Published in final edited form as:

Fam Cancer. 2020 July ; 19(3): 223–239. doi:10.1007/s10689-020-00170-9.

Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Position statement on multigene panel testing for patients with colorectal cancer and/or polyposis

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Abstract

Multigene panel tests for hereditary cancer syndromes are increasingly utilized in the care of colorectal cancer (CRC) and polyposis patients. However, widespread availability of panels raises a number of questions including which patients should undergo testing, which genes should be

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Conflict of interest Dr. Hall has clinical trial support from Merck and Astra Zeneca and research collaborations with Caris, Foundation Medicine, Myriad Genetics Laboratories Inc., Ambry Genetics, and Invitae. Ms. Hampel has performed collaborative research with Ambry Genetics, Invitae, and Myriad Genetic Laboratories Inc., and she is on the scientific advisory boards of Invitae and Genome Medical. She has stock in Genome Medical as an advisory board member. Ms. Heald is on the Speakers Bureau for Myriad Genetics Laboratories Inc. and an advisory board for Invitae. Dr. Yurgelun previously received research funding from Myriad Genetics Laboratories Inc. Ms. Stoll has performed collaborative research with Myriad Genetics Laboratory Inc. and is on an advisory board for Invitae. Dr. Kupfer has performed collaborative research with Myriad Genetics Laboratories Inc. The remaining authors have no potential conflicts of interest to declare.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s10689-020-00170-9>) contains supplementary material, which is available to authorized users.

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included on panels, and the settings in which panels should be ordered and interpreted. To address this knowledge gap, key questions regarding the major issues encountered in clinical evaluation of hereditary CRC and polyposis were designed by the Collaborative Group of the Americas on Inherited Gastrointestinal Cancer Position Statement Committee and leadership. A literature search was conducted to address these questions. Recommendations were based on the best available evidence and expert opinion. This position statement addresses which genes should be included on a multigene panel for a patient with a suspected hereditary CRC or polyposis syndrome, proposes updated genetic testing criteria, discusses testing approaches for patients with mismatch repair proficient or deficient CRC, and outlines the essential elements for ordering and disclosing multigene panel test results. We acknowledge that critical gaps in access, insurance coverage, resources, and education remain barriers to high-quality, equitable care for individuals and their families at increased risk of hereditary CRC.

Keywords

Inherited colorectal cancer; Lynch syndrome; Multigene panel testing; Next-generation sequencing; Polyposis; Position statement

Introduction

Recent advances in genomics have led to significant changes in our understanding of hereditary diseases as well as in the practice of genetic counseling and testing. Next generation sequencing has emerged as a faster and less expensive way of performing clinical genetic testing and supports multigene panel testing. Commercial availability of multigene panel tests has raised a number of questions and concerns, including which patients should undergo multigene panel testing, which genes should be included on panels, which panels should be ordered, and the challenges of managing unanticipated findings and variants of uncertain significance (VUS). Professional society guidelines have yet to address multigene panel testing for colorectal cancer (CRC) [1–3]. The National Comprehensive Cancer Network (NCCN) has, for its part, provided examples of clinical scenarios for which multigene panels should or should not be considered to optimize patient care [4].

In order to address the knowledge gap on appropriate use of multigene panel testing (herein defined as a panel that tests more than one gene or syndrome simultaneously) in the evaluation of hereditary CRC and polyposis, key questions were developed by the authors in conjunction with the leadership of the Collaborative Group of the Americas for Inherited Gastrointestinal Cancer (CGA-IGC). Questions were designed to address major issues in clinical evaluation of hereditary CRC and polyposis related to multigene panel testing, and recommendations are based on review of the existing evidence in conjunction with expert opinion.

Methods

A literature search was conducted of Ovid, MEDLINE, Embase, Cochrane CENTRAL, Scopus, and Web of Science for publications between 1974 and 2017. Search terms are available in Supplemental Table 1. Overall, 986 unique publications were identified, and

each article was reviewed by at least two members of the Position Statement Writing committee for inclusion/exclusion determination. Included articles addressed germline multigene panel testing for CRC, polyposis, or other common cancers; were professional society recommendations for germline testing for hereditary cancers; were related to Lynch syndrome (LS) screening or prediction models; or were landmark articles associating genes with hereditary cancer syndromes. If there was disagreement among the two committee members, the article was discussed and voted upon at an in-person meeting with the committee and CGA-IGC leadership. Committee members also conducted manual literature searches.

Based on emerging research, clinical expertise, and gaps in the literature, the committee developed a list of questions (Table 1) to guide the drafting of this position statement. When weighing which genes should be included on a multigene panel to evaluate hereditary CRC or polyposis, committee members considered the following: evidence of proven causation for hereditary CRC/polyposis; evidence of association, without proven causation, with CRC; evidence of association with non-CRC syndromes; whether CRC/polyposis risks are known; prevalence of pathogenic variants (PV) for a given gene; clinical actionability; and whether professional society recommendations exist that endorse testing of the given gene for CRC or a polyposis syndrome. Genes then were categorized into the minimal set that should be included as well as an additional set of genes that should be considered on a multigene panel for comprehensive assessment of risk. Genes included on the minimal set were those with proven causation, known prevalence and CRC/polyposis risk, and/or have been endorsed by other professional societies. Genes on the consideration list were those shown to be associated with CRC/polyposis without clear data on prevalence and/or CRC risk, or those that have been identified in CRC patients that might not have CRC causality but are otherwise medically actionable. The manuscript was distributed to CGA-IGC members by email, and the membership was given a month to provide comment. These edits were incorporated into the manuscript, and the final manuscript was reviewed and approved by all committee members and leadership.

Results

Question 1: Which minimal set of genes should be included on a multigene panel for evaluation of hereditary CRC or polyposis?

All commercially available panels do not include the same genes, and some panels might fail to include genes relevant to the evaluation of hereditary CRC and/or polyposis. The CGA-IGC defined 11 genes (Table 2) in which PV have been associated with hereditary or familial CRC or polyposis. CGA-IGC considers this list of genes to be the *minimal* set of genes that should clinically be tested in all patients suspected of hereditary CRC or polyposis, and recommends this testing be conducted by multigene panel. Multigene panel testing is recommended over targeted gene testing due to overlapping clinical phenotypes, inconsistent definitions for oligopolyposis, challenges with accurately classifying polyp histology (particularly with hamartomatous polyps), and variable modes of inheritance (both dominant and recessive inheritance). A multi-gene panel approach to classify CRC/polyposis risk helps ensure that rare but clinically actionable genes are not missed,

appropriate management is offered, and inheritance counseling is accurately delivered to the patient and family members. CGA-IGC recommends that multigene panel testing include testing of the mismatch repair (MMR) genes responsible for LS (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*) as well as analysis of six genes which account for a smaller overall fraction of incident CRC but are, nonetheless, associated with elevated cancer risks in carriers (*APC*, *MUTYH*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*). Notably, these latter genes all cause various forms of polyposis. Given the overlapping phenotypes, there has been a call for molecular classification of polyposis syndrome [5]. Clinicians should be aware that all of these genes have gene- and/or syndrome-specific guidelines published by various expert groups and societies to guide management [3, 6, 7]. CGA-IGC also defines an additional group of genes to consider when performing hereditary panel testing in this group of patients (Table 3).

A brief description of the estimated prevalence and clinical phenotype associated with each of the hereditary CRC and polyposis genes considered to be relevant for multigene panel testing by the CGA-IGC is provided below.

Pathogenic variants associated with defective mismatch repair (Lynch syndrome): *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*—LS is the most common hereditary CRC syndrome, with an estimated prevalence of 1/279 in the general population, and underlies approximately 2.8–3.1% of incident CRCs and 2.5–5.8% of incident endometrial cancers [8–13]. Germline PV in the MMR gene family cause LS. Genes included in the MMR family are *MLH1*, *MSH2*, *MSH6*, and *PMS2*, whereas germline deletions in *EPCAM* induce epigenetic silencing of *MSH2*. Patients with LS are at increased risk of CRC, endometrial cancer, and several other cancers with evidence supporting variability in cancer risks by affected gene, sex, ethnicity, and other factors. PV in *MLH1* and *MSH2* are generally associated with higher lifetime risks of CRC other LS cancers, while PV in *MSH6* and *PMS2* are generally associated with later onset cancers and overall lower lifetime cancer risks [1]. LS cancers may be seen as early as young adulthood. The majority of CRCs in LS patients display evidence of microsatellite instability (MSI). Although LS CRCs occur in the absence of polyposis, evidence suggests many, but not all, LS tumors are preceded by a colorectal adenoma [14].

Pathogenic variants associated with polyposis and increased risk of CRC: *APC*, biallelic *MUTYH*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*—Germline PVs in the *APC* gene are rare in the general population, and underlie < 1% of incident CRCs. PVs in *APC* are associated with familial adenomatous polyposis (FAP) and more rarely with attenuated FAP. A low penetrance *APC* variant (p.I1307K) that does not cause polyposis¹⁶ but doubles the risk for colorectal cancers is enriched among individuals with Ashkenazi Jewish (AJ) ancestry (10% carrier rate) but might also been seen in patients without or with unknown AJ ancestry [15, 16].

MUTYH-associated polyposis (MAP) was the first reported autosomal recessive hereditary colorectal cancer syndrome. This syndrome has protean manifestations ranging from early-onset CRC absent of polyposis to mild polyposis (0–50 polyps) similar to attenuated FAP to dense polyposis (hundreds of polyps) similar to classic FAP [17]. Sutcliffe et al. found that 10% of patients with MAP had less than ten polyps while 19.5% had a FAP phenotype, and

almost a quarter had extracolonic cancers and multiple primaries [18]. Monoallelic PV in *MUTYH* are common in the general population, especially among Caucasians where two founder PV are prevalent (p.G396D and p.Y179C) [19]. Some studies have shown that carriers of a monoallelic *MUTYH* PV, have an approximate twofold increased risk of developing CRC (equating to ~ 10% lifetime risk of CRC), although it remains uncertain to what degree family history of CRC modulates risk in these *MUTYH* carriers [20].

Juvenile polyposis syndrome (JPS) is associated with early-onset development of polyps and cancer of the GI tract. In JPS, the polyps are histologically distinguishable as hamartomatous juvenile polyps, and germline PV in the *BMPRI1A* and *SMAD4* genes are the cause [21]. Patients with *SMAD4* PV are also at risk to develop hereditary hemorrhagic telangiectasia and are more prone to profuse gastric polyposis [22, 23]. Patients with *BMPRI1A* mutations have been reported to develop adenomatous polyps and mixed polyposis [24].

PV in the *PTEN* gene cause PTEN-hamartoma tumor syndrome (PHTS), an umbrella term that includes Cowden syndrome and Bannayan–Riley–Ruvalcaba Syndrome. In the GI tract, these syndromes are characterized by a mixed polyposis phenotype, including hamartomas, serrated polyps, adenomas, and ganglioneuromas, as well as an increased risk of CRC [25]. PHTS is also associated with an increased risk of breast cancer, endometrial cancer, thyroid cancer, kidney cancer, and melanoma.

Finally, patients who carry rare germline PV in *STK11* manifest Peutz–Jeghers Syndrome (PJS). PJS causes hamartomatous polyposis of the GI tract, most commonly Peutz–Jeghers polyps in the small bowel. Patients with PJS are at risk for a variety of cancers including breast, pancreas, small bowel, CRC, lung, and rare types of reproductive organ cancers [26].

Question 2: Which additional set of genes should be considered on a multigene panel for evaluation of hereditary CRC or polyposis?

Beyond the minimal list of genes recommended for multigene panel testing for patients with suspected hereditary CRC, CGA-IGC recommends that 16 additional genes be considered (Table 3). While large studies examining the prevalence of PV in these genes are relatively few, early and generally small studies have provided data suggesting that germline PV in these genes are variably associated with hereditary CRC. The additional list includes genes associated with low-moderate CRC risk, genes with limited data, and genes with PV found in CRC patients that are actionable but CRC causation is not proven. Inclusion of these genes on a multigene panel has the potential to increase PV detection rate, clarify future cancer risks, drive management, and clarify inheritance risks. However, there are important data limitations for each of these genes that need to be considered by the clinician and patient before ordering this testing. Brief reviews of the phenotype associated with PV in each of these genes are provided below.

Genes associated with low to moderately increased risk of CRC: *ATM*, *CHEK2*, *TP53*—*ATMPV*s are common in the general population and have been detected in several large studies of multigene panel testing in CRC patients [13, 27, 28]. These results are consistent with older studies that suggested that PV in *ATM* confer a risk for both upper GI cancers and CRC [29]. *ATMPV* were found to be enriched in two large cohorts of CRC

patients and second-hits were found in all cases with matched tumor available for sequencing suggesting causation [30]. Germline *ATMPV* are associated with a 2.81–2.97 odds ratio of developing CRC [30].

PV in *CHEK2* are common in the general population and have primarily been associated with hereditary breast cancer, particularly the common PV, c.1100delC, found in those of northwestern European background [31]. However, an association of *CHEK2* PV and CRC has been reported [32, 33]. Pearlman et al., Stoffel et al., and Yurgelun et al. identified *CHEK2* PV in 0.2% each of their cohorts of early-onset CRC, high-risk CRC, and unselected CRC [2, 13, 27, 28].

Germline PV in the *TP53* gene are associated with Li-Fraumeni syndrome, a highly penetrant hereditary cancer syndrome characterized by very high lifetime cancer risks for breast cancer, sarcoma, leukemia, lung, adrenocortical, and other cancers. More recently, a broader phenotypic spectrum of cancers associated with germline *TP53* PV has been uncovered, including CRC. A study of early-onset CRC identified germline missense variants in *TP53* in 1.3% of cases, none of whom had other manifestations of Li-Fraumeni syndrome [34]. Pearlman et al. however reported no *TP53* carriers in their cohort of early-onset CRC, while Stoffel et al. reported 1 in 430 patients with early onset CRC in a high-risk clinic and Yurgelun et al. reported 1 in 1058 in their series of unselected CRCs [2, 13, 27]. Furthermore, McFarland SP et al. described a single-institution cohort of 93 individuals with pathogenic germline *TP53* variants, of whom 8.6% had a diagnosis of either CRC or an adenoma with high-grade dysplasia [35]. Within this cohort, 4.3% of *TP53* carriers had CRC before age 35 and 3.2% were diagnosed before age 25 [35].

Genes with limited data of CRC risk: *GREM1*, *POLE*, *POLD1*, *AXIN2*, *NTHL1*, *MSH3*, *GALNT12*, *RPS20*—Duplications in the gene *SCG5* upstream of *GREM1* are a rare cause of polyposis known as hereditary mixed polyposis syndrome (HMPS) due to the large variety of intestinal polyp histologies seen in affected carriers (e.g. adenomas, serrated lesions, juvenile polyps). To date, the majority of HMPS cases have been associated with a single founder alteration, a 40 kb upstream duplication in individuals of Ashkenazi Jewish ancestry [36]. However, a 16 kb tandem duplication in the *GREM1* promoter has also now been identified as a cause of HMPS in a non-AJ family [37].

PV in the *POLE* and *POLD1* genes have been associated with a hereditary adenomatous oligopolyposis and early-onset CRC phenotype, reminiscent of FAP in some kindreds and LS in others. The syndrome associated with PV in these genes is known as polymerase proofreading-associated polyposis (PPAP). PV appear to cluster in the genes' internal exonuclease domains, but exceptions have been reported [38]. While the tumor spectrum of PPAP is still being defined, patients with *POLD1* associated PPAP may also have risks of endometrial cancer and PV in both genes have been associated with brain tumors [38].

The phenotype associated with germline *AXIN2* PV is one of gastrointestinal polyposis (adenomatous) and ectodermal dysplasia, including tooth agenesis. PV in *AXIN2* appear to be present, but rare, among patients with diffuse colorectal polyposis that is clinically indistinguishable from FAP [39].

NTHL1 functions in the base excision repair pathway, similar to *MUTYH*. Individuals with biallelic *NTHL1* PV have an attenuated polyposis phenotype (20–50 adenomas and an increased risk of CRC). A broader spectrum of tumors associated with bi-allelic PV in *NTHL1* has also been described [40, 41].

The *MSH3* gene is a member of the DNA MMR family. Biallelic PV in *MSH3* are associated with adenomatous polyposis of the colon and risk of early-onset CRC, and present similar to an FAP phenotype. In the limited number of biallelic *MSH3* PV carriers described, the cancer risk phenotype can also in some ways resemble that of a milder form of constitutional mismatch repair deficiency (CMMRD), including GI adenomas and cancers and central nervous system tumors [42]. There is no known increased risk of CRC in individuals with monoallelic PV in *MSH3*.

Germline PV in *GALNT12*, particularly the c.907G > A variant, result in an attenuated adenomatous polyposis phenotype and familial CRC risk. A small number of carriers have been identified in polyposis patients with adenoma counts ranging from 10 to 100. Families where PV have been found have also included other non-CRC GI tumors (bile duct, gastric, other), but it is unclear if these are related to a hereditary risk syndrome associated with *GALNT12* [43].

RPS20 PV have been associated with early-onset microsatellite stable CRC in a single Finnish family with multigenerational CRC meeting the Amsterdam I criteria. The believed causative variant is a duplication leading to a frame shift and premature termination of the protein (p.V50SfsTer23) [44].

Genes with PV found in CRC patients that are actionable but CRC causation not proven: *BRCA1*, *BRCA2*, *CDKN2A*, *PALB2*—A third group of genes that CGA-IGC believes should be considered for all patients undergoing evaluation for suspected hereditary CRC includes four genes that are not generally considered to be CRC risk genes but have been identified in patients with CRC undergoing hereditary panel genetic testing and are associated with other immediately actionable cancer risks (*BRCA1*, *BRCA2*, *CDKN2A*, *PALB2*).

Several studies in the past 20 years have examined the contribution of PV in *BRCA1* and *BRCA2* to the risk of CRC [45–49]. Studies of multigene panel testing by Pearlman et al. and Yurgelun et al. identified *BRCA1/2* PV among early-onset (1.3%), and unselected patients with CRC (1.0%), at a higher frequency than would be expected by chance, but proof of causation is lacking [2, 13, 27, 28].

Both Pearlman et al. and Yurgelun et al. identified *CDKN2A* PV in their cohorts of early onset (1/450) and unselected patients with CRC (1/1058), respectively [13, 27]. Germline PV in *CDKN2A* (also known as *p16*) are known to predispose to melanoma and pancreatic cancers, and are associated with the familial atypical multiple mole melanoma syndrome.

PV in *PALB2* are associated with moderate to high risks of breast cancer and increased risk of pancreatic cancer. In the series reported by AlDubayan et al., they found an enrichment of germline *PALB2* PVs in patients with CRC; however, no somatic second hits were identified

in the CRC [30]. Like *CDKN2A*, PV variants in *PALB2* were relatively rare in unselected CRC (2/1058), high-risk CRC (1/1260), and early-onset CRC (2/450) [13, 27, 28].

Question 3: Who should undergo multigene panel testing for hereditary CRC syndromes?

Traditional belief holds that inherited cancer syndromes only occur in those with striking personal and/or family histories of cancer. However, in the case of epithelial ovarian cancer [50, 51], metastatic prostate cancer [52], triple negative breast cancer [53, 54], and pancreatic cancer [55–58] it has been shown that the hereditary contribution is relatively high, even in the absence of typical “red flags” (family history of cancer and/or young age of onset). Thus, in these populations, the use of multigene panel testing has been endorsed for all patients [6]. Table 4 shows the contribution of hereditary cancer syndromes for patients with CRC relative to other common cancer types.

Given that traditional criteria fail to identify individuals at risk for hereditary CRC, and in line with recommendations for other hereditary cancer syndromes, CGA-IGC proposes indications for panel testing in Table 5. The rationale for testing in each group is discussed briefly below.

All CRC patients diagnosed under age 50, irrespective of MSI/IHC status—

Young age at CRC diagnosis has always been a red flag for hereditary CRC testing. Pearlman et al. reported 16% of population-based patients under age 50 at CRC diagnosis had a hereditary cancer syndrome [27]. Stoffel et al. also demonstrated that 18.3% patients with CRC age under 50 attending a high-risk clinic had a hereditary CRC syndrome [2]. Therefore, the CGA-IGC supports testing for all CRC patients diagnosed under age 50.

CRC patients diagnosed 50 years, irrespective of MSI/IHC status, who have at least one FDR with CRC or endometrial cancer and consider with at least one FDR with any LS-associated cancer—

Recent studies have shown that family history alone would miss a significant number of CRC patients with hereditary cancers syndromes. Pearlman et al. reported 38.4% of patients with early onset CRC and a FDR with CRC had a PV [27]. Yurgelun et al. reported 36.4% of unselected CRC patients with at least one FDR with CRC had LS and another 13.9% had a PV causing another hereditary cancer syndrome [13]. Since the proportion of CRC patients with an affected FDR relative found to have a PV in a cancer gene is high, we propose that the family history criteria, previously described in the Amsterdam II and Revised Bethesda Guidelines, be relaxed to include patients with CRC 50 years with at least one FDR with CRC or endometrial cancer.

CRC patients diagnosed 50 years, irrespective of MSI/IHC status, with synchronous or metachronous LS-associated cancers—

In the series from Yurgelun et al. 13/59 (22.0%) with CRC and at least one other LS-related primary cancer had a PV and 18/124 (14.5%) of patients with CRC and at least one non-LS-related second primary cancer had a PV (unpublished data Yurgelun) [13]. This recommendation is in alignment with one of the Revised Bethesda Guidelines criterion [59]. As a result, CGA-IGC endorses testing patients with more than one primary LS-related cancer (e.g.,

colorectal, endometrial, ovarian, urothelial, small bowel, gastric, pancreatic/biliary tract, sebaceous carcinoma, glioblastoma).

Any patient with a PREMM₅ score 2.5% or a MMRpro or MMRpredict score 5%—The MMRpredict, MMRPro, and PREMM₅ models have been developed to predict the likelihood of a patient harboring a LS PV [60–62]. Current NCCN guidelines recommend an evaluation to rule out LS in individuals whose risk is at least 5% using MMRpredict, MMRPro, or PREMM₅ models [4, 7]. The PREMM₅ model was developed using clinical and germline MMR data from ~ 18,000 patients, including information about patient gender, age at genetic testing, and personal and family history of cancer [62]. Unlike MMRpredict and MMRPro, PREMM₅ includes data from and prediction for *PMS2* and *EPCAM* carriers in addition to *MLH1*, *MSH2*, and *MSH6*, making it more robust than the other two models. Data have demonstrated that use of both 2.5% and 5.0% PREMM₅ score thresholds to guide germline LS testing has a favorable net benefit versus testing all individuals, though the 2.5% threshold has superior sensitivity (89.4% versus 72.1%) but inferior specificity (49.2% versus 75.1%) than the 5.0% threshold [62]. As such, the NCCN has acknowledged that a threshold of 2.5% could be considered for genetic testing [4]. Further data are needed to evaluate the possibility that the 2.5% threshold is most useful for assessing cancer-unaffected individuals with a family history of LS-associated cancer, and also to assess whether there is value to germline LS testing in individuals with MMR-proficient/microsatellite stable CRC whose PREMM₅ score is 2.5–4.9%. Acknowledging these gaps in knowledge, the CGA-IGC endorses the recommendation of a PREMM₅ score of 2.5% to identify patients for germline genetic testing [62, 63].

CRC patients with MMR-deficient (dMMR) tumor unattributed to *MLH1* promoter hypermethylation—Universal tumor screening for LS, as recommended by the NCCN and Evaluation of Genomic Applications in Practice and Prevention (EGAPP) and endorsed by CGA-IGC, is increasingly being adopted for use among all CRC patients at the time of diagnosis [4, 7, 64]. This screening serves two purposes; (1) identification of patients who are more likely to have LS [65], and (2) identification of patients who may benefit from immune therapy [66]. Universal tumor screening is typically performed using either MSI testing or IHC staining with antibodies to four MMR proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Around 15–20% of CRCs are found to be microsatellite unstable (MSI-high) or have at least one MMR protein that is not present in the tumor [9, 10]. These tumors are considered MMR deficient (dMMR) and could potentially benefit from immune checkpoint inhibitor therapy in the metastatic/palliative setting; however, only a portion of these patients will actually have LS. Patients with dMMR tumors unrelated to *MLH1* promoter hypermethylation should be referred to cancer genetics for an evaluation. If *MLH1* promoter methylation has not been ruled out, this step needs to be performed prior to any germline testing since the majority (75%) of dMMR tumors are due to acquired *MLH1* promoter methylation [65]. If the original tumor screening test utilized IHC staining, then methylation needs to be ruled out for tumors with absence of *MLH1* and *PMS2*. If MSI testing only was performed, either methylation can be ruled out for all MSI-high tumors or IHC can be performed for the MSI-high tumors and only those with absence of *MLH1* and *PMS2* will then need methylation testing. Methylation testing can be performed directly or

inferred by testing the tumor for the *BRAF*V600E mutation (present in ~ 68% of *MLH1* promoter hypermethylated colorectal tumors) [65]. If methylation and/or the *BRAF*V600E mutation are not present in the tumor or the tumor demonstrates loss of MSH2, MSH6 and/or PMS2, then follow-up genetic testing is indicated.

CRC patients diagnosed 50 who meet criteria for another cancer syndrome

—All CRC patients who meet testing criteria for other hereditary cancer syndromes (e.g. hereditary breast ovarian cancer syndrome) should be offered germline testing regardless of their MSI or IHC status [6, 7].

Patients with 10 cumulative adenomatous colorectal polyps—In a select series of 7225 patients with attenuated and classic colonic adenomatous polyposis, Grover et al. reported that 4–5% of patients with 10–19 adenomas had PV in *APC* or *MUTYH* [67]. The mutation detection rate increased to 7–10% among those with 20–99 adenomas and to > 50% for those with more than 100 adenomas [67]. Stanich et al. showed that 7.6% of patients with 10–19 adenomas undergoing a multigene panel test of at least 14 CRC genes harbored a PV increasing to 13.7% in those with 20–99 adenomas and 47.7% for those with at least 100 adenomas [68]. Interestingly, PV were not confined to adenomatous polyposis genes: 4.3% of patients with 10–19 adenomas, 3.0% with 20–99, and 3.2% with 100 had a PV in a LS or non-polyposis CRC gene and 1.0% of patients with 10–19 adenomas, 2.4% with 20–99, and 4.1% with 100 had a PV in a hamartomatous polyposis syndrome gene [68]. Therefore, while polyp burden is an important indication for genetic testing and age at diagnosis influences the likelihood of identifying a PV in polyposis genes, older patients with low adenoma counts (10–19) still had > 5% chance of having a mutation in a CRC gene. There are no studies looking at the increase in mutation detection rate when analyzing the more newly associated polyposis genes. The CGA-IGC endorses testing all patients with at least ten cumulative adenomatous polyps.

Patients with 3 cumulative hamartomatous polyps—Assessment for the hamartomatous syndromes is often more complicated, as there can be prominent physical features associated with these conditions. There are clinical diagnostic criteria for PHTS [6], PJS [69], and JPS [70] that should be thoroughly vetted for a patient suspected of a hamartomatous polyposis syndrome, especially in the absence of a germline PV. However, when solely considering polyp count, a clinical diagnosis of PJS or JPS is established when a patient has at least three Peutz-Jeghers polyps or juvenile polyps, respectively, and “multiple” hamartomas or ganglioneuromas are considered a major criterion for PHTS [6, 69, 70]. Data on multigene panel testing among patients with hamartomatous polyposis are limited. Stanich et al. found a high PV detection rate among patients undergoing multigene panel testing with 10–19 (45%), 20–99 (72.1%), and 100 (58.3%) hamartomas [68]. The majority of PV were found in *BMPR1A*, *SMAD4*, *STK11*, and *PTEN*, but a small number of patients were found to harbor a *CHEK2* PV [68]. The CGA-IGC recommends multigene panel testing for patients with at least three hamartomatous polyps (including hamartomas, Peutz-Jeghers polyps, ganglioneuromas, and juvenile polyps) anywhere in the GI tract but recognizes the absence of data on panel testing for hamartomatous colorectal polyposis.

Comment on testing for serrated polyposis—The World Health Organization has published criteria for SPS [71]. The genetic etiology of SPS remains unclear. Recently, PV in *RNF43* have been identified in 1.4% of patients with serrated polyposis syndrome (SPS) [72, 73]. *RNF43* polyposis is autosomal dominant, and has been described with a variable phenotype that is dominated by early-onset serrated and hyperplastic polyps (anywhere from a few to a mild polyposis phenotype) and increased CRC risk. One study found that 1/40 (2.5%) patients meeting WHO SPS criteria had biallelic *MUTYHPV* [74]. However, these patients also had at least ten adenomas [74]. At this time, the CGA-IGC feels there are insufficient data to support multigene panel testing patients with SPS in the absence of other risk factors for hereditary CRC and/or adenomatous polyposis.

Question 4: How should a patient with a dMMR CRC be evaluated using both germline and somatic testing?

There are currently two approaches to genetic testing for patients with dMMR CRC: (1) order germline genetic testing with a multigene panel; or (2) order paired germline and tumor genetic testing with a multigene panel. In either case, a multigene panel including all CRC genes is the appropriate test since it has been shown that MSI-high and/or dMMR tumors can be caused by biallelic *MUTYHPV* and likely by germline PV in other DNA repair genes (e.g. *POLE* and *POLD1*) when they lead to somatic mutations in the MMR genes [75]. One study found 3.1% of patients with a dMMR CRC actually had biallelic *MUTYH* PV and another study found that germline and somatic *POLE* and *POLD1* PV caused dMMR [76, 77].

If germline genetic testing is ordered alone, it is possible that no PV will be identified. This can occur in 2.5–3.9% of CRC cases [9, 78]. These cases have unexplained MMR deficiency and should no longer be referred to as “Lynch-like syndrome” because this could confuse the risk assessment and management for these patients. It has now been shown that 48–69% of cases with unexplained dMMR have double somatic mutations in an MMR gene, 0–5% have somatic mosaicism for an MMR gene PV, 5–19% are found to have inaccurate tumor screening results (MSI, IHC, and/or methylation), and a small number of cases remain unexplained and could either be due to an unidentified germline or somatic PV in an MMR gene [79–82]. This can be determined by ordering sequencing of the MMR genes on tumor DNA which often also includes MSI testing, *MLH1* methylation testing, and *BRAFV600E* testing that can be used to help verify the original tumor screening results. If two somatic PV or one somatic PV and loss of heterozygosity are found in the tumor, it can be considered sporadic (assuming germline PV in *MUTYH*, *POLE*, *POLD1* and other repair genes have been ruled out). In these cases, the patient and their family should be managed based on the family history and not as if they have LS. If only one somatic PV is found in a MMR gene, it is possible that the patient has either an unidentifiable germline PV (in which case they would have LS) or an unidentifiable somatic PV (in which case they would not have LS). As a result, they should be managed based on their family history. If no somatic PV are found, it is possible that the tumor screening results were incorrect, and the MSI, IHC and/or methylation may need to be repeated to help resolve the case.

Ideally, the CGA-IGC endorses a simultaneous paired germline-somatic panel. However, considerations about whether to order sequential or simultaneous germline and tumor sequencing include a number of factors. If the patient's personal and/or family history are consistent with LS, it is more likely that they will have LS, so it may be efficient to order germline testing alone given that follow-up tumor testing will probably not be necessary. If the patient has an insurance that might only cover one genetic test, it might be best to order paired tumor and normal testing since it may not be possible to reflex to tumor testing if no PV is found on germline testing. In some cases (e.g. older patients with no family history with loss of MLH1 and PMS2 without *MLH1* methylation), it may actually be more likely that the patient has biallelic somatic MMR gene PV rather than a germline MMR gene PV, and paired germline and somatic testing may be a reasonable first approach to testing [83]. Lastly, patient preferences should be taken into account as some may prefer to get a complete answer quickly rather than drawing out the testing process by ordering the tests sequentially.

Question 5: What are the essential elements for delivery and interpretation of multigene panel testing?

Genetic counseling and informed consent—Genetic counseling has played an integral role in hereditary cancer risk assessment with the identification of cancer susceptibility genes, with several societies recommending pre- and post-test genetic counseling [1, 6, 7, 84]. Compared to single gene/syndrome testing, the implementation of panel-based testing has further highlighted the importance of genetic counseling in navigating patients through the complexities of this testing process.

Genetic counseling is “the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease,” and includes interpretation of personal and family history to assess disease risk; education about disease including genetic testing, management, and prevention; and counseling to promote informed decision-making [85]. Genetic counselors are health care providers with specialized training in these areas. Ideally, patients meeting the criteria in Table 5 are referred to a genetic counselor for pre- and post-test genetic counseling. In the absence of a professionally trained genetic counselor, clinicians ordering genetic testing should be aware of and implement the elements of genetic counseling and informed consent prior to ordering any germline testing (Table 6).

As multigene panel testing is increasingly implemented in evaluation of hereditary cancer, genetic counseling with cancer genetics professionals may aide patients in navigating through these complex issues, including selection of the appropriate panel, discussion of possible outcomes of testing (including inconclusive or unexpected results), potentially limited clinical utility of a PV in genes of moderate-penetrance, insurance coverage, genetic discrimination protections, implications for family members, and psychosocial concerns, allowing patients to make informed decisions regarding testing. As part of the post-test genetic counseling process, particularly for patients found to have a PV, it is important to help identify to patients inherited CRC/polypsis registries as well as patient advocacy groups.

Informed consent is a necessary and, in some states, legally required component that should precede genetic testing. The historical approach of informed consent for single gene testing included the following elements: discussion of specific genes, possible outcomes of testing, management specific to test results, and a review of benefits, risks, and limitations of testing [86]. With the transition of multigene panel tests into clinical practice, the American Society for Clinical Oncology has updated their guidelines for informed consent [87]. The introduction of multigene panel testing has made the informed consent process more challenging, given time constraints of most clinicians and the complexity of testing. In these instances, the informed consent process should concentrate on more generalized information with a focus on more likely syndromes, the possible outcomes of genetic testing (i.e. positive, negative, VUS), potential for unanticipated results, an explanation of the lack of information as it pertains to newer genes/syndromes, and reproductive risks related to autosomal recessive genes. Studies have proposed a tiered approach to the consent process, including the following: an explanation that testing can identify varying risks, that the implications of results may vary by gene and personal/family history, that the evidence for medical management recommendations vary by gene, that PV in some genes are associated with childhood cancers, that there is the potential for uncertain test results, that patients should be aware that testing is a choice, and that ongoing communication with the provider is critical [88]. This approach was accepted by most patients in a small study [89], although further research into this and other methods of genetic counseling for panel testing is still needed. Above all, the information provided during the informed consent process should be easily understandable by the patient.

VUS interpretation—Although multigene panel testing increases the identification of clinically actionable PV, it also results in a higher proportion of VUS. Most studies of multigene panel CRC testing report VUS rates between 20 and 30% [2, 13, 27, 28, 90, 91]. Since VUS results pose a clinical challenge, responsible interpretation of their meaning and collaborative efforts to reclassify them are imperative. Collaboration among experts can help reduce VUS frequency and provide an opportunity for resolution of conflicting interpretations [92, 93]. A number of resources are available to clinicians and patients to assist in VUS interpretation and reclassification. ClinVar is a public archive that provides details about the classification of germline genetic variants [94]. Most commercial laboratories, as well as many academic institutions, submit their classifications of individual variants along with supporting evidence to ClinVar. The aggregation of this data in one archive allows clinicians to more easily collate the information available about a specific variant. Patients also have opportunities to contribute to VUS classification efforts through research studies like the Prospective Registry of Multiplex Testing (PROMPT) [95]. Additionally, most commercial testing laboratories have variant classification programs that include offering testing to family members of individuals with VUS to determine how they track with disease phenotype in a family. When specifically considering VUS in genes associated with hereditary CRC, resources like the International Society for Gastrointestinal Hereditary Tumours (InSiGHT) are valuable. InSiGHT is a multidisciplinary organization that maintains a database of variants in genes associated with hereditary gastrointestinal cancers (<https://www.insight-group.org/variants/>) [96]. The InSiGHT expert panel regularly reviews available published and submitted data to determine appropriate classifications for

variants in mismatch repair genes, as well as other genes involved in hereditary gastrointestinal cancers [97]. The CGA-IGC supports the submission of VUS data to public databases like InSiGHT and ClinVar by clinicians and laboratories.

Timing of genetic testing in newly diagnosed CRC patients—The optimal timing of germline testing around surgical management should be individualized and guided by the goal of maximizing actionable information that would impact clinical management, while minimizing anxiety that may arise while waiting for testing results and/or for surgical intervention. Therefore, timing of germline testing in this setting represents a shared decision between the surgeon, the clinical genetics care provider, and the patient. In patients deemed appropriate to await results of genetic testing prior to surgery, results of germline testing can impact surgical decision-making. For patients with germline predisposition to CRC, there is often the consideration for more extensive resection beyond the standard segmental resection [98]. In addition, patients with a hereditary syndrome may benefit from prophylactic resection of other organs at risk within the particular syndrome (e.g. hysterectomy and bilateral salpingo-oophorectomy is considered by women with LS) [99, 100]. Thus, for patients warranting an evaluation for a hereditary cancer syndrome, testing should be completed prior to surgical management so that the risk of germline predisposition can be determined, the patient can be offered segmental versus extended surgical options, and a well-informed decision can be reached.

Discussion

Multigene panel testing for cancer risk assessment has expanded exponentially in recent years. While professional organizations acknowledge this rapid rise in multigene panel testing [6, 7, 87], specific guidance on clinical implementation is currently lacking but urgently needed. This CGA-IGC position statement fills this gap by providing expert opinion for use of multigene panel testing in CRC and polyposis risk assessment. A comprehensive literature review was undertaken to support our recommendations, and we anticipate updating this position statement as new research in this field becomes available.

We acknowledge a number of areas of uncertainty, knowledge gaps and barriers in the application of multigene panel testing for cancer risk assessment (Table 7). The optimal panel of genes for CRC risk assessment is not established, and the field is changing rapidly. The genes recommended in this position statement are based on current knowledge of risk and penetrance estimates and represent the minimal genes to include on a panel. Additional genes could be considered based on individual personal and family history. While risk estimates and management recommendations are established for high-penetrance genes, this is not the case for moderate-penetrance genes and remains a significant area of uncertainty in clinical practice. Furthermore, testing of multiple genes simultaneously amplifies the number of VUS identified. We strongly endorse collaborative variant interpretation efforts and highlight the pioneering work by the International Society of Gastrointestinal Hereditary Tumors (InSiGHT, <https://www.insight-group.org/variants/>) in this area. Uncertainties about low-/moderate-penetrance CRC susceptibility genes and VUS findings underscore the importance of having knowledgeable providers interpreting multigene panel results in clinical practice to avoid potential harms. In the era of precision medicine and novel

therapies, somatic testing of tumors is also rapidly increasing. Simultaneous somatic and germline genetic testing is emerging, though data in this area is still limited with the exception of somatic testing to identify double somatic MMR mutations. Finally, we acknowledge critical gaps in access, resources, and education that impede full realization of the cost-effective benefits of multigene panel testing in CRC [101]. Lack of insurance coverage, genetic counseling resources, and professional education are all barriers that must be addressed to ensure high-quality, equitable care for individuals and their families at increased risk of CRC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The CGA-IGC would like to thank Marian Simonson and Loren Hackett of the Cleveland Clinic for their assistance with the literature search.

Funding None.

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Table 1
Questions about multigene panel testing in colorectal cancer addressed in this position statement

Questions about multigene panel testing in colorectal cancer	
1	Which minimal set of genes should be included on a multigene panel for evaluation of hereditary colorectal cancer or polyposis?
2	Which additional set of genes could be included on a multigene panel for evaluation of hereditary colorectal cancer or polyposis?
3	Who should undergo multigene panel testing for hereditary colorectal cancer or polyposis syndromes?
4	How should a patient with a mismatch repair deficient colorectal cancer be evaluated using both germline and somatic testing?
5	What are the essential elements for delivery and interpretation of multigene panel testing?

Table 2

Minimal and additional genes to include on multigene panel test for evaluation of colorectal cancer and/or polyposis

Genes	Cumulative CRC risk by age 70	Prevalence	Inheritance	Cancer/polyposis phenotype
Genes associated with Lynch syndrome				
<i>MLH1</i>	4–79% [83–85]	1:1946 [16]	AD	CRC, EC, OV, GC, SBC, PC, HTC, UTC, PC, SC, BT
<i>MSH2</i>	35–77% [83–85]	1:2841 [16]		
<i>MSH6</i>	12–50% [83–85]	1:758 [16]		
<i>PMS2</i> ^a	10–19% [85, 86]	1:714 [16]		
<i>EPCAM</i> ^b	75% [85]	Unknown		
Genes associated with polyposis				
<i>APC</i>	69–100% [3]	2.29:100,000 to 3.2:100,000	AD	Adenomatous polyposis, CRC, SBC, GC, TC, HB, desmoids
<i>BMPRIA</i>	38% ^c [87, 88]	1:16,000 to 1:100,000	AD	Juvenile polyposis, CRC, GC, SBC
<i>MUTYH</i>	71.7–75.4% [33]	1:8073 [16] (biallelic); 1:45 [16] (monoallelic)	AR	Adenomatous polyposis, CRC, SBC, TC
<i>PTEN</i>	9–16% [89, 90]	1:200,000 [91]	AD	Mixed polyposis (hamartomas, ganglioneuromas, serrated, adenomatous), BC, TC, EC, CRC, KC, melanoma
<i>STK11</i>	39% [23, 92]	1:25,000 to 1:280,000 [93]	AD	Peutz-Jeghers polypos, CRC, BC, PC, GC, SBC, OC, EC, SCT, LC
<i>SMAD4</i>	38% ^c [87, 88]	1:16,000 to 1:100,000	AD	Juvenile polyposis, CRC, GC, SBC

AD autosomal dominant, *AR* autosomal recessive, *BC* breast cancer, *BT* brain tumor, *CRC* colorectal cancer, *EC* endometrial cancer, *GC* gastric cancer, *HB* hepatoblastoma, *HTC* hepatobiliary tract cancer, *KC* kidney cancer, *LC* lung cancer, *PC* pancreatic cancer, *SBC* small bowel cancer, *SC* sebaceous carcinoma, *SCT* sex cord tumor, *TC* thyroid cancer, *UTC* urinary tract cancer

^aLaboratory analysis should be able to distinguish exons 12–15 in *PMS2* from the transcribed pseudocopy of *PMS2* (*PMS2CL*)

^bLarge rearrangement analysis only

^cEstimated cumulative lifetime colorectal cancer risk

Additional genes with (a) low to moderately increased risk of colorectal cancer (CRC), (b) preliminary but limited data on CRC risk, and (c) genes with pathogenic variants found in CRC patients that are actionable in regard to other cancers but CRC causation not proven. Testing for these genes can be considered in specific circumstances

Table 3

Genes	Odds ratio	Prevalence	Inheritance	Cancer/polypoidosis phenotype
(a) Genes associated with low to moderately increased risk of CRC				
<i>ATM</i>	2.81–2.97 [27]	1:100 [94]	AD	BC, PC
<i>CHEK2</i>	1.56–1.88 ^a [95]	1:100 to 1:200 [28]	AD	BC, CRC
<i>TP53</i>	Not defined, but skewed towards younger age at diagnosis [96, 97]	1:5000 to 1:20,000	AD	ACC, BC, BT, CRC, LC, leukemia, sarcoma
(b) Genes with preliminary but limited data				
<i>SCG5/GREM1</i> ^b	Not defined, presumed to be high	Unknown	AD	Mixed (serrated, juvenile, adenomatous) polypoidosis, CRC
<i>POLD1</i>	Not defined	Unknown	AD	Adenomatous polypoidosis, BT, CRC, EC
<i>POLE</i>	Not defined	Unknown	AD	Adenomatous polypoidosis, CRC
<i>AXIN2</i>	Not defined	Unknown	AD	Adenomatous polypoidosis, CRC
<i>NTHL1</i>	Not defined	Unknown	AR	Adenomatous polypoidosis, CRC
<i>MSH3</i>	Not defined	Unknown	AR	Adenomatous polypoidosis, CRC
<i>GALNT12</i>	Not defined	Unknown	AD	CRC
<i>RPS30</i>	Not defined	Unknown	AD	CRC
(c) Genes with PV found in CRC patients that are actionable but CRC causation not proven				
<i>BRCA1</i>	Not defined	1:400 to 1:500 [98] 1:40 (Ashkenazi Jewish) [99]	AD	BC, OC, PrC, melanoma
<i>BRCA2</i>	Not defined	1:400 to 1:500 [98] 1:40 (Ashkenazi Jewish) [99]	AD	BC, OC, PrC, melanoma
<i>CDKN2A</i>	Not defined	Unknown	AD	PC, melanoma
<i>PALB2</i>	3.42–4.91 [27]	Unknown	AD	BC, PC

ACC adrenal cortical carcinoma, AD autosomal dominant, AR autosomal recessive, BC breast cancer, BT brain tumor, CRC colorectal cancer, GC gastric cancer, LC lung cancer, PC pancreatic cancer, PrC prostate cancer, PV pathogenic variant

^aData limited to *CHEK2* c.1100delC and p.1157T

^bLarge rearrangement analysis only

Table 4
Prevalence of pathogenic or likely pathogenic variants in patients with various cancer types

Cohort	Prevalence of pathogenic or likely pathogenic germline cancer susceptibility gene variants	Most common genes with germline pathogenic variants	References
Epithelial ovarian/fallopian tube cancer	18.1–23.6%	6.4–9.5% <i>BRCA1</i> , 5.1–6.3% <i>BRCA2</i> , 0.6–1.4% <i>CHEK2</i> , 1.1–1.4% <i>BRIP1</i>	[48, 49]
Breast cancer	9.3%	2.3% <i>BRCA1</i> , 2.3% <i>BRCA2</i> , 1.1% <i>CHEK2</i> , 0.9% <i>ATM</i> , 0.9% <i>PALB2</i>	[51]
Breast cancer (stage I–III)	10.7%	3.7% <i>BRCA1</i> , 2.5% <i>BRCA2</i> , 2.1% <i>CHEK2</i> , 0.8% <i>ATM</i> , 0.8% <i>BRIP1</i>	[102]
Breast cancer (triple negative)	14.1–14.6%	7.2–8.5% <i>BRCA1</i> , 2.6–2.7% <i>BRCA2</i> , 1.2–1.3% <i>PALB2</i>	[51, 52]
Colorectal cancer	9.9%	3.1% Lynch, 1.7% monoallelic <i>MUTYH</i> , 1.3% APC p.I1307K, 0.9% <i>ATM</i> , 0.8% <i>BRCA2</i>	[12]
Cohort	Prevalence of pathogenic or likely pathogenic germline cancer susceptibility gene variants	Most common germline variants	References
Colorectal cancer (age < 50 years)	16.0–18.3%	8.4–13% Lynch, 1.6% monoallelic <i>MUTYH</i> , 0.2–2.3% APC, 0.9% APC p.I1307K, 0.9–1.9% bi-allelic <i>MUTYH</i> , 0.5% SMAD4, 0.2% TP53, 0.2% <i>CHEK2</i> , 0.2–0.9% <i>BRCA1/2</i>	[2, 24]
Pancreatic cancer	3.8–8.4%	0.7–4.0% <i>BRCA2</i> , 1.0–2.0% <i>ATM</i> , 0–1.4% Lynch, 0.3–0.4% <i>BRCA1</i>	[53–56]
Prostate cancer (metastatic)	11.8%	5.3% <i>BRCA2</i> , 1.6% <i>ATM</i> , 1.9% <i>CHEK2</i> , 0.9% <i>BRCA1</i>	[50]
Endometrial cancer	9.2%	5.8% Lynch, 1.0% <i>CHEK2</i>	[11]

CGA-IGC recommendations for individuals who should be considered for multigene panel testing for evaluation of hereditary colorectal cancer and/or polyposis

Table 5

Individuals who should undergo multigene panel testing ^a
Colorectal cancer diagnosed age < 50 years ^b
Multiple Lynch syndrome primary tumors ^{b,c}
Colorectal cancer ^b and at least one first degree relative with colorectal or endometrial cancer
PREMM ₅ score 2.5% or MMRpro or MMRpredict score 5%
Mismatch repair-deficient colorectal cancer, not attributed to <i>MLH1</i> promoter methylation
Patients meeting any other genetic testing criteria [4, 6]
10 cumulative colorectal adenomas
3 cumulative gastrointestinal hamartomatous polyps ^d

^aIn some instances, the individual affected with colorectal cancer/polyposis is unavailable for testing. In this case, genetic testing should be offered to any first-degree relative (FDR) with a family history meeting these criteria. Consideration can be given to testing second-degree relatives with a family history meeting these criteria when the affected family member and FDRs are unavailable to be tested

^bIrrespective of microsatellite instability (MSI)/immunohistochemistry (IHC) status

^cColorectal cancer, endometrial cancer, ovarian cancer, urothelial cancer, small bowel cancer, gastric cancer, hepatobiliary cancer, pancreatic cancer, sebaceous carcinoma, glioblastoma

^dIncluding hamartomas, ganglioneuromas, Peutz-Jeghers polyps, and/or juvenile polyps

Table 6
Essential elements of pre-test genetic counseling and informed consent for multigene panel testing

Elements of pre-test genetic counseling and informed consent
Discussion of the risks associated with groupings of genes (high and moderate risk) to be analyzed, including impact on medical care
Implications of testing outcomes: positive, negative, and variant of uncertain significance. This also includes:
Possibility of a pathogenic variant is less well understood or reduced penetrance genes
Incidental pathogenic variant in gene(s) unrelated to the personal or family history
Higher rates of variants of uncertain significance on panels compared to single gene/syndrome testing
Potential reproductive risks for genes associated with autosomal recessive conditions ^a
Possibility the test will be uninformative
Risks to family members and importance of sharing results with at risk relatives
Costs associated with genetic counseling and testing
Potential risks and protection against genetic discrimination by insurers and employers
Confidentiality of the information
Potential future uses of DNA sample
Psychosocial implications
Plans for results disclosure and follow up

^aSuch as *ATM* (ataxia telangiectasia), *BRCA2* (Fanconi anemia), or mismatch repair genes (constitutional mismatch repair deficiency)

Areas of uncertainty, knowledge gaps and barriers in implementation of multigene panel testing for colorectal cancer

Table 7

Areas of uncertainty, knowledge gaps and barriers in multigene panel testing for colorectal cancer
Optimal panel of genes not established
Risk estimates and management for low- and moderate-penetrance genes uncertain
Increased number of variants of uncertain significance
Utility of simultaneous somatic and germline genetic testing not established ^a
Lack of access, resources & education

^aExcept for evaluation of double somatic mismatch repair variants in tumors