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# Gastric Cancer: A Practical Review on Management of Individuals with Hereditary or Familial Risk for Gastric Cancer

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**Keywords**
Gastric cancer · High-risk population · Sporadic cancer risk · Familial cancer risk

**Abstract**
Gastric adenocarcinoma is one of the most frequent and deadly cancers worldwide. However, its incidence is variable, being higher in eastern countries where screening the general population is recommended. On the other hand, in low to intermediate-risk countries, screening the general population may not be cost-effective, and therefore, it is necessary to be aware of high-risk populations that may benefit from adequate screening and surveillance. It is not always easy to identify these individuals, leading to a late diagnosis of gastric adenocarcinoma. In this review, the authors intend to summarize the data required to identify the population at risk of sporadic or familial gastric adenocarcinoma and the beginning of screening and its surveillance, with the final aim of increasing early detection of gastric adenocarcinoma and decreasing morbimortality. The authors highlight the importance to be aware of the several hereditary syndromes and MAPS recommendations and apply screen and surveillance protocols. The high-risk syndromes to gastric adenocarcinoma are gastric adenocarcinoma and proximal polyposis of the stomach, hereditary diffuse gastric cancer, and familial intestinal gastric cancer.



**Cancro gástrico: uma revisão prática na abordagem de indivíduos em risco de cancro gástrico hereditário ou familiar**

**Palavras Chave**
Cancro gástrico · População de alto risco · Risco cancro esporádico · Risco de cancro familiar

**Resumo**
O adenocarcinoma gástrico é um dos cancros mais frequentes e mortais em todo o mundo. No entanto, a sua incidência é variável, sendo maior nos países orientais, onde o rastreio da população geral está recomendado. Por outro lado, nos países de risco baixo a intermediário, o rastreio da população geral pode não ser custo-efetivo e, portanto, é necessário conhecer quais são as populações de alto risco que podem beneficiar de rastreio e

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vigilância adequados. Porém, nem sempre é fácil identificar esses indivíduos levando a um diagnóstico tardio de adenocarcinoma gástrico. Nesta revisão, os autores pretendem resumir a informação necessária à identificação da população em risco de adenocarcinoma gástrico esporádico ou familiar e o início do rastreio e sua vigilância, com o objetivo final de otimizar a deteção precoce do adenocarcinoma gástrico e diminuir a morbimortalidade. Os autores salientam a importância de conhecer as diversas síndromes hereditárias e recomendações MAPS e aplicar protocolos de rastreio e vigilância. As síndromes de maior risco para adenocarcinoma gástrico são GAPPS, HDGC e FIGC.


## Introduction

Gastric adenocarcinoma is the fifth most common and fourth most mortal cancer worldwide [1]. Its high mortality can be explained by the absence of screening and early-diagnosis strategies, resulting in the diagnosis of gastric cancer (GC) at an advanced stage.

Currently, screening for gastric adenocarcinoma in the opposite, in low to intermediate-risk countries (i.e., Western countries), is only recommended for high-risk groups (e.g., extensive preneoplastic conditions, history of GC in a first-degree relative, genetic syndromes associated with GC risk) [2]. Classically, it is usual to aggregate Western countries in GC risk, but it is important to clarify that it differs between the countries, and so it is essential to adjust screening and/or clinical investigation accordingly to the specific country's risk (shown in Fig. 1).

Most cases of gastric adenocarcinoma are sporadic, with a minority of cases (10%) occurring in a context of familial aggregation or heritable syndromes [3]. GC can be classified into several subtypes depending on the classification, being the mostly used Lauren or WHO classifications. Lauren's classification was established in 1965 and specifically subdivided the gastric adenocarcinoma into intestinal (53%), diffuse (33%), or indeterminate histologic type (14%) [4]. The indeterminate type may correspond to other subtypes according to WHO classification. Despite its simplicity, Lauren's classification is useful to guide the investigation of affected or familial individuals with gastric adenocarcinoma.

Sporadic adenocarcinoma is generally of the intestinal type, associated with *Helicobacter pylori* infection, and corresponds to the last stage of the Correa cascade, which represents the progression of precancerous conditions, although family aggregation exists also in this GC subtype. On the other hand, diffuse adenocarcinoma is less frequent and, as it may be associated with a genetic disorder (hereditary diffuse gastric cancer; HDGC), this condition should be carefully evaluated.

High-risk population includes individuals with heritable syndromes associated with GC and individuals with risk factors for sporadic GC (mainly extensive precancerous conditions associated with *H. pylori*). The lack of gastric adenocarcinoma screening in the general population in low to intermediate-risk countries is associated with the lack of firm evidence of cost-effectiveness, although it is important to identify individuals with a higher risk of GC that may benefit from screening/surveillance.

The scarcity of literature on this topic led to this review. We intend to summarize (i) diagnostic criteria of heritable syndromes associated to GC, (ii) risk factors for sporadic GC, (iii) timing to start screening, and (iv) surveillance of high-risk population. Methods of detection, surveillance, and prophylactic or therapeutic interventions will not be discussed in this review.

## Methods

A narrative non-systematic review was performed based on an electronic search through the medical literature using PubMed. The keywords "Heritable Gastric Cancer," "Familial gastric cancer," "Sporadic cancer," "Lynch syndrome," "Li-Fraumeni syndrome," "Gastrointestinal polyposis syndromes," "Gastric Adenocarcinoma and Proximal Polyposis of the Stomach," "Hereditary diffuse gastric cancer," and "Familial intestinal gastric cancer" were used. No publication date restrictions were imposed, but guidelines and systematic reviews in the past 10 years from gastroenterology, endoscopy, oncology, genetics, and histopathology were preferred. When more than one guideline concerning the same subject was available, the most updated one was selected. Only articles published in English were considered. The majority of articles refer to European or North American studies. However, Asian articles were punctually included if relevant to the manuscript.

## Hereditary Cancer

Familial aggregation of gastric adenocarcinoma can occur in up to 10% of the patients, but a deleterious genetic variant is only identifiable in about 1–3% of cases [3]. Familial/hereditary GC may be part of a genetic syndrome involving multiple organs or be exclusive to the stomach.

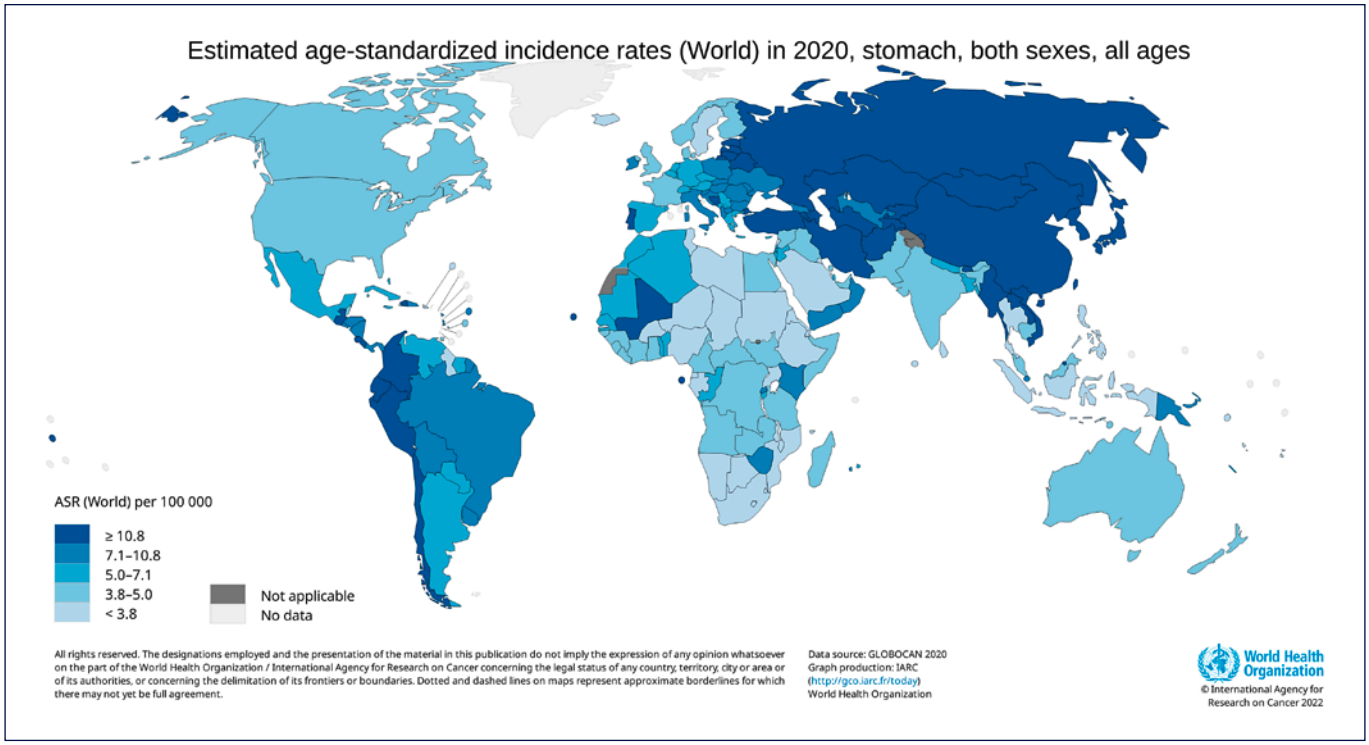


**Fig. 1.** Global incidence rate of GC in 2020.

Familial aggregation is defined through a high prevalence of GC among first-degree relatives (siblings, parents, and children). Indeed, the existence of a first-degree relative with GC confers an increased risk (OR 2–10) of the disease [5].

However, it is important to clarify that familial GC aggregation may be linked to shared environmental and lifestyle factors, thereafter increasing the incidence of cancer in a genetically susceptible family [6]. In fact, first-degree relatives have a higher prevalence of *H. pylori* infection, atrophy, and intestinal metaplasia [7]. This finding validates the recommendation to perform esophagogastroduodenoscopy (EGD) every 3 years in individuals with precancerous conditions (non-extensive) and a family history (1st degree relatives) of GC, and every 1–2 years in patients with a family history of GC and extensive precancerous conditions according to MAPS II [8]. On the other hand, the risk of GC in second-degree relatives is lower [6] and, therefore, there is no indication for screening these individuals [8].

In the initial approach of a familial aggregation of gastric adenocarcinoma, certain topics must be assessed to recognize patients at high risk of hereditary gastric adenocarcinoma: histological type, presence of gastrointestinal polyposis and extra-gastric neoplasms, a detailed family tree of affected family members, and any known inherited mutation/disease in the family (shown in Fig. 2). These elements are essential in the evaluation of the criteria defined to motivate further risk assessment of heritable GC (shown in Fig. 3) [9]. Briefly, these include two or more relatives with the same cancer; cancer in at least two generations; cancer diagnosed at a young age; multiple neoplasia in the same individual; a family with an unusual cancer pattern; and cancer associated with a known heritable syndrome.

Hereditary causes are rare but multiple and, although the diagnoses are mostly clinical, some can be confirmed through genetic tests. Hereditary GC can be included in polyposis and nonpolyposis syndromes. The polyposis syndrome with the highest risk is gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), and those without polyposis are HDGC and familial intestinal gastric cancer (FIGC).

In this section, the main different causes will be discussed with a resume of diagnostic criteria, screening initiation, and surveillance (shown in Table 1, adapted from [10–12]). Prophylactic or therapeutic endoscopic or surgical interventions will not be thoroughly discussed. Ad-

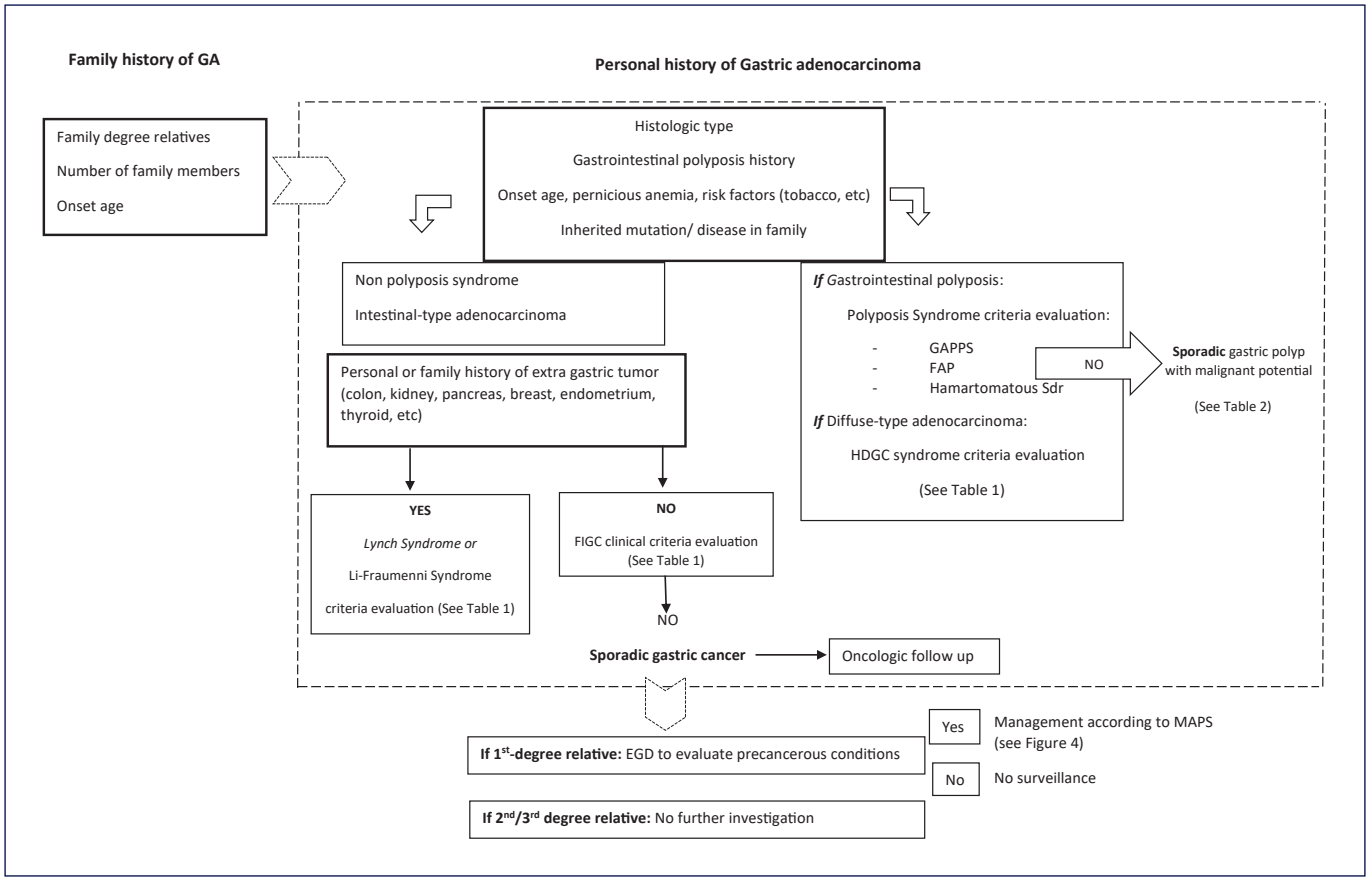


**Fig. 2.** Initial approach to a patient with personal or family history of GC.

| *Referral to a cancer geneticist in the presence of at least one* |
|---|
| **Individual criteria** |
| Gastric cancer before age 40 |
| Gastric cancer before age 50 who had one 1st or 2nd degree relative affected with gastric cancer |
| Gastric cancer at any age who had 2 or more 1st or 2nd degree relative affected with gastric cancer |
| Gastric cancer and breast cancer with one diagnosis before age 50 |
| Gastric cancer at any age and a family history of breast cancer in a 1st or 2nd degree relative diagnosed before age 50 |
| Gastric cancer at any age and a family history of juvenile polyps or gastrointestinal polyposis |
| Gastric cancer at any age and a family history of cancers associated with Lynch syndrome |
| **Familial criteria** |
| Known mutation in a gastric cancer susceptibility gene in a close relative |
| Gastric cancer in one 1st or 2nd degree relative who was diagnosed before age 40 |
| Gastric cancer in two 1st or 2nd degree relatives with one diagnosis before age 50 |
| Gastric cancer in three 1st or 2nd degree relatives independent of age, or |
| Gastric cancer and breast cancer in one patient with one diagnosis before age 50, juvenile polyps, or gastrointestinal polyposis in a close relative |

**Fig. 3.** Criteria for further risk evaluation for high-risk syndromes associated to GC (adapted from [9]).

ditionally, other rarer hereditary syndromes associated with GC (ataxia-telangiectasia, Bloom syndrome, hereditary breast and ovarian cancer syndrome, and xeroderma pigmentosum) will not be described due to the lack of information that supports recommendations on screening and surveillance [9].

## Polyposis Syndromes

*Hamartomatous Syndromes*

The presence of hamartoma polyps in the digestive tract should raise the clinical suspicion of a genetic syndrome and, therefore, there is an indication for genetic study. Hamartomatous syndromes include Peutz-Jeghers syndrome, juvenile polyposis syndrome (JPS), and Cowden syndrome.

Peutz-Jeghers syndrome is characterized by perioral hyperpigmentation and hamartomatous polyps [13] and is mostly associated with *STK11/LKB1* tumour suppressor gene variants [14]. Although most polyps are located in the small bowel (60–90%), 15–30% are located in the stomach [14]. The risk of gastric adenocarcinoma is 29% at 15–64 years of age, with an average diagnosis between 30 and 40 years of age [15]. Screening should start at 8 years of age and, in the absence of lesions, repeated at 18 years of age. Surveillance depends on phenotype and should be performed every 1–3 years [10].

JPS is diagnosed in the presence of at least one hamartomatous polyp in the stomach [11], and in 40–60% of the cases there is a deleterious variant in the *SMAD4* or *BMPR1A* genes [16]. The gastric phenotype is normally associated with variants in the *SMAD4* gene [16], and the risk of extracolonic cancer is difficult to assess, ranging from 20% to 60%, including GC [17]. The current recommendation is to start screening in *SMAD4* variant carriers at 18 years of age and in *BMPR1A* variant carriers at 25 years of age. Surveillance should be performed every 1–3 years according to phenotype [10].

Cowden's syndrome is characterized by the existence of several neoplasms dispersed through multiple organs and, concerning the stomach, gastric hamartomas associated with variants in the *PTEN* gene. The risk of gastric adenocarcinoma is higher, but its incidence is unknown [18]. GC screening and surveillance in these individuals is not consensual. Older guidelines recommended screening at 15 years of age and surveillance every 2–3 years [11]; however, more recent NCCN updates no longer recommend EGD due to lack of evidence [19].

*Adenomatous Syndromes*

Familial adenomatous polyposis (FAP) is mostly a colorectal disease, associated with an autosomal dominant mode of transmission and variants in the *APC* gene, which can be classified as classic or attenuated, according to the number of colorectal adenomas. However, gastric polyps may occur in more than 60% of the patients [20], with different malignant risk.

Most gastric polyps associated with FAP are fundic gland polyps that may present with low-grade dysplasia in up to 40% of the cases [21], with high-grade dysplasia (HGD) and malignant transformation being rare [22, 23]. However, it should be recognized that sporadic fundic gland polyps associated with proton-pump inhibitor can also occur in FAP, and these hardly harbour dysplasia [18].

Up to 20% of polyps correspond to adenomas, encompassing foveolar-type adenomas (85%), pyloric gland adenoma (15%), and intestinal-type adenoma (1–2%), with a corresponding increased risk of malignancy [21, 22]. Foveolar-type adenomas are rare in an absolute matter being the majority associated with *APC* variants and appearing as an isolated sporadic lesion within normal mucosa and, thus, a low progression risk. Pyloric gland adenomas, which are also rare and associated with normal mucosa, present HGD and adenocarcinoma foci at a higher frequency (10–15%). In contrast, intestinal-type adenomas are highly associated with advanced lesions (HGD or adenocarcinoma), intestinal metaplasia, gastritis, and also synchronous adenocarcinoma. This may be explained by other risk factors than *APC* variants, such as *H. pylori* infection. These facts elucidate its lower frequency but high malignancy risk.

The risk of GC in FAP in Western countries is low and was previously described as comparable to the risk of sporadic fundic gland polyps [23]. However, recent case series discovered advanced gastric lesions (including adenocarcinoma) in extensive areas of sporadic fundic gland polyps [24, 25]. This fact may lead to the creation of specific protocols for screening and surveillance of GC in this population, which currently are lacking.

On the other hand, the risk of duodenal adenocarcinoma is known to be highly associated to duodenal polyposis and, therefore, is recommended starting screening at 25 years of age and surveillance according to Spigelman's classification. Consequently, this is an opportunity to surveille gastric mucosa in an attempt to early detection of GC and precursors lesions, as recommended in the ESGE guideline [10].

**Table 1.** Summary of diagnostic criteria and management of hereditable syndromes associated with gastric cancer (GC) risk

| | Gene | GC risk | Diagnostic criteria | Initial screening age | Surveillance |
|---|---|---|---|---|---|
| *Polyposis syndromes* | | | | | |
| Adenomatous | | | | | |
| Familial adenomatous polyposis (FAP) | *APC* promotor IA | 4–7% (Asian population)<br>Not increased in Western countries | ACG guidelines:<br>• At least 10 cumulative colorectal adenomas<br>• History of adenomas and FAP-type extracolonic manifestations*<br>• Family history of one of the adenomatous polyposis syndromes | EGD: 25 years of age | EGD: According to Spigelman score |
| MUTYH-associated polyposis | *MUTYH* | 2% (F) to 5% (M) | >10 colorectal adenomas | EGD: 35 years of age | EGD: According to Spigelman score |
| Hamartomatous | | | | | |
| PJS | *STK11/LKB1* | 29% at 15–64 years | WHO criteria:<br>• At least three Peutz-Jeghers polyps<br>• Any number of Peutz-Jeghers polyps with a family history of PJS<br>• Characteristic, prominent mucocutaneous pigmentation with a family history of PJS<br>• Any number of Peutz-Jeghers polyps and characteristic, prominent mucocutaneous pigmentation | EGD: 8 years of age<br>Repeated at 18 years of age | EGD every 1–3 years if polyps found |
| JPS | *SMAD4* (*BMPR1A*) | 10–30% | WHO criteria:<br>• More than three to five juvenile polyps of the colorectum<br>• Juvenile polyps throughout the gastrointestinal tract<br>• Any number of juvenile polyps with a family history of juvenile polyposis | *SMAD4*<br>EGD: 18 years of age<br>*BMPR1A*<br>EGD: 25 years of age | EGD every 1–3 years<br>Management case-by-case |
| Cowden syndrome | *PTEN* | Rare | ACG guidelines:<br>• Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should be evaluated for Cowden syndrome and related conditions | Not recommended [19]<br>EGD: 15 years of age [11] | Not recommended [19]<br>EGD every 2–3 years<br>If duodenal polyps ECG according to Spigelman score [11] |
| Fundic glands polyps (FGP) | | | | | |
| GAPPS | *APC* promotor IB | 13% | Essential criteria:<br>• Proximal polyposis with antral sparing.<br>• No evidence of colorectal or duodenal polyposis<br>• >100 polyps carpeting the proximal stomach in the index patient or >30 polyps in a first-degree relative of another patient<br>• predominantly FGPs and/or fundic gland-like polyps<br>• Proband or relative with either dysplastic FGPs or GC | Prophylactic gastrectomy in probands (?)<br>EGD in first-degree relatives (age?) | ECG surveillance case-by-case |

**Table 1** (continued)

| | Gene | GC risk | Diagnostic criteria | Initial screening age | Surveillance |
|---|---|---|---|---|---|
| *Nonpolyposis syndromes* | | | | | |
| Intestinal type | | | | | |
| Lynch syndrome | *MSH2, MLH1, MSH6, PMS2, EPCAM* | 13% Global (10%, 9%, 7%, 0%, 0%) | Amsterdam criteria II:<br>• HNPCC-associated cancer† in three or more relatives.<br>• One being a first-degree relative of the other two.<br>• Two or more successive generations affected<br>• HNPCC-associated cancer <50 years in one or more patients<br>• Exclusion of FAP<br>Revised Bethesda criteria:<br>• CRC at age <50 years<br>• Synchronous, metachronous colorectal or other HNPCC-associated tumour‡ regardless of age<br>• CRC with MSI histology§ at age <60 years<br>• CRC in one or more first-degree relatives with a Lynch syndrome-related tumour, with one of the cancers diagnosed at age <50 years<br>• CRC in two or more first-degree or second-degree relatives with Lynch syndrome-related tumours, regardless of age<br>Universal screening for all CRCs and endometrial cancers<br>Computational predictive models:<br>• PREMM Model >5% | EGD: 30–35 years of age | EGD every 2–3 years according to phenotype |
| Li-Fraumeni syndrome (LFS) | *TP53* | 2–5% | Revised Chompret criteria:<br>• LFS tumour¶ at age <46 years and at least one first-degree or second-degree relative with LFS tumour (except breast cancer if the proband has breast cancer) at age <56 years or multiple tumours<br>• Multiple tumours (except breast cancer), two of which belonged to the LFS tumour spectrum and the first of which occurred at age <46 years<br>• Adrenocortical carcinoma or choroid plexus tumour | Disagreement<br>EGD: 25 years of age [19]<br>Not recommended [34] | Disagreement<br>EGD every 2–5 years [19]<br>Not recommended [34] |
| FIGC | Unknown – probable polygenic cause | 66% | IGCLC criteria in high-incidence countries:<br>• Intestinal GC in three or more relatives<br>• One being a first-degree relative of the other two<br>• Two or more successive generations affected<br>• Intestinal GC at age <50 years in one or more patients<br>• Exclusion of gastric polyposis<br>IGCLC criteria in low-incidence countries:<br>• Intestinal GC in two or more first-degree relatives<br>• Intestinal GC in second-degree relatives, one diagnosed at age <50 years<br>• Intestinal GC in three or more relatives at any age<br>Proposal of new criteria:<br>• GC in two or more relatives at any age<br>• At least one intestinal GC | EGD: 40 years of age or 5 years before the youngest case | EGD every 5 years |

**Table 1** (continued)

| | Gene | GC risk | Diagnostic criteria | Initial screening age | Surveillance |
|---|---|---|---|---|---|
| Diffuse type | | | | | |
| Hereditary diffuse gastric cancer (HDGC) | *CDH1*<br>*CTNNA1* | Clinical criteria 2015: 33% (F) to 42% (M) | IGCLC Family criteria (first and second relatives):<br>• At least two cases of GC in family regardless of age, with at least one diffuse GC<br>• At least one case of diffuse GC at any age and one or more cases of LBC at age <70 years in different family members<br>• At least two cases of LBC in family members aged <50 years<br>IGCLC Individual criteria:<br>• Diffuse GC at age <50 years<br>• Diffuse GC at any age in individuals of Maori ethnicity<br>• Diffuse GC at any age in individuals with a personal or family history (first degree) of cleft lip/cleft palate<br>• History of diffuse GC and LBC, both diagnosed at age <70 years<br>• Bilateral LBC, diagnosed at age <70 years<br>• Gastric in-situ signet-ring cells and/or pagetoid spread of signet-ring cells in individuals aged <50 years | • *CDH1* pathogenic: prophylactic gastrectomy at 20–30 years<br>• *CDH1* variant uncertain significance or *CTNNA1* or HDGC-like:<br>-Probands: surveillance at diagnosis (Cambridge protocol)<br>-First-degree relatives: 40 years or 10 years before youngest case | Annually in first 2 years and then every 2 years according to phenotype (Cambridge protocol) |

ACG, American College of Gastroenterologists; CRC, colorectal cancer; EGD, esophagogastroduodenoscopy F, Female; GAPPS, gastric adenocarcinoma and proximal polyposis of the stomach; HNPCC, hereditary nonpolyposis colorectal cancer; IGCLC, International Gastric Cancer Linkage Consortium; LBC, lobular breast cancer; M, male; MSI, microsatellite instability; WHO, World Health Organization; PJS, Peutz-Jeghers syndrome; JPS, juvenile polyposis syndrome. * Duodenal/ampullary adenomas, desmoid tumours (abdominal > peripheral), papillary thyroid carcinoma, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, and osteomas. † HNPCC-associated cancers include CRC, endometrial cancer, small-bowel cancer, and ureteral or renal pelvis cancer. ‡ HNPCC-related tumours include colorectal tumour, endometrial tumour, stomach tumour, ovarian tumour, pancreatic tumour, small-bowel tumour, ureteral or renal pelvis tumour, biliary tract tumour, brain tumour (usually glioblastoma), sebaceous gland adenoma, and keratoacanthoma. § Tumour-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous and signet-ring cell features, and medullary growth pattern. ¶ Soft tissue sarcoma, osteosarcoma, brain tumour, premenopausal breast cancer, adrenocortical carcinoma, leukaemia, and lung bronchoalveolar cancer.

MUTYH-associated polyposis is an autosomal recessive syndrome associated with biallelic variants in the *MUTYH* gene. This syndrome also has an increased risk of duodenal (4%) [21] and GC (2–5%) [12], thus an EGD should be performed at 35 years of age and then maintained similarly to FAP [10].

### *Gastric Adenocarcinoma and Proximal Polyposis of the Stomach*

GAPPS is a recently described gastric polyposis syndrome characterized by an excess of fundic gland polyps that affects the fundus and gastric body, sparing the antrum and small curvature, and no colorectal phenotype. Its diagnosis is clinical and must meet specific criteria (shown in Table 1) [26]. It is an autosomal dominant hereditary disease with incomplete penetrance secondary to variants in the promoter IB of the *APC* gene [27]. This syndrome has a high risk (13%) [26] of intestinal-type gastric adenocarcinoma and HGD, unlike other GC associated polyposis, like FAP and fundic gland polyps [28].

The natural history of GAPPS is variable, and additional mutations can arise that lead to malignant transformation and earlier progression. Thus, affected patients should initiate screening (as their first-degree family members) and endoscopic surveillance. However, there are still no clear recommendations in this issue [26]. There are case-reports where dysplastic, or even neoplastic, lesions are undistinguished within polypoid carpet in patients who present with metastatic disease. This fact may support the recommendation for prophylactic total gastrectomy [28].

## Nonpolyposis Syndromes

*Lynch Syndrome*

Lynch syndrome is the most common cause of heritable gastrointestinal cancer and is an autosomal dominant syndrome linked to germline variants in one of the DNA mismatch repair (MMR) genes (*MSH2*, *MSH6*, *MLH1*, P*MS2*) or exonic deletions in the *EPCAM* gene [29]. Diagnosis of Lynch syndrome can be difficult, so there are different methods to support the diagnostic approach. These include the Amsterdam II criteria (family related clinical criteria; sensitivity 22%, specificity 98%), the Bethesda criteria (individual clinicopathologic criteria; sensitivity 82%, specificity 77%) and, finally, computational predictive models (MMRpredict, MMRpro, and PREMM) (shown in Table 1). The latter can be used when Lynch syndrome is suspected and is impossible to confirm the criteria (dead or distant relatives, etc.). The PREMM model is more practical and applicable to the general population, with higher sensitivity but lower specificity (90% and 67%, respectively). A probability greater than 5% means that the patient is admissible for genetic testing [29].

The lifetime risk of GC in Lynch Syndrome patients remains not deeply studied. An old Finnish study referred to a 13% lifetime risk [30], but a more recent Dutch study reported a lower relative risk (3.4 incidence ratio) [31]. Also, it demonstrated a higher risk in males (8%) compared to females (5.3%) [31]. Since the intestinal type is the most frequent, there is a possibility of surveillance; however, there is a lack of data for robust recommendations [29]. A recent retrospective study has found that patients with MMR deleterious variants have a high prevalence of precursor conditions (HP infection in 58.3%, intestinal metaplasia in 38.2%, and multifocal atrophy in 33.6%). (Raquel Ortigão et al., Eur J Gastroenterol Hepatol, in press).

Thus, it is currently recommended to screen patients with Lynch syndrome or MMR deleterious variants with EGD at 30–35 years of age with biopsies for screening for *H. Pylori* and eradication, if present. Surveillance should be performed every 2–3 years according to individual risk, i.e., family history of gastric adenocarcinoma and/or presence of precancerous conditions [29].

*Li-Fraumeni Syndrome*

Li-Fraumeni syndrome is an autosomal dominant disease characterized by multiorgan neoplasms associated with deleterious germline variants in *TP53* [32]. The risk of GC in these patients does not seem to be completely determined, with older studies showing a high prevalence (26%) [33], while more recent ones showed a non-superior risk in this population compared to the general population [34].

Thus, the recommendations are discordant regarding screening and surveillance of gastric cancer. NCCN 2022 update recommends surveillance at 25 years of age or 5 years before the earliest GC in the family and to be repeated every 2–5 years [19]; on the other hand, the UK 2021 consensus recommends *H. pylori* testing and eradication, if required, but does not recommend EGD for surveillance, due to lack of evidence [35].

*Hereditary Diffuse Gastric Cancer*

HDGC is a rare autosomal dominant syndrome defined by the presence of, at least, one diffuse GC plus lobular breast cancer associated with *CDH1* or *CTNNA1* germinative variants [36]. Additionally, some families have an isolated phenotype of lobular breast cancer, designated as hereditary lobular breast cancer, while others fulfil clinical criteria but do not carry a genetic variant, known as HDGC-like.

In 2020, the International Gastric Cancer Linkage Consortium (IGCLC) updated the practice guidelines on clinical criteria for genetic testing (shown in Table 1) [18]. Each subgroup is assigned a different risk of GC, and therefore a different therapeutic approach and surveillance.

Patients and families with HDGC-*CDH1* should undergo prophylactic total gastrectomy after excluding more advanced lesions on endoscopy at the time of diagnosis. In those who have decided to undergo endoscopic surveillance and in hereditary lobular breast cancer, EGD must be performed annually according to the Cambridge protocol.

In patients with *CTNNA1* variants, *CDH1* variants of uncertain significance, or HDGC-like, EGD should be performed annually in the first 2 years and then the interval may increase according to the features. In first-degree relatives, surveillance should be started at 40 years of age or 10 years before the youngest case.

*Familial Intestinal Gastric Cancer*

FIGC is an autosomal dominant syndrome [37], which remains genetically unexplained but is postulated to be a polygenic syndrome [38]. Diagnosis is clinical and based on GC incidence [38]. In high-incidence countries, the diagnosis respects the Amsterdam criteria, similar to Lynch syndrome, and in low to intermediate-incidence countries the criteria are intestinal GC in two or more

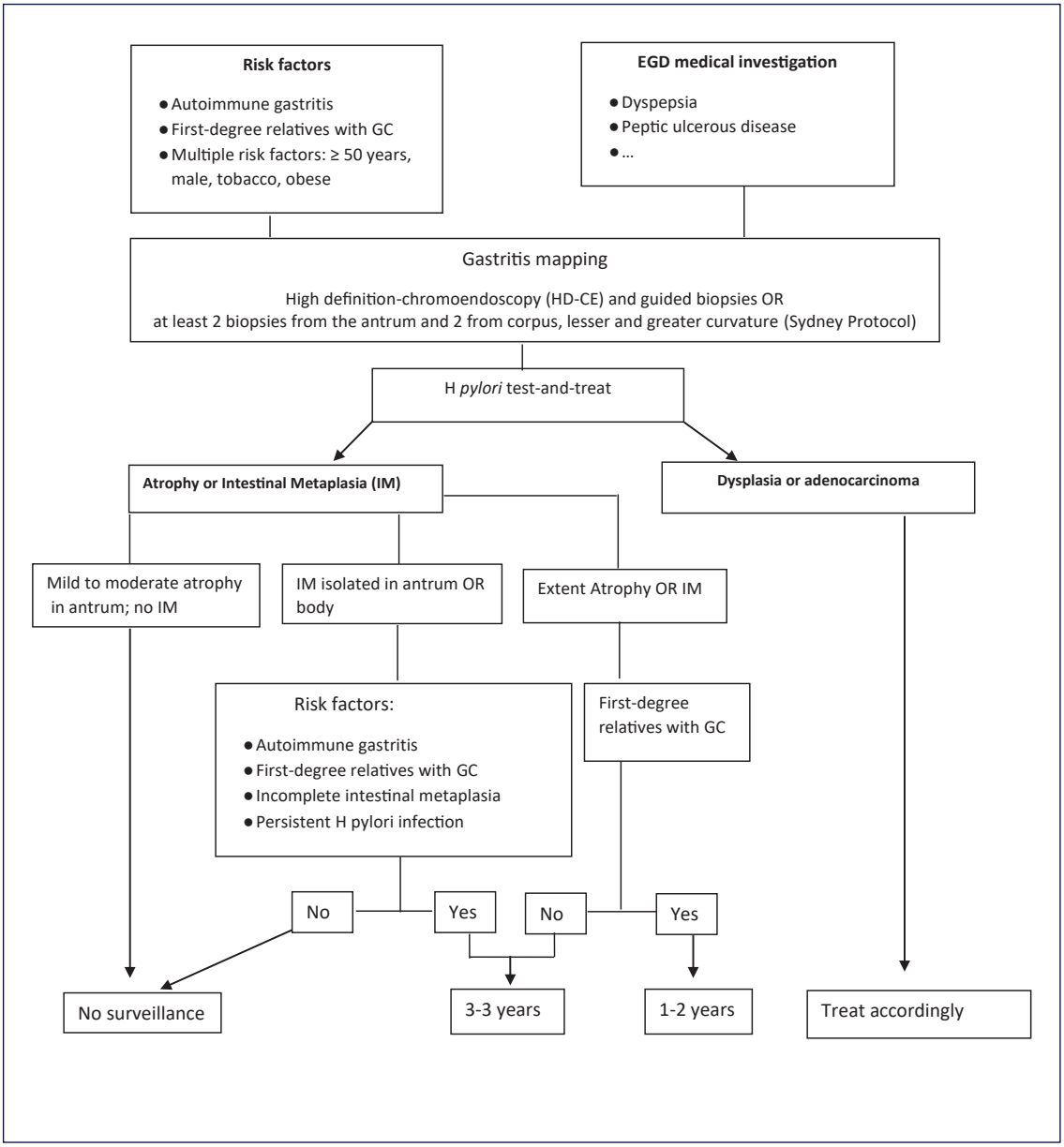


**Fig. 4.** Sporadic gastric cancer (GC) screening and management of precancerous conditions.

first-degree relatives; intestinal GC in second-degree relatives, one diagnosed at age <50 years; and intestinal GC in three or more relatives at any age (shown in Table 1). There are only a few general recommendations such as starting surveillance at 40 years of age or 5 years before the youngest case, *H. pylori* test-and-treat [39] and every 5 years thereafter [40].

## Family History without Heritable Cancer Criteria

So far, recommendations for screening and surveillance of patients with clinical and/or genetic criteria for hereditary syndromes associated with GC have been described. However, with the increase in the incidence of GC, there are more and more individuals with a family history of GC without hereditary criteria, that is, patients with only one relative with GC.

**Table 2.** Sporadic gastric polyps' characteristics associated to gastric adenocarcinoma and their management

| Gastric polyp | Main cause | Typical characteristics | High-risk characteristics | Gastric cancer risk | Management* |
|---|---|---|---|---|---|
| Fundic gland polyps | +++ PPI<br>[FAP see Table 2] | • Fundus and gastric body location<br>• Small size (<10 mm)<br>• Translucent and glossy appearance | • Dysplasia<br>• >10 mm size<br>• Antrum location<br>• Ulceration<br>• Unusual appearance | <1% | • Remove when atypical characteristics<br>• Manage PPI reduction dose/suspension<br>• Reevaluation 12 months<br>• Surveillance according to MAPS II |
| Hyperplastic polyps | Chronic gastritis:<br>+++ *H. pylori*<br>Autoimmune gastritis<br>[GAPPS see Table 2] | • Solitary<br>• Sessile or pedunculated with an eroded surface<br>• Antrum | • >10 mm<br>• Fundus and body | 1.5–8% | • Remove >5 mm<br>• Test-and-treat *H. pylori*<br>• Reevaluation 12 months<br>• Surveillance according to MAPS II[#] |
| Gastric adenomas<br>- Pyloric gland adenomas<br>- Foveolar adenomas<br>- Oxyntic gland adenomas | Atrophy and intestinal metaplasia<br>[FAP see Table 2] | • Solitary<br>• Well delineated often eroded | • >20 mm<br>• Villous | 34% | • Remove<br>• Surveillance according to MAPS II[#] |

* Biopsies in the surrounding area to evaluate background mucosa. [#] High risk of synchronous and/or metachronous lesions.

Concerning this issue, there are no clear recommendations regarding GC screening in family relatives. What is known, as discussed below, is that the existence of a first-degree relative with GC confers an increased risk of GC [5] and a higher prevalence of *H. pylori* infection, atrophy, and intestinal metaplasia [7]. On the contrary, the risk of GC in second-degree relatives is lower [6].

Despite low evidence, the British Society of Gastroenterology Guidelines suggests that endoscopic screening should be considered in individuals older than 50 years of age with a family history [41]. Additionally, in MAPS II, the existence of familial GC modifies the follow-up of precursor lesions [8].

Thus, there may be a proposal for EGD at age 50 years of age (or before if early-onset in a family relative) in individuals with GC in first-degree relatives (but not in second-degree) to evaluate precursor conditions and/or *H. pylori* infection. If present, management according to MAPS II is recommended; if absent, no further screening is recommended [41].

## Sporadic Cancer

As discussed above, the existence of hereditary syndromes and familial risk is responsible for an elevated cancer risk compared to the general population and, therefore, an earlier screening and laborious surveillance is recommended. However, most cancers are sporadic, which increased difficulties in identifying high-risk patients who may benefit from a screening.

The major risk factor associated with sporadic GC is the existence of precancerous conditions (gastric atrophy and intestinal metaplasia), which are mainly caused by chronic *H. pylori* infection. The onset and management of precancerous conditions and their risk factors are elucidated in MAPS II recommendations [8] and summarized in Figure 4.

Other risk factors are autoimmune gastritis; a minority of sporadic gastric polyps; and sociodemographic risk factors. Autoimmune gastritis is a chronic disease with malignant potential for adenocarcinoma or neuroendocrine tumours (OR 2.18 and 11.4, respectively) [42]. A meta-analysis calculated a relative risk of GC of 6.8 and an annual incidence/person of 0.27% [43]. It is recommended to perform an EGD at diagnosis and then every 5 years for GC risk [8].

A minority of sporadic gastric polyps have a malignant potential (even being low) to cause gastric adenocarcinoma. This includes fundic gland polyps, hyperplastic and adenomas; setting aside inflammatory fibroid polyps, which have no malignant potential [44], and sporadic hamartomas that are extremely rare to support data. The main cause and features of the different sporadic gastric

polyps associated with gastric adenocarcinoma and their management are summarized in Table 2 [44–46]. In general practice, biopsies should be performed according to the Sydney protocol to determinate surveillance (independently of polyp histology) and in the surrounding area to detect precancerous conditions or adenocarcinoma [45].

Other risk factors associated with GC risk are age, gender, ethnicity, smoking, and history of gastric surgery for benign disease. The risk of GC appears to be increased after 45 years of age [47, 48], in non-Caucasian individuals [49–51] and in individuals with previous gastric surgery (more than 30 years ago) [52]. However, all of them can be related to *H. pylori* infection chronicity. Additionally, men and current smokers are also at higher risk (1.3–3 times and OR 1.45, respectively) [49, 53, 54]. Despite low evidence, endoscopic screening should be considered in individuals older than 50 years with multiple risk factors for gastric adenocarcinoma, especially in those with family history [41].

## Conclusion

GC remains one of the most prevalent and deadly cancers worldwide, but its screening in the general population is only effective in countries with high incidence. In countries with low to intermediate risk of gastric adenocarcinoma, screening is only cost-effective in high-risk populations. High-risk population includes sporadic precancerous conditions (intestinal metaplasia or atrophy) and several genetic syndromes with different risk to gastric adenocarcinoma, being the highest risk attributable to GAAPS, HDGC, and FIGC.

The management of these patients is hampered by the overlap of genetic and environmental risk factors, which by working synergistically may increase the risk of gastric adenocarcinoma. To conclude, clinicians should recognize high-risk patients, and although hereditary adenocarcinoma is rare, that possibility must be considered and the diagnostic criteria applied. However, the lifetime risk of gastric adenocarcinoma differs, and so screening and surveillance protocols may be adapted to local conditions.

## Key Points

- Importance of a complete personal and family history of gastric (and extra-gastric) cancer.
- Awareness of heritable syndromes with GC risk.
- All individuals with precancerous conditions and/or heritable syndromes should be tested-and-treated to *H. pylori*, especially in high prevalence countries.
- Interaction between environmental factors and heritable syndromes, especially *H. pylori* infection.
- Importance of family history (and others risk factors) in management of precancerous conditions.

## Statement of Ethics

Ethical review and approval was not required as the study is based exclusively on published literature.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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## Author Contributions

All the authors contributed to the concept and design of the article. Marisa Linhares performed the literature review and wrote the manuscript. All the authors critically reviewed and approved the final version to be published.

## Data Availability Statement

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

## References


1 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.

2 Areia M, Dinis-Ribeiro M, Rocha Gonçalves F. Cost-utility analysis of endoscopic surveillance of patients with gastric premalignant conditions. Helicobacter. 2014;19(6):425–36.

3 Oliveira C, Pinheiro H, Figueiredo J, Seruca R, Carneiro F. Familial gastric cancer: genetic susceptibility, pathology, and implications for management. Lancet Oncol. 2015;16(2):e60–70.

4 Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
5 Yaghoobi M, Bijarchi R, Narod SA. Family history and the risk of gastric cancer. Br J Cancer. 2010;102(2):237–42.
6 Safaee A, Moghimi-Dehkordi B, Fatemi SR, Maserat E, Zali MR. Family history of cancer and risk of gastric cancer in Iran. Asian Pacific J Cancer Prev. 2011;12(11):3117–20.
7 Rokkas T, Sechopoulos P, Pistiolas D, Margantinis G, Koukoulis G. Helicobacter pylori infection and gastric histology in first-degree relatives of gastric cancer patients: aA meta-analysis. Eur J Gastroenterol Hepatol. 2010; 22(9):1128–33.
8 Pimentel-Nunes P, Libânio D, Marcos-Pinto R, Areia M, Leja M, Esposito G, et al. Management of epithelial precancerous conditions and lesions in the stomach (MAPS II): European Society of Gastrointestinal Endoscopy (ESGE), European Helicobacter and Microbiota Study Group (EHMSG), European Society of Pathology (ESP), and Sociedade Portuguesa de Endoscopia Digestiva (SPED) guideline update 2019. Endoscopy. 2019; 51(4):365–88.
9 NCCN Clinical Practice Guidelines. Gastric cancer. 2022.
10 Van Leerdam ME, Roos VH, Van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) gGuideline. Endoscopy. 2019; 51(9):877–95.
11 Syngal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110(2):223–62; quiz 263.
12 Gullo I, van der Post RS, Carneiro F. Recent advances in the pathology of heritable gastric cancer syndromes. Histopathology. 2021; 78(1):125–47.
13 Jasperson KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. Gastroenterology. 2010;138(6):2044–58.
14 Utsunomiya J, Gocho H, Miyanaga T, Hamaguchi E, Kashimure A. Peutz-Jeghers syndrome: its natural course and management. Johns Hopkins Med J. 1975;136(2):71–82.
15 Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker SV, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology. 2000; 119(6):1447–53.
16 Latchford AR, Neale K, Phillips RKS, Clark SK. Juvenile polyposis syndrome: a study of genotype, phenotype, and long-term outcome. Dis Colon Rectum. 2012;55(10):1038–43.
17 Howe JR, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol. 1998;5(8): 751–6.
18 Blair VR, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. Lancet Oncol. 2020;21(8): e386–97.
19 NCCN Clinical Practice Guidelines. Genetic/Familial high-risk assessment: breast, ovarian, and pancreatic. 2022.
20 Lynch HT, Smyrk T, McGinn T, Lanspa S, Cavalieri J, Lynch J, et al. Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. Cancer. 1995;76(12):2427–33.
21 Brosens LAA, Wood LD, Offerhaus GJ, Arnold CA, Lam-Himlin D, Giardiello FM, et al. Pathology and genetics of syndromic gastric polyps. Int J Surg Pathol. 2016;24(3):185–99.
22 Wood LD, Salaria SN, Cruise MW, Giardiello FM, Montgomery EA. Upper GI tract lesions in familial adenomatous polyposis (FAP): enrichment of pyloric gland adenomas and other gastric and duodenal neoplasms. Am J Surg Pathol. 2014;38(3):389–93.
23 Arnason T, Liang WY, Alfaro E, Kelly P, Chung DC, Odze RD, et al. Morphology and natural history of familial adenomatous polyposis-associated dysplastic fundic gland polyps. Histopathology. 2014;65(3):353–62.
24 Leone PJ, Mankaney G, Sarvapelli S, Abushamma S, Lopez R, Cruise M, et al. Endoscopic and histologic features associated with gastric cancer in familial adenomatous polyposis. Gastrointest Endosc [Internet]. 2019;89(5): 961–8.
25 Walton SJ, Frayling IM, Clark SK, Latchford A. Gastric tumours in FAP. Fam Cancer. 2017;16(3):363–9.
26 Worthley DL, Phillips KD, Wayte N, Schrader KA, Healey S, Kaurah P, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): aA new autosomal dominant syndrome. Gut. 2012;61(5):774–9.
27 Mitsui Y, Yokoyama R, Fujimoto S, Kagemoto K, Kitamura S, Okamoto K, et al. First report of an Asian family with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) revealed with the germline mutation of the APC exon 1B promoter region. Gastric Cancer. 2018;21(6):1058–63.
28 Rudloff U. Gastric adenocarcinoma and proximal polyposis of the stomach: dDiagnosis and clinical perspectives. Clin Exp Gastroenterol. 2018;11:447–59.
29 Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of lynch syndrome: aA consensus statement by the us multi-society task force on colorectal cancer. Gastroenterology [Internet]. 2014;147(2): 502–26.
30 Aarnio M, Sankila R, Pukkala E, Salovaara R, Aaltonen LA, De La Chapelle A, et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. Int J Cancer. 1999;81(2):214–8.
31 Capelle LG, Van Grieken NCT, Lingsma HF, Steyerberg EW, Klokman WJ, Bruno MJ, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in The Netherlands. Gastroenterology. 2010;138(2): 487–92.
32 Amadou A, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. Curr Opin Oncol. 2018;30(1):23–9.
33 Masciari S, Dewanwala A, Stoffel EM, Lauwers GY, Zheng H, Achatz MI, et al. Gastric cancer in individuals with Li-Fraumeni syndrome. Genet Med. 2011;13(7):651–7.
34 Bougeard G, Renaux-Petel M, Flaman JM, Charbonnier C, Fermey P, Belotti M, et al. Revisiting Li-Fraumeni syndrome from TP53 mutation carriers. J Clin Oncol. 2015;33(21): 2345–52.
35 Hanson H, Brady AF, Crawford G, Eeles RA, Gibson S, Jorgensen M, et al. UKCGG Consensus Group guidelines for the management of patients with constitutional TP53 pathogenic variants. J Med Genet. 2021;58(2):135–9.
36 Hansford S, Kaurah P, Li-Chang H, Woo M, Senz J, Pinheiro H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol. 2015;1(1):23–32.
37 Caldas C, Carneiro F, Lynch HT, Yokota J, Wiesner GL, Powell SM, et al. Familial gastric cancer: overview and guidelines for management. J Med Genet. 1999;36(12):873–80.
38 Carvalho J, Oliveira P, Senz J, São José C, Hansford S, Teles SP, et al. Redefinition of familial intestinal gastric cancer: clinical and genetic perspectives. J Med Genet. 2021; 58(1):1–11.
39 Kluijt I, Sijmons RH, Hoogerbrugge N, Plukker JT, De Jong D, Van Krieken JH, et al. Familial gastric cancer: guidelines for diagnosis, treatment and periodic surveillance. Fam Cancer. 2012;11(3):363–9.
40 Chung SJ, Park MJ, Kang SJ, Kang HY, Chung GE, Kim SG, et al. Effect of annual endoscopic screening on clinicopathologic characteristics and treatment modality of gastric cancer in a high-incidence region of Korea. Int J Cancer. 2012;131(10):2376–84.
41 Banks M, Graham D, Jansen M, Gotoda T, Coda S, Di Pietro M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma. Gut. 2019;68(9):1545–75.
42 Murphy G, Dawsey SM, Engels EA, Ricker W, Parsons R, Etemadi A, et al. Cancer risk after pernicious anemia in the US elderly population. Clin Gastroenterol Hepatol [Internet]. 2015;13(13):2282–9.e1-4.
43 Vannella L, Lahner E, Osborn J, Annibale B. Systematic review: gastric cancer incidence in pernicious anaemia. Aliment Pharmacol Ther. 2013;37(4):375–82.

44 Islam RS, Patel NC, Lam-Himlin D, Nguyen CC. Gastric polyps: a review of clinical, endoscopic, and histopathologic features and management decisions. Gastroenterol Hepatol. 2013;9(10):640–51.
45 Castro R, Pimentel-Nunes P, Dinis-Ribeiro M. Evaluation and management of gastric epithelial polyps. Best Pract Res Clin Gastroenterol. 2017;31(4):381–7.
46 Okamoto Y, Kanzaki H, Tanaka T, Sakae H, Abe M, Iwamuro M, et al. Gastric adenoma: a high incidence rate of developing carcinoma and risk of metachronous gastric cancer according to long-term follow-up. Digestion. 2021;102(6):878–86.
47 de Vries AC, van Grieken NCT, Looman CWN, Casparie MK, de Vries E, Meijer GA, et al. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide Cohort Study in The Netherlands. Gastroenterology. 2008;134(4):945–52.
48 Leung WK, Lin SR, Ching JYL, To KF, Ng EKW, Chan FKL, et al. Factors predicting progression of gastric intestinal metaplasia: results of a randomised trial on *Helicobacter pylori* eradication. Gut. 2004;53(9):1244–9.
49 Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, et al. Cancer statistics, 2006. CA Cancer J Clin. 2006 Mar–Apr;56(2):106–30.
50 Ali R, Barnes I, Cairns BJ, Finlayson AE, Bhala N, Mallath M, et al. Incidence of gastrointestinal cancers by ethnic group in England, 2001–2007. Gut. 2013;62(12):1692–3.
51 Dong E, Duan L, Wu BU. Racial and ethnic minorities at increased risk for gastric cancer in a regional US population study. Clin Gastroenterol Hepatol. 2017;15(4):511–7.
52 Lagergren J, Lindam A, Mason RM. Gastric stump cancer after distal gastrectomy for benign gastric ulcer in a population-based study. Int J Cancer. 2012;131(6):1048–52.
53 Pérez-Rodríguez M, Partida-Rodríguez O, Camorlinga-Ponce M, Flores-Luna L, Lazcano E, Gómez A, et al. Polymorphisms in HLA-DQ genes, together with age, sex, and *Helicobacter pylori* infection, as potential biomarkers for the early diagnosis of gastric cancer. Helicobacter. 2017;22(1):e12326–10.
54 Morais S, Rodrigues S, Amorim L, Peleteiro B, Lunet N. Tobacco smoking and intestinal metaplasia: systematic review and meta-analysis. Dig Liver Dis. 2014;46(11):1031–7.