

# HPV-based cervical cancer screening: Gaining insights in sample preference and cost-effectiveness

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## LIMITATIONS WITH CURRENT CERVICAL CANCER SCREENING METHODS

Cervical cancer can be prevented through vaccination and screening; however, it remains the fourth most common cancer type in women, with over 500,000 cases detected in 2018. Most cases of cervical cancer have been linked to types of high-risk Human Papillomavirus (HPV), a common sexually transmitted infection<sup>1</sup>.

Regular cytology-based screening for cervical cancer via a Pap smear, which look for abnormal cervical cells, has directly shown to improve incidence and mortality rates<sup>2,3</sup>. Despite the benefits, many women are often reluctant to undergo a Pap smear.

### Limitations of Pap smears



Figure 1: Pap smear limitations

## HPV-BASED SELF-COLLECTION METHODS CAN INCREASE CERVICAL CANCER SCREENING COVERAGE

Given the drawbacks with a Pap test, alternative methods, which are easy and can better fit a women's own schedule are needed. In this regard, a number of studies have shown that self-collection methods for HPV testing offer promise and better acceptance for cervical cancer screening.

These methods can improve coverage, especially for women who do not participate in routine screening. A meta-analysis reported an overall 2.14 fold increase in screening coverage due to self-samples<sup>3</sup>. Additionally, studies have shown that the performance of self-samples provided similar results to physician-collected samples for the detection of HPV, highlighting the impact these techniques could have in screening uptake<sup>4</sup>.

### Overall 2.14 fold increase in screening coverage



Figure 2: Screening coverage

## URINE AS A PREFERRED SAMPLE TYPE

Most acceptability studies to date have focused on self-collection through brush- or swab-based cervico-vaginal samples<sup>5</sup>. The evidence-base on urine in comparison to vaginal self-sampling and physician-taken cervical samples is less extensive, but the available studies consistently report urine for HPV testing as the most accepted and preferred sample type. Urine was preferred in almost all studies as the most preferred sampling method over vaginal, vulvar and physician-collected cervical samples for HPV testing to detect high-grade lesions<sup>6</sup>. Additionally, women were more confident about providing a urine sample than a vaginal sample for HPV testing and had limited concerns about the accuracy of the test in these samples<sup>7</sup>. The Belgian VALHUDES study also aims to assess the sensitivity and specificity of particular hrHPV assays in vaginal self-samples as well as first-void urine compared to matched physician-taken samples<sup>8</sup>.

In another study in Korean women, stress was rated lowest for urine sampling (2.04/10), followed by vaginal self-sampling (2.12) compared to clinician-taken samples (5.01), which was rated as the highest stress. While the highest trust rates were observed for the Pap test (93%), women reported more trust in tests with urine sampling (91%) compared to vaginal self-sampling (87.5%). Compared to the Pap test, the odds ratio of associating pain to a urine sample was only 0.05 compared to 0.5 for the vaginal self-sample<sup>9</sup>.

Women in the UK compared five self-sampling methods; urine was rated as easiest to collect. The women were also more confident they had taken the sample correctly with urine<sup>10</sup>.

When evaluating sample acceptance among women across different ethnic groups in the United States<sup>9</sup>, including Hispanic women, and non-Hispanic black and white women, urine self-collection was strongly preferred for future high-risk HPV testing across all ethnic groups. Around 85% of participants reported no concerns with urine collection, compared to 68% for brush-based collection. For vaginal self-sampling, 16% of women were concerned if they performed the collection correctly. Further, 78% of women reported that they would be more likely to attend future cervical cancer screening appointments if screening would be urine based, highlighting the impact urine-based testing could have on certain populations<sup>11</sup>.

### Sample acceptance among women



Figure 3: Sample acceptance

## FIRST-VOID URINE CONTAINS HIGHER CONCENTRATIONS OF HPV DNA

First-void urine has shown to contain higher concentrations of HPV DNA, therefore, collection of this fraction is important to increase sample sensitivity. NovoSanis developed Colli-Pee<sup>®</sup> which allows for standardized, volumetric collection of first-void urine. The device also enables immediate mixing of a urine preservative, which has shown to improve stability of the urine sample<sup>12</sup>. Cup-based urine collections can be awkward, messy and inconvenient for the user.

Several studies reported that first-void urine sampling, using a first-void urine collection device was preferred over a physician-collected cervical sample. Colli-Pee<sup>®</sup> usability data also show more accurate and volumetric collection of first-void urine than a traditional urine cup, and that users find the device easy or very easy to use<sup>13,14</sup>. Colli-Pee<sup>®</sup> has been rated as the most accepted sample type. A proportion of 89.0% of the participants rated convenience of urine sampling as good to excellent compared with physician-taken samples, with no aspect of urine sampling rated as poor<sup>15</sup>. Further, first-void urine sampling with Colli-Pee<sup>®</sup> resulted in good high-risk HPV agreement between paired first-void urine and cervical samples<sup>15,16</sup>.

## URINE AS A SAMPLE TYPE HAS POTENTIAL TO REACH NON-ATTENDERS

All the discussed studies evaluated sample acceptance and preference in women who are already undergoing a Pap smear or colposcopy. Perceptions on urine self-sampling of cervical screening non-attenders remains unclear while the technology is likely to have most value in this population<sup>7</sup>.

Screening attenders may have different preferences to non-attenders who might be more reluctant to provide a physician-taken sample. This is where the importance of studies on participation rates of non-responders comes in, as women are offered different strategies for cervical cancer screening.

In a vaccine impact monitoring study, young women who did not attend their first cervical screening appointment, received a self-collection kit by postal mail. The results showed 14% of urine samples returned compared to 12% of the swabs<sup>17</sup>. In another study in the general population in France, 5000 hard to reach women (40-65) who had not had a Pap smear over the past three years received a urine sampling home-collection kit. 771 returned a urine sample by postal mail. This highlights that urinary HPV testing may be useful to reach women who do not regularly have cervical Pap smears done to find high-grade cervical lesions<sup>18</sup>.

### COST-EFFECTIVENESS OF SELF-SAMPLING METHODS

Successful implementation of HPV self-sampling programs will depend on different factors, including potential costs and health benefits. The most common driver of HPV self-sampling cost-effectiveness is the level of increase in screening attendance<sup>19</sup>. Interventions that encourage HPV self-sampling uptake such as patient education, effective messaging and outreach strategies might benefit response rates.

In a trial in the UK, among previously unscreened women, direct mail HPV self-sampling was considered the most cost-effective strategy. This strategy provided a cost well below the willingness to pay threshold per quality-adjusted life-years (QALY), with higher screening uptake and subsequent increase in CIN2+ detection<sup>20</sup>.

### QALY

A QALY is a measure of disease burden, including both the quality and the quantity of life lived.

Additionally, HPV self-sampling offers opportunities for low-medium income countries (LMIC) where the infrastructure required to underpin screening by cervical cytology is lacking<sup>7</sup>. Five studies modeled HPV self-sampling in LMIC and found that (a) HPV self-sampling was more effective than Visual Inspection with Acetic acid (VIA), (b) once in a lifetime screening could be cost-effective at reducing cervical cancer incidence and mortality, and (c) multiple screenings per lifetime could also be cost-effective for further reductions in cervical cancer<sup>19,21</sup>. Cost-effectiveness of HPV self-sampling at home with cryotherapy for high-risk HPV positive women for all women in Uganda estimated 70% screening coverage. A lifetime cervical cancer risk reduction of 15% was reported for HPV self-sampling compared to 7.2% for VIA based on once in a lifetime screening<sup>19,21</sup>.

The World Health Organization (WHO) also used HPV-self sampling through urine collection to evaluate the impact of HPV vaccination in Rwanda and Bhutan. Young girls in these areas are often reluctant to accept a gynecological examination for collection of a cervical sample. Around 1,000 women were recruited in each country between the ages of 17 and 22, who provided a valid urine sample using Colli-Pee<sup>®</sup>. Only 84 samples were not returned in Bhutan, and 132 in Rwanda<sup>22</sup>, highlighting the high acceptability of urine as a sample type, and feasibility for home-based collection in combination with accessible delivery points in LMIC settings.

HPV self-sampling, including urine-based testing can be cheaper than standard cervical screening tests because it does not require an appointment, a practitioner or any special equipment<sup>7</sup>. Colli-Pee<sup>®</sup> Small Volumes offers an additional benefit since its collector tubes immediately fit carriers of high-throughput machines, eliminating the need for an additional pipetting step and reducing manual handling errors.



**Step 1**  
First-void urine collection by patient



**Step 2**  
Molecular Analysis

WORKFLOW WITH COLLI-PEE SMALL VOLUMES

There are some cost-related challenges with HPV self-sampling methods, however. If HPV self-sampling is used by too few women at high risk of CIN2+ such as never-screened women, it could possibly lead to increased costs from false positives being sent to colposcopy for diagnosis. A related concern is the possibility of 'switching,' in which women who otherwise would have attended Pap decide to self-sample instead. It was reported that HPV self-sampling was most cost-effective when users had a longer time since last screening<sup>23</sup>.

### CONCLUSION

Women prefer easy, and non-invasive techniques that are clinician independent for cervical cancer screening. Overall, the most accepted and preferred specimen for HPV self-sampling is urine. Urine as a sample type offers potential to increase screening uptake and improve cost-effectiveness ratios.

Further, studies have shown that in order to use HPV-based urine sampling for cervical cancer screening, the urine collection process has to be optimized through effective collection of first-void urine and addition of a preservative. Colli-Pee<sup>®</sup> offers great potential in this regard.

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