GIPS Journal Watch July & August 2018

***Helicobacter pylori* Infection Is Associated With Reduced Risk of Barrett's Esophagus: An Analysis of the Barrett's and Esophageal Adenocarcinoma Consortium.**
Wang Z, Shaheen NJ, Whiteman DC, Anderson LA, Vaughan TL, Corley DA, El-Serag HB, Rubenstein JH, Thrift AP.
Am J Gastroenterol. 2018 Aug;113(8):1148-1155.
https://www.ncbi.nlm.nih.gov/pubmed/29880962

This study serves as an interesting contrast to the investigation regarding *Helicobacter pylori* (HP) infection and eosinophilic esophagitis published in this same issue. In this study, the authors sought to better understand the relationship between HP and the risk of developing Barrett's esophagus (BE). To do so, the authors utilized data from 6 previously published case-control studies regarding BE in which individual data was available on HP infection status. In all studies, BE was defined as endoscopic evidence of columnar mucosa in the tubular esophagus with intestinal metaplasia on esophageal biopsy. In the end, individual level data was available for 1308 BE patients as well as 1388 controls patients. The authors found that HP infection was inversely associated with the risk of BE (OR=0.44). Interestingly, the study authors found a stronger inverse association in individuals infected by a CagA-positive stain of HP. These findings held true even when controlling for other factors including body mass index and smoking status. This inverse relationship was not appreciated however in a controlled group of patients with gastroesophageal reflux disease. The authors conclude that HP infection, particularly with a CagA-positve strain, is associated with a lower risk of BE and that this is probably mediated by a decrease in gastroesophageal reflux disease in infected patients.

Improved Progression Prediction in Barrett's Esophagus With Low-grade Dysplasia Using Specific Histologic Criteria.
Ten Kate FJC, Nieboer D, Ten Kate FJW, Doukas M, Bruno MJ, Spaander MCW, Looijenga LHJ, Biermann K; ProBar study group and Palga Group.
Am J Surg Pathol. 2018 Jul;42(7):918-926.
https://www.ncbi.nlm.nih.gov/pubmed/29697438

The authors of this study aimed at improving the prediction of progression in Barrett's esophagus (BE) patients with low grade dysplasia (LGD) by a defined histologic criteria panel. The authors identified that 4 of 12 histologic criteria diagnostic of LGD showed to have a moderate to good interobserver agreement among 4 gastrointestinal pathologists in a cohort of 84 BE patients with LGD (15 progressors and 69 nonprogressors) and these criteria were significantly associated with neoplastic progression. The 4 criteria were loss of surface maturation (defined as no maturation of the epithelium seen on low power from the proliferation zone up to the surface), mucin depletion (defined as almost total to total disappearance of mucus from the surface columnar cells on high power), nuclear enlargement (defined as a nuclear size at least 2× as large as the nuclei of the normal not inflamed columnar epithelium), and increase of mitosis (defined as at least 1 mitosis at the epithelial surface or in the neck of the crypts; mitoses in the base of the crypt are disregarded). Combination of these criteria differentiated high-risk of progression (≥ 2 criteria) and low-risk of progression group (≤ 1criteria) amongst patients with LGD ($P<0.001$). The validation of this panel in predicting progression was performed by two expert pathologists in a cohort of 98 BE patients with LGD (30 progressors and 68 nonprogressors) from a prospective ProBar study. Patients with ≥2 criteria in their index LGD biopsy showed a significantly higher risk of progression to HGD or EAC (HR, 3.52; 95% CI, 1.56-7.97; *P*=0.003) compared to patients

with up to one of the criteria. Additionally, aberrant expression of p53 (overexpression/complete loss) and histologic criteria showed improved area under the curve on ROC analysis. Based on these findings authors concluded that panel of 4 histologic criteria was helpful in segregating BE patients with LGD diagnosis into defined prognostic groups.

Factors Associated With Progression of Barrett's Esophagus: A Systematic Review and Meta-analysis.
Krishnamoorthi R, Singh S, Ragunathan K, Visrodia K, Wang KK, Katzka DA, Iyer PG.
Clin Gastroenterol Hepatol. 2018 Jul;16(7):1046-1055.
https://www.ncbi.nlm.nih.gov/pubmed/29199147

This systematic review and meta-analysis was performed to identify risk factors associated with the progression of baseline non-dysplastic Barrett's esophagus (BE) or BE with low-grade dysplasia to that with high-grade dysplasia or adenocarcinoma. The authors note that surveillance guidelines are available for patients with BE but the cost-effectiveness of these strategies, particularly when they are applied to all BE patients, need to be considered. Therefore, these authors sought to identify specific clinical, endoscopic, and histologic factors that may be associated with future progression in BE so that surveillance protocols may allow for some degree of stratification. The authors utilize data from 20 studies which encompassed 74943 patients. All studies reported on a number of predictors of progression from which pooled estimates (odds ratios) were determined. This analysis demonstrated in association of BE progression with increasing age, male sex, smoking, and increasing BE segment length. Additionally, the use of proton pump inhibitors or status was associated with a reduced risk of progression. Notably, a diagnosis of low-grade dysplasia was associated with a fourfold increase in the risk of BE progression. Several factors did not appear to affect this risk, including alcohol use and obesity. The authors conclude by stating that individuals with these high risk features should perhaps undergo more intensive surveillance or that these factors could potentially be used in the development of future risk scores. They also conclude by suggesting that as a modifiable risk factor, smoking cessation should be discussed with the patient.

Diagnosis and risk stratification of Barrett's dysplasia by flow cytometric DNA analysis of paraffin-embedded tissue.
Choi WT, Tsai JH, Rabinovitch PS, Small T, Huang D, Mattis AN, Kakar S.
Gut. 2018 Jul;67(7):1229-1238.
https://www.ncbi.nlm.nih.gov/pubmed/28642331
The authors investigate whether DNA content abnormality detected by flow cytometry can be used to diagnose dysplasia and aid in stratifying low-grade dysplasia (LGD) and indefinite for dysplasia (IND) formalin-fixed paraffin-embedded tissue samples. The study set included 80 high-grade dysplasia (HGD) samples, 38 LGD, 21 IND, and 14 negative for dysplasia (ND). After sectioning, manual dissection, and flow analysis, DNA aneuploidy was identified in 76 HGD (95%), 8 LGD (21.1%), 2 IND (9.5%), and 0 ND samples. Sensitivity and specificity of DNA content abnormality was estimated as 95% and 85%, respectively. For individuals with DNA aneuploidy detected at baseline LGD or IND, univariate hazard ratios for subsequent detection of HGD or esophageal adenocarcinoma were 7.0 and 20.0, respectively ($p < 0.001$). This methodology can be used to identify a subset of patients with LGD and IND who are at increased risk for future HGD or adenocarcinoma.

Houston Consensus Conference on Testing for Helicobacter pylori Infection in the United States.
El-Serag HB, Kao JY, Kanwal F, Gilger M, LoVecchio F, Moss SF, Crowe S, Elfant A, Haas T, Hapke RJ, Graham DY
Clin Gastroenterol Hepatol. 2018 Jul;16(7):992-1002.
https://www.ncbi.nlm.nih.gov/pubmed/29559361

This article serves as a meeting summary for the Houston Consensus Conference which consisted of a group of 11 experts regarding the diagnosis and treatment of *Helicobacter pylori* infections (HP). This consensus conference utilized the modified Delphi panel approach to provide recommendations regarding HP infections at health care systems across the United States of America. These recommendations were further validated by a separate panel of gastroenterologists. This meeting was convened secondary to perceived performance gaps that exist in the practice of HP diagnosis and treatment in this country. This process led to the development of 28 distinct statements regarding this disease process. The full listing of these recommendations, and the evidence used to support them, can be found within this article. Those directly related to histologic examination of gastric biopsy material include statement 17: "We recommend that validated diagnostic testing of stool or gastric mucosal biopsy by culture and susceptibility, or molecular analysis be universally available (100% agree/strongly agree).", statement 21: "We recommend that, if endoscopy is being performed, biopsies (2 each) from the antrum and corpus (+/- the incisura) should be obtained (100% agree/strongly agree).", and statement 27: "We recommend that all patients receiving treatment for HP receive post treatment confirmation of eradication. We recommend that only tests that evaluate for active infection, such as UBT, HpSAg test, or histology (if endoscopy is required for other reasons), are utilized for this purpose (100% agree/strongly agree)."

Differentiating breast carcinoma with signet ring features from gastrointestinal signet ring carcinoma: assessment of immunohistochemical markers

Hui Y, Wang Y, Nam G, Fanion J, Sturtevant A, Lombardo KA, Resnick MB.
Hum Pathol. 2018 Jul;77:11-19.
https://www.ncbi.nlm.nih.gov/pubmed/29317235

This immunohistochemical study looked at expression profiles of breast vs gastrointestinal primary tumors, with a focus on lobular breast carcinoma vs gastric signet ring carcinoma. After evaluating a total of 93 cases with stains for ER, PR, E-cadherin, CK7, CK20, GCDFP-15, mammaglobin, CDX2, GATA-3 and HepPar, the most useful results show:

Breast origin:

ER	sensitivity/specificity:	81.8% / 100%
	PPV / NPV	100% / 89.3%
GATA3	sensitivity/specificity:	100% / 98%
	PPV / NPV	96.8% / 100%

Gastrointestinal origin:

CK20	sensitivity/specificity:	66.7% / 93.3%
	PPV / NPV	94.1% / 63.6%
CDX2	sensitivity/specificity:	72% / 100%
	PPV / NPV	100% / 68.9%

These stains discriminated lobular breast from GI signet ring in 15/16 cases. The authors recommend a combination of ER and Gata3 with CK20 and CDX2 to discriminate between these differential diagnoses.

Gastrointestinal Tract Vasculopathy: Clinicopathology and Description of a Possible "New Entity" With Protean Features.
Louie CY, DiMaio MA, Charville GW, Berry GJ, Longacre TA
Am J Surg Pathol. 2018 Jul;42(7):866-876.
https://www.ncbi.nlm.nih.gov/pubmed/29624512

In this paper the authors reported the clinical and histopathologic findings in 16 cases of GI tract vasculitis or vasculopathy (excluding the cases of IgA vasculitis) identified over a 20-year period at their institution. Eight patients had associated systemic disease. Two patients with systemic lupus erythematosus showed leukocytoclastic vasculitis in small bowel biopsies. Two patients with dermatomyositis, one patient showed leukocytoclastic vasculitis on colonic biopsies and the second patient on small bowel excision specimen showed vasculopathy involving medium caliber veins and arteries with various degrees of occlusion interpreted as dermatomyositis-associated GI vasculopathy. One patient with rheumatoid arthritis showed necrotizing vasculitis of small and medium vessels of descending colon. One patient with granulomatosis with polyangiitis (Wegener granulomatosis) showed necrotizing granulomatous vasculitis on cecum and gastric biopsies. One patient eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome) showed eosinophilic vasculitis on small bowel resection. One patient with Crohn disease showed venulitis with thrombosis on jejunal resection. In 2 of these patients, GI manifestations were the initial presentation of the disease. Eight patient had vasculitis or vasculopathy isolated to the GI tract. The histologic findings included granulomatous venulitis (1), necrotizing arteritis and venulitis (1), enterocolic lymphocytic phlebitis (4), and idiopathic myointimal hyperplasia of arteries in the rectosigmoid (1), and jejunum (1). Five of the cases involved colectomy specimens, and 2 of the cases involved small intestinal resections. Clinically in these cases resections were curative and the disease was self-limited and appeared to be confined to the GI tract on follow-up. Based on these findings and the current literature authors concluded that isolated GI tract vasculopathy is rare, but may be as common as that associated with systemic disease. The common primary vasculopathies were enterocolic lymphocytic colitis and idiopathic myointimal hyperplasia. Idiopathic myointimal hyperplasia occurs predominantly in the left colon and rarely in small bowel and likely represent a more complex, protean disorder.

***Helicobacter pylori* infection does not protect against eosinophilic esophagitis: results from a large multicenter case-control study.**
Molina-Infante J, Gutierrez-Junquera C, Savarino E, Penagini R, Modolell I, Bartolo O, Prieto-García A, Mauro A, Alcedo J, Perelló A, Guarner-Argente C, Alcaide N, Vegas AM, Barros-García P, Murzi-Pulgar M, Perona M, Gisbert JP, Lucendo AJ; Upper GI Tract Study Group from the Spanish Gastroenterological Association (AEG).
Am J Gastroenterol. 2018 Jul;113(7):972-979.
https://www.ncbi.nlm.nih.gov/pubmed/29545632

The authors of this multicenter prospective study aimed to investigate the association between eosinophilic esophagitis (EoE) in *Helicobacter pylori* (HP) infection. They note that the declining incidence of HP infection, largely in developed nations, has occurred at a time when rates of EoE diagnoses are increasing. The reasons for the latter remain unclear and a direct relationship with decreased HP gastritis rates has been suggested. This study included 808 individuals from 23 medical centers and included 404 patients with EoE and 404 control subjects. Control subjects were considered individuals with esophageal symptoms but without endoscopic and histologic findings of EoE. Each patient was testing for the presence of HP by any one of a number of methods. The authors found that

there was no statistically different prevalence of HP in the EoE group compared to the controls (37% versus 40%, OR 0.97). Additionally, this findings held true even when the groups were subdivided into children and adults. The authors conclude that there is no inverse association between HP and EoE and question the belief that HP infers a protective role against the latter.

Eosinophils in the gastrointestinal tract: how much is normal?
Silva J, Canão P, Espinheira MC, Trindade E, Carneiro F, Dias JA.
Virchows Archiv 2018 Sept;473(3):313–320.
https://www.ncbi.nlm.nih.gov/pubmed/29987614

Eosinophilic gastrointestinal disorders are characterized by excessive numbers of eosinophils infiltrating the mucosa. Since eosinophils are normally present in most sites along the GI tract, establishing the normal range of eosinophils along the GI tract is an interesting topic. Histological criteria for eosinophilic esophagitis have been well characterized and accepted. However, histological criteria for other forms of gastroenteritis are not well-defined. In this study, the authors retrospectively reviewed the eosinophilic density (eos/mm2) in the epithelium and in the lamina propria on H&E slides along the GI tract in 33 normal Portuguese pediatric patients, who did not have endoscopic or microscopic abnormalities. Patients with functional GI disorder were not excluded (n=22). Their results showed that mean eosinophils in the lamina propria along the GI tract have variable eosinophilic count which are much less common in the epithelium. The deep lamina propria of the stomach showed more eosinophils than the superficial layer. Duodenal bulb had a mean density of 18.1±17 eos/mm2 in the lamina propria, while there was only 0.9±2 intraepithelial eos/mm2. The highest eosinophil count was observed in the lamina propria of the ileum (111/mm2, range from 3-111) and cecum (125/mm2, range from 2-125). There was no statistical significance for the mean eosinophilic density between patients with functional GI disorders and those with exclusion of GI pathology. Due to limited sample size, no cut-off criteria are established yet. However, their result may provide a baseline reference and distribution of eosinophils when evaluating pediatric patients with suspicion of eosinophilic gastroenteritis.

Usefulness of gastroduodenal biopsy in the differential diagnosis of systemic AH amyloidosis from systemic AL amyloidosis.
Ichimata S, Kobayashi M, Shimojo H, Katoh N, Yazaki M, Kanno H.
Histopathology. 2018 Aug;73(2):230-239.
https://www.ncbi.nlm.nih.gov/pubmed/29660165

The utility of gastroduodenal biopsy as an adjunct or replacement for biochemical analysis in detection of immunoglobulin (Ig) heavy-chain amyloid deposition is the focus of this paper. Ig heavy-chain amyloidosis (AH amyloidosis) is Ig-related amyloidosis classified together with Ig light-chain amyloidosis (AL amyloidosis). Compared with AL amyloidosis, patients with AH amyloidosis have better prognosis and may not need aggressive therapy. Gastroduodenal biopsy specimens were obtained from three cases of biochemically confirmed AH amyloidosis and 21 cases of immunohistochemically confirmed AL amyloidosis. AH amyloid deposition was detectable with Congo red staining in the gastroduodenal biopsy specimens, and typically was observed on the capillary wall of duodenal villi as dotted line-like deposition in the villi. This pattern was not observed in AL amyloidosis. Submucosal tissue often was not present in the biopsy samples, so the role of submucosal analysis is not yet known in this context. Regardless, mucosal histology may be helpful in helping establish the diagnosis of Ig heavy-chain amyloidosis.

Microscopic ileitis in diverted and nondiverted enteric segments: an underrecognized condition with a multifactorial etiology
Zuo C, Fu Z, Lee EC, Foulke L, Young GQ, Cubero Rego D, Lee H.
Hum Pathol. 2018 Jul;77:80-87.
https://www.ncbi.nlm.nih.gov/pubmed/29596895

These authors reviewed 101 diverted and non-diverted bowel segments (37 loop ileostomies, 16 end ileostomies and 12 colostomies) status post-Hartmann's procedure for microscopic ileitis and microscopic colitis. Two cases showed collagenous ileitis – one in a diverted distal limb and one affecting a non-diverted proximal limb of the loop ileostomy. Two cases showed lymphocytic ileitis –one in a non-diverted proximal limb of a loop ileostomy and the other in an end ileostomy. The authors conclude that microscopic ileitis can occur in a diverted enteric segment, though rare (7.5%), and these patients have risk factors for microscopic colitis. High output ostomy output may be the presenting symptom.

Lymphocytic colitis: pathologic predictors of response to therapy
Setia N, Alpert L, van der Sloot KW, Colussi D, Stewart KO, Misdraji J, Khalili H, Lauwers GY.
Hum Pathol. 2018 Aug;78:1-7.
https://www.ncbi.nlm.nih.gov/pubmed/29452215

This study looks at the secondary features of lymphocytic colitis, beyond the intraepithelial lymphocytosis and surface epithelial damage, to assess for prognostic predictors. A total of 32 cases with complete clinical data and slides were reviewed and could be divided into three groups: (1) improvement with minimal intervention or spontaneous improvement, (2) response to steroid therapy, and (3) improvement with mesalamine, bismuth subsalicylate, and/or cholestyramine. Histologic features reviewed included: surface and crypt lymphocytosis, surface epithelial damage, crypt damage, crypt architectural distortion, irregularity/thickness of collagen table, increased lamina propria cellularity, neutrophilic cryptitis, and eosinophil clusters in the lamina propria. Patients with improvement following minimal intervention were more likely to have mild crypt architectural distortion, whereas the other two groups showed slight differences in their subepithelial collagen table, severity of lamina propria inflammation and presence of eosinophil clusters. The authors suggest that secondary microscopic features of lymphocytic colitis could predict response to therapy.

Endoscopic and Histologic Features of Immune Checkpoint Inhibitor-Related Colitis.
Wang Y, Abu-Sbeih H, Mao E, Ali N, Qiao W, Trinh VA, Zobniw C, Johnson DH, Samdani R, Lum P, Shuttlesworth G, Blechacz B, Bresalier R, Miller E, Thirumurthi S, Richards D, Raju G, Stroehlein J, Diab A.
Inflamm Bowel Dis. 2018 Jul 12;24(8):1695-1705.
https://www.ncbi.nlm.nih.gov/pubmed/29718308

This retrospective review of 53 patients with immune checkpoint inhibitor (ICPI) related diarrhea/colitis gives a descriptive of clinical, endoscopic and histologic findings. Histologically, acute inflammation was found in 23% and chronic inflammation was found in 60%. The histologic spectrum included neutrophil cryptitis and crypt abscess, crypt epithelial apoptosis, basal lymphocytic inflammation, crypt distortion, and lymphocytic colitis pattern of injury. Most patients (82%) had persistent histologic evidence of disease on followup. Patients with acute inflammation, among other factors trended towards better survival. Ulcers on endoscopy were a predictor of steroid refractoriness. The authors also point out that the clinical, endoscopic, histologic, and radiologic findings do not correlate well with each other, and therefore a more comprehensive grading system is needed for assessing ICPI-related GI toxicity.

Tryptophan Metabolism through the Kynurenine Pathway is Associated with Endoscopic Inflammation in Ulcerative Colitis.
Sofia MA, Ciorba MA, Meckel K, Lim CK, Guillemin GJ, Weber CR, Bissonnette M, Pekow JR.
Inflamm Bowel Dis. 2018 Jun 8;24(7):1471-1480.
https://www.ncbi.nlm.nih.gov/pubmed/29796641

This prospective study of 100 UC patients, evenly distributed in each of the 0-3 Mayo endoscopic score categories, evaluated serum and colonoscopic biopsies for tryptophan metabolites by ultra-high performance liquid chromatography (uHPLC) and gas chromatography-mass spectrometry (GC-MS) and by mRNA expression in tissue. The tryptophan metabolites from the Kynurenine pathway (KP) (Indoleamine 2,3-dioxygenase 1 (IDO1), Kynurenic acid (KYNA), Quinolinic acid and 3-hydroxyanthranilic acid (3HAA)) have regulatory effects on immune pathways important in mucosal inflammation. The authors found that serum KYNA is Associated with Endoscopic and Histologic Disease Activity, Mucosal IDO1 is Associated with Mucosal Inflammation and Histologic Disease Activity and that Higher Ratios of KYNA/T and KP mRNA Expression Changes both Predict Hospitalization and Colectomy. Overall, these findings confirm the role of tryptophan metabolism along the KP in active UC and suggest that KYNA may be a noninvasive UC biomarker and possible therapeutic target.

CMV Disease in IBD: Comparison of Diagnostic Tests and Correlation with Disease Outcome.
Johnson J, Affolter K, Boynton K, Chen X, Valentine J, Peterson K.
Inflamm Bowel Dis. 2018 Jun 8;24(7):1539-1546.
https://www.ncbi.nlm.nih.gov/pubmed/29718356

This retrospective chart review included IBD patients who had CMV PCR testing and compared these results to IHC and H&E, with a single viral inclusion considered positive. Only existing H&E and IHC reports were reviewed, slides were not re-reviewed for the purpose of the study. Of 180 total patients, 26 had CMV positive PCR, of these, 10 also had positive IHC, and 5 had both positive IHC and H&E. None were reported as positive H&E and PCR without IHC. CMV treatment rates and subsequent surgery rates were also analyzed. Patients with more positive tests had a higher rate of surgery. The authors also found that when PCR test is negative, IHC was also often negative, and that positive PCR may be an indication for additional IHC testing, which is more likely to result in CMV therapy.

Symptoms Do Not Correlate With Findings From Colonoscopy in Children With Inflammatory Bowel Disease and Primary Sclerosing Cholangitis.
Ricciuto A, Fish J, Carman N, Walters TD, Church PC, Hansen BE, Crowley E, Siddiqui I, Nguyen GC, Kamath BM, Griffiths AM.
Clin Gastroenterol Hepatol. 2018 Jul;16(7):1098-1105.
https://www.ncbi.nlm.nih.gov/pubmed/29378308

This study sought to investigate the possibility that symptomology in primary sclerosing cholangitis - inflammatory bowel disease (PSC-IBD) patients, measured by the pediatric ulcerative colitis activity index (PUCAI), may underestimate the endoscopic and histologic disease activity in pediatric patients. The authors note in their introduction that such patients have an increased risk of developing adenocarcinoma despite a relative paucity of clinical symptoms compared to non-PSC IBD patients. They postulate that this increased risk of neoplasia may be secondary to unrecognized disease activity. This prospective study included children with PSC and non-PSC IBD who underwent colonoscopy over an

approximately 1 year period. PUCAI scores were determined and compared to the endoscopic and histologic findings. Additionally, findings were compared to fecal levels of calprotectin. The authors found that PSC-IBD patients in clinical remission had statistically higher endoscopic activity scores than those of non-PSC IBD patients in clinical remission. The histologic activity scores were also found to be greater in the former group compared to the latter. The authors conclude by saying that symptoms cannot be completely relied upon to determine whether PSC-IBD patients have attained endoscopic or histologic targets of remission. Their analysis also suggests that low levels of fecal calprotectin (less than 100 µg/g) may be useful in correctly identifying such patients.

High Risk of Advanced Colorectal Neoplasia in Patients With Primary Sclerosing Cholangitis Associated With Inflammatory Bowel Disease.
Shah SC, Ten Hove JR, Castaneda D, Palmela C, Mooiweer E, Colombel JF, Harpaz N, Ullman TA, van Bodegraven AA, Jansen JM, Mahmmod N, van der Meulen-de Jong AE, Ponsioen CY, van der Woude CJ, Oldenburg B, Itzkowitz SH, Torres J.
Clin Gastroenterol Hepatol. 2018 Jul;16(7):1106-1113.
https://www.ncbi.nlm.nih.gov/pubmed/29378311

This study aimed to evaluate the risk of advanced colorectal neoplasia (ACRN) in a cohort of patients with primary sclerosing cholangitis - inflammatory bowel disease (PSC-IBD) compared with IBD patients without a concurrent diagnosis of PSC. Additionally, the authors sought to evaluate the rate of ACRN in PSC-IBD patients following a diagnosis of low-grade dysplasia (LGD). A total of 293 PSC-IBD patients and 1618 non-PSC IBD patients were included in this retrospective longitudinal study. All study patients had undergone more than 2 surveillance colonoscopies over a period of 15 years. The study authors found that patients with PSC-IBD had a 2-fold higher risk of developing ACRN that IBD patients without PSC. However, the proportions of patients with a diagnosis of LGD did not differ between these 2 groups (21% of patients with PSC-IBD versus 18% of patients with non-PSC IBD). Furthermore, the rate of a subsequent ACRN diagnoses following a history of LGD was significantly higher in patients with PSC-IBD. The authors conclude that analysis of this large cohort confirms earlier findings of an increased risk of ACRN in PSC-IBD patients. This finding, in addition to the fact that these patients have a high-risk of developing ACRN following a diagnosis of LGD, led the authors to suggest that strict surveillance programs for these patients be followed and that perhaps colectomies following a diagnosis of LGD be considered in this specific population.

Distinct Histopathologic and Molecular Alterations in Inflammatory Bowel Disease-Associated Intestinal Adenocarcinoma: c-MYC Amplification is Common and Associated with Mucinous/Signet Ring Cell Differentiation.
Hartman DJ, Binion DG, Regueiro MD, Miller C, Herbst C, Pai RK.
Inflamm Bowel Dis. 2018 Jul 12;24(8):1780-1790.
https://www.ncbi.nlm.nih.gov/pubmed/29788391

This study compared 35 patients with 47 IBD-associated intestinal adenocarcinoma with 451 patients with sporadic colorectal adenocarcinoma and with published data on sporadic colorectal adenocarcinoma and found that 33% of IBD-associated intestinal adenocarcinoma harbored c-MYC amplification as compared to 8% in sporadic cases. Mucinous and signet ring cell histology was also seen significantly more often in the IBD group and correlated with the presence of c-MYC amplification. Her2 positive IBD cases (found in 11%) were associated with poor survival. Other markers found in IBD cases

were KRAS exon 2 or 3 mutation in 10% of cases and IDH1 mutation in 7% of cases. The authors suggest these findings may help guide therapy for patients with IBD-associated intestinal adenocarcinoma.

Unusual Histopathological Findings in Appendectomy Specimens: A Retrospective Analysis of 2047 Cases.
Unver N , Coban G, Arıcı DS, Buyukpınarbasılı N, Gucin Z, Ümit Malya F, Onaran OI, Topalan K.
International Journal of Surgical Pathology. 2018 Jul 1. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/30021480

In this study, the authors retrospectively evaluated the histopathologic features of appendectomy specimens in 2047 patients (1329 males, 718 females, age range: 1-87 years) who had undergone appendectomy to address an initial diagnosis of acute appendicitis. Histopathologic examination revealed acute appendicitis in 2013 patients (98.34 %). This was considered as group 1. The remaining 34 cases (1.66%), with pathologic findings other than acute appendicitis constituted group 2. The histopathologic examination in group 2 exhibited low-grade mucinous neoplasms (8 cases), mucoceles (7 cases), carcinoid (6 cases), granulomatous inflammation (5 cases), intraluminal Enterobius vermicularis (4 cases), endometriosis externa (1 case), adenocarcinoma infiltrated to serosa (1 case), mesenteric cyst (1 case), and low-grade adenocarcinoma formed in mucinous cystic neoplasm background (1 case). The authors conclude that even if the macroscopic appearance of the specimen is normal or consistent with acute appendicitis, they suggest routine histopathological examination, given that some appendices (1.66%) showed unexpected histopathologic findings, such as neuroendocrine tumors, parasitic infections or malignant neoplasms that may need further exploration and additional treatment.

Histologic and Outcome Study Supports Reclassifying Appendiceal Goblet Cell Carcinoids as Goblet Cell Adenocarcinomas, and Grading and Staging Similarly to Colonic Adenocarcinomas.
Yozu M, Johncilla ME, Srivastava A, Ryan DP, Cusack JC, Doyle L, Setia N, Yang M, Lauwers GY, Odze RD, Misdraji J.
Am J Surg Pathol. 2018 Jul;42(7):898-910.
https://www.ncbi.nlm.nih.gov/pubmed/29579011

Given the evidence that the goblet cell carcinoids are derived from mucin-producing cells and even histologically indolent appearing tumors have malignant potential, the authors proposed that these tumors be considered as adenocarcinomas and should be histologically graded in a similar manner to other tubal gut adenocarcinomas. The authors proposed a grading system based on the proportion of tumor that shows tubular or clustered growth pattern; >75% tubular or clustered growth for low grade (grade 1), 50% to 75% for intermediate grade (grade 2), and <50% for high grade (grade 3). In this study authors aimed at validating the prognostic significance of their proposed grading system as well as other current systems in a large set of goblet cell tumors (N=126; age range 33-86 yrs (Mean 57 yrs); M:F-~1:1). The tumors were classified as low-grade (n=47); intermediate grade (n= 22) and high grade (n=57) goblet cell adenocarcinoma. Median overall survival was 204, 86, and 29 months for low-grade, intermediate grade, and high-grade tumors, respectively and was statistically significant (P<0.0001). On multivariate analysis age (P = 0.016), histologic grade (P= 0.009), and stage (P = 0.001) were significantly associated with overall survival. Regarding the other grading systems (Tang's and Lee's), the overall survival curves between the various grades were significantly different in both systems (P<0.0001). Based on these findings authors concluded that goblet cell carcinoids be reported as goblet cell

adenocarcinomas, and should be staged and graded in a manner analogs with other gastrointestinal adenocarcinomas.

Genomic profile of appendiceal goblet cell carcinoid is distinct compared to appendiceal neuroendocrine tumor and conventional adenocarcinoma
Wen KW, Grenert JP, Joseph NM, Shafizadeh N, Huang A, Hosseini M, Kakar S.
Hum Pathol. 2018 Jul;77:166-174.
https://www.ncbi.nlm.nih.gov/pubmed/29634977

This next-gen DNA sequencing study looked at 479 cancer genes in19 appendiceal tumors: 4 goblet cell carcinoids (GCC), 9 goblet cell carcinoids with associated adenocarcinoma (GCC-AC), 3 neuroendocrine tumors (NET), and 3 adenocarcinomas (2 conventional and 1 mucinous). Mutations in SOX9, THOA and chromatin-modifier genes were found in goblet cell tumors. The authors conclude that the mutation profile of GCC/GCC-AC is distinct from NET and conventional appendiceal AC.

Serrated epithelial colorectal polyps (hyperplastic polyps, sessile serrated adenomas) with perineurial stroma: Clinicopathological and molecular analysis of a new series
Erlenbach-Wünsch K, Bihl M, Hartmann A, Groisman GM, Vieth M, Agaimy A
Annals of Diagnostic Pathology 2018 Aug;35:48–52.
https://www.ncbi.nlm.nih.gov/pubmed/29747061

In this study, the authors describe clinicopathological and molecular features of 21 serrated fibroblastic polyps (FPs) and examined the epithelial and stromal components separately for the presence of BRAF mutations. Serrated colorectal FPs are composed of serrated epithelial crypts separated and distorted by intimately associated bland spindle cell proliferations with perineurial-like phenotype. The 21 FPs in this study (mean age 62 yrs; age range 45 to 80 yrs) originated in the sigmoid colon/rectosigmoid junction (16 cases), rectum (2 cases), and other parts of the colon (n=3). The mean size was 3mm (range: 1 to 6mm).Most patients had additional synchronous or metachronous polyps. Histologically, all lesions were composed of serrated epithelial crypts that were separated and distorted by spindle cell stromal proliferations. The stromal proliferation in this series was consistently positive for EMA, claudin-1 and GLUT-1. The epithelial component displayed features of hyperplastic polyps (HPs) in 17cases and that of sessile serrated adenoma (SSA) in 4 cases. Laser-microdissection-guided molecular testing was successful for 13 epithelial and 9 stromal components (9 paired samples). The BRAF V600E mutation was detected in 54% of the epithelial but in none of the stromal components. Given the above findings, the authors conclude that the epithelial component of FPs represents the genuine neoplastic component which should be carefully classified either as HPs or SSA based on the criteria used for serrated colorectal epithelial polyps in general (irrespective of the presence or absence of perineurial stromal component, and with a note on the presence of the stromal component). A more concise terminology reflecting their epithelial nature is needed to fulfill the requirements for colorectal cancer risk assessment and hence adopt appropriate follow-up strategies. The terminologies “fibroblastic polyps” and “mucosal perineuriomas” should probably be avoided.

Colonic Adenomatous Polyps Involving Submucosal Lymphoglandular Complexes: A Diagnostic Pitfall.
Lee HE, Wu TT, Chandan VS, Torbenson MS, Mounajjed T.
Am J Surg Pathol. 2018 Aug;42(8):1083-1089.
https://www.ncbi.nlm.nih.gov/pubmed/29738362

The aim of this study was to identify histologic features to distinguish colorectal adenomas involving submucosal lymphoglandular complexes (LGC) and true invasive adenocarcinoma. The authors identified seven cases (5 right, 2 left colon; 1 SSA, 6 TA/TVA including 4 high grade dysplasia and 1- focal intramucosal adenocarcinoma) of adenomas involving submucosal LGC and the control group included 7 cases (3 right, 2 left and 2 rectum/rectosigmoid colon) of T1 adenocarcinomas with associated submucosal lymphoid aggregates. The glands in the submucosal LGCs of adenoma cases were invested in lamina propria, showed continuity with surface adenoma, were well rounded and contained within lymphoid tissue, and predominantly lacked classic features of pseudoinvasion such as granulation tissue, hemorrhage, hemosiderin deposits, or inflamed/ruptured cysts. Adenocarcinomas had at least one of the following features: infiltrating single cells/small clusters (n=5), poorly formed, fused, and irregular glands (n=2), solid tumor nests (n=1), desmoplastic reaction (n=5), intraluminal necrosis (n=3), or lymphovascular invasion (n=1) and lacked features of pseudoinvasion. Adenomas had none of these features. Five adenocarcinomas showed connection to the surface tumor. Based on these findings authors concluded that adenomas involving LGCs are a rare, clinicopathologically distinct form of pseudoinvasion that mimics invasive adenocarcinoma; histologic features that distinguish them are a well-rounded contour contained within the lymphoid tissue, and lack of infiltrating single cells/small clusters, poorly formed, fused, and irregular glands, solid tumor nests, desmoplastic reaction, and lymphovascular invasion.

The clinicopathological significance of micropapillary pattern in colorectal cancers

Pyo JS, Park MJ, Kang DW.
Hum Pathol. 2018 Jul;77:159-165.
https://www.ncbi.nlm.nih.gov/pubmed/29634975

In this study, micropapillary pattern (MPP) was defined as tumor cell clusters without fibrovascular cores, with pleomorphic nuclei and eosinophilic cytoplasm, and location in stromal spaces resembling lymphovascular spaces. 266 colorectal carcinomas were evaluated with 27.8% showing any MPP features. Nearly 10% of tumors contained at least 5% MPP. Tumors with MPP showed higher rates of vascular and lymphatic invasion, lymph node metastases, and pT stage. Greater MPP directly correlated with higher rate of vascular and lymphatic invasion. In one third of MPP cases, the foci were observed in mucin pools (mucinous adenocarcinoma was excluded from this study) and these tumors were more right sided and poorly differentiated, but had less lymphovascular invasion and LN metastases. The authors conclude that MPP is a poor prognostic feature and further state that MPP in mucin pools show different tumor behavior than pure MPP.

The significance of tumor budding in T1 colorectal carcinoma: the most reliable predictor of lymph node metastasis especially in endoscopically resected T1 colorectal carcinoma

Lee SJ, Kim A, Kim YK, Park WY, Kim HS, Jo HJ, Oh N, Song GA, Park DY.
Hum Pathol. 2018 Aug;78:8-17.
https://www.ncbi.nlm.nih.gov/pubmed/29447923

This study looked at 133 T1 colorectal cancers resected by either EMR or surgical approach with a focus on risk factors for LN metastasis. Of the 16 cases (12%) with LN metastasis, all were non-pedunculated grossly and most were >1000µm into the submucosa (although this feature was not statistically different from the LN negative cohort). Independent risk predictors of LN metastasis included: (1) The number of tumor budding foci (defined as isolated single cancer cell or cluster <5 cells at the invasive front), (2) positive resection margins, and (3) absence of identifiable precursor adenoma. In this study, the ROC curve cutoff to differentiate LN+ and LN- groups was tumor budding foci of ≥3.5 resulting in a PPV/ NPV of 87.5 and 81.1%. High grade histologic subtypes (including poorly differentiated, signet ring cell and mucinous types) were not associated with a higher risk of LN metastasis in this study.

Tumor Budding in Colorectal Carcinoma: Translating a Morphologic Score Into Clinically Meaningful Results.
Cho SJ, Kakar S.
Arch Pathol Lab Med. 2018 Aug;142(8):952-957.
https://www.ncbi.nlm.nih.gov/pubmed/30040461

This review article concisely yet thoroughly summarizes the known clinical significance of tumor budding in colorectal carcinoma based on the English-language pathology literature, and addresses how tumor budding can be practically implemented in daily work flow. Tumor budding is increasingly recognized as an important independent prognostic factor in colorectal carcinoma, and prominent tumor budding in adenocarcinoma arising in a polyp is a risk factor for lymph node involvement. However, it has not routinely included in pathology reports at many institutions, largely due to variability in methods used to assess tumor budding. In 2017, consensus guidelines were released from the International Tumor Budding Consensus Conference (ITBCC) and are now included in the CAP Colorectal Cancer Protocol , facilitating uniform reporting of tumor budding. Future guidelines need to address difficult situations such as intense inflammation, fibrosis, or gland fragmentation.

Histopathological Predictors of Recurrence in Stage III Colon Cancer: Reappraisal of Tumor Deposits and Tumor Budding Using AJCC8 Criteria.
Landau MA, Zhu B, Akwuole FN, Pai RK.
Int J Surg Pathol. 2018, Jul 1. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/29992847

In this retrospective study, the authors evaluated the implementation of both the American Joint Committee on Cancer (AJCC8) criteria for tumor deposits and the International Tumor Budding Consensus Conference (ITBCC) scoring scheme for tumor budding on predicting recurrence in stage III colon cancer. AJCC8 defines a “tumor deposit” as a discrete focus of tumor within the lymph node drainage area of the primary carcinoma with no identifiable lymph node. Contrary to the AJCC7 tumor deposit definition, the AJCC8 tumor deposit definition excludes tumor foci associated with an

"identifiable vascular or neural structure." Also, College of American Pathologists(CAP) colorectal carcinoma protocol has adopted the ITBCC recommendations and recommends tumor budding assessment in :(1) pT1 tumors, in which it is an independent predictor of lymph node metastases, and (2) stage II tumors, in which it is an independent predictor of survival. However, the prognostic impact of tumor budding, if any, using the ITBCC scoring criteria has not been fully evaluated in stage III colon cancer. To this end, the clinicopathological records of 256 patients with colonic adenocarcinoma, including 150 patients with stage III colonic adenocarcinoma and 106 patients with stage II colonic adenocarcinoma were reviewed. The authors found that the tumor deposits and tumor budding are the only histological variables that independently predict tumor recurrence in stage III colon cancer and were associated with a 2.2- and 1.5-fold increased risk of developing disease recurrence, respectively (95% CI = 1.1-4.2, *P* = .02, and 95% CI = 1.1-2.1, *P* = .01, respectively). The negative independent prognostic effect of tumor deposits is seen even with concurrent positive lymph nodes and is most pronounced in patients with stage IIIB (pT3-T4a N1) tumors. Within the N1 cohort, patients with tumor deposits without concurrent positive lymph nodes (N1c) had a significantly decreased disease-free survival compared with patients with N0 tumors (*P* < .001) and patients with N1a/b tumors (*P* = .02). The authors conclude that the presence of tumor deposits and tumor budding appears to indicate an aggressive colorectal carcinoma phenotype in stage III disease, even in the presence of concurrent positive lymph nodes. Tumor deposits (as defined by AJCC 8) and high tumor budding (using ITBCC criteria) should be included as a part of a routine comprehensive pathologic risk assessment of stage III colon cancer, even in the setting of concurrent positive lymph nodes.

Expression Profile of LGR5 and Its Prognostic Significance in Colorectal Cancer Progression
Jang BG, Kim HS, Chang WY, Bae JM, Kim WH, Kang GH.
Am J Pathol. 2018 Jul 21. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/30036518

This study examined the expression of leucine-rich, repeat-containing, G-protein-coupled receptor 5 (*LGR5)* in 788 human colorectal cancer (CRC) samples using RNA ISH and assessed its prognostic significance. Real-time RT-PCR was performed on 32 pairs of fresh-frozen human CRC samples and adjacent noncancerous colon tissues. LGR5 mRNA expression was higher in CRC samples than in noncancerous tissue in 75% of samples, but its expression was not associated with other cancer stem cell markers. LGR5 RNA ISH was positive in 68% of 788 CRCs and was positively correlated with older age, moderately to well-differentiated cells, and nuclear β-catenin expression. Enhanced LGR5 expression remained persistent during the adenoma-carcinoma transition, but markedly declined in the budding cancer cells at the invasive fronts, which was not associated with altered Wnt or epithelial-mesenchymal transition signaling. LGR5 had negative correlations with microsatellite instability and CpG island methylation phenotype, and was not associated with KRAS or BRAF mutation. Notably, LGR5 positivity was an independent prognostic marker for better clinical outcomes in CRC patients. In ex vivo cell line studies, LGR5 overexpression in CRC cells attenuated tumor growth by decreasing ERK phosphorylation along with decreased colony formation and migration abilities. Knockdown of LGR5 expression in CRC cells resulted in a decline in the colony-forming and migration capacities. These data suggest a suppressive role of LGR5 in CRC progression.

Increased Levels of Oxidative Damage in Liver Metastases Compared with Corresponding Primary Colorectal Tumors: Association with Molecular Subtype and Prior Treatment
van der Waals LM, Jongen JMJ, Elias SG, Veremiyenko K, Trumpi K, Trinh A, Laoukili J, Ubink I, Schenning-van Schelven SJ, van Diest P, Borel Rinkes IHM, Kranenburg O.
Am J Pathol. 2018 Jul 20. [Epub ahead of print]
https://www.ncbi.nlm.nih.gov/pubmed/30031728

It is unclear whether increased oxidative stress persist in metastatic colorectal cancer (CRC). This study used CRC tissue microarray and immunohistochemistry analyzed markers of oxidative damage in primary CRC and their corresponding liver metastases. Markers of generic and oxidative DNA damage (histone 2AX and 8-hydroxy-2'-deoxyguanosine (8-OHdG)) were significantly higher in liver metastases compared with their corresponding primary tumors. Chemoradiation neoadjuvant therapy was associated with increased persistent oxidative DNA damage, especially in metastases. Immunohistochemistry-based molecular classification of CRC into epithelial- and mesenchymal-like molecular subtypes revealed that untreated mesenchymal-like tumors contained lower levels of oxidative DNA damage compared with epithelial-like tumors. However, treated mesenchymal-like tumors, but not epithelial-like tumors, showed significantly higher levels of histone 2AX and 8-OHdG. Mesenchymal-like tumors expressed significantly lower levels of phosphorylated nuclear factor erythroid 2-related factor 2, a master regulator of the antioxidant response, and nuclear factor erythroid 2-related factor 2-controlled genes. Positive 8-OHdG was associated with mesenchymal-like metastases and a poor overall survival. The authors conclude that an increased capacity to tolerate therapy-induced oxidative damage in mesenchymal-like CRC may explain, at least in part, the poor responsiveness of these tumors to chemotherapy and the poor survival of this patient subgroup.

Histopathological variables in liver metastases of patients with stage IV colorectal cancer: potential prognostic relevance of poorly differentiated clusters
Lionti S, Reggiani Bonetti L, Bettelli S, Spallanzani A, Gelsomino F, Barresi V.
Hum Pathol. 2018 Aug;78:115-124.
https://www.ncbi.nlm.nih.gov/pubmed/29715463

Liver metastases were reviewed in 63 patients to assess for histologically poorly differentiated clusters, defined as at least 5 neoplastic cells with no glandular formation (different from isolated tumor cells which are defined as clusters of <5 tumors cells) and not limited to the invasive front. The authors postulate that these poorly differentiated clusters origin in the tumor center and migrate to the periphery to invade outward. Features associated with shorter cancer specific survival included the presence of poorly differentiated clusters, the presence of these clusters at the tumor periphery (rather than contained to the center of the tumor mass) and positive resection margin. The localization of poorly differentiated clusters at the tumor edge was also associated with shorter progression free survival. Given the prognostic significance demonstrated, the authors suggest including this feature in path reports.

Lymph Node Yield After Neoadjuvant Chemoradiotherapy in Rectal Cancer Specimens: A Randomized Trial Comparing Two Fixatives.
Dias AR, Pereira MA, de Mello ES, Nahas SC, Cecconello I, Ribeiro U Jr.
Dis Colon Rectum. 2018 Aug;61(8):888-896.
http://www.ncbi.nlm.nih.gov/pubmed/29944580

This study is a prospective randomized trial to assess the lymph node yield in patients undergoing low anterior resection (LAR) with total mesorectal excision (TME) after neoadjuvant chemoradiation (nCRT) for rectal adenocarcinoma in terms of two different fixatives: formalin (NBF) vs Carnoy's solution (CS). Carnoy's solution has similar efficacy in terms of tissue morphology, ability to perform immunohistochemistry and molecular DNA based studies. It also has been shown to facilitate identification of small lymph nodes during gross dissection. The authors hypothesize that total lymph node recovery is increased in rectal cancer specimens following nCRT by the use of CS. 130 specimens were fixed either in NBF or CF for 24-48 hours, the fat measured and manual dissected for lymph nodes. After dissection the residual fat from the NBF group was immersed in CS for 24-48 hours to search for residual lymph nodes (NBF revision group). Specimens were processed similarly and scored for tumor regression according to CAP guidelines. Overall, the LN count for NBF group was 16.3 and for the CS group 24 ($p < 0.01$). Six cases in the CS and 22 in the NBF group had <12 LNs ($p = 0.001$). A total of 722 LNs were found after treating the residual fat from the NBF group with CS (mean, 11.1 LNs). Interestingly, adding to the NBF group, the findings from the Revision group reduced the number of cases with <12 LNs from 22 (33.8%) to 3 (4.6%). The authors conclude this study proved 1) CS is superior to NBF in terms of cases with less than 12 lymph nodes (9.2% vs 33.8%) 2) CS identifies more smaller lymph nodes 3) CS identifies lymph nodes faster. Of particular importance the study showed that not only were smaller lymph nodes being missed with NBF (less than 3mm) that in some cases those lymph nodes contained metastatic tumor whereby modifying N status in 4 patients and ultimately upstaging 2. Therefore, the authors advocate for examining at least 12 lymph nodes in these specimens.

Histology of colorectal adenocarcinoma with double somatic mismatch-repair mutations is indistinguishable from those caused by Lynch syndrome

Hemminger JA, Pearlman R, Haraldsdottir S, Knight D, Jonasson JG, Pritchard CC, Hampel H, Frankel WL.
Hum Pathol. 2018 Aug;78:125-130.
https://www.ncbi.nlm.nih.gov/pubmed/29723603

The histology of colorectal tumors with double hit MMR mutations (double somatic mutations in the MMR gene, rather than germline mutation such as seen in Lynch syndrome) is identical to the histology found in Lynch syndrome tumors. Since these patients also exhibit loss of MMR protein expression by IHC and a high level of MSI by PCR, tumor sequencing for double somatic mutations should be considered to differentiate sporadic from hereditary MMR deficiency.

Evaluation of the correlation of MACC1, CD44, Twist1, and KiSS-1 in the metastasis and prognosis for colon carcinoma.

Zhu B, Wang Y, Wang X ,Wu S, Zhou L, Gong X, Song W, Wang D.
Diagn Pathol. 2018 Jul 18; 13(1):45.
https://www.ncbi.nlm.nih.gov/pubmed/30021598

The authors explored the expression (by immunohistochemistry) of MACC1, CD44, Twist1, and KiSS-1 in 212 colonic adenocarcinoma (CAC) tissue specimens along with the corresponding normal colon mucosa tissues and their associations with each other. Demographic, clinicopathological, and follow-up data were also collected. Metastasis-associated in colon cancer 1 (MACC1) has been reported to promote tumor cell invasion and metastasis. CD44 is a common biomarker of cancer stem cells (CSTs), and CD44 level are correlated with cell-to-extracellular matrix (ECM) adhesion, cell growth and angiogenesis. Twist

1, is a pivotal transcriptional factor in epithelial-mesenchymal transition (EMT).CSTs and EMT have also been reported to promote tumor cell proliferation, invasion, and metastasis. KiSS-1, a known suppressor of metastasis, has been reported to be down-regulated in various tumors. However, the associations of MACC1, CD44, Twist1, and KiSS-1 in colonic adenocarcinoma (CAC) invasion and metastasis remain unclear. The results of this study showed up-regulation of MACC1, CD44, and Twist1 expression and down-regulation of KiSS-1 expression in CAC tissues. Positive expression of MACC1, CD44, and Twist1 had a positive correlation with invasion, tumor grades, and lymph- node-metastasis (LNM) stages and tumor-node-metastasis (TNM) stages for CAC patients; while positive expression of KiSS-1 was inversely associated with invasion, tumor size, LNM stage, and TNM stage. The KiSS-1-positive group had significantly more favorable overall survival (OS) than the KiSS-1-negative group; while an overexpression of MACC1, CD44, and Twists1 was negatively associated with longer OS time, by univariate analysis. Multivariate analysis suggested that MACC1, CD44, Twist1 overexpression, and low expression of KiSS-1 and LNM and TNM stages should be considered independent predictors affecting CAC patient survival. This study demonstrates that expression levels of MACC1, CD44, Twist1, and KiSS-1 are related to the duration of OS among CAC patients, and these may be suitable for use as biomarkers and therapeutic targets in CAC.

Somatic *POLE* exonuclease domain mutations are early events in sporadic endometrial and colorectal carcinogenesis, determining driver mutational landscape, clonal neoantigen burden and immune response.

Temko D, Van Gool IC, Rayner E, Glaire M, Makino S, Brown M, Chegwidden L, Palles C, Depreeuw J, Beggs A, Stathopoulou C, Mason J, Baker AM, Williams M, Cerundolo V, Rei M, Taylor JC, Schuh A, Ahmed A, Amant F, Lambrechts D, Smit VT, Bosse T, Graham TA, Church DN, Tomlinson I.
J Pathol. 2018 Jul;245(3):283-296.
https://www.ncbi.nlm.nih.gov/pubmed/29604063

The authors begin this article by acknowledging the immense advancements in the molecular understanding of tumorigenesis that has occurred over a short period of time and specifically point out the recently recognized class of tumors with missense mutations in *POLE* and *POLD1*. They note that somatic *POLE* mutations have largely been recognized in cancers of the endometrium and colon and that tumors with such alterations demonstrate considerable genomic instability and are associated with an excellent prognosis. The aim of this particular investigation was to evaluate the timing in which these *POLE* mutations occur during the process of carcinogenesis. Data from a number of publicly available data sets, including the TCGA, in addition to material from institutional cohorts were used study. Specifically in regards to colonic material, 389 FFPE colonic polyps were analyzed. Evaluation of these polyps for *POLE* mutations found such alterations in 3 lesions (1.1%), an incidence which is concordant with published rates in colorectal adenocarcinomas. Histologically, the authors suggest that precursor lesions associated with *POLE* mutated endometrial carcinomas, as well as a single colonic polyp with a *POLE* alteration that was available for testing, demonstrate prominent CD8+ T-cell infiltrates, a finding which has been associated with their invasive counterparts. The authors conclude by a suggesting that somatic *POLE* mutations occur early in the development of neoplasia and may perhaps be the initiating event in this process.

Detection Rate of High-Grade Squamous Intraepithelial Lesions as a Quality Assurance Metric for High-Resolution Anoscopy in HIV-Positive Men.

Siegenbeek van Heukelom ML, Marra E, Cairo I, Van Eeden A, Schim van der Loeff MF, De Vries HJC, Prins JM.

Dis Colon Rectum 2018; 61: 780–786.

http://www.ncbi.nlm.nih.gov/pubmed/29771801

This retrospective review analyzes the high grade squamous intraepithelial (HGSIL) detection rate in HIV positive men who have sex with men (MSM) for the purpose of developing quality assurance measures. This study included 1340 HIV positive MSM in 3 HIV outpatient clinics high-resolution anoscopy (HRA)-guided biopsies were performed. HRA-guided biopsies are the gold standard for identifying anal intraepithelial neoplasia (AIN) which is graded as 1, 2 and 3 and further characterized as low grade squamous intraepithelial lesions (LSILs; AIN1) or high-grade squamous intraepithelial lesions (HSILs; AIN2 and 3). This study examined the HSIL detection rate amongst 7 anoscopists for the purpose of improving HRA quality and the ability to identify HSIL in subsequent biopsy material. None of the anoscopists in the study had performed anoscopy before but all received identical training from an experienced anoscopist. The screening routine was also identical: 1) digital anal rectal exam 2) peri and intra anal inspection using colposcope 3) application of acetic acid and staining with Lugol iodine when appropriate 4) any suspicious lesion was biopsied; no cytology was performed. All biopsies were grade by AIN-experienced pathologists and the highest AIN grade was defined in the final diagnosis. The authors looked at the HSIL detection rate of each anoscopist over time and discovered that there were significant differences. However, the overall HSIL detection rate for all 7 anoscopists combined increased significantly over time, from 27% in the first set of anoscopies to 70% in the 7th set ($p < 0.001$; OR, 1.15; 95% CI, 1.08–1.23 per 50 HRAs). The mean number of biopsies also increased significantly from 1.4 (22% HSIL rate) in the first set and 2.0 (29% HSIL) in the last set ($p < 0.001$). Therefore, a minimum of 50 HRA's per year and the identification of at least 20 HSIL has been proposed as QA metrics for HRA. In conclusion, the authors propose the use of a standardized learning curve as a quality standard for performing HRA.

External Quality Assessment Identifies Training Needs to Determine the Neoplastic Cell Content for Biomarker Testing.

Dufraing K, De Hertogh G, Tack V, Keppens C, Dequeker EMC, van Krieken JH.

J Mol Diagn. 2018 Jul;20(4):455-464.

http://www.ncbi.nlm.nih.gov/pubmed/29625250

This study focuses on identifying different practices of determining neoplastic cell percentage in tumors undergoing biomarker testing. Depending on the assay being performed, the lower limit of detection of mutations varies. Therefore, accurate estimation of tumor percentage is critical for accurate results and interpretations. This is particularly important in specimens with low cellularity where overestimation of tumor percentage can lead to false negative results due to the dilution of wild type DNA into mutant DNA. Currently there is no gold standard to assess tumor percentage. Most pathologists review the H&E stained slide to estimate the percentage of tumor cells to non-neoplastic cells. However, this method is prone to interobserver variation. In the first part of the study, the methods for determining the neoplastic cell content were analyzed. Amongst the different laboratories and pathologists, estimation of tumor percentage varied as well as method of tissue retrieval for eventual DNA extraction. Some laboratories cut sections directly from blocks and others from slides. Some selected an area of tumor based on a corresponding H&E stained slide and either dry scraped, wet scraped or used laser

microdissection to retrieve the tissue. The authors state that in this study the average difference between the highest and lowest estimation of tumor percentage was between 52% and 78% which is similar to previously reported studies. The most accurate way to assess tumor percentage is manual counting of cells in a selected area. However, this study revealed only 3 laboratories reported using this method. In addition, many laboratories had technicians and molecular biologists reviewing material without oversight by a pathologist. In the future, the authors advocate for creating and distributing best practice guidelines. Standardization of tumor estimation is necessary for assuring the minimal percentage of tumor cells is achieved for the corresponding testing method and ultimately accurate interpretation of results.

The outlet patch: gastric heterotopia of the colorectum and anus.
Mannan AASR, Vieth M, Khararjian A, Khandakar B, Lam-Himlin D, Heydt D, Bhaijee F, Venbrux HJ, Byrnes K, Voltaggio L, Barker N, Yuan S, Montgomery EA.
Histopathology. 2018 Aug;73(2):220-229.
https://www.ncbi.nlm.nih.gov/pubmed/29667709

Gastric heterotopia (GH) can occur throughout the GI tract but is rare in the colorectal region. This multi-center study describes clinicopathological features of GH of the colon, rectum and anus. A total of 33 cases were studied (20 from men, 13 from women, median age 54 years). Sites of heterotopia included the rectum (n = 26), anus (n = 4), ileocecal junction (n = 1), ascending colon (n = 1), and descending colon (n = 1). Presenting symptoms (n = 27) included hematochezia (41%) and altered bowel habits (4%); 15 patients (55%) were asymptomatic. On colonoscopy (n = 31), all appeared as solitary lesions (median size = 6.5 mm, range = 2-55 mm), either as polyps (61%), raised erythematous patches (23%), an ulcer (10%), within a rectal diverticulum (3%), or within a hemorrhoid (3%). Patients were managed by polypectomy. One patient with an area of GH had an associated carcinoma and underwent resection. No morbidity related to GH itself was reported following excision. Histologically, heterotopic gastric mucosa was oxyntic (85%), mixed oxyntic and non-oxyntic (12%) and not specified (3%) types. In five patients, a pyloric gland adenoma (PGA) arose from heterotopic gastric mucosa, two of which contained a focus of invasive adenocarcinoma. One case had associated surface foveolar-type low-grade dysplasia. Another had associated adenocarcinoma arising from the heterotopic mucosa. One case contained Helicobacter pylori organisms. In summary, this study thoroughly describes features of gastric heterotopia in the outlet patch (the distal GI tract). Features including association with PGA, surface dysplasia, and adenocarcinoma suggest that GH in the outlet patch can undergo neoplastic transformation.

JOURNALS REVIEWED (MAY-JUNE 2018)
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