Review Article

Advances in Hereditary Colorectal and Pancreatic Cancers

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ABSTRACT

Purpose: Innovations in genetic medicine have led to improvements in the early detection, prevention, and treatment of cancer for patients with inherited risks of gastrointestinal cancer, particularly hereditary colorectal cancer and hereditary pancreatic cancer.

Methods: This review provides an update on recent data and key advances that have improved the identification, understanding, and management of patients with hereditary colorectal cancer and hereditary pancreatic cancer.

Findings: This review details recent and emerging data that highlight the developing landscape of genetics in hereditary colorectal and pancreatic cancer risk. A summary is provided of the current state-of-the-art practices for identifying, evaluating, and managing patients with suspected hereditary colorectal cancer and pancreatic cancer risk. The impact of next-generation sequencing technologies in the clinical diagnosis of hereditary gastrointestinal cancer and also in discovery efforts of new genes linked to familial cancer risk are discussed. Emerging targeted therapies that may play a particularly important role in the treatment of patients with hereditary forms of colorectal cancer and pancreatic cancer are also reviewed. Current approaches for pancreatic cancer screening and the psychosocial impact of such procedures are also detailed.

Implications: Given the availability of new diagnostic, risk-reducing, and therapeutic strategies that exist for patients with hereditary risk of colorectal or pancreatic cancer, it is imperative that clinicians be vigilant about evaluating patients for hereditary cancer syndromes. Continuing to advance genetics research in hereditary gastrointestinal cancers will allow for more progress to be made in personalized medicine and prevention. (*Clin Ther.* 2016;38:1600–1621)

Key words: familial gastrointestinal cancer, genetic testing, Lynch syndrome, multigene panel testing.

INTRODUCTION

Recent innovations in genetic medicine and next-generation sequencing technologies have led to tremendous advances in the understanding of the role that genetics plays in carcinogenesis. An abundance of research on the identification and management of hereditary gastrointestinal cancer, in particular, has led to drastic improvements in cancer prevention and cancer treatment for patients with such hereditary risks. In this review, we summarize recent data and key advances that have improved the diagnosis, screening, and treatment of patients with hereditary colorectal cancer and hereditary pancreatic cancer.

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HEREDITARY COLORECTAL CANCER

Colorectal cancer remains the fourth most incident cancer and the second most common cause of cancer-related mortality in the United States, despite increasing awareness about the efficacy of colorectal cancer screening techniques.[1] The lifetime risk of colorectal cancer for the general population in the United States is estimated to be 4.4% and 4.7% for women and men, respectively.[1] It is thought that ~20% of patients with colorectal cancer have a family history of colorectal cancer and that roughly 5% of colorectal cancers are attributable to identifiable Mendelian genetic syndromes (Table I), such as Lynch syndrome (formerly known as hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis, and *MUTYH*-associated polyposis.[2,3] Over the past decade, scientific knowledge about the genetics of colorectal cancer has grown exponentially, and the coming years promise continued advances in the identification, management, and understanding of patients with hereditary predisposition to colorectal cancer.

Identifying Patients with Lynch Syndrome

Accounting for ~3% of all colorectal cancers, Lynch syndrome is the most common hereditary colorectal cancer syndrome, and it also confers an increased lifetime risk of endometrial cancer, ovarian cancer, gastric cancer, small bowel cancer, pancreatic cancer, biliary tract cancer, urothelial/kidney cancer, brain cancer, and sebaceous gland neoplasms.[3,4] Lynch syndrome is caused by germline mutations in the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, or by germline mutations in *EPCAM* which causes epigenetic silencing of *MSH2*.[5,6] Prospective data indicated that screening colonoscopies beginning in the early 20s can markedly reduce colorectal cancer incidence and colorectal cancer-related mortality in individuals with Lynch syndrome.[7] For women with Lynch syndrome, risk-reducing hysterectomy and salpingo-oophorectomy can drastically reduce the risk of endometrial and ovarian cancers.[9]

In 1991, before the discovery that germline mutations in the MMR genes were the underlying genetic defect in Lynch syndrome, the so-called Amsterdam criteria were published with the purpose of creating a uniform definition of the syndrome to facilitate collaborative research efforts.[10] These intentionally strict criteria focused entirely on a family history of colorectal cancer and were later used to identify individuals for Lynch syndrome genetic testing, but they were ultimately found to have poor sensitivity and specificity. In 1997, the National Cancer Institute sponsored a workshop that generated the Bethesda guidelines,[11] which were a multifaceted list of clinical, histologic, and family history features meant to identify patients with colorectal cancer whose tumors should undergo microsatellite instability (MSI) testing as a screen for Lynch syndrome. These complex guidelines proved to be too cumbersome for clinicians to remember and use in routine clinical practice and have also largely become obsolete.[12]

The primary strategy currently used in routine clinical practice to identify patients with Lynch syndrome involves screening of colorectal cancer tumor specimens for evidence of high-level MSI (MSI-H) and/or DNA MMR deficiency (MMR-D).[4,13,14] Studies have consistently found that so-called universal tumor testing (ie, performing polymerase chain reaction-based MSI testing or immunohistochemical staining for DNA MMR protein expression [MMR IHC]) of all colorectal cancers is an effective way to screen patients with colorectal cancer for evidence of Lynch syndrome, because Lynch-associated cancers virtually always find MSI-H and MMR-D.[15–18] With a growing array of data to indicate that universal tumor testing with MSI or MMR IHC markedly increases the recognition of patients with Lynch syndrome compared with older strategies that used clinical criteria such as the Bethesda guidelines or Amsterdam criteria, guidelines put forth by the National Comprehensive Cancer Network (NCCN), the American College of Gastroenterology (ACG), and others currently endorse universal tumor testing on all colorectal cancer specimens.[4,13–17] Universal tumor testing appears to be highly cost-effective, but its performance in real-world practice ultimately depends on other healthy relatives undergoing genetic testing for Lynch syndrome after an individual with MSI-H and/or MMR-D colorectal cancer is found to have a germline mutation that causes Lynch syndrome.[19,20]

Subsequent studies reported that tumor testing may be equally as effective in screening endometrial cancer specimens for evidence of Lynch syndrome and have led to efforts to implement universal testing of patients with endometrial cancer as well.[6,21–23] Tumor testing of other Lynch-associated cancers, colorectal adenomas, and sebaceous adenomas have all been examined in small cohorts of patients, but it remains unclear as

Table I. Hereditary colorectal cancer syndromes.

Syndrome Name(s)	Linked Gene(s)	Classic Phenotypic Features and Cancer Risks	Key Management Strategies	Refs.
Mismatch repair deficiency syndromes				
Lynch syndrome Alternate name: hereditary nonpolyposis colorectal cancer (HNPCC) Subtypes/variants: Muir-Torre syndrome (sebaceous neoplasia) Turcot syndrome (glioma)	*MLH1, MSH2, MSH6, PMS2, EPCAM*	Colorectal cancer risk, proximal colonic predominance Endometrial adenocarcinoma risk, particularly endometrioid histology Increased risk of cancers of the ovary, stomach, small intestine, pancreas, urinary tract and biliary tree, among other sites Tumors display MSI-H and deficient MMR protein expression	Annual colonoscopy, starting at age 20–25 years TAH-BSO once childbearing is complete Upper endoscopy every 3–5 years, beginning at age 30–35 years Aspirin chemoprevention Dermatology evaluations	7,8,13,14,114–120
Adenomatous polyposis syndromes				
Familial adenomatous polyposis (FAP) Subtypes/variants: Gardner syndrome (extracolonic manifestations)	*APC*	>100 colorectal adenomas, often beginning in teenage years Extremely high colorectal cancer risk Fundic gland polyps of the stomach	Annual colonoscopy or flexible sigmoidoscopy, beginning in puberty Total colectomy whenever polyp burden becomes too high to manage by endoscopy Screening endoscopy and duodenoscopy (with side-viewing scope), starting at age 20–25 years Annual thyroid ultrasound scan	13,14,121–131

(continued)

Table I. (continued).

Syndrome Name(s)	Linked Gene(s)	Classic Phenotypic Features and Cancer Risks	Key Management Strategies	Refs.
		Duodenal/ampullary adenomas and adenocarcinomas Increased risk of gastric cancer, desmoid tumors, papillary thyroid cancer, and brain tumors, particularly medulloblastoma Strong association with congenital hypertrophy of the retinal pigment epithelium, epidermoid cysts, and osteomas		
Attenuated familial adenomatous polyposis (AFAP)	*APC* (present in a minority of cases)	10–99 lifetime colorectal adenomas	Colonoscopy every 1–2 years, starting at age 20 years Colectomy if colonoscopy not adequate for screening	13,14,121-126, 131–133
		Likely increased risk of gastroduodenal and thyroid neoplasia	Screening endoscopy and duodenoscopy (with side-viewing scope), starting at age 20–25 years Consider annual thyroid ultrasound scan	
MUTYH-associated polyposis (MAP)	*MUTYH* (biallelic mutations)	>10 lifetime adenomas	Annual colonoscopy	3,13,14,52,59,134–138
		35%–58% of colorectal cancer diagnoses occur before an individual has had 10 lifetime adenomas	Colectomy if colonoscopy not adequate for screening	

(continued)

Table I. (continued).

Syndrome Name(s)	Linked Gene(s)	Classic Phenotypic Features and Cancer Risks	Key Management Strategies	Refs.
		Autosomal recessive pattern of inheritance Somatic *KRAS* G12C mutations may be present in colorectal cancers/adenomas Cancer risk for monoallelic *MUTYH* mutation carriers is controversial Suspected increased risk of gastroduodenal and thyroid neoplasia	Screening endoscopy and duodenoscopy	
Hamartomatous polyposis syndromes				
Peutz-Jeghers syndrome (PJS)	*STK11*	Mucocutaneous pigmentation	Endoscopy, capsule endoscopy, and colonoscopy every 3 years, starting during childhood/adolescence (small bowel imaging, beginning at age 8–10 years)	13,14,70,139,140
		Multiple hamartomatous polyps of the GI tract	Pancreatic cancer screening with MRI and/or EUS, beginning at age 35 years	
		Colorectal cancer risk	Breast MRI, starting at age 25 years in women	
		Breast and pancreatic cancer risk	Annual pap test and pelvic examination	
		Cervical adenoma malignum Lung adenocarcinoma Sertoli cell tumors	Annual testicular examination	

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Table I. (continued).

Syndrome Name(s)	Linked Gene(s)	Classic Phenotypic Features and Cancer Risks	Key Management Strategies	Refs.
Juvenile polyposis syndrome	*SMAD4, BMPR1A, ENG*	Juvenile polyps of the GI tract Colorectal cancer risk Gastric cancer risk Subset of patients with germline *SMAD4* mutations will have concurrent HHT	Endoscopy and colonoscopy every 1–3 years, starting at age 12–15 years Screen for vascular lesions associated with HHT at birth	13,14,141–143
PTEN hamartoma tumor syndrome Alternate names: Cowden syndrome Bannayan-Riley-Ruvalcaba syndrome	*PTEN*	Multiple GI hamartomas or ganglioneuromas Trichilemmomas and other mucocutaneous lesions Breast cancer risk Endometrial cancer risk Thyroid neoplasia risk Macrocephaly	Colonoscopy at least every 5 years, starting at age 35 years Annual dermatology examination by age 18 years Breast MRI, starting at age 30 years Consider endometrial cancer screening Annual thyroid examination with consideration of thyroid ultrasound scan	13,14,70,144,145
Serrated polyposis syndrome (SPS)	Most cases do not have identifiable germline mutation; debate exists over whether this is a genetic syndrome	>5 serrated polyps proximal to the sigmoid colon with ≥2 over 10 mm OR	Colonoscopy every 1–3 years for individuals with SPS Begin screening colonoscopy at age 40 years for first-degree relatives of patients with SPS	13,14,146,147

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Table I. (continued).

Syndrome Name(s)	Linked Gene(s)	Classic Phenotypic Features and Cancer Risks	Key Management Strategies	Refs.
		Serrated polyps proximal to the sigmoid colon in a patient with a relative with SPS OR > 20 serrated polyps of any size throughout the colon		
Miscellaneous syndromes				
Li-Fraumeni syndrome (LFS)	*TP53*	Early onset malignancies Core cancers: leukemia, brain tumors, sarcomas, breast cancer, and adrenocortical tumors Risk of numerous other primary malignancies over lifetime, including colorectal cancer	Colonoscopy every 2–5 years, starting at age 25 years Breast MRI at age 20 years Consideration of whole-body MRI (ideally as part of a clinical trial)	30,63–65,70,148
Familial colorectal cancer type X (FCCX)	Most cases do not have identifiable germline mutation	Colorectal cancer, distal colonic predominance Family history consistent with Amsterdam criteria but tumors do not find MSI-H/MMR-D	Colonoscopy at least every 3–5 years, starting 10 years before youngest family diagnosis	71

EUS = endoscopic ultrasound; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; MMR = mismatch repair; MMR-D = mismatch repair deficiency; MRI = magnetic resonance imaging; MSI-H = high-level microsatellite instability; SPS = Serrated polyposis syndrome; TAH-BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

to how effective MMR IHC and MSI testing are at screening such neoplasms for underlying Lynch syndrome.[24–28]

A key limitation to the use of tumor testing for identifying patients with Lynch syndrome is that it requires available tumor tissue for MMR IHC and/or MSI polymerase chain reaction. Thus, alternate strategies are needed for Lynch syndrome evaluation among individuals who have not had a prior cancer or for whom tissue is unavailable. As such, multiple clinical prediction models are available that can provide a numeric estimate of an individual's likelihood of having an underlying germline mutation in a DNA MMR gene on the basis of analysis of their personal and family history.[29,30]

MMRpro (available online for free clinical- and research-based use at https://www4.utsouthwestern.edu/breasthealth/cagene) is a prediction model developed with Bayesian statistics, which estimates an individual's likelihood of having a germline mutation in *MLH1*, *MSH2*, and *MSH6*, based on personal and family history of colorectal and endometrial cancers.[31] Similarly, the $PREMM_{1,2,6}$ model (available for free online use at premm.dfci.harvard.edu) was developed with multivariable logistic regression and provides an estimate of an individual's likelihood of having a germline mutation in *MLH1*, *MSH2*, and *MSH6* with the use of personal and family history data about colorectal cancer, endometrial cancer, and other Lynch-associated neoplasms (ovarian, gastric, small intestine, urinary tract, biliary, brain, and pancreatic cancers and sebaceous adenomas).[32] Although they were developed with differing statistical methods, MMRpro and $PREMM_{1,2,6}$ are comparable in their abilities to discriminate Lynch syndrome mutation carriers versus noncarriers, and both appear to have superior performance to the use of clinical criteria such as Amsterdam guidelines and Bethesda criteria.[4,29,30,33] Cost-effectiveness analyses and validation studies found that prediction models such as MMRpro and $PREMM_{1,2,6}$ perform optimally when individuals predicted to have a $\geq 5\%$ likelihood of Lynch syndrome undergo germline testing.[30,34] As such, guidelines from the NCCN and ACG endorse the use of MMRpro and $PREMM_{1,2,6}$ as Lynch syndrome risk assessment tools and recommend that patients with scores $\geq 5\%$ undergo Lynch syndrome genetic testing.[13,14]

Limitations of MMRpro and $PREMM_{1,2,6}$ include that they are not designed to provide prediction for *PMS2* or *EPCAM* mutation carriage. Furthermore, their discriminatory capacity is limited in women with endometrial cancer and in certain ethnic populations.[35,36] Questions were also raised as to whether these models' predictions are specific to detecting patients with Lynch syndrome, or if they instead simply identify patients at high risk of some sort of hereditary cancer.[37] As the use of next-generation sequencing multigene panels continues to supplant phenotype-directed syndrome-specific genetic testing, it is likely that new clinical prediction models will need to be developed to assess for risk of a wide spectrum of hereditary cancer.

Updates in Clinical Genetic Testing

The standard method of hereditary cancer evaluation has classically involved individuals undergoing germline genetic testing for a particular syndrome if they fulfill clinical criteria for that syndrome or have other syndrome-specific features (eg, MSI-H/MMR-D colorectal cancer being a sign of possible underlying Lynch syndrome). Advances in next-generation DNA sequencing technologies have made it efficient and affordable to analyze dozens of genes simultaneously, however, and have led to the commercial availability of multigene panels for hereditary cancer risk assessment.[38,39] Such multigene panels allow patients to undergo germline testing for a wide spectrum of cancer susceptibility syndromes in parallel. Thus, the multigene panels are a potentially attractive alternative to phenotype-directed syndrome-specific testing, although numerous questions and concerns about their use have arisen.[38,40]

One recent study that examined the use of a 25-gene panel found that 5.6% of patients suspected to have Lynch syndrome actually had mutations in non-Lynch cancer susceptibility genes, including high-penetrance genes such as *APC*, *MUTYH*, *STK11*, *BRCA1*, *BRCA2*, and *PALB2*.[37] Interestingly, many of these non-Lynch mutation carriers appeared to have personal and family histories suggestive of Lynch syndrome, illustrating the potential for phenotypic overlap between syndromes.[37] Of concern, however, was the finding of germline variants of uncertain significance (VUSs) in 38% of study subjects and the detection of germline mutations in poorly defined moderate-penetrance genes such as *ATM*, *BARD1*, *BRIP1*, and *NBN*.[37]

A similar study of patients whose clinicians specifically ordered germline testing with a colorectal cancer-focused 14-gene panel found pathogenic

mutations in 10.4% of individuals but also VUSs in 20.4% of individuals.[41] Within this cohort, 69% of the pathogenic mutations identified were deemed "actionable," in that they were in genes linked to well-described phenotypes for which risk-reducing management guidelines are available, although the clinical significance of the other 31% of mutations remains unclear.[41]

Another study examined the use of exome sequencing of 10 genes linked to hereditary colorectal cancer among a cohort of patients in a population-based registry of early-onset and suspected familial colorectal cancer.[42] Within this cohort, 14.2% were found to have a germline mutation in a colorectal cancer susceptibility gene, including 3.3% with a non-Lynch syndrome mutation, although only 10% of patients were found to have a VUS, possibly because of the more limited nature of the germline testing in this study.[42]

The high rate of VUSs and other uncertain findings found by multigene next-generation sequencing in each of these studies creates the potential for added patient anxiety and potential misinterpretation (and overtreatment or undertreatment) by both patients and clinicians, indicating the potential limitations and risks of such broad-based germline evaluation.[38,40] As such, some have expressed caution about the use of multigene panel testing in routine hereditary cancer risk assessment pending further data, and a recent policy statement update by the American Society for Clinical Oncology advised that "providers with particular expertise in cancer risk assessment" be involved in ordering and interpreting the results of multigene panel testing.[43] Currently, NCCN guidelines on familial colorectal cancer risk assessment do not comment specifically on the use of multigene panel testing.[14]

With further research on multigene panel testing, it is likely that the risk of colorectal cancer and other cancers conferred by the various genes found on commercially available multigene panels will be more precisely understood. Furthermore, it is anticipated that the genes available on such panels will continue to evolve as new genes linked to hereditary colorectal cancer risk are discovered.

Refining the Colorectal Cancer Risk from Other Known Hereditary Syndromes

Germline mutations in *BRCA1* and *BRCA2* are a common cause of hereditary breast/ovarian cancer present in ~0.2% to 0.3% of the general population and as many as 2.5% of unselected individuals of Ashkenazi Jewish (AJ) ancestry.[44–47] In addition to the breast and ovarian cancer risks conferred by *BRCA1/2* mutations, mutation carriers are at increased lifetime risk of pancreatic cancer, prostate cancer, and melanoma, and there has long been debate as to whether there is an increased risk of colorectal cancer.[48–50] Recent data that examined the yield of multigene panel testing in patients with suspected Lynch syndrome found a surprisingly high number of individuals with germline *BRCA1* and *BRCA2* mutations, most of whom had personal histories of colorectal cancer.[37] The clinical histories of the *BRCA1/2* mutation carriers in this study, particularly the male mutation carriers, appeared to lack classic signs of hereditary breast/ovarian cancer, although almost all met clinical criteria for Lynch syndrome testing.[37] A recent prospective study of 7015 women with *BRCA1* or *BRCA2* mutations found an excess of incident colorectal cancer diagnoses for women with *BRCA1* mutations aged $\leq$50 years, but not for other subgroups, leading the investigators to propose that women with *BRCA1* mutations begin having screening colonoscopies every 3 to 5 years, beginning at age 40 years.[51] The question of whether *BRCA1* and *BRCA2* mutation carriers benefit from enhanced colorectal cancer screening remains open to debate, however, and further studies will be needed to conclusively address whether these mutations are linked to colorectal cancer risk.

As noted in Table I, patients with biallelic germline mutations in the *MUTYH* base excision repair gene carry a diagnosis of *MUTYH*-associated polyposis and are at markedly increased lifetime risk of colorectal cancer, typically with concurrent colorectal polyposis or oligopolyposis.[52–54] The clinical significance of monoallelic germline *MUTYH* mutations is an important source of debate, especially because some data suggest that the prevalence of monoallelic *MUTYH* mutations may be as high as 1% in the general population.[55] Multiple studies reported a >2-fold increased lifetime risk of colorectal cancer for monoallelic *MUTYH* mutation carriers, compared with the general population, and have found that monoallelic *MUTYH* mutation carriers who also have a family history of early-onset colorectal cancer have a lifetime colorectal cancer risk in excess of 10%.[53,56–58] Numerous other large, well-designed studies, however, have reported no increased risk of colorectal cancer for monoallelic *MUTYH* mutation carriers.[59–61] Thus, the clinical

significance of *MUTYH* mutation carrier status remains questionable, although at the very least it should prompt relatives with a known history of colorectal cancer and/or polyposis to be tested for biallelic mutation carriage.[37]

Li-Fraumeni syndrome (LFS) is a highly penetrant autosomal dominant cancer susceptibility syndrome usually caused by a germline mutation in the *TP53* tumor suppressor gene.[62] Classically, individuals with LFS are at markedly increased risk of early-onset cancers, including female breast cancer, leukemia, sarcomas, adrenocortical cancer, and choroid plexus carcinomas, although a wide variety of other cancers, including colorectal cancer, were linked to LFS.[62–69] In a large registry of 64 families with classic LFS, 16% of families and 2.8% of patients had a reported diagnosis of early-onset (age: <50 years) colorectal cancer.[64] Within that study, the mean age at colorectal cancer diagnosis was 33 years, although 3 patients were diagnosed at age ≤ 15 years.[64] In a separate, large, registry-based cohort of patients with colorectal cancer, 1.3% of patients diagnosed with colorectal cancer at age ≤ 40 years were found to carry a germline *TP53* alteration, although it is not clear that all of these alterations were truly pathogenic mutations.[65] Interestingly, none of the *TP53* alteration carriers in this study had personal or family cancer histories that met clinical criteria for LFS.[65] Despite such data, the true prevalence of germline *TP53* mutations in patients with colorectal cancer remains undefined, and it is unclear how best to identify patients with colorectal cancer who should undergo germline *TP53* testing. In those with LFS with or without a documented germline *TP53* mutation, NCCN guidelines currently recommend that screening colonoscopies begin at age 25 years with future examinations every 2 to 5 years.[70]

Emerging Genes Linked to Hereditary Colorectal Cancer Risk

For the past 10 years, the term familial colorectal cancer type X (FCCX) was used to broadly categorize families that have an obvious hereditary pattern of colorectal cancer without MSI-H/MMR-D or profound polyposis, because the genetic basis of such families' colorectal cancer risk was unknown.[71] Facilitated by advances in genetic sequencing technology, recent studies have identified additional colorectal cancer susceptibility genes that account for a fraction of such cases, and more such genes are likely to be discovered in the near future with ongoing research into familial cancer risk.

Whole-genome sequencing of several families with unexplained autosomal dominant FCCX-like patterns of colorectal cancer and oligopolyposis led to the identification of germline mutations in the proofreading domains of the *POLE* and *POLD1* genes, which encode for DNA polymerases ε and δ, respectively.[72] The syndrome linked to such germline mutations was since termed polymerase proofreading-associated polyposis (PPAP) and appears to be rare, accounting for 0.25% to 0.5% of patients with familial colorectal cancer and/or polyposis in recent studies.[42,73] The colorectal cancers that develop in PPAP demonstrate a hypermutated phenotype, presumably because of their underlying polymerase proofreading defect, and are typically microsatellite stable (MSS) with intact DNA MMR function.[72,74,75] There are reports of PPAP-related colorectal cancers with MSI-H because of somatic biallelic MMR gene alterations,[73,76] demonstrating the potential for PPAP to mimic Lynch syndrome. PPAP appears to confer a high lifetime risk of early-onset colorectal cancer[42] and, in some cases, colorectal oligopolyposis,[74] although data remain relatively limited to date and subject to potential ascertainment bias such that the true penetrance of colorectal neoplasia remains undefined. Multiple studies also reported a link between PPAP and endometrial cancer risk,[72,74] and data suggest risks of duodenal neoplasia,[77] although the full phenotypic spectrum of this syndrome continues to be defined. Some experts have advocated for patients with PPAP to follow the same gastrointestinal cancer screening guidelines used for patients with Lynch syndrome (colonoscopies every 1–2 years, beginning at age 20–25 years and upper endoscopies every 3 years) with consideration of endometrial cancer risk reduction, but such recommendations have not been clinically studied.[74]

Expanding use of strategies such as exome sequencing with linkage analysis has led to the identification of candidate causative germline mutations in other, individual families previously classified as FCCX. In one 4-generation family with FCCX, a germline truncating mutation in the *RPS20* gene that encoded for the S20 component of the ribosomal subunit was identified by exome sequencing and was purported to be the cause of the family's autosomal dominant

colorectal cancer risk.[78] Interestingly, additional data are now also linking Diamond-Blackfan anemia, a rare well-characterized hereditary ribosomopathy, with increased risks of various cancers, including colorectal cancer, particularly in individuals with germline *RPS19* mutations.[79] Exome sequencing of another family with FCCX led to the identification of germline truncating mutations in *FAN1*, a gene involved in the Fanconi anemia DNA crosslink repair pathway whose protein product also interacts with MMR proteins, in 3 individuals with MSS colorectal cancer.[80] Germline alterations in *FAN1* were subsequently identified in 4 additional families with FCCX, and the tumors from affected individuals were not hypermutated and had a predominance of C:G > G:C and T:A > G:C transversions, supporting the hypothesis that these individuals' *FAN1* alterations were indeed causative of their colorectal cancer risk.[80]

Beyond families with FCCX-like patterns of colorectal cancer risk, additional advances were made in the understanding of other apparently rare hereditary colorectal cancer conditions. A large germline duplication upstream of the *GREM1* gene was linked to families with hereditary mixed polyposis syndrome, a rare syndrome with apparent autosomal dominant inheritance in which individuals have an increased risk of colorectal cancer and develop numerous colorectal polyps of varying histologic features, including serrated polyps, hamartomatous polyps, traditional adenomas, and polyps with multiple histologic features.[81] To date, this *GREM1* alteration has only been identified in individuals of AJ ancestry, suggesting it may be a founder mutation.

The contribution of autosomal recessive and non-Mendelian genetic factors to hereditary colorectal cancer risks remain particularly poorly defined, likely because the familial patterns of cancer development are inherently difficult to identify. Within a cohort of 51 patients from 48 families with colorectal adenomatous polyposis suspected to have a hereditary basis, whole-exome sequencing found 7 Dutch individuals from 3 unrelated families with biallelic germline mutations in *NTHL1*, a base excision repair gene like *MUTYH*. In addition to colorectal adenomas, 5 of the 7 patients had multiple primary cancers and 4 had a history of colorectal cancer.[82] A subsequent case report of a Canadian woman of German ancestry with early-onset colorectal oligopolyposis and numerous diverse invasive cancer diagnoses identified biallelic *NTHL1* mutations.[83] In both reports, somatic genetic analysis of the cancers and adenomas from patients with biallelic *NTHL1* mutations found a relative increase in G:C > T:A transitions, similar to what was observed in *MUTYH*-associated polyposis and fitting with the base excision repair defect predicted from loss of normal NTHL1 function.[82,83]

Treatment Considerations in Hereditary Colorectal Cancer

Until recently, the chemotherapeutic management of colorectal cancer diagnosed in the setting of a hereditary cancer syndrome was essentially the same as the treatment of patients with sporadic colorectal cancer. A key exception stems from compelling data that consistently indicate a lack of benefit from 5-fluorouracil monotherapy in the adjuvant treatment of stage II and stage III MSI-H colon cancer.[84,85] Recent data now strongly suggest that MSI-H/MMR-D tumors, including colorectal cancers, may be highly responsive to immune checkpoint blockade with drugs such as pembrolizumab when treated in the metastatic setting.[86] A recent Phase II study of single-agent pembrolizumab reported objective response rates of 40% and 78%, respectively, for heavily pretreated patients with metastatic MSI-H colorectal cancer and metastatic MSI-H non-colorectal cancer.[86] Most of these patients had known diagnoses of Lynch syndrome.[86] In stark contrast, the objective response rate was 0% among patients with metastatic MSS colorectal cancer, and these patients had a median overall survival of only 5 months (whereas neither the MSI-H colorectal cancer nor MSI-H non-colorectal cancer cohorts reached the median overall survival).[86] The study's investigators speculated that immunogenic mutation-associated neoantigens generated by the tumors' MMR deficiency may make MSI-H cancers particularly susceptible to immune-based therapies, and they indeed found that the overall somatic mutational load was significantly associated with outcome in this small study.[86]

Advances were also made in the realm of aspirin chemoprevention for patients with hereditary colorectal cancer. A randomized double-blind, placebo-controlled trial of 861 individuals with Lynch syndrome found that 600 mg aspirin/d was associated with a significantly lower rate of incident colorectal cancer (hazard ratio [HR] = 0.41; 95% CI, 0.19–0.86; $P = 0.02$) and any incident Lynch-associated cancer (HR = 0.45; 95% CI, 0.26–0.79; $P = 0.005$),

when taken for a minimum of 2 years.[8] Subgroup analysis found a significant association between increasing body mass index (BMI) and development of incident colorectal cancer (adjusted HR = 1.10 per kg/m^2 of BMI; 95% CI, 1.03–1.17) in patients randomized to receive placebo, but no significant association between BMI and development of incident colorectal cancer (adjusted HR = 1.00 per kg/m^2 of BMI; 95% CI, 0.90–1.12) in patients randomized to receive aspirin, suggesting that the chemopreventive effects of aspirin in Lynch syndrome may be limited to overweight and obese individuals.[87] Despite such data, both the ACG and NCCN currently state that data are insufficient to justify recommending aspirin to all patients with Lynch syndrome.[13,14] An ongoing follow-up randomized clinical trial is investigating different doses of aspirin (100, 300, and 600 mg/d) in individuals with Lynch syndrome, although the trial is not currently open in the United States (NCT02497820).

HEREDITARY/FAMILIAL PANCREATIC CANCER

It is widely known that pancreatic cancer, although accounting for only 3% of all cancer diagnoses, is a disease that has an exceedingly high mortality rate, making it the fourth leading cause of cancer death in the United States.[1] Most patients with pancreatic cancer are diagnosed at an advanced and incurable stage, and the 5-year survival of such patients is 1% to 3%, the lowest of any solid tumor.[1] Individuals with risk of pancreatic cancer that exceeds the general population lifetime risk of 1.3% are faced with the uncertainty of living with risk of a disease of which no known evidence-based mechanisms for prevention or early detection are known, and of which curative treatment options are often not possible.[88] Thus, strategies to improve the identification of at-risk individuals and to explore mechanisms for pancreatic cancer screening are key points of research.

Defining and Identifying Pancreatic Cancer Risk

No single gene is responsible for hereditary or familial pancreatic cancer risk. Rather, multiple hereditary cancer syndromes and associated genes confer an increased lifetime risk of pancreatic cancer (Table II). In addition to well-established links between pancreatic cancer risk and hereditary breast/ovarian cancer[49] (*BRCA1/2*), Lynch syndrome[89] (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*), Peutz-Jeghers syndrome[90] (*STK11*), familial atypical multiple mole melanoma syndrome[91] (*CDKN2A*), and hereditary pancreatitis[92] (*PRSS1*), studies also reported that germline mutations in *PALB2*,[93] *ATM*,[94] and *TP53*[95] are also linked to increased pancreatic cancer risk, although the magnitude of risk remains unknown.[13,88] Only ~20% of individuals with apparent hereditary pancreatic cancer risk, however, have an identifiable germline mutation in 1 of these genes.[96] The remainder of patients with suspected pancreatic cancer risk are often classified as having familial pancreatic cancer (FPC), which is currently defined as a family with ≥2 individuals who are first-degree relatives of one another with pancreatic cancer, in the absence of an identifiable genetic mutation.[13]

Currently, minimal guidelines are available to select patients with pancreatic cancer who should undergo germline genetic testing (beyond standard guidelines for *BRCA1/BRCA2* mutation testing, Lynch syndrome analysis, etc).[14,70] Recent guidelines put forth by the ACG[13] recommend referral for genetic evaluation for patients with pancreatic cancer who fulfill syndrome-specific clinical criteria for any of the syndromes associated with pancreatic cancer. The ACG defines individuals to be at risk of pancreatic cancer if they have a known hereditary syndrome linked to pancreatic cancer (Table II), have a clinical history of hereditary pancreatitis, or if they have a strong family history of pancreatic cancer (defined as ≥2 relatives with pancreatic cancer if at least 1 is a first-degree relative, or ≥3 total relatives with pancreatic cancer).[13] The ACG also recommends that individuals undergoing genetic testing in the setting of FPC be tested for mutations in *BRCA1*, *BRCA2*, *PALB2*, and *ATM*, with consideration of testing for Lynch syndrome and hereditary pancreatitis if indicated by family history.[13] In addition, PancPro (https://www4.utsouthwestern.edu/breasthealth/cagene) is a clinical prediction model analogous to MMRpro (described in "Identifying Patients with Lynch Syndrome") that uses personal and family history data, including prior genetic testing results, to estimate an individual's future risk of developing pancreatic cancer.[97]

Several recent studies have attempted to quantify the fraction of pancreatic cancer cases that are attributable to specific genetic syndromes. In a clinic-based study of 306 Canadian patients with pancreatic

Table II. Hereditary cancer syndromes linked to pancreatic cancer risk.[13,96,149,150]

Genes Linked to Pancreatic Cancer Risk	Syndrome Name	Relative Risk of Pancreatic Cancer Versus General Population	Phenotypic Features (Beyond Pancreatic Cancer)
BRCA1	Hereditary breast/ovarian cancer	*BRCA1*: 2–3	Early-onset breast cancer Ovarian cancer
BRCA2		*BRCA2*: 3–9	Male breast cancer Prostate cancer Melanoma
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Lynch syndrome	9–11	See Table I
STK11	Peutz-Jeghers syndrome (PJS)	≤132	See Table I
CDKN2A	Familial atypical multiple mole melanoma (FAMMM) syndrome	13–39	Multiple early onset melanomas
PRSS1	Hereditary pancreatitis	>50	Chronic/recurrent pancreatitis
PALB2		Unknown	Increased risk of female breast cancer
ATM		Unknown	Moderately increased risk of female breast cancer
TP53	Li-Fraumeni syndrome (LFS)	Unknown	See Table I
Likely other unknown genes	Familial pancreatic cancer (FPC)	4–7 if 1–2 FDR with pancreatic cancer 17–32 if ≥3 FDRs with pancreatic cancer	By definition, a family (lacking a germline mutation and who does not meet criteria for another hereditary syndrome) with multiple pancreatic cancer diagnoses ≥2 of whom are FDRs of one another

FDR = first-degree relative.

cancer, 14 (4.6%) carried germline mutations in *BRCA1/BRCA2*, most of whom did not fulfill NCCN or other clinical criteria for *BRCA1/2* testing.[70,98] Within this cohort, AJ ancestry was significantly associated with carrying a *BRCA1/2* mutation (12.5% of individuals with AJ ancestry carried a mutation), and mutation carriers did not seem to have particularly young-onset pancreatic cancer (mean age at diagnosis: 64 years).[98]

The same group of investigators also studied a population-based cohort of 290 Canadian patients with pancreatic cancer in which they found the prevalence of germline mutations among 13 genes linked to pancreatic cancer risk to be 3.8%.[99] Within this cohort, personal or family history of breast cancer or colorectal cancer was significant predictors for carrying a germline mutation, with >10% of patients with such histories being mutation

carriers.[99] Age at pancreatic cancer diagnosis did not predict for carrying a mutation, because both carriers and noncarriers were diagnosed at a mean age of 64 years.[99]

Within another cohort of 159 patients with pancreatic cancer that was heavily enriched for individuals with AJ ancestry, multigene germline testing found 15.1% to be mutation carriers, with *BRCA2* mutations accounting for more than one-half of all mutations identified.[100] Individuals with AJ ancestry in this study had an overall mutation prevalence of 15.6%, with all of the identified mutations being known AJ founder mutations in *BRCA1*, *BRCA2*, *MSH2*, and *MSH6*, prompting the investigators to conclude that AJ ancestry alone is enough to warrant genetic testing among patients diagnosed with pancreatic cancer.[100] In large part because of these recent analyses that indicated a mutation prevalence of 12.1% to 15.6%[98,100] in patients of AJ ancestry with pancreatic cancer, NCCN guidelines were recently updated,[70] and they now recommend germline genetic testing for all patients of AJ ancestry with pancreatic cancer, regardless of age or family history.

Therapeutic Considerations in Hereditary Pancreatic Cancer

Given the dismal survival statistics for pancreatic cancer, most patients with pancreatic cancer who are subsequently found to carry a germline mutation in a cancer susceptibility gene will not benefit from additional screening for other metachronous cancers. Although finding a germline mutation may not help the proband for cancer prevention, however, there are therapeutic avenues that can be considered for some individuals with hereditary pancreatic cancer. A recent retrospective analysis of 549 patients with metastatic pancreatic cancer treated with palliative chemotherapy (before the widespread use of newer regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel) found that patients with family histories of cancer had improved survival compared with those without a family history of cancer.[101] Within that study, survival was particularly good for patients with pancreatic cancer with numerous relatives with *BRCA1/2*-associated cancers (breast, ovarian, and/or pancreatic cancer), suggesting that some of these probands may have had underlying mutations, although germline analysis was not performed.[101] The investigators also found that treatment with first-line platinum-based chemotherapy (known to be particularly effective in *BRCA1/2*-associated breast and ovarian cancer) was associated with superior median overall survival (14.8 months) in patients with a family history of ≥ 3 relatives with these cancers, compared with patients without a known family history of cancer (median overall survival: 7.3 months; $P = 0.002$).[101]

Like platinum salts, poly (ADP-ribose) polymerase (PARP) inhibitors have become key strategies for treating advanced breast and ovarian cancers that arise in the setting of germline *BRCA1/2* mutations, and a recent Phase II study of single-agent olaparib reported a 57% disease control rate (stable disease plus partial/complete responses) among patients with *BRCA1/2*-associated pancreatic cancer.[102] Numerous subsequent trials (NCT02184195, NCT1489865, NCT01585805) are investigating a variety of different PARP inhibitors, both as monotherapy and in combination with chemotherapy, in the treatment of pancreatic cancers associated with germline *BRCA1/2* and *PALB2* mutations.[103] Whether platinum agents and PARP inhibitors will prove to have efficacy in patients with pancreatic cancer with germline mutations in other DNA repair genes (eg, *ATM*) remains unknown. As such data emerge, the implications of family history assessment and genetic testing in patients with pancreatic cancer could expand to include benefits beyond hereditary cancer risk assessment.

Pancreatic Cancer Screening

For healthy individuals found to have a germline mutation in a gene linked to pancreatic cancer risk and/or those from families with FPC, the question of how to manage and reduce pancreatic cancer risk is of major importance, particularly because pancreatic cancer is notorious for having a low rate of early-stage diagnosis and cure. As such, pancreatic cancer screening has become a subject of intense research interest. On the basis of data available from the US National Institutes of Health (www.clinicaltrials.gov), there are at least 7 ongoing clinical trials designed to evaluate the efficacy of pancreatic cancer screening in high-risk populations (NCT02309632, NCT02078245, NCT02000089, NCT01662609, NCT02478892, NCT02206360, and NCT02462460).

The multicenter Cancer of the Pancreas Screening 3 study was the first large study to systematically

evaluate pancreatic cancer screening strategies in high-risk individuals.[104] Among 216 high-risk patients, 42% were found to have a radiographic abnormality in the pancreas with the use of magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), or pancreas-protocol computed tomography.[104] Within that study, the prevalence of pancreatic lesions increased significantly after age 50 years. Five individuals (2%) in that study had pancreatic abnormalities detected on screening that led to pancreatic resection, of whom all had histologic evidence of pancreatic intraepithelial neoplasia identified.[104] Of note, computed tomography was markedly less sensitive than MRCP and EUS in this study.[104] A recent Swiss study of MR-based pancreatic cancer screening in high-risk individuals similarly detected pancreatic lesions in 40% of individuals.[105] Within that study, 12.5% of patients underwent pancreatic resection because of abnormalities seen on screening, and 7.5% of the cohort was found to have resectable adenocarcinoma.[105]

In large part because of these data, recent guidelines were published by the ACG and state that EUS and/or MRCP be considered for patients at high risk of pancreatic cancer, beginning at age 50 years or 10 years younger than the earliest pancreatic cancer diagnosis in the individual's family (except for patients with Peutz-Jeghers syndrome, who are recommended to begin screening by age 35 years).[13] The ACG recommends pancreatic cancer screening for all individuals with Peutz-Jeghers syndrome, hereditary pancreatitis, and familial atypical multiple mole melanoma syndrome, regardless of family history.[13] For patients with Lynch syndrome, *BRCA1/2* mutations, *PALB2* mutations, and *ATM* mutations, however, pancreatic cancer screening is recommended only for individuals with a first- or second-degree relative with pancreatic cancer.[13] Similarly, it recommends pancreatic cancer screening for individuals from families with FPC if they have at least 1 first-degree relative with pancreatic cancer.[13]

Patient-reported Psychosocial Outcomes

Despite such recommendations, robust data about the efficacy of such screening are lacking, and pancreatic cancer screening is still considered experimental. It is thus extremely important for patients and providers to give careful consideration to the psychological impact of undergoing screening for such a high-risk cancer, particularly given the uncertainties about the benefits of such screening. As such, the impact that pancreatic cancer risk assessment and screening has on patients' psychosocial well-being has become a key focus of current research.

One study focused solely on patient experiences with genetic counseling related to pancreatic cancer and surveyed 45 at-risk individuals after a genetic counseling session.[106] Overall, patients perceived genetic testing to be helpful and estimated their own risk of pancreatic cancer to be high, with perceptions of lifetime risk being on average 50.8%.[106] It was reported that participants would value genetic counseling more if there was more knowledge about pancreatic cancer risk, personalized risk estimates, and a specific, identified "pancreases cancer gene."[106]

Another recent multicenter prospective observational study evaluated participant experiences and reports of distress related to undergoing EUS and MRCP as part of the Dutch pancreatic cancer surveillance study.[107] Attitudes, experiences, perceived risk, cancer worry, and distress were measured at baseline and then annually for 3 years.[107] The study included individuals unaffected with pancreatic cancer with hereditary syndromes associated with pancreatic cancer risk and 2 affect family members or familial pancreatic cancer risk, defined as ≥ 2 first-degree relatives, ≥ 3 of any sort relatives, or multiple second-degree relatives diagnosed with pancreatic cancer, with 1 diagnosed at the age of ≤ 50 years.[107] Only a small proportion (5%–7%) of the 140 study participants who completed the assessment reported clinically significant distress, and patient worry and dread about screening procedures decreased over time. Participants also felt less risk of pancreatic cancer when they underwent annual surveillance.[107]

A previous cross-sectional study from the same group, reporting on 69 high-risk individuals from 50 families, found that only a small proportion of patients reported significant distress. Interestingly, although all participants were from a high-risk cohort, only 58% felt at high risk compared with the general population. Most felt that screening offered security, 98% felt certain that surveillance would detect cancer, and the benefits to screening outweighed the risk, raising concern about patients' risk perceptions and their understanding of the limitations of pancreatic cancer screening techniques.[108]

Two other prospective studies were completed in a sample of unaffected high-risk individuals, defined as

those with 2 family members affected with pancreatic cancer or with a *BRCA2* gene mutation, who are part of a Canadian pancreatic cancer screening program. In these 2 studies, distress, cancer worry, and risk perception were measured up to 3 months[109] and 1 year.[110] Overall, no significant increases in these outcomes were found over time in these studies, although it was reported that 22.9% of men and 19.9% of women scored above the cutoff for clinical distress at baseline.[109] Distress and cancer worry were higher in patients who were younger and had a strong family history of pancreatic cancer, although individuals with higher baseline distress experienced significant reductions in cancer-related intrusive thoughts over time.[109,110]

Additional studies were performed to evaluate the overall experience reported by individuals living with the knowledge that they are at increased risk of pancreatic cancer,[106,111] their knowledge of pancreatic cancer screening,[112] and their receptivity[113] or intent to engage in pancreatic cancer screening. Two qualitative studies that focused on patient experiences with pancreatic cancer risk[111] and understanding of and intent to engage in pancreatic cancer screening[112] found the family experience was an important factor in how someone viewed their own risk of pancreatic cancer and became motivated to engage in invasive screening. Pancreatic cancer was considered a fatal disease[112]; therefore, screening was viewed as a potential way to catch cancer early.[111] Participants had limited knowledge about the pancreas, pancreatic cancer, and screening,[112] and overall they felt there was a lack of patient-centered resources.[111] More work is needed to understand why a small subset of individuals do have clinically meaningful distress, the impact of having abnormal surveillance results, and how to best intervene to support patients engaging in this process of risk assessment and screening.

SUMMARY

Although a relatively small fraction of patients with colorectal cancer and pancreatic cancer have an identifiable genetic syndrome underlying their cancer risk, the availability of new diagnostic, risk-reducing, and therapeutic strategies that exist for such patients makes it imperative that clinicians be vigilant about evaluating patients for hereditary cancer syndromes. Recent advances in next-generation sequencing have led to the commercial availability of multigene panel testing, which may help increase the number of patients who ultimately undergo germline evaluation, although concerns remain about the high risk of uninformative findings. As genetics research continues at its breakneck pace, our understanding of existing cancer risk genes will certainly improve, whereas new cancer predisposition genes will undoubtedly be discovered, hopefully allowing for ongoing progress toward a goal of personalized cancer medicine and prevention.

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