Lymphocytic Esophagitis in Nonachalasia Primary Esophageal Motility Disorders: Improved Criteria, Prevalence, Strength of Association, and Natural History.

Putra J, Muller KE, Hussain ZH, Parker S, Gabbard S, Brickley EB, Lacy BE, Rothstein R, Lisovsky M. Am J Surg Pathol. 2016 Dec;40(12):1679-1685.
https://www.ncbi.nlm.nih.gov/pubmed/27526295

The primary goal of this study was to investigate the putative association of lymphocytic esophagitis (LE) pattern of injury with nonachalasia primary esophageal motility disorders (PEMD). The authors first established the normal esophageal lymphocytic count from 17 healthy volunteers with normal acid exposure, determined by 48 hr pH monitoring. The cutoffs for high IELs (ie, mean±2 SD) were estimated as 62, 46, and 41 at 0 to 2, 5, and 10 cm above the gastroesophageal junction, respectively; and histologically LE was defined as a lymphocyte count exceeding mean± 2 SD for a given biopsy level with an absence of rare intraepithelial granulocytes, arbitrarily defined as no more than 1 granulocyte per 2 HPF. The authors evaluated the esophageal biopsies from 69 patients with PEMD, including 22 with nutcracker esophagus, 33 with ineffective motility, and 14 with diffuse spasm while the control group consisted of esophageal biopsies from 70 patients with severe dysmotility-negative GERD referred for Nissen fundoplication. PEMD patients were more likely than controls to experience dysphagia (51% vs. 11%) and present with a normal esophageal endoscopy (45% vs. 21%). Moreover, PEMD patients were less likely than GERD controls to report reflux/heartburn symptoms (35% vs. 56%) and have endoscopic evidence of an irregular Z-line/possible Barrett esophagus (26% versus 46%) or ulcer/stricture (0 vs. 8%). LE pattern of injury was observed in 45%, 21%, and 36% of patients with nutcracker esophagus, ineffective motility, and diffuse esophageal spasm, respectively. The remainder of the patients with high IEL had a histologic pattern of reflux esophagitis: 9% with nutcracker esophagus, 18% with ineffective motility, and 14% with diffuse spasm. In contrast, LE was seen only in 6% of patients with dysmotility-negative GERD ($P<0.035$, vs. any type of PEMD). Overall, LE was strongly associated with PEMD in multivariate analysis (OR- 7.93; 95% CI 2.26-27.9; $P=0.001$). Histologically LE was focal in 82% and peripapillary in 68% of patients with PEMD; and the majority of patients with PEMD (64%) had CD4-predominant T cells. 56% of patients with PEMD and LE continued to have LE on follow-up, suggesting a chronic course of LE in a significant proportion of patients with PEMD. Based on these findings, the authors concluded that a strong association exists between PEMD and LE with many patients experiencing a chronic course of LE. The presence of LE in biopsies, especially if persistent, may be useful in increasing the awareness of PEMD.

Alcohol Consumption and Multiple Dysplastic Lesions Increase Risk of Squamous Cell Carcinoma in the Esophagus, Head, and Neck

Katada C, Yokoyama T, Yano T, Kaneko K, Oda I, Shimizu Y, Doyama H, Koike T, Takizawa K, Hirao M, Okada H, Yoshii T, Konishi K, Yamanouchi T, Tsuda T, Omori T, Kobayashi N, Shimoda T, Ochiai A, Amanuma Y, Ohashi S, Matsuda T, Ishikawa H, Yokoyama A, Muto M.
Gastroenterology. 2016 Nov;151(5):860-869.e7. doi: 10.1053/j.gastro.2016.07.040.
https://www.ncbi.nlm.nih.gov/pubmed/27492616

Some patients develop multiple squamous cell carcinomas (SCCs) in the upper aerodigestive tract, attributed to field cancerization; alcohol consumption has been associated with this process. The authors examined the association between multiple areas of dysplastic squamous epithelium with the development of SCC of the esophagus or head and neck cancer, as well as alcohol consumption and smoking. 331 patients with early stage esophageal SCC were examined using Lugol chromoendoscopy to evaluate the dysplastic squamous epithelium in the esophagus. Patients then were assigned to 3 groups, based on the number of Lugol-voiding lesions: A, no lesion; B, 1-9 lesions; or C, 10 or more lesions. Participants completed lifestyle surveys on their history of drinking, smoking, and diet. All participants were evaluated by laryngopharyngoscopy before registration; only those without head and neck cancer were included, except for patients with superficial SCC limited to the subepithelial layer. Lesions detected in the esophagus and head and neck by surveillance were considered to be metachronous. The study end point was the cumulative incidence of metachronous SCCs in the esophagus and head and neck after endoscopic resection of esophageal SCC, according to the grade of Lugol-voiding lesions. At study entry, all patients were instructed to abstain from alcohol and smoking. Over the 2-year study period, metachronous SCCs of the esophagus were detected in 4% of patients in group A, in 9.4% of patients in group B, and in 24.7% of patients in group C ($P < .0001$ for patients in group A vs B or B vs C). Head and neck SCCs were detected in none of the patients in group A, in 1.7% of the patients in group B, and in 8.6% of the patients in group C ($P = .016$ for patients in group A vs C and $P = .008$ for patients in group B vs C). SCC of the esophagus or head and neck developed in 4.0% of patients in group A, in 10.0% of patients in group B, and in 31.4% of patients in group C ($P < .0001$ for group A vs B or A vs C). Alcohol abstinence decreased the risk of multiple SCCs of the esophagus (adjusted hazard ratio, 0.47, 95% confidence interval, 0.25-0.91; $P = .025$), whereas smoking abstinence did not. The authors conclude that multiple dysplastic lesions in the esophagus increase the risk of multiple SCCs. Alcohol abstinence reduces the risk of metachronous SCCs.

Diagnosis and Management of Low-Grade Dysplasia in Barrett's Esophagus: Expert Review From the Clinical Practice Updates Committee of the American Gastroenterological Association

Wani S, Rubenstein JH, Vieth M, Bergman J.
Gastroenterology. 2016 Nov;151(5):822-835. doi: 10.1053/j.gastro.2016.09.040. Review.
https://www.ncbi.nlm.nih.gov/pubmed/27702561

The purpose of this clinical practice update expert review is to define the key principles in the diagnosis and management of low-grade dysplasia (LGD) in Barrett's esophagus patients. The article provides 15 points of practice advice. The advice most directly affecting pathologists are listed below, the first of which mirrors published ACG guidelines:

Practice Advice 2: Given the significant interobserver variability among pathologists, the diagnosis of Barrett's esophagus with LGD should be confirmed by an expert gastrointestinal pathologist (defined as a pathologist with a special interest in Barrett's esophagus-related neoplasia who is recognized as an expert in this field by his/her peers).

Practice Advice 3: Expert pathologists should report audits of their diagnosed cases of LGD, such as the frequency of LGD diagnosed among surveillance patients and/or the difference in incidence of neoplastic progression among patients diagnosed with LGD vs nondysplastic Barrett's esophagus.

Prospective identification of Helicobacter pylori in routine gastric biopsies without reflex ancillary stains is cost-efficient for our health care system.
Pittman ME, Kharajian A, Wood LD, Montgomery EA, Voltaggio L.
Hum Pathol. 2016 Dec;58:90-96. doi: 10.1016/j.humpath.2016.07.031.
https://www.ncbi.nlm.nih.gov/pubmed/27574809

This study evaluated the effectiveness and cost-efficiency of up-front Diff-Quick stain for identification of H. pylori at Johns Hopkins Hospital. For a 1-month period, gastric biopsies were prospectively evaluated for H pylori using routine hematoxylin and eosin (H&E) and a reflex Diff-Quik stain. During this time, 379 gastric biopsies were collected on 326 patients. H pylori organisms were prospectively identified in 23 (7%) patients, all of whom had superficial dense lymphoplasmacytic inflammation expanding the lamina propria. An additional 2 patients with neutrophilic inflammation were found to have H pylori by immunohistochemical staining. One patient diagnosed as having normal gastric mucosa was retrospectively found to have inflammation with rare H pylori organisms originally overlooked on both H&E and Diff-Quik but later identified on immunostain (0.5%). No patients with chemical gastritis (16%) or chronic inflammation (27%) were found to have H pylori. During the study month, 9 immunostains for H pylori were performed in addition to the 379 Diff-Quik. After discontinuation of reflex Diff-Quik, approximately 20 immunostains are performed for H pylori each month, which decreases technical time spent for processing gastric biopsies and reduces cost to the health care system. The authors conclude that in this center's population with a low prevalence of H pylori, reflex staining for organisms is not cost-effective, and discontinuation of up-front ancillary studies is cost-effective without compromising patient care.

Helicobacter pylori vacA transcription is genetically determined and stratifies the level of human gastric inflammation and atrophy
Charlotte G Sinnett,1 Darren P Letley,1 Geetha L Narayanan,1 Sapna R Patel,1
Nawfal R Hussein,1 Abed M Zaitoun,2 Karen Robinson,1 John C Atherton1
Sinnett CG, et al. J Clin Pathol 2016
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4714145/

This prospective study attempts to determine disease risk factors for specific H. Pylori infected individuals. Two important factors in H. Pylori virulence are the cytogoxin associated gene A (cagA) and vacuolating cytotoxin A (VacA). The authors focus on VacA in this study. The vacA gene is present and expressed in virtually all H. Pylori strains, however, not all are cytotoxic. There are three regions with

significant allelic diversity 1) the signal region, s1/s2 2) the mid region, m1/m2 and 3) the intermediate region i1/i2. All forms of the toxin exist, some more prevalent than others. The signal and intermediate regions determine toxin activity where s1i1 forms are fully active and s1i2 and s2i2 forms are less active. In Western Europe and the USA, it is has been reported that s1m1 strains are associated with more gastric inflammation, peptic ulcer disease and gastric adenocarcinoma. However in East Asia most strains are the i1-type. Therefore, based on these findings and the variation of vacA transcription levels grown in vitro, the authors hypothesized that the amount and activity of VacA could have relevant implication in disease severity in addition to the strain type. As such, they analyzed 39 gastric biopsies from patients with known H. Pylori infection to correlate quantification of vacA transcript levels with H&E findings as well as genetic determinants of vacA expression to be used as improved markers of disease risk. Exclusion criteria for this study included 1) proton pump inhibitor use 2) NSAID use 3) >150mg/day aspirin use 4) antibiotics 2 weeks prior to endoscopy. PCR amplification of vacA sequence from nucleotides 520-1055 was used to determine vacA genotype. Reverse transcriptase quantitative PCR (RT-qPCR) with SYBR Green was performed on total RNA to determine expression levels of vacA using 16srRNA as reference. Results of vacA expression by RT-qPCR showed that 21 patients had a wide range of mRNA expression levels whereas 18 patients had no detectable level of expression. Additionally, the level of vacA expression did not correlate with vacA allelic type. Where there was no statistical difference between mRNA levels of toxic i1-type strains and non-toxic i2-type strains. However, in patients who showed increased gastric inflammation and atrophy on H&E, there was an association with mRNA level of toxic vac i1-type strain. After combining cases of grade 2 and 3 inflammation, there was significantly higher level of vacA mRNA than for grade 1 ($p<0.05$) and for those with neutrophilic inflammation compared to those without ($p<0.005$). In comparison to 8 of 10 patients with i2-type strains which showed only had mild inflammation and no atrophy or intestinal metaplasia. Interestingly this association was not found in patients with severe inflammation, considered erosion or ulceration in either the stomach or duodenum. To understand the mechanism responsible for the differences in mRNA expression levels, the authors looked at polymorphisms that may affect expression levels. Polymorphisms within the promoter region did not prove to be associated with differences in expression levels. However, a polymorphism within the 5' UTR of the vacA transcript at nucleotide position +28 was found which is responsible for stability and half-life of mRNA. The authors report that the strains possessing A(+28) had more vacA expression (increased stability) than the G(+28) was associated with decreased expression (less stability). Similarly i1-type toxic strains with the A(+28) polymorphism were associated with more inflammation and neutrophilic infiltration. In summary, this study claims that in addition to previous reports that toxic i1-type strains are associated with increased disease risk so are total levels of vacA expression during infection. Therefore, they suggest vacA expression levels and +28 5'UTR polymorphism status may be important additional markers for risk stratifying patients for severe gastric or duodenal H.pylori disease.

Propionibacterium acnes overabundance and natural killer group 2 member D system activation in corpus-dominant lymphocytic gastritis.

Montalban-Arques A, Wurm P, Trajanoski S, Schauer S, Kienesberger S, Halwachs B, Högenauer C, Langner C, Gorkiewicz G.
J Pathol. 2016;240(4):425-436.
https://www.ncbi.nlm.nih.gov/pubmed/27538697

The authors of this study aimed to identify a potential bacterial trigger for body-predominant lymphocytic gastritis (LyG) through a number of means including comparative microbiota analysis. Additionally, they assessed the activation of the natural killer group 2 member D (NKG2D) system and IL-15 in this disease process. The authors note that LyG, which was initially reported in the context of 'varioliform gastritis', is associated with celiac disease in up to 45% of cases with a minor component of the remaining cases being tied to H. pylori infection. These two disease processes preferentially involve the gastric antrum and a large percentage of body-predominant LyG cases are considered idiopathic. As these cases seem to respond to antibiotic therapy even in the absence of H. pylori, an alternative bacterial cause has been hypothesized. Given this background, the authors compared the microbiota of gastric body biopsies from cases of LyG (n=13), H. pylori gastritis (n=5) and healthy controls (n=6) through the use of amplification and identification of bacterial 16S rRNA. While found at lower levels in H. pylori gastritis (24.8% of bacterial taxa) and normal controls (22.2%), Propionibacterium acnes was over represented in cases of LyG (47.4%). Through the use of RT-PCR, the authors also demonstrated that the NKG2D system and IL-15, major determinants of intraepithelial lymphocyte recruitment in the gastrointestinal tract, were significantly overexpressed in cases of LyG. Finally, the authors inoculated cell cultures of gastric epithelial cells with stomach derived strains of P. acnes and H. pylori and only found upregulation of the NKG2D system and IL-15 in the former. The authors conclude that the NKG2D system and IL-15 likely play a role in body-predominant LyG and overabundance of P. acnes may be a contributing factor.

OsmoPrep-associated Gastritis: A Histopathologic Mimic of Iron Pill Gastritis and Mucosal Calcinosis.
Matsukuma K, Gui D, Olson KA, Tejaswi S, Clayton EF, Thai A.
Am J Surg Pathol. 2016 Nov; 40(11):1550-1556.
https://www.ncbi.nlm.nih.gov/pubmed/27454942

The authors described 8 cases of OsmoPrep (Sodium Phosphate) associated gastritis characterized by purple to black granular inorganic lamina propria deposits and reactive gastropathy mimicking iron pill gastritis and mucosal calcinosis. In 7 prospectively identified patients, the distinctive features included smooth translucent to opaque granular irregularly sized deposits, restricted to the gastric lamina propria, and mucosal changes of mucin loss, nuclear hyperchromasia and no significant inflammation compatible with reactive gastropathy. The endoscopic findings ranged from mild erythema to severe diffuse erosions and mucosal friability. In all cases, the deposits were negative for iron on Perl's stain while 6/7 cases were positive with von Kossa stain, useful in identifying deposits containing calcium. However, the Alizarin red stain, a calcium chelating dye, was negative in all the biopsies. None of the patients were found to have calcium dysmetabolism, but all the patients used OsmoPrep bowel preparation for endoscopy. Another patient with similar histologic findings was identified in a

retrospective review of patients prescribed OsmoPrep for bowel preparation between 2007 and 2014. The von Kossa stain positivity in these biopsies was attributed to sodium phosphate, the active ingredient of OsmoPrep, because this stain identifies the phosphate or carbonate moiety of the calcium salts. In contrast, Alizarin red, a dye that directly binds calcium, was negative in all the cases. Furthermore, the authors observed similar staining profile of Von Kossa positive and Perl's and Alizarin Red negative staining in albumin-embedded OsmoPrep pill fragments, except with H&E stain, the fragments appeared more eosinophilic when compared to the deposits in the gastric biopsies. Thus, OsmoPrep associated gastritis could be a potential diagnostic pitfall, which requires clinicopathologic correlation. The authors did not identify any long-term complications in any of their patients.

Oncocytic variant of malignant gastrointestinal neuroectodermal tumor: a potential diagnostic pitfall
Boland JM, Folpe AL.
Hum Pathol. 2016 Nov;57:13-16. doi: 10.1016/j.humpath.2016.05.026. Epub 2016 Jun 23.
https://www.ncbi.nlm.nih.gov/pubmed/27346570

This is a case report of a gastric malignant gastrointestinal neuroectodermal tumor occurring in a 46-year-old woman and showing striking oncocytic cytoplasmic change, a previously undescribed potential diagnostic pitfall. An initial needle biopsy and the subsequent resection specimen showed areas with large, eosinophilic cells with S100 protein and SOX10 expression and lacking expression of KIT, DOG1, Melan A, keratin, chromogranin, or smooth muscle actin, and was interpreted as representing a malignant granular cell tumor. Subsequent gene expression profiling studies showed an EWSR1-ATF1 fusion, confirmed with fluorescence in situ hybridization for EWSR1, and a final diagnosis of MGNET with oncocytic change was made. This case highlights a previously undescribed pitfall in the diagnosis of MGNET, oncocytic change, and suggests that MGNET should be included in the differential diagnosis for unusual oncocytic neoplasms of the gastrointestinal tract. This article includes gross and microscopic photos of the unusual lesion.

Programmed Death-Ligand 1 Expression Is Common in Gastric Cancer Associated With Epstein-Barr Virus or Microsatellite Instability.
Ma C, Patel K, Singhi AD, Ren B, Zhu B, Shaikh F, Sun W. Am J Surg Pathol. 2016 Nov;40(11):1496-1506.
https://www.ncbi.nlm.nih.gov/pubmed/27465786

The authors of this study hypothesized that gastric tumors with prominent lymphoid stroma especially Epstein-Barr virus infection associated (EBV+) and microsatellite instable (MSI) gastric cancers are more likely to express programmed death Ligand 1 (PD-L1) and to have increased CD8 T-cells in the tumor microenvironment. The authors identified 44 cases of gastric cancer resections, including 7 EBV+, 16 MSI, and 21 microsatellite stable (MSS) from 2004 to 2015. Histologically, 71% (5/7) of EBV+, 63% (10/16) of MSI and 5% (1/21) EBV-/MSS gastric cancers showed lymphoid stroma (medullary carcinoma). PD-L1 (clone SP263; Ventana) expression is considered positive if any membranous staining is identified

in either tumor cells or tumor immune infiltrates. The positive pattern of PD-L1 staining in gastric cancer was classified as: (1) diffuse (Contiguous membranous staining involving 10% or more tumor), (2) invasive front (staining seen predominantly in tumor cells and the associated immune cells at the tumor-stroma interface), (3) immune infiltrates (staining only seen in tumor-associated immune cells), and (4) negative (no staining in either tumor cells or tumor-associated immune cells. 32/44 cases (72%) were PD-L1 positive (PD-L1+). Both EBV+ cancers and MSI cancers were more likely to be PD-L1+ compared with EBV-/ MSS cancers (7/7 [100%], 14/16 [87%], 11/21 [52%]; P=0.013). Diffuse staining was noted in 4/7 [57%] PD-L1+/EBV+, 5/14 [36%] PD-L1+/MSI cancers. Invasive front staining in 2/7 [29%] PD-L1+/EBV+ and, 9/14 [64%] PD-L1+/MSI cancers. In contrast, only immune infiltrate staining was seen in 7/11, 64% PD-L1+/EBV-/MSS cancers. PD-L1 expression was negative in the 2 (100%) mucinous adenocarcinomas and in 4 of 5 (80%) (Including 1 MSI and 3 EBV-/MSS cases) signet-ring cell carcinomas. Regarding the immune infiltrates, PD-L1+ cancers had significantly more T cells at the invasive front than PD-L1- cancers. PD-L1+/EBV+ and PD-L1+/MSI gastric cancers had significantly more CD3, CD8, and PD-1 T cells at tumor invasive front compared with PD-L1+/EBV-/MSS cancers. When stratified by PD-L1 expression, PD-L1+ was not associated with depth of invasion, positive lymph node metastasis, or distant metastasis. In multivariate analysis, PD-L1 expression was not associated with disease free survival, but high stage and MSI both were independent prognostic factors for DFS (P=0.009, 0.043). Based on these findings authors concluded that positive PD-L1 expression in gastric cancer is associated with EBV infection, MSI and abundant CD8 T cells at tumor invasive front. PD-L1 expression is not predictive of patient survival. The findings also suggest that EBV + and MSI should be further investigated for predicting response to PD-1 blockade.

Use of Proton Pump Inhibitors and Risks of Fundic Gland Polyps and Gastric Cancer: Systematic Review and Meta-analysis.

Tran-Duy A, Spaetgens B, Hoes AW, de Wit NJ, Stehouwer CD.
Clin Gastroenterol Hepatol. 2016;14(12):1706-1719.
https://www.ncbi.nlm.nih.gov/pubmed/27211501

The objective of this systematic review with meta-analysis was to evaluate the relationship between proton pump inhibitor (PPI) use and the development of fundic gland polyps (FGPs) and gastric cancer. The authors note that an increasing number of observational studies on the adverse events associated with long-term PPI use have appeared in the literature and a potential association between these medications and the development of FGPs has emerged over time. Additionally, a potential link between PPI use and subsequent gastric cancer has been proposed but not thoroughly examined. Multiple databases were searched for relevant studies which included those which were written in English, reported FGPs or gastric cancer, compared outcomes of PPI users with PPI non-users and provided adequate data to estimate odds ratios or risk ratios. A total of 12 studies, comprising 87,324 patients, met inclusion criteria, 8 of which evaluated gastric polyps and 4 which evaluated the presence of gastric cancer. While there was significant heterogeneity in the reporting of FGPs in these studies, the pooled odds ratios for the development of FGPs in the setting of long term PPI use (>12 months) were 1.43 and

2.45 depending on the statistical model applied. Additionally, while the reported pooled risk ratio for gastric cancer was 1.43, the authors felt that this association may be bias considering the small number of studies evaluating this finding and the lack of reporting of other pertinent findings such as H. pylori infection status. Therefore, while the authors conclude that long-term PPI use is indeed associated with the development of FGPs, the magnitude and statistical significance of the association between PPI use and the risk of gastric cancer remain uncertain.

HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and American Society of Clinical Oncology.
Bartley AN, Washington MK, Ventura CB, Ismaila N, Colasacco C, Benson AB 3rd, Carrato A, Gulley ML, Jain D, Kakar S, Mackay HJ, Streutker C, Tang L, Troxell M, Ajani JA.
Arch Pathol Lab Med. 2016 Dec;140(12):1345-1363.
https://www.ncbi.nlm.nih.gov/pubmed/27841667

This multi-society systematic literature review (116 articles) by an expert panel establishes evidence-based guidelines with recommendations for optimal HER2 testing in patient with gastroesophageal adenocarcinoma (GEA). Eleven recommendations are proposed which have strong agreement from open-comment participants. Among these: that all patients who are candidates for HER2-targeted therapy undergo HER2 assessment prior to initiating such therapy; That ISH should be performed only on equivocal (2+) IHC cases; That the antibodies and probes used for testing be specified and specifically validated for GEA; and that Ruschoff/Hofmann scoring method be used. Additional useful information pertaining to technical considerations and stain interpretation are discussed.

Diagnostic phrasing is independently correlated with the decision to treat for graft-versus-host disease: retrospective review of colon biopsies with rare apoptosis.
Rowan DJ, Hartley CP, Carrillo-Polanco LF, Oshima K, Hagen CE.
Histopathology. 2016 Nov;69(5):802-811.
https://www.ncbi.nlm.nih.gov/pubmed/27237047

Based on a recent proposal of the category “indeterminate for GVHD (iGVHD)” to indicate cases with 6 or fewer apoptotic bodies per 10 crypts, a retrospective study was performed for blind review of maximum number of apoptotic bodies per 10 contiguous crypts, evidence of crypt dropout, and ulceration. In all, 122 biopsies were reviewed, of which 47 met the criteria for iGVHD (a subset of reviewed cases from the reporting institution were from 2013 and beyond, when the authors started using the term iGVHD). The patients categorized as iGVHD were more likely to have been managed conservatively than those with a diagnosis of grade 1 GVHD (25% versus 0%). Eight symptomatic patients who met the diagnostic criteria for iGVHD had resolution of symptoms without increased immunosuppression, suggesting that patients with only rare crypt apoptosis may not need therapy for

GVHD. The authors advocate the use of iGVHD as a distinct diagnostic category to help distinguish cases of possible (indeterminate) GVHD and likely GVHD.

Gastrointestinal Manifestations of Autosomal-Dominant Polycystic Kidney Disease.
Mikolajczyk AE, Te HS, Chapman AB.
Clin Gastroenterol Hepatol. 2017;15(1):17-24.
https://www.ncbi.nlm.nih.gov/pubmed/27374006

While not a research article per se, this paper serves as a succinct review of the manifestations of autosomal-dominant polycystic kidney disease (ADPKD) within the gastrointestinal and pancreaticobiliary tracts. ADPKD, which is most often attributed to mutations on *PKD1* and *PKD2*, affects between 1/400 to 1/1000 people and is among the most common reasons for renal transplant. ADPKD associated polycystic liver disease is the most extensively covered process in this review and is the most common extrarenal manifestation of ADPKD, affecting 94% of diseased individuals over the age of 35. While common, the degree of associated liver cysts is variable with larger cyst burdens being more common in women. This finding has been related to multiple pregnancies and exposure to oral contraceptive pills, the latter of which is discouraged in these patients. The medical and surgical management of liver cysts is variable and includes somatostatin analogues, aspiration-sclerotherapy, fenestration and resection. Diverticular disease is the second most common extrarenal manifestation of ADPKD, affecting between 50-83% of patients with end stage renal disease (ESRD) secondary to ADPKD. Interestingly, this increased prevalence is not noted in ADPKD individuals who have not reached ESRD. This manifestation is thought to be secondary to smooth muscle dysfunction or abnormal extracellular matrix production. This latter hypothesis is also referenced in the discussion of hernias associated with ADPKD. While they often go undetected, pancreatic cysts are noted in 9-36% of these patients and are typically unilocular. While the pathologic findings of these cysts are not discussed, rare reports of intraductal pancreatic mucinous neoplasms and mucinous cystic neoplasms are mentioned in the review. The authors note that with the advances in care for ADPKD patients these gastrointestinal and pancreaticobiliary manifestations may become more relevant.

Clinicopathological characteristics of systemic mastocytosis in the intestine.
Shih AR, Deshpande V, Ferry JA, Zukerberg L.
Histopathology. 2016 Dec;69(6):1021-1027.
https://www.ncbi.nlm.nih.gov/pubmed/27391777

Seven cases of atypical mast cell infiltrate on GI biopsy were studied for clinicopathological characteristics indicative of systemic mastocytosis; all patients met WHO criteria for systemic mastocytosis. Five cases showed involvement of large bowel, one of the small bowel, and one of both by mast cells with varying morphology. The mucosal collection of mast cells could be polypoid (one case), confluent and subepithelial (three cases), or multifocal (three cases). Eosinophils were admixed,

with a relative lack of plasma cells. Four patients had follow-up available, of whom none had disease progression. The lack of clinical suspicion for mast cell disease can make diagnosis difficult.

Immunohistochemical detection of human intestinal spirochetosis
Ogata S, Shimizu K, Oda T, Tominaga S, Nakanishi K.
Hum Pathol. 2016 Dec;58:128-133. doi: 10.1016/j.humpath.2016.07.032.
https://www.ncbi.nlm.nih.gov/pubmed/27581381

Human intestinal spirochetosis (HIS) is a colorectal infection by Brachyspira species of spiral bacteria. Immunohistochemical cross-reaction to an antibody for Treponema pallidum aids its histologic diagnosis. This study's aim was to analyze the immunohistochemical characteristics of HIS. This analysis on 223 specimens from 83 HIS cases, focused on so-called fringe formation (a histologic hallmark of HIS), spiral organisms within mucus or within crypts, and strong immunopositive materials in the mucosa, together with their location and the types of lesions. Fringe formation was found in 81.6% of all specimens and spiral organisms within mucus or within crypts in 97.3% and 57.0%, respectively. Strong immunopositive materials were observed in the surface epithelial layer in 87.9%, in the subepithelial layer in 94.6%, and in deeper mucosa in 2.2% of all specimens. The positive rates in conventional adenomas (24.0%, n = 146) and hyperplastic nodules (100%, n = 17) were each different from that found in inflammation (70.8%, n = 24), and spiral organisms were seen more frequently in the right-side large intestine than in the left (within mucus, 100%, n = 104 versus 95.0%, n = 119; within crypts, 65.4%, n = 104 versus 49.6%, n = 119). Thus, immunohistochemistry was effective not only in supporting the diagnosis of HIS but also in highlighting spiral organisms within mucus or crypts that were invisible in routine histology. Possibly, these spiral organisms may spread throughout the entire large intestine, although there is a potential problem with antibody specificity.

Increased Rates of Clostridium difficile Infection and Poor Outcomes in Patients with IBD with Cytomegalovirus.
McCurdy JD, Enders FT, Khanna S, Bruining DH, Jones A, Killian JM, Tariq R, Smyrk TC, Loftus EV Jr.
Inflamm Bowel Dis. 2016 Nov;22(11):2688-2693.
https://www.ncbi.nlm.nih.gov/pubmed/27755270

This retrospective case control study found that Clostridium difficile infection (CDI) was more common in IBD patients with CMV (17.6%) as compared to matched control IBD patients without CMV (8.25%, p = 0.046). More coinfected patients also required colectomy (colectomy-free survival at 1 year 30% for coinfected vs 71.5% for controls, p<0.001), and most were within 3 months from infection diagnosis. CMV infection was made by H&E and/or IHC and later confirmed by IHC if not performed initially. Five of the 11 (45%) coinfected patients had high-grade CMV (5 or more inclusions on IHC) which was not significantly different from the 12 of 52 IBD patients without CDI co-infection. The authors point out that they were unable to determine the order of infection in co-infected patients. Antiviral therapy was not

protective against colectomy risk in the co-infected group. The authors conclude that IBD patients with CMV more frequently also have CDI occurs which associated with poor outcomes.

Lymphoid Aggregates Remodel Lymphatic Collecting Vessels that Serve Mesenteric Lymph Nodes in Crohn Disease.
Randolph GJ, Bala S, Rahier JF, Johnson MW, Wang PL, Nalbantoglu I, Dubuquoy L, Chau A, Pariente B, Kartheuser A, Zinselmeyer BH, Colombel JF.
Am J Pathol. 2016 Dec;186(12):3066-3073
https://www.ncbi.nlm.nih.gov/pubmed/27746181

This novel study included 17 patients with adult-onset ileal stricturing Crohn's disease (CD) who had intraoperative blue dye lymphatic tracing. They noted aberrant flow of the dye in bowel segments affected by active CD as compared to unaffected segments. There was also expansion of the mesenteric lymphatic vessels. They concluded that remodeling of collecting lymphatic vessels within the mesenteric fat of CD affected segments contain B-cell rich tertiary lymphoid organs (TLOs, which may mediate local immunity when regional lymph node drainage is impaired) which then affected the vessel integrity, and presumably the delivery of lymph to regional lymph nodes.

Histological Disease Activity as a Predictor of Clinical Relapse Among Patients With Ulcerative Colitis: Systematic Review and Meta-Analysis.
Park S, Abdi T, Gentry M, Laine L.
Am J Gastroenterol. 2016;111(12):1692-1701.
https://www.ncbi.nlm.nih.gov/pubmed/27725645

This systematic review and meta-analysis sought to assess whether histologic remission was associated with lower rates of clinical relapse or exacerbation compared to clinical or endoscopic remission in ulcerative colitis (UC) patients. Fifteen studies representing 1,573 patients were included which examined UC patients with extractable data regarding the initial presence or absence of histologic, clinical and endoscopic remission with outcomes including clinical relapse or exacerbation, the latter of which was defined by the study. While the primary definitions of histologic remission and activity were also study defined, separate analyses of additional histologic criteria were performed including the absence of epithelial or lamina propria neutrophils, crypt abscesses, basal plasmacytosis, lamina propria eosinophils, crypt distortion, chronic inflammatory infiltrates and absence of basal lymphoid aggregates. The authors found the incidence of clinical relapse was significantly lower among patients with baseline histological remission than those with histological activity (RR=0.48). Additionally, relapse was less common in this group compared to individuals with clinical and endoscopic remission (RR=0.81). Of note, 31% of patients with endoscopic remission were not in histologic remission. Specific histologic features associated with a lower rate of relapse included the absence of neutrophils in the epithelium, neutrophils in the lamina propria, crypt abscesses, eosinophils in the lamina propria and chronic inflammatory infiltrates. Alternatively, the absence of basal plasmacytosis, basal lymphoid aggregates

and architectural distortion were not associated with decreased rates of relapse. The authors conclude that histologic remission provides clinically important prognostic information in UC patients and is superior to endoscopic and clinical remission in predicting subsequent relapses.

Long-term Outcomes of Sphincter Saving Procedures for Diffuse Crohn's Disease of the Large Bowel.
Li Y, Stocchi L, Mu X, Cherla D, Remzi FH.
Dis Colon Rectum. 2016 Dec;59(12):1183-1190.
https://www.ncbi.nlm.nih.gov/pubmed/27824704

This retrospective study assessed patients with large bowel Crohn's disease (CD) undergoing either total abdominal colectomy with ileorectal anastomosis or ileal pouch-anal anastomosis (IPAA) for long term functional results and permanent stoma. The authors sought to determine how selecting patients to have IRA or intentional IPAA would compare with a control group undergoing total proctocolectomy and end ileostomy (TPC + EI) due to prior published reports of poor pouch function following IPAA in CD. Exclusion criteria included 1) previous segmental colectomy for CD 2) incidental diagnosis of CD established after specimen examination 3) patients with clinical signs of Crohn's ileitis without previous CD diagnosis 4) surgical revision of existing IPAA 5) IRA after repeated resections for ileocolonic disease. Inclusion criteria for IRA included 1) normal rectum 2) mild/moderate proctitis with 'slightly reduced distensibility' and 3) mild perianal disease. Patients selected for IPPA were highly motivated with histologically proven CD involving only the colon and rectum and without anoperineal or fistulizing disease. Patients in the IPAA group were younger, had shorter disease duration from the time of diagnosis to surgery and were more refractory to medical treatment compared to IRA patients. The IPAA group also had less perianal disease and small bowel involvement. Following surgery the IPAA group had a higher risk of readmission than those undergoing IRA. There was no significant association between surgical procedure and postoperative use of immunomodulators, although both the IPAA group and IRA group had a higher rate of steroid and biologics use than the control group TPC +EI. Overall quality of life scores were similar between the sphincter sparing groups but better than the control group. Functional outcomes were similar with IRA and IPAA. Patients undergoing IRA had a higher rate of stoma diversion and surgical recurrence than those with intentional IPAA. In summary, the authors state that the selection of patients with less severe disease to undergo IPAA vs IRA explains the improved quality of life and decreased rates of adverse long term outcomes within the IPAA group. However, they claim that either IRA or IPAA had acceptable functional results and quality of life scores when compared to patients who underwent TPC + EI. Therefore, the authors believe this study confirms that sphincter-saving operations for CD of the large bowel should be acceptable alternatives to TPC +EI in patients who are highly selected, motivated and willing to accept a greater risk of medication use and dietary restrictions.

Comparison of Targeted vs Random Biopsies for Surveillance of Ulcerative Colitis-Associated Colorectal Cancer
Watanabe T, Ajioka Y, Mitsuyama K, Watanabe K, Hanai H, Nakase H, Kunisaki R, Matsuda K, Iwakiri R, Hida N, Tanaka S, Takeuchi Y, Ohtsuka K, Murakami K, Kobayashi K, Iwao Y, Nagahori M, Iizuka B, Hata K,

Igarashi M, Hirata I, Kudo SE, Matsumoto T, Ueno F, Watanabe G, Ikegami M, Ito Y, Oba K, Inoue E, Tomotsugu N, Takebayashi T, Sugihara K, Suzuki Y, Watanabe M, Hibi T.
Gastroenterology. 2016 Dec;151(6):1122-1130. doi: 10.1053/j.gastro.2016.08.002.
https://www.ncbi.nlm.nih.gov/pubmed/27523980

The randomized controlled trial included 246 patients with UC for 7 years or more, seen at 52 institutions in Japan from October 1, 2008 through December 31, 2010. Patients were randomly assigned to the random group (4 random biopsies collected every 10 cm in addition to targeted biopsies, n = 122) or the target group (biopsies collected from locations of suspected neoplasia, n = 124). The primary end point was the number of neoplastic lesions detected in a single surveillance colonoscopy. The mean number of biopsies found to contain neoplastic tissue per colonoscopy was 0.211 (24 of 114) in the target group and 0.168 (18 of 107) in the random group (ratio of 1.251; 95% confidence interval, 0.679-2.306). The lower limit was above the non-inferiority margin of 0.65. Neoplasias were detected in 11.4% of patients in the target group and 9.3% of patients in the random group (P = .617). Larger numbers of biopsy samples per colonoscopy were collected in the random group (34.8 vs 3.1 in the target group; P < .001), and the total examination time was longer (41.7 vs 26.6 minutes in the target group; P < .001). In the random group, all neoplastic tissues found in random biopsies were collected from areas of the mucosa with a history or presence of inflammation. Random biopsies from areas without any signs of present or past inflammation were not found to contain neoplastic tissues. The authors found that targeted and random biopsies detect similar proportions of neoplasias. However, a targeted biopsy appears to be a more cost-effective method.

Gastric Proteins MUC5AC and TFF1 as Potential Diagnostic Markers of Colonic Sessile Serrated Adenomas/Polyps
Magomed Khaidakov, Keith K. Lai, D. Roudachevski, Julietta Sargsyan, Hannah E. Goyne, Rish K. Pai, Laura W. Lamps, Curt H. Hagedorn
Am J Clin Path. 2016 Nov;146(5):530-537.

http://dx.doi.org/10.1093/ajcp/aqw142

The goal of this study was to identify immunohistochemistry markers that might help distinguish hyperplastic polyps (HPs) from sessile serrated adenomas/polyps (SSA/Ps). Currently SSA/Ps are considered to be associated with increased risk of colon cancer while hyperplastic polyps are not. While the distinction between the two lesions is based on morphologic criteria, the authors note that the diagnosis of SSA/P can be challenging in small or fragmented biopsies and that ancillary testing may be of use to help avoid inadequate follow up or unnecessary surveillance for misdiagnosis of an SSA or a HP respectively. The authors state that in previous studies they evaluated the transcriptional signature of SSA/Ps and found that the gastric epithelial associated genes MUC5AC and TFF1 were highly expressed. A study set of 47 HPs, 37 SSA/Ps, and 30 normal colon biopsies were evaluated by immunohistochemistry and immunofluorescence for MUC5AC and TFF1. Both immunohistochemistry and immunofluorescence showed similar results with increased expression, co-expression, and

expression deeper in the crypts for SSA/Ps compared to HPs and normal colon. The authors suggest that evaluating expression of these two markers may be useful for differentiating SSA/Ps from HPs.

Gremlin1 expression associates with serrated pathway and favourable prognosis in colorectal cancer.
Pelli A, Väyrynen JP, Klintrup K, Mäkelä J, Mäkinen MJ, Tuomisto A, Karttunen TJ.
Histopathology. 2016 Nov;69(5):831-838.
https://www.ncbi.nlm.nih.gov/pubmed/27257976

148 surgical cases of colorectal cancer were assessed for Gremlin1 expression, a BMP antagonist postulated to be involved in CRC progression. Gremlin1 is expressed abundantly in lower stage cancers (P=0.044), those with serrated histology (P=0.033 or P=0.053 depending on classification cut-off), and was a stage-independent indicator of longer survival (P=0.029).

Fusobacterium nucleatum in colorectal carcinoma tissue and patient prognosis.
Mima K, Nishihara R, Qian ZR, Cao Y, Sukawa Y, Nowak JA, Yang J, Dou R, Masugi Y, Song M, Kostic AD, Giannakis M, Bullman S, Milner DA, Baba H, Giovannucci EL, Garraway LA, Freeman GJ, Dranoff G, Garrett WS, Huttenhower C, Meyerson M, Meyerhardt JA, Chan AT, Fuchs CS, Ogino S.
Gut 2016;65:1973-1980.
https://www.ncbi.nlm.nih.gov/pubmed/26311717

F. nucleatum activates WNT signalling in colorectal carcinoma cells and may promote cancer growth. Epidemiological analysis of 1069 rectal and colon cancer cases from national databases shows increased *F. nucleatum* DNA in colorectal carcinoma tissue by quantitative PCR analysis from formalin-fixed paraffin blocks, with association with MSI-high (multivariable odds ratio 5.22, 95% CI 2.86-9.55) independent of CIMP and *BRAF* mutation status. Increasing content of *F. nucleatum* DNA is associated with shorter survival and may serve as a prognostic biomarker.

Clinicopathological characteristics predict lymph node metastases in ypT0-2 rectal cancer after chemoradiotherapy.
Bosch SL, Vermeer TA, West NP, Swellengrebel HA, Marijnen CA, Cats A, Verhoef C, van Lijnschoten I, de Wilt JH, Rutten HJ, Nagtegaal ID.
Histopathology. 2016 Nov;69(5):839-848.
https://www.ncbi.nlm.nih.gov/pubmed/27270756

The authors examined factors predictive of residual lymph node metastases in low-stage rectal cancer cases after neoadjuvant chemoradiation (CRT). In this multi-center study of 210 cases of treated ypT0-2 disease, residual nodal disease was found in 44 cases (21%). Independent predictors of residual nodal metastasis were clinical nodal involvement (OR 2.79, 95% CI 1.04-7.48, P=0.042), high-grade histology in

the post-treatment specimen (OR 6.46, 95% CI 1.23-34.02, P=0.028), and residual tumor diameter at least 10 mm (OR 2.54, 95% CI 1.06-6.09, P=0.036). The authors advocate risk stratification based on these factors.

Risk of Colorectal Neoplasia in Individuals With Self-Reported Family History: A Prospective Colonoscopy Study from 16 Asia-Pacific Regions.
Wong MC, Ching JY, Chiu HM, Wu KC, Rerknimitr R, Li J, Wu DC, Goh KL, Matsuda T, Kim HS, Leong R, Yeoh KG, Chong VH, Sollano JD, Ahmed F, Menon J, Ng SC, Wu JC, Chan FK, Sung JJ.
.Am J Gastroenterol. 2016;111(11):1621-1629.
https://www.ncbi.nlm.nih.gov/pubmed/26977757

The objective of this study was to evaluate the risk of colonic adenomas, advanced colorectal neoplasia (ACN) and colorectal carcinoma (CRC) among individuals undergoing screening colonoscopy with a history of CRC in first degree relatives. This was a large multinational, multi-center, prospective study involving 16 Asia-Pacific countries/regions and included 11,797 patients. Asymptomatic subjects aged ≥ 40 years were included while individuals with a previous history of colonic disease, a prior colonic screening test or any contraindication to colonoscopy were excluded. Study participants were asked about a history of CRC in their siblings and parents. Among the subjects, the proportion of adenomas, ACN (defined as adenomas ≥ 10 mm, or those with high-grade dysplasia or a villous component) and CRC was 29.3%, 6.5% and 0.6% respectively. These findings are similar to other large screening colonoscopy cohorts. In regards to the prevalence of CRC in those subjects with a family history of CRC, subjects with affected siblings, parents, or ≥ 2 of those individuals had a higher risk of CRC compared to those without a family history (1.1%, 0.9% and 3.1% respectively compared to 0.6%). While the prevalence was different for these various groups, the risk of CRC was statistically similar among subjects with siblings, parents or ≥ 2 individuals affected. Similar findings were also noted in the prevalence of colonic adenomas and ACN is these groups compared to those subjects without a family history. The authors conclude that, similar to previous studies, a family history of CRC puts individuals at an increased risk of adenomas, ACN and CRC. Furthermore, this study implies that identification of the specific proband with a history of CRC, whether it be siblings or parents, is not significant when assessing the risk of colonic neoplasia.

Patterns and prognostic relevance of PD-1 and PD-L1 expression in colorectal carcinoma
Lee LH, Cavalcanti MS, Segal NH, Hechtman JF, Weiser MR, Smith JJ, Garcia-Aguilar J, Sadot E, Ntiamoah P, Markowitz AJ, Shike M, Stadler ZK, Vakiani E, Klimstra DS, Shia J.
https://www.ncbi.nlm.nih.gov/pubmed/27443512

Programmed death-ligand 1 (PD-L1) immunohistochemistry has been found to be useful in predicting response to anti programmed death-1 (anti PD-1) therapies in several types of cancer and, although anti PD-1 therapy has been found to be effective in mismatch repair deficient colorectal tumors, the

predictive value of PD-L1 immunohistochemistry in colorectal cancer has not yet been determined. The authors of this study aimed to evaluate expression patterns of PD-L1 and PD-1 by IHC on tissue microarrays to explore its clinical utility. The authors found that IHC on colorectal tumors was feasible and, as expected, mismatch-repair-deficient tumors had significantly higher rates of high PD-L1 and PD-1 expression when compared with mismatch-repair-proficient tumors. A secondary aim of the study was to evaluate any prognostic significance of PD-1 and PD-L1 expression in non-treated tumors. For this the authors found that the ratio of PD-1/PD-L1 in mismatch repair deficient tumors was positively correlated with recurrence-free survival, with high levels of PD-1 positive tumor infiltrating lymphocytes showing better outcomes only when the tumors had low-level PD-L1 expression. The authors feel that this work may serve as a basis for further assessment of PD-L1 IHC as a predictive marker for anti-PD-1 therapy in colorectal carcinoma and that the findings may help to understand the prognostic impact of tumor infiltrating lymphocytes in different subsets of mismatch-repair-deficient colorectal carcinomas.

Clinicopathological and Prognostic Evaluations of Mixed Adenoneuroendocrine Carcinoma of the Colon and Rectum: A Case-Matched Study

Watanabe J, Suwa Y, Ota M, Ishibe A, Masui H, Nagahori K, Tsuura Y, Endo I.
Dis Colon Rectum 2016; 59: 1160–1167
https://www.ncbi.nlm.nih.gov/pubmed/27824701

Mixed adenoneuroendocrine carcinoma (MANEC) is defined by the WHO as a neoplasm with dual adenocarcinoma and neuroendocrine differentiation, with each component accounting for at least 30% of the entire tumor. This retrospective case-matched study aimed to evaluate the occurrence, clinicopathologic characteristics and prognosis of MANEC's of the colon and rectum. A review of 1306 consecutive colorectal cancer patients identified 42 patients (3.2%) with MANEC (33 colon, 9 rectum). Routine H&E slides were reviewed for neuroendocrine morphology, and IHC for chromogranin A, synaptophysin, and CD56 were performed to assess percent NE differentiation. Each MANEC patient was case matched with 2 colorectal adenocarcinoma patients based on age, sex, tumor site, tumor diameter and TMN stage (7th edition). Average tumor size was 52.2mm, 88.1% were T3-4 and 61.9% had lymph node metastases. All cases demonstrated lymphovascular invasion. Only one tumor revealed a small cell component and this patient had widely metastatic disease 4 months after LAR and died after 12 months. Within the NEC component, 4.8% of MANEC's revealed Somatostatin receptor type 2A (SSTR2a) positivity within the NEC areas. 46.9% of MANEC patients and 35.3% of adenocarcinoma patients were treated with oxaliplatin based chemotherapy. 5 year DFS rate for MANEC group was 60.5% and 76.2% for the adenocarcinoma group. The 5 year OS was 69% for MANEC group and 82% for the adenocarcinoma group. For the MANEC group both DFS and OS were statistically worse when compared to the adenocarcinoma group ($p=0.032$ and $p=0.048$ respectively). Of the 9 patients who had surgical resection for metastatic disease, the NEC component was demonstrated within 5 metastases. Similar to previous publications this study suggests that MANEC's of the colon and rectum have a worse prognosis than adenocarcinoma, particularly for stage III. Oxaliplatin-based chemotherapy appears to have similar outcomes for MANEC's and adenocarcinomas of the colon and rectum. Given the low rate of SSTR2a positivity, the authors suggest that somatostatin analogs may not be effective for treatment

of MANECs. Overall, the authors recommend performing IHC on any colorectal adenocarcinoma that demonstrates neuroendocrine morphology on H&E given the therapeutic and prognostic implications.

Molecular cytology genotyping of primary and metastatic GI stromal tumors by using a custom two-gene targeted next-generation sequencing panel with therapeutic intent.
Gleeson FC, Kerr SE, Kipp BR, Voss JS, Minot DM, Tu ZJ, Henry MR, Vasmatzis G, Cheville JC, Lazaridis KN, Levy MJ. Gastrointest Endosc. 2016 Dec;84(6):950-958.
https://www.ncbi.nlm.nih.gov/pubmed/27118626

The goal of this study was to investigate the genotypic concordance between paired cytology smears and surgical pathology specimens from GI stromal tumors in patients with primary or metastatic sporadic disease, including the frequency of KIT and PDGFRA and imatinib sensitivity. The authors used a custom designed GIST ion Ampliseq panel to detect both common and rarer somatic mutations within KIT (exons 2, 9, 10, 11, 13, 14, 15, 17, 18) and PDGFRA (exons 12, 14, 15, 18) genes. The cytology specimens from 36 patients with sporadic GIST were evaluated, of whom 24 (66%) had paired surgical pathology specimens available for correlation. Cytology specimens were obtained by EUS (n=28), CT (n= 5), or transabdominal US (n = 3); the sites included gastric (n = 25), primary peritoneal (n =2), metastatic peritoneal (n=2), liver (n=4), duodenum (n =2), and esophagus (n =1). Thirty-four patients (94.4%) had successful targeted NGS sequencing results. Genotyping revealed KIT mutations in 23 of 34 patients (67.6%) in exons 11 (n=20, 58.8%) and 9, 13, and 17 (n=1, 2.9% each). PDGFRA mutations were identified in 5 patients (14.7%) in exons 18 (n =3, 8.8%) and 12 (n =2, 5.9%). KIT/PDGFRA WT/WT status was identified in 6 patients (17.7%). In 20 patients with prior multigene mutation analysis, there was 100% concordance in mutational landscape of these two genes. Based on these findings, it was predicted that 23 patients (67.6%) were likely to be sensitive to imatinib and the remaining 11 patients (32.4%) were predicted to have decreased sensitivity or resistance to imatinib. Regarding concordance between cytology and surgical specimens, 23 patients who had successful paired NGS results, 22 (95.6%) demonstrated complete KIT/PDGFRA mutational concordance. One patient with a discordant result showed WT cytology status, whereas subsequent surgical pathology specimen showed KIT V654A mutation. Of the 6 patients with WT status, 5 had surgical pathology specimen on which 160 gene panel NGS evaluation was performed. One patient had a very rare PDGFRA (1765C >T P589S) mutation and one had a TP53 (724T >A C242S) mutation. No patient harbored mutations in other known genes associated with GIST such as BRAF, RAS family, SDHB, SETD2, or NF1. These findings demonstrated the ability to stratify either primary or metastatic GIST by mutational subtype using a targeted NGS 2 gene mutation panel and use of cytology smear specimens obtained via minimally invasive techniques.

Diagnosis of autoimmune pancreatitis by EUS-guided FNA using a 22-gauge needle: a prospective multicenter study.
Kanno A, Masamune A, Fujishima F, Iwashita T, Kodama Y, Katanuma A, Ohara H, Kitano M, Inoue H, Itoi T, Mizuno N, Miyakawa H, Mikata R, Irisawa A, Sato S, Notohara K, Shimosegawa T.
Gastrointest Endosc. 2016 Nov;84(5):797-804.

https://www.ncbi.nlm.nih.gov/pubmed/27068878

This prospective multicenter study, involving 12 tertiary referral centers in Japan, aimed at investigating the diagnostic utility of EUS-FNA using a 22-gauge needle for the histopathologic diagnosis of type 1 autoimmune pancreatitis (AIP). FNA specimens from 78 patients (M-60; mean±SD age, 65.8± 11.1 yrs) were evaluated for CD38 and IgG4-positive plasma cell counts, storiform fibrosis (SF), and obliterative phlebitis (OP). Of 63/78 patients with elevated serum IgG4 ≥135 mg/dL, 43 patients had level 1 (IgG4 >270 mg/dL) and 20 patients had level 2 (IgG4 135-270 mg/dL) IgG4 levels. With 3.4±1.3 passes, the number of patients whose tissue specimens contained >10, 5 to 10, and 1 to 4 HPFs were 29 (37.2%), 18 (23.1%), and 15 (19.2%) respectively. The CD38 and IgG4-positive plasma cell counts were 23.2 ± 18.8/HPF and 5.1± 6.7/HPF, respectively. 19 patients (24.4%) contained >10 IgG4-positive plasma cells per HPF on an average. SF was observed in 49 patients (62.8%) and OP in 38 patients (48.7%). Overall, 45 of 78 patients (57.7%) had level 1 (3 or 4 criteria) or 2 (2 criteria) histologic criteria for the diagnosis of lymphoplasmacytic sclerosing pancreatitis as per International Consensus Diagnostic Criteria (ICDC). There were no patients with type 2 AIP in this study. Based on these findings, the authors concluded that EUS-FNA with a 22- gauge needle may be useful for the histopathologic diagnosis of type 1 AIP.

Pancreatic cyst epithelial denudation: a natural phenomenon in the absence of treatment.
Gómez V, Majumder S, Smyrk TC, Topazian MD, Chari ST, Gleeson FC, Harmsen WS, Enders FT, Abu Dayyeh BK, Iyer PG, Pearson RK, Petersen BT, Rajan E, Takahashi N, Vege SS, Wang KK, Levy MJ. Gastrointest Endosc. 2016 Nov;84(5):788-793.
https://www.ncbi.nlm.nih.gov/pubmed/27060714

Current nonresection EUS-intracystic therapies for pancreatic cystic lesions (PCLs) aim at ablating the cyst epithelial lining, thereby potentially diminishing or negating the risk of malignant transformation. Many investigators view the presence and degree of denuded epithelium within the surgical pathology specimen as a key measure of successful therapy. However, little is known regarding the incidence and degree of epithelial denudation among ablative therapy treatment–naïve PCLs. Hence, the authors of this study aimed to assess the prevalence, extent, and predictors of epithelial denudation in treatment-naïve PCLs by using a standardized protocol for histopathologic evaluation. Resected pancreatic cysts from 140 patients (F-84; 18-87 years, mean 63 years) were reviewed for histopathology of the cysts, IPMN subtype, presence and degree of dysplasia, and extent (%) of denuded epithelium. Eighty-five cysts (60.7%) were classified as intraductal papillary mucinous neoplasms (IPMN), 33 (23.5%) as mucinous cystic neoplasm (MCN), 11 (7.9%) as serous cystadenoma (SCA), and 11 (7.9%) were made up of other cyst subtypes. The presence of varying degrees of denuded epithelium was identified in 112 PCLs (80%). Extent of denuded epithelium was more prominent in MCN, compared with IPMN and SCA with mean percentage of 45.1%, 10.8%, and 22.4%, respectively ($P < .0001$). There was no statistically significant difference in the extent of denuded epithelium between mixed main-duct with side branch IPMN and main-duct IPMN and also between the various histologic subtypes of IPMN. There was no association between percentage of denuded epithelium and cyst size. However, there was an

association between the extent of denuded epithelium and the degree of epithelial dysplasia for IPMN and MCN combined (mean percentage of denuded epithelium for low-, moderate-, and high-grade dysplasia being 23.3%, 4.5%, and 1.2%, respectively; *P* =.02). There was a significant association between the cyst location and extent of denudation with mean percentage of denuded epithelium in PCLs from neck, body and/or tail (23.9%) vs head and/or uncinate (13.4%) (*P*=.035). Based on these findings, the authors concluded that the presence and extent of cyst epithelial denudation of treatment-naïve PCLs vary with cyst histology and other factors such as degree of dysplasia and importantly the finding of denudation after ablative intracystic therapy may not provide an adequate metric of successful intervention.

Validation of a Proposed Tumor Regression Grading Scheme for Pancreatic Ductal Adenocarcinoma After Neoadjuvant Therapy as a Prognostic Indicator for Survival.
Lee SM, Katz MH, Liu L, Sundar M, Wang H, Varadhachary GR, Wolff RA, Lee JE, Maitra A, Fleming JB, Rashid A, Wang H. Am J Surg Pathol. 2016 Dec;40(12):1653-1660.
https://www.ncbi.nlm.nih.gov/pubmed/27631521

The goal of the study was to validate the clinical importance of a previously proposed 3-tiered histologic tumor regression grading (HTRG) scheme [HTRG 0- no viable tumor, HTRG 1- <5 %viable residual carcinoma (single cells or small groups of tumor cells); and HTRG 2- ≥5% viable residual tumor cells] in a cohort of 167 consecutive patients presenting with pancreatic ductal adenocarcinoma (PDAC) from 2008 to 2012 treated with neoadjuvant therapy and pancreaticoduodenectomy (PD). Among the study patients (84 M, 83 F; age range: 34-85 yrs median age: 65 yrs), 3(1.8%) were HTRG 0 (CAP grade 0), 18 (10.8%) were HTRG 1 (CAP grade 1), and 146 (87.4%) were HTRG 2 responses (95 [56.9%] with CAP grade 2 and 51 [30.5%] CAP grade 3 response). R0 resection was achieved in 162 patients (97%), and R1 resection in 5 patients (3%). Patients with HTRG 0 or 1 had significantly lower frequency of lymph node metastasis (*P*=0.003), recurrence (*P*=0.01), lower ypT (*P*<0.001) and AJCC stage (*P*<0.001) than those with HTRG 2. With a median follow-up of 30.5 months (range 8.2 to 84.2 months), 97 (58.1%) patients died of PDAC; 3 (1.8%) died of other causes; 19 (11.4%) were alive with PDAC; and 48 (28.7%) were alive with no clinical or radiographic evidence of recurrent PDAC. Patients with HTRG 0 or 1 had longer DFS (44.0±5.5 months vs 28.2±2.6 months, *P*=0.004) and OS (54.0±4.2 months vs 44.4±2.5 months, *P*=0.02) than those with HTRG 2. In multivariate analysis, HTRG grade 0 or 1 was an independent prognostic factor for better DFS (*P*=0.03), but not OS. There was no difference in either DFS or OS between CAP grade 2 and CAP grade 3 (*P*>0.05). The authors concluded that the previously proposed 3-tiered HTRG scheme was valid, simple and easily applied by the diagnostic pathologist and had a significant prognostic relevance in evaluation of histologic response in post-therapy PD specimens.

Variations in cancer centers' use of cytology for the diagnosis of unresectable pancreatic cancer in the National Cancer Data Base.
Gansler T, Fedewa SA, Lin CC, Jemal A, Ward EM. Cancer. 2016 Nov;124(11):791-800.
https://www.ncbi.nlm.nih.gov/pubmed/27348076

This study examined the prevalence of definitive cytological diagnosis alone without confirmatory histology in patients with unresectable pancreatic cancer (UPC) among various facilities using National Cancer Data Base (NCDB). A total of 13,657 patients diagnosed with UPC (stages III and IV) in 2011 and 2012 were identified. The prevalence of definitive cytological diagnosis (cytology only, without confirmatory histology) versus histological diagnosis (with or without accompanying cytology) was assessed, along with facility type (classified as community cancer programs (CCPs), comprehensive community cancer programs (CCCPs), academic comprehensive cancer programs (ACADPs), National Cancer Institute-designated cancer center programs (NCIPs) and other cancer programs (OTHERPs)). The most common facility type among UPC patients was CCCPs (44.2% of patients), followed by ACADPs (28.3% of patients), NCIPs (10.9% of patients), CCPs (10.1% of patients), and OTHERPs (6.5% of patients). Overall, 26.8% of UPC cases were definitively diagnosed with cytology. The prevalence of cytological diagnosis by facility type (P<.001) was 16.5% in CCPs, 22.6% in CCCPs, 31.3% ACADPs and 43.2% in NCIPs. In comparison with NCIPs, the multivariable odds ratios for the cytologic diagnosis of UPC were 0.29 for CCPs (95% CI, 0.20-0.42), 0.42 for CCCPs (95% CI, 0.31-0.59), 0.49 for OTHERPs (95% CI, 0.32-0.75), and 0.60 for ACADPs (95% CI, 0.43-0.84). The prevalence of definitive diagnostic cytology was higher in older patients and among patients living in the Northeast (34.4%) compared with other regions (lowest in the South [23.3%]). Regarding treatment modalities, definitive cytological diagnoses were slightly more common (P=.008) among patients who received chemotherapy and were substantially more common (P<.001) in those who underwent radiotherapy. Based on the findings of only 26.8% of UPC being diagnosed definitively with cytology and wide variation in its use by facility type, the authors suggested that opportunities for quality improvement may be helpful for the use of cost-effective cytology as a definitive diagnostic tool.

Reliable Next-Generation Sequencing of Formalin-Fixed, Paraffin-Embedded Tissue Using Single Molecule Tags
Eijkelenboom A, Kamping EJ, Kastner-van Raaij AW, Hendriks-Cornelissen SJ, Neveling K, Kuiper RP, Hoischen A, Nelen MR, Ligtenberg MJ, Tops BB.
J Mol Diagn. 2016 Nov;18(6):851-863.
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This paper describes the development, validation, and implementation of an NGS-based cancer host spot panel of clinically relevant genes utilizing single-molecule molecular inversion probes (smMIPs). The authors state that utilizing smMIP's has the advantage of creating true library diversity from FFPE material. A known limitation of PCR from low quality or low quantity DNA from FFPE material is the inability to differentiate PCR duplicate reads from independent reads originating from separate original template molecules. This phenomenon can overestimate the true number of DNA molecules sequenced and thereby potentially result in higher false negative rates. The smMIP's used in this study are allele specific oligonucleotides that have two complementary arms consisting of an extension probe and a ligation probe joined by a backbone that includes a single molecule tag (SMT). The probe sequences are complementary to sequences surrounding the targeted region, which includes the SNP to be interrogated. When a smMIP hybridizes to genomic DNA, the targeted region is used as template for gap filling through extension which results in a circularized probe. A subsequent exonuclease treatment

removes all linear DNA and leaves only the single stranded circular smMIP's to be amplified by PCR primers complementary to the backbone sequences. The reads can then be grouped by the same SMT to determine reads originating from the same capture event. The authors also claim the ability to distinguish true C:G>T:A mutations from those secondary to cytosine deamination following formalin fixation as a second advantage of this combined technology. Of note a total of 100ng of input genomic DNA was used in this study. Their validation plan was to design a single cancer hotspot panel (CHP) of all clinically relevant coding sequences in 23 genes, covering a total of 41 hotspot regions. This study tested both methods in parallel for 6 weeks and concluded that the smMIP-NextSeq500 approach fulfilled all of the validations requirements and was overall superior to their existing diagnostic platforms of Sanger sequencing and Ampliseq-PGM sequencing. The smMIP-NextSeq500 identified all of the mutations detected in the Ampliseq approach plus two additional mutations (not included in the Ampliseq design), proving similar sensitivities. Interestingly, the false positive rate with an allele frequency greater than 5% was significantly reduced in the smMIP approach (10 fold reduction, $p<0.0001$). The authors attribute this finding to differences in sequencing technology as well as consensus building using SMT's. The use of SMT's allowed the authors to reliably evaluate false library diversity which included determining one sample was of insufficient quality that the Ampliseq platform called sufficient. Conversely there were two samples Ampliseq deemed insufficient that smMIP was able to meet criteria for acceptability. Because SMT's allow for the differentiation between true C>T transitions and C:G>T:A variants secondary to formalin induced deamination of cytosine residues, the smMIP strategy reduces the false positivity rate, thereby allowing for the confident detection of true low level mutation variants down to 1%. TAT was one day longer but still within the criteria of 90% completed within 7 working days. Overall, the authors claim the smMIP-NextSeq500 approach to be superior for FFPE material with low quality/quantity of DNA and should be considered for clinical use.