The Traditional Pap Test versus Liquid Based Cervical Cytology

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The Pap Test

• Widely used for prevention of cervical cancer since the mid 1950s

• Widely acknowledged as the most successful screening test in the history of Medicine

Dr. Papanicolaou
Limitations of the Pap Test

- **Low sensitivity**
  - Review of studies in developed countries cite a sensitivity of 44-65% for a single Pap test
  - Reports range from 30-87% for detecting HSIL

- **False-negative rate of ~14% to 33%**
  - Multifactorial: preanalytic/analytic
    - Sample collection, preparation (2/3 of FN)
    - Screening and interpretation

USA: Liquid-Based Cytology

- **Hologic ThinPrep Pap Test (1996)**
  - The pivotal trial demonstrated a 65% increase \( (P \leq 0.001) \) in the diagnosis of LSIL or greater cytology and improvement in specimen quality compared with the conventional Pap test \( (P \leq 0.001) \).

- **BD SurePath Pap Test (1999)**
  - Pivotal study: increases detection rate of LSIL and HSIL by 47% \( (P \leq 0.0011) \) and 116% \( (P \leq 0.0002) \).
## USA: Impact of Liquid-Based Cytology

The CAP Laboratory Survey: Median Reporting Rates (50th Percentile) for Conventional Papanicolaou (Pap), SurePath Pap, and ThinPrep Pap Cytologic Preparations Across the Major Clinical Cytologic Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Conventional Pap Test</th>
<th>SurePath Pap Test</th>
<th>ThinPrep Pap Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>2.4</td>
<td>4.1*</td>
<td>4.9*</td>
</tr>
<tr>
<td>LSIL</td>
<td>1.3</td>
<td>2.5*</td>
<td>3.0*</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.3</td>
<td>0.3</td>
<td>0.6‡</td>
</tr>
<tr>
<td>UNSATS</td>
<td>1.0</td>
<td>0.3‡</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Advantages of Liquid-based Cytology

**SCREENING**
- **TIME**: Estimated to decrease screening time by 30%
- **EASE**: More uniform, thin-layer distribution of cells
- **COMPUTER ASSISTED IMAGING**: enabled with ease

**ADDITIONAL OUT OF VIAL TESTING**
- HPV testing
- Organisms
  - Gonorrhea, chlamydia
Liquid-Based Cytology Cost-Benefit Analysis

- Liquid-based cytology is more costly in terms of capital investment, operating costs, & disposables.
  - Mitigated to some extent if higher rates of equivocal or mild abnormalities increased due to follow-up costs
- However LBP
  - Decreases unsatisfactory rates/ avoid repeat testing
  - Allows HPV testing (reflex or co-testing) and GC/ chlamydia to be done from same vial
- In the USA, there was no detailed cost-benefit analyses performed for LBP vs. Conventional smears
  - Overall COST savings is not an advantage of using LBP
Eligible studies (9), published from 1991-2007

Conclusions:

- Liquid-based cervical cytology is neither more sensitive nor more specific for detection of high grade cervical intraepithelial neoplasia compared with the conventional Pap test

- Consistent over study design, clinical settings, and LBC systems
Prospective cluster randomized controlled trial involving 89,784 women aged 30-60 in the Dutch cervical cancer program.

Indicated that liquid-based cytology does not perform better than conventional Pap tests in terms of relative sensitivity and PPV for detection of cervical cancer precursors, when applied within a well-organized and quality-controlled cervical screening program.
Nearly universal acceptance of LBC occurred before the completion of definitive comparative effectiveness trials.

- Ideally, for screening tests designed for widespread general use, public health practice should be based on the strongest possible evidence. In reality, this sequence is sometimes not followed.

The choice of conventional cytology or LBP is now less important than comprehensive re-examination of cervical cancer screening programs, with increased consideration of HPV-based technologies.

- Prophylactic vaccines will reduce the efficiency of screening by any method
- Introduction of HPV testing will lead to increased screening sensitivity that should permit lengthened screening intervals.
Current Estimated Status of LBP/HPV/Automation in US Labs

- **Liquid based cytology** - 93%
  - ThinPrep: 70%
  - SurePath: 30%

- **High risk HPV testing**
  - Reflex for ASC-US: 90%
  - Co-testing (Pap+ HPV): 60%

- **Automated/Image Assisted Screening**: 33%

**NOTE:** Estimates ONLY. Based on 2013-14 data from ~1500 labs participating in interlaboratory comparison programs.
USA-Cervical Cancer Rates

Figure 1. Decrease in cervical cancer incidence rates in the United States over the past quarter century. Data from SEER Cancer Statistics Review, 1975-2005.
Benefits of Co-testing: Studies from U.S. and Europe

- Higher sensitivity and NPV than Pap alone. (lower specificity)
- Leads to earlier diagnosis of CIN 3+ and Cancer
- Incorporating HPV finds more AIS than cytology alone
- Negative cytology plus negative HPV allows spacing screening beyond every three years.

Follow-up of 5 yrs of Co-testing
331,818 Women
Kaiser Permanente Northern California

<table>
<thead>
<tr>
<th>5 year cumulative risk of CIN 3+</th>
<th>3 years</th>
<th>5 years</th>
</tr>
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<tbody>
<tr>
<td>&gt;ASC-US Cytol*</td>
<td>3.8%</td>
<td>4.7%</td>
</tr>
<tr>
<td>HPV +**</td>
<td>5.0%</td>
<td>7.6%</td>
</tr>
<tr>
<td>HPV + / Cytol neg</td>
<td>3.1%</td>
<td>5.9%</td>
</tr>
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*Cytology regardless of HPV status
**HR HPV regardless of cytology

Current Screening Options in the USA

- **Cytology (conventional or LBP) for women 21 yrs and older**
  - Reflex HPV testing following an interpretation of atypical cells of undetermined significance (ASC-US).
- **Cytology + HPV co-testing for women 30-65 yrs**
  - Preferred option per 2012 guidelines
- **Primary HPV screening of women 25 years of age or older**

Which triage strategy is most efficacious and cost effective in the US setting?
Why the USA will stay with LBP

1. > 90% labs already converted to LBP
2. Automated screening devices in 1/3\textsuperscript{rd} of labs
3. Professional screening and management guidelines support out of vial testing
   - Screening: cotesting (preferred) / HPV (new option)
   - Follow up: reflex for ASC-US, post-treatment, TOC
   - Genotyping following HR-HPV+/primary HPV testing
4. Cytotechnologist considerations:
   - Workforce shortage and screening limits
The Bottom Line

• The majority of cervical cancers are diagnosed in women who were never screened or not screened within the past 5 years.

• Improvement in cervical cancer prevention and mortality can only be obtained by
  – Screening all eligible women
  – HPV vaccination

• The choice of cervical screening method may vary
  – patient and provider preference, geographic, demographic, and socio-economic considerations can all affect the choice of screening modality in a specific country, area, or practice setting.
“As participation in screening and prevention is the key to reduction in cervical cancer morbidity and mortality, the ASC advocates for screening and vaccination access for all women with consideration of all acceptable screening modalities, patient compliance, test accessibility and overall cost. “

Approved by the ASC Executive Board, Sept 15th, 2014