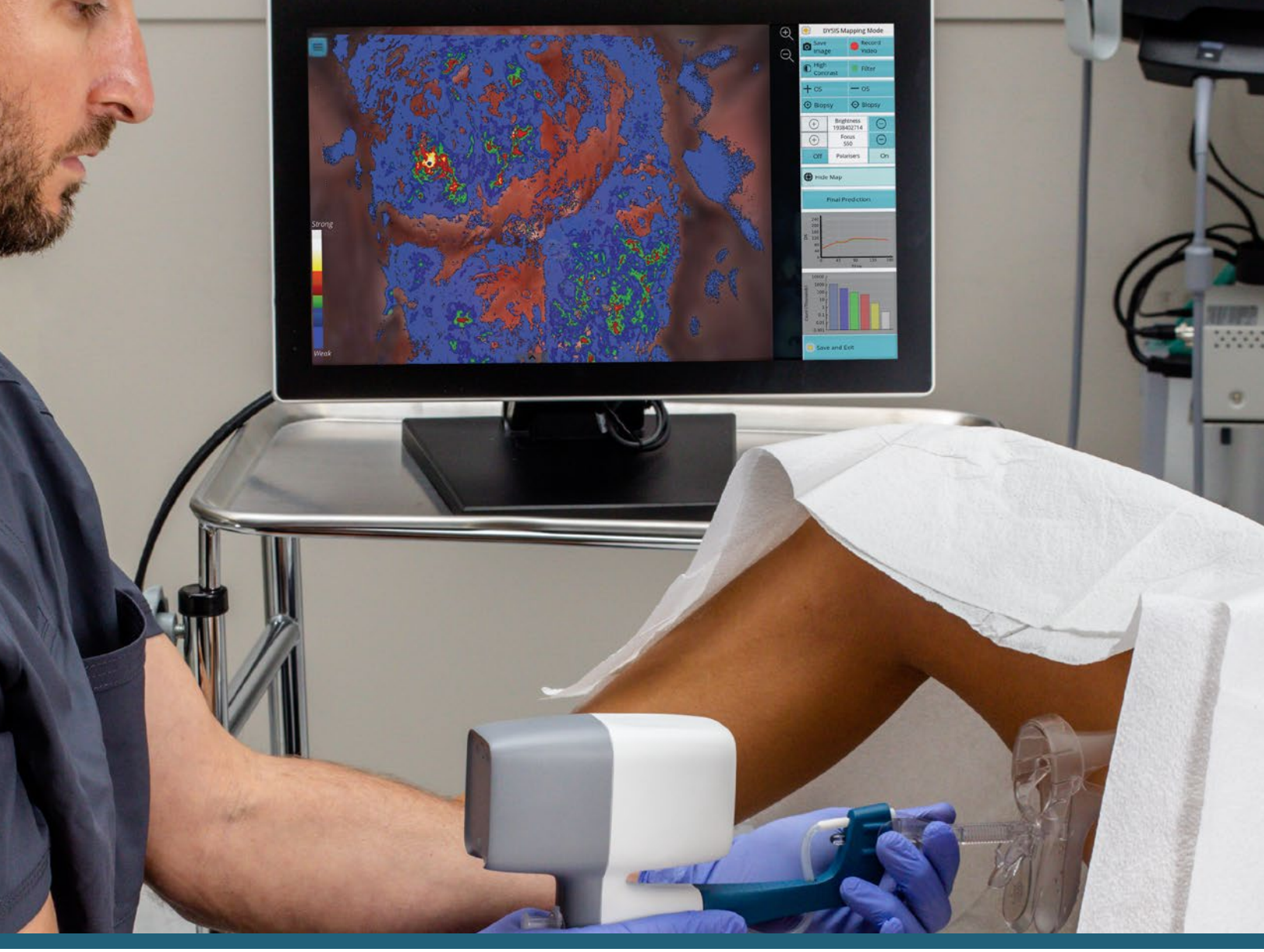

CERVICAL CANCER PREVENTION:

THE CASE FOR CLINICIAN EDUCATION IN SCREENING, COLPOSCOPY AND RISK-BASED MANAGEMENT

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The approach to cervical cancer prevention has seen significant changes in the more than 60 years since the Pap smear was introduced.[1] While the Pap test alone has reduced cervical cancer in well-screened populations, the incidence of cervical cancer in the US in 2021 was still reported to be 14,480 cases with 4,290 deaths, with a higher incidence in unscreened and under-screened women, and with geographic disparities.[2,3]

Identifying and treating high grade disease for cancer prevention improved with the emergence of HPV testing, allowing for the identification of women who are at greatest risk for CIN 3+. The high negative predictive value of a negative HPV test has contributed to widened screening intervals in the general population.[4,5,6] Due to the uptake of HPV vaccines and the decrease in HPV 16 and 18 lesions in the HPV vaccinated population, colposcopic findings have changed with smaller and more subtle lesions that need to be identified.[7] Additionally, new risk-based management guidelines require that clinicians manage patients based on their calculated immediate risk of CIN 3+ from their current and available past history.[8,9]

All of these data and advances in technology have driven changes in evidence-based practice. This article will review some of these changes including current screening and risk-based management guidelines as well as colposcopy standards, challenges in colposcopy, and recommendations for clinician education. Education for clinicians is critical for the adoption and appropriate use of the tools we have to prevent cervical cancer.

HPV Natural History

Cervical cancer is preventable due to its long preinvasive stage and the ability to identify and treat high grade disease. The majority of women will be infected with one or more types of HPV at some point and the virus is usually no longer detected by 24 months due to an immune response.[10,11] Persistence is a greater risk for women infected by HPV 16 which along with HPV 18 causes 70% of cervical cancer.[12,13] Long term persistent infection is necessary for the development of significant neoplasia and for progression to cancer precursor lesions or invasive cancer.[11]

Screening allows for the identification of women at risk for CIN 3+ with cytology and HPV testing, and colposcopy remains the main arbiter for whether significant disease is currently present. HPV testing also allows for an objective measure of not only a woman's current risk but her future risk and whether she requires increased surveillance because of the presence of oncogenic HPV types. Competent colposcopy remains critical to the follow-up of those women with persistent HPV, who have an increasing risk for the development of high-grade disease as long as they remain HPV positive.

Cervical Cancer Prevention

The current approach to cervical cancer prevention requires four separate but linked components including HPV vaccination, screening cytology with or without HPV testing and primary HPV screening.[14] Screen-positive women are evaluated with colposcopy and cervical biopsy and women with biopsy-confirmed high-grade cervical cancer precursors are treated. The goal of cervical cancer screening is to prevent morbidity and mortality from cervical cancer by identifying and treating high-grade cervical cancer precursors, avoiding unnecessary and potentially harmful evaluations and

treatments while minimizing cost to the healthcare system.[15]

Recently published guidelines, recommendations and endorsements have highlighted the importance of HPV testing in initial screening and in the follow-up of screen positive women.[5,16] Recently published guidelines for screening have recommended that improved screening would include expanding access to those who are under screened or unscreened as a top priority.[17] Trends in the use of cervical cancer screening tests in a large data base from 2013 to 2019 showed that there was a decrease in cytology alone among women aged 21-29 and an increase in co-testing among women 30-64. There was little uptake of primary HPV screening among all age groups even though HPV primary screening was FDA approved in the US in 2014.[18] Over-screening adolescents and young women younger than age 21 was seen in the data which estimated that 2.2 million of those young women were screened inappropriately. Educating clinicians in primary care and pediatric settings was suggested to be warranted to increase adherence to clinical guidelines and decrease harms.[18] As the 2020 American Cancer Society (ACS) guideline suggests that primary HPV testing alone is the preferred screening method and ACOG endorses primary HPV screening in 2021, there may be an increase over time, but this will also require increased access to HPV testing and clinician education.[5,16]

Age of Initiation of Screenings

The clinician should be aware that the recommendation for the age for initiation of screening was recently raised to 25 years old by the new ACS Guidelines but the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP) and the Society of Gynecologic Oncologists (SGO) continue to recommend initiation of cervical cancer screening at age 21. ACOG suggests in their April 2021 Practice Advisory that raising the screening start age to 25 years could increase the already high rate of underscreening among individuals aged 25–29 years and exacerbate existing health

inequities in cervical cancer screening, incidence, morbidity, and mortality.[5,16,17]

Cytology

The Pap test revolutionized the ability to screen for cervical cancer prevention and its success has been seen through the decades.[1] Though, the test is subjective and recent studies have shown that there is interobserver variability in the Pap interpretation and a sensitivity that may be as low as 50% in some studies.[19,20] The Pap test is more specific than HPV testing but in screening, the HPV test has superior sensitivity. A positive HPV test with a negative Pap is not a false positive but indicates that woman is at greater risk until the virus is no longer detectable, and she requires diligent follow-up as long as she remains positive.[11,12,21]

HPV Testing

There are currently five FDA approved HPV tests in the US market for use in triage of the ASC-US Pap test, for co-testing with Pap and HPV in initial screening, and for follow-up testing. Two of those tests are FDA approved for stand-alone HPV testing or primary HPV screening. Those tests are the Roche cobas® HPV test (Roche Diagnostics, Indianapolis, IN) and the BD Onclarity™ test (BD, Franklin Lakes, NJ) and those tests report HPV 16 and 18 genotyping on every sample and the cobas test reports the other 12 types in a grouped panel. The Onclarity test has been FDA approved for expanded genotyping that includes 16, 18, 31, 45, 51, 52 and a grouped result of 8 other types, though expanded genotyping is not yet included in management algorithms. Primary HPV screening was approved in the US in 2014 but the adoption has been slow.[18,22,23] The FDA approval was based on data that adding the Pap along with the HPV test was only marginally better as the Pap did not add a significant increase in the detection of high-grade disease.[22]

The Athena trial that led to FDA approval for primary HPV screening, was a prospective, multicenter study of over 47,000 women

that looked at the absolute risk of CIN in cytology negative women and their HPV status. The study supported the importance of genotyping for HPV 16 and 18 in those women for detecting the presence of CIN 2+. Importantly, 28% of the CIN 3 in the Athena trial were in the 25 to 29 years old age group and this is what led to the FDA approval for primary HPV screening to start at age 25.[19] The age for the initiation of co-testing with Pap and HPV is 30, which was FDA approved in 2003 and that age was based on data at the time.[24] The clinician should be knowledgeable about which HPV test their lab is using to report their results and whether they have the option for primary HPV screening. In primary HPV screening, reflex Pap testing is done for all HPV positive women. The addition of cytology to a positive HPV 16 or 18 screen can identify a subset of women with the highest risk for CIN3+ if the Pap is HSIL. HPV negative women are followed with an HPV test in 5 years according to USPSTF and ACS guidelines.[8,17,25]

The ACS in their updated 2020 guidelines recommend primary HPV screening as the preferred screening option for average-risk individuals aged 25 to 65 years old.[5] The ASCCP recognizes the need to move toward primary HPV-based cervical cancer screening and no longer endorses its 2012 guidelines that do not include primary HPV.[17] ACOG in their 2021 practice bulletin suggest that until primary HPV testing is widely available and accessible cytology-based screening methods should remain options in cervical cancer screening guidelines.[16]

The 2019 ASCCP Risk-Based Management Consensus Guidelines

The 2019 ASCCP Risk-Based Management Consensus Guidelines were developed to support a shift from results- based to risk -based guidelines. Clinical action thresholds were developed with the paradigm shift from results to recommendations based on the current risk of CIN3+.

The first fundamental concept in risk-based management is that the longer an HPV infection has been present, the higher the risk of pre-cancer and cancer. Time matters as the persistence of HPV infection increases the risk of the development of neoplasia. HPV type matters and HPV 16 is the most dangerous and if HPV status is known, other patient factors are not significant.

A clinical correlate is that colposcopy is always needed following two consecutive positive HPV tests as this represents persistence of the HPV infection.[8,9] This is an example of the importance of competent colposcopy when a patient may present with a high risk of CIN3+ due to the persistence of HPV infection.

The risk-based management guidelines as developed require HPV based testing with or without a Pap test. The guidelines prefer HPV testing for follow-up and state that surveillance with cytology alone is acceptable only if testing with HPV or cotesting is not feasible.[8]

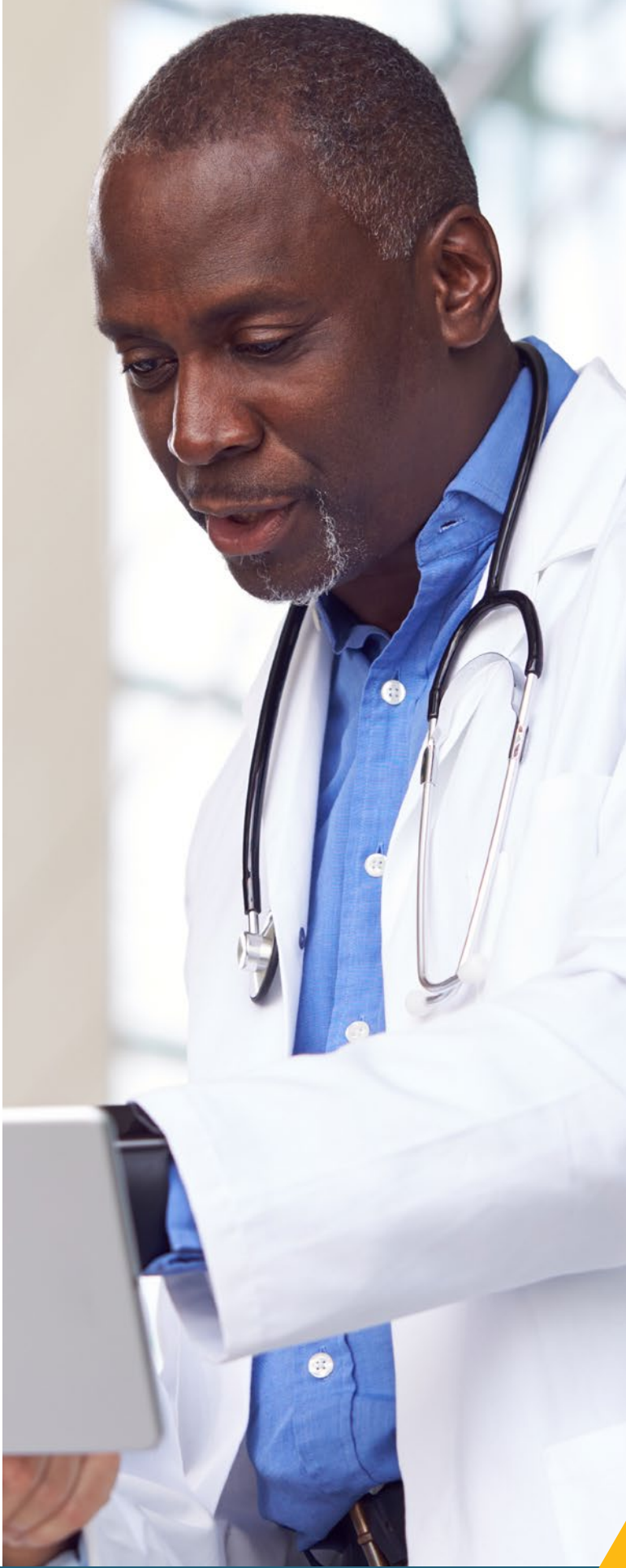
The second fundamental concept is that recommendations of colposcopy, treatment, or surveillance are based on a patient's risk of CIN3+ determined by a combination of current results and past history. This information leads to risk thresholds that are determined through a calculation within

an algorithm accessed on an app (Apple or Android) or on-line. (ASCCP quick start guide. Available at: asccp.org/quickstart).[8]
The new risk-based guidelines were developed to decrease confusion for the clinician and the risk thresholds for CIN3 management are determined easily on the app or computer. Those thresholds are:

- 60% or higher, preferred to proceed directly to expedited excisional treatment without colposcopy
- Between 25% and 59% can choose between expedited treatment or colposcopy
- 4% to 24% risk: colposcopy preferred
- Risk below 4%: managed with surveillance: repeat HPV testing or cotesting at 1, 3, or 5 years that is determined by the estimated 5-year CIN3 risk[8]

In the new screening guidelines, key changes from the 2015 primary HPV testing interim guidance is that all patients who are HPV positive should have a reflex Pap test from the same sample. Additionally, all women who are 16 or 18 positive should have colposcopy with biopsy even when cytology results are negative. If a reflex Pap test is not feasible, the patient should proceed directly to colposcopy. The reflex pap test will identify women who are HPV 16 or 18 positive who have a high-grade abnormal Pap and then those women would qualify for expedited excisional treatment without the step of colposcopy and biopsy. Their risk of current CIN3 would be at the 60% risk threshold.[8]

The 2019 Risk-based management guidelines have been developed to be enduring so that as new technologies are introduced and FDA approved, their data can be evaluated and determined if they should be added to the current risk calculation. These new options include expanded genotyping which allows



for more individualized HPV high risk types to be identified which could be used as HPV 16 and 18 are at this time.[26] Dual stain is the use of testing for two specific proteins p16 and Ki-67, in cytology and histology cervical cell samples. If the testing is done on HPV positive patients, there may be an increase in the identification of high-grade disease on those slides. This would allow for different management for those women who are dual stain positive such as referral for immediate colposcopy and biopsy.[27-29]

Colposcopy

Colposcopy is the critical link between screening and identifying women who would benefit by treatment due to the presence of pre-cancerous cells. If the new risk-based management guidelines and increased HPV testing in the US are adopted, there will be more management scenarios that rely on HPV positive women being evaluated by colposcopy.[8] Increased HPV primary screening will increase the number of women who undergo colposcopy where lesions may be small and harder to detect.[7]

It is incumbent on the colposcopist to use the procedure of illuminated magnification to identify and biopsy the areas of greatest severity. Historically, colposcopy has changed as evidence has shown that the sensitivity of cervical biopsy increases as the number of biopsies goes up.[30] Previously, various grading systems were used to help the colposcopist identify the most significant area of abnormality and taking one biopsy was considered reasonable. Multiple studies have now shown that taking more biopsies leads to increased identification of high-grade disease.[30,31] Several studies have reported a substantial increase in CIN2+ detection moving from one to two targeted biopsies. Studies have shown that taking a single biopsy from the cervix may miss up to 40% of prevalent precancers, leading to a recommendation that at least 2 and up to 4 targeted biopsies are taken for accurate detection of prevalent precancer.[7]

HPV primary screening has some impact on increasing the number of colposcopies such as in HPV 16 and 18 positive women even when the Pap is negative.[8] Though, widened screening intervals and some decreased indication for colposcopy with minor cytologic abnormalities and negative HPV testing means less cases in many clinical settings. The decreased numbers of necessary colposcopies along with the decrease in the size and number of lesions in the vaccinated population means that adequate colposcopy training and mentoring are essential. Colposcopy training is critical as there is some dependence on pattern recognition which means that larger numbers of colposcopies assists the clinician in identifying and taking biopsies appropriately. Training in many cases is not standardized and quality control may be limited.[7]

Colposcopy Standards

Evidence based consensus guidelines for colposcopy practice in the US were developed by an expert working group appointed by the ASCCP's Board of Directors and published in 2017.[7,32-35]

These guidelines were developed to improve on the limitations of colposcopy practice due to factors such as, lack of standardized terminology, lack of recommendations for colposcopy practice and procedure and lack of quality assurance measures. The Evidence-Based Consensus Recommendations for Colposcopy Practice include terminology that has been standardized and recommendations for reporting both a comprehensive number of criteria and a minimum criterion.[7,32-35]

A risk-based colposcopy practice approach is addressed, which allows modification due to knowing a patient's calculated percentage risk for CIN3 +. The approach identifies an adaption of colposcopy to previous risk and colposcopy impression and for the number of biopsies to be taken at colposcopy. There are recommendations for number of biopsies in low-risk women with less than high-grade CIN on cytology, no evidence for HPV 16 /18 and a normal colposcopic impression. Whereas biopsy practice in women with a very high risk of precancer such as with 2 of the high-risk criteria including HSIL cytology, HPV 16 or 18 positive, or a high-grade impression would increase the number of biopsies.[33]

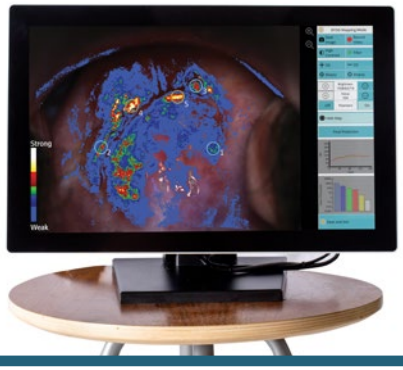
Clinician Education

It is imperative that clinicians who screen and manage women for cervical cancer prevention are aware of the new recommendations that have been described here. These changes will increase the use of HPV testing in screening and surveillance and increase the number of women who require colposcopy when lesions may be more difficult to identify.

Colposcopy education is critical and there are currently training options in residency programs and comprehensive colposcopy courses through ASCCP. There are additional CME courses and on-line options for webinars, cases, and image archives. There is a 3-tiered mentorship program through ASCCP with didactic education followed by mentorship and a competency examination, and information can be obtained on their website. asccp.org

An option for on-line education is through colposcopyskills.com which includes 50 interactive colposcopy cases ranging from normal to cancer where users can compare selections and findings to those of expert colposcopists. The image player allows the user to replicate examinations, mark choice of biopsy sites and record impressions. The user can view the DYSISmap which is the technology of dynamic spectral imaging that shows a color-coded view of acetowhitening to help increase the detection and effective biopsy of most significant areas of abnormal change.[36]

The Dynamic Spectral Imaging involves the standardized and reproducible acetic acid application combined with LED lighting and digital imaging. The DYSISmap™ is generated from measured response curves and red, yellow and white indicate areas of most intense whitening. The Dynamic Spectral Imaging algorithm measures cellular response and the dynamic curves relate to the intensity and duration of acetowhitening.[36-41]



DYSISmap

The changes in cervical cancer prevention from the use of cytology alone to HPV based screening and risk-based management will positively impact cervical cancer prevention, but clinician education remains as a critical part of its success. Colposcopy remains an important procedure in identifying those screen-positive women who need immediate treatment or continued surveillance. Adoption of changes in cervical cancer screening and management by clinicians has been slow in the past and it remains important that clinicians receive education in all aspects of screening, management, and colposcopy to increase benefit and reduce harm to women. Additionally, increasing access to screening to underserved and under insured women will make a difference in reducing the burden of cervical cancer.

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