Cost-Effectiveness of Offering Cervical Cancer Screening with HPV Self-Sampling among African-American Women in the Mississippi Delta

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ABSTRACT

Background: African-American women in the United States have an elevated risk of cervical cancer incidence and mortality. In the Mississippi Delta, cervical cancer disparities are particularly stark.

Methods: We conducted a micro-costing study alongside a group randomized trial that evaluated the efficacy of a patient-centered approach ("Choice" between self-collection at home for HPV testing or current standard of care within the public health system in Mississippi) versus the current standard of care ["Standard-of-care screening," involving cytology (i.e., Pap) and HPV co-testing at the Health Department clinics]. The interventions in both study arms were delivered by community health workers (CHW). Using cost, screening uptake, and colposcopy adherence data from the trial, we informed a mathematical model of HPV infection and cervical carcinogenesis to conduct a cost-effectiveness analysis comparing the "Choice" and "Standard-of-care screening" interventions among un/underscreened African-American women in the Mississippi Delta.

Results: When each intervention was simulated every 5 years from ages 25 to 65 years, the "Standard-of-care screening" strategy reduced cancer risk by 6.4% and was not an efficient strategy; "Choice" was more effective and efficient, reducing lifetime risk of cervical cancer by 14.8% and costing $62,720 per year of life saved (YLS). Screening uptake and colposcopy adherence were key drivers of intervention cost-effectiveness.

Conclusions: Offering "Choice" to un/underscreened African-American women in the Mississippi Delta led to greater uptake than CHW-facilitated screening at the Health Department, and may be cost-effective.

Impact: We evaluated the cost-effectiveness of an HPV self-collection intervention to reduce disparities.

Introduction

Cervical cancer incidence is an indicator of health disparities. Because cervical cancer is largely preventable through organized screening programs that detect and treat precursor lesions, and prophylactic human papillomavirus (HPV) vaccination programs that can prevent infections if administered before sexual initiation, the disease reflects a lack of access to health care. Although cervical cancer disparities based on race have narrowed in the United States in recent years, Black women still have an elevated risk of cervical cancer incidence (8.9 per 100,000 women) and mortality (3.2 per 100,000 women) compared with Non-Hispanic White women (7.1 and 2.0 per 100,000 women, respectively; refs. 1, 2). In the Mississippi Delta, one of the poorest regions in the United States (3), cervical cancer incidence among Black women is 12.5 per 100,000 (compared with 9.2 per 100,000 among White women in the region; ref. 4).

Although 82.3% of women of screening ages 21 to 65 years in Mississippi report that they have received screening in the past three years (5), data on screening coverage among Black women in the Delta region are sparse. A door-to-door recruitment effort found that of 516 women ages 26 to 65 years living in the Delta, 66.9% reported screening in the last three years (6). The prevalence of oncogenic HPV infection—which, if persistent, can progress to cervical precancer and cancer—among women of screening age in the Delta region is 18%, which is higher than similarly aged women in other U.S. locales (7–10).

For women who do not attend the clinic for cervical cancer screening, self-collection at home for HPV testing ("self-sampling") shows similar sensitivity to detect precancer as provider-collection of HPV specimens at the clinic (11). Furthermore, engaging with women through a door-to-door approach by trusted individuals in the community may improve screening uptake (12–14). To examine the efficacy of a patient-centered approach ("Choice" between two cervical cancer screening modalities) versus the current standard of care within the public health system in Mississippi ("Standard-of-care" arm screened at the Health Department clinics)—both delivered by community health workers (CHW)—to improve screening uptake, we conducted a group randomized trial among un/underscreened African-American women in the Mississippi Delta (Clinical Trials Registration: NCT03713710). We found that women in the "Choice" arm were more than five times as likely to adhere to screening compared with women in the "Standard-of-care screening" arm. Among women in the "Choice" arm, screening uptake was 48% among those who selected self-collection at home for HPV testing compared with 7.5% among those who selected screening at the local health department (15).

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Our objective was to estimate the cost and cost-effectiveness of the "Choice" and "Standard-of-care screening" interventions among un/under-screened African-American women in the Mississippi Delta.

Materials and Methods

Model description

To evaluate the cost-effectiveness of the "Choice" intervention versus "Standard-of-care screening," we used a previously published mathematical model of HPV infection and cervical pathogenesis. This individual-based Monte Carlo microsimulation model has been calibrated to fit epidemiologic data from women in the United States, and can be used to simulate the lifetime course of HPV infections under different prevention strategies (16, 17). A cohort of theoretical girls is simulated beginning at age 9 years, before sexual initiation. Each month, members of the cohort face a probability of transitioning between health states [i.e., normal cervix, HPV infection, histologic grade of precancer cervical intraepithelial neoplasia grade 2 or grade 3 (CIN2, CIN3), and stage of cancer] until either death from all-cause mortality or cervical cancer after its onset. As we have previously described, transition probabilities may vary by age, HPV type (HPV 16, 18, 31, 33, 45, 52, 58, other oncogenic types, or non-oncogenic types), duration of infection or lesion status, and prior type-specific HPV infection (15, 16). Uncertain transition probabilities—including HPV incidence, CIN regression, invasion, and type-specific HPV re-infection—were calibrated to data on HPV prevalence and type distribution among women with and without lesions; we used the 50 top-fitting sets of input parameter values (i.e., those with the highest goodness-of-fit score compared against epidemiologic data targets) for cost-effectiveness analysis as a form of probabilistic sensitivity analysis. The model has been validated against data from SEER cancer registries assuming current screening practice patterns in the United States (17).

For this analysis, we assumed that the underlying natural history of HPV infection does not vary by race, and that existing cervical cancer disparities are due to differences in access to health care and screening. We applied background mortality rates and cancer mortality rates specific to Black women in the United States; hysterectomy rates by age were assumed to be the same as for the general population (18–20). Cost data inputs for each arm of the trial were based on a micro-costing study we conducted alongside the group randomized trial; screening uptake and colposcopy adherence in each arm were based on trial findings (**Table 1**; Supplementary Table S1). Test performance, treatment efficacy, and cancer treatment costs were drawn from the literature (21–25).

In accordance with guidelines for conducting cost-effectiveness analysis, all costs and life-years were discounted at an annual rate of 3% to reflect time preferences. We calculated incremental cost-effectiveness ratios (ICER) after eliminating strategies that were more costly and less effective (i.e., dominated) or with a higher ICER than more effective strategies (i.e., extended dominance).

Strategies

Although the trial involved a single round of screening, we assumed the intervention would be offered to a cohort of women every 5 years from ages 25 to 65 years; the five-year interval was selected in accordance with national U.S. Preventive Services Task Force screening guidelines for both HPV primary testing and cytology/HPV co-testing (26). As in the study, we assumed CHWs would go door-to-door and visit community gathering sites, approaching women without prior identification of eligibility; women were eligible to participate if they identified as African-American; were ages 25 to 65 years; resided in participating towns, had no prior history of cervical cancer or hysterectomy, were not currently pregnant, had not given birth in the prior 8 weeks, and had not been screened in the last four years (15). Eligible women would receive a brief educational intervention addressing cervical cancer, risk factors, and the importance of screening. Women in the "Standard-of-care screening" arm (and those in the "Choice" arm who selected screening at the Health Department) were provided with an appointment to receive screening with cytology/HPV co-testing at the Health Department and CHW contact information. Women who missed the first appointment were given a second opportunity; if they missed a second appointment they were considered non-adherent. To simplify subsequent management algorithms for a population in which adherence data are lacking, we assumed that women would be referred to colposcopy if they (i) had a cytology result of low-grade squamous intraepithelial lesion or worse ($LSIL^+$); (ii) had a cytology result of atypical squamous cells of undetermined significance (ASCUS) and a positive hrHPV test result; or (iii) tested positive for HPV types 16 or 18; otherwise, women were assumed to return to routine screening.

Women in the "Choice" arm who selected self-collection at home for HPV testing received an explanation of how to collect the sample along with a self-collection kit, a pre-addressed and stamped envelope for return of the sample, a small absorbent napkin, and CHW contact information. Women were encouraged to self-collect their sample at the time of the CHW visit or to hand-deliver the sample while the CHW was in the neighborhood. If a woman did not return her sample within 30 days, she was contacted by a CHW and given another 30-day window to complete the intervention. Women who tested hrHPV-positive were referred to colposcopy at the Health Department, as in the study. Following colposcopy, women with a histologic diagnosis of cervical intraepithelial neoplasia grade 2 or higher ($CIN2^+$) were assumed to receive treatment with loop electrosurgical excision procedure (LEEP), whereas women with a diagnosis <CIN2 were assumed to return to routine screening (this deviation from screening guidelines, which require surveillance for hrHPV-positive women who are <CIN2 on histology (27), was assumed given low attendance at Health Department facilities).

Although the trial was not powered to evaluate adherence with recommended management for women with abnormal results, we assumed proportions attending colposcopy were the same as in the trial (100% among women in the "Standard-of-care" arm and those in the "Choice" arm who selected screening at the Health Department; 28.6% among women in the "Choice" arm who opted for self-collection at home). None of the participants in the trial were referred to treatment, so we assumed 100% adherence to LEEP.

Cost data

We conducted a micro-costing study alongside the group randomized trial. Data sources included interviews with key informants (i.e., Health Department providers and administrators, CHWs, study coordinator), salary scales, supply contracts, budget spreadsheets, and invoices. We estimated the average cost of the CHW intervention per woman screened in each arm, as well as the cost per procedure for screening and management at the Health Department. We included direct medical costs (i.e., supplies, equipment, personnel time, laboratory transport and processing), direct non-medical costs (i.e., women's transportation to the clinic), women's time, and programmatic costs (i.e., CHW training, intervention quality-control efforts). Because most women drove or received a ride to the Health Department, women's transportation costs were estimated from the approximate round-trip mileage from each county to its respective Health

Table 1. Baseline values and ranges for model variables.

Variable	Baseline value	Sensitivity analyses
Screening ages	Age 25–65 years	Age 35 years
Screening interval	Every 5 years	Every 3 years
Proportion of women in "Choice" arm who select screening at HD (15)	24.2%/75.8%	0%/100%
Screening uptake among eligible women (15)[a]		
"Standard-of-care screening" arm	8.2%	4.6%; 13.4%
"Choice" arm–screening at HD	7.5%	1.6%; 20.4%
"Choice" arm–hrHPV	48.0%	39.9%; 57.1%
Proportion of women who received screening results (15)[a]		
"Standard-of-care screening" arm	100%	76.8%
"Choice" arm–screening at HD	100%	29.2%
"Choice" arm–hrHPV	96.7%	88.5%
Colposcopy adherence (15)[a,b]		
"Standard-of-care screening" arm	100%	2.5%
"Choice" arm–screening at HD	100%	
"Choice" arm—hrHPV	28.6%	8.4%; 58.1%
Treatment adherence[a]		
"Standard-of-care screening" arm	100%	
"Choice" arm–screening at HD	100%	
"Choice" arm–hrHPV	100%	
Test sensitivity/specificity for CIN2$^+$, Pap/HPV co-testing (21–23)	0.963/0.806	
Test sensitivity/specificity for CIN2$^+$, hrHPV self-collection (21)	0.953/0.722	
Test sensitivity/specificity for CIN2$^+$, colposcopy (49)	0.67 CIN2, 0.91 CIN3, 1.0 Cancer/0.89	1.0/1.0
LEEP effectiveness (24)[c]	93%	
Direct medical cost, Health Department[d] (US$)		
Pap/HPV co-test	128.82	47
Colposcopy	142.34	215
LEEP	197.65	537
Direct medical cost, intervention[d] (US$)		
"Standard-of-care screening" arm	1,385.84	452.92; 50%; 901.81;
"Choice" arm–HPV	397.50	190.18; 50%; 273.01;
"Choice" arm–Pap	295.43	88.11; 50%; 244.80
Direct nonmedical cost[d] (US$)		
Woman's transportation, Pap/HPV co-test	2.29	
Woman's transportation, colposcopy	4.08	
Woman's transportation, LEEP	13.29	
Woman's time[d,e]		
Pap/HPV co-test at Health Department	31.82	50%–150%
Self-collection for HPV testing	3.43	50%–150%
Colposcopy	29.80	50%–150%
LEEP	55.38	50%–150%
Cost of cervical cancer treatment (US$; ref. 25)		
Initial year	<65 years: 69,551 ≥65 years: 57,959	
Ongoing	All ages, 1,829	
Death	<65 years: 151,689 ≥65 years: 101,126	

Abbreviations: CIN2$^+$, cervical intraepithelial neoplasia grade II or higher; HD, Health Department; hrHPV, high-risk human papillomavirus DNA testing; LEEP, loop electrosurgical excision procedure; US$, United States dollars, 2019.

[a]Lower and upper bounds for sensitivity analyses were based on the 95% confidence intervals from the trial. Because so few women from the "Choice" arm who selected screening at the Health Department were referred to colposcopy, and because so few women in the study were referred to treatment, we did not estimate a lower bound for these adherence variables.

[b]In the "Standard-of-care screening" arm, 1 of 14 women screened was referred to colposcopy and complied; of the 3 women in the "Choice" arm who chose and attended screening at the Health Department, none was referred to colposcopy. Among the 60 women in the "Choice" arm who self-collected at home for HPV testing, 14 were referred to colposcopy, but only 4 complied.

[c]Although LEEP was assumed to effectively remove 93% of CIN2$^+$ lesions, we assumed 25% of women treated retained an hrHPV infection (50).

[d]These costs were derived from the present study, and include supplies, equipment, personnel time, laboratory transport, and laboratory processing. See Supplementary Data spreadsheet for more detail.

[e]These costs were derived from the present study, and include women's time spent traveling, waiting for, and receiving care. Enrollment time was not counted for either the "Standard-of-care screening" or the "Choice" arms.

Department; miles per gallon associated with a car; and the average cost of fuel in the Gulf Coast during 2019 (28–30). Women's time costs were estimated using the female median year-round full-time earnings and the estimated average time for traveling, waiting for, and receiving each procedure. We used the average personnel time, women's time, and transportation costs across counties and facilities; similarly, to apportion equipment costs per procedure, we used the average number of procedures per year across facilities. Costs were adjusted for inflation using the Consumer Price Index and are reported in 2019 US dollars (31). Detailed costing methods are described in Supplementary Table S2; aggregated costs by category are presented in Supplementary Table S3; detailed costs are provided in the Supplementary Data spreadsheet.

Scenario analyses

To test the robustness of results, we performed scenario analyses to explore the impact of the following scenarios for an intervention offered every 5 years (in accordance with screening guidelines): (i) screening at alternative frequencies or intervals (every 3 years; once in a lifetime); (ii) the upper- and lower-bound 95% confidence intervals around study screening uptake and colposcopy adherence variables; (iii) enhanced uptake (200% of baseline analysis); (iv) all women in the "Choice" arm selecting self-collection at home for HPV testing; (v) performance of cytology only (baseline analysis: cytology and HPV co-testing) at the Health Department; (vi) perfect diagnostic performance of colposcopy; (vii) a modified payer perspective, including Medicare reimbursement costs for procedures and direct medical costs only for the intervention; (viii) training and quality-control costs excluded; (ix) CHW and Coordinator salaries assumed to be similar to the Health Department Aide and Nurse, respectively; (x) CHW time costs for recruitment increased (400% of baseline analysis); (xi) women's time costs varied 50% to 150%; and (xii) treatment costs include the cost of two follow-up cytology tests (**Table 1**).

Results

Results for the baseline analysis are shown in **Table 2**. We present policy scenarios in which screening interventions are offered every 5 years, or every 3 years, or could be available at either of these intervals. When offered every 5 years from age 25 to 65 years, the "Standard-of-care screening" strategy reduced cervical cancer incidence by 6.4% relative to no screening, whereas the "Choice" strategy reduced cancer incidence by 14.8%. "Standard-of-care screening" was not an efficient strategy due to its high cost and relatively small benefit; the "Choice" strategy every 5 years cost $62,720 per YLS. When we assumed the interventions were offered every 3 years, "Standard-of-care screening" remained an inefficient strategy; "Choice" every 3 years reduced cancer risk by 19.5% and cost $74,970 per YLS. When we assumed the interventions could be offered every 3 or 5 years (i.e., competed both intervals and interventions), "Choice" every 3 years was the most effective strategy, reducing cancer risk by 19.5%, but also the most costly ($110,350 per YLS); "Choice" every 5 years remained an efficient strategy and cost $62, 720 per YLS.

Scenario analyses considered "Standard-of-care screening" versus "Choice" every 5 years or no intervention (baseline ICER for "Choice": $62,720 per YLS). "Choice" remained the most effective strategy across scenarios, and the strategy with the most attractive (i.e., lowest) ICER across the scenarios considered (**Fig. 1**). The ICER for "Choice" remained relatively stable when we assumed (i) all women in the "Choice" arm opted for self-collection for HPV testing; (ii) the Health Department performed cytology alone (as in the early study period), as opposed to cytology/HPV co-testing; (iii) perfectly accurate colposcopy performance; (iv) Medicare reimbursement costs for Health Department procedures and excluding women's time and transportation costs (modified payer perspective); (v) CHW recruitment costs increased 400%; (vi) women's time costs varied by 50% to 150%; and (vii) treatment costs included the cost of two follow-up Pap tests.

Table 2. Baseline cost, health, and cost-effectiveness outcomes[a].

Screening strategy	Reduction in lifetime risk of cervical cancer (%)[b]	Discounted lifetime cost per woman (US$)	Discounted life expectancy (years)	ICER (US$/YLS)
Screening interval: Every 5 years				
No screening	—	840 (580–1,060)	27.2633 (27.2484–27.2800)	—
"Standard-of-care screening" arm	6.4 (5.9–6.9)	1,320 (1,080–1,530)	27.2669 (27.2530–27.2826)	Dom
"Choice" arm[c]	14.8 (14.1–15.4)	1,380 (1,160–1,570)	27.2719 (27.2594–27.2859)	62,720 (46,490–96,530)
Screening interval: Every 3 years				
No screening	—	840 (580–1060)	27.2633 (27.2484–27.2800)	—
"Standard-of-care screening" arm	7.2 (6.6–7.6)	1,620 (1,380–1,820)	27.2673 (27.2535–27.2829)	Dom
"Choice" arm[c]	19.5 (18.8–20.0)	1,710 (1,500–1,890)	27.2748 (27.2632–27.2880)	74,970 (56,080–114,160)
All scenarios available (screening interval: every 3 years; every 5 years)				
No screening	—	840 (580–1060)	27.2633 (27.2484–27.2800)	—
"Standard-of-care screening" arm, every 5 years	6.4 (5.9–6.9)	1,320 (1,080–1,530)	27.2669 (27.2530–27.2826)	Dom
"Choice" arm[c], every 5 years	14.8 (14.1–15.4)	1,380 (1,160–1,570)	27.2719 (27.2594–27.2859)	62,720 (46,490–96,530)
"Standard-of-care screening" arm, every 3 years	7.2 (6.6–7.6)	1,620 (1,380–1,820)	27.2673 (27.2535–27.2829)	Dom
"Choice" arm[c], every 3 years	19.5 (18.8–20.0)	1,710 (1,500–1,890)	27.2748 (27.2632–27.2880)	110,350 (83,720–165,080)

Abbreviations: Dom, dominated (i.e., either more costly and less effective or having a higher incremental cost-effectiveness ratio than a more effective strategy); ICER, incremental cost-effectiveness ratio; US$, 2019 United States dollars; YLS, year of life saved.

[a]For reduction in cancer risk, discounted lifetime costs, and discounted life expectancy, the mean value and range is reported across the 50 top-fitting input parameter sets that represent good fit to US epidemiologic targets on HPV type- and age-specific prevalence and HPV type distribution in lesions and cervical cancer. The reported ICER is the ratio of the mean costs divided by the mean effects of one strategy versus another across the 50 sets. "Standard-of-care screening" arm was navigated to Pap/HPV co-test at the Health Department. "Choice" arm could choose Pap/HPV co-test at the Health Department or self-collection at home for HPV testing.

[b]Relative to no screening.

[c]In the trial, 24.2% of enrolled women chose to be screened at the Health Department, whereas 75.8% chose to self-collect an HPV sample at home.

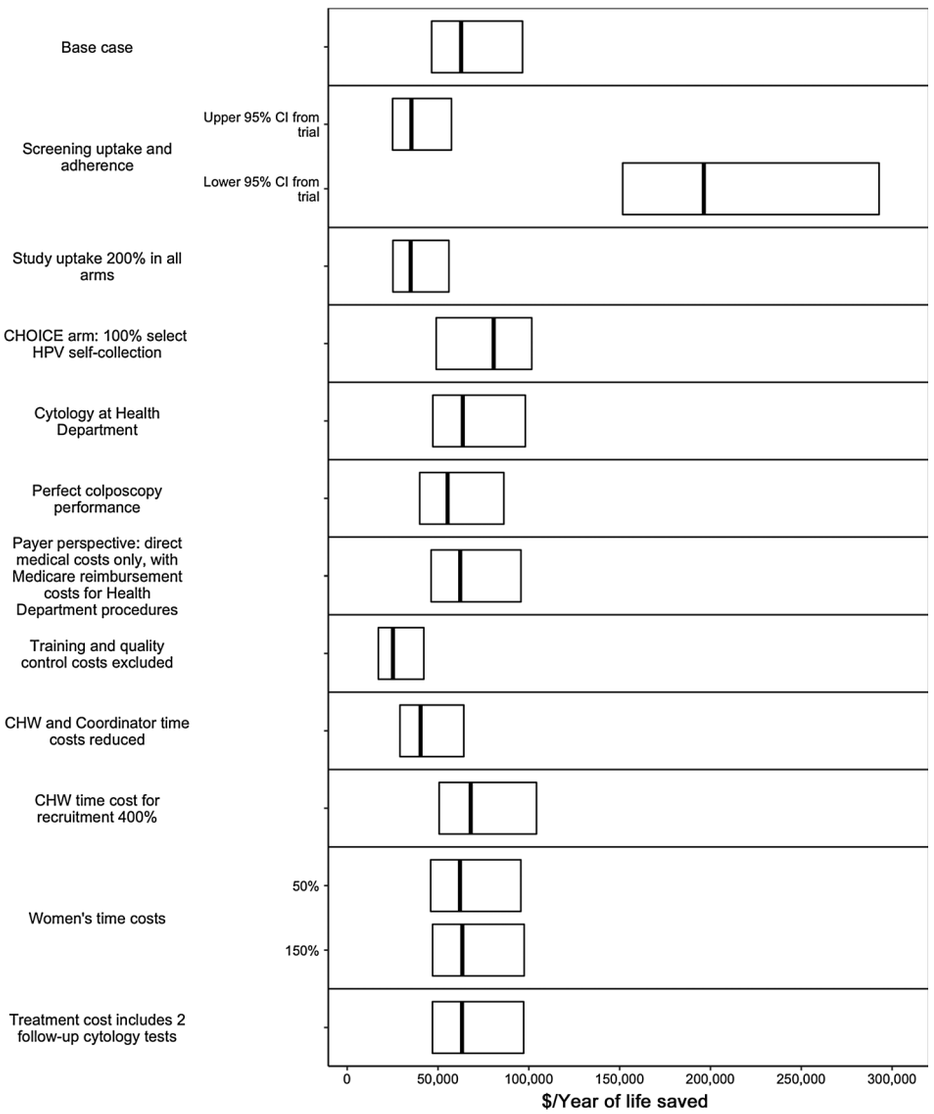

Figure 1.
Cost-effectiveness analysis: Base case and scenario analyses. Incremental cost-effectiveness ratios for "Choice" are presented along the *x*-axis in 2019 US$ per year of life saved (YLS) for the base case analysis and univariate sensitivity analysis (*y*-axis). White bars represent the range of the ICERs for "Choice" across the 50 input parameter sets (compared with no screening, as "Standard-of-care screening" was dominated in these scenarios), with the ICER of the mean costs divided by the mean effects demarcated by a black line. The base case analysis was "Choice" offered every five years compared with no screening (as "Standard-of-care screening" was dominated), with model inputs as indicated in **Table 1**.

Screening uptake and colposcopy adherence were highly influential on health impact and ICERs; when we assumed that screening uptake and colposcopy adherence resembled the lower-bound 95% confidence interval from the trial, "Standard-of-care screening" remained an inefficient strategy and the ICER for "Choice" more than doubled due to decreased effectiveness with fewer women receiving screening and recommended management ($196,350 per YLS). The ICER for "Choice" became more attractive when we assumed the upper-bound 95% confidence interval from the trial represented screening uptake and colposcopy adherence ($35,360 per YLS). When we assumed screening uptake improved by 200% in both arms, "Pap" remained inefficient and the ICER for "Choice" became dramatically more attractive ($39,950 per YLS). When we assumed that all women in the "Choice" arm opted for self-collection at home for HPV testing, the ICER for "Choice" was slightly higher than in the baseline scenario due to the substantially larger number of women screened ($65,940 per YLS). Intervention costs for CHW training and quality control were also highly influential on the ICER; when these costs were excluded, the ICER for "Choice" was $25,190 per YLS. The ICER for "Choice" also became more attractive when we assumed salaries for the CHWs and program coordinator were more in line with comparable Health Department staff salaries rather than research study personnel ($40,390 per YLS).

Discussion

We performed a micro-costing study alongside a group randomized trial comparing "Standard-of-care" screening at the Health Department and "Choice" between screening at the Health Department and self-collection at home for HPV testing, with both arms delivered by CHWs. We then used an existing microsimulation model of HPV infection and cervical pathogenesis to project the lifetime costs and benefits of the intervention at regular intervals in a population of un/underscreened African-American women in the Mississippi Delta. We found that "Choice" was the most effective and cost-effective strategy under all scenarios considered. The ICER for "Choice" was sensitive to

assumptions regarding screening uptake and colposcopy adherence, as well as intervention costs. "Choice" offered every 5 years cost $62,720 per YLS.

The low screening uptake with both "Standard-of-care screening" and "Choice" contributed to the relatively high costs per woman screened. The "Choice" intervention was less costly per woman screened than the "Standard-of-care screening" intervention due to the very low number of women who received screening with "Standard-of-care" (8.2%); by comparison, 38.2% of women in the "Choice" arm were screened. We note that the study population resides in one of the poorest regions in the United States, with vast cervical cancer disparities along racial lines. It is possible that a similar "Choice" intervention could yield lower per-woman costs and higher cancer benefits (and thus a more attractive ICER) in a population with greater screening uptake. In fact, in a scenario analysis in which we examined the impact of a 200% increase in study uptake, the ICER for "Choice" fell to $34,950 per YLS. Of note, if we assumed all women in the "Choice" arm selected self-collection at home for HPV testing, the ICER increased to $65,940 per YLS.

The benchmark for determining whether an intervention is "cost-effective" is controversial. In the United States, this benchmark is not codified. On the basis of World Health Organization guidance of setting the benchmark equal to GDP per capita ($65,120), "Choice" might be considered a borderline cost-effective intervention. The American College of Cardiology and the American Heart Association—which have published statements on cost and value methodology that accompany their clinical practice guidelines—consider an intervention with an ICER between $50,000 and $150,000 per quality-adjusted life-year to have an intermediate value (32, 33). Although "Choice" is indeed a costly intervention due to the intense time requirements of the CHWs and program coordinator to find and educate eligible women about screening, it falls within this "intermediate value" range. Decision makers might prioritize such an intervention due to the fact that it targets a population with significant health disparities. Although there may be trade-offs between improving population health and equity (34, 35), the present analysis does not allow us to determine whether "Choice" involves such a trade-off. To understand the opportunity costs associated with the "Choice" intervention, we would need to understand its funding mechanism—and what interventions would be displaced to fund "Choice"—as well as the cost-effectiveness and equity impact of other available interventions in the Mississippi Delta. To optimize scarce resources, decision makers would first need to select interventions that are both cost-effective and improve equity; with any remaining funds, decision makers would need to prioritize either cost-effectiveness or equity attributes of an intervention.

Despite the potential value of the "Choice" intervention in terms of improved screening uptake, we note that only 28.6% of hrHPV-positive women (who chose self-collection at home) attended colposcopy; 100% of women in the "Standard-of-care" arm and those who selected screening at the Health Department attended colposcopy (15). Thus, it appears that attending Health Department facilities is a substantial barrier for these un/underscreened women, and while offering a choice of screening modalities (including self-collection at home for HPV testing) may improve screening uptake, the vast majority of screen-positive women will not attend recommended follow-up. To further address cancer disparities in the Delta region, it will be critical to identify the specific barriers to clinic attendance and follow-up. In other low-resource populations, barriers to follow-up have included demographic factors [age (ref. 36, 37), race (ref. 36)], economic factors (insurance status; ref. 38), psychosocial factors [health beliefs (ref. 39), fear of cervical cancer diagnosis (ref. 40)], and logistics of healthcare delivery (referral to external facilities; ref. 37). Without identifying and overcoming specific obstacles to treatment, screening programs cannot provide health benefits.

This cost-effectiveness analysis has several limitations. First, the microsimulation model of HPV infection was calibrated to epidemiologic data from the New Mexico HPV-Pap Registry and other large study populations in the United States (10, 41, 42). The prevalence of hrHPV in New Mexico may be slightly lower than a previous study found in the Mississippi Delta (7, 10). Hysterectomy rates are also higher in African-American women, and thus cervical cancer incidence and mortality rates and disparities are likely to be underestimated in this population (43, 44). Despite these limitations, we opted to use the general US model (with background and cancer mortality rates from Black US women) due to the abundance of epidemiologic data from large studies for calibration; comparable data from African-American women in Mississippi were not available. To the extent that HPV prevalence and cervical cancer burden are higher among African-American women in Mississippi than in the general US model, the ICER for "Choice" may be more attractive than this analysis suggests.

An additional limitation of the present study was that our assumed management algorithms did not completely align with US Preventive Services Task Force guidelines at the time of the study. In 2012, guidelines recommended screening with cytology every 3 years beginning at age 21 years, with the option to switch to cytology and hrHPV co-testing every 5 years from age 30 until age 65 years; screening can end at age 65 years if there is no history of abnormalities over the past 10 to 20 years. We evaluated an intervention that would occur every 3 or 5 years from age 25 to 65 years. As with modeling results used to inform recently updated screening guidelines (17), screening every 3 years is only slightly more effective than, and not as efficient as, screening every 5 years with co-testing. Although guidelines require surveillance screening for hrHPV-positive women with normal cytology, hrHPV-negative women with ASCUS, and women who are <CIN2 on histology (27), we instead assumed these women would return to routine screening given low attendance at Health Department facilities. Thus, the present analysis may slightly underestimate the costs and benefits associated with surveillance screening.

Although our micro-costing study attempted to include costs relevant to implementing a CHW-facilitated intervention for "Standard-of-care screening" and "Choice" and exclude costs related to study administration, it is possible that study costs do not represent the costs of implementing a program across multiple counties in the Delta. For instance, the CHWs and program coordinator were study personnel, as was the CHW trainer, and it is unclear how their salaries and enrollment outcomes would compare with individuals employed at the county or state level. The cost of intervention personnel time was influential on the cost-effectiveness of "Choice," and when we assumed local health department personnel salaries, the ICER decreased to $40,390 per YLS. We also did not survey all trial participants to obtain individual time and transportation costs, but instead used average values for distance traveled, cost of fuel, and women's wages. Due to administrative burden on the CHWs, we also did not obtain data on the time spent canvasing to find each eligible woman, which varied by a number of factors such as weather, neighborhood, and time of day; the CHWs also approached many women who were not eligible for the study due to reporting screening in the past 4 years. Thus, CHW time per woman screened may be underestimated, but a sensitivity analysis suggests that even quadrupling CHW time costs for recruiting did not have a large impact on the ICER. In addition, intervention costs for

onetime training were high, but in an actual program, the cost per woman screened would likely fall as more women were screened (provided extensive re-training or training of new CHWs was not necessary).

To the best of our knowledge, this is the first cost-effectiveness analysis conducted alongside a trial of CHW-delivered self-collection for HPV testing in the United States. Previous studies have examined the cost-effectiveness of CHW-delivered interventions promoting self-collection in lower-resource settings, including Uganda and El Salvador, and found the intervention to be cost-effective due to increased screening uptake among un/underscreened women (45, 46). A recent systematic review of cost-effectiveness studies of HPV self-sampling found that screening uptake and screening history are key drivers of cost-effectiveness (47). Findings from our scenario analyses are consistent, suggesting that higher screening uptake and adherence to colposcopy would have improved the ICER dramatically.

A recent public-private partnership between the US National Cancer Institute, academic institutions, and companies that manufacture HPV tests will soon launch a multisite study to evaluate whether self-collection at home for HPV testing is comparable with provider-collection at a clinic (48). If HPV detection is comparable, companies will be able to pursue applications for FDA approval for home-based tests. Further study will be needed to determine culturally tailored interventions for delivering home-based HPV tests and improving colposcopy adherence to different populations of un/underscreened women.

Self-collection for HPV testing has the potential to reduce health disparities and be cost-effective. The group randomized trial in the Mississippi Delta demonstrates the difficulty of achieving high screening uptake and colposcopy adherence in some health disparity populations, but "Choice" improved screening uptake and may be a cost-effective strategy. For African-American women in the Mississippi Delta, an important area for future research will be how to overcome barriers to delivering recommended follow-up.

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Disclaimer

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Authors' Contributions

N.G. Campos: Conceptualization, data curation, formal analysis, methodology, writing–original draft. **I.C. Scarinci:** Conceptualization, resources, funding acquisition, investigation, writing–review and editing. **L. Tucker:** Data curation, investigation, writing–review and editing. **S. Peral:** Data curation, formal analysis, project administration, writing–review and editing. **Y. Li:** Formal analysis, writing–review and editing. **M.C. Regan:** Data curation, formal analysis, writing–review and editing. **S. Sy:** Data curation, formal analysis, writing–review and editing, model programming. **P.E. Castle:** Conceptualization, data curation, supervision, investigation, writing–review and editing. **J.J. Kim:** Conceptualization, resources, formal analysis, supervision, investigation, writing–review and editing.

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