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Colon polyps
Pathologic features with molecular correlation

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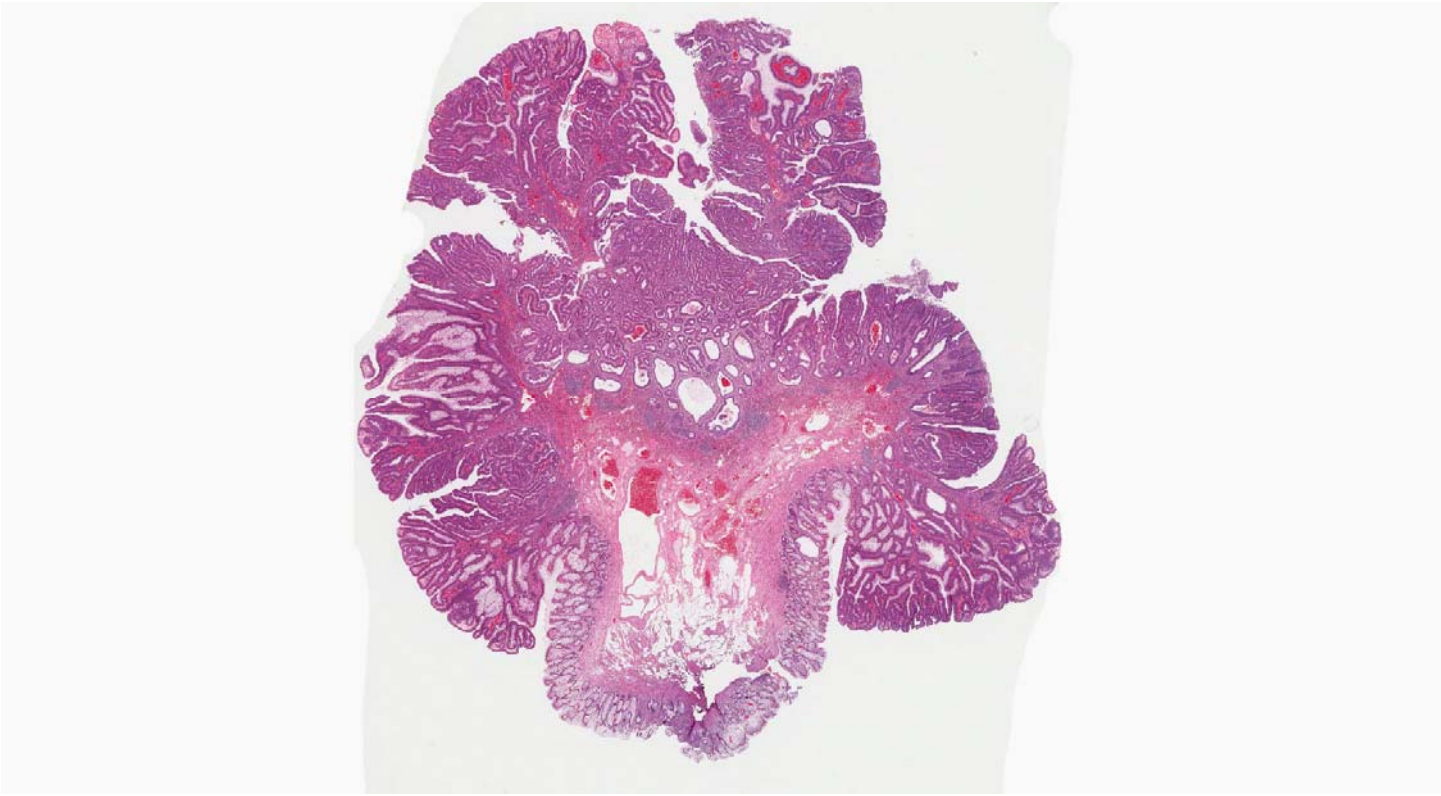
Objectives

- Define colon polyps
- List types of colon polyps
- Identify the pathologic features for a few examples of different types of colorectal polyps
- Discuss the molecular basis and pathways of colon polyps and colorectal cancer

I have nothing to disclose

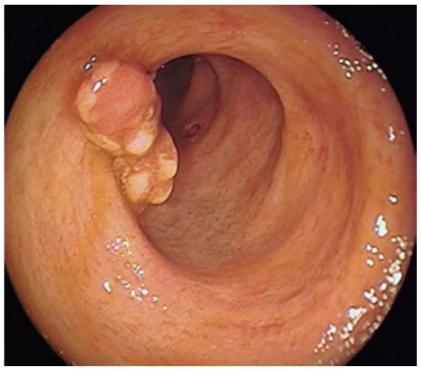

I need courage.
I need a heart.
I need a brain.
I'm over 50. I need a colorectal exam.

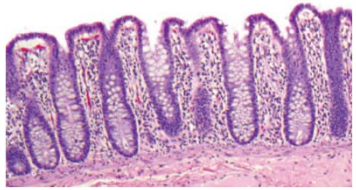
- 56 year old male who was referred to the gastroenterologist by primary care physician for screening colonoscopy
- No Gastrointestinal symptoms
- No history of cancer
- Was found to have a 2.0 cm polyp in the descending colon
- It was amputated from bottom of the stalk

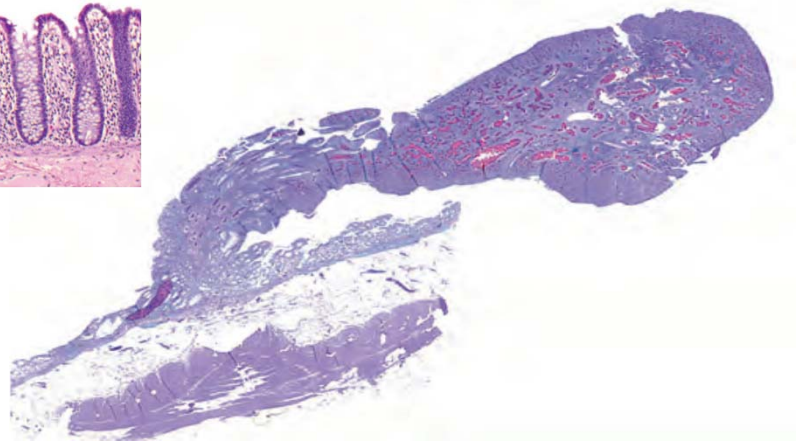


What is a polyp

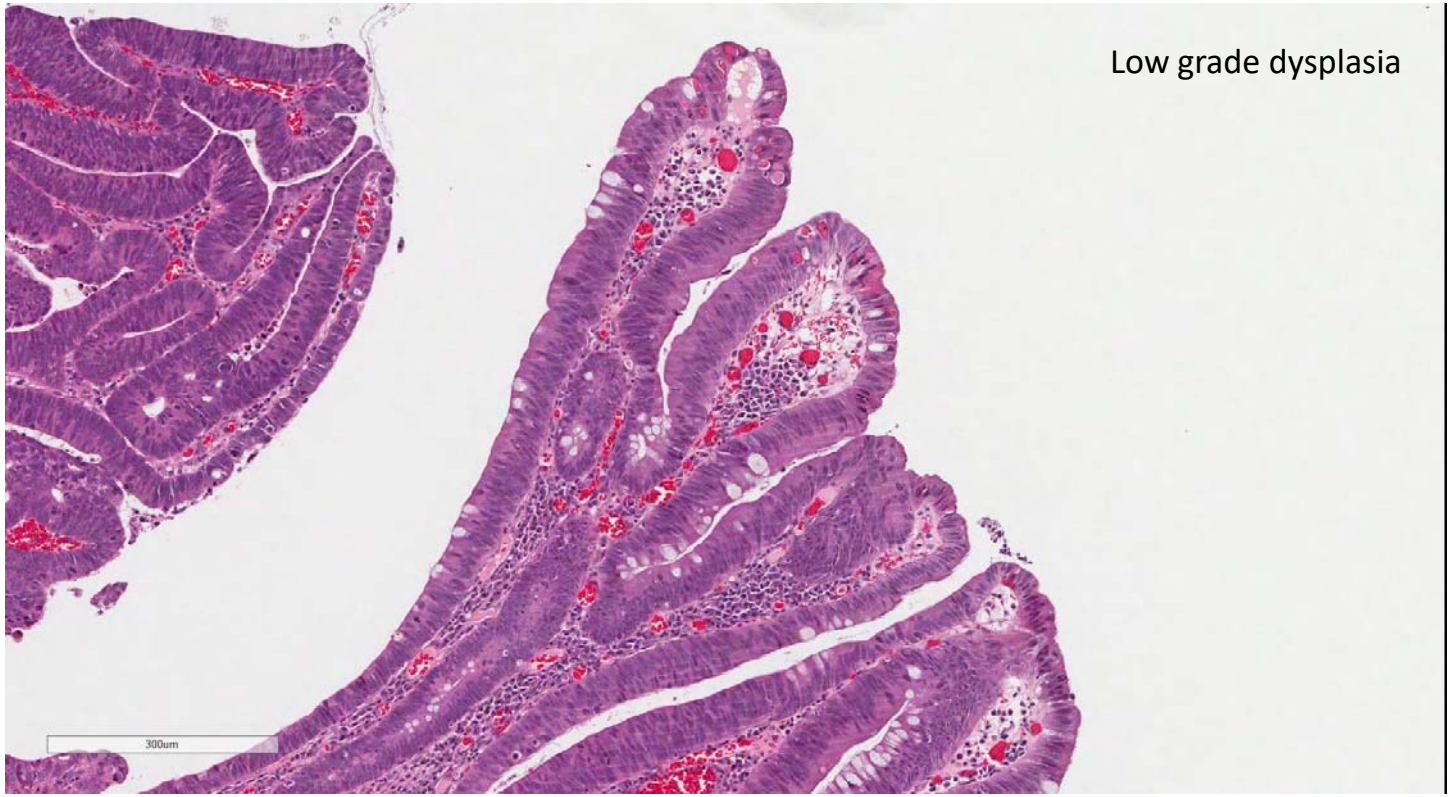
A localized projection above the colonic mucosa



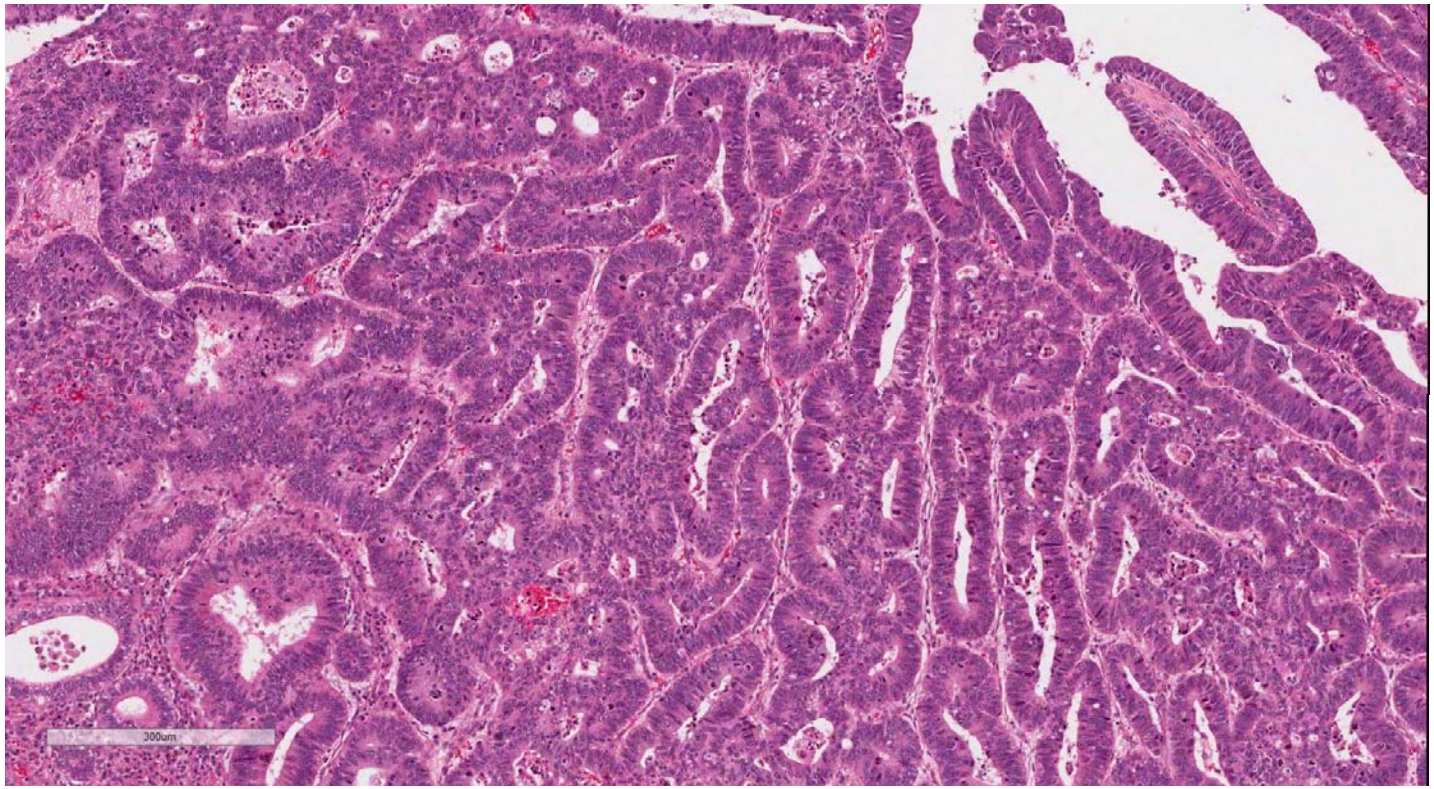




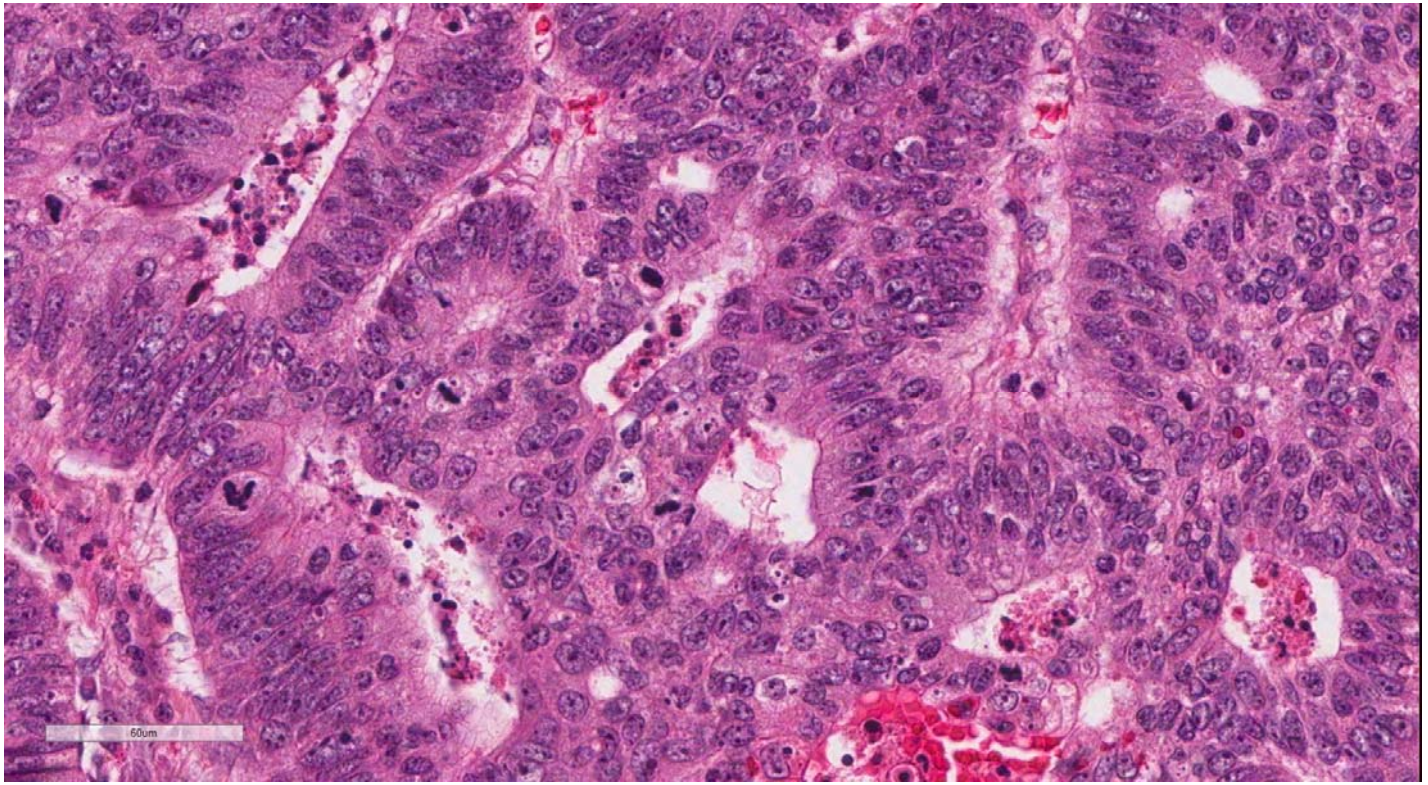
Odz and Goldblum, Surgical Pathology of The GI Tract, 3rd edition, 2015


Low grade dysplasia
300um

High grade dysplasia



High grade dysplasia



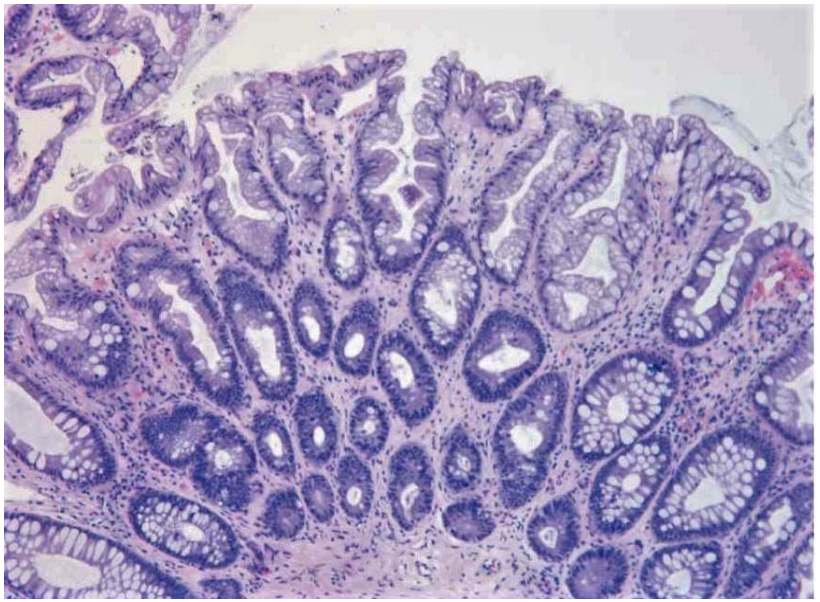
Inflammatory polyps	Hamartomatous Polyps	Epithelial Polyps	Mesenchymal Polyps	Miscellaneous Polypoid Lesions
Inflammatory Pseudopolyp Prolapse-Type Inflammatory Polyp Inflammatory Myoglandular Polyp	Juvenile Polyps and Juvenile Polyposis Peutz-Jeghers Syndrome Cowden Syndrome Cronkhite-Canada Syndrome	Hyperplastic and Serrated Polyps Conventional Adenoma Adenomatous Polyposis Syndromes Adenomas and Adenoma-Like Dysplasia-Associated Lesions or Masses in Inflammatory Bowel Disease Malignant Epithelial Polyps	Ganglioneuroma Neurofibroma Granular Cell Tumor Mucosal Perineurioma Mucosal Schwann Cell Hamartoma Leiomyoma of the Muscularis Mucosae Leiomyosarcoma Gastrointestinal Stromal Tumor Lipoma Lipomatous Ileocecal Valve Inflammatory Fibroid Polyp	Pneumatosis Coli Mucosal Pseudolipomatosis Endometriosis Benign Infiltrative Processes Systemic Mastocytosis Inverted Appendix Mucosal Tag Atheroembolus-Associated Polyp

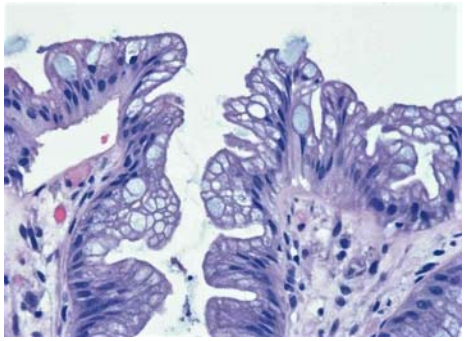
Hyperplastic polyps

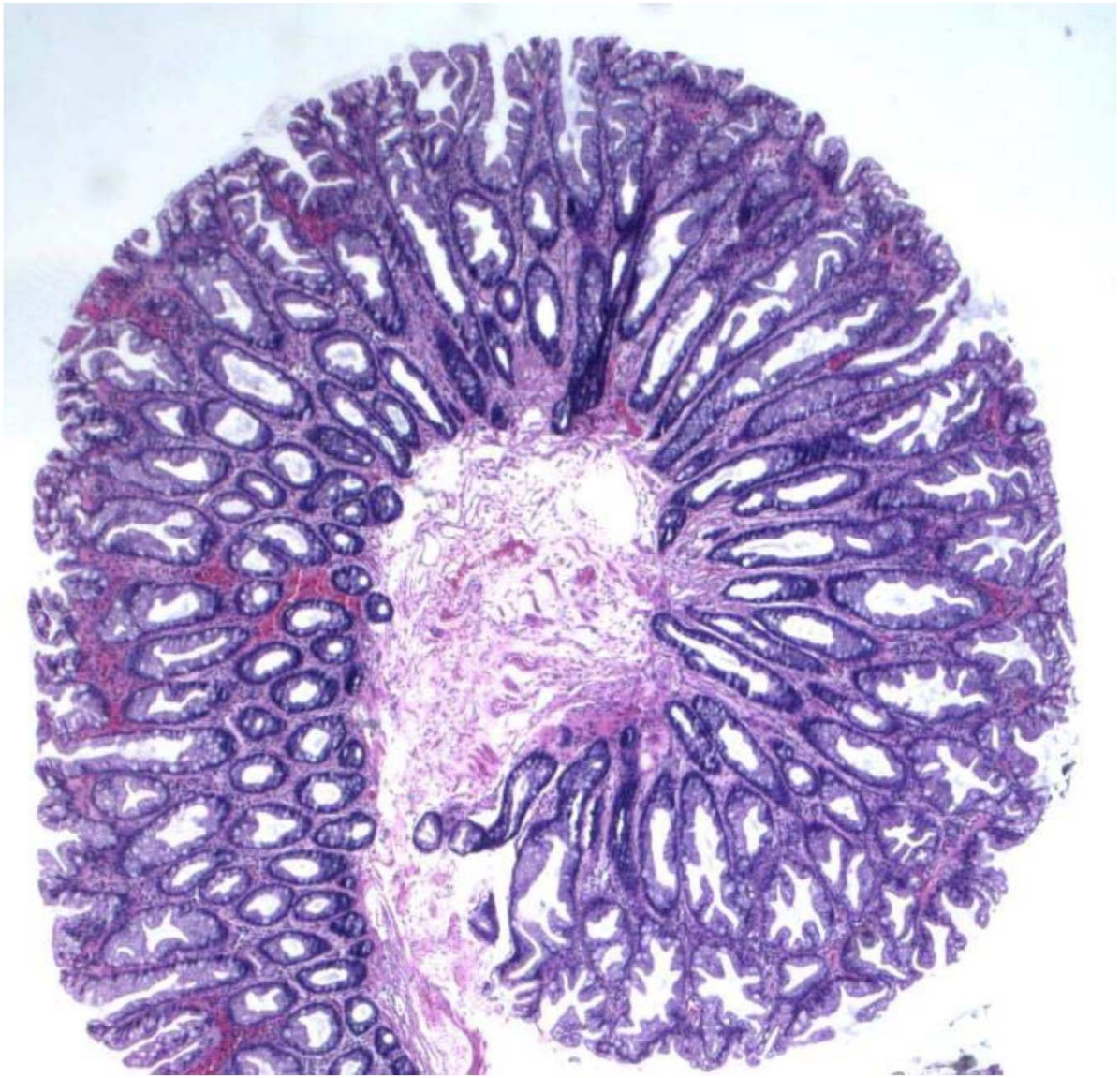
- The most common type of polyps in the colon
- Benign polyps
- Small (<0.5 cm)
- No associated risk of malignant transformation
- No surveillance, only polypectomy

Hyperplastic polyps

- Basal layer proliferative and it can look hyperchromatic
- Saw tooth shaped superficial layer with narrow-base crypts
- Usually left colon







Hyperplastic polyp

Serrated adenomas

- Sessile serrated polyps/adenomas
- Traditional serrated adenomas
- Mixed serrated adenoma and traditional adenoma
- Usually right colon

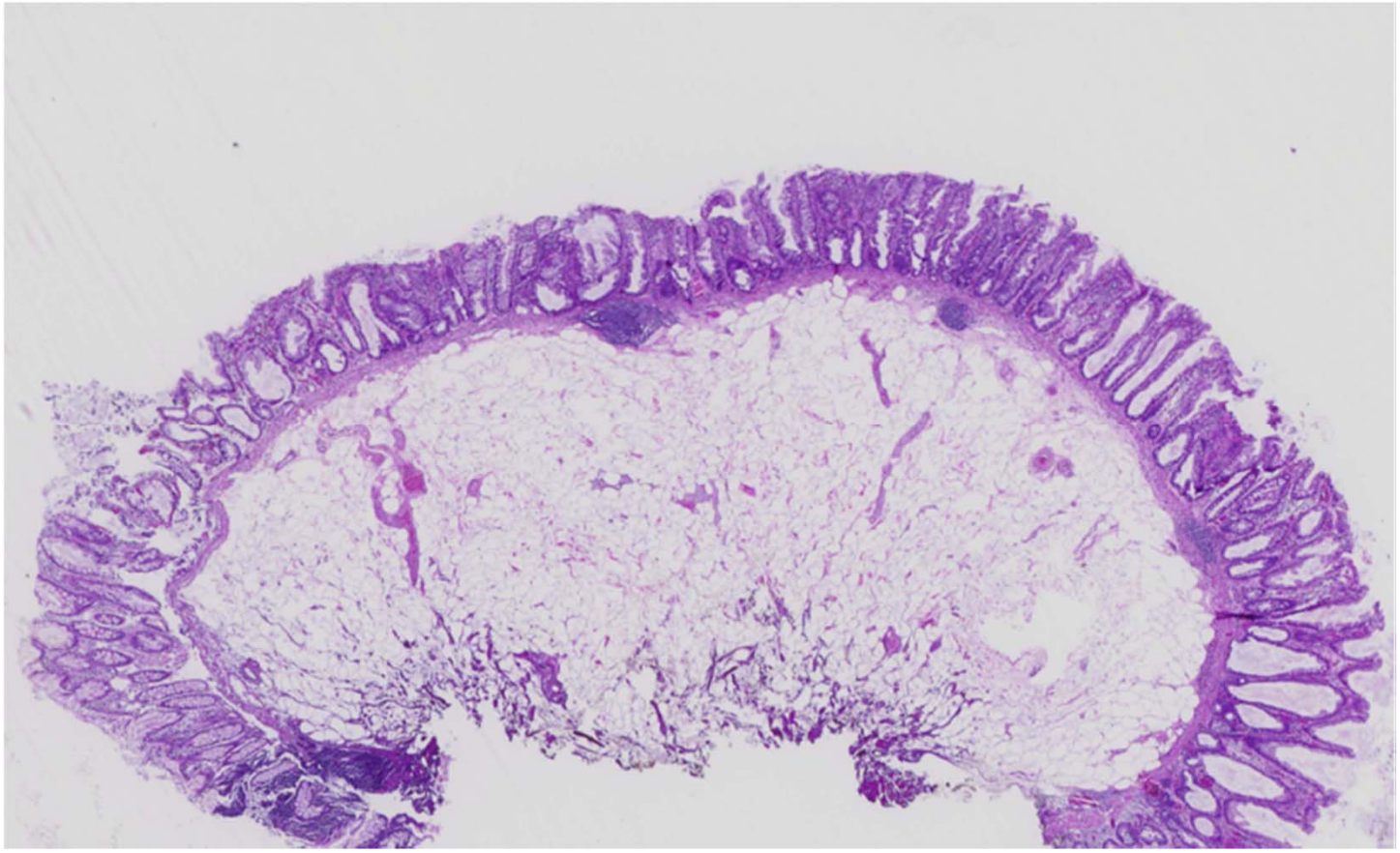
Serrated adenomas

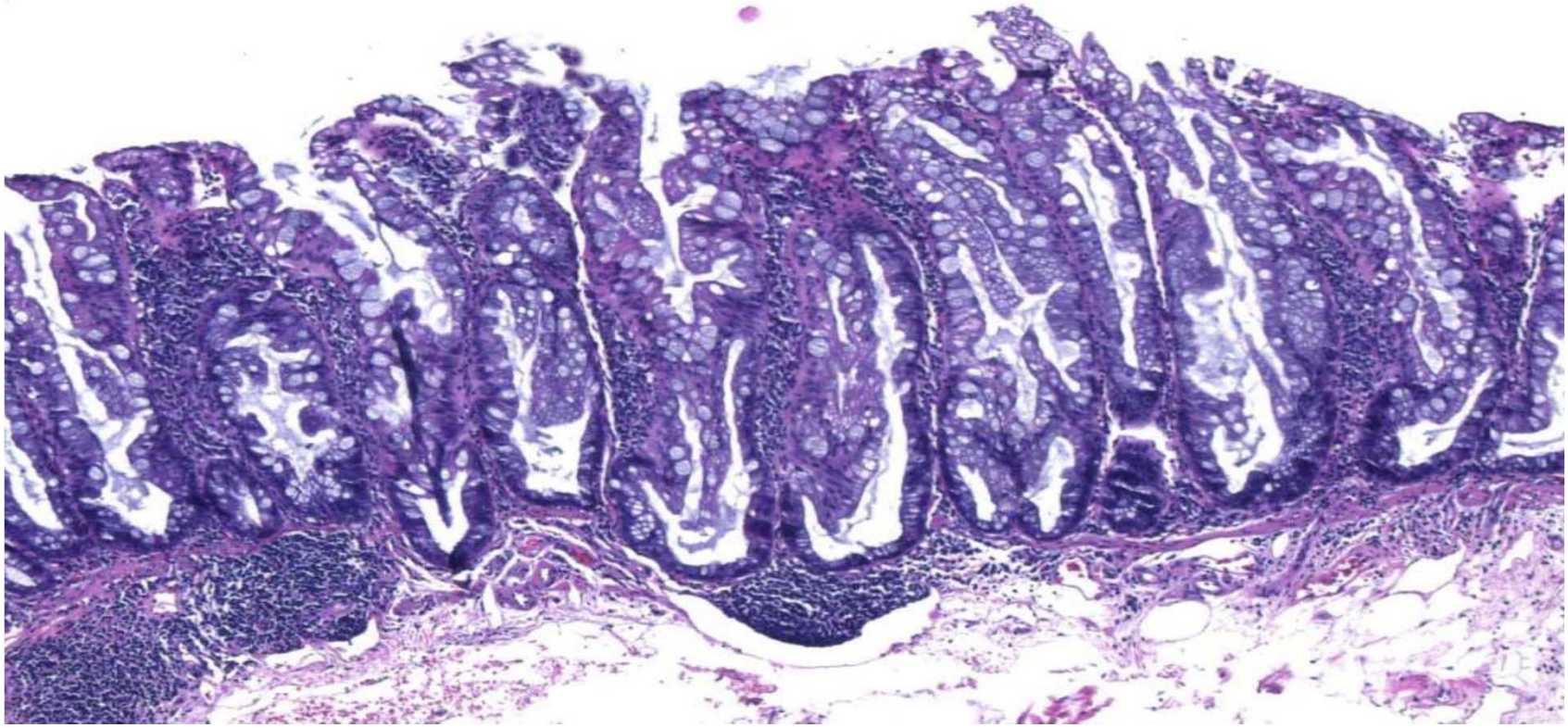
- >0.5 cm
- Crypt distortion
- Basal dilatation of the crypts
- Extension of serrations to the bottom of the crypts
- Nuclear atypia (nuclear enlargement, prominent nucleoli, nuclear hyperchromasia)

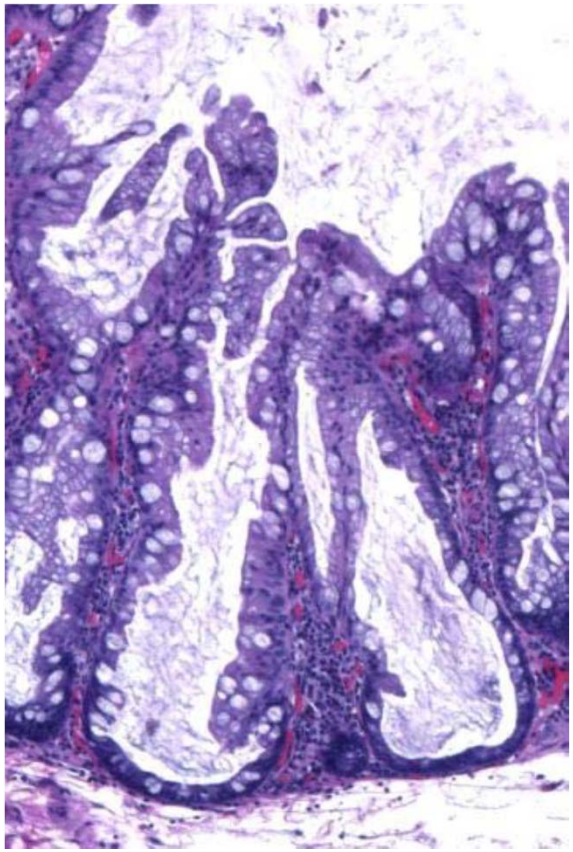
Serrated adenomas

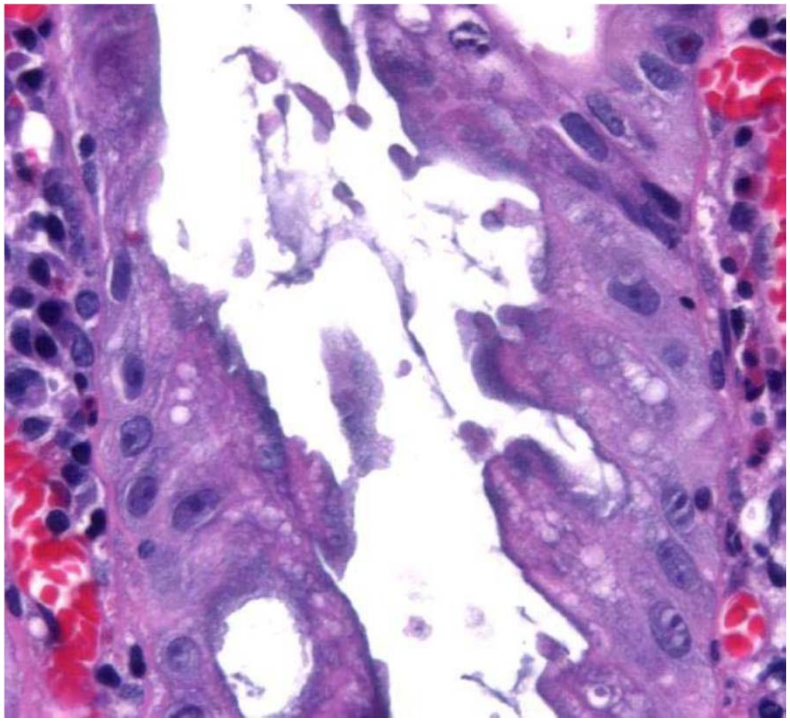
- Proliferation zones moved from the base to the midportion or upper portion of epithelium
- Focal mucin overproduction
- Frequent cytoplasmic eosinophilia

Torlakavic and Snover 1996, Gastroenterology

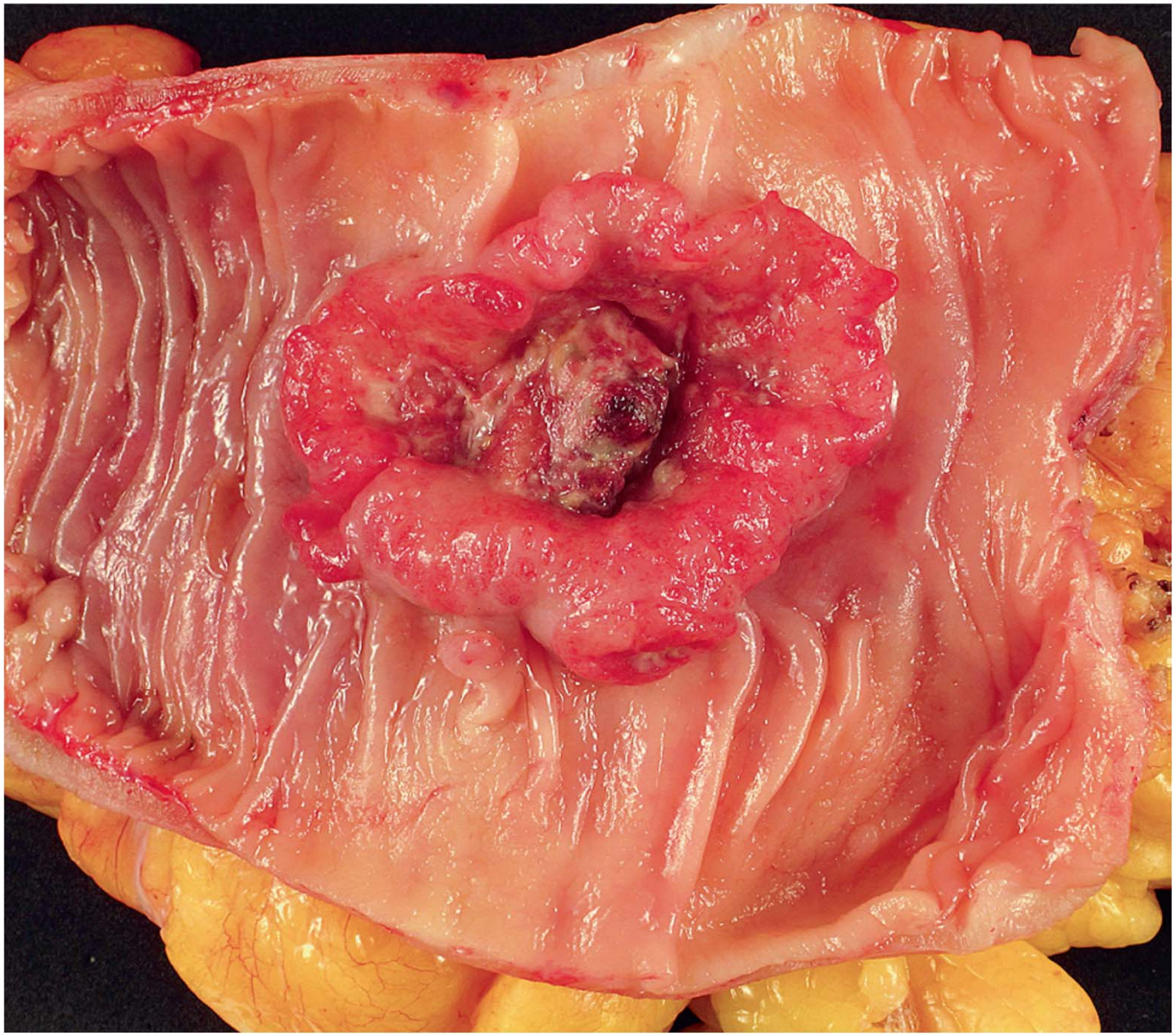








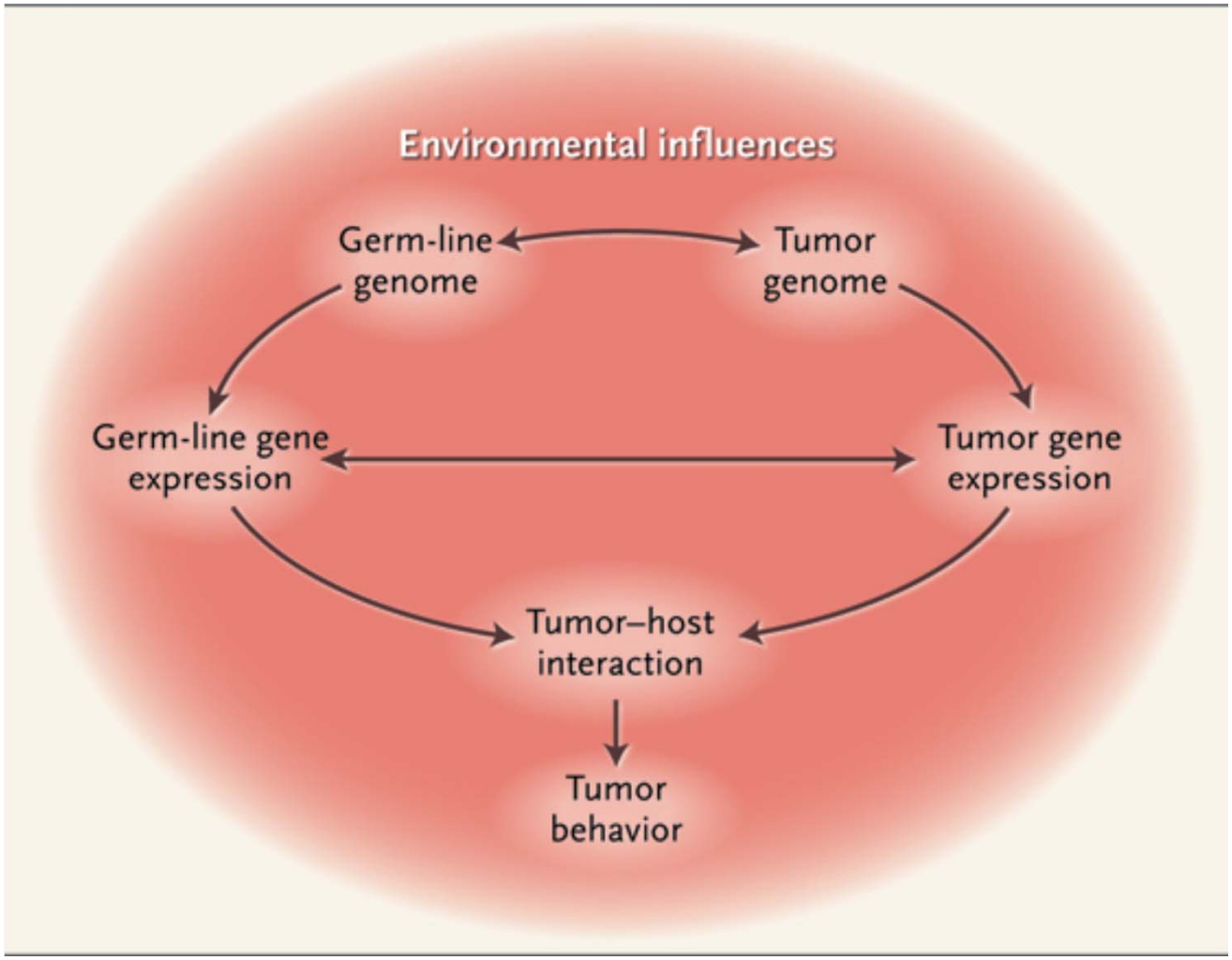
Middle of crypt



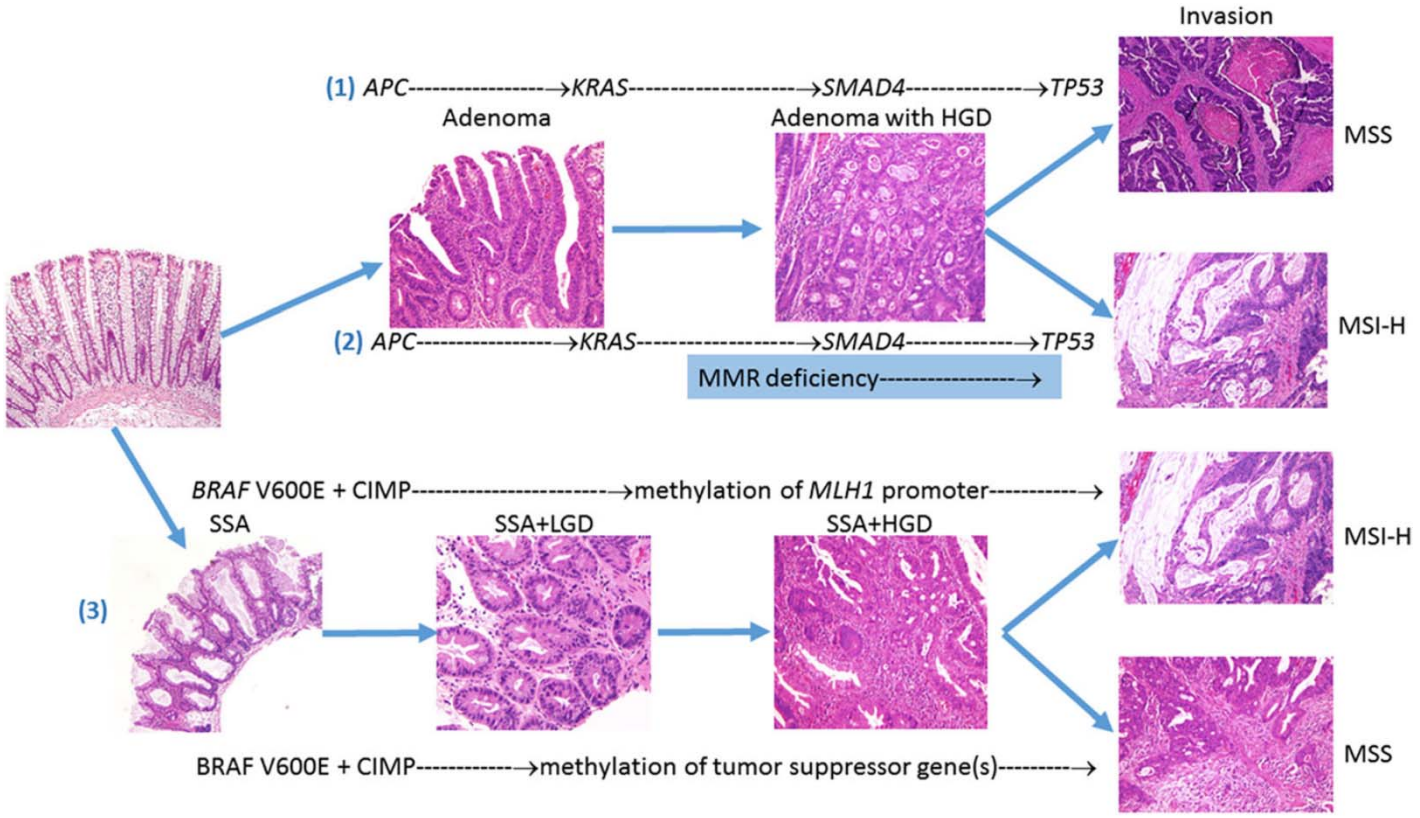
Odz and Goldblum, Surgical Pathology of The GI Tract, 3rd edition, 2015

Colorectal Cancer

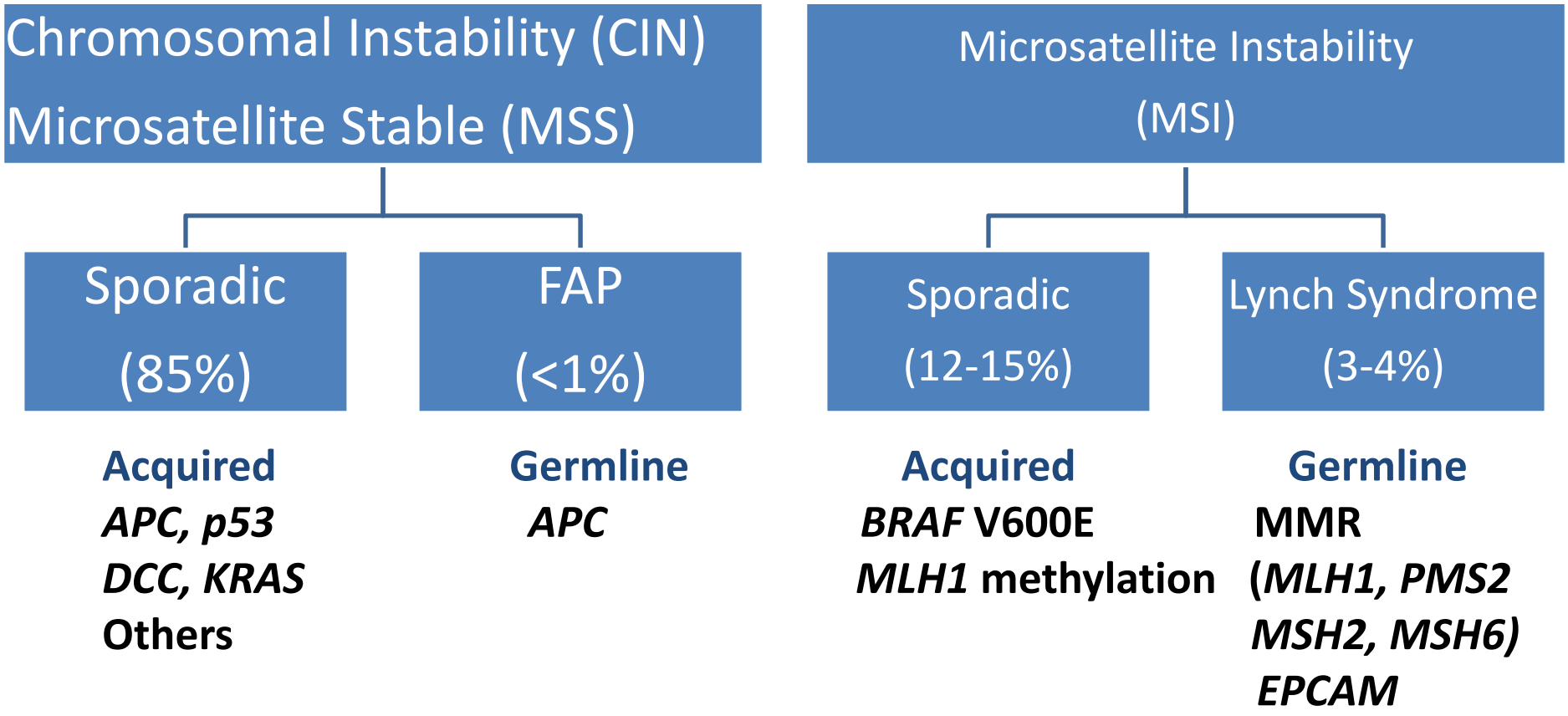
- In the USA, 160000 diagnosed every year
- 57000 people die of disease every year
- Second leading cause of cancer death in adults
- Starts as adenomatous polyp → advanced adenoma → severe dysplasia → invasive adenocarcinoma



Markowitz, SD, et al NEJM 2009;361:2449-60



Gonzalez et al. Applied Cancer Research (2017) 37:13


Chromosomal Instability (CIN)
Microsatellite Stable (MSS)
Microsatellite Instability
(MSI)
Sporadic
(85%)
FAP
(<1%)
Sporadic
(12-15%)
Lynch Syndrome
(3-4%)
Acquired
APC, p53
DCC, KRAS
Others
Germline
APC
Acquired
BRAF V600E
MLH1 methylation
Germline
MMR
(MLH1, PMS2
MSH2, MSH6)
EPCAM

- Microsatellites are short nucleotide repeat sequences (mononucleotide, dinucleotide, ... Penta nucleotides) which are prone to replication errors by DNA polymerase
- Slippage causes insertion-deletion loops
- Mismatch repair (MMR) proteins correct this
- Errors result in varying lengths of these sequences
- If not corrected, second round of replication incorporates mutation → frameshift mutations → nonfunctional proteins

Importance of identifying MSI in colon cancer

- Identification of Lynch syndrome patients
- MSI status has prognostic and predictive significance for therapy
- MSI status is central to many of the molecular classification systems of CRC

Lynch Syndrome (HNPCC)

- Most common hereditary CRC syndrome (3-4% of all CRC)
- Autosomal dominant
- Lifetime risk of developing colorectal cancer is 53%
- Mean age of diagnosis is 45 years
- Extracolonic cancers (endometrium, ovary, renal pelvis, stomach, others)

Lynch Syndrome (HNPCC)

- Colonic screening leads to decreased CRC and death
- Screening of relatives critical
- Difficult to recognize clinically (family history not always obvious or available)
- Lynch CRCs arise from traditional adenomas

Sporadic MSI Tumors

- 10-15% of all colon cancer
- Phenotypically similar to LS tumors
- Right sided, older females
- Commonly arise from sessile serrated adenomas
- MLH1 deficient with wild type BRAF and MLH1 promotor hypermethylation arise from traditional adenomas

Farchoukh *et al* AJSP 2016

MMR Proteins

- Two complexes MLH1/PMS2 and MSH2/MSH6
- Stability of PMS2 and MSH6 depends upon these complexes
- Loss of MLH1 leads to loss of PMS2, loss of MSH2 leads to loss of MSH6
- MLH1 and MSH2 are stable without complex (isolated loss of PMS2 or MSH6)

Universal MSI Testing of CRCs for Lynch Syndrome / MSI

- **Universal testing all CRCs** (Consensus Statement of US Multi-Society Task Force on CRC, EGAPP and other organizations)
- **Either MSI PCR or IHC MMR is valid**

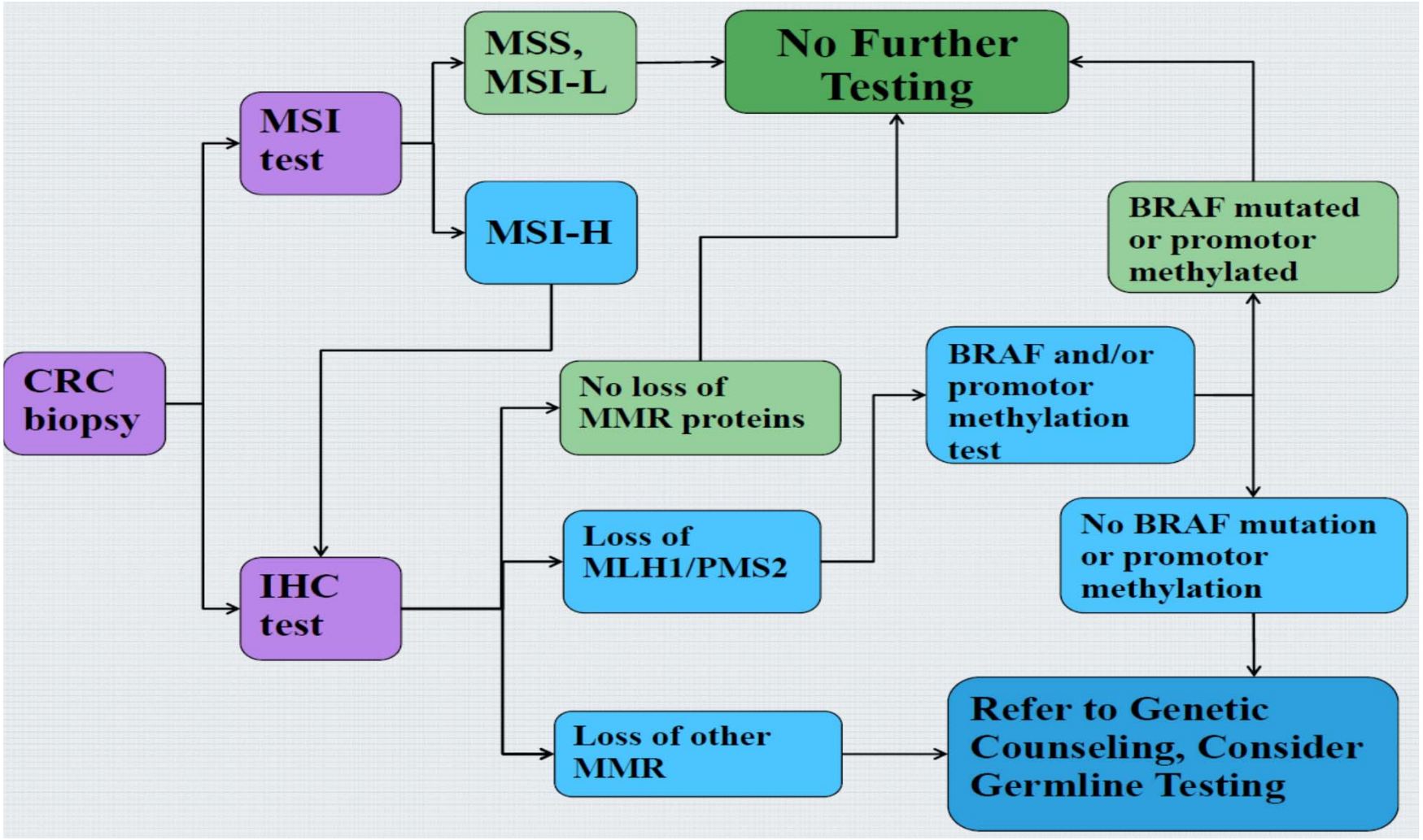
Principles of Lynch Syndrome/MSI Initial Screen

Is tumor mismatch repair (MMR) deficient?

- Directly by IHC of MMR proteins
- Indirectly by measuring MSI status by PCR
- Directly/Indirectly using Next Generation Sequencing

Is MMR deficiency indicative of LS or is this sporadic?

IHC Pattern	Rate of Results	Clinical
All proteins intact	80-85%	most likely not LS
MLH1- /PMS2-	10%	Sporadic (BRAF mutation/MLH1 promotor methylation) (80%) _____ *possibly* germline LS MLH1 (20%)
MSH2- /MSH6-	3%	*possibly* germline LS MSH2
MSH6-	1%	*possibly* germline LS MSH6
PMS2-	1%	*possibly* germline LS PMS2


MSS, MSI-L
No Further Testing
MSI test
MSI-H
BRAF mutated or promotor methylated
CRC biopsy
No loss of MMR proteins
BRAF and/or promotor methylation test
Loss of MLH1/PMS2
No BRAF mutation or promotor methylation
IHC test
Loss of other MMR
Refer to Genetic Counseling, Consider Germline Testing

ASCP/CAP/AMP/ASCO Biomarker Guidelines 2018

- Strongly recommends MSI testing of all stage II and above, screen for LS and prognosis, (and predictive)

- Strongly recommends BRAF (V600E) testing for stage II and above for prognostic stratification (BRAF status in the decision tree for EGFR targeted therapy is optional and still controversial)

- Strongly recommends extended KRAS and NRAS genotyping in all patients with metastatic CRC being considered for EGFR targeted therapy

Sepulveda *et al* AJCP, JMD, JCO 2017

ASCP/CAP/AMP/ASCO Biomarker Guidelines 2018, Pathologists Perspective

- Metastatic or recurrent CRC tissues are preferred specimens for treatment predictive markers. In their absence, primary tumor tissue is accepted
- FFPE tissue is an acceptable specimen for mutation testing, all others including cytology require validation
- Pathologists must validate candidate specimens for adequacy, quality and malignant cell fraction. This needs to be documented in the patient report
- Laboratories should establish policies to ensure efficient allocation and utilization of tissue particularly in small specimens
- Members of the patients medical team, including pathologists, may initiate biomarker testing in accordance with institutionally accepted practices

ASCP/CAP/AMP/ASCO Biomarker Guidelines 2018, Pathologists Perspective

- A benchmark of 90% of specimens should be sent out within 3 working days
- A benchmark of 90% of reports should be available within 10 working days from the date of receipt in the molecular lab
- Reports should include results and interpretation sections readily understandable by pathologists and oncologists.

Sepulveda *et al* AJCP, JMD, JCO 2017


8/27
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