European Journal of Cancer 104 (2018) 91–103

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Screening and surveillance in hereditary gastrointestinal cancers: Recommendations from the European Society of Digestive Oncology (ESDO) expert discussion at the 20th European Society for Medical Oncology (ESMO)/World Congress on Gastrointestinal Cancer, Barcelona, June 2018

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Received 4 September 2018; accepted 6 September 2018
Available online 18 October 2018

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https://doi.org/10.1016/j.ejca.2018.09.004

KEYWORDS
Hereditary GI cancer;
Surveillance;
Screening;
Hereditary diffuse gastric cancer;
Lynch syndrome;
Polyposis;
Familial pancreatic cancer

Abstract Patients with hereditary gastrointestinal (GI) cancers represent a substantial fraction of the overall affected population. Although awareness for hereditary GI cancer syndromes is on the rise, identification of patients and measures of surveillance are often unclear in everyday clinical routine. Therefore, the European Society of Digestive Oncology expert discussion 2018 at the World Congress on Gastrointestinal Cancer focussed on screening and surveillance of hereditary colorectal, gastric and pancreatic cancers. An international panel of experts and opinion leaders developed the here presented recommendations based on published evidence and on profound clinical expertise to facilitate clinical routine in identification and caretaking of patients with familial GI cancers.

1. Introduction

With more than 2.5 million new cases and 1.7 million cancer deaths every year worldwide, colorectal cancer (CRC), gastric cancer (GC) and pancreatic cancer (PC) are the leading causes of gastrointestinal (GI) cancer–related morbidity and mortality [1]. Approximately 15–20% of all CRC, 10% of all GC and 5–10% of PC have got a probable genetic inherited cause [2–6]. Undoubtedly, screening by colonoscopy has led to a reduction of CRC in the general population, as well as in high-risk groups, over the last decades. Much less progress has been achieved for GC, where the detection rate at the early stage remains low [7]. Intriguingly, CRC incidence rates for younger patients are on the rise since the mid 1980s, giving suspicion for genetic and/or environmental causes of disease [8].

For risk populations, such as individuals with a known or suspected inherited disease prone to cancer, a set of guidelines have been proposed and implemented by national and international societies. Nevertheless, owing to the heterogeneity of different disorders causing familial GI cancers, expanding set of genes potentially involved in hereditary cancer syndromes and novel methods in molecular diagnostics such as next-generation sequencing (NGS), strong evidence is still lacking for a set of practical questions that clinicians are facing in routine practice.

Thus, the objective of the European Society of Digestive Oncology (ESDO) expert discussion 2018 at the 20th World Congress on Gastrointestinal Cancer was to review the current approach to patients and individuals at risk for the aforementioned hereditary GI cancers.

An international panel of experts and opinion leaders participated in the discussion. In the run-up for the expert meeting, a questionnaire was developed for every tumour entity. The collected answers where then discussed and consented at the meeting. The recommendations summarised in this article represent the current evidence-based approaches and expert opinions based on profound expertise through substantial clinical experience. The aim of this work is to offer physicians a practical and comprehensive approach to the affected patient and individual at risk in everyday clinical routine, focussing on identification of patients at risk, specific genetic testing and measures of surveillance.

2. General consideration

2.1. Patient history

Key to the identification of any hereditary cancer syndrome is a dedicated patient and family history especially in young patients with cancer.

2.2. Multidisciplinary approach

Patients with (suspected) hereditary cancer syndromes or syndromes prone to cancerous disease should be offered care focussing on all aspects of these complex diseases. Patients should undergo genetic counselling prior to any germline mutational analysis. Surveillance usually is not only performed by a single medical speciality but includes experienced surgeons, gastroenterologists, oncologists, gynaecologists, urologists, dermatologists, geneticists, pathologists and radiologists, as well as psychologists/psycho-oncologists and nutritional experts. Thus, treatment and caretaking is recommended at specialised high-volume centres, whenever possible.

2.3. Third concern

Identification of an individual with a familial cancer syndrome should not only lead to individualised care for the patient but also include the third concern, i.e. relatives not being aware of their risk. This includes clinical and genetic counselling for relatives, predictive genetic testing whenever applicable and surveillance. Surveillance measures regarding the discussed hereditary GI-cancers are summarized in Table 2.

Table 1
GI cancer predisposition syndromes with the affected genes and phenotypes.

Syndrome	Genetic feature	Clinical feature
Lynch syndrome	Tumour: MSI-high, dMMR Germline: *MLH1, MSH2, MSH6, PMS2, EPCAM*	High lifetime prevalence of colorectal, endometrial, ovarian, gastric and small bowel, urinary tract, biliary tract and PC
FAP	*APC*	Adenomatous polyps (usually more than 100) Duodenal polyps Desmoids, hepatoblastoma, cribriform-morular variant of thyroid cancer, congenital retinal pigment hypertrophy
aFAP	*APC*	Adenomatous polyps (usually less than 100) Duodenal polyps
MAP	*MUTYH* (autosomal recessive)	Adenomatous polyps (usually less than 100) Serrated polyps Duodenal polyps
PJS	*STK11*	PJS-type polyps, mucocutaneous hyperpigmentation, risk for PC, breast cancer, gynaecological cancer and testicular tumour
JPS	*SMAD4/BMPR1*	Juvenile polyps throughout the GI tract
Serrated polyposis	*RNF43*	Serrated polyps, usually proximal of the sigmoid colon
HDGC	*CDH1, CTNNA1*	Diffuse gastric cancer, lobular breast cancer, colorectal cancer
FIGC	None	Gastric cancer
GAPPS	*APC*	Gastric cancer and polyposis
Li-Fraumeni	*TP53*	Sarcoma at young age with other tumours such as breast cancer, brain, colorectal and PC
Cowden syndrome	*PTEN*	Colorectal, upper GI, small bowel, thyroid, breast, uterine, renal cell cancer and cutaneous lesions
PPAP	*POLE, POLD1*	Colorectal polyposis, duodenal adenomas, endometrial, ovarian and breast cancer
MSH3-associated polyposis	*MSH3* (autosomal recessive)	Colorectal polyposis
NTHL1-associated polyposis	*NTHL-1* (autosomal recessive)	Colorectal polyposis
Hereditary mixed polyposis	*GREM1*	Colorectal polyposis
HBOC	*BRCA1* and 2	Breast and ovarian cancer, PC predisposition

GI, gastrointestinal; FAP, familial adenomatous polyposis; aFAP, attenuated FAP; MAP, *MUTYH*-associated polyposis; PJS, Peutz–Jeghers syndrome; JPS, juvenile polyposis syndrome; HDGC, hereditary diffuse gastric cancer; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; PPAP, polymerase proofreading-associated polyposis; HBOC, hereditary breast and ovarian cancer; MSI-high, high microsatellite instability; dMMR, deficient mismatch repair; PC, pancreatic cancer.

3. Hereditary colorectal cancer

3.1. Lynch syndrome

3.1.1. Identifying the patient with Lynch syndrome

The accepted criteria for a clinically suspected Lynch syndrome (LS) have been summed up in the Amsterdam II and revised Bethesda criteria [9,10]. LS should also be suspected if any of the following criteria are fulfilled: (a) young age of disease onset, (b) family history of CRC, (c) known mismatch repair (MMR) gene mutation in the family, (d) personal or family history of a LS-associated cancer (see section 3.2.2) or (e) a tumour with high microsatellite instability (MSI-high) or deficient MMR system (dMMR). Although clinical suspicion is higher in young patients, an age limit for screening is not recommended as tumour incidence rates show an age dependency in LS just like in sporadic cancers, with higher incidence rates in older patients [11,12]. Besides, MSI diagnostics have recently been used more extensively because of therapeutic consequences [13].

3.1.2. Lynch syndrome-associated cancers

Cancers associated with LS are colorectal, endometrial, ovarian, gastric, small bowel, urinary tract, biliary tract and pancreatic cancers [14]. For MSH2-mutation carriers, there is a higher risk for cutaneous lesions such as acanthomas or sebaceous lesions (Muir–Torre syndrome) [15] Although described by others, the ESDO expert panel does not consider breast cancer as LS associated as the increased risk in dMMR patients does not seem clinically relevant to date [11,16].

3.1.3. Histopathologic work-up on suspected Lynch syndrome

The first diagnostic step is the analysis of MMR protein expression by immunohistochemistry (IHC) and/or testing for MSI by polymerase chain reaction (PCR) [12]. Both methods should be performed with an appropriate quality. Especially if the IHC results are doubtful, MSI analysis, for example, by multiplex fluorescent PCR amplification of BAT25, BAT26, NR21, NR22, and NR24 replication markers from the DNA extracted from the formalin-fixed paraffin-embedded tumour tissues should be performed [17].

Table 2
GI cancer predisposition syndromes, summary of surveillance recommendations.

Syndrome - Site	Surveillance procedure	Interval	Starting at age
Lynch syndrome			
- colorectal	Colonoscopy (chromoendoscopy)	1–2 years	20–25
- upper GI	EGD	1–2 years	30
- Pancreatic cancer	EUS/MRI (only if FDR is affected)	1 year	50 or 10 years prior youngest affected FDR
- endometrial/ovary	Transvaginal US, endometrial biopsy, consider hysterectomy and oophorectomy	2 years	35
FAP			
- Colorectal	Colonoscopy, proctocolectomy	1 year	Screening age 10 years, surveillance annually at the age of 18 years (earlier according to findings)
- Duodenal	Duodenoscopy	3 years	20–25
- Thyroid	Ultrasound (only in females)	1 year	15
- Pancreatic	EUS/MRI (only if FDR is affected)	1 year	50 or 10 years prior youngest affected FDR
- Desmoids/	Abdominal ultrasound	1 year	till the age of 5 years (hepatoblastoma), then from 20 years
Hepatoblastoma			
aFAP	Similar to FAP	Similar to FAP	No later than 15
MAP			
PJS			
- Colorectal and gastric	Endoscopy	Baseline age 8 years, then every 2–3 years, or if negative, reinitiation at the age of 18 years, every 2–3 years till 50 years, then every 1–2 years	
- Small bowel	MRI enteroscopy or video capsule	45–50 years or 10 years before youngest affected FDR	
- Pancreatic	EUS/MRI	annually at the age of 25 years	
- Breast	MRI		
JPS	EGD/colonoscopy	2–3 years, annually in case of findings	12–15
Serrated polyposis	Colonoscopy	1–3 years	Unclear
HDGC			
- Gastric	Gastrectomy, EGD if surgery is not possible	1 year	20 or 5 years prior to youngest affected FDR
- Breast	MRI	1 year	30
- Colorectal	Colonoscopy (if FH positive)	3–5 years	40
FIGC	EGD	1 year	40 or 5 years before youngest affected FDR
GAPPS	EGD, gastrectomy in unmanageable polyposis	1 year	40 or 5 years before youngest affected FDR
Li-Fraumeni	Laboratories including WBC, LDH, ESR	3 months	With diagnosis, colonoscopy age 25 years
	Whole-body MRI	1 year	
	Breast examination	6 months	
	Abdominal ultrasound	6 months	
	Colonoscopy	2–5 years	

GI, gastrointestinal; FDR, first-degree relative; FAP, familial adenomatous polyposis; MAP, MUTYH-associated polyposis; PJS, Peutz–Jeghers syndrome; JPS, juvenile polyposis syndrome; HDGC, hereditary diffuse gastric cancer; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; PPAP, polymerase proofreading-associated polyposis; WBC, white blood cell; EUS, endoscopic ultrasound; MRI, magnetic resonance imaging; US, ultrasound.

3.1.4. Universal testing of tumours for microsatellite instability

Universal testing for MSI in patients with newly diagnosed Lynch syndrome-associated malignancies is highly recommended. There is not only a substantial fraction of LS patients missed if screening is solely performed on the basis of the clinical criteria but there is evidence for cost-effectiveness of universal MSI testing in patients up to the age of 70 years [16,18,19].

3.1.5. Germline testing

Patients with MSI-high/dMMR tumours should be offered germline testing for MMR mutations after receiving genetic counselling. In the case of CRC, with *MLH1/PMS2* deficiency, *BRAF* mutation and *MLH1*-promotor hypermethylation should be excluded in the tumour before germline mutational testing. An MSI-high/dMMR tumour with *MLH1/PMS2* defect and *BRAF* mutation is classified as sporadic CRC [17,20,21].

Penetrance at the age of 70 years for CRC in LS reaches 50%, depending on the causative germline mutation [22].

3.1.6. Genes to be analysed in suspected Lynch syndrome patients

MLH1, *MSH2*, *MSH6*, *PMS2* and *EPCAM* should be analysed by an appropriated method, preferably NGS, for point mutations and larger rearrangements [17,23,24].

3.1.7. Surveillance for colorectal cancer in Lynch syndrome

Patients diagnosed with a germline mutation in any MMR gene should undergo colonoscopy at least every 1–2 years, as endoscopic surveillance is the only means to reduce mortality [25–28]. Whenever possible, colonoscopy should be performed as chromoendoscopy using indigo carmine [29–32]. A sufficient amount of time should be provided for the endoscopic procedure. Surveillance should start at the age of 20–25 years or even earlier, if the family history suggests an earlier age of disease onset [26,27,33]. LS patients should be preferably followed up in specialised centres.

3.1.8. Colorectal surgery as prophylactic measure in Lynch syndrome

A prophylactic colectomy is not recommended as evidence is lacking. If surgery is performed for a CRC, it should be performed according to oncological principles of surgery [33]. In selected cases, a subtotal colectomy might be discussed with the patient [27]. Patients should be informed about the necessity of surveillance of the remaining colon and rectum after total or subtotal colectomy and surveillance of extracolonic malignant manifestations.

3.1.9. Extracolonic surveillance in Lynch syndrome

3.1.9.1. Gastric cancer and small bowel cancer (SBC). For GC and duodenal cancer, upper GI endoscopy should be performed regularly in mutation carriers starting no later than the age of 30 years. Upper GI endoscopy is recommended, regardless of the family history as recent data do not support any correlation to prior GC/SBC in the family [34,35]. Data on the correct interval of upper GI endoscopy are limited. Therefore, a practical suggestion would be to perform upper GI endoscopy in the same session as colonoscopy. *Helicobacter pylori* testing is mandatory, and eradication should be performed in case of proof. The role of video capsule endoscopy for surveillance of SBC is still unclear.

3.1.9.2. Endometrial and ovarian cancer. For gynaecological surveillance, transvaginal ultrasound and endometrial biopsy should be performed, starting no later than the age of 35 years, at least every other year [26,33]. Hysterectomy and oophorectomy should be discussed with patients after family planning is completed [36,37]. Patients should be accompanied by a multidisciplinary team including psychologists/psycho-oncologists and should be given sufficiently long time for a decision.

3.1.9.3. Pancreatic and periampullary cancer. There is not much evidence for any routine surveillance for PC in LS patients as cumulative risk remains low (3–5% at 70 years). Nevertheless, in case of a family history of PC in mutation carriers, annual *magnetic resonance imaging* (MRI) and/or endoscopic ultrasound (EUS) should be considered, starting at the age of 50 years, or 10 years before the onset of PC in the youngest affected family member [38,39]. Consequences of PC surveillance are discussed in the following section.

3.1.9.4. Others. There is no clear evidence for routine surveillance of urinary tract or biliary tract cancer, although risk factors have been recently described for the former. Thus, in case of a positive family history, an annual urinary cytology could be discussed with the patient, as well as abdominal and renal ultrasound [40,41]. Patients should be informed about an increased lifetime risk for biliary and urinary tract cancer at diagnosis of LS.

3.1.10. Chemoprevention and other preventive measures

In general, patients should be advised to stop smoking, reduce overweight and increase physical activity. Nutritional counselling can be offered.

Regarding chemoprevention, the CAPP2 trial showed a reduction in LS-associated cancers with 600 mg of daily aspirin for at least 2 years [42]. Nevertheless, the results of this trial have to be interpreted with caution as to following caveats: the initial report of the trial did not meet its end-point [43], the dosage of aspirin seems unusually high in comparison to trials in sporadic CRC and clinical experience might suggest an underreporting of GI bleedings. Thus, a critical discussion of the trial results with the patient is warranted. Particularly, it is unknown whether high-dose aspirin (600 mg per day) is necessary to prevent further LS-associated cancers as the inhibition of cyclooxygenase-2 and subsequently decreased prostaglandin E2 synthesis—often the presumed mechanism of the preventative impact of aspirin on different malignancies—requires less then 100 mg daily. Fortunately, dose non-inferiority studies comparing 100 mg, 300 mg and 600 mg of daily aspirin for prevention of LS-associated malignancies in LS carriers (i.e. CAPP-3 and AAS-Lynch) are currently under way, and their results are eagerly awaited (ClinicalTrials.gov identifier NCT02813824 and NCT02497820).

3.1.11. Surveillance in case of Amsterdam/Bethesda positivity but microsatellite stable tumours

For Amsterdam-positive patients without demonstration of high MSI or dMMR, surveillance should start at the age of 25 years with colonoscopies every 3–5 years

[33]. More vigorous surveillance should be guided by the family context and the tumour localisation (for instance, if accumulation of gynaecological tumours, gynaecological surveillance is recommended, and accumulation of early onset CRC may lead to shortening of intervals between examinations).

3.2. Polyposis syndromes

3.2.1. Identifying the patient with polyposis

Patients with more than 10 synchronous adenomatous polyps, at least two hamartomatous polyps or at least five serrated polyps proximal of the sigmoid colon, as well as a family history of any polyposis syndrome, are suspected of having a polyposis syndrome. Patients with a personal history of at least 20 (metachronous) adenomas may also be suspected of polyposis [44]. Patients with less than 20 polyps with a frequent recurrence rate and a young age of onset can be suspected of having a hereditary cause—polyposis or non-polyposis.

Polyposis syndromes with their respective phenotype and genotype are summarised in Table 1.

3.2.2. Genetic work-up

Polyposis work-up is guided by the phenotype. For adenomatous polyposis, germline mutational testing after genetic counselling of *APC* and *MUTYH* is the minimum standard (familial adenomatous polyposis (FAP), attenuated FAP (aFAP), MUTYH-associated polyposis [MAP]). An extended gene panel can be offered if *APC* and *MUTYH* do not show any mutations. Following genes should be considered for testing: *STK11*, *PTEN, BMPR1A*, *SMAD4*, *POLE*, *POLD1*, *MSH3*, *NTHL-1*, *GREM1* and *RNF43* [45]. Associations of genes with specific syndromes are summarised in Table 1.

3.2.3. Diagnosis, surveillance and surgery for familial adenomatous polyposis

FAP is characterised by patients having more than 100 polyps in their large intestine, although at young ages and in patients with aFAP, the number of polyps can be lower. Besides the almost certain lifetime risk of CRC, there is an increased risk of duodenal cancer, hepatoblastoma, thyroid cancer and desmoid tumours (aggressive fibromatosis). Thus, a personal history of desmoid tumours, hepatoblastoma, cribriform-morular variant of thyroid cancer or congenital retinal pigment epithelial hypertrophy should at least raise the suspicion of an underlying FAP. The disease is characterised by a germline mutation in the *APC* gene [44–47].

Patients with FAP should receive early screening and annual colonoscopies (plus chromoendoscopy with indigo carmine) starting at the age of 10 years. According to the burden of polyps, a total (procto)colectomy should be performed, preferably after puberty. Conservation of the rectum should depend on involvement with polyps: if there are less than 20 rectal adenomas without high-grade dysplasia and no confluent polyposis, rectum-conserving surgery can be discussed. In selected cases, colectomy may be carried out later (i.e. less than 20 colorectal polyps on chromoendoscopy) [2,26,27,44].

Annual rectoscopy or pouchoscopy should be carried out after surgery. During colonoscopy, the ileum should be inspected as far as possible. Duodenoscopy including examination of the ampulla using lateral vision should be carried out at least every 3 years according to findings, starting no later than the age from 20 to 25 years. Abdominal ultrasound can be proposed, initially for hepatoblastoma (until the age of 5 years), later for detection of desmoids [26,33,44,47]. Annual thyroid ultrasound can be offered to women, starting at the age of 15 years [48]. Surveillance for PC should be performed if there is a family history of PC and is analogous to PC surveillance in LS patients (see section 3.1.9).

3.2.4. Diagnosis and surveillance for attenuated familial adenomatous polyposis and MUTYH-associate polyposis

The genetic aetiology of aFAP is the same as for FAP with a germline mutation of the *APC* gene and autosomal dominant mode of inheritance. Nevertheless, the load of polyps is lower in aFAP than in FAP. In contrast, MAP is an autosomal recessive condition—thus often with an uninformative family history—leading to polyposis rather in the range of aFAP than in that of FAP. MAP patients carry a higher lifetime risk of duodenal cancer.

For aFAP, surveillance is essentially analogous to FAP, although surveillance may start a little later (latest at the age of 20 years). If a biallelic *MUTYH* mutation has been detected, surveillance should start no later than at the age of 20 years and is similar to the surveillance for FAP. With a phenotypic aFAP without APC mutation, annual colonoscopy by chromoendoscopy should be performed from the age of 20 years. Duodenoscopy by chromoendoscopy should be performed at the age of 20, 25 and 30 years and then at least every other year. In case of significant lesions, intervals should be shortened [17,26,44].

3.2.5. Diagnosis and surveillance in Peutz–Jeghers syndrome

Peutz–Jeghers syndrome (PJS) usually is caused by germline mutations in the *STK11* gene [49]. Clinical diagnosis can be made based on any two of the following criteria: (a) two or more PJS-type polyps of the small intestine, (b) mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes or genitalia or (c) family history of PJS [2,26,44]. Baseline endoscopy (colonoscopy and upper GI endoscopy) should be performed at the age of 8 years. Thereafter, the screening interval may be tailored based on the findings of the first endoscopy: if polyps are detected, screening should be performed at 2- to 3-year intervals; if not, screening may be reinitiated at the age of 18 years, again with 2- to 3-

year intervals. More frequent screening (every 1–2 years) should be performed after the age of 50 years [50].

The small intestine should be examined before the age of 10 years to avoid the risk of intussusception due to large polyps, either with MRI enteroscopy or capsule endoscopy. Follow-up should be based on the initial findings or, analogous to endoscopic surveillance, recommenced at the age of 18 years [44,50].

Extraintestinal manifestations of PJS include breast cancer, PC, gynaecological cancer (ovary, uterus, cervix) and testicular tumours. Surveillance for breast cancer should include annual MRI starting at the age of 25 years. Regular cervical smears and clinical testicular examination can be recommended from the age of 18–20 years [50]. For PC, annual MRI/EUS should be offered from the age of 45 to 50 years or 10 years before the youngest affected first-degree relative.

3.2.6. Diagnosis and surveillance in juvenile polyposis syndrome

Juvenile polyposis syndrome (JPS) is inherited through germline mutations of *BMPR1A* and *SMAD4* in most cases. Clinical diagnosis is established if any of the following criteria are met: (a) at least three juvenile polyps in the colon, (b) multiple juvenile polyps throughout the GI tract or (c) one polyp and family history of JPS [51].

Data on surveillance are scarce, but an increased cancer risk has, nevertheless, been described. Colonoscopy and upper GI endoscopy are recommended starting at the age of 12–15 years. Endoscopic surveillance is guided by findings and should be repeated annually in case of polyps and every 2–3 years otherwise. Monitoring of the small intestine is not recommended [44,52,53].

3.2.7. Surveillance in serrated polyposis syndrome

The World Health Organization criteria for diagnosis of serrated polyposis syndrome include one of the following: (a) at least five serrated polyps proximal of the sigmoid, thereof two larger than 10 mm, (b) at least one serrated polyp proximal of the sigmoid colon and one first-degree relative with serrated polyposis and (c) at least 20 serrated polyps throughout the colon [44,54].

In serrated polyposis, colonoscopy should be performed every 1–3 years. Surgery is indicated in case of endoscopical uncontrollable load of polyps [26,27,44].

3.2.8. Surveillance in polyposis and non-polyposis with unidentified mutation

Surveillance is guided by phenotype in analogy to the syndrome most suitable. Massive polyposis (i.e. presence of more than 100 polyps) warrants the same rigorous surveillance and measures as in FAP.

In Amsterdam-positive patients without MSI, the panel recommends colonoscopic surveillance starting at the age of 25 years, with intervals ranging from 3 to 5 years and shorter according to endoscopic findings. Upper GI endoscopy and endometrial biopsy can be offered to these patients, especially if individuals show a high recurrence rate of colonic polyps.

4. Familial gastric cancer

4.1. Identifying the patient with familial gastric cancer

Patients with a family history of GC, early onset disease (<40 years of age) or a known personal or family history of any of the following conditions are at risk for familial GC: hereditary diffuse GC (HDGC), familial intestinal GC (FIGC), gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), LS, FAP, MAP, PJS or Li-Fraumeni syndrome [3,4,55,56]. Involved genes are summarised in Table 1.

4.2. Hereditary diffuse gastric cancer

4.2.1. Identifying the patient with hereditary diffuse gastric cancer

The clinical criteria for identifying HDGC patients have been described and defined by the International Gastric Cancer Linkage Consortium: (a) families with two or more individuals with GC at any age, in first- or second-degree relatives, with at least one confirmed diffuse GC (DGC), (b) DGC before the age of 40 years without family history or (c) families with diagnosis of both DGC and lobular breast cancer (LBC) with a case before the age of 50 years should be considered for genetic counselling and testing. Genetic testing may also be considered if there is a personal history of bilateral LBC under the age of 50 years or the presence of two or more relatives with LBC under the age of 50, a personal or family history of DGC and cleft palate/lip or *in situ* signet ring cell carcinoma and/or pagetoid spread of signet ring cells [55,57,58].

4.2.2. Genetic work-up for hereditary diffuse gastric cancer

Patients should receive genetic counselling and *CDH1* germline testing. *CDH1* mutational testing in the tumour is obsolete. Germline mutational analysis of *CTNNA1* can be performed, especially if results for *CDH1* are negative or inconclusive [59,60].

Finally, patients should receive an upper GI endoscopy with multiple and random gastric biopsies [57].

4.2.3. Management and surveillance for gastric cancer in confirmed mutation carriers

All patients should have total gastrectomy because failure of endoscopic surveillance occurs in approximately 50% of patients. The lifetime risk of a potential fatal cancer exceeds 80%. Patients should be confronted with these numbers for an informed consent regarding surgery [57,58,61,62].

If surgery is not possible, surveillance should be performed with annual white light high-definition

endoscopy with repeated inflation and deflation in a dedicated session under sedation with at least 30 min allocated. Target areas (pale in appearance) should be biopsied multiple times, and random biopsies should be performed additionally to reach a total number of more than 30 samples per session. Ideally, endoscopic surveillance is performed at specialised centres [57,61,62].

Although a clear association with HDGC is not proven, *H. pylori* testing should be performed and, if positive, the bacteria should be eradicated [57].

Surveillance should commence after genetic counselling and positive genetic test results, with surgery being performed after the age of 20 or 5 years earlier than the youngest affected relative [57,63].

4.2.4. Special surgical aspects in hereditary diffuse gastric cancer

As mentioned previously, total gastrectomy is recommended in any proven *CDH1*-mutation carrier. For patients with a diagnosed DGC, gastrectomy should be carried out according to oncological principles (D2 lymph node dissection). If the patient is undergoing a prophylactic gastrectomy, a D1 lymph node dissection is sufficient. However, if cancerous cells are discovered in the surgically resected specimen, a second surgical procedure according to oncological principles (D2 resection) is recommended. In case of endoscopic surveillance, total gastrectomy is warranted if microscopic foci of signet ring cells or any high-grade dysplasia are detected in the histopathological specimen, confirmed by two pathologists [57,64]. In this scenario, an oncologic D2 lymphadenectomy should be performed as there is a relevant risk of undiscovered invasive adenocarcinoma in the biopsy specimen.

Perioperative counselling should be performed by a multidisciplinary team, including surgeons, gastroenterologists, nutritional experts and psychologists/psycho-oncologists to ensure that the patient receives sufficient information about morbidity and lifestyle as well as nutritional changes (e.g. vitamin B12 supplementation) after gastrectomy [3,63,65].

4.2.5. Management and surveillance of other digestive and extradigestive manifestations of hereditary diffuse gastric cancer

4.2.5.1. Lobular breast cancer. Starting at the age of 30 years, confirmed mutation carriers should examine themselves at least once a month after being trained adequately, receive a clinical breast examination twice a year and an annual breast MRI and mammography. Mastectomy is not recommended but could be considered under certain circumstances, such as a family history for LBC [57,63].

4.2.5.2. Colorectal cancer. If there is a family history of CRC in a proven mutation carrier or with mucinous or signet ring cell histology in a first- or second-degree relative, colonoscopy should be performed 10 years before disease onset in the youngest affected family member, latest at the age of 40 years, and should be repeated every 3–5 years or according to findings. In the absence of a family history, adherence to local guidelines regarding CRC surveillance is recommended [57].

4.2.6. Surveillance of patients with evocative family history but negative mutational status

Endoscopic surveillance should be performed as mentioned previously. Prophylactic surgery is not recommended.

4.3. Familial intestinal gastric cancer

4.3.1. Diagnostic criteria and genetic testing

In countries with high incidence rates of GC, the diagnostic criteria for FIGC are analogous to the Amsterdam criteria for LS. In countries with lower incidence rates of GC, FIGC can be diagnosed if at least two first- or second-degree relatives are affected by intestinal-type GC, one of which before the age of 50 years, or if more than three relatives are affected by intestinal-type GC, regardless of the age [3,55].

4.3.2. Surveillance for familial intestinal gastric cancer

To date, there is no consensus on surveillance for FIGC. The ESDO expert panel recommends surveillance measures analogous to HDGC with upper GI endoscopy starting at the latest at the age of 40 years or 5 years before disease onset in the youngest affected relative. A dedicated session of 30 min with repeated inflation and deflation and mucosal inspection, as well as multiple random biopsies, are recommended. Testing for *H. pylori* is mandatory, and the eradication of bacteria is necessary in case of positive result of testing.

4.4. Gastric adenocarcinoma and proximal polyposis of the stomach

4.4.1. Identifying the patient with gastric adenocarcinoma and proximal polyposis of the stomach

To date, only a limited number of families have been described in the literature. The diagnostic criteria include the following: (a) gastric polyposis restricted to the corpus and fundus of the stomach without evidence of duodenal and colorectal polyposis, (b) more than 100 polyps carpeting the proximal stomach or more than 30 polyps in a first-degree relative, (c) predominantly fundic glandulocystic polyps, some harbouring dysplastic regions and (d) an autosomal dominant pattern of inheritance. Other polyposis syndromes should be excluded [66].

4.4.2. Genetic testing for gastric adenocarcinoma and proximal polyposis of the stomach

As for FAP and aFAP, the *APC* gene is affected in GAPPS, although the mutations are confined to the promoter region of the *APC* gene in GAPPS [17,67].

4.4.3. Surveillance and management of gastric adenocarcinoma and proximal polyposis of the stomach

Endoscopic surveillance should be performed as mentioned previously for FIGC (4.3.2). Nevertheless, prophylactic gastrectomy should be discussed carefully, especially when polyposis cannot be managed by upper GI endoscopy. All first-degree relatives should be advised to undergo upper GI endoscopy and colonoscopy [3,4,66].

4.5. Other familial gastric cancer syndromes

LS, FAP, MAP, PJS and JPS have been discussed previously. For Li-Fraumeni syndrome with proven germline mutation of *TP53*, modalities of surveillance remain controversial. In lack of evidence, the ESDO expert panel recommends the following measures according to the most recent recommendations by the international expert panel on Li-Fraumeni syndrome: annual whole-body MRI, abdominal ultrasound and dermatological surveillance seem suitable. Laboratory tests including complete blood count serum lactate dehydrogenase activity and erythrocyte sedimentation rate may be performed every 3–4 months, and gynaecological examination including clinical examination of breasts should be performed at least twice a year. Prophylactic mastectomy can be discussed. Surveillance by colonoscopy is proposed every 2–5 years, starting at the age of 25 years [68–71].

5. Hereditary and familial PC

5.1. Definition of familial PC and hereditary PC

Hereditary PC (HPC) is defined by an underlying syndrome with possible tumour locations in different organs and a clear association with a causal germline mutation. In contrast, familial PC (FPC) is non-syndromic with a familial clustering of PC (i.e. pancreatic ductal adenocarcinoma) without an identified mutation. The distribution of FPC to hereditary syndromic forms is 90:10 [72].

5.2. Patients at risk and underlying genetic causes

5.2.1. Identifying the patient at risk for familial PC

The non-syndromic form can be diagnosed if two first-degree relatives or if three relatives from the same side were affected by PC [38,73].

5.2.2. Syndromes and genetic mutations associated with HPC

Syndromes associated with HPC include PJS (*LKB1/STK11*), LS (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*), FAP (*APC*), hereditary breast and ovarian cancer (*BRCA1*, *BRCA2*), cystic fibrosis (*CFTR*), familial atypical multiple mole melanoma (*CDKN2A*), hereditary pancreatitis (*PRSS1*, *SPINK1*, *CASR*, *CTRC*), ataxia telangiectasia (ATM), Li-Fraumeni syndrome (*TP53*) or syndromes with *PALPB2* mutations [38,72]. Table 3 illustrates the different mutational syndromes and the cumulative risk at 70 years.

Table 3
Hereditary pancreatic cancer predisposition syndromes, their genetic findings and lifetime risk of pancreatic cancer by the age of 70 years.

Syndrome	Gene	Cumulative risk of pancreatic cancer at the age of 70 years
PJS	*STK11*	20–60%
Hereditary pancreatitis	*PRSS1/SPINK1*	40%
FAMMM	*CDKN2A/p16*	17%
HBOC	*BRCA1, BRCA2*	3–8%
ATM	*ATM*	5%
Cystic fibrosis	*CFTR*	<5%
Lynch syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	<5%
Li-Fraumeni	*TP53*	<5%
FAP	*APC*	2%

PJS, Peutz–Jeghers syndrome; FAMMM, familial atypical multiple mole melanoma; HBOC, hereditary breast and ovarian cancer; ATM, ataxia telangiectasia.

5.2.3. Additional risk factors

Among others, smoking, obesity and chronic pancreatitis are additional risk factors for the development of PC. Patients at risk for HPC or FPC should especially be advised to change their lifestyle if applicable to minimise their anyhow elevated risk for PC [74,75].

5.2.4. Age and ethnic considerations

Although age for disease onset is reported younger (around 10 years) for FPC than for sporadic PC, surveillance usually need not start earlier than the age of 45–50 years. In families with younger affected individuals, screening and surveillance should start before the age of onset of the youngest affected individual [38].

For *BRCA* mutations, there is a higher incidence in individuals with Ashkenazi ancestry [76,77].

5.2.5. General recommendations to individuals from high-risk families

Patients should be advised to stop smoking, control weight, increase physical activity and adapt their diet to be rich in vegetables and fruits. In case of diabetes mellitus, specialist consultation is warranted. Alcohol intake should be limited or ceased [38]. For special preventive measures of PC in LS, see section 3.1.10.

For patients with any suspected syndrome mentioned previously, as well as fulfilling the criteria mentioned in section 5.2.1, referral to genetic counselling is recommended. Patients should be provided with a surveillance and treatment plan in high-volume centres for PC

treatment, as well as counselling on the aforementioned general behavioural measures.

5.2.6. Management of patients with recurrent and/or autoimmune pancreatitis

After referral to genetic counselling, these patients should be tested for mutations in the following genes: *PRSS1*, *CFTR*, *SPINK1*, *CASR* and *CTRC* [78,79].

5.2.7. Gene panel for suspected hereditary and familial PC

Following genes can be included in panel testing: *BRCA1*, *BRCA2*, *STK11*, *ATM*, *PALB2*, *CDK4*, *CDKN2A*, *PRSS1*, *CFTR*, *SPINK1*, *CASR* and *CTRC*. In case of MSI-high/dMMR in the tumour, *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* can be added to document a possible LS [38,78–81].

5.2.8. Universal genetic testing

In case of germline mutation in an affected individual, predictive testing should be offered to the entire family after genetic counselling and after the age of 18 years, according to the local legal issues.

5.3. Screening, surveillance and management

Patients at risk for FPC or HPC should be informed about the intrinsic limitations of surveillance. Hence, the risk–benefit ratio for screening and surveillance is still unclear. Nevertheless, in proven or suspected individuals for FPC or HPC, surveillance is recommended because prevention for PC can only be offered in detection of premalignant lesions, and cure can only be achieved when the disease is detected at an early stage. In families with syndromic and genetically proven disease, and at least one affected family member with PC, i.e. HPC, surveillance should be offered to mutation carriers. In FPC, surveillance can be offered to the entire family [38,72].

5.3.1. Measures and goals of surveillance

In FPC, annual EUS and MRI should be performed to identify target lesions, which are the following: solid nodules, dilated main pancreatic duct, intraductal papillary mucinous neoplasias (IPMN), pancreatic intraepithelial neoplasias (PanIN) or cystic lesions with worrisome features and at risk for high-grade dysplasia [82]. In case of HPC, extrapancreatic surveillance is recommended according to the underlying syndrome [38,72,81].

5.3.2. Age interval for surveillance

Surveillance should start latest at the age of 50 years or 10 years earlier than the onset of disease in the youngest affected individual. Surveillance should be continued until the age of 75–80 years or shorter if the patient is unfit for surgery (i.e. pancreaticoduodenectomy) [38,72]. Annual surveillance is recommended although a 2-year interval was recently proposed for patients with non-CDNK2A HPC (lesser cumulative risk), if the pancreas is unremarkable at baseline screening [83].

5.3.3. Management of findings on EUS or MRI

Any identified resectable adenocarcinoma, PanIN3, high-risk IPMN, cyst >3 cm, solid nodule >2 cm or positive cytology or histology for neoplastic cells should ultimately lead to radical surgery, if the patient is fit, and appropriate staging procedures have been performed to ensure the possibility of a curative-intent resection.

Frontline total pancreatectomy should be avoided as well as enucleation. According to the site of the target lesion(s), usually either partial pancreatectomy or duodenopancreatectomy is performed. In case of highly suspicious solid or high-grade dysplastic lesions, surgery can be offered as a preventive measure, regardless of the size of the lesion.

If surgery cannot be performed, follow-up can be offered by EUS and MRI after 6–12 months [38].

6. Future approaches

If robust evidence is obtained, new diagnostic procedures (liquid biopsy including metabolomics) and novel therapeutic approaches (for instance, Poly (ADP-ribose) polymerase (PARP) inhibitors in BRCA-mutated PC, immune checkpoint controller in dMMR/MSI-high tumours) should be implemented in everyday practice.

Conflict of interest statement

Pascal Hammel has received financial support from AstraZeneca conducting a clinical trial (POLO). None of the other authors has got any conflicts of interest to declare regarding this manuscript.

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