Cobas® 4800 HPV detection in cervical, vaginal, urine and oral samples from women with abnormal cytology before and after treatment in Dumfries and Galloway.

”A cause is Insufficient but Necessary part of a complex of conditions, which is Unnecessary but Sufficient for the effect.”

John Mackie

Grazyna Stanczuk MD, MRCOG, PhD
grazyna.stanczuk@nhs.net
SHINe Meeting, University of Edinburgh, 15th of September 2012.
Aim

To compare prevalence of HR-HPV DNA detection in four concomitant samples: cervical, vaginal, urine and oral; from women with significant cervical lesion (HGCIN) before and after treatment using Cobas® 4800.
Hypothesis

- HR-HPV viremia is higher in clinically significant cervical intraepithelial neoplasia (HGCIN) hence likelihood of detection of HR-HPV in cervical, vaginal and urine samples is high. The same may apply to detection of HR-HPV in oropharynx.

- After removal of HGCIN from the cervix grate majority of women will test negative for HR-HPV in cervical sample. We hypothesis that similar reversal from positive to negative testing will follow in vagina, urine and oropharynx samples.
Material and Methods

- 100 consenting to the study women attending colposcopy clinic with abnormal cervical smear.
- Samples: cervical in 20ml of ThinPrep
  vaginal in 5 ml of ThinPrep
  oral in 2ml of ThinPrep
  urine cells pallet in 5 ml of ThinPrep

Cobas® 4800 HPV test
Cobas® 4800 HPV Detection in Cervical, Vaginal and Urine samples from Women with Abnormal Cervical Cytology in Dumfries and Galloway.

- 32% percent of patients were between 20 and 24 years old.
- More than half (56%) had a borderline or mild dyskaryosis.
- 31% percent of CIN2+ were diagnosed in women younger than 25 years and 64% under age of 30 years.
Cobas® 4800 HPV Detection in Cervical, Vaginal and Urine samples from Women with Abnormal Cervical Cytology in Dumfries and Galloway.

102 patients with abnormal smear

- 32 CIN 1
- 32 CIN 2
- 30 CIN 3
- 2 Cancer

- The majority of patients had LLETZ (70%), 30% had cervical biopsy.
- 30 CIN 3 cases include two women with GCIN 3.
- HPV 16 was detected in 40 women (39%); it was a single detected type in 15 women.
- 52% of women with HPV 16 had CIN2+ and 30% had CIN3+.

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>CIN2+</th>
<th>CIN3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobas</td>
<td>55.7</td>
<td>42.0</td>
</tr>
<tr>
<td>Abbott</td>
<td>56.2</td>
<td>43.2</td>
</tr>
<tr>
<td>Aptima</td>
<td>55.6</td>
<td>44.1</td>
</tr>
</tbody>
</table>

Distribution of HPV types in low and high grade lesions

PPV of testing HPV16 positive in women with abnormal smear (%) Predictors 2, Szarewski A et al., 2012.
Cobas® 4800 HPV Detection in Cervical, Vaginal and Urine samples from Women with Abnormal Cervical Cytology in Dumfries and Galloway.

<table>
<thead>
<tr>
<th>HPV Cobas® positive</th>
<th>Cervical</th>
<th>Vaginal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>29/32 (91%)</td>
<td>27/32 (85%)</td>
</tr>
<tr>
<td>CIN 2</td>
<td>29/32 (91%)</td>
<td>28/32 (88%)</td>
</tr>
<tr>
<td>CIN 3</td>
<td>29/30 (97%)</td>
<td>29/30 (97%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

Cases with partially discordant results

- This is a first report of HPV detection by Cobas® in self-collected vaginal samples.
- Self-collected vaginal sampling is a valid option for cervical screening.
Cobas® 4800 HPV Detection in Cervical, Vaginal and Urine samples from Women with Abnormal Cervical Cytology in Dumfries and Galloway.

<table>
<thead>
<tr>
<th>HPV Cobas® positive</th>
<th>Cervical</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>29/32 (91%)</td>
<td>27/32 (85%)</td>
</tr>
<tr>
<td>CIN 2</td>
<td>29/32 (91%)</td>
<td>24/32 (75%)</td>
</tr>
<tr>
<td>CIN 3*</td>
<td>29/30 (97%)</td>
<td>27/30 (90%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>2/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

82% are urine positive in CIN2+

* Include two cases with GCIN3

<table>
<thead>
<tr>
<th>No.</th>
<th>Pathology</th>
<th>Cervix</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CIN 3</td>
<td>16</td>
<td>Others</td>
</tr>
<tr>
<td>2.</td>
<td>CIN 3</td>
<td>Others+16+18</td>
<td>16</td>
</tr>
<tr>
<td>3.</td>
<td>CIN 2</td>
<td>Others+16</td>
<td>16</td>
</tr>
<tr>
<td>4.</td>
<td>CIN 2</td>
<td>16</td>
<td>Others+16</td>
</tr>
<tr>
<td>5.</td>
<td>CIN 2</td>
<td>Others+16</td>
<td>Others</td>
</tr>
<tr>
<td>6.</td>
<td>CIN 2</td>
<td>Others</td>
<td>Others+16</td>
</tr>
</tbody>
</table>

Cases with discordant results

- This is a first report of HPV detection by Cobas® in urine samples.

- Further work is required in order to optimise and clinically validate use of urine HPV testing in cervical screening scenarios.
Cobas® 4800 HPV detection in cervical, vaginal and urine samples after treatment for HG CIN in Dumfries and Galloway – preliminary results (n=19).

<table>
<thead>
<tr>
<th>No</th>
<th>Pathology</th>
<th>Cervix</th>
<th>Vagina</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CIN3, GCIN3</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>(Others+16+18)</td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
</tr>
<tr>
<td>2.</td>
<td>CIN 3</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
</tr>
<tr>
<td>3.</td>
<td>CIN 3</td>
<td>negative</td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>(Others+16)</td>
<td>(Others+16)</td>
<td>(Others+16)</td>
<td>(Others+16)</td>
</tr>
<tr>
<td>4.</td>
<td>CIN 3</td>
<td>negative</td>
<td>Others+16</td>
<td>Others+16</td>
</tr>
<tr>
<td></td>
<td>(Others+16)</td>
<td>(Others+16)</td>
<td>(Others+16)</td>
<td>(Others+16)</td>
</tr>
<tr>
<td>5.</td>
<td>CIN 2</td>
<td>negative</td>
<td>-</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
</tr>
<tr>
<td>6.</td>
<td>CIN 2</td>
<td>negative</td>
<td>Others+16</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>(Others+16)</td>
<td>(Others+16)</td>
<td>negative</td>
<td>negative</td>
</tr>
<tr>
<td>7.</td>
<td>CIN 2</td>
<td>negative</td>
<td>Others</td>
<td>Others</td>
</tr>
<tr>
<td></td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
<td>(Others)</td>
</tr>
</tbody>
</table>

Cobas® HPV positive

<table>
<thead>
<tr>
<th>Cobas® HPV positive</th>
<th>Cervix</th>
<th>Vagina</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 3 (n=11)</td>
<td>2/11</td>
<td>4/11</td>
<td>4/11</td>
</tr>
<tr>
<td>CIN 2 (n=8)</td>
<td>-</td>
<td>2/8</td>
<td>2/8</td>
</tr>
</tbody>
</table>
Quest for Improved, Women friendly cervical screening continue: Evaluation of HPV DNA testing in primary cervical cancer screening (10,000 women study). Operational Study in Dumfries and Galloway NHS Health Board.

**Aims**

- To evaluate the efficacy of different cervical cancer primary screening strategies.
- To optimise and clinically validate HPV detection in self-collected vagina and urine samples.
- To establish positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of HPV testing in cervical, vaginal and urine samples, in each screening strategy.
- To evaluate cost-effectiveness of each screening strategy.
- To evaluate infrastructure, human resources and equipment needed in different screening strategies.
- Provide choices to women.
Sensitivity of cytology vs. HPV DNA for ≥CIN2

Studies performed in developed countries in women 30 years and older.

*Sensitivity* for ≥CIN2 (%)

- Switzerland Bigras (N=13,842)
- USA Cardenas (N=1,850)
- France Coste (N=3,080)
- USA Kulasingam (N=774)
- Canada Mayrand (N=9,977)
- Germany Petry (N=7,908)
- UK* Cuzick (N=10,358)

Average increase 35.7%


Cumulative incidence rate of CIN 3+ according to baseline test results in the first 72 months of follow up—from an overview of 12 trials

http://www.cancerforum.com/print/articles/new-technologies-for-cervical-cancer-screening/
Cumulative incidence of ≥CIN3 in women with negative cytology over 10 years by hrHPV status at baseline

Women with HPV16 and HPV18 infection* at baseline are at a higher risk of developing cervical disease over time than women positive for the 12 other hrHPV types

* No histological evidence of cervical disease at baseline.

Proposed algorithm for cervical cancer screening

- **High NPV test**
  - **Negative**
    - 5 year recall
  - **Positive**
    - **High PPV test**
      - **Positive**
        - Colposcopy
      - **Negative**
        - **High NPV + high PPV in 6-12 months**
      - **Borderline**
        - **High NPV + high PPV in 6-12 months**
  - **Borderline**
    - **Negative +Borderline**
    - **Positive + Borderline**
    - **High NPV + high PPV in 6-12 months**

- **High NPV + high PPV in 6-12 months**
- **High PPV Positive**
- **High PPV Positive**
Proposed algorithm for cervical cancer screening

HPV test

- Negative
  - 5 year recall

- Positive
  - VIA
  - HPV 16
  - Cytology
  - P16
  - Methylation

<table>
<thead>
<tr>
<th>VIA</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
<td>14-95%</td>
</tr>
<tr>
<td></td>
<td>85%</td>
<td>14-98%</td>
</tr>
</tbody>
</table>
Proposed algorithm for cervical cancer screening

HPV test

Negative

5 year recall

Positive

Cytology

Negative or borderline

HPV+Cytology in 6-12 months

Cyto negative or borderline HPV positive

Cyto borderline HPV negative

HPV+Cytology in 6-12 months

Mild+

Colposcopy

Cyto Mild+
Proposed algorithm for the study

Cytology N=10,000

Cyto-/HPV-

3 year recall

Cervical HPV test

Cyto-/HPV+

HPV in 6-12 months

Approximately 6%

Positive cytology

Colposcopy

Cyto Mild+

Vaginal sample
HPV DNA test

Urine sample
HPV DNA test

Vaginal sample
HPV DNA test

Urine sample
HPV DNA test

220 Colposcopies
57 of CIN 2
44 of CIN3
Proposed algorithm for the study

Cytology  N=10,000

HPV test

Vaginal sample  HPV DNA test
Urine sample  HPV DNA test

Cyto-/HPV+

Approximately 6% (6.3% will have CIN 3+) Petry et al. 2011
N=36

Vaginal sample  HPV DNA test

HPV-16

Approximately 30%  N=200

Colposcopy

HPV in 6-12 months

P16/Ki-67+ve

Approximately 25%  N=150

Vaginal sample  HPV DNA test

Approximately 6%  N=600

Urine sample  HPV DNA test

Approximately 30%  N=200
Thank you