GIPS Journal Watch January & February 2018

Optimal Histologic Cutpoints for Treatment Response in Patients With Eosinophilic Esophagitis: Analysis of Data From a Prospective Cohort Study.
Reed CC, Wolf WA, Cotton CC, Rusin S, Perjar I, Hollyfield J, Woosley JT, Shaheen NJ, Dellon ES.
Clin Gastroenterol Hepatol. 2018 Feb;16(2):226-233.e2.
https://www.ncbi.nlm.nih.gov/pubmed/28987502

This prospective cohort study was performed to determine the optimal histologic eosinophilic density cutpoint following eosinophilic esophagitis treatment that would maximize symptomatic and endoscopic improvement. The authors note that while there is current histologic criteria for the diagnosis of eosinophilic esophagitis, which requires the presence of at least 15 eosinophils per high-power field, there is a lack of prospective studies which have evaluated the usefulness of histologic cutpoints in the post-treatment setting. The study population consisted of 62 consecutive adult patients who underwent upper endoscopy and were found to have eosinophilic esophagitis. At the time of initial diagnosis, and following 8 weeks of standard therapy, eosinophilic density, severity of patient symptoms, and endoscopic findings were quantified. Specific treatments were at the discretion of the primary gastroenterologist and included topical corticosteroids or dietary elimination therapy. To remove it as a confounding factor, patients who received esophageal dilation were excluded from the final data analysis. The authors found that the mean eosinophil count at the time of initial diagnosis was 124 eosinophils per high-power field, which decreased to 35 eosinophils per high-power field following treatment. Measurements of symptoms severity and endoscopic changes showed similar decreases. However, despite having histologic improvement, 53% of patients did not have a decrease in symptoms. By generating receiver operator curves, the authors concluded that post-treatment eosinophil counts of 8, 15, and 5 eosinophils per high-power field best predicted symptomatic, endoscopic, or combined responses. They do note however that their data does highlight the tenuous relationship between clinically relevant symptomatic relief and post-treatment eosinophil counts.

Definition of Barrett Esophagus in the United States: Support for Retention of a Requirement for Goblet Cells.
Salimian KJ, Waters KM, Eze O, Pezhouh MK, Tarabishy Y, Shin EJ, Canto MI, Voltaggio L, Montgomery EA.
Am J Surg Pathol. 2018 Feb;42(2):264-268.
https://www.ncbi.nlm.nih.gov/pubmed/29016405

The authors of this study aimed at determining whether intestinal metaplasia (IM) accompanies esophageal adenocarcinoma (EAC) in a US patient cohort in an effort to aid in establishing an appropriate definition for BE which varies globally. The authors reviewed a series of 139 consecutive patients who underwent EMRs or esophagectomies for EAC. 97/139 (70%) patients were IM+. Of the 97 patients, 87 had IM adjacent to tumor bed (< 1cm) and 2 cases had distant IM. In 8 (8%) the assessment of proximity of IM was complicated due to prominent treatment

effect. Tumors found in IM− patients tended to be more aggressive and were stage pT3 or greater at the time of resection (57%, IM−; 31% IM+; *P* = 0.02). While evaluating the hypothesis if neoadjuvant therapy masks the preexisting IM, authors found that 36/39 patients (92%) of treatment naïve patients had evidence of IM in the current resection (34 patients) or prior biopsies (2 patients). Overall, 70% to 92% of patients in the current study showed evidence of IM in association with EAC in resection specimen. Based on these findings authors concluded that the definition of BE in US should continue to require the presence of IM.

Subsquamous intestinal metaplasia is common in treatment-naïve Barrett's esophagus.
Bartel MJ, Srivastava A, Gordon S, Rothstein RI, Pohl H
Gastrointest Endosc. 2018 Jan;87(1):67-74.
https://www.ncbi.nlm.nih.gov/pubmed/28687439

This cross sectional study aimed at identifying the prevalence and distribution of subsquamous intestinal metaplasia (SSIM) proximal to squamocolumnar junction (SCJ) in patients undergoing Barrett's esophagus (BE) surveillance. 515 squamous epithelial biopsy specimens obtained from 5 mm and 10 mm above the SCJ from 106 (95% men; mean age, 66 years) consecutive patients with biopsy proven BE were reviewed. The mean Barrett's circumferential length was 1.6 cm and maximal length was 3.3 cm. SSIM was present in 39% of patients (95% CI, 29.4-48.6) at 5 mm proximal to the SCJ and in 21% (95% CI, 11.7-32.1) at 10 mm proximal to the SCJ. In the per–biopsy specimen analysis, SSIM was present in 17% of biopsy specimens (95% CI, 13-21.6) at 5 mm proximal to the SCJ and in 8% (95% CI, 4.3-12.2) at 10 mm proximal to the SCJ. In specimen with adequate submucosal stroma (176, 34%) the proportion of biopsy specimens with SSIM increased to 44% (95% CI, 34.7-52.7) and 29% (95% CI, 17.1-43.1) at 5 mm and 10 mm proximal to the SCJ, respectively. SSIM was detected at a higher proportion at the anterior/right lateral position compared with the posterior/left lateral position (21% vs 11%, P = .001) at both levels. Dysplasia was not identified in these biopsies. Clinically, there was no association of SSIM with duration of reflux symptoms, length of BE or PPI use. Overall, the authors found a high proportion of SSIM (approximately 40%) in biopsies <1 cm proximal to the SCJ in treatment-naïve BE patients which raises further questions regarding BE management and the prevalence of SSIM in normal-appearing esophagus.

Increased detection of Barrett's esophagus-associated neoplasia using wide-area trans-epithelial sampling: a multicenter, prospective, randomized trial.
Vennalaganti PR, Kaul V, Wang KK, Falk GW, Shaheen NJ, Infantolino A, Johnson DA, Eisen G, Gerson LB, Smith MS, Iyer PG, Lightdale CJ, Schnoll-Sussman F, Gupta N, Gross SA, Abrams J, Haber GB, Chuttani R, Pleskow DK, Kothari S, Goldblum JR, Zhang Y, Sharma P.
Gastrointest Endosc. 2018 Feb;87(2):348-355.
https://www.ncbi.nlm.nih.gov/pubmed/28757316

In this multicenter, prospective, randomized, tandem study the authors aimed to evaluate the use of novel wide-area transepithelial sampling (WATS) as an adjunct to standard random

biopsy sampling (Seattle protocol) for the detection of high grade dysplasia/ esophageal adenocarcinoma (HGD/EAC) in Barrett's esophagus (BE). WATS is an abrasive brush biopsy technique designed to obtain a wider area of transepithelial specimen. The brush specimens were smeared onto glass slides and stained using modified Papanicolaou stain. Analysis of these smears was aided by a neural network–based, high-speed computer scan that identifies potentially abnormal cells based on cellular morphology. A final diagnosis was rendered using both computer-assisted and manual microscopic examination of the slide. A total of 160 patients undergoing endoscopic surveillance for BE or referred for endoscopic treatment of dysplastic BE completed the trial (mean age, 63.4 years; 76% men; 95% white). The diagnostic yield for biopsy sampling was: HGD/EAC, 7 (4.4%); low-grade dysplasia (LGD), 28 (17.5%); nondysplastic BE (NDBE), 106 (66.25%); and no BE, 19 (11.9%). WATS alone detected 29 cases of HGD/EAC, and 1 case of HGD/EAC was missed by WATS. The addition of WATS led to the diagnosis of 23 cases of HGD/EAC which were biopsy negative (absolute increase, 14.4% [23/160]; 95% CI, 7.9%-19.3%). The biopsy results for 23 WATS HGD/EAC cases were: NDBE, 11; and LGD/indefinite, 12. One case of biopsy HGD/EAC was classified as LGD by WATS. 21 (91.3%) patients diagnosed with HGD/EAC by WATS and biopsy sampling negative had a prior history of dysplasia. Based on these findings authors concluded that WATS increases the detection of HGD and EAC in a high-risk BE surveillance population when used as an adjunct to biopsy sampling compared with biopsy sampling alone suggesting that WATS is a promising tool for the diagnosis of BE-associated neoplasia.

Esophageal Diseases Special Issue
Gastroenterology. 2018 Jan 154(2):A1–A18, 263–452
https://www.sciencedirect.com/journal/gastroenterology/vol/154/issue/2

This issue is the second part of the January journal celebrating the 75th anniversary of *Gastroenterology*. A series of review articles summarize esophagology topics such as GERD, eosinophilic esophagitis, and esophageal carcinoma (both squamous and adenocarcinoma).

PAX9 regulates squamous cell differentiation and carcinogenesis in the oro-oesophageal epithelium.
Xiong Z, Ren S, Chen H, Liu Y, Huang C, Zhang YL, Odera JO, Chen T, Kist R, Peters H, Garman K, Sun Z, Chen X.
J Pathol. 2018 Feb;244(2):164-175.
https://www.ncbi.nlm.nih.gov/pubmed/29055049

The authors of this study aimed to determine the functional role of PAX9 in oro-esophgeal squamous epithelium through the use of tissue specific PAX9-deficient mice and human cell lines and tissue. PAX9 is a transcription factor which has been found to be necessary for the development of the thymus, parathyroid, limbs, palate, and teeth in mice. Retained expression of this protein has been noted to occur in adult humans in endocrine tissues and those of the upper gastrointestinal tract. The authors note that previous studies have suggested that the

absence of this protein plays a potential role in the development of esophageal squamous cell carcinoma and that of the oral cavity. Through a number of experiments involving mouse models, the authors showed that tissue specific Pax9 deficiency was associated with squamous epithelial cell hyperproliferation, delayed cell differentiation, and altered global gene expression within the esophagus. Furthermore, studies of human esophageal squamous cell carcinomas demonstrated downregulation of PAX9, a finding which was more closely associated with individuals with a history of alcohol consumption. In cell line studies, as well as in mouse models, the authors showed that ethanol exposure leads to downregulation of this protein. The authors conclude by suggesting that PAX9 downregulation may contribute to alcohol associated squamous cell carcinoma of the esophagus and that further studies are warranted to investigate the upstream and downstream mechanisms involved in this process.

The notch pathway is activated in neoplastic progression in esophageal squamous cell carcinoma
Lubin DJ, Mick R, Shroff SG, Stashek K, Furth EE.
Hum Pathol. 2018 Feb;72:66-70.
https://www.ncbi.nlm.nih.gov/pubmed/29137934

This immunohistochemical study evaluated Notch intracellular domain (NICD) (a molecule belonging to a signalling pathway that can increase stem cell survival, chemoresistance, and promotion of epithelial-to-mesenchymal transition) in esophageal squamous cell carcinoma (n=60) and compared it to benign esophageal squamous epithelium (n=42) and eosinophilic esophagitis (n=13). NICD staining was scored by digital image analysis, and higher scores were found in SCC compared to normal and reactive. Higher scores also correlated with tumor grade and stage, and shorter patient survival. The authors suggest the Notch pathway may be upregulated in esophageal SCC, contribute to decreased survival, and may be a potential therapeutic target.

Polypoid fibroadipose tumors of the esophagus: 'giant fibrovascular polyp' or liposarcoma? A clinicopathological and molecular cytogenetic study of 13 cases
Graham RP, Yasir S, Fritchie KJ, Reid MD, Greipp PT, Folpe AL.
Mod Pathol. 2018 Feb; 31(2): 337-342.
https://www.ncbi.nlm.nih.gov/pubmed/28984298

This study looks at a set of polypoid, fat containing tumors of the esophagus, and included cases original diagnosed as well-differentiated liposarcoma, dedifferentiated liposarcoma, and "giant fibrovascular polyp." The latter a tumor that has historically been considered a non-neoplastic, reactive lesion. Grossly, all the tumors were pedunculated, polypoid masses that partially obstructed the esophageal lumen. Microscopically the tumors were lined by squamous mucosa, involved the subepithelial stroma, and were composed of admixed adipose and fibrous zones in variable amounts. In all cases, including the "giant fibrovascular polyps" at least rare hyperchromatic stromal cells could be identified in fibrous stroma. MDM2 FISH

demonstrated amplification in all the tumors. The authors suggest that these findings, and their clinical experience, support that most, if not all, "giant fibrovascular polyps" of the esophagus are well-differentiated or dedifferentiated liposarcoma. They also suggest that the diagnosis of "giant fibrovascular polyp" should be made with caution and only after evaluation with MDM FISH.

Neoplastic Lesions of Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS) Are Gastric Phenotype.
de Boer WB, Ee H, Kumarasinghe MP.
Am J Surg Pathol. 2018 Jan;42(1):1-8.
https://www.ncbi.nlm.nih.gov/pubmed/29112017

The authors of this study aimed at systematic description of lesions in a cohort of Gastric Adenocarcinoma and Proximal Polyposis Syndrome (GAPPS) family members and propose diagnostic clues and a possible path of progression based on morphology. The authors reviewed 51 endoscopic biopsies and 5 gastrectomy specimens from 25 patients belonging to a GAPPS family. 10 patients showed normal findings on endoscopy. Gastric body polyposis was identified endoscopically in 14 patients and 1 patient had gastric mass without polyposis. Fundic gland polyps (FGP) were seen in 10 of 14 patients with polyposis. The most frequent pathology (12 patients) was disorganized proliferation (increases Ki67 activity) of specialized/oxyntic glands high up in the mucosa involving the attenuated foveolar region around the gastric pits, forming a polypoid lesion, which was termed by authors as hyperproliferative aberrant pits (HPAPs. Advanced lesion had an appearance of inverted foveolar hyperplasia. In 8 patients HPAPs coexisted with FGP like changes. Neoplastic lesions were seen in 9 patients- 1 patient had invasive adenocarcinoma and 8 patients had dysplastic (premalignant) lesions. Dysplasia was noted in 3 settings: (1) discrete gastric adenomas (6 patients), (2) multifocal "flat" dysplasia in the setting of HPAP +/− FGP-like polyps (8 patients), and (3) adenoma associated with adenocarcinoma (1 patients). All the dysplastic lesions and the adenocarcinoma showed a gastric phenotype which is supported by diffuse expression for MUC5AC and variable expression for MUC6. Based on these findings authors concluded that there was wider spectrum of lesions in GAPPS than previously reported. Hyperproliferative aberrant pits were the earliest microscopic finding. Dysplasia and adenocarcinoma were of gastric phenotype suggesting gastric pathway of carcinogenesis.

Nectin-4 promotes gastric cancer progression via the PI3K/AKT signaling pathway
Zhang Y, Chen P, Yin W, Ji Y, Shen Q, Ni Q.
Hum Pathol. 2018 Feb;72:107-116.
https://www.ncbi.nlm.nih.gov/pubmed/29208564

Using multiple methodologies, including PCR, Western blot, and immunohistochemistry, this study evaluated the expression of Nectin-4 (a cell-adhesion molecule that functions in movement, proliferation, differentiation and polarization and is expressed in embryos and

placenta) in gastric cancer specimens and cell lines. High expression correlated with high TNM stage, lymph node metastasis and poor prognosis. Additional Western blot studies showed the PI3K/AKT signaling pathway is also involved. The authors conclude that Nectin-4 has a promoter effect on gastric cancer cell growth and motility, and may server as a therapeutic target.

SSH1 expression is associated with gastric cancer progression and predicts a poor prognosis
Maimaiti Y, Maimaitiming M, Li Y, Aibibula S, Ainiwaer A, Aili A, Sun Z, Abudureyimu K.
BMC Gastroenterol. 2018 Jan 16;18(1):12.
https://www.ncbi.nlm.nih.gov/pubmed/29338701

Slingshot homolog-1 (SSH1) plays an important role in the development of cancers. This study aimed to determine whether SSH1 is a prognostic biomarker for gastric cancer patients. Immunohistochemistry (IHC) staining of SSH1 was performed on tissue microarrays containing 100 gastric cancer specimens. The authors found that SSH1 expression level in gastric cancer tissues was significantly associated with lymph node metastasis ($p = 0.032$). Kaplan-Meier survival analysis showed that SSH1 expression was significantly correlated with poor survival of patients with gastric cancer ($p = 0.016$) in addition to other parameters such as lymph node metastasis, positive lymph node ratio, pathological grading, tumor size, AJCC staging and tumor infiltration. Multivariate analyses also showed that SSH1 expression and positive lymph node ratio were the best predictors of poor overall survival in patients with gastric cancer ($p = 0.030$ and 0.014). The authors concluded that SSH1 expression is associated with gastric cancer progression and poor prognosis, and therefore it may be a promising target for the treatment of gastric cancer.

Prognostic value of the expression of DNA repair-related biomarkers mediated by alcohol in gastric cancer patients
Zhang Y, Wu H, Yang F, Ning J, Li M, Zhao C, Zhong S, Gu K, Wang H.
Am J Pathol. 2018 Feb;188(2):367-377.
https://www.ncbi.nlm.nih.gov/pubmed/29331492

Alcohol consumption likely induces gastric carcinogenesis by deregulation of RNA polymerase (Pol) III genes and oxidative damage. This study investigated the prognostic value of transcription factor IIB-related factor 1 (BRF1)-a key transcription factor that modulates Pol III transcription through BRCA1, myeloperoxidase (MPO)-an enzyme induced by alcohol-mediated oxidative damage, BRCA1, and BRAC2 upon alcohol induction in 77 primary gastric adenocarcinomas and 69 para-tumor tissues (>2 cm from the tumor edge). The authors found that BRF1 expression was significantly associated with tumor stage and lymph node metastasis. BRCA2 expression was also significantly associated with lymph node metastasis. Additionally, high BRF1 expression ($P = 0.010$) and MPO-positive cell infiltration ($P = 0.004$) in tumor tissues, as well as positive expression of BRCA1 ($P < 0.001$) in para-tumor tissues were more frequent in gastric cancer patients with hazardous or harmful alcohol consumption habits. BRF1, BRCA2,

and MPO were independent prognostic factors for disease-free survival. BRCA1/BRCA2 were independent prognostic factors for overall survival. Furthermore, BRCA2 was an independent poor prognostic factor for disease-free survival and overall survival in patients who underwent platinum-based adjuvant chemotherapy.

High TREM2 expression correlates with poor prognosis in gastric cancer
Zhang X, Wang W, Li P, Wang X, Ni K.
Hum Pathol. 2018 Feb;72:91-99.
https://www.ncbi.nlm.nih.gov/pubmed/29104108

This study utilized real-time PCR and immunohistochemistry to evaluate mRNA and protein expression of TREM2 (a molecule that forms a receptor signaling complex with cell membrane protein TYRO) in 317 samples of gastric cancer matched with normal and non-neoplastic tissue. The authors found that increased TREM2 was found in gastric cancer compared to normal tissue, and higher levels associated with poor differentiation, higher TNM stage, lymph node metastasis and poor prognosis.

The incidence, mutational status, risk classification and referral pattern of gastro-intestinal stromal tumours in the Netherlands: a nationwide pathology registry (PALGA) study.
Verschoor AJ, Bovée JVMG, Overbeek LIH; PALGA group, Hogendoorn PCW, Gelderblom H.
Virchows Arch. 2018 Jan 8.
https://www.ncbi.nlm.nih.gov/pubmed/29308530

In this study, the authors studied the nation-wide incidence of GIST between 2003 and 2012 and the frequency of mutations, risk groups, histological subtypes and immunohistochemistry results in the Netherlands. Result showed that the incidence of GIST has significantly increased from 12.7 per million population in 2003 to 17.7 per million in 2012 in the Netherlands. Mutational analysis was performed in 33.9% of patients with a resection between 2011 and 2012 and showed KIT mutation 67.5%, PDGFRA 16.3%, wild-type 11.4%. The authors hypothesized about the cause of the increase in The Netherlands: 1) increased use of diagnostic procedures such as CT scans, gastroscopy and endoscopic ultrasound, 2) an increased awareness of the diagnosis after the introduction of imatinib as effective treatment, and 3) a real increase in the incidence; although this is a possibility, until now no causal factors or risk factors for the development of GIST are known.

Disease activity indices in coeliac disease: systematic review and recommendations for clinical trials.
Hindryckx P, Levesque BG, Holvoet T, Durand S, Tang CM, Parker C, Khanna R, Shackelton LM, D'Haens G, Sandborn WJ, Feagan BG, Lebwohl B, Leffler DA, Jairath V.
Gut. 2018 Jan;67(1):61-69.
https://www.ncbi.nlm.nih.gov/pubmed/27799282

This systematic review of adult and pediatric celiac disease publications between 1966 and 2015 identified 286 eligible studies, which included celiac disease activity markers as a measure of outcome. Content validity was lacking in all identified histologic and endoscopic scores. Comparing quantitative histologic analysis with qualitative scales, better reliability and responsiveness was found for quantitative morphometric histologic analysis, and the authors recommend this as a secondary or co-primary clinical trial endpoint.

Duodenal Adenomas in Patients With Multiple Colorectal Adenomas Without Germline APC or MUTYH Mutations.
Kallenberg FGJ, Latchford A, Lips NC, Aalfs CM, Bastiaansen BAJ, Clark SK, Dekker E
Dis Colon Rectum. 2018 Jan;61(1):58-66.
https://www.ncbi.nlm.nih.gov/pubmed/29215473

This retrospective study evaluated data from patients with 10-99 colorectal adenomas who were negative for APC and MUTYH germline mutations and had undergone more than 1 endoscopic procedure. Patients with germline mutations have routine upper GI screening and surveillance as they have an increased life time risk of duodenal malignancies (4-12%). However, for patients who have multiple colonic adenomas but no known germline mutation, it is not clear if they should also undergo increased upper GI surveillance. Therefore, this study reviewed data from this patient cohort and found 133 patients who met their inclusion criteria. After careful review, and in certain cases additional testing, 83 patients were ultimately included in the study. Duodenal adenomas were discovered in 9.6% of that patient population. The maximum number of adenomas found in one patient was 3. No patients developed duodenal malignances or high grade dysplasia lesions. The authors identified the lack of full sequencing of MUTYH and lack of unknown mutational status of other genes association with polyposis syndromes, such as POLE and POLD1, as significant limitations to the study. However, based on their results, they do recommend upper GI screening for any patient with multiple colorectal adenomas at the time of initial diagnosis, regardless of age.

The Influence of Tumor Stage on the Prognostic Value of Ki-67 Index and Mitotic Count in Small Intestinal Neuroendocrine Tumors.
Sun Y, Lohse C, Smyrk T, Hobday T, Kroneman T, Zhang L.
Am J Surg Pathol. 2018 Feb;42(2):247-255.
https://www.ncbi.nlm.nih.gov/pubmed/29016403

The authors of this study aimed at assessing the clinical behavior of Small intestinal neuroendocrine tumor (SINET) in relation to stage (based on AJCC 8th edition), Ki67 index, mitotic count (MC) and other pathologic features. A total of 130 patients (Mean age 63.5 yrs; mean tumor size 1.5 cm) with surgically resected ileal and jejunal NETs were reviewed. WHO grade: Grade1- 112 (86%); Grade 2-18 (14%), grade 3- 0. Stage: I- 6 (5%); II-21 (16%); stage III-43 (33%) and IV-60 (46%). Multivariate analysis showed significant association of age, Ki-67 index

>5%, MC >10/50 hpf, stage IV, and liver metastases with increased risk of death in all patients. In patients with stage IV disease, Ki-67 index >5% was significantly associated with increased risk of death (HR, 3.97; 95% CI, 1.41-11.16; P =0.009). In patients with stage I, II and III disease only age and MC >1/50 hpf (HR, 2.23; 95% CI, 1.15-4.34; P = 0.018) were significantly associated with higher risk of death. Ki67 index did not show any significant prognostic value in these patients. Based on these findings authors concluded that stage IV, liver metastasis and increased tumor cell proliferation rate with different cutoff values (Ki-67 >5%, MC >10/50 hpf) were independent prognostic factors for SINETs.

Small bowel stenosis: a manifestation of chronic graft-versus-host disease in children?
Tordjman M, Ouachee M, Bonnard A, Tilea B, Yakouben K, Viala J, Peuchmaur M, Berrebi D.
Hum Pathol. 2018 Feb;72:174-179.
https://www.ncbi.nlm.nih.gov/pubmed/28899741

This case series of 4 pediatric patients with bone marrow transplantation describes the histologic and clinical features of small bowel stenosis following chronic GVHD. All cases showed multiple areas of stenosis (range 2-5) of variable length (ranges 2- 20cm), extensive ulceration, neutrophilic infiltration, apoptotic cells in glands, disorganization of gland architecture, crypt shortfall, submucosal fibrosis, and sclerolipomatosis of serosae. Multinucleated giant cells were seen in 2 cases, and pyloric metaplasia was found in 3 of 4 cases. The authors comment that features were found in all ileal specimens and overlapped with features of Crohn disease. Photos of radiologic, gross and histologic findings are provided.

Molecular classification of Crohn's disease reveals two clinically relevant subtypes.
Weiser M, Simon JM, Kochar B, Tovar A, Israel JW, Robinson A, Gipson GR, Schaner MS, Herfarth HH, Sartor RB, McGovern DPB, Rahbar R, Sadiq TS, Koruda MJ, Furey TS, Sheikh SZ.
Gut. 2018 Jan;67(1):36-42.
https://www.ncbi.nlm.nih.gov/pubmed/27742763

Given the phenotypic heterogeneity of Crohn's disease, these authors used unbiased principal components analysis of gene expression profiles from colon of Crohn's patient's and non-IBD controls. They identified two distinct clusters, one similar to the controls, and one which separated out completely a subgroup of Crohn's patients. This Crohn's subgroup had gene expression patterns more consistent with ileum, rather than the tissue source site of colon, while the group clustering with the controls had expression of colon-specific genes. The authors validated the findings, and also determined that the subclasses were due to stable molecular transformation of colon cell genomes, rather than transient extracellular signalling pathways. They also found similar subclasses in treatment naïve pediatric Crohn's patients, and identified that many upregulated genes were contributing to a basal activation of the immune system, associated with defects in cellular processing. Differences in lipid metabolism dysregulation were found between adult and pediatric patients of otherwise same subclass, indicating an

even greater complexity to the findings. They were able to correlate their subclass findings clinically, in that those with colon gene expression pattern were more likely to have rectal disease, and those with ileal gene expression pattern were more likely to have actual ileal disease. The authors suggest that these findings may be helpful to guide personalized treatment options.

Plasma microRNA Profile Differentiates Crohn's Colitis From Ulcerative Colitis.
Netz U, Carter J, Eichenberger MR, Feagins K, Galbraith NJ, Dryden GW, Pan J, Rai SN, Galandiuk S.
Inflamm Bowel Dis. 2017 Dec 19;24(1):159-165
https://www.ncbi.nlm.nih.gov/pubmed/29272478

Patients with Crohn's colitis (n=8) and ulcerative colitis (n=8) who "had at least part of the inflamed large bowel still in vivo" were screened for expression of 380 human plasma miRNAs. Seven differentially expressed miRNAs were then confirmed in new patient samples (Crohn's colitis, n=12; ulcerative colitis, n=21) to develop a prediction model. Diagnosis was then predicted using the top two miRNAs (miR-598 and miR-642), which were consistently statistically significantly different between the two groups, in 33 blinded patient samples from the confirmation group, yielding an overall accuracy of 75%. The authors indicate that these two plasma-based miRNAs should be further studied in more diverse patient and disease populations, but show potential to differentiate cases of colitis due to either Crohn's or ulcerative colitis, which may also be helpful in cases of indeterminate colitis.

Patients With Ulcerative Colitis and Primary Sclerosing Cholangitis Frequently Have Subclinical Inflammation in the Proximal Colon.
Krugliak Cleveland N, Rubin DT, Hart J, Weber CR, Meckel K, Tran AL, Aelvoet AS1, Pan I, Gonsalves A, Gaetano JN, Williams KM, Wroblewski K, Jabri B, Pekow J.
Clin Gastroenterol Hepatol. 2018 Jan;16(1):68-74.
https://www.ncbi.nlm.nih.gov/pubmed/28756053

The purpose of this retrospective cohort study was to evaluate the presence of subclinical disease activity in ulcerative colitis (UC) patients with primary sclerosing cholangitis (PSC) compared to UC patients without PSC. The authors note that patient's with UC-PSC have a high-risk of developing colonic neoplasia which frequently occurs in the proximal colon. This feature, along with the fact that UC in PSC patients is frequently mild or asymptomatic compared to just UC alone, has suggested that subclinical disease may directly contribute to this increased risk of colorectal carcinoma. To contribute to this hypothesis, the authors measured endoscopic and histologic activity in a cohort of asymptomatic patients with ulcerative pancolitis (143 patients, 205 examinations) which included 36 and 169 examinations from UC-PSC and UC alone patients respectively. Disease activity was measured in relation to specific colon segments including right colon (encompassing cecum, ascending, and transverse colon), left colon (encompassing the splenic flexure, descending colon, and sigmoid colon), and rectum. The authors found that

while the global presence of endoscopic or histologic disease activity did not differ between the two groups, UC patients with PSC were more likely to have subclinical endoscopic disease in the right colon (56%) compared to individuals with UC alone (32%). This difference was also appreciated in regards to histologic activity with the UC-PSC group being more likely to harbor subclinical histologic activity (64%) compared to the UC group (31%). Interestingly, the opposite was true for rectal histologic activity, which was more frequently encountered in UC individuals without PSC. The authors conclude that UC patients with PSC are significantly more likely to harbor clinically silent colitis in the right colon and postulate that this finding may contribute to the increased incidence of colon cancer in these individuals.

Massive Submucosal Ganglia in Colonic Inertia
Naemi K, Stamos MJ, Wu ML.
Arch Pathol Lab Med. 2018 Feb;142(2):208-212.
https://www.ncbi.nlm.nih.gov/pubmed/28981370

The authors describe massively enlarged submucosal ganglia in the setting of colonic inertia, a form of primary chronic constipation without known etiology or diagnostic criteria, but one that often requires pancolectomy. They define massive submucosal ganglia as having at least 20 perikarya, and describe findings in a study group of 8 specimens, 7 of which contained at least 1 massive ganglion. The comparison group of 10 specimens from patients lacking chronic constipation contained only 1 massive ganglion in total. The nature of these ganglia requires further study as to whether they are pathogenetic or secondary findings.

The Role of the Surgical Pathologist in the Diagnosis of Gastrointestinal Polyposis Syndromes
Rosty C.
Adv Anat Pathol. 2018 Jan;25(1):1-13.
https://www.ncbi.nlm.nih.gov/pubmed/28901964

This review article covers the clinical presentation and pathology associated with rare polyposis syndromes to aid the diagnostic pathologist with recognition and improved knowledge base. The author calls out specific histologic and clinical clues of hamartomatous polyposis syndromes that can alert a pathologist to diagnosis of juvenile polyposis syndrome, Peutz-Jeghers syndrome, and Cowden syndrome. The evolving genetic causes of adenomatous polyposis syndromes are described including FAP, MUTYH-associated polyposis, the recently described polymerase proofreading-associated polyposis and NTHL-1 associated polyposis. Also discussed are GAPPS and serrated polyposis syndrome. Lynch syndrome is not discussed in this article.

NTHL1 and MUTYH polyposis syndromes: two sides of the same coin?
Weren RD, Ligtenberg MJ, Geurts van Kessel A, De Voer RM, Hoogerbrugge N, Kuiper RP.
J Pathol. 2018 Feb;244(2):135-142.
https://www.ncbi.nlm.nih.gov/pubmed/29105096

This interesting review article discusses a potpourri of familial polyposis syndromes and their associations with colorectal carcinoma. While familial adenomatous polyposis and its attenuated form are thoroughly discussed, other less frequently encountered syndromes such as polymerase proofreading-associated polyposis are also reviewed. This later entity is an autosomal dominant cancer syndrome associated with monoallelic germline mutations of *POLE* and *POLD1*. A large portion of the article is devoted to describing various autosomal recessive adenomatous polyposis syndromes including *MUTYH*-associated polyposis as well as *NTHL1*-associated polyposis. The molecular underpinnings of these syndromes, which are both related to defects in the process of base excision repair, are described in detail. The authors conclude the review by postulating the existence of additional, as yet undescribed, polyposis syndromes related to alterations in this process.

Lesions of All Types Exist in Colon Polyps of All Sizes.
Turner KO, Genta RM, Sonnenberg A.
Am J Gastroenterol. 2018 Feb;113(2):303-306.
https://www.ncbi.nlm.nih.gov/pubmed/29231190

The object of this retrospective study was to examine the relationship between colonic polyp size and specific histologic features. The authors note that in addition to the number and size of colonic polyps, histologic features such as the presence of high-grade dysplasia or villous architecture currently dictate the recommended follow-up colonoscopy schedule for patients. While it has been established that large colonic polyps are more likely to contain these advanced features, the authors note a lack of significant literature regarding these findings in smaller polyps. The pathology reports from 550,811 polyps acquired from 483,998 patients over a 6 year period were assessed. Polyps were characterized as hyperplastic polyps, tubular adenomas, tubulovillous adenomas, sessile serrated adenoma/polyps, traditional serrated adenomas, and adenocarcinoma. In addition to the endoscopic size, the presence or absence of high-grade dysplasia was also noted on review of the reports. Within this study population, 81% of colonic polyps were noted to be smaller than 1 cm while 19% were larger than this clinically relevant measurement. Additionally, 3.4% of all polyps contained histologic features of advanced neoplasia or malignancy. While a majority of these polyps with advanced features measured greater than 1 cm (75%), 25% of such polyps were less than 1 cm in diameter. The authors conclude that the frequency of advanced features does increase with polyp size, however, a significant proportion of advanced features also occur in smaller polyps. Therefore, endoscopists should be advised to excise all polyps encountered during colonoscopy and submit them for histologic evaluation.

Risk of Metachronous High-Risk Adenomas and Large Serrated Polyps in Individuals with Serrated Polyps on Index Colonoscopy: Data from the New Hampshire Colonoscopy Registry
Anderson JC, Butterly LF, Robinson CM, Weiss JE, Amos C, Srivastava A.
Gastroenterology. 2018 Jan;154(1):117-127.
https://www.ncbi.nlm.nih.gov/pubmed/28927878

This study uses data from the New Hampshire colonoscopy registry (a population-based registry that originated in 2004 that contains demographics and longitudinal colonoscopy data on 5433 patients starting from index scope through subsequent surveillance) to examine the relationship between index serrated polyps and the risk of metachronous high-risk adenomas. A significantly increased risk (odds ratio 5.61; 95% CI, 1.72-18.28) of high-risk adenoma on second colonoscopy was seen in patients who had either A) high-risk adenoma with synchronous large (≥1 cm) serrated polyps, B) high-risk adenoma with synchronous sessile serrate adenoma/polyp (SSA/P), or C) traditional serrated adenoma at index colonoscopy. High risk adenoma alone was also associated with increased risk of metachronous high risk adenoma. Lesions associated with higher risk of metachronous large serrated polyps (but not high-risk adenoma) included: A) large serrated polyps alone, B) SSA/P, or C) TSA. The study provides population-based evidence that patients with these lesions may benefit from closer colonoscopy surveillance.

Colon Pathology Characteristics in Li-Fraumeni Syndrome.
Rengifo-Cam W, Shepherd HM, Jasperson KW, Samadder NJ, Samowitz W, Tripp SR, Schiffman JD, Kohlmann W.
Clin Gastroenterol Hepatol. 2018 Jan;16(1):140-141.
https://www.ncbi.nlm.nih.gov/pubmed/28624650

The authors of this brief research correspondence sought to highlight the colonic pathologic characteristics of patients with Li-Fraumeni syndrome. They note that these patients with germline mutations in the *TP53* tumor suppressor gene are at significantly increased risk for malignancy over their lifetimes which includes increased incidences of early onset colorectal cancer. Because of this, current guidelines suggest that these patients should receive screening colonoscopies every 2-5 years beginning at the age of 25. By searching a cohort of well-documented patients enrolled in an established cancer genetics program, the authors identified 66 individuals with pathogenic germline *TP53* mutations. Of these patients, 31 individuals had undergone colonoscopic evaluations with a total of 72 procedures. The average age at first colonoscopy was 28 years and ranged from 11-53 years. While 52% of patients were found to have no colonic abnormalities, the remaining individuals were found to have various neoplastic lesions with the most common being tubular adenomas (55% of lesions). Additional lesions included hyperplastic polyps (19%), sessile serrated adenoma/polyps (12%), and colorectal carcinoma or high-grade dysplasia (14%), with the latter two being combined in this study. The mean age of patients at diagnosis of colorectal carcinoma (n=4) or high-grade dysplasia (n=1) was 25.4 years, with 4 of 5 diagnosed before the age of 25. Given this data, the authors conclude that screening colonoscopies in Li-Fraumeni syndrome patients should begin at an earlier age given the possibility of early onset advanced neoplasia before the age of 25.

Dual Stain With SATB2 and CK20/Villin Is Useful to Distinguish Colorectal Carcinomas From Other Tumors.

Li Z, Rock JB, Roth R, Lehman A, Marsh WL, Suarez A, Frankel WL.
Am J Clin Pathol. 2018 Feb 17;149(3):241-246.
https://www.ncbi.nlm.nih.gov/pubmed/29471325

This immunohistochemical study on tumor microarrays identified that dual staining with SATB2 and either CK20 or villin had the highest sensitivity and specificity for identifying colorectal carcinoma. The authors propose that these stain combinations are useful for identifying cases of CK20 negative and CDX2 negative colorectal carcinomas, especially when presenting as a metastatic lesion, and for those cases with limited biopsy tissue.

Tumor Budding and PDC Grade Are Stage Independent Predictors of Clinical Outcome in Mismatch Repair Deficient Colorectal Cancer.

Ryan É, Khaw YL, Creavin B, Geraghty R, Ryan EJ, Gibbons D, Hanly A, Martin ST, O'Connell PR, Winter DC, Sheahan K.
Am J Surg Pathol. 2018 Jan;42(1):60-68.
https://www.ncbi.nlm.nih.gov/pubmed/29112018

The authors reviewed 238 mismatch repair deficient (dMMR) colorectal cancers (CRC) for tumor budding, poorly differentiated clusters (PDCs) grade and conventional histopathologic parameters. Tumor budding was assessed using a rapid bud count method where tumor bud counts were generated in 5 hotspot regions at 200X for tumor slide and they were scored as follows (i) Score 0=indicates no evidence of budding, (ii) Score 1=refers to all cases with a budding score >0 but less than 1 bud in at least 50% of fields examined, (iii) Score 2 =cases with at least 1 bud in at least 50% of fields examined. A PDC was defined as the presence of ≥5 cancer cells with no gland formation in a field containing maximum clusters. The PDC's were graded as (i) grade 0=the absence of PDCs, (ii) grade 1=1 to 4 PDCs, (iii) grade 2=5 to 9 PDCs, (iv) grade 3=cases with ≥10 PDCs. 37 of 167 (22.2%) assessed tumors had a high budding (score 2); 41/167 had PDC grade 2 to 3. Tumor budding and PDCs were significantly associated with WHO grade, perineural invasion, lymphovascular invasion, and extramural vascular invasion (EMVI) and infiltrative margin in dMMR CRC. On multivariate analysis only PDC grade (OR, 4.12; 95% CI: 1.69-10.04; P=0.002) and EMVI (OR, 3.81; 95% CI, 1.56-9.19; P=0.003) were independent predictors of lymph node metastasis. Regarding survival outcomes, on multivariate analysis, only pT stage (HR, 4.11; 95% CI, 1.48-11.36; *P*=0.007) and budding (HR, 2.98; 95% CI, 1.72-5.19; *P*<0.000) were associated with worse disease free survival (DFS). PDC grade was significant for DFS (HR, 2.53; 95% CI, 1.65-3.89; *P*=0.042) when budding was excluded from the model. Based on these findings authors concluded that tumor budding and pT stage were the best predictors of worse clinical outcomes in dMMR CRC. PDC grade was an independent predictor of lymph node metastasis and could also be prognostic factor for outcome. Conventional WHO grade did not correlate with clinical outcome in dMMR CRC.

PD-L1 protein expression in tumour cells and immune cells in mismatch repair protein deficient and proficient colorectal cancer: the foundation study using the SP142 antibody and whole section immunohistochemistry.

El Jabbour T, Ross JS, Sheehan CE, Affolter KE, Geiersbach KB, Boguniewicz A, Ainechi S, Bronner MP, Jones DM, Lee H

J Clin Pathol. 2018 Jan;71(1):46-51

https://www.ncbi.nlm.nih.gov/pubmed/28667193

This study assessed PD-L1 expression in mismatch repair proficient (MMR-P) and mismatch repair deficient (MMR-D) colorectal adenocarcinomas (CRC) for the purposes of evaluating response to immune checkpoint inhibitor (ICPI) therapy. The authors utilized the same antibody (Ventana clone SP142) and guidelines published for NSCLC clinical trials. PD-L1 expression was scored in both the tumor cells (TC) as well as infiltrating immune cells (IC). PD-L1 expression was scored according to two algorithms. Positive criteria for algorithm A included 1) >50% expression in TC and any expression in IC 2) Any expression in TC and >10% IC and negative criteria 1) >1% TC and Any IC 2) Any TC and >1% IC and 3) <1%TC and <1%IC. For algorithm B positive criteria included 1) >50% expression in TC and any expression in IC 2) Any expression in TC and >10% IC 2) >1% TC and Any IC 3) Any TC and >1% IC and negative criteria <1%TC and <1%IC. The final results for 104 CRC showed a significant association of positive PD-L1 expression and MMR-D with either algorithm. These tumors had a higher TMN stage and advanced clinical stage. Copy number analysis was performed on select cases and amplification of PD-L1 was only rarely detected. Overall, the authors conclude that evaluating PD-L1 in both TC and IC in whole tissue sections of CRC will enhance the sensitivity of screening patients for ICPI therapy.

Mismatch repair–deficient colorectal cancer: a model of immunogenic and immune cell–rich tumor despite nonsignificant programmed cell death ligand-1 expression in tumor cells

Le Flahec G, Badic B, Guibourg B, Doucet L, Bail JP, Marcorelles P, Schick U, Uguen A.

Hum Pathol. 2018 Feb;72:135-143.

https://www.ncbi.nlm.nih.gov/pubmed/29208565

These authors performed an immunohistochemical study (PD-1, 4 different clones of PD-L1, CD3, CD4, CD8, CD20, CD68, and FOXP3) with tissue microarrays and whole tumor specimens. No significant difference in PD-L1 expression was found between MMR deficient vs. proficient colorectal carcinomas. MMR deficient tumors contained more intraepithelial and stromal lymphocytes, and greater expression of PD-L1 in the stromal immune cells. Based on their observations, the authors conclude that there is insufficient evidence to utilize PD-L1 IHC as a screening method to direct immunotherapy in colorectal carcinoma.

Clinicopathologic and Molecular Characteristics of Synchronous Colorectal Carcinoma With Mismatch Repair Deficiency.

Nakano K, Yamamoto H, Fujiwara M, Koga Y, Tsuruta S, Ihara E, Oki E, Nakamura M, Ogawa Y, Oda Y.

Am J Surg Pathol. 2018 Feb;42(2):172-182.

https://www.ncbi.nlm.nih.gov/pubmed/28877066

The authors reviewed 118 synchronous and 117 solitary colorectal carcinomas CRC patients in a Japanese population. There were no significant differences in clinicopathologic and molecular findings between the synchronous and solitary CRC. The prevalence of MMR protein deficiency in synchronous tumors was higher than that in solitary tumors (10.2% vs. 6.8%; P =0.3333). In synchronous tumors, 9 (7.6%) patients had concordant loss of MMR and 6 (5.1%) had discordant loss of MMR. The frequency of MMR deficiency in synchronous CRCs in current study was lower than that in prior reported studies in Western population (30% to 47%). The Concordant patients showed concurrent MLH1/PMS2 loss (n = 3), concurrent MSH2/ MSH6 loss (n = 4) and isolated MSH6 loss (n = 2) in both tumors, whereas the Discordant patients showed concurrent MLH1/PMS2 loss (n = 2), isolated PMS2 loss (n = 2) and isolated MSH6 loss (n = 2) in a single tumor. *BRAF* mutations were identified in two patients with concordant MMR loss group. Only 1 tumor with isolated loss of PMS2 showed *BRAF* mutation in the discordant group. *KRAS* mutation was identified in only 1 tumor in a single patient in each group. Based on these findings authors concluded that the frequency of MMR protein deficiency in synchronous CRC in the Japanese population may be lower compared to Western populations. Given, the heterogeneity of MMR loss, *BRAF* and *KRAS* mutations in synchronous tumors authors suggested that molecular testing of all synchronous lesions may be necessary.

Clinical and biological significance of miR-193a-3p targeted KRAS in colorectal cancer pathogenesis.

Mamoori A, Wahab R, Islam F, Lee K, Vider J, Lu CT, Gopalan V, Lam AK.

Hum Pathol. 2018 Jan;71:145-156.

https://www.ncbi.nlm.nih.gov/pubmed/29104111

This study investigated the function of microRNA miR-193a3p in colorectal cancer via multiple methodologies, including transfection of colorectal cancer cell lines (matched with nonneoplastic cell lines), measurement of expression level by quantitative real-time PCR, and evaluation of downstream effects on KRAS expression by IHC. The authors found the 70% of colorectal cancer tissues shows down-regulation of miR-193a-3p compared to non-neoplastic colorectal tissue and this correlated with early stage carcinoma.

Optimal detection of clinically relevant mutations in colorectal carcinoma: sample pooling overcomes intra-tumoral heterogeneity.
Nelson AC, Boone J, Cartwright D, Thyagarajan B, Kincaid R, Lambert AP, Karnuth K, Henzler C, Yohe S.
Mod Pathol. 2018 Feb;31(2):343-349.
https://www.ncbi.nlm.nih.gov/pubmed/29027537

This study examines a strategy to overcome false negative results in molecular testing of colon cancer due to intra-tumoral heterogeneity. The authors note that most critically a false negative result for KRAS and NRAS can lead to unnecessary treatment with costly agents that have significant side effects. The study looked for heterogeneity in 99 colorectal carcinomas by sampling 3 different sites within each tumor. Next generation sequencing was performed on each of the three samples as well as a pooled sample. Overall the study found 11% discordant cases across all genes and 2% discordant KRAS. Different reasons were suggested for the discordancy including borderline tumor percentage and heterogeneity. The authors suggest from their findings that intra-tumoral heterogeneity is infrequent but that a pooled strategy, although more labor intensive, might be a way to avoid false negative results.

An Update on the Diagnosis, Grading, and Staging of Appendiceal Mucinous Neoplasms
Valasek MA and Pai RK.
Adv Anat Pathol. 2018 Jan;25(1):38-60.
https://www.ncbi.nlm.nih.gov/pubmed/29016471

The nomenclature and staging criteria of appendiceal mucinous neoplasms has shifted in recent years, and this extremely practical and thorough review article provides pathologists an update on current terminology (the new PSOGI vs WHO vs AJCC) including: serrated polyp with or without dysplasia, LAMN, HAMN, mucinous adenocarcinoma, mucinous adenocarcinoma with signet ring cells, and mucinous signet ring cell carcinoma. Histologic criteria are detailed as well as changes in AJCC staging (8^{th} edition). The article places a practical emphasis on histologic mimics, such as serrated polyps, conventional-like adenomas, ruptured appendiceal diverticula, endometriosis, and mucosal hyperplasia, and it gives guidance on how to handle and report each of these findings. Specific criteria for assessing tumor grade are outlined and the article provides useful charts and numerous photomicrograph examples to accompany each topic.

A study of appendiceal crypt cell adenocarcinoma (so-called goblet cell carcinoid and its related adenocarcinoma)
Nonaka D, Papaxoinis G, Lamarca A, Fulford P, Valle J, Chakrabarty B.
Hum Pathol. 2018 Feb;72:18-27.
https://www.ncbi.nlm.nih.gov/pubmed/28823572

This article proposes the renaming of GCC to “crypt cell adenocarcinoma” after a retrospective study of 105 tumors. The authors found that one third of tumors were pure low grade, and

others contained 5-95% high grade components. There was significant correlation with cancer related survival when the tumors were divided into 3 tiers of high grade component (<40%, 40-90%, and ≥90%). The neuroendocrine cell component ranged from 0-90% (median 5) and showed no difference between low and high grade areas. The mucus cell component ranged from 5-100% (median 70). Cancer related survival also correlated with size and stage. Within this series, 6 patients with localized disease showing pure low grade histology died of disease within 34-98 months after initial surgery. This finding, in combination with their overall results, is cited as evidence that GCC, even in pure low grade form and low stage, should be regarded as a malignant neoplasm. The authors review the history of GCC, how it came upon this name, the confusion that surrounds the term "carcinoid", and previous significant studies of this entity. They conclude that the historical term "crypt cell adenocarcinoma" more appropriately reflects the nature and origin of this tumor, and can prevent some of the confusion regarding the "carcinoid" of the term GCC.

It is notable that another recent study (Wen et. al. Hum Pathol. 2017 Jul;65:187-193) published in this journal shared similar concerns regarding the GCC terminology and showed errors in staging and clinical interpretation when using the term GCC; these authors proposed renaming the tumor mixed GCC-adenocarcinoma.

BRCA1 and BRCA2 expression patterns and prognostic significance in digestive system cancers.
Wang GH, Zhao CM, Huang Y, Wang W, Zhang S, Wang X.
Hum Pathol. 2018 Jan;71:135-144.
https://www.ncbi.nlm.nih.gov/pubmed/29126833

This immunohistochemical microarray study looked at the BRCA1 and BRCA2 expression in 1546 samples of 4 GI cancer types (gastric, colorectal, hepatocellular, and pancreatic). BRCA1 and 2 showed similar expression patterns where low cytoplasmic expression correlated with advanced stage, and high cytoplasmic expression showed favorable overall survival. High BRCA1 nuclear reactivity correlated with advanced stage and poor outcome. The authors suggest that BRCA IHC may be useful in the prognosis and treatment for GI cancers, citing other studies showing that reduced expression of BRCA may be more sensitive to platinum-based chemotherapy.

HPV positive, wild type TP53, and p16 overexpression correlate with the absence of residual tumors after chemoradiotherapy in anal squamous cell carcinoma
Soares PC, Abdelhay ES, Thuler LCS, Soares BM, Demachki S, Ferro GVR, Assumpção PP, Lamarão LM, Ribeiro Pinto LF, Burbano RMR.
BMC Gastroenterol. 2018 Feb 21;18(1):30.
https://www.ncbi.nlm.nih.gov/pubmed/29466950

The aim of this study was to evaluate the association of HPV status, p16 expression level and TP53 mutations with residual tumors (local response) after chemo radiotherapy in anal squamous cell carcinoma (SCC). 78 patients with anal SCC status post chemo radiotherapy were followed for six-month to identify the absence or presence of residual tumors. HPV DNA was identified by PCR and direct sequencing, p16 expression was detected by western blotting, and TP53 mutations were identified by direct sequencing. The outcomes were classified as: a) no response (presence of residual tumor), and b) complete response (absence of residual tumor). Positive HPV, p16 overexpression, wild-type TP53, female gender, and stages I and II were significantly associated with the absence of residual tumor. Only the presence of HPV was independently correlated with the clinical response; this variable increased the chances of a response within six months by 31-fold. The authors concluded that the HPV status in tumor cells can direct future therapeutic strategies in anal SCC.

The January issue of *Archives of Pathology & Laboratory Medicine* contains several practical updates on GI topics in the special section on contributions from the Canadian Anatomic and Molecular Pathology (CAMP) 2017 conference:

Is There a Role for Programmed Death Ligand-1 Testing and Immunotherapy in Colorectal Cancer With Microsatellite Instability? Part I—Colorectal Cancer: Microsatellite Instability, Testing, and Clinical Implications
Marginean EC, Melosky B.
Arch Pathol Lab Med. 2018 Jan;142(1):17-25.
https://www.ncbi.nlm.nih.gov/pubmed/29144791

Is There a Role for Programmed Death Ligand-1 Testing and Immunotherapy in Colorectal Cancer With Microsatellite Instability? Part II—The Challenge of Programmed Death Ligand-1 Testing and Its Role in Microsatellite Instability-High Colorectal Cancer
Marginean EC, Melosky B.
Arch Pathol Lab Med. 2018 Jan;142(1):26-34.
https://www.ncbi.nlm.nih.gov/pubmed/29120224

Celiac Disease and Other Causes of Duodenitis
Owen DR, Owen DA.
Arch Pathol Lab Med. 2018 Jan;142(1):35-43.
https://www.ncbi.nlm.nih.gov/pubmed/28758791

Lymphoproliferative Disorders of the Gastrointestinal Tract
Skinnider BF.
Arch Pathol Lab Med. 2018 Jan;142(1):44-52.
https://www.ncbi.nlm.nih.gov/pubmed/28829152

Journals Reviewed (January & February 2018)

Advances in Anatomic Pathology
American Journal of Clinical Pathology
American Journal of Gastroenterology
American Journal of Pathology
American Journal of Surgical Pathology
Archives of Pathology and Lab Medicine
BMC Gastroenterology
Cancer Cytopathology
Clinical Gastroenterology Hepatology
Diseases of the Colon and Rectum
Gastroenterology
Gastrointestinal Endoscopy
Gut
Histopathology
Human Pathology
Inflammatory Bowel Diseases
Journal of Clinical Pathology
Journal of Gastrointestinal Surgery
Journal of Molecular Diagnostics
Journal of Pathology
Modern Pathology
Virchows Archiv