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CULMINATING EXPERIENCE COVER PAGE

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Culminating Experience Paper or Project Title:

Buen Pastor Clinic Can More Cost-Effectively Screen and Treat for Cervical Cancer by Prioritizing its Current Use of VIA and Adding Cryotherapy Treatment

Abstract (150-300 words)

Background: Although cervical cancer is the leading cause of cancer death among women in Honduras with an incidence of 39.6 new cases per 100,000 women, the country does not have a national screening program for cervical morbidity and cancer; nevertheless, La Clínica Buen Pastor in Olancho has an established cytology-based (Pap smear) screening program that attempts to screen and treat as many women as possible in the region. This policy memorandum provides evidence for simple modifications that can make the clinic's program more efficient and cost-effective.

Methods: For July-August 2008, I assisted Dr. Sheree Lynch and La Clínica Buen Pastor (Olancho, Honduras) with the clinic's cervical cancer screening program. The recommendations I provide in this memo are derived from my fieldwork and from a comprehensive literature review of the most cost-effective screen-and-treat options for low-resource countries, such as Honduras.

Findings: Visual Inspection with 3-5% Acetic Acid (VIA) has been shown to be the most effective, cost-saving, and low-technology (no laboratory needed) alternative to traditional cytology for low-income countries, including Honduras. VIA is more sensitive (up to 96% sensitivity) than Pap smears (though less specific) and identifies more cervical dysplasia cases than cytology. VIA allows for immediate, same-day treatment with cryotherapy, a safe and inexpensive treatment with a notable 89.5-91% cure rate. Single-visit or two-visit strategies are the most effective for the lowest cost. Screening women once every 3-5 years is more cost-effective than doing repeated Pap smears and could reduce the incidence of cervical cancer by 69-81%. VIA and cryotherapy are acceptable to Honduran women.

Conclusions: La Clínica Buen Pastor should use VIA as its primary screening tool (replacing Pap smears) and use cryotherapy for treatment at the same or next visit. These feasible changes will maximize detection of cervical dysplasia, increase treatment rates, and lower regional cervical cancer incidence.

CE Advisor: _____ Date: _____

To : Dr. Lynch - La Clínica Buen Pastor, Olancho, Honduras
From : **Aiesha LaNiece Hill Garrett**
Boston University School of Public Health MPH Candidate; Buen Pastor Consultant
Date : December 17, 2008
Re : **Buen Pastor Clinic Can More Cost-Effectively Screen and Treat for Cervical Cancer by Prioritizing its Current use of VIA and adding Cryotherapy Treatment**

Cervical Cancer devastates many women throughout the world and is a leading cause of death among women in developing countries. Eighty percent of deaths from cervical cancer occur in low resource, developing countries (1-4). Honduras is not exempt from this epidemic. Cervical cancer is the most frequently occurring cancer in Honduras, averaging 24.4% of all cancer cases (5). As the human papillomavirus (HPV) spreads throughout the country's communities - due to early initiation of sexual activity, unsafe sexual practices, and infidelity - new cases of cervical cancer continue to arise. And yet, simple technologies have been developed to make screening and prevention of cervical cancer more feasible, even for areas, such as Olancho, Honduras, where resources and trained medical personnel are limited.

To meet the challenge of cervical cancer and pre-cancer, La Clínica Buen Pastor needs to find the most cost-saving, efficient, and socially acceptable method of screening and treatment for cervical cancer within the community. Modifying the clinic's current cytology (Pap smear) - and visual inspection-based approach and adding cryotherapy as a treatment option may prove crucial in reducing the incidence of cervical cancer and in making the most effective use of the clinic's time, resources, and medical staff.

La Clínica Buen Pastor (6) is a private primary healthcare and preventive services clinic and pharmacy (founded in 1983 under The Luke Society), located in Santa María del Real, Olancho, Honduras. Currently the clinic has: 3 full-time physicians (but no certified nursing staff); and, an on-site pharmacy, basic laboratory (no cytology-reading capabilities), and some advanced equipment (mammography, ultrasound and sonogram, X-ray, echocardiogram,

cauterization machines). Buen Pastor is a trusted clinic within Olancho that treats an average of 21,000 patients from low-income families annually (6). Traveling medical teams provide care to the remote mountain communities. Each day, the clinic serves between 50-100 patients. Due to the high quality of care, service, and support at Buen Pastor, many patients travel hours past local government health centers to attend this private clinic for primary healthcare, emergencies, and basic surgeries* (further details in Appendix A).

Cervical cancer in Honduras is the most common cancer among women (3), with an incidence of approximately 39.6 new cases per 100,000 women in the country each year (7). When compared to developed countries, such as the United States (7.4 new cases per 100,000), and other developing countries, such as India (17.1 new cases per 100,000), the incidence of cervical cancer in Honduras is alarmingly high (8). In fact, cervical cancer is the leading cause of cancer death among women in the country (9). Researchers suggest that Honduras' overall lack of an organized screening program for cervical cancer contributes to the high mortality (9). For this reason, La Clínica Buen Pastor's current program to regularly screen and treat women for cervical pre-cancer and cancer within the communities of the Olancho province is noteworthy. Nevertheless, research on screening and treatment within low resource settings has shown that the cytology-based screening currently employed by the clinic could be more efficient and cost-saving if modified to focus on visual inspection and cryotherapy.

Methods: From July 4, 2008 through August 21, 2008, I assisted Dr. Sheree Lynch and La Clínica Buen Pastor on cervical cancer screening, research, and patient education. Before, during, and after my fieldwork in Honduras, I reviewed the literature on the current cost-effective and accurate screening methods for cervical cancer screening in low-income countries.

* All anecdotal or observational information obtained via my personal communication (e-mail, phone, in-person) and experiences (while working at Buen Pastor clinic) with Dr. Sheree Lynch (both in the U.S. and in Honduras) from April 25, 2008 – October 19, 2008, will be indicated henceforth in this memo by an asterisk (*).

While in Honduras, I shadowed Dr. Lynch during patient consultations, follow-ups, and procedures (including Pap smears, biopsies, colposcopies, cauterizations, etc.), developed and conducted patient surveys, and did "waiting room chats" individually and in groups with women on cervical and breast health. The recommendations I propose in this memo are, thereby, based on my research (further details in Appendix B).

Buen Pastor's current policy on cervical cancer screening is to have each woman receive a Pap smear every 3 months (Appendix C Figure 1). After 1 year, if no abnormalities are detected, the patient may be graduated to a 6-month screening track, at the discretion of the treating physician. If abnormalities are found, a biopsy is performed to determine the level of cervical dysplasia (cervical intraepithelial neoplasia or CIN).[1] CIN-1 and CIN-2 dysplasias are then treated via electric cauterization (cautery) and follow-up. Basic Pap smear screening with no abnormalities requires 2 visits, one for a Pap smear and a follow-up in 15 days for the results.

A woman presenting with an abnormal Pap smear must return for at least two additional visits to receive a biopsy of the affected area of the cervix and to find out the results. If the biopsy is positive for dysplasia, the patient must attend two more clinic visits (before returning to a regular Pap smear schedule) for electric cautery of the dysplastic area and for post-operative follow-up. Thus, a female patient with dysplasia may have a total of six or more visits at the clinic within a two month period to receive screening and treatment for cervical dysplasia and pre-cancer. This consumes a great deal of the time of the three doctors in the clinic and is invasive and inconvenient for the women being screened and treated.

The costs to the patients are as follows: U.S $5.30 for Pap smear; U.S. $29.00 for biopsy and $16.00 for the accompanying colposcopy; U.S $16.00 for cautery; U.S. $ 2.65 for

[1] Cervical dysplasia (also called CIN) is defined as an area of abnormal cells in the anogenital skin (epithelium) of the cervix. Refer to Appendix C Figure 2 for a more detailed description and diagram of CIN.

follow-up visits.[2,3] Olancho is a province of extreme poverty (10), where many people are living on less than one dollar a day and most women are housewives.* Thus, for the women of the community, so many clinic visits each year at such steep prices are not only too financially taxing and time insensitive, but also grounds for ignoring their cervical health. In my interviews with women in the clinic waiting room, I found that several women who were not up to date with their Pap smears knew the importance of getting screened regularly but simply could not afford the visits and procedures involved. Importantly, these women are not the only ones bearing the cost burden; the clinic expenses are also high at U.S. $4.00, $29.00, and $10.60 per Pap smear, biopsy, and cauterization, respectively (these costs are deducted from the above patient costs).

The strengths of Buen Pastor's screening program are that the clinic has an established procedure to screen and treat women for cervical cancer and dysplasia and that women are aware of the steps they must take to be screened and treated in their community. Unfortunately, the clinic's noteworthy efforts may be lost in screening too often and not using the most cost-effective screening and treating procedure; many women are lost to follow-up, because of the burden the program places on them financially and time-wise.*

Evidence-Based Screening: Cytology vs. Visual Inspection

Visual Inspection with 3-5% Acetic Acid (VIA) has been found to be the most effective, cost-saving, and low-technology alternative to traditional cytology for low-income countries (11,12), including Honduras (13). Procedurally, VIA often involves naked-eye (without magnification) examination of the uterine cervix one minute after the cervix is swabbed with acetic acid (11). A bright light source, such as a halogen lamp, is used to illuminate the vaginal area during inspection. The health worker performing the VIA identifies any lesions on the

[2] Colposcopy (at biopsy) uses a lit microscope to examine the cervix for suspicious lesions (Palefsky, 2002).
[3] Cauterization (electrocautery or electric cautery) is the act of using an electrode to burn away problematic tissues.*

cervix that appear dull, opaque white (acetowhite) and are well-defined. Acetowhite lesions indicate a positive VIA[4] test. Detection of these lesions may lead to early diagnosis of high grade CIN and early, asymptomatic (pre-clinical) stages of invasive cancer. Results of VIA are known immediately after the test is performed, allowing for same-day (same-visit) treatment if possible (2,11,12,14). In the developing world, the convenience of getting treatment the same day as screening (screen-and-treat approach) cuts patient and health facility costs, the number of clinic visits and consultation time, travel time, and loss to follow-up (1,12,13,15,16).

The Effectiveness of VIA as a primary screening method in developing countries has been thoroughly tested (10,17-23). The evidence shows that VIA is a viable tool for detecting precancerous cervical lesions (2,11,24,25). In fact, compared to conventional cytology, VIA performs similarly or better than cytology at detecting high-grade lesions or cervical cancer precursors (2,11,25). Studies from around the world consistently show that VIA is at least as sensitive[5] as (and often more sensitive than) cytology (7,11,17,21-23). In other words, VIA better identifies women with high grade dysplasias and cancer than does cytology. The trade-off is that VIA is less specific than cytology, so it may incorrectly identify more non-diseased women as positive than Pap smears would (7,11,17,21-23). However, the studies detailed in the Appendix C, Table 1 and described in Discussion 1, show that identifying more true cases of pre-cancerous dysplasia outweighs the possibility of mislabeling some non-diseased women as cases.

Cytologic screening is less effective than VIA. Even with good Pap smear cell collection (by the health professional) and well-trained cytopathologists, cytology's sensitivity is only moderate, with a mean sensitivity of just 58% (26,27). Thus, with cytology many women will

[4] Visual Inspection with Acetic Acid (VIA) has also been referred to as Direct Visual Inspection (DVI) and, less frequently, as cervicoscopy and aided visual inspection (WHO, 2002).
[5] The sensitivity of a screening test is the probability that diseased individuals will actually test positive when given that test. The specificity of a screening test is the probability that non-diseased people will actually test normal when administered that test.

have false negative Pap smear results and will go untreated for their dysplasia (28). The Pap smears must, therefore, be repeated often (annually to every 2-3 years (29-33)) to lower the probability of not detecting a lesion (28,34). The developed world's citizens can afford these costs of repeated cytologic screening; underdeveloped areas like Olancho, Honduras cannot.

Research in rural Honduras shows that VIA offers an effective alternative to cytology. Perkins et al. (2007) (13) studied 339 women who received both VIA and a Pap smear. Only two of the women (0.6%) tested positive from the Pap smears, whereas forty-nine of the women (14%) tested positive with VIA. Of the 49 positive VIA tests, 23 women were confirmed to have dysplasia through biopsy. The Pap smears missed all of these 23 cases. Also, when the same Pap smears were reviewed in the United States, 14 of them were determined to be positive (compared with only 2 in Honduras) (4%). Thus Pap smears prepared in Honduras, even when read by qualified laboratories in the U.S. still identify fewer cases of dysplasia than VIA. The poor quality of the few laboratories in Honduras contributes to the inaccuracy of the smears (35).

Additionally, the women screened with VIA were twice as likely to comply with follow-up compared with the women screened only via Pap smear (83% follow-up for VIA vs. 38% follow-up for Pap smear). The researchers attribute the difference in follow-up to be due to the real-time nature of VIA that allows women to immediately know the results of their VIA and the necessary steps to treatment (or on-the-spot treatment, if they so choose). In the study, the cost per Pap smear was U.S. $3.00[6] whereas the cost of VIA was only U.S. $0.22. All women offered VIA in the study agreed to undergo the screening test.

Overall, this community-based Honduran study by Perkins et al. illustrates several key points about the success of VIA as a screening tool in Honduras: (1) VIA has a higher sensitivity and is more accurate than even high quality Pap smear readings, thereby identifying more cases

[6] Based on direct purchase of materials and the hourly wage of a Ministry of Health nurse (Perkins et al., 2007).

of dysplasia; (2) VIA yields higher follow-up rate than Pap smears and lends itself to immediate treatment; (3) VIA is more cost-effective than Pap smears in the rural Honduran setting; (4) VIA is acceptable to Honduran women (13). This study was done is a setting similar to Buen Pastor.

A screen-and-treat approach, coupling VIA with cryotherapy[7] is often suggested to maximize treatment and minimize visits and costs in low-resource settings. Cervical cryotherapy involves using a liquid-nitrogen-cooled probe or a liquid nitrogen or nitrous oxide gas 'gun' to freeze and kill the cells of abnormal tissues on the cervix (28). Carbon dioxide gas may be used as the cryotherapy refrigerant in place of nitrous oxide (36). Cryotherapy can be performed immediately after a positive VIA test (2,24,37,37-39) and has been shown to be as effective as other methods of treatment including loop electrosurgical excision procedure (also called LEEP) (40), a more deep-tissue version of the electric cauterization Buen Pastor uses. Research suggests that a single or two-visit strategy to screen and treat cervical lesions with VIA and cryotherapy is safe, acceptable, reliable and cost-effective for low-resource settings (1,2,15,24).

Research shows that the use of conventional, multi-visit, cytologic screening methods in developing countries is impractical, because they are higher in cost and less effective (12,16). The most cost-effective strategies are the screen-and-treat approaches that require the fewest patient visits, because they reduce the loss to follow-up and increase treatment rates (15,16). Screening with VIA and treating acetowhite lesions in the same day has been successfully tested and evaluated as a screen-and-treat approach in low-resource settings (1,2,15,16,24,38); the approach saves time, eliminates extra visits, and reduces costs. Based on studies from India, Kenya, Peru, South Africa, and Thailand, the following conclusions have been made (16): The traditional strategies of three visits or more - such as the current procedure at Buen Pastor - were found to be the least effective strategy for screening and treatment (16). Two-visit strategies

[7] Cryotherapy is sometimes called liquid nitrogen therapy (Palefsky, 2002).

were more effective and less costly than three-visit strategies. Nevertheless, single-visit strategies (VIA and cryotherapy same day) were most effective and least costly (1,15,16). Refer also to Appendix C Figure 3 for the diagramed results of these five studies.

Goldie et al. (2001) note that screening with VIA every 5 years costs about the same as doing cytology only three times in a woman's lifetime, yet it reduces the incidence of cancer by 69%. Screening using VIA every 3 years costs less than performing cytology only five times in a woman's life and reduces cervical cancer incidence by 81%. Refer to Appendix C Figure 4 for the cost differences over a lifetime using cytology vs. VIA (1).

Based on 32 studies reviewed by the Alliance for Cervical Cancer Prevention, cryotherapy has an overall cure rate of 89.5%-91%, demonstrating that cryotherapy is as effective as other standard out-patient treatment methods for CIN (36). In Peru, Luciani et al. found of 472 women treated with cryotherapy for CIN1-3, cryotherapy effectively cured 418 women (88%), of which 49 had CIN-3 before cryotherapy (37). Overall, at the end of the follow-up period of the study, 92% of the women with initial diagnoses of CIN-1 and CIN-2 were cured and 70% of women with CIN-3 were cured. When offered the option of same-day treatment after VIA, 78% of the women agreed (thus, no loss to follow-up for treatment occurred in this group). Of the 345 women who chose to return for treatment at a later date, 140 did not return (40.5% loss to follow-up for treatment with the two-visit approach).

In Ghana, Blumenthal et al. found that only 2.6% of the women treated with cryotherapy (at the same visit as VIA or at a subsequent treatment visit) tested positive 1-year post treatment (38). Almost 100% of the women were satisfied/very satisfied with VIA and cryotherapy (38). Side effects with cryotherapy are minimal and not considered serious (36,37).[8] Thus, VIA and

[8] The strengths and limitations of cryotherapy are provided in Appendix C Figure 5 (41).

cryotherapy are shown to be effective treatment methods, that are safe and acceptable (41). And, reducing the number of visits reduces the loss to follow-up.

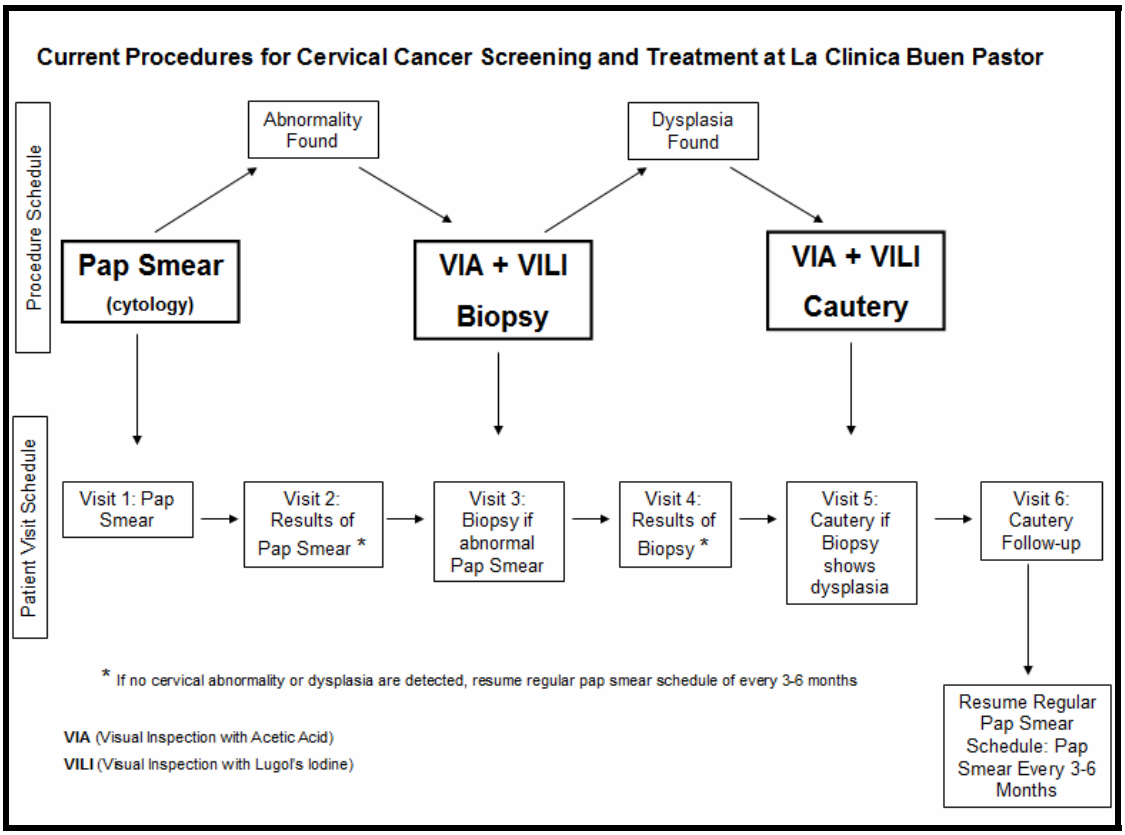
What does the evidence on VIA and cryotherapy mean for Buen Pastor?

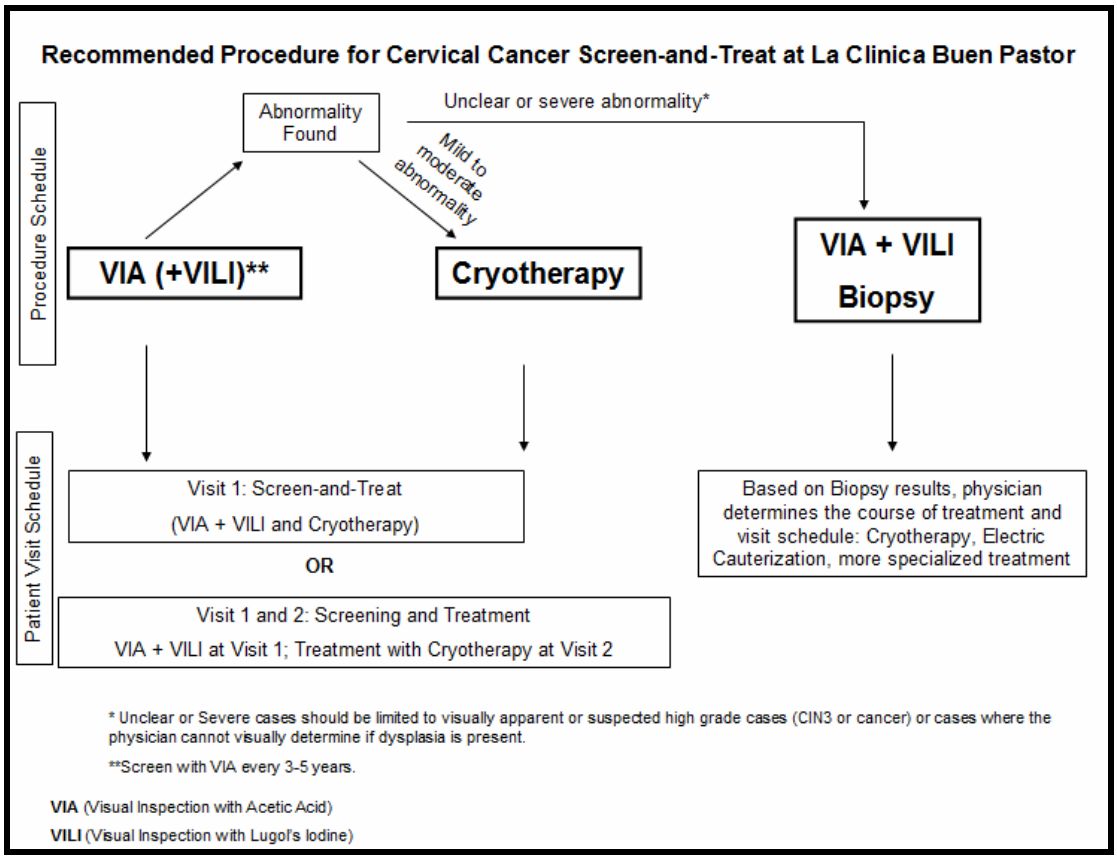
VIA already in-use at Buen Pastor: Fortunately, doctors at Buen Pastor already perform visual inspection with acetic acid during the biopsies and cauterizations (Refer to the diagrams on the following page)[9]. At the clinic, during the initial Pap smear, no acetic acid is applied to the cervix. The physician simply swabs the cervix and smears the cervical cells onto a slide to be sent to the capital (Tegucigalpa) for reading by the cytopathologists.[10] Results are usually returned to the clinic in 15 days, at which point the female patient must make another clinic visit to learn the outcome of her Pap smear. Staff admit that the pathological readings done in the country are subject to inaccuracy, thereby producing false negatives due to mixed up test results and incorrect readings of Pap tests* (13,35). Despite Western medicine recommendations to do Pap smears every 1-3 years (29-32), the clinic feels it must perform 2-6 Pap smears per year on each eligible female patient to ensure that any abnormalities and false negatives are detected.

Doctors admit they must learn to stop relying so heavily on cytology results and use their 'clinical eye' more effectively to assess cervical lesions as well.* The research agrees with this assessment, showing that cytological screening in developing countries (such as Honduras) is often of poorer quality in comparison to developed countries, because of the difficulty of finding and maintaining well-trained cytotechnologists and high quality laboratories (1,2,13,20,35).

No need for Pap smears anymore: When women return to the Buen Pastor for their third-visit biopsy after having a positive or abnormal Pap smear (2 visits), the doctors use acetic acid to visually inspect the cervix to determine (using their 'clinical eye') where the

[9] These diagrams can also be found in Appendix C Figure 1 and Figure 6.
[10] The clinic cannot support an on-site cytopathologist.


Current Procedures for Cervical Cancer Screening and Treatment at La Clinica Buen Pastor
Procedure Schedule
Abnormality Found
Dysplasia Found
Pap Smear (cytology)
VIA + VILI Biopsy
VIA + VILI Cautery
Patient Visit Schedule
Visit 1: Pap Smear
Visit 2: Results of Pap Smear *
Visit 3: Biopsy if abnormal Pap Smear
Visit 4: Results of Biopsy *
Visit 5: Cautery if Biopsy shows dysplasia
Visit 6: Cautery Follow-up
* If no cervical abnormality or dysplasia are detected, resume regular pap smear schedule of every 3-6 months
VIA (Visual Inspection with Acetic Acid)
VILI (Visual Inspection with Lugol's Iodine)
Resume Regular Pap Smear Schedule: Pap Smear Every 3-6 Months


Recommended Procedure for Cervical Cancer Screen-and-Treat at La Clinica Buen Pastor
Procedure Schedule
Abnormality Found
Unclear or severe abnormality*
Mild to moderate abnormality
VIA (+VILI)**
Cryotherapy
VIA + VILI Biopsy
Patient Visit Schedule
Visit 1: Screen-and-Treat (VIA + VILI and Cryotherapy)
OR
Visit 1 and 2: Screening and Treatment
VIA + VILI at Visit 1; Treatment with Cryotherapy at Visit 2
Based on Biopsy results, physician determines the course of treatment and visit schedule: Cryotherapy, Electric Cauterization, more specialized treatment
* Unclear or Severe cases should be limited to visually apparent or suspected high grade cases (CIN3 or cancer) or cases where the physician cannot visually determine if dysplasia is present.
**Screen with VIA every 3-5 years.
VIA (Visual Inspection with Acetic Acid)
VILI (Visual Inspection with Lugol's Iodine)

abnormalities are. The Pap smear results do not indicate where on the cervix the doctors should look; the results simply let the physician know there may be acetowhite lesions to biopsy when VIA is performed. The actual identification of the lesions and their location on the cervix is thereby left to the physicians. At Buen Pastor, the doctors use VIA (with colposcopy magnification), as well as VILI (Visual Inspection with Lugol's Iodine)[11] (39), to find any lesions on the cervix to biopsy. Since Buen Pastor physicians are well trained in VIA (and VILI), if they skip the cytology step for their patients, they should still be able to identify the lesions on the cervix. In fact, since the cytology readings from the capital may be inaccurate and patients may subsequently be lost to follow-up,* doctors at the clinic – to preserve time and resources and to increase the number of true cases they detect – should perform VIA, instead of a Pap smear at the first visit. The truth is that, if there is an abnormality, the physicians will end up having to use VIA anyway to find that abnormality at a later visit.

VIA already effective at Buen Pastor: Screening using VIA and treating with cryotherapy on the same day or at a second visit actually fits well within Buen Pastor's current treatment framework. VIA and VILI are again used at cauterization if the biopsy results indicate dysplasia. Anecdotally, no biopsies performed at Buen Pastor (after VIA and VILI to locate possible lesions) have come back negative for dysplasia.* This observation means that the lesions clinic doctors are identifying through visual inspection are actually the problematic areas of the cervix that require further treatment (i.e. cauterization, etc.). The different tissue samples for various areas of visual dysplasia on the cervix that Buen Pastor doctors assess before biopsy are mixed together (i.e. they are not packaged as separate samples from differing areas on the patient's cervix) and are sent to the capital for collective testing. When the results return

[11] Visual Inspection with Lugol's Iodine (also known as VILI or the Schiller's test), uses an iodine solution to identify precancerous lesions, which appear as well defined, thick, mustard or saffron yellow (compared to the normal black coloring produced by iodine on normal tissues). Sometimes VILI is used in place of or in conjunction with VIA (Alliance for Cervical Cancer Prevention, 2005)

abnormal (as they always do*), the physicians must then reapply acetic acid (and Lugol's iodine) to the cervix to reveal the same lesions previously biopsied. Thus, at cauterization, Buen Pastor doctors are re-doing their own fine work in identifying dysplastic lesions via visual methods.

Forgo the biopsy: The only advantage for the clinic that a biopsy confers is CIN-grade a diagnosis. Simply treating based on VIA without biopsy does not let physicians know if the visual lesions are worse than severe dysplasia (i.e. cancer). However, more severe CIN (such as CIN-3) and cancer may have a different appearance on the cervix than low-level dysplasia (42). Based on anecdotal evidence, Buen Pastor doctors' – using VIA and their 'clinical eye' – have correctly determined that a negative Pap smear result was a false negative*. When the cervix was hard, bleeding, and/or red, showing signs of high grade dysplasia, the subsequent biopsies have confirmed the doctors' suspicions of CIN-3 and cancer*. Thus, as well-trained physicians, a diagnosis from biopsy is merely reassurance that their assessment is correct… but, it comes at a high financial cost to the clinic and to its patients. Biopsies should be reserved for cases that doctors' clinical knowledge and their 'clinical eye' during visual inspection tell them are most severe and may require more advanced treatment than the clinic offers. Recall that studies show that VIA (when performed properly) accurately detects high-grade lesions and invasive carcinomas (11,17-19,21,23).

Since the electric cauterization now used by the clinic requires another round of VIA (and VILI), the biopsy step, like the Pap smear step, can also be skipped. If the clinic offers a screen-and-treat approach, a lesion identified by VIA can be immediately treated at the same visit. Even if a second visit is needed for follow-up or even if the cryotherapy procedure is delayed until the second visit, the screen-and-treat option will require 4-5 less visits for one round of screening than Buen Pastor's current procedure. VIA and cryotherapy will also eliminate the need for women to be screened excessively each year with cytology to ensure that they are cancer-free.

Recommendations: VIA and Cryotherapy in Place of Repeated Pap Smears

Buen Pastor has the option to make its screening techniques more patient-friendly, cost- and time- saving, effective and sustainable. Based on my research at the clinic and considering the published evidence presented for the effectiveness of VIA and cryotherapy in a single or double visit approach, my recommendations for Buen Pastor are as follows (Appendix C Figure 6):

1) **Switch to a one- or two- visit screen-and-treat regimen**. The clinic's current 6-visit regimen for screening and treatment is neither cost- nor time-saving.

2) **Employ VIA as the primary screening tool, replacing the conventional cytologic screening cycle the clinic currently uses.** The clinic already uses VIA to identify lesions for biopsy and cauterization. Skipping the initial Pap smear is actually eliminating the most insensitive part of the screening and treating process at the clinic.

3) **VIA may continue to be accompanied by colposcopy magnification (at the clinic's discretion).** Although VIA with magnification[12] does not seem to increase test accuracy (11), for quality assurance, I recommend the continued use of magnification with VIA.

4) **Use VILI as an additional check for lesions.** Researchers have not yet determined whether sequential application of Lugol's after VIA reduces the false-positives of VIA (10). Since Buen Pastor is accustomed to (and has achieved accuracy) following VIA with VILI, VILI may continue to be used as a double-check mechanism.

5) **Reserve biopsies for unclear and severe cases**. Again, since VIA accurately identifies high-grade lesions, the clinic can skip the VIA + VILI + Biopsy step and move right to VIA (+VILI) + immediate treatment. Biopsies will determine the seriousness of any unclear cases and whether cryotherapy or specialized treatment is needed.

6) **Use cryotherapy immediate post-VIA or at Visit 2.** Cryotherapy can be used in place of electric cauterization to treat women immediately after screening with VIA (or at Visit 2 if women are unable to pay for immediate treatment). This method of screen-and-treat may be particularly useful in the mountain communities Buen Pastor visits, where electricity is not available. Women can be treated upon screening and avoid travel to the clinic, and the medical team can minimize its trips.

7) **Screen women only once a year (unless a cervical problem is suspected).** Although studies show that VIA is most effective and cost-saving every 3-5 years (1,12), the clinic should begin with annual screening and steadily work towards screening every 3-5 years.

A model of the estimated cost differences between Buen Pastor's current screening and treatment program and the recommended VIA + cryotherapy program is located in Appendix C Figure 7.

[12] VIA with magnification is sometimes referred to as VIAM (WHO, 2002)

Potential Challenges

Since VIA is already a part of the general screening and treatment procedures for Buen Pastor, modifying the program to focus primarily on VIA and cryotherapy should not pose many challenges. Potential challenges may arise with respect to equipment procurement, clinician assurance, and patient education.

Women attending the clinic for Pap smears are already accustomed to receiving VIA, so the main concern would be explaining the new procedures to the patients. Female patients tend to be very trusting of physician's advice and decisions at Buen Pastor, so the clinic should expect little resistance to VIA being used as a primary screening method. Women may be reluctant, however, to the immediate additional cost of on-the-spot cryotherapy treatment (though the women are not likely to be opposed to the treatment itself). For this reason, a Visit 2 for treatment is proposed as a secondary option to same day treatment. Overall, however, based on the surveys conducted at Buen Pastor and based on the distance traveled, and the time and costs lost to so many visits for screening (under the current policy), women will most likely be thankful for a shortened and less expensive option for screening and treatment.

New materials and equipment: Although the clinic is already equipped with a steady supply of acetic acid and Lugol's iodine, the clinic will need to procure cryotherapy equipment. Much of the equipment and materials presently used in the clinic are donated, refurbished, or discounted. A new cryosurgical unit may cost about $1700, but the connections the clinic has with U.S. doctors and hospitals may allow for used cryosurgical equipment to be purchased (or even donated or acquired through an international grant) at a much lower cost.

Doctors at the clinic will need no additional training on VIA and will require minimal training (no more than few hours) to learn to perform cryotherapy effectively. The overall concern that Buen Pastor physicians show for their patients most likely indicates that additional

training will not be met with much resistance. The main hurdle is assuring doctors that using VIA and cryotherapy in place of the traditional cytologic cycle is not simply a money-saving technique, but also a highly effective technique (equally or more effective than cytology). A training session will likely be needed to ensure the participation of the clinic's doctors.

Conclusion: Maximize Resources, Case-Identification/Treatment with VIA + Cryotherapy

La Clínica Buen Pastor currently has most of the elements needed to run the most effective and most cost-saving screening and treatment regimen for cervical cancer: VIA and cryotherapy. Considering the proven ability of VIA to detect more dysplasia cases than even well-performed cytology and considering the clinic's already widespread use of VIA as an adjunct screening tool, VIA should now become the primary screening method at Buen Pastor. Cryotherapy should be offered for immediate treatment following a positive VIA test and should replace the expensive electric cauterization procedure presently used for treatment at the clinic. Buen Pastor has the chance to improve its exceptional track record by offering this evidence-based program for effective, sustainable, and accurate cervical cancer screening and treatment.

Appendix A

La Clínica Buen Pastor: History, Background, Resources

La Clínica Buen Pastor (6), is a private primary healthcare and preventive services clinic and pharmacy located in Santa María del Real, Olancho, Honduras. The clinic was founded in 1983 under The Luke Society (43), a medical missions organization that supports the work of indigenous (i.e. local) Christian health professionals practicing in their communities in various countries around the world. Buen Pastor has 3 full-time physicians and no certified nursing staff. Due to donations and active purchasing and advocating, the clinic's on-site pharmacy is well-stocked with medicines and treatments that many local pharmacies do not have and decent equipment (such as cautery equipment). The clinic is also fortunate to have the only mammography machine in all of the Olancho province (mammography is normally performed only in the capital), the only consistently functioning X-ray machine in the region (the only other X-ray machine in the region is in the hospital and often does not work), and the only advanced sonogram and echocardiogram machines (producing images in both black-white and color) in Olancho. The on-site laboratory functions in basic testing - including general blood counts, urine tests, malaria and dengue fever testing - but has neither the capacity nor a trained pathologist to read Pap smears and biopsies.

Buen Pastor is a trusted clinic within Olancho and has an average of 21,000 patients annually, primarily from very low-income families (6). The clinic also has traveling medical teams that extend medical services to the remote mountain communities that otherwise would not have access to care. Each day, the clinic serves between 50-100 patients, most of these patients being women and children. Due to the high quality of care, service, and support provided at Buen Pastor, many patients travel hours past their local government health centers to attend this private clinic for primary healthcare, emergencies, and basic surgeries.*

The clinic also has a program that sends children with major health issues, such as congenital heart disease, to the United States for surgery that Honduras cannot offer them. Many children in the area have been afforded life-saving treatments and surgeries through the program.

Appendix B

Methods of Research

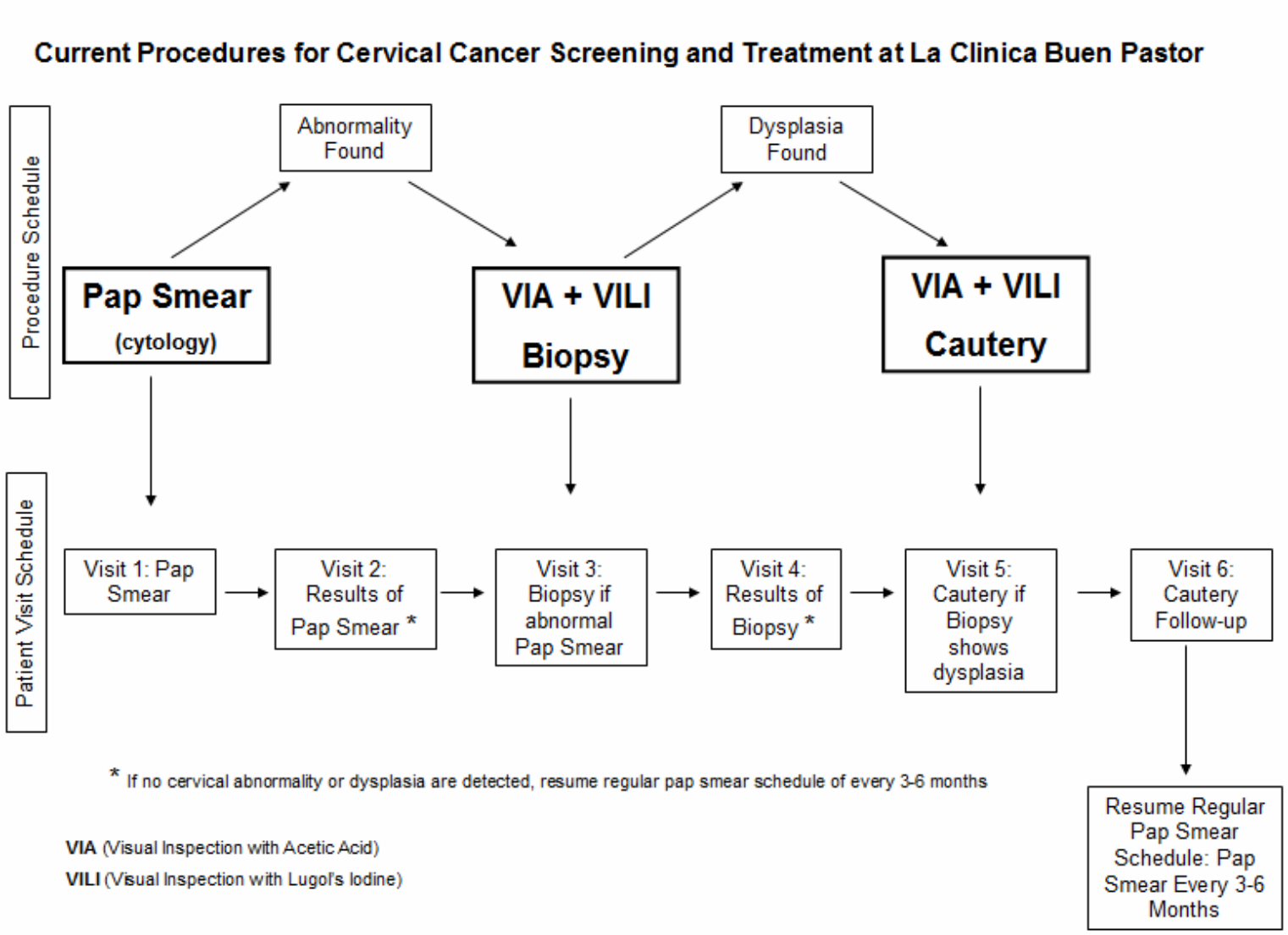
From July 4, 2008 through August 21, 2008, I assisted Dr. Sheree Lynch and La Clínica Buen Pastor (Santa María del Real, Olancho, Honduras) on cervical cancer screening, research, and patient education. Prior to my arrival in July, I reviewed the literature on the current cost-effective and accurate screening methods for cervical cancer screening in low-income countries (such as Honduras) and reviewed the health statistics and history of Honduras. While at the clinic, I shadowed Dr. Lynch during patient consultations, follow-ups, and procedures (including Pap smears, biopsies, colposcopies, cauterizations, ultrasounds, endoscopies, echocardiograms, etc.). In addition to tracking the patients I saw with Dr. Lynch, for the first three weeks, I surveyed most of the female patients in the clinic each day to determine basic demographics (age, parity, smoking status, marital/relationship status, history of cancer and chronic disease, history of Pap smears and other cervical procedures, etc.).

For patient education on cervical and breast health (the final 4 weeks), I spoke with each female patient in the clinic waiting room (whether she was a patient or simply accompanying a patient) about the importance of cervical and breast health, the high prevalence of cervical cancer and breast cancer death in Honduras, and the procedures available to them at the clinic. In my discussions ("waiting room chats") with the women, I sometimes used models and drawings to show how Pap smears and mammograms were done at the clinic. After speaking with me, all women who had not had a Pap smear within the last year were given an information slip to present to their doctor during the consultation (or to the receptionist if they were not at the clinic for a personal consultation). The information slip indicated whether the woman needed a Pap smear, a mammogram, or both. Women could then choose to: (a) have their Pap smear that day, (b) make an appointment for a Pap smear and/or mammogram for a later date, or (c) not present the information slip to the physician or the receptionist.

The recommendations I propose in this memo are, thereby, based on my desktop and field research

Appendix C

Figure 1:



Appendix C

<u>Figure 2</u>: Cervical Epithelium Ranging from Normal to Invasive Cancer
(Palefsky 2002, page 16 Figure 1.3)

Cervical dysplasia (also referred to as cervical intraepithelial neoplasia or CIN) is defined as an area of abnormal cells in the anogenital skin (epithelium) of the cervix. Over time, the abnormal cells may progress to invasive cancer. CIN Grade 1 (CIN 1) represents mild dysplasia, which is not considered precancerous and usually regresses on its own without treatment (25,28). CIN 2 and CIN-3 (moderate and severe dysplasia, respectively), however, may progress to cancer. Figure 2 below shows how HPV infection may lead the cells of the cervical epithelium to transform (through dysplasia stages CIN 1-3) from normal cells to invasive cancer (28).

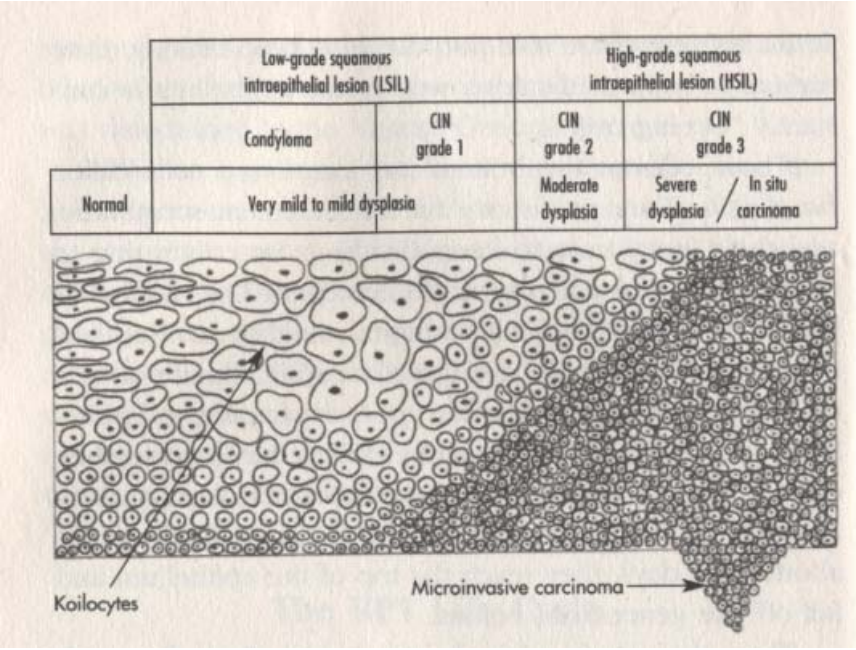


Figure 1.3: Cervical Epithelium Ranging from Normal to Invasive Cancer. *This figure shows what the normal epithelium looks like on the left. The terminology used to describe the abnormal areas, or "lesions," is shown on the top of the diagram. Progressively more advanced changes in the epithelium due to HPV are shown as the diagram moves to the right. Epithelial cells sit on a structure called the basement membrane. The normal epithelium shows cells flattening out and losing their nucleus as they mature and move up to the top of the epithelium. These cells eventually die and fall off. Mild dysplasia is characterized by relatively minor changes in the cells and sometimes by the presence of koilocytes, which are cells with enlarged, irregular nuclei surrounded by a halo. Mild dysplasia does not directly progress to cancer. Moderate and severe dysplasia occur when an increasing proportion of the normal epithelium is replaced by small cells with large nuclei. The most advanced form of severe dysplasia is known as* carcinoma in situ, *in which the entire epithelium is replaced by these cells. Severe dysplasia can progress to cancer, which by definition occurs once the epithelial cells invade the basement membrane and the underlying tissues. (Illustration by Ira C. Smith.)*

Appendix C

<u>Table 1</u>: Studies on the Effectiveness of VIA Compared to Cytology: Specificities, Sensitivities, and Conclusions

Researchers	Year (published)	Country	Study Size	VIA		Pap Smear (cytology)		Conclusions
				Specificity (%)	*Sensitivity (%)*	*Specificity (%)*	*Sensitivity (%)*	
Ceccini et al.	1993	Italy	2105	75.0%	88.0%	99.0%	63.0%	The limited sensitivity of cytology made it less able to detect cases of moderate and severe dysplasia (CIN2-3). Although the specificity of VIA was poor, VIA increased the detection rate of CIN2-3 at relatively low costs.
Londhe et al.	1997	India	372	54.0%	72.4%	96.3%	13.2%	VIA identified 3.5 times more (78%) high-grade lesions (including one case of cancer) than cytology.
Sankaranarayanan et al	1998	India	3000	92.2%	90.1%	91.3%	86.2%	Both VIA and cytology performed similarly in detecting moderate and severe lesions. The differences noted between the two methods were not statistically significant.
Sankaranarayanan et al	1999	India	1351	68.0%	96.0%	89.5%	62.0%	VIA had a higher detection rate of moderate dysplasia or worse lesions than cytology; More than 60% of high-grade SIL was detected by VIA.
University of Zimbabwe (Gaffikin et al.)	1999	Zimbabwe	10,934	64.1%	76.7%	90.6%	44.3%	VIA could correctly identify most of the pre-cancer and cancer cases in the study; the higher sensitivity of VIA allowed the test to identify more cases than cytology.
Denny et al.	2000	South Africa	2944	83.0%	67.0%	94.0%	78.0%	Both VIA and cytology performed similarly in detetcting high-grade lesions (CIN2-3) and invasive carcinoma cases. The differences noted between the two methods were not statistically significant.

Appendix C

Discussion of Table 1: Studies on the Effectiveness of VIA Compared to Cytology: Specificities, Sensitivities, and Conclusions

Ceccini et al (1993) (18) conducted a clinic-based study testing the diagnostic accuracy of VIA[13] compared to cytology in 2105 women in Italy. Of the eight confirmed cases of CIN 2 and CIN 3, cytology only detected five cases, whereas VIA detected seven cases. The limited sensitivity of cytology made it less able to detect cases of moderate and severe dysplasia.

In their prospective study of 372 sexually active, reproductive-aged women in India, ***Londhe et al. (1997)*** (23) tested the sensitivity of the Pap smear and VIA, using colposcopy to diagnose lesion grades. The researchers found the sensitivity of the acetic acid test to be 72.4% compared to 13.2% sensitivity for cytology. The specificity of cytology, however, was 42.3% higher than VIA, meaning there were more false positives with VIA. The WHO cites this study in its report on Cervical Cancer Screening in Developing Countries, explaining that VIA identified 3.5 times more (78%) high-grade lesions (including one case of cancer during the study) than did cytology (11). Thus, despite the false positives with VIA, more cancerous and pre-cancerous lesions were identified using this alternative method to cytology.

Sankaranarayanan et al (1998) (22) performed a clinic-based study and examined 3000 women in India by VIA and cytology. The conclusion was that both methods performed similarly in detecting moderate and severe dysplastic lesions. Although the difference between the two methods of screening in this study were not deemed statistically significant, VIA detected 90.1% of cases, while cytology only detected 86.2% of cases. Five lesions missed by cytology were detected by VIA and only three lesions missed by VIA were detected by cytology. The calculated specificities of VIA and cytology were also similar at 92.2% and 91.3%, respectively. In this study, VIA was (percentage-wise) both more specific and more sensitive than cytology, and, in statistical terms, performed equally as well as cytology.

In a subsequent clinic-based study of 1351 women (ages 22-70) by the same researchers in India, ***Sankaranarayanan et al (1999)*** (11,21) found the detection rate of moderate to severe dysplasia by VIA and cytology were 53.6 per 1000 women (estimated 96% sensitivity) and 37.4 per 1000 women (62% sensitivity), respectively. The ratio of the sensitivities of the two tests (sensitivity ratio = 1.54) showed VIA to be significantly more sensitive than cytology. Although the specificity of VIA was lower than cytology (68% compared to 89.5% respectively), VIA actually detected more mild and moderate dysplasia than the Pap smear by identifying 25 lesions missed by cytology (cytology only detected 1 lesion missed by VIA). Important to note is that both tests detected almost all severe dysplasia cases, demonstrating that VIA, in fact, has the ability to detect mild and moderate, as well as severe CIN cases.

A cross sectional study of VIA screening vs. cytology screening in 10,934 women, conducted by the ***University of Zimbabwe (1999)*** (17), concluded that VIA was more sensitive (sensitivity: 76.7% for VIA, 44.3% for cytology), but less specific than cytology (specificity 64.1% for VIA, 90.6% for cytology). VIA could correctly identify most of the pre-cancer and cancer cases in the study. Similar to the aforementioned studies, in this study, the higher sensitivity of VIA allowed it to identify a greater proportion of diseased cases than cytology.

Although ***Denny et al. (2000)*** (19) did not find a higher sensitivity for VIA during their study of 2944 women (ages 35-65) in South Africa, the researchers reported that VIA[14] and Pap smears detected similar numbers of high-grade lesions (CIN 2 and CIN 3) and invasive carcinoma cases. VIA's specificity, however, was lower than cytology, leading to more women being incorrectly classified as test positive when tested with VIA. Nevertheless, VIA was still as effective as cytology in detecting true cases.

[13] VIA is referred to as cervicoscopy in the published study (Ceccini et al., 1993)
[14] VIA is referred to as DVI (Direct Visual Inspection) in the published study (Denny et al., 2000)

Appendix C

Figure 3: Cost-Effectiveness of Cervical Cancer Screening in Five Developing Countries
(Goldie et al. 2005, page 2164 Figure 2)

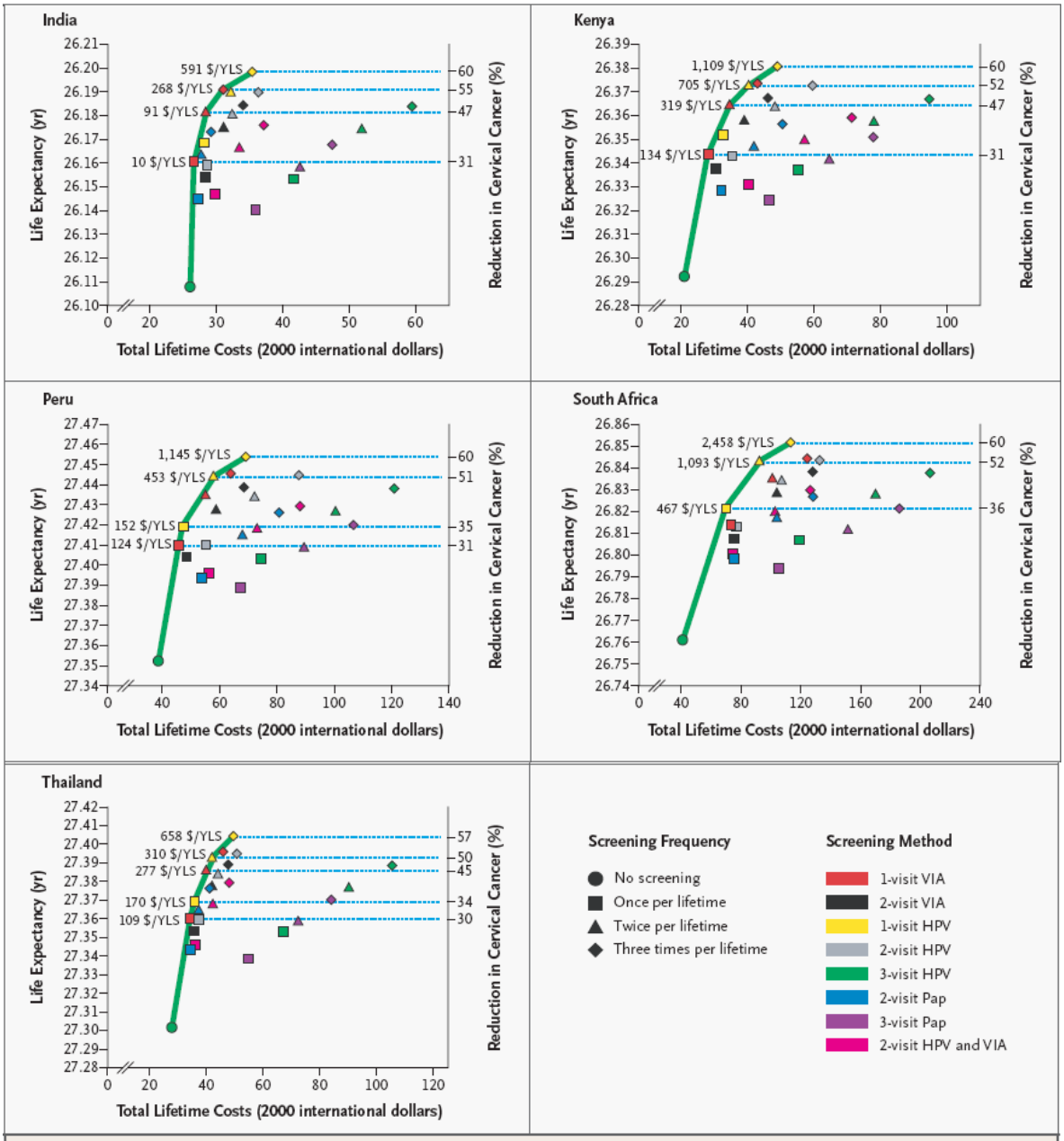


Figure 2. Cost-Effectiveness of Screening for Cervical Cancer.

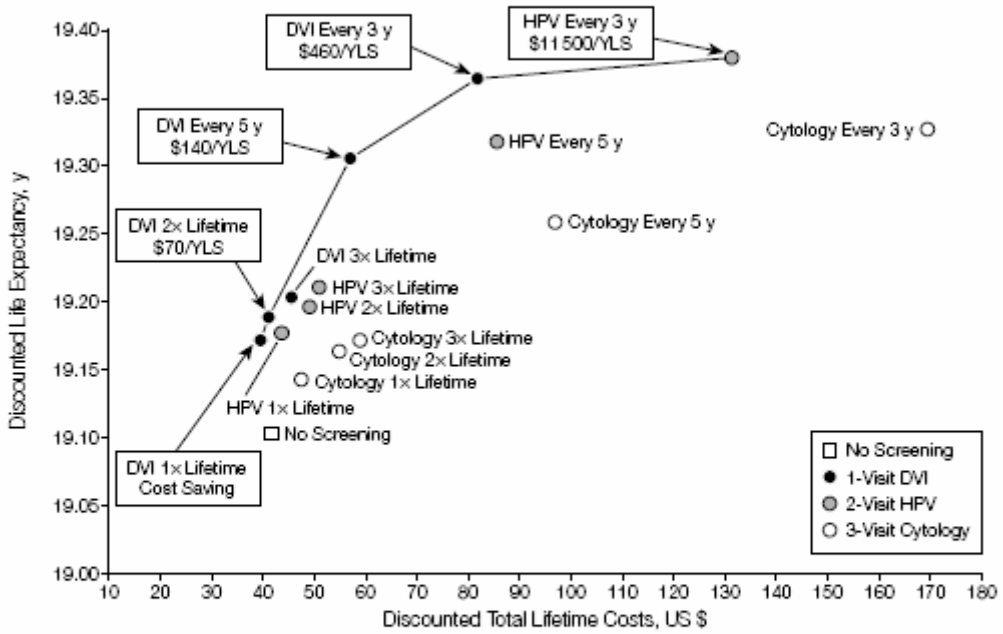
The discounted lifetime costs and life expectancy associated with eight strategies performed at different screening intervals are shown for the five countries. The cost-effectiveness associated with a change from one strategy to a more costly alternative is represented by the difference in cost divided by the difference in life expectancy associated with the two strategies. Strategies that lie on the efficiency curve dominate those to the right of the curve because they are more effective and either cost less (indicating strong dominance) or have a more attractive cost-effectiveness ratio (weak dominance) than the next-best strategy. A cost-effectiveness ratio is shown for each nondominated strategy and is the reciprocal of the slope of the line connecting the two screening strategies under comparison; this slope is steeper when the net gain in life expectancy per dollar is greater. YLS denotes year of life saved, VIA visual inspection of the cervix with acetic acid, HPV human papillomavirus DNA testing, and Pap Papanicolaou smear.

Appendix C

Figure 4: Cost and Benefits of Screening with Cytology and VIA (and HPV Testing[15]) at Different Intervals of Time

(Goldie et al. 2001, page 3112 Figure 2)

Figure 2. Discounted Lifetime Costs and Benefits of Screening at Different Intervals With 1-Visit DVI, 2-Visit HPV DNA Testing of Clinician-Collected Samples, and 3-Visit Cervical Cytology



DVI indicates direct visual inspection; YLS, years of life saved; and HPV, human papillomavirus. Strategies lying on the efficiency curve dominate those lying to the right of the curve because they are more effective and either cost less or have a more attractive cost-effectiveness ratio than the next best strategy. Compared with no screening, the incidence of cancer was reduced by 26% in the 1-visit DVI strategy, by 37% in the 2-visit DVI strategy, by 69% in the DVI every 5 years strategy, by 81% in the DVI every 3 years strategy, and by 85% in the HPV every 3 years strategy. The cost-effectiveness ratio is the reciprocal of the slope of the line connecting the 2 screening strategies under comparison.

[15] HPV Testing is not discussed as an option in this memo, because it is too expensive for low-resource settings such as Honduras.

Appendix C

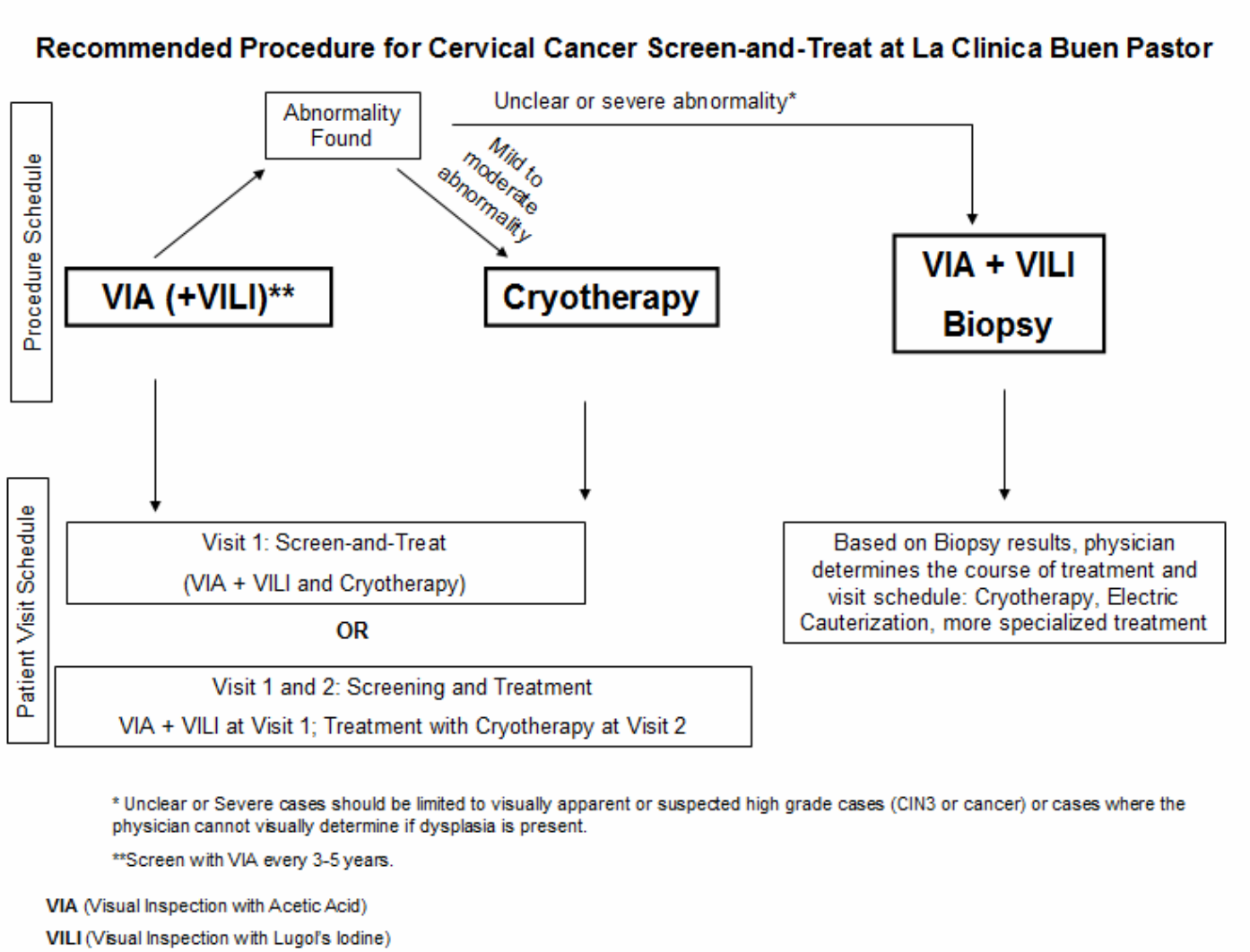
Figure 5: Strengths and Limitations of Cryotherapy
(Jacob et al. 2005, page S15 Table 1)

Table 1 Strengths and limitations of cryotherapy compared to other outpatient methods of treating precancerous cervical lesions

Strengths	Limitations
Overall cure rate of 89–91% at 1-year follow-up.	May be slightly less effective for treating CIN3.
Uses simple and inexpensive equipment, compared with other methods, and requires only few consumable supplies.	Should not be used for lesions extending into the endocervical canal.
Can be performed by a trained and competent nonphysician as an outpatient procedure in a primary care setting.	Because it is an ablative procedure, no tissue sample is available for histological examination to confirm the diagnosis, the grade of the lesion, or the adequacy of treatment. However, a punch biopsy specimen can be taken before the procedure.
Requires approximately 11 min if double-freeze method is used.	Requires access to a supply of carbon dioxide or nitrous oxide.
Anesthesia is not required.	In some cryotherapy instruments, especially with carbon dioxide, problems with the flow of refrigerant may occur, interfering with freeze adequacy and/or requiring technique modification.
Electricity is not required for equipment functioning.	Profuse watery discharge is usual, persisting for up to 6 weeks.
Few complications/side effects are related to the procedure.	
Equipment is easy to decontaminate with high-level disinfection methods.	

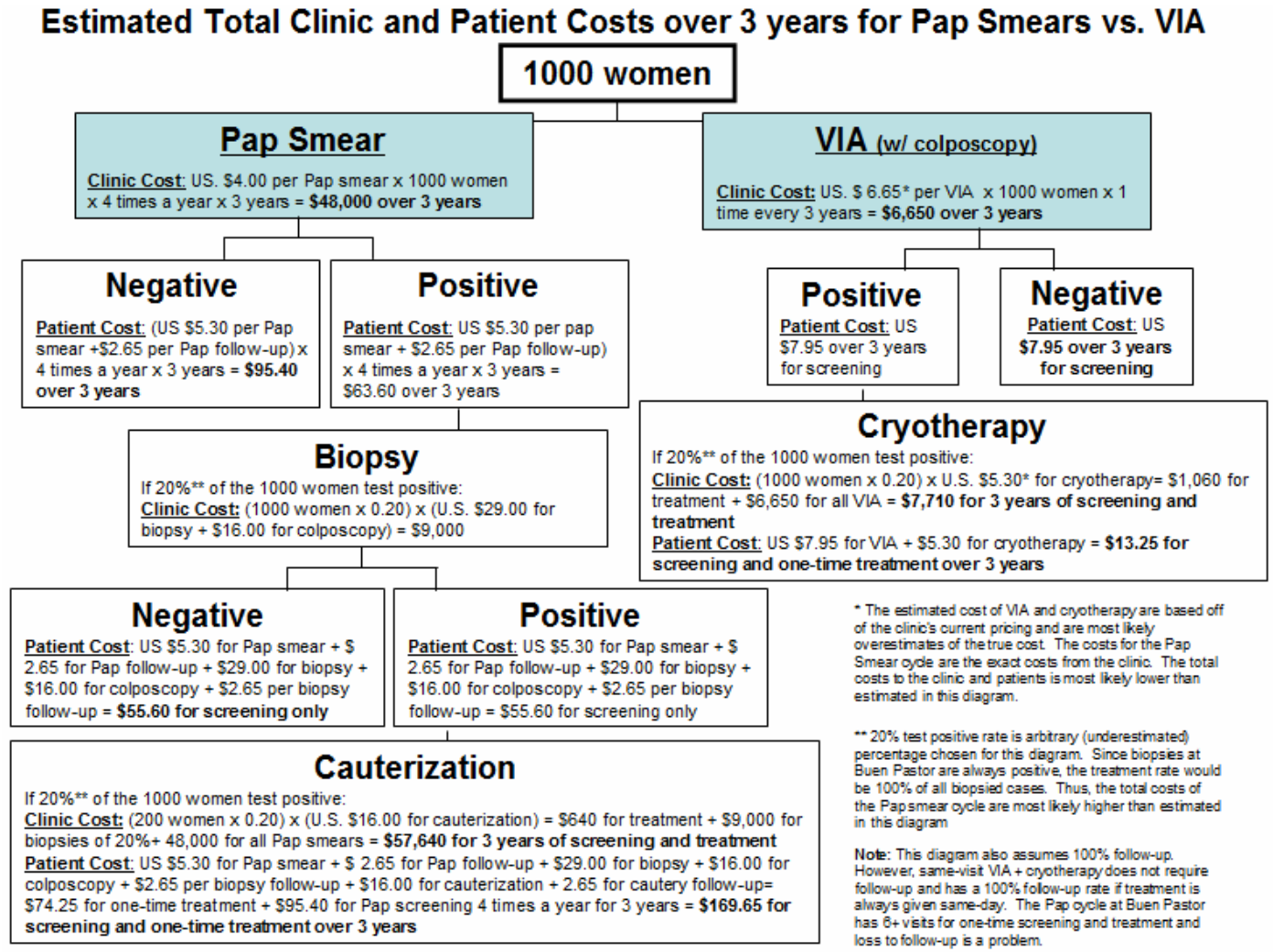
Appendix C

Figure 6:



Appendix C

Figure 7:



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