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Point-Counterpoint: Cervical Cancer Screening Should Be Done by Primary Human Papillomavirus Testing with Genotyping and Reflex Cytology for Women over the Age of 25 Years

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Screening for cervical cancer with cytology testing has been very effective in reducing cervical cancer in the United States. For decades, the approach was an annual Pap test. In 2000, the Hybrid Capture 2 human papillomavirus (HPV) test was approved by the U.S. Food and Drug Administration (FDA) for screening women who have atypical squamous cells of underdetermined significance (ASCUS) detected by Pap test to determine the need for colposcopy. In 2003, the FDA approved expanding the use of the test to include screening performed in conjunction with a Pap test for women over the age of 30 years, referred to as "cotesting." Cotesting allows women to extend the testing interval to 3 years if both tests have negative results. In April of 2014, the FDA approved the use of an HPV test (the cobas HPV test) for primary cervical cancer screening for women over the age of 25 years, without the need for a concomitant Pap test. The approval recommended either colposcopy or a Pap test for patients with specific high-risk HPV types detected by the HPV test. This was based on the results of the ATHENA trial, which included more than 40,000 women. Reaction to this decision has been mixed. Supporters point to the fact that the primary-screening algorithm found more disease (cervical intraepithelial neoplasia 3 or worse [CIN3+]) and also found it earlier than did cytology or cotesting. Moreover, the positive predictive value and positive-likelihood ratio of the primary-screening algorithm were higher than those of cytology. Opponents of the decision prefer cotesting, as this approach detects more disease than the HPV test alone. In addition, the performance of this new algorithm has not been assessed in routine clinical use. Professional organizations will need to develop guidelines that incorporate this testing algorithm. In this Point-Counterpoint, Dr. Stoler explains why he favors the primary-screening algorithm, while Drs. Austin and Zhao explain why they prefer the cotesting approach to screening for cervical cancer.

POINT

In the first quarter of 2014, the FDA appointed an independent expert panel that, after carefully reviewing the evidence, unanimously recommended that the human papillomavirus (HPV) primary-screening algorithm proposed in Roche's ATHENA trial be approved as safe and effective. The FDA in its own independent analysis concurred and recommended that the cobas HPV test be approved for use as a primary-screening test for cervical cancer using the proposed algorithm. As of this writing, the 3-year data from the ATHENA trial are nearing publication, as is the interim guidance commentary organized by the Society of Gynecologic Oncology (1, 2). As one who has been involved in most of the HPV diagnostic trials as well as the HPV vaccine trials, I have been asked to give my perspective on why I favor HPV primary screening rather than cotesting as the best approach to cervical cancer screening. Implicit in this request is the absence from the discussion of cytology alone as an option, yet it is the comparison of cytology to HPV testing, not cotesting, that has provided the data that many others and I have found so convincing that I, a long-practicing cytopathologist, now believe that the best way forward is primary HPV testing. The rationale for my viewpoint can be captured in three words: science, safety, and simplicity.

When I was president of the ASCP, one of the guiding strategies for the organization was the concept of patient-centered advocacy, and it remains a guiding strategy. Advocate for and do what is best for patients, based on the best available medical and scientific data, regardless of cost, including personal cost, cost to one's practice, or cost to one's institution, and that should always be the winning strategy (3). Knowing what is best may not always be simple, but the concept of balancing benefits and harms regardless of cost permeates the current guidelines for cervical cancer screening (4). As one examines the evidence, this emphasis on balance leads one to the nonintuitive concept that more is not always better. For cervical cancer, this means that excess screening, especially for a disease of such low prevalence in screened populations, may do more harm than good. Hence, contemporary approaches to cervical cancer screening seek to balance the benefits of screening with the harms of overreferral and overtreatment.

It is this balance of benefits versus harm that is a primary consideration in comparing the concept of HPV primary screening to that of cotesting. The data influencing these considerations are perhaps some of the most robust in all of medicine. Where else in medicine can one find combined data from published large-scale clinical trials that encompass approximately 1.2 million women in

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6 countries (5–8)? There are six randomized controlled clinical trials, including studies performed in the United States, the Netherlands, Sweden, Italy, England, and Canada, all with a minimum of 3 years of follow-up and some with up to 12 years. Remarkably, the details of the trial designs vary considerably, yet the conclusions are fundamentally the same, cited as strong statistical evidence that we are indeed on the right track (5). HPV testing is superior to cytology alone and dominates in terms of clinical performance. Furthermore, the potential contribution of cotesting over HPV primary screening is extremely limited; i.e., more than 95% of the clinical utility in a cotesting scenario comes from the HPV test. The above-mentioned general conclusions are true not only for the detection of precancerous states (cervical intraepithelial neoplasia grade 2 or worse [CIN2+] or CIN3+) but also now for the prevention of invasive cancer, as detailed in the 2014 meta-analysis of the four European randomized controlled trials (5).

Prior pooled analyses from the European trials showed a 30 to 40% gain in the sensitivity of detection of CIN3+ for HPV over cytology, with minimal if any gain attributable to doing both tests, while suggesting an interval protection of at least 5 years (9). In the updated analysis with a median of 6.5 years of follow-up and data on 176,464 women covering 1,214,415 person years, the data demonstrate that HPV-based screening provided 60 to 70% greater protection against invasive cancer than other forms of screening (5). This expansion to invasive cancer required the pooling of data and long-term analysis, as the prevalence of invasive cancer is so low in screened populations. The effect of HPV testing was not seen in the first 2.5 years but was highly significant thereafter, supporting the concepts that cytology detects disease that the patient has now but that HPV testing not only detects current disease but also is better at predicting the risk of disease development. HPV testing was also superior for detection of adenocarcinoma, a finding not seen in most cytology studies. Importantly, the authors of the British ARTISTIC trial were also authors of this analysis; the initial ARTISTIC report is often cited as evidence that cytology can be as good as or better than HPV testing, a finding later thought to be related to the design of the study and the fact that liquid-based cytology (LBC) was just introduced in the population at the start of the trial (10, 11). This relative inexperience with LBC caused an initial apparent increase in sensitivity due to overdiagnosing of minor cytological abnormalities, and these diagnoses were not sustained in subsequent rounds of the trial (11).

The United States-based ATHENA trial was Roche's FDA prospective registration trial for the cobas HPV test (2, 7, 12–15). The trial was designed to potentially validate a unified and simplified HPV primary-screening algorithm for women who were 25 years old and older. The algorithm capitalizes on the sensitivity and specificity of genotyping to minimize loss to follow-up and maximize disease ascertainment. As noted above, independent reviews support the manufacturer's claims that the proposed primary-screening algorithm is superior to cytology alone and equivalent to or better than cotesting for the prevention of CIN3 and invasive cancer (K. Simon and M. Kondratovich, talk presented at the 2014 Microbiology Devices Advisory Committee Meeting [outline available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/ucm388531.htm]). Much of the improvement in performance relative to cotesting comes from the extension of HPV screening and genotyping to the age group 25 to 30 years, for which current guidelines do not advocate HPV testing except for ASCUS triage. Yet this is a critical age group, as there is more CIN3 in this group than in all of the women 40 years old and older in the ATHENA study (2; Simon and Kondratovich, talk presented at the 2014 Microbiology Devices Advisory Committee Meeting). The potential for overtreatment in this age group needs to be balanced against the fact that without treatment of precancer, there is virtually no benefit to screening. Furthermore, the potential harms of treatments may be overestimated in the literature (16).

Critics of ATHENA conclusions point to the low sensitivity of cytology in the study, but cytology was used such that it had maximum potential for sensitivity, as all patients with abnormal cytology were referred for colposcopy (Simon and Kondratovich, talk presented at the 2014 Microbiology Devices Advisory Committee Meeting). The verification bias-adjusted (VBA) sensitivities of cytology (42.6%) versus HPV primary algorithms (not tests, as in reference 17) at 58.3% seem low to some, relative to results in the literature (17), yet the reader should be cautioned to make apples-to-apples comparisons. The only other large VBA randomized controlled trial comparing cytology testing to HPV testing is the Canadian Cervical Cancer Screening Trial (CCCaST), which found essentially the same relative numbers as those found in the ATHENA study (6). All the other relevant studies include unadjusted numbers, including the original and oft-cited Duke review, where cytology was estimated to have a single-round sensitivity of 50% (18). In addition, verification bias adjustment, because it extrapolates from a population of cotest-negative patients, impacts both tests similarly, thereby not changing the rank order comparisons. The validity of verification bias adjustment for very rare events has also recently been called into question (7, 19). The truth about test performance is probably between the two estimates; the actual rates are more likely in the real world closer to the unadjusted rates. However, the relative performances are the same and, as in all the trials, favor HPV testing over cytology, with performance equivalent to or better than that of cotesting, depending mostly on the frequency of screening.

Since at least 2003, the National Cancer Institute (NCI) in collaboration with Kaiser Permanente of Northern California (KPNC) has been analyzing the screening histories of women who have been tested with both an HPV test and cytology. This data set, now including over a million women, has been widely cited in guideline development (4, 8, 20). As published in 2014, the reassurance provided by primary HPV testing every 3 years against the future risk of precancer and cancer was superior to that provided by Pap testing every 3 years as well as cotesting every 5 years, which serves as independent real-world confirmation of the ATHENA analysis (8). Suggestions in the United States that the 5-year interval for cotesting may be too long might be balanced by the fact that outside the United States, no country is considering any form of cotesting, and some think that 5 years may be too short! In the KPNC analysis, even small differences between very low risks can be statistically significant because of the size of the population. When the cancer risks after an HPV-negative result are compared with cancer risks after a cotest-negative result at the same time point, some of the risks have overlapping 95% confidence intervals. The 3-year cancer risk after an HPV-negative versus cotest-negative result is statistically significant (0.011 versus 0.007, $P = 0.03$). However, the 5-year cancer risk after an HPV-negative re-

sult versus a cotest-negative result is not (0.017 versus 0.014, $P = 0.11$). A 0.004% gain in performance translates to ~1 additional case per 25,000 women, a level that most individual practices would never be able to perceive.

One other very recent independent analysis based on modeling and consideration of the impact of HPV vaccination comes from Australia. My cytopathology colleagues in Australia have proudly presented the quality of their cytology-based screening program and have relatively resisted the need for implementing HPV testing (21). Yet, based on their systematic review and modeling, effective in 2016, algorithmic primary HPV screening every 5 years will replace cytology screening every 2 years because it is deemed to be safer and more effective (National Screening Program Renewal [http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/future-changes-cervical]).

Much of the safety of HPV primary screening is inherent in the science above. Finding more, real disease and treating it to prevent cancer has always motivated the fight against cervical cancer. While some of the potential criticisms or concerns have been addressed, in the United States, many have observed that screening is more opportunistic and less organized, unlike in the much better organized health care settings in Europe. Yet for women who do get screened, should one not use a screening approach that is as safe, effective, and simple to comply with as possible? As they say, "all politics is local," and in the United States, most women are in the hands of their local medical practitioner, who I believe ultimately will want to do the right thing based on the best science. I submit, as would any epidemiologist, that doing the most sensitive test first at the right interval is more likely to achieve these goals, and that demands a change in historical practice. Complexity is the enemy of compliance, and certainly simplicity in screening programs should improve adoption of guidelines (22). One should point out that cotesting was initiated in the United States, without any clinical trial, in order to compensate for the perceived lack of performance of cytology-based screening, yet one of the unintended consequences of cotesting is the creation of significant algorithmic complexity (20). Because we are coming from a cytology-based approach, the algorithms still account for the significance of the numerous Bethesda categories. If one simply multiplies the 7 main cytology interpretations by the 2 main possible HPV results, that yields 14 different outcomes, and that is without genotyping. In contrast, HPV primary screening treats cytology dichotomously, as positive or negative, greatly simplifying the colposcopy versus no-colposcopy decision point. So yes, adding primary HPV testing to the menu of possible approaches to cervical cancer screening, namely, cytology alone, ASCUS triage, and cotesting, each with potentially different frequencies or mixing of approaches depending on age, adds complexity. However, within a main strategy, primary HPV testing has the virtue of a single unified approach for virtually the entire population aged 25 years and older, with the simplest to follow within the algorithm process.

The final concern of many critics is that we have more than 60 years of experience with cytology-based screening, but ATHENA lasted only 3 years and we need more data and long-term follow-up in the United States. Do we really? Do we ignore the assembled wealth of the data discussed above and not appreciate a more global point of view? Do we in the United States, actually care more about our patients than our colleagues in Canada, Europe, and Australia? Or can we not all agree, based on the data, that there should be a reasonable and standard approach to screening for cervical cancer, at least in health care systems that can afford and support it? Furthermore, given the costs involved and the absence of government support, it is unlikely that there will ever be the kind of multiround 6- to 10-year trial in the United States. In my opinion, such a study is not needed because the existing worldwide data are all consistent with the results of the ATHENA study and sufficient.

In summary, the subject of this exchange of viewpoints is focused on the choice between two superior choices, cotesting and HPV primary screening. While the devil is always in the details, it is indeed remarkable that neither of us argues in favor of cytology alone as the primary screening test. However, it should be pointed out, as it was in the FDA review, that more than half of the women screened in the United States are still screened with Pap smears alone. Indeed, the recently published guidelines state that cytology alone every 3 years is acceptable medical practice even though much of the above data were already available before 2012. Perhaps the real debate should focus on moving the standard of care to what we now know is best and then implementing it for all who need it.

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REFERENCES

1. **Huh W, Ault K, Chelmow D, Davey DD, Goulart RA, Garcia FA, Kinney WK, Massad LS, Mayeaux EJ, Saslow D, Schiffman M, Wentzensen N, Lawson HW, Einstein MH.** Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol http://dx.doi.org/10.1097/AOG.0000000000000669.
2. **Wright TC, Stoler MH, Behrens CM, Sharma A, Zhang G, Wright TL.** 2015. 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 **136:**189–197. http://dx.doi.org/10.1016/j.ygyno.2014.11.076.
3. **Stoler MH.** 2010. Pursuing patient centered advocacy. Crit Values **3:**9–11.
4. **Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs LS, Jr, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiffman M, Castle PE, Myers ER, American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology.** 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. Am J Clin Pathol **137:**516–542. http://dx.doi.org/10.1309/AJCPTGD94EVRSJCG.
5. **Ronco G, Dillner J, Elfstrom KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ, International HPV Screening Working Group.** 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet **383:**524–532. http://dx.doi.org/10.1016/S0140-6736(13)62218-7.
6. **Mayrand MH, Duarte-Franco E, Rodrigues I, Walter SD, Hanley J, Ferenczy A, Ratnam S, Coutlée F, Franco EL, Canadian Cervical Cancer Screening Trial Study Group.** 2007. Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. N Engl J Med **357:**1579–1588. http://dx.doi.org/10.1056/NEJMoa071430.
7. **Wright TC, Jr, Stoler MH, Behrens CM, Apple R, Derion T, Wright TL.** 2012. The ATHENA human papillomavirus study: design, methods, and baseline results. Am J Obstet Gynecol **206:**46.e1-46.e11. http://dx.doi.org/10.1016/j.ajog.2011.07.024.
8. **Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, Poitras NE, Lorey T, Cheung LC, Kinney WK.** 2014. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. J Natl Cancer Inst **106:**dju153. http://dx.doi.org/10.1093/jnci/dju153.

9. **Naucler P, Ryd W, Törnberg S, Strand A, Wadell G, Elfgren K, Rådberg T, Strander B, Forslund O, Hansson BG, Hagmar B, Johansson B, Rylander E, Dillner J.** 2009. Efficacy of HPV DNA testing with cytology triage and/or repeat HPV DNA testing in primary cervical cancer screening. J Natl Cancer Inst **101:**88–99. http://dx.doi.org/10.1093/jnci/djn444.
10. **Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, Roberts C, Desai M, Peto J, ARTISTIC Trial Study Group.** 2009. ARTISTIC: a randomized trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess **13:**1–150, iii–iv. http://dx.doi.org/10.3310/hta13510.
11. **Kitchener H, Canfell K, Gilham C, Sargent A, Roberts C, Desai M, Peto J.** 2014. The clinical effectiveness and cost-effectiveness of primary human papillomavirus cervical screening in England: extended follow-up of the ARTISTIC randomised trial cohort through three screening rounds. Health Technol Assess **18:**1–196. http://dx.doi.org/10.3310/hta18230.
12. **Stoler MH, Wright TC, Jr, Sharma A, Apple R, Gutekunst K, Wright TL, ATHENA (Addressing the Need for Advanced HPV Diagnostics) HPV Study Group.** 2011. High-risk human papillomavirus testing in women with ASC-US cytology: results from the ATHENA HPV study. Am J Clin Pathol **135:**468–475. http://dx.doi.org/10.1309/AJCPZ5JY6FCVNMOT.
13. **Wright TC, Jr, Stoler MH, Sharma A, Zhang G, Behrens C, Wright TL, ATHENA (Addressing the Need for Advanced HPV Diagnostics) Study Group.** 2011. Evaluation of HPV-16 and HPV-18 genotyping for the triage of women with high-risk HPV+ cytology-negative results. Am J Clin Pathol **136:**578–586. http://dx.doi.org/10.1309/AJCPTUS5EXAS6DKZ.
14. **Wright TC, Jr, Stoler MH, Behrens CM, Sharma A, Sharma K, Apple R.** 2014. Interlaboratory variation in the performance of liquid-based cytology: insights from the ATHENA trial. Int J Cancer **134:**1835–1843. http://dx.doi.org/10.1002/ijc.28514.
15. **Cox JT, Castle PE, Behrens CM, Sharma A, Wright TC, Jr, Cuzick J, Athena HPV Study Group.** 2013. 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 **208:**184.e1-184.e11. http://dx.doi.org/10.1016/j.ajog.2012.11.020.
16. **Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, Paraskevaidis E.** 2014. Fertility and early pregnancy outcomes after treatment for cervical intraepithelial neoplasia: systematic review and meta-analysis. BMJ **349:**g6192. http://dx.doi.org/10.1136/bmj.g6192.
17. **Austin R, Zhao C.** 2014. Is 58% sensitivity for the detection of cervical intraepithelial neoplasia3 and invasive cancer optimal for cervical cancer screening? Cytojournal **11:**14. http://dx.doi.org/10.4103/1742-6413.132997.
18. **McCrory DC, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, Myers E, Nanda K.** 1999. Evaluation of cervical cytology. Evid Rep Technol Assess (Summ) report no. 5. AHCPR Publication no. 99-E010. Agency for Health Care Policy and Research, Rockville, MD.
19. **Sasieni P.** 2001. Estimating prevalence when the true disease status is incompletely ascertained. Stat Med **20:**935–949. http://dx.doi.org/10.1002/sim.907.
20. **Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, Solomon D, Wentzensen N, Lawson HW.** 2013. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. J Low Genit Tract Dis **17**(5 Suppl 1)**:**S1–S27. http://dx.doi.org/10.1097/LGT.0b013e318287d329.
21. **Farnsworth A.** 2011. Screening for the prevention of cervical cancer in the era of human papillomavirus vaccination: an Australian perspective. Acta Cytol **55:**307–312. http://dx.doi.org/10.1159/000326956.
22. **Roland KB, Benard VB, Soman A, Breen N, Kepka D, Saraiya M.** 2013. Cervical cancer screening among young adult women in the United States. Cancer Epidemiol Biomarkers Prev **22:**580–588. http://dx.doi.org/10.1158/1055-9965.EPI-12-1266.

COUNTERPOINT

Recently, the FDA approved a primary HPV cervical-screening algorithm with only limited sensitivity for detection of cervical intraepithelial neoplasia 3 (CIN3) or cervical cancer (CIN3+) (1).

Very few practitioners seem to realize that the FDA-documented verification bias-adjusted (VBA) sensitivity of the new screening algorithm for CIN3+ detection was only 27% for women 50 years and older and 36% for women 40 years and older (Table 1), age groups with the highest rates of cervical cancer (2). Even for younger women, who have the lowest cervical cancer rates, the FDA-documented VBA sensitivity of the new cervical-screening algorithm was only 53% for women 30 years old and older and 58% for women 25 years old and older (Table 1). When aware of these data, many logically wonder why the FDA would approve a cervical-screening algorithm with such limited sensitivity, given the higher sensitivity of preferred cytology and HPV cotesting for women 30 years old and older (3, 4).

TABLE 1 Sensitivity of cobas HPV primary-screening algorithm for detection of *in situ* carcinoma (CIN3) or invasive cervical cancer (CIN3+) in the FDA ATHENA trial database

Age group in ATHENA trial (yr)	% cobas CIN3+ VBA sensitivity	FDA table(s)[a]
≥25	58.26	A4.1, A8.2
≥30	53.56	12, A4.2
≥40	36.09	13
≥50	27.26	14

[a] See reference 1.

Although VBA CIN2/3+ sensitivity exceeding 90% has been reported in laboratories with optimized cervical-screening practices (5-7), the ATHENA trial compared Roche's new cobas primary HPV screening algorithm to clearly suboptimal cytology performance in four large U.S. laboratories, with VBA CIN3+ age-stratified sensitivity of only 27 to 42% (1). Even though independent British technology assessment studies have concluded that, with quality-optimized liquid-based cytology (LBC) practice, "it is difficult to escape the conclusion that LBC was more sensitive in ARTISTIC than earlier conventional cytology" (8), the ATHENA trial selected four U.S. cytology laboratories with LBC performance below even the "near 50%" VBA sensitivity judged achievable with conventional smear cytology in a 1999 Agency for Healthcare Policy and Research Technology Assessment report (9). Given the FDA instructions to the advisory panel, the panel could reasonably conclude only that the performance of the proposed HPV primary-screening algorithm appeared to be at least equivalent to the suboptimal performance of the four selected cytology laboratories. Even with suboptimal cytology performance, when ATHENA cytology results were added to FDA-approved HPV testing results for women 30 years old and older, significantly higher CIN3+ detection rates were documented with FDA-approved cytology and HPV cotesting of women 30 years and older than with the proposed primary-screening algorithm (1). A recent meta-analysis similarly concluded that "it is well established in the literature that cotesting has a higher sensitivity than HPV DNA testing" (3).

Available clinical trial data have focused on the increased detection of CIN2/3+ in the HPV arms of international trials compared with the detection by cytology (10). The U.S. Preventive Services Task Force (USPSTF), however, has emphasized that "the degree of benefit in preventing invasive cancer cannot be determined from test performance studies alone. The cross-sectional data suffer from determining sensitivity, specificity, and related predictive values for a surrogate outcome (CIN2+) and not invasive cervical cancer" (11). Natural history studies document that most CIN3, particularly in younger women, will never progress to invasive cervical cancer (12). Kaiser investigators have similarly concluded that CIN3+ is not the right endpoint for evaluating cervical-screening algorithms, as it does not reflect cancer risk accurately. Noting that the risk of CIN3 tripled between 2003 and

2012, with unchanged risk for cervical squamous carcinoma, they conclude that "observational studies of large populations over time will be essential to obtain the risk of cancer as an outcome measure to guide clinical practice" (13).

Ronco et al. recently acknowledged that "the effect of HPV testing as an alternative to regular screening on the incidence of invasive cancer has not been assessed adequately" (14). Seeking to collect clinical trials with significant numbers of cervical cancers to evaluate, the authors combined four European trials with a total of 107 cervical cancers diagnosed in either the experimental (HPV) or control (cytology) arms of the trials. Three of the trials (Italian NTCC, Dutch POPOBASCAM, and Swedish SWEDESCREEN) utilized conventional Pap smear cytology, while only the United Kingdom ARTISTIC trial utilized LBC. Furthermore, the largest NTCC trial referred all women with positive HPV test results to colposcopy, resulting in double the colposcopy rate in the HPV arm than in the cytology arm. Noting nevertheless that no differences in cancer rates were evident between the cytology and HPV arms in the first 2.5 years after enrollment, the authors surprisingly discarded from further analysis almost half ($n = 52$) of the painstakingly collected 107 cervical cancer cases. The authors argue, somewhat unconvincingly, that the earlier-detected 52 cervical cancers were predominantly prevalent cervical cancer present before the beginning of the four trials. The authors themselves acknowledge that they "would [have] expect[ed] cancer detection to be higher in the experimental (HPV) arm in the first 2.5 years," which was not the case. The authors then elect to focus solely on the remaining 55 cervical cancers diagnosed 2.5 to 8 years after enrollment. Since 36 of the 55 remaining cervical cancer diagnoses were diagnosed in the cytology arms of the trials compared to 19 in the HPV arms, the authors conclude that HPV-based screening provided "greater protection" and advise extension of screening intervals to "at least 5 years." The authors, however, fail to comment on reported data that the results in the conventional Pap smear trials were virtually the opposite of results in the LBC ARTISTIC trial. Virtually all cervical cancers diagnosed 2.5 to 8 years after enrollment in the United Kingdom LBC trial were diagnosed in the HPV arm of the trial. None were diagnosed during this period in the United Kingdom LBC trial arm! As in the ATHENA trial, cytology quality appears to have been largely bypassed as a possibly significant factor in framing comparisons. Furthermore, the authors do not comment on their reported data documenting that 8 of 19 (42%) cervical cancer cases diagnosed in the HPV trial arms 2.5 to 8 years after enrollment tested HPV negative at baseline, findings which should raise questions about the safety of extended screening intervals. Also, no benefit was documented for HPV testing of women younger than 30 years old, the group with the greatest increased rate of HPV-driven colposcopies. Studies show that FDA-approved HPV screening test results will be negative in around 10% of cervical cancers diagnosed at the same time as HPV testing and that HPV-negative results significantly increase as the time of HPV testing prior to cervical cancer diagnosis lengthens (Table 2).

Available U.S. studies using FDA-approved Hybrid Capture 2 testing from the ThinPrep vial suggest that invasive cervical cancer rates will likely be lowest when FDA-approved cotesting is used for testing women who are 30 to 65 years old (15, 16). Virtually no long-term observational clinical data documenting cervical cancer protection using the recently FDA-approved cobas primary HPV screening algorithm is available. It is revealing that a new definition of "acceptable cervical cancer protection" used in 2012 guidelines (4) shifted from protection achievable with annual conventional smear screening in 2002 and 2006 guidelines to less protection achievable with every 3-year conventional smear screening, despite data showing a consistently increased relative cervical cancer risk with every 3-year conventional smear screening ranging from 1.3 to 4.7 (17). Focus on protection achievable with the conventional Pap smear also ignores significant Surveillance, Epidemiology, and End Results (SEER) Program-documented declines in cervical cancer incidence since the widespread adoption of new cervical screening technologies beginning in 1996. Maximizing cervical cancer protection is simply no longer the priority. The new priority is decreasing testing.

TABLE 2 HPV-negative test rates prior to cervical cancer diagnoses

Time (yr) prior to cervical cancer diagnoses	Rate (%) of negative hrHPV[a] test result	No. of cervical cancers	Reference
0	10	475	22
≤2.5	16	25	14
1–3	23	26	23
≤5	31	87	15
2.5–8	42	19	14

[a] hrHPV, high-risk HPV test results.

Additional cancers detected with cotesting, for example, are characterized as too few and/or too costly to justify preventing (16). This outlook is characteristic of the increasing recent tendency to emphasize cancer screening costs and "harms" rather than maximizing cancer prevention (18). According to this view, many traditional cancer prevention strategies are simply too expensive or too ineffective to justify. Public health officials seem unexpectedly surprised and alarmed, however, when the loss of clear messaging associated with changes in recommended screening intervals coincides with increased nonattendance for cervical screening (19).

Countries considering primary HPV screening, such as Holland and Australia, may soon embark on important national experiments not yet supported by long-term observational studies proving optimal cervical cancer prevention with primary HPV screening (20, 21). Hoped-for cost savings associated with proposed extended screening intervals are clearly a major motivating factor, despite uncertainties about the costs of increased HPV test-driven colposcopic referrals and trial data indicating up to 42% HPV-negative test result rates for cancers diagnosed over the next 2.5 to 8 years. It will be important to follow closely these national experiments to further assess the effectiveness of proposed primary HPV screening policies. For now, in the United States, FDA-approved cytology and HPV cotesting of women 30 years and older offers the greatest screening protection against cervical cancer.

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REFERENCES

1. **FDA.** 12 March 2014. Meeting materials of the microbiology devices panel. FDA, Bethesda, MD. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM388564.pdf.
2. **Rositch AF, Nowak RG, Gravitt PE.** 2014. Increased age and race-specific incidence of cervical cancer after correction for hysterectomy prevalence

in the United States from 2000 to 2009. Cancer **120:**2032–2038. http://dx.doi.org/10.1002/cncr.28548.
3. **Bouchard-Fortier G, Hajifathalian K, McKnight MD, Zacharias DG, Gonzalez-Gonzalez LA.** 2014. 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 **36:**46–55. http://dx.doi.org/10.1093/pubmed/fdt057.
4. **Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs LS, Jr, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiffman M, Castle PE, Myers ER, American Cancer Society, American Society for Colposcopy and Cervical Pathology, American Society for Clinical Pathology.** 2012. Screening guidelines for the prevention and early detection of cervical cancer. Am J Clin Pathol **137:**516–542. http://dx.doi.org/10.1309/AJCPTGD94EVRSJCG.
5. **Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, Pan QJ, Fischer C, Lorincz A, Zahniser D.** 2001. Shanxi Province Cervical Cancer Screening Study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. Gynecol Oncol **83:**439–444. http://dx.doi.org/10.1006/gyno.2001.6370.
6. **Zhao C, Florea A, Onisko A, Austin RM.** 2009. Histologic follow-up results in 662 patients with Pap test findings of atypical glandular cells: results from a large academic women's hospital laboratory employing sensitive screening methods. Gynecol Oncol **114:**383–389. http://dx.doi.org/10.1016/j.ygyno.2009.05.019.
7. **Dudding N, Crossley J.** 2013. Sensitivity and specificity of HPV testing: what are the facts? Cytopathology **24:**283–288. http://onlinelibrary.wiley.com/doi/10.1111/cyt.12104/abstr.
8. **Kitchener HC, Almonte M, Gilham C, Dowie R, Stoykova B, Sargent A, Roberts C, Desai M, Peto J, ARTISTIC Trial Study Group.** 2009. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess **13:**1–150. http://www.journalslibrary.nihr.ac.uk/hta/volume-13/issue-51.
9. **McCrory DB, Matchar DB, Bastian L, Datta S, Hasselblad V, Hickey J, Myers E, Nanda K.** 1999. Evaluation of cervical cytology. Evidence Report/Technology Assessment no. 5. AHCPR Publication no. 99-E010. Agency for Health Care Policy and Research, Rockville, MD. http://www.ncbi.nlm.nih.gov/books/NBK11840/.
10. **Dillner J, Rebolj M, Birembaut P, Petry KU, Szarewski A, Munk C, de Sanjose S, Naucler P, Lloveras B, Kjaer S, Cuzick J, van Ballegooijen M, Clavel C, Iftner T, Joint European Cohort Study.** 2008. Long term predictive values of cytology and human papillomavirus testing in cervical cancer screening: joint European cohort study. BMJ **337:**a1754. http://dx.doi.org/10.1136/bmj.a1754.
11. **Vesco KK, Whitlock EP, Eder M, Lin J, Burda BU, Senger CA, Holmes RS, Fu R, Zuber S.** 2011. Screening for cervical cancer. A systematic evidence review for the U.S. Preventive Services Task Force. Evidence Synthesis, no. 86. AHRQ Publication no. 11-05156-EF-1. Oregon Evidence-Based Practice Center, Portland, OR. http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0016542/pdf/TOC.pdf.
12. **McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, Skegg DC.** 2008. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol **9:**425–434. http://dx.doi.org/10.1016/S1470-2045(08)70103-7.
13. **Kinney W, Fetterman B, Poltras N, Lorey T.** 2014. CIN3+ is not the right endpoint for evaluating screening algorithms, as it does not reflect cancer risk accurately. Gynecol Oncol **133S:**186. http://www.gynecologiconcology-online.net/article/S0090-8258(14)00730-6/abstr.
14. **Ronco G, Dillner J, Elfström KM, Tunesi S, Snijders PJ, Arbyn M, Kitchener H, Segnan N, Gilham C, Giorgi-Rossi P, Berkhof J, Peto J, Meijer CJ, International HPV Screening Working Group.** 2014. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet **383:**524–532. http://dx.doi.org/10.1016/S0140-6736(13)62218-7.
15. **Katki HA, Kinney WK, Fetterman B, Lorey T, Poitras NE, Cheung L, Demuth F, Schiffman M, Wacholder S, Castle PE.** 2011. Cervical cancer risk for women undergoing concurrent testing for human papillomavirus and cervical cytology: a population-based study in routine clinical practice. Lancet Oncol **12:**663–672. http://dx.doi.org/10.1016/S1470-2045(11)70145-0.
16. **Gage JC, Schiffman M, Katki HA, Castle PE, Fetterman B, Wentzensen N, Poitras NE, Lorey T, Cheung LC, Kinney WK.** 2014. Reassurance against future risk of precancer and cancer conferred by a negative human papillomavirus test. J Natl Cancer Inst **106:**1–4. http://jnci.oxfordjournals.org/content/106/8/dju153.full.pdf+html.
17. **Kinney W, Wright TC, Dinkelspiel HE, DeFrancesco M, Cox TJ, Huh W.** 2015. Increased cervical cancer risk with screening at longer intervals. Obstet Gynecol **125:**311–315. http://dx.doi.org/10.1097/AOG.0000000000000632.
18. **Gross CP.** 2014. Cancer screening in older persons. A new age of wonder. JAMA Intern Med **174:**1565–1567. http://dx.doi.org/10.1001/jamainternmed.2014.3901.
19. **CDC Newsroom.** 5 November 2014. Millions of US women are not getting screened for cervical cancer. CDC, Atlanta, GA. http://www.cdc.gov/media/releases/2014/p1105-vs-cervical-cancer.html.
20. **Health Council of the Netherlands.** 2011. Population screening for cervical cancer. Health Council of the Netherlands, the Hague, the Netherlands. Publication no. 2011/07. http://www.gezondheidsraad.nl/sites/default/files/summaryBHMK.pdf.
21. **Australian Government Medical Services Advisory Committee.** 2014. Application no. 1276. Renewal of the National Cervical Screening Program. Australian Government Medical Services Advisory Committee, Canberra, Australia. http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/ncsp-renewal.
22. **Wu Y, Chen Y, Li L, Yu G, Zhang Y, He Y.** 2006. Associations of high-risk HPV types and viral load with cervical cancer in China. J Clin Virol **35:**264–269.
23. **Zhao C, Li Z, Nayar R, Levi AW, Winkler BA, Moriarty AT, Barkan GA, Rao J, Miller F, Fan F, Zhou Z, Si Q, Fischer AH, Sturgis CD, Jing X, Marshall CB, Witt BL, Birdsong GG, Crothers BA.** 2015. 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 **139:**184–188. http://dx.doi.org/10.5858/arpa.2014-0028-OA.

SUMMARY

Points of agreement

1. HPV DNA testing alone or coupled with cytology (cotesting) is more sensitive than cytology alone for cervical cancer screening; however, many women are still screened with cytology alone.
2. When determining the optimal screening approach for cervical cancer in addition to assessing the benefits and harm, the cost-effectiveness of the various algorithms needs to be considered.
3. Cancer screening programs that are simple will be easier to implement and should increase compliance.
4. A more organized approach to cervical cancer screening in the United States that increases the number of women participating in screening programs should be a major public health priority.

Issues to be resolved

1. We must determine the optimal endpoint for cervical cancer screening studies. While CIN3+ does not always reflect cancer risk accurately, the rate of invasive cancer is so low that it may not be a practical endpoint.
2. Large observational studies that follow women over time may provide clarity on the effectiveness of primary screening compared to cotesting.
3. Should the optimal screening approach be based on cost-effectiveness or maximizing cancer prevention?
4. From a population management perspective, identifying a cost-effective screening approach is important. While cotesting may be slightly more sensitive, it also is more expensive than HPV primary screening.
5. The sensitivity of cytology in the ATHENA trial, while lower than may have been expected, is in line with that seen in some studies but lower than that seen in other studies.
6. Guidelines addressing cervical cancer screening will need to consider the appropriate testing algorithms as well as the ideal testing interval.
7. Given the controversies in this field, patient education regarding cervical screening will be important so that increasing testing intervals does not decrease testing compliance.

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