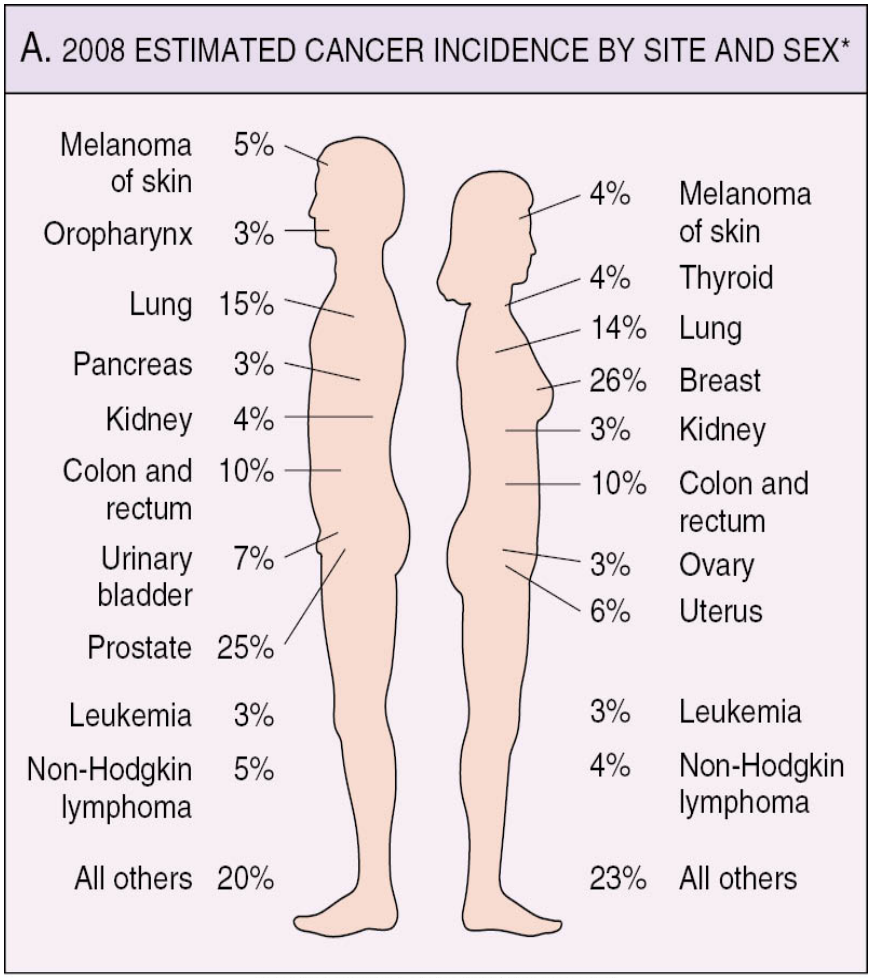
COLON CANCER: "PAST, PRESENT, AND FUTURE" AND FAMILIAL SYNDROMES

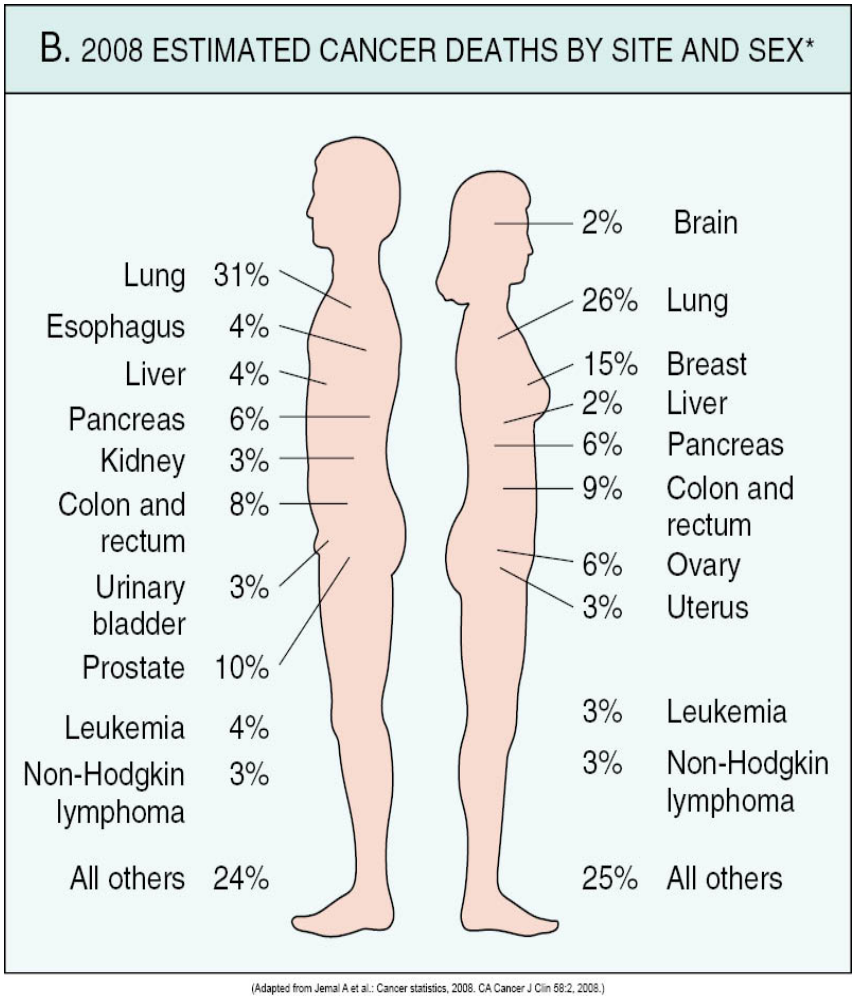
Eun Lee, MD,
Professor & Director of Anatomic Pathology

MCC Affiliate Network Meeting

- Etiology for colon cancer
- “Past, Present, and Future” for colon cancer
- Familial syndromes
- New universal IHC screening protocol for Lynch syndrome

Cancer Incidence & Death Rate in USA





3rd for Incidence & Death in both Male & Female

Colon cancer in Kentucky

- Colon cancer incidence
  - #1 in the nation in 2009
  - 9% higher than the national rate
- Increased statewide colorectal cancer screening (colonoscopy)
  - 34.7% in 2001
  - 63.7% in 2010
  - led by Dr. Thomas Tucker
  - statewide joint effort

Dietary ("Western diet")

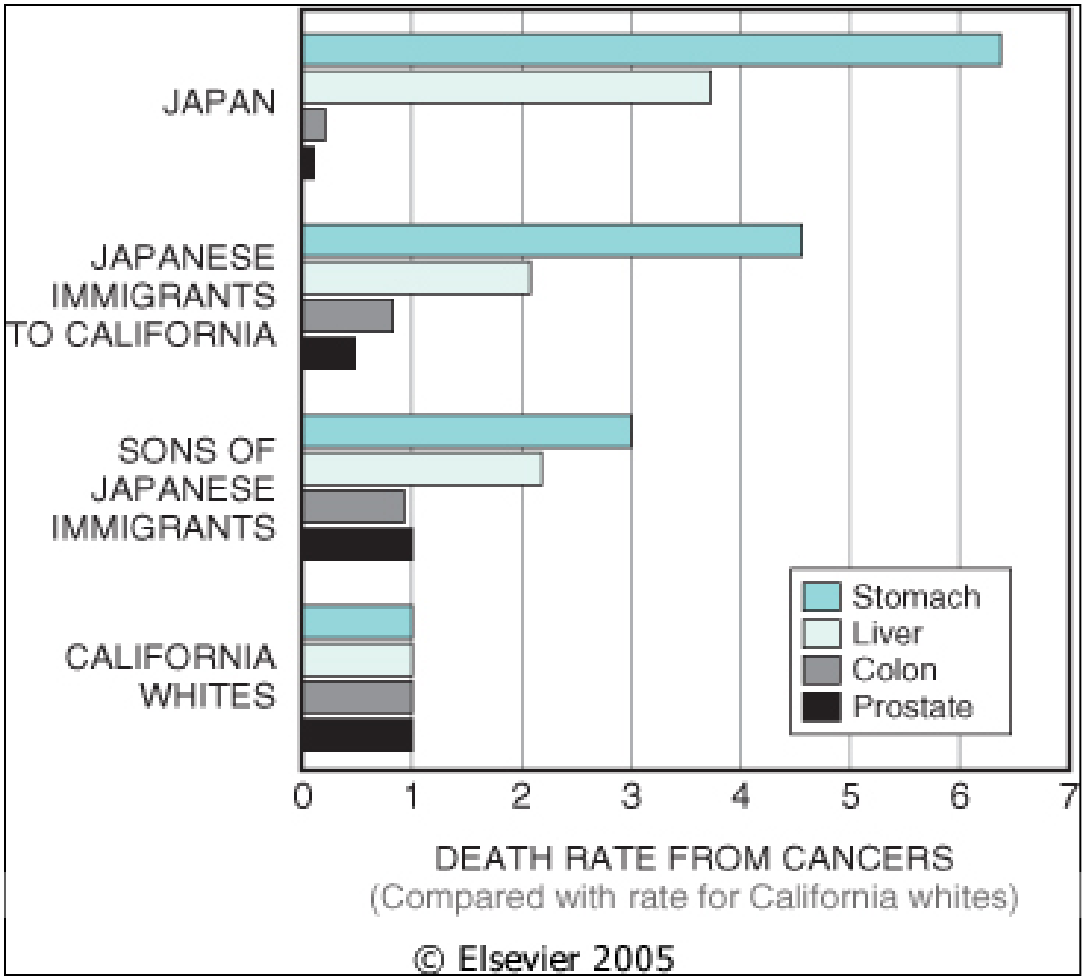
- **Low fiber diet**
- High fat diet
- Decreased intake of vitamins A, C, E

Colon Cancer in Korea

Uncommon in 70's

2nd M/C for male & 4th M/C for female

Immigrants from Japan to the United States



Japan in 2012

- Colon cancer: #2
- Gastric cancer: #3

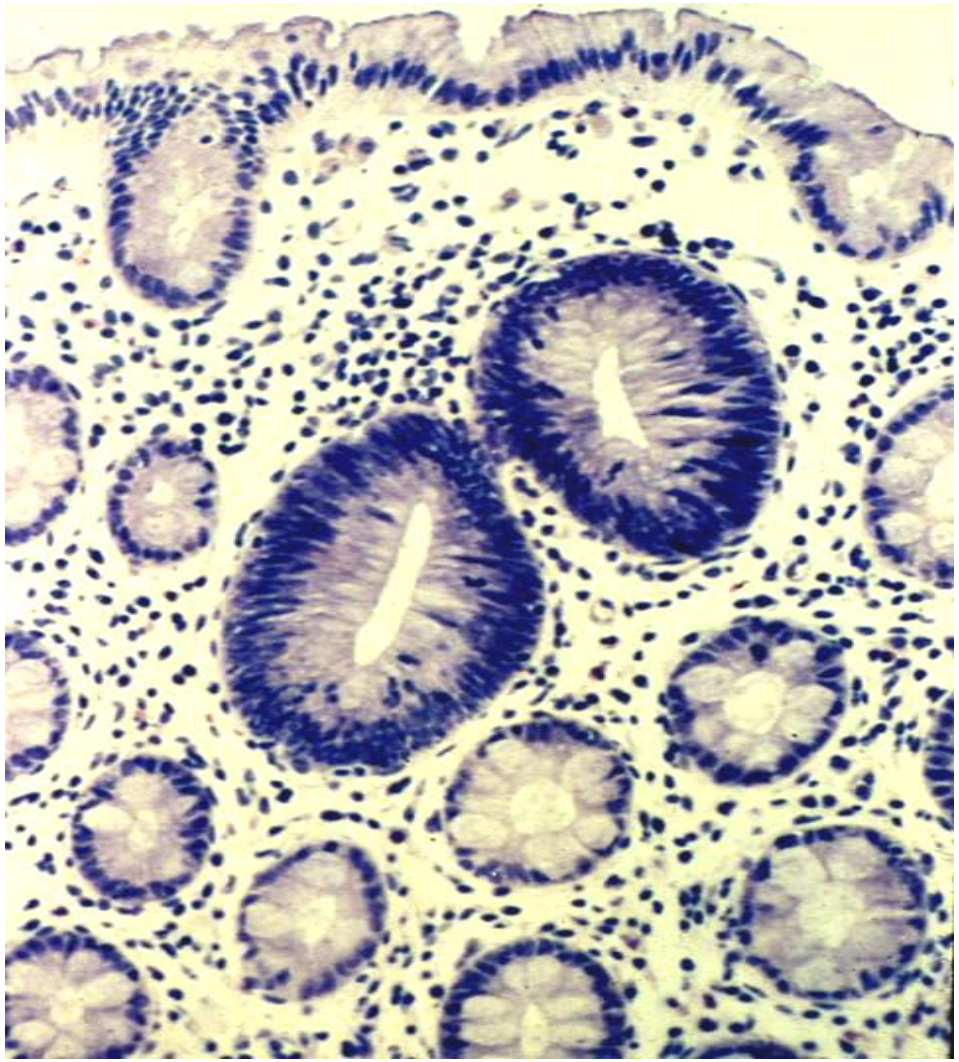
Etiology

- Hereditary
  - 1st degree relative w/ cancer: 2-4 fold ↑ risk
  - Lynch syndrome
  - Familial adenomatous polyposis (FAP)
- Ulcerative colitis
- Colorectal adenomas

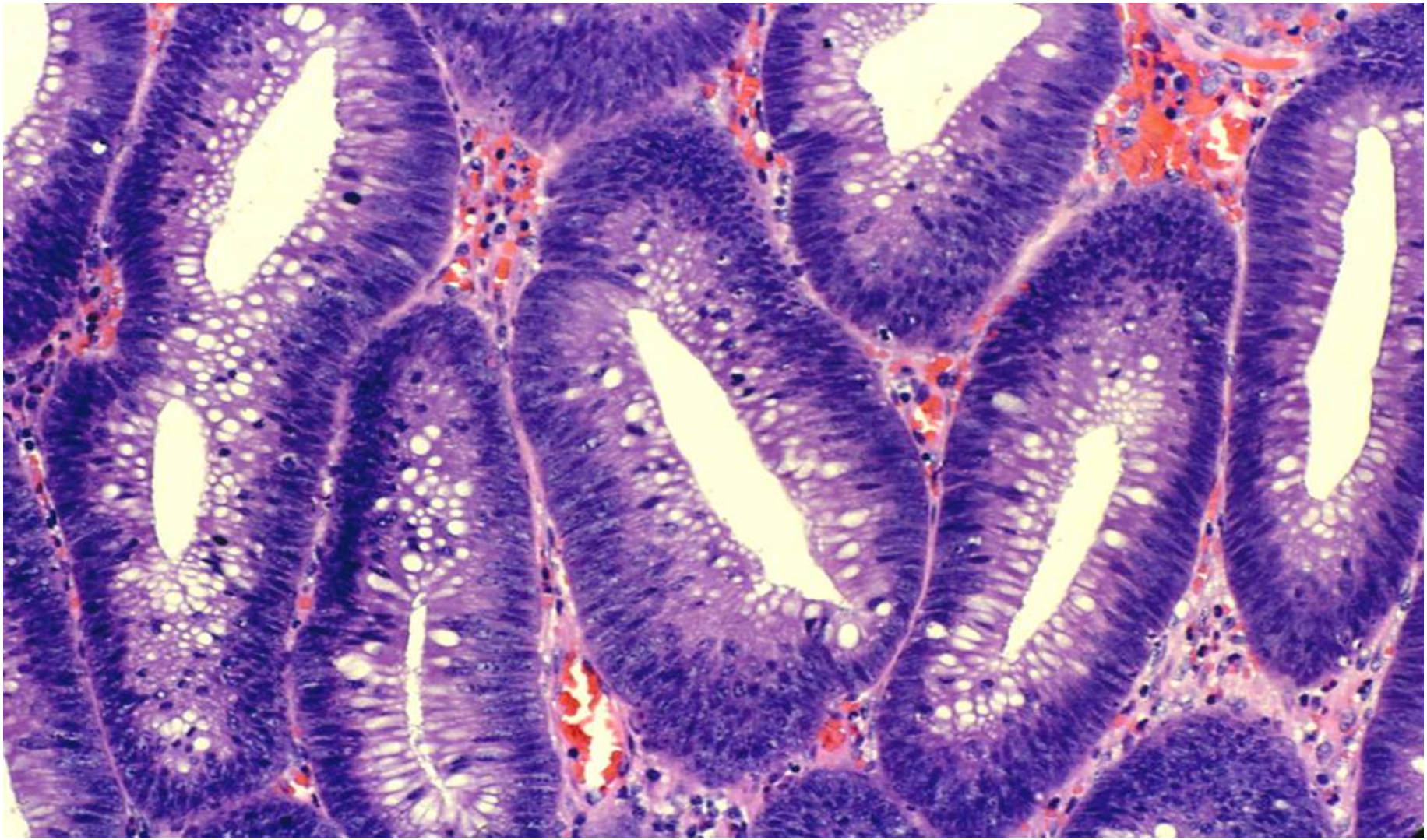
Colonic polyps

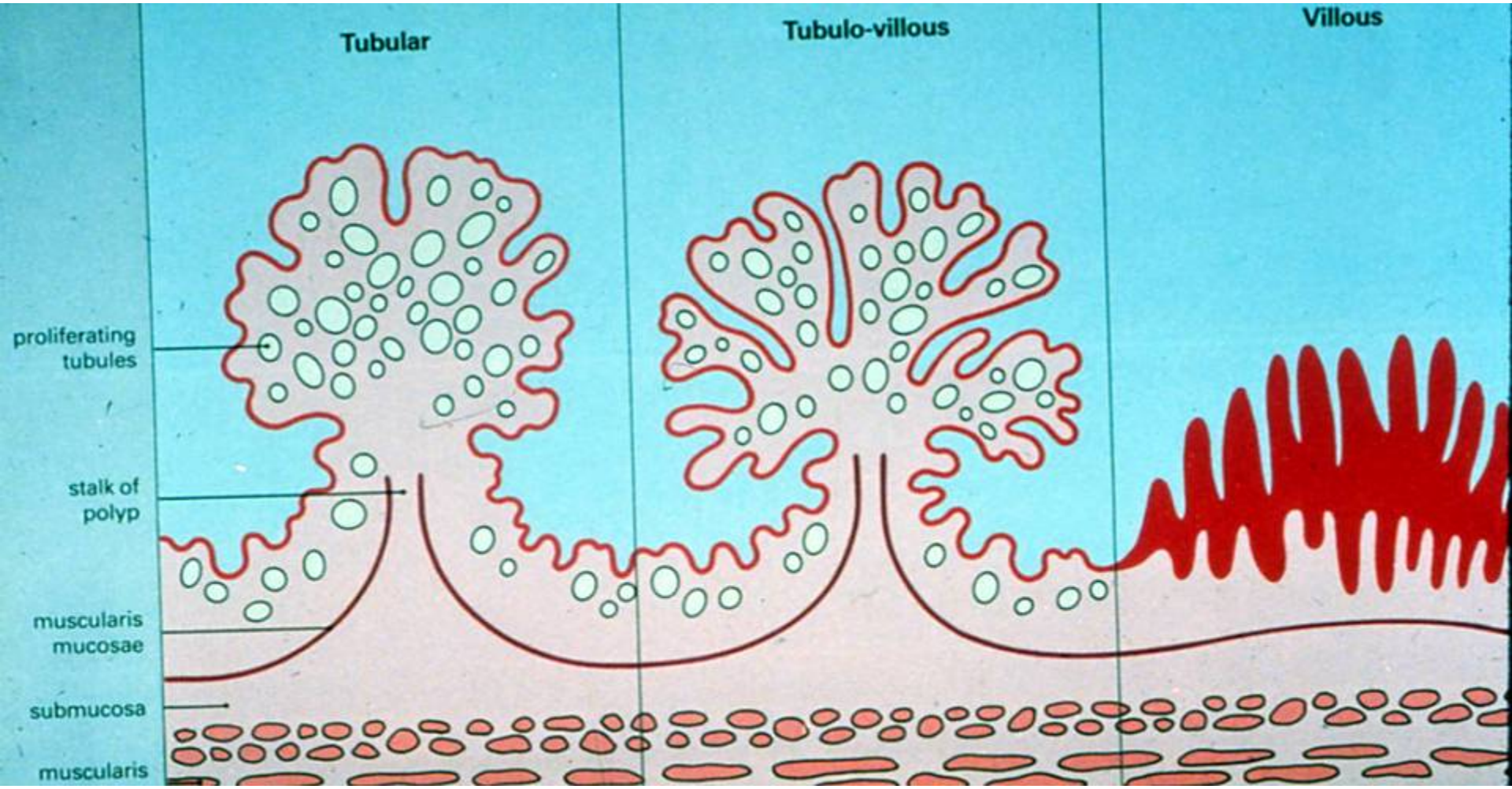
A. **Non-neoplastic polyps** (**NO** malignant potential)
    1. Hyperplastic polyp
    2. Juvenile polyp
    3. Hamartomatous polyp
    4. Inflammatory polyp (pseudopolyp)
    5. Lymphoid polyps
B. **Neoplastic polyps** (**malignant potential**)
    1. Tubular adenoma
    2. Villous adenoma
    3. Tubulovillous adenoma
    4. Traditional serrated adenoma
    5. Sessile serrated adenoma

Adenomatous change

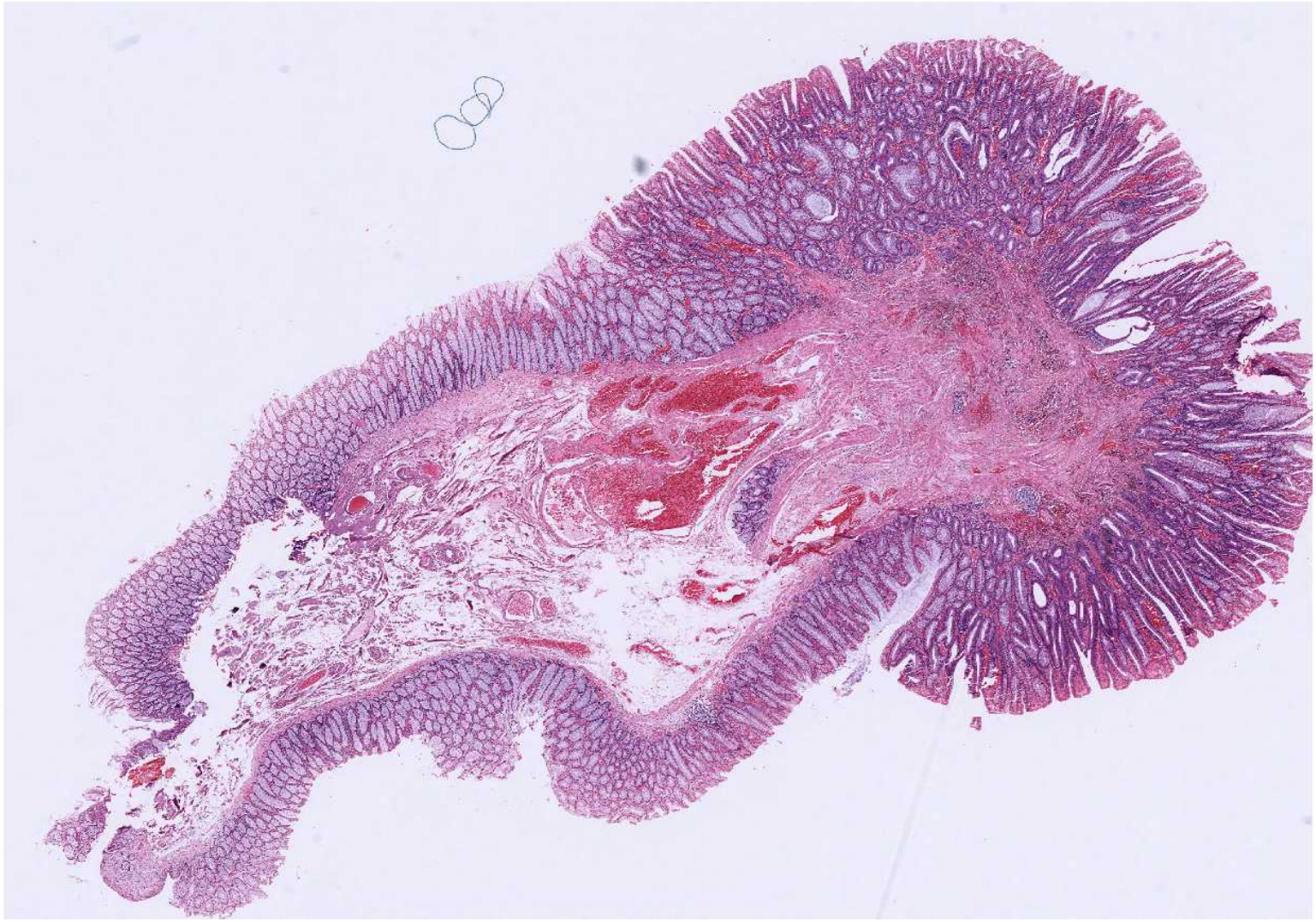


Adenomatous change

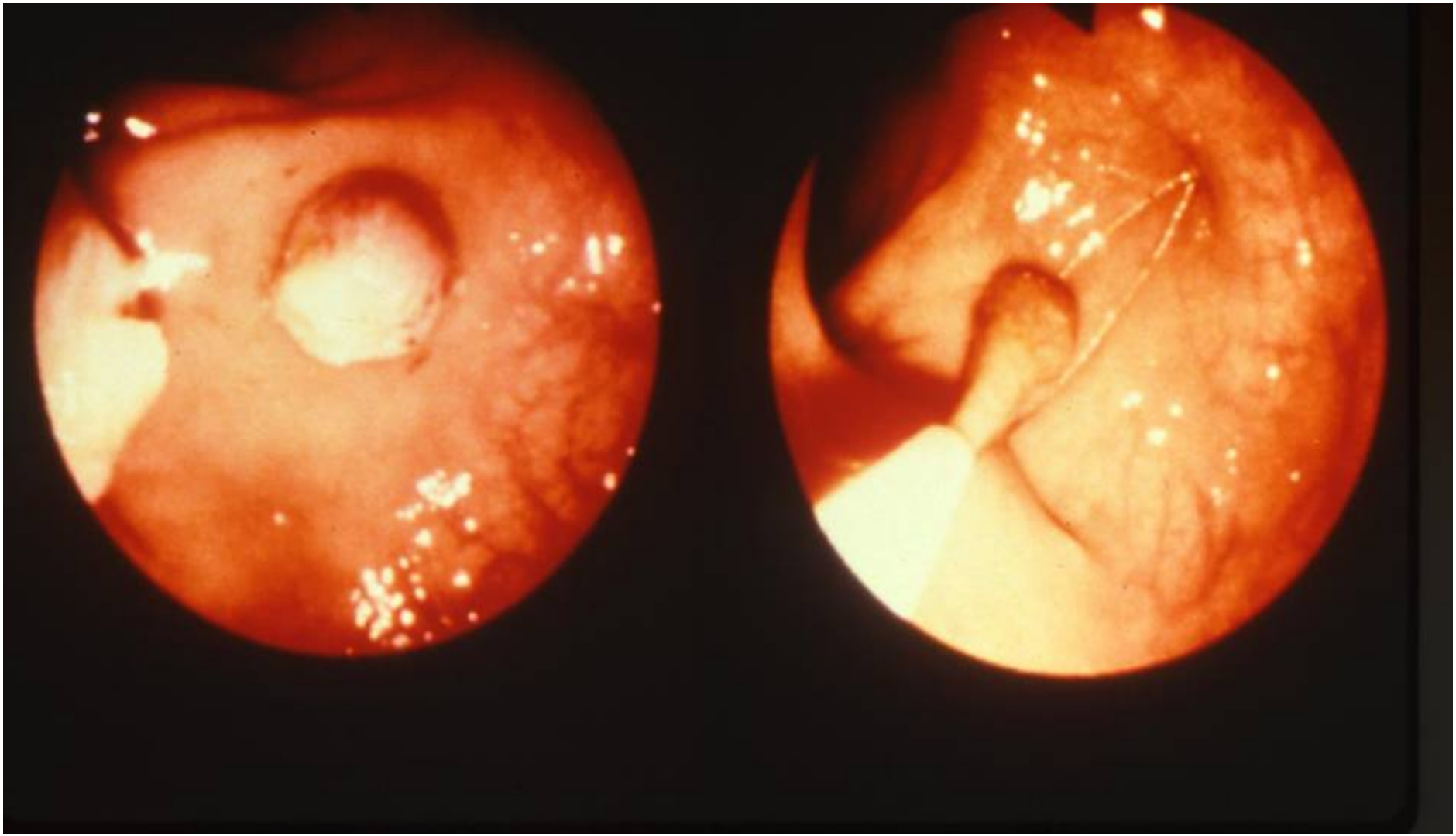



Tubular
Tubulo-villous
Villous
proliferating tubules
stalk of polyp
muscularis mucosae
submucosa
muscularis

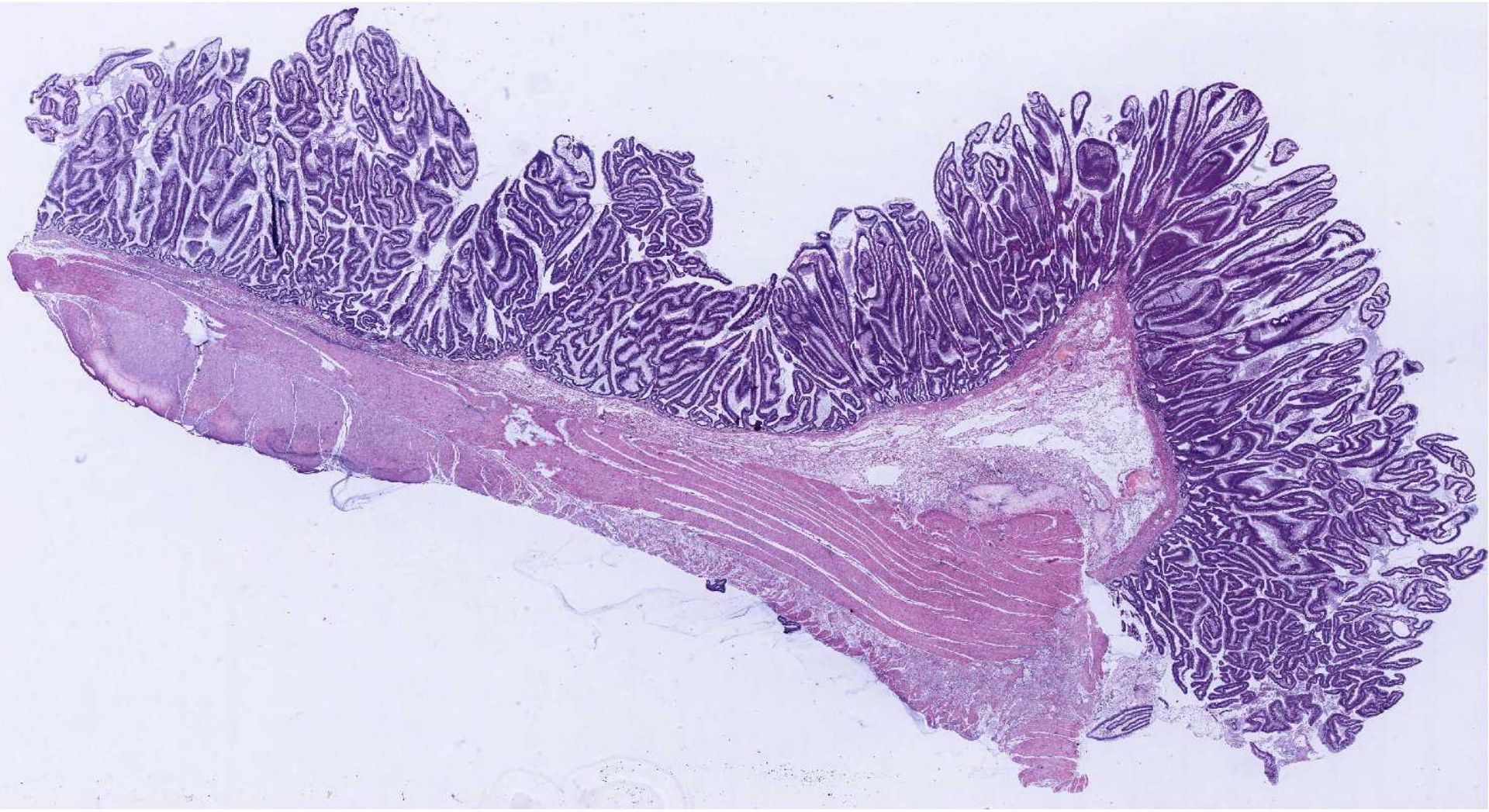
Tubular adenoma



Tubular adenoma



Villous adenoma



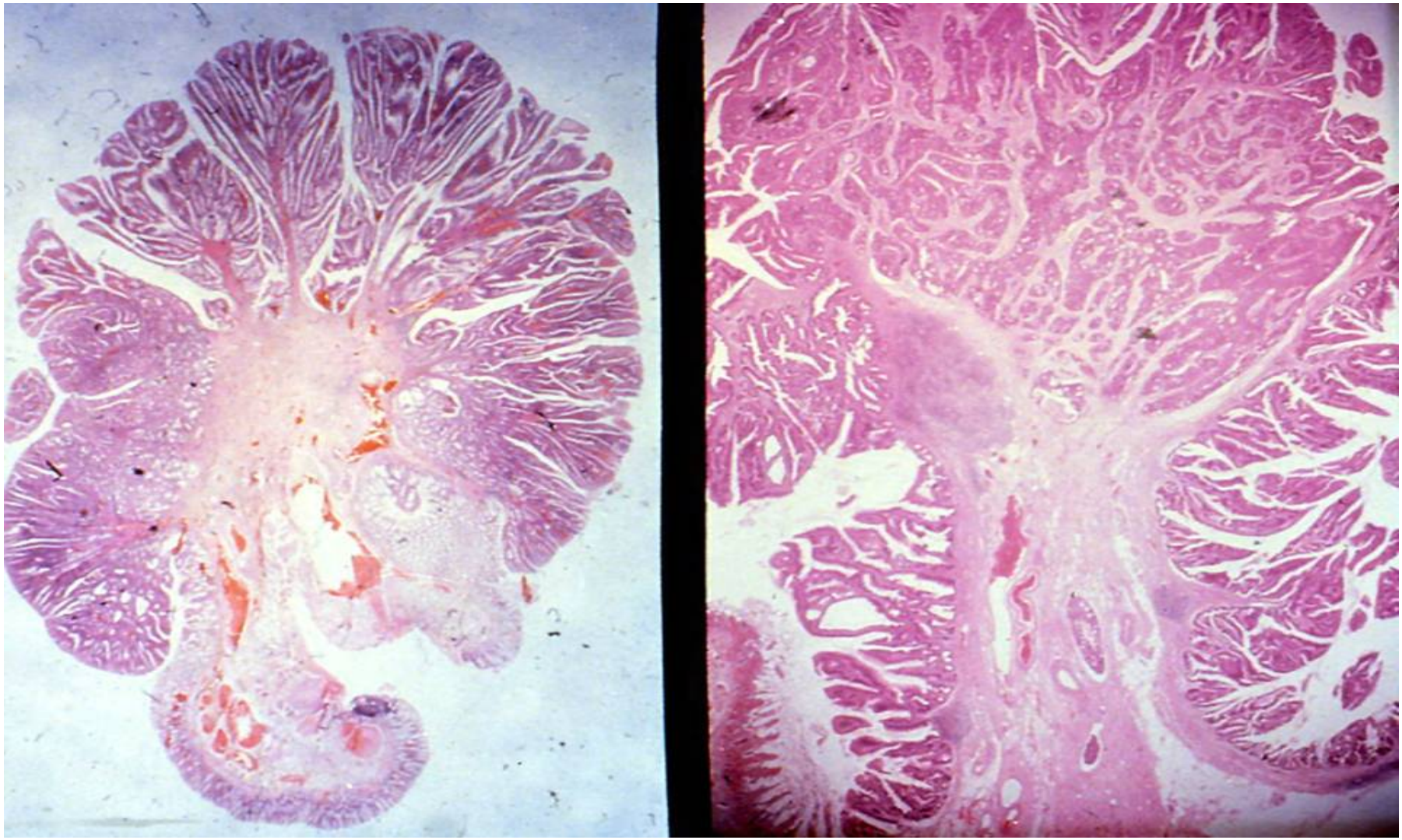
Other etiologies

- ? Heavy metals (e.g.: Arsenic) in Appalachia (Drs. M. Dignan, T. Tucker, X. Shi, G. M. Li)

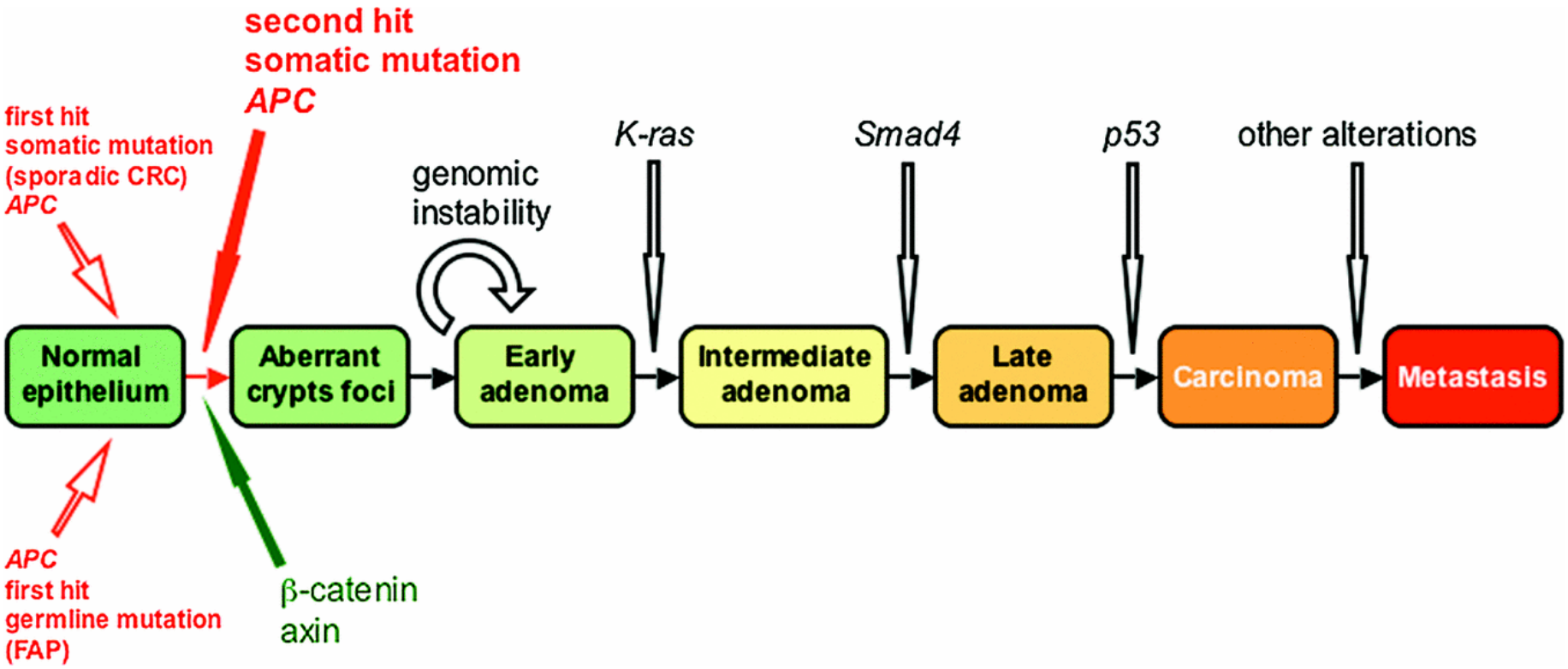
Colon Cancer in 80's

- Hyperplastic polyps: M/C (not true anymore)
- Adenomas
  - tubular, tubulovillous, villous
- Colon cancer
  - diagnosis, histologic type, grading
  - staging (Dukes classification)
- High grade dysplasia (instead of carcinoma-in situ)

Invasive CA in adenoma ("malignant polyp"): up to 5%



Dr. Vogelstein
"Multi-step carcinogenesis"

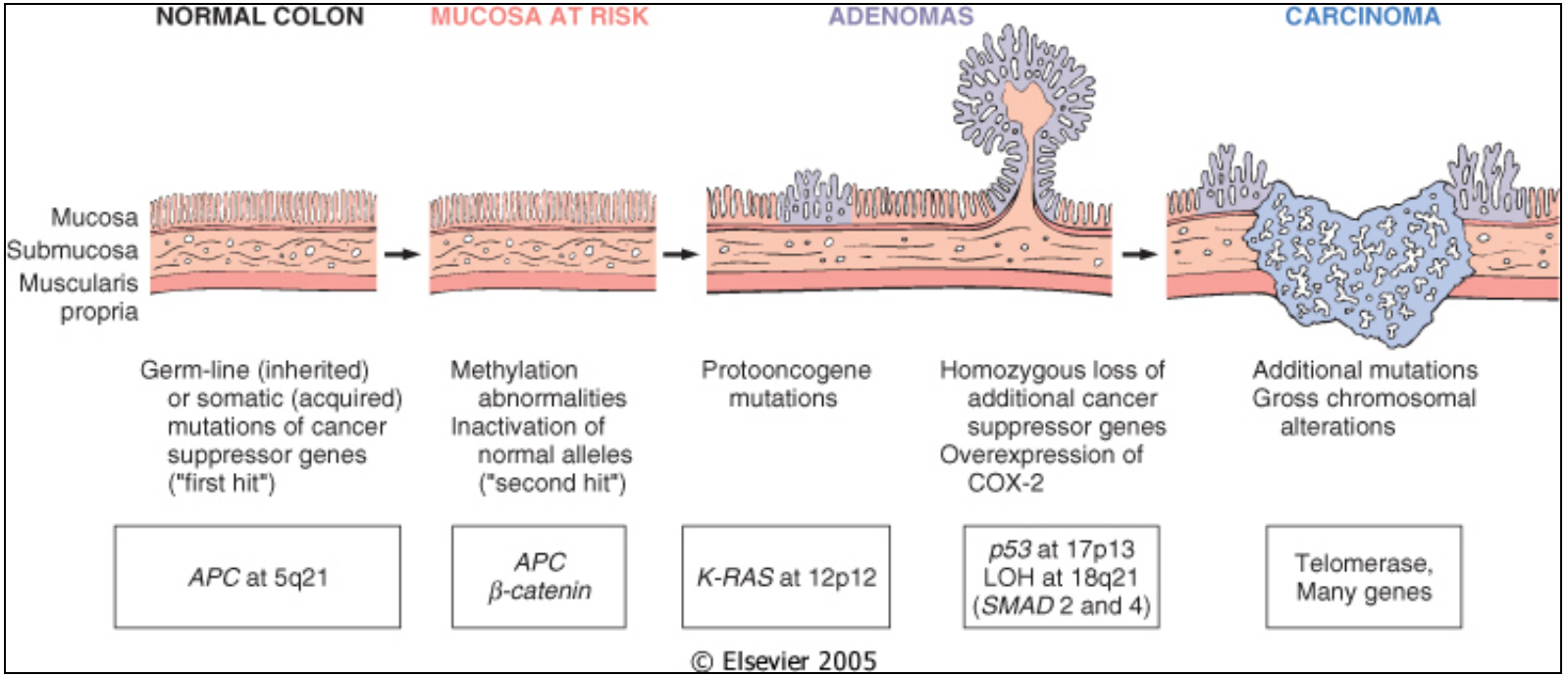


Genetic alterations during colorectal tumor development N Eng J Med 1988

Adenomatous Polyposis Coli (APC) Gene

- Promote cell adhesion and **regulate cell proliferation**
- **Increased & unregulated proliferation**

APC/β-catenin pathway



Classical pathway

Chromosomal instability pathway

Lynch Syndrome (HNPCC)

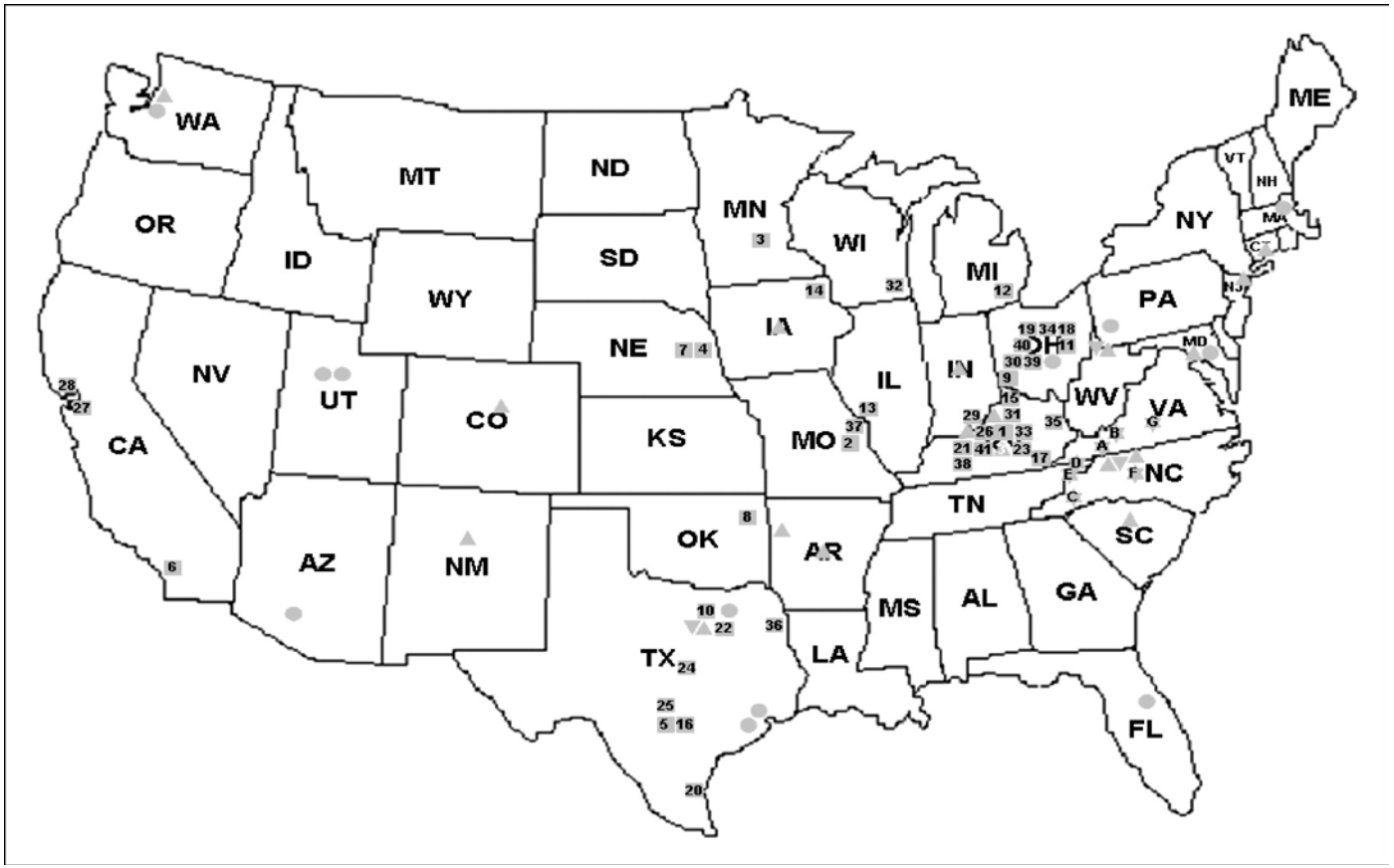
- 3-5% (M/C hereditary) of all colon cancers
- Younger age of onset, right colon, synchronous cancer, strong family history
- Germline (inherited) mutations of DNA **mismatch repair genes** leading to **microsatellite instability**
  -"automatic spelling checker"
- Small increases or decreases in the size of microsatellite throughout the genome
  ("MSI-H tumor")

Lynch Syndrome

- **Lifetime cancer risks:**
  - Colorectal 80%
  - Endometrial 20-60%
  - Gastric 13-19%
  - Ovarian 9-12%
  - Biliary tract 2%
  - Urinary tract 4%
  - Small bowel 1-4%
  - Brain/CNS 1-3%

American Founder Mutation

(76 families; 12 families in Kentucky)

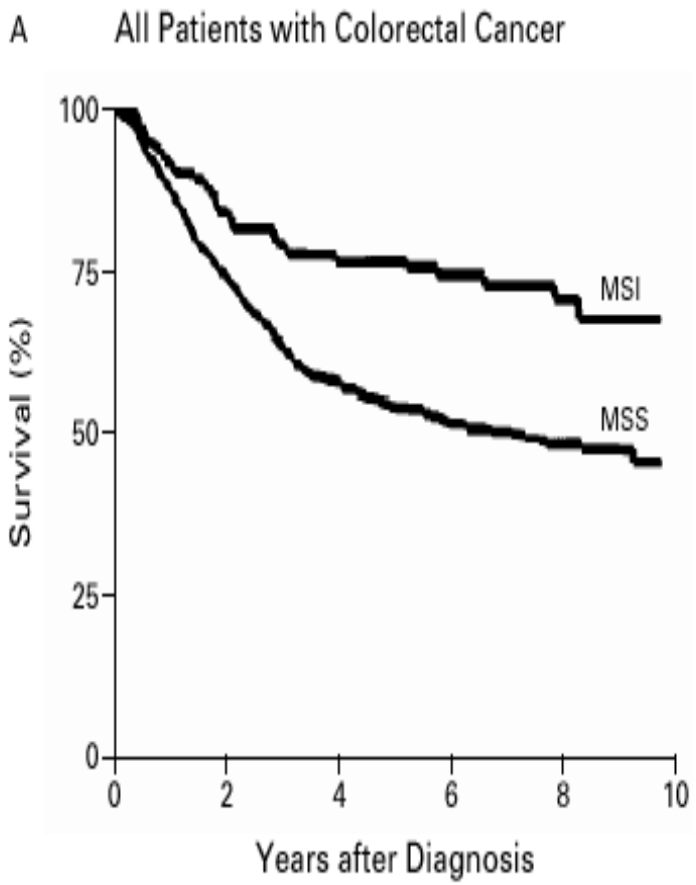


Clendenning M et al. Cancer Res 2008;68:2145-2153

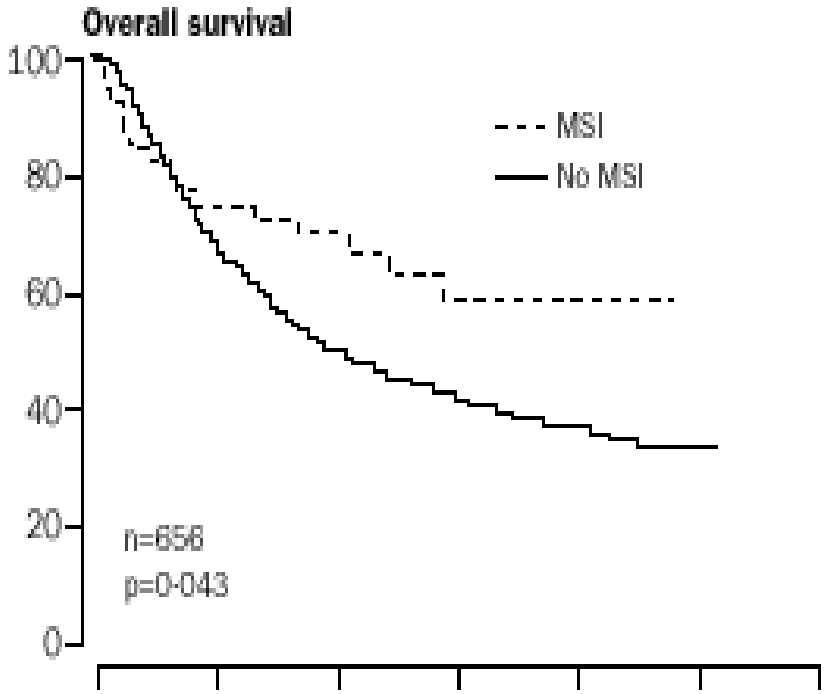
MSI-H Colon Cancers

- Also in 10% of sporadic colon cancers

Microsatellite Instability & Prognosis

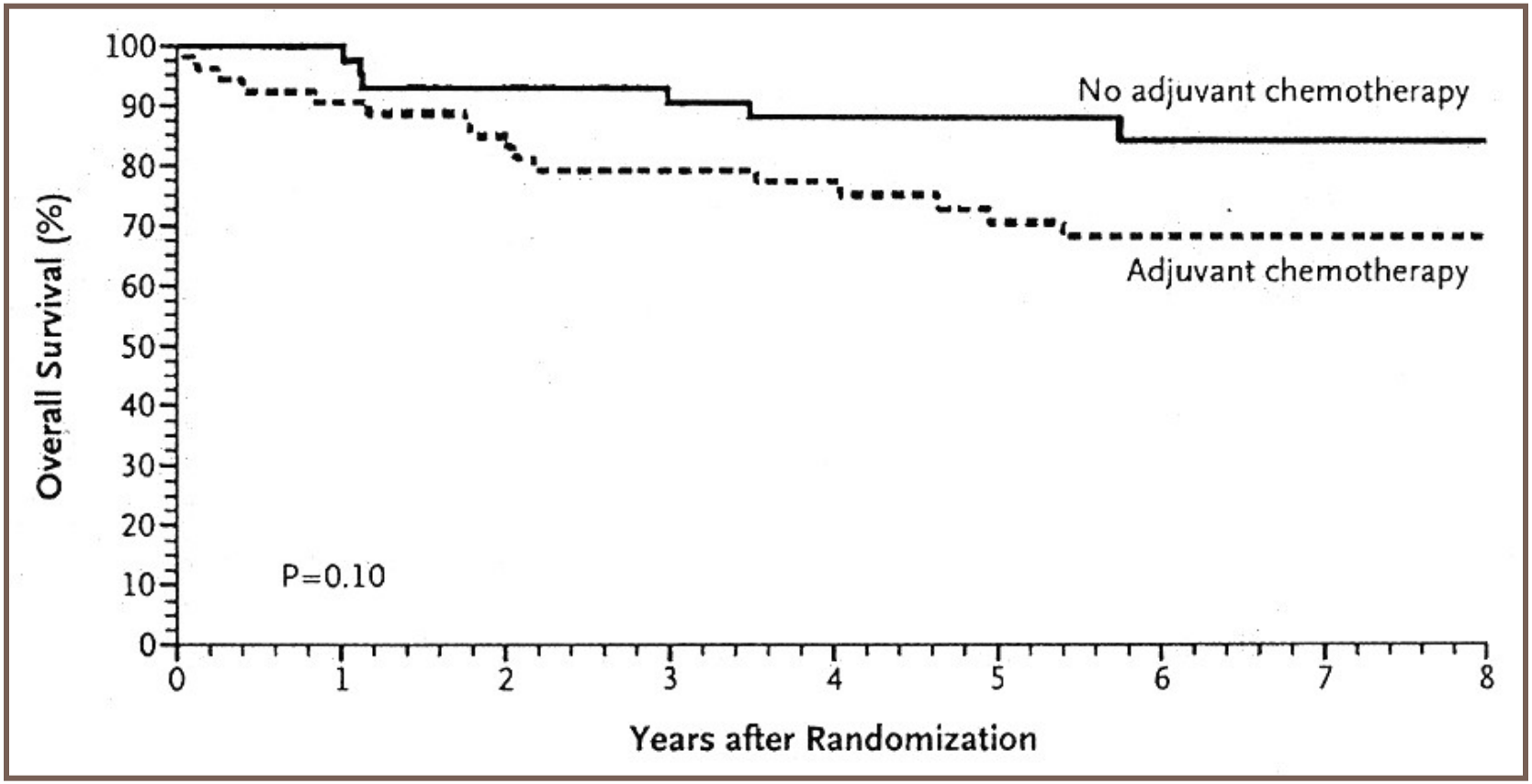


NEJM 342:71, 2000



Lancet 355:1748, 2000

Adjuvant Therapy in MSI-H CRC (stage II & III)



Ribic et al, NEJM 2003;349:247-257

MSI-high Tumors

- Peritumoral lymphoid reaction ("Crohn's-like")
- ↑ intratumoral lymphocytes
- Medullary histology
- Prominent mucinous differentiation
- NO "dirty necrosis"

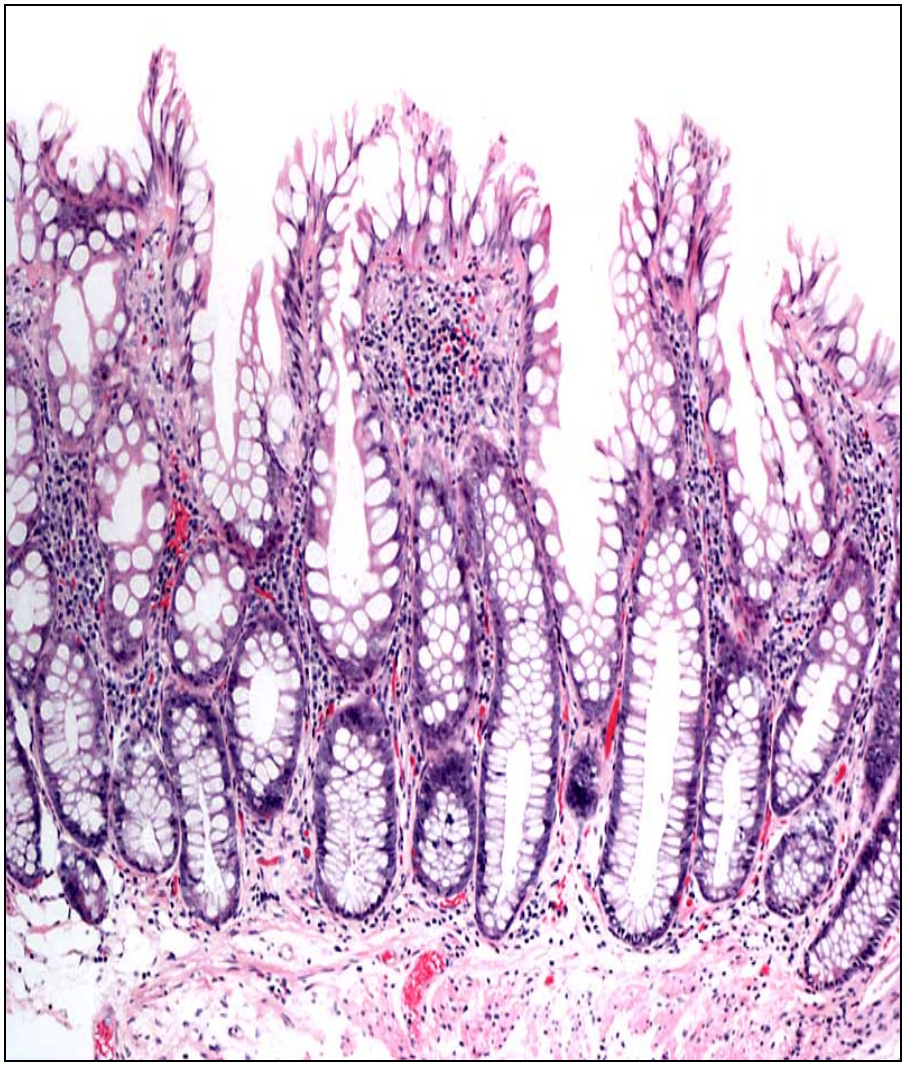
Evolution

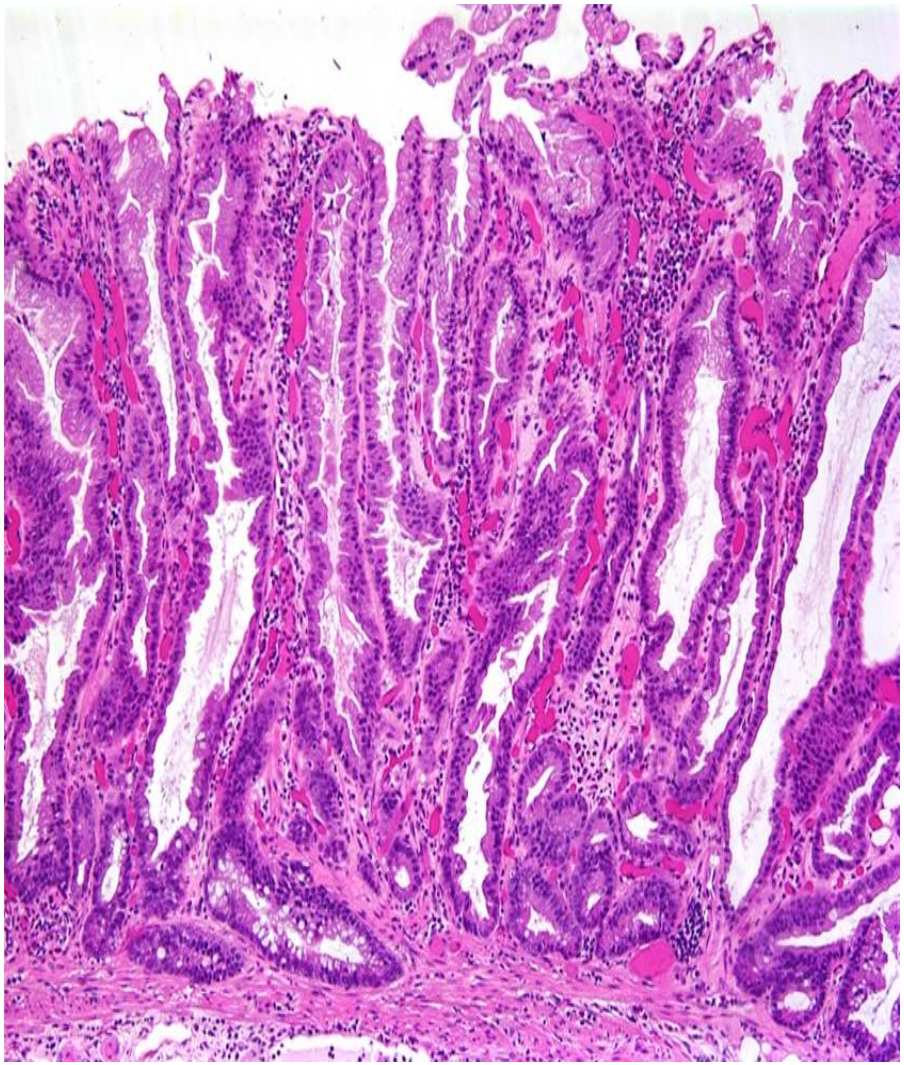
- Changes for AJCC (TMN) staging
  - New AJCC, new WHO Classification next year
  - Molecular information in certain tumors
- Evolution of reporting
  - CAP (College of American Pathologists) cancer protocol/checklist for synoptic reporting
  - Mandatory documentation of all pertinent pathologic findings in pathology reports

New adenomas (5-6 years ago)

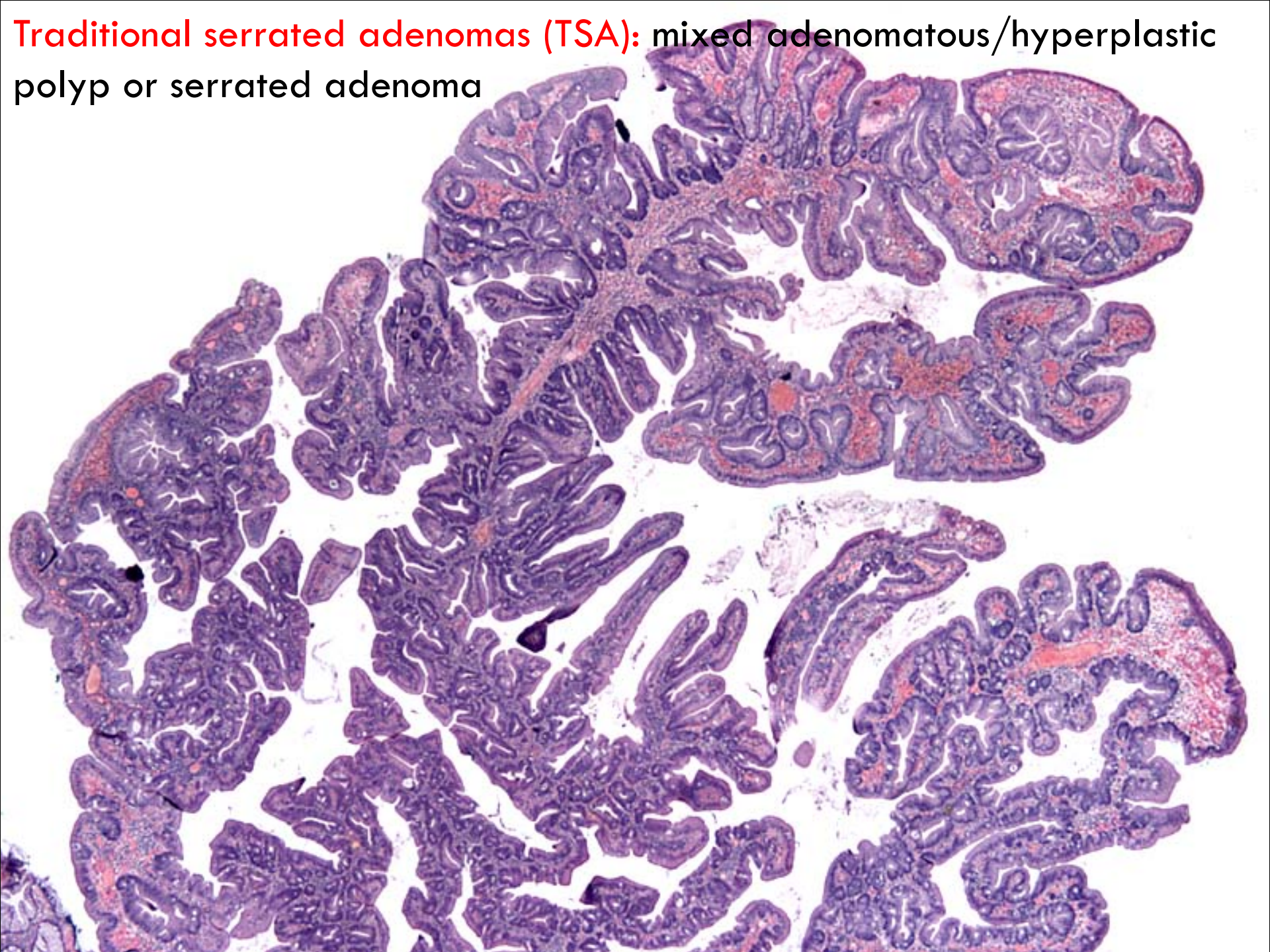
- Tubular adenoma
- Tubulovillous adenoma
- Villous adenoma
- Sessile serrated adenoma (SSA)
- Traditional serrated adenoma (TSA)

HP vs Sessile serrated adenoma





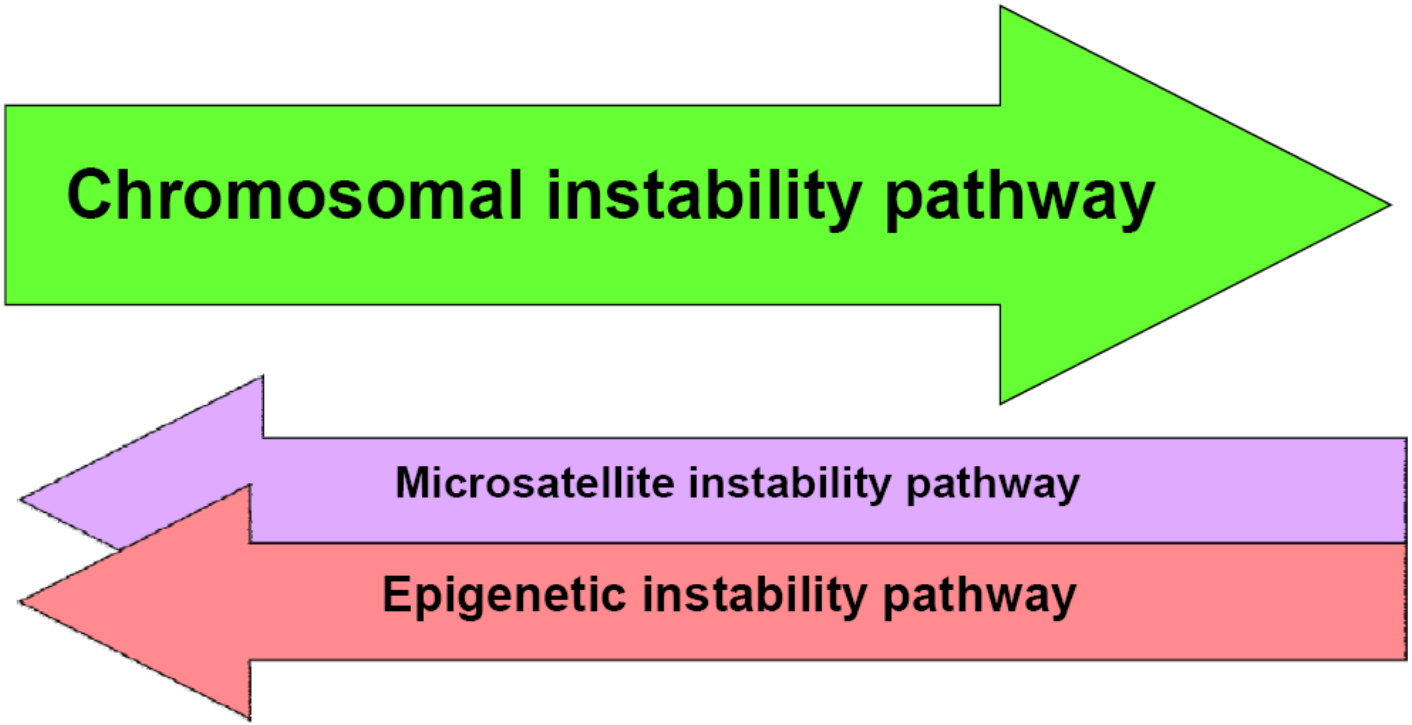
Traditional serrated adenomas (TSA): mixed adenomatous/hyperplastic polyp or serrated adenoma



Extensive DNA methylation

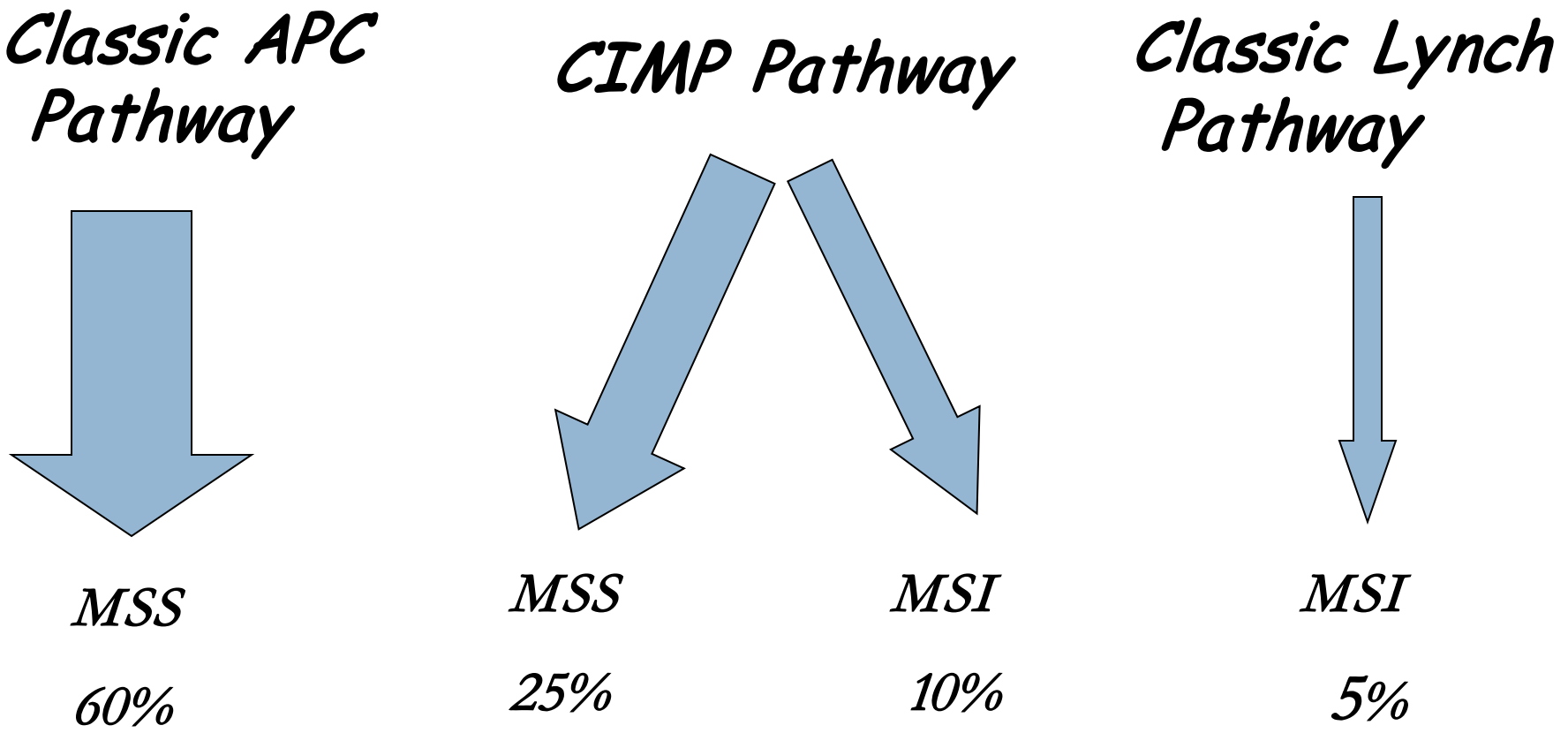
- About 50% of genes have clusters of dinucleotide cytosine guanine (C*p*G) within their promoter regions: C*p*G islands
- Normally unmethylated
- Transcriptional inactivation of genes
- Suppressor genes: ***BRAF***, *TGFβRII*, *BAX*, *IGF2R*
- Epigenetic changes: changes in gene activity
- C*p*G island methylator phenotype (**CIMP** or CIMP-high)

Mutually Exclusive Relationships



Partially Overlapping Two Pathways

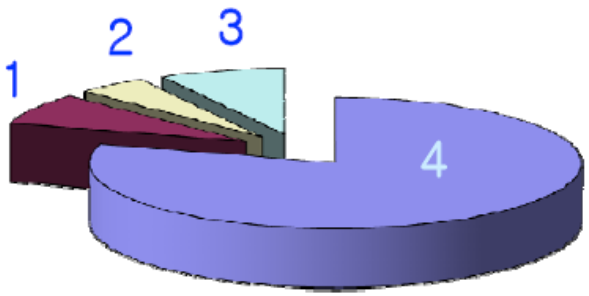
Major Pathways for Colorectal Cancer

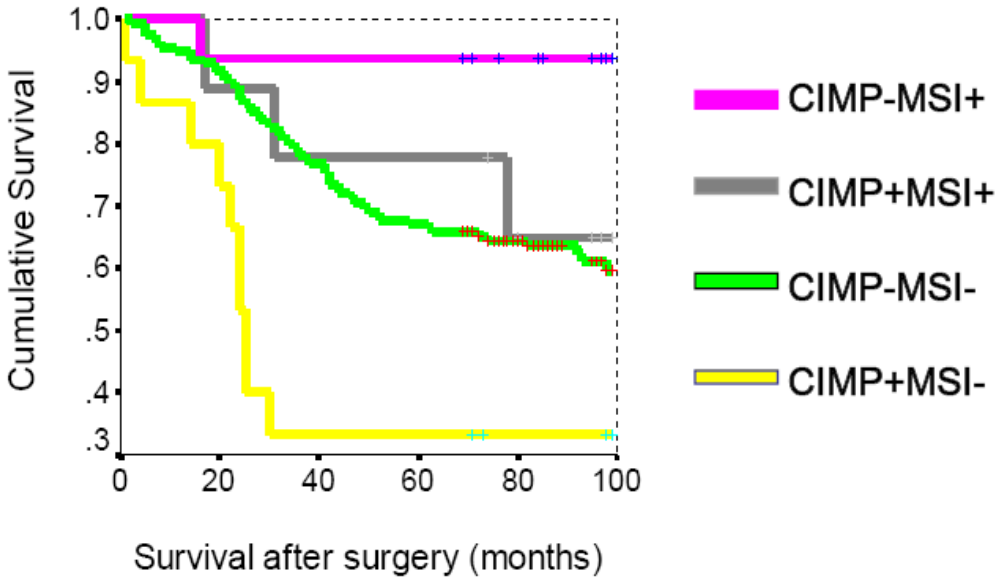


vanRijsoever M, et al. Clin Cancer Res, 2003;9:2898-2903

Four Molecular Subtypes of Colorectal Cancers according to CIMP and MSI status

1. CIMP-/MSI+, 8%
2. CIMP+/MSI+, 5%
3. CIMP+/MSI-, 8%
4. CIMP-/MSI-, 79%





P=0.0006

MSI+ CRC, 1+3, 13%
CIMP+ CRC, 2+3, 13%

Molecular Classification for Colorectal Cancer

Group 1	CIMP-high/MSI-H/ BRAF mutation	serrated polyps	12%	Good
Group 2	CIMP-high/MSI-L or MSS/BRAF mutation	serrated polyps	8%	Bad
Group 3	CIMP-low/MSS or MSI-L/KRAS mutation	adenomas or serrated	20%	?
Group 4	CIMP-neg/MSS	adenomas	57%	Average
Group 5 (Lynch)	CIMP-neg/MSI-H	adenomas	3%	Good

J R Jass, Histopathology 2007

NEJM July, 2004

Table. Estimated Drug Costs for Eight Weeks of Treatment for Metastatic Colorectal Cancer.

Regimen	Drugs and Schedule of Administration	Drug Costs*
		$
Regimens containing fluorouracil		
Mayo Clinic	Monthly bolus of fluorouracil plus leucovorin	63
Roswell Park	Weekly bolus of fluorouracil plus leucovorin	304
LV5FU2	Biweekly fluorouracil plus leucovorin in a 48-hr infusion	263
Regimens containing irinotecan or oxaliplatin		
Irinotecan alone	Weekly bolus	9,497
IFL	Weekly bolus of fluorouracil plus irinotecan	9,539
FOLFIRI	LV5FU2 with biweekly irinotecan	9,381
FOLFOX	LV5FU2 with biweekly oxaliplatin	11,889
Regimens containing bevacizumab or cetuximab		
FOLFIRI with bevacizumab	FOLFIRI with fortnightly bevacizumab	21,399
FOLFOX with bevacizumab	FOLFOX with biweekly bevacizumab	21,033
Irinotecan with cetuximab	Weekly irinotecan plus cetuximab	30,790
FOLFIRI with cetuximab	FOLFIRI and weekly cetuximab	30,675

* Costs represent 95 percent of the average wholesale price in May 2004.

For 8 weeks course; $161,000 for 1 year treatment

KRAS testing before **Anti-EGFR** therapy

- Second & third line therapy for metastatic CRC
- Only effective if *KRAS* is wild type
- ASCO guideline in 2009
- *KRAS* mutation: 30-40%
- Substantial saving for health care system
  - *KRAS* testing: <$500/test
  - Erbitux: $2,491 x 24 infusions = $60,000
- Other mutations in EGFR pathway:
  - *BRAF*, *PIK3CA*

Aspirin use, tumor *PIK3CA* mutation, and colorectal cancer survival

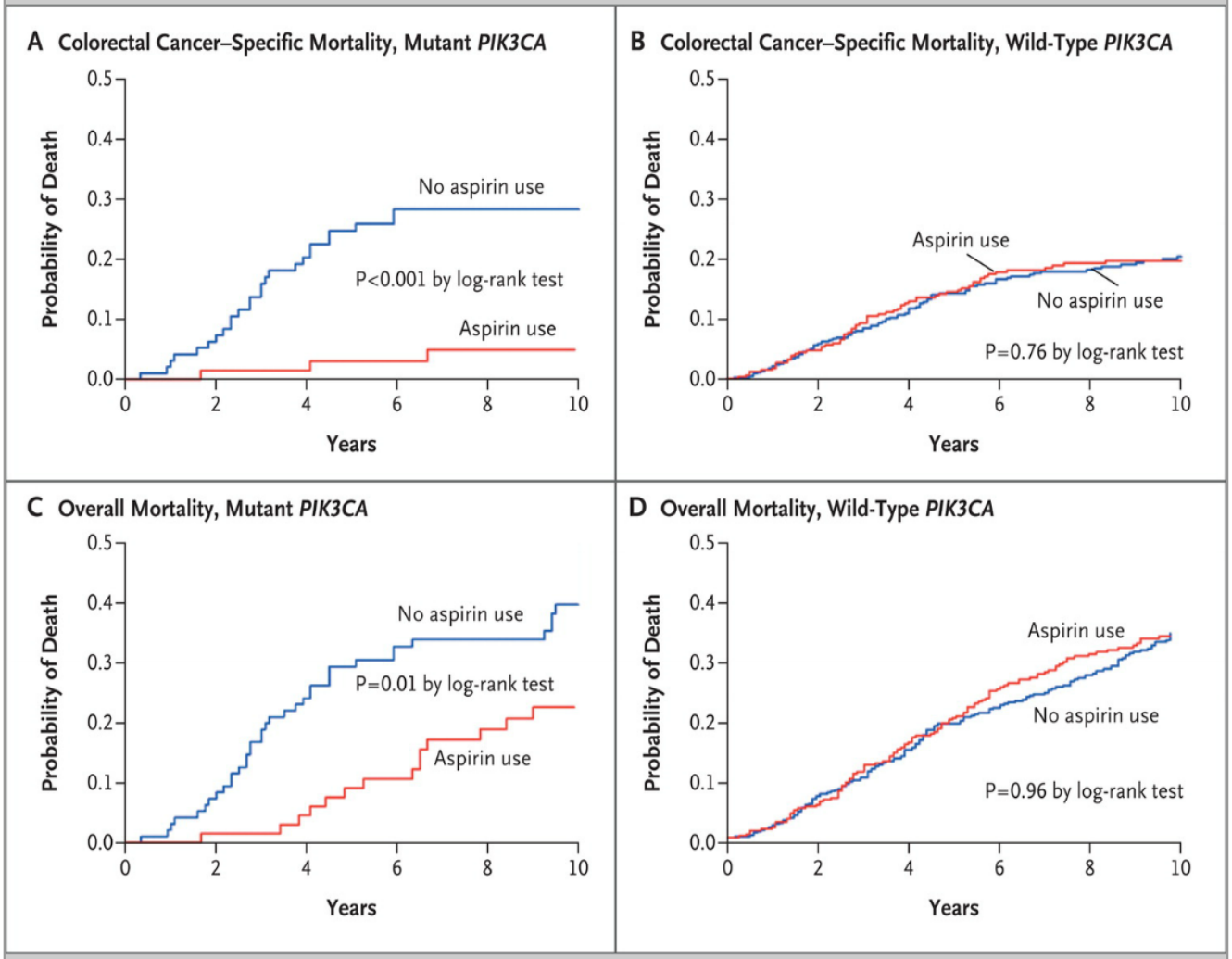


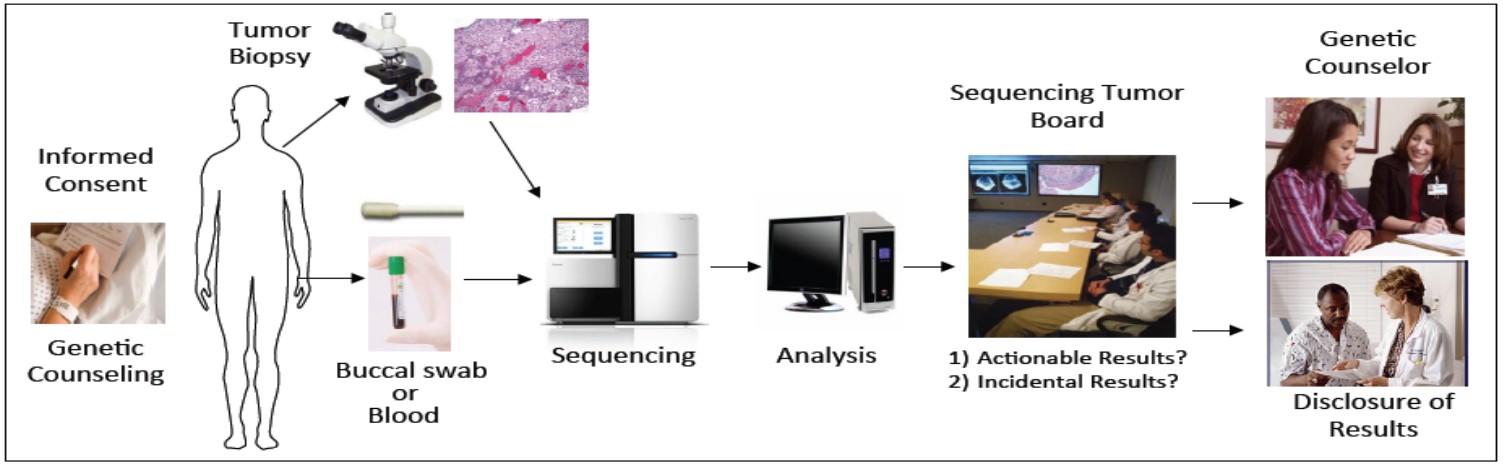
Figure 1. Mortality among Patients with Colorectal Cancer, According to Regular Use or Nonuse of Aspirin after Diagnosis and *PIK3CA* Mutation Status.

Panels A and B show colorectal cancer–specific mortality among patients with mutant-*PIK3CA* tumors and those with wild-type *PIK3CA* tumors, respectively, and Panels C and D show overall mortality in the respective subgroups of patients.

N Engl J Med 2012: 367: 1596

Next Generation Sequencing (NGS) for CRC

MI-ONCOSEQ:
The Michigan Oncology Sequencing Center



Michigan Center for Translational Pathology

University of Michigan Health System

Cost for NGS/whole genomic sequencing

- 1990: 8 years, 3 billions
- 2010: 3-4 months, $100,000
- Near future: several days, >$1,000
- Future: <24 hours, <$1,000

Promise of Genomic Medicine

- Personalized medicine
- Improves patient outcome
  - more effective treatment
  - less toxic drugs
- Reduces cost

Personalized Medicine

- Molecular characteristics of DISEASE
  - molecular classification of tumor
  - characterization of tumor heterogeneity
  - characterization of therapeutic targets
- Molecular characteristics of HOST
  - disease susceptibility
  - treatment efficacy (e.g., pharmacogenomics)

Other –omics Techniques

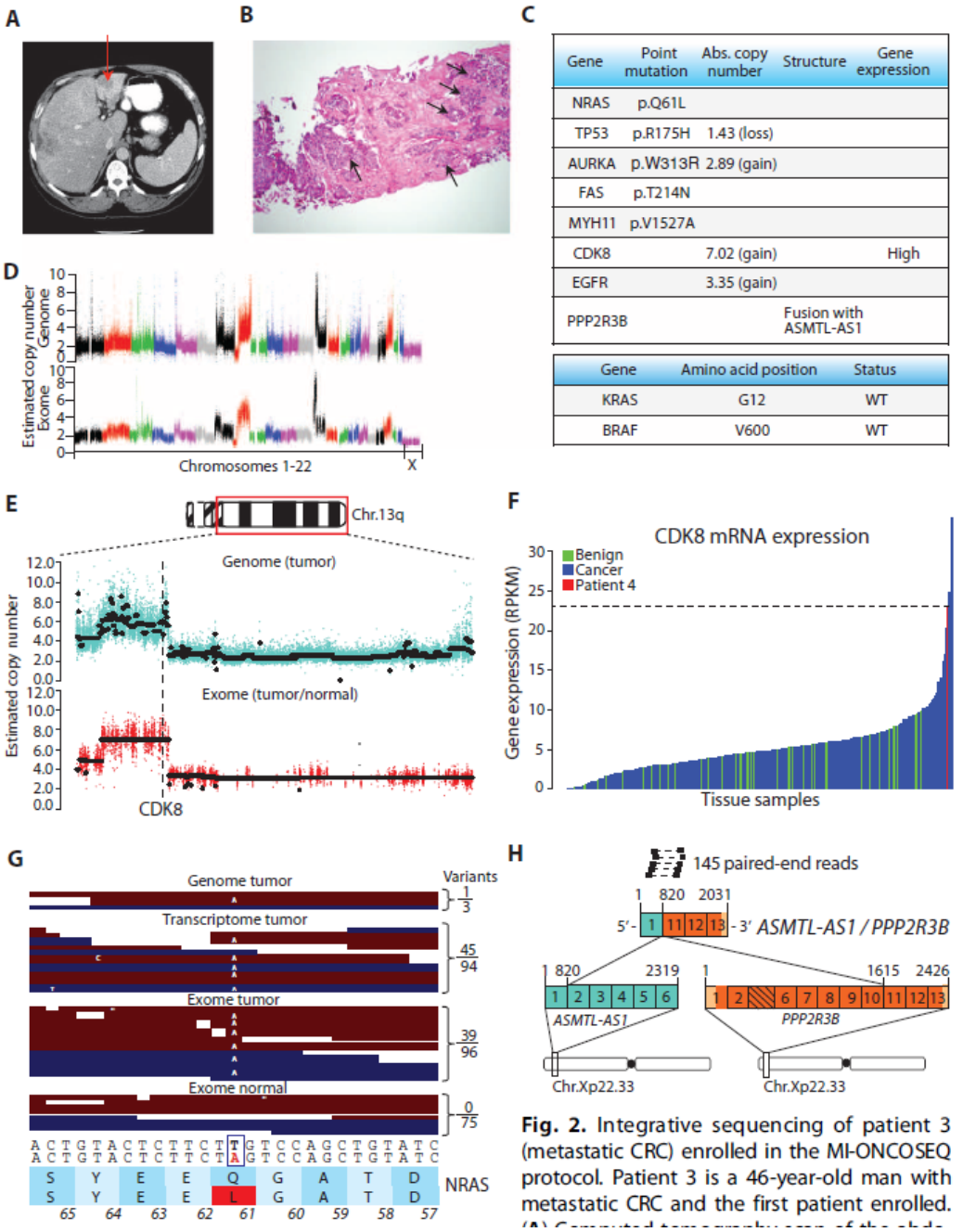
- Transcripomics (mRNA)
- Interferomics (iRNA)
- Epigenomics
- Tumor cells (oncomics) vs stroma (stromics)
- Proteins vs nucleic acids (e.g., proteomics and metabolomics)

“Specialty Pharmacy” services

- “Accredited Specialty Pharmacy” at UK
- FDA approval for 900 new drugs by 2016
- 40%: specialty medications
  - requires associated genetic lab tests
  - majority are cancer drugs
- Pre-authorization for specialty medications and associated genetic lab tests by insurances

What will the pathology report in the future look like?

- Site of biopsy
- Morphology
- Point mutations
- Germline alterations
- Copy number aberrations
- Gene rearrangements
- Gene expression (pathway activation)
- Drugs matched to mutation



Gene	Point mutation	Abs. copy number	Structure	Gene expression
NRAS	p.Q61L			
TP53	p.R175H	1.43 (loss)		
AURKA	p.W313R	2.89 (gain)		
FAS	p.T214N			
MYH11	p.V1527A			
CDK8		7.02 (gain)		High
EGFR		3.35 (gain)		
PPP2R3B			Fusion with ASMTL-AS1	

Gene	Amino acid position	Status
KRAS	G12	WT
BRAF	V600	WT

Fig. 2. Integrative sequencing of patient 3 (metastatic CRC) enrolled in the MI-ONCOSEQ protocol. Patient 3 is a 46-year-old man with metastatic CRC and the first patient enrolled. (A) Computed tomography scan of the abdo

“Information Overload”

“I think we over-ordered”

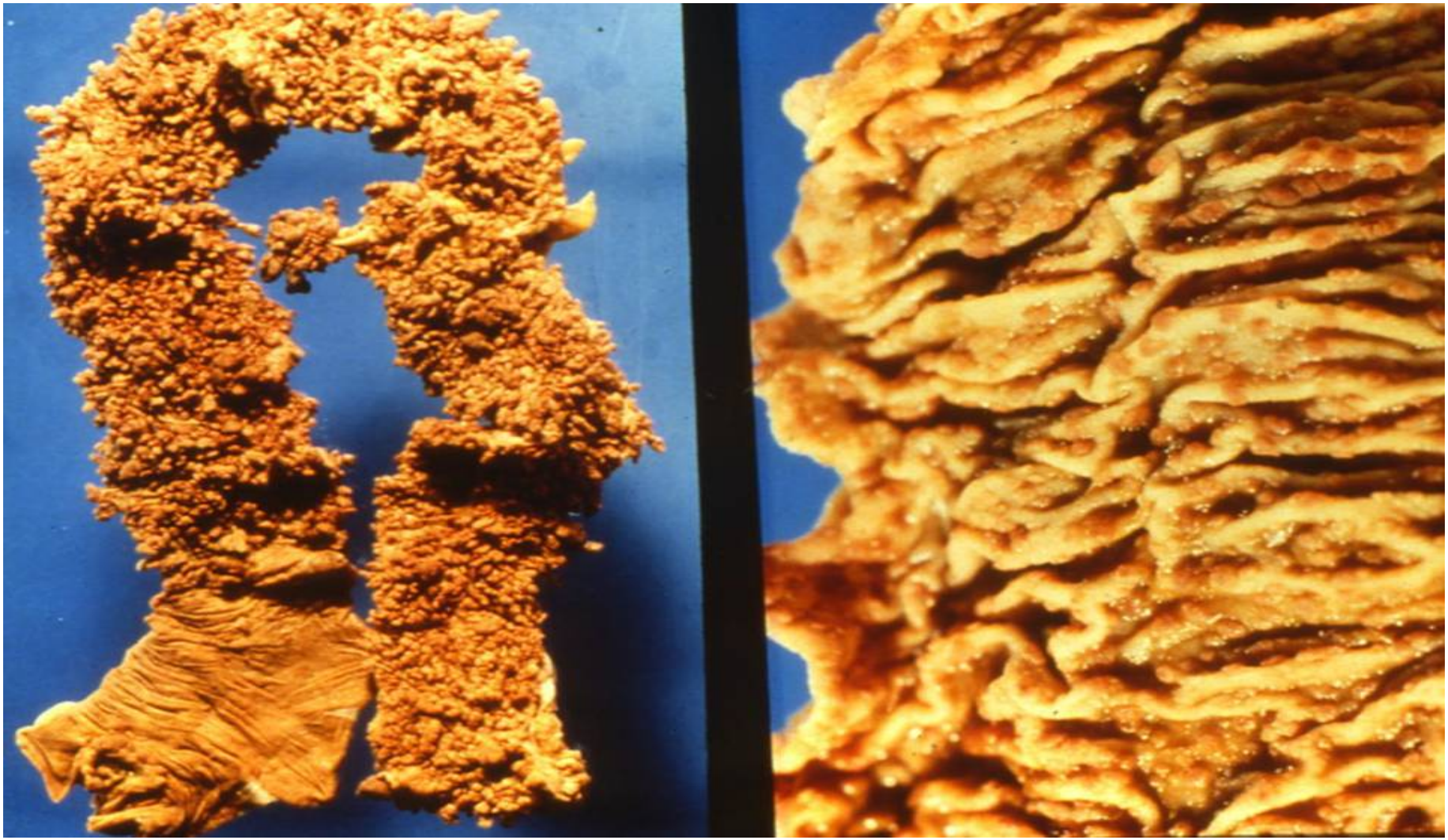
New prognostic DNA tests for colon cancers

- On their way to market
- Onco*type* DX Colon Cancer Assay, ColoPrint
- Similar to Onco*type* DX & Mammaprint for breast cancer
- NONE have shown any proven utility

Familial syndromes

- Familial adenomatous polyposis (FAP)
  a) Classic FAP
  b) Attenuated FAP
  c) Gardner syndrome
  d) Turcot syndrome
- Lynch syndrome (HNPCC)
- Others (e.g.: Serrated adenomatous polyposis, Juvenile polyposis syndrome, etc.)

Familial adenomatous polyposis (FAP)



Classic FAP syndrome

- Usually 1000, **at least 100** adenomas
- **Colon,** small intestine (ampulla), stomach
- Relatively uncommon
- **Germ-line (inherited) APC gene mutation** ("first hit")
- **Adenomas in 2nd and 3rd decades**

Classic FAP syndrome

- **Colon cancer** in 100% of untreated patients
- 10% after 10 years, 100% after 40 years
- Often before age of 30
- **Family screening and early detection**
- DNA marker (APC gene mutation)
- Flexible sigmoidoscopy at age of 12
- **Prophylactic proctocolectomy**

Diagnosis of Lynch Syndrome

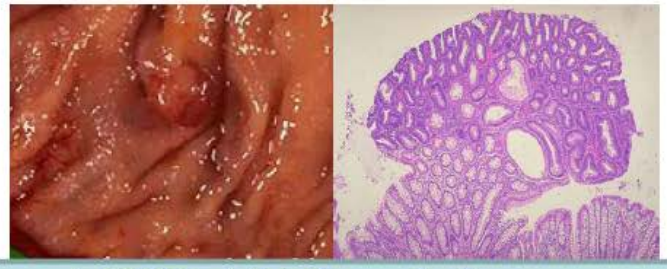
- For other family members
  - Early screening program for CRC
  - Endometrial cancer
- Second tumor in colon (50% within 15 years)
- Differences in prognosis and therapy

Tools to detect MSI (and exclude sporadic tumors)

- Immunohistochemistry
  - mismatch repair proteins: MLH1, MSH2, MSH6, PMS2
- PCR
  - to detect MSI (MSI tesing)
- Sequencing of suspected gene (Genetic testing)
  - to confirm the diagnosis of Lynch syndrome
- *BRAF* mutational analysis (or IHC for *BRAF*)
  - *BRAF* mutation = sporadic CRC
- *MLH1* methylation assay
  - *MLH1* promoter hypermethylation = sporadic CRC

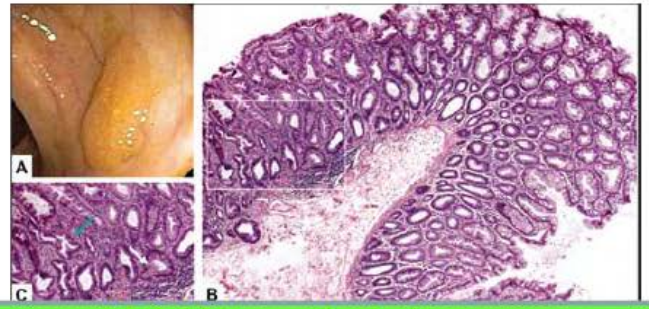
Two Molecular Pathways of MSI

HNPCC

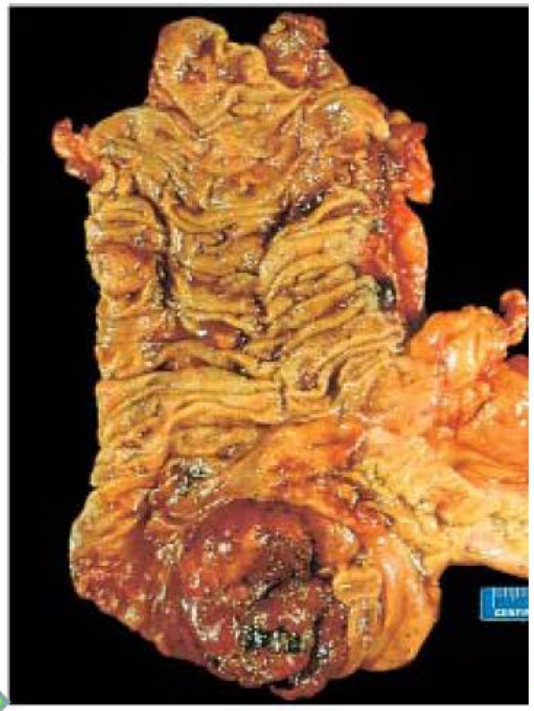


MSH2, MLH1 mutation

Sporadic

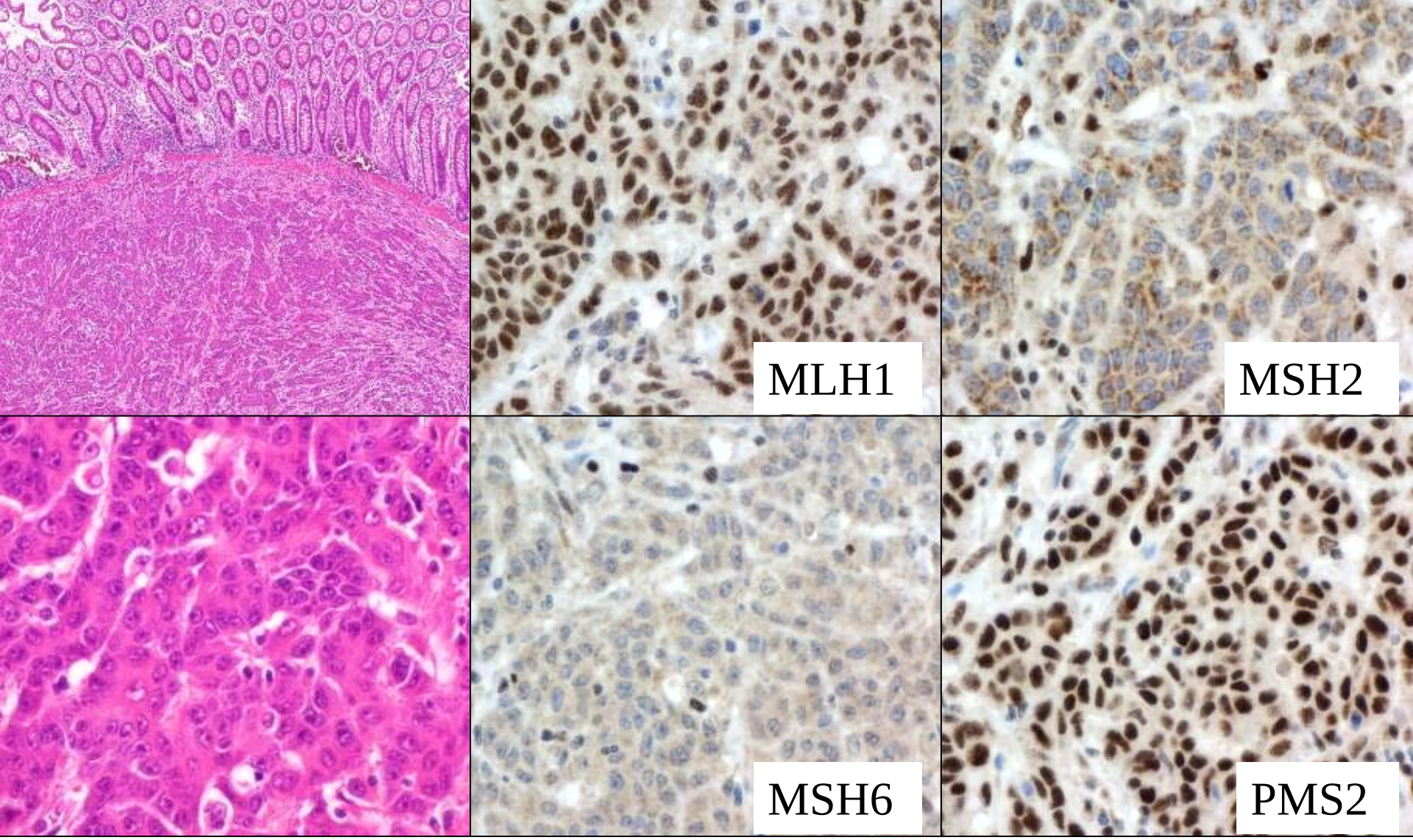


MLH1 methylation



CIMP-/MSI+

CIMP+/MSI+



Loss of MSH2/MSH6 expression

	IHC MLH1	IHC PMS2	IHC MSH2	IHC MSH6
MLH1 Mutation	Loss	Loss	Positive	Positive
PMS2 Mutation	Positive	Loss	Positive	Positive
MSH2 Mutation	Positive	Positive	Loss	Loss
MSH6 Mutation	Positive	Positive	Positive	Loss

A.R. Sepulveda, Medscape Pathology; http://cme.medscape.com/viewarticle/571610

Cleveland Clinic

(J Clin Oncol 31: 1336-40, 2013)

- Only to surgeons (2004-2007)
  - Genetic counseling (GC) for 32% of possible LS
  - Gene sequencing (GT) for 26%
- Surgeons & genetic counselor (2007-2008)
  - GC for 64% & GT for 45%
- Direct contact by genetic counselor (July 2008-)
  - GC for 71% & GT for 66%

Ohio State University

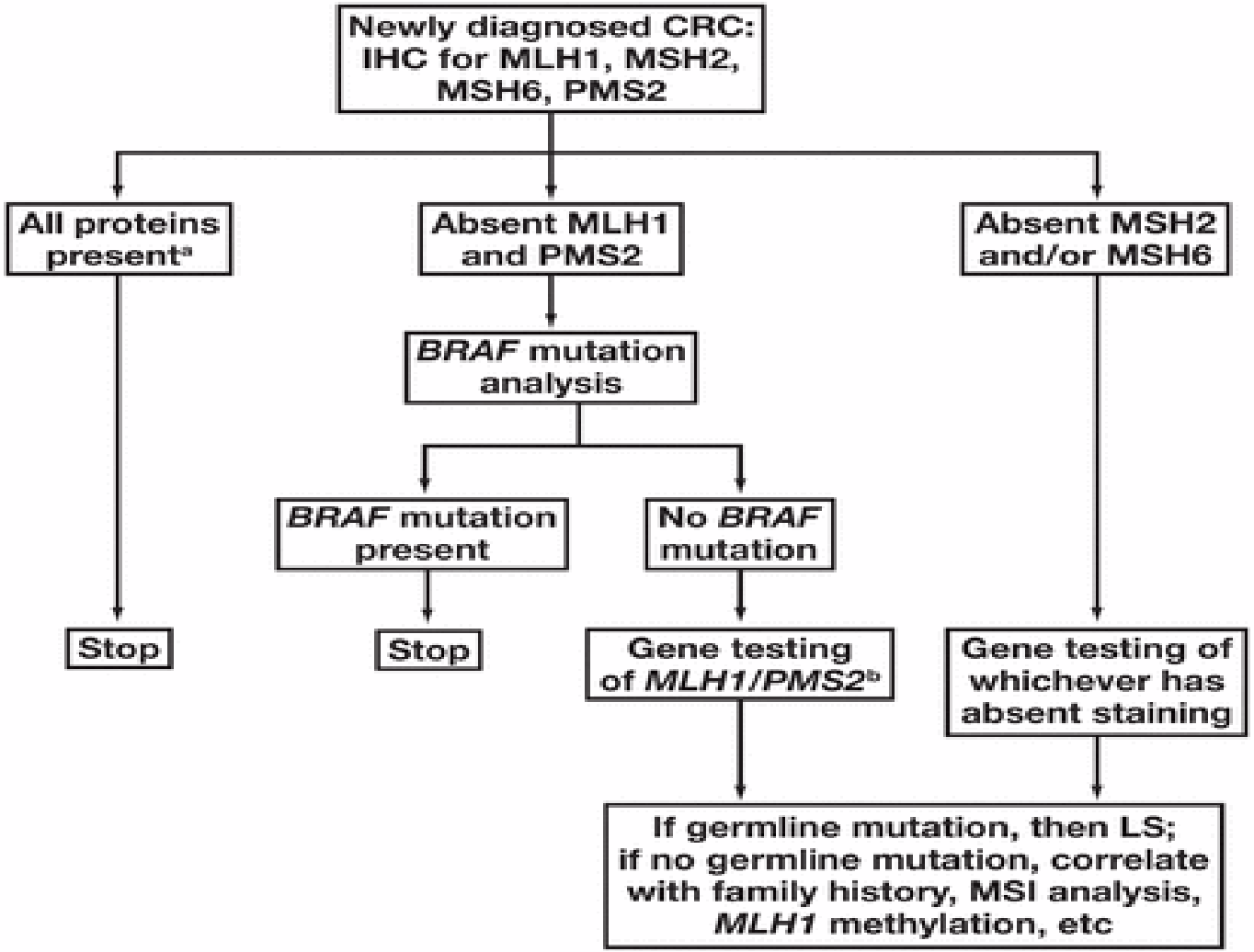
- Excellent Cancer Genetics department
- No good infra structures until 4-5 years ago
- Screening Algorithm
  (Am J Clin Pathol 2013: 140: 177-183)

Old practice at UK

- Only highly suspicious cases
- Genetic counseling first
  - Amsterdam Criteria
  - Bethesda guideline
- MSI test → IHC → genetic testing

Our new protocol

(all new colon resections: 200 cases/yr)



Our new protocol

- Liz Reilly, Genetic Counselor
- Biopsies by clinician's or GC's request
  - e.g.: pre-chemoradiation biopsy for rectal cancer
- MSI testing for certain cases including equivocal IHC cases
- Other tests by GC's request
  - large deletions of *EPCAM* gene (lies next to *MSH2*)

Take home message

- Very common, preventable cancers
- Colonoscopic examination/screening
  - early diagnosis of cancer
  - removal of adenomas
- Lynch syndrome
  - diagnosis
  - screening for family members
  - ? joint efforts in future

MSI Testing

- PCR
- Dissection or micro-dissection
- 2002 Revised Bethesda Panel
  - 2 mononucleotide and 3 dinucleotide repeats
- MSI-High: at least 2 of 5 markers are abnormal
- MSI-Low: 1 of 5 markers is abnormal (unknown clinical significance)

IHC vs MSI

- Similar sensitivities and specificities
- Pros & cons
  - Convenience (e.g.: no micro-dissection)
  - Candidate gene for GT

Ohio State University

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