



LUMA™ Cervical Imaging System

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For approximately 30 years colposcopically directed biopsy of the uterine cervix has been the gold standard for the detection of cervical intraepithelial neoplasia (CIN) and cancer following an abnormal Papanikolaou (Pap) smear. Recent technological advancements utilizing properties of fluorescence, reflectance and spectroscopy intrinsic to *in vivo* tissues, have led to the development of a useful adjunct to improve colposcopic detection of high-grade CIN. The addition of the LUMA™ (MediSpectra, Inc., MA, USA) cervical imaging system to colposcopy has been shown in two prospective, randomized controlled trials to result in a 25% or greater increase in the true positive biopsy rate of colposcopy for patients with atypical squamous cell or low-grade squamous intraepithelial lesions on Pap smear, with only a 4% increase in the false-positive rate, versus that of colposcopy alone. The US FDA approved this device in March 2006 to be used to enhance the sensitivity of colposcopic examinations of women with abnormal cervical cytology, in an effort to further reduce the incidence of cervical cancer.

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In the early 1940s, George Papanikalou developed his technique for cytologic screening of cervical cancer. Prior to this, the Viennese investigators von Franque and Hans Hinselmann were developing a precursor of the modern-day colposcope. In the 1920s, concerned that the current practice of visual inspection with the naked eye and palpation of the cervix were poor methods for identification of early cervical cancers, they devised an instrument that would illuminate and magnify the cervix [1]. Mounting on a stand a binocular dissecting microscope with an attached light source and 3.5- to 30-times magnification capabilities allowed for markedly improved visualization of the cervix [1]. This enabled the colposcopic pioneers to describe characteristics of cervical carcinoma and various grades of intraepithelial neoplasia. In addition, by applying dilute acetic acid to the cervix, they discovered the characteristic acetowhitening effect used to identify neoplastic areas of the cervix [1]. Meanwhile, Walter Schiller proposed the application of an iodine solution to the cervix as a potential alternative screening test, based on the premise that normal tissue stained dark brown, while carcinomatous tissue

stained far less, thereby identifying areas of possible cervical pathology [1]. Schiller's test, as it became known, was eventually incorporated into colposcopic examinations.

Over time, colposcopy was widely accepted as an adjunct to cervical cancer screening and by the late 1970s and early 1980s became firmly entrenched in the screening process of cervical neoplasia and cancer. Thus, routine Pap screening, coupled with colposcopically directed biopsies of suspicious cervical lesions, has been the gold standard for diagnosis of precancerous and cancerous lesions for over 20 years.

Although dramatic decreases in the overall incidence of cervical cancer have been appreciated with this surveillance scheme, new technologies can serve as useful adjuncts to further enhance the sensitivity and specificity of currently accepted colposcopic practices. The current screening process is largely subjective and dependent on three steps, involving three different clinician's assessment of three distinct pathological entities. A cytologist evaluates the Pap smear, a colposcopist examines and forms an impression of the cervix leading to a biopsy, and

a pathologist interprets the degree of neoplasia from the biopsy. Clearly, this allows for a large margin of error that can compromise diagnosis and lead to considerable cost. Thus, less subjective and more concrete diagnostic modalities have been pursued for detecting precancerous lesions. Development of adjunctive colposcopic optical techniques holds promise for real-time, objective, noninvasive detection of cervical neoplasia [2,3].

The ultimate goal of cervical cancer screening is to identify and eradicate significant precancerous lesions with a propensity towards cervical cancer. The Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesions (ASCUS-LSIL Triage Study [ALTS]) Group determined that traditional colposcopy identified only 60–70% of the cumulative cervical dysplasia (cervical intraepithelial neoplasia [CIN])2 or 3 found over 2 years in their large study population [4,5]. There are approximately 55 million Pap tests performed annually in the USA, detecting approximately 3 million women with either ASCUS or LSIL [4,5]. Together, ASCUS and LSIL Pap tests represent 59% of biopsy-proven CIN2 or 3, with atypical glandular cells of undetermined significance (AGUS) and high-grade intraepithelial lesions (HSIL) making up the remaining 41% [6]. Extrapolating the ALTS Group data to the US population, approximately 200,000 women with referral Pap tests of ASCUS or LSIL, will have CIN2 or 3 missed on their initial colposcopy. Recent studies of current colposcopic practice have further confirmed the often poor sensitivity of colposcopically directed biopsy. In a large Chinese screening study, Pretorius and colleagues found that random cervical biopsies of visually normal areas of the cervix performed by gynecological oncologists identified 37.1% of CIN2 or worse lesions [7]. Evaluating the ALTS Group data, Gage and colleagues found that the sensitivity of colposcopy in detecting CIN2 or worse lesions was significantly enhanced when two or more biopsies were obtained, irrespective of the degree of the colposcopist's training or medical specialty [8]. Judging from these studies, it is evident that standard of care in colposcopy and directed biopsy lacks appropriate sensitivity and specificity. Therefore, in an effort to further enhance the effectiveness of colposcopy and improve detection of high-grade neoplasia (CIN2/3), the LUMA™ Cervical Imaging System (MediSpectra, Inc.) was developed.

Overview of the market: device design

Traditionally, evaluation of the cervix takes place by magnified visual inspection of the cervix, via a colposcope, after the application of 3–5% acetic acid to the uterine cervix. Over time, various methods and instruments have been devised as useful adjuncts to the colposcopist or for cervical screening in general.

Cervicography involves simply obtaining a 35-mm photograph of the cervix after the application of acetic acid and having the photograph reviewed by an expert for the presence or absence of a significant lesion.

Speculoscopy utilizes a disposable low-intensity blue–white chemiluminescent light source and 4–6× magnification obtained using a hand-held magnifying device [9]. This screening tool is marketed under the name PapSure® (Watson

Laboratories, CA, USA) and is used in conjunction with a Pap smear. Multiple studies of the PapSure method have shown increased sensitivity for the detection of high-grade (CIN2/3) lesions when compared with cytology alone, but at the expense of an increased false-positive rate [9–12].

Another small, portable device using low-level electrical impulses and light pulses at various frequencies to differentiate normal cervical from neoplastic tissue is the TruScan® device developed by Polartechniques, Ltd, in Sydney, Australia [9]. The TruScan electro-optical device is passed across the cervix, generating a tissue signature from the cervix, which, when analyzed by the TruScan computer, produces a real-time impression of either normal, CIN1 or CIN2/3 [9]. No clinical trials comparing TruScan with other screening methods have been performed, but early studies of the device alone suggest false-positive and -negative rates to the order of 10% [9,13,14].

In vivo spectroscopy utilizes the well-established principle that abnormal epithelial tissues, when illuminated with low-power light of specific wavelengths, produce autofluorescence signatures that differ from those of normal tissues subjected to the same light [9]. These differences, captured and analyzed by electro-optical sensors, are exploited to yield an interpretation of potential clinically significant neoplasia on the cervical epithelium.

Prior to development of the LUMA system, evaluation of intrinsic tissue fluorescence has shown efficacy for the *in vivo* detection of colon, esophagus, bronchus and bladder neoplasia [15–23]. Studies of this nature have also been implemented in cervical tissue. Ramanujam and colleagues evaluated the diagnostic contribution of *in vivo* cervical tissue fluorescence spectra acquired at 380 and 460 nm excitation [24]. Using a multivariate statistical algorithm, they found a 91% sensitivity and 75% specificity in the differentiation of CIN from normal tissue [24]. Unfortunately, fluorescence spectral analysis alone is insufficient to reliably ascertain differences between CIN2/3 and CIN1, or discern the difference between neoplasia and metaplasia or inflammation [3,24–26].

Broadband white light, diffuse reflectance or elastic scattering spectroscopy has been studied and implemented with benefit in the detection of skin, bladder, colon and ovarian neoplasia [3,21,22,27–30]. Combining fluorescence and reflectance, Georgakoudi and colleagues demonstrated complementary diagnostic potential for the evaluation of Barrett's esophagus [3,31]. Similar combined diagnostic modalities have been used to detect *in vivo* cervical neoplasia [3,31–36]. Building on these studies, the integrated, trimodal LUMA Cervical Imaging System was developed and has undergone rigorous testing to obtain US FDA approval.

How the device works

The LUMA system is the first FDA-approved optical imaging device intended to assist clinicians with colposcopic evaluations and subsequent biopsy of the cervix in an effort to improve diagnostic ability for clinically significant lesions (CIN2/3). It is approved for use in all patients referred for colposcopy with a Pap smear result of atypical squamous cell, LSIL, HSIL or

cancer. The LUMA system was not developed to replace colposcopy. The clinician should perform routine colposcopy first, to identify and commit to any suspicious cervical lesions for biopsy. Following this, the LUMA examination takes place. Any additional areas for biopsy may be seen at that time. The LUMA system should not be used to omit a previously selected biopsy site by routine colposcopy.

The device is easily integrated into clinical practice, simple to use and provides a clear, concise display of the data for quick interpretation. It consists of a portable console, noncontact illumination probe and disposable probe cover (FIGURES 1 & 2). The console contains the optical sources, which include a 337-nm ultraviolet nitrogen laser to induce fluorescence, and two xenon flash lamps to provide broadband white light for reflectance measurements [3]. Maximal optical energy delivered is 280 μ J, well below the permissible safety threshold [3]. The optical sources, through a fiber-optic cable, are coupled to the optical probe, where a scanning system illuminates the cervix [3]. The built-in video system visualizes the cervix, aids in alignment and focusing of the probe and captures images during the measurement process [3]. The video image(s) is also used to display the final output or data [3].

During a 12-s, noncontact scan of the cervix, data are collected simultaneously from the three combined optical measurements: tissue fluorescence excitation, white light diffuse reflectance or backscatter and video imaging (FIGURE 3) [3]. The scan of the ectocervix comprises an area with a diameter of 25 mm, and interrogates 499 densely packed spots while the illumination probe is in a fixed position (FIGURE 2) [3]. Each spot is approximately 1 mm in diameter and spaced 1 mm apart, center-to-center [3]. Spectra are sampled at 1-nm resolution across the entire visible spectrum, with a 7-nm spectral bandwidth [3]. Background fluorescence and reflectance values

are subtracted and spectral responses are corrected to responses of previously accepted calibration standards [3,34]. The measured spectra are then submitted to a classification algorithm to determine whether each interrogated area might contain neoplastic squamous epithelium [3]. The system is designed to detect high-grade neoplastic lesions of 2 mm or more [3]. The endocervical canal is not interrogated with this method [3]. The LUMA system does not visualize the entire transformation zone, unless it has receded into the endocervical canal [3].

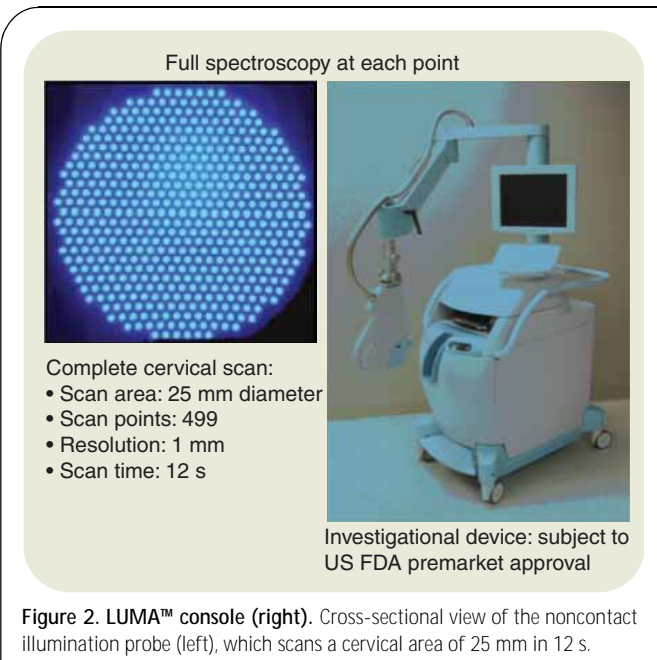
The optical probe is calibrated for reflectance and fluorescence reference targets prior to each scan [3]. To initiate a reading during the colposcopic examination, the illumination probe is placed near the outer opening of the vaginal speculum at a distance of approximately 100 mm from the cervix [3]. An integrated video camera image and a projected green targeting pattern are used to align the probe visually to the center of the cervix and to adjust the optical focus [3]. Focus to within 5 mm is verified and provides further calibration assurance of received spectral signals [3]. The optical interrogation of the cervix is initiated by a foot switch [3].

The objective measurements of optical characteristics are then subjected to a multivariate statistical algorithm to aid in identifying areas of the cervix with the highest likelihood of high-grade CIN on biopsy (FIGURE 4). This information is then presented to the clinician via video display of a static image of the cervix. A color overlay is then superimposed on the digital image of the cervix. A color code (from light yellow to intense blue) is then used to interpret the overlay and indicate areas on the cervix with the highest degree of neoplasia, effectively targeting those locations for biopsy.

The biological basis of the optical characteristics comes primarily from data generated by the reflectance or white light backscatter and the fluorescence of the cervical tissue being examined (FIGURE 5). Reflectance is influenced by several variables. The degree of cervical vascularity, epithelial thickness, size and number of cell nuclei and chromatin content, and the mucosal layer structure all contribute to the reflectance properties of the tissue being interrogated. The stromal component, primarily composed of collagen, is also responsible for the reflectance properties of the cervix [33]. Additional backscatter is due to photons that are singly reflected from the epithelial cell nuclei [33,37]. Neoplastic tissue tends to have higher reflectance intensity at all wavelengths. The opposite is true of fluorescence. Neoplastic tissue tends to have lower fluorescence intensity at all wavelengths. The intensity of fluorescence is influenced by functional components of the cervix, such as hemoglobin, porphyrin, NADPH (the reduced



Figure 1. Scanning head is part of the LUMA™ console. Disposable covers fit within the speculum at a distance of 100 mm from the cervix and a scan is obtained.



form of nicotinamide adenine dinucleotide) and flavins, in addition to structural components, such as collagen and elastin. Hemoglobin is the main tissue absorber of light from the visible spectrum [33]. It is found only in stromal tissue, which is probably more abundant in normal cervical tissue versus neoplastic tissue. The primary fluorophores in the visible region of the spectrum are collagen and NADPH [33,38]. NADPH is most abundant in the epithelial cell layer and is sensitive to the metabolic state of the tissue [33,39]. Collagen dictates the degree of stromal tissue fluorescence [33].

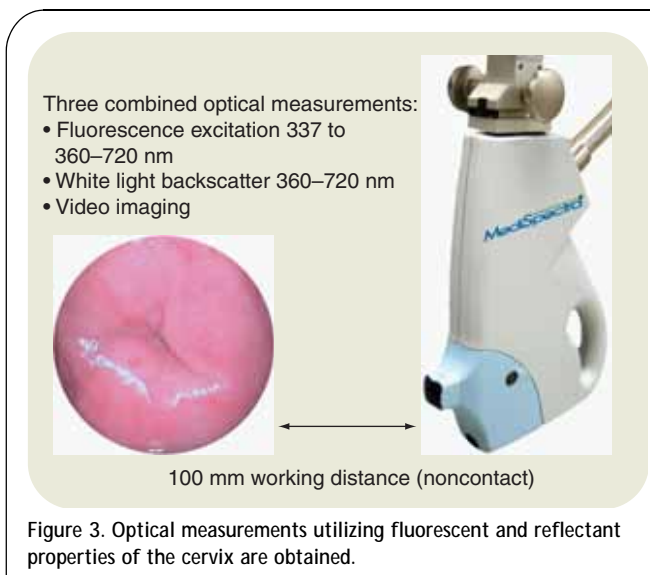
Cost-effectiveness

Owing to the novelty of this technology and the very recent approval of the LUMA Cervical Imaging System, there are currently no available cost estimates of this equipment and/or its integration into the clinical setting. Nonetheless, it is entirely plausible that implementation of this adjunctive technique, over time, could lead to significant healthcare cost savings. Annually, approximately 3 million colposcopic procedures are performed in the USA for ASCUS or LSIL cytology [4,5]. The estimated cost of managing one patient through the process of colposcopy, biopsy and pathology review is approximately US\$1200 [101]. Therefore, technology that increases the sensitivity of cervical biopsy stands to save considerable healthcare dollars. More efficient and accurate detection of clinically significant lesions (CIN2/3) may result in fewer repeated colposcopic evaluations and earlier eradication of precancerous lesions, thus breaking the cycle of repeated colposcopic examinations for women with persistently abnormal Pap smears but erroneously negative (or low-grade) biopsies. With substantial healthcare spending devoted to screening and treatment of cervical pathology, earlier detection of significant neoplasia serves to decrease the burden of neoplastic disease and potentially save considerable healthcare dollars.

Although no training requirements or guidelines for the use of the LUMA Cervical Imaging System currently exist, the device appears to be user-friendly, with easily interpretable data to enhance the colposcopic evaluation by all colposcopists irrespective of skill. A user's guide will be made available to all clinicians utilizing the system, and the device should be easily integrated into clinical practice (FIGURE 6). In addition to the portable main console, which houses the computer and video equipment plus the monitor screen, all that is needed to perform each LUMA evaluation is one disposable probe cover that fits on the scanning probe head and standard equipment for a general colposcopic examination (i.e., speculum, 3–5% acetic acid and colposcope).

Sensitivity & specificity

Results of the effectiveness of this adjunct to colposcopy, when presented to the FDA, paved the way for device approval in March 2006. The initial pilot study, by Huh and colleagues, investigated the optical characteristics of a large clinical population ($n = 604$) to create and train an optical detection algorithm that would identify and discriminate between CIN2/3 and cancer and all other cervical tissue types [3]. Ultimately, more than 10,000 optical measurements were made on colposcopically evaluated tissue from more than 500 patients, together with more than 1500 measurements at tissue sites with pathology-qualified results, which served as the basis for algorithm training and testing [3]. This study also predicted that enhanced sensitivity provided by the algorithm leads to a true-positive detection rate of 32%, which corresponds to a 33% increase in detection of high-grade disease [3]. Once a suitable algorithm had been developed and tested, MediSpectra, Inc. embarked on a large-scale, multisite, randomized, prospective clinical trial comparing the combination of LUMA and colposcopy with colposcopy alone, in addition to a multisite, single-arm, internally controlled study designed to determine the rates of true and false positivity associated with LUMA.



Multispectral, multivariate integration of three optical measurements

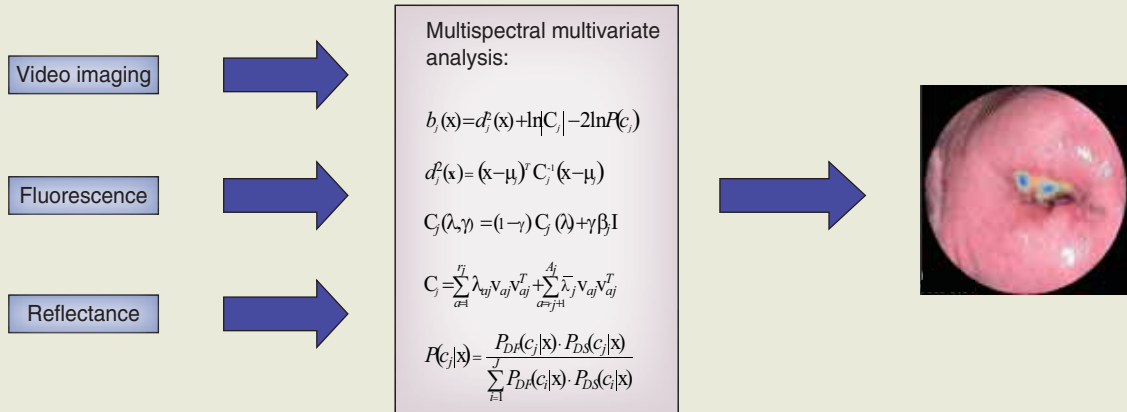


Figure 4. Video imaging, fluorescence and reflectance properties of the cervix are integrated and subjected to the analysis algorithm.

Clinically significant results were found in the study comparing colposcopy alone with colposcopy combined with the LUMA optical detection system [40]. Over 2200 women referred for colposcopy with abnormal cytology were randomized to one of two arms, with differences in true-positive rates (identification of CIN2/3 or cancer) and false-positive rates (negative biopsy) analyzed as the primary outcomes [40]. Among patients referred with ASCUS or LSIL cytology undergoing biopsy, the use of colposcopy combined with LUMA detected 238 cases of CIN2+ out of 1090 women (true-positive [TP] rate of 21.8%), compared with detection of 218 cases of CIN 2+ out of 1096 women (TP rate of 19.9%) in the colposcopy alone arm [40]. This ultimately resulted in a 26.5% gain in the true-positive rate, with only a 4% increase in the false-positive rate [40]. An average increase of 0.27 biopsies per patient occurred in the colposcopy/LUMA arm [40]. In this article, the authors estimate that widespread use of LUMA as an adjunct to colposcopy can result in the identification of over 100,000 cases of CIN2/3 that would not have been detected at the initial colposcopic examination [40]. In this study, the detection rate (sensitivity) of clinically significant lesions was significantly enhanced with LUMA versus colposcopy alone with only a modest difference in specificity (60.5 and 57.4%, respectively) [40]. The positive predictive value of biopsies indicated by colposcopy alone was 15.2%, compared with 18.1% with colposcopy combined with LUMA [40]. Importantly, there were no device-related adverse events in this study. A follow-up study mirroring the intended role of LUMA in the clinical setting was then undertaken [41]. In this

multicenter, internally controlled trial, 193 women underwent a LUMA scan prior to undergoing a colposcopic evaluation. The LUMA results were blinded to the colposcopist until they had completed the initial colposcopy and committed to all biopsy sites. After these sites were annotated on the LUMA computer screen, the LUMA results were unmasked and those areas for biopsy identified by the optical detection system were added to the computer image of the cervix. Colposcopists were then instructed to take at least one biopsy from any area identified by LUMA as high probability for CIN2 or greater, in addition to performing biopsies on those areas identified prior to using the LUMA device. Initial colposcopy was found to yield a true-positive rate (biopsy \geq CIN2) of 21.2% [41]. Adjunctive use of the LUMA device identified an additional number of cases of CIN2 or greater, resulting in a 4.7% increase in the

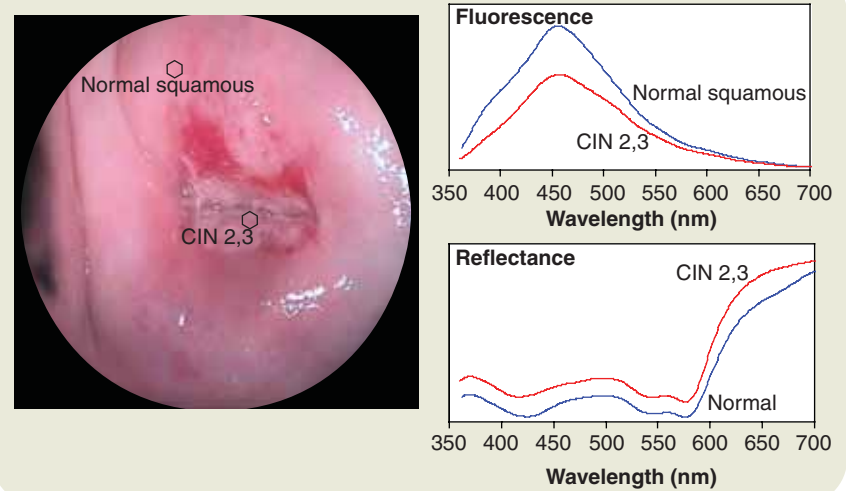
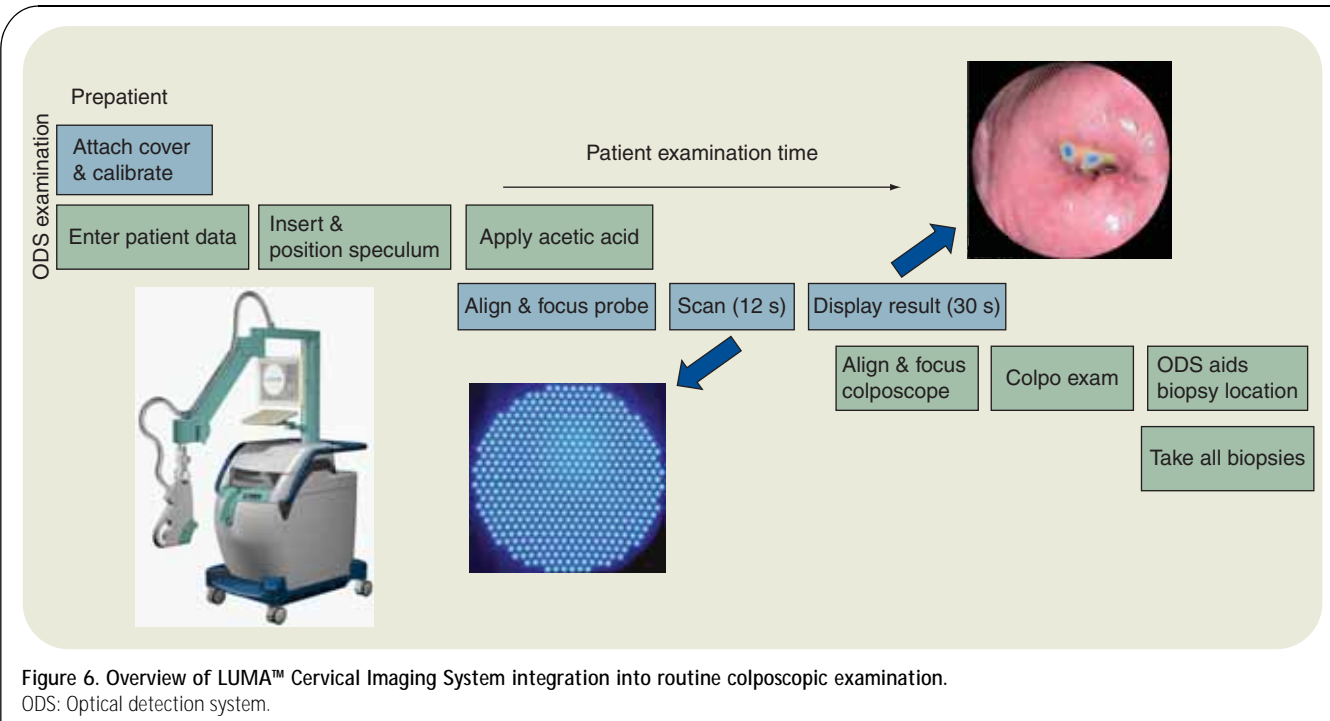


Figure 5. Differences in tissue spectroscopy between normal and neoplastic tissue are identified. A color overlay (not pictured) is added to guide the colposcopic biopsy.



true-positive rate, yielding a 22% relative gain in the identification of lesions over colposcopy alone [41]. In the clinically important ASCUS/LSIL population, the relative gain was found to be 25% [41], in close agreement with the prior study. The false-positive rate for initial colposcopy with biopsy was 51.8%, and the LUMA device led to an incremental false-positive rate of 18.1% [41]. Colposcopy alone resulted in a mean biopsy rate of 0.89 per subject, which increased marginally to 1.02 per subject with the adjunctive system [41]. Postapproval studies are currently underway to further assess the long-term efficacy of this technology.

Owing to the recent approval of the LUMA Cervical Imaging System, the device has yet to make its way into mainstream clinical practice. As a consequence, there is a paucity of postmarketing data to report at this time. Nonetheless, it is highly conceivable that this technology will rapidly garner favor among colposcopists seeking to improve upon the largely subjective nature of current colposcopic practice.

Conclusion

Even in the most experienced hands, the current diagnostic gold standard for cervical neoplasia is imperfect at best. Approximately a third of CIN2/3 lesions are missed by seasoned colposcopists [4,5]. Furthermore, the accepted methodology of cervical cancer screening involves multiple variables, all of which may serve to further lessen its sensitivity and specificity. Assuming the Pap smear correctly identifies ASCUS or worse pathology, thereby triggering a colposcopic evaluation, a sequence of wholly subjective events are set in motion in an effort to diagnose the cervical lesion correctly. Through visual inspection, a colposcopic impression is formulated by the clinician, one or more biopsies are obtained and a pathologist then determines the grade of

neoplasia microscopically. In short, the inherent subjectivity of colposcopically directed biopsy to detect high-grade lesions (\geq CIN2/3) of the cervix provides an excellent opportunity for the development of improved diagnostic modalities. Implementation of an optical detection system, LUMA, exploiting the reflectance and fluorescent properties of the cervix, bolsters the efficacy of established colposcopic technique. Not only may this technology improve the diagnostic yield of colposcopic examinations and further reduce the incidence of cervical cancer, but it may do so at considerable cost savings to the healthcare system by earlier detection and eradication of clinically significant lesions.

Expert commentary

If proven affordable, effective utilization of the LUMA Cervical Imaging System by clinicians in multiple disciplines may dramatically decrease referrals of patients to colposcopy, streamline the diagnostic process for cervical neoplasia and significantly increase the accuracy of colposcopic biopsy for high-grade lesions. For a new device or technology to be widely accepted, it must be easy to use and produce quick, reliable information that the clinician can act upon. The LUMA Cervical Imaging System meets these tenets. Furthermore, if ongoing studies consistently demonstrate high sensitivity and specificity for CIN2/3, the use of LUMA technology can efficiently triage patients into a 'see and treat' cohort that receives an excisional or ablative procedure (i.e., loop electrosurgical excisional procedure or cryosurgery) on the same day high-grade lesions are identified. This would substantially reduce problems associated with poor follow-up, often intrinsic to the population of concern.

This technology is not intended to replace colposcopy, it is intended to improve it, and it should be reiterated that standard colposcopy is performed before utilizing the LUMA device, and

that this technology should not be used to omit any biopsy sites seen prior to the LUMA scan. Despite its many benefits, the LUMA system cannot adequately assess the endocervix. Standard colposcopic evaluation along with an endocervical curettage and possible endometrial biopsy is recommended for glandular cells identified on Pap testing. Nonetheless, in an era where human papilloma virus infection and subsequent cervical neoplasia is increasingly more common, the development of an effective adjunct to colposcopy for the detection of CIN2/3 or cancer is a welcome addition to the armamentarium to fight cervical disease.

Five-year view

The ubiquity of human papilloma virus infection will continue to make the screening and evaluation of abnormal cervical cytology an important aspect of healthcare for women in the near future. Any significant impact on the incidence of cervical neoplasia from various human papilloma virus vaccines (both preventive and therapeutic) is many years from realization. Therefore, our current methods of surveillance and management of cervical disease will remain the diagnostic standard. Adjunctive use of the LUMA Cervical Imaging System can further strengthen the diagnostic potential of colposcopy and holds promise to be incorporated into routine evaluations of those patients presenting with ASCUS, LSIL or HSIL Pap smears. Increasing the diagnostic specificity and

sensitivity of colposcopy could establish safe and more aggressive 'see and treat' protocols, particularly in developing countries where a one-time visit to a clinician may be all that is possible. In the meantime, it will be interesting to assess the degree of acceptance and integration of this technology into current colposcopic management.

Information resources

As the LUMA Cervical Imaging System makes its way into the clinical arena and Phase I–III data become more available, a significant body of information will exist that is directly related to the performance characteristics of LUMA. An easily accessible resource for basic information on the imaging system is www.medispectra.com. A number of pertinent papers dealing with background studies of the technology instrumental in development of LUMA can be found here, and include:

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Key issues

- Colposcopy with directed biopsy is the current gold standard for the diagnosis of high-grade (\geq cervical dysplasia 2/3) cervical lesions.
- Colposcopically directed biopsy misses up to a third of all high-grade lesions.
- Addition of an optical detection system, the LUMA™ cervical imaging system, to standard colposcopy, safely and efficiently increases the sensitivity of colposcopic biopsies.
- The LUMA system exploits the inherent differences of light reflectance and fluorescence between normal and neoplastic tissue to provide a computer-generated 'map' of the cervix that identifies areas with the highest probability of high-grade neoplasia for biopsy.
- A LUMA scan of the cervix takes 12 s, uses a noncontact device and is entirely safe.
- The LUMA system is a useful adjunct to colposcopy – it is not intended to replace it.

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