

Standards Based Utilization of Synoptic Tools for Pathology Reporting of Colorectal Neoplasms

Waqas Amin, MD¹ (aminw@upmc.edu), Anthony L Piccoli³, Lisa J Devine³, Anil V. Parwani, MD, PhD^{1,2}; Departments of ¹Biomedical Informatics and ²Pathology, University of Pittsburgh, Pittsburgh, PA, ³Information Services Division, Clinical Department Systems, University of Pittsburgh Medical Center, Pittsburgh, PA

Content:

Synoptic reporting provides composite documents combining information obtained from gross and microscopic evaluation, and results of molecular and genetic tests. Standardized data elements are presented and captured in the form of check lists which provides accurate structural information as a part of pathology reports in comparison to the conventional narrative pathology reports that show inconsistency in format, context and content. It also allows pathologist to document their finding thereby improving the quality and consistency of the pathology reports.

Design:

The aim of this effort is to develop the complete set of data elements in the synoptic templates or "worksheets" for colorectal neoplasms based on the World Health Organization (WHO) Classification and the College of American Pathologists (CAP) Cancer Checklists. The CAP checklist provides the most updated and is supplemented classification scheme (WHO classification), specimen details, staging and information on various ancillary techniques.

Technology:

For this project we employed a digital synoptic reporting system as part of an existing laboratory information system (LIS), CoPath Plus, from Cerner DHT, Inc. The synoptic elements are provided as distinct data points. For example, a data element such as tumor type is assigned from the synoptic value dictionary under the value of tumor type, allowing the user to search for just those cases that have that value point populated.

Results:

These synoptic worksheets are exploited for use in our LIS. The data is stored as discrete data elements which appear as an accession summary within the final pathology report. In addition, the synoptic data can be exported to research databases for annotating the banked tissues. To date a total of 12285 colorectal synoptic reports have been completed at our institute.

Conclusions:

Synoptic reporting facilitates standard based structured method for entering the diagnostic and prognostic information for a particular pathology specimen, thus reducing transcription services, specimen turnaround time, and typographical and transcription errors that can be imported into the LIS database. This enables swift data access and improved communication for cancer management. Finally, these synoptic templates act as a robust medium for standardized and high-quality data from the colorectal neoplasm specimens which can be stored in virtual biorepositories to enhance translational research.

Tissue Fold Detection and Image Quality in Whole Slide Imaging

Pinky A. Bautista (pbautista@partners.org), Yukako Yagi; Department of Pathology, Massachusetts General Hospital, Boston, MA

Content:

In whole slide imaging the resulting image quality is dependent on several factors such as the optics specifications, hardware and software features of the imaging device, and the quality of the tissue slide itself. It has been observed that the presence of tissue artifacts in a slide can affect the quality of the scanned image, specifically some tissue areas, aside from areas occupied by the tissue artifacts, appear blurred.

Technology:

The main objective of this work is to develop an algorithm to detect tissue artifacts from the thumbnail version of a whole slide image. For this report however, we specifically focus on the detection of tissue folds wherein we proposed an enhancement scheme that utilizes the saturation and luminance components of the pixels as shifting factors to the original color values to localize the presence of folds.

Design:

The fold detection algorithm was applied to the low pixel resolution of the high resolution whole slide, i.e. 14.6µm/pixel. To probe the usefulness of the algorithm, we compared the image quality of the images produced by scanning in automated and manual modes. In the 'automated' mode the fold areas may be selected as focus points by the scanner whereas in manual mode tissue folds are avoided in the selection of the focus points by referring to the resulting enhanced image wherein the location of tissue folds are emphasized.

Results:

To show the viability of the proposed enhancement algorithm in detecting tissue folds, the slides were scanned at 0.43 μm /pixel resolution in manual and automatic modes. Visual comparisons of specific tissue areas from whole slide images produced by automatic and manual modes show that with the manual selection of focus points the resulting images are sharper and not blurry.

Conclusions:

It has been shown in the results of our experiments that referring to the enhanced image, where tissue folds are highlighted, to avoid the tissue artifacts in selecting the focus points helps improve the resulting image quality. Thus, incorporating the proposed enhancement scheme to detect tissue folds to the scanning procedure will effectively increase the efficiency of the scanning devices.

An Informatics Biospecimen Software Suite to Enhance Cancer Cooperative Group Information Management

Dave Billiter, B.A., PMP,
(Dave.Billiter@nationwidechildrens.org); Research Informatics Core, Nationwide Children's Hospital, Columbus, OH

Content:

The importance of biospecimen submission, accessioning, processing, distribution, and monitoring continues to be a significant topic within the biospecimen management and informatics disciplines. The Office of Biospecimen and Biorepositories Research and the International Society for Biological and Environmental Repositories accentuate the need for high-quality specimens and the ability for informatics to manage a specimen throughout the lifecycle. The Biopathology Center, biorepository for the Children's Oncology Group, collaborated with the Research Informatics Core to design and develop a suite of informatics applications to provide the ability to not only track a specimen, but to order and track the biospecimen kit transporting the specimen and monitor the institution submitting the specimen.

Technology:

The Biopathology Center Information Management Suite is a collection of applications comprised of web based data collection tools, databases built in SQL Server 2008. Additionally, co-hosting servers use SQL Reporting Services 2008 to share data across multiple data sources and ultimately make it available for end users. The suite of applications is written using Visual Studio 2008, Asp.Net, LINQ, and Crystal Reports 2008. Design: Kit Management, the first application in the suite, was created to increase the ability for over 250

Children's Oncology Group institutions to order protocol specific kits via a web-based interface and allow the Biopathology Center to fulfill the kit request and to distribute the kit. The second application is the Specimen Tracking and Reporting System. An enterprise application designed to harmonize multiple data sources, track the life cycle of specimen, track the chain of custody of a specimen and promote best practices in lab workflow and integration based on the Common Biorepository Model. Finally, the Institutional Performance Monitoring System was designed to monitor institutional specimen submission, per protocol, for specimen quantity and quality.

Results:

The suite is invaluable in eliminating the problem of information fragmentation, enhancing specimen awareness, and increasing performance while adhering to best practices.

Conclusion:

Informal interviews with Biopathology Center staff and institutional end-users indicate the information exchange effectiveness of the suite. It is the aim to finalize the deployment into production and continue to enhance the suite with continued iterations.

A Histotechnology and Microscopy Curriculum: Evolutionary Steps Toward an Optimal Instructional Resource

Philip J. Boyer, MD, PhD
(philip.boyer@ucdenver.edu), Yao Xu Schmidt, MS, MD, B.K. Kleinschmidt-DeMasters, MD; Department of Pathology, University of Colorado Denver, Aurora, CO

Content:

Anatomic pathology employs a wide spectrum of histotechnologic and microscopic techniques and tools with which few residents have familiarity upon entering residency. We have previously reported initial steps in the development of a curriculum which incorporates both Web-based instructional materials and reference to traditional textbooks with the goal of providing a comprehensive curriculum to (1) meet educational needs of trainees and (2) satisfy Accreditation Council for Graduate Medical Education (ACGME) guidelines. Given the scarcity of formal, didactic instruction hours when residents can be excused from formal duties and the abundance of topics to cover, we have reformulated the content of our curriculum to a series of eight self-guided exercises from a supplement to and infrastructure for formal lectures. In addition, formal skill set proficiency tasks have been added.

Technology:

Resources are compiled on an Intranet-restricted Web server with access through standard Web pages. Instructional content is stored as HTML, Adobe Acrobat PDF, and Articulate Presenter voice-annotated Flash files generated from Microsoft PowerPoint files. Testing and grade book functions are carried out using the Blackboard learning management system maintained university-wide.

Design:

Materials were grouped into eight major histotechnology and microscopy topic units. Each unit includes objectives (knowledge and proficiency); a pretest and a posttest; a voice-annotated PowerPoint lecture; supplemental summary tables and text; PDFs of key references; and additional resources. Proficiency tasks were implemented (e.g. embedding, cutting, and staining of tissue blocks; automated immunohistochemistry tasks; microscopy tasks, etc.).

Results:

This on-line resource has been deployed as part of an "immersion" series for first year residents. Initial resident feedback on a beta testing site has been overwhelmingly favorable. The conversion from paper-based testing and manual grading to automated functionality using Blackboard has reduced administrative time commitment.

Conclusions:

Further modifications and improvement of this curriculum position it as a self-guided instructional and reference resource for trainees that also provides documentation of "instruction" and "assessment" with respect to the ACGME "competency-based education" initiative. Remaining issues include development of a more seamless transition from instructional material to testing.

ImageMiner: A Medical Image Analysis and Image Management UML Data Model

Wenjin Chen, PhD¹ (chenwe@umdnj.edu), Vicky Chu¹, Jun Hu¹, Lin Yang¹, Fusheng Wang, PhD², Tahsin Kurc, PhD², Joel H. Saltz, MD, PhD², David J. Foran, PhD¹; ¹Center for Biomedical Imaging, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ; ²Center for Comprehensive Informatics, Emory University, Atlanta, GA

Content:

In this abstract we report the development of the ImageMiner UML data model. The objective of the ImageMiner project is to design, develop, and evaluate a modular set of tools for performing automated imaging, archiving, analysis, and sharing of medical images, including pathology and radiology images.

Technology:

ImageMiner leverages caGrid to provide an environment in which basic and translational research projects can share image data and analytical resources, while utilizing high-performance computing to support high-throughput analysis. The two major components of the ImageMiner data model are the Core model, which supports information on image acquisition, storage, and analysis results; and the TMAMiner extension, which addresses specific requirements of TMA based research.

Design:

The Core model supports a range of image modalities and formats and provides a platform through which images, gold-standard databases, and image analysis algorithms can be shared with other investigators.

The TMAMiner extension manages information regarding the physical composition and relevant clinical information of TMA blocks and supports high resolution visualization of specimens scanned using whole slide scanners. Other features of this sub-model include customized TMA evaluation support and flexible array data storage, to accommodate a wide range of textual and numerical data types.

Results:

Recently, ImageMiner model v.1, was evaluated by the NCI Enterprise Vocabulary Services team and registered in the cancer Data Standards Repository (caDSR). The imaging algorithms used for automatic segmentation and feature extraction have been deployed to strategic sites at The Cancer Institute of New Jersey, Emory University and the Ohio State University. During a series of performance studies the software was shown to support reliable, grid-enabled content-based image retrieval and clinical decision support.

Conclusions:

ImageMiner model and software are shown to be a reliable imaging and data management toolset providing grid-enabled analytic services and decision support. In the next phase of our work these tools will be deployed to a larger number of sites for prospective performance analysis.

Cell Surface Marker Immunophenotyping by Quantitative Imaging Cytometry: Virtual Slides with Embedded Multiparametric Data in Routine Clinical Use

Eric K. Morgen, MD, William R. Geddie, MD (william.geddie@uhn.on.ca); University Health Network, University of Toronto, Toronto, Ontario, Canada

Content:

Assessment of cell surface markers by quantitative imaging cytometry (QIC) offers several advantages over flow cytometry, including lower cell number requirements, the possibility of iterative re-staining, and, with current technology, retention of multi-parametric fluorescent marker data with digital images in a high-content virtual slide. We have evaluated the enhanced capability and clinical utility of 2nd-generation QIC for hematolymphoid immunophenotyping.

Technology:

Both the 1st- and 2nd-generation CompuCyte[®] QIC systems use multiple lasers and photomultiplier tubes plus stage movement in the x-axis combined with laser beam movement in the y-axis to generate scan fields of 1000 x 748 pixels. The main contrast is that, for morphologic review of events, the 1st-generation system requires physical slide XY-coordinate re-localization and image reacquisition, whereas the 2nd-generation system immediately saves all recorded data as a multi-layered virtual slide. Pixel sets of any recorded parameters (fluorescence, laser light loss, differential interference contrast (DIC)-type data, or algebraic manipulations of these direct measurements) can be reassembled for directed reanalysis or extracted as image galleries of gated cells.

Design:

Fifty clinical immunophenotyping studies (Clatch's method), performed on both the 1st- and 2nd-generation CompuCyte[®] platforms, along with 50 subsequent studies performed on the iCys[®] alone, were evaluated with particular attention to the utility of morphologic review of cell populations. In a subset of cases, iCys[®] DIC-like images were compared with true DIC images on a Leica DMR optical microscope.

Results:

Immunophenotypes generated by the two systems were identical, but visual assessment, useful for differentiating lymphoid from myeloid cells and identifying doublets/aggregates, was dramatically more convenient with virtual slides and galleries, allowing it to be performed routinely. In certain cases, the unique ability of the 2nd-generation system to recalculate event data based on new cell-contouring thresholds proved invaluable. The DIC-like images were comparable to true DIC images.

Conclusions:

Immunophenotypic analysis by QIC has matured in the iCys, providing a method both feasible and valuable for routine clinical use. The resulting combination of morphologic and immunophenotypic data seems superior to the alternative of imaging flow cytometry, with the additional advantage of on-

demand event data recalculation with modified parameters.

Integrating Digital Dictation and Anatomic Pathology LIS

Peter Gershkovich MD, MHA
(peter.gershkovich@yale.edu), John H. Sinard, MD, PhD; Yale University Medical School, New Haven, CT

Content:

Dictation and Transcription Management remains one of the critical bottlenecks of Anatomic Pathology (AP) workflow, and addressing transcription delays continues to be a challenge. Since different vendors have designed the dictation systems and AP LIS software, the events and priorities of one system are not easily linked to the events and priorities of another.

Technology:

We used an off-the-shelf, inexpensive Dictation/Transcription system and integrated it with our existing CoPathPlus AP LIS. The integration required two custom components: a File Management Component and a Dictation Portal for users' access to transcriptions and the Dictation Archive. Both components were built with Java-based Web technologies. Dictation File Management was added to a Scheduling System originally created to manage Pathology image files. "Dictation Portal" is a brand-new Web application created using Google Web Toolkit and delivered via the intranet on Tomcat Servlet container.

Design:

Dictation files are first delivered to two network-based directories for gross descriptions and final diagnoses, respectively. The File Management Component monitors for new files and validates the file name against active cases in CoPath. The CoPath-based priority is appended to the name of the file and the file is moved to a directory accessible via Dictation Portal. An entry is posted into the CoPath "events" table to record the date and time of the dictation.

Results:

The new integrated multi-component system for management and distribution of dictation files was built in one month, which included the time necessary to test and validate the system. The system has been deployed into production, providing the ability to monitor the transcription progress in real time. A dictation "dashboard" facilitates this monitoring.

Conclusion:

Integrating CoPathPlus and the Dictation/Transcription system removed redundancy in specifying dictation priorities and provided a

mechanism for consolidating workflow events into a single table, improving data analysis. Dictations that exceed priority specific thresholds for transcription are readily identified and addressed. In addition, continuous monitoring has improved transcriptionist productivity.

Web-Based Entry of Clinical Pathology Call Events For Quality Assurance Documentation and Educational Purposes

Christopher M. Gilbert, MD¹
(gilbertcm@upmc.edu); William J. Cable, MT²;
¹Department of Pathology, University of Pittsburgh,
Pittsburgh, PA, ²Information Services Division, Clinical
Department Systems, University of Pittsburgh Medical
Center, Pittsburgh, PA

Content:

Improvements to clinical pathology training are a perennial objective with few simple solutions. Prior to this project, pathology residents at our institution communicated call event information in a non-uniform manner that made learning from these events difficult and proper documentation essentially impossible. The CP Call Quality Assurance Documentation application was created to improve call event reporting and enhance resident training in clinical pathology.

Technology:

The application was written in ColdFusion 8, and is housed on an internal Intranet web server running Windows Server 2003 with Oracle 10g. Security technology in use includes secure logon via Access Control List, Secure socket, VPN access from home, and the truncation of medical record numbers. Additional features include search capabilities and dynamic E-mail generation.

Design:

The application features a call submission form, reference material, recently submitted call events, and a searchable database. Following a call event, a resident visits the site, completes the web-based form, chooses E-mail recipients relevant to patient care from a distribution list of faculty and house staff, and previews the entry. Upon submission, the application generates an E-mail that is distributed to the selected recipients with protected health information intact. Simultaneously a record is retained in the database stripped of protected health information. Aesthetically, the application was designed to conform to existing layouts with the same formats and cascading style sheets used by the Department of Pathology.

Results:

All residents were trained and signed user agreements. The application went live in April 2009 and is currently in use by the department. It has already provided a means for quality assurance of calls taken by residents new to clinical pathology and the steadily growing archive of call events is expected to become a valuable reference and teaching resource in the future.

Conclusions:

This informatics project accomplished dual goals of improving call documentation and dissemination while creating a powerful and valuable educational tool.

Barcode-Driven Cassette Printing Dramatically Improves Quality and Efficiency

Erin Grimm, MD
(grimme@u.washington.edu), Kevin Fleming, Rosy Changchien, Dan Luff, MHS, PA (ASCP), Rodney A. Schmidt, MD, PhD; Department of Pathology, University of Washington, Seattle, WA

Content:

Barcode-driven workflow has the potential for improving the efficiency, patient safety and economy of anatomic pathology laboratory operations, yet there is little quantitative data to support its use. Potential benefits are both direct (error reduction, personnel savings, reduced wastage) and indirect (reduced work associated with error correction and decreased medical-legal liability). Efficiency analyses suggest that the most reliable and efficient systems are those that incorporate single-piece continuous workflow with just-in-time printing and avoid any manual labeling steps. This report details benefits and costs associated with implementing cassette barcoding.

Technology:

We developed a C#.Net application (OmniTrax) that interoperates with our AP-LIS (PowerPath, Impac Medical Systems, Mountain View, CA) to print barcodes for all specimens and derived materials. Gross specimen containers are barcoded when accessioned, and these container barcodes drive the real-time printing of barcoded cassettes using the General Data (Cincinnati, Ohio) single hopper cassette imager. Just-in-time single piece workflow is employed throughout.

Design:

We assessed handling steps, error opportunities, required QA steps, cassette wastage, primary cassette labeling error rates, and personnel effort before and after deployment of OmniTrax. Measurement tools

included quality assurance records, workflow analyses, counts of cassettes and user reports (backed by supervisor's confirmation).

Results:

Implementation of OmniTrax reduced cassette handling steps from 11 to 5. Nine of the original steps had an opportunity for sample identification error but only one of the remaining steps did. The primary cassette labeling error rate fell from approximately 988/85,213 (1.16%) to 4/50,016 (0.0080%). Cassette wastage fell from approximately 8% to 3%. Gross room personnel savings was 0.75 - 1.0 FTE due to avoidance of pre-labeling of cassettes and reduced work reconciling labeling errors. Workflow at the gross station was at least as efficient as before. Primary costs were for software development and cassette printer hardware.

Conclusions:

Both patient safety (through reduction in labeling errors) and efficiency are improved profoundly via use of barcode-driven just-in-time single piece workflows. Savings in personnel and reduced wastage offset the costs of hardware with a relatively short expected break-even period.

National Wide Real Time Virtual Slide Conference System

Woo Young Jang, MD, MS
(pathwyl@empal.com); Hangang Sacred Heart Hospital, Hallym University, Seoul, Republic of Korea

Content:

It is very hard to create real time virtual slide conference system because of hardware performance, speed of internet and large data size of virtual slide. We use most recent version of hi-resolution conference system and Government-controlled 1 Giga bps internet (KREONET) and make a successful real time conference. We will extend this system at most of large sized Hospitals, Medical College of Universities and Public Health Care Centers.

Technology:

Virtual Slide Machine, HP Xeon Server, Pentium (Quad Core) Desktop Computer, Pentium (Dual Core) Laptop Computer, Cable Internet (Speed: 1 Giga bps), High Definition Television, High-Resolution Conference Camera, Virtual Slide Controlling Software were used for construction of this system.

Design:

This system was designed for performance, clear vision diagnosis-consultation-conference. We set this system for three parts. The first is virtual slides which was scanned by virtual slide machine and saved at

retail HP Xeon server. The second is desktop and laptop computers which were installed Virtual slide controlling software. The last is high resolution image & voice chatting system which consists of High Definition Television & High-Resolution Conference Camera. The members of 'Medical Informatics of Pathology' were select one of their most convenient conference site (IISan, ChungJu, and JeJu City) and began the conference. The average loading time from server to Desktop and Laptop was 1.2 second. The largest file size was about 800Mbytes and the smallest file size was about 100Mbytes. The most long distance of conference site was about 500km. We can make a real-time conference talking with looking high resolution image of members (high definition television) and high resolution image of virtual slides (desktop and laptop computers). We tossed the 'authority of control' to each other using virtual slide controlling software and could make a successful real time scanning and diagnosis.

Results:

Prototype national wide real time virtual slide conference system made possible to get the excellent conference and diagnosis with ease.

Conclusions:

Prototype national wide real time virtual slide conference system had the following advantages:

- 1) Easy handling of viewer
- 2) High resolution motion image (conference and virtual slide)
- 3) Discussion without echo noise
- 4) Real time access

More technical refinements would be desirable for the more advanced expanded tasks.

Current Status of Pathology Informatics in Korea, 2009

Hee Jae Joo, MD^{1,3} (joodr@hotmail.com); Sang Yeop Yi, MD^{1,2}; ¹The Medical Informatics Study Group of Korean Society of Pathologists, Korea, ²Department of Pathology, Kwandong University College of Medicine, Goyang, Korea, ³Department of Pathology, Ajou University College of Medicine, Suwon, Korea

Content:

Beginning in 2000, aided by a rapid spread and development in computer technology and medical informatics, pathology informatics also progressed quickly. The Medical Informatics Study Group of Korean Society of Pathologists conducted a nationwide survey to compare the current status of pathology informatics in Korea between 2009 and 2007.

Design:

In survey, the diagnosis field includes laboratory information system, bar-code, voice recognition system, digital image acquisition and management, pathology PACS, clinical PACS, electronic medical record, gross description, structured documentation, evidence based report, diagnostic coding system, method of consult, telepathology, teleconference, decision support system, de-identification, and virtual slide. The education field includes e-learning, internet in education, and intradepartmental informatics training for residents. The research field includes data management for biorepository, tissue microarray, and gene array, image analysis, and virtual slide.

Results:

Our survey's respondents consisted of directors of Departments of Pathology across Korea. We surveyed from May to June of 2009 via either online or mail responses. A total of 117 hospitals participated in the survey. Almost institutions (n=114) are implementing laboratory information system. Sixty five were using bar-code system. Many institutions (n=87) used digital camera for gross images. The automatic system (n=46) for take and management of gross images are increased than 2007. Pathology PACS (n=51), clinical PACS (n=92), and electronic medical record (n=58) are also increased. Almost institutions (n=107) still prefer the postal service for consultation to experts. Implementations of telepathology (n=3) and teleconference (n=0) are insignificant. Applications of virtual slide (n=12) and image analysis (=13) for diagnosis are slightly increased. The objects of E-learning is students (n=17) and residents (n=5). The exclusive program (n=11) for data management of biorepository are slightly increased. Data management for tissue microarray or gene array is still weak. Applications of virtual slide (n=9) and image analysis (n=19) for research are slightly increased.

Conclusions:

In comparison with 2007, the speed of implementation of pathology informatics and digitalization is slow, but steady in progress. The growth of education and research filed including telepathology is insufficient than diagnosis field. The application of insurance charge and active support by government is necessary to settle this problem.

Her-2 Signal Enumeration in FISH Image Stacks in Invasive Breast Cancer Specimens

Michael W. Kilpatrick, PhD
(Kilpatrick@ikonisys.com), Changhua Yu, Xiuzhong Wang, Triantafylos Tafas; Ikonisys, Inc. New Haven, CT

Content:

To determine Her-2 status in invasive breast cancer specimens, accurate automated FISH dot counting is highly desirable. Various intensity-based thresholding techniques have been developed for dot segmentation in FISH images. Here we present a gradient-based dot detection method. The proposed method is verified by analysis of several breast cancer slides.

Technology:

Specimen slides were prepared, hybridized with two FISH probes, an orange Her-2 probe and a green control probe and counterstained with Dapi. Slides were imaged in all 3 fluorescence channels, Dapi, orange and green, using an automated epifluorescence microscope equipped with a 100x objective.

Design:

Nuclei are segmented based on the DAPI image and, using the segmented nucleus DAPI mask, the FISH channel cutout stacks of each nucleus are generated. The best focal plane is identified and 5 planes around the best focal plane are then chosen for dot counting. Before searching for FISH signals, top-hat filtering is used to reduce noise introduced by fluorescent residue. Adaptive thresholds are found based on maximum gradient images. Pixels with gradient above threshold grow into dots. Finally, FISH signals are recognized by a trained multi-layer perceptron (MLP) utilizing the 3D features of size, shape and intensity.

Results:

Five breast cancer slides were used to evaluate the automated FISH signal detection method. For each slide, at least 100 nuclei were analysed. The dot feature samples from 2 slides were used for MLP training and samples from the remaining slides were used for testing. Trained personnel manually counted and tabulated the FISH signal in each nucleus. The agreement between automated and manual FISH signal counting for the slide set ranged from 80.26% - 91.15%.

Conclusions:

We have proposed a gradient-based method for the detection of FISH signals using a monochrome FISH image stack. In the 3D image stack, pixels with gradient magnitude above adaptive thresholds grow into dots. Shape, area and relative volume features are extracted. Normalized intensity features reflecting local contrast are also used. A three-layer MLP is trained to discriminate the FISH signals. Experimental results with breast cancer specimen slides demonstrated the automated dot counting ability of the proposed method.

Usability and Interface Design Challenges Encountered in Structured Data Capture of Gross Description

Mark B. Law, PhD (mark.law@mtuitive.com);
mTuitive Software, Inc., Centerville, MA

Content:

It was necessary to answer a number of usability issues particular to the gross room environment during a project for the Massachusetts General Hospital to create a speech-driven software application for structured data entry of the small gross description by gross technicians at the point of performance. Ethnographic observation of gross technicians and an iterative design process involving testing of and retesting of the user interface with those gross technicians revealed an information architecture that was then implemented as a set of templates for structured data capture tailored to specific specimen types. Rule-driven software efficiently directed the data entry session based on the information entered. User interface elements were designed for optimized control using off the shelf Nuance Dragon Medical speech recognition software. Use of forced choice lists and data entry controls that were able to parse certain phases were used to enable structured speech-driven data capture.

Technology:

mTuitive Software xPert rule-based software for structured data capture. Nuance Dragon Medical for speech recognition.

Design:

Ethnographic observation and task analysis was used to gather user interface and information architecture requirements. Iterative design was used to rapidly create, test, update, and retest the user interface until a satisfactory performing implementation was reached.

Results:

Observation and task analysis revealed that a hands-free system was favored because the user often needed both hands to work with the tissue at times when reportable information was discovered. Most of the data that the users entered was uniform and standardized to specimen types allowing a set of specimen-specific templates to be created that could accommodate the majority of reporting using predefined lists of values. Measurements were sufficiently uniform for the software to parse spoken measurement values reliably into structured components, e.g., each dimension and the corresponding unit of measure could be parsed into discrete fields. Analysis of the most frequent data entries for each specimen type allowed default values to be chosen in many cases which sped data entry by

requiring the user to only verify those values and enter only a few others to complete the data entry session.

Conclusions:

Using speech recognition for data entry and application control it was possible to create a hands-free system for the entry of structured gross descriptions that was as efficient as dictated entries for later transcription. Critical to the success of this project was the observation and analysis that led to the construction of data entry templates that were consistent with the information architecture of the small gross descriptions and that were optimized for speech-driven data entry and application control.

DICOM in the XML Schema Design Language

Robert C. Leif, PhD (rleif@rleif.com);
Newport Instruments, San Diego, CA

Content:

In 1998, I proposed that the International Society for Advancement of Cytometry should replace their present Flow Cytometry Standard with an implementation in DICOM and work with the DICOM developers. After this suggestion was rejected, I suggested an XML implementation based upon DICOM to the International Society for Advancement of Cytometry Data Standards Task Force.

Technology:

XML Schema Design Language is the basis for the development of a new standard (CytometryML) for cytometry metadata. The schemas have been validated with XMLSpy and Stylus Studio. The relevance of the composition of the major schemas has been tested by the automated creation of XML pages and the manual entry of data into them.

Design:

Since only data-types including data structures and objects are described in schemas, object oriented design principles were followed in their design, which, wherever possible, was based on DICOM. Strong typing, minimization of the coupling of independent higher-level schemas, and maximization of the cohesion of individual schemas were design principles. Container files for multiple XML pages that included a table of contents were employed instead of mimicking a DICOM directory structure.

Results:

XML schemas that describe the metadata XML documents for two related types of container files have been created. The series container includes the metadata files that are constant for a set of measurements, such as the instrument description.

The instance container includes the metadata and binary data that is specific to an individual or small closely related group of measurements, such as the instrument settings and staining protocols. Schemas for digital microscopes and flow cytometers, as well as image and list-mode (waveform) data have been created.

Conclusions:

It is possible to translate DICOM data-types into conventional, readable, modular XML schemas. Both the XML metadata and binary data files that describe instances can be placed together in a container based upon a ZIP file. The reuse of the well tested DICOM model and descriptions resulted in a great decrease in the design and documentation effort and increased the probability of reliability. The modular structure of the schemas has facilitated the inevitable changes associated with a design by committee.

Data-Mining Time-Events from Free Text in Electronic Health Records

G. William Moore, MD, PhD^{1,2,3}
(George.Moore@va.gov), Lawrence A. Brown, MD^{1,2},
Dong H. Lee, MD^{1,2}; ¹Pathology and Laboratory
Medicine Service, Veterans Affairs Maryland Health
Care System, Baltimore, MD ²Department of
Pathology, University of Maryland Medical System,
Baltimore, MD ³Department of Pathology, The Johns
Hopkins Medical Institutions, Baltimore, MD

<http://www.netautopsy.org/timeline.htm>

Content:

Many time-events in ordering, processing, and reporting clinical laboratory tests have standardized formats. However, some time-events are recorded solely within free-text comments. In a retrospective study of turnaround time, we examined all accessions with critical results, to determine call-back interval to the healthcare provider.

Technology:

VistA public-domain software; commercial spreadsheet; Perl programming language.

Design:

All laboratory tests ordered at the Baltimore Veterans Affairs Maryland Health Care System Pathology and Laboratory Medicine Service from May 1, 2007, through May 31, 2009, were analyzed for time-events in the free-text comment field. Critical results were downloaded from VistA software, and data-mined from an open-source Perl script. A time-event had at least 3 numerals with an embedded colon; 2-4 numerals preceded by at-sign; or 1 numeral preceded

by at-sign, followed by AM or PM, detected by pattern-matching in Perl. Comma-delimited output was analyzed in a commercial spreadsheet.

Results:

Over the 25-month period, there were an estimated 1.81 million accessions; 35,062 (1.9%) accessions with critical results; 19,690 (56.2%) accessions with free-text time-pattern; and 341 (1.7%) time-events flagged as errors: 249 (73%) time-events required visual inspection only; 92 (27%) time-events required manual alteration.

Conclusion:

When the clinical laboratory is asked to provide turnaround time data, one can data-mine existing free-text fields for time-events, using inexpensive, readily-available computer script and spreadsheets. We were able to standardize over 98% of free-text time-events using public-domain software. Retrospective analyses can serve to assess prior performance in the laboratory; and to suggest future software modifications for the laboratory information system.

Hierarchical Algorithm for Diffuse Lymphoid Infiltrates in Tissue and Body Cavity Fluids

Grace F. Kao, MD^{1,2,3}, G. William Moore, MD,
PhD^{1,4,5} (George.Moore4@va.gov); ¹Pathology and
Laboratory Medicine Service, Veterans Affairs
Maryland Health Care System, Baltimore, MD,
²Department of Dermatology, University of Maryland
Medical System, Baltimore, MD, ³Department of
Dermatology, George Washington University School of
Medicine, Washington, DC, ⁴Department of Pathology,
University of Maryland Medical System, Baltimore,
MD, ⁵Department of Pathology, The Johns Hopkins
Medical Institutions, Baltimore, MD

<http://www.netautopsy.org/algolymp.htm>

Content:

A diagnostic classification may be formalized as an algorithm, or hierarchy of instructions. Many existing diagnostic algorithms in human pathology are human-readable, but cannot be understood by computer applications or verified for consistency and completeness. Diffuse lymphoid infiltrates have four major diagnostic categories: benign reactive and atypical lymphoid hyperplasia, and low-grade and high-grade lymphoma, with distinct prognostic and therapeutic implications.

Technology:

Symbolic logic, Perl programming language.

Design:

An open-source theorem prover program solves for true/false variables in a diagnostic hierarchy. An intercalation theorem permits insertion of a subhierarchy for new technologies, such as immunohistochemistry and flow cytometry, without altering inferences in the original hierarchy. A ranking theorem permits re-ordering of the hierarchy, to optimize diagnostic and cost-effectiveness.

Results:

The diffuse lymphoid infiltrate hierarchy has a total of 424 lines and 304 concepts: 83 primary disease concepts for diffuse lymphoid infiltrates; 221 concepts for demographics, clinical findings, gross and microscopic findings, immunophenotypes, and cytogenetics; and a maximum depth of eight subhierarchies. The full hierarchy is mathematically consistent; it satisfies the intercalation and ranking theorems; and the primary classification is compliant with Resource Description Framework (RDF).

Conclusion:

Diffuse lymphoid infiltrates in tissue and body cavity fluids are formalized as a hierarchical diagnostic algorithm. Diagnostic algorithms can organize well-defined subsets of tumor pathology, making them accessible to computer software applications and internet spiders. These public computer applications can enhance collegial information exchange, constructive criticism, and more widespread discussion of pathologic entities.

Pythagorean Transformation in Cell Tessellations: Model for Malignant Growth

G. William Moore, MD, PhD^{1,2,3}
(George.Moore@va.gov), Raimond A. Struble, PhD⁴,
Lawrence A. Brown, MD^{1,2}, Grace F. Kao, MD^{1,5,6},
Grover M. Hutchins, MD³; ¹Pathology and Laboratory
Medicine Service, Veterans Affairs Maryland Health
Care System, Baltimore, MD, ²Department of
Pathology, University of Maryland Medical System,
Baltimore, MD, ³Department of Pathology, The Johns
Hopkins Medical Institutions, Baltimore, MD,
⁴Department of Mathematics, North Carolina State
University, Raleigh, NC ⁵Department of Dermatology,
University of Maryland Medical System, Baltimore,
MD, ⁶Department of Dermatology, George
Washington University School of Medicine,
Washington, DC

<http://www.netautopsy.org/pythtess.htm>

Content:

Tumors of surface epithelium are the most common human malignancies. Benign surface epithelium consists of equal-sized cells, over a uniform surface,

that divided just enough to replace themselves. Malignant transformation has variably-sized cells, a disorganized surface, and the tendency to invade surrounding tissues.

Technology:

Ordinary and synthetic geometry.

Design:

A monolayer of normal surface cells, can be modeled as a planar tiling, or tessellation, of tangent, regular hexagons, with one origin-cell. A Pythagorean transformation maps each point on the plane outside the origin-cell, to a ray in three-dimensional space, arising from the origin-cell center. Pappus hexagon theorem shows that two sets of three collinear cell-nuclei (=centers-of-gravity) on the plane intersect at three collinear points, that lie along other cell-nuclei and cell-edges.

Results:

A generalized Pappus theorem using the Pythagorean transformation, shows that the original three sets of coplanar points transform into three coplanar sets of rays. Transformed ray-planes in 3-space intersect on the original plane unless the origin-cell is disproportionately enlarged by malignant transformation.

Conclusions:

Results suggest that the origin-cell undergoing malignant transformation may disrupt communication with neighboring cells, through altered cell geometry. Therapy for cell-to-cell miscommunication might possibly control malignancy. Mathematical models can explore alternatives to classical hypotheses in pathology, and explore general paradigms.

Application of Focus Fusion Technique to Virtual Slide for Cytopathology in Human Uterus Screening

Hiroyuki Nozaka, MSc¹
(hnozaka@cc.hirosaki-u.ac.jp), Zhongxi Zheng¹, Rie Sakuraba¹, Tomisato Miura¹, Manabu Nakano¹, Tatsusuke Sato¹, Hideki Takami¹, Noriyuki Yamada², Tamotsu Sugai²; ¹Hirosaki University Graduate School of Health Sciences, Japan, ²School of Medicine, Iwate Medical University, Japan

Content:

Recently, many diagnostic imaging systems have been developed for histopathology, however development of the digital imaging tools for cytopathology has delayed. The reason why smear slides for cytology are thicker than paraffin embedded tissue section, the surface of smear slide is not flat and smooth plane. The current virtual slide (VS)

system is optimized for the scanning of flat and smooth plane slide, it is not suitable for the scanning of irregular plane slide such as smear slide. Therefore VS system for cytopathology requires the mechanical function to scan three-dimensional structure of cell clusters, and it also requires the new image-processing technology for display of three-dimensional VS. The aim of this study is development of multi-layer VS scanning system for cytopathology and focus fusion technology for VS.

Technology:

We developed the VS system with focus fusion. The VS system is composed of a microscope (Axioscope A1, CarlZeiss) and an three-dimensional transfer device for glass slide (Original). The three-dimensional transfer device is composed a slide hand which holds a slide glass by air pressure and motorized stage with three-axial transfer. To scan of VS, we developed focus fusion technology which synthesizes mono-layer scanning image from multi-layer scanning image.

Design:

Samples were collected from 20 patients for human uterus screening. Both conventional smear slide and liquid based cytology slide were made from sample which recovered by cervical scraping, and we carried out papanicolaou stain. These slides were scanned by VS system with focus fusion method or non-focus fusion method. And we evaluated the effect to cytopathological diagnosis and findings.

Results:

VS system with focus fusion was more excellent than the current VS system with mono-layer method or movie method in the point of viewing inside cell clusters and image file size. LBC was more suitable than conventional smear slide for VS with focus fusion.

Conclusions:

It is thought that focus fusion technique is useful for VS of cytopathology, and it can be applied to tele-cytology and e-learning.

Acknowledgment:

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Utilizing caGrid Infrastructure for Tissue Microarray Analysis

Alex Wright¹, Tony Pan, MS ScB³
(tspan@emory.edu), Jason Lander², Shiv Kaushal²,
Ashish Sharma³, Joel Saltz, MD, PhD³, Philip Quirke¹,

Darren Treanor MB BSc, MD¹; ¹Section of Pathology and Tumour Biology, Leeds Institute of Molecular Medicine, University of Leeds, United Kingdom, ² National Grid Service, University of Leeds, United Kingdom, ³Center For Comprehensive Informatics, Emory University, Atlanta, GA

Content:

The National Cancer Institute (NCI) Cancer Biomedical Informatics Grid (caBIG[®]) program and the National Cancer Research Institute (NCRI) in the UK are collaborating on the creation of interoperable Grids for sharing data and computing power to facilitate international cancer research. In this abstract we report on the development of a caBIG caGrid-based environment at University of Leeds and its application to facilitate Grid-enabled analysis of TMA images.

Technology:

Tissue microarrays (TMAs) are commonly used in biomedical research. They provide a high-throughput technology for analysis of large number of tissue samples. Scoring TMAs is a time consuming manual process, frequently performed in single site laboratories using microscopes, glass slides, and paper. Grid technology and use of virtual slides for TMAs can facilitate 1) more efficient sharing of images and results; 2) collaborative scoring of TMAs (e.g., by 2 expert pathologists at different institutions); and 3) cooperative development and evaluation of image processing algorithms.

Design:

At University of Leeds, we have employed the caGrid middleware to implement a Grid service for a pixel-based MATLAB[®]. This algorithm detects and quantifies DAB and hematoxylin stained pixels in tissue cores, outputting the percentage of positive stained pixels in the core. caGrid service interfaces allow remote invocation of the pre-compiled algorithm. The analysis outputs are stored locally and accessible to the researcher via a caGrid retrieval interface.

Results:

Remote clients can submit whole-slide TMA images to the caGrid-enabled implementation of the MATLAB[®] stain quantification algorithm for analysis. The service is being deployed at the UK NGS grid at University of Leeds and Emory University to create a testbed Grid environment.

Conclusions:

Studies involving TMA analyses can benefit from Grid technologies to process images much faster, by using combined processing power across multiple sites, and to analyze multiple images simultaneously. In addition, the computing grid can allow a researcher to

utilize diverse image sources in the environment, provide access to a broader set of analytical algorithms, and enable systematic management and collaborative access to analysis outputs.

Reducing Patient Identification Errors Related To Glucose Point of Care Testing

Liron Pantanowitz, MD
(Liron.Pantanowitz@baystatehealth.org), Deborah Bozek, MT (NCA), Joseph Seipel, James H Nichols, PhD; Baystate Medical Center, Tufts University School of Medicine, Springfield, MA

Content:

Patient identification (ID) errors in point-of-care testing (POCT) can cause data to be transferred to the wrong patient's chart and prevent POCT results from being transmitted to the correct patient's medical record and appropriately billed. Despite implementation of patient barcoding and ongoing operator training at our institution, patient ID errors still occur with glucose POCT. The aim of this study was to develop a solution to reduce identification errors with POCT.

Technology:

POCT Glucose Meters (Precision PCx® Point-of-Care System, Abbott Diagnostics). Database Server (QCM3, Abbott Diagnostics). Interface Manager (Telcor PC). Laboratory Information System (Sunquest v6.2, Sunquest Information Systems).

Design:

Glucose POCT is performed by approximately 2400 operators throughout our health system. Patient ID by operators occurs mainly by scanning in wristband barcodes and by manual data entry using PCx glucose meters. Cradled devices upload data to our QCM3 repository which gets transmitted to our Telcor PC where the patient ID (9-digit account number) is checked against patient registration data from an ADT feed. Only matched data is transmitted via our LIS into the patient's electronic medical record. Daily review of the Telcor PC is performed, all patient ID errors tracked and if appropriate reconciled.

Results:

In a 6 month period 119,861 POCT glucose tests using PCx meters were performed. During this period 350 patient ID errors were detected (average 58 errors/month) giving a 0.3% error rate. Errors occurred when incorrect patient account numbers were entered into the POCT device during testing related to improper barcode scanning, transient use of ID numbers (e.g. for emergency department patients), and/or erroneous operator manual data entry.

Conclusions:

Patient ID errors (0.3% error rate) may occur with glucose POCT despite patient barcoding. Identification of these errors should ideally take place at the bedside when they occur so that they can be addressed in real time. Therefore, at our institution, we are introducing an ADT feed directly to our glucose meters in an attempt to eradicate patient ID errors in POCT.

Leveraging the LIS to Monitor Cytopathology Screening and Performance Indicators

Liron Pantanowitz MD
(Liron.Pantanowitz@baystatehealth.org); Maryanne Hornish CT(ASCP), MBA, Robert A. Goulart MD; Baystate Medical Center, Tufts University of Medicine, Springfield, MA

Content:

Cytopathology screening and performance indicators, part of a laboratory's quality assurance program, are critical for the detection, reduction, and correction of deficiencies in Pap test analysis. They also help meet Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements and maintain laboratory accreditation. Our aim is to report the measures by which our cytopathology division utilizes the laboratory information system (LIS) to evaluate various quality indicators.

Technology:

Laboratory Information System (CoPath v3.1, Cerner Corporation); Spreadsheet Application (Microsoft Excel version 2003).

Design:

Ten cytopathology screening and performance indicators are regularly evaluated, including (1) rescreening of random and high risk cases, (2) diagnosis correlation between cytotechnologist and cytopathologist, (3) frequencies of diagnostic categories including ASC-US/SIL rates, (4) HPV DNA positivity rates for ASC-US cases, (5) cytologic-histologic correlation, (6) cytotechnologist reporting errors, (7) specimen turnaround time, (8) productivity (volume of slides/month), (9) 5-year lookback, and (10) diagnosis correlation between cytopathologist and cytopathology fellow. LIS data downloaded into spreadsheets is manipulated for concise data presentation (e.g. pivot tables, charts).

Results:

For pre-reporting rescreening purposes (indicator 1), our LIS automatically marks cases identified as high risk and each 10th consecutive negative Pap test case entered by a primary screening cytotechnologist on a lab-wide basis. The percentage of cases directed for

pre-reporting secondary review is adjusted for individual screeners (e.g. new hirees). For indicators 2 to 8, our evaluation involves cross referencing of LIS data, comparison of findings against laboratory averages, and trend analyses. For the 5-year lookback process (indicator 9), the LIS identifies for review all respective Pap tests that were reported as negative within the last 5 years for current cases diagnosed as high grade squamous intraepithelial lesion or carcinoma. For indicator 10, a comparison of our fellow's diagnoses entered into the LIS and corresponding cytopathology staff provides objective documentation of graduated fellow learning.

Conclusions:

LIS workflow and electronic databases can be utilized to continuously monitor cytopathology screening and performance indicators. This permits potential false negative Pap tests to be identified and assessed for individual feedback, continuing education, and monitoring of overall performance of the cytopathology laboratory.

Interface Problems Caused by Complex Surgical Pathology Reports

Liron Pantanowitz MD (Liron.Pantanowitz@baystatehealth.org), Andrew Ellithorpe, PA (ASCP) MHS, William Lareau, BS MT (ASCP); Baystate Medical Center, Tufts University School of Medicine, Springfield, MA

Content:

The need to provide electronic pathology reports is rapidly increasing with widespread adoption of the electronic medical record (EMR). As a result, there is greater demand for interconnectivity between the laboratory information system (LIS) and disparate EMRs. The complexity of surgical pathology reports has concurrently increased with structured synoptic templates, the incorporation of more detailed diagnostic and prognostic information, and even embedded digital images. HL7 messages containing such reports pose difficulties in crossing interfaces and being displayed correctly in downstream EMRs. Our aim is to report difficulties that we have experienced when electronically transmitting complex surgical pathology reports.

Technology:

Laboratory Information System (CoPath v3.1, Cerner Corporation); EMR (Millennium, Cerner Corporation); Interface engine (eGate Intergrator version ICAN-SRE 5.0.5, Sun Micro Systems).

Design:

Surgical pathology reports created in our LIS use Microsoft Word. Standardized templates are used,

particularly for cancer cases, providing reports with a structured layout (e.g. headings, indenting, spacing). Tables with multiple columns and rows are used in neoplastic breast cases to relay information about multiple specimen resection margins. Electronic reports are transmitted in RTF format via our interface engine into our EMR. Transmissions are regularly monitored to detect reports that fail to post in the EMR.

Results:

Pathology reports with single tables post to our EMR, albeit with an imperfect layout of the table. Retrospective review revealed that 4% of our breast cancer surgical pathology reports contain more than 1 table reporting specimen margins, due to multiple re-excision specimens submitted simultaneously to the laboratory. Despite successful transmission from our LIS after electronic sign out, reports with multiple tables either did not post to the EMR and/or caused the entire interface to fail. Rearrangement of report format preserving tables, and moving data elements into different fields, did not resolve this problem.

Conclusions:

Challenges exist in being able to effectively transmit and display human-readable electronic structured pathology reports. Employing other report formats (e.g. PDF, XML-based clinical document architecture) in order to overcome these difficulties, and replace well formatted LIS printed reports, should be considered.

Utilization of Laboratory Data in the Electronic Medical Record (EMR)

Liron Pantanowitz MD (Liron.Pantanowitz@baystatehealth.org), Julie Gentes RN, Neil R. Kudler MD; Baystate Medical Center, Tufts University of Medicine, Springfield, MA

Content:

Laboratory data takes a central role in the EMR. Lab data populating an EMR can be displayed in several formats including tables (spreadsheets), group listings, or graphic displays, all of which are customizable. Our aim was to determine the various ways in which lab data is utilized by clinicians in our health system's EMR.

Technology:

Electronic Medical Record (Millennium, Cerner Corporation).

Design:

Data from our laboratory information system is transmitted electronically in HL7 and RTF format to the EMR, where it is displayed in a structured folder

layout (laboratory, microbiology, anatomical pathology, and transfusion medicine service tabs). The same lab data is displayed in dashboards and flowsheets and is used to generate decision support alerts, to trigger automated health maintenance reminders, and to populate clinical notes and EMR-generated letters.

Results:

Dashboards and flowsheets (e.g. renal view) can be customized to group relevant lab results to assist in disease-specific management. This eliminates distracting test results on a screen for specific users that are irrelevant to their decision-making process. Lab data also generates interruptive and non-intrusive electronic alerts. Lab results can be associated with medication order entry to generate drug-related alerts that may interrupt workflow, but improve quality and safety. Post hoc modifications of lab data within the laboratory information system triggers an electronic message sent to the ordering provider's EMR inbox. Lab data (e.g. Pap test results) post to the health maintenance tool to create automated reminders that prompt physicians to implement preventive services (e.g. obtain a Pap smear). Clinicians also incorporate lab results, often without accompanying data elements (units, reference ranges, comments), into their clinical notes and EMR-generated letters (e.g. patient follow-up letters).

Conclusions:

Flexible electronic laboratory data in the EMR has many advantages. Users can view, sort and pool lab information to support trend analysis and clinical decision making. Lab data can also be used to trigger clinical decision support systems such as alerts and reminders. Pathologists need to participate in the creation of these EMR tools in order to support the appropriate utilization of laboratory information in the EMR.

Stepwise Approach to Establishing Multiple Outreach LIS-EMR Interfaces

Liron Pantanowitz, MD
(Liron.Pantanowitz@baystatehealth.org), William Lareau, BS, MT(ASCP), Wayne Labranche; Baystate Medical Center, Tufts University of Medicine, Springfield, MA

Content:

Clinical laboratory outreach business is increasing as more physician practices adopt electronic medical records (EMRs). As a result, client connectivity with legacy laboratory information systems (LISs) is becoming more important in competitive geographic environments. We report a stepwise approach used at

our institution to successfully interface our LIS with multiple regional EMRs.

Technology:

Electronic Medical Records (eClinicalWorks, MediNotes, SOAPware, NextGen, Script Sure, Sage Medical manager, SSIMED EMRge, Allscripts, Renal Track, ePro, Practice Manager); Laboratory Information Systems (Sunquest version 6.2, Sunquest Information Systems; CoPath version 3.1, Cerner Corporation), Software As A Service (AE Master Data Synchronization Service and TXM/IXM Reconciler, Accenx Technologies).

Design:

A 4-stage scheme was employed to establish unidirectional and bidirectional interfaces using HL7 messages with multiple physician practice EMRs. Our approach involved planning (step 1), followed by interface building (step 2) with subsequent testing (step 3), and finally ongoing maintenance (step 4).

Results:

Step 1 (planning phase) included financial (budget), infrastructure, test volume (tests/year/practice) and backlog (retrospective LIS data) parameter analysis, identification of resources, roles and responsibilities, and schedule determination. Step 2 (build phase) involved the creation of a test compendium (practice-specific translation table matching test codes and nomenclature) and software installation. Step 3 (production phase) required validating secure connectivity, matching of results to orders, adjustment and endorsement of EMR lab data content and display (electronic screenshots and EMR printed reports), as well as reconciliation of mismatched orders and/or results. For step 4 (monitoring phase), a service agreement with our clients was required, along with a downtime procedure, connectivity monitor, mechanisms to continually check EMR lab data and update our test compendium, as well as a change control procedure for potential software upgrades.

Conclusions:

An organized project management approach is fundamental to successfully establish multiple LIS-EMR interfaces. Software as a service (SAAS) forms a vital component of establishing and maintaining laboratory outreach connectivity. Interoperability standards and improved EMR vendor cooperation are essential for electronically integrating healthcare.

Use of an EMR for Transfusion and Apheresis Medicine Services

Liron Pantanowitz, MD
(Liron.Pantanowitz@baystatehealth.org), Rebecca Levy, MD, Chester Andrzejewski, PhD,MD, Darlene

Cloutier MT(ASCP),HP, Jennifer Stebbins, RN, Suzanne Cronin, RN BSN MBA, Jean Provencher,RN, Eileen Donelan, MT(ASCP),MBA; Baystate Medical Center, Tufts University of Medicine, Springfield, MA

Content:

The Electronic Medical Record (EMR) facilitates communication and accessibility of information across specialty care lines. Pathology transactions in the EMR typically include the transmission and display of laboratory test results as well as computerized physician order entry of lab tests. For Transfusion and Apheresis Medicine Services (TAMS) current laboratory information systems (LIS) are inadequate to record patient care activities like consultations, patient monitoring during transfusion, and capture of hemapheresis procedure notes. Paper documentation of such TAMS activities can be misplaced, overlooked, or not included in a patient's chart. The utilization of an EMR to electronically document TAMS activities may address these issues. We present our institution's approach, strategies and experience in meeting this challenge.

Technology:

Clinical Information System (CIS, Cerner Millennium). Networked workstations (Dell OPTIPLEX GX620 or 745 computers) with Windows operating system (Microsoft Windows XP Professional).

Design:

An EMR working group was assembled comprised of TAMS "content experts" (physicians, technologists, nurses) and information technologists. Team members met regularly to discuss inpatient and outpatient service activities, software and hardware requirements, report format design, impact on staff, and evaluate building of a suitable TAMS folder (tab). Automated EMR data collection was established for data mining of these TAMS activities.

Results:

Areas for electronic documentation in the EMR included the blood unit tag, hemapheresis worksheet, pathologist consult and progress notes. Transfusion and apheresis flowsheets were constructed using select data elements (e.g. vital signs, hematocrit, medications) from the EMR into a truncated display format. Electronic alerts informing physicians about hemotherapy challenges (e.g. transfusion reactions, medication reconciliation) were added. An electronic alert will also be activated when a transfusion is ordered on an "at risk" patient (e.g. renal or cardiac failure patient at risk for fluid overload).

Conclusion:

Creation of a TAMS folder in the EMR may permit transfusion and apheresis medicine services to effectively utilize the EMR for electronic

documentation of activities. Automated data mining of these documented activities will facilitate TAMS quality assurance and biovigilance. Collaboration between TAMS "content experts" and information technologists is key to effectively exploit the EMR. We plan to adopt this strategy at our institution.

Tissue Microarray Facilitated Mechanical Characterization of Cancerous Breast Tissue Using Atomic Force Microscopy

Rajarshi Roy, BS¹ (rroy12@umd.edu), Wenjin Chen, PhD²; Jun Hu²; Lauri Goodell²; David J. Foran, PhD²; Jaydev P. Desai¹; ¹Department of Mechanical Engineering, University of Maryland, ²Department of Pathology and Laboratory Medicine, Robert Wood Johnson Medical School, University of Medicine and Dentistry of New Jersey, New Brunswick, NJ

Content:

Atomic force microscopy (AFM) is an emerging tool in biology. Using its unique nano-indenter AFM measures the elastic characteristics of biomedical materials. It has been shown to be sensitive to the presence of disease in cultured cells. In this pilot study we investigated the use of AFM to perform mechanical characterization of fixed breast tissue sections. A tissue microarray configuration was adopted in the experimental design to facilitate accurate sampling using an AFM probe.

Technology:

The AFM system consists of a micro-cantilever (Novascan Technologies Inc., Ames, IA, USA) of stiffness 2.5 N/m that is piezoelectrically controlled to deform tissue samples by a fixed amount (250 nm or 500 nm). Deformation in the sample causes the cantilever to deflect, which is optically sensed by a laser beam reflected from the back of cantilever. This deflection is related to the stiffness of the tissue probed by the AFM.

Design:

Two adjacent breast cancer tissue microarray slices, A and B, were sectioned from a microarray block and fixed onto glass microscopic slides. Slide A was stained with H&E and scanned using a high-resolution Trestle/Zeiss whole-slide imaging device. Resulting digital images were annotated by a board-certified anatomic pathologist to generate a template which would later be used to guide AFM sampling on slide B. This design allowed accurate probing for specific tissue components throughout the complex cancer tissue architecture.

Results:

These experiments showed that cancer tissue exhibited less stiffness than normal tissue, and that epithelial regions exhibited less stiffness than stromal regions. Statistical differences were highly significant. Cancer epithelial regions were significantly softer than non-cancer epithelial regions, which agreed with previous *in vitro* studies.

Conclusion:

Preliminary feasibility studies indicate that AFM can be used to objectively distinguish between normal and cancerous tissue and in discriminating among different subclasses of tissue in both cancer and benign specimens. One of the appealing aspects of the technology is that it does not require specialized staining or preparation of the tissues under examination. In the next stage of research we plan to build a prototype platform to investigate the use of this approach for performing high-throughput analysis and characterization of pathology specimens.

H&E Digital Staining From the Multispectral Image of a Specimen Stained With Hematoxylin Only

Mitsuyoshi, Tashiro, MS¹
(tashiro.m.ac@m.titech.ac.jp), Rie Yoshida¹,
Tomokatsu Miyazawa¹, Yuri Murakami¹, Masahiro Yamaguchi¹, Nagaaki Ohyama¹, Yukako Yagi²;
¹Tokyo Institute of Technology, Tokyo, Japan,
²Department of Pathology, Massachusetts General Hospital, Boston, MA

Content:

Recently multispectral image (MSI) analysis has been developed and expected as a validity tool for pathological diagnosis support. Some methodologies of digital staining for pathological tissue samples were proposed using spectral information. We confirmed tendency of spectral changes between nuclear and cytoplasm tissue in a same single stained slide. Then in this paper, a digital staining method is proposed for producing Hematoxylin and Eosin (H&E) stained image from a specimen stained with Hematoxylin only (H-only).

Technology:

In the digital staining, the transmittance spectrum is estimated from MSI, and the amount of dye is calculated based on Beer-Lambert law, for each pixel from H-only stained tissue. At this time, the spectral absorption coefficients (SAC's) of H pigment in nucleus and cytoplasm are considered to be different. Thus we measure SAC's of H dye in both nucleus and cytoplasm, and apply least mean technique for estimation of the dye amount of each element. In reproducing scheme, the SAC of Eosin is used instead

of H in cytoplasm, and the spectral absorbance of digitally stained image is calculated based on the Beer-Lambert law. Then we can obtain the spectral transmittance of the H&E digitally stained image, and a color image is obtained with using the color matching function of human vision.

Design:

In this experiment, a multispectral imaging system was utilized to capture the 16-band image in 2000 x 2000 pixels. The system is composed of a CCD camera, 16 band rotation filters, a conventional optical microscope Olympus BX-62 with an objective lens of 20 fold where the light source is a halogen lamp, and a PC based image capturing and displaying unit. Specimens stained with H only were captured by this system and the proposed technique was applied to the 16-band images.

Result:

In preliminary experiments, we compared the dye amount images of H only and H&E stained image. The result shows the tendency of dye amount images are similar. Then a color image of H&E digital staining was generated from the dye amount images of H in nucleus and H in cytoplasm.

Conclusion:

We proposed a H&E digital staining method from H-only stained tissue and the result shows the possibility of the digital staining technique.

Identification of Transcriptional Regulators Associated With a Novel IGF-I Ligand Gene Signature in Breast Cancer

David Tuck, MD^{1,2}, Sudhir Perincheri, PhD¹; Lina Mu, MD⁷, PhD; Emad Ramadan, PhD²; Emmett Sprecher², Vince Schulz, PhD⁵; Dionyssios Katsaros, MD, PhD⁶; Herbert Yu, MD, PhD⁴, Lyndsay Harris, MD³;
¹Yale Center for Medical Informatics, New Haven, CT; Departments of ²Pathology, ³Internal Medicine (Medical Oncology) and ⁴Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT; ⁵Yale Center of Excellence in Molecular Hematology, Yale University School of Medicine, New Haven, CT; ⁶Department of Obstetrics and Gynecology, Gynecologic Oncology and Breast Cancer Unit, University of Turin, Turin, Italy; ⁷Department of Social and Preventive Medicine, School of Public Health and Health Professions, Buffalo, NY.

Content:

Insulin Growth Factor 1(IGF1) signaling mediated by the Insulin Growth Factor Receptor (IGF1R) plays an important role in cellular proliferation and apoptosis. Creighton *et al* recently published an IGF1R-activated gene signature that is highly correlated with poor

prognostic factors in breast cancer. In contrast, it has been shown that higher IGF1 levels were associated with better outcome in a cohort of women with newly diagnosed breast cancer. In order to clarify the role of IGF1 levels and IGF1R activation in breast cancer, we analyzed gene expression profiles from breast tumors whose IGF1 levels had been previously characterized.

Technology:

Microarray data was generated using the Illumina HumanRef8 platform. Statistical analyses were performed using the SAS software (Version 9.1) or the R package (<http://www.r-project.org>).

Design:

Gene expression profiling was done on tumors that were surgically resected in the department of Gynecologic Oncology and Breast Cancer Unit at the University of Turin from two hundred and four primary breast cancer patients who were regularly followed after adjuvant therapy. An ethical review committee at the university approved the study. Genes differentially expressed among patients with high, intermediate or low IGF1 mRNA expression were identified. Statistical analysis was done to determine the association between the IGF1 signature and disease outcome. A motif module methodology was used to identify significantly enriched transcription factor motifs by comparing the profiles of IGF-high to IGF-low patients.

Results:

Findings showed that IGF1 levels were strongly anti-correlated with the IGF1R activation signature. Statistical analyses showed that a gene signature differentiating low, medium and high IGF-1 ligand groups is a predictor of improved outcome in several independent breast cancer datasets. Fifteen transcription factor motif modules with significantly enriched targets in IGF signature high compared to IGF signature low patients were identified.

Conclusions:

The IGF1 gene signature is a predictor of improved outcome in breast cancer and should be factored in therapeutic attempts to target the IGF1R. Significant subsets of the enriched transcription factors have well defined roles in regulating cellular proliferation. Functional analysis of the enriched transcription factors may further delineate deregulated pathways in breast cancer.

Automated Ordering and Resulting of Laboratory Tests: Technical Design, Limitations and Benefits

Joseph Mark Tuthill, MD
(mtuthill1@hfhs.org), Lisa Dwyer, MT(ASCP), Gaurav

Sharma, MD; Department of Pathology & Laboratory Medicine, Henry Ford Hospital, Detroit MI

Context:

Periodic validation of test ordering and result reporting in a laboratory information system (LIS) and its receipt with appropriate display by receiving systems is a regulatory requirement. Pathology Informatics (PI) support staff are increasingly challenged to perform comprehensive testing. Automated software testing applications have emerged as a viable alternative. In 2004, PI purchased an automated software testing application to accomplish this task.

Technology:

LIS: Sunquest Laboratory™ v6.3 (Sunquest Information Systems, Tucson, AZ)
Workstations: Three Dell Optiplex 745 (Dell, Roundrock, TX) running Microsoft Windows XP sp 2 Quality Advantage™ Lab Volume and Scenario Solutions (Software Testing Solutions™, Tucson, AZ)
Remote Connection: PC Anywhere v11.5 (Symantec™, Cupertino, CA)

Design:

Three workstations configured with Windows XP sp2, a static IP address, and PC Anywhere. Two workstations are installed with the Quality Advantage™ Laboratory Scenario Testing and Laboratory Volume Testing Solutions. The third workstation is installed with the Quality Advantage™ Blood Bank Scenario Testing Solution.

Results:

Profiles were created to order/result a subset of the laboratory test menu and send to six different departmental applications. The product has been used during implementation and/or upgrades, calculation review for ninety-eight worksheets and lab web portal validation. It took 3.5 minutes for an analyst and 4.5 minutes for the software to order, result, and screen shoot the average order code. However, the analyst performed this activity during business hours in addition to other duties, were often interrupted and needed breaks. The automated software could be scheduled to run after hours or on weekends and could be remotely operated. PI estimated that 266 man hours were saved during the first five months of 2009 resulting in a \$6100 cost savings.

Conclusion:

Overall, the technology had a good return on investment (ROI) and improved quality of testing. Limitations included capital investment, yearly maintenance fee, time intensive test profile setup, and one user per workstation. Benefits included creation and comparison of comprehensive

customized profiles for different testing scenarios and availability of detailed documentation for regulatory agency inspections.

Use of Digital Image Capture System with Annotation and Measurement Capabilities in Anatomic Pathology: Technical Design, Benefits and Challenges

Joseph Mark Tuthill, MD (mtuthill1@hfhs.org), Gaurav Sharma, MD, Dhananjay Chitale, MD; Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI

Context:

Accurate description of gross appearance and measurements of surgically resected specimens is an integral part of anatomic pathology reports. Gross photographs with annotation of sections and diagrams provide invaluable information during review of slides and re-sampling of specimens. For certain specimen types (example breast lumpectomy) entire specimen may be submitted and topographic information is needed for location of lesion and status of margins. Considerable interobserver variability exists in quality and annotation on images and diagrams. We implemented a user-friendly, high-resolution automated digital image capture system (ADICS) with the aim of providing accurate easily accessible information for pathologists.

Technology:

Laboratory Information System (LIS): Sunquest CoPathPlus, Ver 4.0 (Sunquest Information Systems, Tucson, AZ) ADICS: MacroPath D (Milestone S.r.l. Sorisole, Italy) on Intel Pentium 4 (2.2 GHz, 60 GB hard disk) with Windows XP Professional (Microsoft, Redmond VA).

Design:

Pre implementation, specimen images were captured using digital cameras at the grossing stations and diagrams with section annotations were hand drawn and manually scanned. These were uploaded to a network shared drive in case specific folders and accessed by pathologists at the time of case sign-out. Measurements and gross descriptions were dictated in the report. Post implementation, specimen images were captured on ADICS and the sections and measurements were annotated on system screen. The original image and copies with annotations and measurements were automatically saved in case specific folders.

Results:

ADICS combined 6 processes including hand-drawing diagrams, scanning, creating folders and uploading images case folders (example: 15-20 minutes for a

lumpectomy) and reduced the number of lost images. High quality annotated images provided better topographical information on size and location of lesion with margins and aided re-sampling if needed.

Conclusion:

Single process by ADICS with annotation abilities dramatically reduced the turnaround time at the grossing station with improved efficiency. The benefits of implementing this system in a high volume surgical pathology laboratory outweigh the investment, improve workflow and provide accurate, accessible gross examination information to pathologists complementing final reports including future teaching and clinical purposes. Challenges include the initial capital/ maintenance cost and user training time.

Henry Ford Pathology and Laboratory Medicine Department Website: Evolution from Department Website to Laboratory Portal

Joseph Mark Tuthill MD (mtuthill1@hfhs.org), Gaurav Sharma MD, Jackie Ribbentrop; Department of Pathology and Laboratory Medicine, Henry Ford Hospital, Detroit, MI

Content:

Over the last five years the Henry Ford Department of Pathology and Laboratory Medicine website has evolved from simple web pages to a combination of informational pages and forms and an access point (portal) to web applications that include:

- Lab test ordering and resulting portal (LP)
- Biomaterial repository (BTM)
- Telepathology (TP)
- Laboratory users guide, (eLUG)
- Learning management system (LMS)
- Document management system (DM)
- Links to our helpdesk, forms and surveys
- Customer focused pages including an area for residents

Technology:

Internet Explorer (Redmond, WA)

Web servers: VMware clustered (Hewlett Packard, Palo Alto, CA); Apache TomCat (Los Angeles, CA) and Microsoft IIS 6.0

Web Design: [SiteMaker](#), [Medseek](#) (Birmingham, AL)

BTM: Daedalus software Inc. (Cambridge, MA)

LMS: Healthstream Inc. (Nashville, TN)

LP: Labworks, Atlas Development Corporation (Calabasas, CA)

TP: Mirax AT, Carl Zeiss (Thornwood, NY)

Deployment:

A suite of tools and applications involving: multiple vendors, design and customer focus teams integrated through the portal. Vision: our departmental web site would evolve to become a portal to key applications and information. Common design element: selection of web based applications from vendor partners that allow functions to be integrated into our department web portal. This is critical as we expand from a stand-alone laboratory to an integrated product line across eight hospitals and 33 medical centers across 300 square miles.

Results:

The web portal and associated applications are widely accessed by a variety of customers including the 600 employees of the PALM, physicians, nurses and residents. Some areas experience thousands of hits per week with hundred of unique sessions on the included applications. Usage and penetration of these tools are increasing weekly.

Conclusion:

The site continues to evolve providing single point of entry allowing easy access to PALM information technology services for our employees and customers.

Geometric Approaches For Cancer Detection and Classification Based on Nuclear Structure

Wei Wang, MS (wwang2@andrew.cmu.edu),
John A. Ozolek, MD Dejan Slepcev, PhD, Gustavo K. Rohde, PhD, Carnegie Mellon University, Pittsburgh, PA

Context:

Visual interpretation of histopathology images is the most common method used in diagnostic pathology. Many lesions, both benign and malignant, can be difficult to distinguish from one another based solely on histomorphological grounds and expensive studies may be required. Our study shows that geometric approaches are superior to feature-based methods for discriminating between differential diagnoses in certain pediatric liver tumors and thyroid tumors based on nuclear structure (size, shape, chromatin pattern) from digital images.

Technology:

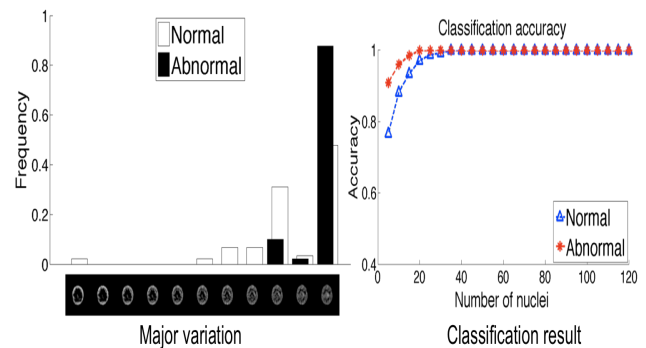
Nuclear segmentation from digital images is performed using a hybrid level set and graph cut method. Classification is performed by quantifying similarities in a group of nuclei to groups of nuclei in a trained database. Group (distribution) distances are computed using novel geometric approaches (based on optimal transportation distances) as well as more commonly used numerical features.

Design:

Analysis was performed on 9 cases of normal and cancers (five hepatoblastoma, two thyroid follicular adenoma and two follicular carcinoma). Representative fields of Feulgen stained sections from routinely processed tissues were imaged at 1000X magnification. Our geometric approaches are able to automatically classify this data with 100% accuracy using both case-based and randomized blindfolded cross validation strategies.

Results:

The figure (right) shows the detection rate for normal and hepatoblastoma as a function of number of nuclei used to perform classification (40 nuclei are needed for perfect classification accuracy). The histogram (left) represents the number of nuclei in each population (normal vs. hepatoblastoma) most similar to the geometric path (provided by the optimal transportation metric) shown at the bottom. The figure also indicates that it is uncommon for hepatoblastoma nuclei to have chromatin concentrated around the edge of the nucleus.



Conclusions:

We propose a novel computer-assisted method for cancer detection and classification based on quantifying distributions of nuclei over mathematical geometries. Validation of our approach with the test data available demonstrated that our methods can distinguish between normal liver and hepatoblastoma and follicular adenoma and follicular carcinoma with 100% accuracy. In addition, our approach can be used to define unique nuclear "signatures" for individual tissues and lesions.

Unified Modeling of Image Annotation and Markup

Fusheng Wang, PhD¹
(fusheng.wang@emory.edu), Tony Pan¹, Tahsin Kurc¹, Ashish Sharma, Joel Saltz, MD, PhD¹, Wenjin Chen, PhD², Vicky Chu², Jun Hu², Lin Yang², David J.

Foran, PhD²; ¹Center for Comprehensive Informatics, Emory University, Atlanta, GA, ²Center for Biomedical Imaging & Informatics, The Cancer Institute of New Jersey, New Brunswick, NJ

Content:

We report our progress on the development of a unified image markup and annotation model to standardize observational and computational descriptions of image features for both radiology and pathology/microscopy images. The objective is to develop a generic and unified data model that enables both syntactic and semantic interoperability for sharing image interpretations in healthcare and clinical trial environments.

Technology:

Image annotation and markup on microscopy images differs from the one on radiology images in several ways: i) more complex microenvironment structures with biological and spatial relationships; ii) different image metadata and additional specimen information; iii) annotations at multiple granularities; iv) new pathology concepts and measurements, and v) more complex geometric shape types for representing pathology annotation targets. We develop the data model through adjusting and extending the caBIG Annotation and Image Markup (AIM) data model, and integrating the Core component developed from ImageMiner data model. We leverage NCI Enterprise Vocabulary Service to describe semantic pathology and biology concepts for annotations.

Design:

The data model consists the following major components: ImageReference, ImageProvenance (the set of information that describes the source of the image, including specimen, equipment, patient, user, group, and the anatomic hierarchy), Annotation (annotation on a target within the image), and AnnotationProvenance (the data analysis process that generates the annotation or markup). An Annotation consists of markup, geometry, feature and assessment, and relationships to other Annotations. AnnotationProvenance captures algorithm and its parameters which generate the annotation results. Attributes used for features and assessments majorly come from the vocabulary, and can also be user defined.

Results:

We have performed a requirement analysis based on a variety of use cases, including tissue microarrays and TCGA Glioblastoma, and developed a preliminary conceptual data model. We are currently aligning the model to AIM and adjusting AIM with revised structures and several new classes.

Conclusions:

Extending AIM data model to support pathology/microscopy not only provides immediate benefit on sharing image information, but also bridges the gap between radiology imaging community and pathology imaging community. Our initial work provides a starting point. Community use cases and requirements are needed for the enrichment of the data model.

wuTissue: Adoption and Use of caTissue Suite in a Multi-Repository Academic Environment

Mark A. Watson, MD, PhD
(watsonm@wustl.edu), Rakesh Nagarajan, David A. Mulvihill; Washington University School of Medicine, St. Louis, MO

Content:

Advances in molecular technologies and clinical trial design have mandated new requirements for the operation of biorepositories. caTissue Suite v1.1 is a caBIG™ application designed to manage the associated complexities of biospecimen annotation data and features new functionalities needed for operation in a multi-repository environment.

Technology:

JBOSS 4.2.2 GA (Red Hat Middleware, LLC); JAVA Development Kit 1.5 (Sun Microsystems, Inc); **Apache Ant 1.7** (The Apache Software Foundation); **MySQL 5.0.45** (MySQL Inc.); Oracle 10.2.0.2.0 (Oracle Corporation); caGRID 1.2 (caBIG®).

Design:

caTissue Suite is an n-tiered application. A web browser submits requests to the application server, which in turn persists or acquires data in a relational database. A JAVA-based Application Programming Interface permits more advanced, automated, and customized access to all of the application's features. The application supports administrative functions (protocol and storage system definition), biospecimen accessioning (including provisions for consent tracking and iterative biospecimen derivation and aliquoting), and investigator queries (advanced query creation and specimen requisition system). A caTIES-like interface allows for import and concept coding of textual based pathology data, and discrete pathology and clinical data entry is support through customized form creation.

Results:

A single instance of the system is tracking tumor biospecimens in the Siteman Cancer Center Tissue Procurement (Tumor Bank) Facility, and more

recently, is being used to track specimens in the Kidney Translational Research Core, the Alzheimer's Disease Neuropathology and Neurogenetics Cores, and several smaller, independent biorepositories within the medical school. In all, eight different repository sites are now represented in the system, which includes approximately 250,000 specimens from 39,000 participants enrolled in 250 protocols.

Conclusion:

To facilitate data sharing, a de-identified, publicly and grid-accessible mirror instance of the system is maintained and updated weekly with production data. We are continuing to integrate inventory data from other biorepositories within our institution. Six new repositories are currently engaged at various points in this process, which includes regulatory and data sharing policy review, laboratory workflow analysis, legacy data mapping activities, data staging and migration, and end-user training and acceptance. Each of these steps poses unique challenges.

One-Stage and Two-Stage Models for Compressing Pathology Image Slides

Saunya M. Williams¹ (saunya@gatech.edu), Sourabh Khire¹, Nikil Jayant, PhD¹, Alexis B. Carter, MD², Uday Srinath¹; ¹School of Electrical and Computer Engineering, Georgia Institute of Technology, Atlanta, GA, ²Department of Pathology and Laboratory Medicine, Emory University, Atlanta, GA

Context:

While mathematical losslessness (ML) in image compression provides maximum fidelity in digital pathology, pervasive digital practice may need a higher level of compression. To this end, we proposed the criterion of diagnostic losslessness (DL) at APIII 2008, with expert-specified diagnostic quality guiding the degree of compression. We extended the DL-idea, focusing on the total bits needed for digitizing pathology images in the alternative approaches of one-stage and two-stage compression.

Technology:

SPOT Digital Cameras (Diagnostic Instruments, Inc) were used to capture uncompressed images from slides of morphologically distinct lesions. Multiple versions of each digital photomicrograph were created using JPEG and JPEG 2000.

Design:

To create a workflow model, we defined another level of compression: Perceptual losslessness (PL), which is not as stringent as DL, but provides adequate image quality to locate a region of interest (ROI) in a pathology image or to identify prominent within-ROI

features. As a pilot study, one pathologist annotated images with ROIs needed for diagnosis. Two levels of magnification, low (XL) and high (XH), as well as the fractional area F of the ROI in an image were postulated and applied to two models: (1) a 1-stage model where the entire image is represented at XH and compression level of DL, and (2) a progressive 2-stage model where (i) the entire image is represented at XL and at the compression level PL (preserving ROI), followed by (ii) a second stage where the ROI is represented at XH and compression level of ML (or DL). The bit-efficiencies of the models are compared as a function of ML, DL, PL, XH, XL and ROI fraction F .

Results:

Analytical results were obtained for the number of bits needed (and therefore the time taken) to represent a digital slide in each model. For $ML=2:1$, $DL=10:1$, $PL=60:1$, $XH=40x$, and $XL=10x$, the 1-stage model was seen to be bit-rate-competitive with, but not always more bit-efficient than, the inherently economical 2-stage model, depending on the ROI fraction F .

Conclusion:

The 1-stage model is viable from an information viewpoint, while offering better workflow by not needing expert intervention for ROI detection.