The Cytopathology & Informatics Partnership: Current and Future Roles of Informatics in Cytopathology

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CURRENT STATE

Field of Cytopathology:
- Area of Anatomical Pathology most akin with Clinical Pathology.
- High volume of specimens, repetitive tasks, & many standards.

Informatics advances:
1. Leveraging the Lab Information System (LIS).
2. Standardized Diagnostic Criteria & Reporting.
3. Adoption of Digital Imaging.
4. Automation (computer-assisted screening).

1. Leveraging the LIS

Lab Information System (LIS) at the core of most cytopathology lab operations.

LIS functions include:
- Workflow management.
- Data entry, Reporting, & Archiving.
- Code capture & Billing.
- Interfacing with other systems.
- Assistance with regulatory compliance.
DATABASES

- LIS represents a large complex electronic relational database.
  - Relational database = multiple related tables linked via common shared files.
  - Ready for harvesting!
- Benefits of electronic data include:
  - Flexible & efficient way to store, retrieve & manipulate data.
  - Rapid transmission & exchange of data.
  - Integration of multiple databases.
  - Decreased storage space requirements.
  - Multiple user access to stored information.
- Manipulation of extracted data (datasets) is feasible with spreadsheet applications, such as Excel.

QC/QA Indicators

- Purpose:
  - Help detect, correct, and reduce lab errors: e.g. potential false negative Pap tests.
  - Meet regulatory requirements: e.g. CLIA '88
  - Maintain accreditation: e.g. CAP, Joint Commission.
  - Provides individual feedback & continuing education for staff.
- Process:
  - Quality of the overall testing process needs to be continuously monitored.
  - Requires utilization of the LIS & electronic databases.
  - Cross referencing of LIS data, comparison of findings against lab averages, and trend analyses.

Screening & Performance Indicators

- Re-screening of random and high risk cases.
- 5-year look back.
- Frequencies of diagnostic categories.
  - e.g. ASC-US/SIL rates.
- HPV DNA positivity rates for ASC-US cases.
- Cytologic-histologic correlation.
  - e.g. Pap test & cervix biopsy.
- Diagnosis correlation between cytotech & cytopathologists.
- Cytotechnologist reporting errors.
- Specimen turnaround time.
- Productivity (volume of slides/month).

Diagnostic Categories

Example of a contingency table

Table: Cytologic/Histologic Correlation

<table>
<thead>
<tr>
<th>Time period</th>
<th>Histologic Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>NILM</td>
</tr>
<tr>
<td></td>
<td>ASC</td>
</tr>
<tr>
<td></td>
<td>ASC-H</td>
</tr>
<tr>
<td></td>
<td>AGC</td>
</tr>
<tr>
<td></td>
<td>LSIL</td>
</tr>
<tr>
<td></td>
<td>LGH</td>
</tr>
<tr>
<td></td>
<td>HSIL</td>
</tr>
<tr>
<td></td>
<td>CA</td>
</tr>
<tr>
<td></td>
<td>UNSAT</td>
</tr>
</tbody>
</table>

Old & New INDICATORS

- Greater utilization of hr-HPV data as a potential cytopathology lab QA indicator.
**Slides per Hour by Cytotechnologist**

<table>
<thead>
<tr>
<th>Lab Average</th>
<th>CT 3</th>
<th>CT 2</th>
<th>CT 1</th>
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<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>10</td>
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<tr>
<td></td>
<td>2</td>
<td>6</td>
<td></td>
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<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fictitious data for presentation purposes.

**Additional Measures**

- Electronically alert providers of patients with a Pap test of HSIL or Cancer without documented follow up after a specific time period (follow-up letters, autofax &/or via EMR mBox).
- Generation of marketing and sales reports. e.g. Turnaround time.
- Tracking resident/fellow vs cytopathologist diagnoses.

**Web-site consortium**

- Example: Genetics Café is an interactive web site to compare one lab's findings to cumulative group results.

**CYTOLOGY LAB LEAN APPROACH**

- Statistical QC is helpful for tasks in which numbers are generated.
- Application of the Toyota Production System process to GYN & Non-GYN Cytology may help identify and eliminate waste.
- Proven reduction in cytology diagnostic errors.
- Improved Papanicolaou test quality.
- Previously implemented initiatives:
  - Continuous pull system workflow process.
  - Adoption of a standardized diagnostic terminology scheme for thyroid FNA.
  - Immediate interpretation FNA service.

**2. STANDARDIZED REPORTING**

- Our core mission is to provide information in a manner most effective for patient care (i.e. for clinical decision support).
  - Information must be accurate, timely, understandable, & available when needed.
- Cervical cytology results were reported using various terminologies during the first 40 years of Pap test screening.
  - Many labs modified reporting to suit their own needs.
  - Terms did not correspond to current knowledge of cervical carcinogenesis.
- Challenge: Establish diagnostic criteria ↔ Standardize reporting ↔ Evaluate Outcomes.
**Papanicolaou’s Classification**

- **1943 “classes” introduced to describe precancerous squamous lesions of the uterine cervix:**
  - **Class I** – Absence of atypical or abnormal cells
  - **Class II** – Atypical cytology but no evidence of malignancy
  - **Class III** – Cytology suggestive of but not conclusive for malignancy
  - **Class IV** – Cytology strongly suggestive of malignancy
  - **Class V** – Cytology conclusive for malignancy

**The Bethesda System (TBS)**

- **A system for uniformly reporting cervical cytology was introduced in 1988, revised in 1991 & 2001.**
- Adopted as the standard of reporting in USA by the Center for Disease Control & Prevention, the executors of CLIA 1988.
- Broad interdisciplinary participation in this consensus process.
- Diagnostic categories tied to rational evidence-based management algorithms (e.g. ASCCP) & outcomes.
- Followed by the recent Bethesda system diagnostic framework for reporting thyroid FNA results.

**ADVANTAGES**

- Conducive to rapid electronic sign out.
- Improves communication among cytologists, surgical pathologists & health care providers.
- Promotes clear management guidelines.
- Facilitates data extraction, exchange and analysis.
- Inspires multi-institutional studies.
- Offers a mechanism for modification & reform.
- An important component to improve cervical cancer screening.
- Ultimately improves patient care.

**“Terms without Borders”**

- Europe still has many different systems of cytology classification and languages.
- European guidelines being developed for different countries to adapt their terminology to make these screening programs comparable.
- British Society for Clinical Cytology (BSCC) closely aligned with TBS.

**Bethesda Interobserver Reproducibility Study (BIRST)**

- **Sharma et al. Cancer Cytopathology 2007; 111:19-25.**
- **Class slides:** Interobserver agreement for SIL on LBP is good & superior to conventional smears.
- **BIRST** Web-based assessment of TBS (2001) for classifying cervical cytology:
  - 77 online images (broad range)
  - 214 Cytotechnologists & 165 Pathologists
  - Compared to TBS panel
  - 55.1% exact agreement - Highest for LSIL
  - Lowest for ASC-US or ASC-H
  - Limited reproducibility of cervical cytologic interpretation.

Can computer-assisted image analysis do a better job?

**3. DIGITAL IMAGING**

- **Applications for Cytology:**
  - Education & Research
  - Telecytology
  - Proficiency Testing
  - Automated Pap Screening
  - Pap Test Replacements
  - Other (e.g. QA/QC, image-enhanced reports, archiving, etc.)
**TELECYTOLOGY**

- Practice of cytology at a distance using telecommunication to transmit images.

- For diagnosis, consultation, conferences, QA review, & education.

- Static imaging (snap shot) involves the capture & sending of selected field of views.

- Robotic microscopy (real-time) uses a video camera, web conferencing &/or remotely operated microscope.

- Virtual microscopy uses images generated with whole slide scanning systems.

- Early efforts limited by computer power & software.

- Early studies were less accurate than light microscopy.

- However, more recent data demonstrate improved accuracy & reproducibility.

- Becoming useful for immediate assessment of FNA.

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**Telecytology Publications**

<table>
<thead>
<tr>
<th>Date</th>
<th>Country</th>
<th>System</th>
<th>Time</th>
<th>Quality</th>
<th>Agreements</th>
<th>Agreement Concordance</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>2006</td>
<td>USA</td>
<td>GYN</td>
<td>30m</td>
<td>Good</td>
<td>Moderate</td>
<td>Poor</td>
<td>Poor images of specimens</td>
</tr>
<tr>
<td>2005</td>
<td>USA</td>
<td>Non-GYN</td>
<td>30m</td>
<td>Poor</td>
<td>Moderate</td>
<td>Poor</td>
<td>Poor quality images (not at home)</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>Non-GYN</td>
<td>30m</td>
<td>Poor</td>
<td>Moderate</td>
<td>Poor</td>
<td>Poor quality images with inability to focus on thick cellular groups</td>
</tr>
<tr>
<td>2003</td>
<td>Japan</td>
<td>GYN &amp; non-GYN</td>
<td>30m</td>
<td>Good</td>
<td>Good (no % recorded)</td>
<td>Moderate</td>
<td>Poor quality images with inability to focus on thick cellular groups</td>
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<tr>
<td>2002</td>
<td>Iran</td>
<td>Non-GYN</td>
<td>30m</td>
<td>Good</td>
<td>Good to excellent</td>
<td>Moderate</td>
<td>Poor quality images with inability to focus on thick cellular groups</td>
</tr>
<tr>
<td>2001</td>
<td>USA</td>
<td>GYN</td>
<td>30m</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
<td>Lengthy time to scan whole slides</td>
</tr>
<tr>
<td>2000</td>
<td>USA</td>
<td>GYN</td>
<td>30m</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
<td>Lengthy time to scan whole slides</td>
</tr>
<tr>
<td>1998</td>
<td>Germany</td>
<td>Non-GYN</td>
<td>30m</td>
<td>Good</td>
<td>Good</td>
<td>Poor</td>
<td>Lengthy time to scan whole slides</td>
</tr>
</tbody>
</table>

*Although a remotely controlled (dynamic) telecytology system was employed in this study, only preselected (static) areas were used.

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**PROFICIENCY TESTING**

- Current gold standard is manual screening or review of glass slides.

- Virtual microscopy is being recommended by several investigators.

- CytoView = prototype computer image-based GYN cytology PT.

- Pros: Cost effective & improved standardization.

- Cons: Prior training is required, lengthy time to examine digital images, connectivity need, & this may not reflect the real-world experience.

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**DIGITAL IMAGING PROCESS**

- Acquisition (e.g. capture)
  - Liquid based cytology offers uniformly fixed & stained cellular areas relatively small to image.

- Archiving (e.g. saving files)
  - Entails image taxonomy & management.

- Image manipulation (e.g. annotation)

- Image utilization (e.g. sharing)
  - Imaged enhanced reports result in improved concordance between Pap tests & cervix biopsies.


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**TODAY’S DIGITAL IMAGING DRAWBACKS**

- Expensive initial set-up costs.

- Workflow interruption.

- Length of time to scan whole slides.

- Large storage size for WSI.

- Bandwidth restrictions.

- Undefined legal implications.

- Professional reluctance.

- Lack of standardization in the imaging process.

- Factors not unique to Cytology.
Impact of Digital Image Manipulation in Cytopathology
Arch Path Lab Med 2009; 133:57-61.

- Manipulation of a digital image affects its interpretation.
- Care needs to be taken when digital cytology images are used, to specifically ensure that their alteration does not affect diagnosis.
- Standards related to the use of digital images in cytopathology are required to avoid the potential for misdiagnosis.

Factors Unique to Cytology

- Problem: 3D cell groups and thick smears.
  - Solution: Z-stack versus scanning at different focal planes (digital zoom, focal plane intercalation).

Virtual Image

Virtual Focus

This particular image pair showed the least correlation in the study with the majority of the test takers overcalling the manipulated image HGSIL compared with the original image’s diagnosis of negative.

Arch Path Lab Med 2009; 133:57-61.

Even with an internal control!

Manipulated Image

Unaltered

Altered

Virtual Image

Virtual Focus

Z-level:
- 1μm
**Virtual Focus**

- Z-level: + 1μm

**Virtual Focus**

- Z-level: + 3μm

**Virtual Focus**

- Z-level: + 5μm

**Video Microscopy**

- Microscope-mounted video cameras.
- Applications include:
  - Conferencing.
  - Telemicroscopy:
    - Dynamic.
    - Video images can improve “focusing” by playing files forward & backward.

**Emerging Imaging Methods**

- Multispectral image analysis:
  - Utilizes spatial and spectral image information to classify images.
- Image cytometry:
  - Image-based measurement of cell properties.
- Still investigational tools.

**Utility of multispectral imaging in differentiating lesions with subtle cytomorphologic differences**

- FNA
  - Follicular Adenoma
  - Parathyroid Adenoma

- Pap Stain

Imaged cells with multispectral solution applied
Growing literature highlights Pap test shortcomings (FNR).

- Direct cervix visualization of the cervix ("optical biopsy")
  - e.g. digital cervicography
  - optical coherence tomography
  - speculoscopy (chemiluminescence)

- Non-visual biophysical analyses
  - e.g. Polarprobe (spectroscopic patterns)

- Non-invasive but complementary (i.e. augment cytology) at best?

Spitzer M. AJOG Reviews 1998; 179:544-46.


Cervicography Digital Camera

Optical Coherence Tomography

- High-resolution cross sectional imaging.
- Resolution approaches the cellular range (1-15 micrometers).
- Analogous to US, but uses light instead.


4. AUTOMATED CYTOLOGY DEVICES

- In 1996 only 12% of cytology labs were engaged in automated cytology.

- Automated Preparation Devices
  - Cell collection from liquid samples, monolayer slide preparation, autostainers, etc.
    - e.g. ThinPrep™ 2000 Processor, BD PrepMate™ Cell Enrichment Processor; MonoPrep® LBP Processor.

- Screening Process Control
  - Computer interface with a microscope stage.
  - Ensures all fields on a slide have been examined.
    - e.g. Accell Series 2000, Pathfinder System, Cytosafe System.

- Computer-Assisted Screening

Manual Pap test screening is difficult, repetitive, labor-intensive, suffers from a significant FNR, carries ergonomic risk, & affected by screening environment.

- Compound by skilled cytotechnologist shortage.

- Early semi-automated screening devices plagued by lack of a standardized process conducive to rapid acquisition and computer processing.

- Resulted in the advent of Liquid Based Cytology with a "monolayer".

- Goal: Improved sensitivity, specificity & productivity over manual screening (that can consistently analyze slides around the clock without fatigue).

- "Manual screening is an art & a science; Automated screening is more science than art!"

Computer-Assisted Screening Timeline

- 1932 – Pap test introduced
- 1938 – Pap test screening implemented
- 1962 – Smear pattern recognition using a cytoanalyser
- 1967 – Cytology screening apparatus using alcohol suspensions
- 1983 – Early neural network (artificial intelligence) algorithms
- 1995 – PAPNET™ System FDA approved for re-screening
- 1996 – ThinPrep™ Pap test FDA approved
- 1996 – BD FocalPoint™ Slide profiler (AutoPap 300 QC) FDA approved as an alternative to traditional dyes
- 1999 – AutoCyte Prep™ (now BD SurePath™) Pap test FDA approved
- 2001 – BD FocalPoint™ Slide profiler approved to screen SurePath™ slides
- 2002 – ThinPrep Imaging System™ FDA approved
- 2006 – MonoPrep™ Pap test introduced
- 2006 – BD FocalPoint™ GS Imaging System approved
**“Graphing Machine”**

Automatic Preparation and Scanning in Cervical Cytology

- **Cell Writing Pen**: A peristaltic pen in the centre deposits a line of cells on a transparent film strip as it passes.
- **Staining Apparatus**: The film strip is looped over a series of rollers. Below is a unit containing individual staining-baths that, when raised, immerse the rollers.
- **Viewing Apparatus**: The prepared film on the left passes under the objective of a microscope (centre) for viewing on a screen or through binoculars.

**LIQUID BASED CYTOLOGY**

**Fluid-Based Technology**

**PROBLEMS SOLVED**

- **Pre-analytic**: Improved sampling, fixation, staining, background & fewer artifacts (e.g. overlapping cells).
  - Variables in slide quality are now under the control of the cytology laboratory.
- **Analytic**: Smaller area on a slide to screen/image.
  - Monolayers easier to read.

**Trade Off**

- **Endocervical cells**: Prior to Imager stain
  - Conventional smear: HSIL in Mucus Strand
  - Liquid Based Pap: HSIL

**Automated Screening Systems**

- **Primary screening systems**
  - e.g. BD FocalPoint™ Slide Profiler (formerly AutoPap).
  - Self-contained onsite unit.
  - Slides scanned at varying objective levels.
  - Computer processors assign scores for each FOV.
  - Negative slides receive no human review & are archived.
  - Abnormalities require human review.
- **Interactive screening systems**
  - e.g. ThinPrep Imaging System™, BD FocalPoint™ GS Imaging System, Monolith™.
  - Slide screening system scans the entire slide (e.g. 120 fields).
  - Data is processed using imaging algorithms.
  - Location guided workflow process (“pap map”).
  - Cytotechnologist attention is driven using X-Y axis relocation to significant fields (e.g. 22 FOVs).

**Practical Issues**

- Imager inserted into workflow (cytotech’s cytotechnologist).
- Initial installation, calibration, & training.
- Abnormal fields may not be the most diagnostic.
- Specimen adequacy & diagnosis of infections limited to FOV.
- Reimbursement (billing) - CPT codes exist for both technical and professional components.
**Imaging Systems Outcomes**

**In General:**
- Increase in abnormal Pap test diagnoses.
- Increase in pathologist-referred cases.
- Overall similar ASC-US HPV+ rates.
- Increased rates of biopsy-proven SIL detection.
- No change in HSIL Cyto-Histo correlation.

**Published Message:**
- Safe & effective technology that improves outcomes in patient care.
- Cost-effective in high volume cytology laboratories.
  - Additional cost to the Pap test (a shift in labor cost from physician office to the lab, hardware, increased sensitivity with more cases for review).

**Cytotechnologist Productivity**

- Initial learning curve.
- Increased cytotech productivity.
- Example of slide screening times:
  - Conventional smear = mean 5.6 min (10.7 slides/hour)
  - TPI = mean 2.9 min (20.6 slides/hour)
- Need for new benchmarks & standards for cytotechnologist performance i.e. maximum workload limits (slides/hour).
- BD FocalPoint™ GS Imaging System = 170 slides/24 hour workload limitation.
- ThinPrep Imaging System™ = 200 slides/24 hour workload limitation

**Imaging System Accuracy in Detecting Glandular Lesions**

- In a minority of cases, computer-assisted imaging devices fail to detect atypical/neoplastic glandular cells of interest within selected FOVs.
- Hence, there are reservations regarding total Pap test screening automation (i.e. without manual review).
- Technology is not perfect, but neither is the Pap test, and nor are we.

**Malpractice Concerns**

- Potential malpractice claims for automated screening imagers include:
  - Appropriate device QC
  - Personnel training
  - Compliance (e.g. with manufacturer standards)
  - Other

**FISH & CHIPS**

- Genetic alterations play an important role in cervix carcinogenesis.
- FISH assays are available for detecting gains (e.g. 3q & 5q) in cytology samples for risk stratification and triaging.

**5. ANCILLARY TESTING**

- Personalized medicine:
  - Involves the use of molecular methods (information) to better manage a patient’s disease or disease predisposition.
- Residual Pap vial & FNA material are available for ancillary testing.
- We should "seize the opportunity"!
- Ancillary tests:
  - HPV, immunocytochemistry, in-situ hybridization, molecular tests, etc.
IT-related issues

- Hierarchy of ordering ancillary tests: (clinicians or the lab?).
- Handling specimens: Aliquots, split samples, & specimen tracking.
- Ordering: e.g. reflex testing.
- Data integration from disparate systems.
CONCLUSIONS
Where are we?

- Cytology has embraced informatics, particularly since CLIA '88.
- Ongoing utilization of LIS electronic databases for continuous QA/QC helps detect, correct, and reduce lab errors (akin to Clinical Pathology).
- Standardized diagnostic criteria & reporting are now expanding beyond GYN cytology.
- FDA approval has promoted the adoption of technology.
- Current digital applications include telecytology, automated Pap test screening, education & potentially proficiency testing.
- Telecytology, like telemedicine, is decentralizing practice.
- Automated Pap test screening has increased productivity & sensitivity.
- Technology is driving our quality monitors (e.g. workload limits, HPV rates). Professional organizations should play a role in developing standards.
- Liquid based cytology is helping meet demands for molecular testing.

Questions & Controversies
Where are we going?

- Are conventional Pap tests (smears) still considered acceptable standard of care?
- Is autoverification (no human review) of imaged abnormal Pap tests feasible?
- Will future re-screening require morphology review or molecular tests?
- Will automated screening be applied to non-GYN specimens and FNA biopsies?
- Once our images are in a computer system will they be outsourced?
- Are new technologies being incorporated into educational programs?
- Can we do it? i.e. keep cytologists in the center of clinical decision-making support?
- Can this technology help provide affordable cytology services in unscreened populations without an effective cytology infrastructure?
- Will disruptive technology (i.e. new technology that transforms markets) "replace" cyto technologists &/or pathologists?

Is this what Dr. Papanicolaou had intended?

<table>
<thead>
<tr>
<th>Pap Tests</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical Cancer</td>
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</tr>
<tr>
<td>Imaging</td>
<td></td>
</tr>
<tr>
<td>HPV</td>
<td></td>
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<tr>
<td>Molecular</td>
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</tr>
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Is IT worth it?

<table>
<thead>
<tr>
<th>Pap Test Technology</th>
<th>TIME</th>
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<tbody>
<tr>
<td>Monolayer</td>
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<tr>
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- Robert A. Goulart MD
- Maryanne Hornish CT(ASCP), MBA