Challenges to "Classic" Esophageal Candidiasis
Alsomali MI, Arnold MA, Frankel WL, Graham RP, Hart PA, Lam-Himlin DM, Naini BV, Voltaggio L, Arnold CA.
Am J Clin Pathol. 2017 Jan 31
https://www.ncbi.nlm.nih.gov/pubmed/28158394

This case control study looked at the incidence, clinical and endoscopic features of, and histologic morphology of esophageal candidiasis (EC). Using histology as the gold standard for diagnosis, the authors found an incidence of 5.2% (40 cases from 770 patients with esophageal biopsies), over half of the cases had no suspicion of EC on endoscopy reported. Only 46% of the cases were submitted with a clinical suspicion of EC and of these "white exudates, and mucosal breaks" were the most common descriptions. Histologically, pseudohyphae were identified in most cases (92.5%), and in most cases these were seen in desquamated parakeratosis or in "hyper-pink parakeratosis". The authors discuss a cost analysis of PAS/D staining to identify EC and conclude that the special stain is not recommended on all esophageal specimens, but a targeted approach in cases with the following: "1) ulcer 2) suspicious morphology and/or 3) clinical impression of EC" might be more cost effective.

Range of pathologies diagnosed using a minimally invasive capsule sponge to evaluate patients with reflux symptoms.
Paterson AL, Lao-Sirieix P, O'Donovan M, Debiram-Beecham I, di Pietro M, Miremadi A, Attwood SE, Walter FM, Sasieni PD, Fitzgerald RC; BEST and BEST2 study groups..
Histopathology. 2017 Jan;70(2):203-210.
https://www.ncbi.nlm.nih.gov/pubmed/27417524

The trademarked Cytosponge is a small sponge ball contained within a soluble gelatin capsule and attached to a string; this apparatus can be swallowed by a patient, the capsule dissolves, the sponge expands, and after an interval of time it is withdrawn by the string. 820 patients from the BEST and BEST2 study groups were included in the study and were administered the Cytosponge, which was then processed for paraffin histology, and underwent EGD with biopsy as clinically indicated per usual clinical criteria. No therapy was initiated as a result of Cytosponge findings; clinical management was adjusted based on the endoscopic findings. In 12% of patients, Cytosponge histology showed abundant acute and chronic inflammatory cells that permeated epithelial fragments or were present in dense clusters separate from epithelial fragments. In 3.9% of cases, dense aggregates of mostly acute inflammation were seen in association with fibrin, taken to represent an ulcer. Commensal organisms like Candida from the oropharynx and Aspergillus from tonsils were noted in some cases. In 0.6% of cases, eosinophilic infiltration of epithelial cells was noted (>15 eos per HPF) occasionally with micro-abscesses, taken as possible EOE pathology. One case showed viral nuclear inclusions from herpes esophagitis. In 78% of the study patients, no significant pathology was seen at endoscopy. The authors discuss in detail the overlap and discrepancy in Cytosponge versus EGD findings; in 73% of cases there was agreement between the findings. In 15% of cases, the Cytosponge was negative but pathology was identified at endoscopy (typically, severe esophagitis or Candida esophagitis). Interestingly, in 11% of cases, endoscopy was negative

whereas Cytosponge identified pathology, including significant inflammation or ulceration, Candida with significant accompanying inflammation, and the single case of herpetic viral inclusions. While this is a preliminary study, the Cytosponge method holds promise for use in a resource-limited or non-endoscopic clinical setting with easy administration by a non-physician.

Discordance Among Pathologists in the United States and Europe in Diagnosis of Low-Grade Dysplasia for Patients With Barrett's Esophagus.
Vennalaganti P, Kanakadandi V, Goldblum JR, Mathur SC, Patil DT, Offerhaus GJ, Meijer SL, Vieth M, Odze RD, Shreyas S, Parasa S, Gupta N, Repici A, Bansal A, Mohammad T, Sharma P. Gastroenterology. 2017 Feb;152(3):564-570.e4.
https://www.ncbi.nlm.nih.gov/pubmed/27818167

This is an interobserver agreement study for dysplasia in Barrett's esophagus (BE). Prior to slide review, the authors attempted to improve interobserver concordance rates among low grade dysplasia (LGD) by agreeing upon criteria for dysplastic changes, including: glandular crowding, cribriform glands, cytologic atypia extending to surface, nuclear enlargement, nuclear hyperchromasia, nuclear crowding, pseudostratification, irregular nuclear contours, and mucin depletion. To account for inflammatory changes, they also developed two new subcategories of LGD:

1) low grade dysplasia with predominant inflammatory features (LGD-I), and
2) low grade dysplasia with predominant dysplastic features (LGD-D)

79 slides from patients with BE (23 samples of non-dysplastic BE, 22 samples of LGD, and 34 samples of high-grade dysplasia) were randomly assigned to 7 pathologists (4 from the United States and 3 from Europe), and interpreted in a blinded fashion. Study pathologists also reported degree of confidence in interpretation, where high is >90% confident in diagnosis. The overall k values are below:

Study category	**Kappa**
Overall diagnosis	0.43
Nondysplastic BE	0.22
LGD	0.11
HGD	0.43
High confidence US pathologists	0.63
High confidence European pathologists	0.80

Kappa values interp (a refresher)
Poor agreement = 0.20 or less Fair agreement = 0.20 to 0.40 Moderate agreement = 0.40 to 0.60 Good agreement = 0.60 to 0.80 Very good agreement = 0.80 to 1.00

The level of interobserver agreement increased with level of pathologist confidence. There was also a difference in reading of histopathology samples of BE tissues between US and European pathologists, with European pathologists showing overall higher concordance rates:

Study category	**US Kappa**	**European Kappa**
Overall diagnosis	0.44	0.65
Nondysplastic BE	0.21	0.37
LGD	0.14	0.32

HGD	0.45	0.63

Pathologists weighted the presence of cytologic atypia, nuclear hyperchromasia and nuclear crowding as highly influencing their LGD interpretations. HGD showed highly weighted glandular crowding, cytological atypia, nuclear hyperchromasia, and nuclear crowding. There was no improvement in level of agreement among experienced pathologists, even after accounting for inflammation. The authors conclude that despite refining the criteria, they were unable to detect expected improvement in overall interobserver agreement.

CDH17 Is a More Sensitive Marker for Gastric Adenocarcinoma Than CK20 and CDX2.
Altree-Tacha D, Tyrrell J, Haas T.
Arch Pathol Lab Med. 2017 Jan;141(1):144-150.
https://www.ncbi.nlm.nih.gov/pubmed/28029907

Immunostaining for CDH17, an oncogene expressed by intestinal epithelium, was tested on 26 normal and 884 neoplastic samples in comparison to CK20 and CDX2. In colon adenocarcinoma, CDH17 was positive in more than 97% of cases in comparison to CK20 (~89%) and CDX 2 (~93%). In metastatic colon cancer, CDH17 stained about 91% of cases (CK20, ~59%; CDX2, ~81%). In gastric adenocarcinomas, CDH17 stained 64% of samples (CK20, ~25%; CDX2, ~47%) and in esophageal adenocarcinomas, CDH17 stained ~39% of samples (CK20, ~26%; CDX2, 29%). This new marker can be considered as a useful tool in workup of GI cancers, particularly gastric cancers.

High-throughput Protein and mRNA Expression-based Classification of Gastric Cancers Can Identify Clinically Distinct Subtypes, Concordant With Recent Molecular Classifications.
Ahn S, Lee SJ, Kim Y, Kim A, Shin N, Choi KU, Lee CH, Huh GY, Kim KM, Setia N, Lauwers GY, Park DY.
Am J Surg Pathol. 2017 Jan;41(1):106-115.
https://www.ncbi.nlm.nih.gov/pubmed/27819872

The goal of this study was to replicate and validate molecular subtyping of gastric cancers, based on high throughput technologies, using simple cost-effective immunohistochemistry (IHC) and in situ hybridization (ISH) in a large Asian cohort (n=349). A recent publication, based on protein and mRNA expression using widely available and inexpensive IHC and ISH, identified 5 clinically relevant subtypes of gastric cancers from a Western cohort (n=149): cluster 1 Epstein-Barr virus (EBV)-positive cancers, cluster 2 -aberrant MLH1 expression (high-MSI), cluster 3 -aberrant E-cadherin expression or epithelial to mesenchymal transition (EMT)/Genome stable (GS), cluster 4 -aberrant p53 expression, and cluster 5 -normal p53 expression. Tissue microarrays constructed from untreated gastric adenocarcinoma in 349 patients were stained with antibodies to MLH1, E-cadherin, p53, and HER2. Tumors showing complete loss of nuclear MHL1 were classified as showing aberrant MHL1 expression. Tumors that showed complete loss or diffuse/strong p53 nuclear positivity were classified as aberrant p53 expression. Complete loss of membranous E-cadherin expression or markedly reduced membranous staining (>30%)

were regarded as aberrant expression, regardless of the nuclear or cytoplasmic staining. The HER2 results were scored according to the recently developed assessment guidelines for HER2-associated gastric cancers. Chromogenic ISH with EBV-encoded small RNA (EBER-ISH) was performed and tumors with strong nuclear staining were considered positive. Among the 349 gastric cancers, loss of MLH1 expression was observed in 26 cases (7.4%), aberrant expression of E-cadherin in 56 cases (16.0%), and aberrant expression of p53 in 221 cases (63.3%) [Diffuse/strong positivity n=64 (18.3%); null phenotype n=157 (45.0%)], EBER-ISH positive in 26 cases (7.4%), and HER2 positive in 11 cases (3.2%). The proportion of the cluster 2 (high-MSI tumors) was lower in the Asian cohort (7% vs. 16% in the Western cohort), whereas the proportion of the cluster 5 (tumors with normal p53 expression) was higher in the Asian cohort (21% vs. 7% in the Western cohort). Similar to the prior study, authors identified distinct clinicopathologic characteristics corresponding to the molecular classifications. EBV-positive (cluster 1) tumors were more often poorly differentiated (61.5%) in males (80.8%) with gastric body cancers (80.8%). Microsatellite-unstable (high-MSI) tumors (cluster 2) occurred at a more advanced age and were predominantly in the antrum (58.3%) with intestinal histology. Both types showed better overall survival than the other types. Gastric cancers with reduced expression of E-cadherin (cluster 3, EMT/GS) had the poorest overall survival and showed a high prevalence of poorly cohesive carcinoma (ie, diffuse type in the Lauren classification system). Clusters 4 and 5 (aberrant or normal p53) had intermediate prognosis. The authors utilized widely available, inexpensive IHC and ISH assays to successfully reproduce previously reported molecular classification of gastric cancers, dividing them into subgroups with targetable molecules amenable to tailored therapy with a potential for improved patient outcomes.

Microscopic gastrointestinal stromal tumours: a clinical and molecular study of 13 cases.
Anderson W, O'Sullivan B, Hughes F, Swift C, Smith M, Deshmukh N, Taniere P.
Histopathology. 2017 Jan;70(2):211-216.
https://www.ncbi.nlm.nih.gov/pubmed/27472829

13 clinically silent micro-GISTs were identified incidentally in patients undergoing management of other diseases. 10/13 were in the stomach, 2 in the duodenum, and 1 in the rectum. Mean size was sub-centimeter, and all were well-circumscribed with predominantly spindle-cell appearance and a very low mitotic index. 12/13 had either KIT mutations (83%) or mutations in PDGFRA (17%), a rate higher than published in other series. A high mutation rate (80%) was noted in the smallest lesions (those measuring less than or equal to 5 mm). The authors speculate that KIT/PDGFRA mutation is common early in GIST development and may not in itself indicate clinical impact.

Mesenteric Tumor Deposits in Midgut Small Intestinal Neuroendocrine Tumors Are a Stronger Indicator Than Lymph Node Metastasis for Liver Metastasis and Poor Prognosis.
Fata CR, Gonzalez RS, Liu E, Cates JM, Shi C.
Am J Surg Pathol. 2017 Jan;41(1):128-133.
https://www.ncbi.nlm.nih.gov/pubmed/27684993

The authors of this study evaluated the prognostic significance of mesenteric tumor deposits (MTDs) in midgut small intestinal neuroendocrine tumors (NETs). The study group consisted of 132 (72- male, 60- female; median age 60 yrs) resected jejunal/ileal NETs. MTDs were defined as discrete but irregular mesenteric tumor nodules frequently located adjacent to neurovascular bundles and discontinuous from the primary neoplasm. Mesenteric deposits with a rounded contour or associated with a surrounding rim of lymphocytes were considered to be lymph node (LN) metastases and not MTDs. LN metastasis, MTDs, and liver metastasis were present in 106, (80.3%), 86 (65.1%), and 77 (58.3%) of patients, respectively. Independent predictors of liver metastasis were MTDs and female gender. In multivariate analysis the odds ratio for liver metastasis with MTDs was 16.68 (95% CI 4.66-59.73;P< 0.001) and 0.81 (95% CI 0.20-3.26; P=0.767) for LN metastasis. Increasing age, liver metastasis, and MTDs all showed increased hazard ratios for disease specific survival (DSS) in univariate Cox proportional-hazards regression. Multivariate analysis of liver metastasis-free survival stratified by tumor grade showed that MTDs were associated with adverse outcomes. Hazard ratio for MTDs was 4.58 (95% CI, 1.89-11.11; P=0.001), compared with 0.98 (95% CI, 0.47-2.05; P=0.967) for LN metastasis. Advanced T stage, LN metastasis, and histologic grade of the primary tumors showed no significant effect on DSS. Based on these findings, the authors concluded that MTDs are common findings in patients with midgut NETs and are a strong predictor for liver metastasis and decreased DSS in contrast to LN metastasis. Therefore, the presence or absence of MTDs should be reported for midgut NETs and be considered for inclusion in the AJCC cancer staging algorithm for these tumors. In the authors' opinion, the midgut NETs with MTDs should be considered as a more advanced stage than stage IIIB (T1-4/N1), perhaps as stage IIIC.

Hydrophilic Polymer-associated Ischemic Enterocolitis.
Chavez JA, Chen W, Frankel WL, Arnold CA.
Am J Surg Pathol. 2017 Feb;41(2):271-276.
https://www.ncbi.nlm.nih.gov/pubmed/27819873

In the first ever reported study, the authors describe a series of 7 specimens (small bowel-2, colon-4, aortic thrombus-1) from 3 patients (pt 1:56/F; pt 2:77/F; pt 3:65/M) with hydrophilic polymer-associated ischemic enterocolitis within a day of aortic repair. Two patients (pts 1 &2) had a fenestrated Endograft repair of a juxtarenal abdominal aortic aneurysm, and 1 patient (pt 3) had an open repair with a 32-mm Hemashield graft of an ascending aortic dissection. All intestinal specimens showed hydrophilic polymers in submucosal vessels in the areas of ischemic injury with the intervening normal mucosa devoid of polymers. In patients who underwent Endograft repair, the hydrophilic polymers appeared as intravascular, serpiginous structures with stippled basophilia in routine H&E, turquoise in colloidal iron, pink in von Kossa and mucicarmine, and pale blue in trichrome. In a subsequent specimen from Patient 1 (89 days post initial resection), these polymers were diminished in number and showed altered morphology being less crisply basophilic, more amorphous in shape, and associated with a foreign body giant cell reaction. In the 3rd patient, who underwent aortic repair with a Hemashield graft, the hydrophilic polymers were serpiginous, gray intravascular structures in submucosal vessels in areas of ischemia, having a smooth texture and lacking stippling. Clinical follow-up was available up to 115 weeks: 1 patient died, and 2 are alive and well. Based on these findings, the authors concluded that this new diagnostic entity has to be considered in the differential

diagnosis of iatrogenic ischemic injuries in the gastrointestinal tract. Awareness of this entity is important in identifying the etiology of the ischemia and in preventing misdiagnosis of the polymers and their associated giant cell reaction as infection, vasculitis, or idiopathic inflammatory bowel disease.

Cytomegalovirus (CMV) in gastrointestinal mucosal biopsies: should a pathologist perform CMV immunohistochemistry if the clinician requests it?
Juric-Sekhar G, Upton MP, Swanson PE, Westerhoff M.
Hum Pathol. 2017 Feb;60:11-15.
https://www.ncbi.nlm.nih.gov/pubmed/27666768

Cost effective immunohistochemistry is important in today's accountable care models. As one example, medicare reimbursement requires review of H&E stained slides prior to the ordering of additional studies. In this retrospective study, clinician driven requests for upfront CMV immunohistochemistry was investigated. Clinical requests for CMV IHC accompanied 449 cases in which CMV was detected in 37 (26 by IHC and 11 by H&E). Pathologist-initiated staining comprised 238 cases with CMV detected in 15 (12 by IHC, 3 by H&E). Among the 38 IHC stained cases, 27 showed overt viral inclusions obvious by H&E. When clinical concern for CMV was expressed and biopsies showed uninflamed mucosa, CMV IHC was always negative. The authors conclude that although clinical suspicion for CMV has a high yield for detection, up front testing is unnecessary.

Postoperative Venous Thromboembolism in Patients Undergoing Abdominal Surgery for IBD: A Common but Rarely Addressed Problem
Brady M, Patts G, Rosen A, Kasotakis G, Siracuse J, Sachs T, Kuhnen A, Kunitake H
Dis Colon Rectum 2017; 60: 61–67
https://www.ncbi.nlm.nih.gov/pubmed/27926558

This study is a retrospective evaluation of medical and pharmacy administrative claims data to determine the use of postoperative prophylactic anticoagulation following discharge for adult patients undergoing abdominal surgery for Crohn's disease and ulcerative colitis. Venous thromboembolism (VTE), including deep VTE, mesenteric VTE and pulmonary embolism occurs in 2-3% of these patients, which is 2-3 times higher than the general population. Evidence based guidelines managing anticoagulation currently do not exist. Therefore, the authors reviewed 7, 078 patients charts to determine the rate of VTE prophylaxis, the 90-day rates of thromboembolic events and risk factors for patients with inflammatory bowel disease undergoing abdominal surgery. The authors discovered 0.6% of patients received postdischarge chemical prophylaxis and 235 patients (3.3%) developed a thromboembolic complication. These adverse events were more common in patients with ulcerative colitis than Crohn's disease (5.8% vs 2.3%) and in those where a stoma was created. Other factors included J-pouch reconstruction, prednisone use and increased hospital stay after surgery. In light of the findings, the authors recommend developing evidence-based guidelines to improve outcomes following abdominal surgery for patients with inflammatory bowel disease.

Development and validation of the Nancy histological index for UC.
Marchal-Bressenot A, Salleron J, Boulagnon-Rombi C, Bastien C, Cahn V, Cadiot G, Diebold MD, Danese S, Reinisch W, Schreiber S, Travis S, Peyrin-Biroulet L.
Gut. 2017 Jan;66(1):43-49.
https://www.ncbi.nlm.nih.gov/pubmed/26464414

This is the first of two articles in this issue of Gut on a standardized histological system for assessing disease activity in ulcerative colitis (UC). 200 biopsies were scored across different centers using the Global Visual Evaluation and other criteria based on detailed literature review. Ultimately, 8 features were assessed: chronic inflammatory infiltrate, epithelial neutrophils, ulceration, acute inflammatory infiltrate, mucin depletion, lamina propria neutrophils, basal plasmacytosis, and serrated architecture. After statistical analysis, three items were selected for the Nancy histological index reported here: ulceration, acute inflammatory infiltrate, and chronic inflammatory infiltrate, resulting in a 5-tier classification from grade 0 (absence of significant activity) to grade 4 (severely active disease). There is high correlation between changes in the Geboes score, another accepted scale for disease activity, and the Nancy index (0.910, range 0.813-0.955).

Development and validation of a histological index for UC.
Mosli MH, Feagan BG, Zou G, Sandborn WJ, D'Haens G, Khanna R, Shackelton LM, Walker CW, Nelson S, Vandervoort MK, Frisbie V, Samaan MA, Jairath V, Driman DK, Geboes K, Valasek MA, Pai RK, Lauwers GY, Riddell R, Stitt LW, Levesque BG.
Gut. 2017 Jan;66(1):50-58.
https://www.ncbi.nlm.nih.gov/pubmed/26475633

This is the second of two articles in this issue of Gut on a standardized histological system for assessing disease activity in ulcerative colitis (UC). 48 UC colon biopsies were scored using the Geboes score (GS), the modified Riley score, and the Visual Analogue Scale (VAS). All components of the GS were shown to be reliable, with the best predictors of VAS being chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in the epithelium, and erosion or ulceration. These items were included in the new Robarts histopathology index reported here (RHI). RHI shows correlation coefficients greater than 0.70 for change scores in VAS.

Comprehensive DNA Methylation Profiling of Inflammatory Mucosa in Ulcerative Colitis.
Tahara T, Hirata I, Nakano N, Nagasaka M, Nakagawa Y, Shibata T, Ohmiya N.
Inflamm Bowel Dis. 2017 Jan;23(1):165-173.
https://www.ncbi.nlm.nih.gov/pubmed/27930411

This study consisted of DNA methylation profiling of 94 colonic biopsies from 84 UC patients without cancer and control groups of 5 patients with high-grade dysplasia and 9 with carcinoma, in order to determine methylation changes that may lead to development of tumorigenesis in UC. Bisulfite pyrosequencing was used to evaluate 45 CpG island (CGI) promoter regions of genes associated with cancer, inflammation, age, and the *LINE1* repetitive element. Hypermethylation of CGIs correlated with increased disease duration, a risk factor for UC-associated cancer development. Genes involved in biosynthetic processes, metabolic regulation, and nitrogen metabolism were affected. The authors suggest that DNA methylation assessment of mucosal

biopsies may be useful as a molecular marker and to identify therapeutic targets for UC-associated neoplasia.

Low rate of dysplasia detection in mucosa surrounding dysplastic lesions in patients undergoing surveillance for inflammatory bowel diseases.
Ten Hove JR, Mooiweer E, Dekker E, van der Meulen-de Jong AE, Offerhaus GJ, Ponsioen CY, Siersema PD, Oldenburg B.
Clin Gastroenterol Hepatol. 2017;15(2):222-228.
https://www.ncbi.nlm.nih.gov/pubmed/27613257

The aim of this study was to assess the rate of dysplasia diagnoses from mucosal biopsies obtained adjacent to confirmed dysplastic lesions. The authors note that most guidelines on inflammatory bowel disease (IBD) surveillance state that biopsies should be taken from the mucosa surrounding lesions suspected of being neoplastic. In the past, these background biopsies were to be negative to refrain from performing a colectomy. With the advent of high-definition endoscopies and chromoendoscopy, the authors questioned whether these biopsies are still necessary. Patients undergoing colonoscopic surveillance for IBD over a period of 15 years were identified from 3 tertiary care facilities. Of these 1065 patients, 196 (18%) had a visible dysplastic lesion. In 140 dysplastic lesions, represented by 71 patients, additional biopsies of surrounding mucosa were taken. Thirty-four patients (48%) had ulcerative colitis, 30 (42%) had Crohn's disease and 7 patients (10%) had indeterminate colitis. Dysplasia was detected in surrounding mucosal biopsies in 7 of 140 neoplastic lesions (5.0%). Of the 4 lesions detected with high-grade dysplasia, 2 had biopsy proven dysplasia in the surrounding mucosa. Conversely, 5 of 136 (3.7%) lesions consisting of low-grade dysplasia had surrounding dysplastic mucosa. Given the rate of surrounding mucosal dysplasia was 5%, the authors conclude that the general ability to endoscopically demarcate lesional margins is suitable. They note that the lack of actionable findings in most cases of surrounding mucosal biopsies casts doubt of the usefulness of this practice.

Genetic instability, CpG island methylator phenotype, and proliferative activity are distinct differences between diminutive and small tubular adenoma of the colorectum.
Nando Y, Watari J, Ito C, Hara K, Yamasaki T, Okugawa T, Kondo T, Kono T, Tozawa K, Tomita T, Ohda Y, Oshima T, Fukui H, Matsubara N, Tomita N, Hirota S, Miwa H.
Hum Pathol. 2017 Feb;60:37-45.
https://www.ncbi.nlm.nih.gov/pubmed/27746269

There has been a growing approach to "predict, resect, and discard" diminutive (≤5 mm) colorectal polyps to avoid the cost of pathological assessment. This approach has been supported by the ASGE and recently by the Japanese Society of Gastroenterology. By comparison, endoscopic resection (ER) with histologic evaluation is recommended for small (6-10 mm) lesions. The size distinction appears arbitrary as advanced lesions are rarely found in subcentimeter polyps, and so the aim of this study was to evaluate the molecular alterations and treatment indications in diminutive vs small tubular adenomas (TA). This study prospectively analyzed 96 TAs for genetic instability (including microsatellite instability and loss of heterozygosity), methylation status, KRAS/BRAF mutations, and Ki-67 staining. Molecular

events and proliferative activity increased from diminutive to small TA's, even in those without advanced histology, supporting the concept of "predict, resect, and discard" for diminutive lesions while further supporting ER with histologic evaluation of small polyps.

Clinicopathological and molecular features of sessile serrated adenomas with dysplasia or carcinoma.
Bettington M, Walker N, Rosty C, Brown I, Clouston A, McKeone D, Pearson SA, Leggett B, Whitehall V.
Gut. 2017 Jan;66(1):97-106.

The authors reviewed 137 SSAs with areas of dysplasia/carcinoma prospectively collected from a community GI practice for BRAF and KRAS mutation, CpG island methylator phenotype (CIMP), and immunostaining for MLH1, p53, p16, beta-catenin, and MGMT. Most polyps were small (less than 10 mm) and proximal (almost 90%). More than 90% were BRAF mutated and more than 90% showed CIMP. Loss of MLH1, indicating mismatch repair deficiency by this assessment, was associated with increased age, female gender, proximal location, CIMP, and lack of aberrant p53 in comparison to MMR-proficient cases (all to statistically significant levels). Loss of p16 and gain of nuclear beta-catenin were relatively common in foci of dysplasia/carcinoma regardless of MMR status (~43% and 56%, respectively). The authors speculate that, since dysplasia is seen at a similar age to carcinoma in SSAs, there may be a rapid transition to malignancy in SSAs.

Diagnosis of T1 colorectal cancer in pedunculated polyps in daily clinical practice: a multicenter study.
Backes Y, Moons LM, Novelli MR, van Bergeijk JD, Groen JN, Seerden TC, Schwartz MP, de Vos Tot Nederveen Cappel WH, Spanier BW, Geesing JM, Kessels K, Kerkhof M, Siersema PD, Offerhaus GJ, Milne AN, Lacle MM.
Mod Pathol. 2017 Jan;30(1):104-112.
https://www.ncbi.nlm.nih.gov/pubmed/27713422

In this study the pathology from a sample of T1 colorectal cancers in pedunculated polyps, diagnosed in 10 Dutch hospitals, were reviewed by expert gastrointestinal pathologists and 16% (20/128) of the cases were downgraded to pseudoinvasion, high grade dysplasia, or equivocal. The authors discuss the difficulties, both for generalists and expert gastrointestinal pathologists, in making the diagnosis of invasive cancer in polyps and recommend secondary review or discussion at multidisciplinary conferences for difficult cases.

Colorectal carcinomas with submucosal invasion (pT1): analysis of histopathological and molecular factors predicting lymph node metastasis.
Pai RK, Chen Y, Jakubowski MA, Shadrach BL, Plesec TP, Pai RK.
Mod Pathol. 2017 Jan;30(1):113-122.
https://www.ncbi.nlm.nih.gov/pubmed/27713420

In this study the authors aim to identify features of pT1 tumors associated with lymph node metastasis. Currently in the United States resection for pT1 tumors are recommended for cases with high-grade morphology, lymphovascular invasion, and/or close or positive resection margins. The authors discuss features considered high risk in Japan (mucinous morphology, depth of invasion, and high tumor budding) and report an analysis on 116 cases pT1 tumors from a western cohort. In univariate analysis high tumor budding (P<0.001), lymphatic invasion (P=0.003), depth of submucosal invasion >1000 μm (P=0.04), and high-grade morphology (P=0.04) were significantly associated with lymph node metastasis; however, on multivariate analysis, only high tumor budding was found to be significant. The authors conclude that tumor budding should be considered when deciding on further resection of pT1 tumors. Molecular alterations were also discussed, but no clear recommendations were given.

Clinicopathological features of a kindred with SCG5-GREM1-associated hereditary mixed polyposis syndrome.
Plesec T, Brown K, Allen C, A Burke C, Church J, Kalady M, LaGuardia L, O'Malley M, Heald B.
Hum Pathol. 2017 Feb;60:75-81.
https://www.ncbi.nlm.nih.gov/pubmed/27984123

Limited clinical and histologic information has been published on hereditary mixed polyposis syndrome (HMPS). This syndrome, which was first characterized in 1997, has been exclusively found the Ashkenazi Jewish population, has a presumed increased risk for colorectal cancer, and is defined by a duplication on chromosome 15 spanning the 3′ end of the SCG5 gene and a region upstream of the GREM1 locus. The authors describe a cohort of 10 HMPS patients with confirmed germline SCG5-GREM1 duplication. Mean age at presentation was 33.3 years. The patients have a unique polyp termed “hyperplastic-inflammatory polyp” which differs morphologically from other hamartomatous polyps. These lesions show an expanded lamina propria filled with inflammatory cells (similar to an inflammatory polyp), but show epithelial serrations (similar to hyperplastic polyps). Tubular adenomas found in these patients also frequently showed an inflammatory backdrop with expansion of the lamina propria. The authors suggest that finding multiple polyps with multiple morphologies should prompt consideration for HMPS, careful prospective follow-up, and re-review of prior procedures, especially since these patients produce low numbers of polyps.

Patients with nonpolypoid (flat and depressed) colorectal neoplasms at increased risk for advanced neoplasias, compared with patients with polypoid neoplasms.
McGill SK, Soetikno R, Rouse RV, Lai H, Kaltenbach T.
Clin Gastroenterol Hepatol. 2017 Feb;15(2):249-256.
https://www.ncbi.nlm.nih.gov/pubmed/27639328

This retrospective longitudinal cohort study was performed to evaluate the long-term outcomes of patients diagnosed with non-polypoid colorectal neoplasia (NP-CRN) on screening colonoscopy. The authors note that NP-CRN, defined as flat lesions with a height of less than half the lesion’s diameter, have been previously linked to the early development of colon cancer

and have been shown to have distinct molecular derangements compared to their polypoid counterparts. The authors sought to investigate the rates at which patients diagnosed with NP-CRN go on to develop subsequent advanced neoplasia. The patient cohort consisted of individuals (4454) undergoing elective colonoscopy over a period of five years at a large academic Veterans' Affairs hospital. Of these patients, 341 (7.7%) were found to have NP-CRN while the overall prevalence of polypoid neoplasms without NP-CRN was 36.3%. Patients from this latter group served as controls for this study. By evaluating the findings from subsequent follow-up colonoscopies, the authors were able to demonstrate that a significantly higher proportion of patients with NP-CRN (16.0%) subsequently developed advanced neoplasia at their follow-up colonoscopies compared to the control group (8.6%). Additionally, the former group was also more likely to develop more NP-CRN at follow-up colonoscopy (17%) than controls (7%). Interestingly, the incidence of invasive carcinomas at follow-up colonoscopy was not significantly different between these groups. The authors conclude that patients with NP-CRN do in fact have a higher risk of developing advanced lesions in the future compared to individuals with polypoid lesions. While the authors note that patients with NP-CRN seem to represent a high-risk group, the current surveillance guidelines for follow-up colonoscopies appear adequate. Of note, the authors mention that during the time period of the study, sessile serrated adenomas/polyps were not recognized as distinct entities and their study does not address how these lesions relate to this process.

Tumor budding at the invasive front of colorectal cancer may not be associated with the epithelial-mesenchymal transition.
Yamada N, Sugai T, Eizuka M, Tsuchida K, Sugimoto R, Mue Y, Suzuki M, Osakabe M, Uesugi N, Ishida K, Otsuka K, Matsumoto T.
Hum Pathol. 2017 Feb;60:151-159.
https://www.ncbi.nlm.nih.gov/pubmed/27836787

Tumor budding is thought to reflect the epithelial-mesenchymal transition (EMT). This tissue microarray study examined the induction of tumor budding and EMT and their association with EMT-related proteins (ZEB1, TWIST, SNAIL, and SLUG) in colorectal cancer (CRC). Low or no expression of any markers was found in tumor budding. In stromal cells surrounding tumor budding, the expression of ZEB1 was more frequent than TWIST, SNAI, and SLUG. In comparison to low-grade areas, the stromal cells surrounding high grade areas of tumor budding showed significantly greater expression. The authors conclude that tumor budding at the invasive front does not represent an epithelial mesenchymal transition. However, the heterogeneous immunophenotype of the stromal cells do show a mixture of benign activated fibroblasts and transformed neoplastic stromal cells.

Micropapillary colorectal carcinoma: clinical, pathological and molecular properties, including evidence of epithelial-mesenchymal transition.
Gonzalez RS, Huh WJ, Cates JM, Washington K, Beauchamp RD, Coffey RJ, Shi C.
Histopathology. 2017 Jan;70(2):223-231.
https://www.ncbi.nlm.nih.gov/pubmed/27560620

The authors studied 42 cases of colorectal cancer (CRC) with micropapillary features (MP; small rounded clusters of malignant cells with reversed polarity, abundant eosinophilic cytoplasm and retraction artifact, features distinct from tumor budding). 27 cases showed prominent cribriforming with dirty necrosis in the non-MP areas; 9 showed mucinous features. 24/29 studied cases showed evidence of epithelial-mesenchymal transition by immunostaining for vimentin and cadherin as well as SMAD4 localization. 36 cases (86%) showed pT3 or pT4 status with 31 (74%) having lymph node metastases and 23 (55%) having distant metastases. KRAS mutations were identified in 11 of 31 cases and BRAF V600E mutations in 4 of 31 cases. All 21 cases tested for MSI were microsatellite-stable. In comparison to a large conventional CRC cohort, MP CRC is more likely to present as stage IV disease ($P<0.001$) but there is no difference in overall survival after adjusting for stage.

Differences in Microsatellite Instability Profiles between Endometrioid and Colorectal Cancers A Potential Cause for False-Negative Results?
Wang Y, Shi C, Eisenberg R, Vnencak-Jones CL.
J Mol Diagn. 2017 Jan;19(1):57-64.
https://www.ncbi.nlm.nih.gov/pubmed/27810331

Many institutions have implemented universal screening for microsatellite instability (MSI) for all newly diagnosed colorectal cancers (CRCs) and endometrial cancers (EMCs) to identify patients with potential Lynch Syndrome (LS). Lynch Syndrome, or hereditary nonpolyposis colorectal cancer, is an autosomal dominant disorder caused by mutations in one of four mismatch repair (MMR) genes or by a deletion in EPCAM locus. Mutations in these genes results in defective mismatch repair, which can be germline, as in the case of LS, or sporadic within the tumor only. LS can be screened either though PCR based testing for instability in DNA extracted from tumor tissue or immunohistochemistry to interrogate expression of mismatch repair proteins. MSI is defined as insertion or deletion of repeated DNA sequences. When MSI is present within at least 30% of the loci analyzed the tumor is considered to demonstrate high frequency MSI (MSI-H). Loss of protein expression of any of the four MMR proteins indicates a possible DNA mutation or hypermethylation of one of the MMR genes. The majority of PCR based testing is now performed with a commercial kit utilizing 5 mononucleotide repeat markers. IHC is the preferred test for EMCs by some institutions due to a reported higher false negative rate with MSI testing. This study consists of two parts. The first is to compare MSI PCR profile patterns between EMCs and CRCs and the second is to look at the relationship between pathologic features of EMCs and MSI status. 311 CRC specimens and 91 EMC specimens were used for analysis. 14.8% of CRC's and 22% of EMCs were MSI-H. However EMCs exhibited smaller repeat number changes when compared to CRCs. Additional studies revealed that tumor percentages less than 30% correlated with smaller repeat changes (one nucleotide shift). The authors therefore suggest that MSI may be missed if each locus is not examined carefully, particularly for tumors with low tumor percentage. In terms of pathologic features and MSI status in EMC's, the authors observed that grade 2 tumors correlated more frequently with MSI-H status. However, there was no correlation with age at diagnosis, stage, tumor site, histologic type, cervix involvement, lymphovascular invasion, tumor margin or myometrial invasion.

Transanal Endoscopic Microsurgery for Early Rectal Cancer: A Single-Center Experience
O'Neill C, Platz J, Moore J, Callas P, Cataldo P
Dis Colon Rectum 2017; 60: 152–160
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280406/

This is a retrospective review at a single center of transanal endoscopic microsurgery (TEM) for early rectal cancer, defined as T1 or T2, N0 and M0. Although there appears to be much controversy regarding local excision for early rectal cancers, the benefits include minimal perioperative morbidity and better functional results when compared to radical resection. Recent literature published regarding TEM report improved outcomes and some patients are selected for local excision. Patients with T3 lesions or node-positive disease were excluded from this study. Patients with adverse histologic features on biopsy, such as poor differentiation or lymphovascular invasion, they were counseled and given a choice of additional chemoradiation or radical resection. Patients were staged preoperatively with either MRI or endoscopic ultrasound. Those with T2 lesions were given adjuvant chemoradiation and those staged as T2 after surgery received post-operative chemoradiation. A total of 137 patients underwent TEM, however 45 were excluded after T3 lesions were identified microscopically. Of the 92 remaining patients, the majority had surgery performed by the same surgeon. 91 of the 92 tumors were resected with negative margins. 75% of patients were discharged the same day as surgery. 10.9% had minor complications and 4.3% had a postoperative bleed, considered a major complication. Overall 58.7% had T1 disease, of which 7.4% received chemoradiation for adverse histologic features. 38 patients had T2 disease, of which 44.7% underwent adjuvant chemoradiation and 42.1% received neoadjuvant chemoradiation. For those undergoing neoadjuvant chemotherapy for T2 disease, 50% achieved a complete pathologic response following surgery (ypT0). The final pathologic stage of tumors for the entire patient population was ypT0 at 8.7% (8/92), pT1 at 58.7% (54/92), pT2 at 23.9% (22/92), and ypT2 at 8.7% (8/92). 7 of 92 patients had disease recurrence of which 2 were local, 2 regional, and 3 distant metastasis. None of those with a complete pathologic response to neoadjuvant therapy recurred. The 3-year predicted disease-specific survival (DSS) was 98.6% and the 3-year overall survival 89.4%. Increased tumor diameter was significantly related to overall survival (p=0.047). Overall, the authors conclude that for appropriately selected patients (T1N0 lesions without adverse histologic features) TEM alone is equivalent to radical resection outcomes. Outcomes for T1N0 lesions with adverse outcomes and T2N0 lesions, TEM combined with chemoradiation, were similar to radical resection and sphincter preservation was improved. The authors highlight the need for better pre-operative imaging to more accurately stage prior to deciding which patients are eligible for TEM.

Proteomic signatures reveal a dualistic and clinically relevant classification of anal canal carcinoma.

Herfs M, Longuespée R, Quick CM, Roncarati P, Suarez-Carmona M, Hubert P, Lebeau A, Bruyere D, Mazzucchelli G, Smargiasso N, Baiwir D, Lai K, Dunn A, Obregon F, Yang EJ, Pauw E, Crum CP, Delvenne P.
J Pathol. 2017;241(4):522-533.

https://www.ncbi.nlm.nih.gov/pubmed/27976366

This multi-institutional study was performed to test the hypothesis that squamous cell carcinoma (SCC) of the anus encompasses more than one tumor type which can be delineated by the site of initial HPV infection. The authors note that recent studies regarding SCC of the uterine cervix have uncovered distinct biologies within these tumors which are dependent on the originally infected cell population. The study population in the current work consisted of 154 primary invasive SCCs, 69 dysplastic lesions, and 31 normal anal canal tissues acquired from hemorrhoidectomies. Through complex proteomic methodologies, the authors were able to identify two distinct subsets of SCCs with unique proteomic signatures. These two populations correlated with the location of the lesions, with those arising from the anal transitional zone appearing distinct from those occurring in the more distal squamous zone. Among the differential proteomic signatures were multiple keratin filaments (including CK7 and CK19), and protein families linked to desmosomes, DNA replication, and the cell cycle. Using this information, the authors were also able to show that immunohistochemical studies for CK7 and CK19 could differentiate these two subsets, with expression of these keratins being almost exclusively seen in cases of SCC arising in the anal transitional zone. Going one step further, the authors were able to show through correlation with the clinical findings, that SCC from the anal transitional zone had lower 5-year DFS and 5-year OS (56.2% and 55.1%) compared to SCC from the squamous zone (85.3% and 80.4%). These finding were only significant when HPV-related lesions were considered, as the rare HPV negative lesions, which exclusively arose in the squamous zone, also had poor outcomes. Finally, the authors were also able to correlate these findings with the microscopic features of these lesions with those arising in the anal transitional zone having a higher likelihood of being poorly-differentiated or basaloid. The authors conclude that SCC of the anus appears to include a heterogeneous group of lesions that can largely be separated based on their precise anatomic location and that these specific groups have prognostic significance.

An S100P-positive biliary epithelial field is a preinvasive intraepithelial neoplasm in nodular-sclerosing cholangiocarcinoma.
Nakanuma Y, Uchida T, Sato Y, Uesaka K.
Hum Pathol. 2017 Feb;60:46-57.
https://www.ncbi.nlm.nih.gov/pubmed/27984121

Nodular-sclerosing cholangiocarcinoma (NS-CCA) occurring in the absence of chronic biliary disease affects the intrahepatic large, perihilar, and distal bile ducts. These lesions are typified by early invasion and metastasis at the time of diagnosis, and precursor lesions are not well characterized. The authors used S100P immunohistochemistry to identify peri-tumoral fields of neoplastic biliary epithelial cells, which were found in 31 of 57 cases and showed flat, micropapillary, or papillotubular configuration. Based on the degree of atypia, these presumed precursor lesions were classified into groups A (low grade and similar to BilIN1-2 lesions), B (high grade dysplasia and consistent with BilIN3 or CIS), and C (overtly malignant and possibly representing cancerization). The authors further showed that groups A and B differed from invasive CCA in the expression of cancer-related molecules and MIB-1 index, whereas these

features in group C were relatively similar to those of invasive CCA. NS-CCA without chronic biliary disease may therefore have precursor lesions that are similar or identical to BilINs.

Nonmucinous Biliary Epithelium Is a Frequent Finding and Is Often the Predominant Epithelial Type in Mucinous Cystic Neoplasms of the Pancreas and Liver.
Zhelnin K, Xue Y, Quigley B, Reid MD, Choi H, Memis B, Adsay V, Krasinskas AM.
Am J Surg Pathol. 2017 Jan;41(1):116-120.
https://www.ncbi.nlm.nih.gov/pubmed/27673548

The goal of this study was to investigate the frequency of nonmucinous epithelium and the clinicopathologic associations in a cohort of 102 pancreatic and 34 hepatic cystic neoplasms characterized by ovarian-type stroma (mucinous cystic neoplasm, MCN). All but 1 patient were female (99.2%) with a mean age of 46.3 years (range, 19 to 81 y); 1 case with unequivocal ovarian-type stroma was found in the pancreas of a male (36 y). Nonmucinous/biliary epithelium characterized by epithelial cells ranging from flat to cuboidal to short columnar without obvious mucin or goblet cells was present at least focally in 102 of 104 (98%) pancreatic and 26 of 32 (81%) hepatic cases. Abundant nonmucinous/biliary epithelium (nonmucinous/biliary-predominant; defined as >50% nonmucinous/biliary epithelium) was noted in 50% and 38% of pancreatic and hepatic lesions, respectively. Of the 71 total cases with ≤50% nonmucinous/biliary epithelium, 8 cases demonstrated high-grade dysplasia (7 pancreas, 1 liver), and 14 demonstrated invasive adenocarcinoma (11 pancreas, 3 liver). Conversely, not a single case of high-grade dysplasia (P=0.007) or invasive carcinoma (P<0.001) was identified in the 58 cases with abundant (>50%) nonmucinous/biliary epithelium. Based on these findings, the authors have concluded that nonmucinous/biliary epithelium frequently occurs in MCNs of the pancreas and liver but there is insufficient evidence to regard cases with predominantly nonmucinous/biliary epithelium as separate entities. Importantly, the findings suggest that mucinous change is a harbinger of "progression" and only when abundant mucinous epithelium is present is there a risk of progression to malignancy.

"Simple Mucinous Cyst" of the Pancreas: A Clinicopathologic Analysis of 39 Examples of a Diagnostically Challenging Entity Distinct From Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms.
Krasinskas AM, Oakley GJ, Bagci P, Jang KT, Kuan SF, Reid MD, Erbarut I, Adsay V.
Am J Surg Pathol. 2017 Jan;41(1):121-127.
https://www.ncbi.nlm.nih.gov/pubmed/27740966

The authors of this study aimed to investigate the clinicopathologic features of the recently proposed entity of simple mucinous cyst of the pancreas, defined as a cyst > 1cm and lined by nonpapillary mucinous epithelium without ovarian-type stroma. Thirty-nine cases (F:M-4:1; mean age 65 yrs) were evaluated. The mean cyst size was 2.4 cm (range, 1.0 to 5.5 cm). Most were located in the body/tail (n=25, 64%) [head (n=8, 20%), uncinate process (n=3, 8%)]. 82% had elevated carcinoembryonic antigen (CEA) levels in the cyst fluid. Grossly, most cysts were unilocular (67%) and did not communicate with the main pancreatic duct (92%). The cysts were most often filled with clear or serous fluid (n=12, 48%). 7 cysts contained mucinous or

thick/viscous fluid (28%). The remainder were filled with "translucent mucoid to serous" (3), brown/green thick material (2), and serosanguinous (1) fluid. All cysts had a smooth internal lining with only one having focal papillary-like excrescences. The majority of the cysts (n=36; 92%) were lined by bland columnar mucinous epithelium qualifying as low-grade dysplasia (low-grade PanIN equivalent, PanIN 1A, 1B or 2). Focal high grade dysplasia (PanIN 3 equivalent) was noted in 3 cases (8%). 26 (67%) cases showed degenerative changes in the cyst wall. The lining epithelium of all of the cysts were CK7+ and had intact SMAD4. Twenty-nine (97%) cysts were lined by mucinous epithelium with a gastric phenotype (MUC5AC and/or MUC6 +). A Ki-67 index ≥10% was identified in 6 (21%) cases. P53 was only positive in 1 case (3%) that had focal high-grade dysplasia. Of the 27 cases tested for KRAS mutations, 15 (55%) harbored KRAS mutations. Based on these findings, the authors concluded that the term "simple mucinous cyst" is useful to apply to >1 cm mucinous cysts that do not have characteristic histologic findings of IPMN or MCN. KRAS mutations can be detected in these typically bland cysts; and, in rare instances, focal high-grade dysplasia may be present. Hence, these cysts should be viewed as neoplastic and treated similarly to other mucinous pancreatic cysts.

A Combination of MUC5AC and CA19-9 Improves the Diagnosis of Pancreatic Cancer: A Multicenter Study.

Kaur S, Smith LM, Patel A, Menning M, Watley DC, Malik SS, Krishn SR, Mallya K, Aithal A, Sasson AR, Johansson SL, Jain M1, Singh S, Guha S, Are C, Raimondo M, Hollingsworth MA, Brand RE, Batra SK.

Am J Gastroenterol. 2017;112(1):172-183.

https://www.ncbi.nlm.nih.gov/pubmed/27845339

The objective of this study was to analyze the effectiveness of utilizing MUC5AC as a biomarker for pancreatic adenocarcinoma in a large patient cohort. The authors note recent studies which demonstrated significant differential expression of MUC5AC in pancreatic adenocarcinoma compared with chronic pancreatitis and duodenal tissue through comparative genomic analysis. Expression of MUC5AC was evaluated through the use of immunohistochemistry while serum levels were assessed through the use of a sandwich ELISA assay. The study populations consisted of multiple independent patient cohorts from three institutions with a single individual training set and two validation sets. Immunohistochemical studies demonstrated MUC5AC expression in 22 of 29 (76%) pancreatic adenocarcinomas without reactivity in normal pancreas or chronic pancreatitis. Positivity was also noted in low and high-grade PanIN lesions. In the evaluation of circulating MUC5AC, the median levels in patients with resectable pancreatic tumors (67.2 ng/ml; IQR: 23.9-382.1) and unresectable lesions (389.7 ng/ml; IQR: 87.7-948.6) were significantly higher than benign controls (7.2 ng/ml; IQR: 0.4-26.5) and chronic pancreatitis (8.4 ng/ml; IQR: 1.5-19.2). After a value of 20.4 ng/ml was determined as the optimal differential cutoff, the sensitivity and specificity of elevated serum MUC5AC was 75%/73% in the differential of adenocarcinoma with benign controls and 75%/79% with chronic pancreatitis. When measured in combination with CA19-9, the diagnostic accuracy of serum MUC5AC increased. The authors conclude that there is differential expression of MUC5AC in pancreatic adenocarcinoma and its precursor lesions and serum MUC5AC levels may be helpful in the detection of pancreatic tumors, with the ultimate goal being assistance in early detection.

Targeted next-generation sequencing of FNA-derived DNA in pancreatic cancer
Mulder B, Mieog J, Handgraaf H, Saraqueta A, Vasen H, Potjer T, Swijnenburg, Luelmo S, Feshtali S, Inderson A, Vahrmeijer A, Bonsing B, van Wezel T, Morreau H
J Clin Pathol 2017;70:174–178
https://www.ncbi.nlm.nih.gov/pubmed/27672215

Next generation sequencing for targeted somatic and germline mutations in patients with pancreatic ductal adenocarcinoma (PDAC) is performed on fine needle aspirate (FNA) material as part of an ongoing study prior to surgery treatment. The authors utilized the AmpliSeq 50 gene Cancer Hotspot Panel V2 to interrogate genes believed to be significant in PDAC (KRAS, TP53, SMAD4 and CDNK2A) and report on one patient who had a primary PDAC seven years ago and then presented with a new pancreatic lesion. The clinical question was whether the new lesion was a separate primary PDAC or a local recurrence of the previous. Therefore, NGS was performed on both lesions and compared. The analysis showed the two lesions to have distinct mutational profiles, which provided support that the new lesion was a separate primary PDAC. The results from these studies altered treatment significantly in that a curative surgical option was chosen versus palliation for metastatic disease. In addition, the 50 gene panel revealed a germline CDKN2A deletion that predisposed the patient to developing PDAC, which was confirmed on a subsequent peripheral blood sample. Total pancreatectomy was performed due to the increased risk of an additional primary PDAC. In conclusion, the authors provide evidence for the benefit of genomic analysis on FNA material for the purposes of identifying possible germline mutations and targeted somatic mutations that may be relevant for treatment decision making. Potential limitations include how patients will be informed of their results regarding germline aberrations as well as lack of insurance reimbursement for testing outside of clinical guidelines.

Journals Reviewed (January & February 2017)
Histopathology
Archives of Pathology and Lab Medicine
Modern Pathology
American Journal of Clinical Pathology
Journal of Pathology
Journal of Clinical Pathology
American Journal of Pathology
Human Pathology
Cancer Cytopathology
American Journal of Surgical Pathology
Advances in Anatomic Pathology
Journal of Molecular Diagnostics
Gastrointestinal Endoscopy
Gastroenterology Clinics of North America
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