FREQUENTLY ASKED QUESTIONS

What is HPV?¹

HPVs, or human papillomaviruses, are common viruses that cause warts and cancers and the most common viral sexually transmitted infection (STI). There are over 200 types, or strains (small mutations of the same virus), of HPV and related viruses, many of which are harmless to humans.

Of the 200 types, or strains, of HPV, roughly 40 can be spread by skin-to-skin contact during vaginal, anal, or oral sex. Many of these HPVs cause warts and certain cancers and pre-cancers of the cervix, mouth, skin lining, anus, and lower genital tract.

What is cervical cancer?²

Cervical cancer is cancer that starts in the cervix, the lower part of the uterus that opens at the top of the vagina.

Cervical cancer frequently starts as a precancerous condition called cervical intraepithelial neoplasia (CIN), or dysplasia, which can be detected by a Pap test (also known as Pap smear) and is 100 percent treatable if caught early.

It can take years for precancerous changes to turn into cervical cancer. These changes are documented by grades from CIN 1 to 3, with CIN 1 representing mild abnormalities and CIN 3 representing severe abnormalities.³ CIN 3 carries the most risk for developing cervical cancer.

According to the American Cancer Society, cervical cancer is the second leading cause of death for women worldwide and one of the most common causes of cancer death for women in the United States; though, the number of women diagnosed with cervical cancer has decreased by 50% in the last 30 years.⁴

How are HPV and cervical cancer related?⁵,⁶

HPV has been implicated in close to 100 percent of all cervical cancers, meaning that almost 100 percent of all cervical cancers are caused by the HPV virus. Of the 200 types, or strains, of HPV, roughly 40 can be spread by skin-to-skin contact during vaginal, anal, or oral sex. Of these strains, 14 types are known to be

linked to cervical cancer and are therefore termed carcinogenic or ‘high risk.’ High-risk HPV infection strongly predicts subsequent cervical pre-cancerous lesions.

HPV infections are common in healthy women and are typically cleared or suppressed successfully by the immune system; only rarely does the infection persist and result in cervical cancer, which happens when HPV converts normal cells on the cervix into cancerous ones.7

Most, though not all, women who are diagnosed with cervical cancer today have not had regular Pap smears or have not followed up on abnormal Pap smear results.

What types of HPV are linked to cervical cancer?

Persistent infection of HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 have been classified as ‘high-risk’ genotypes, with an additional six genotypes (26, 53, 66, 68, 73 and 82) classified as ‘probably high-risk.’8 Types 16 and 18, specifically, are responsible for 70 percent of invasive cervical cancers.9

Is HPV linked to any other types of cancer?10

HPV is linked to cancer of the vulva and vagina in females and cancer of the penis in males. For both sexes, HPV is also linked to cancers of the anus and oropharynx (head and neck). The chart below demonstrates the incidence of such cancers:

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Average Number of Cases Per Year</th>
<th>Estimated Number of Cancer Caused by HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Cervical</td>
<td>--------</td>
<td>11,422</td>
</tr>
<tr>
<td>Vulva</td>
<td>--------</td>
<td>3,168</td>
</tr>
<tr>
<td>Vagina</td>
<td>--------</td>
<td>735</td>
</tr>
<tr>
<td>Penis</td>
<td>1,048</td>
<td>--------</td>
</tr>
<tr>
<td>Anus</td>
<td>1,549</td>
<td>2,821</td>
</tr>
<tr>
<td>Oropharynx (Head and Neck)</td>
<td>9,974</td>
<td>2,443</td>
</tr>
</tbody>
</table>

Who gets cervical cancer?12

Almost all women are at risk for cervical cancer; however it occurs most often in women over the age of 30.

From 2008-2012, the median age at diagnosis for cervical cancer was 49 years of age and the median age at death from cervical cancer was 57 years of age.

Based on rates from 2008-2012, 0.6 percent of women born today will be diagnosed with cervical cancer at some time during their lifetime, which translates to one in 147 women who will be diagnosed with cervical cancer during their lifetime.

What are the key statistics about HPV and cervical cancer?

The most recent estimates have determined that, in the United States, approximately 79 million people, or 25 percent of the population, are currently infected with HPV, with an estimated 14 million new HPV infections diagnosed each year in persons between the ages of 14 and 44 years.13 At least 80-90 percent of sexually active individuals will contract some type of genital HPV at some point in their life.14

The American Cancer Society’s recent estimates for cervical cancer in the United States for 2015 are:15

- An estimated 12,900 new cases of invasive cervical cancer are expected to be diagnosed.
- Approximately 4,100 deaths from cervical cancer are expected.

Rates of cervical cancer incidence and death vary by state. Based on data taken from 2008-2012 the national incidence rate for cervical cancer was 7.7 per 100,000 women.16 During this time, many Southern states had the highest incidence rates of cervical cancer, including Texas, Louisiana, and Florida, ranging from 8.2 to 9.6 per 100,000 women.17

During 2008-2012, the national death rate from cervical cancer was 2.3 per 100,000 women. Death rates, much like incidence rates, also vary by state.18 In this survey, Utah, Colorado, and Massachusetts had some of the lowest incident rates, ranging from 4.3 to 6.4.19

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Cervical cancer also disproportionately affects minority populations, especially African American, Hispanic/Latino, and Alaskan Native populations. African American women are twice as likely to die from cervical cancer as their white counterparts. The chart below demonstrates cervical cancer incidence and mortality rates in the United States by race:

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>African American</th>
<th>Asian American/Pacific Islander</th>
<th>American Indian or Alaska Native</th>
<th>Hispanic/Latino</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence</strong></td>
<td>7.7</td>
<td>9.2</td>
<td>6.3</td>
<td>7.5</td>
<td>9.9</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>2.1</td>
<td>4.0</td>
<td>1.8</td>
<td>3.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*2012 is the most current data on this specific subject.

**Can HPV be prevented?**

Correct usage of latex condoms greatly reduces, but does not eliminate, the risk of contracting or spreading HPV. Currently, three HPV vaccines are licensed in the United States to help prevent HPV infection, which in turn helps to prevent cervical cancer: Cervarix®, Gardasil®, Gardasil-9®. All vaccines offer protection against HPV types 16 and 18. Gardasil-9®, the newest vaccine released in March 2015, protects against HPV-6, 11, 16, 18, 31, 33, 45, 52, and 58.23 HPV types 6 and 11 are responsible for nearly 90 percent of all genital warts cases, while HPV types 16 and 18, specifically, are responsible for 70 percent of invasive cervical cancers.24

The HPV vaccine is licensed, safe, and effective for both males and females aged nine through 26 years. The Center for Disease Control and Prevention’s (CDC) Advisory Committee on Immunization Practices (ACIP) recommends that all 11 or 12 year old boys and girls get the three shot series.25 According to the CDC, in order for the HPV vaccine to work best, it is important for preteens to get all three doses before they become

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sexually active, especially because the vaccine produces a higher antibody count that fights infection when given at this age compared to older ages.26

Despite offering excellent coverage of the most “high-risk” types of HPV, vaccination rates in the United States remain low. In 2014, per the CDC’s report, only 60 percent of female teens, ages 13-17, received one or more of the recommended three-dose HPV vaccination series, with only 39.7 percent completing the three shot series.27 Further, only 41.7 percent of males, ages 13-17 received one or more doses of the vaccine.28

Clinical studies have shown HPV vaccination to be a highly effective and potentially lifesaving tool in the prevention of cervical cancer. Modeling studies have also shown that HPV vaccination can be cost-effective, with an incremental cost effective ratio (ICER) of $100,000 or less per quality-adjusted life year (QALY) gained.29

Is there a cure or treatment for HPV?30, 31

There is no cure for HPV, but a vast majority of HPV infections often clear or become undetectable on their own. If the infection progresses, there are several treatment options for HPV-related diseases such as genital warts and lesions.

Visible genital warts can be removed by the patient with medications or treated by a healthcare provider. Precancerous cells can be removed from the cervix by a healthcare provider through a variety of methods including electrocoagulation, cryotherapy, laser ablation, or local surgery. Invasive cancers are generally treated with surgery, radiation, or both, and with chemotherapy in selected cases.

Screening is vital in preventing HPV infections from becoming cancerous. With screening and vaccination, the tools are currently in place to prevent HPV from becoming cervical cancer, thus preventing cervical cancer entirely.

What types of screening tests are available?

There are two types of tests that screen for cervical cancer, the Pap test (or Pap smear) and the HPV DNA test (also known as the HPV test).

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26 Ibid.
28 Ibid.
• The Pap test helps find abnormal cells on the cervix that might become cervical cancer if they are not treated appropriately.
• The HPV DNA test uses cells from the cervix to test for the virus that can cause these abnormal cell changes on the cervix. The HPV test may be used to provide more information when a Pap test has unclear results.

For women ages 30 or older, the co-testing, which refers to the use of a Pap test and the HPV DNA test, is now the standard of care for cervical cancer screening.

In some cases a colposcopy or cervical biopsy may be appropriate to further examine and diagnose any potential problems.

• A colposcopy is a simple procedure that uses magnification to allow a doctor to better view the cervix and any abnormalities.
• During a cervical biopsy, a doctor takes a small sample of the cervix to better study the tissue more carefully for abnormalities.

**Why is HPV and cervical cancer screening important?**

Cervical cancer often does not cause symptoms until it is advanced and much more difficult to treat. Screening tests for abnormal cells and HPV can detect prospective problems well before this point, lending increased potential to successful treatment options and the prevention of cervical cancer and premature death. When detected at an early stage, cervical cancer has a five-year survival rate of 91.5 percent. However, when cervical cancer is diagnosed at an advanced stage, survival rates plummet to 16.5 percent.32

The addition of HPV DNA testing to cytology enhances the detection of cervical cancer and its precursors, an area where cytology has been largely ineffective in decreasing the incidence of this highly aggressive form of cancer.33 HPV testing can reduce the incidence of cervical cancer within four to five years and reduce the mortality due to cervical cancer within eight years compared to cytology.34

An additional study, known as the ATHENA study, examined a population of almost 42,000 women ages 30+ who had normal Pap results but were positive for HPV 16 and/or 18. Results demonstrated that one in 10 of those women were diagnosed with pre-cancerous lesions (grade CIN2 or greater). If these women had only been tested with Pap alone using the new guidelines for the study of cells alone, they would have been

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34 Rijkart DC, et al. (2011) “Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: Results over two screening rounds of the POBASCAM randomized controlled trial”. Lancet Oncology, 2011
released from screening for another three years, potentially allowing the precancerous lesions to advance to cervical cancer.35

**What are the general recommendations for HPV and cervical cancer screening?**

According to the American Cancer Society (ACS), the American College of Obstetricians and Gynecologists (ACOG), the American Society for Colposcopy and Cervical Pathology (ASCCP), U.S. Preventative Services Task Force (USPSTF) and the American Society for Clinical Pathology (ASCP), screening for cervical cancer should begin at age 21. Women ages 21 to 29 should be screened every three years with a Pap test, receiving HPV DNA testing only in the case of inconclusive Pap test results. Women between the ages of 30 and 65 should have a Pap test and an HPV test (referred to as ‘co-testing’) every five years. See the Sample Guidelines – Screening and Diagnostics page of this toolkit for more information.

The American College of Obstetricians and Gynecologists recently published new guidelines which state that HPV testing should be performed only to detect the presence of high-risk HPV. There is no role for testing for low-risk genotypes, and tests for low-risk HPV should not be performed.36 This recommendation concurs with comments from screening guidelines released in March 2012 by a harmonized group of experts from the American Cancer Society, the American Society for Colposcopy and the Cervical Pathology, and American Society for Clinical Pathology.

**What are the main differences between the Pap test and the HPV test?**

Both the Pap test and the HPV DNA test are done on a sample of cells gathered from the cervix. While the Pap test looks at the general appearance of the cells, the HPV test checks those cells for the presence of the HPV virus itself. Both tests are appropriate for cervical cancer screening, but the HPV test cannot currently be used as a screening tool on its own. Instead, the HPV test must be used with a Pap test for women 30 years of age or older or as a screening test to further analyze an inconclusive Pap test.

Aside from this, there are differences in the sensitivity and specificity of each test. Sensitivity refers to the proportion of actual positive results that are correctly identified by a screening test. Specificity measures how accurately a test diagnoses a particular disease without giving false-positive results.

Compared to the Pap test, HPV DNA testing has a greater sensitivity for the detection of cervical intraepithelial neoplasia (CIN), or the presence of abnormal cells on the cervix. A study published by the *New England Journal of Medicine* demonstrated that the sensitivity, of HPV testing for CIN grade 2 (moderate degree abnormalities) or 3 (severe degree of abnormality) was 94.6 percent, whereas the sensitivity of the Pap test alone was 55.4 percent. The sensitivity of both tests used together was 100 percent, and the specificity was 92.5 percent.37

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HPV DNA testing is substantially more sensitive in detecting CIN 2 or 3 than cytology but less specific (90.7 percent vs. 96.3 percent).38

**How can HPV genotyping be used in screening for HPV and cervical cancer?**

HPV genotyping can give providers more information about the type, or strain, of HPV infection an individual may have in order to determine the best future course of action.

National Cancer Institute studies indicate that women with HPV types 16 and 18 (which are further discussed below), have about a 20 percent risk of CIN 3 over 10 years, despite negative Pap tests. Therefore, women who test positive for either of these strains may benefit from immediate colposcopy in order to determine current and future needs.39

**What are the recommended next steps for an unclear or positive Pap test result?**

Women who receive an “unclear” or “abnormal” Pap test should receive further screening and/or treatment to prevent cervical cancer.

For women who receive an “unclear” or “inconclusive” Pap test result, an HPV DNA test may be helpful to determine if the cell changes are related to HPV. In a study of 11,000 women, the HPV test was shown to be 97 percent sensitive for cervical intraepithelial neoplasia (CIN2), or the presence of moderately abnormal cells on the cervix, compared to 77 percent for conventional Pap tests resulting in abnormal results.40

For women who receive an “abnormal” or “positive” Pap test, regardless of their HPV status, a colposcopy may be recommended in order to further determine if the cells are in fact abnormal and determine the best course of treatment. Colposcopy is not recommended for women who have an ASC-US Pap and negative HPV; rather they should continue with routine screening as per age specific guidelines.

**What is the best course of action for women who receive a normal Pap test but a positive HPV test?**

According to the CDC, women who receive a normal Pap test but a positive HPV test should get another Pap test and HPV test in one year.

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39 Cox JT, et al (2003). “Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy.” American Journal of Obstetrics and Gynecology 2003;188(6)
According to the 2012 ACS/ASCCP/ASCP Guidelines, as well as recommendations from ACOG, women with a positive HPV test but negative/normal Pap test results should be followed with either:

- Option 1: Repeat co-testing in 12 months or
- Option 2: Immediate HPV genotype-specific testing for HPV16 alone or for HPV16/18.

In the case of Option 1: If co-testing is repeated at 12 months, women testing positive on either test (HPV positive or LSIL or more severe cytology) should be referred to colposcopy. Women testing negative on both tests should return to routine screening.

In the case of Option 2: If immediate HPV genotype-specific testing is used, women testing positive for HPV16 or HPV16/18 should be referred directly to colposcopy. Women testing negative for HPV16 or HPV16/18 should be co-tested in 12 months, with management of results as described in Option 1.

**Can men be screened for HPV?**

Currently, there is no HPV test recommended for men. The only approved HPV tests on the market are for screening women for cervical cancer. However, men should be encouraged to check for any abnormalities on their penis, scrotum, or around the anus and report any warts, blisters, sores, ulcers, white patches, or other abnormal areas, even if they are not painful, to their doctor.