

# The cervical cancer screening dilemma: Choosing the optimal screening strategy



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## Faculty

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## Intended audience

This continuing education (CE) activity has been designed to meet the educational needs of women's health nurse practitioners (NPs), adult NPs, family NPs, and certified nurse midwives (CNMs) involved in women's health.

## CE approval period

Now through March 31, 2017

## Estimated time to complete this activity

1 hour

## CE approval hours

1.0 contact hour of CE credit

## Needs assessment

The essence of the cervical cancer screening (CCS) dilemma is which screening test(s) to use and how frequently to screen. Major national health organizations may differ somewhat in terms of their specific recommendations, but their general objectives are to prevent morbidity and mortality from cervical cancer (Saslow et al, 2012 [this article presents recommendations from the American Cancer Society, the American Society of Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology]; U.S. Preventive Services Task Force, 2012; American College of Obstetrics and Gynecology, 2012) and to prevent overzealous management of precursor lesions that most likely will regress or disappear.

## Educational objectives

At the conclusion of this educational activity, participants should be able to:

1. Understand the importance of maximizing the benefits of cervical cancer prevention while minimizing the harms associated with overtreatment.

2. Evaluate current available options for CCS: cervical cytology, primary HPV testing, and co-testing.
3. Determine the optimal interval for CCS for each patient.

## Accreditation statement

This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH), and has been approved for 1.0 contact hour of CE credit.

## Faculty disclosures

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**Kim Choma, DNP, APN, WHNP-BC**, has disclosed that she serves on the Speakers' Bureau and advisory board of Hologic.

**Charles Dubin, MD**, reports that he serves on the Speakers' Bureau of Hologic, Myriad Genetics, and Phenogen Sciences.

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The authors evaluate current available options for cervical cancer screening (CCS), with an emphasis on the importance of maximizing the benefits of cancer prevention while minimizing the harms associated with overtreatment. Two major dilemmas are addressed: Which CCS method is recommended for women aged 30-65? and What is the optimal interval between screenings for women in any age group?

**KEY WORDS:** cervical cancer screening, cytology screening, Pap test, HPV test, co-testing

Cervical cancer screening (CCS) has been one of the most successful screening programs in United States history, reducing cervical cancer-related incidence and mortality by 45% and 49%, respectively, since 1980.<sup>1</sup> Until fairly recently, yearly cytology testing was recommended to maximize detection of pre-cancerous lesions. The discovery that infection with the human papillomavirus (HPV) underlies the pathophysiology of nearly all cervical cancers led to the incorporation of HPV testing in general screenings of women aged 30 years or older, starting in 2003.<sup>2,3</sup>

Unlike few other forms of cancer, cervical cancer is nearly al-

ways preventable.<sup>4</sup> Under optimal circumstances, each potential case of cervical cancer can be forestalled by identifying and treating disease that progresses, at most, to the high-grade cancer precursor stage.<sup>5,6</sup> At the same time, healthcare professionals (HCPs) want to minimize the harms associated with overtreatment of benign lesions not destined to become cancerous.<sup>6</sup>

### The cervical cancer screening dilemma

The essence of the CCS dilemma is which screening test(s) to use and how frequently to screen. Major national health organizations may differ somewhat in their specific

recommendations, but their general objectives are to prevent morbidity and mortality from cervical cancer and to prevent overzealous management of precursor lesions that most likely will regress or disappear.<sup>6,7</sup>

### Which cervical cancer screening tests are available?

Two tests, cervical cytology and the HPV test, are used to screen for cervical cancer. In essence, though, HCPs have three CCS options: cytology alone, the HPV test alone (known as the primary HPV test), and co-testing with both methods.

### Cervical cytology

A sample of cervical cells is examined under a microscope to screen for premalignant cells that could signal the presence of cancer precursors.<sup>8</sup> Cervical cells collected by an HCP are smeared on a glass slide (traditional or conventional cytology—that is, the Pap test) or added to a preservative fluid (liquid-based thin-layer test). Liquid-based cytology, because of its greater sensitivity than conventional cytology in detecting disease, enables extension of the screening interval

from 1 year to up to 3 years—without significantly diminishing CCS effectiveness.<sup>9</sup>

### HPV testing

The causal role of persistent HPV infection in the development of cervical cancer and its precursors has been well documented.<sup>10</sup> A landmark 2010 study showed that, over a 60-year study period, the 8 most common HPV types identified were (in descending order of frequency) 16, 18, 45, 33, 31, 52, 58, and 35.<sup>11</sup> Together, these genotypes account for 91% of all cases of cervical cancer. HPV 16, 18, and 45 were found

## Women aged 21-29 should undergo cervical cytology every 3 years.

in 75% of the most common type of cervical cancer (squamous cell) and in 94% of the second most common form (adenocarcinoma). A study of more than 20,000 women showed that those infected with HPV types 16 and/or 18, versus those infected with other high-risk types, had a 10 times greater risk of developing cervical cancer.<sup>12</sup> Because HPV cannot be cultured, in most cases its accurate identification relies on molecular biology techniques.<sup>13</sup> Molecular assays use primers and probes that identify a region of HPV DNA or HPV mRNA. Of note, HPV tests used in clinical practice need to be FDA approved for validity.<sup>6</sup>

### Co-testing

Recent incorporation of HPV DNA testing into CCS strategies offers the benefits of increasing early disease detection (up to 100% sensitivity)<sup>14</sup> and increasing the length of the interval between screenings—thereby lessening harms such as the adverse psychosocial impact of screening positive, the need for additional visits and procedures, and the treatment of lesions that would have resolved on their own.<sup>6</sup> Even more recently, HPV infection can be identified by HPV mRNA testing, which, like standard HPV DNA testing, has up to 100% sensitivity<sup>15</sup> but also offers improved specificity, with a 24% reduction in false-positive results.<sup>16</sup>

### Which approaches to screening are recommended for women aged 21-29?

According to guidelines issued in 2012 by the American Cancer Society (ACS), the American Society of Colposcopy and Cervical Pathology (ASCCP), and the American Society for Clinical Pathology (ASCP), CCS should begin at age 21.<sup>6</sup> Women aged 21-29 should undergo cervical cytology every 3 years.<sup>6</sup> The same year, the U.S. Preventive Services Task Force (USPSTF) and the American Congress of Obstetricians and Gynecologists (ACOG) issued similar recommendations.<sup>17,18</sup> These organizations all advised against HPV co-testing in women younger than 30; although HPV is commonly present in women in this age group, most of them successfully fight off the infection within

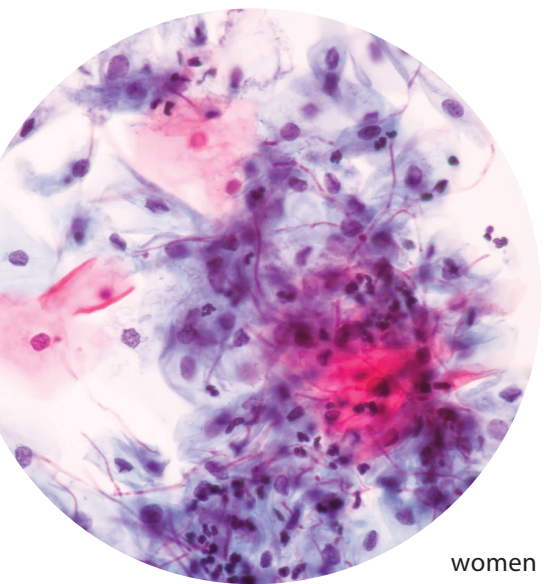
a few years.<sup>19</sup> An updated Practice Bulletin from ACOG published in January 2016 reinforces the recommendations for women aged 21-29 based on level A evidence: Co-testing in these women and annual cytology should not be performed.<sup>20</sup> Until more long-term, level A evidence studies are available to support future updates to the 21-29 age group, HCPs are encouraged to follow the consensus guidelines.<sup>6</sup>

Although primary HPV testing was not recommended at the time of the ACS/ASCCP/ASCP, USPSTF, and ACOG updates in 2012—in fact, its use was specifically discouraged in women in their 20s—the body of evidence supporting this CCS approach has grown. Findings from the Addressing the Need for Advanced HPV Diagnostics (ATHENA) study (2008-2012) supported the safety and effectiveness of primary HPV testing.<sup>21,22</sup> In 2014, the FDA approved the use of the cobas HPV test as a primary screen for cervical cancer in women aged 25 years or older.<sup>23</sup> As a result, interim clinical guidance issued by the Society of Gynecologic Oncology (SGO) and the ASCCP in 2015 supported primary HPV testing as a possible alternative to cytology-based screening and co-testing, but starting no sooner than age 25.<sup>24</sup>

### Which approaches to screening are recommended for women aged 30-65?

Again, HCPs have three CCS options: cervical cytology, primary HPV testing, and co-testing. The ACS/ASCCP/ASCP recommends cytology alone every 3 years or co-testing every 5 years.<sup>6</sup> The USPSTF endorses cytology every 3 years, with co-testing as an option in

Readers can access a chart summarizing CCS guidelines from the ACS/ASCCP/ASCP, the USPSTF, and ACOG and the interim clinical guidance from the SGO/ASCCP by [clicking here](#)<sup>B</sup>.



women  
who want to

extend their screening interval to 5 years.<sup>17</sup> ACOG supports the options of cytology at 3-year intervals and co-testing at 5-year intervals, with the latter preferred.<sup>18</sup> None of these organizations advocates the use of primary HPV testing as an alternative to cytology or co-testing.

Co-testing for women aged 30 or older was approved by the FDA in 2006. But how does co-testing compare with primary HPV testing—as advocated in the interim guidance report—and with cervical cytology alone in predicting outcomes in women in the 30- to 65-year age group?

### Studies supporting co-testing

Blatt et al<sup>25</sup> conducted a retrospective study to assess the sensitivity of various testing options for biopsy-proven cervical intraepithelial neoplasia grade 3 or worse (CIN3+). The authors evaluated 256,648 cervical biopsies from women aged 30-65 who had undergone a co-test and colposcopy within 1 year of each other (colposcopy was performed a mean of 54 days after the co-testing result). Among the samples, 4,090 (1.6%) exhibited CIN3+. A positive co-test result was 98.8% sensitive for diagnosing CIN3+, compared with the 94% sensitivity of a positive

HPV test result and the 91.3% sensitivity of a positive cytology result. Looked at another way, in this group of women, use of cytology alone would have missed 8.7% of the CIN3+ cases and use of the HPV test alone would have failed to catch 6% of the CIN3+ cases, whereas co-testing would have missed only 1.2% of these cases. Therefore, co-testing identified 80% of the CIN3+ cases that would have been missed by screening with the primary HPV test. Of the 526 confirmed cases of cervical cancer in this study, 98 (18.6%) were HPV test negative and 64 (12.2%) were cytology negative, whereas only 29 (5.5%) were co-test negative. Co-testing identified 70% of cervical cancers that would have been missed by screening with the HPV test alone.

Additional studies conducted over the past 11 years showed that primary HPV testing missed a substantial proportion of cervical cancers, and were in concordance with the landmark study by Blatt and colleagues.<sup>11,26-29</sup>

### Studies supporting primary HPV testing

The aforementioned interim guidance from the SGO/ASCCP was based, in large part, on the results of several large trials demonstrating that a negative HPV test result provides greater reassurance of low CIN3+ risk than does a negative cytology result. For example, Dillner et al<sup>30</sup> evaluated primary data from seven HPV screening studies in six European Union countries, each investigating the predictive value of primary HPV testing for future CIN3+. The cumulative incidence rate of CIN3+ after 6 years was considerably lower among women negative for HPV at baseline (0.27%) than

among women with negative results on cytology (0.97%). The cumulative incidence rate among women who were cytology-negative/HPV-positive rose continuously over time, reaching 10% at 6 years, whereas the rate among women who were cytology-positive/HPV-negative remained below 3%.

Other recent studies provided evidence that a negative HPV test result, as compared with a negative cytology result, offers greater reassurance that a woman will be free of CIN3+ over time.<sup>31-33</sup> In these studies, participants underwent co-testing. In essence, the investigators found that the HPV test results, relative to the cytology results, were more predictive of outcomes over 3-5 years. That is, the cytology portion of the co-test did not add much information to the HPV portion, suggesting, to some at least, that HPV testing could be used by itself.

### The first dilemma: Which CCS method is recommended for women aged 30-65?

The findings of the studies supporting primary HPV testing are open to interpretation. For example, Gage et al<sup>32</sup> compared the risks of CIN3+ and of cervical cancer alone for HPV testing every 3 years, cytology testing every 3 years, and co-testing every 5 years among more than 1 million women in the Kaiser Permanente population who were aged 30-64 years and who tested HPV-negative and/or cytology-negative in routine screening. Investigators found that 3-year risks following an HPV-negative result were lower than 3-year risks following a cytology-negative result (CIN3+, 0.069% vs. 0.19%;  $P < .0001$ ;

cancer, 0.011% vs. 0.020%;  $P < .0001$ ) and 5-year risks following an HPV-negative/Pap-negative co-test result (CIN3+, 0.069% vs. 0.11%;  $P < .0001$ ; cancer, 0.011% vs. 0.014%;  $P = .21$ ). That is, the 3-year safety (i.e., reassurance against future risk of pre-cancer and cancer) conferred by a negative HPV test result exceeded the 3-year safety conferred by a negative cytology result or the 5-year safety conferred by a negative co-test result. However, a closer look at the data shows that if HPV testing had been compared with co-testing at the 3-year checkpoint instead of the 5-year checkpoint (the recommended interval), negative co-testing results at baseline were slightly more reassuring than negative HPV results at baseline for CIN3+ and for cancer.

In addition, as HPV-infected cervical cells progress toward cervical cancer, HPV DNA levels *decline*.<sup>34</sup> Depending on the age at which CCS begins and the frequency with which it is performed, relying initially, solely, or mainly on the results of HPV DNA screening tests might miss fast-growing cancers. Although as HPV integrates itself into the human genome and HPV DNA levels decrease, HPV E6/E7 mRNA levels *increase*, suggesting that the assay that particularly targets this protein, as compared with the HPV DNA assays, is more specific in indicating lesion severity.<sup>35</sup>

Furthermore, with cytology alone, adenocarcinoma and its precursors are difficult to identify—simply because of the cervical anatomy and the detection methods used. Cervical adenocarcinoma is usually farther away from the transformation zone, the area targeted most readily with the use of cervical sampling

devices. Cytology alone has been relatively ineffective in identifying glandular lesions associated with adenocarcinoma. Addition of HPV testing to cytology—that is, co-testing—should enhance identification of adenocarcinoma and its precursor, adenocarcinoma in situ (ACIS).<sup>18</sup>

*At this point in time, co-testing seems a reasonable option in women aged 30-65 years because it offers optimal sensitivity and specificity in identifying cervical cancer precursors.*

### What is the optimal screening interval for cervical cancer screening?

The 2012 ACS/ASCCP/ASCP and ACOG guidelines' recommended screening intervals are 3 years for liquid-based cytology testing and 5 years for co-testing.<sup>6,18</sup> The updated Practice Bulletin from ACOG states that co-testing every 5 years is preferred, but that screening with cytology alone every 3 years is acceptable.<sup>20</sup> ACOG recommends against annual testing. The USPSTF recommends cytology every 3 years for women younger than 30.<sup>17</sup> For women aged 30-65 who want to extend their screening interval to 5 years, adding HPV testing is advised. The interim guidance provided by the SGO/ASCCP recommends that re-screening after a negative primary HPV test result occur no sooner than every 3 years—but only in women aged 25 years or older.<sup>24</sup>

For decades in the past, women underwent conventional Pap testing every year—their single best option for identifying cervical cancer precursors in a timely fashion. But there was a distinct downside to this yearly testing, which often yielded results—

atypical squamous cells of undetermined significance (ASCUS) or a higher-grade lesion—that would lead to colposcopy and, depending on the results of the cervical biopsies, a loop electro-surgical excision procedure or conization. Most of these cytologic abnormalities, as well as the HPV infections underlying them, resolve on their own. Screening women every year, then, is bound to lead to unnecessary diagnostic and therapeutic procedures. These procedures are, at the very least, unpleasant and worrisome and at worst, harmful.<sup>36-41</sup>

### The second dilemma: What is the optimal interval between screenings for women in any age group?

Since the CCS guidelines were published in 2012 and the interim guidance was published last year, a different perspective on the CCS interval has been offered. According to a commentary by Kinney et al,<sup>42</sup> which was based on a modeling study for the USPSTF that was published in 2013,<sup>43</sup> women who comply with the CCS recommendations and increase the co-testing interval from 3 years to 5 years are increasing their risk for unfavorable consequences, with an additional 1/369 diagnosed with cancer in her lifetime and 1/1,639 dying of cancer. Adoption of a 3-year co-testing interval instead of a 5-year co-testing interval between screenings would “cost” 409 additional colposcopies and 14.3 additional women treated for each cancer death prevented. Many women and their HCPs might argue that the extra screenings, tests, treatments, and related harms are worth it to save even a small number of lives. In

addition, as noted in the discussion of the first CCS dilemma, results of the study by Gage et al<sup>32</sup> suggest that the optimal interval for co-testing may be 3 years, not 5 years. Finally, there is considerable clinician resistance to the 5-year screening interval recommended for a negative co-test result.<sup>42</sup>

*Based on what is known to date, HCPs should consider the optimal CCS screening interval to be 3 years, both for cytologic testing in women aged 21-29 or older and for co-testing in women aged 30-65.*

### At what age can cervical cancer screening safely be stopped?

According to the ACS/ASCCP/ASCP, CCS can safely be stopped in women older than 65 who have had adequate negative prior screening (three consecutive negative cytology results or two negative co-test results within the previous 10 years, with the most recent test performed within the past 5 years) and no history of CIN2+ within the past 20 years.<sup>6</sup> The USPSTF and ACOG are in general agreement with these criteria.<sup>17,18</sup> For women older than 65 with a history of CIN2, CIN3, or ACIS, routine screening should continue for at least 20 years.<sup>6,18</sup> According to the USPSTF, women older than 65 who have never been screened, women who do not meet the criteria for adequate prior screening, or women for whom the adequacy of prior screening cannot be accurately assessed or documented should undergo routine CCS.<sup>17</sup> Likewise, routine screening should continue for at least 20 years after spontaneous regression or appropriate management of a high-grade pre-cancerous lesion, even

if this extends screening past age 65.

### Conclusion

The best approach to prevent cervical cancer entails screening and vaccination. The goals of maximizing benefits and minimizing harms for patients are guiding principles at the forefront of CCS. To this end, using the evidence to date, which includes the 2012 guidelines, the interim guidance published last year, and the updated ACOG practice bulletin, cytology screening every 3 years in women aged 21-29 and co-testing every 3 years in women aged 30-65 are reasonable recommendations to balance patient harms and clinician resistance to 5-year screening intervals. ●

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#### Web resources

A. [npwh.org/courses/home/details/559](http://npwh.org/courses/home/details/559)

B. [cdc.gov/cancer/cervical/pdf/guide\\_lines.pdf](http://cdc.gov/cancer/cervical/pdf/guide_lines.pdf)

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