



HPV self-sampling in the follow-up of women after treatment of cervical intra-epithelial neoplasia: A prospective study in a high-income country

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ABSTRACT

Current follow-up strategy for women after large loop excision of the transformation zone (LLETZ) for cervical intra-epithelial neoplasia (CIN) is burdened by a low compliance. We evaluated the performance of home-based Human Papillomavirus (HPV) self-sampling (Self-HPV) after treatment for CIN with the aim to assess the (i) feasibility and (ii) follow-up compliance. This study took place at the Geneva University Hospitals between May 2016 and September 2020. Women aged 18 years or older, undergoing LLETZ for a biopsy-proven cervical intraepithelial neoplasia grade 1 or worse (CIN1 +) were invited to participate. Agreement statistics, interpreted according to the scale of κ values, were calculated for Self-HPV and HPV performed by the physician (Dr-HPV). The samples were analyzed using GeneXpert and Cobas. Sample size was calculated to provide a 10% precision to estimate the kappa coefficient. A total of 127 women were included, with a median age of 35 years (interquartile range 30–41 years). There was a substantial agreement between Self-HPV and Dr-HPV using GeneXpert at 6 and 12 months, with a κ value of 0.63 (95%CI: 0.47–0.79) and 0.66 (95%CI: 0.50–0.82), respectively. Up to 9/10 (90%) women who did not come to their follow-up visit did not send their Self-HPV, either. In the follow-up after LLETZ treatment, home-based self-HPV is feasible, with substantial agreement between the two groups, however, concern remains regarding adherence to Self-HPV performance at home and loss to follow-up.

The trial was registered on clinicaltrials.gov with the identifier NCT02780960.

1. Introduction

Cervical cancer (CC) is the second most common gynecological malignancy and the third cause of cancer-related death worldwide (International Agency for Research on Cancer. *Estimated age-standardized incidence and mortality rates (World) in, 2020*). The development of cervical intra-epithelial neoplasia (CIN), which precedes that of CC, is caused by persistent infection with high-risk Human Papillomavirus (HPV) (Cogliano et al., 2005; Bosch et al., 2002). Screening for CC using cytology and/or HPV testing allows the diagnosis and treatment of precancerous cervical lesions with the aim of preventing their progression to CC (von Karsa et al., 2015). As most women are diagnosed with CIN in their childbearing years, management of precancerous lesions is based on the use of ablative (ie thermal ablation) or excisional therapy (i.e. large loop excision of transformation zone (LLETZ)) (Bigrigg et al., 1994). One drawback of conservative techniques is the risk of disease persistence in about 10% of women, which corresponds to treatment

failure and is identified mainly within the first 2 years of follow-up after surgery (Arbyn et al., 2006)

A growing body of literature supports the use of HPV testing alone for surveillance after treatment for CIN (Coupé et al., 2007; Kim et al., 2010; Venturoli et al., 2008; Prendiville and Sankaranarayanan, 2017). Performance of HPV testing alone is comparable, if not superior to, that of cytology, with a sensitivity of 93%, a specificity of 85% and a negative predictive value (NPV) of 99% in the detection of residual CIN after treatment (Gallwas et al., 2010). A prospective study conducted on a cohort of 352 patients found that the most important predictor of persistent disease at 6 months following treatment was a positive HPV test (Odds Ratio (OR) 38.80, 95% confidence interval (95%CI): 14.09–107.05) (Leguevaque et al., 2010). Moreover, a cost-effectiveness analysis conducted in the Netherlands identified HPV testing alone at 6 months following treatment to be the most promising follow-up strategy when compared to co-testing and cytology alone (Coupé et al., 2007)

Regardless of the strategy used, follow-up after LLETZ, which entails

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multiple, subsequent gynecological exams is burdened by low patient compliance (Ostojic et al., 2010). One study conducted in Australia found that only 26.6% of women successfully completed co-testing at 12 months following excisional treatment for CIN (Tan et al., 2020). Previous studies have found that the most frequently cited reasons for avoiding a gynecological consultation in high-income countries were lack of time and the cost of the gynecological exam (Catarino et al., 2016). Sending a vaginal HPV self-sampling kit directly at home has proven effective in increasing participation in CC screening while also maintaining a comparable performance to physician-taken samples, although such method has not been thoroughly studied in the post-treatment setting (Verdoordt et al., 2015; Penaranda et al., 2015; Arbyn et al., 2014)

The objectives of this study were to assess (i) the feasibility, and (ii) the follow-up compliance with Self-HPV at 6 and 12 months after LLETZ for CIN.

2. Material and methods

This study took place at the Geneva University Hospitals between May 2016 and September 2020. Women aged 18 years or older, attending the colposcopy clinic with a biopsy-proven cervical intra-epithelial neoplasia grade 1 or worse (CIN1 +) were invited to participate. Pregnant women and those speaking neither French nor English were excluded. The study was approved by the *Commission Cantonale d'Ethique de la Recherche* (CCER) with the identification number 2015-00121. All participants signed an informed consent form. The study met the institution's guidelines for protection of human subjects concerning their safety and privacy.

2.1. Study procedure

At colposcopy, after having given oral and written consent to participate in the study, participants were asked to collect a vaginal sample for HPV testing using a dry swab. To do this, women were instructed to wash their hands before the procedure. They were taught to hold the swab by the handle and to insert it into the vagina, being careful to avoid contact with external genitalia. Once resistance was met (at least 6 cm), they would gently turn the swab three to five times. Subsequently, the swab was placed back into its plastic tube and kept at a dry state. At the end of the consultation, women completed a questionnaire on socio-demographic characteristics. Once in the operating room and immediately prior to LLETZ, the clinician collected a cervico-vaginal sample (Dr-HPV) using a Cervex-Brush Combi (Rovers, Oss, The Netherlands), which was preserved in a liquid-based medium (Thin-Prep®2000, Hologic Inc, Marlborough, MA, USA). The Dr-HPV samples were analyzed using the GeneXpert (GeneXpert®IV; Cepheid, Sunnyvale, California, USA) device within 24 h of specimen collection. If possible, Self-HPV samples were analyzed within 24 h of their collection. Whenever prompt analysis was not possible, the specimens were stored at a temperature of 2 °C and analyzed within 1 week. Samples having yielded an invalid HPV test result were not retested.

2.2. Follow-up

A 6 and 12-month consultation visit at the colposcopy clinic was scheduled for all participants. Two weeks prior to their appointment, they were sent a Self-HPV kit including a dry swab and written instructions on how to collect the vaginal sample, following the same procedure as the one used preoperatively. The specimens were sent back to the hospital in a pre-paid envelope and analyzed within 24 h of their reception. In case of eventual delays that did not allow HPV testing to be promptly ran, samples were stored in the fridge (2 °C) and were analyzed within 1 week using the GeneXpert HPV test®.

At colposcopy, the clinician collected two cervical samples, which were then each immersed in the PreservCyt® Solution. One sample was

analyzed using Cepheid's GeneXpert HPV test. About 1 mL of the other Dr-HPV sample was analyzed using the Roche Cobas 4800 HPV test (Roche Molecular Diagnostics, Pleasanton, California, USA), and with the remaining part of the sample a cytological analysis was performed.

Women who did not come to their follow-up visit, even if the HPV sample had been sent back, were considered as lost to follow-up, as comparative analyses were not possible without the Dr-HPV test result at follow-up. Nevertheless, the proportion of women having sent back their self-HPV sample but not attended the follow-up visit was included in analyses to evaluate compliance with follow-up.

2.3. HPV analysis

2.3.1 Vaginal self-sampled specimens: In the laboratory, the swab was rinsed in a vial with 5 mL of saline solution (sodium chloride 0.9%) and then vortexed for 30 s. One ml of the solution was collected with a pipette and then transferred into a single-use disposable cartridge that holds polymerase chain reaction (PCR) reagents of the GeneXpert analyzer. The result was available after one hour. The Xpert HPV assay specifically identifies high-risk types HPV 16 and HPV 18-45 in two distinct detection channels, and reports 11 other high-risk types (31, 33, 35, 39, 51, 52, 56, 58, 59, 66 and 68) in a pooled result.

2.3.2 Clinician-collected cervical samples at 6 and 12 months after LLETZ: The specimens were analyzed by the GeneXpert and Roche Cobas 4800 systems. The Roche HPV test is a molecular analysis based on real-time PCR with an automated system for sample processing. Cobas can detect HPV16, HPV18, 12 other high-risk HPVs (31, -33, -35, -39, -45, -51, -52, -56, -58, -59, -66, and -68) in a pooled result.

2.4. Cytology and histology

Women with newly diagnosed cervical intra-epithelial neoplasia grade 2 or worse (CIN2 +) or with a persistent CIN1 lesion were included. CIN1 was considered as persistent after at least 2 years. In selected cases, histological HSIL or AGC with CIN1 at cervical biopsy were also candidates for LLETZ (Navarria and Jacot-Guillarmod, 2010). Similarly, women below the age of 25 years with persistent HSIL were considered candidates for LLETZ.

Thin-layer slides were prepared using the ThinPrep® technology at the laboratories of the Geneva University Hospitals in Geneva, Switzerland. The slides were read by qualified cytotechnologists and the results were classified according to the Bethesda nomenclature system. Each positive (ASC-US +) slide was read by one pathologist. Histological specimens were obtained by qualified gynecologists using punch biopsy, after having identified the cervical pathological area using acetic acid and Lugol iodine. If no pathological area was identified, cervical biopsy was performed at 6 o'clock, thus increasing colposcopy's diagnostic accuracy (Zhao et al., 2015). Endo-cervical curettage was also systematically performed, using an endocervical brush (Pretorius et al., 2004). The specimens were conserved in a formalin-based solution, and the slides were read by pathologists specialized in gynecological pathology and classified according to the international standards. Any lesion detected at follow-up was considered as treatment failure.

2.5. Statistical analysis

Data analysis was performed using the STATA Statistical Software Release 14.2 (StataCorp LP, College Station, TX, USA). The tests were based on the binomial distribution at a confidence interval of 95% (95% CI). All tested hypotheses were two-sided, and p values < 0.05 were considered statistically significant. Pearson's Chi-2 test was used to compare independent proportions, using instead the Fischer-exact test whenever the number of expected frequencies in the contingency table was < 5. Agreement between the Self-HPV and Dr-HPV was assessed using k values, calculating their relative 95% CIs. K values were obtained by calculating the difference between the observed and the expected

agreement and by standardizing the obtained value on a -1 to 1 scale. K values were interpreted according to the commonly adopted scale: when k values < 0 agreement was considered to be less than what would be expected by chance; k values 0.01 – 0.20 corresponded to a slight agreement; for k values 0.21 – 0.40 the agreement was considered to be fair; k values 0.41 – 0.60 corresponded to a moderate agreement; for k values 0.61 – 0.80 agreement was considered substantial and, finally, k values 0.81 – 0.90 corresponded to an almost perfect agreement, which was reached when the value equals to 1 .

2.6. Sample size

The study was powered to assess agreement between Self-HPV and Dr-HPV. A sample size of at least 120 women was considered sufficient to provide a 10% precision to estimate the kappa coefficient, if the κ is 50% (the latter would be the worst-case scenario, as precision would improve if the κ is lower or higher than 50%). Assuming a 10% prevalence of CIN1 + in our selected population, the precision of other measures was presumed to be about 15%.

3. Results

3.1. Participants' baseline characteristics

A total of 127 women undergoing LLETZ for a histological diagnosis of CIN1 + were included in the study. The median age of the participants was 35 years, with an interquartile range (IQR) of 30–41, the total age range varying from a minimum of 22 to a maximum of 67 years. The majority of them lived in Switzerland (124/127, 97.6%) and were employed (82/127, 64.4%). Their median age at first sexual intercourse was 17 (IQR 16–19) years and their median number of sexual partners was 7 (IQR 4–10). More than half of the participants had a preoperative cervical intra-epithelial neoplasia grade 3 (CIN3) diagnosis (72/127, 56.7%), while 41/127 (32.3%) women had CIN2 and 12/127 (9.5%) women had persistent CIN1. Two women (2/127, 1.6%) had a negative biopsy result at the inclusion time, although we chose to include them because of a history of high-grade squamous intra-epithelial lesion (HSIL) at cytology. The participants' baseline characteristics are reported in Table 1.

3.2. HPV positivity agreement

The k value for Self-HPV and Dr-HPV using GeneXpert for both was 0.63 and 0.66 at 6 and 12 months, respectively. When stratifying the agreement statistics for the women's sociodemographic characteristics, the k values maintained a moderate-substantial agreement. At 6 months, the k value for women having had < 5 sexual partners was 0.879 (95%CI 0.46–1.29), while for women aged 35 years or older it was 0.664 (95%CI 0.46–0.87). At 12 months, women with a CIN3 diagnosis at LLETZ had a k value of 0.745 (95%CI 0.54–0.95). Table 2 reports the agreement statistics stratified by women's sociodemographic characteristics between Self-HPV and Dr-HPV when both analyzed using GeneXpert at baseline, 6 and 12 months.

When comparing Self-HPV using GeneXpert and Dr-HPV using Cobas, the obtained k value was 0.52 at 6 months and 0.47 at 12 months. At 6 months, women with < 5 sexual partners had a k value of 0.68 (95%CI 0.30–1.05), while women aged 35 years or older had a k value of 0.55 (95%CI 0.31–0.79). At 12 months, women with a CIN3 diagnosis had a k value of 0.37 (95%CI 0.17–0.57). Table 3 reports the agreement statistics stratified by the women's sociodemographic characteristics at 6 and 12 months between Self-HPV and Dr-HPV using GeneXpert and Cobas.

3.3. Compliance with follow-up tests

The study design and main results are reported in Fig. 1. A mean of 40.3 (IQR 23–50) days elapsed between the colposcopy visit with biopsy

Table 1
Sociodemographic characteristics of the study participants.

Variable	Value*
Age, median (IQR), y	35(30–41)
Gestivity, median (IQR)	1(0–2)
Parity, median (IQR)	1(0–1)
Country, N(%)	
France	3(2.4)
Switzerland	124(97.6)
Educational degree, N(%)	
Elementary school or none	9(7.3)
High school	47(37.0)
University	55(43.3)
Other	14(11.0)
Non specified	2(1.6)
Profession, N(%)	
Employed	95(74.8)
None	32(25.2)
Age at first sexual intercourse, median (IQR), y	17(16–19)
Number of sexual partners, median (IQR)	7(4–10)
Contraception, N(%)	
None	27(21.3)
Pill	46(38.6)
IUD	15(11.8)
Condom	23(18.1)
Other	13(10.5)
Pre-operative biopsy result N(%)	
CIN1	12(9.5)
CIN2	41(32.3)
CIN3	72(56.7)
Negative	2(1.6)

*Column values are expressed as N = number if categorical variables; continuous variables are expressed as means with the interquartile range (IQR). Abbreviations: y = years of age; SD = standard deviation; IQR = inter-quartile range; IUD = intra-uterine device, CIN1/2/3 = cervical intra-epithelial neoplasia grade 1,2 or 3, respectively

and LLETZ. There were a total of 20/98 (20.4%) women positive at Self-HPV at 6 months, which means that, if only women with positive Self-HPV test were to have a colposcopy, up to 78/98 (79.6%) would have avoided a colposcopy visit given the negative Self-HPV test result. According to Dr-HPV using Xpert and Cobas, there were a total of 18/103 (17.5%) and 22/116 (19.0%) women positive for HPV at the same control visit, respectively. When comparing HPV positivity, Self-HPV did not differ significantly neither from Dr-HPV using Xpert ($p = 0.599$) nor when using Cobas ($p = 0.797$). The proportion of women who did not send back their Self-HPV sample (22/127, 17.3%) at 6 months was significantly higher than that of women who did not come for their 6-month control visit (22/127, 17.3% versus 10/127, 7.9%, $p = 0.024$). Up to 9 out of the 10 women (90%) who did not come to their follow-up visit had not sent back their Self-HPV sample, either. Out of women who had not sent back their Self-HPV but who came to their appointment, 11/13 of them were HPV-negative (84.6%).

There were a total of 13/83 (15.7%) women positive at Self-HPV at 12 months, meaning that if only women with a positive Self-HPV were to have colposcopy, up to 70/83 (84.3%) of them would have avoided the full gynecological examination. Up to 48/127 (37.7%) women had a negative Self-HPV at both 6 at 12 months. According to Dr-HPV using Xpert and Cobas, there were a total of 14/97 (14.4%) and 13/108 (12.0%) women positive for HPV at the same control visit, respectively. When comparing HPV positivity, Self-HPV did not differ significantly neither from Dr-HPV using Xpert ($p = 0.807$) nor when using Cobas ($p = 0.459$). At 12 months, 31/127 (24.4%) women did not send back their Self-HPV test and 19/127 (15.0%) women did not come to their 12-month follow-up appointment ($p = 0.060$). Up to 17 out of the 19 women who did not come to their scheduled appointment did not send back their Self-HPV sample, either. Out of the 14 women who came to their colposcopy appointment but had not sent back their Self-HPV, 13/14 of them were HPV-negative (92.9%).

Table 2
Agreement statistics for Self-HPV and Dr-HPV using Xpert according to patient characteristics.

Variable	At baseline			At 6 months			At 12 months		
	κ	95%CI	% Agreement	κ	95%CI	% Agreement	κ	95%CI	% Agreement
Overall agreement	0.520	0.40–0.64	66.7	0.630	0.47–0.79	87.6	0.660	0.50–0.82	90.9
Histological diagnosis*									
Negative	–	–	–	0.286	0.11–0.68	70.0	–	–	–
CIN1	–	–	–	0.615	0.02–1.42	80.0	–	–	–
CIN2	–	–	–	0.747	0.39–1.10	88.9	0.338	0.02–0.65	82.4
CIN3	–	–	–	0.635	0.45–0.82	91.1	0.745	0.54–0.95	94.0
Cytological diagnosis									
Negative	–	–	–	0.427	0.27–0.59	88.9	0.677	0.51–0.85	92.4
ASC-US	–	–	–	0.756	0.30–1.21	90.0	–	–	–
LSIL+	–	–	–	0.631	0.20–1.06	80.0	0.731	0.21–1.26	85.7
Age									
<35	0.637	0.45–0.82	75.0	0.591	0.34–0.84	84.6	0.787	0.51–1.06	96.7
≥35	0.406	0.25–0.57	59.7	0.664	0.46–0.87	90.0	0.615	0.41–0.82	87.2
Number of partners									
<5	0.660	0.42–0.89	76.0	0.879	0.46–1.29	95.5	–	–	–
≥5	0.470	0.33–0.61	63.8	0.522	0.35–0.69	85.1	0.821	0.63–1.01	94.6
Age at first sexual intercourse									
<17	0.470	0.27–0.67	62.2	0.728	0.49–0.97	93.9	0.635	0.36–0.91	91.3
≥17	0.530	0.38–0.69	69.1	0.589	0.38–0.79	83.9	0.669	0.48–0.86	90.7

*Intended as histological diagnosis obtained on the LLETZ specimen

Abbreviations: Self-HPV = home-based HPV sample taken by the patient at home, Dr-HPV = clinic-based HPV sample taken by the physician or nurse at the clinic CIN1/2/3 = cervical intraepithelial neoplasia grade 1/2/3, respectively, 95%CI = 95% confidence interval; LSIL+=low-grade squamous intra-epithelial lesion or worse

Table 3
Agreement statistics for Self-HPV (Xpert) and Dr-HPV (Cobas) according to patient characteristics.

Variable	At 6 months			At 12 months		
	κ	95%CI	% Agreement	κ	95%CI	% Agreement
Overall agreement	0.52	0.37–0.67	83.3	0.47	0.32–0.62	86.3
Histological diagnosis*						
Negative	0.53	0.16–0.90	81.8	0.68	0.14–1.22	85.7
CIN1	0.62	–1.00–1.22	80.0	–	–	–
CIN2	0.56	0.21–0.91	79.1	0.62	0.28–0.95	88.9
CIN3	0.50	0.32–0.68	86.9	0.37	0.17–0.57	86.5
Cytological diagnosis						
Negative	0.594	0.43–0.76	91.2	0.423	0.25–0.59	88.4
ASC-US	0.511	0.03–0.99	81.8	0.583	0.00–1.17	80.0
LSIL+	0.220	0.12–0.54	50.0	0.455	0.00–0.92	66.7
Age						
<35	0.56	0.35–0.75	84.1	0.64	0.40–0.88	93.8
≥35	0.55	0.31–0.79	84.6	0.4	0.20–0.60	81.3
Number of partners						
<5	0.68	0.30–1.05	87.5	–	–	–
≥5	0.50	0.33–0.67	83.3	0.51	0.33–0.69	84.2
Age at first sexual intercourse						
<17	0.75	0.48–1.02	94.7	0.43	0.18–0.68	79.2
≥17	0.48	0.29–0.67	77.6	0.51	0.35–0.67	89.3

*Intended as histological diagnosis on the LLETZ specimen

Abbreviations: Self-HPV = home-based HPV sample taken by the patient at home, Dr-HPV = clinic-based HPV sample taken by the physician or nurse at the clinic CIN1/2/3 = cervical intraepithelial neoplasia grade 1/2/3, respectively, 95%CI = 95% confidence interval; LSIL+=low-grade squamous intra-epithelial lesion or worse

3.4. HPV clearance over time

Considering that 87 women were Self-HPV positive at baseline and that a total of 69 and 56 of them had either a cleared or persistent HPV infection at 6 and 12 months, respectively, the clearance rate at 6 months was 52/69 (75.4%) women, while a total of 17/69 (24.6%) women had a persistent HPV infection. At 12 months, 47/56 (83.9%) women had cleared their initial HPV infection, while 9/56 (16.1%) had a persistent or recurrent HPV infection.

Considering that 85 women were Dr-HPV (GeneXpert) positive at baseline and that a total of 69 and 66 of them had either a cleared or persistent HPV infection at 6 and 12 months, respectively, the HPV clearance rate at 6 months was 54/69 (78.3%), and the persistence rate at the same time was 15/69 (21.7%). At 12 months, 55/66 women

(83.3%) had cleared their HPV infection, whereas 11/66 women (16.7%) had a persistent or recurrent HPV infection. The HPV clearance rates according to Self-HPV and Dr-HPV using GeneXpert are reported in Fig. 2.

3.5. Invalid HPV test results

There were a total of 7/105 (6.7%) Self-HPV invalid test results at 6 months. At 12 months, there were 13/96 (13.5%) invalid Self-HPV test results and 1/98 (1.0%) Dr-HPV invalid test result using GeneXpert ($p = 0.001$), while the Cobas yielded to invalid test results.

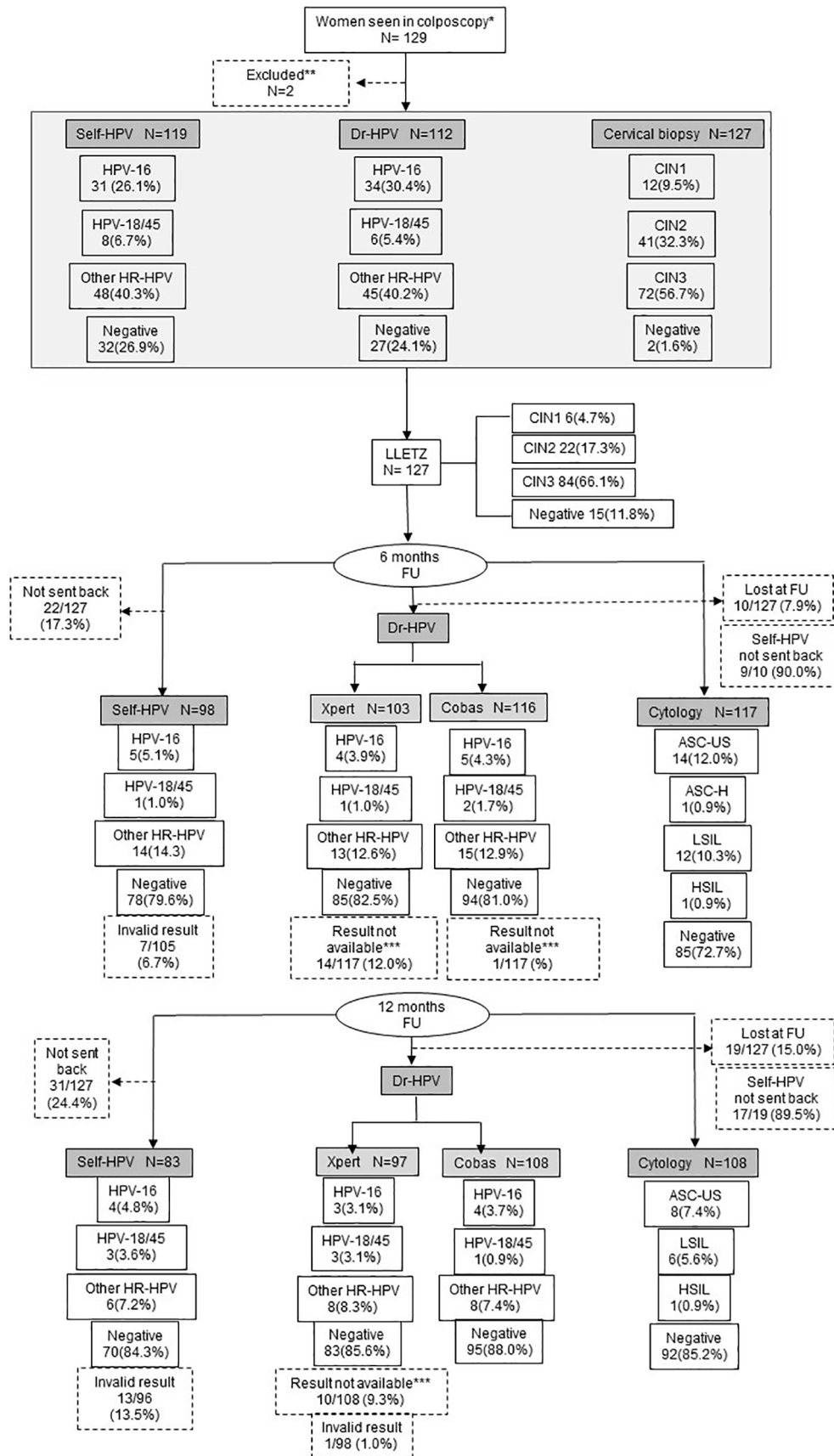


Fig. 1. Study flowchart. Women candidates for LLETZ for cervical dysplasia, including those followed at our clinic and those referred to it from gynecologists working in private practice **2 patients sought a second opinion and chose not to be operated at our clinic ***Reasons for which results may not be available include: sample lost between its collection and the analysis and sample not taken by the physician or nurse.

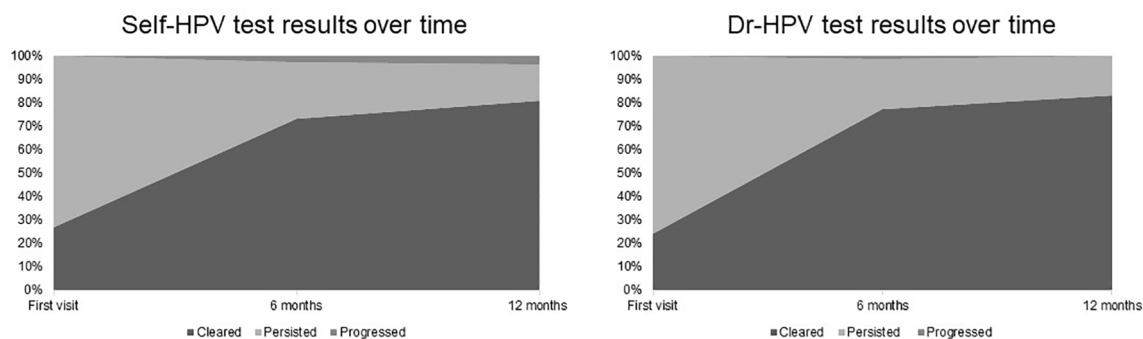


Fig. 2. HPV clearance over time according to Self-HPV and Dr-HPV (Xpert).

4. Discussion

This is one of the first studies comparing home-based Self-HPV to clinic-based Dr-HPV for follow-up after LLETZ. While the literature supports the use of Self-HPV in the context of CC screening, there is little evidence concerning the effectiveness of Self-HPV in the follow-up after treatment for CIN. We found a moderate to substantial agreement between home-based Self-HPV and Dr-HPV at 6 and 12 months after surgical treatment for CIN, with an overall k value of 0.63 and 0.66 for Self-HPV and Dr-HPV using GeneXpert at 6 and 12 months, respectively. Moreover, Self-HPV and Dr-HPV obtained comparable viral clearance rates over time. Similarly, in their systematic review Hoffman SR et al found HPV viral persistence rates after conservative management of CIN to be 21% and 15% at 6 and 12 months, respectively (Hoffman et al., 2017).

The cumulative rate of CC 8 years after CIN treatment is 5.8 per 1000 women, as much as 5 times higher than that of the general population (Soutter et al., 1997). The rate of CIN recurrence or persistence after LLETZ translates into the need to implement a testing strategy that is not only effective in disease detection, but which also ensures high patient follow-up compliance. A retrospective analysis of 251 patients having undergone LLETZ found that only 58.2% of patients came to their scheduled follow-up appointments in the first two years following surgery (Ostojic et al., 2010). A prospective study conducted in Germany found that, among women with scheduled gynecological checkups due to abnormal cytology results, those with a visit scheduled at 6 months following LLETZ were the ones less likely to comply with the scheduled appointments (Rippinger et al., 2019). A randomized controlled trial found that women who were given a self-sampling kit for HPV testing were more likely to participate in CC screening than those who were asked to fix an appointment for a cytological sample to be taken by the physician (35/45, 78% and 22/43, 51%, respectively, $p = 0.009$) (Peeters et al., 2020). Another interesting finding from our study is that if only Self-HPV-positive women had been scheduled for a colposcopy, up to 79.6% and 84.3% would have avoided a colposcopy at 6 and 12 months, respectively. Our results, along with the low compliance with follow-up colposcopy after surgery found in the literature, support the use of home-based Self-HPV, which could narrow down the indication to a gynecological examination only to women with a positive HPV test (So et al., 2019).

We found that the proportion of women who did not send back their Self-HPV sample was significantly higher than that of patients who did not attend their consultation at 6 months, and up to 84.6% of these women were HPV-negative. It needs to be mentioned that all women in our cohort also had a scheduled gynecological exam, which may have discouraged some of them from performing Self-HPV. Indeed, previous works have found that certain women find the gynecological examination reassuring and would rather undergo a gynecological exam than perform vaginal self-sampling (Fargnoli et al., 2015). Andersson S et al. found that 54.3% of women expressed high confidence in performing Self-HPV after LLETZ, and that a greater distance from the colposcopy

clinic and higher knowledge about the natural history of CC were strong independent predictors of willingness to perform Self-HPV (Andersson et al., 2018). Among women in our cohort who did not send back their Self-HPV, up to 9/22 (40.9%) and 17/31 (54.8%) of them did not come to their consultation at 6 and 12 months, respectively, suggesting their unwillingness to comply with the scheduled follow-up altogether. While Self-HPV may be used to circumvent the gynecological examination and to prevent loss at follow-up, these findings highlight the importance of targeted patient education about the benefits of follow-up after treatment for CIN (Srisuttayasathien and Manchana, 2021). Further studies needed to assess reasons for non-attendance at follow-up.

We found a considerably higher number of invalid test results using Self-HPV when compared to Dr-HPV. While all Dr-HPV samples were all analyzed within 2 days of their collection, Self-HPV samples could be sent within an interval of 15 days of their collection. This issue may be overcome by giving women a more limited amount of time to send back their Self-HPV sample, as Catarino R et al have demonstrated that an interval longer than 6 days between the sample's collection and analysis increases the chances of having an invalid test result (Catarino et al., 2017).

This is one of the first studies to explore the feasibility of home-based Self-HPV for the follow-up of women after LLETZ in a high-income setting, presenting a method that may contribute to reduce drop-out rates in a population that runs a higher risk of developing CC. We were able to compare Self- to Dr-HPV, the latter of which was analyzed with two different devices, such as the Xpert and the Cobas.

Main limitation was a higher loss at follow-up using Self-HPV as opposed to Dr-HPV at 6 months follow-up. Such finding may partly be explained by the fact that all women in our cohort also had a scheduled gynecological exam, which may have rendered some of them less motivated to perform and send their Self-HPV test. Further trials should focus exclusively on women who do not come to their scheduled colposcopy appointments, determining whether Self-HPV may help reach this part of the population. We also sought to assess performance of Self-HPV and Dr-HPV at follow-up using cytology (HSIL +), although small numbers hampered the significance of our findings, as only one case of HSIL was detected at 6 months. The same woman had a positive Self-HPV and underwent a second LLETZ procedure, which revealed persistence of CIN3. Further studies should focus on evaluating the tests' performance in terms of HSIL + detection at follow-up.

5. Conclusion

Our study focused on home-based Self-HPV at 6 and 12 months after LLETZ to improve follow-up participation. Our findings suggest that Self-HPV may be used as a triage test to identify women who, due to their high risk of persistent disease, require further investigation. Randomized trials are needed to further establish the reliability of Self-HPV in disease detection, with the aim of introducing an approach potentially capable of reducing loss to follow-up after conservative treatment and, ultimately, reduce CC mortality rates.

CRedit authorship contribution statement

Manuela Viviano: Conceptualization, Methodology, Writing – original draft. **Pierre Vassilakos:** Conceptualization, Methodology, Writing - review & editing. **Ulrike Meyer-Hamme:** Conceptualization, Methodology. **Lorraine Grangier:** Writing - review & editing. **Shahzia Lambat Emery:** Writing - review & editing. **Manuela Undurraga Malinverno:** Conceptualization, Methodology, Writing - review & editing. **Patrick Petignat:** Conceptualization, Methodology, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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