Transformation of Gynaecologic cytology: A Liquid Based Approach

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Carcinoma Cervix

- Used to be the commonest cancer world-wide
- 470,000 new cases per annum world-wide
- 233,000 deaths, 80% in developing countries
- India: Commonest cancer in women
Cervical Cancer in India

New Cervical Cancer Cases
- India ~ 1,34,420
- World ~ 5,29,000

Deaths due to Cervical cancer
- India ~ 73,000
- World ~ 2,74,000

India ~ 27% of new Cervical Cancer cases in world
Rest of World - 73%

India ~ 27% of deaths due to Cervical Cancer in world
Rest of World - 73%

Cervical Cancer – Disease Burden

Cervical Cancer in India

- > 200 women die every day
- 8 women die every hour
- Every 7 minutes a woman dies
Cervical Screening – Pap Test

- Introduced in the 1940’s
- The Pap Test has been the most successful screening test.
- Up to 70% reduction in cervical cancer

“Lady, have you been “Paptized”?
- New York Amsterdam News, on Pap smears, 1957
Birthplace of the Cervical Smear!
Human papillomavirus

German virologist, Harald zur Hausen received award for discovery of HPV

HPV is a relatively small virus containing circular double-stranded DNA within a spherical shell

HPV 6 → Predilection for vulva
HPV 16 → Predilection for cervix
HPV 16/18 → Rapid progression to neoplasia
HPV 6/11 → May remain sub clinical

100 nm
Harald zur Hausen
Progression of cervical carcinogenesis

Mild cytological abnormalities and/or CIN1

Normal cervix -> HPV-infected cervix -> Persistent infection -> Precancer -> Cervical cancer

Clearance: CIN1: 57% (approximate likelihood)
CIN2: 43%
CIN3: 32%

CIN = cervical intraepithelial neoplasia; CIN1 = CIN grade 1
Precancer is equivalent to CIN2/3

Shedding of virus-laden epithelial cells

Viral assembly (L1, L2, E4)

Viral DNA replication (E6 & E7)

Episomal viral DNA in cell nucleus (E1 & E2, E6 & E7)

Infection of basal cells (E1 & E2)

Types of HPV infection

• Latent infection: Episomal DNA ~ 8-16%
  – No morphological change
• Lytic (Productive) infection: L-SIL ~ 0.5-2%
  – E6(p53) and E7 (Rb) under E2 control
• Integrative infection: H-SIL ~ 0.2-0.5%
  – Disruption of control over E6 and E7
HPV Diagnosis by

- Clinical
- Cytology
- Colposcopy
- Histopathology
- Molecular Biology

Considerations about HPV Testing
- Compared to Cytology, HPV testing is ~20-40% more sensitive than cytology
- ≥ 90% sensitive for CIN3+
- But only 5-10% less specific
- CLINICALLY VALIDATED
Screening by Colposcopy

• Clinicians Involvement

• On the spot
  * assessment of Lesion – staging.
  * Distinguish Low grade / High grade.
  * Immediate biopsy / therapy.
  * Valuable for follow up

Comprehensive Health Care Possible.
Cervical transformation zone is the prime target for carcinogenesis
SCREENING BY CERVICAL CYTOLOGY

1. Conventional
2. LBC
The Goal of Pap Testing

THE GOAL OF PAP TESTING IS TO IDENTIFY PRECANCEROUS CELL CHANGES BEFORE THEY PROGRESS TO CANCER
**Conventional PAP**

- Smear taken
- Microscopic evaluation done
- ASCUS or ASC-H suspected
- Ambiguous report issued
- Colposcopy etc needed
- Repeat sampling necessary
- Hence reduced patient compliance

**Thin Prep PAP**

- Smear prepared
- Microscopic evaluation done
- ASCUS or LSIL suspected
- Same sample vial for HPV
- HPV detected eg HPV 16
- LSIL confirmed
- Complete report with Evidence based medicine
- Better patient compliance
3 Steps - Accurate Cyto-diagnosis

STEP 1:
- Time and effort in preparing a good smear sample
- **WHAT IS NOT ON THE SMEAR CANNOT BE DIAGNOSED!!**
- Spreading and uniformity

STEP 2:
- **THERE IS NO SUBSTITUTE FOR CAREFUL SCREENING**
- An atypical cell not seen or misinterpreted is possibly the only chance of avoiding the development of a potentially fatal disease

NO DEFINITE WHITES & BLACKS

STEP 3:
- **POSITIVE OR ATYPICAL SMEAR SHOULD BE FOLLOWED UP BY AN ADEQUATE CONFIRMATORY TEST**
- Good liaison & dialogue between the clinician & cytology department
- Follow up
- **CYTO-HPV- HISTO- CORRELATION**
Limitations of the Conventional Pap Smear

• False Negative Rate
  – Sampling and interpretive errors

• Ambiguous reports
  – ASCUS
  – Limiting factors... Blood, mucus, inflammation

• Unsatisfactory results

Conventional Pap Smear
Source of False Negative Results

• Sampling / Preparation Errors
  – Cells not collected on the sampling device
  – Cells not transferred to the slide
  – Cells poorly preserved

• Screening Errors
  – Screening errors: Abnormal cells are present but not found
  – Interpretive errors: Cells are not classified correctly
Cell Sampling

More than 82% of the sample collected is discarded

Source: AJCP, February 1994
The Problem

Precancerous cells collected (red)

Sample may not reflect patient’s actual condition

Non-representative portion of cells

Over 80% of cells discarded

Missing cells, obscuring elements

Smear spray-fixed and sent to lab
The Solution

- Precancerous cells collected (red)
- Increased opportunity to detect early signs of abnormality
- Virtually 100% of cells collected into ThinPrep® vial
- Cells immediately preserved and sent to lab
- Filtration process disperses, randomizes cells
- More representative and clear thin layer of cells
The ThinPrep System

Collection & Accession

ThinPrep 2000

ThinPrep 5000

Preparation
ThinPrep® Process

1. DISPERSION
2. CELL COLLECTION
3. CELL TRANSFER
The ThinPrep Pap Test
Thin Prep Pap smear
The greatest challenge in cervical screening has been the tedious task of finding a needle in a haystack, where majority of haystacks have no needle!
It’s All About the Sample

Conventional Pap Smear Slide

Blood, mucus and inflammation can obscure cervical cells, making a diagnosis difficult.

ThinPrep Pap Test Slide

Through processing, obscuring elements are removed. The result significantly improves diagnostic review.
Sample Collection Video
The ThinPrep® Process

A Simple Change

- 3-5x CLOCKWISE
- IMMEDIATELY rinse
- THOROUGHLY rinse
Taking the LBC sample

Equipment -

- Speculum – reusable or disposable
- Sterilisation facilities
- Latex gloves
- Sample forms and bags
- Cervex brushes
- Endocervical brushes
- Thin Prep vials
- Waste disposal
- Black marker pen
- Leaflets
Collecting the sample

• Remove the lid from the ThinPrep vial and put the vial in a safe position

• Pass the speculum and visualise & assess the cervix

• Insert Cervex brush into endocervical canal at the os, so that the shorter outer bristles fully contact the ectocervix

• Using pencil pressure rotate the Cervex brush 3-5 times in a clockwise direction (this ensures good contact with the ectocervix )

• IMMEDIATELY fix the sample

• Rinse the Cervex brush into the ThinPrep vial using a vigorous swirling motion

• Agitate the brush forcefully at least 10 times in the preservative liquid

• Check the brush to ensure that no material is clinging to the fronds.

• Screw the lid on until the black marks meet
Reflex HPV testing

- Liquid based cytology is the primary screening modality
- HSIL, ASC-H = direct colposcopic biopsy
- LSIL, ASC-US = HPV test
  - On remaining liquid based cytology specimen
- High risk HPV +ve = Colposcopic biopsy
- High risk HPV -ve = Follow up cytology

- Specific guidelines governing what to do when a woman is found to have HPV were published.
- They were developed by 146 experts representing 29 organizations and professional societies.
- HPV testing is the preferred method of follow-up evaluation for women age 20-30 with inconclusive ("ASC-US") Pap results.
- If testing shows they do not have HPV, a repeat Pap is recommended in 12 months. If HPV is present, a colposcopy exam should be done.
- Routine HPV testing, along with the Pap, is beneficial for women 30 and older.

Centers for Disease Control and Prevention (CDC) in April 2007

- HPV vaccine be given to girls and young women age 11-26
- Ideally, the vaccine should be given before a girl becomes sexually active, and thus exposed to HPV. If given afterwards, the vaccine will only protect her against the HPV type(s) to which she has not yet been exposed.
- In any case, even after vaccination, screening for cervical cancer risk (see the next point) is still needed, since the protection offered by the HPV vaccine is incomplete.
- HPV testing along with the Pap for women age 30 and over.
New Cervical Cancer Screening Recommendations from the U.S. Preventive Services Task Force and the American Cancer Society/American Society for Colposcopy and Cervical Pathology/American Society for Clinical Pathology

March 15, 2012, issue of Annals of Internal Medicine

• What is new about these guidelines?

• 1st time that USPSTF has recommended the combined use of cervical cytology and high-risk human papillomavirus (HPV) DNA testing (“co-testing”). The previous USPSTF guidelines had indicated that evidence was insufficient to make a recommendation regarding the use of co-testing. USPSTF now recommends that women age 30–65 years should be screened by either cytology every 3 years or co-testing every 5 years.

• HPV can take more than a decade to progress to cervical dysplasia or cancer

• In contrast, ACS/ASCCP/ASCP finds that co-testing every 5 years is preferred to cytology alone but that cytology alone every 3 years is an acceptable strategy. In choosing to make co-testing the preferred strategy, ACS/ASCCP/ASCP focused on evidence from multiple randomized trials showing that co-testing has improved performance compared with cytology alone.

• Specifically, co-testing has increased sensitivity for detecting cervical intraepithelial neoplasia grade 3 or greater (CIN3+), and women who have undergone co-testing have a lower risk of CIN3+ and invasive cancer after the first screening round.

• Because of this improved performance, co-testing can be used for screening at less frequent intervals than cytology alone. In addition, co-testing offers greater risk reduction than cytology alone for adenocarcinoma of the cervix and its precursors.
Most surprising of these recommendations is that women under age 21 should not be tested. But it makes sense -- many sexually active women under 21 will develop a human papillomavirus infection, or HPV, which can lead to pre-cancerous lesions.

And when doctors see those lesions on a Pap test, they want to treat them. Yet nearly all of those lesions will disappear on their own without residual effects. And those that do not are easily treated years later.

Treating them as soon as they're spotted can lead to cervical incompetence and miscarriage down the road.

Women who have a normal Pap result and a positive HPV test result should repeat both tests or receive a gene test called genotyping that determines if they have HPV 16 and 18. These types of HPVs are known to cause 70% of cervical cancers. There is no immediate need for a colposcopy.

Mildly abnormal Pap result (called ASC-US) and a negative HPV test result should follow up with either HPV testing plus a Pap test, or HPV testing alone, at intervals of three years or longer.

Women who have been vaccinated against HPV should begin cervical cancer screening at the same age as unvaccinated women.
Clinical details:

**Specimen Type**: Conventional Smear / Liquid based cytology

**SPECIMEN ADEQUACY**: Superficial cells
Intermediate cells
Parabasal cells
Deep parabasal/Basal cells
Endocervical cells
Metaplastic cells
Others

**Inflammation** – Mild / Moderate / Severe

**Organisms**: Doderlein bacilli
Trichomonas vaginalis
Fungal organisms
Others

**EPITHELIAL CELL ABNORMALITIES**: DETECTED / NOT DETECTED
Squamous/Glandular

**RESULT INTERPRETATION**: NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY
LSIL/HSIL
OTHERS

**HPV DNA & Genotyping detection**

Method: DNA isolation followed by PCR amplification and genotyping by direct sequencing

Test Results: HPV: Detected / Not Detected
Genotype:

Interpretation:
1. A result Not detected indicates the absence of HPV in the specimen.
2. A result Detected indicates the presence of HPV in the specimen.

Test Details: The sensitivity of PCR based methods is about 100 HPV viral genomes in a b/g of 100ng cellular DNA with a specificity of >98%. An internal control of 268bp is run for every sample to validate the assay.

Clinical significance: High risk HPV include: 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, 59, 68, 69 of which type 16 & 18 cause 70% of cervical cancers. However the low risk types viz 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73, 81 of which 6 & 11 are the ones linked to 90% genital warts.

Limitation of the assay: Presence of PCR inhibitors in the sample may prevent DNA amplification for HPV.

This test has been validated by the molecular biology section.
RESULTS

• The age range in our study was 20 to 80 years.

• 75% of patients were in the age range of 30 – 60 yrs when abnormal findings were detected.
## Comparison of Conventional & LBC cases

<table>
<thead>
<tr>
<th>Year</th>
<th>Conventional Pap</th>
<th>LBC(Thinprep)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jul-2009</td>
<td>1637</td>
<td>111</td>
</tr>
<tr>
<td>2010</td>
<td>2745</td>
<td>846</td>
</tr>
<tr>
<td>2011</td>
<td>3092</td>
<td>1288</td>
</tr>
<tr>
<td>Till Sept 2012</td>
<td>2661</td>
<td>1650</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10135</strong></td>
<td><strong>3895</strong></td>
</tr>
</tbody>
</table>

**UNEVALUATED:-**
2342 CONVENTIONAL
1789 LBC

A linear increase in the LBC samples is noteworthy.
### Distribution of Abnormal & negative smears (July 2009 to September 2012)

<table>
<thead>
<tr>
<th>NILM</th>
<th>Conv</th>
<th>LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9981(98.45%)</td>
<td>3825(98.2%)</td>
</tr>
<tr>
<td>Abnormal</td>
<td>154(1.55%)</td>
<td>70(1.8%)</td>
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</table>

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Conv</th>
<th>LBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>64</td>
<td>21</td>
</tr>
<tr>
<td>LSIL</td>
<td>37</td>
<td>37</td>
</tr>
<tr>
<td>ASC-H</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>HSIL</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>AGUS</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>154</td>
<td>70</td>
</tr>
</tbody>
</table>
% of distribution of Abnormal findings in Conventional and LBC

A significant increase in LSIL in LBC Compared to conv cyto is evident

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Conv cyto</th>
<th>LBC</th>
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</thead>
<tbody>
<tr>
<td>ASCUS</td>
<td>0.63%</td>
<td>0.54%</td>
</tr>
<tr>
<td>LSIL</td>
<td><strong>0.37%</strong></td>
<td><strong>0.95%</strong></td>
</tr>
<tr>
<td>ASC-H</td>
<td>0.07%</td>
<td>0.05%</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.31%</td>
<td>0.23%</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>0.08%</td>
<td>0.03%</td>
</tr>
<tr>
<td>AGUS</td>
<td>0.07%</td>
<td>0.00%</td>
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### Table of comparison (US CAP)

<table>
<thead>
<tr>
<th>Category</th>
<th>Convention cytology</th>
<th>Thin Prep LBC</th>
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<tbody>
<tr>
<td>ASCUS</td>
<td>2.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>LSIL</td>
<td>1.3%</td>
<td><strong>3.0%</strong></td>
</tr>
<tr>
<td>HSIL</td>
<td>0.3%</td>
<td>0.6%</td>
</tr>
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</table>

### Present study

<table>
<thead>
<tr>
<th>Category</th>
<th>Conv cytology</th>
<th>LBC</th>
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<tbody>
<tr>
<td>ASCUS</td>
<td>0.63%</td>
<td>0.5%</td>
</tr>
<tr>
<td>LSIL</td>
<td><strong>0.37%</strong></td>
<td><strong>0.9%</strong></td>
</tr>
<tr>
<td>HSIL</td>
<td>0.31%</td>
<td>0.2%</td>
</tr>
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</table>

A 2.5 time increase in LSIL
• From the aforementioned slides we can conclude that there is a definite increase in LSIL compared to ASCUS in LBC.

• The differences between conventional and LBC preparations such as absence of obscuring of cellular details by blood, mucus & inflammatory cells aids interpretation.

• Uniform and representative.

• Lower unsatisfactory rate in LBC Preparations due to better sampling.

• A reflex HPV test or co-testing can be carried out which is the greatest benefit (US FDA approved).
## Other findings

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<th>Conventional</th>
<th>LBC</th>
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<tbody>
<tr>
<td>Candida</td>
<td>177 (1.77%)</td>
<td>45 (1.18%)</td>
</tr>
<tr>
<td>Trichomonas</td>
<td>6 (0.06%)</td>
<td>1 (0.02%)</td>
</tr>
<tr>
<td>Reactive cellular changes a/w</td>
<td>736 (7.37%)</td>
<td>331 (8.65%)</td>
</tr>
<tr>
<td>Unsatisfactory</td>
<td>42 (0.5%)</td>
<td>5 (0.13%)</td>
</tr>
</tbody>
</table>

Two cases of granulomatous cervicitis were also reported which on histology were compatible with tuberculous cervicitis. One of them presented as a mass lesion.
HPV RESULTS

• 116 of 177 cases showed the high risk genotypes 16 & 18 i.e. 66%

• 21 of 31 cases were positive for low risk genotypes 6 & 11 i.e. 68%

• The average HPV infection rate was 10 – 11%

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases for HPV screening</th>
<th>Abnormal findings in Cytology</th>
<th>HPV detected in</th>
</tr>
</thead>
</table>
### HIGH RISK HPV(2011)

<table>
<thead>
<tr>
<th>TYPES</th>
<th>CASES DETECTED</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>42</td>
</tr>
<tr>
<td>18</td>
<td>20</td>
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<tr>
<td>35</td>
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<td>68</td>
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<tr>
<td>69</td>
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<td><strong>Total</strong></td>
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### LOW RISK HPV(2011)

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<tr>
<td>11</td>
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<td>73</td>
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<tr>
<td>81</td>
<td>0</td>
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<tr>
<td><strong>Total</strong></td>
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## HIGH RISK HPV (2012)

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<tr>
<td>Total</td>
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## LOW RISK HPV (2012)

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<td>81</td>
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<tr>
<td>Total</td>
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## Data Summary

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<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2012</th>
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</thead>
<tbody>
<tr>
<td>Total no. of pap</td>
<td>3182</td>
<td>3553</td>
<td>4411</td>
<td>4311</td>
</tr>
<tr>
<td>Conventional pap</td>
<td>1637</td>
<td>2745</td>
<td>3092</td>
<td>2661</td>
</tr>
<tr>
<td>LBC</td>
<td>111</td>
<td>846</td>
<td>1288</td>
<td>1650</td>
</tr>
<tr>
<td>% positive Conventional pap</td>
<td>2.01%</td>
<td>2.3%</td>
<td>0.6%</td>
<td>1.4%</td>
</tr>
<tr>
<td>% positive LBC</td>
<td>8.1%</td>
<td>1.5%</td>
<td>1.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>HPV screening</td>
<td>NA</td>
<td>NA</td>
<td>899</td>
<td>989</td>
</tr>
<tr>
<td>% positive in HPV</td>
<td>NA</td>
<td>NA</td>
<td>11.01%</td>
<td>10.31%</td>
</tr>
</tbody>
</table>
HPV infects cells in the cervical transformation zone, area of active cell turnover. Basal cells, which feature the HPV receptor, are a natural target for infection.

The most common diagnostic challenges occur in distinguishing LSIL from benign reactive atypia, CIN 2 from CIN 3, and CIN 3 from atrophy & immature metaplasia (Do not have the mitotic activity, nuclear pleomorphism, loss of cell polarity, nuclear hyperchromasia, or clumped chromatin of HSIL).

The distinction between CIN 2 and CIN 3 is not as crucial, because both lesions are in the high-grade category.

Studies have shown that the subjective criteria used for separating the different grades and the fact that the thickness of the immature basaloid cells can vary within the same lesion lead to failures in reproducible diagnosis of CIN 2.
ANCILLARY STUDIES

• **p16INK4a** is a tumor suppressor gene that encodes a protein involved in cell cycle regulation. Diffuse, strong, cytoplasmic and/or nuclear staining in squamous and glandular lesions associated with high-risk HPV infection.
• Interpreting p16 immunostaining is complicated.

• **Mib–1**: HSIL (CIN 2 and CIN 3) usually shows diffuse nuclear positivity scattered throughout all layers of the epithelium.

• **ProEx C** is a recently developed IHC assay that targets the expression of topoisomerase II-α and minichromosome maintenance protein-2.
• The assay is a nuclear stain that is positive in cervical dysplasia and has been validated in cytologic specimens for the detection of HSIL. It is comparable to p16 and Mib-1 in the detection of high-grade lesions in formalin-fixed tissue sections and in distinguishing them from benign mimics.

• **In situ hybridization (ISH)** is a direct signal detection assay that allows visualization of HPV DNA within infected cells. Episomal forms result in blocklike nuclear labeling, whereas integrated forms result in punctate, nuclear signals. Punctate signals are most frequently found in HSILs and invasive carcinomas.
Chromogen in situ hybridization (CISH) offers a real advantage by providing a cytomorphologic link in assessing HPV Positivity which is seen as either in or not in, the abnormal cells.

It also provides additional information as to whether the virus is integrated or not in the host genome (discrete nuclear dots imply that virus is in the chromosomal DNA & now able to effect the genetic aberration almost always a marker of a high risk HPV).

It is even possible to detect and localize single or very few HPV copies within infected nuclei.

It can be tested real time.
Comparison between methods used for test validation

HPV IHC Genotype includes – 1, 6, 11, 16-16, 18 & 31
HPV CISH Genotype – 16, 18, 31, 33, 35, 45, 51, 82.
HPV DNA by PCR – High Risk :16,18,31,33,35,39,45,51,52,, 56, 58,59,68 and 69.
Low risk : 6, 11,40,42.43,44,53,54,61,72,73 and 81

<table>
<thead>
<tr>
<th>Parameter / test</th>
<th>CISH</th>
<th>PCR</th>
<th>IHC</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>97 %</td>
<td>*98%</td>
<td>40%</td>
</tr>
<tr>
<td>Specificity</td>
<td>86 – 89 %</td>
<td>44 – 95 %³</td>
<td>Variable according to genotype included.</td>
</tr>
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</table>

The PPV and NPV of PCR are 41% and 97.5% respectively

The PPV and NPV of CISH are 52% and 99% respectively.
INTERESTING CASES

Case 1
ML G 2398/10
Clinical details

• 61 yr, female
• Colposcopy - Abnormal
• Thin Prep Pap smear
Diagnosis

HIGH GRADE SQUAMOUS INTRAEPITHELIAL LESION
SIGNIFICANCE OF HSIL

• HSIL indicates moderate or severe dysplasia.

• Chance of a Pap smear showing HGSIL and of there being an invasive cancer of the cervix already present is less than 1%.

• In fact only about 1.5% of women with a HGSIL Pap smear will progress to having invasive cancer of the cervix within the next 24 months.

• The next step is to have a colposcopically directed biopsy of the cervix to see whether the changes on the cervix are the same as the Pap, worse than the Pap indicates (carcinoma in situ, or invasive cancer) or less severe (mild dysplasia, inflammation) than the Pap indicated.

• The biopsy result is the "gold standard"
Final diagnosis

CERVICAL INTRAEPITHELIAL NEOPLASIA, CIN III
CASE - 2

ML G – 2123/12
Diagnosis

LSIL

REFLEX TESTING DONE

HPV Genotype -16
CASE - 3

ML G - 797/12 & ML – 2935/12
ML G – 797/12 (Convention pap)
ML G – 797/12 (Convention pap)
Diagnosis

ASC-H
Diagnosis

Cervical Intraepithelial Neoplasia Grade III (CIN-III)
ML – 2935/12 CISH - Positive
CASE - 3

ML G- 1285/12 & ML – 4633/12
ML G – 1285/12 Conventional Pap
ML – 4633/12
Diagnosis
HPV 16 DETECTED
HISTO CYTO NEGATIVE
Rationale For Co-testing

• Co-testing increases prevalently detected CIN3+ (in comparison to cytology) in the initial screening round and results in decreased CIN3+ in subsequent rounds

• Co-testing significantly reduced the invasive cancer rate in the second screening round in one RCT

• A negative co-test has a high negative predictive value for CIN3+ and cancer in subsequent 5 to 6 years.

• Screening at short intervals leads to unnecessary procedures and potentially harmful treatment of lesions destined to clear without intervention
Management of Women with HPV-Positive, Cytology- Negative Co-tests

Women cotesting HPV positive, cytology negative should be followed with either

- **Option 1**: Repeat co-testing in 12 months or

- **Option 2**: Immediate HPV genotype-specific testing for HPV16 alone or for HPV16/18.

If co-testing is repeated at 12 months, women testing positive on either test (HPV positive or LSIL or more severe cytology) should be referred to colposcopy; women testing negative on both tests (HPV-negative and ASCUS or negative cytology) should return to routine screening.

If immediate HPV genotype-specific testing is used, women testing positive for HPV16 or HPV16/18 should be referred directly to colposcopy; women testing negative for HPV16 or HPV16/18 should be co-tested in 12 months, with Mx of results as described in option 1.

Women cotesting HPV positive, cytology negative should not be referred directly to colposcopy. Furthermore, they should not be tested for individual HPV genotypes other than HPV16 and HPV18.
CASE - 4

ML G - 922/12
LBC, Vault smear
LBC, Vault smear
Diagnosis

LSIL
THANK YOU