

## AGA Clinical Practice Update on Young Adult–Onset Colorectal Cancer Diagnosis and Management: Expert Review



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- DESCRIPTION:** The objectives of this expert review are: (1) to prepare clinicians to recognize the presentation and evidence-based risk factors for young adult–onset colorectal cancer (CRC), defined as CRC diagnosed in individuals 18 - <50 years of age; (2) to improve management for patients with young onset CRC. This review will focus on the following topics relevant to young adult–onset CRC: epidemiology and risk factors; clinical presentation; diagnostic and therapeutic management including options for colorectal and extra-colonic surgical intervention, chemotherapy and immune-oncology therapies; genetic testing and its potential impact on preimplantation genetics; fertility preservation; and cancer surveillance recommendations for these individuals and their family members.
- METHODS:** The evidence reviewed in this manuscript is a summation of relevant scientific publications, expert opinion statements, and current practice guidelines.
- BEST PRACTICE ADVICE 1:** With the rising incidence of people developing CRC before 50 years of age, diagnostic evaluation of the colon and rectum is encouraged for all patients, irrespective of age, who present with symptoms that may be consistent with CRC, including but not limited to: rectal bleeding, weight loss, change in bowel habit, abdominal pain, iron deficiency anemia.
- BEST PRACTICE ADVICE 2:** Clinicians should obtain family history of colorectal and other cancers in first and second degree relatives of patients with young adult–onset CRC and discuss genetic evaluation with germline genetic testing either in targeted genes based on phenotypic presentation or in multiplex gene panels regardless of family history.
- BEST PRACTICE ADVICE 3:** Clinicians should present the role of fertility preservation prior to cancer-directed therapy including surgery, pelvic radiation, or chemotherapy
- BEST PRACTICE ADVICE 4:** Clinicians should counsel patients on the benefit of germline genetic testing and familial cancer panel testing in the pre-surgical period to inform which surgical options may be available to the patient with young adult–onset CRC
- BEST PRACTICE ADVICE 5:** Clinicians should consider utilizing germline and somatic genetic testing results to inform chemotherapeutic strategies
- BEST PRACTICE ADVICE 6:** Clinicians should offer hereditary CRC syndrome specific screening for CRC and extra-colonic cancers only to young adult–onset CRC patients who have a genetically or clinically diagnosed hereditary CRC syndrome. For patients with sporadic young adult–onset CRC, extra-colonic screening and CRC surveillance intervals are the same as for patients with older adult–onset CRC.

*Abbreviations used in this paper:* ACS, American Cancer Society; AA, African American; CI, confidence interval; CMS, consensus molecular subtyping; CRC, colorectal cancer; FAP, familial adenomatous polyposis; LS, Lynch syndrome; MACS, microsatellite and chromosome stable; MAP, MYH-associated polyposis; MMR, mismatch repair; MSI, microsatellite instability; NAP, *NTHL1*- associated polyposis; NHW, non-Hispanic White; PAPP, polymerase proofreading-associated polyposis.



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Over the past 30 years, colorectal cancer (CRC) has become an increasingly common diagnosis and cause for cancer-related death for young adults (18 to <50 years of age),<sup>1,2</sup> and is the most commonly diagnosed cancer and cause of cancer death for young adult men in the United States.<sup>3,4</sup> Of the approximately 140,000 cases of CRC diagnosed in the United States annually, 11% of colon cancers and 18% of rectal cancers occur in young adults.<sup>1</sup> In the same time frame, the incidence of CRC declined by 20% for people over 50 years of age, and their CRC mortality decreased by 34%. These decreases in older adult-onset CRC incidence and mortality in large part have been attributed to implementation of average-risk CRC screening beginning at 50 years of age. This rise in young adult-onset CRC is not fully accounted for by the declines in incidence of older adult-onset CRC nor the increase in known hereditary CRC syndromes, as only 20% of young adult-onset CRC patients will have a pathogenic mutation.<sup>5</sup>

The purpose of this clinical practice update is to highlight the importance of the rise of CRC in young adults, summarize the epidemiological and genetic features of young adult-onset CRC, and present an approach for the work up and treatment in young adults with CRC. That 1 in 10 colon cancers and 1 in 5 rectal cancers are projected to develop in people under the 50 years of age by 2030 indicates the need to improve our understanding of the best clinical practices to recognize and treat young adult-onset CRC.<sup>1,2</sup>

## Epidemiology of Young Adult-Onset CRC

### *Incidence*

In the United States, the incidence of CRC has increased 51% in people 18 to <50 years of age over the past 30 years, while at the same time, the incidence for older age onset CRC has decreased by 20%.<sup>6</sup> The incidence of young adult-onset CRC is 9.2 to 12.2 per 100,000 compared with an incidence of 40 per 100,000 for people  $\geq$ 50 years of age.<sup>7</sup> The inflection time point when CRC incidence began to increase in young adults and decrease in older adults occurred in the 1990s, coincident with the adoption and increased use of average-risk CRC screening.<sup>8</sup> Though projections based on the yearly percent increases seen in young adult-onset CRC cases from 1975 to 2010 predict that the highest increases in incidence of both colon and rectal cancer will occur in people 18–34 years of age,<sup>1</sup> currently 75% of young adult-onset CRC arises in people 40 to <50 years of age.<sup>9,10</sup> Young adult-onset CRC is significantly more likely to develop in the rectum and distal colon compared with the proximal colon, and rectal and distal colon tumors account for the overall increased incidence of young adult-onset CRC.<sup>11</sup>

Increases in the incidence of young adult-onset CRC is not restricted to the United States. Analysis of the incidence of young vs older adult-onset CRC in 36 countries from 3 continents highlight that young adult-onset CRC is a global problem.<sup>2</sup> Rates of young adult-onset CRC (18 to <50 years of age) from 2008 to 2012 increased in 19 countries (range, 3.5 per 100,000 in India to 12.9 per 100,000 in Korea) but decreased in only 3 countries (Italy, Austria, and Lithuania)—2 of which endorse that CRC screening begin in the fourth decade.<sup>2</sup>

### *Racial Differences in Incidence and Mortality*

Though the incidence of young adult-onset CRC increased in all racial and ethnic groups in the United States from 2000 to 2014, non-Hispanic White (NHW) individuals had a 47% relative increase in incidence—the highest increase in incidence during this time. Despite the rising incidence in NHW individuals, the overall incidence of young adult-onset CRC (18 to <50 years of age) is still higher in African American (AA) individuals not classified by Hispanic ethnicity (12.7 per 100,000 persons) compared with NHW individuals (11.0 per 100,000 persons).<sup>6</sup> This rise in incidence among young adult-onset CRC in NHW individuals is largely attributable to the greater increase in rectal cancer incidence in NHW individuals (from 2.7 to 4.5 per 100,000 persons) compared with AA individuals not classified by Hispanic ethnicity (from 3.4 to 4 per 100,000 persons) from 2000 to 2010.<sup>9</sup> Despite these trends among NHW individuals, AA individuals still have the highest overall incidence of young adult-onset CRC (12.7 per 100,000) and highest incidence of both distal and proximal colon cancer.<sup>9,11</sup> In the 40- to <50-year-old age group in which the greatest increases in young adult-onset CRC incidence have occurred, the incidence remained higher in non-Hispanic AA individuals (29 per 100,000 persons) than in NHW individuals (23 per 100,000 persons).<sup>12</sup> Young adult-onset CRC has steadily increased by 15% annually among Hispanics in the 20- to 29-year-old and Hispanic individuals who develop young adult-onset CRC present on average 10 years earlier than NHW individuals with young adult-onset CRC.<sup>13</sup>

Non-Hispanic AA individuals with young adult-onset CRC have lower overall survival and a higher risk for cancer specific death compared with NHW individuals (hazard ratio: 1.35 for colon and 1.51 for rectal and rectosigmoid cancer). The overall survival of Hispanic and NHW individuals is not significantly different.<sup>14</sup> However, among young adult-onset rectal cancer patients, survival rates were similar for AA individuals not classified by Hispanic ethnicity and NHW individuals due to significant increases in survival for both Hispanic and non-Hispanic AA individuals with rectal cancer.<sup>6</sup> For NHW individuals, survival rates for proximal colon

cancer significantly increased from 50% in 1992–1996 to 70% in 2010–2014, but for proximal colon cancer in AA individuals not classified by Hispanic ethnicity, the survival rate of 55% did not improve.<sup>9</sup> For stage IV CRC, overall survival was poorer in AA individuals not classified by Hispanic ethnicity than in NHW individuals.<sup>6</sup>

## Molecular Epidemiology

Genetic, transcriptional and methylation features characterize CRC and subdivide it into several distinct molecular subtypes based on somatic profiles that inform better chemotherapy options and correlate with cancer survival.<sup>15</sup> Next-generation sequencing efforts have identified high frequencies of somatic mutations in histone modifier genes, higher tumor mutation burdens, and a greater proportion of microsatellite instability (MSI) in 350 tumors from patients with young adult-onset vs older adult-onset distal colon and rectal cancers.<sup>16</sup> MSI is the phenomenon of cancer DNA to exhibit extra microsatellite nucleotide repeats compared with matched normal cells secondary to deficient DNA mismatch repair (MMR). Deficient MMR cancers arise from constitutional pathogenic mutations in 1 of the 4 DNA MMR genes including MLH1, MSH2, MSH6, and PMS2 causing Lynch syndrome (LS) or from hypermethylation of the promoter (most commonly MLH1) seen in up to 20% of sporadic colon cancers. Deficient MMR tumors are typically chromosomally stable, while roughly half of microsatellite stable CRCs are chromosomally unstable and the other half are microsatellite and chromosome stable (MACS).<sup>17</sup> MACS tumors often arise in the distal colon and rectum and are less likely to produce the immune response of many MSI tumors with tumor-infiltrating lymphocytes that may be prompted by the higher cancer antigen burden that results from the underlying genome wide MSI. Young adults with MACS CRC may be more likely to have a family history of CRC, though an underlying genetic etiology has not been identified. *BRAF* V600E mutations and *APC* mutations have been reported to be less frequent in young adult-onset CRC,<sup>18</sup> and in one series, somatic tumor mutations in *MYCBP2*, *BRCA2*, *PHLPP1*, *TOPORS*, and *ATR* occurred more frequently in young adult-onset CRC than in older adult-onset cases.<sup>19</sup> Young adult-onset CRC is more likely to have LINE-1 hypomethylation than older adult-onset tumors.<sup>20</sup>

Consensus molecular subtyping (CMS) using gene expression transcription has emerged as a prognostic tool with associations with overall and progression-free survival.<sup>21</sup> CMS subtyping is also predictive for response and survival benefits for specific chemotherapeutic agents for patients with stage III CRC.<sup>15</sup> **Overall, CRC patients <40 years of age are more likely to have subtypes CMS1 (MSI/immune) or CMS2 (canonical APC/ $\beta$ -catenin) tumors as compared with CMS3 (metabolic) or CMS4 (mesenchymal) tumors.**<sup>18,22</sup>

## Diagnosis and Management

### *Clinical Presentation and Endoscopic Features of Young Adult-Onset CRC*

Regardless of the age of onset, CRC is often clinically silent in its earliest stages. Because 70% of sporadic young adult-onset CRC patients have no family history of CRC and thus are not eligible for high risk CRC screening, the majority of patients with young adult-onset CRC will present with symptoms.<sup>23–25</sup> Symptoms may include rectal bleeding, abdominal pain, weight loss, or anemia.

Currently, the diagnosis of underlying CRC may be delayed on average for 6 months in young compared with older patients. Possible contributors to this delay in diagnosis include low awareness of alarm symptoms by patients, low clinical suspicion by health care providers, and inadequate or lack of health care access, among others.<sup>23,26</sup> Compared with patients >50 years of age, patients with young adult-onset CRC are more likely to present with advanced cancer, stage III or IV (61% of young adult-onset CRC patients <50 years of age; 76% <30 years of age vs ~50% older adult-onset CRC).<sup>27,28</sup> Signet ring cell histology is found in <1% of all CRC, but is present in at least 3–13% of young adult-onset CRC and is most likely to be present in CRC patients  $\leq$ 30 years of age.<sup>18,28,29</sup> Additionally, tumors are also more likely to be poorly differentiated<sup>30</sup> and are more likely to involve the distal colon and rectum.<sup>29,31</sup>

### *Prevention and Early Detection*

Though the use of CRC screening has contributed significantly to the decrease of CRC in people  $\geq$ 50 years of age, CRC screening among asymptomatic young adults who are <50 years of age has not been recommended outside of known hereditary CRC syndromes in the United States. This is with the exception of the recent American Cancer Society (ACS) guidelines that recommend average-risk CRC screening begin at 45 years of age,<sup>32</sup> utilize the same screening modalities and intervals for subsequent screening or surveillance recommended for people  $\geq$ 50 years of age. Unlike the existing CRC screening recommendations for asymptomatic people  $\geq$ 50 years of age which have been based on randomized controlled trials and prospective cohort studies, the data supporting the ACS guideline to start screening at 45 years of age are based on MISCAN-Colon (Microsimulation Screening Analysis-Colon) modeling that identified an acceptable risk benefit of screening to potential life-years gained via this intervention.<sup>32,33</sup> The U.S. Preventive Services Task Force decision not to expand average screening to start at 45 years of age was based on a benefit being found in 2 of the models (SimCRC and CRC-SPIN) but not the third (MISCAN), which was tested and originally applied to CRC incidence from 1975 to 1979, which predated both CRC screening

and the increase in young adult-onset CRC.<sup>34</sup> Proponents for the ACS recommendation to begin average-risk screening at 45 years of age purport the potential to contain the rising incidence of young adult-onset CRC, while those in opposition to this guideline cite concern that by expanding the screening population may divert resources from medically underserved people, incur excessive financial health care costs, inhibit proper randomized screening to test this guideline recommendation, and be limited because the basic biology of young adult-onset CRC may differ and thus not be amenable to the current screening modalities.<sup>35-37</sup> Though the impact of lowering the screening age will likely remain under debate for some time,<sup>38-40</sup> it is worth reiterating that 2 of the only 3 countries with declining incidence of young adult-onset CRC were the only countries that endorsed that average-risk CRC screening begin at 44 years of age (in Italy) and at 40 years of age (in Austria).<sup>2,41</sup>

### Risk Factors

Though the reasons for the increased incidence of young adult-onset CRC are not known, having inflammatory bowel disease,<sup>42</sup> harboring a pathogenic germline mutation for a known hereditary cancer syndrome,<sup>43,44</sup> and having a history of irradiation<sup>23</sup> are each associated with a higher risk for young adult-onset CRC. A family history of CRC in a first-degree relative is associated with an odds ratio for young adult-onset CRC of 4.50, with the highest odds ratio of 11.68 related to having a sibling with CRC compared with an odds ratio of 3.75 if a parent has CRC.<sup>45</sup> Subpar family history ascertainment including failure to inquire about family history of extracolonic cancers and age of cancer onset may limit early recognition of individuals at risk for young adult-onset CRC.<sup>46</sup> Additional environmental exposures and health behaviors are also likely to relate to young adult-onset CRC. Given that the most significant increases of young adult-onset CRC arise in countries that have established high-income economies or are in the process of transitioning to a high-income economy and adopting a Westernized approach to life, a higher-calorie, lower fruit and vegetable-based, meat-predominant diet, higher body mass index and a decreased activity level may contribute to the rise of young adult-onset CRC.<sup>2</sup> Excessive sedentary time measured as hours of television watching is also associated with an increased risk for young adult-onset CRC, particularly rectal cancer.<sup>47</sup> However, having a high body mass index in childhood or young adulthood is associated with an increased risk for colon cancer but not for rectal cancer.<sup>48</sup>

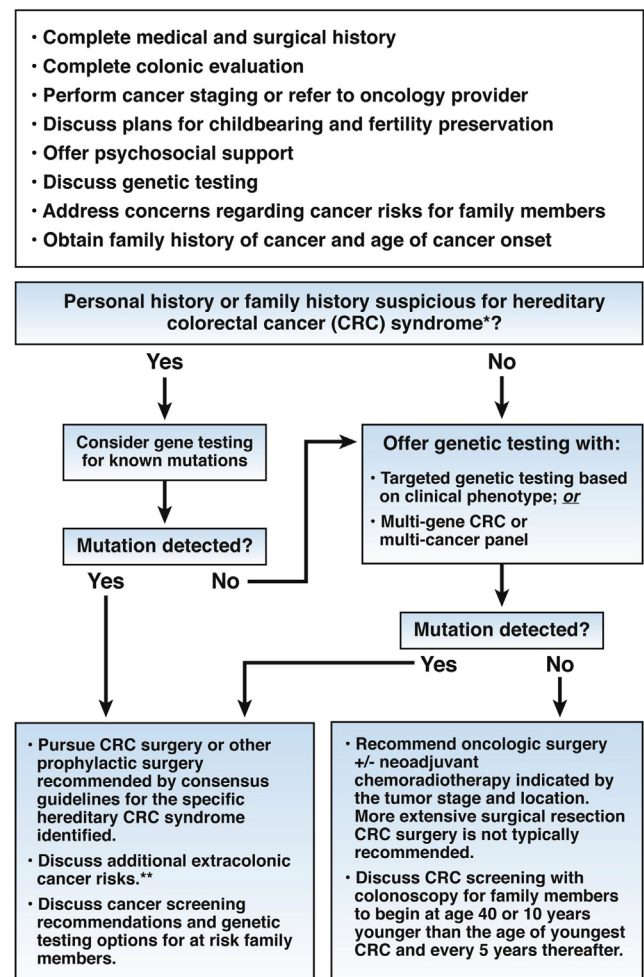
### Hereditary CRC Syndromes

Roughly 1 in 5 young adult-onset CRCs will be caused by a germline mutation and among those with a

detectable hereditary condition, half of those patients with young adult-onset CRC will have LS (Figure 1).<sup>49,50</sup> Recognition of a hereditary CRC syndrome and the need for genetic testing is imperative because surgical options vary depending upon the presence and type of known hereditary syndrome a young adult-onset CRC patient may have (Table 1).

LS is the autosomal dominant hereditary CRC syndrome that results from defective DNA MMR. It is associated with young adult-onset MSI CRC, and patients with this condition have an increased risk for endometrial, gastric, ovarian, small bowel, renal pelvis, and ureteral cancers.

Familial adenomatous polyposis (FAP) results from constitutional pathogenic mutations in *APC*, and is the second most common hereditary cause for young adult-onset CRC. Patients with FAP develop hundreds to thousands of colorectal adenomas and have a nearly



\*Hereditary CRC syndromes with known constitutional pathogenic mutations include Lynch Syndrome, Familial Adenomatous Polyposis (classic and attenuated), MYH-associated polyposis, NTHL1-associated polyposis, Peutz-Jeghers Syndrome, Juvenile Polyposis Syndrome, PTEN Hamartoma Tumor Syndrome, Polymerase proofreading associated polyposis.

\*\*At the time of initial cancer diagnosis and treatment the discussion of extracolonic cancer risk and future screening may be introduced but may be more completely addressed and future testing planned until after cancer treatment.

**Figure 1.** Management of young adult-onset colorectal cancer patients

100% risk of developing CRC by 40 years of age without a prophylactic total colectomy/proctocolectomy.<sup>51,52</sup>

Some constitutional pathogenic *APC* mutations predispose to attenuated FAP, which has a to a less severe colon polyp burden (<100 polyps) and lower risk for and later age of onset for CRC.

The autosomal recessive condition called MYH-associated polyposis (MAP) clinically resembles attenuated FAP because constitutional pathogenic homozygous mutations of the MYH base excision repair gene may lead to *APC* mutations. *NTHL1*-associated polyposis (NAP) is another autosomal recessive hereditary CRC syndrome. Typical age of polyp onset is in the 40s, polyp burden is generally under 50 polyps, but cancer risk is increased significantly with most CRC arising under the 60 years of age.<sup>53,54</sup> Polymerase proofreading-associated polyposis (PAPP) is an autosomal dominant hereditary CRC syndrome caused by mutations in *POLE* and *POLD1* genes. PAPP is associated with young adult-onset CRC and polyposis, though PAPP-associated young adult-onset CRC may arise even in the absence of polyposis.<sup>55,56</sup>

Familial CRC syndrome X refers to patients who fulfill Amsterdam or Bethesda criteria for consideration of genetic testing for LS but are not found to have constitutional pathogenic mutations in the DNA MMR genes.<sup>57,58</sup> In a group of young adult-onset CRC patients who met Amsterdam criteria II but did not have LS, 60% had constitutional pathogenic mutations in *BRCA2*.<sup>59</sup>

### Genetic Screening

It is highly recommended to offer genetic testing to all young adult-onset CRC patients because 20% of patients with young adult-onset CRC will have an underlying constitutional pathogenic mutation.<sup>49</sup> As well outlined in National Comprehensive Care Network guidelines, one option for genetic evaluation is a targeted approach based on several features including the patient's family history of hereditary CRC, other cancer syndromes, and the patient's polyp burden and histology.<sup>60</sup> Tumor testing for MSI or immunohistochemistry for *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be done on all young adult-onset CRC as a screen for LS and be performed on all CRC regardless of age of onset, given the prognostic value among early stages (stage I and II) and the predictive value for treatment with immunotherapy in stage IV disease.

With the advent of next-generation sequencing, decreasing costs in the consumer market place, and recent studies highlighting the limitations of guideline based genetic testing,<sup>61,62</sup> it may be reasonable to offer young adult-onset CRC patients direct genetic (germline) testing. They are better than targeted testing for people who do not fit clinical criteria for one hereditary syndrome, who have clinical criteria that may fit more than 1 hereditary cancer syndrome, or who have no or a limited family history of cancer.

However, by testing more genes, the chances of finding genetic variants of unknown significance or a pathogenic variant that does not have a clear management guideline increase and may lead to confusion for the patient and the provider. This reinforces the concept of early integration of genetic counselors and genetic specialists in the care of young adult-onset CRC cases to deliver appropriate interpretation of results through counseling, thus providing accurate interpretation of results and reducing patient-provider anxiety and uncertainty. Though data on this approach of universal genetic testing in CRC are limited, recent studies have highlighted the limitation of a guideline-based approach in breast,<sup>61</sup> pancreas,<sup>63</sup> and prostate<sup>64</sup> cancers, leading to the advocacy for more broad-based genetic testing in these cancer types by professional organizations and the National Comprehensive Care Network in some cases.

### Treatment Options For Young Adult-Onset CRC

Surgical and chemotherapeutic recommendations for young adult-onset CRC that arises outside of a known hereditary condition vary, and there are no consensus guidelines currently available.

#### *Multimodal Surgical and Oncologic Management*

For the subset of young adult-onset CRC patients who demonstrate evidence of an inherited genetic predisposition syndrome, the surgical management not only treats the index CRC, but also considers prevention of other syndromic malignancies. Preoperative assessment includes not only appropriate clinical staging of the index CRC to allow for stage-appropriate treatment recommendations, but also comprehensive screening of other organs considered to harbor high risk of malignancy due to the underlying cancer syndrome. The surgical management of the most common hereditary CRC syndromes including LS and FAP have been well summarized elsewhere.<sup>65</sup> The choice of chemotherapy is influenced by somatic mutations that are characteristic of some hereditary syndromes.

Though more likely to receive adjuvant chemotherapy for stage I or II CRC,<sup>66</sup> survival for stage I and II young adult-onset CRC was not better than that of stage-matched older-onset CRC patients who did not receive chemotherapy and only slightly improved for stage III and IV cancer.<sup>28</sup> However, another study found that young adult-onset patients were more likely to have >12 lymph nodes examined, to receive systemic therapy (chemotherapy or immunotherapy) within 6 months of diagnosis and to have a reduced risk of CRC-specific death compared with those with older-onset CRC.<sup>67</sup> In fact, multiple studies have demonstrated a more favorable prognosis of tumors displaying MSI among stage II

**Table 1.** Cancer Risks, Genes Associated, and Recommendations for Management of Hereditary CRC Syndromes

Syndrome	Gene(s)	Mode of inheritance	Lifetime cancer risks	% (95% CI)	Screening/surveillance	CRC and preventative surgery
Lynch syndrome	MSH2 <sup>1</sup> EPCAM	Autosomal dominant	Colorectal	49 (29–85)	Age 20–25 y: Colonoscopy every 1–2 y	Consider IRA for CRC Consider prophylactic hysterectomy once child bearing complete
			Endometrial	57 (22–82)	Flexible sigmoidoscopy every 1–2 y post-IRA	
			Ovary	20 (1–66)	Consider annual endometrial biopsy for premenopausal women and annual endometrial ultrasound for postmenopausal women	
			Stomach	11–19		
			Hepatobiliary	2–7		
			Upper urinary tract	4–5	Age 30–35 y: Consider upper endoscopy every 3–5 years	
			Pancreas	3–4		
			Small Bowel	1–4	Annual urinalysis	
			CNS (Glioblastoma)	1–3		
Lynch syndrome	MLH1 <sup>1</sup>	Autosomal dominant	Colorectal	52 (31–90)	Age 20–25 y: Colonoscopy every 1–2 y	Consider IRA for CRC Consider prophylactic hysterectomy once child bearing complete
			Endometrial	21 (9–82)	Flexible sigmoidoscopy every 1–2 y post-IRA	
			Ovary	38 (3–81)	Consider annual endometrial biopsy for premenopausal women and annual endometrial ultrasound for postmenopausal women	
			Stomach	11–19		
			Hepatobiliary	2–7		
			Upper urinary tract	4–5	Age 30–35 y: Consider upper endoscopy every 3–5 y	
			Pancreas	3–4		
			Small Bowel	1–4	Annual urinalysis	
			CNS (Glioblastoma)	1–3		
Lynch syndrome	MSH6 <sup>1</sup>	Autosomal dominant	Colorectal	18 (13–30)	Age 20–25 y: Colonoscopy every 1–2 y	Consider IRA for CRC Consider prophylactic hysterectomy once child bearing complete
			Endometrial	17 (8–47)	Flexible sigmoidoscopy every 1–2 y post-IRA	
			Ovary	1(0–3)	Consider annual endometrial biopsy for premenopausal women and annual endometrial ultrasound for postmenopausal women	
			Stomach	≤3		
			Urinary Tract	<1		
Lynch syndrome	PMS2 <sup>2</sup>	Autosomal dominant	Colorectal	15–20	Age 20–25 y: Colonoscopy every 1–2 y	Consider IRA for CRC Consider prophylactic hysterectomy once child bearing complete
			Endometrial	15	Flexible sigmoidoscopy every 1–2 y post-IRA	
					Consider annual endometrial biopsy for premenopausal women and annual endometrial ultrasound for postmenopausal women	
Familial adenomatous polyposis: classic	APC <sup>3–5</sup>	Autosomal dominant	Colorectal	100	Age 10–12 y: Colonoscopy every 1–2 y	Consideration for IPAA colectomy when polyp burden too great for endoscopic control, IRA for women in child-bearing years with conversion to IPAA after child bearing complete
			Duodenum/Periampullary	4–12	Annual pouchoscopy post-IPAA	
			Stomach	<1	Flex sig q 6 mo post IRA	
			Pancreas	2	Age 18–25 y: Upper endoscopy every 1–3 y	
			Thyroid	1–2	Symptom-based evaluation	
			Liver (hepatoblastoma)	1–2	Consider thyroid ultrasound	
			CNS (Medulloblastoma)	<1	Symptom based evaluation	

Familial adenomatous polyposis: attenuated	APC <sup>5-10</sup>	Autosomal dominant	Colorectal	70	Age 20–25 y: Colonoscopy every 1–2 y	Consideration for IRA for CRC or when polyp burden too great for endoscopic control
			Duodenum/Periampullary	4–12	Flex sig q 6 months post-IRA	
			Thyroid	1–2	Age 20–25 y: Upper endoscopy every 1–3 y Consider annual thyroid ultrasound	
MutYH polyposis (MAP)	MUTYH <sup>5,6,11-15</sup>	Autosomal Recessive	Colorectal	80	Age 20–25 y: Colonoscopy every 1–2 y	Consideration for IRA or colectomy for CRC or when polyp burden too great for endoscopic control
			Duodenum	4	Age 20–25 y: Upper endoscopy every 1–3 y	
Peutz Jeghers syndrome	STK11 <sup>5,16,17</sup>	Autosomal dominant	Breast	54	Age 25 y: Mammogram and breast MRI yearly	
			Colorectal	39		
			Pancreas	11–36	Late teens Colonoscopy every 2– y	
			Stomach	29	Age 25–30 y: MRCP or EUS every 1–2 y	
			Ovary	21	Late teens Upper endoscopy every 2–3 y	
			Uterine/cervix	13	Age 18 y: Annual transvaginal ultrasound	
			Lung	15	Age 20 y: Annual chest CT	
			Small bowel	9–10	Age 8–10 y: Small bowel screening (CT/MR enterography, small bowel follow-through, capsule endoscopy) every 1–3 y	
			Testicular	<1	Age 10 y: Testicular exam and ultrasound yearly	
Juvenile polyposis syndrome	SMAD4 <sup>5,18-21</sup> BMPR1A	Autosomal dominant	Colorectal	39	Age 15 y: Colonoscopy every 1–3 y	
			Stomach, pancreas, and small bowel	21	Age 15 y: Upper endoscopy every 1–3 y	
Serrated polyposis syndrome	Unknown <sup>22-24</sup>		Colorectal	16–42	Colonoscopy every 1–3 y	Consideration for colectomy for CRC or when polyp burden too great for endoscopic control
PTEN hamartoma tumor syndrome	PTEN <sup>25,26</sup>	Autosomal dominant	Colorectal	16–20	Colonoscopy every 1–3 y	Consider bilateral mastectomy Total thyroidectomy for benign lesions and cancer Consider prophylactic hysterectomy once child bearing complete
			Breast	30–50% (Female)	Age 18 y: Self-exam annually	
			Thyroid	5–10	Age 25 y: Clinical exam every 6 months	
			Endometrial	5–20	Age 30 y: Mammogram and breast MRI annually	
			Lung	12	Age 18 y: Baseline then annually	
			Renal	2–8	Annual endometrial biopsy for premenopausal women Annual endometrial ultrasound for postmenopausal women Urinalysis annually Urine cytology and renal ultrasound if family history of renal cancer annually	

CI, confidence interval; CRC, colorectal cancer; CT, computed tomography; EUS, endoscopic ultrasound; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; IPAA, ileal pouch anal anastomosis; IRA, ileorectostomy.

and III CRC cases, thus recommending against the use of adjuvant chemotherapy among patients with MSI stage II CRC.<sup>68</sup> This recommendation still applies to young-onset CRC patients. In addition, the classical use of oxaliplatin-based chemotherapy for 6 months has been limited to cases with larger primaries (T4) and abundant lymphatic node involvement (N2), thus limiting the use to 3 months in the rest of stage III cases due to the high rates of neuropathy.<sup>68</sup> Careful consideration of side effects needs to be carefully factored in a young adult-onset population with potential longer impacts upon their quality of life. More aggressive surgery to extend surgical resection beyond standard oncological guidelines or more intensive chemotherapy in several studies was not recommended because of the potential risk for overtreatment.<sup>69,70</sup>

### Psychological Impact

Because more young adult-onset CRC patients present with stage III and IV disease that requires multimodality therapy, they likely face higher risks for long-term treatment-related sequelae. Even long-term survivors face ongoing functional deficits and symptoms, and have disproportionately reported worse anxiety, body image, and embarrassment with bowel movements.<sup>71</sup> Thus, their cancer survivorship needs may differ and likely require long-term attention.

### Fertility Preservation

Based on current evidence, surgery for CRC does not appear to negatively impact fertility. That said, the moderate risk for impaired fertility associated with chemotherapy based on type, dose and duration warrant discussion, particularly because patients might wish to pursue fertility preservation prior to beginning treatment for CRC.<sup>72</sup> Though banking of cryopreserved sperm is recommended prior to gonadotoxic chemotherapy<sup>73</sup> it is not universally offered to cancer patients.<sup>62</sup> In women, embryo cryopreservation is the most established option for women, but unfertilized oocyte cryopreservation is available for those women without a partner who do not want to use donor sperm or who have beliefs that do not allow freezing of embryos. Ovarian tissue cryopreservation and later transplantation is not yet approved beyond use in clinical trials, but has the potential to restore fertility even in young girls who have not yet ovulated. Ovarian translocation away from radiation fields and use of a gonadotropin-releasing hormone agonist to prevent chemotherapy induced ovarian failure are 2 more components of a complete discussion about fertility preservation.<sup>63</sup>

### Summary and Conclusions

Young adult-onset CRC is increasing in incidence globally, particularly in developed countries. As borne out by the story of CRC screening among adults  $\geq 50$

years of age in the United States, early detection is the key to improving CRC-related outcomes. **The signs and symptoms that prompt health care providers to consider a diagnostic colon exam for a person over 50 should prompt a diagnostic colonoscopy exam for the person <50 years of age.** Collecting family history and referring for genetic evaluation are important first steps for patients with young adult-onset CRC, though most young adult-onset CRC patients do not have a known hereditary CRC syndrome. For young adult-onset CRC patients without an apparent underlying genetic syndrome, better understanding of the molecular make-up of young adult-onset CRC may lead to more tailored surgical and chemotherapy treatment options in the future, but at this point, more extensive surgery or more aggressive chemotherapy cannot be recommended. As cancer treatments evolve to use patient tumor specific therapeutics, our management of patients with young adult-onset CRC will improve.

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**Conflicts of Interest**

The authors disclose no conflicts.