 278–284
- [15] Rivero-Sanchez L, Lopez-Ceron M, Carballal S et al. Reassessment colonoscopy to diagnose serrated polyposis syndrome in a colorectal cancer screening population. *Endoscopy* 2017; 49: 44–53
- [16] van Herwaarden YJ, Verstegen MH, Dura P et al. Low prevalence of serrated polyposis syndrome in screening populations: a systematic review. *Endoscopy* 2015; 47: 1043–1049
- [17] Colussi D, Zagari RM, Morini B et al. Prevalence of serrated polyposis syndrome in an FIT-based colorectal cancer screening cohort in Italy. *Gut* 2017; 66: 1532–1533
- [18] Rosty C, Brosens LAA, Dekker E et al. Serrated polyposis. In: WHO Classification of Tumours Editorial Board Digestive System Tumours. WHO Classification of Tumours series. 5th edn. Lyon, France: IARC; 2019
- [19] Rodriguez-Alcalde D, Carballal S, Moreira L et al. High incidence of advanced colorectal neoplasia during endoscopic surveillance in serrated polyposis syndrome. *Endoscopy* 2019; 51: 142–151
- [20] Carballal S, Rodriguez-Alcalde D, Moreira L et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. *Gut* 2016; 65: 1829–1837
- [21] Parry S, Burt RW, Win AK et al. Reducing the polyp burden in serrated polyposis by serial colonoscopy: the impact of nationally coordinated community surveillance. *N Z Med J* 2017; 130: 57–67
- [22] Hazewinkel Y, Tytgat KM, van Eeden S et al. Incidence of colonic neoplasia in patients with serrated polyposis syndrome who undergo annual endoscopic surveillance. *Gastroenterology* 2014; 147: 88–95
- [23] Bisgaard ML, Fenger K, Bulow S et al. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat* 1994; 3: 121–125
- [24] Rivera B, González S, Sánchez-Tomé E et al. Clinical and genetic characterization of classical forms of familial adenomatous polyposis: a Spanish population study. *Ann Oncol* 2010; 22: 903–909
- [25] Win AK, Reece JC, Dowty JG et al. Risk of extracolonic cancers for people with biallelic and monoallelic mutations in *MUTYH*. *Int J Cancer* 2016; 139: 1557–1563
- [26] Lubbe SJ, Di Bernardo MC, Chandler IP et al. Clinical implications of the colorectal cancer risk associated with *MUTYH* mutation. *J Clin Oncol* 2009; 27: 3975–3980
- [27] Aretz S, Stienen D, Uhlhaas S et al. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum Mutat* 2005; 26: 513–519
- [28] Volikos E, Robinson J, Aittomäki K et al. LKB1 exonic and whole gene deletions are a common cause of Peutz-Jeghers syndrome. *J Med Genet* 2006; 43: e18
- [29] Atkins D, Best D, Briss PA et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1490
- [30] Dumonceau JM, Hassan C, Riphaus A et al. European Society of Gastrointestinal Endoscopy (ESGE) Guideline Development Policy. *Endoscopy* 2012; 44: 626–629
- [31] Linstone HA, Tuoff M. The Delphi Method: Techniques and Applications. Boston: Addison-Wesley Pub. Co; 1975
- [32] Jones J, Hunter D. Qualitative Research: Consensus methods for medical and health services research. *BMJ* 1995; 311: 376–380
- [33] Likert R. A technique for the measurement of attitudes [microform]. 1932
- [34] Wennberg JE. Time to tackle unwarranted variations in practice. *BMJ* 2011; 342: d1513
- [35] Karstensen JG, Burisch J, Pommergaard HC et al. Colorectal cancer in individuals with familial adenomatous polyposis, based on analysis of the Danish Polyposis Registry. *Clin Gastroenterol Hepatol* 2019; doi:10.1016/j.cgh.2019.02.008

- [36] Kinzler KW, Nilbert MC, Su LK et al. Identification of FAP locus genes from chromosome 5q21. *Science* 1991; 253: 661–665
- [37] Syngal S, Brand RE, Church JM et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; 110: 223–62; quiz 63
- [38] Dutch Society for Clinical Genetics. CBO Guideline Hereditary Colorectal Cancer 2015. Version 2.0. Updated 2015-12-31. Available from: <https://oncoline.nl/erfelijke.darmkanker>. Accessed: 17 June 2019
- [39] Sutcliffe EG, Bartenbaker Thompson A, Stettner AR et al. Multi-gene panel testing confirms phenotypic variability in *MUTYH*-associated polyposis. *Fam Cancer* 2019; 18: 203–209
- [40] Papp J, Kovacs ME, Matri Z et al. Contribution of *APC* and *MUTYH* mutations to familial adenomatous polyposis susceptibility in Hungary. *Fam Cancer* 2016; 15: 85–97
- [41] Bulow S. Results of national registration of familial adenomatous polyposis. *Gut* 2003; 52: 742–746
- [42] Gibbons DC, Sinha A, Phillips RK et al. Colorectal cancer: no longer the issue in familial adenomatous polyposis? *Fam Cancer* 2011; 10: 11–20
- [43] Booij KA, Mathus-Vliegen EM, Taminiau JA et al. Evaluation of 28 years of surgical treatment of children and young adults with familial adenomatous polyposis. *J Ped Surg* 2010; 45: 525–532
- [44] Cohen S, Gorodnichenko A, Weiss B et al. Polyposis syndromes in children and adolescents: a case series data analysis. *Eur J Gastroenterol Hepatol* 2014; 26: 972–977
- [45] Kennedy RD, Potter DD, Moir CR et al. The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. *J Ped Surg* 2014; 49: 82–86
- [46] Vasen HF, Moslein G, Alonso A et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008; 57: 704–713
- [47] Vasen HF, Griffioen G, Offerhaus GJ et al. The value of screening and central registration of families with familial adenomatous polyposis. A study of 82 families in The Netherlands. *Dis Colon Rectum* 1990; 33: 227–230
- [48] Bulow S, Bulow C, Nielsen TF et al. Centralized registration, prophylactic examination, and treatment results in improved prognosis in familial adenomatous polyposis. Results from the Danish Polyposis Register. *Scand J Gastroenterol* 1995; 30: 989–993
- [49] Nieuwenhuis MH, Vogt S, Jones N et al. Evidence for accelerated colorectal adenoma–carcinoma progression in *MUTYH*-associated polyposis? *Gut* 2012; 61: 734–738
- [50] Win AK, Dowty JG, Cleary SP et al. Risk of colorectal cancer for carriers of mutations in *MUTYH*, with and without a family history of cancer. *Gastroenterology* 2014; 146: 1208–1211.e1–e5
- [51] Win AK, Hopper JL, Jenkins MA. Association between monoallelic *MUTYH* mutation and colorectal cancer risk: a meta-regression analysis. *Fam Cancer* 2011; 10: 1–9
- [52] Friedl W, Caspari R, Sengteller M et al. Can *APC* mutation analysis contribute to therapeutic decisions in familial adenomatous polyposis? Experience from 680 FAP families *Gut* 2001; 48: 515–521
- [53] Ricciardiello L, Ahnen DJ, Lynch PM. Chemoprevention of hereditary colon cancers: time for new strategies. *Nature Rev Gastroenterol Hepatol* 2016; 13: 352–361
- [54] Moussata D, Nancey S, Lapalus MG et al. Frequency and severity of ileal adenomas in familial adenomatous polyposis after colectomy. *Endoscopy* 2008; 40: 120–125
- [55] Koskenvuo L, Renkonen-Sinisalo L, Jarvinen HJ et al. Risk of cancer and secondary proctectomy after colectomy and ileorectal anastomosis in familial adenomatous polyposis. *Int J Colorectal Dis* 2014; 29: 225–30
- [56] Sinha A, Tekkis PP, Rashid S et al. Risk factors for secondary proctectomy in patients with familial adenomatous polyposis. *Br J Surg* 2010; 97: 1710–1715
- [57] Church J, Burke C, McGannon E et al. Predicting polyposis severity by proctoscopy: how reliable is it? *Dis Colon Rectum* 2001; 44: 1249–1254
- [58] Vasen HF, van Duijvendijk P, Buskens E et al. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: a Dutch-Scandinavian collaborative study including 659 patients. *Gut* 2001; 49: 231–235
- [59] Friederich P, de Jong AE, Mathus-Vliegen LM et al. Risk of developing adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; 6: 1237–1242
- [60] Smith JC, Schaffer MW, Ballard BR et al. Adenocarcinomas after prophylactic surgery for familial adenomatous polyposis. *J Cancer Ther* 2013; 4: 260–270
- [61] von Roon AC, Will OC, Man RF et al. Mucosectomy with handsewn anastomosis reduces the risk of adenoma formation in the anorectal segment after restorative proctocolectomy for familial adenomatous polyposis. *Ann Surg* 2011; 253: 314–317
- [62] Zahid A, Kumar S, Koorey D et al. Pouch adenomas in Familial Adenomatous Polyposis after restorative proctocolectomy. *Int J Surg* 2015; 13: 133–136
- [63] Patel NJ, Ponugoti PL, Rex DK. Cold snare polypectomy effectively reduces polyp burden in familial adenomatous polyposis. *Endosc Int Open* 2016; 4: E472–E474
- [64] Sansone S, Nakajima T, Saito Y. Endoscopic submucosal dissection of a large neoplastic lesion at the ileorectal anastomosis in a familial adenomatous polyposis patient. *Dig Endosc* 2017; 29: 390–391
- [65] Saurin JC, Napoleon B, Gay G et al. Endoscopic management of patients with familial adenomatous polyposis (FAP) following a colectomy. *Endoscopy* 2005; 37: 499–501
- [66] Bjork J, Akerbrant H, Iselius L et al. Periampullary adenomas and adenocarcinomas in familial adenomatous polyposis: cumulative risks and *APC* gene mutations. *Gastroenterology* 2001; 121: 1127–1135
- [67] Groves CJ, Saunders BP, Spigelman AD et al. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. *Gut* 2002; 50: 636–641
- [68] Saurin JC, Ligneau B, Ponchon T et al. The influence of mutation site and age on the severity of duodenal polyposis in patients with familial adenomatous polyposis. *Gastrointest Endosc* 2002; 55: 342–347
- [69] Bulow S, Bjork J, Christensen IJ et al. Duodenal adenomatosis in familial adenomatous polyposis. *Gut* 2004; 53: 381–386
- [70] Sourrouille I, Lefevre JH, Shields C et al. Surveillance of duodenal polyposis in familial adenomatous polyposis: should the Spigelman score be modified? *Dis Colon Rectum* 2017; 60: 1137–1146
- [71] Vasen HF, Bulow S, Myrholm T et al. Decision analysis in the management of duodenal adenomatosis in familial adenomatous polyposis. *Gut* 1997; 40: 716–719
- [72] Wallace MH, Phillips RK. Upper gastrointestinal disease in patients with familial adenomatous polyposis. *Br J Surg* 1998; 85: 742–750
- [73] Lepisto A, Kiviluoto T, Halttunen J et al. Surveillance and treatment of duodenal adenomatosis in familial adenomatous polyposis. *Endoscopy* 2009; 41: 504–509
- [74] Bulow S, Christensen IJ, Hojen H et al. Duodenal surveillance improves the prognosis after duodenal cancer in familial adenomatous polyposis. *Colorectal Dis* 2012; 14: 947–952
- [75] Latchford AR, Neale KF, Spigelman AD et al. Features of duodenal cancer in patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2009; 7: 659–663

- [76] Thiruvengadam SS, Lopez R, O'Malley M et al. Spigelman stage IV duodenal polyposis does not precede most duodenal cancer cases in patients with familial adenomatous polyposis. *Gastrointest Endosc* 2019; 89: 345–354.e2
- [77] Spigelman AD, Williams CB, Talbot IC et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989; 2: 783–785
- [78] Kashiwagi H, Spigelman AD, Debinski HS et al. Surveillance of ampullary adenomas in familial adenomatous polyposis. *Lancet* 1994; 344: 1582
- [79] Kallenberg FGJ, Bastiaansen BAJ, Dekker E. Cap-assisted forward-viewing endoscopy to visualize the ampulla of Vater and the duodenum in patients with familial adenomatous polyposis. *Endoscopy* 2017; 49: 181–185
- [80] Alarcon FJ, Burke CA, Church JM et al. Familial adenomatous polyposis: efficacy of endoscopic and surgical treatment for advanced duodenal adenomas. *Dis Colon Rectum* 1999; 42: 1533–1536
- [81] Cordero-Fernandez C, Garzon-Benavides M, Pizarro-Moreno A et al. Gastroduodenal involvement in patients with familial adenomatous polyposis. Prospective study of the nature and evolution of polyps: evaluation of the treatment and surveillance methods applied. *Eur J Gastroenterol Hepatol* 2009; 21: 1161–1167
- [82] Hamada K, Takeuchi Y, Ishikawa H et al. Safety of cold snare polypectomy for duodenal adenomas in familial adenomatous polyposis: a prospective exploratory study. *Endoscopy* 2018; 50: 511–517
- [83] Inoki K, Nakajima T, Nonaka S et al. Feasibility of endoscopic resection using bipolar snare for nonampullary duodenal tumours in familial adenomatous polyposis patients. *Fam Cancer* 2018; 17: 517–524
- [84] Jaganmohan S, Lynch PM, Raju RP et al. Endoscopic management of duodenal adenomas in familial adenomatous polyposis—a single-center experience. *Dig Dis Sci* 2012; 57: 732–737
- [85] Morpurgo E, Vitale GC, Galandiuk S et al. Clinical characteristics of familial adenomatous polyposis and management of duodenal adenomas. *J Gastrointest Surg* 2004; 8: 559–564
- [86] Moussata D, Napoleon B, Lepilliez V et al. Endoscopic treatment of severe duodenal polyposis as an alternative to surgery for patients with familial adenomatous polyposis. *Gastrointest Endosc* 2014; 80: 817–825
- [87] Soravia C, Berk T, Haber G et al. Management of advanced duodenal polyposis in familial adenomatous polyposis. *J Gastrointest Surg* 1997; 1: 474–478
- [88] Yachida T, Nakajima T, Nonaka S et al. Characteristics and clinical outcomes of duodenal neoplasia in Japanese patients with familial adenomatous polyposis. *J Clin Gastroenterol* 2017; 51: 407–411
- [89] Balmforth DC, Phillips RK, Clark SK. Advanced duodenal disease in familial adenomatous polyposis: how frequently should patients be followed up after successful therapy? *Fam Cancer* 2012; 11: 553–557
- [90] Walton SJ, Kallenberg FG, Clark SK et al. Frequency and features of duodenal adenomas in patients with MUTYH-associated polyposis. *Clin Gastroenterol Hepatol* 2016; 14: 986–992
- [91] Vogt S, Jones N, Christian D et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology* 2009; 137: 1976–1985.e1–e10
- [92] Nielsen M, Poley JW, Verhoef S et al. Duodenal carcinoma in MUTYH-associated polyposis. *J Clin Pathol* 2006; 59: 1212–1215
- [93] Gluck N, Strul H, Rozner G et al. Endoscopy and EUS are key for effective surveillance and management of duodenal adenomas in familial adenomatous polyposis. *Gastrointest Endosc* 2015; 81: 960–966
- [94] Ma T, Jang EJ, Zukerberg LR et al. Recurrences are common after endoscopic ampullectomy for adenoma in the familial adenomatous polyposis (FAP) syndrome. *Surg Endosc* 2014; 28: 2349–2356
- [95] Ouaisi M, Panis Y, Sielezneff I et al. Long-term outcome after ampullectomy for ampullary lesions associated with familial adenomatous polyposis. *Dis Colon Rectum* 2005; 48: 2192–2196
- [96] Ito K, Fujita N, Noda Y et al. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. *Gastrointest Endosc* 2007; 66: 740–747
- [97] Napoleon B, Gincul R, Ponchon T et al. Endoscopic papillectomy for early ampullary tumors: long-term results from a large multicenter prospective study. *Endoscopy* 2014; 46: 127–134
- [98] Menzel J, Hoepffner N, Sulkowski U et al. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT—a prospective, histopathologically controlled study. *Gastrointest Endosc* 1999; 49: 349–357
- [99] Bianchi LK, Burke CA, Bennett AE et al. Fundic gland polyp dysplasia is common in familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; 6: 180–185
- [100] Church JM, McGannon E, Hull-Boiner S et al. Gastroduodenal polyps in patients with familial adenomatous polyposis. *Dis Colon Rectum* 1992; 35: 1170–1173
- [101] Iida M, Yao T, Itoh H et al. Natural history of gastric adenomas in patients with familial adenomatous coli/Gardner's syndrome. *Cancer* 1988; 61: 605–611
- [102] Walton SJ, Frayling IM, Clark SK et al. Gastric tumours in FAP. *Fam Cancer* 2017; 16: 363–369
- [103] Mankaney G, Leone P, Cruise M et al. Gastric cancer in FAP: a concerning rise in incidence. *Fam Cancer* 2017; 16: 371–376
- [104] Offerhaus GJ, Giardiello FM, Krush AJ et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. *Gastroenterology* 1992; 102: 1980–1982
- [105] Campos FG, Martinez CAR, Bustamante Lopez LA et al. Advanced duodenal neoplasia and carcinoma in familial adenomatous polyposis: outcomes of surgical management. *J Gastrointest Oncol* 2017; 8: 877–884
- [106] van Heumen BW, Nieuwenhuis MH, van Goor H et al. Surgical management for advanced duodenal adenomatosis and duodenal cancer in Dutch patients with familial adenomatous polyposis: a nationwide retrospective cohort study. *Surgery* 2012; 151: 681–690
- [107] Alderlieste YA, Bastiaansen BA, Mathus-Vliegen EM et al. High rate of recurrent adenomatosis during endoscopic surveillance after duodenectomy in patients with familial adenomatous polyposis. *Fam Cancer* 2013; 12: 699–706
- [108] Latchford AR, Neale K, Phillips RK et al. Peutz-Jeghers syndrome: intriguing suggestion of gastrointestinal cancer prevention from surveillance. *Dis Colon Rectum* 2011; 54: 1547–1551
- [109] Korsse SE, Dewint P, Kuipers EJ et al. Small bowel endoscopy and Peutz-Jeghers syndrome. *Best Pract Res Clin Gastroenterol* 2012; 26: 263–278
- [110] van Lier MG, Mathus-Vliegen EM, Wagner A et al. High cumulative risk of intussusception in patients with Peutz-Jeghers syndrome: time to update surveillance guidelines? *Am J Gastroenterol* 2011; 106: 940–945
- [111] Latchford AR, Phillips RK. Gastrointestinal polyps and cancer in Peutz-Jeghers syndrome: clinical aspects. *Fam Cancer* 2011; 10: 455–461
- [112] Giardiello FM, Brensinger JD, Tersmette AC et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. *Gastroenterology* 2000; 119: 1447–1453

- [113] Giardiello FM, Trimbath JD. Peutz-Jeghers syndrome and management recommendations. *Clin Gastroenterol Hepatol* 2006; 4: 408–415
- [114] Resta N, Pierannunzio D, Lenato GM et al. Cancer risk associated with *STK11/LKB1* germline mutations in Peutz-Jeghers syndrome patients: results of an Italian multicenter study. *Dig Liver Dis* 2013; 45: 606–611
- [115] Chen HY, Jin XW, Li BR et al. Cancer risk in patients with Peutz-Jeghers syndrome: A retrospective cohort study of 336 cases. *Tumour Biol* 2017; 39: 1010428317705131
- [116] Goverde A, Korsse SE, Wagner A et al. Small-bowel surveillance in patients with Peutz-Jeghers syndrome: comparing magnetic resonance enteroclysis and double balloon enteroscopy. *J Clin Gastroenterol* 2017; 51: e27–e33
- [117] Maccioni F, Al Ansari N, Mazzamurro F et al. Surveillance of patients affected by Peutz-Jeghers syndrome: diagnostic value of MR enterography in prone and supine position. *Abdom Imaging* 2012; 37: 279–287
- [118] Gupta A, Postgate AJ, Burling D et al. A prospective study of MR enterography versus capsule endoscopy for the surveillance of adult patients with Peutz-Jeghers syndrome. *AJR Am J Roentgenol* 2010; 195: 108–116
- [119] Urquhart P, Grimpén F, Lim GJ et al. Capsule endoscopy versus magnetic resonance enterography for the detection of small bowel polyps in Peutz-Jeghers syndrome. *Fam Cancer* 2014; 13: 249–255
- [120] Schulmann K, Hollerbach S, Kraus K et al. Feasibility and diagnostic utility of video capsule endoscopy for the detection of small bowel polyps in patients with hereditary polyposis syndromes. *Am J Gastroenterol* 2005; 100: 27–37
- [121] Caspari R, Friedl W, Mandl M et al. Familial adenomatous polyposis: mutation at codon 1309 and early onset of colon cancer. *Lancet* 1994; 343: 629–632
- [122] Chen TH, Lin WP, Su MY et al. Balloon-assisted enteroscopy with prophylactic polypectomy for Peutz-Jeghers syndrome: experience in Taiwan. *Dig Dis Sci* 2011; 56: 1472–1475
- [123] Belsha D, Urs A, Attard T et al. Effectiveness of double-balloon enteroscopy-facilitated polypectomy in pediatric patients with Peutz-Jeghers syndrome. *J Ped Gastroenterol Nutr* 2017; 65: 500–502
- [124] Bizzarri B, Borrelli O, de'Angelis N et al. Management of duodenal-jejunal polyps in children with Peutz-Jeghers syndrome with single-balloon enteroscopy. *J Ped Gastroenterol Nutr* 2014; 59: 49–53
- [125] Akarsu M, Ugur Kantar F, Akpınar H. Double-balloon endoscopy in patients with Peutz-Jeghers syndrome. *Turkish J Gastroenterol* 2012; 23: 496–502
- [126] Serrano M, Mao-de-Ferro S, Pinho R et al. Double-balloon enteroscopy in the management of patients with Peutz-Jeghers syndrome: a retrospective cohort multicenter study. *Rev Esp Enferm Dig* 2013; 105: 594–599
- [127] Latchford AR, Neale K, Phillips RK et al. Juvenile polyposis syndrome: a study of genotype, phenotype, and long-term outcome. *Dis Colon Rectum* 2012; 55: 1038–1043
- [128] Ma C, Giardiello FM, Montgomery EA. Upper tract juvenile polyps in juvenile polyposis patients: dysplasia and malignancy are associated with foveolar, intestinal, and pyloric differentiation. *Am J Surg Pathol* 2014; 38: 1618–1626
- [129] Aretz S, Stienen D, Uhlhaas S et al. High proportion of large genomic deletions and a genotype phenotype update in 80 unrelated families with juvenile polyposis syndrome. *J Med Genet* 2007; 44: 702–709
- [130] Wain KE, Ellingson MS, McDonald J et al. Appreciating the broad clinical features of *SMAD4* mutation carriers: a multicenter chart review. *Genet Med* 2014; 16: 588–593
- [131] Alimi A, Weeth-Feinstein LA, Stettner A et al. Overlap of juvenile polyposis syndrome and Cowden syndrome due to de novo chromosome 10 deletion involving *BMPRIA* and *PTEN*: implications for treatment and surveillance. *Am J Med Genet A* 2015; 167: 1305–1308
- [132] Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol* 1998; 5: 751–756
- [133] Gonzalez RS, Adsay V, Graham RP et al. Massive gastric juvenile-type polyposis: a clinicopathological analysis of 22 cases. *Histopathology* 2017; 70: 918–928
- [134] Jee MJ, Yoon SM, Kim EJ et al. A novel germline mutation in exon 10 of the *SMAD4* gene in a familial juvenile polyposis. *Gut Liver* 2013; 7: 747–751
- [135] Postgate AJ, Will OC, Fraser CH et al. Capsule endoscopy for the small bowel in juvenile polyposis syndrome: a case series. *Endoscopy* 2009; 41: 1001–1004
- [136] Snover DC, Ahnen DJ, Burt RW et al. Serrated polyps of the colon and rectum and serrated polyposis. In: Bosman T, Carneiro F, Hruban R et al., eds. *WHO classification of tumours of the digestive system*. Lyon, France: IARC; 2010: 160–165
- [137] Rubio CA, Stemme S, Jaramillo E et al. Hyperplastic polyposis coli syndrome and colorectal carcinoma. *Endoscopy* 2006; 38: 266–270
- [138] MacPhail ME, Thygesen SB, Patel N et al. Endoscopic control of polyp burden and expansion of surveillance intervals in serrated polyposis syndrome. *Gastrointest Endosc* 2019; 90: 96–100
- [139] Pellise M, Burgess NG, Tuticci N et al. Endoscopic mucosal resection for large serrated lesions in comparison with adenomas: a prospective multicentre study of 2000 lesions. *Gut* 2017; 66: 644–653
- [140] Boparai KS, Mathus-Vliegen EM, Koornstra JJ et al. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut* 2010; 59: 1094–1100
- [141] Bleijenberg AG, Ijspeert JE, van Herwaarden YJ et al. Personalised surveillance for serrated polyposis syndrome: results from a prospective 5-year international cohort study. *Gut* 2019; doi:10.1136/gutjnl-2018-318134
- [142] Heresbach D, Barrioz T, Lapalus MG et al. Miss rate for colorectal neoplastic polyps: a prospective multicenter study of back-to-back video colonoscopies. *Endoscopy* 2008; 40: 284–290
- [143] Boparai KS, van den Broek FJ, van Eeden S et al. Increased polyp detection using narrow band imaging compared with high resolution endoscopy in patients with hyperplastic polyposis syndrome. *Endoscopy* 2011; 43: 676–682
- [144] Hazewinkel Y, Tytgat KM, van Leerdam ME et al. Narrow-band imaging for the detection of polyps in patients with serrated polyposis syndrome: a multicenter, randomized, back-to-back trial. *Gastrointest Endosc* 2015; 81: 531–538
- [145] Lopez-Vicente J, Rodriguez-Alcalde D, Hernandez L et al. Panchromoendoscopy increases detection of polyps in patients with serrated polyposis syndrome. *Clin Gastroenterol Hepatol* 2018; doi:10.1016/j.cgh.2018.10.029
- [146] Rivero-Sánchez L, López Vicente J, Hernandez Villalba L et al. Endo-cuff-assisted colonoscopy for surveillance of serrated polyposis syndrome: a multicenter randomized controlled trial. *Endoscopy* 2019; doi:10.1055/a-0925-4956
- [147] Chow E, Lipton L, Lynch E et al. Hyperplastic polyposis syndrome: phenotypic presentations and the role of *MBD4* and *MYH*. *Gastroenterology* 2006; 131: 30–39
- [148] Lage P, Cravo M, Sousa R et al. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. *Am J Gastroenterol* 2004; 99: 1779–1784

- [149] Boparai KS, Reitsma JB, Lemmens V et al. Increased colorectal cancer risk in first-degree relatives of patients with hyperplastic polyposis syndrome. *Gut* 2010; 59: 1222 – 1225
- [150] Win AK, Walters RJ, Buchanan DD et al. Cancer risks for relatives of patients with serrated polyposis. *Am J Gastroenterol* 2012; 107: 770 – 778
- [151] Egoavil C, Juarez M, Guarinos C et al. Increased risk of colorectal cancer in patients with multiple serrated polyps and their first-degree relatives. *Gastroenterology* 2017; 153: 106 – 112.e2
- [152] Caetano AC, Ferreira H, Soares J et al. Phenotypic characterization and familial risk in hyperplastic polyposis syndrome. *Scand J Gastroenterol* 2013; 48: 1166 – 1172
- [153] Oquinená S, Guerra A, Pueyo A et al. Serrated polyposis: prospective study of first-degree relatives. *Eur J Gastroenterol Hepatol* 2013; 25: 28 – 32
- [154] Hazewinkel Y, Koornstra JJ, Boparai KS et al. Yield of screening colonoscopy in first-degree relatives of patients with serrated polyposis syndrome. *J Clin Gastroenterol* 2015; 49: 407 – 412
- [155] Cohen S, Hyer W, Mas E et al. Management of juvenile polyposis syndrome in children and adolescents: a position paper from the ESPGHAN Polyposis Working Group. *J Ped Gastroenterol Nutr* 2019; 68: 453 – 462
- [156] Hyer W, Cohen S, Attard T et al. Management of familial adenomatous polyposis in children and adolescents: position paper from the ESPGHAN Polyposis Working Group. *J Ped Gastroenterol Nutr* 2019; 68: 428 – 441
- [157] Latchford A, Cohen S, Auth M et al. Management of Peutz-Jeghers syndrome in children and adolescents: a position paper from the ESPGHAN Polyposis Working Group. *J Ped Gastroenterol Nutr* 2019; 68: 442 – 452