Clinical & Translational Correlation Colorrectal Cancer

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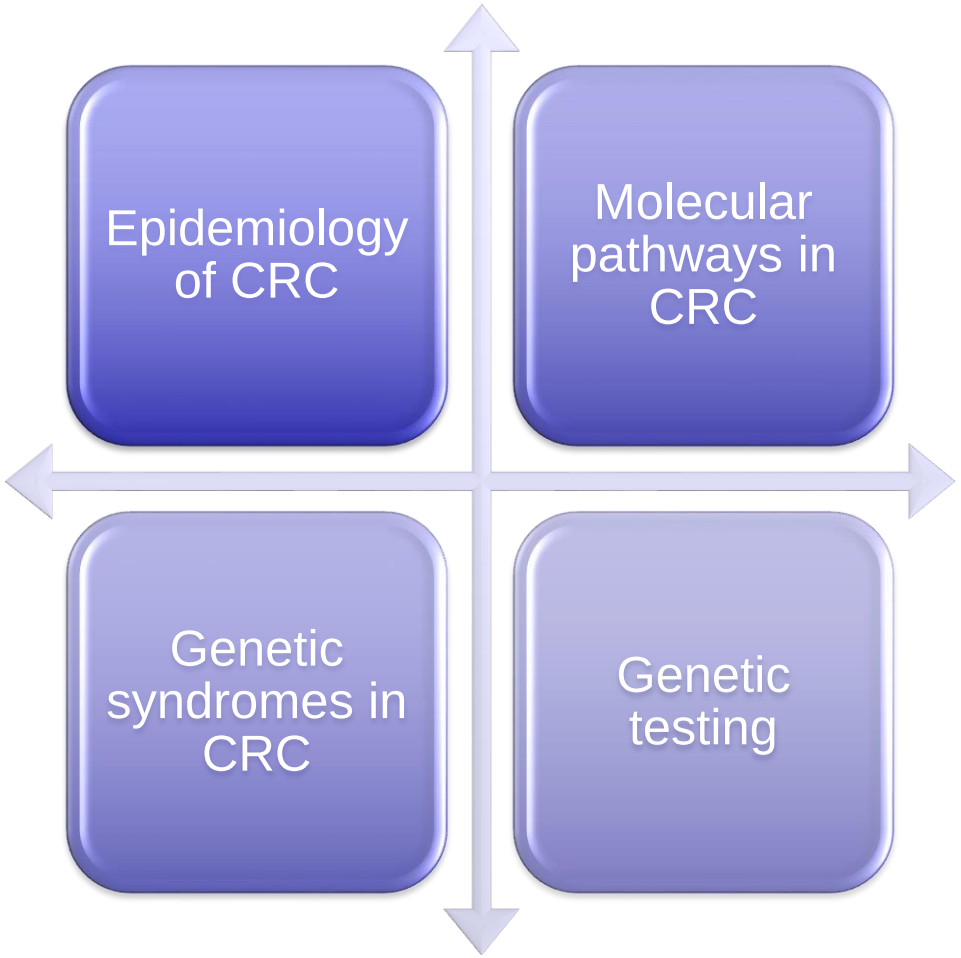
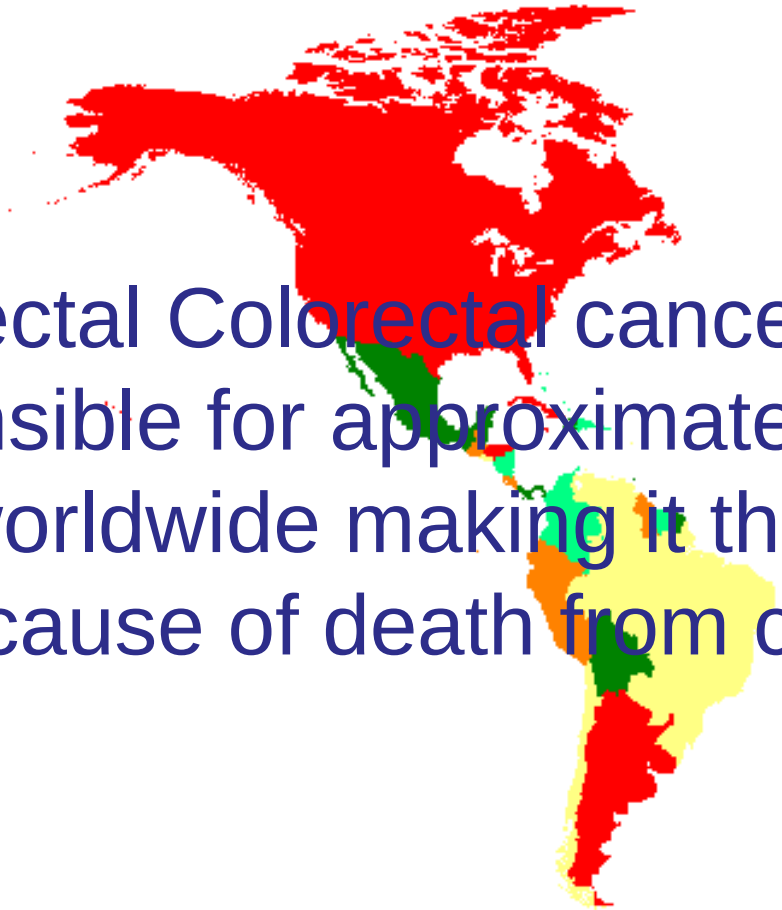
CENTRO COMPRENSIVO DE CÁNCER
universidad de puerto rico

colorectal cancer coalition
PUERTO RICO

No Financial Disclosures

What We Will Learn…



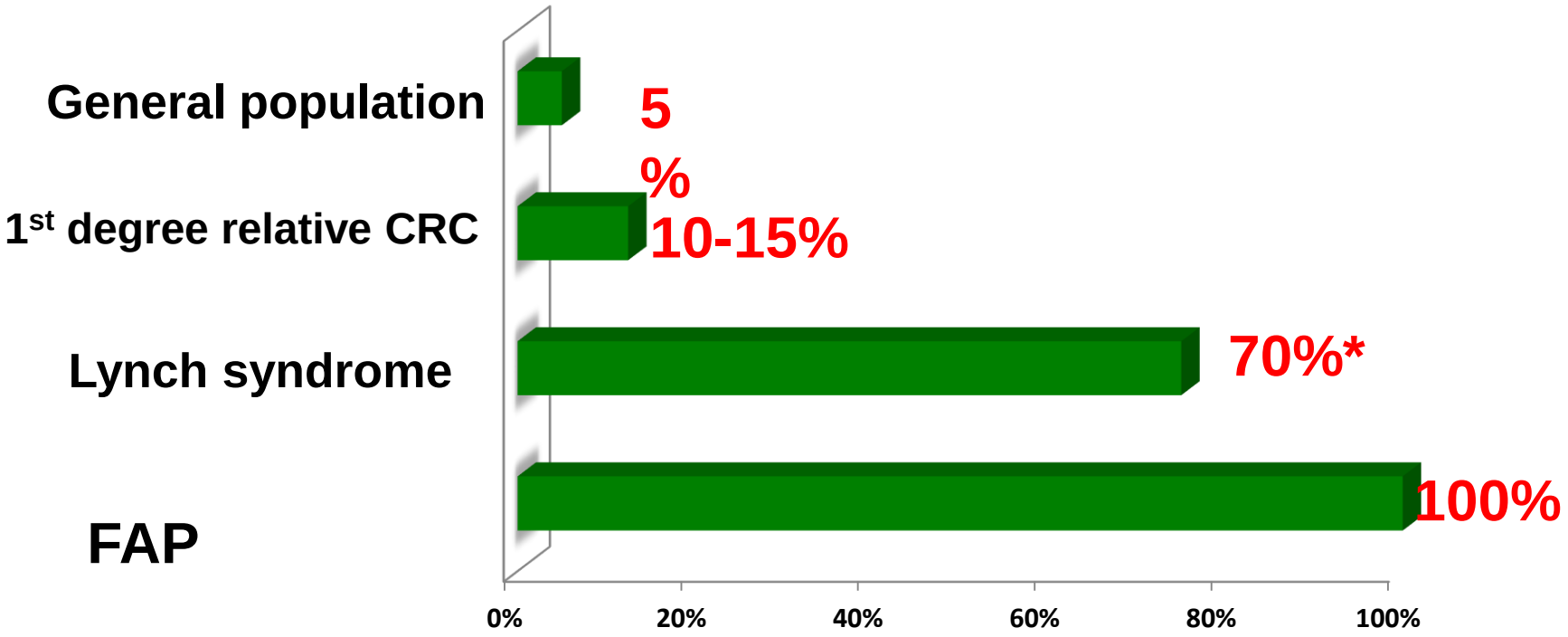


Colorectal Colorectal cancer (CRC) is responsible for approximately 608,000 deaths worldwide making it the fourth most common cause of death from cancer in 2008

< 141.8 < 152.2 < 162.1 < 174.9 < 275.0

GLOBOCAN 2008 (IARC) - 14.2.2013

Colorectal Cancer Life time risk



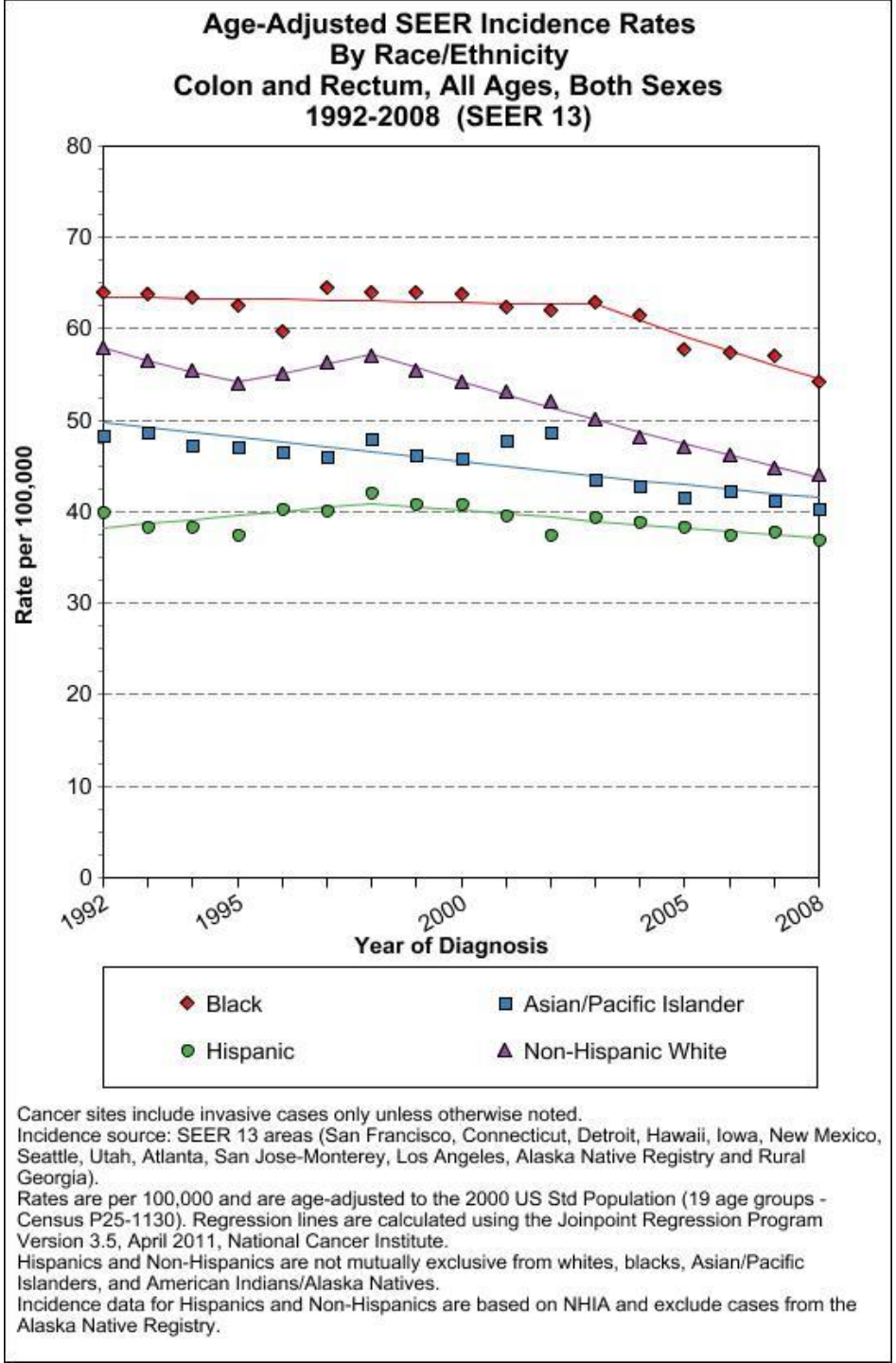
*Stoffel E, *et al*. *Gastro*. 2009; 137: 1621-1627

Age-adjusted SEER CRC Incidence Rates (2006-2010)

Race/Ethnicity	Male	Female	Both sexes
All Races	52.2	39.3	45.8
White	51.3	38.4	44.9
Black	64.3	49.2	**56.8**
Asian/Pacific Islander	43.8	32.7	**38.3**
American Indian/Alaska Native	44.1	36.6	**40.4**
Hispanic	45.5	31.6	**38.6**

From 2006-2010, the median age at diagnosis for colorectal cancer was 69 years of age

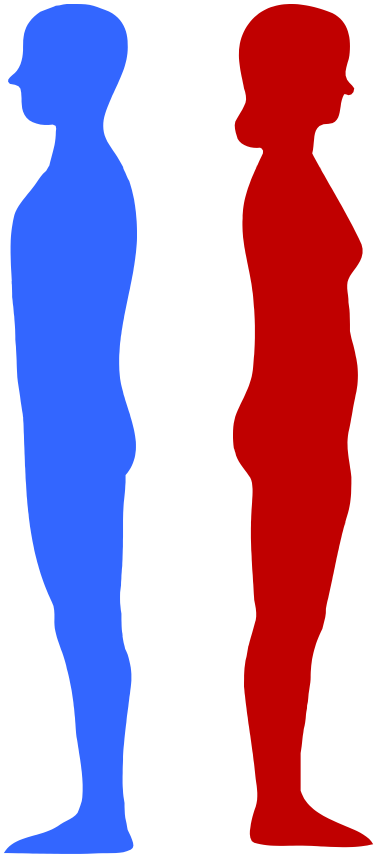
Age-Adjusted US Incidence Rates (SEER 13)



Cancer sites include invasive cases only unless otherwise noted.
Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130). Regression lines are calculated using the Joinpoint Regression Program Version 3.5, April 2011, National Cancer Institute.
Hispanics and Non-Hispanics are not mutually exclusive from whites, blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives.
Incidence data for Hispanics and Non-Hispanics are based on NHIA and exclude cases from the Alaska Native Registry.

Top Ten Incidence Cancer Sites, 2005-2009*

Males (N=32,714)	%
Prostate	40.2
Colon and Rectum	13.4
Lung and Bronchus	6.4
Urinary Bladder	4.1
Oral Cavity and Pharynx	4.0
Non-Hodgkin Lymphoma	3.4
Stomach	2.9
Liver and Intrahepatic Bile	2.8
Kidney and Renal Pelvis	2.1
Leukemia	2.1
Other Locations	18.4



Females (N=27,935)	%
Breast	30.6
Colon and Rectum	14.0
Thyroid	8.1
Corpus and Uterus	7.1
Lung and Bronchus	4.2
Non-Hodgkin Lymphoma	3.8
Cervix Uteri	3.7
Stomach	2.6
Ovary	2.6
Leukemia	1.9
Other Locations	21.3

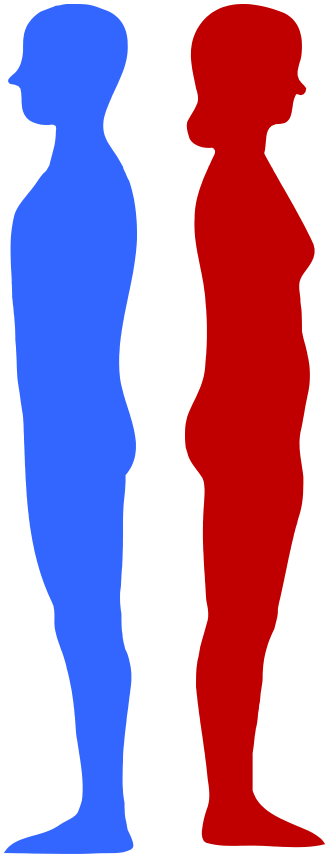
*Statistics are from an average of the years 2005-2009/statistics that presents the year 2009 are preliminary.
Cases with age unknown were included/ Statistics were generated from malignant cases only

Rates are per 100,000 and age-adjusted to the 2000 PR population

Data Source: Puerto Rico Central Cancer Registry, Preliminary Puerto Rico Cancer Incidence File (December, 2011)

Top Ten Mortality Cancer Sites, 2007-2008*

Males (N=5,653)	%
Prostate	18.4%
Lung and Bronchus	13.2%
Colon and Rectum	12.8%
Liver and Intrahepatic Bile Duct	6.4%
Stomach	4.8%
Oral Cavity and Pharynx	3.8%
Pancreas	3.7%
Esophagus	3.6%
Lymphoma	3.6%
Leukemia	3.3%
Other Locations	26.5%



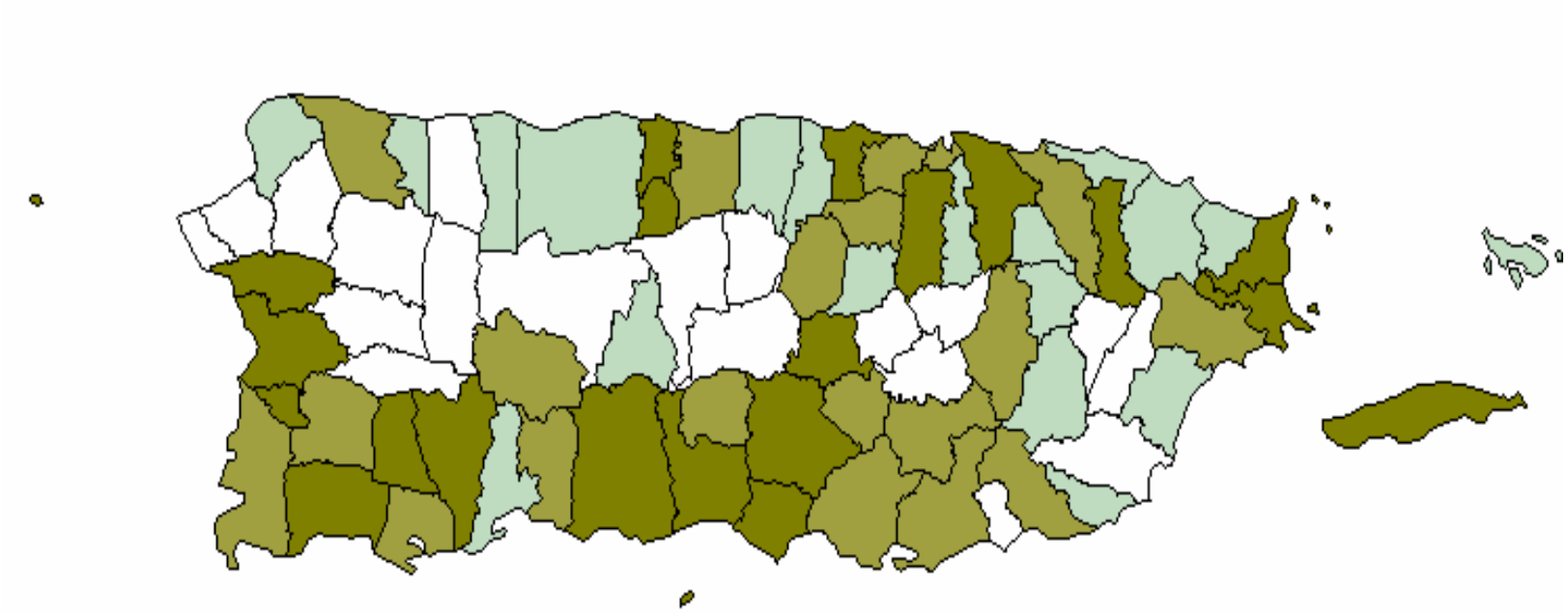
Females (N=4,319)	%
Breast	19.3%
Colon and Rectum	12.8%
Lung and Bronchus	10.2%
Liver and Intrahepatic Bile Duct	5.5%
Pancreas	5.3%
Corpus and Uterus, NOS	4.6%
Ovary	4.2%
Lymphoma	3.9%
Stomach	3.8%
Leukemia	3.5%
Other Locations	26.9%

*Cases with age unknown were included/ Statistics were generated from malignant cases only/ Statistics are an average of the years 2007-2008

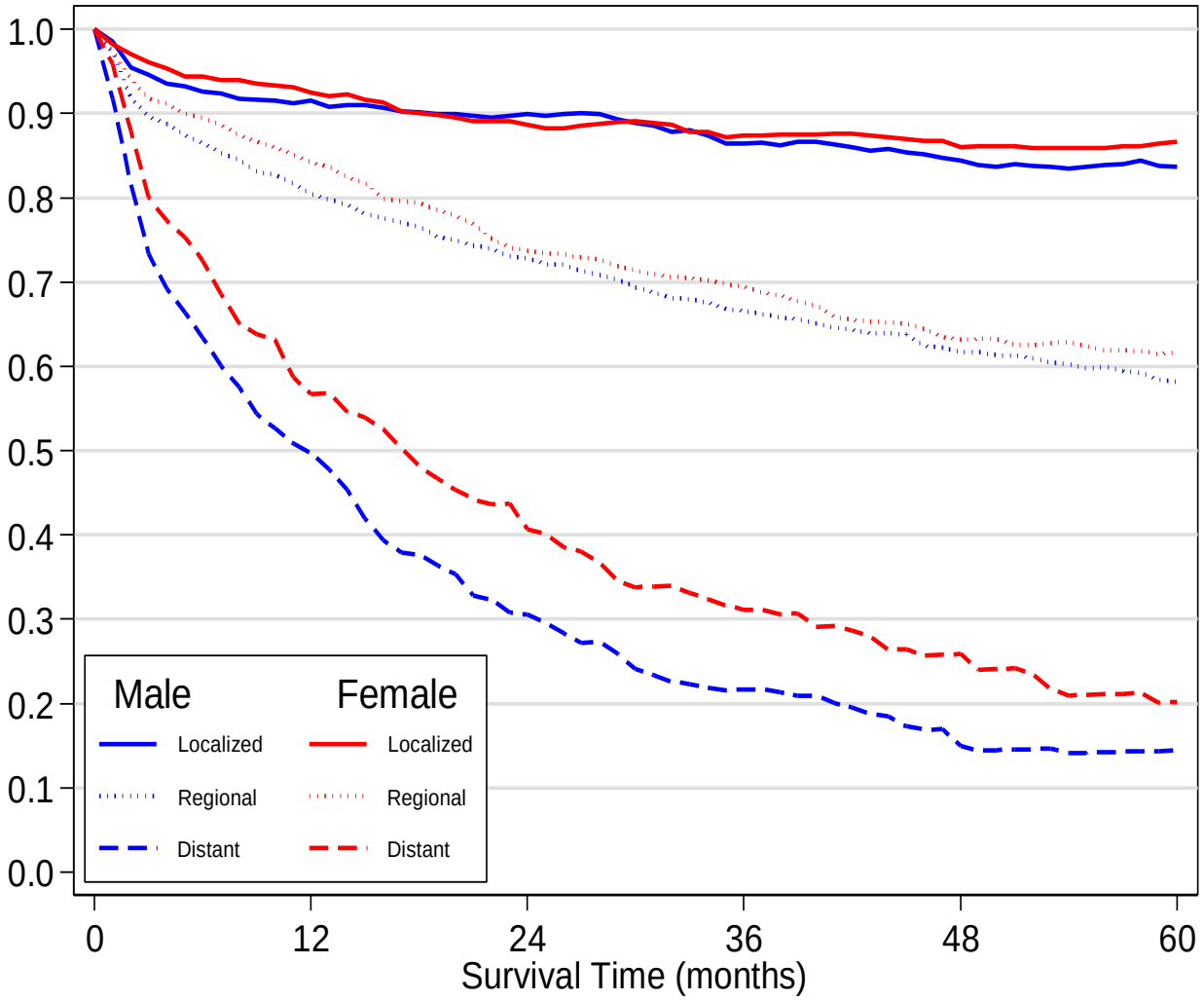
Rates are per 100,000 and age-adjusted to the 2000 PR population

Data Source: Puerto Rico Department of Health and National Center for Health Statistics using the Medical Mortality Data System (MMDS) for the years 2000-2008.

Age-Adjusted CRC Incidence Rates PR Municipalities

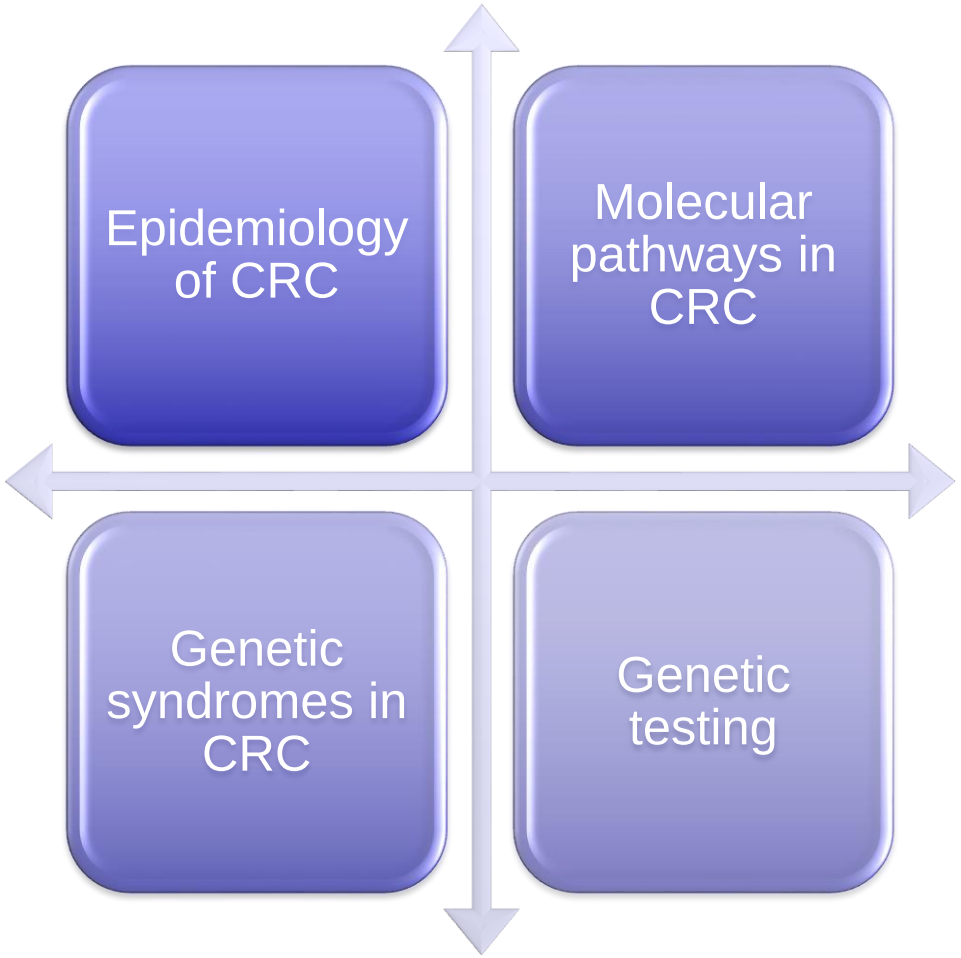


5-Yr CRC Stage Specific Survival in PR

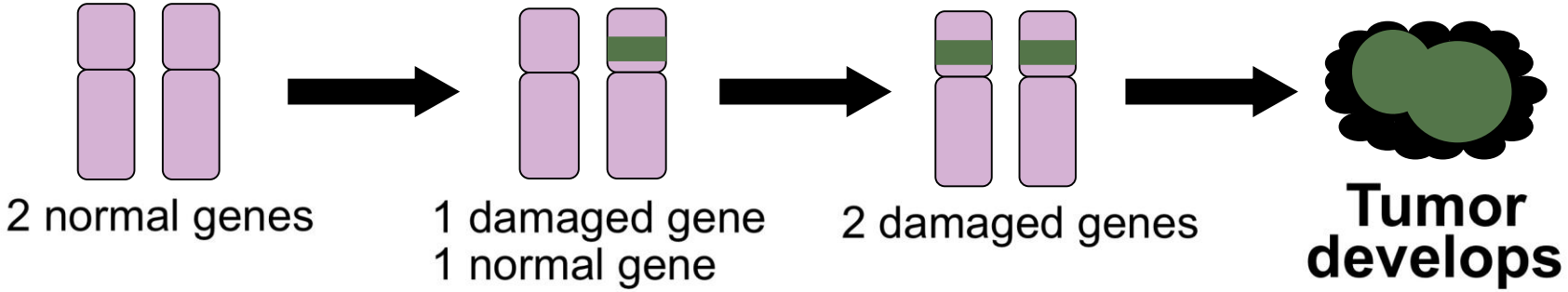


Cruz-Correa et al, Gastro 2011

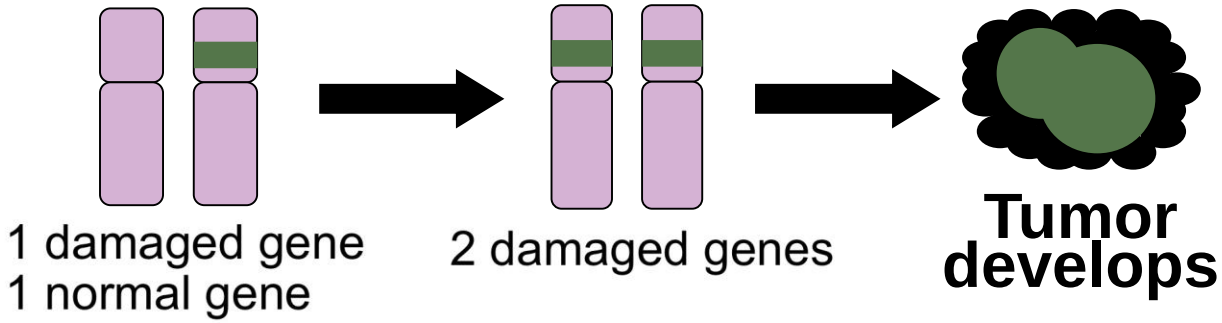
What We Will Learn…



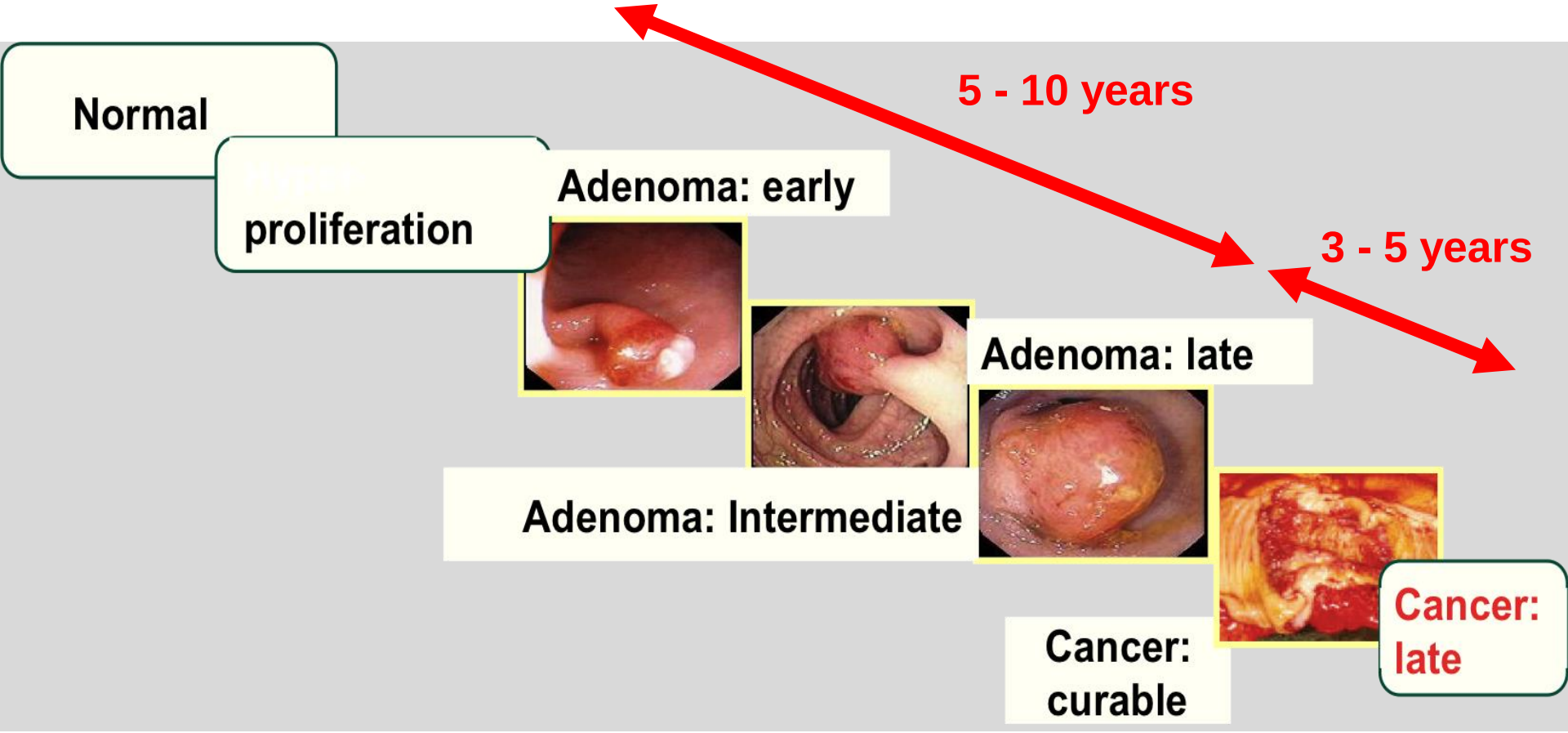
The Development of Hereditary Cancer



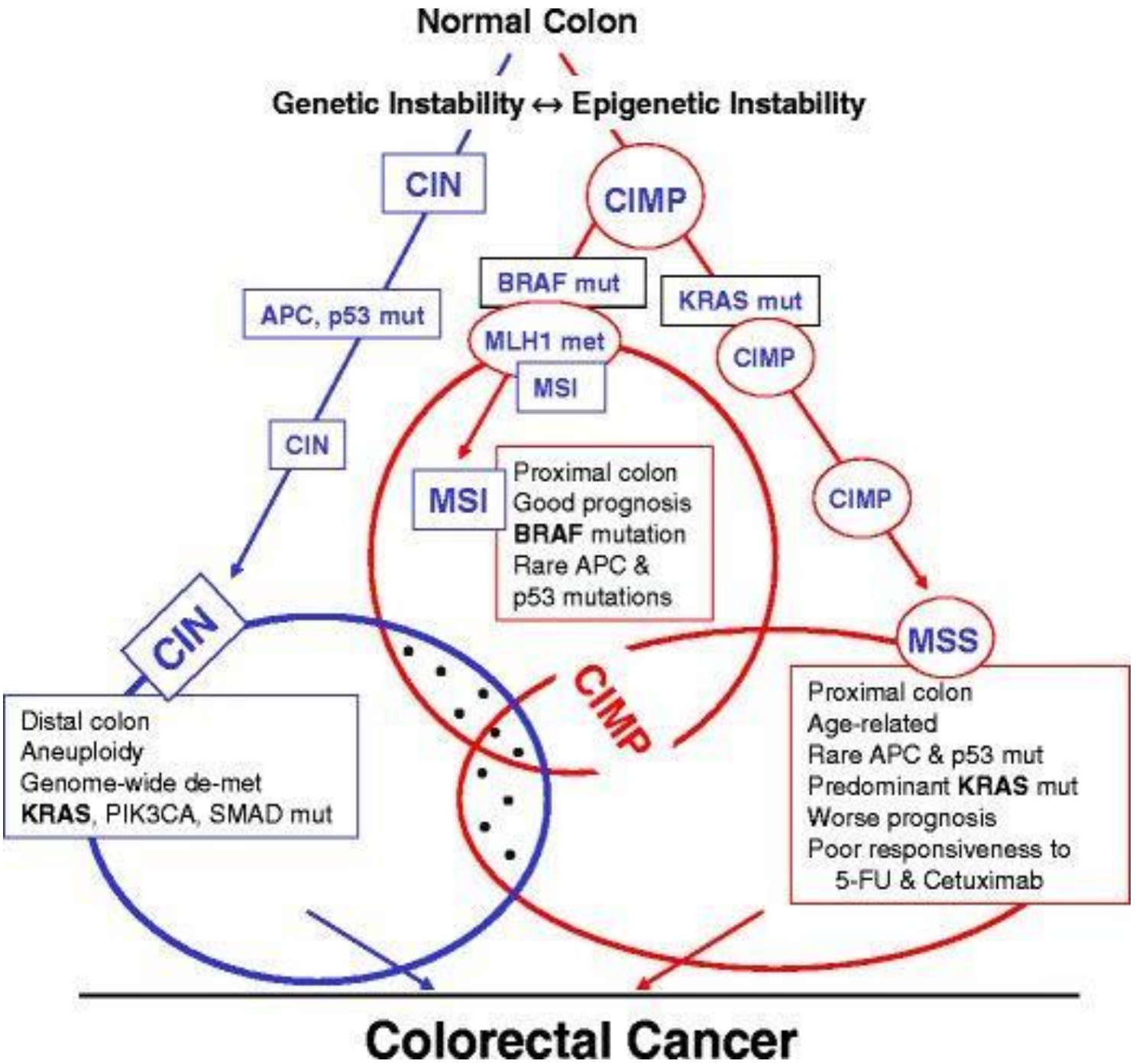
In hereditary cancer, one damaged gene is inherited.



Natural History of CRC



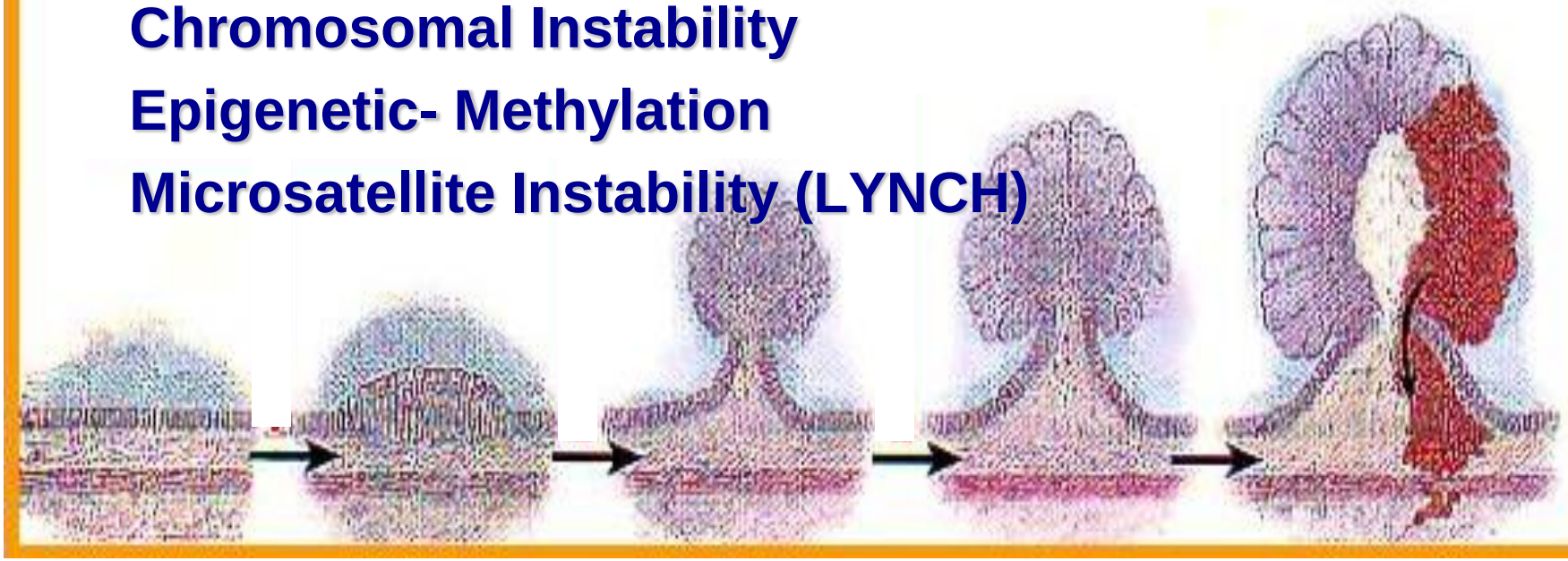
From: Rozen, Young, Levin, Spann (2002)


Normal Colon
Genetic Instability ↔ Epigenetic Instability
CIN
CIMP
APC, p53 mut
BRAF mut
KRAS mut
MLH1 met
MSI
CIMP
CIN
MSI
Proximal colon
Good prognosis
BRAF mutation
Rare APC &
p53 mutations
CIMP
CIN
MSS
CIMP
Distal colon
Aneuploidy
Genome-wide de-met
KRAS, PIK3CA, SMAD mut
Proximal colon
Age-related
Rare APC & p53 mut
Predominant KRAS mut
Worse prognosis
Poor responsiveness to
5-FU & Cetuximab
Colorectal Cancer

Adenoma-Carcinoma Sequence

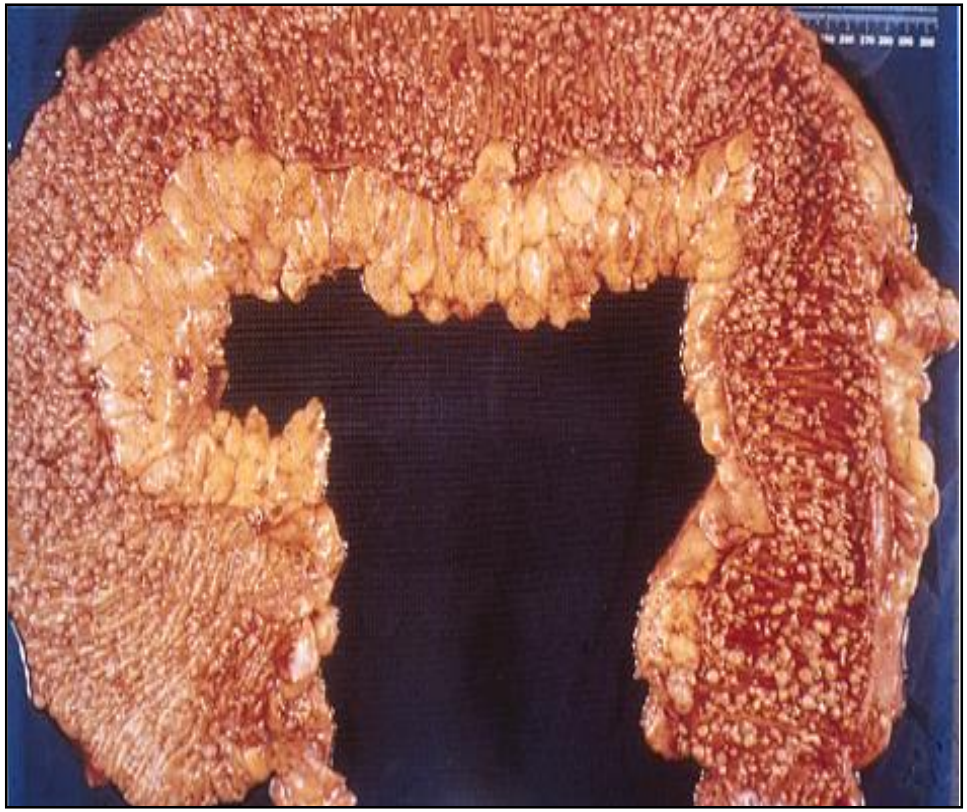
Molecular Pathways to CRC

- **Chromosomal Instability**
- **Epigenetic- Methylation**
- **Microsatellite Instability (LYNCH)**

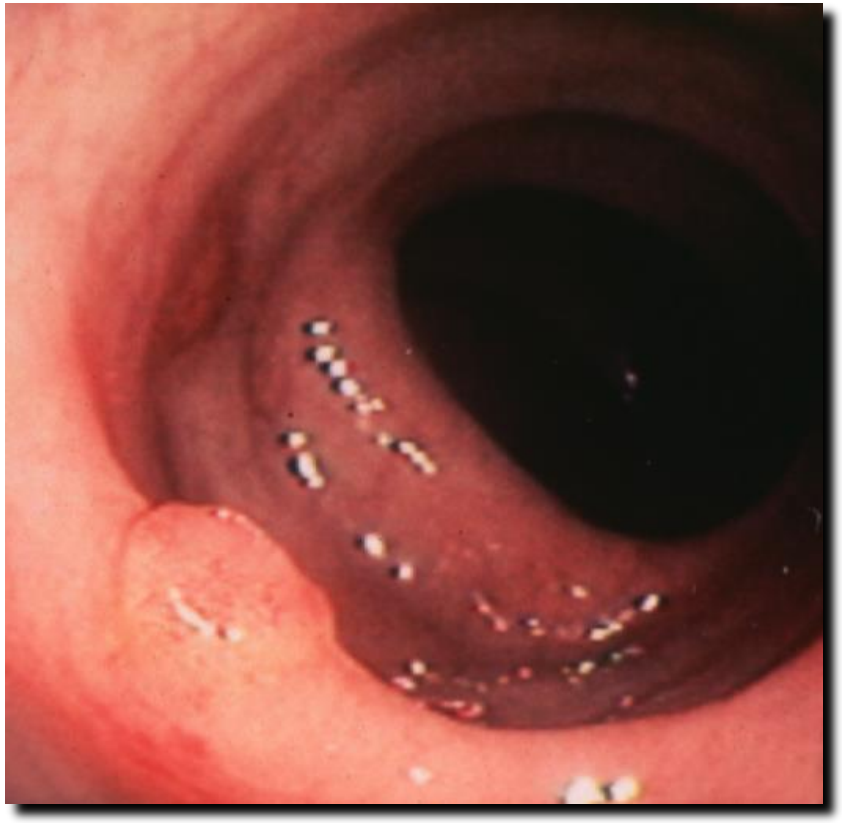


Normal Epithelium | Small Tubular Adenoma | Intermediate Adenoma | Advanced Adenoma | Adenocarcinoma

Chromosomal Instability Pathway

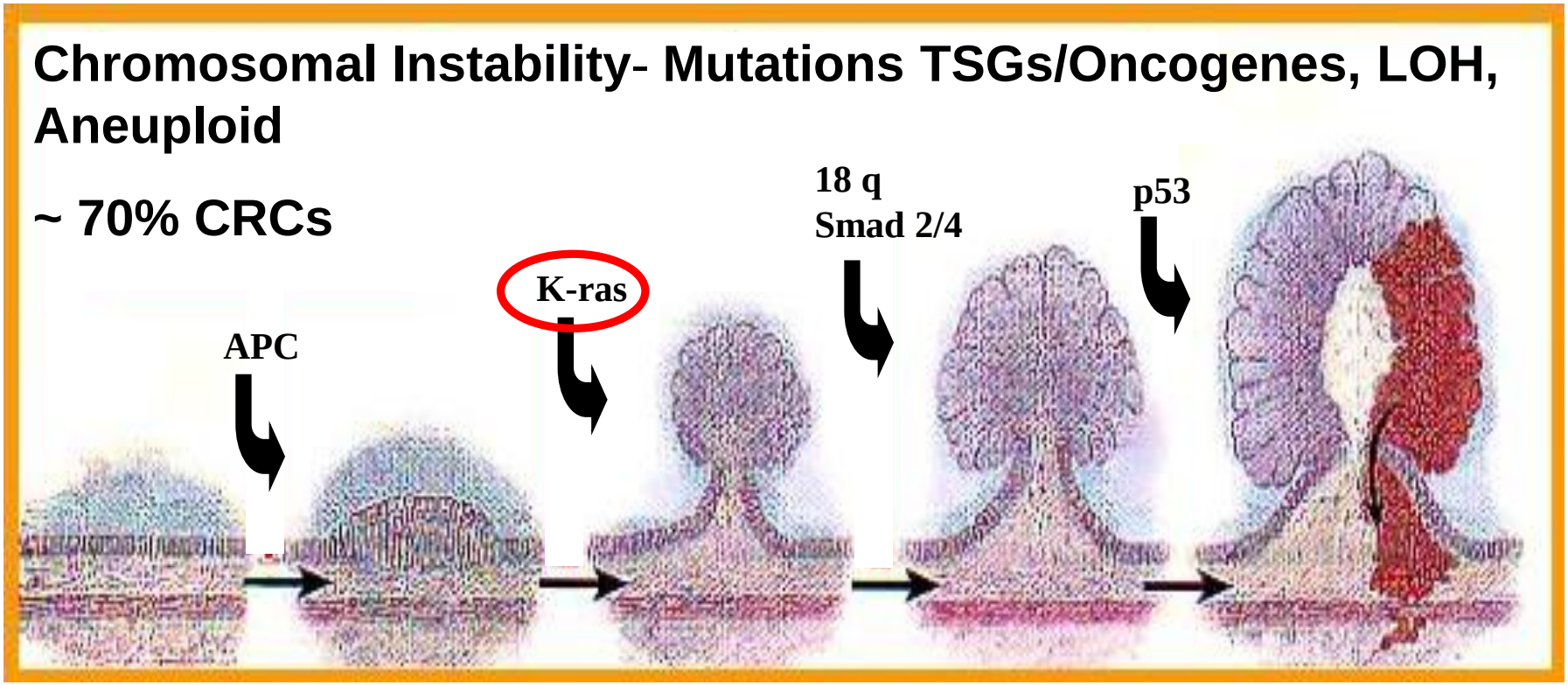


Familial Adenomatous Polyposis



Sporadic Adenomas

Chromosomal Instability Pathway to CRC



CASE 1

- 69 yo Male presented with iron deficiency anemia
  - Stage IV CRC with multiple mets to liver
  - Liver mets not amendable to surgery
  - Sigmoid colectomy to prevent obstruction
  - Clearing colonoscopy showed 2 diminuitive polyps
- Patient wants aggressive non-surgical therapy
- Oncologist recommends:
  - 5-Fluorouracil/Leukovorin
  - Bevacizamab (Avastin)

CASE 1: Your Treatment Approach?

A. Standard chemotherapy (FOLFOX)

B. Add NSAIDs

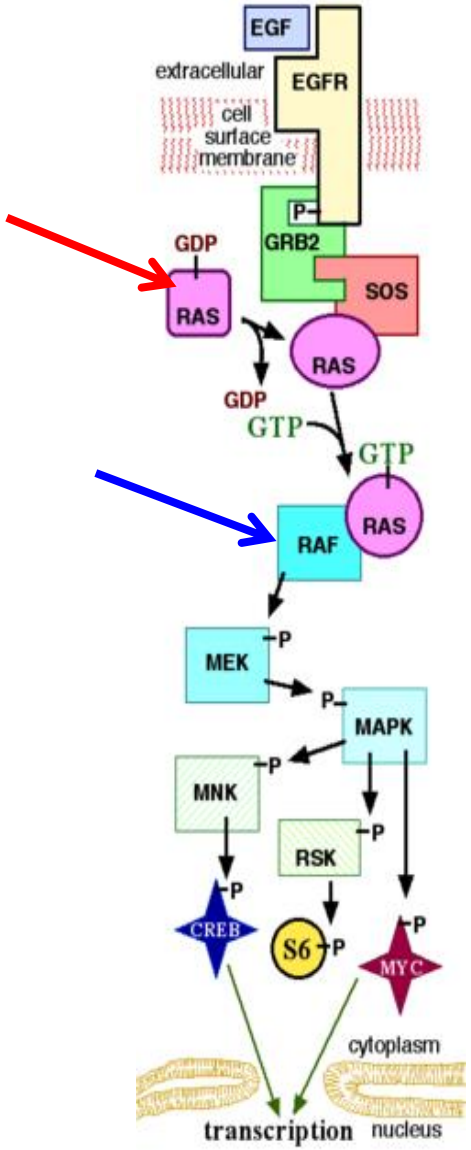
C. Genotype tumor for *RAS* and *RAF*

D. No therapy

Drugs for Advanced Colorectal Cancer

Drug	***Target***	***Stage for Treatment***	***Comments***
5-fluorouracil (5-FU)	antimetabolite	III, IV	Used with leukovorin
Irinotecan (Camptosar)	Topo-isomerase I inhibitor	III, IV	
Oxaliplatin (Eloxitin)	platinates DNA	III, IV	
Avastin (bevacizimab)	VEGF	IV	
Erbitux (**cetuximab**)	EGFR/HER1/c-ERB1	IV	**WT *KRAS* (and *BRAF)***
Vectibix (**panitumab**)	EGFR	IV	**WT *KRAS* (and *BRAF)***

RAS Signaling in Colon Cancer

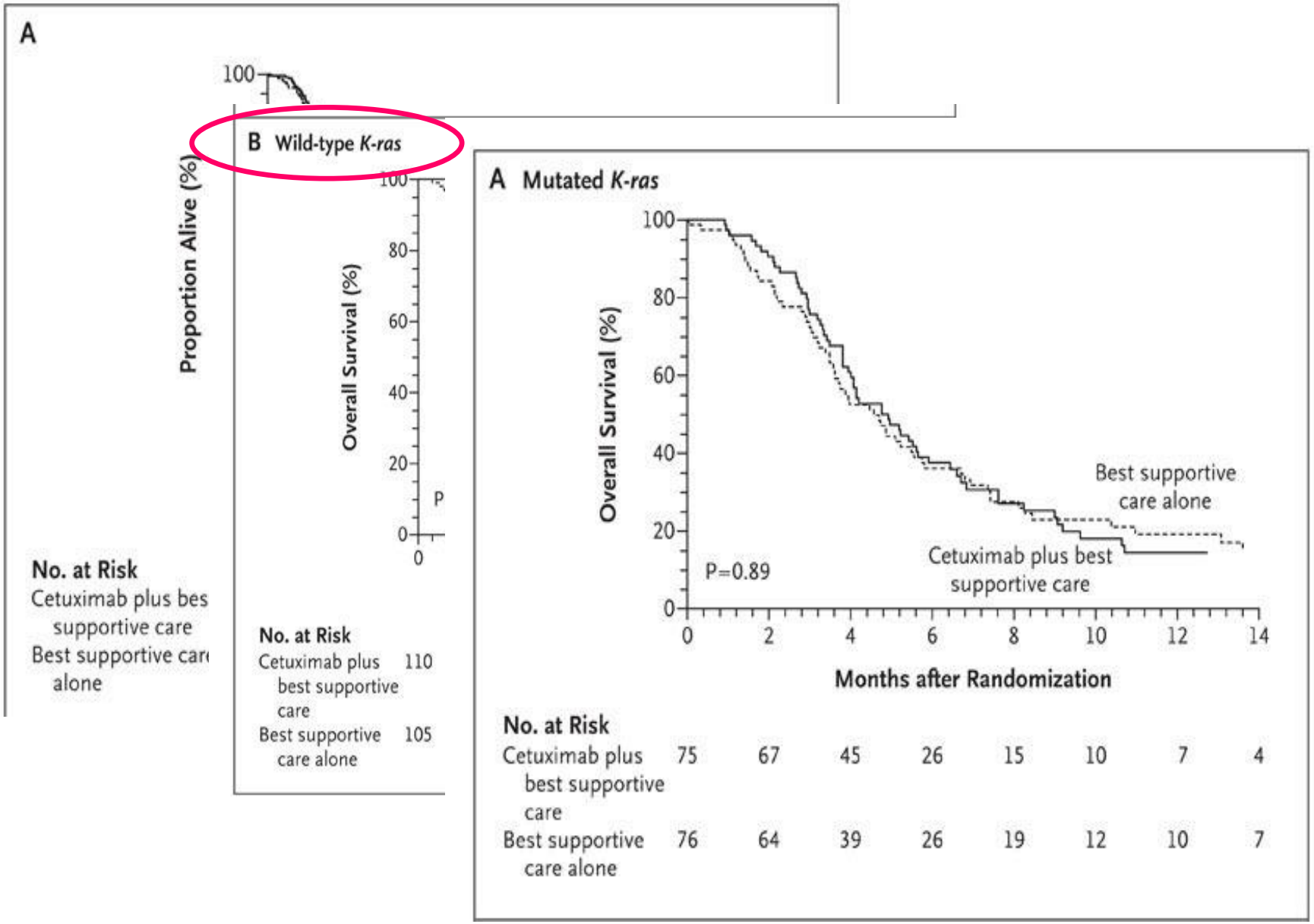


EGFR: overexpressed
RAS/RAF: mutational activation

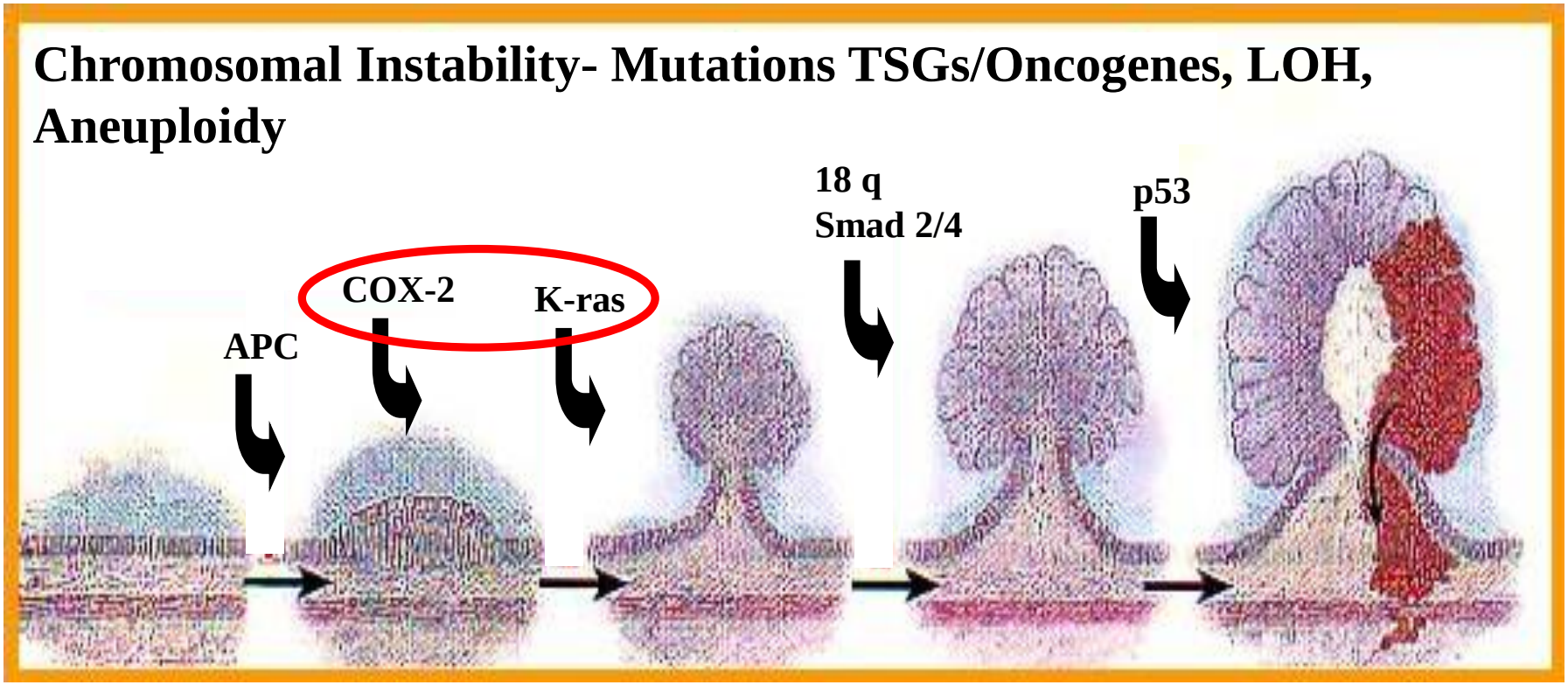
RAS: 50% CRC
RAF: in MMR-deficient sporadic tumors

Facilitates size growth
EGFR inhibitors ineffective with mutant *RAS*

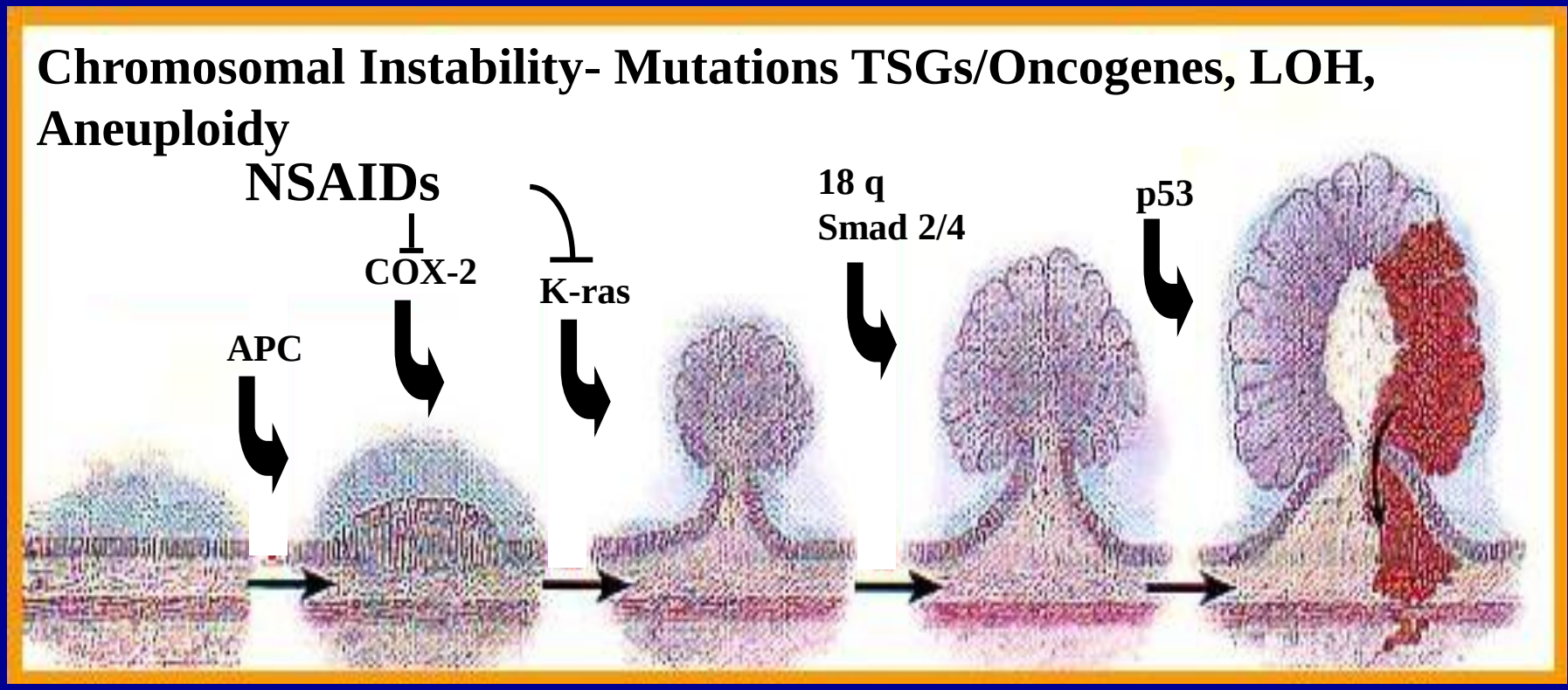
Cetuximab (Erbitux) for Metastatic CRC



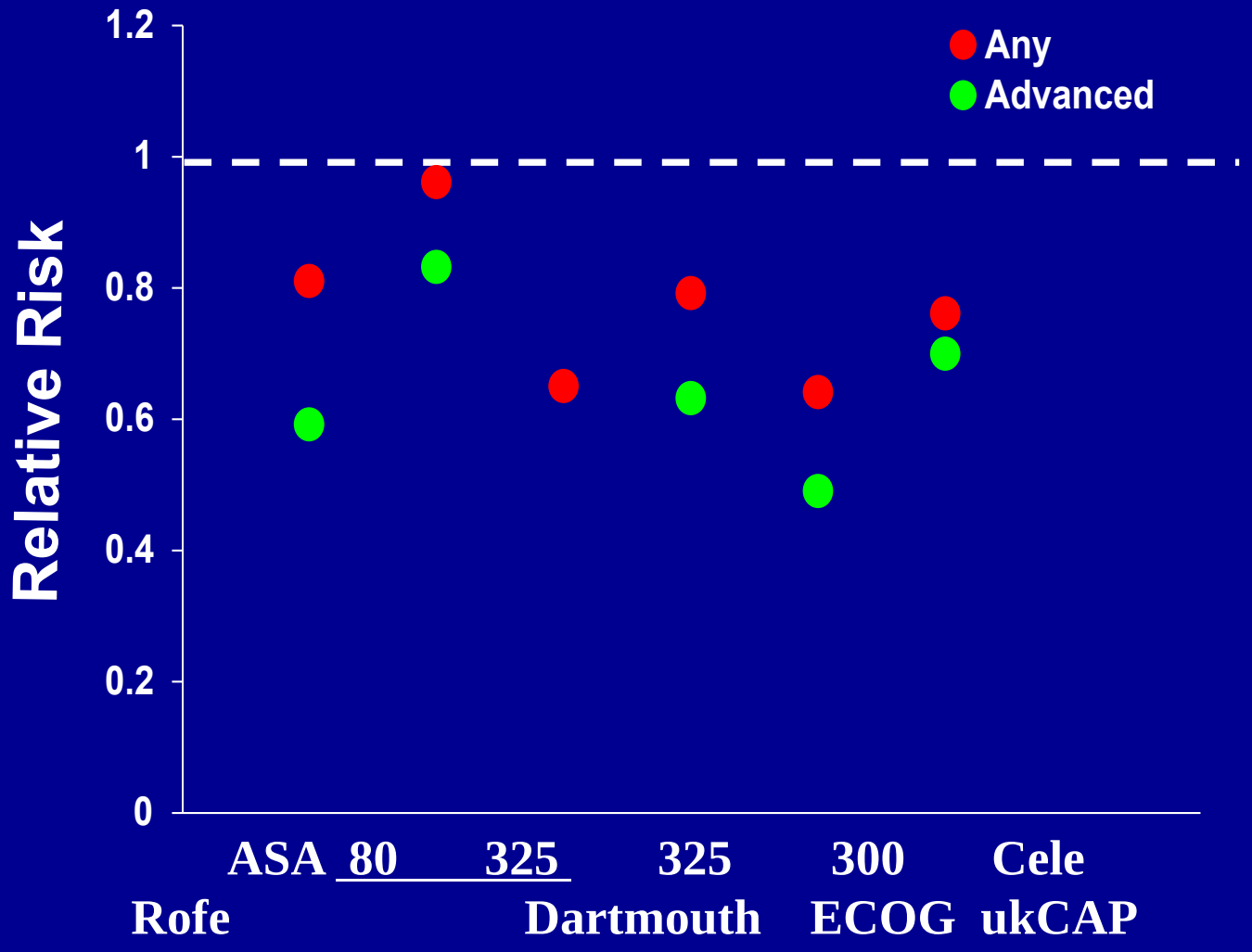
Chromosomal Instability Pathway to CRC



NSAIDs Inhibit CIS Pathway to CRC



NSAID Adenoma Prevention Trials

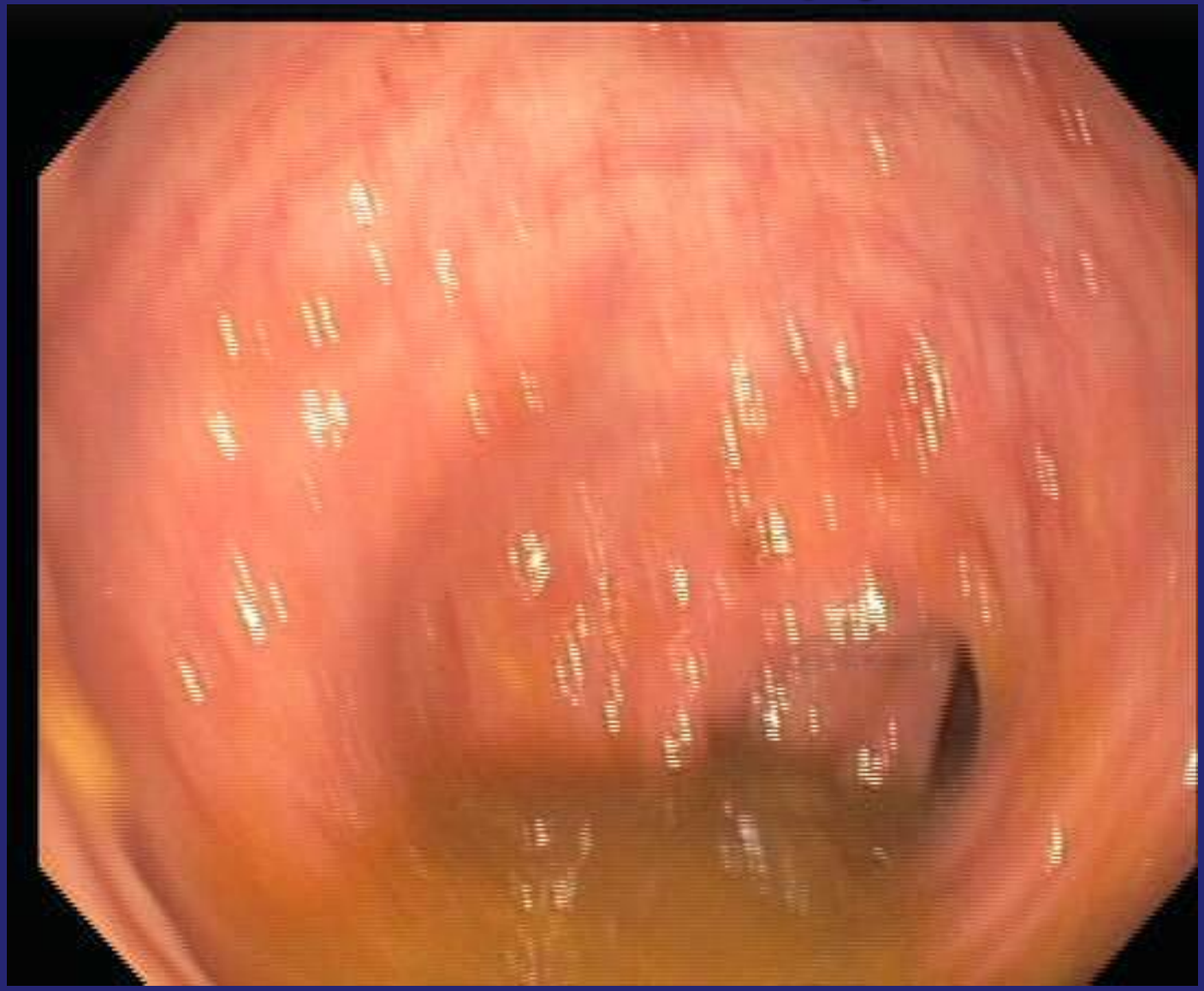


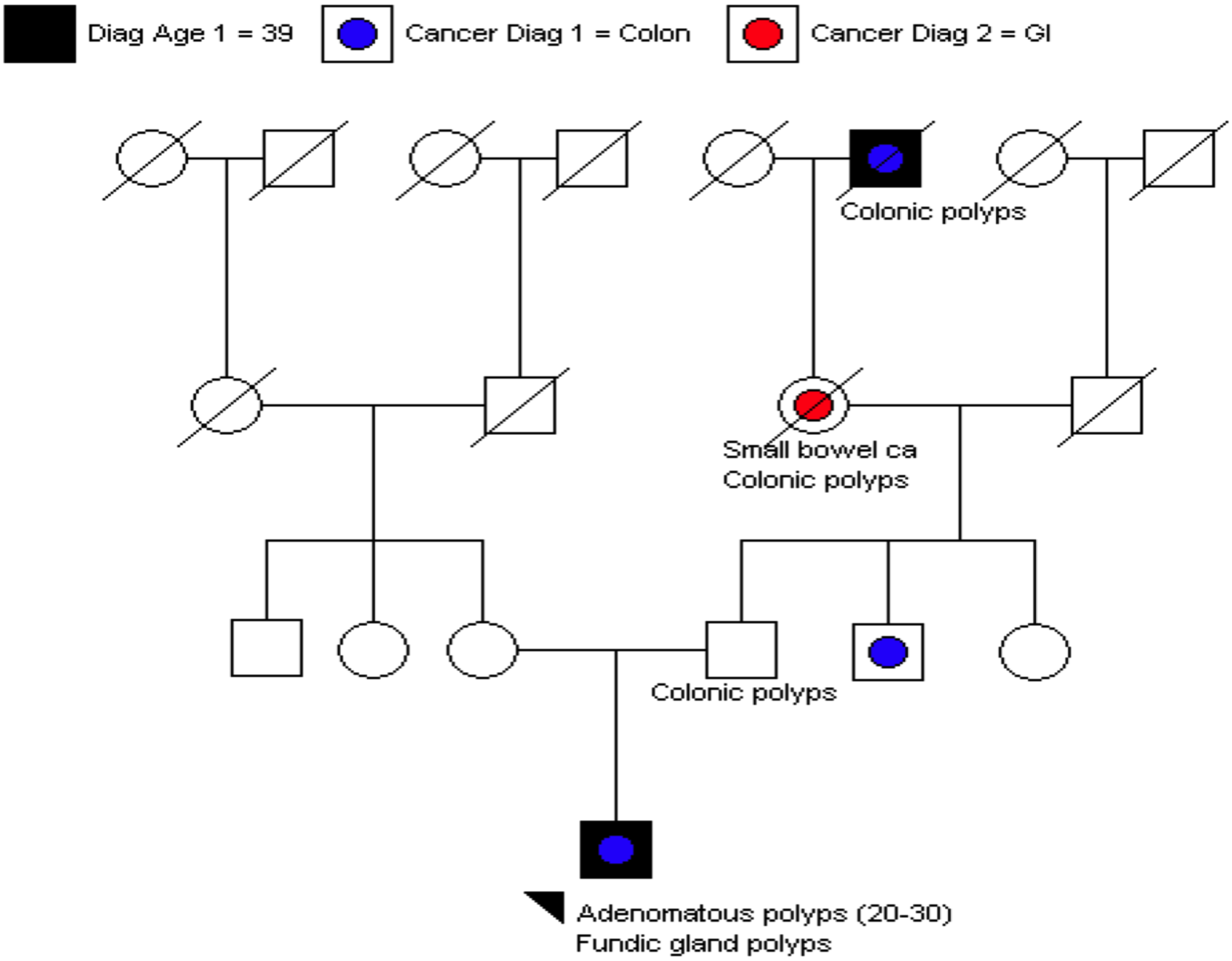
Baron et al N Engl J Med 2003 and Sandler et al ibid
Arber et al N Engl J Med 2006, Baron et al Gastroenterology 2006

Case 2

- 39 y/o anesthesiologist of Jewish ancestry presents with history of painless rectal bleeding for several months
- Family history is significant for father with colonic polyps and paternal uncle with colon cancer
- PE unremarkable

Colonoscopy

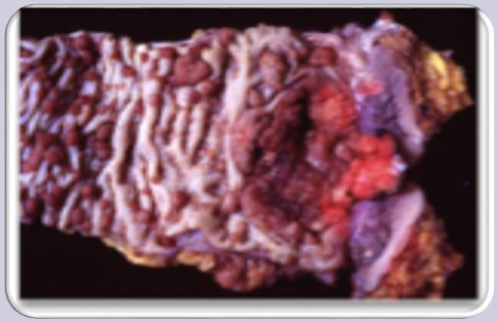


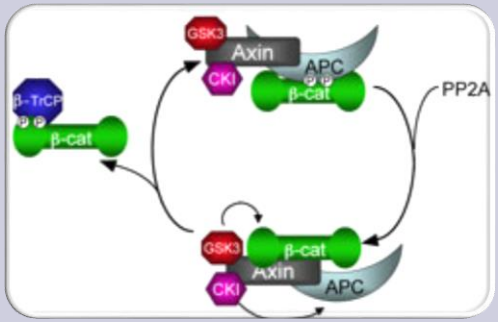

Diag Age 1 = 39
Cancer Diag 1 = Colon
Cancer Diag 2 = GI
Colonic polyps
Small bowel ca
Colonic polyps
Colonic polyps
Adenomatous polyps (20-30)
Fundic gland polyps

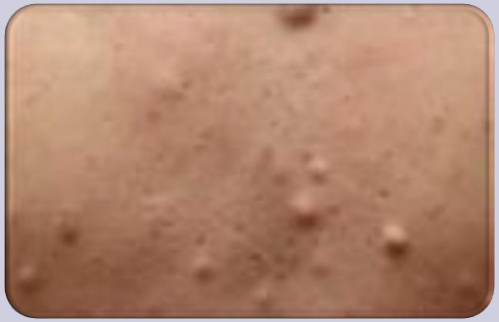
Case 2. Your next step is…

A. Referral to colorectal surgery
B. Genetic counseling/testing
C. Chemoprevention
D. Surveillance colonoscopy in 6 months

Adenomatous Polyposis Syndrome







Autosomal Dominant

Incidence 1:10,000

100% CRC risk

***APC* Gene**

(Tumor Suppressor Gene)

Hundreds of mutations

Epidermal Cysts

Desmoids

CHERPE

Various Presentations of Adenomatous Polyposis Syndromes

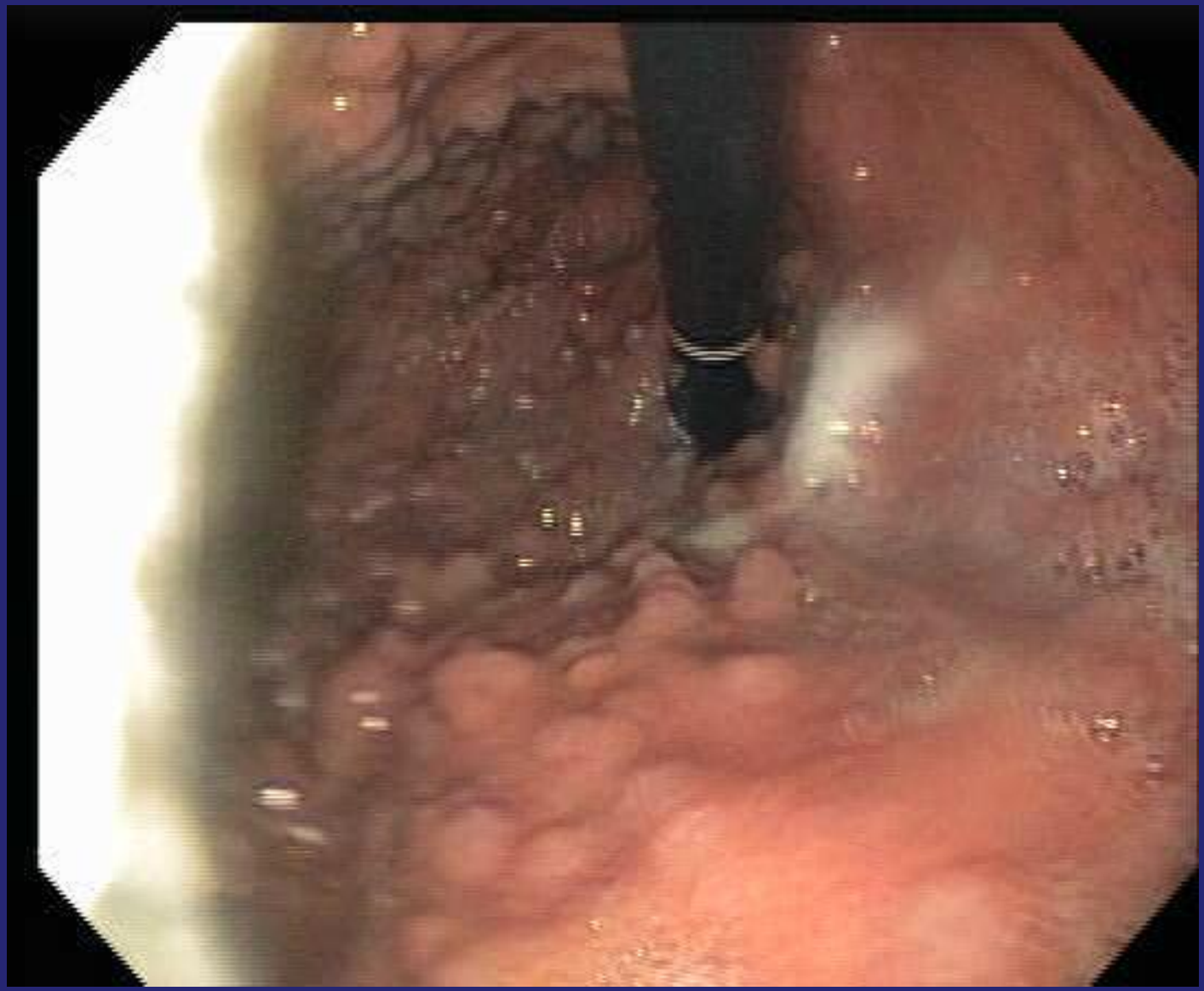
Condition	**FAP**	**AFAP**	**MAP**
Gene	*APC*	*APC*	*MYH*
Inheritance	Autosomal Dominant	Autosomal Dominant	Autosomal *Recessive*
Polyp Number	100 or more	< 100	1-1000

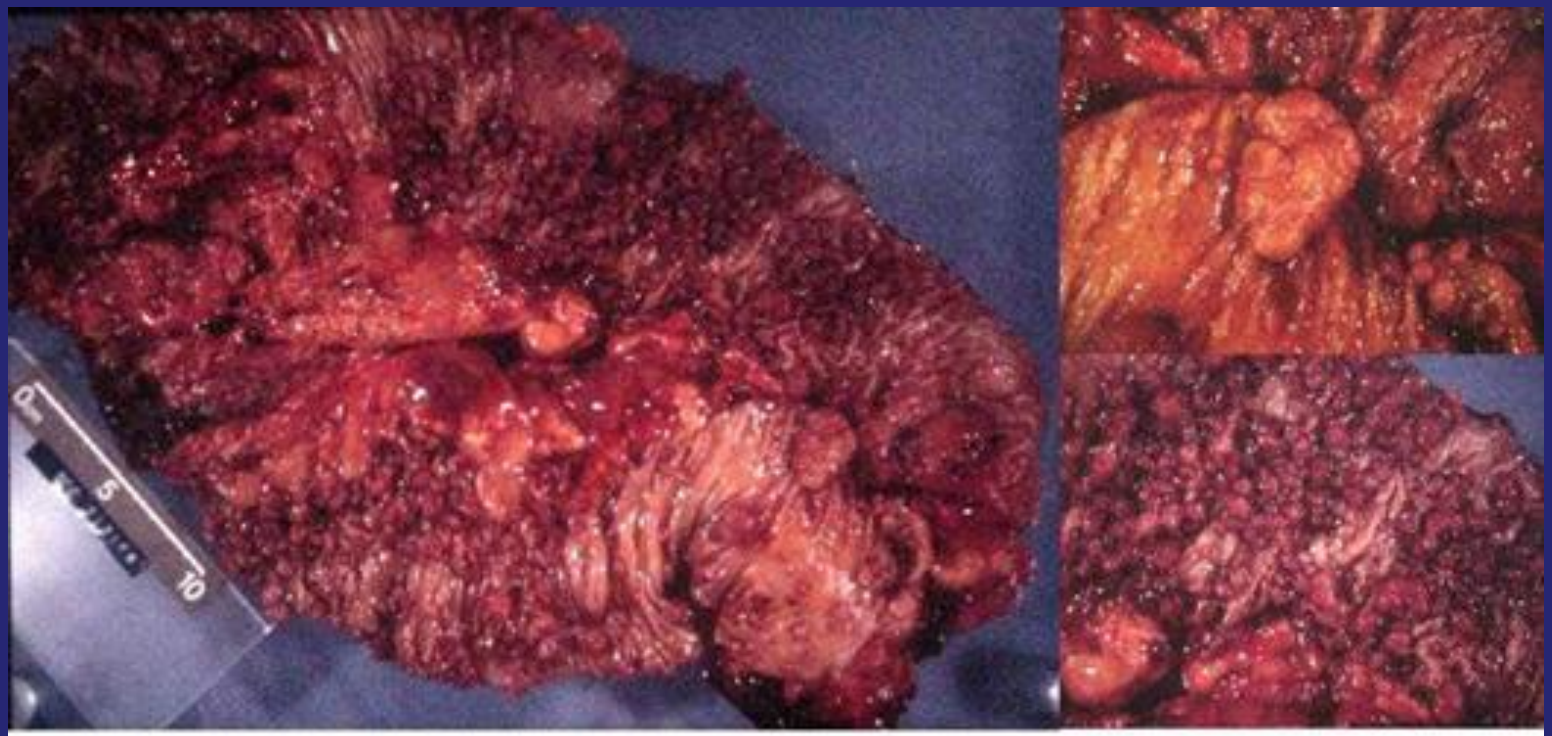
Case 2. Surveillance for which cancers should be consider in this patient?

A. Thyroid cancer
B. Pancreatic cancer
C. Stomach cancer
D. Duodenal cancer

Cancers in Classic FAP

Cancer	Lifetime Risk
Colon	100%
Duodenal	5-11%
Pancreatic	2%
Thyroid	2%
Brain (medulloblastoma)	< 1%
Hepatoblastoma	<1% (< 5y/o)





Colectomy specimen with multiple polyps.

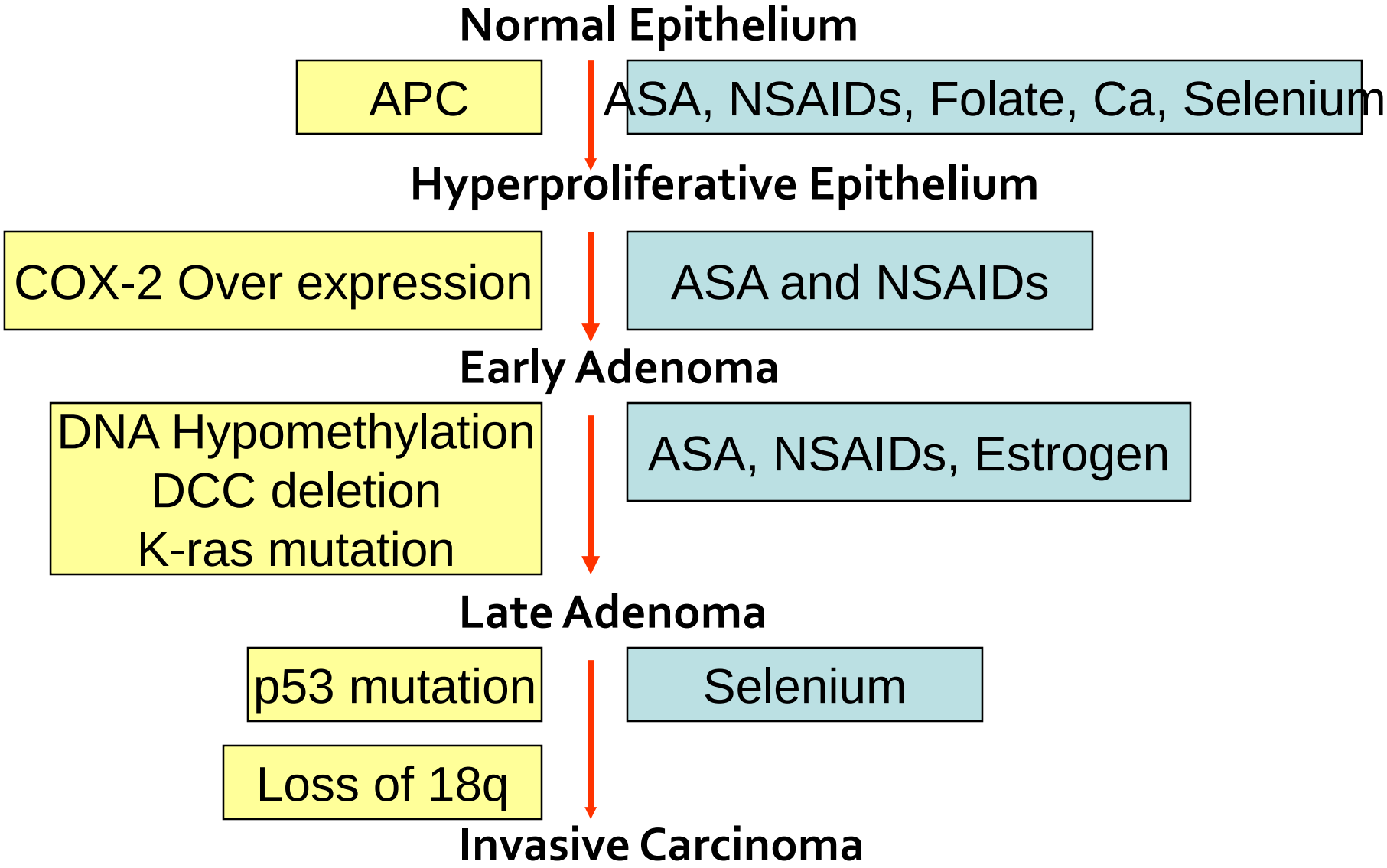
RED Flags for Adenomatous Polyposis Syndromes

- ≥ 10 cumulative colorectal adenomas
- Colorectal cancer associated with multiple polyps

CASE 2. Chemoprevention options for CRC in FAP include:

A. Aspirin or NSAIDs for rectal/colonic adenomas
B. Bioflavinoids (curcumin) 2-3 gram/day
C. Celecoxib for desmoid tumors
D. Not routinely given to patients with FAP

Chemoprevention Intervention



Cruz-Correa, DCR 2006

The Effect of Celecoxib in FAP

RCT Placebo-controlled double-blind;
77 patients with FAP randomized for Six Months
Endoscopy at baseline and 6-months

N=77	Percent Reduction Mean No. polyps	Reduction Polyp Burden
Placebo (n=15)	4.5%	4.9%
100 mg/bid (n=32)*	11.6%	14.6%
400 mg/bid (n=30)	28%	31%

*p > 0.05; *Steinbach et al*., NEJM 2000;342

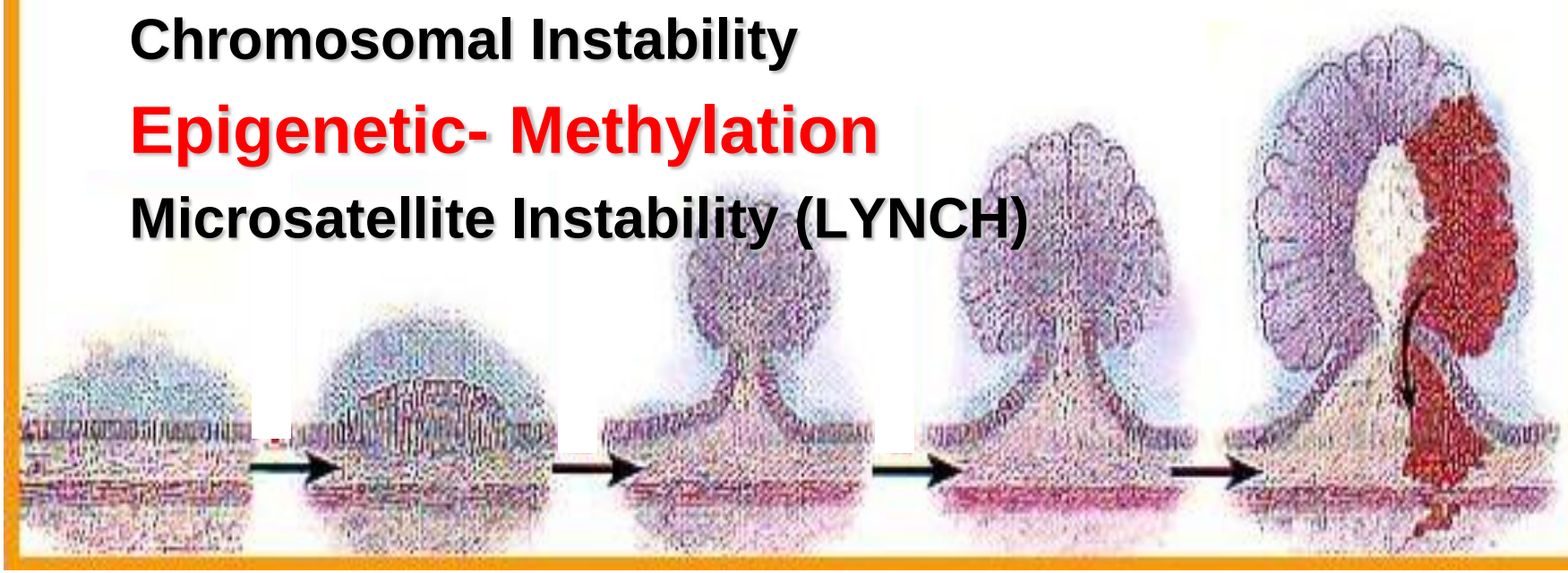
Adenoma-Carcinoma Sequence

Molecular Pathways to CRC

Chromosomal Instability

Epigenetic- Methylation

Microsatellite Instability (LYNCH)



Normal Epithelium

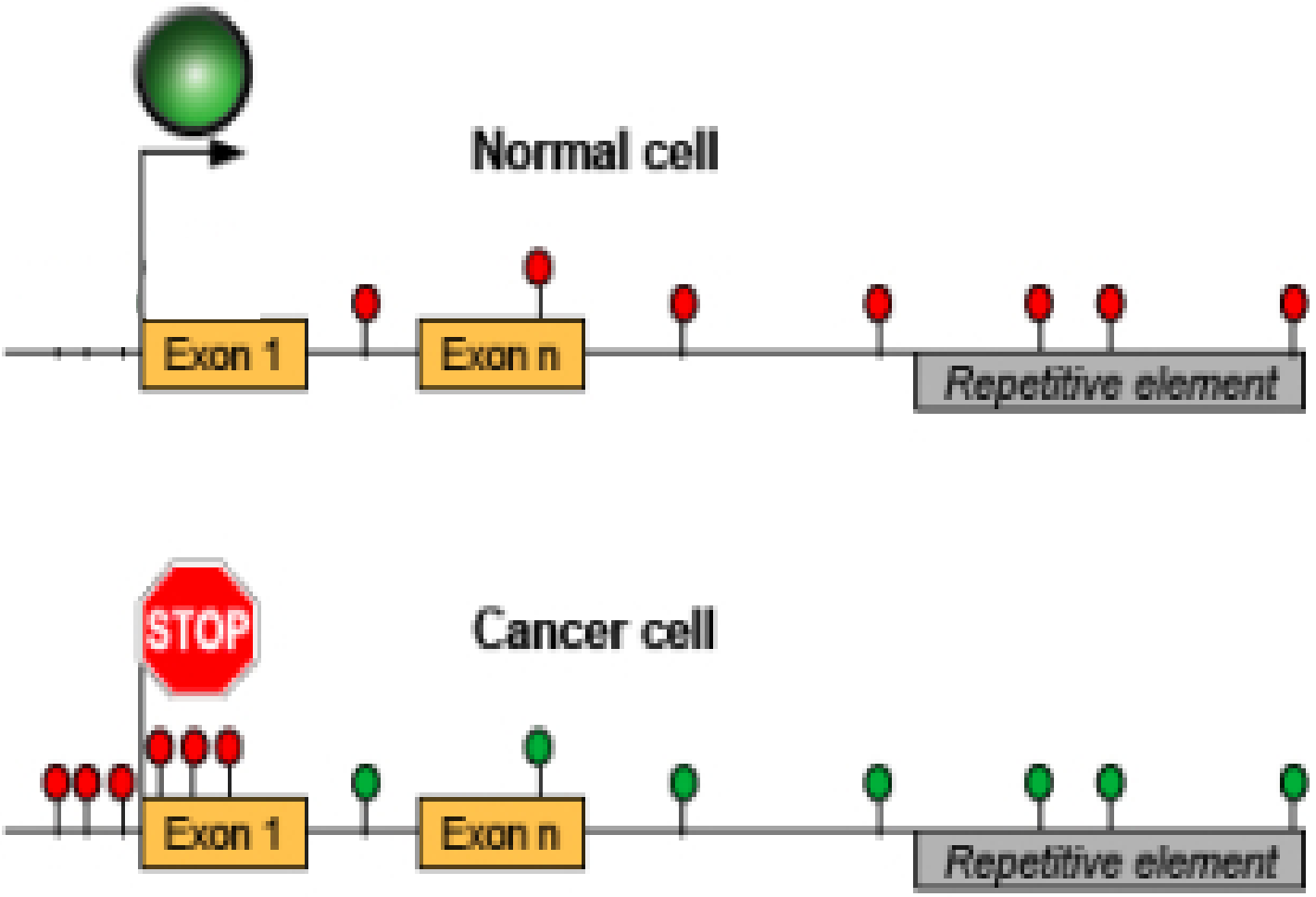
Small Tubular Adenoma

Intermediate Adenoma

Advanced Adenoma

Adenocarcinoma

Epigenetics - Methylation



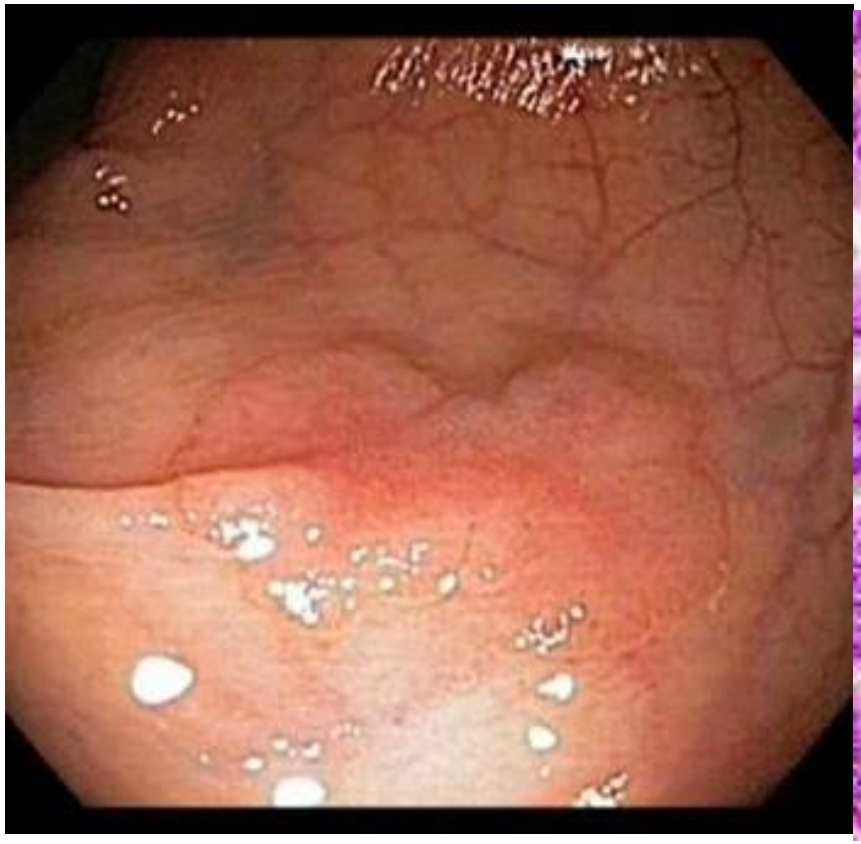
CpG-Island Methylator Phenotype (CIMP)

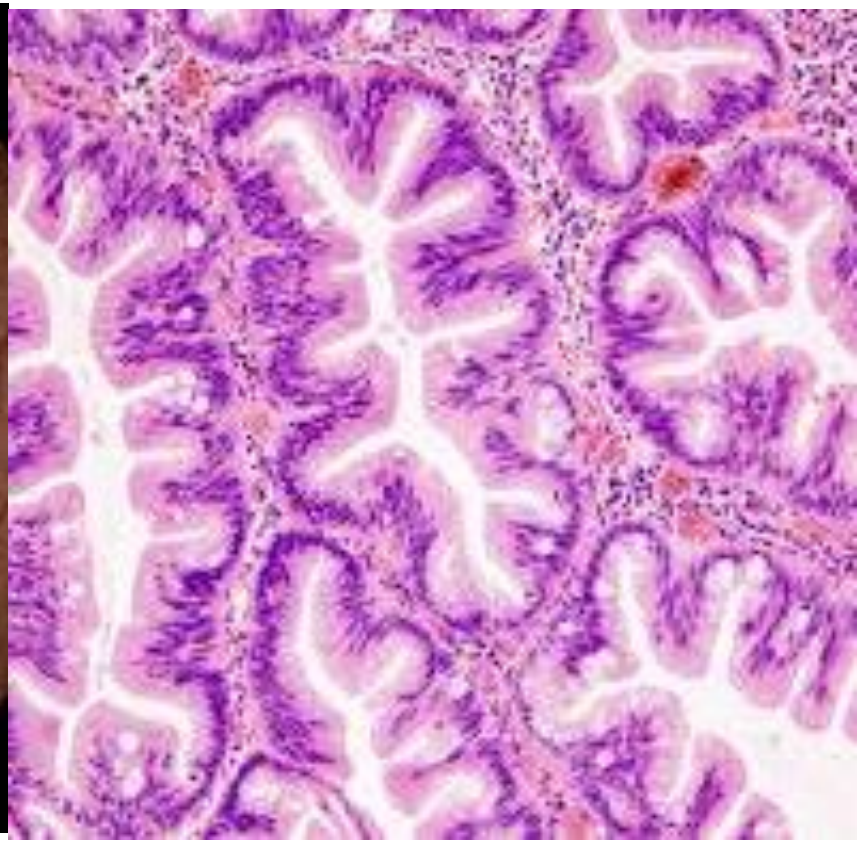
- CIMP was defined by CpG island promoter hypermethylation of ≥3 out of five markers (*CACNA1G, IGF2, NEUROG1, RUNX3 and SOCS1*) gene panel

- **Phenotype** - proximal tumor location, poor differentiation, mucinous histology, MSI, higher prevalence in women, high *BRAF* mutations and low *TP53* mutations

Ogino S and Goal A, J Mol Diagn 2008

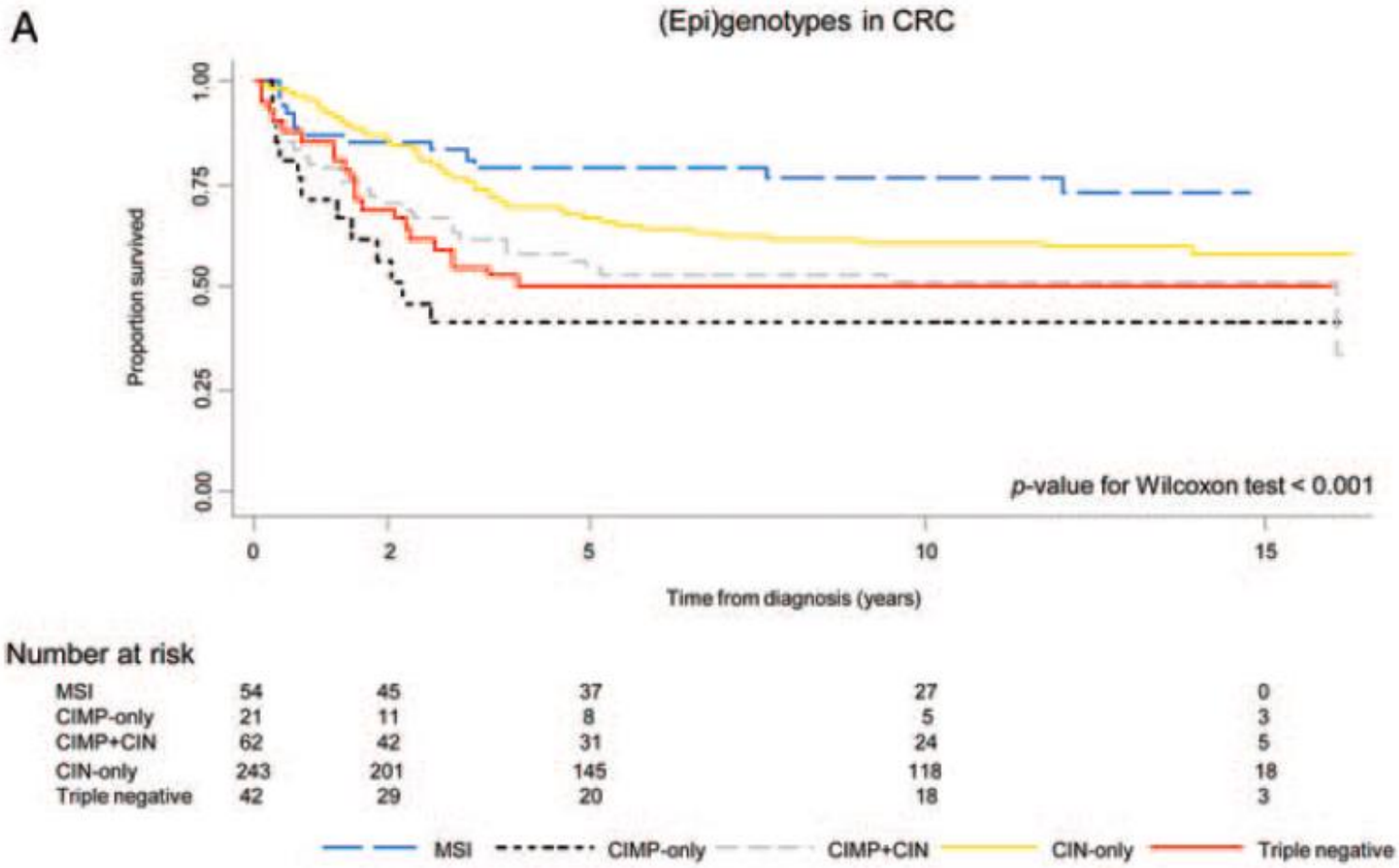
Endoscopy-Histology





CRC Survival According to (epi)genotype (Netherlands Cohort Study)

Higher Mortality HR = 4.07 (95% CI 1.86-8.91)



Simmons et al, Annals of Oncology 2003

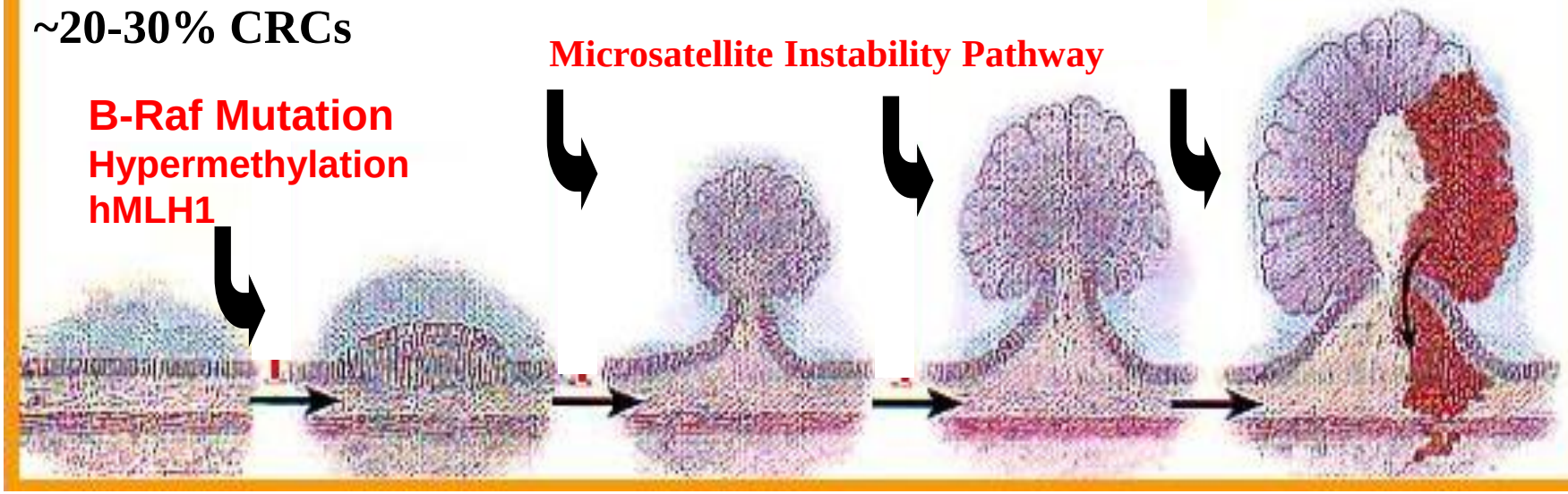
Epigenetic Pathway

Methylation- CpG island hypermethylation → gene silencing

~20-30% CRCs

Microsatellite Instability Pathway

B-Raf Mutation
Hypermethylation
hMLH1



Normal epithelium

Hyperplastic Polyp

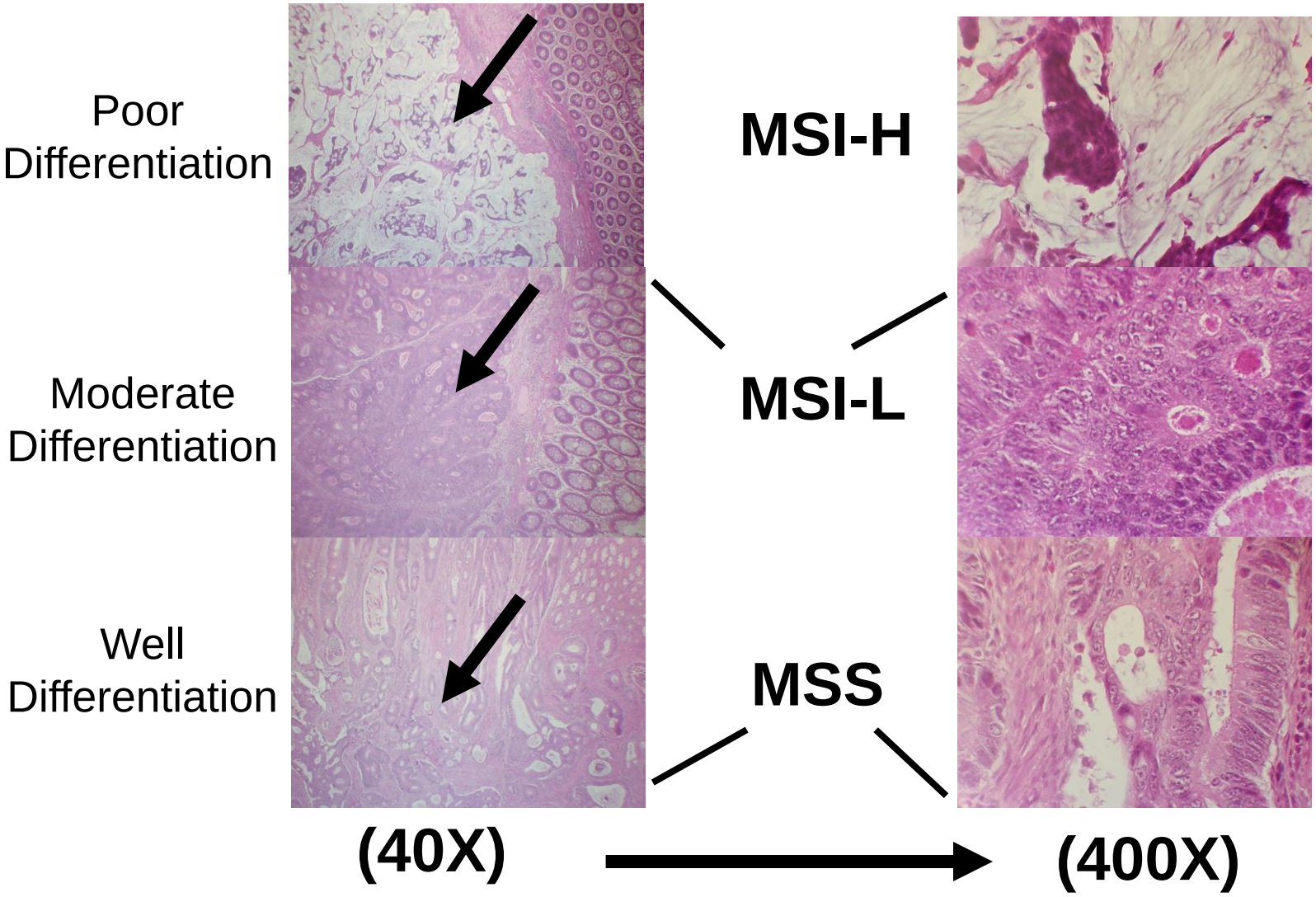
Sessile Serrated Adenoma

Mixed Polyp

Adenocarcinoma
Diploid
Microsatellite Unstable

Modified from Jänne PA, Mayer RJ. *N Engl J Med*. 2000;342:1960-8.

Histology and MSI Classification



MSI vs. MSS Colorectal Tumors

MSI	MSS
Microsatellite instability	Loss of heterozygosity (LOH)
Diploid	Aneuploid
Frequently mucinous	Few mucinous tumors
Poor differentiation	Well differentiation
Proximal colon	Fewer proximal tumors
Young (germline) / Old (hypermethylated ***hMLH1***) patients	Few young patients
Few p53 mutation/LOH	p53 mutation/LOH
Lymphoid Crohn's-like histology	
Better survival matched for stage	

MSI in Hispanics

Characteristics	MSI (n= 5) %	MSS (n=80) %	P-Value
Tumor Differentiation			
well/moderate	80.0	90.3	0.37
poorly/undifferentiated	20.0	9.7	
Proximal Colon Location	80	24.7	0.02
Stage Stage			
I/II	75.0	45.0	
III/IV	25	55.0	0.20
Family History of CRC	50	30	0.58
Median Age @ diagnosis			
< 60 years	40.0	53.8	0.66
> 60 years	60.0	46.3	

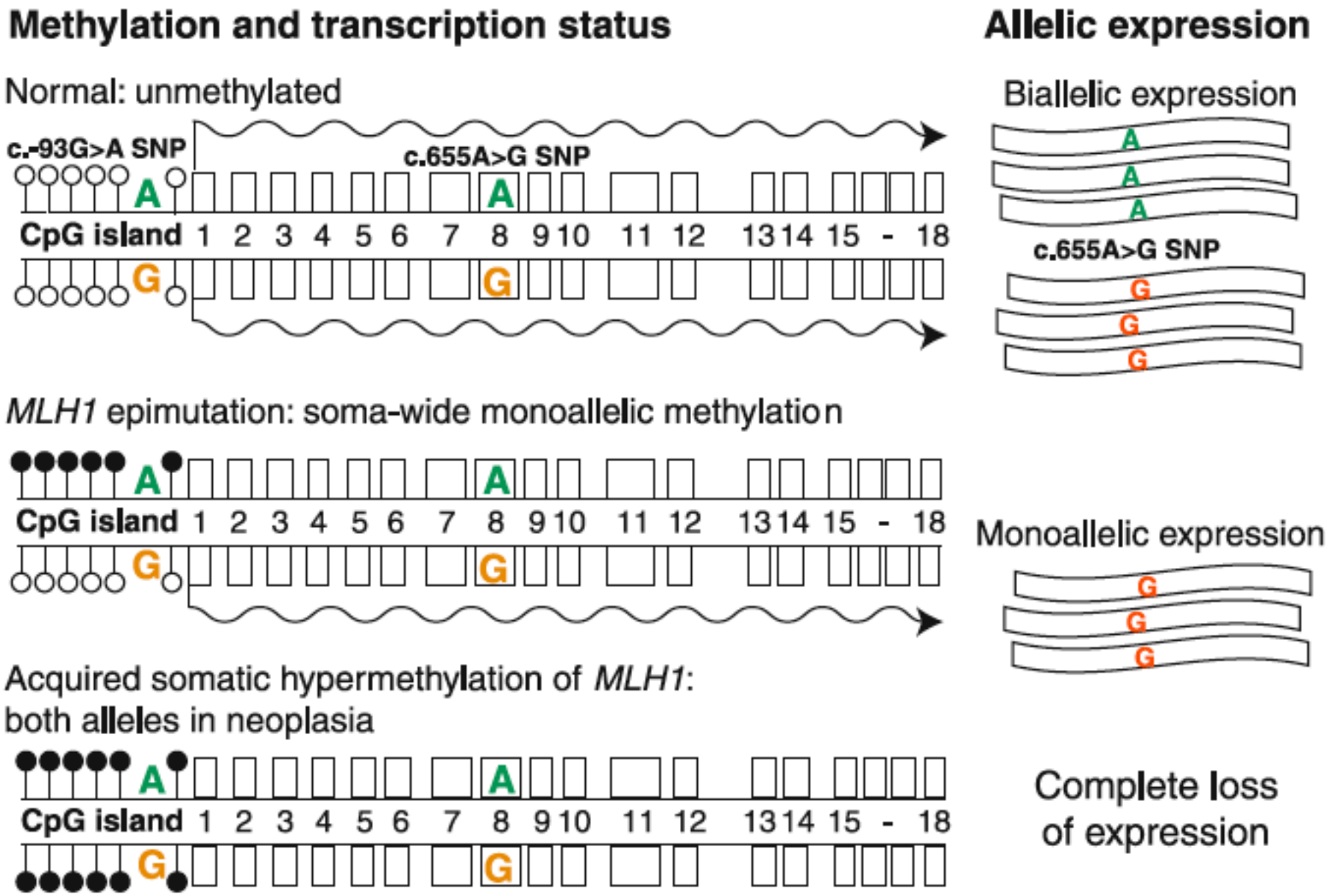
Cruz-Correa, DDW 2013

Constitutional Epimutations *MLH1* and *MSH2*

- Constitutional epimutation is an **epigenetic aberration** present within normal somatic tissues that results in the silencing of a gene that is normally active, or conversely, the reactivation of a gene that is normally silent

- Confers an elevated risk of developing ***mismatch repair deficient tumors*** at a young age of onset, synonymous with Lynch syndrome

MP Hitchins. Familial Cancer 2013



MP Hitchins. Familial Cancer 2013

MLH1 Epimutation

- *De novo* constitutional *MLH1* epimutations have been described in ***early-onset, MSI CRC tumors***

- Identified initially by dense methylation of a ***single allele*** of the *MLH1* promoter in the peripheral blood lymphocytes of a patient with MSI and MLH1 protein loss at 25 years

- 3-9% of cases with absence MLH1 protein and negative *MLH1* sequence mutation

Gazzoli et al. Cancer Research 2002

MLH1 Epimutation Carriers

- Primary epimutations are labile in the germline and thus ***reversible*** between successive generations, giving rise to unpredictable non-Mendelian patterns of inheritance

- Distribute evenly through out somatic cells, with a grade of mosaicism (10-100% cells)

- The mechanism(s) unclear; occurs mostly from the maternal allele

Case 3. 52 y/o female patient with CRC Stage IIB, MSI tumor. True statements regarding management

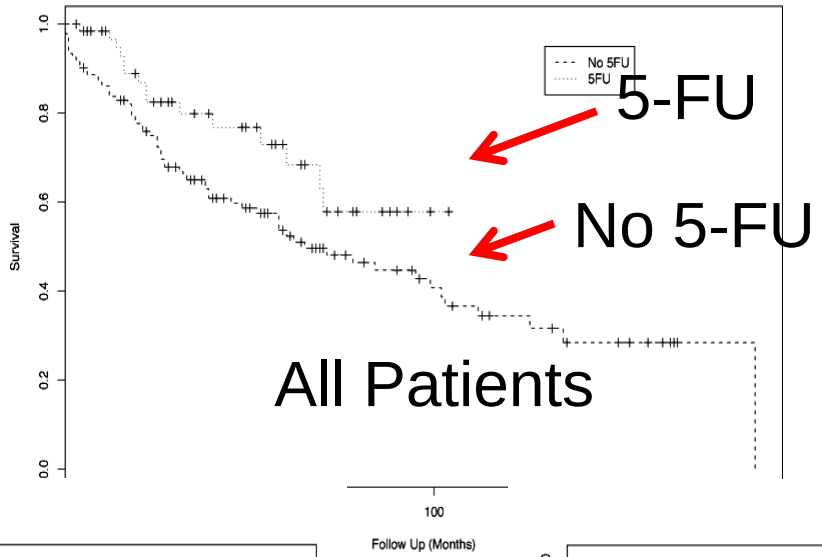
A. Use of chemotherapy is **not** indicated based on MSI status.

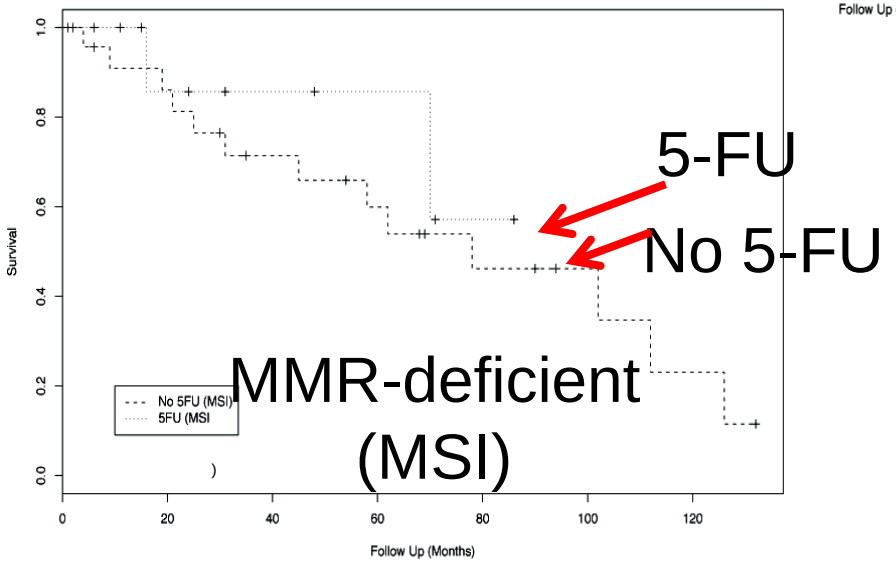
B. Suspect Lynch Syndrome case.

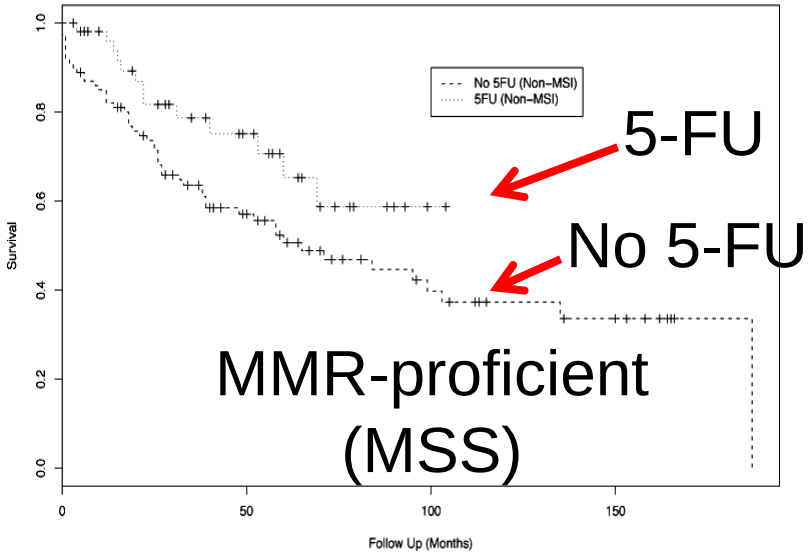
C. Chemoprevention is indicated at this point.

D. Surveillance for other non-CRC tumors is not indicated.

Kaplan-Meier: Survival and 5FU







Carethers, *et al.* Gastroenterology 126:394-401, 2004

Studies of 5-FU Treatment, Survival and MSI Status

Table 3. Chemotherapy in Colorectal Cancer with Microsatellite Instability

First author	Year	Study design	Adjuvant chemotherapy regimen	No. of patients (MSI/MSS)	Benefit of chemotherapy in patients with MSI
Elsaleh[135]	2000	Consecutive patients	5-FU	63/669	Yes
Ribic[141]	2003	Randomized controlled study	5-FU	95/475	No
Carethers[94]	2004	Consecutive patients	5-FU	36/168	No
de Vos tot Nederveen Cappel[143]	2004	Lynch syndrome patients	5-FU	28/0	No
Storojeva[136]	2005	Randomized controlled study	5-FU/mitomycin	21/139	No
Benatti[142]	2005	Consecutive patients	5-FU	256/1007	No
Popat[51]	2005	Pooled data from multiple studies	5-FU	1277/6365	No
Lanza[137]	2006	Consecutive patients	5-FU	75/288	No
Jover[138]	2006	Consecutive patients	5-FU	66/688	No
Kim[126]	2007	Prospective study	5-FU/leuocovorin	98/444	No
Des Guetz[139]	2009	Meta-analysis	—	454/2871	No
Bertagnolli[140]	2009	Randomized controlled study	5-FU/irinotecan/leucovorin	106/677	No

5-FU, 5-fluorouracil; MSS, microsatellite stable.

5FU may shorten survival in some MMR-deficient patients.

Boland and Goel. *Gastroenterology* 2010;**138**:2073-2087.

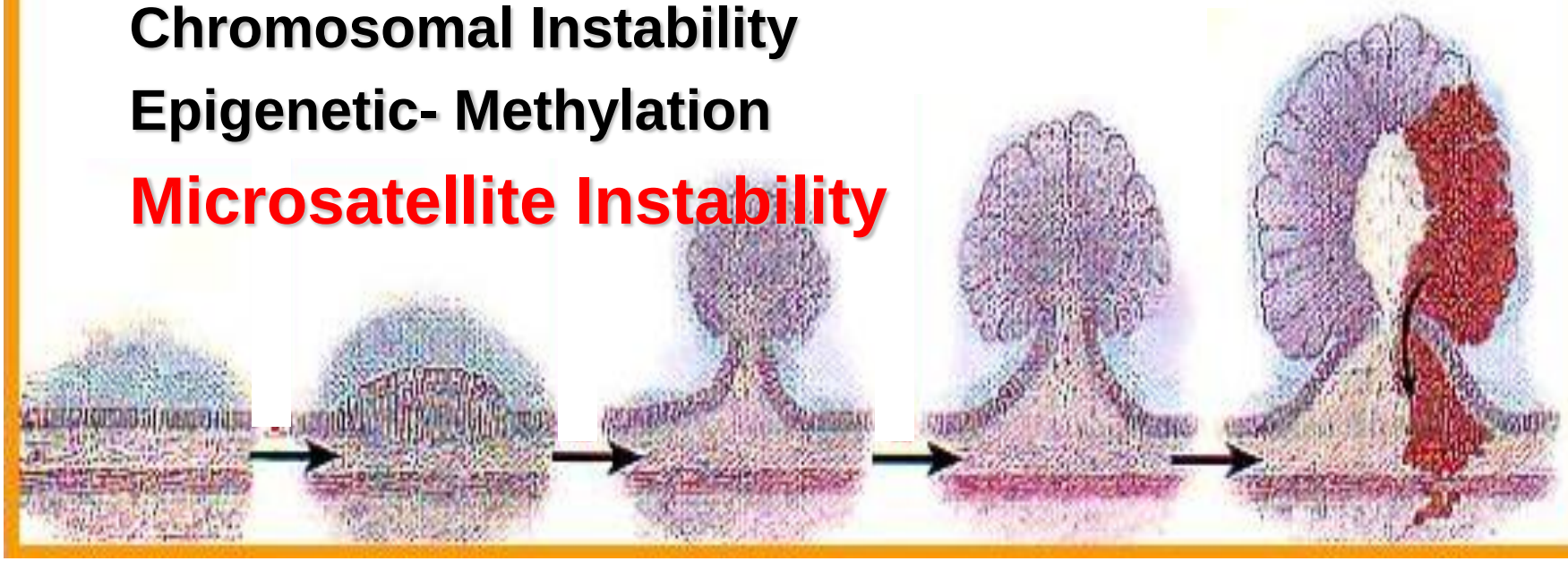
Adenoma-Carcinoma Sequence

Molecular Pathways to CRC

Chromosomal Instability

Epigenetic- Methylation

Microsatellite Instability



Normal Epithelium

Small Tubular Adenoma

Intermediate Adenoma

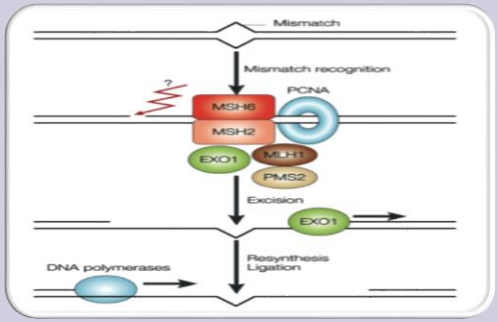
Advanced Adenoma

Adenocarcinoma

Lynch Syndrome

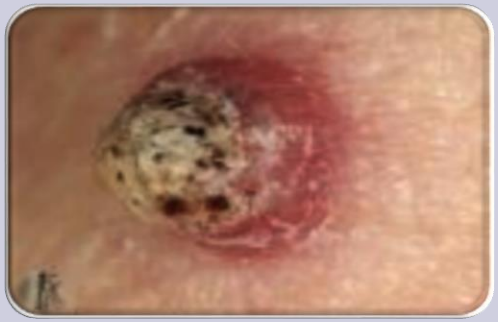
Autosomal Dominant

1:250-500 individuals



MMR Gene Defect

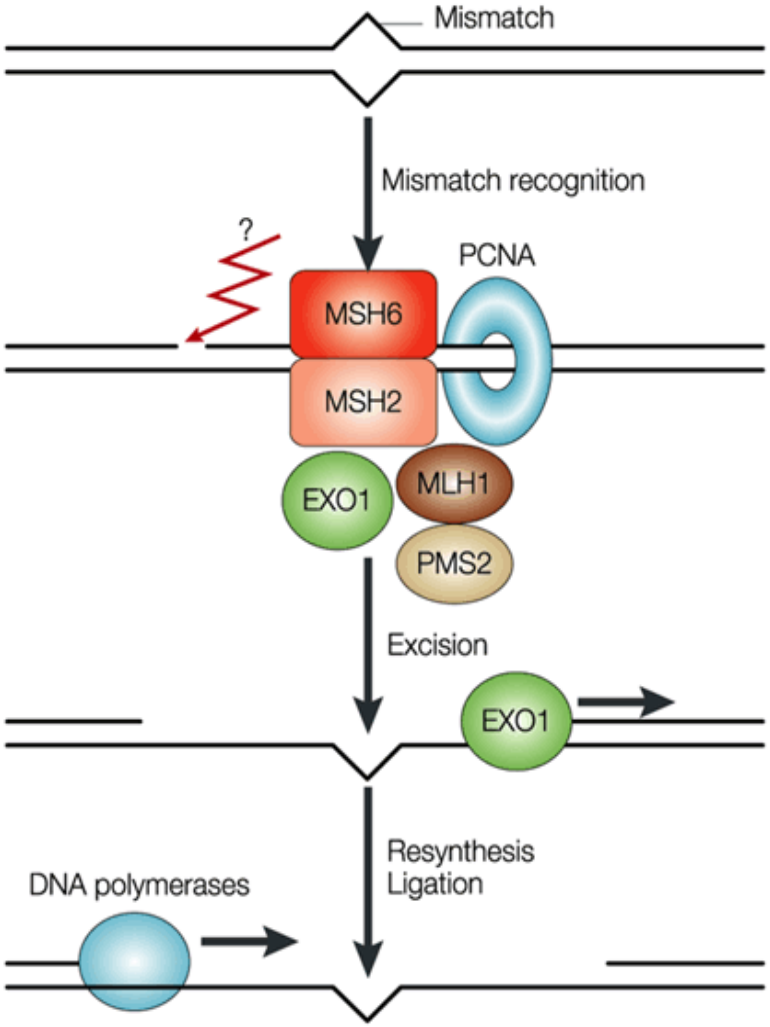
Microsomal Instability



Kerato-Acantomas

Sebaceous neoplasms

Lynch Syndrome



Mismatch Repair System

hMSH2

hMLH1

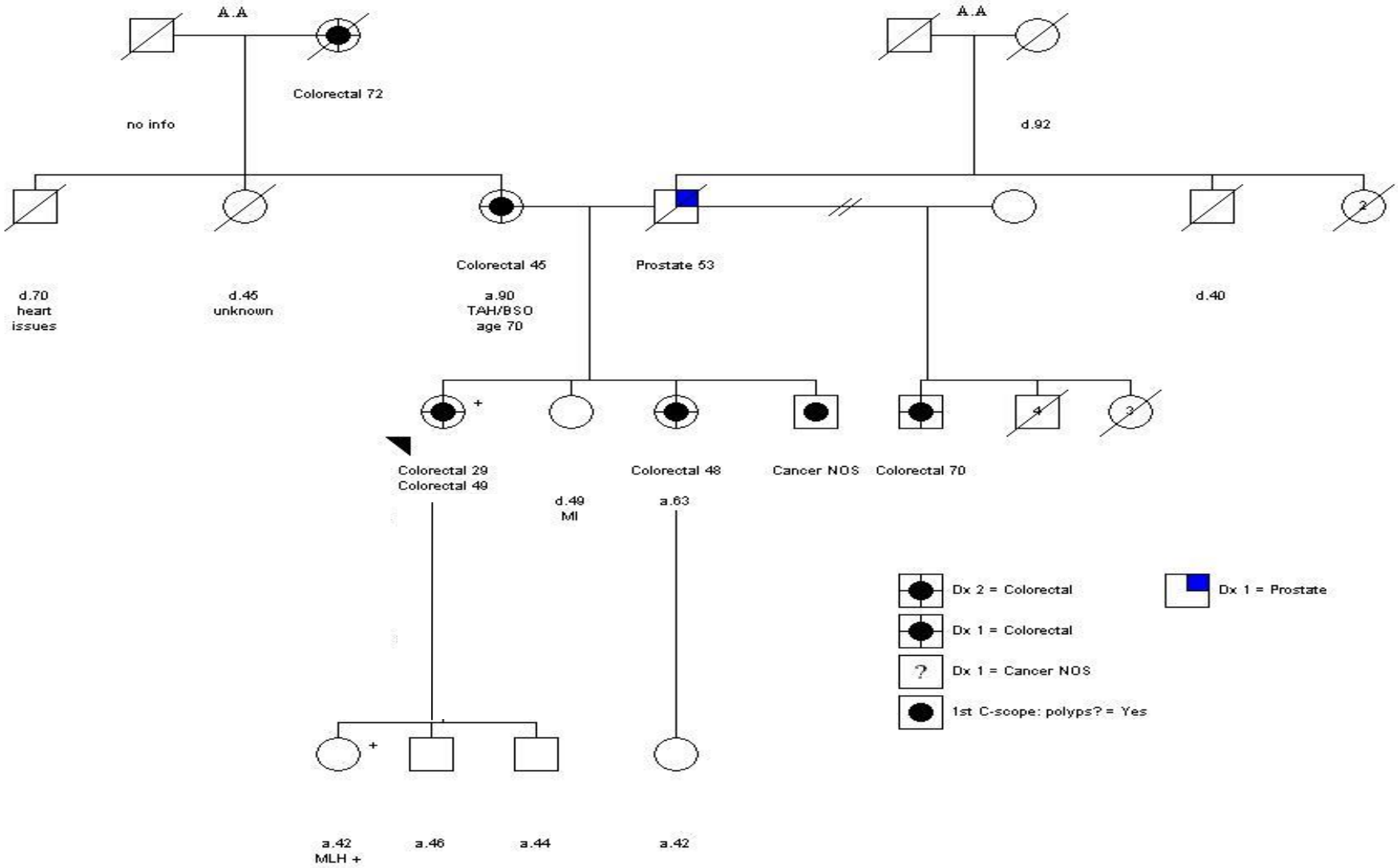
hMSH6

hPMS2

EPCAM

Martin A., Scharff, MD. Nature Reviews, Immunology 2002, 2: 605-614


Billabong

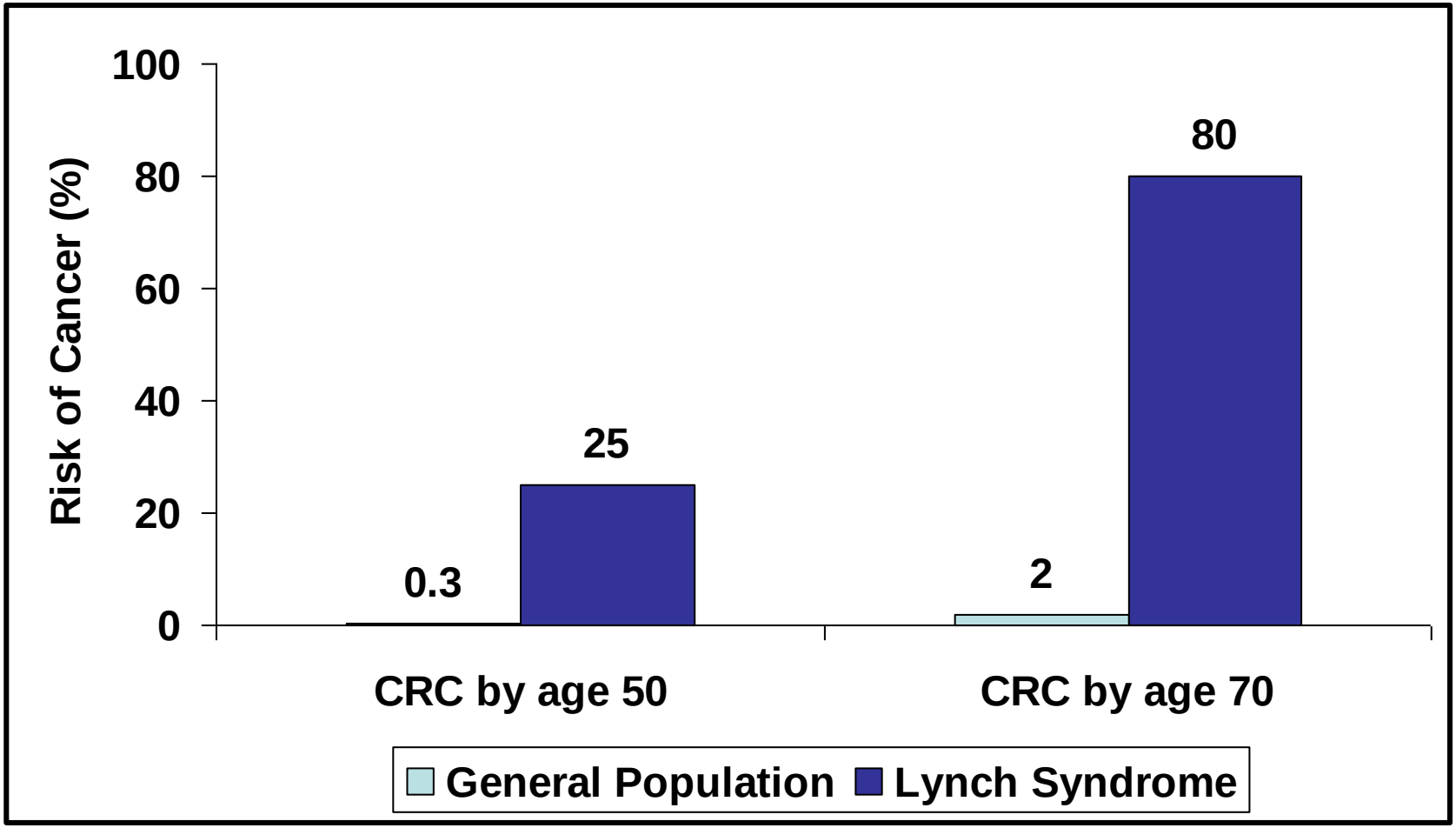

A.A
Colorectal 72
no info
A.A
d.92
d.70
heart
issues
d.45
unknown
Colorectal 45
a.90
TAH/BSO
age 70
Prostate 53
d.40
+
Colorectal 29
Colorectal 49
d.49
MI
Colorectal 48
a.63
Cancer NOS
Colorectal 70
+
a.42
MLH +
a.46
a.44
a.42
Dx 2 = Colorectal
Dx 1 = Colorectal
Dx 1 = Cancer NOS
1st C-scope: polyps? = Yes
Dx 1 = Prostate

Study ID	Mutation for Lynch	Age at primary CRN	Family history of CRC	# Relatives with CRC	AMSTERDAM I/II
9009	MLH1 c.2044_2045del	58	Yes	5	Yes
9009-02	MLH1 c.2044_2045del	42	Yes	5	Yes
9306	MLH1 1024del6	39	Yes	3	Yes
9306-01	MLH1 1024del6	35	Yes	3	Yes
9162	MSH2 1705delGA	-	Yes	1	No
9249	MSH2 1457del4	38	Yes	1	Yes
9109	MSH2 L302X (905T>A)	51	No	0	No
8397	MSH2	59	Yes	2	Yes
8313	MSH2	74	No	0	No
8252	MSI+BRAF	54	No	0	No
9258	MSH2	57	Yes	1	Yes

Cancers in Lynch Syndrome

Cancer	Lifetime Risk (%)
Colon	80
Endometrial	39-60
Stomach	13
Ovarian	<5
Ureters/renal	<5
Brain (glioblastoma)	<5

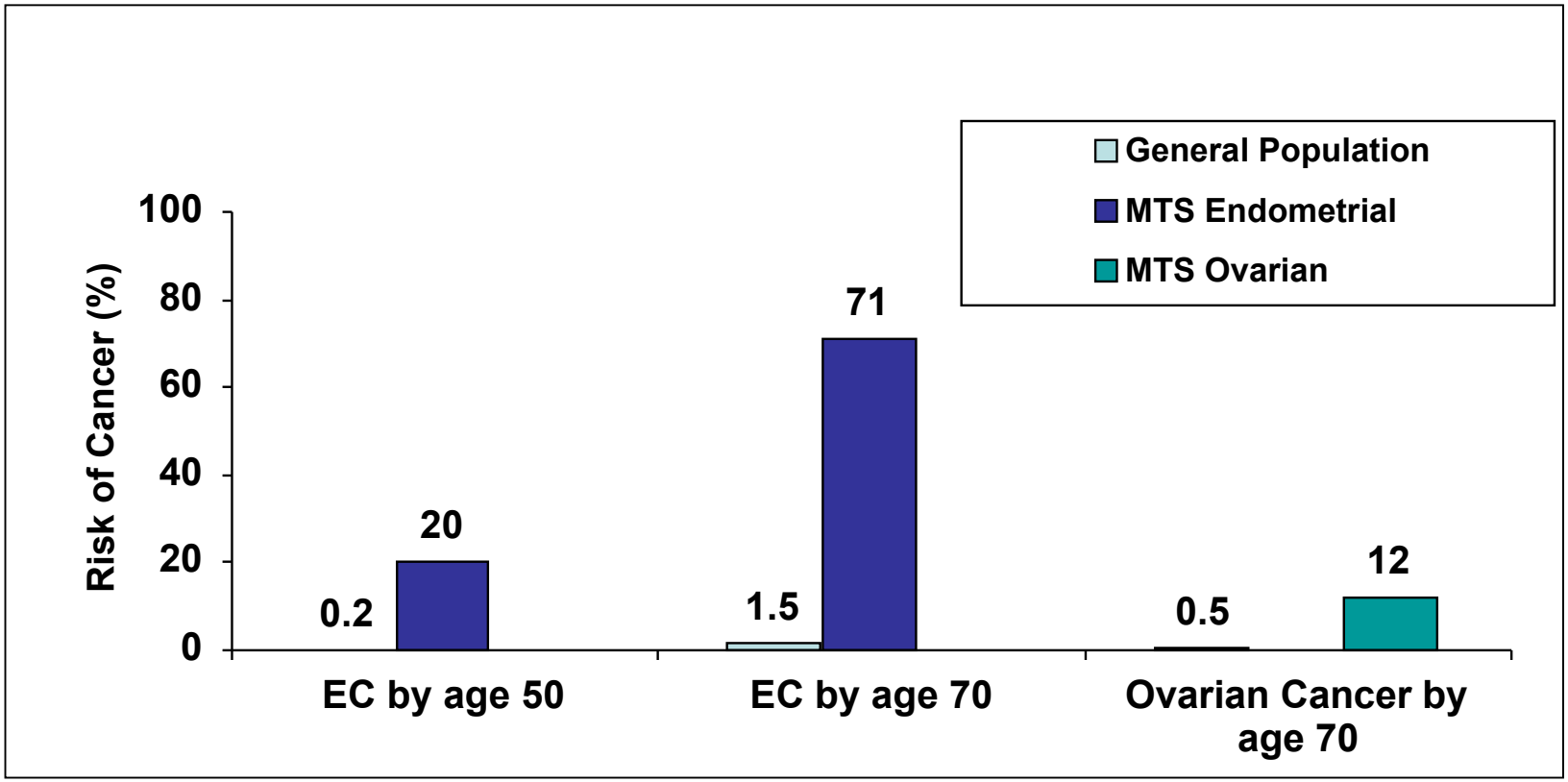
Lynch Syndrome Increases Colorectal Cancer Risk



Lu K, et al. Obstet Gynecol 2005, Vasen HF et al. J Clin Oncol 2001
Hampel H, et al. Gastroenterology 2005

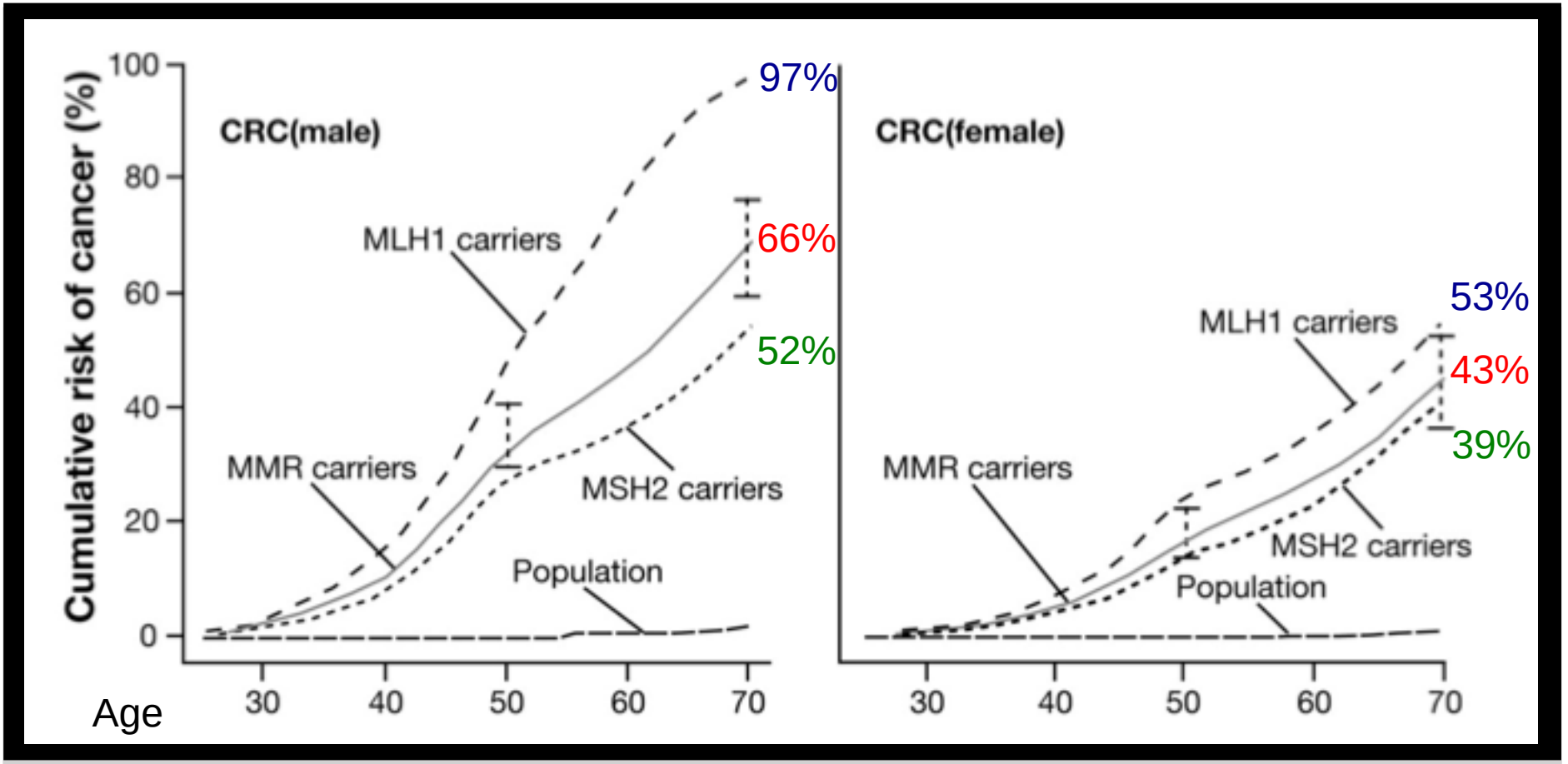
Lynch Syndrome Increases Gynecologic Cancer Risks

Women with LS Syndrome may present with a gynecologic cancer first



Lu K, et al. Obstet Gynecol 2005, Vasen HF et al. J Clin Oncol 2001
Hampel H, et al. Gastroenterology 2005

Cumulative risk of CRC by Sex



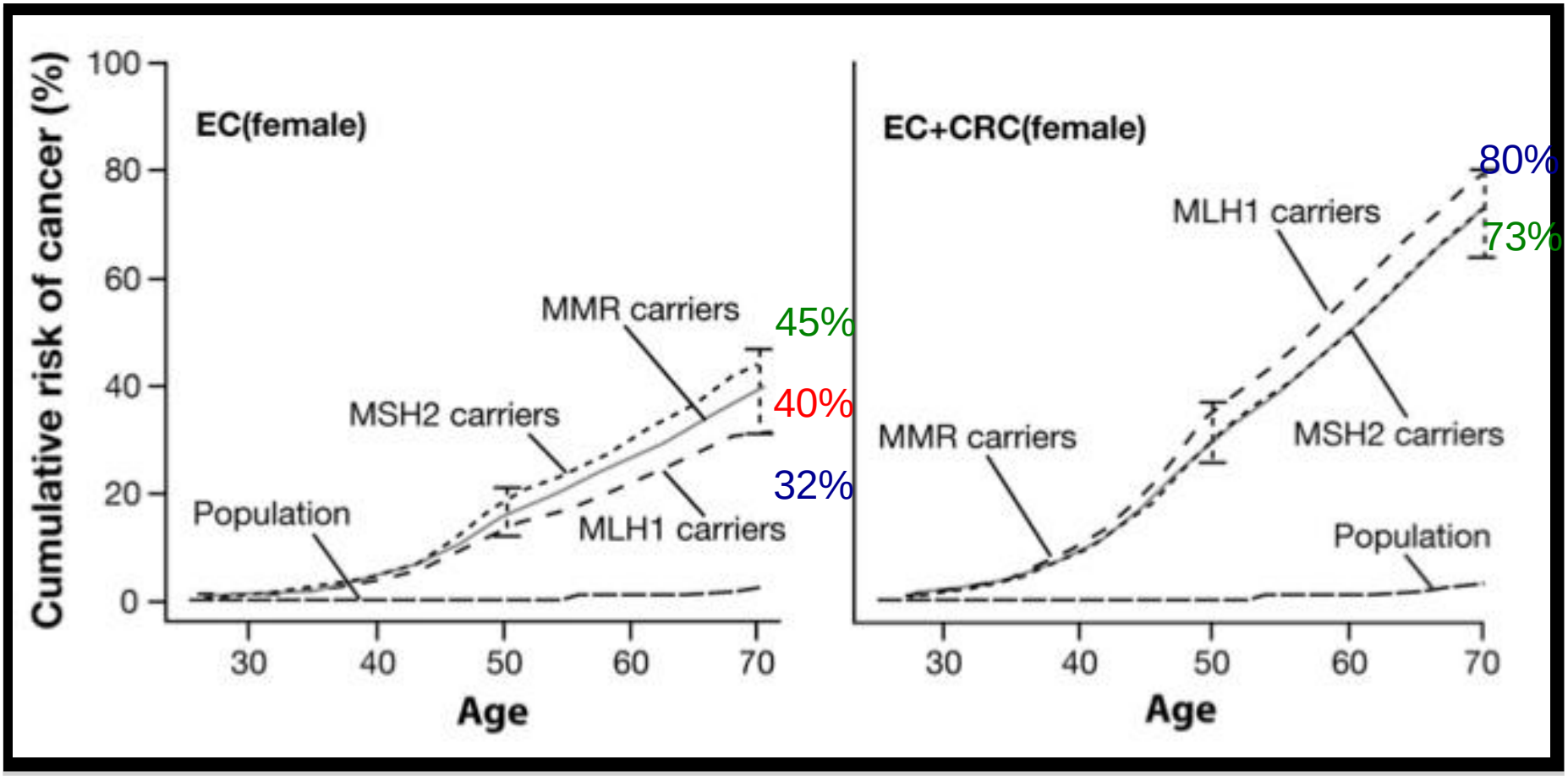
Stoffel E, *et al*. *Gastro*. 2009; 137: 1621-1627

Risk MMR mutation carriers

Risk *MLH1* mutation carriers

Risk *MSH2* mutation carriers

Cumulative risk of Endometrial CA (EC) and CRC in females



Risk MMR mutation carriers

Risk *MLH1* mutation carriers

Risk *MSH2* mutation carriers

Stoffel E, *et al*. *Gastro*. 2009; 137: 1621-1627

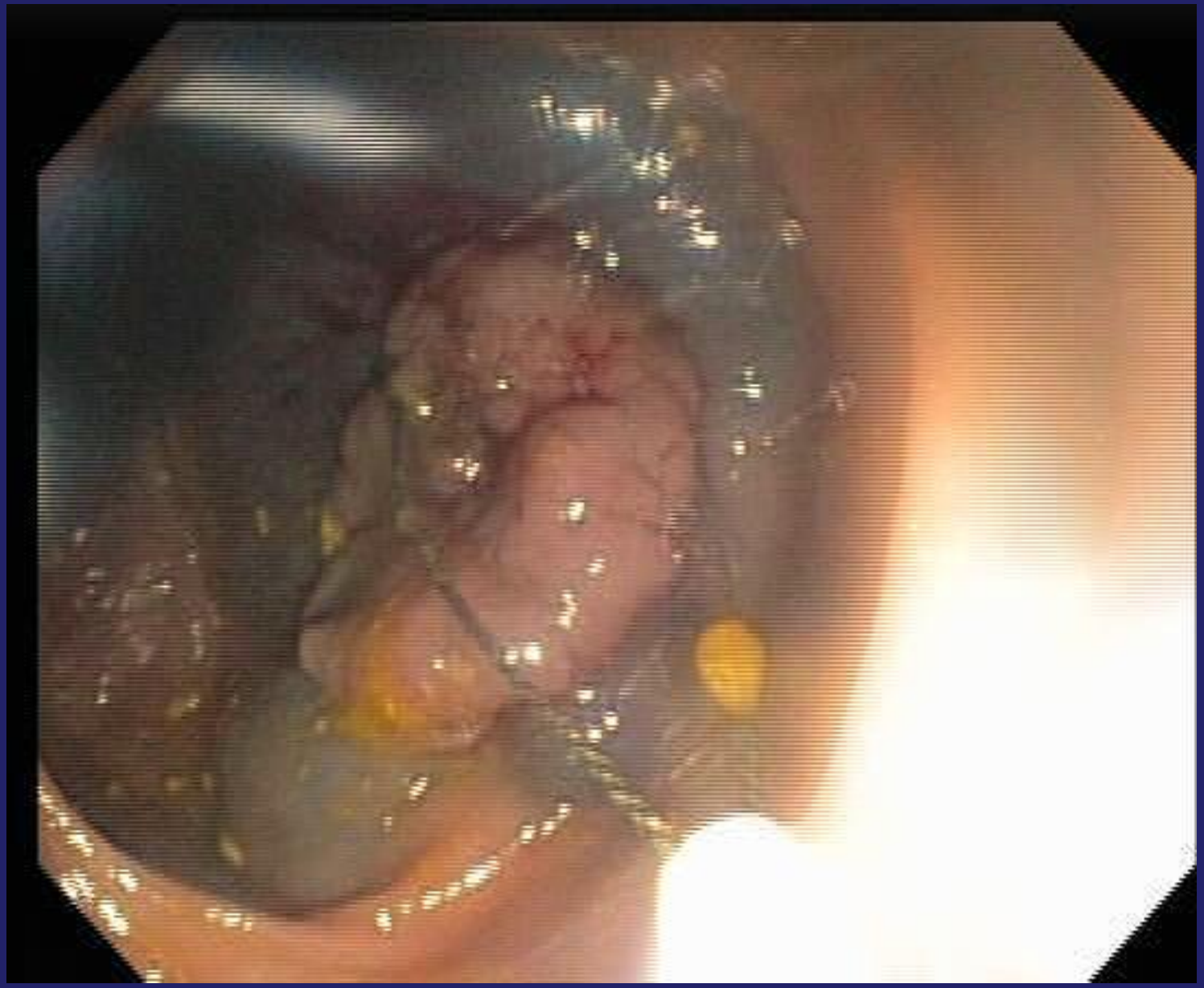
Lynch Syndrome Management

Colorectal Cancer Surveillance

Procedure	Age to Begin	Interval
Colonoscopy	**20-25 years**	**1-2 years**
	40 years	**Annually**

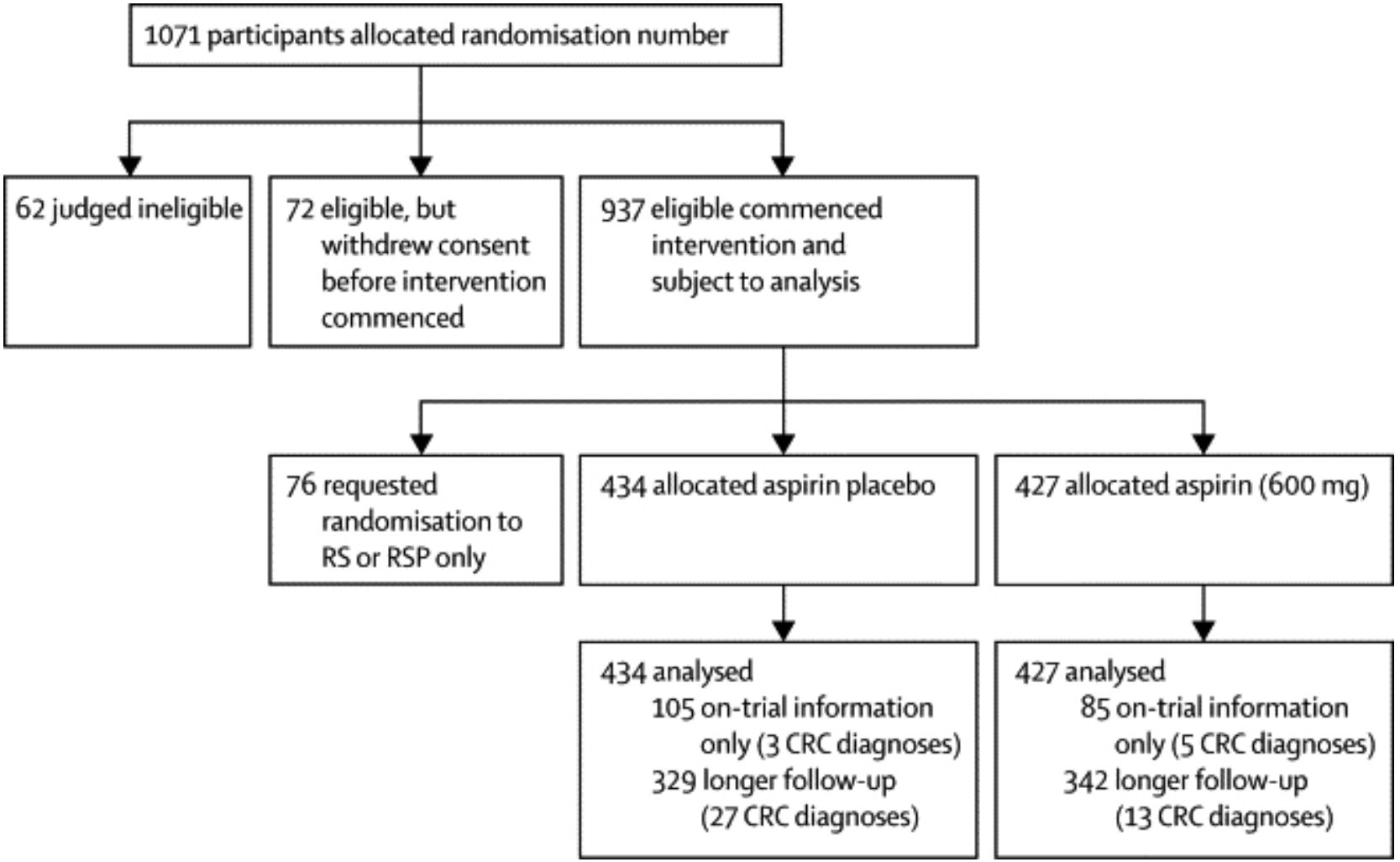
- Adenomas/cancers are often right-sided in MT syndrome
- Reduces CRC risk by over 50% and overall mortality by 65%
  - Results in diagnosis of earlier stage cancers

Gastroenterology 1993; Dis Colon Rectum 2002; Gastroenterology 2000



Chemoprevention in Lynch Syndrome

The Colorectal Adenoma/carcinoma Prevention Program (CAPP)

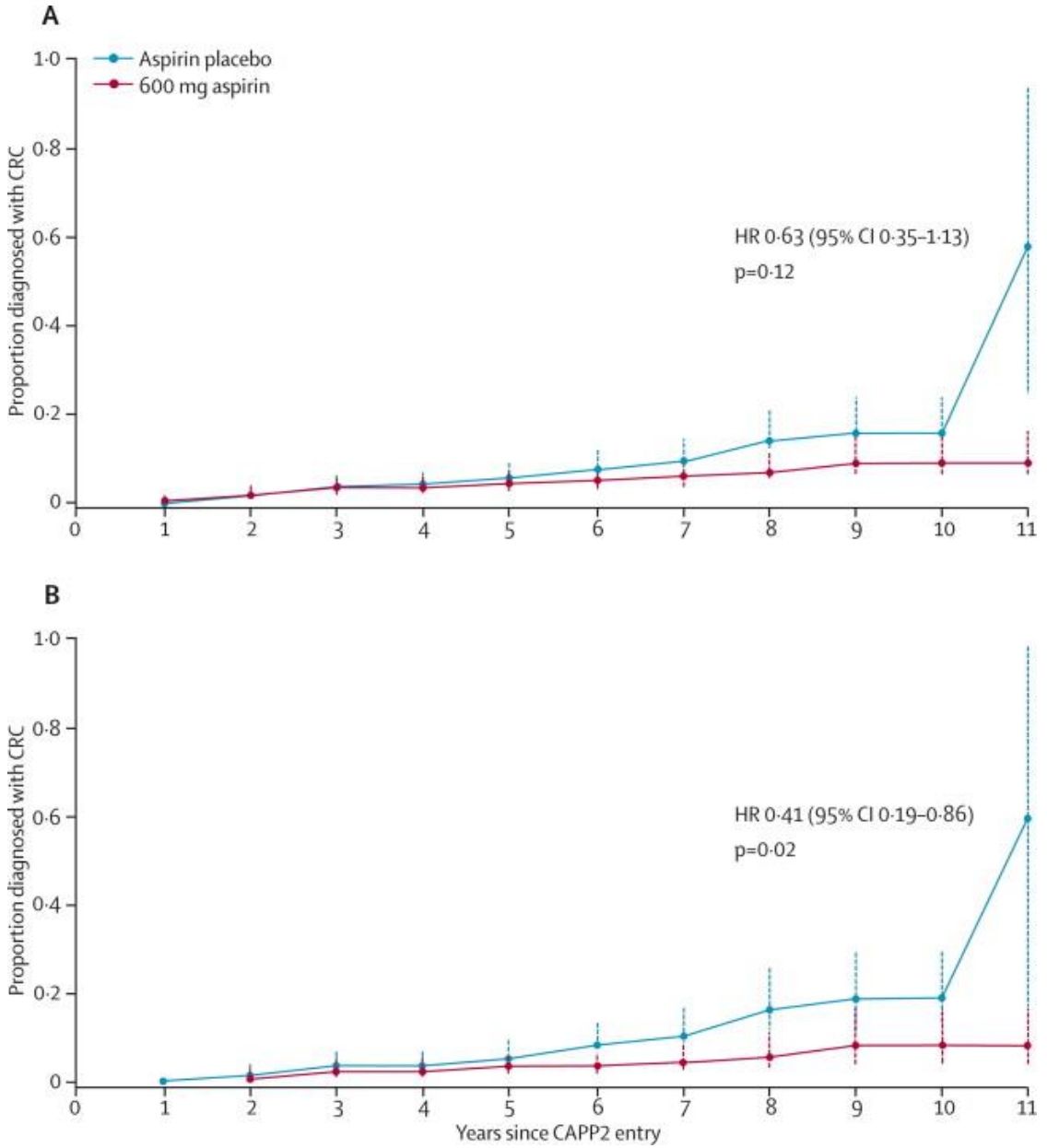


Burn J, et al. Lancet 2011

Decreased Incidence of CRC for ASA Users

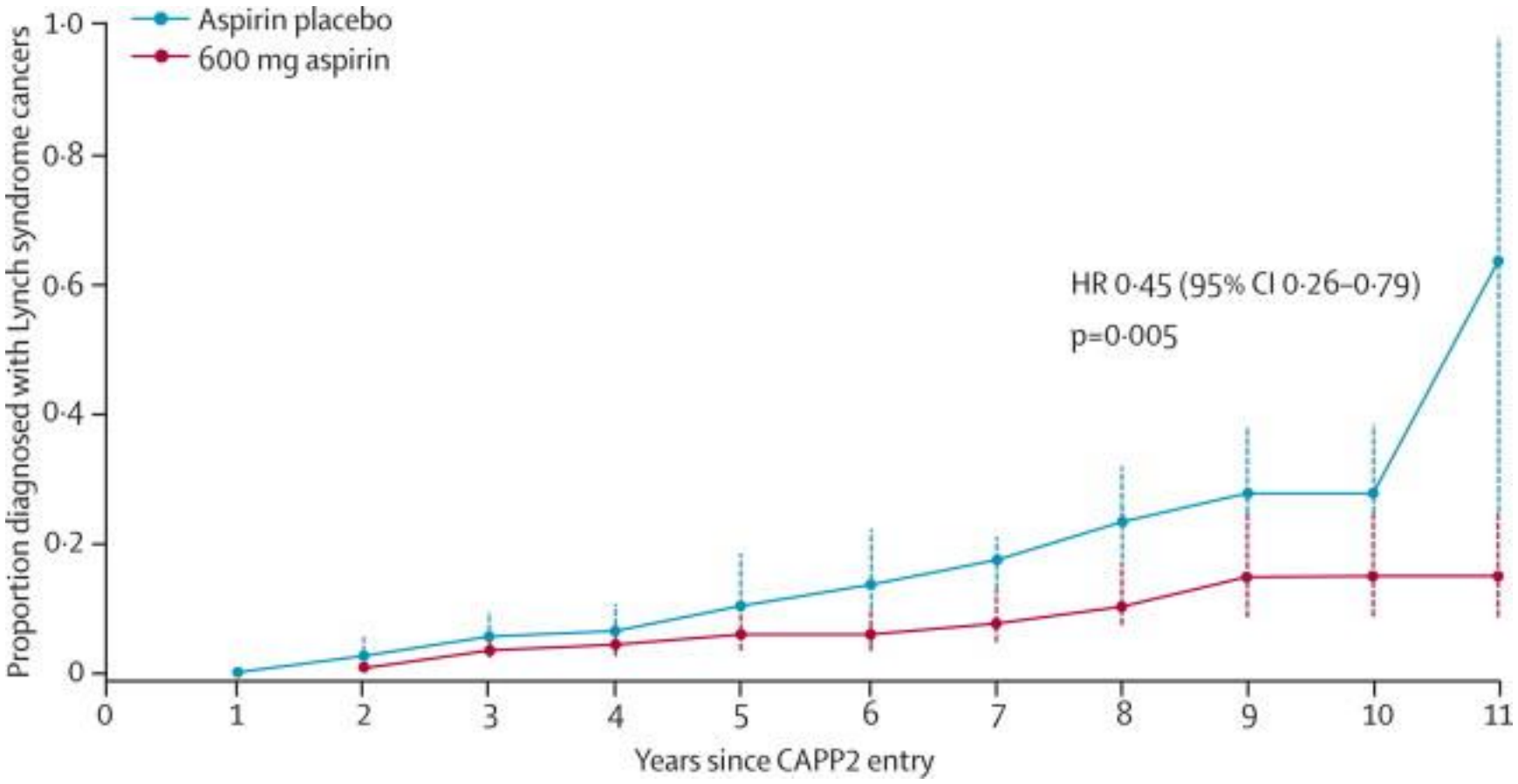
Intention to treat

Per-Protocol



Burn J, et al. Lancet 2011

Decreased Risk of Lynch-Cancers Among ASA Users



Burn J, et al. Lancet 2011

Case 3. 52 y/o female patient with CRC Stage IIB, MSI tumor. True statements regarding management

A. Use of chemotherapy is **not** indicated based on MSI status.

B. Suspect Lynch Syndrome case.

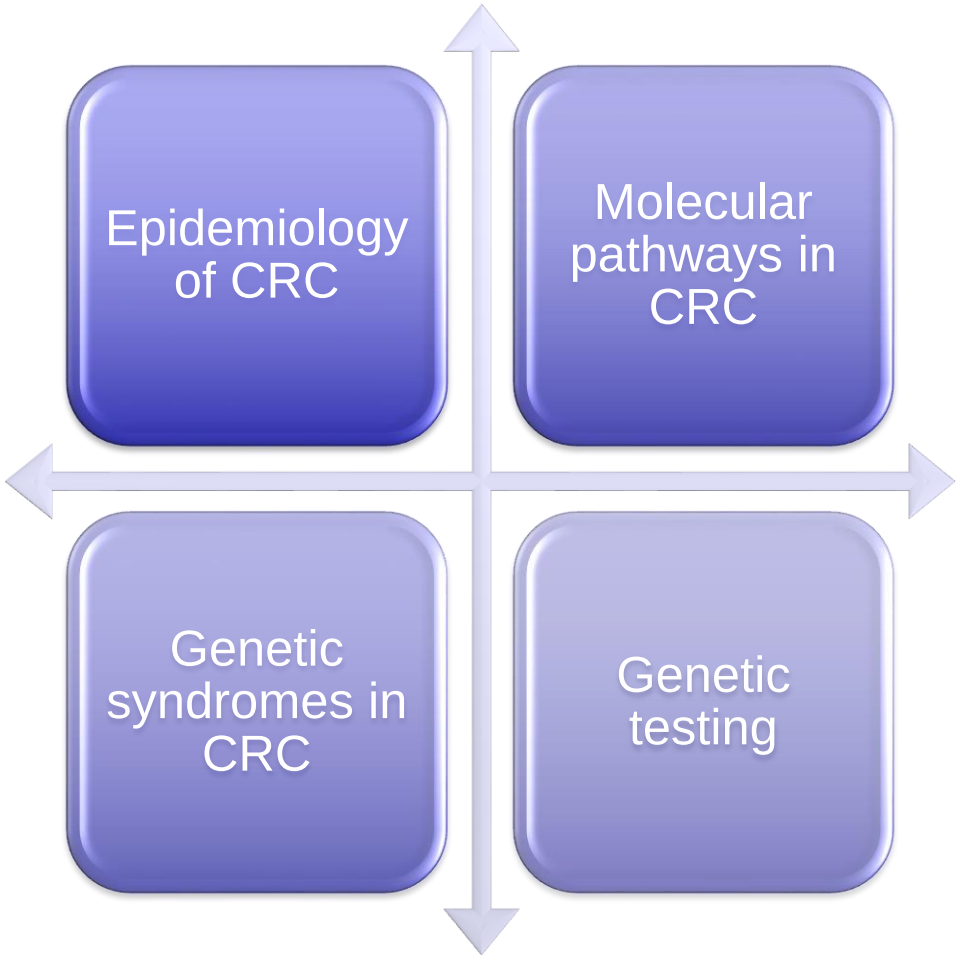
C. Chemoprevention is indicated at this point.

D. Surveillance for other non-CRC tumors is not indicated.

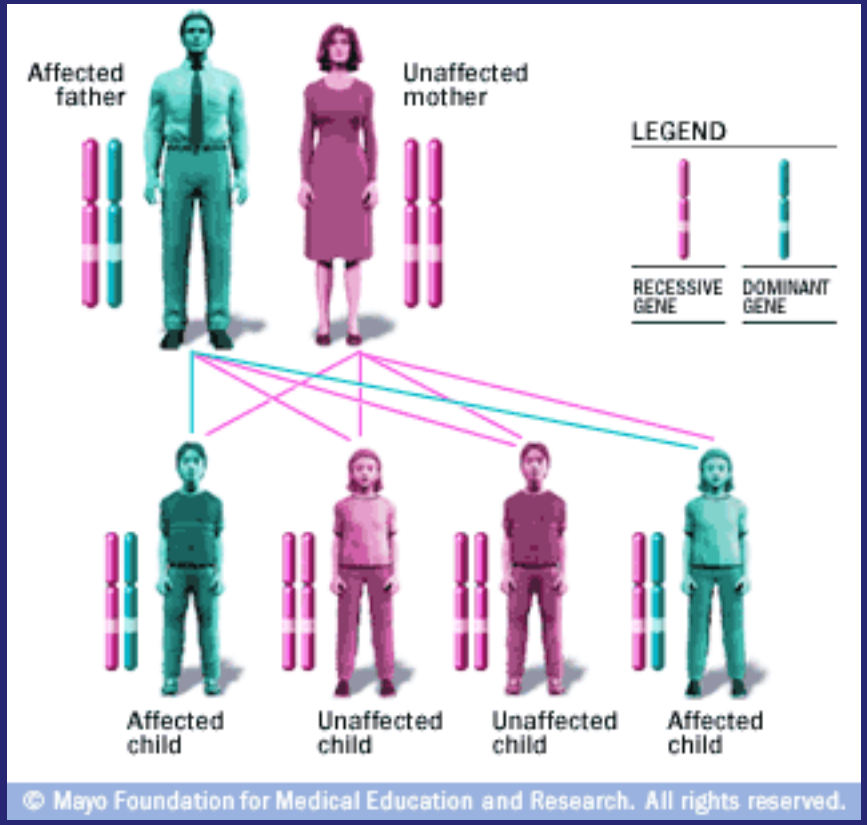
Red Flags for Lynch Syndrome

- Early onset colorectal cancer (<50 years)
- Early onset endometrial cancer (<50 years)
- Two or more Lynch syndrome cancers
  - In the same individual
  - Among close relatives

What We Will Learn…



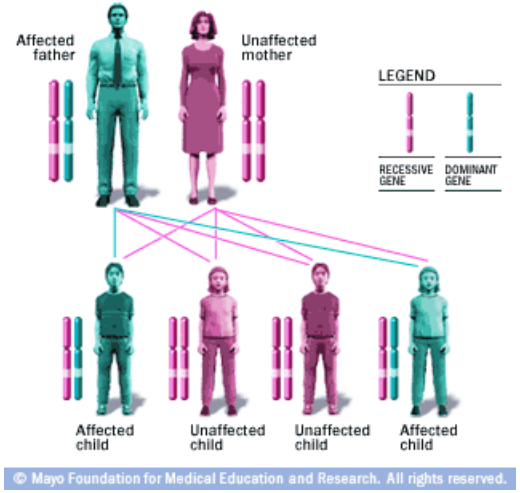
Genetic Testing



American Society of Clinical Oncology
Guidelines for Genetic Testing

- Personal or family history suggestive of hereditary cancer risk
- Test can be adequately interpreted
- Test results will aid in diagnosis or influence medical management of the patient and/or family

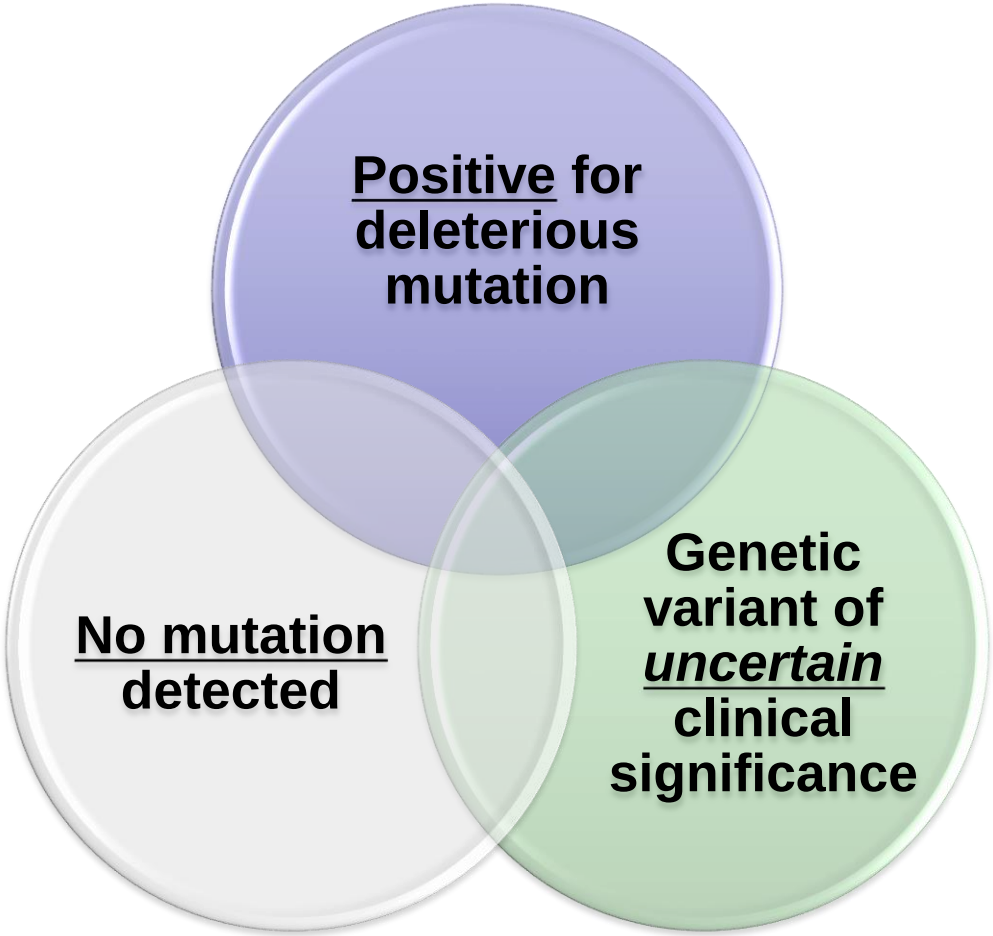
J Clini Oncology 2003



Who May Benefit from Genetic Testing?

- People with multiple primary cancers
- People with multiple family members affected by cancer of any type
- People with cancer at *young age* of onset
- Ashkenazi Jewish people with an interest in genetic testing for familial cancer
- First-degree relatives of known mutation positive individuals

Interpreting Genetic Testing Results



Interpreting Genetic Testing Results

Positive for deleterious mutation

Test Results and Interpretation

POSITIVE FOR A DELETERIOUS MUTATION

Test Performed	Result	Interpretation
MLH1 sequencing	No Mutation Detected	No Mutation Detected
comprehensive rearrangement	No Mutation Detected	No Mutation Detected
MSH2 sequencing	1705delGA	**Deleterious**
comprehensive rearrangement	No Mutation Detected	No Mutation Detected
MSH6 sequencing	No Mutation Detected	No Mutation Detected

Take Home Points

- Molecular diagnostic in CRC is essential for medical and surgical treatment
  - Chemotherapy (KRAS/BRAF/MSI)
  - Surgery (MMR/APC germline mutations)
- Suspect Familial Cancer
  - Individuals with cancer < age 50
  - Individuals with multiple family members with cancer
- Consider genetic counseling & testing
- Establish appropriate & individualized medical/surgical management plan

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coalición de cáncer colorrectal
PUERTO RICO

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UNC (Drs. Robert Sandler and John Baron
VA Caribbean (Dr. Doris Toro)
PR Colorectal Cancer Coalition
PR Gastroenterology Association