The Frontiers of Serrated Polyps

PRESENTED BY

Amitabh Srivastava, MD

USCAP 109TH ANNUAL MEETING
2020 EYES ON YOU

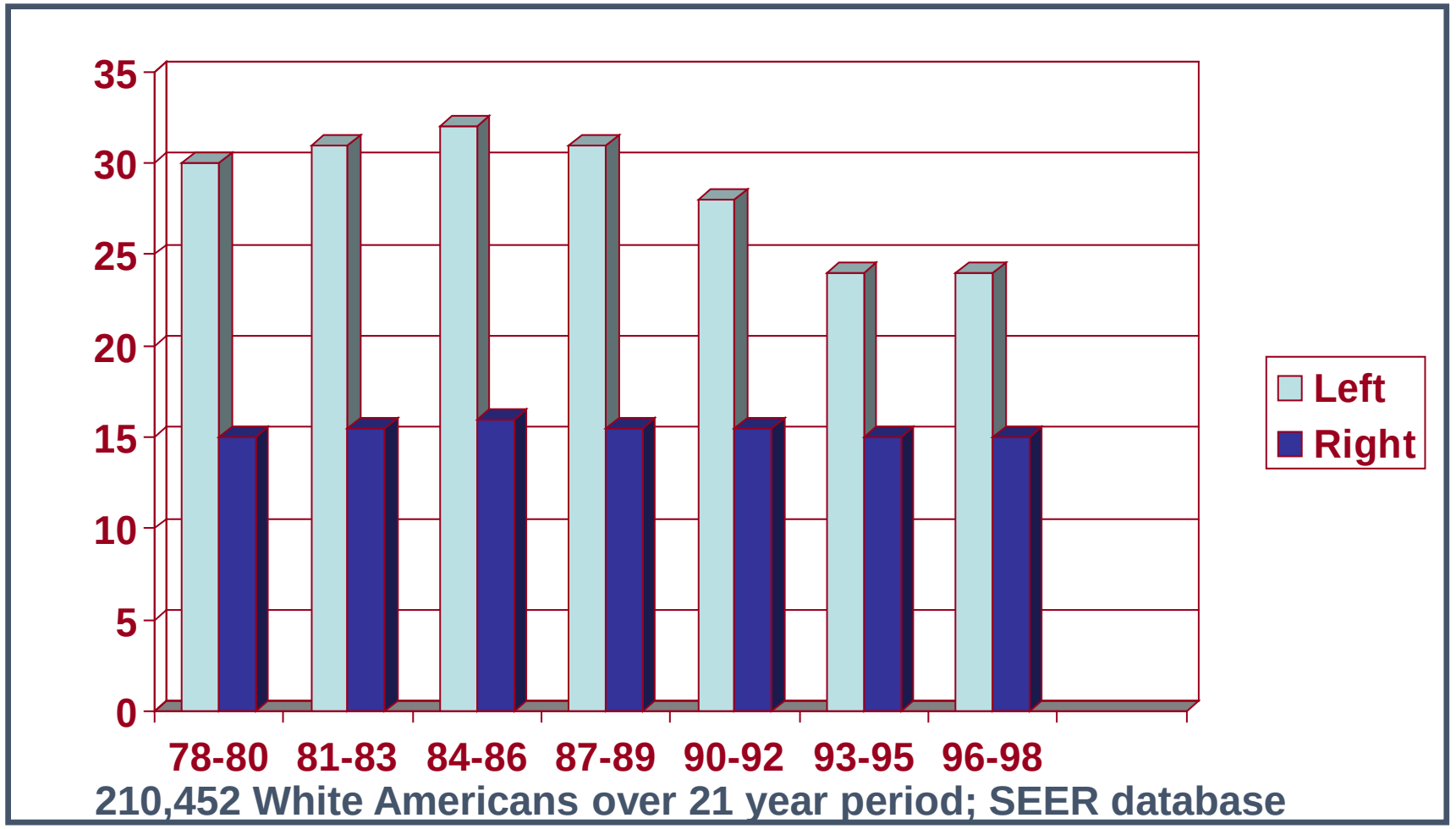
No Disclosures

USCAP

Relevance of Serrated Polyps

- **Estimated to be precursors of up to 30% of all CRC**
- **Occur concurrently with advanced conventional adenomas**
- **Variability in histologic diagnosis; variability in detection**
- **Miss rate based on tandem studies is 27% (95% CI: 16-40%; *Zhao et al Gastroenterology 2019*)**
- **Regarded significant for pathogenesis of interval colon cancer**

Incidence of Colon Cancer

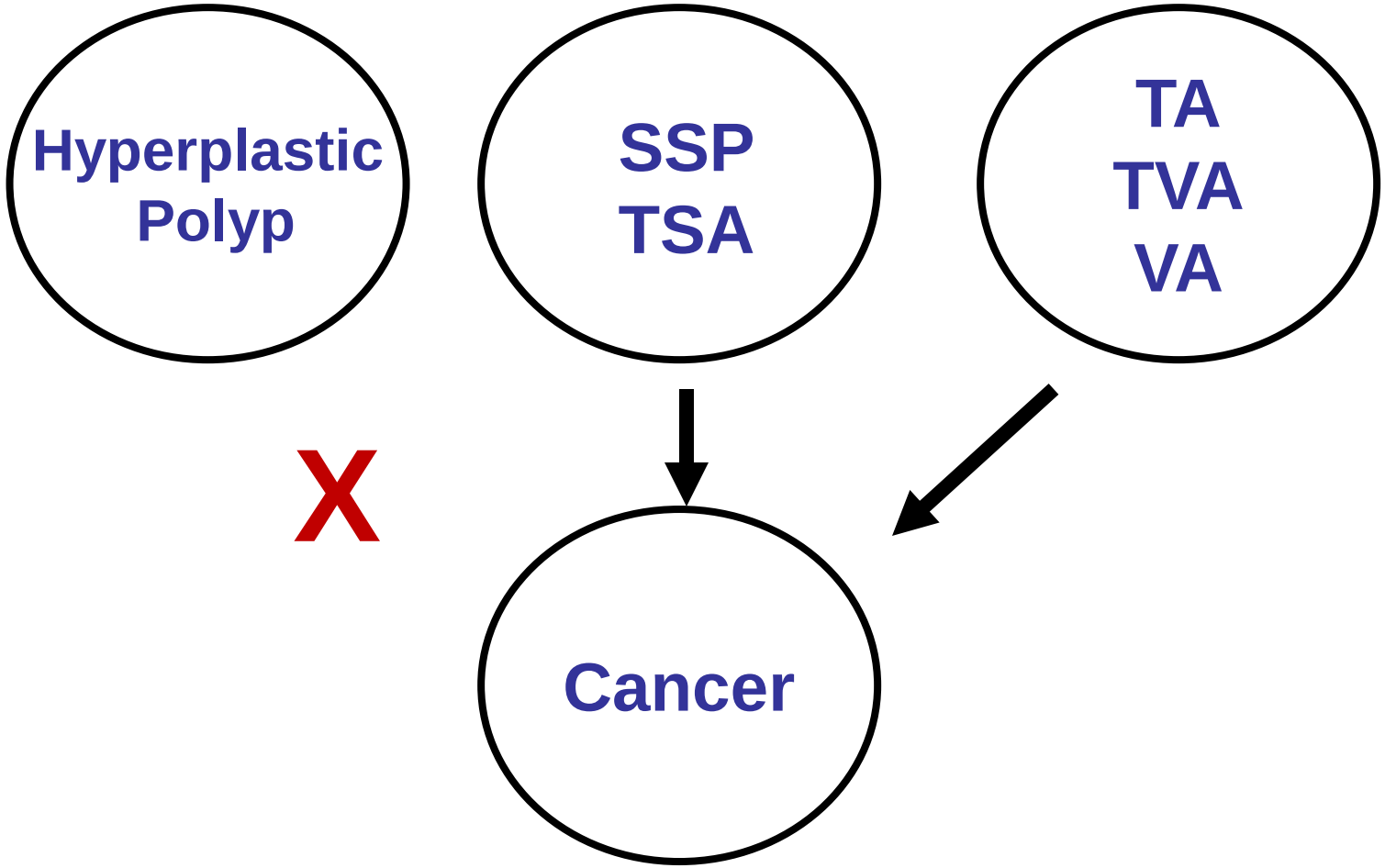


Rabeneck et al. Is there a true "shift" to the right colon in the incidence of colorectal cancer? Am J Gastro 2003; 98:1400-9

Outline

- **Relationship of hyperplastic polyps to:**
  - **Traditional serrated adenomas**
  - **Sessile serrated polyps**
- **Surveillance protocols for serrated polyps**

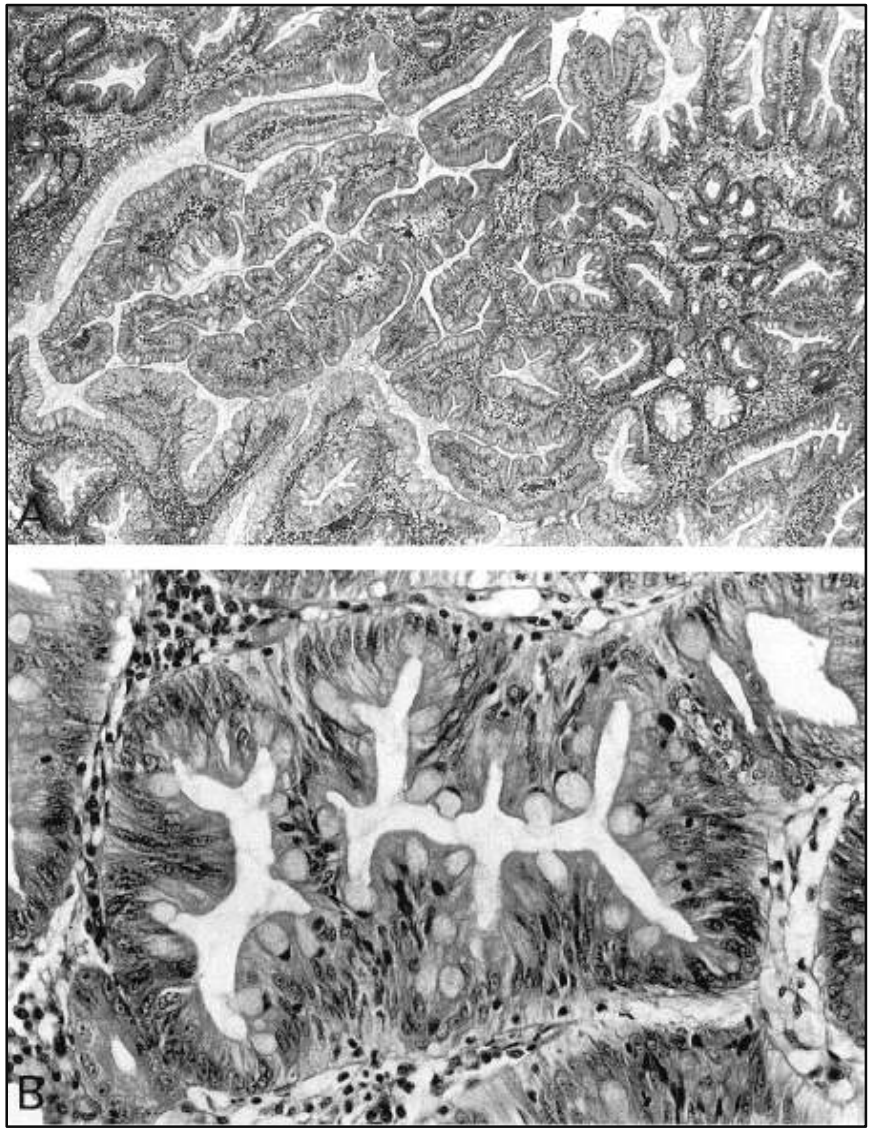
Current understanding of precursors of colorectal cancer



Traditional Serrated Adenoma

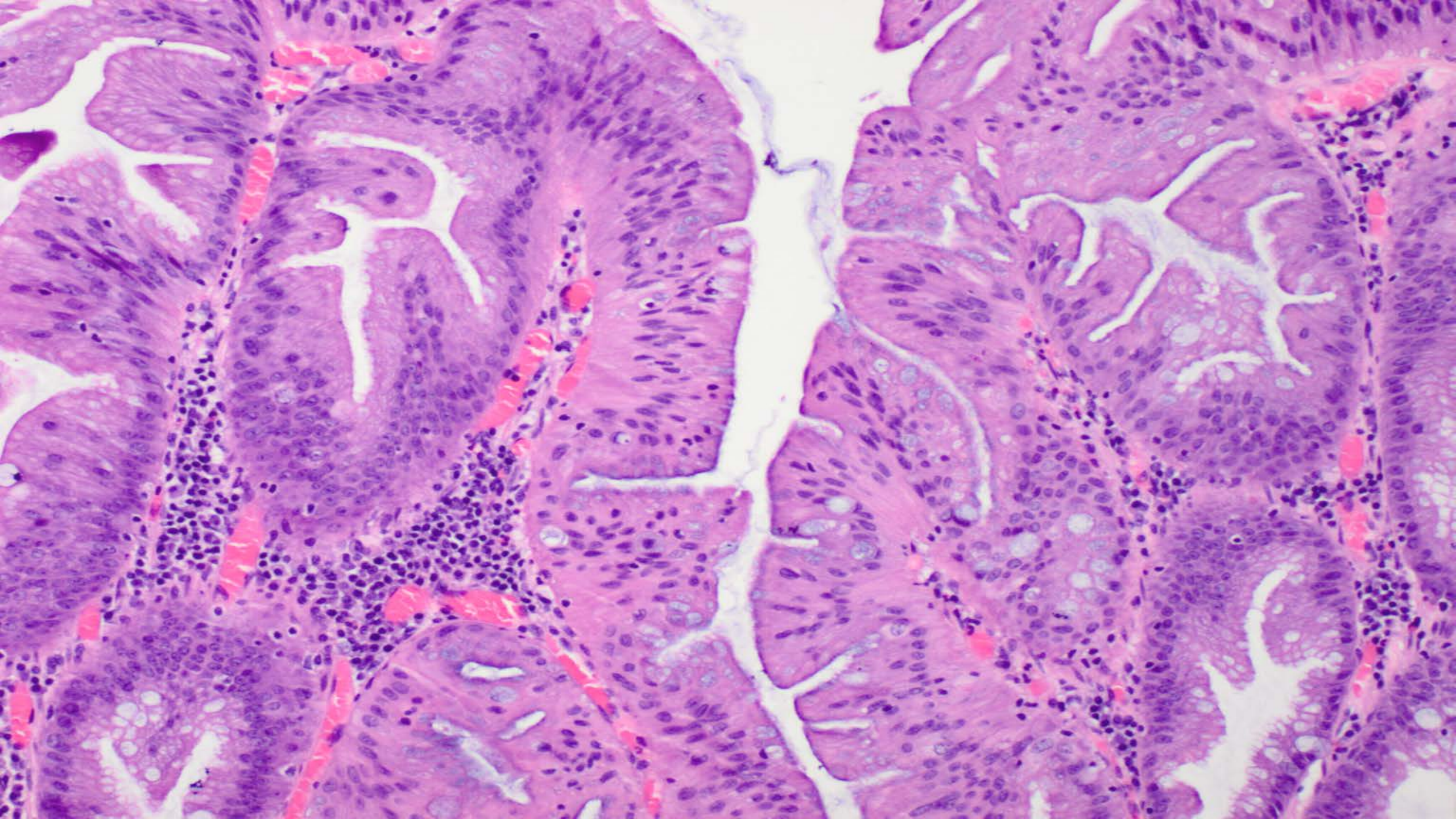
Mixed Hyperplastic Adenomatous Polyps/Serrated Adenomas: A Distinct Form of Colorectal Neoplasia

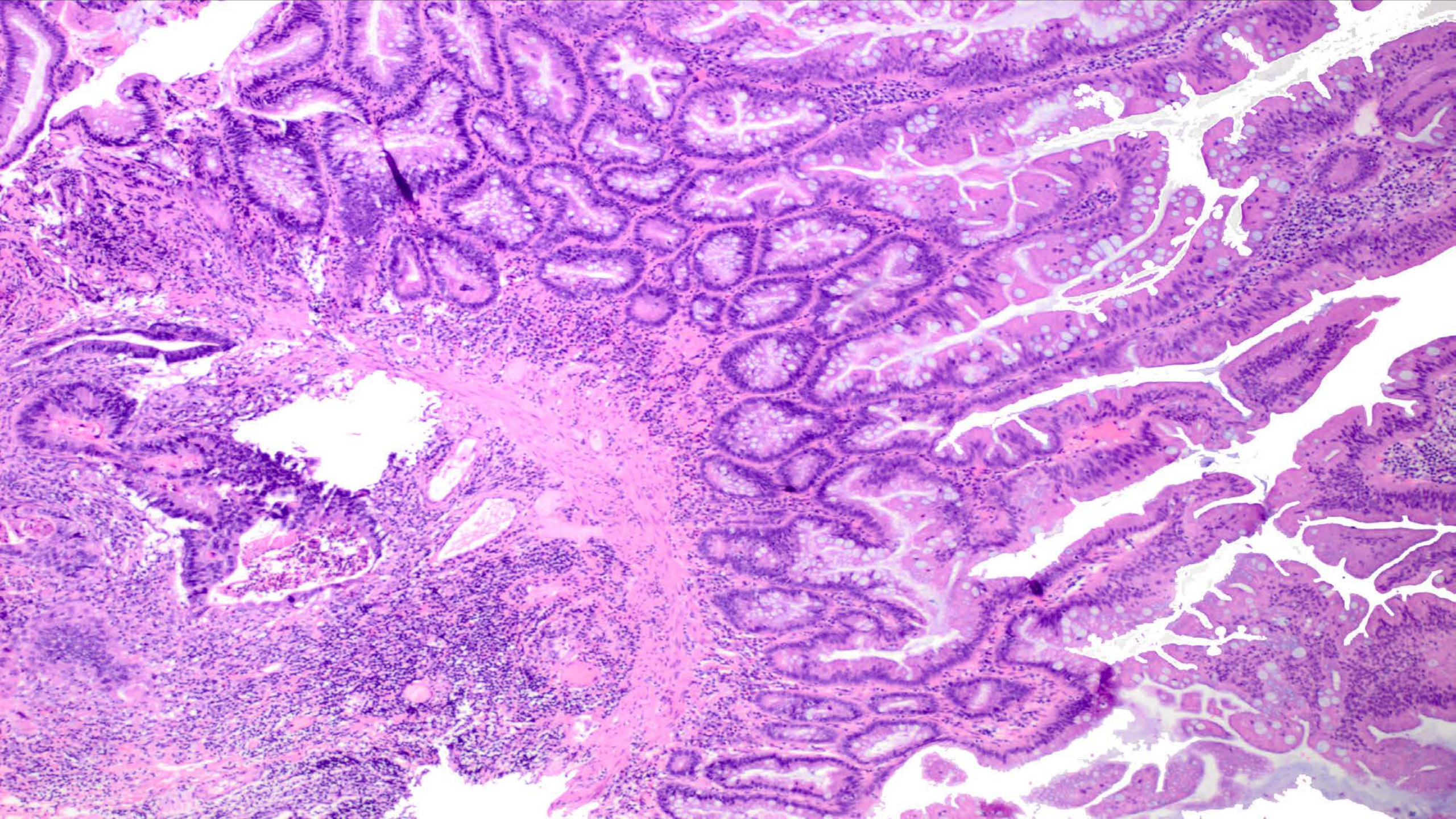
Teri A. Longacre, Cecilia Fenoglio-Preiser, Am J Surg Pathol 1990;14:524-537



- 110 distinct polyps
- Serrated architecture like HP
- Cytology of an adenoma
- 59/110 in rectosigmoid
- 37% with HGD
- 11% with intramucosal Ca.
- Proposed designation SA

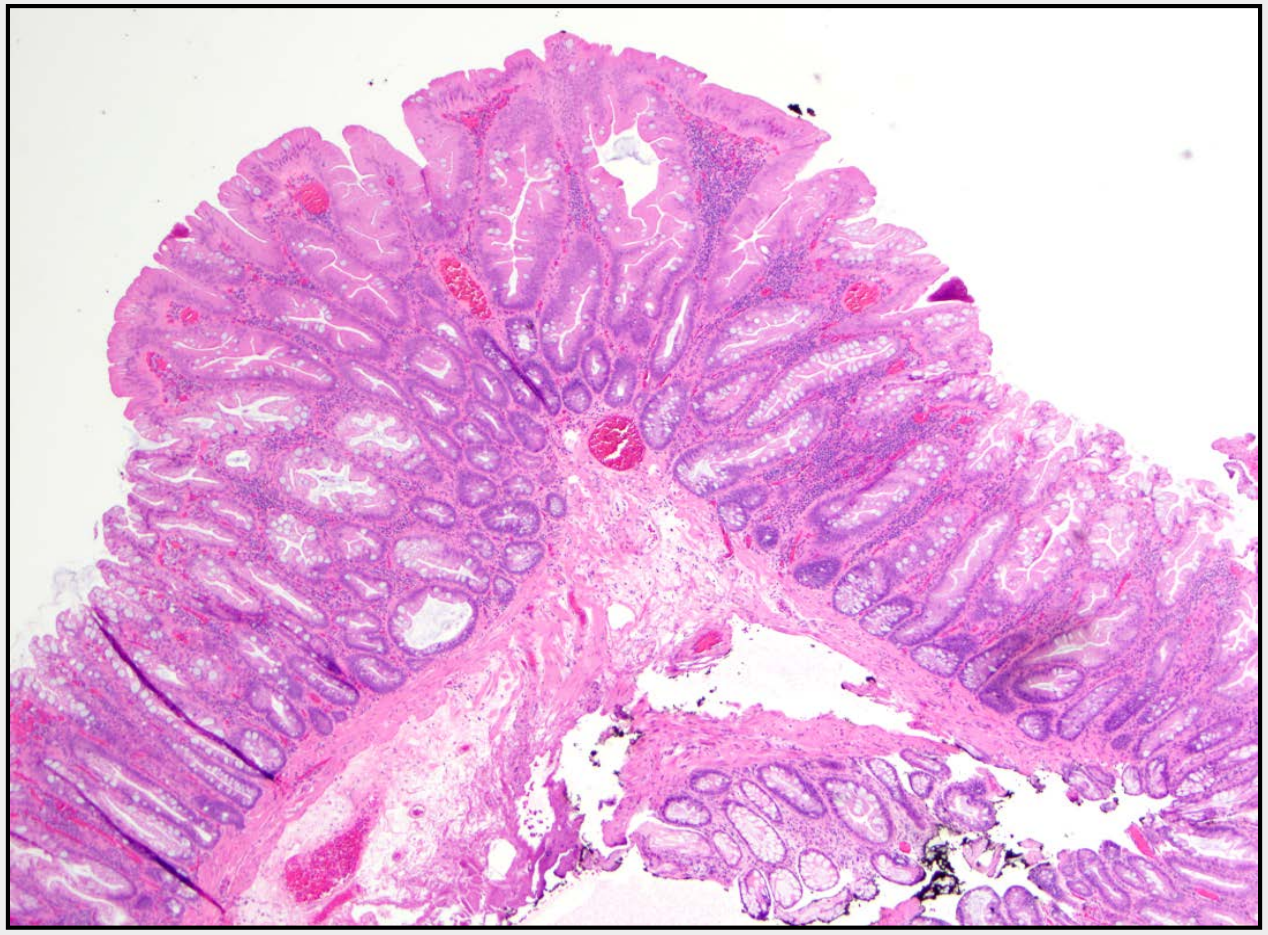
("traditional" serrated adenoma)



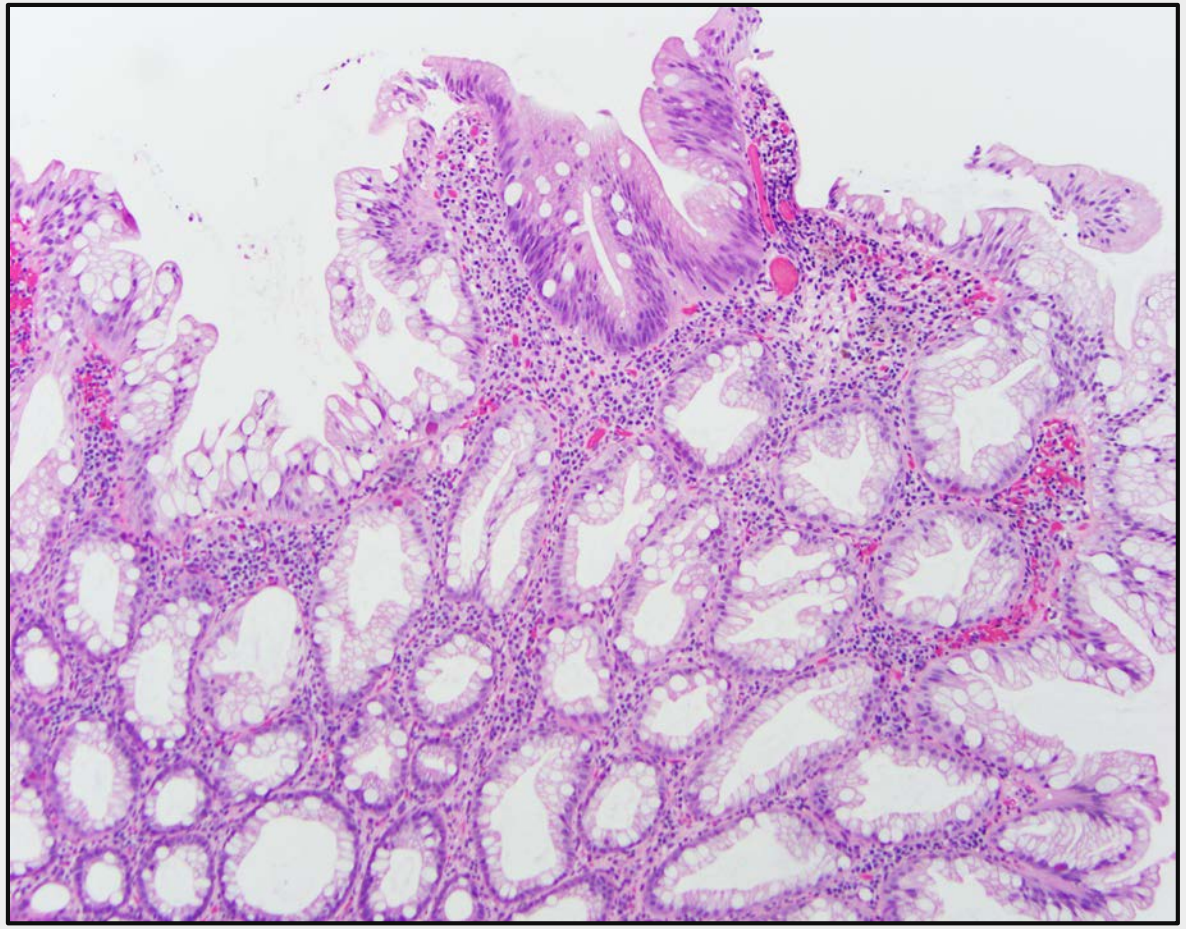


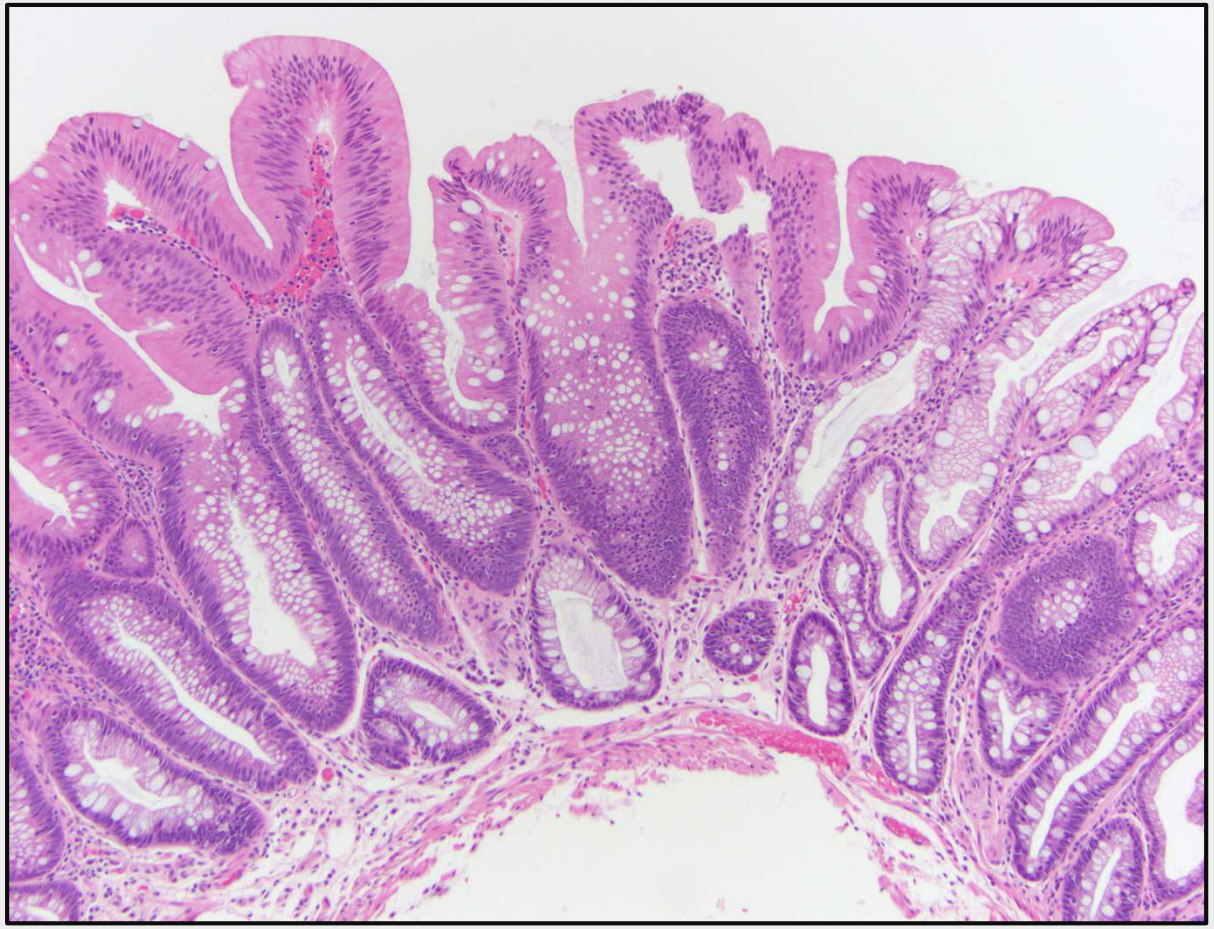
Subset of Traditional Serrated Adenoma of the Colorectum Arise From Non-Dysplastic Precursor Lesions

A subset shows non-dysplastic SP in background



Traditional Serrated Adenoma of the Colorectum Arise From Non-Dysplastic Precursor Lesions





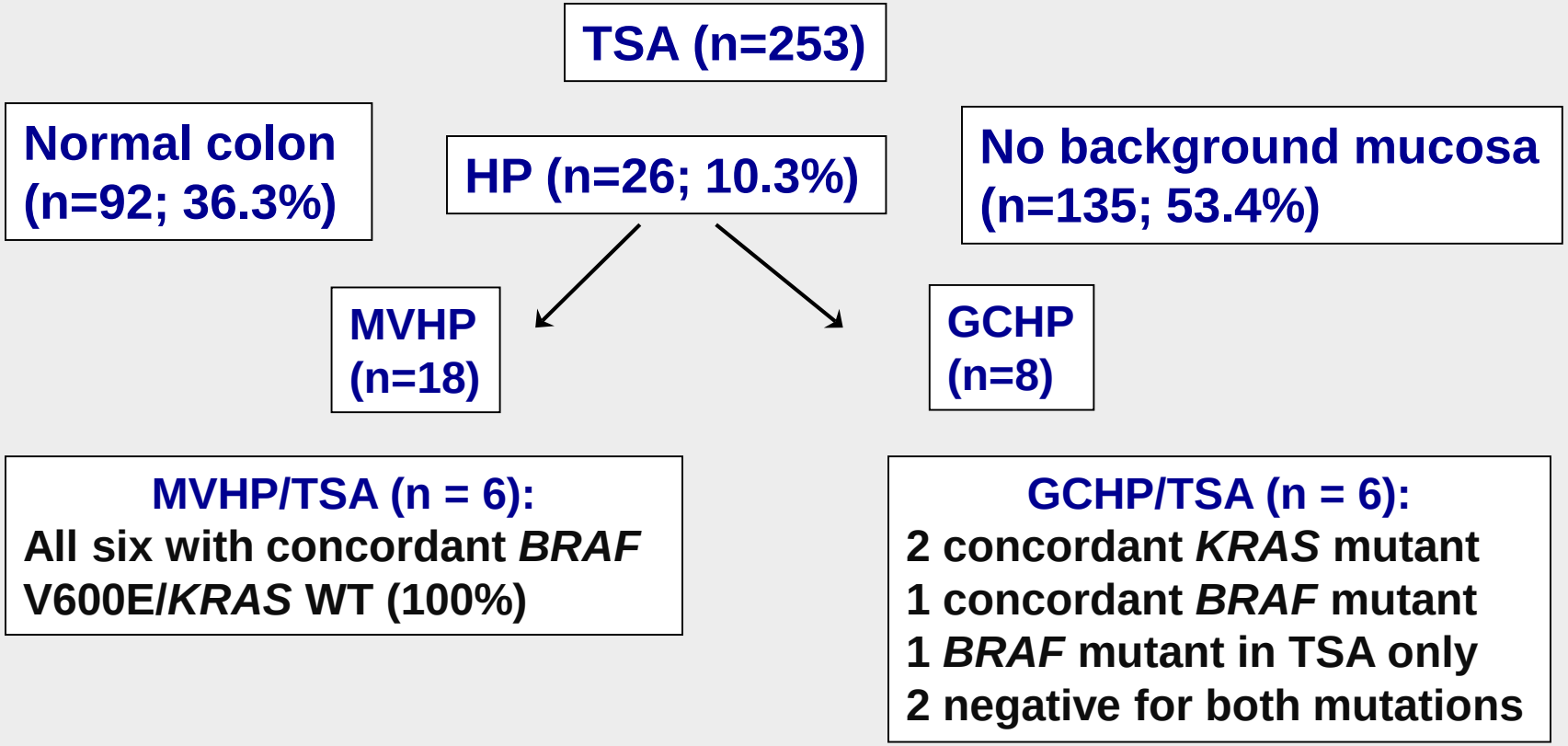
Traditional Serrated Adenoma of the Colorectum Arise From Non-Dysplastic Precursor Lesions

- **Non-dysplastic HP or SSA/P present in 52.3% of TSA**
- **TSA with SSA/P precursor more common in proximal colon**
- **TSA with precursor lesions:**
  - **Lower frequency of *KRAS* mutation (15-25%) compared to those without precursor (51%)**
  - **Higher frequency of *BRAF* mutation (72-75%) compared to those without precursor (35%)**

Kim M-J et al, Am J Clin Pathol 2013, 140: 898-911

Traditional Serrated Adenoma of the Colorectum Arise From Non-Dysplastic Precursor Lesions

Concordant mutations in background non-dysplastic HP and TSA

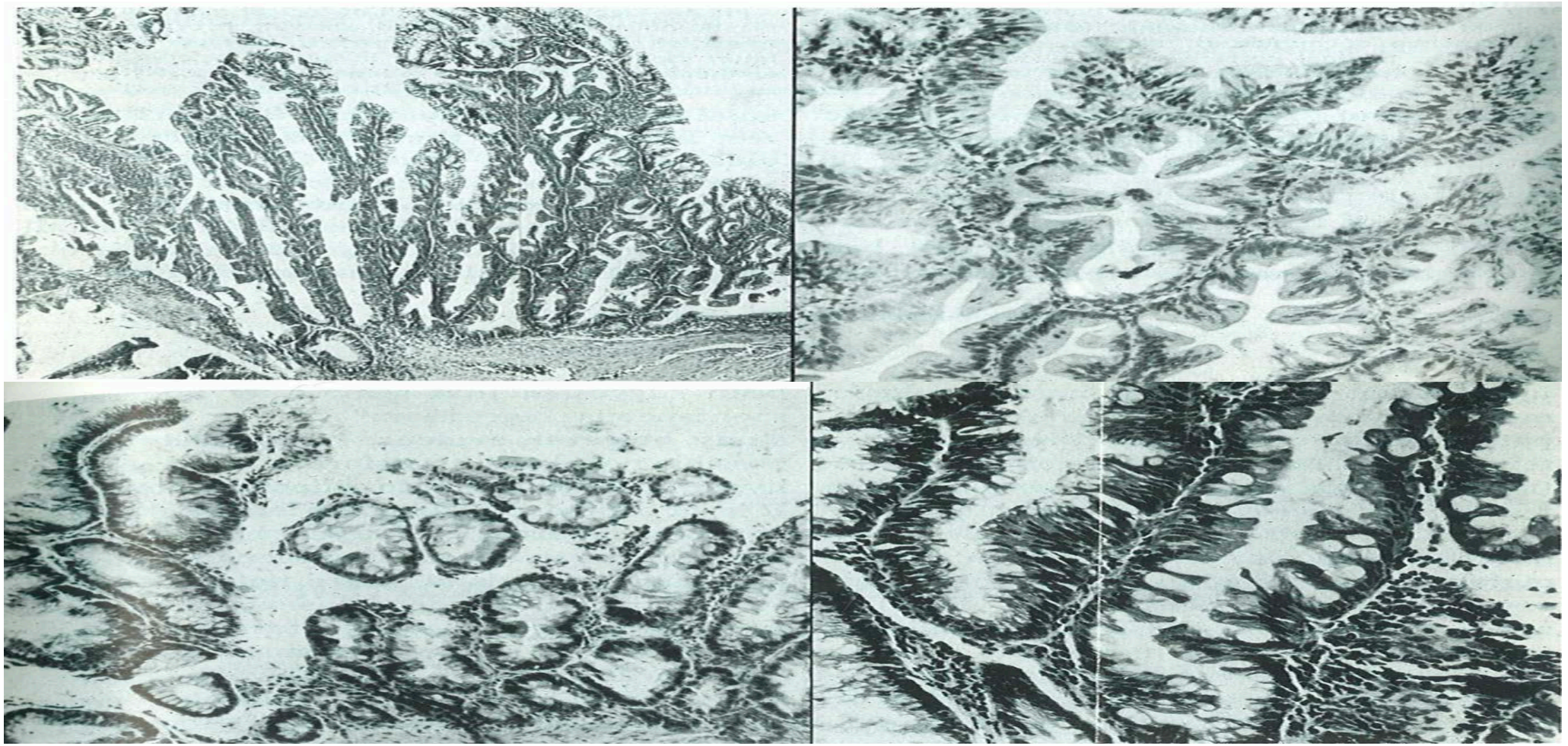


Viani K et al, USCAP 2015

Mixed Hyperplastic Adenomatous Polyps/Serrated Adenomas: A Distinct Form of Colorectal Neoplasia

Teri A. Longacre, Cecilia Fenoglio-Preiser, Am J Surg Pathol 1990;14:524-537

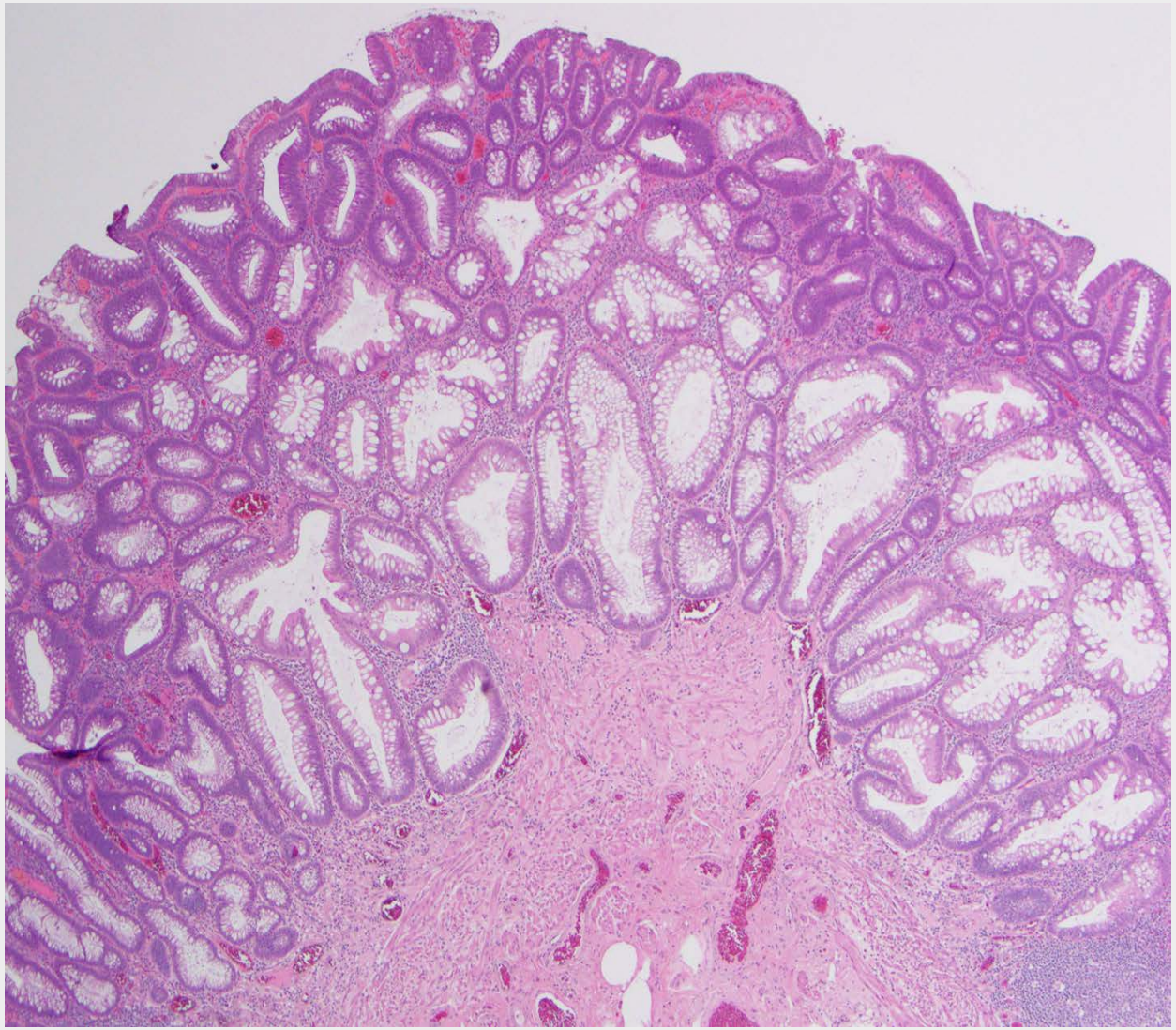
“It is possible, ….that the polyps containing admixed hyperplastic and adenomatous glands represent adenomatous transformation of a hyperplastic polyp.”

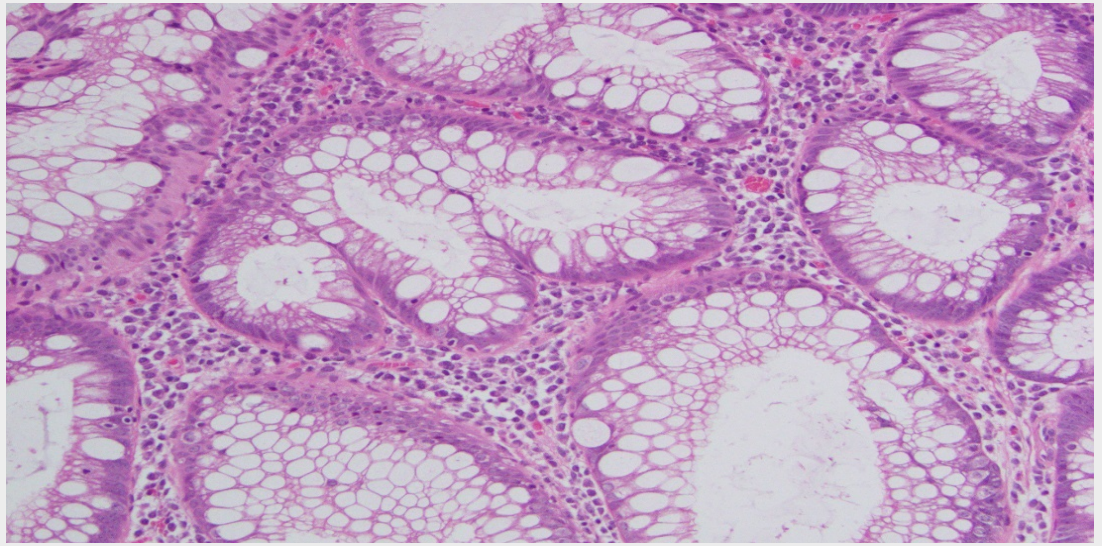


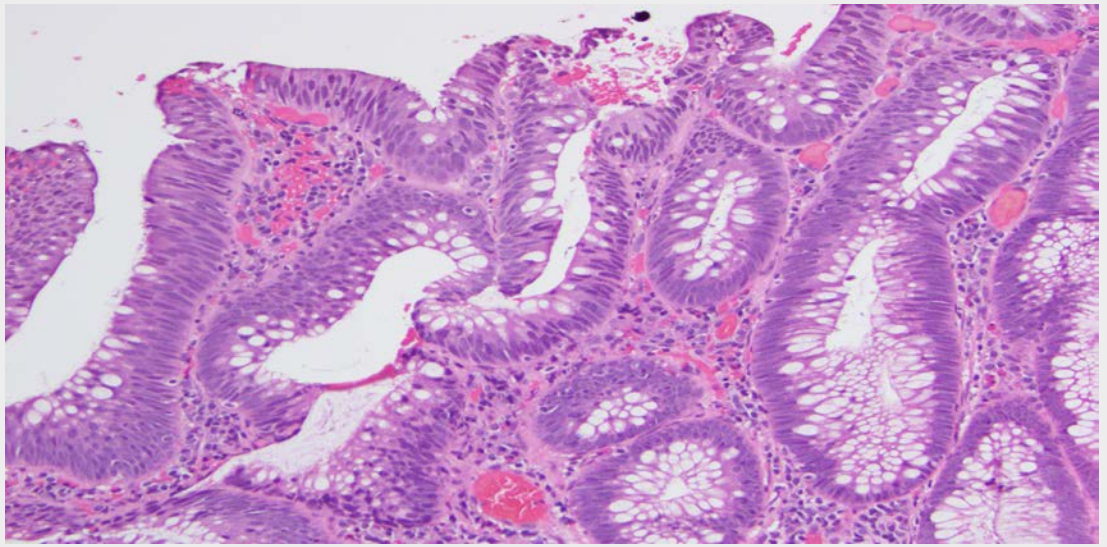
“It is, therefore, proposed that hyperplastic polyps of the human colon, although usually non-progressive, may nevertheless represent a reservoir from which some of the villose adenomas may be derived.”

Harvey Goldman, Arch Pathol:1970 !!

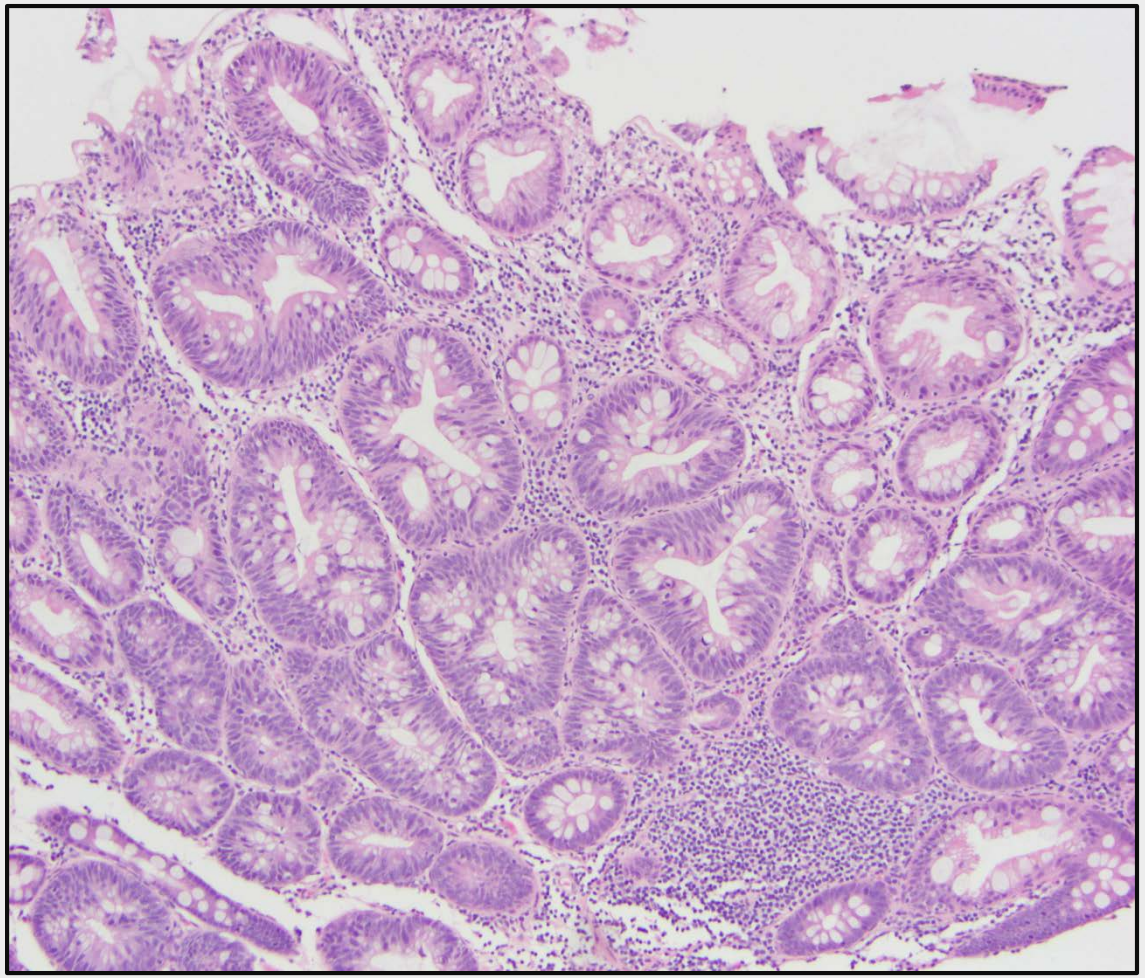
Conventional adenoma-like dysplasia in rectosigmoid ‘hyperplastic polyps’

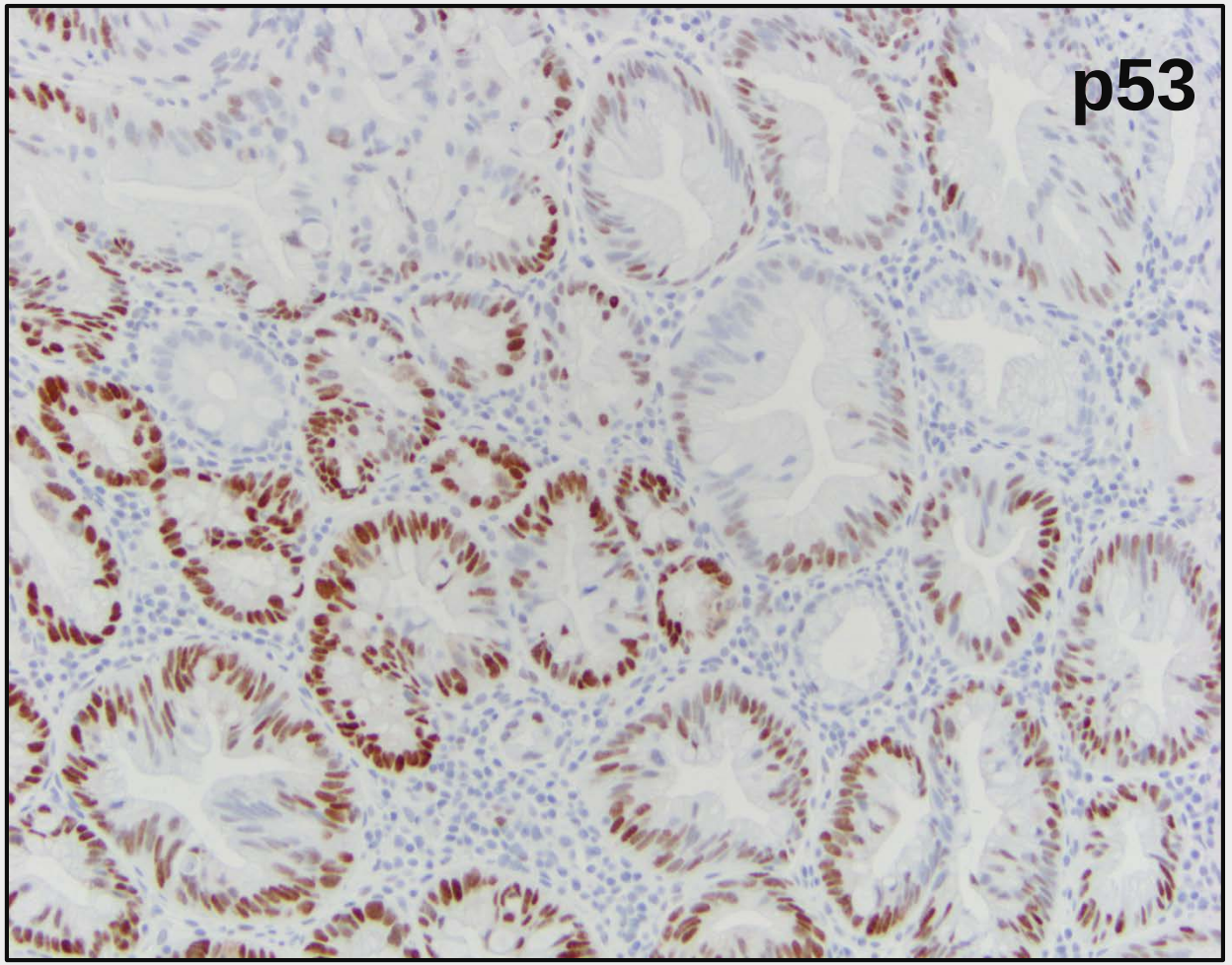




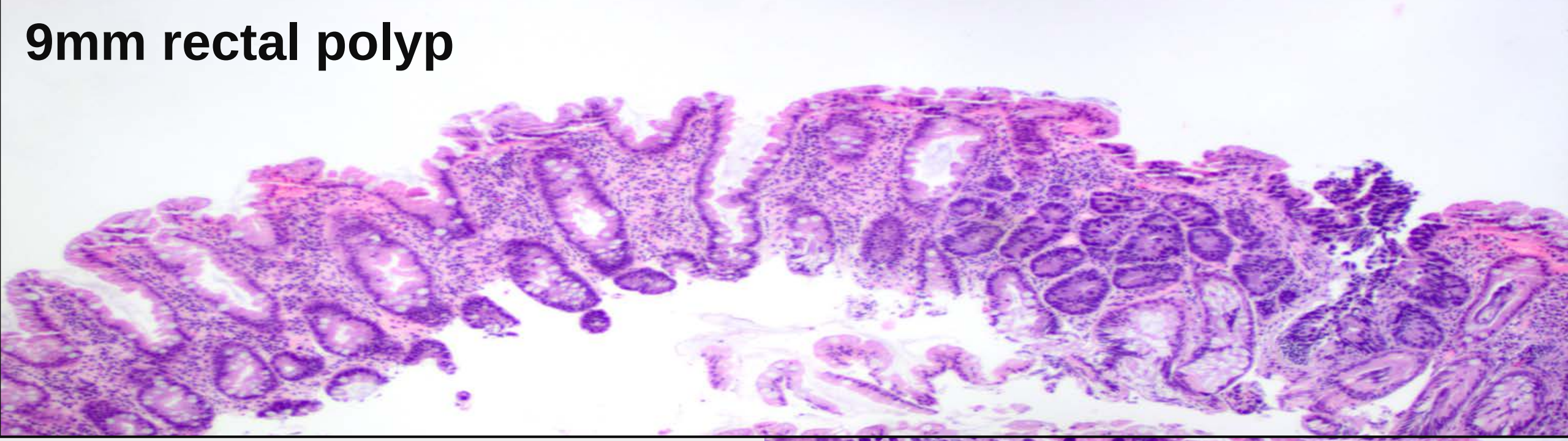


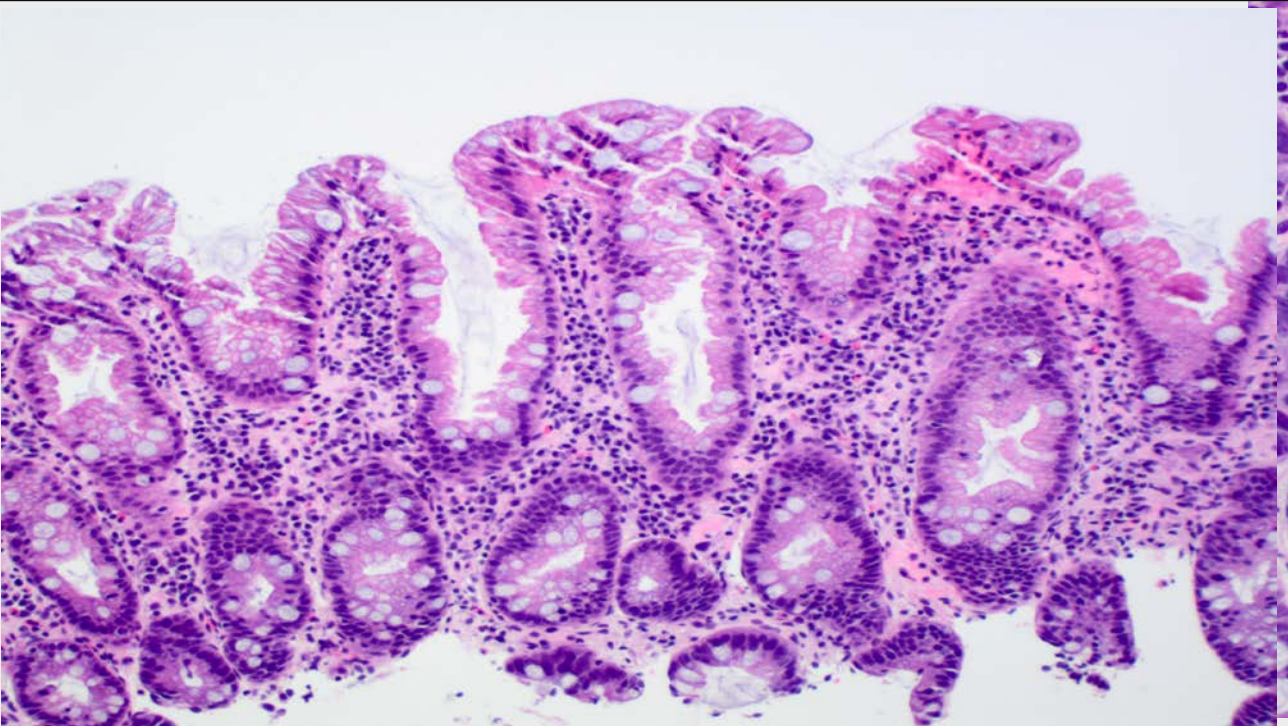
Conventional adenoma-like dysplasia in rectosigmoid ‘hyperplastic polyps’

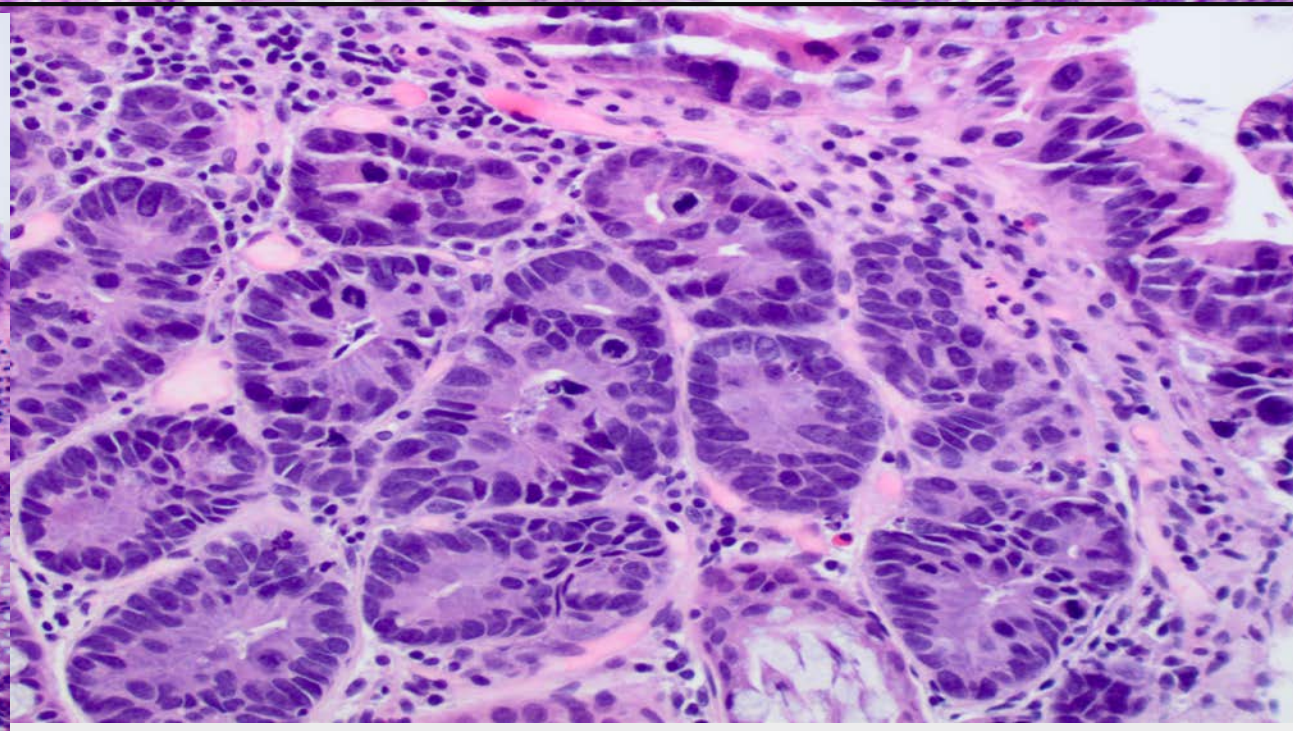




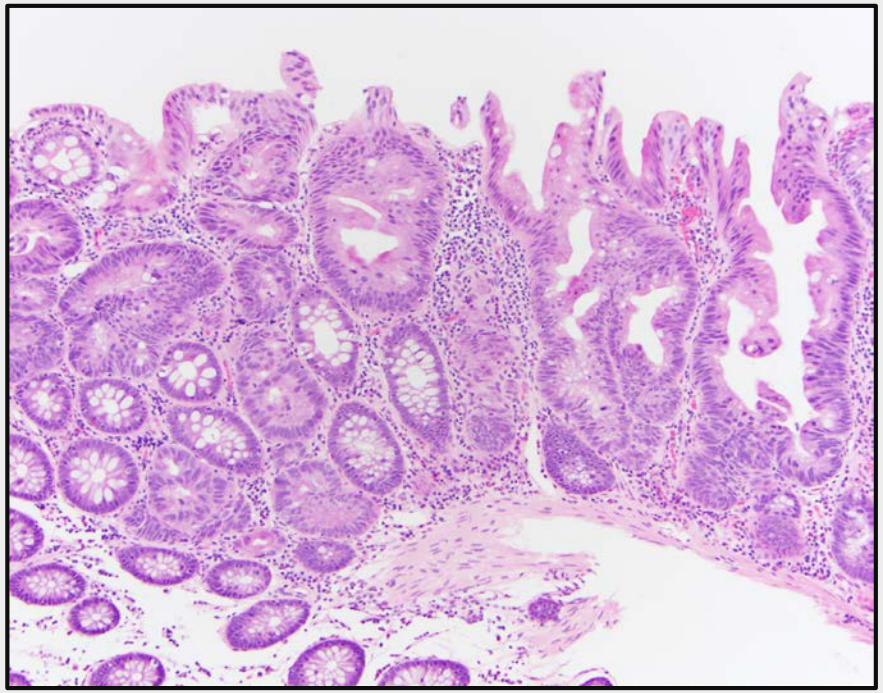
9mm rectal polyp

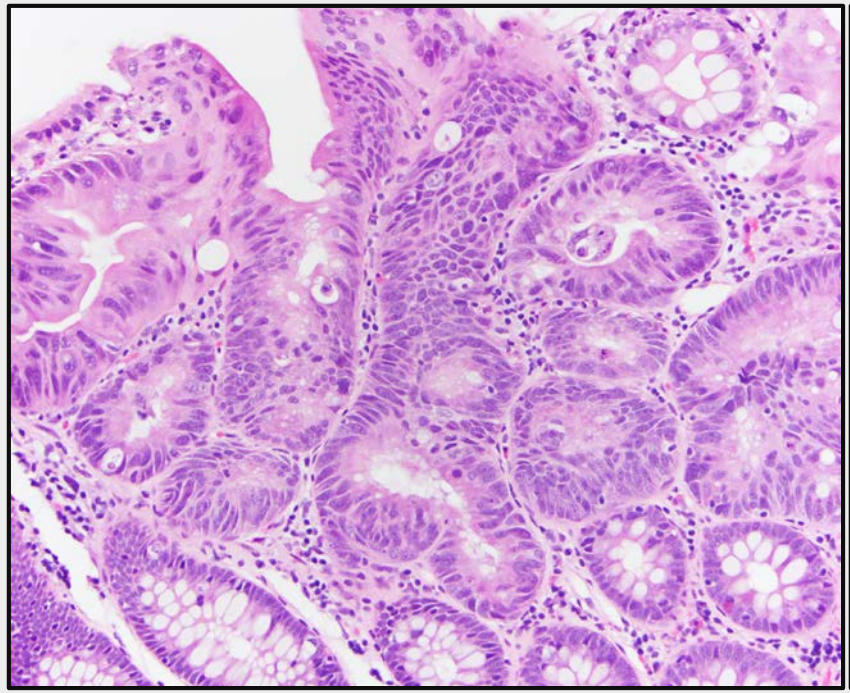


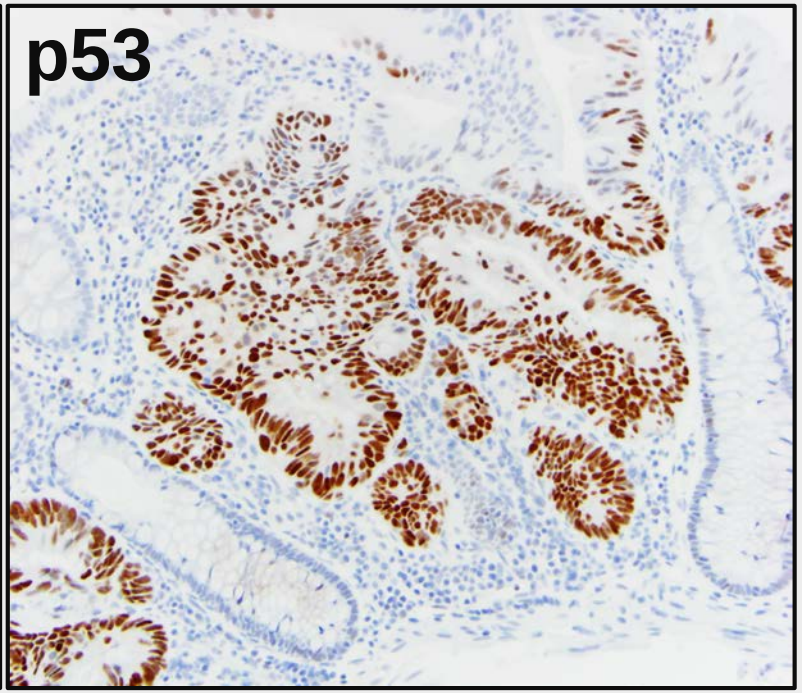




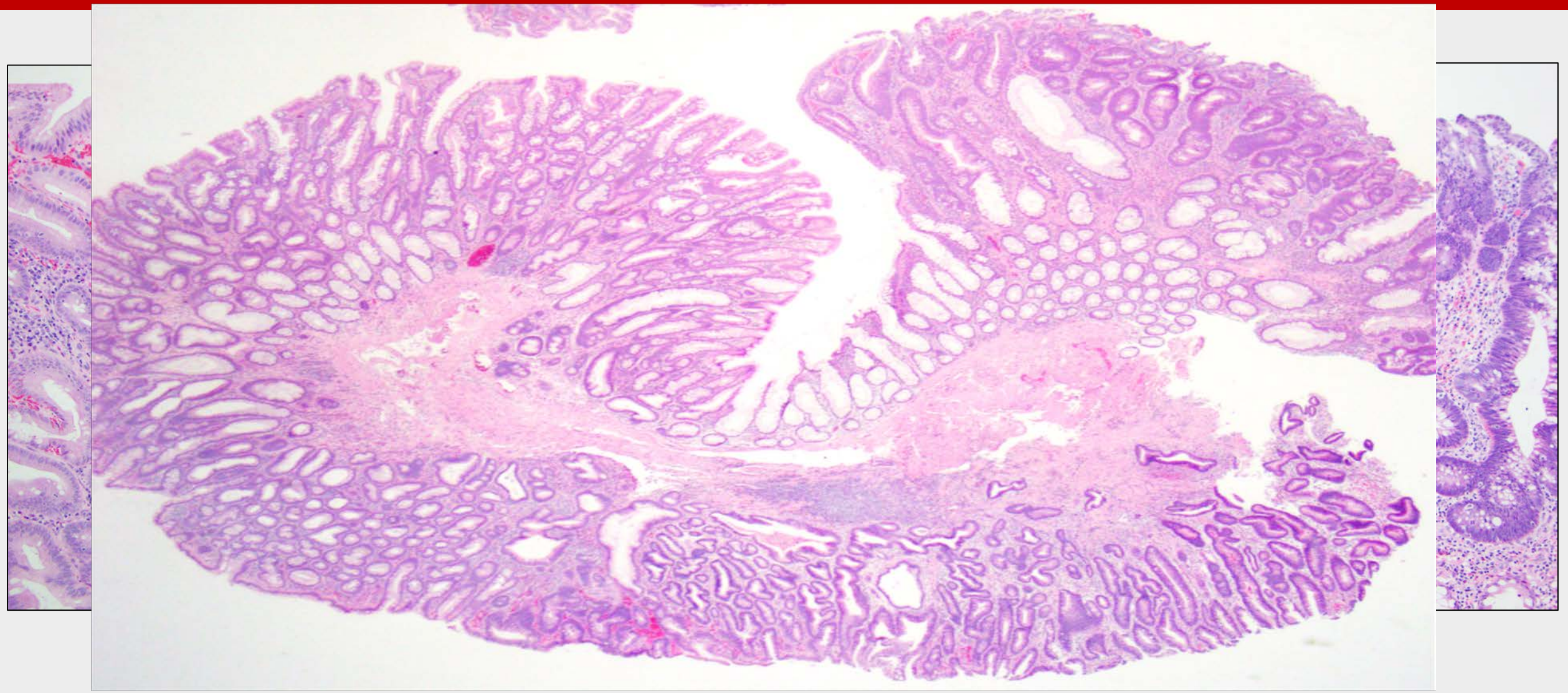
‘Advanced’ TSAs may show cytologic high-grade dysplasia with retention of serrated architecture



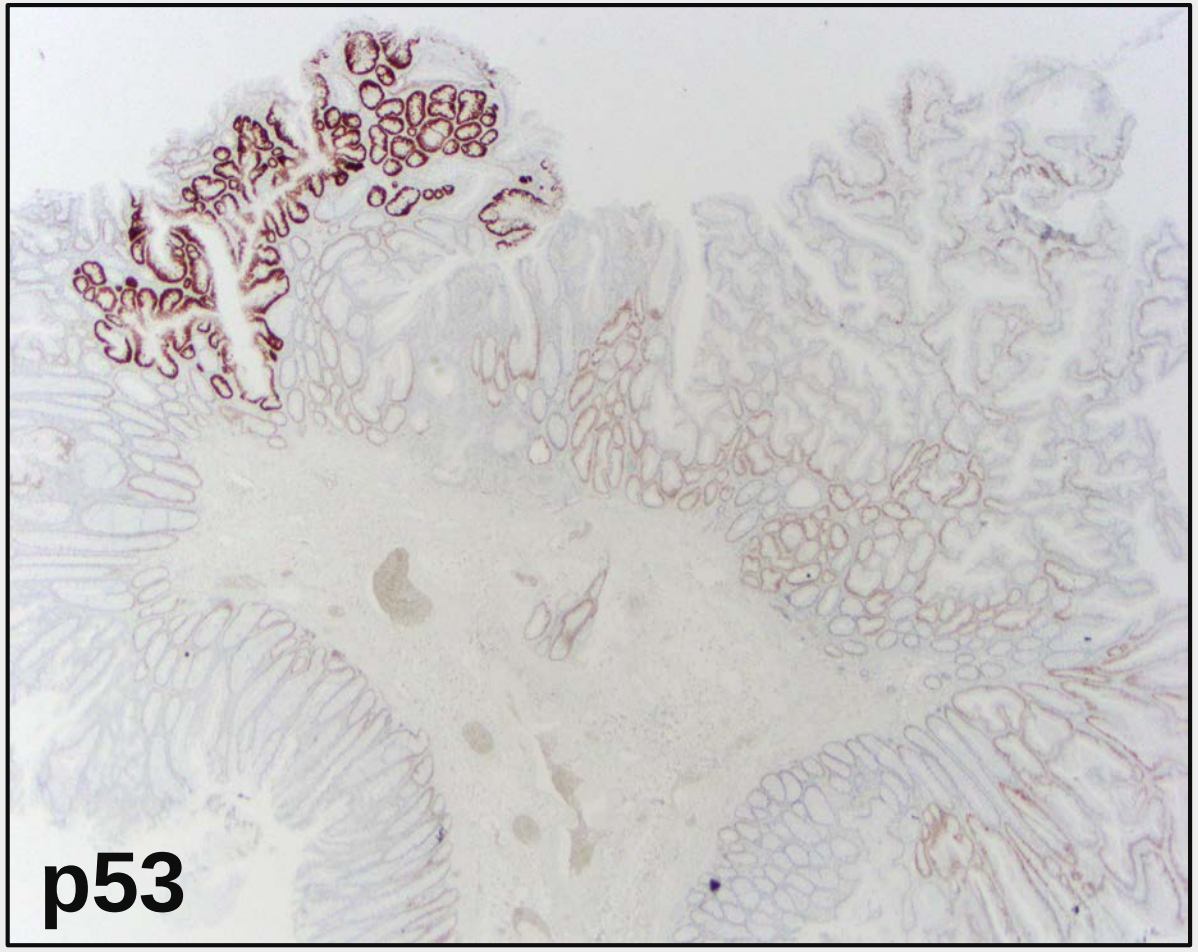




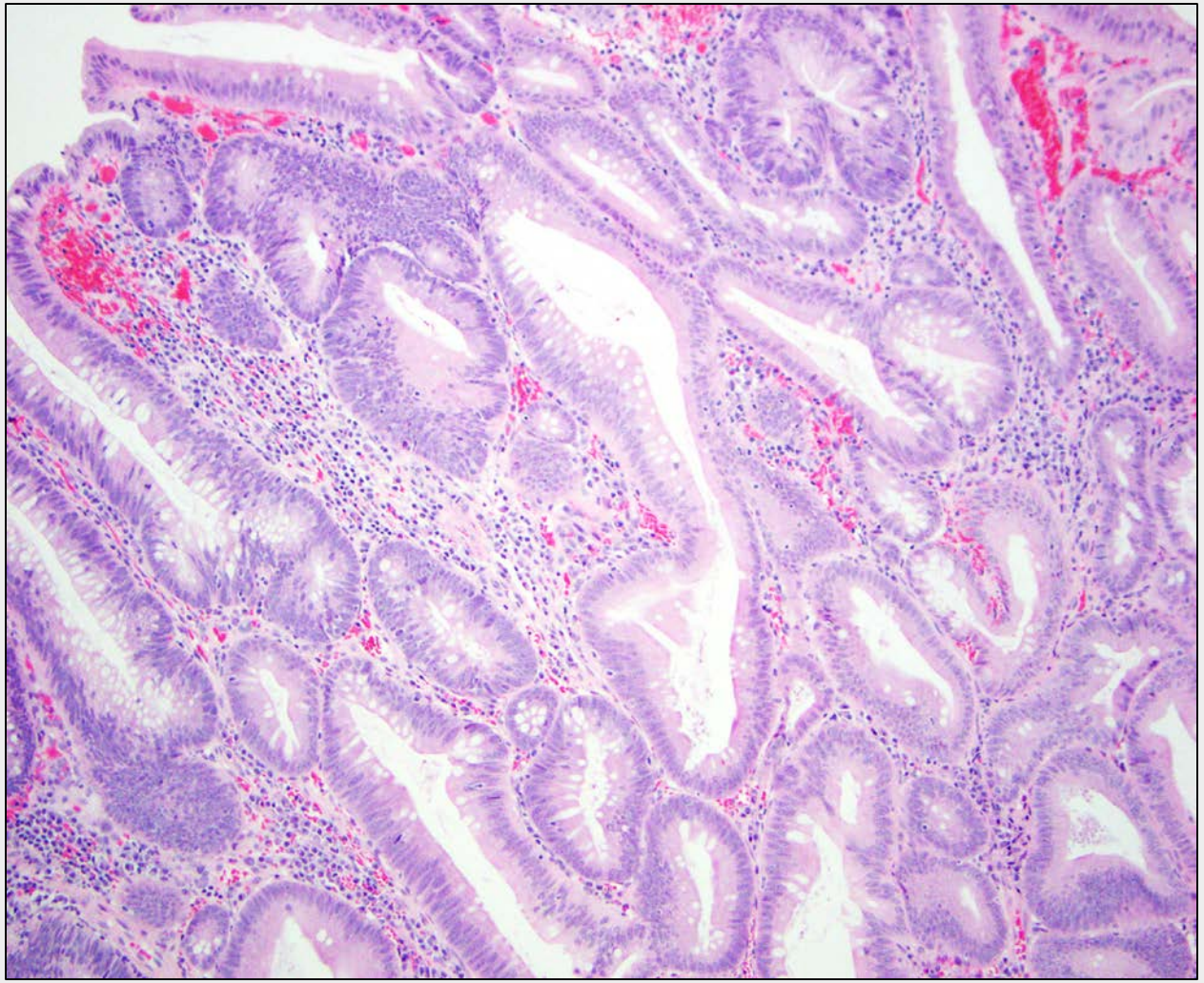
‘Advanced’ TSAs show foci resembling conventional adenomas

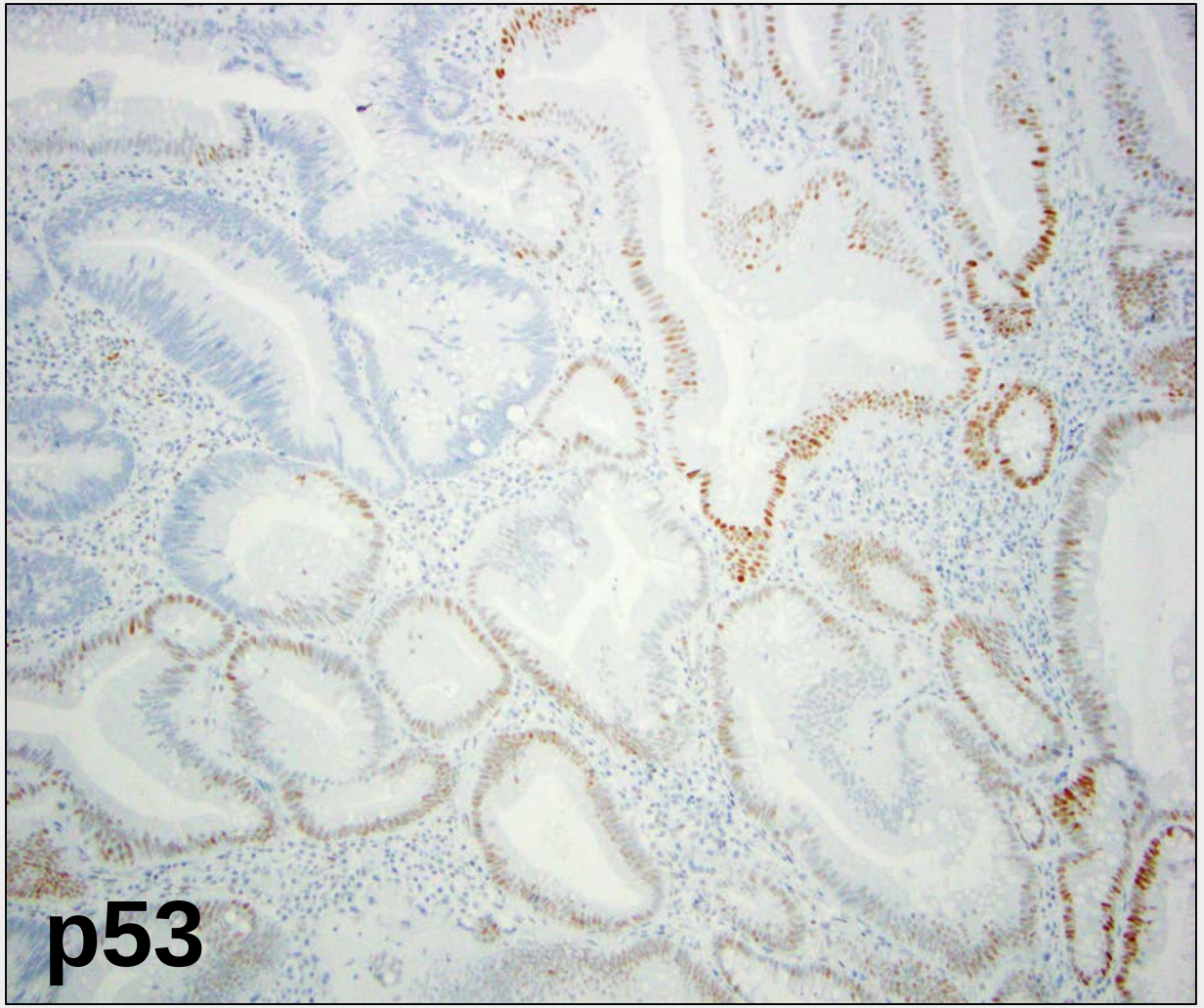


‘Advanced’ TSAs show foci resembling conventional adenomas

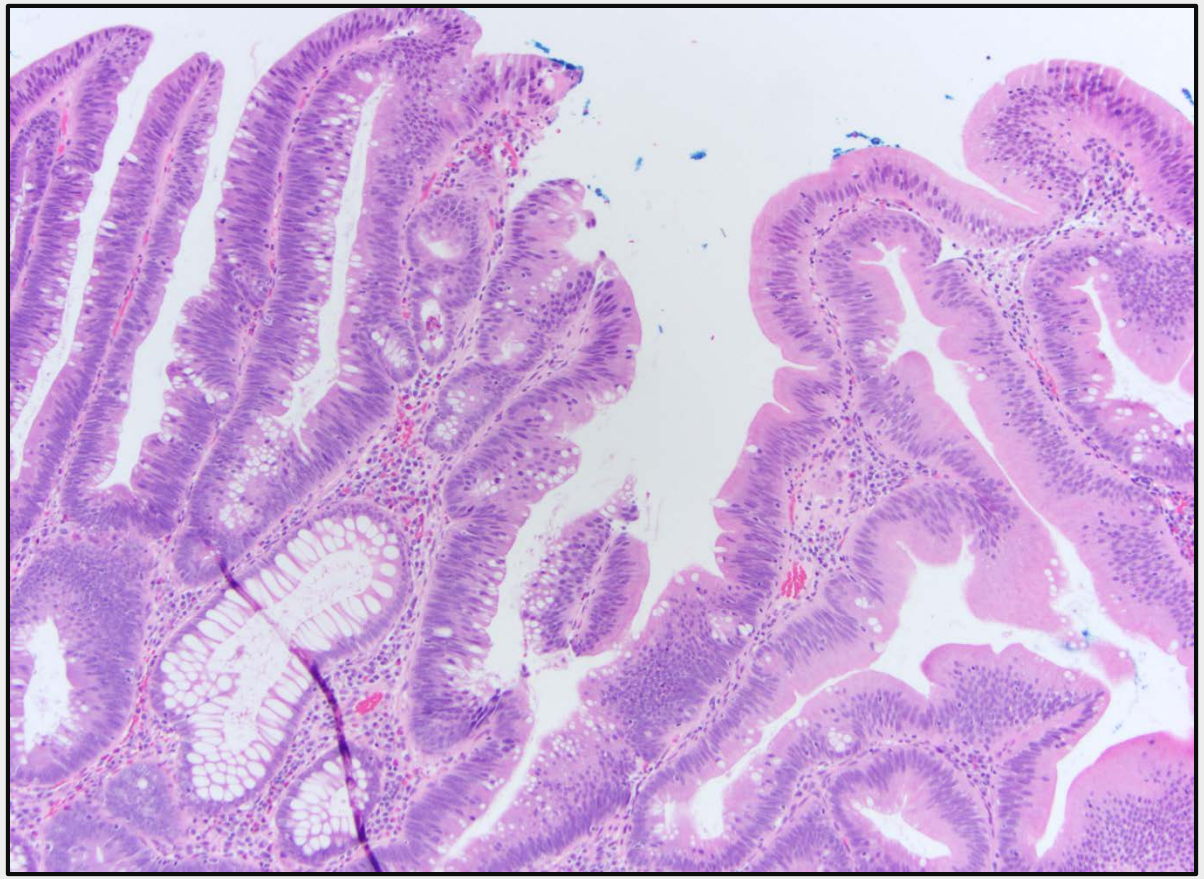


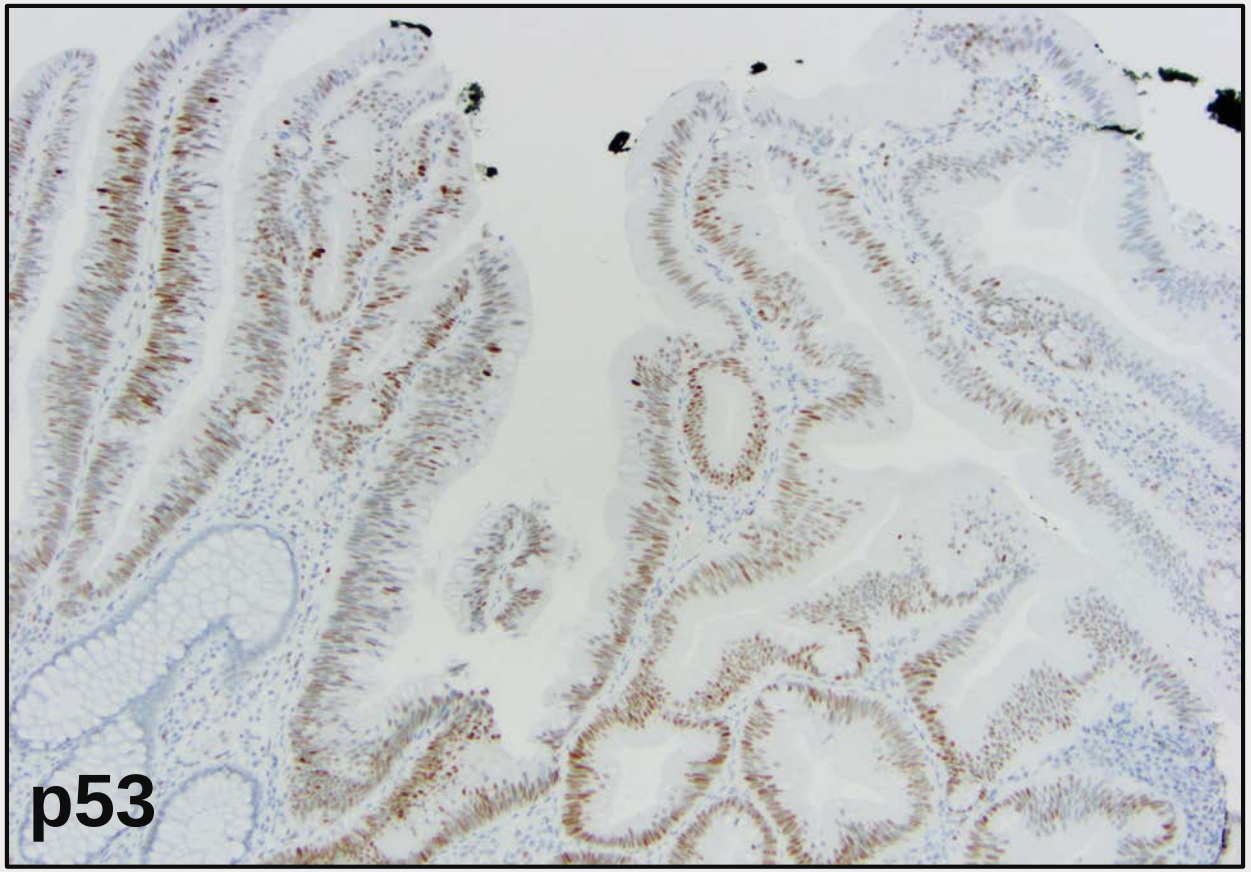
‘Advanced’ TSAs show foci resembling conventional adenomas





‘Advanced’ TSAs show foci resembling conventional adenomas



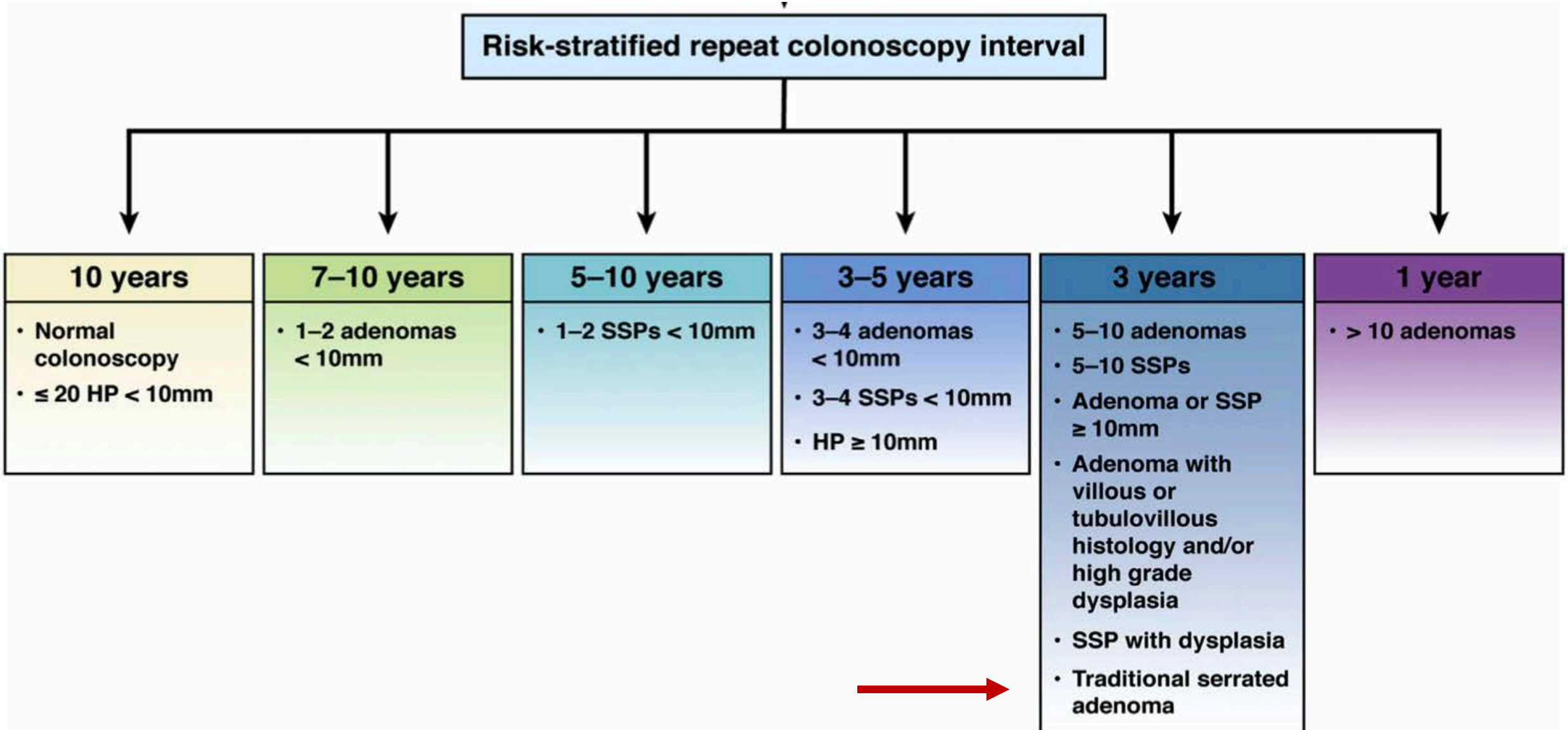


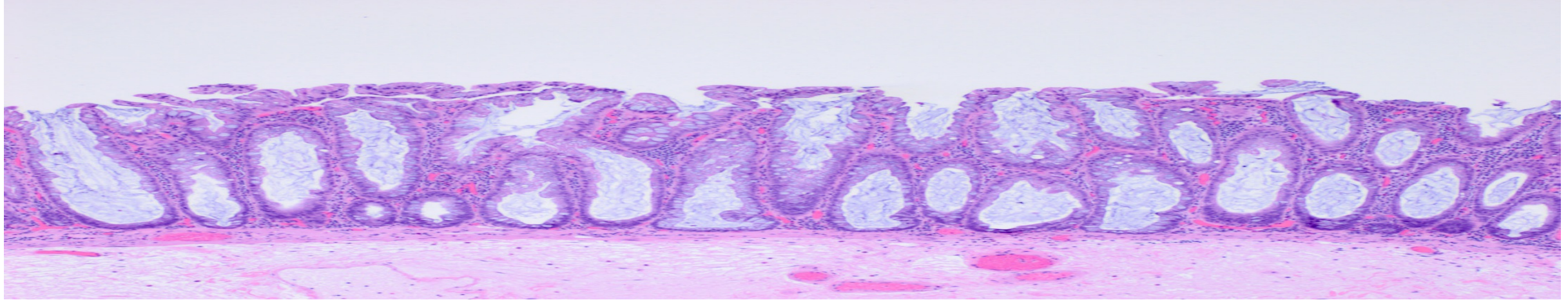
Metachronous outcomes in patients with traditional serrated adenoma

- **Danish Study (Erichsen et al Gastroenterology 2016)**
  - Nested case control (n=10,150; serrated polyps 931)
  - Outcome of interest: CRC
  - TSA one of the highest risk factors for CRC (OR=4.84; 95% CI: 2.36-9.93)
  - 10 yr CRC risk: 4.4% for SSP-D, 4.5% for TSA, 2.3% for conventional adenomas
  - Only 31 TSA; patients not part of routine screening/surveillance colonoscopy

- **Korean Study (Yoon et al, GIE 2015)**
  - Retrospective case control (n=558; 186 TSA)
  - Outcome of interest: AA
  - Metachronous AA more common in baseline TSA group vs. conventional adenoma (OR=2.37)
  - Outcome data available only in 186/420 initial baseline group

Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer (Gastroenterology 2020)





- **Hyperplastic polyp (pre-2003)**

- **Sessile serrated adenoma**
- **Sessile serrated polyp**
- **Serrated polyp with abnormal proliferation**
- **‘Non-dysplastic’ serrated polyp**
- **Sessile serrated adenoma/polyp (WHO)**

2003-18

- **Sessile serrated *lesion* (WHO 2019)**

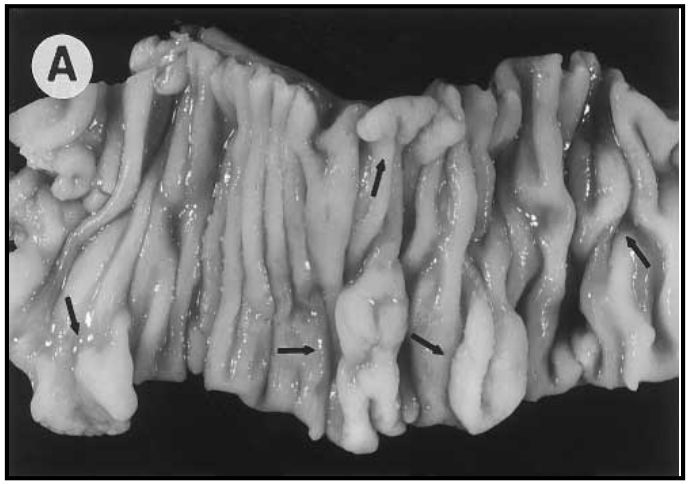
Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer (Gastroenterology 2020)

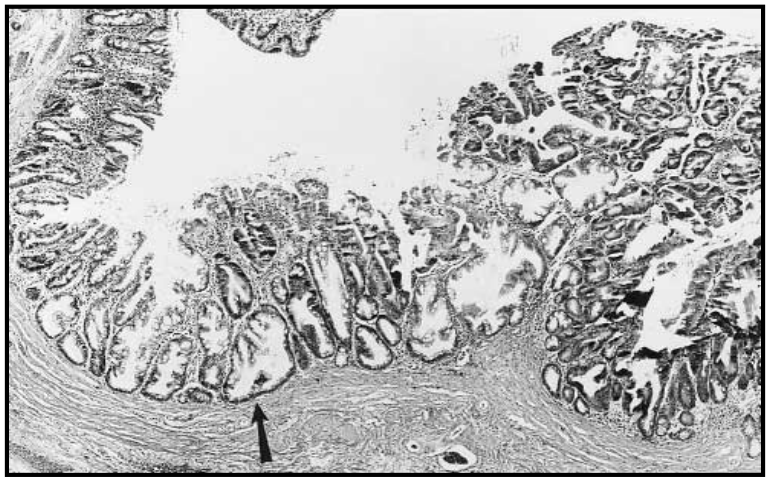
Table 5. US Multi-Society Task Force Recommendations for Post-Colonoscopy Follow-Up in Average-Risk Adults With Serrated Polyps[a]

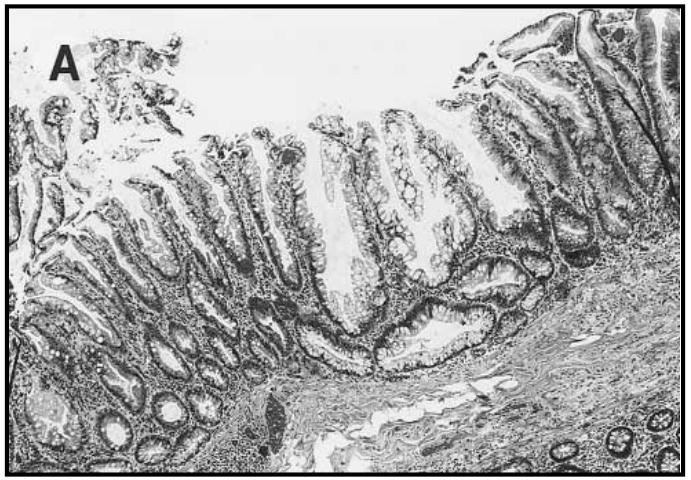
Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
≤20 HPs in rectum or sigmoid colon <10 mm[f]	10 y[b]	Strong	Moderate
≤20 HPs proximal to sigmoid colon <10 mm[f]	10 y	Weak	Very low
1–2 SSPs <10 mm	5–10 y	Weak	Very low
3–4 SSPs <10 mm	3–5 y	Weak	Very low
5–10 SSPs <10 mm	3 y	Weak	Very low
SSP ≥10 mm	3 y	Weak	Very low
SSP with dysplasia[e]	3 y	Weak	Very low
HP ≥10 mm	3–5 y[c]	Weak	Very low
TSA	3 y	Weak	Very low
Piecemeal resection of SSP ≥20 mm	6 mo	Strong	Moderate[d]

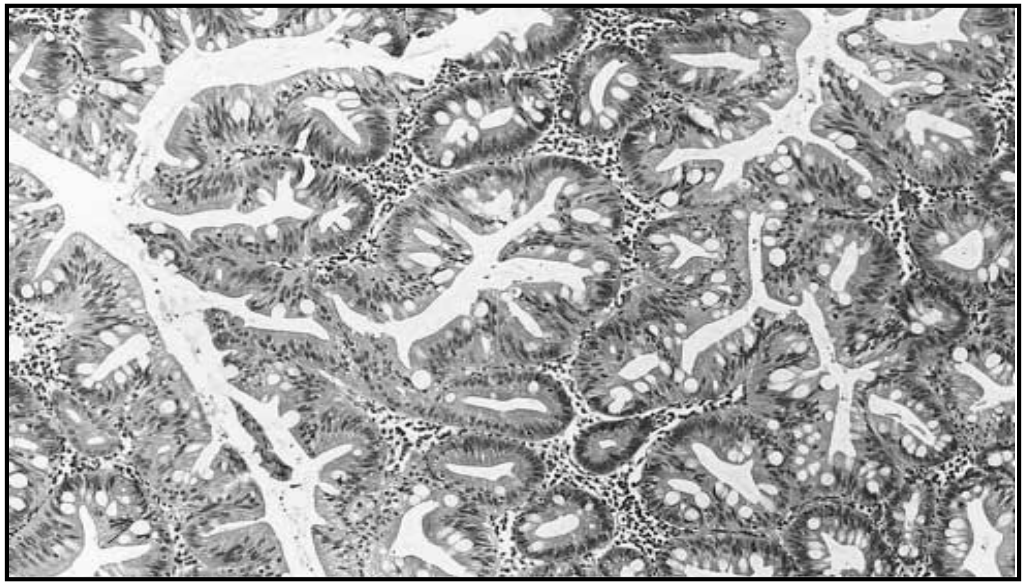
Serrated Adenomatous Polyposis in Humans

Emina Torlakovic, Dale C. Snover, Gastroenterology 1996, 110:748-755





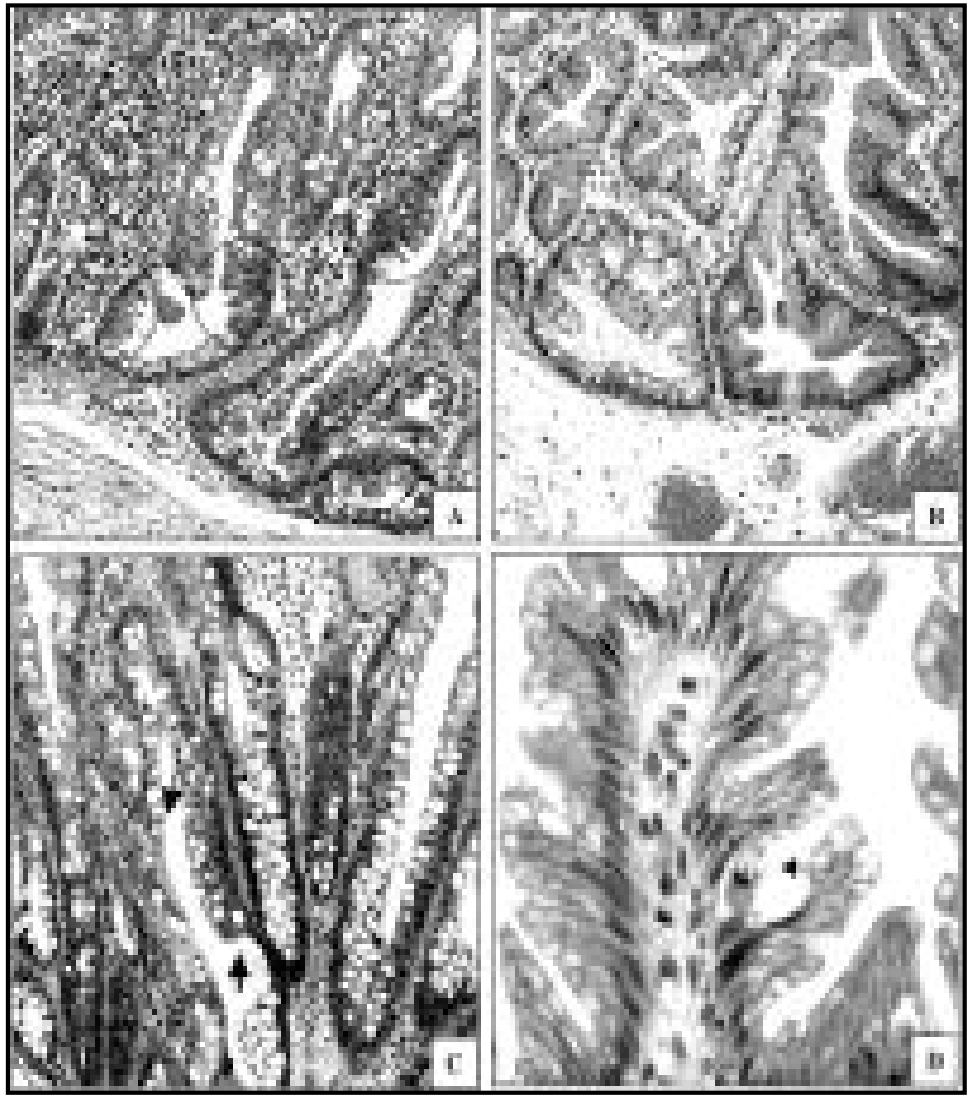




- 6 Patients; Age: 39-85yrs
- >50 polyps; 0.5-4.5cm
- Majority *sessile*
- Four with cancer

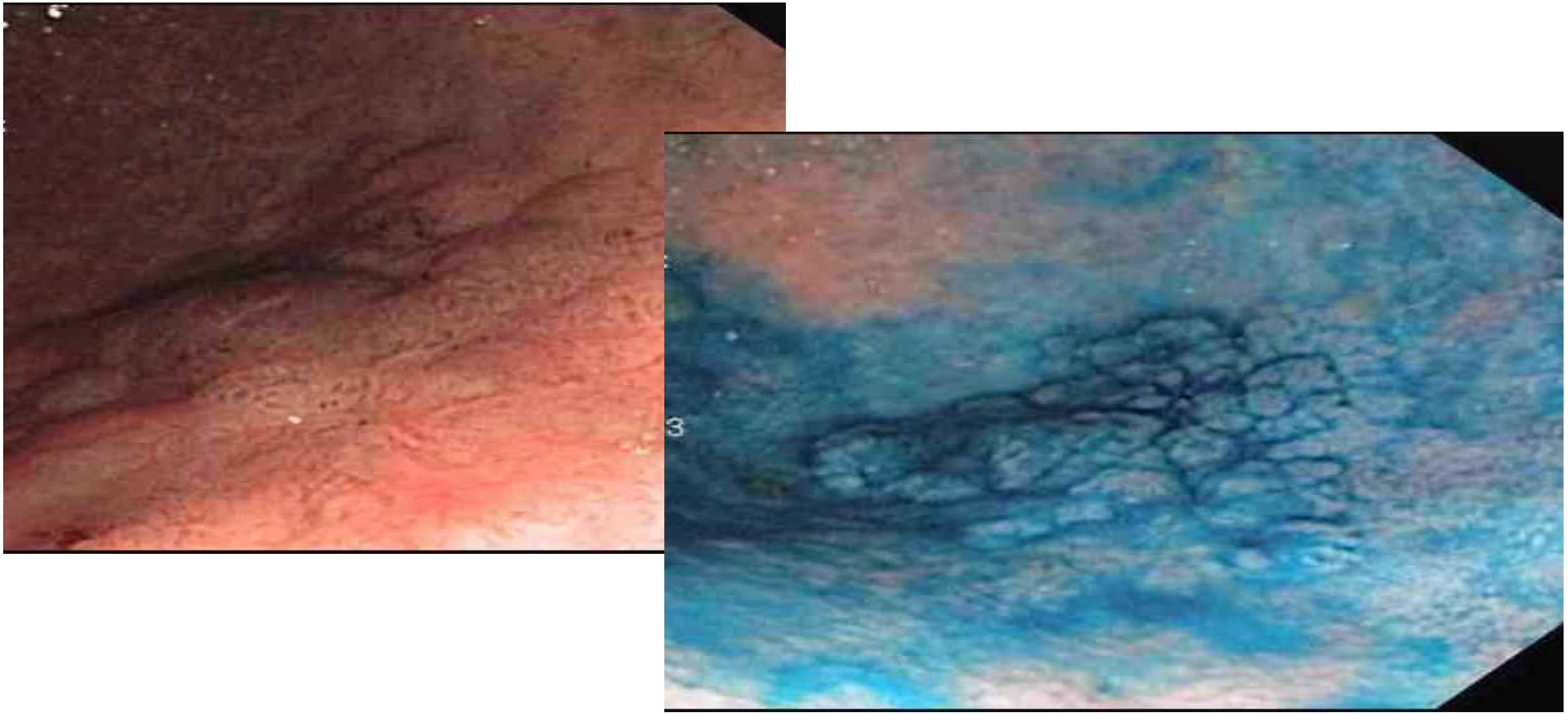
Morphological reappraisal of serrated colorectal polyps

Torlakovic E et al, Am J Surg Pathol 2003; 27:65-81

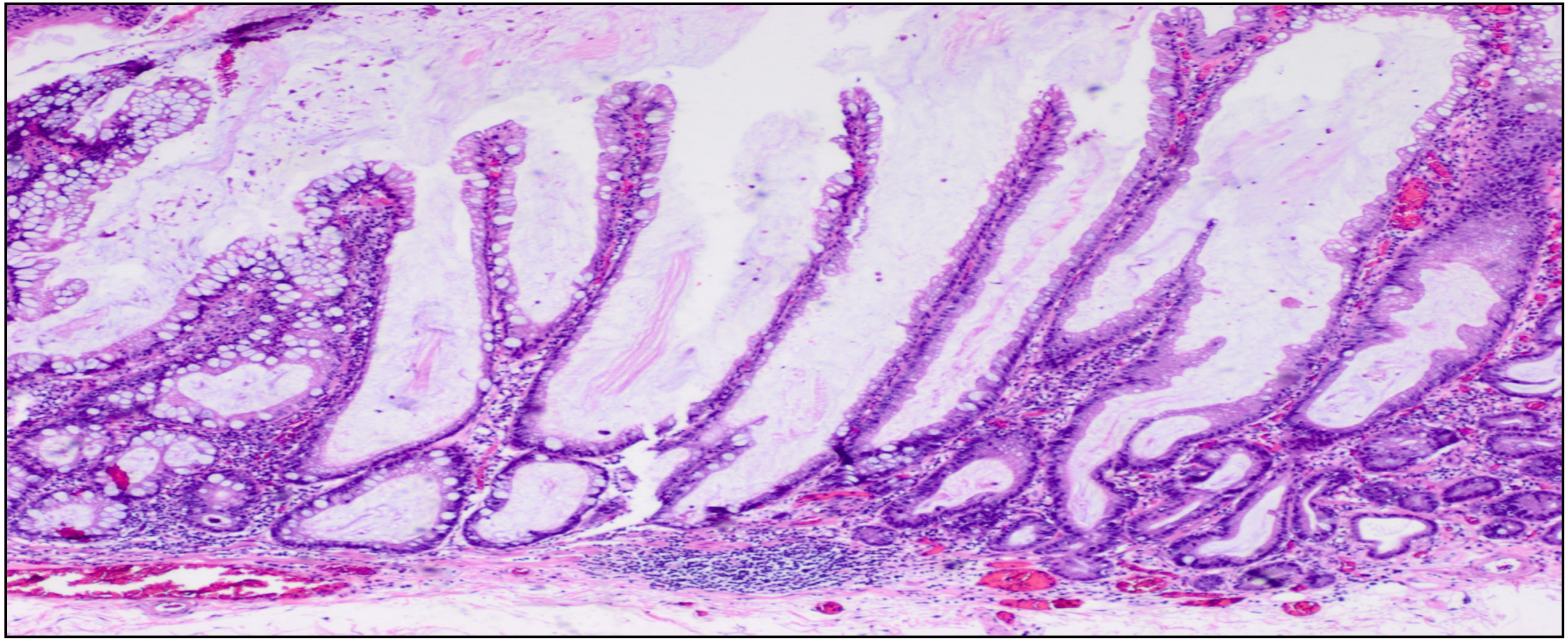


- 289 serrated colorectal polyps
- Cluster analysis of 24 variables
- 3 distinct types of HPs
- Another subset similar to HP seen in ‘hyperplastic polyposis’
  - Right sided
  - Abnormal proliferation
  - Distinct from “TSA”
  - Proposed designation
    Sessile Serrated Adenoma

Sessile Serrated Adenoma/Polyp

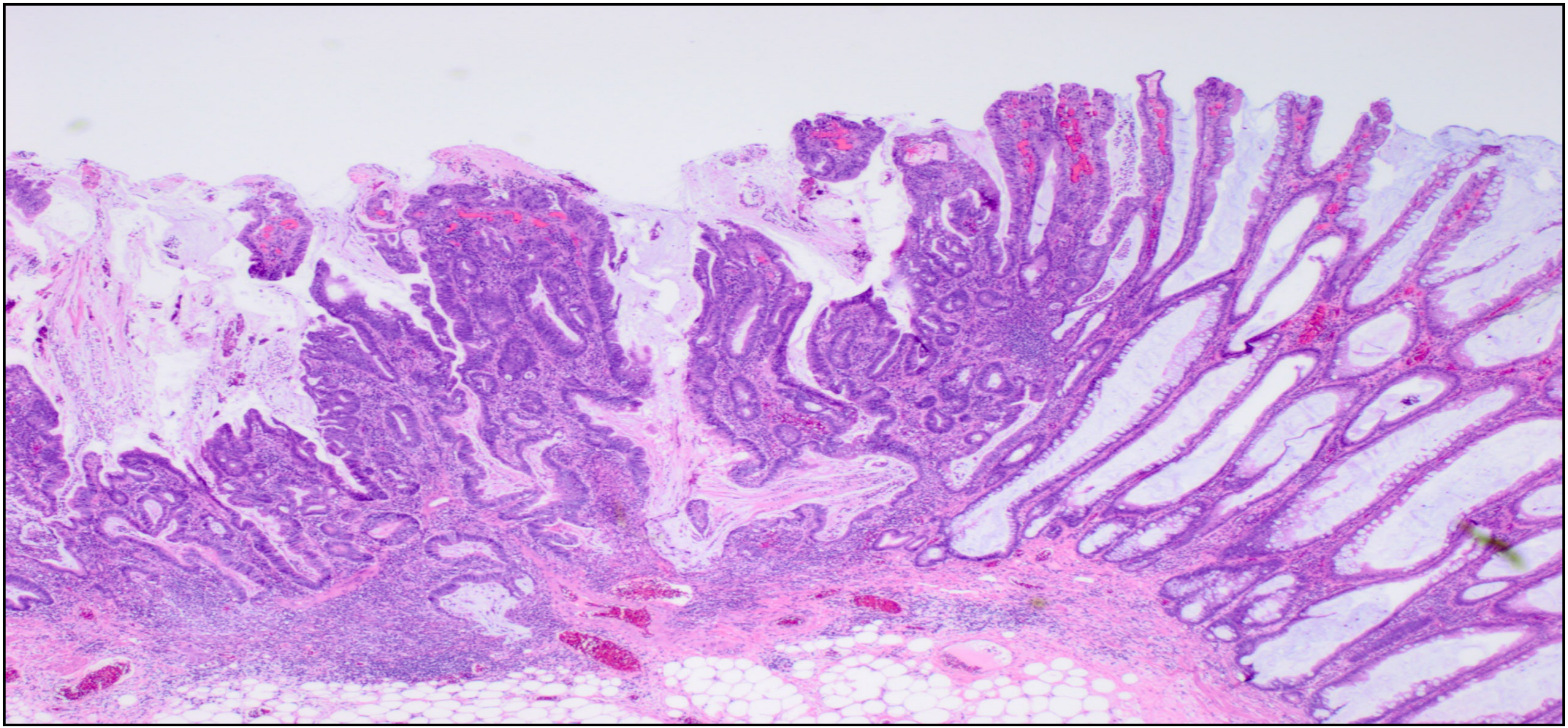


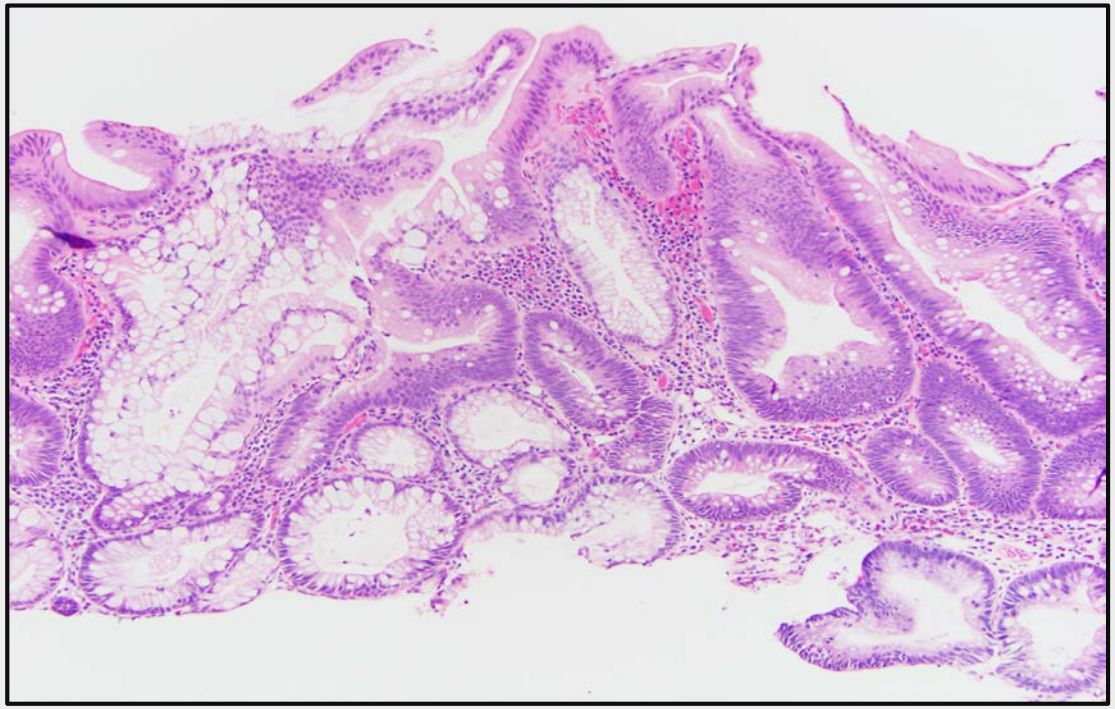
Microscopic Features of SSA/P

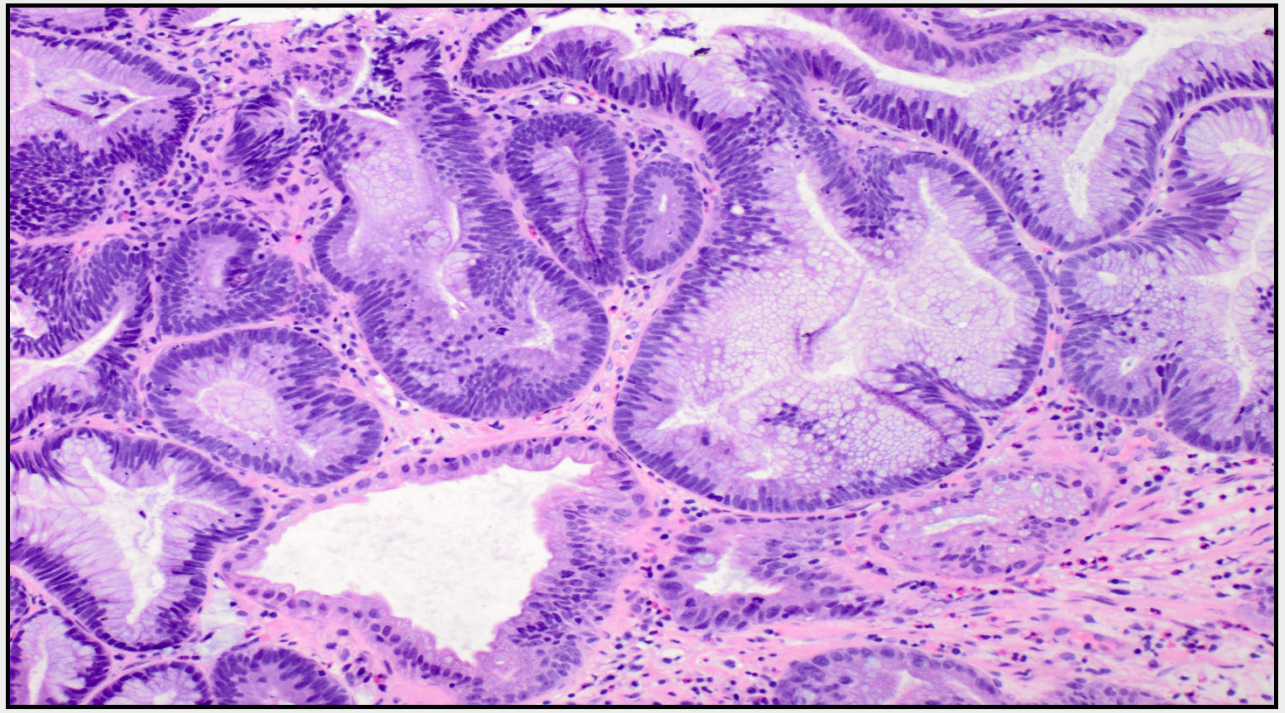


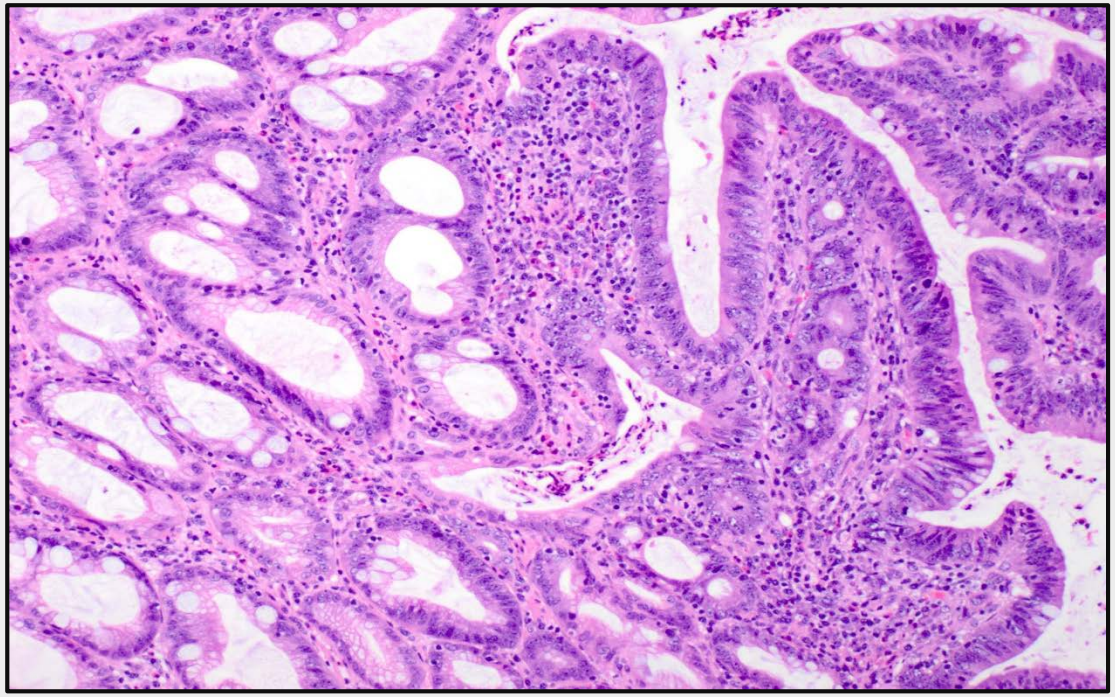
Architectural disarray at the base most commonly used feature for diagnosis

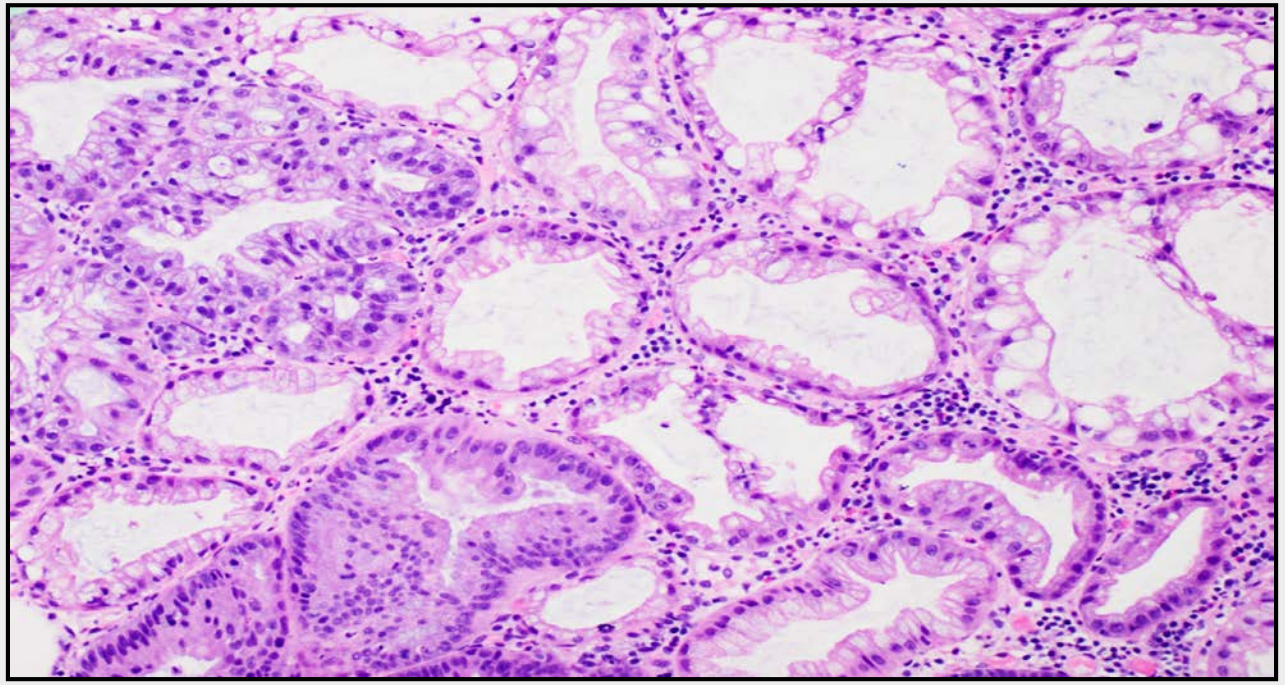
Invasive Carcinoma in SSA/P



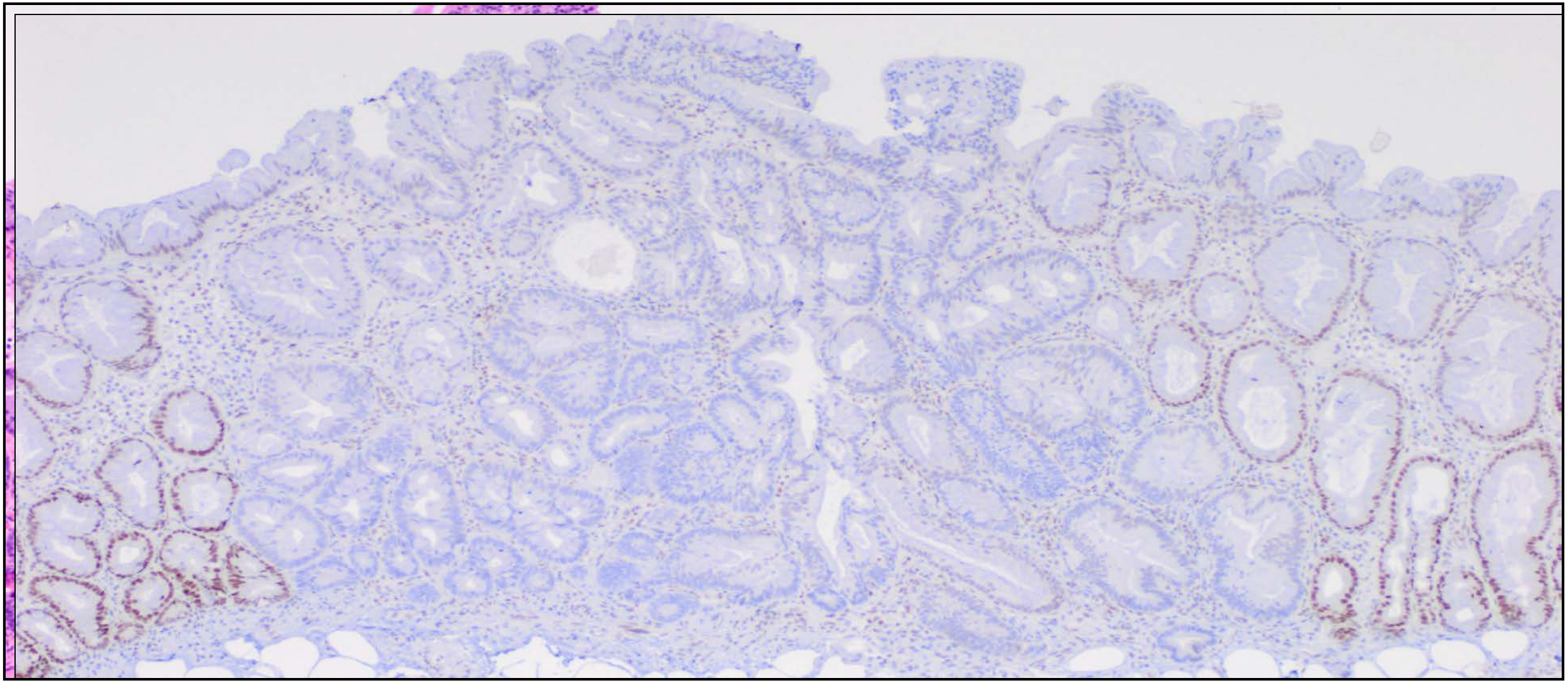


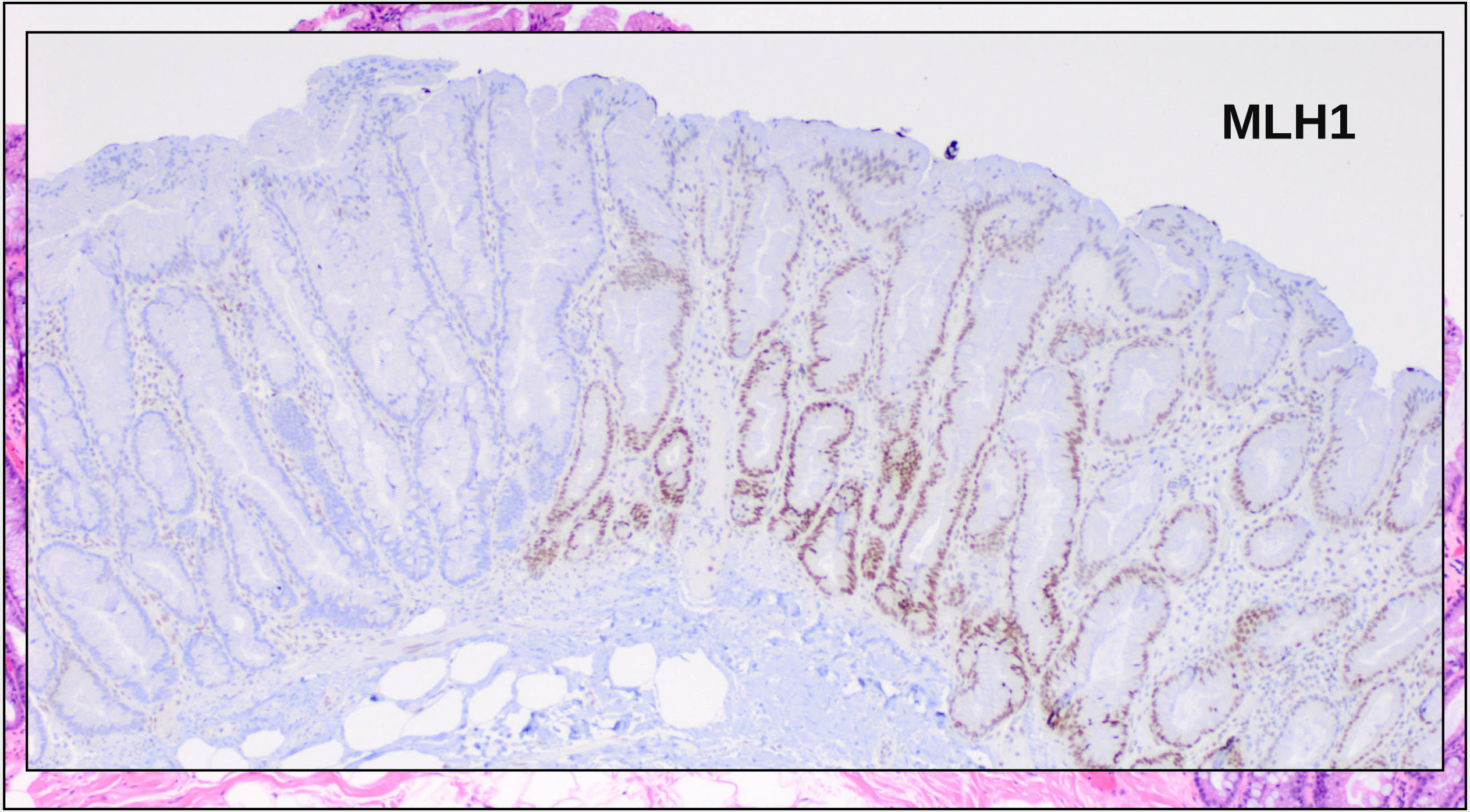






SSA/P with cytologic dysplasia




MLH1

HP vs. SSA/P

Interobserver Reproducibility			
Category	**1st Round**	**2nd Round**	**3rd Round**
TSA	**0.81**	**0.78**	**0.83**
SSA/P	**0.45**	**0.32**	**0.47**
HP	**0.51**	**0.42**	**0.53**
Overall	**0.56**	**0.47**	**0.58**

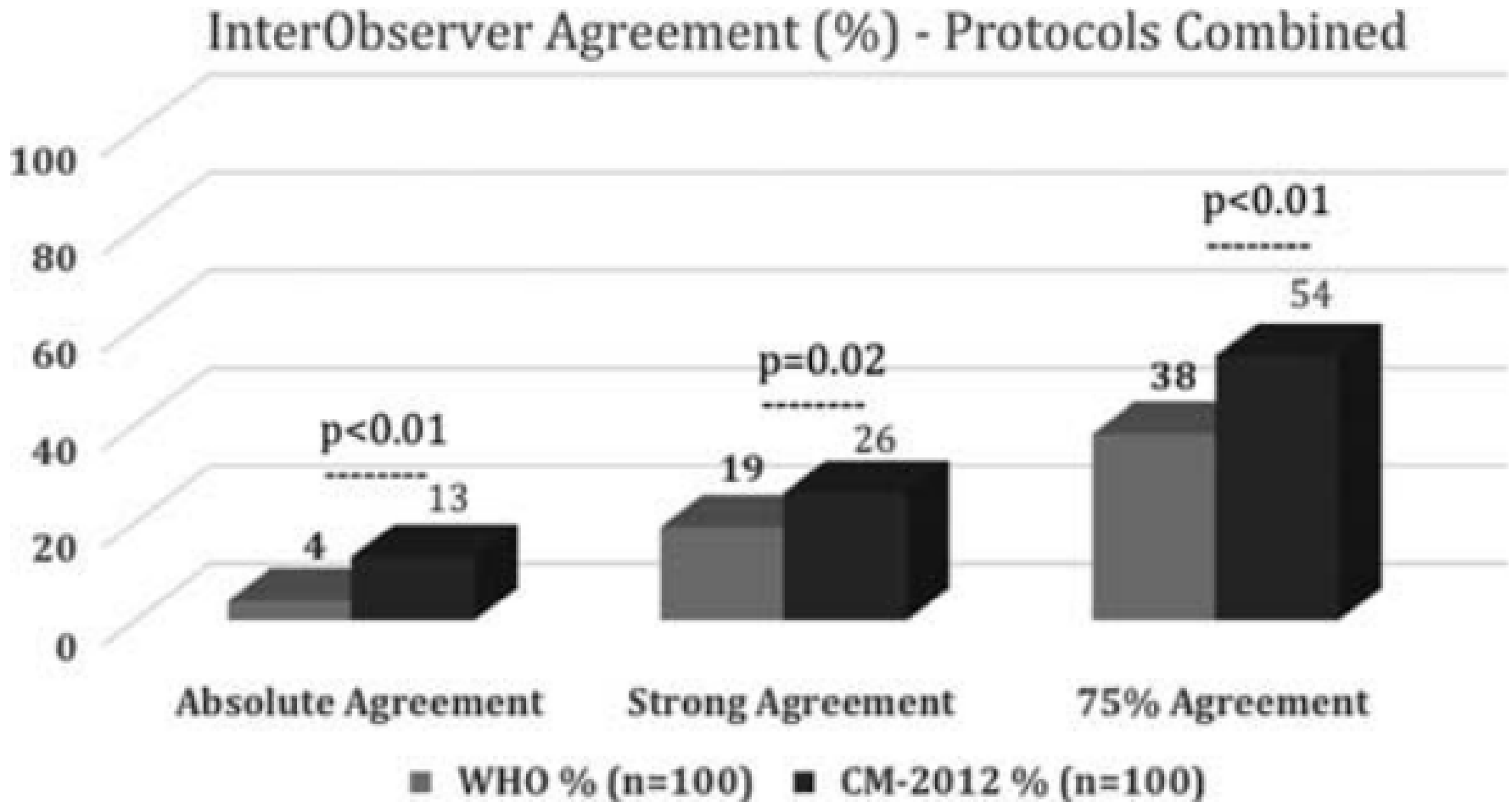
Farris A et al, Am J Surg Pathol 2007

Reproducibility of diagnosis of serrated polyps

Reference	Cases (n)	# Observers	Kappa (overall)
Farris et al 2007	185	5	0.56
Bustamente-Balenet et al 2009	195	2	0.14
Wong et al 2009	60	4	0.38
Khalid et al 2009	40	3	0.16
Gunia et al 2011	19	3	0.29-0.65
Ensari et al 2012	70	20	0.57

“Single unequivocal architecturally distorted, dilated, and/or horizontally branched crypt’ criteria for SSP is better but not enough

100 polyps; 21 pathologists



Kolb JM, J Clin Gastro 2016

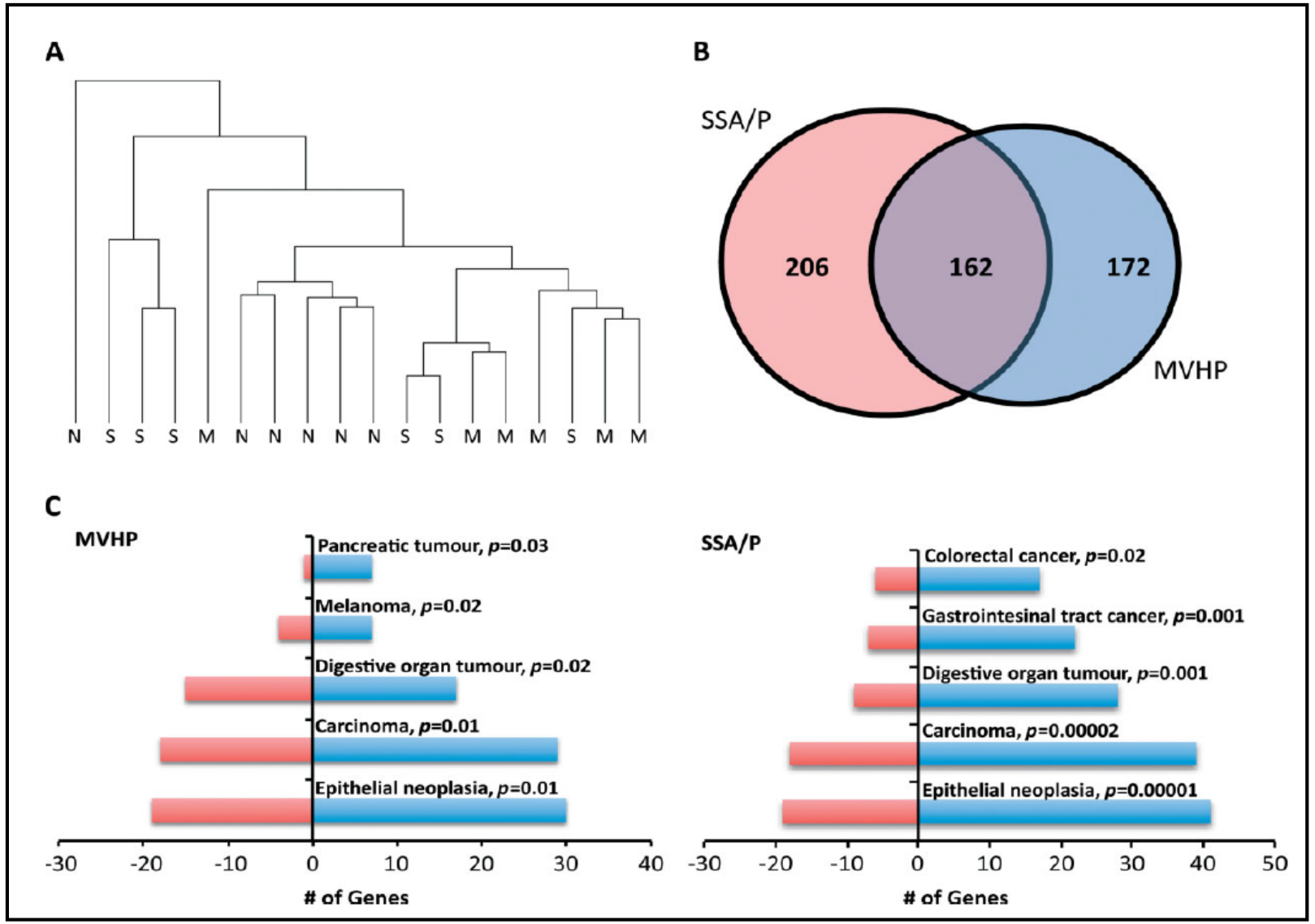
Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: The molecular profile of HP and SSA/P is:

Gene expression profiling of serrated polyps identifies annexin A10 as a marker of a sessile serrated adenoma/polyp

Gonzalo DH et al, J Pathol 2013; 230: 420–429

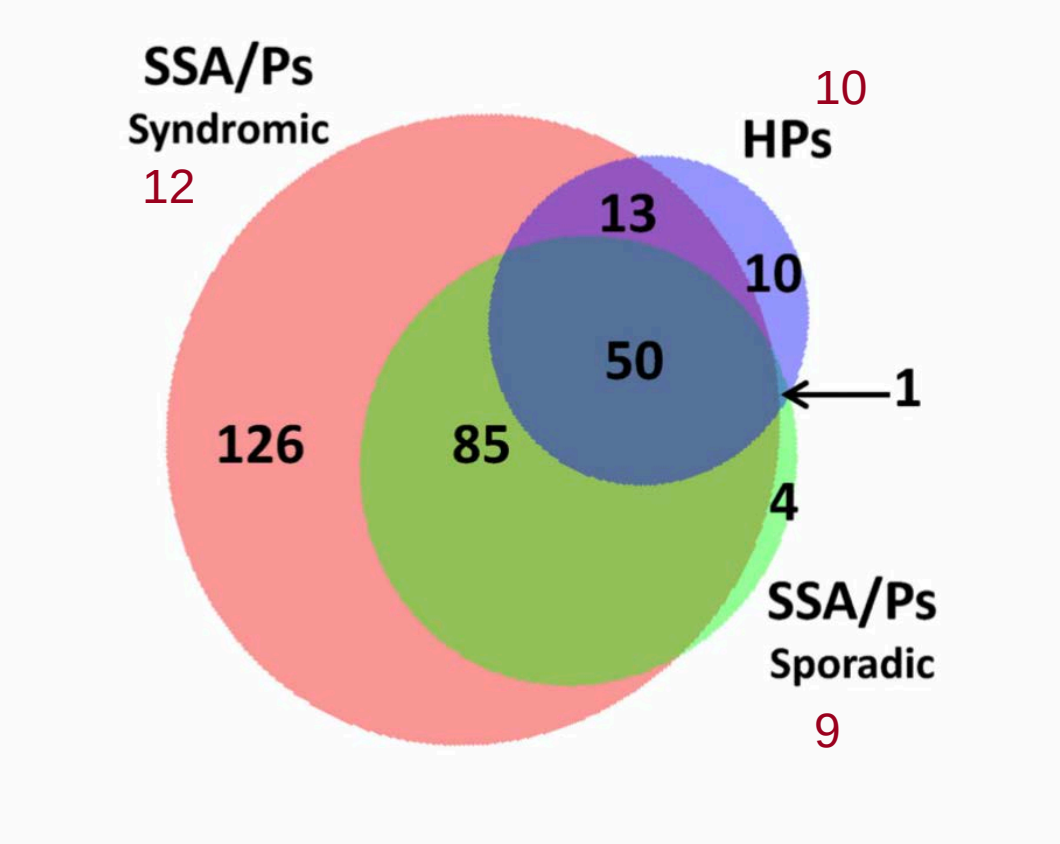


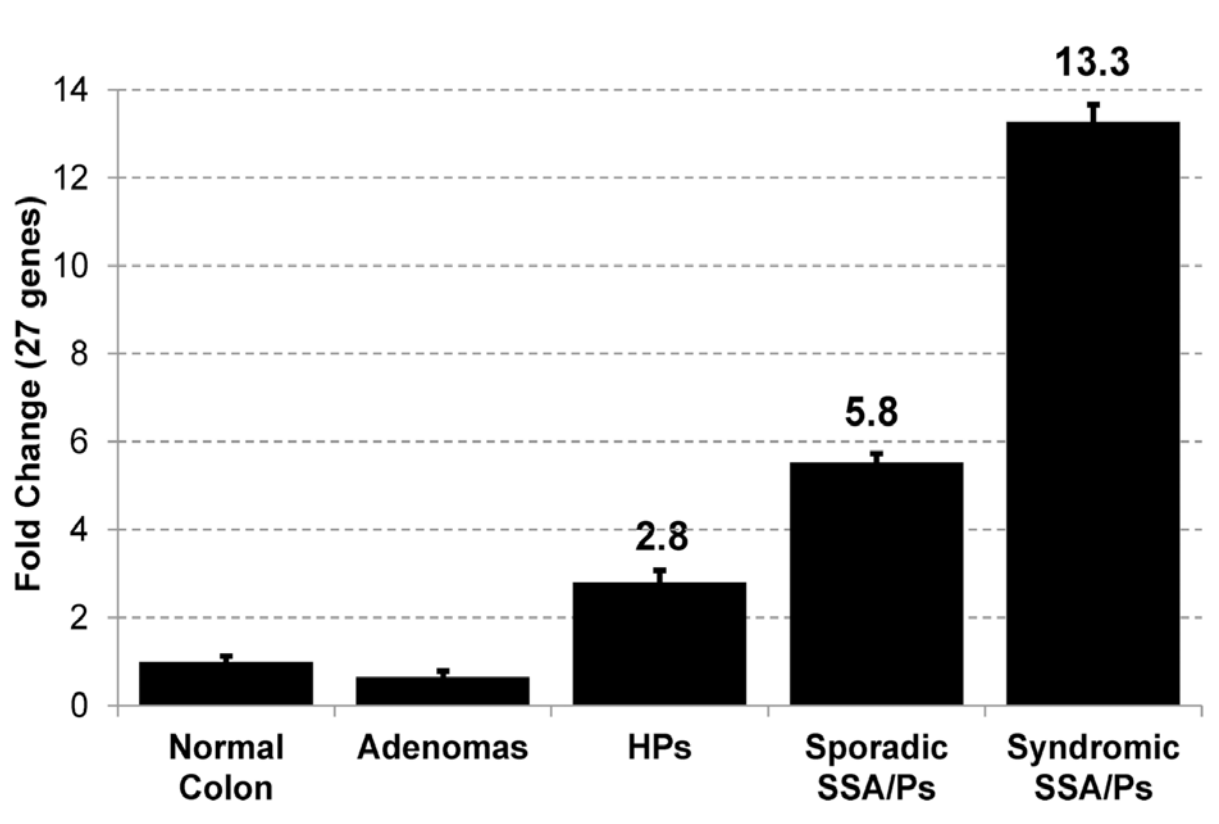
Distal MVHP <9mm (n=6)
Proximal SSP >9mm (n=6)
Normal (n=6)

Gene signature in SSP identifies colon cancer subtype

Kanth P et al, Cancer Prev Res (Phila) 2016

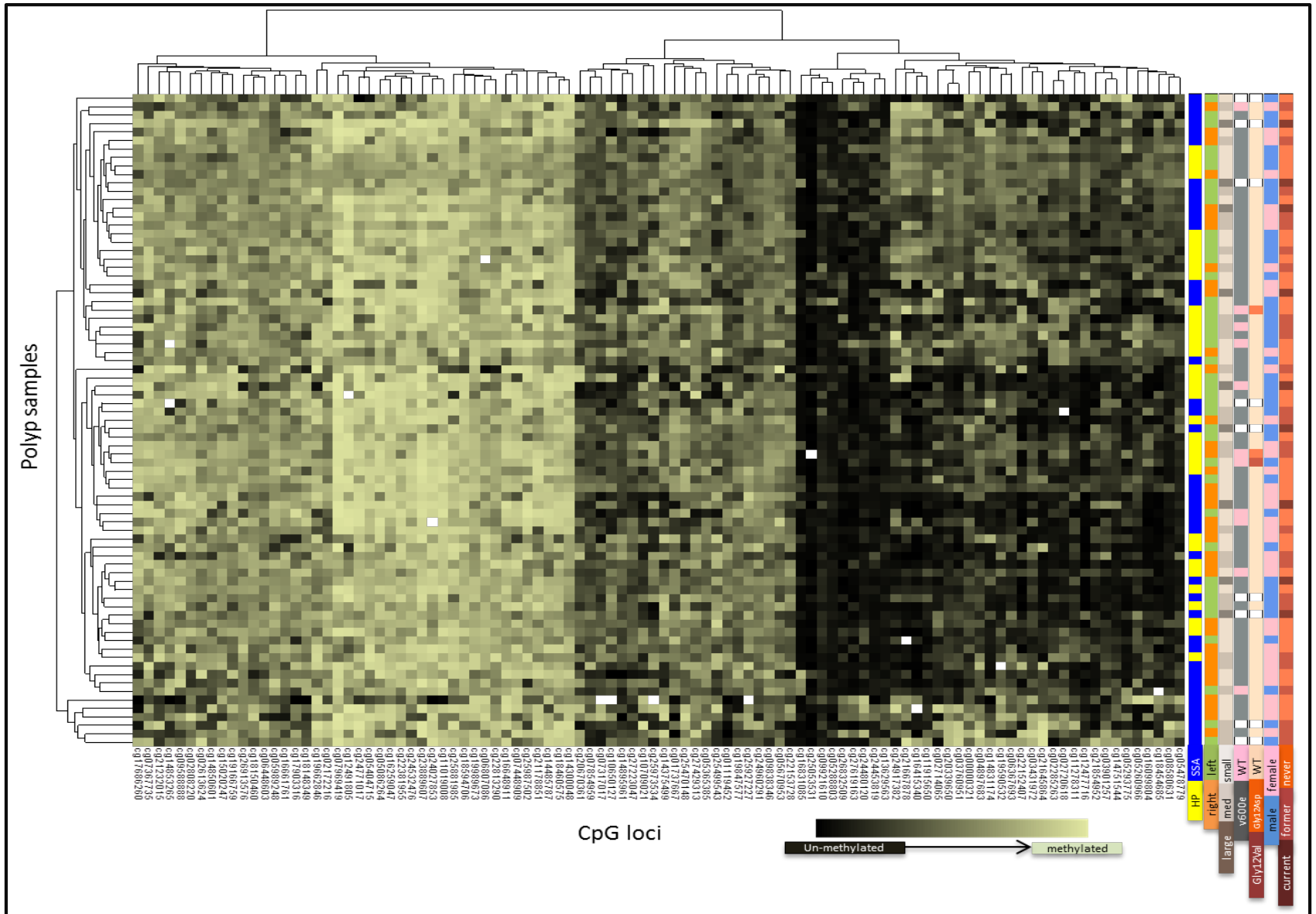
86% of the differentially expressed genes in HPs overlapped with SSA/Ps





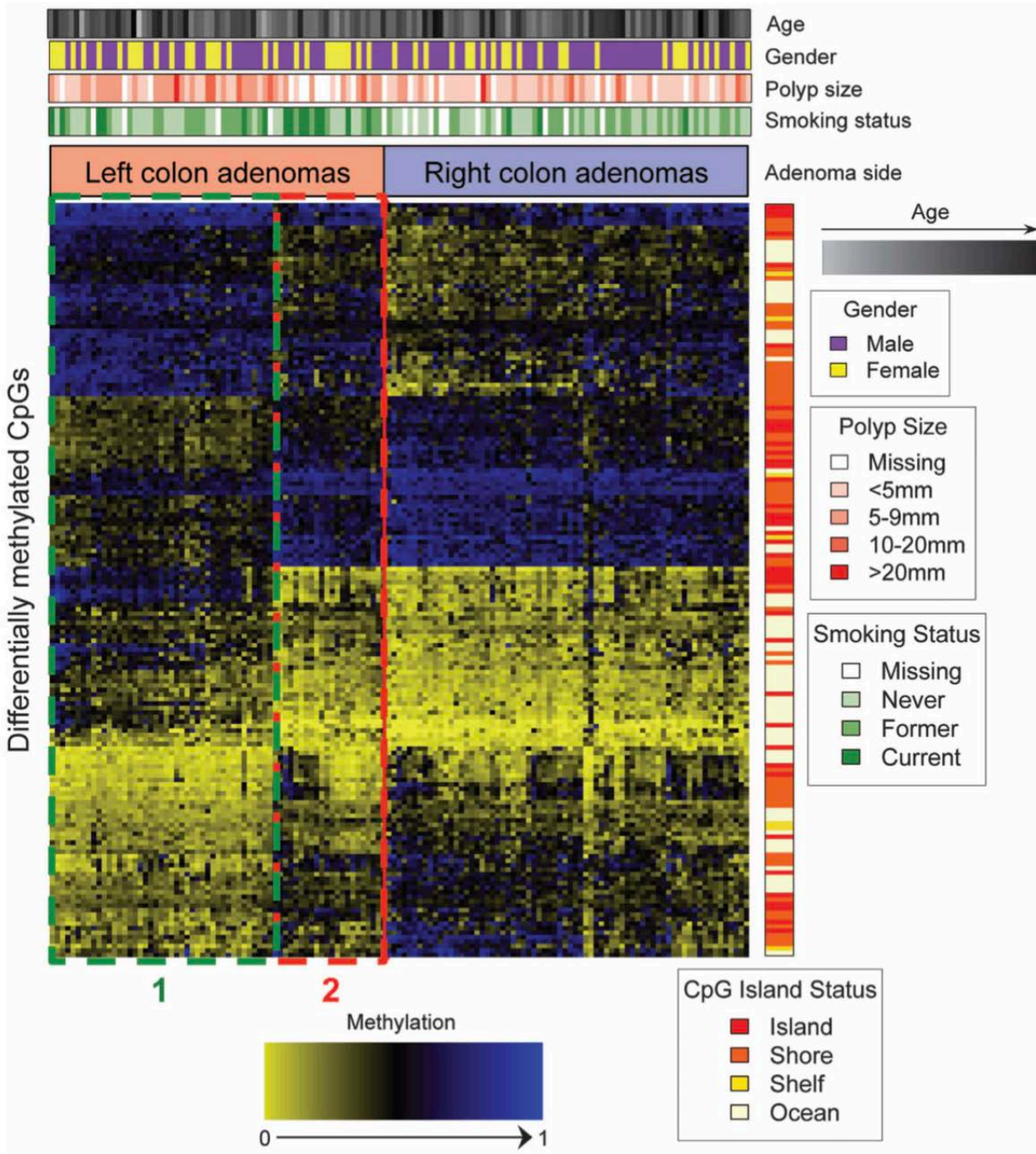
"This suggests that the molecular phenotype in HPs (considered at little or no risk for progression to colon cancer) is surprisingly similar to that of SSA/Ps (considered high risk)"

Overlapping methylation profiles of HP and SSA/P: 100 most differentially methylated CIMP probes (n=96; 48 right/48 left colon; 24 each)



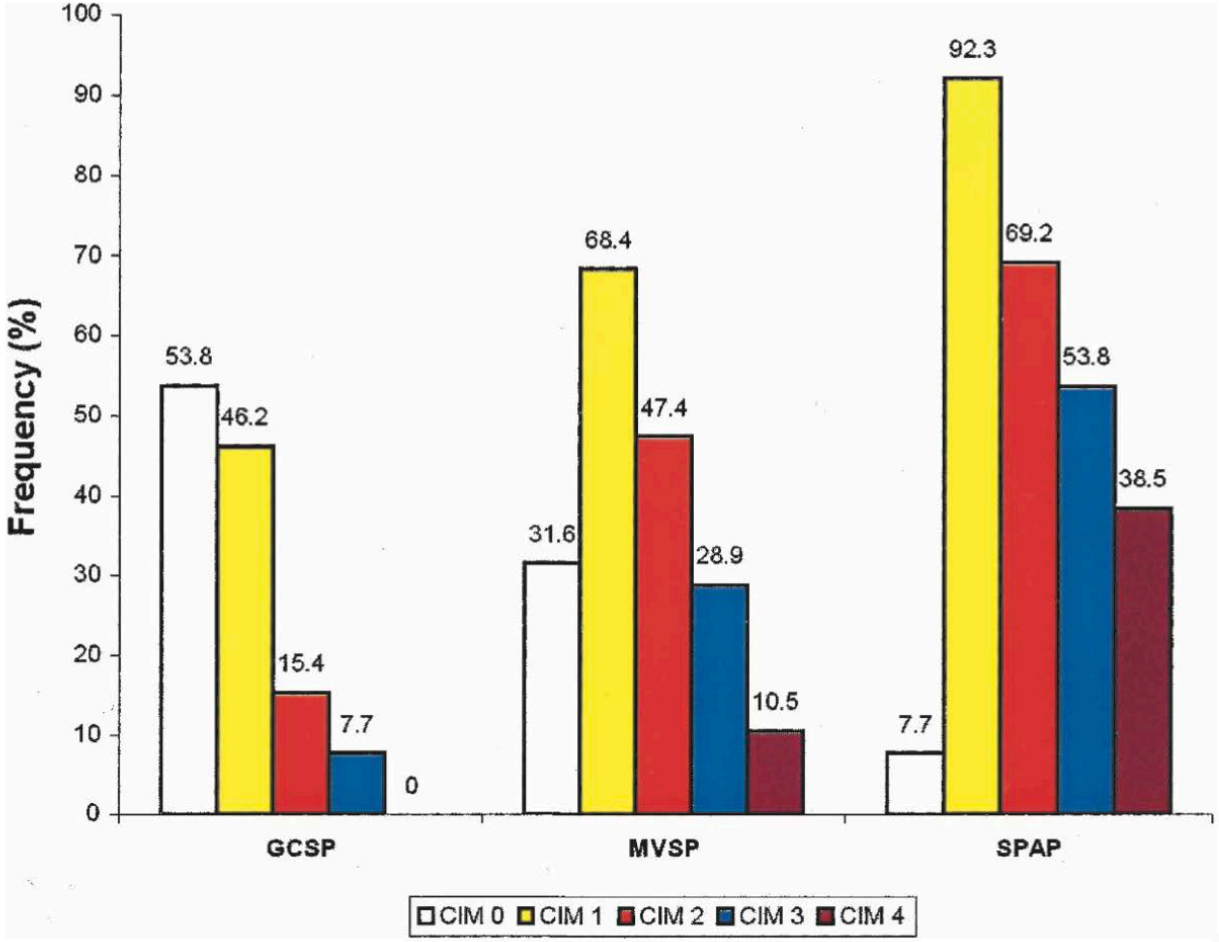
Methylation in conventional adenomas involves non-CIMP genes and shows distinct signature in right and left colon adenomas

Koestler D et al Mod Pathol 2014



Hyperplastic (Serrated) Polyps of the Colorectum

Relationship of CpG Island Methylator Phenotype and K-ras Mutation to Location and Histologic Subtype

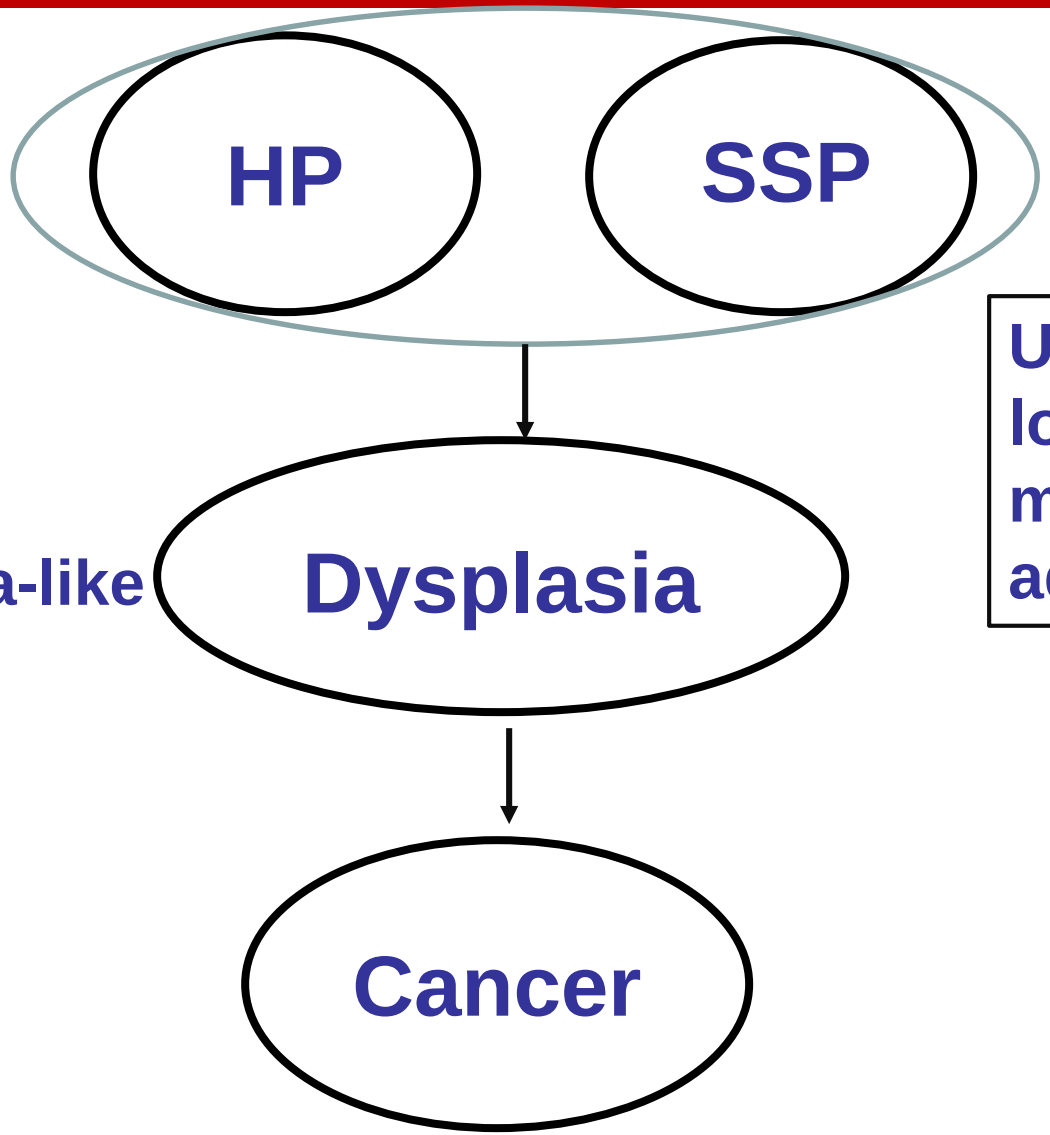


"We postulate that MVSP and GCSP may be precursor lesions that, if proximally located or larger, can progress to SPAP"

O'Brien MJ et al Am J Surg Pathol 2004

Serrated Precursors of Colorectal Cancer

Harvey's reservoir!



- TSA-like
- Conventional adenoma-like
- MLH1/p53

Use size, number and location to stratify metachronous risk of advanced outcomes

Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy

Hazewinkel Y et al, Endoscopy 2013

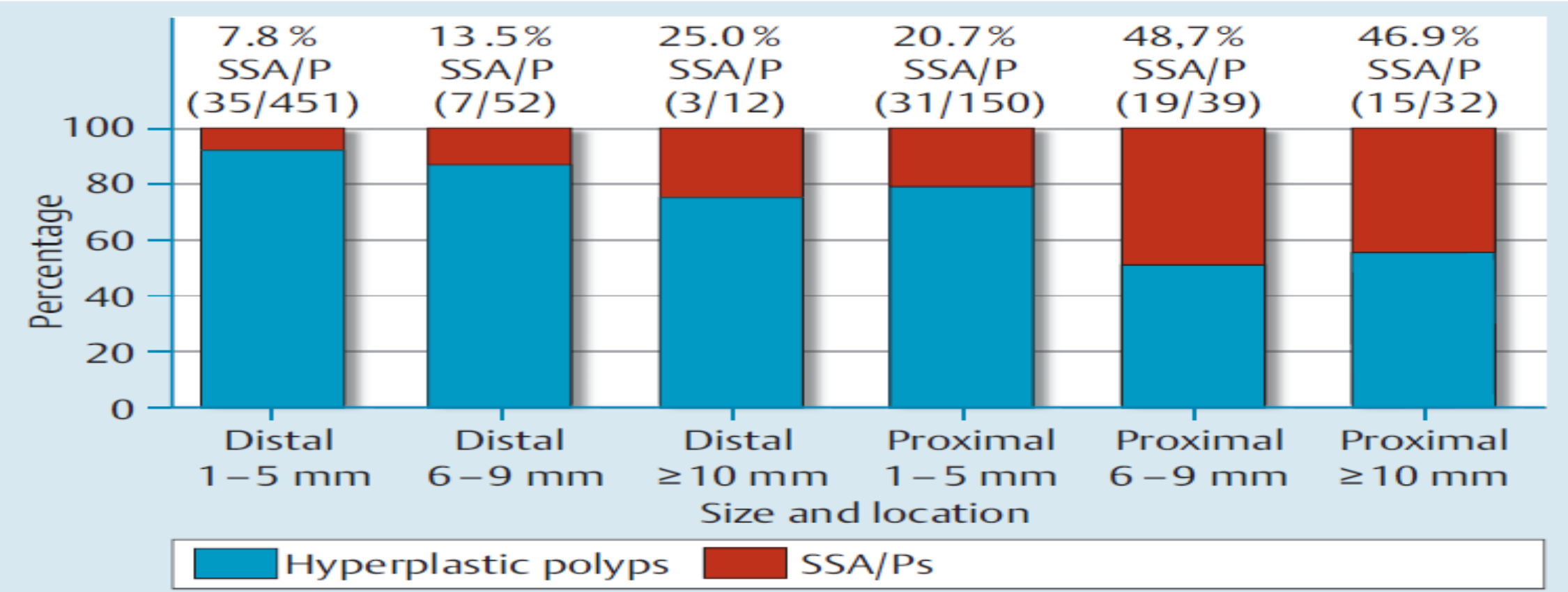


Fig. 1 Ratio between hyperplastic polyps and sessile serrated adenoma/polyp (SSA/P) histology stratified per size group and colonic location.

Likelihood of SSA/P diagnosis (n=50,156)

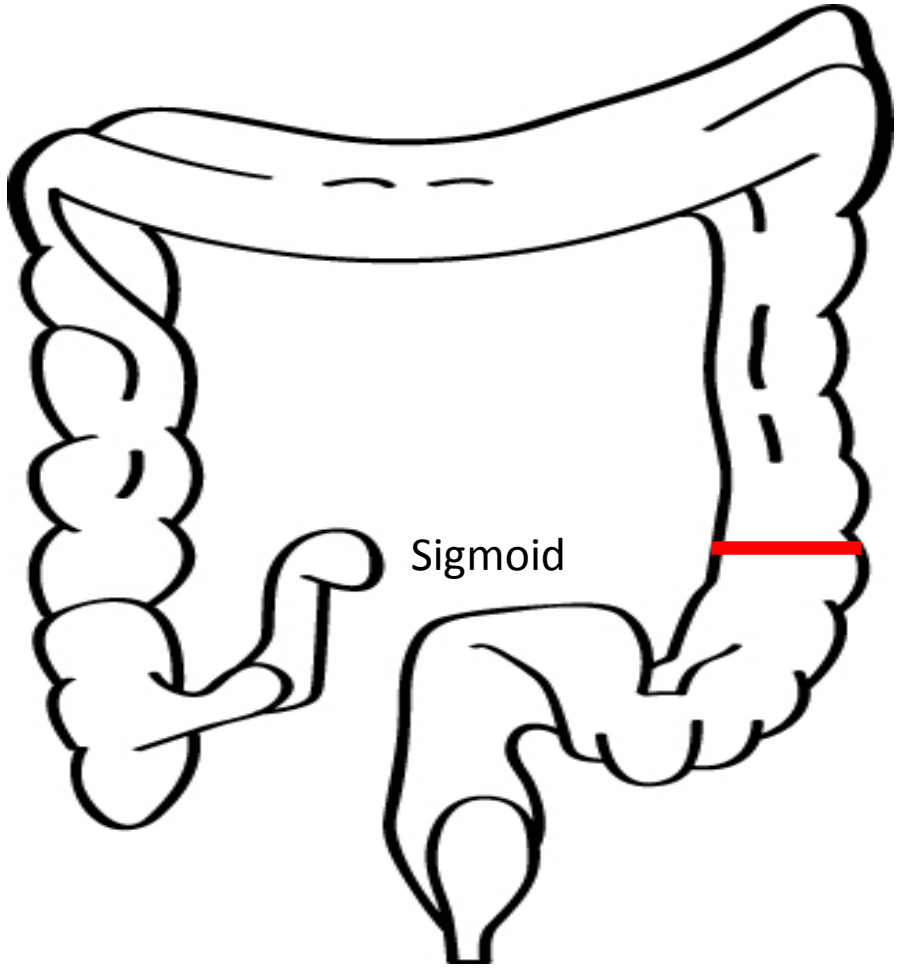
Range of diagnosis per center: 1.5-18.5%

		OR	95% CI	p
Time period tertile	1 (2004-11)	1.0	---	---
	2 (2012-14)	4.01	3.50 - 4.59	0.0001
	3 (2015-18)	8.65	7.58 - 9.86	0.0001
Size of serrated polyp	<5 mm	1.0	---	---
	5-9 mm	2.92	2.68 - 3.15	0.0001
	≥ 10 mm	8.44	7.49 - 9.51	0.0001
Proximal versus distal		11.88	10.92 - 12.92	0.0001
High versus low volume path center		1.73	1.55 - 1.94	0.0001

Adjusted for age, gender, BMI, family history, smoking

NHCR data 2018

Proximal Serrated Polyp Detection Rate (PSDR)



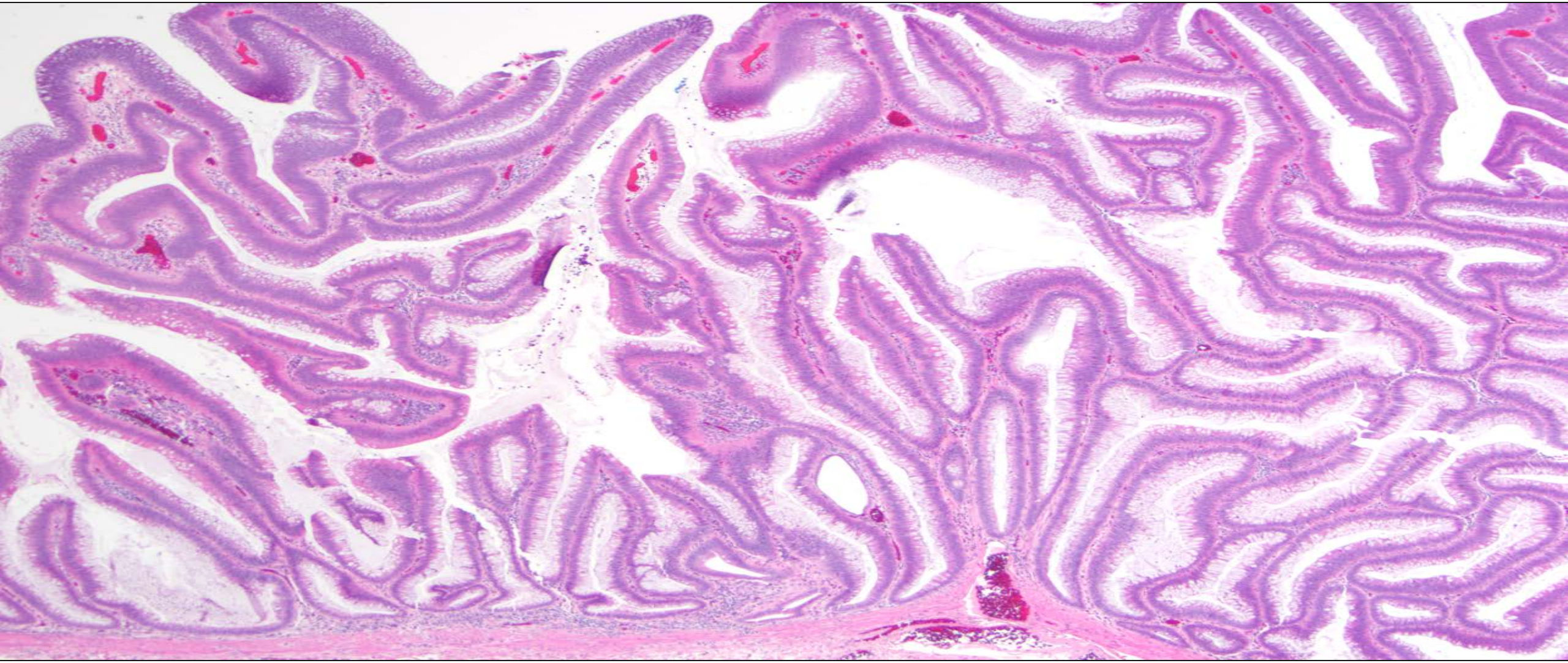
- **Any serrated polyp proximal to the sigmoid regardless of size or histological subtype**
- **Simpler since it only involves anatomy**
- **Correlated with ADR (Anderson J et al Gastrointest Endosc. 2017 Jun;85(6):1188-1194)**

We already use size, number, location to define risk of cancer associated with serrated polyps

WHO Criteria for SPS:

- **> 5 SPs proximal to the sigmoid colon with at least two greater than 1.0cm *(all at least 5mm)***
- **> 20 SPs, any size, distributed throughout colon *(at least 5 proximal to the rectum)***
- ~~**Any HPs proximal to sigmoid colon in a patient with family history of hyperplastic polyposis syndrome**~~

Basal crypt changes are related to endoscopic (sessile) appearance and are prevalent in flat adenomas in the right colon



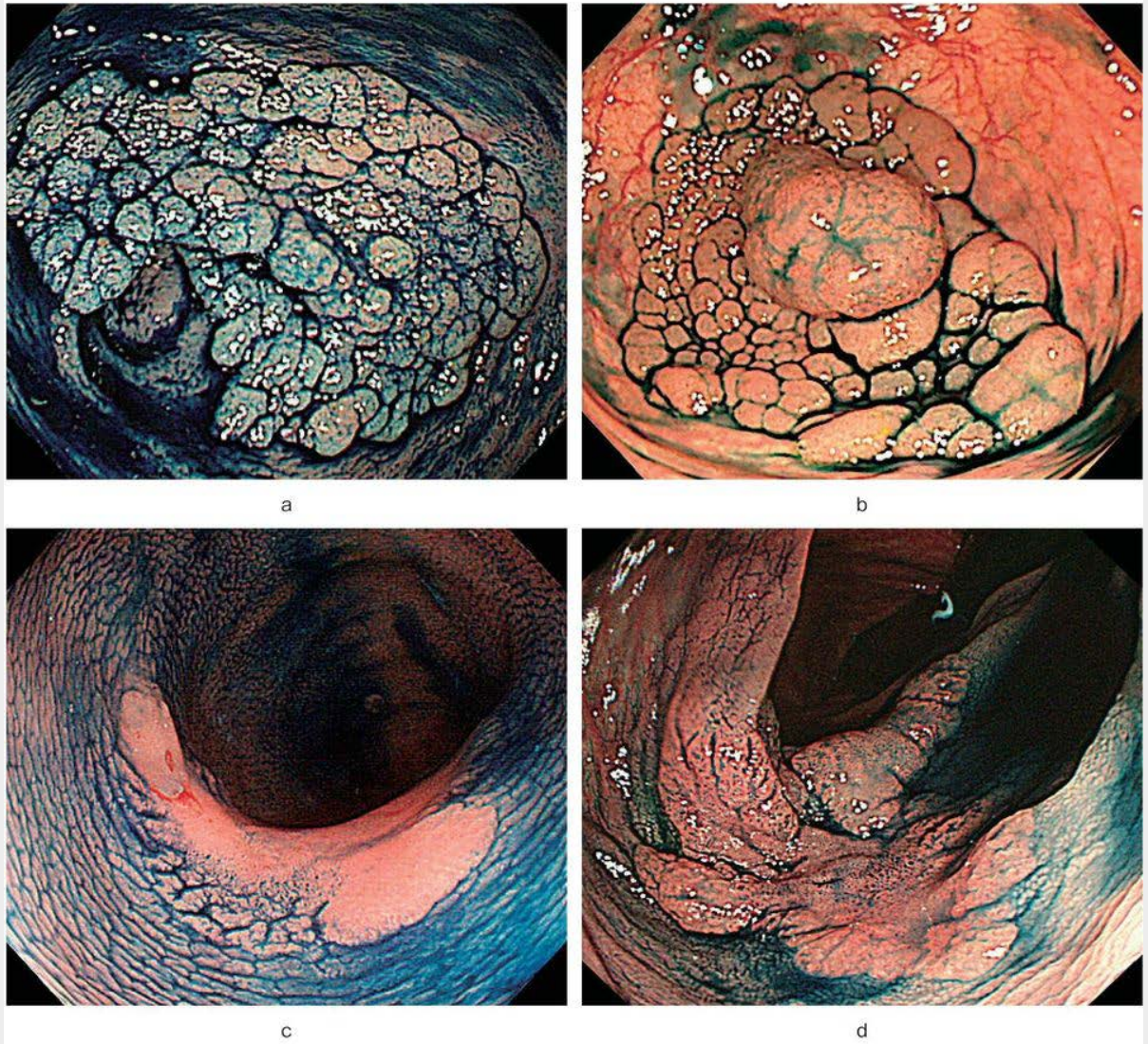
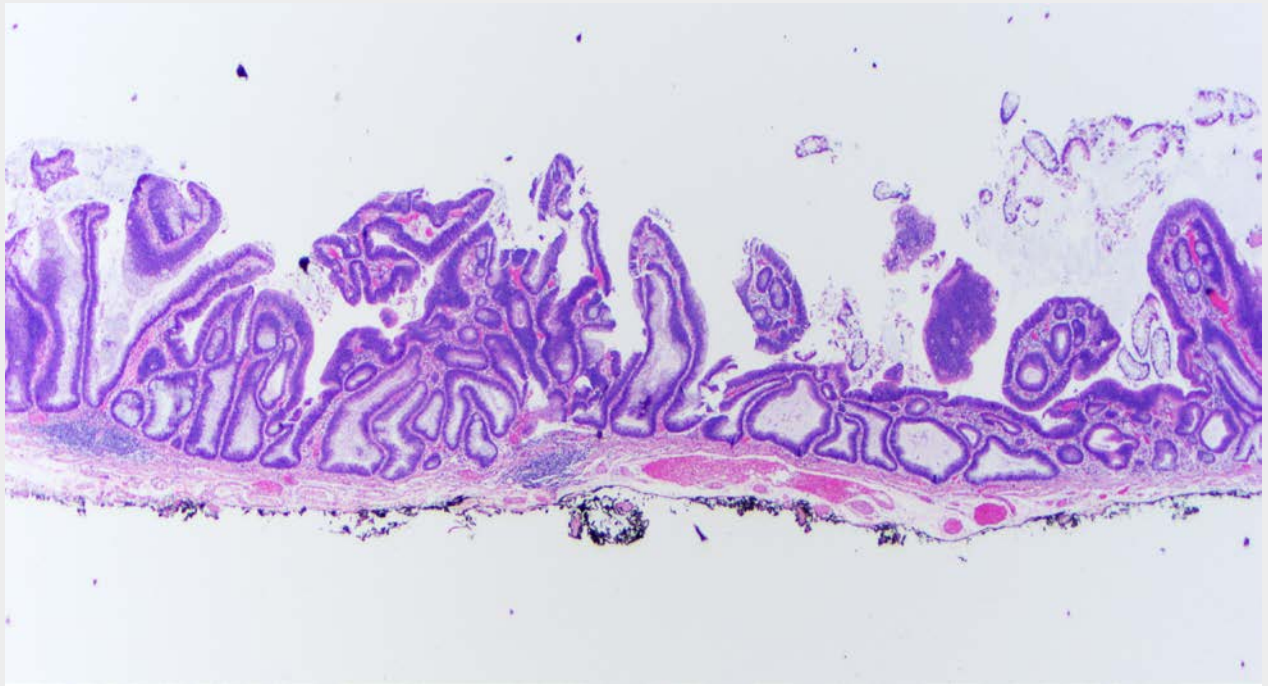
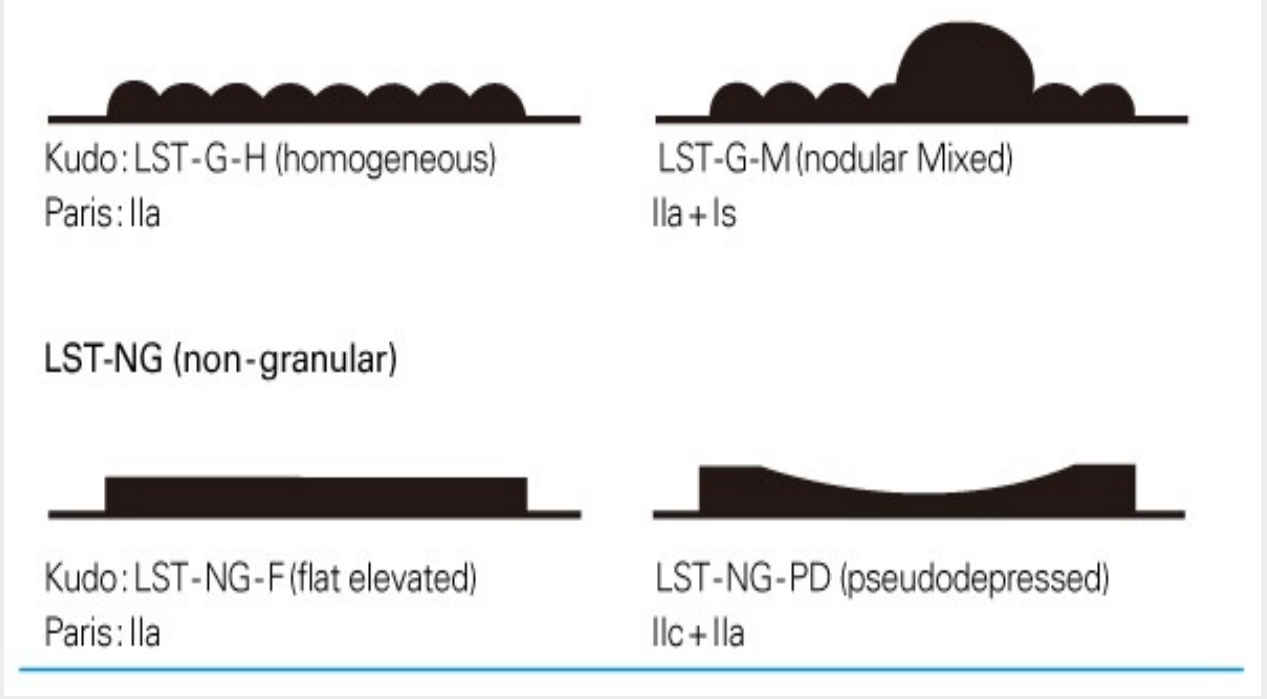


Figure 1 LST の病型亜分類（インジゴカルミン散布像で判定する）.
a：顆粒均一型 homogeneous type；LST-G（Homo）.
b：結節混在型 nodular mixed type；LST-G（Mix）.
c：扁平隆起型 flat-elevated type；LST-NG（F）.
d：偽陥凹型 pseudo-depressed type；LST-NG（PD）.





Long term CRC risk large (≥ 1 cm) serrated polyps similar to conventional adenomas

Group	N	CRC cases	HR ratio (95% CI)	Time to diagnosis (yrs)
Polyp free	10,685	99	1.0 (reference)	7.7
Advanced Adenoma	701	24	3.3 (2.1-5.2)	7.1
Large SP	81	3	4.2 (1.3-12.3)	7.5

Large serrated polyps in 24 adults were only biopsied and CRC developed in only one at another site

Holme et al Gut. 2015 Jun;64(6):929-36

Surveillance for patients with serrated polyps

Live Content Slide

When playing as a slideshow, this slide will display live content

Poll: The increased risk of cancer in patients with serrated polyps is related to :

Proximal and Large Hyperplastic and Nondysplastic Serrated Polyps Detected by Colonoscopy Are Associated With Neoplasia

Schreiner M et al, Gastroenterology 2010;139:1497–1502

Prevalence of Advanced Adenoma or Multiple Tubular Adenomas in Patients With and Without Proximal or Large Non-dysplastic Serrated Polyps

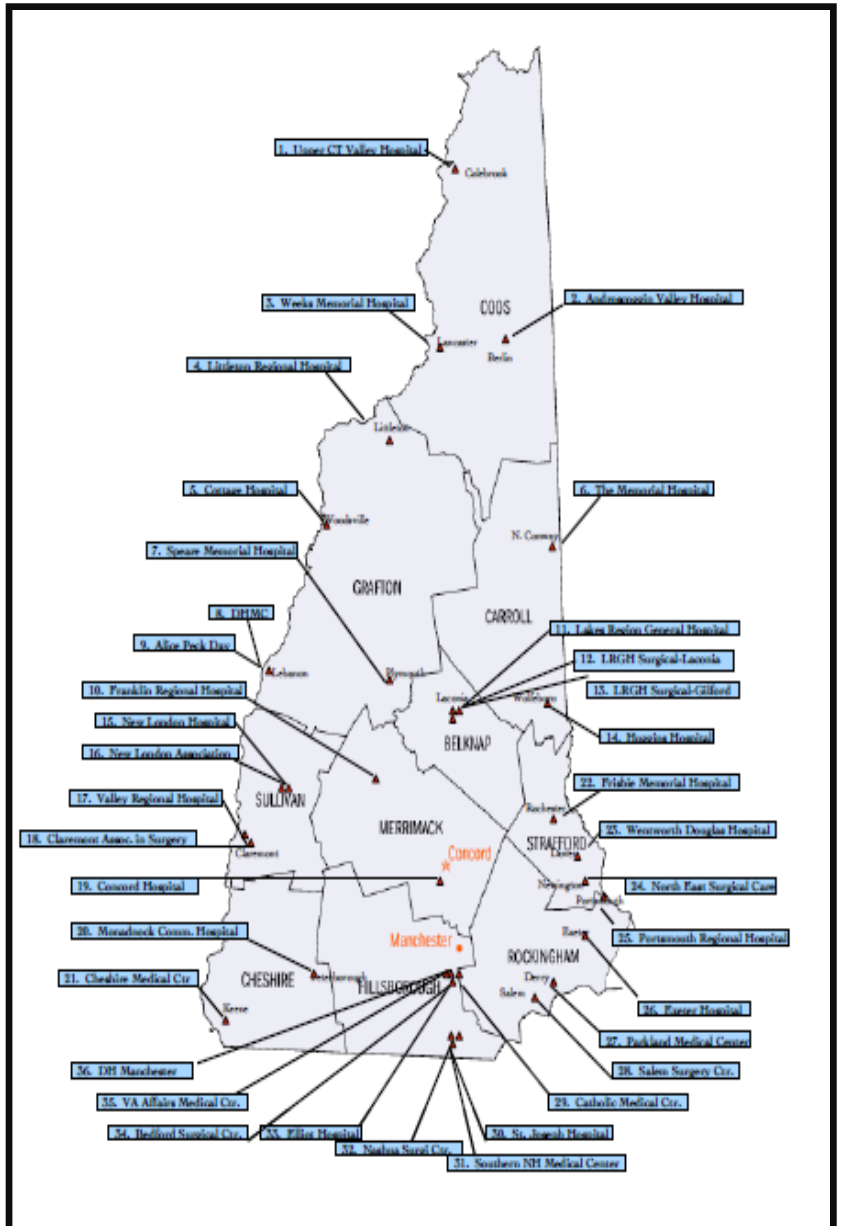
Baseline	Advanced adenoma	≥ 3 Tubular adenomas
Proximal ND-SP (n = 248), %	17.3	10.7
No Proximal ND-SP (n = 2873), %	10.0	5.3
OR (95% CI)	1.90 (1.33-2.70)	2.19 (1.36-3.52)
Large ND-SP (n = 44), %	27.3	9.4
No Large ND-SP (n = 3077), %	10.3	5.6
OR (95% CI)	3.37 (1.71-6.65)	1.72 (0.52-5.73)

Prevalence of serrated polyps and association with synchronous advanced neoplasia in screening colonoscopy

Hazewinkel Y et al, Endoscopy 2013

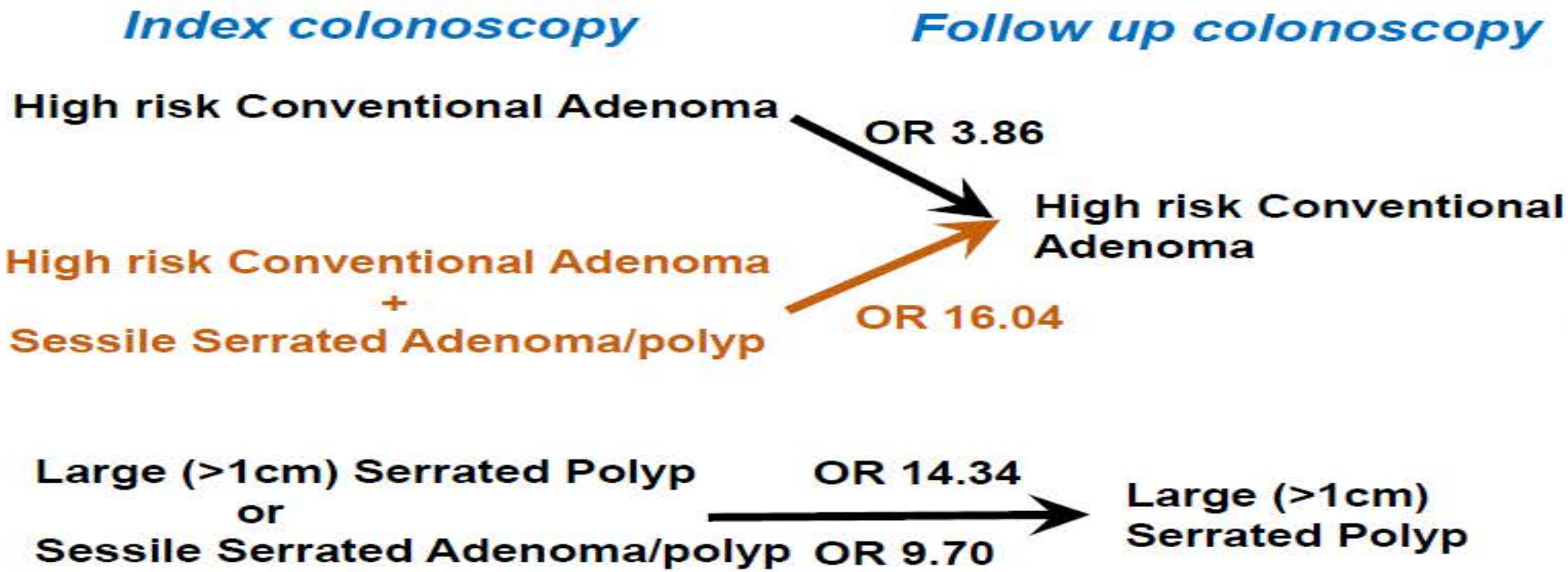
Individuals with at least one:	n	Individuals with advanced neoplasia, n (%)	Adjusted OR [95%CI]	*P*
Proximal serrated polyp				
No	1254	99 (7.9)	1.00	
Yes	174	31 (17.8)	2.44 [1.55-3.84]	<0.001
Proximal hyperplastic polyp				
No	1299	110 (8.5)	1.00	
Yes	123	20 (16.3)	1.95 [1.13-3.36]	0.02
Proximal SSA/P				
No	1375	119 (8.7)	1.00	
Yes	51	11 (21.6)	3.04 [1.50-6.15]	0.002
Large serrated polyp (≥10mm)				
No	1389	120 (8.6)	1.00	
Yes	37	10 (27.0)	4.02 [1.87-8.62]	<0.001
Large hyperplastic polyp (≥10mm)				
No	1405	125 (8.9)	1.00	
Yes	21	5 (23.8)	3.18 [1.11-9.07]	0.03
Large sessile SSA/P (≥10mm)				
No	1410	125 (8.9)	1.00	
Yes	16	5 (31.3)	5.02 [1.69-14.86]	0.0004

New Hampshire Colonoscopy Registry



- >30 participating sites
- >100 endoscopists
- 130,000 patients enrolled
- 150,000 colonoscopies
- 12000 patients with 10 year follow up
- 4700 with baseline serrated polyps
- 500 with large (>1cm) serrated polyps
- Projected enrollment 230,000 by 2020

Metachronous Polyps in patients with index serrated polyps



Anderson J et al, Gastroenterology 2018

Longitudinal outcome analysis: patients with right sided “HP” diagnosed prior to 2003 (n=655)

Variable	*OR	95% Confidence Interval	p value
Risk of conventional advanced adenomas/cancer			
Age at index colonoscopy	1.05	1.02-1.07	0.001
Advanced adenoma on index colonoscopy	1.83	1.02-3.28	0.04
Large or proximal HP on index colonoscopy	0.63	0.37-1.07	0.09
Time to surveillance colonoscopy (months)	1.07	1.00-1.02	0.21
Risk of large serrated polyps			
Age at index colonoscopy	1.0	0.96-1.04	0.97
Advanced adenoma on index colonoscopy	0.33	0.07-1.59	0.17
Large or proximal HP on index colonoscopy	2.93	1.09-7.86	0.03
Time to surveillance colonoscopy (months)	0.98	0.96-1.00	0.06

Hagen C. et al, (Unpublished data)

Cancer in Serrated Polyposis Syndrome

- Presence of at least one conventional adenoma associated with cancer (p=0.003)
- Non-significant trend between polyp count and CRC (p=0.06)
- No association with:
  - Age, gender
  - Polyp size, distributions
  - SSA/P or villous component

Rosty C. et al, Am J Surg Pathol. 2012 Jun;36(6):876-82.

BSG/PHE/ACPGBI Guidelines for Post-polypectomy and Post-cancer-resection Surveillance

Baseline colonoscopy

fulfilling all of: caecal intubation, adequate bowel prep and clearance of all premalignant polyps (consider site-check for 10-19mm NPCPs without histological confirmation of complete excision)

≥2 premalignant polyps including ≥1 advanced colorectal polyp

OR

≥ 5 premalignant polyps

Premalignant polyps

- Serrated polyps (excluding diminutive 1-5mm rectal HP) and adenomatous polyps

Advanced colorectal polyps

- Serrated polyps ≥ 10mm, serrated polyps with dysplasia, adenoma ≥ 10mm, adenoma with high-grade dysplasia

≥10mm, adenoma with high-grade dysplasia
(L)NPCP: (Large; ≥20mm) non-pedunculated colorectal polyp

Serrated Polyposis Syndrome:
- ≥5 serrated polyps ≥5mm prox to rectum, with ≥2 of ≥10mm; or
- ≥20 serrated polyps (any size) including ≥5 prox to rectum

Rutter et al., Gut 2020

Genotype of interval and non-interval CRC similar once matched for location

Soong TR et al, Mod Pathol 2018

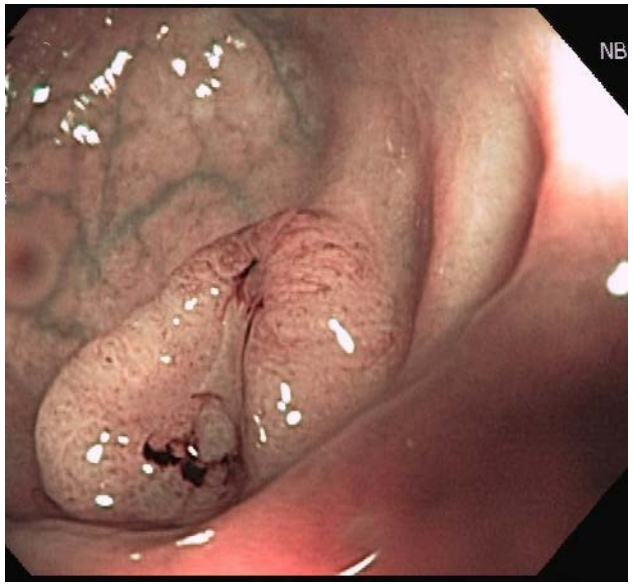
Table 4 Genetic alterations in interval and non-interval tumors involving the five major pathogenetic pathway in colorectal cancer (CRC)

Signaling pathway (genes[a])	Interval colon cancer $N = 20$ n (%)	Matched non-interval colon cancer[b] $N = 40$ n (%)	P (matched comparison)
Wnt *(APC, CTNNB1, TCF7L2, TCF7L1, FBXW7, ARID1A, SOX9)*	18 (90)	37 (93)	0.73
P53 *(ATM, TP53, CDKN1A, CDKN2A)*	16 (80)	38 (95)	0.81
RTK/RAS *(EGFR, ERBB2, NRAS, KRAS, BRAF)*	14 (70)	35 (88)	0.13
PI3K *(IGF1R, PIK3CA, PIK3C2B, PTEN, PIK3R1, AKT1, PRKDC, MET)*	17 (85)	30 (75)	0.38
TGF beta *(SMAD2, SMAD4, MYC, MECOM)*	13 (65)	20 (50)	0.26

Modeling data on interval cancers: 52% due to missed lesions; 19% due to incompletely excised lesions; 24% possible new lesions (Robertson DJ et al, Gut 2014)

Incomplete Polyp Resection During Colonoscopy—Results of the Complete Adenoma Resection (CARE) Study

Pohl H et al, Gastroenterology 2013;144:74-80



Incomplete Resection Rates:

- 10.1% overall (95% CI: 6.9-13.3%)
- Large (17.3%) more than small (6.8%) polyps
- SSA/P (31.0%) more than other (7.2%) polyps
- Nearly half (47.6%) of SSA/P between 10-20 mm size

Summary

- Serrated polyp size, location and number best guide for developing optimal surveillance guidelines
- Short term risk of cancer is very low, even in patients with large, proximal serrated polyps
- Patients with concurrent HRA and proximal/large serrated polyps are the highest risk group that will benefit from close surveillance
- Low risk of malignant transformation does not imply HP is not a precursor of CRC

Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer (Gastroenterology 2020)

Table 4. US Multi-Society Task Force Recommendations for Post-Colonoscopy Follow-Up in Average-Risk Adults With Normal Colonoscopy or Adenomas[a]

Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
Normal	10 y[b]	Strong	High
1–2 tubular adenomas <10 mm	7–10 y[c]	Strong	Moderate
3–4 tubular adenomas <10 mm	3–5 y	Weak	Very low
5–10 tubular adenomas <10 mm	3 y	Strong	Moderate
Adenoma ≥10 mm	3 y	Strong	High
Adenoma with tubulovillous or villous histology	3 y[d]	Strong	Moderate
Adenoma with high-grade dysplasia	3 y[d]	Strong	Moderate
>10 adenomas on single examination[e]	1 y	Weak	Very low
Piecemeal resection of adenoma ≥20 mm	6 mo	Strong	Moderate[f]

Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer (Gastroenterology 2020)

Table 5. US Multi-Society Task Force Recommendations for Post-Colonoscopy Follow-Up in Average-Risk Adults With Serrated Polyps[a]

Baseline colonoscopy finding	Recommended interval for surveillance colonoscopy	Strength of recommendation	Quality of evidence
≤20 HPs in rectum or sigmoid colon <10 mm[f]	10 y[b]	Strong	Moderate
≤20 HPs proximal to sigmoid colon <10 mm[f]	10 y	Weak	Very low
1–2 SSPs <10 mm	5–10 y	Weak	Very low
3–4 SSPs <10 mm	3–5 y	Weak	Very low
5–10 SSPs <10 mm	3 y	Weak	Very low
SSP ≥10 mm	3 y	Weak	Very low
SSP with dysplasia[e]	3 y	Weak	Very low
HP ≥10 mm	3–5 y[c]	Weak	Very low
TSA	3 y	Weak	Very low
Piecemeal resection of SSP ≥20 mm	6 mo	Strong	Moderate[d]

The Frontiers of Serrated Polyps

PRESENTED BY

Amitabh Srivastava, MD