GIPS Journal Watch November & December 2018

Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review.
Ma C, van Rhijn BD, Jairath V, Nguyen TM, Parker CE, Aceves SS, Furuta GT, Gupta SK, Katzka DA, Safroneeva E, Schoepfer AM, Straumann A, Spergel JM, Pai RK, Feagan BG, Hirano I, Dellon ES, Bredenoord AJ.
Clin Gastroenterol Hepatol. 2018 Nov;16(11):1714-1729.e3.
https://www.ncbi.nlm.nih.gov/pubmed/29908360
This is a somewhat similar article to one published in September of 2018 by many of the same authors regarding evaluation of endpoints and outcome measures in Crohn's disease (https://www.ncbi.nlm.nih.gov/pubmed/29596987). In this current publication, the authors examine the inconsistencies in outcome measures reported in clinical trials evaluating therapies for eosinophilic esophagitis (EoE). They note that with the development of novel therapeutic regimens, a core outcome set for evaluating primary endpoints will be efficacious for comparison purposes and may be required for regulatory standards in the future. This paper serves as a meta-analysis of works reporting efficacy in placebo-controlled EoE randomized control trials. While patient reported outcomes, endoscopic endpoints, and histologic findings are all discussed only the latter will be summarized here. Of the 22 publications identified, 21 reported eosinophil density in some manner. While most reported peak eosinophil counts, methods varied widely with some being quantified by field size, high-power fields (HPF), and specific locations within the esophagus. Definitions of histologic remission also varied and ranged from peak eosinophil counts of 0-6/HPF. One study used a more comprehensive scoring system (EoE-HSS) which takes into account eosinophil density, basal hyperplasia, eosinophilic abscesses, and surface epithelial changes among others. The authors conclude by stating that there is considerable heterogeneity in endpoint reporting. They also suggest that future histologic endpoints may want to consider the evaluation of other factors beyond peak eosinophil count since this measure appears to correlate poorly with patient reported outcomes. It may be that other factors such as degree of subepithelial fibrosis or basal cell hyperplasia, as captured by the EoE-HSS described above, may be more telling.

Mucosal inflammation in Candida esophagitis has distinctive features that may be helpful diagnostically.
Martin IW, Atkinson AE, Liu X, Suriawinata AA, Lefferts JA, Lisovsky M.
Mod Pathol. 2018 Nov;31(11):1653-1660.
https://www.ncbi.nlm.nih.gov/pubmed/29921901
The stated goal of this study was to identify specific features of mucosal inflammation in the esophagus that might help identify cases of Candida esophagitis when fungal forms are not easily identified. The study was retrospective and looked at a study group of 99 consecutive cases of Candida esophagitis compared with a control group of 64 cases of reflux esophagitis. Evaluation of histologic features of the two groups, among other findings, identified concurrent superficial band-like neutrophils and increased intraepithelial lymphocytes (usually peripapillary and consisting of CD4 predominant lymphocytes) as the most suggestive feature of Candida

esophagitis and might warrant additional stains and clinical correlation to help support the diagnosis.

Methylation panel is a diagnostic biomarker for Barrett's oesophagus in endoscopic biopsies and non-endoscopic cytology specimens.
Chettouh H, Mowforth O, Galeano-Dalmau N, Bezawada N, Ross-Innes C, MacRae S, Debiram-Beecham I, O'Donovan M, Fitzgerald RC.
Gut. 2018 Nov;67(11):1942-1949
https://www.ncbi.nlm.nih.gov/pubmed/29084829
This study utilized biopsy and cytosponge samples from the BEST2 trial, and identified eighteen differentially methylated genes from whole methylome data, which were confirmed by PCR, which distinguished Barrett's esophagus from squamous and cardia controls. A pilot and validation cohort on Cytosponge samples narrowed the field to four potential biomarkers (methylation of TFPI2, TWIST1, ZNF345, and ZNF569). The authors propose that this technique could be a cost effective alternative to endoscopy and biopsy.

Low-grade dysplasia diagnosis ratio and progression metrics identify variable Barrett's esophagus risk stratification proficiency in independent pathology practices.
Davison JM, Shah MB, Deitrick C, Chennat J, Fasanella KE, McGrath K.
Gastrointest Endosc. 2018 Nov; vol 88(5):807-815.e2.
https://www.ncbi.nlm.nih.gov/pubmed/29944863
The aim of this study was to compare multiple, independent pathology practices under a single large health system using objective measures of BE risk stratification proficiency, including LGD/BE diagnosis ratio, and relative risk of neoplastic progression in patients diagnosed with LGD versus nondysplastic BE. The authors retrospectively identify 4734 patients under endoscopic biopsy surveillance for BE in a healthcare system with 16 independent pathology practices including 1 group of subspecialized GI pathologists (SSGI) and 15 general surgical pathology (GSP) practices. The 4 highest volume practices (SSGI, GSP1-3) averaged 56 to 162 BE cases per pathologist annually. In contrast, the low-volume general surgical pathology groups (LVGSPs) combined averaged approximately 10.6 BE cases per pathologist annually. The LGD/BE diagnosis ratio ranged from 1.1% to 6.8% in various practices ($P<0.001$). The cumulative proportion of patients with HGD or EAC within 2 years of the first diagnosis of LGD was 35.3% in the SSGI and ranged from 1.4% to 14.3% in the GSPs ($P < .001$). GSP1 with the lowest LGD/BE diagnosis ratio had an adjusted risk of progression similar to LGD diagnosed by subspecialists (hazard ratio, .42; 95% CI, .06-3.03). However adjusted risk of progression was 79% to 91% lower than subspecialists in GSP2, GSP3, or LV-GSPs. When LGD was diagnosed in a LVGSP practice, the risk of progression was not significantly increased relative to patients with nondysplastic BE. Based on these findings authors concluded that GSP and subspecialist practices show highly significant differences with respect to LGD/BE ratio, risk of progression relative to nondysplastic BE, crude annual progression rates, and the cumulative 2-year progression rate after LGD. These metrics can be used to assess proficiency in BE risk

stratification in historical cases. Some general practitioners were able to achieve results similar to subspecialists. LVGSP did not successfully risk stratify patients with BE.

Refined Criteria for Separating Low-grade Dysplasia and Nondysplastic Barrett Esophagus Reduce Equivocal Diagnoses and Improve Prediction of Patient Outcome: A 10-Year Review.
Waters KM, Salimian KJ, Voltaggio L, Montgomery EA.
Am J Surg Pathol. 2018 Dec;42(12):1723-1729.
https://www.ncbi.nlm.nih.gov/pubmed/30234520
The authors in 2012 implemented institutional criteria that Barrett esophagus with maintained cell polarity and surface gastric-type mucin vacuoles is considered negative for dysplasia (NFD) rather than indefinite for dysplasia (IFD) even with mild to moderate nuclear enlargement. The current study was aimed at examining the effect of new diagnostic criteria in categorization of cases as IFD as well as the short-term follow-up on these cases over a 10-year span from 2007 to 2016 (1549 cases from 1130 patients). The increased diagnostic threshold led to a decreased frequency of cases categorized IFD by nearly 50% (8.4% from 2007 to 2011 vs. 4.3% from 2012 to 2016). There was also a slight decrease in the frequency of LGD (3.9% to 2.5%), HGD (1.4% to 1.3%), and IMC (2.3% to 1.6%) between the 5-year periods. The IFD cases from 2012-2016 were more frequently dysplastic (3/21, 14.3%) on the next biopsy than earlier cases from 2007-2011 (1/48, 2.1%). Dysplasia on the next biopsy for NFD cases was lower in cases from 2012-2016 (6/222, 2.7%) than the cases from 2007-2011 (16/360, 4.4%). Based on these findings the authors concluded that improved diagnostic criteria reduced the proportion of IFD cases as well as better risk stratification of patients on the next biopsy.

International development and validation of a classification system for the identification of Barrett's neoplasia using acetic acid chromoendoscopy: the Portsmouth acetic acid classification (PREDICT).
Kandiah K, Chedgy FJQ, Subramaniam S, Longcroft-Wheaton G, Bassett P, Repici A, Sharma P, Pech O, Bhandari P.
Gut. 2018 Dec;67(12):2085-2091.
https://www.ncbi.nlm.nih.gov/pubmed/28970288
This prospective observational study sought to develop and validate a classification system accessible to all endoscopists for Barrett's esophagus (BE) using acetic acid chromoendoscopy (AAC), a technique reported to have high sensitivity and specificity for identifying BE high-grade dysplasia and intramucosal carcinoma in the hands of expert BE endoscopists. Four study phases were included: Phase 1 - development of descriptive criteria, which were agreed upon by 3 experts, Phase 2 - Development of a simple AAC classification, based on a total of 560 observations by 7 endoscopists and resulting in the PREDICT classification, Phase 3 - validation of PREDICT by 13 endoscopists on 780 observations, and Phase 4 - validation of PREDICT by 9 non-endoscopists on 360 observations, using images and videos. The sensitivity and negative predictive value were significantly increased by using the PREDICT criteria, by both endoscopists in Phase 3 and non-endoscopists in Phase 4. The authors suggest that the PREDICT Classification has clinical value to a range of providers and is easy to apply.

Identification of Prognostic Phenotypes of Esophageal Adenocarcinoma in 2 Independent Cohorts

Sawas T, Killcoyne S, Iyer PG, Wang KK, Smyrk TC, Kisiel JB, Qin Y, Ahlquist DA, Rustgi AK, Costa RJ, Gerstung M, Fitzgerald RC, Katzka DA; OCCAMS Consortium. Gastroenterology. 2018 Dec;155(6):1720-1728.e4.
https://www.ncbi.nlm.nih.gov/pubmed/30165050

This study looked at two distinct cohorts of esophageal adenocarcinoma (EAC) patients comprising over 1800 cases: 1. Mayo Clinic Rochester (single institution) and 2. A European Consortium (multicenter). These two independent cohorts showed some similarities: Over half of EACs in both occurred *without* endoscopic or pathologic evidence of Barrett's esophagus/intestinal metaplasia (BE/IM), and these patients had reduced survival compared to those with BE/IM. EAC in the setting of BE/IM was identified at earlier stage, associated with longer survival independent of patient age or sex, tumor stage or location, and BE length. While both cohorts demonstrated improved survival in BE/IM, the Mayo cohort showed longer median overall survival compared to the European cohort (4 yrs vs 1.3 yrs), which the authors attributed to more early-stage tumors (17% vs 6%), younger age (64 yrs vs 66 yrs) and more aggressive neoadjuvant therapy use. The study raises compelling evidence for 2 phenotypically different EACs (one with grossly visible or histologically identifiable IM, and one without) that could correlate with a more rapid pathway – or one independent of the BE pathway. The authors suggest this could have ramifications for tumor behavior and/or response to therapy and therefore prognosis, and call for additional molecular study.

OLGA Gastritis Staging for the Prediction of Gastric Cancer Risk: A Long-term Follow-up Study of 7436 Patients.

Rugge M, Genta RM, Fassan M, Valentini E, Coati I, Guzzinati S, Savarino E, Zorzi M, Farinati F, Malfertheiner P.
Am J Gastroenterol. 2018 Nov;113(11):1621-1628.
https://www.ncbi.nlm.nih.gov/pubmed/30333540

This retrospective study sought to examine the gastric carcinoma risk associated with gastritis as graded by the Operative Link for Gastritis Assessment (OLGA) system. This scoring system incorporates histologic assessment of the degree of mucosal atrophy within the gastric body as well as the antrum. The authors note that previous studies have established that individuals with higher OLGA stages were at an increased risk for the development of subsequent neoplasia. They sought to better quantify this risk over time by exploring a large cohort of patients with whom baseline OLGA stages were available. A total of 24,753 individuals were initially considered for the study with a final study population of 7436. Inclusion criteria were (1) age older than 18; (2) no previous gastrointestinal surgery or neoplasia; (3) histologic assessment of *H. pylori* status was available; (4) material was sufficient for determining OLGA stage. Patients who developed gastric neoplasia less than one year following the index endoscopy were excluded. The authors found that the distribution of OLGA stages were such that lower stages were more frequently encountered (stage 0= 80.8%; stage I: 12.6%) compared to higher stages (stage III: 2.0%; stage IV: 0.3%). Higher stages correlated positively with patient age. With a median follow-up of 6.6 years, 28 incidences of gastric neoplasia were

encountered including 7 invasive carcinomas. These were significantly associated with an initial higher OLGA stage. Multivariate analysis which evaluated patient age, gender, OLGA stage, and *H. pylori* status demonstrated that only the OLGA stage to be an independent predictor of subsequent neoplasia. The authors also noted that the cases that progressed to neoplasia usually did so within a period of 3 years. Given these results, the authors suggest that gastritis staging is an important predictor of the development of neoplasia and should be utilized in developing endoscopic follow-up protocols.

Endoscopic and clinicopathological features of intramucosal, histologically mixed-type, low-grade, well-differentiated gastric tubular adenocarcinoma with the potential for late-onset lymph node metastasis.
Saitoh T, Takamura A, Watanabe G.
BMC Gastroenterol. 2018 Dec 27;18(1):189.
https://www.ncbi.nlm.nih.gov/pubmed/30587141
This study aims to investigate the endoscopic and clinocopathological features of intramucosal histologically mixed type low-grade well-differentiated gastric tubular adenocarcinoma (tub1s; LG-tub1s). 185 early gastric cancer (EGC) lesions were evaluated in this retrospective observational study. Among these EGC lesions, 60 intramucosal LG-tub1s were divided into 53 tub1 (44 pure LG-tub1s and 9 LG-tub1s containing HG-tub1) lesions and 7 LG-tub1 > tub2 (LG-tub1 containing LG- and HG-tub2) lesions. The frequencies of the superficial depressed type (P = 0.026), reddish color (P = 0.006), HG of contained tub2s (P = 0.006), and gastrin-mucin phenotype (G-phenotype, P = 0.028) were found significantly higher in the LG-tub1 > tub2 group than those in the tub1 group. However, the largest lesion of the LG-tub1 > tub2 group had a superficial flat appearance, an isochromatic color, an HG-tub2 and an undifferentiated component, a large diameter greater than 30 mm, and a G-phenotype. The authors conclude that intramucosal G-phenotype LG-tub1s > HG-tub2 are potential premalignant stomach neoplasms that may have specific endoscopic and clinicopathological features. However, G-phenotype LG-tub1s > HG-tub2 with undifferentiated component, which potentially show higher malignancy than those without undifferentiated components might change from a reddish to isochromatic color. Accurately diagnosing, treating, and following-up G-phenotype LG-tub1s > HG-tub2 might decrease the number of patients who experience late-onset metastasis after endoscopic submucosal dissection.

PD-L1 expression and the prognostic significance in gastric cancer: a retrospective comparison of three PD-L1 antibody clones (SP142, 28–8 and E1L3N).
Ma J, Li J, Qian M, Han W, Tian M, Li Z, Wang Z, He S.
Diagn Pathol. 2018 Nov 21;13(1):91.
https://www.ncbi.nlm.nih.gov/pubmed/30463584
The authors compared IHC staining of PD-L1 in gastric cancer (GC) by using three commercially available antibody clones (clones SP142, 28–8 and E1L3N), and analyzed the correlation with the prognosis. IHC using PD-L1 antibodies in 315 formalin-fixed paraffin-embedded samples was qualitatively compared at the 1, 5 and 10% cut-off by two

pathologists on total, tumor and immune/ stromal cells and computer – assisted scoring was used to quantitatively analyze and compare the "H-score" of PD-L1 expression in 66 samples on total cells. PD-L1 clones SP142 and 28–8 displayed great concordance by qualitative and quantitative analyses. PD-L1 clone SP142 showed the highest positivity in immune/stromal cells staining (18.41%) compared to 28–8 (7.62%), while clone E1L3N showed poor staining in both tumor and immune/stromal cells. Clone SP142, but not 28–8 and E1L3N, predicted a worse prognosis at the 5% cut-off ($p = 0.0243$). Both the clone SP142 and 28–8 had high inter-pathologist correlation for tumor staining, but a moderate correlation for stromal/immune cell staining. Furthermore, a higher density of PD-L1^{+}CD8^{+} T cells was correlated with a shorter survival time. The authors conclude that PD-L1 antibody clone SP142 was superior in cell staining, particularly in immune/stromal cell and prognosis. These findings are important for selection of PD-L1 antibody clones in the future diagnostic test.

Pathological features of total gastrectomy specimens from asymptomatic hereditary diffuse gastric cancer patients and implications for clinical management.
Rocha JP, Gullo I, Wen X, Devezas V, Baptista M, Oliveira C, Carneiro F.
Histopathology. 2018 Dec;73(6):878-886.
https://www.ncbi.nlm.nih.gov/pubmed/30014492
In this paper, the authors aimed to obtain a better understanding of Hereditary diffuse gastric cancer (HDGC) syndrome by exploring the histopathological findings of total gastrectomy (TG) specimens from asymptomatic HDGC patients. A comprehensive literature review was carried out, searching for TGs performed in asymptomatic HDGC patients. Fourteen unpublished cases, analyzed in the authors institution were also included. The series encompassed 174 CDH1 carriers. Preoperative endoscopic biopsies were positive in 28.3%. A macroscopic lesion was apparent in 11.7% of TGs. Histopathological analysis revealed intraepithelial lesions and/or intra- mucosal signet ring cell carcinoma in 87.9% of TGs. Microscopic cancer foci were detected in 95.3% of TGs when a total-embedding protocol (assessment of the totality of gastric mucosa) was applied, and only in 62.5% when no specific protocol was used ($P < 0.001$). The authors conclude that thorough histopathological examination of gastric mucosa remains the gold standard for detection of cancer foci in HDGC gastrectomy specimens, requiring experienced pathologists for an accurate diagnosis.

Discriminant value of IEL counts and distribution pattern through the spectrum of gluten sensitivity: a simple diagnostic approach
Kirmizi A, Kalkan C, Yuksel S, Gencturk Z, Savas B, Soykan İ, Cetinkaya H, Ensari A.
Virchows Arch. 2018 Nov;473(5):551-558.
https://www.ncbi.nlm.nih.gov/pubmed/30094491
Increased intraepithelial lymphocytes (IEL) in the duodenal epithelium with or without villous architectural changes can be associated with a spectrum of conditions, including celiac disease (CD), non-CD gluten sensitivity, food allergies, infections, drug, IBD, GVHD, autoimmune enteropathy and CVID. The normal range of IEL has been debated and varies between 20 and 40 per 100 enterocytes in the literature. Based on H&E stain and CD3 immunostain, the authors

investigated the IEL counts of 374 distal duodenal biopsies from normal control (n = 82), non-CD with normal villous architecture and increased IEL (n = 112), Marsh type 1 CD (n = 88), and type 3 CD group (n = 92). IEL counts showed increasing tendency among these groups on H&E and CD3-immunostains. Non-CD typically showed focal/uneven and tip-increased distribution of IELs, while Marsh type 1 CD typically showed diffuse/even distribution pattern in both tip and side epithelium. IEL count of 20.5 on H&E and 28.5 on CD3 as the normal cut-off showed a sensitivity of 95.9 and 87.7% and a specificity of 98.8% and 93.9%, respectively for the diagnosis of celiac disease.

Associations of Microscopic Colitis With Other Lymphocytic Disorders of the Gastrointestinal Tract.

Sonnenberg A, Turner KO, Genta RM.

Clin Gastroenterol Hepatol. 2018 Nov;16(11):1762-1767.

https://www.ncbi.nlm.nih.gov/pubmed/29535059

The authors of this study sought to examine what association there may be between microscopic colitis (MC) (lymphocytic colitis [LC] and collagenous colitis [CC]) and lymphocytic infiltrates involving the upper gastrointestinal tract. The authors acknowledge that a relationship between LC and celiac disease is well established but associations with other lymphocytic disorders have not been well established. This retrospective study utilized pathologic diagnoses rendered from a large national laboratory covering material obtained from providers throughout the country and interpreted by pathologists with subspecialty training in gastrointestinal pathology. For the purposes of this study, only individuals who received bidirectional endoscopies were included, which comprised 228,506 patients. Of these, 3456 were diagnosed with microscopic colitis (LC: 1864; CC: 1592). Of these, 14% had a concomitant lymphocytic disorder of the upper gastrointestinal tract (which included lymphocytic esophagitis, lymphocytic gastritis, duodenal intraepithelial lymphocytosis, and celiac disease). LC was more commonly associated with upper tract findings than CC and duodenal intraepithelial lymphocytosis was the most common condition (8%). This was followed by celiac disease, lymphocytic gastritis, and lymphocytic esophagitis. Concurrent finding within the colon as well as the upper gastrointestinal tract was more common in younger individuals compared to patients with solitary MC. The authors conclude that lymphocytic disorders of the upper tract are more common in patients with MC than those without. They also propose that there may be a unifying etiology contributing to lymphocytic disorders of the upper and lower gastrointestinal tracts.

Apoptotic colopathy: a pragmatic approach to diagnosis.

Karamchandani DM, Chetty R

J Clin Pathol. 2018 Dec;71(12):1033-1040.

https://www.ncbi.nlm.nih.gov/pubmed/30275102

Due to overlapping features, this review paper analyzes key histologic findings in colonic injury demonstrating crypt apoptosis, or “apoptotic colopathy”. Clinically relevant etiologies where apoptotic colopathy is observed are GVHD, drug-induced injury, infection, immune disorders

and a variety of other rare miscellaneous causes. The purpose of this review is to identify defining features in each category to be combined with clear and careful communication between the pathologist and clinical team for an accurate diagnosis. **GI-GVHD**: 1) Apoptosis with 'exploding crypt cells' 2) Apoptotic microabscesses and hypereosinophilic crypts 3) Neutrophilic cryptitis and crypt abscess 4) Neuroendocrine cell clusters 5) Occasional scattered eosinophils (typically <15/10 HPF*) 6) Frequent crypt distortion 7) Endothelial cell injury (lamina propria pericapillary hemorrhage). **Mycophenolate mofetil (MMF/CellCept)-induced colitis**: 1) Apoptosis 2) Mixed lamina propria infiltrate typically with >15 eosinophils/10 HPF 3) Normal or mild crypt architectural distortion 4) Isolated crypt damage (degenerated crypts) 5) Typically, absent apoptotic microabscess and absent neuroendocrine cell clusters. **Check point inhibitor therapy:** 1) Apoptosis 2) Neutrophilic abscess/cryptitis 3) Atrophic crypts and apoptotic microabscess 4) Variable increase in intraepithelial lymphocytes. **CMV:** 1) Apoptosis 2) Crypt atrophy and dropout 3) Variable inflammatory response (ranging from minimal/mild to severe with mucosal ulcers) 4) Viral inclusions (intranuclear and/or intracytoplasmic) seen in endothelial cells, but also in glandular epithelial cells or stromal cells. **CVID** 1) Apoptosis (not present in all cases) 2) Paucity of plasma cells 3) Intraepithelial lymphocytosis typically more pronounced in the deep mucosa 4) Presence of lymphoid aggregates 5) Variable foci of architectural distortion.

The emerging role of histologic disease activity assessment in ulcerative colitis.
Pai RK, Jairath V, Vande Casteele N, Rieder F, Parker CE, Lauwers GY.
Gastrointest Endosc. 2018 Dec; vol 88(6):887-898.
https://www.ncbi.nlm.nih.gov/pubmed/30142351
This comprehensive review summarizes the current treatment targets, histologic scoring indices, and evidence highlighting the importance of measuring histologic activity in Ulcerative colitis. The authors also discussed the practical considerations regarding histologic evaluation in routine clinical practice.

Late-Onset Crohn's Disease Is A Subgroup Distinct in Genetic and Behavioral Risk Factors With UC-Like Characteristics.
Li D, Haritunians T, Landers C, Potdar AA, Yang S, Huang H, Schumm LP, Daly M, Targan SR, McGovern DPB.
Inflamm Bowel Dis. 2018 Oct 12;24(11):2413-2422.
https://www.ncbi.nlm.nih.gov/pubmed/29860388
By examining polygenetic risk score (PRS) in 2344 Caucasian Crohn's disease (CD) patients across all ages, the authors identified a group of patients aged 55 years and older, who had late-onset (LO) CD, associated with low PRS and smoking cessation, who more often had colonic CD with less penetrating disease and less need for surgery. The findings were also true in an independent validation cohort of CD patients from the International Inflammatory Bowel Disease Genetic Consortium (n=13,065). The findings add to the existing literature regarding the LO CD subgroup as a distinct and real entity.

Localization of TNF alpha in ileocolonic biopsies of patients with inflammatory bowel disease
Villanacci V, Cadei M, Lanzarotto F, Ricci C, Antonelli E, Cannatelli R, Gulotta T, Fontana L, Pasquali V, Sigala S, Salviato T, Nascimbeni R, Bassotti G.
Ann Diagn Pathol. 2018 Oct 27;38:20-25.
https://www.ncbi.nlm.nih.gov/pubmed/30388432
The proinflammatory cytokine TNFα plays an important role in the pathogenesis of inflammatory bowel disease (IBD), and previous studies showed that TNFα expression correlated to the degree of colonic inflammation in patients with ulcerative colitis (UC), and tissue levels of TNFα may predict response to infliximab treatment. In this study, the authors investigated TNFα expression by immunostain in the biopsies of patients with IBD including both active Crohn's disease (CD) and UC, and aimed to establish the anatomic distribution and cellular localization in the inflamed mucosa. Results showed that TNFα reactivity was constantly and selectively detected in the affected mucosa. TNFα expression was heterogenous and focal in CD and more diffuse and homogeneous in UC. TNFα was expressed in plasma cells, lymphocytes and, and to a lesser extent, macrophages. TNFα expression in plasma cells was further verified by co-localization of MUM1 with TNFα. There was a strong association between the grade of inflammation and the TNFα positivity. TNFα may be a predictive marker for IBD patients for the anti-TNFα therapy.

Refractory inflammatory bowel disease: is there a role for Epstein-Barr virus? A case-controlled study using highly sensitive Epstein-Barr virus–encoded small RNA1 in situ hybridization
Pezhouh MK, Miller JA, Sharma R, Borzik D, Eze O, Waters K, Westerhoff MA, Parian AM, Lazarev MG, Voltaggio L.
Hum Pathol. 2018 Dec;82:187-192.
https://www.ncbi.nlm.nih.gov/pubmed/30120969
This retrospective study evaluated 67 colectomy specimens from patients with refractory IBD for EBV-encoded RNA (EBER) by in situ hybridization and quantified this detection as either focal or diffuse. The control group included 12 colectomy specimens resected for dysplasia or endometriosis. EBER was detected in 60% of refractory IBD cases (15% diffuse) and 25% of controls (0% diffuse). Ulceration and greater depth of inflammation correlated with EBER detection. There was no statistically significant correlation between EBER positivity and duration of the disease or the medications used in treatment (anti–TNF-α therapy, azathioprine, or 6-MP). The authors raise the possibility that EBV infection may contribute to ongoing inflammation and lack of response to therapy in refractory IBD. They also suggest that targeting the EBV infection may be a useful therapeutic tool in treating refractory IBD.

New Methylation Biomarker Panel for Early Diagnosis of Dysplasia or Cancer in High-Risk Inflammatory Bowel Disease Patients.
Azuara D, Aussó S, Rodriguez-Moranta F, Guardiola J, Sanjuan X, Lobaton T, Boadas J, Piqueras M, Monfort D, Guinó E, Moreno V, Capellá G, de Oca J.
Inflamm Bowel Dis. 2018 Nov 29;24(12):2555-2564.

https://www.ncbi.nlm.nih.gov/pubmed/30099509
The authors identify a panel of 5 methylated genes which may be markers for early identification of neoplasia in high-risk inflammatory bowel disease patients (IBD). A discovery phase using 73 samples from 28 patients with and without neoplasia identified the five markers using high-throughput unbiased methylation analysis of CpG sites. A validation of the markers was then performed by methylation-specific melting curve analysis in 4 independent groups, including non-IBD controls with normal colonoscopy, sporadic colorectal cancer patients, and IBD patients with and without neoplasia. The authors found that methylation patterns in 2 of the 5 genes, *SLIT2 and EYA4*, were sufficient to stratify patients for cancer risk, and also point out that methylation levels in non-neoplastic IBD mucosa are an important component, as these are much higher than in the non-IBD and CRC controls.

SATB2 Is Superior to CDX2 in Distinguishing Signet Ring Cell Carcinoma of the Upper Gastrointestinal Tract and Lower Gastrointestinal Tract.
Ma C, Lowenthal BM, Pai RK.
Am J Surg Pathol. 2018 Dec;42(12):1715-1722.
https://www.ncbi.nlm.nih.gov/pubmed/30212392
The authors of this study evaluated the expression of SATB2 and CDX2 in 159 primary (n=93) and metastatic (n=66) upper and lower GI tract signet ring cell adenocarcinomas and 13 metastatic breast carcinomas with signet ring cell features. SATB2+ was identified in 88% (43/49) of colorectal, 82% (27/33) of appendiceal, 13% (7/54) of gastric, and 35% (8/23) of esophageal/ esophagogastric junction signet ring cell carcinomas. SATB2 + was more frequent in primary and metastatic signet ring cell carcinomas of lower GI tract origin than those from upper GI tract (70/82, 85% vs. 15/77, 19%, P<0.01). Compared with CDX2, SATB2+ and SATB2 +/CDX2+ had higher specificities for signet ring cell carcinomas from the lower GI tract (81% vs. 49% and 86% vs. 49%, respectively, P<0.01). 2/13 (15%) metastatic breast carcinoma were SATB2+, but all were CDX2-. Based on these findings authors concluded that SATB2 is a relatively specific immunohistochemical marker for both metastatic and primary signet ring cell carcinomas of lower GI tract origin and is more specific than CDX2 in distinguishing signet ring cell carcinomas of the lower and upper GI tract.

Mesenteric tumour deposits arising from small-intestine neuroendocrine tumours are frequently associated with fibrosis and IgG4-expressing plasma cells.
Roberts J, Gonzalez RS, Revetta F, Shi C.
Histopathology. 2018 Nov;73(5):795-800.
https://www.ncbi.nlm.nih.gov/pubmed/29943407
Mesenteric tumor deposits (MDTs) frequently occur in small-intestine neuroendocrine tumors. MTDs are defined as discrete but irregular mesenteric tumor nodules discontinuous from the primary neoplasm; they are associated with frequent liver metastasis and a poor prognosis. In addition, MTDs are frequently associated with dense fibrosis, which can radiographically simulate IgG4-related sclerosing mesenteritis. In this study, the authors examined whether mesenteric tumor deposits in patients with small-intestine NETs neuroendocrine tumors

showed histological and immunophenotypic overlap with IgG4-related sclerosing mesenteritis. Sixty-six mesenteric tumor deposits from 66 patients with small-intestine neuroendocrine tumors were assessed for clinicopathological features and the presence of IgG4-positive and IgG-positive plasma cells by immunohistochemistry. Seventeen mesenteric tumor deposits (26%) showed >40 IgG4- positive plasma cells per high-power field(HPF), and the majority of cases (68%) showed at least some staining of IgG4-positive plasma cells. Mesenteric tumor deposits with >20 IgG4-positive plasma cells/HPF tended to be larger and had more IgG-positive plasma cells and a higher IgG4-positive/IgG-positive plasma cell ratio. All but one mesenteric tumor deposit with >20 IgG4-positve plasma cells had a ratio of >40%. IgG4 expression is frequent in mesenteric tumor deposits from small-intestine neuroendocrine tumors. The authors conclude that MTDs seen in small-intestine NETs can be impressive mimics of IgG4-related sclerosing mesenteritis clinically and radiographically. Furthermore, the adjacent fibrosis, lymphoplasmacytic inflammation and significant numbers of IgG4-positive PC can cause histological confusion in the absence of sampled tumor cells. Undersampling of tumor on biopsies of mesenteric tumor deposits could potentially cause diagnostic confusion with IgG4-related sclerosing mesenteritis. It is important to be aware of this potential pitfall when dealing with a biopsy of a mesenteric mass.

Mixed Adenoma Well-differentiated Neuroendocrine Tumor (MANET) of the Digestive System: An Indolent Subtype of Mixed Neuroendocrine-NonNeuroendocrine Neoplasm (MiNEN).

La Rosa S, Uccella S, Molinari F, Savio A, Mete O, Vanoli A, Maragliano R, Frattini M, Mazzucchelli L, Sessa F, Bongiovanni M.

Am J Surg Pathol. 2018 Nov;42(11):1503-1512.

https://www.ncbi.nlm.nih.gov/pubmed/30001239

The authors investigated the clinico-pathologic and molecular features of 12 GI tract (1-stomach, 3- duodenum and 8 –colon) mixed adenoma and well-differentiated neuroendocrine tumor (MANETs). In all cases, the adenoma (8 low grade dysplasia, 4 high grade dysplasia) accounted for the largest component and the NET was localized in the deep central portion of polyps. Neuroendocrine hyperplasia was identified in the adjacent adenomatous component in 5 cases. NET was confined to mucosa or muscularis mucosae, with only one case showed infiltration into submucosa. NET component was grade 1 in 9 cases, grade 2 in 2 cases and grade 3 in 1 case based on KI67 index. The NET component was p53 negative in all cases and 3 of 9 cases showed variable nuclear positivity for β-catenin in both components. Both tumor components in all cases were negative for *KRAS, BRAF*, and *PIK3CA* gene mutations and microsatellite instability. All patients with follow-up data were alive and free of disease after a mean follow-up time of 9 years. Review of the literature identified 59 previously reported GI MANETs with no tumor-related death. Based on these findings authors concluded that MANETs represent indolent neoplasms and need to be distinguished from aggressive high-grade MiNENs.

A morphological and molecular study of proposed early forms of traditional serrated adenoma.

Bettington M, Rosty C, Whitehall V, Leggett B, McKeone D, Pearson SA, Walker N.
Histopathology. 2018 Dec;73(6):1023-1029.
https://www.ncbi.nlm.nih.gov/pubmed/3007084

Traditional serrated adenoma (TSA) is the least common subtype of serrated colorectal polyp, and is characterized histologically by tubulovillous architecture, ectopic crypt formations, slit-like serrations, and typical cytology (cells with abundant intensely eosinophilic cytoplasm and centrally placed pencillate nuclei). The authors state that some large TSAs present with a flat 'shoulder' component surrounding the central protuberant component and hypothesize that small polyps with the same histology as these shoulder regions may represent early TSAs and hence will probably have morphological, immunohistochemical and molecular features similar to those of the shoulder areas of large TSAs. At present, many of these polyps would be diagnosed as 'odd-looking' tubular adenoma (KRAS-mutated forms) or possibly as sessile serrated polyps with dysplasia (BRAF-mutated forms).To this end, they collected 70 small (<10 mm) polyps that may represent early TSAs on the basis of typical TSA cytology covering the luminal surface and 12 large TSAs with a shoulder component resembling these small polyps. Morphologically, slit-like serrations were present in 81%, ectopic crypt formations were present in 67%, and a villous component was present in 47%. These histological features were similar to those of the 12 shoulder lesions. Immunohistochemical stains showed an absence of b-catenin nuclear expression in 96% of the small polyps, retained expression of MLH1 in 100%, and Ki67 positivity restricted to the crypt bases and ectopic crypt formations. BRAF and KRAS mutations were identified in 47% and 31% of the polyps, respectively. These morphological, immunohistochemical and molecular findings are similar to what has been reported in large TSAs, and support the hypothesis that these polyps represent early forms of TSA.

Smoking and Other Risk Factors in Individuals With Synchronous Conventional High-Risk Adenomas and Clinically Significant Serrated Polyps.

Anderson JC, Calderwood AH, Christensen BC, Robinson CM, Amos CI, Butterly L.
Am J Gastroenterol. 2018 Dec;113(12):1828-1835.
https://www.ncbi.nlm.nih.gov/pubmed/30385834

Although this is an essentially a pure clinical paper, it seemed rather appropriate to include it here for anyone considering a New Year's resolution. The authors of this article sought to examine the risk profile of individuals who had been diagnosed with high-risk colonic adenomas (HRA) and clinically significant serrated polyps (CSSP). The former was defined as adenomas measuring larger than 1.0 cm, containing a villous component, having high-grade dysplasia or carcinoma, or consisting of greater than 2 polyps. The latter was defined as sessile serrated adenomas/polyps, traditional serrated adenomas, and any hyperplastic polyps measuring greater than 1.0 cm. Data was extracted from a statewide registry and included information from a final cohort of 18,354 patients receiving their first screening colonoscopy. Of these, 1309 had HRA alone, 461 had CSSP alone, and 89 individuals had synchronous HRA+CSSP. Various clinical variables were examined including age, sex, body mass index (BMI), family history,

aspirin use, educational level, marital status, exercise, and alcohol and smoking habits. Of these, higher BMI, older age, and smoking were associated with an increased risk of having HRA+CSSP with the latter imparting an eight fold-increase risk compared to non-smokers. The authors note that smoking has already been shown to be associated with the development of HRAs in other studies. Factors associated with a reduced risk of HRA included exercise and aspirin use. The authors conclude that a patient's smoking status may need to be considered in future surveillance guidelines and as a modifiable risk factor smoking cessation should be encouraged.

Clinical Practice Guideline on Screening for Colorectal Cancer in Individuals with a Family History of Nonhereditary Colorectal Cancer or Adenoma: The Canadian Association of Gastroenterology Banff Consensus

Leddin D, Lieberman DA, Tse F, Barkun AN, Abou-Setta AM, Marshall JK, Samadder NJ, Singh H, Telford JJ, Tinmouth J, Wilkinson AN, Leontiadis GI.
Gastroenterology. 2018 Nov;155(5):1325-1347.e3.
https://www.ncbi.nlm.nih.gov/pubmed/30121253

These consensus recommendations were developed by the Canadian Association of Gastroenterology and further endorsed by the American Gastroenterological Association with the purpose of providing guidelines for patients with a family history (FH) of non-hereditary colorectal cancer (CRC). The group makes "strong recommendations" for CRC screening for all individuals with a family history of CRC or documented adenoma. However, they acknowledge the limited and "very low quality" evidence used to develop additional guidelines, such as interval follow-up or age at first screening. As such, 16 of the 19 specific guidelines are "suggestions" rather than "recommendations". Some of these suggestions include:

- Colonoscopy is suggested (recommended in individuals with ≥2 first-degree relatives [FDRs]), with fecal immunochemical test as an alternative.
- The elevated risk associated with an FH of ≥1 FDRs with CRC or documented advanced adenoma suggests initiating screening at a younger age (eg, 40–50 years or 10 years younger than age of diagnosis of FDR).
- A shorter interval of every 5 years was suggested for individuals with ≥2 FDRs, and every 5–10 years for those with FH of 1 FDR with CRC or documented advanced adenoma compared to average-risk individuals.
- It is suggested that individuals with an FH of ≥1 second-degree relatives only, or of nonadvanced adenoma or polyp of unknown histology, be screened according to average risk guidelines.

Consensus molecular subtype classification of colorectal adenomas.

Komor MA, Bosch LJ, Bounova G, Bolijn AS, Delis-van Diemen PM, Rausch C, Hoogstrate Y, Stubbs AP, de Jong M, Jenster G, van Grieken NC, Carvalho B, Wessels LF, Jimenez CR, Fijneman RJ, Meijer GA; NGS-ProToCol Consortium.
J Pathol. 2018 Nov;246(3):266-276.
https://www.ncbi.nlm.nih.gov/pubmed/29968252

This paper examines whether colonic adenomas can be reliably stratified into the consensus molecular subtype (CMS) classes. This classification system was developed for colorectal carcinomas by the CRC Subtyping Consortium and is based on RNA expression of a number of genes. The authors begin this publication by saying that only a minority of adenomas progress through the adenoma to carcinoma sequence and that this can occur by developing microsatellite instability or by DNA copy number aberrations. The authors hoped to determine whether CMS classes can already be determined at the adenoma stage and whether adenomas with a high-risk of progression (have DNA copy number aberrations) would have different CMS classes. A total of 62 adenomas with available snap-frozen material were analyzed by DNA copy number analysis, MSI assay, and RNA sequencing. With the latter results, 54 (87%) of the adenomas could be CMS classified with the most prevalent subtype being the CMS3 (metabolic subtype) group (73%). Interestingly, this was the least common CMS subtype identified in a larger cohort of colorectal carcinomas that were simultaneously analyzed. A smaller proportion of adenomas (13%) were classified as CMS2 (canonical subtype), a group which appeared to be enriched for adenomas considered to be at a higher risk of progression having DNA copy number changes. No statistical difference between histologic type or grade of dysplasia was identified between these two groups. The authors conclude by saying that CMS classification of colorectal adenomas is possible and the frequency of subtypes appreciated in their study is consistent with what would be expected of adenomas which have the potential to progress to carcinoma.

Molecular characterization of sessile serrated adenoma/polyps with dysplasia/carcinoma based on immunohistochemistry, next-generation sequencing, and microsatellite instability testing: a case series study.

Murakami T, Akazawa Y, Yatagai N, Hiromoto T, Sasahara N, Saito T, Sakamoto N, Nagahara A, Yao T.

Diagn Pathol. 2018 Nov 20; 13(1):88.

https://www.ncbi.nlm.nih.gov/pubmed/30458818

In this study, the authors evaluated the molecular biological features of colorectal sessile serrated adenoma/polyps **(**SSA/Ps) with dysplasia/carcinoma, representing relatively early stages of the serrated neoplasia pathway. Immunostaining for β-catenin, MLH1, mucins, CD10; targeted next-generation sequencing; and microsatellite instability (MSI) testing was performed in 8 SSA/P lesions comprising of 4 SSA/Ps with high-grade dysplasia and 4 SSA/Ps with submucosal carcinoma. 5 cases showed lost MLH1 expression. All lesions studied showed positivity for nuclear β-catenin expression, and MUC2, and were negative for CD10. MUC5AC and MUC6 positivity was observed in 7 cases. Genetically, the most frequently mutated gene was BRAF (7 cases), and other mutations were detected in FBXW7 (3 cases); TP53 (2 cases), and KIT, PTEN, SMAD4, and SMARCB1 (1 case each). 4 of 8 lesions were MSI-high and the remaining 4 lesions were microsatellite-stable (MSS). All 4 MSI-high lesions displayed MLH1 loss, 3 of which harbored a FBXW7 mutation, but not a TP53 mutation. However, 2 MSS lesions harbored a TP53 mutation, although none harbored a FBXW7 mutation. Colorectal SSA/Ps with dysplasia and invasive carcinoma frequently harbored BRAF mutations and showed nuclear β-catenin

expression. Furthermore, these lesions might not only be associated with MSI-high colorectal cancer, but also MSS, and MSI-high and MSS serrated lesions might have distinct genetic features (such as FBXW7 and TP53 mutations). BRAF-mutant MSS colon carcinomas are particularly important because they have a dismal prognosis and an aggressive clinical course with adverse histologic features, such as lymphatic and perineural invasion and high tumor budding.

Gut microbiota modulate T cell trafficking into human colorectal cancer.
Cremonesi E, Governa V, Garzon JFG, Mele V, Amicarella F, Muraro MG, Trella E, Galati-Fournier V, Oertli D, Däster SR, Droeser RA, Weixler B, Bolli M, Rosso R, Nitsche U, Khanna N, Egli A, Keck S, Slotta-Huspenina J, Terracciano LM, Zajac P, Spagnoli GC, Eppenberger-Castori S, Janssen KP, Borsig L, Iezzi G.
Gut. 2018 Nov;67(11):1984-1994.
https://www.ncbi.nlm.nih.gov/pubmed/29437871
This study fills in a gap in understanding of the mechanism of tumor infiltrating lymphocyte (TIL) recruitment. Using 16S ribosomal RNA (16SrRNA) expression by quantitative reverse transcription PCR in fresh colorectal cancer samples and healthy control tissue, they evaluated genes encoding chemokines and bacterial markers. Both in vitro and in vivo (mouse) studies were performed. The authors found that distinct chemokine signatures were associated with specific TIL, for example CCL5, CXCL9, and CXCL10 with cytotoxic T cells and T-helper-1 cells, and that expression was dependent on defined gut bacteria. The overall effect being that gut microbiota stimulates colorectal cancer cells to secrete specific chemokines which recruit beneficial T cells, and ultimately resulting in improved patient survival.

Discovery of methylated circulating DNA biomarkers for comprehensive non-invasive monitoring of treatment response in metastatic colorectal cancer.
Barault L, Amatu A, Siravegna G, Ponzetti A, Moran S, Cassingena A, Mussolin B, Falcomatà C, Binder AM, Cristiano C, Oddo D, Guarrera S, Cancelliere C, Bustreo S, Bencardino K, Maden S, Vanzati A, Zavattari P, Matullo G, Truini M, Grady WM, Racca P, Michels KB, Siena S, Esteller M, Bardelli A, Sartore-Bianchi A, Di Nicolantonio F.
Gut. 2018 Nov;67(11):1995-2005.
https://www.ncbi.nlm.nih.gov/pubmed/28982739
The authors identified a five-gene methylation panel for colorectal cancer (CRC) in cell-free circulating DNA (cfDNA) which could be used for non-invasive treatment monitoring in clinical trials or in practice. 149 CRC cell lines were used to prepare methylation arrays. After identifying five cancer-specific methylation loci, digital PCR was used to measure methylation of the five genes in 82 cases of tumor tissue DNA and in 182 cfDNA samples from patients with metastatic CRC. All tumor tissues and 85.7 % of cfDNA samples had methylation of at least one of the five markers, which was unrelated to treatment, and which correlated with progression-free survival. The authors point out that this method alleviates the need for personalized assays since the markers are broadly expressed.

Tumor Grade Is Prognostically Relevant Among Mismatch Repair Deficient Colorectal Carcinomas.

Johncilla M, Chen Z, Sweeney J, Yantiss RK
Am J Surg Pathol. 2018 Dec;42(12):1686-1692.
https://www.ncbi.nlm.nih.gov/pubmed/30179899

The authors of this study evaluated the prognostic significance of conventional tumor grade in 116 [77 localized (stage I to II) and 39 advanced (stage III to IV)] mismatch repair deficient colorectal carcinomas. High grade (<50% gland formation) mismatch repair-deficient tumors were more often of advanced stage than low-grade tumors (46% vs. 23%, P=0.01). Tumor budding was absent in most (83%) mismatch repair deficient tumors. High grade and tumor budding were significantly associated with decreased disease-free survival (P=0.01 and 0.04, respectively). Tumors with predominantly solid component were significantly associated with decreased disease-free survival compared with low-grade tumors (HR =6.1, P<0.01). There was no association between nuclear grade and tumor infiltrating lymphocytes with tumor stage or clinical outcome. Based on these findings authors concluded that histologic grade is an important prognostic factor among mismatch repair deficient colorectal carcinomas and mismatch repair status should not supplant histologic grade in the assessment of colorectal carcinomas.

Two-stain immunohistochemical screening for Lynch syndrome in colorectal cancer may fail to detect mismatch repair deficiency.

Pearlman R, Markow M, Knight D, Chen W, Arnold CA, Pritchard CC, Hampel H, Frankel WL.
Mod Pathol. 2018 Dec;31(12):1891-1900.
https://www.ncbi.nlm.nih.gov/pubmed/29967423

This study looks at a strategy, used by some, for universal screening for Lynch syndrome using as two immunohistochemistry stain panel of MSH6 and PMS2 rather than the four-stain panel of MLH1, PMS2, MSH2, and MSH6. The strategy relies on the observation that MLH1 and PMS2 as well as MSH2 and MSH6 form dimers and, if MLH1 or MSH2 are lost, their respective partners are thought to be unstable and appear negative by immunohistochemistry. According to current published literature, loss of MSH2 with intact MSH6 staining would not be expected; however, the authors state they were made aware of a case of a patient with germline MSH2 expression, found after gene sequencing due to high clinical suspicion, that failed to be identified by the two antibody panel. The authors hypothesize that a subset of patients with MSH2 related Lynch syndrome could be missed by the two-stain screening panel due to apparent expression of MSH6 by immunohistochemistry. Thy looked at a set of cases from the Ohio Colorectal Prevention Initiative and out of 33 cases with absence of MSH2, 14 had no MSH6 expression, 8 had ambiguous staining, and 11 had convincing staining that could be interpreted as positive. The authors concluded that the two-stain method fails to detect some patients with Lynch syndrome and that the four-stain method is recommended for optimal screening.

Assessing colorectal cancer mismatch repair status in the modern era: a survey of current practices and re-evaluation of the role of microsatellite instability testing.
Hissong E, Crowe EP, Yantiss RK, Chen YT.
Mod Pathol. 2018 Nov;31(11):1756-1766.
https://www.ncbi.nlm.nih.gov/pubmed/29955148
The stated goals of this study were to identify the current sate of mismatch repair gene testing in pathology practices in the United States, Canada, Europe, and Australia as well as to re-evaluate discordant rates between immunohistochemistry and PCR within the authors own institution. For the first part of the study, 96 institutions were surveyed and 86% reported universal screening (76% used immunohistochemistry and 20% PCR). The majority of the institutions that employed PCR were academic institutions that used both immunohistochemistry and PCR due to the stated discrepancy rate of 5% between the two methods in older literature. The second part of the study evaluated 809 colorectal cancers from the authors home institution, which tests by both PCR and immunohistochemistry. The authors found and extremely low discordance rate between PCR and immunohistochemistry and suggest that, in the modern era, immunohistochemistry is the preferred single screening test with PCR used only in cases with equivocal immunohistochemistry patterns.

Worldwide Practice Patterns in Lynch Syndrome Diagnosis and Management, Based on Data From the International Mismatch Repair Consortium.
Pan JY, Haile RW, Templeton A, Macrae F, Qin F, Sundaram V, Ladabaum U.
Clin Gastroenterol Hepatol. 2018 Dec;16(12):1901-1910.e11.
https://www.ncbi.nlm.nih.gov/pubmed/29702294
This is an interesting overview of the broad scope of practices used throughout the world to identify and manage patients with Lynch syndrome (LS). Data was collected via a questionnaire that was sent to institutional members of the International Mismatch Repair Consortium. With information obtained from 55 complete questionnaires, the authors report the diversity of practices representing Asia, Australasia, Europe, North America, and South/Central America. While the centers reported a wide range of annual referrals for suspected LS (<25 to >500), LS was newly diagnosed in roughly 1 of 5 of all referred patients. A relative majority of centers (56%) performed routine tumor testing to identify new cases with 100% of these institutions carrying out universal testing of all new cases of colorectal carcinoma. A smaller number of these institutions evaluated all new endometrial (50%) or ovarian (13%) cases. Nearly all respondents reported using MMR testing by immunohistochemistry (98%) with 78% also using microsatellite instability testing. To identify sporadic cases, 75% of institutions test for *BRAF* mutations while 56% test for *MLH1* promoter hypermethylation. The remaining portions of the article pertain to management practices once LS patients are identified. The authors conclude by saying that there is widespread heterogeneity in the management practices for LS on a worldwide scale and that this is likely related to the availability of rapidly emerging testing modalities.

Cost Effectiveness of Intraoperative Gross Examination in Colorectal Resections: A Retrospective Review of 200 Consecutive Cases.

Khararjian A, Mathew P, Choudhary A, Baras A.
Arch Pathol Lab Med. 2018 Nov;142(11):1403-1406
https://www.ncbi.nlm.nih.gov/pubmed/29902068

In this study, the authors evaluated the utility of intraoperative gross examinations of colorectal resections, and their effect on immediate surgical management and associated costs. They reviewed 270 cases of colorectal resections for primary disease during a 15-month period. The cases were separated into 3 categories: frozen section performed, intraoperative gross examination performed, and no intraoperative consultation. Of the 270 cases, 200 (74.1%) had an intraoperative gross examination. In 34 of the 200 cases (17%), additional specimens were taken and, therefore, required operative note review to ascertain whether the additional specimens taken were based on the findings from the intraoperative gross examination. After reviewing the operative notes for those 34 cases, none (0%) were a result of the gross findings reported. The average associated time for intraoperative gross examinations was 27.67 minutes (including transport). The billable costs exceeded $7000 during the study period, and the cost of the pathology assistant's time per case was $22.10. Importantly, the study demonstrated that no change in surgical management was a result of gross examination of colorectal resection specimens and that the associated costs were significant. Although the direct costs (reimbursement and pathology staff time) were not particularly high for intraoperative gross examinations, indirect costs (such as pathology assistants time which could have been used for grossing other specimens and/or increase in operating time and/or unnecessarily prolonged patient exposure to anesthetic agents) could make them low-yield procedures. The study shows that decreasing unnecessary consultations will directly save the health care system money by eliminating billable services and will also increase the efficiency of the pathology department by reducing the opportunity costs for the time of the pathologist and the pathology staff.

Predictors of Metastases in Rectal Neuroendocrine Tumors: Results of a National Cohort Study.

Concors SJ, Sinnamon AJ, Folkert IW, Mahmoud NN, Fraker DL, Paulson EC, Roses RE
Dis Colon Rectum. 2018 Dec;61(12):1372-1379.
https://www.ncbi.nlm.nih.gov/pubmed/30312223

This retrospective study analyzed risk factors for metastasis in patients with rectal neuroendocrine tumors (rNETs). The incidence of early and smaller rNET's has increased due to the increased use of screening colonoscopies. Local excision is commonly recommended for small tumors, less than 2cm, and resection for lesions greater than 2cm. However, the evidence supporting this approach is limited to small studies. Although the 5 year overall survival rate for rNET is high, it drops considerably when regional and/or distant metastases are present. Therefore, these authors sought to identify factors that could predict local and distant metastatic disease. To that end, 4893 rNET's were reviewed for size, degree of differentiation, and presence of local or distant metastatic disease. Of those patients 79.3% had well-differentiated tumors, 11% had moderately differentiated tumors and 9.7% had poorly differentiated tumors. 75% were less than 1cm and median tumor size was 0.6 cm. 8% of

patients had distant disease at time of presentation. Using multivariable logistic regression, larger size was associated with higher risk of lymph node involvement and both size and differentiation were associated with increased risk for metastatic disease. Cut point analysis showed a difference in risk above and below 1.15cm which was rounded to 1.00cm. Well differentiated, non-metastatic, patients had the best 5-and 10- year overall survival rates at 93.6% and, as expected, distant metastatic disease resulted in the poorest overall survival, 15.4%. In conclusion, the authors propose that tumors >1.5cm are more likely to metastasize to regional lymph nodes and less-differentiated and larger tumors are more likely metastasize to distant sites. They note specifically that a 1.15 cm cut point appears more relevant than 2 cm as an indication for resection over local excision.

Morphologic and Immunohistochemical Characteristics of Anorectal Melanoma.
Charifa A, Zhang X.
Int J Surg Pathol. 2018 Dec; 26(8):725-729
https://www.ncbi.nlm.nih.gov/pubmed/29759015
The authors reviewed histologic features and immunohistochemical stains of 19 anorectal melanoma cases. Epithelioid histopathologic morphology was observed in 63.2% of the cases followed by 47.4% of the cases with spindle- cell, 26.3% with lymphoma-like, and 26.3% with pleomorphic morphologies. Junctional melanocytic activity was seen in almost half of the cases. Melanin pigment was absent (amelanotic) in nearly 40% of the cases. Immunohistochemically, diffuse positive expression of Sox10, S100 protein, melan-A, and HMB-45 was seen in 100%, 40%, 53.3%, and 38.5% of the cases, respectively. Cytokeratins were negative and CD56 was positive in 2 cases. In summary, anorectal melanoma often presents with a variety of histologic morphologies and lacks the diagnostic clues such as junctional melanocytic activity and melanin pigment. Anorectal melanoma should be kept in mind in the differential diagnosis of malignant neoplasms of anorectal region with epithelioid, spindle-cell, lymphoma- like, and pleomorphic morphologies. Sox10 immunohistochemistry stain can be used as a first-line screening tool to avoid extensive or unnecessary workups and/or potential misdiagnosis.

Treatment Effects Can Mimic Recurrent Extramammary Paget Disease in Perianal Skin.
Pittman ME, Milsom J, Yantiss RK.
Am J Surg Pathol. 2018 Nov;42(11):1472-1479.
https://www.ncbi.nlm.nih.gov/pubmed/30045063
The aim of the study was to evaluate the therapy-related changes and possible diagnostic pitfalls in patients with long standing primary perianal Paget disease. The authors reviewed 412 post-treatment tissue samples from 3 women with primary perianal Paget disease who underwent wide excision, skin grafting, and topical 5-fluorouracil therapy. Biopsy samples from engrafted skin often displayed single and clustered cells dispersed in the deep epidermis with hyperchromatic nuclei surrounded by a clear halo or cytoplasmic pallor simulating basophilic mucin. Similar vacuolated cells were scattered throughout all levels of the epidermis in biopsy samples following topical chemotherapy. These abnormal cells in both situations were negative

for CK7 and mucicarmine. All patients showed disease recurrence and in some biopsies showed classic features, whereas others were smaller with less conspicuous nuclear atypia and not overtly mucinous cytoplasm. All Paget cells showed strong, membranous CK7 staining. Based on these findings authors concluded that treatment of perianal Paget disease can elicit cytologic abnormalities in benign epithelial cells that simulate the cytologic features of recurrent disease, and can diminish the atypia of Paget cells. Immunohistochemical stains for CK7 can be helpful in evaluating for recurrence from these patients.

Testing for Human Papillomavirus Strains 16 and 18 Helps Predict the Presence of Anal High-Grade Squamous Intraepithelial Lesions.

Sambursky JA, Terlizzi JP, Goldstone SE

Dis Colon Rectum. 2018 Dec;61(12):1364-1371.

https://www.ncbi.nlm.nih.gov/pubmed/30308526

Recommended screening for anal high-grade squamous intraepithelial lesions (HSIL) for the prevention of invasive squamous cell carcinoma (SCCA) currently includes digital rectal examination (DRE) and anal cytology. Similar to cervical SCCA, HR-HPV causes over 90% of all anal SCCA. However routine high-risk HPV (HR-HPV) testing is not FDA recommended and therefore, not always included. Therefore, the authors of this study retrospectively reviewed the addition of HR-HPV to the current anal dysplasia screening protocols in an attempt to improve specificity, PPV and NPV. Ranging from 18-89 years old, the study included 896 patients, including 45 women, and the rest being men, half who were HIV positive with median viral load undetectable. Patients with a history of anal cancer, inadequate cytology and less than 18 years old were excluded. In this study, two HPV assays were used: The older, gold standard, HC2 which detects 1 or more of 13 HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and the newer Cobas assay which detects those same 13 strains plus HPV-66 while concurrently genotyping for 16/18 specifically. Patients also underwent DRE and had both anal cytology and high-risk anoscopy (HRA) performed. Patients with benign cytology who were negative for HR-HPV were used as the baseline comparison to calculate relative risk (RR). Ultimately 894 patients were included in the study, of which 45% had normal cytology and 45.3% showed ASCUS. There was no difference between HIV positive and negative patients. The incidence of HR-HPV was 58.6% of which 34% were genotyped as HPV16/18. HIV positive patents did test positive more often than HIV negative patients (65.7% vs 53%; p=0.0001). Within the HR-HPV positive group, HSIL was detected in 24% of patients and those positive for genotypes 16/18 had HSIL more often than those positive for other HR strains. SCCA was not found in any patients. As all patients also underwent HRA, regardless of cytology, 3.7% of those with normal cytology were found to have HSIL, the majority of which were positive for HPV 16 or 18 (13.8% vs 1.8%). Similarly patients with ASCUS cytology had an increased incidence of HSIL when combined with HR-HPV positivity (41.7% vs 19.9%). As such, these authors conclude that the addition of testing for HR-HPV strains 16 and 18 to routine screening for anal dysplasia should be performed on all patients with benign cytology. Furthermore, it is recommended that those patients that test positive for HPV16/18 should undergo HRA. For those patients with benign cytology and negative for HR-HPV the proposed recommendation is to repeat screening

in 1 year as the risk of HSIL is significantly less when HPV 16/18 negative. The authors state that testing for HR-HPV, including genotypes 16 and 18 can identify patients at high risk for HSIL.

Journals Reviewed November-December 2018

Advances in Anatomic Pathology
American Journal of Clinical Pathology
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American Journal of Pathology
American Journal of Surgical Pathology
Annals of Diagnostic Pathology
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