GIPS Journal Watch July-August 2016

Do Ancillary Studies Aid Detection and Classification of Barrett Esophagus?
Panarelli NC, Yantiss RK.
Am J Surg Pathol. 2016 Aug;40(8):e83-93.
http://www.ncbi.nlm.nih.gov/pubmed/27096258

This review summarizes existing data regarding the utility of ancillary techniques in the evaluation of biopsies for Barrett's esophagus and/or associated neoplasia. The authors discussed the role of ancillary stains in identification of goblet cells, distinguishing Barrett's esophagus from intestinal metaplasia of the gastric cardia and Barrett's esophagus-related dysplasia. Authors also reviewed the role of molecular techniques and advanced endoscopic techniques in identification and risk stratification of Barrett's esophagus and/or associated dysplasia.

Oxyntic gastric atrophy in Helicobacter pylori gastritis is distinct from autoimmune gastritis.
Venerito M, Varbanova M, Röhl FW, Reinhold D, Frauenschläger K, Jechorek D, Weigt J1, Link A, Malfertheiner P.
J Clin Pathol. 2016 Aug;69(8):677-85.
http://www.ncbi.nlm.nih.gov/pubmed/26729016

This prospective study of 384 eligible patients compared features of oxyntic gastric atrophy (OGA) arising in two different settings: autoimmune gastritis (AIG) and Helicobacter pylori infection. OGA, independent of etiology, is associated with increased risk for iron deficiency anemia, pernicious anemia, neuroendocrine tumors and gastric adenocarcinoma. Histologically OGA is diagnosed as decreased density or loss of appropriate glands within gastric mucosa and their replacement with extracellular matrix and/or metaplastic epithelium. In this study the authors not only performed histologic examination of gastric biopsies, they also analyzed serum for gastrin (gastrin-17), pepsinogen I and II, antibodies against H. pylori and cytotoxin associated gene A protein (CagA) to determine the diagnostic performance of these markers as screening for moderate to severe OGA. The inclusion criteria included age older than 18 years, not receiving antibiotic treatment and no use of proton pump inhibitor therapy for at least 2 weeks prior to endoscopy. If patients ever had evidence of H. pylori infection (serology, rapid urea test or histology), they were considered H. pylori positive. If they always had negative H. pylori results and denied receiving H. pylori eradication therapy they were considered H. pylori negative. Patients underwent EGD and 2 biopsies were taken from the antrum, one from the angularis and two from the corpus. Histologic examination included analysis of several H&E sections, PAS histochemical stain, chromogranin IHC and modified Giemsa by two gastrointestinal pathologists. Mucosal atrophy was scored according to the updated Sydney system (0=absent, 1-mild, 2-moderate, 3=severe). ECL hyperplasia was defined as up to 5 adjacent cells labeled with chromogranin A. OGA was defined as moderate to severe based on both corpus biopsies. AIG was defined as the presence of ECL hyperplasia in patients without previous long-term PPI use. Of the 384 eligible patients, 34 (8.9%) patients had advanced OGA

by histology. 22 of which had AIG, and among this group 18 were H. pylori negative. Within the group of 12 patients which did not show AIG features, 10 were H. pylori positive. The authors conclude that H. pylori negative AIG is distinct from OGA arising in H. pylori gastritis based on the following characteristics: H. pylori negative AIG is more likely to 1) be associated with other autoimmune diseases 2) have severe corpus atrophy and 3) to develop corpus intestinal metaplasia. In terms of the utilization of serum biomarkers as an early screening tool for gastric carcinoma, this paper discovered the need to exclude patients with early stage OGA to increase diagnostic performance.

Risks and Predictors of Gastric Adenocarcinoma in Patients with Gastric Intestinal Metaplasia and Dysplasia: A Population-Based Study.
Li D, Bautista MC, Jiang SF, Daryani P, Brackett M, Armstrong MA, Hung YY, Postlethwaite D, Ladabaum U..
Am J Gastroenterol. 2016;111(8):1104-13.
http://www.ncbi.nlm.nih.gov/pubmed/27185078

To investigate the incidence of noncardia gastric adenocarcinoma among patients with a previous diagnosis of gastric intestinal metaplasia or dysplasia, the authors performed a retrospective cohort study that compared these incidences to the general population. A review of Kaiser Permanente Northern California members revealed 4,146 individuals with a diagnosis of gastric intestinal metaplasia and 141 patients with low-grade dysplasia which met the authors' inclusion criteria. Among the individuals with intestinal metaplasia, 37 cases of noncardia gastric adenocarcinoma subsequently developed with a median time of progression of 6.1 years and a relative risk of 2.56 compared to the Kaiser Permanente general population. 11 cases of adenocarcinoma developed in the 141 patients with low-grade dysplasia with a median time required to progress of 2.6 years. Multiple clinical parameters were examined as predictors for progression in the subsequent portion of this study. Of these, Hispanic patients were found to have a 4.2 times higher risk of progression compared to Whites. In the end, the authors noted that the risk of adenocarcinoma in patients with intestinal metaplasia was not sufficiently elevated to warrant routine endoscopic surveillance, however, this practice may be reasonable in higher risk patients including those with dysplasia or Hispanic race.

A protein and mRNA expression-based classification of gastric cancer.
Setia N, Agoston AT, Han HS, Mullen JT, Duda DG, Clark JW, Deshpande V, Mino-Kenudson M, Srivastava A, Lennerz JK, Hong TS, Kwak EL,Lauwers GY
Mod Pathol. 2016 Jul;29(7):772-84.
http://www.ncbi.nlm.nih.gov/pubmed/27032689

This study aims to address the need for a new classification system for gastric cancer that might account for potential therapeutic targets. The authors discuss recent work by three groups that have attempted to develop a classification based on genetic and epigenetic features using advanced molecular techniques (DNA sequencing, RNA sequencing, whole-exome sequencing,

copy number variation analysis, and DNA methylation arrays). The authors argue that while these studies are a significant step in understanding the biology of gastric tumors, the advanced molecular methods, at least currently, are not cost effective for routine practice. The stated goal of this study was to test the validity of the molecular classifications by focusing on protein and mRNA expression using cheaper in situ and immunohistochemistry biomarkers and to try and develop an algorithm to aid in distinguishing molecular subtypes using the results. 14 biomarkers (EBER ISH, MLH-1, PMS2, MSH2, MESH6, E-cadherin, PD-L1, MUC2, CDX2, CD10, MUC5AC, MUC6, AND HER2) were evaluated and, by hierarchical clustering, five groups were identified: EBV-positive; MSI-H; aberrant E-cadherin; remaining with aberrant p53; and remaining with normal p53. The authors claim that this algorithm may be able to reproduce the molecular based classification using ISH and immunohistochemistry alone.

Ethnic Variations in Duodenal Villous Atrophy Consistent With Celiac Disease in the United States.
Krigel A, Turner KO, Makharia GK, Green PH, Genta RM, Lebwohl B.
Clin Gastroenterol Hepatol. 2016;14(8):1105-11.
http://www.ncbi.nlm.nih.gov/pubmed/27155557

This cross-sectional retrospective review aimed to investigate the prevalence of celiac disease among various ethnic groups in the United States. Data was sourced from a large national pathology reference laboratory database and evaluated 454,885 patients who had undergone a duodenal biopsy over an approximately 8 year period. As only the pathology reports were available for review and no clinical or serologic data was obtainable, the authors used the presence of duodenal villous atrophy as a surrogate for celiac disease (CD). However, the authors did acknowledge that some cases may have represented alternative causes of villous atrophy. They found the overall prevalence of CD to be 1.74% with an essentially equal distribution of men and women. Significantly fewer East Asian and Hispanic patients were found to have villous atrophy, a finding which is consistent with previous literature. While the overall prevalence of CD in South Indians (0%) and North Indian (1.51%) was relatively low, patients identified as having ancestry in the Punjab region of northern India were found to have the highest prevalence of CD (3.08%). This finding has also been reported in patient populations outside of the United States.

A comparison of endoscopy versus pathology sizing of colorectal adenomas and potential implications for surveillance colonoscopy.
Taylor JL, Coleman HG, Gray RT, Kelly PJ, Cameron RI, O'Neill CJ, Shah RM, Owen TA, Dickey W, Loughrey MB.
Gastrointest Endosc. 2016 Aug;84(2):341-51.
http://www.ncbi.nlm.nih.gov/pubmed/27102832

This nationwide study aimed at comparing endoscopy and pathology sizing of intact colorectal adenoma, removed at colonoscopies, performed as part of the Northern Ireland Bowel Cancer

Screening Program, from 2010 to 2015. The authors assessed the potential impact of discordant adenoma sizing on colonoscopy surveillance and used the findings to make a recommendation for more accurate sizing of adenomas. Authors identified 2521 intact adenomas from 1467 individuals with both endoscopy and pathology measurements in a cohort of 10,008 histopathologic specimens from 4256 colonoscopy procedures. Of the 2521 polyps, 73% were tubular adenomas and 27% had a villous component. Overall there was good agreement between endoscopy and pathology sizes with a mean size difference of 0.1 mm (95% limits of agreement, −4.45 to 4.65 mm); endoscopy sizing tended to be greater than pathology sizing as adenoma size increased. Adenomas with a villous component were larger than tubular adenomas. No significant differences in median values were observed between endoscopy and pathology sizes for tubular or tubulovillous/villous adenomas. Endoscopic sizing showed significantly greater clustering to the nearest 5 mm versus pathology sizing (30% vs 19%, P < .001), which was suspected to be a reason for lower accuracy. Using the 10 mm size as the cut-off for risk stratification, the overall agreement for endoscopy and pathology size classification in the study was very high (92.7%). However, the discordance in sizing was much higher 28.3%, when the analysis was restricted to those in the 8- to 12-mm size range. Based on different guidelines, 4.8% to 9.1% of individuals had differing risk stratification for surveillance recommendations; and the use of pathology sizing resulted in 1.1% to 2.3% more individuals being stratified as low risk. The authors concluded that pathology sizing appeared to be more accurate than endoscopy sizing; and preferential use of pathology size would result in a small reduction in surveillance colonoscopies.

Mismatch repair deficiency in Lynch syndrome-associated colorectal adenomas is more prevalent in older patients.
Tanaka M, Nakajima T, Sugano K, Yoshida T, Taniguchi H, Kanemitsu Y, Nagino M, Sekine S. Histopathology. 2016 Aug;69(2):322-8.
http://www.ncbi.nlm.nih.gov/pubmed/26826556

IHC was performed for MLH1, PMS2, MSH2, and MSH6 in 134 adenomas obtained from 26 Lynch syndrome patients confirmed by genetic testing. MMR deficiency (defined as the loss of any mismatch repair protein) was found in 84% of cases or 113 adenomas). All MMR-deficient adenomas should homogeneous loss of MMR proteins, supportive of underlying germline mutation. MMR deficiency was more frequent in adenomas from older patients (at least 60 years old, 81 of 86 cases, 94%), larger tumor size (more than 5 mm, 71 or 73 cases, 97%), and in a background of high-grade dysplasia (50 of 51 cases, 98%). Increased age and larger tumor size were independently associated with MMR deficiency. Age of patient, tumor size, and presence of high-grade dysplasia should be taken into consideration during Lynch syndrome screening after colonoscopy with biopsy.

Diagnostic Challenges Caused by Endoscopic Biopsy of Colonic Polyps: A Systematic Evaluation of Epithelial Misplacement With Review of Problematic Polyps From the Bowel Cancer Screening Program, United Kingdom.

Panarelli NC, Somarathna T, Samowitz WS, Kornacki S, Sanders SA, Novelli MR, Shepherd NA, Yantiss RK.

Am J Surg Pathol. 2016 Aug;40(8):1075-83.

http://www.ncbi.nlm.nih.gov/pubmed/26975041

The aim of the study was to describe the spectrum of histologic features of epithelial misplacement in adenomas due to prior biopsy before complete excision. The study group was comprised of sixteen (16) endoscopically manipulated adenomas (mean age: 72; M/F-3/1; Right colon-11; left colon-5; sessile-13; mean size-34 mm). The clinical and morphologic findings and the Ki67 and P53 immunoexpression of the study group cases were compared with similar findings in ten (10) pedunculated adenomas with misplaced epithelium (pseudoinvasion) secondary to torsion (mean age: 62; M/F-3/7; sigmoid-9, rectum-1; mean size-28 mm), and ten (10) adenomas containing invasive adenocarcinoma (mean age: 62; M/F-2/3; right colon-6, left colon-4; mean size-35 mm, sessile-5, pedunculated 5; stage I-9, Stage III-1). In the study group, submucosal misplaced epithelium showed two morphologic patterns, circumscribed (5 cases) and ill-defined aggregates simulating adenocarcinoma (11 cases). 6 of 11 polyps showed single cells or small clusters dispersed in inflamed, fibrotic stroma. The misplaced epithelium in these polyps showed only low-grade cytological features and was associated with extruded mucin (75%), tattoo pigment (63%), scant lamina propria (88%), muscularis mucosae (44%) and misplaced normal epithelium (38%). Additional findings suggestive of trauma included erosion, ruptured crypts, hemorrhage/hemosiderin and granulation tissue. The misplaced epithelium in pedunculated polyps had lobular contour with a rim of lamina propria, hemorrhage, and/or hemosiderin. Malignant polyps showed high-grade cytology, infiltrative border, and desmoplasia; most (70%) lacked features of trauma. Ki67 and p53 staining was patchy and weak in the misplaced epithelium, whereas malignant polyps showed diffuse staining for one or both markers. The authors also evaluated 64 cases of polyps from United Kingdom bowel cancer screening program (BCSP) with expert consensus diagnosis of misplaced epithelium. The histologic findings identified in the current study were frequently identified in the BCSP cases and supported the consensus diagnosis of benign epithelial misplacement. Based on these findings the authors suggested that the findings of close proximity of worrisome epithelium to ruptured, inflamed crypts, discontinuous foci of lamina propria and muscularis mucosae around the epithelium, extruded pools of mucin, and tattoo pigment are helpful clues to benign diagnosis of misplaced epithelium in endoscopically manipulated adenomas. Ki67 and P53 immunohistochemical stains may also be helpful in selected cases.

Interlaboratory Variability in the Histologic Grading of Colorectal Adenocarcinomas in a Nationwide Cohort.

Kuijpers CC, Sluijter CE, von der Thüsen JH, Grünberg K, van Oijen MG, van Diest PJ, Jiwa M, Nagtegaal ID, Overbeek LI, Willems SM.

Am J Surg Pathol. 2016 Aug;40(8):1100-8.

http://www.ncbi.nlm.nih.gov/pubmed/26975039

Histologic grade of colorectal cancer (CRC) is a prognostic factor independent of stage. In patients with stage II colon cancer, poor differentiation (PD) is an indication for adjuvant chemotherapy. Given the importance of grade, this nationwide study aimed at assessing the variability between Dutch pathology laboratories and individual pathologists in grading poorly differentiated colon cancer. Rectal cancer cases were excluded because national guidelines recommend neoadjuvant therapy. By reviewing the synoptic reports of CRC resections from 2010 to 2013 in the Dutch pathology registry (PALGA), the authors identified 11,781 resections from 11,681 patients processed at 35 laboratories, of which 1427 (12.2%) were PD adenocarcinomas. In a multivariate analysis adjusting for the differences in case mix between laboratories, 2 laboratories reported a significantly lower proportion of PD adenocarcinoma and 2 laboratories a significantly higher proportion of PD adenocarcinoma compared with the reference laboratory. Among the 2813 stage II tumors, in which grade is the sole indicator of eligibility for adjuvant chemotherapy, 258 (9.2%) were PD adenocarcinomas. In this cohort, after multivariate logistic regression analysis, 4 laboratories diagnosed significantly more PD adenocarcinomas when compared to the reference laboratory, thus increasing the number of colon cancer patients eligible for adjuvant therapy. Among the 45 pathologists from these 8 laboratories, substantial variation in grading between individual pathologists was observed in 7 of 8 laboratories; however, the difference in the number of PD adenocarcinomas between pathologists was not statistically significant, possibly because of the relatively low numbers of cases per pathologist. All pathologists, responding to a questionnaire regarding criteria used to determine differentiation/grade, stated that they used architectural criteria to determine the differentiation/ grade; and 17 (32.7%) stated that they used cytologic criteria as well. Based on these findings, the authors concluded that considerable interlaboratory and intralaboratory variation exists in differentiation grading and suggested that grading criteria needs to be standardized for optimal determination of prognosis and treatment selection.

Driver Gene Mutations in Stools of Colorectal Carcinoma Patients Detected by Targeted Next-Generation Sequencing

Armengol G, Sarhadi VK, Ghanbari R, Doghaei-Moghaddam M, Ansari R, Sotoudeh M, Puolakkainen P, Kokkola A, Malekzadeh R, Knuutila S.

J Mol Diagn. 2016 Jul;18(4):471-9.

http://www.ncbi.nlm.nih.gov/pubmed/27155048

This paper discusses stool based molecular assays for the detection of mutations in exfoliated colorectal adenocarcinoma (CRC) cells. The authors utilized the Ion Torrent next generation sequencing platform (NGS) and AmpliSeq library kit to detect 504 mutational hotspots and targeted regions in 22 genes known to have clinical relevance (diagnostic, prognostic or therapeutic) in CRC and NSCLC: AKT1, ALK, BRAF, CTNNB1, DDR2, EGFR, ERBB2, ERBB4, FBXW7, FGFR1, FGFR2, FGFR3, KRAS, MAP2K1, MET, NOTCH1, NRAS, PIK3CA, PTEN, SMAD4, STK11, and TP53. DNA was extracted from 65 stool samples from patients with known CRC at the time of diagnosis, prior to any treatment. Ultimately 52 stool samples were successfully analyzed as the

other 13 had either poor quality DNA or unsatisfactory sequencing data. Between 1-5 genes were found to have mutations in 75% of cases whereas the remaining specimens had no reportable mutations. Sanger sequencing was performed on 11 cases however, mutations were confirmed in only 3 of those 11 cases. Stool samples where mutations were not detected were not analyzed by other methods. The authors suggest poor quality PCR and a lower sensitivity by Sanger sequencing as explanations for the discrepancy. In one case, an FFPE block from the patient's resected tumor was sequenced and did reveal the same mutations detected in the corresponding stool sample. To that end, the mutation pattern identified within the stool samples of patients with CRC was similar to those reported in resected colorectal adenocarcinomas (TP53, KRAS, FBXW7 and SMAD4) supporting their claim that fecal DNA mutations are representative of mutations from tumor cells. The authors conclude that performing NGS on stool samples is a potential noninvasive approach with diagnostic, prognostic and therapeutic importance in patients with CRC. However, they state that technical improvements are necessary to increase success rate and quality of sequencing results.

The expression profiles of the galectin gene family in colorectal adenocarcinomas.
Gopalan V, Saremi N, Sullivan E, Kabir S, Lu CT, Salajegheh A, Leung M, Smith RA, Lam AK.
Hum Pathol. 2016 Jul;53:105-13.
http://www.ncbi.nlm.nih.gov/pubmed/27001434

We aim to investigate the expression profiles of galectin family genes (galectins-1, 2, 3, 4, 7, 8, 9, 10, and 11) in colorectal carcinomas. Messenger RNA (mRNA) expression of galectin family members (1, 2, 3, 4, 7, 8, 9, 10, and 12) was analyzed by real-time polymerase chain reaction in colorectal tissues from 201 patients (54 noncancer colorectal tissues, 49 adenomas, and 98 adenocarcinomas). Galectin-1 and galectin-3 protein expressions were determined by immunohistochemistry. In general, high galectin mRNA expression was noted in colorectal carcinomas in early stages of their pathogenesis. Significant differences in galectins-2, 3, 7, 8, and 10 mRNA expression were associated with pathologic stages ($P<.05$). Increased prevalence of galectins-2, 7, 8, and 10 mRNA overexpression was noted in nonmetastatic colorectal carcinomas ($P<.05$). Galectin-1 and galectin-3 proteins were present in the nucleus and cytoplasm of the colorectal tissues and expressed significantly higher in colorectal carcinomas when compared to colorectal adenomas (61% and 95%, respectively). Patients with colorectal carcinoma with high levels of galectin-3 mRNA and protein expression showed better prognosis ($P=.052$). To conclude, many novel correlations between the deregulation of galectin family genes and various clinicopathological features in colorectal adenocarcinoma were noted. Overexpression of galectins at the mRNA level and proteins were predominant in earlier stages of colorectal carcinomas. These altered expression patterns of galectin genes suggest the multifunctional role of galectin genes in the regulation of colorectal cancer development, progression, and metastasis.

Reappraisal of hMLH1 promoter methylation and protein expression status in the serrated neoplasia pathway.
Lee EJ, Chun SM, Kim MJ, Jang SJ, Kim DS, Lee DH, Youk EG.
Histopathology. 2016 Aug;69(2):198-210.
http://www.ncbi.nlm.nih.gov/pubmed/26713412

33 sessile serrated lesions with cytologic dysplasia (SSL/Ds) were assessed for methylation levels and protein expression of hMLH1 using the MassARRAY EpiTYPER assay and immunohistochemistry as well as IHC for Ki-67. 20 cases had areas of low-grade dysplasia and 11 cases had high-grade dysplasia. Controls were hyperplastic polyps and SSLs without dysplasia. The dysplastic component had a significantly higher methylation level of hMLH1 overall (P=0.005) with significant difference in methylation based on degree of dysplasia (mean hMLH1 methylation level 9.89% for LGD, 14.4% for HGD, and 2% for two cases of submucosal invasive carcinoma). Loss of hMLH1 expression was found in 13/33 (about 39%) of dysplastic lesions. The loss of protein expression does not necessarily precede the development of dysplasia within SSL.

Distribution of the c-MYC gene product in colorectal neoplasia.
Baker AM, Van Noorden S, Rodriguez-Justo M, Cohen P, Wright NA, Lampert IA.
Histopathology. 2016 Aug;69(2):222-9.
http://www.ncbi.nlm.nih.gov/pubmed/26826706

Attempts to study MYC distribution have had variable results since different antibodies have been used (targeting the N-terminus or targeting the C-terminus of the MYC protein). The authors use mRNA ISH on paraffin-embedded normal colon (n=15), hyperplastic polyp (n=4), and neoplastic colon samples (n=55) using the N-terminally directed antibody Y69 and the C-terminally directed antibody 9E10. mRNA localized correlated well with Y69 protein detection, more so than with 9E10 protein detection, and caution is suggested when using 9E10 in analysis of MYC localization and expression.

Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study.
Mayo E, Llanos AA, Yi X, Duan SZ, Zhang L.
Histopathology. 2016 Aug;69(2):230-8.
http://www.ncbi.nlm.nih.gov/pubmed/26802566

The authors examined incidental CRC cases with known tumor deposit (TD) or perineural invasion (PNI) status in the SEER database diagnosed in 2010 and 2011. Overall survival (OS) and cancer-specific survival (CSS) were estimated. 6.71% (2774 of 41,323) CRC cases were positive for TD. 9.61% (3970 of 41.215) CRC cases had PNI. Positive status for TD or PNI correlated independently with worse 3-year OS (hazard ratios 1.68 and 1.24) and 3-year CSS (hazard ratios 1.79 and 1.28, respectively). Other independent prognostic factors were age, T

status, N status, tumor location, and tumor grade, but not gender. Rare TD-positive CRC cases assigned as N0 should have been assigned to N1c per the authors. The authors note that the limited 3-year follow-up time makes extrapolation of results difficult. TD and PNI status for CRC has only been collected since 2010 in SEER, so the results are within the "short or intermediate follow-up" period. However, the association of positive TD status with worse 3-year OS regardless of N stage is compelling.

Medullary carcinoma in the colorectum: a systematic review and meta-analysis
Pyo JS, Sohn JH, Kang G.
Hum Pathol. 2016 Jul;53:91-6.
http://www.ncbi.nlm.nih.gov/pubmed/27001432

This study investigated clinicopathological characteristics of colorectal medullary carcinoma (MC) through systematic review and meta-analysis including 16 eligible studies. The study found an incidence of 0.027 for MC with predilection in the right colon and in female patients. As compared to poorly differentiated or undifferentiated adenocarcinoma, MC had higher overall survival rate, lower lymph node metastasis, higher mismatch repair deficiency rate, higher BRAF V600E mutation rate, and lower KRAS mutation rate.

Robot-Assisted Abdominoperineal Resection: Clinical, Pathologic, and Oncologic Outcomes
Eftaiha SM, Pai A, Sulo S, Park JJ, Prasad LM, Marecik SJ.
Dis Colon Rectum. 2016 Jul;59(7):607-14
http://www.ncbi.nlm.nih.gov/pubmed/27270512

This is a prospective 5-year database review of robot-assisted abdominoperineal resections (APRs) of rectal cancers to assess long term outcomes. Standard APRs are associated with high rates of positive circumferential margins and intraoperative perforations when compared to low anterior resections (LARs). Extralevator APR was implemented to achieve wider excision of the levator muscle perineally after total mesorectal excision abdominally (TME) to improve these adverse outcomes. Levator transection can also be performed transabdominally-robotically (RILT, robotic intra-abdominal levator transection). The authors followed 51 patients with rectal adenocarcinomas over a 5-year period who underwent APR, 22 of which were performed with some form of robotic assistance. All patients were evaluated by endoscopy, endoscopic ultrasound, CT scan for metastatic disease and were presented for multidisciplinary tumor board review. Patients with positive mesorectal lymph nodes or evidence of mesorectal infiltration were treated with neoadjuvant chemoradiation and resection was performed 8-10 weeks later (91% of patients). The mean tumor distance from the anal verge was 4.6cm. Of the 22 patients who had robotic assistance, all underwent robot assisted total mesorectal excision. 5 had levator resections performed by the RILT approach (22.7%) and 16 patients underwent robotic colon mobilization. Comparison of postoperative, pathologic and oncologic outcomes in patients who received robot assisted APRs to those who received open and laparoscopic APRs showed similar 3-5 year overall survival and disease free

survival rates between the two groups. Circumferential margin positivity and intraoperative perforation rates were also similar. In comparing approaches to levator transection, RILT versus perineal dissection, the authors note a better short term oncologic outcome within the RILT group. However, state that the numbers of patients are too small to draw a definitive conclusion. Overall, this paper concludes that robot-assisted APR for low rectal cancer is feasible and safe with short and mid term outcomes comparable to open and laparoscopic procedures. More studies are needed to elucidate the differences in abdominal versus perineal levator transections in terms of long term damage to neurovascular bundles within the lateral pelvic wall and the implications on function and wound complications.

Genomic Alterations Observed in Colitis-Associated Cancers Are Distinct From Those Found in Sporadic Colorectal Cancers and Vary by Type of Inflammatory Bowel Disease

Yaeger R, Shah MA, Miller VA, Kelsen JR, Wang K, Heins ZJ, Ross JS, He Y, Sanford E, Yantiss RK, Balasubramanian S, Stephens PJ, Schultz N, Oren M, Tang L, Kelsen D.

Gastroenterology. 2016 Aug;151(2):278-287.e6.

http://www.ncbi.nlm.nih.gov/pubmed/27063727

The authors of this study compared the spectrum of genomic alterations in colitis-associated cancers with those of sporadic colorectal cancers, and also investigated the differences of these tumors in patients with Crohn disease vs. ulcerative colitis. Genomic analysis of 47 colitis-associated cancers were analyzed via hybrid capture-based next-generation sequencing, interrogating >300 cancer-related genes. Of these 47 cases, 29 were from patients with UC and 18 with CD; 43 were primary tumors and 4 metastases. Primary tumors were from the ileum (2), right colon (18), left colon (6), and rectosigmoid/rectum (21). The authors found genomic alterations in TP53, IDH1, and MYC to be significantly more frequent, and mutations in APC to be significantly less frequent, than those reported in sporadic CRCs by The Cancer Genome Atlas or Foundation Medicine. The study identified genomic alterations that might be targeted by a therapeutic agent in 17 of 47 (36%) colitis-associated carcinomas. These included the mutation encoding IDH1 R132; amplification of FGFR1, FGFR2, and ERBB2; and mutations encoding BRAF V600E and an EML4-ALK fusion protein. Alterations in IDH1 and APC were significantly more common in colitis-associated carcinomas from patients with CD than UC. In summary, the study found significant differences in the spectrum of genomic alterations in colitis associated carcinomas compared with sporadic CRCs. A high frequency of IDH1 R132 mutations were found in patients with CD but not UC, as well as a high frequency of MYC amplification in colitis associated carcinomas. Many of these genetic alterations could serve as therapeutic targets.

Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease.
Parian A, Koh J, Limketkai BN, Eluri S, Rubin DT, Brant SR, Ha CY, Bayless TM, Giardiello F, Hart J, Montgomery E, Lazarev MG.
Gastrointest Endosc. 2016 Jul;84(1):87-95.e1.
http://www.ncbi.nlm.nih.gov/pubmed/26709112

The aim of this study was to understand the significance of serrated epithelial changes (SEC) and its relationship to dysplasia in IBD patients. SEC is identified in flat mucosal biopsies as goblet cell rich hyperplastic mucosal change with significant crypt distortion and crypts often failing to reach the muscularis propria. The epithelium may show eosinophilic change but lack conventional dysplasia. The authors investigated the incidence of dysplasia or colorectal cancer (CRC) and, the concordance between the locations of SEC and dysplasia or CRC in 187 IBD patients (mean age: 48.4 y; UC-98, CD-73, IBDU-16; mean age at diagnosis: 31.5y; mean duration of IBD: 16 y; mean follow-up; 28 mo.) with 1 or more histologic findings of SEC without prior dysplasia. 8.0% (15/187) had synchronous SEC and dysplasia. Of these, 13 patients had LGD and 2 had CRC. Additionally, 3 patients with LGD developed HGD or CRC on further follow-up. 112 of 172 patients had follow-up for metachronous dysplasia. 21% (24/112) patients had new dysplasia on follow-up; 6 (5%) had HGD or CRC and 18 (16.1%) had LGD. Of the 40 patients evaluated for concordance between location of the index SEC and any dysplasia 27 (68%) showed concordances and these were predominantly found in the sigmoid/descending colon (44%). On follow-up examination, older age at IBD diagnosis, male gender, and a first-degree relative with CRC and at least 1 follow-up SEC were associated with dysplasia in IBD patients with SEC. Based on the findings of this uncontrolled study authors concluded that there is an increased frequency of dysplasia in patients with the histologic finding of SEC. SEC seen on successive endoscopic examinations further increased the risk of dysplasia. However, this association needs further study.

A Biomarker Panel to Detect Synchronous Neoplasm in Non-neoplastic Surveillance Biopsies from Patients with Ulcerative Colitis.
Garrity-Park MM, Loftus EV Jr, Bryant SC, Smyrk TC.
Inflamm Bowel Dis. 2016 Jul;22(7):1568-74.
http://www.ncbi.nlm.nih.gov/pubmed/27135485

This retrospective study included 220 ulcerative colitis patients with low-grade dysplasia (UC-LGD), 114 UC patients with colorectal carcinoma (UC-CRC) and 114 UC controls, with a goal of determining if any biomarkers (SNP or methylation) could predict which UC-LGD cases would progress to UC-CRC. Biopsy and resection tissue with LGD, CRC, and non-adjacent non-neoplastic were analyzed. They developed a predictive model including genetic and epigenetic biomarkers and clinical parameters with an area under the curve of 0.92. They also report finding an epigenetic profile (i.e. RUNX3 methylation) that distinguishes UC-LGD which is likely to progress to UC-CRC as compared to UC-LGD non-progressors. The authors propose that

changes in non-adjacent non-neoplastic tissue are present and may be predictive of risk of progression to UC-CRC years before histologic abnormalities are identified.

DNA Methylation and Mutation of Small Colonic Neoplasms in Ulcerative Colitis and Crohn's Colitis: Implications for Surveillance.
Johnson DH, Taylor WR, Aboelsoud MM, Foote PH, Yab TC, Cao X, Smyrk TC, Loftus EV Jr, Mahoney DW, Ahlquist DA, Kisiel JB.
Inflamm Bowel Dis. 2016 Jul;22(7):1559-67.
http://www.ncbi.nlm.nih.gov/pubmed/27104828

This case-control study of archival frozen tissue and cohort study of paraffin embedded tissue assessed DNA from small neoplasms (lesions < 1 cm) in IBD, including tissue and stool, to look for DNA mutations or methylation patterns associated with adenomatous or serrated neoplasia pathways. The small lesions included 29 low-grade dysplasia, 19 serrated epithelial change, and 10 sessile serrated adenomas. Compared to IBD controls, the prevalence of methylated bone morphogenetic protein 3 (BMP3) or methylated N-Myc downstream-regulated gene 4 (*NDRG4*) was significantly higher in cases with low-grade dysplasia. Cases with sessile serrated adenoma showed aberrant DNA methylation and *BRAF* mutations consistent with the serrated neoplasia pathway. In cases with serrated epithelial change, KRAS mutations were significantly more prevalent, leading the authors to hypothesize that this histologic feature is a hyperplastic phenomenon, rather than a precursor neoplastic process. This could be a useful type of adjunctive non-invasive testing to study IBD tumorigenesis.

Higher Risk for Hematological Malignancies in Inflammatory Bowel Disease: A Nationwide Population-based Study in Taiwan.
Wang LH, Yang YJ, Cheng WC, Wang WM, Lin SH, Shieh CC.
Am J Gastroenterol. 2016;111(9):1313-9.
http://www.ncbi.nlm.nih.gov/pubmed/27296944

In an effort to examine the association between inflammatory bowel disease (IBD) and the development of malignancies in the Taiwanese population, the authors performed a retrospective review of that nation's comprehensive health database. Previous studies have examined this association in Western patients but no comprehensive study has assessed this in Asian countries. A review of the national health database revealed the average annual incidence of IBD was 1.38 per 100,000 persons and was male predominant for both Crohn's disease (CD) and ulcerative colitis (UC). Median age at diagnosis was 34.9 for CD and 43.1 for UC. The authors' cancer risk analysis demonstrated a significantly higher risk of hematological malignancies in this population compared to the nationwide cohort with no significantly elevated risk of colorectal carcinoma. The authors postulate that this finding may only apply to Asian populations as the characteristics of IBD in these countries are distinctly different than in Western countries.

Predictive Factors for Differentiating Between Crohn's Disease and Intestinal Tuberculosis in Koreans.
Jung Y, Hwangbo Y, Yoon SM, Koo HS, Shin HD, Shin JE, Moon HS, Kang SB, Lee JR, Huh KC.
Am J Gastroenterol. 2016;111(8):1156-64.
http://www.ncbi.nlm.nih.gov/pubmed/27296940

The authors performed a retrospective review in an effort to develop a predictive risk score model for differentiating Crohn's disease (CD) from intestinal tuberculosis (ITB) in a population of Korean patients utilizing clinical, endoscopic, and histologic features. 256 participants were identified from multiple tertiary care centers including 158 CD patients and 98 ITB patients. An extensive review of the patients' demographic information, clinical symptoms, laboratory findings, endoscopic impressions and histologic features was performed and compared between these cohorts. Multiple significant parameters were used in the development of a risk score model which was validated on a select portion of the cohorts. Overall, CD tended to occur in younger patients than ITB (28.5 versus 49.3), had a higher male to female ratio (110:48 versus 38:60), and presented with diarrhea (67.7% versus 20.4%). Endoscopically, ring shaped ulcers were more frequent in ITB than CD (72.5% versus 14.0%) while longitudinal ulcers were more common in CD (63.3% versus 7.1%). Histologically, granulomas were identified in both groups (53.9% of CD, 67.4% of ITB) however, caseous necrosis was only observed in cases of ITB (38.8% of cases). The authors' seven-marker risk score model utilizing most of these features was found to be reliable in differentiating ITB from CD.

Significance of Paneth Cells in Histologically Unremarkable Rectal Mucosa.
Pezhouh MK, Cheng E, Weinberg AG, Park JY.
Am J Surg Pathol. 2016 Jul;40(7):968-71.
http://www.ncbi.nlm.nih.gov/pubmed/26900817

The goal of this study was to assess the frequency and clinical significance of isolated Paneth cells in normal rectal biopsies from pediatric patients. The authors reviewed the slides and clinical findings of 245 pediatric rectal biopsies from 245 patients (mean age of 8.9±6.2 years, 109 male and 136 female patients) with reported normal endoscopic and histologic evaluations and no prior abnormal biopsies. 193 were pinch biopsies with the most common clinical indications being abdominal pain (30.1%), bloody stools (23.8%), and diarrhea (23.3%). 52 were rectal suction biopsies from patients being evaluated for Hirschsprung disease presenting with constipation (84.6%). All the suction biopsies showed ganglion cells and the patients were clinically determined to be negative for Hirschsprung disease. Paneth cells were identified in biopsies from 42 patients (17.1%) ranging from 1 to 14 Paneth cells per 100 crypts and 1 to 3 Paneth cells per affected crypt. Paneth cells were commonly identified in younger patients with decreasing incidence in increasing age. Paneth cells were more often identified in suction biopsies than pinch biopsies (40.4% vs 10.9%). The most common clinical indication in biopsies with Paneth cells was constipation (52.4%) and this was true for both suction and pinch biopsy groups. Also, constipation was highly associated (odds ratio of 4.5; CI 2.2-9.0; 95%) with identification of rectal Paneth cells. During a mean overall follow-up of 756 days only 1 of 42

patients with Paneth cells developed IBD (Crohn's disease). In this first study to report isolated Paneth cells in the rectum, authors concluded that Paneth cells in rectal biopsies were associated with young age and clinical constipation and did not show significant association with current or future development of IBD.

Intraepithelial lymphocytosis is a frequent finding in biopsies from ileal pouch–anal anastomoses
Schaeffer DF, Walsh JC, Tyler AD, Ben-Bassat O, Silverberg MS, Riddell RH, Kirsch R.
Hum Pathol. 2016 Aug;54:31-6.
http://www.ncbi.nlm.nih.gov/pubmed/27063473

The study authors found that 18% of 230 patients with functioning ileal pouch-anal anastomosis (IPAA) showed an increase in IELs (defined as ≥ 20 IELs/100 enterocytes) in the pouch and/or afferent limb biopsies. None of these patients had positive celiac specific serology. IELs were more commonly observed in afferent limb compared to pouch biopsies, and in familial adenomatous polyposis compared to ulcerative colitis. Cases with increased IELs did not show severe villous blunting or any association with age, sex, ethnicity, smoking history, time since ileostomy, use of antibiotics, biologic agents, anti-diarrhea agents or probiotics, C-reactive protein levels or differential white count. Intraepithelial lymphocytosis in pouch biopsies may represent a subclinical response to an altered bacterial microenvironment. Pathologists should be aware that intraepithelial lymphocytosis is part of the spectrum of changes in pouch biopsies, and only rarely is due to celiac disease.

Pouchitis Is a Common Complication in Patients With Familial Adenomatous Polyposis Following Ileal Pouch-Anal Anastomosis.
Quinn KP, Lightner AL, Pendegraft RS, Enders FT, Boardman LA, Raffals LE.
Clin Gastroenterol Hepatol. 2016;14(9):1296-301.
http://www.ncbi.nlm.nih.gov/pubmed/27085760

This retrospective cohort study was performed to access the overall frequency of pouchitis in familial adenomatous polyposis (FAP) patients who had undergone an ileal pouch-anal anastomosis (IPAA). Previous investigations into this topic have reported pouchitis as a rare complication following IPAA in this population, particularly in comparison to ulcerative colitis patients. A total of 113 patients met the inclusion criteria and their medical records were reviewed. Pouchitis was defined as an episode of typical clinical pouchitis symptoms combined with evidence of endoscopic inflammation. Twenty-five (22.1%) patients met these criteria and the mean time to pouchitis was 4.1 years. This prevalence was higher than has been previously reported in FAP patients with these episodes occurring more remotely to the initial surgery than in reported cases of pouchitis in ulcerative colitis patients.

Juvenile Polyps in Denmark From 1995 to 2014
Jelsig AM, Ousager LB, Brusgaard K, Qvist N.
Dis Colon Rectum. 2016 Aug;59(8):751-7
http://www.ncbi.nlm.nih.gov/pubmed/27384093

This register-based retrospective study aimed to determine the incidence of juvenile polyps within the adult and child population in Denmark from January 1, 1995, until December 31, 2014. Children were defined as <18 years old. Juvenile polyps (JPs) are hamartomatous polyps with characteristic histologic features including cystically dilated mucus-filled glands, prominent lamina propria, and increased inflammation. JPs account for the majority of polyps found in children and are associated with rectal bleeding. JPs also arise within the adult population, although less frequently then other types of polyps, and therefore the terminology "JP" reflects morphologic features rather than age of diagnosis. Distinguishing JPs from other types of polyps, such as IBD associated inflammatory polyps, is important for identifying patients with juvenile polyposis syndrome (JPS). Patients with JPS have a high risk of cancer within the GI tract and therefore require genetic counseling and surveillance. To this end the authors of this paper searched the Danish Pathology Data Bank (DPDB) using a code for "juvenile polyp" and an additional code for anatomic location. From this search they extracted sex, age at diagnosis, number of polyps, and reoccurrences in the 20-year period. An additional search was performed for "adenocarcinoma in the colon and rectum" in patients with juvenile polyps to determine age at cancer diagnosis, number of JPs, and the occurrence of adenomas. From these searches the patients were divided into 3 groups according to the number of polyps: 1) single JP (SJP) 2) between 2 and 5 polyps (MJPs) 3) Juvenile polyposis syndrome (more than 5 polyps). Of the detected juvenile polyps approximately 75% were found in adults and 25% in children. 96% had a single juvenile polyp without reoccurrence, 1% met criteria for juvenile polyposis syndrome and 5% had between 2–5 polyps. Therefore, the incidence of juvenile polyps within the Danish population can be estimated to be between 1:45,000 and 1:65,000. The authors acknowledge the lack of histologic review for confirmation of the pathologic diagnosis of juvenile polyp as a limitation to the study.

Histologic analysis of eosinophils and mast cells of the gastrointestinal tract in healthy Canadian children
Chernetsova E, Sullivan K, de Nanassy J, Barkey J, Mack D, Nasr A, El Demellawy D.
Hum Pathol. 2016 Aug;54:55-63.
http://www.ncbi.nlm.nih.gov/pubmed/27045513

This study aimed to establish a benchmark reference of mucosal eosinophils and mast cells in the Canadian pediatric population. 356 mucosal biopsies from 38 pediatric patients in eastern Ontario revealed higher eosinophil counts in the lower GI tract as compared to upper GI: low of 7.6±6.5/HPF in the gastric body to a high of 50.3±17.4/HPF in the cecum. Similarly, the number of mucosal MC was different in the various regions of the GI tract ranging from 0.04±0.2/HPF in the duodenal cap to 0.9±2.6/HPF in the ileum.

RNA sequencing distinguishes benign from malignant pancreatic lesions sampled by EUS-guided FNA.
Rodriguez SA, Impey SD, Pelz C, Enestvedt B, Bakis G, Owens M, Morgan TK.
Gastrointest Endosc. 2016 Aug;84(2):252-8.
http://www.ncbi.nlm.nih.gov/pubmed/26808815

This prospective study aimed at determining whether RNA sequencing (RNAseq) of endoscopic ultrasound-FNA biopsy samples of undiagnosed pancreatic masses can reliably discriminate between benign and malignant tissue. RNA required for RNAseq was extracted from a single additional EUS-FNA biopsy from 48 patients. The results of RNAseq were compared with cytologic diagnosis, surgical pathology diagnosis, or benign clinical follow-up of at least 1 year. The first 13 specimens yielded 10 adequate samples of 5 benign and 5 malignant cases which were used to construct a distinguishing classifier. The classifier profile was composed of 85 genes of which some were over-expressed and some under-expressed in malignant compared with benign cases. Most of the highly upregulated genes were highly enriched for genes previously implicated in pancreatic malignancy. The training set classifier was applied to 23 test cases. Of the 15 cancers, the classifier correctly classified 13 as malignant and 2 incorrectly as benign. Of the 8 benign specimens, the classifier correctly classified 6 as benign and misclassified 2 as malignant. Overall, the RNAseq-based classifier had a sensitivity for malignancy of .87 (.58-.98; 95% CI) and a specificity of .75 (.35-.96; 95% CI). Based on these findings the authors concluded that RNAseq may reliably distinguish pancreatic ductal adenocarcinoma from reactive pancreatitis in EUS-FNA biopsy specimens and may also be a new method to evaluate more diagnostically challenging pancreatic lesions.

Allograft pancreas: pale acinar nodules
Troxell ML, Drachenberg C.
Hum Pathol. 2016 Aug;54:127-33.
http://www.ncbi.nlm.nih.gov/pubmed/27063474

The authors of this study retrospectively studied the characteristics of pale acinar nodules in allograft pancreata and compared them to native pancreas specimens. Pale acinar nodules were present in 13% (9/69) of allograft biopsies from 22% (7/32) of transplant patients, and 23% (5/22) of native pancreas surgical specimens, although more nodules per pancreas area were present in allograft needle biopsies. Acinar nodules had size of 100 to 700 µm, were periodic acid-Schiff pale, were synaptophysin negative, stained more weakly with keratin CAM 5.2 compared to surrounding parenchyma, and had a low proliferative rate. Ultrastructural evaluation revealed paucity of zymogen granules with dilated cistern-like structures. These pale acinar nodules have similar features in allograft and native pancreas specimens, yet remain of uncertain etiology and significance.

Novel immunohistochemical markers differentiate intrahepatic cholangiocarcinoma from benign bile duct lesions.

Bertram S, Padden J, Kälsch J, Ahrens M, Pott L, Canbay A, Weber F, Fingas C, Hoffmann AC, Vietor A, Schlaak JF, Eisenacher M, Reis H, Sitek B, Baba HA.

J Clin Pathol. 2016 Jul;69(7):619-26.
http://www.ncbi.nlm.nih.gov/pubmed/26729014

The goal of this immunohistochemical study was to distinguish benign bile duct lesions from intrahepatic cholangiocarcionoma (ICC). The study included 77 ICC's, 33 bile duct adenomas (BDA) and 47 "ductular reactions in liver cirrhosis (DR)" and analyzed for eight immunohistochemical markers: stress-induced phosphoprotein 1 (STIP1), SerpinH1, 14-3 3Sigma, CD56, HSP27, HSP70, BCL2, p53, and ki67. Of the ICC's the majority were early stage. However, there was a wide range of TMN stages represented. Tissue microarrays were created for the ICC's and DR's. Bile duct adenomas were assessed by whole mount sections to avoid sampling error. Stains were analyzed by two blinded, experienced pathologists. Quantity was scored as (0%: 0 points; 1–5%: 1point; 6–10%: 2 points; 11–50%: 3 points; >50%: 4 points) and staining intensity (none: 0 points; weak: 1 point; moderate: 2 points; marked: 3 points). The product of these two scores was calculated similar to the immune reactive score (IRS) modeled after Remmele and Stegner. Ki67 was assessed by the percentage of stained nuclei in a semi-quantitative scoring system (0%: 0 points; 1–5%: 1 point; 6–10% 2 points; 11–50%: 3 points; >50%: 4 points). The authors found that STIP1, an HSP-organizing protein, expression was significantly higher in ICC's than DR's but not compared to the BDA group. SerpinH1 (or HSP47) is a serine proteinase inhibitor believed to play a role in collagen maturation and function. Other studies have shown an association with increased expression and tumor progression. In this study there was no difference in expression of SerpinH1 within fibroblasts and endothelial cells within the three different lesions. However, protein expression within tumor cells was significantly higher in ICC's compared to BDA's and DRs. Similar results were observed with 14-3-3Sigma (SFN), an adaptor protein involved in various signaling pathways. Additional studies with a three marker immunohistochemical panel including SerpinH1, 14-3-3Sigma and ki67 was performed which showed a 91.8% diagnostic accuracy in distinguishing between ICC and BDA or DR. Compared to the previously published marker panel of p53, BCL-2 and ki67, which had a reported accuracy of 89.9%, the authors claim their panel to be at least equal or marginally superior in distinguishing ICC's from BDAs and DRs.