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Gastrointestinal Cancer Precursor Conditions and Their Detection

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INTRODUCTION

Gastrointestinal (GI) cancers are a leading cause of cancer morbidity and mortality.[1] In the United States, GI cancers are predicted to lead to over 170,000 deaths in 2023 alone, accounting for 28% of cancer-related deaths.[1] Many GI cancers arise from distinct precursor lesions, presenting an opportunity for cancer prevention and interception. Hereditary cancer syndromes, in which precursor lesions are common, have informed our understanding of basic biological principles of cancer development and progression, as well as the clinical management of precursor lesions in the broader population. Deleterious monogenic germline variants are thought to lead to approximately 5% to 10% of GI cancers.[2] Polygenic variation also contributes to the risk of GI cancer, including among individuals with a monogenic germline variant.[3] This review will focus on the leading causes of hereditary GI cancer, as well as the management of common precursor lesions of the GI tract.

We review hereditary predisposition to and precursor conditions of the colorectum, stomach and esophagus, and pancreas. Hereditary cancer syndromes often predispose to neoplasm in more than one organ and may be discussed later in more than one section. Hereditary neuroendocrine cancer syndromes and syndromes with insufficient evidence to guide management are outside the scope of this review.

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COLORECTAL CANCER PREDISPOSITION AND PRECURSOR CONDITIONS

Lynch Syndrome

Lynch syndrome (LS) is an autosomal dominant syndrome caused by germline deleterious variants in one of the DNA mismatch repair (MMR) genes—*MLH1*, *MSH2*, *MSH6*, and *PMS2*.[4] Epigenetic silencing of *MLH1* and *MSH2* can also cause LS, the latter secondary to deletions in the *EPCAM* gene.[4] LS is the most common hereditary cause of GI cancer.[5] The population prevalence of LS and the relative frequencies of alterations in each of the MMR genes vary by population.[5-10] In the United States, LS is estimated to affect approximately 1 in 300 to 400 individuals.[5,7,8]

Within the GI tract, LS is associated with colorectal cancer (CRC), small bowel, gastric, and pancreaticobiliary cancers[11,12] (Table 1). The cancer risks associated with LS extend, however, beyond the GI tract and include endometrial, ovarian, urinary tract, prostate, skin, and brain cancers.[11-14] It is important to note that female individuals with LS have a cumulative risk of gynecologic cancers that is of similar or larger magnitude as the risk of colon cancer.[12]

While historically regarded as a single syndrome, there is variation in the cancer risks associated with germline alterations in each of the MMR genes (see Table 1), and management recommendations vary accordingly.[15,16] *MLH1*-LS and *MSH2*-LS are highly penetrant, with a lifetime cumulative risk of LS-cancer of over 70% for both male and female individuals.[12] *MSH2*-LS likely has the broadest spectrum of cancer risk, with a particularly high risk of urinary tract cancer. *EPCAM*-LS is thought to have a similar phenotype as *MSH2*-LS but data are limited. *MSH6*-LS is characterized by a higher lifetime risk of gynecologic cancers than colorectal cancer. *PMS2*-LS is the most common form of LS in the United States, leading to a lifetime risk of LS-cancers of approximately 35%. The cancer risks associated with *PMS2*-LS pertain predominantly to the colon and the endometrium.[12]

Most LS-associated cancers acquire a second, somatic, alteration in the affected MMR gene, leading to DNA MMR deficiency (MMRD) of the tumor. MMRD results in a high rate of mutations of both single nucleotide variations and insertion/deletion mutations, particularly at DNA microsatellites (termed microsatellite instability [MSI]).[4] MMR proficient tumors can also occur in individuals with LS, particularly in *MSH6*-LS and *PMS2*-LS.[17]

The precursor lesions associated with LS and their contribution to cancer risk have been studied primarily in the colon and rectum.[18] Emerging data suggest that there are several molecular pathways of CRC development in LS, underpinning distinct precursor lesions[11,12,19] (Fig. 1). MMRD can occur either early, before the acquisition of key driver mutations, or at a later stage in adenoma development.[18,20] Recent data suggest that early MMRD is the more common pathway.[18,21] Indeed, MMRD has been detected in nondysplastic colonic crypts, suggesting that MMRD can be a very early event, preceding adenoma formation.[21-23] *MSH2*, *MSH6*, and *PMS2* associated CRC is thought to develop commonly by acquisition of somatic mutations in the *APC* gene, leading to adenomatous polyp growth via activation of Wnt signaling (see “Polyposis Syndromes” section).[19,24]

However, some *MLH1*-associated CRCs are hypothesized to evolve directly from colonic crypts, independent of *APC*. These tumors are thought to acquire mutations in *CTNNB1* (beta-catenin) and bypass the adenomatous polyp phase.[18,25,26] Further studies are needed to validate and refine these models of carcinogenesis in LS and determine the associated implications for colonoscopic surveillance.

Frequent colonoscopic surveillance is the mainstay of CRC early detection and prevention in LS (see Table 1). *MLH1*-LS and *MSH2*-LS are characterized by accelerated carcinogenesis, which is thought to develop within 2 to 3 years, in comparison with 10 or more years in sporadic CRC.[27,28] High-quality colonoscopy with polypectomy at frequent intervals reduces the incidence of CRC in individuals with LS.[29]There are limited data regarding the outcomes of upper GI endoscopic surveillance and pancreatic cancer screening among individuals with LS.[30-32] Screening recommendations are discussed in Table 1 and under “Pancreatic cancer predisposition and precursor conditions”.

Beyond the prevention afforded by colonoscopies, high-quality data support the use of aspirin for the prevention of colorectal cancer among individuals with LS.[33,34] The randomized CAPP2 trial demonstrated a reduction in colorectal cancer incidence for individuals with LS who were randomized to aspirin treatment versus placebo (9% vs 13%, HR = 0.65).[33] The CAPP3 trial is ongoing with the goal of determining if lower doses of aspirin are equally effective for chemoprevention in LS (NCT02497820). Recent data suggest that resistant starch, also studied in the CAPP2 trial, may be beneficial for the prevention of upper GI cancers in LS.[35] The mechanisms driving the preventative effects of aspirin and resistance starch in individuals with LS have not been definitively established.

Immunoprevention is actively being explored for individuals with LS. As discussed above, MMRD leads to a high somatic mutational burden in LS-associated cancers. Neoantigens that arise from MMRD are thought to elicit an immune reaction that can restrict cancer growth or lead to cancer regression, both spontaneously and in response to T-cell immune checkpoint inhibitors.[36-38] While immune checkpoint inhibitors are effective for treating established LS-associated cancers with MMRD, it is unclear if they offer a preventative benefit. A study of patients with LS who received immunotherapy for an established malignancy suggests a persistent risk of precursor lesions and malignancy.[39] Cancer vaccines for the prevention of LS-associated cancers are also in clinical development.[40] These include vaccines that target tumor-associated antigens that are not specific to LS (NCT05419011), as well as LS-specific vaccines that target neoantigens that arise as a result of MMRD (NCT05078866).

Polyposis Syndromes

Multiple hereditary cancer syndromes result in polyposis of the GI tract,[41,42] most involving the colon and rectum. Polyposis syndromes vary clinically in their inheritance pattern, molecular etiology, polyp type and burden, and extracolonic manifestations **(**Table 2).

Familial adenomatous polyposis (FAP) is the most common hereditary polyposis syndrome of the GI tract. FAP is an autosomal dominant syndrome caused by pathogenic germline variants in the *APC* gene. Classic FAP is highly penetrant, leading to hundreds to thousands

of adenomatous polyps in the colon and rectum, and a lifetime CRC risk of virtually 100%. Attenuated FAP is clinically distinguished from classic FAP as a syndrome with less than 100 colonic polyps; it is associated with germline alterations in the 3′ or 5′ portion of the *APC* gene.[43] Individuals with FAP often have polyposis of the upper GI tract, as well, leading to cancers of the stomach, small bowel, and ampulla of Vater.[44-47] Additional tumors associated with FAP include desmoid tumors, thyroid cancer, hepatoblastoma, and medulloblastoma.[48-50]

CRC carcinogenesis in FAP is driven by a somatic second hit in the *APC* gene.[51,52] This in turn leads to unopposed β-catenin activity, activating the Wnt signaling pathway, as well as chromosomal instability.[24] Germline alterations in *RNF43* and *AXIN2* also lead to polyposis via the Wnt signaling pathway, though they cause phenotypically distinct syndromes from FAP.[53] Acquired somatic mutations in additional oncogenes (eg, *KRAS*) or tumor suppressor genes (eg, *TP53*) are thought to drive tumorigenesis, in a process similar to the sporadic adenoma to carcinoma process.[54,55] Spatially separated tumors can originate from the same cancer-primed cell in patients with FAP, indicating that somatic alterations may occur in a macroscopically normal epithelium, before the appearance of clinically identifiable adenomas.[56] Multiple other mechanisms of polyposis exist, including alterations in kinase and phosphatase activity, DNA base excision repair, DNA polymerase activity, TGF-β signaling, and others (see Table 2).

Esophagogastroduodenoscopy (EGD) and colonoscopy are the mainstay of cancer early detection for individuals with polyposis syndromes (see “Management of precursor lesions” below). Small bowel visualization with video capsule endoscopy or CT/MRI enterography is recommended for syndromes with a high risk of small bowel cancer (see Table 2). In polyposis syndromes with a low to moderate polyp burden, endoscopic management serves as the primary prevention strategy. However, when endoscopic management is not feasible because of a high polyp burden, prophylactic surgery, including colectomy/proctocolectomy, pancreaticoduodenectomy, and/or gastrectomy, may be considered.

Chemoprevention and chemointerception trials have been conducted almost exclusively for FAP. Sulindac and other NSAIDs have been evaluated in several trials as monotherapy or in combination with other agents.[57,58] The combination of the NSAID sulindac and the EGFR inhibitor erlotinib has been shown to reduce colorectal and duodenal polyp burden in FAP over short-term follow-up.[59,60] An irreversible inhibitor of ornithine decarboxylase, eflornithine, has been suggested to have a role in the prevention of colonic disease progression in FAP, but further studies are needed to confirm these findings.[61] Despite demonstrating a reduction of polyp burden, these regimens have not been definitively shown to alter clinical management for individuals with FAP and have not received Food and Drug Administration approval for this indication.

Management of precursor lesions

Colorectal polyps.—CRC screening is recommended for all asymptomatic adults aged 45 years or older who are at an average risk of CRC.[62,63] The recommended age to initiate screening was changed from 50 to 45 years in recent years because of an increasing incidence of young-onset CRC. The causes of this increase in CRC incidence are poorly

understood, but they have been largely attributed to lifestyle and environmental factors, as this increased risk is associated with a birth-cohort effect. Individuals born around 1990 have up to 4 times the risk of rectal cancer and twice the risk of colon cancer of individuals born around 1950.[64-66] Various screening strategies are now recommended for individuals at average risk for CRC, including stool-based tests, CT colonography, sigmoidoscopy, and colonoscopy.[63]

Colonoscopy is performed in the setting of routine colon cancer screening, but also as follow-up of abnormal CRC screening tests, surveillance postpolypectomy or CRC resection/treatment, or for diagnostic purposes.[67] Colonoscopy can prevent CRC through the disruption of precursor lesions, such as polyps, including tubular adenomas and sessile serrated polyps (SSPs).[68] The sensitivity of stool-based and blood-based tests for precursor lesions is limited,[62,69,70] and positive findings require follow-up with a colonoscopy. The development of these polypoid lesions and CRC occurs through 3 distinct pathways, the chromosomal instability, the MSI, and the CpG island methylator phenotype.

Risk factors for the development of traditional adenomas and SSPs include smoking, obesity, and heavy alcohol use.[71] Physical activity and the use of aspirin is associated with a lower risk of developing adenomas and an advanced adenoma or large SSP, respectively. These risk factors largely mirror risk factors for CRC development,[71] although the association of aspirin use with a decreased risk of CRC has been called into question.[72] The presence of one or more of these risk factors does not typically alter CRC surveillance recommendations.[63] Apart from the hereditary syndromes discussed earlier, there are additional personal and familial risk factors that warrant specialized surveillance, the specifics of which are outside the scope of this review. These include a personal history of inflammatory bowel disease, cystic fibrosis, and childhood cancer treated with chemotherapy or abdominal radiation therapy and a family history of CRC without a detectable pathogenic germline variant.[73-77]

Individuals with precancerous colorectal polyps have a higher risk for colorectal cancer compared to the general population and thus interval surveillance colonoscopy will be based on age, personal history, genetic susceptibility, family history, procedural findings, prep quality, examination quality, and comorbidities.[67]

Overall, individuals that are found to have an adenoma at baseline colonoscopy, have a 1.3 fold risk of developing CRC compared to the general population.[78] Adenomas can be risk stratified as a low-risk adenoma (<10 mm in size), advanced adenoma (≥10 mm in size, tubulovillous or villous histology, high-grade dysplasia), advanced neoplasia (advanced adenoma or CRC), or high-risk adenoma (advanced neoplasia or ≥3 adenomas).[67] Patients who are found to have an advanced adenoma compared to a non-advanced adenoma have a higher risk of developing CRC compared to the general population (Standardized incidence ratios of 2.23 and 0.68, respectively).[78] Patients undergoing routine recommended surveillance colonoscopy for an advanced adenoma have a 2.05% 10-year cumulative risk of developing CRC.[78] Furthermore, among patients found to have an SSP or SSP with dysplasia compared to no polyps, the odds of developing CRC are 3 fold and 5 fold, respectively.[79]

Risk-stratification as well as timing of surveillance colonoscopy after baseline colonoscopy for both adenomas and SSPs are based on number of polyps, size of polyps, and histology (Fig. 2). These recommendations have been previously summarized and well described.[67]

Importantly, the recommended interval for the second-surveillance colonoscopy among postpolypectomy patients is based on the risk-stratification of findings identified on baseline and first-surveillance colonoscopies.[67] Overall, colonoscopy provides the opportunity to remove precursor CRC lesions and to intercept CRC early when it is more amenable to treatment and surgical options.

GASTROESOPHAGEAL CANCER PREDISPOSITION AND PRECURSOR CONDITIONS

Hereditary Syndromes

Several hereditary cancer syndromes predispose to gastric cancer (Table 3). The prevalence of any germline alteration in cancer predisposition genes among patients with gastric cancer is in the range of 10%,[80-82] but causality has only been established for a limited number of genes. Overall, it is estimated that 3% to 5% of gastric cancers can be attributed to monogenic hereditary cancer syndromes.

Hereditary diffuse gastric cancer (HDGC) is a gastric-cancer predominant syndrome.[83,84] HDGC is caused by germline deleterious alterations in *CDH1*, encoding the E-cadherin gene, a major component of the adherens junction of epithelial cells.[85] HDGC is associated with diffuse type gastric cancer with signet ring cell morphology, as well as lobular breast cancer. The cancer risk associated with HDGC is still being refined. Initial estimates were likely inflated because of ascertainment bias; a large proportion of families with germline alterations in *CDH1* do not meet clinical criteria for HDGC and are found incidentally.[86-88] Germline alterations in *CTNNA1* also predispose to diffuse gastric cancer,[83,84,89,90] but the risk of lobular breast cancer has not been established.[91] *CTNNA1* encodes the alpha-catenin protein, also an adherens junction protein.[92]

The precursor lesions of HDGC are microscopic signet-ring cell foci. These include lesions replacing the normal gland cells (in situ signet-ring cell carcinoma) or pagetoid spread of signet-ring cells below the preserved epithelium.[85] In approximately 95% of cases of HDGC associated with *CDH1* germline alterations, foci of signet-ring cells are detected in the lamina propria (stage T1a). The discrepancy between the nearubiquitous finding of T1a lesions and the partial penetrance of diffuse gastric cancer suggests that many T1a lesions have indolent behavior and do not progress rapidly to advanced cancer. The recommended management for individuals with HDGC has been to consider a prophylactic total gastrectomy at an early age (see Table 3), before invasive cancer develops.[85,93] Specialized endoscopic surveillance protocols, which include multiple biopsies, have been proposed as a method of cancer interception for individuals who do not undergo prophylactic gastrectomy.[94-96] Accumulating experience from the implementation of such protocols suggests that endoscopic surveillance may be an alternative to surgery in individuals with *CDH1* alterations who decline total gastrectomy. However, predictors of progression are not

well defined, and there are no sufficiently reliable methods to detect progression when it occurs.

There are no established nonoperative interventions to prevent gastric cancer in HDGC. As a presumed modifiable risk factor, *Helicobacter pylori* detection and eradication are recommended,[85] and this recommendation extends to other hereditary cancer syndromes that may predispose to gastric cancer, such as LS.

Hereditary predisposition to esophageal cancer is less well characterized. Rare syndromes that predispose to *squamous cell* carcinoma of the esophagus have been described, including Tylosis with esophageal cancer,[97-99] Bloom syndrome,[100] and Fanconi anemia.[101] Screening recommendations are based on limited data but include consideration of an upper endoscopy starting at early adulthood.[102] Hereditary predisposition to esophageal *adenocarcinoma* (EAC) is less well understood, and there is no consensus regarding specific screening recommendations. There is notable overlap between the genes proposed to predispose to EAC and gastric adenocarcinoma. Recent data suggest that pathogenic variants in *ATM* and *TP53* predispose to EAC, as well as to progression from its precursor lesion, Barret's esophagus (BE), to adenocarcinoma.[103] Genes involved in the DNA homologous recombination pathway (eg, *BRCA1/2*) have also been suggested to predispose to gastroesophageal cancer[80-82,103] but causality has not been definitively established.

Management of Precursor Lesions

Gastric intestinal metaplasia—Gastric intestinal metaplasia (GIM) is a precursor lesion for gastric adenocarcinoma as it may develop into dysplasia, which may progress to gastric cancer.[104] GIM can be further characterized by histologic subtype as incomplete (has some colonic type intestinal metaplasia [IM]) versus complete (small intestinal type IM) and anatomic location as extensive (involves the gastric body and either the antrum and/or incisura) versus limited (only involves the gastric antrum and/or incisura). Individuals with incomplete and/or extensive GIM have the highest risk of progressing to gastric cancer.[105] Higher risk patients with GIM include individuals with incomplete and/or extensive GIM or individuals with a family history of gastric cancer. In addition, patients at an overall increased risk for gastric cancer, include individuals who immigrated from high gastric cancer incidence regions and individuals from historically marginalized racial/ethnic backgrounds.[105]

Among patients who have had gastric biopsies, the prevalence of GIM is approximately 4.8%.[106] At 5 year follow-up, the cumulative incidence of gastric cancer among individuals with GIM is 1.1% and 1.6% at 10 years.[107] Importantly, this prevalence and incidence data were drawn from studies conducted in North America, South America, Europe and Asia, where population risk differs across regions.[107]

In Asian countries, particularly Eastern Asia, there is a higher incidence and mortality rate associated with gastric cancer, with some risk factors including higher rates of *H pylori* infection, diet, and hereditary predisposition, as mentioned above.[108] As a result, some countries in that region have implemented national screening guidelines that are associated with reductions in gastric cancer mortality.[109]

However, the United States is considered a low-incidence country with 26,500 gastric cancer cases diagnosed in 2023, with the most common location of gastric cancer being noncardia gastric cancers.[110] As a result, population-based screening initiatives have not been implemented. However, incidentally identified GIM on endoscopic biopsies has led to the development of practice guidelines on how to best manage these findings routinely.[105]

Eradication of *H pylori* with eradication confirmation is recommended for patients with GIM and *H pylori*.[105] Among patients with incidentally identified GIM, endoscopic surveillance every 3 to 5 years with random biopsies of the gastric body and antrum as well as targeted biopsies of any concerning lesions, can be considered based on informed discussions regarding the risks/benefits of the procedure as a reduction in gastric cancer mortality has not yet been delineated.[105]

Lastly, guidelines also do not recommend short-interval endoscopy to risk stratify patients with incidentally identified GIM. However, based on informed clinical discussions, patients who are at higher risk, as delineated earlier, or patients who had any high-risk lesions or concerns regarding the thoroughness of their initial endoscopic evaluation can undergo a repeat upper endoscopy in 1 year for further risk stratification (ie, anatomic extent and histologic subtype).[105]

Barrett's esophagus—BE describes the replacement of normal esophageal squamous epithelium by metaplastic columnar epithelium with goblet cells.[111] This metaplastic mucosal change in the distal esophagus is also denoted as IM and is associated with chronic gastroesophageal reflux disease (GERD).[112] Approximately 5% to 12% of patients with chronic GERD develop BE.[113,114] BE is considered the precursor lesion for EAC with histologic progression from BE with no dysplasia to low-grade dysplasia, high-grade dysplasia, and ultimately EAC.[115]

As BE can be a clinically silent disease, prevalence estimates are predominately based upon patient populations that present for endoscopic evaluation in the setting of GERD symptoms. In the United States, the prevalence of BE is estimated to be 5.6%, with other estimates ranging from 0.4 to greater than 20% in the general population based on the population studied and diagnosis study criteria.[116-120] Compared to the general population, individuals with BE have a 10 fold to 55 fold risk of developing EAC.[121] Among individuals with high-grade dysplasia (HGD) specifically, the incidence of developing EAC within the first 7 years of diagnosis is 6.58 per 100 patient-years.[122]

Risk factors for BE include age over 50 years, central obesity, tobacco use, and family history.[112] In addition, White race and male sex are risk factors for BE with BE being more common in White and male populations and uncommon in Black, Asian/Pacific Islander, and female populations.[112,123] As a result, the American College of Gastroenterology recommends screening endoscopy for individuals with chronic GERD symptoms and 3 or more of the risk factors delineated above including a family history of BE or EAC in one or more first-degree relatives.[124] The American Gastroenterological Association has similar recommendations.[125]

Endoscopic suspicion of BE requires that columnar epithelium be identified at least 1 cm or more proximal to the gastroesophageal junction.[112] When BE is suspected on initial white-light endoscopy, this mucosal change is characterized by a salmon-colored mucosa.[112] Once suspected, at least 8 endoscopic biopsies are recommended to identify the presence of IM.[112] The Seattle Biopsy Sampling Protocol is recommended by multiple societies and targeted biopsies of any identified mucosal abnormalities are also indicated.[112,126] If IM is not identified, a repeat endoscopy with biopsies is recommended in 1 to 2 years.[112] However, if IM is identified, this mucosal change is further stratified into BE with no dysplasia, BE with indefinite dysplasia (IND), and BE with low-grade dysplasia (LGD), HGD, or early EAC.[112] If dysplasia or EAC is suspected, pathologic confirmation by a second pathologist with GI expertise is recommended for appropriate risk-stratification.[112,127]

The surveillance interval for BE with no dysplasia is based on the length of the BE segment. Among individuals with a BE segment of less than 3 cm, a repeat surveillance endoscopy is recommended in 5 years.[112] Among individuals with a BE segment of 3 cm or greater, a repeat endoscopy is recommended in 3 years.[112] In patients found to have BE with IND, treatment with a twice daily proton pump inhibitor and a repeat endoscopy within 6 months is recommended.[112]

Surveillance and management of individuals found to have LGD, HGD, intramucosal carcinoma (T1a), or submucosal cancer (T1b) are well described and briefly summarized here.[68,82] For individuals found to have LGD, an informed discussion regarding the risks and benefits of surveillance versus endoscopic eradication therapy (EET) is recommended.[112] Among patients who proceed with EET the primary endpoint is complete eradication of IM (CEIM), with ongoing surveillance endoscopy at specified intervals thereafter.[112] Among patients with HGD or intramucosal carcinoma (T1a), EET with a goal of CEIM is recommended followed by ongoing surveillance endoscopy also at specified intervals thereafter.[112,127]

Importantly, among patients with BE, chemoprophylaxis with proton pump inhibitor therapy can reduce the progression to EAC and remains an integral part of clinical management.[128]

PANCREATIC CANCER PREDISPOSITION AND PRECURSOR CONDITIONS

Hereditary Syndromes

Several distinct syndromes predispose to hereditary pancreatic cancer (HPC), including alterations in the DNA double-strand break repair pathway (specifically in the *ATM*, *BRCA2*, *BRCA1*, and *PALB2* genes), Lynch syndrome, Li-Fraumeni syndrome, and others (Table 4). Taken together, these syndromes account for approximately 10% of pancreatic adenocarcinoma (PDAC) cases.[129-131] The lifetime risk of PDAC differs significantly depending on the affected gene, with a particularly high risk with germline alterations in *STK11* and *CDKN2A*. There are insufficient data regarding PDAC risk modifiers among individuals with HPC; family history is used in clinical practice to guide screening recommendations.[132,133]

The precursor lesions of PDAC include pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN).[134,135] PanIN is a microscopic lesion that is thought to be the precursor lesion for most PDACs. Pan-INs can be classified based on their histologic appearance as low grade and high grade; the latter is considered carcinoma in situ. The progression from PanIN to PDAC is thought to occur via sequential acquisition of somatic alterations in key oncogenes (*KRAS*) and tumor suppressor genes (*CDKN2A*, *TP53*, and *SMAD4*). *KRAS* alterations are thought to represent the earliest somatic driver, with over 90% of PDAC harboring a somatic *KRAS* alteration. IPMNs are macroscopic cystic lesions arising from the pancreatic ductal system (see “Management of Precursor Lesions” section for additional details). IPMNs are thought to harbor somatic alterations similar to PDAC but an enrichment of alterations in *GNAS* and *RNF43* in IPMNs has been described.[136] PanIN and IPMN can co-occur.[137] Mucinous cystic neoplasms (MCNs) can also progress to pancreatic cancer; MCNs are less common than IPMNs.[138]

Accumulating data from clinical trials demonstrate that screening for PDAC among individuals with HPC can detect PDAC at earlier stages. Correspondingly, screen-detected PDAC is associated with dramatically improved long-term survival.[137,139,140] Screening is associated with a high rate of detection of pancreatic cysts that require further imaging or biopsies,[141,142] as well as a less than 5% chance of undergoing surgery that is of low yield or deemed not necessary after review of final pathology.[143,144] Current screening criteria and methods are presented in Table 4. There is no high-quality data regarding PDAC prevention among individuals with HPC, but vaccines targeting common somatic *KRAS* alterations are being developed.[145]

Management of Precursor Lesions

Intraductal papillary mucinous neoplasms—Pancreatic IPMNs are mucinous cystic lesions that are a precursor for PDAC. IPMNs may progress from a benign IPMN to IPMN with LGD, IPMN with HGD, and invasive carcinoma.[146] These mucinous neoplasms are characterized based on the location of pancreatic duct involvement as a main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), or mixed type IPMN. It is difficult to discern the incidence of IPMNs, as individuals may be asymptomatic and/or have very small lesions. Previous studies assessing the prevalence of pancreatic cystic lesions that were found incidentally on cross-sectional abdominal imaging, found a prevalence ranging from 2.6% to 13.5% and a mean cyst diameter from 7.4 to 8.9 mm.[147,148]

Among those diagnosed with an IPMN, the median age at time of diagnosis is 66 to 67 years with BD-IPMNs being more commonly an incidental finding compared to MD-IPMNs or mixed-duct IPMNs.[149] In addition, most individuals with IPMNs do not have a family history of PDAC.[149] Despite this, patients with MD-IPMN or mixed-type IPMN have a 57% to 92% risk of developing an IPMN-associated carcinoma whereas patients with BD-IPMN have a 6% to 46% risk.[149,150]

Given the malignant potential of IPMNs, there are various national and international guidelines highlighting management considerations including surveillance and surgical recommendations for pancreatic cysts.[150-153] The most recently published Kyoto guidelines focus specifically on IPMNs and will be discussed in more detail. The Kyoto guidelines

recommend considering surgery among individuals found to have “high-risk stigmata” of HGD or malignancy. These high-risk features include main pancreatic duct (MPD) of 10 mm or greater, an enhancing mural nodule of 5 mm or greater, obstructive jaundice in an individual with a pancreatic head cystic lesion, or patients with suspicious or positive cytology.[154] Worrisome features prompting additional evaluation can be subdivided as clinical (acute pancreatitis, elevated CA 19-9, newly diagnosed or acutely exacerbated diabetes in the last year) or imaging features (cyst ≥3 cm, enhancing mural nodule <5 mm, thickened/enhancing cystic walls, MPD 5–9 mm, abrupt change in pancreatic duct caliber with distal pancreatic atrophy, lymphadenopathy, cystic growth rate of ≥2.5 mm/12 mo).[154] Subsequent potential surgical evaluation versus surveillance is based on patient symptoms, including repeated bouts of acute pancreatitis, the presence of more than one worrisome feature, surgical candidacy and cystic size. Surveillance intervals with multidetector computed tomography, magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) are based on the largest cyst size.[154] Overall, other guidelines, also provide surgical, endoscopic, or imaging recommendations based on risk stratification and IPMN size criteria.[151,153]

However, the Kyoto guidelines are not specifically designed for high-risk individuals, who have a personal or familial/genetic risk for PDAC. The Cancer of the Pancreas Screening Studies Consortium has released a consensus statement on the management of pancreatic cysts in high-risk populations.[137] As a result, it is imperative to interpret cystic guidelines within the context of the populations they are targeted for.

SUMMARY

Hereditary cancer syndromes of the GI tract result in a wide variety of precursor lesions and biological processes of cancer development and progression. Individuals with hereditary predisposition to cancer are ideal candidates for efforts aimed at improving early detection, such as those leveraging blood-based cancer detection. Similarly, cancer surveillance and interception are suited for individuals with nonhereditary precursor lesions. Further clinical and preclinical research is needed to inform future studies in these fields.

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KEY POINTS

- Many gastrointestinal cancers arise from detectable precursor lesions, presenting an opportunity for cancer prevention and interception.
- Hereditary cancer syndromes inform our understanding of cancer development and progression, as well as the management of cancer precursor lesions.
- Further research is needed to advance chemoprevention and immunoprevention strategies for individuals with hereditary cancer syndromes and individuals with nonhereditary cancer precursor lesions.

CLINICS CARE POINTS

- Hereditary cancer syndromes predispose to a variety of GI malignancies and precursor lesions. Screening, surveillance, and management recommendations differ based on the gene in which a germline pathogenic variant is identified, as well as clinical factors.
- LS is the most common GI cancer hereditary syndrome. LS increases the risk of malignancy in multiple GI organs, requiring multimodality surveillance, often at an early age. LS-specific cancer prevention with aspirin and resistant starch has been shown to be effective.
- Predisposition to gastric cancer is particularly high in HDGC syndrome. Prophylactic gastrectomy should be considered in young adulthood.
- The most common hereditary cancer syndromes, including LS and *BRCA1/2*-associated hereditary breast and ovarian cancers, also predispose to pancreatic cancer. Pancreatic cancer surveillance can detect cancer at earlier stages, leading to favorable long-term outcomes, but these encouraging results have only been demonstrated for high-risk populations undergoing screening at specialized centers.
- Multiple hereditary syndromes lead to colonic polyposis, with varying malignancy risk of extracolonic and extra-GI tract organs.
- Precursor lesions of the GI tract, including colorectal polyps, BE, GIM, and IPMNS, can occur in the absence of a diagnosed hereditary cancer syndrome, and warrant specialized surveillance and management.

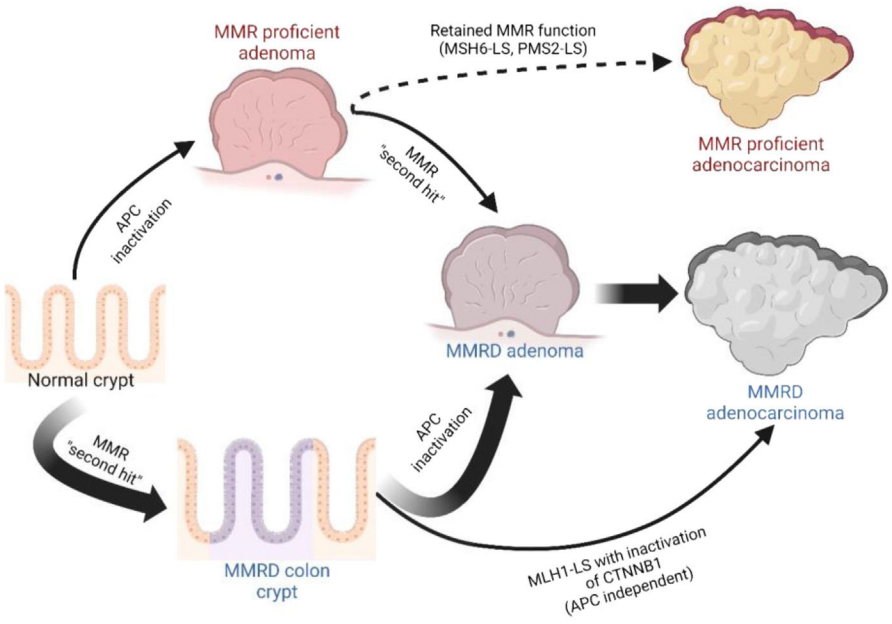

Fig. 1.

LS colorectal cancer development and progression differs across MMR genes. Most LS-associated colorectal cancers are thought to arise via early acquisition of somatic MMRD, followed by progression to MMRD adenoma and carcinoma. In *MLH1*-LS, direct progression to carcinoma without an intermediate adenoma phase may occur. MMRD can also be acquired after an adenoma has developed. In a minority of cases, MMR-proficient adenomas may progress to MMR-proficient adenocarcinomas, particularly in *MSH6*-LS and *PMS2*-LS. Figure created with BioRender.com.

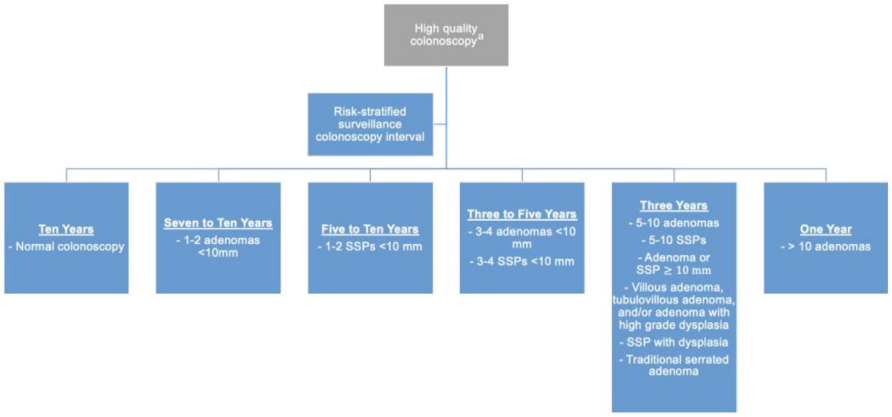

Fig. 2.

Recommendations for timing of surveillance colonoscopy after polypectomy of an adenoma or SSP. [a]High quality colonoscopy as defined by the 2020 US Multi-Society Task Force on Colorectal Cancer (*Adapted with permission from* Elsevier: Gupta S, Lieberman D, Anderson JC, et al. Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc. 2020;91(3):463-485.e5. https://doi.org/10.1016/j.gie.2020.01.014. Please refer to the US Multi-Society Task Force on Colorectal Cancer for additional recommendations on follow-up colonoscopy for hyperplastic polyps.)

Table 1

Lynch syndrome gastrointestinal cancer risk and management recommendations [2,15,16,41]

	MLH1		MSH2/EPCAM		MSH6		PMS2	
GI organ	**Cancer risk estimate**	**Screening recommendations**	**Cancer risk estimate**	**Screening recommendations**	**Cancer risk estimate**	**Screening recommendations**	**Cancer risk estimate**	**Screening recommendations**
Colon and rectum	46%–61%	Colonoscopy every 1–2 y, starting at age 20–25 y[a]	33%–52%	Colonoscopy every 1–2 y, starting at age 20–25 y[a]	10%–44%	Colonoscopy every 1–3 y, starting at age 30–35 y[a]	8.7%–20%	Colonoscopy every 1–3 y, starting at age 30–35 y[a]
Stomach	5%–7%	EGD every 2–4 y, starting at age 30–40 y[b]	0.2%–9.0%	EGD every 2–4 y, starting at age 30–40 y[b]	≤1%–7.9%	EGD every 2–4 y, starting at age 30–40 y[b]	Insufficient data	*Consider* EGD every 2–4 y, starting at age 30–40 y[b]
Small bowel	0.4%–11 %	See stomach	1.1%–10%	See stomach	≤1%–4%	See stomach	0.1%–0.3%	See stomach
Pancreas	6.20%	Consider annual screening starting at age 50, if meeting family history criteria[c]	0.5%–1.6%	Consider annual screening starting at age 50 y, if meeting family history criteria[c]	1.4%–1.6%	Consider annual screening starting at age 50 y, if meeting family history criteria[c]	≤1% to 1.6%	Insufficient data to recommend screening[c]
Biliary tract	1.9%–3.7%	No specific recommendations	0.02%–1.7%	No specific recommendations	0.2%≤1%	No specific recommendations	0.2% to ≤1%	No specific recommendations

[a] Or 2–5 y earlier than the earliest CRC in the family, whichever is earlier.

[b] Testing for *H pylori* and eradication, if positive, is recommended.

[c] Pancreatic cancer (PDAC) screening is currently to be considered in the setting of ≥1 first-degree or second-degree relative with pancreatic cancer. Screening is performed annually, alternating between MRCP and EUS. Screening should begin 10 y before the earliest PDAC in the family or at the age of 50 y, whichever is earlier.

Table 2

Polyposis syndromes of the gastrointestinal tract [2,15,41,42]

Polyposis Syndrome	Gene(s)	Molecular Pathway	Colonic Polyposis Phenotype	Colon Cancer Risk	Colon Cancer Risk management[a]	Extracolonic GI Polyposis/Cancer Risk and management[a]	Extra-GI Cancer Risk
Classic FAP	APC	Wnt signaling	≥100 adenomas	100%	Colectomy with ileorectal anastomosis, or total proctocolectomy with ileal pouchanal anastomosis, or proctocolectomy with end ileostomy. When applicable, the remaining bowel should undergo endoscopic surveillance every 6–12 mo	Gastric, duodenal, and ampullary cancer: EGD including complete visualization of the ampulla of Vater at age 20–25 y or earlier based on family history, with further intervals dependent on findings. Pancreatic cancer: no specific screening recommendations	Intra-abdominal desmoid tumors, thyroid cancer, hepatoblastoma, medulloblastoma, and other central nervous system (CNS) cancers
Attenuated FAP	APC	Wnt signaling	10–<100 adenomas	70%	Colonoscopy every 1–2 y. Surgical approaches as in classic FAP may be warranted depending on phenotype	Gastric, duodenal, and ampullary cancer: EGD including complete visualization of the ampulla of Vater at age 20–25 y or earlier based on family history, with further intervals dependent on findings	Thyroid cancer
GAPPS	APC	Wnt signaling	No polyposis	Insufficient data	Colonoscopy at time of diagnosis to exclude colon polyposis	Stomach fundic gland polyposis and cancer risk: annual gastroscopy from age 15 y. Consider risk-reducing total gastrectomy from third decade. Pancreatic cancer: no specific screening recommendations	No definitive risk
MAP	Biallelic MUTYH (AR)	DNA base excision repair	10–100; adenomas and hyperplastic polyps > serrated, sessile serrated, mixed polyps	70%–90%	Colonoscopy every 1–2 y. Surgical approaches as in classic FAP may be warranted for an adenoma burden that cannot be handled endoscopically	Gastric, duodenal and ampullary cancer: EGD including complete visualization of the ampulla of Vater at age 20–25 y or earlier based on family history, with further intervals dependent on findings	No definitive risk
Juvenile polyposis	SMAD4, BMPR1A	TGF-β/BMP signaling	≥5 Hamartomatous/ juvenile polyps	50%	Colonoscopy starting at 12–15 y. If polyps are found, repeat every 2–3 y or sooner based on findings. If no polyps, then resume at 18 y every 1–3 y	Stomach cancer: EGD starting at 12–15 y. If polyps are found, repeat every 2–3 y or earlier based on findings. If no polyps, then resume at 18 y every 1–3 y	No definitive risk
Polymerase proofreading associated polyposis	POLD, POLE	DNA proofreading and replication	30 – >100 adenomas	>20%	Colonoscopy at 25–30 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y	Insufficient data	Insufficient data

Polyposis Syndrome	Gene(s)	Molecular Pathway	Colonic Polyposis Phenotype	Colon Cancer Risk	Colon Cancer Risk management[a]	Extracolonic GI Polyposis/Cancer Risk and management[a]	Extra-GI Cancer Risk
Peutz-Jeghers	STK11 (LKB1)	Serine/ threonine protein kinase activity	≥2 Peutz-Jeghers-type hamartomatous polyps	39%	Colonoscopy starting at 8–10 y. If polyps are found, repeat every 2–3 y. If no polyps, then resume at age 18y	Stomach and small intestine cancer: EGD at intervals as colonoscopy. Small bowel visualization (video capsule endoscopy or CT/MRI enterography) at baseline with follow-up interval based on findings, but at least by age 18 y, then every 2–3 y. Pancreatic cancer: MRCP/EUS annually, starting at 30–35 y or 10 y earlier than the earliest diagnosis in the family	Breast, endometrial, cervical, lung, ovarian, and testes
PTEN hamartoma tumor syndrome	PTEN	Phosphatase activity, PI3K/AKT	0 – >100; mixed polyposis: hamartomas, hyperplastic, adenomas, inflammatory, ganglioneuromas	11%–20%	Colonoscopy, starting at age 35 y unless symptomatic or if close relative with CRC before age 40 y, then start 5–10 y before the earliest known CRC in the family. Colonoscopy should be done every 5 y	No definitive risk	Breast, thyroid, endometrial, kidney cancer, and melanoma
NTHL1 tumor syndrome	Biallelic NTHL1 (AR)	DNA base excision repair	1–100; adenomas > serrated, sessile serrated, hyperplastic polyps	>20%	Colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y	Duodenal cancer: insufficient data	Breast, endometrial, urothelial carcinomas, hematologic malignancies, squamous cell carcinoma of the head, neck, and cervix
Serrated polyposis syndrome	RNF43, (MUTYH)	Wnt signaling, (DNA base excision repair)	5 – >100; serrated lesions/polyps (hyperplastic polyp, sessile serrated lesion without or with dysplasia, traditional serrated adenoma, and unclassified serrated adenoma)	Insufficient data	Colonoscopy until all polyps ≥5 mm are removed, then colonoscopy every 1–3 y depending on findings	Insufficient data	Insufficient data
Hereditary mixed polyposis syndrome	GREM1	TGF-β/BMP signaling	Mixed polyposis; adenomas and a unique polyp composed of a mixture of hyperplastic polyp and inflammatory polyp–type changes are the most frequent	11%–20%	Colonoscopy at age 25–30 y and repeat every 2–3 y if negative If polyps are found, colonoscopy every 1–2 y	Insufficient data	Insufficient data
Constitutional MMR deficiency	Biallelic PMS2, MSH6, MLH1, MSH2 (AR)	DNA MMR	0 - > 100	Insufficient data	Annual colonoscopy starting at age 6 y. Once polyps are identified, repeat every 6 mo	Small intestine polyposis and cancer: EGD and video capsule endoscopy starting at 8 y	Hematologic, CNS, sarcomas, and genitourinary

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Polyposis Syndrome	Gene(s)	Molecular Pathway	Colonic Polyposis Phenotype	Colon Cancer Risk	Colon Cancer Risk management[a]	Extracolonic GI Polyposis/Cancer Risk and management[a]	Extra-GI Cancer Risk
AXIN2	AXIN2	Wnt signaling	0 – >100, mainly adenomas	Insufficient data	Colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y	Insufficient data	Insufficient data
MBD4-associated neoplasia syndrome	Biallelic MBD4 (AR)	DNA base excision repair	15–100+ adenomas	Insufficient data	Colonoscopy at age 18–20 y or date of diagnosis and repeat every 2–3 y if negative	Insufficient data	Acute myeloid leukemia, uveal melanoma
MSH3-associated polyposis syndrome	Biallelic MSH3 (AR)	DNA mismatch repair	30 – >100 adenomas	Insufficient data	Colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y	Insufficient data	Insufficient data
MLH3-associated polyposis syndrome	Biallelic MLH3 (AR)	DNA MMR	30 – >100 adenomas	Insufficient data	Begin high-quality colonoscopy at age 25–30 y and repeat every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y	Insufficient data	Insufficient data

[a]Surgical resection should be considered for high-risk lesions or when polyps cannot be managed endoscopically in the colon, stomach, and small bowel. AR, autosomal recessive.

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Table 3

Hereditary cancer syndromes predisposing to gastric cancer [2,85,93]

Gene/s	Gastric Cancer Risk	Gastric Cancer Risk management[a]	Other Cancer Risks
CDH1	33%–42%	Prophylactic total gastrectomy at age 18–40 y, or earlier if there is a family history of gastric cancer at an age <25 y. Individuals who elect not to undergo prophylactic gastrectomy should be offered screening every 6–12 mo by upper endoscopy with multiple random biopsies	Lobular breast cancer
CTNNA1	49%–57%	Insufficient data to guide management. Consider management similar to CDH1	Insufficient data
Lynch syndrome (MLH1, MSH2/ EPCAM, MSH6, PMS2)	See Table 1	See Table 1	See Table 1
Juvenile polyposis syndrome (SMAD4)	21%	See Table 2	See Table 2
Peutz-Jeghers syndrome (STK11)	29%	See Table 2	See Table 2
FAP (APC)	2%	See Table 2	See Table 2
Li-Fraumeni syndrome (TP53)	10.7%	EGD every 2–5 y starting at age 25 y	See Table 4
BRCA2, ATM, PALB2, BRCA1	Insufficient data	Insufficient data to guide management	See Table 4

[a]Testing for *H pylori* and eradication if positive can be considered regardless of recommendations for endoscopic surveillance or surgery.

Table 4

Hereditary pancreatic cancer syndromes[2,132,133]

Gene	PDAC Risk	Additional Criteria Suggested for PDAC Screening eligibility[a]	Age of Initiating PDAC screening[b]	Extrapancreatic GI Cancer Risk	Extra-GI Cancer Risk
STK11	32%–54%	No additional criteria	30–35	See Table 2	See Table 2
CDKN2A	>15%	No additional criteria	40	Insufficient data	Melanoma; limited data suggests sarcoma, nerve sheath tumors, and other cancers
ATM	5%–10%	Family history	50	Possibly gastric and colon cancer	Breast, prostate, and ovarian
BRCA2	5%–10%	Family history	50	Possibly gastric	Breast (female and male), ovarian, prostate, and possibly melanoma
BRCA1	<5%	Family history	50	Possibly gastric	Breast (female and male), ovarian, prostate, and possibly melanoma
PALB2	2%–10%	Family history	50	Possibly gastric	Breast (female and male), ovarian, prostate, and possibly melanoma
TP53	7.30%	Family history	50	Colorectal, gastric	Breast, sarcoma, CNS, leukemia, adrenocorticoid carcinoma, lung, thyroid, and others
MLH1	See Table 1	Family history	50	See Table 1	Uterine, ovarian, skin, urothelial, CNS, and prostate
MSH2/EPCAM	See Table 1	Family history	50	See Table 1	Uterine, ovarian, skin, urothelial, CNS, prostate, and others
MSH6	See Table 1	Family history	50	See Table 1	Uterine, ovarian, skin, urothelial, CNS, and prostate
PRSS1, SPINK1	Insufficient data	Clinical hereditary pancreatitis	40 or 20 y after onset of pancreatitis	Insufficient data	Insufficient data

[a] Family history is defined as ≥ 1 first-degree or second-degree relative with pancreatic cancer.

[b] Or 10 y younger than the earliest PDAC diagnosis in the family.