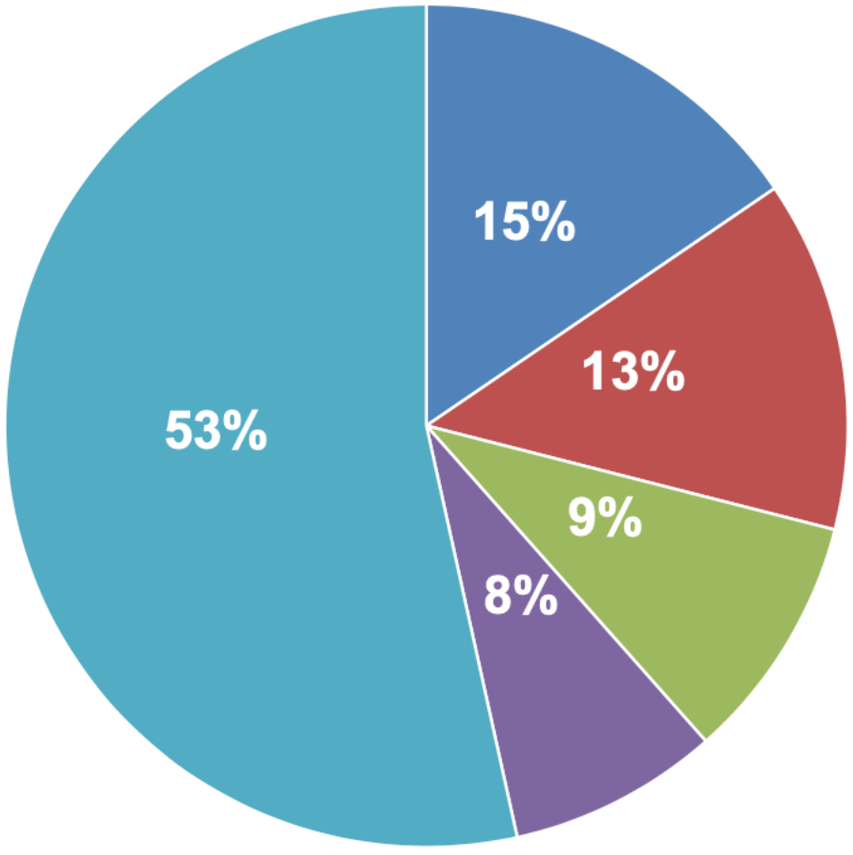
Colon Cancer
Medical Grand Rounds

Warren Brenner M.D
GI Medical Oncology

At a Glance

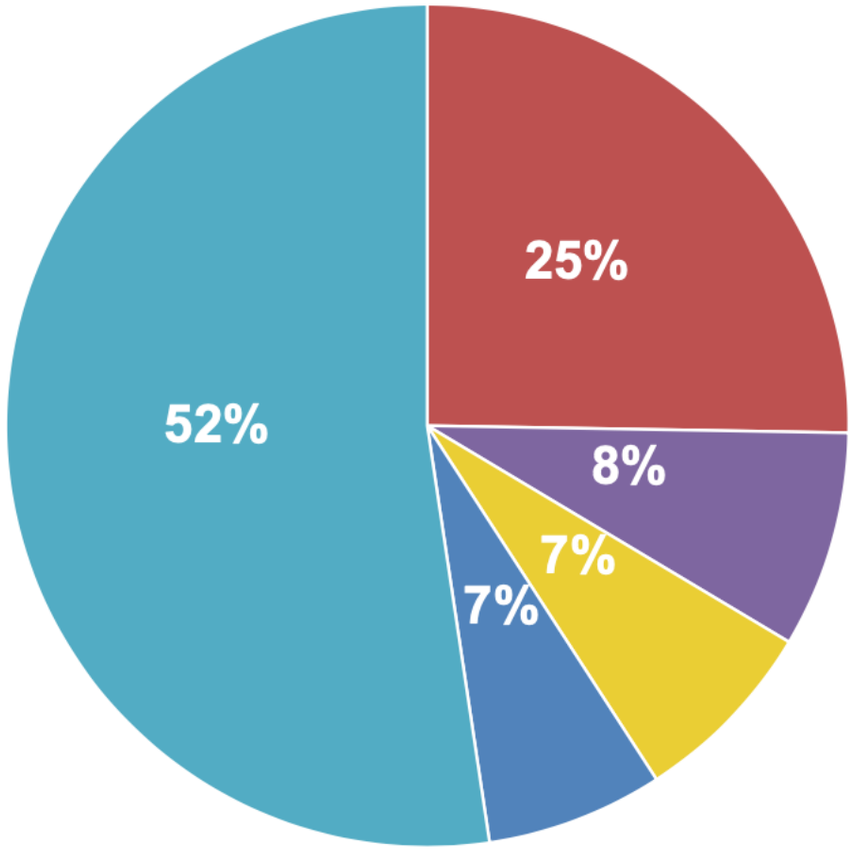
Breast, lung and bronchus, prostate, and colorectal cancers account for almost 50% of all new cancer cases in the United States. Lung and bronchus, colorectal, pancreatic, and breast cancers are responsible for nearly 50% of all deaths.

New Cancer Cases, 2018



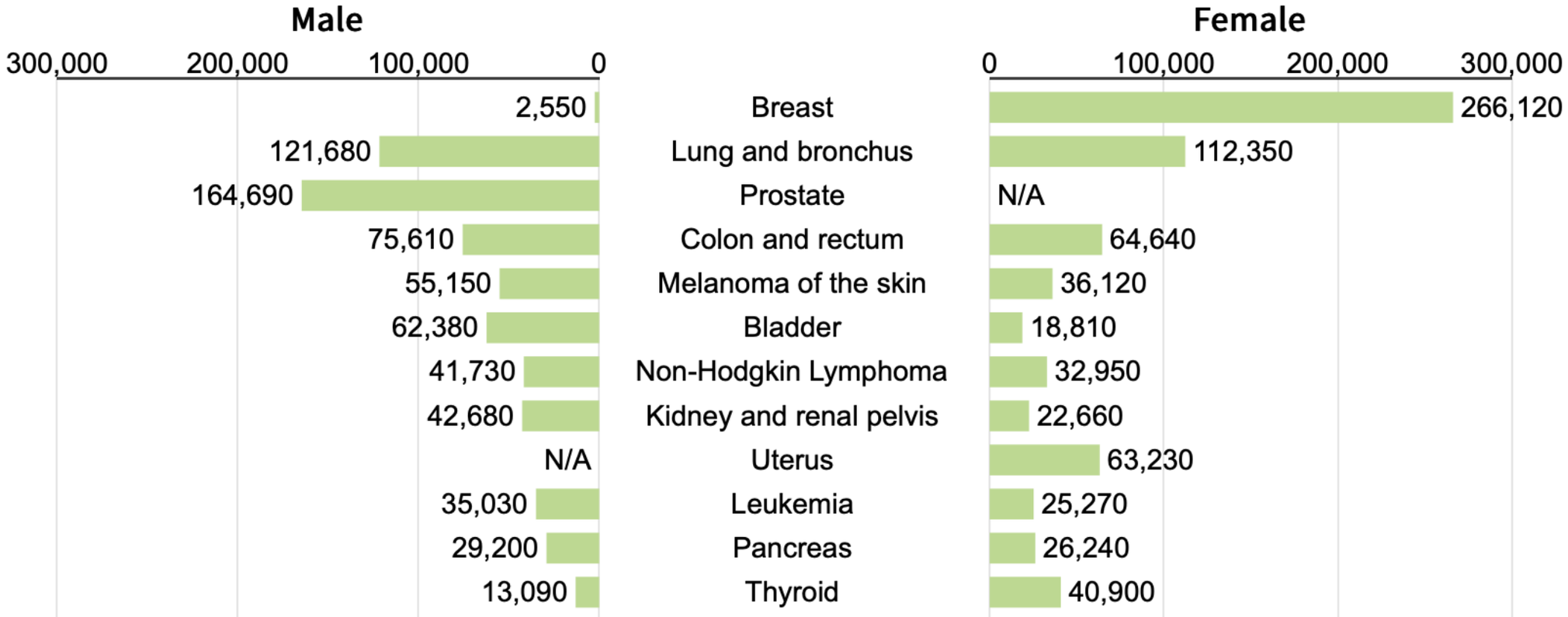
- Breast: 268,670
- Lung and bronchus: 234,030
- Prostate: 164,690
- Colon and rectum: 140,250
- Other: 927,710

Cancer Deaths, 2018

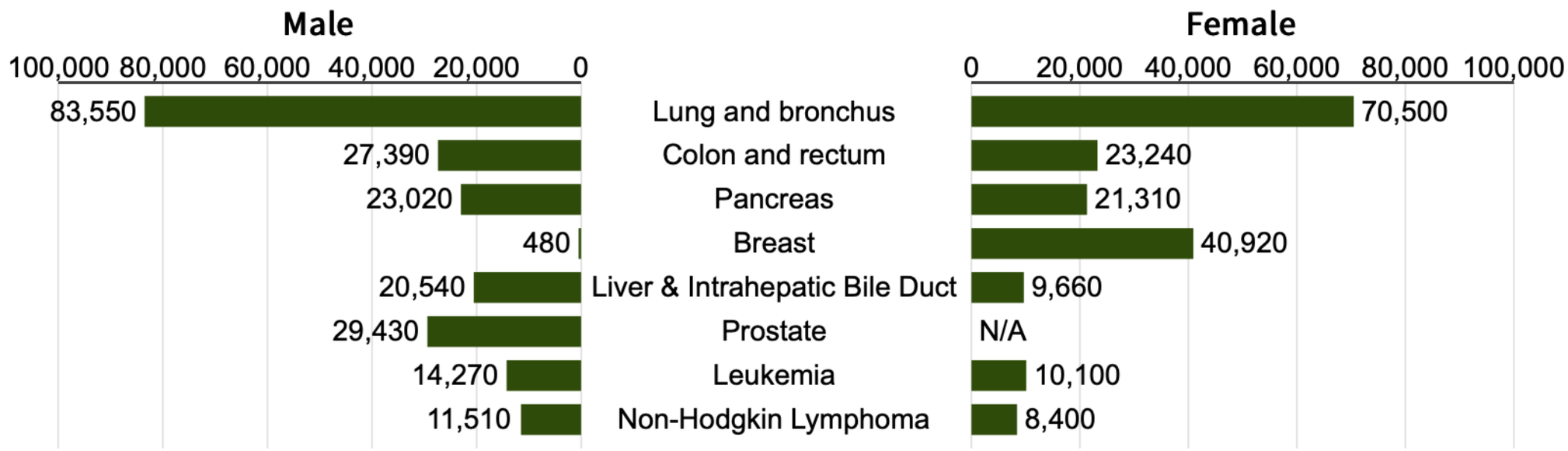


- Lung and bronchus: 154,050
- Colon and rectum: 50,630
- Pancreas: 44,330
- Breast: 41,400
- Other: 319,230

seer.cancer.gov - accessed May 2019



Source: Estimated New Cancer Cases and Deaths for 2018



Source: Estimated New Cancer Cases and Deaths for 2018

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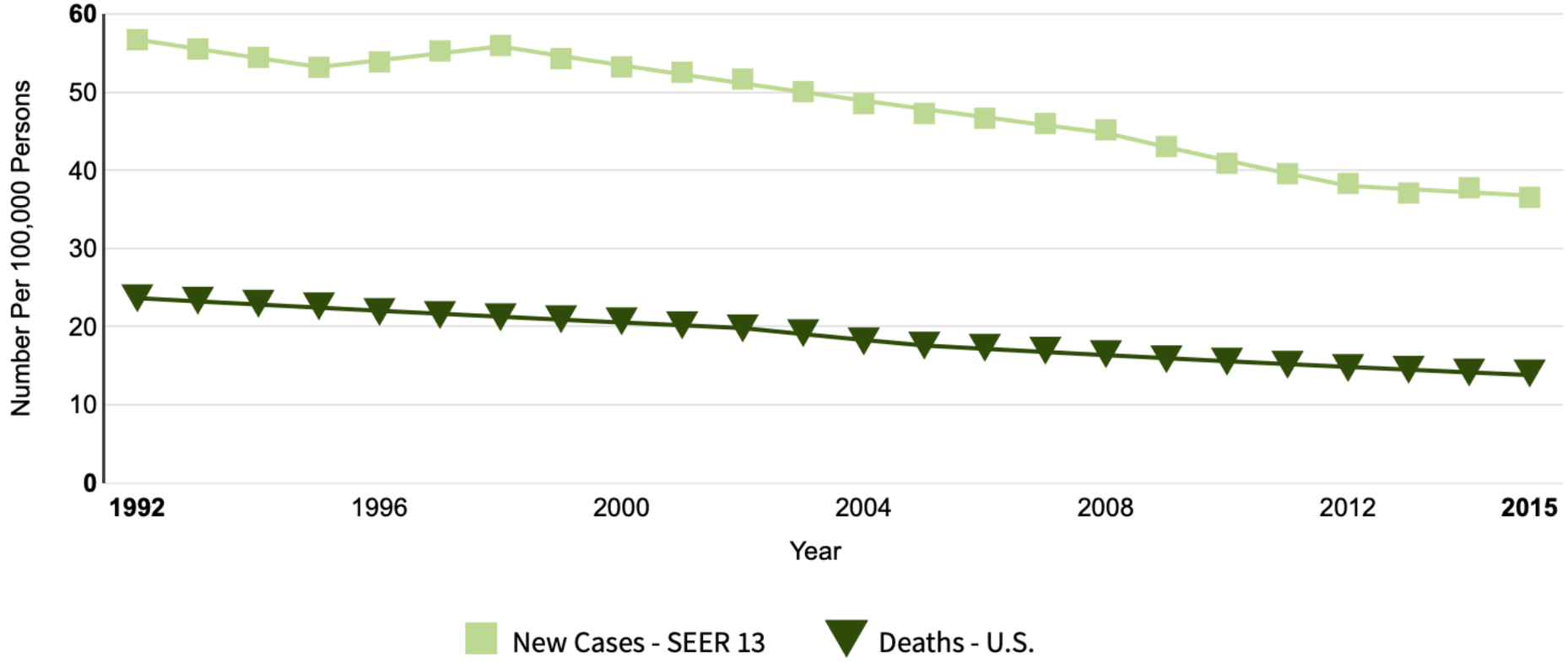
Estimated New Cases in 2018	140,250
% of All New Cancer Cases	8.1%

Estimated Deaths in 2018	50,630
% of All Cancer Deaths	8.3%

Percent Surviving 5 Years
64.5%
2008-2014



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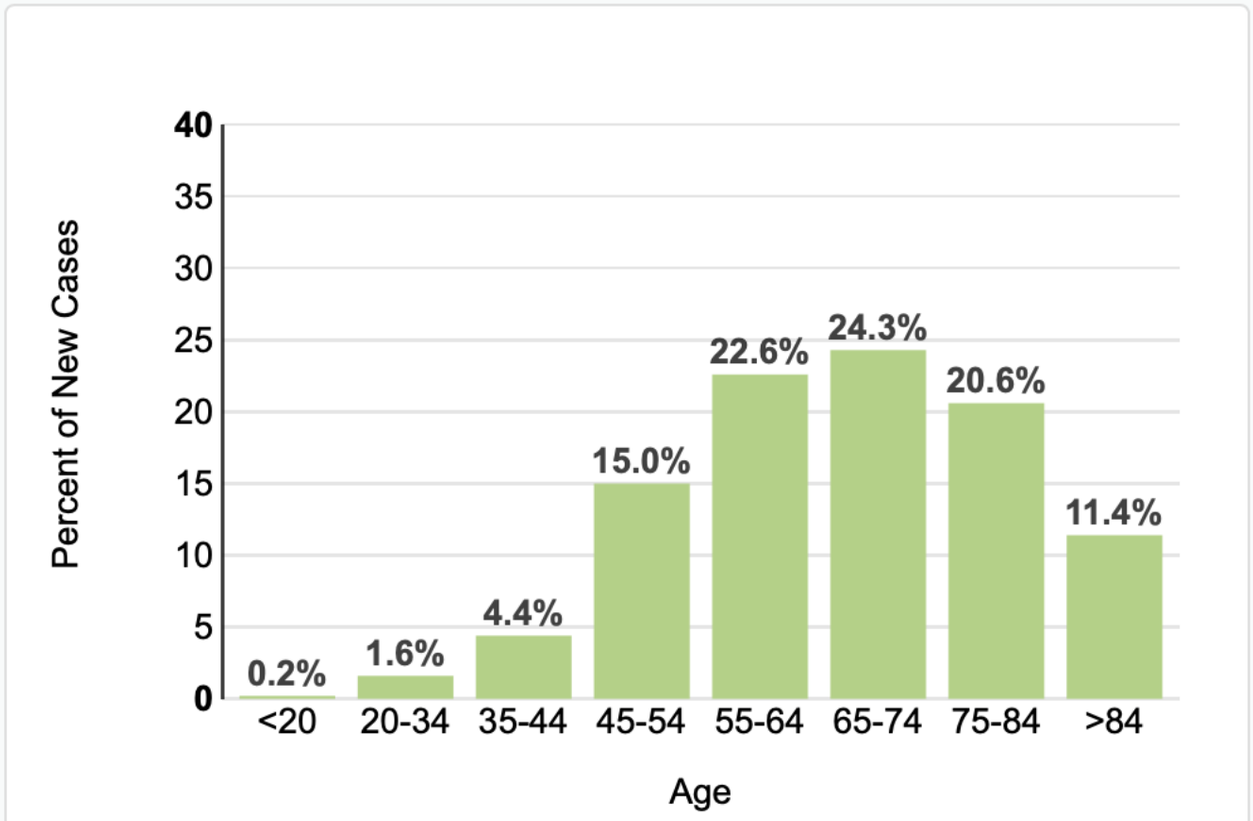
Percent of New Cases by Age Group: Colorectal Cancer



Colorectal cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis

67

SEER 18 2011-2015, All Races, Both Sexes

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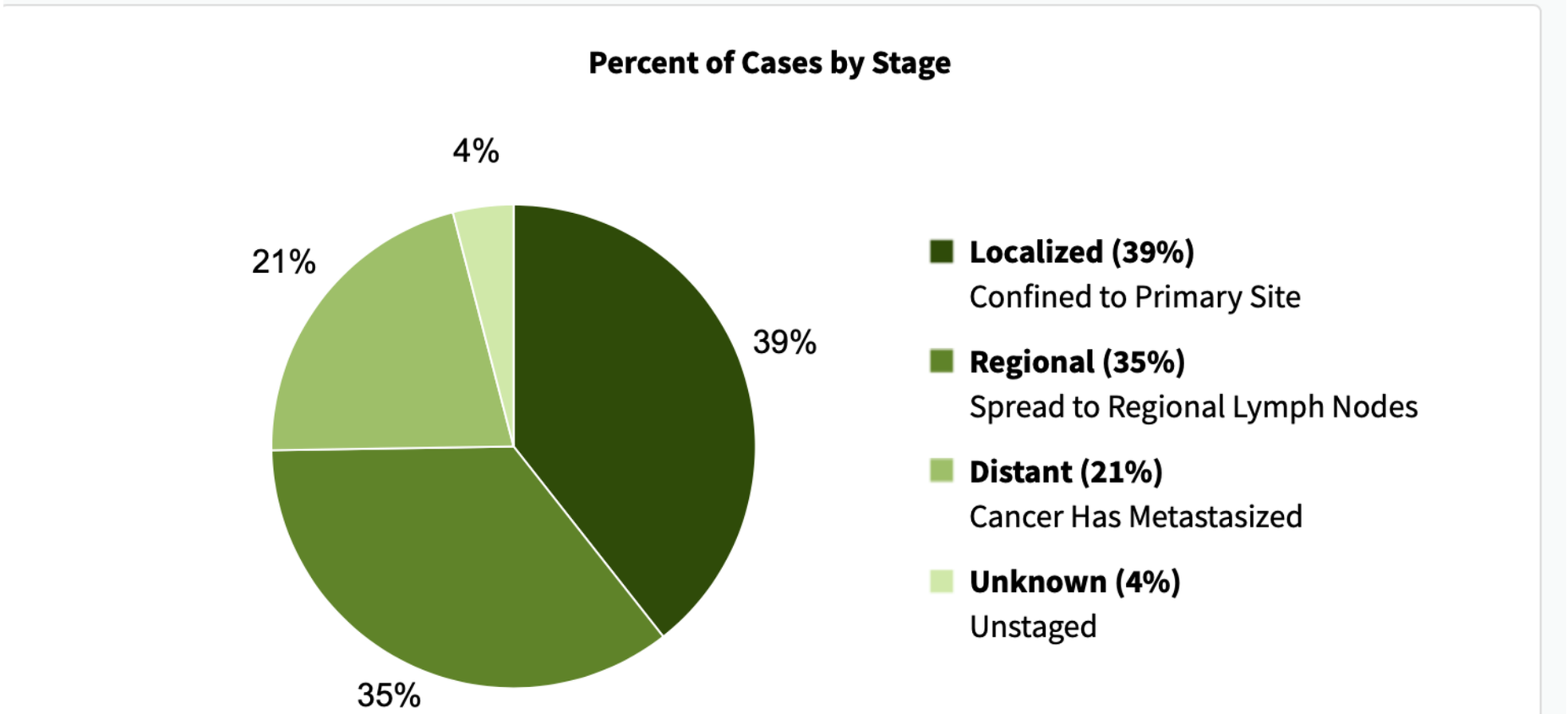

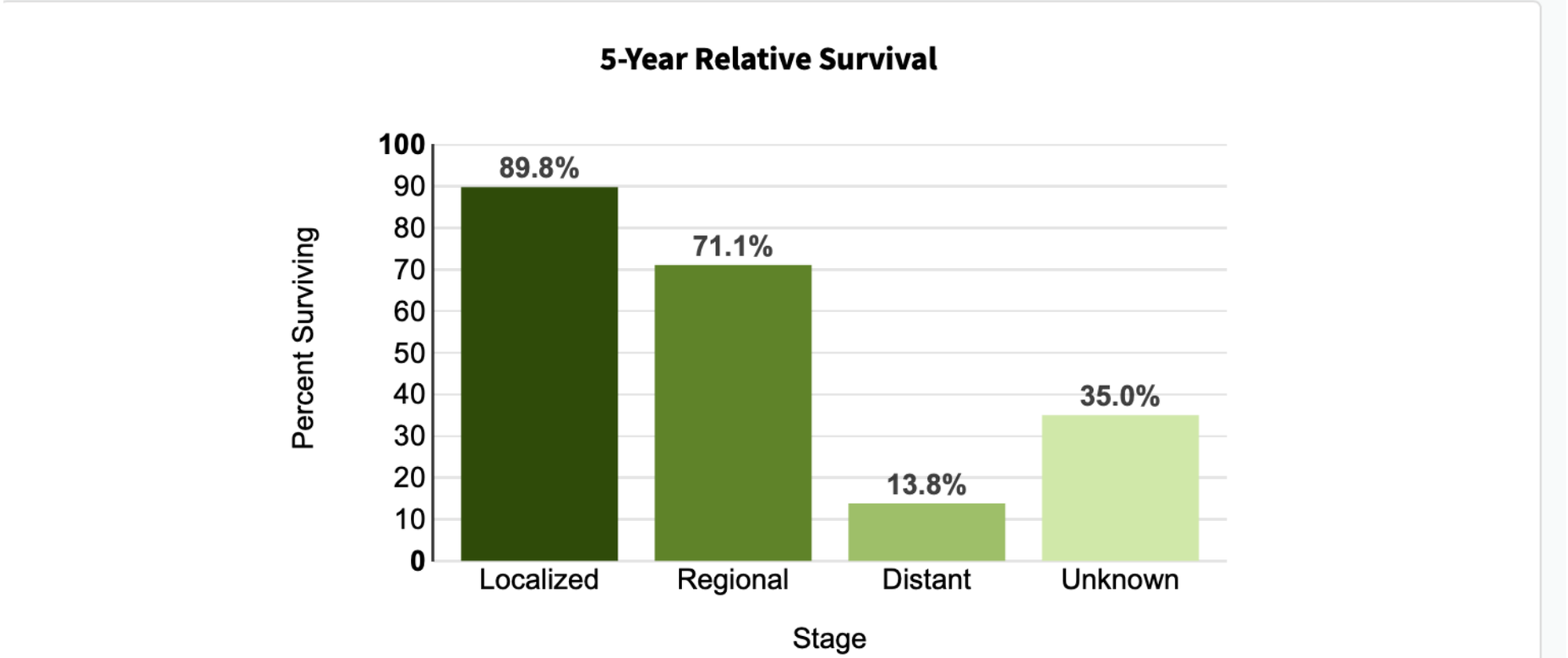

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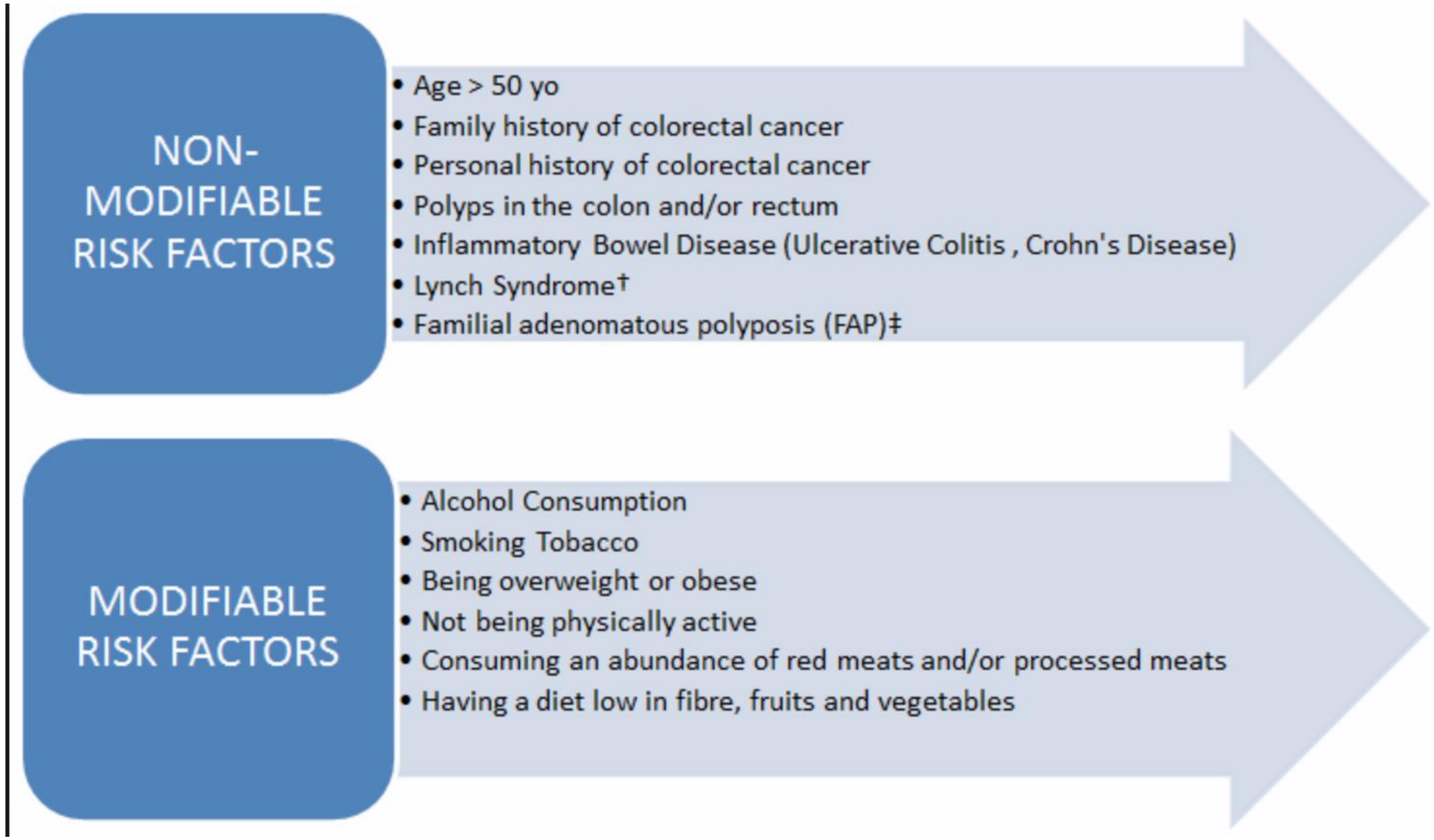
Epidemiology

- Lifetime risk of developing CRC is 5%
- Males have a 25% higher risk than females
- African Americans have a 20% higher risk
- Rising incidence of CRC in younger age group <50
- Shift in right sided colon cancer

Uptodate-accessed May 2019

Risk and Protective Factors



Decreased risk
Multivitamins containing folic acid
Aspirin and other NSAIDs
Postmenopausal hormone use
Calcium supplementation
Selenium
Consumption of vegetables, fruits, and fiber

Uptodate-accessed May 2019

Screening

ACS screening options for adults age 45 years and older who are at average risk of colorectal cancer include either a high-sensitivity, stool-based test or a visual exam

	Test	Frequency
Stool-based	FIT	Every year
	Highly-sensitive-guaiac-based fecal occult blood test (HSgFOBT)	Every year
	Multi-targeted stool DNA test (mt SDNA)	Every 3 years
Visual exams of the colon and rectum	Colonoscopy	Every 10 years
	CT colongraphy (CTC) (virtual colonoscopy)	Every 5 years
	Flexible sigmoidoscopy (FS)	Every 5 years

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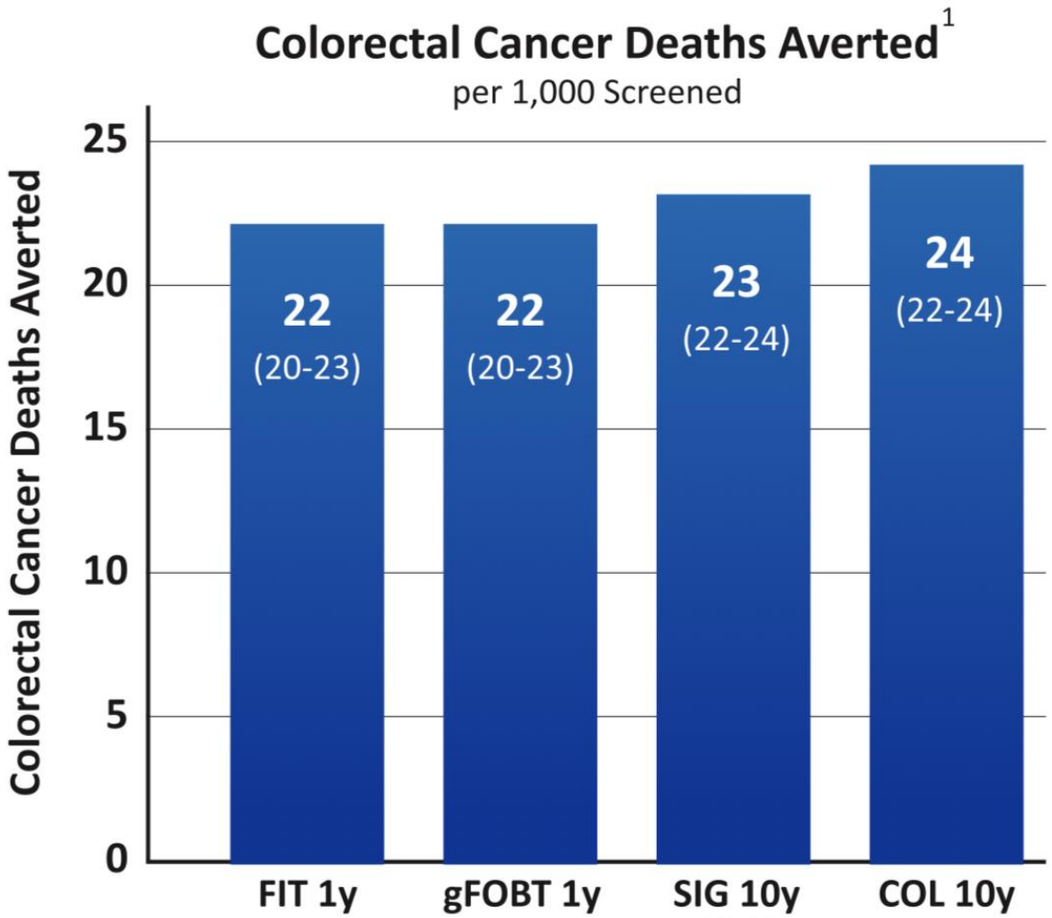

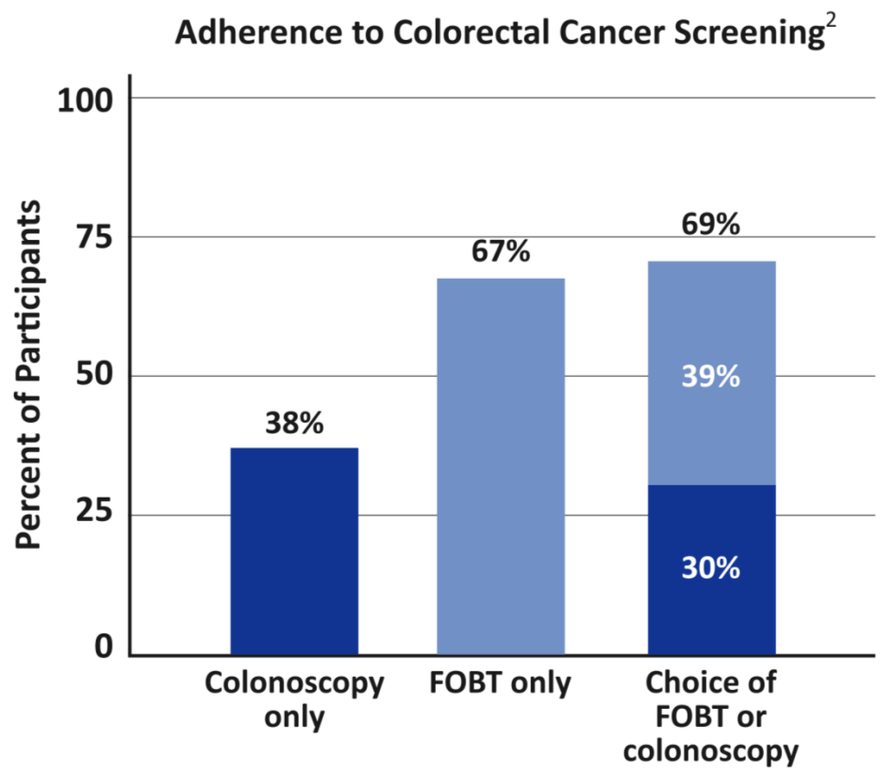

FIT-DNA BRAND NAME	MANUFACTURER	SENSITIVITY FOR CANCER	SPECIFICITY FOR CANCER	NUMBER OF STOOL SAMPLES
Cologuard	Exact Sciences	92.3%[7]	84.4%[7]	1

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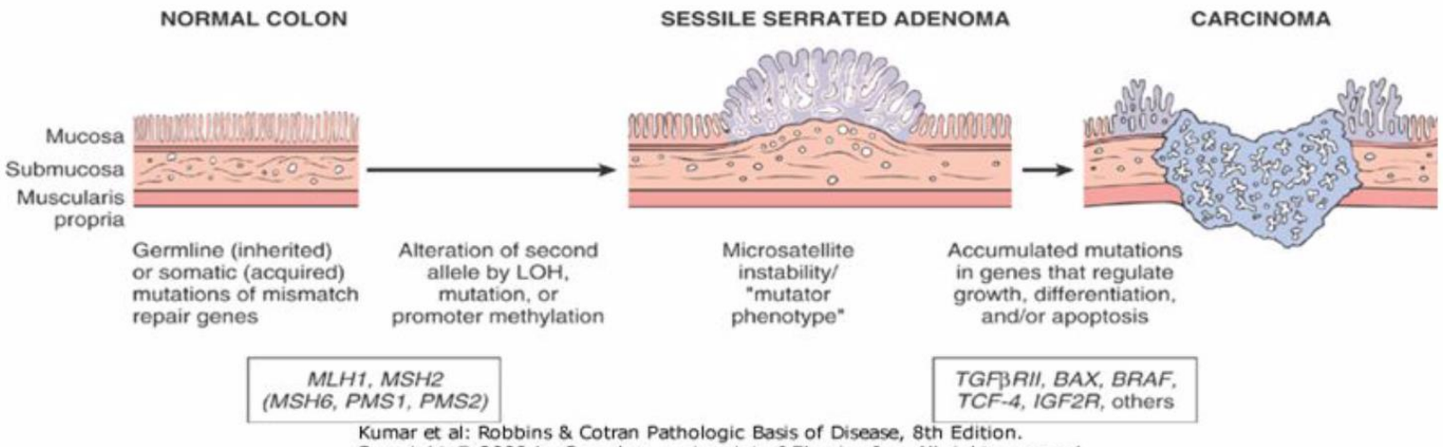
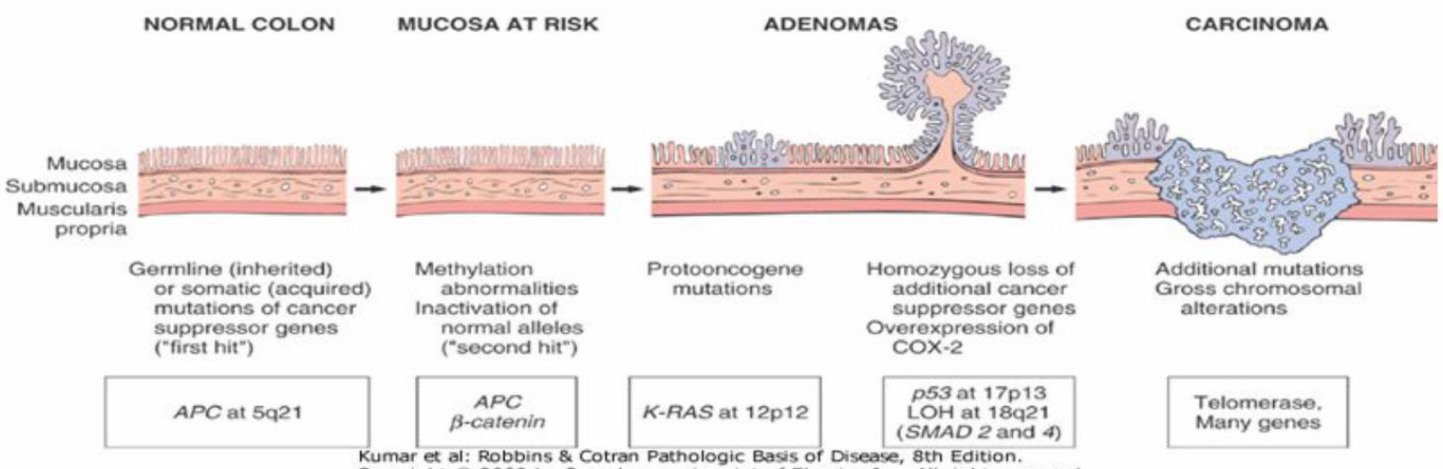
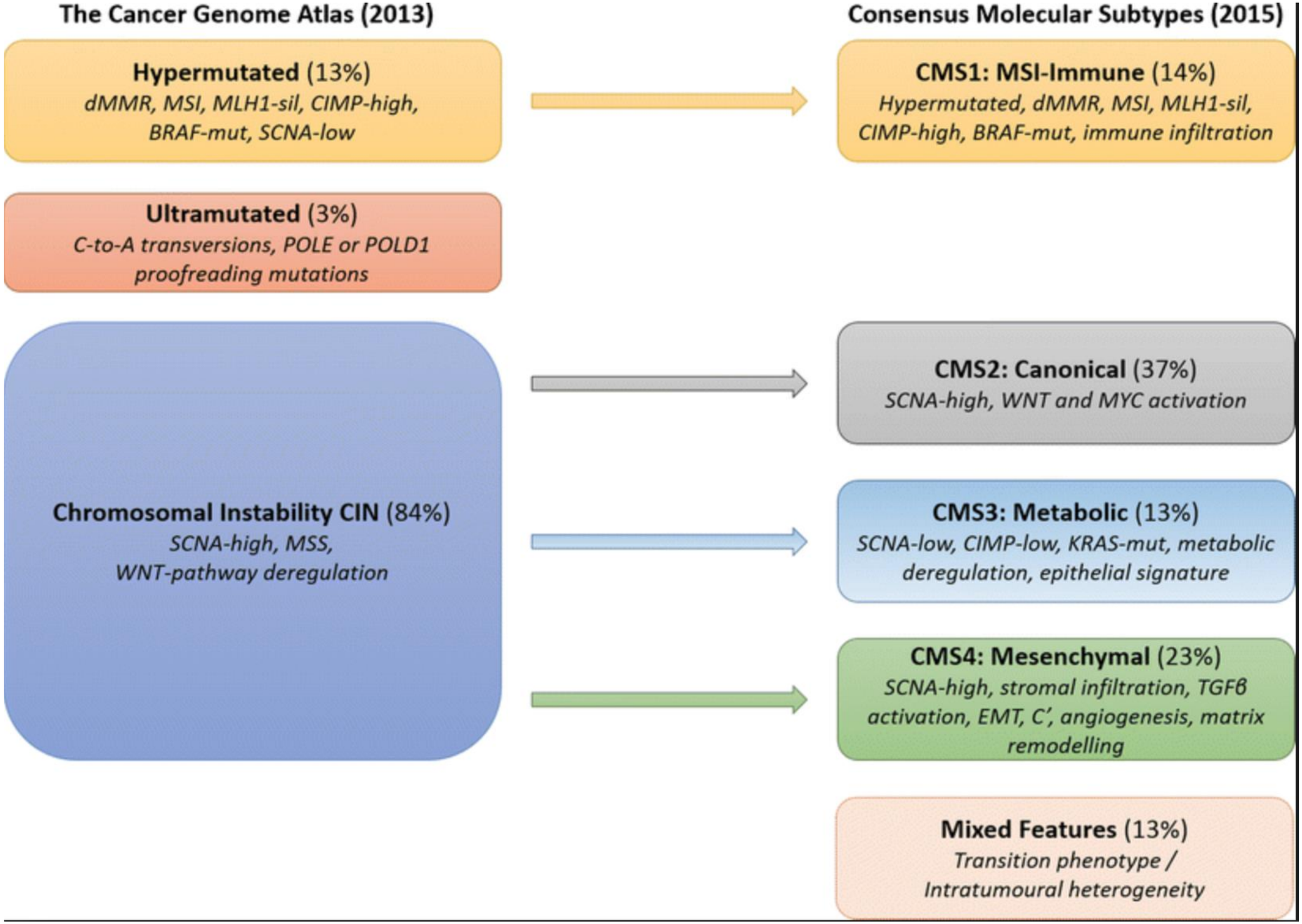
Genetics of CRC

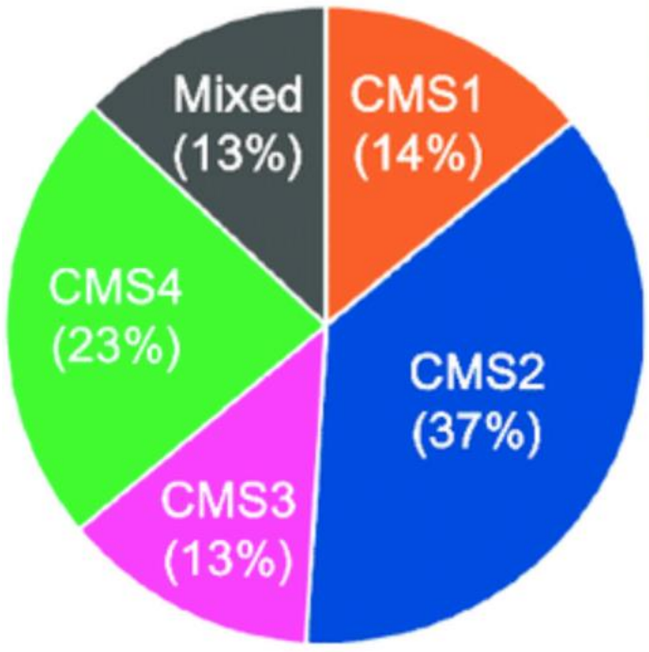
Molecular pathways in colon cancer







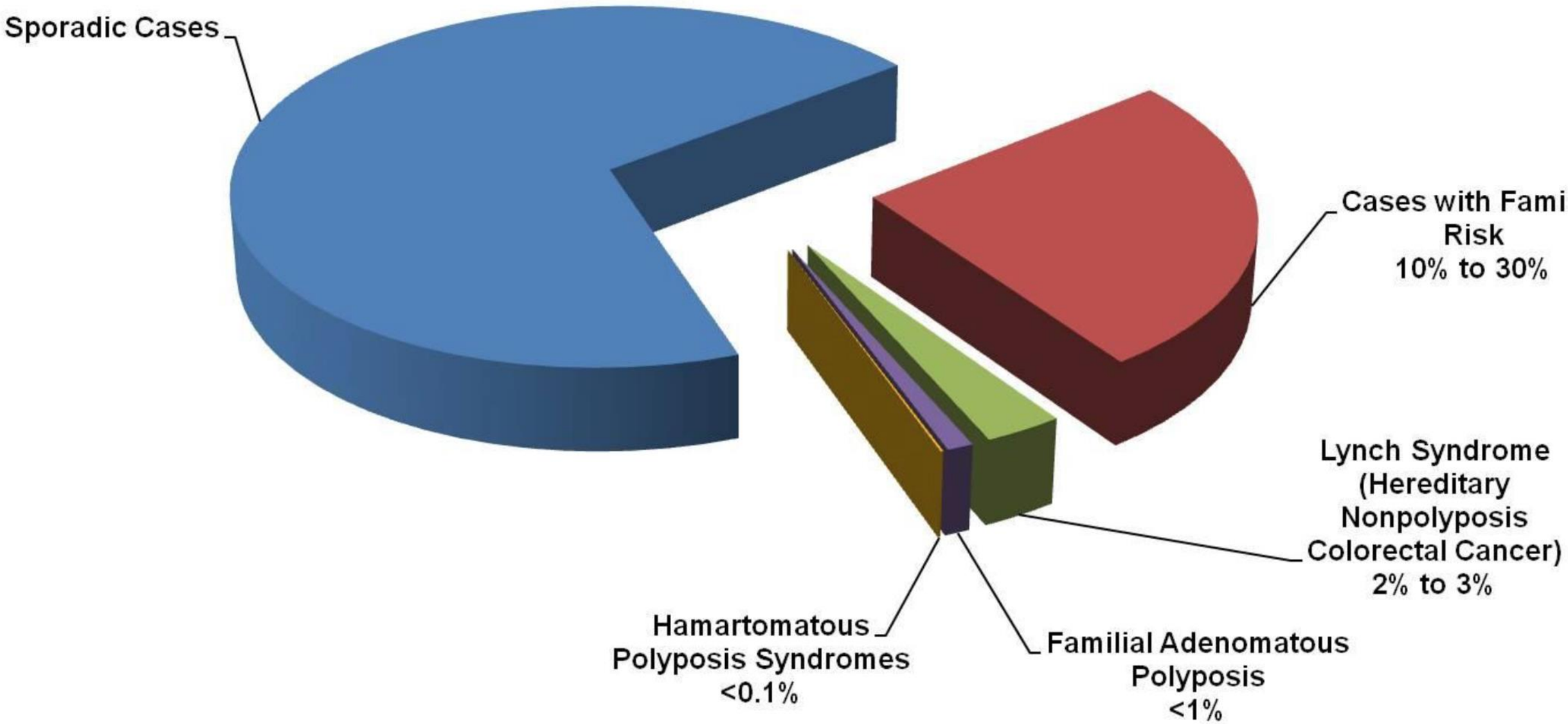
Muller et al Virchows Arch(2016) 469;125-134



Normal colorectal mucosa			
Proximal colon	Distal colon to rectum	Colorectum	Distal colon to rectum
MSI CIMP-positive *BRAF* mut Hypermethylation	Canonical pathway with *APC* & *TP53* mut SCNA-high *HNF4A* amplification	*KRAS & APC* mut	SCNA-high
CMS1 **MSI-immune**	**CMS2** **Canonical**	**CMS3** **Metabolic**	**CMS4** **Mesenchymal**
MSI; CIMP-positive; Hypermethylation; SCNA-low	MSS; CIN CIMP-negative; SCNA-high	MSS; CIMP-low; SCNA-intermediate	MSS; CIMP-negative; SCNA-high
BRAF & *TGFBR2* mutations	*APC* & *TP53* mutations	*KRAS* & *APC* mutations	
High expression of the *miR-17–92* cluster	Low expression of *let-7* miR family	Low expression of *miR-200* family	
Immune activation; JAK-STAT and Caspases pathway	WNT and MYC activation; Cell cycle pathway	Metabolic dysregulation; Epithelial signature	TGF-β activation; Stromal infiltration; EMT activation; Matrix remodeling; Angiogenesis
Worse survival after relapse; Female; Old-onset; Higher histological grade; Proximal colon	Superior survival after relapse; Dostal colon to rectum		Worse relapse- free and overall survival; Advanced stages (III and IV)

Muller et al Virchows Arch(2016) 469;125-134

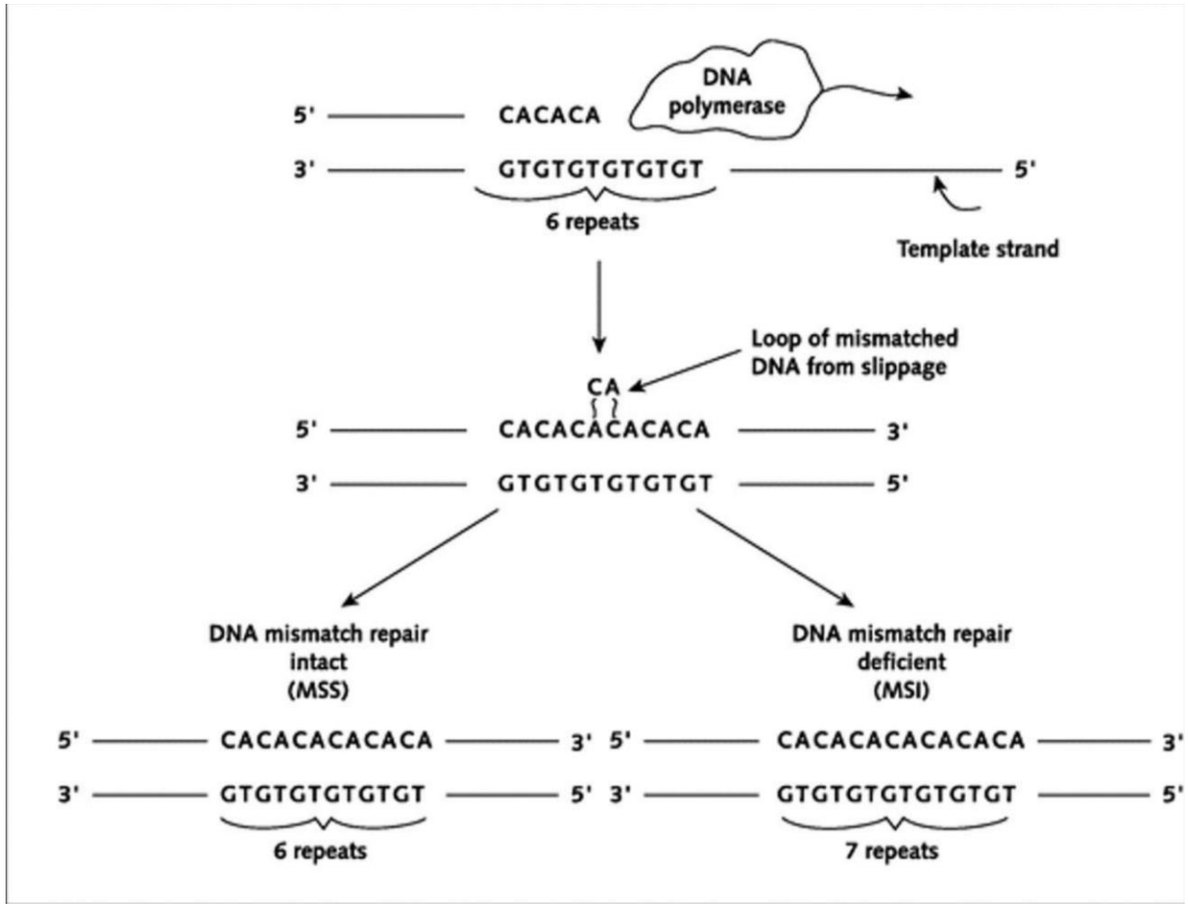
Colon Cancer Cases Arising in Various Family Risk Settings



Lynch et al; NEJM 2003;348:919-932

Lynch Syndrome

First described by Aldred Warthin in 1895 and reported in 1913
Lynch described 2 Midwestern kindred's as having a “cancer family syndrome” in 1966
Germline mutation in DNA mismatch repair genes resulting in microsatellite instability inherited in AD manner
Accounts for 1-3% of all cases of CRC (based on detection of germline mutations)
Various repair mechanisms are available to correct any errors occurring during DNA replication
One type of error called “ slippage” can occur during the replication of microsatellite sequences by DNA polymerase
Microsatellite DNA sequences are defined as short dinucleotide or mononucleotide repeats.
These sequences are usually within non coding regions although some genes contain microsatellites within coding regions
Primary function of the MMR system is to eliminate these mismatches and insertion-deletion loops



Lynch et al; NEJM 2003;348:919-932

Lynch Syndrome CRC

Poorly differentiated, mucinous and increased incidence of signet cells

Diploid, peritumoral lymphocyte infiltration and Crohn's like reaction

Adenomas found in 20% of colons in HNPCC patients with CRC

Colonic adenomas tend to occur earlier, are larger and more often villous with more high grade dysplasia

Accelerated rate of adenoma to carcinoma

Lynch et al; NEJM 2003;348:919-932

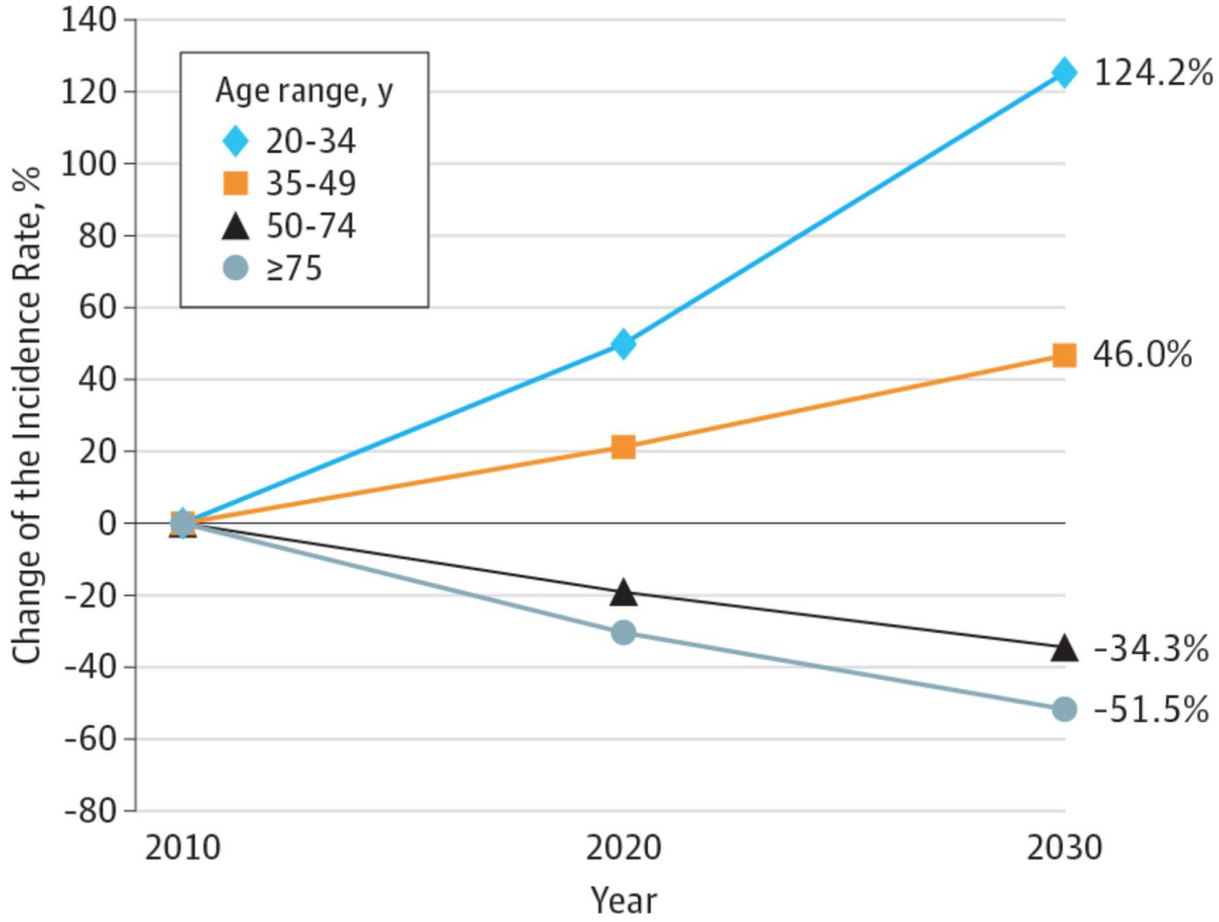
Table 2. Number of Different Germ-Line Mutations and Polymorphisms Identified in Patients with Hereditary Nonpolyposis Colorectal Cancer.*

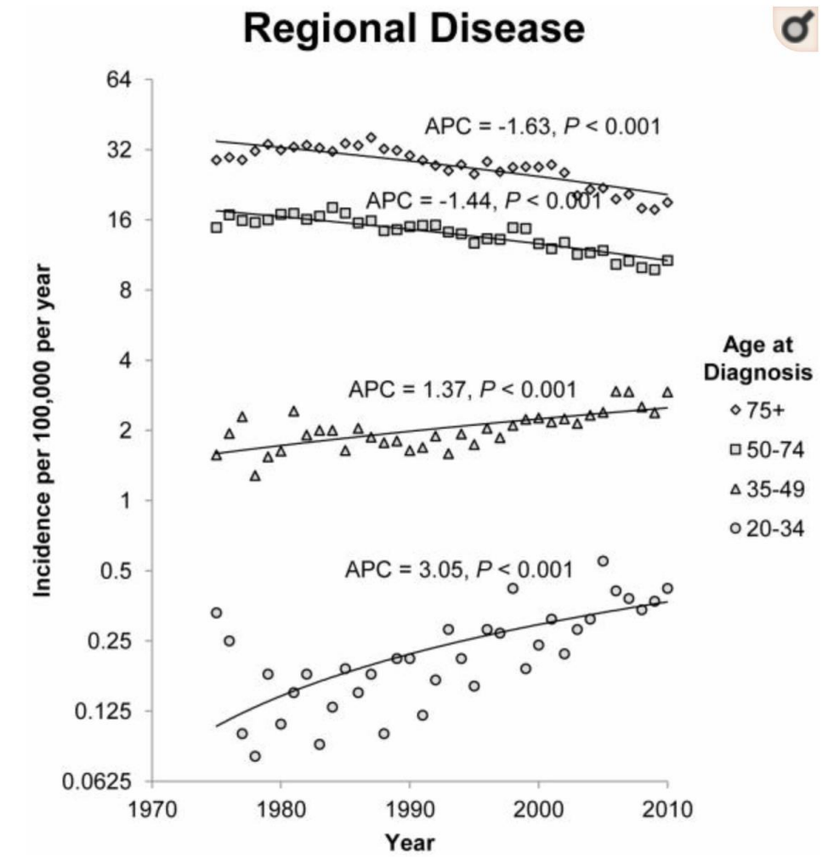
Gene	Total No. of Mutations†	No. of Missense Mutations (% of total)	No. of Polymorphisms‡
MLH1	164	47 (29)	20
MSH2	121	19 (16)	24
MSH6	31	12 (39)	43
PMS1	1	0	0
PMS2	5	1 (20)	5
Total	322	79 (25)	92

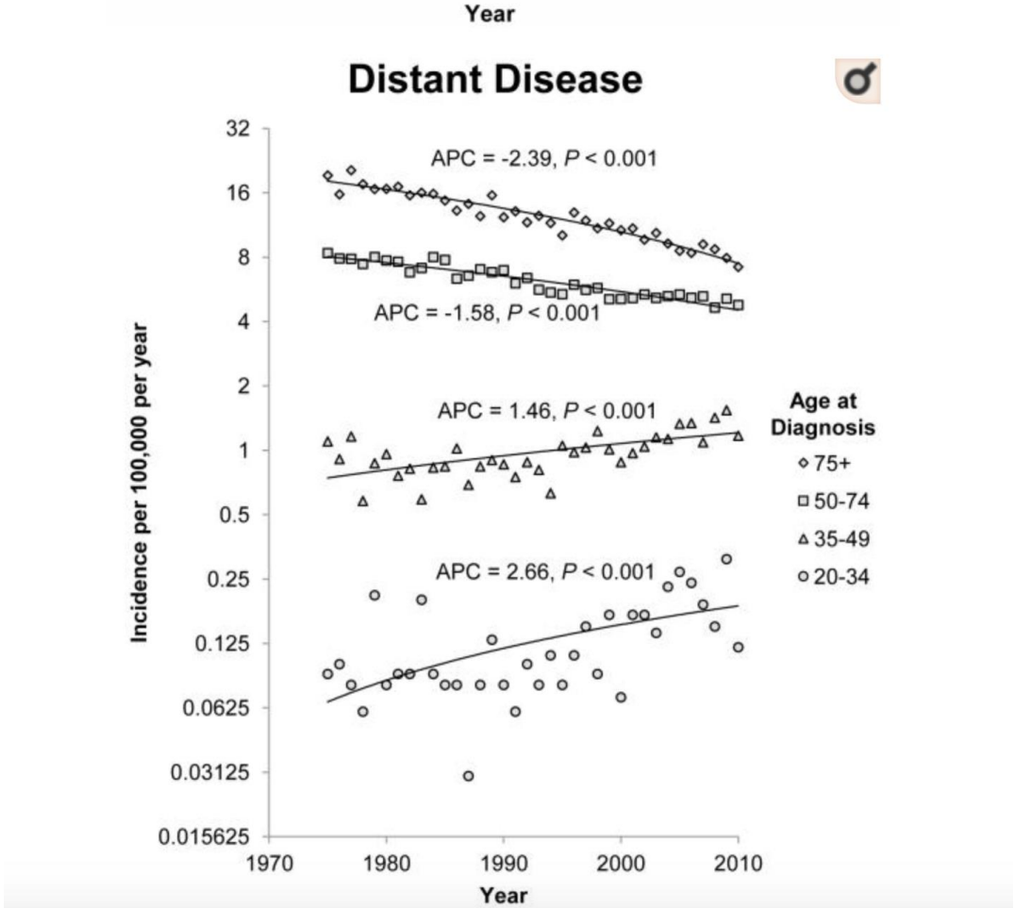
* The mutations are from the data maintained by the International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (http://www.nfdht.nl). The data base also lists 10 mutations in the *MLH3* gene; all but 1 are missense mutations and have so far been reported by a single laboratory.[64] Their putative pathogenetic role remains to be determined.
† The mutations listed are considered disease-causing.
‡ The polymorphisms listed are not considered disease-causing.

Rising Incidence of younger age onset CRC

Ages 20-39 - Colon cancer incidence increased by 1-2.4% per annum and rectal cancer by 3.2%
Proportion of rectal cancer cases that were diagnosed in adults younger than age 55 doubled from 14.6% between 1989 and 1990 to 29.2% between 2012 and 2013.







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Features of Young Age onset CRC

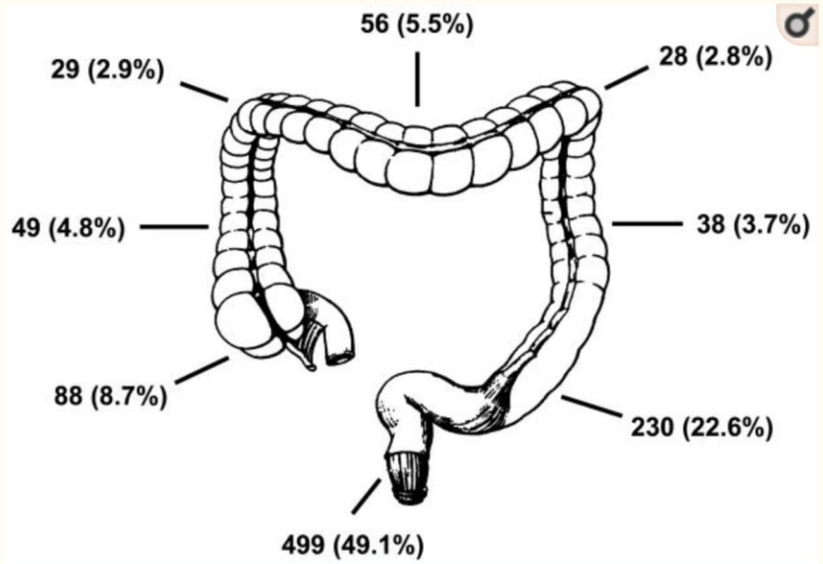


FIGURE 1

Specific subsite locations of tumors in the colorectum.

Demographic and Clinical Features*

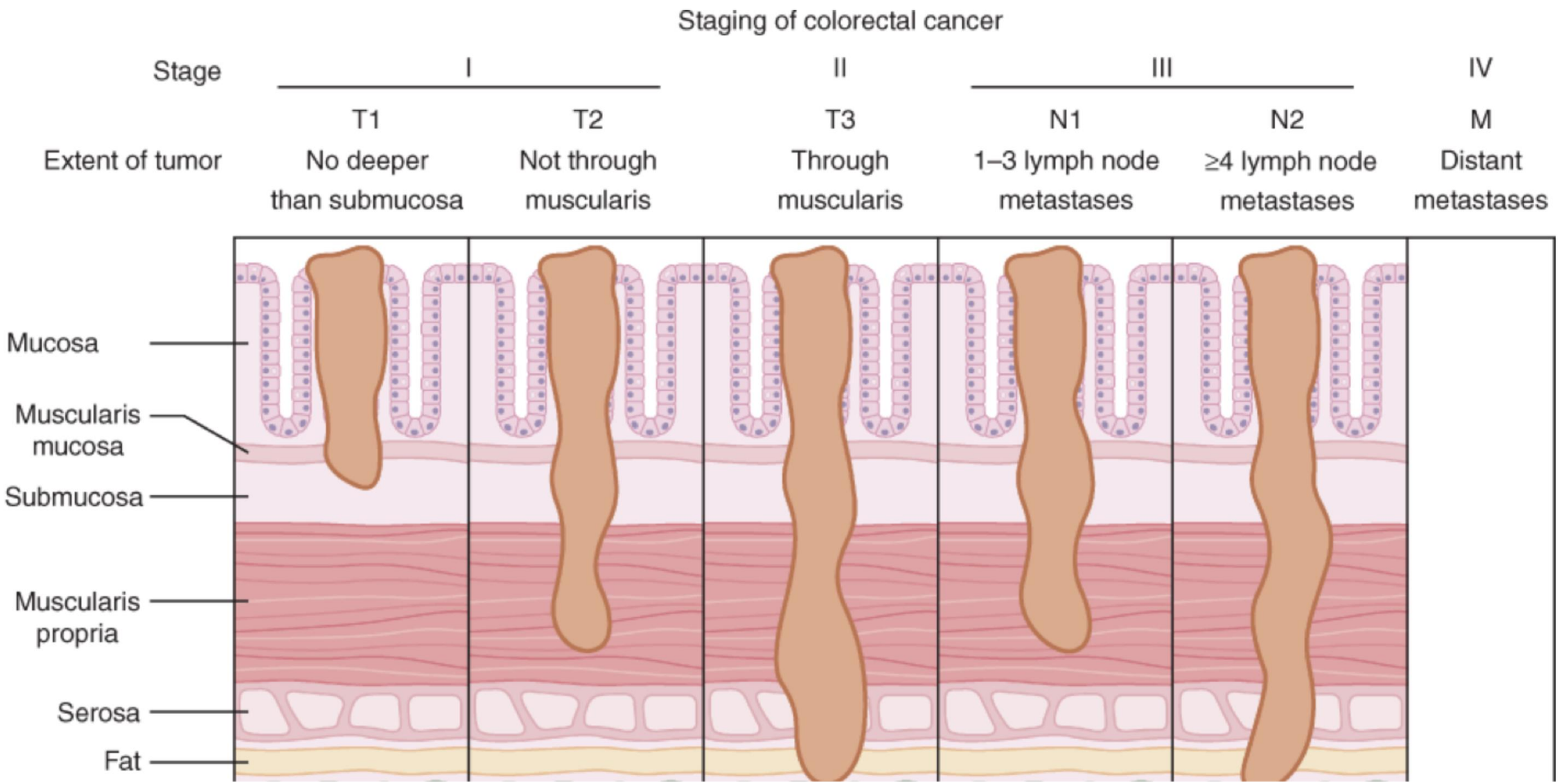
Feature	Colon Cancer (n = 524)†	Rectal Cancer (n = 499)‡	p Value§
Sex			
Male	275 (52.5)	308 (61.7)	0.003
Female	249 (47.5)	191 (38.3)	
Mean age (SD, minimum)	42.6 (6.2, 17.9)	42.2 (6.6, 17.8)	0.26
Symptomatic at presentation	434 (82.8)	450 (90.2)	<0.001
Presenting clinical features at first diagnosis‖			
Rectal bleeding	176 (33.6)	344 (68.9)	<.001
Abdominal pain			
Acute	22 (4.2)	1 (0.2)	<.001
Chronic	236 (45.0)	74 (14.8)	<.001
Change in bowel habits	77 (14.7)	108 (21.6)	0.004
Diarrhea	60 (11.5)	75 (15.0)	0.09
Positive fecal blood test	28 (5.3)	18 (3.6)	0.18
Rectal Pain	6 (1.1)	66 (13.2)	<.001
Bloating	51 (9.7)	24 (4.8)	0.003
Constipation	40 (7.6)	46 (9.2)	0.36
Weight loss	74 (14.1)	61 (12.2)	0.37
Nausea or vomiting	55 (10.5)	13 (2.6)	<.001
Melena	10 (1.9)	10 (2.0)	0.91
Other	153 (29.2)	108 (21.6)	0.006

Pathologic Features*

Feature	Colon Cancer (n = 524)†	Rectal Cancer (n = 499)‡	p Value§
Synchronous malignant lesions	7 (1.4)	2 (0.4)	0.11
Grade			
Grade 1	9 (1.7)	12 (2.4)	0.25
Grade 2	267 (51.0)	282 (56.5)	
Grade 3	191 (36.5)	158 (31.7)	
Grade 4	43 (8.2)	31 (6.2)	
Unknown grade	14 (2.7)	16 (3.2)	
Pathologic staging			
Stage 1	42 (8.0)	95 (19.0)	<.001
Stage 2	110 (21.0)	99 (19.8)	
Stage 3	155 (29.6)	174 (34.9)	
Stage 4	217 (41.4)	131 (26.3)	

Medicine. 87(5):259-263, SEP 2008

Staging


Staging of colorectal cancer
Stage
I
II
III
IV
T1
T2
T3
N1
N2
M
Extent of tumor
No deeper than submucosa
Not through muscularis
Through muscularis
1–3 lymph node metastases
≥4 lymph node metastases
Distant metastases
Mucosa
Muscularis mucosa
Submucosa
Muscularis propria
Serosa
Fat

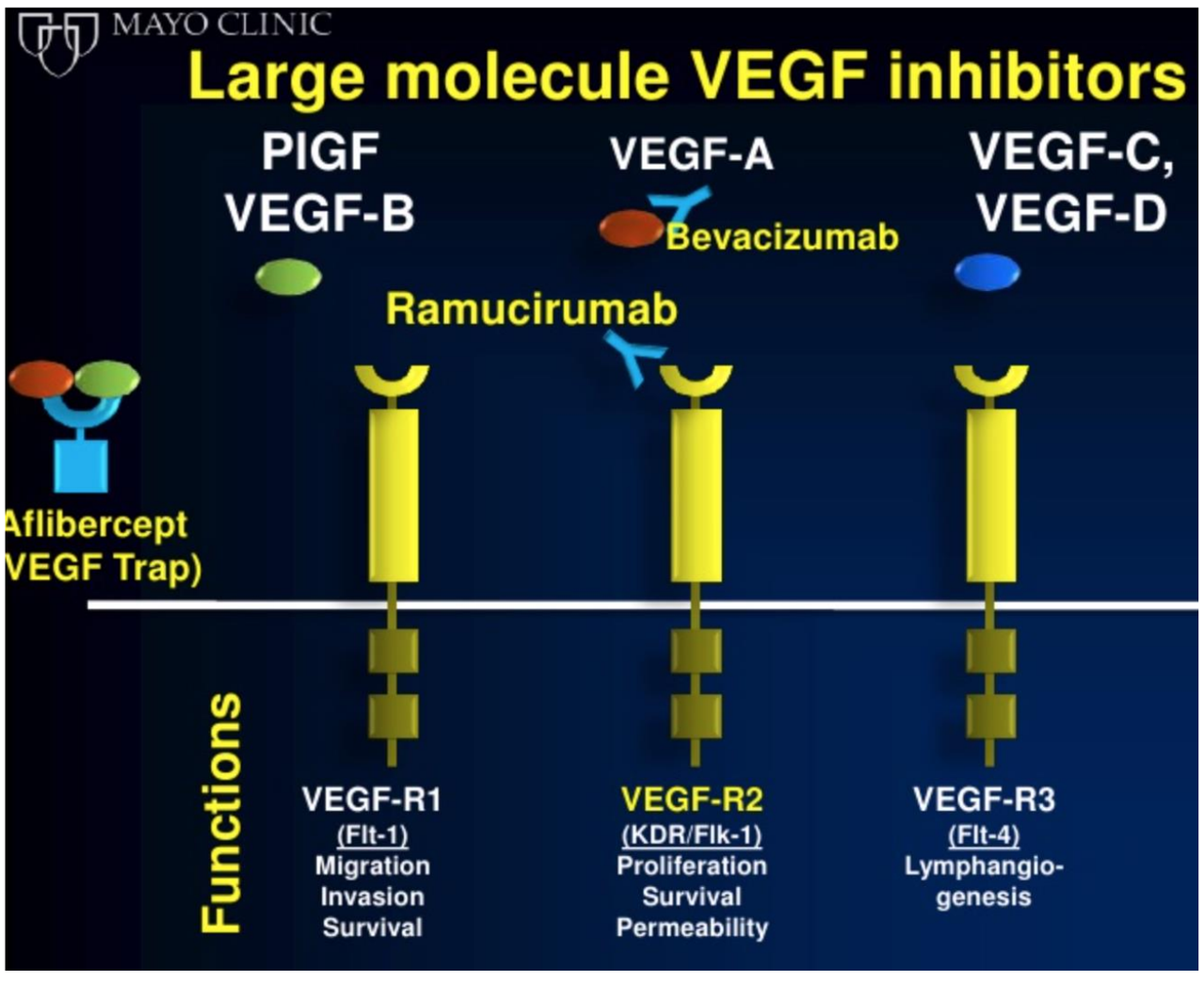
Treatment

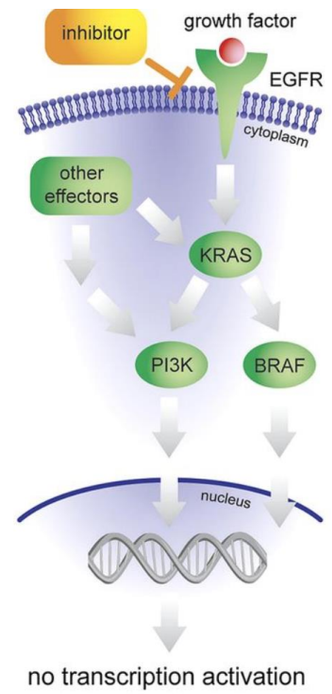
- Stage 1 - surgical resection - No role for adjuvant therapy
- Stage IIA - Benefit of adjuvant chemotherapy modest - ?colon cancer oncotype Dx
- Stage IIB - Recommend chemotherapy
- Stage III - chemotherapy -3 months for lower risk and 6 months for higher risk
- Stage IV - chemotherapy with/out surgical resection/ablative techniques - subset can be cured
- Rectal cancer - increasing use of total neoadjuvant therapy and possible avoidance of surgery

11 FDA Approved Drugs for Colorectal Cancer

"Cytotoxics"	Mechanism
1. 5-Fluorouracil (5-FU)	-> pyrimidine analog
2. capecitabine	-> oral 5-FU pro-drug
3. TAS-102	-> 5-FU drug with metabolism inhibitor
4. irinotecan	-> topoisomerase I inhibitor
5. oxaliplatin	-> 3rd generation platinum

"Biologics/Targeted"	Mechanism
1. cetuximab	-> antibody against EGFR
2. panitumumab	-> antibody against EGFR
3. bevacizumab	-> antibody against VEGF
4. ziv-aflibercept	-> VEGF trap
5. regorafenib	-> tyrosine kinase inhibitor
6. ramucirumab	-> antibody against VEGFR2





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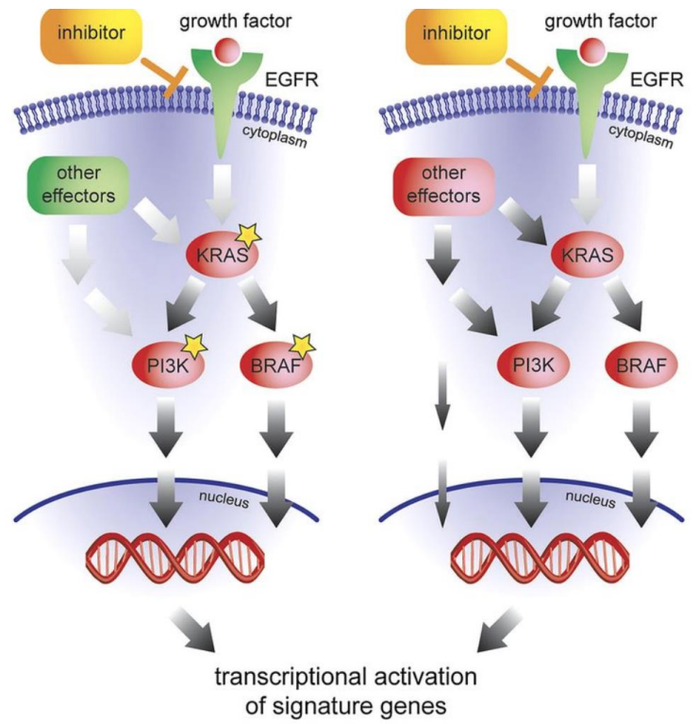
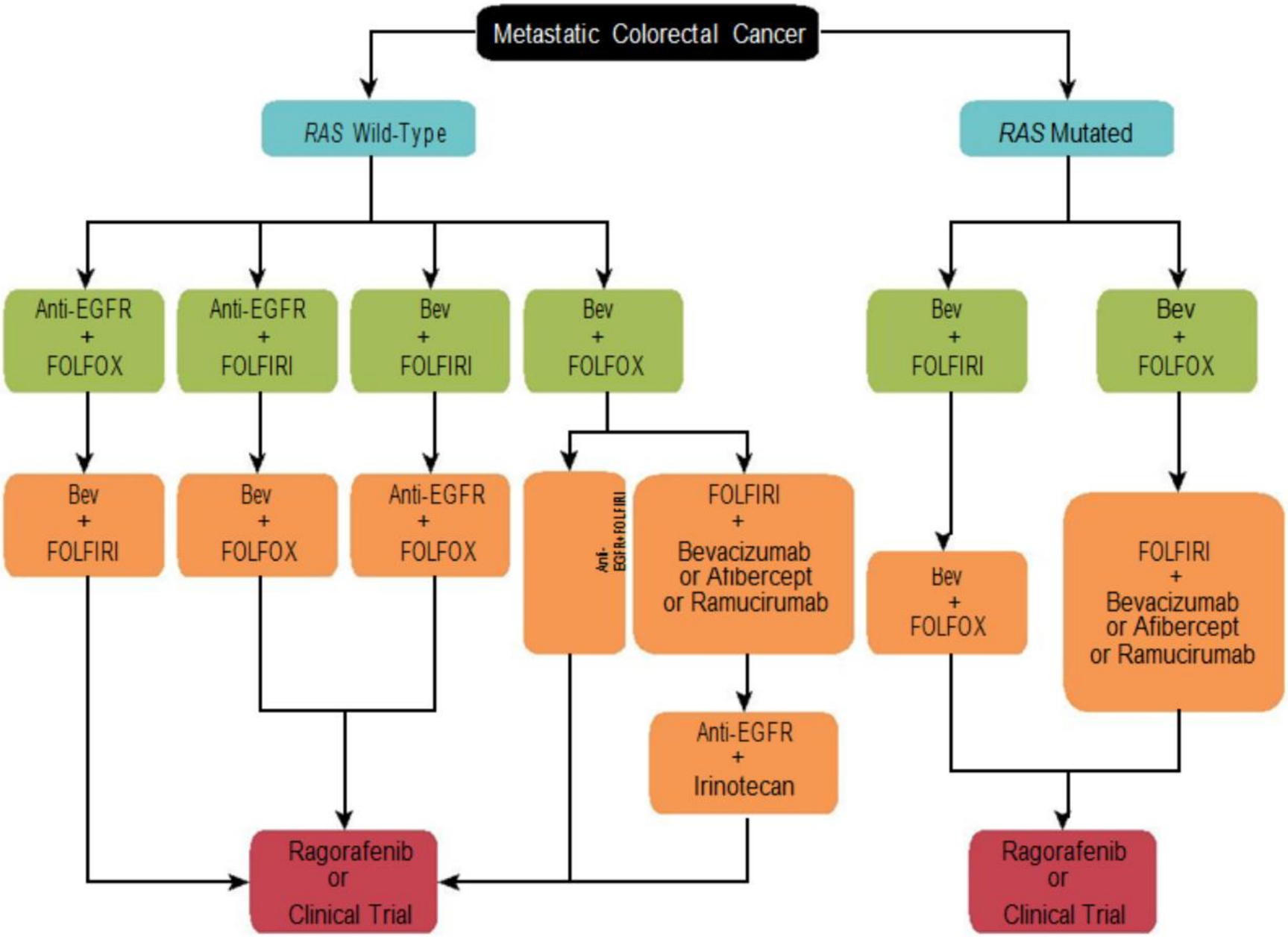


transcriptional activation
of signature genes

Wildtype	Mutant	Wildtype
Wildtype-like signature	Activated oncogenic signature	
Responsive to EGFR inhibition	Resistant to EGFR inhibition	

Figure. Schema for Contemporary Therapy of Unresectable Metastatic Colorectal Cancer

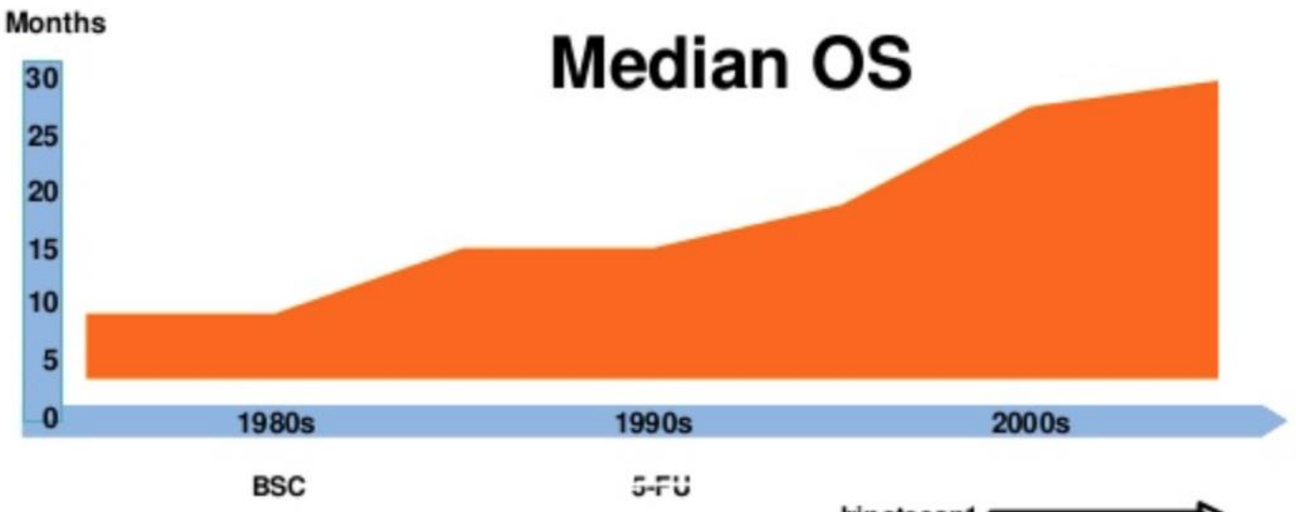


Anti-EGFR represents either cetuximab or panitumumab. 5-fluorouracil (5-FU) can be substituted with capecitabine.

Bev indicates bevacizumab; FOLFIRI, 5-FU and irinotecan; FOLFOX, 5-FU and oxaliplatin.

mCRC:

Improved Survival Over Time:



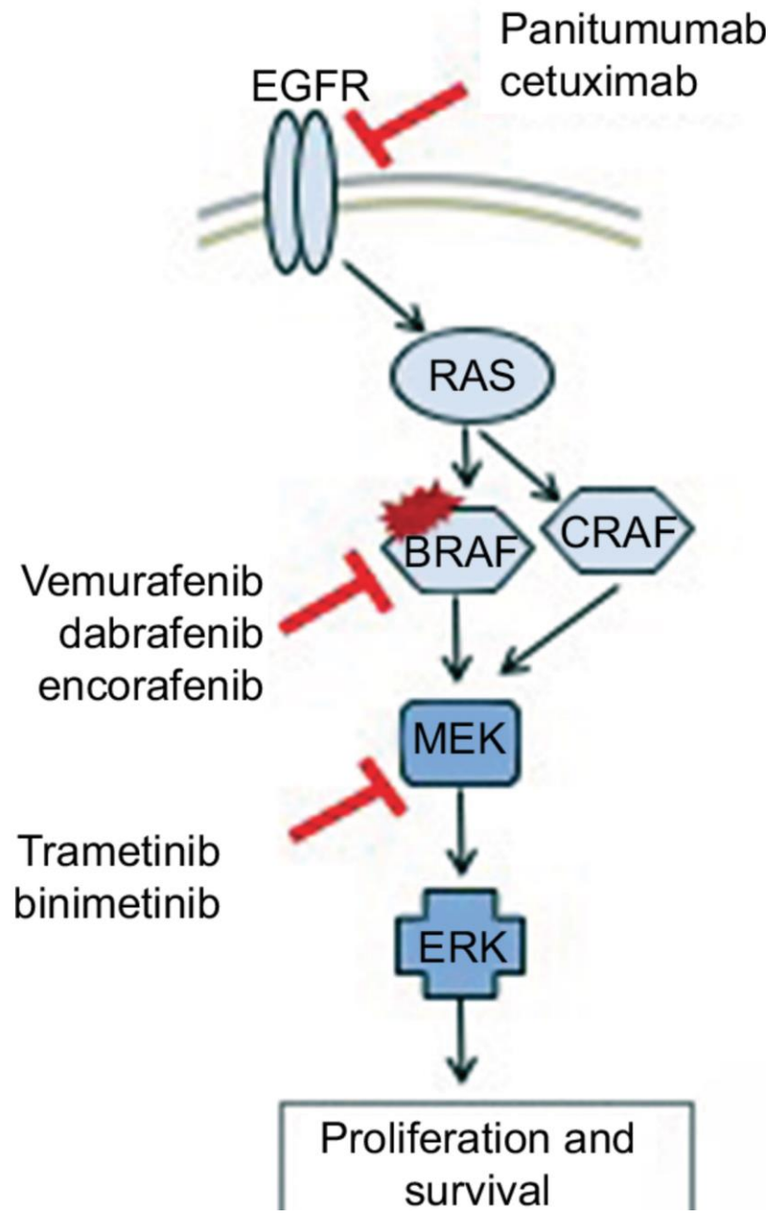
1. Cunningham D, et al. *Lancet*. 1998;352(9138):1413-1418. 2. Van Cutsem E, et al. *Br J Cancer*. 2004;90(6):1190-1197. 3. Rothenberg M, et al. *J Clin Oncol*. 2003;21(11):2059-2069. 4. Hurwitz H, et al. *N Engl J Med*. 2004;350(23):2335-2342. 5. Cunningham D, et al. *N Engl J Med*. 2004;351(4):337-345. 6. Van Cutsem E, et al. *N Engl J Med*. 2009;360(14):1408-1417. 7. Van Cutsem E, et al. *J Clin Oncol*. 2007;25(13):1658-6164. 8. Van Cutsem E et al. *J Clin Oncol*. 2012;30(28):3499-3506. 9. Grothey A, et al. *Lancet*. 2013;381(9863):303-312.

Whats new in biology of CRC

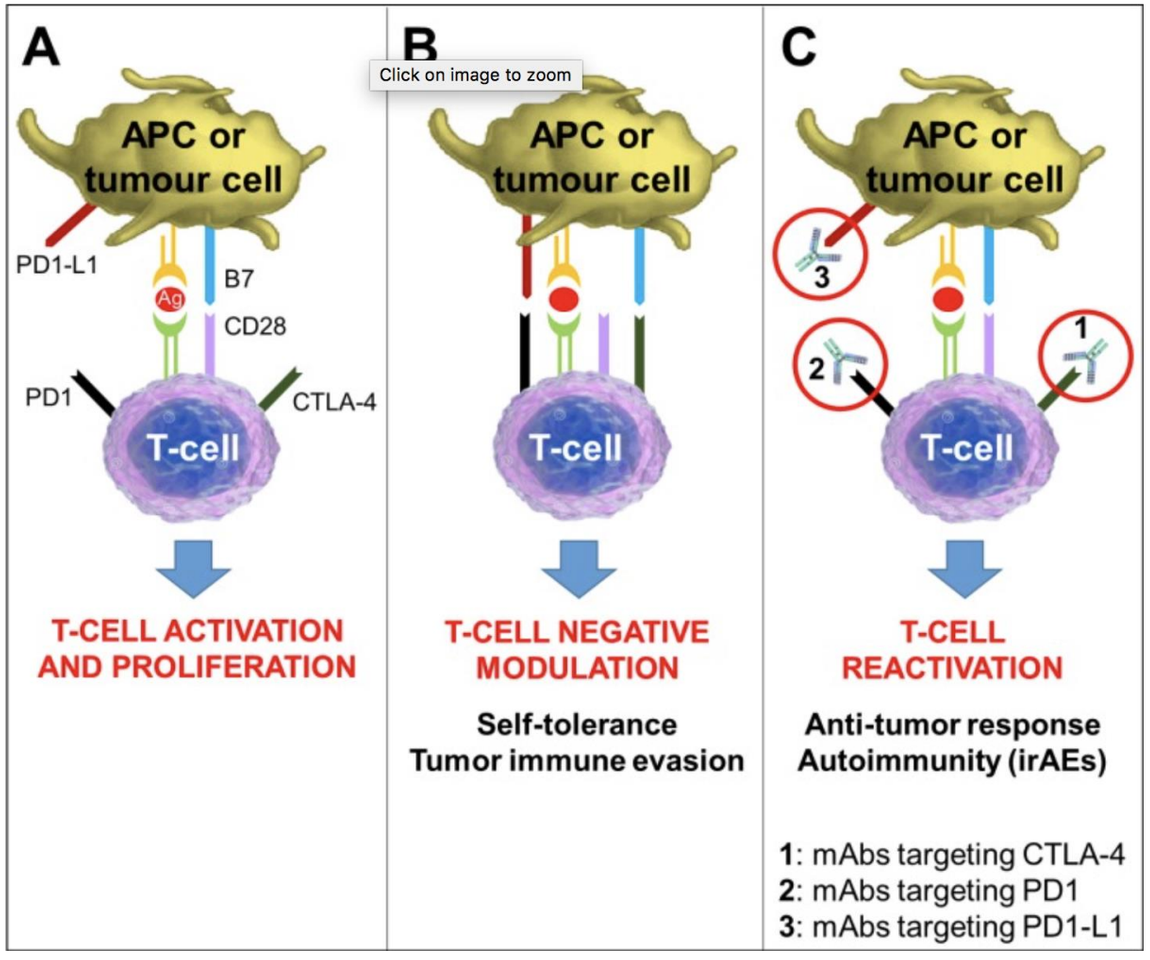
- Right sided tumors and left sided tumors have different biology
- CALGB/SWOG 80405
- Right sided tumors have MOS of 19.4 months cf 33.2 months for left sided tumors
- Left sided tumors treated with cetuximab have OS of 36 vs 31.4 months
- OS worse when right sided tumors treated with cetuximab 16.7 months

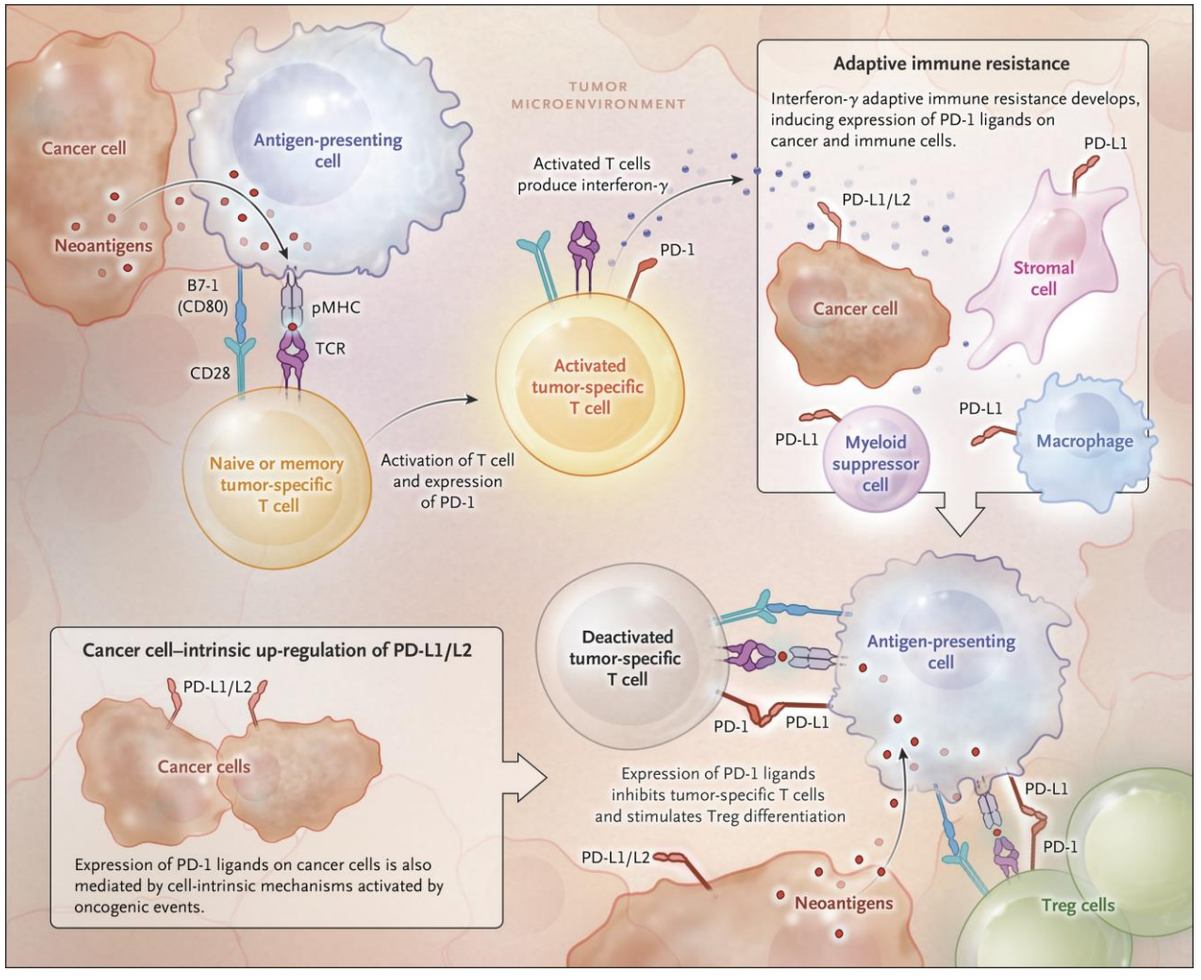
Braf Mutated CRC

- 6-8% of metastatic CRC
- Usually right sided
- Higher incidence of peritoneal disease
- Aggressive phenotype with poor prognosis
- Median OS +- 12 months



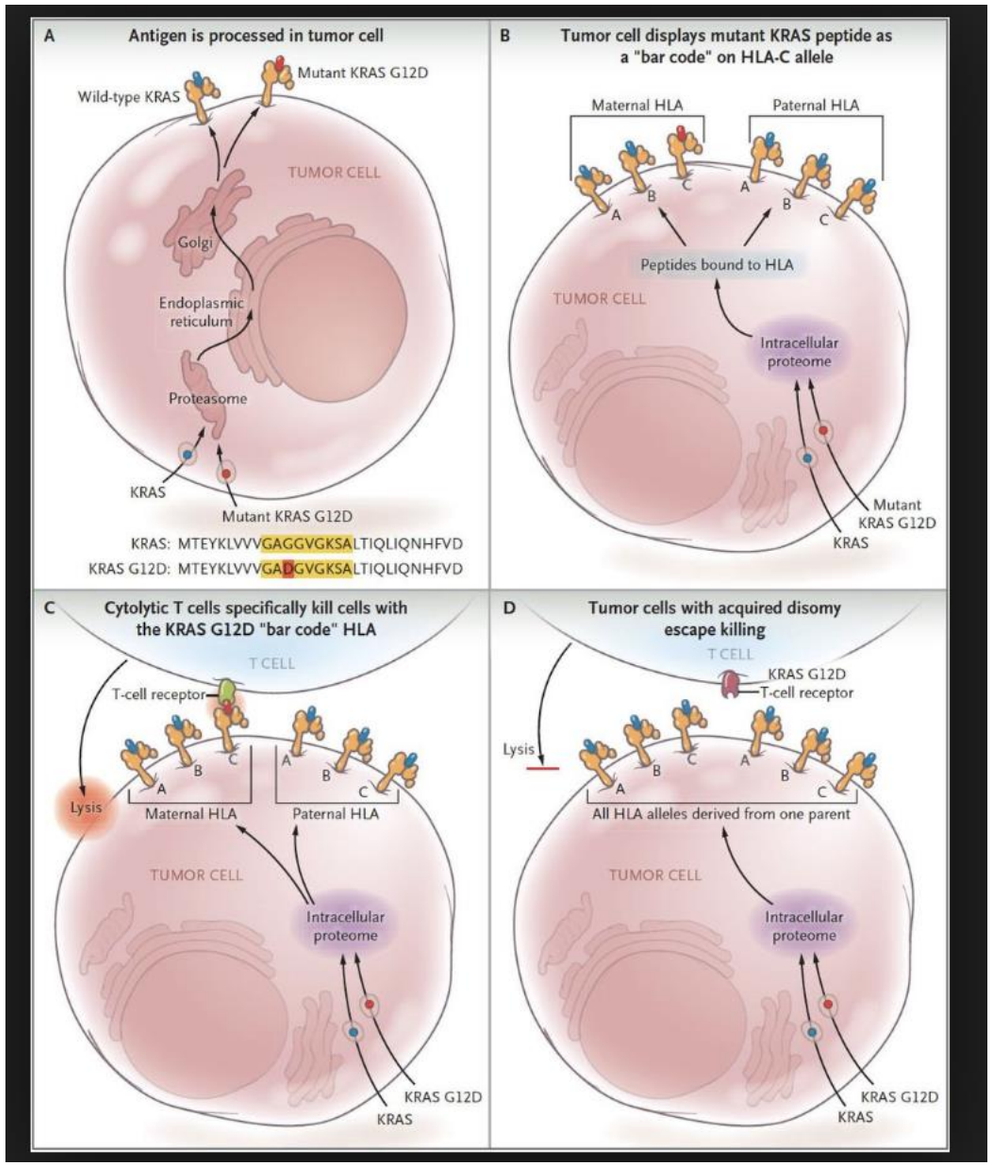
Immunotherapy and CRC

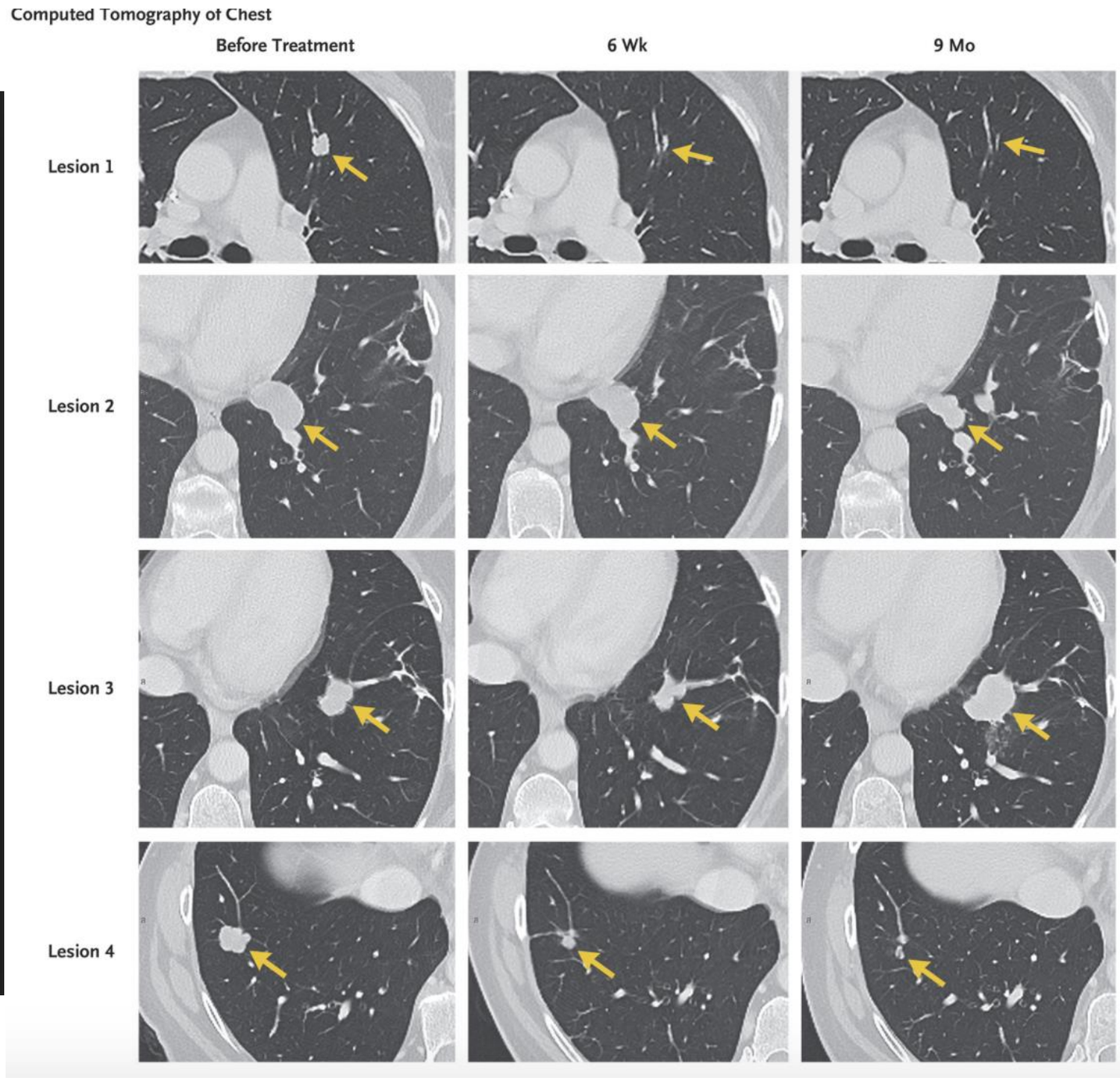




- MSI high tumors 3-5% of metastatic CRC
- Increased cell surface epitopes leading to increased immunogenicity
- Treatment with immunotherapy in second or later lines of therapy

T cell therapy to target cancer cells





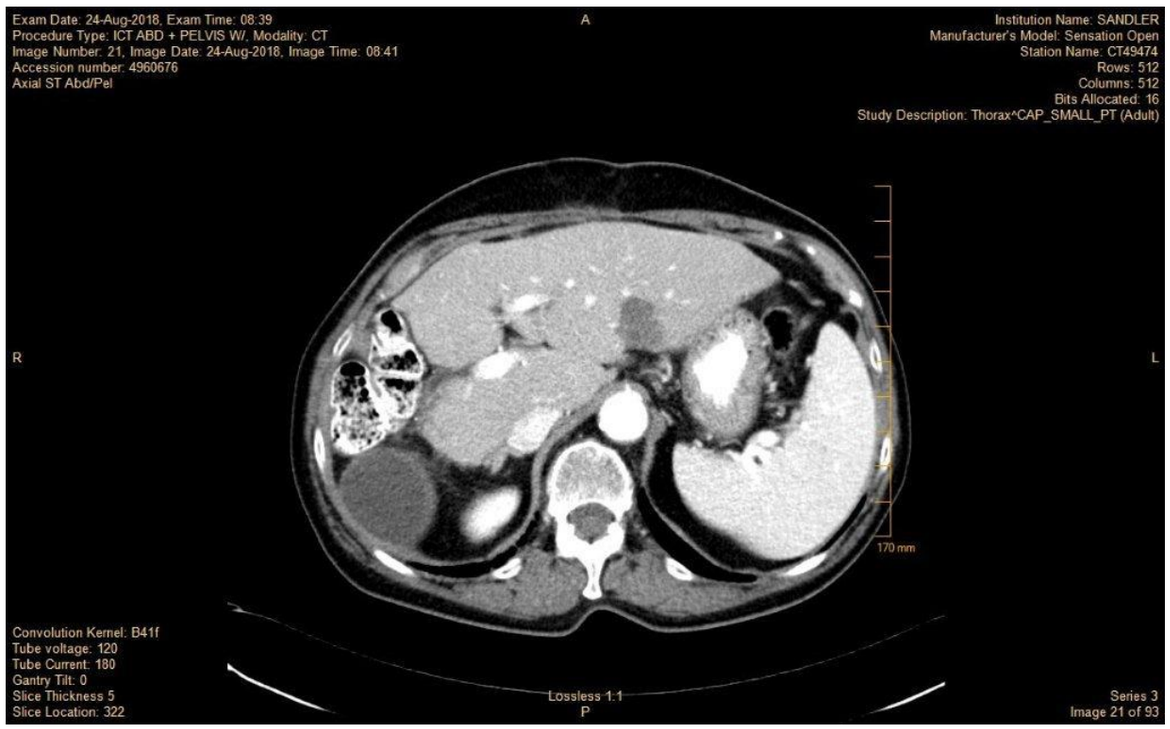
Tran et al; NEJM 2016;Dec 8;375(23):2255-2262

Gastrointestinal Multimodlity Clinic at Lynn Cancer Institute

- Multidisciplinary management of GI malignancies with medical oncology, radiation oncology, surgical disciplines, pathology,radiology and interventional radiology

Cases

- 69 year old female
- Diagnosed with rectal cancer with bilobar liver metastases, ?lung nodules and adrenal nodule 10/2016
- KRAS,NRAS and BRAF wild type and MSI stable
- FOLFIRI/panitumumab 10/2016-10/17
- Rectal surgery 11/2017 - T2N0
- Reintroduction chemotherapy 12/17-1/18
- Portal vein embolization 1/18
- Right liver lobe lobectomy 2/18 and microwave ablation of left lateral segment lesion
- Progression of left sided liver lesion 4/18
- FOLFOX/bevacizumab 4/18-8/18
- Fiducial placement in left sided liver lesion with SBRT to left sided liver tumor
- Patient currently disease free on observation



- 44 year old female
- Metastatic left sided sigmoid CRC with liver metastases , MSI stable, Pan Ras wild type
- 6 cycle of FOLFOX
- Surgical resection with left sided colectomy (12/15 + LN) and left liver lobectomy
- continuation of Folfox for planned 6 cycles