and compared EGFR and Akt pathway activation with EGFR mutation status. Slides were immunostained with activation-state specific antibodies, including antibodies to phospho-EGFR, phospho-tyrosine and phospho-Akt.12 cases were subjected to EGFR DNA sequencing.

Results: High EGFR phosphorylation of all the tyrosine sites probed and phosphorylated Akt were detected in mutant EGFR cell xenografts but not in xenografts containing cell lines with wild type EGFR. IHC analysis of general phospho-tyrosine, phospho-EGFR and phospho-Akt on a NSCLC TMA found phosphorylated EGFR in 15%-25% of patient samples, depending on the tyrosine site. Phosphorylated EGFR was more frequent in adenocarcinomas (20%-30%) and in bronchoalveolar carcinomas (BAC)(28%-50%) than in squamous cell carcinomas (SCC)(5%-10%). The phospho-EGFR reactivity was closely correlated with high general phospho-tyrosine reactivity. There was also a strong correlation between high phospho-EGFR staining and high phospho-Akt staining in patient specimens. EGFR kinase domain DNA sequencing revealed that a majority of these samples were mutant.

Conclusions: These results suggest that mutant EGFR is constitutively phosphorylated and activates downstream Akt in NSCLC; therefore, IHC analysis of phosphorylated EGFR and Akt may reflect the activation of mutant EGFR signaling in patient samples.

1492 Adhesion Molecules (α-Catenin, β-Catenin, and E-Cadherin), and EGFR Expression in Thymic Neoplasms with Clinicopathologic Correlation

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Background: To investigate the expression of α-catenin, β-catenin, E-cadherin and EGFR in thymic neoplasms, and analyze their interrelationship with cliniopathological variables and their effect on prognosis.

Design: A series of 61 thymic neoplasms were reviewed and classified according to World Health Organization (WHO) scheme. Key clinical information including patient survival, Masaoka's staging, disease local recurrence, treatment modality, and WHO histology subtype was obtained. Percentage of membranous expression of α-catenin, β-catenin, E-cadherin and EGFR were recorded. While staining <80% of the cells was considered reduced expression for α-catenin, β-catenin, and E-cadherin, EGFR was considered positive when >10% of tumor cells expressed the antibody. Correlation of expression of markers and clinicopathologic variables was statistically analyzed using Spearman rank correlation and Kaplan-Meier analysis.

Results: Fifty seven patients had available long follow up records. There were 6 type A, 15 type AB, 7 type B1, 6 type B2, 17 type B3, and 9 type C tumors. Six of fifty seven patients died of the disease. Six patients developed local relapse. The reduced expression rate of α-catenin, β-catenin, E-cadherin was 77.2%, 78.9%, and 89.5% respectively in all subtypes. Expression of α-catenin was significantly reduced (<30%) in patients who died of the disease (p=0.04). Expression of β-catenin closely correlated with α-catenin, and E-cadherin (p<0.001 each). Epidermal growth factor receptor was positive in 56.1% of total cases with no significant correlation with various prognostic variables.

Conclusions: The reduced expression of α-catenin, but not β-catenin, and E-cadherin, implies more aggressive malignant behavior of thymic neoplasms regardless of tumor subtype. EGFR is moderately expressed in thymic neoplasms, and therapeutic targeting EGFR in thymomas warrants further investigation.

Quality Assurance

1493 Assessment of Specimen Adequacy in Bronchial Washings and Brushings: Correlation of Diagnostic Yield with Number of Benign Bronchial Epithelial Clusters, Bronchoscopic Findings and Tumor Size

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Background: Bronchial washings (BW) and brushings (BB) are valuable in the diagnosis of lung neoplasia. Adequacy is a challenging issue in nongynecologic cytology; in negative bronchial cytology, specimen adequacy is not well defined and a large number of well-preserved bronchial epithelium is recommended. The purpose of this study is to determine if the number of benign bronchial epithelial clusters (BEC), bronchoscopy visualization of lesion, or tumor size correlates with positive diagnosis.

Design: We reviewed 107 sequential bronchial cytology specimens (48 BB, 59 BW) and corresponding biopsy (Bx) from 54 different patients, obtained between Jan.-Jun. 2003. All patients have biopsy proven lung carcinoma. We defined BEC as a group of ≥3-10 well-preserved respiratory epithelial cells. Cytology slides were reviewed and correlated with histology. According to number of BEC, cases were subdivided into two groups: category I <10 BEC, II ≥10 BEC. Sample quality (poor fixation, inflammation, blood or mucous) was recorded. Patient records were reviewed for bronchoscopic findings and tumor size.

Results: Number of BEC, bronchoscopic findings and tumor size are summarized in table I. The most important predictor of positive cytology was bronchoscopic visualization of lesion in BB (P<0.001) and lack of visualization in BW (P <0.04). The number of BEC and tumor size did not correlate with positive diagnosis in either BB or BW. When compared to BB, BW is more likely to have positive diagnosis in non-visualized lesion (10 versus 5 cases). Bronchoscopy findings for 4 cases and tumor size for 2 cases were not available. Drying artifact was present in most BB smears. Blood, inflammation, or mucous didn't preclude a diagnosis in any case.

Conclusions: 1- In this limited study there is no correlation between the number of BEC and diagnostic yield. 2- Bronchoscopic visualization of lesion is predictive of positive diagnosis. BB is most diagnostic in visualized lesions and BW in non-visualized lesions. Utilization of bronchoscopic findings may allow for specimen enrichment by the bronchoscopist and/or specimen triage by the cytology lab.

BEC number, bronchoscopic finding and tumor size in BB and BW

	# BEC		Bronchoscopic finding		Tumor size	
	< 10	≥10	Lesion	No lesion	< 3 cm	≥3 cm
BB (n=48)						
Positive(n=15)	5	10	9	5	1	12
Negative(n=26)	8	18	2	23	5	19
BW(n=59)						
Positive(n=17)	11	6	6	10	3	12
Negative(n=28)	23	5	3	24	6	20
	BB P value=NS		BB P< 0.001		BB P= NS	
	BW P=NS		BW P< 0.04		BW P=NS	

1494 Efficacy of On-Site Specimen Adequacy Evaluation of Image-Guided Non-Thyroid Fine and Core Needle Biopsies

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Background: Cytology labs upon request provide on-site specimen adequacy evaluations assuming that they improve diagnostic yield. So far, the literature on this issue has been controversial and the cost-effectiveness of this practice remains unclear. Therefore, we have examined our own experience to assess its efficacy.

Design: Cytology reports on all image-guided non-thyroid fine needle (FNA) and core biopsies from January through June 2005 were retrieved. The specimens were divided into two categories: those with and without adequacy evaluations. Organ site, type of specimen (FNA or core), and final cytologic diagnosis were recorded for all specimens. For those with evaluations, the result of evaluation, and number of passes were recorded.

Results: 250 specimens were accrued during the study period from kidney (16), liver (42), lung (50), pancreas (51), retroperitoneum (7), and soft tissue (84). 204 were FNA, 38 were core, and 8 had both. 136 had adequacy evaluations and 114 did not. A definitive positive diagnosis was rendered on 96 (38%), i.e. 66 (49%) of the 136 with evaluations and 30 (26%) of the 114 without (P<0.001 by chi-square). When we stratified the analysis by organ, on-site evaluations significantly improved the diagnostic yield (as compared to those without evaluations) for liver (75% v 10%, P<0.001) and lung (67% v 30%, P=0.01), but not for kidney (64% v 60%, P=0.89), pancreas (13% v 11%, P=0.83), retroperitoneum (20% v 100%, P=0.05), or soft tissue (41% v 27%, P=0.19). No difference was noted in the total number of passes between the 99 specimens that were deemed adequate on evaluation versus the 37 deemed inadequate (2.72 v 2.76, P=0.89 by t test). Of the specimens deemed adequate at on-site evaluations, 77 (78%) were adequate on the first pass and 90 (90%) on the first two, but more passes were obtained in 55 (56%) either for ancillary studies or just to assure adequacy. Of the specimens deemed inadequate at on-site evaluations, 35 (95%) procedures stopped after 4 passes.

Conclusions: On-site adequacy evaluations were helpful for liver and lung but not for tumors of other organs. Since 90% of the adequate materials were obtained on the first two passes and 95% procedures stopped after 4 passes regardless of the adequacy result, on-site evaluations should be used selectively for the purpose of minimizing the number of passes instead of increasing the diagnostic yield.

1495 A Practical Multi-Step Approach To Reduce Errors in Surgical Pathology Specimen Handling and Processing

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Background: In recent years, medical errors and patient safety have become pressing national health care problems. In 2003 our anatomic pathology service experienced a sentinel event resulting from transposition of two breast core biopsies and subsequent inappropriate surgery. We report a multi-prong approach to prevent such errors.

Design: A multidisciplinary committee performed a thorough root-cause analysis and failure mode analysis following JCAHO guidelines. Following are some of the major changes implemented to ensure patient identity at each step of specimen handling: - Additional space was added to the accessioning area to improve workflow. - Batch entry was abandoned mandating individual handling of each specimen. - Besides the surgical number, two unique patient identifiers (name and date of birth) have been added to cassettes. - Cassette and slide labeling is now automated. - Each specimen is now placed in a separate plastic bin along with the requisition slip and cassettes. - Multiple patient identifiers are verified and dictated at the beginning of grossing. - High-risk cases (e.g. breast and prostate cores) are not handled back-to-back. - Pathologists receive one case per slide-tray. - Multiple monthly quality assurance indicators have been introduced to monitor the effectiveness of the corrective actions. - Continuous in-service education is given to residents, pathology assistants, laboratory assistants and histology technologists.

Results: Significant improvements were noted in quality control parameters compared between a 31-month period preceding and a 10-month period following implementation of the new specimen handling policy (see table).

	Average/ Month			Maximum/ Month		% Reduction in,	
	Cassettes Labeled	Error Events	Mislabeled Blocks	Error Events	Mislabeled Blocks	Error Events	Mislabeled Blocks
Before	7649.8	2.8	7.9	6	24		
After	8021	1.1	2.2	2	5	61%	72%
p-value		< 0.002	< 0.014				

Conclusions: Overall, the approach of maintaining the chain of patient identity at each step resulted in significant improvements. Specifically, non-batching, verification of multiple patient identifiers, physical separation of specimens and the culture of increased awareness have been particularly effective. The practice of proper specimen handling is being enforced with routine in-service education to eliminate the human error, still a significant risk factor despite marked improvement in the specimen handling process.

1496 Are Routine Step Sections of All Bronchoscopic Biopsies Required?

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Background: Step sectioning is a common practice in surgical pathology that has proven useful in increasing the diagnostic yield of biopsy material. The manner and extent of step sectioning varies by practice. Conservative step sectioning may limit diagnostic sensitivity, while extensive step sectioning may generate extraneous numbers of glass slides, especially in high volume practices. At our institution, we routinely step section all bronchoscopic biopsies, generating 3 H and E stained slides and 3 unstained slides on each tissue block. We sought to clinically validate this protocol with regard to diagnostic yield.

Design: Retrospective blinded review of routinely step sectioned bronchoscopic biopsies (39 cases, 52 total tissue blocks). Each of the following were documented: 1) pathologic diagnosis; 2) the number of step sections required to reach the diagnosis in an unequivocal manner; and 3) whether the saved unstained step sections were utilized for ancillary studies.

Results: The pathologic diagnoses of each tissue block were categorized as follows: malignancy, 30 blocks; reactive and/or dysplastic squamous changes, 6 blocks; granulomatous inflammation and/or specific organism, 10 blocks; no diagnostic abnormality, 6 blocks. In the cases of malignancy, 97% (29 of 30) were detected on the first section, and 100% by the second. In contrast, all three step sections were required for unequivocal diagnosis in 3 cases of granulomatous inflammation (see table). Ancillary studies were performed in 17 cases, but in only 5 of these were the unstained step sections utilized for the ancillary studies.

Diagnostic yield as a function of number of step sectioned slides

	Malignant (30)	Reactive/dysplasia (6)	Granuloma/organism (10)
Slide 1	29/30 (97%)	5/6 (83%)	7/10 (70%)
Slide 2	30/30 (100%)	6/6 (100%)	7/10 (70%)
Slide 3	30/30 (100%)	6/6 (100%)	10/10 (100%)

Conclusions: The data indicates that routine step sectioning increases diagnostic yield in bronchoscopic biopsies. However, the extent of step sectioning required varied by diagnostic category, and importantly all malignancies and dysplasias were detected by step two. A routine two-slide step sectioning protocol would be most appropriate in the evaluation of bronchoscopic biopsies, with additional sections performed in cases that reveal findings suspicious for granulomatous type inflammation. The protocol should also include a statement regarding the use of unstained steps for ancillary studies.

1497 Impact of False Positive FNA Cytology on Management: Learning from Our Mistakes and Prevention of Medical Errors

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Background: Fine needle aspiration (FNA) has extremely low rates of false positive diagnosis in experienced hands. Correlation of cytology with consecutive surgical pathology diagnosis is an essential part of quality assurance. The aim of our study was to assess the impact of false positive diagnosis on patient care management and review cytologic errors.

Design: Quality assurance (QA) data from 1997 to 2005 was reviewed to identify cases with false positive cytology. Clinical history and findings, aspirate smears, histologic slides and management in these cases was reviewed.

Results: Out of 1712 FNA cases included in the QA data 8 were identified with false positive cytology (0.005%). These are summarized in the table below. Retrospective review revealed cytologic atypia in each case. Prior history of malignancy (case 1,2,6 and 8) and highly suspicious clinical findings (case 2, 3, 4 and 5) resulted in interpretation of cytologic atypia as evidence of malignancy. In retrospect reclassification of cytologic diagnosis as "atypical" in all cases would have resulted in similar management in quest for accurate diagnosis. Diagnosis of benign process not responding to treatment was delayed in two cases (case 3 and 8).

Conclusions: In the presence of clinical findings suspicious for malignancy, cytologic atypia in aspirate smears may result in over diagnosis of malignancy. False positive cytology in such cases does not result in serious adverse outcome. However diagnosis of a benign outcome in a few cases may be delayed.

Case	Age/ Gender	Site	History	Cytologic diagnosis	Management	Histologic diagnosis	Clinical Impact
1	24/M*	Left breast	H/o Acute leukemia	Ductal Carcinoma	Incisional biopsy	Gynecomastia with atypia	None
2	48/F*	Lung	H/o non-small cell carcinoma. New opacity.	Bronchio-alveolar carcinoma	Wedge resection	Alveolar bronchiolitis	None
3	48/M	Lymph node	Lympha-denopathy	Malignant B-Cell Lymphoma	Excisional biopsy	Reactive	Delay
4	54/M	Pancreatic head mass	Persistent pain, weight loss	Islet cell tumor	Pacreato-duodenectomy	Chronic pancreatitis	Extensive surgery
5	57/M	Parotid gland	Two neck masses	Mucoepidermoid carcinoma	Excision, Frozen Dx- negative	Warthin's tumor	None
6	76/M	Lung	Left arm malignant myxoid fibrous histiocytoma (MFH)	Metastatic malignant MFH	Lobectomy	Solitary fibrous tumor	Extensive surgery
7	81/M	Parotid gland	10 year old mass, recent size increase	Adenocarcinoma with oncocytic features	Excision, Frozen Dx- negative	Oncocytoma	None
8	25/M	Lung	Ewing's sarcoma of shoulder	Metastatic Ewing's sarcoma	Excision, Frozen Dx- negative	Chronic inflammation	Extensive surgery

*M = Male, F = Female.

1498 Enhancement of Imprint Cytology with Immunohistochemistry and Fine Needle Aspiration in Intraoperative Evaluation of Sentinel Lymph Nodes for Metastatic Malignant Melanoma

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Background: Staging of malignant melanoma (MM) by intraoperative evaluation of sentinel lymph nodes (SLNs) allows for a one-step regional lymph node dissection to be performed when the SLN findings are positive. Frozen section examination of the SLNs in MM is not recommended because of the potential loss of SLN tissue containing a small micrometastatic focus. Intraoperative imprint cytology (IIC) has been recommended as an alternative to frozen section and has become a routine practice for evaluation of SLNs at our institution. The limitation of IIC for evaluation of SLNs for MM is its low sensitivity (10-30%). The reason for this could be a low yield of neoplastic cells by IIC, or a decreased recognition of cells by cytologic methods. This study was done to determine 1) the sensitivity of IIC at our institution as well as whether 2) immunohistochemistry on routinely negative slides could play a role to enhance detection and 3) whether a bench top fine needle aspiration (FNA) could increase yield of neoplastic cells over use of the IIC.

Design: Routine evaluation of SLN including IIC, H&E permanent sections and immunohistochemistry (HMB 45) was performed for 354 patients with MM from November, 2002 to September, 2005. At the time of intraoperative consultation, after routine IIC slides were prepared, bench top FNA was performed in 25 patients with MM starting from July of 2005. These sections were immunostained with HMB 45 and melan A. Results were compared with those of the IIC, H&E and HMB 45 immunostained sections.

Results: SLN positivity was 10.7% (38/354). IIC was helpful in detecting occult MM in 32% (in 12 of the 38 positive SLNs identified on permanent sections). There was one false positive IIC (specificity of 97%). Of the 25 patients with a negative routine IIC, one showed micrometastasis on H&E stained sections. This was detected by immunostains with HMB 45 and melan A on additional touch preparations and on bench top FNA which was confirmed by H&E and HMB 45 immunostained sections.

Conclusions: Although it has a low sensitivity, IIC is a valuable method of intraoperative evaluation of SLNs, which can spare nearly one-third of the patients with clinically occult regional metastases from a second surgery. At this stage, a low positivity rate in our accrued cases does not allow any conclusion as to the efficacy of additional cytologic sampling and immunocytochmical procedures. Further studies are in progress to assess this.

1499 Follow-Up of Diagnoses of High Grade Squamous Intraepeithelial Lesion [HSIL]

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Background: Diagnoses of high grade squamous intraepethelial lesions [HSIL] routinely lead to follow up— repeat pap smears or a variety of more invasive procedures: cervical biopsies, cone biopsies, and endocervical currettage. These strategies attempt to remove patients from the indeterminant HSILdiagnostic category, either "upgrading" diagnoses to those more suspicions for carcinoma, indicating more aggresive monitoring or treatment, or "downgrading" them to benign diagnoses that require less monitoring and treatment. In this study we measured prospectively how often follow-up" upgraded", left "unchanged/equal", or " downgraded" HSILs.

Design: Initial HSIL diagnoses were identified and followed for a peroids of 6-24 months. All repeat pap smear, cervical biopsy, cone biopsy, and endocervical currettage diagnoses that followed up HSILs were reviewed. Patient diagnoses were "upgraded" when they became suspicious or diagnostic for carcinoma, "unchanged/equal" if remaining HSIL or similar indeterminant histological diagnoses, and "downgraded" if becaming low grade squamous intraepethelial lesion [LSIL], negative, or benign. We expressed the yield of HSIL through the outcomes of the follow-up procedures.

Results: Between Jan. 2003 and Jan. 2005, HSIL was diagnosed from 229 pap smears. 11/229 [5%] of HSIL diagnoses received no recorded follow-up during the 24- month study period. Otherwise, HSIL diagnoses trigered 426 follow-up manouvers: 194 repeat pap smears, 151 cervical biopsies, 64 cone biopsies and 17 endocervical currettages. Thus, there were 1.9 procedures/HSIL diagnosis, with 62% of these procedures more invasive than pap smear. The follow-up procedures yielded no dignoses of carcinoma, 4 cases [1.7%] were upgraded to "suspicious for carcinoma", 85 [37%] diagnoses remained "unchanged/equal," and 140 diagnoses [61%] were "downgraded" to LSIL or less worrisome categories.

Conclusions: This prospective study found the yield of more suspicious diagnoses from initial LSIL pap smears to be very low [< 2%]. The persistenace of indeterminant "unchanged/equal" diagnoses, despite further procedures, was disapointingly high [37%]-more than a third of cases. Patients' diagnostic classifications were downgraded in only 3/5 of cases [61%]. Given the low frequency of "upgrades", the high rate of persistent "unchanged/equal"diagnoses, and the relative intensity of invasive manouvers that HSIL entails, it remains an inefficient diagnostic category.

1500 Correlating Clinical Impression with Pathologic Diagnosis of Pulmonary Malignancy

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Background: Undertaking procedures, pulmonologists often estimate the likelihood of malignancy of lung lesions. We compared a clinician's estimates of procedures' yield of diagnoses of malignancy to corresponding cytological or histological diagnoses, by measuring procedure-specific and overall correlation of estimates made at the time of procedures with diagnostic results of: bronchial brushings (BBs), bronchial washes (BWs) , fine needle aspirations (FNAs), and lung biopsies (BXs).

Design: Of 103 specimens, 7 were excluded for acellularity.[4 BBs and 3FNAs]; 2 BBs and 2 FNAs were excluded for yielding indeterminant diagnoses, a tertium quid the clinician never chose. For the remaining 92 specimens [9BBs, 37BWs, 29FNAs and 17Bxs], the pulmonologist catagorized the results he anticipated as either likely or unlikely to be malignant. Concordances with cytologic or histologic diagnoses were then calculated by procedure type and overall.

Results: All 9 BBs were projected to be malignant, 6/9 BBs were [66%]. Of 37 BWs, 30 were projected as malignant, only13/37 BWs were[35%]. Of 21 discordant BWs, 17 clinician-classified positives were cytologically negative; 4/7 projected negatives were cytologically positive. All 29 FNAs were projected to be malignant, only 15/29 were[52%]. Of 17 BXs,16 were projected malignant,13/16 were[81%]. The single BX case projected as negative was histologically positive. The remaining 4/17 BXs projected as unlikely to be malignant were all positive for malignancy. Overall, the clinician's diagnostic sensitivity was 90% [47/52], but specificity was only 8% [3/37] .

Conclusions: Where definite diagnoses were forthcoming, projections at the time of procedures overestimated positivity in all specimen types. For BB,and FNA, the clinician always projected positive results, leading to low predictive values of positive estimates: 66% for BB, 51% for FNA; this rate was even lower for BW [43%]. For BX, the predictive value of a positive estimate was the best among the four groups [76%]. In BW and BX categories, false negative were 24% for BW and 7% for BX, despite 45% prevalance of positivity in the BW group [17/37], and 93% positivity for BX [13/14]. Poor correlation of clinical impressions with pathologic diagnoses of pulmonary neoplasms was due to persistent bias toward malignancy, quantitated by very low specificity [8%].

1501 The Changing Blood Transfusion Practice in Minimally Invasive Robotic-Assisted Prostatectomies

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Background: Robotic prostatectomy is a minimally invasive and sophisticated surgical method for removing the prostate using a robotic device. As far as we know, there have been no published studies comparing blood loss in robotic and non-robotic prostatectomies. In our institution, all elective prostatectomies (robotic and non-robotic) automatically trigger 2 units of typed and crossmatched blood reserved for these patients in anticipation of blood loss, according to the institution's Maximum Surgical Blood Order Schedule (MSBOS).

Design: All radical prostatectomies in our institution from January 2003 to August 2005 were analyzed for intraoperative blood usage.

Results: Blood loss during the da Vinci (Intuitive Surgical, Inc., Sunnyvale, CA) robotic assisted prostatectomies was minimal. None of the 31 (0%) robotic prostatectomies required blood transfusion. On the other hand, each of the 12 traditional open radical prostatectomies performed (100%) required 2 units of crossmatched blood intraoperatively. One (1) laparoscopic radical prostatectomy was performed during this period, for which transfusion of 2 units of crossmatched blood was also required (100%).

Conclusions: Robotic prostatectomy is gaining popularity around the nation as a less invasive way of removing the prostate for cancer than open surgery. It allows the surgeon to remotely and precisely control the movements of instruments positioned inside the patient through small incisions. Our findings indicate that robotic prostatectomy has the advantage of reducing intraoperative blood loss (0% transfusion requirement) compared to non-robotic procedures (100% transfusion requirement). While most blood products are safe and most transfusions are uneventful, blood transfusions are not entirely risk-free. This study suggests that preoperative typed and crossmatched blood for robotic prostatectomy may be safely replaced by a simpler "type and screen" process in the blood bank. This could represent an opportunity for improving efficiency in the blood bank by decreasing unnecessary crossmatching and decreasing wastage of expired blood products. However, additional blood usage data based on a larger series of robotic prostatectomy would be necessary to ultimately effect a change in our blood order protocol. Future studies should also include blood usage in other types of minimally invasive robotic-assisted surgeries.

1502 Image Analysis of Her-2/neu Expression Improves Case Selection for Reflex FISH Testing in Breast Cancer

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Background: Herceptin is an important therapeutic option for breast cancer patients with a positive Her-2/neu status. Current protocols recommend reflex FISH gene amplification testing for immunohistochemistry (IHC) cases with an intermediate staining pattern (2+). Inter- and intraobserver variability with IHC evaluation can affect the number of FISH assays performed. As diagnostic algorithms are expensive and impact patient care, we evaluated the effects of assisted cellular image analysis (ACIS) on reflex Her-2/neu FISH testing.

Design: ACIS was standardized using 40 cases interpreted with Her-2/neu IHC that covered the spectrum of 0+ to 3+ staining with 2+ FISH correlation. Standardized IHC for Her-2/neu was performed on 373 sequential cases that were divided into two groups: 1. traditional interpretation (Pre-ACIS group; retrospective cases); and 2. imaging assisted interpretation (ACIS group; prospective cases). Testing was performed according to the manufacturers' recommendations (Ventana Medical Systems and ChromaVision, Clarient Inc.). Pre-ACIS group demographics (n=137): Age: 59±13 yrs; Tumor size: 2.6±2.2 cm; modified Bloom-Richardson grade 1 (22%), 2 (44%), and 3 (34%); ER-positive 71%; and PR-positive 63%. ACIS group demographics (n=236): Age: 58±13 yrs; Tumor size: 2.5±2.2 cm; modified Bloom-Richardson grade 1 (16%), 2 (53%), and 3 (31%); ER-positive 77%; and PR-positive 62% (Pre-ACIS vs ACIS demographics p = 0.414).

Results:

Comparision of Her-2/neu Scoring with FISH Amplificaton

		Her-2/neu Score (% of Cases)				% 2+ Cases With
	n=	0+	1+	2+	3+	FISH Amplification
Pre-ACIS	137	28%	34%	25%	13%	7%
ACIS	236	31%	37%	19%	13%	21%
p=				0.487		<0.001

While the percentage of 2+ cases in the ACIS group deceased slightly (p = 0.487), their correlation with Her-2/neu gene amplification increased significantly ($p < 0.001$). Compared to the pre-ACIS group, the average overall cost per patient in the ACIS group decreased by 8 percent.

Conclusions: Compared to traditional interpretation, ACIS can assist pathologists to reduce the percentage of 2+ Her-2/neu cases and significantly increase their correlation with FISH-detected amplification. In addition, the average overall cost per patient can be decreased. In conclusion, the use of automated staining with cellular imaging provides a cost-effective method that pathologists can use to improve the evaluation of a breast cancer patient's Her-2/neu status.

1503 Improved Patient Care through a Pathology Panel Review of Breast Specimens

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Background: Assessment of benign and malignant breast lesions can be difficult, particularly on needle biopsy. Assessment of breast lesions using a breast pathology panel has been advocated to address quality assurance and quality improvement issues. The aim of this study, therefore, is to evaluate the effectiveness of a breast pathology panel double review over an extended period (2yrs) in the assessment of breast lesions with subsequent impact for improved patient care.

Design: Baseline (pre-intervention) evaluation (voluntary intradepartmental consults) of all breast specimens received at the Henry Ford Health System (including needle biopsy, localizations, mastectomy specimens, sentinal and axillary lymph nodes) from Jan 2002- July 2003 (surgical pathology volume=78,000). Error verification sources included clinician and tumor board review. Intervention included prospective double slide review of all breast specimens facilitated by a Breast Review Panel comprised of 4 pathologists with an interest in breast pathology (including one specialist breast surgical pathologist) over a 2 year period (Aug 2003-Aug 2005 surgical pathology volume =96,523; breast cases = 5,416). All slides from each case were double reviewed by at least one of the panel pathologists. All tumor cases were reviewed by the panel pathologist involved in tumor board presentation (in most cases the specialist breast surgical pathologist).

Results: Over the baseline period a total 37 revised diagnoses were rendered overall of which 5 (13.5%) were revised breast diagnoses. During the intervention (breast review panel) assessment period a total 30 revised diagnoses were rendered with only 1 breast diagnosis revision (small focus of invasive ductal carcinoma missed on one needle biopsy level within a lesion with extensive high-grade DCIS). The only other corrections to breast specimen reports during the intervention period were for typographical errors (2 stage, 1 margin and 1 side designation change) and a case of invasive carcinoma seen on additional sections submitted following case sign out.

Conclusions: This study shows that a Breast Review Panel facilitated double review of breast specimens has a very low diagnostic error rate (only 1 of 5, 416 breast cases; <0.001%). A panel approach has the potential to minimize erroneous breast cancer diagnoses prior to clinician/tumor board review with subsequent reduction in potential patient over or under treatment. This approach continues to demonstrate merit in some practice settings as an effective patient safety initiative.

1504 Critical Values in Surgical Pathology – Survey Results from ADASP (Association of Directors of Anatomic and Surgical Pathology)

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Background: Analogous to "critical values" (CVs) in clinical pathology, occasional diagnoses (dx) in surgical pathology (SP) could require immediate contact of the physician to initiate treatment.

Design: To propose guidelines on CVs in SP, a survey was sent to 225 ADASP members for grading 17 different possible CVs from 1 to 3 as follows: (1) No phone call necessary, (2) The clinician should be called within 24h; (3) A phone call should be made as soon as possible (ASAP). Respondents could also list additional dx they believed constituted a CV.

Results: There were 73 responses, the majority (ranging from 55 to 91%) agreed on the need for a phone call ASAP for the following dx: crescents in kidney biopsy, vasculitis, bacteria in heart or bone marrow, organisms in immunocompromised patients, uterine contents without villi or trophoblasts, fat in endometrial curettage, mesothelial cells in heart biopsy, fat in endoscopic colon polypectomies, transplant rejection, malignancy in superior vena cava syndrome, and neoplasms causing paralysis. For new dx of malignancy with clinical suspicion and for new dx of metastasis with known primary malignancy, most participants agreed that there was no need for a phone call. In some dx (organisms in immunocompetent patients, and large vessel in core biopsy specimen), there was disagreement about the need for a phone call. For disagreement between frozen section and final dx and for completely unexpected malignancy, most participants agreed on the need for a phone call, but disagreed on the degree of urgency. Several additional CVs were suggested as well as discussion of best terminology for critical values, appropriate documentation of phone calls, urgency of call depends on details of dx (which microorganism; grade of transplant rejection; if disagreement between frozen section and final dx is significant, etc). 5 of 73 pathologists said they didn't

believe in the concept of CV in SP, 3 of which expressed concern about medicolegal implications.
Conclusions: There was good agreement about most of the possible CVs, although there was difference of opinion for some dx. The results of this survey will help an ADASP committee to develop national guidelines for critical values in surgical pathology.

1505 Double Slide Viewing as a Quality Improvement Initiative

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Background: Few studies have measured the effect of double viewing of cytology cases as a means to decrease error.
Design: Three Agency for Healthcare Research and Quality-funded project sites performed pre-sign out double viewing of consecutive pulmonary cytology cases (n=431). Interobserver variability between the first and second cytologist diagnosis was measured using the kappa statistic. Two-step or more differences in diagnosis were arbitrated as interpretive errors and the effect of double viewing was measured by comparing the frequency of cytologic-histologic correlation-detected errors in the previous 2 years to the double viewing period. The use of non-definitive diagnoses (e.g., atypical and suspicious) also was measured in the project sites.
Results: Using double viewing, the number of interpretive errors detected for the institutions was 2.7%, 0%, and 1.9%, respectively. The pairwise kappa values between the first and second cytologist varied from 0.81 and 0.95, indicating excellent agreement. Double viewing did not lower the frequency of cytologic-histologic correlation false negative errors when data from the double viewing period were compared to data from the previous 2 years. During the double viewing period, the aggregated 2-step diagnostic error proportion was 25.2% of all cytologic-histologic correlation pairs. Based on the cytologic-histologic correlation process, a 2-step or greater difference in diagnosis was observed in 23.8%, 14.7%, and 27.1% of cytologic-histologic correlation pairs in the project sites. A statistically significant assocation existed between project site and use of diagnostic category ($P<0.001$), and some project sites had a high frequency (23.2%) of non-definitive diagnostic category use.
Conclusions: Double viewing detects an error in approximately 1 of every 37 cases, although biases in performing double viewing limit the effectiveness of the process. Double viewing does not significantly lower the cytologic-histologic correlation error frequency, indicating that the majority of possible errors are not prevented. The use of non-definitive diagnoses varies considerably across project sites.

1506 The Value of Monitoring Frozen Section-Permanent Section Correlation Data over Time

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Background: There is little published data on the value of measuring frozen-section discordant and deferral rates by multiple institutions over time.
Design: Participants in the College of American Pathologists' Q-TRACKS program self-reported the number of anatomic pathology frozen-permanent section discordant and deferred cases in their laboratory by prospectively performing secondary review of intra-operative consultations. One hundred seventy-four laboratories self-reported data. Laboratories participated in the program from 1 to 5 years and reported their data every quarter. We calculated mean and median discordant and deferred case frequencies and used mixed linear modeling to determine if length of participation in the program was associated with improved performance.
Results: The mean and median frozen-permanent section discordant frequencies were 1.36% and 0.70%, respectively. Longer participation in the Q-TRACKS program was significantly associated (P = .0401) with lower discordant frequencies; 4 or 5 year participation showed a decrease in discordant frequency of 0.99% whereas 1 year participation showed a decrease in discordant frequency of 0.84%. Longer participation in the Q-TRACKS monitor was associated with lower microscopic sampling frequencies for discordant diagnoses (P = .0351). The mean and median deferred diagnostic frequencies were 2.35% and 1.20%, respectively. Increased length of participation in the Q-TRACKS program was significantly associated (P = .0437) with lower deferred diagnostic frequencies.
Conclusions: Long term monitoring of frozen-permanent section correlation is associated with sustained improvement in performance.

1507 Evaluating the Amended Report in Surgical Pathology

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Background: Quality assurance in surgical pathology evaluates the impact on patient care of errors in the delivery of diagnosis and aims at improving pathologists' and departmental performance. This study focuses on one indicator, the amended report.
Design: A laboratory information system (LIS) search of 18,000 accessions located 121 amendments, which were categorized by the reason for the revision as recorded by the reporting pathologist. Errors were analyzed for their potential impact on patient care.
Results: Amendments occurred in 0.7% of accessioned cases, mainly involving breast (34/121-28%) and skin (14/121-12%) cases. Table 1 shows the reasons for amendments. Changes to the final diagnosis, laterality, specimen site and patient demographics amounted to 49 (40.2%)cases and were considered of significant impact on patient care if undetected. The majority of final diagnosis changes remained within the same diagnostic category (15/27-55.6%) and had no effect on patient care. Two (7.4%) final diagnoses were prematurely released and 2 (7.4%) lacked explanatory information. However in 8/27 (29.6%) cases a change from benign to malignant, from neoplastic to non-neoplastic or vice versa was made and carried a potential impact on patient care. Modification of 43 (35.5%) reports lacked a clear categorization of the error ("typographical error," or no documentation provided). The remaining 29 (23.9%) cases involved minor issues. Overall a statement reconciling original and amended report was lacking and significant differences in documentation practices were observed among pathologists.
Conclusions: Review of amended reports is a useful QA indicator to evaluate errors in surgical pathology. This study documents a low incidence of errors requiring amendment of surgical pathology reports and ultimately no significant impact on patient care. It detected serious flaws in the LIS documentation of amended reports, mainly lack of retention/accessibility of the original report, the absence of a detailed log of each amendment, and overall incomplete or ambiguous documentation by the pathologists of the reason for amendment. Such practices may be avoided by establishing well-defined categories for reasons for amendment, and explicit, possibly templated, documentation of the modifications.

	Amended Reports	
Reason	Number of cases	percentage %
Final diagnosis change	27	22.3
Typographical error	24	19.8
No information provided	19	15.7
Laterality	11	9.1
Specimen site	7	5.8
Procedure	6	5.0
Gross description	6	5.0
Margin clarification	5	4.1
LIS error	4	3.3
Patient demographics	4	3.3
History	3	2.5
Ancillary studies	3	2.5
Attending	2	1.6
Total	121	100

1508 AP Quality and Safety Monthly Conference: The Pathology Version of Morbidity and Mortality Conference

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Background: Since January 2005, we have conducted a monthly Anatomic Pathology (AP) Quality and Safety Conference for education and process improvement, using a multihead microscope with video monitor, and attended by all the anatomic pathologists and more recently by residents and fellows. We report our experience with this conference and propose it as an additional useful QA activity.
Design: The cases presented at the conference are selected by the AP director based on: discordance between final diagnosis (dx) and preliminary FNA or frozen section dx ; amended dx; discordant second opinion dx; discordance between cytology and surgical pathology dx; technical problems; reporting and terminology issues; and physician complaints. For the current study, we reviewed the cases presented at the past 6 months conferences and classified as to problem type and implemented further action.
Results: During this 6 month period, there were 110 cases presented at the conference: 95 surgicals, 13 non-gyn cytology, 1 gyn cytology and 1 bone marrow. During this 6-month period there were a total of 8656 surgicals, 1547 non-gyn cytology and 5002 gyn cytology specimens. The cases were categorized into 15 different types of problems: terminology (11 cases); clerical error (15 cases); technical error (0 cases); incomplete examination – gross or micro (5 cases); incomplete or inadequate report (23 cases); incorrect tumor classification (12 cases); incorrect tumor grade (1 case); incorrect tumor staging (8 cases); overcall (10 cases); undercall (11 cases); incorrect outside dx (4 cases); other clinically significant incorrect dx (5 cases); other clinically insignificant incorrect dx (3 cases); inappropriate use of stains (1 case); and consult should have been obtained (1 case). Also analyzed for each case was further actions taken: amended report (31 cases); addendum (35 cases); additional immunostains (7 cases); additional gross examination (4 cases); additional levels (2 cases); review of case (2 cases); comment in the dx (2 cases); physician contacted (14 cases) and no action (41 cases).
Conclusions: The institution of a monthly AP Quality and Safety Conference is pathology's version of the educational and process improvement "Morbidity and Mortality" clinical conference. Although many of the issues presented are also handled on an individual basis, we believe there is educational value for group presentation and discussion when conducted in a constructive, non-threatening environment.

1509 Amended TNM Staging of Synchronous Lung Cancers after Molecular Analysis

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Background: Multiple lung carcinomas (CAs) of the same histologic type are considered synchronous if they involve separate lobes with no evidence of extra-thoracic disease, mediastinal lymph node metastases, or of nodal metastases with a common nodal drainage. Synchronous tumors should be staged separately. However, if multiple tumors are in the same lobe, they are staged as T4 and therefore represent stage IIIB disease. However, metastatic CA (M1) would be stage IV. In this study, we evaluated changes in TNM staging based on molecular analysis of synchronous lung CA.
Design: We retrieved paraffin blocks of 24 CA from 12 patients. The CA in each patient were of the same histologic type (10 adenocarcinomas, 8 squamous cell carcinomas, 4 large cell carcinomas, and 2 small cell carcinomas). 4-8 microdissection targets from neoplasm and non-neoplastic controls were removed under stereoscopic guidance and analyzed by PCR for LOH at 1p, 3p, 5q, 9p, 10q, 17p, 17q, 21q, 22q and point mutation determination in k-ras-2 . The tumors were classified as de novo or metastasis based on 3 levels of concordance: (1) marker affected - tumors were considered concordant if 50% of more of the same markers were mutated, (2) same gene copy affected, and (3) temporal sequence of mutation. The tumors were staged according to the 6th edition of the AJCC Cancer Staging Manual.

Results: 11 patients had multiple CA of the same histologic type in the same lobe (stage IIIB) and 1 patient had CA involving different ipsilateral lobes and positive subcarinal lymph node (stage IV). By molecular analysis, 5/12 CA were classified as metastases, including the 1 CA in different lobes. These metastatic CA would have the same original stage. However, 7/12 CA were re-classified as de novo by molecular analysis, therefore each CA should have a separate T classification instead of being classified as T4 for both CA. After reclassification, 7 patients were staged as follows: IA (2 patients), IB (3 patients), and IIB (2 patients)

Conclusions: Molecular analysis downstaged 7/12 (58%) patients with multiple lung tumors involving the same lobe by demonstrating that they are de novo tumors and not metastases, which has prognostic implications. We believe that when multiple lung carcinomas of same histologic type are encountered, molecular analysis may contribute to a more acurate TNM staging. In our series 7/12 (58%) patients would need an ammended TNM classification in the surgical pathology report.

1510 MISFISHIE: A Specification for Reporting Immunohistochemical Findings. Assessment of Compliance in Publications

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Background: A goal of the biomedical literature is to report results in sufficient detail so that the study can be independently replicated. To ensure that a sufficient level of detail is provided, a minimum information specification is needed for reporting data. A data content specification has already been widely accepted by the microarray community - MIAME. However, no specification exists for immunohistochemistry experiments. In this study, we developed and evaluated a specification for immunohistochemical studies. This specification details the minimum information that should be provided when reporting immunohistochemistry experiments. Compliance to this standard should provide other investigators enough information to reproduce the experiments and/or to evaluate data upon which results are based.

Design: A specification that consists of 6 sections – Design (e.g. number of cases, number of stains), Processing (e.g. tissue type, fixative), Antibody Data, Staining Protocol, Imaging Data , and Image Characterization (e.g. method of image evaluation) - was developed. This specification does not dictate a specific format for data reporting. A selection of immunohistochemistry articles from the past 5 years reporting studies was assessed for compliance with the six sections of the specification. Each reviewer assessed each of 32 assigned articles. Compliance for each MISFISHIE subsection was rated on a scale of 0 to 10. Score of 10 indicates that all information the reviewer needed to reproduce the experiment was provided; scores <10 correspond to how incomplete the information was that the reviewer thought necessary to reproduce the work. Scores of 8 and 9 were considered a low pass, e.g. the reviewer could reproduce the experiment with only a few assumptions.

Results: Of the papers, only 4 (13%) were deemed MISFISHIE compliant in all sections. 28% were out of compliance in only one section. 31% did not comply in two sections. More than 90% complied with sections on Design and Specimen Processing. 75% complied with sections on Antibody Information and Staining Protocol. Only 16% of articles were compliant with Section 5 (Imaging Data).

Conclusions: Many papers lack sufficient detail for independent investigators to reproduce the studies with complete confidence. We propose that investigators and journal editors evaluate immunohistochemical studies using the MISFISHIE specification.

1511 High-Throughput Image Analysis of Tissue Microarrays Based on a Public Domain Software Program

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Background: Visual assessment of IHC staining of TMA can be time-consuming and laborious. Several companies offer TMA-scanning platforms with image-analysis software; however, these are hardware-specific and expensive.

Design: We created Java-based software for the public domain image analysis program, ImageJ (http://rsb.info.nih.gob/ij/). This plugin utilizes a novel algorithm for nuclear IHC staining analysis. It performs colour deconvolution (G. Landini) and works separately with the DAB and hematoxylin channels. Thresholding can be manual or automatic. A watershed algorithm separates touching objects. Multiple parameters of the segmented objects are then analysed, including area, Feret's diameter, circularity, and roundness. Texture analysis is performed using the 21 parameters as described in R. Haralick et al., 1983. Those objects that do not meet the tumor cell criteria are excluded. The output file presents percent of positive nuclei, percent of positive area, optical density of positive objects, and a number of other features. The program saves result images showing positive and negative nuclei outlined by different colors, thereby allowing visual quality control of tumor nuclei identification.

Results: The plugin was tested on breast TMA containing 4648 tissue cores, stained for ER (clones SP1 and 1D5), Ki67, and p53. Visual examination of the output images shows that our program allows accurate selection of positive and negative tumor nuclei. The programme does not make any assumptions about the average size or shape of tumor cells, allowing parallel analysis of pleomorphic tumors with usual ductal and lobular carcinomas. Texture analysis filters out the majority of lymphocytes and stromal cell nuclei, greatly increasing the accuracy of tumor cell identification. ER staining was positive in 66.14% using the SP1 antibody, and 62.11% for 1D5. Percent of positive tumor nuclei in ER staining is associated with better disease specific survival (p = 2.4E-06), and in Ki67 (p = 7.6E-016) and p53 (p = 9.36E-012) with worse survival, as determined by univariate Cox regression analysis.

Conclusions: We developed a robust image analysis programme specifically designed for nuclear staining analysis of IHC slides, whether TMA or whole section. This freeware provides quantitative scoring of nuclear immunostaining digital images.

1512 A Proposal for Improved Quality Assurance in Flow Cytometry Using the Rmax Statistic for Kappa-Lambda Testing

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Background: Flow cytometric analysis of percent κ and λ surface immunoglobulin (sIg) light chains is important for determining B-cell clonality. However, it has been problematic to compare data within one laboratory over time or among different laboratories because there is no generally agreed upon statistical approach.

Design: For evaluating sIg light chain restriction, we transformed all κ /λ ratios to maximum ratios. That is, Rmax=max (κ/λ , λ/κ), so that all resulting ratios were at least 1. Percent κ and λ lymph node data were obtained from four medical centers during 2002, 2003, and 2004. Both inter-institutional differences and year-to-year variations in optimal Rmax statistic cut-off value and in sensitivity and specificity of the same R-max cut off value were analyzed.

Results: 938 κ, λ data pairs from four institutions were converted to maximum ratios. The Rmax cut-off values were chosen to optimally separate reactive lymphoid hyperplasia from B-cell lymphoma. To compare the sensitivity and specificity across years and sites, a cut-off value of 2.84 was used. A separate logistic regression was used for sensitivity and specificity with institution, year and their interaction as covariates. The results show that there were no interaction effects between sites and years. However, within each site, there was variation in sensitivity across years (p=0.0090), but for a given year there was no variation in sensitivity between sites (p=0.1023). No statistically significant difference was found in specificity across years and between sites.

Site	Year	N	Rmax cut-off value	Sensitivity	Specificity
1	02	100	2.84	0.95	0.92
	03	85	3.01	0.95	0.94
	04	111	2.84	0.96	0.94
2	02	87	2.50	0.96	0.76
	03	93	2.84	0.97	0.92
	04	110	2.50	0.98	0.82
3	02	59	3.33	1.00	0.85
	03	78	2.84	1.00	0.85
	04	90	2.33	0.97	0.90
4	02	21	2.84	1.00	0.86
	03	45	2.84	1.00	0.93
	04	59	2.84	0.95	0.97

Conclusions: We propose that the Rmax statistic, which can reveal previously unsuspected variations in κ, λ data, may improve quality assurance within a single facility over time and may promote sharing of data among institutions.

Techniques

1513 Real-Time Region-of-Interest-Based Image Database Query and Differential Diagnosis Generation Utilizing Third-Generation Vector Quantization Techniques in Concert with N-Space Voronoi Mapping

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Background: The advent of whole slide digital imaging allows for exploration of histologic datasets by automated methods for determination of similarity with prior stored images. Additionally, if established image repositories are pre-coordinated with diagnostic data, as linked metadata, there exists the opportunity to construct region-of-interest-based query tools, that use image content itself (and not text) as the predicate for carrying out searches.

Design: An image query and retrieval engine was constructed using C++ 6.0 (Microsoft Corporation, Redmond, WA) as the development environment for the 3rd generation Vector Quantization Discovery Toolset (VQDT) already in place at the MGH Pathology Digital Imaging Laboratory. This system consists of an N-space Sparse Matrix mapping system, an advanced Voronoi projective filter for carrying out principle component analysis (PCA), a Voronoi Visualization tool suite and a highly-optimized VQDT Bayesian Inference matching filter to provide for real-time matching of predicate regions of interest with established vocabularies and associated diagnostic metadata.

Results: Histologic digital imagery content was acquired from 157 different slides and subsequently parsed through the VQDT in training mode, allowing for generation of a general class of VQ principle-component elements (vectors) spanning eight organ systems. Of each organ system selected, baseline "normal histology" cases were included in addition to histopathologic entities. Submitted imagery was tagged with pre-coordinated diagnostic data, allowing for spatially-tagged vocabulary metadata. An additional 25 wide-field slides were scanned with their content used as the predicate for testing of the specificity and sensitivity of the N-space VQ inference engine. This was carried out by selecting diagnostically archetypal regions of interest from these 25 images for query against the established vocabulary. Resultant Bayesian clusters of vectors returned from the Voronoi mapping were evaluated in terms of their confidence intervals for returning one or more tagged diagnoses which correlated with the objectively deemed diagnoses of the test set. Resultant sensitivity and specificity for the test set was 93% and 97% respectively.

Conclusions: Vector Quantization with N-Space Voronio mapping demonstrates utility in providing for satisfactory sensitivity and specificity as an automated image matching and differential diagnosis generation tool.