



LUMA™ Cervical Imaging System Information for Prescribers

CAUTION: FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN OR LICENSED HEALTH CARE PROVIDER WHO HAS COMPLETED TRAINING IN THE USE OF THE DEVICE

CAUTION: THE USER SHOULD READ AND UNDERSTAND THE OPERATING INSTRUCTIONS, INCLUDING INDICATIONS, WARNINGS AND PRECAUTIONS, BEFORE PERFORMING ANY PROCEDURE. FAILURE TO DO SO MAY RESULT IN INJURY TO THE PATIENT OR THE OPERATOR, OR DAMAGE TO THE SYSTEM.

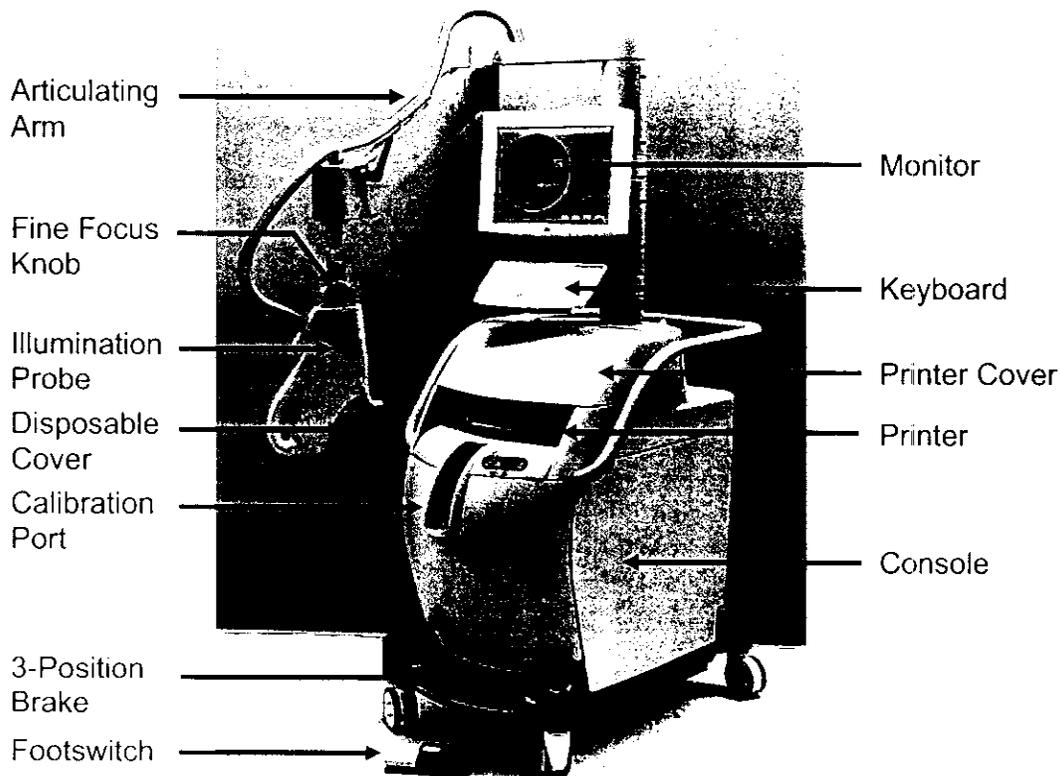
I. DEVICE DESCRIPTION AND BACKGROUND INFORMATION

LUMA Device Description

The MediSpectra LUMA™ Cervical Imaging System is a stand-alone, non-contact optical analysis system. It is used following a thorough colposcopic examination of the cervix as an adjunct to colposcopy. Scans of the cervix are performed by interrogating a 25 mm diameter circular area of the ectocervix in a dense grid pattern using laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The cervix is scanned by the illumination probe, which is positioned near the proximal opening of the speculum as part of a colposcopy examination, following the application of acetic acid. The scan is a hands-free operation that takes approximately 12 seconds.

The key elements of the system are:

- console (and accessories),
- illumination probe, and
- disposable probe cover.



The **console** contains a computer, control electronics, ultraviolet laser, broadband flashlamp assembly, camera controller, spectrometer, and the visible “targeting” laser used for centering and focusing. Interaction with the system is by way of a keyboard, touchpad and/or foot-actuated dual-pedals. The touchpad allows the user to control system operations by drawing a finger across the pad to position the screen cursor, and then clicking either the left or right touchpad button. The foot pedals allow hands-free operation of the software screens.

Output data are provided to the user by way of an LCD monitor and a printer. The LCD monitor is used to display the software control screens and cervical images captured during the scan. A color printer produces a report containing the cervical image captured during the scanning process, as illustrated in Appendix A of the *User Manual*.

A **calibration port** is located in the front center of the console, and is used to calibrate the system prior to each patient exam; it can also be used to store the probe when not in use.

The **illumination probe** is attached to the console by way of an articulating arm. The articulating arm allows the user to manipulate and position the illumination probe during the exam. The probe can be moved in several different axes for optimum positioning, and contains the fine focus assembly. The **disposable probe cover** is a single-patient use accessory that minimizes the risk of contamination to the system. It consists of a molded plastic housing with an anti-fog coated optical window. A protective plastic strip over the anti-fog window is removed after the disposable cover is placed on the probe, but prior to inserting into the calibration port.

The *LUMA User Manual* should be consulted for more detailed descriptions of the system, as well as the system user interface and procedures for use.

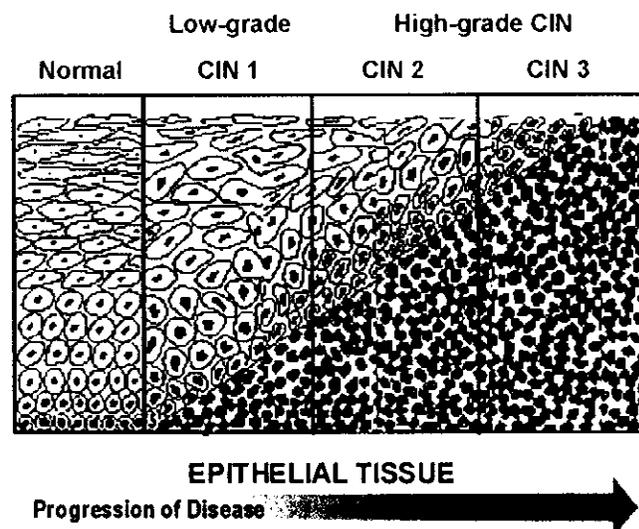
Cervical Neoplasia and Colposcopy

Development of Cervical Cancer

Prospective follow-up studies have documented that cervical cancer develops from histologically-defined precursor lesions that are referred to as cervical intraepithelial neoplasia or CIN (reviewed in Wright 2002). These precursor lesions are caused by infection with anogenital types of human papillomavirus (HPV)(IARC 2005). Although criteria for identification of cervical intraepithelial neoplasia (CIN) vary somewhat among pathologists, the common pathological differences identified in CIN lesions are epithelial immaturity, cellular disorganization, nuclear abnormalities, and increased mitotic activity (Wright 2002). The degree of CIN is determined from the extent of the mitotic activity, delayed maturation, and nuclear atypia.

Currently, several different classification systems for CIN are in use by pathologists. The one most widely used and the one that correlates best with clinical management divides

CIN lesions into low-grade CIN (CIN 1) and high-grade CIN (CIN 2,3), which combines what was previously referred to as CIN 2, and CIN 3 together into a single entity (see figure)(Wright 2002). Low-grade CIN (CIN 1) lesions are heterogeneous with respect to their associated HPV types and, most importantly, biological behavior (IARC 2005). CIN 1 lesions represent the cytopathic effects of HPV infections and usually spontaneously regress in the absence of clinical intervention. In contrast, high-grade cervical neoplasia including invasive cancer (CIN 2,3+) lesions are usually associated with infection with specific "high-oncogenic risk" types of HPV which are the HPV types that are found in invasive cervical cancers. These are HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. CIN 2,3 lesions are much more likely to persist than are CIN 1 lesions and CIN 2,3 lesions place a patient at risk for developing invasive cervical cancer if not detected and appropriately treated (IARC 2005).



Progression of Disease and Corresponding Cell Morphology Changes

Role of Colposcopy in the Prevention of Cervical Cancer

Cervical cancer prevention programs utilize cervical cytology, with or without adjunctive "high-risk" HPV DNA testing, to identify women at risk for having CIN 2,3 lesions. Women who have abnormal cervical cytology results or persistent "high-risk" HPV infections are referred for a colposcopic evaluation at which time the clinician examines the cervix using a colposcope which is a long-focal point magnifying device that illuminates the cervix using broadband white light. The cells in CIN 2,3 lesions are smaller and more crowded, with more notable condensed nuclear material compared to the cells of the normal epithelium or CIN 1 lesions. These changes alter the optical properties of the tissues, and as a result CIN 2,3 lesions typically appear densely white after the application of a solution of 3% to 5% acetic acid (i.e., acetowhite)(Sakuma 1985, Burke 1991). In addition, CIN 2,3 lesions often result in neovascularization and have characteristic vascular changes which can be identified with the colposcope. This combination of acetowhitening and vascular changes allows the clinician to identify areas

of the cervix that may represent CIN 2,3 lesions using the colposcope. Once such areas are identified the clinician obtains a cervical biopsy in order to allow a definitive histopathological diagnosis. Typically, one to two biopsies are taken. If a CIN 2,3 lesion is identified by histopathology, the patient can be treated using a variety of ablative or excisional techniques. If a cancer is identified either by colposcopy or on histopathology the patient is usually referred for definitive therapy.

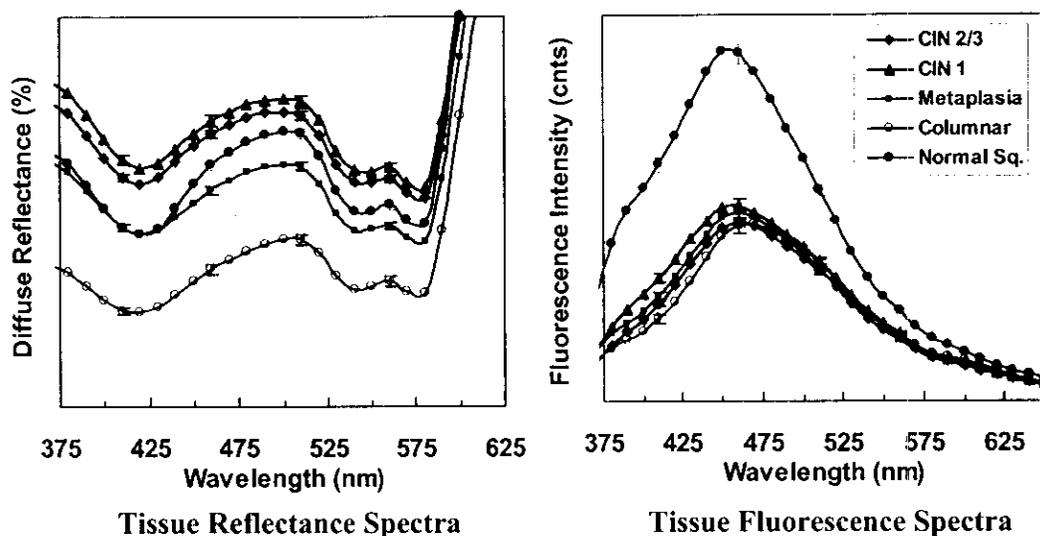
LUMA Principle of Operation

Optical Characteristics of Cervical Tissue

The structural and biochemical properties of the tissue that change with the development of CIN lead to corresponding changes in the optical characteristics of the tissue. These optical changes have been investigated extensively in the literature (Richards-Kortum 1996, Wagnieres 1998, Ramanujam 2000, Drezek 2003). For example, the development of high-grade CIN is associated with nuclear condensation that results in the acetowhitening effect. These changes also affect the properties of optical signals in general. Optical absorption of hemoglobin is also observed in tissue reflectance spectra, and these signals can change with CIN development. Reflectance optical signals measured from various intact cervical tissues are shown in the accompanying figures. The effect of hemoglobin absorption is seen in the reflectance spectra as minima near 415, 540 and 575 nm.

The predominant biochemical effect of CIN development is seen in the fluorescence optical signals. Fluorescence signals from diseased tissue are significantly reduced compared to those for normal squamous tissue. This is interpreted as a shift in the oxidation-reduction equilibrium of the metabolic protein nicotinamide adenine dinucleotide phosphate (NADPH), which is characterized by an emission maximum near 460 nm following excitation by 337 nm light. Acetowhitening also affects the fluorescence signals, resulting in a reduction of the observed fluorescence signal overall. The combined result is that the fluorescence signals from normal squamous tissue are significantly more intense than those from most other tissues (seen figure).

In these ways the morphological and biochemical changes associated with CIN development are exhibited in the optical measurements of intact cervical tissue. Optimally exploiting these characteristics can therefore be used to provide enhanced identification of CIN 2,3 tissue.



The LUMA Optical Scan

In the LUMA system diagnostic scans of the cervix are performed by interrogating the ectocervix using a combination of laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The cervix is scanned by the illumination probe, which is positioned near the proximal opening of the speculum as part of a colposcopy exam, following the application of acetic acid. The scan is a hands-free operation that takes approximately 12 seconds.

The fluorescence measurements are made by illuminating the cervix with ultraviolet (UV) light pulses at 337 nm from a nitrogen laser and recording the spectrally resolved intensities (spectra) of longer wavelength UV and visible light (360-720 nm) emitted from the cervix. Reflectance measurements are made by illuminating the cervix with pulses of broadband light from xenon flash lamps and recording the spectra of reflected light at those same wavelengths. Fluorescence and reflectance spectra are obtained from 499 distinct, closely-packed sites on the cervix by way of a computer-controlled scanning mechanism.

Prior to and during the measurement sequence, the cervix is also illuminated with the flashlamps for capturing video images of the cervix. The video images prior to the measurements provide a method to align the device, with four green spots of 532 nm visible light. The video images are used for alignment, to control for movement during a scan, and as an element in the overall device output. An interrogation point is rescanned if there is movement greater than 0.55 mm; an entire rescan is performed if accumulated movement is greater than 2.5 mm.

Following the optical scan of the cervix, the device analyzes the calibrated spectra and images of the cervix with a mathematical algorithm encoded in its software. Final output results are then calculated and displayed within approximately 30 seconds.

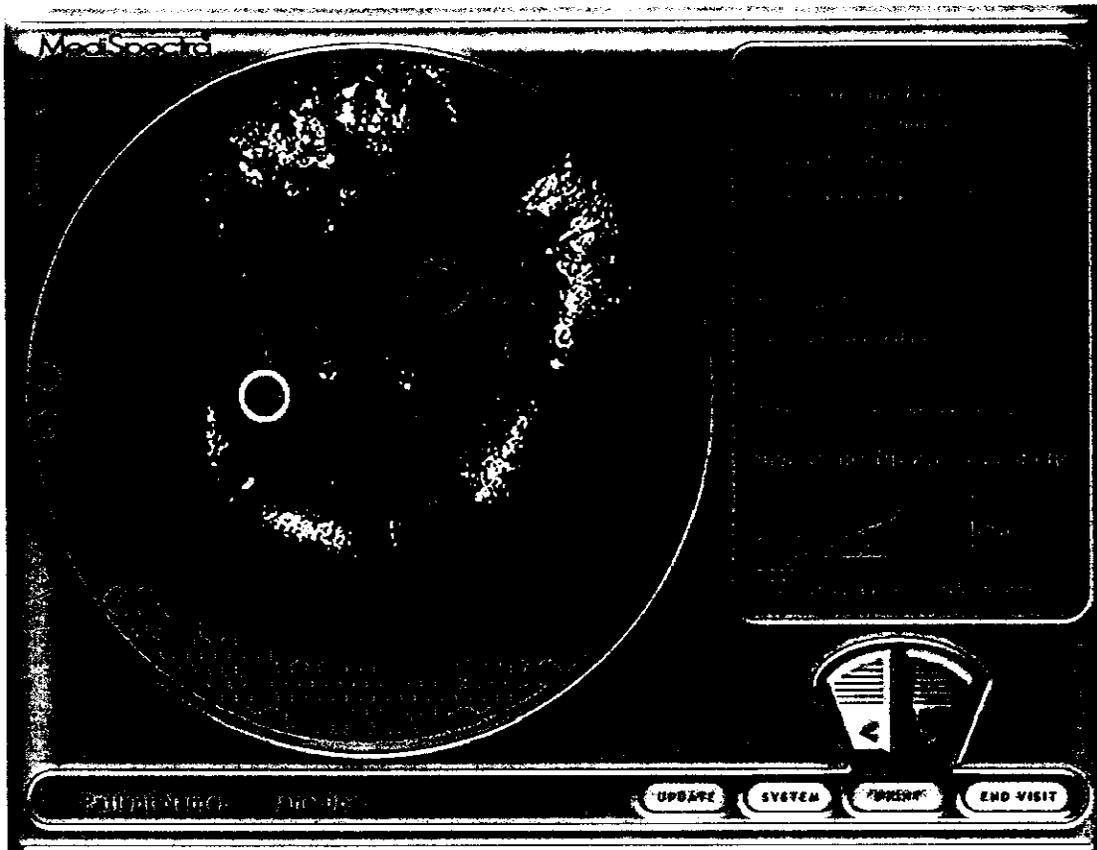
LUMA Algorithm

The LUMA algorithm combines the fluorescence, white light backscatter and video measurements in an integrated real-time algorithm. The LUMA classification algorithm consists of three main components: image masks, spectral masks, and a spectral classifier. The “masks” identify areas of the cervix that are necrotic or have obstructions or poor signal due to fluids, foam, blood, mucus or vaginal wall. A logistic classification with fluorescence spectra is combined with a multivariate statistical analysis of backscattered white light employing principal component and feature extraction analyses methods to yield a final tissue classification and associated LUMA score. The algorithms were optimized to differentiate high-grade cervical intraepithelial lesions (CIN 2,3+) from all other tissue types.

Results are displayed as a false-color overlay superimposed on a digital image of the cervix obtained during the scan. This overlay is color-coded to indicate the classifier score for high-grade disease (CIN 2,3+) at different locations on the cervix as follows:

- Blue: highest score for CIN 2,3+ ;
- Yellow: lower score for CIN 2,3+ ;
- Green square cross-hatching: necrotic tissue (rare); and
- Gray diamond-shaped cross-hatching: indeterminate, i.e., a LUMA result is not being made.

This color coding corresponds to a LUMA score representing the likelihood that high grade disease is present. It does not represent a definitive diagnosis of CIN 2,3+.



Biopsy Site Annotation Software

The colposcopist is asked to commit to any colposcopically-directed biopsy sites prior to viewing the LUMA display by annotating an electronic image.

Colposcopy Directed Annotations

Using the touchpad on the system keyboard, the colposcopist annotates biopsy site (s) by centering the green annotation circle over the targeted tissue. Left clicking or tapping the touchpad places the circle onto the displayed image of the cervix. Once annotated, the colposcopically directed site is depicted as a yellow circle. The colposcopist is allowed to adjust location of biopsy sites while in the colposcopy biopsy site selection mode. Once the colposcopist confirms (by pressing a keypad or foot pedal) that all colposcopically-directed biopsy sites have been entered, the annotated colposcopy biopsy sites cannot be changed. These sites should be biopsied regardless of the subsequent LUMA display.

LUMA Directed Annotations

The colposcopist commits to any LUMA-directed biopsy sites using the same process. With respect to the second annotation (after the LUMA display is viewed), the device software will:

- allow placement of annotation circles on the cervical image in areas marked with green crosshatch, blue or yellow false-color overlay;
- allow the colposcopist to change LUMA biopsy site locations while in the LUMA biopsy site location mode; and
- disallow annotation of LUMA biopsy sites that would overlap with any previously annotated colposcopically-directed or LUMA-directed biopsy site.

Once annotated, the LUMA-directed site is depicted as a green circle.

II. INDICATION, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS

INDICATION FOR USE

The LUMA Cervical Imaging System is indicated for use as an adjunct to colposcopy for the identification of high-grade disease (CIN 2,3+) in women referred to colposcopy with a Pap test result of atypical squamous cells (ASC), low-grade squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion or cancer (HSIL+).

CONTRAINDICATIONS

There are no contraindications for the LUMA system.

WARNINGS

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| <ul style="list-style-type: none"> • WARNING: LUMA is not to be used as a substitute for colposcopy. When using the LUMA system, <u>always</u> conduct a colposcopic examination first and both identify and commit to any/all biopsy sites. The LUMA examination is begun <u>only after</u> commitment to these colposcopically-directed biopsies. <u>Never</u> use the LUMA system to omit a biopsy selected by colposcopy. |
|---|
- **WARNING:** The illumination probe contains both laser and broadband light sources. Never stare directly into the illumination probe output window, or point the probe toward the eyes of anyone present when the system is active.

- **WARNING:** To achieve optimal results:
 - Take at least one biopsy when LUMA displays blue shading over an area not targeted by the colposcopic exam, provided that the area is in the transformation zone, not an artifact of mucus, pooled fluids, or noncervical structures; and
 - Biopsy yellow areas not already targeted by colposcopy if clinically suspicious.
- **WARNING:** LUMA misses some CIN 2,3+ lesions detected by colposcopy. Therefore, colposcopic-indicated biopsy sites should not be omitted based on LUMA output. This could result in a missed diagnosis of CIN 2,3+.
- **WARNING:** The optical resolution of the LUMA system is not sufficient to evaluate atypical blood vessels. Therefore, it is essential to perform a thorough colposcopy in order to identify vascular lesions which may be present.
- **WARNING:** LUMA relies on an unobstructed scan of the ectocervix and the device may miss lesions or deliver a false positive signal in areas where the cervix is obscured. These include:
 - Areas of the ectocervix obscured by mucus, blood (heavy menstrual flow), or pooled fluids. In many instances, these obstructions can be removed by gentle wiping of the cervix with a cotton-tipped applicator.

Do NOT vigorously rub the cervix. Do NOT take a Pap test or a colposcopic biopsy prior to scanning as this may cause bleeding.
 - Areas that are obscured by vaginal walls or noncervical structures such as an IUD string, speculum, or intravaginal contraceptive device. In many instances, these obstructions can be gently moved out of the way with a cotton-tipped applicator and the patient rescanned. The colposcopist should rely solely on colposcopic visualization and not on LUMA for evaluation of obscured areas (see Interpreting the LUMA Display in the User Guide).

Do NOT perform a LUMA scan on:

- Patients who have used vaginal creams or medication (including douches except saline douches) within the 48 hour period prior to the LUMA;
- Patients in whom Monsel's solution (ferric subsulfate) or iodine solutions (such as Lugol's) has been applied to the cervix prior to

scanning;

Do NOT insert objects such as cotton swabs or ring forceps into the vagina while focusing the probe and scanning the cervix.

- **WARNING:** Areas of the cervix identified by LUMA as “obstructed” are masked by the software and are reported as *indeterminant* by the LUMA (i.e., they show grey crosshatching). In addition, the endocervical canal and cervical edges are often reported as *indeterminant* by LUMA. It is important to note that whenever a region is reported as *indeterminant* a lesion in this region will be missed by LUMA. Therefore the colposcopist should rely solely on colposcopy when evaluating *indeterminant* (grey crosshatched) areas.
- **WARNING:** Failure to apply acetic acid to the cervix prior to performing a LUMA scan could result in missed diagnosis of CIN 2,3+.
- **WARNING:** There is a theoretical risk based on cell culture studies that, compared to uninfected cells, HPV-infected cells may be preferentially damaged following ultraviolet (UV) exposure. Research reports indicate damage at UV energy levels that are at least four times higher than those emitted by the LUMA device.
- **WARNING:** To minimize optical exposure, do not perform more than one complete LUMA procedure per day on any patient.
- **WARNING:** LUMA should not be used in patients who have taken photosensitizing drugs within 72 hours (such as a sulfa drug, ampicillin or tetracycline) or had a history of photosensitivity (e.g. porphyria, Systemic Lupus Erythematosus (SLE)). Although not included in the clinical trials of LUMA, the use of LUMA in these patients may result in erythema of the cervix or vagina.

PRECAUTIONS

Clinical Precautions

- **CAUTION:** Use of LUMA may result in one or more additional biopsies from regions of normal tissue or CIN 1. In the Intended Use Clinical Trial of LUMA, the rate of “false positive” biopsies (i.e. CIN 1 or normal) was 82% for LUMA and 74% for colposcopic-directed biopsies.
- **CAUTION:** The safety and effectiveness of the LUMA System have not been evaluated in the following:
 - Patients younger than 18 years of age;

- Patients who are pregnant through 6 weeks post-partum;
 - Patients with untreated gynecological infections, such as acute cervicitis, acute inflammation, and acute vaginitis;
 - Patients who have exposure to diethylstilbestrol (DES) *in utero*;
 - Patients who have used vaginal creams or medications (including vaginal contraceptive delivery systems and douches except saline douches) within the 48 hours preceding the examination;
 - Patients who have received a Pap test 1-7 days before the LUMA scan
 - Tissue other than the ectocervix (e.g., vagina, vulva, endocervix). Thus women who have no cervix (i.e., history of total hysterectomy) should not be scanned;
 - Congenital anatomical cervical variants (e.g., double cervix);
 - Cervices that have undergone surgical procedures within the last 6 weeks, including but not restricted to, dilatation and curettage (D&C), therapeutic abortion, or ablative or excisional therapeutic procedures;
 - Cervices that have been anesthetized just prior to scanning;
 - Glandular lesions of the cervix, including adenocarcinoma *in-situ* and invasive adenocarcinoma, and therefore may not diagnose these lesions.
- **CAUTION:** The patient, the speculum, the probe or the probe's articulating arm should not be touched while the system is scanning. Excessive motion will cause a cancelled scan and require a rescan.
 - **CAUTION:** In clinical trials, the comparative performance of LUMA in patients with and without high-risk HPV was not evaluated.

Electrical Safety Precautions

- **CAUTION:** Use of controls, adjustments, or performance of procedures other than those specified herein may result in hazardous radiation exposure.
- **CAUTION:** Connect the system's electrical cord only into a grounded 110-120 VAC electrical outlet. Failure to do so may result in electrical shock to the patient or operator, or in damage to the equipment.
- **CAUTION:** Never use a converter adapter to connect the three-pronged AC plug into a two-pronged, ungrounded wall outlet. Doing so may result in electrical shock to the patient or operator, or in damage to the equipment.

- **CAUTION:** To avoid fire or explosion, do not operate the system in the presence of open flammable vapors or explosive gases, open chemicals, or in rooms where such materials have been stored.
- **CAUTION:** The LUMA system cannot be used simultaneously with other patient-connected electrical treatment or diagnostic devices, such as a Loop Electrosurgical Excision Procedure (LEEP). However, system shutdown is not needed before performing a LEEP.
- **CAUTION:** Use of cell phones near the probe during device scanning may interfere and result in a system shutdown. A message will appear on the screen that the scan has failed. If this problem occurs, you should confirm that all cell phones in the examination room have been turned off. It will then be necessary to turn off and then restart the system.
- **CAUTION:** Do not use any spray or liquid solution on the system in a manner that is not specifically defined in Section 5.2 of the User Manual (“Wiping System Surfaces”). Many important parts of the system are not water resistant. Do not allow any fluid to drip or run down surfaces. Avoid the possibility of electrical shock and device damage by always shutting down the system and unplugging the power cord prior to wiping surfaces.
- **CAUTION:** The LUMA System should not be used adjacent to or stacked with other equipment and that if adjacent or stacked use is necessary, the LUMA System should be observed to verify normal operation in the configuration in which it will be used.
- **CAUTION:** Never attempt to unplug or move the system until the shutdown sequence is complete, and the power has been turned OFF.
- **CAUTION:** Routinely inspect all components, including the power cord, before using the system. Never use any component that appears damaged.
- **CAUTION:** Use only MediSpectra-qualified peripheral devices, including the printer, footswitch, and touchpad control.
- **CAUTION:** Only a qualified MediSpectra service representative can service the system or perform preventive maintenance. Never attempt to repair the system yourself. Disassembly could result in electrical or optical hazards.

Probe Cover Precautions

- **CAUTION:** Always inspect the disposable probe cover prior to use. If it appears damaged in any way, or if there are fingerprints or other marks visible on the window, do not use. Replace with a new disposable probe cover. Never touch the lens at the tip of the illumination probe, or the window of the disposable probe cover.

- **CAUTION:** Failure to use a new disposable for each patient exam may result in cross-contamination between patients.
- **CAUTION:** Only authorized MediSpectra disposable covers should be used with the LUMA system. Contact MediSpectra for ordering.
- **CAUTION:** Always wear gloves when removing a used disposable cover at the end of an exam.
- **CAUTION:** Never insert the probe into the calibration port with a used disposable cover still in place. In the event the calibration port becomes contaminated, a pop-up message directs you to the *User Manual* (Section 5.2, “Wiping System Surfaces”), for instructions on removing and disinfecting the detachable calibration port door assembly.

Optical Exposure Precautions

- **CAUTION:** The scanning laser may be disabled at any time during the scanning by pressing either footswitch, or pressing any key (except Fn) on the keyboard, tapping the keyboard touchpad or by turning the Laser Enable Key (located on the front of the console) to the OFF position (clockwise).
- **CAUTION:** Unauthorized disassembly of the illumination probe could result in electrical and/or optical hazards. Disassembly of the illumination probe is not necessary during operation and maintenance procedures.
- **CAUTION:** While the LUMA system is a Class 1 (non-hazardous) laser product, the internal lasers are rated as Class 3B (acute hazard to skin/eye) and their emission levels are higher than the levels emitted from the probe during a LUMA scan. Unauthorized disassembly of the console could result in optical hazards. Disassembly of the console is not necessary during operation and maintenance procedures. All procedures that require access to the Class 3B level of laser energy are to be performed by trained MediSpectra personnel or authorized service agent.

General Technical Precautions

- **CAUTION:** If any of the system’s diagnostic tests fail, the system displays an error message and stops initializing. The system cannot be used—contact a MediSpectra service representative.
- **CAUTION:** The illumination probe delivers and receives the UV and broadband light sources, projects the alignment pattern for focusing, and houses the lens for the camera. It must be handled with extreme care.
- **CAUTION:** Before lifting the LUMA printer cover, remove the illumination probe from the calibration port and swivel the keyboard and monitor all the

way to the side.

- **CAUTION:** Always power the system down before unplugging it by pressing the System Power Button on the right of the front panel.
- **CAUTION:** Be sure the casters are fully locked (lowest position of the brake) prior to system operation.
- **CAUTION:** Be sure all electrical connections are secure prior to operating the system.
- **CAUTION:** Never block the cooling vents or fans located on the rear panel while system is operating.
- **CAUTION:** Be careful not to trip over the footswitch cable or main power cord.
- **CAUTION:** Prior to use, visually inspect the system for external damage. If damage is found, do not use the system—report damage to MediSpectra.
- **CAUTION:** The wrap-around handles are designed to provide assistance for pushing and maneuvering the system when it needs to be moved. Do not attempt to lift the system with these handles.
- **CAUTION:** Avoid extreme environmental conditions in storing or using this system. Adhere to the operating and storage conditions specified in this manual.
- **CAUTION:** The LUMA system contains two fuses, located in the fuse holder on the power inlet connector on the rear panel. Replace only with MediSpectra fuse (part number 3-00838) or equivalent.
- **CAUTION:** The *optical window area* of the probe head is normally protected by the disposable probe cover while the system is in use. It should only be wiped with **70% isopropyl alcohol**. Except as described here, avoid contact with the *optical window area* of the probe head since contact could result in damage that may lead to inaccurate display results.

III. ADVERSE EVENTS

In all clinical studies to date, involving 3527 enrolled subjects, there were 17 reports of adverse events. None of these events was serious and none was believed to be related to the LUMA device.

The 17 reported minor adverse events occurred in 11 women and consist of the following:

- cramping (2)
- vomiting (1)
- weakness (1)
- vaginal bleeding (3)
- dizziness/fainting (6)
- nausea (1)
- abdominal pain (1)
- dysuria (1)
- burning sensation after application of acetic acid (1)

Risks associated with the intended use of the LUMA system are inadvertent contact of the probe with the vaginal speculum, resulting in minor discomfort. While not observed in clinical studies, failure to follow operating instructions could result in ocular damage, hazardous optical radiation, electrical shock, damage to the system or other hazards.

IV. CLINICAL STUDIES ON THE SAFETY AND EFFECTIVENESS OF THE LUMA CERVICAL IMAGING SYSTEM

Background: Overview of Colposcopy Performance

Colposcopy with colposcopically-directed biopsy is considered the standard of care for diagnosing significant cervical cancer precursors and invasive cervical cancer (CIN 2,3+). However, colposcopy is a subjective clinical science, with an accuracy that is dependent upon the training and experience of the colposcopist [Buxton 1991, Massad 2003]. Estimates for the performance of colposcopy in clinical practice vary widely depending on a number of factors, including the grade of the referral cytologic abnormality and whether or not women with negative colposcopic findings are followed prospectively.

Cox *et al.* recently analyzed the data from the ASCUS/LSIL Triage Study (ALTS) clinical trial specifically to address the performance of initial colposcopy among the ASCUS/LSIL referral population [Cox, 2003]. They concluded that in the ASCUS/LSIL referral population 18% of women would have biopsy-confirmed CIN 2,3+ identified at initial colposcopy, and that cumulatively about 27% of the women would be diagnosed with CIN 2,3+ over a two year period. Therefore the sensitivity of a single colposcopic examination in the ALTS study was only about 67% (18%/27%). Similarly, histopathologic correlation studies between the preoperative diagnosis and the diagnosis made on loop electrosurgical excision (LEEP) specimens demonstrate that colposcopically-directed cervical biopsies miss approximately a third of cases of CIN 2,3. Massad *et al.* summarized the findings of eight histopathologic correlation studies correlating histopathology findings in LEEP specimens in women undergoing a LEEP for a preoperative diagnosis of CIN 1 (based on preoperative colposcopically-directed cervical biopsy) [Massad 1996]. The prevalence of CIN 2,3+ in the LEEP specimens in the eight studies ranged from 18% to 55%. In six of the eight studies, a third or more of the women with a preoperative diagnosis of CIN 1 were subsequently found to have undiagnosed CIN 2,3+, and the average detection of CIN 2,3+ in the eight studies, combined, was 36%. Other studies have reported false negative rates of colposcopy ranging from 15% to 31% for CIN 2,3 lesions [Skehan 1990, Denny 1995].

Clinical Studies of LUMA

A total of nine clinical studies, enrolling over 3500 subjects, have been completed to date. The first seven studies were executed to support system development and optimization of the LUMA algorithm. One study included data that can be used to assess instrument reproducibility, as described below. Two additional studies provided clinical evaluation in the colposcopy referral population of the safety and efficacy of LUMA when used in combination with colposcopy as reported in more detail below.

LUMA Reproducibility

To assess the reproducibility of the LUMA results, fifty women with no evidence of cervical disease underwent multiple LUMA procedures, once per week for four to five weeks. Two to five regions of each woman's cervix were monitored to determine if the LUMA classifications for those regions changed from no evidence of disease to a blue or yellow LUMA reading or vice versa. The study had data on 189 regions, and a total of 899 assessments, 28 of which were falsely positive. An indirect measure of reproducibility is the probability of a falsely positive outcome in these putatively negative women. The false positive rate was estimated by a generalized estimating equation (GEE) model for the probability of a positive (yellow or blue) reading that takes into account that repeated measures within each woman are correlated. From the model, the false positive rate was estimated to be 3.02% with 95% confidence interval 1.75% to 5.12%. Reproducibility can be directly estimated as the probability of discordant results within women between all possible pairings of visits for each region. The total number of visit pairings was 1707, of which 71 were discordant. The probability of discordance between visit pairs was estimated from a GEE model that takes into account that repeated measures within each woman are correlated. The probability of discordance between visit-pairs was estimated to be 4.03% with 95% confidence interval from 2.08% to 6.29%.

This study did not include women known to have cervical disease, so no conclusions can be made regarding the repeatability of the LUMA System for women with cervical disease. That is, no information is available on how many true positives could become false negatives, or vice versa, upon repeated LUMA procedures.

Concurrent-use Clinical Study

An initial clinical study was designed to evaluate the performance of the LUMA system in an alternate use model in which LUMA is used concurrently with colposcopy. In this study women were randomized to one of two arms: Routine Colposcopy (a LUMA scan was performed but the colposcopist was blinded to the results) or Colposcopy with LUMA (the colposcopist was able to visualize the LUMA result while performing the colposcopic examination). While this does not reflect the adjunctive intended use of the LUMA system, it does provide supporting evidence of the safety and effectiveness of the LUMA system when used in a colposcopy referral population.

Study Sites, Patient Characteristics and Exclusions

A total of 2299 women referred to colposcopy on the basis of an abnormal Pap test (ASC, LSIL, HSIL, or cancer) were enrolled at 13 centers with a total of 51 participating colposcopists. One hundred thirteen (113) subjects (4.9%) were lost because of either investigator withdrawal or exclusions, leaving 2186 evaluable subjects. Of the 113 subjects removed, 27 subjects (1.2%) were withdrawn by the investigator before randomization. There were a total of 86 (3.7%) subjects excluded after randomization; 37 subjects (1.6%) were lost from the Routine Colposcopy arm and 49 subjects (2.1%) from the Colposcopy with LUMA arm. The primary reasons for subject loss were no majority pathology diagnosis (1.8%) and device malfunctions (1.6%). The median age of women was 30.4 years. The most common reason for referral to colposcopy was a LSIL cytology (44%), followed by ASC cytology (36%) and HSIL/Cancer (20%). Other demographic data is similar to that for the intended use study reported below.

Study Results

The primary trial endpoints were the comparison of subject-level true positives (TP) (women with CIN 2,3+ on cervical biopsy) and subject-level false positives (FP) (women with cervical biopsies but no CIN 2,3+ diagnosed) between the two arms. The primary TP hypothesis was that the TP rate would be significantly greater in the Colposcopy with LUMA arm compared to the Routine Colposcopy arm. Overall, TP rates were 19.9% in the Routine Colposcopy arm versus 21.8% in the Colposcopy with LUMA arm, corresponding to a 1.9% (95% CI -1.5% to 5.3%) increase (Table 1). This increase represents a 9.8% relative gain (95% CI -6.8% to 29.3%) in the TP rate. The overall study hypothesis was not met because neither 95% CI indicates a statistically significant increase.

While pooling of ASC/LSIL subjects was not prespecified, the TP findings were similar in the ASC and LSIL Pap strata, as might be expected since these groups have similar CIN 2,3+ disease prevalence and associated clinical management practices. Among women referred for evaluation of ASC and LSIL combined, the TP rate was 11.4% for Routine Colposcopy versus 14.4% for Colposcopy with LUMA arm. This represents a 3.0% (95% CI -0.1% to 6.1%) difference in TP rate, corresponding to a 26.5% relative gain (95% CI -1.1% to 61.8%).

Table 1: Concurrent-use Study - Subject-level True Positive Rates

Pap Strata (% total)	Routine Colposcopy Arm % (n/N)	Colposcopy with LUMA Arm % (n/N)	Difference (95% CI)
Overall (100.0%)	19.9% (218/1096)	21.8% (238/1090)	1.9% (-1.5%, 5.3%)
ASC (36.3%)	10.9% (42/387)	13.8% (56/407)	+2.9% (-1.7%, 7.5%)
LSIL (43.6%)	11.8% (57/484)	14.9% (70/469)	+3.1% (-1.2%, 7.4%)
HSIL (20.1%)	52.9% (119/225)	52.3% (112/214)	-0.6% (-9.9%, 8.7%)

The primary FP hypothesis was that the FP rate would be greater in the Colposcopy with LUMA arm compared to the Routine Colposcopy arm by an amount significantly less than 8%. Overall, the FP rate was 57.4% in the Routine Colposcopy arm versus 60.5% in the Colposcopy with LUMA arm, for a FP difference of 3.1% (95% CI -1.0% to 7.2%) (see Table 2). The 95% CI is below 8%, indicating that the FP rate hypothesis was met.

Table 2: Concurrent-use Study - Subject-level False Positive Rates

Pap Strata (% Total)	Routine Colposcopy Arm % (n/N)	Colposcopy with LUMA Arm % (n/N)	Difference (95% CI)
Overall (100.0%)	57.4% (629/1096)	60.5% (659/1090)	3.1% (-1.0%, 7.2%)
ASC (36.3%)	54.3% (210/387)	62.4% (254/407)	+8.1% (1.3%, 14.9%)
LSIL (43.6%)	66.7% (323/484)	67.6% (317/469)	+0.9% (-5.1%, 6.9%)
HSIL (20.1%)	42.7% (96/225)	41.1% (88/214)	-1.6% (-10.8%, 7.6%)

Overall, 22.7% of subjects had no biopsies in the Routine Colposcopy arm, while 17.7% had no biopsies in the Colposcopy with LUMA arm. Thus 5% more women received biopsies in the Colposcopy with LUMA arm. The average number of biopsies for all subjects was also greater in the Colposcopy with LUMA arm than in the Routine Colposcopy arm. In the Routine Colposcopy arm the average number of biopsies per patient was 1.03, while in the Colposcopy with LUMA arm it was 1.30, for an average gain of 0.27 biopsies per patient. The proportion of biopsies that were positive for CIN 2,3+ was 24.0% (268/1115) in the Routine Colposcopy arm and 21.9% (306/1397) in the Colposcopy with LUMA arm.

Intended Use Pivotal Trial

The intended use study was a single-arm evaluation of the ability of LUMA to identify additional cases of women with CIN 2,3+ who had been definitely missed by the initial colposcopic examination. The study was terminated after approximately 30% of the planned enrollment was reached and without knowledge of the study results.

In the intended use pivotal trial of 193 women referred for colposcopy, examination of the LUMA results was preceded by colposcopy with selection of and commitment to colposcopically-indicated biopsy sites. In the study, 21.2% of the women had CIN 2,3+ diagnosed by the colposcopically-directed biopsies. LUMA-directed biopsies taken afterwards led to detection of CIN 2,3+ in an additional 4.7% of the women. This corresponds to a relative gain of 22.0% (95% CI 6.1% to 37.8%). On average, women in this study had one colposcopically-directed biopsy and one LUMA-directed biopsy. This study was not designed to determine the relative contribution of LUMA compared to the value of additional colposcopically-directed biopsies after initial colposcopy was completed.

Study Sites, Patient Characteristics and Exclusions

This trial enrolled 227 subjects at 7 centers with a total of 16 participating colposcopists including nurse practitioners, generalist obstetrician/gynecologists and gynecologic oncologists. The subjects were at least 18 years of age (or age of consent) and referred to colposcopy on the basis of an abnormal Pap test (ASC, LSIL, HSIL or cancer). Thirty-four (15%) of the 227 subjects were not evaluable, including 7 subjects (3.0%) withdrawn by the investigator before examination was completed and 27 (11.9%) subjects excluded post examination. The primary reason for post examination exclusions was incomplete pathology (16 subjects). The final evaluable population was 193 subjects. Demographic and clinical information of the enrollees is presented in Table 3. The mean age was 28.5 years. The most common reason for referral to colposcopy was LSIL cytology (47%), followed by ASC cytology (39%) and HSIL/Cancer cytology (14%).

Table 3: Intended Use Study - Demographic and Clinical Characteristics

Characteristic	Overall
N, evaluable	193
Age (years)	
Mean (SD)	28.5 (10.6)
Range	18 - 64
Race	
Caucasian	83 (43.0%)
Hispanic	60 (31.1%)
African American	41 (21.2%)
Native American	3 (1.6%)
Asian	3 (1.6%)
Other	3 (1.6%)

Characteristic	Overall
Clinical History	
Referral Pap	
ASC*	76 (39.4%)
LSIL	91 (47.2%)
HSIL/Cancer	26 (13.5%)
Menstrual status	
Menstrual (cycling)	181(93.8%)
Post-menopausal	12 (6.2%)
No prior history of abnormal Pap	99 (51.3%)
Mean gravidity (SD)	2.0 (2.1)
Mean parity (SD)	1.5 (1.8)

*Includes ASC-US and ASC-H cytology

Definition of Study Endpoints

The primary trial endpoints were the incremental true positive (TP) subjects (subjects with CIN 2,3+ on a LUMA-directed biopsy, but no CIN 2,3+ detected on a biopsy indicated by colposcopy) and incremental false positive (FP) subjects (subjects with LUMA-directed cervical biopsies that were not diagnosed as CIN 2,3+, and who did not have a biopsy indicated by colposcopy). The primary TP trial hypothesis was that overall TP rates for the LUMA increment would be significantly greater than 2%. The primary FP trial hypothesis was that overall FP rates for the LUMA increment would be significantly less than 15%.

True Positive Detection Rates

Initial colposcopy identified 41 cases of CIN 2,3+ for a TP rate of 21.2% (see Table 4). Among those women not identified by colposcopy to have CIN 2,3+ an additional 9 cases were identified by the use of the LUMA system. This corresponds to an incremental LUMA TP rate of 4.7% (95% CI 2.2% to 8.7%). In this *intended use* trial the overall TP hypothesis was therefore met ($p = 0.0164$). Use of the LUMA system therefore resulted in a 22.0% (95% CI 6.1% to 37.8%) relative gain in the number of subjects with CIN 2,3+ compared to colposcopy alone.

The study results can be used to estimate the sensitivity of LUMA-aided colposcopy relative to colposcopy alone. Sensitivity is the percent of women with CIN 2,3+ disease that are detected to have CIN 2,3+ from colposcopy-indicated biopsies. While the sensitivities of colposcopy and LUMA cannot be estimated directly from the study because the total number of women with CIN 2,3+ is unknown, the relative increase in sensitivity when LUMA is added to colposcopy can be estimated by the ratio of the incremental TP rate to the initial colposcopy TP rate. The estimate of a 22% relative gain in TP rate reported above therefore also corresponds to the same relative gain in the sensitivity.

Table 4: Intended Use Study - Subject Level Outcomes

Strata	Outcome	Initial Colposcopy		LUMA Increment	
		Rate (n/N)	95% CI	Rate (n/N)	95% CI
Overall	True Positive	21.2% (41/193)	15.7%, 27.7%	4.7% (9/193)	2.2%, 8.7%
	False Positive	51.8% (100/193)	44.5%, 59.0%	18.1% (35/193)	13.0%, 24.3%

False Positive Detection Rates

The FP rate for initial colposcopy was found to be 51.8% (100 of 193 subjects), Table 4. An additional 35 subjects had a LUMA-directed biopsy that was not diagnosed as CIN 2,3+, yielding an incremental FP rate of 18.1% (95% CI 13.0% to 24.3%). The 95% CI includes 15%, indicating that the FP hypothesis was not met.

Because the clinical consequence of a false positive LUMA reading is an increase in the number of biopsies taken, the impact of the FP rate on the patient can best be assessed based on the increase in biopsy rates. The mean biopsy rate for the LUMA increment was 1.02 (197 biopsies in 193 subjects), which was comparable to the mean biopsy rate for colposcopy of 0.89 (172 biopsies in 193 subjects). The percent of subjects not biopsied in the LUMA increment was 22.3% (43/193), which was comparable to the no biopsy rate in the colposcopy phase of 26.9% (52/193). The percent of subjects biopsied increased from 73.1% (141/193) for initial colposcopy to 92.2% (178/193) with the addition of the LUMA increment.

The study results can be used to obtain limited information on the specificity of colposcopy with adjunctive LUMA relative to colposcopy alone. Specificity is the percent of women without CIN 2,3+ that are not biopsied. While the specificities of colposcopy and LUMA cannot be estimated directly from the study, the relative increase in (100%-specificity) when LUMA is added to colposcopy can be estimated by the ratio of the incremental FP rate to the initial colposcopy FP rate. The estimate is 18.1%/51.8%, or 35.0% (95% CI 21.5% to 48.5%).

True Positive and False Positive Trade-off

Taken together, the incremental TP and FP rates of 4.7% and 18.1% for the LUMA phase represent a trade-off of approximately 4:1 (18.1/4.7) in the ratio of the number of subjects regarded as unnecessarily biopsied in search of CIN 2,3+ to the number of subjects in which incremental biopsy detected CIN 2,3+. By comparison, this ratio was approximately 2.5:1 (51.8/21.2) in the initial colposcopy phase. A smaller ratio for the colposcopy phase than the LUMA phase is expected, because by virtue of going last, the LUMA phase is a search only for the remainder of women with CIN 2,3+ disease that were not detected with disease in the colposcopy phase.

The proportion of biopsies that were positive for CIN 2,3+ was 26.2% (45/172) in the colposcopy phase and 18.3% (36/197) in the incremental LUMA phase. That is, the ratio

of true positive to false positive biopsies was approximately 3:1 in the colposcopy phase and 4.5:1 in the LUMA phase. The larger ratio in the LUMA phase is expected because in that phase a search is made only for the remainder of high-grade disease that was not detected in the colposcopy phase.

Analysis of LUMA Readings

The LUMA score is a measure between 0 and 1 of the LUMA system reading at a specified biopsy location, and was calculated using the LUMA output data from the intended use study. Although a specific score is not reported to the user, the “strength” of the score is reflected in the color display (i.e., blue areas represents those with highest LUMA scores). The LUMA score was evaluated in relation to the likelihood of a positive biopsy by mixed effect logistic regression models with biopsy as the unit of analysis. The goal was to assess the degree of relationship between the LUMA score and the logarithm of the odds of a positive biopsy while taking into account Pap referral stratum (ASC, LSIL, HSIL), study phase (colposcopy or LUMA), interactions between stratum, study phase, and LUMA score, and clinical site and colposcopist variability.

The primary finding from these analyses is that the LUMA score has a direct and significant relationship to the likelihood of a positive biopsy ($p = 0.0135$). This relationship is homogeneous across strata and study phase. According to the model, the odds of a positive biopsy is estimated to increase 1.39 fold (95% CI 1.07 to 1.80) for every 0.25 increase in the LUMA score. There is evidence of a significant interaction between LUMA score and study phase with $p = 0.0622$ (using 0.1 as criterion for significance of an interaction). A model including the interaction between study phase and the LUMA score yields estimates of the relationship between LUMA score and odds of a positive biopsy that is specific for LUMA phase biopsies. Using the model that includes this interaction, the odds of a positive biopsy for LUMA phase biopsies is estimated to increase 2.46 fold (95% CI 1.27 to 4.78) for every 0.25 increase in the LUMA score. The corresponding estimate for Colposcopy phase biopsies is 1.28 (95% confidence interval from 0.96 to 1.72).

Conclusions Drawn from the Studies

The results of the intended use study discussed above indicated an estimated relative gain of approximately 22.0% (95% CI 6.1% to 37.8%) in identification of true positive cases of high-grade CIN 2,3+ across the study population. This benefit was observed with an increase of approximately one biopsy per subject, about a fifth of which were positive for CIN 2,3+ (compared to about a fourth for colposcopic-indicated biopsies), and with no significant adverse events noted. Further, the effectiveness of the LUMA system was supported by a statistically significant relationship between LUMA score and positive biopsy rate, with positive biopsy locations tending to have higher LUMA scores across all Pap strata and for both LUMA-directed and colposcopically-directed biopsies. A smaller, statistically insignificant, yet similarly favorable risk/benefit profile was observed in the dual-arm study under different conditions of use, providing additional supportive evidence of the safety and effectiveness of the device.

V. Patient Counseling Information

A number of studies have demonstrated that patients who are referred for colposcopy experience considerable anxiety [Orbell, 2004; Rogstad, 2002]. Most women experience high levels of anxiety because of fear that they have cancer or fear of colposcopy itself [Jones, 1996; Maissi, 2005]. Moreover, many women have learned for the first time that they are infected with a "high-risk" type of human papillomavirus (HPV) and have numerous questions regarding when and from whom they got the HPV infection, will they ever clear the infection, and will they develop cervical cancer [Anhang, 2004]. Therefore it is important that clinicians take time to counsel patients prior to performing a colposcopic examination. This counseling should take into account:

- the role that cervical cytology plays in cervical cancer screening programs [Wright, 2004]
- the natural history of high-risk HPV infections – focusing on the fact that HPV infections are ubiquitous among sexually active women and most infections spontaneously resolve within 12 months and have no significant clinical sequelae [Baseman, 2005]
- that very few women who have either an abnormal cervical cytology or who are "high-risk" HPV DNA positive will actually have or ever develop cancer [Wright, 2004]
- a description of the colposcopic examination focusing on the fact that colposcopy is a relatively quick procedure and that taking a cervical biopsy causes only minor discomfort similar to having blood drawn

Clinicians utilizing LUMA as an adjunct to colposcopy need to explain that using LUMA:

- reduces the likelihood that a high-grade cervical cancer precursors (i.e., CIN 2,3) will be missed during colposcopy;
- slightly prolongs the amount of time it takes to perform the examination; and
- increases the number of biopsies that are obtained from a woman by an average of one biopsy. Cervical biopsy usually produces only minor discomfort, however some women may experience more pain. Minor bleeding is common after a cervical biopsy, however significant bleeding or other complications are extremely uncommon [Ferris, 2005].

VI. LUMA TRAINING PROGRAM

The LUMA™ Cervical Imaging System training program provides colposcopists the knowledge and skills necessary for utilizing LUMA as an adjunct to colposcopy. The program also provides information to support staff who set up and maintain the system. The LUMA Cervical Imaging System education program consists of two training modules which are described below.

LUMA™ Cervical Imaging System Information for Prescribers

Training Module #1- System Overview & Set-up

This training module will review the components of the LUMA™ Cervical Imaging System as outlined in current labeling. The target audience for this session are all colposcopists and personnel who support the system set-up. The following is an outline of the topics covered. A more detailed description of each topic covered by Training Module #1 can be found in the *LUMA™ Cervical Imaging System User Manual*:

- *Basic Use Information*: limits of device operation, specula options, conditions affecting results
- *System Overview*: Console, articulating arm, illumination probe, disposable probe cover, calibration port, monitor, keyboard, printer, footswitch, 3-position brake
- *Detailed System Operation*: plugging system in, power up, warnings, cautions and notes
- *Troubleshooting the system*
- *Basic System Maintenance*

Training Module #2- LUMA Use

This training module will review patient scan and biopsy annotation using the training mode of the system. This is a hands on-training session during which the colposcopist will calibrate, focus the instrument and review/annotate the training cases provided by the system software. The target audience for this training are the colposcopists who may potentially use the system. This training will be done prior to the first patient use.

The following is an outline of the topics covered. A more detailed description of each topic covered by Training Module #2 can be found in the *LUMA™ Cervical Imaging System User Manual*:

- Setting up the scan after acetic acid application: acetic acid timer, pooled fluid removal, focusing of illumination probe, performing scan
- Annotation of biopsy sites: colposcopy annotation, displaying LUMA results, interpreting LUMA results, LUMA annotation, full annotation display
- Biopsy: Always/never rule
- Record-keeping: LUMA Report

VII. GENERAL

Manufacturer:

MediSpectra, Inc.
 45 Hartwell Avenue
 Lexington, MA 02421
 www.medispectra.com
 Phone: 888-544-0471
 FAX: 781-674-0002

Other Manuals provided with the system:

LUMA™ Cervical Imaging System User Manual,
LUMA™ Cervical Imaging System Quick Reference Guide

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