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Primary HPV Testing vs. Co-testing for Cervical Cancer Screening

Outcome and Economic Support that Co-testing is Superior

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Introduction and Overview

Consensus in US cervical cancer screening guidelines currently state that Pap plus human papillomavirus (HPV) testing for women aged 30 to 65 years is recommended; cytology alone is recommended for women aged 21 to 29.* In 2014, the FDA approved a DNA HPV test for primary cervical cancer screening in women 25 years and older. This article provides foundational evidence demonstrating the diagnostic superiority of co-testing compared with primary high-risk HPV testing alone (HPV testing). Using an extensive modeling analysis, a screening span of up to 40 years, and a constructed cohort of 1 million women, we predicted that co-testing would result in thousands of fewer invasive cervical cancer cases and deaths and would save the healthcare system $39 million over the 40 years, as compared to a strategy using primary HPV testing alone. These findings are not only relevant when considering Women's Healthcare policies, but they also direct attention to real-world outcomes and economics critical to selecting the best strategies for cervical cancer screening.

Where the Story Begins

The incidence of cervical cancer in the US has declined dramatically over the last half century and continues to decline to this day. In 1975, the incidence of cervical cancer was 14.8 per 100,000 women; by the year 2013 that number was only 6.4 per 100,000. Similarly, the mortality due to cervical cancer during the same period was reduced from 5.6 to 2.3 women per 100,000.**
It is widely accepted that secondary prevention of cervical cancer, i.e., the detection and eradication of precancerous lesions, is almost entirely responsible for this observed reduction, and clearly the most important step at which to intervene.[1]

The Pap test, developed by George Papanicolau in 1941, gained widespread use in the 1960s and became a part of a well-woman exam. Although many have questioned the clinical sensitivity of the Pap test, its efficacy in reducing cervical cancer is unchallenged. In the US, the Pap test is thought to be responsible for an 80% reduction in the incidence of cervical cancer.[2] Comparing rates of cervical cancer from countries that have implemented national screening programs, such as Great Britain, to countries where no such programs exist, such as Brazil, shows astonishing differences. While the incidence in both countries is similar in women under the

*Available at: http://www.cdc.gov/cancer/cervical/pdf/guidelines.pdf

**Available at: http://seer.cancer.gov/statfacts/html/cervix.html

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age of 30, the incidence of cervical cancer in the unscreened population becomes more than triple that of the screened population by the sixth decade of life *(Figure 1)*.[3]

The role of HPV in the development of precancerous and cancerous lesions of the cervix is now well established. HPV is accepted as the single, necessary cause of all cervical cancers.[4] The presence of high-risk or oncogenic HPV is predictive of the presence or development of cervical cancer and its precursor lesions.[5] Therefore, it is reasonable to conclude that detection of HPV in the genital tract would be of great use in the identification of women at risk for developing cervical precancer and cancer. But is that really the end of the story? What have findings in real-world clinical practice taught us about how best to incorporate HPV testing into cervical cancer screening?

Getting Beyond Smoke and Mirrors

The concurrent use of a Pap and HPV test reduces the incidence of cervical precancers and cervical cancers significantly more than the use of either test by itself. Using pooled data from seven HPV screening studies in Europe, Dillner and colleagues[6] showed a greater reduction in CIN3+ disease in women who were cotested than women who were screened with HPV testing alone. More specifically, CIN3+ disease was found in 24% fewer women who were cotest-negative compared with women who were HPV-negative at baseline over a 6-year follow-up.

Recently, two large US clinical laboratories extracted cervical cancer screening results and follow-up data from their databases with the aim of providing insight into the "real-world" performance of Pap only, HPV only and Pap+HPV screening approaches.[7,8] The results revealed that co-testing with Pap+HPV identified more cervical precancers and invasive cancers than the HPV or Pap test alone.

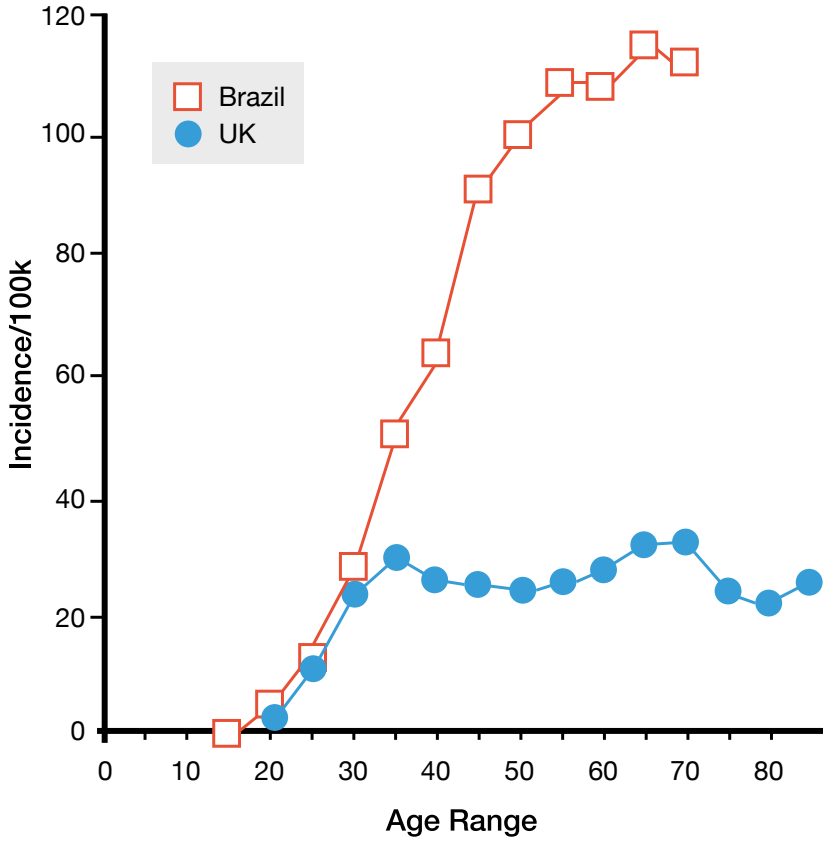


Figure 1. Modified from Bosch FX and de Sanjose S.[3]

Data from an earlier study examining real-life screening scenarios had already challenged the sensitivity of HPV testing alone in the detection of precancer and cancer, which was published in more formally conducted clinical trials. In the study of more than 1 million women, Gage and colleagues[9] demonstrated that risk of developing CIN3+ disease within 3 years of screening was 29% lower in women who were cotest-negative, as compared with women who tested HPV negative. Furthermore, among 405 cases of cervical cancer detected during the study, nearly 19% were HPV-negative compared with just over 12% of women who were cotest-negative.

The case in favor of primary HPV screening has been made largely on the basis of cost. The obvious assumption is that adding the cost of an additional test would result in a higher financial burden to the screening program. Furthermore, when tests are run concurrently it is assumed that they render a higher number of positive results, leading to increased numbers of women who are sent to follow-up. This then lowers clinical specificity and further increases cost to the system. That said, cost effectiveness studies challenging these assumptions have only recently emerged and additional studies are likely needed in the future.

Patient Outcomes and Economic Superiority for Co-testing vs. Primary HPV Screening

With a deep understanding of the clinical aspects of cervical cancer screening and the need to better parce out the financial ramifications of any proposed changes to screening, our group undertook a detailed cost-effectiveness analysis.[10] When comparing these strategies there are several

factors to consider. In this analysis, we focused on a comparison of currently available screening algorithms in women >30 (cytology alone, co-testing, and HPV primary screening).

The cobas® HPV test (Roche Holding AG) is the only HPV assay currently approved by the FDA for primary HPV screening in the US. For this reason, only data generated with the cobas® HPV test should be used when evaluating cost-effectiveness of primary HPV screening in the US. Although four HPV assays currently have an indication for use as an adjunct test in women over 30, making it possible to utilize additional data sets for cost-effectiveness analyses of a co-testing approach, not all HPV assays have the same performance characteristics. Data from clinical studies show that the sensitivity of all FDA-approved HPV assays is similar, but that an increased clinical specificity is observed with the mRNA-based Aptima HPV assay (Hologic, Inc) compared to the three DNA-based HPV assays.[11-15] In addition, the mRNA HPV test is currently the most widely used test in clinical practice in the United States [College of American Pathologists (CAP).[16] For these reasons, it is reasonable and appropriate to utilize the mRNA test when comparing the different screening strategies. Doing so will provide more real-world estimates for related test and treatment costs.

A 3-year interval for both strategies was employed as there is a known increase in the risk of invasive cervical cancer when extending the interval or co-testing to 5 years.[17] Use of the 3-year interval is not only within the recommended guidelines for screening outlined by the US Preventative Services Task Force (USPSTF) but it is also the most commonly adhered to strategy in the US.[18-20] Finally, we chose to model the co-testing group to include genotyping for not only women with negative Pap test, but those with positive HPV tests, as well. This is concordant with ASCCP guidelines and current clinical practice, since its inclusion streamlines patients at high risk for already harboring a lesion to immediate colposcopy. We used a health state transition (Markov) model, incorporating epidemiologic, clinical and economic data from healthcare databases and published literature, to enter a hypothetical cohort of one-million 30 year-old women receiving triennial cervical cancer through age 70.

Screening strategies compared screening with HPV alone to co-testing. Outcomes included: total and incremental differences in costs, invasive cervical cancer cases and deaths, number of colposcopies, and quality-adjusted life years for cost-effectiveness calculations.

In terms of total cost, a key focus for this article, our cost accounting included:

- All costs associated with diagnostic tests and procedures (including colposcopy and biopsy), additional and repeat testing, medical office visits, cancer treatment costs, and end-of-life care.
- Costs for diagnostic tests and procedures derived from current payment levels using the Truven Health Analytics MarketScan Research Databases (Truven Health Analytics).
- Treatment costs for CIN2 or CIN3 were taken from a recent study on the costs of care for these patients, and treatment of CIN2/3 was assumed to be 100% successful. CIN1 was assumed to not be treated and therefore did not incur added costs if discovered.[21]
- Costs for treating invasive cervical cancer were split into three components to account for high initial costs of care and lower costs in subsequent years for surviving patients.[22]
- For terminal invasive cervical cancer, an additional cost accounting for end-of-life care was added to either the initial or subsequent year depending on the age of death.[22]

Modeling Analysis Supports Co-testing as Preferred Cervical Cancer Screening Strategy[10]

The results of our analysis shows co-testing with the use of a highly specific HPV assay is not only clinically superior but also provides a cost-effective and potentially long-term cost-saving way of screening for cervical cancer compared to primary HPV screening. The model reveals that screening women with HPV testing alone would result in an additional 21 cases and an additional 20 deaths from cervical cancer per 100,000 women. It also predicts that the costs associated with screening and managing women using this strategy are higher than those using co-testing. In fact, when using co-testing, there was a $39 savings per woman over the 40-year screening period when compared to screening using HPV testing alone. When projected to the one-million woman cohort, the model predicts that using co-testing results in 2,141 fewer cases and 2,041 fewer deaths from cervical cancer, while achieving $39 million in savings when compared to screening using HPV testing alone. Co-testing also resulted in slightly fewer lifetime colposcopies per woman, fewer false positive colposcopies, and a higher number of true positive colposcopies. If one applies the results of this model to the total screening population of the US, the model predicts that using HPV testing alone, rather than co-testing, would result in approximately 150,000 additional cases of cervical cancer and more than 100,000 cervical cancer deaths, while costing an additional $4.4 billion in health care costs over the 40-year screening period.

What about women ages 25 through 29?

Our study also evaluated the strategy of primary HPV screening in a population of 25-29 year old women and compared it to screening with the Pap alone with reflex to HPV for an ASCUS result. The model predicted a slight decrease in the incidence of cervical cancer in that age group (0.51 vs. 0.26 per 10,000 women); however, it failed to predict a significant decrease in mortality (0.03 vs. 0.02 per 10,000 women). In this age group, the cost-efficacy of primary HPV screening as calculated using an incremental cost-effectiveness ratio (ICER) shows that the strategy of screening women with HPV alone has an ICER of over

$425,000 when the accepted ICER in the United States is considered to be $50,000. This shows that the strategy of screening women in this age group may not be cost-effective.

Although mathematical models, such as the one used by our group, are highly dependent on the conditions and data utilized, there is little argument that co-testing is more effective than primary HPV screening at preventing the incidence of mortality from cervical cancer. Huh and colleagues found a slight cost benefit of HPV testing alone using an algorithm that did not include the use of the Aptima HPV assay or genotyping, and followed a 5-year interval in the co-testing arm.[23] In contrast, we chose a more clinically-relevant path that uses the current standard of care screening interval in the US, genotyping for Pap negative/HPV-HR positive cotests, and an mRNA HPV test with greater specificity.[10] Under these conditions, our findings are in contrast to the findings by Huh and colleagues and demonstrates that in a setting more closely representing clinical practice in the US, co-testing represents a cost-effective screening method over HPV alone.

In conclusion, co-testing has been successfully implemented into practice in the United States and recent data shows a continued decline in cervical cancer rates. Prior to changing such a successful strategy, it is incumbent on all of us to ensure that any replacement strategy performs equally as well or at least in a similar fashion, and indeed, presents tangible cost-savings. The results of our study, summarized above, does just that. In fact, the model strongly supports that co-testing remains the preferred approach for cervical screening in women aged 30 to 65, since this strategy, when compared with screening using HPV testing alone, decreases invasive cervical cancer cases and deaths and provides substantial long-term cost savings to the healthcare system. As clinicians and laboratory directors, it is time to refocus attention on the merits of selecting cervical cancer screening strategies that, in clinical practice, reflect real-world outcomes.

References

1. Schiffman M, Castle PE. The promise of global cervical-cancer prevention. N Engl J Med. 2005;353:2101-04.
2. Herrero R. Epidemiology of cervical cancer. J Natl Cancer Inst Monogr. 1996;21:1-6.
3. Boche FX, de Sanjose S. Chapter 1. Human Papillomavirus and cervical cancer. Burden and assessment of causality. J Natl Cancer Inst Monogr. 2003;31:3-13.
4. Wright TC Jr, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screeing. N Engl J Med. 2003;348(6):489-90.
5. Clavel C, Masure M, Bory J-P et al. Human papillomavirus testing in primary screening for the detection of high-grade cervical lesions: a study of 7932 women. Br J Cancer. 2001:84:1616-23.
6. Dillner J, Rebolj M, Birembaut P, et al. Long-term predictive values of cytology and human papillomavirus testing in cervical cancer screening: Joint European cohort study. BMJ. 2008:337:a1754.
7. Blatt AJ, Kennedy R, Luff RD, Austin RM, Rabin DS. Comparison of cervical cancer screening results among 256,648 women in multiple clinical practices. Cancer Cytopathol. 2015; 123(5):282-88.
8. Zhou H, Mody RR, Luna E, et al. Clinical performance of the food and drug administration-approved high-risk HPV test for the detection of high-grade cervicovaginal lesions. Cancer Cytopathol. 2016;124:317-23.
9. Gage JC, Schiffman M, Katki HA, et al. Reassurance against future risk of precancer and cancer conferred by a negative human Papillomavirus test. J Natl Cancer Inst. 2014;106(8): dju153 doi:10.1093/nci/dju 153.
10. Felix JC, Lacey MJ, Miller JD, Lenhart M, Spitzer GM, Kulkarni R. The clinical and economic benefit of co-testing versus primary HPV testing for cervical cancer screening: A modeling analysis. J Womens Health. 2016;25(6):606-16.
11. Dockter J, Schroder A, Hill C, Guzenski L, Monsonego J, Giachetti C. Clinical performance of the APTIMA HPV assay for the detection of high-risk HPV and high-grade cervical lesions. J Clin Virol. 2009;45(Suppl 1):S55-61.
12. Overstad IT, Vennestrom U, Andersen L, et al. Comparison of different commercial methods for HPV detection in follow-up cytology after ASCUS/LSIL, prediction of CIN2-3 in follow-up biopsies and spontaneous regression of CIN2-3. Gynecol Oncol. 2011;123(2):278-83.
13. CuzickJ, Cadman L, Mesher D, et al. Comparing the performance of six human papillomavirus tests in a screening population. Br J Cancer. 2013;108(4):908-13.
14. Szarewski A, Ambroisine L, Cadman L, et al. Comparison of predictors for high-grade cervical intraepithelial neoplasia in women with abnormal smears. Cancer Epidemiol Biomarkers Prev. 2008:17(11):3033-42.
15. Szarewski A, Mesher D, Cadman L. et al. Comparison of seven tests for high-grade cervical intraepithelial neoplasia in women with abnormal smears: the Predictors 2 study. J Clin Microbiol. 2012;50(6):1867-73.
16. College of American Pathologists (CAP). Human papillomavirus for cytology laboratories CHPVD, CHPVM, CHPVK, CHPVJ Participant Summary. Washington, DC: CAP, 2015.
17. Kinney W, Wright TC, Dinkelspiel HE, DeFrancesco M, Cox TJ, Huh W. Increased cervical cancer risk associated with screening at longer intervals. Obstet Gynecol. 2015;125(2):311-5.
18. Verilli L, Winer RL, Mao C. Adherence to cervical cancer screening guidelines by gynecologists in the Pacific Northwest. J Low Genit Tract Dis. 2014;18(3):228-34.
19. King NR, Kasper KM, Daggy JK, Tucker-Edmonds B. Current practice patterns in cervical cancer screening in Indiana. AJOG. 2014;210(3):265.e1-e8.
20. Kulasingan SL, Havrilesky LJ, Ghebre R. Myers ER. Screening for cervical cancer: a modeling study for the US Preventive Services Task Force. J Low Genit Tract Dis. 2013:17(2):193-202.
21. Vijayaraghavan A, Efrusy MB, Goodman KA, Santas CC, Huh WK. Cost-effectiveness of using human papillomavirus 16/18 genotype triage in cervical cancer screening. Gynecol Oncol. 2010;119:237-42.
22. Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML. Projections of the cost of cancer care in the United States: 2010-2020. J Natl Cancer Inst. 2011;103:117-28.
23. Huh WK, Williams E, Huang J, Bramley T, Poulios N. Cost effectiveness of human papillomavirus-16/18 genotyping in cervical cancer screening. Appl Health Econ Health Policy. 2015:13(1):95-107.

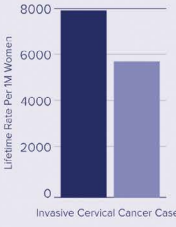
NEW CLINICAL-ECONOMIC MODELING STUDY SHOWS:
PAP+HPV TOGETHER™ COULD PROVIDE BETTER CLINICAL AND ECONOMIC OUTCOMES THAN SCREENING WITH HPV-ALONE*[1]

Co-testing could prevent more cases of invasive cervical cancer and cost the health care system less money over time, study shows.

The power of Pap+HPV Together is easy to see...

...when based on clinical and economic data modeling.†[1]

Adopting screening with HPV-Alone* and eliminating the Pap test from frontline screening could result in a:



37% increase‡ in invasive cervical cancer cases for women age 30-70

...when measured in cervival cancer cases prevented. †[1]

Compared to screening with HPV-Alone*, the model predicted that over the next 40 years, screening with Pap+HPV Together using the Aptima HPV assay could:

Prevent nearly 150,000 cases of invasive cervical cancer

Save approximately $4 billion in U.S. health care costs§

...when new data strengthen the already strong case for Pap+HPV Together.[2]

Results from the largest retrospective study of cervical cancer screening strategies (the Quest Study) reinforce screening with Pap+HPV Together as the preferrred method for women ages 30-65.[3]

1 in 5

1 in 5 women (18.6%) with cervical cancer could be missed by screening with HPV-Alone*[2]

Cost Effectiveness = Clinical Benefit + Cost Savings { The cost of treating cancer was found to be the largest contributor to increased costs associated with screening with HPV-Alone.[1]

Why use mRNA?

mRNA-Based HPV Screening
Assesses the presence *and* activity of a high-risk HPV infection[4,5]

– VS –

DNA-Based HPV Screening
Assesses the presence of a high-risk HPV infection

24% Reduction in false positives[6]

mRNA-based screening provides the same excellent sensitivity as DNA-based screening, but offers increased specificity, which results in a 24% reduction in false positives.[6] Combined with the better sensitivity of the image-guided Pap test, this was the most influential factor in the incremental difference in cost savings.

The increased rate of false-positive results with DNA-based HPV testing could lead to:

- Unnecessary procedures and overtreatment[6]
- Increased anxiety and emotional burden[7]
- Higher health care costs[8]

The Bottom Line

The increased specificity of an mRNA-based HPV test and the higher sensitivity when paired with the image-guided Pap test was the main driver for cost-effectiveness.

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This data is intended for insurers.

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

†**About The Study:** Researchers from the University of Southern California and Truven Health Analytics performed a clinical-economic modeling analysis of screening with the Aptima HPV assays in combination with the ThinPrep® Pap test and compared these results to screening with HPV alone using a DNA-based test with HPV 16/18 genotyping and reflex cytology. The study simulated the lifetime effects of each screening strategy on a cohort of 1 million 30-year-old women modeled up to 70 years old, based on all women receiving cervical cancer screening every three years. The results of the model were then applied to the 78.9 million 30- to 70-year-old women in the United States. Funding for the study was provided by Hologic, Inc.

‡Disease prevalence and progression taken from USPSTF sources; Sensitivity estimates for HPV alone derived from the ATHENA trial. Sensitivity estimates for co-testing derived from the ATHENA trial and the ThinPrep Imager package insert.

§Based on a $39 difference for each 30-year-old woman modeled in the study.

References: 1. Felix J, et al. Accepted for presentation at ISPOR 18th Annual European Congress, Milan, Italy, Nov. 7-11, 2015. **2.** 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. (Study included ThinPrep® Pap Test, SurePath Pap Test, and Hybrid Capture 2 assay). **3.** Saslow et al. Journal of Lower Genital Tract Disease. November 2012. **4.** Tinelli A, et al. HPV viral activity by mRNA HPV molecular analysis to screen the transforming infections in precancer cervical lesions. Curr Pharm Biotechnol. 2009;10(8):767-771. **5.** Cuschieri K, et al. Human Papillomavirus Type Specific DNA and RNA Persistence—Implications for Cervical Disease Progression and Monitoring. J Med Virol. 2004;73(1):65-70. **6.** Aptima HPV Assay Aptima HPV Assay [package insert]. AW-12820 Rev.001. San Diego, CA: Hologic, Inc., 2015. (Data in PI included ThinPrep Pap Test, Aptima HPV assay, Hybrid Capture 2 assay). **7.** Sawaya G, et al. Identifying a "range of reasonable options" for cervical cancer screening. Obstet Gynec. 2015;125:308-310. **8.** Cost-effectiveness of High-risk Human Papillomavirus Testing with Messenger RNA versus DNA under United States Guidelines for Cervical Cancer Screening. J Low Genit Tract Dis. 2015;19(4):333-9.