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ORIGINAL ARTICLE

Outcomes of disease-specific next-generation sequencing gene panel testing in adolescents and young adults with colorectal cancer

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Abstract

Purpose: Adolescents and young adults with colorectal cancer (CRC) have attracted recent attention, with a hereditary syndrome identified in one-third of patients diagnosed ≤ 35. We aimed to study this population to determine if a CRC-specific gene panel increased the yield of testing.

Methods: Patients with CRC ≤ 35 evaluated from 05/2014–11/2017 were identified from the genetic counseling database. Records were reviewed for personal/family history and genetic counseling outcomes.

Results: One hundred forty-three patients with CRC ≤ 35 were included. One hundred four (72.7%) underwent CRC panel testing. Thirty-nine (27.2%) had syndrome-directed testing, declined, or were lost to follow-up. Forty-two patients had a genetic syndrome (29.4%). Twenty-four of the 42 hereditary patients (57.1%) were identified via syndrome-directed testing. Mutations identified via panel testing were consistent with patient personal/family history. Thirty-three patients had at least one variant of uncertain significance.

Conclusion: Hereditary syndromes were identified in 29.4% of patients. Panel testing in patients without a phenotype did not increase diagnostic yield, but identified variants in one-third. Disease-specific panel testing is of low yield in young patients without a suggestive personal/family history. Testing broader panels may increase the yield of mutation pick-up in this population, although at the expense of identifying variants.

Keywords Colorectal cancer, Hereditary cancer syndromes, Panel testing, Adolescents, Young adults.

Introduction

Colorectal cancer (CRC) has typically been considered a disease affecting individuals older than age 50. However, recent data has demonstrated a trend of increasing numbers of patients under age 50 diagnosed with CRC. In fact, the rate of CRC in individuals between ages 20–34 is anticipated to increase 90.0–124.2% by 2030 if current rates continue [1]. Although the cause for this increase is not fully understood, potential risk factors include obesity, physical inactivity, increased red meat intake, and decreased vegetable consumption. Early age of onset of CRC also raises the question of the role of genetic predispositions to CRC among this young population, although inherited predispositions are unlikely to play a major factor in the increasing incidence of CRC.

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Our previous work has demonstrated the increased frequency of hereditary predispositions to CRC among young individuals with CRC. One-third of patients with CRC diagnosed at age 35 and younger were identified to have a hereditary CRC syndrome via traditional phenotype-driven genetic workup [2]. The implementation of next generation sequencing (NGS) panel-based testing has allowed for broader genetic evaluation beyond traditional testing, and has been utilized in wider CRC populations. In populations below age 50, the incidence of high-penetrant hereditary CRC syndromes is approximately 10–17% [3–6].

Although panel-based testing is increasingly implemented in clinical practice, the utility of a disease-specific gene panel in the context of an extreme phenotype of adolescents and young adults (AYA) with CRC has not been studied. This raises the possibility that patients without a syndrome identified via traditional phenotype-driven testing may still have an underlying inherited predisposition to CRC. We aimed to evaluate the yield of disease-specific gene panel testing in AYA with CRC, especially in patients without a suggestive clinical phenotype or family history of the disease.

Material and methods

Patient selection

We included 143 patients who were diagnosed with CRC at 35 years or younger and were evaluated by genetic counseling within the period of 05/2014 to 11/2017. This time frame was selected because our institution initiated NGS panel testing with CLIA-certified laboratories beginning in 05/2014. This patient population is derived from the catchment area of The University of Texas MD Anderson Cancer Center (UTMDACC), which is focused in the State of Texas. Approximately 45 new patients meeting this criteria are seen each year at UTMDACC. Patients were referred to genetic counseling by UTMDACC providers per established referral criteria or at provider's discretion. All patients diagnosed with CRC at 35 years or younger met our referral criteria regardless of family history. All genetic counseling patients diagnosed with CRC at an age in that range were included, regardless of whether the patient was newly diagnosed during that time period or was referred due to a previous diagnosis at age 35 or younger, even if the patient was over the cut-off age at the time of genetic counseling.

Clinical data, including medical history and pathology data, were obtained from the electronic medical record. Family history was obtained by a genetic counselor and recorded in a pedigree. This study was approved by the Institutional Review Board.

Genetic evaluation

All patients underwent genetic counseling by board-certified genetic counselors. Patients with a clear clinical phenotype or family history pattern for a hereditary cancer syndrome (i.e., tumor studies consistent with Lynch syndrome, polyposis) underwent syndrome-specific genetic testing based on phenotype, although some of these patients with a syndromic presentation opted to pursue panel testing in tandem with the increased clinical implementation of panel-based testing.

Table 1 Clinicopathologic characteristics of patients ($N = 143$).

Characteristics	No. of patients (%)
Age at diagnosis, years (range)	29.6 (19–35)
Female	78 (54.5)
Race/ethnicity	
White	98 (68.5)
Black	10 (7.0)
Hispanic	25 (17.5)
Asian	10 (7.0)
Colorectal cancer site	
Right colon	39 (27.3)
Left colon	48 (33.5)
Rectum	50 (35.0)
Not specified	6 (4.2)
Tumor stage at diagnosis	
0/Tis	1 (0.7)
I	19 (13.3)
II	9 (6.3)
III	37 (25.9)
IV	66 (46.1)
Unknown	11 (7.7)
Grade of differentiation	
Well differentiated	1 (0.7)
Moderately differentiated	102 (71.3)
Poorly differentiated	21 (14.7)
Unknown	19 (13.3)
Signet ring cells	
Yes	7 (4.9)
No	120 (83.9)
Unknown	16 (11.2)
Family history	
Amsterdam I/II	9 (6.3)
FDR with CRC	12 (8.4)
FDR with other cancer	45 (31.5)
SDR with CRC	42 (29.4)
SDR with other cancer	106 (74.1)
Personal history of other cancer	21 (14.7)
Colorectal panel testing	104 (72.7)
Hereditary syndrome	42 (29.4)

CRC, colorectal cancer; FDR, first-degree relative; SDR, second-degree relative.

Patients without a clear clinical phenotype [i.e., mismatch repair (MMR)-proficient tumors, no evidence of polyposis, no family history of colorectal cancer] were recommended a broader genetic workup, including testing for single genes or more commonly, a panel of colorectal cancer genes (including at minimum *APC, BMPR1A, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11*, and *TP53*) or *ad-hoc* panels potentially combining the CRC-focused panel with other genes based on the personal and/or family history (i.e., *BRCA1*/*BRCA2* for a family history of breast or ovarian cancer). All genetic testing was performed by CLIA-certified laboratories; variants were classified as variants of uncertain significance (VUS), likely pathogenic or pathogenic by the genetic testing laboratories. Type of testing (single-gene versus panel) and outcomes of genetic testing (including frequency of pathogenic mutations and variants of uncertain significance) were recorded.

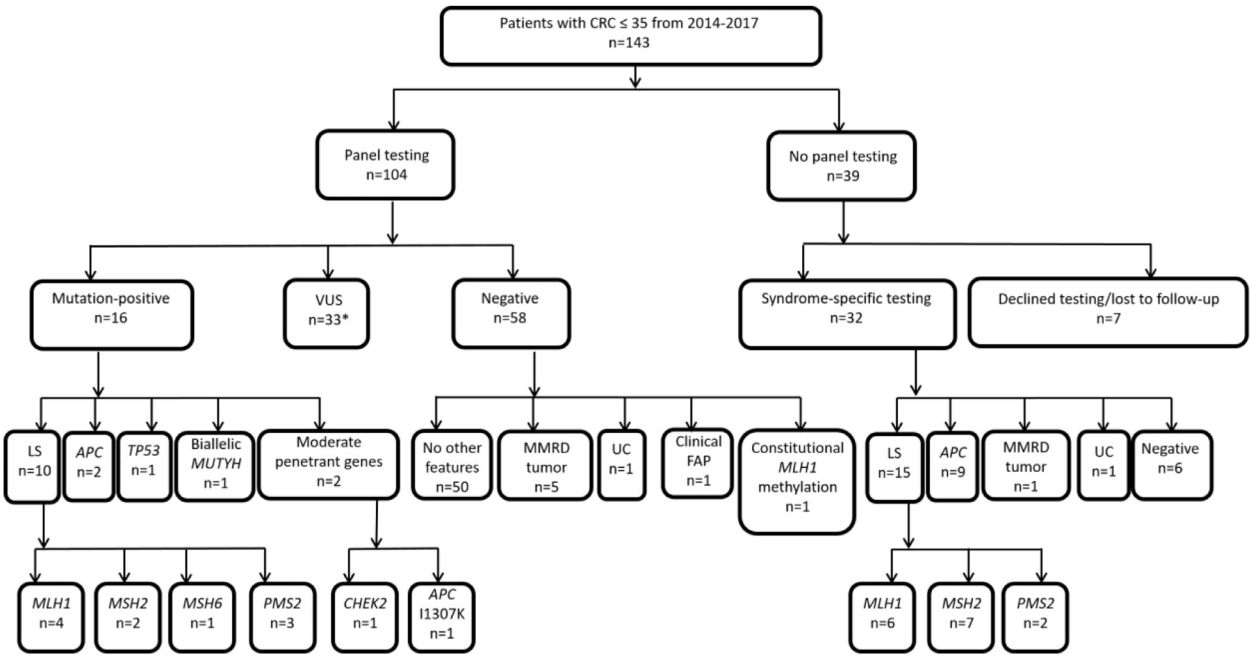

Fig. 1 Patient selection and grouping.
CRC, colorectal cancer; VUS, variant of uncertain significance; LS, Lynch syndrome; UC, ulcerative colitis; FAP, familial adenomatous polyposis.
*Three VUS detected in patients with pathogenic mutations.

Results

Patients

One hundred forty-three patients with CRC diagnosed at 35 years or younger were seen for genetic counseling over a period of 30 months. The clinicopathologic characteristics of this population are described in Table 1. The average age of diagnosis was 30 years, with most patients being female and white. The rectum was the most common site followed by the left colon. Patients most frequently presented with metastatic disease at diagnosis. Twenty-one patients had poorly differentiated tumors, and seven patients presented with signet ring cells. All patients met the Revised Bethesda guidelines solely on the basis of their ages at diagnosis [7] and nine met Amsterdam I or II criteria [8]. Microsatellite instability (MSI) and/or immunohistochemistry (IHC) results were available for 120 patients (83.9%). Of the 120 patients with tumor test results, 24 (20.0%) had MSI-high tumors and/or tumors demonstrating MMR deficiency. Twelve patients had a first-degree relative with CRC, 42 had a second-degree relative with CRC, and 18 had no relatives with any cancer (12.6%).

Of the 143 patients, 96 (67.1%) did not have a phenotype (i.e., microsatellite-stable tumor, no evidence of polyposis) or family history consistent with a hereditary cancer syndrome.

Outcomes of patients undergoing panel testing

Of the 143 patients seen for genetic counseling, 104 (72.7%) underwent a colon-specific gene panel (Fig. 1). Sixteen patients who underwent panel testing were identified to have a germline mutation associated with hereditary CRC (15.4%). Mutations associated with high CRC penetrance included two in *APC*, four in *MLH1*, two in *MSH2*, one in *MSH6*, three in *PMS2*, one in *TP53*, and one with biallelic *MUTYH* mutations. Two additional patients had germline mutations of moderate penetrance, one in *CHEK2* and the other with the *APC* I1307K variant. Of the mutation-negative patients on panel testing, five had MMR-deficient tumors but no germline mutation detected. Somatic testing for biallelic MMR mutations was not pursued and therefore may have been present in these patients [9]. However, one such mutation-negative patient with loss of MLH1 and PMS2 staining reported a family history consistent with Amsterdam criteria, with several relatives' tumors also demonstrating loss of MLH1 and PMS2; therefore, an undetectable germline mutation was suspected in this family. One additional mutation-negative patient was confirmed to have constitutional *MLH1* promoter hypermethylation, while another mutation-negative patient had greater than 100 tubular adenomas, consistent with a clinical diagnosis of familial adenomatous polyposis (OMIM #175100). Another patient in this mutation-negative group had a diagnosis of ulcerative colitis. Germline mutations in high penetrance genes that were detected in this group were anticipated as these patients exhibited tumor studies (MSI and/or IHC), clinical phenotype, and/or family histories consistent with the identified syndromes. Forty-two VUS were identified among 33 patients (31.7% of those undergoing panel testing), including in three patients who also harbored pathogenic germline mutations (Fig. 2).

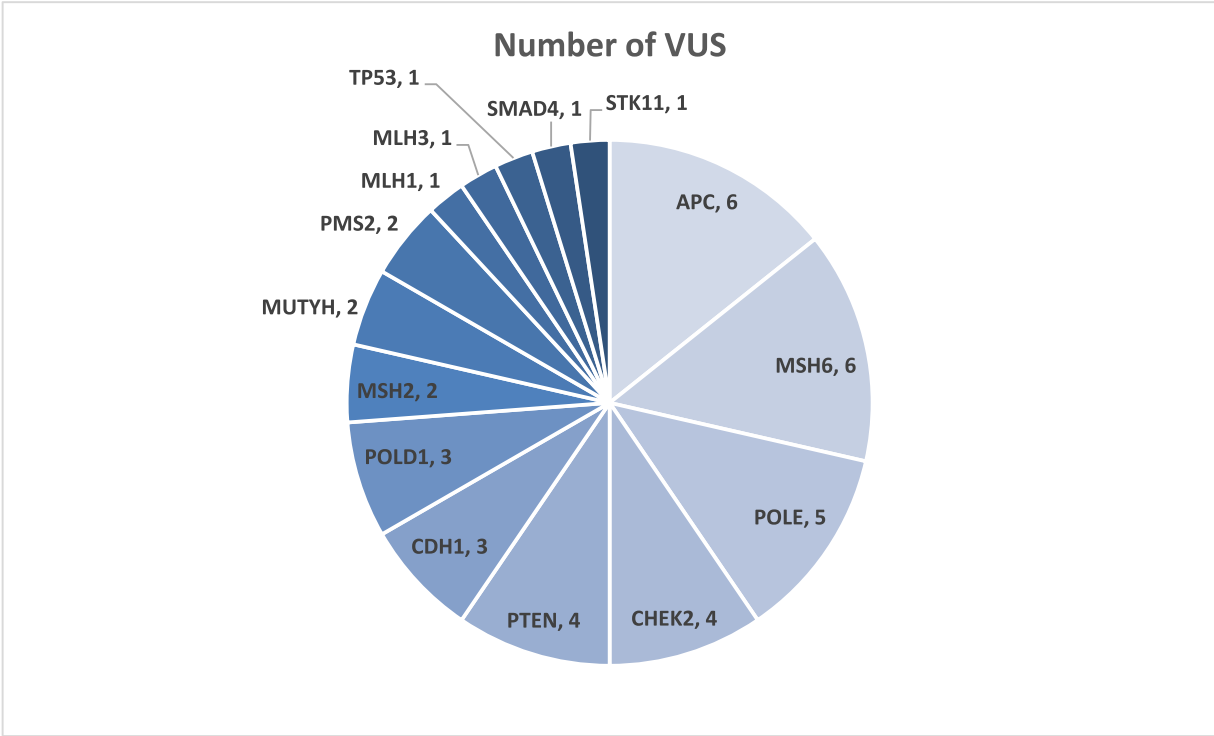

Fig. 2 Variants of uncertain significance identified in patients undergoing panel testing
42 variants of uncertain significance (VUS) identified in 33 patients.

Table 2 Clinical phenotype and family history of mutation carriers.

ID	Sex	Age at CRC	Other clinical features	Family history	Mutation
69	M	33	Multiple colon adenomas, desmoids, multiple congenital anomalies, cognitive impairment	No family history of CRC	20.5 megabase deletion of chromosome 5, including *APC*
95	F	25	Multiple colon adenomas, odontomas, supernumerary teeth	Unknown (adopted)	*APC* c.4348C>T
45	F	21	N/A	FDR with colon polyposis	*APC* c.3147G>A
55	M	33	N/A	Ashkenazi Jewish, no family history of CRC	*APC* p.I1307K
142	M	28	Multiple colon adenomas	FDR with CRC and colon polyposis	*APC* c.-190G>A
140	M	35	Multiple colon adenomas	No family history of CRC	*APC* c.835-1G>A
8	F	22	Multiple colon adenomas	FDR with CRC and polyposis	*APC* c.2309C>G
10	M	34	Multiple colon adenomas	No family history of CRC	*APC* c.3927_3931delAAAGA
48	M	27	Multiple colon adenomas, synchronous CRC, desmoids, gastric cancer	No family history of CRC	*APC* c.3927del5
12	F	35	Multiple colon adenomas, desmoids	No family history of CRC	*APC* c.5854delC
60	M	29	Multiple colon adenomas	No family history of CRC	*APC* c.2888del5
139	M	31	Multiple colon adenomas, synchronous CRC	No family history of CRC	*APC* c.1312+1G>C
132	F	27	N/A	No family history of CRC	*CHEK2* c.507delT

(*continued on next page*)

Table 2 (*continued*)

ID	Sex	Age at CRC	Other clinical features	Family history	Mutation
116	F	27	Loss of MLH1/PMS2, MLH1-methylated tumor	No family history of CRC	Constitutional *MLH1* promoter hypermethylation
61	M	35	Loss of MLH1/PMS2, MSI-high, synchronous CRC	No family history of CRC	*MLH1* deletion exons 9–13
20	M	32	Metachronous CRC, sarcoma	FDR with CRC, SDR with CRC (AI)	*MLH1* c.790+4A>C
104	F	33	Loss of MLH1/PMS2	SDR with CRC	*MLH1* c.199G>A
64	M	29	MSI-high, prostate cancer	SDR with CRC	*MLH1* p.R265G
15	F	31	Loss of MLH1/PMS2, synchronous CRC	FDR with EC	*MLH1* c.589-2A>G
103	F	29	EC, metachronous CRC	FDR with EC and sebaceous adenomas	*MLH1* deletion exons 2–6
40	F	22	EC, ovarian cancer	FDR with CRC, SDR with CRC (AI)	*MLH1* c.199G>A
57	F	34	Loss of MLH1/PMS2	FDR with CRC, SDR with CRC (AI)	*MLH1* p.C39Y
119	M	35	Loss of MLH1/PMS2, metachronous CRC	No family history of CRC	*MLH1* c.1491dupG
23	M	33	Loss of MLH1/PMS2	Unknown (adopted)	*MLH1* p.C39Y
72	M	33	Loss of MSH2/MSH6	No family history of CRC	*MSH2* c.1867delG
100	F	27	Loss of MSH2/MSH6	Known family history of LS; SDR with EC	*MSH2* c.1661G>A
44	M	35	Loss of MSH2/MSH6, sebaceous neoplasms, small bowel cancer, prostate cancer	FDR with CRC	*MSH2* p.R711*
63	M	35	Wilms tumor, gastric cancer	FDR with EC, SDR with CRC (AII)	*MSH2* c.1251_1254insAGTT
24	F	28	Loss of MSH2/MSH6	SDR with CRC	*MSH2* IVS5+3A>T
84	M	35	Loss of MSH2/MSH6	FDR with CRC, SDR with CRC (AI)	*MSH2* whole gene deletion
35	F	24	Loss of MSH2/MSH6	SDR with CRC	*MSH2* c.1068delA
101	F	34	Loss of MSH2/MSH6	FDR with kidney cancer, SDR with CRC, SDR with stomach cancer	*MSH2* deletion exons 1–6
56	F	34	N/A, tumor not available for MSI/IHC	Known family history of LS; FDR with CRC, FDR with EC (AII)	*MSH2* c.2634+5G>C
105	F	26	N/A, tumor not available for MSI/IHC	No family history of CRC	*MSH6* c.3261dupC
144	F	35	Multiple colon adenomas	No family history of CRC	*MUTYH* p.Y179C/p.Y179C
134	F	26	Loss of PMS2	No family history of CRC	*PMS2* c.631C>T
145	F	33	Loss of PMS2	No family history of CRC	*PMS2* c.710_714delAAAGC
130	M	34	Loss of PMS2	No family history of CRC	*PMS2* c.538-2A>G
31	F	32	EC	No family history of CRC	*PMS2* p.E41X
34	F	17	Loss of PMS2	No family history of CRC	*PMS2* c.1831insA
138	F	18	Osteosarcoma	No family history of CRC or young cancers	*TP53* p.C242Y

AI, Amsterdam I; AII, Amsterdam II; CRC, colorectal cancer; EC, endometrial cancer; FDR, first-degree relative; IHC, immunohistochemistry; LS, Lynch syndrome; MSI, microsatellite instability; SDR, second-degree relative.

Outcomes of patients undergoing other testing

Thirty-nine patients did not undergo panel genetic testing. Twenty-four patients (61.5%) underwent syndrome-specific testing due to clinical evidence of a genetic syndrome and were all found to have pathogenic mutations, including nine in *APC*, six in *MLH1*, seven in *MSH2*, and two in *PMS2*. Seven of the 39 patients were offered panel testing and declined or were lost to follow-up (18.0%). The remaining eight patients (20.5%) underwent other targeted genetic testing, with no mutations or VUS identified in this group. This group of eight contained one patient with loss of PMS2 staining in the tumor but no germline mutation, as well as one patient with ulcerative colitis who underwent *TP53* testing based on a personal history of multiple primary cancers. Another patient with a personal and family history suspicious for FAP had a microsatellite-stable tumor with two somatic *APC* mutations; germline *APC* testing was negative. The remaining five patients in this group all had MMR-proficient tumors with no significant family history of colorectal cancer nor synchronous polyps; they were evaluated soon after the implementation of panel testing and were offered only *MUTYH* germline testing. All five were negative for mutations.

Table 2 lists the personal and family history features of mutations carriers identified by both panel testing and syndrome-directed testing.

Discussion

Our study aimed to evaluate whether testing young patients with CRC with a disease-specific gene panel would increase the yield of patients identified to have a hereditary syndrome, in particular those patients without a clear syndromic phenotype or family history of cancer. The majority of our cohort underwent panel testing; however, only patients previously suspected to have a hereditary predisposition were identified to have a highly-penetrant germline mutation via panel testing. No mutations in genes of high-penetrance were identified in patients without a personal or family history suggestive of a specific hereditary CRC syndrome. Although one patient with no family history of cancer was found to have an *MSH6* mutation via panel testing, this is not entirely unexpected given the lower penetrance of *MSH6* mutations [10]; this patient's tumor was unavailable for testing and therefore MSI-status is unknown.

We again confirmed the high prevalence of hereditary syndromes among young patients with CRC, 29.4% overall [2]. However, disease-specific panel testing did not appear to increase the yield of patients diagnosed with an inherited syndrome any more than phenotype-drive genetic testing. Panel testing did additionally identify two patients with mutations in moderate-penetrant genes that would not have been identified via phenotype-driven testing; however, the extent of the benefit of surveillance recommendations and their effect in cancer prevention in the context of these moderate-penetrant genes is largely unknown. Panel testing also identified 33 patients with VUS results.

It is important to highlight that most patients in our cohort underwent disease-specific panel testing, although 25 patients had broader panel testing based on their personal and/or family history of cancer. Several recent publications have reported outcomes of pan-cancer panel testing in patients with CRC diagnosed under 50, with 16–18.6% identified to have germline mutations including in genes of moderate penetrance and in genes not traditionally associated with CRC risk [3–5]. Therefore, although disease-specific panel testing did not identify any unexpected highly-penetrant mutations in our cohort, expanding to a broader panel may increase the mutation detection rate via opportunistic population screening for other hereditary cancer syndromes, although the role of these mutations in the development of CRC is still an unanswered question. This broader testing strategy may increase the yield of mutations identified, but at the cost of identifying VUS in this population.

One limitation of our study is that not all members of our cohort underwent uniform panel testing, although most patients who did not undergo panel testing were identified to have a germline mutation consistent with their personal and/or family history of cancer. Therefore, we cannot rule out the possibility of unanticipated mutations in the population of patients who did not have a CRC gene panel. In addition, because our patients underwent disease-specific panel testing, mutations in non-CRC genes may have been missed.

In conclusion, disease-specific gene panel testing for AYA with CRC does not appear to increase the yield of germline mutations over patients undergoing traditional testing driven by phenotype and/or family history. Panel testing did identify mutations in genes of moderate penetrance, as well as VUS in nearly a third of patients. Broader pan-cancer gene testing may increase the mutation detection rate in non-CRC genes, although the extent of their association with CRC risk is still undefined. In addition, broader panel testing would be likely to further increase the rate of VUS. Despite this, the use of panel testing is still an important consideration in the young CRC population, given the high yield of testing as well as impact of mutation identification for a patient and/or family members. The benefits and limitations of panel testing in this population, including the size and extent of the selected panel and the high likelihood of identifying VUS results, should be considered when making clinical recommendations for genetic testing. Further research into the use of broader panels in the cohort of AYA with CRC is indicated.

Conflict of interest

The authors disclose no potential conflicts of interest.

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