FROM GUIDELINES TO PRACTICE:

NEW INSIGHTS IN CERVICAL CANCER SCREENING

CURRENT CERVICAL CANCER SCREENING GUIDELINES

- The American Cancer Society (ACS), American Society for Colposcopy and Cervical Pathology (ASCCP), and American Society for Clinical Pathology (ASCP) recommend the following[1]:
  - o Women should begin cervical cancer screening at 21 years of age
  - o Women 21 to 29 years old should be screened with Pap testing alone every 3 years
  - o Women age 30 to 65 years should be screened with Pap testing plus human papillomavirus (HPV) testing (co-testing) every 5 years or Pap testing alone every 3 years
  - o Women with adequate negative prior screening should discontinue screening after age 65
- While interim guidance suggesting intervals for use of screening with HPV alone has been published, primary HPV screening, also referred to as HPV alone* in this document, is not currently recommended by major societies, as 2015 guidelines from the American College of Physicians include only Pap testing and co-testing as recommended strategies[2,3]

*A positive HPV screening result may lead to further evaluation with cytology and/or colposcopy.

Pap plus HPV testing is the preferred cervical cancer screening method for women 30 to 65 years old

AGE GROUP	RECOMMENDATIONS
<21 Years	No routine speculum exam or cytology regardless of age of onset of intercourse or other risk factors.
21–29 Years	Screening with cytology alone every 3 years.
30–65 Years	Co-testing every 5 years (preferred), or cytology alone every 3 years (acceptable).
>65 Years	Discontinue screening after age 65 following adequate negative prior screening. However, women with a history of cervical intraepithelial neoplasia grade 2 or worse diagnosis should continue screening for at least 20 years.

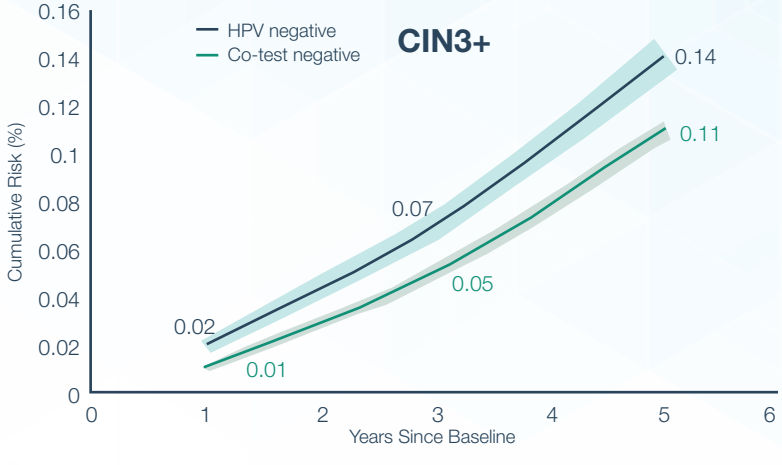
REFERENCES

1. Saslow D, et al. *CA Cancer J Clin*. 2012;62(3):147-72.
2. Huh WK, et al. *Gynecol Oncol.* 2015;136(2):178-82.
3. Sawaya GF, et al. *Ann Intern Med.* 2015;162(12):851-9.

RECOMMENDATION: Screening with Pap Plus HPV Together (Co-testing) Should Remain the Preferred Method of Screening for Women 30 to 65 Years of Age

- Co-testing detects more precancerous lesions (cervical intraepithelial neoplasia and worse, CIN3+) than screening with HPV alone
- In a study of more than a million women, the risk of developing CIN3+ within 3 years of screening was 29% lower in women who were co-test negative vs women who tested HPV negative (Figure A)[1]
- In 7 European studies, CIN3+ was later detected in 24% fewer women who were co-test negative compared with women who tested negative for HPV at baseline screening over a 6-year follow-up period[2]

A. Risk of women developing CIN3+ following screening with HPV alone vs co-testing at 1-, 3-, and 5-year intervals[1]



Pap plus HPV testing together is more sensitive for detecting precancerous lesions than screening with HPV alone[1]

REFERENCES

1. Graph adapted from: Gage JC, et al. *J Natl Cancer Inst*. 2014;106(8). pii: dju153.

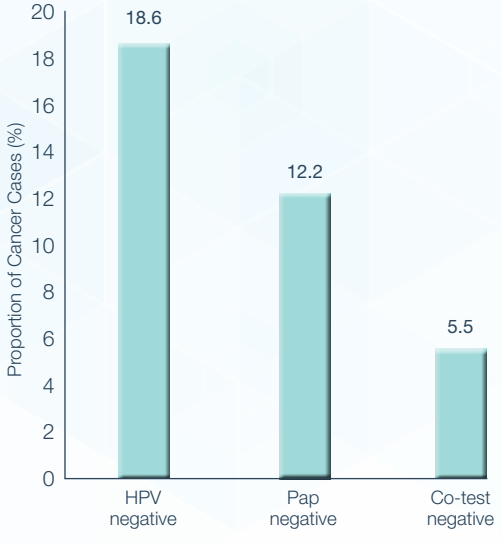
2. Dillner J, et al. *BMJ*. 2008;337:a1754.

Pap HPV Together

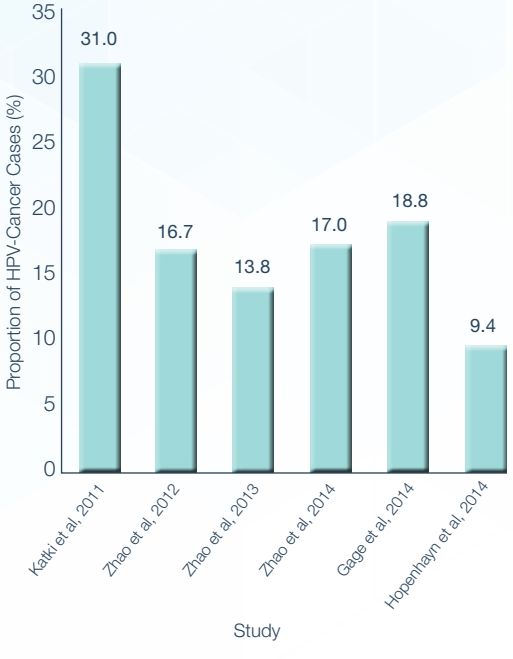
Screening with Pap Plus HPV Together (Co-testing) Provides Greater Reassurance against Cervical Cancer than Screening with HPV Alone

- Studies have consistently shown that screening with HPV alone misses more cases of cervical cancer than screening with co-testing[1–7]
- A study of over a million women in the Kaiser Permanente Health System found that, among 405 cases of cervical cancer detected during the study, 18.8% were HPV negative compared with 12.3% that were co-test negative[1]
- Investigation of screening results from over 250,000 women in the Quest Diagnostics Health Trends study found that, among 526 women with cancer, 18.6% tested negative for HPV less than 1 year prior to cancer detection, while only 5.5% were co-test negative less than 1 year before diagnosis (Figure A)[2]
- Several studies have reported similar results, with HPV testing alone failing to detect between 9% and 31% of cervical cancer cases (Figure B)[1,3–7]

A. Number of cases of cervical cancer with various screening results <1 year prior to diagnosis.[2] Graph adapted from Blatt et al.[2]



B. Summary of cervical cancer cases that tested negative for HPV over several recent studies[1, 3–7]



The clinical studies represented within these sources were conducted using different study designs and various assays. Products included hc2, cob as 4800, ThinPrep®, SurePath, Linear Array, INNO-LiPA Genotype test.

REFERENCES

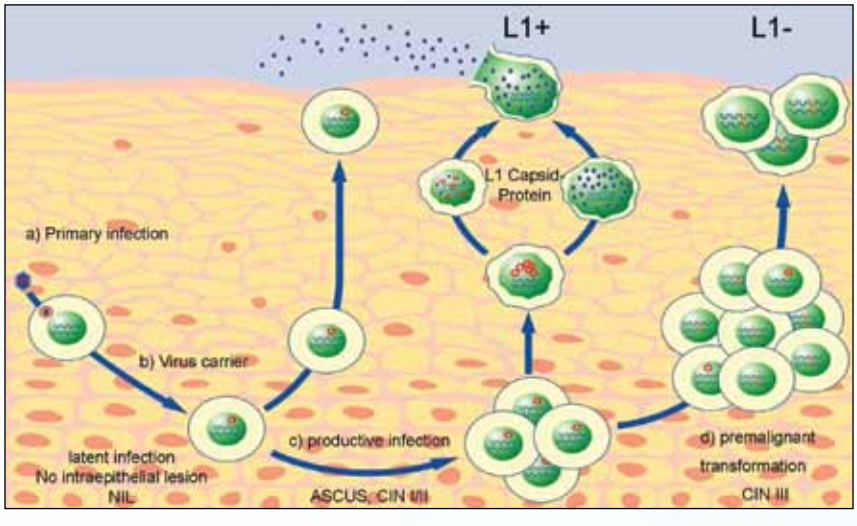
1. Gage JC, et al. *J Natl Cancer Inst*. 2014;106(8). pii: dju153.
2. Graph adapted from: Blatt AJ, et al. *Cancer Cytopathol*. 2015;123(5):282-8.
3. Katki HA, et al. *Lancet Oncol*. 2011;12(7):663-72.
4. Zhao Y, et al. *J Med Virol*. 2012;84(12):1920-7.
5. Zhao C, et al. *Am J Clin Pathol*. 2013;140(1):47-54.
6. Zhao C, et al. *Arch Pathol Lab Med*. 2014;138(1):16-24.
7. Hopenhayn C, et al. *J Low Genit Tract Dis*. 2014;18(2):182-9.

Additional Benefits of Pap Testing

- In the Quest Diagnostics Health Trends study, among 169 adenocarcinomas detected, 26.6% were HPV negative less than one year prior to diagnosis compared with 8.3% that were co-test negative[1]
- Levels of HPV L1 DNA decrease as cancer progresses, suggesting that advanced cervical diseases could be missed with an L1 DNA HPV test (Figure A)[2]

Detecting adenocarcinoma and providing additional reassurance are among the additional benefits conferred by **Pap plus HPV testing** together[1,2]

A. Schematic of HPV L1 deletion. Figure from Hilfrich[3]



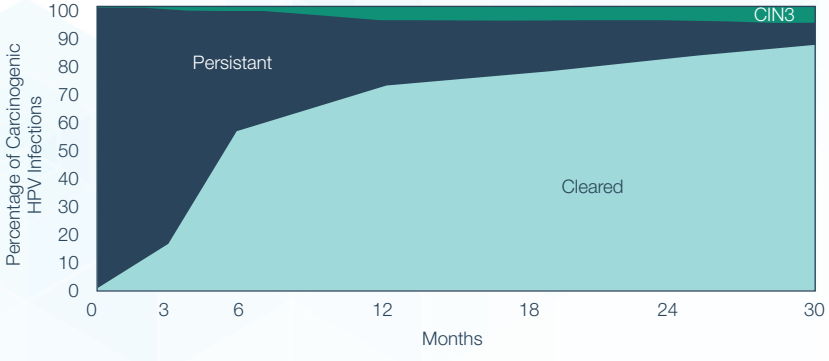
REFERENCES
1. Blatt AJ, et al. *Cancer Cytopathol*. 2015;123(5):282-8.
2. Tjalma WA, et al. *Eur J Obstet Gynecol Reprod Biol.* 2013;170(1):45-6.
3. "Ralf Hilfrich (2013). HPV L1 Detection as a Prognostic Marker for Management of HPV High Risk Positive Abnormal Pap Smears, Human Papillomavirus and Related Diseases From Bench to Bedside A Diagnostic and Preventive Perspective, Dr. Davy Vanden Broeck (Ed.), InTech, DOI: 10.5772/55902. Available from: http://www.intechopen.com/books/human-papillomavirus-and-related-diseases-from-bench-to-bedside-a-diagnostic-and-preventive-perspective/hpv-l1-detection-as-a-prognostic-marker-for-management-of-hpv-high-risk-positive-abnormal-pap-smears"

Pap HPV Together

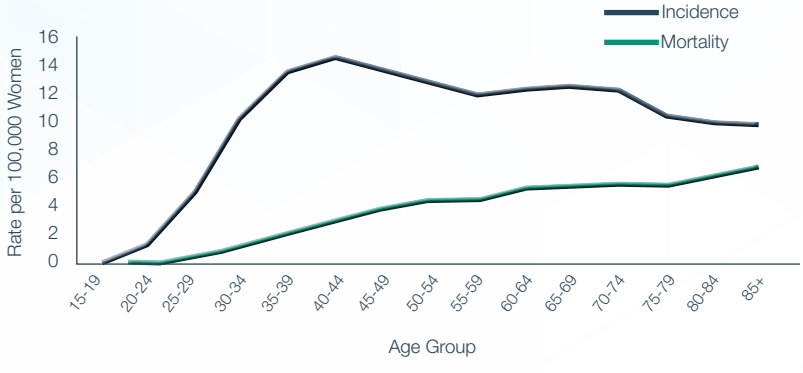
Recommendation: Pap Testing Every 3 Years Should Remain the Primary Screening Strategy for Women 21 to 29 Years of Age

- Cervical cancer is associated with persistent HPV infections. In young women who have recently become sexually active, the rate of HPV infection is high, but the large majority of those infections clear on their own (Figure A)[2]
- Women under age 30 are unlikely to develop cervical cancer (Figure B),[3] and overtreatment of these women may represent a clinical concern because treatment of cervical lesions can be associated with pregnancy complications such as preterm birth[4,5]
- Positive HPV results have been associated with increased anxiety shortly after testing[6] and can result in women reporting worse feelings about their previous and future sexual relationships[7]
- The New Technologies for Cervical Cancer study found that screening with HPV alone resulted in overdiagnosis of cervical lesions in women 25 to 34 years old[8]
- In 2012, the ACS, ASCCP, and ASCP recommended that, "because of the high prevalence of HPV in women under the age of 30, HPV testing should not be used to screen women in this age group due to the potential harms"[9]

A. Clearance of high-risk HPV infections over 30 months in women aged 21 to 29 years[1]



B. Cancer incidence and mortality per 100,000 women by age in the United States[10]



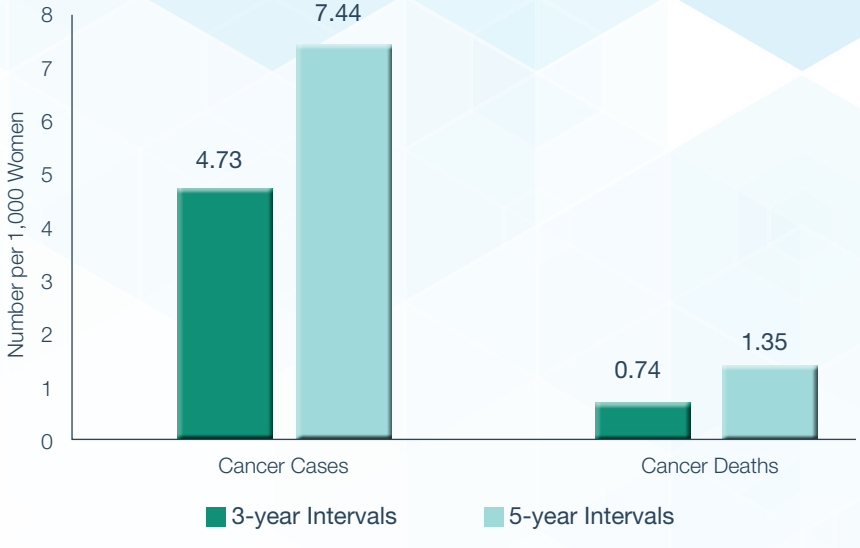
REFERENCES

1. Rodriguez AC, et al. *J Natl Cancer Inst.* 2008;100(7):513-7.
2. Markowitz LE, et al. *J Infect Dis.* 2013;208(3):385-93.
3. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Cancer Stats 2000-2006. Bethesda, MD: National Cancer Institute; 2015.
4. Kitson SJ, et al. *Eur J Obstet Gynecol Reprod Biol.* 2014;180:51-5.
5. Miller ES, et al. *AJOG*. 2014;211(3):242 e1-4.
6. McCaffery KJ, et al. *BMJ*. 2010;340:b4491.
7. McCaffery K, et al. *BJOG*. 2004;111(12):1437-43.
8. Ronco G, et al. *Lancet*. 2014;383:524-32.
9. Saslow D, et al. *CA Cancer J Clin*. 2012;62(3):147-72.
10. National Cancer Institute. Cervix Uteri Cancer. http://seer.cancer.gov/statfacts/html/cervix.html. Accessed March 30, 2016.

Recommendation: The Interval for Screening Women Over 30 with Pap Plus HPV Together (Co-testing) Should be Changed from 5 Years to 3 Years

- A model of the outcomes associated with various cervical cancer screening strategies published by the United States Preventative Services Task Force in 2013 found that lengthened screening intervals may result in appreciable increases in cervical cancer cases[1]
- Lengthening screening intervals from 3 years to 5 years is estimated to double cervical cancer cases (Figure A), with an additional 1/369 women in the United States being diagnosed with cervical cancer using a 5-year interval[1,2]

A. Estimated cancer cases and deaths per 1,000 women over a lifetime for a screening strategy beginning with Pap testing every 3 years at age 21, then co-testing at 3- vs 5-year intervals beginning at age 30[2]



Lengthening screening intervals from 3 to 5 years may substantially increase cervical cancer cases and deaths[1–3]

SCREENING INTERVALS

REFERENCES

1. Kinney W, et al. *Obstet Gynecol.* 2014;125(2):311-5.

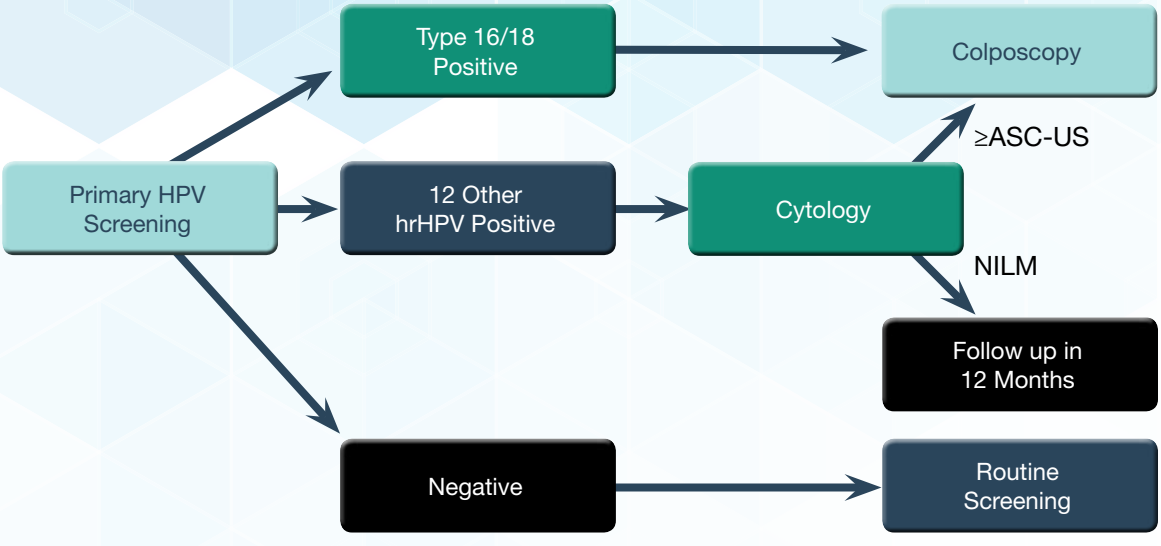
2. Kulasingam SL, et al. *J Low Genit Tract Dis*. 2013;17:193-202.

Pap HPV Together

COMMON PERCEPTIONS
"SCREENING WITH HPV ALONE IS EASIER"

- The screening algorithm put forth by the interim guidance document is complicated, confusing, and invites more risk of disease than screening with Pap plus HPV together (Figure A)[1]

A. Screening algorithm for screening with HPV alone



Current interim guidance for **screening with HPV alone** is complex and adherence may be a challenge

REFERENCES

1. Huh WK, et al. *Gynecol Oncol*. 2015;136(2):178-82.

COMMON PERCEPTIONS

"PATIENTS WILL BE UNAFFECTED BY ADDITIONAL CHANGES IN CERVICAL CANCER SCREENING"

Screening with HPV Alone and Extended Screening Intervals Cause Patient Anxiety

- A survey of women's perceptions of cervical screening practices found that the majority of women screened reported that they would prefer to continue to receive Pap testing, with approximately 40% reporting that they would be anxious if they received screening with HPV alone[1]
- Another study found that 68.4% of women surveyed were willing to attend cervical screening every 3 years, while only 25.2% were willing to adopt a 5-year screening interval[2]
  - o The stigma surrounding a positive HPV test has been found to affect anxiety, but cancer risk and the potential for cervical lesions are of greater concern[3,4]
  - o There is some evidence that HPV testing does not increase women's anxiety when it is combined with Pap testing[5]

Women may be resistant to changes in screening intervals and methodology associated with changes in cervical screening technology

PERCEPTIONS

REFERENCES

1. Cooper CP, et al. *Am J Prev Med.* 2015;49:e99-e107.
2. Silver MI, et al. *Obstet Gynecol.* 2015;125(2):317-29.
3. Giorgi Rossi P, et al. *Front Oncol*. 2014;10(4):20.
4. O'Connor M, et al. *BJOG*. 2014;121(11):1421-30.
5. Kitchener HC, et al. *Int J Gynecol Cancer*. 2008;18(4):743-8.

Pap HPV Together

COMMON PERCEPTIONS

"SCREENING WITH HPV ALONE IS CHEAPER"

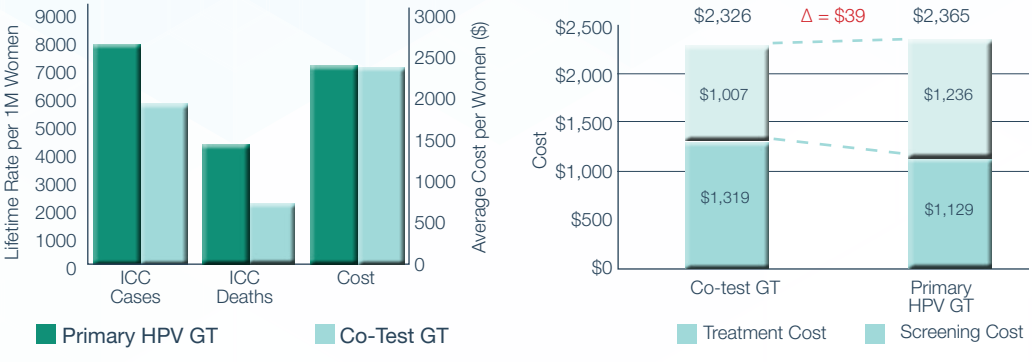
One Screening Test is not more Cost-Effective than Two

- Several factors affect the relative costs of screening with HPV alone vs with Pap plus HPV together (co-testing):
  - o Test performance (sensitivity/specificity)
  - o Test costs
  - o Treatment costs
- A cost-effectiveness model comparing different cervical screening strategies found that an HPV-alone screening strategy that included genotyping for 2 high-risk strains, HPV 16/18, reduced costs with similar effectiveness to a co-testing strategy that did not include genotyping for HPV 16/18[1]
- Further investigation of the cost-effectiveness of co-testing with HPV 16/18 genotyping compared with screening with HPV with HPV 16/18 genotyping alone found that co-testing provided greater clinical benefit at similar costs (Figure A)[2]

Model assumptions:

- Co-testing at 3 years vs 5 years
- Screening with an mRNA-based HPV test and liquid-based cytology, compared to HPV alone screening with a DNA-based test

A. Lifetime cervical cancer incidence and mortality, and average cost per woman, for co-testing with HPV 16/18 genotyping vs screening with HPV alone with HPV 16/18 genotyping.[2]



This data is intended for insurers.
1M: 1 million — HPV: Human papillomavirus — ICC: Invasive Cervical Cancer

REFERENCES

1. Huh WK, et al. *Appl Health Econ Health Policy*. 2015;13:95-107.

2. Felix JC, et al. *Journal of Women's Health*. 2016 [epub ahead of print]

CERVICAL CANCER SCREENING: THE FUTURE

Summary of Recommendations

- **Maintain Pap plus HPV together (co-testing)** as the preferred method for cervical cancer screening in women ≥30 years old
- **Change the interval for co-testing** women ≥30 years old from every 5 years to every 3 years
- **Recommend that women 21 years of age** begin cervical cancer screening with Pap testing every 3 years and not begin HPV screening until ≥30 years old

Pap + HPV Together

REFERENCES

1. Blatt AJ, et al. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. *Cancer Cytopathol.* 2015;123(5):282-8. doi:10.1002/cncy.21544
2. Cooper CP, et al. Acceptable and Preferred Cervical Cancer Screening Intervals Among U.S. Women. *Am J Prev Med*. 2015;49:e99-e107. doi: 10.1016/j.amepre.2015.04.02
3. Dillner J, et al. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. *BMJ*. 2008;337:a1754. doi:10.1136/bmj.a1754
4. Felix J, et al. The Clinical and Economic Benefits of Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening: A Modeling Analysis. *J Womens Health* (Larchmt). 2016 Mar 29. [Epub ahead of print.]
5. Gage JC, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. *J Natl Cancer Inst*. 2014;106(8): pii: dju153. doi:10.1093/jnci/dju153
6. Giorgi Rossi P, et al. The Possible Effects on Socio-Economic Inequalities of Introducing HPV Testing as Primary Test in Cervical Cancer Screening Programs. *Front Oncol.* 2014;4:20. doi: 10.3389/fonc.2014.00020
7. Hilfrich R (2013). HPV L1 Detection as a Prognostic Marker for Management of HPV High Risk Positive Abnormal Pap Smears, Human Papillomavirus and Related Diseases From Bench to Bedside A Diagnostic and Preventive Perspective, Dr. Davy Vanden Broeck (Ed.), InTech, DOI: 10.5772/55902. Available from: http://www.intechopen.com/books/human-papillomavirus-and-related-diseases-from-bench-to-bedside-a-diagnostic-and-preventive-perspective/hpv-l1-detection-as-a-prognostic-marker-for-management-of-hpv-high-risk-positive-abnormal-papsmears
8. Hopenhayn C, et al. Prevalence of human papillomavirus types in invasive cervical cancers from 7 US cancer registries before vaccine introduction. *J Low Genit Tract Dis*. 2014;18(2):182-9. doi: 10.1097/LGT.0b013e3182a577c7
9. Huh, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. *Gynecol Oncol*. 2015;136(2):178-182. doi:10.1016/j.ygyno.2014.12.022
10. Huh WK, et al. Cost effectiveness of human papillomavirus-16/18 genotyping in cervical cancer screening. *Appl Health Econ Health Policy*. 2015;13:95-107. doi: 10.1007/s40258-014-0135-4
11. Katki HA, Kinney WK, Fetterman B, et al. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. *Lancet Oncol*. 2011;12(7):663-72. doi:10.1016/S1470-2045(11)70206-6
12. Kinney W, et al. Increased cervical cancer risk associated with screening at longer intervals. *Obstet Gynecol*. 2015;125(2):311-5. doi: 10.1097/AOG.0000000000000632
13. Kitchener HC, et al. The psychosocial impact of human papillomavirus testing in primary cervical screening-a study within a randomized trial. *Int J Gynecol Cancer.* 2008 Jul-Aug;18(4):743-8.
14. Kitson SJ, et al. Predictive value of volume of cervical tissue removed during LLETZ on subsequent preterm delivery: a cohort study. *Eur J Obstet Gynecol Reprod Biol*. 2014;180:51-5. doi: 10.1016/j.ejogrb.2014.06.011
15. Kulasingam SL, et al. Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. *J Low Genit Tract Dis.* 2013;17:193-202. doi: 10.1097/LGT.0b013e3182616241
16. Markowitz LE, et al. Reduction in human papillomavirus (HPV) prevalence among young women following HPV vaccine introduction in the United States, National Health and Nutrition Examination Surveys, 2003-2010. *J Infect Dis*. 2013;208(3):385-93. doi: 10.1093/infdis/jit19
17. McCaffery KJ, et al. Psychosocial outcomes of three triage methods for the management of borderline abnormal cervical smears: an open randomised trial. *BMJ*. 2010;340:b4491. doi: 10.1136/bmj.b4491
18. McCaffery K, et al. Testing positive for human papillomavirus in routine cervical screening: examination of psychosocial impact. *BJOG*. 2004;111(12):1437-43.
19. Miller ES, et al. The association between cervical excisional procedures, midtrimester cervical length, and preterm birth. *Am J Obstet Gynecol.* 2014;211(3):242 e1-4. doi: 10.1016/j.ajog
20. National Cancer Institute. Surveillance, Epidemiology and End Results (SEER) Cancer Stats 2000-2006. Bethesda, MD: National Cancer Institute; 2015 Accessed March 30, 2016.
21. NCI's Division of Cancer Control and Population Sciences. Cancer of the Cervix Uteri (Invasive). Cancer Statistics National Cancer Institute. Cervix Uteri Cancer. http://seer.cancer.gov/statfacts/html/cervix.html. Accessed March 30, 2016. http://seer.cancer.gov/csr/1975_2012/browse_csr.php?sectionSEL=5&pageSEL=sect_05_table.07.html. Accessed February 4, 2016.
22. Rodriguez AC, et al. Rapid clearance of human papillomavirus and implications for clinical focus on persistent infections. *J Natl Cancer Inst*. 2008;100(7):513-7. doi: 10.1093/jnci/djn044 2008;100:513-7
23. Ronco G, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383:524-32. doi: 10.1016/S0140-6736(13)62218-7
24. Saslow D, et al. ACS-ASCCP-ASCP Cervical Cancer Guideline Committee (2012), American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *CA: A Cancer Journal for Clinicians*. 2012;62(3):147–72. doi: 10.3322/caac.21139
25. Sawaya GF, et al. Cervical Cancer Screening in Average-Risk Women: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians. *Ann Intern Med.* 2015;162(12):851-9. doi:10.7326/M14-2426 4
26. Silver MI, et al. Patient concerns about human papillomavirus testing and 5-year intervals in routine cervical cancer screening. *Obstet Gynecol*. 2015;125(2):317-29. doi:10.1097/AOG.0000000000000638
27. Tjalma WA, et al. Cervical cancer screening: which HPV test should be used--L1 or E6/E7? *Eur J Obstet Gynecol Reprod Biol*. 2013;170(1):45-6. doi: 10.1016/j.ejogrb.2013.06.027
28. Zhao C, et al. Cervical screening test results associated with 265 histopathologic diagnoses of cervical glandular neoplasia. *Am J Clin Pathol*. 2013;140(1):47-54. doi: 10.1309/AJCPIP9M8HPVBSSC
29. Zhao C, et al. Prior High-Risk Human Papillomavirus Testing and Papanicolaou Test Results of 70 Invasive Cervical Carcinomas Diagnosed in 2012: Results of a Retrospective Multicenter Study. *Arch Pathol Lab Med*. 2015 Feb;139(2):184-8. Epub 2014 Apr 2 2014;138(1):16-24 . doi.org/10.5858/arpa.2014-0028-OA
30. Zhao, Y., Cao, X., Zheng, Y. et al. Relationship between Cervical Disease and Infection with Human Papillomavirus Types 16 and 18, and Herpes Simplex Virus 1 and 2. *J Med Virol*. 2012 84(12):1920-7. doi: 10.1002/jmv.23353

Pap HPV Together