

## Cervical Cancer Screening: Updated Recommendations for the Efficient Use of Pap and HPV Testing in Women

The incidence and mortality of cervical cancer has decreased in the United States more than 50% in the last 30 years due to widespread screening with cervical cytology (Pap testing). The majority of deaths from cervical cancer in the US are now among women that are screened infrequently or not at all. New technologies for performing cervical cancer screening, including the development of molecular testing for human papilloma virus (HPV) DNA directly from the cytology specimens, has evolved quickly as have recommendations for classifying and interpreting the results. As a result of this evolving technology, the American College of Obstetricians and Gynecologists (ACOG) updated their recommendations for cervical cancer screening in December of 2009. Based on good scientific data, ACOG concluded that women can now be screened less frequently than previously recommended which epidemiologic data has shown prevents cervical cancer as effectively but decreases costs and prevents unnecessary interventions that could potentially be harmful.

ACOG issued their revised evidence-based guidelines in December 2009 in *Obstetrics & Gynecology*. Their Level A

recommendations now include:

- Initiating cervical cancer screening at age 21 (regardless of the age of onset of sexual intercourse) with a screening Pap test every two years until the age of 29.
- Pap test screening in women age 30 and older every three years after three consecutive negative Pap tests if there is no history of CIN 2 or greater, HIV infection, immunocompromise, or exposure to diethylstilbestrol (DES) in utero.
- Co-testing (Pap test + high-risk HPV testing) as an acceptable screening option for cervical cancer screening every three years in women 30 years of age and older.

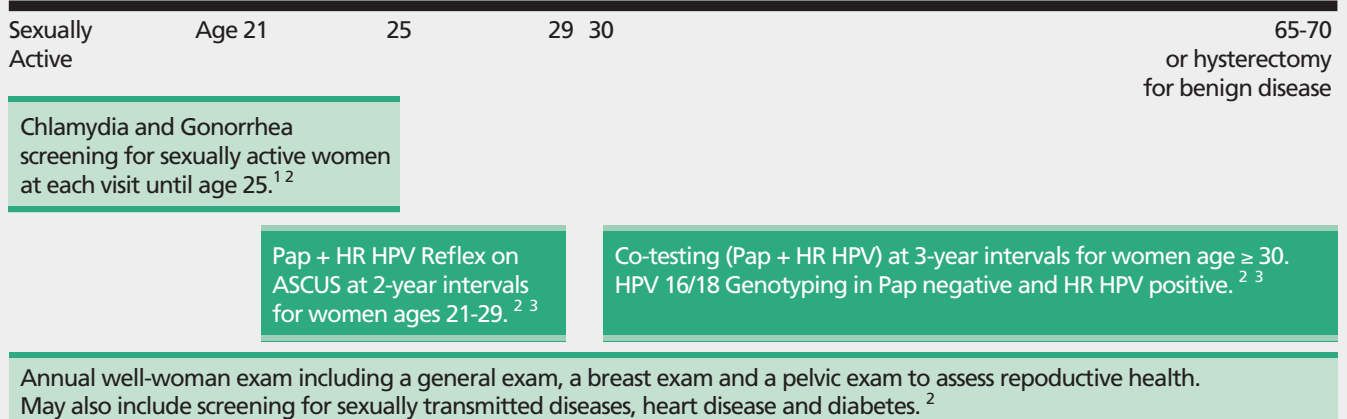
Infection with HPV is a necessary factor in the development of squamous cervical neoplasia, but most HPV-infected women will not develop cervical abnormalities. Most immunocompetent women will clear the infection in an average of 8-24 months. HPV type and persistence of infection appear to be the most important determinants of the risk of progression to squamous cervical neoplasia. There are approximately 15 recog-

nized "high-risk" HPV types (HR-HPV) that show an increased propensity to cause clinically significant cervical lesions.

HPV is a common infection in women and the highest incidence of HPV infections are seen in adolescents and women in their early 20s. However, HPV infections are likely to resolve spontaneously in this age group. Due to the immaturity of the adolescent cervix, the incidence of dysplastic changes is also higher in this age group, but the large majority of these lesions also resolve on their own without treatment. Although the rate of HPV infection is high among adolescents, the rate of invasive cervical cancer is very low. Only 0.1% of cervical cancer cases occur before the age of 21. Delaying cervical cancer screening until the age of 21 is a conservative approach designed to avoid unnecessary follow-up and treatment of women with abnormal cytology results that can have economic, emotional and future childbearing implications. However, sexually active women younger than 21 should be counseled and tested for sexually transmitted infections and counseled regarding safe sex practices and contraception.

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### Guidelines for Women's Health Screening



1. Centers for Disease Control (CDC) 2. American College of Obstetricians and Gynecologists (ACOG) 3. American Society for Colposcopy and Cervical Pathology (ASCCP)

## Updated Recommendations for the Efficient Use of Pap and HPV Testing in Women (*continued*)

HPV positivity in women older than 30 is more likely to reflect persistent and therefore potentially cancerogenic infections. Since the incidence of cervical cancer in women increases as women age, it becomes increasingly important to determine which women have persistent HPV infections and which women have either cleared an infection or never became infected in the first place. New ACOG clinical guidelines reflect this as women 30 or over with a low risk of persistent HPV infections can now undergo less frequent screenings at an interval of only once every three years. Women considered to have a low risk of persistent HPV infections are those with three consecutive negative Pap tests or a single negative Pap + HR-HPV co-test. Of note, this screening interval can be utilized in this age group even if the women have new sexual partners. As the screening interval decreases, the Pap + HPV co-test is an important option to consider since liquid-based cytology can miss up to 15-35% of CIN 3 or invasive cancer. Adding HPV to the three year screening cycle may provide added assurance that a high-grade cervical lesion is not present in these women and is an acceptable screening option according to the ACOG recommendations.

However, the Pap test + HR-HPV co-test is not recommended for women in their 20s because they are more likely to have HPV infections that will be cleared and not be of long-term clinical consequence. HR-HPV positivity in this set of patients could potentially lead to invasive testing that is unnecessary and not without side effects (like cervical incompetence). Reflex HR-HPV testing, however, is used in this age group for ASC-US Pap test results.

The HPV DNA test currently in use at Bronson is the *digene*<sup>®</sup> HPV test (also known as the Hybrid Capture<sup>®</sup> 2 HR HPV Test) which is FDA approved for use on ThinPrep Pap tests utilizing residual sample taken after the cells have been extracted for cytology. Specimens for HPV testing only (without concurrent cytology) can also be collected using the *digene* Cervical Sampler kit. The *digene* HPV Test determines whether a patient sample has DNA from one of the 13 most important high-risk types of HPV associated with the development of cervical cancer. It has been recommended by various professional medical organi-

zations including the American Society for Colposcopy, ACOG, and American Cancer Society among others. Multiple domestic and international clinical trials involving the Pap + HPV co-test have shown sensitivity for CIN 2 and greater of 97% and sensitivity for CIN 3 and greater of 100% in women 30 and older. Conversely, women who receive a negative result from a co-test have a less than 1 in 1000 risk of having CIN 2 or greater. Follow-up studies in women with a negative co-test have shown the risk of developing CIN 3 over the next 10-year period is less than 2%. The *digene* HPV Test does not test for low-risk HPV types (HPV types associated with genital warts and other clinical diseases) as testing for these HPV types is not recommended in clinical guidelines and may not be reimbursed by insurance.

Aside from using an HPV test as an adjunct to cytology for primary screening in women age 30 or older, HPV testing can also be utilized four other ways:

- Triage test to stratify risk to women aged 21 or older with a diagnosis of ASC-US,
- Triage test to stratify risk to postmenopausal women with a diagnosis of LSIL,
- Follow-up test after CIN 1 or negative findings at colposcopy following a prior cytology diagnosis of ASC-US, ASC-H, LSIL or AGC, or
- Follow-up test after treatment for CIN 2 or CIN 3.

An HPV test is not recommended for women younger than 21 and if inadvertently done, the results should not influence clinical management.

Recently a vaccine targeting HPV-16 and HPV-18, the HPV types associated with approximately 70% of the cases of cervical cancer in the US, has been introduced. However, the vaccine does not protect against all types of high-risk HPV. Women who have been immunized against HPV-16 and HPV-18 should be screened using the same regimen as women that have not been immunized for HPV. Of note, routine cervical cytology testing can be discontinued in women, regardless of age, who have had a total hysterectomy (i.e. removal of the uterus and cervix) for noncancerous reasons so long as they have never had a history of high-grade cervical intra-epithelial neoplasia. ACOG's upper age limit for cervical cancer screening remains at 65 or 70 among women who

have had 3 or more negative cytology results in a row and no abnormal results in the past 10 years.

It is important to stress that routine periodic gynecologic examinations may still be appropriate even if cervical cytology is not performed annually. And while the new screening intervals apply to many women, higher-risk women such as those with previous cervical abnormalities (CIN 2, CIN 3, or cancer), HIV infection, immunosuppression or those exposed to diethylstilbestrol (DES) in utero may need more frequent screening, however. Additionally, any abnormal cytology result requires appropriate follow-up as advised by the American Society for Colposcopy and Cervical Pathology (ASCCP).

The annual volume of Pap tests at Bronson is approximately 29,000 with roughly 1300 HPV DNA tests performed in the same time frame (4.5% of Pap



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tests). The majority of these HPV tests are reflex tests following an ASCUS cytology result. In medical communities that have initiated Pap + HPV co-testing in women 30 and over, the rate of HPV testing in a laboratory often approaches 30% of Pap tests. With the updated ACOG recommendations and Pap + HPV co-testing emerging as the standard of care for primary screening of women 30 and over, the HPV testing rate is likely to increase in this laboratory as well.

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