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Original Study

Cost Savings of HPV Testing Alone Versus Co-Testing for Cervical Cancer Screening at a Student-Run Free Clinic

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Abstract

Background: Primary high-risk human papillomavirus (hrHPV) testing is an approved alternative method of cervical cancer screening by the United States Preventative Services Task Force. The University of South Florida BRIDGE (Building Relationships and Initiatives Dedicated to Gaining Equality) Clinic is a student-run free clinic with limited screening resources, serving patients below the poverty line. This study aimed to determine the potential cost benefit of primary hrHPV testing in this population.
Methods: A retrospective observational study of clinic invoices and patient charts from January 2014 to December 2018 of women receiving cervical cancer screening by co-testing was performed.
Results: BRIDGE spent $29,122.37 on screening over the five-year period for 128 patients. By eliminating cervical cytology, the clinic would have saved $11,594.34. Fifteen patients had abnormal results, ten of which were hrHPV-positive.
Conclusions: The $11,594 saved would allow BRIDGE to screen 110 more patients by primary hrHPV testing and another three by eliminating follow-up for atypical squamous cells of undetermined significance, hrHPV-negative results. One patient with low-grade squamous intraepithelial lesion and negative hrHPV represents a 0.8% risk of missing precancerous lesions the clinic would assume by adopting primary hrHPV testing.

Introduction

Although primary high-risk human papilloma virus (hrHPV) DNA testing is an approved alternative method of cervical cancer screening for patients over the age of 30, its cost and clinical outcome benefits over the use of concurrent cervical cytology and hrHPV testing (co-testing) are debated.[1] Current strategies for the screening of women at average risk of cervical cancer between the ages of 30 and 65 include primary hrHPV testing every five years, co-testing every five years, or cervical cytology every three years. It is generally agreed upon that women between 21 and 29 years of age should be screened with cervical cytology alone, and women over the age of 65 with two prior normal tests no longer need cervical cancer screening. Primary hrHPV testing was endorsed by the United States Preventative Services Task Force (USPSTF) in 2018 as a grade-A recommendation for cervical cancer screening in women ages 30 to 65, but the American College of Obstetricians and Gynecologists (ACOG) and the American Society for Colposcopy and Cervical Pathology (ASCCP) recommend co-testing as their preferred screening method.[2-4] In July 2020, the American Cancer Society (ACS) published new guidelines for cervical cancer screening of patients at average risk, with primary hrHPV testing as the preferred choice.[5]

Four European trials demonstrated greater than 30% improvement in sensitivity for detecting cervical intraepithelial neoplasia grade 3 (CIN 3) or worse with hrHPV-based testing compared to cervical cytology, without appreciable gain by using both tests in combination.[6] Some

retrospective cohort studies suggest primary hrHPV testing is less expensive than primary cervical cytology and equally effective to co-testing; the most robust study by Jin et al., comprised of nearly 100,000 patients, demonstrated that primary hrHPV testing detected more CIN 3 or worse results and was less expensive than primary cervical cytology.[7] The majority of these patients were white, married, and privately insured. Proponents of co-testing argue that primary hrHPV testing produces more false-negative results for earlier disease, thereby requiring more follow-up visits and colposcopies, and contributes to increased cost and burden of disease.[8] This is supported by a hypothetical economic model developed by Felix et al., which demonstrated a savings of $39 per patient using co-testing screening.[9]

Free clinics commonly serve demographically distinct populations from those studied in recent trials, and uninsured minorities with poor access to healthcare are likely more at risk for highly preventable disease including cervical cancer. However, these clinics are also limited in the services they can provide to their at-risk patients due to cost and resource availability. BRIDGE (Building Relationships and Initiatives Dedicated to Gaining Equality) is a student-run free clinic through the University of South Florida Morsani College of Medicine which serves those in Tampa's University Community Area below the poverty line. The clinic's patient population is predominantly Hispanic, Spanish-speaking only, and uninsured. Since its founding in 2007, BRIDGE has grown to include services from the majority of the university's health professions schools and provides more than 1,000 patient visits annually. Clinic visits, limited procedures, and diagnostic and screening tests are offered at no cost to the patient, including testing for cervical cancer, accounting for nearly one million dollars of healthcare cost each year.

The purpose of this study is to determine the potential screening cost benefit of primary hrHPV testing in this uninsured, minority population over a retrospective five-year period and use rates of abnormal testing to examine clinical outcome benefits in a free clinic setting, which lacks the financial and diagnostic resources available in previously conducted studies.

Methods

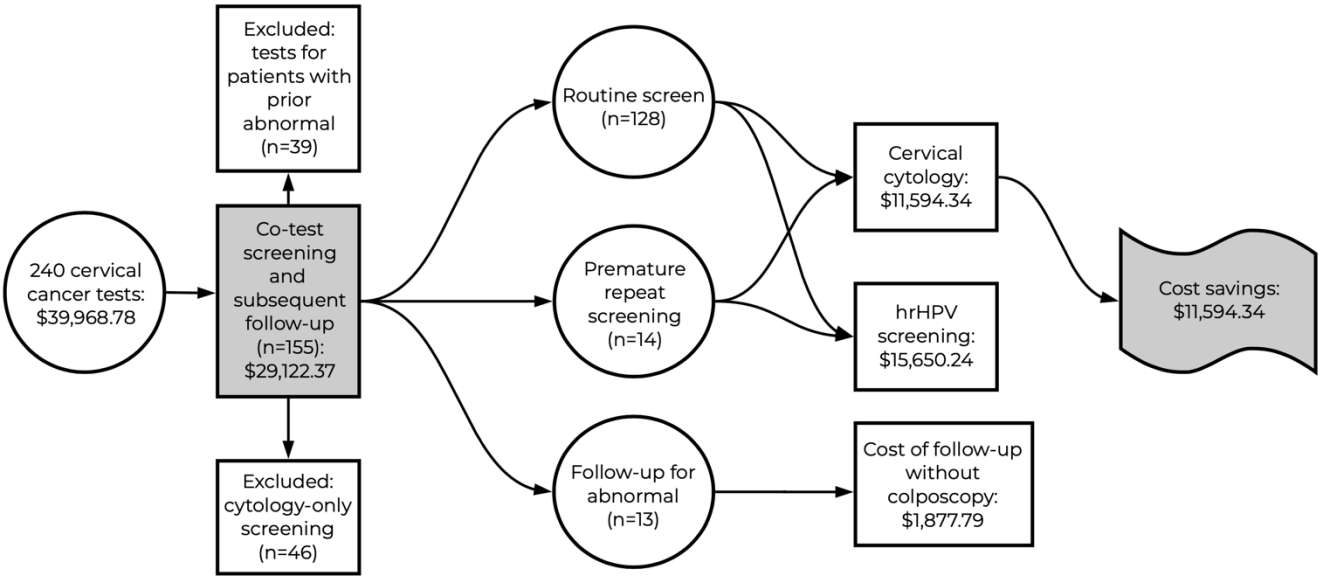
A retrospective observational study of all women receiving cervical cancer screening at BRIDGE clinic from 2014 to 2018 was performed. This study was deemed exempt from review by the USF Institutional Review Board. Monthly laboratory invoices from Quest Diagnostics spanning the five-year study period were reviewed; invoices detailed all laboratory orders itemized patient-by-patient for patients who received testing within a month-long billing period, including distinct orders for cervical cytology and hrHPV DNA testing. Patients receiving cervical cytology testing only were excluded; only women who received both cervical cytology and hrHPV DNA testing were included. If a patient underwent multiple cervical cancer screenings via co-testing within the five-year study period, each instance was recorded.

Corresponding patient charts were then reviewed for history of prior abnormal cervical cytology, which were excluded; only women with no history of prior abnormal results were included, thereby representing the patient population undergoing screening rather than diagnostic testing. Charts were then reviewed for results of patients' co-testing. Any necessary follow-up required due to abnormal testing was recorded. Patient demographic factors such as race/ethnicity, marital status, and smoking history were abstracted at that time. The total cost of cervical cancer screening via co-testing was determined, as well as that of hrHPV DNA testing alone. If results were unable to be found or indicated unsatisfactory samples, these tests were included in the total cost. Chi-squared analysis was used to assess demographic differences between patients with normal results and those with abnormal results.

Results

Fifty-one invoices were retrieved for the period between January 2014 and December 2018; there were no invoices for months corresponding with student winter breaks (December), and four invoices across this five-year interval were missing from the electronic medical record. A total of 240 cervical cancer tests were performed, amounting

Figure 1. BRIDGE Clinic's distribution of cervical cancer testing costs over a five-year period



hrHPV: high-risk human papillomavirus

to $39,968.78. After exclusion of cervical cytology-only tests (n=46) and co-testing for patients with prior abnormal results (n=39), cervical cytology and hrHPV co-testing cost $29,122.37. These 155 co-tests represent the initial screening of 128 patients, 14 premature repeat screens within the five-year period, and four cervical cytology tests and nine co-tests performed for follow-up evaluation of abnormal results. The results of five patients' tests were unavailable, either due to error in handling or inadequate sampling; this expense remains included in the total. The total cost for screening of these 128 patients was $27,244.58, with $15,650.24 (57%) attributed to hrHPV testing and $11,594.34 (43%) to cervical cytology. The total cost of follow-up testing excluding colposcopy was $1,877.79. Figure 1 demonstrates the breakdown of clinic cost based on inclusion criteria and type of test performed. Yearly totals and average price of both tests are demonstrated in Table 1.

Put simply, the dollar amount that would have been spent on a primary hrHPV screening strategy in our patient population from 2014 to 2018 was $15,650, while the co-testing cost $27,245. Of the 128 patients receiving these tests, the majority were Hispanic (85%), married or with a monogamous partner (63%), multiparous (81%), and nonsmoking (85%), with an average age of 45.7 years at the time of testing; all were uninsured (Table 2).

Of the 14 premature repeat co-tests performed earlier than recommended by current screening guidelines, five were done sooner than two years after the prior test in the absence of risk factors. Three premature tests bore abnormal results: two atypical squamous cells of undetermined significance (ASCUS), hrHPV-negative and one cervical cytology-negative, hrHPV-positive. One patient underwent a third screening test, which was normal and negative.

Fifteen patients had abnormal cervical cytology and/or positive hrHPV testing at some point over the five-year study period, seven of whom were either screened late enough in the study

Table 1. Annual cost of BRIDGE Clinic co-testing

Year	Patients Screened	Average Cost of Cervical Cytology Per Patient	Average Cost of hrHPV Testing Per Patient	Total Cost
2014	19	$78.00	$102.11	$3,421.97
2015	37	$77.18	$110.26	$6,935.49
2016	38	$79.91	$111.45	$7,271.94
2017	36	$82.82	$105.88	$6,793.13
2018	25	$82.11	$105.88	$4,699.84
		Five-Year Total:		$29,122.37

Table 2. Patient demographics

Characteristic	N=128	%
Race		
White	115	90
American Indian	2	2
Asian	4	3
Black	7	5
Ethnicity		
Hispanic	109	85
Non-Hispanic	19	15
Insurance Status		
Insured	0	0
Uninsured	128	100
Marital Status		
Single	23	18
Married/Monogamous	80	63
Separated/Widowed	25	20
Parity		
None	10	8
One	14	11
Two or More	104	81
Smoking		
Never	109	85
Current	10	8
Former	9	7
Age, years		
21-29	4	3
30-64	122	95
65+	2	2

period that follow-up testing was performed outside the review window (43%, n=3) or were lost to follow-up (57%, n=4), defined as having no subsequent visits or communication after the encounter in which testing occurred. Four patients had cervical cytology results of ASCUS with negative hrHPV testing, two of whom received repeat testing the following year and were normal and negative. One patient's results indicated low-grade squamous intraepithelial lesion (LSIL) with hrHPV-negative testing in 2017. No follow-up was documented for this patient at the time of data collection. One patient's testing showed LSIL cervical cytology and positive hrHPV in 2016; repeat cervical cytology testing in 2017 yielded the same results, and the patient was then sent for colposcopy at a partner clinic. Two patients had ASCUS with positive hrHPV. One received repeat co-testing in the two subsequent years with normal and negative results both times; the other had this first abnormal result in 2018 and had not received follow-up testing at the time of data collection. Seven patients had normal cervical cytology with positive hrHPV testing, with three lost to follow-up. Four of these underwent follow-up testing, and three had persistent positive hrHPV at the end of the study period. There were statistically significant differences in marital status and age between patients with abnormal testing and those with normal results (p=0.001), as well as race but not ethnicity (p=0.003 and p=0.317, respectively) (Table 3).

Table 3. Demographics of patients with normal versus abnormal results

Characteristic	Normal N=108* (%)	Abnormal N=15† (%)	p
Race			
White	95 (88)	15 (100)	0.003
American Indian	2 (2)	0 (0)	-
Asian	4 (4)	0 (0)	-
Black	7 (6)	0 (0)	-
Ethnicity			
Hispanic	90 (83)	14 (93)	0.317
Non-Hispanic	18 (17)	1 (7)	-
Marital Status			
Single	15 (14)	8 (53)	0.001
Married/Monogamous	68 (63)	7 (47)	-
Separated/Widowed	25 (23)	0 (0)	-
Parity			
None	8 (7)	2 (14)	0.430
One or More	100 (93)	13 (86)	-
Smoking			
Never	93 (86)	11 (73)	0.237
Current	4 (4)	2 (13)	-
Former	11 (10)	2 (13)	-
Average Age, years (SD)	45.0 (9.3)	36.4 (9.0)	0.001

SD: standard deviation
**Total patients in this table sum to 123 due to 5 patients having missing results*
†*Abnormal results were defined as atypical squamous cells of undetermined significance or worse cervical cytology and/or positive high-risk human papillomavirus testing*

Discussion

To our knowledge, this is the first manuscript examining cost savings via primary hrHPV testing based on actual expenses of a free student-run clinic for the underserved. Our results demonstrated a potential cost savings of $11,594 by foregoing cervical cytology for cancer screening. Using the test's most recent average cost, the $11,594 saved would allow the clinic to perform 110 additional cervical cancer screens by primary hrHPV testing, an increase of up to 85% more patients. Three additional patients could have been screened with the $359.20 that would have been saved without follow-up on ASCUS, hrHPV-negative results as the atypical cervical cytology would not have been noted by primary hrHPV testing.

The results reflect elements of variability not accounted for by hypothetical models, namely lost or inadequate samples, loss of patients to follow-up, premature screening by patient preference, and change in practice trends. Five patients underwent repeat screening earlier than the two-year interval allowed by Medicare, all of whom had no apparent history concerning for high-risk of developing cervical cancer. Although charts were not reviewed for patients receiving cervical cytology alone and therefore age was not determined, 30 patients received cervical cancer screening by this method in 2014 compared to one in 2018. This suggests the clinic's adoption of new screening recommendations for the use of co-testing began in 2014, but explicit documentation of this change is not available. Additionally, the results show deviation from guidelines for follow-up of abnormal results because BRIDGE must refer to partner clinics to have colposcopies performed. Guidelines for abnormal results suggest colposcopy for any hrHPV-positive results, ASCUS cervical cytology without hrHPV that persists at three-year follow-up, or LSIL without hrHPV that persists at one-year follow-up. Repeat co-testing for hrHPV-positive, abnormal cervical cytology was instead performed because this was more readily available to the patients. BRIDGE uses closer surveillance for abnormal results by repeating co-testing in six months to a year, requiring the patient to test negative for hrHPV two consecutive times before returning to normal co-testing schedule, per the clinic's supervising gynecologist's recommendation.

Given the clinic's limited access to colposcopy, if primary hrHPV testing had been performed, the management of 10 of the 15 patients with abnormal results would have been the same: co-testing within a year. The four patients who had ASCUS cervical cytology and negative hrHPV would not have had abnormal results by primary hrHPV-screening. For the one patient with LSIL cervical cytology and negative hrHPV, as a 25-year-old, her cervical dysplasia may have resolved or progressed to invasive disease without being tested for another five years. Estimates for disease regression of LSIL with negative hrHPV testing among patients in their early to mid-twenties are greater than 58% in one year and greater than 80% in three years; the risk of progression to CIN 2 and 3 is 3% and 0.2%, respectively. This represents a 0.8% risk of missing a precancerous lesion over a five-year period that the clinic would assume by adopting primary hrHPV testing (one test out of 123 available results); the yearly risk would be 0.16%. This risk would not change significantly if the patients with missing results all had negative results. If all missing results were assumed to be positive, given the same proportion of various abnormal findings seen in the 15 patients described above, the risk of missing a precancerous lesion would only increase to 1.0% (0.33 out of 5, for a total of 1.33 out of 128).

The primary limitation of this study is the narrow time period observed, capturing only one screening interval and failing to include cost of follow-up for abnormal results at the end of the observed window. Additionally, data from 2014 is more reflective of screening by cervical cytology alone as the clinic was just beginning to offer co-testing at that time. Four patients under the age of 30 received co-testing rather than guideline-concurrent cervical cytology-only testing. This study does not include cost of diagnostic testing (colposcopy and biopsy) or treatment in the total cost, as these are not services the free clinic is able to provide at this time. Additionally, this study is not able to account for our patients' HPV vaccination status, as this is infrequently documented in the chart or recalled by patients. Patients are assumed to be unvaccinated given their average age and insurance status. This does not limit the cost analysis for our patient

population as it would not change the need for or schedule of hrHPV screening. Cost savings for cervical cancer screening and follow-up may be greater in a cohort of HPV-vaccinated patients, but there have not yet been any studies demonstrating this level of efficacy of the vaccine.

Reducing costs is only one factor in how free clinics could provide cervical cancer screening to a greater number of underserved patients. As discussed by Stoler et al., the combination of seven possible cervical cytology results and two HPV results yields 14 potential outcomes, thus 14 starting points for the follow-up algorithm.[10] Simplifying this to two would be easier on volunteer providers and may increase patient understanding of and compliance with cervical cancer screening.[11] In the future, patient willingness to undergo cervical cancer screening may increase dramatically if they are able to self-swab for hrHPV. In a review conducted by Arbyn et al., self-sampling for hrHPV demonstrated similarly accurate results compared to clinician sampling.[12] This may be beneficial for free clinics such as BRIDGE by shortening the length of a gynecologic visit and allowing more patients to be seen and screened in a single clinic session. BRIDGE relies on providers across specialties to provide care for its patients, including gynecologists, internists, and family physicians. Implementing a change in policy for cervical cancer screening requires discussion among these groups whose governing bodies have differing opinions on primary hrHPV testing. However, these results present a persuasive argument.

Conclusion

Based on these results, primary hrHPV testing can be a significant cost benefit with slightly increased risk of missed detection of a precancerous lesion. This would allow for simplification of the follow-up algorithm, potentially increase patient compliance, and provide funds to screen a greater number of patients in an underserved population.

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Disclosures

The authors have no conflicts of interest to disclose.

References

1. Huh WK, Ault KA, Chelmow D, et al. Use of primary high-risk human papillomavirus testing for cervical cancer screening: interim clinical guidance. Obstet Gynecol 2015;125:330–7. LINK
2. Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer: US Preventive Services Task Force Recommendation Statement. US Preventive Services Task Force. JAMA 2018;320:674–86. LINK
3. Gynecologists ACoOa. Practice Advisory: Cervical Cancer Screening [Internet]. 2019. LINK
4. Huh W, Ault KA, Chelmow D, et al. Use of Primary High-Risk Human Papillomavirus Testing for Cervical Cancer Screening: Interim Clinical Guidance. J Lower Gen Tract Dis. 2015;19:91-6. LINK
5. Fontham ET, Wolf AM, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. CA: Cancer J Clin. LINK
6. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: fol- low-up of four European randomised controlled trials. Lancet. 2014;383:524-32. LINK
7. Jin X, Lipold L, Foucher J, et al. Cost-Effectiveness of Primary HPV Testing, Cytology and Co-testing as Cervical Cancer Screening for Women Above Age 30 Years. J Gen Intern Med. 2016;31(11):1338-44. LINK
8. Randall M. Cervical Cancer & Co-testing: What is the Economic Impact? [Internet]. ReachMD; 2021. LINK
9. Felix J, Lacey, MJ, Miller, JD. The Clinical and Economic Benefits of Co-Testing Versus Primary HPV Testing for Cervical Cancer Screening: A Modeling Analysis. J Women's Health. 2016;25(6):606-16. LINK
10. Barron S, Austin RM, Li Z, Zhao C. Follow-up outcomes in a large cohort of patients with HPV-negative LSIL cervical screening test results. Am J Clin Pathol. 2015;143:(4)485–491. LINK
11. Stoler M, Austin, RM, Zhao, C. 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. J Clin Microbiol. 2015;53(9):2798-804. LINK
12. Arbyn M, Smith SB, Sultana F, et al. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018;363. LINK