

SCREENING FOR CERVICAL CANCER

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Introduction:

Cervical cancer screening through the Pap smear is probably the most effective cancer screening program ever developed. 50 years ago, cervical cancer was the leading cause of cancer death in women in the US. The Pap smear was introduced in 1943 and since then cervical cancer risk has been reduced by 70%. In contrast to other screening techniques like mammography which detects cancer at an early stage, the Pap smear is designed to prevent invasive cancer by detecting precursor lesions. Now only about 5,000 women yearly in the US die of cervical cancer. The decrease in invasive cervical cancer incidence and mortality since the introduction of the Pap smear has been so impressive, that it is one of the few interventions to receive an “A” from the US Preventive Services Task Force, even though there have been no randomized trials.

Recently however, this rate of decline in cervical cancer mortality has leveled off and it may even be increasing slightly in young women. There is persuasive evidence of the role of human Papillomavirus (HPV) in the etiology of preinvasive and invasive cervical cancer and there has been a dramatic increase in the incidence of HPV infection in young women. Approximately one-third of American female college students now harbor HPV. Currently, there is interest in exploring cervical cancer screening strategies that combine HPV DNA testing with more conventional screening techniques.

The cost of detection and treatment of low grade cervical lesions has recently escalated probably with marginal cancer prevention benefit. Most of the recent efforts to improve Pap smear performance (driven by the Clinical Laboratory Improvement Amendment [CLIA] mandate that a random sample of slides read as normal be rescreened) have focused on reducing the number of false-negatives. Approximately 2.5 million women each year are diagnosed with low grade cervical abnormalities (approx 50,000,000 Pap smears are done annually). The associated costs of colposcopic evaluation and intervention for these low grade abnormalities approaches \$6 billion annually.

Epidemiology of Cervical Cancer

Most cases of cervical cancer are squamous cell carcinoma. The mean age at diagnosis is 54 years. Most precursor lesions are now detected in women < age 40. Precursor lesions are cervical intraepithelial neoplasia or CIN.

Role of Human Papillomavirus in the Development of Cervical Cancer

CIN lesions as well as cervical cancer lesions often contain HPV. There are several types of HPV which vary in their ability to transform cervical epithelium. The low risk varieties (6,11) are associated with viral condylomata and mild dysplastic changes such as CIN I. The high risk types (16,18,33,35) are associated with moderate dysplasia (CIN II) and severe dysplasia or carcinoma-in-situ (CIN III). Here the viral genome is commonly integrated into the host DNA.

A model has been developed by Meijer and others: When women start sexual intercourse, an infection with high risk HPV is acquired. About 80% of the women clear this infection without developing cervical lesions. The rest (20%) of the women develop CIN lesions. Most of these women with abnormal smears (about 80%) show spontaneous regression of the cervical lesion and obtain normal cytology when high risk HPV is cleared. Those women who cannot clear the virus and have a persistent high risk HPV infection will develop invasive cervical cancer, but additional genetic changes, such as activation of cellular oncogenes or loss of tumour suppressor genes, are necessary for this progression from CIN III to invasive carcinoma. Thus the detection of high risk HPV in cervical smears is a powerful tool for detecting those at risk of developing cervical cancer.

Risk Factors for Cervical Neoplasia

Risk factors for cervical neoplasia include:

1. Early age of first intercourse
2. Multiple male sexual partners
3. Male sexual partners who themselves have had multiple sexual partners
4. Known exposure to HPV
5. Cigarette smoking
6. Immunosuppression of any cause
7. A history of neoplasia anywhere on the lower genital tract
8. Low socioeconomic status

Frequency of Pap smear screening:

Some experts feel that it is more important to get the first Pap smear on a woman who has never had one than to get another Pap smear on a woman who has had many. Most cases of cervical cancer occur in women who have not been screened. Pap smear screening detects vastly more dysplasia than outright carcinoma with dysplasia being a failure of the epithelial cells to mature fully. A large proportion of women with CIN will not progress on to cancer but it is difficult to distinguish those who will from those who won't. Frequency of screening guidelines may change in the future as newer technologies are incorporated into long-term surveillance strategies.

Adolescents may be at high risk because the squamocolumnar junction is generally on the ectocervix where it has great potential for interaction with a carcinogen (e.g. HPV).

Current guidelines for cytologic screening and optimal screening interval include:

1. **All women who are sexually active or age aged 21 or older should have annual screening.** The incidence of cervical cancer in women who have never had sexual intercourse is low to non-existent. Also, it establishes a pattern of health care at a formative age and allows for communication between a young woman and her provider about sexuality issues, contraception etc. If the hymen is intact or if the history of no sexual intercourse is believable, screening is not indicated.
2. **After at least 3 annual satisfactory smears, the frequency of screening may be decreased to every 3 years in low-risk women at the discretion of the provider.** An every 3-5 year screening interval exists in most of the Western world without an increase in the incidence of cervical cancer.
3. **Screening depends upon choice of test.** If conventional pap is used annual screening is recommended, if liquid based cytology is used then screening can occur every two years.
4. **If the woman is high-risk, annual screening should continue.** Some experts feel that any woman with one or more risk factors should be considered high-risk. A woman who has had a normal pap but has started a new relationship needs to be screened.
5. **If previous screening has revealed atypical cells, annual screening should continue.** (See specific qualifiers below)
6. **Pelvic exam warranted every year if not doing a pap smear.**

When to stop screening:

Women over the age of 65 who have had consistently normal smears may have cytologic screening discontinued. However, since almost half of the deaths from cervical cancer in the US come in women over the age of 65, this recommendation can only be made for women who have been carefully screened over the preceding decades. Almost all women with cervical cancer over the age of 65 have had no recent screening or no screening at all.

1. **After the age of 65, routine screening may be discontinued if findings are normal on two consecutive Pap smears.**
2. **If a woman over age 65 has an abnormal Pap smear, screening should be performed annually until two consecutive Pap smears are normal.**

Dr. Wheelock of MCV OB/Gyn favors continuing screening every 3 years even though it may not be cost-effective as this is the only way to pick up vaginal dysplasia and early vaginal cancers. Additionally, periodic screening is prudent for those women on hormone replacement therapy.

Post-hysterectomy screening:

Pap smear screening in women who have undergone complete hysterectomies for benign disease is not cost-effective. There are two exceptions to this rule:

1. **Women operated on before the early 1960's** (when subtotal hysterectomies were

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common, leaving the cervix intact)

2. Women who have had laparoscopic hysterectomies without removing the cervix

A speculum exam is necessary to assure that no cervix is present before discontinuing screening. Dr. Wheelock of MCV Ob/Gyn Dept. favors continuing Pap smear screening in patients who have had a hysterectomy for cervical dysplasia to screen for vaginal dysplasia (field effect and HPV).

Weaknesses of Pap smear screening:

Although the false-negative rate of a single Pap smear has been widely accepted to be 20% (that is 2 out of 10 women with disease will not be detected by the smear), recent meta-analyses suggest it may be far higher, approaching 50%. However, this false-negative rate drops significantly, perhaps to a low as 1-2%, if three consecutive negative smears are obtained. There are several possible causes of false-negative smears:

1. The lesion may not be shedding an adequate number of cells to be detected.
2. The lesion may be not adequately sampled because of its location (i.e. within the cervix), anatomy of the cervix (i.e. scarring), or inadequate technique.
3. The cells may be on the slide but uninterpretable because of the thickness of the smear, drying artifact, excess blood or inflammation.
4. The abnormal cells may be missed by the cytotechnologist.

Factors 2 and 3 account for about 50% of false-negative smears. Whereas the sensitivity of an individual smear varies from 30-87%, the specificity of an abnormal smear is much higher, 86-100%. This means that very few women with abnormal Pap smears will not have a related finding on colposcopy. However, since the Pap smears screen for dysplasia as well as cancer, most abnormal smears will not lead to a diagnosis of cancer.

Improving Pap smear quality:

Several steps can be taken to improve Pap smear quality:

1. The pt should not be menstruating, using any vaginal creams, or have douched or had sex within 24 hours of the Pap. A small amount of blood will not invalidate a Pap but full menstrual flow will.
2. Lubricate the speculum only with water and visualize the entire cervix.
3. Take the Pap smear before the digital exam to avoid contaminating the specimen with lubricant gel and glove powder. Take the Pap smear before obtaining any cultures.
4. Do not wipe the cervix unless there is excess mucous as you will be actually wiping away cells. If the patient clearly has a vaginal discharge and no obvious signs of a cervical disorder, consideration should be given to treating the vaginitis first and having the patient return for her Pap smear at a later date.
5. Scrape the ectocervix first to minimize the effect of bleeding which almost inevitably occurs after sampling the endocervix. Place the spatula firmly into the cervical os and rotate 360 degrees to ensure sampling the entire ectocervix.
6. Use a cytobrush to sample the endocervix. Place the cytobrush firmly in the cervical os and rotate 90-180 degrees and then spread the resultant scrapings on a slide. Most dysplasia arise in the squamocolumnar junction and for many women this resides in the

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anatomic endocervix.

7. Spread the material from the spatula and the cytobrush evenly and thinly on the slide(s).

8. Fix the sample immediately (within seconds) to avoid drying artifact. If a spray fixative is used, hold the device no closer than 10 inches from the slide to avoid damage to the cells. If a single slide is used, obtain the spatula specimen first but do not plant it on the slide until the cytobrush specimen has been gathered. Then plant them both in rapid succession and fix immediately.

Spotting is expected after use of the cytobrush so patients should be warned. Pregnant patients may be more likely to bleed and although this may not jeopardize the pregnancy, I usually defer the Pap smear in the pregnant patient and leave this in the hands of the obstetrician.

Interpreting the Report:

Several classification systems have been in place in the past. The five point numerical grading scale (Class I, normal; Class II, atypical; Class III, dysplasia...) gave way to the cervical intraepithelial neoplasia system (CIN I, CIN II...). This has now been replaced by the Bethesda system. This new system gives a description of the adequacy of the smear as well as possible causes of atypia. The Bethesda system was revised in 2001 and current terminology follows.

I. Statement of Adequacy of Specimen for Interpretation:

One of three general responses will be given:

1. **Satisfactory:** the sample can be interpreted without any qualification. The presence or absence of endocervical cells is noted. Endocervical cells or squamous metaplastic cells indicate that the transformation zone has been adequately sampled. Failure to sample the transformation zone increases the likelihood of a false negative smear. However, it is up to the clinician to determine the next course of action. If the woman's risk is perceived to be low (and previous smears are normal), the clinician may elect to repeat the smear in a year. If the previous smear was abnormal, s/he may wish to repeat the smear in a few months.

2. **Unsatisfactory:** All unsatisfactory smears must be repeated.

a. specimen rejected/not processed (specify reason, eg unlabelled)

b. specimen processed and examined, but unsatisfactory for evaluation of epithelial cell abnormality because of (specify reason, eg > 75% of epithelial cells are obscured by blood or inflammation)

II. General Categorization: (Optional)

This categorization is designed to allow clinicians and/or their staff to triage reports readily. It divides reports into those that are “**negative for intraepithelial lesion or malignancy**” (combines the previous category headings of “within normal limits” and “benign cellular changes”) vs “**epithelial cell abnormalities**” vs “**other**”. The “other” category includes cases in which there are no morphological abnormalities in the cells; however, the findings may indicate some increased risk. **Endometrial cells, cytoplasmically benign, in a post-**

menopausal woman” can indicate serious disease. This diagnosis may indicate a polyp or hyperplasia or adenocarcinoma of the endometrium. **“Endometrial cells out-of-phase or in the second half of the cycle”** can also be associated with serious pathology unless the woman is on oral contraceptives and either missed pills or is having break-through bleeding. In this latter case, this diagnosis is not a problem unless present on repeat Pap or associated with atypical cells.

III. Interpretation/Result:

Negative for Intraepithelial Lesion or malignancy: Reported here are organisms and other non-neoplastic findings.

Organisms: Examples include “*Trichomonas vaginalis*,” fungal organisms morphologically consistent with *Candida* spp”, “shift in flora suggestive of bacterial vaginosis”, “bacteria morphologically consistent with *Actinomyces*”, “cellular changes consistent with herpes simplex virus”. If the organism is not considered sexually transmitted and the pt is asymptomatic, and the sample is satisfactory, nothing further need be done as these organisms normally colonize the vagina.

If the organism is sexually transmitted (*Trichomonas*, *HSV*), and the pt is asymptomatic, you may either recall the patient for further testing and treatment or simply treat based on the Pap smear interpretation.

If the inflammation associated with the infection has reduced the adequacy of the specimen making it “unsatisfactory for evaluation”, the pt should be treated and the Pap smear repeated in 2 weeks. Some experts recommend treating with a week-long course of doxycycline and/or oral or vaginal metronidazole if an etiologic agent cannot be identified and inflammation is interfering with the Pap smear interpretation. Others discourage empiric treatment.

Actinomyces may be seen on the Pap smears of women using IUD’s. These organisms are considered distinctive so this diagnosis is definitive. Most women are asymptomatic. Referral to a gynecologist is prudent for removal of the IUD and/or treatment with penicillin.

Changes owing to infection with HPV are specifically excluded from this category recognizing the current understanding of the biology of HPV. Changes associated with HPV are now grouped under “Low-grade squamous intraepithelial lesions” or **LSIL** (see below).

Other Non-Neoplastic Findings (optional):

These are not premalignant conditions but normal reactions to some vaginal change. Changes that cause reactivity include reactive cellular changes associated with inflammation (includes typical repair), radiation, and IUD’s. Other categories here include “glandular cells status posthysterectomy” and “atrophy.” The underlying problem should be corrected if possible and the pt should be followed in the usual manner.

Epithelial Cell Abnormalities

Squamous Cell:

“**Atypical squamous cells (ASC)**” is used when the cellular abnormalities seen are more marked than those attributable to reactive changes but that quantitatively or qualitatively fall short of a designation of “squamous intraepithelial lesion (SIL)”. There are two possible categories of ASC:

1. **Atypical squamous cells of undetermined significance (ASC-US):**

2. **Atypical squamous cells, cannot exclude HSIL (ASC-H):**

It is generally agreed that all ASC Paps need some form of additional workup or follow-up because 10-20% of women with ASC have underlying CIN II or III and 1 in 1000 have invasive cancer; 24-94% of women with ASC-H will have CIN II or III.

Repeating the Pap smear at specified intervals, performing immediate colposcopy, examining the specimen for HPV DNA of high-risk type, or combining a single repeat Pap with another method are all widely used strategies in the US. The 2001 consensus group guidelines published in JAMA, (see refs) detail the risks/benefits of each strategy and conclude that in an ideal world, “reflex” HPV DNA testing is the optimal approach. Here, the original specimen is either collected as a liquid based sample or co-collected for HPV DNA testing but only processed if the **ASC-US** result is obtained on the original specimen. Reflex HPV DNA testing eliminates the need for a second visit, spares 40-60% of women from a colposcopic exam, and if negative, assures women that they do not have a significant lesion.

An acceptable alternative for the management of **ASC-US** is repeat cervical cytological testing. Here, the patient is treated for any underlying infection and either a conventional or liquid-based Pap test is repeated at 6 month intervals until 2 consecutive “negative for intraepithelial lesion or malignancy” are obtained. After 2 repeat “negative for intraepithelial lesion or malignancy” tests are obtained, women are returned to the routine cytological screening program. If any repeat test results is an **ASC-US** or greater abnormality during the intensive follow-up period, the woman should be referred for colposcopy. After colposcopy (where presumably the lesion is no higher grade than CIN II) Pap tests should be repeated every 6 months x 2 until there have been two consecutive negative smears. At this point, the patient may be returned to routine screening. In all follow-up strategies, the tests must not only be negative but satisfactory for interpretation.

The OB-Gyn Dept at MCV (our colposcopy referral center) interprets the 2001 consensus recommendations slightly differently. They require **2 consecutive** abnormal Paps, 6 months apart before colposcopy is recommended. These may be two **ASC-US** or two **LSIL** or a combination of both. Criteria for re-referral during the follow-up period is the same as for initial referral; two consecutive abnormal Paps, 6 months apart. USHS follows the MCV guidelines.

A diagnosis of **ASC-US** in postmenopausal women may result from atrophic changes of estrogen deficiency and treatment with topical estrogen may cause reversal of this abnormality. If the repeat Pap after treatment again shows **ASC-US**, colposcopy is warranted. Follow-up as listed above.

Squamous Cell: noninvasive squamous cervical abnormalities are categorized into two groups, **LSIL** or **HSIL**:

1. **“Low-grade squamous intraepithelial lesion” (LSIL)** (encompassing HPV, Mild Dysplasia, CIN I). There is considerable virological, molecular, and clinical evidence that **LSIL** is generally a transient infection with HPV while **HSIL** is more often associated with viral persistence and higher risk for progression to cervical CA.

Most women with **LSIL** will have changes that spontaneously revert to normal. Some women however will develop precancerous lesions. Certain HPV types are associated with high oncogenic risk (16,18,45 and 56), some with intermediate risk (31,33,35,51,52 and 58) and others with low risk (6,11,42,43,44). However, HPV typing as a screening tool is not widely in use yet.

1. As detailed above, the approach favored by the Department of Obstetrics and

Gynecology at MCV varies slightly from the 2001 consensus recommendations. For all patients with **LSIL**, the Pap should be repeated in 6 months. If the repeat Pap also shows **LSIL or ASC-US**, the patient should be referred for colposcopy. Individual biopsies of atypical areas or colposcopically directed loop electrobiopsy using a small-size loop may be accomplished. Routine electroexcision of the transformation zone of nonstaining areas as a method of evaluating a positive Pap smear diagnosed as **LSIL** or **ASC-US** is not recommended. If CIN I is diagnosed on colposcopic biopsy, no further treatment need be done as the majority of these lesions revert spontaneously.

2. Follow-up after CIN I or II includes Pap smears at 6 and 12 months by the primary care provider. Criteria for re-referral for colposcopy during the follow-up period is the same as for initial referral; two consecutive abnormal Paps, 6 months apart. These may be two **ASCUS** or two **LSIL** or a combination of both. If both follow-up Pap smears are normal, the patient may then be returned to yearly screening. The pt must be reliable and agree with this plan.

Squamous Cell: “High-grade squamous intraepithelial lesion” or HSIL (encompassing Moderate and Severe Dysplasia, Carcinoma-in-Situ, CIN II, CIN III)

Women with this designation should all be referred for colposcopy. Following biopsy confirmation of **HSIL**, excisional or ablative therapy aimed at removal or destruction of the entire lesion is usually performed in nonpregnant women. Cervical conization may be performed if the limits of the lesion and the transformation zone are not entirely visualized. If **HSIL** is identified during pregnancy, treatment is usually deferred unless invasive carcinoma is present.

Follow-up after cryotherapy for CIN II will include a Pap smear at 6 and 12 months performed by the primary care provider. If these Pap smears are normal, the patient may be screened again at yearly intervals. If the patient had a LEEP treatment, Paps should be repeated every 4 months x 3 for 1 year.

Follow-up after treatment for CIN III will include a Pap smear at 4 months performed by MCV. If this Pap smear is normal, the patient will be referred back to the primary care provider for repeat Pap smears at 4 months x 2. If these Paps are normal, the patient may return to yearly Paps.

Squamous Cell: “Squamous cell carcinoma” Immediate referral for colposcopy and definitive therapy is indicated.

Glandular Cell: “Atypical glandular cells of undetermined significance”

Adenocarcinoma is being detected more frequently, especially in women under 35 years of age. The management of this category is somewhat gray and therefore some experts recommend that all pts be referred for evaluation by a gynecologist.

Glandular Cell: “Endocervical adenocarcinoma” or “Endometrial adenocarcinoma” or “Other adenocarcinoma” should be referred immediately for evaluation. Pap smears contain malignant cells in 25-30% of women with endometrial cancer.

Other Malignant Neoplasms: Malignant cells from the fallopian tube or peritoneal cavity occasionally can be found on Pap smears. Unusual malignancies such as sarcomas and melanomas can also be detected on the Pap smear.

Abnormal Pap Smears in the HIV+ Patient: HIV positive patients should be referred for colposcopy for any Pap smear that is **ASC-US, LSIL, AGUS, HSIL or CIS.**

Abnormal Pap Smears in the Pregnant Patient: Management of the pregnant patient with an abnormal Pap smear is beyond the scope of this handout. See MCV guidelines included in this section of your handbook.

Alternative Screening Strategies: Detailed cost-effectiveness analysis have been published on the use of HPV testing alone (instead of Pap smear) and the use of reflex HPV testing in conjunction with Pap smears.^{1,2} Both analyses suggest biennial or triennial screening with one of these newer techniques is more cost-effective than annual screening with conventional Pap. However, neither analysis takes into consideration the other benefits of annual screening: STD screening, safer sex counseling, breast exam and reinforcement of BSE techniques, etc. Additionally, college students are highly sexually active and less frequent screening may cause a significant delay in the diagnosis of new HPV infections. For now, USHS will continue with conventional Pap smear screening with repeat cytology for abnormal Paps.

Other Diagnostic Modalities:

1. Colposcopy:

Colposcopy is the examination of the lower genital tract using illuminated magnification. Specific visual patterns have been correlated with histologic abnormalities. Abnormal epithelium becomes white in color when dilute acetic acid is applied. A mosaic vascular pattern can also be seen after acetic acid wash. By grading these colposcopically visible patterns, targeted biopsies can be performed. Lesions suspicious for cancer include areas of ulceration, necrosis, friability, nodularity or stony firmness.

2. Endocervical Curettage:

Most colposcopists perform routine endocervical curettage under direct inspection except if the patient is pregnant.

3. Diagnostic Conization:

A cone specimen suitable for histologic evaluation can be obtained by surgery (cold knife cone), laser, or loop electrode excision procedure (LEEP). A diagnostic conization is indicated if:

- A. Cytologic assessment indicates an abnormality that is not consistent with the tissue diagnosis
- B. The entire transformation zone is not visible.
- C. Microinvasive carcinoma is present on directed biopsy.
- D. Cytologic or biopsy evidence of a premalignant or malignant glandular epithelium is detected. In general, conization is not indicated as an initial diagnostic procedure. Colposcopy has reduced the incidence of conization to approximately 5-20% of pts with atypical cytology.

¹ Kim JK, Wright TC, Goldie SJ Cost-effectiveness of alternative triage strategies for atypical squamous cells of undertermined significance. JAMA, 2002;287:2382-2389

² Mandelblatt JS, et al. Benefits and costs of using HPV testing to screen for cervical CA. JAMA, 2002;287:2372-2379.

4. Endometrial Sampling of Atypical Glandular Cells:

Women with atypical glandular cells should undergo endocervical curettage directed by colposcopy. Further diagnostic modalities indicated may be endometrial biopsy, fractional dilation and curettage, or hysteroscopy to exclude the possibility of endometrial adenocarcinoma.

Therapeutic Modalities: The following is a brief description of therapeutic modalities and is not intended as an in-depth discussion. For a more extensive discussion of treatment modalities, see Cannistra and Niloff's article "Cancer of the Uterine Cervix", *NEJM*, 1996;334:1030-1038. Ambulatory therapy is appropriate when the lesion is located on the ectocervix and when there is no involvement of the endocervix as determined by colposcopic examination and endocervical curettage.

1. Local Excision: Local excision may be accomplished by excision or punch biopsy of the entire lesion.

2. Cryocautery: Cryocautery using nitrous oxide or carbon dioxide as a refrigerant may be used to treat lesions which can be completely covered by the probe and which do not extend into the canal.

3. Carbon Dioxide Laser Vaporization: Laser vaporization is used for the treatment of lesions too large to be covered by the cryocautery probe or which extend into the canal or which have deep gland involvement. Tissue should be vaporized to a depth of 7 mm which will be effective for over 99% of pts.

4. Loop Electrode Excision Procedure (LEEP): Recently, thin wire loop electrodes which permit excision of the entire transformation zone have been developed. Following removal of the specimen, the base of the area is cauterized and silver nitrate is applied. This procedure provides a tissue sample for histologic evaluation.

5. Hysterectomy: Some individuals with **HSIL** or with recurrent **HSIL** or with lesions not adequately treated with local therapies may be candidates for hysterectomy.

Enhancements in Pap smear screening:

The FDA has approved several devices that use **computerized image analysis to rescreen Pap smears that have already been examined by cytotechnologists.** A *JAMA* article (O'Leary T, et.al. PAPNET-Assisted Rescreening of Cervical Smears, *JAMA*, 1998; 279:235-237) reports cost and accuracy of one of these techniques. With PAPNET-assisted technology, cytotechnologists review computerized images of slides read as "normal", select a proportion (typically 20-30%), and manually rescreen them using microscope technology. PAPNET screening identified 29% of slides (1614) requiring additional microscopic review. On further review, 8% (448) had possible abnormal cells. Ultimately 11 of these cases were reviewed by a consensus panel as having possibly atypical cells. Of these 11, 5 were eventually reclassified as Atypical Squamous Cells of Undetermined Significance (ASCUS) and 1 as Atypical Glandular Cells of Undetermined Significance (AGUS). The patient with AGUS was eventually diagnosed as having Low Grade Squamous Intraepithelial Lesion (LSIL). **Costs were estimated at \$5,825-\$33,781 to detect 1 additional ASCUS or AGUS and \$17,475-\$101,343 to detect 1 additional LSIL!** The manufacturer of Papnet has elected not to support this technology in the future and instead has brought out the AutoPap 300 QC system.

AutoPap, is another computerized image system that has been approved by the FDA for both rescreening and for primary screening. This system divides smears into five classes, varying from very suspicious of cervical cancer to normal. Depending on the sensitivity of the system and the populations screened, 25-40% of the smears in a population based screening program can be passed without further screening. This technique also identified 5x more false-negative results than did a random manual rescreening of a 10% sample!

Thin-prep is a liquid-based method of specimen collection and preparation which has been approved by the FDA. The clinician uses a sampling device (a broom-type tool or a spatula and endocervical brush) to collect the cervical specimen. The device is then rinsed in a vial of fixative solution to dislodge the cervical cells. At the lab, the vial is agitated to mix the cells in solution and a predetermined number of cells are placed on a filter membrane. A thin monolayer of cells is then transferred to a glass slide, stained, and examined the same way the conventional Pap smear is examined. One clinical trial found that both specimen adequacy (less mucus and fewer cellular clumps) and diagnostic sensitivity for low-grade lesions was increased. However, cytotechnologists have to be specially trained to read these slides and the laboratory processing is labor intensive and more expensive. Advantage of thin prep is HPV testing can be done.

Autocyte PREP and AutoCyte SCREEN combines a liquid-based, thin-layer slide system with an automated screening technique. Superior sensitivity for squamous intraepithelial lesions has been demonstrated and the thin-layer slides are easier to read by both conventional and automated microscopy systems.

Speculoscopy is a technique whereby a blue-white chemiluminescent light is activated and attached to the upper dilator blade of the vaginal speculum before speculum insertion. The cervix is first washed with 5% acetic acid, the room lights are dimmed or extinguished, and the cervix is observed using low power magnification (using a hand-held monocular optic with 4-6x magnification). The speculoscopy exam is considered positive if any acetowhite areas are detected. Results of two studies indicate that speculoscopy improves the detection of both low-grade and high grade lesions. Speculoscopy may prove useful as an adjunct to Pap smear screening, particularly for those high-risk women who may not have continuing access to routine gynecologic care. **Speculoscopy adds an additional \$5 in cost per patient screened.**

Cervicoscopy refers to visual inspection of the cervix for evidence of abnormality after an acetic-acid wash (VIA). It is used as an alternative to the Pap smear in developing countries that do not have the resources to perform widespread cytologic screening.

Cervicography refers to a system of cervical cancer screening that uses a static photographic image (Cervigram slide) of the ectocervix taken with a specially designed camera after application of acetic acid. The image is subsequently studied to evaluate for abnormality and provide photo documentation of visual findings. Although cervicography was intended to complement the Pap smear, the technique has also been evaluated as a primary method for detection of high grade lesions and cervical cancer in resource poor settings.

HPV testing Because persistent infection with one of the high-risk HPV types is necessary for development and maintenance of CIN lesions and the subsequent progression to cervical cancer, testing cells for the presence of HPV DNA may enhance cervical cancer screening. There are new recommendations for ASCUS if HPV testing occurs with a Pap smear. If high risk strain identified, then refer for colposcopy. If low risk strain, can repeat Pap in 12 months.

The American College of Obstetricians and Gynecologists (ACOG) does not currently recommend any of these new techniques as the standard of care. No large, population-based prospective study has been completed to determine whether any of these techniques lowers the incidence of invasive cervical cancer or improves survival rate.

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