ACG Clinical Guideline: Genetic Testing and Management of Hereditary Gastrointestinal Cancer Syndromes

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Abstract

This guideline presents recommendations for the management of patients with hereditary gastrointestinal cancer syndromes. The initial assessment is the collection of a family history of cancers and premalignant gastrointestinal conditions and should provide enough information to develop a preliminary determination of the risk of a familial predisposition to cancer. Age at diagnosis and lineage (maternal and/or paternal) should be documented for all diagnoses, especially in first- and second-degree relatives. When indicated, genetic testing for a germline mutation should be done on the most informative candidate(s) identified through the family history evaluation and/or tumor analysis to confirm a diagnosis and allow for predictive testing of at-risk relatives. Genetic testing should be conducted in the context of pre- and post-test genetic counseling to ensure the patient's informed decision making. Patients who meet clinical criteria for a syndrome as well as those with identified pathogenic germline mutations should receive appropriate surveillance measures in order to minimize their overall risk of developing syndromespecific cancers. This guideline specifically discusses genetic testing and management of Lynch syndrome, familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), *MUTYH*-associated polyposis (MAP), Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden syndrome, serrated (hyperplastic) polyposis syndrome, hereditary pancreatic cancer, and hereditary gastric cancer.

Introduction

Hereditary gastrointestinal (GI) cancer syndromes represent a phenotypically diverse group of disorders that exhibit distinct patterns of inheritance in an individual's progeny. Over the past few decades, the expansion of familial cancer registries and advancement in genomics have led to the development of clinical diagnostic criteria for specific hereditary syndromes as well as the discovery of multiple genes in which germline mutations predispose individuals to syndrome-associated neoplastic manifestations. This guideline first discusses essential elements of a patient's personal and family history that allow for risk assessment for potential inherited cancer susceptibility. It then addresses the currently most well-characterized GI cancer susceptibility syndromes: Lynch syndrome (LS), familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), *MUTYH* -associated polyposis (MAP), Peutz–Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), Cowden syndrome (CS), serrated (hyperplastic) polyposis syndrome, hereditary pancreatic cancer, and hereditary gastric cancer. For each of these syndromes, we outline diagnostic criteria and indications

for genetic evaluation, describe the currently known associated underlying genes, and make recommendations for surveillance and management of at-risk individuals and those found to carry a definitive disease-causing mutation. Finally, we discuss the elements of informed consent that must accompany genetic evaluation as well as currently evolving genetic testing technologies that may change how genetic testing is conducted in the near-term future.

Each section of the document presents summary statements, the key recommendations related to the section topic, followed by a summary of the supporting evidence (**Tables 1** and **2**). A search of MEDLINE via the OVID interface using the MeSH term "hereditary cancer syndrome" limited to clinical trials, reviews, guidelines, and meta-analysis for the years 1966–2013 was performed to develop the document and create summary statements and recommendations. "Summary statements" and "recommendations" are distinguished by whether it was possible to address the quality of evidence supporting the statements based on an objective grading system. An objective measure that provides assessment of the strength of data regarding prognostic indicators does not currently exist, and similarly, "motherhood" statements (such as the importance of obtaining a family history) that are based on sound clinical judgment are oft en not subject to systematic clinical studies as they are understood to reflect sound clinical practice. The summary statements therefore reflect consensus opinion by the authors and a thorough literature review that reflects expert opinion by leaders in the field and other consensus guidelines. For management recommendations, where alternative strategies are and should be subject to rigorous assessment, the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system was used to grade the strength of recommendations and the quality of evidence (1). An explanation of the quality of evidence and strength of recommendations is shown in **Table 3**. The quality of evidence, which influences the strength of the recommendation, ranges from "high" (further research is very unlikely to change our confidence in the estimate of effect) to "moderate" (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate) to "low" (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), and to "very low" (any estimate of effect is uncertain). The strength of a recommendation is graded as strong when the desirable effects of an intervention clearly outweigh the undesirable effects and is graded as conditional when uncertainty exists about the trade-offs.

The field of cancer genetics poses some challenges with respect to the GRADE system. Because of the rarity of the syndromes, and the relatively recent discovery of cancer susceptibility genes, data regarding long-term outcomes regarding optimal management strategies at this time are limited to observational studies. Randomized clinical trials, which are the gold standard of systems such as GRADE, are difficult to conduct in rare diseases, where the main objective outcome, reduction in cancer mortality, takes years to assess and large patient numbers. The reader, therefore, should take the assessments of quality of evidence with caution— the often "low" or "very low" quality gradings reflect primarily a lack of available data and not that the quality of studies conducted thus far has been poor.

Table 1. Summary statements
Standard for minimal cancer family history assessment in gastrointestinal (GI) practice
A family history of cancer and premalignant GI conditions that provides sufficient information to develop a preliminary determination of the risk of a familial predisposition to cancer should be obtained for all patients being evaluated in outpatient gastroenterology and endoscopy practices.
Essential elements of a family history include presence and type of cancer diagnoses in first- and second-degree relatives, and presence and (ideally) type of polyps in first-degree relatives; age and lineage should be noted for each diagnosis.
Lynch syndrome (LS)
All newly diagnosed colorectal cancers (CRCs) should be evaluated for mismatch repair deficiency.
Analysis may be done by immunohistochemical testing for the *MLH1/MSH2/MSH6/PMS2* proteins and/or testing for microsatellite instability. Tumors that demonstrate loss of *MLH1* should undergo BRAF testing or analysis for *MLH1* promoter hypermethylation.
Individuals who have a personal history of a tumor showing evidence of mismatch repair defi ciency (and no demonstrated BRAF mutation or hypermethylation of *MLH1*) , a known family mutation associated with LS, or a risk of $\geq$5% chance of LS based on risk prediction models should undergo genetic evaluation for LS.
Genetic testing of patients with suspected LS should include germline mutation genetic testing for the *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* genes or the altered gene(s) indicated by immunohistochemical (IHC) testing.
Adenomatous polyposis syndromes
Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis/attenuated polyposis
Individuals who have a personal history of >10 cumulative colorectal adenomas, a family history of one of the adenomatous polyposis syndromes, or a history of adenomas and FAP-type extracolonic manifestations (duodenal/ampullary adenomas, desmoid tumors (abdominal>peripheral), papillary thyroid cancer, congenital hypertrophy of the retinal pigment epithelium ((CHRPE), epidermal cysts, osteomas) should undergo assessment for the adenomatous polyposis syndromes.
Genetic testing of patients with suspected adenomatous polyposis syndromes should include *APC* and *MUTYH* gene mutation analysis.
Hamartomatous polyposis syndromes
Peutz–Jeghers syndrome (PJS)
Individuals with perioral or buccal pigmentation and/or two or more histologically characteristic gastrointestinal hamartomatous polyp(s) or a family history of PJS should be evaluated for PJS.
Genetic evaluation of a patient with possible PJS should include testing for *STK11* mutations.
Juvenile polyposis syndrome (JPS)
Individuals with five or more juvenile polyps in the colorectum or any juvenile polyps in other parts of the GI tract should undergo evaluation for JPS.
Genetic evaluation of a patient with possible JPS should include testing for *SMAD4* and *BMPR1A* mutations.
Cowden syndrome (PTEN hamartoma tumor syndrome)
Individuals with multiple gastrointestinal hamartomas or ganglioneuromas should be

evaluated for Cowden syndrome and related conditions.
Genetic evaluation of a patient with possible Cowden syndrome should include testing for *PTEN* mutations.

Table 1. Summary statements *continued*
Serrated/hyperplastic polyposis syndrome
Individuals who meet at least one of the following criteria have the clinical diagnosis of serrated polyposis syndrome (SPS): (i) at least 5 serrated polyps proximal to the sigmoid colon with ≥2 of these being >10 mm; (ii) any number of serrated polyps proximal to the sigmoid colon in an individual who has a first-degree relative (FDR) with serrated polyposis; and (iii) >20 serrated polyps of any size, distributed throughout the large intestine.
A clear genetic etiology has not yet been defined for SPS, and therefore genetic testing is currently not routinely recommended for SPS patients; testing for *MUTYH* mutations may be considered for SPS patients with concurrent adenomas and/or a family history of adenomas.
Hereditary pancreatic cancer
Individuals should be considered to be at risk for familial pancreatic adenocarcinoma if they (i) have a known genetic syndrome associated with pancreatic cancer, including hereditary breast–-ovarian cancer syndrome, familial atypical multiple melanoma and mole syndrome (FAMMM), PJS, LS, or other gene mutations associated with an increased risk of pancreatic adenocarcinoma; or (ii) have two relatives with pancreatic adenocarcinoma, where one is a FDR; (iii) have three or more relatives with pancreatic cancer; or (iv) have a history of hereditary pancreatitis.
Genetic testing of patients with suspected familial pancreatic cancer should include analysis of *BRCA1/2*, *CDKN2A*, *PALB2*, and *ATM*. Evaluation for PJS, LS, and hereditary pancreatitis-associated genes should be considered if other component personal and/or family history criteria are met for the syndrome.
Hereditary gastric cancer
Hereditary diffuse gastric cancer (HDGC)
Individuals with (i) ≥2 cases of diffuse gastric cancer, with at least one diagnosed at <50 years; (ii) ≥3 cases of documented diffuse cancer in first- or second degree relatives independent of age of onset; (iii) diffuse gastric cancer diagnosed at <40 years; (iv) a personal or family history of diffuse gastric cancer and lobular breast cancer with one diagnosed at <50 years should be evaluated for HDGC.
Genetic testing of individuals who fulfill HDGC clinical criteria should include analysis of *CDH1* mutations.

Table 2. Summary of recommendations
Lynch syndrome (LS)
1. In individuals at risk for or affected with LS, screening for colorectal cancer by colonoscopy should be performed at least every 2 years, beginning between ages 20 and 25 years. Annual colonoscopy should be considered in confirmed mutation carriers (strong recommendation, moderate quality of evidence for screening, and very low quality of evidence for annual surveillance and age of initiation).
2. Colectomy with ileorectal anastomosis (IRA) is the preferred treatment of patients affected with LS with colon cancer or colonic neoplasia not controllable by endoscopy. Segmental colectomy is an option in patients unsuitable for total colectomy if regular postoperative surveillance is conducted (conditional recommendation, moderate quality of evidence).
3. Hysterectomy and bilateral salpingo-oophorectomy should be offered to women who are known LS mutation carriers and who have finished child bearing, optimally at age 40–45 years (conditional recommendation, low quality of evidence).
4. Screening for endometrial cancer and ovarian cancer should be offered to women at risk for or affected with LS by endometrial biopsy and transvaginal ultrasound annually, starting at age 30 to 35 years before undergoing surgery or if surgery is deferred (conditional recommendation, very low quality of evidence).
5. Screening for gastric and duodenal cancer can be considered in individuals at risk for or affected with LS by baseline esophagogastroduodenoscopy (EGD) with gastric biopsy at age 30–35 years, and treatment of *H. pylori* infection when found. Data for ongoing regular surveillance are limited, but ongoing surveillance every 3–5 years may be considered if there is a family history of gastric or duodenal cancer (conditional recommendation, very low quality of evidence).
6. Screening beyond population-based recommendations for cancers of the urinary tract, pancreas, prostate, and breast is not recommended unless there is a family history of the specific cancers (conditional recommendation, low quality of evidence).
7. Although data suggest that daily aspirin may decrease the risk of colorectal and extracolonic cancer in LS, currently the evidence is not sufficiently robust or mature to make a recommendation for its standard use (conditional recommendation, moderate quality of evidence).
Adenomatous polyposis syndromes
Familial adenomatous polyposis (FAP)/MUTYH-associated polyposis (MAP)/attenuated polyposis
8. In individuals at risk for or affected with the classic AP syndromes, screening for colorectal cancer by annual colonoscopy or flexible sigmoidoscopy should be performed, beginning at puberty. In families with attenuated familial adenomatous polyposis (AFAP) or MAP, surveillance should be by colonoscopy (strong recommendation, moderate quality of evidence).
9. Absolute indications for immediate colectomy in FAP, AFAP, and MAP include: documented or suspected cancer or significant symptoms. Relative indications for surgery include the presence of multiple adenomas >6 mm, a significant increase in adenoma number, and inability to adequately survey the colon because of multiple diminutive polyps (strong recommendation, low quality of evidence).

Table 2. Summary of recommendations *continued*
10. Screening for gastric and proximal small bowel tumors should be done using upper endoscopy including duodenoscopy starting at age 25–30 years. Surveillance should be repeated every 0.5–4 years depending on Spigelman stage of duodenal polyposis: 0=4 years; I=2–3 years, II=1–3 years, III=6–12 months, and IV=surgical evaluation. Examination of the stomach should include random sampling of fundic gland polyps. Low-grade dysplasia is common in fundic gland polyps, and surgery should be reserved for high-grade dysplasia or cancer (strong recommendation, very low quality of evidence).
11. Annual thyroid screening by ultrasound should be recommended to individuals affected with FAP, MAP, and attenuated polyposis (conditional recommendation, low quality of evidence).
12. Biannual screening should be offered to affected infants until age 7 years with α-fetoprotein and ultrasounds (conditional recommendation, very low quality of evidence).
13. Postsurgical surveillance should include yearly endoscopy of rectum or ileal pouch, and examination of an ileostomy every 2 years (strong recommendation, low quality level of evidence).
Hamartomatous polyposis syndromes
Peutz–Jeghers syndrome (PJS)
14. Surveillance in affected or at-risk PJS patients should include monitoring for colon, stomach, small bowel, pancreas, breast, ovary, uterus, cervix, and testes cancers. Risk for lung cancer is increased, but no specific screening has been recommended. It would seem wise to consider annual chest radiograph or chest computed tomography (CT) in smokers (conditional recommendation, low quality of evidence).
Juvenile polyposis syndrome (JPS)
15. Surveillance of the gastrointestinal (GI) tract in affected or at-risk JPS patients should include screening for colon, stomach, and small bowel cancers (conditional recommendation, very low quality of evidence).
16. Colectomy and ileorectal anastomosis or proctocolectomy and ileal pouch-anal anastomosis is indicated for polyp-related symptoms, or when the polyps cannot be managed endoscopically (conditional recommendation, low quality of evidence).
17. Cardiovascular examination for and evaluation for hereditary hemorrhagic telangiectasia should be considered for *SMAD4* mutation carriers (conditional recommendation, very low quality of evidence).
Cowden syndrome (PTEN hamartoma tumor syndrome)
18. Surveillance in affected or at-risk Cowden syndrome patients should include screening for colon, stomach, small bowel, thyroid, breast, uterine, kidney, and skin (melanoma) cancers (conditional recommendation, low quality of evidence).
Serrated/hyperplastic polyposis syndrome
19. Patients with serrated polyposis should undergo colonoscopies every 1–3 years with attempted removal of all polyps >5 mm diameter (conditional recommendation, low quality of evidence).
20. Indications for surgery for serrated polyposis syndrome (SPS) include an inability to control the growth of serrated polyps, or the development of cancer. Colectomy and ileorectal anastomosis is a reasonable option given the risks of metachronous neoplasia (conditional recommendation, low quality of evidence).

Table 2. Summary of recommendations *continued*
21. There is no evidence to support extracolonic cancer surveillance for SPS at this time. Screening recommendations for family members are currently unclear pending further data and should be individualized based on results of baseline evaluations in family members (conditional recommendation, very low quality of evidence).
Hereditary pancreatic cancer
22. Surveillance of individuals with a genetic predisposition for pancreatic adenocarcinoma should ideally be performed in experienced centers utilizing a multidisciplinary approach and under research conditions. These individuals should be known mutation carriers from hereditary syndromes associated with increased risk of pancreatic cancer (Peutz–Jeghers, hereditary pancreatitis, familial atypical multiple melanoma and mole syndrome (FAMMM)) or members of familial pancreatic cancer kindreds with a pancreatic cancer affected first-degree relative. Because of a lower relative risk for pancreatic adenocarcinoma development in *BRCA1*, *BRCA2*, *PALB2*, *ATM*, and LS families, surveillance should be limited to mutation carriers with a first or second-degree relative affected with pancreatic cancer (conditional recommendation; very low quality of evidence).
23. Surveillance for pancreatic cancer should be with endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) of the pancreas annually starting at age 50 years, or 10 years younger than the earliest age of pancreatic cancer in the family. Patients with PJS should start surveillance at age 35 years (conditional recommendation, very low quality of evidence).
24. Because of the increased risk for pancreatic cancer development when compared with a pancreatic cyst in the sporadic setting, cystic lesion(s) of the pancreas detected during surveillance of a hereditary pancreatic cancer-prone family member requires evaluation by centers experienced in the care of these high-risk individuals. Determining when surgery is required for pancreatic lesions is difficult and is best individualized after multidisciplinary assessment (conditional recommendation, low quality of evidence).
Hereditary gastric cancer
Hereditary diffuse gastric cancer
25. Management for patients with hereditary diffuse gastric cancer should include: (i) prophylactic gastrectomy after age 20 years (>80% risk by age 80); (ii) breast cancer surveillance in women beginning at age 35 years with annual mammography and breast MRI and clinical breast examination every 6 months; and (iii) colonoscopy beginning at age 40 years for families that include colon cancer (conditional recommendation, low quality of evidence).

Table 3. GRADE (Grading of Recommendations Assessment, Development and Evaluation) system of evidence and strength of recommendation	
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of the effect is very uncertain.