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Looking ahead: a case for HPV testing of self-sampled vaginal specimens as a cervical cancer screening strategy

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Abstract

Even in the era of highly effective HPV prophylactic vaccines, substantial reduction in worldwide cervical cancer mortality will only be realized if effective early detection and treatment of the millions of women already infection and the millions who may not receive vaccination in the next decade can be broadly implemented through sustainable cervical cancer screening programs. Effective programs must meet three targets: 1) at least 70% of the targeted population should be screened at least once in a lifetime, 2) screening assays and diagnostic tests must be reproducible and sufficiently sensitive and specific for the detection of high-grade precursor lesions (i.e., CIN2+), and 3) effective treatment must be provided. We review the evidence that HPV DNA screening from swabs collected by the women in their home or village is sufficiently sound for consideration as a primary screening strategy in the developing world, with sensitivity and specificity for detection of CIN2+ as good or better than Pap smear cytology and VIA. A key feature of a self-collected HPV testing strategy (SC-HPV) is the move of the primary screening activities from the clinic to the community. Efforts to increase the affordability and availability of HPV DNA tests, community education and awareness, development of strong partnerships between community advocacy groups, health care centers and regional or local laboratories, and resource appropriate strategies to identify and treat screen-positive women should now be prioritized to ensure successful public health translation of the technologic advancements in cervical cancer prevention.

Introduction

Each year, about 500,000 new cases of cervical cancer are diagnosed worldwide. Recognition that human papillomavirus (HPV) infection causes practically all invasive cervical cancers (ICC) has revolutionized cervical cancer prevention strategies. One of these revolutions was the development of highly effective prophylactic vaccines targeting the most carcinogenic HPV types: 16 and 18[1]. However, these vaccines do not protect against all carcinogenic HPV types nor adequately protect those who are already infected, and their high cost may render them largely unavailable in resource-poor countries for years. Further,

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the millions of women with prevalent pre-cancers and early cancers would not benefit from vaccines but would benefit from early detection and treatment through screening.

Historically, cervical cancer screening has relied on morphological evaluation of exfoliated cells scraped from the transformation zone of the cervix to identify cytological abnormalities. While application of cervical cytology has led to a remarkable reduction in cervical cancer incidence in many high-income countries[2], it has been difficult to establish and maintain effective cervical cytology programs in low and middle income countries[3]. Cytology screening programs require resources and infrastructure that are simply not available in the developing world[4].

To meet screening needs in developing nations, direct naked-eye visualization of the cervix after acetic acid application (VIA) has been widely evaluated as a screening strategy[5]. The test is simple and requires few resources. Since the results of the VIA screening are available immediately, it is possible to follow testing with cryotherapy of the transformation zone for VIA-positive women in a single visit. This “see and treat,” or “single visit” approach can overcome the loss to follow-up inherent in testing and treatment programs that require repeated visits. Findings on the efficacy of a VIA screen in reducing cervical cancer incidence are mixed. Denny et al[7] and Sankarnarayanan et al[9] reported modest successes with the use of VIA screening, but the landmark Osmanabad intervention trial in India[10] found that VIA screening was not successful in decreasing the incidence of advanced cervical cancer, or of cervical cancer deaths.

There can be many reasons for the inconsistency in efficacy of VIA[11]. Interpretation of VIA positivity is highly subjective and even in studies conducted with a common training protocol and test definition, the sensitivity estimates vary widely[12]. Further, common conditions like cervical inflammation reduce the specificity of VIA[13]. Poor performance of VIA is often attributed to inadequate training, yet it is difficult to monitor its performance across providers in real time. Its positive predictive value is low, and if one were to treat all VIA-positive women with cryotherapy, as is recommended in the “see and treat” policy, the number of women receiving unnecessary cryotherapy would be many times the number receiving cryotherapy for cervical cancer precursors. Since cryotherapy is not a harmless procedure[14], such an approach would cause more harm than benefit if the program could not deliver a significant reduction in cervical cancer incidence.

Due to these drawbacks of morphologic screening, a paradigm shift toward molecular screening for ICC through HPV DNA detection is evident. HPV DNA tests performed on cells collected by the clinician from the cervical transformation zone (CC-HPV) have the potential to replace cervical cytology as the primary screening test in both developed and developing countries[15]. They can reproducibly detect >90 % of precancers and cancers, and their use as the primary screen significantly reduced cervical cancer incidence in randomized controlled trials[10, 16].

Yet like Pap screening, CC-HPV imposes a burden on both clinics and women; the woman needs to attend the clinic and undergo a speculum examination from a skilled provider. Several researchers have therefore investigated whether HPV DNA detection in self-sampled vaginal specimens would be an effective primary screen for cervical cancer prevention[19–23]. In this procedure, the woman can self-collect a vaginal swab in the privacy of her home. She would be spared the need for a formal clinic visit and a speculum examination. Only those women whose swabs test positive for high risk HPV DNA would attend a dedicated clinic for diagnosis and/or treatment. This scheme would provide an objective screening test with a performance at least as good as the best cytology, and it could expand coverage far beyond what is now possible and reach women who would benefit the

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most from screening. Most importantly, it would move screening from the clinic into the community (Fig 1).

In this review, we will describe the performance characteristics of HPV detection in self-sampled vaginal specimens, and present our view of how HPV testing using samples self-collected at home can translate into successful reduction in cervical cancer mortality in world regions harboring the largest ICC burden.

Self-sampling for genital HPV DNA

For self-sampling, the subject is instructed to insert a brush or swab as high as possible into the vagina until it meets with resistance, rotate it three times and then remove it and place it into the tube containing the transport medium[19]. These self-collected samples for HPV assays (SC-HPV) can be obtained in the clinic[19, 21, 24] or at home[22]. Women are given verbal or diagrammatic instructions by the health-care provider, but the specimens are collected in privacy.

Comparison of SC-HPV with CC-HPV for HPV DNA detection

In 2007, Petignat et al[25] conducted a systematic review of 18 studies which compared the prevalence of HPV infection obtained from SC-HPV and CC-HPV. They concluded that the two methods of obtaining specimens gave comparable HPV prevalence values. Results from an additional 15 studies published subsequent to this review are shown in Table 1. These studies varied greatly in the collection devices used and in the DNA detection systems. However, within the individual studies, there was good overall agreement between the results of SC and CC samples. Discordant results were generally equally distributed between SC+/CC- and SC-/CC+ for HR-HPV. In contrast, low risk (LR) HPVs were more commonly detected in the SC swab[25–28].

SC-HPV as a screening strategy - comparison with cytology and CC-HPV

The first study comparing SC-HPV with cytology and CC-HPV for the detection of CIN2+ was conducted in South Africa and published in 2000[19]. This was followed by similar studies in China, Mexico and the United Kingdom (Table 2). While these studies varied with respect to case definition and the ascertainment of verification bias for detection of CIN2+, the sensitivity of SC-HPV was comparable to Pap in most studies. Specificity using SC-HPV was generally lower than that for Pap cytology, with one exception[24]. Clearly, performance of subjective tests such as Pap cytology is heavily influenced by the quality of the cytology programs at each test site.

The sensitivity of CC-HPV was consistently the highest of any screening method in all six studies, with values between 84% and 100%. The sensitivity of SC-HPV was 10–19% below that of CC-HPV. The differences in the specificity between SC-HPV and CC-HPV were minimal. When choosing between tests with different performance characteristics, it is best to evaluate not only the individual performance estimates of sensitivity and specificity, but their relative relationship (i.e., how much loss in specificity was realized with each incremental gain in sensitivity?). The ‘best test’ will thus depend on the relative importance of missing cases (lower sensitivity) to over-referral or over-treatment (lower specificity). In the context of once- or twice-in a lifetime cervical cancer screening where there are minimal opportunities for intervention, maintaining a high level of sensitivity is critical.

Why is HR-HPV prevalence similar, yet clinical sensitivity lower, in SC-HPV samples compared to CC-HPV samples?

This apparent paradox is easily understood when carefully considering the anatomical source of cells sampled from CC-HPV versus SC-HPV. Specifically, the speculum-assisted

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clinician-collected swab directly samples the cervical epithelium, avoiding vulvovaginal epithelial sampling. In contrast, the self-collected sample contains a mixture of vulvar, vaginal, and cervical epithelial cells. Because HR-HPV DNA is detected in cervical and vaginal epithelium with equal or greater frequency[27, 28], the overall HR-HPV prevalence will often mirror these findings. However, since CIN2+ is restricted to cervical cells, the ability to detect HR-HPV associated with CIN2+ is completely dependent on the adequacy of *cervical* epithelial sampling. The adequacy of cervical sampling vis-à-vis self-collection will be dependent on the depth of insertion of the swab (i.e., sufficient to touch the cervix), the extent of cervical epithelial cell exfoliation into the vaginal vault, and the rigor of sample collection (i.e., rotating the swab 3–5 times versus 1 time before removing).

As expected, data show that the SC-HPV collects a less adequate cervical HPV sample compared to CC-HPV. For example, in a study in Shanxi Province, China, HPV viral load estimates from directed sampling of 3 different lower genital tract sites were compared among 34 women who were hc2 positive at all sites. The mean hc2 signal strength (RLU/CO) was highest at the endocervix (688), about six-fold lower in the upper vagina (118), and still lower in the lower vagina (51). The viral load estimates from the self-collected specimens from the same women (RLU/CO=273) were remarkably close to the average of the 3 sites (RLU/CO=286), supporting that the self-collected sample reflects a combination of all cell types[29], and less efficiently samples infection at the cervix.

A large screening study in Mexico evaluated the relative contribution of viral load differences in detection of CIN2+ (Salmeron, personal communication). The correlation of viral loads in SC-HPV and CC-HPV for the over 7000 participants in this study is shown in Figure 2 and the 101 participants diagnosed with CIN2+ are identified in the figure. A majority (n=69, 68.3%) of the women with CIN2+ were positive in both CC-HPV and SC-HPV, 25 (24.8%) were positive only in CC-HPV, 3 (3.0%) were positive only in SC-HPV and 4 (4.0%) were negative in both. Among the 69 CIN2+ cases who were positive in both assays, the signal strength was higher in CC-HPV in 59 (85.5%). The median hc2 signal strength of the 94 women with CIN2+ who were positive in CC-HPV was sevenfold higher than that of the 72 women who were positive in SC-HPV. Among the disease-negative women, the median signal strength in the CC-HPV positive specimens was 1.3 times higher than that in the SC-HPV positive specimens (Table 3). Taken together, these data suggest that the lower HR-HPV viral load observed in the SC-HPV samples results from sampling fewer HR-HPV infected cervical cells, leading to the reduced sensitivity of SC-HPV compared to CC-HPV for the detection of cervical lesions.

Improving the performance of SC-HPV

The reduced adequacy of cervical cell collection using self-sampling results in a clinical sensitivity for the detection of CIN2+ that is 10–19% lower than CC-HPV. Attempts to improve the sensitivity of SC-HPV have taken many forms: (a) modification of the collection device to pick up more cervical and fewer vaginal cells (Belinson, unpublished data), (b) use of an analytically more sensitive PCR-based HPV assay[29] and (c) lowering the cut-points for currently used assays[30, 31]. However, improvements to the sensitivity of SC-HPV must be balanced to avoid unacceptable decreases in clinical specificity. While the preliminary data from the SHENCCAST studies suggest that the relative balance of sensitivity and specificity of SC-HPV by PCR is similar to CC-HPV by hc2, further targeted improvements to the specificity are possible. High-risk HPV probes which hybridize with low-risk HPVs produce false positive results[32], and this may happen more frequently with self-collected vaginal specimens which have a higher prevalence of LR-HPV[2, 27, 28]. Use of high-risk HPV probes which do not cross-hybridize with low-risk HPVs would eliminate this problem. The major problem and the most difficult to solve is that of high-risk HPVs

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which are present only in the vagina, and therefore not likely to produce cervical disease. Use of a device that favors collection of cervical cells would lessen this problem[33–35].

Acceptability of SC-HPV

Women all over the world have readily accepted self-sampling to collect vaginal specimens. Studies published in the past decade show that tens of thousands of women have provided self-sampled specimens. Self-sampling has been employed satisfactorily to collect specimens from “hard-to-reach” women in Appalachia[36], the US military[37] and the inner city[38], and for follow-up in prospective studies[39, 40] in the USA and Uganda[41].

Acceptability of self-sampling has been extensively evaluated in many developing countries[42–46]. Women generally preferred self-sampling to clinician-collected sampling, although some were concerned that they “may not take as good a specimen as a clinician may take”. Use of collection devices with indicators of proper sample collection that would be visible to the woman may reduce concerns that the self-collected sample was inferior to one collected by the doctor (e.g., FTA elute micro cards[47, 48]). In addition, some questioned why they should collect a specimen since they were not ill, and in the Chinese study, the majority of women preferred to do the self-sampling at the clinic rather than at home[43]. In practice, we found that participation in screening by home-based self-sampling was significantly higher than by clinic-based sampling (71.5% vs. 53.8% respectively, $p< 0.001$) in South Indian women aged 30–45 years[22].

HPV assays-there are many options

The optimum assay for self-sampled specimens should have a high analytical sensitivity for high-risk HPVs, and the high-risk HPV probes should not hybridize with low-risk HPVs. It should also be affordable and its performance must be easy to monitor. The assays listed in Table 4 meet some of these requirements. Whichever HPV assays are chosen, it will be necessary to provide them to the community either free or at affordably low prices, and to monitor their performance for quality assurance.

HPV assays utilizing multiple platforms at varying cost and infrastructural requirements have been developed or are under development (Table 4). The technical aspects of the assays have been discussed extensively elsewhere[49–58]. With one exception, all of the screening studies based on HPV assays listed in Table 2 were performed with hc2, the test for high-risk HPVs developed by Digene and approved by the FDA in 2000. However, the study by Qiao et al used a new test, C*are*HPV, which was designed to be simpler to use and more affordable in poor-resource settings, and has performance characteristics comparable to hc2[49]. *Care*HPV needs a small footprint of bench-top work space, does not need electricity or running water and can be performed almost anywhere by low level technical staff in 2.5 hours. *Care*HPV was designed to be available at the cost of less than US $5 per test, compared with the cost of hc2 at US $40–60 per test.

Different tests will be appropriate in different settings. Low-tech tests like *Care*HPV obviate the need for sophisticated laboratories, and are thus appropriate for small-scale, local testing using minimally trained technicians and few resources. Such tests will offer a reasonable option for SC-HPV screening in remote environments or regions where transport to a regional testing laboratory presents a significant barrier. However, many middle-income countries may be able to effectively utilize high-throughput regional testing in a centralized laboratory, which can maintain quality control and standardization. These environments may offer an economy of scale, and except for an initial capital investment for instrumentation (which can be offset by charitable donations), will offer a cost-effective solution in many regions.

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Whatever test is used, for SC-HPV to be a successful primary screening strategy, it will be critical to seamlessly link the collection of the samples in the community to laboratory testing for HPV. This includes (1) stable transportation of SC-samples to the laboratory or testing site, (2) ensuring a link between the patient identification, the sample, and the test result, (3) quality controlled HPV testing, and (4) efficient delivery of test results with appropriate counseling and management of test positives. Samples are currently collected with a swab or brush and placed into a liquid transport medium. Transportation of liquid samples can pose problems, particularly in remote areas with extreme temperatures. Options for collection of dry specimens should be a priority research target, with an aim to eliminate liquid mediums, stabilize DNA, render specimens non-infectious, withstand extreme temperatures and humidity, and be resistant to cross-contamination. The FTA micro elute card by GE Bioscience is one option that meets many of these requirements[48]. Other possible inexpensive solutions include fixation with common materials such as hairspray, or simply air-drying on the collection brush. Barcoding is an increasingly affordable means to ensure that specimen identity is maintained during transport and testing, especially when a traditional chain of command is difficult to control.

Follow-up and treatment

The proportion of screened women 30 years and older who will test positive for HR-HPV will vary between populations. In Mexico and India, the reported HR-HPV prevalence is ~10–12%[10, 59, 60], whereas in sub-Saharan Africa the HR-HPV prevalence can be over 20%[7]. As illustrated in Figure 1, two broad approaches to management of HR-HPV positive women can be envisioned, depending on resource availability.

In the first approach all HR-HPV positive women would be referred for additional testing to differentiate those with cervical cancer precursors (i.e., CIN2/3) and cancer that need treatment from those who are simply HPV infected. This is traditionally achieved using colposcopy and directed biopsy, requiring the availability of highly skilled clinicians. These will not be available in the low-resource countries. As an alternative, several molecular tests are currently under evaluation for differentiating HPV-associated disease from HPV infection[61]. For example, detection of the cellular protein p16 in cells by immunostaining or ELISA[62–65] has been found to be more specific for detection of CIN2+ compared to HR-HPV DNA testing alone. The E6 protein test, a lateral flow, antibody capture assay, is still in early stage evaluation[66], but holds particular promise as a point-of-care rapid test to differentiate CIN3/cancer patients requiring immediate treatment from HR-HPV positive patients without high grade disease. Most women identified as having CIN2+ can be treated using outpatient clinic-based procedures like cryotherapy and LEEP (loop electroexcision procedure), while the rest would require referral to a tertiary care hospital or regional cancer center for appropriate treatment. A large proportion of women identified as HR-HPV positive will not be found to have any disease, reducing the overall specificity of a HR-HPV-based screening strategy. However, these women are clearly at a higher risk of subsequent disease compared to the HR-HPV negative women. In a study in Portland, Oregon, it was estimated that the risk of future disease in a woman who is infected with HPV16 or HPV18 is about 20%, compared to a risk of <1% for women who are HR-HPV negative[67]. Management of the HR-HPV positive women might include a 12-month repeat screen, whereas HR-HPV negative women can either be rescreened once more in 5 to 10 years, or removed from screening.

The second approach assumes there is no practical method for differentiating diseased from non-diseased women, which is the probable scenario in the most resource poor areas. In this case, it may be preferable to treat all HR-HPV positive women with low-cost and easily implemented methods such as cryotherapy[7]. It will remain necessary to rule out by clinical

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examination cancers or large lesions that would be inadequately treated by cryotherapy; these women will still need referral as described above[68].

The way forward

Successful reduction of cervical cancer incidence through early detection and treatment must meet three crucial targets: 1) at least 70% of the targeted population should be screened at least once in a lifetime, 2) screening assays and diagnostic tests must be reproducible and sufficiently sensitive and specific for the detection of high-grade precursor lesions (CIN2+), and 3) effective treatment must be provided. In this review, we have demonstrated that the performance data (Target 2) is sufficiently sound to support use of SC-HPV as a primary screening strategy in the developing world. However, studies have not assessed the population effectiveness of this strategy, which is conditionally dependent on success in all three target areas. We attempted to estimate the impact of the screening program at the population level in our evaluation of the efficacy of 3 different cervical cancer screening tests in peri-urban India by carefully monitoring participation in screening and follow-up protocols in addition to individual test performance. A population-based sample of women was invited to participate in a screening visit at the local clinic via house-to-house recruitment. Using only locally available resources, 58.4% of eligible women refused participation. In addition, 59.5% of the screen-positive women were considered inadequately screened because of refusal to comply with follow-up procedures. Using inverse-probability weighting, we estimated that 68% of the underlying prevalent disease in the population remained undiagnosed as a result of failure to be screened, and 28% undiagnosed due to incomplete screening and follow-up[69]. Despite our use of the best performing screening assay (CC-HPV), we were able to detect and prevent only a minor fraction of disease in the population. Thus, *successful* implementation of an SC-HPV strategy still requires advances in 4 primary areas: 1) availability of HPV DNA tests, 2) education/awareness of community members to promote screening participation, 3) development of partnerships between communities, health care centers, and laboratories, and 4) strategies to identify and treat the women selected based on the positive test rate and resource availability.

Availability of HPV DNA tests

Where effective technology is available, it is imperative that governments and industry work together to ensure that technologies such as HPV DNA assays be made affordable. Antiretroviral therapy for HIV treatment became available in resource-poor countries as a result of such partnerships[70, 71].

Improve screening participation and development of partnerships

A strategy based on self-collection has an excellent chance to improve coverage over traditional speculum-based strategies; this hypothesis should be tested. High coverage of screening (80%) has been highlighted by the WHO as one of the most critical elements necessary for successful mortality reduction through screening[72, 73]. However, a recent analysis of cervical cancer screening in 57 countries reported substantial inequities in coverage of current screening programs. Crude coverage in developing countries was less than half that of developed countries (44.7% vs. 93.6%, respectively), and there was an alarmingly low rate of effective coverage (18.5%)[74]. Formative research to assess infrastructural barriers and community acceptance should be conducted before implementing a screening program, in order to develop the most useful and culturally appropriate educational and awareness materials. Targeting education to influential community advocacy and women's groups has the potential to mobilize a larger number of unpaid community volunteers to recruit, register, educate, and organize the collection of the samples under the supervision of a community health worker. This could have a substantial

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impact on screening coverage rates. The health workers engaged in mobilizing and organizing the community-based self-collection will also need to be trained in delivery of test results, including counseling of both test positive and test negative women, and effectively providing a link between HPV positive women and appropriate medical follow-up. The most effective results delivery and counseling messages may be regionally dependent, and qualitative research efforts in this area should be prioritized.

Diagnosis and treatment

Once HR-HPV positive women are identified, the best follow-up strategy remains uncertain, and is a clear research priority. As discussed previously, choice of diagnosis and/or treatment measures will be constrained by resources and in the most resource poor regions, the best strategy may be treatment of all HR-HPV positive women with a relatively straightforward and accessible method such as cryotherapy. The consequences of a large amount of overtreatment have not been fully evaluated, and demonstration projects utilizing this approach should evaluate longer-term effects of screen and treat programs.

In summary, future research should focus on evaluating implementation strategies, with careful measurement of endpoints such as percent of eligible population screened, turn-around time for dissemination of lab results, clinical follow-up of screen-positive women, and long term effectiveness of treatment. Many NGOs would welcome the opportunity of trying out these methods in their communities. Where a strategy falls short of expectations, multidisciplinary teams should work together to identify barriers, evaluate alternative strategies addressing the barriers, and most critically, broadly disseminate their findings. Implementing widespread SC-HPV screening, particularly in low-resource settings will continue to be challenging. However, the challenges should be viewed as impetus, not a deterrent, to broad implementation of proven cervical cancer prevention tools such as SC-HPV.

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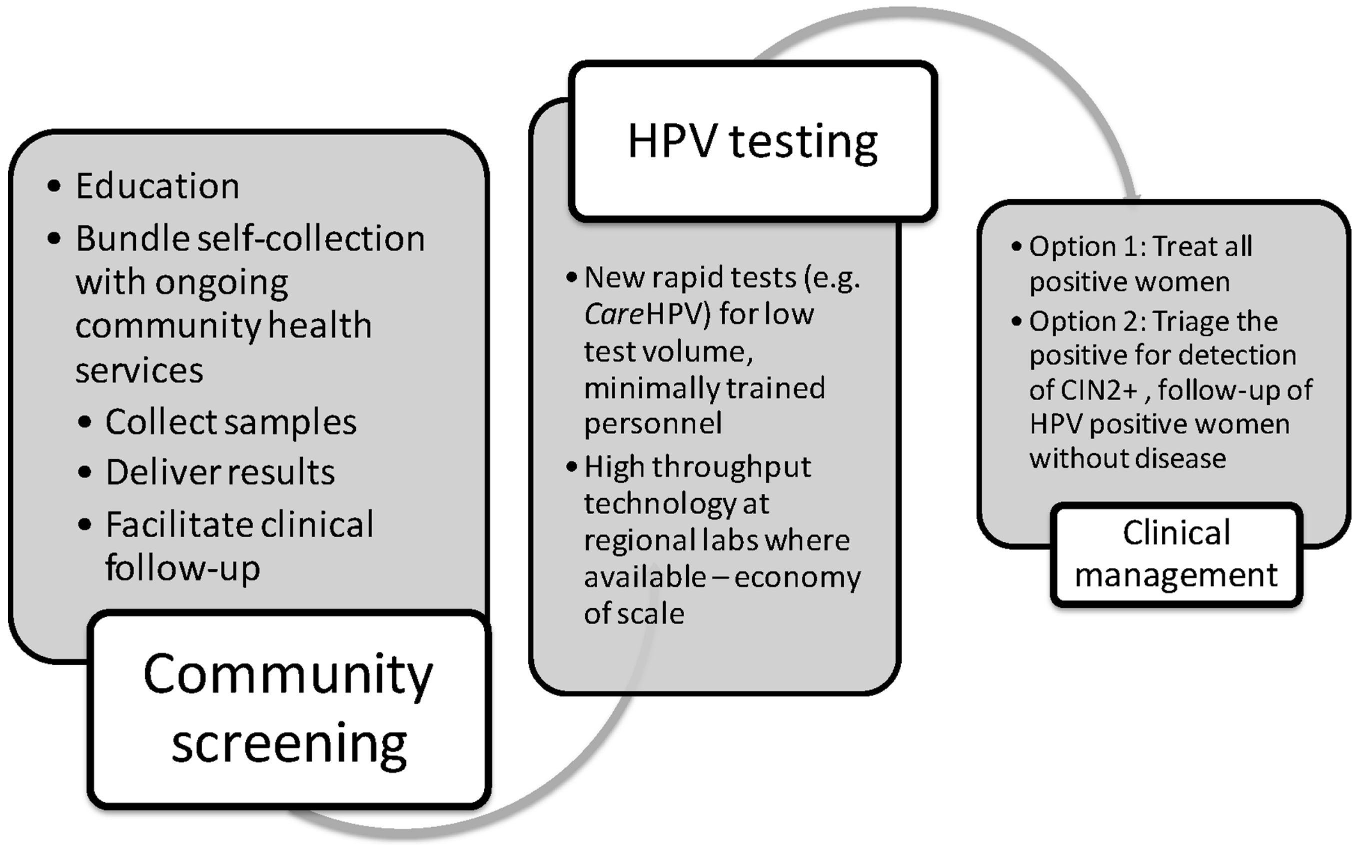

Figure 1.
Example of self-sampling HPV testing strategy for cervical cancer screening, highlighting requirements for primary community screening, HPV testing, and clinical management according to resource availability.

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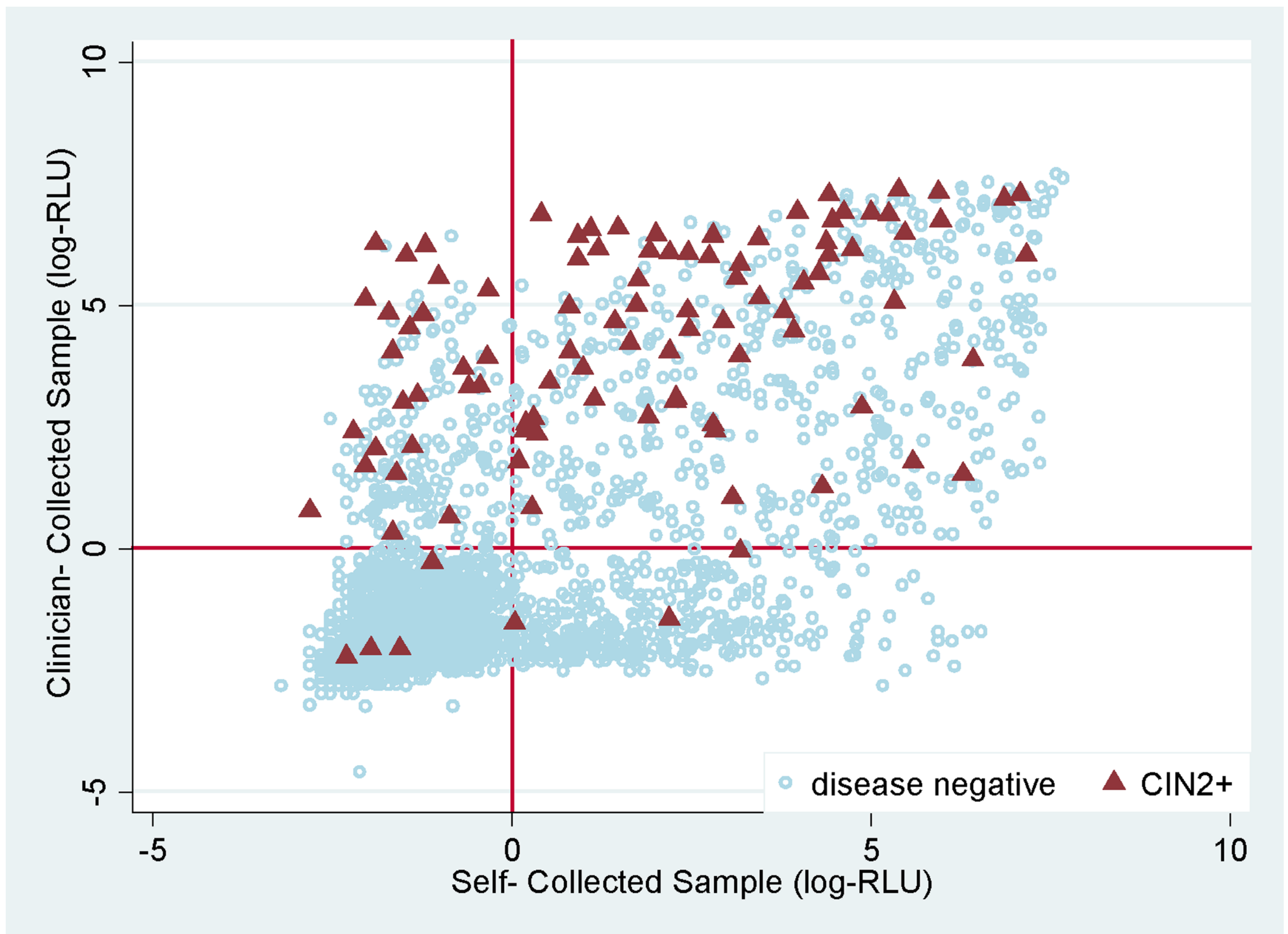

Figure 2.
Pair-wise correlation of HPV viral load (log-RLU) in SC-HPV and CC-HPV in women with and without CIN2+.

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Table 1

Comparison of HPV DNA Detection in CC-HPV and SC-HPV Samples*

Reference	Country	# Pts	Population sampled	Device-self	Device-clinician	SC-HPV HR Prevalence	CC-HPV HR Prevalence	Kappa (95% CI)
Sowjanya[22] et al. 2009	India	432	25 years; population based, but enriched for screen+	Digene cervical sampler	Digene cervical sampler	14.1	20.1	0.7
De Alba[75] et al. 2008†	USA	386	18 years, Hispanic, no pap in last year	cotton swab	Not reported	18.1	7.0	.47**
Khanna[76] et al. 2007 ‡	USA	398	18 years, routine gynecologic care	Digene cervical sampler	Digene cervical sampler	26.1	16.3	.53**
Safaeian[77] et al. 2007	Uganda	606	15–49 years, population based	Dacron swab	Dacron swab	19.0	19.1	0.75 (0.68–0.82)
Holanda[78] et al. 2006 §	Brazil	878	15–70 years, from poor rural areas	collection brush	conical brush	33.9	28.6	0.7
Karwalajtys[79] et al. 2006	Canada	307	15–49 years, follow-up for previous HPV+ result, random sample of HPV–	Dacron swab	Digene cervical sampler	20.8	17.6	0.54 (0.42– 0.66)
		152	>49 years, due for annual cytology	Dacron swab	Digene cervical sampler	9.9	8.6	0.37 (0.13– 0.62)
Bhatla[23] et al. 2009	India	546	>=30 years, gynecologic symptoms, married	Digene cervical sampler	Digene cervical sampler	12.3	13.1	0.76 (0.65– 0.82)
Qiao[49] et al. 2008	China	2388	30–54 years, population based	Digene cervical sampler	Digene cervical sampler	19.5	18.0	not reported
Jones [26] et al. 2007¥	South Africa	450	>18 years, 1/3 with gynecologic symptoms	tampon, vaginal swab	Digene cervical sampler	33.4	36.3	0.61 (0.50– 0.72)
Szarewski[80] et al. 2007	UK	920	due for routine screening	cotton swab	Digene cervical sampler	19.2	17.4	not reported
Wright[19] et al. 2000	South Africa	1415	35–60 years, previously unscreened	Dacron swab	conical brush	21.1	21.3	0.45
Belinson[24] et al. 2001	China	1997	35–45 years, population based	Dacron swab	endocervical brush	17.0	18.2	not reported
Belinson[20] et al. 2003¶	China	8497	35–50 years, population based	Digene cervical sampler	Digene cervical sampler	25.6	23.7	0.489
Salmeron[21] et al. 2003	Mexico	7868	25–60 years, attending clinic for cx ca screening	Dacron swab	conical cytobrush	11.6	9.4	not reported

*all HPV testing performed with hc2 (RLU/CO 1 as threshold for positivity) except Qiao et al, which used careHPV

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** calculated from data reported

† SC-HPV and CC-HPV samples collected on different days

‡ Restricted to the 398 women with both SC-HPV and CC-HPV samples

§ CC-HPV sample collected within 1 week of SC-HPV sample

¥ SC-HPV prevalence & kappa are reported for swab sample only (not tampon)

¶ CC-HPV sample collected at least 3 months after SC-HPV

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Table 2

Comparison of SC-HPV with CC-HPV and cervical cytology as a screening strategy for the detection of CIN2+

Article	Pap[§]		SC-HPV[¥]		CC-HPV[¥]		Population	Collection Device	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity		Self	Clinician
Wright[19] et al. 2000	67.9* (53.9–79.4)	87.7* (85.8– 89.5)	66.1 (52.1– 77.8)	82.9 (80.7–84.9)	83.9 (71.2– 91.9)	84.5 (82.3– 86.4)	1415 unscreened black South African women aged 35–65	Dacron swab	special conically shaped brush
Belinson[24] et al. 2001	94*	78*	83	86	95	85	1997 women aged 35–45 from Shanxi province	Dacron swab	plastic spatula and endocervical brush
	confidence intervals not provided								
Belinson[20] et al. 2003	88.3 * (85.0– 90.8)	81.2* (80.4– 82.0)	87.5 (84.2– 90.8)	77.2 (76.2– 78.2)	96.8 (95.0– 98.6)	79.7 (78.9– 80.5)	8497 women aged 35–50 in Shanxi province	Digene Cervical Sampler brush	Conical shaped brush similar to self-test
Salmerón[21] et al. 2003	59.4 * (49.2– 68.9)	98.3 * (98.0– 98.6)	71.3 (61.3– 79.6)	89.2 (88.5– 89.9)	93.1 (85.8– 96.9)	91.8 (91.2– 92.4)	7868 women, aged 15–85, attending cx ca screening in Mexico	Dacron swab	conical cytobrush (Digene)
Szarewski[80] et al. 2007	81 * (60– 92)	96 * (95– 97)	81 (60–92)	82 (80– 85)	100 (85–100)	85 (82– 87)	922 women attending routine pap smears in the UK	cotton swab (Digene kit)	Digene Cervical Sampler brush
	*mild dyskaryosis and above								
Qiao[49] et al. 2008	85.3 * (76.9– 93.7)	97.0 * (96.3– 97.7)	72.9 ** (62.4– 83.3)	87.7 ** (86.3– 89.0)	84.3 ** (75.8–92.8)	87.5 ** (86.1–88.8)	population-based, 2530 women aged 30 to 54 in Shanxi province, China	vaginal-brush (Cervical Sampler, Qiagen)	cervical brush (Cervical Sampler, Qiagen)
	*ASC-H+								

[§]threshold for Pap positivity was ASCUS+ unless otherwise specified

[¥]all HPV testing performed with hc2 (RLU/CO 1 as threshold for positivity) except Qiao et al, which used careHPV

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Table 3

Comparison of hc2 signal strength in HR-HPV positive CC-HPV and SC-HPV specimens for women with and without CIN2+, Morelos State, Mexico

	CC-HPV		SC-HPV		
	No. of Samples	**Median RLU (IQR)**	**No. of Samples**	**Median RLU (IQR)**	**P- Value**
Women with CIN2+	94	131.5 (20.9–485.2)	72	16.5 (4.3–82.9)	<0.001
Women without CIN2+	626	17.9 (3.7–110.0)	823	13.5 (3.2–119.2)	<0.001

(Salmerón, personal communication)

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Table 4

HPV assays with potential for screening

Assay	Target	Methodology	Comment
Hybrid Capture 2	DNA	signal amplification using hybrid capture technology	most widely used assay to date
CareHPV	DNA	as above	designed for low-resource areas
Cervista HPV HR	DNA	signal amplification using invader chemistry	for all HR-HPVs
Cervista HPV 16/18	DNA	as above	for HPV 16 and 18
Roche Amplicor HPV	DNA	PCR-based with micro-well plate detection	for all HR-HPVs
Abbott Real time HR HPVs	DNA	PCR-based with Taqman probe cleavage detection	for all HR-HPVs
Gen Probe Aptima HPV	mRNA	TMA and chemiluminescent probe detection	for all HR-HPVs
PreTect HPV-Proofer	mRNA	NASBA amplification with molecular beacon detection	results type-specific
NucliSENS Easy Q HPV v1 test	mRNA	as above	results type-specific
MALDI-TOF	Type Specific DNA	Multiplex Primary PCR with Mass Spectrometry	Technically complex with high throughput