Quality Assurance

1612 Comparison of ZAP-70 Expression and Cytogenetic Risks in CLL Patients: A New Practical Insight for Their Molecular Risk Stratification

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Background: Adequate molecular risk stratification is crucial for modern management of chronic lymphocytic leukemia (CLL) patients. Expression of zeta associated protein - 70 (ZAP-70) has been proposed as a surrogate marker for the immunoglobulin variable region (VH) mutation status, and is associated with poor prognosis in CLL. Although recent studies have shown that presence of high-risk cytogenetic/ molecular factors (del11q, del17p, V3-21 usage) can result in discordance between ZAP-70 expression and VH mutation status, a direct comparison of ZAP-70 expression as measured by multiparametric flow cytometry, with low to intermediate cytogenetic risk factors (del13q and trisomy 12), has not been characterized. Understanding this relationship has practical significance since the VH mutation status can not be evaluated as a routine clinical test.

Design: Data was retrospectively collected from 81 CLL patients who had both ZAP-70 and cytogenetic studies performed between 01/2005 and 09/2007. Patients with the following characteristics were excluded: presence of high risk cytogenetics as mentioned above; lack of either trisomy 12 or del 13q; simultaneous expression of trisomy 12 and del 13q; plus more than 2 concurrent cytogenetic abnormalities. The remaining patients (n = 38) were then separated into two groups, based on the presence of either trisomy 12 or del13q, identified by FISH. The average percent of ZAP-70 expression by multiparametric flow cytometry was compared using the student T test. Molecular genetic studies for the VH mutation status were not performed in this study.

Results: There was a statistically significant lower level of ZAP-70 expression in the del13q group (mean ZAP 70 % expression=9.16%) when compared with the trisomy 12 group (mean ZAP 70% expression=19.90%) (p=0.005).

Conclusions: We observed a statistically significant decrease of ZAP-70 expression in CLL patients with del13q when compared to those with trisomy 12. This finding is of practical value in molecular risk stratification and management of CLL patients, where routine measurement of VH mutation status is not possible. In addition, the finding provides insights in establishing practical quality control standards for measurement of ZAP-70 by flow cytometric immunophenotyping.

1613 Is a Negative Immunohistochemical Control (No Primary Antibody) Routinely Needed?

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Background: Immunohistochemical stains are used for localisation of proteins in cells and tissues. Negative immunohistochemical controls are routinely used to test for the specificity of the staining, but there is no generally accepted protocol for the use of negative controls.

Design: We sought to perform a preliminary assessment of the utility of negative control done by omission of the primary antibody through the use of a tissue microarray consisting of 0.6 mm cores of normal tissue from 138 cases. These included 69 different normal tissues. Unstained tissue microarray slides were stained in four different laboratories, using three different automated immunostainers, and different commercial detection kits, including both avidin-biotin and polymer-based detection systems.

Results: We found that all slides showed no staining except for endogenous cytoplasmic or extracelluar pigments (lipofuscin, melanin, or hemosiderin) detected in cardiomyocytes, macrophages, substantia nigra cells, hepatocytes, seminal vesicle cells and skin. Weak diffuse staining of cells from the anterior pituitary gland was also detected in the slide of one of the laboratories.

Conclusions: Negative controls done with omission of the primary antibody showed no precipitation of chromogenic substrate in the normal tissues, with the exception of very faint staining of the anterior pituitary in a slide from one of four laboratories participating in this study. These results are preliminary but, if validated, suggest that some or all negative controls could be eliminated from routine use.

1614 Process Improvement of Surgical Pathology Turnaround Time: A Departmental Effort at a Regional Veterans Affairs Medical Center

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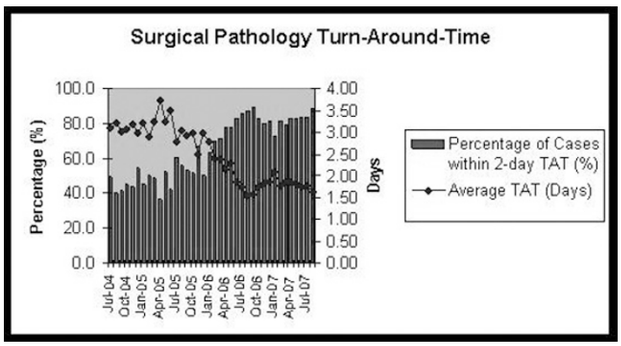
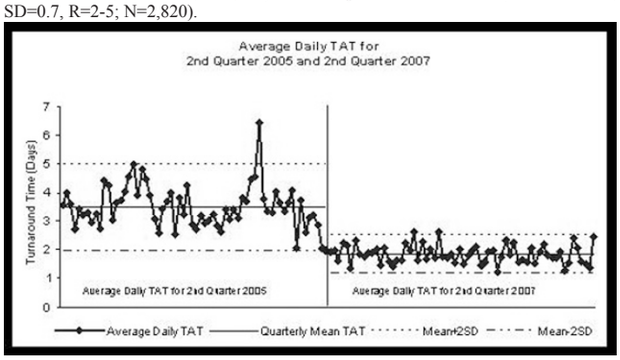
Background: Surgical Pathology (SP) turnaround time (TAT) is a visible parameter of a pathology service and Veterans Affairs Medical Centers across the nation are striving for improvement.

Design: In early '06, we benchmarked our SP TAT data against Carey Award winning laboratories that reported an average (ave) TAT of <2 days. Process improvement measures were taken and impact evaluated by retrospective review of QA data. Dictation templates were created for microscopic exam - a result of several staff meetings and input from all pathologists. Secretarial work flow changes were made to enhance timely transcription. Availability of templates enabled more pathologists to self-transcribe, thereby decreasing secretarial workload. Measures were taken to improve staffing. Templates provided new staff members a jumpstart with daily sign-outs. All SP cases accessioned between 7/04 and 8/07 were included. TAT QA data from 1/06-8/07 was compared with data from 7/04-12/05. TAT variability over a quarter was compared between '05 and '07 using ave daily TAT. Audit data of randomly selected oncologic SP reports for data elements from CAP Cancer Protocols was reviewed for '06.

Results: Ave TAT of <2 days with a <2-day (d) TAT in >80% cases was achieved within 6 months. Ave TAT between 7/04 and 12/05 was 3 d (R=2.5-3.7); it declined to 2 d (R=1.5-2.8) in '06 and to 1.8 d (R=1.6-2.0) in '07.



Comparative 2nd quarter daily ave TAT showed decreased variability in '07 (ave=1.8 d/case; SD=0.3, R=1.2-2.5; N=3,017) when compared with that of '05 (ave=3.5 d/case; SD=0.7, R=2-5; N=2,820).



Audit of 58 randomly selected cases from '06 demonstrated 100% compliance with CAP Cancer Protocols.

Conclusions: Departmental effort with multifaceted approach helped reduce TAT by almost half, approaching numbers better than the gold standard set by previous Carey Award winners.

1615 Process Improvement in the Histology Laboratory Using a Collaborative Problem Resolution Tool

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Background: The histology laboratory has little opportunity for automation and is largely run through manual processes. Process improvement, therefore, relies on team investment in changes and dedicated follow through. Tools exist in the business community for directed process improvement and these can be used in the histology laboratory. In our laboratory, the time delay in obtaining recut hematoxylin and eosin (H&E) stains and in obtaining special stains significantly delayed case signout. We used a performance improvement tool called FasTrac™ (Orion Advisory, Inc, Charlotte, NC) to address this gap.

Design: The FasTrac™ methodology is a six step collaborative problem solving tool that capitalizes on a cross-functional team. FasTrac™ begins by clearly defining a quantifiable problem and ends with implementation of solutions. During the process, the team members identify the root causes of the problem, implement corresponding solutions, and the result is expected to be closing the performance gap. The entire process takes place in a 12-week time period. Success is judged by improvement in the metric – turnaround time of recut and special stains, in our case.

Results: Analysis of average turnaround time from ordering of recut H&E to slide delivery was 24 hours and the average for special stains was 27 hours. Through the collaborative process, solutions were suggested and implemented, including obtaining running logs of orders, distributing recut blocks across all members of the lab, and more frequent batching of special stains. After the 12 week FasTrac™, the recut H&E turnaround time was 4 hours and the special stain turnaround time was 6 hours, on average. The turnaround times have met target for the past 9 months.

Conclusions: Gaps in laboratory performance in the laboratories can be addressed using simple, but highly effective collaborative process improvement tools. We demonstrate the use of the FasTrac™ process to close the specific gap of a delay in recut and special stain turnaround times. We were able to significantly reduce both turnaround times and improve overall case sign-out turnaround time. The tool also improved morale in the laboratory by engaging the front-line employees in the process.

1616 Utility of Molecular Fixative UMFIX in Preservation of Morphology and Nucleic Acid Integrity in Paraffin Embedded Surgical Specimens

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Background: Gene and protein expression profiling are used to understand disease process and to identify new prognostic and therapeutic markers. Formalin-fixed paraffin embedded (FFPE) specimens represent the most abundant archival source. Tissues fixed in 10% neutral buffered formalin (NBF) retain good morphologic and protein preservation, but the quality of nucleic acids (DNA and RNA) is compromised. We

evaluated utility of a molecular fixative (UMFIX, Sakura Finetek USA, Inc, Torrance, CA) for its effect on quality of tissue morphology and on preservation of DNA and RNA integrity.
Design: Forty surgical specimens: colon (11), breast (13), lung (6), prostate (8), kidney (1), and skin (2) were split in 3 equal parts, and tissues were immediately fixed in a) UMFIX, b) NBF, and c) snap frozen. The tissues were all quality controlled morphologically. DNA and RNA were isolated from approximately equal number of tissue sections. Quality and quantity was evaluated by spectrophotometry and agarose gel electrophoresis. Integrity of isolated DNA was assessed by amplification of 100, 200, 300, 400, and 600 base pair (bp) amplicons. For assessment of RNA integrity, amplification of β-Actin (343 and 705 bp fragments) and β2 microglobulin (less than 200 bp fragment) transcripts was utilized.
Results: The histomorphology of UMFIX-fixed tissues was similar to that of matched FFPE tissues. UMFIX fixation preserved integrity of small and intermediate DNA fragments, as demonstrated by successful amplification of 400 bp amplicons in all samples, and 600 bp amplicons in 17/40 (43%) samples. RNA integrity of UMFIX-fixed tissue was 45% and 43% of that observed for frozen tissue in amplification of 243 and 705 bp β-Actin fragments, respectively. UMFIX fixation proved inferior to both freezing and formalin fixation in amplification of β2 microglobulin transcripts (104 versus 215,168 and 1,047 copies, respectively). Length of fixation time did not seem to influence the quality of nucleic acids.
Conclusions: Histomorphology of UMFIX-fixed tissues was similar to that of FFPE tissues, and was diagnostic. UMFIX also proved superior to formalin in preservation of DNA integrity, yet was only 40% as effective as snap freezing in preserving larger DNA fragments. UMFIX performed poorly in preservation of RNA. Overall, while UMFIX proved acceptable for tissue morphology, it failed to preserve total nucleic acid integrity to a degree that would justify its use as a universal molecular fixative.

1617 Lean Process Improvement Shortens Total Molecular Diagnostic Testing Time

M Cankovic, L Whiteley, R Brown, R D'Angelo, RJ Zarbo. Henry Ford Hospital, Detroit, MI.
Background: Diagnostic molecular test results are often important for subsequent therapeutic decision making, yet delays during the pre-analytic phase of test ordering and specimen retrieval greatly influence the overall turnaround times (TAT). These delays are often caused by lack of co-ordination in specimen hand-offs between different sections of the lab. In this study we share our experience with the Henry Ford Production System's implementation of Lean process improvements across different disciplines that resulted in significantly reduced TAT for antigen rearrangement (AR) assays.
Design: We compared total test times and individual steps in 3 time periods, and measured the time it took to complete different steps. Period I - By looking at a two year period, we estimated average times needed to complete the following steps: 1. Pathologist realizes the AR testing is needed; 2. Pathologist orders the test; 3. Molecular Diagnostic lab requests Histology to cut appropriate tissue sections; 4. Histology assigns low priority to task; 5. Molecular Diagnostic lab completes the testing. Period II – Lean Process improvements were implemented across different disciplines; we measured the time it took to complete the 5 steps defined in Phase I. Period III – Several "Rapid Process Improvement" modifications were added to further increase efficiency.
Results: Period I – The entire process, from the time the pathologist realizes the testing is needed to the time the test results are generated took from 33.5-145 hours (1.4-6.0 days); average 64.8 hours (2.7 days). A lot of this time was wasted on hand-offs between different lab sections. In Period II, electronic test ordering became available, and Lean process improvement was implemented in Histology for continuous work process. This resulted in elimination of 2 pre-analytical steps, and significant reduction in time for 2 additional steps. In Period III, visual aids were made available to Histology personnel in order to reduce misunderstanding of electronic requests and reduce need for re-cuts. This resulted in additional time saving, and TATs of 24.2-49 hours (1-2 days); average 36.5 hours (1.5 days).
Conclusions: By implementing Lean processes across laboratory disciplines, total molecular diagnostic time for AR assays was reduced from an average of 2.7 days to an average of 1.5 days, a 45% improvement. Because of the more timely molecular diagnostic test results, pathologists were able to rapidly integrate this information in a final report without need for an addendum report.

1618 The Routine Pap Test for the Detection of High-Grade Cervical Neoplastic Lesions: A Contemporary Re-Evaluation Based on Rates of Diagnostic Discordance in 356 Pap Tests Obtained Concurrent with a Cervical Biopsy

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Background: Studies evaluating the routine papanicolaou (pap) test have traditionally used as the reference gold standard, the diagnoses on the follow-up cervical histologic samples. Since the latter are typically obtained days to weeks after the cytologic sample, the accuracy of the resultant comparison may be affected by intervening factors, such as regression of human papillomavirus or colposcopy-associated variability. A subset of our clinicians have routinely obtained cervical cytology samples immediately prior to their colposcopic procedures, which presented a unique opportunity to re-evaluate the test performance of the pap test in detecting the most clinically significant lesions (i.e cervical intraepithelial neoplasia 2 or worse: CIN2+), using as gold standard, diagnoses on cervical biopsies that were essentially obtained simultaneously.
Design: Our database was searched for all women with a cervical biopsy (bx) and pap test accessioned within 24 hours of each other for the period 1/3/06-7/27/07. For each patient, diagnostic discordance between the pap test and bx was considered to be present when either modality displayed HSIL/CIN2+ while the other modality displayed no dysplasia/NILM/LSIL (i.e. a less severe lesion).Therefore, HSIL/CIN2+ was present in both the pap and bx in true positives (TP), and absent in both modalities in true negatives (TN). In false positives (FP), the pap showed HSIL while the bx showed less than a CIN2+. In false negatives (FN), paps displaying less than a HSIL were associated with biopsies displaying CIN2+. Combinations associated with ASC-US or ASC-H interpretations were excluded. All cytologic preparations were liquid-based.
Results: A diagnostic discordance was present in 17 (4.8%) of 356 such pap test/bx combinations. The discordance was attributed, by virtue of having the less severe interpretation, to the pap test in all 17 cases. Using the cervical bx diagnoses as the gold standard, the sensitivity, specificity, positive predictive value and negative predictive value of the pap test in identifying a CIN2+ lesion was 50%, 100%, 100% and 95% respectively. There were 17, 322, 0, and 17 TP, TN, FP and FN respectively.
Conclusions: In 4.8% (17/356) of cases, a bx-proven CIN2+ was not captured by the concurrently obtained pap test. This figure essentially represents the contemporary false-negative rate of the pap test in liquid-based cytologic preparations, and should be a consideration in screening programs.

1619 Best Practices in Breast Pathology: Practical Quality Assurance/ Patient Safety Program in a Womens Hospital. A Descriptive Study

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Background: The Susan G Komen for the Cure white paper (Breast J 13(5), 2007 443-47) identifies key issues that affect quality practice in breast pathology, including diagnostic accuracy, reimbursement, tissue banking, pathologist training, clinical team integration, and maintenance of the highest standards of practice. The purpose of this study is to describe how the above issues are addressed in an integrated quality assurance/ patient safety program in a pathology department of a womens hospital.
Design: Preanalytic handling of biopsies include 10% formalin fixation time of 8-48 hours and 5 levels on each block. Analytic items include mandatory review of internal and referred material and halting scheduled surgery if there are diagnostic discrepancies. Daily review of difficult cases is documented for patient safety CME. Uniform problem-oriented panels for IHC studies are utilized. There is real-time review of FNAs accompanied by biopsies and secondary reviews of positive and negative biopsies. A postanalytic radiology-pathology correlation report is issued by radiology. Predictive/prognostic marker results are monitored to detect drift. Preanalytic resection specimen handling includes review of the core biopsy report to direct specimen handling. All tissue is submitted for a diagnoses of ADEH/DCIS in the absence of a gross lesion. Tissue banking is routine for all tissues. Postanalytic review includes tumor boards, OR consults and 5% random review. Pathologists and assistants are held to a quality program for recredentialling.
Results: Discrepancies in breast biopsy diagnoses from outside institutions are 7%, with 50% of discrepancies potentially impacting patient management. Internal peer review measures indicate a very low incidence of significant discrepancies compared to the published literature.
Conclusions: (1) Preanalytic measures assure optimal specimen handling and predictive/prognostic factor outcomes and uniform practice. (2) The quality analytic measures provide for an active collegial environment and exposure for trainees that fosters patient safety, maximizes diagnostic accuracy and reproducibility and minimizes risk. (3) Postanalytic analysis assures integration of radiology (rad-path correlation), surgery and oncology (tumor boards), and teaching function, by being a part of the entire process. (4) These measures, along with the complex specimen reporting requirements, have never been addressed from the reimbursement perspective, and there is a critical need for this to be done.

1620 Critical Values in Surgical Pathology: Continuous Monitoring To Improve Patient Safety

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Background: Critical values (CVs) are used in the area of clinical pathology to ensure patient safety; however, such practice has not been well-established in anatomic pathology. Recently, guidelines proposed by the Association of the Directors of Anatomic and Surgical Pathology (ADASP) were adopted and modified by our department. To evaluate our performance within these new guidelines, we monitored CVs in surgical pathology to improve patient safety.
Design: In 2005, we established policies regarding timely communication and documentation of urgent surgical pathology findings, which has led to guidelines requiring immediate notification of primary clinicians. In 2006, we performed a 6-month, retrospective study for documentation and notification of CVs. To assess our progress, we studied a similar time frame this year and compared the results to determine the validity of our CVs and our compliance using newly revised/customized guidelines.
Results: Of the 28,298 surgical pathology cases examined, excluding gynecologic pathology, neuropathology and cytology, 1,048 cases (3.7%) prompted urgent physician notification (3.2% in 2006). In over half of the cases (694 cases, or 66.2%), the physician was contacted by telephone within 24 hours of receiving the specimen and the notification was documented in the report. The top three reasons that required physician notification were consistent with the previous year: kidney biopsies (321, 30.6%), malignancies (174, 15.3%) and transplant biopsies (245, 21.6%). 391 of the 1,048 cases (37.3%) fell within the ADASP proposed CV categories. Other cases which also prompted urgent contact include graft-versus-host disease (23), acute tubulo-interstitial nephritis (102), and acute ischemic colitis (6). Our new policy requires CVs to be documented and "flagged" using our electronic system. 840 cases (80.2%) were both flagged and documented, while 191 cases (18.2%) were either documented (141) or flagged (50). 17 cases (1.6%) were not properly documented. By way of comparison, only 76.4% of the cases had proper documentation during 2006.
Conclusions: Our findings demonstrate an increased rate of notification and documentation, suggesting enhanced awareness of our pathologists in responding to CVs and compliance with newly established guidelines. Based on 2006 findings, our

customized guidelines were satisfactory in identifying most of the urgent diagnoses, with the new addition of acute ischemic colitis. The continuous monitoring of our policies regarding CVs allows improvement in patient care and safety.

1621 Monitoring Critical Values in Medical Kidney Diseases: A Step Towards Quality of Care

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Background: The Division of Renal Pathology, in collaboration with nephrology, established guidelines for proper notification and documentation of urgent diagnoses, which required immediate communication. In addition to quality assurance purposes, these guidelines were established to improve patient care, safety and clinician satisfaction.

Design: In 2005, we customized a list of critical diagnoses in renal pathology which requires immediate physician communication. To monitor our compliance and the effectiveness of these guidelines, we performed a retrospective study of a 6-month period (2007) and compared to the previous data (2006). The study included a systematic analysis of all kidney biopsy reports to document the critical values and to monitor adherence to our established policy.

Results: Of the total 733 kidney biopsies, the clinicians were communicated in 321 cases (43%) of the total kidney biopsies this year as compared to 218 cases (32%) last year. There were an increased in number of cases in many of the categories of critical value list, including crescentic glomerulonephritis, allograft biopsies and active interstitial nephritis (Table). All cases were communicated within 24 hours based on the findings of the light and immunofluorescence microscopy. The average time spent by the pathologist in communication and documentation was estimated approximately over 8 minutes per case or 43 extra work hours over the 6 month period. Per our guidelines, all the cases were documented and "flagged" in our electronic system.

Conclusions: Critical diagnoses in renal pathology requiring immediate physician notification represent a significant fraction (30.6%) of the total number of surgical pathology cases communicated in our department. This study demonstrates an increased awareness among the renal pathologists to relay critical values in an emergent fashion. Many medical kidney diagnoses require time-sensitive management; thus, our compliance to the guidelines facilitates the clinicians to expedite the treatment protocols, minimize further kidney damage, and ultimately improve patient care and safety.

Critical Diagnoses	2006	2007
Crescentic GN	19%	26%
Anti-GBM	2	4
Immune complex	26	57
Pauci-immune	12	22
Allograft biopsies	23%	29%
Active rejection	34	36
No rejection	10	56
BK virus infection	7	2
Acute Tubular Injury	43 (20%)	40 (12%)
Active Interstitial Nephritis	29 (13%)	62 (19%)
Acute Vascular Injury	8%	3%
Acute thrombotic injury	10	5
Vasculitis	5	1
Athero emboli	2	2
Paraprotein Deposition Disease	11 (5%)	17 (5%)
Obstructive Uropathy	1 (1%)	0 (0%)
Collapsing Glomerulopathy	23 (10%)	16 (5%)
Unexpected Findings	1%	1%
Neoplasm	3	10
Other tissue in the biopsy (colon, liver, spleen)		
Total	218	321

1622 Mandatory Second Opinion in Cytopathology Referral Material

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Background: Mandatory review of outside pathologic material is intended to detect interpretive errors that may have a clinically significant impact on patient care. Prior to definitive treatment of referred patients, our institution requires a review of pertinent pathologic material previously obtained at outside institutions. The aims of this study were to determine if this local standard of practice has a measurable impact on patient care.

Design: The pathologic diagnoses of 499 second opinion cytology cases seen at the University of Iowa Hospitals and Clinics were studied. Each second opinion was classified as 'no diagnostic disagreement', 'minor disagreement', or 'major disagreement' with respect to the originating institution's interpretation. A major diagnostic disagreement was defined either as: 1) a two step difference in opinion on a scale of "benign, atypical, suspicious and malignant" or 2), a diagnostic disagreement with a potential for a change in treatment or prognosis. The clinical impact of major disagreement cases was determined by pathologic and clinical follow-up via chart review.

Results: Second opinion cytology resulted in 37 cases (7.4% of total cases) with major diagnostic disagreements and 55 cases (11.0%) with minor diagnostic disagreements. Clinical and pathologic follow-up was available in 30 of the major disagreement cases, and the second opinion diagnosis was better supported in 22 of these cases compared to the outside diagnosis. The second opinion in 6 major disagreement cases prompted changes in clinical management. The case-types that prompted a change in clinical management included: thyroid fine needle aspirations (3 cases), cervical-vaginal cytology (2 cases), and parotid fine needle aspiration (1 case).

Conclusions: Major disagreements in second opinion cytology are common, likely reflective of the challenges inherent in the interpretation of cytologic specimens. Although mandatory second opinion of outside cytologic material prompted changes in clinical management in only a small fraction of cases (1.2%), this rate is similar to those previously published for surgical pathology second opinion. These findings support the notion that mandatory second opinion policy is an important part of patient care.

1623 High Risk for Carry-Over Artifacts in Routine Hematoxylin and Eosin Stainers

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Background: Carry-over artifacts (floaters) can be introduced at every step in tissue processing. The Hematoxylin & Eosin (H&E) staining process has been implicated as a source for contaminants, but little experimental evidence exists. This study sought to experimentally address the question of whether a routine linear H&E stainer (so-called "dip and dunk") is a source for significant carry-over artifact.

Design: Two staining machines were used to assess carry-over artifacts in the H&E staining process: A linear stainer (Leica Systems, Bannockburn, IL) and an automated discrete slide H&E stainer (Symphony, Ventana Medical Systems, Inc., Tucson, AZ). We extracted 20 ml of fluid from each staining bath on the linear stainer at the end of the day, three separate days. Cytospins were prepared and the slides were stained using the automated Symphony stainer and examined for tissue contaminants. In a second experiment, 3 blocks containing ten fragments of different types of tissue were created. 40 slides were cut from each block and alternating levels were stained on the Symphony discrete slide stainer and the linear stainer. The 120 slides were examined for carry-over artifact.

Results: The staining solutions in the linear stainer were contaminated with tissue fragments. The fragments vary in size from 5-10 cells up to 50 or more cells. Many of the contaminating fragments were morphologically malignant. The contaminating fragments were concentrated in the first xylenes and first alcohols, but were seen occasionally all the way through the stain set up. In the second experiment, tissue from the sections could be seen displaced, presumably from discohesion or lifting of the sections. 45% of the slides stained on the linear stainer had these displaced tissue fragments and 22% of the slides stained on the Symphony stainer had displaced tissue fragments (p=0.007). Two slides from the linear stainer (3%) had foreign tissue fragment contaminants that were not from the tissue in the blocks (true tissue floaters). None of the slides from the discrete slide stainer had true tissue floaters.

Conclusions: The linear H&E stainer is a source for potential carry-over artifacts and the contaminating tissue fragments in the stain solutions can be malignant. Because the early solutions are most frequently contaminated, efforts to change or clean solutions should concentrate on the initial xylenes and alcohol baths. The discrete slide stainer, with single use reagents, does not have the same risk of foreign contaminants.

1624 Using a Validated Taxonomy of Amended Reports To Study and Improve Surgical Pathology Practice

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Background: Amendments change released surgical pathology reports. They confuse report readers and cause rework. Previously, the authors validated a taxonomy that divided causes of amendments into misinterpretations (MIS-INTERP), misidentifaction (MIS-ID), specimen defects (SPEC.DEFECT), and report defects (REPORT DEFECT).

Design: In 2004-07 we tracked: surgical cases, amended reports, amendments per thousand cases, and amendment fractions by cause. In 2004 a report transcription step was eliminated, in 2005 the amendment process was standardized, in 2006 a Lean quality assurance initiative, the Henry Ford Production System (HFPS), was introduced, and in the first half of 2007, HFPS became fully operational. We compared yearly rates and fractions.The 2004 measures were also compared to those in 2003, and the indices for the first half of 2007 were annualized (*ann*).

Results: Annual cases: 47,153 (2003), 46,468 (2004), 46,880 (2005), 48,010 (2006), 49,326 (2007) *ann*. Amended reports: 158 (2003), 225 (2004), 475 (2005), 374 (2006), 280 (2007) *ann*. Amended reports/1000 surgical cases: 3.4 (2003), 4.8 (2004), 10.1 (2005), 9.8 (2006), 5.7 (2007) *ann.* See table below for yearly fractions of defects. Transcription's elimination modestly increased detected defects, standarization doubled them, but total defects fell 20 % with HFPS introduction and 40% more with its full integration into practice. Report defects rose to 2/3 of amendments with standardization, then to 3/4 of amendments with HFPS's integration. MIS-INTERP fell slightly with HFPS integration. MIS-ID rose with systematic amendment handling, and then fell with HFPS introduction and fell strikingly with HFPS's integration into practice operations. Sample defects remained few throughout.

Conclusions: Removing transcription increased report defects and introducing systematic classification increased detection of defects in all categories. Introduction of the HFPS Lean intiative began to reduce defects in all categories and its full integration into practice reduced them further in MIS-INTERP and Report Defect categories. The amendment taxonomy identifies pathology defects and specifies outcomes of improvements aimed to reduce them.

YEARLY DEFECT FRACTIONS

YEAR	MIS-INTERP	MIS-ID	SPEC. DEFECT	REPORT DEFECT
2004	53 (23.5%)	44 (19.5)	20 (9)	108 (48)
2005	87 (18.3%)	74 (15.6)	9 (1.9)	305 (64.2)
2006	59 (15.8%)	46 (12.3)	16 (4.3)	253 (67.6)
2007	18 (6.4%)	36 (12.9)	16 (5.7)	210 (75)

1625 Lean Redesign of Digital X-Ray of Breast Biopsies for Calcifications – Reduction of Turn around Time and Wasteful Recuts in the Henry Ford Production System

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Background: Breast biopsies are performed for analysis of mammographic calcifications which may be associated with cancer. Occasionally, the confirmation of calcifications in initial slides isn't possible. This necessitates multiple recuts and may ultimately lead to conventional x-ray (XR) to assist in the identification. In our environment, the current XR process for calcifications is tedious and time-consuming as specimen imaging is accommodated in a busy radiology service. This increased turn around time (TAT) delayed the final reporting up to 7 days. Our response was to use Lean process redesign in the Henry Ford Production System to implement an intradepartmental digital X-Ray (DXR) imaging system to identify these targeted calcifications. This improvement dramatically decreased the TAT by allowing for earlier calcification identification in the gross pathology process which, in turn, allowed the pathologist to report a more timely final diagnosis.

Design: Data were collected from a search of breast biopsies categorized into masses versus calcifications from March 2- April 5, 2006. Calcifications were further divided into those that required additional recuts for calcification identification and those that needed XR localization. The TAT and number of recuts for these cases were calculated from accession to signout in the CoPath information system. After implementation of the DXR, all cases for calcifications were imaged prior to histologic submission. Data were collected for TAT and recut data were compared subsequently from February 28-March 31, 2007.

Results: In 2006, from 164 biopsy cases, there were 118(72%) masses and 46(28%) calcifications. Of the calcifications category, 31% required additional recuts (12 slides-median) and 40% of those cases required XR localization. The median TAT was 5 days. In 2007, of 193 biopsy cases, there were 145(75%) masses and 48(25%) calcifications. Of the calcification cases, 10% needed additional recuts (3 slides-median) and 100% of those cases were DXR prior to histologic submission. The median TAT was 2 days.

Conclusions: Lean process redesign utilizing DXR up-front in the gross examination process of breast biopsies, has significantly improved TAT by 60% and number of recuts has reduced by 75% for breast biopsies for calcifications. This improvement in TAT and decrease in laboratory waste associated with unneeded recuts, has allowed our pathologists to report the final diagnosis in a timelier manner.

1626 Intraoperative Consultation (IOC) for Axillary Sentinel Lymph Node Biopsy (ASLNB): An 8-Year Audit

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Background: SLNB has emerged as an alternative to axillary lymph node dissection (ALND) in the staging of clinically node-negative breast cancer patients since it has less morbidity without compromising survival. We summarize our 8-year institutional experience and address a wide range of quality assurance questions around this practice.

Design: Surgical pathology database was searched in the period 1999 to 2007 for all cases with IOC on SLNB in breast cancer patients. The complete operative procedure including additional surgery on the ipsilateral axilla was recorded. Number of sentinel nodes processed at the time of IOC, frozen and permanent section diagnoses, number of additional non-sentinel nodes and their status, tumor type, and whether the IOC diagnosis was rendered by a breast pathologist were analyzed. Chi square and Fisher's exact tests were used to determine differences between the groups.

Results: 707 IOCs performed by frozen sections were identified. The median age was 58 years old (Range: 23-87). The mean number of sentinel nodes harvested was 2.4 per case. IOC was positive for metastatic carcinoma in 117/707 cases (16.5%) and the final pathology was positive in 158/707 cases (22.3%) with an overall false negative rate of 25.5% and accuracy of 94%. There were no false positive cases. The rate of false negative was not significantly associated with the histologic type (p = 0.76). When a breast pathologist rendered the IOC (n = 211), the false negative rate was 15.3%, sensitivity 84.5% and accuracy 97%. When a non-breast pathologist rendered the diagnosis (n = 496), the false negative rate increased to 29.4% (p = 0.08), sensitivity decreased to 70.6% and accuracy to 93%. The likelihood of missing a micrometastatic focus (≤2 mm) was not significant when the two groups were compared, but it was significantly higher for macrometastasis (> 2 mm) when non-breast pathologists rendered the diagnosis (p = 0.009). In 113/117 cases with positive IOC the surgeon proceeded with ALND and additional metastases in non-sentinel nodes were identified in 59 cases (52.2%).

Conclusions: Regardless of the tumor histologic type, IOC for SLNB is a safe practice that can reliably save clinically node-negative patients a second surgery for lymph node dissection. In slightly more than half of the intraoperatively positive cases, other axillary lymph nodes will have metastases. It is less likely to miss a macrometastasis when breast pathologists render the IOC consultation.

1627 Improving Patient Safety and Quality of Care through Continuous Monitoring of Surgical Pathology Amended Reports

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Background: Error and error reduction are a main focus of attention in quality assurance and quality improvement (QAI) programs in surgical pathology. Despite its importance, there have been few studies that utilize amended reports as quality improvement instruments. Amended reports provide crucial data, as they are the result of identified discrepancies by pathologists, clinicians, or any consultant reviewing this clinicopathologic correlation.

Design: Our study evaluates the consequences of errors and develops methods for reducing them. We assessed the 455 amended reports (out of 107,642 surgical pathology cases or 0.42%) in a 2-year period using a computer program that identifies amended reports for future review. Analysis was based on a comparison between each original report and the corresponding amended report. Each of these reports was classified into 1 of 5 error types derived to facilitate prompt assessment of the causes for amendment. Errors related to diagnosis (types I and II) were sub-classified according to patient management effects. Gross description/clinical history errors (type III), typographical mistakes (type IV), misidentification errors (type V) and the quality of documented changes and report format were also studied.

Results: Proposed classification categories and improvement actions are listed in the table, according to phase of report-processing (pre-analytical, analytical and post-analytical).

Conclusions: Structured, continuous review of revised surgical pathology reports is a necessity. We propose a system of classification for amended report error type (five types) as a means for improving departmental quality and communication with clinicians. Depending upon error type, direct action may be taken to prevent recurrence. In addition to documentation of exact changes made within amended reports, notation of communicated report revisions to the clinician, within the revised document, is essential. A clear explanation of changes and consistent documentation of clinician notification standardizes error reporting and improves clinician-consultant communication, ultimately reflecting in quality of patient care.

	Classification						Quality improvement action		
	Error			Effect			Pre-analytical	Analytical	Post-analytical
	Type	#	%	Type	#	%			
Patient Safety	I and II	137	30	A	96	70		Review each case with pathologist	Inform clinician that additional consultation and testing may be required and may change preliminary dx
				B	30	22			
				C	11	8			
Quality of reports	III	11	2.4				Correct assessment of clinical data and		Reinforce proofreading before sign out
	IV and V	307	67.5				Reinforce proofreading		
	Total	455	100						
	Explanation of changes (types I-V)			Yes	302	66.4			Reinforce appropriate explanation and clinician utility
				In	129	28.4			
				No	24	5.3			
	Notification documented (types I and II only)			Yes	21	15.3			Reinforce documentation
				No	116	84.7			

Type I = Change in the main diagnosis. Type II= Change that affects the diagnosis (staging, grading, margins). Type III= Change that does not affect the diagnosis (clinical history, gross description). Type IV = typographical error (not diagnosis). Type V = Case, patient, specimen misidentification. Effects: A= no harm. B= moderate harm. C= severe harm. In = Insufficient (no clear explanation).

1628 To Count or Not To Count: That Is the Question

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Background: Lymph node (LN) status, the single most important prognostic indicator of survival in a patient with cancer, is traditionally based on the number and location of tumor positive LNs. However, recent studies have shown that the total lymph node count is also of prognostic significance, and have stressed the importance of retrieving a minimal number of lymph nodes in order for the patient to be considered optimally staged. Despite these findings, the actual process of counting lymph nodes is currently not standardized.

Design: The study was undertaken to determine the degree and significance of variations in the process of lymph node dissection and counting. A set of 15 H&E slides was circulated on two separate occasions with an intervening period of 2-30 days amongst 10 pathologists, 7 of whom practiced in a community hospital setting. Inter- and intra-observer differences amongst the pathologists were analyzed. This was followed by a targeted review session in which 4 areas were marked and re-circulated with a questionnaire to better understand the used individual criteria. Gross dissection was evaluated by reviewing the lymph node dissecting practices at two independent institutions participating in the study.

Results: The total lymph node counts rendered on the submitted slide set ranged from 62-101, with no two pathologists giving the same total count. Slides with more than ten fragments and slides with the gross description of "single node palpated" had the greatest counting variability. Intra-observer disagreement was frequent, occurring 32% of times. The targeted review showed that different pathologists had different criteria about what constituted a lymph node. Size, the presence/absence of a capsule and subcapsular sinus, and the proximity two nodal structures were issues that the pathologists used to determine whether or not to count a lymphoid aggregate as a LN. The gross dissection of lymph nodes appeared to be relatively standardized at both institutions, with both using a combination of fat clearing, visualization techniques and palpation for the detection of lymph nodes.

Conclusions: This study documents significant inter and intra-observer variation in LN counting amongst pathologists. We recommend that no more than five fragments of tissue be submitted in a single cassette and that all lymphoid tissue be counted as LN. Unless the actual process of LN counting is standardized, the minimal node count is likely to vary significantly between studies and a true minimal node count for staging cannot be reliably set.

1629 Analysis of a Standardized Pathology Reporting Process Based on the College of American Pathology Checklists

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Background: Traditional narrative and descriptive pathology reports in free text format have significant variability. More often, such variability results in pathology reports missing important data elements critical to clinical decision-making processes by other members of the healthcare team. Standardized pathology reporting processes, or Synoptic Reportingensures reporting uniform critical pathologic factors through standardized data elements in forms of checklists and coded variables for the relevant data elements.

Design: The focus of this project was to examine the utility, quality and completeness of synoptic reports of the lung, colon, and endometrium. As of 2003, our institute has used a digital synoptic reporting system as part of existing laboratory information system (LIS), CoPathPlus. One hundred and Fifty cases were randomly selected from the LIS representing cases from lung and endometrium resections.A total of 100 reports were evaluated for the required CAP checklist elements in the free text and synoptic sections of the reports.

Results: For the lung resection specimens, data indicated that majority of the 12 required CAP checklist elements were present in both the free text and the synoptic sections \ with the exception of 2 elements: surgical margin involvement (deficiency in 1 report) and surgical margin site (deficient in 11 reports). For endometrial carcinomas, deficiency is noted for 4 of 14 required CAP checklist elements including tumor type (2% deficient reports), nuclear grade (12% deficient reports), and tumor size (2% deficient report), and depth of invasion (4% deficient reports).

Conclusions: Since the implementation of CAP checklists, there is paucity of information regarding the use of the checklists and their impact on reporting pathology data to the health care team, including the cancer registry, quality improvement departments, marketing, public health agencies and research databases. Our study illustrates that inspite of implementation of CAP checklists in our pathology reports, there are considerable deficiencies in the reports and 1 or more the required CAP checklist elements are missing from the pathology reports.

1630 The Significance of Intraoperative Gross Examination of Margins on Patient's Management: A Breast Model

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Background: Local control is compromised in patients with positive or close margins after breast conserving surgery (BCS). Assessment of adequacy of margins on lumpectomy specimens with palpable lesions is a common indication for intraoperative consultation (IOC) in our practice. Inadequate resection margins that are identified intraoperatively can be immediately revised, potentially saving the patient a separate surgical procedure. We aimed to determine the accuracy of intraoperative margin assessment by gross inspection and estimate the rate of spared re-excisions in patients with invasive breast cancer undergoing BCS for which IOC was requested.

Design: We identified 150 consecutive cases of BCS for invasive breast carcinoma in which the adequacy of margins was grossly assessed intraoperatively between 2005-2007. The size and status of the closest margin rendered at the time of IOC were compared with those of the final pathology of the initial specimen. Revision of margins in the same surgery and any re-excision at a later date were recorded. For the purpose of this analysis we defined potentially saved re-excisions as cases with positive or "close" margins that are 2 mm or less at the time of IOC.

Results: IOC identified 30 cases with close/positive margins. The false negative rate was 45%, false positive rate 9%, sensitivity of gross assessment 54%, specificity 91%, and the accuracy was 82%. The initial margins were revised intraoperatively in 28/150 cases: in 17 cases due to the grossly assessed close/positive margins and in 11 cases at the surgeon's discretion. Ultimately, definite negative margins after intraoperative revision were achieved in 123/150 cases. In 14 cases re-excision was performed as a second surgical procedure. Based on gross assessment, there were 20 cases in which gross assessment identified correctly close/positive margin, in which a second re-excision operation could have been spared; 11/20 (55%) were revised in the same surgery all with definitive negative margins. Margins were not revised (9/20) whenever the involved margin was anterior or posterior.

Conclusions: IOC using gross assessment of margins has low sensitivity. A second re-excision was avoided in 7% (11/150) of our patients sparing the cost and morbidity of additional surgery.

1631 The Benefits of Hospital-Wide Electronic Safety Reporting Systems in Developing Pathology-Based Quality Improvement Projects

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Background: To increase utilization and efficiency and decrease turnaround time of evaluation of safety reports (SR), an institutional electronic safety reporting system (ERS) was implemented in 2006. Each SR was distributed to hospital administration and appropriate departments for investigation.

Design: The Pathology Quality Assurance (QA) team reviewed all relevant electronically reported safety incidents and analyzed them according to origin, cause and type of event. SR examination identified important quality improvement projects (QIP).

Results: Between October 2006 and June 2007, 464 SR were filed. Events were categorized by location and classified as intra or extra-departmental in origin (Table 1). Eleven event types were identified based upon perceived cause or association; the frequency of each was calculated (Table 2). The potential severity and frequency of reported events were used to develop QIP focusing on specimen collection and handling, delayed reporting of results, transportation problems, failure to follow protocol, and enhancement of informational services.

SAFETY REPORTS BY LOCATION

	Event Originated Within Pathology	Extra-Departmental Event	Total
Core Lab	50	93	143
Anatomic Pathology	16	69	85
Blood Transfusion Service	16	66	82
Microbiology	7	31	38
Blood Banking Services	5	31	36
Diabetes Lab	11	10	21
Off-Site Locations	8	6	14
Immunology	3	0	3
Other	0	2	2
Not Involving Pathology Lab	n/a	40	40
Total	116	348	464

SAFETY REPORTS BY EVENT TYPE

	Number	Percentage of Total	# QIP Initiated
Labeling Problem	99	21.3	0
Specimen Collection and Handling	63	13.6	4
Delayed Reporting of Results	56	12.1	1
Employee Event	52	11.2	0
Transportation Issues	49	10.6	2
Failure to Follow Protocol	48	10.3	3
Data Entry Errors	32	6.9	1
Adverse Patient Outcome	19	4.1	0
Product Dispensation Error	8	1.7	0
Miscommunication with Provider	5	1.1	0
Other	33	7.1	2
Total	464	100	13

Conclusions: Implementation of an ERS has provided real-time notification of SR, facilitating the rapid accrual of valuable data. This information serves as the focus for investigation and analysis by the QA team and allows for the construction of QIP in a timely fashion with the goal of enhancing patient safety.

1632 Effect of Double Viewing Needle Core Prostate Biopsy Tissues on Error Reduction

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Background: The effectiveness of using a standardized double case viewing protocol for prostate biopsy error detection across multiple institutions has not been established.

Design: Four institutions (Loyola University, University of Iowa, University of Pittsburgh, Wake Forest University) implemented a standardized case-control study, in which specimens from the case period were blindly reviewed (pre-signout) by a second in-house pathologist. The cases from the control period were not double viewed. A total of 712 cases and 2459 case parts were double viewed. One institution previously reported their data, although this study focused on comparative findings and overall cancer proportion. We measured the malignancy and high grade prostatic intraepithelial neoplasia (HGPIN) rate by part and case, the number of total diagnostic disagreements, disagreements leading to major changes in clinical management (e.g., change from routine follow-up to rebiopsy or cancer treatment), and diagnostic disagreements from benign to malignant (or vice versa).

Results: The mean institutional proportional difference between first and second reviewer diagnosis per case and part was 14.0% (range: 9.8%-16.5%) and 6.6% (range: 3.8%-11.8%), respectively. The mean institutional proportional diagnostic difference that had a major impact on clinical management per case and part was 10.6% (range: 5.8%-14.7%) and 5.1% (range: 3.4%-9.8%), respectively. The mean institutional proportional difference of a change from a benign to a malignant diagnosis (or vice versa) per case and part was 0.8% (range: 0%-2.9%) and 0.3% (range: 0%-1.0%), respectively. The detection of malignancy increased from the control to the case period at only one institution, although case malignancy (34.0%-49.1%) and HGPIN (2.1%-13.5%) rates were highly variable.

Conclusions: Double case viewing had a variable institutional impact on error detection, most likely reflecting differences in pre-existing diagnostic standardization. Double case viewing had a high impact on changing clinical case management and rarely resulted in a change of diagnosis from benign to malignant (or vice versa). A larger study is needed to determine if double viewing affects overall malignancy rates; our data indicate that in some cases, the diagnosis is upgraded and in other cases it is downgraded, balancing out the overall malignancy rate.

1633 Effectiveness of Random and Focused Review in Detecting Anatomic Pathology Error

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Background: Different error detection methods yield different error proportions and have variable benefits for anatomic pathology divisions with limited quality assurance resources. We compared error detection proportions of a random review process and a focused review process.

Design: We performed a non-concurrent cohort study at a large institution that practices subspecialty surgical pathology sign-out to compare the effectiveness of error detection using a targeted 5% pseudo-random review process and a focused review process. In the focused process, pathologists selected specific areas to review (e.g., core biopsy specimens from a particular organ type or an area of perceived high diagnostic interobserver variability). The institution was deidentified to encourage error reporting. From 2001 to 2006, pathologists reviewed 7,444 cases (3.5% of all surgical pathology cases) using a targeted 5% pseudo-random review process, and in 2006, pathologists reviewed 380 cases (0.70% of all cases) using a focused review process. Previously, individual errors detected by both processes have been presented, although this study was focused on the effectiveness of the method of case review. Reviewers subjectively classified errors as having potentially minor or major impact

on patient care. We performed medical record reviews to determine the effect of major impact errors and graded impact severity using the categories of harm (subclassified by degree), no harm, and near miss.

Results: The number of errors detected by the targeted 5% pseudo-random and focused review processes was 195 (2.6% of reviewed cases) and 50 (13.2%), respectively ($P < 0.001$). The number of major errors for the targeted 5% pseudo-random and focused review processes was 27 (0.36%) and 12 (3.2%), respectively ($P < 0.001$). Harm was seen in 17 (43%) of all major errors and moderate harm was associated with 2 (5.1%) major errors (0.026% of all reviewed cases).

Conclusions: We conclude that compared to a targeted 5% pseudo-random review process, focused review detects a higher proportion of errors and may be more effectively used for design of error reduction initiatives such as diagnostic standardization procedures. The lack of diagnostic standardization rarely causes catastrophic events, but may be associated with low grade harm, such as repeat testing or diagnostic delays.

1634 Interobserver Variability in the Diagnosis of Extranodal Extension of Malignancy

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Background: The diagnosis of extranodal extension (ENE) of malignancy has become important in providing information of prognostic and therapeutic value for many oncology patients. This includes patients with malignancies commonly seen in the practice of surgical pathology, including patients with invasive duct carcinoma of breast, non-small cell carcinoma of lung, renal cell carcinoma, stage 3 colonic adenocarcinomas and squamous carcinomas of the head and neck. The usual definition of extranodal extension is tumor spreading beyond the lymph node capsule. Despite the frequency of this task for surgical pathologists we could find no study of the reliability of this diagnosis.

Design: We presented 18 digitized images of lymph nodes containing metastatic tumor to 26 academic pathologists at 4 institutions, all affiliated with the University of Toronto. The images were drawn from cases of squamous carcinoma of the head and neck (5 cases) and colonic adenocarcinomas (4 cases). Pathologists were instructed to specify whether ENE was present or absent using the criteria they use in daily practice. Their answers were recorded on data sheets anonymously and no time restrictions were imposed.

Results: The observed agreement for each image ranged from a high of 92% to a low of 54%. Although not offered as an option some pathologists diagnosed images as indeterminate for ENE. These diagnoses were offered 9 times in a total of 468 diagnoses. We counted these judgments as negative as no definite diagnosis of ENE had been made. The kappa statistic thus calculated was 0.44 (moderate agreement), $p<0.0001$.

Conclusions: Our results showed moderate reliability between pathologists in diagnosing ENE. As we gave no instructions as to the definition of ENE, our results should closely approximate the daily practice of these academic pathologists. The major criticism of our study is that we used images rather than slides. We did this deliberately in order to present exactly the same image to our subjects. Our results are in the range of other studies of reliability in histological diagnosis, although most of these studies compare the original diagnosis to review diagnoses. In addition these studies often concern what are usually thought of as more difficult diagnoses (example Hodgkin's disease, cervical neoplasia). We suggest that a more precise and easily applied definition of ENE is necessary to disseminate among pathologists, in order to issue this diagnosis with more reliability.

1635 High Concordance between Local and Central Laboratory Testing of Biomarkers in the Capcetabine (C) + Docetaxel (D) +/-Trastuzumab (T) Neoadjuvant (XENA) Breast Cancer (BC) Clinical Trial

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Background: Previous studies have reported an alarmingly low concordance between local laboratories and central laboratories in BC clinical trials for the determination of ER/PR and HER2 status. The objective of the XENA® trial was to show the rates of pathological complete (pCR) and near (npCR) and to confirm that the C+D (+/- trastuzumab) regimen known to be effective in the treatment of metastatic disease would also be efficacious when used in the neoadjuvant setting.

Design: The XENA trial enrolled patients with newly diagnosed invasive HER2–/+ BC, T2N0-1M0 and T3N0-1M0, to determine the rate of (pCR) and npCR (T1a) in the affected breast after 4 cycles of neoadjuvant treatment with C+D (+T for HER2+ cases). 30 local laboratories determined the estrogen receptor (ER) and progesterone receptor (PR) by IHC and the HER2 status by either IHC or FISH on FFPE needle core biopsies. The central laboratory re-determined the ER/PR by IHC and HER2 by FISH (Inform®, Ventana Medical Systems, Tucson, AZ) on unstained slides of the core biopsies submitted by the local labs. Central lab HER2 FISH signals > 4.0 was considered as HER2+.

Results: Of the 164 patients enrolled in the XENA trial, 155 (94%) were evaluable for all 3 biomarkers. For ER, 7 (5%) were discordant with 5/7 (71%) featuring local ER- and central ER+. For PR, 20 (13%) were discordant. If weak PR positivity by central testing was considered negative, PR discordance was 16 (10%). For HER2, 1 (1%) were discordant with local reporting HER2- and central HER2+.

Conclusions: In contrast with previous breast cancer clinical trial studies, the discordance between local and central labs for determining ER, PR and HER in patients enrolled in the XENA trial was extremely low. Of the 3 measured biomarkers, discordance in PR testing was highest (13%), intermediate for ER (5%) and lowest for HER2 (1%). Approaches to reduce discordance by the central lab in the XENA trial included 1) confirming that both labs tested the same tumor block, used similar techniques and cut-offs for ER and PR IHC, agreed upon thresholds for HER2+ by both IHC and FISH and that central lab used HER2+ gene copy only, not HER2/CEP17 ratio to judge concordance with local IHC.

1636 Low Lymph Node Count after Neoadjuvant Chemotherapy for Breast Cancer Should Not Be Assumed To Represent Complete Axillary Dissection

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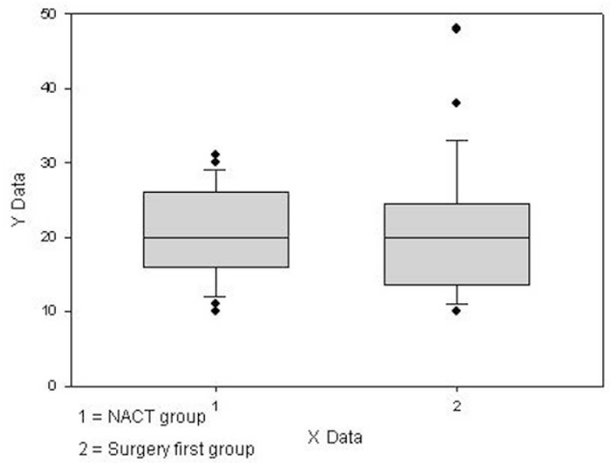
Background: In patients with locally advanced breast cancer, neoadjuvant chemotherapy (NACT) has become the preferred initial treatment modality, followed by definite surgical therapy directed to the breast and the axilla. Although it is well documented that NACT reduces the number of tumor-involved lymph nodes, it s not clear how NACT affects the overall lymph node count in an axillary lymph node dissection (ALND).

Design: Patients who received NACT followed by ALND were compared with patients who received surgery first. All patients received a level I and II axillary lymph node dissection at single institution by one breast surgeon. The number of lymph nodes between the two groups was compared using Mann-Whitney Rank Sum Test and Box plot.

Results: A total of 36 neoadjuvant (age range 34 to 77 years, mean 52±10 years) and 38 surgery-first patients (age range 29 to 85 years, mean 53±11 years) were studied. The mean number of lymph node count in NACT group is 20±6, SEM 1.04 whereas the mean number of lymph node count in surgery first group is 20±9, SEM 1.4 (P=0.96).



Conclusions: There is no significant difference in the number of axillary lymph node count retrieved at ALND in patients treated with NACT in comparison to surgery-first patients. Low lymph node count may be more common with NACT at certain institution as reported (Am J Surg 2006;191:827-29) but may not be necessarily true at other institutions. Therefore, care should be followed to perform an adequate ALND as well as pathologic evaluation to obtain maximum yield of lymph node count to provide accurate information for staging.

1637 Standard Procurement, Processing and Reporting of Thyroid Fine Needle Aspiration (FNA) Improves Patient Care

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Background: Thyroid nodules (TN) occur commonly (Prevalance: 4-7%) and are assessed by FNA +/- ultrasound (U/S) guidance. A satisfactory sample that includes well-made smears is essential for interpretation and diagnosis. In our institution, we standardized collection, making and number of smears and reporting format for TN FNAs and evaluate the effect in the pre- and post- standardization (ST) groups.

Design: Computer assisted search for all TN FNAs was performed between 9/24/04 and 8/29/07, including pre-ST data (TN FNAs performed by multiple MDs, +/- U/S guidance, smears made by different people) and post-ST data (U/S guided TN FNAs performed by a single endocrinologist yeilding 2 needle passes with 4 standard smears made by a single designated/trained nurse with additional pass material submitted in Cyto-rich red for cell block and H&E stain). Standard staining techniques were used (Papianicolou and diff-quick stain). Pathology reports were reviewed for satisfactory vs unsatisfactory procedure, satisfactory vs limited interpretation (LI), cytopathologic diagnosis and surgical follow-up (f/u).

Results: 100 cases were identified in both groups with 120 pre-ST and 142 post-ST sites aspirated. The number of unsatisfactory specimens post-ST was reduced by 50% (Table 1).

Table 1 Rate of unsatisfactory and LI in the pre- and post- ST groups

	Pre- ST	Post- ST
No of sites	120	142
Unsatisfactory for diagnosis	13 (10.8%)	8 (5.6%)
Interpretation limited*	25 (20.8%)	18 (12.6%)

*obscuring blood/ inadequate follicular cells/ drying artifact

Surgical f/u in post-ST cases reveals a 21.1% increase in true positive diagnosis of papillary carcinoma and a 16.2% decrease in surgical excision of benign thyroid disease (Table 2) thereby improving patient care.

Table 2 Surgical outcomes in pre- and post- ST groups

			Surgical diagnosis		
	Cytology diagnosis requiring surgery*	Patients with surgical f/u	Benign**	Hurthle cell/ Follicular Neoplasms***	Papillary carcinoma
Pre- ST (%)	36	33	16 (48.4)	8 (24.2)	9 (27.3)
Post- ST (%)	35	31	10 (32.2)	6 (19.3)	15 (48.4)

*Microfollicular/ Hurthle cell lesions/ Suspicious for Papillary carcinoma **MNG, Thyroiditis, Intrathyroid parathyroid ***Adenoma/ Carcinoma

Conclusions: Standardization markedly reduced unsatisfactory/ non-diagnostic TN FNA specimens and the number of limited cytopathologic interpretations. Standardization of TN FNAs improves cytologic-histological correlation and patient care.

1638 Distinctive Morphometric Signatures Exist within Nuclei of Gleason Pattern 4 Areas in Gleason 7 Prostate Cancer with Differing Primary Grades on Needle Biopsy

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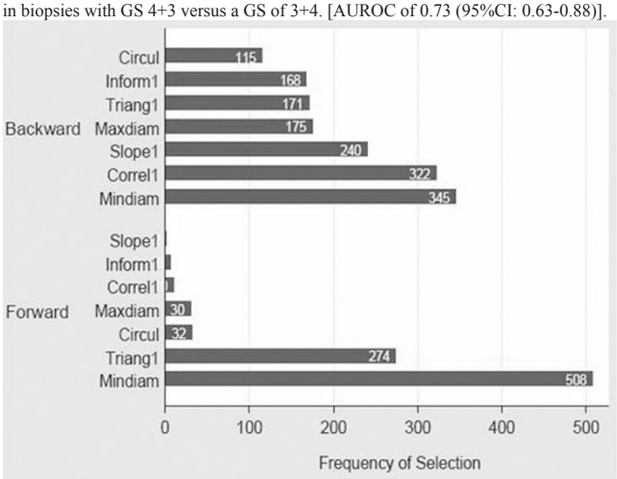
Background: The Gleason score (GS) 7 group of prostate cancer represents a heterogenous group with a wide variation in clinical outcome. Since upgrading of biopsy GS has adverse clinical impact, ancillary tools, besides visual determination of primary Gleason pattern (pGP) are essential to aid in better risk stratification of this unique group.

Design: Sixty one prostate biopsies from patients with a diagnosis of GS7 adenocarcinoma, including 41 with pGP3 and 20 with pGP4 were selected. Slides from these tissues were stained using Feulgen. Areas of GP4 in all these cases were analyzed for 40 nuclear morphometric descriptors of the size, shape and chromatin using the CAS-200 system (Bacus Labs., Lombard, IL). Primary outcome analyzed was the ability of morphometric features to distinguish GP4 areas in the two subsets of GS7 tumors. Initial exploratory logistic regression (LR) analyses was performed to identify the best 1- through 4-parameter model. Discriminative ability of algorithms was tested using Receiver Operator Characteristic (ROC) curves.

Results: There was no significant difference in the mean age, PSA and percentage of cancer between these two groups. LR yielded seven features that were significantly different (figure 1). Minimum nuclear diameter was selected as the most informative single-parameter model with a significant discriminative ability to distinguish GP4 areas in biopsies with GS 4+3 versus a GS of 3+4. [AUROC of 0.73 (95%CI: 0.63-0.88)].



Conclusions: In this small cohort, we report presence of distinctive morphometric features in GP4 areas in the two sub-groups of GS7. These findings may aid in better risk stratification of the GS7 group by supplementing visual estimation of the percentages of pGP3 and pGP4 on the biopsy.

1639 The Value of Double Viewing Urine Cytology Specimens

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Background: The practice of incorporating a double review process into anatomic pathology practice has demonstrated variable benefits, with some studies showing marginal benefit and others showing greater benefit. We measured the effectiveness of pre-sign out double review of urine cytology specimens diagnosed by the cytotechnologist or first pathologist as atypical.

Design: Specimens in which the screening cytotechnologist or initial pathologist used a diagnosis of atypical were flagged for review by a second pathologist at a deidentified institution. In 2006, a total of 222 consecutive specimens were double viewed, 49% because of a screening cytotechnologist diagnosis, 23% because of an initial pathologist diagnosis and 28% because of an atypical diagnosis from both the screening cytotechnologist and initial pathologist. We performed clinical record review to measure the patient outcomes of downgraded and upgraded diagnoses.

Results: The screening cytotechnologist diagnosed 170 urine specimens as atypical. The initial pathologist disagreed 64% of the time, downgrading the diagnosis 76% of the time and upgrading it 24% of the time. After the two pathologists reached consensus, the final sign-out diagnosis deferred from the screened diagnosis 68% of the time, with the diagnosis being downgraded to benign 72% of the time and upgraded to suspicious or malignant 28% of the time. The initial pathologist used the diagnosis of atypical in 114 cases. The review pathologist disagreed in 42% of the cases, downgrading the diagnosis 63% of the time and upgrading it 37% of the time. After the two pathologists reached consensus, the final sign-out diagnosis was changed from atypical 19% of the time; of these diagnoses 58% were downgraded to benign and 42% were upgraded to suspicious or malignant. Clinical outcome, based on medical record review, correlated with the changed diagnosis in 80% of cases.

Conclusions: We conclude that double viewing initially diagnosed atypical urine cytology specimens resulted in a high degree of variability in diagnostic interpretation. Double viewing atypical urine specimens lowered the percentage of cases diagnosed as atypical in approximately 1 of every 5 cases. We found that double viewing improved diagnostic accuracy, resulted in improved patient triage that correlated with the clinical outcome, and resulted in greater diagnostic standardization. These data indicate that double viewing improved patient care for this specific indeterminate diagnosis.

1640 Comparison of Thinprep and Conventional Smear Preparations in the Diagnosis of Thyroid Nodules by Fine Needle Aspiration Biopsy: A 10-Year Experience

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Background: Pre-operative diagnosis by fine needle aspiration biopsy (FNAB) is the standard of care in the management of thyroid nodules. Over the last decade there has been a change in the cytopreparatory techniques for evaluation of FNAB specimens. While earlier on it was mainly examination of conventional direct smears (smear) made by spreading the aspirated material on the glass slide, more recently for the past several years liquid based cytology for the thinprep process (Cytyc, Boxborough, MA) has become the preferred method of evaluating FNAB. The aim of our study was to compare the two methods in the diagnosis of thyroid FNAB specimens.

Design: All thyroid cytology and surgical pathology (lobectomy and total thyroidectomy) specimens received in our department over a 10-year period (1997-2007) were retrieved from the archives. Thyroid surgical pathology specimens with the final pathological diagnosis served as the gold standard for comparing thyroid FNAB diagnosis. Patient's who had both the surgical pathology specimen and the FNAB formed the study group. Cytology reports were reviewed to make a note of the diagnosis and cytopreparatory method used for every case. Sensitivity and specificity for diagnosis of thyroid malignancy by FNAB was calculated and compared for both (thinprep & smear) cytological preparations.

Results: In our department from 1997-2007 total of 693 patients' had both thyroid FNAB and surgical resection specimens accessioned, of these 290 were smear and 403 thinprep specimens. In the 5-year period from 1997-2002 out of a total of 308 thyroid FNAB specimens only 13 (4%) were thinprep, for the later 5-year period (2002-2007) the number of thinprep specimens increased to 361 out of 385 (94%). Of the total 403 thinprep cases 20 (5%) were unsatisfactory, while this figure for smear type specimens was 36/290 (12%). The sensitivity for diagnosing thyroid malignancy with thinprep and smear was 87% and 84% and the specificity was 93% and 89% respectively. There were 12/194 (6%) false positive thyroid FNAB diagnosis by thinprep compared to 15/166 (13%) by smear.

Conclusions: There has been a dramatic change in the cytopreparatory technique from conventional smear to thinprep cytology for the past 5 years. Thinprep processing is a better than smear technique for evaluation of thyroid FNAB specimens with better sensitivity, specificity and fewer non-diagnostic specimens.

1641 Digging Deeper: An Analysis of Cutting Deeper Levels on Skin Specimens

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Background: Pathologists obtain step sections (deeper levels) when initial sections are not considered fully diagnostic. While often necessary, serial sectioning leads to increased turnaround time, labor, and material costs, and sometimes tissue loss due to re-trimming of the paraffin block. In our laboratory, skin specimens are the most common tissue type on which deeper levels are requested (14.9 % overall). We analyzed multiple parameters which might contribute to the necessity of examining deeper levels in the hope of developing strategies to decrease the deeper level ordering rate.

Design: Data analysis was performed on the first 200 skin specimens from 2005 which had deeper levels ordered and the first 200 which did not (controls). The following factors were analyzed: specimen type (shave, punch, excision), specimen size, whether the specimen was submitted whole or sectioned, the clinical impression, the final diagnosis, and the experience of the pathologist. We also compared the turnaround times between the two groups.

Results: Smaller specimen size ($p<0.0001$), punch biopsies ($p<0.0001$), specimens submitted whole ($p<0.0001$), and cases with a clinical impression of cancer/dysplasia ($p=0.0002$) correlated with a higher rate of deeper levels. There were 102 punch biopsies; 77% had deeper levels. Of the 200 specimens submitted for deeper levels, 76% had been submitted whole. Of specimens which required deeper levels, 80% measured 0.5 cm or less; additionally, 60% of specimens which measured 0.5 cm or less required deeper levels. Pathologists with more years of experience ordered more deeper levels ($p<0.0001$), as did the board-certified dermatopathologist ($p<0.0001$). Deeper levels were ordered more frequently when the final diagnosis did not match the clinical impression ($p<0.0001$). A benign or malignant final diagnosis did not affect the deeper level ordering rate. The turnaround time was significantly longer in specimens with deeper levels compared with controls (average of 3.96 and 1.45 days, respectively, $p<0.0001$).

Conclusions: The factors most closely associated with ordering deeper levels on skin specimens include small specimen size (0.5 cm or less), punch biopsies, specimens submitted whole, and those with a clinical impression of cancer or dysplasia. We conclude that prospective ordering of deeper levels on such specimens and/ or sectioning specimens currently submitted whole, will improve turnaround time by decreasing the delays encountered when ordering deeper levels after initial review.

1642 Using a Business Review and Scorecard To Manage the Business of Surgical Pathology

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Background: Surgical Pathology operations can be extremely complex and a variety of factors impact performance. These include personnel, processes, technology, and a host of external pressures. In the business of pathology, these factors must be managed to ensure optimal performance, including clinical service, quality, financial indicators, and productivity. Tools exist in the business arena to manage such performance metrics, but they have not been widely adopted in medicine and are particularly absent in pathology.

Design: We developed a Surgical Pathology scorecard through a collaborative group process. The scorecard tracks data for 15 key volume metrics and 44 performance-related metrics in four categories: Service, Employee Satisfaction and Teamwork, Quality/Risk/Innovation, and Productivity/Financial. A target was set for each metric and performance against the targets discussed in a monthly business review meeting of laboratory supervisors and medical directors, a data analyst, an informatics specialist, the quality officer, and the administrative and physician leadership of Surgical Pathology. Identified gaps between targeted and actual performance levels for a given metric, were analyzed, and a plan to close the gap was developed and implemented.

Results: At the time of scorecard development, only 18% of the metrics were at target. One-year later, most metrics have shown positive trends towards closing gaps, with 58% of the metrics now meeting target. One major benefit of this tool is that it allowed us to quickly recognize increases in the surgical pathology workload and take decisive action to ensure continued efficient and effective laboratory operation .

Conclusions: The performance metric scorecard and monthly business review meeting are very effective management tools for surgical pathology. These tools enable identification and response to trends in key volume metrics. They also enable the surgical pathology leadership to identify metrics that are critical to operational success and to manage performance gaps between current and target values. These tools are excellent for managing productivity, quality, and patient safety data.

1643 Just-in-Time Surgical Pathology Specimen Workflow with Comprehensive Barcode Tracking and Lean/Six Sigma Software Design as a Prototypic Next Generation Laboratory Information System for Comprehensive Error Reduction

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Background: The laboratory workflow associated with anatomic pathology (unlike clinical labs) has significantly lagged in the use of advanced and automated specimen tracking technology, with pre- and post-analytical error rates associated with asset identification (for requisitions, specimens, blocks and slides), exceeding 1.5 percent of all accessions for combined intra-case and inter-case misidentification. While the majority of errors are detected, the remaining undetected fraction represents a very real and continuous threat as significant diagnoses may be generated from incorrect source material.

Design: Just-in-time barcode tracking of all specimen materials was developed and implemented in one large academic center (MGH) with knowledge gained from this exercise used to refine a more granular and fault-tolerant process at a second institution (U. of Michigan). The refined process benefited from Value Stream Mapping and quantitative pre- and post-analytical quantitative inference of risk analysis, whereby individual process steps were ranked by both severity of having the potential to cause harm and by frequency of occurrence. Subsequently designed software was itself designed according to Lean principles, with use of Extreme Programming (XP) methodology, to mitigate the seven or more forms of waste that occur with inefficient design models. With insights gained from the above, a further refined AP workflow system was made possible, using a three-tier client-server architecture model.

Results: Initial deployment of the aforementioned just-in-time approaches reduced misidentification errors to undetectable levels. Remaining difficulties in workflow were associated with a small (but finite) non-reading rate of generated barcodes -- an issue resolved by the selection of higher fidelity printing technologies for both slide labels and blocks.

Conclusions: Comprehensively barcode-driven workflow developed in concert with just-in-time methodologies for label generation and lean software design can reduce intra-case and inter-case asset misidentification to undetectable limits. This finding alone can easily justify the assertion that automated tracking techniques should become the new standard of care for anatomic pathology lab workflow.

1644 Reduction of Surgical Pathology In-Process Mis-Identification Defects by Bar-Code Specified Work Process Innovation in the Henry Ford Production System

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Background: Our implementation of a Lean continuous quality improvement initiative in Surgical Pathology (SP) at Henry Ford Hospital, known as the Henry Ford Production System, enabled workers to identify sources of waste, defects & mis-identifications (mis-ID) arising in all phases of production. In advance of implementing a barcode specified approach to workflow with an integrated identification system of barcoded lab tags, blocks and slides, we defined the baseline of defects causing mis-IDs arising from specimen collection to report generation.

Design: The internal mis-ID rate in SP was assessed using a visual data display for all workers to document defects, as described (AJCP 2007;128:423-429) for 3 weeks in July 2006 (baseline) compared to August 2007 after 200 process improvements and an internally developed bar-coded work system was implemented.

Results: We documented a 63% reduction in mis-ID cases from the baseline rate of 1.67% in 2006 (45 defects in 2694 cases) compared to 0.63% in 2007 (18 defects in 2877 cases). The 2 measurement intervals had comparable numbers of specimen parts (4413 v. 4725), blocks (8776 v. 9167) and slides (14,270 v. 17,927). Defects types remaining in 2007 were 14 encountered in the accessioning process, 4 of which involved blocks, 2 in gross tissue exam, 2 in histology affixing wrong labels to slides and 1 from signout pathologist transposing slides when opening the case in the computer. Slide labeling alone accounted for 2 defects and blocks another 4. These 6 slide and block mis-ID defects accounted for 1/3 of the 18 defects. Blocks and slides formerly accounted for 78% of the defects. The rate of mis-ID blocks and slides was reduced by 85%.

Conclusions: The successes here are attributed to: 1) the management approach known as the Henry Ford Production System, where empowered workers redesigned over 200 surgical pathology laboratory processes in 1.5 years in pursuit of tolerating zero defects, 2) implementation of a bar-code system that maintained identity, specified and standardized work from lab tag to report, and 3) worker design of quality control checks at each workcell to eliminate mis-ID defects. While we have shown marked improvement in creating and maintaining identification of specimens and associated information throughout SP processes, 22% of the case mis-IDs were derived from erroneously labeled specimens sent to the lab, thereby uncovering additional external opportunities.

Techniques

1645 Whole Genome Amplification (WGA) by Strand Displacement Amplification Introduces Significant Errors in Copy Number Alternation Calls in 500K Single Nucleotide Polymorphism (SNP) Array Analysis

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Background: Recently, limited studies using SNP genotyping micrroarrays have detected cytogenetically-cryptic uniparental disomy (UPD) and copy number alternations (CNA) in cases of MDS and AML. However, prior studies used unsorted bone marrow samples to perform their analysis. To further specifically study the genetic alternations in different lineages of marrow cells in MDS, we aim to use novel integration of multicolor flow cytometry (FCM) sorting and genome-wide profiling using SNP microarrays. This approach, however, is limited by the amount of sorted cells and thus WGA is needed to obtain enough DNA for SNP analysis in some cases.

Design: Four bone marrow samples from MDS patients were fractionated into erythroid (CD71 bright and CD34-), immature myeloid (CD10- and high side-scatter), blastic (CD34+) and lymphoid fractions (CD45 bright and low side-scatter) using FCM sorting. Genomic DNA from the fractionated cells was extracted. About 10 ng of genomic DNA of each fraction was then amplified by WGA using strand displacement amplification. SNP microarray (GeneChip Human Mapping 500K Set, Affymetrix) was performed using paired amplified and unamplified DNA. Analysis was done using CNAG software.

Results: Monosomy 7 and trisomy 8 were detected by SNP array in one case each using either amplified or un-amplified samples. This finding was consistent with conventional cytogenetic study results. UPD region (16q22.1 to 16q23.2) was identified in one case in both amplified and non-amplified samples. Gains of small chromosomal regions were noted in 2 samples with one sample each showing one CNA region using un-amplified DNA. In contrast, numerous gains or losses (ranging from 9 to more than 30 CNAs) of small chromosomal regions (in range of Mega bases) were noted in all samples using WGA amplified DNA.

Conclusions: SNP analyses using WGA amplified DNA identify UPD or numerical changes of large fragments chromosomal regions as reliable as unamplified DNA. However, the WGA approach introduces abundant errors regarding gains or losses of small chromosomal regions likely due to the non-homogenous amplification of certain segments of genome.

1646 Use of Normal B-Cells as a Negative Control Significantly Impacts the Results of ZAP-70 Expression as Detected by Multiparametric Flow Cytometry

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Background: ZAP-70 serves as a surrogate marker for immunoglobulin VH mutation status (iVHms) in CLL patients and is widely used in molecular risk stratification of CLL. ZAP-70 expression as detected by flow cytometry was originally defined as being positive if greater than 20%; such results can be seen in about 50% of CLL cases. Although the technology of ZAP-70 detection by flow cytometry has evolved significantly since 2003, it remains extremely challenging due to lack of proper controls, meaningful thresholds, and standardized analysis and reporting of results. Most labs use T/NK-cells, where ZAP-70 is constitutively expressed, as the positive and sole control for ZAP-70 levels in neoplastic B-cells. Consequently, far more CLL cases are positive for ZAP-70 than the 50% predicted by iVHms. In order to establish consistent quality control standards and provide insight in standardizing the detection of ZAP-70