Colli-Pee® - Performance of a game-changing sampling device for HPV-based cervical cancer screening

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INTRODUCTION

Cervical cancer is the fourth most common cancer in women, worldwide leading to over 300,000 deaths per year.[1] Introduction of screening programs has allowed for an increased detection of pre-cancer lesions, resulting in a 50% reduction of premature deaths. Yet, non-attendance rates are high: on average 40% of women living in developed countries are not participating in screening, and 80% in developing countries.[2]

The golden standard to screen for pre-cancer lesions has been cytologic evaluation based on clinician-taken cervical smears. Reasons for reluctance to gynaecological examinations are the relative invasive character of cervical sampling, ethnicity and culture, lack of time and the need to visit a clinician. The principal cause of cervical cancer are high-risk infections with the human papillomavirus (HPV) and a significant evidence-base has been established to indicate that HPV-based cervical cancer screening is more effective and efficient.[3]

This is where Novosanis' Colli-Pee®, a user-friendly, self-sampling urine-capturing device fits in with the opportunity to offer a complete molecular approach towards cervical cancer screening. Colli-Pee® collects first-void urine (first 20 mL of urine flow) for the detection of HPV infections. The same sample also has great potential for molecular-based triage testing to differentiate between a transient productive infection and a persistent transforming infection.[4]

STANDARDIZED FIRST-VOID AND VOLUMETRIC SELF-SAMPLING

First-void urine contains washed away mucus and debris from exfoliated superficial cell layers of a cervix carcinoma. Colli-Pee® allows for volumetric and standardized collection of first-void urine and different variants enable collection of different volumes ranging from 45 mL to 4 mL. The volumetric collection capabilities of the device has been validated - 84.8% and 89.4% of the collected samples are within the specified range of 20±2 mL and 10±1 mL respectively.[5] This is significantly more standardized compared to a regular urine cup, where collected sample volumes are only 15.1% within the specified range. Moreover, Colli-Pee® outperforms a regular urine cup with regards to the number of both human and HPV DNA copies found in urine.[6,7] This is illustrated on Figure 1 for HPV 16 DNA copies specifically.

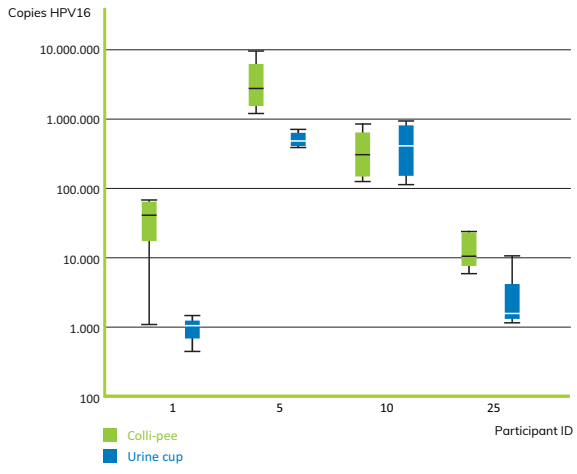

Figure 1
Boxplots of HPV 16 DNA copies, for all patients where an infection with HPV 16 was detected, found in Colli-Pee® versus copies found in a urine cup.

Novosanis' usability study also showed that Colli-Pee® is a well-accepted solution for home-based collection: 96% of users rated the device as easy-to-use and 87% preferred postal delivery to visiting a physician.[8]

CLINICAL PERFORMANCE

Five clinical trials have been set-up to address the performance of Colli-Pee® collected first-void urine for HPV detection in cervical cancer screening programs, which include more than 2500 women referred to colposcopy.

The EVAH study, using the analytically sensitive SPF10-DEIA-LiPA25 assay and the clinically validated GP5+/6+ assay (EIA) for HPV detection, showed that urine samples collected with Colli-Pee® enabled almost perfect detection of HPV infections in women with CIN2+ lesions.[9] This is illustrated on Figure 2 by an absolute sensitivity ranging from 95% to 100%. The quality of clinician-taken smear and a vaginal swab self-sample were also assessed within the EVAH study. These samples provided perfect sensitivity, similar to first-void urine collected with Colli-Pee®.

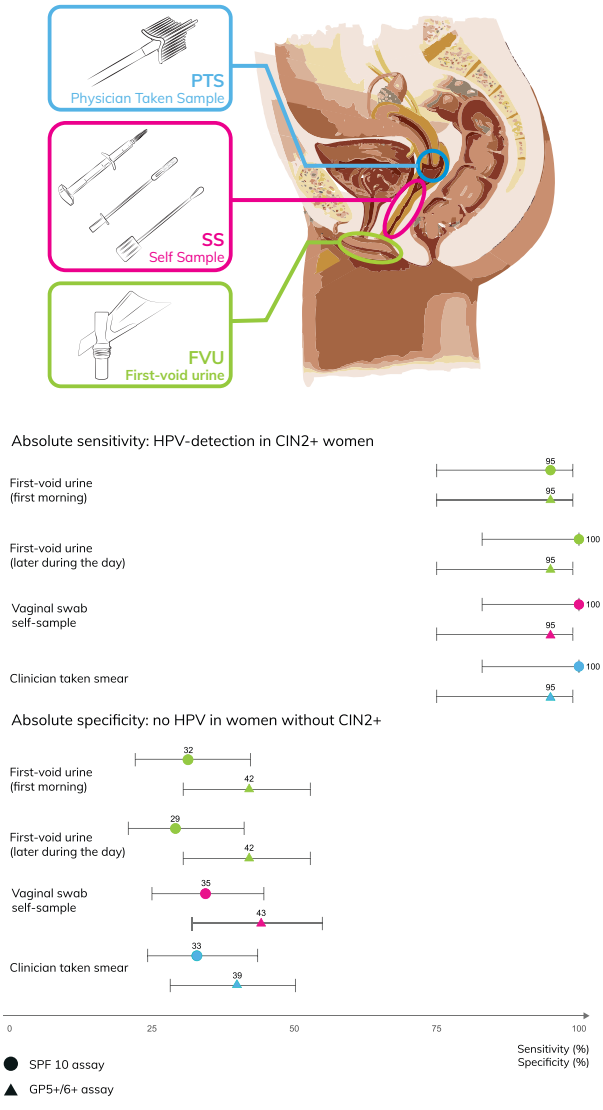

Figure 2
Absolute sensitivity and specificity results of the EVAH study in clinician-taken smear, vaginal swab self-sample and first-void urine with CIN2+ diagnosis as reference. Sensitivity i.e. HPV detection rate in CIN2+ women; specificity i.e. percentage not infected with HPV and not diagnosed with CIN2+.

The EVAH study also showed high concordance between HPV detection in first-void urine and clinician-taken smears illustrated by kappa-values ranging from 0.75 to 0.85. This corresponds to preliminary results of ongoing clinical trials where kappa-values up to 0.80 have been observed.[10,11]

About 90% of HPV infections clear within two years and only a small proportion of infections can persist and progress to cervical cancer.[12] Hence, HPV-based primary screening provides low specificity for the selection of clinically relevant lesions. Results of the EVAH study also showed modest specificity rates for all sample types i.e. 33% to 39% for clinician-taken smear, 35% to 43% for the vaginal swab self-sample and 29% to 42% for first-void urine collected with Colli-Pee® (Figure 2).

Novosanis invests time and research on the potential of first-void urine samples for screening purposes and methods to identify clinically relevant disease based on only one sample. Different approaches are under development i.e. (1) the usability of clinical cut-off values of commercially available, automated screening assays and (2) triage tests based on methylation markers i.e. early signs of cancer development.

FEASIBILITY OF COMMERCIAL AVAILABLE DIAGNOSTIC ASSAYS

Several pilot studies confirmed feasibility of HPV DNA detection in first-void urine with commercially available diagnostic assays for automated screening (Roche Cobas® HPV, BD Onclarity™ HPV, Aptima® HPV Hologic Panther, Cepheid Xpert® HPV) or genotyping (Genefirst Papilloplex™ HR-HPV, Anyplex™ II HPV HR Seegene, Fujirebio Innolipa™, High+Low Papillomastrip Operon).

These studies have been carried out with Colli-Pee® prefilled with Urine Conservation Medium (UCM®), enabling general urine preservation for transport and storage at ambient temperature for up to 7 days. Detection of HPV DNA in Colli-Pee® collected first-void urine was assessed with commercial, diagnostic assays and both an in-house and a commercially available genotyping assay as a reference.

NucliSENS®easyMag® extraction was used for analysis with the two comparator assays that were developed to provide maximal analytical sensitivity: (1) a lab developed HPV type specific qPCR method i.e. the Riatol assay (UAntwerp, Belgium) and (2) the Optiplex HPV genotyping kit (Diamex, Germany).

Concordance between the tested and comparator assays show a high level of agreement for genotyping tests with kappa-values ranging from 0.67 to 0.82.[13-15] Automated screening assays also demonstrate fair to good concordance with kappa-values ranging from 0.24 to 0.76 for detection of all HPV types.[16-19] When HPV 16 and HPV 18, the most commonly detected high-risk types in cervical cancer, were under investigation, kappa-values slightly increased i.e. 0.56 to 0.73.[16,17,19] This already shows the clinical feasibility of first-void urine in primary screening.

The next step is to validate clinical cut-off values of commercial assays on clinically annotated first-void urine samples. This is one of the goals of the VALHUDES[1] trial, set-up in cooperation with different manufacturers of diagnostic assays.[20]

[1] VALidation of Human papillomavirus assays and collection DEvices for HPV testing on Self-samples and urine samples

MORE EXCITING RESULTS IN THE PIPELINE

Our first clinical trial – the EVAH study showed that first-void urine offers nearly perfect sensitivity for the detection of clinically relevant disease. More results are expected from the VALHUDES and Predictors 5.1 projects where we further evaluate the clinical accuracy of first-void urine, the performance compared to other sample types and in different commercially available assays.

In the ongoing CASUS trial new molecular approaches are being developed that enable triage on the same urine sample based on methylation markers. These findings forecast the development of fully molecular cervical cancer screening approaches where Colli-Pee® delivers a solid sampling solution.

Our new Colli-Pee® small volume variants (10 mL and 4 mL) reduce downstream processing time since collection tubes are compatible with high-throughput machines. The CASUS trial also investigates the technical performance of our new variants focusing on the increase in DNA concentration compared to the collection of 20 mL first-void urine. The best available Colli-Pee® variant will be selected to validate a complete molecular screening approach for cervical cancer.

For more information: www.novosanis.com

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