Short Abstract Presentations

Thursday, May 7, 2015

8:00 am – 9:00 am

Locations:

Wyndham Grand Pittsburgh Hotel

Grand Ballroom 1

King's Garden 1

King's Garden 2/3

Brigade Room

Imaging Informatics
Ballroom 1

From Two to Three Dimensions in Digital Pathology: Three-Dimensional Analysis And Volume Rendering Using Routine Histology Sections

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Content:
Pathologists render a diagnosis from thin tissue sections mounted on glass slides. The ability to then infer three-dimensional structure from these two-dimensional tissue sections is crucial for the diagnosis and full characterization of many disease processes. This is dependent on the skill and experience of the individual pathologist. With advances in digital methods, it is now feasible to have a new workflow in which pathologists are presented with aligned whole slide images (WSIs) of serial sections. We are developing web-based tools for aligning and viewing WSI datasets generated from renal needle core biopsies as our test system. The expectation is for faster evaluation, greater objectivity, and improved diagnostic accuracy.

Technology:
Serial sections from renal needle core biopsies were scanned at x40 using a Philips Ultra Fast Whole Slide Scanner. The WSIs were viewed using our high performance web-based client server system (https://slide-atlas.org). Tools were developed for local adaptive alignment of the WSIs and incorporated into Slide Atlas. Aligned WSIs are displayed side by side, and can be quickly manipulated and stepped through to find a region of interest that can be compared simultaneously in adjacent sections. Alignment information is stored with the images and applied interactively for display. Precise alignment is computed and maintained at different zoom levels. Structures of interest (e.g. glomeruli, tubular deposits) can be segmented and volume rendered.

Design:
Serially sectioned renal needle core biopsies received in the routine diagnostic workflow were stained with our standard panel of histochemical stains and then digitized. Serial sections (up to ~70 per biopsy) were aligned, inspected and structures of interest segmented, extracted and volume rendered.

Results:
The serial WSIs from renal biopsies can be aligned, and the algorithms can compensate for artifacts intrinsic to paraffin-processed tissue. Alignments can be made from a few or many serial WSIs, creating "short" and "long" image stacks. Large regular structures such as glomeruli as well as variably sized and irregular tubular crystalline deposits can be aligned, segmented and rendered into three-dimensional structures.

Conclusion:
Serial WSIs from routine specimens can be can be aligned and viewed, facilitating three-dimensional analyses.

Biomarkers for pancreatic cancer--Identification through meta-analysis and validation on tissue microarrays utilizing digital pathology for potential clinical application

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Content:
Pancreatico-biliary adenocarcinomas (PBA) have a poor prognosis. Diagnosis is usually achieved by imaging and/or endoscopy with confirmatory cytology. Cytological interpretation can be difficult especially in the setting of chronic pancreatitis/cholangitis. Immunohistochemistry biomarkers could act as an adjunct to cytology to improve the diagnosis. Thus, we performed a meta-analysis and selected KOC, S100P, mesothelin and MUC1 for further validation in PBA resection specimens.

Technology:
Hamamatsu (Japan)
- NanoZoomer Digital Pathology Scanner Leica Biosystems (UK) Ltd and SlidePath (Dublin, Ireland)
- Digital Image Hub
- Distiller (Slidepath Digital Slide Solutions)

Design:
Tissue microarrays containing tumour and normal cores in a ratio of 3:2, from 99 surgically resected PBA patients, were used for immunohistochemistry. Immunohistochemistry was performed on an automated platform using antibodies against KOC, S100P, mesothelin and MUC1. Stained slides for each antibody were scanned in NanoZoomer Digital Pathology Scanner and uploaded as dynamic digital images in Digital Image Hub and Distiller. Tissue cores were then digitally scored for staining intensity and proportion of tissue stained using Histoscore method (range, 0–300). Sensitivity and specificity for individual biomarkers, as well as biomarker panels, were determined with different cut-offs for positivity.

Results:
The expression of all four biomarkers was high in PBA versus normal ducts, with a mean Histoscore of 150 vs. 0.4 for KOC, 165 vs. 0.3 for S100P, 115 vs. 0.5 for mesothelin and 200 vs. 14 for MUC1 ($p < .0001$ for all comparisons). Five cut-offs were identified for sensitivity/specificity analyses, namely 5%, 10% or 20% positive cells, Histoscore 20 and moderate-strong staining intensity using receiver operating characteristics curves. Using 20% positive cells as a cut-off achieved higher sensitivity/specificity values: KOC 84%/100%; S100P 83%/100%; mesothelin 88%/92%; and MUC1 89%/63%. Analysis of a panel of KOC, S100P and mesothelin achieved 100% sensitivity and 99% specificity if at least 2 biomarkers were positive for 10% cut-off; and 100% sensitivity and specificity for 20% cut-off. The panel approach was facilitated in Distiller.

Conclusion:
A biomarker panel of KOC, S100P and mesothelin with at least 2 biomarkers positive was found to be an optimum panel with both 10% and 20% cut-offs in resection specimens from patients with PBA.

DPIP – Digital Pathology Integrative Platform

Ilker Ersoy, PhD1,2; Mikhail Kovalenko, MSc1; Chi-Ren Shyu, PhD2,3,4; William Krause, PhD1; Donald Doll, MD5,6; Richard Hammer, MD1; Dmitriy Shin, PhD (shindm@health.missouri.edu) [1,2,3]

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Content:
We present Digital Pathology Integrative Platform (DPIP) that unifies Whole Slide Imaging (WSI) technology with web-based interactive WSI viewing, annotation, workflow/logic processing framework, gaze tracking and bio-objects detection and identification module to support educational and research tools in pathology informatics. Collected Human Computer Interaction (HCI) data facilitate best practices in learning/training experience and allows capturing visual diagnostic heuristics from WSI.
We demonstrate utility of DPIP using a WSI web-based interactive hematopathology atlas with game-like training workflow and WSI web-based interactive histology atlas, in which learning of histological structures is facilitated by their functional annotations.

Technology:
Aperio ScanScope CS was used to digitize glass slides. DPIP platform was developed in-house using Javascript and PHP technologies. Open-source based software such as "Openseadragon" viewer, "VIPS" library, "IIPImage" server were incorporated into DPIP using custom-built software.

Design:
DPIP consists of several software modules that are depicted in Figure 1. The first volume of hematopathology atlas was developed using DPIP based on 60 patient cases from Ellis Fischel Cancer Center, Columbia, MO and includes complete set of diagnostic materials such as H&E/IHC slides, flow cytometry, radiographs and patient history. Penalty-based diagnostic training scheme was developed for each of these cases.
The proof-of-concept version of the interactive histology atlas includes tissue images from male and female reproductive organs. Biological objects (cells, follicles, tissues, etc.) have been delineated and functionally annotated for training and research purposes.

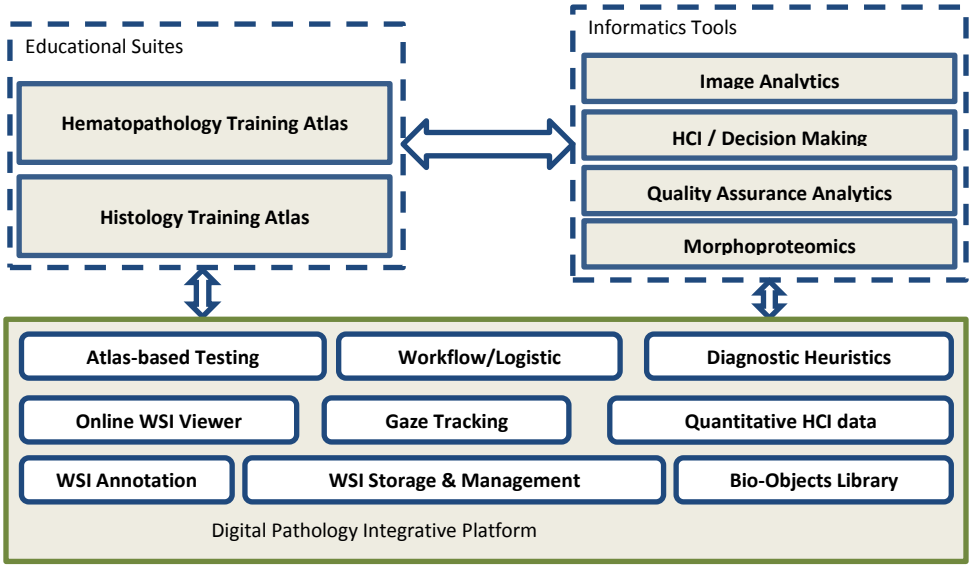

Figure 1. Digital Pathology Integrative Platform

Results:
DPIP-based educational suites were evaluated by hematopathology, oncology and histology experts and educators. There has been high inter-expert agreement that DPIP-based tools provide significant improvement over traditional WSI based educational and research resources. DPIP-based tools create a

synergetic effect that enables conducting trainee behavior analysis, expert vs. novice, specialist vs. generalist pathologist studies as well as WSI image analytics for pathology diagnosis and quality assurance purposes.

Conclusions:
We conclude that DPIP provides a means to build new generation of WSI tools where HCI data is exploited to design more effective applications for educational, research and clinical purposes.

Novel Label-Free Chemical Imaging for the Identification of Biomarkers of recurrent Diabetic Nephropathy

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Content:
Kidney transplantation is the main treatment for end-stage renal disease, however close monitoring of post-transplant biopsies is required to monitor and identify subclinical complications. In high risk patients surveillance biopsies are acquired approximately every 6 to 12 months post transplantation to examine tissue histology to find markers associated with complications. Recent technological advances in developing high resolution imaging approaches has allowed for the interrogation of the biochemical status of glomerular and tubular structures to identify markers of disease processes.

Technology:
We focused on identifying biochemical markers associated with recurrent diabetic nephropathy using the chemical imaging approach, Fourier Transform Infrared (FT-IR) spectroscopic imaging. FT-IR imaging is an emerging approach to obtain label-free images of the biochemical composition of tissue biopsies (including proteins, lipids, collagen, DNA and glycation).

Design:
A study was performed on native kidney tissues in order to identify biochemical markers associated with diabetic nephropathy. Serial sections were acquired and stained with PAS or imaged using chemical imaging. The histological parameters used for diagnosis was compared to the biochemical markers. Finally, a follow up studied was performed on renal transplant patients to replicate the first study.

Results:
Biomarkers were identified that were changed in renal structures associated with the progression of diabetic nephropathy, including increased levels of glycation. Using these two biomarkers alone, it is possible to diagnose the disease with specificity of 91% and sensitivity of 88%. In comparison, using the histological parameter, mesangial fractional surface area, alone gives a specificity of 82% and sensitivity of 89%. When all the biochemical information is used to diagnose the cases, we obtained a 100% specificity and 100% sensitivity. These biomarkers were found to be increasing in the cohort of transplant patients that underwent rapid diabetic nephropathy recurrence. In addition, the early biopsies from the patients that underwent later diabetic nephropathy progression were biochemically different from the non-progressive patients, suggesting that chemical imaging may identify pre-histological biomarkers that will predict outcome.

Conclusion:
We have demonstrated that a number of biomarkers are associated with the advancement of diabetic nephropathy and that we can track the early recurrence of diabetic nephropathy in surveillance biopsies.

Applied Pathology Informatics
Brigade Room

Critical Value Notification in Downstream Systems

Douglas J. Hartman, MD (hartmandj@upmc.edu)[1], Darlene Sutara[2], James Blumer[2], Shangcong Zeng[2], Anthony Piccoli[2], Richard Ambrosino, MD PhD[3]

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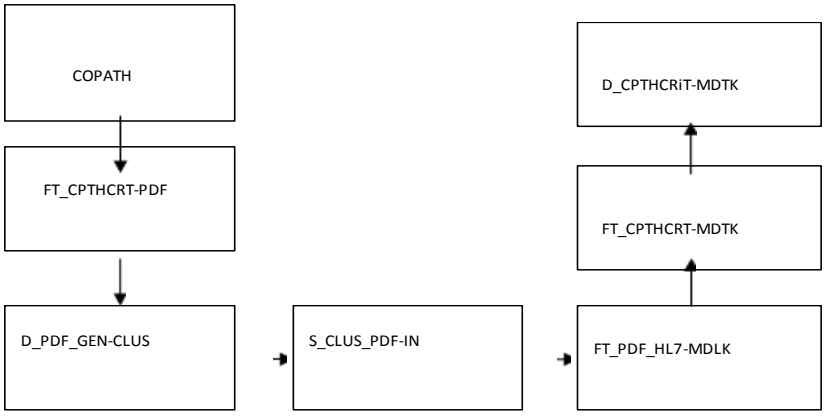
Content:
Criteria for values within anatomic pathology that constitute critical value results have been described. In the increasingly demanding field of medical delivery communication of critical values can be lost within the day-to-day demands of clinical service.

Technology:
We have identified a mechanism to notify the clinical teams when a critical value in anatomic pathology has been identified. The critical value is assigned within the Pathology Laboratory Information System (Cerner CoPath) by "TC66". We expanded a pre-existing structure for notifying clinicians of post-discharge lab values for notification of critical values in anatomic pathology.

Design:
We generated a signal within the headers of our outgoing anatomic pathology reports that could be parsed. Using the outbound HL7 report feed, the Message Router monitors the feed for the critical result indicator, TC66 using a string search. When encountered, Message Router directs this data to a separate flow. Key fields in the message are used to determine MedTrak logic: Attending Doctor Last^First Send as is; Referring Doctor Last^First Send as is; Consulting Doctor Last^First Send as is; Admitting Doctor #####^Last^First Send as is; Results Copies To ######^Last^First~ Send as is.

Results:
When the critical value string is identified, two things occur: a) the report content is formatted into a PDF based on a predefined template and b) the HL7 message is transformed into the agreed format for the notification system (MedTrak). A diagram of the process is below. The reformatted message is directed to MedTrak for delivery thru the Automated Notification process. Following is a visual of the process:



Conclusion:
This notification system represents an improved mechanism to notify clinicians when a critical anatomic value is identified. The solution for this problem required an interdisciplinary team of both medical directors and directors both within the originating system, the downstream systems and the notification systems. Future changes in healthcare are going to necessitate more projects across interdisciplinary teams such as this project to provide a safer healthcare environment, effective/efficient communication between clinical team members and optimize clinical care delivery.

An Open-Source Database Application for Clinical Pathology Consults

Patrick C. Mathias, MD, PhD, (pcm10@uw.edu)[1]; Cigdem H. Ussakli, MD[1]; Daniel S. Herman, MD PhD[1]; Sinan Ussakli[2]; Noah G. Hoffman, MD, PhD[1]

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Content:
Clinical pathology consults elicit valuable information about patients and laboratory tests that are not routinely captured in the electronic health record.
At our institution, clinical pathology consults are a significant service component of residency, so in 2004 we developed an online call database to capture resident effort and knowledge and serve as a resource when residents are consulted. Because of technical problems from its growth and outdated software components, we recently updated our database to achieve better performance and add new features.

Technology:
The revised database was built using open-source components. The application was built with a Python web framework called Flask (http://flask.pocoo.org) and used an Apache web server (http://httpd.apache.org) and a department-hosted PostgreSQL database (http://www.postgresql.org). We used our institution's pubCookie web authentication services combined with account management within the application to ensure appropriate levels of access for users. The application is available to download at https://github.com/compumaster/oncalldb and a demo is available at http://oncalldb.azurewebsites.net.

Design:
The primary functions of the database are to capture both structured and narrative on-call data, and to track progress of consultations. Based on resident input, multiple features were added: frequent auto-saving, robust full-text search, alerts indicating a patient has been previously consulted on, views of records without structured protected health information, commenting capabilities for faculty and other residents, tagging calls for classification purposes, and multiple user privilege levels.

Results:
More than 6000 resident consults have been logged since the new database went live in July 2013. Throughout the more than 1.5 years of use, there have been no unscheduled downtimes. More than 30% of calls were for resident approval of laboratory tests, and another 23% of calls were for clinical consultations. Other frequent categories of calls included transfusion reactions (13%), requisition clarifications (8%), and critical values (8%).

Conclusions:
We have built and deployed a freely available application to log resident consults that includes case tracking capabilities, auto-saving, full-text search, the ability to comment on cases, and multiple user privilege levels.

Utilizing structured data in pathology reporting for clinical flow cytometry

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Content:
Pathology reporting is well-suited to templating, due to the structured nature of the information being conveyed. For complicated reports, such as clinical flow cytometry, an underlying data structure is of great benefit compared to "fill-in-the-blanks" style templating, both in terms of ease of use for the operator as well as the ability to extend the system as new capabilities are added.

Technology:
A web-based interactive form was designed using HTML 5, Javascript, and the publicly available jquery library, with templates stored in custom XML files.

Design:
The form was designed with underlying data structures that included classes for flow cytometry markers, cell types, and marker panels. Interaction between the classes was modeled so that, for example, a description of B lymphocytes would only include the subset of markers performed that were relevant for that cell type. The class structures also included attributes that automatically generate diagnostic lines and interpretive comments.

Results:
The software tool was designed for use by pathologists reviewing the flow cytometry data. Emphasis was placed on the ability to generate reports with complex diagnostic lines and comments that were easily readable while minimizing the amount of effort required for report generation. Commonly encountered diagnostic scenarios (for example, a new diagnosis of acute leukemia) were included in a set of templates which would pre-populate fields in a manner depending on the other variables selected (such as the panels of tubes used). Extensibility of the system (for example, adding a new marker to a panel) was ensured via design of the data structures to allow addition or subtraction of new members without the need for major reformatting. The tool was placed into general clinical practice in July 2014. Users reported increased efficiency and reproducibility with no major drawbacks.

Conclusion:
As the information being conveyed in pathology reports grows increasingly more complicated, traditional synoptic-style reporting becomes less and less efficient as a method for generating reports in a templated manner. Although it requires a greater initial investment, designing custom data structures for a reporting tool greatly increases its utility for the user.

Developing a pseudo-bidirectional order entry interface using Lab Information System

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Content:
CPOEs ensure proper collection and exchange of patient's health data between laboratories and clinics and promote continuity of care. However, there is ongoing challenge of adoption by clinicians due to interruption to workflow. Customizing the order entry interface based on specific needs of practice routine process will improve the usability and increase adoption.

Technology:
LIS: Cerner Copath v2013.01.1.136 (Kansas city, MO, USA); Outreach vendor: 4Medica v15.10 (Culver City, CA, USA); Practice EMR: Athena v1.2 (Marina Del Rey, CA, USA)

Design:
The main objective of this work is to streamline the ordering process and result retrieval. We created a complete set of combined tests for pap smears and gynecology biopsies. A new set of part types was also built in LIS corresponding to test orders. The new part types contain both the test names and test codes. Our outreach vendor did customized programming to strip out the test names and codes and place them in target segments of OBR designated by EMR.

Results:
Clinician places the orders in EMR and prints the requisition. The lab accessions the received specimen in LIS using new part types. The result output includes part type name containing test name and code which will be parsed out. The returned test name and code values will link the result back to the original order and change the status of ordered test from "order" to "review result". When clinician checks the lab information, the result displays with exact label of original order with new status. Without this customization, the result would create a separate value with a general label such as "surgical pathology" or "cytology" which requires clinician to review the previous progress notes to find the original orders and open multiple reports to find the corresponding result.

Conclusion:
Flexible, customized order entry is the key to high adoption and successful implementation. We found the followings as the most important factors for the success of this project:
1. Focus on automating physician's ordering process
2. Customizing the design to improve efficiency
3. Minimize the impacts to ancillary workflow
4. Allowing for a flexible rollout strategy.

Imaging Informatics
King's Garden 1

Webpage Graphical Animations for Pathology Education

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Mercer University School of Medicine, Department of Biomedical Sciences

Content:
Animations to enhance health science education were added to webpages in general and organ systems pathology (http://library.med.utah.edu/WebPath/webpath.html). Selected webpages emphasizing educational constructs that could be enhanced with a simple graphical animation were modified. Constructs included pathophysiologic mechanisms of disease, diagnostic characteristics, and complications of disease.

Technology:
Graphical animations were developed with World Wide Web 3 (WWW3) guidelines for the HyperText markup Language version 5 (HTML5), Cascading Style Sheets version 3 (CSS3), and Scalable Vector Graphics (SVG) standards and coded into .html files with TexEdit 4.10 (http://www.tex-edit.com). The svg-edit-2.7 program (https://code.google.com/p/svg-edit/) was used with the Safari 7.1.3 web browser to develop the coding for SVG animations.

Design:
Standards to create the HTML5, CSS3, and SVG coding were taken from http://www.w3schools.com. A total of 150 animations were developed. Their display size ranged from 25 X 50 pixels to 200 X 250 pixels. Each of these animations was placed onto a single webpage adjacent to an existing gross or microscopic pathologic image of a disease condition. There were 50 animations utilizing either mouseOver or touch screen on a mobile device to initiate the animation. The animations were set to a play length between 1 to 9 seconds, and they could repeat indefinitely.

Results:
The animations required from 10 minutes to 1 hour each to develop. Webpage .html markup with the animation and uploading to the website server took less than 5 minutes per webpage. Learners using these webpages stayed on a webpage with animation an average of 20 seconds longer than pages with equivalent size of text and images without animation.

Conclusion:
CSS3 animations let a webpage element gradually change from one style to another. SVG can display complex, irregular shapes. These animations use coding created and edited with any text editor and presented via a common open source interface displayed via a web browser without the need for additional software or plugins. Animations can be added to webpages with minimal time and resources. Animations encourage active learning via interaction to lengthen attention span and hold learner interest on the page. Animations support conceptualization of visual models for learning.

Applied Telemicroscopy for Microbiology: Comparing the Accuracy of Whole Slide Images to Static Photomicrographs

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Content:
Telemicroscopy has the potential to improve the rapidity of microbiology-related consultations, but the optimal imaging modalities have not been thoroughly investigated for this application, particularly in regard to interpretive accuracy. This study compares 40x whole slide imaging (WSI) and static photomicroscopy for telemicrobiology.

Technology:
The Aperio XT system (Leica Biosystems, Nussloch, Germany) was used for 40x WSI acquisition. An Olympus (Center Valley, Pennsylvania, USA) system (BX46 microscope, DP73 camera, cellSense Standard 1.11 software) was used to obtain digital photomicrographs.

Design:
Four evaluators (pathologists and clinical microbiologists) each evaluated 30 microbiology-relevant slides using 3 modalities: 40x WSI, representative 10x and 100x static digital photomicrographs, and glass slides. A minimum 2 week wash-out period was employed between evaluations. Various specimens (cytology, histology, laboratory preparations) containing viruses, bacteria, mycobacteria, fungi, parasites, and negative controls using different stains were studied. Evaluators provided a diagnosis and assessed the imaging technology for all cases. Statistical analyses were performed using two-tailed Student T-tests in Microsoft Excel 2010 (Redmond, Washington, USA).

Results:
Diagnoses using glass slides and static images were more accurate than 40x WSI ($p=0.02$ & 0.03, respectively). Diagnostic accuracy using glass slides and static images were equivalent ($p=0.83$). Evaluators perceived image resolution and focus to be limiting factors in photomicrographs and WSI. False negative interpretations occurred less frequently when using static images (3%) than glass slides (8%) or 40x WSI (7%).

Conclusion:
Image resolution and suitable focus appear to be limitations of digital imaging for telemicrobiology. If photographed appropriately, the accuracy of static telemicrobiology is comparable with glass slide analysis. For telemicrobiology, the diagnostic accuracy of 40x WSI is inferior to using representative static images. Better imaging technology is required to facilitate telemicrobiology.

Google Glass Imaging Modality for Integrated Gross Pathology Workflow

Jeffrey Taylor[1], Brian Kolowitz[1], Ishtiaque Ahmed[2], Anil V. Parwani[2], Liron Pantanowitz[1]

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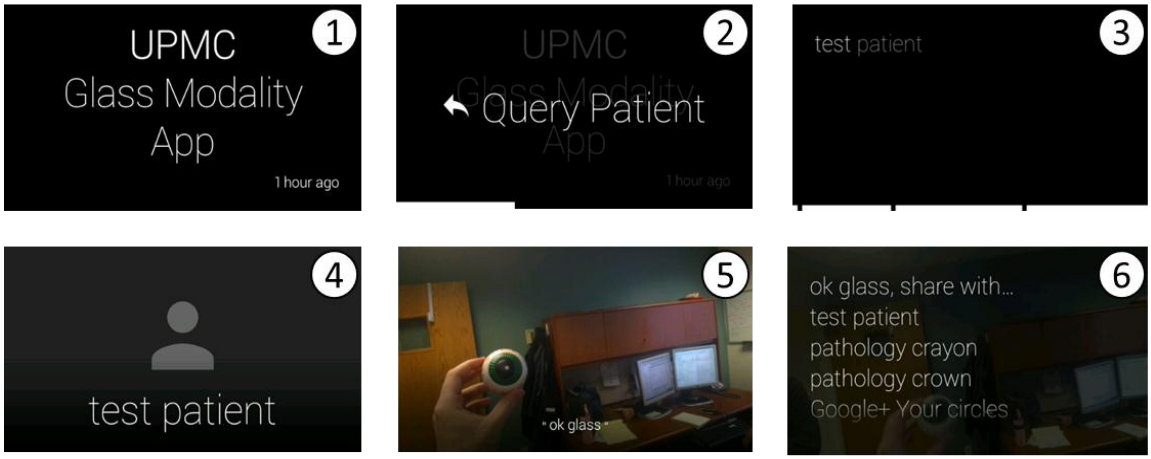
Content:
Google glasses (Glass™) have great potential in healthcare. Several proofs of concept have been tested such as enhanced patient interaction, telemedicine and education. Glass has also been used for telepathology. Current imaging in gross pathology requires a hands-on approach, cameras capable of macrophotography, and computers to import captured images into the laboratory information system. Our aim was to use Glass to develop a hands-free imaging modality integrated into gross pathology workflow.

Technology:
Google Glass (explorer prototype) device. Glass web application program interface (HTML5, CSS, JavaScript, Google Glass Mirror API). Glass application server (Microsoft .Net 4.5, Microsoft ASP.Net MVC 3, Google Glass Mirror API, Object Store API, Patient & Exam Query API).

Design:
Using Google Glass connected to Google cloud a user activates our Glass Modality App inside the glass display (Figure). Using a Glass App Server the user can query a patient by searching the master patient index on our local institution server. After saying "ok glass" to take a snapshot, the static image with associated metadata is then stored in the laboratory information system.



Results:
Through the use of our Glass Modality App, a user is able to capture and upload pathology images acquired with the wearable Glass device into a patient's electronic record by means of voice commands.

Conclusions:
The Glass Modality App is useful in situations such as grossing where the user cannot use their hands, mobility and point-of-view are beneficial, and static images of gross pathology are needed. These custom interfaces allow abstract query of patient and metadata, storage of captured images using the Glass device, and integration with the laboratory information system.

Independent, Student-Led Software Engineering at a Free Medical Student-Run Clinic: Pathology Informatics Leads the Way

Timothy Kennell Jr., BS (tikenn@uab.edu)[1]; Omar Ramadan, BS[2], L. Nicholas Herrera, BS[2], Nathan Haywood, BS[2], Jae Sung, BS[2], Robin Lorenz, MD, PhD[1]; Seung Park, MD[3]

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Content:
In this era of Big Data in medicine, independent software engineering capabilities have emerged as key drivers of health care innovation. While many student-run clinics have informatics committees, few have the infrastructure and support that would allow for meaningful clinical software engineering. Creation of such infrastructure, as well as training of students to serve in software engineering roles, therefore became a key focus for our clinic in academic year 2014-2015. In this abstract, we present the one-year impact that pathology informatics has had at our institution's student-run clinic.

Technology:
Server Hardware: Dell PowerEdge 2590; Host Virtualization Hypervisor: VMWare ESXi 4.1.0; Guest Operating System: Ubuntu Linux Server 14.04 LTS 64-bit; Web Server: nginx 1.7; Database Management System: MariaDB 10.0; Server-Side Programming Language: PHP-FPM 5.5; User Interface Library: Twitter Bootstrap 3.3.

Design:
We designed and led a one-week-long boot camp in clinical informatics and software engineering. The students performed a survey of the informatics landscape at our clinic, identifying unmet needs and engaging with stakeholders. We chose to design and implement a custom, Web 2.0, real-time volunteer signup, tracking, and training management platform as the first critical subsystem of a future laboratory information system and electronic medical record.

Results:
Within one year of the boot camp, under pathology informatics faculty guidance, the students designed, built, and deployed the platform. 100% of users have converted over, and greater than 30% of users take advantage of the smartphone-optimized layout. It has reduced clinic coordinator burden from 20+ hours/week to under 1 hour/week, and has driven down human error in scheduling. Furthermore, our underlying databases have been increasingly useful for advanced analytics.

Conclusion:
Pathology Informatics has set the vision and led the way for an informatics and Big Data-driven future at our institution's student-led clinic. In one year we have gone from using off-the shelf, ill-fitting software systems to generating our own custom solutions. Our finalized platform is an integral part of our clinic's patient care. This effort shows the utility of informaticist-supervised student software engineering both as a learning opportunity and as a driver of cultural change.

Advanced Pathology Informatics
King's Garden 2

A New Theory of Reference Intervals Based on Clinical Risks

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Content:
Reference intervals are usually determined by statistical methodology unrelated to clinical outcomes: a "healthy" cohort's central 95% of test values are the "Reference Interval"; others are "Low" or "High". Methodological problems include defining "healthy" and illogic of flagging outer values when entire cohort is *defined* as healthy. These problems arise from methodology established before modern electronic medical records (EMR). We seek replacement methodology from perspectives of informatics.

Technology:
Data extracted from AllScripts SCM version 5.0 (Sunrise Clinical Manager); statistical analysis performed with JMP version 11.2.1 (SAS Corporation, Cary, NC).

Design:
We extracted discharge dispositions; laboratory test results and demographics for 375,747 adult patient admissions at Sarasota Memorial Hospital (Florida). Similar smaller extracts were obtained from an academic medical center (Northeast USA) and a regional hospital (Southwest USA). For each analyte, we calculated an Outcome Risk function:
$OR(x) = (ONO_{within \cdot x}) / (ONO_{without \cdot x})$
where $ONO_{within \cdot x}$ ‥‥odds of *Negative Outcome* for test results within ·*x;*
$ONO_{without \cdot x}$ = odds of *Negative Outcome* for results not within ·*x;*
x = mean value of test results within an interval ·*x;*
Logistic regression, adjusted for confounding variables, determined final OR(x) for each analyte .

Results:
Risks of both mortality and unfavorable discharge are below average within intervals reported in Table 1. Further, this approach provides clinical risks (e.g.,mortality odds ratios) for values outside cut-points. Concurrence was found with other Negative Outcomes (e.g., 1-year post-discharge mortality), and among various medical centers.

Conclusions:
We devised novel method to associate risks of negative patient outcomes, independent of diagnosis, with analyte test values. Clinical risk analyses determine reference interval cut-points and quantitative risks beyond them. In first approximation, outcome risk functions and cut-points can be calculated by spreadsheet in the lab from readily available EMR data.

Table 1. Risk-based Reference Intervals for Common Analytes

Analyte	*Standard Reference Interval*	*Risk-based reference interval (95% C.I.)*
Potassium	3.5 - 5.1 *mEq/L*	3.3 (-0.4,+0.1) - 4.4 (±0.1) *mEq/L*
Sodium	136 – 145 *mEq/L*	135 (-0.2,+0.7) - 142 (±0.1) *mEq/L*
Chloride	94 – 110 *mEq/L*	100 (±0.1) - 109 (-0.8,+0.2) *mEq/L*
BUN	7-18 *mg/dL*	0 (+4,-0)-24 (±1.0) *mg/dL*
Creatinine	0.5-1.4 *mg/dL*	0.6 (±0.1)- 0.9 (±0.1) *mg/dL*

Use of no-SQL data model to address complexity of Tumor DNA sequencing analysis.

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Context:
Tumor DNA Sequencing generates complex datasets that require even more complex phenotype annotations. Adequate data models are critical for efficient storage, retrieval, exchange, and rapid understanding of interrelationships between various data elements that come from a range of sources used in bioinformatics pipelines and in pathological evaluation of variants. Relational models that have been dominating systems design for the last 30 years have been criticizes for being too rigid, too fragmented, and incongruent to the needs of service oriented information exchange. No-SQL databases and document-based principles of data modeling may be more suitable to support the needs of molecular pathology.

Technology:
MongoDB – a modern no-SQL database was used to store data for Downstream Reporting software - a Java based reporting tool that integrates Anatomic Pathology LIS, bioinformatics pipelines, and external resources such as Pubmed, Enembl, OMIM, KEGG, GeneCards, and Uniprot via RESTful API to facilitate creation of Pathology Reports for Tumor DNA Sequencing tests.

Design:
MongoDB provides storage for "Downstream Reporting" – a web application deployed on Apache Tomcat servlet container. Users of the system upload results of two parallel bioinformatics pipelines to filter artifacts, select and annotate driver mutations, and generate molecular pathology reports. Four core tables and a handful of cached dictionaries were created to support all data needs of the application. Classic one-to-many and many-to-many relationships were replaced with document based embedded data model.

Results:
Most relationships between entities in DNA sequencing data that a relational model would consider as one-to-many appear to be rather one-to-few (e.g. a few genes in CNV region, or a few literature references for predicted effects of a variant). Keeping them together by means of embedded data model helped to reduce systems complexity and speed up development time. This data model worked well with JSON based information exchange and required less code to create desired functionality.

Conclusions:
The complexity and flexibility of data in cancer genomics requires new approaches to simplify data models, facilitate understanding of data, and speed up the development process. No-SQL databases and MongoDB in particular appear to be well suited to address these needs.

Strategies to Optimize Data Storage for Clinical Next Generation Sequencing

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Content:
Data storage for Next Generation Sequencing (NGS) based assays constitutes a significant component of clinical laboratory operations. Scalable, redundant and secure infrastructure solutions are essential to manage analyzed NGS data. With continuously evolving sequencing technology, laboratory workflow and cumulative experience with data

analytics, strategies for optimal utilization of storage infrastructure resources is surfacing as an important aspect of data management. The aim of this study is to present our institution's experience with data storage for NGS.

Technology:
The Molecular and Genomic Pathology laboratory houses six NGS sequencers with or without accompanying high-performance workstation servers for data analytics and local storage (7-10 terabytes per server). Resource intensive data analytics (e.g. whole transcriptome) is performed on a high performance compute (HPC) cluster, provisioned by our institution's HIPAA-compliant data center with onboard "hot" storage. Scale out network attached storage (SONAS) and high-performance enterprise storage (HPES) at our data center were used for archiving clinical NGS test data (cold storage).

Design:
Using high-bandwidth network connections, raw signal files were moved to the SONAS archives whereas intermediate data (FASTQ-BAM-VCF) were stored in the HPES pool. The latter provided low-latency access to FASTQ and other files for alternate bioinformatics analyses that were run on virtual machines and the HPC cluster. Downstream test results, including annotated genomic alterations and knowledgebase, generated by custom developed web applications were hosted and stored in virtualized database servers in our data center.

Results:
With initial NGS based testing, raw data files (100-250GB per run) and intermediate data (100-500MB) were archived to allow re-analysis and alternative analysis, respectively. However, increasing test volumes and introduction of new NGS assays (new gene panels, gene fusion and copy number variation analysis) and novel workflows required optimization of allocated storage. Such strategies included creation of data retention policies to limit storage of relevant raw data, data compression, and optimal use of our low-latency storage pool. Institution wide disaster recovery (DR) plans enhanced storage reliability and security, but also helped define data types based on relevance to patient care. All NGS data were stored off-site in our data center as part of this DR plan.

Conclusion:
The steady plummet of storage cost has greatly facilitated large-scale NGS data storage. However, strategies to optimally manage stored data are becoming increasingly important because of the increasing demand for NGS testing, competing capital needs, complexity of big data, and need to re-analyze archival data.

Harnessing Web Application Programming Interface (Web API) for Optimizing Clinical Next Generation Sequencing (NGS) Workflow

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Content:
Application programming interface (API) is a set of protocols that facilitate software development by exposing useful functions and content for consumption by other applications either at a system level or across a network (Web API). The latter is a popular component of modern data-driven web applications that has recently gained popularity for sharing large-scale genomic datasets. The aim of this project was to use Web API based messaging for transfer of genomic data to improve our laboratory's NGS workflow.

Technology:
Our pipeline consisted of servers performing primary bioinformatics analysis on semiconductor-based raw sequence data and custom developed web applications, VariantExplorer and SeqReporter, for downstream data analytics. VariantExplorer also used novel algorithms for processing copy number variation (CNV) and gene fusion data. The sequencing servers and VariantExplorer were hosted in an Ubuntu Linux operating system. SeqReporter was deployed in Microsoft Windows Server operating system. Django framework v1.5 and ASP.NET framework v4.5 were used to develop VariantExplorer and SeqReporter, respectively. The web API was hosted by VariantExplorer and used

JavaScript Object Notation format for messaging. All data communications occurred over high-bandwidth secure network (1Gb/sec).

Design:
Upon completion of primary bioinformatics analysis, technologists submitted analysis jobs to VariantExplorer, which extracted the genomic data (BAM and VCF files) from the sequencing servers. Subsequently, VariantExplorer enabled asynchronous consumption of the annotated DNA variants as well as CNV and gene fusion analyses results by SeqReporter using a set of web APIs. The received data was then further annotated with our in-house knowledgebase and converted into a LIS-compatible clinical report.

Results:
A total of 344 cases across different NGS gene panels (thyroid, advanced solid tumor and brain tumor panels) were analyzed using the new framework. In contrast to the older method that relied on manual uploads of genomic data, the web API based method substantially streamlined the data analysis workflow in our molecular laboratory. There was a significant decrease in user interaction and input during the entire process enabling more hands-off time, which also significantly decreased probability of human errors, especially with constantly increasing test volumes. A real time monitoring interface enabled easy tracking of background data analytic processes in both applications.

Conclusion:
High-complexity and high-volume clinical testing with NGS assays requires close interactions between bioinformatics and clinical informatics systems to optimize laboratory workflow. Web API employed in our laboratory's NGS workflow successfully bridged this gap to enable seamless communications in an operating system agnostic manner with promising preliminary results.