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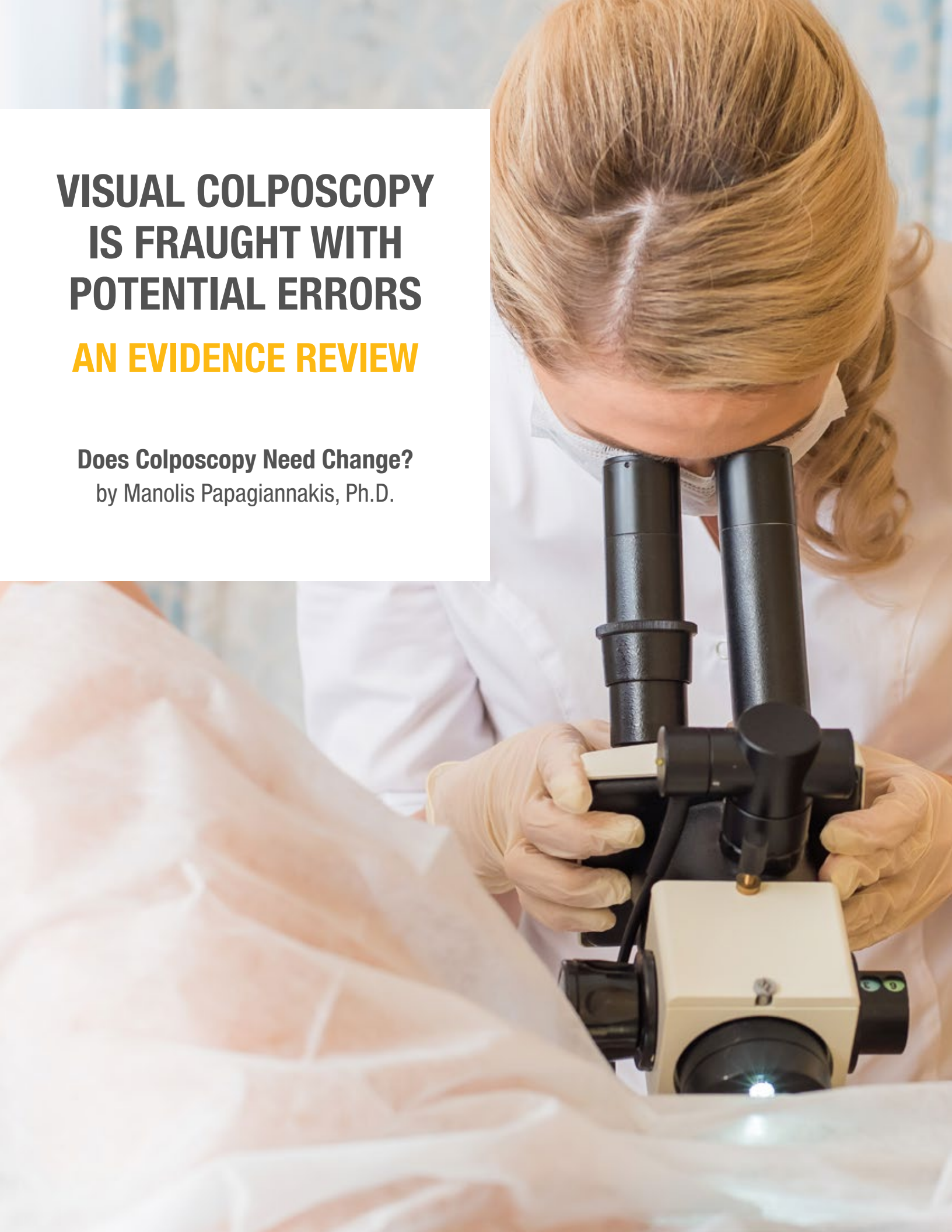
AN EVIDENCE REVIEW

Does Colposcopy Need Change?

by Manolis Papagiannakis, Ph.D.



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OBJECTIVE

To discuss standard colposcopy, its limitations and its role in the current cervical screening setting.

METHOD

Presentation of results from large clinical studies that assessed the performance of colposcopy and quantified the correlations between impression, biopsy performance and excisional treatment outcomes.

CONCLUSION

Standard colposcopy is a subjective, clinician-dependent examination, but plays a crucial role in the cervical cancer screening process. Accurate colposcopy is critical in stratifying patient risk and has significant impact on patient management decisions. Published research demonstrates that standard colposcopy frequently fails to recognize high-grade disease and biopsy sampling often does not represent the most atypical area. The need for standardization and improvement is recognized in the literature.

Organized population screening for cervical cancer prevention in the developed world reduced the incidence and mortality of cervical cancer significantly. In recent years, the prevention and screening systems are being revisited and optimized for performance and cost-effectiveness. Significant changes include the introduction of liquid-based cytology, HPV-DNA testing, HPV genotyping and vaccination, re-design of the screening algorithms, increasing intervals between screens, etc., that make the system more cost-effective and sensitive for detecting and preventing disease.

In every setting, colposcopy remains the significant link between the screening system and the diagnosis and treatment of disease. Colposcopy is the visual inspection of the cervix with a special low-magnification microscope, with the purpose of identifying abnormalities, excluding invasive disease and deciding the appropriate patient management strategy. This may include identifying and sampling the most atypical site for biopsy, treating or discharging. Colposcopy was "invented" by Dr. Hans Hinselmann in the 1920's in Germany, and essentially remains unchanged to date. It is generally recognized as a subjective technique that depends on the skills and practice of the colposcopist.

"As women are referred to colposcopy based on increasingly sensitive tests, there is a need to have a diagnostic examination with the best accuracy possible."

— Gage et al[1]

The performance of colposcopy to identify cervical pathology and especially high-grade disease is reported in numerous publications, with contradicting results, and is often debated. In general, studies that assess the performance of colposcopy are conducted differently, are presented in different ways and use different end-points and definitions of the metrics they present, making comparisons difficult. The main limitation of most colposcopy studies is that the gold standard of full histological assessment (i.e. an excisional specimen) for all evaluated patients is unethical, and thus, impossible to achieve. Therefore comparisons have to rely on available biopsy results (ironically, with biopsies decided by colposcopy!), extensive biopsy protocols (e.g. by having a very low threshold for taking a biopsy or adding random biopsies), by introducing an alternative or adjunctive technique to traditional assessment (e.g. dynamic spectral imaging) or additional follow-up examinations.

This article will present and discuss clinical evidence (in no way exhaustive) on the performance and limitations of colposcopy, using as sources established, major and thorough peer review publications, with significant emphasis on the ASCUS-LSIL Triage Study (ALTS), the 5000 patient, three-arm randomized controlled trial, conducted by the National Cancer Institute (NCI) to determine the best management option for women with ASC-US or LSIL Papanicolaou (Pap) smear results.

COLPOSCOPY

The actual colposcopic examination depends largely on “pattern” recognition. During colposcopy several different morphological aspects are considered that include the uptake of acetic acid, the size, margins and surface of any observed lesions, the presence of atypical vessels, mosaic and punctation and iodine staining. Additionally,

the decisions that need to be taken during colposcopy consider several other factors such as patient age & demographics, family and personal health history, smoking status, family plans, screening test results, HPV type, etc.

Colposcopy sources of error.
There are at least ten sources of colposcopic exam errors including, to name just a few, failure to wait for the full effect of acetic acid, failure to take a biopsy when in doubt, failure to take the biopsy sample from the intended site, using a blunt, non-sharp biopsy punch to obtain tissue specimens, and failure to properly and legibly record colposcopic findings.[2]

Importance of colposcopic impression.
During colposcopy, the clinician forms an "impression" (or opinion, prediction) based on visualizing the aforementioned aspects. This is far from standardized, and suffers from significant levels of inter- and intra-observer disagreement as demonstrated in different studies.[3-5] Ferris and Litaker[5] who did an inter-observer agreement study based on the ALTS data commented that "the results were disappointingly poor." Different scoring systems have been introduced to colposcopy (Reid index, Swedescore), but they only guarantee that different factors are evaluated, not how they are evaluated, so their impact is limited.[6]

Even though colposcopic impression is not a final outcome of colposcopy, it does play a significant role. Impression is easily biased by knowledge of the referral cytology, as the expectation is that patients with high-grade cytology abnormalities are more likely to have disease. For example, when a lesion in a high-grade referral patient appears to the colposcopist as "High-Grade," excisional treatment may be performed without biopsying first. Furthermore, impression of lesions plays a significant role in deciding how many biopsies should be taken and the exact biopsy placement to ensure that the most atypical site is sampled.

Colposcopic impression plays its most significant role in the low-grade cytology patients, that represent the majority of cases seen at colposcopy, and most of the CIN2+ is found in this population.[7] For example in the case of a "Normal" impression in a low-grade Pap smear, biopsy is often omitted; 25% of patients with ASC-US were not biopsied during ALTS.[8]

Sensitivity of colposcopic impression.
The sensitivity of colposcopic impression for high-grade neoplasia (i.e. the accuracy to predict confirmed CIN2+ disease) is low (see Table 1).

Table 1. Sensitivity of colposcopic impression to predict CIN2+

Study	Sample Size (N)	Population	Sensitivity
Massad & Collins[10]	2825	All referrals	56%
ALTS colposcopists[11]	2085	ASC-US/LSIL	35.4%
ALTS QC expert reviewers[11]	2085	ASC-US/LSIL	23.2%
ALTS digital image review[13]	919	ASC-US/LSIL	39%

A meta-analysis[9] analyzed several earlier studies and found a weighted means for sensitivity of 85%; however, in general, the studies included in this meta-analysis were of different designs, from an era preceding organized screening and suffered from disease verification bias.

In a study that included 2825 women of mixed referral smear results, Massad and Collins[10] found that "a colposcopic impression of high-grade disease identified only 56% of high-grade lesions." Ferris and Litaker[11] performed quality control for colposcopy during ALTS by comparing colposcopic diagnosis during the exam, to histology and to the diagnosis of an expert panel based on reviewing digital images from the exams. The sensitivity of the colposcopists for CIN2+ was 34.7% and of the expert reviewers 23%, and the overall accuracy for identifying between normal, CIN1 and CIN2+ was 36.6% and 54.8% respectively.

"The practice of colposcopy has undergone scientific scrutiny over the past decade, and it is clear that this procedure is far from perfect and likely misses clinically significant (and perhaps clinically insignificant) disease."

— Huh et al[12]

Table 2. Misses of directed biopsy to find worst atypia compared to LEEP on same patient

Study	Sample Size (N)	Disease	Missed
Gardasil placebo arm, all cases[18]	737	CIN2+/AIS CIN3+/AIS	26% 42%
Gardasil placebo arm, same day LEEP[18]	594	CIN2+/AIS CIN3+/AIS	57% 66%
Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED)[17]	74	CIN3+	53%

Another analysis of the ALTS colposcopy data[13] assessed the accuracy of colposcopic grading for detection of high-grade cervical intraepithelial neoplasia (CIN) using colposcopy case images, and concluded that "The sensitivity of a global on-line assessment using a diagnostic threshold of high grade disease was only 43% for CIN3+ and 39% for CIN2+," which was comparable to the impression recorded at the time of colposcopy.

Effectiveness of colposcopically-directed biopsy.
Colposcopic impression is not a final outcome for colposcopy, but punch biopsy is. In most cases, the result of punch biopsies will determine the further management of the patient (e.g. ASCCP guidelines[14]), so it is important that biopsies are performed when needed and that they capture the most atypical area. At the same time, excessive biopsying is not advisable, as it impacts patients (pain and bleeding, induced anxiety) and adds a significant financial burden.[15]

Arguably, colposcopic impression does not matter for patient care, as long as the biopsy decisions are right, and biopsy samples are collected from the right sites on the cervix. In several trials, the measured sensitivity for colposcopy reflects just that, the effectiveness of colposcopically-directed punch biopsy. For example, even if the provider's impression of a cervix is low-grade or negative, as long as the right spot is biopsied and a high-grade CIN is found, then the patient is further managed according to that and not the impression.

However, as shown during ALTS, where colposcopists were asked to biopsy any suspicious area, biopsy fails to detect a significant amount of high-grade disease. In the immediate colposcopy arm of the study, the sensitivity for CIN3+ was 56% for women with LSIL[16] and 54% for women with ASC-US smear.[8] Even when the results from all colposcopies over the two years of the study were considered (some patients having up to five colposcopies!) only 70% of the 408 women with CIN3+ were found by colposcopically-directed biopsy.[1]

Sensitivity of colposcopically-directed biopsies when compared to LEEP.
The limitations of directed biopsies are best highlighted in studies that compare histological outcomes of directed punch biopsies to those of a subsequent Loop Electrosurgical Excision Procedure (LEEP) (see Table 2). Massad et al[17] commented that "half of the women with CIN1 on directed biopsy had high-grade lesions found in loop excision specimens" and that "significant

discrepancies may be found between the results of colposcopically directed biopsy and loop excision."

When comparing directed punch biopsy results to LEEP outcomes for women with CIN3+, Wentzensen et al[18] found that "although collected from an undisputed CIN3 or cancer case, almost a third of the samples had =<CIN1 histology" and determined that discrepancy was larger when the lesions were smaller indicating that they were either not correctly identified by the colposcopy or not sampled accurately.

Stoler et al[19] used the colposcopy data from the placebo arm of the Gardasil HPV vaccine trial to compare the results of 737 women who had directed biopsy before LEEP, with expert panel adjudication of both

"Half the women with CIN1 on directed biopsy had high-grade lesions found in loop excision specimens."

— Massad et al[17]

biopsy and LEEP specimens. They found that directed biopsy fails to find the most atypical site in 42% of the cases with CIN3+ or Adenocarcinoma in situ (AIS) and 53% when only one biopsy was taken. Even when 2-4 biopsies were taken, 31% of CIN3/AIS was missed. In 594 cases where biopsy was performed on the same day as LEEP, 66% of the CIN3/AIS disease was underestimated by the biopsy and 48% was missed even when 2-3 biopsies were taken. After adjudication

of the CIN3/AIS histological results of the definitive therapy specimen by the study pathology panel, "the colposcopy-directed biopsy diagnosis was less severe 42–66% of the time."

To overcome the limitations of colposcopic judgment and colposcopically-directed biopsy, it is becoming acceptable to increase the number of biopsies taken by collecting multiple random biopsies (i.e. from areas where no disease is suspected) from every patient in routine practice[20] or by collecting multiple biopsies from any lesion observed.[21] However, as described above, even with 2-4 colposcopically-directed biopsies in the Gardasil trial, 31-48% of CIN3/AIS found in the LEEP had been missed.[19] It is clear that without an improvement in colposcopic accuracy, this may be the only way to ensure that disease is not missed, despite the vast amount of unnecessary biopsies with their impact on patients and economics that this brings.

"The practice of colposcopy has undergone scientific scrutiny over the past decade, and it is clear that this procedure is far from perfect and likely misses clinically significant (and perhaps clinically insignificant) disease."[12]

CONCLUSIONS

Today, colposcopy remains as it was in the 1920's, a subjective procedure dependent on pattern recognition, clinician judgment and skills. Furthermore, it is expected that "colposcopy might become more challenging when HPV testing becomes more common in the United States, as the high sensitivity of HPV testing leads to the detection of earlier and smaller CIN3 lesions."[22]

"At the present time in the United States, there is no "standard" for colposcopy regarding the number of biopsies that should be taken. Clinical practice can range from taking one biopsy from the worst visible lesion to performing four quadrant biopsies, irrespective of the presence or absence of colposcopic abnormalities."[12]

"These findings highlight the need to improve both the sensitivity and specificity of colposcopy."

— Stoler et al[19]

Even with extensive biopsy-taking (2-4 biopsies), LEEP procedures performed on the same patients revealed that 31-48% of CIN3/AIS had been undetected.[18,19] While one could argue that the disease may eventually be detected in subsequent follow-up exams, this is highly dependent on access to care, patient compliance and accuracy of Pap smears which are also subjective,[23,24] not to mention the cost and patient anxiety of repeat follow-up exams.

Recently, recommended screening intervals have been extended to 3-5 years in low-risk women, thus putting more pressure on the accuracy of colposcopy. There is a clear need to improve the objectivity and standardization of colposcopy.

ACKNOWLEDGMENTS

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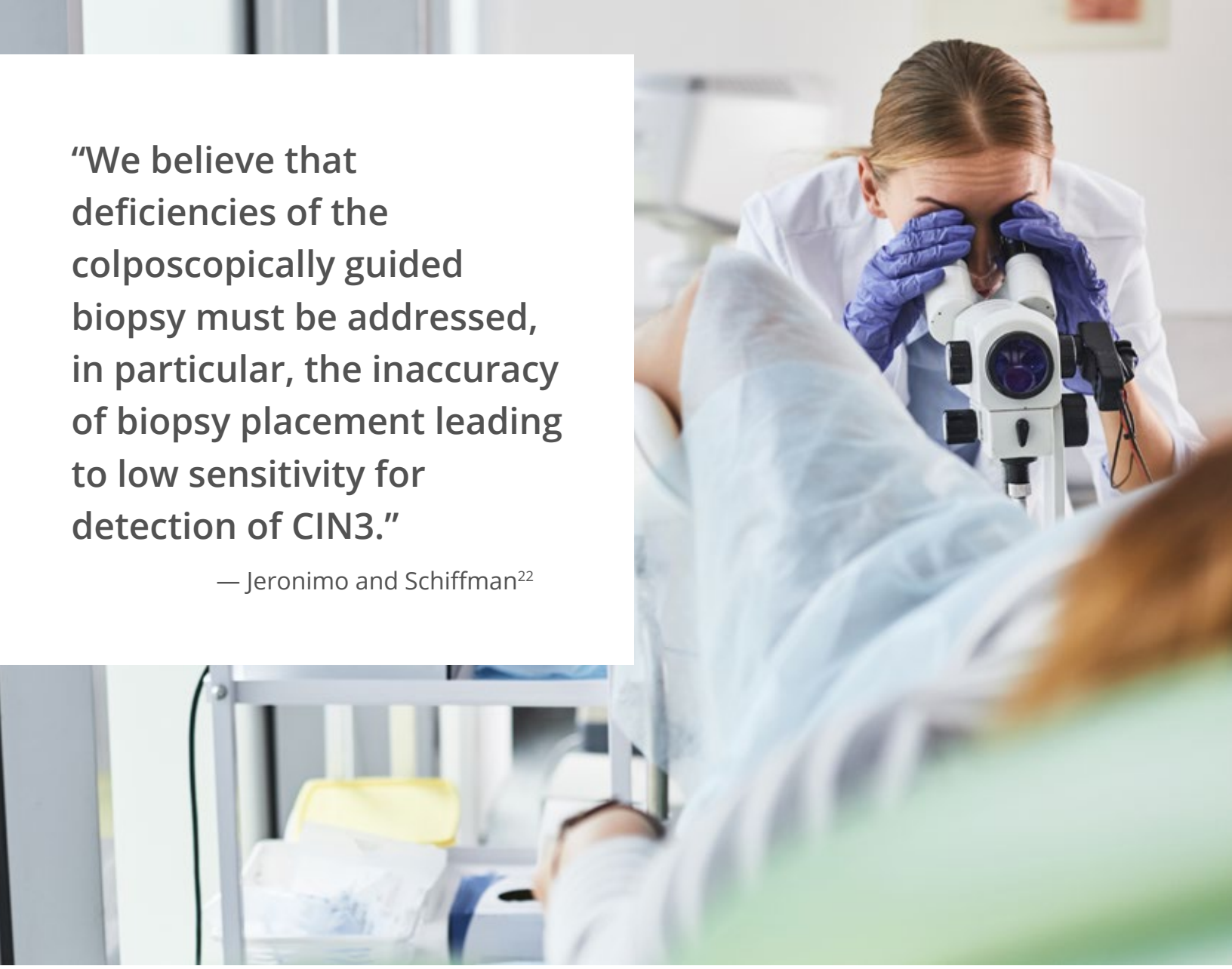

"We believe that deficiencies of the colposcopically guided biopsy must be addressed, in particular, the inaccuracy of biopsy placement leading to low sensitivity for detection of CIN3."

— Jeronimo and Schiffman[22]

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