Banner MD Anderson Cancer Center
Making Cancer History®

COLON CANCER

Presented to: Banner University Medical Center-Internal Medicine

Presented by: **Madappa N. Kundranda. MD. PhD**.

Date: March 15th 2016

Banner MD Anderson Cancer Center
Making Cancer History®

What is the significance of this month in the context of todays talk?

DISCLOSURES

- No Relevant Financial Disclosures
- Will Discuss Investigational Techniques
- Will mainly be using USPSTF guidelines

Banner MD Anderson Cancer Center
Making Cancer History®

Objectives

- Understand the pathophysiology of CRC
- Importance of screening
- Evaluate common presentations of suspected CRC
- Management of CRC
- Newer innovative therapies

Banner MD Anderson Cancer Center
Making Cancer History®

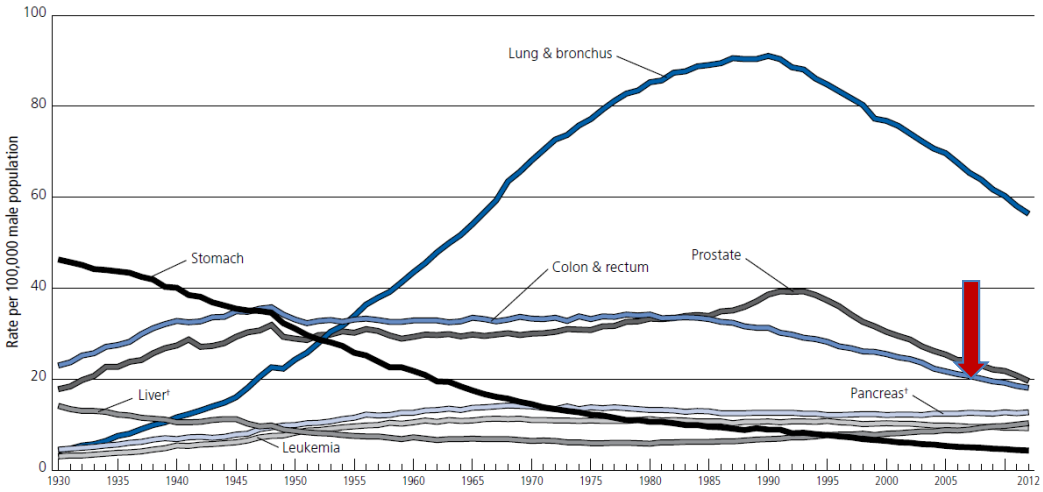
The Problem

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2016 Estimates

Estimated New Cases		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 180,890 (21%)	Breast 246,660 (29%)	Lung & bronchus 85,920 (27%)	Lung & bronchus 72,160 (26%)
Lung & bronchus 117,920 (14%)	Lung & bronchus 106,470 (13%)	Prostate 26,120 (8%)	Breast 40,450 (14%)
Colon & rectum 70,820 (8%)	Colon & rectum 63,670 (8%)	Colon & rectum 26,020 (8%)	Colon & rectum 23,170 (8%)
Urinary bladder 58,950 (7%)	Uterine corpus 60,050 (7%)	Pancreas 21,450 (7%)	Pancreas 20,330 (7%)
Melanoma of the skin 46,870 (6%)	Thyroid 49,350 (6%)	Liver & intrahepatic bile duct 18,280 (6%)	Ovary 14,240 (5%)
Non-Hodgkin lymphoma 40,170 (5%)	Non-Hodgkin lymphoma 32,410 (4%)	Leukemia 14,130 (4%)	Uterine corpus 10,470 (4%)
Kidney & renal pelvis 39,650 (5%)	Melanoma of the skin 29,510 (3%)	Esophagus 12,720 (4%)	Leukemia 10,270 (4%)
Oral cavity & pharynx 34,780 (4%)	Leukemia 26,050 (3%)	Urinary bladder 11,820 (4%)	Liver & intrahepatic bile duct 8,890 (3%)
Leukemia 34,090 (4%)	Pancreas 25,400 (3%)	Non-Hodgkin lymphoma 11,520 (4%)	Non-Hodgkin lymphoma 8,630 (3%)
Liver & intrahepatic bile duct 28,410 (3%)	Kidney & renal pelvis 23,050 (3%)	Brain & other nervous system 9,440 (3%)	Brain & other nervous system 6,610 (2%)
All sites 841,390 (100%)	All sites 843,820 (100%)	All sites 314,290 (100%)	All sites 281,400 (100%)

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Figure 1. Trends in Age-adjusted Cancer Death Rates* by Site, Males, US, 1930-2012

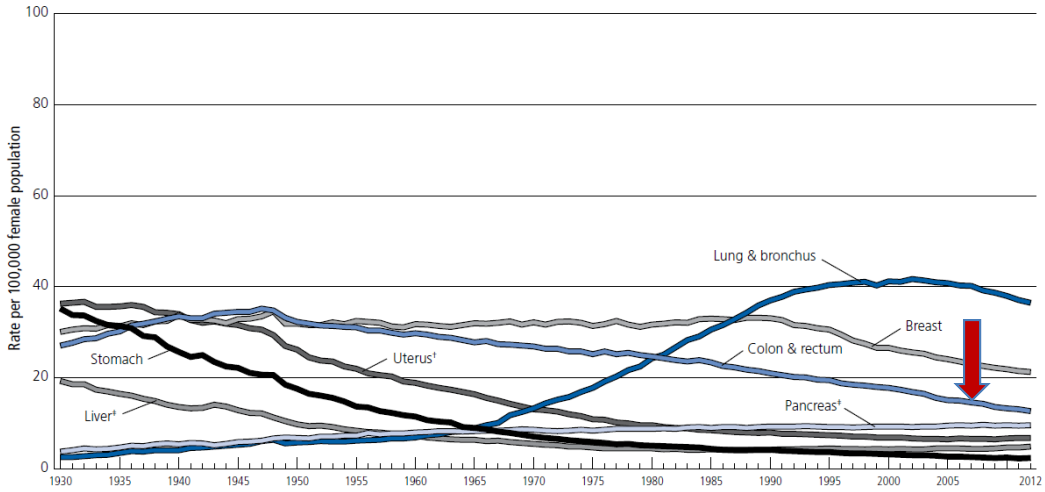


*Per 100,000, age adjusted to the 2000 US standard population. †Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959 and US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

Figure 2. Trends in Age-adjusted Cancer Death Rates* by Site, Females, US, 1930-2012

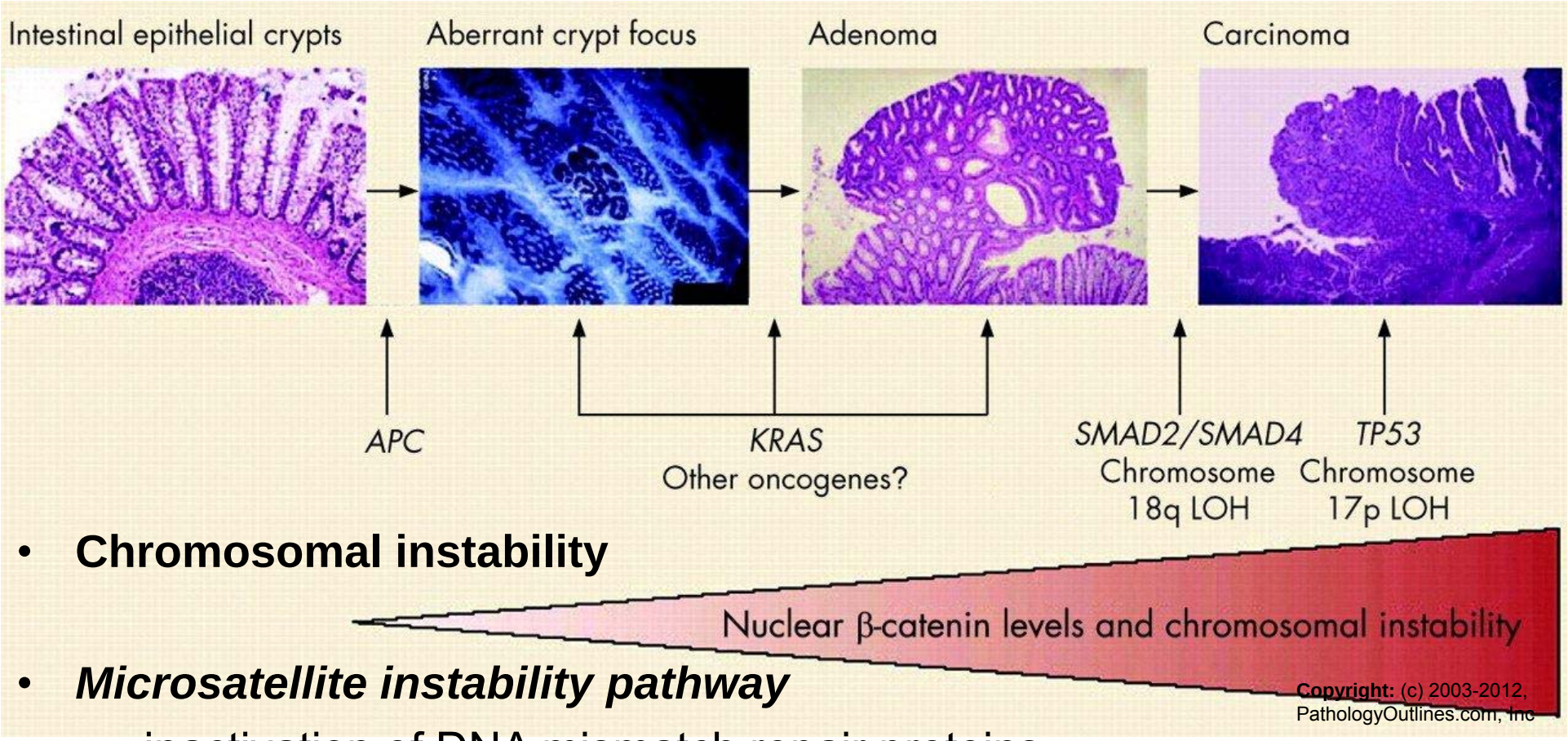


*Per 100,000, age adjusted to the 2000 US standard population. †Uterus refers to uterine cervix and uterine corpus combined. ‡Mortality rates for pancreatic and liver cancers are increasing.

Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the liver, lung and bronchus, and colon and rectum are affected by these coding changes.

Source: US Mortality Volumes 1930 to 1959, US Mortality Data 1960 to 2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

The ‘Suspected’ Cause - Pathogenesis



- **Chromosomal instability**
- ***Microsatellite instability pathway***
  - inactivation of DNA mismatch repair proteins
- ***CpG island methylator pathway (CIMP)***
  - underlies MSI associated with MLH1 hypermethylation

Banner MD Anderson Cancer Center
Making Cancer History®

Why is screening important?

- Lifetime Risk for CRC ~6%
  - >90% diagnosed >50 yrs
  - 5-7% diagnosed between 40-50 yrs

- Familial CRC
  - 5-10%
  - Majority is first degree relative (2-4 fold increase)
  - CRC syndromes can increase the lifetime risk – 80%*

- 1/3 of Americans report not being current on their screening†

Banner MD Anderson Cancer Center
Making Cancer History®

*Losi L et al , AJG, 2005; †US MMWR 2012

ARE **ALL** ADENOMAS ALIKE?

- Terminology can be confusing and misleading

- **Hyperplastic Polyp** – BENIGN
- **Advanced Adenoma**
  - 1cm or > with Villous component (villous or tubulovillous)

    OR
  - High-grade dysplasia
- **Serrated lesions**
  - Precursor esp. in the proximal bowel*

ADR: As a quality metric

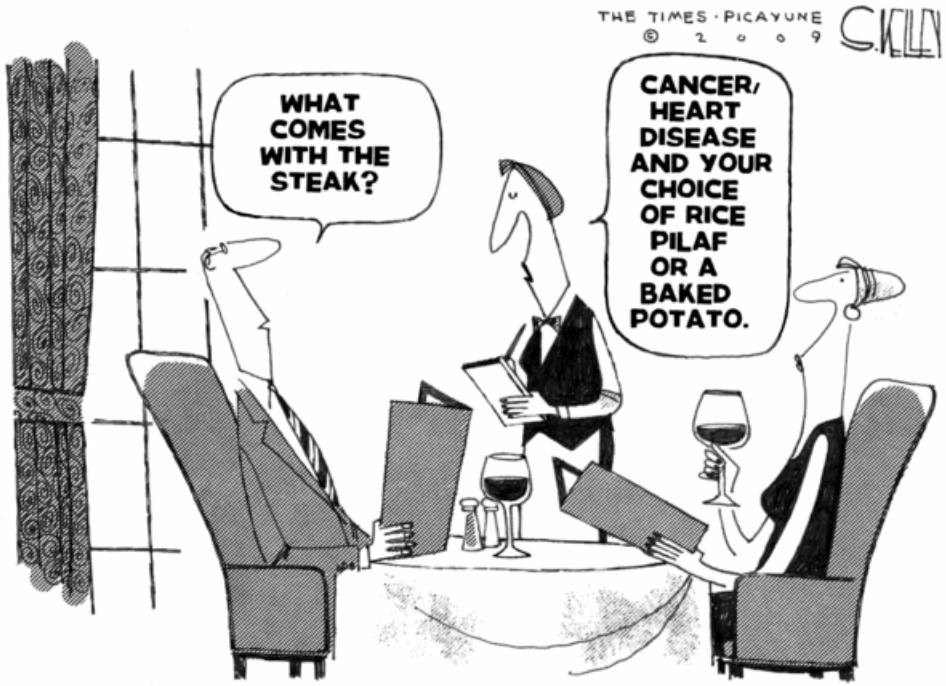
- <20%was assoc with a 11-fold increase in detecting CRC in 5 yrs†

Banner MD Anderson Cancer Center
Making Cancer History®

*Ferlitsch M et al;JAMA, 2011.†Kaminski MF et al;NEJM; 2010

Potential Risk Reduction Strategies

- Less Red



- Regular PE
- BMI
- Avoidance of ETOH
- 5-7 servings of fresh fruits and vegetables

NONE OF THESE HAVE SHOWN TO BE AS EFFECTIVE AS SCREENING

Banner MD Anderson ~~Cancer~~ Center
Making Cancer History®

Therefore the Key is Prevention!

- SCREENING
  - REDUCES INCIDENCE
  - PREVENTS CR MORBIDITY
  - MORTALITY

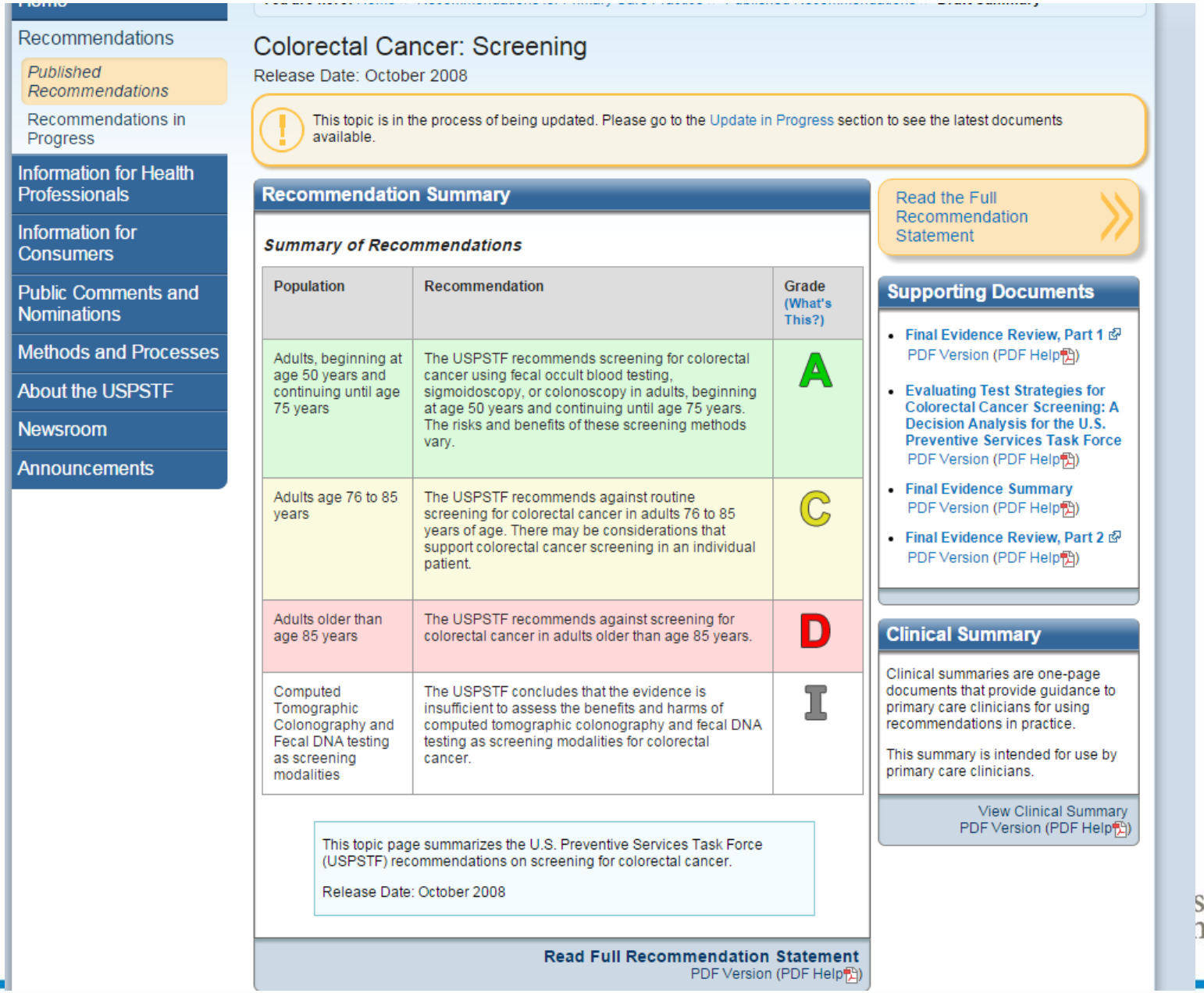
- More Recommendations Than Societies!!!!

Banner MD Anderson Cancer Center
Making Cancer History®

Ordinarily, that wouldn't bother me, except Doc did the same blindfold trick last week, when he did my colonoscopy.

MD Anderson Cancer Center
Making Cancer History®

"Current" USPSTF Guidelines



Recommendations

Published Recommendations

Recommendations in Progress

Information for Health Professionals

Information for Consumers

Public Comments and Nominations

Methods and Processes

About the USPSTF

Newsroom

Announcements

Colorectal Cancer: Screening

Release Date: October 2008

This topic is in the process of being updated. Please go to the Update in Progress section to see the latest documents available.

Recommendation Summary

Summary of Recommendations

Population	Recommendation	Grade (What's This?)
Adults, beginning at age 50 years and continuing until age 75 years	The USPSTF recommends screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until age 75 years. The risks and benefits of these screening methods vary.	A
Adults age 76 to 85 years	The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be considerations that support colorectal cancer screening in an individual patient.	C
Adults older than age 85 years	The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years.	D
Computed Tomographic Colonography and Fecal DNA testing as screening modalities	The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer.	I

This topic page summarizes the U.S. Preventive Services Task Force (USPSTF) recommendations on screening for colorectal cancer.

Release Date: October 2008

Read Full Recommendation Statement
PDF Version (PDF Help)

Read the Full Recommendation Statement

Supporting Documents

- Final Evidence Review, Part 1
  PDF Version (PDF Help)
- Evaluating Test Strategies for Colorectal Cancer Screening: A Decision Analysis for the U.S. Preventive Services Task Force
  PDF Version (PDF Help)
- Final Evidence Summary
  PDF Version (PDF Help)
- Final Evidence Review, Part 2
  PDF Version (PDF Help)

Clinical Summary

Clinical summaries are one-page documents that provide guidance to primary care clinicians for using recommendations in practice.

This summary is intended for use by primary care clinicians.

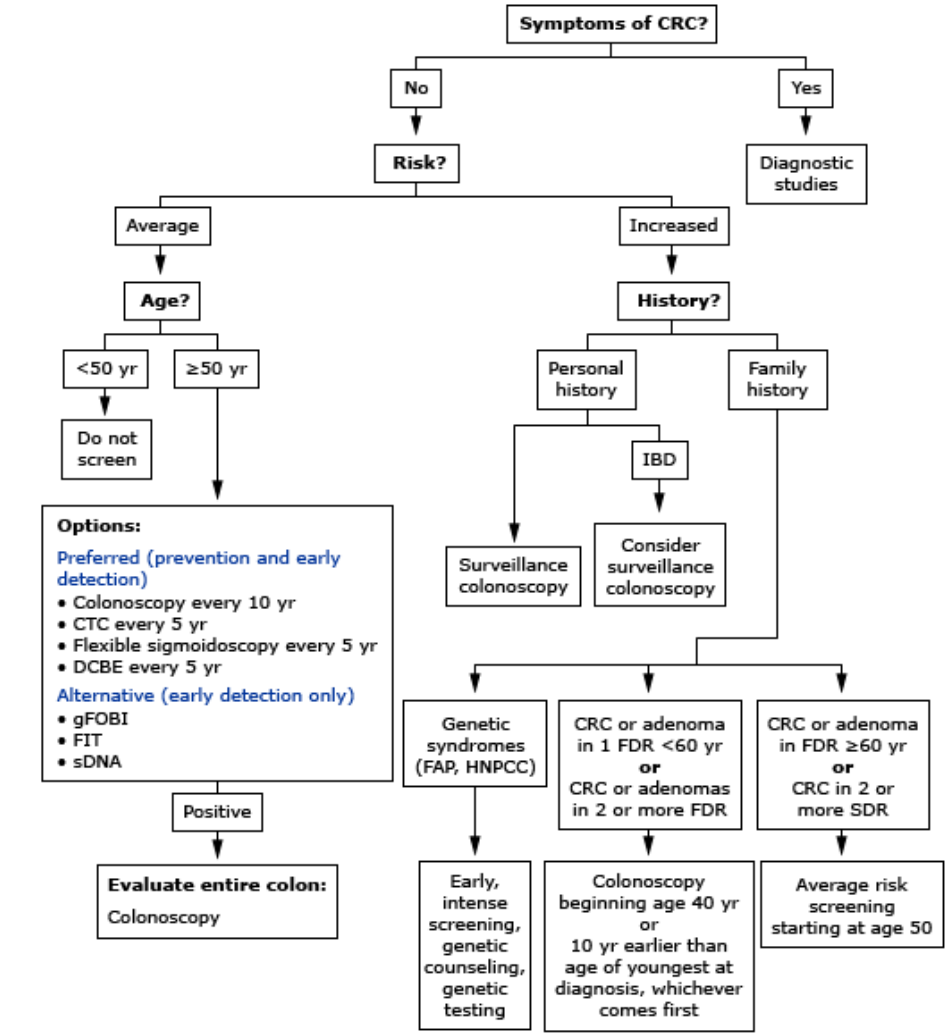
View Clinical Summary
PDF Version (PDF Help)

General Consensus

- Asymptomatic, neg family history, >50yrs
  - Colonoscopy every 10 OR
  - Flexible sigmoidoscopy (5yrs) **AND** FOBT yearly OR
  - CT colonography every 5
- Tests that detect cancer (varying sensitivity)
  - FIT
  - Guaic based tests
  - Stool DNA

Banner MD Anderson Cancer Center
Making Cancer History®

Algorithm for CRC screening and surveillance in average-risk and increased-risk populations



IBD: inflammatory bowel disease; CRC: colorectal cancer; FDR: first degree relative; SDR: second degree relative; CTC: computed tomographic colonography; FAP: familiar adenomatous polyposis; HNPCC: hereditary nonpolyposis colorectal cancer; DCBE: double-contrast barium enema; gFOBT: guaiac fecal occult blood test; FIT: fecal immunochemical tests; sDNA: stool DNA tests.

Banner MD Anderson Cancer Center
Making Cancer History®

"I read that vegetarian diets are associated with lower risk for colorectal cancer, so I made you a large salad to make up for lost time."

Banner MD Anderson Cancer Center
Making Cancer History®

What about CEA?

- Causes for elevated CEA in an individual without cancer
  - Biliary disease
  - Hepatic injury
  - Pulmonary infections
  - Smokers
  - Bowel disease

Banner MD Anderson Cancer Center
Making Cancer History®

Key points about serum biomarkers

- Look at trends not a single number
- NOT an absolute diagnostic tool
- Maybe a monitoring tool

Banner MD Anderson Cancer Center
Making Cancer History®

Newer biomarkers

- Holy grail of onco-monitoring
- Several modalities of testing incl:
  - Quantitatively or structurally-altered proteins
  - Cancer-associated autoantibodies
  - Cell-free nucleic acids (cfNAs)
  - Circulating tumor cells (CTCs)
  - Cancer derived extracellular vesicles (EVs)

Banner MD Anderson Cancer Center
Making Cancer History®

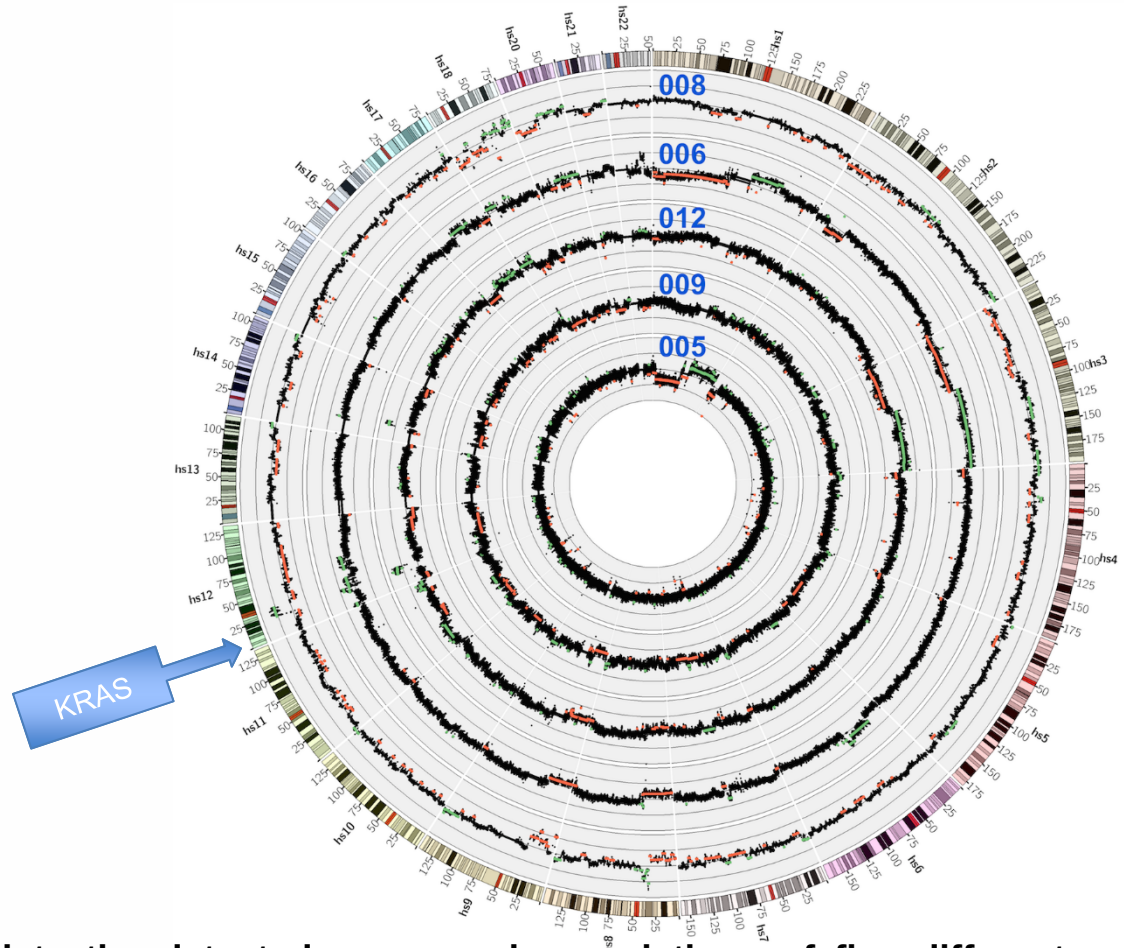
cf-DNA as a potential biomarker

- Tumor genome shotgun sequencing to evaluate the genomic change index as predictor of therapy response

- Tumor-specific somatic mutations were followed in cell-free circulating DNA

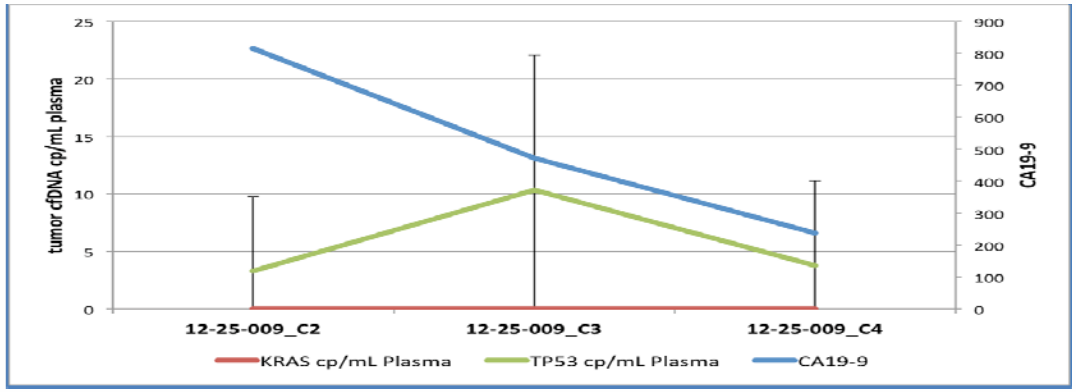
Banner MD Anderson Cancer Center
Making Cancer History®

Copy-Number Analyses

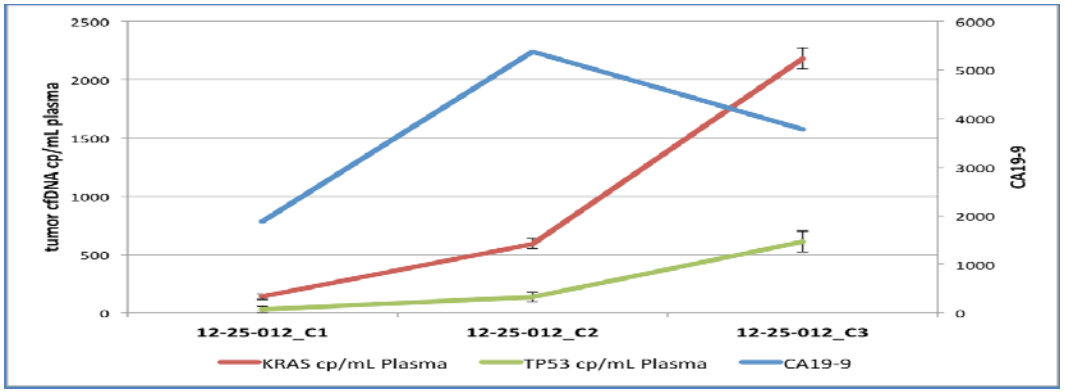


Circos Plot depicts the detected copy-number variations of five different patient tumors. Recurrent copy-number variations were detected for chromosomes 3p, 3q, 8p, 9p and the KRAS gene region on 12p.

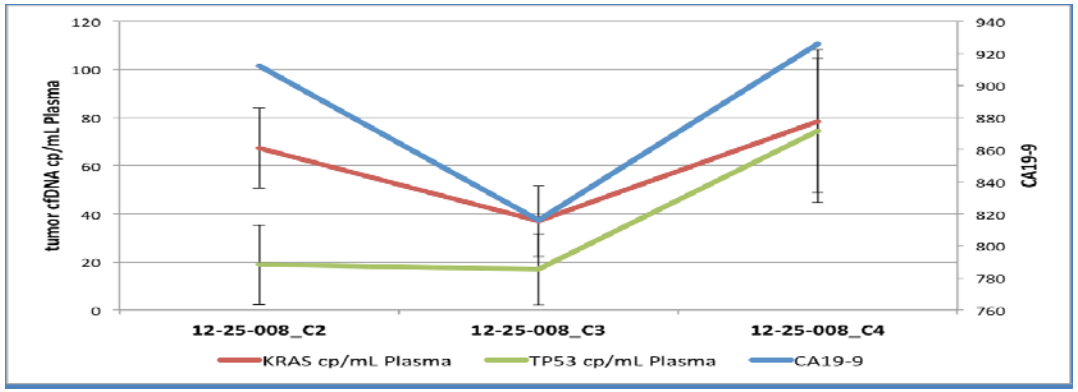
Banner MD Anderson Cancer Center
Making Cancer History®



CR and >70% decrease in CA19-9; no copies of mutKRAS and 4-10 cp/mL mutTP53 were detected at the 3 time points measured.



PR and rising CA19-9, there was also an increase in mutKRAS and mutTP53 cp/mL.



SD and mutKRAS and mutTP53 cfDNA copies of 20-80 per mL plasma (cp/mL) did not significantly change over time.

Banner MD Anderson Cancer Center
Making Cancer History®

Banner MD Anderson Cancer Center
Making Cancer History®

Staging

TNM staging for colorectal cancer, 7th edition

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum¶
T4b	Tumor directly invades or is adherent to other organs or structures¶Δ
Regional lymph node (N)◇	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2-3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more regional lymph nodes
N2a	Metastasis in 4-6 regional lymph nodes
N2b	Metastasis in seven or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

MD Anderson Cancer Center
Making Cancer History®

Management

- Stage I: surgery alone
- Stage II:
  - low risk vs. high risk

  Surgery +/- Adjuvant chemo
- Stage III: Surgery plus adjuvant chemotherapy
- Stage IV: Palliative Chemotherapy

Banner MD Anderson Cancer Center
Making Cancer History®

Stage II

- High Risk:
  - T4 primary
  - Inadequately sampled lymph nodes (less than 13 in the surgical specimen)
  - Bowel obstruction or perforation
  - High-grade/poorly differentiated histology
  - Lymphovascular invasion (LVI)
  - Perineural invasion (PNI)
  - Close, indeterminate, or positive margins
  - High preoperative serum carcinoembryonic antigen (CEA) level

What about MSI and Stage II

- MSI-H:
  - Hypermutability that occurs due to a deficiency in the DNA MMR
  - DNA Replication with accumulated errors
  - Microsatellites aka repeated sequences of DNA
  - MSI can be
    - Sporadic-15%; due to hypermethylation of the MLH1 gene promoter
    - Genetic-Lynch syndrome; germline mutation in MLH1, MSH2, MSH6, PMS2

Banner MD Anderson Cancer Center
Making Cancer History®

- MSI-H (IHC or PCR) portends to a better prognosis and don't respond to 5-FU based regimens*
- Popat et al# in a systematic review of 32 studies of CRC demonstrated that MSI-H pts derived no benefit from adjuvant FU-containing chemotherapy
- Sargent et al^ demonstrated that MSI-H pts treated with chemotherapy was associated with a reduced OS

*Ribic CM, NEJM,2003; #Popat S, JCO,2005;^Sargent DJ, JCO 2010

Banner MD Anderson Cancer Center
Making Cancer History®

Adjuvant therapy

- 5FU (or capecitabine) and Oxaliplatin
- **NO** BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB
- **NO** Radiation unless its rectal cancer

Banner MD Anderson Cancer Center
Making Cancer History®

Stage IV

- Palliative intent

- 5FU (or capecitabine) and Oxaliplatin
- 5FU (or capecitabine) and Irinotecan
- YES-BEVACIZUMAB, CETUXIMAB, PANITUMUMAB, ziv-AFLIBERCEPT, RAMUCIRUMAB
- NO Radiation

Banner MD Anderson Cancer Center
Making Cancer History®

Follow up Colonoscopy

- After curative intent -

Initial in 1 year, subsequent based on findings.

Banner MD Anderson Cancer Center
Making Cancer History®

Questions?

Banner MD Anderson Cancer Center
Making Cancer History®