

Disclosures

- Research support from Pfizer (Study PI)
- Research support from PTEN Research Foundation (Study PI)
- Research support from Janssen (Site PI)
- Research support from Emtora (Site PI)
- Research support from Freenome (Site PI)
- Research support from Guardant (CO-I)

Agenda

- 1. Definitions
- 2. Why is CRC important?
- 3. Early onset CRC
- 4. CRC screening options
- 5. Discussion of colonoscopy for screening
- 6. Surveillance recommendations
- 7. Genetic testing criteria

Definitions

- Screening
 - To identify polyps/cancer in a patient without a personal history of cancer or precancerous lesions
 No signs/symptoms of suspected colorectal disease
- Surveillance
 To identify polyps/cancer in an individual with previously identified polyps/cancer
 No signs/symptoms of suspected colorectal disease
- Diagnostic
 Signs/symptoms of suspected colorectal disease

Baron et al. Recommended Intervals Between Screening and Surveillance Colonoscopies. Mayo Clin Proc. 8.2013.

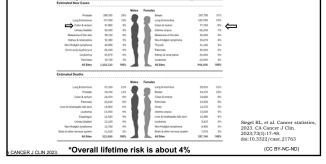
Definitions

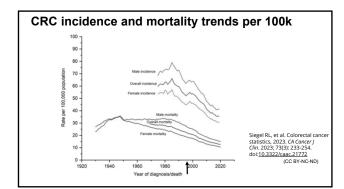
Average risk

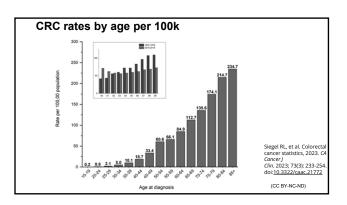
- No personal history of colon neoplasia
- No family history of CRC or advanced adenoma in a first degree relative (parents, siblings, children)
- High risk
 - This definition varies by guideline, but for USMSTF and today's lecture this is:

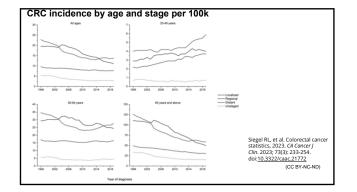
First degree relative with CRC, advanced adenoma or advanced serrated adenoma

Why is colon cancer important?









How can we reduce advanced EOCRC?

Small steps any healthcare provider can take

- Aggressively investigate red flag symptoms of CRC, even in young people
- Be aware of family history of colorectal cancer and how this will impact screening for your patient

Red flag symptoms in young people

It is clear that diagnosis of CRC under age 45 is delayed

- Patients frequently report symptoms being dismissed by their providers... this needs to change
- 4 red flag symptoms were significantly associated with early-onset CRC in a large study
 - Abdominal pain, Rectal bleeding, Diarrhea, IDA
 - 1, 2, or ≥3 of were was associated with a 1.9-,

3.6-, and 6.5- fold increased risk respectively. Fritz et al. Red-flag signs and symptoms for earlier diagnosis of early-onset colorectal cancer. JNCI 2023

Colon Cancer Screening

- Multiple modalities available
 - Colonoscopy
 - Flexible sigmoidoscopy
 - Fecal immunochemical testing (FIT)
 - Multi-target stool DNA
- * Remember Any screening is better than none...

Screening modality	Frequency	Mean CRC cases averted Per 1,000 individuals
FIT	Yearly	50
FOBT	Yearly	42
sDNA-FIT	Yearly	57
sDNA-FIT	every 3 years	47
Colonoscopy	every 10 years	58
CT colonography	every 5 years	53
Flexible sigmoidoscopy	every 5 years	49

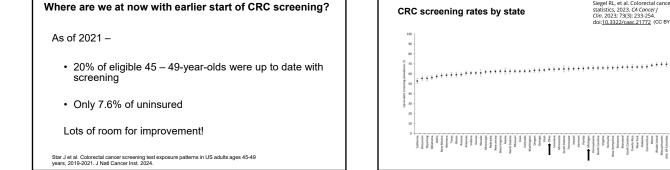
Colon cancer screening

- Multiple guidelines exist:
 - American College of Gastroenterology (2021)
 - National Comprehensive Cancer Network (continuously updated)
 - US Multi-Society Task Force on Colorectal Cancer (updated 2021)
 - US Preventative Services Task Force (2021)
 - American College of Physicians (2023)**

olds w	hen CRC screer				incidence observed i led.	n 50-yea
	Table 3.Life-Years Screening per 100 Screened at Ages	0 Individual			Required, and Adverse Events	of
		Additional life-years gained	CRC prevented	CRC death averted	Additional tests required	Additional adverse events
Tier 1	Colonoscopy every 10 y	16-34	1-4	1-2	Colonoscopy: 756-800	2
Data is per 1,000 individuals	Annual FIT	17-33	1-4	1	FIT: 3387-3520 Colonoscopy: 175-205	1
	Triennial sDNA-FIT	16-31	1-4	1	sDNA-FIT: 1166-1201 Colonoscopy: 177-196	<1
	Flexible sigmoidoscopy every 5 y	13-30	1-3	1	Flexible sigmoidoscopy: 743- 801 Colonoscopy: 170-192	<1
	CT colonography every 5 y	14-31	1-3	1	CT colonography: 798-806 Colonoscopy: 153-165	1

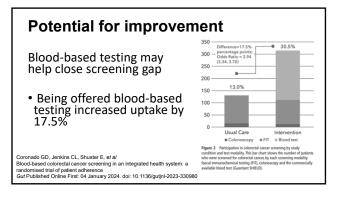
Recommen	dation Summary	
Population	Recommendation	Grade
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years.	A
	See the "Practice Considerations" section and Table 1 for details about screening strategies.	
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years.	В
	See the "Practice Considerations" section and Table 1 for details about screening strategies.	
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 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, prior screening history, and preferences.	C

Siegel RL, et al. Colorectal cancer statistics, 2023. CA Cancer J Clin. 2023; 73(3): 233-254. doi:10.3322/caac.21772 (CC BY-NC-ND)



Blood-based testing is coming

- Tests detect genomic or epigenomic changes in cell-free DNA shed by colorectal tumors into blood
- Similar sensitivity and specificity for CRC to stool based testing had been reported
- Many project approval in 2024 or 2025



Non-Endoscopic options

- FIT preferred to FOBT
 - Better performance
 - Less reliance on dietary restrictions
 - Single sample to collect (FOBT is supposed to be 2-3 samples)
 - Remember FOBT in the office with rectal exam is <u>NOT ACCEPTABLE</u>

Levin et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Math-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA: A Cancer Journal For Orliniona, 2004

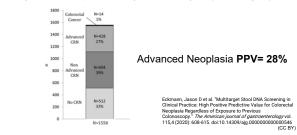
Why is FIT preferred over mt-sDNA?

 Annual FIT is more effective and less costly than Fecal DNA every 3 years (...and colonoscopy every 10)

Modality	Interval	QALY/person	\$/person
FIT	Yearly	18.747	2,407
sDNA-FIT	every 3 y	18.7423	5,190
Colonoscopy	every 10 y	18.7455	4,173

Adapted from Ladabaum U , Mannalithara A . Comparative effectiveness and cost-effectiveness of a multi-larget stool DNA test to screen for colorectal neoplasia. Gastroenterology 2016.

What to expect after a positive FIT or mt-sDNA Study of all mt-sDNA patients at Mayo Clinic over 3 years (16,469 subjects)



Timeline after positive stool screening

- Colonoscopy by <u>6 months</u>
 - This is when risk for colorectal cancer becomes significantly increased

Corley JAMA 2017

What needs done with + FIT/mt-sDNA and – colonoscopy?

- Guidelines: If colonoscopy high quality, <u>no further testing</u> <u>needs done</u> and recommend following standard screening/surveillance
- Study of 205 patients with this situation:
 - 5 (2.4%) aerodigestive cancers during follow-up
 - The expected number of cancers was 6
 Risk ratio of 0.8 (95% Cl, 0.3–1.9) relative to SEER population

Rex AJG 2017 and Berger CGH 2020.

USMSTF High-Risk Screening Guidelines (ACG 2021 is similar) Table 5. MSTF recommendations for persons with high-risk family histories not associated with polyp syndromes District another or an advanced advence in the first-degree relative stig age of degree relative stig

How effective is screening colonoscopy?

In a meta-analysis of 43 publications and more than 15,000 tandem colonoscopies, **miss rates** were:

- 26% for adenomas (95% confidence interval [CI] 23%-30%)
- 9% for advanced adenomas (95% CI 4%-16%)
- 27% for serrated polyps (95% CI 16%-40%).

Gastroenterology 2019 1561661-1674.e11DOI: (10.1053/j.gastro.2019.01.260)

LISHED IN 1812 OCTOBER 27, 2022 VOL. 387 NO. 17

Effect of Colonoscopy Screening on Risks of Colorectal Cancer and Related Death

Bretthauer, M. Loberg, P. Wieszczy, M. Kalager, L. Emilsson, K. Garborg, M. Rupinski, E. Dekker, M. Spaander M. Bugajski, Ø. Holme, A.G. Zauber, N.D. Pilonis, A. Mroz, E.J. Kuipers, J. Shi, M.A. Hernán, H.-O. Adami, J. Regula, G. Hoff, and M.F. Kaminski, for the Nord/CS Tudy Group⁶

- NORDICC study is a very controversial publication
 Discussed in popular press on day of release
- People 55-64 years, trial from 2009 2014
- Pragmatic randomized trial
- 84.5k participants
- 1:2 ratio either to be invited for a single screening colonoscopy (the invited group) or to receive no invitation or screening (the usual-care group)



Results

- 28,220 invited for colonoscopy but only 11,843 (42%) had procedure
- ADR variable between countries 14% in Sweden, 27- 35% in others
- ITT risk reduction of 18% for CRC, no change in mortality
- But in per protocol analysis –
 31% reduction in CRC risk and 50% reduction in mortality

NORDICC take home points

- Colonoscopy for CRC screening works when people get the test
- Further benefit may be seen when data analyzed again in 5-10 years as further benefit of polypectomy is realized
- Colonoscopy benefit may be overestimated and more in line with other methods like sigmoidoscopy

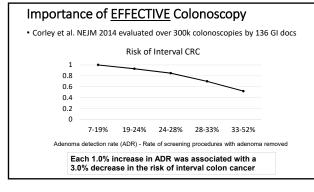


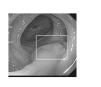
Table 2. Risk Factors for Interval PCCRC: Multivariable Cox Regression Model*				
Variable	HR	95% CI	P Value	
Center				
Academic	Reference	Reference	Reference	
Nonacademic hospital	3.74	1.31-10.66	0.014	
Endoscopy center	3.87	1.31-11.43	0.014	
ADR, per 1% increase	0.95	0.92–0.97	<0.001	

Adenomatous colon polyps

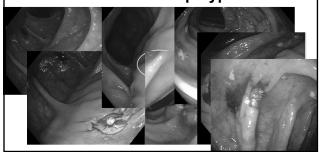
Classifications:

- Endoscopic appearance
- Sessile: Base is attached to the wall
- Pedunculated: Mucosal stalk from polyp to wall
- Pathology
- Tubular (80% of adenomas)
- Tubulovillous (mixed)
- Villous (finger-like glands, higher risk)





Sessile adenomatous polyps



Adenomatous colon polyps

- Even the small tubular adenomas that don't have it

• By definition, they are all dysplastic

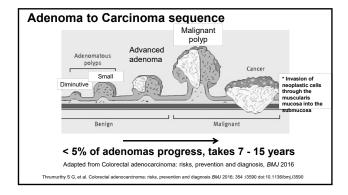
mentioned on pathology reports

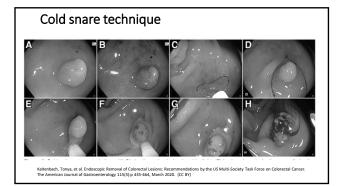
- lastic
- Adenomatous colon polyps

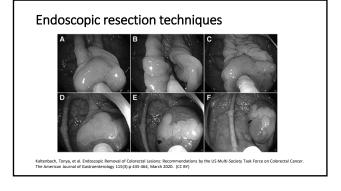
Classifications:

- <u>Advanced</u> adenomas:
- 1. High-grade dysplasia
- 2. > 1 cm size
- 3. Villous histology (ie. villous or tubulovillous)
- These are higher risk for progression to CRC and development of future CRC

*3 or more adenomas at a single colonoscopy is also a risk factor

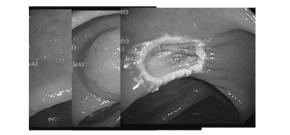


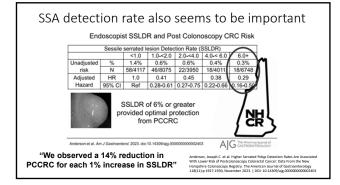


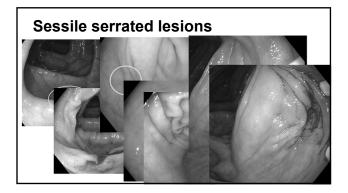


Sessile serrated lesions

• They can be very hard to see!





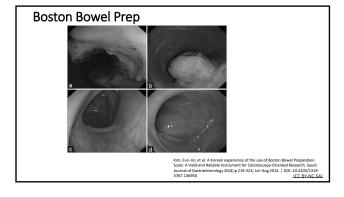


Why is bowel prep adequacy important?

 If patients rated as inadequate (any section under a 0 or 1 on BPPS), they should be coming back in less than 1 year

Optimizing Adequacy of Bowel Cleansing for Colonoscopy: Recommendations From the US Multi-Society Task Force on Colorectal Cancer David A. Sohmon', Alan N. Barkun', Lavry R. Cohen', Ianne A. Dominitz', Toury Kahenhach', Morian Martel', Douglas I. Rober C. Richard Boland', Frances M. Gazdelle', David A. Lieberman'', Theodore R. Levin'' and Douglas K. Rex¹⁰ EFFECT OF INADEQUATE PREPARATION ON POLYP/ ADENOMA DETECTION AND RECOMMENDED FOLLOW-UP INTERVALS Recommendations

Recommendations
 If the colonoscopy is complete to cecum, and the preparation ultimately is deemed inadequate, then the examination should be repeated, generally with a more aggressive preparation regime, within 1 year, intervals shorter than 1 year are indicated when advanced neoplasia is detected and there is inadequate preparation (*Strong recommendation, low-quality veriface*).
 If the preparation is deemed adequate and the colonoscopy is completed then the guideline recommendations for screening or surveillance should be followed (*Strong recommendation, high-quality evidence*).



Comparing the Real-World Effectiveness of Competing Colonoscopy Preparations: Results of a Prospective Trial

Phillip Gu, MD¹⁰, Daniel Lew, MD¹⁰, Sun Jung Oh, MD¹, Aarshi Vipani, MD¹, Jeffrey Ko, MD¹, Kevin Hsu, MD¹, Ebrahim Mirakhor, MD¹, Varun Patisapa, MD¹, Ta Bulen, NN¹⁰, Garth Toller, MS^{14,4}, Brennan M. R. Spiegel, MD, MSH6^{3,3,6,2} and Christopher V. Marina, MD, MSH^{10,4,5,4}

Am J Gastroenterol 2019;114:305-314.

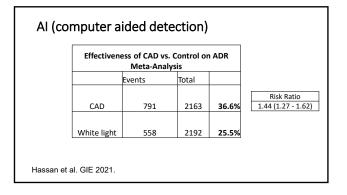
METHODS: We included patients aged ≥18 years, who presented for an outpatient colonoscopy at a large medical center serving more than 70 academic and community-based endoscopsists who are free to perscribe the bewel prep of their choice. The primary outcome was bowel cleansing quality as measured by the Boston Bowel Preparation Scale. We performed regression models with random effects on the outcomes to Bowel Preparation Scale.

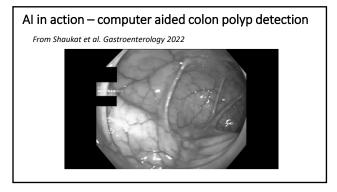
Tolerability

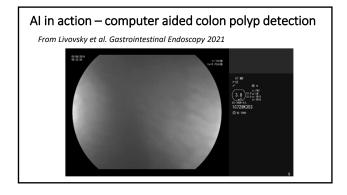
- After adjusting for prep-, provider-, and patient-related factors in multivariable logistic regression analysis with random effects, we found that patients receiving the below were all significantly more likely to complete the prep compared with those prescribed GoLYTELY.
- Prepopik/Clenpiq (P < 0.001)
- Magnesium citrate (P = 0.014)
- Suprep (P < 0.001)
- OsmoPrep (P = 0.003)
- MiraLAX with Gatorade (P < 0.001)
- MoviPrep (P = 0.001)

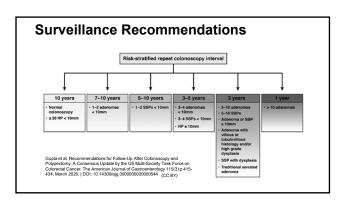
Variable	BBPS total score, mean ± s.d.	Adjusted P value ^a	Adequate bowel cleansing, ^b n (%)	OR (95% CI) ^a
Prescribed bowel prep				
GoLYTELY	6.67 ± 1.87	Reference	430 (84.0)	Reference
MoviPrep	7.11 ± 1.62	0.004	267 (91.1)	1.44 (0.85-2.44)
MiraLAX with Gatorade	7.09 ± 1.64	< 0.001	2,499 (92.5)	1.76 (1.24-2.49)
Prepopik/Clenpiq	7.01 ± 1.59	0.18	205 (90.7)	1.24 (0.70-2.21)
Suprep	7.28 ± 1.66	< 0.001	426 (90.6)	1.37 (0.86-2.16
Magnesium citrate	6.89 ± 1.56	0.39	48 (90.6)	1.54 (0.57-4.17
OsmoPrep	7.04 ± 1.86	0.27	67 (81.7)	0.70 (0.36-1.37
Bowel prep completion				
Did not complete prep	6.89 ± 1.88	Reference	298 (86.6)	Reference
Fully completed the prep	7.07 ± 1.66	0.23	3,606 (91.2)	1.36 (0.96-1.93
Unknown	7.43 ± 1.52	0.07	38 (95.0)	2.82 (0.64-12.3
Bowel prep dosing				
Day-before dosing	6.97 ± 1.70	Reference	2,392 (89.4)	Reference
Split dosing	7.18 ± 1.63	0.001	1,550 (93.2)	1.35 (1.05-1.74

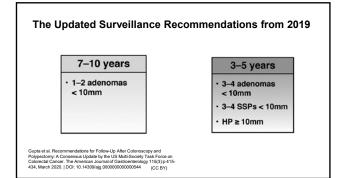
Table 2.	ADR for screening	ng colonoscopy per p	hysician
		Overall	
	Physician N	Mean ADR (SD) ^a	Adjusted ADR ^b
Overall	1,140	36.80 (10.21)	39.08
2014	1,025	33.93 (11.76)	36.36
2015	1,131	35.80 (11.06)	38.25
2016	1,131	36.95 (11.16)	39.36
2017	1,130	38.01 (10.82)	40.62
2018	1,103	38.12 (10.98)	40.01
^a Per physici		aged 50 years and older p	er 2010 US census data,











Colon cancer surveillance

Baseline finding	Recommended interval for first surveillance	Finding at first surveillance	Recommended interval for next surveillance
1-2 tubular adenomas <10 mm	7–10 y	Normal colonoscopy ⁸ 1-2 tubular adenomas <10 mm 3-4 tubular adenomas <10 mm Adenoma ≥10 mm in size; or adenoma with tubulovilous/vilous histology; or adenoma with high grade dyspissia; or 5-10 adenomas <10 mm	10 y ◀ 7-10 y 3-5 y 3 y
8-4 tubular adenomas <10 mm	3-бу	Normal colonoscopy ⁸ 1-2 tubular adenomas <10 mm 3-4 tubular adenomas <10 mm Adenoma ≥10 mm in size; or adenoma with tubuloillouu+lifulous histology; or adenoma with high grade dysplasia; or 5-10 adenomas <10 mm	10 y ◀ 7-10 y 3-5 y 3 y
Adenoma ≥10 mm in size, or adenoma with tubulovillous/villous histology; or adenoma with high-grade dysplasia; or 5–10 adenomas <10 mm	Зу	Normal colonoscopy ⁸ 1-2 tubular adenomas <10 mm 3-4 tubular adenomas <10 mm Adenoma ≥10 mm in size; or adenoma with tubuloullous/Nitlous histology; or adenoma with high grade dysplasia; or 5-10 adenomas <10 mm	5y ◀ 5y 3-5y 3y

When to stop?

- Screening:

 USPSTF recommends stopping at 75, with consideration of continuing through 85 based on comorbidities
 USMSTF has similar recommendations with individualized recommendations from 76-85 and no screening after age 85

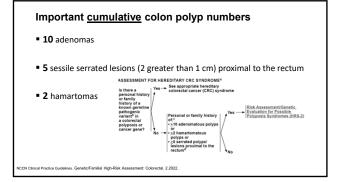
 Surveillance – No formal recommendations. Should be individualized, based on assessment of risks, benefits and comorbidities • 75-85 is likely reasonable

- If color cancer found, would patient accept/be offered surgery and/or chemotherapy?

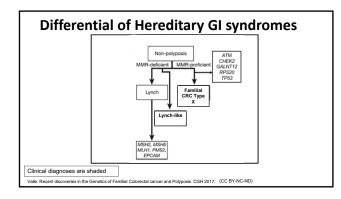
US Preventive Bankes Task Fores. Screening for colonical cancer: US Preventive Services Task Fores recommendation statement: JAMA 2021. var here at a 5 hould colonical cancer convening to condicate in tealing partners when previous convening? A coad-technices adapta. An intern Med. 2014 Listement at di cubitato to Calconaugo Services AMS Services Targetorium, A Comment Jama 2014, Sorte Targetorium, A Comment

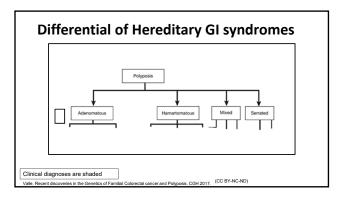
When to refer patients to GI Genetics in 2023

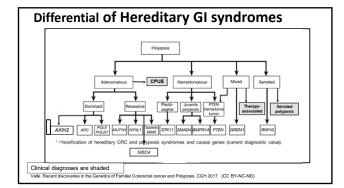
- Colorectal cancer at any age
- Personal and family history suspicious for Lynch syndrome
- More than 10 cumulative colon adenomas
- More than 2 cumulative GI hamartomas
- Family members with a known hereditary cancer syndrome

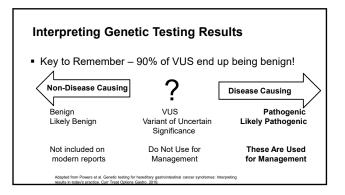


Dif	ferentia	l of Here	editary GI	syndrome	S
	Non-polyposis	7	Polyposis		
e. Recent disc	coveries in the Genetics of	Familial Colorectal cancer	and Polyposis. CGH 2017.		









Summary

- Colorectal cancer screening and surveillance is important and beneficial
- Be mindful of red flag symptoms at any age
- Multiple options for screening exist
- High quality colonoscopy is key