

# Comparison of Cervical Cancer Screening Results Among 256,648 Women in Multiple Clinical Practices

Amy J. Blatt, PhD<sup>1</sup>; Ronald Kennedy, MD<sup>1</sup>; Ronald D. Luff, MD, MPH<sup>2</sup>; R. Marshall Austin, MD, PhD<sup>3</sup>; and Douglas S. Rabin, MD<sup>1</sup>

**BACKGROUND:** In the United States, human papillomavirus (HPV) and Papanicolaou (Pap) testing (*cotesting*) for cervical screening in women ages 30 to 65 years is the preferred strategy, and cytology alone is acceptable. Recently, a proprietary automated test for identifying high-risk HPV types for primary cervical screening was approved by the US Food and Drug Administration. The objective of the current study was to document extensive cervical screening among these screening options. **METHODS:** To investigate the sensitivity of various testing options for biopsy-proven cervical intraepithelial neoplasia grade 3 or worse ( $\geq$ CIN3) and cancer, the authors reviewed 256,648 deidentified results from women ages 30 to 65 years at the time of cotest who had a cervical biopsy specimen obtained within 1 year of the cotest. **RESULTS:** A positive cotest result was more sensitive (98.8%; 4040 of 4090 cotests) for diagnosing  $\geq$ CIN3 than either a positive HPV-only test (94%; 3845 of 4090 HPV-only tests) or a positive Pap-only test (91.3%; 3734 of 4090 Pap-only tests;  $P < .0001$ ). A positive Pap-only result was more specific (26.3%; 66,145 of 251,715 Pap-only tests) for diagnosing  $\geq$ CIN3 than a positive HPV-only test (25.6%; 64,625 of 252,556 HPV-only tests) or a positive cotest (10.9%; 27,578 of 252,558 cotests;  $P < .0001$ ). Of 526 cervical cancers, 98 (18.6%) were HPV-only negative, 64 (12.2%) were Pap-only negative, and 29 (5.5%) were cotest negative. **CONCLUSIONS:** Compared with HPV-only testing, cotesting was more sensitive for the detection of  $\geq$ CIN3 in women ages 30 to 65 years. The current data suggest that approximately 19% of women with cervical cancer may be misdiagnosed by an HPV-only cervical screen. It is important to consider these data as the guidelines for cervical cancer screening undergo revision. *Cancer (Cancer Cytopathol)* 2015;123:282-8. © 2015 The Authors. *Cancer Cytopathology* published by Wiley Periodicals, Inc. on behalf of American Cancer Society. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

**KEY WORDS:** cervical cancer; cervical intraepithelial neoplasia 3; cotest; guideline; human papillomavirus; Papanicolaou.

## INTRODUCTION

In the United States, concurrent human papillomavirus (HPV) and Papanicolaou (Pap) testing (*cotesting*) is recommended for cervical cancer screening among women ages 30 to 65 years.<sup>1-3</sup> These guidelines were developed based on the success of Pap test screening in decreasing cervical cancer incidence and mortality in the United States over the last several decades. In addition, guideline development relied on the success of adding US Food and Drug Administration (FDA)-approved HPV testing to routine cervical screening with a Pap test in women aged  $\geq 30$  years, which further decreased the incidence of cervical intraepithelial neoplasia grade 3 or worse ( $\geq$ CIN3) cervical biopsy results.<sup>1-7</sup>

**Corresponding author:** Douglas S. Rabin, MD, Medical Director, Women's Health-Medical Affairs, Quest Diagnostics, 3 Giralda Farms, Madison, NJ 07940; Fax: (973) 520-2890; douglas.s.rabin@questdiagnostics.com

<sup>1</sup>Quest Diagnostics, Madison, New Jersey; <sup>2</sup>Clinical Trials, Quest Diagnostics, Madison, New Jersey; <sup>3</sup>Department of Cytopathology, Magee-Women's Hospital of the University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

**Received:** January 27, 2015; **Revised:** March 17, 2015; **Accepted:** March 18, 2015

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Published online April 10, 2015 in Wiley Online Library (wileyonlinelibrary.com)

**DOI:** 10.1002/cncy.21544, wileyonlinelibrary.com

Recent studies have argued that HPV-only screening may be more effective than Pap-only screening for cervical precancer and cancer at screening intervals  $\geq 3$  years.<sup>4-10</sup> However, those prospective trials were performed among selected populations in well defined, controlled circumstances and usually compared HPV-only testing with Pap-only testing rather than guideline-recommended cotesting.<sup>6,9</sup> Two publications from 1 US longitudinal study in a clinical practice setting attempted to estimate results from HPV-only screening compared with cotesting. Those reports indicated that cotesting afforded better protection from developing CIN3 and cancer when performed at similar screening intervals compared with HPV-only testing.<sup>10,11</sup>

In April 2014, the cobas HPV test (Roche Molecular Systems, Inc, Pleasanton, Calif) was approved by the FDA for primary cervical cancer screening in women aged  $\geq 25$  years.<sup>12</sup> To more fully investigate the potential benefits of HPV-only screening, HPV-only test results must be compared with cotest results in the detection and prevention of invasive cervical cancer in real-world clinical practice with clinical populations that are not preselected. Furthermore, to determine the impact of changes to a screening program that has decreased the incidence of cervical cancer to 7.0 per 100,000 women per year (2011),<sup>13</sup> large sample numbers are needed to establish cancer risks for each cytologic abnormality and HPV test result, particularly for women who are negative for HPV and/or cytology testing.<sup>11</sup>

HPV-only primary screening for cervical cancer presents many challenges for clinicians. Questions arise regarding its effectiveness, its long-term risk, and when it is the best option for a particular patient.<sup>14</sup> Clinicians had similar questions when cotesting was first recommended for women aged  $\geq 30$  years in 2006. Since then, the adoption of cotesting has steadily increased, with approximately 50% of physicians cotesting women aged  $\geq 30$  years, but it still is not done at the recommended level.<sup>15,16</sup> In addition, as we seek to further prevent cervical cancer, we must be mindful to maximize disease detection while minimizing the harms associated with screening and overtreatment.<sup>17,18</sup>

The objective of this Quest Diagnostics Health Trends study was to provide a real-world, retrospective comparison between 3 screening approaches for cervical cancer (Pap-only testing, HPV-only testing, and Pap/HPV cotesting). With more than 250,000 samples, we

sought to compare the 3 screening approaches based on cervical biopsy results, including squamous cell carcinoma, adenocarcinoma, and cervical intraepithelial neoplasia (CIN) grade 3 or greater ( $\geq$ CIN3). Our objective was to provide practical clinical data to inform the discussion regarding the choice of an appropriate cervical cancer screening methodology and to help determine the most effective screening method for the early detection and appropriate treatment of cervical cancer.<sup>12-21</sup>

## MATERIALS AND METHODS

Quest Diagnostics (Madison, NJ) has more than 145 million patient encounters each year across the United States. For this study, we extracted testing data from women as described below. All data were deidentified before analysis. This study was determined to be exempt by the Western Institutional Review Board.

Woman ages 30 to 65 years at the time of cotesting were included in the study if they had a cervical cancer biopsy (Current Procedural Terminology [CPT] code 88305) and a cotest (a Pap test [with or without imaging, as ordered] and an HPV test; CPT codes 88175 or 88142 and 87621, respectively) performed at Quest Diagnostics within 1 year before their cervical biopsy. A positive cotest was defined as either a positive Pap result paired with an HPV result, or a positive HPV result paired with a Pap result, or when both tests were positive and paired. All cotest samples in the study had an HPV result and a Pap result on the same accession. If the accession had an order name indicating reflex testing and the Pap result was positive, then it was not included. Data were collected during an 81-month period beginning January 1, 2005 and ending September 30, 2011. Cotest results that were not paired with a biopsy result in our database were not included in this analysis; approximately 75% of all cotests with a positive result were not followed up at Quest Diagnostics.

Cervical biopsy, HPV, and Pap test results from the study population were extracted from the Informatics Data Warehouse. Pap slides were prepared according to the manufacturers' guidelines (ThinPrep Pap test and ThinPrep Imaging system [Hologic Inc, Bedford, Mass]; SurePath Pap test and BD FocalPoint Imaging [Becton Dickinson, Burlington, NC]) and then reviewed in accordance with protocols approved by the FDA. The Digene Hybrid Capture HPV DNA test (HC2) (Qiagen,

**TABLE 1.** Results of Human Papillomavirus-Only Testing, Papanicolaou-Only Testing, and Cotesting in Women Ages 30 to 65 Years

Test	No. of Women	No. of Test Results						Total Cancers <sup>a</sup>
		Negative Cervical Biopsy or <CIN2	CIN2	CIN3	AIS	SCC	Adenocarcinoma	
Total	256,648	241,662	10,896	3365	199	310	169	526
Baseline HPV test								
Indeterminate	2	2	0	0	0	0	0	0
HPV negative	64,870	64,172	453	140	7	34	45	98
HPV positive	191,776	177,488	10,443	3225	192	276	124	428
Baseline Pap test								
UNSAT	866	825	18	11	0	6	3	12
Pap negative	66,478	65,173	972	230	39	24	35	64
Total Pap positive	189,304	175,664	9906	3124	160	280	131	450
Baseline HPV/Pap cotest <sup>b</sup>								
HPV negative/Pap negative	27,123	27,017	62	19	1	7	14	24
HPV negative/Pap positive	37,243	36,658	390	120	6	26	29	69
HPV positive/Pap negative	39,290	38,093	909	211	37	17	21	40
HPV positive/Pap positive	152,124	139,067	9517	3004	155	254	102	381
HPV negative/Pap UNSAT	504	497	1	1	0	1	2	5
HPV positive/Pap UNSAT	362	328	17	10	0	5	1	7
HPV indeterminate/Pap negative	1	1	0	0	0	0	0	0
HPV indeterminate/Pap positive	1	1	0	0	0	0	0	0
HPV indeterminate/Pap UNSAT	0	0	0	0	0	0	0	0

Abbreviations: AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; Pap, Papanicolaou; SCC, UNSAT, unsatisfactory.

<sup>a</sup> SCC, adenocarcinoma, adenosquamous carcinoma, and cervical cancer of unknown histology are included under "Total Cancers."

<sup>b</sup> The cotest results include unsatisfactory and indeterminate results in which HPV-only or Pap-only data were used for total biopsy counts.

Gaithersburg, Md) was used to test for the presence of HPV types with a known high risk for cancer according to the manufacturer's instructions. All cytology and testing for HPV were performed at Quest Diagnostics. Quest Diagnostics has validated modifications to FDA-cleared/FDA-approved assays for the detection of HPV in Sure-Path liquid-based cytology fluid in accordance with Clinical Laboratory Improvement Amendments regulations. These assay modifications have not been approved or cleared by the FDA.

Histologic findings at biopsy were classified (in order of increasing severity) as no lesion found, CIN1, CIN2, CIN3, adenocarcinoma in situ, squamous cell carcinoma, or adenocarcinoma. All cervical biopsy results were further reviewed for confirmation of findings and for language and were excluded when information was not complete. Twenty-four biopsies and patient results were removed from the final data set because they were not considered to be primary cervical disease. Any misclassified CIN1/CIN2 specimens, lymphomas, endometrial adenocarcinomas, metastatic adenocarcinomas, melanomas, or malignancies were removed.

We calculated the distribution of cervical biopsy results for all women ages 30 to 65 years who had a biopsy preceded by a cotesting result during our study period. In

addition, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value for the tests within the study population. Statistical comparisons were made using the Pearson chi-square test to assess the difference between proportions. All statistical analyses were performed with the SAS statistical software package (SAS version 9.4; SAS Institute Inc, Cary, NC).

## RESULTS

We evaluated 256,648 samples from women ages 30 to 65 years who had a cotest and a cervical biopsy within 1 year of each other at Quest Diagnostics. In this population, 74.7% (191,776 of 256,648 samples) were positive for HPV, 73.8% (189,304 of 256,648 samples) had an abnormal Pap test (atypical squamous cells of undetermined significance or worse), 89.2% (229,020 of 256,648 samples) had a positive cotest, and 1.6% (4090 of 256,648 samples) exhibited  $\geq$ CIN3 (Table 1). Higher sensitivities for  $\geq$ CIN3 were detected in women who had positive cotest results (98.8%; 4040 of 4090 samples) compared with those who had a positive HPV-only test (94%; 3845 of 4090 samples) or a positive Pap-only test (91.3%; 3734 of 4090 samples;  $P < .0001$ ) (Table 2). Higher specificity for  $\geq$ CIN3 was detected among

**TABLE 2.** Sensitivity and Specificity With 95% Confidence Limits and Positive and Negative Predictive Values of Human Papillomavirus-Only Testing, Papanicolaou-Only Testing, and Cotesting for Cervical Intraepithelial Neoplasia Grade 3 or More Severe Results<sup>a</sup>

Test	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV, %	NPV, %
Pap only	91.3 (91-92.6)	26.3 (26.1-26.4)	1.97	99.50
HPV only	94 (93.3-94.7)	25.6 (25.4-25.8)	2	99.62
Cotesting	98.8 (98.6-99.2)	10.9 (10.8-11)	1.76	99.83

Abbreviations: CI, confidence interval; HPV, human papillomavirus; NPV, negative predictive value; Pap, Papanicolaou; PPV, positive predictive value.

<sup>a</sup>Of 256,648 women, 4090 (1.6%) had cervical intraepithelial neoplasia grade 3 or more severe biopsy results. The distributions of positive and negative screening results by biopsy finding are summarized in Table 1.

women who had a positive Pap-only test (26.3%; 66,145 of 251,715 samples) compared with those who had a positive HPV-only test (25.6%; 64,625 of 252,556 samples) or a positive cotest (10.9%; 27,578 of 252,558 samples;  $P < .0001$ ) (Table 2). The average age of all women who had a SurePath Pap specimen was 45.8 years (95% confidence interval [CI], 44.6-47.1 years;  $N = 91,375$ ), and the average age of all women who had a ThinPrep Pap specimen was 45.8 years (95% CI, 44.8-46.9 years;  $N = 165,042$ ;  $P = 1.0000$ ; 231 were conventional Pap tests).

In this population, 37,243/256,648 women (14.5%) had an abnormal Pap test but were negative for HPV. Of the women who had an abnormal Pap test and a  $\geq$ CIN3 cervical biopsy result, 195 of 3735 (5.2%) were negative for HPV. Among women who had an abnormal Pap-test result, a negative HPV-test result, and a  $\geq$ CIN3 cervical biopsy result, 69 of 195 (35.4%) had cervical cancer. On average, women with HPV-negative cervical cancer were older compared with all HPV-negative patients studied. The average age of patients who had HPV-negative cervical cancer SurePath specimens was 52.7 years (95% CI, 50.1-55.2 years;  $N = 36$ ), and, for those who had HPV-negative cervical cancer ThinPrep specimens, it was 52.4 years (95% CI, 50.2-54.6 years;  $N = 50$ ;  $P = .5698$  for SurePath vs ThinPrep; 12 tests were performed by conventional pathology for which the HPV transport media were not identified); whereas the average age of *all* patients who had HPV-negative SurePath specimens was 44.2 years (95% CI, 44.1-44.3 years;  $N = 22,082$ ), and the average age of *all* patients who had HPV-negative ThinPrep specimens was 43.5 years (95% CI, 43.4-43.6 years;  $N = 42,722$ ;  $P = 1.0000$  for SurePath vs ThinPrep). Of the specimens in which  $\geq$ CIN3 was detected from 2005 to 2011, 63.3% (2589 of 4090 specimens) were associated with ThinPrep tests, 33.7% (1377 of 4090 specimens) were associated with SurePath tests, and 3% (124 of 4090 specimens) were

associated with conventional Pap tests. Of the specimens in which HPV-negative cancers were identified, 15.2% (50 of 329 specimens) were received in ThinPrep media, and 18.3% (36 of 197 specimens) were received in SurePath media ( $P = .5572$ ).

In this study population, cotesting detected 98.8% (4040 of 4090 specimens) of all  $\geq$ CIN3 cervical biopsy results compared with 94% (3845 of 4090 specimens) for HPV-only testing and 91.3% (3734 of 4090 specimens) for Pap-only testing. Among the 526 cancers that were detected in this study, 18.6% (98 of 526 cancers) were HPV negative, 12.2% (64 of 526 cancers) were Pap test negative, and 5.5% (29 of 526 cancers) were cotest negative (Table 1). Adenocarcinoma verified as cervical in origin was detected in 169 women, of whom 45 of 169 women (26.6%) had negative HPV tests, 35 of 169 women (20.7%) had negative Pap tests, and 14 of 169 women (8.3%) had negative cotests (Table 1).

## DISCUSSION

The primary objective of this study of cervical cancer screening and cervical biopsy results from more than 250,000 women was to provide a systematic and real-world comparison of 3 screening options for cervical cancer detection in women ages 30 to 65 years: the Pap-only test, the HPV-only test, and the Pap/HPV cotest. We examined the results from all cervical biopsies that were performed within 1 year of a cotest in women ages 30 to 65 years and observed that cotesting identified  $\geq$ CIN3 cervical biopsy results more frequently than Pap-only or HPV-only testing (98.8% vs 91.3% vs 94%, for cotesting, Pap-only testing, and HPV-only testing, respectively). The higher sensitivity associated with cotesting indicates that it identifies more women who have  $\geq$ CIN3 cervical biopsy results compared with Pap-only or HPV-only testing. The studies by both Katki et al and Gage et al demonstrated

complementary findings, indicating that a negative cotest was more protective against  $\geq$ CIN3 for up to 4 years compared with HPV-only or Pap-only testing.<sup>8,10,11</sup>

In the current study, cotesting identified more  $\geq$ CIN3 cervical biopsy results in women who tested negative for HPV within 1 year before cervical biopsy, consistent with other reports.<sup>11,13</sup> The current results suggest that 6% of women who have  $\geq$ CIN3 cervical biopsy results might receive a false-negative screening result if they were tested with HPV only. Because most CIN3 does not progress to cancer,<sup>21</sup> it is of more concern that approximately 19% of women with biopsy-documented cancer in our study tested negative for HPV. The largest available cervical cancer series to date have documented similar patterns, reporting negative HC2 HPV results in approximately 10% of women with biopsy-confirmed cancer.<sup>22-25</sup> This is probably because of lower viral loads below the test cutoff point, older age (as demonstrated in our data), and the presence of adenocarcinoma.<sup>26-28</sup> However, HPV-negative cancers in older patients may reflect an increased time before cancer diagnosis, the issue of true-negative or false-negative results, a smaller lesion size, or lower viral titers during earlier periods.<sup>26,27</sup> Finally, qualitative and/or quantitative changes that may occur during some persistent high-risk HPV infections might be sufficient to cause persistently high-risk HPV-infected patients to have negative test results for HPV.<sup>26,27</sup> Our current findings are also consistent with other reports in which a negative baseline HPV-test result occurred in 16% to 42% of women with cervical cancer who were diagnosed from 2.5 to 8 years later after a cotest.<sup>7,10,27</sup>

Extrapolating our results to the US population suggests that nearly 2400 women with cervical cancer (of the 12,360 women who are estimated by the American Cancer Society to be diagnosed with cervical cancer each year) could be misdiagnosed annually if they were screened with HPV-only testing.<sup>29</sup> It is particularly striking that 26.6% of women who were diagnosed with adenocarcinoma in our study population were HPV negative. A recent, large, worldwide analysis of 682 paraffin-embedded cervical adenocarcinoma specimens reported polymerase chain reaction-detectable HPV DNA in only 428 of 682 (62.8%) cervical tumors,<sup>30</sup> similarly suggesting significant limitations for HPV testing in the detection of increasingly prevalent cervical glandular neoplasms.

There are limitations to this study. We cannot confirm that the cervical biopsy results were from women

who did not have an intervening screening test or treatment with a different provider during the study period. Also, because we investigated the screening results of women who underwent biopsies, we were unable to draw conclusions based on the overall population of women who were screened for cervical cancer. Approximately 75% of all positive cotests performed at Quest Diagnostics did not have follow-up biopsies that we could identify.

This study used the Qiagen HC2 assay for detection of high-risk HPV. A recent interim clinical guidance report has now emphasized that, between the 4 available HPV assays, assumptions should not be made that the assays are comparable and that an FDA-approved test should not be used by clinicians without a specific indication for primary HPV screening.<sup>31</sup> Therefore, estimates of possible levels of cervical cancer protection based on HC2 data (theoretically used in a non-FDA-approved manner) may not be transferrable to primary screening outcomes using the Roche cobas high-risk HPV testing algorithm (Roche Molecular Systems, Inc). Currently, almost all risk estimates of possible protection from developing cervical cancer with primary HPV testing rely mainly on HC2 testing data.<sup>7,10,11</sup> Finally, we reviewed these data to make sure there were no differences between SurePath and ThinPrep testing in  $\geq$ CIN3 results for HPV-only or Pap-only testing by age and negative results, and no significant differences were observed. Additional strengths of this study include its real-world population of more than 250,000 women and more than 500 cervical cancers and its unselected clinical results rather than those from a controlled study population.

## Conclusion

In this Quest Diagnostics Health Trends study, HPV/Pap cotesting identified more women whose cervical biopsy result revealed a finding of  $\geq$ CIN3 than HPV-only testing when offered as a primary screening test for cervical cancer. These data highlight that up to 19% of women with cancer may be falsely reassured of a negative screening result when they are screened using HPV-only testing. The results of our current study, as well as limitations of the study that led to FDA approval of an HPV-only primary test, including abnormally low cytology performance, lack of a cotesting comparator algorithm, the inclusion of women aged  $<30$  years, requiring up to 3 follow-up visits, and no long-term follow-up, all raise

concerns regarding the suitability of HPV-only testing as a primary cervical cancer screen.<sup>32,33</sup> Because early detection and treatment of cervical cancer are critical to the overall health of women, it is important that the best and most sensitive diagnostic tools for cancer detection be identified and made available to all women. Our data support cotesting in women ages 30 to 65 years as the most effective screening test for detecting cervical cancer.

## FUNDING SUPPORT

The source of this work was Quest Diagnostics Health Trends. Editorial support was provided by Jill See, PhD, and Ed Shifflett, PhD, of AlphaBioCom and was funded by Quest Diagnostics Inc.

## CONFLICT OF INTEREST DISCLOSURES

Drs. Blatt, Kennedy, Luff, and Rabin are full-time employees of Quest Diagnostics.

## REFERENCES

- Saslow D, Solomon D, Lawson HW, et al. 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 Cancer J Clin.* 2012;62:147-172.
- Bouchard-Fortier G, Hajifathalian K, McKnight MD, Zacharias DG, Gonzalez-Golzone LA. Co-testing for detection of high grade cervical intraepithelial neoplasia and cancer compared with cytology alone: a meta-analysis of randomized controlled trials. *J Public Health (Oxf).* 2014;36:46-55.
- Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin Number 131: screening for cervical cancer. *Obstet Gynecol.* 2012;120:1222-1238.
- Cox JT, Castle PE, Behrens CM, et al. Comparison of cervical cancer screening strategies incorporating different combinations of cytology, HPV testing, and genotyping for HPV 16/18: results from the ATHENA HPV study. *Am J Obstet Gynecol.* 2013;208:184.e181-184.e11.
- Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 2+ and CIN 3+ among women with HPV-positive and HPV-negative LSIL Pap results. *J Low Genit Tract Dis.* 2013;17(5 suppl 1):S43-S49.
- Castle PE, Stoler MH, Wright TC Jr, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol.* 2011;12:880-890.
- Ronco G, Dillner J, Elfstrom KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet.* 2014;383:524-532.
- Katki HA, Schiffman M, Castle PE, et al. Five-year risks of CIN 3+ and cervical cancer among women who test Pap-negative but are HPV-positive. *J Low Genit Tract Dis.* 2013;17(5 suppl 1):S56-S63.
- Kitchener HC, Gilham C, Sargent A, et al. A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: extended follow up in the ARTISTIC trial. *Eur J Cancer.* 2011;47:864-871.
- 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;12:663-672.
- Gage JC, Schiffman M, Katki HA, et al. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test [serial online]. *J Natl Cancer Inst.* 2015;107;pii.dju153.
- US Food and Drug Administration. FDA approves first human papillomavirus test for primary cervical cancer screening FDA [news release]. Silver Spring, MD: US Food and Drug Administration; 2014. [www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm](http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm394773.htm). Accessed September 19, 2014.
- National Cancer Institute; Surveillance, Epidemiology, and End Results (SEER) Program. SEER Program US Population Data (1969-2012). Release date, March 2014. Bethesda, MD: National Cancer Institute; 2014. [www.seer.cancer.gov/statfacts/html/cervix.html](http://www.seer.cancer.gov/statfacts/html/cervix.html). Accessed October 14, 2014.
- Austin RM, Zhao C. Is 58% sensitivity for detection of cervical intraepithelial neoplasia 3 and invasive cervical cancer optimal for cervical screening [serial online]? *Cytojournal.* 2014;11:14.
- Bekker JB, John TS, Leiman G. Confirming suboptimal adherence to HPV cotesting guidelines in an academic center in Vermont. *Am J Clin Pathol.* 2013;139:259-260.
- Tatsas AD, Phelan DF, Gravitt PE, Boitnott JK, Clark DP. Practice patterns in cervical cancer screening and human papillomavirus testing. *Am J Clin Pathol.* 2012;138:223-229.
- Smith-McCune K. Choosing a screening method for cervical cancer: Papanicolaou testing alone or with human papillomavirus testing. *JAMA Intern Med.* 2014;174:1027-1028.
- Kulasingam SL, Havrilesky L, Ghebre R, Myers ER. Screening for Cervical Cancer: A Decision Analysis for the US Preventive Services Task Force [Internet]. US Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews. Rockville, MD: US Agency for Healthcare and Quality; 2011. Report No. 11-05157-EF-1.
- Nauder P, Ryd W, Tornberg S, et al. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. *J Natl Cancer Inst.* 2009;101:88-99.
- Cuzick J, Clavel C, Petry KU, et al. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer.* 2006;119:1095-1101.
- McCredie MR, Sharples KJ, Paul C, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical neoplasia 3: a retrospective cohort study. *Lancet Oncol.* 2008;9:425-434.
- Wu Y, Chen Y, Li L, Yu G, Zhang Y, He Y. Associations of high-risk HPV types and viral load with cervical cancer in China. *J Clin Virol.* 2006;35:264-269.
- Kang WD, Kim CH, Cho MK, et al. Comparison of hybrid capture II assay with the human papillomavirus DNA chip test for the detection of high-grade cervical lesions. *Int J Gynecol Cancer.* 2009;19:924-928.
- Moreira MA, Longato-Filho A, Taromus E, et al. Investigation of human papillomavirus by hybrid capture II in cervical carcinomas including 113 adenocarcinomas and related lesions. *Int J Gynecol Cancer.* 2006;16:586-590.
- Poljak M, Kovanda A, Kocjan BJ, Seme K, Jancar N, Vrtacnik-Bokal E. The Abbott RealTime High Risk HPV test: comparative evaluation of analytic specificity and clinical sensitivity for cervical carcinoma and CIN 3 lesions with the Hybrid Capture 2 HPV DNA test. *Acta Dermatoven Alp Pannonica Adriat.* 2009;18:94-103.

26. Li Z, Austin RM, Guo M, Zhao C. Screening test results associated with cancer diagnoses in 287 women with cervical squamous cell carcinoma. *Arch Pathol Lab Med.* 2012;136:1533-1540.
27. Zhao C, Li Z, Nayar R, 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;139:184-188.
28. Hopenhayn C, Christian A, Christian WJ, 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;18:182-189.
29. American Cancer Society. Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society; 2014. [www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf](http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-041770.pdf). Accessed August 5, 2014.
30. Pirog EC, Lloveras B, Moljin A, et al. HPV prevalence and genotypes in different histologic subtypes of cervical adenocarcinoma: a worldwide analysis of 780 cases. *Mod Pathol.* 2014;27:1559-1567.
31. Huh WK, Ault KA, Chelnow D, et al. Use of primary high risk human papillomavirus testing for cervical cancer screening. interim clinical guidance. *Obstet Gynecol.* 2015;125:330-337.
32. Nayar R, Goulart RA, Tiscornia-Wasserman PG, Davey DD. Primary human papillomavirus screening for cervical cancer in the United States—US Food and Drug Administration approval, clinical trials, and where we are today. *Cancer Cytopathol.* 2014;122:720-729.
33. Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL. Primary cervical cancer screening with human papillomavirus: end of study results from the ATHENA study using HPV as the first-line screening test. *Gynecol Oncol.* 2015;136:189-197.