

# Risk Assessment and Genetic Testing for Inherited Gastrointestinal Syndromes

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**Abstract:** A number of inherited syndromes affect the gastrointestinal tract, including Lynch syndrome and other hereditary colorectal cancers, hereditary polyposis, hereditary gastric cancer, hereditary pancreatic cancer, and hereditary pancreatitis. Recognition and diagnosis of these syndromes are paramount because affected individuals and family members can be offered life-saving screening, risk-reducing surgeries, and other therapies. Genetic counseling and testing are critical components of risk assessment and diagnosis of inherited syndromes. With the advent of next-generation sequencing, multigene panels have significantly changed the practice of genetic counseling and testing. Gastroenterology providers interface with patients who are at risk for inherited gastrointestinal syndromes; thus, providers should learn to recognize these syndromes and know when to refer their patients. Additionally, gastroenterology providers should have an understanding of genetic counseling and be able to interpret multigene panel test results. This article provides an overview of and practical tips for the assessment and diagnosis of hereditary gastrointestinal cancer syndromes and pancreatitis.

Inherited gastrointestinal syndromes include cancer predisposition syndromes such as Lynch syndrome and polyposis as well as hereditary gastric cancer, hereditary pancreatic cancer, and hereditary pancreatitis (Table). Identification of at-risk relatives through genetic testing is actionable through intensive screening, surgery, and/or medical treatments. Moreover, finding a pathogenic variant (ie, mutation) in an individual has implications for family members and cascade testing. Despite knowledge of inherited gastrointestinal syndromes and clinical criteria for diagnosis, high-risk individuals and their family members often remain undiagnosed. Gastroenterology providers should learn to recognize patients at increased risk and ensure they undergo genetic counseling and possibly testing, preferably with a genetic counselor. Over the last decade, genetic testing for hereditary syndromes has become more complex.

#### Keywords

Genetic counseling, genetic testing, hereditary gastrointestinal cancers, hereditary pancreatitis, direct-to-consumer testing

**Table.** Hereditary Gastrointestinal Syndromes and Indications for Genetics Referral

	<b>Syndrome(s) (Implicated Genes)</b>	<b>Indications for Referral</b>
<b>Hereditary Colorectal Cancer</b>	<ul style="list-style-type: none"> <li>Lynch syndrome (<i>MLH1</i>, <i>MSH2</i>, <i>MSH6</i>, <i>PMS2</i>, <i>EPCAM</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Lynch syndrome–associated cancers under age 50 years (eg, colorectal, endometrial, gastric, ovarian)</li> <li>Multiple relatives with Lynch syndrome–associated cancers</li> <li>Individuals with multiple primary Lynch syndrome–associated cancers</li> <li>Distinguishing pathologic features (ie, microsatellite instability–high)</li> <li>Abnormal mismatch repair universal tumor screening</li> <li>Known germline Lynch syndrome mutation in the family</li> </ul>
<b>Adenomatous Polyposis</b>	<ul style="list-style-type: none"> <li>Familial adenomatous polyposis (<i>APC</i>)</li> <li><i>MUTYH</i>-associated polyposis (<i>MUTYH</i>)</li> <li>Polymerase proofreading–associated polyposis (<i>POLE</i>, <i>POLD1</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Multiple colorectal adenomatous polyps</li> <li>Small bowel and gastric polyps or cancers</li> <li>Extraintestinal features (eg, desmoid tumors, congenital hypertrophy of the retinal pigment epithelium, extra or missing teeth, osteomas, epidermoid cysts, hepatoblastomas)</li> </ul>
<b>Hamartomatous Polyposis</b>	<ul style="list-style-type: none"> <li>Peutz-Jeghers syndrome (<i>STK11</i>)</li> <li>Juvenile polyposis syndrome (<i>BMPRIA</i>, <i>SMAD4</i>)</li> <li>Cowden syndrome (<i>PTEN</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Multiple gastrointestinal hamartomatous polyps</li> <li>Personal or family history of other cancers, including breast, thyroid, renal, endometrial, and pancreatic</li> <li>Perioral or buccal pigmentation</li> <li>Macrocephaly</li> </ul>
<b>Hereditary Gastric Cancer</b>	<ul style="list-style-type: none"> <li>Hereditary diffuse gastric cancer (<i>CDH1</i>, <i>CTNNA1</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Diffuse-type gastric cancer (particularly early onset)</li> <li>Lobular breast cancer</li> </ul>
<b>Hereditary Pancreatic Cancer</b>	<ul style="list-style-type: none"> <li>Hereditary breast and ovarian cancer syndrome (<i>BRCA1/2</i>, <i>PALB2</i>)</li> <li>Familial atypical multiple mole melanoma syndrome (<i>CDKN2A</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Pancreatic cancer at any age</li> <li>Personal or family history of other cancers, including breast, ovarian, prostate, and melanoma</li> </ul>
<b>Hereditary Pancreatitis</b>	<ul style="list-style-type: none"> <li>(<i>PRSS1</i>, <i>CFTR</i>, <i>SPINK1</i>, <i>CTRC</i>, <i>CASR</i>)</li> </ul>	<ul style="list-style-type: none"> <li>Idiopathic chronic or recurrent acute pancreatitis (particularly early onset)</li> <li>Family history of pancreatitis or pancreatic cancer</li> <li>Personal or family history of cystic fibrosis, male infertility, chronic sinusitis, nasal polyps, diabetes, and/or exocrine insufficiency</li> </ul>

Instead of testing for a specific syndrome gene by gene, multigene panel testing now enables testing of multiple genes simultaneously. This multiplexed testing allows for a cost-effective evaluation for hereditary gastrointestinal syndromes but can also lead to unexpected or uncertain results. In addition, direct-to-consumer genetic testing has gained in popularity but should be interpreted with caution. This article provides practical tips for risk assessment and genetic testing considerations for hereditary gastrointestinal syndromes.

### Key Elements of Family History for Risk Assessment

Family history is a key component of assessing hereditary syndromes. A thorough and accurate family history

allows practitioners to identify patterns of disease and formulate a differential diagnosis, not only for the patient as an individual but for the family as a whole.<sup>1</sup>

Ideally, in order to accurately assess an individual's genetic risk, a 3- to 4-generation family history should be obtained to identify patterns of inheritance. Typically, this is part of a genetic counseling session, but a family history can also be gathered by the patient's provider. All relatives should be included with their current age or age at death, if known. Additionally, both maternal and paternal ethnic backgrounds should be acquired, paying particular attention to Ashkenazi Jewish ancestry, as founder mutations exist in this population.<sup>2</sup> For any suspicion of genetic disease, specific diagnosis as well as age at diagnosis should be noted for each relative. The indication for genetics evaluation will determine the

line of specific questioning for family history assessment. During a busy clinic or endoscopy visit, it might not be feasible to obtain a complete family history as described previously. In this situation, providers can ask more directed questions to screen for the possibility of a hereditary syndrome, such as the 3-question survey for Lynch syndrome validated by Kastrinos and colleagues.<sup>3</sup>

## Genetic Testing Considerations

### *Panel Testing for Cancer Risk Assessment*

For many hereditary cancer syndromes, the personal and/or family history of cancer can be helpful in dictating which syndrome or gene(s) to test for. However, in some cases, this distinction may not be so apparent, as there can be overlapping phenotypes and syndromes with multiple types of associated cancers. This overlap can present challenges, particularly when the personal and family histories present atypically.<sup>4,5</sup> Additionally, the number of genes implicated in hereditary cancer syndromes can create a lengthy and expensive evaluation process if all genes are tested for individually.

Next-generation sequencing technology enables the analysis of multiple genes simultaneously, effectively reducing cost and turnaround times for cases in which multiple hereditary syndromes are in the differential diagnosis.<sup>6,7</sup> Currently available hereditary cancer panels include cancer site-specific panels, high- or moderate-risk gene panels, guideline-based panels, and pancancer panels.<sup>8</sup> Panel testing has the benefit of providing a more comprehensive, cost-effective method of sequencing multiple genes concurrently,<sup>9,10</sup> and has been shown to be a more effective method of genetic testing for families with overlapping phenotypes. Given the complexity of panel testing, consultation with an experienced cancer genetic specialist may be of benefit, especially when the testing strategy or test results are unclear.<sup>11</sup>

### *Cascade Testing for At-Risk Family Members*

In addition to patients being counseled about the complexities related to multigene panel testing, patients should be informed of the importance of family testing when a mutation is identified. Cascade testing in family members relies heavily on efforts by both the patient and the clinician to inform relatives and encourage them to undergo their own testing.<sup>12</sup> The identification of a mutation in the family allows for risk stratification of at-risk relatives, as relatives who test positive for a familial mutation can then initiate increased screening and risk-reduction strategies while relatives who test negative (ie, true negatives) can then be reassured that they are not at increased risk for cancer and can follow general population screening guidelines.

### *Direct-to-Consumer Genetic Testing*

In recent years, direct-to-consumer genetic testing for health information has become increasingly available, and consumer interest and demand for testing has risen. Currently available direct-to-consumer panels include specific markers in *BRCA1*, *BRCA2*, and *MUTYH*. Patients utilizing direct-to-consumer genetic testing should be informed of the limitations of testing. In particular, the possibility of both false-positive and false-negative results should be reinforced, as these have the potential to provide false reassurance or increase anxiety related to risk. In a study evaluating 49 patients undergoing confirmatory testing of variants reported on direct-to-consumer genetic testing, 40% of variants in clinically actionable genes were false-positive results.<sup>13</sup> Additionally, 8 variants had discordant classifications. These results highlight the need for clinical confirmation of all potentially actionable variants detected on direct-to-consumer genetic testing at this point in time.

## Genetic Testing and Counseling for Hereditary Colorectal Cancer and Hereditary Polyposis

### *Risk Assessment for Hereditary Colorectal Cancer and Hereditary Polyposis*

When obtaining a family history for the evaluation of hereditary colorectal cancer, particular attention should be paid to cancer and colon polyp history in first- and second-degree relatives as well as the history of colonoscopy and number and types of polyps found, if known.<sup>4</sup> A number of features in a family history should raise suspicion for Lynch syndrome (Table).

For patients being evaluated for hereditary polyposis, additional information about intestinal and extraintestinal manifestations should be obtained. For familial adenomatous polyposis (FAP) and *MUTYH*-associated polyposis, additional questions should be asked about small bowel and gastric polyps or cancers, desmoid tumors, extra or missing teeth, osteomas, hepatoblastomas, and a retinal finding called congenital hypertrophy of the retinal pigment epithelium. For hamartomatous polyposis syndromes, such as Peutz-Jeghers syndrome and Cowden syndrome, any history of breast cancer, thyroid cancer, endometrial cancer, renal cancer, macrocephaly, skin findings, and hyperpigmentation of the buccal mucosa should be obtained.<sup>14</sup>

### *Testing and Counseling for Hereditary Colorectal Cancer and Hereditary Polyposis*

There are several important considerations when performing genetic testing for hereditary colorectal cancer and hereditary polyposis. Criteria from multiple professional

organizations, including the National Comprehensive Cancer Network, the American College of Gastroenterology, and a joint statement from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors, are available to help guide testing for these conditions, among other hereditary cancer syndromes.<sup>15-17</sup>

For individuals with colorectal (or endometrial) cancer, testing the tumor for evidence of a defective DNA mismatch repair is widely advocated. So-called universal tumor screening can be performed using microsatellite instability testing and/or immunohistochemical staining for mismatch repair protein expression. Given that there are several explanations for microsatellite instability or abnormal immunohistochemistry, algorithms have been developed to guide follow-up testing for Lynch syndrome (Figure 1). While a step-by-step approach may still be taken to determine the etiology of abnormal tumor screening, laboratories also offer paired germline and somatic testing to determine the likely etiology in a single comprehensive test.<sup>18</sup> In the presence of normal tumor testing, genetic testing may still be indicated in the case of early-onset colorectal cancer and/or the presence of other Lynch syndrome-associated tumors in the individual or family.

One challenge related to genetic counseling for hereditary polyposis includes syndrome heterogeneity. Up to 90% of individuals with classic FAP carry mutations in *APC*, and biallelic mutations in *MUTYH* are found in an additional one-third of *APC* mutation-negative FAP cases.<sup>19</sup> Of note, the *APC* I1307K variant is an increased risk allele commonly found in Ashkenazi Jewish individuals.<sup>20</sup> While many genetic testing laboratories classify this variant as pathogenic, it does not cause a FAP phenotype and classic polyposis, but rather is associated with a 2-fold increased risk of colorectal cancer.<sup>21</sup> To that end, carriers of this particular variant do not need to be managed as FAP but should proceed with colonoscopies every 5 years beginning at age 40 years or based on the earliest age of colorectal cancer in the family.<sup>15</sup> Additionally, phenotypic overlap in the adenomatous polyposis syndromes may require consideration of additional genes for testing. Mutations in *POLE* and *POLD1* have been associated with polymerase proofreading-associated polyposis, which has been seen with an attenuated polyposis phenotype that carries an increased risk for colorectal and endometrial cancer.<sup>22</sup> Biallelic mutations in *NTHL1* and *MSH3* have also been associated with adenomatous polyposis, although additional research is needed to fully clarify the phenotypes associated with these genes.<sup>23,24</sup> Hamartomatous polyposis syndromes include juvenile polyposis syndrome (*SMAD4*, *BMPRIA*), Peutz-Jeghers syndrome (*STK11*), and Cowden syndrome (*P TEN*).<sup>25-28</sup>

Additional genes associated with polyposis include *GREM1* (hereditary mixed polyposis syndrome), *AXIN2* (polyposis and oligodontia), and *RNF43* (serrated polyposis syndrome).<sup>29-31</sup> Given the significant heterogeneity of these polyposis syndromes, simultaneous sequencing of multiple genes utilizing a panel approach allows for a comprehensive, efficient testing strategy.<sup>4</sup>

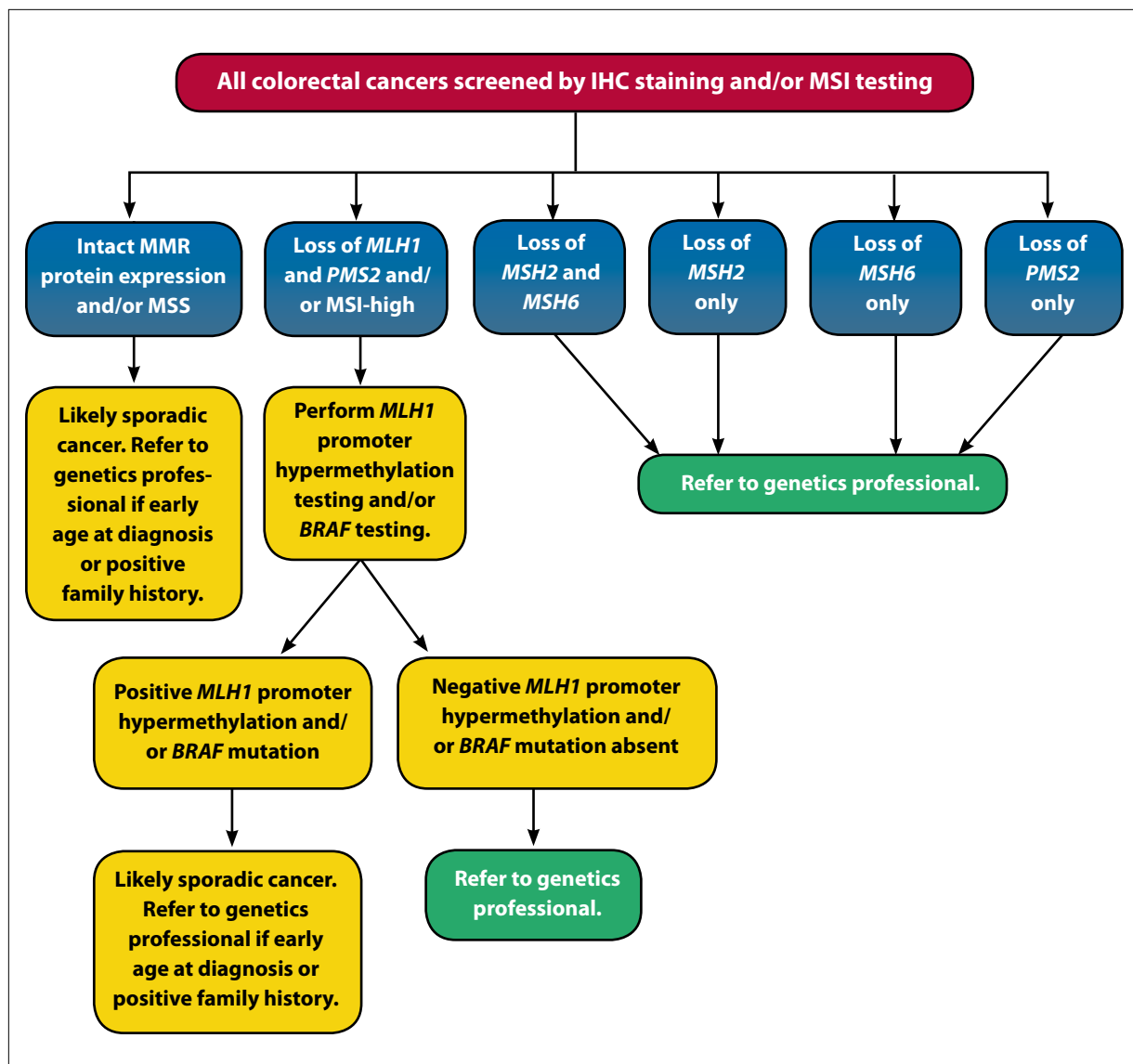
An additional challenge of genetic counseling for hereditary polyposis and Lynch syndrome can be the pattern of inheritance. While most polyposis syndromes appear to follow an autosomal dominant pattern of inheritance, there are some syndromes that are inherited in an autosomal recessive pattern, including *MUTYH*-, *NTHL1*-, and *MSH3*-associated polyposis. Additionally, approximately 30% of individuals harboring *APC* mutations will have de novo mutations,<sup>32</sup> so a lack of family history does not exclude the diagnosis of FAP. For individuals of reproductive age carrying mutations in the mismatch repair genes, additional discussion of reproductive risk for constitutional mismatch repair deficiency may need to be addressed.<sup>33</sup> In these situations, genetic testing for the partner may be indicated to allow for prenatal diagnosis and/or preimplantation genetic diagnosis.

Testing using a multigene panel can present a challenge because of the possibility of identifying mutations in genes not traditionally associated with colorectal cancer. Studies utilizing multigene panel tests in colorectal cancer patients identified the prevalence of germline mutations to be between 14% and 18%. Mutations were identified in genes not usually related to colorectal cancer, including *ATM*, *CHEK2*, *BRCA1*, *BRCA2*, *CDKN2A*, and *PALB2*.<sup>34-36</sup> Notably, one-third of mutation carriers did not meet testing criteria for the gene(s) in which they were found to carry a mutation. These studies highlight the need to evaluate not only hereditary colorectal cancer genes but also additional cancer predisposition genes when providing genetic testing to a patient with a colorectal cancer diagnosis.

## Genetic Testing and Counseling for Hereditary Gastric Cancer

### *Risk Assessment for Hereditary Gastric Cancer*

Familial gastric cancer has been associated with a number of syndromes, including hereditary diffuse gastric cancer (HDGC), gastric adenocarcinoma and proximal polyposis of the stomach, and familial intestinal gastric cancer. Syndromes associated with intestinal gastric cancer include Lynch syndrome, Li-Fraumeni syndrome, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer syndrome, FAP, and juvenile polyposis syndrome.<sup>37</sup> The family history and age of onset of any gastric cancer diagnosis help inform the differential



**Figure 1.** Algorithm for universal tumor screening for Lynch syndrome.

IHC, immunohistochemistry; MMR, mismatch repair; MSI, microsatellite instability; MSS, microsatellite stable.

diagnosis. Family history assessment for hereditary gastric cancer should focus on the type of gastric cancer (eg, diffuse-type gastric cancer), history of breast cancer (lobular breast cancer in particular), and family history of other syndrome-specific cancers (ie, Lynch syndrome) or gastrointestinal polyposis.

Inherited gastric cancers are more commonly of the diffuse type (ie, HDGC), and approximately 40% of families meeting HDGC diagnostic criteria will harbor mutations in *CDH1* (E-cadherin).<sup>38</sup> Mutations in *CDH1* confer a cumulative risk of gastric cancer by age 80 years of 70% for men and 56% for women. Additionally, the cumulative risk of lobular breast cancer is 42%

for women carrying *CDH1* mutations.<sup>39</sup> The current guidelines suggest following a protocol that includes prophylactic total gastrectomy beginning at age 20 years or endoscopic surveillance following the Cambridge protocol,<sup>40</sup> with a minimum of 30 biopsies in targeted anatomic zones in patients opting not to undergo gastrectomy. Finally, breast cancer screening should include annual mammogram and breast magnetic resonance imaging beginning at age 35 years.<sup>40</sup>

#### **Testing and Counseling for Hereditary Gastric Cancer**

In 2010, the International Gastric Cancer Linkage Consortium (IGCLC) broadened the consideration of



genetic testing for HDGC for families meeting any of the following criteria: (1) 2 cases of diffuse gastric cancer, with 1 confirmed case of diffuse gastric cancer in an individual younger than age 50 years, (2) 3 confirmed cases of diffuse gastric cancer in first- or second-degree relatives independent of age, (3) 1 case of diffuse gastric cancer in an individual younger than age 40 years, or (4) personal or family history of diffuse gastric cancer and lobular breast cancer, with 1 diagnosis of diffuse gastric cancer or lobular breast cancer in an individual younger than age 50 years.<sup>40</sup> Genetic testing should include both sequencing and deletion or duplication analysis of *CDH1*, with consideration of testing for *CTNNA1* variants, which have been reported in a handful of families meeting IGCLC criteria who were negative for *CDH1* mutations.<sup>41</sup> Other genes have been implicated in familial gastric cancer, such as *ATM*, *BRCA2*, and *STK11*, so panel testing may be indicated for families without *CDH1* mutations, particularly those with other cancer histories.<sup>39</sup>

Unique genetic counseling challenges for HDGC primarily stem from the recommendation of prophylactic total gastrectomy. Due to the lack of effective endoscopic surveillance, prophylactic total gastrectomy has been strongly recommended for *CDH1* mutation carriers.<sup>40</sup> Gastrectomy has typically been recommended beginning at age 20 years given the relatively small risk of diffuse gastric cancer prior to this age,<sup>42</sup> which brings up the issue of when to begin testing offspring for known mutations. There is no well-established recommended age at which to offer testing, but the IGCLC agrees that testing could be considered at the age of consent (age 18 years in the United States) or based on family history of gastric cancer.<sup>40</sup>

## Genetic Testing and Counseling for Hereditary Pancreatic Cancer

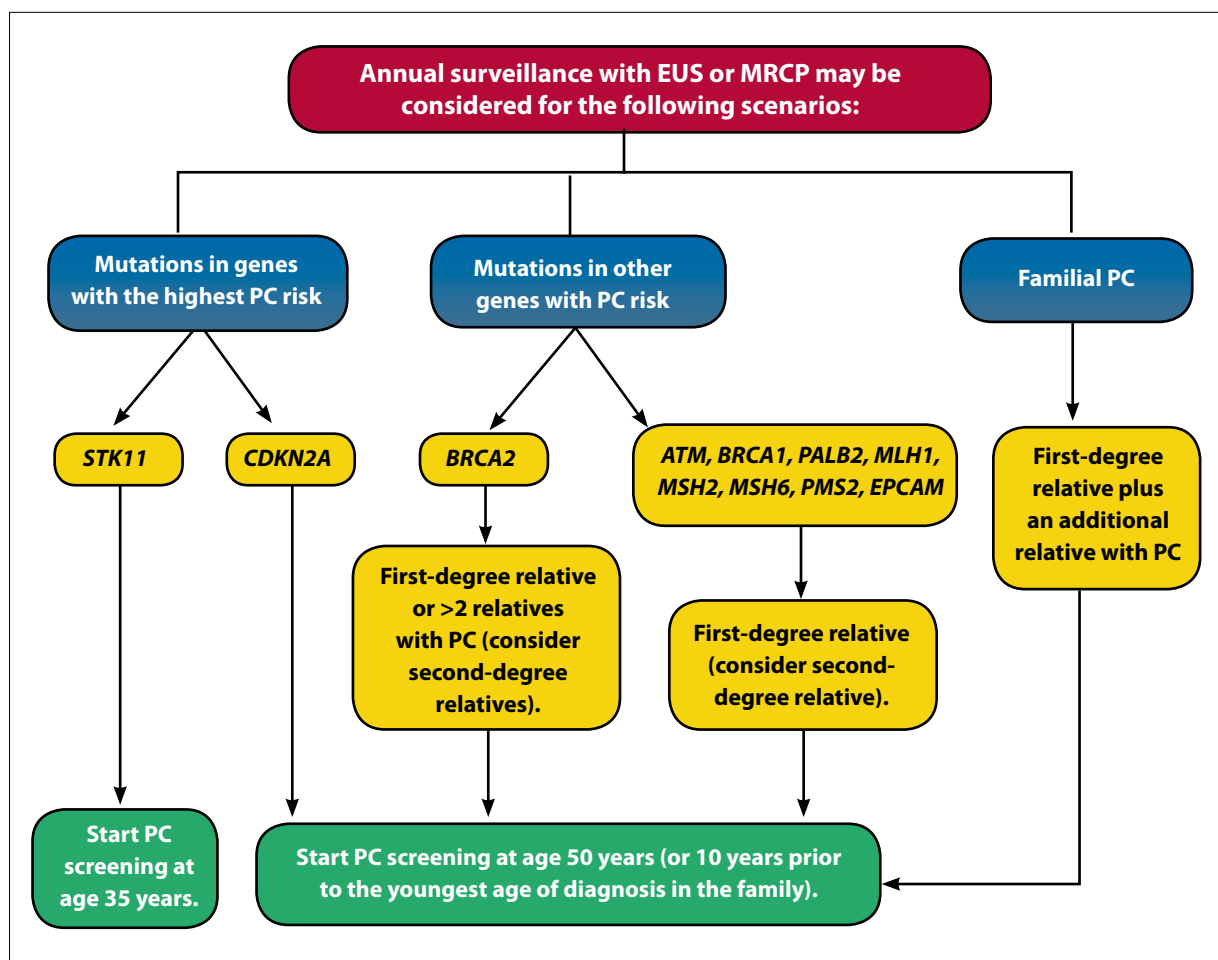
### Risk Assessment for Hereditary Pancreatic Cancer

There are a number of hereditary syndromes that involve pancreatic cancer, including hereditary breast and ovarian cancer syndrome (*BRCA1* and *BRCA2*), familial atypical multiple mole melanoma syndrome (*CDKN2A*), hereditary pancreatitis (*PRSS1*), Peutz-Jeghers syndrome (*STK11*), Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), and Li-Fraumeni syndrome (*TP53*).<sup>16</sup> Additionally, many families with multiple cases of pancreatic cancer without a known genetic etiology have been identified as familial pancreatic cancer.<sup>43</sup> Familial pancreatic cancer is defined as families with at least 2 affected first-degree relatives, with some practices expanding these criteria to 1 affected first-degree relative and 1 affected second-degree relative for screening purposes.

### Testing and Counseling for Hereditary Pancreatic Cancer

In recent years, several studies have reported the prevalence of deleterious germline mutations in patients with pancreatic cancer to be between 4.0% and 13.5%.<sup>44-47</sup> Mutations in these cohorts included genes previously known to be associated with an increased risk of pancreatic cancer, but also included mutations in other genes, such as *ATM*, *CHEK2*, and *RAD50*, which do not confer an increased risk of pancreatic cancer but are associated with other cancers for which modified management recommendations may be made.<sup>46</sup> Age at diagnosis and family history of pancreatic or other cancers appear to be poor predictors for mutation detection.<sup>44,46</sup> In fact, in a cohort of suspected sporadic pancreatic cancer patients, 3.9% of patients carried deleterious mutations, many of which would have been missed if guidelines for hereditary cancer susceptibility testing had been utilized.<sup>45</sup> These findings led the National Comprehensive Cancer Network to recommend consideration of germline testing for all pancreatic cancer patients, regardless of age at diagnosis or family history of cancer.<sup>48</sup> Genetic testing for all pancreatic cancer patients not only provides information about the cause of disease and treatment options,<sup>49</sup> but also allows for cascade testing of unaffected relatives, which aids in determining relatives who may benefit from pancreatic cancer surveillance.

The main challenge of genetic counseling for pancreatic cancer is that screening for early detection is not well established. Presently, expert opinion is that annual endoscopic ultrasound and/or magnetic resonance cholangiopancreatography may be offered to high-risk patients.<sup>50</sup> Figure 2 depicts the algorithm to determine the individuals who are eligible for pancreatic cancer screening. Although more studies are needed to prove the efficacy of pancreatic cancer screening, early data are promising. In a study of 345 patients undergoing pancreatic cancer screening, 24 subjects (7%) had neoplastic progression over a 16-year follow-up period (14 pancreatic adenocarcinomas and 10 high-grade dysplastic lesions).<sup>51</sup> Ten out of 14 pancreatic adenocarcinomas were detected on routine surveillance, and 9 out of those 10 were surgically resectable. Overall, 85% of resectable pancreatic adenocarcinomas survived 3 years. The mortality rate for high-risk individuals developing pancreatic adenocarcinoma was 64% (9/14), whereas none of the 10 individuals who developed high-grade dysplastic lesions had died as of the last follow-up. Larger studies are needed to further refine pancreatic cancer screening guidelines. For patients at highest risk due to family history or mutation status, screening appears to aid in detecting lesions at localized, resectable stages, with the potential to increase survival rates. Ideally, screening for



**Figure 2.** Eligibility criteria for pancreatic cancer (PC) screening.

EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography.

pancreatic cancer should be performed under a study protocol.

## Genetic Testing and Counseling for Hereditary Pancreatitis

### *Risk Assessment for Hereditary Pancreatitis*

Chronic pancreatitis (CP) and recurrent acute pancreatitis (RAP) have both been associated with hereditary factors, often with unusual presentations, including childhood onset, chronic pancreatitis in young adulthood, and a high risk of pancreatic cancer.<sup>52-54</sup> Affected individuals may be considered for evaluation of hereditary pancreatitis and genetic testing in the case of idiopathic CP or RAP, particularly in the context of a family history of disease.<sup>55</sup> Specific questions should be asked regarding the family history, such as whether the patient has any relatives with pancreatitis (including age at diagnosis and amylase and

lipase levels, if available), pancreatic cancer (including age at diagnosis), or diagnoses of diabetes, exocrine insufficiency, male infertility, chronic sinusitis or nasal polyps, or cystic fibrosis. It is also helpful to ascertain any history of smoking or alcohol abuse in family members.<sup>56</sup>

### *Testing and Counseling for Hereditary Pancreatitis*

To date, there are 5 genes known to be associated with hereditary pancreatitis, with the strongest risk associated with mutations in *PRSS1*, *CFTR*, and *SPINK1*, and lesser risk associated with variants in *CTRC* and *CASR*.<sup>57</sup> Genetic testing is generally considered first for individuals who have already manifested symptoms of CP or RAP, who have a family history of pancreatitis, who have early-onset idiopathic CP or RAP, or who have asymptomatic relatives of a mutation carrier.<sup>56</sup> With panel testing readily available, genetic testing should consist of full gene sequencing and deletion or duplication analysis of all 5

genes, as both sequence changes and copy-number variants have been associated with hereditary pancreatitis.<sup>58</sup>

The primary genetic counseling challenges pertaining to hereditary pancreatitis relate to the risk of pancreatitis for family members. Recurrence risk is dependent on genotype, as *PRSS1* mutations are inherited in an autosomal dominant pattern, whereas *CFTR*, *SPINK1*, *CTRC*, and *CASR* mutations may be inherited in either a dominant or recessive pattern and are often cotransmitted.<sup>56</sup> *CFTR* mutation carriers should be counseled not only about risk of pancreatitis for family members, but also about reproductive risk for cystic fibrosis. Additionally, testing positive for a hereditary pancreatitis gene mutation does not guarantee manifestation of symptoms due to incomplete penetrance; in fact, asymptomatic relatives who choose to undergo genetic testing should be informed that while penetrance is high, there is a 20% chance they may never develop symptoms and may continue to have normal pancreatic function throughout their lifetime.<sup>59</sup> The risk of pancreatic cancer in these individuals appears to be contingent upon the history of pancreatitis itself, and carrying a gene mutation alone does not necessarily result in an increased risk of pancreatic cancer in the absence of pancreatitis.<sup>52,54</sup>

## Conclusion

Many genetic conditions exist that affect risk of gastrointestinal disease, including hereditary gastrointestinal cancer syndromes and hereditary pancreatitis. As genetic testing becomes increasingly utilized in a clinical setting, particular attention should be paid to how patients are counseled with regard to this testing and the information provided by such tests. Additionally, public interest in genetic testing and genetic information continues to grow with the increasing availability of direct-to-consumer testing. Recognition and prompt referral to a genetic counselor for at-risk patients and their families should be routine in every gastrointestinal practice.

*Ms Stoll and Dr Kupfer have conducted research with Myriad Genetic Laboratories. Ms Stoll is also on the advisory board for Invitae.*

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