Concordance Between the Generation 3 Point-of-Care Tampon (Pocket) Digital Colposcope and Standard-of-Care Colposcope Using Acetic Acid and Lugol's Iodine Images in Lima, Peru

by

Denali K. Dahl

Global Health Institute
Duke University

Date:_______________________
Approved:

____
Nimmi Ramanujam, Supervisor

____
John Schmitt

____
Lawrence P. Park

Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the
Global Health Institute in the Graduate School
of Duke University

2017

ABSTRACT

Concordance Between the Generation 3 Point-of-Care Tampon (Pocket) Digital Colposcope and Standard-of-Care Colposcope Using Acetic Acid and Lugol's Iodine Images in Lima, Peru

by

Denali K. Dahl

Global Health Institute
Duke University

Date:________________________
Approved:

____
Nimmi Ramanujam, Supervisor

____
John Schmitt

____
Lawrence P. Park

An abstract of a thesis submitted in partial
fulfillment of the requirements for the degree
of Master of Science in the
Global Health Institute in the Graduate School of
Duke University

2017

Abstract

Cervical cancer is the second leading cause of death for women worldwide with 85% of deaths occurring in low and middle-income countries, despite being both preventable and treatable if detected early enough. The burden of disease persists primarily due to a lack of access to early diagnostics and significant proportion lost to follow-up. In Peru specifically, the rates of cervical cancer are among the highest in the world with an annual incidence of 48.2 per 100,000.

To provide low-cost and accessible colposcopy while maintaining image quality, the point of care tampon like (Pocket) digital colposcope is being developed in the Tissue Optical Spectroscopy (TOpS) Lab at Duke University. As part of the ongoing Pocket colposcope development and validation, the Generation 3 Pocket colposcope was tested for concordance to the standard-of-care Goldway SLC-2000 digital colposcope in a pilot study conducted in Lima, Peru. The goal of this study is to demonstrate equivalence in clinical diagnostic performance of the Generation 3 Pocket colposcope versus the standard-of-care digital colposcope.

100 patients were enrolled under the IRB approved study protocol Pro00052865. Paired images of cervices were collected with the standard digital colposcope and the Pocket colposcope for each patient using acetic acid and Lugol's iodine as contrast agents. Biopsies were taken as part of routine clinical care when indicated. The paired

images were blinded by device, randomized, and sent with an electronic survey to three Duke affiliated physicians who are highly trained in colposcopy.

The primary outcome measured was level of agreement using an unweighted kappa statistic between 1) overall predicted diagnosis and 2) Reid Colposcopic Index scores for the Generation 3 Pocket colposcope and Goldway colposcope. The secondary outcome measured was sensitivity, specificity, positive predictive value, and negative predictive value.

The percent agreement for all physicians combined between systems for the overall diagnosis was 83.78% with a kappa of 0.5786 and p-value of <0.0000, and the percent agreement for the Reid Colposcopic Index score comparison was 72.3% with a kappa of 0.4366 and p-value of <0.0000 indicating strong concordance. Both systems performed similarly when compared to gold-standard pathology, with level of agreement of approximately 66% and a kappa statistic of ~0.3, and p-values <0.0000.

The Generation 3 Pocket colposcope performed similarly to the standard Goldway colposcope and can be used to increase access to colposcopy, thereby reducing the burden of cervical cancer morbidity and mortality in Peru and around the world.

Contents

List of Tables

List of Figures

Acknowledgements

I would like to offer my sincere thanks to Dr. Nimmi Ramanujam my primary advisor and my committee members Dr. Larry Park and Dr. John Schmitt for all their mentorship and support during my thesis research. I would also like to acknowledge and thank Elizabeth (Betsy) Asma, Chris Lam, Dr. Jenna Mueller, Marlee Krieger, Dr. Lisa Muasher, Dr. Peyton Taylor, Dr. Gino Venegas, Dr. Ernesto Ortiz, Yenny Bellido, La Liga de Lucha Contra el Cancer, the Duke Global Health Institute, and the Department of Biomedical Engineering in Pratt School of Engineering at Duke University for making this project possible.

1. Introduction

Cervical cancer is prevalent around the world, but the majority of the disease burden is felt by low and middle-income countries where 85% of all cervical cancer related deaths occur [1]. With an extremely high mortality rate of 16.3 per 100,000, cervical cancer is the second leading cause of mortality for women in developing countries, resulting in 270,000 deaths in 2012 [1, 2].

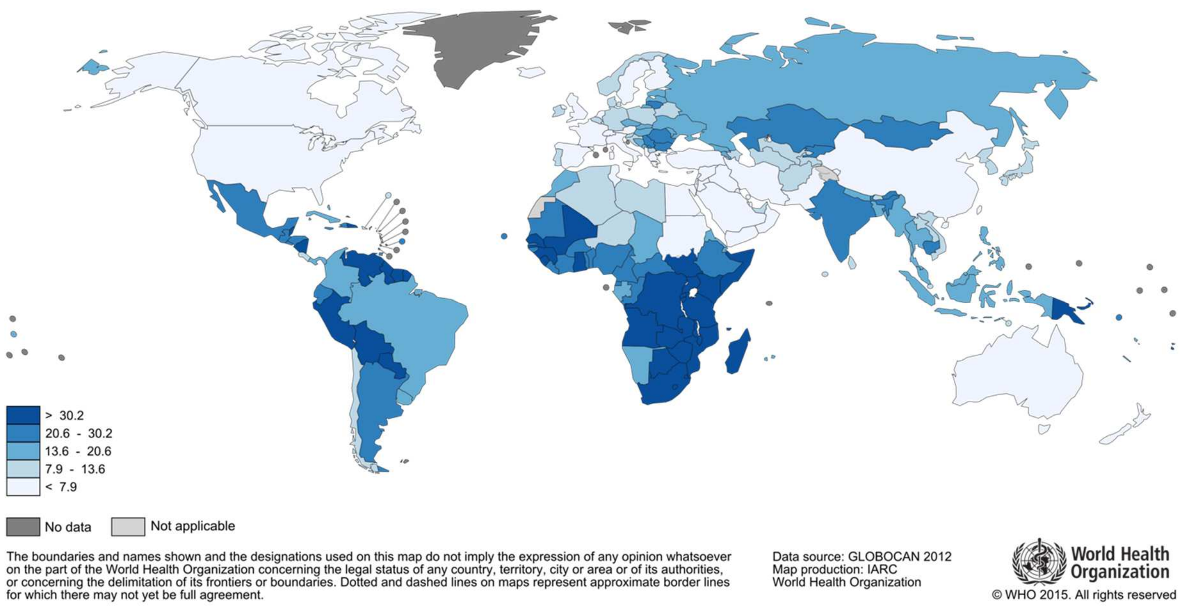


Figure 1: WHO Estimation of Cervical Cancer Incidence Worldwide in 2012[3]

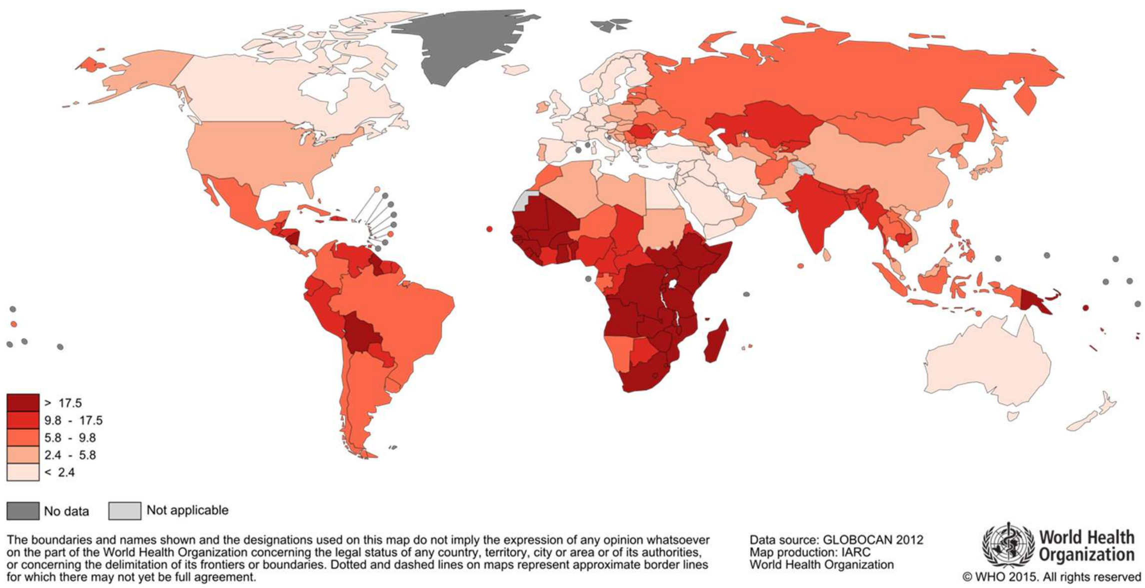


Figure 2: WHO Estimation of Cervical Cancer Mortality Worldwide in 2012[3]

Cancerous lesions in the cervix can develop when certain strains of high-risk human papillomavirus (HPV) are transmitted through sexual contact [4]. The majority of sexually active men and women will be infected with HPV at some point in their lives, but only a small percentage of these infections develop into cancer [5]. Other cofactors often increase the development of HPV infection to cancerous lesions, such as tobacco use, high parity, long-term hormonal contraceptive use, and co-infection with HIV [6].

Unlike many other types of cancer, cervical cancer is both preventable and treatable when detected early. The burden of disease persists because access to screening, preventative care, early diagnostic tests, and treatment are not readily available in many low and middle-income countries [7]. The most effective form of preventing the development of cervical cancer is the HPV vaccine Gardasil 9 which is

97% effective at preventing cervical cancer by protecting against infection from HPV strains 6, 11, 16, 18, 31, 33, 45, 52, and 58 [8]. The HPV vaccine protects against the HPV strains that most commonly cause cancer, but the vaccine does not eliminate an individual's risk of developing cervical cancer. As a result, periodic screenings for cervical cancer are necessary for all adult women regardless of vaccination status.

To visually examine the cervix for cancerous lesions, acetic acid is applied to the cervix where abnormal tissue will temporarily appear white. Acetic acid causes swelling of the epithelial tissue and reversible precipitation of the nuclear proteins and cytokeratins. Precancerous or cancerous cells contain high concentrations of nuclear proteins, resulting in high precipitation when acetic acid is applied, therefore appearing white [9]. Normal squamous epithelium is sparsely nucleated and so little precipitation or 'acetowhitening' is seen. When available, Lugol's iodine is also applied to the cervix to enhance visual inspection. Squamous epithelium cells contain glycogen, while precancerous or cancerous lesions contain little or no glycogen. Iodine is glycophilic, so squamous epithelium cells will have a high iodine uptake and appear dark brown, while precancerous and cancerous lesions will have little or no iodine uptake resulting in a yellow color [10].

In developing countries, the most common form of diagnosis is performed with visual inspection with acetic acid (VIA) unassisted by optics or naked eye. When available, visual inspection with acetic acid and magnification (VIAM), which includes colposcopy and cervicography [11], is preferred over VIA. Traditional colposcopy provides the best form of magnification but is expensive and not readily available in low-resource settings. Cervicography, or taking pictures with a camera by an untrained provider, is often substituted for a colposcope. When no form of magnification is available, the WHO recommendation for diagnosing lesions on the cervix is VIA [7]. Colposcopy as a diagnostic tool has high sensitivity and low specificity, which means it can accurately identify cancer in patients who pathologically have cancer, but also generates a high number of false positive diagnoses, i.e., mistakenly identifying healthy patients as having cancer or precancerous lesions [12]. A high number of false positive diagnoses lead to a large number of women being treated for cervical cancer when they do not actually pose a risk for developing cancerous lesions. This results in unnecessary treatment, which wastes time and limited medical resources.

For many precancerous lesions, cryotherapy is the WHO recommended treatment. For larger lesions, loop electrosurgical excision procedure (LEEP) is recommended when available [13]. Both treatment methods effectively treat the precancerous cells from the cervix. True invasive cervical cancer requires chemotherapy, radiation treatments, and or radical hysterectomies to treat [14].

1.1 Cervical Cancer in Peru

Rates of cervical cancer in Latin America are among the highest in the world. In Peru, cervical cancer is the leading cause of female cancer and cancer-related deaths, especially for women of reproductive age between fifteen to forty-four years old [6].

Since 2000, Peru has had national guidelines for cervical cancer screening for women aged twenty-five to fifty-nine. National guidelines include Pap smear tests and VIA as the indicators for screening methods. However, only 40.3% of women in this age range were screened between 2000 and 2003 [15]. The rates of cervical cancer screening were disproportionate across the country, with women in costal areas like the capital city of Lima getting screened at significantly higher rates than women in other parts of the country [15]. This disparity is not surprising, as the majority of health care and medical professionals are concentrated in Lima. The even lower rates of screening in rural areas of Peru compared to the country overall suggest a significant unmet need and contributes to a large number of preventable cancer deaths in these areas of the country[15].

The high morbidity and mortality of cervical cancer is partly due to a lack of screening, but also largely due to a significant lack of follow up after an abnormal screnning. Only 25% of women who had an abnormal Pap smear followed up to receive colposcopy to characterize the cervical abnormalities, meaning that many women did not receive treatment for precancerous or cancerous lesions [16]. Part of the lack of follow-up is due to inaccessible and costly services, systemic issues with the handling of samples and dissemination of results, a lack of comfort and privacy in health centers, anxiety related to test results, and overall fear of cancer [17].

National initiatives like Project ESPERRANZA have been incorporated by the Ministry of Health to try and reduce the incidence and mortality of cervical cancer in

Peru. Project ESPERANZA trains health professions and works to vaccinate preteen girls against HPV [18]. Even with the HPV vaccination, routine screenings are required to ensure the continued cervical health. To truly reduce the rates of cervical cancer morbidity and mortality, preventative screenings for Pap smear tests and colposcopy need to become more affordable and accessible, particularly outside of the main costal cities.

La Liga Peruana Contra el Cáncer (La Liga) [19] is a nonprofit organization that aims to fill this gap by providing subsidized healthcare services, specifically for women's cancer screenings. Their motto is, "porque prevenir es vivir" which means 'to prevent is to live". La Liga has three main health centers near the Lima city-center, and operates several mobile healthcare units to screen women in the impoverished outskirts of Lima. In the mobile health clinics, the midwives and nurses provide Pap smears, VIA unassisted by magnification, and exams for breast and skin cancer. The mobile clinics also have social workers that provide patients with counseling and social services. Women who have abnormal screenings are referred to the main health clinics in the center of Lima for follow-up diagnostic testing and treatment, which can be over four hours away by bus. La Liga provides some assistance with transportation, but loss to follow-up continues to be a large problem for women with abnormal Pap smears and only about 20-30% of the women referred actually travel to Lima for colposcopy or treatment [20].

1.2 Development of the Generation 3 Pocket Colposcope

Standard colposcopes (Figure 3a) cost up to $20,000 USD and rely on a constant supply of electricity while in use. The standard colposcope views the cervix externally, about 300mm away from the cervix, requiring a high megapixel camera with extreme zooming capabilities. Due to the high cost of the machine, colposcopy can only be performed in medical facilities with substantial resources.

To address this need, the Tissue Optical Spectroscopy (TOpS) Lab in Duke University's Department of Biomedical Engineering has developed a low-cost, portable colposcope to increase access to cervical cancer screenings in low-resource settings [21]. The Pocket (Point-of-Care Tampon) colposcope (Figure 3b) was inspired by the tampon, which is a transvaginal feminine hygiene product. By placing a camera on the end of a tampon-like probe, images of the cervix can be captured from about 30mm away, which dramatically decreases the megapixel and zooming requirements of the camera. Using a low-powered camera in a tampon design allows the device to be manufactured at a significantly lower cost than standard colposcopy, on the magnitude of several hundred USD rather than several thousand USD.

Additionally, the Pocket colposcope can be powered by connecting directly to a laptop or smart phone using a USB connection. The ability to have a battery-powered colposcope means that colposcopy is not restricted to a medical facility with a constant supply of electricity, but can be used in a mobile clinic or remote health care setting where plugging a large machine into a wall is not feasible.

The Pocket colposcope is built with a waterproof casing, which allows for easy and quick sterilization of the probe between patients with 0.0675% bleach [22]. Ease of sterilization is essential in mitigating patient-to-patient transfer of pathogens [23].

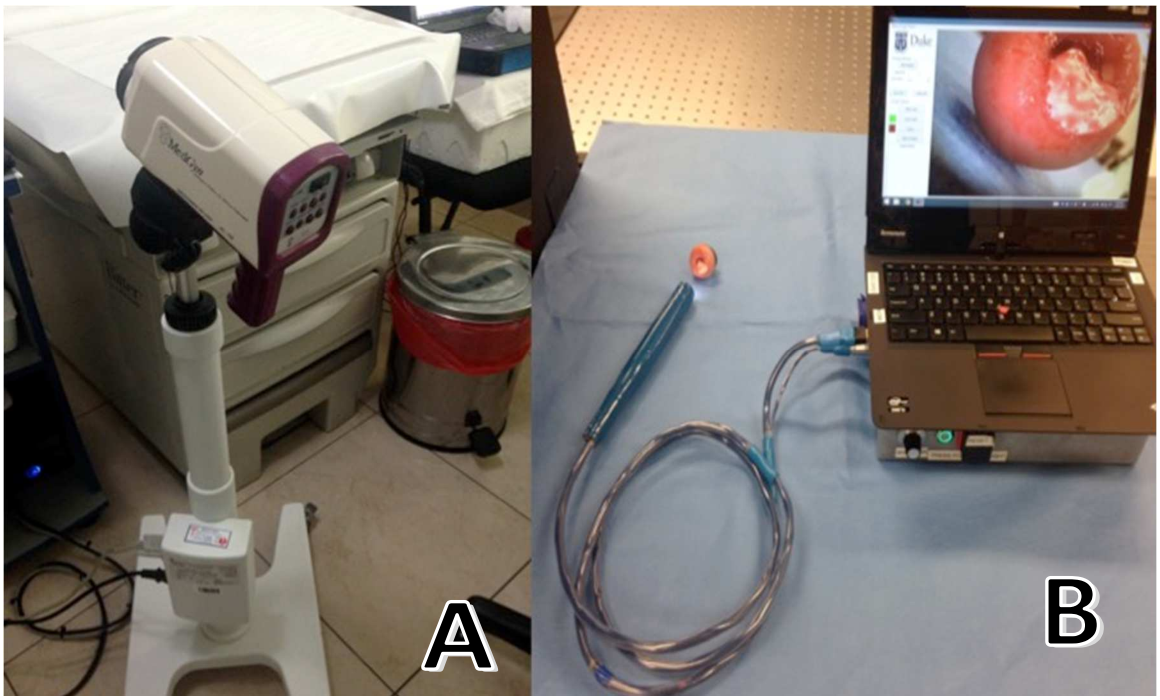


Figure 3: A) Standard-of-care Goldway SLC-2000 digital colposcope at La Liga Peruana de Lucha Contra el Cancer B) Generation 3 Pocket digital colposcope. Set-up includes transvaginal probe, blue power box, and laptop

The Generation 3 Pocket colposcope used in this study is part of the ongoing development of the Pocket colposcope that maintains the quality of standard colposcopy while reducing equipment cost and increasing accessibility. Currently, the Pocket colposcope is being used in clinical investigations in hospitals in the U.S. (n=183), Peru (n=198), Kenya (n=50), and Tanzania (n=50). The goal is to compare the iterations of the Pocket colposcope to the standard-of-care colposcopes in order to demonstrate equivalence between the devices in different settings.

1.3 Research Question

The primary research question for this study is: Is the Generation 3 Pocket colposcope equivalent to the standard-of-care Goldway SLC-2000 colposcope in Lima, Peru at providing acetowhitening and Lugol's iodine images for colposcopy diagnoses of precancerous and cancerous lesions by OBGYN specialists who are trained in colposcopy?

Two primary outcomes were analyzed to show concordance between the Goldway standard-of-care colposcope and the Pocket colposcope 1) level of agreement with an unweighted kappa statistic for overall diagnosis, and 2) level of agreement with an unweighted kappa statistic for Reid Colposcopic Index scores.

2. Methods

This is a pilot diagnostic concordance cohort study conducted in collaboration with obstetric gynecologist specialists at La Liga Peruana de Lucha Contra el Cáncer. The study is comprised of two parts: 1) clinical data collection in Lima, Peru and 2) retrospective cervical image analysis by physicians affiliated with Duke University.

Women are initially screened for cervical abnormalities with a Pap smear. La Liga administers Pap smears in their main clinics as well as in their mobile clinic locations. If the Pap smear is abnormal, the woman is referred for colposcopy (Figure 4) to visually examine the cervix for abnormalities. This study recruited patients undergoing a colposcopy exam, in order to compare the Generation 3 Pocket colposcope to the Goldway standard-of-care colposcope.

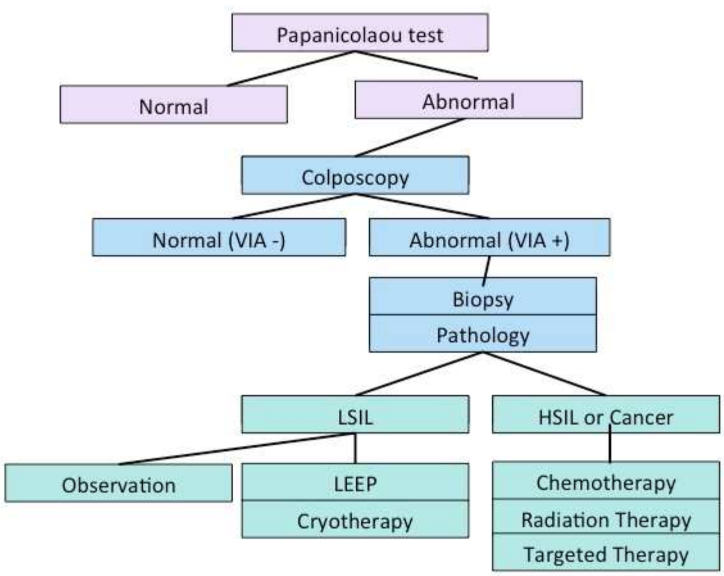


Figure 4: Flow chart for the screening and treatment of precancerous and cancerous cervical lesions.

2.1 Setting

Patient enrollment and image collection with the Generation 3 Pocket digital colposcope and the standard Goldway SLC-2000 digital colposcope occurred at La Liga Peruana de Lucha Contra el Cáncer cervix clinic in Pueblo Libre, Lima, Peru. Lima is the largest city in Peru, and the second largest city in Latin America with a population of about 10 million people [24]. The population of Lima is a mixture of ethnic groups due to years of being colonized and waves of immigration. The predominate ethnic group is comprised of European and Indigenous Peruvian mixes, although minority populations includes a high percentage of Chinese immigrants. The the official language is Spanish. Lima is home to one third of the Peruvian population, and two-thirds of the major industries. Lima is a costal city comprised of forty-three densely populated districts [24].

La Liga Peruana de Lucha Contra el Cáncer is a nonprofit organization dedicated to improving women's health by providing screening and treatment services for a variety of health conditions, including cervical cancer. La Liga has three main locations near the city center of Lima in addition to several mobile clinics that provide basic care to districts on the outskirts of the city. Many of the patients who receive care at La Liga are from Lima, but it is not uncommon for women and families to travel for days to seek care in Lima since the majority of the healthcare facilities are concentrated in the capital city. La Liga works with families who are traveling from a distance to ensure they have access to housing accommodations and the resources they need while they are receiving medical care.

Evaluation of the cervical images by the physicians was done remotely using REDCap electronic database that is HIPPA compliant and encrypted. A web portal hosts a digital survey (Appendix A) that clinicians enter their clinical interpretations of the randomized image panels into. The randomized and de-identified image panels were sent via email as de-identified Microsoft PowerPoint slides.

2.2 Participants

Peruvian women who had been referred for colposcopy or loop electrosurgical excision procedure (LEEP) were recruited for this study. 100 women were consented and enrolled in the study, 98 from colposcopy exams and 2 from LEEP procedures. In the case of the LEEP procedures, the cervix is examined using colposcopy before the surgery is performed. The women ranged in ages from 20 to 67 years old, with the average age being 37 years old.

Obstetric gynecologists at La Liga Peruana de Lucha Contra el Cáncer were trained on how to use the Generation 3 Pocket colposcope by members of the Duke study team in order to capture in vivo cervical images. First, physicians were shown how the device worked by taking practice images of their hands or office supplies. The physicians were given the opportunity to hold the Generation 3 Pocket colposcope to see where the camera focuses and how the image-capture process works. During the first couple uses of the Generation 3 Pocket colposcope in the clinic, each new physicians was reminded of how to orient the device and then guided through the image capture process.

To evaluate the cervical images, de-identified images and electronic surveys were sent to three physicians. All three physician participants are affiliated with Duke University Medical Center, and were trained as obstetrics and gynecology specialists in the United States. The three physicians have many years of clinical experience and trained experts at identifying cervical abnormalities using colposcopy.

2.3 Procedures

The patients from the referred population were presented with the opportunity to be a part of the study following an explanation of the purpose, background of the study, the patient's involvement, benefits, risks, compensation (for injury), cost, alternatives, and confidentiality. Informed written consent was obtained from each patient who was willing to participate. As part of the consent process, patients agreed to allow researchers access to their medical record, including but not limited to cervical pathology and age. The patients verbally answered a short questionnaire (Appendix C) about their demographic information and family history of cancer.

Once enrolled in the study, patients proceeded with the normal colposcopy exam. To begin the colposcopy or LEEP exam, the doctor first inserted a speculum into the patient's vagina to open the vaginal walls in order to view the cervix. The cervix was cleaned of excess mucus so a clear visual could be obtained. Acetic acid was applied to the cervix for one minute, and then an image of the cervix was captured with the Goldway colposcope and the Generation 3 Pocket colposcope. 3-5 images were captured with the Goldway colposcope and 3 images were captured with the Pocket colposcope. Iodine was then applied to the cervix and 3 more images were captured with the Pocket colposcope, and then 1-2 images were captured with the Goldway colposcope. The images captured with the Goldway colposcope were automatically saved in each patient's electronic medical record file at La Liga Peruana de Lucha Contra el Cáncer. Images captured with the Generation 3 Pocket colposcope were saved in files on a secure clinical laptop with study identification codes.

Paired acetic acid and Lugol's iodine images were captured for each patient enrolled in the clinical study. The pair of images consists of the best acetic acid and Lugol's iodine images captured with the Pocket colposcope and with the Goldway colposcope. The best images were determined by the author based on physician guidance of what elements were required for a complete diagnosis of the cervix. For each patient, multiple images were captured for both acetic acid and Lugol's iodine with the Pocket and standard-of-care colposcope, so the best image from the set was considered to be the most in-focus image.

Since this study was a pilot study at La Liga Peruana de Lucha Contra el Cáncer, not all of the patient images captured were high quality, as there was a learning curve on operating the Pocket colposcope and its integration into the clinical workflow. Figure 9 identifies what about the low quality and not usable images deemed them unsuitable for analysis, and an example of a low-quality image excluded from the analysis is shown in Figure 7. From the 100 patients enrolled in the study, 73 image pairs were of high enough quality for further evaluation. Figure 5 shows the criteria used to determine the quality of the Pocket images captured, and Figure 6 shows the criteria used to determine the quality of the Goldway images captured. The criteria were determined based on the elements of a cervical image required to make a diagnosis: clear visibility of the entire cervix. Figure 8 shows the overall breakdown of image quality grading for all 100 patients enrolled in this study.

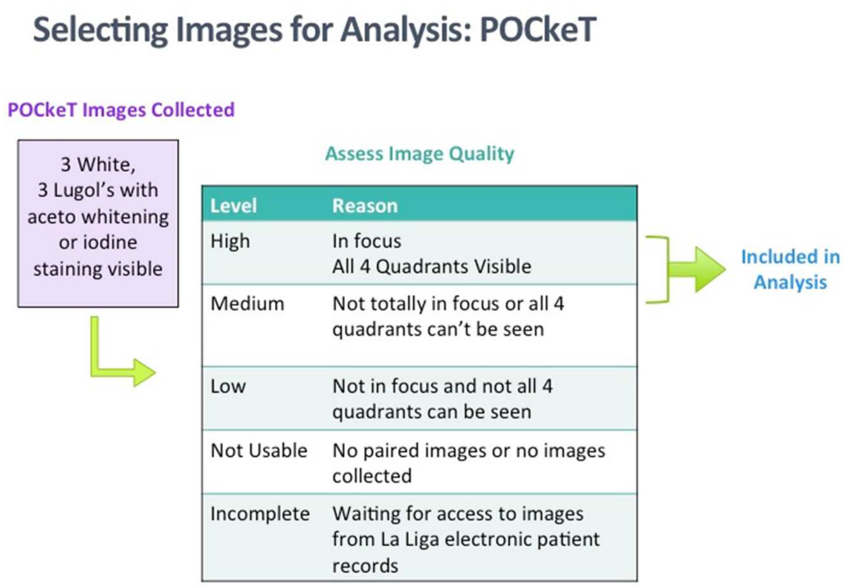


Figure 5: Determining image quality and ability to interpret image for diagnosis for images collected with the Generation 3 Pocket colposcope for patients enrolled at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

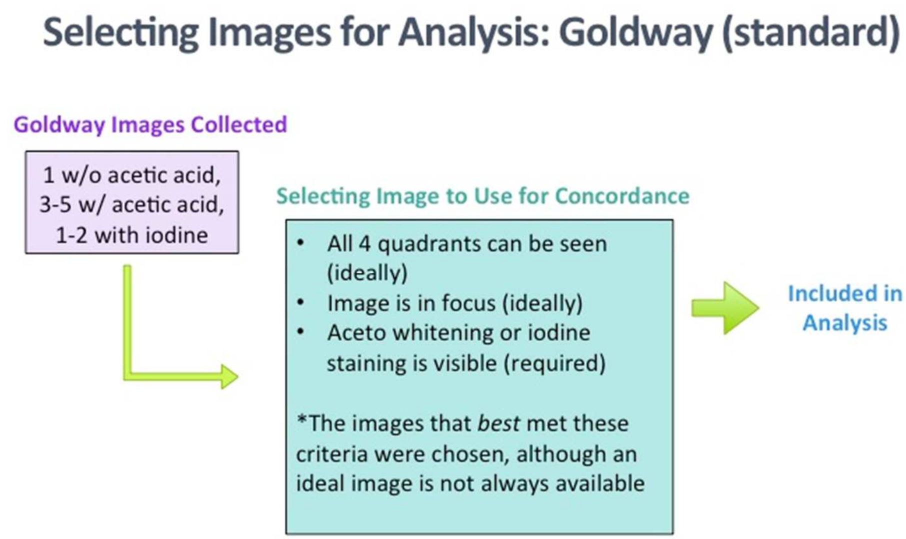


Figure 6: Determining image quality and ability to interpret image for diagnosis for images collected with the Goldway colposcope for patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

Figure 7: Example of cervix image captured with the Generation 3 Pocket colposcope at La Liga Peruana de Lucha Contra el Cáncer that is both out of focus and lacks visibility of all four quadrants. This image is considered low quality.

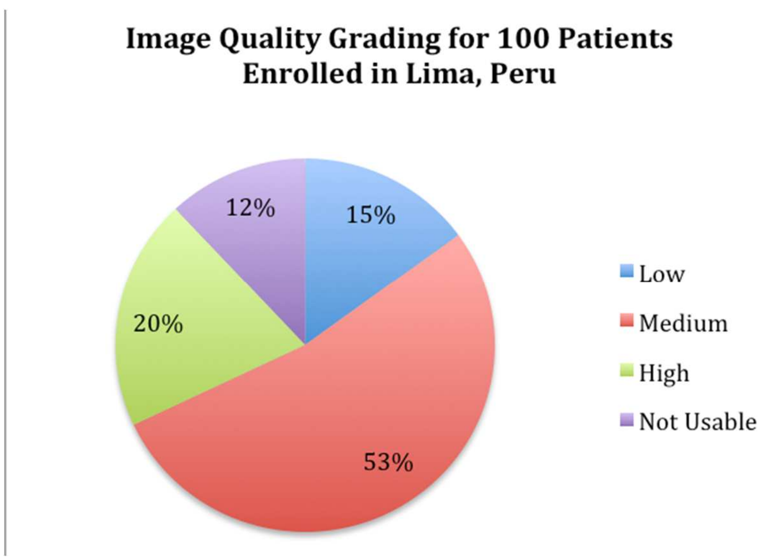


Figure 8: Overall grading of image pairs for 100 patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

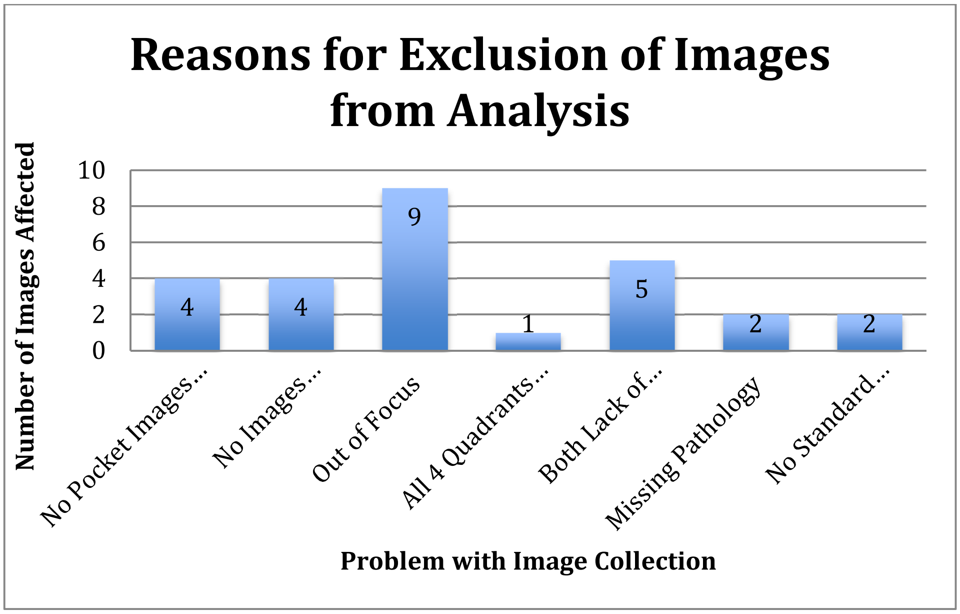


Figure 9: Reasons images were not included in analysis and fell into "Not Useable" or "Low" categories for 100 patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

For the analysis, 27 image pairs were deemed not interpretable and excluded from the analysis (Figure 9). The primary cause for low image quality was lack of focus in the Generation Pocket colposcope images. The Generation 3 Pocket colposcope has a set working distance of 30mm and it takes a couple of seconds to capture the images, so the physician needs to find the exact working distance where the cervix appears in focus on the computer screen and hold that position while images are captured. Some motion artifact is anticipated with the physician holding the Pocket colposcope, so three images are captured sequentially to reduce the effect of a blurry image being captured. Despite this precaution, out of focus images was still the primary cause of low-quality images captured. Another factor that led to out of focus image capture occurred in one patient where the speculum could not open wide enough to fully insert the Pocket colposcope, and so the probe could not reach the required working distance.

The primary factor contributing to a lack of full quadrant visualization was the cervix being at an angle. In some women cervix is pointed at an angle and so adjusting the Pocket or standard-of-care colposcope to be at an angle confined by the vaginal canal is a challenge. In extreme cases, the colposcopes could not be maneuvered enough to capture the full front face of the cervix.

In four patients images were not collected with either the Pocket or standard-of-care colposcope due to heavy menstruation. If a woman was bleeding to heavily to obtain a clear visual of her cervix, she was told to return in two-weeks for another colposcopy exam. Another four patient images were deemed unusable because Pocket images were not captured due to software glitches. In two patients, standard-of-care images were not captured with Lugol’s iodine and so fully paired images could not be compiled for that patients.

From the 73 interpretable image pairs, 71 had their associated patient pathology available. At La Liga Peruana de Lucha Contra el Cáncer, the pathology information for a patient only becomes available when the patient returns to the clinic and pays for their results. Two of the patients enrolled in the study did not return to obtain their pathology results, and so a final of 71 interpretable image pairs with matching pathology were included in the analysis. Figure 10 shows the breakdown of number patients enrolled in the study and number of patients included in the analysis.

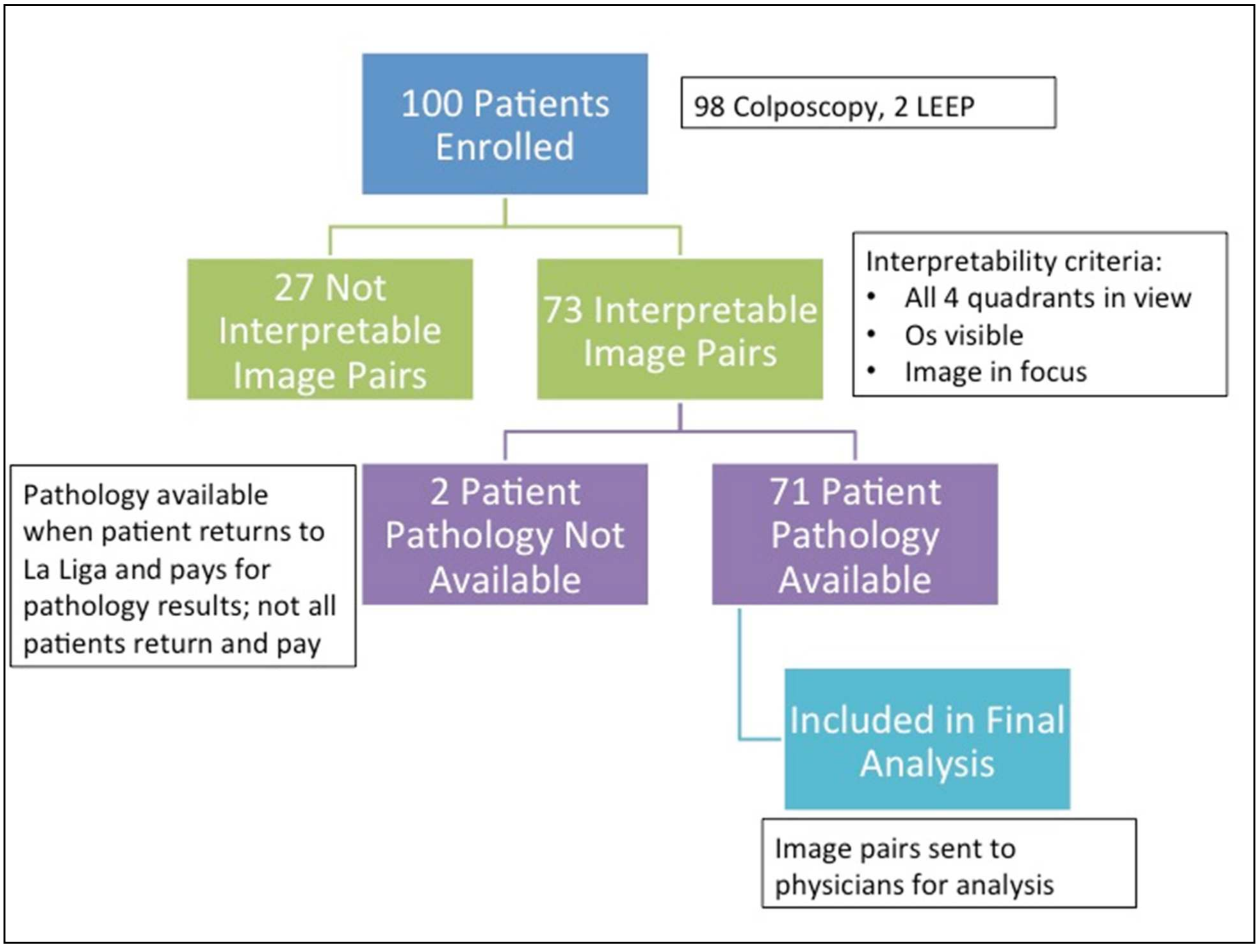


Figure 10: Enrollment tree showing the breakdown of the 100 patients enrolled to the 71 image pairs included in the analysis, for the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

2.4 Measures

This study is based on the technical and clinical questions answered by physicians in the REDcap electronic survey as they evaluated the images of cervices. The survey (Appendix A) includes the image identifier code, technical questions about the image quality, and clinical questions evaluating the properties of the cervix necessary to make a colposcopic diagnosis. Technical questions include field of view, magnification, and focus of the image.

Clinical questions include the VIA diagnosis, whether or not the external os and or transformation zone could be seen, qualitative assessments of the four main components considered when diagnosing a cervix: acetowhitening, surface characteristics, vascularization, and iodine uptake, number of lesions visible, and overall diagnosis of the cervical image. The physicians were also asked whether or not the image provided enough information to make a confident diagnosis.

Precancerous cervical lesions are classified based on the cervical intraepithelial neoplasia (CIN). In the physician's evaluation of the cervix, they gave a diagnosis of Normal, CIN0, CIN1, CIN2, CIN3, or cancer. The diagnosis of CIN0 is sometimes given for a woman who is HPV positive but has a normal cervix free of dysplasia. CIN1-3 refers to the grade of precancerous lesion, and beyond CIN3 is classified as cancer. The grading of precancerous and cancerous lesions can also be divided into low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL). Table 1 shows this re-classification of the CIN gradings, where LSIL includes CIN1 and HSIL includes CIN2+.

Table 1: Classification of image and pathology results into normal, LSIL, and HSIL

	Normal	**LSIL**	**HSIL**
Physician evaluation of the cervix	Normal CIN0	CIN1	CIN2 CIN3

[Normal, CIN0, CIN1, CIN2, CIN3, or Cancer]			Cancer
Pathology Results interpreted at La Liga Contra el Cancer [Normal, CIN1, CIN2, CIN3, Invasive Cancer, Cervicitis, Condyloma, No Biopsy]	Normal Cervicitis Condyloma No Biopsy	CIN1	CIN2 CIN3 Invasive Cancer

Figure 11 demonstrates the difference among normal, LSIL, and HSIL lesions for paired images of the cervix captured with the Generation 3 Pocket and Goldway colposcopes after using acetic acid staining.

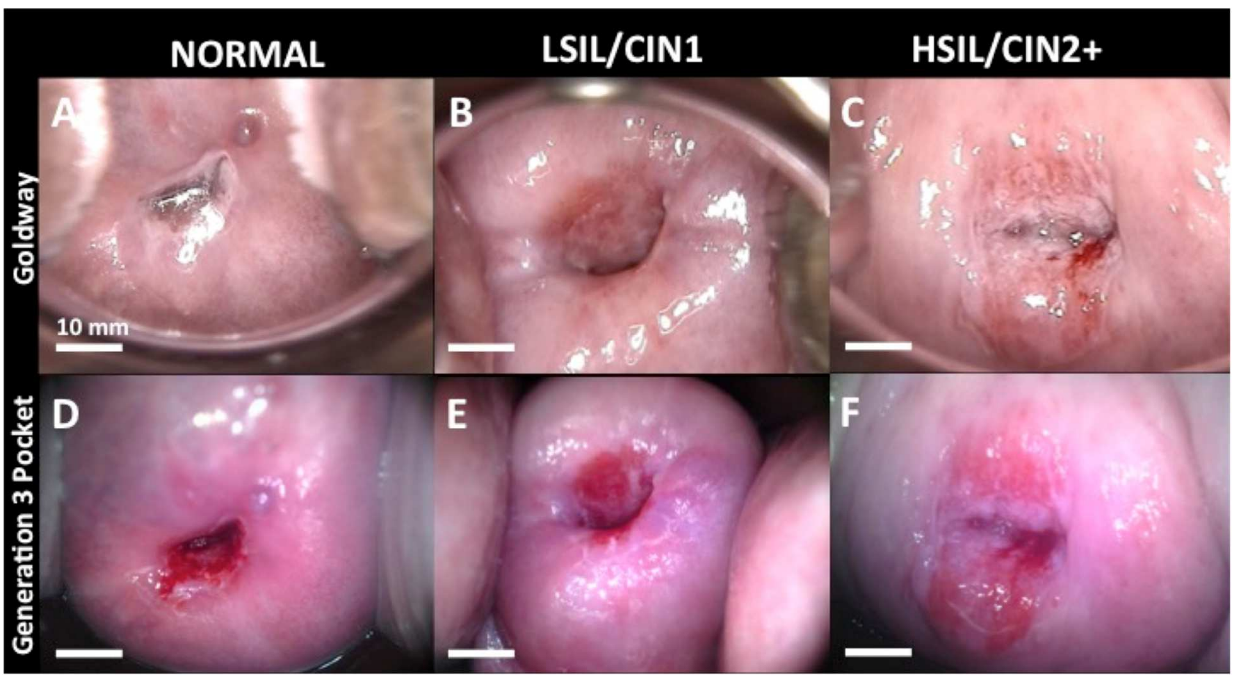


Figure 11: Representative acetowhitening concordant images captured with Goldway SLC-2000B and Pocket colposcope with external LEDs and external box at 35mm working distance, the scale bar is 10mm.

Pathology confirmed diagnosis were Normal (AD), LSIL/CIN1 (BE), and LSIL/CIN2+ (CF). In the normal panel (AD) note the distinct lack of aceto-whitening in the transformation zone. In the low-grade panel (BE) note the small white lesion. In the high-grade panel (CF) note the significant aceto-whitening indicating a 360-degree lesion outside the transformation zone.

Figure 12 demonstrates the difference in normal, LSIL, and HSIL lesions for paired images of the cervix captured with the Generation 3 Pocket and Goldway colposcopes using Lugol's iodine.

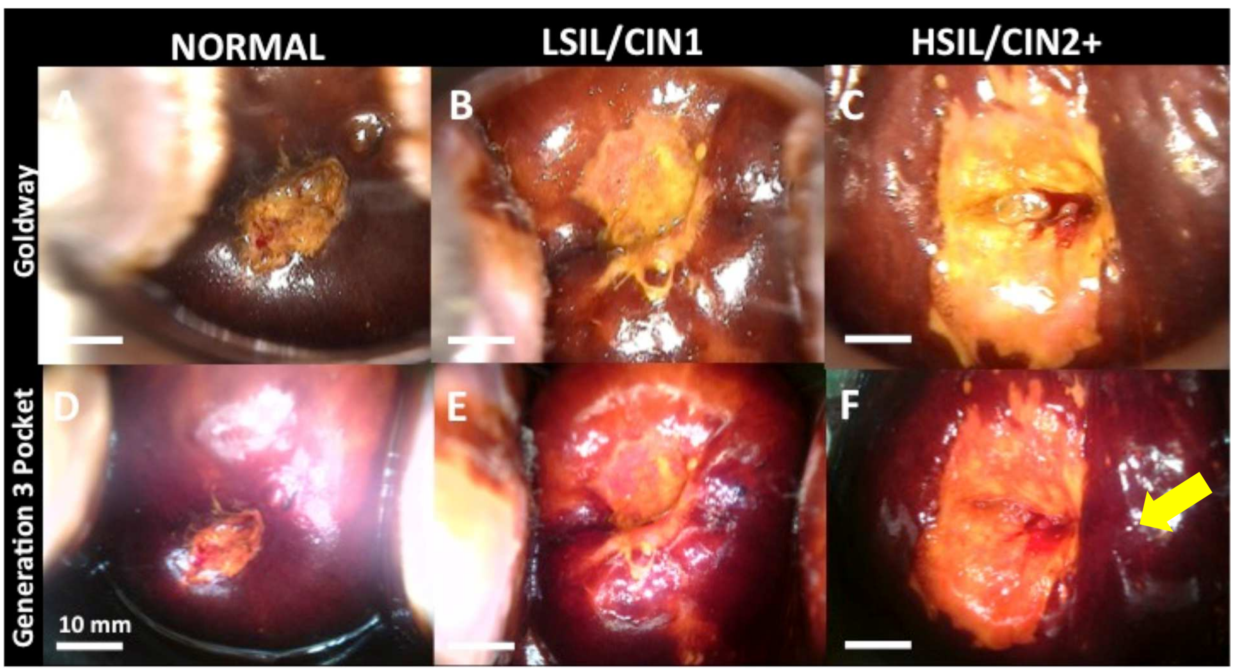


Figure 12: Representative Lugol's Iodine concordant images captured with Goldway SLC-2000B and Pocket Colposcope with external LEDs and external box at 35 mm working distance, the scale bars ate 10mm.

Pathology confirmed diagnosis were Normal (AD), LSIL/CIN1 (BE), and LSIL/CIN2+ (CF). In the normal panel (AD) note the distinct lack of staining in the transformation zone, which presents as the yellowing centered around the os. Note the distinct brown positive staining in the glycogen outside of the transformation zone. In the low-grade panel (BE) note the small lesion stained yellow surrounded by the dark brown staining. In the high-grade panel (CF) note the broad lack of staining indicating a 360-degree lesion outside the transformation zone.

2.5 Data Management

Paired patient images were captured in the cervix clinic at La Liga Peruana de Lucha Contra el Cáncer, and transferred to REDCap using the data management plan highlighted in Figure 13. All of the patient images were labeled with a study identification code in order to protect patient confidentiality. Images captured with the Pocket colposcope were saved onto a secure clinical laptop in Lima, and images captured with the Goldway colposcope were automatically uploaded to the patient's electronic health record. For patient data that was collected and had to be accessed remotely, the software TeamViewer was used to access the clinical laptop in Lima. By remotely accessing the clinical laptop, the research team at Duke University was able to access the patient electronic records to obtain Goldway colposcope images and pathology information, in addition to transferring the Pocket colposcope images saved on the laptop. The clinical laptop in Peru also automatically uploaded images to a secure Duke Dropbox site.

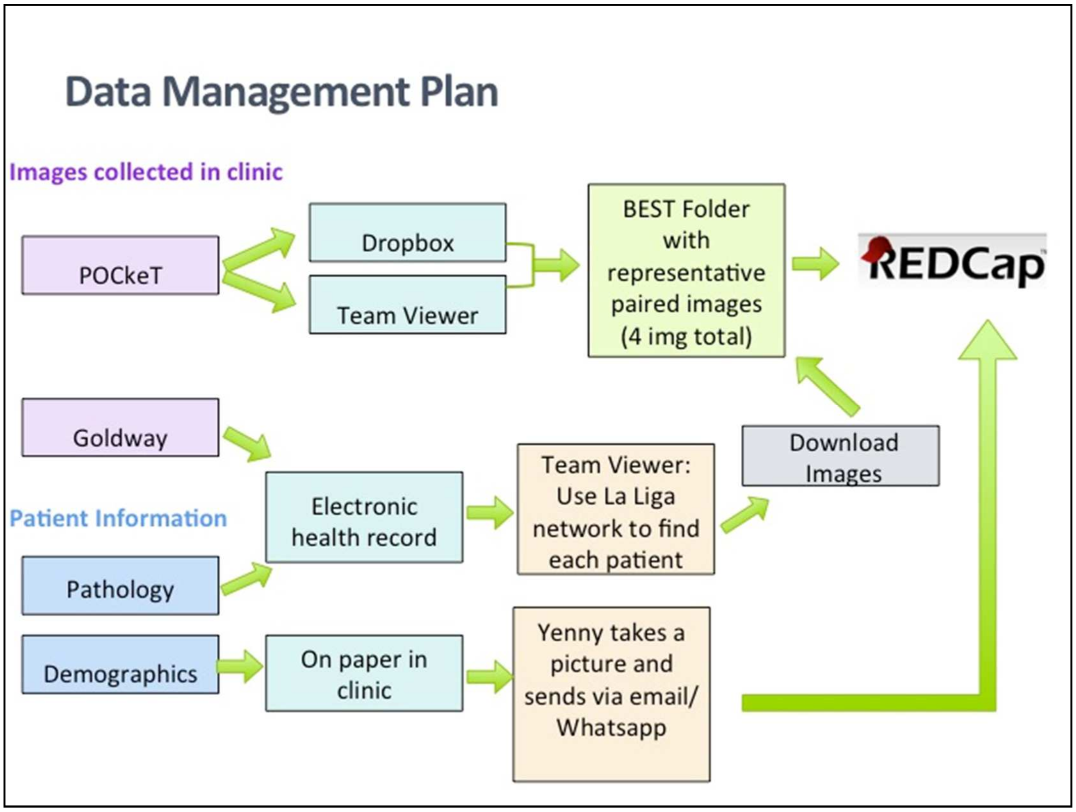


Figure 13: Data Management Plan - to collect and manage the patient images, pathology, and survey responses for patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer, where paired images were captured with acetowhitening and Lugol's iodine.

2.6 Data Analysis

The 71 interpretable pairs of images with associated pathology were blinded by device, randomized with a unique identification code, and grouped into seven sets of images panels. Electronic surveys (Appendix A) and fully de-identified cervix image panels were sent via email to three physicians affiliated with Duke University. The physician responses were matched to the image and device during the analysis using a master key. Images were collected and shared under Duke University Medical IRB approved protocol Pro00052865. Electronic surveys were completed using a secure link, and automatically saved into the data tool Research Electronic Data Capture (REDCap)[25] hosted at Duke University. REDCap is a secure web-based application that provides tools for data collection and management. From REDCap the data was exported for analysis using Stata SE 14.0 [26].

All of the data from the hard copies of the patient questionnaires were entered manually into REDCap so the information could be aggregated and analyzed in Stata. Data entry was verified by checking the questionnaires with the REDCap database output. The patient responses to the questionnaire were summarized for all 100 women enrolled in the study.

2.6.1 Concordance of Overall Diagnosis

To examine concordance between the Generation 3 Pocket colposcope and Goldway standard-of-care colposcopes was evaluated with two measures. First, the physician diagnoses of the paired images were compared for level of agreement using an unweighted kappa statistic.

The level of agreement is calculated using the following equations [27]:

$$\kappa = \frac{n_a - n_\varepsilon}{n - n_\varepsilon}$$

κ = Cohen's kappa

n = number of subjects

n_a = number of agreements

n_ε = number of agreements due to chance

The physicians provided a diagnosis of Normal, CIN 0, CIN1, CIN2, CIN3, or Cancer for each cervix image. The level of agreement between the diagnosis from the Pocket image and Goldway image were calculated by grouping the diagnoses in three ways. The levels of agreement were calculated between the Pocket and Goldway colposcopes for: 1) normal, LSIL, HSIL 2) normal vs. abnormal (LSIL, HSIL) and 3) non-HSIL (normal, LSIL) vs. HSIL.

By classifying the evaluation of the cervix as normal and abnormal (Table 2), the results could be interpreted like a VIA positive or VIA negative evaluation, which is the distinction between whether or not a woman needs a biopsy to explore cervical abnormalities. VIA positive is equivalent to an abnormal classification where a woman would require a biopsy to determine if the abnormalities on her cervix are precancerous or cancerous lesions. VIA negative is equivalent to a normal classification where a woman would not require a biopsy because there are no abnormalities on her cervix despite abnormal Pap smear results.

The physician diagnoses of the cervical images were also compared to the actual pathology confirmed diagnosis provided by the clinic, given as: Normal, Cervicitis, Condyloma, No Biopsy, CIN1, CIN2, CIN3, or Invasive Cancer. These pathology diagnoses were also classified as LSIL/HSIL (Table 1) and abnormal/normal (Table 2).

Table 2: Classification of image, pathology results, and RCI scores into Normal and Abnormal

	Normal	**Abnormal**
Physician evaluation of the cervix [Normal, CIN0, CIN1, CIN2, CIN3, or Cancer]	Normal CIN0	CIN1 CIN2 CIN3 Cancer
Pathology Results interpreted at La Liga Contra el Cancer [Normal, CIN1, CIN2, CIN3, Invasive Cancer, Cervicitis, Condyloma, No Biopsy]	Normal Cervicitis Condyloma No Biopsy	CIN1 CIN2 CIN3 Invasive Cancer
Reid Colposcopic Index Score [Qualitative characteristics of the cervix received quantitative scores based on the Reid Index]	0-2	3-8

2.6.2 Concordance of Reid Colposcopic Index Scores

The second method of concordance analysis was based on the Reid Colposcopic Index (RCI)[28]. The RCI is the WHO-recommended scoring system for evaluating precancerous and cancerous cervical lesions. In theory, the RCI score is used to determine the overall diagnosis and the clinical interpretation would be the same as the

RCI score indicates. However, due to the subjective nature of colposcopy different physicians use the RCI scoring system differently. In addition, exploring the RCI allows further examination of the components to a colposcopic diagnosis to determine what about the physicians' interpretations might have differed.

In the electronic surveys, the physicians completely reviewed the cervical image and provided their qualitative description of the cervix for each of the four categories: color, lesion margin, vascularization, and iodine uptake. The RCI scores were calculated based on the physician responses by converting the qualitative response to the associated quantitative value of 0-2 for each category (Table 3). All four categories were added together to get a total RCI score for each image, which ranges from 0-8. A kappa statistic was used to determine the level of agreement between the RCI scores for the paired Goldway and Pocket images. Scores that match exactly count towards the percent agreement, although individual categories may differ. Table 4 shows the predicted histology or diagnosis given the total RCI score calculated from summing the point values across the four categories. The level of agreement was calculated by comparing raw RCI scores, in addition to grouping the RCI scores into normal vs. abnormal categories (Table 2).

Table 3: The World Health Organization modified Reid Colposcopic Index (RCI) for grading and diagnosis of precancerous and cancerous cervical lesions The colposcopic grading is performed with 5% aqueous acetic acid and Lugol's iodine solution [9]

Colposcopic Diagnosis Categories	Zero Points	One Point	Two Points
Color of Aceto Whitening	Transparent, pure white	Grey/white, shiny surface, semi-opaque	Dull, fully opaque, oyster white, grey
Lesion Margin	Flat, indistinct, feathered, scalloped	Smooth	Rolled, peeled
Vascularization	Vessels – fine punctuation/mosaicism	No Vessels	Vessels – coarse punctuation/mosaicism
Iodine Uptake	Positive iodine uptake: Chestnut-colored mahogany	Partial iodine uptake: Mottled, marbled	Negative iodine uptake: Yellow staining

Table 4: Prediction of histologic diagnosis using the Reid Colposcopic Index score

RCI (overall score)	Histology
0-2	Likely to be CIN1
3-4	Overlapping lesion: likely to be CIN1 or CIN2
5-8	Likely to be CIN2-3

To explore the similarities and differences between the RCI scores for each of the four categories, a kappa statistic was also used to compare the individual category scores for the Goldway and Pocket images for each physician. The RCI scores for each category were split into normal and abnormal by groupings where abnormal was a total score of 3 or more, and a normal RCI score was a total of 2 or less (Table 2).

2.6.3 Secondary Measure

The secondary measures for concordance were: the sensitivity, specificity, positive predictive value, and negative predictive value for the Generation 3 Pocket colposcope compared to pathology and Goldway compared to pathology. The clinical pathology was used as the standard and the physician-evaluated diagnosis of the image was the comparative reference.

Sensitivity and specificity were calculated using the following equations:

$$Sensitivity = \frac{a}{a+c} \qquad Specificity = \frac{d}{b+d}$$

		Pathology		
		Normal	Abnormal	Total
Physician Evaluated Diagnosis of Image (Generation 3 Pocket or Goldway)	Normal	a	b	a+b
	Abnormal	c	d	c+d
	Total	a+c	b+d	a+b+c+d

The positive (PPV) and negative predictive (NPV) values were calculated using the following equations:

$$PPV = \frac{TP}{TP+FP} \text{ x } 100\%$$

$$NPV = \frac{TN}{FN+TN}\ x\ 100\%$$

		True Values (Pathology)	
		Abnormal	Normal
Predicted Values (Physician Evaluated Diagnosis of Image)	Abnormal	True Positive (TP)	False Negative (FN)
	Normal	False Positive (FP)	True Negative (TN)
		TP+FP	FN+TN

3. Results

3.1 Participant Demographics

This section summarizes the demographic information for the 100 patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer in Lima, Peru. Patients ranged in age from 20-67 years old, with the mean age being 37.96 ± 10.94 years old. The average height and weight were 1.57 ± 0.064 m and 62.73± 10.21 kg respectively. All of the patients enrolled had an abnormal Pap smear test and only 12% had HPV testing done. The majority of women were pre-menopausal (90%) and 61% had one or more children. About half of the patients enrolled had a family history of cancer, and the most commonly noted type of familial cancer was cervical (Table 5).

About half of the patients enrolled (49%) had a family history of cancer (Table 6), and the most common form of familial cancer was cervical cancer (Figure 14).

Table 5: Patient Demographics for 100 patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer

Gen3 | n=100		
Pap Test	Normal	0 (0%)
	Abnormal	100 (100%)
Procedure	Colposcopy	98 (98%)
	LEEP	2 (2%)
Age	Mean ± SD	37.96 ± 10.94 years
	Range	20-67 years
Menopausal Status	Pre	90 (90%)
	Post	10 (10%)
Oral Contraceptives	Yes	11 (11%)
	No	89 (89%)
HIV Status	Positive	0 (0%)
	Negative	43 (43%)
	Not Available	57 (57%)
Neo-Adjuvant Therapy	Yes	0 (0%)
	No	100 (100%)
HPV Status	Positive	5 (5%)
	Negative	7 (7%)
	Not Available	88 (88%)
Parity	0	39 (39%)
	1	25 (25%)
	2	18 (18%)
	3+	18 (18%)
Currently taking medication	Yes	18 (18%)
	No	82 (82%)
Country of Residence	Peru	100 (100%)
Weight	Mean ± SD (n=98)	62.73 ± 10.21 kg
	Range	37-95 kg
	Not Available	2 (2%)
Height	Mean ± SD (n=98)	1.57 ± 0.064 m
	Range	1.40-1.71 m
	Not Available	2 (2%)
Personal History of Cancer	Yes	12 (12%)
	No	88 (88%)

Table 6: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer were asked about their Family History of Cancer as part of the oral questionnaire. This table shows the frequency of cancer in their family.

Family History of Cancer (n=100)	# of patients with relatives who have cancer (%)
No Cancer	51 (51%)
Cancer	49 (49%)
1 family member	22 (22%)
2 family members	23 (23%)
3+ family members	4 (4%)

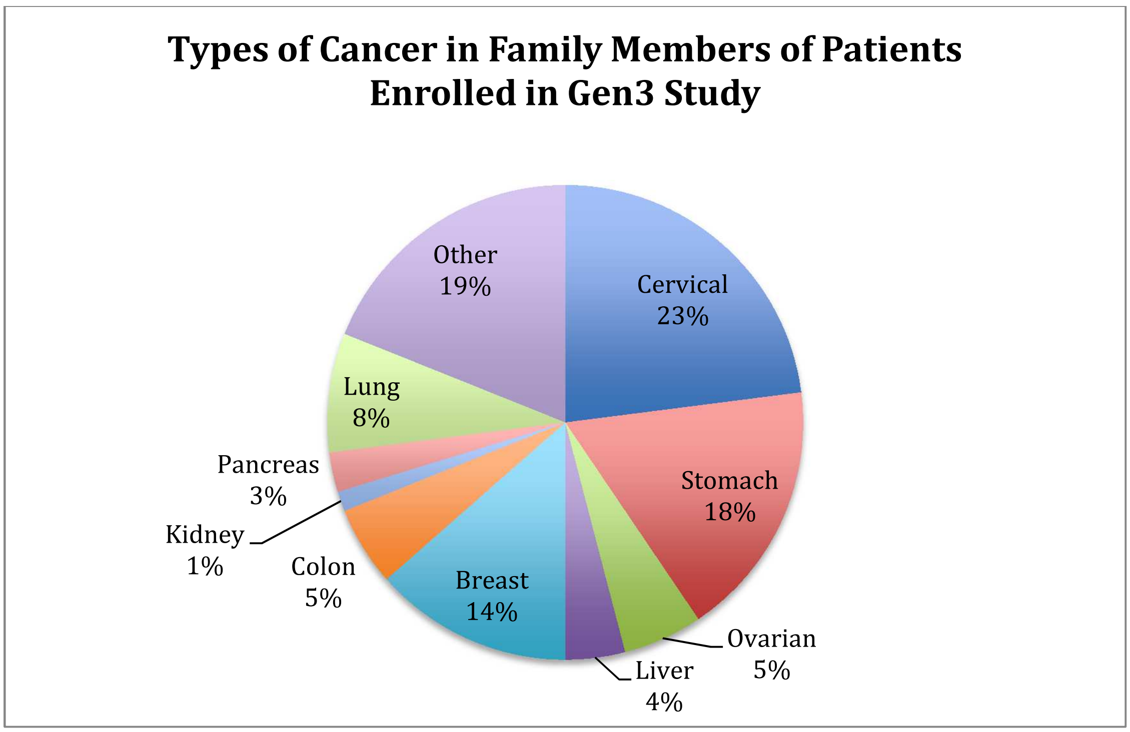


Figure 14: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer were asked about their family history of cancer as part of the oral questionnaire. This pie chart shows the breakdown of types of cancer in the families of the patients enrolled in the study.

Table 7 shows a summary of the pathology for the 100 patients enrolled in the study and the subset of 73 patients with interpretable image pairs to be included in the analysis. The percent breakdown for the pathology grading in the subset of 73 interpretable image pairs reflects the percent breakdown of the pathology grading in the full 100 patient set. This means that a complete representation of the different stages of precancerous and cancerous lesions were included in the final analysis, even though not all of the patient information was used.

Table 7: This table summarizes the clinical pathology for the patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer. Results are based on laboratory analysis of cervical biopsy specimens. Patients who did not receive a biopsy are considered to have normal pathology.

Total Pathology (n=100)	Normal	45 (45%)
	CIN1	32 (32%)
	CIN2	6 (6%)
	CIN3	4 (4%)
	Invasive Cancer	7 (7%)
	Not Available	6 (6%)
Pathology for Interpretable Image Pairs (n=73)	Normal	31 (42.47%)
	CIN1	26 (35.62%)
	CIN2	4 (5.48%)
	CIN3	4 (5.48%)
	Invasive Cancer	6 (8.22%)
	Not Available	2 (2.74%)

3.2 Colposcopy Concordance

3.2.1 Concordance of Diagnosis

This section summarizes the concordance statistics for the Generation 3 Pocket colpocope compared to the standard-of-care Goldway SLC-2000. The primary outcome measure was level of agreement. The level of agreement between the colposcopes was assessed by 1) overall diagnosis (Figure 15) and 2) Reid Colposcopic Index Score (Figure 16) for all physicians combined. The fully stratified results by physician are reported in Appendix D-H. The average level of agreement from both methods for all physicians combined was 78.04% (Figure 17).

When calculating the percent agreement for the overall diagnosis, the highest levels of agreements were when the diagnoses were grouped as normal vs. abnormal (LSIL, HSIL) (Table 10). Figure 12 shows the trends for each physician, in addition to the overall combined physician result for each of the three comparisons done with normal vs. abnormal. For the Pocket vs. Goldway colposcopes the level of agreement was 83.78% with a kappa statistic of 0.5786 and significant p-value (<0.05) for all physicians combined. The level of agreement for Pocket compared to pathology was 64.40% with a kappa statistic of 0.2531 for all physicians combined and the Goldway vs. pathology had a level of agreement of 68.2% with a kappa of 0.3184 for all physicians combined. All three physicians showed the same trends with their individual scores (Appendix D).

When the diagnoses were grouped as non-HSIL (normal, LSIL) vs. HSIL (Table 11), the levels of agreement demonstrated the same trend although the levels of agreement were lower for all three comparisons. The Pocket vs. Goldway colposcopes had a 75.68% level of agreement with a kappa statistic of 0.5116, Pocket vs. pathology had a level of agreement of 62.30% with a kappa of 0.2229, and Goldway vs. pathology had a level of agreement of 60.10% with a kappa of 0.1674 for all physicians combined.

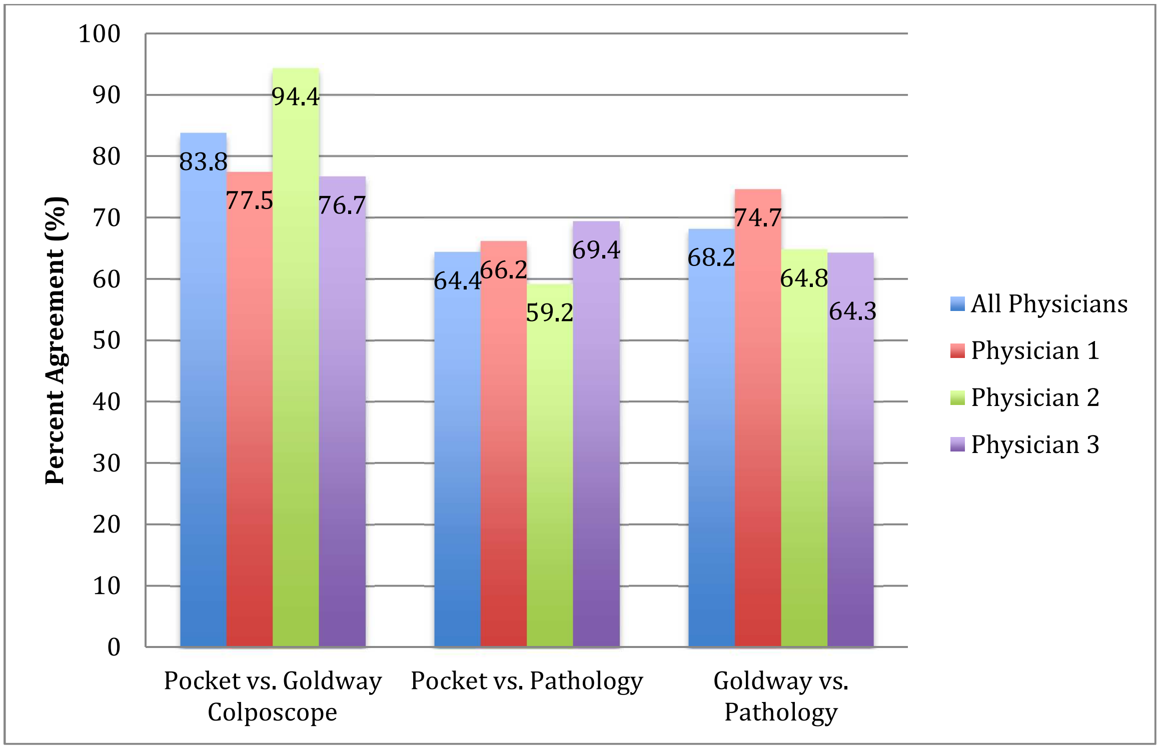
Examining the diagnoses as normal, LSIL, and HSIL demonstrated the same trend with the lowest percentages of agreement (Table 12). The level of agreement for Pocket vs. Goldway was 64.32% with a kappa statistic of 0.4430, Pocket vs. pathology was 45.03% with a kappa statistic of 0.1948, and Goldway vs. pathology was 45.45% with a kappa statistic of 0.2054 for all physicians combined.

The Reid Colposcopic Index comparison demonstrated high levels of agreement between the Pocket and Goldway colposcopes. In Table 13, the RCI scores were compared as normal (0-2) and abnormal (3-8) and had higher levels of agreement then the colposcopes compared in Table 14 where the RCI scores were not grouped. For all physicians combined, calculating the level of agreement in RCI scores between the Pocket and Goldway colposcope was 72.30% with a kappa statistic of 0.4366. The range of physician responses was relatively narrow (67.61-77.46%). When the RCI scores were not grouped, the level of agreement for all physicians was 59.62% with a kappa statistic of 0.3691.

The components of the RCI scores were also compared between devices for level of agreement (Table 15). Color, lesion margin, and iodine uptake had similar levels of agreement with 73.56% kappa 0.4721, 72.17% kappa 0.3752, and 73.11% kappa 0.5694 respectively for all physicians combined. The lowest component was vascularization with a level of agreement of 58.49% with a kappa of 0.3429.

The correlation between RCI score and diagnoses were also explored for level of agreement (Table 16). When the RCI score using the Pocket device was compared to the physician's diagnosis of the image, the level of agreement was 86.39% with a kappa statistic of 0.7005, although when the RCI score for Pocket was compared to the pathology the level of agreement was only 54.93% with a kappa of 0.0861. The RCI score from the Goldway colposcope showed a similar trend, with the level of agreement between the RCI score and the physician diagnosis being 81.31% with a kappa of 0.5861 and RCI score compared to the pathology with a level of agreement of 58.22% with a kappa of 0.1476.

Figure 14 shows a summary of the levels of agreement for the overall diagnosis and RCI score analyses, and an average level of agreement between the two methods for demonstrating concordance between the Pocket and Goldway colposcopes. For all physicians combined, the average level of agreement between the two methods is 78.04% between the Pocket and Goldway colposcopes.



All Physicians	Pocket vs. Goldway	Pocket vs. Pathology	Goldway vs. Pathology
Kappa	0.5786	0.2531	0.3184

Figure 15: Concordance between Generation 3 Pocket and Goldway Colposcope: Diagnosis Comparison, The level of agreement between systems when using the VIA+ diagnostic cut-off (LSIL or HSIL vs. normal) with acetic acid and Lugol's Iodine was 83.78% with a kappa of 0.5786 and p-value of <0.0000 indicate strong concordance from 3 independent blinded reviewers of n=71 randomized image pairs (blue bar). Individual clinician results are coded in red, green, and purple bars. The level of concordance when compared to gold standard histopathology was similar for both systems (64.4% vs 68.18%) and is consistent with prior reports of the performance of colposcopy with moderate level of agreement kappa statistic of 0.2531 and 0.3184 for the Pocket Colposcope and Goldway standard-of-care system, respectively.

Table 8: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with a kappa statistic for normal vs. abnormal (LSIL, HSIL) precancerous and cancerous cervical lesions.

All 3 Physicians Combined

Generation 3 (n=213)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	83.78	0.5786	<0.0000
Pocket Colposcope vs. Pathology	64.40	0.2531	0.0001
Goldway vs. Pathology	68.18	0.3184	<0.0000

Table 9: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with kappa statistic for non-HSIL (normal, LSIL) vs. HSIL precancerous and cancerous cervical lesions.

All 3 Physicians Combined

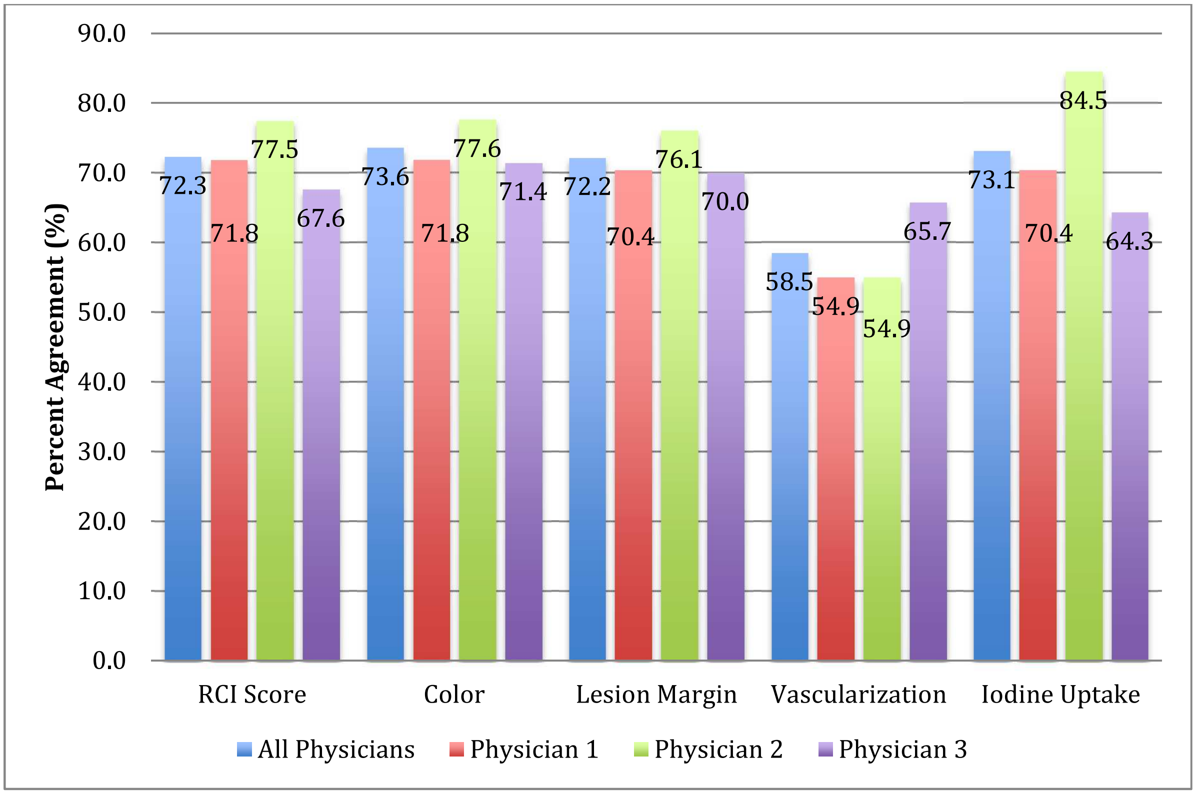
Generation 3 (n=213)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	75.68	0.5116	<0.0000
Pocket Colposcope vs. Pathology	62.30	0.2229	0.0002
Goldway vs. Pathology	60.10	0.1674	0.0041

Table 10: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with kappa statistic for normal, LSIL, and HSIL precancerous and cancerous cervical lesions.

All 3 Physicians Combined

Generation 3 (n=213)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	64.32	0.4430	<0.0000
Pocket Colposcope vs. Pathology	45.03	0.1948	<0.0000
Goldway vs. Pathology	45.45	0.2054	<0.0000

3.2.2 Concordance of Reid Colposcopic Index Scores



All Physicians: Pocket vs. Goldway RCI Scores	Total RCI Score	Color	Lesion Margin	Vascularization	IodineUptake
Kappa	0.4366	0.4721	0.3752	0.3429	0.5694
P-Values	<0.0000	<0.0000	<0.0000	<0.0000	<0.0000

Figure 16: Concordance between Generation 3 Pocket and Goldway Colposcope: RCI Comparison, Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. RCI scores were compared as normal (0-2) and abnormal (3-8). The percent agreement of total RCI scores was calculated using a kappa statistic for paired images between the Generation 3 pocket and Goldway standard-of-care colposcopes.

Table 11: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. RCI scores were compared as normal (0-2) and abnormal (3-8). The percent agreement of total RCI scores was calculated using a kappa statistic for paired images between the Generation 3 Pocket and Goldway colposcopes.

Generation 3 (n=71) RCI Pocket vs. RCI Goldway	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
All 3 Physicians Combined	72.30	0.4366	<0.0000
Physician 1	71.83	0.3831	0.0006
Physician 2	77.46	0.3238	0.0032
Physician 3	67.61	0.1698	0.0696

Table 12: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. The percent agreement of total RCI scores was calculated using a kappa statistic for paired images between the Generation 3 Pocket and Goldway colposcopes.

Generation 3 (n=71) RCI Pocket vs. RCI Goldway	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
All 3 Physicians Combined	59.62	0.3691	<0.0000
Physician 1	54.93	0.311	0.0001
Physician 2	57.75	0.341	<0.0000
Physician 3	66.20	0.153	0.0765

Table 13: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. The percent agreement of the RCI component scores were calculated using a kappa statistic for paired images between the Gen3 Pocket and Goldway colposcopes.

All Physicians

Generation 3 (n=71) Pocket Score vs. Goldway Score	**Level of Agreement (%)**	**Agreement Coefficient (κ)**	**p-value**
Color	73.56	0.4721	<0.0000
Lesion Margin	72.17	0.3752	<0.0000
Vascularization	58.49	0.3429	<0.0000
Iodine	73.11	0.5694	<0.0000

Table 14: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. The percent agreement of the RCI scores for the Gen3 Pocket and Goldway colposcopes were compared to 1) the physician diagnosis and 2) the clinical pathology using a kappa statistic. RCI scores were grouped into normal (0-2) vs. abnormal (3-8), compared to the pathology of normal vs. abnormal (LSIL, HSIL), and physician diagnosis normal vs. abnormal (CIN1+).

All Physicians

Generation 3 (n=71)	**Level of Agreement (%)**	**Agreement Coefficient (κ)**	**p-value**
RCI Pocket vs. Pathology	54.93	0.0861	0.1045
RCI Goldway vs. Pathology	58.22	0.1476	0.0156
RCI Pocket vs. Physician Diagnosis	86.39	0.7005	<0.0000
RCI Goldway vs. Physician Diagnosis	81.31	0.5861	<0.0000

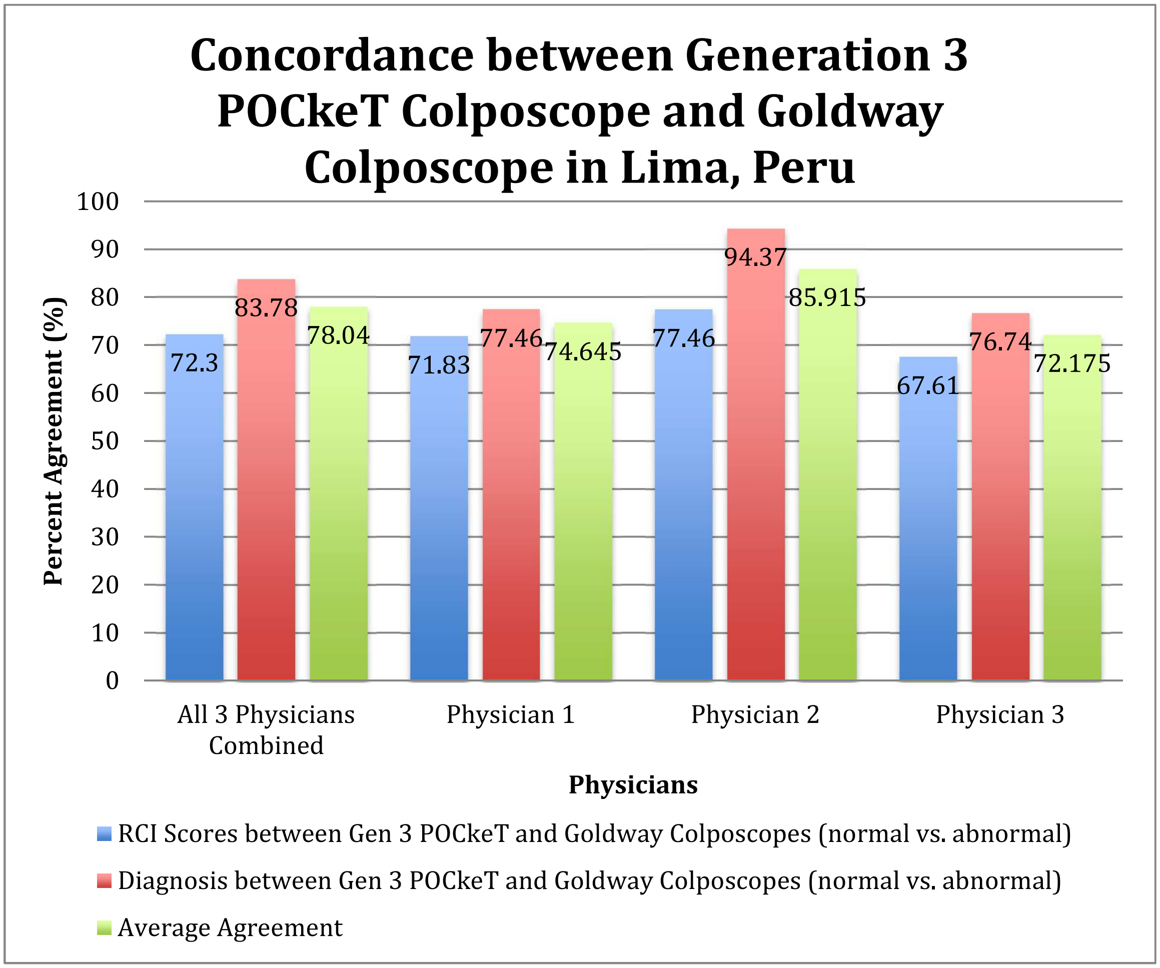


Figure 17: Comparing overall concordance between the Generation 3 Pocket colposcope and Goldway colposcope by comparing the RCI score percent agreement and the diagnosis percent agreement between the devices.

3.2.3 Secondary Measure: Accuracy of Colposcopy

The secondary outcome measure sensitivity, specificity, PPV, and NPV (Table 15) also demonstrated comparable performance between the Generation 3 Pocket and standard-of-care colposcope.

Table 15: The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for Generation 3 Pocket compared to pathology and standard-of-care Goldway colposcope to pathology when the pathology is grouped as normal vs. abnormal (LSIL, HSIL).

Generation 3 Pocket	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All 3 Physicians Combined	82.1	42.4	64.0	65.5
Physician 1	80.0	48.4	66.7	65.2
Physician 2	92.5	16.1	58.7	62.5
Physician 3	69.2	69.6	72.0	66.7

Goldway	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
All 3 Physicians Combined	82.5	45.7	66.4	66.7
Physician 1	87.5	58.1	72.9	78.3
Physician 2	97.5	22.6	61.9	87.5
Physician 3	78.1	45.8	65.8	61.1

4. Discussion

The purpose of this study was to explore whether the Generation 3 Point-of-Care Tampon (Pocket) colposcope was equivalent to the standard-of-care Goldway SLC-2000 digital colposcope in Lima, Peru at providing acetowhitening and Lugol's iodine images for colposcopy diagnoses of precancerous and cancerous lesions by OBGYN specialists who are trained in colposcopy.

4.1 Colposcope Concordance

Overall, the Generation 3 Pocket colposcope performed as well as the standard Goldway colposcope when used to identify precancerous and cancerous lesions using acidic acid and Lugol's iodine during colposcopy. Both the level of agreements calculated by examining the overall diagnosis and RCI scores demonstrated moderate agreement between the Generation 3 Pocket and Goldway colposcopes. The overall diagnosis had a level of agreement of 83.78% with a kappa coefficient of 0.5786 and the RCI score comparison had a level of agreement of 72.30% with a kappa coefficient of 0.4366, indicating moderate agreement (Appendix B, [29]). The average percent agreement for the two statistical methods of assessment for all three physicians combined was 78.04%. This means that the Generation 3 Pocket colposcope performs equally as well as the Goldway standard colposcope 78.04% of the time, which given the variable nature of colposcopy is pretty good.

To better understand the areas of discordance between the colposcopes, the component scores for color, lesion margin, vascularization, and iodine uptake, the RCI were examined for paired images between devices. Color, lesion margin, and iodine had similar percent levels of agreement ranging from 72.17-73.56% for all three physicians combined. The largest source of difference was due to the vascularization category, which had a combined percent agreement of 58.49%. Examining the individual physician responses showed the same trend, where vascularization had low agreement between the Generation 3 Pocket colposcope and Goldway colposcope RCI scores.

One commonly used colposcopy method to enhance the visualization of vascularization is colposcopy with a green filter. In the United States, standard colposcopy exams include imaging the cervix with both white and green light. At La Liga Peruana de Lucha Contra el Cáncer, green light colposcopy is available but rarely used by the physicians in making a diagnosis. The Generation 3 Pocket colposcope can capture images with both white and green light, but paired green images were not captured because green light is not part of the routine standard-of-care diagnosis in Peru. Hemoglobin in the blood absorbs more blue and green wavelengths, so when green light is used the blood-carrying vessels and vasculature appear black [30]. While the use of green filters in colposcopy and the importance of vascularization in contributing to the diagnosis of cervical abnormalities differ between countries, future iterations of the transvaginal digital colposcope should continue to provide green light for optional physician use.

Additionally, further research should be done to understand what is causing the remaining ~20% discordance between the Pocket colposcope and the standard colposcope. Since the images are based on interpretation of the physician at a given time, it would be interesting to explore whether the physician comes to the same conclusion about an image if the image is viewed at different time periods. For example, the physician could be shown the same image four separate times over the course of a year and the responses could be compared for differences.

4.1.1 Improved Concordance with Lugol's Iodine

In a previous study comparing the Pocket colposcope to the standard colposcope at the Duke University Medical Center in Durham, NC, the level of agreement between devices was an average of 70% when comparing the overall diagnosis made between paired images. This level of concordance was calculated using only white light images with acetic acid, or white light and green light images [31]. In the current study, the addition of screening with Lugol's iodine greatly increased the concordance between the devices by raising the percent agreement from an average of about 70% to an average of 83.78%. While the use of Lugol's iodine images improves the concordance between the Pocket colposcope and the standard colposcope, further research should be done to explore whether the use of Lugol's iodine improves the accuracy of the diagnosis.

4.2 Colposcopy and Pathology

Comparing the normal and abnormal Generation 3 Pocket and Goldway diagnoses to the pathology as a secondary outcome for concordance resulted in a high sensitivity and a low specificity, although there were some inter-physician differences that resulted in different numbers. The combined sensitivity for the three physicians was 82.1% and the specificity was 42.4%. A high sensitivity means that there were few false negative results and so few cases of abnormal cervical lesions were missed. The low specificity means that there was a relatively high false positive result, meaning that the physicians evaluated the cervix as abnormal when the pathology classification was normal. However, the specificity varied dramatically between physicians with the lowest specificity being Physician 2 with 33.7% and the highest specificity being Physician 3 with 86.8%. The difference in physician responses is expected due to the subjective nature of colposcopic diagnoses [32].

The sensitivity and specificity numbers were also calculated with a selection bias toward women with cervical abnormalities, because the population of women being evaluated have already been confirmed to have an abnormal Pap smear and therefor are more likely to have cervical abnormalities then the average woman across the entire at-risk population.

The secondary outcome measure for concordance of sensitivity, specificity, PPV, and NPV demonstrated comparable performance between the standard-of-care colposcope and Pocket colposcope. When the Goldway colposcope was compared to the clinically verified pathology groups as normal vs. abnormal, for all physicians combined the sensitivity was 82.5% and the specificity was 45.7%.

Comparing the physician evaluated diagnosis from the images captured with the Generation 3 Pocket colposcope and Goldway colposcope to the clinically verified pathology was equivalently discordant. When examining the overall diagnosis to the pathology for all physicians combined, the level of agreement was fair for both the Generation 3 Pocket colposcope, 64.40% agreement and 0.2531 kappa statistic, and Goldway colposcope, 68.18% with a kappa statistic of 0.3184. When the RCI scores were compared to the pathology, the level of agreement between the Generation 3 Pocket colposcope was 53.05% and the Goldway colposcope was 52.11%. By both measures, the colposcope performed similarly although their diagnoses of the cervical images matched the clinical pathology only a little more then half the time. Additionally, Physician 3 actually increased in accuracy when using the Pocket colposcope as opposed to the standard colposcope.

These results are not unexpected, because colposcopy by nature is a subjective form of diagnosis and can vary drastically between physicians. A population-based study with colposcopy and biopsy results for 2466 women showed the overall strength of agreement between colposcopy and histology was poor (K = 0.17) [33]. For this reason, colposcopy should be used as part of the screening and diagnosis of cervical cancer in conjunction with Pap smear tests, and confirmed by biopsy analysis when available. Colposcopy should not be used alone to diagnose the stage of precancerous or cancerous cervical lesion [12], but is a critical component to the screening and diagnosis process.

4.3 Other Findings

On the demographic questionnaires for each patient, one of the questions asked about their family history of cancer, noting how many family members had cancer and what types. Almost half (49%) of the patients enrolled in the study had one or more family members who had cancer, resulting in a total of 74 affiliated family members having experienced some type of cancer. Of the 74 family members, the most commonly cancer cited was cervical cancer accounting for 23% of the familial cancer burden. While the hereditary predisposition of developing cervical cancer or shared familial risk factors may be a factors to consider, these findings most likely indicate the prevalence of cervical cancer among Peruvian women.

4.4 Study Strengths and Limitations

One of the strength of this study lies in the randomizing and blinding of the paired cervical images before being evaluated by the physicians. By blinding the images by device, the physicians did not know which device was used to capture the image and could evaluate the cervical image based on the image itself without bias for or against one of the colposcopes. Using a new clinical device requires learning how to optimize the image capture in a different way, so the images captured at the beginning of the study are lower quality than the images captured at the end of the study. By randomizing the images, the physicians saw a mixture of images with a slight variation in quality so the evaluation could be fair across all images.

One major limitation in the analysis is the inherent flaw of the Reid Colposcopic Index. The Reid Colposcopic Index was implemented to create a uniform standard by which all colposcopists could evaluate a cervix for precancerous and cancerous lesions. The inherent flaw of the RCI is that it assumes that an abnormal Pap smear means there are abnormal precancerous or cancerous cells on the cervix, when in some cases an abnormal Pap smear can result in a normal visual inspection of the cervix. Due to this assumption, the RCI does not have the scoring capacity for normal visual inspections and the lowest RCI score possible of zero is an indicator for LSIL.

The RCI provides a universal standard for colposcopists to make a diagnosis, but the RCI needs to be improved. As indicated by the numbers, the level of agreement between the physician's RCI score agreeing with the diagnosis was lo, while the agreement between the physician's diagnosis with the clinically verified pathology was high. This means that the physicians are including or excluding other factors in their diagnosis of the cervix that are not being included in the RCI. The RCI should be adapted to better suit the elements of the cervix that the physicians are actually using to make a diagnosis.

Another limitation is that the images being evaluated by the physicians were static images, while real-time diagnoses are made with live video feed of the cervix. A study conducted in 2009 also used static images, but eventually found that there was no clinically significant different in using static vs. dynamic images to make a clinical diagnosis [34].

The largest flaw with colposcopy is that it is a subjective form of diagnosis and is mediocre at identifying the severity of the cervical abnormalities. In high-resource areas where women have regular access to laboratory equipment for pathology testing, this shortcoming is not a large issue because the clinical diagnosis is made by visual inspection in addition to laboratory testing of the biopsied sample. In low-resource settings, the accuracy of colposcopy becomes an issue because unnecessarily referring women for further screening and treatment based on high false positive results is a waste of limited time and resources. To improve colposcopy, one method that is being explored in the TOpS lab is the use of an algorithm to analyze a cervical image for abnormalities. By removing the human variability, the algorithm is able to more accurately identify the stage of precancerous or cancerous lesion.

4.5 Implications for Policy and Practice

The development of a low-cost, portable colposcope has the potential to dramatically increase access and availability of cervical cancer screenings. The portability of Pocket colposcope means it could be used as a point-of-care diagnostic tool in order to visually inspect the cervix in a mobile setting when a Pap smear test is being administered. Even if the Pap smear were abnormal, viewing a normal cervix would prevent the woman from being unnecessarily referred to a major health clinic for colposcopy. The efficiency of referrals for advanced screening and treatment would be limited to the women who are actually in need of biopsies and treatment for precancerous or cancerous lesions. Of the 100 patients enrolled in the study, 31 did not receive a biopsy, which means that if this technology had been available in conjunction with their Pap smear they would not have had to make the trip into the center of Lima for a second medical exam. Increasing the accessibility and efficiency of cervical cancer screenings is an essential component to reducing the high morbidity and mortality rates of cervical cancer in Peru and around the world.

5. Conclusion

In conclusion, the Generation 3 Pocket colposcope performed similarly to the standard Goldway colposcope at identifying precancerous and cancerous lesions in Lima, Peru when images were captured using acetic acid and Lugol's Iodine. These findings have the potential to increase access to colposcopy by providing a lower cost and much more portable system, that could potentially reduce the burden of cervical cancer morbidity and mortality in Peru and around the world. Colposcopy is a critical part of the screening, diagnosis, and early detection of precancerous and cancerous cervical lesions. To reduce the barriers to accessing care and increase follow-up for cervical abnormalities, this type of point-of-care diagnostic should continue to be developed and implemented as a means of reducing the morbidity and mortality of cervical cancer.

Appendix A

Electronic survey emailed to each physician. Physicians completed this survey for every image, resulting in a colposcopic diagnosis and qualitative descriptions of the precancerous or cancerous lesions.

Confidential

Page 1 of 2

Clinical Evalution Of Cervix

Please complete the survey below.

Thank you!

Reviewer: (Please Select from List)	◯ John Schmitt ◯ Lisa Muasher ◯ Peyton Taylor ◯ Olalo Oneko ◯ Gino Venegas ◯ Johanna Halfon ◯ J.S. Malliga ◯ Anthony Wanyoro ◯ Bariki Mchome ◯ Roopa Hariprasad ◯ Rose Kosgei ◯ Other
Name/Title:	__________________________
Image Letter: (Please select from list to match letter displayed on image)	◯ A ◯ B ◯ C ◯ D ◯ E ◯ F ◯ G ◯ H ◯ K ◯ L ◯ P ◯ Q ◯ R ◯ S ◯ T ◯ U ◯ V ◯ W ◯ X ◯ Y ◯ Z
Image Number: (Please enter number to match number displayed on image)	__________________________
What is the VIA diagnosis?	◯ Positive ◯ Negative ◯ Inconclusive
Field of view - How many of the four quadrants of the cervix can you see in a single view?	◯ 1 ◯ 2 ◯ 3 ◯ 4
Magnification - Does a single image / visual provide adequate magnification?	◯ Yes ◯ No
Is the image/visual in focus?	◯ Yes ◯ No
Can you see the os?	◯ Yes ◯ No
If present, can you see the transformation zone?	◯ Yes ◯ No ◯ NA
Can you see aceto-whitening?	◯ Yes ◯ No ◯ NA
If there are aceto-whitened sites, what is the opacity?	◯ transparent ◯ semi-opaque ◯ fully opaque ◯ NA
If there are aceto-whitened sites, what is the color?	◯ pure white ◯ grey white ◯ oyster grey ◯ NA

Surface shine - is the cervical surface shiny?	◯ intense shiny ◯ shiny ◯ dull ◯ NA
Lesion margin - describe the lesion margin	◯ flat/indistinct/feathered/scalloped ◯ smooth ◯ rolled/peeled ◯ NA
Vascularization - describe, if present	◯ yes vessels, fine punctuation/mosaicism ◯ no vessels ◯ yes vessels, coarse punctuation/mosaicism ◯ NA
Iodine Uptake	◯ chestnut-colored mahogany ◯ mottled, marbled ◯ yellow staining ◯ NA
How many lesions are visible?	______________________________
Please check the location of the lesion(s) on the shown clock face. The cervix, viewed as a circle, is divided into 12 segments denoted by 1-12 and separated into four quadrants denoted by dashed blue line for spatial reference.	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10 ☐ 11 ☐ 12 ☐ NA
What is your grading of this cervix?	◯ Normal ◯ CIN0 ◯ CIN1 ◯ CIN2 ◯ CIN3 ◯ Cancer
Did the image provide enough information to make a confident diagnosis?	◯ Yes ◯ No
Why or why not?	______________________________
Other Comments	______________________________

Appendix B [29]

Interpretation of Kappa

	Poor	Slight	Fair	Moderate	Substantial	Almost perfect
Kappa	0.0	.20	.40	.60	.80	1.0

Kappa	Agreement
< 0	Less than chance agreement
0.01–0.20	Slight agreement
0.21– 0.40	Fair agreement
0.41–0.60	Moderate agreement
0.61–0.80	Substantial agreement
0.81–0.99	Almost perfect agreement

Appendix C

Demographic survey given orally to participants who consented to be enrolled in the study.

Duke University Colposcopy Study ID #____________________________

Estudio de Colposcopia a Universidad de Duke

Patient Identification ***Identificación de la paciente***	**Identification #** ***Número de identificación:***	Age: *Edad*
Menopausal status ***Estado de menospausia***	Post- ☐ -o- Pre- ☐ If post, hormone replacement therapy? *En caso de post, está con terapia hormonal*? Yes/*Si* ☐ No ☐ If yes, length of time ____________ *En caso que sí, cuánto tiempo*	If post, surgical menopausal? *En caso que sí, la menospausia fue por cirugía?* Yes/*Si* ☐ No ☐
Oral Contraceptives ***Anticonceptivos orales***	Yes/*Si* ☐ No ☐	
HIV Status ***Estado de HIV***		
Neo-Adjuvant Therapy ***Terapia neo-adyuvante***	Length and Type of Therapy: *Duración y tipo de terapia:*	
HPV Test Result ***Resultados de exámen HPV***	Positive ☐ (Strain(s):) *Positivo (Cepa(s):)*	Negative ☐ *Negativo* Not available ☐ *No disponible*
Pregnancy (self-reported) ***Embarazo (auto-informada)***	Yes/*Si* ☐ No ☐	Parity: *Paridad:*
Current Medications ***Medicaciones actualmente tomando***		
Date of last menstruation ***Fecha de la última menstruación (regla)***	(M/D/Y) *(M/D/A)*	
County of residence ***País de residencia***		
Weight ***Peso:***		**Height** ***Altura:***
History of Cancer ***Antecedientes de cáncer***		
History of Cancer within Family ***Antecedentes familiares de cáncer***		

Appendix D

Table 16: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with a kappa statistic for normal vs. abnormal (LSIL, HSIL) precancerous and cancerous cervical lesions. (Table 10 breakdown)

Physician 1

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	77.46	0.86	<0.0000
Pocket Colposcope vs. Pathology	66.20	0.292	0.0056
Goldway vs. Pathology	74.65	0.470	<0.0000

Physician 2

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	94.37	0.718	<0.0000
Pocket Colposcope vs. Pathology	59.15	0.094	0.1270
Goldway vs. Pathology	64.79	0.219	0.0040

Physician 3

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	76.74	0.523	0.0002
Pocket Colposcope vs. Pathology	69.39	0.387	0.0034
Goldway vs. Pathology	64.29	0.247	0.0287

Appendix E

Table 17: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with kappa statistic for non-HSIL (normal, LSIL) vs. HSIL precancerous and cancerous cervical lesions. (Table 11 breakdown)

Physician 1

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	73.24	0.4580	<0.0000
Pocket Colposcope vs. Pathology	59.15	0.1647	0.0557
Goldway vs. Pathology	71.83	0.3340	0.0018

Physician 2

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	77.46	0.5470	<0.0000
Pocket Colposcope vs. Pathology	59.15	0.2120	0.0148
Goldway vs. Pathology	53.52	0.1033	0.1445

Physician 3

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	76.74	0.5376	0.0001
Pocket Colposcope vs. Pathology	71.43	0.3391	0.0067
Goldway vs. Pathology	53.57	0.0714	0.2685

Appendix F

Table 18: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. This table shows the concordance between Gen3 Pocket colposcope and Goldway standard-of-care colposcope at La Liga calculated with kappa statistic for normal, LSIL, and HSIL precancerous and cancerous cervical lesions. (Table 12 breakdown)

Physician 1

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	57.75	0.362	<0.0000
Pocket Colposcope vs. Pathology	45.07	0.192	0.0779
Goldway vs. Pathology	63.38	0.453	0.0821

Physician 2

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	71.83	0.512	<0.0000
Pocket Colposcope vs. Pathology	38.03	0.125	0.0359
Goldway vs. Pathology	33.80	0.066	0.1724

Physician 3

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Pocket vs. Goldway Colposcopes	62.79	0.4110	0.0001
Pocket Colposcope vs. Pathology	55.10	0.298	0.0014
Goldway vs. Pathology	37.50	0.081	0.1775

Appendix G

Table 19: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. The percent agreement of the RCI component scores were calculated using a kappa statistic for paired images between the Gen3 Pocket and Goldway colposcopes. (Table 15 breakdown)

Physician 1

Generation 3 (n=71) Pocket Score vs. Goldway Score	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Color	71.83	0.393	0.0005
Lesion Margin	70.42	0.368	0.0002
Vascularization	54.93	0.214	0.0063
Iodine	70.42	0.090	<0.0000

Physician 2

Generation 3 (n=71) Pocket Score vs. Goldway Score	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Color	77.61	0.559	<0.0000
Lesion Margin	76.06	0.433	<0.0000
Vascularization	54.93	0.331	<0.0000
Iodine	84.51	0.621	<0.0000

Physician 3

Generation 3 Pocket Score vs. Goldway Score	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
Color (n = 70)	71.43	-0.020	0.5738
Lesion Margin	70.00	0.266	0.0050
Vascularization	65.71	0.211	0.0128
Iodine	64.29	0.349	0.0001

Appendix H

Table 20: Patients enrolled in the Generation 3 Pocket colposcope study at La Liga Peruana de Lucha Contra el Cáncer had paired images captured with acetowhitening and Lugol's iodine. Total RCI scores were calculated for each image based on qualitative responses provided by the physicians in the survey they completed for each image evaluating the cervix for: color, lesion margin, vascularization, and iodine uptake. Each RCI component received a numerical value giving each image a total RCI score. The percent agreement of the RCI scores for the Gen3 Pocket and Goldway colposcopes were compared to 1) the physician diagnosis and 2) the clinical pathology using a kappa statistic. RCI scores were grouped into normal (0-2) vs. abnormal (3-8), compared to the pathology of normal vs. abnormal (LSIL, HSIL), and physician diagnosis normal vs. abnormal (CIN1+). (Table 16 breakdown)

Physician 1

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
RCI Pocket vs. Pathology	64.79	0.2656	0.0111
RCI Goldway vs. Pathology	73.24	0.4460	0.0001
RCI Pocket vs. Physician Diagnosis	98.59	0.9682	<0.0000
RCI Goldway vs. Physician Diagnosis	95.77	0.9067	<0.0000

Physician 2

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
RCI Pocket vs. Pathology	57.75	0.0882	0.1976
RCI Goldway vs. Pathology	63.38	0.2098	0.0215
RCI Pocket vs. Physician Diagnosis	90.14	0.6432	<0.0000
RCI Goldway vs. Physician Diagnosis	87.32	0.5413	<0.0000

Physician 3

Generation 3 (n=71)	Level of Agreement (%)	Agreement Coefficient (κ)	p-value
RCI Pocket vs. Pathology	42.25	-0.0762	0.8024
RCI Goldway vs. Pathology	38.03	-0.1824	0.9605
RCI Pocket vs. Physician Diagnosis	63.27	0.2723	0.0146
RCI Goldway vs. Physician Diagnosis	55.36	0.2170	0.0155

References

1. Levinson, K.L., et al., *The Peru Cervical Cancer Prevention Study (PERCAPS): the technology to make screening accessible.* Gynecologic oncology, 2013. **129**(2): p. 318-323.

2. *WHO-Human papillomavirus (HPV) and cervical cancer*. Vol. 6 SRC - GoogleScholar. 2015.

3. *GLOBOCAN (IARC), Cancer Fact Sheets: Cervical Cancer.* World Health Organization International Agency for Research on Cancer, 2012.

4. Bosch, F., et al., *The causal relation between human papillomavirus and cervical cancer.* Journal of clinical pathology, 2002. **55**(4): p. 244-265.

5. *HPV | What is HPV | Human Papillomavirus | CDC.* 2017.

6. Bruni L, B.-R.L., Albero G, Serano B, Mena M, Gomez D, Munoz J, Bosch FX, de Sanjose S, *Human Papillomavirus and Related Diseases in Peru.* ICO Information Centre on HPV and Cancer, 2016.

7. Sherris, J., *Evidence-based, alternative cervical cancer screening approaches in low-resource settings.* Int Perspect Sex Reprod Health p, 2009. **35**(3 SRC - GoogleScholar): p. 147-54.

8. Release, F.N., *FDA approves Guardasil 9 for prevention of certain cancers caused by five additional types of HPV*. 2014.

9. Lucas, E. *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia: A Beginner's Manual*. 2017; Available from: http://screening.iarc.fr/colpochap.php?chap=4.

10. (ACCP), A.f.C.C.P. *Visual Inspection with Lugol's Iodine (VILI): Evidence to Date*. Available from: http://screening.iarc.fr/doc/RH_vili.pdf.

11. Parham, G.P., et al., *Cronjé, H. S., & A comparison of four screening methods for cervical neoplasia in a developing country.* American Journal of Obstetrics and Gynecology, 2003. **188**(2): p. 395-400.

12. Cantor, S.B., et al., *Cárdenas- … Accuracy of Colposcopy in the Diagnostic Setting Compared With the Screening Setting: Obstetrics & Gynecology, , .* http://doi.org/10.1097/01.AOG.0000295870.67752.b4. Vol. 111. 2008. 7-14.

13. *WHO guidelines: Use of cryotherapy for cervical intraepithelial neoplasia* 2011, World Health Organization.

14. *Treating Cervical Cancer*. 2017; Available from: https://www.cancer.org/cancer/cervical-cancer/treating.html.

15. Soldan, V.A.P., et al., *Who is getting Pap smears in urban Peru?* International journal of epidemiology, 2008. **37**(4): p. 862-869.

16. Abuelo, C.E., et al., *The Peru Cervical Cancer Screening Study (PERCAPS): The Design and Implementation of a Mother/Daughter Screen, Treat, and Vaccinate Program in the Peruvian Jungle.* J Community Health, 2014. **39**(3): p. 409-15.

17. Almonte, M., et al., *Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru.* International Journal of Cancer, 2007. **121**(4): p. 796-802.

18. Aguilar, A., et al., *Control of cervical cancer in Peru: Current barriers and challenges for the future (Review).* Molecular and Clinical Oncology, 2016. **5**(2): p. 241-245.

19. *LIGA CONTRA EL CANCER - Inicio.* 2017.

20. Hunter, J.L., *Cervical cancer in Iquitos, Peru: local realities to guide prevention planning.* Cadernos de Saúde Pública, 2004. **20**(1): p. 160-171.

21. Lam, C.T., et al., *Design of a Novel Low Cost Point of Care Tampon (POCkeT) Colposcope for Use in Resource Limited Settings.* PloS one, 2015. **10**(9): p. e0135869.

22. Health, C.f.D. and Radiological, *Reprocessing of Reusable Medical Devices: Information for Manufacturers - FDA-Cleared Sterilants and High Level Disinfectants with General Claims for Processing Reusable Medical and Dental Devices - March 2015.* 2017.

23. U.S. Department of Health and Human Services, F.a.D.A., *Guidance for Industry: Electro-optical Sensors for the In Vivo Detection of Cervical Cancer and its Precursors: Submission Guidance for an IDE/PMA*, in *Center for Devices and Radiological Health*. 1997.

24. *The District Pueblo Libre - LimaEasy*. 2017; Available from: http://www.limaeasy.com/lima-info/districts-of-lima/the-district-pueblo-libre.

25. Harris, P.A., *Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of Biomedical Informatics p. **42**(2 SRC - GoogleScholar): p. 377-381.

26. Stata, S., T.X. Station, and L.P. StataCorp, *Software: Release 13.* College, 2013.

27. *Cohenâ ™s Kappa | Real Statistics Using Excel*. 2017; Available from: http://www.real-statistics.com/reliability/cohens-kappa/.

28. Daron G. Ferris, M., Mark S. Litaker, PhD, for the ALTS Group, *Prediction of cervical histologic results using an abbreviated Reid Colposcopic Index during ALTS.* American Journal of Obstetrics & Gynecology, 2005.

29. Viera, A.J. and J.M. Garrett, *Understanding interobserver agreement: the kappa statistic.* Fam Med, 2005. **37**(5): p. 360-363.

30. Ferris, D.G., W. Willner, and J. Ho, *Colposcopes: a critical review.* The Journal of family practice, 1991. **33**(5): p. 506-515.

31. Jenna L. Mueller, E.A., Christopher T. Lam, Marlee S. Krieger, Jennifer E. Gallagher, Alaattin Erkanli, Roopa Hariprasad, J.S. Malliga, Lisa Muasher, Bariki Mchome, Olola Oneko, Peyotn Taylor, Gino Venegas, Anthony Wanyoro, Ravi Mehrotra, John W. Schmitt, Nimmi Ramanujam, *International Image Concordance Study to Compare a Point of Care Tampon Colposcope to a Standard-of-Care Colposcope.* Journal of lower genital tract disease, 2016.

32. *Image Capture at Colposcopy | The British Society for Colposcopy and Cervical Pathology*. 2017; Available from: https://www.bsccp.org.uk/colposcopy-resources/image-capture-at-colposcopy/.

33. Ghosh, I., *Study of accuracy of colposcopy in VIA and HPV detection-based cervical cancer screening program.* Australian and New Zealand Journal of Obstetrics and Gynaecology p, 2014. **54**(6 SRC - GoogleScholar): p. 570-575.

34. Massad, L.S., *The accuracy of colposcopic grading for detection of high grade cervical intraepithelial neoplasia.* Journal of lower genital tract disease p 137, 2009. **13**(3 SRC - GoogleScholar).