INFORMED CONSENT FORM

Title of the Study: Validation of a lab-free low-cost screening test for prevention of cervical cancer: automated visual evaluation
Sponsor: National Institutes of Health, National Cancer Institute (NCI), USA, **4R44CA247137**
Principal Investigator: Dr. David Levitz, DL Analytics, EUA
Site Principal Investigator: Dra. Karla Alfaro, Basic Health International, El Salvador

What should I know about a research study?
The following is summary of this research study that will help you to decide if you want to participate. You are free to decide whether you want to participate or not. You can agree to participate and then change your mind. You can ask as many questions as you want before you decide to participate and during the study. Your decision to accept or decline your participation will not affect you in any way.

What is the purpose, procedures and duration of this study?
This study will be conducted by DL Analytics, Basic Health International (BHI) and the Ministry of Health of El Salvador. The purpose of this study is to investigate the performance of a new test for cervical pre-cancer and cancer detection. This test can be performed outside a laboratory facility and provide results on the same day. The research will be led by researchers from DL analytics, BHI and the Ministry of Health of El Salvador.

Cervical cancer is caused by the human papillomavirus (HPV). There are many types of HPV, but only some types can cause infections that can develop into pre-cancer. Cervical **pre-cancer is not cancer, but it can develop into cancer over the years if not treated in early stages.** It is important for women to be tested regularly to determine if there is an HPV infection or if there are any signs of pre-cancer and get appropriate treatment. These types of tests are called screening tests. There are several types of screening tests used around the world. In El Salvador, cytology (Pap smears) and HPV test are available. Cytology is a test that collects cells that are analyzed under a microscope, and the HPV test is a sample from the cervix that is analyzed with a machine at the laboratory. In other countries, visual inspection with acetic acid (VIA) is also used, where a health provider applies a liquid to the cervix and can directly observe if there is any lesion. The purpose of this study is to determine the performance of a new screening test. This new test is called automated visual assessment, or AVE. AVE is based on a computer program that can analyze a digital image of the cervix to detect pre-cancer. We will explain later in detail how the AVE works.

You are here today because you are scheduled to have the current HPV test as part as the routine screening program in El Salvador. If you decide to participate in this study, today you will have the regular HPV test and two additional tests, a visual inspection with acetic acid (VIA) and the AVE. In approximately 30 days depending on the results, you will be referred for a second visit, or you will be advised to follow your regular screening.

Women who return for the second visit will have additional tests to determine if they truly have a pre-cancer or cervical cancer diagnosis. As part of the study, you will be compensated for the cost of transportation for this second visit. The tests that will be performed are HPV genotyping, VIA and AVE, colposcopy and biopsy. Colposcopy involves looking at your cervix through a device with a special magnifying lens. Biopsy involves taking a very small piece of the cervix that will be analyzed at the pathology lab and it's considered the most accurate way to detect pre-cancer or cancer. Some women who return for this second visit will be referred for further treatment depending on the biopsy results. If that's the case for you, we will coordinate the most appropriate treatment based on your diagnosis. Fewer women who are negative on first-visit tests will also be asked to undergo VIA, AVE, colposcopy, and biopsy, but will not be treated. We will compare

the results of different AVE tests to determine how effective this new test is for detecting cervical cancer or pre-cancer. Your participation in this study end until you receive your biopsy results within 2 weeks, or when you are referred for further care depending on the biopsy results.

DETAILED INFORMATION

Below you will find more information about this research study:

Why is the research study being done?
This study is comparing the new AVE screening test, that does not require a laboratory infrastructure to other tests that do require laboratory analysis. The AVE test consists of taking an image of the cervix to be analyzed by a computer program. If the AVE test is effective, this can help us detect pre-cancer or cancer in women without waiting for results to come back from a laboratory and will allow more women to have access to prevention and appropriate treatment if needed.

How Many People Will Take Part in this Study?
Approximately 10,000 women will participate in this study. Women that will be recruited are women that are being tested at the MOH facilities as part of the regular cervical cancer screening program at the health units from the Metropolitan region.

Why am I being invited to participate in this study?
You are being invited to participate in this study because you are eligible for cervical cancer screening with HPV testing in El Salvador. This means that you are a woman between the ages of 30 and 59, have not had an HPV test in the past 5 years, have not had surgery to remove your cervix, and have not been previously diagnosed with cervical cancer.

What will happen if you decide to participate in this research study?
If you decide to participate in the study, you will sign this consent form, and the following activities will take place today. You will be first asked to share general information about your life and health though a questionnaire. You don't have to answer any questions if you don't want to. A nurse will take you to an examination room and a gynecological exam will be performed by a doctor. The doctor will use a speculum to visualize your vagina and cervix. Then he/she will use a small brush to take a sample of your cervix. This sample will be sent to the lab for HPV testing. Your doctor will then put a liquid solution similar vinegar on your cervix. The cervix is normally pink, but this solution causes any pre-cancerous lesions to turn white. The doctor will record your opinion on a portable device that has a camera and a screen to store information. Finally, the doctor will take digital images of the cervix with this same device and with a mobile phone that is for clinical use only. These images will not show any other part of your body. The images will be analyzed by the AVE program to determine if there is any type of pre-cancer or cancer. That is the end of this first exam. You can ask any questions to make sure you understand the process. Questionnaire and the clinical exam should take overall 20 to 30 minutes.

Approximately 30 days after the first visit, you will be contacted by a research assistant who will tell you if you should return for the second visit depending on your test results. We expect that approximately 30% or about 3,000 women will be referred to the second visit, as well as inviting 5% (approximately 500) of women with negative results. These women will receive a compensation for the transportation cost to this second visit. The rest of women with negative results on all their tests (6,500) will be instructed to return to routine screening at the Moh facilities according to the guidelines.

At the second visit, the doctor will conduct another gynecological exam using and speculum and will perform the following tests:

- ScreenFire HPV Test: This is an HPV test that can specifically detect which types of HPV are present in the cervix. The test consist in performing a provider collected sample from your cervix using a small brush. The sample will be analyzed in a lab facility.
- VIA: The doctor applies a liquid similar to vinegar on the cervix. The cervix is usually pink, but the color can turn white if any area has an HPV infection or cervical pre-cancer. The doctor will record his diagnosis on a portable device that also includes a special lens and camera.
- AVE: A portable device will be used to take images of your cervix, which then will be analyzed by AVE algorithm. No other images will be taken of any other part of your body.
- Colposcopy and biopsy: A colposcopy is a procedure in which the doctor uses a special lens to get a better view of the cervix. The doctor will use the portable device to perform the colposcopy and record diagnostic impressions. During colposcopy, your doctor will perform a biopsy, which involves taking small pieces of your cervix. These samples will be sent to a private pathology lab to be analyzed. The biopsy results will be ready in approximately 2 weeks. You will be contacted by a research assistant to receive your results or to schedule an additional appointment for further treatment according to the doctors recommendations.

How will my data/specimens be used?
Your data and samples will be analyzed by study researchers. Your de-identified data will be stored with passwords to protect your privacy. Researchers will maintain a document that links your personal data to the research data, but this document will be kept protected and secure through passwords and will only be available to researchers or individuals at agencies that are responsible of maintaining that data secured. Any information that can identify you will remain confidential. Any personal information that can identify you will be deleted or changed before it's shared with other researchers. The results of the study, without containing personal information that identifies any woman, will be made public through medical journals, professional conferences, and similar venues.

How will my cervical images be used?
You will be able to review the images of your cervix before you authorize their use. The images of your cervix will be stored in a virtual file managed by DL Analytics, one of this study collaborators. That file will only be accessible to researchers of this study and authorized experts from DL Analytics. Images will not be shared publicly.

The images could be used to train other health care providers who work on cervical cancer and to make sure that screening and treatment are done correctly. Images can also be used to build or improve computer programs such as AVE that can help identify cervical cancer and pre-cancer through this technology. Images that are shared will not contain identifiable information, including your name or any identification numbers from your medical records. No woman can be identified through images of her cervix.

Why might you choose to volunteer for this study?
If you participate in this study, several test will be performed therefore you have more chances that if you really have pre-cancer or cervical cancer, one of those tests will identify it. Participants who undergo cervical biopsies as part of the study have the potential benefit to have a more accurate diagnosis. What we learn in this study may benefit other women around the world as it will help us to improve cervical pre-cancer screening.

What are my other choices if I do not take part in this study?
If you decide not to participate in the study, you will only be offered HPV testing at the first visit as this is the test available at the clinic. Any subsequent medical care will be determined by the clinic doctor based on the result of that HPV test.

What are the risks of participating in the research study?
HPV, VIA, AVE, colposcopy, and biopsy tests are very common and safe. None of those procedures in have been shown to affect women's ability to continue to have their normal menstruation and have children in the future. You may feel discomfort or feel embarrassed about the speculum that will be placed in your vagina. If you receive a colposcopy and biopsy, you may feel pain or cramping. We will provide pain medication if you need it.
You may have some vaginal discharge and mild vaginal bleeding or spotting after the colposcopy and biopsies. Sometimes a solution is put on your cervix to stop the bleeding. This can look like coffee grounds and can stain your underwear. It is not dangerous. It is recommended that you wear pads for a few days after the colposcopy. You should seek medical attention if the vaginal discharge is foul smelling, if you have a fever of higher than 38°C (100°F), bleeding more than a normal period, or pain that is not lessened with over-the-counter pain medication.

Confidentiality Risks

If you decide to be in this study, the study researchers will get information that identifies you and your personal health information. This may include information that might directly identify you, such as your name and address. This information will be kept for the length of the study.
Every effort will be made to ensure the confidentiality and privacy of your data. During the study, we will use codes to identify participants, and the information will be stored in secured files and password-protected databases. Only team members and other authorized individuals will have access to your information. After that time, it will be destroyed or de-identified, meaning we will replace your identifying information with a code that does not directly identify you. This research is covered by a Certificate of Confidentiality from the United States National Institutes of Health. This means that most people outside the research team will not see your name on your research information. Exceptions are if you agree that we can give out research information with your name on it, information about child abuse, or neglect and harm to yourself or others.

Unknown Risks

There may be risks or side effects related to the study or tests that are unknown at this time. You will be notified of any significant new findings that become known that may affect your willingness to continue in the study.

Are there any payments to you if you participate in this study?
If you need a colposcopy and biopsy, you will receive a compensation for your transportation to the clinic. There are no other fees related to your participation in this study.

Are there any costs to you if you participate in this study?
Other than your time and additional transportation, there are no cost to you if you participate in the study. The costs of the study procedures are paid by the study.

What will happen if you are injured as a result of taking part in the research?
All medical procedures carry the risk of injury. The procedures in this study are commonly performed at national health facilities, so the risk of injury is remote. However, if you suffer an injury as a result of your participation in this study, go to the nearest health care unit which will provide appropriate medical treatment for the injury in a timely manner. Provision of such medical treatment does not imply any negligence or other wrongdoing on the part of your assigned Ministry of Health clinic or any of the physicians or other personnel involved in the study. If you believe that you have been injured as a result of participating in the study, please immediately contact the study doctor even if you may have already been seen or treated by another doctor. If you are seen or treated by a doctor other than the study doctor,

you should inform such doctor that you are in this study and, if possible, take this document with you as it may help such doctor treat you. If you believe that you have suffered an injury from being in this study, contact the local PI Dr. Karla Alfaro (you will find the information contact later in the document).

What will happen to your information that is collected for this research?
The research team may share your study information, without anyone knowing that it is related to you specifically, with others or use it for research projects not listed in this form. Your samples and data may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and birth date, are removed.
Study results may be shared in medical journals, at scientific meetings, and in other mediums without your identifying information.

What are your rights as a research participant?
Your participation in this study is voluntary. You are free to say no to any part of the study or to leave the study at any time.

What will happen if you decide to withdraw from the study?
If you decide to leave the study before it ends, it is important that you notify the research team in person or using the phone number listed at the end of this document. It is also important to talk to your doctor to ensure safe removal. When you leave the study, if you tell us to, your data and images of the cervix will be destroyed. The research team will do their best to inform you of any findings that may impact your health even if you decide to leave the study. If you leave the study before it ends, but the team is not notified, you will be considered a missed follow-up participant. Researchers may use your study data and images of your cervix unless you indicate otherwise.

Do the researchers or institution have any conflicts of interest relating to this study?
Dr. Miriam Cremer is the founder of the non-profit Basic Health International, Inc. (BHI). Dr Cremer, BHI, and BHI consultants are collaborator on this study and could benefit financially from positive publicity if this research is successful. Neither Dr. Cremer nor Basic Health International have any financial interest in AVE and will not profit from the use of these tests. These financial interests are being managed and are within permissible limits established by the local institution Conflict of Interest Policy. If you have any questions regarding conflict of interests, please ask your doctor or call the Cleveland Clinic Institutional Review Board at (216) 444-2924.

Who to contact if you have questions:
At any point, you can contact the study coordinator to talk with the researchers about any part of the study.

- If you have questions about this study or if you believe you have been hurt as a result of this study, please call:
  Local PI, Karla Alfaro: 2283-8731 or kalfaro@basichealth.org
- If you have questions about your rights as a research participant, please call:
  Comité de Etica e Investigación en Salud IRB (National Committee of Ethics in Health Research of El Salvador): 2561-2559
  National Directorate of Medicines: 2522-5000
- A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

SIGNATURES

Research participant:

I have read, or had read to me, this entire consent for research. I have had the opportunity to ask all my questions about the study. All of the questions I asked were answered to my satisfaction. If I do not choose to participate in this research, or if I choose to withdraw from this research at any time, this will not affect my ability to receive medical care outside of this research study. I hereby volunteer to participate in this research.

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Research participant signature: _____

Name: _____
Print Name

Date: (DD/MM/YR):_____ Time:_____

Thumbprint
(If non-literate)

Consent witness (for non-literate participants)**:**

I was present for the entire consent process and observed that the potential volunteer had an opportunity to ask questions, appeared to understand what was involved and voluntarily agreed to take part in the research.

Consent witness signature: _____

Name: _____
Print Name

Date: (DD/MM/YR): _____ Time:_____

Research investigator or delegate:

I have fully explained to the potential participant the nature and purpose of this research study. I have explained the potential benefits. I have explained the possible discomforts and risks. I believe that the potential volunteer understands the nature, purposes, benefits, and risks of participation in this research. I have also offered to answer any questions and have fully and completely answered all such questions. I have provided the participant with a copy of the consent form.

_____

Signature of Investigator/Delegate (person who obtained consent)

_____

Print Name of person who obtained consent Title

Date: (DD/MM/YR): _____ Time: _____