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Concurrent Session 2: Early Age Onset Colorectal Cancer Screening Updates

November 16, 2020 3:15 to 4:15 p.m. EST





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PANELISTS

- Heather Hampel, MS, LGC, Associate Director, The Ohio State University Comprehensive Cancer Center, Human Genetics, NCCRT Steering Committee (Moderator)
- Rebecca L. Siegel, MPH, Scientific Director, Surveillance Research, American Cancer Society, Inc.
- Samir Gupta, MD, MSCS, AGAF, Professor, Division of Gastroenterology, Department of Internal Medicine; Co-Lead, Cancer Control Program, Moores Cancer Center; University of California San Diego; Chief, GI Section, San Diego Veterans Affairs Healthcare System
- Jordan J. Karlitz, MD, Director, GI Hereditary Cancer and Genetics Program, **Tulane University Cancer Center; NCCRT Steering Committee**

The epidemiology of early-onset colorectal cancer: **Opportunities for Action**



Rebecca Siegel, MPH Sr Scientific Director of Surveillance Research American Cancer Society NCCRT Annual Meeting November 16, 2020



Preventive Services October 2020

Adults ages 50 to 75 yearsThe USPSTF recommends screening for colorectal cancer in all adults ages 50 to 75 years.AAdults ages 45 to 49 yearsThe USPSTF recommends screening for colorectal cancer in adults ages 45 to 49 years.BAdults ages 45 to 49 yearsThe USPSTF recommends to colorectal cancer in adults about screening strategies.BAdults ages 76 to 85 yearsThe USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health and prior screening history.C	Population	Draft Recommendation	Grade
Adults ages 45 to 49 yearsThe USPSTF recommends screening for colorectal cancer in adults ages 45 to 49 years.BSee the "Practice Considerations" section and Table 1 for details about screening strategies.See the "Practice Considerations" section and Table 1 for details about screening strategies.CAdults ages 76 to 85 yearsThe USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults ages 76 to 85 whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health and prior screening history.C	Adults ages 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults ages 50 to 75 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	A
Adults ages 76 to 85 years The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults ages 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small. In determining whether this service is appropriate in individual cases, patients and clinicians should consider the patient's overall health and prior screening history.	Adults ages 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults ages 45 to 49 years. See the "Practice Considerations" section and Table 1 for details about screening strategies.	В
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American Cancer Society®

September 2018

The ACS recommends that adults aged 45 y and older with an average risk^b of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be followed up with timely colonoscopy.

The recommendation to begin screening at age 45 y is a qualified recommendation.

The recommendation for regular screening in adults aged 50 y and older is a *strong recommendation*.

The ACS recommends that average-risk adults in good health with a life expectancy of greater than 10 y continue CRC screening through the age of 75 y (qualified recommendation).

The ACS recommends that clinicians individualize CRC screening decisions for individuals aged 76 through 85 y based on patient preferences, life expectancy, health status, and prior screening history (qualified recommendation).

The ACS recommends that clinicians discourage individuals over age 85 y from continuing CRC screening (qualified recommendation).

CRC incidence & mortality in the U.S.





Siegel et al. March 2020, CA A Cancer Journal for Clinicians

CRC incidence trends <65 y



APC = annual percent change



50-64 yr

Siegel et al. March 2020, CA A Cancer Journal for Clinicians

CRC mortality trends <50 y

#1 cancer COD in men <50 y



APC = annual percent change



CRC mortality trends <65 y

#1 cancer COD in men <50 y



APC = annual percent change



50-64 yr



Siegel et al. March 2020, CA A Cancer Journal for Clinicians

CRC incidence age <50 yr by stage at diagnosis





APC = annual percent change

APC, +2.5

APC, -0.8 (nonsignificant)

APC, +2.5

CRC stage at diagnosis by age







Risk of advanced stage <50 40% higher after accounting for screening

Chen et al. 2017, Clin Gastro and Hep

CRC 5-year relative survival by age





Data Source: SEER 18, diagnoses during 2009-2015, all followed through 2016.



Median age at CRC diagnosis, 1990-2016



YEAR OF DIAGNOSIS



Siegel et al. March 2020, CA A Cancer Journal for Clinicians







- 17,930 new cases ightarrow=49 per day
 - 3,640 deaths =10 per day



CRC < 50 y in the US 2020

80% have children <18 y

Source: Siegel et al. March 2020, CA A Cancer Journal for Clinicians

CRC subsite distribution by age







CRC subsite distribution by age







65+ y



CRC age distribution <50 yr



American Cancer Society®



22% 30-39 years

CRC age distribution <50 yr

Kopetz et al. Clinical and Molecular Characterization of Early-onset Colorectal Cancer. Cancer 2019.

American Cancer

"unique molecular and clinicopathologic features in patients younger than 30 years and with predisposing conditions."





22% 30-39 years

Key Take-away

Substantial opportunity to mitigate burden:

- Screen average-risk at 45 go FIT!
- Earlier for high risk (fam history)
- Reducing delays in diagnosis/tx
 - Educate
 - Reduce stigma





Thank you!



A Different Perspective on the Utilization of SEER Cancer Data to Understand EAOCRC

JORDAN J. KARLITZ, MD ASSOCIATE PROFESSOR OF MEDICINE, DIVISION OF GASTROENTEROLOGY TULANE UNIVERSITY SCHOOL OF MEDICINE

Analyzing SEER Cancer Data in One-year Age Increments

- Traditionally, SEER data has been analyzed in age group blocks (age) 30-39, 40-49 etc.)
- Pooling of ages can increase statistical power for analyses
- However, can potentially overlook important trends in cancer incidence
- Large size of SEER database allows analyses in one-year age intervals
 - Allows for "high definition" view of incidence rate trends in those approaching screening age (key group given rising IRs in young patients)



SEER (Surveillance, Epidemiology, and End Results Program) Database: Overview



* Subcontract under New Mexico ** Three regions represent the state of California: Greater Bay, Los Angeles, and Greater California ***Research support registry only; not under contract to submit data

•SEER 9 - Available for cases diagnosed from 1975 through the current data year.

•SEER 13 - Available for cases diagnosed from 1992 through the current data year and includes expanded races.
•SEER 18 - Available for cases diagnosed from 2000 through the current data year and includes expanded races.
•SEER 21- Available for cases diagnosed from 2000 through the current data year and includes expanded races.
•SEER21 has a more limited set of available variables than other groupings and is only available for limited statistics
•Detroit and New Jersey are no longer in the SEER Program, but are included in the current data release.
•Ref: https://seer.cancer.gov/registries/terms.html

Georgia includes Atlanta, Rural Georgia and Greater Georgia

Trends in the incidence of colorectal cancer in the U.S. among those approaching screening age

- Unique methodology: analyze SEER 18 CRC incidence rates in one year age increments
- Question: What is the increase in the CRC incidence rate from 49 to 50 years of age, when large segments of the population begin average-risk screening?
- 170,434 cases of CRC were analyzed
- Incidence rate increase of 46.1% from 49 to 50 years of age
- Findings consistent with preexisting CRCs diagnosed via screening uptake
- Supports the presence of a large undetected preclinical case burden in patients younger than 50 years that is not reflected in observed SEER incidence rates

JAMA Network

From: Trends in Incidence of Early-Onset Colorectal Cancer in the United States Among Those Approaching **Screening Age**

JAMA Netw Open. 2020;3(1):e1920407. doi:10.1001/jamanetworkopen.2019.20407

100 80 Findings support large undetected Case counts: there were approximately pre-clinical CRC burden prior Incidence Rate 129,226 CRCs (*extrapolated to all 50 60 to age 50 (not reflected in SEER IRs) states) from patients aged 45 to ultimately diagnosed with 40 screening at age 50 50 years from 2000 to 2015 20 Argues for screening at age 45 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 Age, y

> Colorectal Cancer Incidence Rates per 100 000 Population in 1-Year Age Increments in the US Surveillance, Epidemiology, and End Results 18 Registries Among Patients Aged 30 to 60 Years, 2000-2015. Only adenocarcinomas were analyzed. The arrowhead indicates the incidence rate increase from 49 to 50 years of age (46.1% increase: 34.9 [95% CI, 34.1-35.8] to 51.0 [95% CI, 50.0-52.1] per 100 000 population).

Abualkhair W, Zhou M, Ahnen D, Yu Q, Wu X, Karlitz JJ. JAMA Network Open 2020

Age 49 to 50 Incidence Rate Increase Reproducible Across Different Patient Groups

- All U.S. Regions
- Men and Women
- Whites and Blacks
- Colon and Rectal Cancers
- Screening at age 50 unifies these disparate populations, supporting that this increase in incidence from 49 to 50 is due to screening detection as opposed to advancing age alone

Geographic Regions

IR



Yearly Age

54	55	56	57	58	59	60

Men and Women



IR

Yearly Age

52	53	54	55	56	57	58	59	60

Race Stratification

IR



Yearly Age

Colon and Rectal Cancer



Yearly Age

Rectal cancer % increase lower than colon cancer because rectal more likely to present with symptoms prior to screening detection

IR

Stage Stratification



Key Points

- 92.9% of CRC diagnosed at age 50 are invasive (beyond in situ stage)
- Localized cancers: 10% to 11% 5-year mortality, and most require surgery (argues against length time bias in which slower growing and potentially less clinically significant tumors are detected with screening)
- Localized and regional CRCs may be associated with psychological distress, economic burden, and impaired quality of life
- Expected distant CRCs would not have steep rate increases from 49 to 50 years of age as more likely to present with symptoms prior to screening

Take Home Points From This Study

- Steep age 49 to 50 incidence rate increase supports presence of large pre-clinical cancer burden in those in their 40's not reflected in observed SEER incidence rates
- Arguments historically posed against earlier screening at age 45 include much lower incidence rates in 45-49 (34/100,000) versus 50-54 (60.2/100,00)
 - Misconception as those 45-49 do not have the advantage of having CRCs picked up by screening (mainly only by symptoms or FH) compared to 50-54 year-olds
 - Comparing apples to oranges





Prevalence of colorectal neoplasia by age in an average risk cohort: Further Evidence that risk in 45-49-year-olds is similar to 50-54-year-olds

	< 40	40-44	45-49	50-54
	(n=2451	(n=1288	(n=1870	(n=2216
				O)
Advanced	1.1%	3.0%	3.7%	3.6%
neoplasia	(n=28)	(n=38)	(n=70)	(n=804)
Clinically significant	3.0%	5.1%	5.9%	6.1%
serrated polyp	(n=/3)	(n=66)	(n=110)	(1350)

Utilized the New Hampshire Colonoscopy Registry to compare the prevalence of advanced neoplasia (AN) in an "average-risk screening equivalent" group aged 45-49 years with patients aged 50-54 years and older receiving screening colonoscopy

Butterly et al. Aug 2020, Am J Gastroenterology





NCCRT 2020: Early Onset CRC Screening Updates Current opportunities based on family history and symptoms

Samir Gupta MD, MSCS Professor, Department of Medicine, UC San Diego Chief, GI Section, VA San Diego s1gupta@health.ucsd.edu @samirguptaGI

UC San Diego Health Sciences



Family history increases risk and "left shifts" age of diagnosis

≥ 1 first degree relative with CRC at age:	Relative Risk (95% CI)	(cases/10,000)	600 500 400
<50 y	3.31 (2.79–3.89)	Incidence	300-
>50 y	2.02 (1.93–2.11)	mulative I	100
>60 y	1.99 (1.90–2.09)	Cu	30 35



Family history-based recommendations well established

	Criteria	
Joint Guideline by American Cancer Society, US Multi-Society Task Force on Colorectal	CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or adenoma in a single first degree relative < age 60 years	Colonoscopy ev prior to age of fi 40
Cancer (USMSTF ^a) and American College of Radiology, 2008 ⁵	CRC or adenoma in single first degree relative diagnosed age >=60 OR CRC in 2 second degree relatives at any age	Begin screening
National Comprehensive Cancer Network 2019	CRC >=1 first degree relative with CRC at any age	Colonoscopy at diagnosis of CR



Recommendation

very 5 years beginning 10 years irst degree relative diagnosis or age

g at age 40 with any test

age 40 or 10 years before earliest C, repeat every 5 years

Potential effectiveness of implementation of family history based guidelines unclear

- Aims:
 - Estimate performance of family-history based guidelines for identifying individuals ulletwith early onset CRC
- Methods:
 - Population-based case control study individuals age 40-49 in the Colon Cancer \bullet Family Registry 1998-2007
 - Compared sensitivity and specificity of guidelines from major groups ightarrow
 - Estimated proportion with CRC who could have been recommended screening \bullet initiation younger than age of diagnosis

Original Article

Potential Impact of Family History–Based Screening Guidelines on the Detection of Early-Onset Colorectal Cancer

Samir Gupta, MD, MDCS, AGAF (1) 12.3; Balambal Bharti, MBBS, MPH, PhD^{2,3}; Dennis J, Ahnen, MD^{4,5}; Daniel D. Buchanan, PhD^{6,7,8}; Iona C. Cheng, PhD, MPH⁹; Michelle Cotterchio, PhD¹⁰; Jane C. Figueiredo, PhD 😳 ¹¹; Steven J. Gallinger, MD, MSc¹²; Robert W. Haile, DrPH, MPH¹¹; Mark A. Jenkins, PhD^{7,13}; Noralane M. Lindor, MD¹⁴; Finlay A. Macrae, MD, AGAF¹⁵; Loïc Le Marchand, MD, PhD¹⁶; Polly A. Newcomb, PhD, MPH¹⁷; Stephen N. Thibodeau, PhD¹⁸; Aung Ko Win, MBBS, MPH, PhD^{7,13}; and Maria Elena Martinez, PhD 🔟 ^{3,19}

Cancer July 1, 2020



Figure 1. Potential impact of family history-based guidelines on time of colorectal cancer (CRC) diagnosis. Of 2473 cases of CRC, approximately 25% met the criteria for early screening. Among 614 CRC cases meeting the criteria for early screening, approximately 98% could have been recommended to initiate screening at an age younger than the actual age at the time of diagnosis of CRC.

Impact of Family History on CRC Detection/Gupta et al

Current opportunities: on-time evaluation of symptoms

- Small single center case control study, younger vs older rectal cancer patients had longer median time from
 - Symptom onset to healthcare provider evaluation: 121 vs 21 days
 - Symptom onset to first course of treatment : 217 vs 58 days
- Single center retrospective study, younger vs older CRC patients had longer time from
 - Symptom onset to diagnosis: median 128 vs 79 days, with average 243 vs 154 days
 - First medical visit to diagnosis: median 31 vs 22 days, with average of 91 vs 67 days



Figure 1 Time from symptoms to treatment in patients with rectal cancer.

Scott et al Am J Surg 2016; Chen et al Clin Gastro Hep 2017

Strategy for timely evaluation of signs and symptoms

ID Red Flags

- **Rectal bleeding** \bullet
- **Abdominal Pain**
- Weight Loss
- **Iron Deficiency Anemia**
- Constipation
- Diarrhea

Triage

To immediate colonoscopy vs other work up or treatment using:

- **Clinical Guidelines**
- Symptom/Sign Severity
- **Clinical context**

Timely Early-Onset CRC Diagnosis

Burnett-Hartman AN; Lee JK; Demb J; Gupta S under review; Figure concept courtesy of Josh Demb, PhD; Credit to Jeff Lee, MD for "clinical loop"

Close the Loop

Example Strategy: Mandatory 30 day clinic follow up to ensure resolution

Thank You!

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 - Grant Support: ullet
 - NCI 1UG3CA233314-01A1
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 - **Colon Cancer Family Registry** \bullet
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 - @samirguptaGI \bullet

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UC San Diego Health Sciences

Family history-based recommendations

	Criteria	
Joint Guideline by American Cancer Society, US Multi-Society Task Force on Colorectal Cancer	CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or adenoma in a single first degree relative < age 60 years	Colonoscopy eve degree relative di
(USMSTF ^a) and American College of Radiology, 2008 ⁵	CRC or adenoma in single first degree relative diagnosed age >=60 OR CRC in 2 second degree relatives at any age	Begin screening a
USMSTF 2017	CRC or advanced adenoma in 2 first degree relatives at any age OR CRC or advanced adenoma in a single first degree relative < age 60 years	Colonoscopy eve degree relative di
	CRC or advanced adenoma in single first degree relative diagnosed age >=60	Begin screening a
National Comprehensive Cancer Network 2019	CRC >=1 first degree relative with CRC at any age	Colonoscopy at a CRC, repeat ever
	CRC in 2 or more first degree relatives	Colonoscopy eve age of diagnosis of whichever is earlier
Canadian Association of Gastroenterology, endorsed by American Gastroenterological	CRC in 1 first degree relative	Colonoscopy eve younger than age earlier. FIT every 1-2 yea
Association ¹⁶	1 or more first degree relative with documented advanced adenoma	No recommendat both options. Colonoscopy eve younger than age earlier. FIT every

Recommendation

ery 5 years beginning 10 years prior to age of first iagnosis or age 40

at age 40 with any test

ery 5 years beginning 10 years prior to age of first iagnosis or age 40

at age 40 with any test

age 40 or 10 years before earliest diagnosis of ry 5 years

of earliest diagnosed first degree relative,

ery 5-10 years at age 40-50 years or 10 years or of diagnosis of first degree relative, whichever is

ars is suggested as 2nd line option

tion for a preferred test. Colonoscopy or FIT are

ery 5-10 years at age 40-50 years or 10 years e of diagnosis of first degree relative, whichever is 1-2 years is suggested as 2nd line option

Despite recommendations, proportion up-to-date probably low

- Aim: estimate colonoscopy exposure using US National Health Interview Survey data from 2005 and 2010
- Age 40 and older ightarrow
- Survey included questions about whether a mother/father/sibling, or child had \bullet cancer, and type of cancer



Results



Figure. Study sample selected from respondents to the National Health Interview Surveys, 2005 and 2010. Abbreviation: CRC, colorectal cancer.

Key Finding 38.3% individuals age 40-49 reporting first degree relative with CRC were up to date with colonoscopy in 2010

Limitations and Strengths:

- No data below age 40
- Data from 2010
- **Population-based estimate**

TABLE 3. Sensitivity and Specificity of Family History-Based Criteria Issued by the ACS, NCCN, USMSTF, and CAN for Identifying Patients Aged 40 to 49 Years With Early-Onset CRC

Criteria	Sensitivity	
ACS 2008 ^a	25%	
NCCN 2017	21%	
USMSTF 2017	21%	
CAN 2018	21%	

Abbreviations: ACS, American Cancer Society; CAN; Joint Canada/American Gastroenterological Association; CRC, colorectal cancer; NCCN, National Comprehensive Cancer Network; USMSTF, US Multi-Society Task Force on Colorectal Cancer.

^aJoint recommendations by the ACS, USMSTF, and American College of Radiology in 2008.

Specificity

90% 92% 92% 92% Population Screening for Common Inherited Diseases

- CDC Tier 1 Diseases: Lynch syndrome, Hereditary Breast-Ovarian Cancer syndrome, & Familial Hypercholesterolemia
 - Common
 - Easy, Accurate Testing Available
 - Actionable
- Several ongoing projects offering genetic testing for these diseases to the general public
 - Geisinger MyCode assessed for Tier 1 conditions in 50,000 participants
 - 1.32% (1 in 76 individuals) had one of these conditions
 - Compare to the 1 in 800 positive rate in newborn screening The James programs

Population Screening for Common Inherited Diseases

- Healthy Nevada Project: March 2018 phase two expanded to an additional 40,000 participants with genetic testing partner Helix
- Notifying study volunteers at risk for CDC Tier 1 conditions: Hereditary Breast Ovarian Cancer, Lynch syndrome, and Familial Hypercholesterolemia
- 299 (1.26%) of 23,713 participants have a P/LP variant in the 9 genes responsible for these conditions (1 in 79 individuals) >90% of carriers were undetected under current medical practice <20% had documented suspicion for inherited genetic disease in EMR <40% had family history of relevant disease
 - A population preventative genetic screening approach for people <45 may improve outcomes

The James

Points for Discussion

- Incidence of EOCRC is increasing, particularly rectal cancer and cause is not known (Siegel)
- Steep jump in incidence of CRC from age 49 to 50 indicates that these cancers begin prior to age 50 but are not detected until general population screening begins at age 50 – will start age of 45 help? (Karlitz)
- 25% of CRC patients have a FDR with CRC and could have been recommended to start screening early; 98% would have started screening prior to their age at diagnosis (Gupta)

Should population screening be considered to identify individuals with hereditary cancer syndromes who need to start colonoscopy the earliest and repeat it every 1-2 years (Hampel)

For those without family history, early symptom identification & promp follow-up is our best option (Gupta)





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