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Polyposis Syndromes: Recognition & Action

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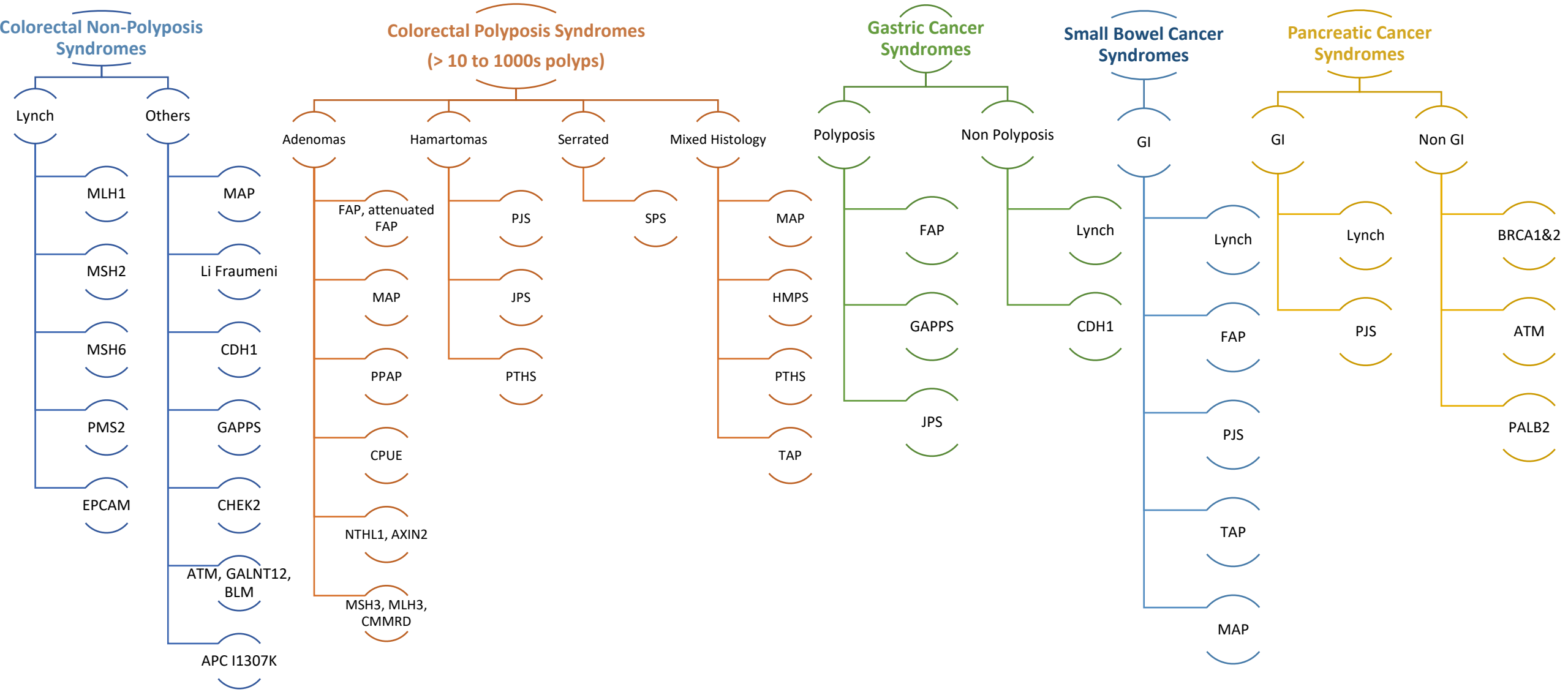
Disclosures

Olympus America (research support)

@SwatiPateIMD



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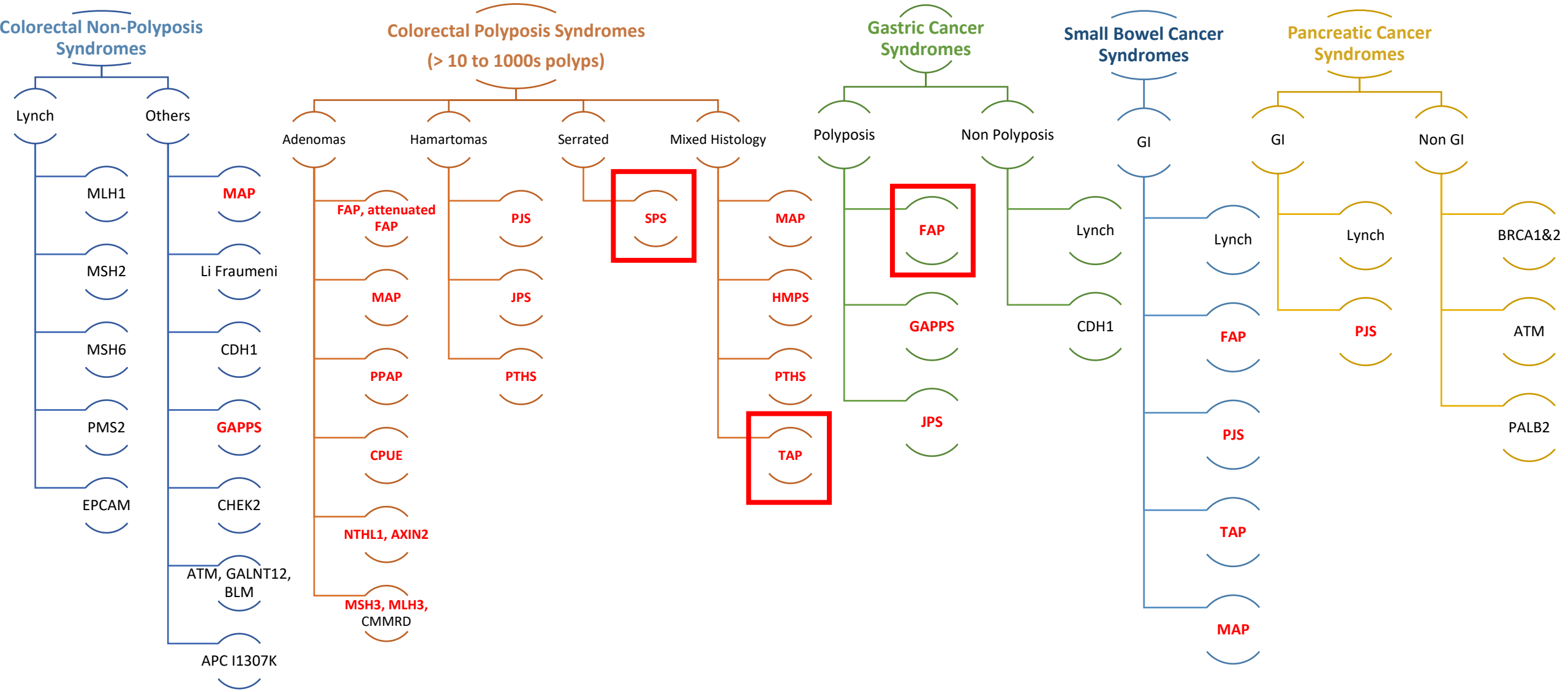

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Agenda

I. Serrated Polyposis Syndrome

II. Gastric Cancer in Familial Adenomatous Polyposis

Agenda

I. **Serrated Polyposis Syndrome**

II. Gastric Cancer in Familial Adenomatous Polyposis

2019 WHO Criteria

I. ≥5 serrated lesions proximal to the rectum, all ≥ 5mm, two or more ≥10 mm

II. ≥ 20 serrated lesions throughout the colon, at least 5 proximal to the rectum

2010 WHO Criteria

I. ≥5 serrated lesions proximal to the sigmoid, two or more ≥10 mm

~~II. Any serrated polyp proximal to sigmoid in FDR of SPS patient~~

III. ≥ 20 serrated lesions throughout the colon

Crockett & Nagtegaal. Gastroenterology 2019;157:949-66.
World Health Organization. Histopathology 2020; 76: 182-88.
IJspeert et al. Gut 2017;66(7):1225-32.

Risk Factors & Etiology

- Smoking paradox
  - 48-86.8% of SPS patients current/former smokers
  - Current smokers OR 0.35 (0.14-0.88) CRC
- Genetics
  - *RNF43* (1.76%)
  - Mixed histology—MUTYH Associated Polyposis
- Therapy Associated Polyposis

Table 2. Association between smoking, adenoma, sex, age and CRC in patients presenting with multiple serrated polyps.

	Univariate		Multivariate*	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
Cigarette smoking				
Never	1.00 (Referent)		1.00 (Referent)	
Former	1.28 (0.57 to 2.87)	0.550	0.71 (0.29 to 1.77)	0.463
Current	0.35 (0.15 to 0.82)	0.015	0.35 (0.14 to 0.88)	0.026
Never	1.00 (Referent)		1.00 (Referent)	
Ever#	0.67 (0.34 to 1.32)	0.247	0.50 (0.24 to 1.07)	0.075
Adenoma				
No	1.00 (Referent)		1.00 (Referent)	
Yes	4.52 (1.47 to 13.97)	0.009	4.09 (1.27 to 13.14)	0.018
Sex				
Female	1.00 (Referent)		1.00 (Referent)	
Male	1.49 (0.76 to 2.90)	0.247	1.57 (0.73 to 3.36)	0.245
Age (year)	1.03 (1.00 to 1.05)	0.033	1.01 (0.98 to 1.04)	0.510

*adjusted for other variables in the table.
#both former or current smokers.
doi:10.1371/journal.pone.0011636.t002

Carballal et al. Gut 2016;65:1829-37.
Muller at al. Clin Gastroenterol & Hepatol 2022;20:622-630.

Risk Factors & Etiology

- Smoking paradox
  - 48-86.8% of SPS patients current/former smokers
- C
  - Mixed histology—MUTYH Associated Polyposis
- Therapy Associated Polyposis

"Genetic testing may be favored based on patient preference, family history of CRC, or presence of features (such as adenomas) that could overlap with other hereditary CRC syndromes."

NCCN 2024

Table 1 Clinical and molecular characteristics of the reported *RNF43* mutation carriers

Family	*RNF43* mutation (NM_017763)	Polyps/cancer (age at diagnosis)	Cosegregation with the disease in the family	Somatic second hit
Fam-1 Gala *et al*[4]	c.338C>A (p.R113*)	>30 SSA (51)	n.a.	n.a.
			siblings polyps)	n.a.
				n.a.
				n.a.
				†Yes 100%
	c.953–1G>A (p.E318fs)	Normal colonoscopy (44) No possibility of colonoscopy (age 44 to 60)		
Fam-5 Buchanan *et al*[6]	c.640C>G (p.L214V)	>100 SP (18)	n.a.	n.a.
Fam-6 Buchanan *et al*[6]	c.443C>G (p.A148G)	34 SP (57)	n.a.	n.a.
Fam-7 Current study	c.394C>T (p.R132*)	CRC (55) >40 polyps (serrated)	Inconclusive	‡Yes

Buchanan et al. PLOSOne 2010; https://doi.org/10.1371/journal.pone.0011636.
NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

Risk Factors & Etiology

- Smoking paradox
  - 4
  - C
- Gen
  - R
  - Mixed histology – MUTYH Associated Polyposis
- Therapy Associated Polyposis

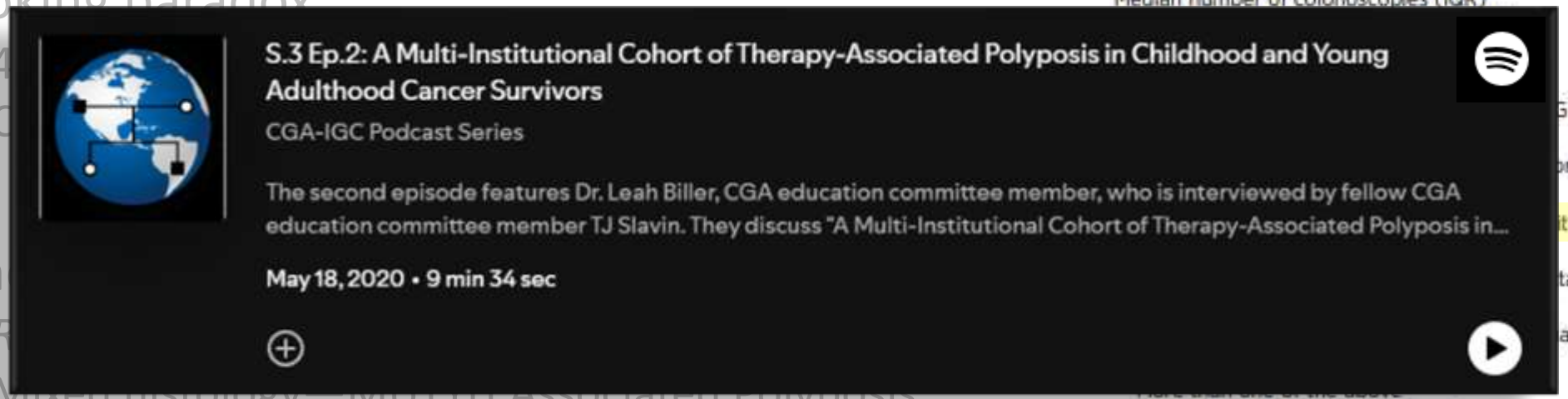
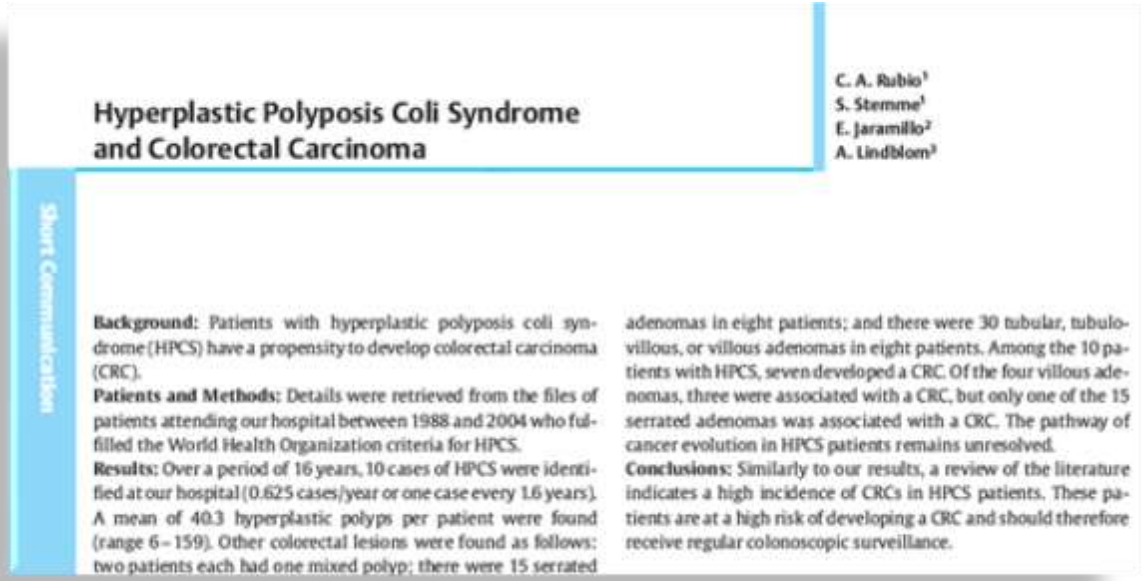


Table 2. Gastrointestinal polyposis and other clinical manifestations of TAP ($n = 34$).

	N	(%)[a]
Median time (years) from initial cancer treatment to first colorectal polyp (IQR)	27(20–33)	
Median age (years) at first polyp (IQR)	49(37–54)	
Median number of colonoscopies (IQR)	4(2–6)	
	32(16–52)	
	23	(68)
	12	(35)
GI	25	(74)
rectal	18	(53)
teria)	10	(29)
	6	(18)
tal	3	(9)
atous	1	(3)
	8	(24)
Presence of gastroduodenal polyps[c]	7	(30)[d]
Gastric hamartoma	2	(9)[d]
Gastric hyperplastic polyps	2	(9)[d]
Duodenal adenoma	1	(4)[d]
Duodenal hyperplastic/serrated polyp	1	(4)[d]
Duodenal inflammatory polyp	1	(4)[d]
Colorectal cancer diagnosis	10	(29)
Median age (years) at colorectal cancer diagnosis (IQR)	46(33–57)	

Biller et al. Cancer Prev Res 2020;13(3):291-8.

Colorectal Cancer risk in SPS



Short Communication

Hyperplastic Polyposis Coli Syndrome and Colorectal Carcinoma

C. A. Rubio[1]
S. Stemme[1]
E. Jaramillo[2]
A. Lindblom[3]

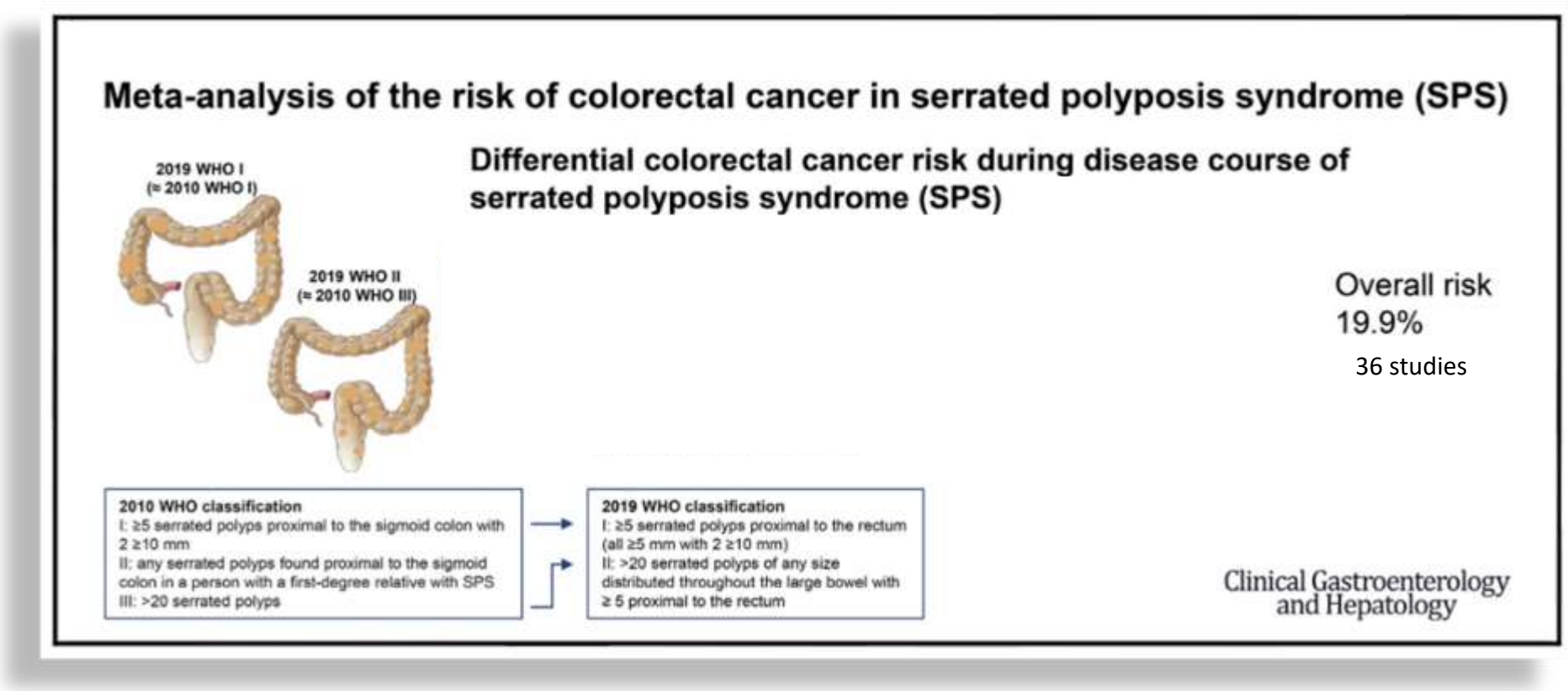
Background: Patients with hyperplastic polyposis coli syndrome (HPCS) have a propensity to develop colorectal carcinoma (CRC).
Patients and Methods: Details were retrieved from the files of patients attending our hospital between 1988 and 2004 who fulfilled the World Health Organization criteria for HPCS.
Results: Over a period of 16 years, 10 cases of HPCS were identified at our hospital (0.625 cases/year or one case every 1.6 years). A mean of 40.3 hyperplastic polyps per patient were found (range 6–159). Other colorectal lesions were found as follows: two patients each had one mixed polyp; there were 15 serrated adenomas in eight patients; and there were 30 tubular, tubulovillous, or villous adenomas in eight patients. Among the 10 patients with HPCS, seven developed a CRC. Of the four villous adenomas, three were associated with a CRC, but only one of the 15 serrated adenomas was associated with a CRC. The pathway of cancer evolution in HPCS patients remains unresolved.
Conclusions: Similarly to our results, a review of the literature indicates a high incidence of CRCs in HPCS patients. These patients are at a high risk of developing a CRC and should therefore receive regular colonoscopic surveillance.

Table 2 Summary findings from publications including patients that fulfil World Health Organization criteria of serrated polyposis syndrome

Author	Patients (*n*)	Age at diagnosis (median, yr)	CRC (%)	CRC family history (%)
Lage *et al*[12]	14	54	43	36
Ferrández *et al*[10]	15	52	7	0
Rubio *et al*[13]	10	61	70	10
Chow *et al*[9]	38	44	26	50
Boparai *et al*[7]	77	56	35	NR

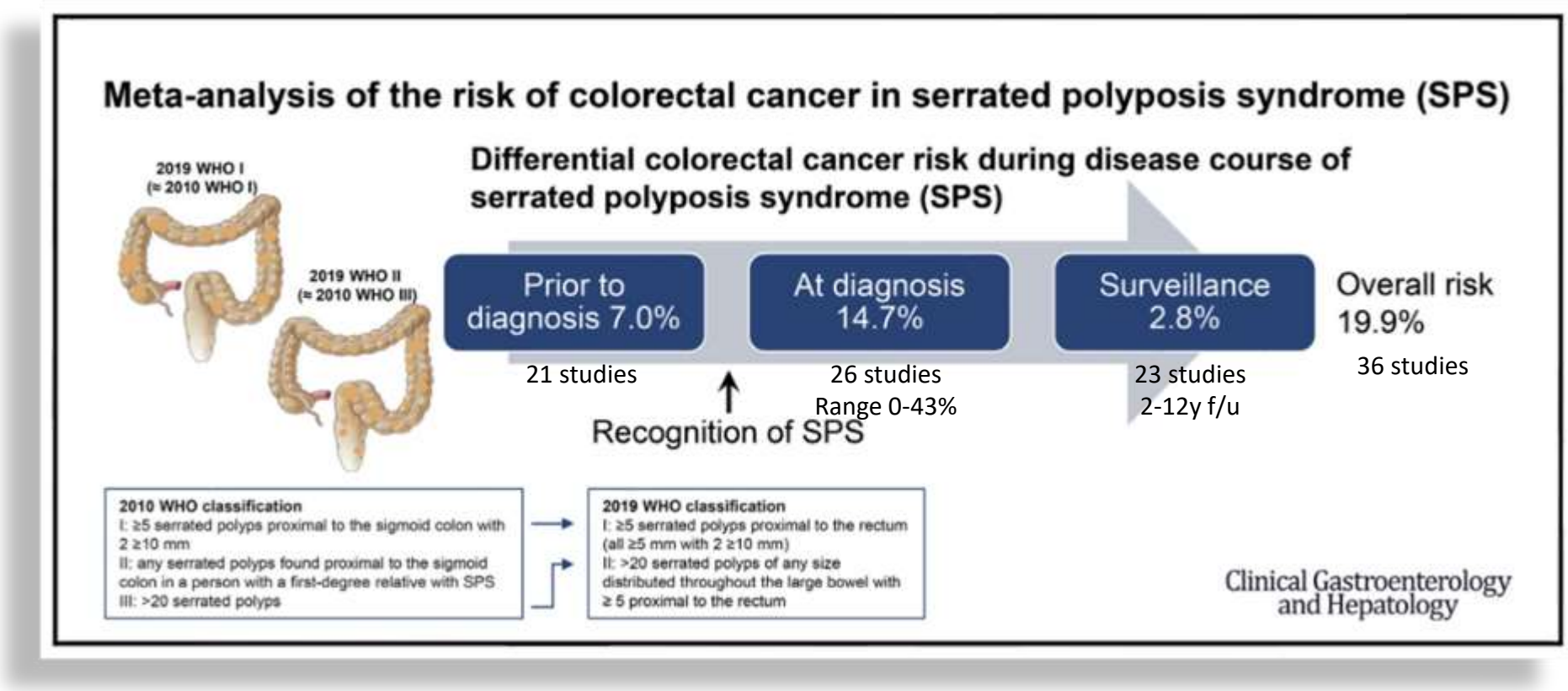
Rubio et al. Endoscopy 2006;38(3):266-70.
Guarinos et al. W J Gastroenterol 2012;18(20):2452-61.

Colorectal Cancer risk in SPS



Muller at al. Clin Gastroenterol & Hepatol 2022;20:622-630.

Colorectal Cancer risk in SPS



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Surveillance recommendations for individuals with serrated polyposis:

- **High-quality colonoscopy with polypectomy until all polyps ≥5 mm are removed, then colonoscopy every 1 to 3 y depending on number and size of polyps. Clearing of all polyps is preferable but not always possible.**
- **Consider surgical referral if colonoscopic treatment and/or surveillance is inadequate.**

NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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My Approach

Index exam:

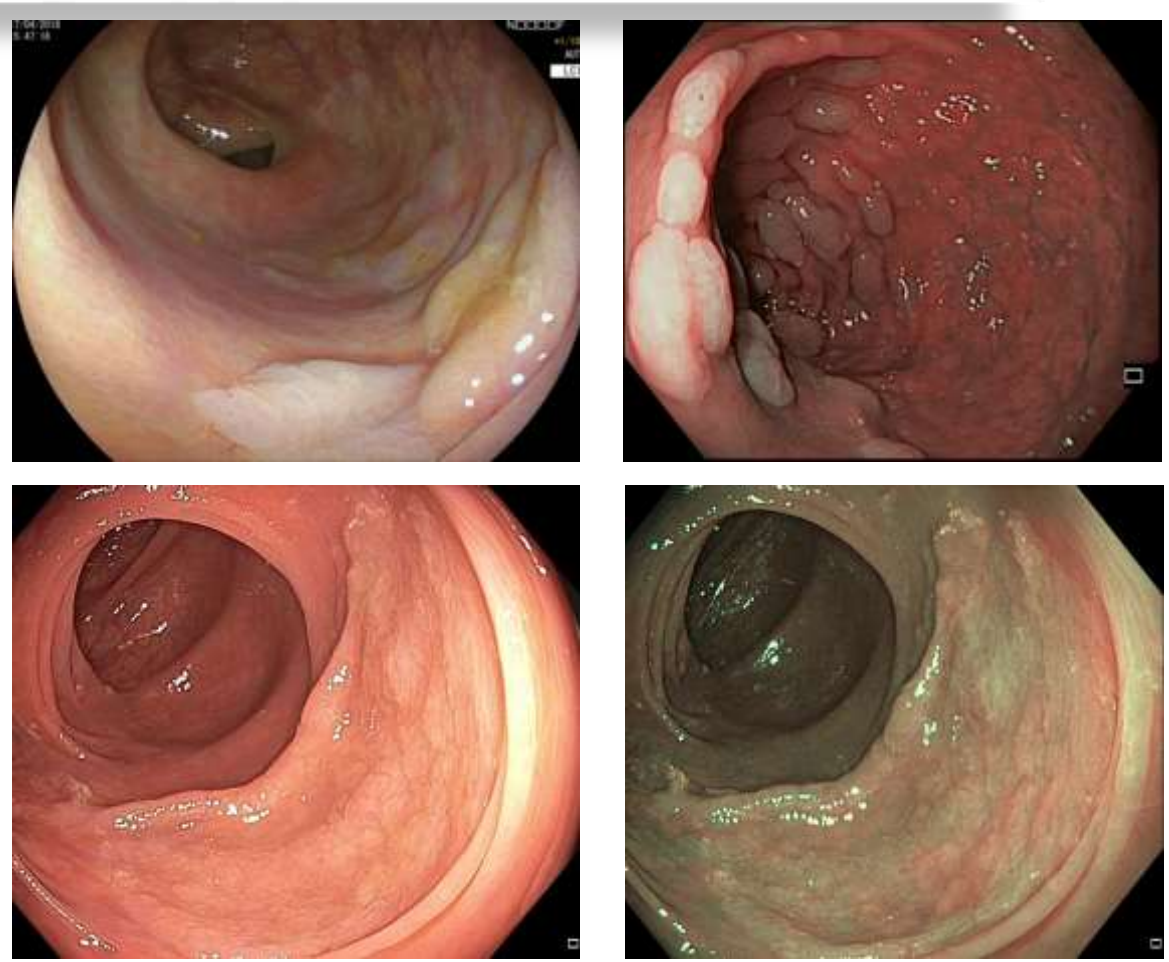
- Full withdrawal only looking for cancer and dysplastic lesions
- If no cancer, remove dysplastic lesions

Clearance Phase:

- Depending on whether high-risk histology, clearance exams every 3-6 months until all polyps ≥ 5mm removed
- Piecemeal cold snare
- Find a buddy!

Surveillance Phase

- Advanced lesion, >5 lesions →1 year
- Otherwise →2-3 years



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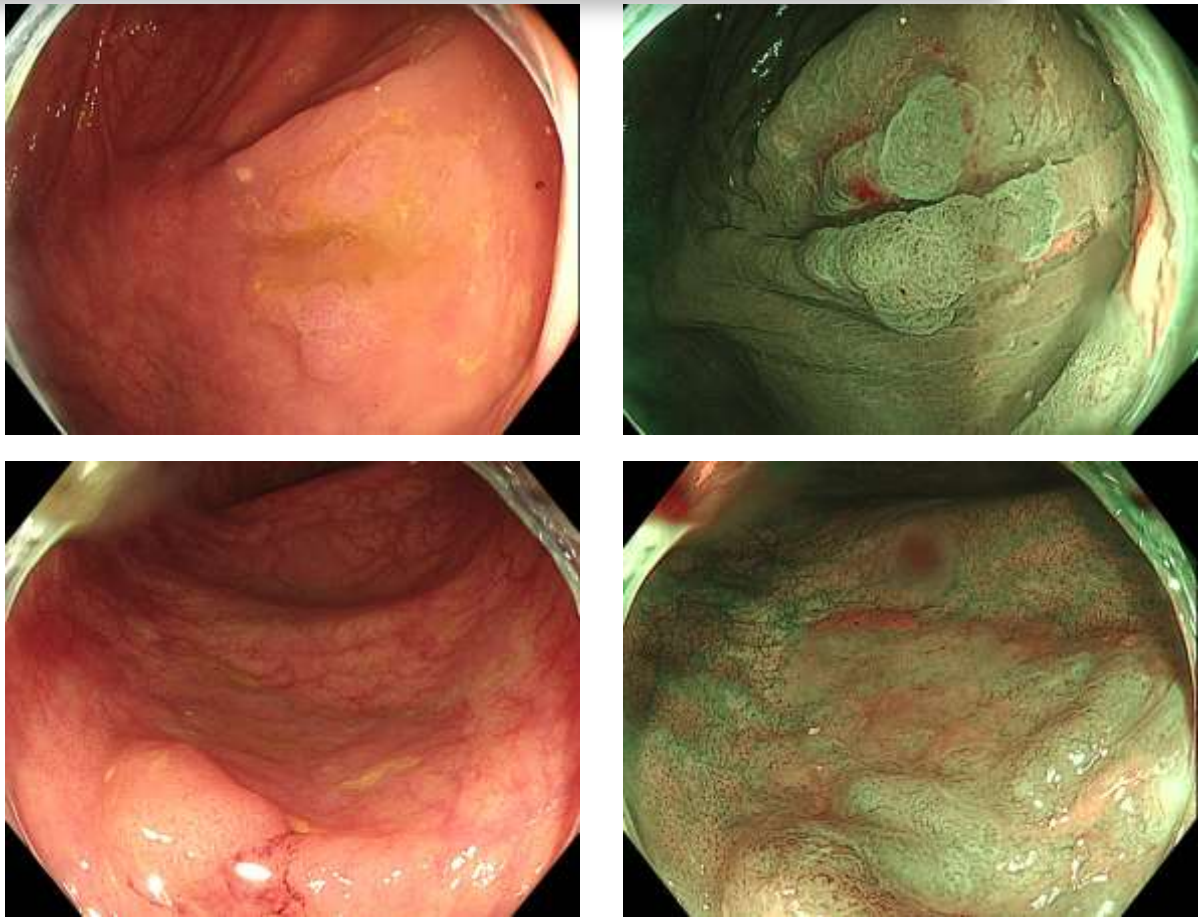

NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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Piecemeal cold snare polypectomy versus conventional endoscopic mucosal resection for large sessile serrated lesions: a retrospective comparison across two successive periods

Cold snare polypectomy without submucosal injection: safety and efficacy in 615 large serrated lesions

OPEN ACCESS

Clearance Phase:

- Depending on whether high-risk histology, clearance exams every 3-6 months until all polyps ≥ 5mm removed
- Piecemeal cold snare
- Find a buddy!

Surveillance Phase

- Advanced lesion, >5 lesions →1 year
- Otherwise →2-3 years

Van Hattem et al. Gut 2021;70(9):1691-97.
Barros et al. Endoscop Int Open 2021;9(9):1421-26.
Patel et al. Evidence Based GI 2021.
NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

Surveillance recommendations for individuals with serrated polyposis:

Can only be done safely if endoscopies are performed with high quality equipment in centers within expertise and interest in the treatment of serrated polyps. The polyp burden in SPS patient can be overwhelming in a subset of cases, but surgery for other reasons than CRC should be considered as last resort and are hardly ever necessary if patients are endoscopically treated by endoscopists with stamina to resect all relevant lesions.

Sabela Carballal, Francesc Balaguer & Joep E G IJspeert

Index

- Full
  lesi
- If n

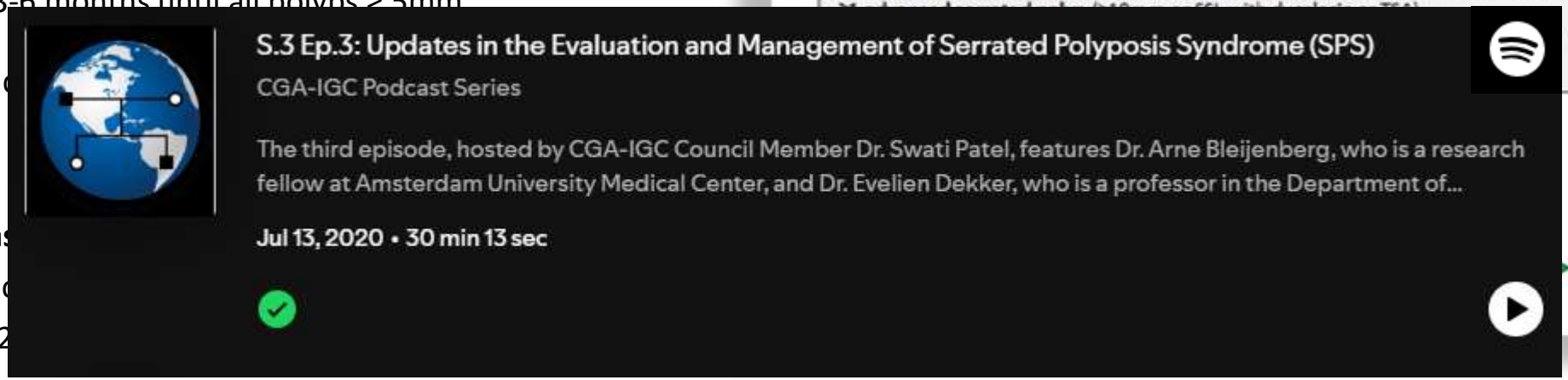
Clearan

- Depending on whether high-risk histology, clearance exams every 3-6 months until all polyps > 5mm removed
- Piecemeal col
- Find a buddy!

Surveillance Pha

- Advanced lesi
- Otherwise →2

Endoscopic findings (confirmed by pathology) include at least one of the following:



Carballal et al. B Prac & Res Clin Gastro 2022;58-59.
NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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II. Gastric Cancer in Familial Adenomatous Polyposis

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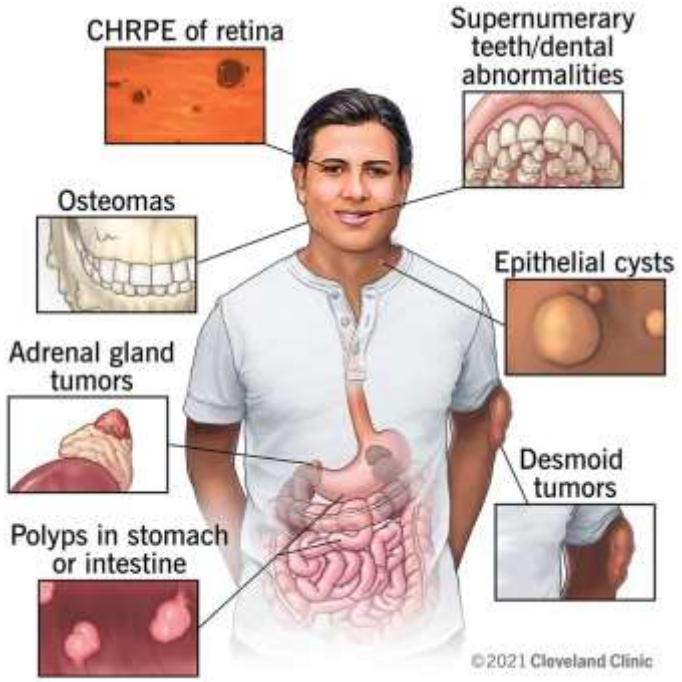

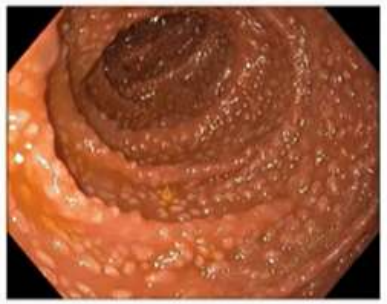

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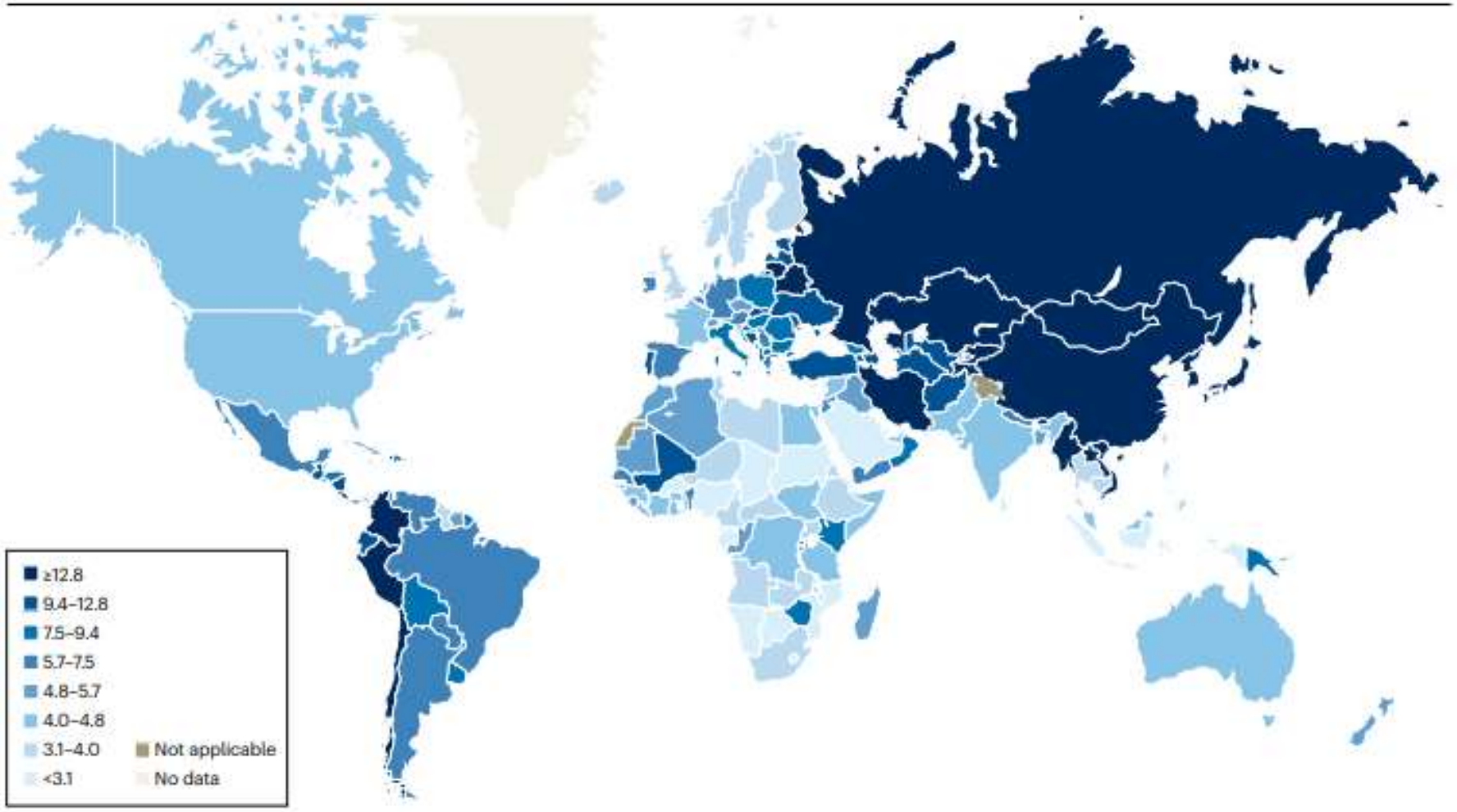

Fig. 1 | Worldwide gastric cancer incidence in 2020. The shading indicates estimated age-standardized incidence rates per 100,000 persons based on data from GLOBOCAN 2020 (ref. 1), https://go.nature.com/3Jolkd5 (accessed 26 July 2022; ©International Agency for Research on Cancer, 2020).

Thrift et al. Nat Rev Clin Onc. 2023(20):338-49.

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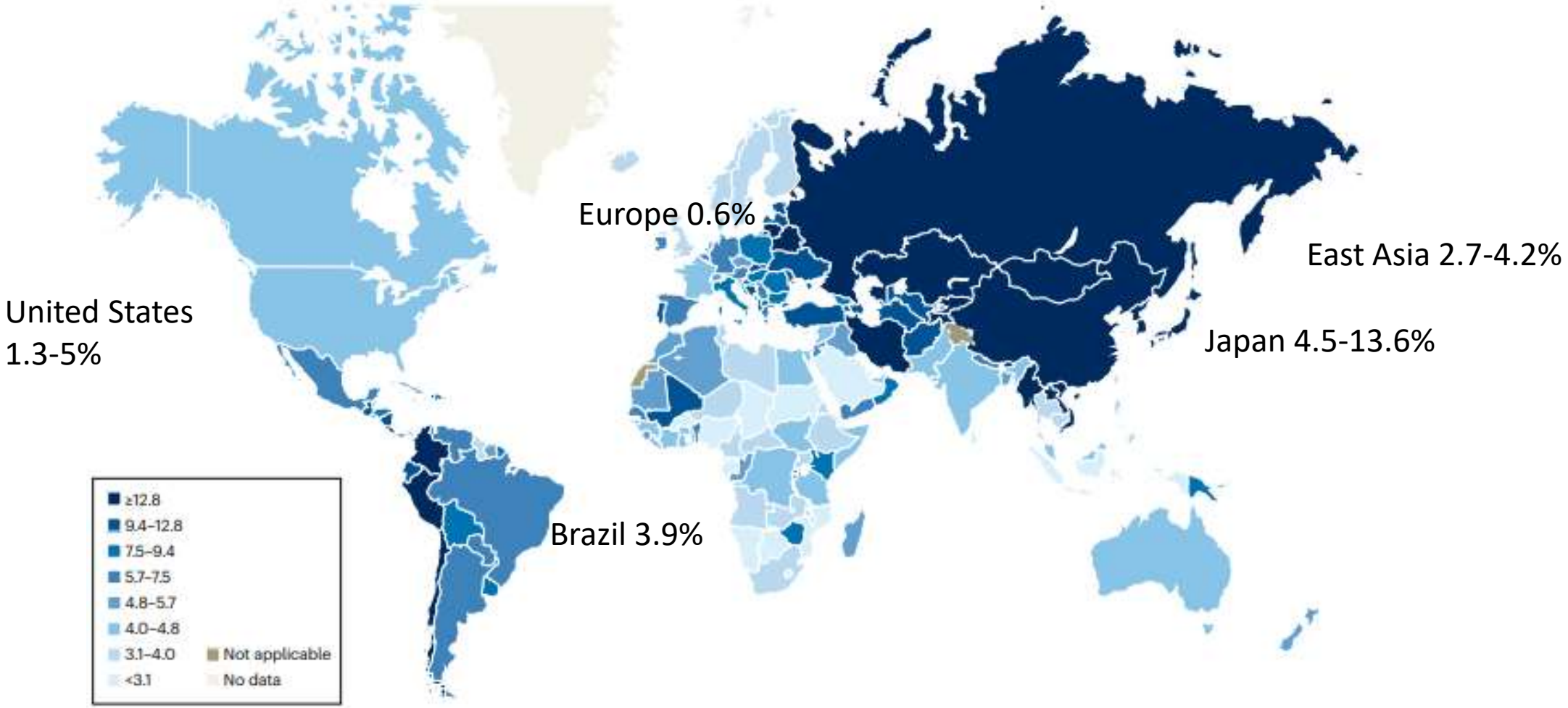

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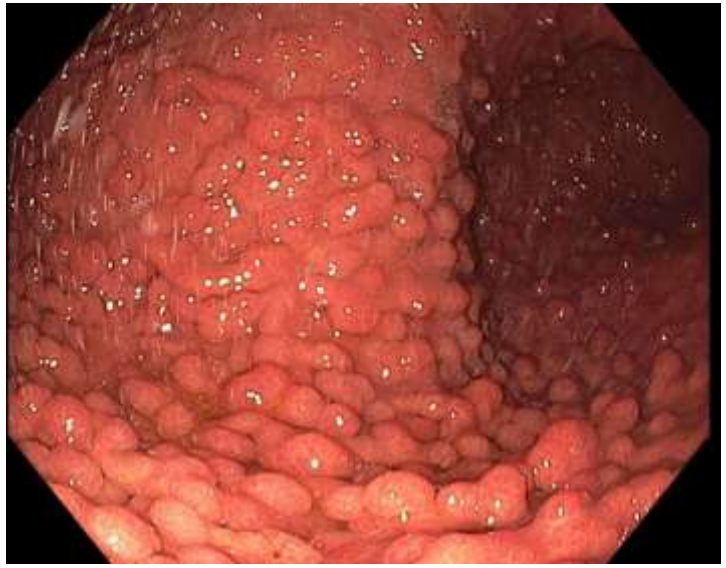
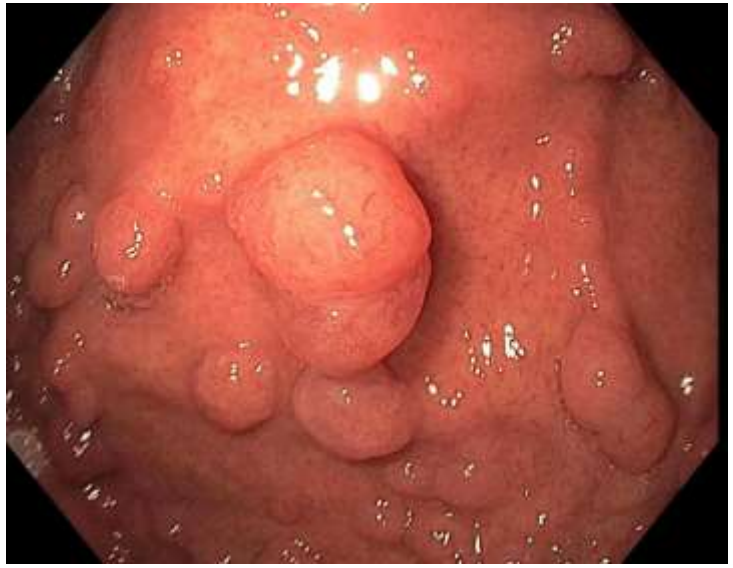
Thrift et al. Nat Rev Clin Onc. 2023(20):338-49.
Iwama et al. Int J Clin Onc 2004;9:308-16.
Park et al. Gut Liver 2011;5:45-51.
Campos et al. J Gastro Oncol. 2019;10(4):734-44.
Shibata et al. J Exp Med 2013;229:143-46.
Mankaney et al. Fam Cancer 2017;16:371-76.
Yamguchi et al. Jpn J Clin Oncol. 2016;46(4):310-15.

Features associated with gastric cancer



Carpeting



Polyps ≥ 10 mm

Mounds ≥ 20 mm

No difference: H. Pylori (west), duodenal polyp burden

Leone et al. Gastrointest Endosc 2019;89(5):961-68.
Christenson et al. J Gastrointest Surg 2024;28(11):1890-96.

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TABLE 1. Gastric polyp pathology

High-risk pathology
Pyloric gland adenoma
Tubular adenoma
Fundic gland polyp with high-grade dysplasia
Hyperplastic polyp
Intestinal metaplasia

Mankaney et al. Gastrointest Endosc 2020;92(3):755-62.

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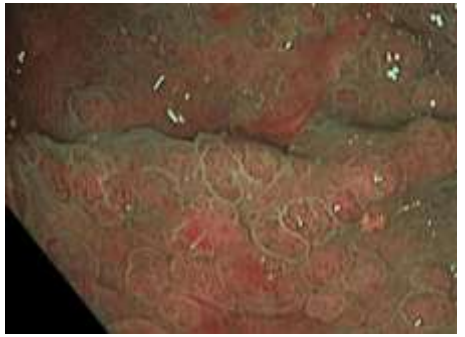
TABLE 1. Gastric polyp pathology

High-risk pathology	Low-risk pathology
Pyloric gland adenoma	Fundic gland polyp with low-grade dysplasia
Tubular adenoma	Fundic gland polyp without dysplasia
Fundic gland polyp with high-grade dysplasia	
Hyperplastic polyp	
Intestinal metaplasia	



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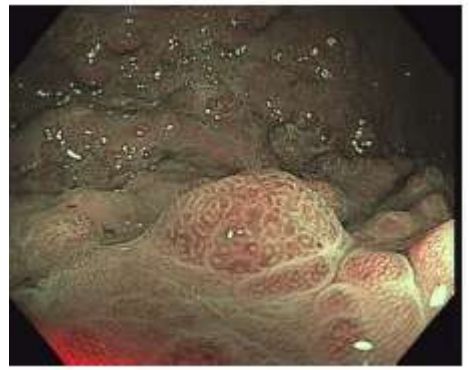


Sensitivity 79.0%
Specificity 78.8%
NPV 96.2%
PPV 38.0%

White patches
Darker than surrounding mucosa
Open pit pattern
Irregular, nodular surface

Interobserver Agreement
0.45 (all)
0.65 (FAP Experts)

Mankaney et al. Gastrointest Endosc 2020;92(3):755-62.
Kunnathu et al. Gastrointest Endosc 2018;88(3):569-70.

Management[d,e,f]

- Recommend representative sampling of polyps <10 mm that appear as FGP by multiple biopsies or endoscopic resection at baseline exam to determine histology.
- Resect polyps ≥10 mm, as well as any polyps with endoscopic markers of advanced pathology or high-risk features. If there is suspicion for malignancy in a lesion, recommend referral to an expert center for management (endoscopic submucosal dissection [ESD] vs. surgery).
- Recommend considering referral to an expert center for management by endoscopists with expertise in FAP for management of mounds of gastric polyps that are limiting accuracy, and resection of polyps with high-risk/advanced pathology. Mounds of gastric polyps may limit accuracy of endoscopic surveillance. If other high-risk characteristics are present, consider endoscopic management to debulk proximal polyposis.
- Due to the fact that adenomas and hyperplastic polyps are the predominant polyp in the antrum, recommend resection of all polyps in the antrum.
- Patients with high-risk lesions that cannot be removed by standard endoscopic techniques (including snare removal with or without endoscopic mucosal resection [EMR]) should be referred to a specialized center for consideration of ESD versus gastrectomy.
- Gastrectomy is indicated for multifocal high-grade dysplasia and intramucosal or invasive cancer (see NCCN Guidelines for Gastric Cancer).
- Roux-en-Y esophago-jejunostomy reconstruction after total gastrectomy may require balloon-assisted enteroscopy for continued duodenal polyposis and ampullary surveillance.

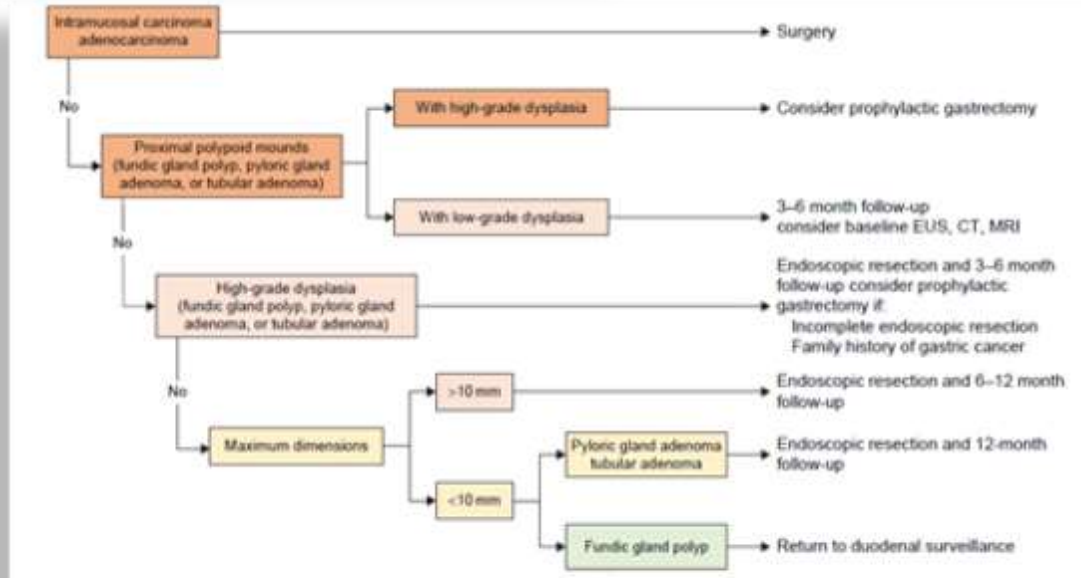
GASTRIC FINDINGS AND MANAGEMENT

Gastric Polyp Characteristics and Recommended Surveillance Intervals[g,h]

Histology	Size	Dysplasia	Surveillance Interval[i]
Fundic gland polyps (FGP)	<1 cm	None or low grade	3 y
	≥1 cm	None or low grade	1 year (6 mo if piecemeal resection or unable to remove all large polyps in a single procedure)
	Any size	High grade*	3–6 mo and consider endoscopic management at an expert center or surgical evaluation
Gastric adenomas (GA) or Pyloric gland adenomas (PGA)	<1 cm	—	1 y
	≥1 cm	—	1 year (6 mo if piecemeal resection or unable to remove all large polyps in a single procedure)
	Any size	High grade*	3–6 mo and consider endoscopic management at an expert center or surgical evaluation
Any proximal polypoid mounds – FGP, PGA, GA	N/A	None or low grade	3–6 mo
		High grade*	Referral for endoscopic management at expert center and surgical evaluation
Intramucosal or invasive adenocarcinoma	N/A	N/A	Surgical evaluation for possible gastrectomy

* Multifocal high-grade dysplasia should prompt referral for surgical evaluation for possible gastrectomy.

- If partial gastrectomy is performed for antral neoplasia, then continue surveillance of the remaining stomach as above.
- Intervals for upper endoscopy surveillance should be determined based on gastric and/or duodenal findings and whichever requires more frequent surveillance should be applied.



Zaffaroni et al. Brit J Surg 2024; 111(5):1-71.
NCCN 2024. Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

1. **Endoscopic goals & expectations with the patient/family**
2. Ensure adequate sedation, ample time
3. Equipment on hand
4. Thoroughly clean/wash, clear bubbles
5. First pass exam: carpeting, mounds, excavated lesions, ulcerated lesions—targeted sampling
6. Subsequent passes: Segmental white light & NBI exam for high-risk features
7. Remove all polyps in antrum, ≥ 1cm, high-risk features

Nearly all patients with FAP have stomach polyps, however **only 5% develop cancer**. Our goal today is to determine whether you are potentially at risk of being in that 5%.

Today's objective is to **map out your upper GI tract**. I will do a careful exam to see if there are any areas that have **turned into cancer** or are at increased risk of becoming cancer. Depending on what we find, we may need to arrange **additional testing** to further evaluate and/or **remove** those areas.

We will determine when you need your **next upper endoscopy based on what we find** today. This can be anywhere from very soon (1-3 months) or as far out as 4-5 years.

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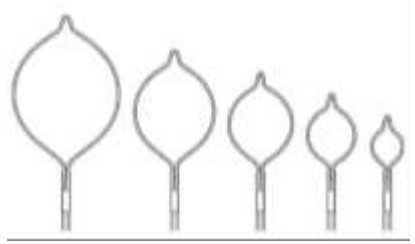

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2. Ensure adequate sedation, ample time
3. Equipment on hand
4. **Thoroughly clean/wash, clear bubbles**
5. First pass exam: carpeting, mounds, excavated lesions, ulcerated lesions—targeted sampling
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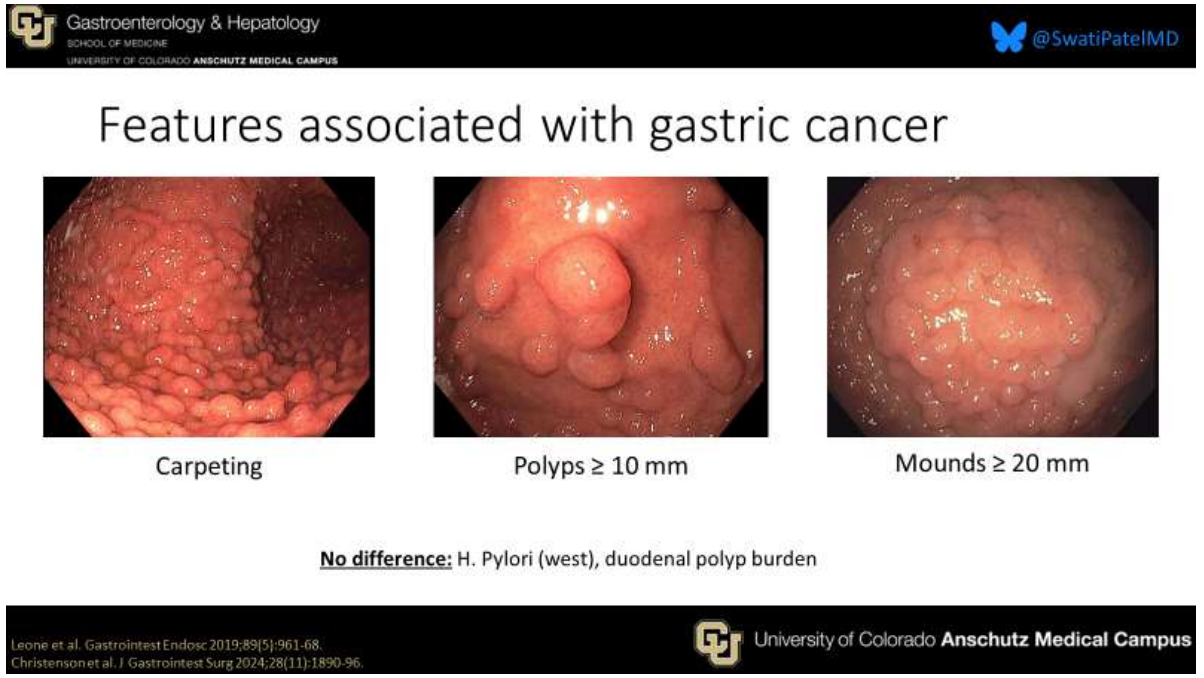

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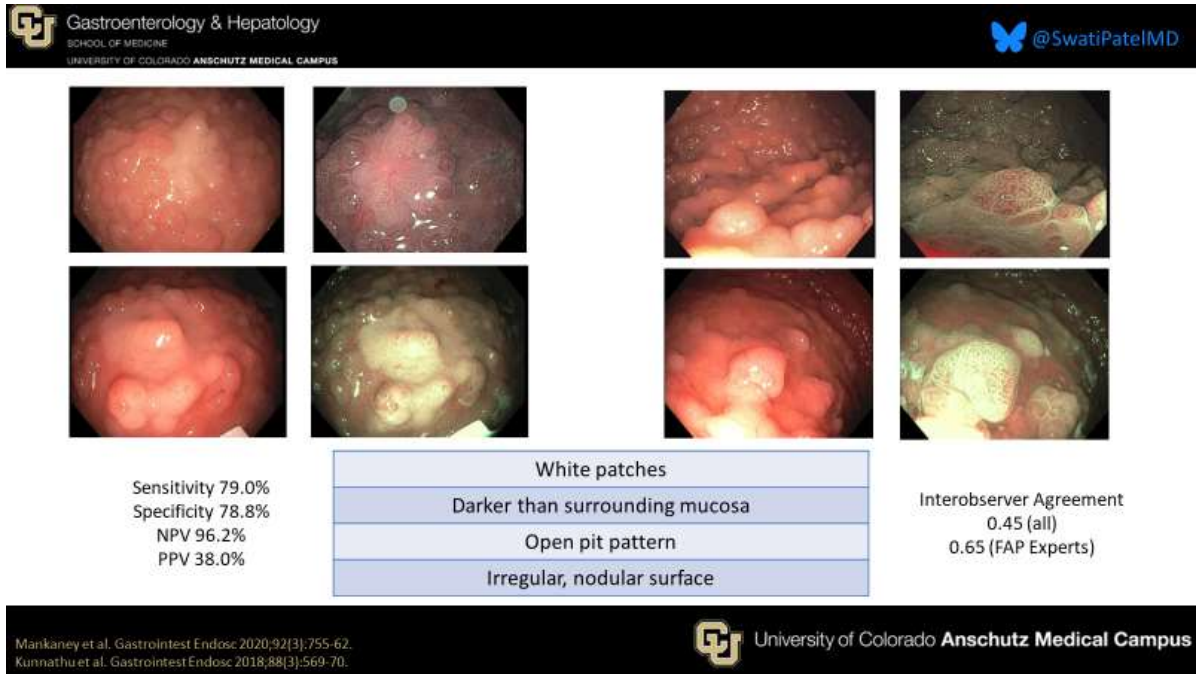

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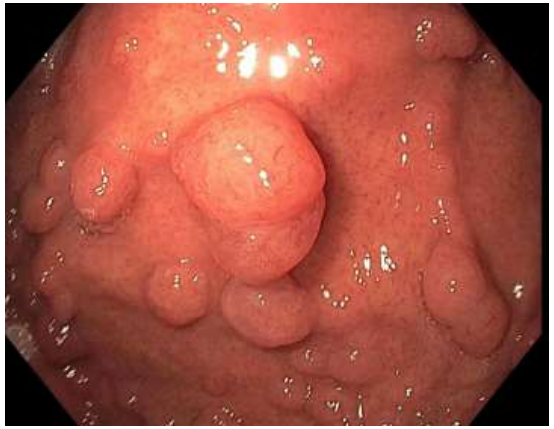

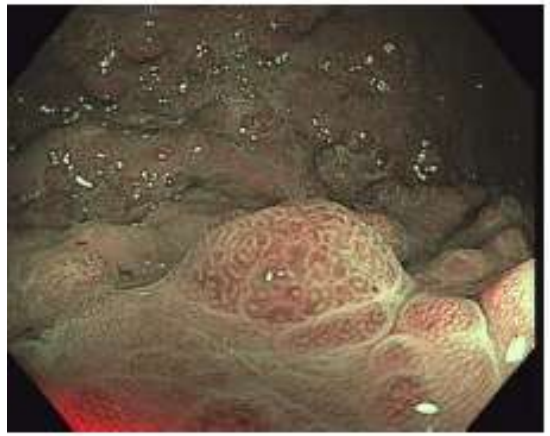

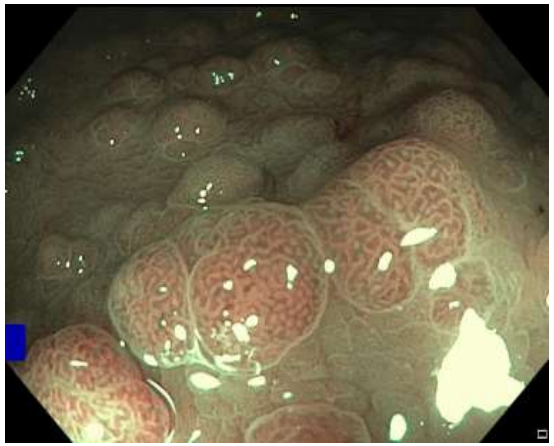

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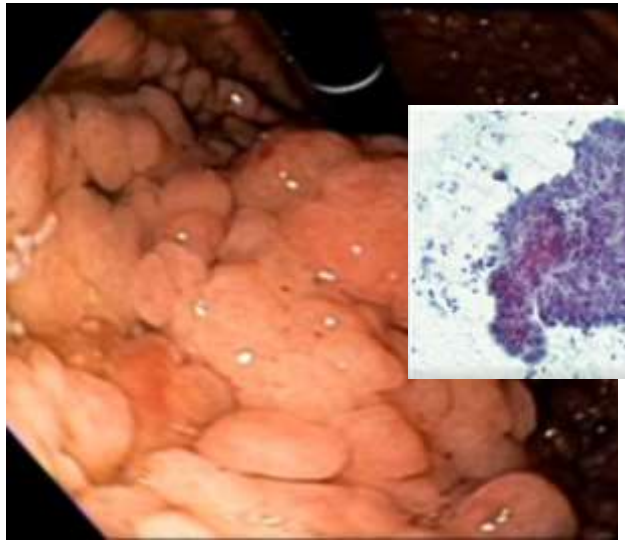

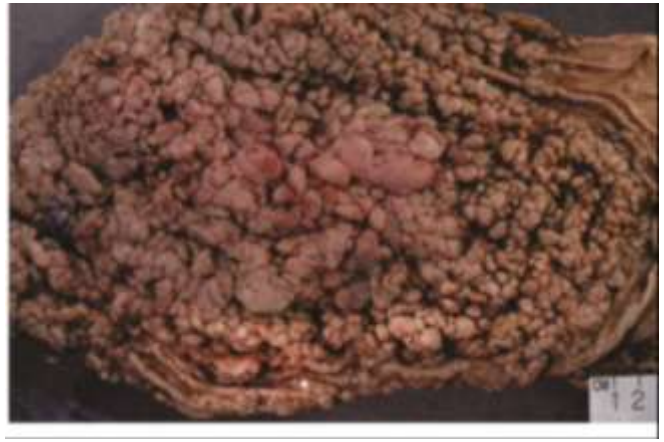

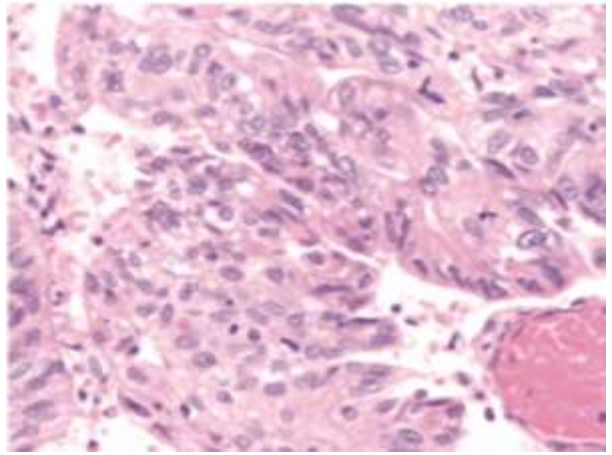

Mankaney et al. Gastroenterol 2017;153:353-54.

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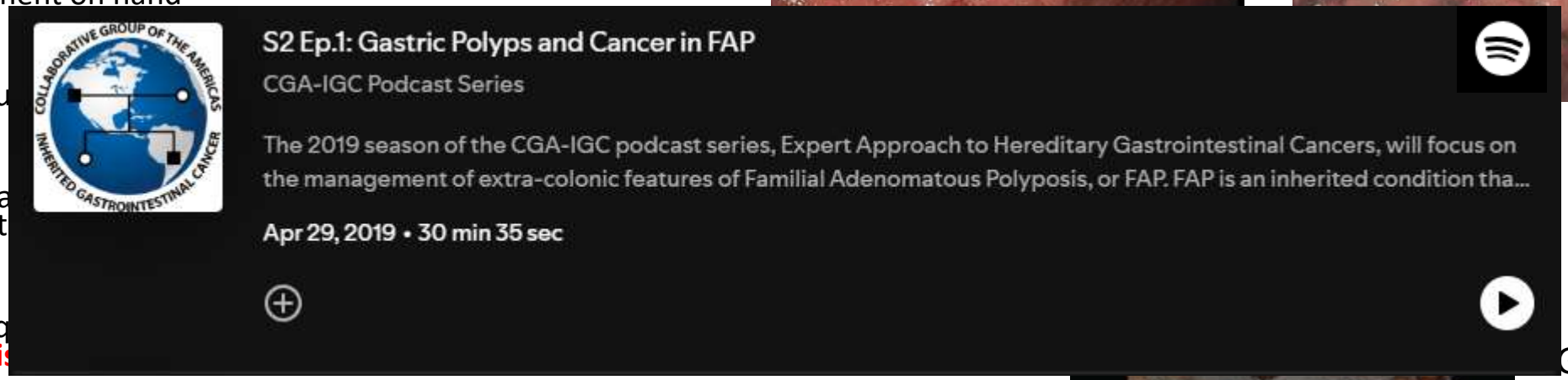

Gastric Adenoma
No HGD

Joseph et al. Am J. Gastroenterol 2022;117(6):835.

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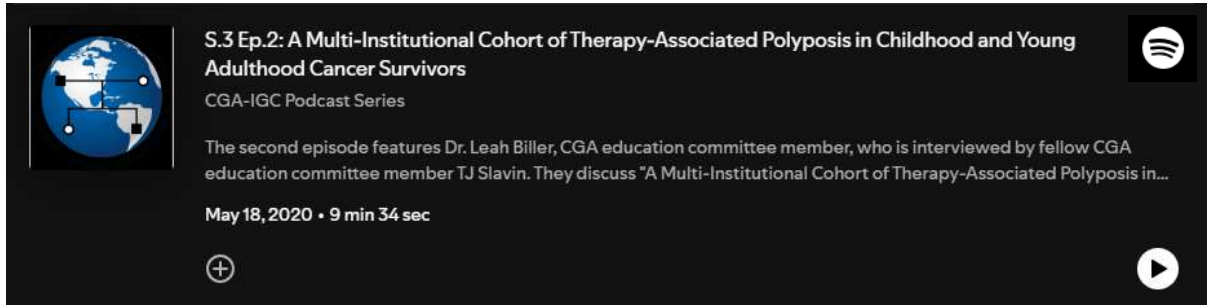
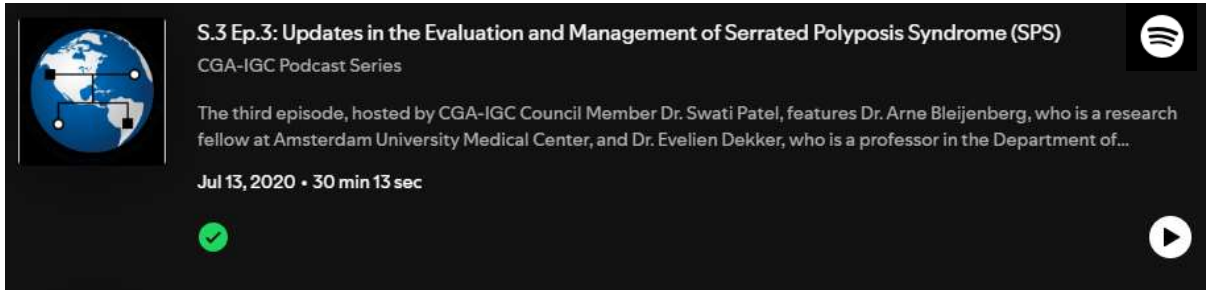
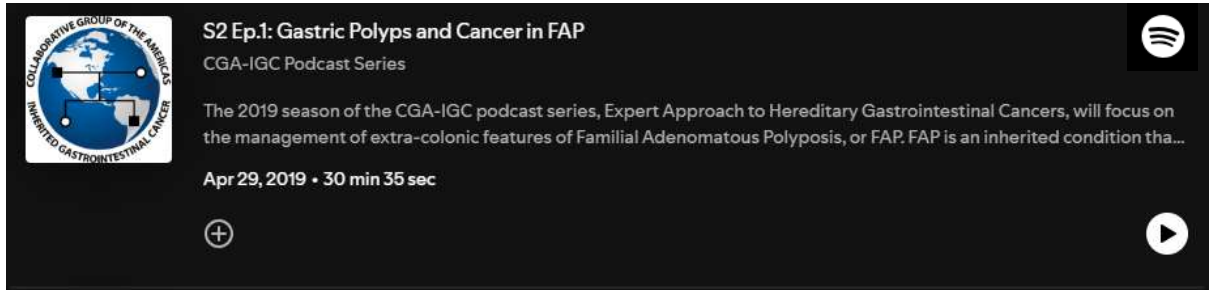
Take home points

- Polyposis can be overwhelming!
- If you only have time for 1 thing—
  FIND THE CANCER!
- Polyposis is a team sport







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