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REVIEW

Endoscopic Surveillance in Patients with the Highest Risk of Gastric Cancer: Challenges and Solutions

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Abstract: Gastric cancer is one of the most significant causes of cancer-related morbidity and mortality worldwide. Recognized modifiable risk factors include *Helicobacter pylori* infection, geographic location, select dietary factors, tobacco use and alcohol consumption. In addition, multiple hereditary cancer predisposition syndromes are associated with significantly elevated gastric cancer risk. Endoscopic surveillance in hereditary gastric cancer predisposition syndromes has the potential to identify gastric cancer at earlier and more treatable stages, as well as to prevent development of gastric cancer through identification of precancerous lesions. However, much uncertainty remains regarding use of endoscopic surveillance in hereditary gastric cancer predisposition syndromes, including whether or not it should be routinely performed, the surveillance interval and age of initiation, cost-effectiveness, and whether surveillance ultimately improves survival from gastric cancer for these high-risk individuals. In this review, we outline the hereditary gastric cancer predisposition syndromes associated with the highest gastric cancer risks. Additionally, we cover current evidence and guidelines addressing hereditary gastric cancer risk and surveillance in these syndromes, along with current challenges and limitations that emphasize a need for continued research in this field.

Keywords: hereditary diffuse gastric cancer syndrome, Lynch syndrome, familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, Li-Fraumeni syndrome

Introduction

Globally, approximately 1.1 million new gastric cancer cases occurred in 2020, along with 768,793 deaths, making it the fourth most common cause of cancer-related death worldwide.[1] In the United States, the cumulative lifetime risk for gastric cancer is estimated to be 0.8%, while a higher incidence is typically observed in East Asia, Eastern Europe, South America and Central America.[2] Certain dietary (salted fish/meat and pickled vegetables, processed and grilled/charcoaled meats, fewer fruits/vegetables), occupational (coal, metal and rubber industries), and lifestyle (obesity, alcohol, tobacco) risk factors have been recognized, in addition to *Helicobacter pylori (H. pylori)* infection as a primary risk factor.[2,3] While gastric surveillance is not routinely recommended in Western societies, it can increase survival rates from gastric cancer in select populations. In South Korea, where surveillance frequently identifies gastric cancers at early stages, the 5-year survival rate was 69%, in contrast to the 33% and 21% 5-year survival rate in the United States and United Kingdom, respectively.[4] Knowledge of which individuals are most susceptible to gastric cancer is important to help guide appropriate surveillance recommendations and improve gastric cancer survival.

Beyond the geographic, environmental and lifestyle influences on gastric cancer risk, approximately 5–10% of gastric cancer cases exhibit familial clustering with a suspected genetic basis.[5] Multiple known hereditary cancer predisposition syndromes are associated with increased gastric cancer risk (Figure 1). These conditions are heterogeneous, caused by a pathogenic or likely pathogenic variant (PV) in one of multiple different gastric cancer risk genes, and concurrently

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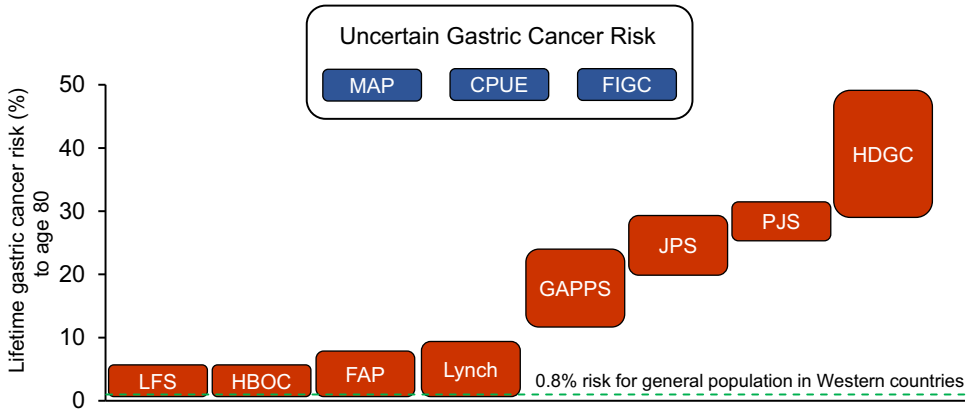

Figure 1 Cumulative gastric cancer risk of hereditary gastric cancer risk syndromes.
Abbreviations: LFS, Li-Fraumeni syndrome; HBOC, hereditary breast and ovarian cancer syndrome; FAP, familial adenomatous polyposis; Lynch, Lynch syndrome; GAPPS, Gastric adenocarcinoma and proximal polyposis of the stomach; JPS, juvenile polyposis syndrome; PJS, Peutz-Jeghers syndrome; HDGC, hereditary diffuse gastric cancer syndrome; MAP, *MUTYH*-associated polyposis; CPUE, colonic polyposis of unknown etiology; FIGC, familial intestinal gastric cancer.

raise the likelihood of a spectrum of other cancer types in a gene-specific manner (Table 1). Identification of a PV associated with a known hereditary cancer predisposition syndrome allows generation of more precise gastric cancer risk estimates and enables tailoring of surveillance recommendations deemed appropriate for the condition (Table 2). As well, predictive genetic testing for a known familial PV is a highly informative strategy to determine which relatives may also be at increased gastric cancer risk. Herein, we review the hereditary cancer predisposition syndromes associated with increased gastric cancer risk, outline current gastric cancer surveillance strategies for each, as well as highlight challenges in the field and the need for continued research.

Hereditary Diffuse Gastric Cancer Syndrome

Genetics and Gastric Cancer Risk

Hereditary diffuse gastric cancer (HDGC) syndrome increases risk for both diffuse gastric cancer (DGC) as well as invasive lobular breast cancer. HDGC is inherited in an autosomal dominant manner most commonly due to a PV in the *CDH1* gene, though other families harbor a PV in the *CTNNA1* gene and a subset of families considered "HDGC-like" fulfill HDGC genetic testing criteria but lack a detectable PV.[6–9] First characterized in 1998 via a large family of Māori ethnicity with early-onset DGC,[10] the incidence of HDGC is currently estimated as 5–10 per 100,000 births.[9] In addition to DGC and lobular breast cancer risk, cleft lip and/or palate has also been noted in select families with *CDH1* PVs.[11]

Prior to 2010, consensus genetic testing criteria to evaluate for HDGC required at least one case of DGC in a family, and lifetime risk estimates suggested a greater than 80% chance of DGC by age 80.[12] Following inclusion of *CDH1* on commercial multigene hereditary cancer panels, the increasing number of tested families with greater phenotypic variability led to reduced penetrance estimates, as well as identification of families lacking DGC (now classified as hereditary lobular breast cancer or HLBC syndrome).[9,12,13] Among families with at least one case of DGC, thus meeting 2010 HDGC clinical criteria, one study estimated cumulative gastric cancer risk as 70% for males and 56% for females.[14] In 2019, two studies reported on cohorts ascertained on the basis of a *CDH1* PV, regardless of whether HDGC clinical criteria were met, thus generating significantly reduced estimates for cumulative lifetime gastric cancer risk, ranging from 37% to 42% for males and 25–33% for females.[15,16] Although more recent gastric cancer risk estimates in HDGC are lower than initial estimates, HDGC still remains one of the highest known gastric cancer predisposition syndromes. In sum, gastric cancer risk in HDGC likely varies depending on family history of DGC and the individual's genetic background, which are important points to consider when personalizing genetic counseling and surveillance recommendations for individuals newly diagnosed with HDGC.

Table 1 Hereditary Cancer Predisposition Syndromes Associated with Increased Gastric Cancer Risk

Syndrome	Gene(s)	GC Risk*	Other Cancer Risks	Benign Syndromic Findings
Hereditary diffuse gastric cancer (HDGC)	*CDH1* *CTNNA1*	33–80% for *CDH1*; unknown for *CTNNA1*	Breast (invasive lobular carcinoma)	Cleft lip/palate
Lynch syndrome (LS)	*MLH1* *MSH2* *MSH6* *PMS2* *EPCAM*	≤1–9.0% (varies by gene)	Colon, endometrial, ovarian, urothelial (renal pelvis, ureter, and/or bladder), small bowel, pancreatic, prostate, brain (typically glioblastoma), skin (sebaceous neoplasms)	-
Familial adenomatous polyposis (FAP)	*APC*	0.1–7.1%	Colon, duodenal/periampullary, thyroid (typically papillary), small bowel, hepatoblastoma, brain (typically medulloblastoma), pancreatic, desmoid tumors	Congenital hypertrophy of the retinal pigment epithelium (CHRPE), epidermal cysts, osteomas
MUTYH-associated polyposis (MAP)	*MUTYH (biallelic)*	Uncertain	Colon, duodenal	-
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	*APC* (promoter 1B)	12–25%	-	-
Peutz-Jeghers syndrome (PJS)	*STK11*	~29%	Breast, colon, stomach, small intestine, pancreatic, cervical, ovarian (sex cord tumor with annular tubules), and lung	Mucocutaneous hyperpigmentation (may fade with age)
Juvenile polyposis syndrome (JPS)	*BMPR1A* *SMAD4*	21–30%**	Colon	Hereditary hemorrhagic telangiectasia (HHT)***
Li-Fraumeni syndrome (LFS)	*TP53*	~3%	Adrenocortical carcinoma, breast, central nervous system, osteosarcomas, soft-tissue sarcomas, in addition to others	-
Colonic polyposis of unknown etiology (CPUE)	Uncertain	Uncertain	Colon	-
Hereditary breast and ovarian cancer syndrome (HBOC)	*BRCA1* *BRCA2*	0.7–3.5%	Breast, ovarian, pancreatic, prostate, melanoma	-
Familial intestinal gastric cancer (FIGC)	Uncertain	Uncertain	-	-

Notes: *Cumulative lifetime risk, as compared to 0.8% cumulative risk by age 80 among general population in Western countries. **Pertains to individuals with a molecular diagnosis of JPS with a confirmed PV in *SMAD4* or *BMPR1A*, as opposed to a clinical diagnosis without a detectable PV. ***Pertains to a subset of individuals with a *SMAD4*-associated JPS.

Surveillance

DGC, the less common histologic subtype compared to intestinal-type gastric cancer, is particularly challenging to detect endoscopically as it often presents as *linitis plastica* with gastric wall thickening as opposed to a protruding luminal mass. Microscopically, foci of signet-ring cell carcinoma (SRCC) are characteristic features of HDGC and are found in nearly all individuals with HDGC who undergo gastrectomy.[17,18] Identification of SRCC is often considered one of the

Table 2 Authors' Approach to Gastric Cancer Surveillance in Hereditary Gastric Cancer Predisposition Syndromes

Syndrome	Gastric Cancer Surveillance Strategy*
Hereditary diffuse gastric cancer (HDGC)	Upper endoscopy at age 18–20 or time of HDGC diagnosis, and then repeated annually until risk-reducing total gastrectomy is pursued. Gastric biopsies should be performed using the IGCLC protocol including 28–30 non-targeted biopsies as well as additional targeted biopsies of any mucosal abnormalities. Inlet patches should be documented, examined, and biopsied.
Lynch syndrome (LS)	Upper endoscopy starting at age 30, repeating every 2–3 years, with biopsies of the gastric antrum and body. Non-invasive *H pylori* testing at time of LS diagnosis if under age 30.
Familial adenomatous polyposis (FAP)	Upper endoscopy starting at age 20 with ampulla visualization (with either a side-viewing duodenoscope or standard upper endoscope with a clear cap). Repeat upper endoscopy interval is based on Spigelman stage and gastric findings and should be no longer than 5 years. Baseline upper endoscopy should be performed prior to age 20 if colectomy is being planned at an early age.
Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS)	Upper endoscopy every 1 year until the time of total gastrectomy. Surveillance should start at the time of diagnosis or at age 15.
MUTYH-associated polyposis (MAP)	Although gastric cancer risk is uncertain, upper endoscopy is needed for duodenal surveillance. Upper endoscopy starting at age 30 with ampulla visualization (with either a side-viewing duodenoscope or standard upper endoscope with a clear cap). Repeat upper endoscopy interval is based on Spigelman stage and should be no longer than 5 years.
Peutz-Jeghers syndrome (PJS)	Baseline upper endoscopy between age 8–10. If polyps are present repeat at least every 2–3 years, and if no polyps resume upper endoscopy at age 18, repeating at least every 2–3 years.
Juvenile polyposis syndrome (JPS)	Baseline upper endoscopy between age 12–15. If polyps are present repeat at least every 2–3 years, and if no polyps resume upper endoscopy at age 18, repeating at least every 2–3 years. If no detectable PV in *SMAD4* or *BMPR1A*, and no gastric polyps, can consider increasing the interval to every 5 years.
Li-Fraumeni syndrome (LFS)	Upper endoscopy starting at age 25, repeating every 2–3 years, with biopsies of the gastric antrum and body.
Colonic polyposis of unknown etiology (CPUE)	Although gastric cancer risk is uncertain, upper endoscopy is needed for duodenal surveillance. Upper endoscopy starting at the time of diagnosis with ampulla visualization (with either a side-viewing duodenoscope or standard upper endoscope with a clear cap). Repeat upper endoscopy interval is based on Spigelman stage and should be no longer than 5 years.
Hereditary breast and ovarian cancer syndrome (HBOC)	Routine gastric surveillance is not currently recommended. However, if pancreatic cancer surveillance is being performed with EUS, a dedicated upper endoscopy should also be performed simultaneously.
Familial intestinal gastric cancer (FIGC)	Upper endoscopy with biopsies of the gastric antrum and body starting at age 50 or 5 years prior to the youngest gastric cancer. Repeat upper endoscopy every 1–3 years.

Notes: *Age of surveillance initiation and frequency of surveillance may be altered by presence of symptoms, family history of polyps and/or cancer, and/or other personal factors including endoscopic findings.

goals of surveillance in HDGC as these foci serve as the precursors of invasive DGC.[19] Endoscopic surveillance in HDGC typically begins in adulthood at the time of HDGC diagnosis or at age 18–20, with annual upper gastrointestinal (GI) endoscopy following a modified Cambridge protocol[20] of targeted biopsies of visible abnormalities (with special attention paid to pale patches of mucosa) as well as approximately 28–30 non-targeted biopsies (3–5 biopsies from the cardia, 5 biopsies each from the fundus, transition zone, and antrum, and 10 biopsies from the body).[9] Additionally, all gastric inlet patches should be documented, inspected, and biopsied. While this protocol is included in the 2020 International Gastric Cancer Linkage Consortium (IGCLC) consensus guidelines for HDGC management,[9,12] the significant limitations of this approach must be emphasized. In one single-center study of 20 individuals with a *CDH1* PV from 13 families who pursued endoscopy and/or gastrectomy, none had visible abnormalities on endoscopy, yet 12

individuals (60%) were found to have SRCC on microscopic review.[21] Among a larger cohort of 67 individuals with *CDH1* PVs who elected prophylactic total gastrectomy, 75% had foci of SRCC on final gastrectomy pathology despite only 25% having SRCC foci detected on random endoscopic biopsy.[22] Strikingly, Cambridge protocol biopsies were not found to improve the detection rate of SRCC foci.[22] More recently in 2021, a comparison of the Cambridge protocol with the expanded gastric mucosal sampling protocol known as the Bethesda protocol (minimum 88 biopsies from 22 gastric sites) suggested the latter method improved detection of occult DGC, however the false negative rate remained 38%.[23] Other advanced endoscopic techniques have also not been particularly effective;[24] as one example, a single-center study of 47 individuals with *CDH1* PVs concluded use of endoscopic ultrasound (EUS) did not lead to any increased gastric cancer detection with EUS.[25]

Another challenging aspect in HDGC is the lack of clarity regarding which SRCC will progress to cancer, versus those that will remain indolent.[26] Given these limitations and unknowns related to gastric cancer surveillance in HDGC, consensus recommendations from IGCLC and the National Comprehensive Cancer Network (NCCN) continue to recommend prophylactic total gastrectomy between ages 18–40 for individuals with HDGC (*CDH1* PV plus a family history of DGC) with the aforementioned surveillance offered every 6–12 months for those who decline surgery.[9,27] For individuals who pursue prophylactic total gastrectomy, consensus recommendations for follow-up care were recently published from the Life after Prophylactic Total Gastrectomy Study Group.[28]

Decisions regarding gastric surveillance versus prophylactic surgery remain particularly challenging for families where reduced penetrance has been suggested, including HLBC families with a *CDH1* PV who lack family history of DGC as well as families with a *CDH1* PV with neither a family history of DGC nor lobular breast cancer.[29] For these families, updated 2020 IGCLC guidelines advise annual endoscopic surveillance with careful consideration of total gastrectomy in light of the uncertain DGC risk.[9] Families deemed HDGC-like (lacking a *CDH1* PV but meeting genetic testing criteria for HDGC) were recommended to undergo yearly endoscopic surveillance for two years (with the option to prolong the interval thereafter if normal exams), avoiding prophylactic gastrectomy as long as endoscopies remain negative.[9] At present, this remains one of the more challenging areas of current clinical practice related to hereditary gastrointestinal syndromes with a strong need for further study.

Lynch Syndrome

Genetics and Gastric Cancer Risk

Lynch syndrome (previously referred to as hereditary non-polyposis colorectal cancer or HNPCC) is the most common hereditary gastrointestinal cancer risk syndrome, estimated to affect approximately 1 in 279 individuals.[30] Germline PVs in the DNA mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*) and deletions of the 3' end of *EPCAM* (which leads to epigenetic inactivation of the downstream *MSH2* gene) underlie the molecular mechanism of this syndrome, leading to mismatch repair deficiency and microsatellite instability in Lynch syndrome-associated tumors.[31,32] The highest lifetime cancer risks associated with Lynch syndrome are colorectal cancer (46–61% vs 4.2% for average-risk) and endometrial cancer (34–54% vs 3.1% for average-risk), although there is a broad cancer spectrum with penetrance differing by gene, sex assigned at birth and age.[33–35] Estimates of the lifetime gastric cancer risk by age 80 in Lynch syndrome vary from 5% to 7% for *MLH1*, 0.2–9.0% for *MSH2*/*EPCAM*, and ≤1–7.9% for *MSH6*, while insufficient data is available at this time to estimate gastric cancer risk for *PMS2* carriers.[35] Notably, the estimated gastric cancer risk varies by geographic region. Studies of populations with Lynch syndrome in Japan and Korea have reported cumulative incidence of gastric neoplasia (including dysplasia and cancer) as high as 41%, often associated with *H. pylori* infection.[36–39] Other patient-specific characteristics associated with greater gastric cancer risk in Lynch syndrome include male sex at birth, older age and having a first-degree relative with gastric cancer.[40]

Surveillance

Multiple professional societies have developed guidelines addressing management of gastric cancer risk in Lynch syndrome.[35,41–48] However, significant heterogeneity exists at present between these guidelines regarding whether gastric surveillance should be performed, the age of initiation, and recommended interval for upper GI surveillance in Lynch syndrome, which has been well-summarized in a recent review by Kumar et al.[49] In part, the variability of different guidelines has resulted from limited data demonstrating clinical effectiveness of gastric cancer surveillance in Lynch

syndrome, as well as uncertainty regarding which high-risk individuals are most in need of surveillance. Fortunately, this is an area of ongoing active research, with recent studies of upper endoscopic surveillance in Lynch syndrome supporting surveillance as effective at detecting pre-cancerous lesions and early-stage gastric cancers.

A study of 217 individuals with Lynch syndrome who underwent a total of 660 upper endoscopies showed 2.8% were diagnosed with gastric adenocarcinoma, while others were found to have either duodenal (n = 4) or esophageal (n = 1) cancer.[50] For a majority of the gastric cancers identified during active surveillance, the interval between the prior negative screening examination and the cancer diagnosis was 2 years or less,[50] indicating that gastric carcinogenesis may occur rapidly in Lynch syndrome, similar to colorectal carcinogenesis.[51,52] Endoscopic surveillance in Lynch syndrome also leads to detection of precancerous and other high-risk, clinically actionable findings, including duodenal adenomas (1.8%), Barrett's esophagus (3.2%), gastric intestinal metaplasia (8.3%) and *H. pylori* (2.8%).[50] Importantly, this series noted that of the upper GI cancers identified on surveillance, 80% were diagnosed at stage I.[50] Another study of a multi-center, French cohort included 172 individuals with Lynch syndrome having diagnostic or surveillance upper endoscopy; 3% were diagnosed with gastric adenocarcinoma, and 20% with normal findings on initial upper endoscopy later developed precancerous findings on follow-up exams.[53] An additional recent study of 323 asymptomatic individuals with Lynch syndrome with 717 total surveillance upper endoscopies performed, reported 1.5% with an upper GI cancer including one gastric adenocarcinoma and one gastric neuroendocrine tumor, and 17.6% with clinically actionable findings.[54] Finally, in a large German cohort of 1128 individuals with Lynch syndrome undergoing upper GI endoscopies, the gastric cancers identified via surveillance were significantly more likely to be stage I (83%), compared to symptomatic gastric cancers detected outside of surveillance (25% were stage I).[55] Furthermore, for 5 of 6 individuals diagnosed with gastric cancer on surveillance, the interval since last upper endoscopy was less than 2 years.[55] In sum, these studies demonstrate that upper GI surveillance in Lynch syndrome detects gastric cancers at early stages and suggest the importance of shorter interval surveillance, although further research is needed to determine if upper GI surveillance reduces death from gastric cancer.

It is the authors' practice that all individuals with Lynch syndrome, regardless of the causative gene, initiate surveillance upper endoscopy at age 30 (or 2–5 years before the youngest age of diagnosis if there is a family history of gastric cancer under age 35), repeating every 2–3 years with consideration of shorter intervals with a family history of upper GI cancer or in the presence of precancerous lesions (incomplete or extensive gastric intestinal metaplasia, gastric/duodenal adenoma or Barrett's esophagus with dysplasia).[49] NCCN recently adopted a similar approach by recommending upper GI surveillance starting between ages 30–40 and repeating every 2–4 years for all *MLH1, MSH2/EPCAM*, and *MSH6* PV carriers with consideration of upper GI surveillance in *PMS2* PV carriers.[35] Surveillance should also be performed with use of high definition, white light endoscopy, ideally performed at the time of surveillance colonoscopy, with inclusion of random biopsies of the proximal and distal stomach to evaluate for *Helicobacter pylori*, intestinal metaplasia and autoimmune gastritis. Whether these gastric biopsies should be performed on only the initial exam or on each surveillance exam remains uncertain. Push enteroscopy may also be considered instead of standard upper endoscopy to improve the extent of small bowel visualization, however more study is needed addressing the yield in Lynch syndrome.[35,49,56] Future research in upper GI surveillance in Lynch syndrome needs to focus on whether upper GI surveillance leads to a survival benefit and is cost-effective, as well as understanding the mechanism of Lynch syndrome-associated gastric carcinogenesis.

Adenomatous Polyposis Syndromes

Familial Adenomatous Polyposis (FAP)

Genetics and Gastric Cancer Risk

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome resulting from PVs in the *APC* gene, with an estimated population prevalence of 1 in 10,000.[57] Up to 20–30% of cases of FAP are *de novo*, arising from a new pathogenic variant in *APC* and therefore may lack family history of FAP.[58] Classic FAP leads to 100s to 1000s of colonic adenomas, beginning in childhood, while attenuated FAP (AFAP) typically presents later in life with cumulative polyp burden in the 10s – 100s.[59] FAP accounts for approximately 1% of all colorectal cancers, and without appropriate intervention, the lifetime risk for colorectal cancer in FAP is virtually 100%.[60] Options for FAP colonic management include frequent endoscopic surveillance, chemoprevention and risk-reducing surgery (eg, proctocolectomy).

Importantly, extra-colonic manifestations of FAP must also be addressed as part of a comprehensive healthcare plan, including risks for duodenal/ampullary cancer, thyroid cancer, and gastric cancer[42,61]

Cumulative gastric cancer risk by age 80 in FAP has been estimated between 0.1% and 7.1%.[35,62] Of note, the rate of FAP-associated gastric cancer reported is higher among Asian populations in Japan (2.6–7.1%) and Korea (4.2%), compared to populations in the United States (as low as 0.6% in one study of 1255 individuals), although a rising incidence has been recently reported among Western populations with a standard incidence ratio of 140 as compared to SEER data.[63–68] The vast majority of individuals with FAP develop fundic gland polyposis, often with low-grade dysplasia, although fundic gland polyps are not considered the precursor lesions for most gastric adenocarcinomas in FAP.[69] Recent efforts by Leone et al to characterize endoscopic and histologic features of gastric cancers in FAP identified 10 individuals with gastric cancer out of 767 individuals in an FAP registry database; these ten individuals with gastric cancer were age-matched to 40 controls with FAP. While the prevalence of gastric polyposis was similarly high in both groups (100% vs 93%), gastric adenomas, pyloric gland adenomas and gastric polyps with high-grade dysplasia (including fundic gland polyps), were more frequent among those with gastric cancer.[70] Endoscopically, solitary gastric polyps ≥2cm, a carpeting of proximal gastric polyps and polypoid mounds within the proximal carpeting were three features observed more commonly among individuals with gastric cancer and FAP.[70] Another high-risk gastric lesion in FAP are gastric white patches, which may reflect underlying adenomatous mucosa and likely portend a higher gastric cancer risk.[71–73]

Surveillance

Current upper GI surveillance guidelines from both the American College of Gastroenterology (ACG) and the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG), published in 2015 and 2020, respectively, strongly recommend earlier initiation of upper GI surveillance at age 25–30 with interval every 0.5–4 years according to Spigelman classification of duodenal polyposis.[41,42] Random sampling of gastric fundic gland polyps is also recommended, although fundic gland polyps with low-grade dysplasia are common in FAP and do not warrant more aggressive management in the absence of other concerning findings.[42,69] Furthermore, criteria exist to help endoscopists identify high-risk gastric polyps in FAP, thus providing guidance on which polyps to target during surveillance.[74] NCCN guidelines recommend initiation of upper GI endoscopy slightly earlier at age 20–25, given concern for the morbidity and mortality associated with duodenal/periampullary cancers in FAP.[35] Additionally, with the recent recognition of the high-risk endoscopic and histologic gastric findings described earlier, current NCCN guidelines note specialized surveillance is recommended if these features are present, and consideration may be given to gastrectomy if high-risk lesions cannot be removed endoscopically; ideally, these procedures should occur at a specialized center with expertise in FAP management and should account for patient-specific factors.[35] Although not yet included in national guidelines, there are proposed surveillance recommendations by Mankaney et al for FAP patients with gastric polyps that many have adopted into clinical practice.[68] These guidelines include gastric polyp number, size, histology, level of dysplasia, and presence of other high-risk features in order to determine appropriate surveillance intervals that are not dependent on duodenal findings.[75] Additionally, if a patient with FAP needs to undergo colectomy at an age before upper GI surveillance is typically recommended to begin, a baseline upper endoscopy to rule out gastric neoplasia should be performed prior to colectomy.

Gastric Adenocarcinoma and Proximal Polyposis of the Stomach (GAPPS)

Genetics and Gastric Cancer Risk

Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS) is a rare autosomal dominant condition characterized by fundic gland polyposis and increased risk for intestinal-type gastric adenocarcinoma. In 2012, the first case series described three families with GAPPS, wherein the youngest individual with gastric polyposis was 10 years old and the earliest gastric cancer occurred at age 33; in contrast to FAP/AFAP, colonic polyposis and duodenal adenomas were not detected in these families.[76] The gastric polyposis in GAPPS typically spares the gastric antrum, instead affecting the oxyntic mucosa of the gastric body and fundus.[76,77] Worthley et al proposed clinical diagnostic criteria for GAPPS as follows: (1) gastric polyps restricted to the body and fundus with no evidence of colorectal or duodenal polyposis; (2) >100 polyps carpeting the proximal stomach in the index case or >30 polyps in a first-degree

relative of another case; (3) predominantly fundic gland polyps (FGPs), some having regions of dysplasia (or a family member with either dysplastic FGPs or gastric adenocarcinoma); and (4) an autosomal dominant pattern of inheritance.[76] In 2016, the genetic basis of GAPPS was identified as point mutations in promoter 1B of the *APC* gene, after sequencing confirmed segregation of these variants with GAPPS in all families evaluated.[78] As more individuals and families have been identified with GAPPS in recent years, the estimated risk of gastric cancer remains high with estimates ranging from 12% to 25%, and the age of onset, degree of dysplasia and penetrance appears variable.[76,79]

Surveillance

Given the relatively recent identification of GAPPS and incomplete understanding of the natural history of this disease, evidence-based consensus recommendations are not available at this time, with recommendations currently driven by expert-opinion. In light of the elevated gastric cancer risk and the challenges inherent in attempting to identify invasive cancer amid florid gastric polyposis, the NCCN and others have suggested annual gastroscopy from age 15 with consideration of risk-reducing total gastrectomy in the 30s.[35,80]

MUTYH-Associated Polyposis (MAP)

Genetics and Gastric Cancer Risk

MUTYH-associated polyposis (MAP) is an autosomal recessive condition caused by biallelic PVs in the *MUTYH* gene, with the affected individual inheriting one PV from each parent. It is estimated that up to 1 in 45 individuals (~2%) is a monoallelic *MUTYH* PV carrier with an estimated population frequency of MAP of 1 in 8073.[30] Since the phenotype of MAP overlaps with FAP yet cancer risk management differs, it is important to confirm the underlying molecular diagnosis in an individual presenting with colonic polyposis and/or early onset colon cancer.[81] Additionally, risk estimation for relatives is also impacted depending on whether the polyposis syndrome is inherited in a recessive (eg, MAP) versus dominant (eg, FAP/AFAP) manner.

To evaluate extra-colonic risk in MAP, a European multi-center study in 2009 reviewed data from 276 individuals with MAP from 181 unrelated families and identified 150 individuals who had undergone upper GI endoscopy.[82] Gastric polyps were identified in 11% (17/150) with 9 having gastric fundic gland polyps only and 4 having gastric adenomas.[82] Three individuals had gastric cancer, but ultimately, the gastric cancer incidence (SIR 4.2, 95% CI: 0.9–12.3) was not statistically significant from the general population incidence.[82] It is important to note the limitation of small sample size, given the difficulty of identifying large cohorts for a rare, recessive condition typically affecting only one generation per family. In 2016, Win et al interrogated a large data set from the Colon Cancer Family Registry and identified 41 individuals with biallelic *MUTYH* PV, along with 138 relatives confirmed as monoallelic *MUTYH* PV carriers. Given the small numbers, it was not possible to assess gastric cancer risk in those with MAP, although increased gastric cancer risk was suggested for those with monoallelic *MUTYH* PV with an estimated cumulative lifetime risk of 2.3% (95% CI, 1.7–3.3%).[83] More studies remain needed to clarify the gastric cancer risk for both biallelic and monoallelic *MUTYH* PV carriers.

Surveillance

Given the uncertainty surrounding gastric cancer risk estimation in MAP, current guidelines are not tailored to gastric cancer risk management, yet upper endoscopy is recommended for duodenal surveillance in light of several studies reporting 5–34% of individuals with MAP having duodenal adenomas or cancer.[84–86] NCCN guidelines for MAP recommend baseline upper endoscopy (including complete visualization of the ampulla of Vater) starting between age 30–35 with follow-up interval determined by the overall Spigelman score of duodenoscopic findings; this approximates guidelines from both the American Society of Colorectal Surgeons (ASCRC) and BSG/ACPGBI/UKCGG, although the ASCRC notes use of the Spigelman criteria is extrapolated from FAP and was not developed from MAP patients.[35,41,87] For ACG and European Society of Medical Oncology (ESMO) guidelines, the recommended age of initiation is slightly earlier at 25–30 years of age, consistent with FAP surveillance, despite the reduced penetrance for duodenal neoplasia with MAP.[42,81,85]

Hamartomatous Polyposis Syndromes

Peutz-Jeghers Syndrome (PJS)

Genetics and Gastric Cancer Risk

Peutz-Jeghers syndrome (PJS) is an autosomal dominant condition characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation. PJS is also associated with increased risk for multiple cancers including breast, colon, gastric, small intestine, pancreatic, cervical, ovarian (sex cord tumor with annular tubules), and lung cancers. PJS is a rare condition and the prevalence is estimated to be between 1 in 50,000–200,000 people.[88] PJS is typically caused by PVs in the *STK11* (also referred to as *LKB1*) gene, however a clinical diagnosis of PJS can be made when an individual meets two or more of the following criteria: 1) Two or more Peutz-Jeghers polyps; 2) Mucocutaneous hyperpigmentation of the lips, mouth, nose, eyes, genitalia, or fingers; 3) Family history of PJS.[89]

Individuals with PJS develop hamartomatous polyps throughout the GI tract including in the stomach, small intestine, and colon.[90] Peutz-Jeghers polyps are histopathologically characterized by interdigitating smooth muscle bundles in a branching tree appearance throughout the lamina propria, and more specifically have lobular organization of the crypts.[91] It can remain challenging to distinguish PJS polyps from juvenile or hyperplastic polyps in the stomach based on histologic criteria.[92] In PJS, the gastric cancer risk is estimated as ~29% by the age of 65, with a mean age of diagnosis between 20 and 40.[93–95]

Surveillance

Current clinical guidelines for the management and surveillance for individuals with PJS are based on expert opinion, but have limited prospective data regarding the efficacy of various surveillance modalities. An asymptomatic individual with PJS should begin upper endoscopy at the age of 8–10 years old.[35,41,93,96] If individuals with PJS have symptoms including GI blood loss, intussusception/obstruction, screening should be initiated at an earlier age or repeated more frequently.[35,41] If the baseline upper endoscopy is without polyps, the next exam can be deferred until age 18.[35,41,93] If polyps are found, polypectomy is recommended with a repeat endoscopy every 2–3 years.[35] After age 18, upper endoscopy should be performed at least every 2–3 years. Shorter screening intervals may be indicated based on polyp size, number, and pathology.

Juvenile Polyposis Syndrome (JPS)

Genetics and Gastric Cancer Risk

Juvenile polyposis syndrome (JPS) is characterized by juvenile polyps in the GI tract, which are a specific histopathological type of hamartomatous polyp, and increased risk of colon and gastric cancers. JPS is rare with an incidence of 1 in 100,000 to 1 in 160,000 individuals.[97] A clinical diagnosis of JPS is made when an individual meets at least one of the following criteria: 5 or more juvenile polyps in the colon, multiple juvenile polyps throughout the GI tract, or any number of juvenile polyps in a person with a known family history of JPS.[35] Pathogenic variants in the *SMAD4* or *BMPR1A* genes (autosomal dominant inheritance pattern) are identified in about 40–50% of individuals meeting clinical criteria for JPS, leaving the remaining large portion of individuals without a known underlying etiology.[98] Individuals with a *SMAD4* pathogenic variant may also demonstrate features of hereditary hemorrhagic telangiectasia, which has additional medical management considerations.[99] There are other further phenotypic differences in JPS between individuals with either a *SMAD4* or *BMPR1A* PV, and those without an identified molecular explanation.[97,100]

Juvenile polyps can appear in the first decade of life and can occur in both the stomach as well as the colon; typically juvenile polyps do not develop in the small intestine.[101] Defining histologic features of a juvenile polyp include cystically dilated glands and inflammatory stroma; however, distinguishing between inflammatory and juvenile polyps can be challenging.[102] Individuals with JPS are more likely to have polyps identified in the colon (~90%) compared to the stomach (~30–60%), although a subset of individuals with *SMAD4* PV have significant involvement of the stomach.[103,104] Notably, gastric juvenile polyps can also be easily confused with hyperplastic polyps histologically.[105] The number of gastric juvenile polyps can vary, ranging between a few (1–4 polyps), multiple (5–99 polyps) or massive (>100 polyps) – with "few" being most common in patients with *BMPR1A* PV and "multiple" in *SMAD4* PV.[103] Gastrectomy may be required in a subset of JPS to due to the enormous polyp burden or cancer,[100,106] and there are

reports of individuals with *SMAD4*-related JPS presenting with massive gastric polyposis with obstructive symptoms and hypergastrinemia.[103,107] Further, *SMAD4* PV have been identified in some cases of Ménétrier disease, which is characterized by hypertrophic gastropathy resulting in giant mucosal folds in the proximal part of the stomach.[108] This suggests the differential diagnosis for Ménétrier disease should include JPS given overlapping phenotypes and important downstream implications of JPS for both the patient and family members. Interestingly, a recent multicenter cohort showed that in individuals with a clinical diagnosis of JPS without a *SMAD4* nor *BMPR1A* PV, none of these individuals had any gastric polyps nor was there any reported gastric cancer, indicating that the gastric phenotype in JPS is dependent on genotype.[100] In individuals with gastric polyps, the incidence of gastric cancer is estimated to be about 21–30%, with an average age of onset of 54–58.[93,103]

Surveillance

For gastric surveillance in JPS, the NCCN and US Multi-Society Task Force on Colorectal Cancer (USMSTFCC) recommends initiating upper endoscopy between ages 12 to 15.[35,93] Of note, the USMSTFCC proposes that in pediatric patients without *SMAD4* or *BMRP1A* PV, gastroscopy is not indicated before age 18 based on current data unless the child is symptomatic.[93] If polyps are found, endoscopy should be repeated every 1 to 3 years, with shorter intervals determined by polyp size, number and pathology for those with a *SMAD4* or *BMPR1A* PV. If no polyps are found, then the recommendation is to resume upper endoscopy at the age of 18 and repeat every 1–3 years.[35] For those with clinical JPS without a molecular explanation, guidelines suggest a consideration for increasing upper GI surveillance interval to every 5 years if no polyps were identified.[35] Alternatively, British guidelines suggest delaying upper endoscopy for gastric screening until age 25 for all non-*SMAD4* carriers.[41] In adults, partial or complete gastrectomy should be considered in individuals with gastric cancer, high-grade dysplasia, and inability to endoscopically control polyp burden or polyp symptoms (eg, anemia).[35,93]

Li-Fraumeni Syndrome (LFS)

Genetics and Gastric Cancer Risk

Li-Fraumeni syndrome (LFS) is a highly penetrant, autosomal dominant hereditary cancer predisposition syndrome with a broad spectrum of cancer risk, often with cancers diagnosed at a younger than expected age. The most common cancer types in LFS include adrenocortical carcinomas, breast cancers, central nervous system malignancies, osteosarcomas and soft-tissue sarcomas.[109] Beyond these core cancer risks, there remains a variety of additional cancer risks, including cancers in the GI tract. The overall lifetime risk of cancer in individuals with LFS is estimated over 80% for both men and women,[109–110] and the diagnosis of LFS is established by either meeting classic clinical criteria or carrying a PV in the *TP53* gene, a key tumor suppressor gene.[112] The prevalence of a germline PV in the *TP53* gene is 1 in 3555–5476 individuals.[113] Of note, a shift to refer to LFS as a wider cancer predisposition syndrome, designated heritable *TP53*-related cancer syndrome, has occurred to acknowledge families that do not fit the classically defined phenotype.[112]

Limited data exist regarding the absolute risk of gastric cancer in LFS, although 3.3% of individuals with LFS (and 5.9% of families) in the International Agency for Research on Cancer (version R20) database were reported to have gastric cancer.[114] A higher incidence of gastric cancer (~15%) is reported in Asian individuals with LFS, with an average age of onset of 39 years.[115] As mentioned previously, however, gastric cancer incidence among the general population is about five times higher in East Asian countries compared to Western countries, which may confound the risks observed among East Asian populations with LFS.[112]

Surveillance

Few organizations provide recommendation for upper GI surveillance for LFS-associated gastric cancer risk. The NCCN and the American Association for Cancer Research organization include recommendations for upper endoscopy every 2–5 years starting at the age of 25, or 5 years prior to the earliest gastric cancer in the family.[116,117] Currently, European groups do not routinely include recommendations for upper GI surveillance in individuals with LFS.[41,112] As for surveillance outcomes, a recent small study examining upper GI surveillance in LFS showed the most common findings on surveillance being fundic gland polyps and gastritis.[114] Although no upper GI cancers were identified in this study,

concerning pathologic and premalignant findings were observed in 8.6% of the cohort, providing early evidence to support upper GI surveillance in this high-risk population.[114]

Other Syndromes

Colonic Polyposis of Unknown Etiology (CPUE)

Colonic polyposis of unknown etiology (CPUE) is defined as ≥10–20 cumulative lifetime colonic adenomas in the absence of a detectable PV in a polyposis gene. Compared to well-established, defined hereditary polyposis syndromes like FAP and MAP, CPUE can be clinically challenging to manage for both patients and their families, since for this potentially heterogeneous group, guidelines vary and predictive genetic testing is not available to determine which relatives are or are not at risk. Additional background on CPUE with suggested management recommendations based on the cumulative number of polyps have been detailed in another recent review.[118] Furthermore, a recent multicenter study highlighted that 7% of patients with CPUE had evidence of upper GI neoplasia on an index endoscopy, highlighting that consideration of upper GI surveillance should be made in these individuals.[119] Given limited data the absolute risk of gastric cancer in CPUE remains uncertain.

Hereditary Breast and Ovarian Cancer (HBOC)

While PVs in *BRCA1* and *BRCA2* cause hereditary breast and ovarian cancer (HBOC) syndrome, other risks include prostate cancer, pancreatic cancer and melanoma as part of the disease spectrum. Data regarding gastric cancer risk in HBOC has been limited, but several early studies reported increased relative risk, ranging from approximately 2 to 6-fold.[120–122] Recently, the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) evaluated 7618 families with germline *BRCA1/2* PV from 26 study groups to calculate age-specific cancer risks by decade for cancers other than breast or ovarian.[123] After adjusting for ascertainment, 3184 *BRCA1* families and 2157 *BRCA2* families were considered informative for analysis, which amounted to 14,979 carriers and 9296 non-carriers.[123] From this expansive dataset, CIMBA quantified the cumulative gastric cancer risk to age 80 as 1.6% for male and 0.7% for female *BRCA1* carriers and approximately 3.5% for both male and female *BRCA2* carriers, suggesting a modestly increased risk compared to the general population, particularly for males and those with *BRCA2* PVs.[123] Additionally, a large-scale, case-control study from a Japanese biobank of 63,828 patients with common cancer types and 37,086 controls also associated *BRCA1/2* PV with increased gastric cancer risk and estimated the cumulative lifetime risk by age 85 as up to 21.3% for *BRCA1* and 19.3% for *BRCA2*, which reflects the higher gastric cancer rates observed in East Asian countries.[124]

In light of the uncertain absolute risk and the lack of evidence regarding surveillance outcomes, at this time there are no specific recommendations for gastric cancer surveillance in HBOC syndrome. However, it is worth noting that some HBOC guidelines have recently included pancreatic cancer surveillance, which can occur via EUS. It remains unknown whether this will have any impact on detection of malignant or premalignant lesions of the stomach and related outcomes, but careful inspection of the gastric epithelium with a standard upper GI endoscopy should be strongly considered if EUS is being performed.[116,125] More research is needed in this area to understand the mechanisms of gastric carcinogenesis in *BRCA1* and *BRCA2* carriers, as well as whether gastric surveillance should be recommended routinely.

Familial Intestinal Gastric Cancer (FIGC)

Familial intestinal gastric cancer (FIGC) encompasses a clinically defined hereditary gastric cancer risk syndrome without a known molecular etiology.[126] It is characterized by an autosomal dominant inheritance pattern of intestinal-type gastric cancer (IGC) without polyposis.[127] Despite scientific advancements, the underlying genetic explanation remains elusive in FIGC.[128]

Diagnostic criteria for FIGC was proposed by the International Gastric Cancer Linkage Consortium with two sets of criteria depending on the local incidence of gastric cancer.[129] In areas with a high incidence of gastric cancer (eg, East Asia), diagnostic criteria include: (1) at least three relatives diagnosed with IGC with one being a first-degree relative of the other two; (2) two successive generations with IGC; (3) in at least one relative, IGC is diagnosed before the age of 50.[129] In areas with low incidence (eg, North America) diagnostic criteria include: (1) at least two first- or second-degree

relatives diagnosed with IGC, with one diagnosed under age 50; or (2) three or more relatives with IGC diagnosed at any age.[129]

More recently, another group proposed that any family presenting with two GC cases, with one confirmed as IGC, regardless of age of onset, could be considered FIGC.[128] Using these criteria, their analysis showed that FIGC index patients developed GC an average of 10 years earlier than sporadic GC and that 38% of FIGC tumors demonstrated microsatellite instability, compared to 8% of all individuals with sporadic GC.[128,130]

At this time, there are no consensus guidelines to dictate medical management of FIGC. Therefore, surveillance should be individualized based on personal and family history. Some authors have suggested that upper endoscopy should start between the ages of 40–60 years old or 5 years prior to the earliest diagnosis of gastric cancer, with *H. pylori* testing and treatment for all at risk.[126,131] The optimal interval of upper endoscopy is also ill-defined, but could be considered every 1–3 years, with annual endoscopic screening potentially being the most effective at detecting early stage, endoscopically treatable GC.[126,132]

Current Challenges, Limitations and Future Directions

Hereditary cancer predisposition syndromes conferring moderate to high risk of gastric cancer are rare, and for some of these syndromes, gastric cancer remains less prevalent than other cancers in the risk spectrum. This creates challenges to prospectively collect data with sufficient sample sizes to accurately estimate lifetime gastric cancer risks and to assess the outcomes of gastric cancer surveillance, especially with regard to survival.

Additionally, there are no robust prospective case-controlled studies comparing effectiveness of endoscopic management strategies for these syndromes, which are necessary to verify surveillance guidelines successfully reduce cancer risks, prevent complications and are cost effective. Further, there is limited data that supports upper GI surveillance improving survival. At this time, clinicians must rely on expert-led, consensus statements to guide medical management decisions. Although inconsistently mentioned in guidelines related to hereditary gastric cancer risk, there should be a consideration for routine assessment of *H. pylori*, with treatment if positive, to decrease gastric cancer risk for individuals at increased risk of gastric cancer.

Upper endoscopy is the current standard for evaluating for gastric adenocarcinoma. This procedure is considered invasive, typically requires anesthesia, and poses a small, but serious risk for complications, and therefore finding effective non-invasive methods of gastric cancer screening would be valuable. With scientific advances, there is increasing interest in non-invasive screening for cancer using cell-free DNA derived from peripheral blood. A non-invasive multi-cancer early detection test was evaluated through a prospective, case-controlled, observational study; this study reported a 16.7% sensitivity of detecting a stage I gastric cancer.[133] Additional non-invasive screening techniques with higher sensitivity for early stage gastric cancers are thus direly needed.

Further research is also needed to understand the mechanisms of gastric carcinogenesis for these different hereditary syndromes, as these mechanisms will likely differ given the differing genetic etiologies of these syndromes. Better understanding of the mechanisms of carcinogenesis may provide insights for cancer prevention for those individuals who are at highest risk but also could provide insights useful for other populations at risk for gastric cancer as well.

Conclusion

While many factors are associated with increased gastric cancer risk, select hereditary cancer predisposition syndromes confer some of the highest gastric cancer risks among affected individuals. Recognition of these underlying hereditary syndromes in patients can allow for improved estimation of the cumulative lifetime gastric cancer risk and enables tailored gastric cancer surveillance recommendations as per current evidence- and/or consensus-based guidelines. Additionally, detection of a PV in a specific gastric cancer risk gene provides the option for highly informative predictive genetic testing in at-risk relatives, thus identifying affected individuals at highest risk for gastric cancer who may require enhanced gastric surveillance and sparing those who did not inherit the familial PV from unnecessary medical intervention.

However, multiple challenges remain in hereditary gastric cancer predisposition syndromes including the need to more accurately estimate gastric cancer risk amongst and within these syndromes, as well as to better understand how to employ gastric surveillance with respect to age of initiation, surveillance interval, and surveillance modality. Furthermore, understanding whether surveillance is effective in decreasing death from gastric cancer as well as whether it is cost-effective are both critical questions to answer. Developing non-invasive methods for gastric surveillance will be critical as more individuals are identified to carry hereditary cancer predisposition syndromes; continued mindfulness of potentially modifiable environmental (eg, *H. Pylori*) and lifestyle risk factors also remains relevant. As research in this field continues to progress, it remains important to closely follow patients with a hereditary gastric cancer predisposition syndrome, developing a personalized gastric cancer surveillance strategy accounting for evolving guidelines and consensus recommendations, personal history and genetic testing results, family history, as well as patient preferences.

Abbreviations

AFAP, attenuated familial adenomatous polyposis; ACG, American College of Gastroenterology; ASCRC, American Society of Colorectal Surgeons; ACPGBI, Association of Coloproctology of Great Britain and Ireland; BSG, British Society of Gastroenterology; CIMBA, Consortium of Investigators of Modifiers of BRCA1/2; CPUE, colonic polyposis of unknown etiology; DGC, diffuse gastric cancer; ESMO, European Society of Medical Oncology; EUS, endoscopic ultrasound; FAP, familial adenomatous polyposis; FGPs, fundic gland polyps; FIGC, familial intestinal gastric cancer; GAPPS, gastric adenocarcinoma and proximal polyposis syndrome; GI, gastrointestinal; HBOC, hereditary breast and ovarian cancer; HDGC, Hereditary diffuse gastric cancer syndrome; hereditary hemorrhagic telangiectasia, HHT; HLBC, Hereditary Lobular Breast Cancer; HNPCC, hereditary non-polyposis colorectal cancer; IGC, intestinal-type gastric cancer; IGCLC, International Gastric Cancer Linkage Consortium; JPS, juvenile polyposis syndrome; LFS, Li-Fraumeni syndrome; MAP, *MUTYH*-associated polyposis; NCCN, National Comprehensive Cancer Network; PJS, Peutz-Jeghers syndrome; PV, pathogenic or likely pathogenic variant; SRCC, signet-ring cell carcinoma; UKCGG, United Kingdom Cancer Genetics Group; USMSTFCC, US Multi-Society Task Force on Colorectal Cancer.

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