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PROJECT TITLE

Validation of a lab-free low-cost screening test for prevention of cervical cancer: automated visual evaluation

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1. BACKGROUND AND SIGNIFICANCE

Effective prevention measures have lowered cervical cancer rates in high-income countries, but the disease remains a leading cause of death in in low- and middle-income countries (LMICs) where up to 80% of the disease burden and 90% of global deaths occur.[1] The World Health Organization (WHO) launched a call to action in May of 2018 for the global elimination of cervical cancer by 2030 through a combination of vaccination, screening, and treatment.[2] Screening women a single time in their lifetimes at the age of 35 can reduce the risk of developing cervical cancer by up to 36%, while two screening visits per lifetime reduces the risk by a further 40%[3] However, the traditional multi-step screening strategy of cytology (Pap smear), colposcopy and treatment of women diagnosed with high-grade cervical abnormalities is not always feasible in LMICs due to limited resources and patient barriers to access and follow-up.[4,5] Thus, there is an urgent need for a true low-cost point of care test to detect high-grade cervical precancer so women can be treated immediately. **The purpose of this study is to validate Automated Visual Evaluation (AVE), a point-of-care screening and triage diagnostic tool based on the assessment of digital images through artificial intelligence.** AVE has been in development since 2021. The current study will consist of a clinical trial to compare the sensitivity of AVE with traditional screening and triage tests.

1.1 Existing Screening and Triage tests

The most widely used cervical cancer screening and triage tests used around the world are unaided visual inspection with acetic acid (VIA), cytology (the Pap smear or test), and human papillomavirus (HPV) testing. However, each of these methods has significant drawbacks. VIA uses 3% to 5% acetic acid applied to the cervix, which turns cervical abnormalities white ("acetowhite"), so the provider is able to identify them with the naked eye. While simple and low-cost, there is a large variation of sensitivity and quality control is difficult.[6,7] Although VIA programs are widely utilized in LMICs, the method has not made the impact that advocates had hoped for in reducing cervical disease burden. Cytology programs have been highly effective in high resource settings but have not led to a decrease in mortality from cervical cancer in LMICs.[8,9] In some regions, adherence to screening programs is as low as 6%, and loss to follow-up is higher in limited-resource settings.[10,11] HPV testing has higher sensitivity and lower specificity than VIA or cytology.[12,13] However, the high cost and complex processing of currently available HPV assays have been barriers for their widespread use.[14,15] In addition, programs that rely on HPV testing to determine patient management result in high degrees of overtreatment. In El Salvador, where about 12% of screen-eligible women are HPV positive, only about 2% have biopsy-confirmed high-grade cervical precancer (cervical intraepithelial neoplasia or CIN2+).[16,17] The use of accurate triage methods for HPV-positive women could notably decrease the amount of overtreatment.

1.2 Innovations in Screening and Triage

In recent years, there have been significant advances in the development of new cervical cancer prevention technologies. Digital cervicography (DC) is an alternative to VIA that involves obtaining a digital image of the cervix to allow for magnified visualization by the provider. DC adds very little to the cost of cervical visualization and produces a permanent image for documentation, quality control and remote consultation. Images for DC can be taken with a colposcope but also with easily accessible tools such as a smartphone. The Enhanced Visual Assessment (EVA) System (Fig. 1) developed by MobileODT (Tel Aviv, Israel) is a portable colposcope that utilizes a smartphone which can be used to capture cervical images for DC (Fig. 3). The EVA System has been utilized in several large clinical trials, including two led by members of our group (NCT03084081 and NCT 03429582).

Fig. 1. The EVA System: a portable colposcope

1.3 Automated Visual Evaluation (AVE)

We will expand the functionality of the existing EVA System by adding Automated Visual Evaluation (AVE), a software with artificial intelligence (AI) capabilities. AVE consists of an image classifier that has "learned" to differentiate precancerous lesions from normal tissue. In other words, AVE software can evaluate a digital image to determine if a cervix is normal or presents high-grade pre-cancer. There are multiple teams around the world developing and testing different versions of AVE. Preliminary data suggest that AVE technology has a higher detection rate for disease in comparison to other methods, both as a screening test in the general population and as a triage test in an HPV positive population. One study using natural history data from an earlier Costa Rica trial revealed that AVE was able to predict abnormal pathology years before cytology or the HPV tests that were available at that time.[18] Another analysis on global images using human annotations to define positives showed similar results.[19] A recent study in Zambia using HPV screening and AVE triage was able to identify stratified risk groups when combining HPV genotyping and AVE data.[20] Data collection is also ongoing for a much larger study using a version of AVE as an HPV-triage tool in 9 countries, including El Salvador.[21]

The version of AVE that we are validating in this study was developed in a previous phase of the project (NCI R44CA247137) and includes three main components: 1) a **diagnostic classifier** that indicates the possibility of CIN2+ ("CINFinder") and which is the main component of AVE, 2) a **quality assurance module** ("CerVisibility") that evaluates the quality of images, provides a score depending on how clear and free of obstructions the cervix appears, and provides live feedback

on what corrective steps can be taken to capture clear images that are adequate for diagnosis, and 3) a **patient management module** to input and save patient information ("CervManager"). To generate a result, CINFinder uses an ensemble of three best-performing neural networks or AI models (i.e., EfficientNet, DenseNet Multiple Instance Learning and MobileNetv2 Fine-Tuned) selected based on results from the initial phase. To mitigate overfitting, these models are combined using a weighted average of 50%-25%-25% in favor of EfficientNet. The result is a numeric value ranging from 0 to 1, which is interpreted as the probability of CIN2+. The optimal threshold to classify participants as positive or negative is .45, as data from the development phase shows it maximizes sensitivity (84%) while maintaining good specificity (72%). Our AVE software (including CINFinder, CerVisibility, and CervManager modules), will be installed as user-friendly features that can be easily accessed by authorized users on the screen interface of the EVA System device.

If confirmed to be valid for cervical precancer detection, AVE has the potential to dramatically change screening in LMICs because it is low-cost and does not require laboratory facilities. Instead, AVE needs to be installed on a device that can both capture images and which has computational abilities to run AI classifiers, such as certain types of smartphones. The EVA System, which is commercially available in over 50 countries, offers an optimal platform to install and use AVE because it is built around an Android smartphone. While our version of AVE will be able to run on any mobile Android device (e.g., phone, tablet), the colposcope component of the EVA System allows the user to capture high-quality images. However, we are also refining our AVE technology to run on a smartphone with minimal hardware requirements. This would make AVE a uniquely affordable and accessible solution for global cervical cancer screening and triage.

2. STUDY DESCRIPTION

2.1 Study Aims

Aim 1. Validate AVE as a primary screening test compared to VIA for the detection of high-grade cervical pre-cancer (cervical intraepithelial neoplasia grade 2 or higher, or CIN2+).

Aim 2. To compare AVE as a triage test compared to VIA for detecting CIN2+ among HPV-positive women.

2.2 Study Design

Non-randomized prospective study to test the difference in sensitivities between AVE and VIA to detect CIN2+ as a primary screening method.

2.3 Study Population

A total of 10,000 women participating in El Salvador's national HPV screening program will be recruited for the study (see Section 3 below for power calculation estimates). The non-profit organization Basic Health International (BHI), which has a long-standing collaboration with the Ministry of Health (MoH) will be the coordinating organization. Women will be approached at MoH municipal health units in the Metropolitan region. Clinical procedures, including capture of cervical images using the EVA System, will be performed by trained study staff in coordination with MoH healthcare workers at the clinics. Eligibility criteria will follow those of the national HPV screening program, including:

Inclusion

- Women aged 30-59 years at the time of screening

Exclusion

- Pregnancy at time of colposcopy/biopsy
- Hysterectomy with surgically absent cervix
- HPV testing in the past five years
- Prior diagnosis or treatment of invasive cervical cancer

2.4 Study General Description

Women will be recruited at MoH local clinics ("health units") where HPV screening takes place as part of the national cervical cancer control program. Informed consent procedures and data collection will be performed by BHI nurse research assistants with extensive experience in previous studies. During the screening visit, participants will undergo routine HPV sample collection, VIA, AVE with the EVA System, and cervical image capture with an Android smartphone. Women with a positive screening result on any of the three screening tests (HPV, VIA, or AVE with the EVA System) will be referred to a second study visit to undergo HPV testing with a genotyping test, VIA and AVE with the EVA System for the second time, and colposcopy with biopsy. In addition, 5% of screen-negative women will undergo the same procedures. Women will be referred to treatment within the public health system as necessary according to biopsy results. Results from VIA and AVE with the EVA System during the first and the second visit will be compared to determine AVE performance as a screening and triage test, respectively. Histopathology findings will serve as the reference to establish the true diagnosis of each case.

2.5 Provider Training

All clinical procedures will be conducted by study personnel in coordination with MoH clinic staff. General physicians will conduct screening and image capture during the first visit, while

colposcopists will conduct second visit procedures. Study providers will receive training in the use of the EVA System device, the installed AVE software, and image capture using a mobile telephone prior to study start-up. Training will be provided by BHI staff familiar with the EVA System and AVE, including an experienced colposcopist who has used these technologies in several previous projects.

2.6 Enrollment

Given our previous experience it will be feasible to enroll 10,000 women in 18 months (78 weeks). An estimate of approximately 556 women per month (129 per week) results in a total of 10,008 women in the study period (556 X 18 = 10,008). As per routine practice, MoH community health promoters will engage in community outreach and schedule screening appointments for eligible women at participating health units. Research assistants will visit health units on screening days and invite eligible women to participate in the study. Those who agree will complete informed consent procedures and will be assigned an alphanumeric identification code to preserve confidentiality ("study ID"). They will also complete a brief intake questionnaire before proceeding to the speculum exam and screening.

2.7 Speculum exam and screening (first visit)

After intake procedures are completed, women will proceed to an exam room. A study provider will place a speculum and conduct the procedures explained below. All procedures, including VIA and AVE results, will be recorded on paper forms by a nurse research assistant. In addition, the provider will input clinical information on the CervManager application installed on the EVA System.

- **HPV sampling:** The provider will obtain a cervical sample for HPV testing with careHPV (Qiagen, Gaithersburg, MD). HPV samples will be placed in a tube linked to the participant's study ID.
- **VIA:** Following HPV sampling, the provider will clear the cervix of any mucus or blood and place a 5% acetic acid solution on the cervix. The provider will wait one full minute for any acetowhite lesions to appear and then record the unaided VIA impression (observed with the naked eye) on CervManager. The nurse research assistant will also record the VIA impression on paper forms. VIA will be recorded as "satisfactory" or "unsatisfactory", and if satisfactory, either "positive" (signs of cervical disease) or "negative" (normal cervix). If VIA is unsatisfactory, the reason will be indicated.
- **AVE with the EVA System:** The provider will re-apply acetic acid and wait another full minute before capturing cervical images using the EVA System. During this time, while the device's lens is pointed at the cervix, the CerVisibility module will sharpen the image using auto-focus and will assess the present or absence of 6 common obstructions (i.e., blur, blood, mucus, collapsed vaginal walls, squamocolumnar junction [SCJ] inside the os, incorrect orientation of the cervix). A notification will appear on the screen to notify the provider if corrective actions need to be taken to ensure the image is free of

obstructions (for example, the provider may need to re-position the speculum or clean the cervix). If no obstructions are detected, a notification will also indicate that the image is ready and adequate for analysis by CINFinder, the diagnostic component of AVE. The provider will then capture at least two cervical images that are adequate for analysis. All information (images, obstructions, diagnostic score, etc.) will be automatically stored in each patient's CervManager profile and uploaded to the CervManager cloud server. Images are analyzed by CINFinder when the image-capturing device (in this case the EVA System) is connected to the server. AVE results will display as a score from 0 to 1 and scores at or above a threshold of .45 will be considered positive for CIN2+, as explained in section 1.3. To avoid introducing bias, the software will calculate results in the background but the device will not display them until after the provider's VIA impression has been inputted into the CervManager database. The result will also be recorded on paper forms.

- **Image Capture with Mobile Phone:** Immediately after image capture for AVE, a final set of at least two images will be captured using an Android smartphone. The CervManager app will be installed on the phone so that images can be captured, stored, and merged with all additional patient information. To ensure image quality, the provider will utilize a previously arranged external light source. This will be done to compare performance of AVE installed on a mobile phone vs. on the EVA System colposcope as a secondary analysis, but will not guide patient management in any way.

2.8 Colposcopy and biopsy (second visit)

In El Salvador, women must return after 30 days to receive their HPV test results in-person. Women who test positive are usually contacted during that time by community health promoters to ensure they return for results, counseling, and ablation treatment if eligible. A team of research assistants will coordinate efforts with community health promoters to ensure that women with any positive screening result (HPV test, VIA, or AVE) schedule an appointment at a designated clinic. In addition, 5% of screen-negative women will also be invited to the second visit to undergo the same procedures to estimate the proportion of false negative screening results. At this visit, speculum exams will be conducted by study colposcopists in coordination with MoH staff. Procedures will include:

- **Urine pregnancy test:** Women with a positive pregnancy test will be excluded from the study and referred to routine care in the public health system.
- **HPV Genotyping test:** During the speculum exam, providers will first collect a cervical sample for testing with the ScreenFire HPV genotyping assay (Atila BioSystems, Mountain View, CA). This test identifies four groups of HPV types by oncogenic risk: highest risk (16), high risk (18/45), moderate risk (33/31/52/58/35) and low risk (39/51/59/56/68). Tests will be processed at the BHI laboratory facilities as is currently being done for another clinical trial (NCT05431699).
- **VIA:** Following HPV sampling, the provider will clear any mucus or blood and apply a 5% acetic acid solution on the cervix to conduct VIA in the same way as described in Section

2.7. The VIA impression will again be recorded on the CervManager application and on paper forms.

- **AVE:** AVE image capture will be performed and the result will be recorded following the same steps as described previously (section 2.7). Secondary analysis may be performed utilizing different AVE thresholds and different neural network models but none of these will impact patient management.
- **Assessment of ablation eligibility:** Treatment will not be offered during this visit as it will depend on biopsy findings, but providers will inspect the cervix for contraindications for ablation treatment, including: lesion that cover over 75% of the cervix, lesion that extends into the endocervical canal, a SCJ that is not fully visible, atrophied or disfigured cervix, hard to reach cervix, or suspicion of cancer. If a woman is found to be ineligible for ablation, she will be referred to appropriate care once her results are available.
- **Colposcopy and biopsy:** The EVA System digital colposcope will be used to check for lesions under cervical magnification and the colposcopic impression will be recorded. If cervical lesions are noted, the physician will take directed biopsies of each lesion (between two and four biopsies) as well as perform an endocervical curettage (ECC). If no cervical lesions are observed, the physician will take two random biopsies from the 10 and 2 o'clock areas in the squamocolumnar junction and also perform an ECC.[22] This two-biopsy protocol results in a better sensitivity for CIN2+ detection than taking a single random cervical biopsy.[23] Some women will have inadequate colposcopy and biopsies will not be able to be taken. These women will be referred for Loop Electro Excision Procedure (LEEP).

2.9 Biopsy results and patient management

Patient management will depend on local histopathology findings of biopsied specimens. All women will be contacted to receive their biopsy results. At least three attempts via phone call will be made to contact each participant, although additional phone calls, texts, or home visits to invite women to a result delivery appointment may also be made. We will keep a record of women who are lost to follow-up and the reasons why.

Participants with histologically confirmed CIN2+ will be referred to treatment by ablation, if eligible. Based on previous studies, we anticipate that approximately 10% of women will be ineligible for ablation; these women will be offered LEEP. Participants with suspected invasive cancer will be referred to the public health system for follow-up care. Data on treatment and/or referral, including histopathology findings from any LEEP specimens, will also be collected. Study staff will track referred patients to maximize adherence to further care.

2.10 Laboratory analysis and histopathology

HPV samples taken with careHPV will be analyzed at MoH laboratories as they are part of the standard of care. Results will be obtained in coordination with MoH laboratory personnel.

ScreenFire HPV test results will be analyzed and stored at BHI facilities. Cervical biopsy specimens obtained during the colposcopy visit will be processed and evaluated by a local study pathologist. These results will be communicated to study coordinators to contact women who will need treatment or further care. Local pathology results will be used for referral to treatment per standard-of-care guidelines.

2.11 Pathology quality assurance

An expert gynecologic pathologist will evaluate slides with CIN2+ diagnoses and those of the 5% screen-negative sample on a regular basis for confirmation of underlying diagnosis. Local pathology will guide patient management, but primary analysis will be based on the results of the review by the expert pathologist. This expert evaluation may be done in person or remotely using a slide scanner. If the expert pathologist upgrades the local diagnosis, the MoH and patient will be informed and offered treatment as appropriate. It will also be important to differentiate CIN2 from CIN3 diagnoses, given recent epidemiological evidence that CIN3 is more likely to progress to invasive cervical cancer.[24]

3. POWER CALCULATIONS AND DATA ANALYSIS

3.1 Aim 1: Validate AVE as a primary screening test compared to visual inspection with acetic acid (VIA) for the detection of high-grade cervical pre- cancer (CIN2+).

A study with 10,000 women will be able to detect a minimum difference of 10% between VIA and AVE with 80% power and a Type I error rate of 5%, assuming a minimum sensitivity of VIA of 65% and a correlation coefficient of the tests in the diseased population (Rho) of at least 50%. Based on the study design, all participants who test positive on any test will be referred to colposcopy with biopsy (i.e., proportion of verification = 1), as opposed to only 5% of those who are double negative being referred (i.e., proportion of verification = 0.05). Finally, based on our previous experience working in El Salvador, we estimate the prevalence (lambda) of CIN2+ in the general screening population at 2%.

3.2 Aim 2. To compare AVE as a triage test compared to VIA for detecting CIN2+ among HPV-positive women.

3.2.2 Data analysis

Since all women who test positive with careHPV, VIA or AVE will undergo colposcopy with biopsy, the positive predictive value (PPV) for CIN2+ will be estimated directly using the women who test positive with a particular screening test. An unbiased estimate of NPV will be obtained by using only results for the 5% of women who are negative for the three screening tests who

are randomly selected to receive colposcopy and a minimum of two biopsies. Methods that account for verification-biased sampling will be used to obtain unbiased estimates of sensitivity and specificity for CIN2+ detection.[25] A method developed by Leisenring et.al. [26] will be used to test for significant differences in PPV and NPV.

4. DATA COLLECTION AND MANAGEMENT

4.1 Data collection

All data will be recorded in real time on paper forms filled out by a nurse research assistant. All forms will include the date and study ID to link information to specific patients and visits. Collected data will include eligibility criteria, a background questionnaire including relevant sociodemographic and medical history traits, clinical procedures, and laboratory results. In addition, providers conducting speculum exams during the first (screening) and second (colposcopy and biopsy) visits will use the CervManager application to create a profile for each patient to input clinical information. Thus, study data will be collected on both paper forms and CervManager for added back-up security. Providers will also capture cervical images using the CervManager application on both the Eva System and an Adroid mobile phone. Images belonging to the same patient will be synchronized under the same study ID. Other clinical data (e.g., HPV test results, histopathology) will also be inputted into the CervManager patient profile.

4.2 Data Management

For storage and management, data from paper forms will be transferred to REDCap,[27-28] an electronic data management system widely used for clinical research. CerwvManager and REDCap can be downloaded and merged periodically to easily identify and correct any entry errors, duplications, or missing data on either database. All AVE algorithms implemented as part of this project and used for subsequent analyses will run on DL Analytics servers.

4.3 Non-participant documentation

We will document the number of eligible women who decline to participate in the study (including main reasons why). If individuals agree, we will collect general, de-identified information (i.e., age range, education, and previous screening). This will be done to identify any potential source of sampling bias.

5. DATA SAFETY AND CONFIDENTIALITY

Data collection forms will be stored in locked filing cabinets in an office with a lock at BHI facilities. Informed consents and any documents with personally identifying information will be stored separately also in locked filing cabinets for a 5 year period after the study ends. All data from paper forms will be transferred to REDCap, which will be housed at an authorized BHI server that manages several other projects. Access to REDCap and the CervManager database is password-protected and restricted to authorized users. Both databases will only be accessible to selected study team members and providers will only be able to enter and access information about their own patients on CervManager. DL Analytics servers are HIPAA compliant, password protected and encrypted to ensure that participant's information remains private. All individuals with access to study data will be certified in protection of research human subjects.

Participant confidentiality will be maintained through the use of an alphanumeric study ID to de-link personal information from study data. Digital cervical images will be saved automatically in the CervManager database under each participant's study ID. The images along with the results of VIA, HPV tests, AVE, colposcopy, and biopsy, de-linked from any personnel or identifiable data, can be utilized in the further development of AVE technology or shared with other research teams working in the same field. Finally, data audits will be conducted every 6 months to guarantee the accuracy of collected data and troubleshoot any potential issues.

5.1. Dissemination of findings

Findings for this investigation will be shared in aggregated and/or summarized form with corresponding authorities in El Salvador and disseminated in medical journals and national and international conferences, as is routine in scientific investigations. In case of data or specimen transfer for research objectives, information will only be shared with the consent of participants and with the express approval of the ethical committee of reference, as appropriate.

6. OTHER RISKS AND SAFETY CONSIDERATIONS

6.1 Clinical risks

The clinical risks of this study to individual patients are minimal. Provider sampling for HPV testing, VIA, AVE and ablation treatment are all very safe. HPV testing and thermal ablation are the standard of care in El Salvador, and VIA and AVE involve only a visual assessment and capturing an image, respectively, during a standard speculum exam. It is possible that the use of VIA and AVE as additional screening tests increase the possibility of detecting HPV infections

and precancer cases. Colposcopy and biopsy are routine proceedings in gynecological care that will provide greater confidence in the results of screening tests.

6.2 Monitoring and adverse events

A monitoring plan consisting of site visits and weekly teleconferences will be carried out by study investigators, local personnel, general and local coordinators. Adverse events (AEs), serious adverse events (SAEs), unanticipated problems, and any protocol deviation or violation will be registered with appropriate documentation by local investigators or coordinators, who will notify principal investigators and coordinators within 24 hours after learning about them. Similarly, principal investigators must report SAEs to the ethics committee in 48 working hours after learning about the event.

6.3 Data Safety and Monitoring Board

A Data Safety and Monitoring Board (DSMB) will be convened. Participants will include at least four physicians, statisticians, and/or other investigators that are not directly involved in the study. After participant enrollment begins, the group will include a telephone conference every six months and on additional occasions if there is a SAEs. Evaluating enrollment, loss to follow-up, participant safety, confidentiality violations, side-effects or other problems or concerns that may arise during the study.

6.4 Ethics Committees

The study protocol will be submitted to the consideration of the corresponding Salvadoran ethics committee, and this will be the committee of record for this study. The protocol will be presented also to the committees that oversee the participation of co-investigators as necessary.

7. TIMELINE AND MILESTONES

Enrollment and data collection will take place over 18 months. Data audits will be carried out regularly during the project. Final analyses will begin after enrollment visits are completed. Project timelines and milestones are presented below.

Timeline and Milestones

	Year 1				**Year 2**			
Milestone	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**

Enrollment/screening (555 women/mo.)								
Colposcopy and biopsy visits								
Local pathology and treatment								
QA pathology review								
Data audits								
Analysis								

8. REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2024;74(3):229-263. doi:https://doi.org/10.3322/caac.21834
2. World Health Organization. WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer. 2018. Accessed August 29, 2021. https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/
3. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al. Cost-Effectiveness of Cervical-Cancer Screening in Five Developing Countries. *New England Journal of Medicine*. 2005;353(20). doi:10.1056/nejmsa044278
4. Maine D, Hurlburt S, Greeson D. Cervical cancer prevention in the 21st century: Cost is not the only issue. *Am J Public Health*. 2011;101(9). doi:10.2105/AJPH.2011.300204
5. Martinez-Gutierrez J, Chima S, Boyd L, et al. Failure to follow up abnormal test results associated with cervical cancer in primary and ambulatory care: a systematic review. *BMC Cancer*. 2023;23(1). doi:10.1186/s12885-023-11082-z
6. Basu P, Mittal S, Banerjee D, et al. Diagnostic accuracy of IVAA and HPV detection as primary and sequential screening tests in a cervical cancer screening demonstration project in India. *Int J Cancer*. 2015;137(4). doi:10.1002/ijc.29458
7. Blumenthal PD, Gaffikin L, Chirenje ZM, McGrath J, Womack S, Shah K. Adjunctive testing for cervical cancer in low resource settings with visual inspection, HPV, and the Pap smear. *International Journal of Gynecology and Obstetrics*. 2001;72(1). doi:10.1016/S0020-7292(00)00329-5
8. Denny L, de Sanjose S, Mutebi M, et al. Interventions to close the divide for women with breast and cervical cancer between low-income and middle-income countries and high-income countries. *The Lancet*. 2017;389(10071). doi:10.1016/S0140-6736(16)31795-0
9. Davies-Oliveira JC, Smith MA, Grover S, Canfell K, Crosbie EJ. Eliminating Cervical Cancer: Progress and Challenges for High-income Countries. *Clin Oncol*. 2021;33(9). doi:10.1016/j.clon.2021.06.013
10. Zhang W, Gao K, Fowkes FJI, et al. Associated factors and global adherence of cervical cancer screening in 2019: a systematic analysis and modelling study. *Global Health*. 2022;18(1). doi:10.1186/s12992-022-00890-w
11. Lopez Varon M, Geng Y, Fellman BM, et al. Interventions to increase follow-up of abnormal cervical cancer screening results: A systematic literature review and metaanalysis. *PLoS One*. 2024;19(2 February). doi:10.1371/journal.pone.0291931
12. Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. *Cochrane Database of Systematic Reviews*. 2017;2017(8). doi:10.1002/14651858.CD008587.pub2
13. Mustafa RA, Santesso N, Khatib R, et al. Systematic reviews and meta-analyses of the accuracy of HPV tests, visual inspection with acetic acid, cytology, and colposcopy. *International Journal of Gynecology and Obstetrics*. 2016;132(3). doi:10.1016/j.ijgo.2015.07.024

14. Okunade KS, Adejimi AA, John-Olabode SO, Oshodi YA, Oluwole AA. An Overview of HPV Screening Tests to Improve Access to Cervical Cancer Screening Amongst Underserved Populations: From Development to Implementation. *Risk Manag Healthc Policy*. 2022;15. doi:10.2147/RMHP.S296914
15. Kundrod KA, Jeronimo J, Vetter B, et al. Toward 70% cervical cancer screening coverage: Technical challenges and opportunities to increase access to human papillomavirus (HPV) testing. *PLOS Global Public Health*. 2023;3(8). doi:10.1371/journal.pgph.0001982
16. Cremer ML, Maza M, Alfaro KM, et al. Introducing a High-Risk HPV DNA Test Into a Public Sector Screening Program in El Salvador. *J Low Genit Tract Dis*. 2016;20(2):145-150. doi:10.1097/LGT.0000000000000188
17. Cremer M, Maza M, Alfaro K, et al. Scale-Up of an Human Papillomavirus Testing Implementation Program in El Salvador. *J Low Genit Tract Dis*. 2017;21(1):26-32. doi:10.1097/LGT.0000000000000280
18. Hu L, Bell D, Antani S, et al. An Observational Study of Deep Learning and Automated Evaluation of Cervical Images for Cancer Screening. *JNCI: Journal of the National Cancer Institute*. 2019;111(9):923-932. doi:10.1093/jnci/djy225
19. Xue Z, Novetsky AP, Einstein MH, Marcus JZ, Befano B, Guo P, Demarco M, Wentzensen N, Long LR, Schiffman M, Antani S. A demonstration of automated visual evaluation of cervical images taken with a smartphone camera. International Journal of Cancer. 2020 Nov 1;147(9):2416-23
20. Hu L, Mwanahamuntu MH, Sahasrabuddhe V V, et al. Internal Validation of Automated Visual Evaluation (AVE) on Smartphone Images for Cervical Cancer Screening in a Prospective Study in Zambia. *medRxiv*. Published online 2024. doi:10.1101/2023.07.19.23292888
21. Sanjosé S de, Perkins RB, Campos NG, et al. Design of the HPV-Automated Visual Evaluation (PAVE) Study: Validating a Novel Cervical Screening Strategy. *medRxiv*. Published online January 1, 2023:2023.08.30.23294826. doi:10.1101/2023.08.30.23294826
22. Richart RM. Colpomicroscopic studies of the distribution of dysplasia and carcinoma in situ on the exposed portion of the human uterine cervix. *Cancer*. 1965;18(8). doi:10.1002/1097-0142(196508)18:8<950::AID-CNCR2820180805>3.0.CO;2-T
23. Gage JC, Hanson VW, Abbey K, et al. Number of Cervical Biopsies and Sensitivity of Colposcopy. *Obstetrics & Gynecology*. 2006;108(2). doi:10.1097/01.AOG.0000220505.18525.85
24. Papoutsis D, Underwood M, Parry-Smith W, Panikkar J. ¿Tiene CIN2 el mismo potencial agresivo que CIN3? Un análisis secundario de la recidiva citológica de alto grado en mujeres tratadas con tratamiento cervical con coagulación fría. Geburtshilfe und Frauenheilkunde. 2017; 77(3). doi:10.1055/s-0042-119993
25. Alonzo TA, Pepe MS. Assessing accuracy of a continuous screening test in the presence of verification bias. *J R Stat Soc Ser C Appl Stat*. 2005;54(1). doi:10.1111/j.1467-9876.2005.00477.x

26. Leisenring W, Alonzo T, Pepe MS. Comparisons of predictive values of binary medical diagnostic tests for paired designs. *Biometrics*. 2000;56(2). doi:10.1111/j.0006-341X.2000.00345.x
27. Harris PA, Taylor R, Thielke R, Payne J, González N, Conde JG. Captura electrónica de datos de investigación (REDCap): una metodología basada en metadatos y un proceso de flujo de trabajo para proporcionar apoyo informático de investigación traslacional. *J Biomed Inform*. 2009; 42(2). doi:10.1016/j.jbi.2008.08.010
28. Harris PA, Taylor R, Minor BL, et al. El consorcio REDCap: Construyendo una comunidad internacional de socios de plataformas de software. 2019;95. doi:10.1016/J.JBI.2019.103208