Screening and Diagnosis of Colorectal Cancer:

Early Detection for Corrections and Public Health

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Faculty Disclosure

I do not have any relevant financial relationships with any commercial interests.

I am a full time employee of Corizon Health

LEARNING OBJECTIVES

- Identify current screening methods and define the appropriate patients for non invasive screening
- Recognize the clinical signs that can assist with early detection
- Appreciate the measures the body takes to ensure iron conservation
- Review therapy for GI cancer

Table 1 Major guideline recommendations addressing colorectal cancer screening for average risk populations; all recommend screening from a certain age, and some recommend against screening in older age; none explicitly incorporates shared decision making based on individual risk and perceived benefits, harms, and burdens. For simplicity, the table includes only the preferred test or first-tier recommendations

Organisation	Screening age	GRADE strength of recommendation	Recommended test and timing
American College of Gastroenterology, 2009	Start 50 years	Strong, for screening	Colonoscopy every 10 years
American College of Physicians, 2015*	Screening for 50-75 years Not recommended >75 years	N/A	High sensitivity gFOBT or FIT every year
			gFOBT or FIT every 3 years *or* Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
US Preventive Services Task Force, 2016	Screening for 50-75 years For 76-85 years, an individual decision	N/A	gFOBT or FIT every year
			FIT-DNA every 1-3 years
			FIT every year *or* Sigmoidoscopy every 10 years
			Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
			CT colonography every 5 years
National Comprehensive Cancer Network Guidelines, 2017	Screening for 50-75 years For 76-85 years, an individual decision	N/A	Colonoscopy every 10 years
			gFOBT or FIT every year
			Faecal DNA test every 3 years
			Sigmoidoscopy every 5-10 years ± gFOBT or FIT every 3 years
			CT colonography every 5 years

			CT colonography every 5 years
United States Multi-Society Task Force of Colorectal Cancer Guidelines, 2017	Screening for age 50-75 years For 76-85 years, consider for those without prior screening	For screening: strong for 50-75, weak for 76-85 years	FIT every year
			Colonoscopy every 10 years
American Cancer Society, 2018	Screening from 45 years Screening for 50-75 years For 76-85 years an individual decision based on preference, life expectancy, and overall health	For screening: weak for 45-49, strong for 50-75, weak for 76-85 years	High sensitivity gFOBT or FIT every year
			Multi-targeted stool DNA every 3 years
			Colonoscopy every 10 years
			CT colonography every 5 years
			Sigmoidoscopy every 5 years
Canadian Task Force on Preventive Health Care, 2016	Screening for 50-74 years Not recommended for >75 years	For screening: weak for 50-59, strong for 60-74 Weak against screening >75 years	gFOBT or FIT every 2 years
			Sigmoidoscopy every 10 years
German Guideline Program in Oncology, 2019	Start 50 years	N/A	Colonoscopy every 10 years
Spanish Society of Medical Oncology, 2014	Screening for 50-74 years	N/A	FIT every two years
			gFOBT every 1-2 years
			Sigmoidoscopy every 5 years
			Colonoscopy every 10 years
National screening programmes in Sweden, New Zealand and United Kingdom†	Screening for 60-74 years	N/A	FIT every 2 years
National screening programmes in Denmark and France	Screening for 50-74 years	N/A	FIT every 2 years

Korean Guidelines for Colorectal Cancer Screening and Polyp Detection, 2012	Start 50 years	Strong, for screening	Colonoscopy every 5 years
Chinese Society of Gastroenterology, 2014	Screening for 50-74 years	N/A	FIT and questionnaire every 3 years
Updated Asia Pacific Consensus Recommendations on colorectal cancer screening, 2015	Screening for 50-75 years	N/A	FIT, interval not mentioned
National Guidelines for Colorectal Cancer Screening in Saudi Arabia, 2015	Screening for 45-70 years Not recommended >70 years	Strong, for screening 54-70 Weak against screening >70 years	Colonoscopy every 10 years
World Gastroenterology Organisation, 2007	Start 50 years	N/A	Colonoscopy every 10 years
NHMRC, Clinical Guidelines for Prevention, Early Detection and Management of Colorectal Cancer, Australia, 2017	Screening for 50-74 years	N/A	FIT every 2 years
National guideline in Japan	Start 40 years	N/A	FIT every year

gFOBT = guaiac faecal occult blood test. FIT = faecal immunochemical test.
The recommendations listed is a selection of recommendations identified through two systematic surveys: one found 15 colorectal cancer screening guidelines published in English between 2007 and 2017 (6 from North America, 4 from Europe, 5 from Asia)[8] ; the other survey in high income countries found another 19 guidelines.[9]
* Update of guideline in progress (Amir Qaseem, ACP, personal communication).
† In addition to FIT screening every two years, a one-time sigmoidoscopy is currently being rolled out for people at age 55 in the UK.[10]

SCREENING STRADEGIES

- SCREEN EVERYONE
- SCREEN ACCORDING TO RISK CATEGORY
- DIFFERENT SCREENING FOR DIFFERENT RISK CATEGORIES

SCREENING STRADEGIES

- SCREEN EVERYONE
- SCREEN ACCORDING TO RISK CATEGORY
- DIFFERENT SCREENING FOR DIFFERENT RISK CATEGORIES

COLONOSCOPY

- SCREENING COLONOSCOPY
  - Needed for all patients with elevated risk of cancer
- DIAGNOSTIC COLONOSCOPY
  - Needed for all patients with + findings on non invasive screening methods

Summary of Recommendations

doi:10.1001/jama.2021.6238AJAMA. 2021;325(19):1965-1977.
doi:10.1001/jama.2021.6238 Corrected on August 24, 2021

Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer in all adults aged 50 to 75 years.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years.	B
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

See Figure 1 for a more detailed summary of the recommendations for clinicians. See the Practice Considerations section and Table 1 for details about screening strategies. USPSTF indicates US Preventive Services Task Force.

NCCN COLON CANCER SCREENING

- AVERAGE RISK → DEALER'S CHOICE ON SCREENING METHOD
- INCREASED RISK
  - PERSONAL HISTORY
    - ADENOMA OR SSP
    - COLORECTAL CANCER
    - INFLAMMATORY BOWEL DISEASE
  - FAMILY HISTORY
- HIGH RISK

COLONOSCOPY INDICATED

Increased risk:

- Personal history
  - Adenoma or SSP[c] → See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)
  - CRC → See Increased Risk Based on Personal History of Colorectal Cancer (CSCR-7)
  - IBD (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-8)
- Positive family history → See Increased Risk Based on Positive Family History (CSCR-11)

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INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

(Appropriate testing for a hereditary syndrome is non-diagnostic or not done[vv])

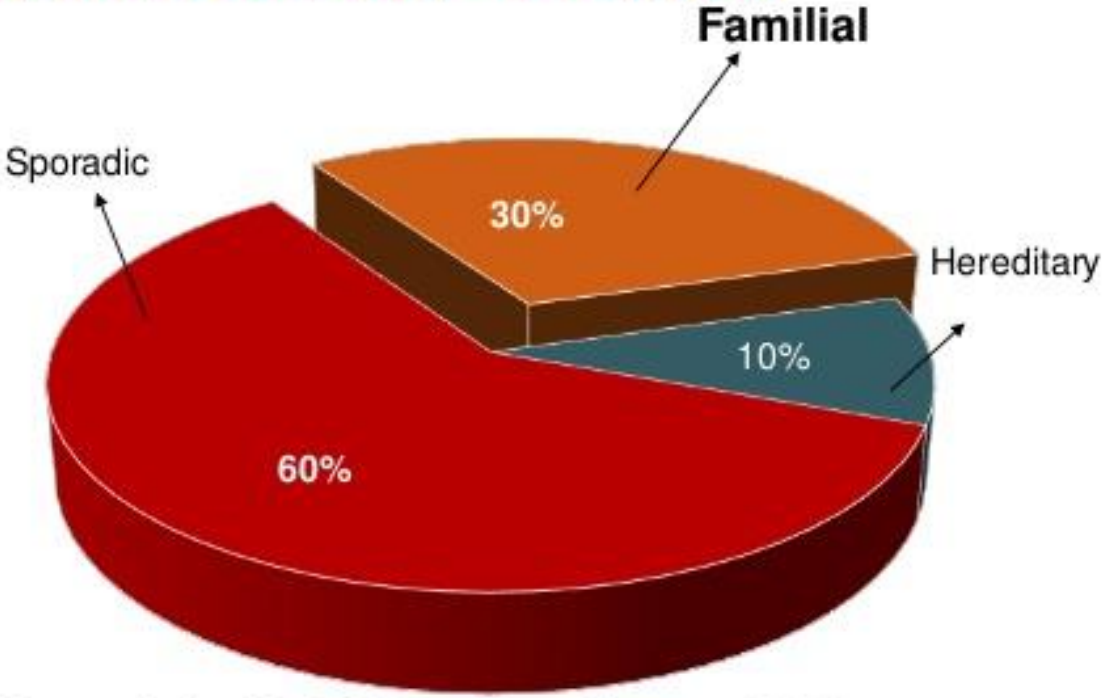
FAMILY HISTORY CRITERIA[ww]	SCREENING[zz,aaa]	
≥1 first-degree relative with CRC at any age	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[ww,zz,bbb,ccc] or if positive, repeat per colonoscopy findings
Second- and third-degree relatives with CRC at any age	Colonoscopy beginning at age 45–50 y	Repeat every 10 y or if positive, repeat per colonoscopy findings
First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology, TSA), or advanced SSPs (≥1 cm, any dysplasia)[xx,yy]	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[zz,bbb] or if positive, repeat per colonoscopy findings

[ww] It is important for endoscopists to add specific recommendations to reports for

Causes of Colorectal Cancer - Familial

Familial Colon Cancer

- Environmental/lifestyle risk factors
- Minor genetic changes
- Some Family history



Risk for colon cancer if close relative had CRC <50 y of age = 18.2%

Risk for colon cancer if close relative had CRC 50-59 y of age = 13.9%

Risk for colon cancer if close relative had CRC ≥60 y of age = 10.9%

***Close relative = parent, brother, sister, or child**

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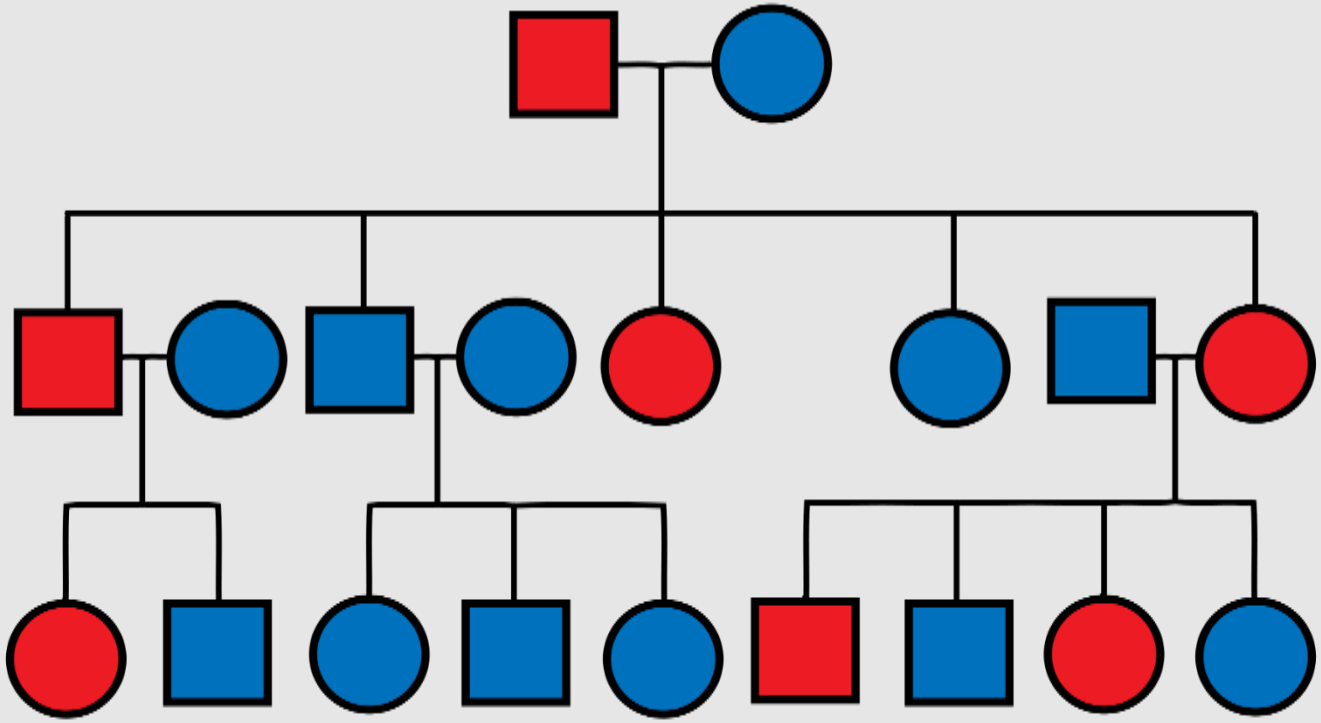

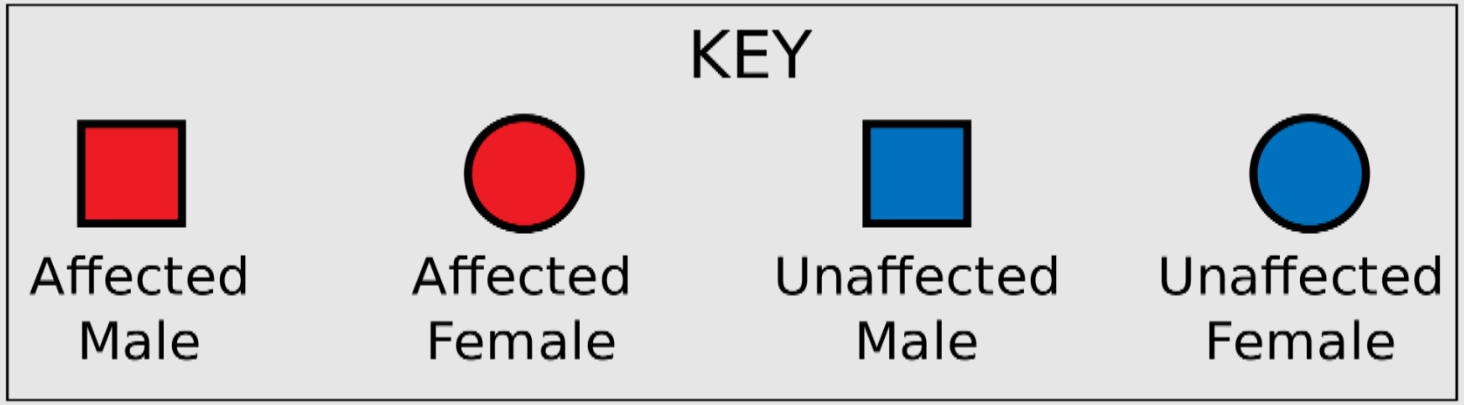
KEY
Affected Male
Affected Female
Unaffected Male
Unaffected Female

First, Second and Third Degree Relative

- A **first-degree relative** is defined as a close blood relative which includes the individual's parents, full siblings, or children
- A **second-degree relative** is defined as a blood relative which includes the individual's grandparents, grandchildren, aunts, uncles, nephews, nieces or half-siblings
- A **third-degree relative** is defined as a blood relative which includes the individual’s first-cousins, great-grandparents or great grandchildren

FULL VS HALF SIBLINGS

Familial colorectal cancer risk in half siblings and siblings: nationwide cohort study

Yu Tian,[1,2*] Elham Kharazmi,[1,3*] Kristina Sundquist,[3,4,5] Jan Sundquist,[3,4,5] Hermann Brenner,[1,6,7] Mahdi Fallah[1,3]

BMJ 2019;364:l803
http://dx.doi.org/10.1136/bmj.l803

COLORECTAL SCREENING- HIGH RISK

HIGH RISK CANCER SYNDROMES

- LYNCH SYNDROME
- POLYPOSIS SYNDROMES
  - FAP FAMILIAL ADENOMATOUS POLYPOSIS SYNDROME
  - PEUTZ-JEGHERS SYMDROME
  - JUVENILE POLYPOSIS SYNDROME
  - SERRATED POLYPOSIS SYNDROME
  - MUTYH ASSOCIATED POLYPOSIS-THE FDA clearance for 23andMe's *MUTYH*-Associated Polyposis Genetic Health Risk report demonstrates substantial equivalence, through the FDA's 510(k) submission pathway, to its predicate device 23andMe's*BRCA1/ BRCA2 (*Selected Variants) Genetic Health Risk report. For this newest clearance, the *MUTYH*-associated polyposis report achieved more than 99% accuracy and utilization of key informational concepts that achieved 90% or greater comprehension in a demographically diverse population.-
- COWDEN SYNDROME
- LI-FRAUMENI SYNDROME

OPTIONS

- COLONOSCOPY + TESTING FOR OTHERS TUMORS AS DETERMINED BY CLINICAL SYNDROME

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RISK ASSESSMENT FOR COLORECTAL CANCER

Average risk:

- Age ≥45 years[a]
  - The data supporting lowering the age to initiate screening are largely from modeling studies.
  - Between 1992 and 2015 there was a relative increase of 30% in the incidence of CRC in 40 year olds. However, this translates into an absolute difference in incidence of 8.2 cases per 100,000.[b]
  - We currently lack empirical data to support screening in those <50 years, as screening studies in average-risk individuals have been limited to those aged ≥50 years.
  - Considerations for the age to initiate CRC screening may be dependent on race/ethnicity, patient preference, and resources available. Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability.
- No history of adenoma or sessile serrated polyp (SSP)[c] or CRC
- No history of inflammatory bowel disease (IBD)
- Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP[d] (≥1 cm, any dysplasia)

→ See Average-Risk Screening and Evaluation (CSCR-3)

Increased risk:

COLORECTAL SCREENING **AVERAGE** RISK

AVERAGE RISK PATIENTS

- AGE ≥ 45 (ACS age 45-76)
- NO ADENOMA, SERRATED SESSILE POLYPS (SSP) OR CRC
- NO PERSONAL H/O IBD
- NEGATIVE FAMILY HISTORY OF CRC OR ADVANCED ADENOMA (HIGH GRADE DYSPLASIA ≥I CM VILLOUS OR TUBULOVILLOUS HISTOLOGY)

OPTIONS

- **FOBT GUAIAC**
- **FECAL IMMUNOCHEMICAL (FIT)**
- MULTI-TARGET STOOL DNA (MT-SDNA) COLOGUARD
- SCREENING COLONOSCOPY
- SIGMOIDOSCOPY +/- FIT
- CT COLONOGRAPHY (CTC)

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NCCN Guidelines Index
Table of Contents
Discussion

RISK STATUS

Average risk:
- Age ≥45 y[a,g]
- No history of adenoma or SSP[h] or CRC
- No history of IBD
- Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP[d,h] (≥1 cm, any dysplasia)

SCREENING MODALITY AND SCHEDULE[i,j,k] / EVALUATION OF SCREENING FINDINGS

Colonoscopy[l]
- No polyps[n] → Rescreen with any modality in 10 y[l]
- Polyp(s)[n] → Polypectomy
  - Hyperplastic polyps <1 cm in size[q] → Rescreen with any modality in 10 y[l]
  - Adenomas or SSP of any size or hyperplastic polyps ≥1 cm in size[r] → See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)

or

Stool-based:
- Guaiac-based testing
- Fecal immunochemical test (FIT) [m]
- Multitargeted stool DNA (mt-sDNA)–based testing

  - Negative → Rescreen with any modality in 1 y[l]
  - Positive → Colonoscopy[l,o,p] → Follow pathway above
  - Negative → Rescreen with any modality in 3 y[l]

or

Flexible sigmoidoscopy → See CSCR-4

or

CT colonography (CTC) → See CSCR-4

[a] The panel has reviewed existing data for beginning screening of average-risk individuals at age <50 years. Based on their assessment, the panel agrees that the data are stronger to support beginning screening at 50 years, but acknowledges that lower-level evidence supports a benefit for screening earlier. When initiating screening for all eligible individuals, the panel recommends a discussion of potential harms/risks and benefits, and the consideration of all recommended CRC screening options. Ladabaum U, et al. Gastroenterology 2019;157:137-148.

[d] Advanced SSPs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas, rather than high-risk adenomas, a definition which includes multiplicity.

[g] CRC screening is recommended in adults aged 45–75 years who might have a life expectancy of ≥10 years. The decision to screen between ages 76–85 years should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Eligible individuals who have not been previously screened are most likely to benefit in this age group.

[h] For details on classification, see footnote c on CSCR-1. For definition of commonly used terms, see CRC-GLOS-1.

[i] See Screening Modality and Schedule (CSCR-A).

[j] A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities. Based on current data, the panel concludes that the interval for repeating testing is unknown/unclear. The panel will continue to review this strategy and monitor data as they emerge.

[l] If colonoscopy is incomplete or the preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality (Johnson DA, et al. Gastroenterology 2014;147:903-924).

[m] Based on recent evidence, FIT has been shown to have superior sensitivity to guaiac-based tests. However, guaiac-based testing has been shown to reduce mortality from CRC and high-sensitivity fecal occult blood test (FOBT) is a reasonable alternative if an immunochemical test cannot be used (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Scholefield JH, et al. Gut 2012;61:1036-1040).

[n] The term "polyp" refers to both polyp and nonpolypoid (flat) lesions.

[o] When a screening stool-based test is positive, a colonoscopy is recommended for further evaluation. Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study and a meta-analysis reported significantly higher risks for CRC and advanced-stage disease when follow-up occurred 10 months or later with a trend towards increased cancer risk observed as early as 6 months after an abnormal result. Thus, we recommend that follow-up colonoscopy is completed ideally within 6 to 10 months after an abnormal stool-based test. (Corley DA, et al. JAMA 2017;317:1631-1641; Forbes N, et al. Clin Gastro Hepatol 2020).

[p] If the colonoscopy is negative after a FIT or mt-sDNA and no additional symptoms are present, there is no need for further tests.

[q] There are iconflicting data to suggest that hyperplastic polyps (<1 cm) proximal to the sigmoid colon pose an increased risk and whether they should be managed differently.

[r] There are limited data to support whether individuals with hyperplastic polyps ≥1 cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs, particularly if they have not been reviewed by an expert gastrointestinal pathologist.

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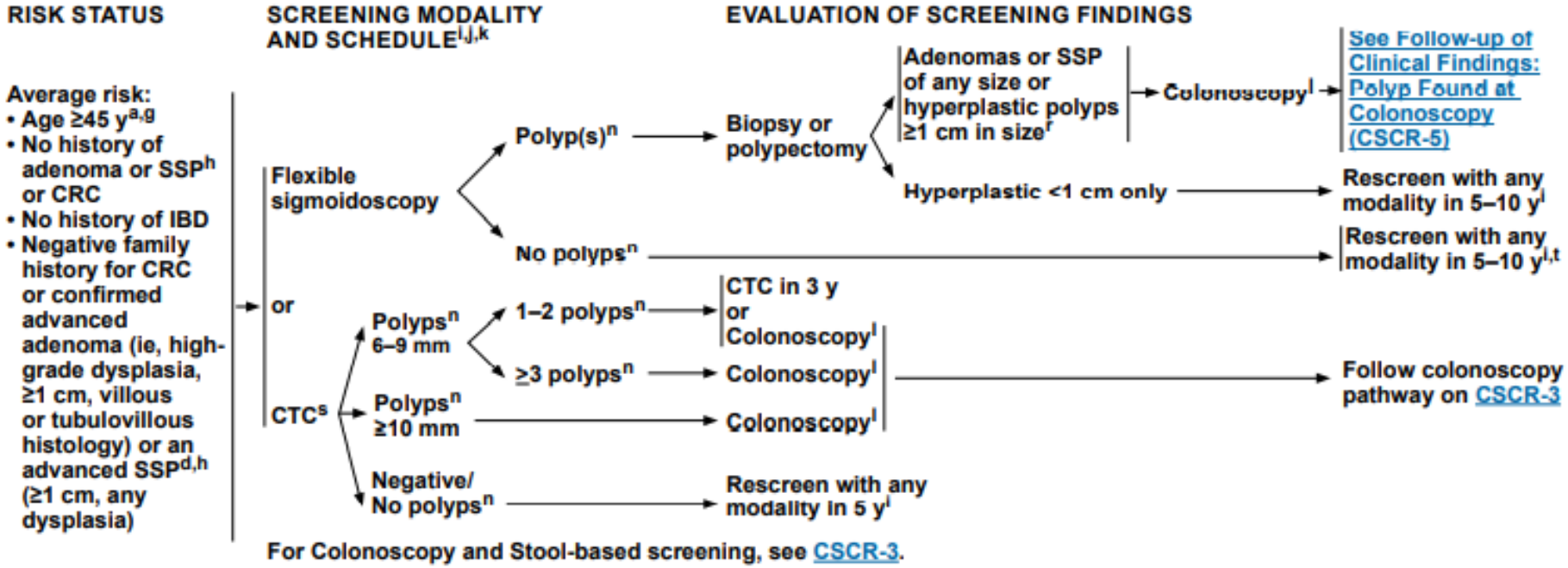
NCCN Guidelines Index
Table of Contents
Discussion



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[k] Screening should be individualized and include a discussion of the risks and benefits of each modality.

[l] If colonoscopy is incomplete or the preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality (Johnson DA, et al. Gastroenterology 2014;147:903-924).

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[r] There are limited data to support whether individuals with hyperplastic polyps ≥1 cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs, particularly if they have not been reviewed by an expert gastrointestinal pathologist.

[s] Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The American College of Radiology has recommended that reporting of polyps ≤5 mm in size is not necessary. If polyp(s) of this size are reported, a decision to refer for colonoscopy with polypectomy versus surveillance CTC should be individualized.

[t] There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years with annual FIT or considering longer interval flexible sigmoidoscopy without FIT (Knudsen AB, et al. JAMA 2016;315:2595-2609).

COLORECTAL CANCER RISK BY AGE

The risk of bowel cancer increases with age, as indicated in the table below:

30	40	50	60	70
Men: 1 in 1,350 risk of bowel cancer over the next 10 years	**Men: 1 in 313** risk of bowel cancer over the next 10 years	**Men: 1 in 87** risk of bowel cancer over the next 10 years	**Men: 1 in 36** risk of bowel cancer over the next 10 years	**Men: 1 in 22** risk of bowel cancer over the next 10 years
Women: 1 in 1,390 risk of bowel cancer over the next 10 years	**Women: 1 in 370** risk of bowel cancer over the next 10 years	**Women: 1 in 125** risk of bowel cancer over the next 10 years	**Women: 1 in 57** risk of bowel cancer over the next 10 years	**Women: 1 in 34** risk of bowel cancer over the next 10 years

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COLORECTAL CANCER INCIDENCE

- INCIDENCE PER 100,000 HAS DECREASED BETWEEN 1976 (60.5/100,000) AND 2005 (46.4/100,000)
- INCIDENCE DOWN 2.7% IN MEN FROM 2004 – 2008
- MORTALITY HAS DECREASED 35% FROM 1990-2007
- 2014 MORTALITY DOWN 51% FROM PEAK MORTALITY

Cases of young-onset colorectal cancer have increased by 51 percent since 1994

In the United States, 11% of colon cancer diagnoses and 18% of rectal cancer diagnoses occur in those under 50

In 2017, The American Cancer Society (ACS) investigators published in the Journal of the National Cancer Institute that (CRC) incidence rates are continuing to rise in young and middle-aged adults, including people in their early 50s. In addition, rectal cancer rates are increasing particularly fast, as 3 in 10 rectal cancer diagnoses are in patients younger than age 55.

Published in 2014, researchers at MD Anderson looked at Surveillance, Epidemiology, and End Results SEER program (on more than 393,000 patients with histologically confirmed CRC between 1975 and 2010) and made incidence rate predictions by 2030. The trends indicate that by 2030:

- 1 in 10 colon cancers will be diagnosed in people under 50
- 1 in 4 rectal cancers will be diagnosed in people under 50

Sedentary behavior increases the risk of certain cancers

Physical inactivity has been linked with diabetes, obesity, and cardiovascular disease, but it can also increase the risk of certain cancers, according to a study published June 16 in the *JNCI: Journal of the National Cancer Institute*.

To assess the relationship between TV viewing time, recreational sitting time, occupational sitting time, and total sitting time with the risk of various cancers, Daniela Schmid, Ph.D., M.Sc., and Michael F. Leitzmann, M.D., Dr.P.H., of the Department of Epidemiology and Preventive Medicine, University of Regensburg, Germany, conducted a meta-analysis of 43 observational studies, including over 4 million individuals and 68,936 cancer cases. Data in the individual studies had been obtained with self-administered questionnaires and through interviews.

When the highest levels of sedentary behavior were compared to the lowest, the researchers found a statistically significantly higher risk for three types of cancer—colon, endometrial, and lung. Moreover, the risk increased with each 2-hour increase in sitting time, 8% for colon cancer, 10% for endometrial cancer, and 6% for lung cancer, although the last was borderline statistically significant. The effect also seemed to be independent of physical activity, suggesting that large amounts of time spent sitting can still be detrimental to those who are otherwise physically active. TV viewing time showed the strongest relationship with colon and endometrial cancer, possibly, the authors write, because TV watching is often associated with drinking sweetened beverages, and eating junk foods.

COLON CANCER RISK FACTORS

RESEARCH ARTICLE | MARCH 01 2022

Adult-Attained Height and Colorectal Cancer Risk: A Cohort Study, Systematic Review and Meta-Analysis FREE

Elinor Zhou; Lin Wang; Celina N. Santiago; Julie Nanavati; Samara Rifkin; Emma Spence; Linda M. Hylind ; Joell J. Gills; Louis La Luna; David R. Kafonek; David M. Cromwell; Julia L. Drewes ; Cynthia L. Sears ; Francis M. Giardiello; Gerard Mullin

Conclusions

Greater adult attained height is associated with an increased risk of colorectal cancer and adenoma.

Impact: Height should be considered as a risk factor for colorectal cancer screening.

Yogurt consumption and risk of conventional and serrated precursors of colorectal cancer

http://gut.bmj.com/

Gut Month 2019 Vol 0 No.0

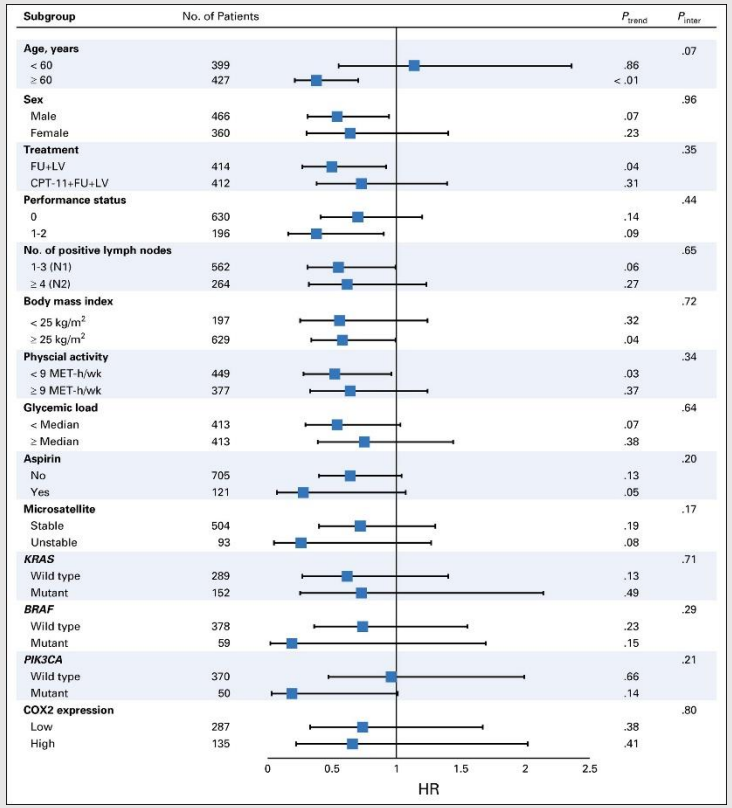

Fig 2. Multivariable hazard ratios (HRs) and 95% CIs for cancer recurrence or mortality across strata of various factors. The analyses used five categories of total nut intake (never, less than one serving per month, one to three servings per month, one serving per week, and two or more servings per week). The forest plot represents the HRs of the comparison of never nut consumers versus consumers of two or more servings of nuts per week, adjusting for calorie intake, age, sex, depth of invasion through bowel wall, number of positive lymph nodes, baseline performance status, treatment group, body mass index, physical activity, aspirin use, and glycemic load. P values are two-sided; Pinter indicates P for interaction between strata and nut intake; Ptrend indicates P for trend across levels of nut intake. COX2, cyclooxygenase-2; CPT-11, irinotecan; FU, fluorouracil; LV, leucovorin; MET-h/wk, metabolic equivalent task hours per week.

Published in: Temidayo Fadelu; Sui Zhang; Donna Niedzwiecki; Xing Ye; Leonard B. Saltz; Robert J. Mayer; Rex B. Mowat; Renaud Whittom; Alexander Hantel; Al B. Benson; Daniel M. Atienza; Michael Messino; Hedy L. Kindler; Alan Venook; Shuji Ogino; Kimmie Ng; Kana Wu; Walter Willett; Edward Giovannucci; Jeffrey Meyerhardt; Ying Bao; Charles S. Fuchs; *Journal of Clinical Oncology* 2018 361112-1120.
DOI: 10.1200/JCO.2017.75.5413
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Welcome to the QCancer®(15yr,colorectal) risk calculator: http://qcancer.org/15yr/colorectal

About you

Age (25-84): 66

Sex: Male Female

Ethnicity: White or not stated

UK postcode: leave blank if unknown

Postcode:

Clinical information

Smoking status: non-smoker

Alcohol status: 3-6 units per day

Do you have a family history of ...

gastro-intestinal cancer?

Women only: have you had any of these cancers?

breast cancer?

uterine cancer?

ovarian cancer?

cervical cancer?

Men only: have you had any of these cancers?

(These cancers did not pass our statistical test for significance for women.)

oral cancer?

lung cancer?

cancer of the blood?

Do you currently have...

Diabetes: none

ulcerative colitis?

colonic polyps?

Leave blank if unknown

Body mass index

Height (cm): 177

Weight (kg): 75

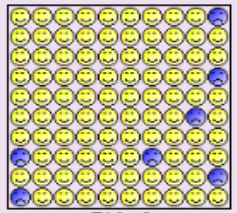
Calculate risk over 15 years. Calculate risk

Your results

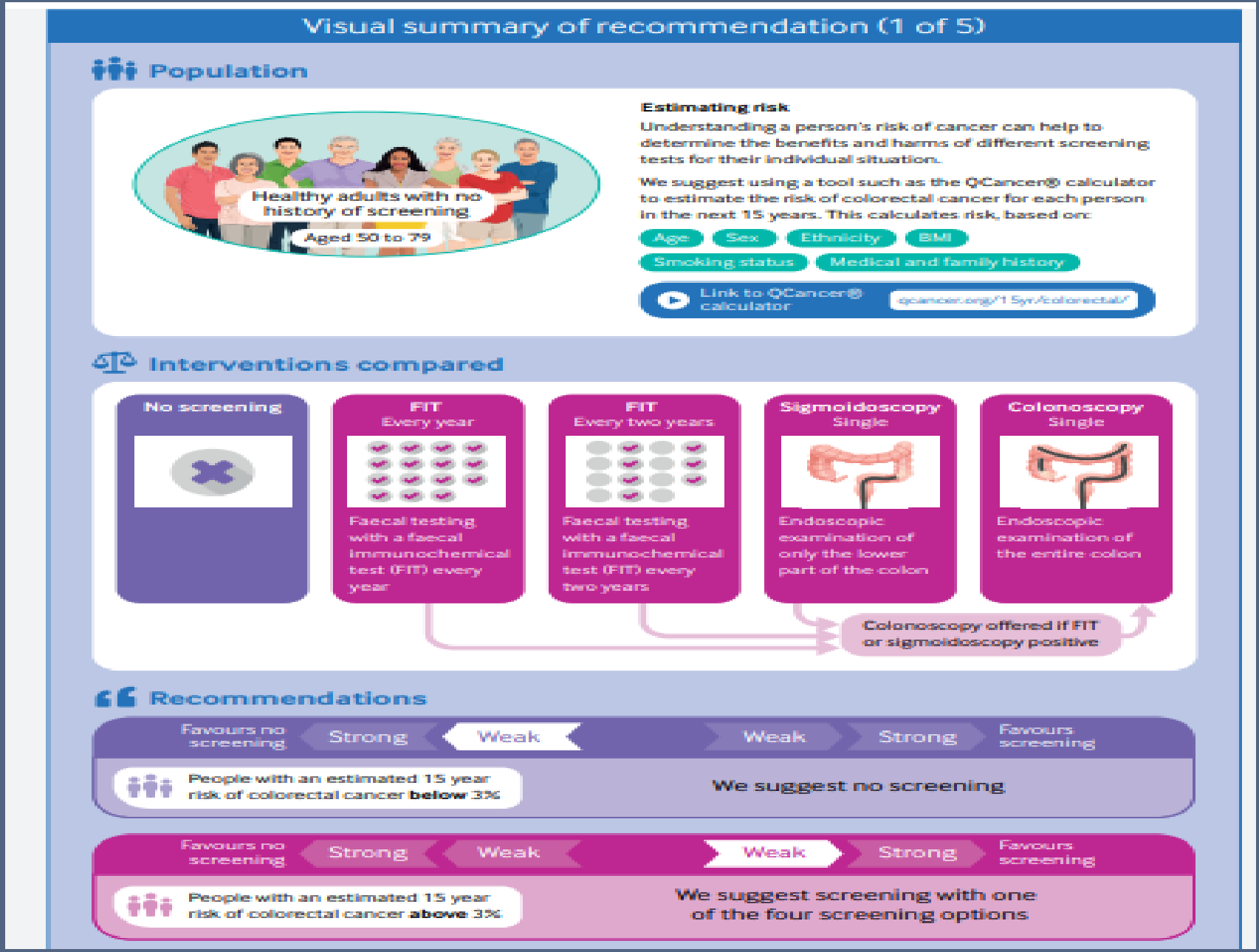
Your risk of having colorectal cancer within the next 15 years is:

6.7%

In other words, in a crowd of 100 people with the same risk factors as you, 7 are likely to develop colorectal cancer within the next 15 years.



Risk of developing colorectal cancer



BMJ 2019;367:l5515

Non-Invasive Colorectal Cancer Screening

Fecal Occult Blood Test (FOBT-Heme)	Fecal Immunochemical Test (FIT-Globin protein)	Stool DNA
Limited by intermittent bleeding	Limited by intermittent bleeding	Precancerous/Cancerous cells continuously exfoliated
Requires 3 separate Stool samples	Single stool specimen	Single stool specimen
Dietary restrictions	No dietary restrictions	No dietary restrictions

Cologuard Biomarkers

2 DNA Methylation Markers
NDRG4 and BMP3

7 DNA Mutation Markers
All KRAS

DNA Normalization Marker
Beta Actin (Quantitative DNA)

Molecular Assay (DNA)

Fecal Hemoglobin Marker
FIT

Hemoglobin Assay (Protein)

gutCARE

26

Practical issues for the different methods for colorectal cancer screening.

PRACTICAL ISSUES

	Feacal testing	Sigmoidoscopy	Colonoscopy
MEDICATION ROUTINE	Continue medication routine as prescribed	Some medicines, especially blood thinners, may be paused	
TEST & VISIT	Done every or every two years at home Individuals with a positive test will be referred for colonoscopy	Done once at an outpatient clinic/hospital	
PROCEDURE & DEVICE	Stool from one bowel movement is collected by a stick and then mailed for analysis Can be uncomfortable to access stool	Bowel enema same day sometimes combined with cleansing of bowel with laxatives Thin, flexible tube with a small camera is passed into the rectum and guided around in the lower part of the large bowel	Need for cleansing of bowel by specific preparation regime with laxatives starting the day before procedure Depending on country, region, clinic; different levels of sedation from light to deep sedation, or no sedation at all Thin, flexible tube with a small camera is passed into the rectum and guided around in the large bowel
RECOVERY & ADAPTATION	No recovery time necessary		Need for some recovery time after procedure, dependent on level of sedation (no recovery necessary if no sedation)
COORDINATION OF CARE	Help can be needed if eyesight or dexterity is poor	Need for nursing, security and transportation	
ADVERSE EFFECTS, INTERACTIONS & ANTIDOTE			Adverse effects are rare, but sedation may slightly increase risk of perforation of colon
SOCIAL LIFE & RELATIONSHIPS	Can be done in the privacy of own home and fit into own schedule	Should be near a toilet during preparation	
WORK & EDUCATION	Will not influence work/education	Need to take time off work for procedure day	Need to take time off work during preparation time and procedure day
TRAVEL TIME & DRIVING			If sedated, not possible to drive directly after procedure, need for transportation

Lise M Helsingen et al. BMJ 2019;367:bmj.l5515

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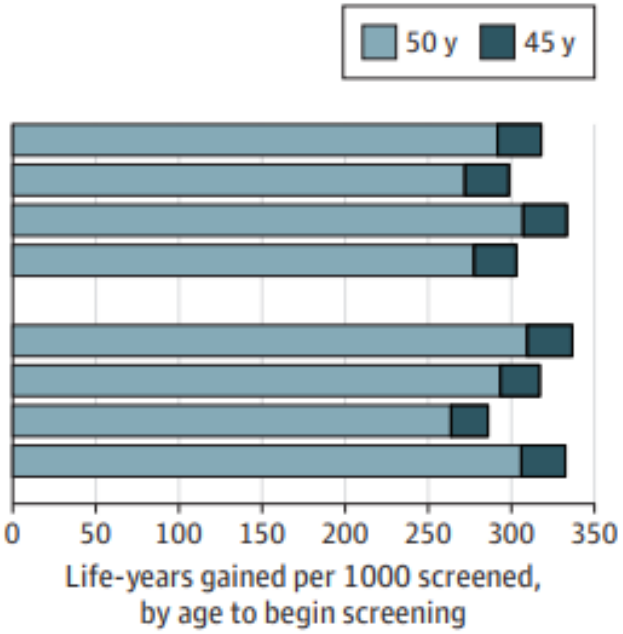
Figure 2. Benefits of Colorectal Cancer Screening

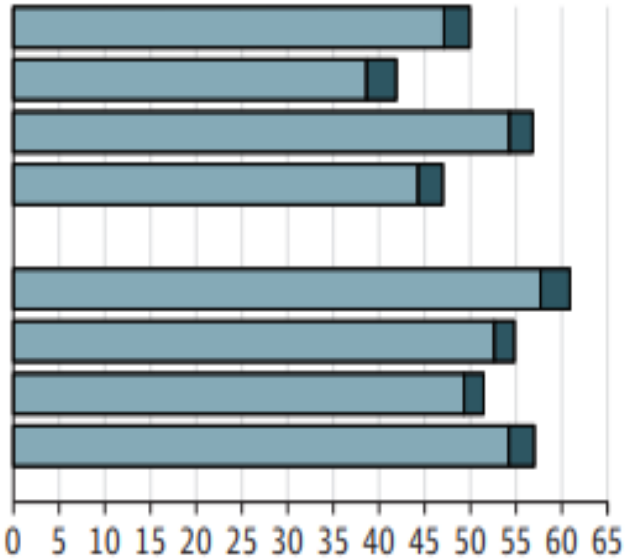
A Benefit: Estimated life-years gained per 1000 individuals screened[a]

Screening modality and frequency	Mean life-years gained if start screening[b]		Additional life years gained if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	292	318	26
HSgFOBT every year[c,d]	272	298	26
sDNA-FIT every year	307	333	26
sDNA-FIT every 3 y[d]	278	303	25
Direct visualization tests			
COL every 10 y	310	337	27
CT colonography every 5 y	293	317	24
Flexible SIG every 5 y	264	286	22
Flexible SIG every 10 y plus FIT every year	306	332	26



B Benefit: Estimated No. of CRC cases averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC cases averted if start screening[b]		Additional CRC cases averted if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	47	50	3
HSgFOBT every year[c,d]	39	42	3
sDNA-FIT every year	54	57	3
sDNA-FIT every 3 y[d]	44	47	3
Direct visualization tests			
COL every 10 y	58	61	3
CT colonography every 5 y	53	55	2
Flexible SIG every 5 y	49	51	2
Flexible SIG every 10 y plus FIT every year	54	57	3



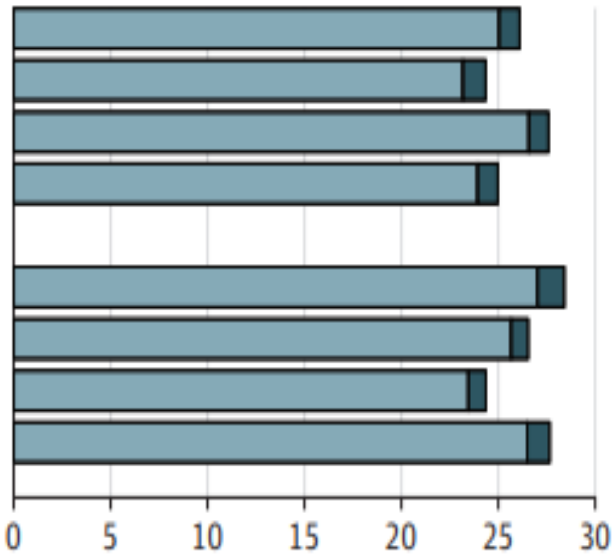
No. of CRC cases averted per 1000 screened, by age to begin screening

CRC indicates colorectal cancer; CT, computed tomography; FIT, fecal immunochemical test (with positivity cutoff of 20 μg of hemoglobin per gram of feces); HSgFOBT, high-sensitivity guaiac fecal occult blood test; sDNA-FIT, stool DNA tests with FIT (multitarget stool DNA test); SIG, sigmoidoscopy; COL, colonoscopy.

[a] Outcomes are expressed per 1000 40-year-olds who start screening at age 45 or at age 50.

C Benefit: Estimated No. of CRC deaths averted per 1000 individuals screened[a]

Screening modality and frequency	Mean CRC deaths averted if start screening[b]		Additional CRC deaths averted if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	25	26	1
HSgFOBT every year[c,d]	23	24	1
sDNA-FIT every year	27	28	1
sDNA-FIT every 3 y[d]	24	25	1
Direct visualization tests			
COL every 10 y	27	28	1
CT colonography every 5 y	26	26	0.9
Flexible SIG every 5 y	23	24	0.9
Flexible SIG every 10 y plus FIT every year	26	28	1



No. of CRC deaths averted per 1000 screened, by age to begin screening

[b] Mean estimate across the 3 Cancer Intervention and Surveillance Modeling Network colorectal cancer models. See modeling report[12,13] for additional details and model-specific estimates.

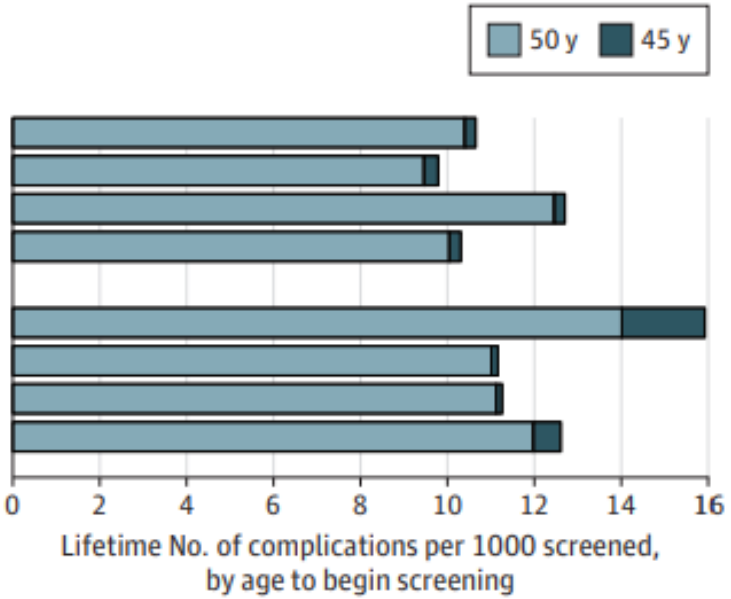
[c] Because of imprecision in sensitivity and specificity, there is considerable uncertainty in model predictions for HSgFOBT strategies. See modeling report[12] for more information.

[d] Compared with other options for stool-based screening, these strategies do not provide an efficient balance of the benefits (life-years gained) vs harms and burden (ie, lifetime number of colonoscopies) of screening. See modeling report[12,13] for more information.

Figure 3. Harms and Burden of Colorectal Cancer Screening

A Harms: Estimated lifetime number of complications (gastrointestinal and cardiovascular) of CRC screening and follow-up procedures per 1000 individuals screened[a]

Screening modality and frequency	Mean estimate of complications if start screening[b]		Additional complications if start screening at age 45 y
	At age 50 y	At age 45 y	
Stool tests			
FIT every year	10	11	0.2
HSgFOBT every year[c,d]	9	10	0.3
sDNA-FIT every year	12	13	0.2
sDNA-FIT every 3 y[d]	10	10	0.3
Direct visualization tests			
COL every 10 y	14	16	2
CT colonography every 5 y	11	11	0.2
Flexible SIG every 5 y	11	11	0.1
Flexible SIG every 10 y plus FIT every year	12	13	0.6



PREVENTION

- ASA

Annals of Internal Medicine

CLINICAL GUIDELINE

Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer: U.S. Preventive Services Task Force Recommendation Statement

Kirsten Bibbins-Domingo, PhD, MD, MAS, on behalf of the U.S. Preventive Services Task Force*

Description: Update of the 2009 USPSTF recommendation on aspirin use to prevent cardiovascular disease (CVD) events and the 2007 recommendation on aspirin and nonsteroidal anti-inflammatory drug use to prevent colorectal cancer (CRC).

Methods: The USPSTF reviewed 5 additional studies of aspirin for the primary prevention of CVD and several additional analyses of CRC follow-up data. The USPSTF also relied on commissioned systematic reviews of all-cause mortality and total cancer incidence and mortality and a comprehensive review of harms. The USPSTF then used a microsimulation model to systematically estimate the balance of benefits and harms.

Population: This recommendation applies to adults aged 40 years or older without known CVD and without increased bleeding risk.

Recommendation: The USPSTF recommends initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years. (B recommendation)

The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin. (C recommendation)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years. (I statement)

The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older. (I statement)

Ann Intern Med. doi:10.7326/M16-0577 **www.annals.org**
For author affiliation, see end of text.
This article was published at www.annals.org on 12 April 2016.

* For a list of members of the USPSTF, see the **Appendix** (available at www.annals.org).

Offer daily aspirin to those with inherited genetic condition to reduce the risk of colorectal cancer

Aspirin taken daily for 2 years or more could reduce the risk of colorectal cancer in people with Lynch syndrome (LS), says NICE in new draft updated guidance.

02 August 2019 Share

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

IndyStar | The Indianapolis Star

Zionsville and IU grad, distance runner Caitlin Engel dies after battle with cancer

Matthew VanTryon, Indianapolis Star

Wed, January 26, 2022, 2:33 PM · 1 min read

Caitlin Engel, who was a distance runner at Zionsville and IU, and was an assistant cross country/track coach at Carmel High School, died Tuesday morning after a long battle with cancer. She was 32.

Chadwick Boseman
@chadwickboseman

1976-2020
Dx colon cancer stage III in 2016

It is with immeasurable grief that we confirm the passing of Chadwick Boseman.

Chadwick was diagnosed with stage III colon cancer in 2016, and battled with it these last 4 years as it progressed to stage IV.

A true fighter, Chadwick persevered through it all, and brought you many of the films you have come to love so much. From Marshall to Da 5 Bloods, August Wilson's Ma Rainey's Black Bottom and several more, all were filmed during and between countless surgeries and chemotherapy.

It was the honor of his career to bring King T'Challa to life in Black Panther.

He died in his home, with his wife and family by his side.

The family thanks you for your love and

7:11 PM · Aug 28, 2020

RISK ASSESSMENT FOR COLORECTAL CANCER (CONT.)

Evaluation of alarm symptoms in patients <45 years:

Signs and symptoms of CRC such as iron deficiency anemia, rectal bleeding, or a change in bowel habits presenting in individuals <45 years warrant prompt evaluation with a colonoscopy or at least with flexible sigmoidoscopy.

- Half of the patients who present with early-onset CRC are <45 years of age.[b,e] The incidence of CRC in individuals <50 years has increased 22% between 2003 and 2013.[f]
- The majority of CRCs in these younger individuals appear to be sporadic but an inherited cancer syndrome should be ruled out given the higher incidence of inherited CRC syndromes in younger patients when compared to older patients.[f]

Clinical Presentation

- This bleeding from the GIT can present in 5 ways;

  a) Haematemesis:- Vomitus of red blood or 'coffee-grounds' material.

  b) Melaena:- Black, tarry foul smelling stool.

  c) Haematochezia:- Is the passage of bright red or maroon blood from the rectum.

  d) Occult GIB:- This is identified in the absence of overt bleeding by special examination of the stool (e.g. Guaiac testing)

  e) Symptoms of blood loss/anaemia:- Light-headedness, syncope, angina or dyspnoea.

Mild anemia in young patients is usually asymptomatic!!

Bristol Stool Chart

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on its surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges (passed easily)
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

KNOW YOUR POOP
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do
Chalky-grey
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Greenish black
Streaks of red
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do
Yellow/Slightly green
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Yellow green Brown
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do
Bright green
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Rainbow Brown
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Peanut butter
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Brown
Lorem ipsum dolor sit amet, consectetur adipiscing elit, sed do
Dark green
Lorem ipsum dolor sit amet, consectetur adip-iscing elit, sed do eius-
Red
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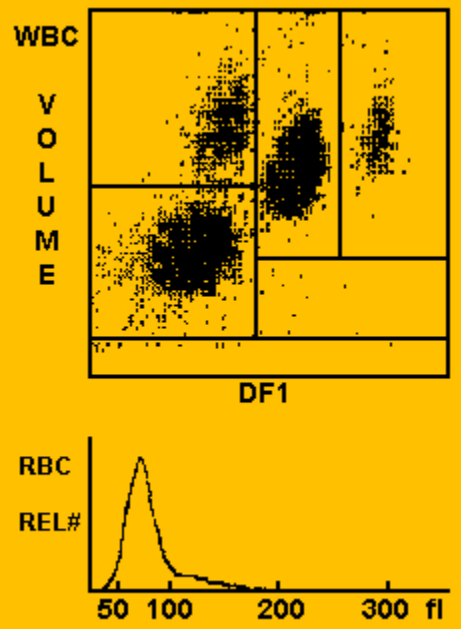
Fe def cbc



WBC	5.5		
	%		#
NE	54.7		3.0
LY	34.1		1.9
MO	7.5		0.4
EO	3.0		0.2
BA	0.7		0.0
RBC	4.28	L	
HGB	9.7	L	
HCT	29.9	L	
MCV	69.7	L	
MCH	22.6	L	
MCHC	32.4	L	
RDW	18.4	H	
PLT	331		
MPV	8.8		

IDA – Special Tests

Iron related tests	Normal	IDA
Serum Ferritin (pmo/L)	33-270	< 33
TIBC (µg/dL)	300-340	> 400
Serum Iron (µg/dL)	50-150	< 30
Saturation %	30-50	< 10
Bone marrow Iron	++	Absent

Iron Deficiency Anemia – Lab Findings

- Serum Iron
  - LOW (< 60 micrograms/dL)
- Total Iron Binding Capacity (TIBC)
  - HIGH (> 360 micrograms/dL)
- Serum Ferritin
  - LOW (< 20 nanograms/mL)
  - Can be “falsely”normal in inflammatory states

Anaemia Workup - MCV

MCV

Microcytic	Normocytic	Macrocytic
Iron Deficiency IDA	Chronic disease	Megaloblastic anemias
Chronic Infections	Early IDA	Liver disease/alcohol
Thalassemias	Hemoglobinopathies	Hemoglobinopathies
Hemoglobinopathies	Primary marrow disorders	Metabolic disorders
Sideroblastic Anemia	Combined deficiencies	Marrow disorders
	Increased destruction	Increased destruction

MICROCYTIC ANEMIA

- FE DEFICIENCY
- FE DEFICIENCY
- FE DEFICIENCY
- THALLESEMIA
- LEAD INTOXICATION
- SICKLE CELL

MCV

- MCV (Mean corpuscular volume)
- $$MCV = \frac{\text{PCV in 100 ml of blood x 10}}{\text{RBC count in million per cc}}$$

This is the average volume of the RBC

Useful to classify the anaemia

- Microcytic, MCV < 80 cu.microns
- Normocytic, MCV 80 – 100 cu.microns
- Macrocytic, MCV > 100 cu.microns

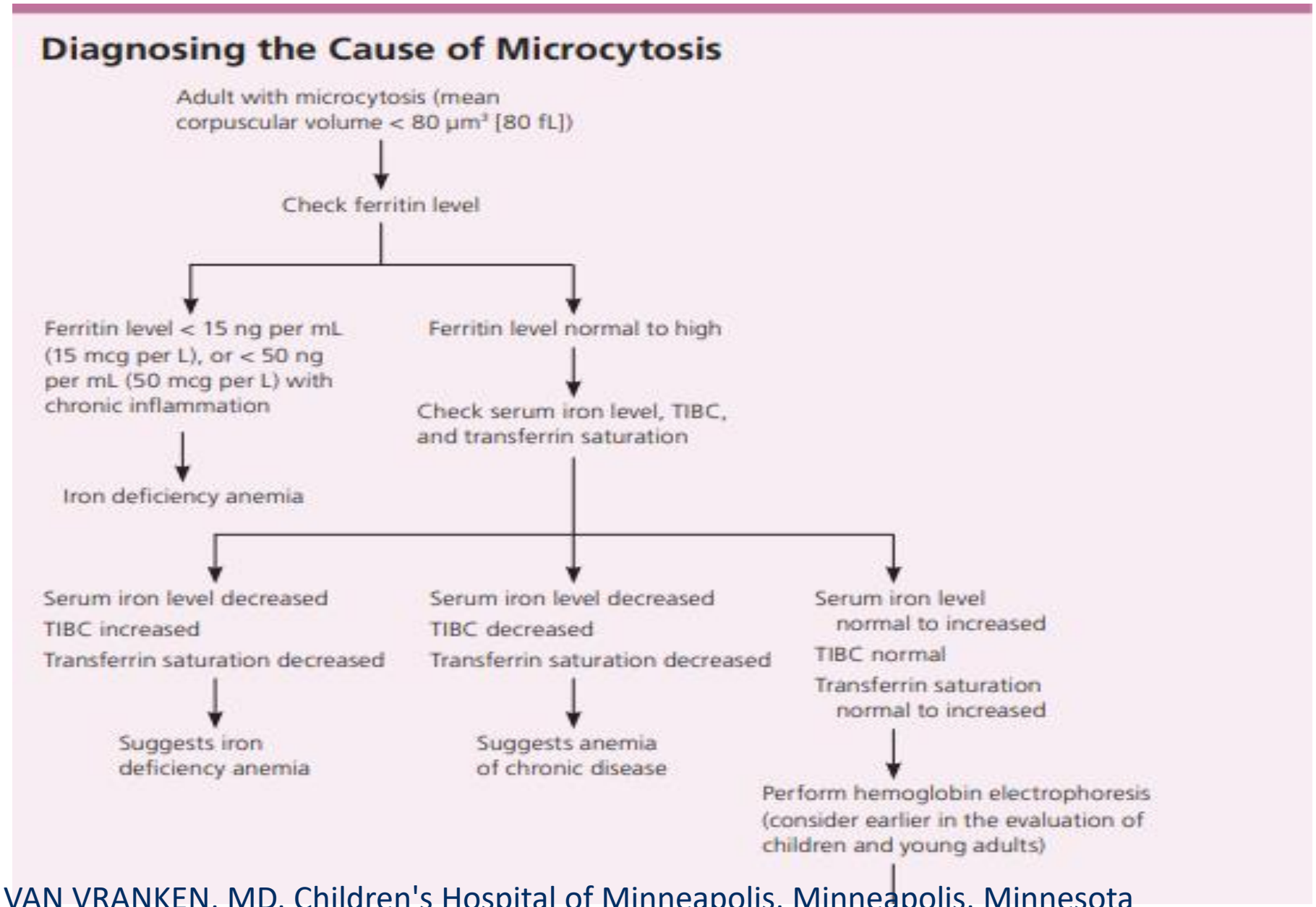
CBC (Collection date/time: 12/7/2018 6:26:00AM)

PLATELET COUNT	578 TH/CUMM	H	140-400
WHITE BLOOD COUNT	6.91 TH/CU MM	N	4.0-10.0
ABSOLUTE NEUTROPHIL CT	4.06 x10-3/uL	N	1.56-8.10
NEUTROPHILS	58.8 %	N	39-81
LYMPHOCYTE	32.0 %	N	14-51
MONOCYTES	6.2 %	N	0-13.3
EOSINOPHIL	2.0 %	N	0-8
BASOPHILS	0.4 %	N	0-2
RED BLOOD CELLS	5.22 M/CU MM	N	4.41-5.51
MANUAL SLIDE REVIEW 1+ MICRO 1+ OVAL 1+ SPHEROCYTES			
HEMOGLOBIN	13.5 G/DL	N	13.5-17.5
HEMATOCRIT	40.6 %	LL	41-53
MCV	77.8 FL	L	80-100

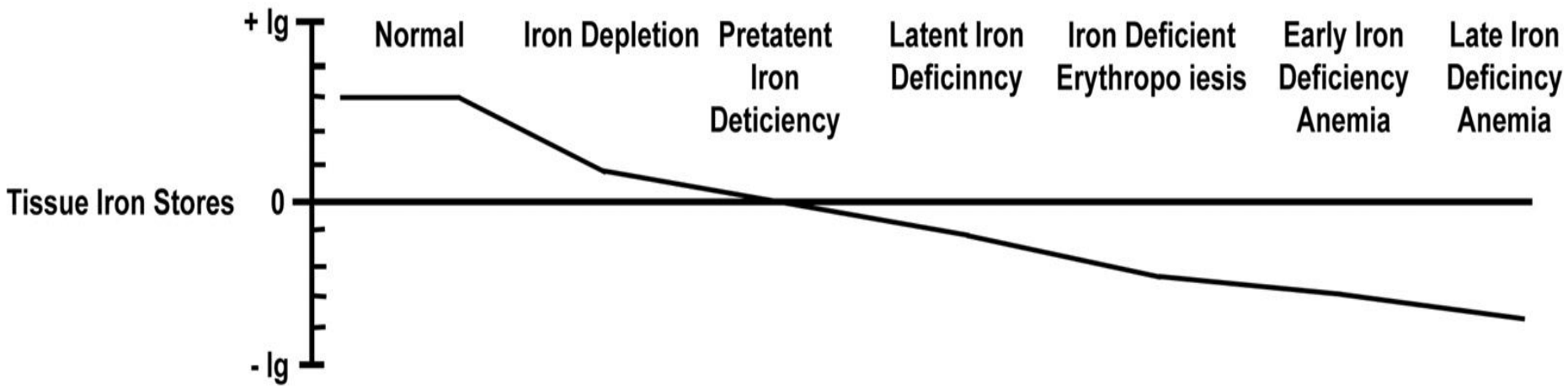
CBC (Collection date/time: 12/7/2018 6:26:00AM)

PLATELET COUNT	578 TH/CUMM	H	140-400
WHITE BLOOD COUNT	6.91 TH/CU MM	N	4.0-10.0
ABSOLUTE NEUTROPHIL CT	4.06 x10-3/uL	N	1.56-8.10
NEUTROPHILS	58.8 %	N	39-81
LYMPHOCYTE	32.0 %	N	14-51
MONOCYTES	6.2 %	N	0-13.3
EOSINOPHIL	2.0 %	N	0-8
BASOPHILS	0.4 %	N	0-2
RED BLOOD CELLS	5.22 M/CU MM	N	4.41-5.51
MANUAL SLIDE REVIEW 1+ MICRO 1+ OVAL 1+ SPHEROCYTES			
HEMOGLOBIN	13.5 G/DL	N	13.5-17.5
HEMATOCRIT	40.6 %	LL	41-53
MCV	77.8 FL	L	80-100

1. Check prior CBC's
2. Obtain serum ferritin



MICHELE VAN VRANKEN, MD, Children's Hospital of Minneapolis, Minneapolis, Minnesota
Am Fam Physician. 2010 Nov 1;82(9):1117-1122



Serum Ferritin (µg/1)	60	20	<12	<12	<12	<12	<12
Stainable Tissue Iron (0-4+)	2+	1+	0	0	0	0	0
Transferrin Saturation (%)	35	35	35	20	<16	<16	<16
Free Erythrocyle Protoporhyrin (µg/dl)	30	30	30	75	>100	>100	>100
Hemoglobin (g/dl)	14	14	14	14	13	<12	<12
Mean Corpuscular Volume (μ^3)	90	90	90	90	88	86	<82
Mean Corpuscular Hemoglobin Concentration (0/0)	33	33	33	33	33	31	<28

CBC (Collection date/time: 12/7/2018 6:26:00AM)

PLATELET COUNT	578 TH/CUMM	H	140-400
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NEUTROPHILS	58.8 %	N	39-81
LYMPHOCYTE	32.0 %	N	14-51
MONOCYTES	6.2 %	N	0-13.3
EOSINOPHIL	2.0 %	N	0-8
BASOPHILS	0.4 %	N	0-2
RED BLOOD CELLS	5.22 M/CU MM	N	4.41-5.51
MANUAL SLIDE REVIEW 1+ MICRO 1+ OVAL 1+ SPHEROCYTES			
HEMOGLOBIN	13.5 G/DL	N	13.5-17.5
HEMATOCRIT	40.6 %	LL	41-53
MCV	77.8 FL	L	80-100

COLORECTAL CANCER

IRON METABOLISM

IRON STORES

- TOTAL BODY CONTENT OF 4 GMS
- 0.5 – 1 GM STORED IN LIVER/MACROPHAGES
- 2/3 OF IRON CONTENT IN THE RED CELLS
- 20-25 MG IRON ARE NEEDED TO MAINTAIN ERYTHROPOESIS
- 1-2 MG REQUIRED DAILY TO MAINTAIN RED CELL PRODUCTION
- MOST IRON IS RECYCLED

IRON HOMEOSTASIS

NO MECHANISM FOR IRON EXCRETION

- INTESTINAL ABSORPTION IS THE MEANS OF REGULATION
- HEPCIDIN CONTROLS IRON ABSORPTION
- HEPCIDIN IS THE ‘INSULIN’ OF ELEVATED IRON LEVELS

HEPCIDIN

- INHIBITS IRON EXPORT BY FERROPROTEIN FROM GUT AND MACROPHAGES
- INCREASED HEPCIDIN PRODUCTION LEADS TO A DECREASE IN PLASMA IRON
- HEPCIDIN REGULATED BY TOTAL IRON BODY STORES, INFLAMMATION, RED CELL IRON DEMAND AND HYPOXIA

HEPCIDIN

- INCREASED IRON LEVELS STIMULATE HEPCIDIN PRODUCTION WHICH BLOCKS IRON ABSORPTION IN THE DIET AND ITS FURTHER STORAGE
- HEPCIDIN PRODUCTION IS SUPPRESSED IN FE DEFICIENT STATES
- HEPCIDIN IS ELEVATED IN INFECTION/INFLAMMATION
- EPO REDUCES HEPCIDIN LEVELS

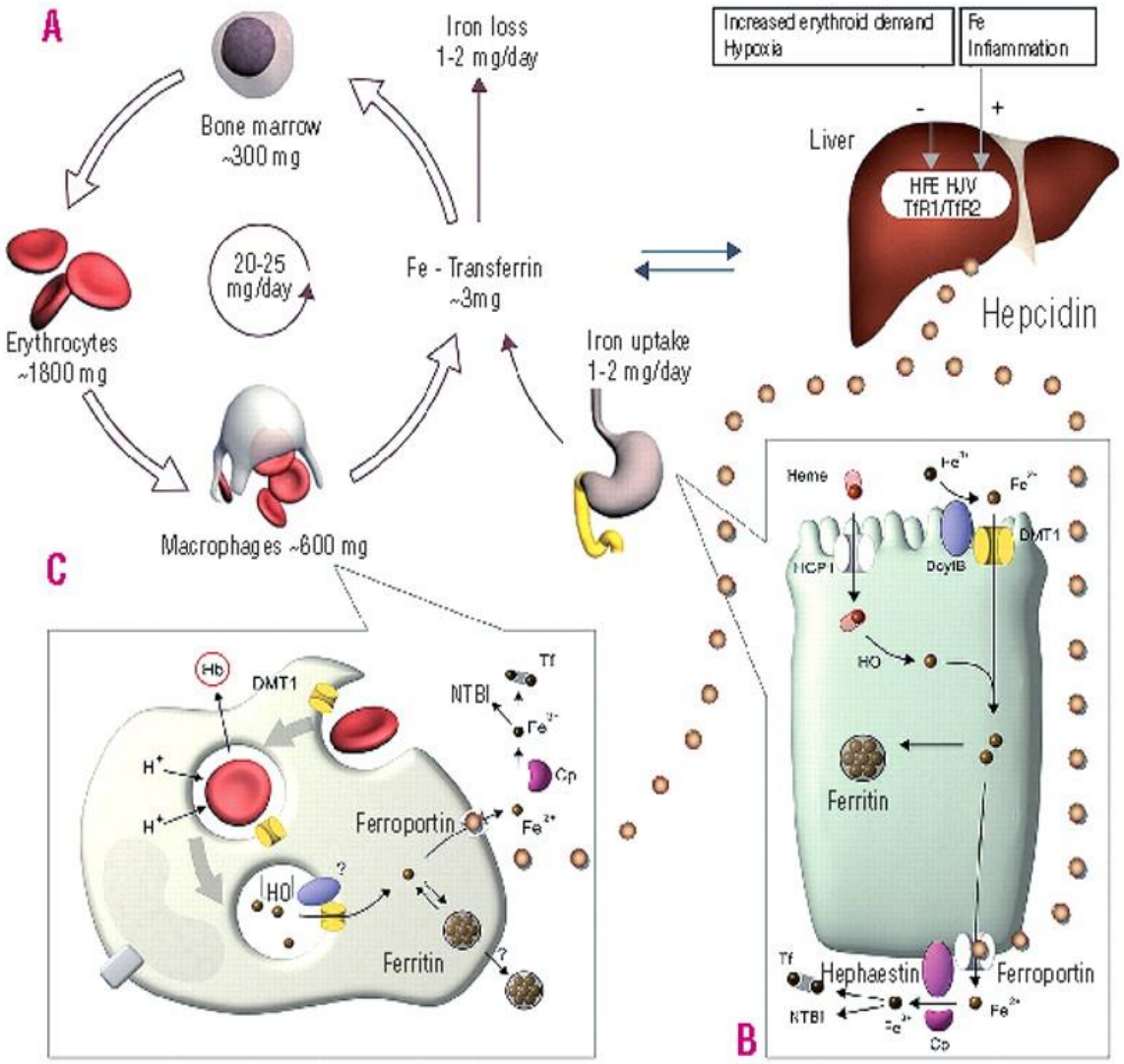


Figure 1. Iron uptake and recycling. A. Most of the utilized body iron is recycled from senescent erythrocytes by macrophages, and returned to the bone marrow for incorporation in erythroid precursors. The liver and reticuloendothelial macrophages function as major iron stores. 1-2 mg of iron is absorbed and lost every day. Only duodenal absorption is regulated by transporters such as DMT1 and HCP1, whereas iron loss occurs passively. The liver-produced peptide hepcidin controls the plasma iron concentration by inhibiting iron export by ferroportin from enterocytes (B) and macrophages (C). This means that an increased hepcidin production leads to a decrease in plasma iron concentrations. Hepcidin expression is regulated by body iron stores, inflammation, erythroid iron demand, and hypoxia via regulation pathways involving expression of *HFE, TfR2, TfR1* and *HJV* genes. Details are discussed in the text and in figure 3. DMT1: divalent metal transporter 1; Hb: hemoglobin; HO: heme oxygenase; NTBI: non-transferrin bound iron; Tf: transferrin; Cp: ceruloplasmin; HCP1: heme carrier protein 1; DcytB: duodenal cytochrome B. *Adapted and reproduced with permission from Swinkels et al. Clin Chem 2006.*[1]

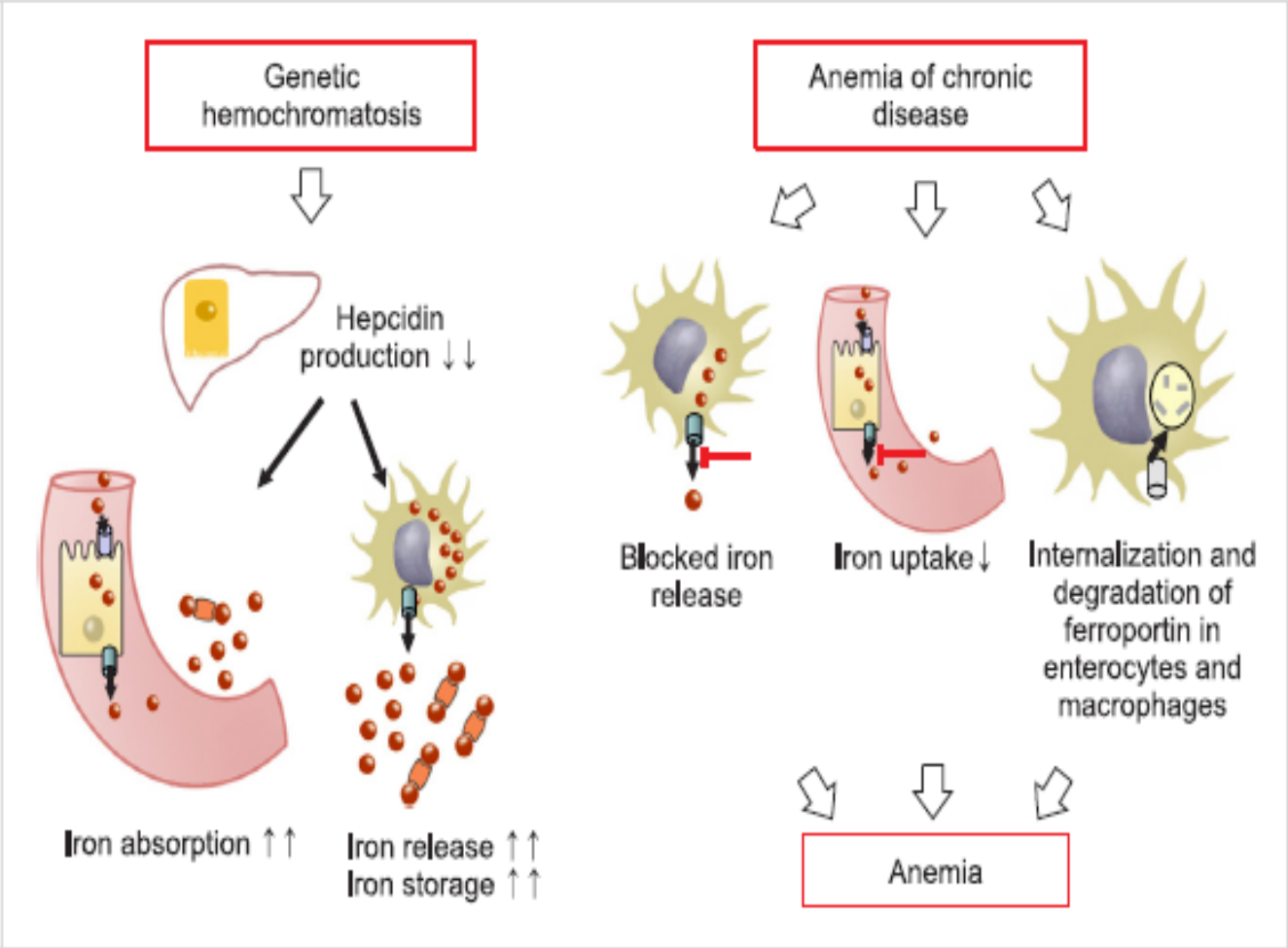


Fig. 2. Pathophysiology o
chromatosis and anemia
nic disease.

Early detection of colorectal cancer

- Determine risk status
- Determine best screening modality
- Determine when to start screening
- Determine interval of testing
- For cause evaluation appropriate at ANY time
  - Iron deficiency anemia
    - Low ferritin
    - Microcytic/hypochromic rbc's
    - Elevated TIBC, low serum iron
  - Change in bowel habits
  - Blood in stool
  - Iron deficiency without anemia

Evaluating the Patient with Anemia

– If MCV < 80, then it's a microcytic anemia

- **The three most common causes for microcytic anaemia are:**
  - **Iron deficiency**
  - **Thalassaemia**
  - **Anaemia of Chronic disease**

    - Check serum iron, ferritin, TIBC
      - If iron-deficiency anemia, look for sources of chronic bleeding – heavy menstrual bleeding, consider colonoscopy
    - Consider lead poisoning, copper deficiency, thalassemias.

PICA

- INGESTING FOREIGN MATERIAL
- FE DEFICIENCY IS ASSOCIATED WITH PICA FOR ICE
- NO MECHANISM HAS BEEN ESTABLISHED FOR THIS BEHAVIOR

IRON DEFICIENCY

- THROMBOCYTOSIS
- THROMBOCYTPENIA

KOILONYCHIA

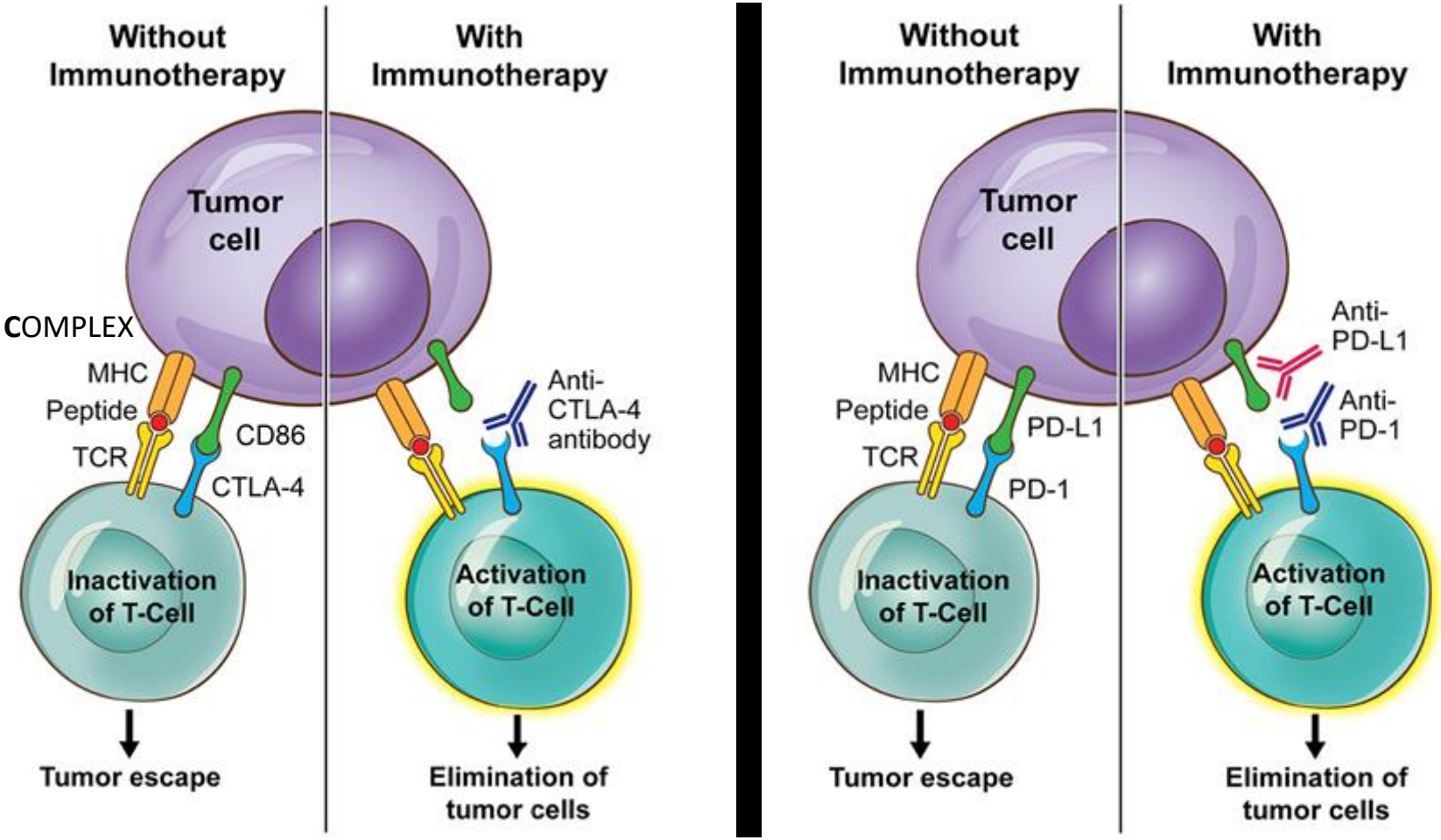
COLORECTAL CANCER

THERAPY

Mechanism of Action of Immune Checkpoint Inhibitors

Anti-CTLA-4 Pathway

Anti-PD-1/PD-L1 Pathway



MAJOR **H**ISTOCOMPATIBILITY **C**OMPLEX

Adapted from Soularue et al. *Gut.* 2018. For educational purposes only.

PD-1/PD-L1 Checkpoint Inhibition

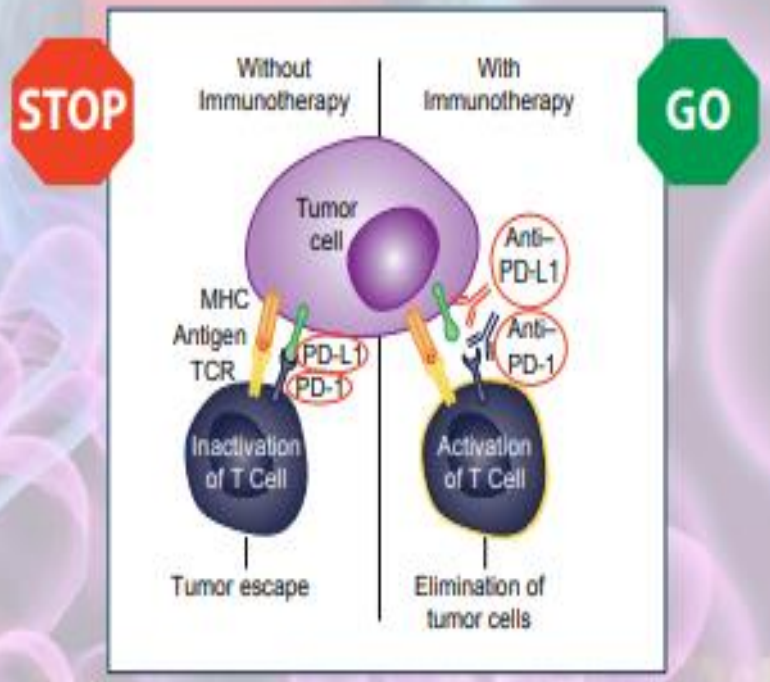
Tumor Microenvironment

PD-1 pathway inhibits signaling downstream of TCR

- TCR triggered by antigen presented by tumor cell
- Negative regulatory receptor PD-1 expressed and PD-L1 reactively expressed
- PD-L1 binds to PD-1

T cell inactivated

Tumor escape



Anti-PD-1 or anti-PD-L1 monoclonal antibodies block the interaction and negative regulation

T cell activated

Tumor attack

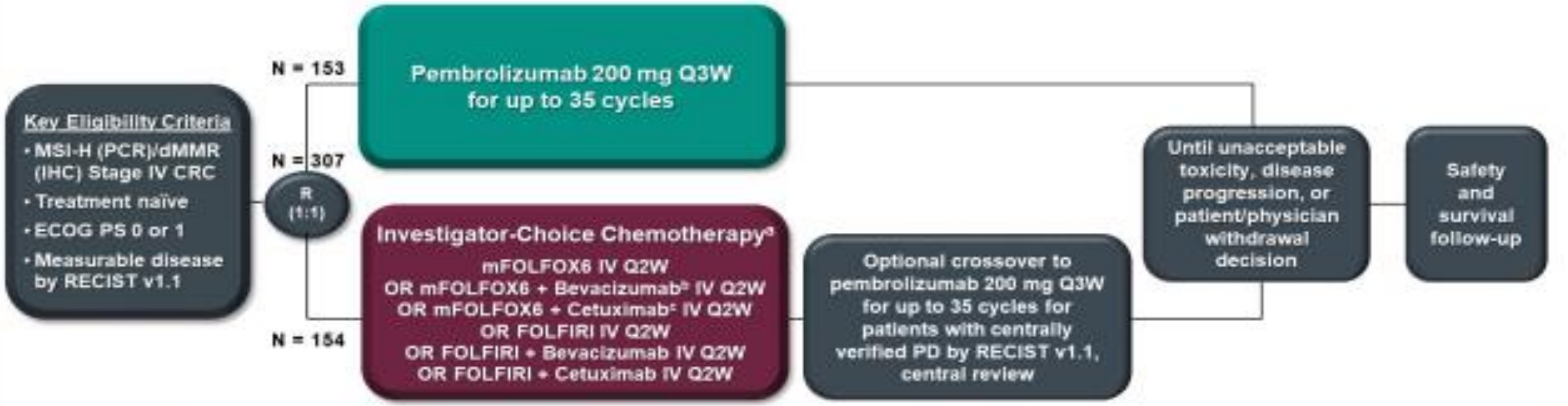
FDA-Approved Therapies

Anti-PD-1: Nivolumab, Pembrolizumab, Cemiplimab-rwlc

Anti-PD-L1: Atezolizumab, Avelumab, Durvalumab

Andre KN177FA ASCO 2021

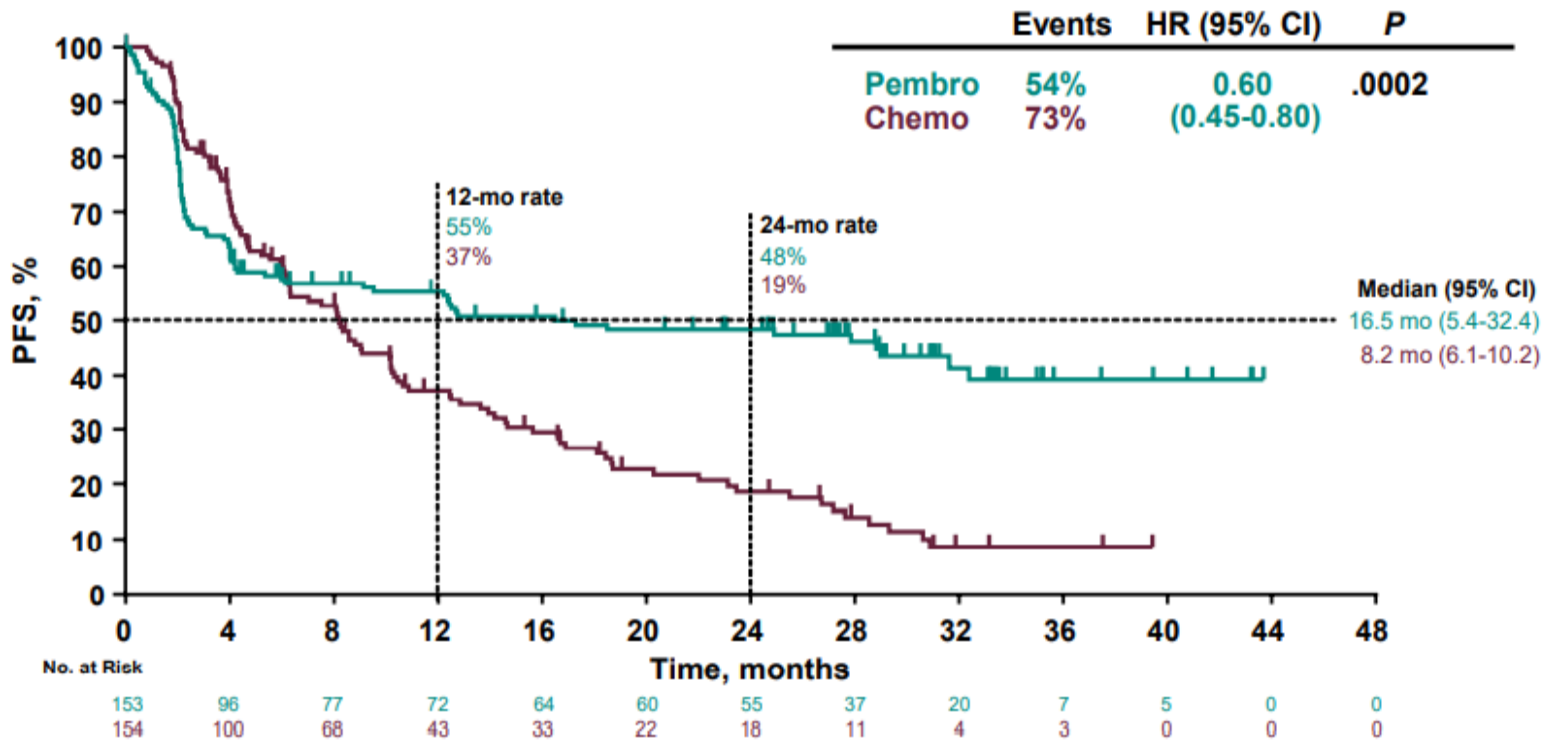
KEYNOTE-177 Study Design
(NCT02563002)



- Dual-Primary endpoints: PFS per RECIST v1.1, BICR; OS
- Secondary endpoints: ORR per RECIST v1.1 by BICR, PFS2, HRQoL, safety
- Tumor response assessed at week 9 and Q9W thereafter per RECIST v1.1 by BICR

[a]Chosen before randomization; [b]Bevacizumab 5 mg/kg IV; [c]Cetuximab 400 mg/m2 over 2 hours then 250 mg/mg^2 IV over 1 hour weekly.
BICR, blinded independent central review; IHC: immunohistochemistry with hMLH1, hMSH2, hMSH6, PMS2; PCR: polymerase chain reaction; PFS, progression-free survival; OS: overall survival; ORR: overall response rate; Q9W: every 9 weeks.

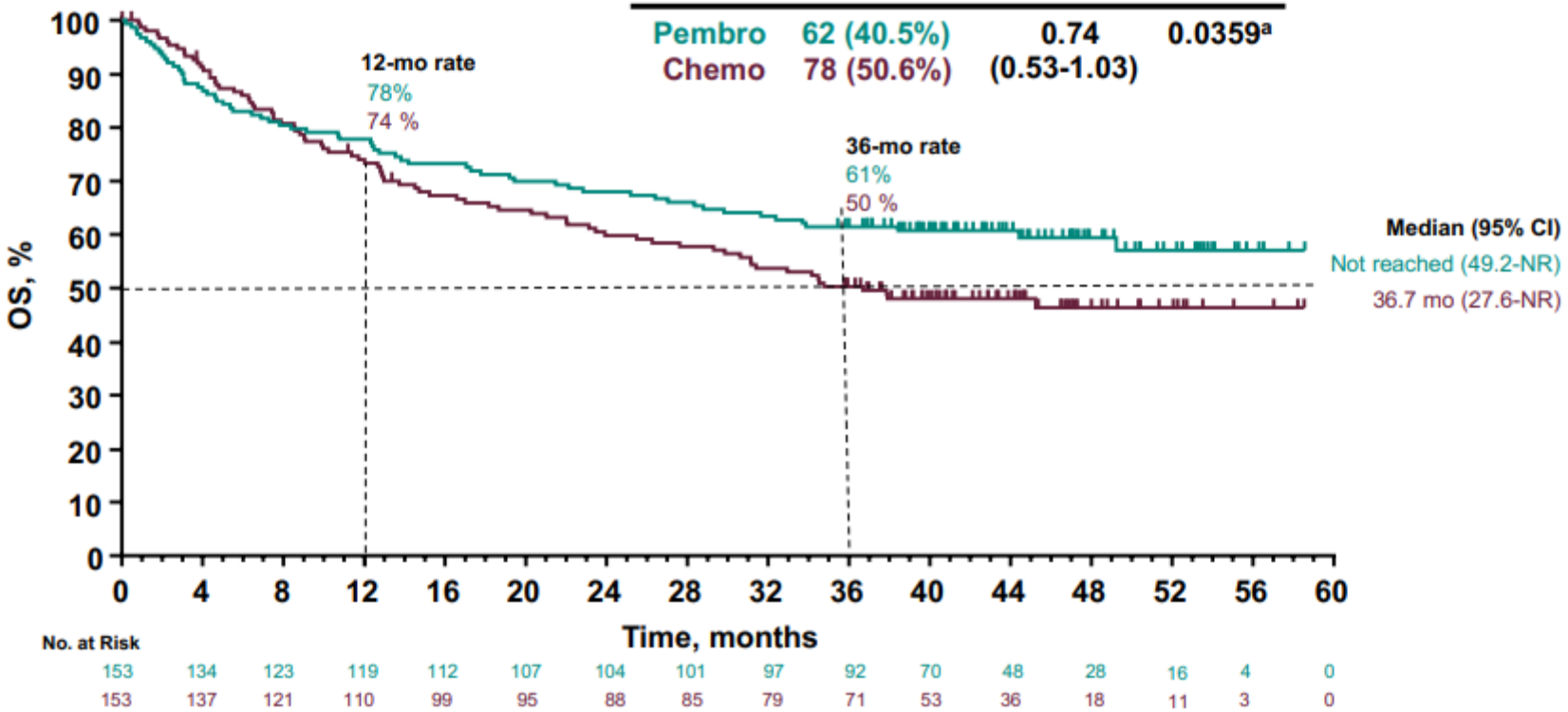
Progression-Free Survival



Median study follow-up: 32.4 months (range, 24.0–48.3); PFS (time from randomization to first documented disease progression or death) assessed per RECIST v1.1 by BICR.
Superiority of pembrolizumab vs chemotherapy for PFS was demonstrated at the prespecified one-sided α = 0.0117. Data cutoff: 19 Feb 2020.
Andre et al. *N Engl J Med.* 2020.

Overall Survival

	Events, n (%)	HR (95% CI)	*P*
Pembro	62 (40.5%)	0.74	0.0359[a]
Chemo	78 (50.6%)	(0.53-1.03)	

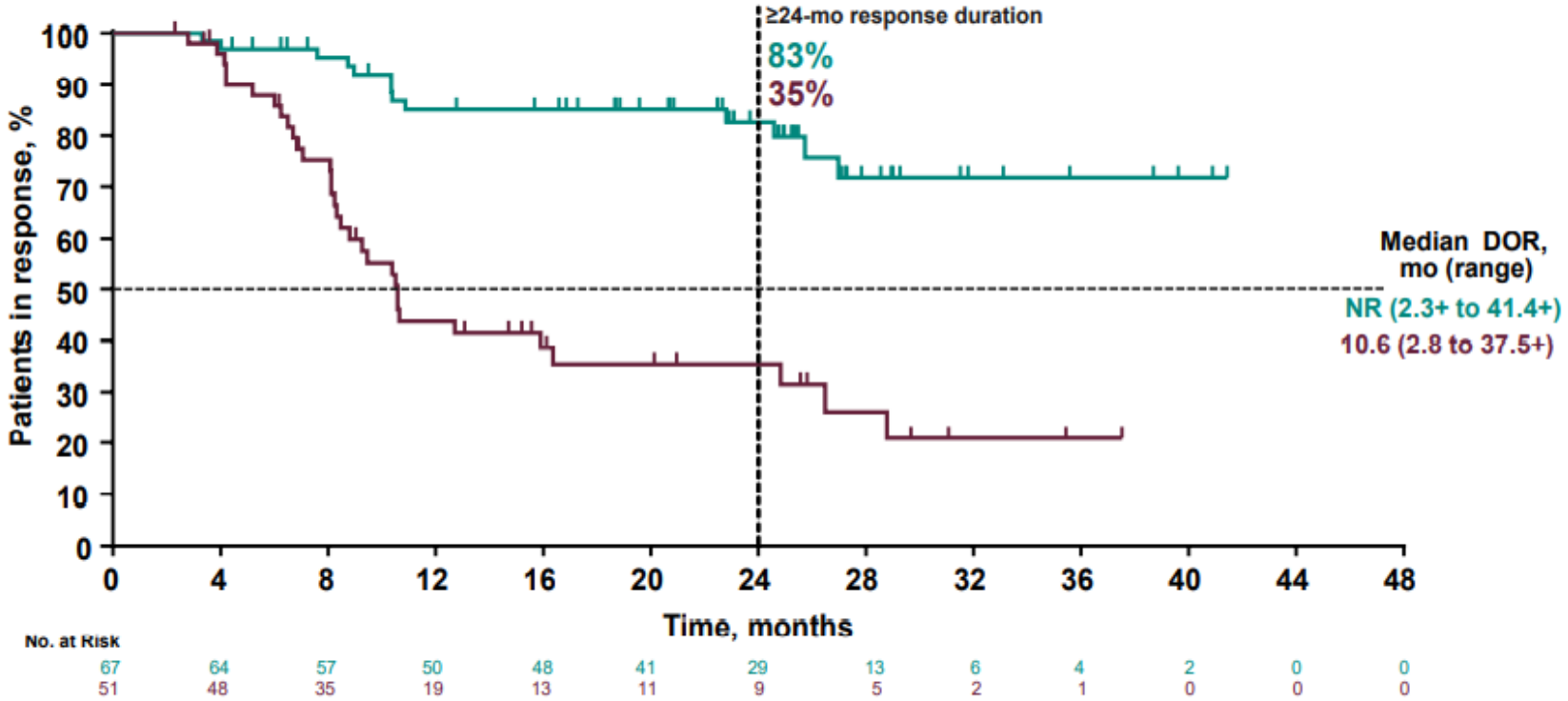


[a]Pembrolizumab was not superior to chemotherapy for OS as one-sided α > 0.0246. Pre-specified sensitivity analyses to adjust for crossover effect by rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38). Data cut-off: 19Feb2021.

Andre et al; NEJM 2020

VANDERBILT-INGRAM CANCER CENTER

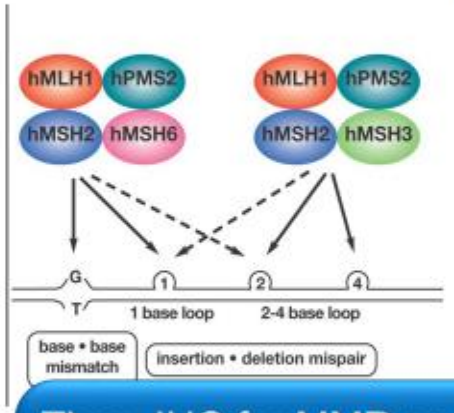
Duration of Response



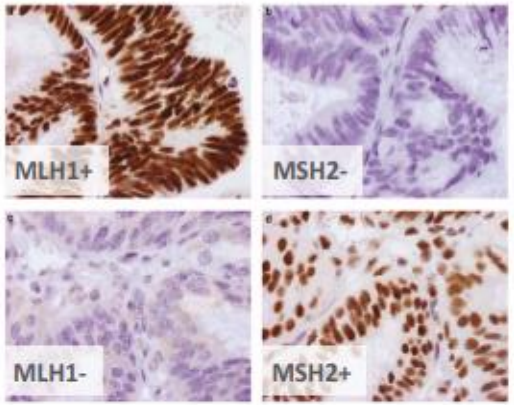
APTITUDE HEALTH

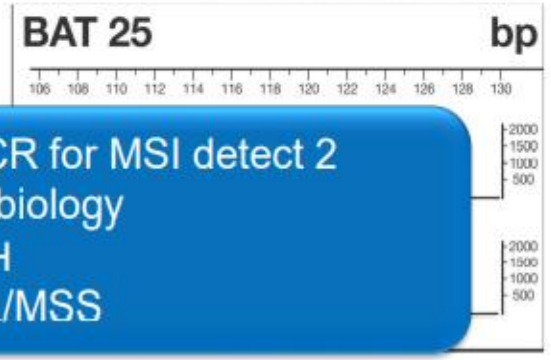
Duration of response assessed per RECIST v1.1 by BICR; data cutoff: 19 Feb 2020.
Andre et al. *N Engl J Med*. 2020.

Mismatch Repair Deficiency (MMR-D): Unique Biologic Subgroup of Colon Cancer



IHC for MMR protein status



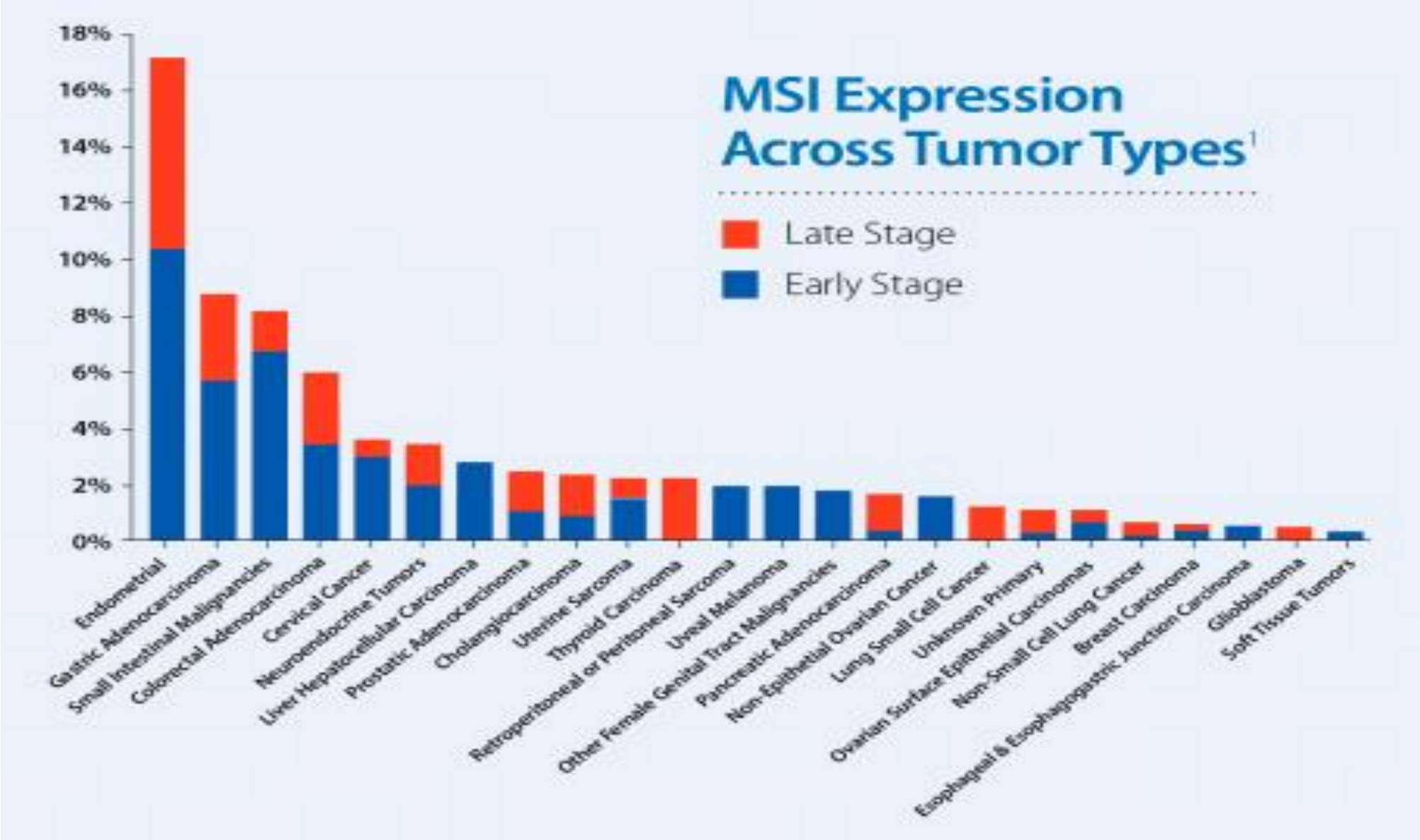


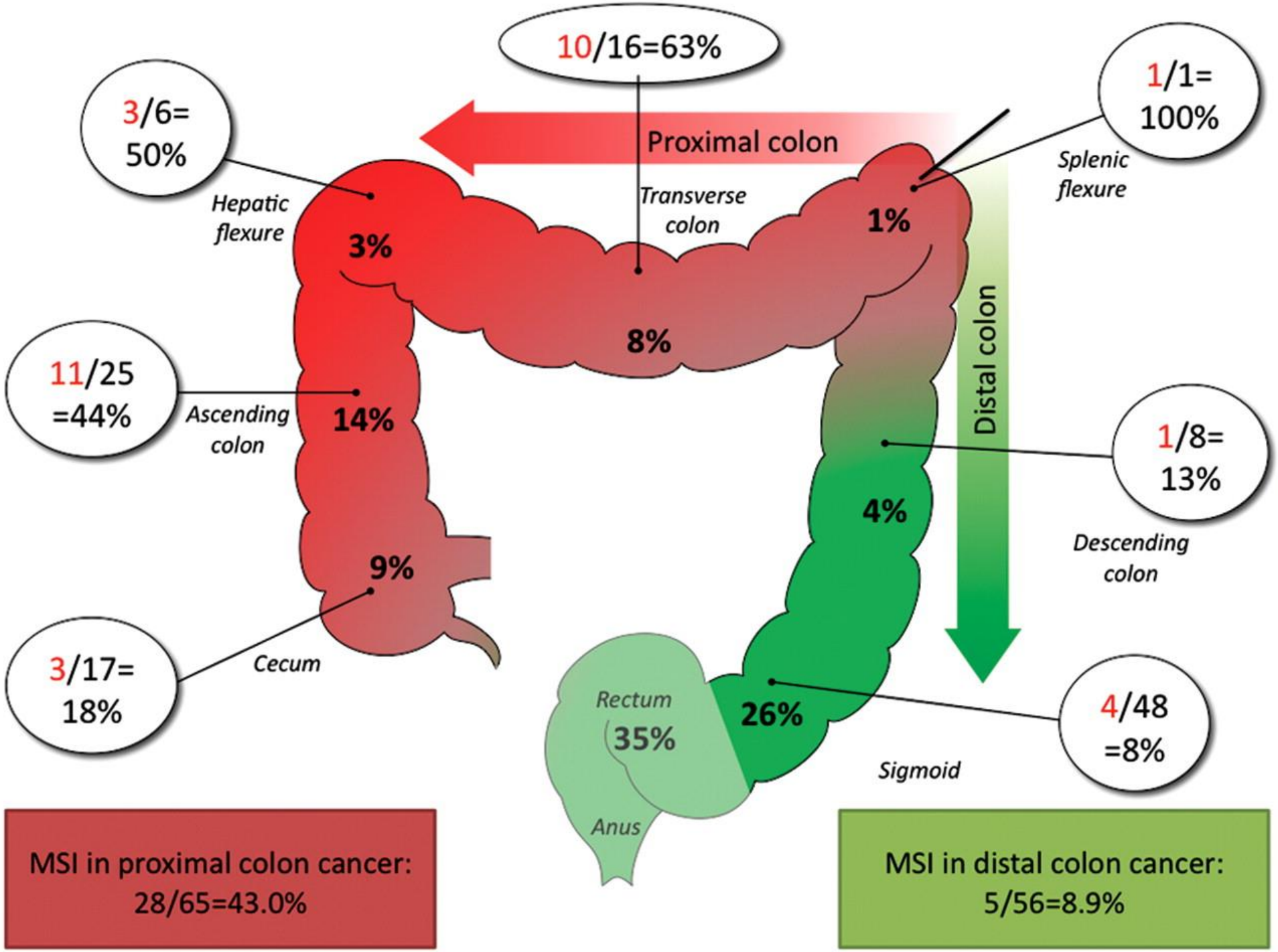
Thus, IHC for MMR proteins and PCR for MSI detect 2 manifestations of the same tumor biology

- MMR-D is synonymous with MSI-H
- MMR-P is synonymous with MSI-L/MSS

APTITUDE HEALTH

Imai K, et al. *Carcinogenesis*. 2008;29:673-680; Umetani N, et al. *Ann Surg Oncol*. 2000;7:276-280; Rosen DG, et al. *Mod Pathol*. 2006;19:1414-1420.


MSI Expression Across Tumor Types[1]
Late Stage
Early Stage
18%
16%
14%
12%
10%
8%
6%
4%
2%
0%
Endometrial
Gastric Adenocarcinoma
Small Intestinal Malignancies
Colorectal Adenocarcinoma
Cervical Cancer
Neuroendocrine Tumors
Liver Hepatocellular Carcinoma
Prostatic Adenocarcinoma
Cholangiocarcinoma
Uterine Sarcoma
Thyroid Carcinoma
Retroperitoneal or Peritoneal Sarcoma
Uveal Melanoma
Other Female Genital Tract Malignancies
Pancreatic Adenocarcinoma
Non-Epithelial Ovarian Cancer
Lung Small Cell Cancer
Unknown Primary
Ovarian Surface Epithelial Carcinomas
Non-Small Cell Lung Cancer
Breast Carcinoma
Esophageal & Esophagogastric Junction Carcinoma
Glioblastoma
Soft Tissue Tumors

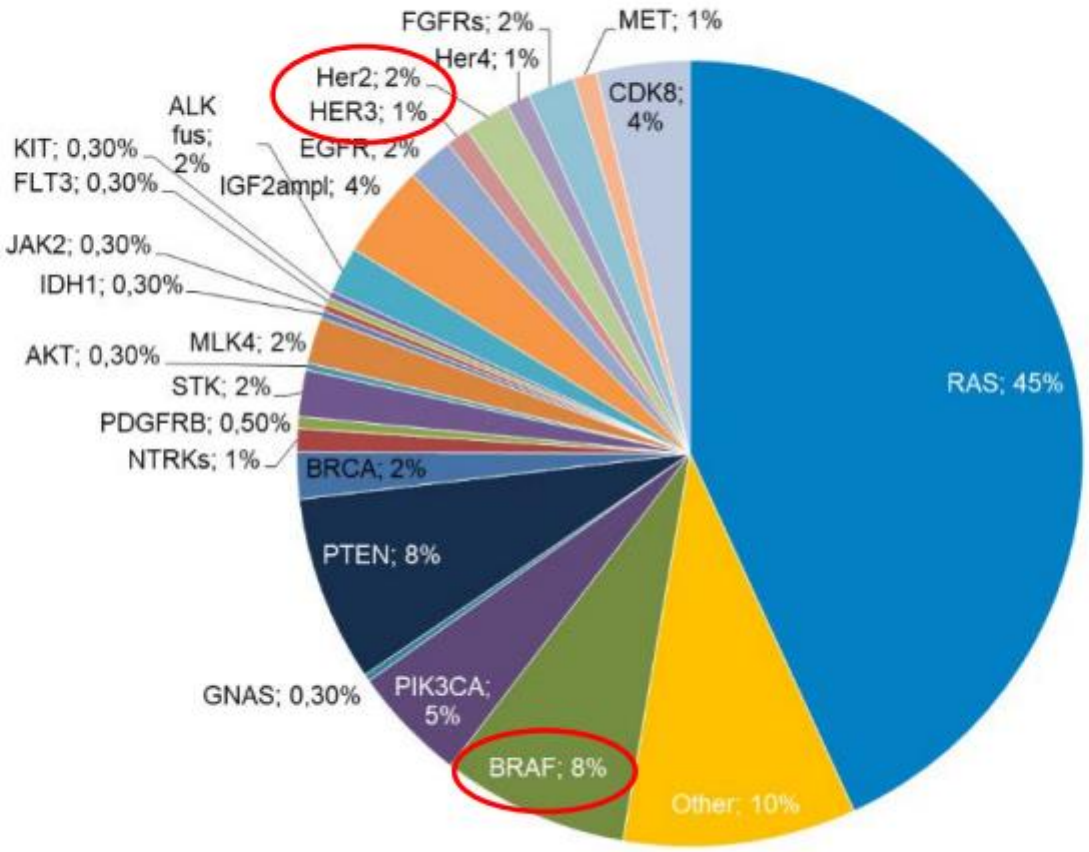

10/16=63%
Proximal colon
Transverse colon
8%
3/6= 50%
Hepatic flexure
3%
1/1= 100%
Splenic flexure
1%
Distal colon
11/25 =44%
Ascending colon
14%
1/8= 13%
Descending colon
4%
9%
Cecum
3/17= 18%
Rectum
35%
26%
Sigmoid
4/48 =8%
Anus
MSI in proximal colon cancer: 28/65=43.0%
MSI in distal colon cancer: 5/56=8.9%

THE HUMAN GENOME PROJECT (HGP) 1990 - 2003

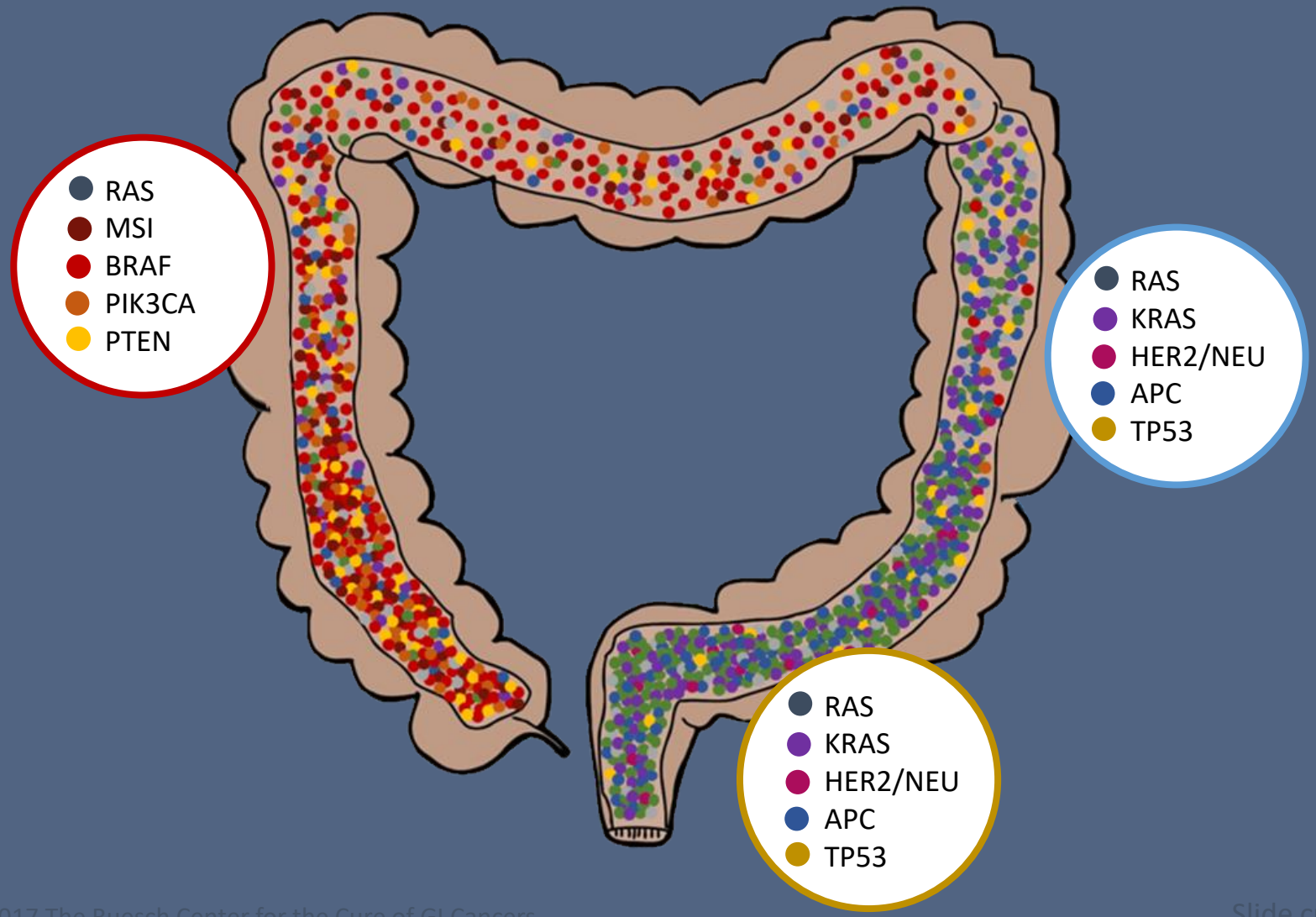
"The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity. In a symbolic sense, it is the heritage of humanity."

Universal Declaration on the Human Genome and Human Rights

Gene Mutations / Fusions in Colorectal Cancer



Molecular Heterogeneity by Sidedness

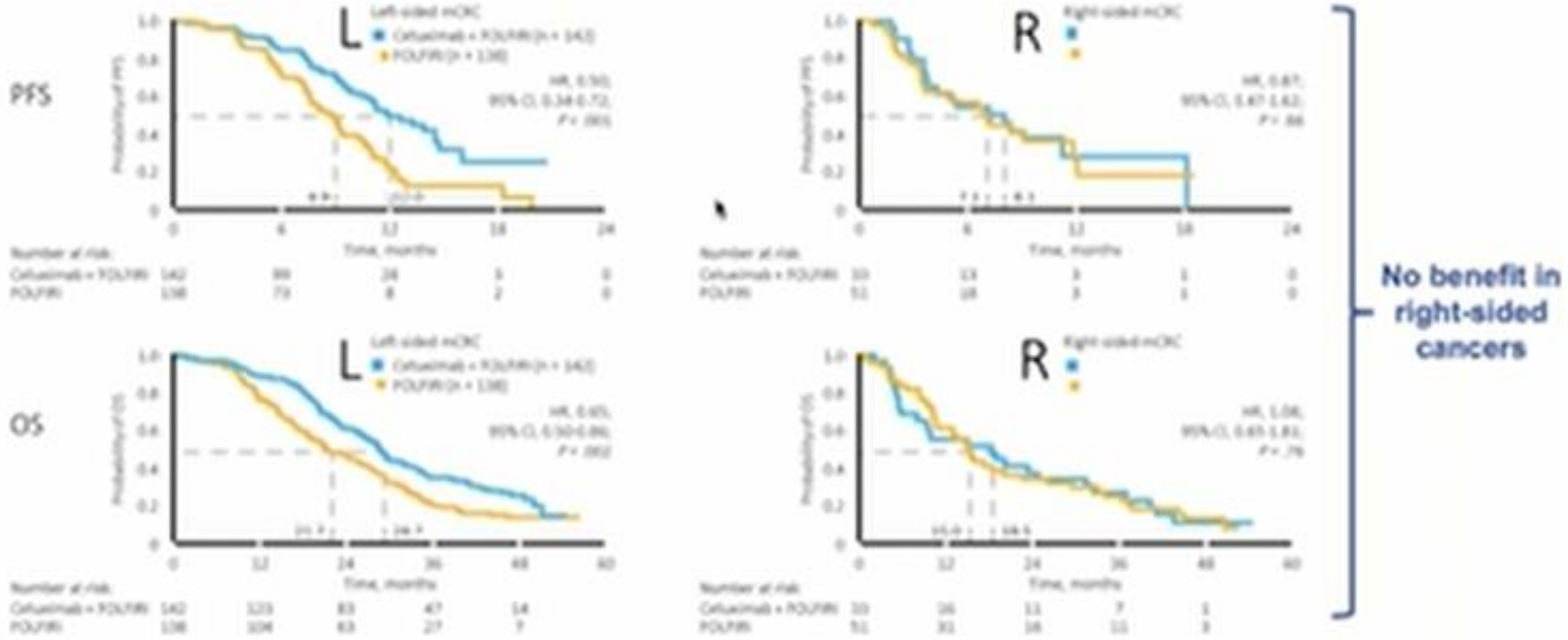


Reprinted with permission. © 2017 The Ruesch Center for the Cure of GI Cancers.

Slide credit: clinicaloptions.com

Impact of sidedness on frontline chemotherapy trials in mCRC (prediction)

CRYSTAL: *FOLFIRI +/- Cetuximab*



Tejpar S, et al. JAMA Oncol. 2017;3:194-201.

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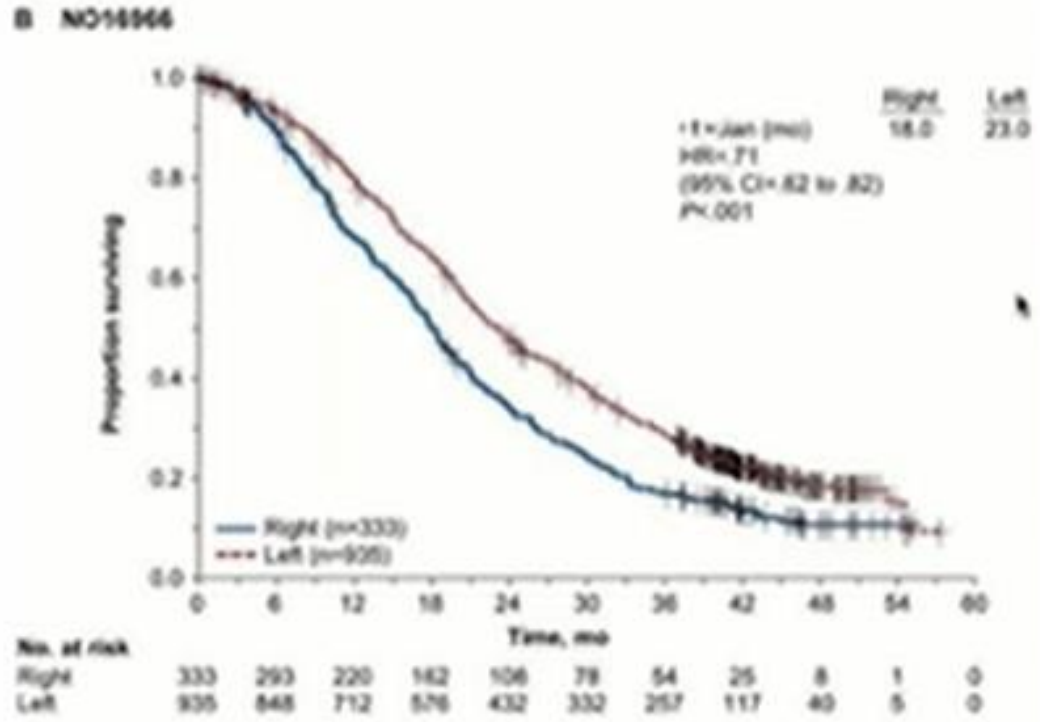
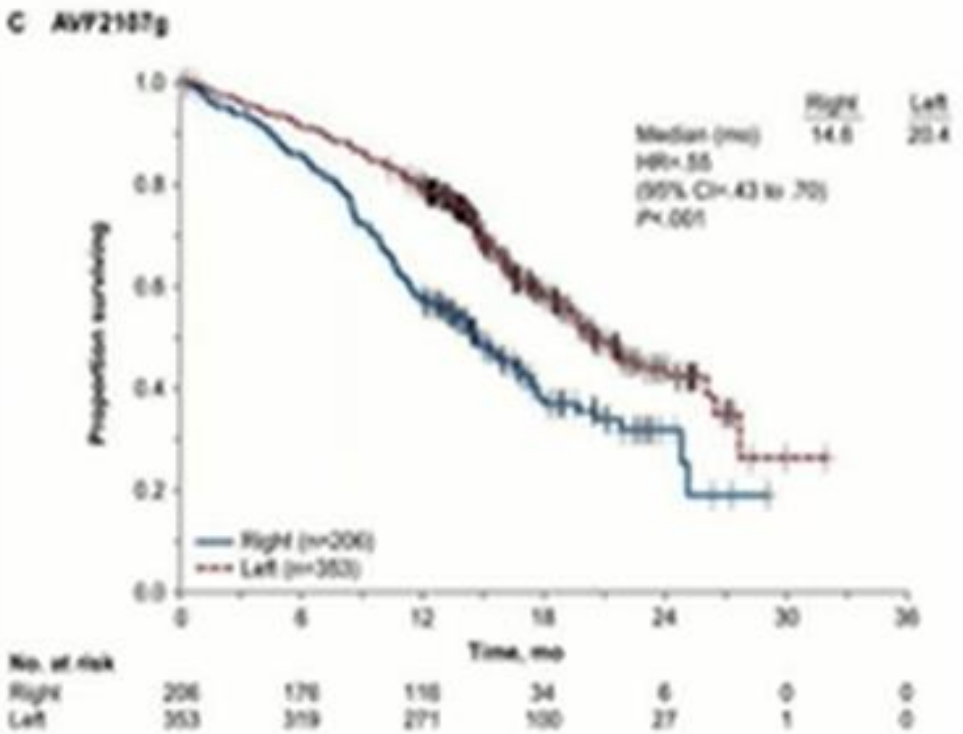
Impact of sidedness on frontline chemotherapy trials in mCRC (prognosis)





Loupakis et al. J Natl Can Net 2015;107(3)

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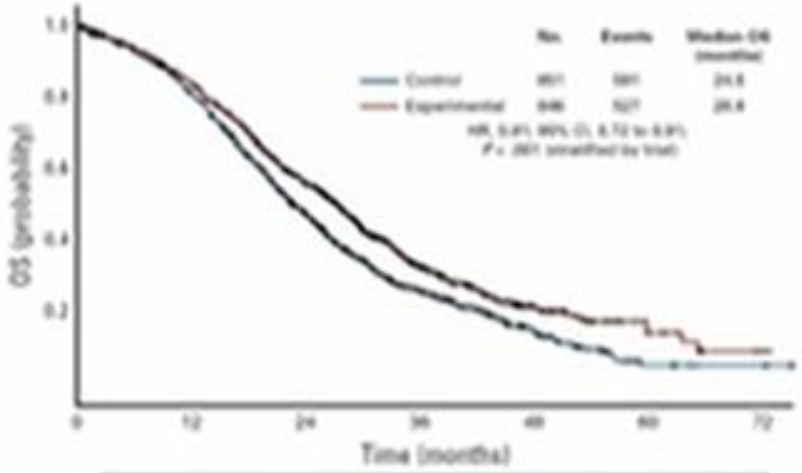
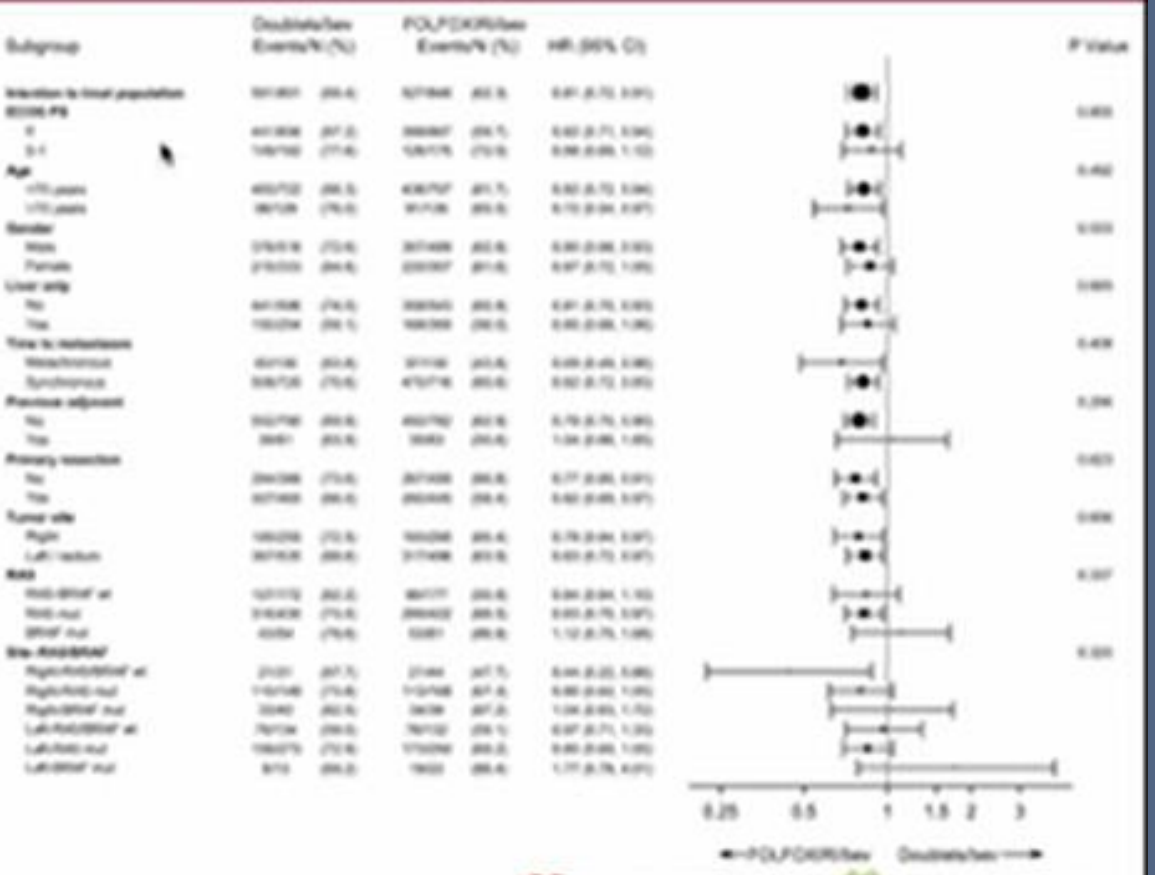
FOLFOXIRI/Bev vs. doublet/Bev (meta-analysis)

- 5 RCTs, N=1697

Median OS: 28.9m vs 24.5m
P<0.001



R0 resection
Folfoxiri vs doublet: 16.4% vs. 11.8%
P =0.007



Cremolini et al. JCO 2020

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31

Conclusion I (Frontline Treatment)

- Bev + FOLFOXIRI represents a new SOC for mCRC
  - Feasible and consistently superior to doublet therapy for overall survival
  - Though, not for all patients (Good PS; Caution in Elderly; no adjuvant oxaliplatin)
- Left-sided CRC have better OS than right sided CRC
- The Ideal anti-EGFR patient is left-sided RAS wt, HER2 non-amplified
- dMMR/MSI-H patients should get PD1 based therapy as frontline

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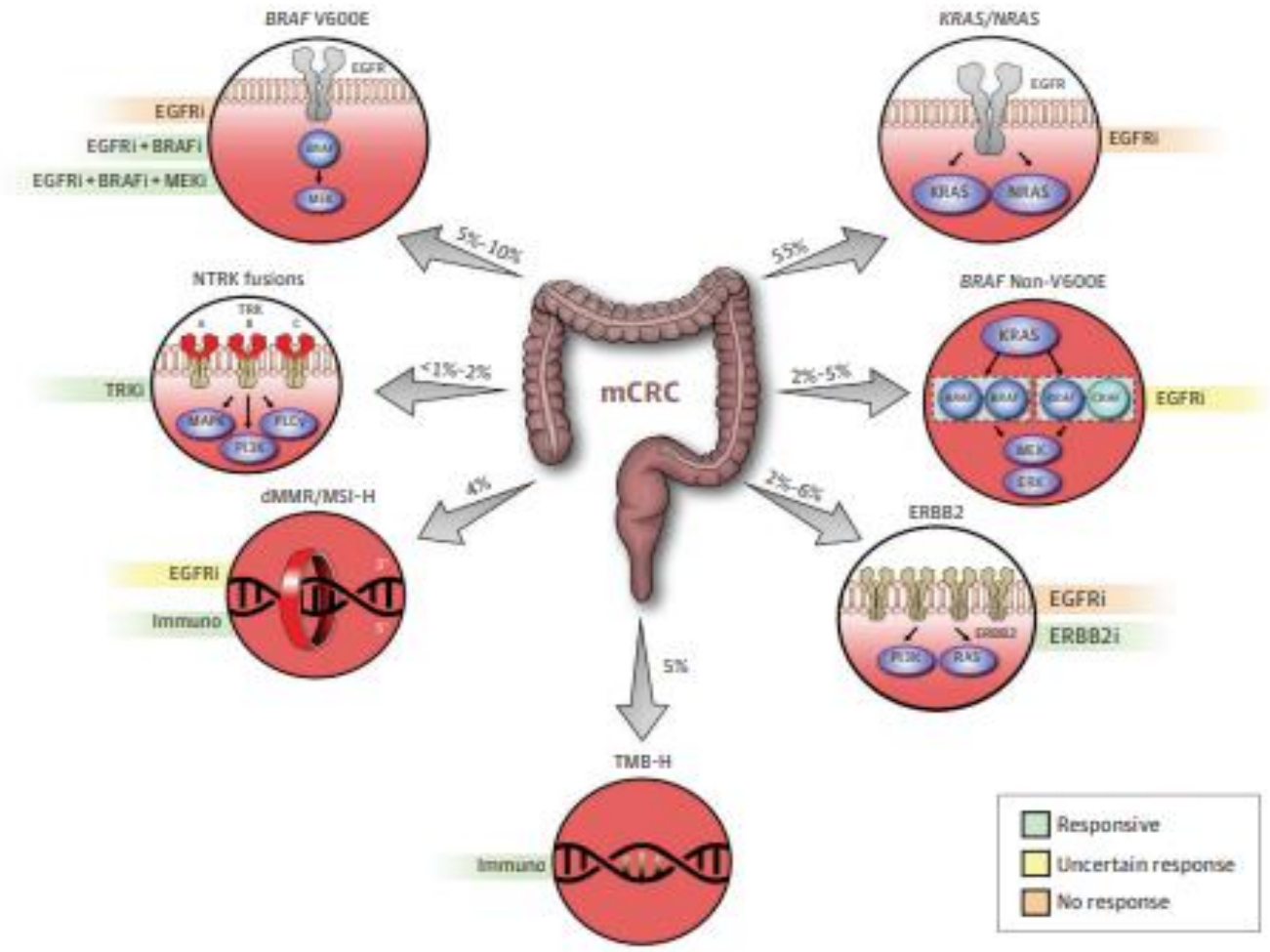
Figure 1. Established or Investigational Biomarkers for Treating Metastatic Colorectal Cancer (mCRC)

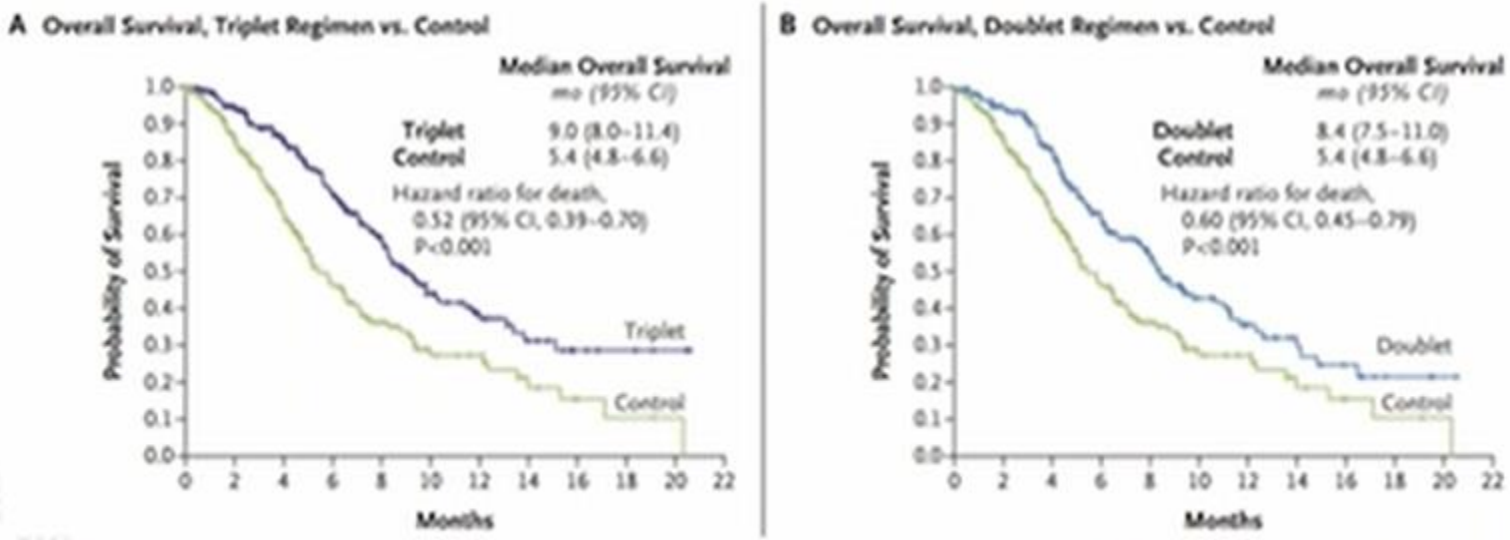


Colored boxes display the treatment approaches associated with each biomarker and if patients were responsive to the treatment (green), if the treatment was under investigation and response was uncertain (yellow), and if patients were not responsive (orange). Adapted from Lee et al (published as Open Access).[3] BRAFi, indicates BRAF inhibitor; dMMR, deficient mismatch repair; EGFRi, epidermal growth factor receptor inhibitor; ERBB2i, human epidermal growth factor receptor 2 inhibitor; Immuno, immunotherapy; MSI-H, microsatellite instability high; NTRK, neurotrophic tyrosine receptor kinase; TMB, tumor mutation burden; TRKi, tropomyosin receptor kinase inhibitor.

39

BRAF V600E: BEACON Regiment (Encorafenib + Cetuximab)

- Response Rate: 26% triplet vs. 20% doublet vs. 2% chemotherapy
- PFS: 4.3m triplet vs 4.2m doublet vs. 1.5m chemotherapy



Kopetz et al. NEJM 2019

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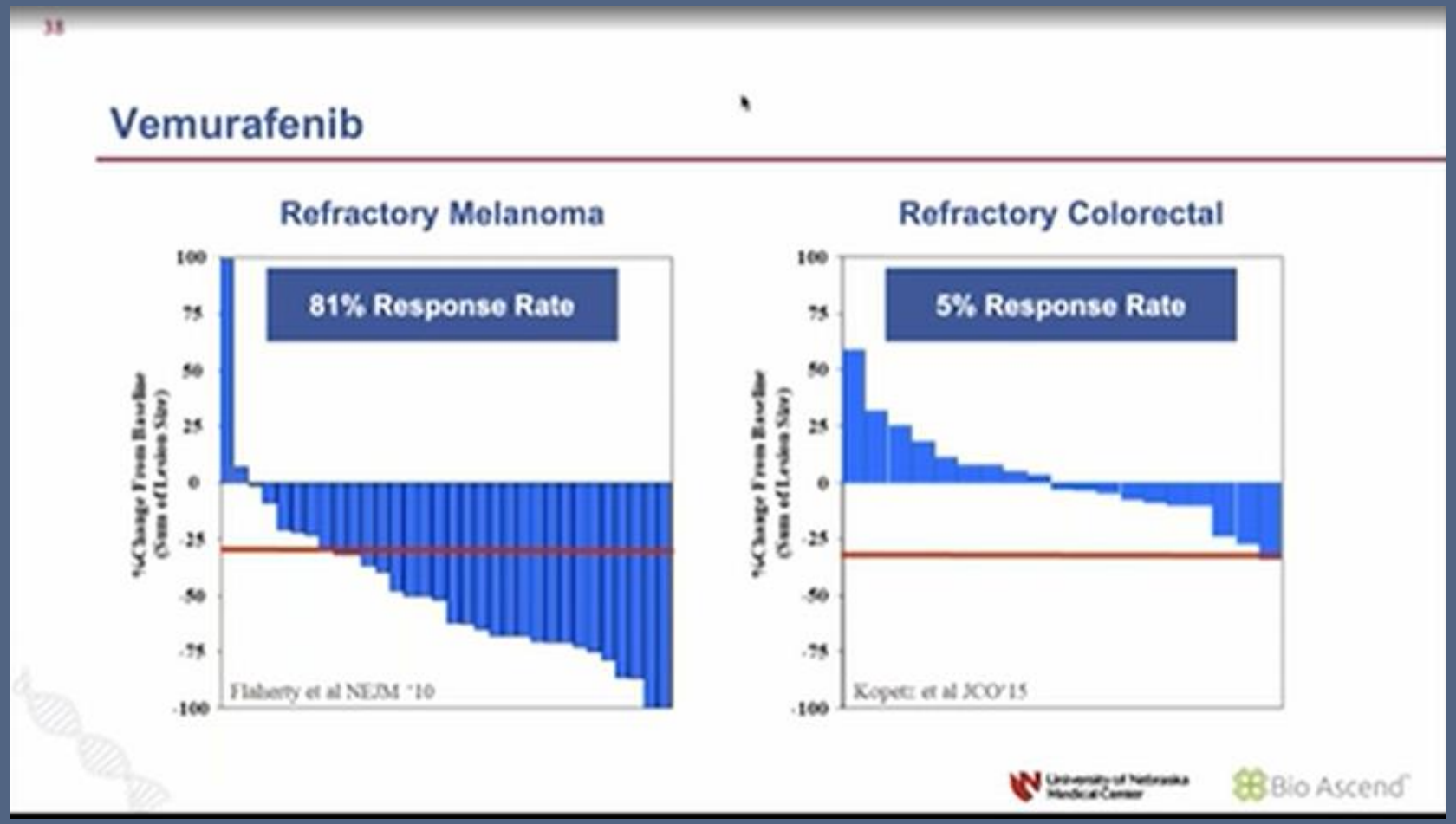
Vemurafenib
Refractory Melanoma
81% Response Rate
%Change From Baseline (Sum of Lesion Size)
100
75
50
25
0
-25
-50
-75
-100
Flaherty et al NEJM '10
Refractory Colorectal
5% Response Rate
%Change From Baseline (Sum of Lesion Size)
100
75
50
25
0
-25
-50
-75
-100
Kopetz et al JCO'15
University of Nebraska Medical Center
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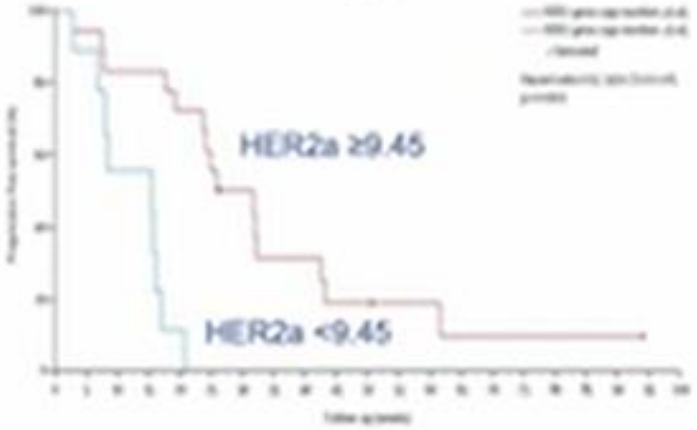
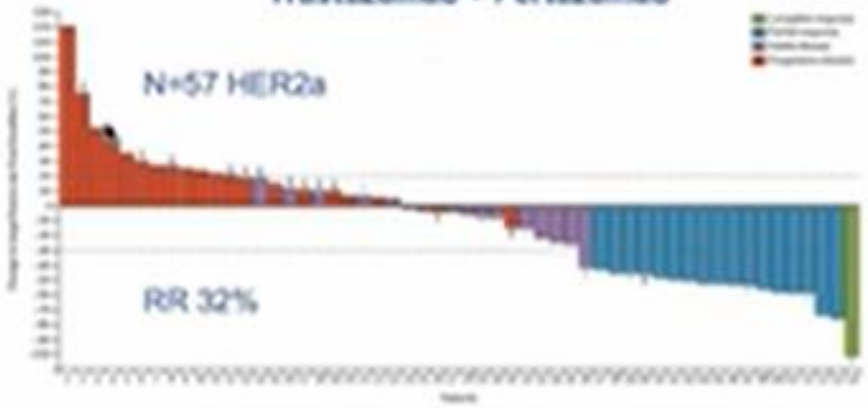
Dual HER2 Inhibition in HER2 Amp CRC

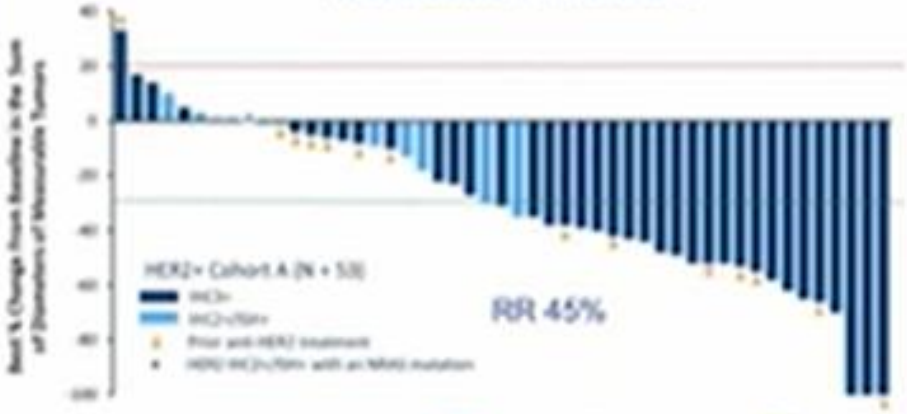
HERACLES Trial
Trastuzumab + Lapatinib



MyPathway Trail
Trastuzumab + Pertuzumab



DESTINY-CRC01
Trastuzumab-deruxtecan



Siena Lancet Oncol. 2017, Meric-Bernstam Lancet Onc 2019, Sienna ASCO 2020

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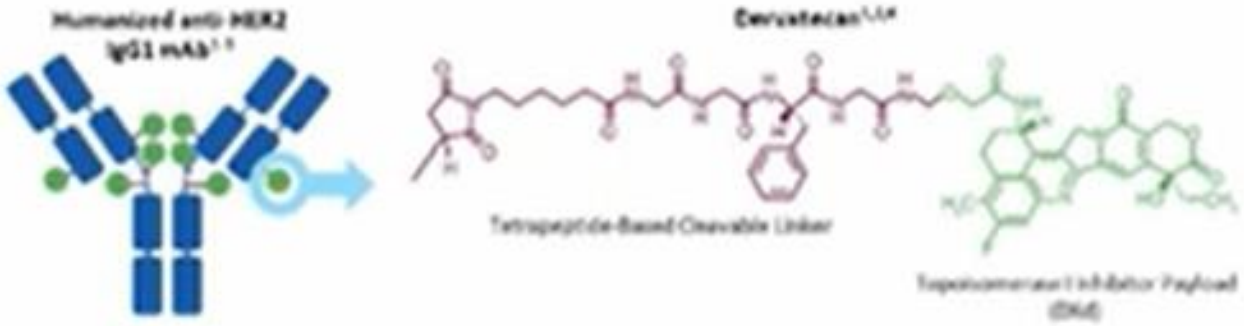
T-DXd Is a Novel ADC Designed to Deliver an Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



- Payload mechanism of action: topoisomerase I inhibitor
- High potency of payload
- High drug to antibody ratio = 8
- Payload with short systemic half-life
- Stable linker-payload
- Tumor-selective cleavable linker
- Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.

1. Nakada T, et al. Chem Pharm Bull (Tokyo). 2019;67(3):179-185. 2. Ogitani Y, et al. Clin Cancer Res. 2016;22(20):5097-5108. 3. Trail PA, et al. Pharmacol Ther. 2018;181:126-142. 4. Ogitani Y, et al. Cancer Sci. 2016;107(7):1039-1046.

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DESTINY-CRC01

AEs of Special Interest: Interstitial Lung Disease

	All Patients (N = 78)					
Preferred Term, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade/ Total
Interstitial Lung Disease	0	2 (2.6)	1 (1.3)	0	2 (2.6)	5 (6.4)

Among the 5 total events:

- Median time to investigator-reported onset was 80 days (range, 22-132)
- 5 of 5 patients with grade ≥ 2 ILD received corticosteroids
- 2 patients recovered, 1 did not recover (later died due to disease progression), and 2 died
- In the 2 fatal cases, onset was from 40-126 days, both received steroids as part of treatment, and death occurred 6-18 days after diagnosis

Protocol recommendations: Monitor for symptoms. Hold T-DXd and start steroids as soon as ILD is suspected

Drug related ILD was determined by an Independent ILD Adjudication Committee based on 44 preferred terms.
One additional grade 5 ILD case in Cohort B was reported after the data cutoff. This case was adjudicated after data cutoff as drug-related ILD.

Presented by: Prof Salvatore Siena, Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

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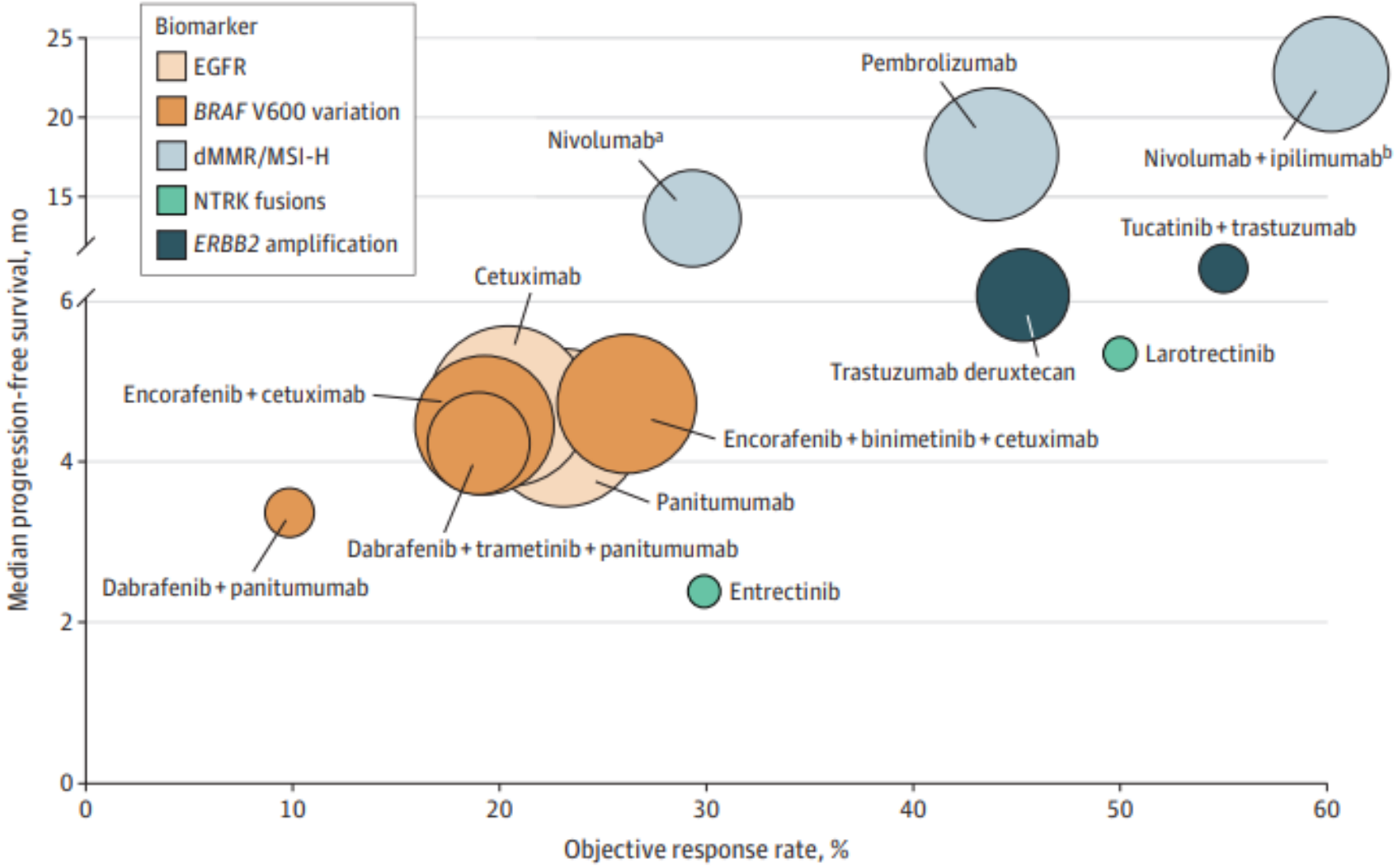
Figure 2. Studies of Biomarker-Driven Therapies in Metastatic Colorectal Cancer (mCRC)



Key efficacy data for treatment regimens in mCRC targeting epidermal growth factor receptor (EGFR),[4] *BRAF* V600 variation,[5,6] deficient mismatch repair (dMMR)/microsatellite instability high (MSI-H),[7-9] neurotrophic tyrosine receptor kinase (NTRK) fusion,[10,11] and *ERBB2* amplification.[12,13] The sizes of the circles represent the relative sample sizes. PFS indicates progression-free survival.

[a] Median PFS not reached. At 12 months, the estimated rate of PFS was 50.4% (95% CI, 38.1%-61.4%).

[b] Median PFS not reached (95% CI, 23 months-not estimable) at a median follow-up of 25.4 months.

BRAF and HER-2 Targeted Treatment mCRC

BRAF V600E mt

- Encorafenib / Cetuximab standard 2nd-line
- 1st-line ANCHOR trial: yet to be determined if favorable results

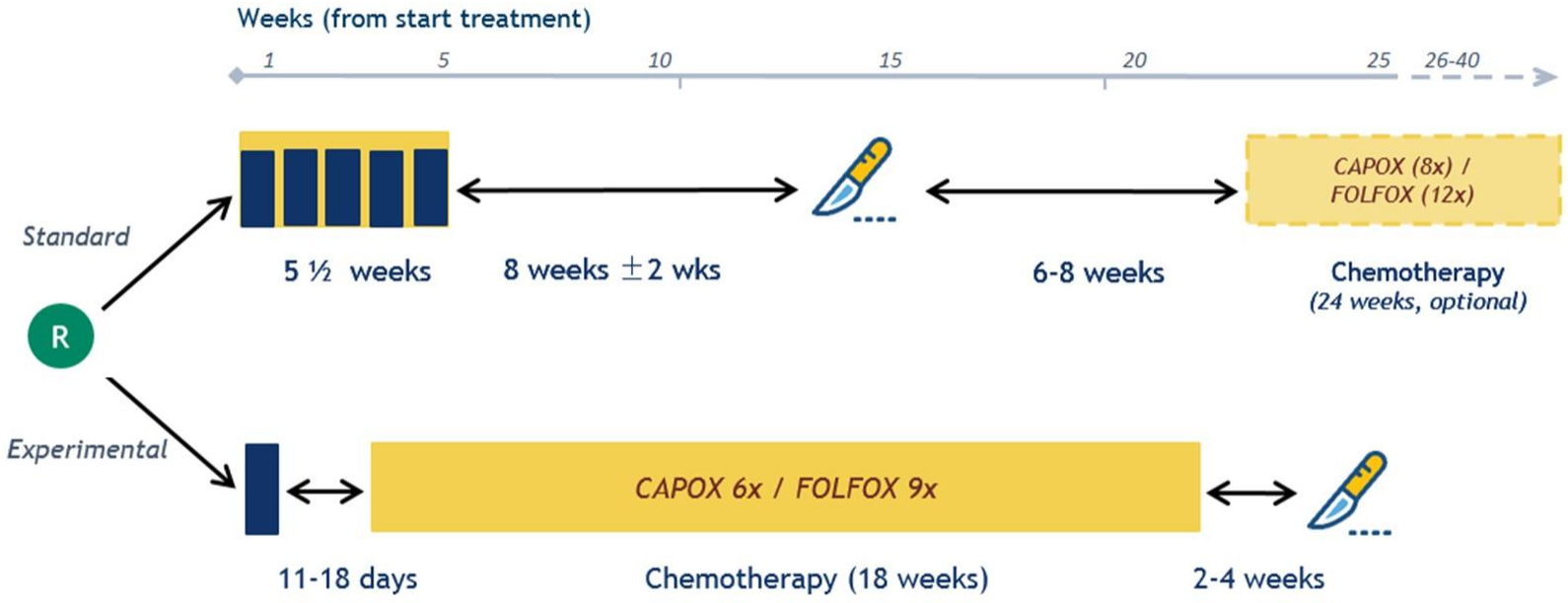
HER-2 amplification

- Variety of combinations with activity in subsequent line
- Trastuzamab/Deruxtecan promising but unique toxicity

CONCLUSIONS AND RELEVANCE The results of this review suggest the ERBB2 receptor is a promising target for patients with metastatic colorectal cancer; however, to date, no therapies are approved for use in this patient population. Therefore, it is imperative to continue to work to address this unmet need so that patients with ERBB2-positive metastatic colorectal cancer have therapeutic options should they become refractory to treatment with standard therapies.

JAMA Oncol. doi:10.1001/jamaoncol.2021.8196
Published online March 3, 2022.

Study design



Standard: week 1-6: 28x1.8 Gy or 25x2 Gy at working days combined with capecitabine b.i.d. 825 mg/m^2 (twice daily) day 1-33-38.
Experimental: week 1: 5x5 Gy, week 3-20: 6x CAPOX (capecitabine b.i.d.1000 mg/m^2 (twice daily) day 1-14 every 3 weeks orally, oxaliplatin 130 mg/m^2 day 1 every 3 weeks iv or alternatively 9x FOLFOX4 (folinic acid, fluorouracil and oxaliplatin all iv every 2 weeks)

Stay at home messages

SCRT → CAPOX → TME

- ✓ 7% lower Disease-related Treatment Failure: 30.4 to 23.9%
- ✓ 7% lower Distant Metastases rate: 26.8 to 20.0%
- ✓ Doubled pCR rate: 14 to 28%
- ✓ 3-year overall survival 89% in both treatment groups
- ✓ No unexpected toxicity
- ✓ No differences in surgery, postoperative complication and QoL