The Cost-Effectiveness of Visual Triage of Human Papillomavirus-Positive Women in Three Low- and Middle-Income Countries

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Abstract

Background: World Health guidelines support HPV testing alone (followed by treatment with cryotherapy) or in conjunction with visual inspection with acetic acid (VIA) triage testing. Our objective was to determine the cost-effectiveness of VIA triage for HPV-positive women in low-resource settings.

Methods: We calibrated mathematical simulation models of HPV infection and cervical cancer to epidemiologic data from India, Nicaragua, and Uganda. Using cost and test performance data from the START-UP demonstration projects, we assumed screening took place either once or three times in a lifetime between ages 30 and 40 years. Strategies included 1) HPV alone, followed by cryotherapy for all eligible HPV-positive women; and 2) HPV testing with VIA triage for HPV-positive women, followed by cryotherapy for eligible women who were also VIA-positive (HPV-VIA). Model outcomes included lifetime risk of cancer and incremental cost-effectiveness ratios (ICER; I$/year of life saved).

Results: In all three countries, HPV alone was more effective than HPV-VIA. In Nicaragua and Uganda, HPV alone was also less costly than HPV-VIA; ICERs associated with screening three times in a lifetime (HPV alone) were below per capita GDP. In India, both HPV alone and HPV-VIA had ICERs below per capita GDP.

Conclusions: VIA triage of HPV-positive women is not likely to be cost-effective in settings with high cervical cancer burden. HPV alone followed by treatment may achieve greater health benefits and value for public health dollars.

Impact: This study provides early evidence on the cost-effectiveness of HPV testing followed by VIA triage versus an HPV screen-and-treat strategy.

Introduction

Cervical cancer is a leading cause of cancer death among women worldwide (1), despite the potential for prevention through organized screening programs that detect and treat precancerous lesions. While routine screening with Pap smear testing has reduced the burden of cervical cancer in the United States and other high-income countries (2), the implementation of Pap-based screening programs has not been feasible in low-resource settings due to a lack of healthcare delivery infrastructure and limited health budgets. Consequently, nearly 90% of cervical cancer deaths worldwide occur in the developing world (1).

The knowledge that cervical cancer is caused by persistent cervical infection with one or more oncogenic human papillomavirus (HPV) types (3) has led to advances in screening technology, including HPV DNA tests (4). HPV testing is more sensitive and reliable for detection of precancer and cancer than Pap testing (5-10). This increased sensitivity for detection of cervical intraepithelial neoplasia grade 3 and higher (≥CIN3) translates into two important benefits: 1) earlier detection of CIN3 lesions that, if treated, results in reduced cervical cancer incidence and mortality (11, 12); and 2) sustained lower risk of cancer following a negative HPV test result, permitting safe extension of screening intervals (12-15). Thus, when HPV testing is used as the primary screening test, women only need one to several screens in their lifetimes to significantly reduce the burden of cervical cancer (16). Where resources are available, the World Health Organization (WHO) thus recommends screening with HPV testing in a "screen-and-treat" strategy for women aged 30 to 49 years, and treating eligible HPV-positive women with timely cryotherapy (17).

One drawback of HPV testing is that only a small proportion of women who test positive for oncogenic HPV have, or would develop, precancer or invasive cervical cancer in the future, as the vast majority of infections clear spontaneously within one year (18). The high prevalence of oncogenic HPV infections coupled with the relatively low prevalence of precancer leads to a high "false positive rate"

with current HPV DNA testing. Consequently, potentially high rates of overtreatment and its associated economic costs may burden healthcare systems in low-resource settings. For countries with sufficient resources to implement a sequence of tests, the WHO recommends that women with positive HPV test results may receive a triage test such as visual inspection with acetic acid (VIA) (17), with treatment provided only to women who also test positive on the triage test. Women who are HPV-positive but VIA-negative are recommended for re-screening in one year. Although there are few studies that have evaluated the diagnostic accuracy or health outcomes associated with HPV testing followed by VIA triage, countries in the early stages of implementing HPV-based screening are employing this strategy (19).

As cervical cancer screening programs are implemented and scaled in low-resource settings, decision-makers need information on the long-term health and economic consequences of screening algorithms to develop evidence-based guidelines. Our objective was to determine the cost-effectiveness of VIA triage for HPV-positive women in resource-limited settings with different epidemiologic profiles.

Materials and Methods

Analytic overview

We used an existing individual-based Monte Carlo simulation model of the natural history of HPV and cervical cancer to estimate the lifetime health and economic outcomes associated with screening with either *care*HPV testing alone or *care*HPV testing followed by VIA triage of HPV-positive women. The model was calibrated to epidemiologic data from India, Nicaragua, and Uganda (20).[1] Test performance for *care*HPV and cost data were drawn from the START-UP multi-site demonstration project conducted in India (Hyderabad), Nicaragua (Masaya Province), and Uganda (Kampala); a fourth site in India was not included in this evaluation (7, 21). Model-projected outcomes included health

[1] The model parameterization process for each setting, including calibration and costing data, is available at: http://www.sciencedirect.com/science/article/pii/S240585211500004X.

benefits— in terms of reductions in lifetime risk of cervical cancer incidence and gains in life expectancy— and lifetime costs (in 2011 international dollars [I$]). Cost-effectiveness ratios were expressed using incremental cost-effectiveness ratios (ICERs), defined as the additional cost of a particular strategy divided by its additional health benefit, compared with the next most costly strategy. Dominated strategies (defined as more costly and less effective, or having higher ICERs than more effective options) were eliminated. While there is no universal criterion that defines a threshold cost-effectiveness ratio, we considered per capita gross domestic product (GDP) as a benchmark; an intervention with an ICER less than the country's per capita GDP would be "very cost-effective" and less than three times per capita GDP would be "cost-effective" (22). Consistent with guidelines for cost-effectiveness analysis (23-25), we adopted a societal perspective, including costs irrespective of the payer, and discounted future costs and life-years at a rate of 3% per year to account for time preferences.

Mathematical simulation model

The natural history model of cervical carcinogenesis comprises mutually exclusive health states, including type-specific HPV infection status, grade of precancer (i.e., CIN grade 2 [CIN2] or CIN3), and stage of invasive cancer (20, 26). Individual girls enter the model at age 9 years with a healthy cervix and transition between health states on a monthly basis until death. Transition probabilities may vary by age, HPV type, duration of infection or precancerous lesion status, and prior HPV infection. Cancer detection can occur through symptoms or via screening. Death from all-cause mortality can occur from any health state, and excess stage-dependent mortality can occur from cervical cancer after its onset. The model tracks disease progression and regression, clinical events, and economic outcomes over the lifetime for each individual woman, which are then aggregated for analysis.

The model parameterization process, including calibration and model fit to epidemiologic data, has been previously described (20, 26-28). Briefly, we established baseline parameter values for the natural history component of the model using longitudinal data from a variety of settings, including age- and type-specific HPV incidence data and time-dependent rates of HPV clearance and progression by genotype (18, 29-32). To reflect heterogeneity in age- and type-specific HPV incidence between settings, as well as natural immunity following initial infection and uncertainty in progression and regression of precancer, we set plausible ranges around these input parameter values. Repeated model simulations in the absence of any intervention selected a single random value from the plausible range for each uncertain parameter, creating a unique natural history input parameter set. We then computed a goodness-of-fit score by summing the log-likelihood of model-projected outcomes for each unique parameter set to represent the quality of fit to country-specific epidemiologic data on age-specific HPV prevalence and cancer incidence (i.e., calibration targets). For each country, we selected the top 50 input parameter sets that produced good fit to the epidemiologic data to use in analyses as a form of probabilistic sensitivity analysis (26, 28, 33). We report results as the mean of outcomes across these top 50 parameter sets.

Strategies

We assumed screening took place once in a woman's lifetime at age 35 years or three times in a lifetime at ages 30, 35, and 40 years, with 80% coverage of the target population. We compared the following strategies, which are outlined in **Figures 1 and 2**: 1) screening with 2-visit HPV testing (hereafter referred to as "HPV alone"), in which a provider administered the *care*HPV test at an initial clinic visit; women who complied with recommended follow-up returned for a second visit to receive results and, if HPV-positive and eligible, immediate cryotherapy (**Figure 1**); and 2) screening with 2-visit HPV testing at the clinic with VIA triage for HPV-positive women at the subsequent results visit (referred

to as "HPV-VIA"), followed by same-day cryotherapy for eligible women who were both HPV-positive and VIA-positive (**Figure 2**). In the HPV-VIA strategy, women who were HPV-positive but VIA-negative in a given screening episode were assumed to be referred to repeat screening with *care*HPV in one year; we assumed 80% of women complied with follow-up screening, with HPV-positive women sent to cryotherapy (if eligible) or to further diagnostic testing (if ineligible for immediate cryotherapy) and HPV-negative women returning to routine screening intervals. For both the HPV alone and HPV-VIA strategies, we assumed that all eligible women complied with the referral to same-day cryotherapy, and that women who were ineligible for cryotherapy were referred to colposcopy and, if necessary, further treatment for women with a histological diagnosis of CIN1+, with compliance rates of 85% for each clinical contact after screening (i.e., visits for receiving screening results, colposcopy, and treatment following colposcopy). The test performance of *care*HPV was based on the START-UP demonstration projects (7), but the performance of VIA in known HPV-positive women was not evaluated in START-UP. Therefore, sensitivity and specificity of VIA as a triage test for HPV-positive women (**Table 1**) were informed from the published literature. To bias the analysis in favor of the strategy of interest, we optimistically assumed that VIA sensitivity to detect cervical intraepithelial neoplasia grade 2 or more severe diagnoses (CIN2+) was 0.70 in women known to be HPV-positive. Based on the available literature, we assumed that VIA specificity was 0.85. Model input parameters are summarized in **Table 2**.

Cost data

Cost data have been published elsewhere (20, 21) but are summarized in **Table 2**. Direct medical costs of screening, diagnosis, and treatment of precancerous lesions were drawn from the START-UP study sites, and included staff time, clinical supplies, drugs, clinical equipment, laboratory staff time, laboratory supplies, and laboratory equipment. We converted local currency units to 2011 I$, a

hypothetical currency that provides a means of translating and comparing costs among countries, taking into account differences in purchasing power. We assumed the *care*HPV test kit was a tradable good valued at US$5 per test.

Transportation costs and the cost of women's time spent traveling to, waiting for, and receiving care were dependent upon the facility level and were derived from START-UP data and the published literature, as previously described (7, 21, 27, 34, 35). With the HPV-VIA strategy, women who tested HPV-positive incurred the direct medical costs associated with the VIA test, but we assumed that women's time spent waiting for and receiving VIA (following receipt of HPV results) was minimal. Thus, women did not incur additional time costs associated with triage testing, but women who screened positive on VIA in the HPV-VIA strategy or positive on the HPV alone strategy did incur additional waiting and procedure time for cryotherapy. Costs associated with cancer care by stage included direct medical costs, women's time costs, and transportation costs.

Scenario analysis

To explore the impact of uncertainty in cost, test performance, and treatment parameters, we evaluated the following scenarios: 1) alternative sensitivity/specificity pairs of VIA performance in HPV-positive women; 2) a lower compliance rate per visit; 3) HPV self-collection (as opposed to provider-collection) at the clinic; 4) decreased direct medical costs of cryotherapy; 6) elimination of the direct medical cost of VIA triage test in HPV-positive women; 7) elimination of repeat HPV testing in 1 year for HPV-positive VIA-negative women; 8) simultaneously decreased eligibility for same-day cryotherapy and increased direct medical and women's time costs for treatment of ineligible women (i.e., cryotherapy following histological confirmation in India; LEEP procedures in Nicaragua and Uganda) (36). To derive alternative sensitivity/specificity pairs for VIA performance in HPV-positive women, we considered the inherent tradeoff between sensitivity and specificity by computing Youden's J index values (sensitivity +

specificity – 1). Assuming the highest Youden's J index value suggested by the literature on VIA triage was a ceiling (37), we derived sensitivity/specificity pairs with Youden's J index values between this maximum index and indices found in the remaining studies identified by our literature review. The following pairs were selected because they also explore less optimistic sensitivity values than the base case, while also varying specificity across the reasonable ranges suggested by the literature: 0.70/0.75; 0.60/0.85; 0.50/0.90.

Results

Reduction in cancer risk

Reduction in cervical cancer risk is presented, for each country, in **Table 3**. In all three countries, HPV alone reduced the lifetime risk of cervical cancer more than HPV-VIA, as more women with CIN2+ and HPV infections destined to progress to CIN2+ received treatment; this finding held true whether screening occurred once or three times in a woman's lifetime. HPV alone once in a lifetime at age 35 years reduced cancer risk by 27.0% (India), 29.8% (Nicaragua), and 30.5% (Uganda), whereas HPV-VIA at age 35 years reduced cancer risk by 24.2% (India), 27.2% (Nicaragua), and 28.5% (Uganda). Screening three times in a lifetime at ages 30, 35, and 40 years was associated with substantially greater reductions in cancer risk in each country, with HPV alone yielding reductions of 48.4% in India (compared to a 44.2% reduction with HPV-VIA), 51.3% in Nicaragua (compared to a 48.6% reduction with HPV-VIA), and 52.3% in Uganda (compared to a 50.0% reduction with HPV-VIA).

Reduction in cryotherapy procedures

In all three countries, the number of immediate cryotherapy procedures associated with HPV-VIA (relative to HPV alone), was reduced. For once in a lifetime screening with HPV-VIA, the reduction in immediate cryotherapy procedures was 50.7% in India, 38.3% in Nicaragua, and 37.7% in Uganda.

Reductions in cryotherapy procedures were very similar when screening was assumed to take place with HPV-VIA three times in a lifetime.

Cost-effectiveness analysis

Cost-effectiveness results for each country are displayed in **Table 3**. In India, where the burden of HPV and cervical cancer is lower than in the other settings considered, the average lifetime cost per woman was lower with HPV-VIA than with HPV alone, whether screening once or three times in a lifetime. Screening once in a lifetime with HPV-VIA had the lowest ICER (I$240 per year of life saved [YLS]). Screening once in a lifetime with HPV alone was more costly but also a more effective strategy (I$460 per YLS), as more women with HPV infections or precancer received treatment. Screening three times in a lifetime with HPV-VIA cost I$770 per YLS, while screening three times in a lifetime with HPV alone was the most effective strategy considered and cost I$840 per YLS. Thus, screening three times in a lifetime with either HPV alone or HPV-VIA would be considered "very cost-effective" in India, with ICERs considerably less than India's per capita GDP of I$5,490; while the ICER for HPV-VIA was slightly lower (i.e., more attractive) than for HPV alone, HPV alone reduced cancer risk by an additional 4.2%.

Unlike India, where HPV-VIA was less costly than HPV alone, the HPV-VIA strategy was both more costly and less effective than (i.e., dominated by) HPV alone in Nicaragua. Because cancer incidence and the cost of cancer treatment are high in Nicaragua, HPV-VIA was associated with higher costs than HPV alone due to the cost of missing HPV infections and precancers that will eventually progress to cancer. We found that screening with HPV testing alone once in a lifetime was cost-saving, while HPV testing alone three times in a lifetime cost I$200 per YLS, well below Nicaragua's per capita GDP of I$4,690.

In Uganda, as in Nicaragua, HPV-VIA was more costly and less effective than (i.e., dominated by) HPV testing alone, whether screening occurred once or three times in a lifetime. Screening once in a

lifetime with HPV alone cost I$130 per YLS, while screening three times in a lifetime with HPV alone cost I$410 per YLS. Both strategies with HPV alone would be considered "very cost-effective" in Uganda, with ICERs well below the per capita GDP of I$1,690.

Scenario analysis

Cost-effectiveness results for scenario analyses in India are presented in **Table 4**; results from scenario analyses in Nicaragua and Uganda— where HPV alone consistently dominated HPV-VIA as baseline assumptions were varied— are presented in **Supplementary Tables S1** and **S2.**

In India (**Table 4**), ICERs were fairly stable as VIA test sensitivity and specificity were varied relative to baseline assumptions. When VIA specificity was reduced to 0.75 (base case: 0.85) while sensitivity was held constant, ICERs remained stable as both the lifetime costs and life expectancy associated with HPV-VIA increased slightly (due to more women receiving immediate treatment with cryotherapy). When VIA sensitivity was reduced to 0.60 (base case: 0.70) and specificity held constant, screening three times in a lifetime with HPV-VIA was no longer an efficient strategy; the ICERs associated with HPV alone declined from I$460 per YLS to I$400 per YLS for once in a lifetime screening, and from I$840 per YLS to I$780 per YLS for screening three times in a lifetime. When VIA sensitivity was further reduced to 0.50 (base case: 0.70) and specificity increased to 0.90 (base case: 0.85), the ICER associated with HPV alone once in a lifetime fell to I$340 per YLS.

HPV-VIA was not an attractive strategy when we reduced visit compliance to 60% per visit (base case: 0.85%), as fewer women received follow-up HPV results in one year.

When we assumed that HPV test sensitivity was reduced due to self-collection (base case: provider-collection) at the clinic, HPV-VIA remained less costly and also less effective than HPV alone in India, but had a slightly higher ICER than HPV alone, and was thus not an efficient strategy.

As we reduced the direct medical cost of cryotherapy by 50% in India, the ICER associated with HPV-VIA once in a lifetime and HPV alone once or three times in a lifetime remained stable, but HPV-VIA three times in a lifetime was inefficient (i.e., was less effective and had a higher ICER) relative to HPV alone three times in a lifetime (**Table 4**). When we eliminated the direct medical cost of the VIA triage test, the ICERs associated with HPV alone once or three times in a lifetime increased slightly (for screening once: from I$460 per YLS to I$520 per YLS; for screening three times: from I$840 per YLS to I$930 per YLS) as the incremental costs relative to HPV-VIA increased. However, the ICERs for all strategies considered remained well below India's per capita GDP.

When we assumed there would be no repeat HPV testing in one year, the health benefits associated with HPV-VIA in India fell dramatically as women with persistent HPV infections did not receive necessary treatment, and HPV alone was more effective and more efficient (i.e., had a lower ICER) than HPV-VIA.

When we simultaneously reduced eligibility for same-day cryotherapy and increased the cost of treatment for ineligible women by 150%, the costs increased and health benefits decreased slightly for all strategies. HPV alone once in a lifetime was no longer an efficient strategy, and the ICERs for HPV-VIA once or three times in a lifetime rose to $270 per YLS and $760 per YLS; HPV alone three times in a lifetime remained the most effective strategy and cost $1,260 per YLS.

Discussion

This study represents one of the first cost-effectiveness analyses of HPV testing followed by visual triage in low-resource settings. We found that using VIA as a triage test to determine which HPV-positive women receive immediate treatment with cryotherapy is less effective at reducing cervical cancer than sending all HPV-positive women to treatment in India, Nicaragua, and Uganda. We found that HPV with VIA triage was consistently more costly and less effective than (i.e., dominated by) HPV

alone in Nicaragua and Uganda, due to the costs of repeating HPV screen-and-treat in one year and the costs of missing some precancers that are destined to progress. In India, where the burden of HPV and cervical cancer is lower and the specificity of HPV testing in the START-UP study was high, HPV-VIA was an efficient strategy under baseline assumptions. Even in India, however, screening with HPV alone was a more effective strategy, and very cost-effective with an ICER well below India's per capita GDP. In both Nicaragua and Uganda, findings from scenario analyses indicated that HPV alone robustly dominated HPV-VIA whether we assumed altered VIA test performance, reduced visit compliance, HPV self-collection at the clinic, reduced direct medical costs of cryotherapy, elimination of the additional cost of the VIA triage test, or elimination of repeat HPV testing at one year for HPV-positive/VIA-negative women. Similar scenario analyses in India found that while both the HPV-VIA and HPV alone strategies would be very cost-effective if specificity of VIA was reduced or the direct medical cost of VIA was eliminated, HPV alone consistently remained the more effective strategy. When VIA test sensitivity was reduced or when the direct medical cost of cryotherapy was reduced by 50%, HPV-VIA three times in a lifetime was no longer an efficient strategy. Under circumstances when visit compliance was reduced, HPV specimens were self-collected, or when there was no repeat HPV testing in one year for HPV-positive/VIA-negative women, HPV-VIA was not an efficient strategy in India.

There were several limitations to this analysis. Data on the performance of VIA in HPV-positive women were limited, but indicate its high variability based on setting. As the START-UP demonstration projects did not evaluate VIA as a triage test for HPV-positive women, we based VIA performance characteristics on available literature. Our review of the literature found that VIA sensitivity to detect CIN2+ in HPV-positive women was as low as 25% in Cameroon (38, 39). The highest VIA sensitivity in HPV-positive women was 82% in a study from India (40), but this was considerably higher than the next highest sensitivity rate of 67% in Madagascar (37). We set VIA sensitivity in HPV-positive women at 70% in order to observe outcomes under a scenario of high performance. Even under these optimal

conditions, HPV with VIA triage was less effective than HPV testing alone in all three countries, and was only a potentially efficient strategy in India.

While the START-UP demonstration projects did not evaluate VIA as a triage strategy, we analyzed the site-specific data to determine the proportion of *care*HPV-positive women with CIN2+ that were also positive on VIA (i.e., the proportion that might theoretically be referred to cryotherapy with VIA triage of HPV-positive women). We found that, at the START-UP sites, 56% (57%), 63% (64%), and 71% (76%) of women with CIN2+ who were HPV-positive with provider(self)-collection in Hyderabad, Nicaragua, and Uganda, respectively, also screened positive on VIA. These data support our assertion that VIA sensitivity to detect CIN2+ in HPV-positive women is indeed optimistic at 70%.

We did not consider the quality of life implications of rare adverse events associated with treatment, and we assumed only a small proportion of women (who were ineligible for cryotherapy and had histologically confirmed CIN2+ in Nicaragua; 20% of confirmed CIN2+ in Uganda) received LEEP. While cryotherapy is generally a safe procedure, LEEP may be accompanied by such complications as infection, bleeding, cervical stenosis, and risk of infertility or preterm birth (41, 42); the risk of these outcomes may be higher in low-resource settings, where LEEP is performed infrequently. Where the burden of HPV is high, even a slight risk of serious adverse events among the relatively small proportion of women referred to LEEP for CIN2+ may lead to a substantial number of cases at the population level, particularly if eligibility for cryotherapy is low. In our scenario analysis of reduced eligibility for same-day cryotherapy and increased costs of either LEEP (in Nicaragua and Uganda) or cryotherapy following histologic confirmation (in India, where LEEP was assumed to be unavailable), HPV alone three times in a lifetime remained the most effective strategy with an ICER below per capita GDP in all settings. However, we note that further data on the frequency, safety, and quality of life implications of LEEP are needed to determine whether the benefits outweigh the risks of potential over-treatment in low-resource settings.

Our costing estimates were drawn from the START-UP demonstration projects, and thus represent real-world data, albeit in a study setting. We did not include programmatic costs, but note that to achieve high test performance standards as a triage test, VIA will require substantial quality assurance and control measures that will be costly (in terms of human resources) to implement on a large scale. Due to limited data, we also did not account for changes in costs based on volume at the clinic that would accompany changes in the number of women referred to treatment.

As screening programs are implemented and scaled in low-resource settings, countries will need to design screening algorithms based on many factors in addition to the cost-effectiveness profile of a screening strategy, including acceptability, feasibility, existing infrastructure, anticipated gains relative to competing healthcare priorities, and affordability. The chronic shortage of healthcare workers in low-resource settings is a potential barrier to scale-up of HPV-based screening programs that recommend treatment for all HPV-positive women. Furthermore, gas-based cryotherapy relies on consistent resupply of gas, which is expensive to transport and not always available. We found that HPV followed by VIA triage may reduce the number of cryotherapy procedures by approximately 38% to 50%, but due to the low sensitivity of VIA and imperfect follow-up of HPV-positive/VIA-negative women, there is a corresponding decline in health benefits as fewer women with persistent HPV infection and precancer receive treatment. In Nicaragua and Uganda, the cost savings associated with fewer cryotherapy procedures were outweighed by increased costs of cancer treatment. Our findings in all three countries also indicate that, when HPV-positive/VIA-negative women did not attend recommended follow-up at one year, the health benefits associated with screening were markedly reduced. In low-resource settings where clinic visits may require substantial time and travel over long distances, compliance with follow-up screening in one year's time may be low, but the consequences of not receiving recommended follow-up may be serious for these women at high risk of precancer. Of note, both HPV alone and HPV-

VIA may have less than the reported impact on cancer risk if cryotherapy is considerably less effective than we assume here.

While HPV testing alone may be a more effective and efficient strategy in many settings, the costs and feasibility of facilitating widespread access to cryotherapy in primary health centers may reduce the real-world effectiveness of this strategy. New treatment technologies may lessen the burden of treating all HPV-positive women, if feasibility and cost-effectiveness can be demonstrated. New ablative technologies currently undergoing testing are smaller, portable, and do not require gas. Thermal-coagulation has been used as part of a "screen-and-treat" program in Malawi (43), and for treatment of HIV-infected women in India (44), with interim cure rates comparable to cryotherapy (41).

The World Health Organization recommends HPV testing for countries with sufficient resources (17). HPV testing with VIA triage has received consideration as a screening algorithm in order to reduce the costs and logistical demands of cryotherapy in low-resource settings. We found that HPV testing followed by VIA triage is not necessarily less costly than HPV testing alone in settings with a high burden of HPV and cervical cancer, despite reductions in the number of immediate cryotherapy procedures. Additionally, HPV testing followed by VIA triage is less effective than HPV testing alone, as fewer women with precancer or HPV infections that would progress to precancer receive treatment, even with an optimistically sensitive VIA triage test. This analysis highlights the need for more accessible treatment options for women in low-resource settings with a high burden of HPV; only when treatment is widely available to HPV-positive women will an HPV screen-and-treat strategy be feasible. Our findings also demonstrate that, if program planners opt to use a triage strategy to reduce the number of women referred to treatment, there is a need for improved genotype restriction, biomarkers, and triage tests with better ability to predict cervical cancer risk that are also adaptable to low-resource settings. Based on current data on the performance of VIA as a triage test for HPV-positive women, this screening and triage algorithm is not likely to be cost-effective in settings with a high burden of cervical cancer.

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Table 1. Literature review on the performance of HPV DNA testing with VIA triage.[a]

Study (Setting)	Performance for CIN2+ Detection: Sensitivity (95% CI); Specificity (95% CI)
Performance of Sequential HPV, VIA Testing System	
Joshi et al. (India)(44)[b]	0.80 (0.67, 0.90)
	0.96 (0.95, 0.97)
Kamal et al. (Egypt)(45)	0.59 (CIN2); 0.75 (CIN3)
	0.98 (CIN2); 0.99 (CIN3)
Tebeu et al. (Cameroon)(39)	0.33 (0.15, 0.58)
	0.97 (0.95, 0.98)
Performance of VIA in HPV-Positive Women	
Bigoni et al. (Cameroon)(38)	0.25 (0.07, 0.59)
	0.74 (0.64, 0.82)
Catarino et al. (Madagascar)(37)[c]	0.67 (0.30, 0.90)
	0.86 (0.77, 0.92)
Muwonge et al. (India)(40)[d]	0.82 (0.77, 0.86)
Tebeu et al. (Cameroon)(39)	0.36 (0.15, 0.64)
	0.87 (0.79, 0.93)
Qiao et al. (China)(46)	0.46 (0.37, 0.56)
	0.87 (0.85, 0.90)
Model Inputs for Performance of VIA in HPV-Positive Women[e]	
	Sensitivity/specificity: 0.70/0.85
	Scenario analysis: 0.70/0.75; 0.60/0.85; 0.50/0.90

[a] CI: confidence interval; CIN2+: cervical intraepithelial neoplasia grade 2 or higher; HIV: human immunodeficiency virus; HPV: human papillomavirus; VIA: visual inspection with acetic acid; VILI: visual inspection with Lugol's iodine. The table presents data stratified on whether the reported test performance describes the testing system (i.e., HPV testing followed by VIA) or the performance of VIA in HPV-positive women.

[b] Study participants were HIV-infected women.

[c] Reported test performance includes both VIA and VILI.

[d] Data were analyzed retrospectively, so test performance is theoretical. Specificity estimates were not available.

[e] The model inputs reflect the performance of VIA in *care*HPV-positive women, with HPV-positivity determined by site-specific START-UP *care*HPV test performance (provider- or self-collection) (see **Table 2**). Because the base case test performance parameters assumed optimistically high VIA sensitivity, we explored alternative combinations of sensitivity and specificity in scenario analyses. To reflect the inherent tradeoff between sensitivity and specificity, we assumed the study with the highest value of Youden's J index (sensitivity + specificity – 1) (Catarino et al. (37)) represented a maximum Youden's J index for VIA performance in HPV-positive women. We then explored several sensitivity and specificity pairs with Youden's J index values between the maximum index and the indices found in the remaining studies.

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Table 2. Baseline values for model parameters.[a]

Variable [Reference]	India	Nicaragua	Uganda
Population coverage of screening program	80%	80%	80%
Compliance rate per visit[b]	85%	85%	85%
Proportion of eligible women receiving immediate cryosurgery following positive *care*HPV result[b]	100%	100%	100%
*care*HPV (provider-collection) sensitivity/specificity for CIN2+[c] (7)	0.89 / 0.95	0.79 / 0.89	0.89 / 0.80
*care*HPV (self-collection) sensitivity/specificity for CIN2+[c] (7)	0.75 / 0.95	0.67 / 0.87	0.76 / 0.80
VIA sensitivity/specificity for CIN2+ in HPV-positive women (37, 40)	0.70/0.85	0.70/0.85	0.70/0.85
Test sensitivity/specificity for CIN1+, colposcopy[d]	0.50 / 0.96	0.95 / 0.68	0.95 / 0.51
Eligibility for cryotherapy (27)[e]			
No lesion or CIN1	100%	100%	100%
CIN2	85%	85%	85%
CIN3	75%	75%	75%
Cancer	10%	10%	10%
Effectiveness of cryotherapy (27, 41, 47, 48)	92%	92%	92%
Effectiveness of cryotherapy/LEEP following colposcopy (27, 48)[e]	96%	96%	96%
Direct medical costs by procedure (7, 21)[f]			
*care*HPV (provider-collection)[g]	9.24	15.61	8.78
*care*HPV (self-collection at the clinic)[g]	8.90	13.48	8.48
VIA	3.55	9.61	2.90
Colposcopy[h]	9.86	15.25	7.08
Colposcopy and biopsy[h]	30.06	39.48	32.90
Cryotherapy[i]	38.13	33.04	13.49
LEEP[i]	NA	133.64	139.54
Cytology (follow-up post-treatment)[j]	15.15	13.71	12.25
Direct non-medical costs[f]			
Transportation (round-trip, clinic)(27, 34, 35)	0.08	0.69	4.46
Transportation (round-trip, secondary facility)(27, 34, 35)	15.29	2.75	10.87
Women's time (per hour)(49)	1.14	1.41	0.68
Treatment of local cancer (FIGO stages 1a-2a)(27, 34, 35)[f,k]	1,821	3,322	888
Treatment of regional/distant cancer (FIGO stages ≥2b)(27, 34, 35)[f,k]	2,652	4,268	1,176

[a] CIN: cervical intraepithelial neoplasia; FIGO: International Federation of Gynecology and Obstetrics; LEEP: loop electrosurgical excision procedure; VIA: visual inspection with acetic acid.

[b] Women who received a positive *care*HPV result and were deemed eligible were assumed to receive immediate cryotherapy. Compliance rate is defined as the proportion of women who do return for each subsequent clinical encounter, relative to the previous visit. Compliance applies to the results/cryotherapy visit for all women screened, as well as the diagnostic confirmation and treatment visits among women who are ineligible for immediate cryosurgery.

[c] Because the test performance characteristics of *care*HPV are dependent upon the prevalence of high-risk HPV in the model, test sensitivity to detect CIN2+ and specificity have been calibrated to test performance in the START-UP demonstration projects. Values in the table are the average test sensitivity/specificity values across 50 input parameter sets for *care*HPV testing once in a lifetime at age 35 years. Reported test sensitivity/specificity for provider-collection in the START-UP studies were as follows: 0.90/0.95 (India); 0.78/0.89 (Nicaragua); and 0.89/0.82 in Uganda. Reported test sensitivity/specificity for self-collection (used in scenario analysis) were as follows: 0.76/0.95 (India); 0.67/0.86 (Nicaragua); and 0.77/0.82 (Uganda).

[d] Test performance characteristics of colposcopy in START-UP were derived from the worst diagnosis of the local pathologist relative to the worst diagnosis by a quality control pathologist (gold standard); we applied the treatment threshold of CIN1+, although this was not the treatment threshold in START-UP. To derive test performance of colposcopy, we excluded histological classifications that were inadequate or with a histological classification other than negative, CIN1, CIN2, CIN3, or cancer. Because CIN1 is not a true underlying health state in the model, performance of colposcopy in the model is based on the underlying health states of no lesion, HPV infection, CIN2, or CIN3. For a treatment threshold of CIN1, we weighted sensitivity of colposcopy for women with HPV based on the country-specific prevalence of CIN1 among women with HPV infections in the START-UP studies.

[e] Women who screened positive but who were deemed ineligible for cryotherapy were assumed to be referred to a secondary facility for colposcopy and subsequent treatment. As described elsewhere (20), treatment protocols were based on information from in-country clinicians familiar with standard of care and availability of and preferences for treatment options. In Hyderabad, we assumed that, upon a histologic diagnosis of CIN1, CIN2, or CIN3, women received cryotherapy at a secondary facility. In Nicaragua, we assumed that a histologic diagnosis of CIN1 was followed by cryotherapy and CIN2/3 was followed by LEEP at a secondary facility. In Uganda, we assumed that, upon a histologic diagnosis of CIN1, women received cryotherapy at a secondary facility; a histologic diagnosis of CIN2/3 was followed by cryotherapy for approximately 80% of women, and LEEP for approximately 20% of women, and treatment occurred at a secondary facility.

[f] All costs are in 2011 international dollars (I$). In the START-UP study, procedures were performed at secondary or tertiary facilities, and costs may over- or under-estimate costs at primary health facilities due to differences in volume of procedures and overhead costs. Further details on costs are published elsewhere (20).

[g] This includes the cost of the careHPV test, which was assumed to be I$5. Self-collection was assumed to occur at the clinic, and the difference in costs is attributable to personnel time.

[h] The proportion of colposcopies that were accompanied by a biopsy was drawn from START-UP data as follows: 93.1% (India); 95.6% (Uganda); and 99.5% (Nicaragua), in the absence of data from actual practice in low-resource settings.

[i] We did not consider complication rates for cryotherapy or LEEP, as treatment complications were very rare in the START-UP demonstration projects.

[j] Protocols for follow-up after treatment varied by country, and are published elsewhere (20).

[k] All cancer costs presented include the value of women's time spent pursuing care and transportation to health facilities.

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Table 3. Incremental cost-effectiveness ratios for 2-visit HPV versus 2-visit HPV-VIA in India, Nicaragua, and Uganda.[a]

Strategy[b]	Reduction in cervical cancer risk, %[c]	Discounted lifetime cost per woman[c]	Discounted life expectancy, mean[c]	ICER (I$/YLS), mean[c]
India (GDP per capita: I$5,450)				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.2	13.09	27.80300	240
HPV 1x	27.0	13.66	27.80425	460
HPV-VIA 3x	44.2	23.48	27.81695	770
HPV 3x	48.4	25.23	27.81903	840
Nicaragua (GDP per capita: I$4,690)				
No screening	--	42.67	28.58210	--
HPV 1x	29.8	40.67	28.64935	CS
HPV-VIA 1x	27.2	42.12	28.64393	Dom
HPV 3x	51.3	51.15	28.70094	200
HPV-VIA 3x	48.6	53.24	28.69458	Dom
Uganda (GDP per capita: I$1,690)				
No screening	--	12.42	25.20221	--
HPV 1x	30.5	20.08	25.26293	130
HPV-VIA 1x	28.5	20.54	25.25940	Dom
HPV 3x	52.3	38.37	25.30774	410
HPV-VIA 3x	50.0	39.04	25.30337	Dom

[a] GDP: gross domestic product; HPV: human papillomavirus; HPV-VIA: human papillomavirus testing followed by triage with visual inspection with acetic acid; I$: 2011 international dollars; ICER: incremental cost-effectiveness ratio; VIA: visual inspection with acetic acid; YLS: year of life saved; 1x: once in a lifetime screening at age 35; 3x: screening three times in a lifetime at ages 30, 35, and 40 years.

[b] Strategies are listed in order of increasing cost.

[c] Cancer incidence reduction for each strategy reflects percentage reduction in lifetime risk of cervical cancer compared with no screening. Cancer incidence reduction, discounted lifetime cost per woman, and discounted life expectancy represent the mean across 50 input parameter sets. Dominated strategies are defined as those that are more costly and less effective or have higher ICERs than more effective options.

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Table 4. Scenario analyses for 2-visit HPV versus 2-visit HPV-VIA in India (GDP per capita: I$5,450).

Strategy[b]	Cancer incidence reduction, %[c]	Discounted lifetime cost per woman[c]	Discounted life expectancy, mean[c]	ICER (I$/YLS), mean[c]
Base case[d]				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.2	13.09	27.80300	240
HPV 1x	27.0	13.66	27.80425	460
HPV-VIA 3x	44.2	23.48	27.81695	770
HPV 3x	48.4	25.23	27.81903	840
VIA test sensitivity/specificity in HPV-positive women: 0.70/0.75 (Youden's J index: 0.45)				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.6	13.16	27.80316	240
HPV 1x	27.0	13.66	27.80425	460
HPV-VIA 3x	44.7	23.71	27.81717	780
HPV 3x	48.4	25.23	27.81903	820
VIA test sensitivity/specificity in HPV-positive women: 0.60/0.85 (Youden's J index: 0.45)				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.0	13.10	27.80286	240
HPV 1x	27.0	13.66	27.80425	400
HPV-VIA 3x	43.9	23.50	27.81669	Dom
HPV 3x	48.4	25.23	27.81903	780
VIA test sensitivity/specificity in HPV-positive women: 0.50/0.90 (Youden's J index: 0.40)				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	23.6	13.08	27.80257	250
HPV 1x	27.0	13.66	27.80425	340
HPV-VIA 3x	43.4	23.39	27.81630	Dom
HPV 3x	48.4	25.23	27.81903	780
Compliance rate per visit: 60%				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	16.1	13.23	27.79646	Dom
HPV 1x	18.4	13.53	27.79769	380
HPV-VIA 3x	34.8	22.87	27.80907	Dom
HPV 3x	38.9	23.82	27.81149	750
HPV self-collection[e]				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	20.0	13.23	27.79987	Dom
HPV 1x	23.9	13.75	27.80185	300
HPV-VIA 3x	40.2	23.28	27.81381	Dom
HPV 3x	45.7	24.98	27.81679	750
Direct medical cost of cryotherapy: Reduced by 50%				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.2	12.90	27.80300	230
HPV 1x	27.0	13.27	27.80425	300
HPV-VIA 3x	44.2	23.00	27.81695	Dom
HPV 3x	48.4	24.25	27.81903	740

Direct medical cost of VIA: I$0				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	24.2	13.01	27.80300	240
HPV 1x	27.0	13.66	27.80425	520
HPV-VIA 3x	44.2	23.29	27.81695	760
HPV 3x	48.4	25.23	27.81903	930
No repeat HPV testing in 1 year for HPV+/VIA- women				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	14.7	13.18	27.79671	Dom
HPV 1x	27.0	13.66	27.80425	250
HPV-VIA 3x	36.8	22.64	27.81208	Dom
HPV 3x	48.4	25.23	27.81903	780
Decreased eligibility for same-day cryotherapy and increased cost of treatment for ineligible women[f]				
No screening	--	8.87	27.78539	--
HPV-VIA 1x	22.3	13.33	27.80164	270
HPV 1x	23.0	13.80	27.80167	Dom
HPV-VIA 3x	41.9	23.88	27.81549	760
HPV 3x	44.0	25.14	27.81649	1260

[a] GDP: gross domestic product; HPV: human papillomavirus; HPV-VIA: human papillomavirus testing followed by triage with visual inspection with acetic acid; I$: 2011 international dollars; ICER: incremental cost-effectiveness ratio; VIA: visual inspection with acetic acid; YLS: year of life saved; 1x: once in a lifetime screening at age 35; 3x: screening three times in a lifetime at ages 30, 35, and 40 years.

[b] Strategies are listed in order of increasing cost.

[c] Cancer incidence reduction for each strategy reflects percentage reduction in lifetime risk of cervical cancer compared with no screening. Cancer incidence reduction, discounted lifetime cost per woman, and discounted life expectancy represent the mean across 50 input parameter sets. Dominated strategies are defined as those that are more costly and less effective or have higher ICERs than more effective options.

[d] Base case assumptions for the parameters on which sensitivity analyses were conducted are listed in Table 1 and are as follows: HPV provider-collection (sensitivity for CIN2+/specificity: 0.89/0.95); VIA sensitivity in HPV-positive women: 0.70; VIA specificity in HPV-positive women: 0.85; Compliance rate per visit: 0.85; Direct medical cost of cryotherapy: I$38.13; Direct medical cost of VIA: I$3.55.

[e] HPV self-collection test performance (sensitivity for CIN2+/specificity: 0.79/0.95). The direct medical cost of HPV self-collection at the clinic was slightly reduced relative to HPV provider-collection due to reduced provider time.

[f] Eligibility for cryotherapy was reduced to 75% of women with no lesion or CIN1, 60% of women with CIN2, 49% of women with CIN3, and 15% of women with cancer (36). The direct medical and women's procedure time cost for treatment following colposcopy and histologic confirmation were increased by 150% of the base case.

Figure legends.

Figure 1. Screening algorithm for the 2-visit HPV (HPV alone) strategy. We assumed screening took place either once in a woman's lifetime at age 35 or three times in a lifetime at ages 30, 35, and 40 years, with screening coverage of the target population at 80%. In the 2-visit HPV strategy, a provider administered the *care*HPV test at an initial clinic visit. Women who complied with recommended follow-up returned for a second visit to receive results and, if HPV-positive and eligible, same-day cryotherapy. We assumed that all eligible women complied with the referral to same-day cryotherapy, and that women who were ineligible for cryotherapy were referred to colposcopy and, if necessary, further treatment for women with a histological diagnosis of CIN1+. Each clinical contact for receiving results, colposcopy or treatment (for women ineligible for cryotherapy) was associated with compliance rates of 85%.

Figure 2. Screening algorithm for the 2-visit HPV-VIA strategy. We assumed screening took place either once in a woman's lifetime at age 35 or three times in a lifetime at ages 30, 35, and 40 years, with screening coverage of the target population at 80%. In the 2-visit HPV-VIA strategy, a provider administered the *care*HPV test at an initial clinic visit. Women who complied with recommended follow-up returned for a second visit to receive results and HPV-positive women received VIA triage, followed by same-day cryotherapy for eligible women who were both HPV-positive and VIA-positive. In the HPV-VIA strategy, women who were HPV-positive but VIA-negative at a given screening episode were assumed to be referred to screening within 1 year with *care*HPV at the clinic, with compliance of 80%; following receipt of results, all HPV-positive women were sent to cryotherapy (if eligible) or to further diagnostic testing (if ineligible for immediate cryotherapy) and HPV-negative women returning to routine screening intervals. We assumed that all eligible women complied with the referral to same-day cryotherapy, and that women who were ineligible for cryotherapy were referred to colposcopy and, if necessary, further treatment for women with a histological diagnosis of CIN1+. Each clinical contact for

receiving results, colposcopy or treatment (for women ineligible for cryotherapy) was associated with compliance rates of 85%.

Figure 1

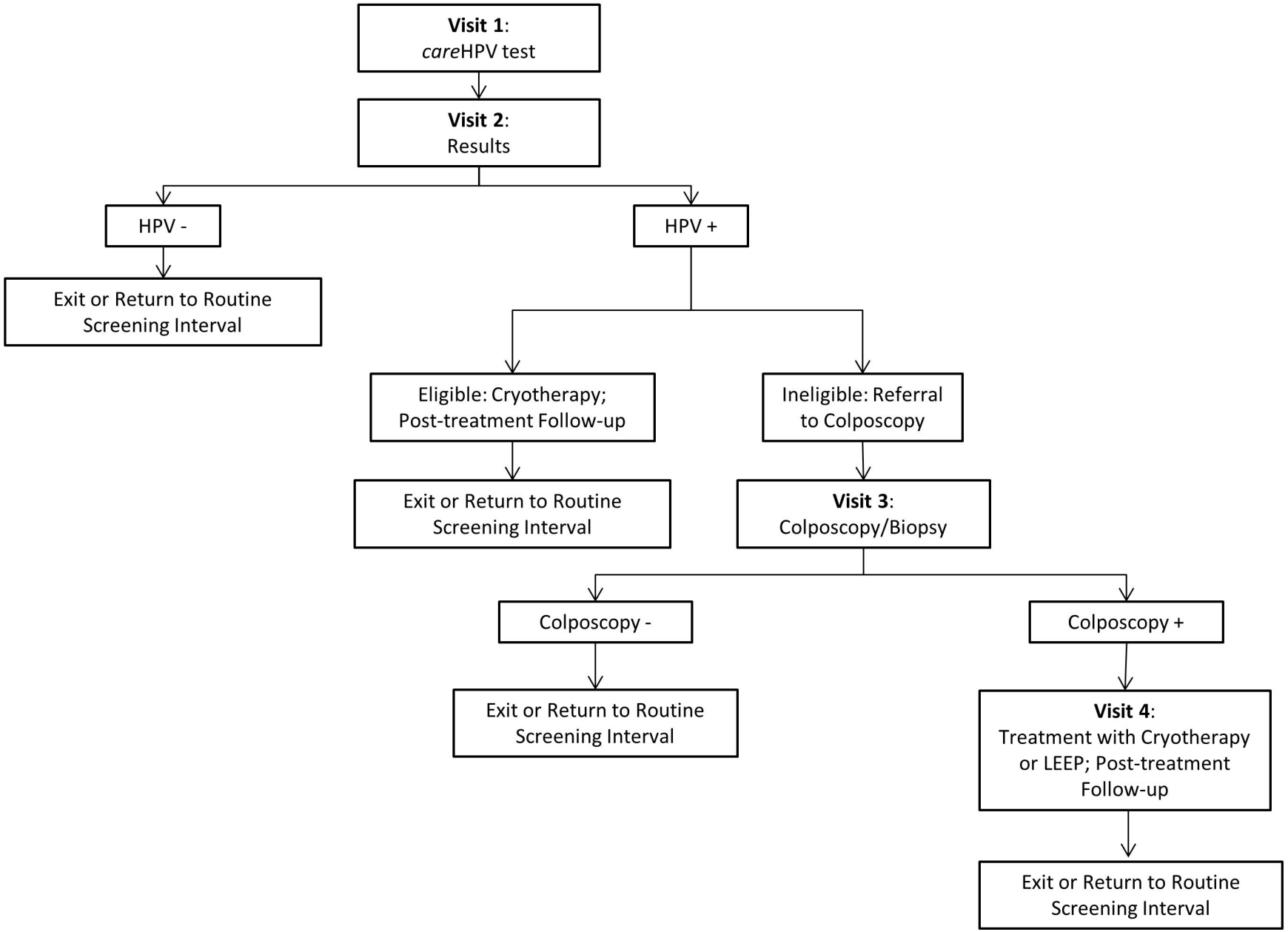
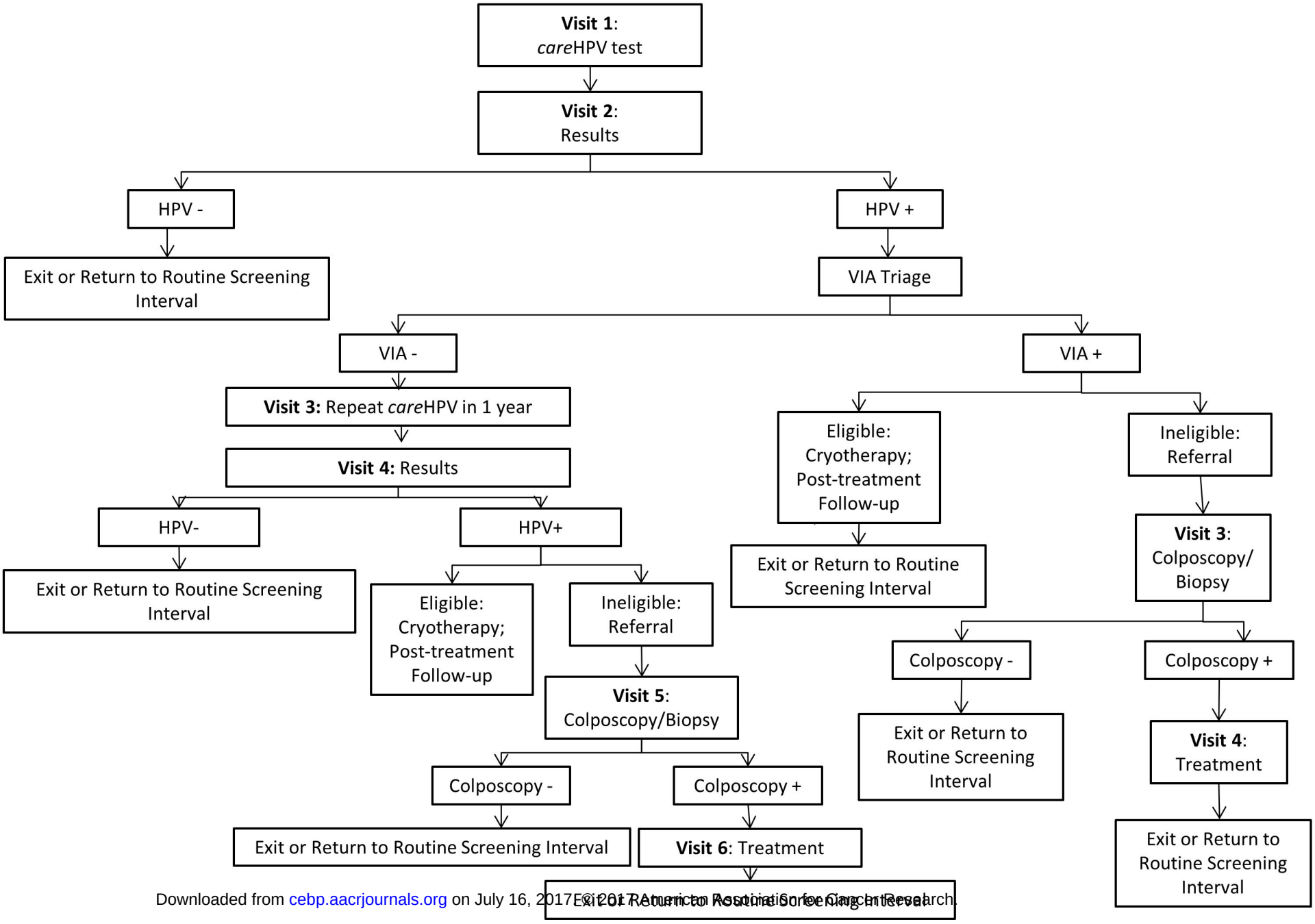


Figure 2



Cancer Epidemiology, Biomarkers & Prevention

AACR American Association for Cancer Research

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