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RESEARCH ARTICLE

# REVISED A pilot study of risk-stratified cervical cancer screening

[version 2; peer review: 2 approved]

Jiangrong Wang[1], K. Miriam Elfström[2,3], Christer Borgfeldt[4], Joakim Dillner[1,3]

[1]Department of Laboratory Medicine, Karolinska Institute, SE-141 52 Stockholm, Sweden
[2]Regional Cancer Center Stockholm Gotland, Lindhagensgatan 98, SE-102 39 Stockholm, Sweden
[3]Karolinska University Laboratory, Karolinska University Hospital, Anna Stecksénsgata 49, SE-171 76 Stockholm, Sweden
[4]Department of Obstetrics & Gynecology, Skåne University Hospital, Department of Clinical Sciences, Lund University, Klinikgatan 12, SE-222 42 Lund, Sweden

**v2** **First published:** 27 Jul 2021, **1**:84
https://doi.org/10.12688/openreseurope.13398.1
**Latest published:** 01 Sep 2022, **1**:84
https://doi.org/10.12688/openreseurope.13398.2

## Abstract

**Background:** Cervical screening programs target entire populations, although it is well established that cervical cancer risks can vary >100-fold based, in particular, on the woman's screening history. Since cervical screening switched to Human Papillomavirus (HPV) testing as the primary screening method, the risk differences are even larger as different HPV types may vary in associated cancer risk by 100 times. Furthermore, HPV infections with the most oncogenic types are declining dramatically because of HPV vaccination programs. Tailoring screening intensity based on the known cancer risk of the individual (risk-stratified screening) therefore has great potential to increase both the sensitivity and specificity. Within Horizon 2020 a major project for Risk-stratified Screening for Cervical Cancer (RISCC) has therefore been launched. We performed a pilot study of risk-stratified screening to evaluate feasibility and acceptability of offering vaginal HPV self-sampling tests to women with a higher risk of cervical cancer.
**Methods:** We identified resident women who had had either i) atypical glandular cells in screening tests during the past six years (risk >150/100,000 woman-years) or ii) abnormal screening findings above the age of 50, but without sufficient follow-up (risk >65/100,000). The women were invited, either by short message service (SMS) or physical letters, to order an HPV self-sampling kit via the study web-platform. The returned self-collected samples were tested for HPV. If positive, women were invited for clinical follow-up.
**Results:** Among 920 targeted women, 191 (21%) placed an order and 163 (18%) returned a self-collected sample. Among all tested samples, 19 (12%) were positive for hrHPV and 18 of these women attended clinical follow-up.
**Conclusions:** SMS invitations to high-risk women complemented with physical letters are feasible and result in substantial requests for kits and submission of samples. Future work will focus on improving the efficiency of the procedure and further increasing attendance.

**Open Peer Review**

**Approval Status** ✓ ✓

| | 1 | 2 |
|---|---|---|
| **version 2** (revision) 01 Sep 2022 | ✓ view | ✓ view |
| **version 1** 27 Jul 2021 | ? view | ? view |

1. **Raúl Murillo**, Hospital Universitario San Ignacio, Bogotá, Colombia

2. **Jean-Luc Prétet**, CHU Besançon, France, Besançon, France

Any reports and responses or comments on the article can be found at the end of the article.

**Keywords**
Human Papillomavirus, self-sampling, SMS-based screening invitations



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This article is included in the Horizon 2020 gateway.



This article is included in the Cancer collection.

**Corresponding author:** Joakim Dillner (joakim.dillner@ki.se)

**Author roles: Wang J**: Data Curation, Formal Analysis, Investigation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Elfström KM**: Data Curation, Investigation, Writing – Review & Editing; **Borgfeldt C**: Investigation, Resources, Writing – Review & Editing; **Dillner J**: Conceptualization, Funding Acquisition, Investigation, Methodology, Resources, Supervision, Writing – Review & Editing

**Competing interests:** JD has received grants to his institution for studies on HPV tests from Roche and Genomica, manufacturers of HPV tests. JW receives part of her salary from a research grant from Merck & Co. for project on HPV vaccine evaluation.

**Grant information:** This research was financially supported by the European Union's Horizon 2020 research and innovation programme under the grant agreement No 847845 (project RISCC) and the Stockholm County regional healthcare provider.
*The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.*

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**How to cite this article:** Wang J, Elfström KM, Borgfeldt C and Dillner J. **A pilot study of risk-stratified cervical cancer screening [version 2; peer review: 2 approved]** Open Research Europe 2022, **1**:84 https://doi.org/10.12688/openreseurope.13398.2

**First published:** 27 Jul 2021, **1**:84 https://doi.org/10.12688/openreseurope.13398.1

**REVISED** **Amendments from Version 1**

The major difference between the old and new version is adding the underlying risk profiles of the selected high-risk groups, and explaining the considerations of group selection for this pilot study as well as future planning. We have added a new Table 1, outlining the absolute risk of invasive cervical cancer by risk groups, identified using the cervical screening registry. The previous tables have been re-numbered.

**Any further responses from the reviewers can be found at the end of the article**

## Introduction

With high coverage of cervical screening and vaccination against the causative agent human papillomavirus (HPV), elimination of cervical cancer is possible. WHO has launched a global strategy to accelerate the elimination of cervical cancer as a public health problem, defined as an incidence below 4 women per 100,000 women per year[1,2]. As the spread of the causative agent is declining, further optimization of cervical screening programs becomes even more important. Risk-stratified screening programs are increasingly discussed as a strategy for obtaining the expected benefits of screening while also containing resource use.

Cervical cancer incidence has decreased by more than 50% after the implementation of organized cervical screening, which detects and treats cervical pre-cancerous lesions[3].

Around 15% of the annual cervical cancer cases in Sweden have had a history of abnormal screening results, prior to the screening test that diagnosed the cancer[4]. Sufficient follow-up and management of women with abnormal screening findings are essential to prevent the progression from precancerous lesion to invasive cervical cancer. Our previous studies identified two groups of women who have a particularly high risk of cervical cancer: women who have had atypical glandular cells (AGC) detected in cervical screening. These women had a risk of 150 per 100,000 person-years in the subsequent 6.5 years, but many of them had not had sufficient follow-up[5]. The other group was women older than the upper age limit of organized cervical screening but who had had abnormalities after age 50 years, exhibiting risk around 60–100 per 100,000 person-years[6]. Many of these women were not sufficiently followed-up.

Performing risk-stratified screening targeting these women is thus urgent. However, with the conventional screening, it is difficult to fit an additional strategy within the available system that summons women for sampling at defined screening stations. Offering vaginal self-sampling for HPV testing to the high-risk women is a potential solution, as women may be resident far away from a screening station - but the women can be reached by SMS and by the postal service subsequently delivering an HPV self-sampling kit. HPV self-sampling has been found to be an acceptable, effective, reliable and lower-cost method to increase screening coverage[7,8]. For the two identified risk groups, HPV testing is particularly beneficial, because the HPV status can effectively distinguish the risk following AGC[9], and may outperform the unsatisfactory cytology for post-menopausal women[10,11].

We therefore performed a pilot study of risk-stratified screening to offer vaginal self-sampling HPV testing to all women who were resident in Southern Sweden and who had AGC or older aged women with previous abnormalities, but without sufficient follow-up.

## Methods

This study targeted the women in the population that, based on data in the screening registry, had the highest risk of cervical cancer. The absolute risks of cervical cancer among the different risk groups in the population are presented in Table 1. The identification of these groups as being the groups at highest risk of cervical cancer is described in previous publications[5,6]. The present project describes the initial piloting of a risk-stratified screening strategy and is therefore targeting only rather small, very high-risk groups. Inclusion criteria of this pilot study were women 1) living in Southern Sweden (Skåne region) up to age 80 years at the end of 2018, with a cytological diagnosis of AGC in the past 0.5–6.5 years, and without a follow-up test on record (cytology, HPV or cervical histology test) in the past two years by the end of 2018; 2) living in Southern Sweden, aged 65–70 years at the end of 2018, with a high-grade abnormality after age 50 and without any follow-up test in the past three years, or having had low-grade abnormalities after age 50 and without any subsequent normal test result. We identified these women from the Swedish National Cervical Screening Registry (NKCx.se) and linked them to the Swedish Total Population Register, through the women's unique Swedish personal identification number (PNR). Details of study inclusion and exclusion criteria are presented in Figure 1.

We have previously found that sending an invitation to order an HPV self-sampling kit is an efficient strategy for achieving increased participation at low costs[12]. We sent SMS to women who fulfilled the inclusion criteria and had a registered cellphone number. The message stated that they were invited to a free HPV self-sampling test, organized by Karolinska Institutet and Region Skåne. They were invited to read more about the study, provide consent, and order the test kit for home delivery via our kit ordering platform (https://www.hpvcenter.se/kit/index.php)[13]. On the platform, women could place the order by typing in their PNR. Only the women whose PNR was included in the project database could order a kit, and only one kit per PNR was permitted by the platform. The SMS invitation was sent on August 19, 2019. Two SMS reminders, on September 16 and October 7, 2019, were sent to the women who had not ordered a kit by these dates. In December 2019, a physical letter was sent to the home addresses of women who did not have a registered cellphone number or who had received three SMS but had still not placed an order.

We sent cervical HPV self-sampling kits (cobas® PCR Female Swab Sample Packet) to the registered home address of

**Table 1. Absolute risk of invasive cervical cancer by risk groups, identified using the cervical screening registry.**

| High-risk groups | Description | Absolute risk (Incidence rate per 100,000 person-years) |
|---|---|---|
| **Atypical glandular cells (AGC)** | Women having had AGC found in cytology in the past 6.5 years | ~150/100,000 person-years[a] |
| **Women aged 65–70** | | |
| **History of high-grade abnormality** | Women having had high-grade abnormality[b] since age 50 years, but no biopsy. | ~100/100,000 person-years[c] |
| **History of low-grade abnormality** | Women having had low-grade abnormality[d] since age 50 years but no follow-up[e] | ~ 65/100,000 person-years[c] |
| **Not screened** | Women not having any cervical test[e] since age 50 years | ~30/100,000 person-years[c] |
| **Long-term non-attenders at screening ages** | Women aged 30-64 and not having any cervical test[e] in the past 10 years | ~25-30/100,000 person-years[f] |

a. Wang *et al.* BMJ 2016 (DOI: 10.1136/bmj.i276)
b. Including cytological diagnosis of CIN2, CIN3, AGC, AIS, AUO (atypia of unknown origin) and invasive cancer in cytological screening
c. Wang *et al.* PLOS Medicine 2017 (DOI: 10.1371/journal.pmed.1002414) and related analyses
d. Including cytological diagnosis of ASCUS and CIN1 in cytological screening
e. Having no cytology, no HPV testing nor histology test
f. Wang *et al.* Acta Oncologica 2020 (DOI: 10.1080/0284186X.2020.1764095)

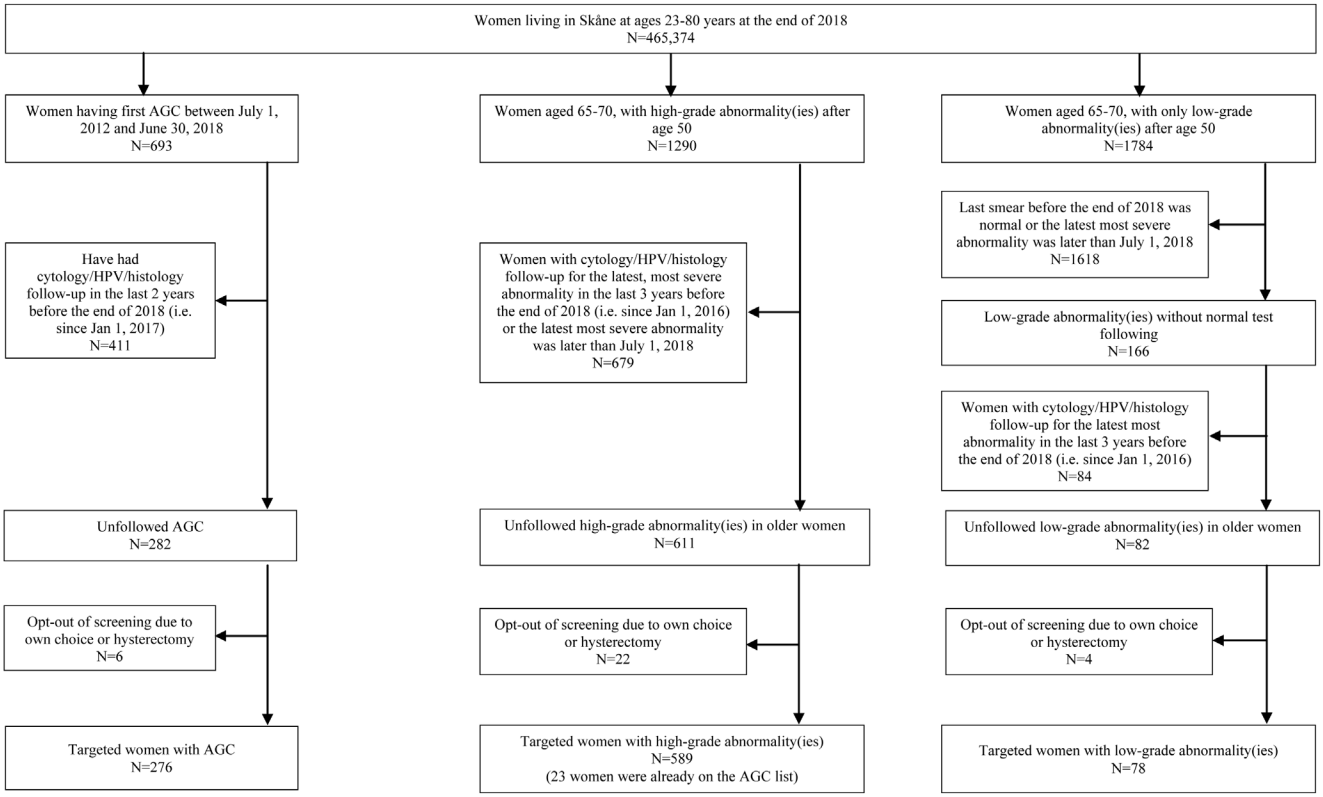



**Figure 1. Flow-chart of inclusion and exclusion of study population.**

women who either i) placed an order on the web platform, or ii) called the contact phone number of the project written on the web platform. Women who received a kit performed vaginal self-sampling following step-by-step picture-based instructions[12,13], and sent the sample back in a pre-paid return envelope included in the package. The samples were sent to the Center of Cervical Cancer Prevention at Karolinska University Hospital in Stockholm, and tested on the cobas® 4800 HPV Test platform (Roche Molecular Systems, Inc, South Branchburg, NJ) for HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68, as high-risk HPV genotypes (hrHPV). The result was reported as being positive or negative for HPV 16, HPV 18, or "other" hrHPV types. Samples that were tested positive for "other" high-risk HPV were further genotyped by Luminex[14,15]. Further details of ordering platform, kit, and HPV testing platform have been described in a previous randomized study[12]. Women who tested positive for any of the targeted HPV types were contacted by the gynecologist who was regionally responsible for cervical screening (CB) for diagnostic workup, including HPV mRNA test, cytology test, colposcopy, and biopsy.

We evaluated this pilot study of risk-stratified screening by measuring the participation (defined as the number and proportion of kits ordered and returned), the proportion of HPV positivity among returned samples, and the number of cervical intraepithelial neoplasia grade 2 or above (CIN2+) diagnoses in histopathology. These measures were compared between type of screening history (AGC or abnormalities at older ages) and age groups, using chi-square or fisher's exact tests. SAS version 9.4 (SAS Institute, Cary, NC) is used for data management and analysis. Statistical analyses used two-sided tests and P-value <0.05 as the significance limit.

Ethical approval of this project was granted by the Swedish Ethical Review Authority (Decision number DNR 2019–03166). The website homepage provided the patient information and possibility to electronically provide Informed consent. This was required before being able to order self-sampling kits. The consent included permission to manage and analyse personal data and the biological specimens. The broader project of SMS-based Summons in Cervical Screening in Sweden is registered on ClinicalTrials.gov with Identifier NCT04061967 (20th August 2019).

## Results

We identified 920 women having had AGC, or had an abnormal screening result after age 50, without sufficient follow-up. The details of inclusions are presented in Figure 1.

Among 920 women, 531 had a registered cellphone number and hence were sent invitations and reminders through SMS. Non-responders after two reminders, as well as 389 women without a registered cellphone number were contacted through physical letters. Among all 920 women, 24 requested to be excluded, and 191 (20.8%) ordered the HPV self-sampling kit on the platform or through calling the contact phone number of the study. The orders were concentrated right after the invitation SMS was sent, the SMS reminders and the physical letter (Figure 2). The orders increased in particular after sending the second SMS (Table 2).

Among 191 women who placed an order, 163 sent the sample back for HPV testing. The HPV testing results were as follows, 19 samples were HPV positive (11.7% out of tested), eight were HPV16/18, 10 were other hrHPV types including 31, 33, 51 and 56 (Table 3). Nearly all women that tested positive attended the clinical follow-up and diagnostic work up (18 out of the 19 HPV-positive women). Eleven tested positive for HPV mRNA, seven had no lesions, two had low-grade lesions, and one had a CIN2+ diagnosis (Adenocarcinoma *in situ*, a 36-year-old woman who had had AGC before). The clinical follow-up was inconclusive for eight women, where a biopsy could not successfully be taken mostly because of cervical stenosis.

The proportion of participating women tended to be slightly higher among those aged 41–75 years, but the difference was not statistically significant. The proportion HPV positivity was particularly high in women with a history of low-grade abnormalities (Table 3, probability=0.0031, P=0.02).

## Discussion

This pilot project invited women to HPV self-sampling with previous abnormal screening results lacking sufficient follow-up. Sending invitations and reminders through SMS for ordering a self-sampling kit online, complemented by sending physical letters to women who did not have a registered cellphone number or did not respond to three SMS invitations, was feasible and resulted in an acceptable participation rate. Clinical follow-up reached almost all women who tested HPV positive.

The participation in this study was higher than in our previous randomized trial of offering self-sampling kits to long-term non-attenders, where 12.9% of women ordered a kit and 10.7% returned a sample for testing in the arm that was invited to order a kit[12]. A likely reason is that previously we sent only one invitation and it was sent only by physical letter. SMS invitations with reminders may outperform the traditional invitation letter. With SMS invitations, kit ordering is simpler because one can directly click the link to the web platform, without copying the web address written on a paper letter. Weaknesses of the SMS invitation strategy are that it may not appear as formal as the physical letter because of limited information and no stamp of authority such as a letterhead. The limited number of orders right after the initial SMS invitation may reflect that women were not used to receiving such invitation-SMSes. However, orders increased after an SMS reminder, suggesting that trust in the message can be strengthened simply by sending reminders of the invitation.

A majority of the study population was aged above 65 years and managing the kit ordering through cellphone and internet may be challenging. Nevertheless, the proportion of kit ordering in the older age group targeted in this study was not

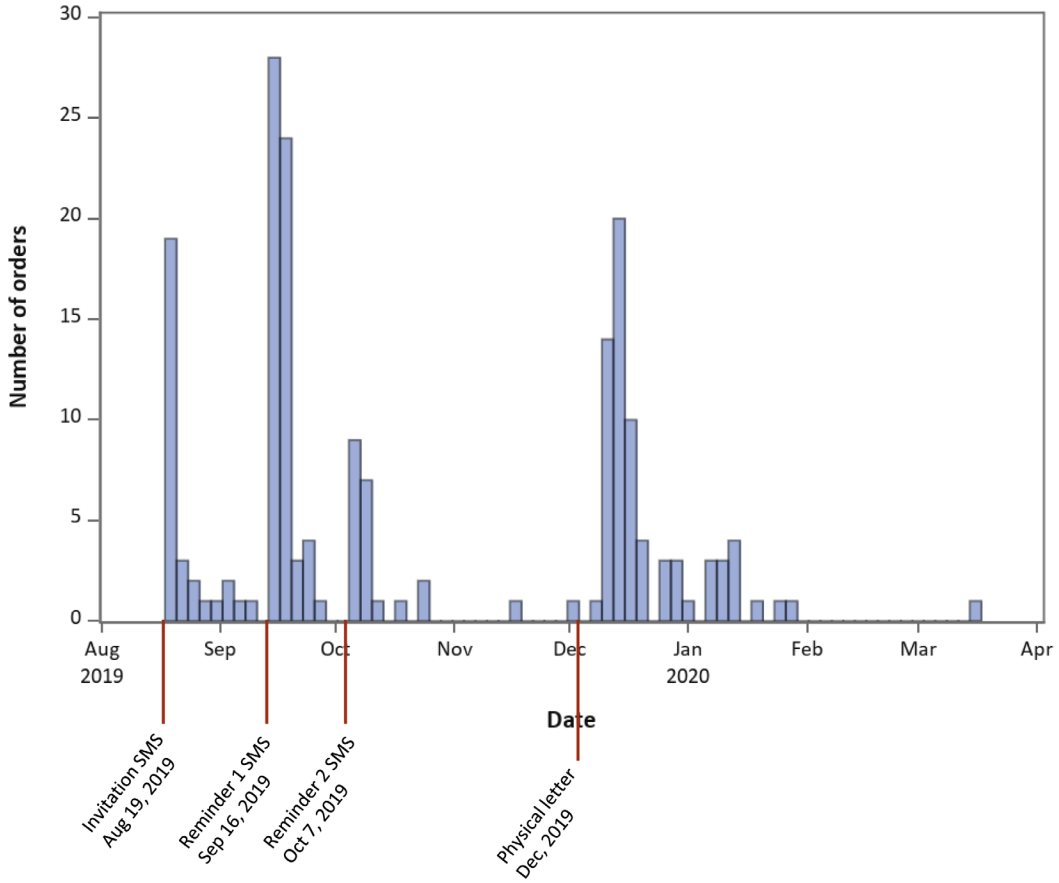



**Figure 2. Number of kits ordered over time.** Each bar represents 3 days.

**Table 2. Number of messages sent and orders by round and type of message.**

| | No. of messages sent | No. of orders* (%) |
|---|---|---|
| SMS invitation | 531 | 30 (5.6) |
| SMS reminder 1 | 501 | 61 (12.2) |
| SMS reminder 2 | 440 | 21 (4.8) |
| Physical letter | 808 | 70 (8.7) |

*Nine women ordered through calling the contact phone number. Date of the order was not recorded.

considerably lower than the younger group. There were only nine women who ordered the kit through contacting the research study by phone call. All of them were aged above 65 years, suggesting that the alternative ordering method is important, especially among older populations.

Only 1/10 women with an adequate colposcopy had a CIN2+ lesion. This was fewer than expected since these women were expected to have a high risk of cervical cancer due to their previous abnormal screening findings. The reasons behind this may include that 1) there was overall improvement in the routine clinical follow-up and management of women with abnormalities, especially after our publications indicating the high risk of these women, and with HPV testing becoming widely available. Under this circumstance, women with historical abnormality but without frequent follow-up, as are included in this project, may be the group with relatively lower risk triaged by previous clinical follow-up, e.g. negative in

**Table 3. Study population, participant and HPV positivity.**

| | No. of women | No. of drop-off | No. of ordered (%) | No. of tested (%) | No. of hrHPV+ve (% out of tested) | No. of HPV 16/18 positive | Genotypes of other hrHPV+ve | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 31 | 33 | 51 | 56 | Negative |
| Total | 920 | 24 | 191 (20.8) | 163 (17.7) | 19 (11.7) | 8 | 3 | 1 | 4 | 2 | 1*** |
| By age group | | | | | | | | | | | |
| 23-40 | 47 | 2 | 5 (10.6) | 3 (6.4) | 1 (33.3) | 1 | | | | | |
| 41-64 | 144 | 4 | 38 (26.4) | 30 (20.8) | 3 (10.0) | 2 | 1 | | | | |
| 65-70 | 673 | 16 | 139 (20.7) | 121 (18.0) | 14 (11.6) | 5 | 1 | 1 | 4 | 2 | 1 |
| 71+ | 56 | 2 | 9 (16.1) | 9 (16.1) | 1 (11.1) | 0 | 1 | | | | |
| By screening history** | | | | | | | | | | | |
| AGC | 276 | 8 | 54 (19.6) | 44 (15.9) | 6 (13.6)* | 3 | 2 | | | | |
| High-grade abnormality | 566 | 16 | 123 (21.7) | 108 (19.1) | 9 (8.3)* | 4 | | | 4 | | |
| Low-grade abnormality | 78 | 0 | 14 (18.0) | 11 (14.1) | 4 (36.4)* | 1 | 1 | 1 | | 1 | |

* Statistically significant on two-sided chi-square test P-value <0.05. **Based on cytological screening finding. HPV, human papillomavirus; hrHPV, high risk HPV; AGC, atypical glandular cells. ***One woman tested positive for Other HPV in the Cobas test, but this could not be confirmed in theHPV genotyping

reflex HPV test; and 2) majority of the study population were post-menopausal, which makes the colposcopic and histopathological evaluation more challenging. Several HPV-positive women had cervical stenosis, and therefore the colposcopy was considered inadequate. These women will be followed with continuous surveillance. Nonetheless, the prevalence of HPV positivity in this study is higher than the general population, especially among older ages[16,17]. Identifying them and keeping them under surveillance may help to find precancer lesions or early staged invasive cervical cancer in time.

Another study also reported acceptance of self-sampling HPV testing after treatment of CIN lesions[18]. To further improve participation in the target population in our study, we could consider sending physical letters to remind women and provide more information regarding the necessity of close follow-up, especially with HPV testing, after previous abnormalities. To optimize sample returns after kit ordering, we will consider sending an SMS reminder and a new kit to women who placed an order but did not return the sample.

Among the 3 very high-risk groups targeted in this study, 2 of these groups are women with insufficient follow-up after abnormal smears. Our assumption is that these women represent a group with non-attendance to follow-up, but the alternative explanation that management guidelines have not been followed cannot be excluded. Regardless of the explanation, the risk is high and targeting these women with risk-stratified screening is therefore motivated. For future strategies, much larger groups are planned to be targeted. A limitation with basing the identification of risk groups on the screening registry is that risk determinants that are not registered are not included, for example immunosuppressed women such as women living with HIV. The possibility to obtain not registered information on risk by asking the women will be explored. There were different HPV prevalences in the different risk groups, but as numbers are limited and biases by e.g. self-selection are possible caution is advised in interpreting these different HPV prevalences. An important outcome of the present pilot is that the response rates and HPV prevalences found will enable a cost-effectiveness evaluation of risk-stratified strategies that are planned for the future.

As a pilot of risk-stratified cervical cancer screening, this study explored several procedures including the identification of certain risk groups from a well-established register database; efficient invitation strategies; systems to order, distribute and collect self-testing tools/samples; and clinical follow-up according to test results. Further efforts to improve risk-stratified screening strategies should be directed to improving the risk stratification algorithm; to developing an integrated system for invitation, test ordering and dispensing, sample collecting and testing, as well as result registration and delivery.

## Conclusion

This pilot study demonstrates that offering self-sampling HPV tests to high-risk women is feasible. We envision that such catch-up screening for high-risk groups could be performed in a whole country, and be a regular process complementing the routine screening program.

## Data availability

### Underlying data

B2SHARE: A pilot study of risk-stratified cervical cancer screening. http://doi.org/10.23728/b2share.10c44a0fe6f84f05b8f3c88b5681a4fc[13].

This project contains the following underlying data:

- datashare_JW20210423.xlsx (data underlying the study results)

### Extended data

B2SHARE: A pilot study of risk-stratified cervical cancer screening. http://doi.org/10.23728/b2share.10c44a0fe6f84f05b8f3c88b5681a4fc[13].

This project contains the following extended data:

- SMS invitation translation_JD20210524.docx (SMS invitation and reminder messages in English and Swedish).
- Step_by_step_instruction.pdf (step-by-step sampling instructions provided to participants)

Data are available under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International license (CC BY-NC-ND 4.0).

### Acknowledgements

We thank Yasmin Hussain and Sadaf Sakina Hassan for helpful technical assistance. We also thank Zurab Bzhalava and Suyesh Amatya for the website programming.

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# Open Peer Review

## Current Peer Review Status: ✔ ✔

**Version 2**

Reviewer Report 09 September 2022

https://doi.org/10.21956/openreseurope.16261.r30010

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✔ **Raúl Murillo**
Centro Javerinao de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia

I think the authors fairly responded to my comments, so I would not have additional comments. Anyway, I am surprised that the authors do not have information on the sociodemographic characteristics of the patients despite stating that their study is based on a well-established registry, I think this is restricting a proper data analysis.

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Cancer early detection

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 02 September 2022

https://doi.org/10.21956/openreseurope.16261.r30009

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✔ **Jean-Luc Prétet**
Centre National de Référence Papillomavirus, CHU Besançon, France, Besançon, France

I would like to thank the authors for their reponses to my comments and the modifications done on the manuscript.

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** HPV-associated diseases, cervical cancer screening, HPV oncogenesis

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

**Version 1**

Reviewer Report 18 November 2021

https://doi.org/10.21956/openreseurope.14468.r27948

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**Jean-Luc Prétet**
[1] Centre National de Référence Papillomavirus, CHU Besançon, France, Besançon, France
[2] Centre National de Référence Papillomavirus, CHU Besançon, France, Besançon, France

The study by Wang and collaborators is a pilot project to test the feasibility and acceptability of offering a vaginal self-sampling for HPV testing in women with a high risk of cervical cancer. This pilot project is part of a larger one entitled RISCC (Risk-stratified Screening for Cervical Cancer). Women from a southern Sweden region (Skane region) with a high risk of cervical cancer were identified from the Swedish National Cervical Screening Registry according to two criteria: (i) women who had had an AGUS cytology during the past six years and (i) women above 50 years who had had an abnormal cytology but with an insufficient follow-up. These women were contacted by SMS and invited to order an HPV self-sampling kit on a dedicated internet platform. Two additional SMS were sent in the case the women did not respond and finally a physical invitation letter was sent after the two reminders by SMS if no order had been placed. A physical invitation letter was also sent to the women who did not have a registered cell phone number in the database. The main conclusions are that SMS invitations are feasible and resulted in an acceptable response rate. Furthermore, women who tested HPV positive were adequately followed-up.

This is an interesting pilot project because it targets specific populations of women at high risk of cervical cancer. From a public health point of view, reaching these populations is important because they are certainly the ones who will benefit the most from a proactive cervical cancer screening program.

Some points deserves to be highlighted and discussed.

According to the methodology used it is difficult to determine whether the acceptable response rate is due to the SMS invitations or to the invitation letters. This is especially true after the last reminder by a physical letter (sent on Dec, 2019) since women who responded were either receiving the letter because they could not be reached by SMS or because they did not respond to

the 3 SMS. I think that it could be interesting to distinguish in the figure 2 these two groups using stacked bar chart for example. The results then should be interpreted and discussed accordingly. As well, the conclusion paragraph in the abstract should be adapted because it is stated that “SMS invitations are feasible and result in substantial request”; invitation letters are not mentioned.

The authors focused on two groups of “at risk” women. What about other “at risk” groups of women (immunosuppressed, HIV…). This was partly discussed when authors compared the results of the pilot study with those obtained with long-term non-attenders.

One important point deals with the age of the study population and the authors pointed out that these women may not be comfortable with cell phone and internet. Can other means of ordering/picking-up self-sampling kits be considered (general practitioners, pharmacists, associations…).

Does a cost-effectiveness study is planned? If not this should be at least discussed since cost-effectiveness analysis will help policy makers to take decision to implement public-health programs.

Some minor points should also be addressed:

- page 4 first §: Can you indicate the name of test used to analyse genotypes by Luminex?
- page 4 second §: “kits” not “kids”?
- page 4 last §: 19 samples were HPV positive, with eight samples HPV16/18 and ten other HR HPV. One sample is lacking. Also clarify the “Total line” in the table 2.
- page 5 first §: “low-grade lesions” not “low-risk lesions”?
- page 5 second §: the proportion of HPV positivity in women with a history of abnormal cytology is high, but the number of women tested is very low.
- Figure 2: each bar seems to represent 3 days, is this correct?

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and does the work have academic merit?**
Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Partly

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Partly

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** HPV-associated diseases, cervical cancer screening, HPV oncogenesis

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 16 Aug 2022

**Jiangrong Wang**

This is an interesting pilot project because it targets specific populations of women at high risk of cervical cancer. From a public health point of view, reaching these populations is important because they are certainly the ones who will benefit the most from a proactive cervical cancer screening program.
*Reply: We are grateful for these supportive comments.*

Some points deserves to be highlighted and discussed. According to the methodology used it is difficult to determine whether the acceptable response rate is due to the SMS invitations or to the invitation letters. This is especially true after the last reminder by a physical letter (sent on Dec, 2019) since women who responded were either receiving the letter because they could not be reached by SMS or because they did not respond to the 3 SMS. I think that it could be interesting to distinguish in the figure 2 these two groups using stacked bar chart for example. The results then should be interpreted and discussed accordingly. As well, the conclusion paragraph in the abstract should be adapted because it is stated that "SMS invitations are feasible and result in substantial request"; invitation letters are not mentioned. *Reply: This would have been interesting, but this exact data was not available (not registered because it was not specified in the ethical permission) and this subsplitting would have resulted in small groups. For future projects on advancing risk-stratified screening, we will include this in the projects. We have revised the conclusion in the abstract adding the role of physical letter.*

The authors focused on two groups of "at risk" women. What about other "at risk" groups of women (immunosuppressed, HIV...). This was partly discussed when authors compared the results of the pilot study with those obtained with long-term non-attenders.
*Reply: We discussed that women at high risk of cervical cancer can be readily identified by ordinary screening databases. The groups mentioned by the reviewer (HIV-positive and immunosuppressed women) would not be routinely registered in cervical screening databases and would be difficult to identify by registry linkages. This is now discussed in an added paragraph in the discussion section.*

One important point deals with the age of the study population and the authors pointed out that these women may not be comfortable with cell phone and internet. Can other means of ordering/picking-up self-sampling kits be considered (general practitioners, pharmacists,

associations...).
*Reply: As we discussed in the third paragraph of the Discussion section, the proportion of kit ordering in the older age group targeted in this study was not significantly lower than in the younger group. Strategies using pick-up of self-sampling kits are difficult to target for the small group of very high risk women targeted in this study.*

Does a cost-effectiveness study is planned? If not this should be at least discussed since cost-effectiveness analysis will help policy makers to take decision to implement public-health programs.
*Reply: We have added a sentence about this in the discussion, the message being that such calculations cannot be done before data from a pilot on the response rate is available.*

Some minor points should also be addressed: page 4 first §: Can you indicate the name of test used to analyse genotypes by Luminex?
*Reply: It is an in-house test and the references to the detailed method is now given.*

page 4 second §: “kits” not “kids”?
*Reply: Corrected.*

page 4 last §: 19 samples were HPV positive, with eight samples HPV16/18 and ten other HR HPV. One sample is lacking. Also clarify the “Total line” in table 2.
*Reply: Indeed, there was one sample that had tested positive for “Other HPV” in the Cobas test, where the positivity could not be confirmed by Luminex. This is now noted in the Table.*

page 5 first §: “low-grade lesions” not “low-risk lesions”? *Reply: Corrected.*

page 5 second §: the proportion of HPV positivity in women with a history of abnormal cytology is high, but the number of women tested is very low.
*Reply: We have pointed out that the paper describes a pilot study with a limited number of women.*

Figure 2: each bar seems to represent 3 days, is this correct?
*Reply: Correct. Now described in the Figure legend.*

***Competing Interests:*** No competing interests were disclosed.

Reviewer Report 14 September 2021

https://doi.org/10.21956/openreseurope.14468.r27461

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**Raúl Murillo**

[1] Centro Javerinao de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia
[2] Centro Javerinao de Oncología, Hospital Universitario San Ignacio, Bogotá, Colombia

Risk stratified screening is an innovative approach to find a more cost-effective way to implement population-based screening, and its main characteristic is the use of different screening protocols and algorithms for different subgroups within the target population according to the differential risk. Thus, risk stratified screening is based on risk, not on test results.

In that sense, despite relevance, I consider the proposal by the authors actually an intervention for follow-up of non-adherent women with abnormal screening results rather than risk stratified screening as claimed in the title. Nonetheless, the lack of adherence could be *per se* a risk factor for developing CIN3+, but in my opinion, a proper risk approach should result in characterizing the non-adherent populations as part of the basis for risk estimates and contrasting screening modalities for the different risk categories identified.

Still, the risk stratification implicit in the analysis deserve some clarification since it was defined based on the date of analysis instead the date of test results (diagnosis):

- The first group corresponds to women aged up to 80 years old with diagnosis of glandular atypia within the previous 0.5 to 6.5 years, but having no follow-up in the previous 2 years (ending on 2018). In my understanding, a given woman could have a diagnosis of glandular atypia 5 to 6 years ago with proper follow-up and negative results during 2 years after diagnosis, but according to the definition she would be at high risk because she does not have follow-up within the two years previous to the analysis.

- Similarly, the second group corresponds to women aged 65 to 70 years old with HSIL diagnosis after age 50 and no follow-up in the previous 3 years (ending on 2018). Again, a given woman could have an HSIL diagnosis 10 years ago (age 55) with proper follow-up and negative results during 5 years after diagnosis, but according to the definition she would be at high risk given the lack of records within the 3 years previous to the analysis.

- Finally, the third group, which would be from a clinical perspective the one with the lowest risk among the three, is defined based on the total lack of adherence regardless the time since diagnosis.

In my view, a proper risk approach should be based on the elapsed time without follow-up since diagnosis: the longer the time the higher the risk. As the study design apparently did not take this condition into account, I kindly suggest to include it in the analysis either in a prospective approach, ideal in my opinion (time without follow-up on record after diagnosis), or in a retrospective approach (time since the last follow-up test on record). I believe this approach would allow a better selection of at risk population and would provide a more accurate idea of losses to follow-up. At present, according to the definitions provided there are 276 women without follow-up out of 693 women with AGC (39.8%), 589 women without follow-up out of 1290 women with HSIL (45.7%), and 78 women without follow-up out of 1784 with LSIL (4.4%). Data of the two former groups resemble non-organized programs from low and middle income countries rather than highly organized programs with good call and recall systems in place, and apparently, losses to follow-up are lower among the lower risk populations (LSIL) which would not be expected on regular basis either. However, for a better assessment by the reader a brief description of the screening algorithm in the program analyzed would be highly desirable: regular screening interval (women at an average risk and women returning to normal after AGC or HSIL management), as

well as follow-up protocols after AGC, HSIL and LSIL findings.

The risk stratification based on date of data analysis instead of date of diagnosis explain the finding of higher high-risk HPV prevalence among the LSIL population, a result not discussed by the authors. Since the definition for this category is based on the absolute absence of any normal follow-up, they actually represent the group with the highest risk. Similarly, the finding of low CIN2+ prevalence contradicts the high-risk definition. On this regard, the authors hypothesized an improvement in routine follow-up as the main reason but they are defining risk precisely based on lack of follow-up, which is contradictory as indicated.

In summary, I think the reported work better correspond to an acceptability study on HPV self-sampling among reluctant-to-follow-up women; although, I also think the acceptability analysis could be improved to get the most from the data. The characteristics of the study population are not reported regarding the basic approach: SMS vs postal mail. It is possible that women having no identified cell phone differ from those having cell phone in terms of age, income level, education level, and technology literacy. Such characteristics could be also related to the willingness to adopt new technologies making a difference between those who did and did not ordered the kit. Previous reports have shown that early and late technology adopters do not differ in age but they differ in income and education level, technology literacy, and social support and mobility (social networks). I am aware that not all variables of interest would be available in the data sources reported by the authors, but certainly some of them would be. I believe such kind of analysis would allow a better segmentation of the target population for planning future interventions.

Regarding the intervention, the authors should take into account that one group had three reminders (two by SMS and one by postal mail), while the other group had only the initial invitation. This difference added to differences in baseline characteristics should be considered to properly interpret the results, and more relevant, the authors should not mix those receiving a postal mail as an additional reminder after two missing SMS with those having only the initial invitation by postal mail (physical letter). Indeed, analyzing the response rate after the additional reminder by postal mail would be worthy.

Given the limitations described, interpreting the acceptability results is challenging. A 20.8% response rate to the invitation is low, but I am not certain about the risk of the population as previously noted. Having 18 out of 19 positive women attending the diagnostic workup is a very positive result, but as a reader I am not certain if those women are actually non-adherent (time without follow-up since diagnosis or time since the last follow-up test). In addition, I consider the clinical benefit uncertain not only because just one CIN2+ was found but also because 8 out of the 18 women attending the diagnostic workup had inconclusive results due to cervical stenosis, a condition associated with the age of the target population at risk as defined by the authors (women aged up to 80 years old). Thus, given the high frequency expected for such condition an alternative approach should be proposed otherwise unethical to keep the inclusion criteria.

A basic question regarding acceptability of HPV self-collection is the consideration of this technology only for “high-risk” women versus an alternative for all women lost to follow-up, meaning even those without abnormal results but non-adherent to the regular screening interval. Although useful, if the latter the data of the present report should be ideally supplemented and contrasted with analyses on acceptability in the remaining groups of the target population. This

contrast might be out of the scope of the publication, but a better characterization of the study population to allow such comparison with previously and future published literature is anticipated.

**Is the work clearly and accurately presented and does it cite the current literature?**
Partly

**Is the study design appropriate and does the work have academic merit?**
Partly

**Are sufficient details of methods and analysis provided to allow replication by others?**
Yes

**If applicable, is the statistical analysis and its interpretation appropriate?**
Partly

**Are all the source data underlying the results available to ensure full reproducibility?**
Yes

**Are the conclusions drawn adequately supported by the results?**
Yes

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Cancer early detection

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**

Author Response 16 Aug 2022

**Jiangrong Wang**

Risk stratified screening is an innovative approach to find a more cost-effective way to implement population-based screening, and its main characteristic is the use of different screening protocols and algorithms for different subgroups within the target population according to the differential risk. Thus, risk stratified screening is based on risk, not on test results. In that sense, despite relevance, I consider the proposal by the authors actually an intervention for follow-up of non-adherent women with abnormal screening results rather than risk stratified screening as claimed in the title. Nonetheless, the lack of adherence could be per se a risk factor for developing CIN3+, but in my opinion, a proper risk approach should result in characterizing the non-adherent populations as part of the basis for risk estimates and contrasting screening modalities for the different risk categories identified.

Still, the risk stratification implicit in the analysis deserve some clarification since it was defined based on the date of analysis instead the date of test results (diagnosis): The first group corresponds to women aged up to 80 years old with diagnosis of glandular atypia

within the previous 0.5 to 6.5 years, but having no follow-up in the previous 2 years (ending on 2018). In my understanding, a given woman could have a diagnosis of glandular atypia 5 to 6 years ago with proper follow-up and negative results during 2 years after diagnosis, but according to the definition she would be at high risk because she does not have follow-up within the two years previous to the analysis. Similarly, the second group corresponds to women aged 65 to 70 years old with HSIL diagnosis after age 50 and no follow-up in the previous 3 years (ending on 2018). Again, a given woman could have an HSIL diagnosis 10 years ago (age 55) with proper follow-up and negative results during 5 years after diagnosis, but according to the definition she would be at high risk given the lack of records within the 3 years previous to the analysis.

Finally, the third group, which would be from a clinical perspective the one with the lowest risk among the three, is defined based on the total lack of adherence regardless the time since diagnosis. In my view, a proper risk approach should be based on the elapsed time without follow-up since diagnosis: the longer the time the higher the risk. As the study design apparently did not take this condition into account, I kindly suggest to include it in the analysis either in a prospective approach, ideal in my opinion (time without follow-up on record after diagnosis), or in a retrospective approach (time since the last follow-up test on record). I believe this approach would allow a better selection of at risk population and would provide a more accurate idea of losses to follow-up. At present, according to the definitions provided there are 276 women without follow-up out of 693 women with AGC (39.8%), 589 women without follow-up out of 1290 women with HSIL (45.7%), and 78 women without follow-up out of 1784 with LSIL (4.4%). Data of the two former groups resemble non-organized programs from low and middle income countries rather than highly organized programs with good call and recall systems in place, and apparently, losses to follow-up are lower among the lower risk populations (LSIL) which would not be expected on regular basis either. However, for a better assessment by the reader a brief description of the screening algorithm in the program analyzed would be highly desirable: regular screening interval (women at an average risk and women returning to normal after AGC or HSIL management), as well as follow-up protocols after AGC, HSIL and LSIL findings.

*Reply: We are very grateful for these careful and detailed comments. Regarding only targeting women with previous abnormality in this risk-stratified screening pilot, we simply targeted the women with highest risk in the population. The risk profile calculations were retrieved from previous publications, but to make the procedure more clear to the readers we added an extra Table with the exact algorithm and the exact cervical cancer risk of the targeted risk groups. We also added an extra description at the beginning of the Method section. Of course, future projects with risk stratified screening will use much larger risk groups. In response to the series of comments, we added explanations of the risk group identification in the discussion (see the added paragraph in the discussion section).*

The risk stratification based on date of data analysis instead of date of diagnosis explain the finding of higher high-risk HPV prevalence among the LSIL population, a result not discussed by the authors. Since the definition for this category is based on the absolute absence of any normal follow-up, they actually represent the group with the highest risk. Similarly, the finding of low CIN2+ prevalence contradicts the high-risk definition. On this regard, the authors hypothesized an improvement in routine follow-up as the main reason

but they are defining risk precisely based on lack of follow-up, which is contradictory as indicated.
*Reply: Indeed, an intervention to find women at high risk starts when the intervention is launched and identifies the women with risk profiles in their screening history. This is in contrast to the gynecological follow-up which starts when abnormalities are detected. As the study was not about optimal follow-up, but about risk-stratified screening, identification of risk women should start when the screening is launched. This is now clarified. On the difference in HPV prevalences between various groups, we did not want to speculate too much because of small numbers. Nevertheless, we added a brief explanation in the discussion section (see the added paragraph in discussion section).*

In summary, I think the reported work better correspond to an acceptability study on HPV self-sampling among reluctant-to-follow-up women; although, I also think the acceptability analysis could be improved to get the most from the data. The characteristics of the study population are not reported regarding the basic approach: SMS vs postal mail. It is possible that women having no identified cell phone differ from those having cell phone in terms of age, income level, education level, and technology literacy. Such characteristics could be also related to the willingness to adopt new technologies making a difference between those who did and did not ordered the kit. Previous reports have shown that early and late technology adopters do not differ in age but they differ in income and education level, technology literacy, and social support and mobility (social networks). I am aware that not all variables of interest would be available in the data sources reported by the authors, but certainly some of them would be. I believe such kind of analysis would allow a better segmentation of the target population for planning future interventions.
*Reply: Comparting social- and demographic characteristics between women who responded to SMS and postal mail would have been interesting, but this data was unfortunately not available.*

Regarding the intervention, the authors should take into account that one group had three reminders (two by SMS and one by postal mail), while the other group had only the initial invitation. This difference added to differences in baseline characteristics should be considered to properly interpret the results, and more relevant, the authors should not mix those receiving a postal mail as an additional reminder after two missing SMS with those having only the initial invitation by postal mail (physical letter). Indeed, analyzing the response rate after the additional reminder by postal mail would be worthy.
*Reply: This is a valuable suggestion and we will certainly collect such data in future studies. It was, however, not collected in this study.*

Given the limitations described, interpreting the acceptability results is challenging. A 20.8% response rate to the invitation is low, but I am not certain about the risk of the population as previously noted. Having 18 out of 19 positive women attending the diagnostic workup is a very positive result, but as a reader I am not certain if those women are actually non-adherent (time without follow-up since diagnosis or time since the last follow-up test). In addition, I consider the clinical benefit uncertain not only because just one CIN2+ was found but also because 8 out of the 18 women attending the diagnostic workup had inconclusive results due to cervical stenosis, a condition associated with the age of the target population at risk as defined by the authors (women aged up to 80 years old). Thus, given the high frequency expected for such condition an alternative approach should be proposed

otherwise unethical to keep the inclusion criteria.
*Reply: In the discussion (the second paragraph), we now compared this 20.8% response rate to similar trials among non-attenders (which was 10.7% under the same kit-order manner). In the discussion section, we have now underlined that women with inconclusive follow-up because of cervical stenosis will continue to be followed up. Indeed, it would have been unethical to just let these women go.*

A basic question regarding acceptability of HPV self-collection is the consideration of this technology only for "high-risk" women versus an alternative for all women lost to follow-up, meaning even those without abnormal results but non-adherent to the regular screening interval. Although useful, if the latter the data of the present report should be ideally supplemented and contrasted with analyses on acceptability in the remaining groups of the target population. This contrast might be out of the scope of the publication, but a better characterization of the study population to allow such comparison with previously and future published literature is anticipated.
*Reply: Indeed. We did compare the response rate in this pilot study with the previous trials among non-attenders. In the new Table we compare the cancer risk to the non-attenders without previous abnormal smears. Direct comparison with these long-term non-attenders without abnormal smears will be subject of future projects.*

***Competing Interests:*** No competing interests were disclosed.