

Assessment of Current Cervical Cancer Screening Practice and Responses to a Novel
Screening Device, Transvaginal Digital Colposcopy, Among Gynecologists in

Hyderabad, India

by

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

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Abstract

Background: India has the highest burden of cervical cancer mortality, globally, with 67,477 deaths in 2012. A novel device, the transvaginal digital colposcope (TVDC), or a small handheld colposcope, could potentially improve quality of care and address barriers to cervical cancer screening, by reducing patient discomfort and aiding practitioners in screening. Studies which validate India-WHO guidelines for cervical cancer screening report wide ranges of sensitivity and specificity for techniques currently used in low-resource settings, all of which are contingent on numerous factors from patient awareness to receptivity to user training, suggesting that the context is paramount to improving cervical cancer detection. To that end, assessment of the healthcare and physician environment in terms of practice and reaction to the new device is essential prior to device implementation in order to anticipate benefits or negative consequences of device use.

Methods: A survey was developed to explore experiences, practice, and approaches to cervical cancer screening based on a new technology, and administered to 15 gynecologists in various clinical settings in Hyderabad, India. First, participants answered questions about past and current practices for cervical cancer screening, diagnosis, and treatment procedures. Next, physicians assessed images from a clinical trial involving imaging of cervix by the TVDC and with standard colposcopy. To check physician interpretation of images from the clinical trial, biopsy or histologic

confirmation was used for positive results, while colposcopy was used as the reference standard for negative results.

Results: Colposcopy and magnification for visualization of the cervix were preferred by all physicians, in spite of low frequency of in-house use or referrals for the procedure. Accuracy among physicians interpreting TVDC images ranged from 25%-100%, while accuracy with colposcopy images ranged from 38%-100%. Sensitivity for TVDC images and corresponding colposcopy images was 72% and 91% respectively, while specificity was 54% and 38% respectively. Physicians were more likely to report suspicion for cancer in positive cases with a false negative rate with TVDC images and corresponding colposcopy images at 19% and 0%. Images with the new device were either considered comparable to or were preferred to colposcopy images, but disagreement in interpretation between TVDC and colposcopy for the same patient ranged from 13%-63%.

Conclusion: This study shows how observation-based cervical cancer screening or diagnostic techniques, without preceding, adjunct screening or diagnostic tests, may have low specificity in disease detection. However, a new technology TVDC may be appropriate for this type of setting. Further research into patient attitudes, physician motivation, physician experience with colposcopy and clinical decision-making is required prior to implementation if gains in reduction of cervical cancer incidence and deaths are to be realized.

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1. Introduction

1.1 Cervical cancer in India

Cervical cancer causes more than a quarter of a million deaths worldwide, with 527,600 new cases diagnosed in 2012, but more than 90% occur in lower and middle income countries or regions without the infrastructure and trained personnel to deal with the condition.(1,2) Global estimates are projected to rise by 25% in the next decade, if screening and treatment coverage are not increased. But more women die from this cancer in India, where most cases are detected at advanced disease states, than anywhere else in the world. In 2010, there were 141,768 new cases, with 77,100 deaths, accounting for nearly 20% of all cancer deaths in women from age 30-69. GLOBOCAN 2012 shows reduction in incidence and mortality at 122,844 cases and 67,477 deaths respectively.(1,2)

1.2 Cervical cancer biology

Cervical cancer is mostly a squamous cell cancer (with 10%-15% adenocarcinomas) of the cervix that arises primarily from a persistent infection from sexually transmitted, high-risk HPV or human papillomavirus strains. In 2011, International Agency for Research on Cancer (IARC) formally reported 12 HPV strains as high risk oncogenic strains.(3) The 3-cm long cervix, where the virus attacks and which changes in length based on the individual and stage of pregnancy if relevant, begins at the end of the vagina with only the lower part of the ectocervix visible with a

speculum, while the rest or the endocervix, which follows the cervical canal, is inside. Cancers typically originate at the juncture between the endocervix and the ectocervix, a significant challenge in disease diagnosis as the pre-cancerous/cancerous lesion visibility varies drastically. The site of the majority of cervical carcinogenesis and area of the cervix where columnar epithelium changes into squamous epithelium, the transformation zone is on the ectocervix for premenopausal women but can recede into the endocervix in older women, making all visual techniques in screening and diagnosis that much more challenging (Figure 1).(4,5)

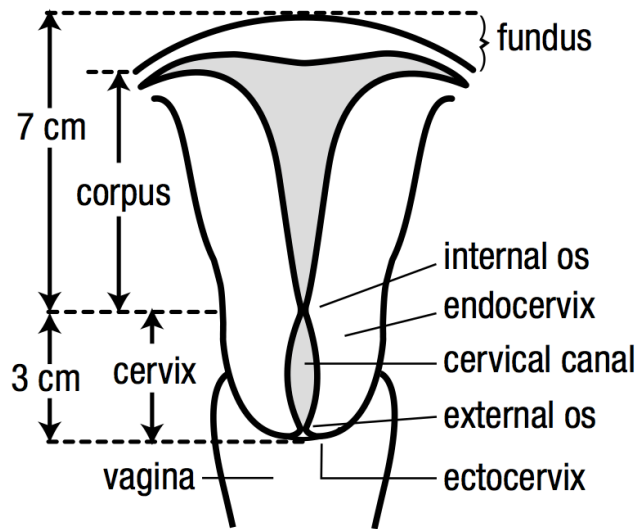
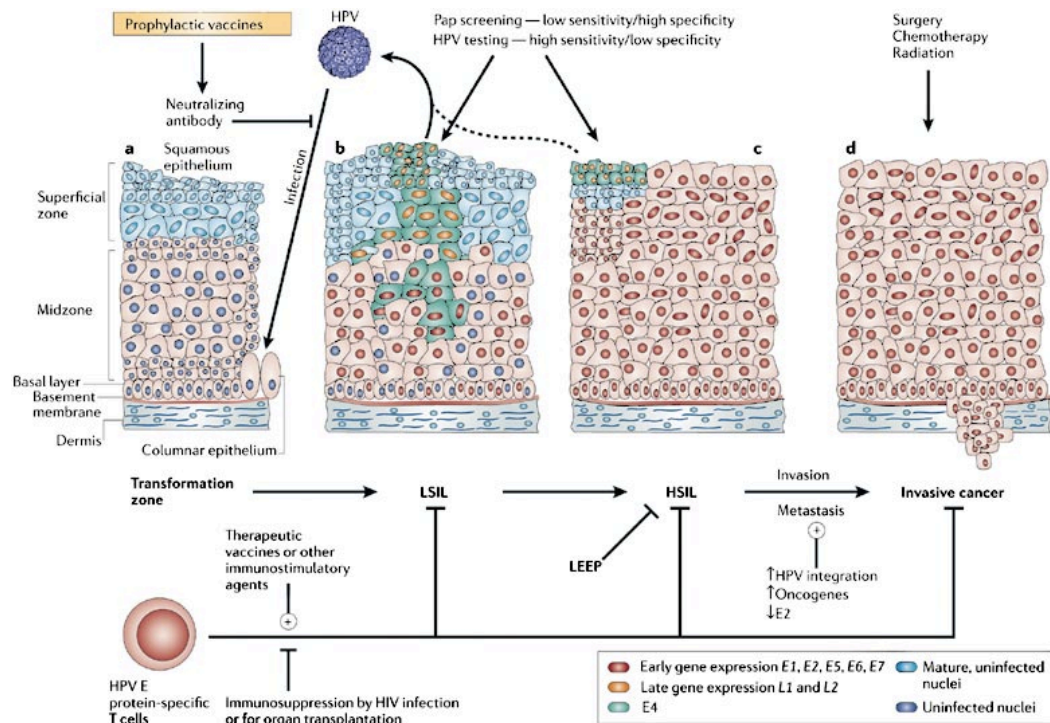


Figure 1: Diagram of the cervix and uterus.(5)

In the US and in India, two naming systems are important in cervical cancer determination via cytology or histology. Squamous dysplasia is first categorized through cytology with the Pap test as either mild or severe dysplasia. Mild dysplasia is categorized as ASC-US, atypical squamous cells of unknown significance, or LSIL, low-

grade squamous intraepithelial lesion) while severe dysplasia is divided ASC-H, “cannot rule out HSIL;” HSIL, high-grade squamous intraepithelial lesion; or CIS, squamous carcinoma *in situ*. Histology or tissue sample analysis, uses the following three stage classification of cervical intraepithelial neoplasia (CIN): CIN1, CIN2, and CIN3. The latter two or CIN2+ are at the highest risk, if undetected or untreated, to advance to cancer. However, in non-immunocompromised women, 10-20 years can pass before premalignant lesions transform to cancer and before it becomes possibly invasive and fatal. CIN1 on the other hand may resolve on its own, as is the case in most infections in women, especially those younger than 25. The development of cervical cancer from these stages is summarized in Figure 2.(5–8)



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Figure 2: Progression to cervical cancer after HPV infection. a) The cervical squamocolumnar junction or transformation zone. b) Point of HPV infection. c) High-risk HPV infections progress to HSILs. d) Progression of untreated lesions to microinvasive and invasive cancer. Immunosuppressed patients who might have HIV infection or have undergone organ transplantation suffer more frequent and severe HPV-related disease.(9)

1.3 Risk factors

HPV spreads from one partner to another very easily, with most sexually active individuals contracting it at some point in their adult lives. Infection from high-risk HPV does not spell out an automatic trajectory to invasive cervical cancer. In fact, in addition to possible spontaneous resolution by the body within a two-year period, only a certain percentage of infections which remain chronic actually advance to cancer. WHO estimates that no more than 2% of women in low-resource settings will actually develop

cervical cancer.(5) In India, the risk factors for cervical cancer include high oncogenicity of HPV, low or compromised immunity, other sexually transmitted co-infections, parity and age at birth of first child.(10) Women with primary level of education or less were seven times more likely to develop cervical cancer than those with secondary education. Rural women also have much poorer survival rates than their urban counterparts.(5,11,12)

1.4 Cervical cancer screening in India

In Kerala, one study revealed only 6.9% of women had undergone any screening and those who had been screened had had a Pap test or cytology. In Dindigul, Tamil Nadu and Osmanabad, Maharashtra only 8 of 13,1746 women aged 30-59 had undergone previous cervical cancer screening. Screening was thought to be higher in Kerala than other states in India because of improved awareness and literacy in the state. One study showed high-risk HPV strains were characterized in 88% of a peri-urban population 20 km outside of Hyderabad, with strains similar to those reported throughout India, with a specific burden caused by HPV 16 that could account for more than 50% of cases. Many studies in India have found no connection between HPV prevalence and age, with the expectation that younger women have a greater burden of disease. The prevalence in this study was 10.4%, while studies elsewhere in India range from 4.8% to 7.8% in cities in the south and north.(5,13)

1.5 Screening & diagnostic methods overview

Recent developments have led to the first HPV vaccines which guard against some of the most common strains, HPV type 16 and 18, which cause 70% of cervical cancer cases globally. In India, Gardasil (quadrivalent) and Cervarix (bivalent) vaccines were licensed in 2011.(10,14) In February 2015, the CDC added a new Gardasil-9 or 9-valent vaccine to recommendations for women, aged 13-26, while it has yet to be approved in India.(15) GAVI Alliance has negotiated to reduce the price of Cervarix from the market price \$130 to \$4.50, which will make vaccination through public programs financially feasible.(16) However, India has had a tragic history with HPV vaccine trials and deployment, in addition to varying acceptance among parents to vaccinate young girls or boys.(17–19) Moreover, with certain viral strains excluded from licensed vaccines' scope of targets, which still can cause cervical cancer, screening therefore remains imperative.

Cervical cancer detection follows the process of screening, diagnosis, and treatment. In the US, according to the guidelines set by the American College for Obstetricians and Gynecologists (ACOG), gold standard practice calls for the following order: Papanicolaou smear or Pap test (cytology), HPV-DNA test (genotyping), colposcopy, biopsy and treatment for patients who are deemed positive for precancerous or cancerous lesions. A patient goes through these steps with some room for adjustment with adjunct co-testing, which is now encouraged; specifically,

gynecologists should use the HPV-DNA test along with the Pap test to interpret either inconclusive results or mild dysplasia observable in colposcopy. Along with the change in co-testing, though routine testing using a Pap test is recommended, the frequency was reduced with new guidelines released in 2013 for most age groups.

An abnormal Pap test is usually followed up by colposcopy, a form of cervix visualization using a colposcope, or a type of low-power light microscope, that includes a green illumination filter for changes in tissue reflectance that can be enhanced with the use of contrast agents—acetic acid or Lugol's iodine. The instrument remains directly outside of the patient's vaginal opening and a speculum is used to expand the vagina to allow observation of the cervix. In addition to assessment of abnormal screening results, the procedure is used to assess genital warts on the cervix, cervicitis, polyps or benign growths, or if there is pain or bleeding. Because of low specificity associated with visualization, biopsy or histologic confirmation of abnormal sites follows colposcopy.(20,21)

However, the burden in middle- and low-income countries has different barriers compelling a different protocol. The WHO has continued to provide several possible frameworks to increase screening coverage that optimizes cost, training, and number of visits. In a minimum resource environment, testing should involve VIA and at maximum, the screening regiment should involve VIA, cytology (Pap test), and HPV test (Appendix A).(5,8)

Guidelines in India suggest the same gold standard protocol, recognized in the US; however, in 1992, the Indian Council of Medical Research (ICMR) called a need for alternatives as existing infrastructure was wholly inadequate for sufficient Pap test screening coverage.(7) The overall regimen relies on good follow-up or repeated visits, with variability in waiting times for turnaround on testing. Moreover, traditional cytology and biopsy necessitates training and pathology facilities. In response, the Government of India partnered with the World Health Organization (WHO) to establish new cervical cancer screening guidelines. The WHO and the ICMR have made a call for a screen-and-treat paradigm, where treatment options are consulted and used on an outpatient basis in the same screening appointment. The guidelines establish a pipeline from community to public health center to district hospital to medical college (tertiary care) to identify cases and direct them to higher care if needed. At the community level, female community health workers are tasked with identifying and handing out screening cards to women who are eligible for cervical cancer screening, with a target population of age 30-59. PHCs are supposed to advertise and dedicate two days a week for screening, where female community health workers are to perform VIA screenings in a separate clinic. At the district hospital, facilities for cytology, colposcopy, biopsy, cryotherapy, and LEEP are to be established and available on all days the hospital is open. Patients who have invasive cancer or specialized are to be referred to Medical

College or a Regional Cancer Center. Unfortunately large-scale programs observing these guidelines have yet to be implemented.(7,8,10)

Barriers to care are not limited to laboratory or personnel capacity alone. Positive health decision-making plays a significant role in incidence as well. Women are making decisions to 1) pursue (multiple) screening(s), 2) comply with follow-up appointments, and 3) follow through with treatment if necessary. Many of these known barriers to screening have not been sufficiently addressed.(22–24) Before a woman ever reaches the physician, the following reasons typically impede that decision: lack of symptoms of any health problem, fear of testing, fear of a cancer diagnosis, community gossip and perceptions, refusal of family or husband, and presence of male doctors.(7) Another major barrier and area for innovation concerns either perceived or previously experienced pain and discomfort during pelvic exams. Women are less likely to get screened for cervical cancer because of perceived or previously experienced pain and discomfort during pelvic exams. The impact and cost-effectiveness of screening, once accomplished, hinges on compliance with receiving treatment, yet another outstanding challenge in India. One qualitative study included specific reasons for refusing treatment because fear of treatment, persisting lack of symptoms, inability to go to the hospital, lack of permission from husband or family to receive treatment, or an understanding from health professional or community health worker that she did not have to receive treatment.(7,25–27) Additional studies are concordant in describing the

following barriers to all points of entry: knowledge about the disease or its prevention, transportation, access to screening, need for culturally adapted resources for prevention/treatment, literacy, misconceptions of cancer and medical terminology, fear of pain in pelvic exams, perceptions of futility of preventive healthcare and finally, household obligations.(24,25,28,29)

1.6 Diagnostic versus screening tests

Before moving ahead, it is important to note a blurring of the divide between a screening and a diagnostic tool, provided in Table 1.(30) The difficulty lies in establishing guidelines and thresholds for disease diagnosis for a tool that can function for both ends. More than merely an issue of semantics, this choice can determine chances of increased referral in low health capacity settings, overtreatment, and misuse of resources. Possible screening methods include VIA/VILI or visual inspection using acetic acid/Lugol's iodine, VIAM (which is VIA with magnification), cytology, and genotyping. When studies compare different modalities of cervical cancer detection, sensitivity, specificity, and other diagnostic accuracy measures are reported, which have different implications based on the goals of the tool. For example, colposcopy can be used in a diagnostic or screening context, for instance. Cantor et al. (2008) performed a large patient study comparing the accuracy of colposcopy used for those two different purposes. Patients were divided into diagnostic or screening groups, while colposcopy and biopsies (of normal and abnormal sites) were performed, with histology results set

for the accuracy threshold. The results show that when the test threshold was LSIL, the sensitivity decreased and specificity increased (Appendix B). As a result, even the area under the receiver operator curve (AUC) decreased from 0.821 to 0.587, when the threshold changed from diagnostic to screening, which translates to a “worse” test, since the closer the AUC values is to 1.0 the better.(31,32) Although the diagnostic role was validated and found to coincide with other meta-analyses, colposcopy’s use for screening was found inferior regardless of the threshold used.(33) This study was also unique in considering screening in the primary care setting and conducting biopsies for areas of the cervix that had already been deemed normal by colposcopy including a large sample size. Unlike the vast majority of studies, work-up or verification bias was reduced here because the gold standard did not differ based on the results of participants’ referral (colposcopy) test.(34,35)

Table 1: Differences between diagnostic and screening tests

	Diagnostic Test	Screening Test
Result	The cutoff is set towards high specificity, with more weight given to diagnostic precision and accuracy than to the acceptability of the test to patients	The cutoff is set towards high sensitivity. As a result many of the positive results are false positives. This is acceptable, particularly if the screening test is not harmful or expensive.
Cost	Patients have symptoms that require accurate diagnosis and therefore higher costs are justified.	Since large numbers of people will be screened to identify a very small number of cases, the financial resources needed must be justified carefully.

Test Result	The test provides a definitive diagnosis (e.g. a definite diagnosis of Meningitis through blood test or lumbar puncture.	The result of the test is an estimate of the level of risk and determines whether a diagnostic test is justified.
Invasiveness	May be invasive	Often non-invasive.
Population offered the test	Those with symptoms or who are under investigation following a positive screening test.	Those at some risk but without symptoms of disease.

1.7 Novel screening device: Transvaginal digital colposcope (TVDC)

A new point-of-care device called the transvaginal colposcope, developed by Nimmi Ramanujam, PhD at Duke University, has the form factor of the feminine hygiene product, the tampon, and seeks to reduce patient discomfort and facilitate implementation in community health and clinical settings for cervical cancer detection. Unlike standard colposcopy, the device is inserted into vagina and has a much shorter working distance. This is one motivation for its use in the primary screening context, but it could be used to address lack of colposcopy in the diagnostic setting as well. The design also makes it possible for use in mobile screening settings and for home use and/or by women for self-testing, with assistance from community health workers if necessary. Currently, at Duke University, a clinical trial entitled, “Cervical Cancer Detection using Optical Spectroscopy” is being conducted to establish the technology’s viability and desired specificity and sensitivity for clinical use (Protocol ID:

Pro00008173). This version of the technology does not employ spectroscopy. Patient and physician experience at Duke University is being used to modify and update the device.

1.8 Purpose of study

Gold standard methods are not widespread because of a host reasons, as discussed, including costs of testing for patients, need for follow-up, and women's decision-making. VIA as recommended, by the WHO, has wide range of sensitivity (67%-79%) and specificity (49%-86%), leading to lower quality of care for patients without access to gold standard methods.(5,21,35-39) These large trials were performed in South Africa, India, Zimbabwe, China, Burkina Faso, Congo, Guinea, Mali and Niger. Other studies in India found sensitivity of VIA to range from 26.3%-86.7%, and specificity has ranged 6.4%-90.9%.(7,40-42) In view of current challenges to cervical cancer screening practice from the literature, new cost-effective technologies such as the TVDC, which may still follow cost-effective see-and-treat paradigms, can promote higher standards of care for women with poor access to cervical cancer screening.

In this paper, we present findings from studying current practice of physicians in South India and their responses to a new screening device, TVDC. The specific aims for this study are as follows:

- 1) Characterize physician preferences of cervical cancer screening and diagnostic methods

- 2) Estimate diagnostic accuracy among physicians using standardized colposcopy images
- 3) Estimate diagnostic accuracy of physicians using a new screening device, TVDC
- 4) Establish whether there is a role for TVDC as an appropriate medical screening device in this setting

The overall goal of this study was to assess the potential for TVDC implementation in an urban, South Indian environment, where the cervical cancer burden is comparable to the nation's high average, by administering a quantitative survey among physicians to assess current practice and responses to the TVDC.

2. Methods

2.1 Study setting

The study was conducted in public and private clinical settings in Hyderabad, Telangana, or in what was previously the capital of Andhra Pradesh until June 2014, and is now shared with the new state, Telangana. Hyderabad has a population of over 7.8 million and is the fourth most populous city in India, boasting a heterogeneous society with the vast majority of its populace younger than 30. As a result, be it a business owner or a practicing physician, in order to work and live in this metropolis, the onus is on the individual to be multilingual and to move seamlessly among cross-cultural differences.(43,44)

15 small, private clinics, 3 private hospitals, and one large public teaching medical center were invited to participate in the study. The smaller clinics were often run by a single gynecologist or by a few physicians, while the hospitals and larger institutions had gynecology departments with 3 to more than 15 physicians. Only the larger institutions had financial schemes for incoming patients from Below Poverty Line households, who were either attending on their own or had been referred through community outreach campaigns. All site names have been omitted from the study as per the study participation agreement. The region visited for the study is in Figure 3.

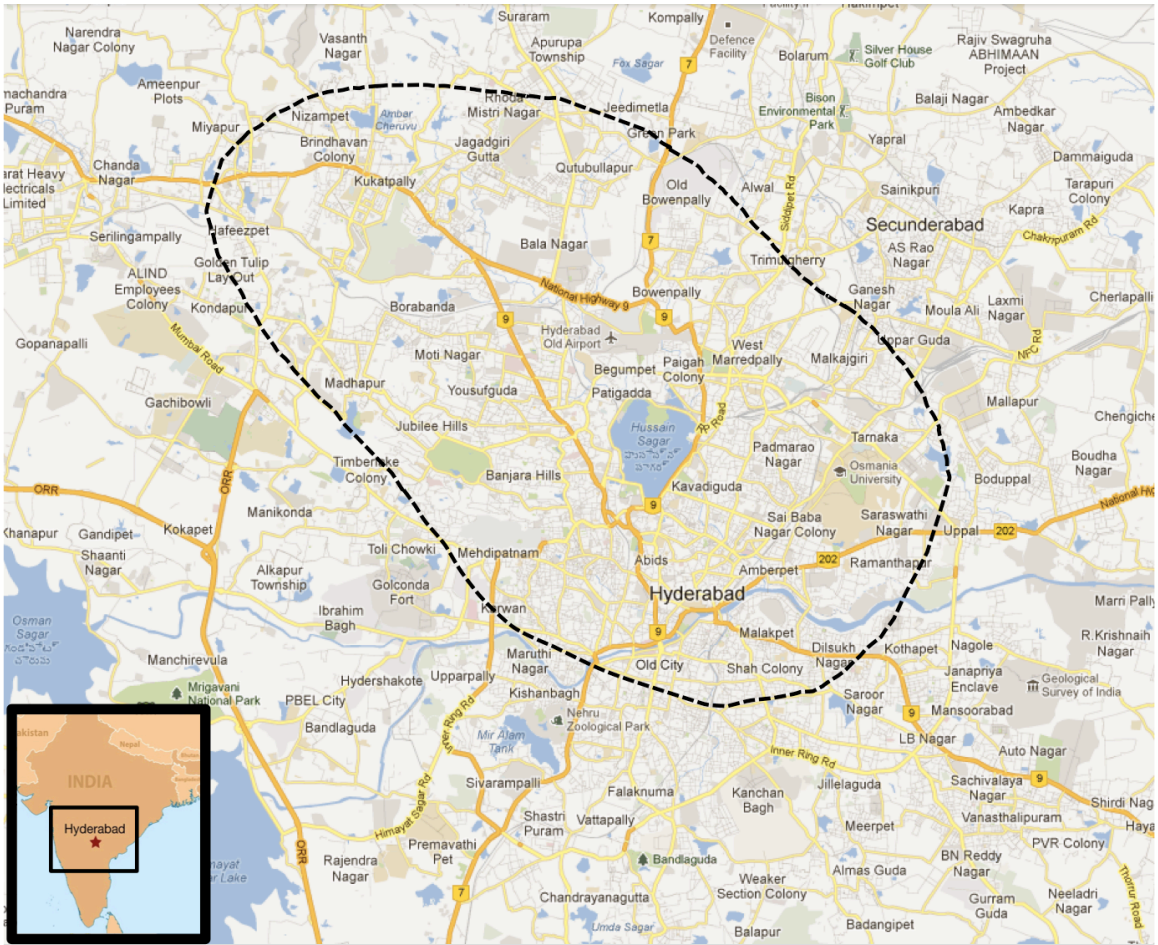


Figure 3: Map of Hyderabad and region visited for recruitment (Google Maps, 2015)

2.2 Participants & recruitment

Gynecologists in Hyderabad were the target population for this study (Table 2). Online listings and personal connections to academic hospitals were used to start recruitment. From those initial contacts, a nonprobability sampling method was developed through referrals (or snowball sampling), wherein each physician was asked to name at least three gynecologists in Hyderabad. This study included visiting doctors who had varying levels of experience, different types of patient populations, and offered diverse financing options. All physicians were contacted directly, after which appropriate departmental or institutional representatives were contacted for study approval.

In India, a physician specializing in gynecology can either pursue a 2-year course and receive a Diploma in Gynecology/Obstetrics (DGO) or a 3-year course and receive a Medical Degree (MD), and pursue further training for a Masters of Science (MS). Completion of exceptionally competitive entrance exams precede either track, with the MD program as the more selective program that opens up job growth and faculty positions, whereas DGOs are limited. A physician who has completed a Bachelor of Medicine, Bachelor of Surgery (MBBS) or has only completed medical school also performs basic pelvic/cervical health exams. A key difference between an MBBS and practicing gynecologists is undergoing training in colposcopy and use of contrast agent training (acetic acid or Lugol's Iodine) for cervical cancer diagnosis in their post-medical

school years. However, in spite of the varying experience with VIA, colposcopy, and other methods, the physicians listed were all possible candidates because the images selected for interpretation are supposed to give rise to the same end result: a positive or negative screening based on a visual representation.

Table 2: Recruitment Criteria

Type of criteria	Study participant criteria
Inclusion Criteria	<ul style="list-style-type: none"> • Currently practicing physicians in Hyderabad • Following certifications: MBBS, DGO, MD, MS • To agree to 15-30 minute anonymized interview
Exclusion Criteria	<ul style="list-style-type: none"> • No experience with VIA (Visual inspection using acetic acid cervical cancer screening technique)

2.3 Procedure

After physicians had been introduced to the project, all were asked for institutional approval to participate in the study in addition to their signature of an informed consent form. In addition to the general agreement to participate, institutional representatives were asked to sign a Data Transfer Agreement, which covered the proprietary information in the form of anonymized cervix images used from the Duke University clinical trial “Cervical Cancer Detection using Optical Spectroscopy” regarding use and nature of the information (Protocol ID: Pro00008173). The informed

consent form was first explained concisely, verbally, before the participant was then asked to read the form, ask questions if necessary, and sign if they agreed to participate. All participating physicians and institutions were made clear of the absence of any connection between career assessment or opportunities and the study, and that the participant could discontinue at any time without fear of any consequences. Most importantly, absolute confidentiality was assured, wherein no identifying information for either the physician or institution would be included in the study (Appendix C).

After this process was completed, each participant was again approached to respond to the survey. With assistance from the researcher, each doctor completed the survey on a computer using Qualtrics software, Version 61331(45). In order to avoid issues with image clarity or resolution, Internet connection, or Qualtrics survey software, all physicians completed the surveys on the researcher's computer. No compensation was given for participation, which was entirely voluntary and dependent on participant's convenience. All surveys were administered in one sitting in the participant's office.

The study was exempted from further review by the Duke University Institutional Review Board, as it was deemed to pose minimal risk (IRB: C0461). A file of informed consent forms with signatures was kept separate from the survey data. All information was kept anonymous using Qualtrics software and no identifying information was ever requested during the survey.

2.4 Survey

2.4.1 Development of survey

The survey was developed using cognitive interviewing and pre-testing in order to ensure internal validity of the instrument and determine whether the respondent understands the questions for their intended purpose. It was pre-tested at three stages before the final survey instrument was used for the study. The first version of the survey was administered to physicians in the US, and revised for instrument length and clarity and verified for accurate representation of decision-making process to determine presence of cervical precancerous lesions or cancer. The second version of the survey was vetted by physicians in India who were teaching faculty or held senior positions in gynecology departments for the same issues, with language and proper wording paramount. Next, initial weeks of research in Hyderabad involved speaking with other Indian gynecologists from different training backgrounds to explore the possibility of adding new sections to reflect practice in Hyderabad. Revisions from cognitive interviewing, exploratory interviews, and the first administration to Indian physicians led to the penultimate form of the instrument, after which it was tested a third time with Indian physicians before being implemented in the field.

2.4.2 Part I: Characterizing cervical cancer screening/diagnostic procedures among physicians

The survey first poses questions about cervical cancer screening/diagnostic methods the physician uses and overall experience in the field. The former was divided

into questions regarding previous exposure and current use of screening/diagnostic methods. They were also asked to rate attributes of screening and diagnostic tools: speculum exam without staining, VIA, Pap test, HPV-DNA test, cervicography, colposcopy, and biopsy. Answer choices for reasons to screen and for treatment options were expanded after initial pretesting and revealed less obvious responses than the literature would suggest. For example treatment options even for mild dysplasia might include a hysterectomy. In addition to specific tool use, screening and treatment protocol in terms of order of steps was determined for each participant. These characteristics were intended to establish common modes of practice and guideline awareness and adherence. The overview of the questions is as follows (Appendix D):

- Age, training, years in screening practice
- Patient population: Number of screened patients per week and reasons to screen
- Screening/Diagnostic methods currently and previously used
- Screening/Diagnostic Method Preference: Guidelines, methods, magnification, biopsy/colposcopy routine
- Actions following a positive/negative screening

2.4.3 Part II: Matched transvaginal digital colposcope (TVDC) and standard colposcopy image interpretation

The second part comprised of 14 cervix images taken of 7 patients, from the clinical trial at Duke University (Protocol ID: Pro00008173). In other words, each patient had been imaged twice, once with the new device or TVDC and once using the gold standard or standard colposcopy. Those 14 images were randomized, used to make a diagnosis/screening decision, and rated on a Likert scale of 0 to 5, or Very Dissatisfied,

Somewhat Dissatisfied, Neutral, Somewhat Satisfied, Satisfied, and Very Satisfied for image quality and reflected their confidence in their decision. This section was only administered after the host institution had signed an agreement that authorized the release of the images (Appendix D).

The TVDC has a 2.0 megapixel camera, 1 to 6X magnification, 60-20 mm working distance, 55-33 mm field of view, weighs less than 4lbs, uses a 12V battery pack and costs under \$200. The colposcope is the Leisegang Optik 2 and it has a 18.1 megapixel camera; magnification of 3.75, 7.5, and 15; 300 mm working distance; 76-19 mm field of view; weighs 130lbs; uses AC power and costs \$20,000.(46)

2.5 Analysis

Data was analyzed by provider experiences, provider preferences, image analysis answers, device preference, disagreement caused by different screening devices, and group experiences (Figure 4).

- 1) **Part I:** All demographics and practice preferences of the participants were summarized.
- 2) **Part II:** Each screening result was confirmed against results from pathology and/or Duke gynecology in the case of a positive colposcopy. If the patient was colposcopically determined negative, then biopsy was not taken. All results that had cytology of LSIL or HSIL, or histology of CIN1+ (CIN1, CIN2, or CIN3) were considered

positive. This decision was made with the low-resource settings in mind where repeated follow-up for low grade or CIN1 lesions may not be possible.(7,31,36–38,47,48)

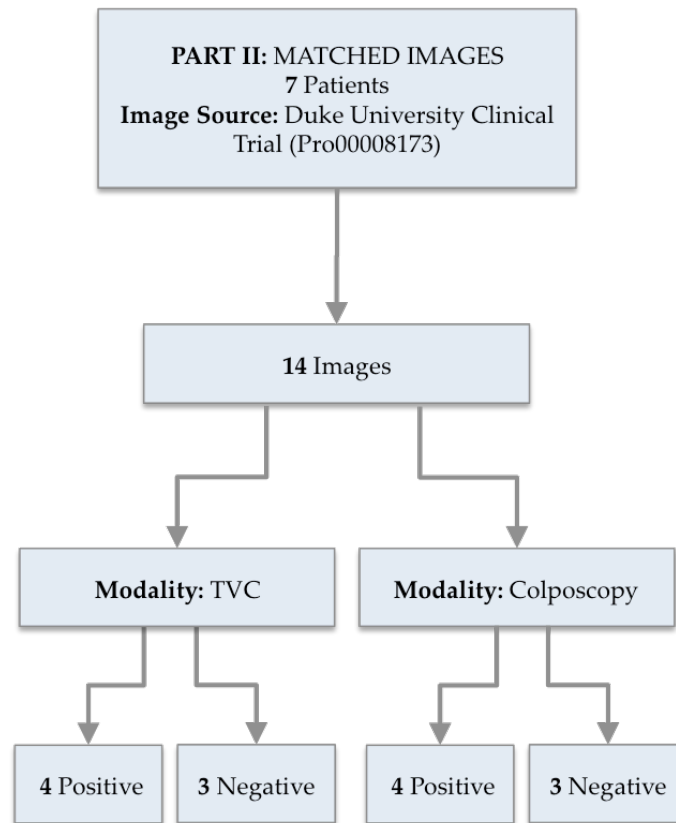


Figure 4: Survey instrument outline of Part II

Sensitivity, specificity, false-positive rate, false-negative rate was calculated for TVDC or new screening device images and images from standard colposcopy or the gold standard from Part II. Device (TVDC vs. colposcopy) preference and decision-making was described through calculating differences on the Likert scale presented in the survey. Percent disagreement was calculated and a 2x2 matrix comparing decisions

from each device, with and without accounting for confirmation by biopsy to note how often the new device was able to (or unable to) improve decision-making. All data was entered and analyzed in Microsoft Excel® 2011.

3. Results

Out of all the clinical sites that were consulted, ultimately 15 participants were able to complete Part I of the survey, while 8 of those 15 signed the agreement covering the Duke University images and completed Part II as well. The first section of results describe physician profiles and their current and former exposure to cervical cancer screening, diagnostic, and treatment procedures.

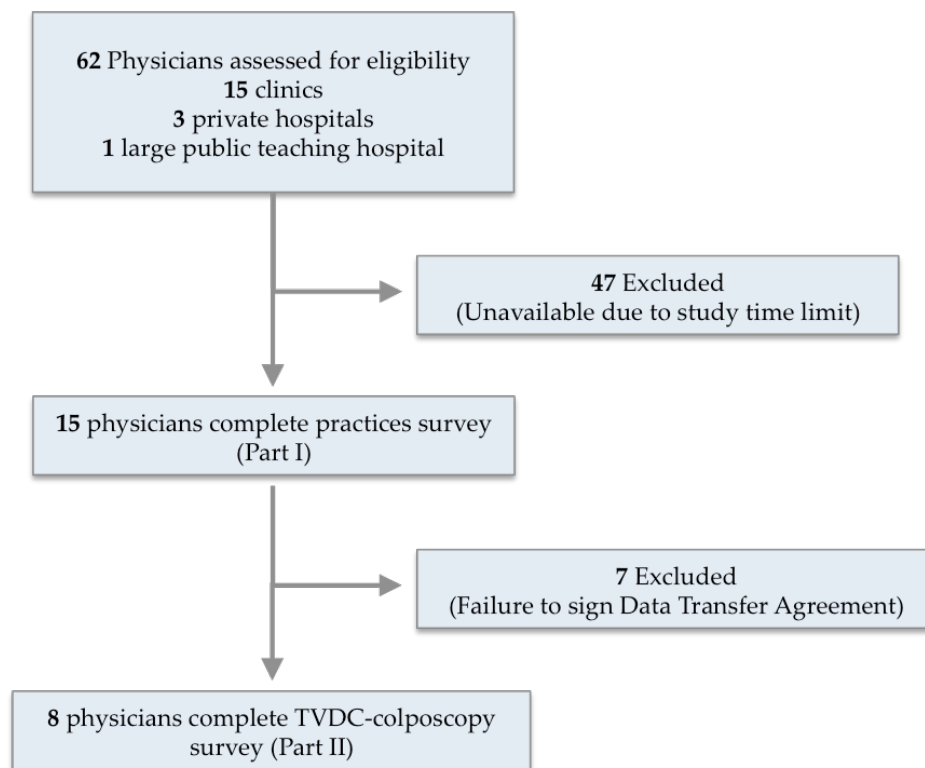


Figure 5: Study diagram of participants

3.1 Part I: Characteristics of providers

All gynecologists who were approached for the study were female and each spoke multiple local languages including English, and a summary of their basic characteristics is presented in Table 3. Of the fifteen participating physicians, there was a range of experience of 5-34 years, with an average of 17 years and an age range of 30-57, with an average of 46. The physicians either were MDs (60%) or DGOs (30%). Only three cited following or adhering to any named cervical cancer guidelines, while they all mentioned the importance of training during their medical school training. Physicians saw a range of 1-100 patients per week, with a mean and median patients per week screened for cervical cancer at 14.0 and 6.0, respectively.

Table 3: Provider characteristics

Characteristics of providers (N=15)	Frequency (%)
Age	
30-39	4 (26.7)
40-49	4 (26.7)
50-57	7 (46.7)
Years of Experience	
5-14	7 (46.7)
15-24	4 (26.7)
25-34	4 (26.7)
Training Level	
MD	9 (60.0)
DGO	6 (30.0)
Adherence to Screening Guidelines	
ACOG	1 (6.7)
Johns Hopkins	1 (6.7)
State guidelines	1 (6.7)
No explicit statement	12 (80.0)

3.2 Part I: Cervical cancer screening protocol

3.2.1 Patient population

Some details were elicited about the patient population because physicians mentioned a cyclical relationship between patients' attitudes and physicians' attitudes; patient populations differed by income level and literacy. The most common reasons for physicians to screen a patient for cervical cancer were "Sexually active patients" (60%), "Family history" (60%), "Excess vaginal discharge" (73%), and "Symptomatic" (73%). Specific reasons that patients declined included "those newly married or nulliparous" and "knowledge." When physicians were asked how many patients on average out of 10 patients declined screening because they did not like the speculum during the gynecological exam, a range of one to four patients was reported.

In these cases, 8 out of 15 physicians reported that it is not uncommon for hysterectomy to be offered as an option for women who are not interested in having more children, regardless of age; however, only 1 out of 15 chose hysterectomy as a possible option if a patient was unwilling to go for colposcopy after a positive Pap test or VIA test.

3.2.2 Cervical cancer screening method and protocol preferences

A detailed summary of the method and protocol preferences is summarized in Table 4. Twelve (80%) physicians described magnification to be useful during a speculum-based cervical exam with or with use of a contrast agent, and all 15 stated VIA as less accurate than colposcopy. When comparing VIA and Pap test, 9 (60%) stated that VIA was more accurate than cytology based Pap test, independent of cost or other attributes that might affect that choice. Responses to positive and negative attributes of cervical cancer screening and diagnostic tools are provided in Appendix E.

Following a positive screening, neither colposcopy nor staining was used for biopsy for 10 (67%) members. Following a negative screening, 14 (93%) physicians would request a patient to come back for screening regardless of symptomatic changes. Finally, following a clinically suspicious cervix, 10 (67%) do not state colposcopy should be used to improve their decision.

Table 4: Screening protocol and decision-making in cervical cancer screening

Screening protocol decision-making	Frequency (%)
Screening provided for	
All sexually active patients	9 (60.0)
Family history	9 (60.0)
Excess vaginal discharge	11 (73.3)
Symptomatic	11 (73.3)
Methods currently being used	
Pap test	14 (93.3)
Speculum Exam	13 (86.7)
Biopsy	13 (86.7)
HPV-DNA	6 (40.0)
Colposcopy	4 (26.7)
VIA	3 (20.0)
Biopsy method	
Speculum exam – no staining	10 (66.7)
Colposcopy	3 (20.0)
Speculum exam – with staining	2 (13.3)
Action following negative screenings	
Patient asked to return within 1 year	11 (73.3)
Patient asked to return within 3 years	3 (20.0)
Patient asked to return with symptoms	1 (6.7)
Action following positive screenings	
Biopsy without colposcopy	9 (60.0)
Biopsy aided by colposcopy	4 (26.7)
VIA	1 (6.7)
Hysterectomy	1 (6.7)
Screening protocol summary	
Pap test → Biopsy → Treatment	8 (53.3)
Pap test → VIA → Colposcopy → Biopsy → Treatment	4 (26.7)
Pap test → VIA → Biopsy → Treatment	2 (13.3)
Pap test → VIA → Treatment	1 (6.7)

3.3 Part II: Matched new device-gold standard image analysis

3.3.1 Difference in sensitivity and specificity of TVDC and colposcopy image interpretation

Sensitivity was highest for colposcopy images at 91%. Specificity, however, in TVDC evaluation was higher than that of matched colposcopy at 54% vs. 38%. False positive rate was higher in colposcopy images (58% vs. 38%) while false negative rate was higher in TVDC images (19% vs. 0%). Differences in accuracy of interpretation broken down by each physician respondent is presented in Appendix F. TVDC accuracy ranged from 43% to 71% and matched colposcopy accuracy ranged from 43% to 100%. All measures are summarized in Tables 5-7.

Table 5: Matched colposcopy image confusion matrix

	Predicted Positive	Predicted Negative	Total
Respondent: Positive	29	14	43*
Respondent: Negative	0	9	9
Total	32 [†]	24	56

* Table values, not including column totals or grand total, for respondent choices in screening survey do not include instances when "Unsure" was selected.

† Column totals include the maximum possible cases that could have been selected in the positive or negative category of cases.(49)

Table 6: Matched TVDC image confusion matrix

	Predicted Positive	Predicted Negative	Total
Respondent: Positive	23	9	32
Respondent: Negative	6	13	19
Total	32	24	56

Table 7: Matched TVDC and colposcopy screening estimates

Screening Test Estimates	Matched TVDC Image Analysis 95% CI	Matched Colposcopy Image Analysis 95% CI
Sensitivity	71.9% [0.530, 0.856]	90.6% [0.739, 0.975]
Specificity	54.2% [0.332, 0.738]	37.5% [0.195, 0.592]
FPR	37.5% [0.195, 0.592]	58% [0.369, 0.772]
FNR	18.7% [0.078, 0.370]	0% [0, 0.133]

3.3.2 TVDC vs. standard colposcopy device preference

Likert scale choices for each of the 14 images is summarized in Figures 6-7. More than half the group in six of the seven image sets rated TVDC as the same if not better quality as the colposcopy images. Since the Likert scale actually asks the rater to use a scale of 0-5, the differences yielded 23 (41%) ratings as TVDC equal to colposcopy, or 51 ratings (91%) as the TVDC image either only one point lower than its respective colposcopy image or equal to it (Appendix G).(50) TVDC images were on the whole favorable in to this group of physicians. One physician, however, also added a comment that a “green filter” for vessel differentiation would have been preferred.

Three images prompted less than 30% disagreement between TVDC and colposcopy images, while four images prompted between 30-63% disagreement. In a context without biopsy confirmation and considering colposcopy as the “true” positive or negative, there is high concordance for true positives between TVDC and colposcopy

at 91%, which drops to 69% with the true result adjusted to biopsy results. 54% of screenings were total disagreement without biopsy confirmation and 26% of screenings were different with biopsy confirmation (Tables 8-9). TVDC accuracy was either the same as or better than colposcopy accuracy for three images, although for one image set, both TVDC and colposcopy accuracy was low (38%). TVDC reduced accuracy of physicians in three other images (Table 10). On the other hand, if these results are interpreted based on respondent instead, 4 out of 8 physicians were either equally or more accurate using TVDC (Appendix F).

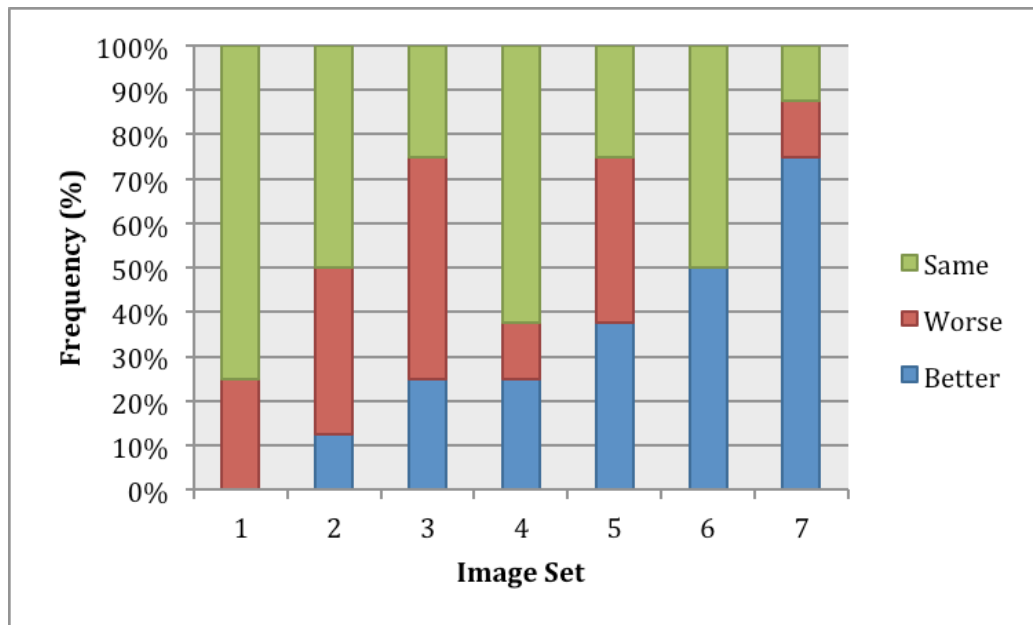


Figure 6: Rating TVDC Images as better, worse, or same as matched colposcopy images

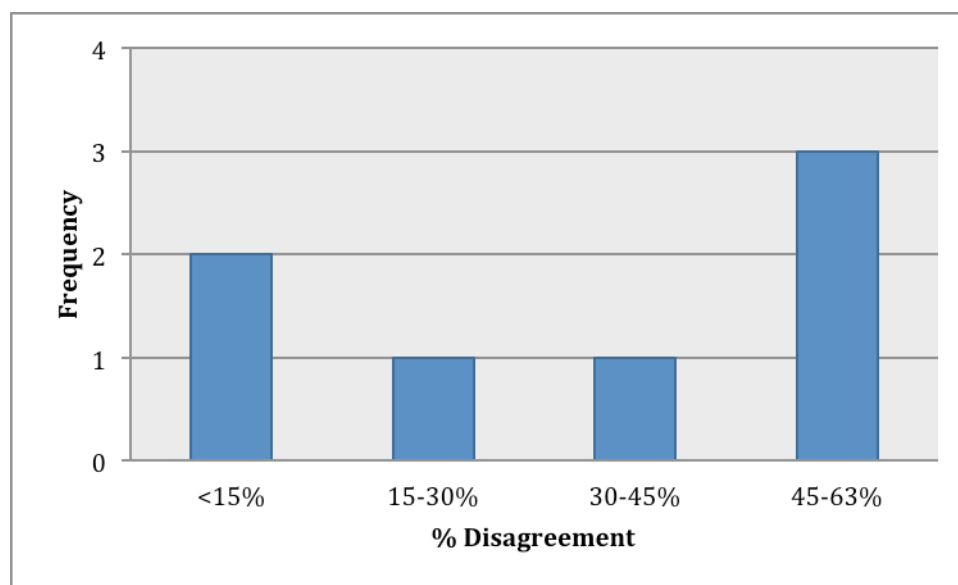


Figure 7: Frequency of percent disagreement between TVDC and matched colposcopy images

Table 8: Concordance/confusion matrix for matched TVDC and colposcopy images, without confirmed biopsy

	Colposcopy: Positive	Colposcopy: Negative	Total
TVDC: Positive	29	2	32
TVDC: Negative	11	5	24
Total	32	24	56

Table 9: Concordance/confusion matrix for matched TVDC and colposcopy images, with confirmed biopsy

	Colposcopy: Positive	Colposcopy: Negative	Total
TVDC: Positive	22	2	32
TVDC: Negative	5	6	24
Total	32	24	56

Table 10: Percent disagreement and accuracy comparison between matched TVDC and colposcopy images

% Disagreement	TVDC	Colposcopy	Test Result
	Accuracy	Accuracy	
13%	100%	88%	Positive
13%	88%	88%	Positive
25%	38%	38%	Negative
38%	50%	88%	Positive
50%	50%	100%	Positive
63%	25%	38%	Negative
63%	100%	38%	Negative

4. Discussion

This study describes current practice of gynecologists in Hyderabad, India and demonstrates possible factors that could point to whether transvaginal digital colposcopy should be studied in this context for use in screening: low in-house standard or referral colposcopy, prevalence of Pap test, and preferences described by the physician. According to the matrix of positive and negative attributes of cervical cancer screening and diagnostic methods, the prohibitive costs of colposcopy prevent the use of the standard diagnostic in the clinics. A disconnect that remains to be explored is the issue of compliance and loss to follow-up. Preventive screening is not conventional practice and the reasons may or may not be due to continued incursion of healthcare costs. Because the TVDC can be applied to a screen-and-treat paradigm this barrier may prove not to be insurmountable. In method preferences, VIA was considered largely more accurate than Pap tests, even though in reported current practice, contrast agents were not used regularly in clinic. Since all physicians indicated that magnification was important in cervix visualization, stated colposcopy as more accurate than VIA, and typically seem to prefer TVDC images or at least consider them comparable to colposcopy images, the TVDC may be able to unite these diverging opinions and allow for acetic acid use with magnification.

Overall diagnostic accuracy for TVDC was largely comparable to colposcopy, but with a wide range of accuracy. There was also a wide range of disagreement in

interpretation between TVDC and colposcopy, which could be related to differences in image interpretation difficulty. However, given the small sample size, the significance of the absence of a correlation cannot be over-interpreted. The range of sensitivity and specificity for both sets of images match what has been reported in the literature and was presented earlier.(5,21,35–39). As Cantor et al. (2008) note in their study, verification bias exists in our study because the same gold standard or criterion standard was not applied equally to all cases.(31,33,48) Moreover, by choosing a low threshold for disease, the sensitivity was higher given the overall tendency to score an image as positive for disease. In a see-and-treat paradigm, the physician prioritizes treatment during the same appointment so as not to lose a patient in follow-up. This paradigm may not be suitable for this context nor does it have to be given the use of Pap tests.

Many studies from India cited by Krishnan et al. (2013) use the IARC training manual and offer retraining or refresher courses in addition to a possibly high patient load. Re-education or re-training is a key variable that was not covered here, as this was a cross-sectional study concerning current or past behavior. Studies should also look into the diagnostic process of Indian physicians based on visual features, even though it is commonly accepted that image based techniques have tremendous variability in diagnosis when there is no clear threshold for the operator to use.(40,42,51) Thus, implementation of the device needs further research to distinguish future challenges that are attributable to the TVDC versus existing practice. Unfortunately, the seemingly

vast number of large studies which have covered all screening techniques, different user populations, different public health campaigns and approach to patients, urban or rural access, and so on, the “real world” effect can be extremely localized.(7)

4.1 Study limitations

This study had both a small sample size and an engineered prevalence because images were chosen as proxies for imaging modalities of interest, namely the new method, TVDC, and the standard method, colposcopy. Although questions about general use or prior use of colposcopy was included, the sample was further compromised because of the lack of information about each individual’s use of colposcopy on a monthly or yearly basis. The data could not be stratified based on physician expertise with colposcopy. Because of the non-representative prevalence created by the images chosen for the survey, the data also could not be stratified based on image disease state in any meaningful way. Even though 8 physicians analyzed 22 images, seven of those images were taken of the same patient but with another modality, causing nesting within the aggregated numbers for sensitivity, specificity, and other diagnostic measures. Those are the types of estimates, which should be intrinsic to a new diagnostic system. However both the lack of a uniform physician sample and image set did not allow for that. Furthermore the image disagreement that was found could also have resulted from “good” or “bad” cases (ease of diagnosis) as opposed to “good” or “bad” images (quality).

Recruitment was based on snowball sampling, which although appropriate, should be changed into a more reliable respondent-driven sampling method. At the pace set at the beginning of the project, by the end of 10 weeks, a sample of 100-200 physicians could have been included, non-response rate notwithstanding; however, in this study the non-response rate was zero. Logistical reasons stymied progress in getting sufficient number of signatures for a larger sample size.

The timeline for this study covered 10 weeks for survey development, pretesting, and administration for the study. Pretesting in this study was completed with the help of American physicians and Indian physicians. However, the pretest group was small, and the third version of the survey was vetted by the same group of Indian physicians. In the future, the timeline would have to accommodate pretesting or a pilot of the study; for example, 1-2 months could be allotted for pretesting and piloting, followed by a 4-6 month period for survey completion.

4.2 Future work

The next version of this study would have four components to analyze: in-depth interviewing of physician experience, quantitative scoring of the images in terms of disease management protocol, interviewing of physician decision-making in determination of disease/diagnosis. This would require a mixed-methods analysis plan. Qualitative methods analysis would probably include the “immersion crystallization” approach as a concise way to inform practice guideline overview in Hyderabad since no

physician seemed to answer that they followed any guidelines whatsoever besides the training received during their post-graduate education; this was also in similar study of physicians by Fox et al.(52)

Quantitative analytical tools that can be used with a better sample size include percent agreement, kappa statistic, and weighted kappa statistic. In addition to diagnostic accuracy measures, calculation of receiver operating characteristic curve (ROC curve) should be included, as it is useful if not necessary for findings associated with images, when the confidence level of the participant varies and there is no clear cutoff for diagnosis. There are many ways to use the ROC, with the most common being the AUC or area under the curve, as presented earlier.(32,53) Percent positive agreement may be used instead of percent agreement, which looks at the number of times a positive result is noted. Typically, diagnostic studies enroll a large pool of patients and often capture the true population prevalence of disease; this is important because accuracy measures such as negative or positive predictive value in addition to sensitivity/specificity are limited by prevalence of the condition. In a study with images, prevalence could be engineered to reflect real-world estimates.

To understand the nature of physician interpretation, a more detailed assessment of the correlation between accuracy and selection of certain visual indicators of disease would be necessary. Physicians could also be matched based on experience and volume of patients screened for cervical cancer. Weighted kappa statistic will be useful if

gynecologists are consulted regarding the prioritizing of indicators used in the survey. The weighted kappa and kappa statistic are reported in cases of comparison between a new process and its corresponding gold standard. Finally, a Bland-Altman plot may be useful, given the lack of almost any hypothesis or prediction of trends in this study and even in current literature, and would function to illuminate a better regression model. In a future study where the sample size is large enough, a predictive model could be designed with covariates of age, experience, patient volume, VIA experience, and similar physician characteristics.

New work should incorporate decision-making science and the theory of reasoned action. Variables representing decision-making should include intention, attitude, role belief, perceived norms, perceived self-efficacy, and perceived risk. These have been identified as necessary components by work developed by Azjen and Fishbein, who have published on how to operationalize reasoned action.⁽⁵⁴⁾ This effort could better characterize protocols and disease management, or more importantly the inconsistencies in practice.

5. Conclusion

Prior to TVDC implementation, a new study, if conducted with a larger sample size that adequately covers different types of clinical settings and patient populations, could illustrate whether this method would have comparable reports of sensitivity and specificity of visualization based tests for cervical cancer. No current studies in India have established the variability in screening and diagnosis among physicians with colposcopy in a context of decision-making factors, let alone lesser-trained health workers who are often charged with the task of screening and in some cases treating on site as well.

It takes decades for cervical neoplasia to progress to invasive cancer, leaving ample time for detection and treatment. This type of research can unmask barriers to better and frequent screening in the healthcare setting and the possible benefits of a new device to change that paradigm.

Appendix A: WHO cervical cancer screening guidelines

The expert panel¹ recommends against the use of CKC as a treatment in a screen-and-treat strategy. Therefore, all screen-and-treat strategies below involve treatment with cryotherapy, or LEEP when the patient is not eligible for cryotherapy.

The expert panel suggests:

- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with VIA and treat. In resource-constrained settings, where screening with an HPV test is not feasible, the panel suggests a strategy of screen with VIA and treat.
- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. However, in countries where an appropriate/high-quality screening strategy with cytology followed by colposcopy already exists, either an HPV test or cytology followed by colposcopy could be used.
- ▶ Use a strategy of screen with VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat. The recommendation for VIA over cytology followed by colposcopy can be applied in countries that are currently considering either programme or countries that currently have both programmes available.
- ▶ Use a strategy of screen with an HPV test and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.
- ▶ Use either a strategy of screen with an HPV test followed by VIA and treat, or a strategy of screen with an HPV test and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with VIA and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with cytology followed by colposcopy (with or without biopsy) and treat.
- ▶ Use a strategy of screen with an HPV test followed by VIA and treat, over a strategy of screen with an HPV test followed by colposcopy (with or without biopsy) and treat.

Figure A1. WHO cervical cancer screening guidelines contingent on resource availability(5)

Appendix B: Example of colposcopy in diagnostic or screening settings

Table B1. Values adapted from Cantor et al., 2008 (31)

Test Threshold	Diagnostic Accuracy Estimate	Diagnostic	Screening
HSIL	Sensitivity	0.983	0.286
	Specificity	0.451	0.877
LSIL	Sensitivity	0.714	0.191
	Specificity	0.813	0.961

Appendix C: Informed consent form for Survey Part I-III



Duke Global Health Institute & Center for Global Women's Health Technologies

Consent To Participate In A Research Study

Cervical Cancer Screening Methods & New Technology Evaluation

IRB No.: C0461 – EXEMPTION FROM DUKE UNIVERSITY IRB REVIEW

INTRODUCTION

You are being asked for your consent to participate in a study about cervical cancer screening. Your participation on this study is voluntary and there is no compensation for participation. Please read this form carefully and ask the researcher if you have any concerns or questions.

PURPOSE OF STUDY

We are interested in understanding current methods of cervical cancer screening and how a new technology called the transvaginal colposcope (TVC) may be implemented from the perspective of healthcare workers. The TVC is a small, handheld colposcope, seeks to reduce patient discomfort, and can aid the practitioner in screening. Ultimately we hope it will facilitate more screenings in community health settings for cervical cancer prevention. We would like to know your opinions on cervical cancer screening technologies to improve the instrument design and studies.

WHAT IS INVOLVED IN THE STUDY?

All information will be gathered through this survey.

1. You will answer questions about general cervical cancer screening methods you use and your experience in this field.
2. A series of images of the cervix taken with a digital camera will have questions regarding your opinions. All images are taken from approved training material that is in the public domain. If there are any questions regarding the images, please contact the researcher.
3. The third and final part will pose the same questions but with a randomized group of pictures which will include those taken with a digital camera and with a transvaginal colposcope (TVC). This last part will be administered only after your host institution has signed an agreement that authorizes the release of the images.

HOW LONG WILL THE STUDY TAKE?

This survey should take you approximately 15 minutes. You may choose not to participate at all or to stop participating at any time. *This will not affect you in any way personally or professionally.*

CONFIDENTIALITY & USE OF STUDY DATA

There is no risk to you in participating in this study. We only ask for your time. This information will only be used for the purposes of research and planning for technology implementation and clinical studies. All answers will be anonymized and will not be associated with your name or participation.

COSTS OR BENEFITS OF PARTICIPATION

There are no costs associated with this study except the use of your time. If you agree to take part in this study, there will not be direct financial or career related benefit. We hope the information learned from this study will benefit patients in the future by providing information about current and new cervical cancer screening methods including the transvaginal colposcope.

ADDITIONAL QUESTIONS?

If you have any further questions or concerns, you may contact Sisira Gorthala at sisira.gorthala@duke.edu

Appendix D: Survey questions & structure

PART I

1. What is your age?
2. What is your level of education?
 - a. MBBS
 - b. MD
 - c. DGO
 - d. MS
3. What national or state level cervical cancer screening guidelines do you follow if any?
4. How many years have you conducted cervical cancer screening?
5. How many patients do you screen for cervical cancer each week? (Please fill in a number)
6. Do you screen all of your female patients who are sexually active for cervical cancer screening?
 - a. Yes
 - b. No
7. For which of the following reasons do you choose to screen for cervical cancer?
 - a. Family History
 - b. Excessive vaginal discharge
 - c. Bleeding
 - d. Preventive screening performed on regular basis
 - e. Symptomatic
 - f. Other: Please type in any other situations that call for screening
8. Approximately out of 10 women you recommend for cervical cancer screening, how many refuse because they do not like the speculum?
9. Which cervical cancer screening methods do you use first when a patient agrees to be screened?
 - a. Speculum Examination - no staining and only naked eye observation
 - b. Visual Inspection with Acetic Acid (VIA) - Naked eye observation
 - c. Pap Smear Test
 - d. HPV-DNA testing
 - e. Colposcopy
 - f. Cervicography - (VIA with Photos)
 - g. Biopsy
10. Which cervical cancer screening methods have you ever used before?
 - a. Speculum Examination - no staining and only naked eye observation
 - b. Visual Inspection with Acetic Acid (VIA) - Naked eye observation
 - c. Pap Smear Test
 - d. HPV-DNA testing
 - e. Colposcopy
 - f. Cervicography - (VIA with Photos)
 - g. Biopsy

11. Which other cervical cancer screening methods do you currently use?
- Speculum Examination - no staining and only naked eye observation
 - Visual Inspection with Acetic Acid (VIA) - Naked eye observation
 - Pap Smear Test
 - HPV-DNA testing
 - Colposcopy
 - Cervicography - (VIA with Photos)
 - Referral for colposcopy
 - Referral for biopsy
12. Please choose if the following factors are advantages of each of the following methods?

	Cost			Easy to use			Patient comfort			Image quality		
	Yes	No	N/A	Yes	No	N/A	Yes	No	N/A	Yes	No	N/A
Speculum Examination	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
VIA	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Pap Smear Test	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
HPV-DNA testing	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Colposcopy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Cervicography	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Biopsy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

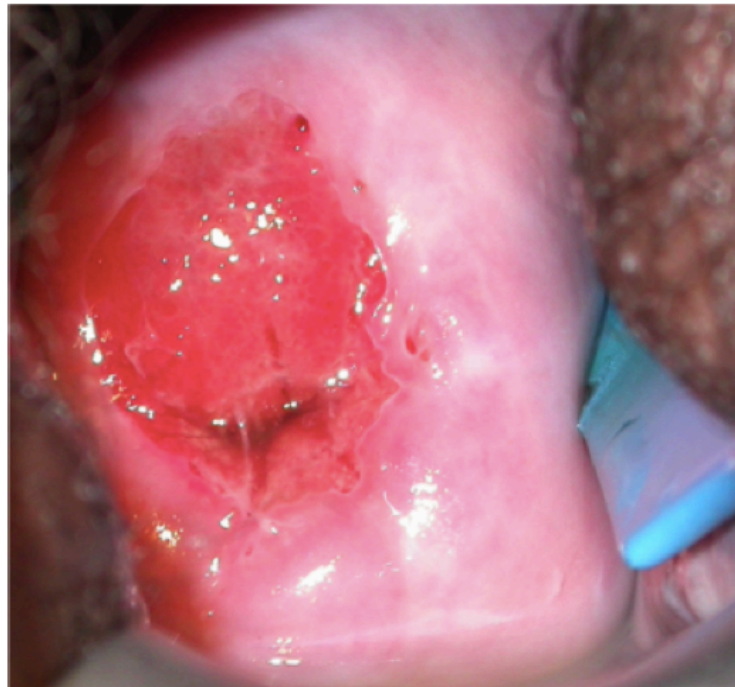
13. What do you use to aid in biopsy?
- None - referral to outside clinic
 - Colposcopy
 - Speculum exam - NO acetic acid and/or iodine preparation
 - Speculum exam - WITH acetic acid and/or iodine preparation
14. Which of the following treatments do you use with colposcopy?
- Not applicable - Referral to another clinic for treatment
 - LEEP
 - Cryotherapy
 - All of the above
 - None
 - Other
15. In your opinion, is VIA more or less accurate than Pap smear test?
- I don't know
 - More accurate
 - Equally accurate
 - Less accurate
16. In your opinion, is VIA more or less accurate than colposcopy?
- I don't know

- b. More accurate
 - c. Equally accurate
 - d. Less accurate
17. For patients who are screened negative, what do you do next?
- a. Ask patient to come back for screening in 3 years
 - b. Ask patient to come back for screening in 1 year
 - c. Ask patient to come back if they have any symptoms
 - d. Nothing
 - e. Other: (please type in your next step)
18. For patients who are screened positive using a Pap smear, what do you do next?
- a. VIA (Acetic Acid)
 - b. Biopsy (no colposcopy)
 - c. Colposcopy aided biopsy
 - d. Referral for colposcopy aided biopsy
 - e. Treatment (e.g. LEEP, cryotherapy, etc)
 - f. Hysterectomy
 - g. Referral to another clinic
 - h. Other: (please type in your next step)
19. If you have a clinically suspicious cervix which of the following regimens do you follow?
- a. Pap smear --> VIA --> colposcopy --> biopsy --> treatment
 - b. Pap smear --> VIA --> biopsy --> treatment
 - c. Pap smear --> biopsy --> treatment
 - d. Pap smear --> treatment
 - e. Pap smear --> VIA --> treatment
 - f. VIA --> biopsy --> treatment
 - g. VIA --> treatment
 - h. Other: Any other option?
20. If the patient has an inconclusive Pap smear and they are unlikely to go for colposcopy?
- a. Perform hysterectomy
 - b. Ask patient to return for testing
 - c. Nothing
 - d. Other: Any other option?
21. Do you use any form of magnification to see the cervix during a only-speculum examination?
- a. Yes (if so what type:)
 - b. No
22. In your opinion, does magnification help VIA (naked eye observation) or speculum examinations?
- a. Yes
 - b. No
23. What light source do you normally use for naked eye observation of the cervix?
- a. Torchlight
 - b. Headlamp
 - c. Medical exam light

24. How far from the entrance to the vagina is the light source in centimeters during naked eye observation of the cervix?
25. Which of the following is used to capture images, if any during naked visualization of the cervix?
 - a. Camera
 - b. Cell phone
 - c. None
26. Do you use anesthesia during colposcopic examination?
 - a. General anesthesia – sometimes
 - b. General anesthesia – often
 - c. Local anesthesia – sometimes
 - d. Local anesthesia – often
 - e. None
 - f. Not applicable - referral for colposcopy in another clinic
27. Do you refer your patients for colposcopy outside of your clinic/hospital?
 - a. Never
 - b. Rarely
 - c. Sometimes
 - d. Often
 - e. Very often

PART II

Example Image: IARC Technical Publication No. 41



1. Is there mosaicism?
 - a. None
 - b. Fine
 - c. Coarse
 - d. Unsure
2. What kind of border to the acetowhitening is there if any?
 - a. Sharp
 - b. Indistinct
 - c. None
 - d. Unsure
3. What kind of color is the acetowhitening, if any?
 - a. Bright White
 - b. Dull White
 - c. None
 - d. Unsure
4. Do you see the transformation zone?
 - a. Recedes into endocervix Yes
 - b. No, this is an inadequate screening/colposcopy
 - c. No, this is not an inadequate screening/colposcopy
 - d. Unsure
5. Other descriptors for suspicion for invasion?
 - a. Atypical vessels
 - b. Fragile vessels
 - c. Irregular surface
 - d. Bleeding
 - e. Ulceration
 - f. Cobblestoning
 - g. None
 - h. Other - please fill in anything else
6. Is this VIA test negative, positive, or inconclusive?
 - a. Positive
 - b. Negative
 - c. Inconclusive
7. What would your next step be?
 - a. Perform cryotherapy
 - b. Perform LEEP
 - c. Refer to another hospital
 - d. Consult another physician
 - e. Ask patient to return in 3 years
 - f. Ask patient to return in less than 3 years
 - g. No further action required
 - h. Unsure
 - i. Other:
8. Any other comments on this cervix?

PART III

Example Image EXCLUDED –

Images from Duke University Clinical Protocol: Pro00008173

14 Matched Images taken with TVDC and Leisan Optik 2 Colposcopy

1. Is there mosaicism?
 - a. None
 - b. Fine
 - c. Coarse
 - d. Unsure
2. What kind of border to the acetowhitening is there if any?
 - a. Sharp
 - b. Indistinct
 - c. None
 - d. Unsure
3. What kind of color is the acetowhitening, if any?
 - a. Bright White
 - b. Dull White
 - c. None
 - d. Unsure
4. Do you see the transformation zone?
 - a. Recedes into endocervix Yes
 - b. No, this is an inadequate screening/colposcopy
 - c. No, this is not an inadequate screening/colposcopy
 - d. Unsure
5. Other descriptors for suspicion for invasion?
 - a. Atypical vessels
 - b. Fragile vessels
 - c. Irregular surface
 - d. Bleeding
 - e. Ulceration
 - f. Cobblestoning
 - g. None
 - h. Other - please fill in anything else
6. Is this VIA test negative, positive, or inconclusive?
 - a. Positive
 - b. Negative
 - c. Inconclusive
7. What would your next step be?
 - a. Perform cryotherapy
 - b. Perform LEEP
 - c. Refer to another hospital
 - d. Consult another physician

- e. Ask patient to return in 3 years
 - f. Ask patient to return in less than 3 years
 - g. No further action required
 - h. Unsure
 - i. Other:
8. Any other comments on this cervix?
9. How satisfied are you with this image?
- a. Very Dissatisfied
 - b. Somewhat Dissatisfied
 - c. Neutral
 - d. Somewhat Satisfied
 - e. Satisfied
 - f. Very Satisfied

Appendix E: Positive and negative attributes of screening and diagnostic tools for cervical cancer

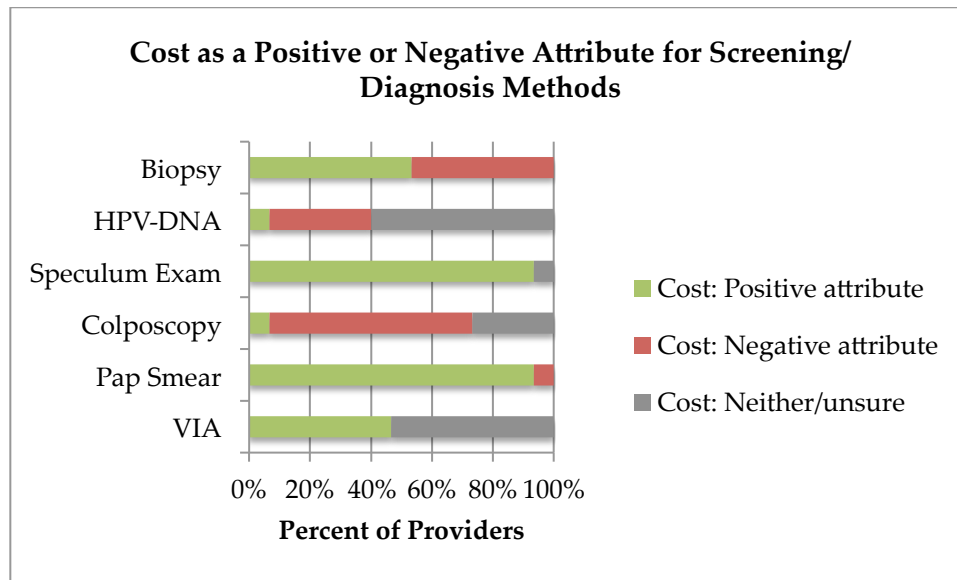


Figure E1. Cost chosen as positive or negative attribute for screening/diagnosis methods

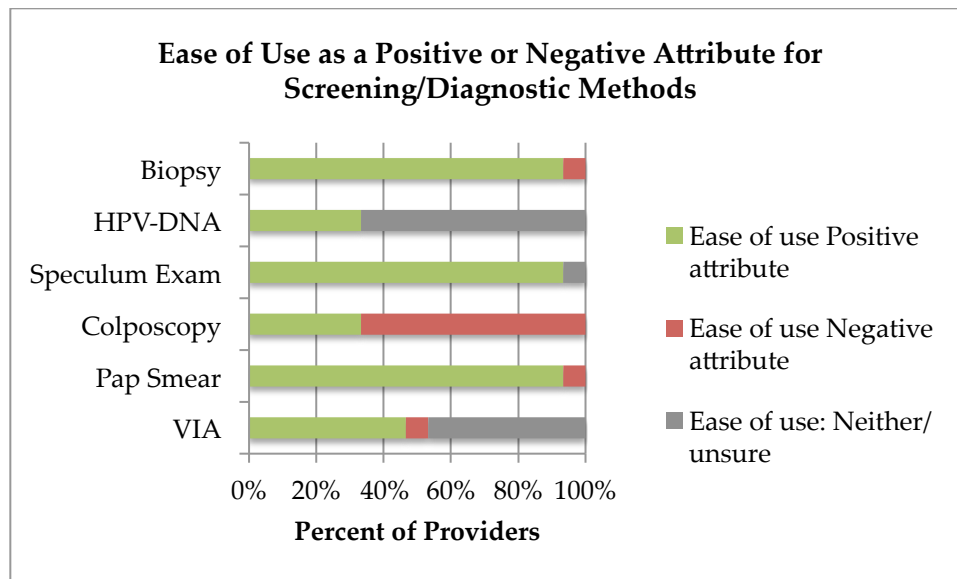


Figure E2. Ease of use chosen as positive or negative attribute for screening/diagnosis methods

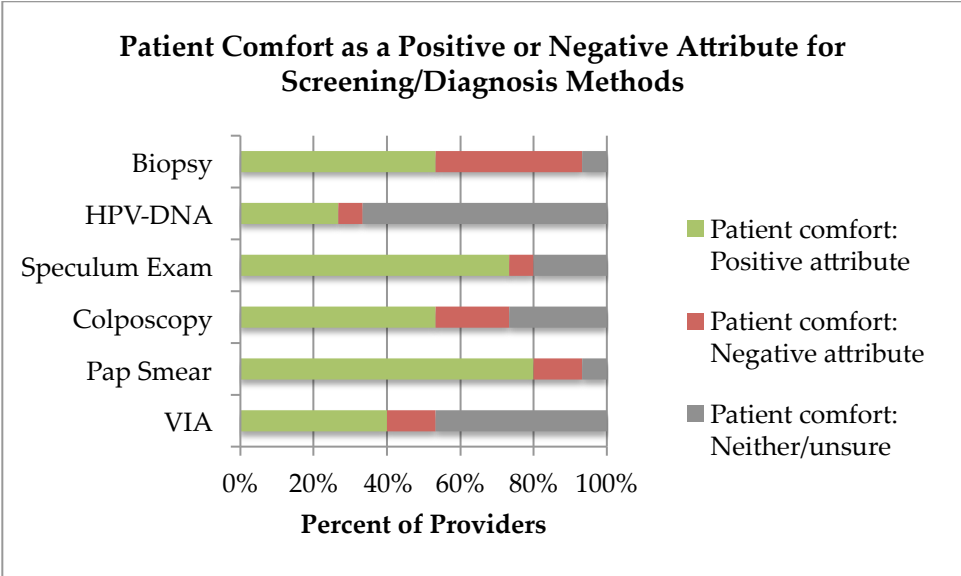


Figure E3. Patient comfort chosen as positive or negative attribute for screening/diagnosis methods

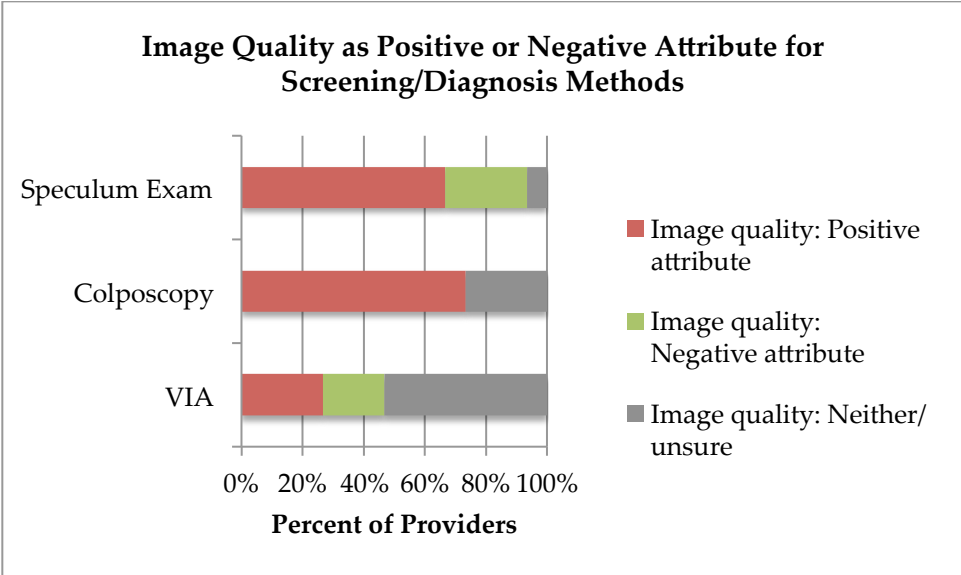


Figure E4. Image quality chosen as positive or negative attribute for screening/diagnosis methods

Appendix F: Accuracy of TVDC and matched colposcopy images by each physician

Table F1. Accuracy of TVDC and matched colposcopy images

Participant	TVDC Accuracy	Matched Colposcopy Accuracy
A	43%	57%
B	57%	71%
C	57%	71%
D	57%	43%
E	71%	57%
F	71%	71%
G	71%	71%
H	86%	100%

Appendix G: Likert scale differences between TVDC and matched colposcopy images

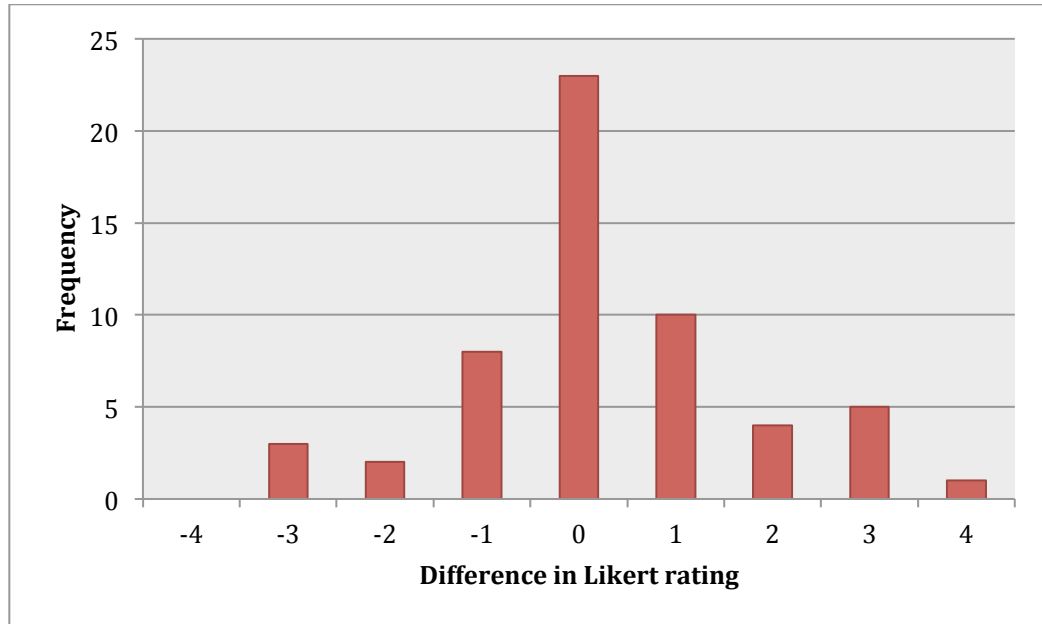


Figure G1. Difference on Likert scale in preference for TVDC and colposcopy.

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