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Darwin L. Conwell, MD, MS, FACP
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Disclosures:

Joseph C. Anderson, MD, MHCDS, FACG
No conflicts of interest.

Brooks D. Cash, MD, FACG
No conflicts of interest.
Making the Case for Screening 45-Year-Old Adults for CRC

Joseph C. Anderson, MD, FACG, MHCDS
WRJ VAMC
Dartmouth College
New Hampshire Colonoscopy Registry
UCONN Health Center

In Memoriam
Dennis J. Ahnen, MD, FACG
(1946 – 2020)
Denver, CO

Figure created by seer.cancer.gov/explorer/application.php


Courtesy of Douglas Robertson, MD

Trends in CRC incidence in the US by age, 1975-2016

50+ years

38% since 1995

20-49 years

55% since 1995

American College of Gastroenterology
Colorectal Cancer Incidence rate by age

Increase incidence highest for rectal cancer


Courtesy of Douglas Robertson, MD

Median CRC age at diagnosis has decreased from 72 to 66 years
Possible Risk factors

- Excess body weight
- Smoking
- Sedentary lifestyle
- Red meat consumption
- High fructose corn syrup
- Antibiotic; microbiome
- Higher risk groups; genetic and IBD

Siegel et al 2020 ASCO

Global trends

- Data from 5 continents
- CRC incidence rates ranged from 3.5/100k in India to 12.9/100k for Korea
- US SEER incidence was 10.0/100k

Age adjusted incidence rate (per 100k) for adults 20-49 years

2008-12

Global incidence adults 20-49 years


Average Annual % Change (AAPC)

Change (AAPC) in CRC incidence over 10 years for adults 20-49

Screening adults in 40’s since 1980’s

American Cancer Society Guidelines 2018

<table>
<thead>
<tr>
<th>Age</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>45-75 years</td>
<td>Screen</td>
</tr>
<tr>
<td></td>
<td>&quot;Qualified&quot; Starting at age 45</td>
</tr>
<tr>
<td></td>
<td>&quot;Strong&quot; Starting at age 50</td>
</tr>
<tr>
<td>76-85 years</td>
<td>Screening Should be Individualized</td>
</tr>
<tr>
<td>&gt; 85 years</td>
<td>Discourage</td>
</tr>
</tbody>
</table>

Appendix A

American Cancer Society Guidelines

· Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society

American College of Gastroenterology
Qualified

"Indicates that there is clear evidence of benefit (or harm) of screening but less certainty about the balance of benefits and harms or about patients’ values and preferences, which could lead to different decisions about screening”

There are no data for screening regarding harms/benefits in 45-49 year age group*

Colonoscopy Outcomes in Average-Risk Screening Equivalent Young Adults: Data From the New Hampshire Colonoscopy Registry

• Panel of volunteers: generalists, biostatisticians, epidemiologists, economists, patient rep
• Lack of RCT data
  • Most RCTs begin at 50 years
  • 2 gFOBT trials started at age 45 years
  • These studies were underpowered
• Recommendations placed heavy emphasis on:
  • Burden of CRC in young adults
  • Results of models
  • Life saved
  • Anticipation of increasing rates
Challenges in implementing ACS recommendations

- Confusion as previous recommendation of 50 years had unanimous support
- Lag between publication of recommendation and insurance coverage
- US health care infrastructure will be unduly strained by lowering the starting age to 45 years
- Efforts should focus instead on increasing screening rates in adults aged 50 years and older?

USPSTF

• Recommends screening at 50 years of age
• Previous models were not unanimously in favor of screening at 45 years
• Currently having new assessment with results 2020-21
• Draft plan 1/19 includes “Adults age ≥40 years in average-risk or unselected populations”
• ACA requires coverage for USPSTF services

USMSTF Statement (June 2018)

• Evidence from screening studies to support lowering the screening age is very limited at this time.
• Beginning screening at 45 years addresses only part of the increasing risk of CRC in young persons.
• For all persons under 50 years, it remains critical to promptly assess symptoms consistent with CRC.
• In particular, rectal bleeding and unexplained iron deficiency anemia should be thoroughly evaluated.
Case control study of patients with rectal CRC
Rectal bleeding most common symptom
Time from symptom onset to diagnosis was 29.5 days if older than 50
Time was 217 days for < 50 year group
Reasons to consider 45 years as starting age

- Sophisticated models used to support recommendations
- Large burden CRC in young adults
- Incidence of 45-49 year olds similar to 50-54 year olds
- Increase is not artifactual
- Screening 45-49 benefits 50-54 year olds
- Screening 45-49 year olds can be cost effective
- Complications in this age group are low
Concerns about screening 45-49

- Incidence is lower than older adults
- Concerns about models
- Divert resources from older adults?
- Will the people at greatest risk attend screening?
- Do we have the capacity?
- No RCT data supporting screening 40-49 year old adults
- Is biology of CRC in young different?

If biology differs—screening may be less effective

Screen #1  Screen #2

Courtesy of Douglas Robertson, MD
If biology differs—screening may be less effective

- Little is known about true nature given lack of screening data
- Clinically tend to be distal
- Later stage than older adults
- Signet cell ring histology
- Mucinous, mostly IBD related
- < 20% have germline mutations

Willauer et al CANCER June 15 2019
Models used by ACS

- USPSTF used models for previous lung/CRC guidelines
- Used 3 Cancer Intervention and Surveillance Modeling Network (CISNET)
  - SimCRC
  - Microsimulation Screening Analysis (MISCAN)
  - CRC-SPIN
- 2/3 models used by USPSTF showed GREATER benefit for initiation at 45 than 50
- All but MISCAN had previously shown benefit for screening 45-49
- When updated using birth cohort all models showed benefit
Heavy CRC burden in adults < 50 years

- CRC most common cancer and cancer death in men < 50 years
- Accounts for about 10-12% of all CRC for men and women
- SEER 9 data (2015); 15% of all rectal cancer in adults < 50 years
- ½ of these rectal cancers are in 45-49
- 3/4 of CRC in adults < 50 are in 40-49 year age group
- Younger adults present at a later stage than older adults
- SEER data shows life years lost comparable for 45-49 and 50-54

In 2020, 12% (17,930/147,950) will be in < 50

- In adults < 50 years of age incidence increased by 2% for all anatomic sites
- Increase largely in non Hispanic whites
- In adults 50-64 years of age incidence rose by 1%
- CRC mortality increased 1.3% in <50 group
- CRC mortality decreased by 3% annually in 65+ group and by 0.6% in those 50-64 years
Is the increase in young CRC artifactual?

- Detection bias from more endoscopic evaluation of younger adults?
- Late-stage CRCs increasing in younger adults at a rate that is more rapid than early stage CRC
- Delay in diagnosing CRC in younger individuals does not fully explain late stage

### Past-year colonoscopy, ages 40-49 yrs, 2000-2015

- **40-44 years**: No Increase, 2015 vs 2000 (absolute diff) 0.1, p=0.77
- **45-49 years**: Doubled, 2015 vs 2000 (absolute diff) 2.7, p<0.001

Fedewa/Siegel/Jamal J Med Screen 2019
Which patients are receiving colonoscopies?

- Among those 45-49 years of age
  - Those with a family history of CRC
  - Black respondents 30% more likely than whites
  - Hispanic had lower rates
- Among those 50-54 years
  - Higher in college grads
  - Higher in obese
- Uninsured had lower rates in all age groups

CRC incidence, ages 40-49 yrs, 2000-2015

40-44 years
(No increase in colonoscopies)

45-49 years
(Doubled colonoscopies)

*Annual percent change is statistically significantly different from zero (P<0.05) Siegel et al J Med Screen 2019
Early-onset CRC by stage at diagnosis

**40-44 years**
- Localized APC, 1.1*
- Distant APC, 2.9*

**45-49 years**
- Localized APC, 0.4
- Distant APC, 2.3*

*Annual percent change is statistically significantly different from zero (P<0.05) Siegel et al J Med Screen 2019

Increase in distant disease in adults 40-49 years

Figure 1. Trends in Colorectal Cancer (CRC) Incidence by Stage in Adults Aged 40 Through 49 Years

Disease stage
- Local
- Regional
- Distinct
- Unstaged

Distant
Increase in distant disease in adults 40-49 years

Distant Advanced CRC stage in younger adults not associated with longer duration of symptoms

- Retrospective analysis from US
- Compared symptoms and time to diagnosis between < 50 years of age (253) and > 50 years (232)
- Younger adults had longer duration of symptoms (128 versus 79) and time to diagnosis (60 versus 30 days)
- BUT those with Stage III or IV had shorter duration/time to diagnosis

Chen et al CGH 2017; 15:728-37
Attendant benefits of screening adults 45-49 years

- Positive impact for those 50-54 years who also have had increased CRC incidence and mortality
- Screening with attendant polypectomy takes about 10 years for benefit
- Therefore screening those 45 years of age (perhaps younger) will help reduce CRC in 50-54 year age group
- Earlier screening of < 50 year group will increase screening awareness and enhance discussion for 50-54 age group

Cost effectiveness of screening at 45 years

- Analysis comparing strategies using Markov model
- Screening colonoscopy at age 45 (per 1000)
  - Averted 4 CRCs and 2 CRC deaths
  - 10.7 million colonoscopies required in US
  - Gained 14 QALYs at cost $33,900/QALY
- Therefore screening at 45 years is cost effective
- However if lower risk patients self selected for screening, the numbers could decrease benefit
- If colonoscopies diverted to unscreened 55 year olds
  - Averted more CRCs and prevented more deaths
  - Gain more QALYs and save up to $445,800

Ladabaum et al Gastro 2019 157; 137-148
Complication rates in adults < 50 years are low

- Younger adults in HMO setting have low rates of complications, especially when compared to older individuals (Levin et al Ann Intern Med. 2006;145:880–6.)

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Population</th>
<th>Age</th>
<th>N</th>
<th>Perforation</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arora/2009</td>
<td>California Medicaid Database</td>
<td>18-50</td>
<td>49,678</td>
<td>33 or 0.7/1000</td>
<td>N/R</td>
</tr>
<tr>
<td>Rutter/2012</td>
<td>Integrated healthcare system WA</td>
<td>40-49</td>
<td>2641</td>
<td>0 or 0/1000</td>
<td>6 or 2.3/1000</td>
</tr>
</tbody>
</table>

Do we have capacity to screen more adults?

- Major factor in ACS Guidelines
  - List of all US medical facilities who purchased endoscopic equipment
  - Random sample of 2100 facilities (31%)
- Facilities asked current # exams & additional # that can be done
- US endoscopic capacity can absorb 10.5 million more exams
- Although screening = colonoscopy in the US, 45-49 population in particular could benefit from stool testing
  - 40% rectal tumors
  - Inexpensive/noninvasive
Recent data

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

Wesal H. Abuakhair, MD, MS; Meijiao Zhou, PhD; Dennis Ahnen, MD; Qingzhao Yu, PhD; Xiao-Cheng Wu, MD, MPH; Jordan J. Karlitz, MD

Figure 1. Colorectal Cancer Incidence Rates per 100,000 Population in 1-Year Age Increments in the US Surveillance, Epidemiology, and End Results (SEER) Registries Among Patients Aged 30 to 60 Years, 2000-2015
The New Hampshire Colonoscopy Registry (NHCR) is a statewide, population-based registry collecting data for over 15 years. Currently includes 200,000 colonoscopies and 400 variables per patient: comprehensive patient risk factors, procedure findings, and pathology. Thousands of patients with 2 or more exams allows investigation of longitudinal outcomes.
**Methods: Sample Selection**

- NHCR patients with first colonoscopy
- Excluded known high risk groups: FDR CRC, genetic syndromes, IBD, high risk symptoms, surveillance indications, as well as poor prep, incomplete exams
- Adults < 50 usually have colonoscopy for diagnostic indications of varying significance (risk):
  - Low ‘average risk screening equivalent’ Risk (*included*): abdominal pain, constipation
  - High Risk (*excluded*): GI bleeding, occult blood, iron deficiency anemia and abnormal imaging

Cha et. al. GIE 2015; 82: 138-145
Table 4. Risk factors for advanced colorectal neoplasia in adults aged 45–49 years

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (F vs M)</td>
<td>0.60 (0.35–1.03)</td>
</tr>
<tr>
<td>BMI (continuous)</td>
<td>1.04 (1.01–1.07)</td>
</tr>
<tr>
<td>Family history (non-first-degree relative)</td>
<td>1.50 (0.76–2.96)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Past</td>
<td>1.91 (1.03–3.55)</td>
</tr>
<tr>
<td>Current</td>
<td>3.18 (1.56–6.48)</td>
</tr>
<tr>
<td>5 drinks or more/wk</td>
<td>0.85 (1.07–1.21)</td>
</tr>
<tr>
<td>Aspirin (1–3 times/wk)</td>
<td>0.97 (0.47–2.02)</td>
</tr>
</tbody>
</table>

BMI, body mass index; F, female; M, male; ref, reference.
How do we screen young adults?

TABLE 2. Model-Estimated Benefits and Burdens of CRC Screening Starting at Age 45 Versus 50 Years, per 1000 Screened Over a Lifetime

<table>
<thead>
<tr>
<th>SCREENING TEST</th>
<th>LYG</th>
<th>NO. OF CSY</th>
<th>MODEL RECOMMENDABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSY every 10 y, 45-75</td>
<td>429</td>
<td>5646</td>
<td>Yes</td>
</tr>
<tr>
<td>CSY every 10 y, 50-75</td>
<td>404</td>
<td>4836</td>
<td>No</td>
</tr>
<tr>
<td>CTC every 5 y, 45-75</td>
<td>390</td>
<td>2666</td>
<td>Yes</td>
</tr>
<tr>
<td>CTC every 5 y, 50-75</td>
<td>368</td>
<td>2430</td>
<td>No</td>
</tr>
<tr>
<td>FSG every 5 y, 45-75</td>
<td>403</td>
<td>3761</td>
<td>Yes</td>
</tr>
<tr>
<td>FSG every 5 y, 50-75</td>
<td>380</td>
<td>3426</td>
<td>No</td>
</tr>
<tr>
<td>FIT yearly, 45-75</td>
<td>403</td>
<td>2698</td>
<td>Yes</td>
</tr>
<tr>
<td>FIT yearly, 50-75</td>
<td>377</td>
<td>2402</td>
<td>No</td>
</tr>
<tr>
<td>HSgFOBT yearly, 45-75</td>
<td>403</td>
<td>3364</td>
<td>No</td>
</tr>
<tr>
<td>HSgFOBT yearly, 50-75</td>
<td>377</td>
<td>2956</td>
<td>No</td>
</tr>
<tr>
<td>mt-sDNA every 3 y, 45-75</td>
<td>375</td>
<td>2640</td>
<td>No</td>
</tr>
<tr>
<td>mt-sDNA every 3 y, 50-75</td>
<td>350</td>
<td>2331</td>
<td>No</td>
</tr>
</tbody>
</table>
Rectal Bleeding predicts left sided conventional adenomas and CRC but not serrated polyps in NHCR patients

Table 1. Absolute and adjusted risks for advanced neoplasia, CRC and serrated polyps stratified by anatomical location

(Results for separate models)

<table>
<thead>
<tr>
<th></th>
<th>Left sided Advanced Neoplasia OR=1.0</th>
<th>Right Sided Advanced Neoplasia OR=1.0</th>
<th>Left sided CRC OR=1.0</th>
<th>Right sided CRC OR=1.0</th>
<th>Left Sided Serrated Polyps OR=1.0</th>
<th>Right Sided Serrated Polyps OR=1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Risk</td>
<td>1.8% (n=105)</td>
<td>0.6% (n=37)</td>
<td>0.1% (n=4)</td>
<td>0.1% (n=9)</td>
<td>0.6% (n=33)</td>
<td>0.8% (n=48)</td>
</tr>
<tr>
<td>Screening Equivalent (Reference group) (n=5855)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference OR=1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (n=2814)</td>
<td>3.0% (n=85)</td>
<td>0.6% (n=17)</td>
<td>0.4% (n=10)</td>
<td>0.2% (n=6)</td>
<td>0.4% (n=11)</td>
<td>0.7% (n=20)</td>
</tr>
<tr>
<td>95% CI</td>
<td>(1.28-2.34)</td>
<td>(0.55-1.82)</td>
<td>(1.47-15.81)</td>
<td>(0.50-5.11)</td>
<td>(0.31-1.29)</td>
<td>(0.94-1.60)</td>
</tr>
</tbody>
</table>

Models adjusted for age, sex, BMI and smoking

*Advanced neoplasia: Adenomas ≥ 1 cm, those with villous elements, high-grade dysplasia, and CRC

**Serrated Polyps: HPs ≥ 1 cm, any sessile serrated polyp, and any traditional serrated adenomas

Anderson et al 2020 ACG

Most advanced neoplasia on left side

8 CRCs

75-80% Conventional advanced neoplasia

4 CRCs
What should we do with young people diagnosed with adenomas?

<table>
<thead>
<tr>
<th>Age group</th>
<th>Metachronous advanced adenomas</th>
<th>Metachronous large serrated polyp</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted odds ratio (95% confidence interval)</td>
<td>Adjusted odds ratio (95% confidence interval)</td>
</tr>
<tr>
<td>&lt;40 (n = 266)</td>
<td>0.19 (0.05-0.80)</td>
<td>0.38 (1.129-1.29)</td>
</tr>
<tr>
<td>40-49 (n = 1063)</td>
<td>0.61 (0.41-0.92)</td>
<td>1.12 (0.69-1.83)</td>
</tr>
<tr>
<td>50-59 (n = 5288)</td>
<td>0.71 (0.58-0.86)</td>
<td>1.02 (0.76-1.38)</td>
</tr>
<tr>
<td>60+ (n = 5813)</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
</tr>
</tbody>
</table>

Can use same recs as for older adults!
Summary recommendations

- Data demonstrate increased prevalence AN in 45-49 year
- Insurance will likely dictate age to start
- More data are needed
- Collect family history including advanced adenomas
- For now EVALUATE ALL SYMPTOMATIC ADULTS < 50 ESPECIALLY RECTAL BLEEDING

Thank you for your attention
Questions?

Joseph C. Anderson, MD, MHCDS, FACG

Brooks D. Cash, MD, FACG

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