Preparation and Screening Automation in Cervical Cytology

AP108 Current Issues in Gynecological Cytology

David C. Wilbur, M.D.
Director, Cytopathology
Massachusetts General Hospital
Boston, Massachusetts

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1) Liquid-Based Cytology
2) Computerized Screening Technology
   - Location Guided Screening
3) CPT Coding for Automation
Causes of False-Negatives

1. Inadequate sampling
2. Inadequate preparation
   - air-drying
   - poor fixation
3. Associated infection
4. Screening errors
5. Interpretation errors
Liquid Based Cytology

General Features

Improved Specimen
  (+) fixation, (-) obscuration
Homogeneity
  (+) cell distribution
Randomization
  (+) abnormality capture
Productivity
  (+) screening efficiency
Liquid Based Cytology

- both FDA labeled at ~ 60% improved detection of HSIL or HSIL+
- both show significant improvements in specimen adequacy (SP>TP)
- both show productivity enhancements
- subtle morphologic differences
- both have automation available
Liquid Based Cytology

Differences

**Cytyc ThinPrep Pap Test**
- Flatter prep/less dense cellularity
- Preprocessing with bloody specimens
- Broom and brush/spatula
- Methanol fixative
- Digene HPV - FDA approved

**TriPath SurePath**
- 3-dimensionality/dense cellularity
- Reduction of blood and inflammation
- Broom only
- Ethanol fixative
- Digene HPV - not FDA approved (study submitted)
Liquid Based Cytology

Morphologic Features

- homogeneity of cellularity
- increased 3-dimensionality (SP>TP)
- more isolated HSIL cells
- distinct tumor diathesis
- loss of geographic localization
Semi-Automation

Human decision retained

- Abnormal triage to full manual review and human interpretation

Full Automation

Device made decision

- Negative interpretation - NFR population
- Full interpretation
Screening Approaches

1) Machine Classification
   TriPath – NFR/Review Populations*

2) Location Guided Screening
   Cytyc – LGS Review and Triage*

3) Combination of 1 & 2
   TriPath – NFR/Review with LGS#

*FDA approved
# in development
Best Cellular Features

- Nuclear size (area)
- Nuclear shape (roundness)
- Chromatin distribution (texture)
- Nuclear darkness (optical density)
- Nuclear & cytoplasmic comparisons (N/C ratio)
- Contrast variations
- Statistical assessments
**Step-Wise Evaluation**

Classifiers → Accumulation of evidence → Slide Score
Detection Sensitivity
Primary Screening

<table>
<thead>
<tr>
<th>Condition</th>
<th>CP Arm</th>
<th>AP Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS+</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>LSIL+</td>
<td>85</td>
<td>92</td>
</tr>
<tr>
<td>HSIL+</td>
<td>93</td>
<td>97</td>
</tr>
</tbody>
</table>
Vassilakos Study - 2002

FocalPoint/SurePath Study

9,665 cases studied

9.2% Process Review

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
<th>4th</th>
<th>5th</th>
<th>NFR</th>
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</thead>
<tbody>
<tr>
<td>HSIL+</td>
<td>85</td>
<td>22</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LSIL</td>
<td>47</td>
<td>21</td>
<td>11</td>
<td>10</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>ASC/GC</td>
<td>54</td>
<td>23</td>
<td>12</td>
<td>5</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

Total ASC+ ≥ 3rd rank = 84%

# Table 1

<table>
<thead>
<tr>
<th>Quintile</th>
<th>HSIL+ (%)</th>
<th>HSIL(%)</th>
<th>AIS(%)</th>
<th>Carcinoma(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60(58)</td>
<td>19(66)</td>
<td>0(0)</td>
<td>41(59)</td>
</tr>
<tr>
<td>2</td>
<td>25(24)</td>
<td>7(24)</td>
<td>1(20)</td>
<td>17(25)</td>
</tr>
<tr>
<td>3</td>
<td>11(11)</td>
<td>3(10)</td>
<td>2(40)</td>
<td>6(9)</td>
</tr>
<tr>
<td>4</td>
<td>6(6)</td>
<td>0(0)</td>
<td>2(40)</td>
<td>4(6)</td>
</tr>
<tr>
<td>5</td>
<td>1(1)-21*</td>
<td>0(0)-3*</td>
<td>0(0)</td>
<td>1(1)-18*</td>
</tr>
</tbody>
</table>

| NFR      | 0(0)      | 0(0)    | 0(0)   | 0(0)         |

| Total    | 103-21*   | 29-32*  | 5      | 69-87*       |

| Q1+Q2    | 85(83)    | 26(90)  | 1(20)  | 58(84)       |
Initial User Interface - PapMap Illustration
Taipei Study

Location Guided Screening

Sensitivity comparison to US FDA Trials

<table>
<thead>
<tr>
<th>Category</th>
<th>US FDA</th>
<th>Taipei</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS+</td>
<td>85.8%</td>
<td>89.9%</td>
</tr>
<tr>
<td>LSIL+</td>
<td>92.2%</td>
<td>95.7%</td>
</tr>
<tr>
<td>HSIL+</td>
<td>97.1%</td>
<td>98.1%</td>
</tr>
</tbody>
</table>

**85% WL reduction**

Acta Cytol 1999;43:363-8
### Chang Study - Hong Kong

#### 1007 Cases Studied

<table>
<thead>
<tr>
<th>Interpretation</th>
<th>Manual Review</th>
<th>LGS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS+</td>
<td>93</td>
<td>111</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>LSIL+</td>
<td>37</td>
<td>29</td>
<td>p=0.9</td>
</tr>
<tr>
<td>Unsat</td>
<td>29</td>
<td>17</td>
<td>p=0.07</td>
</tr>
</tbody>
</table>

Time to Screen: 5.74min. vs 2.71min. (-47%)

AJCP 2001
SurePath - FocalPoint GS Screening System

≥75% (R)

≤25% NILM (NFR)

Database
DISTRIBUTED SCREENING: FOCALPOINT™ GS

Local GS Platform

Database

Distributed GS Platforms

For Use Outside the US Only
Not FDA approved in US
FocalPoint™ GS* Monitor

- Ability to view image of what FocalPoint “sees” to verify live image
- Electronic dotting or manual dotting
Location Guided Screening

FocalPoint System

1) 25% No Further Review Population = NILM
2) LGS Screen of Review Population - 10 FOV’s
3) Full Manual Screen if Potential Abnormality Identified
<table>
<thead>
<tr>
<th>Path</th>
<th>CP Arm</th>
<th>LGS Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FN’s</td>
<td>Triage to Path</td>
</tr>
<tr>
<td>ASCUS+</td>
<td>26</td>
<td>87.9%</td>
</tr>
<tr>
<td>LSIL+</td>
<td>11</td>
<td>91.5%</td>
</tr>
<tr>
<td>HSIL+</td>
<td>11</td>
<td>91.1%</td>
</tr>
</tbody>
</table>
# False-Positive Cases and Specificity

<table>
<thead>
<tr>
<th></th>
<th>CP Arm</th>
<th>LGS Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCUS+</strong></td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td><strong>LSIL+</strong></td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td><strong>HSIL+</strong></td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>FP Rate</strong></td>
<td>4.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>95.1%</td>
<td>96.1%</td>
</tr>
<tr>
<td><strong>QC</strong></td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

*AJCP 2002*
Potential Productivity Impact Model

**CP Arm Screening Worktime**

(4.9 \times 230 \text{ ABNL}) + (3.8 \times 1045 \text{ WNL}) = 5098 \text{ m}

**LGS Arm Screening Worktime**

- 218 No Review Slides = 0m
- 619 FOV - only = 619m
- 418 FOV + FMR = 418 + (4.9 \times 234) + (3.8 \times 204) = 2339.8m

Total LGS Screening Worktime = 2958.8m (58\% of CP Arm)

Mod Pathol 2003
**ENRICHED QC POPULATION CONCEPT MODEL**

**Manual Practice**
- Random QC selection
- 10% Random Rescreening
- Abnormal Distribution in Random Population
- Abnormal Distribution in FocalPoint™ Classified Population
- Q5, Q4, Q3, Q2, Q1
- = false-negatives
- = negatives

**FocalPoint™ Assisted Practice**
- Enriched QC selection
- 25% No Further Review
- 75% Review
- ≥ 75% Review
ThinPrep Imaging System* - Image Processor (IP)
ThinPrep Imaging System

Image Processor

Review scope
ThinPrep Imaging System Review Scope (RS)*
Location Guided Screening
ThinPrep Imaging Directed Cytology System™

• Equipment
  – Staining machine: optimized Feulgen-like hematoxylin
  – Image processor: stores coordinates
  – 3 to 6 custom microscopes with motorized stage, each at no more than 328 feet from the processor
  – Ergonomic pod
• 300 slides processed per day
Location Guided Screening
ThinPrep Imaging Directed Cytology System™

- 22 FOV (20% of slide) presented to technologists in geographic order
- FOV’s selected using algorithms to detect high nuclear optical density (dark nuclei)
- Fiducial marks assure cytotechnologist is viewing same FOV as processor
- Operates in Autolocate™ mode for 22 FOV
- Operates in Autoscan if an abnormality is found
Autolocate Mode

Review 22 Fields:

Shown in “geographic” order, not in ranked order

Slide review is complete if all 22 are negative

Perform complete slide review if any cells within the 22 are positive
Object(s) of Interest - OOI

Target Zone

OOI (s) inside Target Zone
ThinPrep Imaging System Performance

- Four center two-armed study to evaluate primary screening capability
- 10,359 slides with 7.1% eliminated due to process incompatibility
- 9,550 slides reviewed using TP system and conventional screening
- Adjudication by three cytopathologists
### Results

**ThinPrep Imaging System vs. Conventional Screening**

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCUS+</strong></td>
<td>increased</td>
<td>no difference</td>
</tr>
<tr>
<td><strong>LSIL+</strong></td>
<td>no difference</td>
<td>no difference</td>
</tr>
<tr>
<td><strong>HSIL+</strong></td>
<td>no difference</td>
<td>increased</td>
</tr>
</tbody>
</table>
Cytyc Imaging System

**Sensitivity**
ASCUS+ - statistically significant improvement
LSIL+/HSIL+ - equivalent

**Specificity**
HSIL+ - statistically significant improvement
ASCUS+ and LSIL+ - equivalent

**Workload Limits**
Established at 200 Imager-assisted slides in no less than an 8-hour workday

June 2003
CPT Coding and Automation

88142  Manual screening of cervical cytology specimens using liquid-based preparation methods (ThinPrep/SurePath)

88147  FocalPoint primary screening of conventional slides - no manual screening (No Further Review population)

88148  FocalPoint primary screening of conventional slides - full manual review (Review population)

88174  FocalPoint primary screening of liquid-based slides (SurePath only) - no manual screening (No Further Review population)

88175  FocalPoint/Cytyc Imager primary screening of liquid-based slides (SurePath or ThinPrep, respectively) - full manual review (FocalPoint Review population, Cytyc Imager triage to full manual review population, respectively)

- ?FOV only review

88XXX – FocalPoint/Cytyc Imager primary screening of liquid-based slides with FOV-only review (no full manual screening)
Cost/Benefit – Imaging Systems

• Cost
  – TPI – estimated 2x, FPPS – est $5, GS - NA
  – Equipment: no direct cost (included)
  – Preparation time (minutes/case – not CT)

• Savings:
  – productivity estimated to be doubled - TPI, GS
  – productivity estimated at 25% workload - FPPS
  – CLIA workload limit 200 slides per day (TPI only)

• Reimbursement
  – Highly variable by region (88174/75)
# Reimbursement

<table>
<thead>
<tr>
<th>CMS National Limitation Amount (Medicare)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88164</td>
<td>14.76</td>
<td></td>
</tr>
<tr>
<td>88147</td>
<td>15.90</td>
<td></td>
</tr>
<tr>
<td>88148</td>
<td>21.23</td>
<td></td>
</tr>
<tr>
<td>Liquid-Based</td>
<td></td>
<td></td>
</tr>
<tr>
<td>88142</td>
<td>28.31</td>
<td></td>
</tr>
<tr>
<td>88174</td>
<td>29.85</td>
<td></td>
</tr>
<tr>
<td>88175</td>
<td>37.01</td>
<td></td>
</tr>
</tbody>
</table>
# Actual Time Data

<table>
<thead>
<tr>
<th>Manual Screening (TP)</th>
<th>Cytyc Imager</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>5-8 min</td>
</tr>
<tr>
<td>Abnormal</td>
<td>8-15 min</td>
</tr>
<tr>
<td></td>
<td>2-5 min (22 FOV)</td>
</tr>
<tr>
<td></td>
<td>5-10 min</td>
</tr>
</tbody>
</table>

Knapp, R – Personal Communication