2015 Increased IgG4 Density and IgG4:IgG Ratios in Interstitial Lung Disease Are Associated with Rheumatologic Diseases and Usual Interstitial Pneumonia

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Background: IgG4-related lung disease has expanded to include an interstitial inflammatory pattern similar to non-specific interstitial pneumonia (NSIP) and even usual interstitial pneumonia (UIP). It is unknown how often NSIP or UIP have IgG4 plasma cell infiltrates, or what defines an abnormal number of IgG4+ cells in interstitial lung disease (ILD).

Design: We selected 14 cases of cellular NSIP, and 6 cases of UIP based on the presence of numerous plasma cells on routine staining. No patient had a history of IgG4 disease. Immunohistochemical staining identified IgG positive and IgG4 positive plasma cells. In areas of maximal numbers, IgG4 density and IgG4:IgG ratios were quantitated per high-power field (hpf) and averaged over 4 hot spots. There were 9 explants and 11 wedge biopsies.

Results: There were 9 women and 11 men; five patients had a history of autoimmune disease. No case had fibroinflammatory lesions suggestive of IgG4-related masses. Mean IgG4 density was 3.9 ± 4.8 in cases of NSIP (highest 14) vs. 8.2 ± 7.6 in cases of UIP (highest 22) (p=0.15). Mean IgG4 ratio was 6.8% (range 0-31) in cases of NSIP vs. 19.3% (range 5-32) in cases of UIP (p= 0.016). The highest IgG4 ratio in the NSIP group (31%) was in a woman with an elevated serum IgG4 level. There was a significant increase in mean IgG4+ plasma cells between patients with rheumatologic disease and those without (p=0.04). By multivariate analysis, a history of autoimmune disease (p=.006) and UIP histologic pattern (p=0.01) were associated with increased IgG4 ratio, as well as between autoimmune disease and IgG4 density (p=0.01).

Conclusions: IgG4+ cells are associated with autoimmune ILD, and are more numerous in UIP vs. NSIP. Although there is a wide range, an upper normal limit of interstitial plasma cells would be approximately 20/hpf, with an IgG4:IgG ratio of over 25%.

Quality Assurance

2016 Detecting Incidental Gallbladder Adenocarcinoma: When to Submit the Entire Gallbladder

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Background: Gallbladder adenocarcinomas are rare and a substantial proportion is detected incidentally in routine cholecystectomy specimens. It is currently unclear which findings in initial sections are associated with incidental adenocarcinoma, and sampling practices are highly variable when intestinal metaplasia (IM), low-grade dysplasia (LGD), or high–grade dysplasia (HGD) are found upon routine review. The purpose of this study was to correlate findings in initial sections of cholecystectomy specimens with final diagnoses, in order to determine whether detection of any of these features warrants more extensive sampling.

Design: We retrospectively reviewed all cholecystectomy specimens over a 26-month period in order to identify those that had additional sections submitted following review of the original slides. Four pathologists with an interest in gastrointestinal pathology, who were blinded to the original diagnoses and findings on the additional sections, reviewed the initial slides (mean: 2, range 1-7) to assess for the presence or absence of IM, LGD (including BilIN 1 and 2), HGD (BilIN 3), or adenocarcinoma. Diagnostic discrepancies were resolved by consensus.

Results: Additional sections were submitted in 51 of 4059 (1%) cases. These contained IM (n=44, 86%), LGD (n=18, 35%), and HGD (n=5, 10%). A mean of 10 additional cassettes were submitted (range: 2-26). All cases with dysplasia were submitted entirely. Interobserver agreement was fair (κ=0.4) for LGD and high (κ=0.8) for HGD. The diagnosis of IM was agreed upon by all pathologists in all cases. Five incidental adenocarcinomas were detected, including 2 (40%) that were not present in initial sections. These two cases displayed HGD in the original slides, which was independently diagnosed by all four pathologists. The remaining 3 adenocarcinomas were associated with HGD in the background mucosa. Incidental cancers were not detected in cases with only IM or LGD on initial sections; LGD was detected in 8 cases with IM on initial sections, and 2 cases with LGD displayed HGD upon further sampling.

Conclusions: The presence of HGD should prompt complete submission of cholecystectomy specimens, as they may harbor adenocarcinoma and require further treatment. Pathologists should consider seeking a second opinion when LGD is present and submitting additional sections that target abnormal areas; examination of the entire specimen is needed if these yield HGD. Cases that show IM are adequately examined with routine sampling in the absence of gross abnormalities.

2017 Should the Prenatal Cell-Free DNA Screening Test Replace the Quad Screen for Detection of Fetal Trisomies?

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Background: Cell-free DNA (cfDNA) Screening Test is a non-invasive genetic test that is used to identify chromosomes 13, 18, and 21 and the sex chromosomes. The assay can detect the most common autosomal trisomies and some sex chromosome abnormalities. The test utilizes a maternal blood sample, can be used from 10 weeks through the duration of the pregnancy, and is the only 3rd trimester screening test. The assay is significantly more expensive than the Quad Screen and is currently not covered by most third party payers or Louisiana Medicaid.

Design: We routinely receive requests for either a Quad screen or a cfDNA Screening Test. Our department recently noticed an increase in cfDNA test requests. Retrospectively, we reviewed requests for the Quad Screen or Cell-Free DNA Screening Test over the last 9 months.

Results: There were 57 requests identified. Forty-three were for cfDNA testing with alpha-fetoprotein (AFP), and 14 were for Quad screen with cfDNA testing. Thirteen of 14 Quad screen test results were negative and correlated with cfDNA findings. One patient had a positive Quad Screen suspicious for trisomy 18 but a negative cfDNA result. Fifty-five patients had negative cfDNA results. Two patients had positive cfDNA test for Trisomy 21. Results of cfDNA tests accurately predicted clinical outcome.

Conclusions: Our study suggests that the cfDNA test has higher sensitivity and lower false positive rate than a Quad Screen. The utilization of cfDNA test may decrease the use of more invasive testing such as amniocentesis. Ordering cfDNA test combined with AFP appears to have a greater accuracy, is a more cost effective approach for the evaluation of fetal trisomies, and is available in the first trimester.

2018 Discordances in Evaluation of Melanocytic Lesions and Its Impact on Management: A Study of 1518 Cases

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Background: Accurate diagnosis of melanocytic lesions carries a significant clinical implication as appropriate management does not only depend on the correct diagnosis but varies according to the pathologic stage. The objective of this study is to evaluate the degree of discordance between primary histopathologic diagnosis and secondary review of melanocytic lesions, parameters of melanoma, and the subsequent impact on clinical management and follow-up.

Design: In a retrospective review of 1518 referral cases to MD Anderson Cancer Center (MDACC) of melanocytic lesions from 1/2010 to 1/2011, initial diagnoses from the referring institution were compared to the MDACC second opinion reports. If any discordance was noted at time of review, a consensus diagnosis by at least 4 different dermatopathologists was rendered prior to approving the discordance. The discordances were classified as (i) major discordance if they resulted in change in diagnosis and stage of melanoma and thus, the clinical management and (ii) minor discordance if there was no impact on clinical management.

Results: The concordance rate was 100% among metastatic melanoma, (n=214 cases, 14%). Discordance in primary melanocytic lesions occurred in 10.7% of cases (140/1304). Minor and major discordances were found in 38% (n= 53) and 62% (n=87) of the primary melanocytic lesions, respectively. Major discordance categories included inaccurate mitotic count 40/87 (46%), followed by change in diagnosis 39/87 (44.9%), change in Breslow thickness 6/87 (6.9%), change in Breslow thickness and mitotic count 1/87 (1.1%), and change in Breslow thickness, mitotic count and ulceration 1/87 (1.1%). Follow-up ranged between 6 to 131 months (mean 52 months). Among cases with major discordance, 80% (n=69) showed no evidence of residual/recurrent disease, 7% (n=6) died of disease, 2% (n=2) died of other causes, 2% (n=2) are alive with disease, and 9% (n=8) were lost to follow-up.

Conclusions: Our results show that critical review of melanocytic lesions may lead to significant changes in the diagnosis of melanoma, tumor classification as well as staging, thus resulting in critical changes in clinical management and impacting patient survival.

2019 Checklist Implementation for Intraoperative Consultations: Improved Quality and Safety

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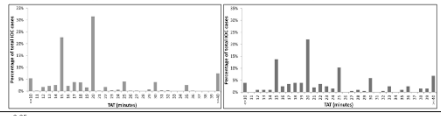
Background: Intraoperative consultation (IOC) is a fundamental part of surgical pathology, providing surgeons with real-time information central to patient care. Correct IOC slide labeling, typically manually performed in a time pressured setting, is critical to avoid patient harm. A recent serious adverse event due to IOC labeling mixup prompted workflow redesign. A checklist was implemented aimed at standardizing slide labeling and monitoring other data points central to quality management. Checklist effects on slide labeling defect rates and frozen section TAT were studied.

Design: Data were collected for all IOC cases over a 9 month period. Slide labeling defect rates and IOC TAT were recorded and compared for the pre and post implementation periods. A slide labeling defect was defined as a lack of any 3 elements on a slide label per hospital policy: patient name, medical record number (MRN), and specimen designation by surgeon.

Results: 839 IOC cases were analyzed. Pre-intervention slide labeling showed that the patient's name, MRN and specimen designation were absent in 23%, 39% and 84% of cases, respectively, with 85% of cases containing at least one defect (n=565). Post intervention, labeling data revealed that the patient's name, MRN and specimen designation were absent in in 18%, 15% and 24% of cases, respectively, with 27% of cases containing at least one defect (n=274). There was statistically significant improvement in all aspects of slide labeling (P<0.001 on all 3 elements). Mean TAT was 21.55 minutes pre-intervention versus 23.21 minutes post-intervention and the change was insignificant (P=0.071). Post-implementation, there was a significant decrease in the number of cases with TATs of exactly 15 or 20 minutes (55% pre and 35% post, p=0.024). This suggests more honest TAT reporting with a shift towards normally distributed values.

Quality Metric	Pre-Intervention (6 months, N=565) no. of defects (rate, %)	Post-Intervention (3 months, N=274) no. of defects (rate, %)	Defect Reduction (%)	P*
Slide Labeling				
Patient name	130 (0.23)	32 (0.08)	65.22	P<0.001
MRN	218 (0.39)	41 (0.15)	61.54	P<0.001
Specimen designation	472 (0.84)	65 (0.24)	71.43	P<0.001
Missing at least one identifier	481 (0.85)	74 (0.27)	68.24	P<0.001
	Pre-Intervention (6 months, N=521)	**Post-Intervention (3 months, N=204)**		**P****
TAT mean (minutes)	21.55	23.21		p=0.071
TAT of 15 or 20 minutes (%)	55%	35%		p<0.024
TAT distribution				

* χ^2 test at significance level $\alpha = 0.05$
** Two-tailed t-test at significance level $\alpha = 0.05$

Conclusions: The implementation of a standardized IOC checklist improved slide labeling quality and safety, with a significant reduction in slide labeling defects at our large academic medical center. In addition, this improvement did not affect mean TAT and may have increased quality of IOC TAT data reporting.

2020 Assessing Accuracy of HIV and HCV Testing Using Sigma-Metrics

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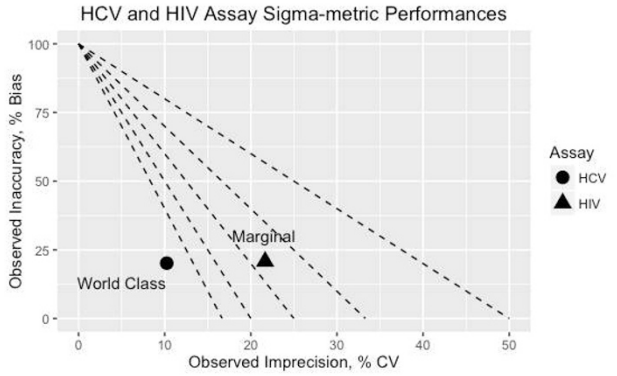
Background: Molecular viral load testing is used for clinical decisions when physicians monitor patients who are infected with HCV and HIV. For response-guided management of patients, assays should be accurate and precise. Sigma-metrics is a popular quality management system which provides a single number to demonstrate the bias and precision of the test. We aimed to see our laboratory's sigma-metrics values for HCV and HIV assays based on our QC data.

Design: To evaluate our HCV and HIV-1 viral load (Abbott Molecular's m2000sp for sample prep and m2000rt for real-time amplification and detection) assays, we used company provided controls at two analyte concentrations to calculate precision and bias data. Our pathology report uses log-copies/mL as units for both assays. We transformed log-copies/mL to copies/mL for our calculations. There aren't set total allowable errors (TEas) for these assays. In our study, TEas were accepted as 100% for both assays since this value was used in previous studies (1). Sigma-metrics were calculated as follows: Sigma-metric = (TEa-bias)/CV (values expressed as %).

Results: HCV results showed that for 6.12 copies/mL standard value, average bias was 24.49, CV was 8.41 and sigma-metric was 9.0; for 2.74 copies/mL standard value, average bias was 15.79, CV was 12.07 and sigma-metric was 7.0. Our HIV results showed that, for 4.87 copies/mL standard value, average bias was 16.33, CV was 16.97 and sigma-metric was 4.9; for 2.87 copies/mL standard value, average bias was 25.22, CV was 26.35 and sigma-metric was 2.8. Average sigma-metric values for HCV and HIV were 8.0 and 3.9, respectively.



Conclusions: HCV assay showed an average of >6 sigma-metric value, a 'world-class' performance. HIV assay's average sigma-metric value was in the 3 to 4 sigma-metric value bracket, a 'marginal' performance. Monitoring HCV and HIV levels in response-guided management requires high performing assays. As commonly used in controlling various analytical methods, sigma-metrics could also be utilized for the assessment of quantitative molecular assays' performances. Ref: (1) Westgard S. et al. Sigma Metrics for Assessing Accuracy of Molecular Testing. Clin Microbiol News. 2015;37:103–10.

2021 Antinuclear Antibody (ANA) 2016 Statistical Analysis. A Comparison of Laboratory Practice and Result Reporting Between the US and International Labs

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Background: ANA detection is a cornerstone in diagnosis of autoimmune diseases. Laboratories utilize different methods and diverse protocols in determining ANA status. IFCC, American College of Rheumatology and several other professional organizations have published guidelines for testing and reporting ANA, preferentially by immunofluorescent method (IFA) using Hep-2 cells. Little data exists describing the actual laboratory practice amongst US (USL) and international laboratories (IL).

Design: The CAP provides the world's largest diagnostic immunology proficiency (PT) testing survey, distributed to 5847 laboratories worldwide in 2016. Participants are sent blind specimen. A questionnaire was sent to laboratories with the ANA PT sample SA 2016. After data adjustments, there were 1206 surveys for analysis (942 USL, 264 IL).

Results: The overall response rate was 21% (1206 out of 5847 kits) and the secondary response rate based on the ANA products was 66% (924 out of 1403 ANA kits). There was a significantly higher % of IL using indirect IFA to screen for ANA. More IL indicated the method of testing in the name of the test or mention specifically in the report compared to USL – test name USL 25% vs IL 55% and test report USL 35% vs IL 53%. Multiplexed bead immunoassay had a much lower concordance rate compared to other two methods for expected positive ANA. Percentage of USL using multi-bead immunoassay was significantly higher than that in IL.

There was a significantly higher % of IL reporting Hep-2 substrate used as indicated by professional guidelines: 175 (92%) vs. 342 (75%). Most USL screen ANA IFA at a titer of 1:40 (72%) compared to IL (39%) while more IL (58%) screened at 1:80 or greater compared to USL (27%). Clinical pathologists reviewed and interpreted the ANA IFA in (IL 25%) compared to USL (7%).

Conclusions: IL participants have adopted the guidelines for reporting ANA tests using Hep-2 (IFA) and reported the method used for ANA testing in their reports more quickly than USL, all statistically significant. *P*-value < .001.

2022 Flow Cytometry Provides a Quantitative Benchmark for the Utility of Diagnostic Tests

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Background: The utility of new diagnostic testing modalities, particularly molecular methods, are best assessed by comparing them to existing testing. Flow cytometry is a time tested diagnostic tool for the diagnoses of hematopoietic malignancies and quantitative assessment of its utility would serve as a useful benchmark for new methods in any diagnostic laboratory. To create such a benchmark, we quantified the diagnostic utility based on the failure and the redundancy of the flow result in the context of histologic and immunohistochemical studies, and the cost of flow cytometry on 100 sequential cases of lymphoma.

Design: In our practice, all biopsies performed for a concern of lymphoma are studied by flow cytometry. Reports for 100 sequentially diagnosed cases of lymphoma (7 months in 2015) were reviewed. The Flow results were scored as contributory based on these criteria: 1) detection of a morphologically occult clone; 2) aided in typing /subtyping of the lymphoma; 3) detection of a coexisting lymphoma; 4) lack of redundancy with histological and immunohistochemical results. Billing codes were tabulated for all cases; charges were estimated from the 2016 charge master.

Results: Flow cytometry was performed on 78% of the cases with a final diagnosis of a lymphoma. A mode and median for the flow markers were 13 ($2184); the mode and median for the number of immunohistochemical stains were 8 and 9.5 ($2076). 2 cases had neither IHC nor flow, 38 had IHC or flow, 60 had both. Flow was scored as contributory in 35 cases and non-contributory to 43 cases.23 of the non-contributory flow studies were due to limited specimens (poor preservation or small size). Flow was scored as non-contributory for the remaining 20 cases because the results were redundant with those obtained by other methods.

Conclusions: Among the 100 cases of lymphoma studied, flowcytometry was found to be diagnostically contributory in 35% of cases.

Assuming that all specimens concerning for lymphoma are studied by flow cytometry, there is an additional charge of $830/specimen attributable to non-contributory flow studies.

These data provide a quantitative benchmark for consideration of new testing modalities: 35% likelihood of contributing to a diagnosis and an expectation of about $800 for non-contributory findings.

2023 Analysis Four-Years into a Universal Lynch Syndrome Screening Program Highlights Challenges and Opportunities

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Background: In October 2012 we instituted a universal Lynch syndrome (LS) screening program in colon cancer (CRC). All CRCs are screened for deficient (d) DNA mismatch repair (MMR) function with immunohistochemistry (IHC). For IHC results suggestive of LS (i.e., MSH2d, MSH6d, PMS2d), the pathologist emails the treating clinician and a genetic counsellor with the abnormal result. For MLH1d tumors, the pathologist initiates *BRAF*-mutation testing; our MMR IHC interpretive comment for these cases states that, especially given wild-type *BRAF*, genetic counselling and/or *MLH1* promoter methylation testing should be considered, both of which are clinician-initiated. Reported rates of *BRAF* mutation in MLH1d CRCs range from 40-83%. We initiated this retrospective chart review of our LS screening program to determine the frequency of *BRAF* mutation in our MLH1d cohort (which impacts the relative value of *MLH1* promoter methylation testing). Based on somewhat surprising results, we expanded the lookback to all dMMR tumors, which will inform decisions about our screening program going forward.

Design: Cases were identified based on searching the pathology database for all MMR IHC results. For each case, patient charts were reviewed for the following: MMR IHC, *BRAF* mutation, *MLH1* promoter methylation, and germline mutation testing results; and whether a patient saw a genetic counsellor.

Results: Of 678 CRCs screened, 104 (15%) had abnormal MMR IHC: 77 MLH1d (11%) (2 with secondary loss of MSH6), 15 MSH2d (2.2%) (1 with concurrent EpCAM loss), 7 MSH6d (1.0%), 4 PMS2d (0.6%), and 1 null (0.1%) (all 4 proteins lost). *BRAF*-mutation testing was successfully initiated in 89% of MLH1d tumors, **63%** of which were *BRAF*-mutant. Among 25 *BRAF* wild-type patients, only 9 (36%)

saw a genetic counsellor, 8 (32%) had *MLH1* germline testing (positive in 2; 25%), and 1 (4%) had *MLH1* promoter methylation testing (which was positive). Among 25 in-house patients with other dMMR patterns, 11 (44%) saw a genetic counsellor and 12 (48%) had germline mutation testing (positive in 9; 75%).

Conclusions: Our MMR IHC-based universal LS screening program in CRC successfully identifies dMMR tumors at the expected frequency of abnormal patterns. There are several challenges after this initial step. Based on our results, we will implement the following: 1. maintain a prospective LS screening database, following up on appropriate patients having not seen a genetic counsellor, 2. re-educate pathologists on the role of *BRAF*-mutation testing in MLH1d tumors, and 3. bring *MLH1* promoter methylation testing in-house and make it pathologist-initiated.

2024 Establishing and Improving Diagnostic Precision in an Academic Non-Subspecialized Practice

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Background: In many practices, interpathologist diagnostic variability generally is unknown, often under estimated, and leads to disagreements in secondary review activities (e.g., conference review), which may compromise patient care. We developed a method to improve agreement by measuring a baseline precision level, assessing root causes of disagreement, and developing daily practice improvement methods.

Design: We measured the level of precision of six pathologists for endometrial biopsy diagnoses of benign, simple hyperplasia without atypia, complex hyperplasia with and without atypia, and FIGO 1 adenocarcinoma. From our slide files, we prepared a 25 case test set of five cases of each of the five diagnoses. Each pathologist, blinded to the original and study group diagnoses, examined the case set and selected one of the five diagnoses and expressed a level of diagnostic certainty on each case. We measured pairwise κ with confidence interval and correlated pathologist, group, diagnostic category and level of certainty with level of agreement. We performed root cause analysis using a categorical Fishbone method to assess causes of pairwise disagreement to design improvement strategies.

Results: The pairwise κ ranged from .24 to .58 with essentially all pairwise κ having a confidence interval of .12, representing fair to moderate agreement. The mean pathologist pair disagreement frequency was 45.6% and the mean two-step disagreement frequency (e.g., complex hyperplasia without atypia to adenocarcinoma) was 11.4%. Individual case confidence level poorly correlated with agreement. Root cause analysis indicated that latent factors contributing to disagreement were variability in pathologist use of specific diagnostic categories, existence of pathologist subgroups with similar diagnostic patterns (e.g., more conservative patterns of diagnosis), moderate differences in criteria/pattern mental maps, bias, and specimen artifact compromising the interpretation.

Conclusions: Fair to moderate pairwise pathologist agreement may be seen in practices that use specific methods to improve individual case diagnostic agreement, such as secondary pre-signout review, but these methods are unable to eliminate latent factors that contribute to error. Methods for improvement involve broad team consensus strategies, using pre-signout review for pathologists pairs who have dissimilar diagnostic patterns, targeting borderline diagnostic categories, and focusing on bias secondary to artifact.

2025 Implementation of a Quality Assurance (QA) Initiative for Improving Pathology Diagnosis and Molecular Subtype Characterization of Breast Cancer in Zambia

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Background: Breast cancer is the second most common female cancer in Zambia, a low resource sub-Saharan African country. Studies from neighboring sub-Saharan countries report a high incidence of triple negative disease (ER-/PR-/HER2-). However, accuracy of immunohistochemistry (IHC) results is of concern due to the lack of QA. Chain of custody can be disrupted and times critical to IHC performance are not recorded. Thus, reported incidence of TNBC may not be accurate.

Design: Data was not available to insure specimen and antigen integrity prior to this collaboration. A Quality Assurance (QA) program was implemented with new workflows that incorporated CAP/CLIA requirements for recording chain of custody and critical times during processing. An on-site workshop was held to introduce the QA program with continuing monthly web-based meetings to review results. Manual IHC was introduced. Allred scoring and CAP/ASCO guidelines were used to determine ER/PR status, which was considered valid only in the presence of positive internal controls. Luminal A (Lum A) cancers were defined as ER+/PR+/HER- with a Nottingham mitotic score of 1 while mitotic scores of 2 or 3 were classified as Luminal B (Lum B). HER2 type was defined as any HER2+ (>10%, 3+), and triple negative as ER-/PR-/HER2- (TNBC). FISH was not available and so equivocal HER2 were considered negative.

Results: QA and IHC data have been collected for 10 patients to date, ranging in age 29-80 years (average and median 51 and 50.5 years). Fixation times were all within CAP recommendations. One patient had no residual tumor after neoadjuvant therapy. The remaining 9 patients tested had positive internal ER/PR controls. Results are given in Table 1 for disease subtype distribution and in Table 2 for fixaiton and turnaround times.

ER+/PR+	5/9 (55%)
Lum A	1/9 (11%)
Lum B	2/9 (22%)
HER2+	2/9 (22%)
TNBC	4/9 (44%)

Times:	Warm Ischemic (hh:mm)	Formalin Fixation (hh:mm)	Turnaround (d)
Average	1:17	23:03	7
Median	0:30	23:00	7
Maximum	4:43	27:30	11

Conclusions: A QA program for breast cancer specimens to insure IHC accuracy and improve turnaround times has been implemented in Zambia as a model for low resource countries. Low cost protocols, an on-site workshop, close engagement of the Zambian physician team, and continuing communications are believed to have contributed to its success.

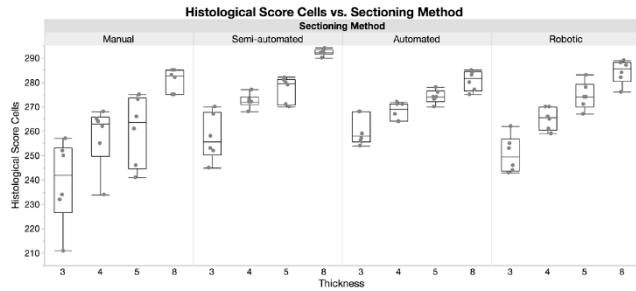
2026 Robotic and Semi-Automated Microtomy Can Decrease Variability in HER2 Staining Intensity

Elizabeth Chlipala, Scott Crawford, Joshua Johnson, Kevin Chu, Alyicia Rios, Farah Patell-Socha, Karen Copeland, Allen M Gown, Regan Fulton. Premier Laboratory, Longmont, CO; Array Science, Sausalito, CA; Sakura Finetek, Torrance, CA; Horizon Discovery, Cambridge, United Kingdom; Boulder Statistics, Boulder, CO; PhenoPath, Seattle, WA.

Background: Advancements in targeted therapeutics demand increasingly quantitative evaluation of biomarker expression in prognostic and predictive assays. Calibration of such assays is critical for accurate results. Pre-analytic variables, such as section thickness, are known to influence IHC staining intensity. We hypothesized that the variability of HER2 IHC staining intensity would correlate inversely with the degree of automation of microtomy instrumentation

Design: We investigated the influence of automated microtomy methods on the intensity of IHC staining using genetically defined HER2 cell line reference standards. We compared four methods: manual (Leica, RM2145), semi-automated (Microm, HM355S with Cool-Cut attachment), automated (Tissue-Tek AutoSection, Sakura Finetek), and fully robotic (Tissue-Tek SmartSection, Sakura Finetek). Cell culture microarray blocks with cell lines expressing HER2 protein at controlled levels were sectioned at 3, 4, 5 and 8um using the four methods. Six sections from each method were split into two staining runs using the HercepTest assay. Whole slide imaging was performed with an APERIO ScanScope XT. Image analysis was performed with a modified cell simulation algorithm to detect membrane staining using Definiens Tissue Studio ver4.2. An H-score was generated. A 2+ HER2 expressing cell line was chosen for analysis.

Results: MeanHER2 staining intensity increased with section thickness with all methods. The coefficient of variation for staining intensity decreased with increasing section thickness across all methods. Variation was observed to decrease with greater levels of sectioning automation.



Conclusions: Cell line reference standards and digital image analysis can be used to assess the reproducibility of IHC assays. Greater staining variability is seen among thinner sections. In borderline cases for HER2 and other assays, these variations may be clinically significant warranting further investigation. Automation in microtomy may provide a means to decrease variability in immunohistochemical assay results.

2027 High Sensitivity and Specificity Exists Between Frozen and Permanent Sections in Renal Transplant Biopsies

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Background: Frozen sections are used to evaluate tumors and margins as daily practice in Pathology with high specificity and sensitivity (>90 % for both indices at the national level and in our department). The correlation between frozen section tissue for immunofluorescent (IF) studies and permanent sections for light microscopy, along with electron microscopy, is critical for determining a final diagnosis in renal pathology. Therefore, we studied the correlation between the frozen sections for IF studies and separate fragments of tissue for permanent sections in our renal transplant biopsies for quality control purposes.

Design: We gathered a total of 122 renal transplant biopsy cases for analysis. The frozen sections of renal transplant biopsies were divided into two categories: group 1 - no inflammation (n = 63), and group 2 - with inflammation (n = 59). Subsequently, the permanent sections were categorized as either having no inflammation (such as is seen in acute tubular injury) or with inflammation (such as is seen in acute cellular rejection or BK virus infection). Finally, the findings between the frozen and permanent sections were correlated to calculate sensitivity and specificity.

Results: For group 1 (no inflammation), the correlation between the frozen and permanent section diagnoses was 92.1 % (58/63); the five non-correlated cases showed either borderline changes or mild acute cellular rejection on the permanent sections. For group 2 (with inflammation), the correlation between the frozen and permanent sections diagnoses was 94.9 % (56/59); the 3 non-correlated cases showed no significant inflammation on the permanent sections. Using frozen section technique as a "new test" to detect inflammation while taking permanent sections as the gold standard gives a sensitivity and specificity of 91.8 and 95.1%, respectively.

Conclusions: Our data suggests that renal biopsy tissue dissected into sections to freeze for IF studies and sections for light microscopy was adequately correlated, based on the high sensitivity and specificity identified in the renal transplant biopsies.

2028 XIST as a Tool for Resolving Specimen Contamination Events

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Background: In a busy surgical pathology laboratory, the prevention of specimen cross-contamination is crucial. However, contamination events such as specimen mix-ups, cross-overs, and floaters are not fully avoidable. Previous work has shown that up to 13% of these events may involve the transfer of malignant tissue. This can create serious diagnostic challenges for the pathologist, with corresponding implications for patient care. The work-up of contamination events involves confirming the presence of a marker in either the contaminant or the patient tissue, but not both. Sequencing-based assays are the standard of care, but can be hampered by low cellularity and the challenges of microdissection.

Markers chosen for working up contamination cases should normally occur only in a well-defined population. *XIST*, the gene which silences an X chromosome in human female cells, has the potential to serve as such a marker, as it is normally expressed in all nucleated female cells and absent in male cells. Furthermore, *XIST* expression can be evaluated using RNA in situ hybridization (ISH), a technique amenable to automation and available in most laboratories. In this study, we evaluated the utility of ISH for *XIST* RNA in the work-up of suspected specimen contamination.

Design: Sections from excisions and biopsies of 151 gastrointestinal carcinomas, including colorectal, esophageal, hepatocellular, and pancreatic ductal carcinomas, and 39 breast carcinomas were evaluated microscopically for expression of *XIST* RNA by ISH (Affymetrix, CA), performed on an automated platform (Leica, IL). Tumor and benign stroma were present on all slides. Positivity was visualized as a large red intranuclear dot.

Results: Intratumoral stromal cells and lymphocytes were uniformly negative in male patients (n=96). In every female patient (n=94), 60-70% of all cells demonstrated *XIST* positivity. In two male patients with hepatocellular carcinomas, representing 2% of all evaluated male tumors, *XIST* expression was observed in tumor cells. 21% of tumors (n=20) arising in female patients demonstrated loss of *XIST* expression exclusively in tumor cells.

Conclusions: RNA ISH for *XIST* is an easily implementable and accessible platform to differentiate male and female cells, and thus assist in resolving specimen mix-ups and cross-contamination. Although this assay is less reliable if only neoplastic contaminant cells are available for analysis, it could serve as a useful first-line test in the 50% of cases which involve a gender mismatch between the patient and the contaminant tissue.

2029 Root Cause Analysis of Bone Marrow Biopsy Processing to Increase Efficiency, Quality, and Interdisciplinary Communication

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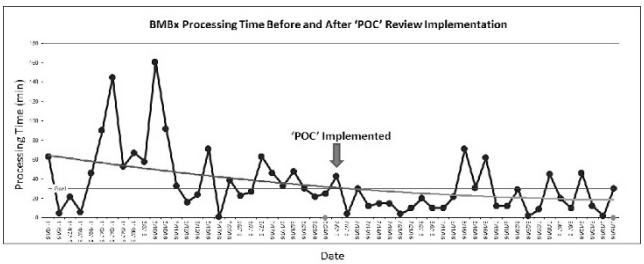
Background: In our pediatric hospital, it was observed that approximately 40% of bone marrow samples encountered delays in processing following adoption of a new electronic medical record (EMR). Samples are held by the clinical laboratory until order discrepancies are resolved, which can lead to cellular degradation, repeat procedures, increased costs, and undue stress to the patient. The diagnosis of pediatric hematologic disorders is highly interdisciplinary, involving physicians, operating room (OR) staff, nurses, clinical laboratory scientists (CLS), and pathologists. To approach this problem, a multidisciplinary team was assembled to analyze the bone marrow biopsy (BMBx) process and identify the cause of delays and to create solutions for decreasing processing time.

Design: Root cause analysis (RCA) was performed through direct observation of the entire BMBx process, from OR to pathology sign out. Focus group interviews were held with physicians, nurses, OR staff, and CLSs to identify potential issues. Sample processing was documented, and time between receipt of specimens in pathology and accessioning of specimens was determined. Data was collected for 45 weeks. Specimens that were received overnight were not included.

Results: The primary delay in BMBx processing was determined to be discrepancies between paper requisitions and EMR orders, which required the laboartory to contact the clinical teams. To resolve this, we implemented mandatory review of the patient's 'Plan of Care' (POC), an existing EMR feature. The POC is entered by the clinical team and documents the testing required for each patient. This change eliminated redundant paper requisitions, which removed an additional source of error. Time spent in processing BMBx was reduced from an average of 48.5 minutes to 21.8 minutes (44.9% reduction; p=0.004) over a 45 week period.



Conclusions: Delays in processing BMBx specimens at our hospital were primarily due to discrepancies in EMR orders and paper requisitions. Implementing review of an EMR feature eliminated redundant paperwork and significantly decreased processing time in the clinical laboratory by almost half. These results demonstrate the benefit of RCA in the clinical laboratory, and may direct efforts towards future improvements.

2030 One H&E Stain Is Sufficient for Evaluation of Sentinel Lymph Nodes in Breast Cancer

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Background: The optimal method of evaluating sentinel lymph nodes (SLN) has not been standardized. Common methods are to perform 3 H&E levels and/or cytokeratin staining, despite College of American Pathologists' recommendations in 2000 that a single H&E is sufficient. 200-500 microns between levels has been suggested; however, how many labs execute this protocol for SLN is questionable as this protocol can be challenging for histology labs. In breast cancer (BC), metastases are divided into macrometastases (> 2 mm), micrometastases (>0.2 mm to 2 mm), and isolated tumor cells (ITC) (≤0.2 mm or <200 cells), with small metastases having minimal clinical significance. The aim of this study was to evaluate the diagnostic utility and clinical impact of 3 H&E sections in SLN in BC.

Design: The databases of two different hospitals were searched for the period of January to September 2016 for BC excisions with positive SLN. All SLN were grossly serially sectioned perpendicular to the long axis into 2-3 mm slices and 3 H&E levels were cut. For H&E sections, in hospital A, the SLN protocol is 30-40 microns between levels and in hospital B, it is 150 microns between levels. The 3 H&E levels of positive SLN were reviewed and pathologic data recorded.

Results: 59 total cases were identified with 29 cases eligible for the study with a total of 50 SLN. Of the 50 SLN, 27 were macrometastases, 18 micrometastases, and 5 ITC. 44 SLN (88%) showed tumor cells in all 3 levels while 6 SLN (12%) in 6 different cases did not show metastases on all 3 levels – 3 ITC, 2 micrometastases, and 1 macrometastasis measuring 2.5 mm. The macrometastasis and 2 ITC all involved cases in which there were several positive SLN. The 2 micrometastases were 0.25 mm and 0.4 mm and interestingly, both cases were tubular carcinomas. One ITC case did not show other metastases. In the latter 3 cases, subsequent ALND was not performed.

Conclusions: The three levels for SLN rarely show metastasis on only one or two levels and even when it does, has essentially no impact on clinical treatment. In our study, there were two different SLN block cutting protocols with no difference in the results, although the distance between levels in both protocols are smaller than recommended. Half the cases where tumor cells were not seen on all 3 levels had concomitant positive SLN. In the other half without concomitant positive SLN, subsequent ALND was not performed. Based on these findings and data showing minimal clinical impact of small metastases, one H&E should be sufficient for SLN evaluation.

2031 Dual-Purpose Biopsy Container and Tissue Processing Cassette

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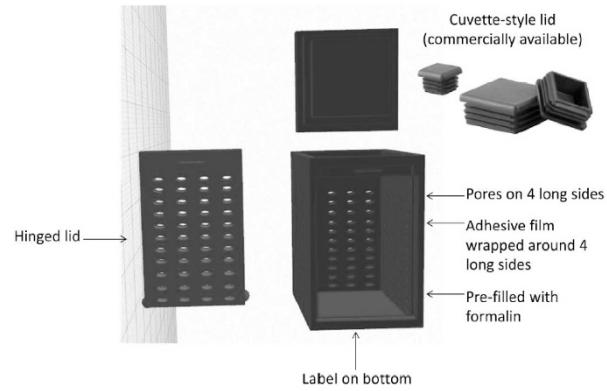
Background: Sources of error from grossing a biopsy are numerous. The "Dual-Purpose Biopsy Container and Tissue Processing Cassette" (Patent Pending) described here aims to eliminate specimen loss, contamination, and incorrect specimen identification arising from the process of grossing a biopsy while improving turn-around time and decreasing hands-on time.

Design: This container (Figure 1) is rectangular, approximately 2.6 x 1.7 x 1.7 cm, pre-filled with formalin and made of optically clear plastic. Mesh openings on four sides are covered with removable adhesive film. Histology personnel access the specimen through the larger, hinged lid. Clinicians place the specimen in the container through the press-in cuvette-style lid. The bottom comes pre-printed with a QRS code and unique alpha-numeric code, which is copied onto the requisition sheet. Additional configurations will also be presented.



Results: The clinician prints an adhesive label and places it on top of the removable film, then sends the specimen to the pathology laboratory. Laboratory personnel label the bottom of the container with the case number and the patient's name with a modified cassette printer or adhesive label. The clinician's label and the adhesive film are removed and placed on the requisition sheet. The mesh-like holes are now exposed and the container is placed on a negative-pressure surface or paper towel to remove formalin. The specimen is measured and described through the clear container and a gross description is generated. The dual purpose container is now ready for the tissue processor without opening the container in the pathology laboratory.

Conclusions: This dual-purpose container eliminates opportunities for specimen contamination, loss and mis-identification.

2032 Comparison of Breast Carcinoma Nottingham Grading by Glass Slides versus Digital Whole Slide Images: Variability Increases Using Digital Format

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Background: While diagnostic variability in histopathological Nottingham grading of breast cancers has been reported, little is known about how evaluation of tumor grade using digital images might affect concordance among pathologists (inter-observer agreement) or how it might affect reproducibility (intra-observer agreement).

Design: Test sets of breast biopsy cases were independently reviewed by 208 U.S. pathologists in two phases separated by ≥ 9 months. In each phase, pathologists were randomly assigned to interpret cases using either glass microscopy slides or digital whole slide imaging. Included in this study were Nottingham Grade interpretations of 22 invasive carcinoma cases from those sets. Cases were independently interpreted by pathologists in each format and phase totaling 2045 interpretations for our analysis. Inter- and intra-observer percent agreement and kappa values were calculated.

Results: The Nottingham Grade intra-observer agreement was highest when the glass format was used in both phases (73%, 95%CI: 68%,77%), intermediate with digital in both phases (68%, 95%CI: 61%,75%) and lowest when the format changed between phases from glass to digital (61%, 95%CI: 55%,67%). In Phase I, Nottingham Grade inter-observer agreement was significantly higher (p<.001) using glass format versus digital (68%, 95%CI: 66%,70% vs. 60%, 95%CI: 57%,62%, respectively). Notably, within all phases and formats nuclear pleomorphism had the lowest percent agreement and mitotic count had the highest. However, in at least 2 cases, highly variable mitotic scores reflected a different mitotic appearance between formats. Mitotic count shifted towards under-diagnosis on digital due to difficulty identifying atypical mitotic figures. Nottingham Grade evaluated using the digital format trended towards more intermediate grade interpretations then reported on glass format.

Conclusions: Digital format had significantly lower Nottingham Grade inter-observer agreement than glass slides. Quality assurance protocols validating the diagnostic reproducibility of digital formats should include grading schemes.

2033 Initial Experience with an Internal Review Process for Achieving Consensus Diagnosis of Atypical Barrett's Esophagus Biopsies within a Large Multi-Hospital Pathology Practice

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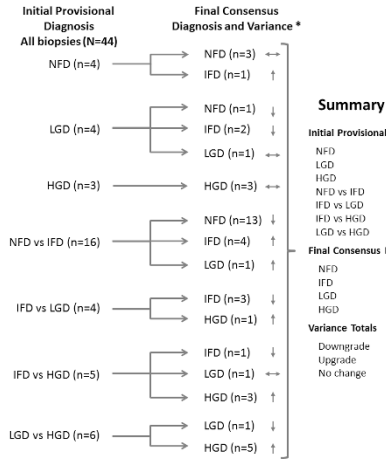
Background: The American College of Gastroenterology recommends that diagnoses of dysplasia of any grade in Barrett's esophagus (BE) undergo review by at least one "expert" gastrointestinal (GI) pathologist [PMID: 26526079]. As a large multi-hospital pathology practice comprised of a subspecialized academic center and several independent community general practices, we developed a consensus reporting process for diagnosing dysplasia in BE.

Design: During a 16 week period in 2016, we asked general pathologists within our multi-hospital system to refer all atypical BE biopsies for internal review by two designated subspecialist GI pathologists. The referring pathologist was asked to make a provisional dysplasia diagnosis (negative, NFD; indefinite, IFD; low-grade, LGD; or high-grade dysplasia, HGD) or differential diagnosis within one of 4 categories (NFDvsIFD, IFDvsLGD, IFDvsHGD, LGDvsHGD). Diagnoses of cancer and non-atypical NFD BE biopsies were excluded. Two subspecialists reviewed each case to achieve a final consensus diagnosis. We compared initial diagnosis with final consensus diagnosis.

Results: During the 16 week period, a total of 32 cases representing 44 separate biopsies were referred for consultation. A flow diagram illustrating changes from provisional diagnosis to final consensus diagnoses is shown in Figure 1. Initial diagnoses ranged across all categories with the most common being IFD/LGD vs HGD (n=11) and NFD vs IFD (n=16). The final consensus diagnosis represented a downgrade in 48% or an upgrade in 34%. In biopsies referred for consultation with a differential diagnosis (n=31), the final diagnosis was represented in the differential in 94%. All 3 diagnoses of HGD were confirmed. Three of four provisional LGD diagnoses were downgraded to either IFD or NFD.

Conclusions: This quality assurance study developed a consensus process for the diagnosis of dysplasia in Barrett's esophagus within a multi-practice system. In the large majority of cases the initial differential diagnosis was reflected in the final consensus diagnosis. The most common atypical cases selected for consultation related to differentiating NFD from IFD and IFD/LGD from HGD.



2034 Prospective Testing for Her2 Using Simultaneous Immunohistochemistry (IHC) and Chromogenic In Situ Hybridization (CISH)

Javier De Luca-Johnson, Britni RE Bryant, Jeannette Mitchell, Valerie Cortright, Donald L Weaver, Andrew Goodwin, Maureen Harmon, Abiy Ambaye. University of Vermont College of Medicine, Burlington, VT.

Background: Our study reports the results following concurrent use of immunohistochemistry (IHC) and chromogenic in situ hybridization (CISH) in all invasive breast cancers diagnosed in our institution during the study period. While multiple studies have validated the use of either IHC or CISH in a retrospective manner, to our knowledge, this is the only study investigating the concurrent use of both Her2 assays in a prospective manner.

Design: We performed a retrospective review of prospectively collected data at a tertiary care academic medical center. During the years 2013-2016, all new invasive breast cancers were simultaneously tested for Her2 using both IHC and CISH. Interpretation was performed using published ASCO/CAP criteria. Patients with discordant IHC and CISH results were identified. The following clinical data were collected: patient demographics, significant medical and treatment history.

Results: 1735 patients underwent Her2 testing by both IHC and CISH. A total of 38 patients (2.2%) demonstrated discordant results: among patients scoring 3+ by IHC, 16 of 191 (8.7%) had non-amplified (negative) results by CISH; among patients scoring 1+ by IHC, 22 (2.7%) had amplified (positive) results by CISH. All patients scoring 0 by IHC were non-amplified by CISH; among patients scoring 2+ by IHC, 23 (12%) were amplified by CISH.

Table 1: Prospective Testing for Her2 using Simultaneous IHC and CISH

IHC Score	Amplified (>2)	Non-Amplified (<2)	No ISH Data
All (n: 1735)	213 (12.9%)	1442 (87.1%)	80
3+ (n: 191) 11%	168 (91.3%)	16 (8.7%)	7
2+ (n: 194) 13%	23 (12%)	169 (88%)	2
1+ (n: 864) 50%	22 (2.7%)	797 (97.3%)	45
0 (n: 486) 26%	0	460 (100%)	26

Conclusions: 2.7% of patients with 1+ on IHC demonstrated amplification of Her2 by CISH, with potential benefit from anti-Her2 therapy. 8.7% of patients with 3+ on IHC were non-amplified for Her2 by CISH. This suggests that CISH may not be suitable as a primary testing method, because a significant proportion would have been given a non-amplified result, and no anti-Her2 therapy. There is little data on the clinical outcome and treatment response rates to Her2 blocking therapy in patients with discordant IHC and CISH results. While IHC and CISH testing have been compared in a retrospective manner, no studies to date have reported the results on simultaneous prospective testing for Her2 IHC and CISH for invasive breast carcinoma.

2035 Excision Biopsy Diagnosis of Patients with Breast Core Needle Biopsy Findings Reported as Atypical Intraductal Epithelial Proliferations

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Background: Core needle biopsies (CB) of palpable and or screen detected breast lesions are done to provide a pathologic diagnosis that will aid in optimal patient management. However, due to the limited tissue sample size, borderline lesions that are difficult to definitely classify as benign or malignant are sometimes encountered. This includes atypical intraductal epithelial proliferations (ADEP) which encompasses atypical epithelial proliferations and atypical duct hyperplasias. Positive predictive rate (PPR) for carcinoma in these lesions varies in different series from 25-36%. Correlation with pathologic and radiologic features at the time of biopsy may provide useful information that will aid in the stratification and management of these patients.

Design: A computer-based search was used to identify patients with initial diagnosis of ADEP on CB with subsequent excision biopsy performed for final diagnosis from 2000-2004. Radiologic correlates were additionally recorded. Data analysis utilized standard statistical methods.
Results: 96 cases diagnosed as ADEP on CB were identified. 84% (81) of these were screen-detected lesions with a BIRADS category of 4 or 5. On excision biospy, 61% were upgraded to a diagnosis of carcinoma – 25% invasive ductal carcinoma, 34% ductal carcinoma in situ, and 2% lobular carcinoma in situ; with a PPR of 25%, 36%, and 2%, respectively. Overall PPR for carcinoma was 61%
Conclusions: Breast CB is a screening test that permits identification of women needing further work up or not. Our initial results show that excision biopsy for ADEP finding on CB is reasonable given the high PPR for carcinoma. Significant emphasis is given on further management options of patients in this equivocal group. The PPR could be increased by identifying pathologic and radiologic features that will allow better identification of cases that should be referred for surgical excision or that will be more appropriately managed by close follow-up. Our findings would support recommendations that could be significant in better triaging patients into more appropriate management algorithms, specifically with respect to an initial ADEP diagnosis.

2036 Common CPT Coding Corrections in an Academic Center

Audrey Deeken-Draisey, Allison Ritchie, Timothy Carll, Guang-Yu Yang, Kruti P Maniar. Northwestern Medicine, Chicago, IL; Medical College of Wisconsin, Milwaukee, WI.
Background: Current Procedural Terminology (CPT) coding provides standardized language to describe services rendered by medical personnel. In our anatomic pathology practice CPT codes are assigned to specimens at accessioning and are later audited by pathologists and billing personnel. Accurate assignment of CPT codes is essential for accurate/appropriate compensation. The aim of this study is to investigate common causes of CPT coding changes in a busy academic practice.
Design: We performed a retrospective analysis of the past 5 months of CPT coding changes, revealing 307 total coding changes. 150 cases requiring correction to either higher code or lower code (75 cases each) were randomly selected from the available data for further analysis of the nature of the change.
Results: Of the 307 total cases, 188 changed to lower codes and 119 changed to higher codes. Of the former, the most common scenarios included the presence of only one lymph node (37%), tissue/margins without neoplasia (21%), and a final diagnosis of lipoma (17%).

Event	# of Cases
Single lymph node	28
Margin/tissue, no tumor present	16
Lipoma	13
Soft tissue, no lymph node present	5
	5
Skin, scar/debridement	3
Epidermal inclusion cyst	3
Gross only	2

The most common scenarios requiring correction to a higher code included the presence of >1 lymph node (44%), skin resections for reasons other than plastic surgery (20%), and tissue with neoplasia or complex margins (17%).

Event	# of Cases
Multiple lymph nodes	33
Skin, other than plastic/cosmetic	15
Tissue with neoplasia/complex margins	13
Multiple organs present	5
Lipoma of cord	3
Major specimen, wrong code	3
Twin gestation, placenta	1
Complex resection	1

Conclusions: The most common cause of CPT coding change was the final lymph node count, which in our practice determines coding as either 88307 (>1 node) vs. 88305 (1 node, or fibroadipose tissue only) for non-sentinel nodes. These events accounted for 44% of the total number of cases corrected and may be a potential area of improvement when assigning initial CPT codes at accessioning. Of the remaining causes, diligence in identifying the specimen(s) properly at receipt in the lab may improve initial CPT code assignment and result in fewer coding changes after diagnosis is made. It is useful for medical coders/pathologists to be aware of the most common coding corrections. Familiarity with CPT system and in-house billing guidelines facilitate accurate professional billing.

2037 Simulated Partial Sampling of Radical Prostatectomy Specimens: A Prospective Study

Jessica Dillon, Jason Pettus. Dartmouth-Hitchcock Medical Center, Lebanon, NH.
Background: There is no accepted standard for gross sampling of radical prostatectomy specimens, and strategies range from selective partial sampling to whole prostate submission. Our laboratory has traditionally submitted entire prostates; however, considering the laboratory strains of this intensive strategy, we aimed to identify a safe and unbiased partial sampling approach.
Design: Consecutive radical prostatectomy cases were sequentially enrolled at the time of primary diagnosis. No changes were made to routine gross examination, and the entire prostate was submitted, including apex margin, bladder neck margin, seminal vesicles, and all sequential transverse sections. A genitourinary subspecialty pathologist first examined slides representing apical and bladder neck margins, seminal vesicles, and even-numbered transverse sections. Preliminary diagnostic parameters were recorded, including Gleason Score (Grade Group), staging criteria, and margin status. Next, odd-numbered transverse slices were reviewed, and concordance/discordance among parameters was recorded before the final diagnosis was rendered.
Results: Twenty-one cases were enrolled during the study period. A range of Grade Groups were present: Group 1 (3 cases); Group 2 (8 cases); Group 3 (9 cases); and Group 5 (1 case). pT stages included pT2a (2 cases); pT2c (9 cases); and pT3a (10 cases). Two cases had a positive margin. With regard to comparing pre- and post-assessment of odd-numbered transverse slices, one disagreement was found in which a focal positive margin was identified on odd-section review (incised lateral capsular margin in a pT2c case). Another case with very low-volume disease showed no tumor upon first review, but a single focus of carcinoma was identified in one slide during the odd-section review. The overall slide count for odd-numbered transverse sections ranged from 12-30 slides per case, with a mean of 20.7 slides.
Conclusions: Our prospective strategy for simulated systematic partial examination of radical prostatectomy specimens appears to represent a safe strategy with minimal patient care risk; however, additional study is needed to better understand potential risks. Partial sampling may become safer as low-volume, low-risk disease is decreasingly likely to be resected in the era of active surveillance. Only one discrepancy was identified during our whole-prostate comparison, which did not result in additional patient therapeutic intervention. From a laboratory cost-per-test standpoint, a reduction of 20.7 slides per case could result in substantial improvement.

2038 Accurate Assessment of Tumor Size in Breast Cancer Patients: Comparison of Different Radiological Modalities with Final Pathology

Carolina Dominguez, Yin Xiong, Laila Khazai, Marilin Rosa, Emmanuel Agosto-Arroyo. Moffitt Cancer Center, Tampa, FL.
Background: Multiple imaging techniques such as mammogram, MRI, ultrasound, or digital mammography are utilized in the evaluation of tumor size for the preoperative treatment planning of patients diagnosed with breast cancer. We have observed discrepancies regarding the size reported by different imaging techniques, compared to the pathology tumor size, which is the gold standard for pathologic staging. The aim of this study is to compare the tumor size measurement reported using the different available imaging modalities and pathology tumor size in excision for breast cancer.
Design: All breast invasive carcinoma resections (i.e. lumpectomy and mastectomies) with associated imaging studies performed at Moffitt Cancer Center from 11/01/14 to 06/30/15 were included. ANOVA and kappa tests were performed using the final report pathology tumor size as the gold-standard.
Results: A total of 397 excisions were identified during the study period. Table 1 summarizes the number of available radiology reports and reasons for absence of tumor size measurement. Statistical analysis revealed that the mammogram and MRI tumor size measurement were significantly bigger than the pathology tumor size, with a p-value of 0.002 and <0.0001, respectively. There was no statistical difference observed between the ultrasound and tomosynthesis tumor size measurement and the pathology tumor size. Kappa test revealed a better correlation between ultrasound and pathology tumor size (74.2%).

Imaging Modality	Available Reports	Report not available or study not performed	No size stated in report	No lesion detected	Total
Ultrasound	349	41	0	7	397
Mammogram	267	90	26	14	397
MRI	219	175	0	3	397
Tomosynthesis	49	327	13	8	397

Conclusions: We observed a better correlation between the ultrasound and tomosynthesis tumor size measurement when compared to the pathology tumor size. Mammogram and MRI results overestimated the tumor size. Although different studies have assessed the correlation between the different radiographic modalities, only few evaluate the digital tomosynthesis accuracy. Adequate radiographic evaluation of breast cancer tumor size is important in preoperative plan, therefore, utilizing the most accurate technique, or a combination of techniques such as ultrasound and digital tomosynthesis, can accurately guide clinicians in this endeavor.

2039 A One Slide GI Biopsy Protocol Does Not Impact Clinical Care and Provides Substantial Cost/Time Savings

Sarah Dry, Bita V Naini. UCLA, Los Angeles, CA.
Background: Protocols for small biopsy specimens often include multiple levels and slides, and often are historic, without current data to support their use. Additional slides require histotechnologists' and pathologists' time. Our institutional protocol calls for 2 slides on each in-house GI biopsy. We evaluated the clinical consequences of examining the first slide only.
Design: Two GI-specialty pathologists prospectively tracked all their GI biopsy cases over 5 weeks. Cases where only the second slide showed diagnostic features were identified. Our histotechnologists average 20-25 slides/hour, which was used to determine time savings. A histotechnologist at mid-salary, including benefits (benefits paid by Department), receives $132,329.60 annually.
Results: In 24 days (5 weeks, with 1 holiday week), 490 cases with 1751 parts were reviewed (mean 20.4 cases/day, 3.6 parts/case). Each slide contained 2-8 tissue sections. Clinical indications included small bowel transplant, surveillance (Barrett's, inflammatory bowel disease), suspected carcinoma, suspected GVHD, colon polyps,

dyspepsia, GERD and diarrhea. Four parts/cases (4/1751, 0.06%), all colon polyps, showed diagnostic features (tubular adenoma (TA)) only on the second slide. In three cases, this would not have affected clinical care, as a TA was present in other parts of the same case. In the fourth case, the patient had no other TAs nor prior history of TAs; our protocol in this situation is to cut 3 additional slides and this would have detected the TA not present in the first slide. Not performing a second level would have saved 70 – 87.6 total hours of histologist time (2.9 –3.6 hours/day, about 40% of 1 full time technician). Histotechnologist cost savings would be $52,931.84 annually. Pathologists would have avoided examination of 70 additional slides per day.

Conclusions: Exceptionally (0.06% of all parts; 0.8% of all cases), findings were present on the second slide only, and all were TAs. In all cases, patient management would not have been affected, either because one TA was already present or because Departmental protocol would mandate additional levels on the case. No critical diagnoses (ie, cancer, rejection, GVHD, dysplasia) would have been missed. Cost savings would include about 40% of a histotechnologist, as well as a pathologist's time to review an average of 70 additional slides/day (latter not calculated). We will continue to monitor this indicator; if further data is similar, we would feel confident eliminating the second routine slide on GI biopsy cases.

2040 Optimization of *MET* FISH Reporting Criteria in Non-Small Cell Lung Cancer: MD Anderson Experience

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Background: *MET* amplification (*MET*amp) is a therapeutic target for non-small cell lung cancers (NSCLC). Although *MET* copy number (*MET*CN) is universally assessed by fluorescence *in situ* hybridization (FISH), the criteria used to define *MET*amp have not been consistent in the clinical setting. Some investigators have used 3 or 5 or more *MET* copies/cell for *MET*amp by FISH whereas others have proposed that a *MET*/CEP7 ratio of 1.8 or 2 can be interpreted as positive for *MET*amp. Our historic criteria for *MET*amp include *MET* copy number ≥ 20 copies/cell in ≥10% tumor cells or a *MET*/CEP7 ratio ≥ 2.0. The clinical significance of NSCLC patients with borderline *MET*CN is incompletely understood.

Design: We retrospectively evaluated 416 consecutive patients with NSCLC tested for *MET*amp by FISH at MD Anderson Cancer Center between 2011-2015. We sought to optimize the *MET* FISH reporting criteria according to clinical outcome.

Results: Using the optimized *MET* FISH reporting criteria, 33 (7.9%) were interpreted as *MET*amp (*MET*/CEP7 ratio ≥ 2.0; or *MET*CN ≥ 5 copies/cell; or *MET*CN ≥20/clusters in 10% cells); 17 (4.1%) as *MET*CN gain/*MET*cng (*MET*/CEP7 ratio < 2.0 and *MET*CN ≥ 4 and < 5); and 366 (88%) as *MET* negative/*MET*neg (*MET*/CEP7 ratio < 2.0 and *MET*CN < 4). Median overall survival (OS) was 21.8 *vs*. 65.75 *vs*. 36.5 months in patients with *MET*amp, *MET*cng and *MET*neg, respectively ($P = .0005$). OS was better in patients ≤ 64 years of age ($P = .039$) and in patients with adenocarcinoma ($P = .0011$), but was worse in patients with advanced stage disease ($P < .0001$). Multivariate analysis identified age ($P = .008$), histology ($P = .005$), stage ($P = .0001$) and *MET* status ($P = .013$) as independent prognostic factors in NSCLC. Interestingly, patients with *MET*cng showed a significant lower risk of death than *MET*neg patients (hazard ratio [HR], 0.58; $P = .034$).

Conclusions: The optimized *MET* FISH reporting criteria improves the accuracy of *MET* testing in patients with NSCLC. We also suggest that these criteria may be a useful guide to identify patients who would potentially benefit from the MET inhibitors.

2041 Modeling of Effectiveness of Addition of New Antibodies in Panel Immunohistohistochemistry

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Background: Diagnostic immunohistochemistry with multiple antibodies in a panel format is a cost effective tool in the identifications of metastatic tumors of unknown primary site. The rapid proliferation of new antibodies with debatable specificity and sensitivity analysis raises the need for a modeling tool to predict the efficacies of expanding established panels. We sought to establish a modeling approach using results of antibody staining analysis of the von Hippel-Lindau gene product in metastatic tumors to the liver that could take into consideration cost as also utility into current models.

Design: The surgical pathology electronic medical record system at our institution identified 280 cases of metastatic tumor to the liver between 2014-2016. Primary sites confirmed included the following carcinomas: 86 colon, 32 breast, 25 lung, 38 pancreatic, 2 squamous (lung and head and neck), 4 cholangiocarcinoma, 5 renal, 4 from prostate, 3 urothelial, 2 esophageal, 9 gastric/GE junction, 1 hepatocellular carcinoma, 1 intestinal, and 1 sarcomatoid carcinoma. Additional non-carcinoma tumors included 7 melanomas, 2 GISTS's, and 1 liposarcoma. In the rest, a definitive site of origin was not confirmed.

Results: Analysis for immunoreactivity yielded the following: 100% of metastatic cholangiocarcinoma showed positive staining, while 50% of primary cholangiocarcinoma samples stained positive. 80% of the biopsies with metastatic renal cell carcinoma exhibited positive staining for VHL. Patchy positivity was observed with 33% of breast, 17% of lung, 28.5% of prostate, 50% of urogenital and the adrenocortical tumor having immunoreactivity for VHL. 100% of the metastatic pancreatic adenocarcinomas were negative for VHL as expected.

Conclusions: Using probability based modeling we evaluated different scenarios to determine optimum utility of VHL stains for evaluation metastatic carcinoma. Given the low prevalence of primary site carcinomas that were positive for VHL in our population and the incremental cost of $150 per case incorporation of VHL in preliminary basic panel was determined to be inappropriate. Incorporating it in second tier testing would be most cost-effective strategy.

2042 Intradepartmental Consultations in Surgical Pathology: Review of a Standardized Process and Factors Influencing Consultation Rates and Practices

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Background: Intradepartmental consultations (ICs) are important for quality assurance (QA) and ensuring diagnostic accuracy in surgical pathology. Our department has instituted a formal process for documentation of ICs and anonymized quarterly data are published within the department. Pathologists are encouraged to use an IC form and to document ICs in their final report; however, informal ICs also take place. This study reviews IC data and documents factors that influence formal (written) and informal (verbal) IC rates.

Design: Formal IC records from January to December 2015 were reviewed and percentage of consultations provided and requested by each pathologist were determined and correlated with years of experience and office location. Pathologists were invited to complete an anonymous online survey about their formal and informal IC practice.

Results: Data were analyzed for 25/30 pathologists (neuropathologists and oral pathologists were excluded). Ninety-six percent completed the online survey. Formal IC was requested on 2769 surgical pathology cases (5% of total cases for 2015). Ninety-two percent sometimes requested informal, usually undocumented ICs. Formal ICs were documented in the final report always (76%) or most of the time (24%). Mean formal:informal IC rates were 79:21% (pathologist estimates). With increased years of experience, the ratio of requested to provided ICs tended to decrease. Perceived level of expertise of a colleague was the highest ranked reason for colleague selection for both formal (100%) and informal (83%) IC. Other highly ranked factors for formal ICs were years of experience of a colleague and speed at which a colleague was likely to return the case. Sixteen percent of respondents chose good/friendly relationship with a colleague as their number 1 reason for selecting a colleague for informal IC. Office proximity was a higher ranked factor for informal IC. A poor relationship with a colleague was a potential deterrent to formal IC for 32% and informal IC for 65%. Publication of IC rates led 27% to increase their formal IC rate.

Conclusions: We provide a framework for a formal IC process. Written documentation of IC aids in QA and determination of IC metrics; however, informal, undocumented ICs still occur. Reasons for IC and choice of consulting pathologist are multifactorial with interpersonal relationships and office proximity having a greater impact on informal IC practice.

2043 An Effective and Multidisciplinary Utilization Framework for Esoteric/ Referred Tests in Molecular Pathology

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Background: In the emerging Value-Based Payment healthcare model, Pathology's governance of referral (send-out) testing is a prime opportunity to demonstrate domain expertise and reduce costs. However, in the absence of an institutional governance mechanism, pathologists have limited influence on utilization of novel, expensive, and esoteric molecular genetic tests. This unchecked utilization may place undue financial burden on the laboratory. To overcome these challenges, we designed and deployed a multidisciplinary and collaborative framework to ensure cost-effective and medically relevant utilization.

Design: We approached our institutional apex governance council and chartered an executive-level Medical Laboratory Formulary (MLFC) to govern the laboratory utilization framework for the entire health system. Clinical Evaluation and Technical Assessment Committee (CETAC), an MLFC subcommittee, is led by Pathology's Vice-Chair. It comprises of pathologists, clinical scientist, laboratory administrators, and representatives from billing and specimen handling. A specified workflow was developed to perform an exhaustive medical, scientific and operational analysis including (1) FDA Clearance (2) National Guidelines (3) Impact on diagnosis/treatment (4) Test cost (5) Coverage by insurance carriers. Subsequently, CETAC invited clinician experts. Based on their input and (1-5), utilization parameters were defined as (a) No restrictions (b) Available after medical review and (c) Off-formulary (i.e. not available through laboratory's referral channels).

Results: In total, 14 germline and nine somatic testing requests were reviewed over 33 CETAC meetings. The final utilization parameters were: No restriction (n=0), Available after medical review by CETAC expert (n=8), and Off-formulary (n=15). For individual tests within the medical review category, utilization was limited to four medical specialties (Genetics, Transplant, Neurology and Oncology). The prices of these requests ranged from $50- $5800. A distinct Off-formulary ordering pathway was created for patients or providers still wishing to access such tests. MLFC endorsed 22/23 CETAC determinations and revised only one.

Conclusions: CETAC has been successful because of its inclusive nature, well-defined pathways and deriving its legitimacy under system-level MLFC. We have managed to deploy an objective and cost-effective utilization framework. Through its work, it has provided an effective and visible role to pathologists. Based on our experience, we highly recommend deploying similar frameworks at other Pathology departments.

2044 Value of Ultrastaging via Additional Sections and Cytokeratin Immunostain for Sentinel Lymph Node Evaluation in Gynecologic Malignancies

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Background: Sentinel lymph node (SLN) biopsy is becoming a standard diagnostic procedure for gynecologic tumors (endometrial, cervical and vulvar cancer). Ultrastaging protocols have been recommended to improve sensitivity of the examination, although less rigorous study is accepted for non-sentinel lymph nodes. We examined the performance of multiple H&E levels and of cytokeratin immunostains to determine whether these procedures increase the sensitivity of SLN examination.

Design: SLNs from gynecologic cases were prospectively evaluated using three H&E sections, 50 µm apart, and a cytokeratin stain on each block. Each slide was reviewed to determine the presence and size of any metastatic tumor. A leave-one-out analysis was conducted to estimate the effectiveness of a more minimal ultrastaging protocol. The endpoint was accurate classification of each SLN block for status (negative, positive) and tumor size if positive (macrometastasis, micrometastasis, isolated tumor cells) according to categories expected to be included in AJCC 8th edition staging.

Results: 8/63 cases (1 vulvar, 7 endometrial) and 10/181 SLN tissue blocks were positive for metastasis as determined by the ultrastaging protocol. These included two blocks with macrometastases, three with micrometastases and five with isolated tumor cell deposits (ITCs). Leave-one-out analysis showed that examining a single H&E level and examining two H&E levels would have resulted in accurate classification of 99.4% (95% CI 98.3–99.9) and 99.8% (95% CI 98.9–99.9) of blocks for both status and size. Examining one H&E and one cytokeratin stain would have resulted in accurate classification of 100% of blocks for both status and size (95% CI 99.4-1.00). For one block, the reviewing pathologists noted that the ITCs were present by H&E but inconspicuous; thus, cytokeratin immunostain was essential to identifying them prospectively.

Conclusions: Multiple H&E levels, as compared to a single level, did not significantly improve the detection of metastatic carcinoma in SLNs associated with GYN malignancies. Routine performance of a cytokeratin stain may better highlight ITCs but did not significantly increase sensitivity. More minimal ultrastaging with one H&E and CK would result in correct classification of an estimated 100% of cases. These data may serve to inform future SLN processing protocols.

2045 Evaluating Clinical Utility of Actionable Genomic Alterations Identified by Comprehensive Genomic Profiling in Advanced or Recurrent Solid Tumors: A Tertiary Academic Hospital Review

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Background: In this era of cancer genomics, comprehensive genomic profiling (CGP) is increasingly utilized to classify cancers by genomic alteration (GA) in an attempt to identify potential molecular targets of therapy. Identifying tumor's underlying GA could provide additional therapeutic option in patients with advanced or recurrent disease, but the clinical actionability remains unclear in clinical practice. The purpose of this study is to evaluate if the use of CGP leads to implementation of genomically guided therapy in patients with advanced or recurrent solid tumors and attempt to address the barriers associated with implementation.

Design: Advanced or recurrent solid tumors from the head and neck, aerodigestive tract, genitourinary, gynecologic, and soft tissue pathology archive were searched which had been evaluated by extended next generation sequencing (NGS) assays. A total of 105 such cases were identified which had been referred for Foundation One (FO) testing (Foundation Medicine, Cambridge, MA). A retrospective chart review was performed to identify therapies implemented in these patients and possible barriers associated with implementation.

Results: A total of 104 advanced or recurrent solid tumors were sent to FO testing. 7 samples were not adequate for FO testing. The Foundation One platform revealed a total of 420 GA in 97 tumors (4.33 GA and 1.21 actionable GA per each tumor). The most commonly detected GA were AKT, CDKN2A/B, CTNNB1, EGFR, ERBB, KRAS, NF1, PIK3CA, PTEN, TERT, and TP53. 76 out of 97 cases (78%) harbored actionable GA. 4 of these patients received genomically-targeted therapy; targeting RPTOR, ERBB, EGFR, and EWSR1 FLI1 fusion.

Conclusions: A diverse list of altered genes and involved genomic pathways were identified in our tumor cases. 78% (76/97) of the tumors analyzed harbored actionable GA, however, only 5.2% (4/76) of these patients received personalized targeted therapy. Barriers to implementing targeted therapy appear multifactorial. FDA approved targeted therapies are often reserved as 2nd line treatment to be used after standard-of-care protocols and data on the efficacy of these drugs in advanced or recurrent solid tumors is limited. In addition, access to the medication can be a time-consuming hurdle. Identifying and addressing key factors that facilitate the use of actionable CGP results in routine clinical practice could benefit patients with difficult to treat tumors.

2046 A Practical Quality Control Procedure for Decalcified Bone Specimens in Evaluation of ER/PR/HER-2 Immunohistochemistry

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Background: Bone is a common metastatic site in patients with breast cancer and is frequently biopsied to reassess receptor status in order to optimize treatment. Acid based decalcification of bone modifies epitopes of several antigens, which is problematic in the assessment of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER-2) immunohistochemistry (IHC). We propose a simple control method for ER, PR and HER-2 testing on decalcified specimens.

Design: We compared ER, PR and HER-2 concordance in 69 cases of primary breast carcinoma and associated decalcified bony metastases between 2013-2016. Discrepancy was defined as a loss or gain of receptor expression in the metastatic site. We then subjected benign breast tissue from reduction mammoplasties to our decalcification protocol and graded antigen expression in paired specimens with and without decalcification. Assessment of ER and PR was done using the Allred scoring system (0-8) and HER-2 via standard semiquantitative scoring (0-1+, 2+ or 3+).

Results: In 69 cases with biomarker testing on primary and metastatic bone tumors, 47 cases showed concordance (68%). Among the 22 discrepant cases (32%), PR showed the highest discrepancy rate, 20/22 cases (91%). ER and HER-2 showed discrepancies in 5/22 and 2/22 cases (23% and 9%, respectively). Receptor changes were primarily due to lost expression within bony metastases; 19/22 cases (86%). All reduction mammoplasty cases had the same HER-2 staining intensity (0-1+) and 3 of 4 cases (75%) retained the same staining intensity for ER and PR (Allred 7); 1 case (25%) showed a minimal decrease in ER/PR staining (Allred 7 to Allred 6 following decalcification).

Conclusions: Biomarker discrepancy among primary tumors and bony metastases occurred in 32% of cases. While a proportion of these discrepancies may be attributable to receptor conversion within the metastatic tumor, decalcification also may decrease immunoreactivity in predictive biomarkers. Validation for ER, PR and HER-2 testing on decalcified specimens has not been pursued as a routine measure for most laboratories. We propose a novel method for assessment of decalcification-induced antigenic changes by using tissue from reduction mammoplasties as a control. In our experience, there was no significant impact of decalcification on benign breast parenchyma using our protocol. Use of reduction mammoplasty specimens is practical as these specimens are relatively accessible as controls.

2047 Molecular Alterations and Pattern of Clinical Utilization of Targeted Next Generation Sequencing for Malignant Lymphoma at the University of Pennsylvania

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Background: The University of Pennsylvania Center for Personalized Diagnostics (CPD) established a targeted next generation sequencing (NGS) panel to evaluate relevant genes in myeloid neoplasms. To assess utilization of this panel for lymphoma, we reviewed the ordering pattern and molecular alterations of cases submitted over a 37 month period.

Design: Cases where the diagnosis could not be confirmed or where the final CPD report was not available were excluded. The CPD database was reviewed to assess the number and pattern of normal, variant and abnormal results. Cases with pathogenic results were compiled and categorized by lymphoma subtype to analyze the frequency and pattern of mutations.

Results: 361 cases of suspected or confirmed lymphoma were submitted over 37 months. 335 cases (93%) were ordered by the clinical team, 23 cases (6%) were ordered by the pathologist and 3 cases (1%) were ordered by both. 17 cases were excluded. Result categories included normal, variants of uncertain significance (VOUS) and abnormal. 54 (16%) cases were canceled for undefined reasons. Of the 290 analyzed specimens, 4 (1%) failed to yield results due to degraded or insufficient DNA, 155 (53%) were abnormal, 71 (24%) were normal and 60 (21%) were VOUS. 62% of cases were chronic lymphocytic leukemia (CLL), 10% diffuse large B cell lymphoma, 6% marginal zone lymphoma, 4% mantle cell lymphoma, 4% B cell lymphoma not further characterized by histology, 3% lymphoplasmacytic lymphoma (LPL), 3% follicular lymphoma, 5% T cell lineage and 3% others. 260 pathogenic mutations were seen. Overall, mutations of *TP53* (22%), *NOTCH1* (10%), *MYD88* (10%), *SF3B1* (10%), and *ATM* (8%) were frequent. In the CLL group there were 180 mutations, most frequently *TP53, SF3B1, NOTCH1, ATM* and *XPO1*. In the non-CLL group there were 80 mutations, most frequently *MYD88, TP53, TET2* and *DNMT3A*. In the T cell group there were 19 mutations, most frequently *TET2, DNMT3A* and *NRAS*.

Conclusions: The majority of NGS testing was ordered by the clinical team. Over half of cases showed abnormal molecular findings. The most frequently analyzed diagnostic category was CLL. The mutation pattern in CLL is consistent with published studies and confers prognostic value. *MYD88* alterations, which have diagnostic and prognostic value in LPL and small B cell lymphomas, were commonly seen in the non-CLL group. Development of a lymphoma-specific NGS targeted panel that provides diagnostic, prognostic and therapeutic information is warranted.

2048 Impact of Feedback and an Educational Intervention on Academic Pathologists' Rates of Helicobacter Pylori (HP) Immunostain Use and HP Detection Rates

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Background: Current guidelines and CMS local coverage determinations recommend the use of HP immunohistochemistry (IHC) only when biopsies show chronic, or chronic active gastritis without detectable HP in H&E stained sections, or in roughly 20% of gastric biopsies examined in a pathology practice. Our institution switched from "upfront" to "on demand" use of HP IHC stains. Due to relatively high initial use rates, we decided to discuss the issues related to HP detection with all pathologists, monitor their HP IHC stain use and provide them with confidential feedback. The aim of this study was to determine the impact of this educational intervention and feedback.

Design: Our electronic database was searched for gastric biopsies reported from 4/15/2014 to 7/13/2016; the presence of HP and HP IHC stain use were extracted for the period before (P1) and after (P2) the feedback on prior utilization and educational intervention (9/21/2015). The rate of HP IHC use and total HP detection rates were tabulated for each pathologist and the numbers were compared to the laboratory means for P1 and P2. The HP primary antibody used was polyclonal rabbit (Cell Marque 215A-78).

Results: 6496 gastric biopsies were reported during the study interval: 4207 in P1 and 2289 in P2. The HP detection rate was 8.8% (372/4207) in P1 and 11.4% (262/2289) in P2. Despite significantly lower utilization of IHC stains (-31.2%, p<0.01), the HP detection rate showed a slight increase (+29.4%, p<0.01).

HP diagnosis					
Pathologist	P2	P2 % [95%CI]	P1	P1 % [95%CI]	% difference, P value
Path1	15/138	10.9% [6.6,17.3]	58/587	9.9% [7.7,12.6]	+10.02%, NS
Path2	19/196	9.7%[6.2,14.7]	19/236	8.0%[5.1,12.2]	+20.42%, NS
Path3	26/324	8.0%[5.5,11.5]	45/488	9.2%[6.9,12.1]	-12.96%, NS
Path4	19/238	7.9%[5.1,12.1]	15/150	10.0%[6.0,15.9]	-20.16%, NS
Path5	24/220	10.9%[7.3,15.7]	24/374	6.4%[4.3,9.4]	+69.92%, NS
Path6*	56/376	14.8%[11.6,18.8]	78/914	8.5%[6.8,10.5]	**+74.60%, 0.0012**
Path7*	71/549	2.9%[10.3,16.0]	80/799	10.0%[8.1,12.3]	+29.19%, NS
All 7 included Path	233/2069	11.2%[9.9,12.7]	338/3822	8.8%[7.9,9.7]	**+27.36%, 0.0031**
Entire laboratory	262/2289	11.4%[10.2,12.8]	372/4207	8.8%[8.0,9.7]	**+29.48%, 0.0009**

* With GI subspecialty; NS= Non Significant

HP IHC use					
Pathologist	P2	P2 % [95%CI]	P1	P1 % [95%CI]	% difference, P value
Path1	28/138	20.3%[14.3,27.8]	311/587	53.0%[48.9,56.9]	**-61.75%, <0.0001**
Path2	42/196	21.4%[16.2,27.7]	154/236	65.2%[58.9,71.0]	**-67.15%, <0.0001**
Path3	222/324	68.5%[63.2,73.3]	207/488	42.4%[38.1,46.8]	**+61.52%, <0.0001**
Path4	11/238	4.6%[2.5,8.1]	30/150	20.0%[14.3,27.1]	**-76.89%, <0.0001**
Path5	31/220	14.0%[10.0,19.3]	101/374	27.0%[22.7,31.7]	**-47.83%, 0.0002**
Path6*	108/376	28.7%[24.3,33.5]	298/914	32.6%[29.6,35.7]	-11.89%, NS
Path7*	145/549	26.4%[22.8,30.2]	383/799	47.9%[44.4,51.4]	**-44.89%, <0.0001**
All 7 included Path	590/2069	28.5%[26.6,30.5]	1551/3822	40.5%[39.0,42.1]	**-29.74%, <0.0001**
Entire laboratory	624/2289	27.2%[25.4,29.1]	1667/4207	39.6%[38.1,41.1]	**-31.19%, <0.0001**

* With GI subspecialty; NS= Non Significant

Conclusions: Despite the decline in use of HP IHC, there was an increase in HP detection. Pathologists with the most extreme rates of HP IHC use had the lowest HP detection rates. HP reporting rates and especially HP IHC use rates can be successfully used as a target of quality improvement efforts by monitoring the rates and providing confidential feedback.

2049 Successful Implementation of Standard Dictation Templates for Routine Specimens in a County Hospital: Time and Cost Analysis

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Background: The use of templates for diagnostic reporting has become common practice (i.e. synoptic cancer pathology reports). Their use has increased completeness and consistency in diagnostic reporting. However, template use is not limited to diagnostic reporting but can also be used for the gross descriptions of routine specimens. Analysis of the benefits of using gross templates has not been reported to our knowledge. Our institution has historically used "free text dictation" for the gross descriptions of routine specimens. Analysis of the gross descriptions showed minimal substantive variation from specimen to specimen. However, significant time and energy was spent on verbalizing these gross descriptions as well as transcribing them into the final pathology report. In order to reduce gross dictation time and transcription time and fatigue, we implemented pre-transcribed structured templates for our routine specimens and analyzed the effects.

Design: Templates were formulated and approved by the subspecialty groups for routine specimens. These included the majority of biopsies, curettages, and tubal ligation specimens. The total time of dictation and transcription from patient identifiers to the end of the gross description was recorded using the free text version and the new templates. The time differences between using free text versus templates were analyzed and extrapolated for a given year.

Results: Analysis showed an average 30% (13.8 sec) reduction in gross dictation time and 27% (37.8 sec) reduction in transcription time for each use of a gross template compared to free text. At our institution, it is estimated that the templates are utilized approximately 28,000 times in a given year. This would result in a savings of 104 hours of dictation time and 286 hours of transcription time.

Conclusions: The use of structured and pre-transcribed templates shows a significant reduction in gross dictation time and transcription. Given the high cost of labor in both pathologist assistants' time and transcription, the use of gross templates can result in significant savings.

2050 Improving Test Utilization in Factor V Leiden Assessment

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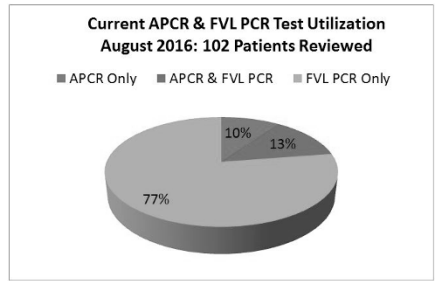
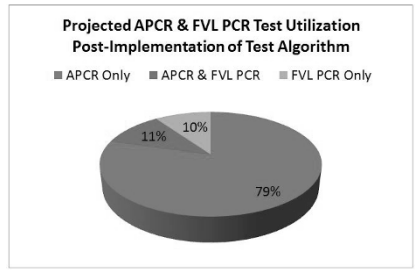
Background: Activated protein C resistance (APCR) is a significant risk factor for venous thromboembolism. Approximately 95% of APCR is a result of Factor V Leiden (FVL), the most common type of inherited thrombophilia. At our institution, we use an aPTT-based assay to assess APCR and a PCR-based test to identify FVL mutations. The most cost-effective and recommended testing strategy is primary screening for APCR followed by confirmation of abnormal results with FVL mutation analysis.

Design: To evaluate routine testing practices at Cleveland Clinic, we performed a retrospective analysis of all stand-alone APCR and FVL PCR tests ordered in August 2016 and determined the patient setting for all FVL PCR ordered in the last year (09/01/2015-09/01/2016).

Results: In August 2016, only 14% (14/102) of FVL assessments were ordered using the recommended test algorithm. In 9% of patients (9/102), APCR assays were ordered concurrently with FVL PCR and in 77% (79/102), FVL PCR was ordered without prior APCR screening (Figure 1). 11% of patients tested (11/102) were heterozygous or homozygous for the FVL mutation. A one-year review (09/01/2015-09/01/2016) revealed that 35% of all FVL PCR orders (560/1604) came from the ED/inpatient setting.



Conclusions: To improve test utilization at Cleveland Clinic, we plan to implement an embedded test algorithm with primary APCR screening, and secondary reflex testing for FVL mutations. Clinicians may bypass the algorithm under certain conditions: prior abnormal APCR results, family history of FVL, known antiphospholipid syndrome, or current therapy with specific anticoagulants. In addition, we will introduce a *Best Practice Alert* to discourage orders from the ED/inpatient setting. Using *Best Practice Alerts* and an integrated test algorithm, we hope to limit submission of inpatient orders, increase utilization of the APCR screening test, decrease unnecessary FVL PCR, and eliminate test redundancy (figure 2). The intervention is expected to result in a 57% reduction in overall cost per diagnosis.



2051 Clinical Impact of Pediatric Gastrointestinal Endoscopy

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Background: Endoscopic studies (endo) play an important role in evaluation of pediatric gastrointestinal disease. However, the findings from these studies are often unremarkable. Furthermore, studies that directly examine the therapeutic impact of endo and biopsy (bx) are sparse.

Design: 419 non-therapeutic upper endo (171 with combined lower endo) and clinical and pathologic data from 419 patients (pts) between August 2014-2015 were collected. Changes in therapy (tx) and post-endoscopic diagnosis (dx) were prospectively recorded. All pathologic dx were categorized as "significant", descriptive (ex. mucosal edema), or no abnormality, and contribution of biopsy for each endo were also categorized into the following: (1) confirmed/consistent with pre-endoscopic dx, (2) changed/provided additional dx, (3) narrowed differential dx, or (4) not contributory (not mutually exclusive).

Results: The pts were between 7 months to 17 years old (mean 11.2 years) and 187 (44%) were male. Abdominal pain (68.5%) and nausea/vomiting (38%) were the most common presenting symptoms. Clinical symptoms were poor predictor for "significant" histologic dx (Youden's J statistics = -0.13 to 0.14). Spearman's correlation between presence of any endoscopic and "significant" histologic change at different sites was poor (0.21) for the antrum, but ranged from 0.39 to 0.72 for other sites.

Overall, 47.0% of endo was normal in all examined sites. Nevertheless, bx confirmed the pre-endo dx in 36% of pts, changed or provided additional dx in 15% and narrowed the differential in 56% (not mutually exclusive). The most common clinically unsuspected "significant" dx included non-*H. pylori* gastritis, eosinophilic esophagitis, Candida esophagitis, *H. pylori* gastritis, and Celiac disease. Overall, endoscopic and bx findings changed tx in 35.6% of pts.

However, endo with bx were unable to provide any organic dx in 35.8% of pts. These pts may have had functional diseases, and they were less likely to have elevated celiac serology (0.082 vs. 0.20, p=0.0433) or fecal calprotectin (0.04 vs. 0.29, p=0.0323) compared to pts with an organic post-endoscopic dx. Moreover, there was no subsequent dx of organic etiology on available follow-up.

Conclusions: Endo with bx changed tx in 35.6% of pts and bx appeared to be clinically useful even when normal. However, 35.8% of endo with bx did not result in an organic dx. These data suggest there may be opportunity to develop improved non-invasive strategies to increase the diagnostic yield of pediatric endo.

2052 Microcytic Anemia Work-Up: Utilization, Quality, and Evaluation of Serum Iron Studies

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Background: Microcytic anemia (MA) is defined as a red blood cell mean corpuscular volume (MCV) less than 80 fL (normal, 80 – 100 fL). MA results from insufficient or failure of hemoglobin synthesis. Iron-deficiency anemia (IDA), anemia of chronic inflammation (AOCI), thalassemia and lead poisoning are the most common causes of MA. Causes of IDA are blood loss, decreased iron absorption and/or intravascular hemolysis; causes of AOCI include infection, inflammation and/or malignancy. Initial MA work-up includes evaluating MCV values from a complete blood count (CBC)).

An MCV <80 fL detected on CBC guides clinicians towards investigating serum iron indices (iron, ferritin, total iron binding capacity (TIBC) levels) to further classify the type of anemia. The purpose of the current study was to outline patient demographics and characteristics of serum iron indices in patients where serum iron studies were ordered to work-up MA from an initial MCV <80 fL on CBC.

Design: This is a retrospective, cross-sectional study comparing serum iron indices and demographics in adult patients (>18 years) who are being evaluated for MA (MCV <80 fL). Data extrapolated from our laboratory information system spanned a one-year period (January 2015 to January 2016). The patient population is diverse, at a medium-sized academic medical center located in a major urban population. Descriptive statistical analyses were utilized.

Results: A total of 5,495 iron, 5,132 ferritin and 5,252 TIBC tests were ordered on 3,108 unique patients (1,136 males, 1,972 females; F:M ratio, 1.7:1; median age 57.1 years; age range 18 to 98 years). All patients had previous MCV values <80 fL on CBC prior to additional iron studies. Serum iron, ferritin and TIBC levels descriptive statistics are outlined in Table 1.

	Iron (mcg/dL)	Ferritin (ng/mL)	TIBC (mcg/dL)
Mean	62	552.9	280
Median	56	189.1	269
Mode	43	4.4	267
SD	36	186.4	83
Minimum	10	1.5	79
Maximum	438	59275.0	813

Conclusions: Serum iron studies are frequently ordered tests as part of the MA algorithm work-up. This study outlined patient demographics and characteristics of serum iron indices in patients where serum iron studies were ordered to work-up MA from an initial MCV <80 fL on CBC. Our study showed a female-predominance and a wide-range of serum iron, ferritin and TIBC values. The current study sheds light into the patient demographics and characteristics of serum iron indices from a diverse patient population, at a medium-sized academic medical center located in a major urban population.

2053 Impact of Consensus Conference Review on Diagnostic Disagreements in the Evaluation of Cervical Biopsies

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Background: Quality assurance with the aim of error reduction is an important component in the oversight of anatomic pathology practices. The College of American Pathologists has issued a guideline for interpretive diagnostic error reduction which recommends review of pathology cases to detect potential interpretive errors. When poor interobserver agreement is discovered, members of the practice should use specific improvement methods to increase overall consensus including the use of consensus conferences. During a thirteen month period, the Department of Pathology and Anatomical Sciences undertook a consensus conference approach to improve diagnostic agreement for cervical disease.

Design: Between September 1, 2014 and September 30, 2015 all cervical biopsies and curettage specimens underwent weekly consensus conference review. Six hundred and ninety-six specimens underwent review. The opinion of each reviewer was recorded before the case was discussed. Percentage agreement was calculated for each meeting and plotted monthly over the 13 month period. For inter-rater agreement, both absolute agreement (number of concordant diagnoses divided by the total number of comparisons) and chance corrected agreement (kappa statistic) were calculated. The consensus diagnosis was the most frequent diagnosis for each case. For each case, diagnoses provided by the raters were compared against the consensus diagnosis. Percentage agreement was compared between the first and last months of the consensus conference program.

Results: The percentage of discrepancies fell as additional correlation conferences were held. The highest percentage of discrepant diagnoses occurred in the first month of conferences. Total percentage of discrepancies in September 2014 was 31% with clinically significant discrepancies in 6% of cases. The percentage of discrepant cases in the last month of the study was approximately a third of the percentage seen in the first month of the study (2% vs. 6% for clinically significant discrepancies and 8% vs. 31% for total discrepancies).

The absolute agreement rate increased from 91.2% in period 1 (September 2014) to 98.4% in period 2 (September 2015). This increase was statistically significant ($z = -7.63$, $p<0.001$). Diagnostic accuracy (relative to the consensus diagnosis) increased from 93.9% in period 1 to 99.0% in period 2.

Conclusions: The consensus conference technique appears to be a useful method to reduce intradepartmental diagnostic discrepancies.

2054 High Rate of Inappropriate Orders for a Hematologic Malignancy Next-Generation Sequencing Panel Does Not Improve with Educational Interventions: A Role for Continued Test Utilization Management

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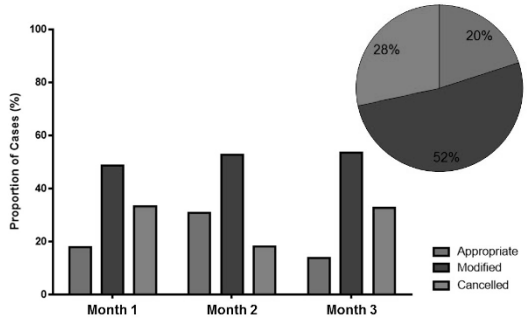
Background: Our Molecular Pathology (MP) Division launched a 44 gene next-generation sequencing (NGS) panel for hematologic malignancies (HM) this year. Preceding the launch, we worked closely with hematologists and hematopathologists to solidify appropriate clinical indications for testing. We evaluated appropriateness of test orders.

Design: All HM NGS panel requests are reviewed by a pathology trainee and a molecular pathologist and/or a hematopathologist to consider clinical, laboratory, and pathologic results. This team determines if the request is appropriate, needs modification, or should be cancelled, and discusses this determination with the ordering clinician. Test request appropriateness determinations, and the performed test(s) are logged in a spreadsheet.

Results: During the first 3 months, 170 requests were received (40, 56 and 74 in months 1, 2 and 3, respectively) and 34 (20%) were appropriate. More than half (N=88, 52%), required modification by the internal review process, while 48 (28%) of the requests were deemed inappropriate and cancelled. Cancellations require clinician agreement and acknowledgement that the requested test is not clinically indicated. The pool of ordering clinicians remained stable during this period. Despite on-going review and feed-back to clinicians, the data do not show a trend towards improved ordering practices. The percentage of appropriate orders fluctuates widely between months (14-31%) with no apparent cause, while the number of orders that require modification stays relatively constant around 50% (49-54%).



Conclusions: Our review process results in cancellation of more than 1 in 4 orders and pathologist-initiated order-modifications for 1 in 2 orders. This leads to a significant cost-saving for the lab, hospital, patient, and insurance companies, and ensures appropriate tests are performed. Despite individual evaluation and cross-talk with clinical colleagues regarding each order, the vast majority of orders require modification and/or cancellation, which re-enforces the role for internal review. We will continue to track monthly results, and incorporate these data into select clinical conferences in the hopes of improving appropriate test utilization practices.

2055 Squamous Cell Carcinoma in Serous Effusions: Avoiding Pitfalls in This Rare Encounter

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Background: With the advent of personalized medicine, precise identification of neoplasms becomes essential. Squamous cell carcinoma (SCC), one of the most common neoplasms, is rarely found in serous effusions (0.4-2.7% in literature). Identification in fluids is difficult due to morphologic and immunohistochemical (IHC) overlap with other neoplasms. The purpose of this study is to review positive effusion samples to determine causes of possible cytology errors and design specific practice changes.

Design: As part of our quality improvement program, a 17-year pathology database review identified 49 fluids (smears and cell-blocks) from 26 patients where SCC was recognized. The available smears and histologic sections as well as IHC stains were reviewed and cyto-histo correlation was performed.

Results: SCC was more often seen in pleural fluid (84%) and rarely in ascites or pericardial fluids (4 cases each). Lung SCC was most frequent (65%), followed by head and neck (16 %), with rectal, vulvar and esophageal origins being less represented. 40% of positive samples were clearly identified as positive (3 smears, 16 cellblocks). In 12 fluids, malignancy was reported as non-small cell carcinoma (9 smears, 3 cellblocks) and further differentiation could not be made with certainty. In 13 samples, an atypical/suspicious diagnosis was rendered (11 smears, 2 cellblocks). Two samples were false negative (on hypocellular smears) and one was false positive (smear with small orangeophilic squamous-like cells). Two fluids were diagnosed as adenocarcinoma on smears and SCC on cellblocks after IHC. A chi-square test showed the correct diagnosis more often on cellblocks compared to smears (p-value =0.0005) and all false positive, negative or misclassification of the neoplasm were done on cytology smears. Ber EP4 and MOC 31 immunostains were positive in all cases when performed, and the most specific immunostains for SCC were p63 and p40. Demonstration of negative mucin production was helpful in challenging cases.

Conclusions: Cytology smears are imperfect tools in evaluation of body fluids. Due to its rarity and morphologic features (cytoplasmic vacuoles, and signet ring cells), SCC can be misclassified as adenocarcinoma on cytology smears. Orangeophilic cytoplasm in some mesothelial cells can lead to false positive results. IHC stains can confuse the subclassification; the most useful stains for identification were p40, p63 and mucicarmine. We found that the combination of clinical history with cellblock preparation and appropriate IHCs is the best method to ensure a correct diagnosis.

2056 Integration of Whole Slide Digital Imaging (WSDI) for Primary Diagnosis: A Validation of Its Utility in Gastrointestinal Pathology Biopsy Workflow at a Multi-Center Academic Institution

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Background: Our medical center has one histology lab that serves three distant sites, which necessitates a courier service. Whole slide digital imaging (WSDI) may improve routine workflow, but its utility as a primary diagnostic tool has not been validated. We sought to validate the integration of WSDI for GI biopsy service into routine workflow for primary diagnosis at a multicenter academic setting.

Design: GI biopsies (n=95) were scanned by Phillips UFS (at 40X) over 5 days. The glass slides were then couriered to another site for signout. An expert GI pathologist (G.L.) independently made his diagnosis on WSDI. Our goals were 1) to assess the turnaround time (TAT) for WSDI and to have them available at the start of the routine work hour (8AM), 2) to compare the accuracy of the diagnoses made with WSDI to those made with glass slides.

Results: A prospectively designed workflow was devised to validate WSDI in routine workflow (Fig 1). In the conventional workflow, slides were delivered for preview by 7:15AM (TAT: ~75 min). In WSDI workflow, all slides were available to view before 7:10AM (TAT: ~61 min). No technical errors occurred. WSDI workflow met deadline for resident review and for attending sign out (Table 1). The accuracy of the diagnoses made on WSDI was compared with the final diagnoses. 1 case (~1%) had a diagnosis error on WSDI in which H. pylori were missed. Review of images and glass slides showed the organisms were present on WSDI but less clearly resolved (Table 2).

Figure 1: Integration of WSDI into GI biopsy workflow compared to conventional workflow

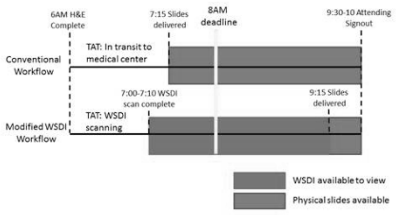

Table 1: Turnaround time (TAT) for WSDI compared to Glass slide delivery		
	WSDI	Glass slide
Median total TAT for review by the resident	61 +/- 5 min	75 +/- 10 min
WSDI scanning time vs slide transport time (20 slides)	40 min (2min/slide)	45 min
Deadline to resident preview met?	Yes	Yes
Deadline to attending sign out time met?	Yes	Yes
Maximum # slides capable of scanning to meet deadline	~60 slides (2min/ slide)	N/A

Table 2: Validation of WSDI		
Technical errors	0/95 (0%)	
Minor interpretation errors	0/95 (0%)	
Major interpretation error	1/95 (1%)	H. pylori organisms not completely visualized

Conclusions: We demonstrated integration of WSDI as a primary diagnostic tool into the GI service. The TAT of WSDI for 20 slides was faster than slide delivery; an estimated 60 slides can be scanned without delay of workflow with one machine. Although the diagnoses made with WSDI was nearly the same as those made with glass slides, the current digital resolution may be suboptimal for small organisms like H. pylori.

2057 Immunohistochemical Evaluation of Sentinel Lymph Nodes in Breast Cancer

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Background: Cytokeratin immunohistochemistry (IHC) has been variably used, in conjunction with routine hematoxylin and eosin (H&E) staining, to facilitate detection of small metastatic breast cancer deposits in lymph nodes. However, IHC increases costs and demands on laboratory resources. In particular, IHC is redundant if metastasis is seen on H&E. The objective of this study was to determine the utility of upfront cytokeratin IHC as a component of the standard protocol used to evaluate sentinel lymph nodes (SLNs) in breast cancer.

Design: An email survey of multiple institutions of the USA and Canada was performed to inquire these institutions' current protocols for evaluation of breast cancer SLNs. The pathology database at Penn State Hershey Medical Center (PSHMC) was searched to identify all SLN excisions performed on patients with breast cancer from March 2014 to June 2015. Thorough histologic evaluation of all available H&E and CAM 5.2 slides from these cases was completed. Metastases were classified as macrometastasis (>2.0 mm), micrometastasis (0.2-2.0 mm) or isolated tumor cells (ITC, <0.2 mm).

Results: Of the 14 institutions participated in the survey, 5 (including PSHMC) order IHC upfront as a protocol before evaluating H&E slides, 3 order IHC only if H&E appears negative, atypical or suspicious, 4 do not order IHC if the H&E is negative, and 2 utilize other protocols. 150 consecutive female breast cancer patients (median age: 56 years; range 26-83 years) with associated 526 SLNs (left: 285, right: 241) submitted in 533 tissue blocks were evaluated. Of the 526 SLNs, 32 (associated 40 blocks) were positive on H&E (6.1%), showing macrometastasis (n=18), micrometastasis (n=12), and ITCs (n=2). CAM 5.2 identified an additional 14 (associated 11 blocks) positive SLNs (2.7%), which were all ITCs and were not recognizable on initial, H&E review. The majority of SLNs (480, 91.2%) and associated blocks (482, 90.4%) were negative on both H&E and CAM 5.2.

Conclusions: Protocols for SLN examination in breast cancer appear heterogeneous among health care centers. H&E stain alone was able to identify all SLNs with macro and micrometastases and some with ITCs, and upfront CAM 5.2 performed in these cases (40 blocks, 7.5%) was probably not required. Although CAM 5.2 staining enhances detection of small cell groups, upfront ordering of CAM 5.2 generates significant incremental costs and efforts that is probably not justified by benefits to patient care.

2058 The Spectrum of Histopathological Findings in Patients Undergoing Colonoscopy for Chronic Diarrhea

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Background: Chronic diarrhea is a common clinical presentation, and in clinical practice these patients typically undergo colonoscopy for evaluation of potential underlying etiology. While in some cases colonoscopy reveals grossly identifiable lesion(s), in others it does not. Frequently, random mucosal biopsies of grossly unremarkable colonic mucosa are taken for further histopathological evaluation. The objective of this study was to assess the diagnostic yield of histopathological evaluation of random colonic biopsies.

Design: We retrospectively reviewed institutional pathology database between 2006 and 2010, for patients (age range: 18-90 years) with a clinical history of chronic diarrhea who have undergone colonoscopy with random mucosal biopsies of grossly unremarkable colonic mucosa. Diarrhea was defined as loose, frequent bowel movements for a minimum of 4 weeks. To minimize selection biases, patients with a known history of inflammatory bowel disease or concurrent symptoms/signs such as abdominal pain, nausea, vomiting, or anemia were excluded.

Results: This study included 409 patients composed of 280 females and 129 males aged (mean ± SD) 51.5 ± 17.4 years. The histological findings were as follows: 303 patients (74.6%) with normal histology; 16 patients (3.9%) with microscopic colitis (including lymphocytic colitis and collagenous colitis); 15 patients (3.7%) with chronic active colitis suggesting idiopathic inflammatory bowel disease; 15 patients (3.7%) with active colitis; 2 patients (0.5%) with melanosis coli; and 58 patients (14.2%) with nonspecific miscellaneous findings (including nonspecific mild lamina propria chronic and acute inflammation, mild architectural disarray, and lymphoid aggregates).

Conclusions: Random mucosal biopsies in patients with chronic diarrhea and normal appearing colonoscopy have yielded a histological diagnosis in about one-fifth of all patients, of which many were clinically significant. Our study reaffirms the usefulness of colonoscopy associated with random mucosal biopsy as a useful diagnostic tool in the workup of chronic diarrhea and early diagnosis of clinically significant gastrointestinal diseases.

2059 Evaluation of Body Fluids: Detection of Malignancy in Specimens Submitted for Cell Count and Differential in the Hematology Laboratory

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Background: Body fluid specimens are regularly submitted to the hematology laboratory for cell count and differential. Often, a concurrent cytology specimen is also submitted if the clinical suspicion for malignancy is high. As part of an initiative to enhance our hematology laboratory's ability to detect malignancy in body fluid specimens, we sought to determine the laboratory's rate of detecting malignancy based on review of the fluid smear/cytospin in comparison to our cytology laboratory's concurrent cytology specimen.

Design: Data was prospectively collected for body fluids submitted to the cytology laboratory in an 8-week period and was correlated with the concurrent hematology specimen. Discrepant cases were flagged for review by the hematology laboratory supervisors, hematopathologist and cytopathologists.

Results: From a total of 1185 body fluid specimens processed in the hematology laboratory during the 8-week review period (July 2016 to August 2016), 464 have concurrent cytology and hematology specimens. 137 (29.5%) were pleural, 123 (26.5%) bronchoalveolar lavage, 97 (20.9%) cerebrospinal, 88 (18.9%) peritoneal, 18 (4%) pericardial and 1 (0.2%) miscellaneous fluids. 50 (10.8%) were diagnosed as malignant by cytology. The hematology laboratory detected 35 of those cases (sensitivity 72.9%). Of the 15 discrepant cases, malignancy was not seen in 2 hematology fluid slides on review. The other 13 cases showed definite features of malignancy.

Factors Contributing to Discrepancy	N
Thick and/or cellular and under-stained smears	4
Hemodilution; focal area with clusters of tumor cells	1
Tumor cells in the periphery of the smear	1
Scant tumor cells in both the cytology and hematology specimens	7
Bland, small, and discohesive tumor cells	1
Inadequate specimen review	6

Conclusions: Our study provides evidence of the comparatively lower rate of malignancy detection for body fluid specimens processed in our hematology laboratory and highlights a number of opportunities for improvement. Quality assurance measures in the form of education or regular review of morphology for the hematology technologists and stricter adherence to slide quality indicators may improve the rate of malignancy detection. This is particularly important for institutions that process a high number of body fluids in the hematology laboratory, a subset of which may not have a concurrent cytology specimen.

2060 Comparison of Two Methods for Cytologic Evaluation of Cerebrospinal Fluids

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Background: Cerebrospinal fluid (CSF) samples are often split for concurrent evaluation by several methods. One portion is reviewed by cytopathologists in Anatomic Pathology (AP). A second portion is evaluated with a hematologic manual cell count in the Clinical Pathology (CP) laboratory. Because CSF specimens are often low volume specimens with low cellularity, splitting these specimens may compromise diagnosis and unnecessarily add to healthcare costs.

Design: 200 consecutive CSF specimens evaluated concurrently by both AP and CP methods from January to June 2010 was included in our study. All cases were reviewed by an AP board-certified pathologist and a CP board-certified pathologist. Concordance of AP and CP diagnoses was calculated. Discordant atypical diagnoses in both AP and CP were followed to see if there was any impact on clinical management. White blood cell (WBC) count reporting in the CP samples was correlated with cytology diagnoses.

Results: Of 200 total cases, AP and CP results were discordant in 42 (21%). The following abnormal results were identified by AP evaluation only: 4 carcinomas, 2 lymphomas, 10 with increased lymphocytes, and 6 with atypical cells. The following abnormal results were reported only by CP review: 1 with blasts, 1 with bone marrow elements, 2 cases of "other cells" identified as macrophages, 2 with atypical cells, and 9 with increased lymphocytes. 5 malignant cases (1 lymphoma, 2 with blasts, and 2 metastatic carcinomas) were identified by both modalities. Of the 46 cases that have confirmed increased WBC by cell count in CP, 32 (70%) were qualitatively called increased lymphocytes and/or neutrophils by AP. 8 out of 9 (89%) of the meningitis cases were called on both AP and CP and 1 case of presumptive viral meningitis was called on CP only.

Conclusions: CSF diagnoses were concordant in 79% of cases, suggesting that evaluating CSF specimens with both methods is unnecessary in most cases. However, in discordant cases, AP cytologic review was more sensitive than CP examination for the diagnosis of malignancy when evaluated in this split-sample method. In cases where infection or an inflammatory process is suspected, AP examination is comparatively sensitive in detecting increased lymphocytes and/or neutrophils. Follow up of all the atypical AP and CP discordant diagnoses revealed no significant impact on clinical management of these cases.

2061 Histopathologic Discordance Between Tumor Grade and Hormone Receptor/HER2 Status in Breast Cancer: An Institutional Experience

Malary Mani, Abul Ala Syed Rifat Mannan, Wen Fan. Mount Sinai Health System, New York, NY.

Background: Hormone receptor(ER/PR) and HER2 status are two of the most important prognostic indicators in breast cancer. HER2 is amplified/overexpressed in 15-20% of primary breast cancers. With the emergence of highly effective HER2 directed therapy, accurate identification of HER2 positive tumors has become critically important. Histopathologic discordance can occur when a well-differentiated tumor is ER/PR negative and HER2 positive or a poorly differentiated tumor is ER/PR positive and HER2 negative (per revised 2013 ASCO/CAP guidelines). In this study, we sought to determine the discordance rate between tumor grade and ER/PR/HER 2 status in a cohort of breast cancer patients diagnosed at our institute.

Design: Department database was searched for all invasive breast cancers, which were subject to ER/PR and HER2 testing (between January 2013 and December 2015). Pathology reports were reviewed to record tumor grade and hormone receptor/HER2 status(either overexpressed or amplified). Tumors were compared based on histologic grade and ER/PR/HER2 status.

Results: 524 breast cancer cases were retrieved from our database, which included 17.2% (90/524) grade 1, 45% (236/524) grade 2 and 37.8%(198/524) grade 3 tumors. Hormone receptor status evaluation revealed: ER+ 80.9% (424/524), PR+ 68.5%(359/524). HER2 was positive in 23.1% (121/524) cases. Triple negative tumors represented 22.6% (98/434), comprising 9.3%(22/236) grade 2 tumors and 38.4% (76/198) grade 3 tumors. Correlation of hormone receptor/HER2 status with tumor grade revealed a discordance rate of 2.2% (2/90) in grade 1 tumors, when the tumors were ER/PR negative and HER2 positive. It was 13.1% (26/198) for grade 3 tumors, when the tumors were ER/PR positive, but HER2 negative. Overall discordant rate was 5.3%(28/524).

Tumor grade and hormone receptor/HER2 status								
	ER		PR		HER2			Total
	+	-	+	-	+	-	Equivocal	
Grade I	88	2	77	13	2	87	1	90
Grade II	214	22	181	55	31	197	8	236
Grade III	122	76	101	97	88	102	8	198

Conclusions: HER2 testing is an important tool in prognostic stratification of breast cancers. As our data reveals, there exists a significant subset of tumors, which demonstrate histopathologic discordance between hormone receptor status and HER2 amplification/overexpression, most of which are grade 3 tumors. It is important to identify this group of tumors, as they require further analysis per revised ASCO/CAP guidelines.

2062 Practice of HER2 Testing in Invasive Breast Cancer: A Single Center Experience

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Background: HER2 is amplified in 15-20% of invasive breast cancers. Accurate determination of HER2 status is critical in identifying patients who will benefit from anti-HER2 targeted therapy. In 2013 American Society of Clinical Oncology (ASCO) and College of American Pathologist (CAP) revised the guidelines for HER2 testing in breast cancer. This study aims to assess compliance to ASCO/CAP guidelines from a single institution experience.

Design: We retrospectively reviewed all invasive breast cancer cases (between January 2014 to December 2015), which were subject to HER2 testing. Pathology records were reviewed for HER2 results on immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH).

Results: A total of 858 cases were identified. Analysis of HER2 results by IHC revealed : negative (0,1+) in 60.3%(517/858), positive(3+) in 9.4%(81/858) and equivocal (2+) in 30.3% (260/858). HER2-FISH was performed in 32.7% (282/858) cases. It was negative in 78.0%(220/282), positive in 13.8% (39/282) cases, equivocal in 6.4% (18/282) and indeterminate in 1.8% (5/282). Overall, HER2-positivity was 14.0% (120/858, which were either HER2 over expressed on IHC [n=81] or amplified on FISH[n=39]). The data shows that FISH was requested in 22 (7.8%) additional cases, when HER2-IHC was not equivocal. On review, all these cases were negative (0,1+) on IHC and were confirmed as negative on FISH. After excluding these 22 cases, corrected HER2-FISH positivity rate is 15% (39/260).

HER2-IHC results					Total (n)
0 (n)	1+ (n)	Total negative (n)	2+ (n)	3+ (n)	
233	284	517	260	81	858

HER2-FISH results						Total (n)
Negative (n)	Positive (n)	Equivocal (n)	Indeterminate (n)	Total Performed (n)	Total not performed (n)	
220	39	18	5	282	576	858

Conclusions: Prevalence of HER2 positive status observed in our study (15%) is similar to previous studies cited in the ASCO/CAP guideline. In a subset of cases (7.8%) HER2- FISH was requested when IHC was negative. The fact that all these cases subsequently returned negative on FISH, validates the utility of IHC as a useful modality for HER2 testing. The study emphasizes the usefulness of continued monitoring of quality assurance in improving current practice and therefore overall patient care.

2063 Six Sigma - A Metric for Quality Improvement in Anatomic Pathology

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Background: Anatomic Pathology departments collect and track various errors that occur within their departments. Data analysis over a long time period is necessary in order to implement appropriate protocols to reduce/eliminate these errors. In our department, we decided to use the "Six Sigma" model to objectively quantify these error rates and evaluate its effect as a quality improvement project. Sigma is a statistical measurement which indicates how well a process is working and higher values equate to higher performance. Sigma is calculated by counting number of defects per million opportunities (DPMO). Six Sigma (3.4 DPMO) is considered a benchmark of quality by many organizations; thus minimizing variability in manufacturing and business processes.

Design: As a pilot project, we focused on evaluating the reported number of specimen mix-up errors in our histology laboratory, in which tissue on glass slide does not match the appropriate tissue block. Histology laboratory staff, trainees, and faculty detect these errors while reviewing their slides. Data collected from July 2013 to April 2016 was analyzed. In 2015, an Advanced Barcode and Tracking (AB&T) system, to scan and match tissue blocks and slides before sectioning, was installed in our histology laboratory. Sigma was calculated before, during, and after implementation of AB&T system, using specimen mix-up errors to calculate DPMO.

Results: In the 19 month period prior to implementation of AB&T, 137 incidents of specimen mix-up were reported (7.2 incidents/month), equating to a sigma of 4.96 (using errors/total blocks) and 5.26 (using errors/total slides). During the 10 month period of transition to AB&T, 63 incidents of specimen mix-up were reported (6.3 incidents/month), equating to a sigma of 5.01 (block metrics) and 5.31 (slide metrics). In the 5 months following implementation of AB&T, only 13 incidents of specimen mix-up were reported (2.6 incidents/month), equating to a sigma of 5.2 (block metrics) and 5.55 (slide metrics). Tracking performed through AB&T revealed that over a 1 month period following implementation, there were 592 flagged specimen mix-ups.

Conclusions: Using specimen mix-up error rates and the AB&T system, we have shown that the sigma calculation can be used to evaluate error rates for process improvement in Anatomic Pathology. Sigma improved both during and after institution of the AB&T system. Continued monitoring of sigma for different processes in anatomic pathology can highlight those processes that need intervention as we strive to provide the best patient care possible.

2064 Financial Impact of Non-Diagnosis Coding for Current Procedural Terminology 88305 Following ICD10 Implementation

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Background: The transition from ICD9 to ICD10 has been challenging for most healthcare institutions. Because of this, Centers for Medicare and Medicaid (CMS) has allowed more flexible coding practices to accommodate this transition. The present flexibility rules end October 1, 2016 and most accurate and specific coding will be required to receive payment. This new rule can specifically impact pathology by denying claims that are submitted without a confirmatory diagnosis. For example, "consistent with" or "suggestive of" are not definitive diagnoses. If the pathology report diagnosis line does not contain a defined diagnosis, the claim will likely be rejected and payment will be denied. This study evaluates the financial impact of the use of pathologist language on the possible reimbursement of small biopsy Current Procedural Terminology (CPT) code 88305.

Design: The total surgical cases signed out on six separate days from January through June of 2016 within the Baylor Scott and White Central Texas Division were analyzed (n = 950). The cases were evaluated for: non-diagnostic codes, organ system, specimen type, CPT filing code, and whether use of pathologist language was speculative or definitive.

Results: Of the 950 cases analyzed, 278 cases included at least one non-diagnostic code (29%). Of these cases, 41 cases did not have a definitive diagnosis in the diagnosis line of the final pathology report, representing 15% of the cases with non-diagnostic codes and 4% of all cases analyzed. The organ system of these small biopsies were predominantly: skin n = 17 (41%), gastrointestinal tract n = 9 (22%), soft tissue n = 7 (17%), and female reproductive tract n = 6 (15%). Reimbursement by CMS for CPT code 88305 (Central Texas) is $84.38 per specimen. The average language related non-diagnostic code case per day is 7 cases, resulting in a reimbursement value per day of $576.60. Projected reimbursement over the course of one year is $146,455.55.

Conclusions: The change in CMS policy for reimbursement of surgical pathology cases could have a significant impact on pathology practice. How pathologists phrase their reports could specifically impact whether a claim gets denied. This could have a large impact on pathology practice nationwide and require a cultural shift to decrease the risk of non-payment by CMS. Further investigation into the knowledge and practice of pathologists with regard to coding rules and regulations could also shed light on the scope of the potential impact of ICD10 implementation and reimbursement through agencies such as CMS.

2065 Critical Communication Between Pathologists and Surgeons During Intraoperative Consultations: Direct Face-to-Face Interaction

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Background: Intraoperative frozen section consultations (IFS) play an important role of daily surgical pathology practice. Common practice at our institution was via intercom phone communication with readback by the medical staff in nearly all cases. Occasionally, direct face-to-face interaction (DFI) happened when surgeons came to review the slides during IFS. We initiated this project due to an incident of miscommunication over the phone on 1 case of axillary sentinel lymph node (SLN) IFS resulted in reporting 2 of 2 lymph nodes positive, but surgeon misunderstood as 1 of 2 positive, which led to a limited axillary dissection versus a more extensive dissection. This incident was re-evaluated with institutional Operating Room (OR) Safety Committee.

Design: Aim to change our communication practice of IFS by requiring DFI with ORS in cases of positive diagnosis impacting surgical management and complex diagnosis that required back and forth dialogue with ORS. The study was conducted for a period of 3 months. Cases with prior known malignant diagnosis, neurosurgical cases confirming the presence of tumor, "curiosity" IFS, and those without significant surgical management changes were not included in the DFI requirements. Attending pathologist and/or resident were responsible for communications of IFS results to ORS. The parameters examined were: accuracy of communication, turn-around time of IFS and ORS satisfaction.

Results: A total of 603 IFS (218 cases) with 60 (~10%) positive/malignant diagnosis and 29 (5% of IFS) cases were reported via DFI to the OR. These included 9 GYN, 7 ENT, 5 pancreas/biliary, 4 breasts SLN, 2 neurosurgical, and 1 each for orthopedic and thoracic cases. No communication errors were reported during this time. Average additional time for reporting results was increased by 2 minutes. Of significance, vast majority of ORS reported marked satisfaction with the added personalDFI (>90%), with few indifferent reports per OR committee. Our data shows no miscommunication leading to adverse outcomes using modified reporting method.

Conclusions: Accuracy in communicating IFS results is critical to impact best patient care. Although this preliminary review showed 5% IFS rate with DFI with ORS, there was a drastic increase in ORS satisfaction with pathologists. Our hybrid communication method is an option for quality assurance without compromising patient care or straining personnel resources. Residents also gain experience in gathering first hand clinical information and communication skills.

2066 The Addition of Cytospins from Needle Rinses Does Not Improve Specimen Adequacy on Thryoid Fine Needle Aspiration

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Background: Rapid onsite evaluation (ROSE) of adequacy is often performed during thyroid fine needle aspiration (FNA) to improve diagnostic yield. During the procedure, at many institutions, conventional smears are prepared from the FNA material. Following smear preparation, residual material left in the FNA needle can be "rinsed" out and additional preparations – such as cytospins – may be prepared from pooled rinses. While these additional preparations may contain material that improves the adequacy of a specimen, their creation requires extra technician time and may not be reimbursed in combination with ROSE. Furthermore, only a fraction of the total specimen slides may be reviewed onsite, meaning that a non-diagnostic ROSE may become diagnostic after all slides are reviewed after the procedure. Here, we retrospectively examine the utility of these cytospins at our institution.

Design: We searched our pathology archives for thyroid FNA specimens for which ROSE was performed. For each specimen, we determined whether or not a cytospin was created from the rinse material and whether this had an effect on specimen adequacy and/or diagnosis. Statistical analysis was performed which controlled for multiple variables (specimen year, patient race, patient age, number of smears created). Specimens were classified according to the Bethesda System for Reporting Thyroid Cytopathology (TBSRTC).

Results: 326 specimens were found to be inadequate on ROSE; of those, 91 had a cytospin created and 235 did not. The adequacy rate of the final specimen was 62.6% (147/235) for specimens without cytospinds and 61.5% (56/91) for those with cytospins (P = 0.90). Improvement in adequacy was also not seen among specimens called "less than optimal" on ROSE (P = 0.6). Furthermore, among these specimens the distribution of diagnoses did not significantly differ (P = 0.2 and 0.8, respectively).

Conclusions: The addition of a cytospin did not improve the likelihood of an adequate specimen following FNA procedures with inadequate or less than optimal ROSE. The addition of the cytospin specimen also did not impact TBSRTC diagnosis frequency among specimens that were found to be adequate after an inadequate ROSE. Given the additional cost of cytospin preparation in terms of technician time, it may be more practical to hold needle rinses until all specimen smears can be reviewed, thus sparing the creation of unnecessary cytospins.

2067 Laboratory Developed Tests and Risk Stratification Proposals – An Application

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Background: The Food and Drug Administration (FDA) has proposed regulation of laboratory developed tests (LDTs). Recommendations aimed at improving the FDA's proposal have come from the College of American Pathologists (CAP), the Association for Molecular Pathology (AMP), and the Diagnostic Test Working Group (DTWG), among others. Specifically, risk stratification of LDTs is an important consideration in these proposals as greater regulation is required of high risk tests. Our objective was to compare the risk stratification methods of four proposals.

Design: LDT regulation proposals were identified from governmental and laboratory community professional society websites. 4 proposals were identified with specific methods for risk stratification. The 4 methods were applied to 4 representative high-risk LDTs. Each method was assessed with respect to clarity and ease of use.

Results: 4/4, 0/4, 0/4 and 1/4 LDTs were classified as high-risk when the proposed FDA, CAP, AMP and DTWG methods were applied, respectively.

	BCR-ABL1 Mutation Analysis by NGS	Serotonin Release Assay (Heparin Dependent Platelet Antibody), Unfractionated Heparin	Cytomegalovirus by Qualitative PCR	ERBB2 (HER2) (HercepTest) by Immunohistochemistry
FDA	High	High	High	High
CAP	Exempt	Moderate	Exempt	Exempt
AMP	Low	Moderate	Moderate	Moderate
DTWG	High	Moderate	Moderate	Moderate

Methods presented by the CAP, AMP and DTWG were all fairly straightforward to implement, although additional recommendations and clarifications may be warranted; FDA methods were more difficult to implement in this exercise.

	FDA	CAP	AMP	DTWG
Clarity of Classification	Unclear	Fairly Clear	Fairly Clear	Fairly Clear
Ease of Use	Challenging	Fairly Easy	Fairly Easy	Fairly Easy
Recommendations	Provide Clear Criteria	Improve definition of traditional LDT	Consider making 4th category for waived and exempt and consider including traditional LDTs in criteria	Consider making 4th category for waived and exempt
*Recommendation for all proposals	Define more clearly what is high morbidity/mortality			

Conclusions: The risk stratification method proposed by the FDA is more difficult to apply than alternative methods proposed by professional societies. More research is needed to clarify the ideal methods for risk stratifying LDTs and improve ease of use.

2068 Impact of College of American Pathologists Evidence-Based Guideline on Immunohistochemistry Assay Validation Practices

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Background: To address inconsistent practices in immunohistochemical (IHC) assay validation, the College of American Pathologists (CAP) published an evidence-based laboratory practice guideline (LPG) on analytic validation of IHC assays in 2014. To study the impact of this LPG on laboratory practices, a cooperative agreement between CAP and the US Centers for Disease Control and Prevention was undertaken to measure laboratories' awareness and implementation.

Design: A detailed survey on IHC assay validation practices and on the awareness and adoption of the CAP's validation LPG was sent in 2015 to laboratories subscribed to one or more relevant CAP proficiency testing (PT) programs and to additional non PT subscribing laboratories that perform IHC testing. The results were compared with a 2010 survey that assessed validation practices sent to one specific CAP PT program.

Results: The analysis was based on 1085 respondents that perform IHC staining out of 1624 completed surveys. 65.4% of respondents reported being aware of the guideline recommendations and 79.9% of those respondents indicated adoption of some or all of the recommendations. The following statistically significant improvements ($p<0.05$) since 2010 were found: laboratories were more likely to have written validation procedures for both predictive marker assays (73.8% versus 45.9%) and non-predictive assays (80.4% versus 68.3%), and were more likely to specify minimum numbers of challenges needed for validation (93.4% versus 66.3% for predictive assays and 92.3% versus 55% for non-predictive assays). 99% of laboratories reported validating their most recently introduced predictive marker assay compared with 74.9% in 2010. The number of validation cases needed for rare antigens and resource limitations were cited as the biggest challenges in implementing the guideline.

Conclusions: This evidence-based LPG
has significantly improved IHC validation processes and provides broader confirmation that LPGs increase the quality of laboratory practices.

2069 New Benchmark Data from College of American Pathologists for Immunohistochemical Assay Validation

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Background: To study the impact of a College of American Pathologists (CAP) evidence-based laboratory practice guideline (LPG) on analytic validation of IHC assays, the CAP and the US Centers for Disease Control and Prevention developed a survey via a cooperative agreement to measure laboratories' awareness and implementation and to establish new benchmark data on laboratory practices.

Design: In 2015 a survey on IHC assay validation practices was sent to labs participating in one of three relevant CAP proficiency testing programs or had billed for IHC testing. Questions captured laboratory practices not addressed in a 2010 survey.

Results: The analysis was based on 1085 respondents that performed IHC staining out of 1624 completed surveys. 96% of labs always document validation of IHC assays. 60% had separate procedures for predictive and non-predictive markers, 24.4% had procedures for lab-developed or -modified tests, 38.1% for cytologic specimens, and 40.4% for decalcified specimens. For non-predictive markers, 85.9% specified a minimum case number (median 20, 5th to 95th percentile range, 5-40). For predictive markers, 76% specified a minimum case number (median 25, 5th to 95th percentile range, 8-50). Median concordance requirements were 95% for both types. For initial validation, 75.4% of laboratories were compliant with 20 cases for non-predictive markers and 45.9% were compliant with 40 cases for predictive markers. The most common primary method for validation was correlation with morphology and expected results (61.1% for non-predictive, 46.5% for predictive). For predictive assays, labs more frequently compared results with another lab. The survey also documented which assay changes necessitated re-validation of an antibody and case requirements for each re-validation.

Conclusions: This survey revealed specific items within the LPG that needed further refinement and adoption and it established benchmarking data on cytology specimens, decalcified specimens and re-validation procedures.

2070 Improved Quality and Number of Platelet Count in Apheresis-Platelet Concentrate > Buffy Coat–Platelet Concentrate & Platelet Rich Plasma-Platelet Concentrate, Assessed by Study of Quality Parameters in 119 Units of Platelet Concentrate. Why Is That?

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Background: A successful transfusion requires whole blood to be separated into components that can be removed based on specific gravity via centrifugation. Platelet quality can then be determined using *in vitro* analysis of the following parameters: volume, swirling, platelet count (PLC), WBC count, and pH. This study was performed to assess the platelet concentrate (PC) quality obtained by three different methods as per the recommended quality norms at our blood bank.

Design: Random donor platelets by platelet rich plasma-platelet concentrate (PRP-PC), Buffy coat poor-platelet concentrate (BC-PC), and single donor platelets by Apheresis-PC (APH-PC) were prepared and examined. A total of 119 units (58 BC-PC, 36 PRP-PC, and 25 APH-PC) were assessed using the following parameters: volume, swirling, PLC, and pH.

Results: The mean volume of PRP-PC, BC-PC and APH-PC was 73.04±4.35 ml, 75.01±3.27 ml and 272±2.98 ml and ranged from 68-88 ml, 55-82 ml and 263-276 ml, respectively. The mean PLC of PRP-PC, BC-PC, and APH-PC were $7.95±2.31×10^{10}$/unit, $8.66±2.29×10^{10}$/unit, and $4.19±0.45×10^{11}$/unit and ranged from $4\text{-}13.6×10^{10}$/unit, $5.4\text{-}15.4×10^{10}$/unit and $3\text{-}4.7×10^{11}$/unit, respectively. The mean pH was 6.23±0.15 (range: 6.0–6.8). No significant difference was observed among the three PC types. All units had a pH well above the recommended norm. PRP-PC and BC-PC units were comparable in terms of swirling, PLC per unit, and pH.

Quality Parameters	PRP-PC	BC-PC	A-PC
Volume (ml)	73.04±4.35	75.01±3.27	272±2.98
Swirling (each day)	Present	Present	Present
PLC (4th day)	7.95±2.31x1010/unit	8.66 ±2.29x1010/unit	4.19 ±0.45x1011/unit
pH (5th day)	6-6.4	6.3-6.8	6-6.6
WBC contamination	5.48 ±3.75x107/unit	4.30 ±3.52x107/unit	-
Culture	Sterile	Sterile	Sterile

Conclusions: All of the APH-PC units fulfilled the desired quality control criteria of volume, better swirling, and PLC than PRP-PCs and BC-PCs. There was greater volume variation in PRP-PC than BC-PC units, which suggested that further standardization is required for PRP-PC prep. After meeting with the Blood Bank Director/Team, it is hypothesized to be due to manual sealing of PRP-PCs. Thereafter, automatic sealing (machine) of PRP-PCs took place and we are currently finding improvements in the volume of PRP-PCs.

2071 To Consult or Not to Consult? That Is the Question! Second Opinion in Surgical Kidney Specimens

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Background: Obtaining second opinions in pathology is intended to reduce clinically significant errors which directly affect patient care. Therefore, slide reviews of cases refered for clinical care and "true" consults of cases have become routine within referral medical centers. However, these slide reviews and consults are time consuming and expensive. Revisions and updates of ISUP/WHO categories of tumors & CAP worksheets have further increased the number of both diagnostic discrepancies and second opinions, thereby increasing the overall cost of patient care. This is the first systematic study of the rate of discrepant diagnoses of renal tumors.

Design: We undertook a retrospective analysis of 518 consecutive review & consult cases from 2010-2015 from both outside hospitals and from within our institution. All cases were categorized as follows: A) No disagreement, B) No disagreement but pertinent information was not included, C) Minor disagreement (minimal impact on treatment or prognosis), D) Major disagreement with patient impact of patient care.

Results: The overall rate of discrepant kidney tumor diagnoses was 53%. The frequency of category B discrepancies in true consults was 19% and for slide reviews 13%. The discrepancy rate for category C was 5% for true consults and 17% for the slide reviews. In the clinically significant category D, the discrepancy rate was 53% for true consults and 14% of slide reviews. Most of the discrepancies were significant reclassifications of tumor type and tumor mis-staging.

Category	Subcategory	True consult	Slide review	Total Cases
A- No Disagreement		32	212	244
2- Disagreement		100	174	274
B - Missed Pertinent Finding	B1 Clear cell papillary RCC present/missed	1	2	3
	B2 Papillary RCC subtypes type1 and 2	2	4	6
	B3 Necrosis	0	9	9
	B4 Other histologic finding	3	2	5
	B5 Diagnostic Improvement (Clarity)	15	30	45
	B6 Not enough slides to review	4	5	9
	TOTAL	25	52	77
C - Minor Disagreement Missed Significant Pertinent Finding	C1 Missed staging	2	1	3
	C2 Upgrading	1	37	38
	C3 Downgrading	1	17	18
	C4 Rhabdoid	2	5	7
	C5 CIS missed if urothelial carcinoma	1	1	2
	C6 Consult Error (Omitted significant finding)	0	6	6
	TOTAL	7	67	74
D - Major Disagreement Patient Management Impact	D1 Clear cell RCC vs non-clear cell RCC	6	7	13
	D2 Histotype re-classification	29	13	42
	D3 Neoplastic vs reactive; benign vs malignant	11	3	14
	D4 Upstaging	0	4	4
	D5 Downstaging	1	9	10
	D6 Sarcomatoid componcnt	2	8	10
	D7 Oncocytoma vs Chromophobe	19	5	24
	D8 Upgrading by 2 grades (e.g. G2 to G4)	1	5	6
	D9 Consult Error (Typographic)	1	0	1
	TOTAL	70	54	124
Grand Total		132	386	518

Conclusions: The clinically significant discrepancy rate in 2nd opinion kidney cases was substantially higher than the reported rate of diagnostic error of 2%. The high discrepancy rate suggests a need for 2nd opinions for kidney tumors and attendance at CME courses to acquire current diagnostic and staging knowledge. The potential impact on patient care justifies the cost of 2nd opinions. To reduce diagnostic errors, we suggest developing guidelines for feedback loop, evidence-based educational resources for generalist pathologists, and standardization of both special stains for working up borderline cases and templates for reporting renal tumors.

2072 Using Root Cause and Human Factors Analysis to Investigate and Reduce Errors in Pathology- A Pilot Project

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Background: Most errors occur due to a series of failures in a chain of events. The cumulative effect of these failures culminates in an error event. Human factors/failures play a greater role as contributor to errors in situations where decision making (e.g. diagnostic decisions) and collaborative team effort (communicating a result) are needed to perform a task. We used a modified cause and human factors analyses to study analytic and post-analytic errors in our laboratory. Common causes of human failures that contributed to error were identified, with an eye towards developing targeted educational activities to improve outcomes.

Design: Cases with potential for patient harm or patient harm, and cases where there were complaints from either patients or clinicians were dissected to causes, including root causes. A modified HFACS based classification was created to allow for granular classification of failures and identify specific opportunities for targeting, so as to reduce errors in the department.

Results: In this preliminary analysis of 10 cases, a total of 36 failure/gap events were identified that contributed to the causation of error. Of these 17 were identified as events pertaining to culture, where behaviors (collegial, hierarchical) other than patient safety behaviors were prioritized. 12 were communication failure events of which 4 consisted of use of reporting language that was not understood by the clinician and led to inappropriate actions by the clinician. 4 were true interpretive diagnostic errors (1 anchoring bias, 3 education/expertise). 3 system level failures were identified.

Conclusions: Multiple factors contribute to the genesis of error. Even errors classified as diagnostic errors have multiple contributors. Cognitive/decision making errors may be hard to target. However, cause analysis of diagnostic errors can identify contributory causes which can be targeted to reduce/minimize the impact of error. Culture and communication are significant contributors of errors in the analytic and post analytic errors in pathology. Targeted educational activities are being developed to improve communication skills and promote a culture of patient safety in the department.

2073 Diagnostic Accuracy of Intraoperative Frozen Section Diagnosis: A Retrospective Review of 11,860 Frozen Sections

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Background: Intraoperative consultation with frozen section is critical to surgical management and remains a challenging area within surgical pathology. To improve the accuracy of frozen section diagnosis and quality assurance within the laboratory, periodic review of current practices should be performed.

Design: A retrospective review of frozen section diagnoses was performed between January 2012 and December 2014. Frozen section diagnoses were compared to final diagnoses. Discrepant and deferred cases were reviewed.

Results: A total of 11,860 frozen sections were identified with 93 (0.8%) deferrals and 258 (2.2%) discrepancies. 98% were concordant with the final diagnosis. The most common specimens sent for frozen section diagnosis were from head and neck, breast and genitourinary sites. Of the discrepancies, 146 (1.2%) were due to sampling error and 112 (0.9%) were due to interpretation error. 40% of deferrals were neurosurgical specimens. The organ system showing the greatest discrepancy due to either sampling (23%) or interpretation error (33%) was head and neck. The number of false positive diagnoses in this group was 7 and false negative diagnoses was 58. All false positive cases were discrepancies due to interpretation of squamous lesions. Of the discrepancies due to sampling error the majority (20%) were from lymph nodes.

Conclusions: Periodic review and quality assurance can highlight major causes of discrepancies between frozen section and final diagnosis. Head and neck specimens contributed to a large percentage (25%) of discrepancies. In addition, lymph nodes comprised up to 20% of discrepancies due to sampling error. Awareness of these specimen types can tailor practice modifications and help improve diagnostic accuracy. As such, concordance may be improved by the use of additional levels on lymph nodes and peer review of all squamous lesions. Nevertheless, frozen section continues to be an accurate method of diagnosis at our institution with a high concordance rate, comparable to values reported in the literature.

2074 Establishment of Helicobacter Pylori Detection Protocol in Patients Undergoing Laparoscopic Sleeve Gastrectomy

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Background: Preoperative *Helicobacter pylori* (HP) screening is routinely performed at our hospital to lower the potential risk of HP-related postoperative complications. Stool antigen (SA) test has been used as the main screening test due to its high sensitivity and specificity. Patients with positive screening test are usually treated before the surgery. There is no established HP detection protocol for laparoscopic sleeve gastrectomy (LSG) specimens in our department. Some pathologist order ancillary stains based on the presence of inflammation while others order them based on the prior SA test. The aim of this study was to evaluate the accuracy of preoperative SA test and to set up the HP detection protocol for LSG specimens.

Design: We retrospectively searched our database for all LSG performed from 01/01/2016 to 06/30/2016. Data regarding patients' clinical information including SA test and HP gastritis treatment, presence of inflammation on LSG specimens, and ancillary stains (Warthin-Starry stain or immunostain) were analyzed.

Results: We received 351 LSG specimens during the study period. Out of 351 patients, 340 were tested preoperatively for SA, 4 were tested for HP serology test. Among 7 patients not tested for HP, 2 were positive by Warthin-Starry stain on LSG specimens. Patients with preoperative SA test were further divided into three groups based on the SA result: Group A-SA positive (either persistently positive or no follow-up HP test after treatment); Group B-SA negative; Group C-SA initially positive but became negative after treatment. Among 321 patients with negative SA, 16 cases (5%) were positive by ancillary stain (group B + C).

Categories	Recieved treatment (n)	Presence of inflammation on LSG (n)	Ancillary stains ordered (n)	HP detected (n)
Group A(19)	12	13	7	3
Group B (262)	0	108	75	13
Group C (59)	59	40	29	3
Total (340)	71	161	101	19

Ancillary stains were ordered in only 111/161(67%) cases with inflammation. To note, ancillary test was not ordered in 3 patients from group A with persistent positive SA; even though 2 had chronic inactive inflammation.

Conclusions: Monitoring of SA test and corresponding histology and ancillary stains is helpful for establishment of HP detection protocol in LSG specimens. Although HP stool antigen test is useful in preoperative HP screening, it is important to correlate with histology features (e.g. inflammation) to help determine the need of ordering ancillary test.

2075 20 Months of Block Quality Feedback to Residents: Are We Getting Better?

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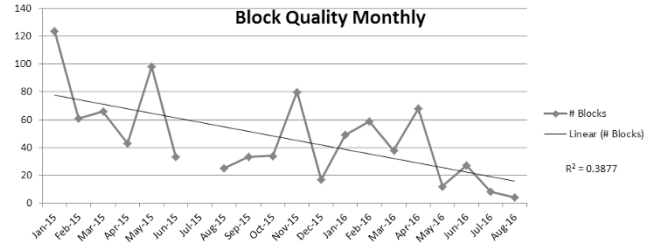
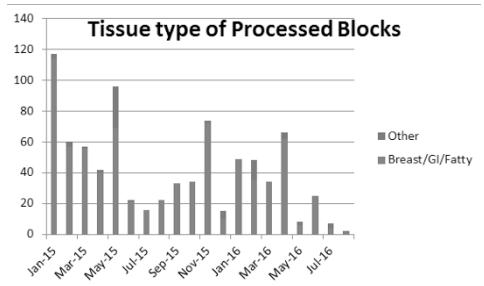
Background: Laboratory management and quality assurance is receiving increased emphasis as a component of pathology resident education. As part of our training program, residents devised a data-driven quality project targeting a problem area in surgical pathology: sub-optimally processed tissue blocks. Herein, we describe the process, results, benefits and obstacles to success of a quality project directed at assessing and reducing the number of sub-optimally processed tissue blocks.

Design: For 20 months, beginning January 2015, poorly processed blocks were recorded on paper. Date, specimen number and blocks affected were reported, along with category of suboptimal processing: fixation/processing, clips/staples, and other. A monthly summary report with tissue type, grosser and sign-out pathologist added was sent to all grossers, histology managers and attending pathologists. Within the report were tips on use of appropriate processors, proper section thickness and importance of removing staples and clips from tissue. For grossers with high number of reported deficiencies, a senior resident provided hands-on observation and feedback.

Results:



Trended blocks by month.



Proportion of blocks according to tissue type.

Conclusions: A trend of fewer poorly processed blocks occurred over time. Improvements were seen among senior and junior residents, highlighting the value of feedback even for seasoned grossers. The majority of poorly processed blocks are due to inadequate fixation of fatty tissue samples such as breast. We conclude that monthly provision of feedback data to grossers provides an opportunity for improved block quality, higher histology lab efficiency and potentially earlier case sign-out. To reduce reporting variability and to maximize analysis of adverse events, a streamlined digital method of data capture in the histology lab should be implemented. For sustained improvement, quality reports of these types can be used as a component of resident evaluation.

2076 Immunohistochemical Detection of Cytomegalovirus Particles in Patients with Suspected CMV Colitis: The Effect of Chromogen Method on Diagnostic Accuracy

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Background: The clinical differential diagnosis for colitis is wide and the detection of cytomegalovirus (CMV) inclusions in tissue biopsy plays a significant role in managing patients with suspected active CMV infection. Immunohistochemistry is often utilized in establishing the diagnosis in these cases. Recent observations in our practice demonstrated variability in immunostaining pattern associated with the chromogen method used to detect antibody binding. We evaluated the diagnostic accuracy of two different chromogens methods, the commonly used DAB and the infrequently used alkaline phosphatase red.

Design: 40 most recent cases of colon biopsies performed for suspected CMV colitis were identified. Immunohistochemical staining was performed using the Ventana Benchmark Ultra automated system, utilizing 2 primary monoclonal mouse CMV antibodies (M854;CCH2+DDG9,Dako A/S,Glostrup, Denmark) combined with 2 indirect detection kits: ultraView Universal DAB Dection Kit (Roche, Indianapolis) and ultraView Universal Alkaline Phosphatase Red Detection Kit (Roche, Indianapolis) that produce brown and red color respectively for light microscopic observation. All cases were stained with both chromogenic methods and reviewed by two independent pathologists along with routine H&E slides. Plasma CMV titers were obtained from electronic medical records.

Results: Eleven of 40 cases demonstrated unequivocal viral cytopathic changes on H&E sections in addition to CMV plasma titre >137 IU/ml or >100 CMV DNA copies/ml. Thirteen of 40 cases had undetectable plasma CMV DNA as well as absence of viral cytopathic changes. These were considered positive and negative gold standards. The red chromogen had sensitivity and specificity of 72.73% and 100% with positive predictive value of 100% and negative predictive value of 81.25%. The brown chromogen had sensitivity and specificity of 100% and 46.15% with positive predictive value of 61.11% and negative predictive value of 100%. Background staining of fecal material as well as enhancement of hemosiderin and melanosis were seen in 15(mild) and 20(moderate) cases with the brown chromogen. A clean pattern was observed in only 5 cases. Using the red chromogen, minimal background staining was observed in 7 of 40 cases.

Conclusions: Given the clinical relevance of a specific diagnosis and the ease of interpretation in a clean background, our results indicate an alkaline phosphatase based red chromogen is a superior method of CMV detection compared to the DAB detection method despite the latter's higher sensitivity.

2077 Addressing Clinician's Concern for Lack of Transformation Zone in Cervical PAP Tests: A Quality Assurance Initiative

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Background: The current Bethesda guidelines do not require presence of transformation zone (TZ) for a cervical PAP test to be deemed adequate. However, clinicians are concerned with reports that lack TZ. Our goal was to evaluate these concerns and guide clinicians with appropriate management.

Design: The rate of lack of TZ was studied in the following cohorts over a period of 6 months: the PAP tests received from the concerned clinician, the group practice of the concerned clinician and our laboratory in general. These rates were compared to published rates in the literature. Samples lacking TZ
received from the concerned clinician's practice were rescreened. In addition we analyzed 353 archived cases from 5 years back that were reported as negative for intraepithelial lesion or malignancy. These cases had no cervical abnormality in the preceding 4 years and were divided into those with and
without TZ. The rates of follow up, subsequent cytology and biopsy diagnoses were studied over the next 5 year period.

Results: The rate of lack of TZ in the PAP tests over a period of 6 months received from the concerned clinician was 6.5%, for the group practice was 11.4% and for our lab was 12.5%. Published rates in the literature ranged between 11.7 to 16%. The rescreening resulted in reporting presence of TZ in 11.8% of cases.
Of the 353 archived cases analyzed, TZ was present in 310 cases (87%) and absent in 43 cases (13%). The presence and absence of TZ distributed by age shows that the largest group in which TZ was absent was between the ages 45-54 years. There was no follow up in 21% and 23% of cases with and without TZ respectively. The percentage of cases with follow up within 1 year was slightly higher in the group without TZ as compared to with TZ. Within 1-3 years both groups had similar percentages. A similar distribution of number of cases within each diagnostic category (NILM, ASCUS, LSIL and HSIL) for the two groups was noted during follow up.

Conclusions: Pap smears without TZ were not at higher risk for subsequent detection of cervical abnormalities compared to smears with TZ, making earlier repeat testing unnecessary. Rescreening cases without TZ is not cost effective. The concerns of the clinicians were alleviated by comprehensive data analysis, literature review and education.

2078 Rapid FNA Diagnosis of Lymphadenopathy

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Background: Lymphadenopathy is commonly approached by fine needle aspiration (FNA). Rapid FNA (RFNA) diagnosis immediately after FNA provides for efficient triage. In this study, we assessed the diagnostic value of RFNA in lymphadenopathy in our hospital.

Design: 130 cases were studied. Rapid FNA were subclassified into 5 categories: negative for malignancy, positive for malignancy, suspicious for lymphoma, atypical cells and non-diagnostic. Comparison between RFNA with final FNA (FFNA) diagnosis was studied.

Results: The level of concordance of RFNA and FFNA was 100% for metastatic carcinoma (54 cases) or melanoma (2 cases). Of the "negative for malignancy" (31 cases) by RFNA, 29 cases were consistent with FFNA diagnosis; 2 cases were positive for malignancy in FFNA diagnosis. One showed small lymphocytes only at RFNA, but Reed-Stenberg cells were present in additional smears at FFNA. The other one was cystic fluid with inflammation and squamous cells; FFNA showed malignant squamous cells. In the category of "suspicious for lymphoma", flow cytometry was performed in each case. Of 16 cases in this category, 3 cases were positive for lymphoma and 12 cases were negative for lymphoma, and 1 case was seminoma in the final FFNA diagnosis. In the atypical category (5 cases), 4 cases were positive for malignancy in the final FNA diagnosis and 1 case was negative for malignancy. Of the non-diagnostic cases (22 cases), 5 cases were non-diagnostic in the FFNA diagnosis; 1 case was non-small-cell-lung-carcinoma in FFNA diagnosis but on review of the RFNA smear, no lesional cells were present in the rapid smear. The remainder of the non-diagnostic cases were negative for malignancy in FFNA diagnosis. The overall correct diagnosis including " atypical cells" and "suspicious for lymphoma" by RFNA was 71.5%.

Conclusions: Although RFNA is limited by less material available, it shows a high predictive value for "negative for malignancy" and "positive for malignancy" cases such as metastatic carcinoma and melanoma. RFNA efficiently selected cases for flow cytometry study only if lymphoma is suspected. In summary, RFNA saves time and is cost-effective in patient care.

2079 A Web-Based Pathology Reporting System Enhances Efficiency and Promote Standardization in Routine Practice

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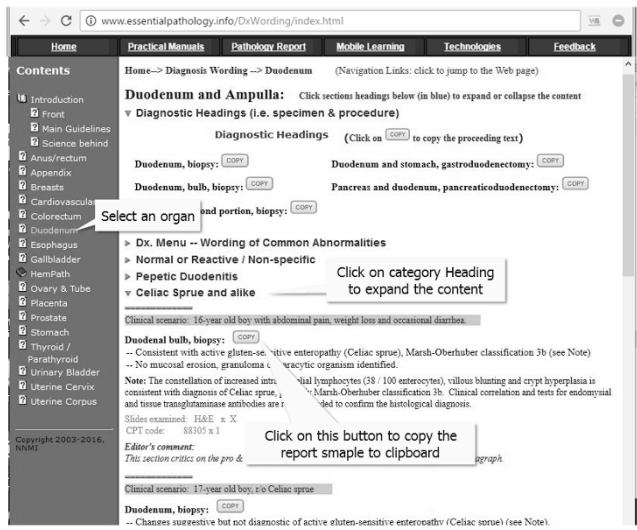
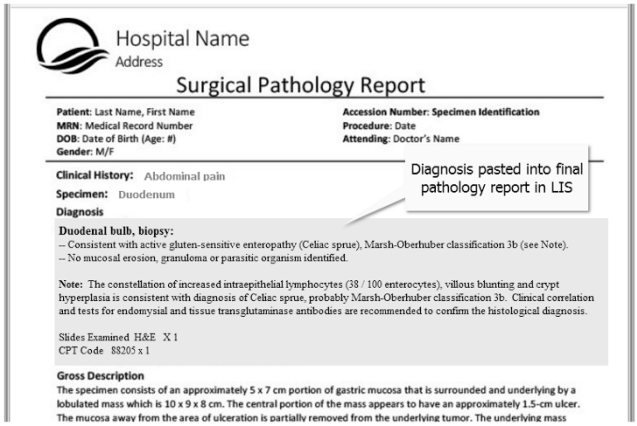
Background: Interrogation of a large number (>100,000) of pathology reports shows that a small number (<20%) of diseases accounts for the vast majority (>80%) of daily caseload. Thus pre-formulated reports for the small set of frequently encountered diseases can help pathologists effectively handle daily workload. Pathology reports are highly individualized with variable styles, semantics and formats, contributing to confusion, misunderstanding, medical errors, and difficulties in data-mining. However, standardization of routine pathology reports is believed to be an impossible task. Our decade-long attempts has uncovered three likely obstacles: 1) lack of specific guidelines for reports; 2) the need for report examples/ templates, and 3) lack of a convenient tool to facilitate the efforts. We present a reporting system that addresses these issues.

Design: A set of guidelines for formulating reports is created based on cognitive science, linguistic principles, and clinicians' feedbacks. Commonly used report examples/templates for each organ/site are formulated following the guidelines and organized in a database. The reporting system is freely accessible online at: http://www.essentialpathology.info/DxWording/index.html

Results: Users can find appropriate report samples for a specific organ/site in the "Contents" list. Sample reports are organized under expandable headings of common diseases.



Desired sample reports can be copied and pasted into laboratory information system.


Hospital Name
Address

Surgical Pathology Report

Patient: Last Name, First Name
MRN: Medical Record Number
DOB: Date of Birth (Age: #)
Gender: M/F

Accession Number: Specimen Identification
Procedure: Date
Attending: Doctor's Name

Diagnosis pasted into final pathology report in LIS

Clinical History: Abdominal pain
Specimen: Duodenum
Diagnosis

Duodenal bulb, biopsy:
-- Consistent with active gluten-sensitive enteropathy (Celiac sprue), Marsh-Oberhuber classification 3b (see Note).
-- No mucosal erosion, granuloma or parasitic organism identified.

Note: The constellation of increased intraepithelial lymphocytes (38 / 100 enterocytes), villous blunting and crypt hyperplasia is consistent with diagnosis of Celiac sprue, probably Marsh-Oberhuber classification 3b. Clinical correlation and tests for endomysial and tissue transglutaminase antibodies are recommended to confirm the histological diagnosis.

Slides Examined H&E X 1
CPT Code 88305 x 1

Gross Description
The specimen consists of an approximately 5 x 7 cm portion of gastric mucosa that is surrounded and underlying by a lobulated mass which is 10 x 9 x 8 cm. The central portion of the mass appears to have an approximately 1.5-cm ulcer. The mucosa away from the area of ulceration is partially removed from the underlying tumor. The underlying mass

Conclusions: With hundreds of sample reports and a convenient on-line tool, this system can markedly enhance users' reporting efficiency in daily service. The guidelines can help users formulate pathology reports with consistency as a key step toward standardization.

2080 Cost-Effective Triaging of Prostatectomy Specimens Using Light-Sheet Microscopy

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Background: Today's pathology laboratories walk ever-shrinking lines between operational budget, quality of care and turnaround time. To remain competitive, labs must keep overhead costs down while maintaining standards of practice. Business models including LEAN and Six Sigma have been widely incorporated to improve efficiency, with metrics such as "value-adding time" joining the vernacular alongside "submitted in *toto*". Because laboratories are reimbursed per-case, rather than by work volume, processing more tissue per case has a negative economic impact on the laboratory. Conversely, inadequate tissue sampling can adversely affect the patient's care, i.e. false negative margins, inaccurate grading and staging. Prostatectomy specimens represent an especially challenging tissue to sample since most prostate carcinomas are not grossly visible. Thus, a thorough sampling method with quick turnaround time and minimal overhead cost is of great importance.

Design: We describe an inverted light-sheet microscope (LSM) system for non-destructive imaging of surgical resection specimens, using prostatectomy tissue as an example. A clinical validation study of acridine orange-stained fresh prostate slices measuring approximately 3x3 cm (N=5 training set, N=24 validation set) was performed. LSM-generated images were compared to corresponding H&E-stained slides for sensitivity and specificity analyses.

Results: The LSM system images a shallow depth (~50 microns) of resected tissue (up to 10x10 cm) at high speed (<1 min/cm^2) at cellular resolution (~2 microns). The system had high sensitivity (> 90%), specificity (> 90%), and overall accuracy (> 90%) for classification of tissue as either positive (N=12) or negative (N=12) for carcinoma. Misclassified images contained small areas (~1 mm) of low grade carcinoma. Surface extraction techniques increased the total length of margin positivity in 2 cases.

Conclusions: Assessment of fresh prostate tissue, using our LSM system, showed high accuracy for detection of carcinoma and increased ability to detect positive margins. Tissue classified as negative for carcinoma need not be submitted for processing, while carcinomatous tissue can be processed for detailed examination of H&E stained slides. Thus, the LSM system with its quick scanning speed, low consumable use and ease of operation presents the rare opportunity to decrease costs while maintaining high quality of care, a feature of increasing importance in the evolving healthcare landscape.

2081 Comparing UroVysion and Urine Cytology as a Quality Assurance Metric and to Evaluate the Relevance of the Paris System for Reporting Urinary Cytology in Our Institution

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Background: The Paris System (TPS) is a new standardized international reporting system for urinary tract cytology that was introduced in early 2016. UroVysion (UV) is a multiprobe FISH assay that detects common genetic abnormalities in bladder cancer and has been shown in multiple prior studies to have a high sensitivity for detection of urothelial cell carcinoma (UCC). In this study, we compare UV results to urine cytology as a cytology quality assurance metric and to determine the relative value of implementing TPS for urine cytology in our institution.

Design: All concurrent UV and urine cytology reports from the same urinary tract samples over the past 6 years were reviewed. The electronic medical record was utilized to determine if the patients were clinically positive or clinically negative for UCC at the time of sample collection. The discrepant cases in which UV was positive and urine cytology was negative were reviewed blindly by two cytopathologists.

Results: The results of UV, cytology and clinical diagnoses are listed in Table 1:

Clinical Diagnosis	Total Number of Cases	Number of cases				
		UroVysion Fish Diagnosis		Urine Cytology Diagnosis		
		Positive	Negative	Positive/ suspicious	Atypical	Negative
Positive	15	13	2	9	6	0
Negative	58	7	51	0	15	43
Total	73	20	53	9	21	43

The overall sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in detecting UCC at our institution were 60%, 74.1%, 100%, and 100% respectively for cytology and 86.7%, 88%, 65%, 96.2% for UV. A total of 5 cases were identified in which UV was positive and urine cytology was negative. Review and reclassification of these cases utilizing TPS showed no evidence of malignancy. All 5 discrepant cases and 2 additional cases that were positive on UV were clinically negative.

Conclusions: Implementation of TPS may not add much value at our institution since urine cytology showed 100% PPV and 100% NPV. UV testing shows good sensitivity but poor PPV due to multiple false positive tests. UV should not be utilized alone as a screening test but can be useful in combination with urine cytology, particularly with atypical diagnoses. Additional studies and review will be necessary to determine if UV comparison to urine cytology results will make a good quality assurance metric.

2082 A Comparison of Freeze Artifact Using Three Frozen Section Techniques

Nida Safdar, Melissa Straub, Christopher Bantz, Kathleen Montgomery, Hernan Correa, Emily Reisenbichler. Vanderbilt University, Nashville, TN.

Background: Frozen section analysis, commonly used for rapid intraoperative microscopic evaluation, guides surgical decision-making. Artifact, resulting from ice crystal formation in tissue, represents a common challenge for interpretation. Various frozen section techniques are utilized across institutions and to date have not been directly compared.

Design: Twelve fresh tissue types were prepared using 3 techniques. For each tissue, 3 slides were prepared per method. In method 1, Optimum Cutting Temperature (OCT) embedding medium and tissue were transferred from a dispensing plastic slide into an empty well. The well was then filled with OCT, a chuck placed over the OCT, and freezing block over the chuck. In method 2, tissue was placed atop a previously frozen OCT mold with a heat extractor then lowered over the tissue. Method 3 was similar to the first, except the dispensing slide was omitted and tissue placed directly into an empty well. Blinded to method, 8 pathologists independently assigned each slide a freeze artifact score: 0 none; 1 mild; 2 moderate; 3 severe. Non-parametric Kruskall-Wallis test was used to compare scores.

Results: The median (mean) artifact scores for methods 1, 2, and 3 across all tissue types were 1.33 (1.56), 2.0 (1.78) and 1.67 (1.64), respectively (p=0.14). A significant difference in scores between methods was only seen for colon and skeletal muscle (Table). For these tissues, method 1 had the lowest median (mean) artifact score: 1 (0.79) and 1 (1.08), respectively. Artifact scores for all tissues and associated p-values are included in Table 1.

	Mean Artifact Score (Range) by Method			
Tissue	1	2	3	p-Value
Ileum	2.0(1-3)	2.0(1-3)	2.3(1-3)	0.57
Epidermis	1.1(0-3)	1.0(0-3)	1.0(0-3)	0.99
Dermis	2.3(1-3)	1.8(1-3)	1.5(1-3)	0.12
Skeletal Muscle	1.1(1-2)	2.3(1-3)	1.6(0-2)	0.0025*
Tonsil	1.0(0-2)	1.7(0-3)	0.7(0-2)	0.09
Vessel	2.1(1-3)	2.5(2-3)	2.4(1-3)	0.40
Kidney	1.3(0-3)	1.5(1-3)	1.7(1-3)	0.48
Tonsil	1.7(0-3)	1.5(0-3)	2.0(1-3)	0.22
Kidney	2.0(0-3)	1.8(0-3)	1.8(1-3)	0.74
Heart	2.5(1-3)	2.3(1-3)	2.1(1-3)	0.41
Liver	1.1(0-2)	1.1(0-3)	1.2(0-2)	0.89
Colon	0.8(0-2)	1.8(1-3)	1.3(0-3)	0.042*

Conclusions: For most tissue types, there was no significant difference in artifact score between methods. While in our study, method 1 had a significantly lower artifact score in colon and skeletal muscle, further studies should address whether this difference is clinically significant by examining discrepancies between frozen section and final diagnoses made on paraffin-embedded tissue.

2083 Introduction of an Asset-Tracking System: Flagging for Laboratory Improvement

Christine J Salibay, Javier Sedillo, Manmeet Singh, Elizabeth Wiley, Tushar Patel. University of Illinois Hospital and Health Sciences System, Chicago, IL.

Background: The advent of laboratory information systems (LIS) revolutionized monitoring of the workflow in anatomic pathology laboratories. With the implementation of an asset-tracking system module to our surgical pathology LIS system, pathologists, residents and pathology staff were readily able to "flag" errors using a standardized reporting template menu or free-type errors made during pre-analytical and analytic tasks. The use of an asset-tracking system allowed for efficient collection and analysis of "flags" in every step of the workflow, such as accessioning and histology processing,

thus ensuring higher quality process management and allowing for a more granular evaluation of laboratory operations. Therefore, enabling us to enact effective quality management changes in the future.
Design: Embedded within the LABLION® LIS interface, standardized templates or free-type text boxes were accessible to all pathologists and pathology staff to "flag" errors. The errors were then captured in electronic format and standardized to a master problem list with emphasis on accessioning and histological processing errors. Monthly monitoring of each "flag" was then conducted using Microsoft Excel®.
Results: The total number of "flags" divided into major sub-groups/workflow process was conducted for each month. Figure 1 is an example of the total "flags" divided into major sub-groups for the month of January 2016. The trend for each problem list was then followed per month. Figure 2 is an example of "tissue sectioning poorly" from November 2015 to August 2016.

Figure 1. Flags by Station (January 2016)

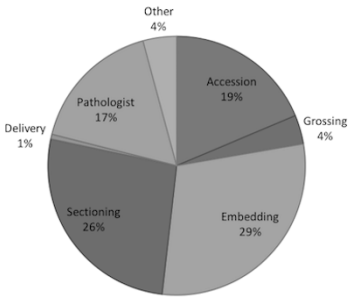
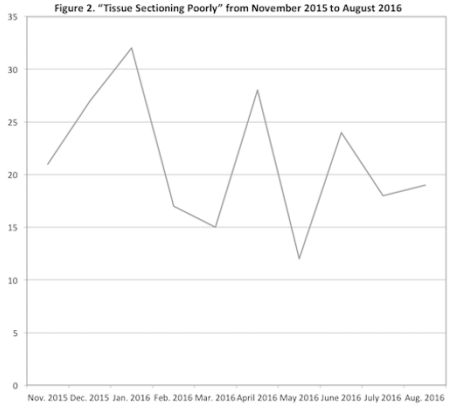


Figure 2. "Tissue Sectioning Poorly" from November 2015 to August 2016



Conclusions: Monitoring quality and process improvement is of great importance to improving pathology laboratory performance. Proper implementation of an LIS system allows for an automated evaluation of pre-analytic and analytic tasks. Review of the data highlights specific areas of improvement needed and thus allows for measured laboratory workflow enhancements.

2084 Inter-Observer Reproducibility in PD-L1 Immunohistochemistry Interpretation Improves with Training

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Background: PD-L1 immunohistochemistry (IHC) is a biomarker predicting some tumors that respond to anti-PD-1/PD-L1 immunotherapy, leading to FDA approval of PD-L1 clones as companion or complimentary diagnostics. The IHC assays have variable interpretive cut-offs, mostly including the percentage tumor cells with various acceptance criteria for membranous staining. Others have proposed that staining of immune cells may also be predictive of therapy response. With no established literature regarding the reproducibility of these interpretations, our objective was to measure inter-observer variability before and after training.
Design: Study cases (n=50) included melanomas, mesotheliomas, and carcinomas from lung, endometrium, pancreas, and liver with various quantities of PD-L1 staining (clone E1L3N;Cell Signaling). Percentage of viable tumor cells (<1, 1-5, 6-49, ≥50%) and percentage of tumor infiltrating immune cells (lymphocytes + macrophages, 0 to 100, rounded to nearest 10th percentile) showing partial or complete membrane staining of any intensity were scored. Six pathologists of varying experience with PD-L1 IHC scored all cases in random order before and after training. Training involved reviewing an educational presentation illustrating interpretive challenges and snapshots of study cases with poor agreement in the first round of scoring. Krippendorff's alpha was used to measure inter-observer agreement (scale of 0/no agreement to 1/perfect agreement).
Results: Prior to training, 36% of specimens were in complete agreement for tumor score across all reviewers compared to 40% following training (p=0.41, McNemar's test). There was significant improvement (p=0.02) in agreement for tumor scores within 1 level (64% versus 82%). For inflammatory score, 64% of specimens were within 1 level of agreement prior to training versus 56% following training (p=0.32).

Agreement	Without Training	With Training	p-value
Tumor Score			
Complete	36%	40%	0.41
Within 1 level	64%	82%	0.02
Krippendorf alpha	0.73	0.79	
Inflammatory Score			
Complete	20%	6%	0.03
Within 1 level	64%	56%	0.32
Krippendorf alpha	0.37	0.38	

Conclusions: Variability for tumor score improved with training, but variability for inflammatory score increased following training. These findings suggest that adequate training and pathologist monitoring may be required to successfully implement PD-L1 IHC and tumor scoring may be more practical than immune cell scoring using a manual interpretation process.

2085 Institutional Experience with the Bethesda System for Reporting Thyroid Cytology (TBSRTC) and Performance Parameters of Cytopathologists

Maryam Shahi, Sandhya Dasaraju, Matthew Root, Rupendra Shrestha, Lynn A Burmeister, Maria Evasovich, Khalid Amin. University of Minnesota, Minneapolis, MN.
Background: TBSRTC consists of 6 diagnostic categories: Non-diagnostic (DC I), benign (DC II), atypia of undetermined significance (DC III), suspicious for follicular neoplasm/follicular neoplasm (DC IV), suspicious for malignancy (DC V) and positive for malignancy (DC VI), each carrying an expected malignancy risk and recommended management. TBSRTC has set some performance expectations, however studies from various institutions have shown significant variability in categorization. We report 5 years institutional experience using TBSRTC and performance parameters of our pathologists.
Design: 2613 thyroid fine needle aspiration (FNA) specimens were performed from mid 2010 to mid 2015 and read by 7 cytopathologists. The follow up rate (repeat FNA, surgical intervention) and malignancy rate for each TBSRTC category was determined. The performance of 5 cytopathologists who signed out more than 200 cases was examined by calculating sensitivity, specificity, positive and negative predictive values, false positive and false negative rates, underdiagnosis (UDR) (malignancy rate of DC II) and overdiagnosis rates (ODR) (Benignity rate of DC IV, V or VI) and clinically significant error (CSER) rates that includes UDR and ODR (the errors that change the clinical management, dramatically).
Results: Our case distribution based on BSRTC was as follows: DC I 6.8%, DC II 78.8%, DC III 11.3%, DC IV 2.5%, DC V 2.1% and DC VI 4.6%. The overall follow up rate and surgical follow up was as follows respectively: DC I: 34.5%, 11.3%; DC II: 14.4%, 9.3%; DC III: 55.6%, 37%; DC IV: 66.7%, 59.1%; DC V: 85.2%, 81% and DC VI: 81.7%, 81.7%. Malignancy rate of FNAs and resections for each TBSRTC category are as follow: ND 1.7%, 5.0%; Benign 0.9%, 9.6%; AUS 12.5%, 33.9%; SFN 16.7%, 27.5%; Susp 69.5%, 84.1%; Pos 76.7%, 93.9%. Performance of cytopathologist (ranges) are as follow: total case sign out: 218-734 ; Sens: 89.4%-97.1%; Spec: 99%-96.8%; NPV: 98.7%-99.4%; PPV: 87.2%-93.7%; FPR: 0.75%-3.23%; FNR: 2.86%-10.61%; UDR: 0.004%-0.010%; ODR: 0.006%-0.023%; CSER: 0.011%-0.028%.
Conclusions: The results suggests that malignancy rate is best concordant with proposed TBSRTC malignancy rate if the recommended management approach is complied with. A slightly lower malignancy rate for DC VI (94%) suggest a tendency for undercalling positive cases in our institution. We also suggest CSER as possible performance parameter, however a larger cohort of cases are needed to extract a more meaningful performance data.

2086 Lymph Node Counting Practices by Trainees: A Pilot Study

John P Sherbeck, Lili Zhao, Richard Lieberman. University of Michigan, Ann Arbor, MI.
Background: The enumeration of lymph nodes (LNs) from oncologic surgical specimens plays a critical role in the staging of patients with solid organ malignancies. Depending on the location and histology of the tumor, the number of nodes assessed can affect TNM staging, adequacy of surgical resection, and/or eligibility for clinical trials. However, there is no standard method for counting LNs. Most studies in the literature site the pathology report as the source of LN data, without further discussion of the counting criteria. A prior multivariate study demonstrated the signing pathologist to be the strongest variable in the final LN count. However, to our knowledge, there have been no studies that prospectively evaluate lymph node enumeration by pathologists.
Design: Four microscopic slides, each from a separate routine pelvic LN dissection, were selected. All slides were negative for carcinoma. Slides were digitally scanned and uploaded with their gross descriptions to an online library. For each slide, respondents were asked how many LNs they would count as part of a staging procedure. The survey was distributed to pathology trainees (PGY1-4 AP residents and AP trained fellows) at our institution via email and completed independently.
Results: 25 trainees responded to the survey, with 24 surveys entirely completed. LN counts for each slide varied widely.

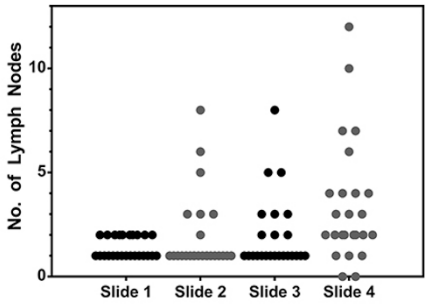

Figure 1. Distribution of lymph node counts for each slide. Each circle represents one respondent.

The consensus count for each slide (the most frequent response) was selected by 60%, 72%, 62.5%, and 32% of respondents, respectively. The intra-class correlation coefficient (ICC) for all four cases was very low (ICC=0.148).

Conclusions: LN counting is a critical part of tumor staging, yet there is wide variability in the methods used to arrive at a final count. In our prospective study, we have demonstrated a very low concordance rate in 4 routine pelvic lymphadenectomy slides. We postulate that this variability arises from differences in pathologist's definition of discrete LNs, assessment of multiple LN fragments within a single tissue piece, and importance they place on the gross description. As LN counts continue to drive clinical decision-making, we believe our data provides impetus for establishing uniform protocols for the counting of LNs to ensure inter-pathologist reproducibility.

2087 An Anorectal Cytology Quality Assurance Study of 43 Patients with Anal High-Grade Squamous Intraepithelial Lesions

Theresa Smith, Sarah Jamshed, Xiaofei Wang. UMass Memorial Medical Center, Worcester, MA.

Background: The detection of High-grade Squamous Intraepithelial Lesions (HSIL) on anorectal cytology (ARC) is low nationwide. As part of our QA program, we performed a cytohistological correlation study to identify possible factors that may affect detection of HSIL in ARC.

Design: 43 patients with biopsy-proven high-grade Anal Intraepithelial Neoplasia (AIN2 or AIN3) were selected for this study. Of 43 patients, 33 are males and 10 are females. HIV serology was positive in 38 patients and HPV was detected in the ARC samples of 37 patients. The ARC specimens were all liquid-based preparations (ThinPreps). All patients' biopsies and their prior cytology slides were reviewed blinded to the original diagnosis.

Results: Of 43 patients, the original cytologic diagnosis included 7 NILM, 12 ASCUS, 9 LSIL, 1 ASC-H, 4 LSIL-H, 9 HSIL and 1 AGUS. Based on the presence or absence of high-grade dysplastic cells in the original diagnosis, patients were divided into two groups: Group A with high-grade dysplastic cells (ASC-H, LSIL-H, HSIL and AGUS), including 15 patients. Group B without high-grade dysplastic cells (NILM, ASCUS, LSIL), including 28 patients. Upon review, all cases in both groups had adequate number of squamous cells present for evaluation. In Group A, 12 of 15 had anal transformation zone (TZ) sampling (80%). All original diagnoses were confirmed without any change. In GroupB, 12/28 had TZ sampling (43%). 22/28 cases had no high-grade dysplastic cells identified. 6/28 cases were found to have high-grade dysplastic cells. Of these 6 cases, one case which was originally diagnosed as NILM, showed enough evidence to diagnose HSIL. The other five cases had rare high-grade dysplatic cells consistent with ASC-H. The original diagnoses of these five cases were 2 NILM, 2 ASCUS and 1 LSIL. The original biopsy diagnoses of AIN2 or AIN3 on 43 patients were confirmed after reviewing the slides.

Conclusions: TZ sampling is important for detecting HSIL on ARC. Our data showed that there was significant difference of TZ sampling between Group A and Group B ($P<0.05$), although all cases in the two groups had adequate number of squamous cells present for evaluation. In addition, a second cytopathologist review may be helpful to improve the detection of HSIL in high-risk patients. In our 6 cases which originally failed to identify high-grade dysplastic cells, 5 cases had only rare high-grade dysplastic cells found on slides during our retrospective review.

2088 Evaluation of Mismatch Repair Immunohistochemistry Followed by Microsatellite Instability Testing in Colorectal Carcinoma

Anthony Snow, Amelia Fierro-Fine, Andrew M Bellizzi. University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Our institution implemented a universal Lynch Syndrome (LS) screening protocol as is supported by recommendations from Evaluation of Genomic Applications in Practice and Prevention (EGAPP) and the Association for Molecular Pathology (AMP). Our protocol involves mismatch repair immunohistochemistry (MMR IHC) for MLH1, PMS2, MSH2, and MSH6 applied to every newly diagnosed colorectal adenocarcinoma (CRC), frequently from biopsy material as the first step in screening. As a component of our screening protocol, cases which are MMR proficient (MMRp) by IHC have microsatellite instability (MSI) testing performed when tissue is available from subsequent resections. MSI testing is put in place to avoid missing a potential small percentage of cases which may have immunohistochemically identifiable mismatch repair proteins which are non-functional. The precise percentage of this case type is not well documented in the literature, but an estimated 5-11% of all LS cases will be MMRp by IHC and MSI-high. We assessed the efficacy and cost of this component of our screening approach.

Design: 980 charts were reviewed based on an information system search for mismatch repair IHC test codes. From these charts, cases of CRC which had MMR IHC and MSI testing performed on the same tumor were identified. The results were compared for concordance. Time and cost comparisons were performed.

Results: 678 CRC cases had MMR IHC performed since October of 2012. Of those, 574 were MMR IHC normal with 104 abnormal. Abnormal patterns included MLH1 deficient (MLH1d) (71%), MSH2d (14%), MSH6d (5.7%), PMS2d (4.8%), other (3.8%). Of the 574 MMRp by IHC cases, 308 were in-house cases and the remainder were referral material. 135 MMR IHC normal cases had MSI testing performed with 125 cases MS-stable and 10 cases MSI-low. No MSI-high cases were detected.

Conclusions: After review of approximately 4 years of material, clinical value was not added by MSI follow up testing. MSI testing resulted in laboratory material and technical personnel costs of $19,150. MMR IHC costs are 33.8% of the cost of MSI testing at our institution. MMR IHC requires 0.11% of the quantity of cells as starting material, 11.1% of time for case interpretation, 14.3% of the turnaround time of MSI. Additionally, MMR IHC is not restricted to the requisite 40% tumor cell composition relative to non-tumor nuclei needed for MSI molecular testing. Based on these results we strongly recommend discontinuance of secondary MSI testing from our LS screening protocol.

2089 Is Chemical Analysis of Recurrent Urinary Calculi Necessary?

Justin Snow, Francesca Khani, Theresa Scognamiglio, Brian Robinson. New York Presbyterian/Weill Cornell Medicine, New York, NY.

Background: Urinary calculi are routinely sent for pathologic examination and chemical analysis of the crystalline components. The makeup of these calculi include many different compounds, but most are composed primarily of calcium (75%), uric acid (10%), or struvite (10%). The aim of this study was to compare the crystalline content of recurrent urinary calculi to the index calculi to determine if there is a benefit to routinely sending subsequent calculi for chemical analysis.

Design: We retrospectively reviewed outside reference laboratory results of chemical analyses of all urinary calculi sent from our pathology laboratory from March 2014 to September 2016. In patients with more than one chemical analysis, we compared the chemical composition of each patient's primary calculi and subsequent calculi.

Results: A total of 808 patient samples were submitted. 89 of 808 (11%) of these patients were found to have recurrence of urinary calculi (1 or more subsequent urinary stones; median: 1 additional stone, range: 1 to 5 subsequent stones). 76 (85%) of these 89 patients had their calculi re-examined, for a total of 176 stones. Of these 76 patients, only 11 (14.4%) were found to have a change in calculi composition. 2 of 11 (18.2%) patients had a change in composition from struvite to calcium; 4 of 11 (36.4%) changed from calcium to struvite; and 5 of 11 (45.4%) changed from uric acid to calcium.

Conclusions: We conclude that a relatively small percentage [14.4% (11/76)] of patients at our institution with recurrent urinary calculi demonstrate a change in the chemical composition of their stones. Seven of these 11 patients were found to have calculi that changed from struvite or uric acid composition to the more common calcium, while 4 of 76 patients (5.2%) were found to have stones that changed from calcium to struvite. These data suggest that routine chemical analysis of recurrent urinary stones is not indicated in patients unless clinical suspicion of a different pathogenesis is suspected, e.g. struvite calculi in upper urinary tract infections. This could, in turn, save pathology departments valuable time and resources without compromising patient care.

2090 The Value of Structured Prospective Intradepartmental Consultation (SPIDC) in a General Anatomic Pathology Practice

John Srigley, Keiyan Sy, Janice Zeng. Trillium Health Partners, Mississauga, ON, Canada.

Background: Prospective intradepartmental consultation (PIDC) is a common component of pathology QA programs. PIDC may involve multi-headed microscopic slide reviews, casual ("curbside") consultations and SPIDC programs. There is limited data on the clinical value of SPIDC. The current study reports outcomes of a SPIDC program in general anatomic pathology practice.

Design: A PIDC form was designed with fields for demographics, requesting pathologist (RP) comments, consulting pathologist (CP) comments and RP classified outcomes of SPIDC. Four categories were used: A. No change in report; B. minor enhancements to report; C. major changes affecting clinical care and D. external opinion. Data was accumulated over an 18 month period and results assimilated on a master spreadsheet.

Results: 1968 SPIDC's accounting for 7% of surgical pathology and 2% cytopathology cases were performed. All 16 pathologists and fellows participated as RPs and/or CPs. 70% of cases were related to cancer and 30% non-cancer. The five commonest anatomic sites were breast (604 cases), GI (339), Gyn (221), lung (159) and GU (147). Consultations related to diagnosis (1485 cases), tumour subtyping (250), changes for threshold of diagnosis (104), grading (65) and stage or margin status (31). In 1962/1968 (99.6%) outcomes were recorded and in 1679/1962 (85.5%) cases, no change in the report was made. However, in 283 cases (14.4%), SPIDC resulted in a minor change in the report (11.6%) or a decision to refer out (1.9%). In 17 cases (0.87%), a major change in reporting affecting patient care was made.

Conclusions: The study demonstrates that SPIDC is of value in improving the quality of diagnostic pathology reporting. Importantly, the study suggests that in just under 1% of SPIDC a major change in pathology reporting with significant clinical implications is detected. Furthermore, the process identifies cases that are best referred out for additional consultation.

2091 Pan-Canadian Quality Assurance Recommendations for Interpretive Pathology – Development of a National Framework

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Background: In response to recent adverse sentinel events and the identified lack of a standardized approach to quality assurance (QA) for interpretive pathology (IP) in Canada, the Canadian Partnership Against Cancer facilitated the assembly of a pan-Canadian thought leaders group to develop a recommendations framework for IP QA.

Design: Following a comprehensive literature review, a three-stage modified-Delphi process, including pre-meeting survey, in-person Delphi meeting and post-meeting survey, wasused to achieve consensus on recommendations,. The document subsequently underwent targeted and public reviews, seeking input from a wide range of stakeholders, including patients.

Results: There were 73 initial recommendations drafted after the literature review. The modified-Delphi process resulted in 54 final recommendations divided into 5 areas: 1) Foundational elements, including governance, linkage to existing QA programs, and resources, such as human resource planning, documentation systems, and informatics (27 recommendations); 2) The pathology testing cycle from an interpretive perspective (11 recommendations); 3) Internal QA policies and procedures (12 recommendations); 4) External QA (3 recommendations); 5) An approach to expressions of concern regarding a pathologist's performance (1 recommendation). Over 100 individuals and groups from across Canada participated in the targeted and public review phases.

Conclusions: To enable robust, consistent and high-quality pathology QA in Canada, we have developed a comprehensive set of recommendations for IP which can be implemented within existing provincial QA programs. To ensure uniform quality of diagnostic care for patients, the framework will help guide healthcare providers and senior decision-makers in implementing IP quality programs provincially and locally. Future plans include knowledge mobilization related to the recommendations and the development of system-level indicators.

2092 Genomic Testing Using Cytology vs Surgical Specimens: A Comparative Study

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Background: The demand for adequate and well preserved tissue for genomic analysis has dramatically increased in the past few years with the emergence of precision medicine and targeted therapy approaches for the management of diseases, specifically cancer. Since some of the tumors are either deep-seated or unresectable, we are relying heavily on cytology material for these studies. The goal of this study is to evaluate our cohort of patients who underwent genomic analysis and compare the data for surgical and cytology specimens.

Design: We performed a retrospective review for patients who underwent FoundationOne testing in our medical center and compared genetic alteration data for surgical and cytology specimens. We also compared major tumor types, and multiple specimens from the same patients.

Results: Of the 446 specimens (from 439 unique patients) sent for testing, 146 (33%) were cytology and 300 (67%) were surgical. Patients ranged in age from 11 to 87 years old (average = 60). 255 (58%) patients were males and 184 (42%) were females. Six patients had multiple specimens tested including 4 patients with both surgical and cytology specimens. The majority of tumor types were represented in the cohort. Overall, there were 18.4 non-synonymous (protein altering) genetic alterations per specimen. There average number of alterations for all tumor types was 18.2 and 18.8 for surgical and cytology specimens, respectively. The same trend was also true for major tumor types; for example, the average number of alterations for surgical and cytology specimens was 22 and 23, respectively, for both colorectal and lung tumors. The limited number of cases with both surgical and cytology specimens showed a relatively similar number of alterations. Both cytology and surgical specimens showed similar variant allele fraction (VAF), however, the average read depth was significantly higher for cytology specimens (P= 0.000005).

Conclusions: Our preliminary results show that genomic testing for tumor specimens resulted in a similar number of mutations detected in cytology and surgical specimens. Additionally, the data suggests that material obtained from cytology specimens could be of better quality (DNA integrity). Further analysis is needed to correct for any inherent bias and compare the collection and processing techniques for both specimen types, and ultimately help guide specimen selection for best patient care.

2093 p16 Immunohistochemistry Is Not Required for Accurate Diagnosis of Cervical Intraepithelial Neoplasia, Grade 2 (CIN 2), When Histologic Features Suggest a Definite High-Grade Squamous Intraepithelial Lesion

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Background: Preinvasive squamous neoplasms of the lower genital tract are currently classified using a two-tier system (low-grade squamous intraepithelial lesion, LSIL, vs. high-grade squamous intraepithelial lesion, HSIL), but for clinical management are also still subclassified under a three-tiered scheme (intraepithelial neoplasia grade 1, 2 or 3; -IN1, -IN2 or –IN3). The clinical need is to distinguish –IN2 and above (precancer, HSIL) from –IN1 and below (not considered precancer). The Lower Anogenital Squamous Terminology (LAST) working group recommended in 2012 that all –IN2 diagnoses be supported by immunohistochemistry (IHC) for p16, a high-risk human papillomavirus surrogate marker. We hypothesized that this testing is not necessary when HSIL is obvious on H&E.

Design: The study cohort consisted of lower female genital tract biopsies and resections in which initial H&E findings suggested either a diagnosis of –IN2 or a differential diagnosis that included –IN2. The study intervention was IHC for p16 and Ki-67. We recorded the preanalytic differential diagnosis (using H&E alone), IHC results, and postanalytic diagnosis (incorporating IHC findings). H&E slides and immunostains from all cases were reviewed by the authors in blinded consensus.

Results: 93 specimens met inclusion criteria. In 35 cases, the H&E findings were equivocal (e.g., -IN1 vs. -IN2) so that IHC was medically necessary. In the other 58 cases, a diagnosis of HSIL was considered histologically apparent by the reviewing pathologist. 55/58 (95%) were maintained at –IN2 or higher after incorporating p16 and Ki-67 results, while 3 (5%) were reclassified as less than –IN2. Of the 11 specimens with a preanalytic differential of -IN2 vs. -IN3, none were downgraded after IHC. In 5 cases, IHC results contradicted obvious histologic –IN2 (i.e., clear moderate dysplasia), introducing a diagnostic dilemma.

Conclusions: We conclude that the LAST recommendation to support all diagnoses of –IN2 with p16 IHC will result in performing the immunostain in many circumstances where it is not medically necessary, especially in cases where the underlying differential diagnosis is between –IN2 and –IN3. Ordering clinicians should recognize that in such cases -IN2 can be reliably diagnosed without ancillary p16 staining.

2094 Analysis of Diagnostic Breast Biopsies with Atypical Ductal Proliferation: A Quality Assurance Measure

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Background: Atypical ductal hyperplasia (ADH) is defined as proliferation of cells in terminal duct lobular units showing both characteristic monotypic cytology and abnormal polarization resulting in cribriform architecture. Atypical ductal proliferation (ADP) is a diagnostic term developed in our practice to denote ductal proliferative lesions lacking full criteria of ADH in core needle biopsies (CNB). The aim of our study was to assess the outcome and impact on clinical management for patients who were diagnosed with ADP on core biopsies.

Design: A retrospective study of breast CNB over a 10-year period was conducted to identify cases of atypical ductal proliferation (ADP). Clinical history, patient demographics, and radiological findings were recorded for all cases. Follow-up excision specimens were reviewed and the findings were categorized as benign, atypical, or malignant.

Results: Of 13,827 patients who underwent breast CNB, 131 patients (1%) were diagnosed as ADP. All the patients were women, with an average age of 55 years (range: 28-82 years). The indication for biopsy was calcifications (n=71; 54%), mass lesion (n=29; 22%) asymmetry, abnormal enhancement, focal density (n=22; 17%) or unknown (n=9; 7%). Of the 131 cases, surgical procedure was performed in 111 patients, of whom 89 patients (80%) underwent excisional biopsy, 15 patients (14%) underwent mastectomy, and 7 patients (6%) underwent repeat CNB. After review of additional specimens, the cases were classified as benign (n=73, 66%), atypical (n=30, 27%), or malignant (n=8, 7%). 5 of the 8 cases upgraded to DCIS or invasive cancer had malignancy in a different quadrant than the focus of ADP seen on CNB and were hence excluded.

Follow-up Diagnoses of Patients with ADP	
	Number of patients (n=106)
Benign	Non-proliferative FCC (n=24)Proliferative FCC (n=49)
Atypical	FEA (n=2)ADH (n=13)ALH (n=10)ADH and ALH (n=5)
Malignant	DCIS (n=1)Invasive (n=2)
FCC = fibrocystic changes; FEA = flat epithelial atypia; ALH = atypical lobular hyperplasia; DCIS = ductal carcinoma in situ	

Conclusions: A significant number of cases diagnosed as atypical ductal proliferation were atypical (27%) on subsequent follow-up, and only a small percentage (3%) of these cases was upgraded to malignancy. The use of ADP as a diagnostic term should be considered in challenging breast core needle biopsies in which criteria for ADH are not met.

2095 Comparison of Immunohistochemistry Staining Performed on Cell Blocks versus Surgical Blocks from the Same Tumor

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Background: The purpose of this study is to compare immunohistochemical stains performed on the cell block (CB) versus the histology blocks (HB) collected from the same specimen. We seek to validate that immunohistochemical stain results obtained from CB are consistent with those obtained from surgical specimen blocks.

Design: We prospectively collected cytologic and histologic material from 57 surgical cases between 2015 and 2016. For the HB, a piece of tumor was removed and processed routinely after formalin fixation. The tumor was scraped with a preparation blade and the blade was rinsed in saline. The rinse was then subjected to a standard protocol for CB preparation and fixed in formalin. Both the CB and the HB had the same vacuum infiltration processing, embedding, microtomy and antibody staining procedures.

The slides were reviewed by a cytopathologist and data was collected based on the presence or absence of stains. Focal staining of the CB tumor comparable to the HB correspondent section was counted as concordant.

Results: Of the total 57 cases sampled, 16 were disqualified, due to paucity of cells of interest in the cell block. On the remaining 41 specimens, 118 stains were performed with adequate controls.The CB staining pattern matched that of the HB on 113 stains. The table reviews the findings.

Organs	Stains	CB vs HBNo. of stains with similar staining pattern	CB vs HBNo. of stains with discordant staining pattern
Lung	panCK, p63, TTF-1, CK5, MOC31, Ber-EP4, CD56, AE1+3, chromogranin,synaptophysin	15	0
Kidney	NSE, synapto, CD56, chromo, PAX8, RCC, Vim, CD10, WT-1, CD34	13	2
Pancreas	Beta-catenin, TTF-1, synapto, CK19, CEA, chromo, CA19-9	11	0
Liver	Hepar-1,Glypican-3, CK20, CDX2	5	0
Breast	ER, PR, GATA-3	4	2
Skin	S100, HMB45, SOX-10, Melan-a, p40	17	0
Soft tissue	TTF-1, napsin-a, CK7, CK20, MOC-31, CK7, CD99, EMA, CD34, BCL-2, Vimentin,S100, HMB45, SOX-10, Melan-a	18	0
Hematopoietic system	Cyclin-D1, CD5, CD20, BCL-6, CD10, CD34, CD117, CD20, CD79a, C-myc	15	0
Testis germ cell tumor	CD30, PLAP	1	1
Other Organs	CK7, p63, CEA, CK20, CK7, CDX2,ER, PR, CA125, Vim, PAX-8, Thyroglobulin, TTF-1, panCK	16	0

Conclusions: The concordance rate obtained between the cytology cell block and the histology block immunohistochemical staining results is a good 95.7%. The immunohistochemical stains on cell blocks yield similar results to histology blocks.

2096 Leaning Out the Clinical Trials Process: Optimizing the Last Hope in Cancer Care

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Background: Henry Ford Cancer Center offers clinical trials to cancer patients unresponsive to usual therapies. In this end-game, time to enrollment is critical as any delay in patient enrollment is significant. Our starting condition was a much delayed process initiated by Clinical Trials Office with connections to Surgical Pathology File Room to Pathologist for case review and block selection and then back to Clinical Trials Office. This resulted in much clinician and patient dissatisfaction with Surgical Pathology. We began by listening to the voice of the customer- disgruntled oncologists- and then addressing this flawed value stream using Lean problem solving approaches. The goal was to quickly and dramatically reduce the time delay to patient enrollment for clinical trials requests.

Design: We held an initial kick-off meeting with 2 sponsors- Chair of Neurosurgery/ Cancer Center Director and Chair of Pathology and held weekly customer-supplier meetings with the multidisciplinary team of stakeholder oncologists, research administrator, surgical pathologists, histotechnologists, clinical trials nurses and Lean facilitators from Pathology. We focused on educating the Kaizen methodology, agreeing on a formal Kaizen Charter, developing a Value Stream Map to identify bottlenecks and time waste, defining customer requirements for routine and urgent clinical requests. In this team-based approach we redesigned workflow and implemented standard work.

Results: Within 3 weeks we achieved a 76.5% time improvement for routines clinical trials requests and 82.4% for STAT requests. We also reduced process steps by 42%, from 12 to 7 steps. From time of clinical request, routine clinical trials cases were turned around in average of 8.2 days down from 17 days and STAT requests were reduced to 1.7 days from 4 days. This improvement has sustained for over 8 months based on transparent daily metrics shared between stakeholders.

Conclusions: Taking a chronic frustration resulting from a broken process owned by 2 or more groups to a sustained resolution requires collaboration to define customer requirements and agreement to mutually redesign and accept new processes based on data. The keys to our success were understanding Kaizen methodology for process improvement that enabled resolution by defining customer requirements, building relationships with customers to foster regular communication, mapping current state of the process, simplifying and standardizing process steps. To sustain the improvement we designed Daily Management Metric Boards, Daily Huddles and implemented visual controls with 5S cards.

2097 Incidental Prostate Cancer in Cystoprostatectomy Specimens, a Clinical Effectiveness and Quality Improvement Study

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Background: Incidental prostatic adenocarcinoma (IPA) is found in 25-46% of cystoprostatectomy resections (CPR) performed for bladder cancer (BCa). Despite this, no metastases or mortality related to IPA have been reported. We examined current grossing practices at our institution, which include submitting the remainder of the prostate in all cases with IPA, additional information gained from these extra sections, and the impact of IPA on patient care.

Design: 58 radical CP cases from 2013-2015 were reviewed. Grossing methods and turnaround times (TAT) were examined for all cases. For cases with IPA, initial (average 8.3 sections) and subsequently submitted prostate sections were evaluated for histologic grade and impact on tumor staging. Clinical history was examined for all patients with a focus on post-operative course, follow-up (f/u) for IPA and mortality.

Results: IPA was found in 44.8% of CPR. When IPA was seen on initial sections, submitting the remainder of the prostate significantly increased TAT by 2.7 days (7.9±0.8 vs 5.3±1.1 days, $p<0.05$) and led to additional lab costs. Clinically significant IPA (Gleason score ≥ 7/ Grade group ≥ 2) was found in 12% of cases (maximum Grade group 4). Only 15% of cases showed a change in diagnostic parameters with additional sections. Positive urethral margins were seen in 8% of cases and occurred when the margin was not frozen and was submitted *en face*. 42% of patients were found to have metastatic BCa or be deceased upon clinical f/u. Of the patients with IPA and documented f/u, 65% had post-op PSA measurements while 35% have no documented f/u for IPA. No correlation between rate of f/u and clinically significant IPA was seen.

Conclusions: Clinically significant IPA is seen in a minority of CPR. Examination of the entire prostate did not change the diagnostic parameters in 85% of cases but significantly increased TAT and led to additional cost. Little or no f/u for IPA was documented in the medical records, largely because patients had high morbidity and mortality secondary to BCa. When IPA was found at the urethral margin, these margins had been submitted *en face* and intraoperative frozen sections had not been requested. We conclude that all urethral margins should be sectioned perpendicularly to best assess margin status. For most cases of IPA, examining additional prostate does not significantly alter the initial diagnosis or affect patient care, and an institutional protocol should be established to prevent unnecessary sectioning.

2098 Effect of Discontinuing Reflex Testing for Helicobacter Pylori by Immunohistochemistry

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Background: Recognizing and reporting Helicobacter pylori (H. pylori) infection in gastric biopsy specimens is an important part of surgical pathology due to its association with gastritis, ulcers, adenocarcinoma, and mucosal associated lymphoid tissue (MALT) lymphoma. Previously, our institution performed immunohistochemistry (IHC) for H. pylori on every gastric biopsy. The value of reflex testing has recently been questioned in a position paper by the Roger C. Haggitt Gastrointestinal Pathology Society[1]. Subsequently, our institution discontinued reflex IHC for H. pylori and left the decision to the discretion of the individual pathologist based on the hematoxylin and eosin (H & E) findings as part of a quality initiative and opportunity for cost reduction. We then conducted a retrospective review to see what effect, if any, this change in policy had on the detection of H. pylori.

Design: We analyzed two three-month periods, one with reflex testing and one without, and reviewed all gastric biopsy reports. For the reflex period we recorded the number of cases positive for H. pylori by IHC. For the non-reflex period we recorded the number of cases both positive and negative by IHC as well as the number of cases positive on H & E alone.

Results: During the reflex period, there were 1012 total gastric biopsy cases all of which received IHC, and 57 of which were positive for H. pylori for a rate of 5.6%. During the non-reflex period, there were 984 total gastric biopsy cases. IHC was ordered 190 times, 19 of which were positive. H. pylori was reported as present on 25 cases with H & E only. The overall rate of reporting H. pylori was 4.8% (44/984) during the non-reflex period, which was not statistically significant from the reflex period ($p= 0.4346$). The ordering of IHC for H. pylori dropped from 100% (1012/1012) to 19.3% (190/984) of total cases.

Conclusions: Discontinuing reflex IHC for H. pylori in gastric biopsies led to large decrease in IHC utilization, representing a substantial cost-savings for patients. It also did not significantly affect the rate of reporting H. pylori. In our experience, reflex IHC in gastric biopsies does not significantly improve detection of H. pylori and therefore, there is no evidence that it is necessary.

2099 Three FDA Approved PD-L1 Assays Demonstrate Concordant PD-L1 Expression in Various Solid and Hematologic Tumors, with Higher Expression in Hodgkin and Diffuse Large B-Cell Lymphomas

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Background: The FDA has approved three PD-L1 assays with DAKO (22C3), DAKO (28-8), and VENTANA (SP142), for evaluating the PD-L1 status to guide immunotherapy with different anti-PD-1/anti-PD-L1 drugs, respectively. We investigated whether different PD-L1 antibodies will reveal distinctive PD-L1 status and the association between PD-L1 expression and oncogene mutations in lung adenocarcinoma and melanoma.

Design: The studied tumors included 95 cases from 9 entities (Table 1), including lung adenocarcinoma without oncogene mutations (n=13), or with mutated *KRAS* (n=8), or with mutated *EGFR* (n=8), and melanoma with (n=10) or without *BRAF (V600E)* mutation (n=10). PD-L1 immunohistochemical (IHC) staining was performed on the Autostainer Link 48 and its expression was examined in tumor cells (TC) and tumor-infiltrating immune cells (IC). Cases with positive PD-L1 expression in TC (>1%) were further categorized into low- or high-level based on 1-49% or ≥50% of TC showing membrane staining.

Results: IHC staining with three PD-L1 antibodies showed concordant PD-L1 expression in TC (Table 1) and IC, except for lower PD-L1 staining in one lung adenocarcinoma with 22C3 and in one DLBCL with SP142 clones, respectively. There was no definite correlation between PD-L1 expression and oncogene mutations in lung adenocarcinoma and melanoma (Table 2). Interestingly, significantly higher PD-L1 staining was noted in high-grade versus low-grade lymphomas *(*$p<0.01$) and in Reed-Sternberg (RS) cells of all Hodgkin lymphomas.

Conclusions: The concordant PD-L1 expression with different antibody clones in various tumors makes it unnecessary to evaluate PD-L1 status with different antibodies. The significantly higher PD-L1 staining in high-grade lymphomas and in RS cells makes PD-L1 a good candidate marker for diagnostic purpose.

Table 1		SP142		22C3		28-8	
		PD-L1 expression					
Tumors	n	Low	High	Low	High	Low	High
Lung	29	4	6	5	5	4	6
Melanoma	20	8	1	8	1	8	1
Breast	5	2	0	2	0	2	0
Colon	5	0	0	0	0	0	0
RCC	5	0	1	0	1	0	1
Urothelial	4	1	0	1	0	1	0
Classic Hodgkin lymphoma	10	0	10	0	10	0	10
DLBCL	10	5	3	4	4	4	4
Low grade lymphoma (FL, MALT, marginal zone)	7	1	0	1	0	1	0
Total	95	21	21	21	21	20	22

Table 2		PD-L1 expression		
		-	Low	High
Lung Adenocarcinoma	Wild typeKRAS/EGFR/ALK	6	3	4
	KRAS mutant	6	1	1
	EGFR mutant	7	0	1
Melanoma	Wild type BRAF	5	4	1
	BRAF (V600E)	6	4	0

2100 What Is the Optimal Flow Cytometric Screening Panel for Our Patients? An Evidence-Based Approach

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Background: As healthcare reform efforts align quality, outcomes, and cost into a value-based reimbursement system,a greater need for efficient,cost-effective testing is emerging.Flow cytometry is an important tool in the diagnosis of hematologic malignancies, used to rapidly characterize expression of cellular antigens.Given recent technological advances,many laboratories have adopted comprehensive antibody panels in the initial evaluation. However, it is unclear if this strategy will be viable in a value-based reimbursement climate.The goal of this study was to determine the optimal combination of markers that balance efficiency and accuracy for our patient population.

Design: Leukemia/lymphoma (L/L) flow cytometry testing from January 2016-July 2016 at our institution was reviewed.

Results: Of the 611 cases in which L/L testing was performed,357 were negative for an abnormal hematolymphoid population,154 were bronchoalveolar lavages (BAL),and the remainder showed abnormal B lymphoid (50),blast(20),plasma cell (17),T cell (7), or monocytic (6) populations.Pitfalls included:8 aberrant plasma cell populations buried within the myeloid compartment in the CD45 vs side scatter plot, requiring CD38 or CD138 for identification;6 monotypic B cell populations buried within a polytypic background on kappa:lambda plot,requiring additional analysis with CD10 or light scatter; 3 CD19- or CD20- B cell lymphoid populations;3 aberrant T cell populations buried within reactive T cells. Minimum antibody requirements for L/L screening were: CD45, CD19, CD20, kappa, lambda, CD10, CD3, CD5, CD4, CD8,CD56. Characterization of B cell populations requires assessment of both CD19 and CD20, and identification of plasma cell neoplasms requires CD138 and/or CD38.

In comparing the current vs a screening approach, the elimination of unnecessary antibody expenditure results in an average of 10 fewer antibodies/case, with an estimated cost savings of $61,100/year.

Diagnosis	Percentage of cases	Number of antibodies to characterize (current)	Number of antibodies to characterize (proposed future)
BAL	25%	10	4
Negative or CD10+ B cell lymphoma	64%	24	11
Acute leukemia	4%	32	32
Plasma cell neoplasm	3%	25	19
CD10- B cell lymphoma	3%	23	18
T cell lymphoma	1%	27	19
Average	--	21	11

Conclusions: We present a framework for developing an evidence-based screening panel that allows for tailoring of the flow cytometric evaluation to the diagnostic need, resulting in cost-effective testing without a reduction in quality.

2101 HER2/*ERBB2* Testing in Breast Carcinoma by Next Generation Sequencing

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Background: A proportion of primary breast carcinomas (10-20%) shows HER2 protein overexpression due to *ERBB2* gene amplification which predicts response to targeted treatment. The current standard for HER2/*ERBB2* testing is based on immunohistochemistry (IHC) and in-situ hybridization techniques. Using an amplicon based sequencing technique (anchored multiplex PCR, AMP), we investigate the concordance rates of our standard HER2 IHC and *ERBB2* fluorescence in-situ hybridization (FISH) testing with *ERBB2* CNV results of the institutionally developed next generation sequencing (NGS) SNAPSHOT assay.

Design: 143 clinically annotated specimens from 134 patients with metastatic breast carcinoma were tested. HER2 IHC, *ERBB2* FISH and NGS were performed on either formalin-fixed paraffin-embedded (FFPE) tissue blocks (N=101) or FFPE cytology cell blocks (N=42) using standard protocols for HER2 IHC (Leica Bond automated IHC) and FISH (Vysis *ERBB2*:CEP17 Dual Color Probe) as per guidelines. FISH was amplified if *ERBB2*:CEP17 ratio was ≥ 2, and equivocal if *ERBB2* copy number per cell was 4-6. For NGS SNAPSHOT using the Illumina platform, we determined the CNV relative log(2)ratios of 0.75-1 as equivocal and >1 as amplified in *ERBB2*.

Results: Seventeen patients (13%) were HER2/*ERBB2* positive, 109 (85%) HER2/*ERBB2* negative, and 2 (2%) HER2/*ERBB2* equivocal by IHC and/or FISH. NGS testing was positive for *ERBB2* gene amplification in 13 patients (10%), negative in 110 (86%), and equivocal in 5 (4%). NGS results were discordant from IHC/FISH HER2/*ERBB2* status in 2%: two HER2/*ERBB2* positive patients were *ERBB2* negative by NGS, one HER2/*ERBB2* negative patient was *ERBB2* positive by NGS. 2 patients with equivocal *ERBB2* by FISH were negative by *ERBB2* NGS, and 2 HER2/*ERBB2* positive patients were *ERBB2* equivocal by NGS. NGS failed in 8 specimens from 6 patients (5%) due to insufficient DNA. Overall sensitivity of *ERBB2* NGS when compared with standard HER2/*ERBB2* testing was 86% with specificity of 99%.

	Positive	Equivocal	Negative	Total
HER2/ERBB2 IHC/FISH	17 (13%)	2 (2%)	109 (85%)	128 (100%)
ERBB2 NGS	13 (10%)	5 (4%)	110 (86%)	128 (100%)

Conclusions: The SNAPSHOT NGS assay, although not designed for CNV detection, provided a high HER2/*ERBB2* concordance rate of 98% for satisfactory samples when compared with standard HER2/*ERBB2* testing by IHC/FISH. Two cases of equivocal *ERBB2* by FISH were negative by *ERBB2* NGS. NGS may be useful in HER2/*ERBB2* testing of breast cancer.

2102 Defining True Cellularity in Age-Matched Marrows

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Background: Bone marrow biopsies from the posterior iliac crest are used for diagnosis, staging, and treatment evaluation. Knowledge of the normal variations in marrow cellularity is critical for evaluating the adequacy of hematopoiesis. Unfortunately, a simple linear and unit decrease in cellularity with age is often used to determine normal cellularity. This "100% minus the age" model is an oversimplification. Accurate assessment of hypo-, normo-, or hyper-cellularity is important for effective patient management, and a better understanding of normal cellularity is required. Bone marrow biopsy in healthy individuals is precluded by its invasiveness. Normal staging marrows could represent marrows from "normal" individuals, which has the benefits of a large sample size, associated medical history, peripheral blood evaluation, and follow-up.

Design: A large "normal" patient study (>500 cases) was conducted by reviewing pathology reports for staging bone marrows from January 1990 to August 2016. Only specimens with adequate clot or trephine biopsies, normal marrow morphology, and without dysplastic changes, abnormal maturation, fibrosis, or osteodystrophy were included. Exclusion criteria included myeloproliferative disorders, involvement by malignancy (including lymphomas, carcinomas, and sarcomas), congenital hematologic disorders, prior hemopoietic stem cell transplantation, and cytokine effect. Cases with erythrocyte microcytosis and macrocytosis as well as abnormal peripheral blood counts were also excluded because they may reflect nutritional deficiencies or treatment effect. Reported cellularities were based on direct visual estimates by experienced hematopathologists.

Results: The observed variation in cellularity with age demonstrated only a small decrease in cellularity of approximately 3% per decade from age 20-90. The calculated cellularity mean and two standard deviations are approximately 50% and 25%, respectively. Variations in cellularity for fifteen healthy donors fell within the 95% prediction limits of the patient sample. Different disorders showed expected biases for age, but demonstrated a scattered distribution for cellularity. The sample means for patient age and cellularity in cases reviewed by four hematopathologists were not significantly different.

Conclusions: Normal marrow cellularity does not decrease by 10% per decade. Instead, only a small decrease in cellularity of approximately 3% per decade is observed from age 20-90. Moreover, 95% of all cellularities fall between 25-75%. This study shows that normocellular marrows without cytopenias can range from 25-75% regardless of age.

2103 Breast Carcinoma Biomarkers: Effects of Hydrochloric Acid and Formic Acid Decalcification on Immunohistochemistry and *In Situ* Hybridization

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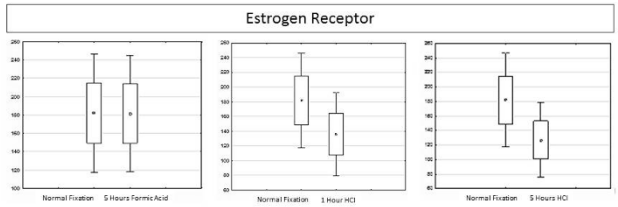
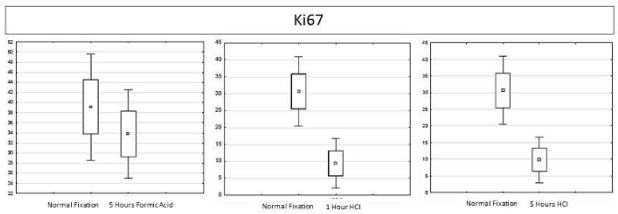
Background: Biomarker analysis of metastatic breast carcinoma (MBC) is routinely recommended by ASCO/CAP guidelines, and establishing a diagnosis of MBC often requires immunohistochemistry (IHC). The reliability of breast tumor biomarkers and breast-specific markers on decalcified tissues has not been extensively studied. We performed IHC studies on breast tumors exposed to hydrochloric acid and formic acid decalcification solutions and HER2 fluorescence in situ hybridization (FISH) on a subset of these tumors in order to establish a protocol for handling bone specimens with suspicion for MBC.

Design: Fifteen fresh cases of primary breast carcinoma and 8 HER2+ paraffin-embedded core biopsy cases were studied. Fresh tissue was divided into five fragments to approximate a bone core biopsy. One fragment (control) was fixed in 10% neutral buffered formalin (NF). Remaining fragments were also exposed to formic acid (FA) or hydrochloric acid (HCl) decalcification for 1 or 5 hours. All fragments were embedded in one block and stained for an IHC panel. The known HER2+ cases were exposed to either 1 or 5 hours of FA, and HER2 FISH was also performed. Results were interpreted as follows: H-scores for ER, PR, and GATA-3 were assigned from 0-300, HER2, CK7, GCDFP-15, Pax-8, TTF-1, CK20, and mammaglobin were scored from 0-3+, and Ki67 from 0-100%. Mean scores were compared using t-test for paired samples.
Results: Mean scores for ER, PR, HER2, Ki67 and GATA-3 were significantly lower than NF in tissue after either 1 or 5 hours of HCl. Mean scores for GCDFP-15 staining in tissue after 5 hours of HCl were significantly lower than NF. No significant differences in mean score were seen between NF and 1 hour FA for any IHC staining. After 5 hours of FA, only Ki67 average score was significantly less than NF.





Three of 5 HER2 equivocal cases (2+ by IHC) were negative (0 or 1+) following 5 hours of HCl and 1/5 was negative following FA exposure. All HER2+ cases were amplified by FISH.
Conclusions: Decalcification with HCl but not FA has significant effects on IHC staining. HER2 FISH was not affected by FA exposure. Breast cancer biomarker interpretation in samples exposed to HCl should be avoided, but formic acid may be used for 5 hours or less with caution.

Techniques (including Ultrastructure)

2104 Diagnostic Utility of Fourier Transform Infrared (FT-IR) Spectroscopic Imaging of Preeclamptic Placenta Tissue

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Background: The diagnostic criterion for preeclampsia is hypertension (blood pressure ≥ 140/90 mmHg) and proteinuria (> 300 mg/24 hours) after 20 weeks gestation. Various etiologies including fetal growth restriction, diabetes mellitus and antiphospholipid syndrome share similar histological features of maternal malperfusion. This has made morphological analysis of the placenta via standard optical microscopy limited in diagnostic potential. A recent study demonstrated a 2-fold yield of histological findings compatible with maternal malperfusion with increased sampling of the preeclamptic (P) placenta. However, increase sampling methodology and nonspecific histological features still leaves a robust biochemical signature unanalyzed. The aim of this study is to assess the biomolecular signature of preeclampsia tissue and propose a novel methodology of evaluating placenta tissue for diagnostic application.
Design: We utilized a placenta tissue microarray (TMA) that were constructed based on the functional anatomy of the placenta into individual cores of the chorionic plate (P1), middle chorionic villi (P2), and basal plate (P3) for both preeclamptic (n = 23) and nonpreeclamptic (NP) tissue (n = 26). Multivariate techniques such as principal component analysis and linear discrimination analysis were utilized to differentiate the two groups.
Results: Analysis of P1, P2 and P3 were performed independently of one another. We collected FT-IR data from the TMA and extracted biochemical signatures from the structures of the placenta. P1 showed the best biochemical distinction between normal (n=24) and preeclamptic (n=20) placenta, with a misclassification rate of 3 out of 44 samples. P3 also showed good biochemical distinction between P (n=13) and NP (n=21) with a misclassification rate of 4 out of 34 samples. Lastly, P2 showed the least discrimination compared to the other regions of the placenta. P (n=19) and NP (n=17) groups showed misclassification rate of 5 out of 36 samples.
Conclusions: FT-IR spectroscopy imaging of placenta tissue with statistical pattern recognition of spectra is a novel methodology. Our data suggest that spectra changes can be reliably distinguished when discriminating preeclamptic versus nonpreeclamptic placenta. Although we do not predict that this method will be necessary for routine pathology practice, it may be a useful research discovery tool once the spectral signature is decoded to identify specific molecular markers.

2105 Nicotinamide Phosphoribosyltransferase a Novel Marker for Cervical Dysplasia

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Background: Invasive cervical squamous cell carcinoma (SCC) is the second most common gynecologic malignancy world-wide. Histologically it is almost invariably preceded by progressive grades of in situ dysplasia. Nicotinamide phosphoribosyl transferase (Nampt) catalyses the rate-limiting step of nicotinamide adenine dinucleotide synthesis. Nampt protein levels are elevated in number of epithelial and mesenchymal malignancies in which higher levels of NAMPT expression correlate with advanced tumor grade and worse prognosis. Here we report Nampt expression in a range of cervical epithelial lesions.
Design: We used Tissue microarrays (TMAs) contained 12 benign cervical squamous epithelial samples, 15, 15, and 13 samples of cervical intraepithelial neoplasia (CIN) I, II, III respectively. Tissue cores also included cases of SCC, 5 low grade, 67 intermediate, and 81 high grade. 7 cases of endocervical adenocarcinoma. Additionally, 13 sections of benign endocervical epithelium were also identified within the TMA tissue and used in this analysis. The concentration of primary Nampt antibody was optimized to normal kidney as control tissue. Mouse monoclonal antibody to human Nampt was used at a 1:1000 concentration. Relative Nampt protein expression was determined as immunostain intensity scored on a 0-3 scale. The final IHC score was the product of the percentage of cells stained multiplied by the intensity score, allowing for a maximal score of 9 and a minimal score of 0.
Results: Nampt is a marker for cervical dysplasia which increases in a grade-dependent manner in CIN and invasive SCC. Nampt is also highly expressed in cervical adenocarcinoma in comparison to benign endocervical epithelium (Table 1). In contrast to p16 which is expressed in only 54% of CIN I, immunoreactivity for Nampt is found to be doubled in CIN I when compared to benign sequamous epithelium.

Tissue Type	Sample Number	Average Nampt IHC Score	SEM
Benign Cervical Sequamous Epithelium	14	1.57	0.14
CIN I	11	3.45	0.49
CIN II	9	3.86	1.02
CIN III	8	4.91	0.76
SCC Grade I	5	4.00	0.55
SCC Grade II	56	4.91	0.32
SCC Grade III	53	6.43	0.37
Benign Cervical Columnar Epithelium	13	1.77	0.23
Adenocarcinoma	7	7.71	0.95

Conclusions: Nampt is a reliable marker of progression in cervical dysplasia that may contribute towards evaluation of cervical epithelial abnormalities.

2106 Application of Hematoxylin and Eosin Staining as Counter Stain to Improve Immunohistochemistry Interpretation

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Background: Common progressive hematoxylins like Mayer's or common regressive hematoxylins like Harris are used as counterstain for IHC, despite the fact that hematoxylin/eosin (H&E) combination is the most common staining technique in histology. The aim of the current study is to investigate the clinical utility of H&E as counter staining for IHC (HE-IHC) to facilitate the interpretation of a marker on small biopsies.
Design: The HE-IHC protocol was optimized to ensure quality as well as technical efficiency. With the optimized protocol, we stained multiple prostate and liver cases with class 1 IHC markers (Ck5/6, 34BE12, p63, p504S, p53, Ck7). We also stained tissue microarrays from the *Canadian Immunohistochemistry Quality Control* (cIQc) proficiency testing exercises for ER, PR, Her2 (Run 59), and p53 (Run 54). Scoring was done by 2 independent pathologists in blind experiment settings. Our staining was considered optimal if results were completely concordant with reference.
Results: The biggest strength of HE-IHC is its ability to identify morphology as in routine HE. Class 1 markers, including dual stains (red/brown), were easily interpretable (Fig 1). Our staining was considered optimal for ER, PR and Her2. There were no false results for Her2. Even cores with weaker staining for ER were stained and interpreted properly. Our staining was considered optimal for 41/42 cores stained with p53 (Fig 2); The missed core was interpreted correctly by only 2/50 laboratories participating in the cIQc.