



## Increased detection of high-grade cervical intraepithelial neoplasia utilizing an optical detection system as an adjunct to colposcopy

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### Abstract

**Objective.** To evaluate the impact of using a novel optical detection system (ODS) as an adjunct to colposcopy.

**Methods.** A multicenter internally controlled trial designed to evaluate the performance of an ODS system (LUMA MediSpectra, Lexington, MA) used as an adjunct to colposcopy among women referred for the evaluation of an abnormal cervical cytology result was conducted at 7 colposcopy clinics in the United States and enrolled 227 women. After exclusions, 193 women remained in the analysis. The main study outcomes were incremental increases in true positives (CIN 2,3 and cancer, or CIN 2+) and false positives (women with additional cervical biopsies not found to be CIN 2+).

**Results.** Initial colposcopy identified 41 cases of CIN 2+ for a true positive (TP) rate of 21.2%. Adjunctive use of ODS identified an additional 9 cases of CIN 2+ which corresponds to an incremental ODS TP rate of 4.7% (95% CI 2.2% to 8.7%). Adjunctive use of ODS therefore resulted in a 22.0% (95% CI 6.1% to 37.8%) relative gain in the number of women with CIN 2+ compared to colposcopy alone. The false positive (FP) rate for initial colposcopy was 51.8% (100 of 193 women). An additional 35 subjects had an ODS-directed biopsy that was not diagnosed as CIN 2+, yielding an incremental FP rate of 18.1% (95% CI 13.0% to 24.3%).

**Conclusions.** Adjunctive use of ODS with colposcopy provides a significant increase in the detection of CIN 2+ in women referred for the evaluation of abnormal cytology results.

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### Introduction

Although colposcopy with colposcopically directed biopsy has been considered the standard of care for evaluating women with abnormal cervical cytology results for several decades, it is now becoming increasingly obvious that a standard colposcopic examination with cervical biopsy has a much lower sensitivity than previously recognized. Several recent studies have convincingly demonstrated that a single colposcopic examination fails to identify 33% to 40% of women with high-grade cervical intraepithelial neoplasia (CIN 2+). For example, the

ASCUS/LSIL Triage Study (ALTS) has reported that 33% to 36% of cases of CIN 2+ were not identified at the initial enrollment colposcopic examination [1,2]. Similarly, a large study conducted in China found that colposcopy alone failed to detect 40% of CIN 2,3 lesions [3]. The results from these recent studies confirm the findings of earlier studies of women undergoing loop electrosurgical procedures for an abnormal cervical cytology which found that colposcopy missed 18%–55% of CIN 2+ [4].

Quantitative optical spectroscopy and imaging techniques that include intrinsic tissue fluorescence, white light backscatter, and video imaging offer considerable promise as a means to increase the sensitivity of colposcopy [5]. These new optical methods exploit the structural and biochemical alterations that occur within tissues during the development of a neoplastic lesion in order to identify areas of the cervix likely to

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represent a CIN 2+ lesion. In March 2006, the Food and Drug Administration of the United States approved a stand-alone optical detection system (ODS) that utilizes optical spectroscopy and imaging techniques as an adjunct to colposcopy for the identification of high-grade disease (CIN 2+) in women referred to colposcopy with a cervical cytology result of atypical squamous cells (ASC), low-grade squamous intraepithelial lesion (LSIL), and high-grade squamous intraepithelial lesion or cancer (HSIL+) [6]. In this report we provide the results obtained in the intended use pivotal trial of this ODS device as an adjunct to colposcopy.

## Materials and methods

The study was a multicenter internally-controlled clinical trial in which women referred for colposcopy underwent a ODS scan prior to undergoing a colposcopic evaluation. The results of the ODS scan were masked to the colposcopist until after they had completed colposcopy and committed to any colposcopically directed biopsy sites. Colposcopists were instructed to annotate all sites that they would normally biopsy during a routine colposcopic examination. Only after sites for colposcopically directed biopsies had been annotated on the ODS's computer screen were the results of the ODS scan unmasked. After inspecting the ODS result, the colposcopist then annotated any additional biopsy sites identified based on the ODS result. Colposcopists were instructed to annotate and take at least one biopsy from any area identified as a high probability for CIN 2+ (e.g., "blue" region) based on the ODS result. The study involved 7 clinical centers and 16 colposcopists including gynecologists and gynecologic oncologists who ranged in colposcopy experience from just having completed their residency training to over 30 years of experience. The study was approved by each local institutional review boards.

Females 18 years or older referred for evaluation of an abnormal cervical cytology result of atypical squamous cells (ASC) or greater were eligible for enrollment. Exclusion criteria included pregnancy through 6 weeks post-partum, current menstruation, previous hysterectomy, cervical stenosis, history of diethylstilbestrol exposure, cervical biopsy or therapeutic procedure since the referral cervical cytology, cervical cytology tests within the prior seven days, use of vaginal medications within the last 48 h or photosensitizing agents within 72 h, history of photosensitivity or other diseases affected by UV radiation, or an observable and untreated gynecological infection.

Pre-commercial optical detection system devices (MediSpectra Inc., Lexington, MA) were used in this study [7]. The devices consist of a console, display monitor, a "non-contact" illumination probe, and a disposable probe cover. The devices utilize two different types of optical sources: a 337 nm UV nitrogen laser to induce fluorescence and two xenon flash lamps to provide broadband white light used for reflectance measurements and video imaging. A fiber optic cable couples the optical sources to the optical probe. Scans of the cervix are performed by positioning the illumination probe near the proximal opening of the speculum after an acetic acid solution has been applied to the cervix. The optical scan interrogates a 25 mm diameter circular area of the ectocervix in a dense grid pattern that includes 499 regions at an approximately 1 mm resolution using laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The scan takes approximately 12 s.

The algorithm employed in this study was developed in a previously described study and uses a logistic classification based on fluorescence spectra combined with a multivariate statistical analysis method based on the diffuse reflectance spectra [7]. The fluorescence spectra at specific wavelengths (360 nm to 590 nm) were used to determine thresholding rules using absolute and relative spectral intensities to produce a likelihood measure of normal squamous tissue. The diffuse reflectance data (370 nm to 650 nm) were analyzed using singular value decomposition using both principal component and feature extraction analysis techniques. The output of the ODS algorithm is a numerical probability reading or "score" between 0 and 1 which is translated for clinical use into a false-color overlay that is superimposed on a digital image of the cervix obtained during the scan. Although a specific score is not provided to the user, the false-color overlays reflect the score. "Blue" false-color overlays

correspond to ODS probability scores of 0.7 to 1.0, "yellow" overlays to ODS probability scores of 0.2 to 0.5, with an intermediate zone between 0.5 and 0.7 (Fig. 1). Visible endocervical tissue is not depicted with a false-color overlay unless there is a likelihood that CIN 2+ is present. The ODS system has a built in calibration system to assure that the device is correctly functioning. Complete details of the system and the classification algorithm employed are described more fully elsewhere [8].

Each cervical biopsy was processed separately and reviewed independently by at least two reference pathologists in a blinded fashion. The study endpoint for histopathological diagnosis was CIN 2,3 or cervical cancer (CIN 2+) that was diagnosed using standard histopathologic criteria [9]. If the diagnoses made by the two reference pathologists did not agree, the biopsy was reviewed by a third reference pathologist in order to obtain a majority opinion.

The study was initiated in July 2003 and was originally designed to enroll 576 subjects based, in part, on an assumption that the underlying prevalence of CIN 2+ was 33% and there would be a loss of 20% of subjects. Because the underlying prevalence of CIN 2+ was found to be lower in an early study from the same clinical sites, the sample size was subsequently revised to take into account the lower expected rate of CIN 2+ (27%). As a result, sample size was increased to 788 subjects to maintain 85% power. However, due to budget limitations, the study was closed to enrollment in October 2003 at 227 subjects. The decision to close the study to enrollment was made before any analysis of the data was undertaken.

The primary study endpoints were the incremental true positive (TP) subjects (subjects with biopsy-confirmed CIN 2+ on an ODS-directed biopsy, but no CIN 2+ detected on a biopsy indicated by colposcopy) and incremental false positive (FP) subjects (subjects with ODS-directed cervical biopsies that were not diagnosed as CIN 2+ and who did not have a biopsy indicated by colposcopy). The primary trial hypothesis for the TP rate was that the overall TP rate for the ODS increment would be significantly greater than 2%. The study was tested using a superiority design with 2.5% Type I error and 85% power. The primary trial hypothesis for the FP rate was that the overall FP rate for the LUMA increment would be significantly less than 15% using a non-inferiority approach with 2.5% Type I error and 97% power.

The per-protocol population is defined as the subset of the intent-to-diagnose population who completed the protocol, met all eligibility criteria, and had a definitive central pathology finding for all cervical biopsies.

## Results

### Patient characteristics and adverse events

There were 34 subjects excluded from the final per-protocol population. Reasons for exclusion include withdrawal due to

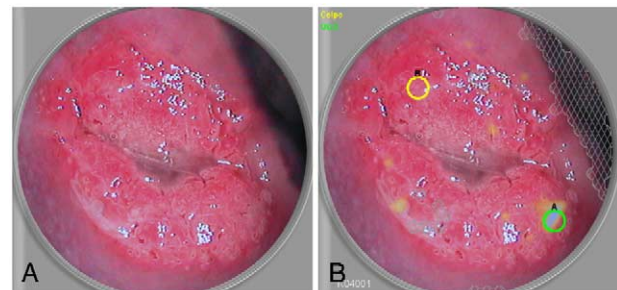


Fig. 1. Example of ODS display output. The first image that the colposcopist sees with the ODS is a digital image of the cervix (A). Sites for colposcopically directed biopsy are annotated on the digital image with yellow circles that are labeled "A" (B). The ODS result is provided as a pseudocolored overlay with blue indicating a high probability of high-grade neoplasia. Once the ODS result is reviewed, sites for ODS-directed biopsies are annotated as green circles that are labeled "B". (B) The colposcopically identified biopsy obtained at 11:00 was diagnosed as "no evidence of disease" whereas the ODS-identified biopsy obtained at 4:00 was diagnosed as CIN 2+.

subject withdrawing consent ( $n=1$ ), the colposcopist being unable to adequately view the cervix ( $n=2$ ), patient unable to remain still during scan ( $n=1$ ), atrophy/bleeding ( $n=1$ ), device failure ( $n=3$ ), failure to meet inclusion/exclusion criteria ( $n=6$ ), failure to obtain or annotate all biopsies ( $n=8$ ), and incomplete pathology results ( $n=16$ ). The most frequent single reason for exclusion was incomplete pathology results. This is because patients were excluded if a diagnosis could not be rendered on any of their cervical biopsies. Some subjects had more than one reason for exclusion. The final per-protocol population of 193 women had a mean age of 28.5 years (range 18–64). LSIL was the most common reason for referral to colposcopy (47%), followed by ASC cytology (39%) and HSIL/cancer cytology (14%). Race/ethnicity were 43% Caucasian, 31% African American, 21% Native American, and 2% Hispanic. Only 6% of women were post-menopausal and 51% had no previous abnormal cervical cytology.

There were only three adverse events among the 227 subjects and no device related adverse events. The adverse events are those typically associated with colposcopy and include fainting ( $n=1$ ), abdominal pain ( $n=1$ ), and dysuria ( $n=1$ ).

#### *Impact of adjunctive ODS on TP and FP rates and relative sensitivity of colposcopy*

The initial colposcopic examination identified a total of 41 cases of CIN 2+ among the 193 per-protocol subjects for a TP rate of 21.2% (95% CI 15.7–27.7%) (Table 1). An additional 9 cases of CIN 2+ were identified using adjunctive ODS. This corresponds to an incremental ODS TP rate of 4.7% (95% CI 2.2–8.7%). Therefore, the overall TP hypothesis which was that the incremental increase in TP with the use of adjunctive ODS is significantly greater than 2% was met ( $p=0.0164$ ). When stratified by referral cytology result, similar results were observed for both women referred for ASC/LSIL and those for HSIL (Table 1).

Another way to interpret the effect of adjunctive ODS is to determine the relative gain in the number of subjects with CIN 2+ identified using colposcopy with adjunctive ODS compared to colposcopy alone. Use of adjunctive ODS resulted in a 22.0% (95% CI 6.1–37.8%) relative gain in the number cases

of CIN 2+ identified compared to colposcopy alone. Although sensitivity cannot be directly measured using this study design because the total number of women with CIN 2+ cannot be known unless all women undergo either a diagnostic excisional procedure or a hysterectomy, the relative increase in sensitivity that is achieved when ODS is used as an adjunct to colposcopy can be determined by the ratio of the incremental ODS TP rate to the initial colposcopy rate. Thus the 22% relative gain in TP rate achieved using ODS as an adjunct to colposcopy also corresponds to the same relative gain in sensitivity.

The other primary study endpoint was the FP rate. Based on the initial colposcopy, 100 women received a biopsy but were not found to have CIN 2+ among the 193 per-protocol subjects evaluated. Thus the FP rate for initial colposcopy was 51.8% (95% CI 44.5–59%) (Table 1). Based on adjunctive ODS, an additional 35 women without CIN 2+ underwent a cervical biopsy yielding an incremental FP rate of 18.1% (95% CI 13.0–24.3%) for adjunctive ODS. Therefore the overall FP study hypothesis which was that incremental increase in FP with use of adjunctive ODS is less than 15% was not met. When stratified by referral cytology result, similar results were observed for both women referred for ASC/LSIL and those for HSIL.

The clinical consequence of a false positive ODS reading is that additional cervical biopsies are taken in women without CIN 2+. Therefore we evaluated the impact of adjunctive ODS results on the number of cervical biopsies. Initial colposcopy resulted in 172 biopsies being taken from the 193 subjects for a mean biopsy rate of 0.89 per subject. Based on the results of adjunctive ODS, an additional 197 biopsies were obtained from the 193 subjects for a mean biopsy rate of 1.02 per subject which is comparable to that of initial colposcopy. With initial colposcopy 73.1% of the subjects (141 of 193) received a cervical biopsy. This increased to 92.2% (178 of 193) when adjunctive ODS was utilized.

#### *Trade-off between TP and FP*

The clinical benefits of adjunctive ODS need to be considered in terms of the trade-off between increases in TP

Table 1  
True positive and false positive subjects by study phase and referral cytology<sup>a</sup>

Referral cytology	Outcome <sup>b</sup>	Initial colposcopy		Adjunctive ODS	
		No.	Rate (95% CI) <sup>a</sup>	No.	Rate (95% CI) <sup>a</sup>
All women ( $n=193$ )	TP	41	21.2% (15.7–27.7%)	9	4.7% (2.2–8.7%)
	FP	100	51.8% (44.5–59.0%)	35	18.1% (13.0–24.3%)
ASC/LSIL ( $n=167$ )	TP	24	14.4% (9.4–20.6%)	6	3.6% (1.3–7.7%)
	FP	93	55.7% (47.8–63.3%)	34	20.4% (14.5–27.2%)
HSIL ( $n=26$ )	TP	17	65.4% (44.3–82.8%)	3	11.5% (2.5–30.2%)
	FP	7	26.9% (11.6–47.8%)	1	3.8% (0.1–19.6%)

ASC, atypical squamous cells; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion.

<sup>a</sup> Subject level analysis of per-protocol subjects.

<sup>b</sup> A true positive (TP) for initial colposcopy is defined as a woman having biopsy-confirmed CIN 2+ on a colposcopy-indicated biopsy. An incremental TP for adjunctive ODS is defined as a woman without CIN 2+ on a colposcopy-directed biopsy who has CIN 2+ on a ODS-directed biopsy. A false positive (FP) for initial colposcopy is defined as a woman with at least one colposcopy-indicated biopsy taken, none of which is diagnosed as CIN 2+. An incremental FP for adjunctive ODS is defined as a woman with no colposcopy-directed biopsies who has at least one ODS-directed biopsy, none of which is diagnosed as CIN 2+.

(detection of CIN 2+) and increases in FP (additional biopsies in women without CIN 2+). The incremental TP and FP rates of 4.7% and 18.1%, respectively, for adjunctive ODS represent a trade-off of approximately 4:1 (18.1:4.7). This means that approximately 4 women without CIN 2+ receive an additional biopsy for every additional woman with CIN 2+ that is identified using adjunctive ODS. For comparison, initial colposcopy provides a trade-off of approximately 2.5:1 (51.8% FP; 21.2% TP). Another approach to evaluating this trade-off is to compare the proportion of the biopsies that are diagnosed with CIN 2+. For initial colposcopy 26.2% (45 of 172) of biopsies were diagnosed as CIN 2+. For adjunctive ODS 18.3% (36 of 197) of biopsies were diagnosed as CIN 2+.

#### Analysis of ODS readings

To evaluate the relationship between the ODS probability score and the likelihood of CIN 2+ on a biopsy, an analysis was taken of the ODS probability scores at annotated biopsy sites. Among the per-protocol population, there were a total of 197 ODS-directed biopsies obtained from 144 women. Of these, 18.3% (36 of 197) were CIN 2+. By definition, ODS-directed biopsy sites were selected by the colposcopist as those with the highest ODS probability scores. As the ODS probability score increased, the TP rate increases ( $p=0.0035$ ) (Table 2). Only 5.6% (2 of 36) of the TPs detected overall were obtained from “yellow” sites (scores of 0.2 to 0.5). In contrast, 80.6% (29 of 36) were obtained from distinctly “blue” sites (scores of 0.7 to 1.0).

We also utilized mixed effect logistic regression models to evaluate the relationship between likelihood of CIN 2+ and the ODS probability score at all annotated biopsy sites (e.g. for both colposcopy-indicated biopsies and ODS-indicated biopsies). These analyses demonstrated that while taking into account the referral cervical cytology (ASC, LSIL, or HSIL/cancer), study phase (e.g., colposcopy-indicated or ODS-indicated), clinical site, and colposcopist variability that the ODS probability score was significantly related to the probability of a CIN 2+ biopsy ( $p=0.0135$ ). Using this regression model, it was found that the

odds of a CIN 2+ biopsy increased 1.4 fold (95% CI 1.1–1.8) for every 0.25 increase in the ODS probability score. When a mixed effect logistic regression model was used that includes the interaction between the study phase and the ODS probability score, the odds of a CIN 2+ biopsy for ODS-directed biopsies was found to increase 2.5-fold (95% CI 1.2–4.8) for every 0.25 increase in the ODS probability score.

#### Discussion

This study was designed to evaluate an ODS device as an adjunct to colposcopy in the manner in which it will be used in a real clinical practice setting. To insure that ODS was used as an adjunct to, rather than as a replacement for, colposcopy, in this study the results of the ODS scan were not displayed until after the colposcopic examination was completed and the colposcopist had committed to, and electronically annotated, sites for colposcopically directed biopsies. When ODS is used in this manner the result is a statistically significant increase in the detection of women with biopsy-confirmed CIN 2+ compared to colposcopy alone. Among 193 per-protocol subjects undergoing colposcopy, initial colposcopy identified 41 with biopsy-confirmed CIN 2+. With adjunctive ODS an additional 9 women with CIN 2+ were identified. This corresponds to a 22.0% (95% CI 6.1–37.8%) increase in the detection of biopsy-confirmed CIN 2+ using colposcopy with adjunctive ODS compared to colposcopy alone. The benefit of an increased detection of CIN 2+ was achieved at a “cost” of requiring approximately one additional biopsy per subject, of which about 20% were diagnosed as CIN 2+. The results achieved in this trial using ODS as a strict adjunct to colposcopy are similar to those found in an earlier trial that used a combination of ODS with colposcopy to evaluate women with either an ASC or LSIL cervical cytology [10]. In the earlier trial a combination of ODS with colposcopy produced a 25% relative increase in the detection of biopsy-confirmed CIN 2+ compared to colposcopy alone among women referred for the evaluation of either ASC or LSIL.

The pre-commercial ODS device that was evaluated in this study has recently been approved for routine clinical use as an adjunct to colposcopy by the Food and Drug Administration [6]. This device interrogates the ectocervix using a combination of laser-induced fluorescence spectroscopy, white light diffuse reflectance spectroscopy, and video imaging. The scan takes approximately 12 s. The concept of utilizing a combination of fluorescence spectroscopy, reflectance spectroscopy, and video imaging to detect cervical intraepithelial neoplasia is derived from earlier research that demonstrated the potential to utilize fluorescence spectroscopy to diagnose cervical neoplasia [11–14]. Subsequently, others have shown that the performance of fluorescence spectroscopy can be enhanced by combining it with other forms of spectroscopic analysis [15,16]. However, the ODS device utilized for this study is the first to receive FDA approval for use as an adjunct to colposcopy.

The potential of an ODS device to improve clinical care needs to be viewed in terms of the performance of routine colposcopy. Until recently colposcopy was widely considered

Table 2  
Histological results of ODS-directed biopsies stratified by ODS probability score

ODS probability score	Total no. biopsies in range	No. TP <sup>a</sup> in range	TP rate <sup>b</sup> (%)	Cumulative TP	Cumulative TP percentage (%)
0.90–1.00	47	17	36.1	36	100
0.80–0.89	34	8	23.5	19	52.8
0.70–0.79	24	4	16.7	11	30.6
0.60–0.69	38	4	10.5	7	19.4
0.50–0.59	28	1	3.6	3	8.3
0.40–0.49	15	0	0	2	5.6
0.30–0.39	7	1	14.3	2	5.6
0.20–0.29	2	0	0	1	2.8
0.10–0.19	2	1	50	1	2.8
0.00–0.09	0	0	0	0	0

<sup>a</sup> True positive (TP) is defined as a cervical biopsy that is diagnosed as CIN 2+.

<sup>b</sup> TP rate is defined as No. TP in range/Total no. biopsies in range.  $p=0.0035$  using chi-square for trend.

to be a relatively sensitive, but rather non-specific, method for identifying high-grade cervical neoplasia. This was based on studies in the older literature which reported that a single colposcopic examination missed relatively few cases of high-grade neoplasia. A comprehensive meta-analysis of the performance of colposcopy, that was based primarily on older studies, estimated that the weighted mean sensitivity of colposcopy for distinguishing normal tissue from abnormal tissue is 0.96 (95% CI 0.95–0.97) and that the weighted mean specificity of colposcopy is 0.48 (95% CI 0.47–0.49) [17]. However, the fact that colposcopy is highly subjective and that its accuracy is highly variable has been emphasized by many [18–22]. Several studies have reported that the false negative rate of colposcopy for CIN 2+ ranges from 15% to 36% [2,23]. One large U.S.-based trial of the management of women with mild cytologic abnormalities found that even when well-trained clinicians performed colposcopy under carefully monitored conditions that only 64% of the cumulative cases of biopsy-confirmed CIN 2+ were identified by a single colposcopic examination among women referred for the evaluation of ASC cervical cytology [1]. Similarly, a single colposcopic examination identified only 67% of the cumulative cases of biopsy-confirmed CIN 2+ among women referred for evaluation of a LSIL cytology result [2].

Two other large, recent studies that have evaluated the performance of colposcopy in a screening, as opposed to a referral population, have also reported that the sensitivity of colposcopy is lower than previously thought. In these studies, all women underwent colposcopy and cervical biopsies were taken of any areas classified as abnormal by colposcopy. In addition, random cervical biopsies were obtained from regions of the cervix that appeared by colposcopy to be normal. The overall sensitivity of colposcopy for identifying CIN 2+ in one of the studies was 78% [24]. In the other study the sensitivity of colposcopy for identifying CIN 2+ among women with an ASC or LSIL cytology result was only 60% [3]. In both studies taking random biopsies from areas that were colposcopically normal increased the detection of CIN 2+ lesions. The yield of CIN 2+ identified per random biopsy can be calculated for the study of Pretorius et al. In that study the yield of CIN 2+ for a colposcopically-directed biopsy was 26.5%, but random biopsies had a yield of only 5.5%. For comparison, the yield of CIN 2+ for colposcopically directed biopsies in the current study was 26.2% which is similar to the results obtained by Pretorius et al.. In contrast, the yield for ODS-directed biopsies in the current study was 18.3% which is over 3-fold higher than that of random biopsies. A recent analysis from ALTS of women eventually diagnosed as having CIN 3+ found that the sensitivity of the enrollment colposcopy was improved when two or more biopsies were obtained compared to a single biopsy [25]. It is important to note that based on our regression modeling, there is a significant relationship between the ODS probability score and the detection of CIN 2+. Therefore even though the current study did not directly compare the increase in detection of CIN 2+ achieved using adjunctive ODS with what would have been obtained by taking an additional, random biopsy of the cervix, it is unlikely that an equivalent increase in

the detection of CIN 2+ would be obtained by simply taking an additional biopsy. A similar conclusion was reached in an earlier randomized trial that evaluated the same ODS used in this trial [10]. In that study the positive predictive value (PPV) of biopsies indicated by ODS among women with ASC or LSIL was the same as that for biopsies indicated by colposcopy, whereas biopsies that were indicated by both the ODS result and colposcopy had a higher PPV.

Increasing the performance of colposcopy through the routine use of an ODS system could have important clinical benefits. Approximately 3 million women require a colposcopic evaluation each year in the United States [26,27]. Based on the results of the current study we estimate that the use of adjunctive ODS would increase the sensitivity of colposcopy by approximately 22%. This could result in the identification of over 100,000 cases of CIN 2,3 that would have not been detected by routine colposcopic examination.

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#### Appendix A

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## References

- [1] Results of a randomized trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol* 2003;188:1383–92.
- [2] A randomized trial on the management of low-grade squamous intraepithelial lesion cytology interpretations. *Am J Obstet Gynecol* 2003;188:1393–400.
- [3] Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X, et al. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. *Am J Obstet Gynecol* 2004;191:430–4.
- [4] Massad LS, Halperin CJ, Bitterman P. Correlation between colposcopically directed biopsy and cervical loop excision. *Gynecol Oncol* 1996;60:400–3.
- [5] Drezek RA, Richards-Kortum R, Brewer MA, Feld MS, Pitris C, Ferenczy A, et al. Optical imaging of the cervix. *Cancer* 2003;98:2015–27.
- [6] U.S. Food and Drug Administration. New Device Approval: LUMA™ Cervical Imaging System; 2006 [Accessed at: <http://www.fda.gov/cdrh/mda/docs/p040028.html> Accessed at: <http://www.fda.gov/cdrh/mda/docs/p040028.html>, vol. May 2006, 2006].
- [7] Huh WK, Cestero RM, Garcia FA, Gold MA, Guido RS, McIntyre-Seltman K, et al. Optical detection of high-grade cervical intraepithelial neoplasia in vivo: results of a 604-patient study. *Am J Obstet Gynecol* 2004;190:1249–57.
- [8] Schomacker KT, Meese TM, Jiang C, Abele CC, Dickson K, Sum ST, et al. Novel optical detection system for in vivo identification and localization of cervical intraepithelial neoplasia. *J Biomed Opt* 2006;11:34009.
- [9] Wright TC, Ferenczy AF, Kurman RJ. Precancerous lesions of the cervix. In: Kurman RJ, editor. *Blaustein's Pathology of the Female Genital Tract*. 5th ed. New York: Springer-Verlag; 2002. p. 253–354.
- [10] Alvarez RD, Wright TC. Effective cervical neoplasia detection with a novel optical detection system: a randomized trial. *Gynecol Oncol* 2007;104:281–9.
- [11] Ramanujam N, Mitchell MF, Mahadevan A, Thomsen S, Malpica A, Wright T, et al. Spectroscopic diagnosis of cervical intraepithelial neoplasia (CIN) in vivo using laser-induced fluorescence spectra at multiple excitation wavelengths. *Lasers Surg Med* 1996;19:63–74.
- [12] Ramanujam N, Mitchell MF, Mahadevan-Jansen A, Thomsen SL, Staerckel G, Malpica A, et al. Cervical precancer detection using a multivariate statistical algorithm based on laser-induced fluorescence spectra at multiple excitation wavelengths. *Photochem Photobiol* 1996;64:720–5.
- [13] Brookner CK, Utzinger U, Staerckel G, Richards-Kortum R, Mitchell MF. Cervical fluorescence of normal women. *Lasers Surg Med* 1999;24:29–37.
- [14] Ramanujam N, Mitchell MF, Mahadevan A, Thomsen S, Malpica A, Wright T, et al. Development of a multivariate statistical algorithm to analyze human cervical tissue fluorescence spectra acquired in vivo. *Lasers Surg Med* 1996;19:46–62.
- [15] Georgakoudi I, Sheets EE, Muller MG, Backman V, Crum CP, Badizadegan K, et al. Trimodal spectroscopy for the detection and characterization of cervical precancers in vivo. *Am J Obstet Gynecol* 2002;186:374–82.
- [16] Ferris D, Lawhead RA, Dickman ED, Holtzapple N, Miller JA, Grogan S, et al. Multimodal hyperspectral imaging for the noninvasive diagnosis of cervical neoplasia. *J Lower Gen Tract Dis* 2001;5:65–72.
- [17] Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol* 1998;91:626–31.
- [18] Buxton EJ, Luesley DM, Shafi MI, Rollason M. Colposcopically directed punch biopsy; a potentially misleading investigation. *Br J Obstet Gynaecol* 1991;98:1273–6.
- [19] Chenoy R, Manohar S, Redman CWE, Luesley DM. Cervical cytologic abnormalities and negative colposcopy: histologic assessment. *Int J Gynecol Cancer* 1994;4:348–51.
- [20] Massad LS, Collins YC. Strength of correlations between colposcopic impression and biopsy histology. *Gynecol Oncol* 2003;89:424–8.
- [21] Massad LS. More is more: improving the sensitivity of colposcopy. *Obstet Gynecol* 2006;108:246–7.
- [22] Jeronimo J, Schiffman M. Colposcopy at a crossroads. *Am J Obstet Gynecol* 2006;195:349–53.
- [23] Skehan M, Soutter WP, Lim K, Krausz T, Pryse-Davies J. Reliability of colposcopy and directed punch biopsy. *Br J Obstet Gynecol* 1990;97:811–6.
- [24] Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. Shanxi province cervical cancer screening study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. *Gynecol Oncol* 2001;83:439–44.
- [25] Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, et al. Number of cervical biopsies and sensitivity of colposcopy. *Obstet Gynecol* 2006;108:264–72.
- [26] Davey DD, Neal MH, Wilbur DC, Colgan TJ, Styer PE, Mody DR. Bethesda 2001 implementation and reporting rates: 2003 practices of participants in the College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytology. *Arch Pathol Lab Med* 2004;128:1224–9.
- [27] Wright Jr TC, Cox JT, Massad LS, Twigg LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002;287:2120–9.