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Uptake of Co-testing with HPV and Cytology for Cervical Screening: A population-based evaluation in the United States

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Abstract

Objectives.—Human papillomavirus (HPV) testing for cervical screening has been shown to increase the yield of precancerous disease and reduce the incidence of cervical cancer more than

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Conflict of Interest:
JC and CMW have received funds from grants, cooperative agreements or subcontracts related to cervical screening and triage through their respective institutions. JC reports personal fees from Hologic and grants from Becton Dickinson (BD), Qiagen and Gene First all outside the submitted work. CMW reports receiving reagents and equipment from Roche Molecular Systems, Roche/Ventana Medical Systems, Hologic and Genera Biosystems, research funding from Hologic all through her institution and outside of the submitted work, personal fees from BD. All other authors report no potential conflicts of interest.

cytology alone. Here we document the state-wide uptake of co-testing with HPV and cytology in women aged 30–64 years as recommended by national and international bodies.

Methods.—Registry-based study of all screening cytology and HPV tests in New Mexico from 2008–2019 among women aged 21–64 years, with a focus on cytology negative tests to distinguish co-testing from reflex HPV testing to triage equivocal or mildly abnormal cytology.

Results.—A total of 1 704 055 cervical screening tests from 681 440 women aged 21–64 years in the state of New Mexico were identified. The proportion of screening tests which were co-tests rose from 5.6% in 2008 to 84.3% in 2019 among women aged 30–64 years with a marked change from the near exclusive use of the Hybrid Capture II HPV test, (a signal amplified test method) to the use of target amplified HPV tests. The largest increases were seen between 2013 and 2015, reflecting the introduction and adoption of new clinical guidelines. Increases in co-testing were also seen in younger women.

Conclusions.—Co-testing is now well established in women aged 30–64 years, but smaller increases have also been seen at younger ages, although this is not currently recommended. The impact of co-testing on cervical disease outcomes and number of colposcopies and biopsies in routine population settings remain important, especially in young women.

Introduction.

Although cancer screening with cervical cytology was the standard for decades, co-testing using both cervical cytology and human papillomavirus (HPV) testing was introduced in the United States (U.S.) for cervical screening in 2002. [1] Since then, various recommendations for cervical co-testing have been supported by several studies and randomized trials showing higher detection rates of precancerous lesions [2–4] and lower subsequent cancer rates following a negative screen when HPV testing was compared to cytology only screening. [5, 6]

Co-testing was recommended for women aged 30 years and over by the U.S. Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), the American Society of Colposcopy and Cervical Pathology (ASCCP) and the American Society for Clinical Pathology (ASCP) in 2012–2013. [7, 8] Subsequently, in 2018, the USPSTF recommendation was updated to include primary HPV screening alone in women aged 3065 years. [9] In 2020, the ACS recommended HPV screening alone as the preferred method of screening for women aged 25–65 years. [10]

Co-testing uptake has previously been reported in two hospital-based systems, one from Johns Hopkins in 2006–2013 [11] and one from Olmsted County up to 2016, [12] one health care claims database [13] and one telephone survey where testing was not laboratory confirmed. [14] Here we provide data on the state-wide uptake of co-testing from 2008 through 2019, using the New Mexico HPV Pap Registry (NMHPVPR), which is the only population-based surveillance system for cervical cancer screening and outcomes in the U.S. The NMHPVPR collects information on all HPV and cervical cytology tests and all cervical, vaginal and vulvar biopsies in women who reside in New Mexico, capturing cervical cancer prevention delivery across the full diversity of patients, providers, clinics, systems and payers.

Methods.

All HPV and cervical cytology tests taken from women between the ages of 21–64 years residing in the state of New Mexico between 2007 and 2019 were studied. A cervical screening test was defined as a cytology test without cytology or HPV tests, or biopsy in the previous 300 days, without a concurrent biopsy (within −7 or +5 days) and excluded women with prior hysterectomy or loop electrosurgical excisional procedure (LEEP). In addition, women under active surveillance were excluded including those with a cytology following 1) a prior LEEP; 2) a high-grade cytology (Atypical Squamous Cells – cannot exclude High grade lesions [ASC-H], Atypical Glandular Cells [AGC], or High grade Squamous Intraepithelial Lesion [HSIL] or greater [HSIL+]) or high-grade biopsy (Cervical Intraepithelial Neoplasia (CIN) grade 2 (CIN2)/CIN3/cancer) without LEEP in the prior 3 years; 3) a high-risk HPV positive or cytology following a equivocal or low-grade cytology (Atypical Squamous Cells of Undetermined Significance [ASC-US] or Low grade Squamous Intraepithelial Lesions [LSIL]) or CIN1 biopsy without LEEP in the prior 18 months.

As reflex HPV tests for equivocal or mildly abnormal cytology have been recommended previously, to distinguish co-tests from these reflex tests, we focused on women who had negative cytology, where reflex testing should not have been performed. As the HPV test was ordered without knowledge of the cytology result, these results will reflect co-testing usage for all women. Within this group, an HPV test reported within −5 and +28 days of the cytology test report was considered to be a ‘co-test’. This range of days is a function of the difference in timing of when HPV versus the corresponding cytology test is performed using a single liquid-based cytology (LBC) sample. All other screening tests were assumed to be ‘cytology only’. HPV testing alone without cytology was very uncommon and was therefore not included in our evaluations.

Only the first screening test for each woman within any calendar year was included. The primary objective was to study trends in the use of co-testing over the period of 2008 to 2019. Additional analyses evaluated trends in all screening tests, changes in the type of HPV tests used and HPV positivity rates per test by age.

Results.

Between 2008 and 2019, the total number of cervical screening tests (cytology alone or co-test) in women aged 21–64 years was 1 704 055, of which 1 254 568 were in women aged 30–64 years. In this group there was a 49.8% overall decline in the annual number of screening cytology tests (with or without HPV tests) over this period from 145 281 in 2008 to 72 957 in 2019 (Figure 1 and Table S1) and the median interval between screening tests increased from 15.0 to 39.0 months in women aged 30–64 years. The total number of HPV tests (co-tests or reflex HPV tests performed within −5 and +28 days of cytology) increased from 12 559 in 2008 to 61 991 in 2019.

In women aged 30–64 years with negative cytology, the proportion of screening tests which were co-tests rose from 5.6% (N = 7807) in 2008 to 84.3% (N = 57 369) in 2019 (Figure

2 and Table S2), a year-on-year annual increase of 7.15% (95%CI: 7.06, 7.24). There was a slightly larger co-testing uptake in 2019 in the younger age groups, being 85.6% at ages 30–39 years, 85.2% at 40–49 years and 82.5% at 50–64 years. The largest increases were seen between 2013 and 2015. Smaller increases were also seen in women younger than 30 years of age increasing from 2.7% in 2008 to 19.4% in 2019 among women aged 25–29 years, and from 2.9% to 11.5% among women aged 20–24 years.

HPV positivity in women aged 30–64 years with negative cytology was relatively constant over the evaluation period, ranging from 6.4% in 2008 to 6.6% in 2019. Decreases in HPV positivity were seen in women aged 21–24 years from 23.5% in 2008 to 17.0% in 2019 and in women aged 25–29 years from 14.6% in 2008 to 12.3% in 2019.

A major change in the type of HPV tests used over this period was observed (Figure 3). In 2008 nearly all of the 12 559 tests performed (co-test or reflex HPV test) used the Qiagen Hybrid Capture II (HC2) HPV test (95.9%). HC2 usage was fairly constant until 2013, when the Roche COBAS HPV test became the most common test type (N = 23 318, 52.5%), and this remained so through 2019. However, in 2013 the Hologic APTIMA HPV test began usage, and currently is used almost as often as the COBAS HPV test. In 2019 out of a total of 61 991 tests, there were 28 263 (45.6%) APTIMA HPV tests vs 30 287 (48.9%) COBAS HPV tests, with HC2 HPV test now being much less often used (3 398 tests, 5.5%). A few other HPV tests have also been used, notably Seegene and Cervista, but none were used more than 2500 times in any one year, and all are very rarely used now.

Conclusions and relevance.

Co-testing was introduced in 2002 but was not rapidly and widely adopted until high-level national recommendations for its use in 2012. By 2016, 72.2% of screening tests in women aged 30–64y were co-tests and by 2019 it was 84.3%. We evaluated HPV co-testing trends in women with negative cytology, but, as HPV tests are ordered before cytology results are available, these trends will very likely also represent those for all screening cytology results, including those with positive results. HPV testing alone was uncommonly observed, supporting little to no usage of primary HPV screening through the end of 2019. Previous reports have looked at changes in co-testing up to 2013 or 2016 but these evaluations were in the context of limited localized settings and were not population-based. Different practices may prevail in different U.S. areas, influenced by laboratory's choices, HPV test compatibility and the overall menu of test platforms offered.

The NMHPVPR is able to provide reliable cervical screening trends regardless of screening modalities used and is the only population-based source of co-testing data in the U.S., or indeed anywhere. This population-based evaluation establishes a baseline for comparison across an entire state as cervical screening guidelines continue to evolve with adoption of HPV primary screening representing the next anticipated milestone in cervical screening improvements.

Most cervical disease identified is in HPV positive women [15] so the role of cytology will become largely limited to the triage of these women and not a primary screening.

This is supported by the modelling results of Kim and colleagues [16–18], indicating that a move to primary HPV testing will maintain the high sensitivity of co-testing, reduce the harms of over referral and be more cost-effective. The move to HPV primary screening has been recommended by the USPSTF [9] and the ACS [10], and implementation of these recommendations as quickly as possible should be a priority for the gynecologic community. Uptake of co-testing was significantly delayed before high population coverage was achieved which suggests continuing education of both providers and patients to support adoption of primary HPV screening will be important. It is also only reasonable to anticipate the adoption of HPV primary screening may suffer extended delays as a result of the recent pandemic. The NMHPVPR offers an opportunity to document the year-on-year adoption of primary screening following national recommendations.

It is important to acknowledge that optimal benefits versus harms associated with primary HPV screening will only be realized through coincident lengthening of screening intervals and adherence to recommendations for follow-up of abnormal/positive HPV results. Partial HPV genotyping is expected to play a significant role in follow-up strategies and risk stratification of women who are screened by co-testing or primary HPV screening. Colposcopists need to be aware of the HPV status (including genotype, especially HPV16/18) of women referred to them, as it will have a major impact on the llikelihood of having a high-grade lesion. Efforts to estimate the impact of co-testing on short-term and long-term follow-up practices including biopsy rates and detection of cervical intraepithelial neoplasia grades 2 and 3 and cancer remain essential.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

New Mexico HPV Pap Registry Steering Committee Collaborators:

NMHPVPR Steering Committee members listed contributed to the content, reviewed and gave input, approved the manuscript and participated in the final decision to submit to the journal. The NMHPVPR Steering Committee members participating in this effort are as follows: Nancy E. Joste, MD, University of New Mexico Health Sciences Center and Tricore Reference Laboratories, Albuquerque, New Mexico; Walter Kinney, MD, Sacramento California; Cosette M. Wheeler, PhD, University of New Mexico Comprehensive Cancer Center; Charles Wiggins PhD MSPH, University of New Mexico Comprehensive Cancer Center; Michael Robertson BS, University of New Mexico Comprehensive Cancer Center; Ruth McDonald, MS, University of New Mexico Comprehensive Cancer Center; Alan Waxman, MD MPH, University of New Mexico Health Sciences Center; Steven Jenison, MD, University of New Mexico Health Sciences Center; Philip E. Castle, PhD MPH, Albert Einstein College of Medicine (member through October 1, 2019); Jean Howe MD MPH, US Indian Health Service; Debbie Saslow, PhD, American Cancer Society; Jane J. Kim PhD, Harvard TH Chan School of Public Health; Mark H. Stoler MD, University of Virginia; Jack Cuzick, PhD, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, England; Rebecca B. Perkins, MD MS, Boston University; Janice L. Gonzales, MD MPH FAAP, New Mexico Department of Health; Salina Torres PhD MPH, New Mexico Department of Health; Giovanna Rossi, MSc, Collective Action Strategies, Community Member; and Kevin English, DrPh MPH, Albuquerque Area Southwest Tribal Epidemiology Center (AASTEC). No compensation was received for contributions to this manuscript by any named authors or by the NMHPVPR Steering Committee members.

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References

[1]. Saslow D, Runowicz CD, Solomon D, et al.American Cancer Society guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin2002;52(6):342–62. [PubMed: 12469763]

[2]. Schiffman M, Herrero R, Hildesheim A, et al.HPV DNA testing in cervical cancer screening: results from women in a high-risk province of Costa Rica. Jama2000;283(1):87–93. [PubMed: 10632285]

3. 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 Cancer2006;119(5):1095–101. [PubMed: 16586444]

4. Bulkmans NW, Berkhof J, Rozendaal L, et al.Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer: 5-year follow-up of a randomised controlled implementation trial. Lancet2007;370(9601):1764–72. [PubMed: 17919718]

5. Ronco G, Dillner J, Elfström KM, et al.Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. Lancet2014;383(9916):524–32. [PubMed: 24192252]

6. Sankaranarayanan R, Nene BM, Shastri SS, et al.HPV screening for cervical cancer in rural India. N Engl J Med2009;360(14):1385–94. [PubMed: 19339719]

7. 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 Clin2012;62(3):147–72. [PubMed: 22422631]

8. Moyer VA. Screening for cervical cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med2012;156(12):880–91, w312. [PubMed: 22711081]

9. Curry SJ, Krist AH, Owens DK, et al.Screening for Cervical Cancer: US Preventive Services Task Force Recommendation Statement. Jama2018;320(7):674–686. [PubMed: 30140884]

10. Fontham ETH, Wolf AMD, Church TR, et al.Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA: A Cancer Journal for Clinicians2020;70(5):321–346. [PubMed: 32729638]

11. Silver MI, Rositch AF, Phelan-Emrick DF, et al.Uptake of HPV testing and extended cervical cancer screening intervals following cytology alone and Pap/HPV cotesting in women aged 30–65 years. Cancer Causes Control2018;29(1):43–50. [PubMed: 29124542]

12. MacLaughlin KL, Jacobson RM, Radecki Breitkopf C, et al.Trends Over Time in Pap and Pap-HPV Cotesting for Cervical Cancer Screening. J Womens Health (Larchmt)2019;28(2):244–249. [PubMed: 30614380]

13. Watson M, Benard V, Flagg EW. Assessment of trends in cervical cancer screening rates using healthcare claims data: United States, 2003–2014. Prev Med Rep2018;9:124130.

14. Watson M, Benard V, King J, et al.National assessment of HPV and Pap tests: Changes in cervical cancer screening, National Health Interview Survey. Prev Med2017;100:243–247. [PubMed: 28502575]

15. Katki HA, Schiffman M, Castle PE, et al.Five-year risk of recurrence after treatment of CIN 2, CIN 3, or AIS: performance of HPV and Pap cotesting in posttreatment management. J Low Genit Tract Dis2013;17(5 Suppl 1):S78–84. [PubMed: 23519309]

16. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of human papillomavirus DNA testing in the United Kingdom, The Netherlands, France, and ItalyJ Natl Cancer Inst. 2005615;97(12):888–95. [PubMed: 15956650]

17. Burger EA, Ortendahl JD, Sy S, et al.Cost-effectiveness of cervical cancer screening with primary human papillomavirus testing in Norway. Br J Cancer. 2012424;106(9):1571–8. [PubMed: 22441643]

18. Kim JJ, Campos NG, Sy S, et al.New Mexico HPV Pap Registry Steering Committee. Inefficiencies and High-Value Improvements in U.S. Cervical Cancer Screening Practice: A Cost-Effectiveness Analysis. Ann Intern Med. 20151020;163(8):589–97. [PubMed: 26414147]

Highlights

- Cervical cancer screening by co-testing increased from 5.6% in 2008 to 84.3% in 2019 among women ages 30–64 years.
- Smaller increases in co-test usage were observed in women of younger ages, although not currently recommended.
- The median screening interval increased from 15 to 39 months as screening guideline recommendations were adopted.
- The near exclusive use of the Hybrid Capture II HPV test has changed to the use of target amplified HPV tests.

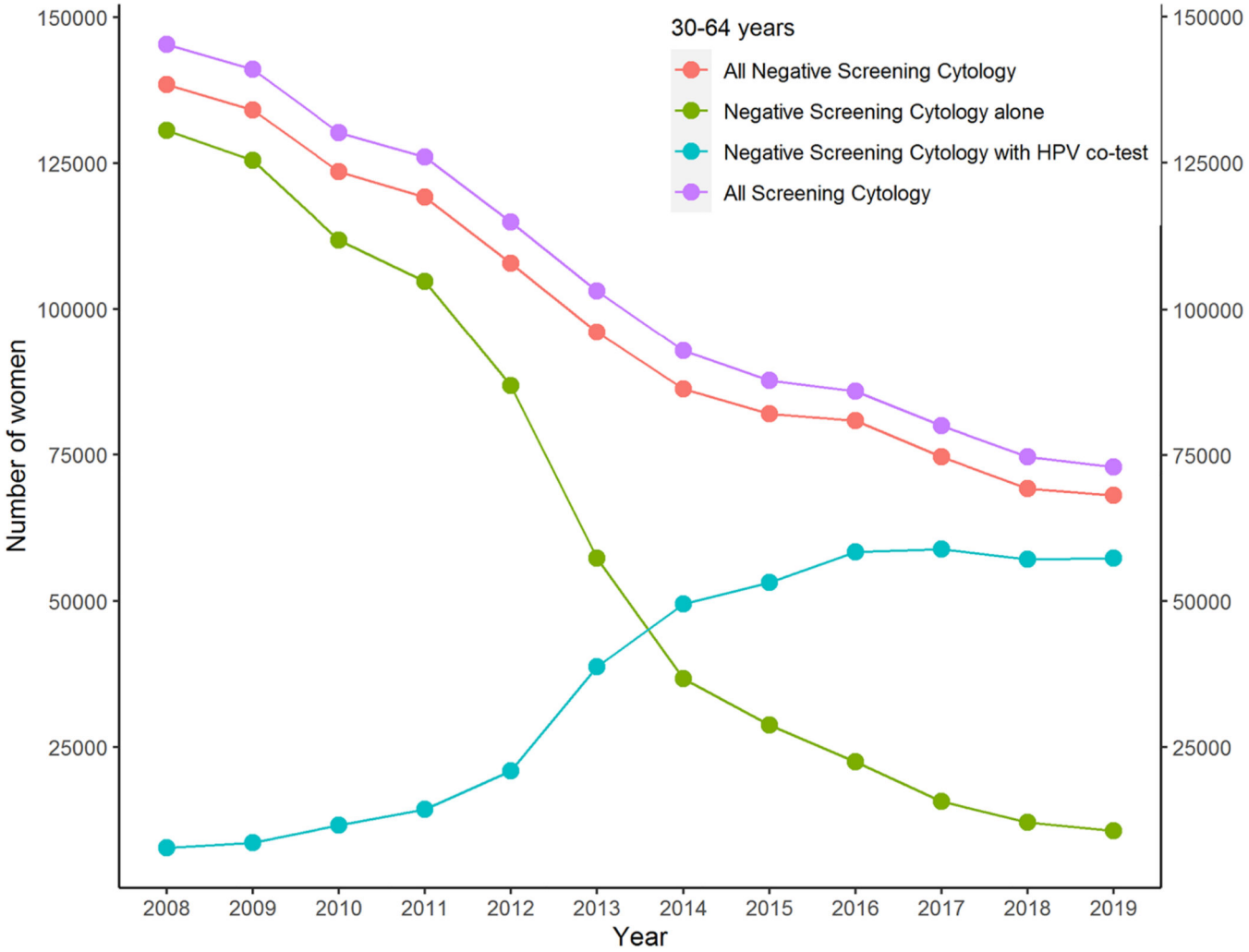

Figure 1:

Number of women with negative screening cytology with or without HPV co-tests, aged 30–64 years, by year. See Methods for the definition of a screening cytology. All screening cytology including positive results also shown.

The change in number of women with negative screening cytology, by year (2008–2019), is plotted for women screening with negative cytology regardless of testing method, for women with negative cytology alone, and women co-tested with negative cytology. Screening cytology is restricted to the first per women in each calendar year. For comparison number of negative screening cytology in all women screening is also plot as is all screening cytology including positive results.

. Numbers screening are restricted to women aged 30–64 years.

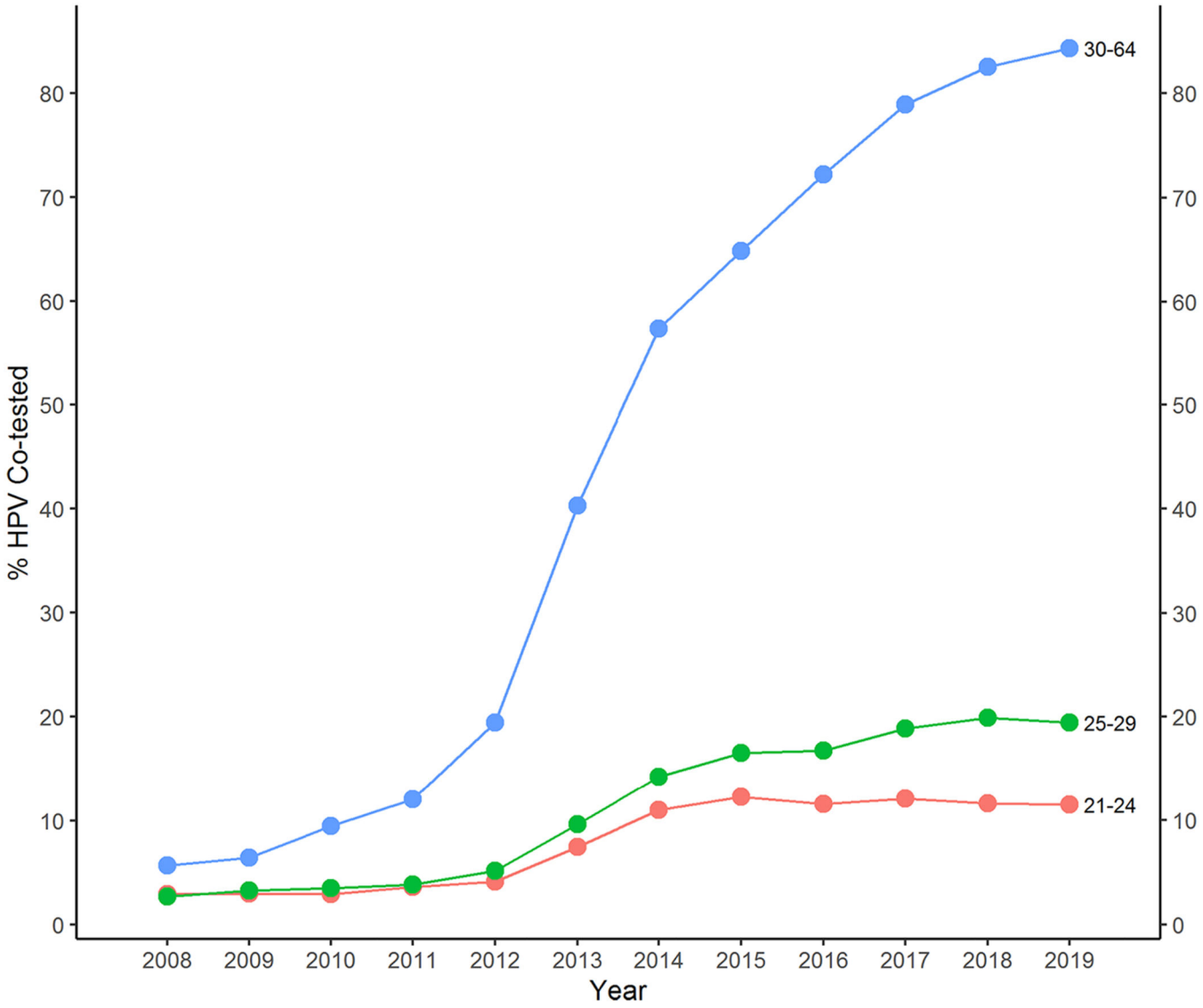

Figure 2:

Proportion of women with negative screening cytology co-tested (HPV and cytology), by year and age group.

The proportion of women who were co-tested out of all women with negative screening cytology is plotted, by year (2008–2019). Curves are plotted separately for women aged 21–24 years, 25–29 years and 30–64 years.

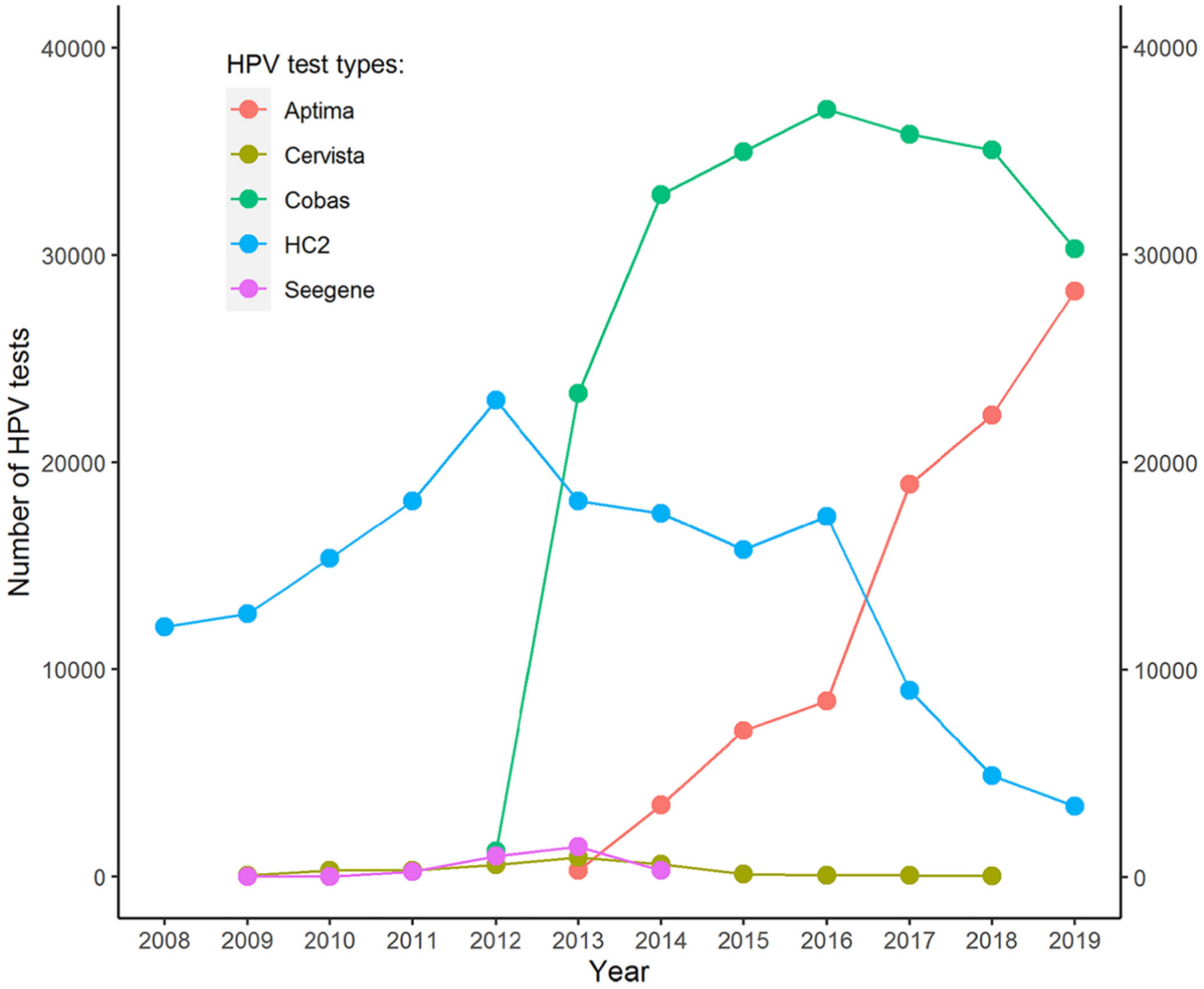

Figure 3:

Number of HPV tests within −5 and +28 days of cytology (co-test or reflex HPV) by assay in New Mexico, 2008 – 2019

Total number of HPV tests performed within −5 and +28 days of cytology (co-test or reflex HPV test) by assay type are plot by year (2008–2019). HPV assay types include the most used in New Mexico (Aptima, Cervista, Cobas, HC2 and Seegene).