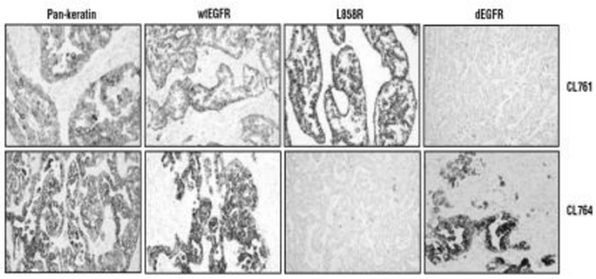
Results: There was high concordance in the assessment of EGFR gene copy number between CISH and FISH tests and between observers ($p<0.000$). Also, there was substantial consistency between immunohistochemical results and CISH results, showing correlation of protein overexpression and gene amplification.
Conclusions: There was nearly perfect agreement between the CISH and corresponding FISH results, and interpretation of CISH results were highly reproducible among the pathologists. In conclusion, EGFR gene amplification status can be reliably assessed by CISH.

1651 Mutation-Specific Antibodies for the Detection of EGFR Mutations in Non-Small-Cell Lung Cancer

J Yu, E Benedettini, DQ Li, T Gu, H Herebert, B Smith, R Polakiewicz, XM Zhou, M Loda, M Comb. Cell Signaling Technology, Inc, Danvers, MA; Dana-Farber Cancer Institute, Boston, MA; Second Xiangya Hosptial, Changsha, Hunan, China.
Background: Activating mutations within the tyrosine kinase domain of the epidermal growth factor receptor (EGFR) are found in approximately 10-20% of non-small cell lung cancer (NSCLC) patients and are associated with response to the EGFR inhibitors Gefitinib and Erlotinib. The most common NSCLC-associated EGFR mutations are the 15 nucleotide in-frame deletion in exon 19 (E746-A750del) and the point mutation in exon 21 (L858R), together accounting for 90% of EGFR mutations. The ability to detect mutated gene products in cancer cells can identify patients most likely benefit from such therapies.
Design: We generated rabbit monoclonal antibodies (RmAb) against EGFR with E746-A750 deletions and L858R point mutation. We tested the antibodies by western blot, Immunofluorescence (IF) and immunohistochemistry (IHC) and used the antibodies staining 40 molecularly pre-typed tumors by IHC. Then, we used IHC by a panel of four antibodies (two EGFR mutation-specific antibodies, a control EGFR antibody and a pan-keratin antibody) to screen 340 cases of tumor samples with unknown genotype.
Results: The mutation-specific antibodies detect the corresponding mutant form of EGFR but not wild type EGFR by Western blotting, immunofluorescence (IF), and immunohistochemistry (IHC). IHC screening of a large panel of paraffin-embedded tumor samples of Non-Small-Cell Lung Cancer (NSCLC) patients shows that antibody reactivity is highly correlated with the presence of EGFR mutations.



DNA Sequencing and IHC Result of EGFR Mutation

	DNA Sequencing			
IHC	L858R (+)	dEGFR (+)	Wild Type	Failed
L858R (+)	24	0	2	2
dEGFR (+)	0	23	0	1
L858R (-)	2	0	193	25
dEGFR (-)	0	3	196	23

Conclusions: This simple assay for detection of EGFR mutations in diagnostic human tissues provides a rapid, sensitive, specific and cost-effective methodology to identify lung cancer patients responsive to EGFR-based therapies.

Quality Assurance

1652 Do Amended Reports Get to Where They Should?

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Background: Amended pathology reports (AmR) are issued to correct erroneous information. To avoid improper treatment based on the original incorrect report, the AmR needs to reach, and come to the attention of, the treating physician (phyT). However, the physician of record (phyR) is often not the phyT. Frequently, especially in cases with malignant diagnoses, the phyR is a radiologist or a surgeon who performed the biopsy or surgery, and the phyT is an oncologist or radiation therapist. Pathology offices typically send AmR to the phyR, and do not have measures in place to ensure that a copy of the corrected report gets to the phyT.
Design: All AmR with a change in the "final diagnosis" field of the report, and were issued >21 days after the original signout, were tracked. A chart review to determine receipt of AmR was performed in the phyR's office. The phyT was identified, and a similar chart review was done at the phyT's office. Both sets of physicians were asked to answer a short questionnaire.
Results: Of a total of 194 AmR over an 18 month period, 60 reports were amended due to changes in the final diagnosis field. Of these, 21 were amended 21 days or more after sign-out with a range of 3 weeks to 4 months. Of these, 16 pertained to malignant diagnoses - including 7 breast, 4 hematopathology, 2 gynecologic, and 1 each pulmonary, soft tissue and genitourinary cases. The phyT was the phyR (either as a primary or secondary clinician) in 9 cases. The remaining 7 had only the phyR listed in the pathology files. 5 of these had an AmR in the chart of the phyR. ONLY 1 had an AmR in the phyT chart. The phyR questionnaire revealed that, in general, phyR submitted AmR to the phyT if the AmR was received prior to the patient's referral to the phyT, but did not necessarily send it along if the AmR was received after the patients referral. Fortunately, only 1 case had a major amendment (a negative to positive lymph node (N0 to N1(mic)), and although this case did not have an AmR in the chart, the corrected stage was entered in the chart based on a discussion at Tumor Board. The phyT questionnaire revealed that failing to receive the AmR was not rare, but in general, major changes were communicated via Tumor Board conferences or other mechanisms.
Conclusions: An understanding of error-prone steps in a system is fundamental to achieving a planned and organized system for error reduction. We have identified an error prone step in the AmR transmission system that needs to be addressed.

1653 A Comparison of Sampling Techniques in the Pathologic Staging of Radical Prostatectomy Specimens: Part II

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Background: The lack of standardized processing evaluating radical prostatectomy (RP) is well recognized, with only 12% of surveyed laboratories submitting the entire specimen (ES) for microscopic examination. (Am J Clin Pathol 1994;102:572-579). Employing 222 consecutive separate RP specimens (110 entire submission (ES) vs 112 representative sampling (RS)) we have previously demonstrated (Mod Pathol 2007; 20(supp2):340A) that complete submission of the entire prostate gland identified extraprostatic extension of tumor twice as often when compared to RS [40% ES vs 21% RS]; resulting in escalation of tumor stage from pT2 to pT3 (AJCC). The present study examines a cohort of ES RP, comparing ES vs RS within the same specimens.
Design: A consecutive series of ES RP specimens from 71 patients were reviewed. Slides/blocks were chosen per RS (representative blocks from apex, superior, mid, inferior, base, seminal vesicles) protocol and compared with the ES of the same RP specimen. This was conducted blindly without knowledge of the previously reported findings. The criteria for comparison included the following: extraprostatic spread, positive surgical margin, prostatic intraepithelial neoplasia (PIN), lymphovascular and perineural invasion, tumor volume and total Gleason score.
Results: The ages ranged from 43 – 78 years (mean 62 yrs). Weights ranged from 16 - 108 grams (mean 42g.).

ES vs RS

Sampling Method	Extraprostatic Extension	Perineural Invasion	Margin (+)	PIN	LVI	Mean Tumor Volume (%)	Total Gleason score
ES (n=71)	27 (38%) [p=0.003]	54 (76%)	25 (35%)	62 (87%)	5 (7%)	14.50	6.81
RS (n=71)	18 (25%) [p=0.003]	28 (39%)	17 (24%)	48 (68%)	0 (0%)	7.00	7.01

Conclusions: Both our previous study (Mod Path 2007; 20(supp2):340A) and the present study clearly demonstrate that total submission of the entire specimen of radical prostatectomy improves detection of extraprostatic spread (ES 38% vs RS 25%), [p=0.003], thereby escalating AJCC tumor staging pT2 to pT3, and positive surgical resection margins (ES 35% vs RS 24%). The detection of perineural and lymphovascular invasion was also higher in the ES than the RS RP specimens. Therefore, it would seem prudent that until such time that protocols for sampling RP have been standardized and management strategies for pT2 vs pT3 ironed out, it is best that the entire specimen of RP be subjected to histological examination.

1654 Amended Report Worksheets in Surgical Pathology

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Background: Amended reports represent a valuable resource for identifying and tracking deficiencies in the practice of surgical pathology. An amended report worksheet is a form that can be completed by the pathologist and allows the pathologist to document the discoverer of the error/deficiency, the mechanism of discovery, the error/deficiency type, and the type of revision made to the original report. We performed an audit of one year's worth of amended report worksheets in order to determine: 1) if pathologists were compliant with this tracking tool and; 2) if useful data could be obtained for the purposes of quality improvement in surgical pathology.
Design: Retrospective analysis of the amended report worksheets in general surgical pathology for the calendar year of 2007 at the University of Iowa Hospitals and Clinics. In addition, there was review of clinical records of all cases in which the amended report changed either the primary or secondary diagnostic characteristics to assess the clinical impact of such changes.
Results: A total of 170 amended reports were issued in general surgical pathology in 2007. Of these, amended report worksheets were completed for 151 cases (89% pathologist compliance). Clinician initiated review of a case was the most often marked mechanism of error discovery (35.5%). Defective reports, which includes erroneous and missing non-diagnostic information and errors in dictation and/or typing was the most common deficiency type (52%), which corresponded with editorial changes that do not change primary or secondary diagnostic information as the most common type of revision (78%). Revisions that changed either primary or secondary diagnostic information accounted for only 7.2% and 13.2% of amended reports, respectively. The most common types of deficiency in amended reports with revisions to either primary or secondary diagnostic information were interpretive errors (40%), followed by defective reports (31.4%) and inadequate specimen handling (20%). Review of clinical records of all cases that had revisions to either primary or secondary diagnostic information did not reveal any negative impact on clinical outcome.
Conclusions: Amended report worksheets appear to provide an easy and convenient mechanism of compiling categorical quality data related to amended reporting in surgical pathology. This type of data can be of use in targeting recurrent or over-represented deficiencies in surgical pathology reporting, and can serve as a bench mark for quality improvement programs.

1655 Who Owns the Specimen?

R Coriat, J Melamed. NYU, NY.

Background: Specimens are submitted to pathology for diagnosis. Additional activities (education, research) are performed with these specimens with the understanding that they are not to compromise the diagnostic process. Explicit consent for this is almost never exiged. In an era where patient autonomy and self determination have given rise to many legal battles, an unequivocal understanding of specimen ownership is essential. The study examines whether a consensus on specimen ownership exists amongst pathologists. Derivative behaviors as to various approaches to specimen ownership are tallied.

Design: The following questions were asked of 30 pathologists promised anonymity of identity and institution: Who owns the specimen? Have you ever made a slide for a "personal collection"? Have you used pathology material for teaching? Research? Would you ever consider discussing directly with a patient what becomes of their specimen? Have you ever heard of a case where a negative legal outcome had resulted as a result of non diagnosis related activity? If you did, would it change your current approach? Do you feel this study is exposing legal gray zones? Would you have agreed to answer these questions in a format that would include identifying information about yourself?

Results: 40% said the specimen is owned by the patient, 33%-jointly by the patient and the department, 20% -solely the department, and 6% did not know. 100% have made a slide for a "personal collection", and used material for teaching and research. 97% stated they would never speak directly with a patient. 80% never heard of a negative outcome ensuing. 60% stated that hearing of a negative outcome would alter their behavior. 40% said it would not. 93% felt the study is exposing legal grey zones. 6% did not. 50% would have agreed to participate had their answers been recorded with identifying parameters. 50% would not.

Conclusions: No consensus exists as to who owns the specimen. Nevertheless, everyone treats specimens beyond diagnosis as if they are owned by the department. Pathologists do not speak with patients about their preferences. Although this practice is tradition, there was concern patients would not agree, causing a compromise of research and education. A possible conflict of interest is therefore avoided by avoiding communication. A negative outcome would encourage many to change their approach, but not all. Many felt a lost lawsuit would not convince them they are wrong. Despite standing ground on the ethical front, most recognized legal grey zones in these practices. Nearly half were so concerned with the ambiguity surrounding these issues they would not have participated had anonymity not been promised.

1656 Periodic Review of Training Program Teaching Files: A Quality Improvement Study

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Background: Pathology training programs typically retain teaching materials derived from classic and/or difficult diagnostic cases. In many institutions, these files may extend back for decades. However, diagnostic criteria are mutable, and a diagnosis made some years previously may not be considered correct today, or may not use up-to-date terminology. We reviewed a teaching file in order to determine if the archived materials continued to provide a high quality teaching experience.

Design: Each of the reviewed cases was originally reported during the years 2001-2003, and consisted of 1-2 representative H and E slides and a 3x5 card with brief clinical information and the diagnosis; a significant special stain or immunohistochemistry was sometimes included. During the study period, 2-4 cases were reviewed daily at a Faculty Consensus Conference, which was typically attended by 3-5 faculty. Following review, cases were classified into one of three categories: No diagnostic change; diagnosis added; or changed diagnosis. Cases considered less than optimal for interpretation were returned to Conference for final disposition after additional information was obtained.

Results: Of the 112 cases reviewed, 19 had slides missing. Of the remaining 93 cases, 19 cases (20%) required the addition of key clinical information and/or additional slides in order to make an appropriate diagnosis. The final disposition of the 93 reviewed cases was as follows: Diagnosis unchanged - 78 cases (84%); diagnosis added - 9 cases (10%); diagnosis changed - 6 cases (6%). Changed diagnoses are listed in Table 1.

Table 1.

Organ System	Original Diagnosis	Changed Diagnosis
GI, Esophagus	Reflux esophagitis	Eosinophilic esophagitis
Testis	Leydig cell tumor	Adrenal rest
Prostate gland	Adenocarcinoma, grade 2+2; Epineurial invasion	Adenocarcinoma, grade 3+4; Perineural pseudoinvasion
Prostate gland	Prostatic intraepithelial neoplasia, high grade	Adenocarcinoma, small focus
Colon	Hyperplastic polyp	Serrated adenoma
Colon	Pseudomembranous colitis	Favor ischemic changes

Conclusions: Pathology teaching files may contain cases with incorrect or incomplete diagnoses, or diagnoses that do not reflect current concepts of pathophysiology or terminology. In addition, critical information may be incomplete or altogether missing, thereby yielding an unsatisfactory teaching experience. Theft of these valuable materials can be a significant problem. Teaching files deserve periodic review if the quality of the educational experience is to be maintained.

1657 A Taxonomy of Amended Reports Assesses Impact of Henry Ford Production Sysytem [HFPS] a Lean Quality Initiative in Surgical Pathology

FA Meier, RC Varney, R D'Angelo, A Gandhi, RJ Zarbo. Henry Ford Hospital, Detroit, MI.

Background: Amendments change previously issued surgical pathology reports, to cause re-work, confusion, distrust. In 2002-2005 we developed and validated a taxonomy of defects using amendments. Since 2005, this classification has provided information about HFPS LEAN initiatives for eliminating defects in surgical pathology.The objective is to use real-time, ongoing identification, classification, and root cause analysis to study defects causing amended reports and to assess effects of LEAN process improvements on patient and specimen identification, specimen adequacy, diagnostic interpretation, and report generation by applying our validated, standard taxonomy.

Design: For 2006, 2007, and through August 2008, we identified all amended reports, gathered systematically information about them in real time, classified using the taxonomy, determined root causes, and used this information to inform interventions. HFPS LEAN initiative included, goal-directed education of clinicians identifying patients, specimens, redesign of specimen accession, and introduction of double reading (internal, pre-sign-out review) of all breast and prostate cases. During these interventions we recorded: total amended reports, amendments/1000 surgical reports, and fractions of defective reports due to mis-interpretation, mis-identification, specimen defects, and report defects.

Results: Total amendments deceased from 374 on 2006 to 306 in 2007 to 261 (annualized) in 2008: an overall reduction of 18%. This was reflected in yearly amendments/1000 reports rates decreasing from 7. 8 to 6.3 to 5.5 (annualized). Misinterpretation fraction declined from 16% to 7% to 2% of defects: an overall 8-fold decrease. Mis-IDs remained at 12% in 2006 and 2007, but appear to have more than halved, to 5%, in 2008. Specimen defects, 4% in 2006, rose to 11% in 2007, and reduced to 3% in 2008. Because of these reductions, report defects now account in 2008 for 90% of defects, after accounting for 68% and 70% in 2006 and 2007.

Conclusions: Although undetected confounding factors cannot be excluded in real practice situations, it appears that focused double review, of a relatively small faction of cases [800/47,500 (2%)], has had a high return in decreased misinterpretations. By our measures, the return from goal-directed clinician education on misidentification has been modest, and accession redesign has not shown an effect on these indices of quality. Overall, however, the impact of HFPS LEAN has been to drive down amendments.

1658 The Cost of Not Having Clinical Information

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Background: Inadequate clinical data (ICD) on requisition forms ranges up to 20% depending on the institution. Well-recognized negative consequences of ICD include delays in signout and substantial changes in diagnoses. Cases with malignant diagnoses and tissues from certain anatomic areas are more prone to incur a diagnostic change due to ICD. ICD also creates additional cost due to potentially unnecessary testing of tissues in order to arrive at a definitive diagnosis. This cost has not been estimated to date.

Design: A retrospective search over a 6 month period (Jan 08- July 08) revealed 14 cases coded as endobronchial or liver needle biopsy for tumor. Liver and lung biopsies were chosen because these are the two most likely sites of metastatic disease, and therefore most likely to generate a broad differential. Of these, 10 cases did not have an adequate clinical history. These cases were circulated amongst four pathologists to determine the number of immunohistochemical stains (IHC) that each would order to evaluate the case in the absence of additional information. History was then obtained on these patients, in the forms of radiology reports, chart review or phone call to the clinician. The slides were re-circulated, and the pathologists listed the IHC stains they would order with knowledge of the new clinical data. A cost difference between the two scenarios was calculated based on Medicare reimbursement rates for IHC.

Results: When these 10 cases were reviewed with ICD, the number of stains per pathologist ranged from 36 to 64. The pathologist who ordered 36 stains would have ordered additional panels depending on the outcome of staining with the first panel. On average the number of stains per case was 5.6 (range 3-14). When the cases were reviewed with additional detailed history, the number of stains ranged from 24 to 53, with an average of 2.8 stains per case. In three cases, at least two pathologists felt that no stains were necessary. At a global medicare reimbursement of $109 per stain, this resulted in a reduction of $305 per case. At a professional reimbursement of $44 per stain, $123 was saved. Two pathologists, each for one case, would have exceeded the maximum billable stains for a local insurance company in the absence of adequate clinical data.

Conclusions: Inadequate clinical history imposes a cost on the health care system in the form of dollars spent by pathologists to perform additional studies on tissue biopsies.

1659 Grading of Ileal Carcinoid Tumours – Is a Ki-67 Proliferation Index Necessary?

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Background: Our ability to predict the behaviour of gastrointestinal carcinoid tumours is limited. Attempts have been made to identify factors associated with outcome to more accurately identify patients at risk of disease progression. One proposed marker is the proliferation index, quantified by immunohistochemistry (IHC), using Ki-67. Criteria for the staging and grading of carcinoid tumours of the mid and hindgut were recently established by the European Neuroendocrine Tumour Society (G. Rindi et al. Virchows Arch 2007). The proposed grading system is three-tiered: G1:<2mitoses/10HPF and/or Ki-67 index<2% G2: 2-20 mitoses/ 10 HPF and/or Ki-67 index between 2 and 20% G3: >20 mitoses/10 HPF and Ki-67 index >20% Few studies have examined the relationship between Ki-67 and mitotic count in ileal carcinoids.

Design: Nineteen ileal carcinoids were identified. Ki-67 IHC was performed on a representative paraffin block. The proliferation index was assessed in 2,000 tumour cells in areas of highest nuclear labelling ("Hot-spots"). A mitotic count per 10 HPF was performed in areas of greatest mitotic activity on the same H&E stained slide.

Results: 11 patients were female, 8 were male. Patient ages ranged from 39-78 years (mean=63 years). Ki-67 proliferation index was found to correlate with mitotic count using a Spearman test, ($r=0.75$), $p < 0.0001$. The tumour grade was not altered in any case by Ki-67 staining. Using the proposed grading system, eight tumours were grade 1, 10 were grade 2 and none were grade 3. The Ki-67 proliferation index ranged from

0-293/2000 cells (0-15%) and the mitotic count ranged from 0-15/10HPF. No correlation was found between the Ki-67 index and tumour size or lymph node positivity.
Conclusions: In this patient population with ileal carcinoid tumours, Ki-67 strongly correlated with mitotic count. Tumour grade was not altered by Ki-67 staining in any case. Given that there were no grade 3 tumours, a two-tier grading system may be more appropriate. The quality of pathology reporting may not be improved by Ki-67 IHC as mitotic count is an adequate surrogate marker of proliferation.

1660 Root Cause Analysis of Surgical Pathology Identification and Information Defects

SS Raab, AM King, DM Grzybicki. University of Colorado Denver, Aurora, CO.
Background: Anatomic pathology identification defects may lead to catastrophic patient outcomes. The best known examples are those associated with the switch of one patient specimen with another. More commonly, these defects are secondary to incorrect or incomplete patient information. We determined the frequency, root causes, and effect on laboratories of identification/information defects.
Design: We used a direct observational method to determine the frequency of surgical pathology and cytopathology identification and information defects. By observing the accessioning process, a trained individual recorded the presence of accurate information for 8 fields on the specimen containers and 10 fields on the requisition forms (e.g., patient name, second patient identifier, date of collection) over a two week period of time (570 surgical pathology and 76 non-gynecologic cytopathology specimens). We determined the frequency of specific field defect and performed root cause analysis to determine the causes of specific defect types occurring at individual pre-analytic specimen procurement sites (n=33). During the observational process, we determined accessioner responses to specific field defects and the time in performing work-around activities.
Results: No specimen (container and requisition) was defect free, although the frequency of defect varied considerably by container (e.g., 1.7% lacked an accurate patient name or second identifier, 3.4% lacked a date of collection, 7.3% lacked a physician name, and 99% did not report the location of specimen procurement) and requisition (e.g., 1.6% lacked a specimen description and 15% lacked clinical history). The frequency of specific defect types varied considerably by pre-analytic collection site (e.g., patient name defects occurred only in some clinics). Root cause analysis showed that the overwhelming majority of these defects occurred as a result of the lack of standardized pre-analytic processes and lack of redundant checks. Accessioners spent considerable time (15 minutes to 45 minutes) in fixing specific individual defects, ignored the lack of information in most cases, and made assumptions to correct information other defects.
Conclusions: Specimen identification and information defects occur at a high frequency and are secondary to the lack of pre-analytic protocols and processes. These defects generally result in laboratory workers spending considerable time in performing work-arounds and making potentially risk-associated assumptions.

1661 Antibody Expiration in the Context of Resource Limitation: What Is the Evidence Basis?

EC Savage, BR DeYoung. University of Iowa, Iowa City, IA.
Background: The recent implementation and enforcement of CAP Survey Checklist ANP 22432 has renewed attention on the issue of outdating of antibodies for immunohistochemistry. The requirement for this position is rooted in CLIA '88 and its granting of anylate specific reagent status to primary antibodies as well as the CAP's role as laboratory accrediting agency as deemed by CMS with the primary driver likely being patient safety. However, in a time of limited resources, one questions the evidence base for this position. Two previous older studies have investigated the issue of expired antibodies, although both in a limited manner.
Design: Methods and Materials: The staining patterns of 26 recently acquired primary antibodies and their expired counterparts (ranging from 6-24 months with an average expiration interval of 13 months) were examined sequentially by two independent reviewers on formalin-fixed paraffin embedded tissue sections utilizing standard immunohistochemical technique. Both staining intensity (ranging from 1 to 3+) and percent of cells stained (I = <25%, II = 25-50%, III = 50-75%, and IV = >75%) were recorded. Positive and negative controls stained appropriately for all antibodies.
Results: Twenty of the twenty-six antibodies tested exhibited no difference in either percent positive cells or staining intensity (76.9%). Of the remaining six, three showed better performance with the expired cohort and three with non-expired antibodies. It should be noted, no antibody's staining characteristics varied by more than one step, and there were no cases where positive staining was lost secondary to antibody expiration.
Conclusions: In concordance with a small number of previous reports, there are negligible differences in immunostaining when comparing outdated antibodies to "current" ones. Given the current constraints on healthcare resources, efforts to procure exemption for primary antibodies from existing regulations may prove beneficial and would not adversely impact patient care assuming.

1662 Implementation of a "Macro/Autotext" Format in FISH Reporting Significantly Reduces Errors

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Background: Error detection in anatomic pathology is well-described, and reporting errors may impact patient outcome (reference). Identifying sources of error and devising targeted approaches to reduce/eliminate error is critical. One approach is to use a standardized report (a.k.a. macros, autotext). In contrast to typical report preparation, our autotext program works by selecting items from an in-depth template rather than entering raw data. We evaluated the impact of using autotext on error reduction in fluorescence in situ hybridization (FISH) reporting.
Design: 250 consecutive FISH reports from before and after autotext implementation were identified (500 total). All reports were reviewed independently for errors (KR,NS). Raw data sheets from which these reports were generated were not reviewed. Errors were classified according to Zarbo *et al*. (ref). Categories included defective patient identification, specimen, report and interpretation. Error outcome severity included no impact on care; minimal harm; minor harm; moderate harm; major harm; and unknown.
Results: From pre- and post-autotext FISH reports, 27% and 15% had errors, respectively (Table 1). There were no errors of patient identification or specimen in either group. Pre-autotext errors included 51 defective reports (14 typographical, 3 punctuation, 12 date errors, 4 mathematical, 18 nomenclature) and 17 interpretation errors (4 false positive, 6 false negative, 7 not further classifiable). 14 had a minimal or minor impact. Post-autotext errors were typographical or grammatical, and none had clinical impact. 33 were due to integral errors in templates, while 5 occurred from manual entry.

Type of FISH report	# cases	# (%) cases with errors	Types of errors (# cases)	Error outcome severity (# cases)(%)
Pre-autotext	250	68 (27%)	Defective report (51) Defective interpretation (17)	No impact (48)(70%); minimal (11)(16%); minor (3)(5%); unknown (6)(9%)
Post-autotext	250	38 (15%)	Defective report (38)	No impact (38)(100%)

Conclusions: Implementation of autotext resulted in an almost 50% reduction in error rate in FISH reporting. This was due principally to decreased opportunity for error during manual entry. In addition, elimination of unnecessary and redundant data reduced the rate of interpretive error. Our study indicates that the overall clinical impact of error may be reduced to 0 primarily due to reduced interpretive error, although original data sheets must be reviewed to verify this finding. Zarbo RJ *et al. Arch Pathol Lab Med*. 2005:129.

1663 Near-Miss Event Rates in a Traditional Surgical Pathology Accessioning and Gross Examination Laboratory

ML Smith, SS Raab. University of Colorado Denver, Aurora, CO.
Background: The rate of near-miss event errors in the pathology gross examination laboratory has not been evaluated. Independent of the diagnostic abilities of the pathologist, errors in the laboratory may lead to catastrophic patient injury if not recognized and addressed. We hypothesize that the characterization of near-miss events in a traditionally designed surgical pathology laboratory will guide optimal re-design of work flow to minimize the potential for error.
Design: Via five days of direct observation of the laboratory process, we collected detailed data on the frequency of near-miss events during the receiving, accessioning, set-up and gross examination of specimens in an academic hospital which batches its work (annual volume: 22000 specimens). Near-miss events were those that if not caught and corrected may lead to a patient specimen being mixed-up with a different patient specimen. Events were categorized as *process dependent* (defined as near-miss events that occurred as a result of the work-flow process [e.g. cassettes from multiple patients are printed and dropped into the same container requiring technical staff to sort them out, specimens separated from requisition forms for accessioning, all biopsies set-up on one large tray]), and *operator dependent* (defined as near-miss events not associated with the work-flow [e.g. a patient specimen was inadvertently placed into another patient's cassette]). Twenty-four different operator dependent error categories were identified. Rates of events were calculated as: frequency of events divided by the number of specimens processed.
Results: 335 cases with 421 specimens were submitted to the laboratory for processing. The rate of operator dependent near-miss events was 0.6 events per specimen (more than one every other specimen). Operator dependent errors were sub-categorized into accessioning (6, e.g. wrong accession number written on requisition form), set-up (14, e.g. requisition paired with incorrect specimen container), and grossing (4, e.g. two different requisition forms in grossing area at the same time). 2310 process dependent near-miss events were identified, a rate of 5.5 events per specimen. The total near-miss event rate was 6.1 events per specimen.
Conclusions: Traditional batched work-flow design in the surgical pathology gross laboratory leads to an unacceptably high rate of process and operator dependent near-miss events. The dramatic number, identification, and categorization of near-miss events will aide substantially in the re-design of work-flow using lean methodologies.

1664 Implementation of a Canadian External Quality Assurance Program for Breast Cancer Biomarkers: An Initiative of Canadian Quality Control in Immunohistochemistry (cIQc) and Canadian Association of Pathologists (CAP) National Standards Committee/Immunohistochemistry

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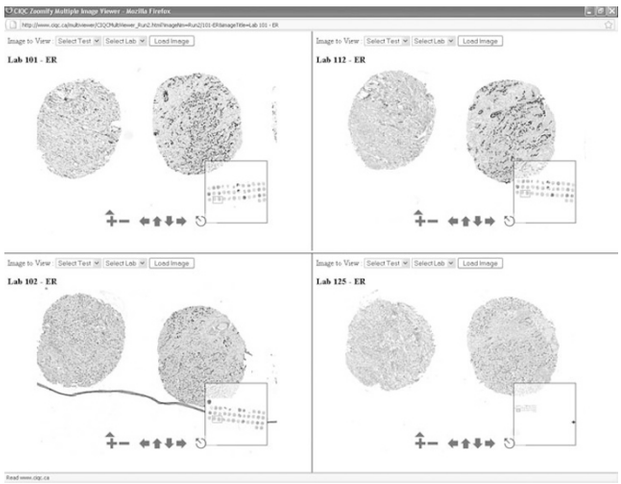
Background: Immunohistochemistry (IHC) results for ER, PR, and HER2 are used to guide breast carcinoma patient management. To obtain fewest false-positive or false-negative results, it is essential to monitor laboratory performance through participation in external quality assurance (EQA) programs. Canadian Immunohistochemistry Quality Control (cIQc, www.ciqc.ca) is the first web-based independent EQA program for Canadian laboratories.
Design: Slides from TMA with 38 tissue cores were sent to 18 Canadian diagnostic IHC laboratories. All results were de-identified for the source and posted for viewing including protocols, Garrattograms, and virtual microscopy at www.ciqc.ca. Sensitivity, specificity, Kendall's W Test for concordance, and kappa statistics were calculated. MultiViewer" enables side-by-side comparison of up to four different results by virtual microscopy. This feature is specific to virtual microscopy, more specifically to the "MutiViewer", as this is not possible using actual microscopy.



Results: High average observed agreement, sensitivity, and specificity in ER, PR, and HER2 testing was observed (all > 90%). Kappa values were within the target range (> 0.8, or "near perfect" agreement) for all participating laboratories except the following: 1 laboratory for ER, 6 laboratories for PR, and 1 laboratory for HER2. Kendall's coefficient of concordance between the 18 laboratories was 0.942 for ER, 0.930 for PR, and 0.958 for HER2. False positive and false negative results could be identified as either interpretive or technical errors.
Conclusions: The first Canadian IHC EQA testing for ER, PR, and HER2 showed very high concordance between laboratories. The anonymous participation and unrestricted full access provides a means for rapid insight into technical or interpretive deficiencies, allowing appropriate corrective action to be taken.

1665 Use of Formal Root Causes Analysis of Anatomic Pathology Errors to Classify System and Active Components

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Background: Anatomic pathology error evaluation and root cause analysis historically has focused on the misdiagnoses of unusual entities or diagnostic pitfalls for more common diseases, suggesting that error cause is associated with cognitive or performance deficiencies of specific pathologists or clinicians. We evaluated the effectiveness of formal root cause analysis to determine the frequency of specific causes in errors detected by the cytologic-histologic correlation process.
Design: We examined 50 consecutive cytologic-histologic correlation-detected errors in 34 gynecologic and 16 non-gynecologic specimens over a 3 month interval. initially, we used a method that graded discrepant histologic and cytologic specimens in terms of quality and the amount of tumor. We then performed a modified Eindhoven method of root cause analysis to determine latent (system) and active (personnel) causes of error. These causes were then evalauted to examine which error causes could be addressed by process improvement.
Results: In our initial assessment, 48% of cytology/surgical specimens were of low quality consisting of the relative absence of tumor cells, obscuring blood, or other artifacts that limited interpretation. In 33% of these cases, some reviewers retrospectively identified possible tumor although generally classified the sample as non-definitive. Of cases in which the specimen was of sufficient quality, at least some tumor cells were identified in 78% of cases and generally was of low volume. The overwhelming cause of error was multiple system failures. Laboratory sources of error included poor preparation (40% of cases), lack of standardized criteria for classifying specimens as less than optimal (50%), lack of training in the interpretation of challenging samples (60%), and lack of protocols to handle small samples (10%). Clinical sources of error included inadequate handling of bloody samples (30%), lack of clinical standardization in obtaining samples (100%), inexperience, and inadequate transport techniques. Although redesign could address many of these factors, overall systems that resulted in busy schedules, lack of a patient safety focus, and inadeqaute training in improvement techniques hampered actual reorganization.
Conclusions: Pathology errors are almost always multifactorial and results from defective laboratory and clinical systems. Although there is a tendency to attribute error to personnel failures, 100% of individual diagnostic errors occur when systems do not address a vast array of error-prone processes and protocols.

1666 A Cost Efficient Strategy for Deeper Levels on Skin Specimens

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Background: The optimal number of levels to perform on skin biopsy specimens to reduce turnaround time and minimize cost has yet to be determined. In a previous study, we found that small specimen size (0.5 cm or less), punch biopsies, and those with a clinical impression of cancer or dysplasia were more likely than other specimen types to require deeper levels to arrive at a final diagnosis. In this study we examine a strategy aimed at optimizing efficiency in the handling of skin biopsy specimens.
Design: 199 consecutively accessioned skin biopsy specimens which measured 0.5 cm or less or were punch biopsies formed the study group. These samples were cut prospectively at 4 levels. The control group consisted of 277 skin specimens meeting the same criteria from our 2005 study which were cut at a single level. We compared the turnaround time for the two groups. We also performed a cost analysis comparing this targeted method with prospectively cutting deeper levels on all skin specimens.
Results: In the study group, 13/199 (6.5%) cases required additional levels. The same group of specimens in our prior study in which a single level was performed had a significantly higher requirement for deeper levels, 167/277 (60%) ($p<0.0001$). The turnaround time between the study cases and controls was also significantly different (mean =1.31 days vs. 2.83 days, respectively, $p<0.0001$). Accounting for the initial production of slides and the cutting of additional levels, the projected cost of performing prospective deeper levels on skin specimens measuring <=0.5 cm or punch biopsies is $2.18 less per case than performing prospective deeper levels on all skin specimens. For our hospital, with an average of 20,000 skin specimens a year, this amounts to saving $33,689 per year, or approximately one half of a full time employee equivalent (histotechnologist). Additionally, the projected number of slides for one year cutting selective levels on all specimens is 77,051 vs. 114,077 with prospective levels, resulting in decreased storage requirements.
Conclusions: Cutting prospective deeper levels on skin specimens which measure <=0.5 cm and punch biopsies significantly reduces the need for additional levels and greatly improves turnaround time. Targeting this select group of specimens for prospective deeper levels is more cost effective than performing deeper levels on all skin specimens and reduces storage requirements.

Special Category - Pan-genomic/ Pan-proteomic Approaches to Cancer

1667 Quantitative Assessment of Change in Protein Phosphorylation as a Function of Ischemic Time before Formalin Fixation

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Background: Post-translational modifications and especially phosphorylation has been shown in preclinical studies to be an excellent method of signaling pathway activation and predicting response to targeted therapies. However, there is evidence that phospho-proteins are dephosphorylated as a function of ischemic time prior to fixation, as is seen in routine processing of surgical pathology specimens. Core Needle Biopsies (CNBs) are typically very rapidly fixed. Here we use this conventional difference in ischemic time to determine the effect of delayed fixation on phospho-specific markers of pathway activation.
Design: Two series of matched CNBs and resections were collected. In series one, 20 cases were examined as a tissue microarray where each specimen was examined in two fold redundancy. The TMA was analyzed by the AQUA® method of immunofluorescent analysis using antibodies to Ki67, p53 and Estrogen Receptor (ER) as controls and antibodies to phospho-Erk (p-ERK), phospho-AKT(p-AKT) and phospho-tyrosine (p-tyr) as the test set. The second cohort was analyzed as whole sections where between 5 and 29 20x fields were assessed on each tissue with an antibody to phospho-AKT.
Results: Both ER and p53 as assessed on the TMA cohort showed no overall trend toward decreased or increased expression in the core biopsy vs the resection specimen. However p-AKT, p-ERK, p-tyr and Ki-67 all showed lower expression in resection specimens. To rule out TMA sampling artifact, whole sections were assayed with an average of 12 and 19 fields for biopsies and resections respectively. In each case, there was consistently and significantly lower levels of pAKT in the resection than in the biopsy (Wilcoxon Signed-Ranks test $p=0.0069$).
Conclusions: This study shows that phospho-proteins are present at decreased levels as a function of ischemic time. This pattern is seen in both TMAs and whole sections. Surprisingly, Ki67 also shows this trend, which could have implications for its use in evaluation of efficacy of neoadjuvant therapy. CNBs appear to be the preferred method for analysis of phospho-proteins for use as a predictor for pathway activation and to assess response to targeted therapies.

1668 Genomic Identification of Biomarkers of Behavior of Pancreatic Endocrine Tumors

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Background: Endocrine tumors of the pancreas are difficult to classify into benign and malignant categories, and as such are often diagnosed as pancreatic endocrine tumors (PETs). The recent WHO classification has improved this situation, but there is still a need for additional molecular biomarkers to provide independent assessment of the risk of malignant behavior.
Design: To identify potential biomarkers of malignant behavior, genome-wide transcriptional profiles were generated for a cohort of 45 PETs using commercially available DNA microarrays. PETs analyzed represented sporadic and syndromic (MEN-1) forms, and primary metastasizing and non-metastasizing tumors, and metastatic tumors.
Results: Using F-tests and selection criteria of $p<0.01$ and fold change > 1.5 in either direction, comparison of 8 PETs with proven metastases (PET-M) to 6 PETs without metastases (PET-N) yielded 255 unique genes whose expression was increased in the PEN-M group and 142 unique genes whose expression was decreased in the PEN-M group. Differentially expressed genes included genes related to tumor invasion and metastasis, as well as other biological processes. Preliminary results from immunohistochemical and AQUA-based validation for several of these biomarkers using tissue arrays containing an independent set of PETs are promising and ongoing.
Conclusions: Genomic investigation of pancreatic endocrine tumors will yield novel biomarkers that will permit a more refined assessment of their risk of malignant behavior. Application of these biomarkers to pathology practice will improve the management of patients with PETs.