# Reaching underscreened women: correlates of cervical cancer underscreening, reactions to mailed HPV self-sampling kits, and cost-effectiveness of HPV self-sampling programs

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**Abstract**

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Underscreening is a major risk factor for the development of cervical cancer. This dissertation examines factors associated with clinic-based Pap screening and human papillomavirus (HPV) self-sampling in a U.S. healthcare system and summarizes the existing evidence on the cost-effectiveness of HPV self-screening in order to support health system implementation of new strategies to increase cervical cancer screening.

The first chapter is an analysis of electronic health record data from Kaiser Permanente Washington (KPWA) to identify correlates of underscreening among 48,711 women aged 30-64 years, with different levels of interaction with the health care system, namely primary care visits and/or use of an online health portal. Recent healthcare interactions were associated with lower odds of underscreening. Compared to screening-adherent women, underscreening was associated with older age, higher body mass index (BMI), current smoking, and non-

adherence to breast and colorectal cancer screening guidelines. These screening disparities persisted even among women who interacted with the healthcare system.

The second chapter identifies attitudes, experiences, and reactions to mailed HPV self-sampling kits among women who were enrolled in a pragmatic randomized trial at KPWA. Using a web-based survey, women who did and did not use and return a kit were queried about potential psychosocial correlates of HPV self-sampling (including knowledge, barriers to Pap screening, trust in physicians, and perceived risk), their experiences with using a kit (or reasons for non-return), and their reactions to the kit (trust in HPV self-sampling, screening preferences, and future intentions). Most kit returners had positive reactions to using a kit and would use them again, and many non-returners reported openness to using a kit in the future. Many kit returners and non-returners, however, lacked trust in HPV self-sampling as a cervical cancer prevention method.

The third chapter is a systematic literature review on the cost-effectiveness of HPV self-sampling to prevent cervical cancer. Sixteen eligible studies were identified, eleven conducted in high-income countries and five set in low/middle-income countries. Fourteen of sixteen studies reported that HPV self-sampling was cost-effective under certain conditions. Overall, studies found that the most important factor for cost-effective HPV self-sampling implementation was the observed increase in screening uptake, with HPV self-sampling kit cost, sensitivity for detecting cervical precancers, and the screening status of self-sampling users also having an impact. There are gaps in the literature on the effects of vaccination and new HPV self-sampling triage strategies on cost-effectiveness in high-income settings, as well as a need

for additional studies based on real-world implementation of HPV self-sampling, especially in low/middle-income countries.

New technologies such as HPV-self-sampling offer health systems opportunities to increase screening uptake among underscreened women. The results of this study suggest that existing health care interactions (such as those between patient and provider) may be an important avenue for building women's trust and confidence in HPV self-sampling. Many women are open to using HPV self-sampling; to optimize the effectiveness and cost-effectiveness of HPV self-sampling programs, health systems should focus on leveraging existing points of patient interaction and continuing to research ways to reach those women who persistently do not engage with the health care system.

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# Chapter 1. Out of reach? Correlates of cervical cancer underscreening in women with varying levels of healthcare interactions in a United States integrated delivery system


**Abstract**

One in five U.S. women with health insurance are underscreened for cervical cancer. We sought to identify whether underscreening correlates differed between women with different levels of health care interaction. Among women age 30-64 who were members of an integrated U.S. health system, we used 2014-2015 electronic health record data to identify underscreened women (≥3.4 years since last Pap, n=3,352) and screening-adherent controls (<3.4 years since last Pap, n=45,359) and potential underscreening correlates related to demographics, health history, and healthcare utilization. We calculated the odds of underscreening in the total population and by subgroups defined by healthcare visits and online health portal usage in the prior 12 months. Underscreening was associated with older age (50-64 vs. 30-39; odds ratio (OR)=1.6; 95%CI=1.4-1.8), current tobacco use (vs never use; OR=2.1; 95%CI=1.8-2.3), higher BMI (≥35 kg/m2 vs <25kg/m2, OR=2.0; 95%CI=1.8-2.2) , screening non-adherence for breast cancer (OR=5.1; 95%CI=4.6-5.7) and colorectal cancer (OR=8.1, 95%CI=7.3-9.0), and having no recent visit with their primary care provider (PCP) or recent health portal use (vs. recent PCP visit and portal use; OR=8.4, 95%CI=7.6-9.4). Underscreening correlates were similar between the total study population and within all healthcare interaction subgroups. Interaction with the healthcare system is associated with lower odds of

underscreening, but sociodemographic and health status correlates are similar regardless of primary care visits or online portal use. These data support the need for additional interventions to reach women who remain underscreened for cervical cancer.

**Introduction**

Papanicolaou (Pap) screening for cervical cancer has dramatically reduced cervical cancer incidence in developed nations.(1–3) In the U.S., adherence to guideline-recommended cervical cancer screening has declined from a high of 82% (2007) to 74% (2016).(4) Non-adherent women ("underscreened") are at increased risk of developing cervical cancer; approximately half(5–8) of the 12,000 U.S. women who develop cervical cancer annually(9) are underscreened. Insurance status is a predictor of underscreening,(10) but despite the inclusion of cervical cancer screening as an essential health insurance benefit in the Affordable Care Act,(11) underscreening has not decreased significantly among insured women, demonstrating that other barriers need to be addressed to increase uptake.(10) Other underscreening predictors include demographics (e.g. older age, Black/African-American or Asian race, Hispanic ethnicity),(10) socioeconomic status (e.g. low income,(12) low educational attainment),(13) obesity,(14) tobacco use,(15) emotional factors (e.g. embarrassment),(16) structural/logistical factors (e.g. competing time demands),(17) and healthcare-related factors (e.g. infrequent health care visits,(18) non-adherence to other cancer screening tests,(19,20) and male provider gender).(21)

Health systems encourage cervical cancer screening through multiple pathways including patient reminders (via mailed letters(22–24) and telephone calls)(24) and physician alerts.(25) These interventions increase screening uptake,(22,26) but gaps persist even in

health systems with robust outreach efforts.(23,27) Women who are nonresponsive to reminders have been described as “hard to reach,”(28,29) but may have existing points of health care interaction that present opportunities for additional screening outreach.

Primary care provider (PCP) recommendations are important motivators for screening(30,31) and PCPs as well as obstetrician/gynecologists (OBGYNs) can provide opportunistic screening during clinic visits. There may be additional room to increase screening during clinic visits(32) especially in hard-to-reach women. (28) PCPs are important to the ongoing shift in the U.S. toward the patient-centered medical home (PCMH) healthcare model, in which PCP teams coordinate all dimensions of a patient’s care.(33) In practice, women may still receive primary care services from different PCPs for reasons of convenience or scheduling, or prefer to receive some primary care services from an OBGYN.(34)

Health information technology is another screening promotion tool. Online health information portals facilitate patient engagement(35) by allowing patients to review health records, exchange messages with providers, receive reminders, and schedule appointments.(36) As availability of online portals expands, researchers and health care systems are seeking ways to promote preventive services uptake using portals for reminders(37) and decision tools.(38)

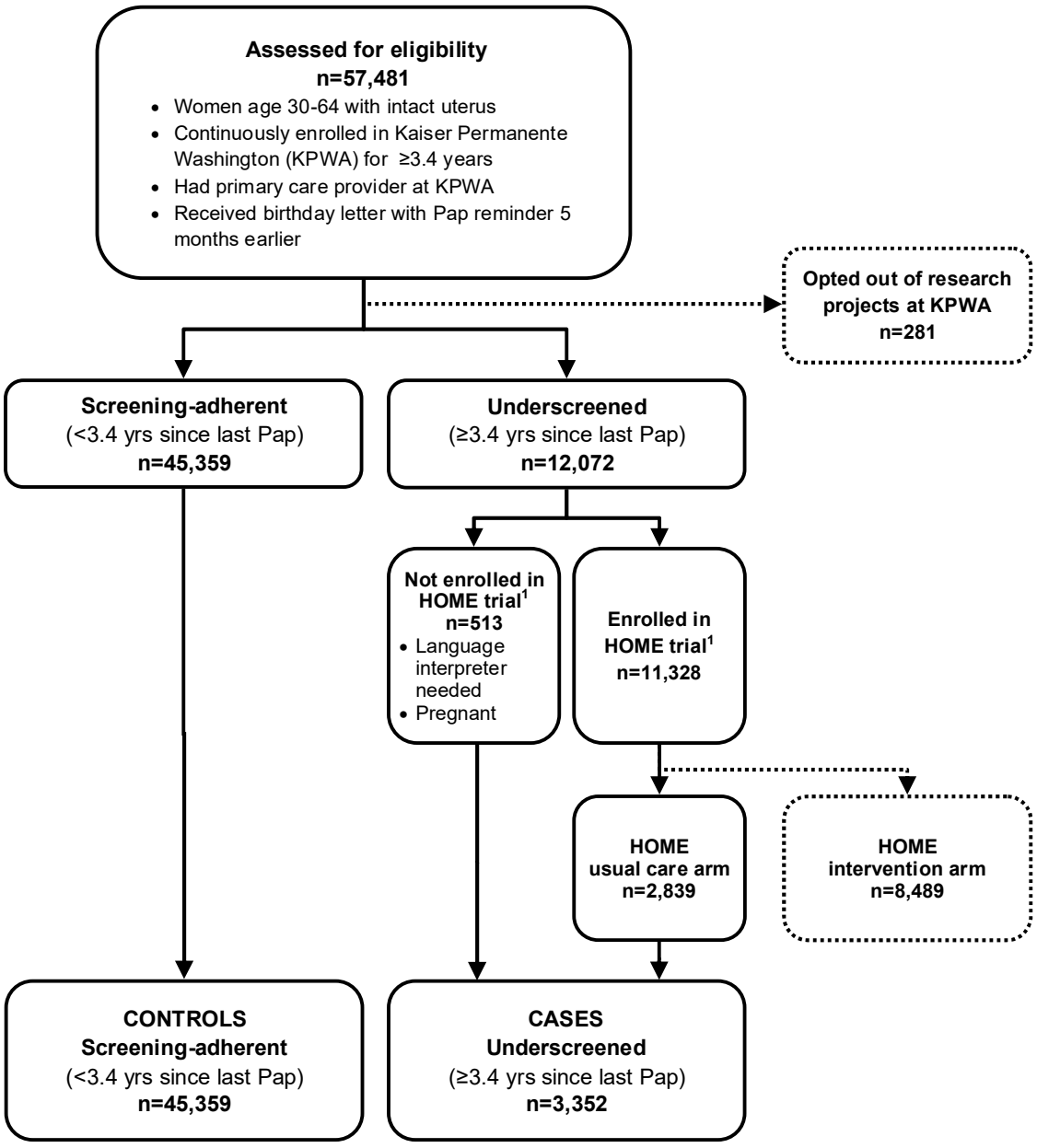
To our knowledge, previous research has not characterized correlates of cervical cancer underscreening among women who have insurance coverage, a PCP, and/or receive regular screening reminders. Identifying underscreening correlates in these women will show whether commonly identified screening barriers vary by different health system interactions. Results could help inform future screening interventions by health systems and researchers.

## Methods

This retrospective case-control study used electronic health record (EHR) data from 2014-2015 to identify correlates of cervical cancer underscreening among insured members of Kaiser Permanente Washington (KPWA), an integrated healthcare system, to evaluate whether underscreening varies across levels of health system interaction. Each year, on or near their birthday, KPWA members are mailed a personalized "birthday letter" with preventive service reminders including upcoming or past-due screenings(23); additional outreach strategies, including patient reminders via telephone and secure email message, targeted EHR reminder alerts to care provider teams, and same-day opportunistic screening; and additional reminders every ~90 days for women who do not complete recommended screening tests. All data were collected under a waiver of consent and HIPAA authorization with approval by the KPWA IRB.

We identified 57,481 women aged 30-64 years (as of September 2013-September 2014) with an intact uterus, a KPWA PCP, at least three years and five months (3.4 years) of continuous KPWA enrollment, and who received a birthday letter five months prior (**Figure 1-1**).(39,40) We excluded women who previously opted out of permitting KPWA to use their data for research (n=281). Concurrent with our study time frame, a randomized trial evaluating mailed human papillomavirus (HPV) self-sampling kits for underscreened women was ongoing at KPWA;(39) due to data sharing agreements with the trial, women randomized to receive HPV self sampling in the trial were excluded (n=8,489).

**Figure 1-1: Flow of eligibility assessment and classification into cervical cancer screening-adherent and underscreened groups among women in a U.S. health care system, 2013-2014**




1 The study period aligned with the first year of a KPWA pragmatic trial (HOME) designed to evaluate a mailed HPV kit strategy for increasing cervical cancer screening uptake in underscreened women. Similar eligibility criteria were applied for HOME participants and underscreened cases in this study, with the additional HOME exclusions for women who were pregnant or needed a language interpreter. HOME women randomized to the data-only usual care arm were included as cases in this study, whereas those randomized to the mailed kit intervention arm were excluded.

We defined cases and controls by cervical cancer screening adherence. We defined controls (screening-adherent) as having had a Pap test <3.4 years prior to data collection. Cases (underscreened) had their last recorded Pap test ≥3.4 years prior to data collection or had no recorded Pap test. Our operational definition of 3.4 years for a Pap screening interval was chosen to match with the definition of screening adherence used in the trial,(39) which added an additional five months (0.4 years) to the recommended three year Pap screening interval to give women time to respond to a birthday letter notification that they were due for Pap testing. Our adherence definition does not include a five-year screening interval because Pap+HPV co-testing at five-year intervals did not become standard-of-care at KPWA until August 2013,(41) and thus no woman who received a co-test could have been considered underscreened during our study time frame of 2014-2015.

We selected independent variables that have been associated with underscreening in different populations(10,12,14,42,43). All independent variables were modeled categorically. Electronic health data were used to define age, race and ethnicity, tobacco use (current, former, never), body mass index (BMI, $kg/m^2$), and Charlson comorbidity index (CCI) score (0, 1-2, ≥3)(44).

Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of census blocks and geocoded street address using women's home addresses. Median household income was calculated for women's census block.(45)

Insurance generosity (as a proxy for an individual's cost burden) was defined based on deductible and copay amounts, categorized from least to most generous as "high deductible" (annual deductible ≥$1,350 for an individual or ≥$2.700 for a family), "not high deductible,

specialty copay ≥$30" (annual deductible <$1,350 for an individual or <$2,700 for a family), and "not high deductible, specialty copay <$30." Cutoffs were based on the observed distribution of copay and deductible costs. We included specialty copay to capture the cost burden of potential follow-up colposcopy.

We defined screening intervals and eligible age groups for breast and colorectal cancer screening adherence using Healthcare Effectiveness Data and Information Set (HEDIS) definitions.(46) Breast cancer screening adherence was defined as receiving a screening mammogram in the two years before data collection for women age 52-64.(46,47) Colorectal cancer screening adherence was defined as having a fecal immunochemical test (FIT) in the previous year before data collection, flexible sigmoidoscopy in the previous five years, or colonoscopy in the previous ten years for women age 51-64.(46,48) We collected enrollment duration and time since last recorded Pap test (stratified by enrollment duration).

For recent health service interactions, we defined recent own PCP visits using visit records to classify whether women visited their PCP designated in the EHR in the 12 months before the most recent birthday letter mailing. We defined recent other PCP/OBGYN visits as visiting an OBGYN or PCP not designated as their primary provider in in the 12 months before the most recent birthday letter mailing(without a visit to their own PCP within that timeframe). We defined active portal use based on women's use of clinically relevant online portal functions that relate directly to clinical encounters or health communication: receiving or sending a message through the portal, viewing lab results, or using appointment scheduling features.(49) Active portal use had three categories: 1) "active" portal use, or logging into the portal on at least two days in the in the 12 months before the most recent birthday letter mailing, 2) "not

active" portal use, or logging in on one or fewer days in the in the 12 months before the most recent birthday letter mailing and/or not using a clinically relevant portal function, and 3) **"**no ID verified," for women who had not verified their identity in the online portal system and thus could not log in.(50)

We analyzed data as an unmatched case control study. For the entire study population, we calculated summary statistics, crude odds ratios (ORs), and 95% confidence intervals (CIs) for associations between Pap underscreening and all independent variables (including health service interactions). We subdivided our population into six groups based on recent healthcare interactions: 1) recent own PCP visitors and active portal users, 2) recent own PCP visitors without active portal use, 3) recent visitors to another PCP/OBGYN (not their own PCP) and active portal users, 4) recent visitors to another PCP/OBGYN (not their own PCP) without active portal users, 5) active portal use without recent visits to any PCP/OBGYN, and 6) neither recent visits to any PCP/OBGYN, nor active portal use. We calculated crude ORs and 95% CI of underscreening for each independent variable within each healthcare interaction group. We used a complete case analysis and dropped missing values when calculating ORs. Analyses were performed using Stata 15 (College Station, Texas).

**Results**

After applying study eligibility criteria, including the exclusion of n=8,489 underscreened women who were randomized to the intervention arm of a concurrent randomized trial, our study population included n=45,359 screening-adherent controls and n=3,352 underscreened cases. Among both screening-adherent and underscreened women, most women were White, Non-Hispanic and age 50-64 years (**Table 1-1**). Most reported never having smoked, had CCI=0

and lived close to their primary care clinic. Most were enrolled in KPWA for ≥10 years; among underscreened women enrolled for ≥10 years, 11% had ≥10 years since last Pap, and 14% had no recorded Pap test.

Comparing underscreened to screened women, odds of underscreening were significantly higher in older age groups (vs. age 30-39), higher BMI categories (vs. <25kg/$m^2$), current tobacco users (vs. former users), lower incomes <$100,000 (vs. ≥$100,000), CCI scores of 3 or greater (vs. CCI=0) and lower for women with >5 years of KPWA enrollment (vs. ≥3.4-5 years, **Table 1-1**). Odds of underscreening rose with increasing BMI, with the highest OR in the highest category (BMI ≥35 kg/$m^2$ vs. <25kg/$m^{2:}$ OR=2.0, 95%CI=1.8-2.2). Current tobacco users were two times more likely to be underscreened compared to never-users (OR=2.1, 95%CI=1.8-2.3). Age-eligible underscreened women had more than five times greater odds of being colorectal cancer screening non-adherent (OR=5.1, 95%CI=4.6-5.7) and more than eight times greater odds of being breast cancer screening non-adherent (OR=8.1, 95%CI=7.3-9.0).

**Table 1-1: Summary and odds ratios of underscreening for potential cervical cancer underscreening correlates among women in a U.S. health care system, by cervical cancer screening status**

| | Total study population | | | | | |
|---|---|---|---|---|---|---|
| | Screening-adherent[1] n=45,359 | | Under-screened[2] n=3,352 | | Odds ratio (OR) of underscreening | |
| **Potential underscreening correlates** | n | % | n | % | OR | 95% CI |
| **Age group, years** | | | | | | |
| 30-39 | 10,146 | 22.4 | 535 | 16.0 | 1.0 | ref |
| 40-49 | 11,965 | 26.4 | 862 | 25.7 | **1.4** | **1.2-1.5** |
| 50-64 | 23,248 | 51.3 | 1,955 | 58.3 | **1.6** | **1.4-1.8** |
| **Race** | | | | | | |
| White | 33,479 | 75.4 | 2,313 | 73.9 | 1.0 | ref |
| Asian | 5,439 | 12.2 | 389 | 12.4 | 1.0 | 0.9-1.2 |
| Black/African American | 2,003 | 4.5 | 148 | 4.7 | 1.1 | 0.9-1.3 |
| Other[3] | 3,503 | 7.9 | 280 | 8.9 | **1.2** | **1.0-1.3** |
| *Unknown[4]* | *935* | *2.1* | *222* | *6.6* | | |
| **Ethnicity** | | | | | | |
| Non-Hispanic | 41,776 | 94.0 | 2,970 | 94.6 | 1.0 | ref |
| Hispanic | 2,675 | 6.0 | 168 | 5.4 | 0.9 | 0.8-1.0 |
| *Unknown[4]* | *908* | *2.0* | *214* | *6.4* | | |
| **Tobacco use** | | | | | | |
| Never | 30,650 | 68.3 | 1,832 | 63.6 | 1.0 | ref |
| Current | 3,280 | 7.3 | 404 | 14.0 | **2.1** | **1.8-2.3** |
| Former | 10,933 | 24.4 | 646 | 22.4 | 1.0 | 0.9-1.1 |
| *Unknown[4]* | *496* | *1.1* | *470* | *14.0* | | |
| **Body mass index (kg/m$^2$)** | | | | | | |
| <25 | 16,868 | 37.6 | 822 | 28.6 | 1.0 | ref |
| 25-29.9 | 12,922 | 28.8 | 740 | 25.7 | **1.2** | **1.1-1.3** |
| 30-34.9 | 7,446 | 16.6 | 555 | 19.3 | **1.5** | **1.4-1.7** |
| ≥35 | 7,654 | 17.1 | 757 | 26.3 | **2.0** | **1.8-2.2** |
| *Unknown[4]* | *469* | *1.0* | *478* | *14.3* | | |
| **Charlson comorbidity index score[5]** | | | | | | |
| 0 | 36,342 | 80.1 | 2,738 | 81.7 | 1.0 | ref |
| 1-2 | 7,793 | 17.2 | 496 | 14.8 | 0.8 | 0.7-0.9 |
| ≥3 | 1,224 | 2.7 | 118 | 3.5 | **1.3** | 1.1-1.6 |
| **Travel time from primary care clinic** | | | | | | |
| <10 minutes | 14,968 | 33.1 | 1,172 | 35.1 | 1.0 | ref |
| 10-19 minutes | 19,326 | 42.7 | 1,349 | 40.4 | 0.9 | 0.8-1.0 |
| 20-29 minutes | 6,889 | 15.2 | 489 | 14.6 | 0.9 | 0.8-1.0 |
| ≥30 minutes | 4,102 | 9.1 | 331 | 9.9 | 1.0 | 0.9-1.2 |
| *Unknown[4]* | *74* | *0.2* | *11* | *0.3* | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Insurance plan generosity** | | | | | | |
| Specialty copay <$30, not high deductible | 34,075 | 75.1 | 2,564 | 76.5 | 1.0 | ref |
| Specialty copay ≥$30, not high deductible | 7,903 | 17.4 | 521 | 15.5 | 1.1 | 1.0-1.3 |
| High deductible[6] | 3,381 | 7.5 | 267 | 8.0 | 1.2 | 1.0-1.4 |
| **Median household income (Geocoded)**[7] | | | | | | |
| <$50,000 | 8,822 | 20.8 | 788 | 25.3 | **1.6** | **1.4-1.8** |
| $50,000-$74,999 | 15,097 | 35.5 | 1,158 | 37.1 | **1.3** | **1.2-1.5** |
| $75,000-$99,999 | 12,397 | 29.2 | 819 | 26.3 | 1.2 | 1.0-1.3 |
| ≥$100,000 | 6,189 | 14.6 | 354 | 11.3 | 1.0 | ref |
| *Unknown* | *2,854* | *6.3* | *233* | *7.0* | | |
| **Breast cancer screening (age 52-64)**[8] | | | | | | |
| Not Guideline Adherent | 2,373 | 11.9 | 872 | 52.1 | **8.1** | **7.3-9.0** |
| Guideline Adherent | 17,586 | 88.1 | 801 | 47.9 | 1.0 | ref |
| *Unknown*[4] | *537* | *1.2* | *74* | *2.2* | | |
| **Colorectal cancer screening (age 51-64)**[9] | | | | | | |
| Not Guideline Adherent | 4,958 | 23.1 | 1,086 | 60.6 | **5.1** | **4.6-5.7** |
| Guideline Adherent | 16,534 | 76.9 | 707 | 39.4 | 1.0 | ref |
| *Unknown*[4] | *449* | *1.0* | *69* | *2.1* | | |
| **<u>Health system history</u>** | | | | | | |
| **Duration of health plan enrollment** | | | | | | |
| ≥3.4 - <5 years | 9,800 | 21.6 | 842 | 25.1 | 1.00 | ref |
| 5 to <10 Years | 13,597 | 30.0 | 1,017 | 30.3 | **0.9** | **0.8-1.0** |
| ≥10 years | 21,962 | 48.4 | 1,493 | 44.5 | **0.8** | **0.7-0.9** |
| **Time since last Pap test (Stratified by duration of enrollment)** | | | | | | |
| Enrolled ≥3.4 - <5 years | | | | | | |
| 3.4-5 years since last Pap | -- | -- | 236 | 28.0 | *n/a* | *n/a* |
| No recorded Pap | | | 606 | 72.0 | | |
| Enrolled 5-<10 years | | | | | | |
| 3.4-<5 years since last Pap | | | 447 | 44.0 | | |
| 5-<10 years since last Pap | -- | -- | 198 | 19.5 | *n/a* | *n/a* |
| No recorded Pap | | | 372 | 36.6 | | |
| Enrolled ≥10 years | | | | | | |
| 3.4-<5 years since last Pap | | | 626 | 41.9 | | |
| 5-<10 years since last Pap | -- | -- | 489 | 32.8 | *n/a* | *n/a* |
| 10+ years since last Pap | | | 169 | 11.3 | | |
| No recorded Pap | | | 209 | 14.0 | | |

1 Any recorded Pap screening test in the prior <3.4 years

2 Last recorded Pap test ≥3.4 years prior to data collection, or no recorded Pap

3 Other race includes American Indian/Alaska Native, Pacific Islander/Native Hawaiian, more than one race, and other race categories

4 The percentage of unknown values is the proportion of women with unknown values from among all screening-adherent or underscreened women. Percentages for known variable categories represent the proportion from all known values (excluding unknowns)

5 Generated from an additive index of comorbid conditions(44)

6 High deductible = annual deductible ≥$1350 for an individual or ≥$2700 for a family

7 Median household income at the census block level using women's home address

8 HEDIS adherence definitions were used to define guideline adherence for screening mammography(46,47)

9 HEDIS adherence definitions were used to define guideline adherence for colorectal cancer screening(46,48)

Underscreened women were less likely than screening-adherent women to be active online health portal users (36.7% vs. 65.5%), have a recent own PCP visit (33.9% vs 59.4%), and have a recent other PCP/OBGYN visit (18.4% vs. 21.4%, Table 2). Compared to women with a recent own PCP visit and active portal use, women with only one type of interaction had higher odds of underscreening (e.g. recent own PCP visit only: OR=2.2, 95%CI=2.0-2.5; portal use only: OR=2.8, 95%CI=2.4-3.2) and women with neither a recent PCP/OBGYN visit nor active portal use had the highest odds of underscreening (OR=8.4, 95%CI=7.6-9.4).

**Table 1-2: Summary and odds ratios for selected recent health care interactions and underscreening among women age 30-64 in a U.S. integrated health care system**

| | | Screening-adherent[1] n=45,359 | | Underscreened[2] n=3,352 | | Crude odds ratio (OR) of underscreening | |
|---|---|---|---|---|---|---|---|
| **Health care interactions** | | n | % | n | % | OR | 95% CI |
| **Active health portal user[3]** | | | | | | | |
| | Inactive | 10,227 | 22.5 | 1,095 | 32.7 | **2.6** | **2.4-2.8** |
| | Active | 29,693 | 65.5 | 1,231 | 36.7 | 1.0 | ref |
| | No ID Verified[4] | 5,439 | 12.0 | 1,026 | 30.6 | **4.6** | **4.2-5.0** |
| **Recent own primary care provider (PCP) visit (Visited own PCP in previous 12 months)** | | | | | | | |
| | No | 18,394 | 40.6 | 2,214 | 66.1 | **2.9** | **2.6-3.1** |
| | Yes | 26,965 | 59.4 | 1,138 | 33.9 | 1.0 | ref |
| **Recent other PCP/OBGYN visit (Visited PCP (NOT own) or OBGYN in previous 12 months)** | | | | | | | |
| | No | 35,638 | 78.6 | 2,735 | 81.6 | **1.2** | **1.1-1.3** |
| | Yes | 9,721 | 21.4 | 617 | 18.4 | 1.0 | ref |
| **Combined Portal Use and PCP/OBGYN Visits** | | | | | | | |
| Active Portal User | Recent own PCP visit | 19,373 | 42.7 | 605 | 18.0 | 1.0 | ref |
| AND: | Recent other (NOT own) PCP/OBGYN visit | 6,410 | 14.1 | 285 | 8.5 | **1.4** | **1.2-1.6** |
| | No recent PCP/OBGYN visit | 3,910 | 8.6 | 341 | 10.2 | **2.8** | **2.4-3.2** |
| Not Active Portal User | Recent own PCP visit | 7,592 | 16.7 | 533 | 15.9 | **2.2** | **2.0-2.5** |
| AND: | Recent other (NOT own) PCP/OBGYN visit | 3,311 | 7.3 | 332 | 9.9 | **3.2** | **2.8-3.7** |
| | No recent PCP/OBGYN visit | 4,763 | 10.5 | 1,256 | 37.5 | **8.4** | **7.6-9.4** |

1 Any recorded Pap screening test in the prior <3.4 years

2 Last recorded Pap test ≥3.4 years prior to data collection, or no recorded Pap

3 Active health portal use is defined as ≥2 days in the past year with a clinically relevant login to the online portals (includes sending viewing messages from health provider, viewing lab results, or scheduling an appointment)

4 Women without a verified ID cannot access the online health portal

Underscreening correlates were similar across health care interaction groups (**Table 1-3**). However, underscreened women with ≥1 form of healthcare interaction were more likely to have a CCI score ≥1, compared to screening-adherent women.

**Table 1-3: Summary distributions of potential cervical cancer underscreening correlates among women with and without selected recent health care interactions in a U.S. health care system**

| | Active Portal Users[1] | | | | | | Not Active Portal Users | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recent Own PCP Visit[2] | | Recent Other PCP/OBGYN visit (Not Own PCP)[3] | | No Recent PCP/OBGYN Visit[4] | | Recent Own PCP Visit[2] | | Recent Other PCP/OBGYN visit (Not Own PCP)[3] | | No Recent PCP/OBGYN Visit[4] | |
| **Variables** | Screening-adherent[5] | Under-screened[6] | Screening-adherent[5] | Under-screened[6] | Screening-adherent[5] | Under-screened[6] | Screening-adherent[5] | Under-screened[6] | Screening-adherent[5] | Under-screened[6] | Screening-adherent[5] | Under-screened[6] |
| | n=19,373 | n=605 | n=6,410 | n=285 | n=3,910 | n=341 | n=7,592 | n=533 | n=3,311 | n=332 | n=4,763 | n=1,256 |
| **Potential underscreening correlates** | % | % | % | % | % | % | % | % | % | % | % | % |
| **Age Group (years)** | | | | | | | | | | | | |
| 30-34 | 17.8 | 13.9 | 27.9 | 18.6 | 22.6 | 13.5 | 23.0 | 13.5 | 32.0 | 21.1 | 25.7 | 16.7 |
| 40-49 | 24.6 | 22.6 | 26.5 | 26.3 | 27.8 | 27.6 | 25.6 | 25.7 | 29.3 | 26.5 | 31.6 | 26.4 |
| 50-64 | 57.6 | 63.5 | 45.6 | 55.1 | 49.6 | 58.9 | 51.4 | 60.8 | 38.7 | 52.4 | 42.8 | 56.9 |
| **Race** | | | | | | | | | | | | |
| White | 80.0 | 81.0 | 80.1 | 83.3 | 81.0 | 84.3 | 63.9 | 66.0 | 67.4 | 68.6 | 68.8 | 68.6 |
| Asian | 9.6 | 4.6 | 9.1 | 7.2 | 10.2 | 10.0 | 18.3 | 16.6 | 15.5 | 13.0 | 17.4 | 16.4 |
| Black/African American | 3.8 | 3.6 | 3.5 | 1.8 | 2.7 | 2.4 | 7.4 | 6.4 | 6.2 | 4.8 | 4.7 | 5.9 |
| Other[7] | 6.6 | 7.9 | 7.3 | 7.6 | 6.0 | 3.3 | 10.4 | 10.9 | 10.9 | 13.7 | 9.2 | 9.1 |
| *Unknown*[8] | *1.3* | *2.8* | *1.6* | *3.2* | *1.4* | *2.9* | *2.4* | *3.9* | *2.7* | *5.1* | *5.2* | *11.8* |
| **Ethnicity** | | | | | | | | | | | | |
| Non-Hispanic | 94.7 | 93.1 | 94.3 | 95.7 | 95.7 | 97.0 | 91.8 | 94.8 | 92.4 | 93.1 | 93.9 | 94.9 |
| Hispanic | 5.3 | 6.9 | 5.7 | 4.3 | 4.3 | 3.0 | 8.2 | 5.2 | 7.6 | 6.9 | 6.1 | 5.1 |
| *Unknown*[8] | *1.3* | *2.1* | *1.4* | *3.2* | *1.4* | *3.2* | *2.3* | *3.4* | *2.7* | *3.6* | *5.3* | *12.0* |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tobacco use** | | | | | | | | | | | | |
| Never | 66.2 | 59.0 | 68.6 | 63.0 | 72.4 | 63.7 | 68.5 | 63.6 | 70.6 | 66.1 | 71.6 | 66 |
| Current | 6.2 | 9.2 | 5.4 | 9.6 | 5.2 | 13.7 | 10.3 | 17.1 | 10.1 | 15.5 | 9.7 | 16.5 |
| Former | 27.6 | 31.8 | 26.1 | 27.4 | 22.4 | 22.6 | 21.2 | 19.2 | 19.3 | 18.3 | 18.7 | 17.5 |
| *Unknown*[8] | *0.1* | *0.8* | *0.1* | *1.4* | *0.9* | *7.9* | *0.2* | *1.5* | *0.5* | *3.0* | *8.5* | *33.1* |
| **Body mass index (kg/m$^2$)** | | | | | | | | | | | | |
| <25 | 35.8 | 19.2 | 38.5 | 26.2 | 44.0 | 35.7 | 35.3 | 28.4 | 36.7 | 27.6 | 43.1 | 34.1 |
| 25-29.9 | 27.8 | 23.1 | 28.5 | 28.0 | 28.9 | 26.0 | 30.1 | 24.2 | 30.0 | 26.6 | 30.2 | 27.4 |
| 30-34.9 | 17.2 | 20.9 | 16.6 | 21.3 | 14.4 | 19.2 | 17.1 | 21.2 | 17.3 | 17.6 | 14.3 | 17.0 |
| ≥35 | 19.2 | 36.8 | 16.4 | 24.5 | 12.7 | 19.2 | 17.4 | 26.1 | 16.0 | 28.2 | 12.5 | 21.5 |
| *Unknown*[8] | *0.0* | *0.2* | *0.1* | *1.1* | *0.6* | *9.7* | *0.1* | *0.9* | *0.6* | *2.7* | *8.5* | *34.0* |
| **Charlson comorbidity index score**[9] | | | | | | | | | | | | |
| 0 | 73.2 | 62.1 | 83.2 | 74.7 | 91.7 | 88.9 | 77.1 | 70.2 | 87.3 | 81.3 | 94.4 | 95.7 |
| 1-2 | 22.9 | 28.9 | 15.1 | 21.4 | 7.3 | 9.7 | 19.6 | 23.3 | 11.5 | 16.0 | 5.0 | 4.0 |
| ≥3 | 3.9 | 8.9 | 1.7 | 3.9 | 1.0 | 1.5 | 3.3 | 6.6 | 1.2 | 2.7 | 0.6 | 0.3 |
| **Travel time from primary care clinic** | | | | | | | | | | | | |
| <10 minutes | 32.1 | 34.1 | 31.3 | 31.2 | 29.9 | 28.4 | 37.5 | 38.3 | 35.1 | 37.8 | 33.4 | 36.1 |
| 10-19 minutes | 43.4 | 39.7 | 43.2 | 44.0 | 43.4 | 41.6 | 40.9 | 41.0 | 41.0 | 40.5 | 42.3 | 39.2 |
| 20-29 minutes | 15.6 | 16.1 | 15.8 | 15.6 | 16.7 | 17.6 | 13.3 | 11.8 | 15.4 | 12.4 | 14.5 | 14.7 |
| ≥30 minutes | 8.9 | 10.1 | 9.7 | 9.2 | 10.0 | 12.3 | 8.2 | 8.8 | 8.6 | 9.4 | 9.8 | 9.9 |
| *Unknow*n | *0.2* | *0.2* | *0.1* | *1.1* | *0.3* | *0.0* | *0.2* | *0.2* | *0.1* | *0.3* | *0.2* | *0.4* |
| **Insurance plan generosity**[10] | | | | | | | | | | | | |
| Specialty copay <$30, not high deductible | 75.7 | 75.9 | 74.8 | 76.1 | 72.0 | 75.1 | 77.0 | 84.1 | 76.9 | 79.2 | 71.6 | 73.3 |
| | 18.1 | 17.7 | 17.7 | 17.9 | 19.7 | 17.0 | 15.2 | 10.7 | 15.8 | 12.3 | 17.0 | 16.5 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Specialty copay ≥$30, not high deductible | 6.2 | 6.4 | 7.5 | 6.0 | 8.3 | 7.9 | 7.8 | 5.3 | 7.2 | 8.4 | 11.5 | 10.2 |
| High deductible | | | | | | | | | | | | |
| **Median household income (Geocoded)**[11] | | | | | | | | | | | | |
| <$50,000 | 19.3 | 24.0 | 17.9 | 22.2 | 16.1 | 19.0 | 26.8 | 29.5 | 24.3 | 32.5 | 22.4 | 24.7 |
| $50,000-$74,999 | 34.9 | 37.2 | 35.6 | 33.1 | 32.7 | 36.5 | 36.6 | 38.2 | 38.6 | 30.8 | 36.4 | 39.4 |
| $75,000-$99,999 | 30.2 | 28.6 | 30.4 | 29.3 | 33.2 | 25.8 | 26.2 | 23.2 | 25.9 | 26.3 | 27.2 | 25.9 |
| ≥$100,000 | 15.7 | 10.2 | 16.1 | 15.4 | 18.0 | 18.7 | 10.4 | 9.1 | 11.3 | 10.4 | 14.0 | 10.1 |
| *Unknown* | 6.3 | 6.3 | 6.5 | 6.7 | 5.4 | 4.4 | 6.6 | 7.7 | 5.9 | 7.2 | 6.4 | 7.6 |
| **Breast cancer screening (age 52-64)**[12] | | | | | | | | | | | | |
| Not Guideline Adherent | 7.1 | 28.6 | 10.3 | 38.7 | 13.7 | 43.0 | 15.6 | 44.0 | 21.2 | 56.6 | 26.9 | 73.6 |
| Guideline Adherent | 92.9 | 71.4 | 89.7 | 57.7 | 86.3 | 57.0 | 84.4 | 56.0 | 78.8 | 43.4 | 73.1 | 26.4 |
| *Unknown*[7] | *2.4* | *5.6* | *2.1* | *3.5* | *1.5* | *4.4* | *3.7* | *5.4* | *3.6* | *3.3* | *3.1* | *3.2* |
| **Colorectal cancer screening (age 51-64)**[13] | | | | | | | | | | | | |
| Not Guideline Adherent | 15.5 | 34.1 | 20.4 | 51.0 | 29.0 | 60.1 | 26.4 | 48.3 | 35.5 | 68.1 | 49.5 | 81.2 |
| Guideline Adherent | 84.5 | 65.9 | 79.6 | 49.0 | 71.0 | 39.9 | 73.6 | 51.7 | 64.5 | 31.9 | 50.5 | 18.8 |
| *Unknown*[7] | *1.8* | *4.6* | *1.4* | *2.6* | *1.1* | *5.7* | *3.2* | *4.2* | *3.1* | *2.4* | *2.5* | *3.0* |
| **Health care interactions** | | | | | | | | | | | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Active Health Portal User**[1] | | | | | | | | | | | | |
| No | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 62.1 | 51.0 | 65.3 | 50.3 | 70.2 | 52.2 |
| Yes | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| No ID Verified[14] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 37.9 | 49.0 | 34.7 | 49.7 | 29.8 | 47.8 |
| **Recent OWN PCP visitor**[2] | | | | | | | | | | | | |
| No | 0.0 | 0.0. | 100.0 | 100.0 | 100.0 | 100.0 | 0.0 | 0.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| Yes | 100.0 | 100.0 | 0.0 | 0.0 | 0.0 | 0.0 | 100.0 | 100.0 | 0.0 | 0 | 0.0 | 0 |
| **Recent Other PCP/OBGYN Visitor**[3] | | | | | | | | | | | | |
| No | 0.7 | 0.8 | 0.0 | 0.0 | 100.0 | 100.0 | 0.6 | 0.8 | 0 | 0 | 100.0 | 100.0 |
| Yes | 99.3 | 99.2 | 100.0 | 100.0 | 0.0 | 0.0 | 99.4 | 99.2 | 100.0 | 100.0 | 0.0 | 0 |
| **<u>Health system history</u>** | | | | | | | | | | | | |
| **Duration of health plan enrollment** | | | | | | | | | | | | |
| ≥3.4-<5 years | 15.1 | 18.3 | 16.6 | 19.6 | 12.5 | 14.4 | 36.8 | 40.3 | 35.3 | 34.0 | 28.4 | 23.7 |
| 5-<10 years | 29.0 | 26.4 | 32.3 | 35.4 | 31.7 | 28.4 | 27.4 | 23.3 | 30.8 | 30.6 | 32.9 | 34.8 |
| ≥10 years | 55.9 | 55.2 | 51.1 | 44.9 | 55.8 | 57.2 | 35.7 | 36.4 | 33.9 | 34.2 | 38.7 | 41.5 |
| **Time since last Pap Test (By duration of enrollment)** | | | | | | | | | | | | |
| Enrolled ≥3.4 - <5 years | | *n=111* | | *n=56* | | *n=49* | | *n=215* | | *n=113* | | *n=298* |
| 3.4-5 years | | 52.3 | | 53.6 | | 46.9 | | 20.9 | | 19.5 | | 19.5 |
| No recorded Pap | -- | 47.7 | -- | 46.4 | -- | 53.1 | -- | 79.1 | -- | 80.5 | -- | 80.5 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Enrolled 5-<10 years | | *n=160* | | *n=101* | | n=97 | | *n=124* | | *n=98* | | *n=437* |
| 3.4-<5 years | | 60.6 | | 51.5 | | 56.7 | | 48.4 | | 43.9 | | 32.0 |
| 5-<10 years | -- | 15.0 | -- | 24.8 | -- | 15.5 | -- | 21.8 | -- | 22.4 | -- | 19.5 |
| No recorded Pap | | 24.4 | | 23.8 | | 27.8 | | 29.8 | | 33.7 | | 48.5 |
| Enrolled ≥10 years | | *n=338* | | *n=128* | | *n=195* | | *n=194* | | *n=121* | | *n=521* |
| 3.4-<5 years | | 49.7 | | 51.6 | | 55.9 | | 39.7 | | 38.8 | | 28.6 |
| 5-<10 years | | 30.5 | | 32.8 | | 29.2 | | 35.6 | | 38.8 | | 20.4 |
| ≥10 years | -- | 11.4 | -- | 10.9 | -- | 7.2 | -- | 7.7 | -- | 10.7 | -- | 6.0 |
| No recorded Pap | | 8.4 | | 4.7 | | 7.7 | | 17.0 | | 11.6 | | 45.0 |

1 Active portal use is defined as ≥2 days in the past year with a clinically relevant login (includes sending or viewing messages from health provider, viewing lab results, or scheduling an appointment) to the online health portal
2 Defined as ≥1 visit with their own PCP in the previous 12 months
3 Defined as no visits to their own PCP and ≥1 visit with a different PCP or OBGYN in the previous 12 months
4 Defined as no visits to any PCP or OBGYN in the previous 12 months
5 Any recorded Pap screening test in the prior <3.4 years
6 Last recorded Pap test ≥3.4 years prior to data collection, or no recorded Pap
7 Other race includes American Indian/Alaska Native, Pacific Islander/Native Hawaiian, more than one race, and other race categories
8 The percentage of unknown values is the proportion of women with unknown values from among all screening-adherent or underscreened women. Percentages for known variable categories represent the proportion from all known values (excluding unknowns)
9 Generated from an additive index of comorbid conditions(44)
10 High deductible = annual deductible ≥$1350 for an individual or ≥$2700 for a family
11 Median household income at the census block level using women's home address
12 HEDIS adherence definitions were used to define guideline adherence for screening mammography(46,47)
13 HEDIS adherence definitions were used to define guideline adherence for colorectal cancer screening(46,48)
14 Women without a verified ID cannot access the online health portal

Across health care interaction groups, associations between potential correlates and underscreening were similar (**Table 1-4**). Age group 50-64 years (vs. 30-39 years), current vs. former tobacco use, and BMI of ≥35 kg/m2 (vs. <25kg/m2) all showed significant positive associations with underscreening in all groups with one or more health care interactions. Underscreening was associated with CCI scores of ≥1 (vs. CCI score=0) among women with recent PCP/OBGYN visits regardless of online portal use. Breast and colorectal cancer screening non-adherence remained strongly associated with cervical cancer underscreening in all healthcare interaction groups. Some associations differed among the health care interaction groups. For active portal users who recently visited their own PCP, Asian women had lower odds of underscreening than White women (OR=0.5, 95%CI=0.3-0.7). For not active portal users with a recent own PCP visit, odds of underscreening were lower among Hispanic women (vs non-Hispanic, OR=0.6, 95%CI=0.4-0.9) and among women with high deductibles vs. those with the most generous health plans (OR=0.6, 95%CI=0.4-0.9). In the no recent PCP/OBGYN + not active portal user group, underscreening was associated with longer duration of enrollment (e.g. ≥10 years vs. ≥3.4-5 years, OR=1.3, 95%CI=1.1-1.5).

**Table 1-4: Odds ratios (OR) for cervical cancer underscreening among women with and without selected healthcare interactions in a U.S. health care system**

| | Active Portal User[1] | | | | | | Not Active Portal User[1] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Recent Visit to Own PCP[2] | | Recent Visit to Other PCP/OBGYN (Not Own PCP)[3] | | No Recent PCP/OBGYN Visit[4] | | Recent Visit to Own PCP[2] | | Recent Visit to Other PCP/OBGYN (Not Own PCP)[3] | | No Recent PCP/OBGYN Visit[3] | |
| **Variables** | OR of underscreening[5] | | OR of underscreening[5] | | OR of underscreening[5] | | OR of underscreening[5] | | OR of underscreening[5] | | OR of underscreening[6] | |
| **Potential underscreening correlates** | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| **Age group, years** | | | | | | | | | | | | |
| 30-39 | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| 40-49 | 1.2 | 0.9-1.6 | 1.5 | 1.0-2.1 | **1.7** | **1.2-2.4** | **1.7** | **1.3-2.3** | 1.4 | 1.0-1.9 | **1.3** | **1.1-1.5** |
| 50-64 | **1.4** | **1.1-1.8** | **1.8** | **1.3-2.5** | **2.0** | **1.4-2.8** | **2.0** | **1.5-2.6** | **2.1** | **1.5-2.7** | **2.0** | **1.7 -2.4** |
| **Race** | | | | | | | | | | | | |
| White | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | | |
| Asian | **0.5** | **0.3-0.7** | 0.8 | 0.5-1.2 | 0.9 | 0.6-1.4 | 0.9 | 0.7-1.1 | 0.8 | 0.6-1.2 | | |
| Black/African | 0.9 | 0.6-1.5 | 0.5 | 0.2-1.2 | 0.9 | 0.4-1.8 | 0.8 | 0.6-1.2 | 0.8 | 0.4-1.3 | *not reported*[8] | |
| American | 1.2 | 0.9-1.6 | 1.0 | 0.6-1.6 | 0.5 | 0.3-1.0 | 1.0 | 0.8-1.4 | 1.2 | 0.9-1.7 | | |
| Other[7] | | | | | | | | | | | | |
| **Ethnicity** | | | | | | | | | | | | |
| Non-Hispanic | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | *not reported*[8] | |
| Hispanic | 1.3 | 1.0-1.8 | 0.8 | 0.4-1.4 | 0.7 | 0.4-1.3 | **0.6** | **0.4-0.9** | 0.9 | 0.6-1.4 | | |
| **Tobacco use** | | | | | | | | | | | | |
| Never | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | | |
| Current | **1.7** | **1.2-2.2** | **2.0** | **1.3-3.0** | **3.0** | **2.1-4.3** | **1.8** | **1.4-2.3** | **1.6** | **1.2-2.3** | *not reported*[8] | |
| Former | **1.3** | **1.1-1.5** | 1.1 | 0.9-1.5 | 1.2 | 0.9-1.5 | 1.0 | 0.8-1.2 | 1.0 | 0.7-1.4 | | |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Body mass index (kg/m$^2$)** | | | | | | | | | | | | |
| <25 | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | | |
| 25-29.9 | **1.6** | **1.2-2.0** | 1.4 | 1.0-2.0 | 1.1 | 0.8-1.5 | 1.0 | 0.8-1.3 | 1.2 | 0.9-1.6 | *not reported*[8] | |
| 30-34.9 | **2.3** | **1.8-2.9** | **1.9** | **1.3-2.7** | **1.6** | **1.2-2.3** | **1.5** | **1.2-2.0** | 1.4 | 1.0-1.9 | | |
| ≥35 | **3.6** | **2.8-4.5** | **2.2** | **1.6-3.1** | **1.9** | **1.3-2.6** | **1.9** | **1.5-2.4** | **2.3** | **1.7-3.2** | | |
| **Charlson comorbidity index score**[9] | | | | | | | | | | | | |
| 0 | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| 1-2 | **1.5** | **1.2-1.8** | **1.6** | **1.2-2.1** | 1.4 | 0.9-2.0 | **1.3** | **1.1-1.6** | **1.5** | **1.1-2.0** | 0.8 | 0.6-1.1 |
| ≥3 | **2.7** | **2.0-3.6** | **2.6** | **1.4-4.8** | 1.6 | 0.6-4.0 | **2.2** | **1.5-3.1** | **2.4** | **1.2-5.0** | 0.5 | 0.2-1.5 |
| **Travel time from primary care clinic** | | | | | | | | | | | | |
| <10 minutes | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| 10-19 minutes | 0.9 | 0.7-1.0 | 1.0 | 0.8-1.3 | 1.0 | 0.8-1.3 | 1.0 | 0.8-1.2 | 0.9 | 0.7-1.2 | 0.9 | 0.7-1.0 |
| 20-29 minutes | 1.0 | 0.8-1.2 | 1.0 | 0.7-1.4 | 1.1 | 0.8-1.6 | 0.9 | 0.6-1.2 | 0.7 | 0.5-1.1 | 0.9 | 0.8-1.1 |
| ≥30 minutes | 1.1 | 0.8-1.4 | 1.0 | 0.6-1.5 | 1.3 | 0.9-1.9 | 1.1 | 0.8-1.5 | 1.0 | 0.7-1.5 | 0.9 | 0.7-1.2 |
| **Insurance plan generosity**[10] | | | | | | | | | | | | |
| Specialty copay <$30,not high deductible | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| Specialty copay ≥$30, not high deductible | 1.0 | 0.8-1.2 | 1.0 | 0.7-1.4 | 0.8 | 0.6-1.1 | **0.6** | **0.5-0.9** | 0.8 | 0.5-1.1 | 0.9 | 0.7-1.1 |
| High deductible | 1.0 | 0.7-1.4 | 0.8 | 0.5-1.3 | 0.9 | 0.6-1.4 | **0.6** | **0.4-0.9** | 1.1 | 0.7-1.7 | 0.9 | 0.8-1.1 |
| **Median household income (Geocoded)**[11] | | | | | | | | | | | | |
| <$50,000 | **1.9** | **1.4-2.6** | 1.3 | 0.9-1.9 | 1.1 | 0.8-1.6 | 1.2 | 0.9-1.8 | 1.5 | 1.0-2.3 | **1.5** | **1.2-1.9** |
| $50,000-$74,999 | **1.6** | **1.2-2.2** | 1.0 | 0.7-1.4 | 1.1 | 0.8-1.5 | 1.2 | 0.9-1.7 | 0.9 | 0.6-1.3 | **1.5** | **1.2-1.9** |
| $75,000-$99,999 | **1.5** | **1.1-2.0** | 1.0 | 0.7-1.5 | 0.7 | 0.5-1.1 | 1.0 | 0.7-1.4 | 1.1 | 0.7-1.7 | 1.3 | 1.0-1.7 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥$100,000 | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| **Breast cancer screening (age 52-64)**[12] | | | | | | | | | | | | |
| Not Guideline Adherent | **5.2** | **4.1-6.7** | **5.8** | **4.1-8.4** | **4.8** | **3.4-6.6** | **4.2** | **3.3-5.5** | **4.8** | **3.4-6.9** | **7.6** | **6.1-9.3** |
| Guideline Adherent | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| **Colorectal cancer screening (age 51-64)**[13] | | | | | | | | | | | | |
| Not Guideline Adherent | **2.8** | **2.2-3.5** | **4.1** | **2.9-5.7** | **3.7** | **2.7-5.0** | **2.6** | **2.1-3.3** | **3.9** | **2.7-5.5** | **4.4** | **3.5-5.5** |
| Guideline Adherent | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| **Duration of health plan enrollment** | | | | | | | | | | | | |
| ≥3.4 - <5 years | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref | 1.0 | ref |
| 5 to <10 Years | 0.8 | 0.6-1.0 | 0.9 | 0.7-1.3 | 0.8 | 0.5-1.1 | 0.8 | 0.6-1.0 | 1.0 | 0.8-1.3 | **1.3** | **1.1-1.5** |
| ≥10 years | 0.8 | 0.7-1.0 | 0.7 | 0.5-1.0 | 0.9 | 0.6-1.2 | 0.9 | 0.8-1.1 | 1.1 | 0.9-1.5 | **1.3** | **1.1-1.5** |

1 Active portal use is defined as ≥2 days in the past year with a clinically relevant login (includes sending or viewing messages from health provider, viewing lab results, or scheduling an appointment) to the online health portal
2 Defined as ≥1 visit with their own PCP in the previous 12 months
3 Defined as no visits to their own PCP and ≥1 visit with a different PCP or OBGYN in the previous 12 months
4 Defined as no visits to any PCP or OBGYN in the previous 12 months
5 Includes women who had <2 days in the 12 months prior with a clinically relevant login AND women who do not have an ID verified to login to the online portal
6 Last recorded Pap test ≥3.4 years prior to data collection, or no recorded Pap
7 Other race includes American Indian/Alaska Native, Pacific Islander/Native Hawaiian, more than one race, and other race categories
8 Odds ratios not reported due to high levels of unknown variable data
9 Generated from an additive index of comorbid conditions(44)
10 High deductible = annual deductible ≥$1350 for an individual or ≥$2700 for a family

11 Median household income at the census block level using women's home address

12 EDIS adherence definitions were used to define guideline adherence for screening mammography(46,47)

13 HEDIS adherence definitions were used to define guideline adherence for screening colonoscopy or Fecal Immunochemical Testing(46,48)

**Discussion**

All women in our study had health insurance, a PCP, and a health system that used a variety of outreach strategies to promote cervical cancer screening. We corroborated several previously identified correlates of underscreening, including higher BMI,(10) current tobacco use,(15) older age,(51) and non-adherence to breast and colorectal cancer screening.(19,20) Many of these underscreened women interacted with the health system through primary care visits and/or online portal use and remained unscreened. Women who interacted with the health care system were more likely to be screened but correlates of underscreening among women with health system interactions were similar to the total population. Addressing the barriers common among people who have these correlates of underscreening could enhance the effectiveness of future portal- or PCP-based interventions.

Underscreening for breast, cervical, and colorectal cancer screening have been linked in many studies,(20,43,52–54) including settings with organized screening programs.(55,56) Cervical, breast, and colorectal cancer underscreening share several common correlates, including Black/African-American race,(10,20) Hispanic ethnicity,(57) lower education,(10,52,57) lower income,(10,55) obesity(14,58), recent health care visits,(59) and provider recommendations(58,60–62). We found stronger associations between cervical and breast cancer underscreening than between cervical and colorectal cancer screening, suggesting that barriers for these two female cancers may be especially tightly linked; both require an in person visit to receive these screenings, whereas colorectal cancer screening can be completed through self-collected FIT kits. From a health system perspective, underscreening across multiple cancer sites represents an important gap in care. Successful

screening interventions for one cancer could also have positive effects for other cancers. An analysis from the UK found evidence for a "spillover effect," in which women may be more receptive to screening promotion after completing another type of screening.(63) More research into shared barriers across screening sites could support the development of combined screening promotion interventions.

The strong relationship between higher BMI and underscreening, particularly among obese women (BMI>30kg/$m^2$), could have implications for cervical cancer screening interventions in primary care, as many barriers to screening among these women relate to experiences in health care. Obese women report that negative healthcare experiences related to their size can be barriers to screening(64,65) and report less trust in their provider when they feel judged for their size.(66) As overweight and obese women are likely to be overrepresented among underscreened women visiting primary care, researchers investigating future PCP-based interventions could evaluate the effectiveness of adding a messaging component to ensure that providers use best practices for respectful, patient-centered interactions with overweight and obese women.

Other underscreening correlates from our study are associated with barriers linked to women's health care system interactions. Smokers are less likely to use primary care and preventive services than former or non-smokers.(15,67) Smokers' pessimistic or fatalistic beliefs about cancer could contribute to the lower uptake of cancer screening among smokers.(68) It is possible that successful tobacco cessation efforts may help reduce women's resistance to cancer screening promotion. Among women age 50-64, commonly reported barriers include negative prior experiences with screening,(69) and negative attitudes toward

health care.(17) In this study and others, comorbidities have been associated with higher use of health services overall,(70) but lower use of cancer screening, including Pap screening.(71,72) Competing health priorities and limited provider time could be factors in this difference, as physicians can be less likely to recommend screening to women with multiple comorbidities.(73)

Since our study was performed, primary HPV screening has been added as a recommended screening option in the U.S.,(74) opening up the possibility for women to self-collect samples for HPV testing. HPV self-sampling could address multiple screening barriers associated with health care interactions, including embarrassment at receiving Pap tests, structural/logistical barriers, and previous negative Pap experiences. Mailed HPV self-sampling kits have increased screening uptake in multiple international trials,(75) including a recent pragmatic randomized trial of HPV self-sampling for underscreened women at KPWA.(40) HPV self-sampling could also be offered in-clinic as in the Australian national screening program.(75,76) Offering women the opportunity to self-collect during a visit or to take home a self-sampling test could free up time during visits, allowing providers to focus on other health priorities and giving women an opportunity to ask questions about HPV self-sampling kits. Self-sampling kits could also be used as part of combined screening interventions that target several cancer sites.

Our findings point to the importance of the patient-provider relationship to cervical cancer screening. The lower odds of underscreening among women who visited their own PCP vs. those who visited another PCP/OBGYN aligns with previous evidence that having a regular source of care is important for screening uptake.(10) We conducted a survey of women who

received HPV self-sampling kits and found that underscreened women at KPWA had high trust in their physician's recommendations,(77) suggesting that it is important to continue to focus on encouraging providers to recommend and offer screening. Many aspects of the patient-provider relationship that could impact screening uptake, such as continuity of care,(78) provider trust,(79) and patient-provider communication,(80) were outside the scope of our study. The relationship between these factors and the extent to which they determine screening behavior among women who visit their PCP is not fully understood.(81–83) Continued research into these factors could contribute to the development of better screening promotion interventions in primary care.

Online portal use was associated with decreased odds of underscreening even among women without recent healthcare visits. While current models of patient-centered care point to EHR use as an important measure of patient interaction, there is still much to learn about patterns of EHR use and the most effective ways to use online portals to promote screening.

Our study was limited by the lack of access to some known predictors of screening (individual-level household income and education), detailed information about the patient-provider relationship (e.g. length of time with same PCP, the number of interactions with PCP or other providers, patient trust in PCP), or complete data on English language proficiency (which would have helped clarify patterns of online portal use). Data sharing requirements from the concurrent trial of HPV self-sampling meant that a randomized subset of underscreened women were excluded from our study.(40) This exclusion meant that the proportion of underscreened women in our study sample did not match the prevalence of underscreening in the KPWA population at large. Due to the amount of unknown values for

some variables, especially among underscreened women, we chose not to present ORs for all variables in women with neither PCP/OBGYN visits nor online portal use because of concerns about biased estimates.(84)

Our study's strengths included our high-quality data sources. The integrated nature of KPWA facilitated completeness of data on cervical cancer screening history. Finally, our study focuses on an important population of women, as PCP visits and portal use provide useful, unexplored avenues of contact for underscreened women, compared to those who do not frequently use health services.

**Conclusions**

Some underscreened women who are hard to reach with screening reminders have existing points of interaction with health care that may make it easier for the health system to engage them in screening. Cancer screening gaps exist even with access and in-person and online interactions, and correlates of underscreening are the same even among women who have these interactions. When designing and implementing new interventions in primary care and using online portals, health systems and researchers should be cognizant of potential provider and system-level barriers that exist among groups that are overrepresented among underscreened women. Health systems should explore new interventions to address cervical cancer screening barriers, such as offering HPV self-sampling kits during PCP visits.

# Chapter 2. Experiences and reactions among underscreened women who did and did not return unsolicited mailed HPV self-sampling kits for cervical cancer screening


**Abstract**

Our objectives were to evaluate experiences and reactions after receiving an unsolicited human papillomavirus (HPV) self-sampling kit in the mail and identify psychosocial correlates of using kits. Survey participants were underscreened women aged 30-64 years who were mailed HPV kits as part of a pragmatic trial at Kaiser Permanente Washington, a U.S. integrated health care system. Six months after the HPV kit mailing, we invited kit returners and non-returners to complete a web survey that measured psychosocial factors (e.g., cervical cancer/HPV knowledge, attitudes toward screening), experiences, and reactions to kits. We compared responses between kit returners and non-returners. Comparing 116 kit returners (272 invited) and 119 non-returners (1083 invited), we found no clinically significant differences in psychosocial factors. Overall, survey respondents showed knowledge gaps in HPV natural history (82% did not know HPV infection can clear on its own) and interpreting HPV test results (37% did not know an HPV-negative result indicates low cancer risk). Kit returners found kits convenient and easy to use (>90%). The most common reason for non-return was low confidence in ability to correctly use a kit, although many non-returners (49%) indicated they would consider future use. Women reported low trust in HPV testing to identify women at high risk for cervical cancer (52% in returners, 42% in non-returners). Screening programs could improve uptake and acceptability of HPV self-sampling through outreach materials that

emphasize the high efficacy of HPV testing for cervical cancer screening and educate patients about how to interpret results.

**Introduction**

Women who never or rarely attend Pap screening are at increased risk for cervical cancer.(5,6,8) Pap screening barriers include sociodemographic factors (e.g. race/ethnicity),(10) poor health status,(13,72) logistical difficulties,(16,85) embarrassment,(16,86) and fear of abnormal results.(16,86) Recently expanded U.S. cervical cancer screening guidelines include primary HPV screening (i.e., HPV alone) as an additional recommended option for women aged 30-65 years.(87) With primary HPV screening, samples for HPV tests (unlike Pap tests) can be self-collected with comparable accuracy to clinician-collected samples.(75) HPV self-sampling (HPV-SS) is an emerging option that may address known Pap screening barriers.

Numerous studies have shown that women find HPV-SS acceptable,(88) and mailing HPV-SS kits directly to underscreened women in an organized screening program increases screening rates compared to traditional invitations or reminders for Pap screening.(75) However, little is known about women's reactions to receiving unsolicited HPV-SS kits in the mail, their preferred screening options, future screening intentions after receiving a kit, and how much their willingness to use an HPV-SS kit may be impacted by psychosocial factors such as HPV/cervical cancer knowledge, trust in HPV-SS results, or trust in their physician.(89–91) Better understanding these factors can help healthcare systems optimize mailing HPV-SS kits as a cervical screening outreach strategy.(92–95)

Our objectives were to: (1) measure potential psychosocial correlates of HPV-SS uptake among underscreened women who were randomized to receive a mailed HPV-SS kit as part of a pragmatic trial within a U.S. healthcare system; (2) compare correlates between women who returned and did not return HPV-SS kits; (3) characterize experiences with HPV-SS kit use; (4) identify reasons for non-return; and (5) characterize women's reactions to receiving kits, including screening preferences, future intentions, and trust in HPV-SS.

**Methods**

We conducted this study among women randomized to the intervention arm of the Home-Based Options to Make screening Easier (HOME) pragmatic trial (ClinicalTrials.gov ID:NCT02005510).(39) HOME evaluated whether direct mailing of HPV-SS kits to underscreened women increases cervical cancer screening uptake and cervical pre-cancer detection/treatment compared to usual care. Trial design has been discussed in detail elsewhere.(39) Briefly, from 2014-2017, 16,590 underscreened women (≥3.4 years since last Pap) aged 30-64 years with a primary care provider at Kaiser Permanente Washington (KPWA, a large integrated healthcare system in Washington State) were randomized to a control arm (usual care consisting of annual patient reminders to attend Pap screening and ad-hoc outreach by clinics), or an intervention arm (usual care plus a mailed, unsolicited HPV-SS kit and reminders). Kits included an invitation letter, a research information sheet, instructions, two Dacron-tipped swabs, a collection tube, and a pre-paid return envelope to the KPWA lab. HPV test results were entered into the electronic health record (EHR) and provided to women's primary care teams for appropriate follow-up. The study protocol was reviewed and approved by the KPWA Institutional Review Board.

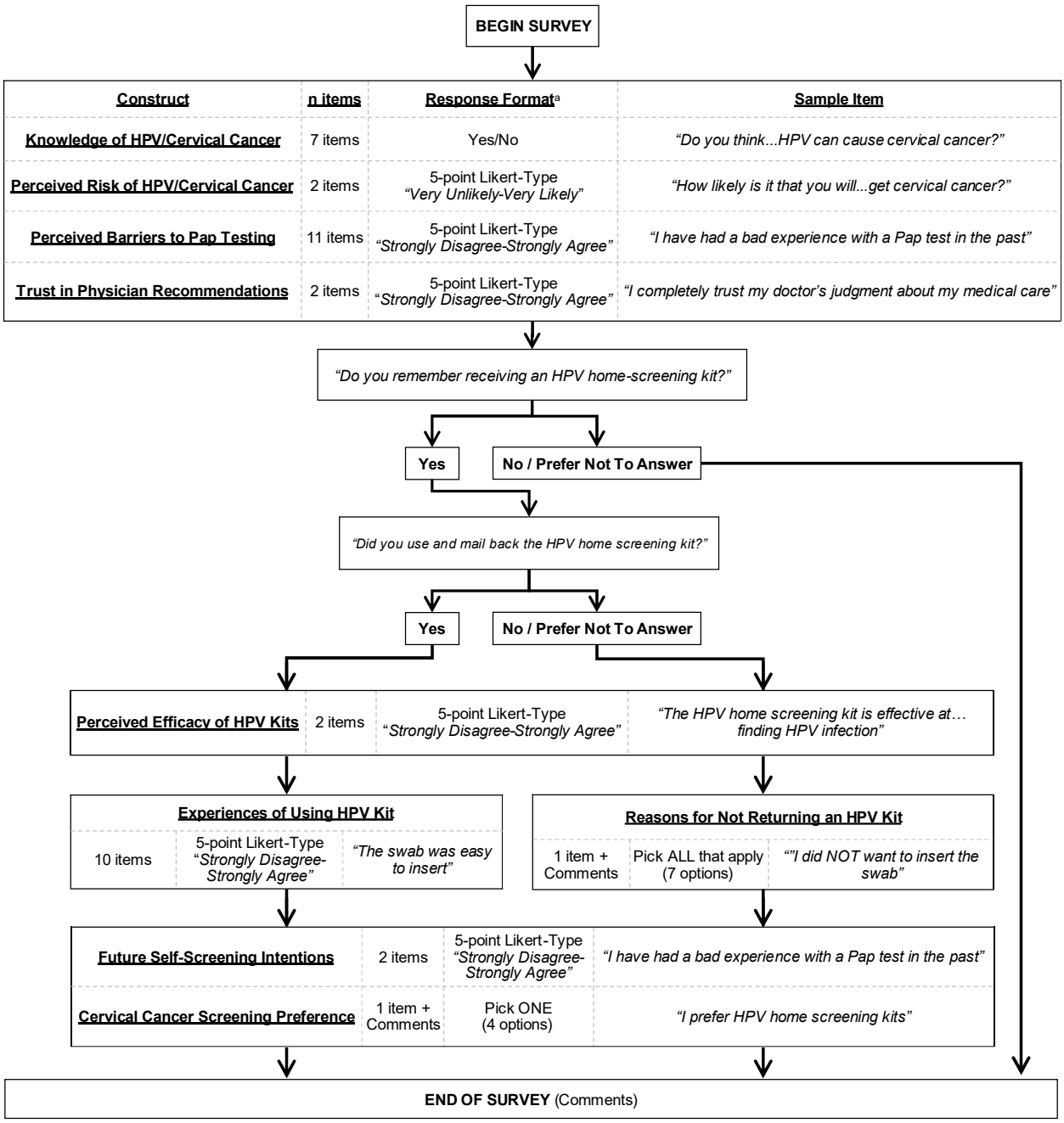
From January-July 2015, we mailed survey invitations six months after trial randomization. We used the EHR to identify and recruit women in two groups based on kit return status (hereafter called "kit returners" and "non-returners"). The target sample size (100 per group; 200 total) was determined based on study resources; we estimated 80% power to detect between-group mean scale score differences as small as 0.4 standard deviations. We excluded women who opted out of EHR review after receiving a kit, were undergoing diagnostic follow-up, or were invited to participate in a qualitative interview after an HPV-positive kit result.(95)

We invited women to complete a 5-10-minute web survey about their experience with a "health screening kit" mailed six months prior. The letter included a survey URL, personalized access code, cash incentive, and a toll-free number to request a paper survey or opt out. We randomized women 1:1 to one of two cash incentives: $5 pre-incentive only or $2 pre-incentive plus $10 post-incentive after survey completion. A paper version was mailed if the web survey was not completed within six weeks. We mailed invitations weekly until we reached the target sample size. In total, 1355 invitations were mailed: 272 to kit returners and 1,083 to non-returners. The web survey was hosted on Qualtrics (Provo, UT).

We assessed sociodemographic characteristics, health status, length of health plan enrollment, and time since last Pap through EHR data.

**Figure 2-1** outlines the order of survey constructs. Unless otherwise noted, item responses used a 5-point Likert scale format. We adapted items from validated questionnaires when possible.(17,96–103)

**Figure 2-1: Flow diagram for survey of HPV kit experiences among underscreened women in a U.S. health care system**




*a All web survey questions included a "Prefer not to answer" option*

The first section measured constructs hypothesized to be correlates of underscreening: knowledge of HPV/cervical cancer (seven items; yes/no response scale);(96) perceived risk of HPV infection and cervical cancer (two items);(104) perceived barriers to Pap testing, (physical, emotional, and structural issues, 11 items), (17,97) and trust in physician recommendation for new health technologies and medical care (two items).

The second section used a skip pattern based on whether the woman remembered 1) receiving a kit, and 2) using the kit and returning it. A picture of the kit was included as a memory aid. Women who did not remember receiving a kit were skipped to the end. We asked kit returners about their experiences (10 items, 8 from a previous study(99) and 2 new items) with the kit itself (instructions, ease of use), including physical (pain, discomfort) and emotional (embarrassment) responses, and feelings about the HPV-SS modality (trust, confidence, convenience). Exploratory factor analysis(105) supported a single factor (eigenvalue=4.47; all factor loadings >0.3). Cronbach's alpha was 0.88, indicating high internal consistency. We assessed reasons for not returning a kit with seven statements covering similar domains to kit returner experience questions, based on items from a previous study.(99) In addition, we identified additional reasons among open-ended responses. Two investigators (CM and RLW) independently reviewed each response before reaching a consensus.

The third section asked women who remembered receiving a kit about three constructs: perceived efficacy of HPV-SS kits to detect HPV infection and women at risk of developing cervical cancer (2 items); intentions to use kits in the future or recommend to others (2

items);(99,103) and screening preference (1 item), with four response options: Pap, HPV-SS kits, both (no preference), or neither.

Data analysis:

Using chi-square tests, we compared personal characteristics between survey responders and non-responders by kit return, and personal characteristics of responders to identify differences between surveyed kit returners and non-returners. For personal characteristics comparisons, we used the EHR to define kit return.

For the following comparisons of psychosocial correlates, we used women's self-reported status to define kit returners and non-returners because we were interested in women's subjective experiences based on their own recall. To compare HPV/cervical cancer knowledge between kit returners and non-returners, we combined responses into an additive index (higher score indicates more correct responses) and compared scores by group using a chi-square test. For women with one (n=17) or two (n=6) missing or "prefer not to answer" responses, those responses were coded as incorrect. Women with more than two missing or "prefer not to answer" knowledge items were dropped from the index (n=2). We estimated average scale scores to compare perceived risk of HPV/cervical cancer and physician trust by kit return and used two-sided *t*-tests to test for differences.

Because our perceived barriers to Pap screening questions encompassed different structural and emotional barriers rather than a single underlying theoretical construct, we evaluated each item's association with kit return individually. We compared item responses by kit return using chi-square tests or Fisher's exact test for comparisons with cell sizes <5.

To compare HPV-SS reactions, we compared average scores for perceived efficacy of HPV-SS kits and future HPV-SS intentions by kit return using t-tests. We used chi-square tests to identify significant differences in reported screening preference between kit returners and non-returners.

Analyses were conducted using Stata 15 (College Station, TX).

**Results:**

Survey response was 43% among kit returners (116/272) and 11% among non-returners (119/1,083). One returner and four non-returners opted out of EHR review after receiving a survey invitation and were excluded from EHR comparisons**.** Among returners, survey respondents were more likely to be White, non-smokers, and have a longer duration of KPWA enrollment than non-respondents (**Table 2-1**). Among non-returners, survey respondents were more likely to be non-smokers than non-respondents. Overall, most survey respondents were non-Hispanic, white, and 50-64 years of age.

**Table 2-1: Sociodemographic, health status, and cervical cancer screening history of underscreened women in a U.S. healthcare system who were invited to complete a survey 6 months after receiving an unsolicited mailed HPV kit, by kit return and survey response**

| | Kit returners invited to survey | | | | | Kit non-returners invited to survey | | | | | All survey respondents |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Non-respondents | | Respondents | | Non-respondents vs. Respondents | Non-respondents | | Respondents | | Non-respondents vs. Respondents | Kit returners vs. Non-returners |
| | n=155[a] | | n=116 | | | n=960[b] | | n=119 | | | |
| **Covariates[c]** | **n** | **%** | **n** | **%** | **$\chi^2$ p-value** | **n** | **%** | **n** | **%** | **$\chi^2$ p-value** | **$\chi^2$ p-value** |
| **Age group (years)** | | | | | | | | | | | |
| 30-39 | 21 | 13.6 | 13 | 11.2 | 0.68 | 161 | 16.8 | 24 | 20.2 | 0.55 | **0.03** |
| 40-49 | 35 | 22.6 | 23 | 19.8 | | 254 | 26.5 | 33 | 27.7 | | |
| 50-64 | 99 | 63.9 | 80 | 69.0 | | 545 | 56.8 | 62 | 52.1 | | |
| **Race** | | | | | | | | | | | |
| White | 110 | 71.0 | 103 | 88.8 | **0.01**[e] | 689 | 71.8 | 86 | 72.3 | 0.80[e] | **0.02**[e] |
| Black/African-American | 10 | 6.5 | 1 | 0.9 | | 33 | 3.4 | 2 | 1.7 | | |
| Asian/Pacific Islander | 14 | 9.0 | 6 | 5.2 | | 86 | 9.0 | 13 | 10.9 | | |
| Other[d] | 14 | 9.0 | 5 | 4.3 | | 81 | 8.4 | 11 | 9.2 | | |
| Unknown | 7 | 4.5 | 1 | 0.9 | | 71 | 7.4 | 7 | 5.9 | | |
| **Ethnicity** | | | | | | | | | | | |
| Hispanic | 6 | 3.9 | 3 | 2.6 | 0.15[e] | 43 | 4.5 | 6 | 5.0 | 0.85[e] | 0.06[e] |
| Non-Hispanic | 141 | 90.9 | 112 | 96.6 | | 848 | 88.3 | 106 | 89.1 | | |
| Unknown | 8 | 5.2 | 1 | 0.9 | | 69 | 7.2 | 7 | 5.9 | | |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Tobacco use** | | | | | | | | | | | |
| Current | 28 | 18.1 | 7 | 6.0 | | 143 | 15.0 | 10 | 8.4 | | |
| Former | 28 | 18.1 | 19 | 16.4 | **0.02** | 183 | 19.1 | 20 | 16.8 | **0.01** | 0.91 |
| Never | 86 | 55.5 | 76 | 65.5 | | 459 | 47.8 | 75 | 63.0 | | |
| Unknown | 13 | 8.4 | 14 | 12.1 | | 175 | 18.2 | 14 | 11.8 | | |
| **Body mass index (in kg/m$^2$)** | | | | | | | | | | | |
| <25 | 42 | 27.1 | 43 | 37.1 | | 235 | 24.5 | 35 | 29.4 | | |
| 25-29.9 | 39 | 25.2 | 28 | 24.1 | 0.47 | 195 | 20.3 | 20 | 16.8 | 0.15 | 0.21 |
| 30-34.9 | 23 | 14.8 | 16 | 13.8 | | 126 | 13.1 | 21 | 17.7 | | |
| ≥35 | 34 | 21.9 | 19 | 16.4 | | 237 | 24.7 | 31 | 26.1 | | |
| Unknown | 17 | 11.0 | 10 | 8.6 | | 167 | 17.4 | 12 | 10.1 | | |
| **Charlson comorbidity score**[f] | | | | | | | | | | | |
| 0 | 118 | 76.1 | 93 | 80.2 | | 773 | 80.5 | 98 | 82.4 | | |
| 1 | 20 | 12.9 | 15 | 12.9 | 0.64[e] | 105 | 10.9 | 13 | 10.9 | 0.91[e] | 0.90[e] |
| 2 | 8 | 5.2 | 5 | 4.3 | | 51 | 5.3 | 6 | 5.0 | | |
| ≥3 | 9 | 5.8 | 3 | 2.6 | | 31 | 3.2 | 2 | 1.7 | | |
| **Health Plan Enrollment Duration (years)**[g] | | | | | | | | | | | |
| 3.4-<5 | 38 | 24.5 | 24 | 20.7 | **0.04** | 194 | 20.2 | 20 | 16.8 | 0.29 | **<0.01** |
| 5-<10 | 44 | 28.4 | 20 | 17.2 | | 297 | 30.9 | 45 | 37.8 | | |
| ≥10 | 73 | 47.1 | 72 | 62.1 | | 469 | 48.9 | 54 | 45.4 | | |
| **Time Since Last Pap (years)**[h] | | | | | | | | | | | |
| 3.4 to <5 | 72 | 46.5 | 61 | 52.6 | 0.57[e] | 326 | 34.0 | 50 | 42.0 | 0.38[e] | 0.12[e] |
| 5 to <10 | 37 | 23.9 | 27 | 23.3 | | 220 | 22.9 | 25 | 21.0 | | |
| ≥10 | 18 | 11.6 | 8 | 6.9 | | 91 | 9.5 | 8 | 6.7 | | |
| No Prior Pap in EHR | 28 | 18.1 | 20 | 17.2 | | 323 | 33.7 | 36 | 30.3 | | |

a One kit returner opted out of medical record review after receiving a survey invitation and was excluded.
b Four kit non-returners opted out of medical record review after receiving a survey invitation and were excluded
c Electronic Health Record covariates are measured as of HOME trial randomization
d Includes American Indian/Alaska Native/Native Hawaiian, More than one race, and Other race categories
e Used Fisher's Exact Test because cell size<10
f Calculated from a weighted index of 19 comorbid conditions
g HOME trial eligibility criteria required ≥3.4 years enrollment in health plan
h HOME trial eligibility criteria required ≥3.4 years since last Pap

Potential correlates of HPV-SS kit uptake:

Self-reported kit return was mostly concordant with EHR data. Five women reported returning a kit with no record in the EHR, and one woman reported not returning a kit despite one documented in the EHR. The following comparisons use self-report to define kit return for a total of 120 kit returners and 115 non-returners.

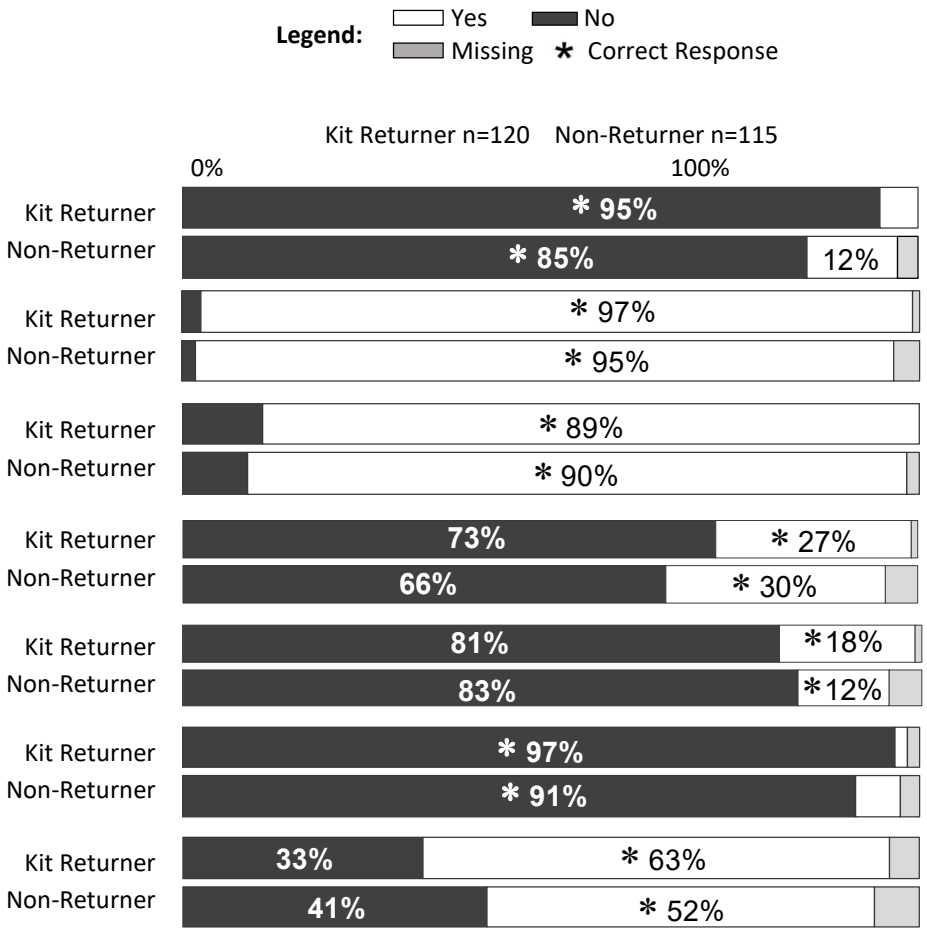
Knowledge scores were similar between kit returners and non-returners (**Table 2-2**). Most (89%) knew HPV is sexually transmitted and can be asymptomatic (90%), were aware of the link between HPV and cervical cancer, and knew that a positive HPV test does not necessarily indicate cancer (94%). However, most women did not know HPV infection can resolve without treatment (82%), or that most sexually active women will get HPV (69%), and 37% were not aware that HPV-negative tests indicate low cervical cancer risk. Kit returners were more likely than non-returners to know HPV infection can be asymptomatic (95% vs. 85%) and that an HPV-negative test indicates low cancer risk (63% vs. 52%).

Overall, respondents perceived themselves at low risk for cervical cancer, and even lower risk for future HPV infection; no difference by kit-return (p=0.94, **Table 2-2**).

Most women trusted their provider's medical judgment (60%) and recommendations about new technologies (73%, **Table 2-2**). Kit returners were slightly less likely than non-returners to say they trusted their doctor's judgment (53% vs 67%) or recommendations about new technologies and treatments (68% vs 79%).

**Table 2-2: Scores and item responses for potential correlates of HPV self-sampling, by self-reported kit return**

**HPV/Cervical Cancer Knowledge**



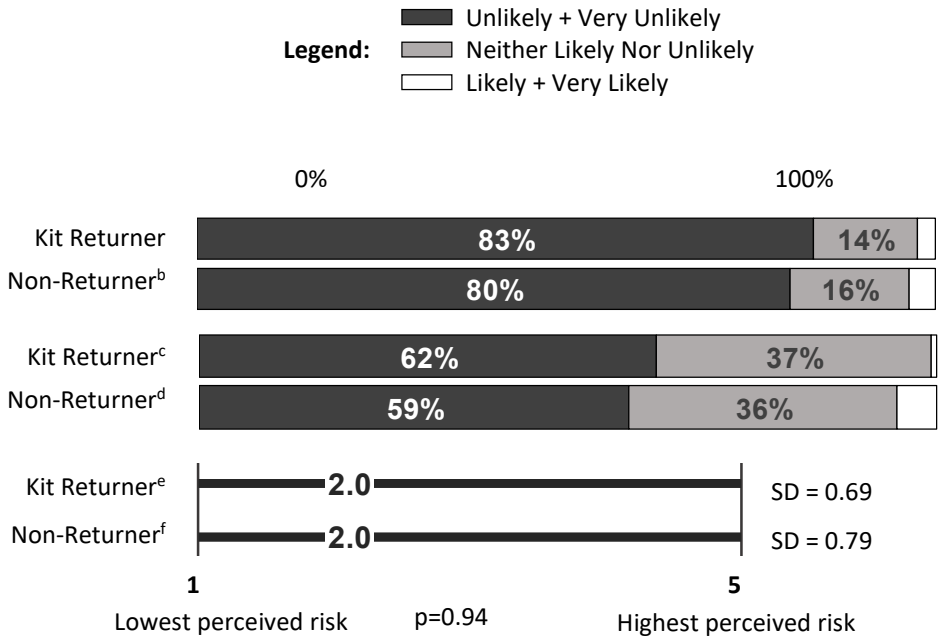

**Summary Knowledge Index**
*(missing items coded as incorrect)*

| Total knowledge items answered correctly | Kit Returner n (%) | Non-Returner[a] n (%) |
|---|---|---|

| | | |
|---|---|---|
| 0-3 items correct | 10 (8%) | 9 (8%) |
| 4-5 items correct | 81 (68%) | 83 (73%) |
| 6-7 items correct | 29 (24%) | 21 (19%) |
| | | p = 0.56 |

**Perceived Risk of HPV/Cervical Cancer**

**Perceived Risk Items**




*Prompt: How much do you agree or disagree with each statement?*

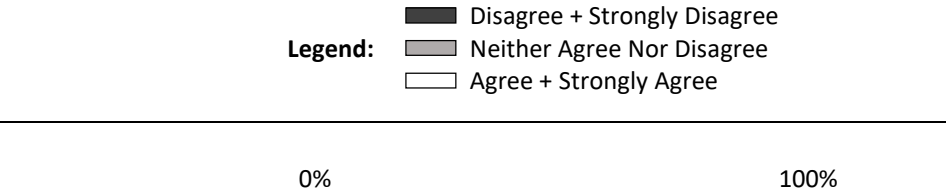
*"How likely is it that you will become infected with HPV?"*

*"How likely is it that you will get cervical cancer?"*

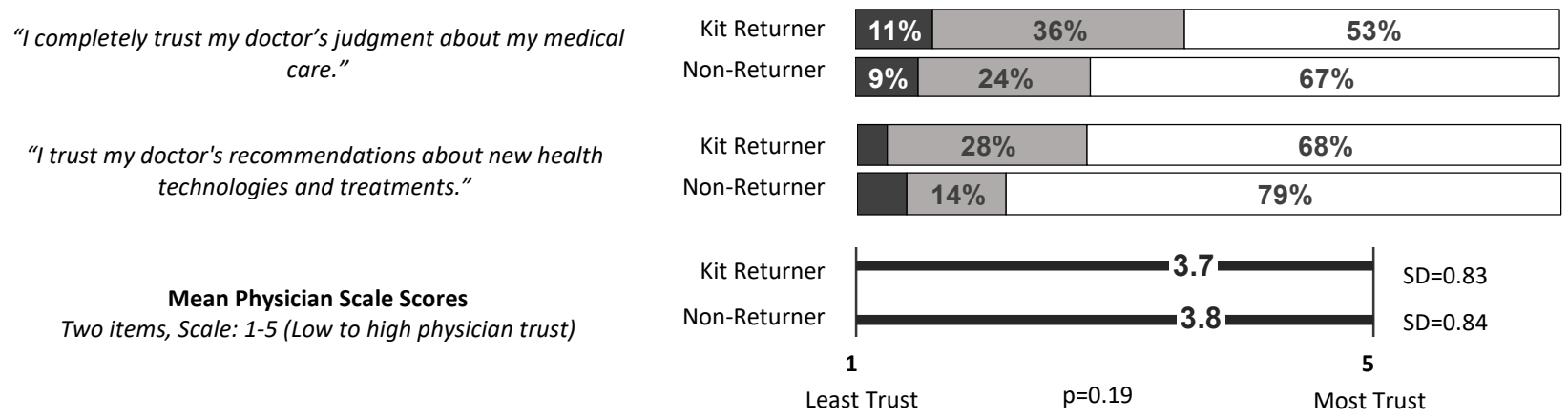
**Mean Perceived Risk Scale Scores**
*Two items, Scale: 1-5 (Low to high perceived risk)*

**Trust in Physician Recommendations**

**Physician Trust Items**




*Prompt: How much do you agree or disagree with each statement?*




HPV: human papillomavirus.

[a]Index was not calculated for 2/115 non-returners who answered <5 of 7 knowledge questions.

[b]Three respondents did not answer this question.

[c]Two respondents did not answer this question.

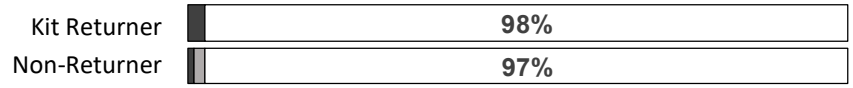
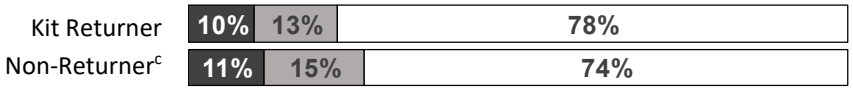
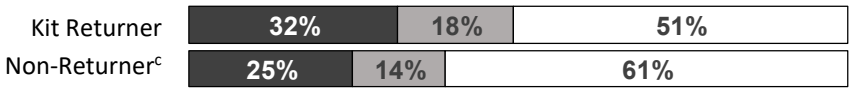
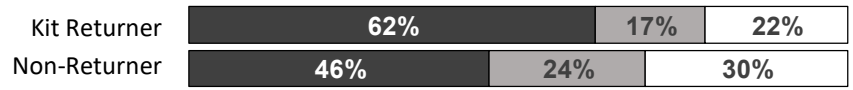
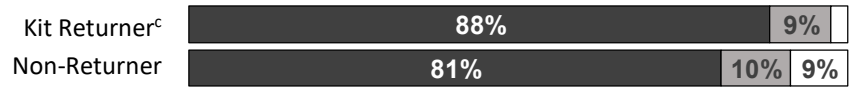
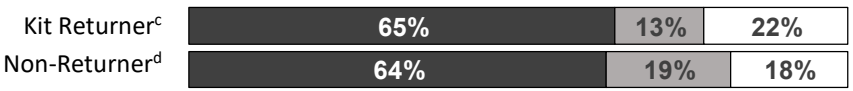
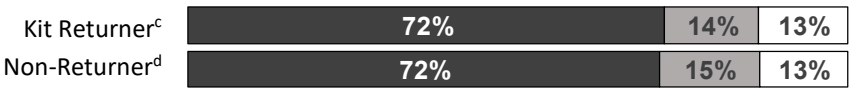
[d]Four respondents did not answer this question.

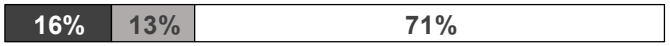
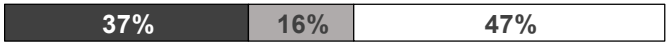
[e]Scale scores dropped for two respondents (<80% of items answered).

[f]Scale scores dropped for five respondents (<80% of items answered).

There were few differences between kit returners and non-returners. Most women believed Pap screening is needed in the absence of symptoms (85%) or sexual activity (72%), and agreed that the benefits of screening outweigh the difficulties (76%) (**Table 2-3**). Over half (56%) found Pap tests embarrassing. Most said they intended to get a Pap test despite not always getting around to it (72%), and 42% reported difficulties fitting Pap tests into their schedule. More kit non-returners than returners worried about Pap results (31% vs 20%), found them embarrassing (61% vs. 51%), and worried that Pap tests are painful (30% vs. 22%).

**Table 2-3: Perceived Pap barriers item responses, by self-reported kit return**

| Perceived Pap Barriers Items | Legend: Disagree + Strongly Disagree; Neither Agree Nor Disagree; Agree + Strongly Agree | p-value[a] |
|---|---|---|
| <u>*Prompt: How much do you agree or disagree with each statement?*</u> | Kit Returner n=120 Non-Returner n=115 | |
| *"Finding cervical cancer early gives you a better chance for a cure."* |  | 0.31[b] |
| *"I am worried that a Pap test might find something wrong."* |  | 0.14 |
| *"The benefits of a Pap test outweigh any difficulty I might have getting it done."* |  | 0.79 |
| *"Pap tests are embarrassing."* |  | 0.33 |
| *"I worry that a Pap test will be painful."* |  | 0.06 |
| *"I only need a Pap test if I have symptoms."* |  | 0.10[b] |
| *"I have had a bad experience with a Pap test in the past."* |  | 0.48 |
| *"I only need a Pap test if I'm sexually active."* |  | 0.99 |
| *"I trust Pap test results."* |  | 0.52[b] |

| | | | |
|---|---|---|---|
| *"I intend to get a Pap test when I am due for one, but I don't always get around to it right away."* | Kit Returner[d] |   | 0.72 |
| | Non-Returner[e] |   | |
| *"It is hard to fit a Pap test in with other commitments such as work or child care."* | Kit Returner[c] |   | 0.23 |
| | Non-Returner |   | |

[a]Chi-squared test unless noted.
[b]Fisher's exact test (cell size <5).
[c]One respondent did not answer this question.
[d]Two respondents did not answer this question.
[e]Three respondents did not answer this question.

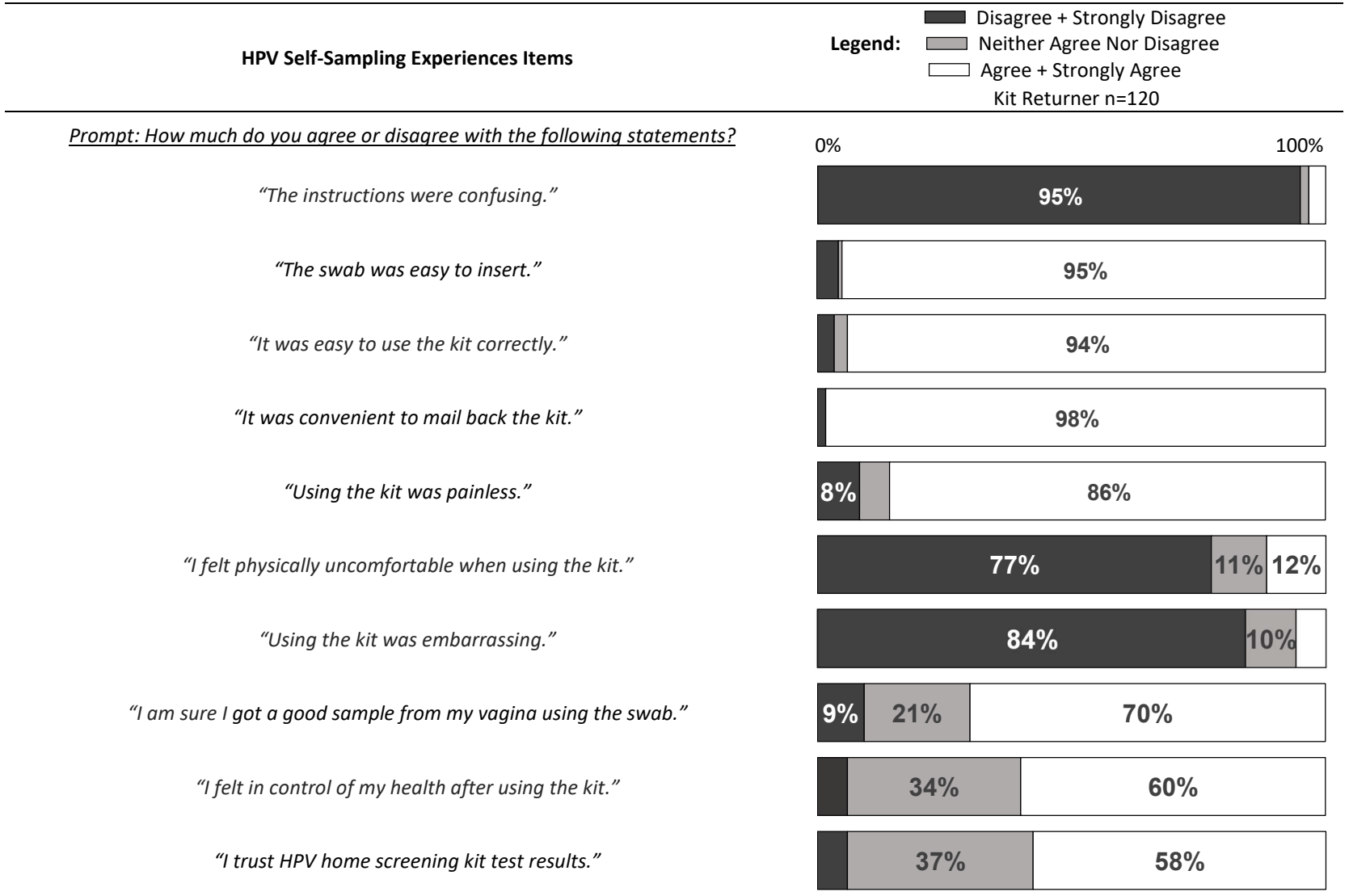
Kit returner experiences:

Kit returners were positive about their experiences (**Table 2-4**). Most believed the instructions were easy to follow (95%); the kits were easy to use, (94%) convenient (98%), and painless (86%); and swabs were easy to insert (95%). Fewer (70%) were confident they had gotten a good sample, and just over half (58%) said they trusted HPV-SS results.

Reasons for non-return:

Among non-returners, 94 (82%) said they remembered receiving a kit in the mail. Of these 94 women, 87 (93%) chose at least one of seven listed reasons for non-return and/or wrote in an open-ended response. Listed reasons included being unsure they could use the kit correctly (38%), not wanting to insert the swab (20%), being embarrassed to use the kit (14%), not trusting kit results (13%), not finding it convenient to use the kit (10%), finding the instructions confusing (9%), and fear that using the kit would be painful (9%). Additional reasons identified in open-ended responses included forgot/did not get around to it (17%) and low perceived risk due to sexual behavior (11%).

**Table 2-4: Experiences with using HPV self-sampling kits**



Reactions to HPV-SS kits:

Kit returners were significantly more confident than non-returners about HPV-SS efficacy ($p<.01$, **Table 2-5**). More than half of kit returners believed kits effectively detected HPV infection or identified women at high risk for cervical cancer, compared to roughly 40% of non-returners.

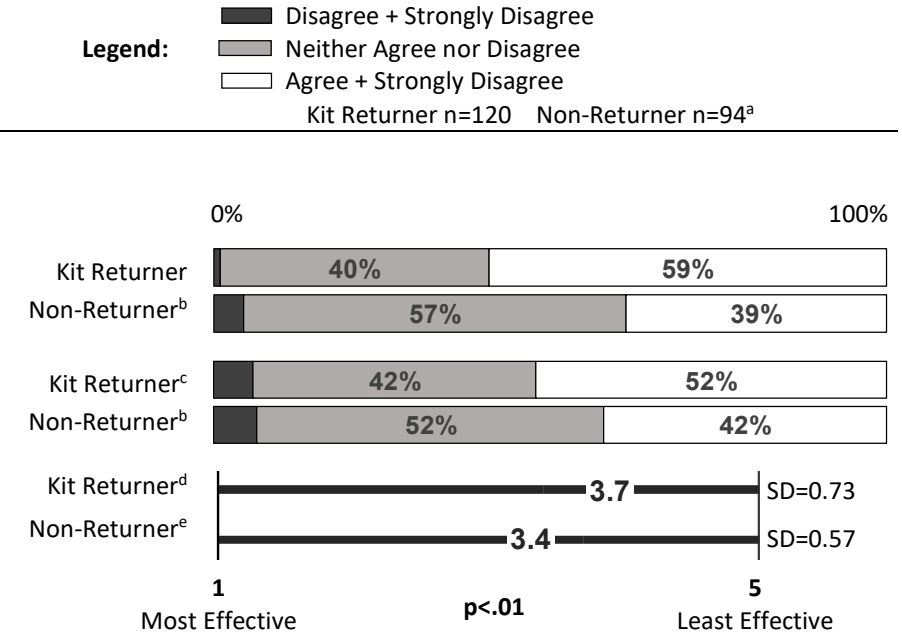
Most kit returners *(*89%) said they would use a kit in the future and would recommend HPV-SS to a friend (79%) (**Table 2-5**). Scores were higher among kit returners than women who did not use the kit ($p<.01$), but 49% of non-returners expressed a willingness to try a kit in the future.

Most kit returners preferred HPV-SS to Pap tests; 66% preferred HPV-SS over Pap; and 21% stated they liked both equally (**Table 2-5**). Despite not having used a kit, 30% of non-returners preferred HPV-SS to Pap testing.

**Table 2-5: Scores and item responses for reactions to HPV self-sampling kits, by self-reported kit return**

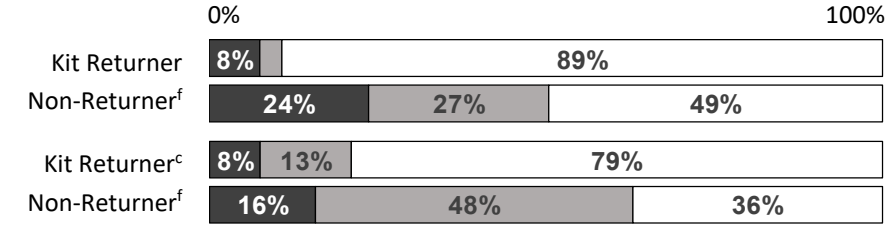
**Perceived Efficacy of HPV Self-Sampling**

**HPV Self-Sampling Efficacy Items**

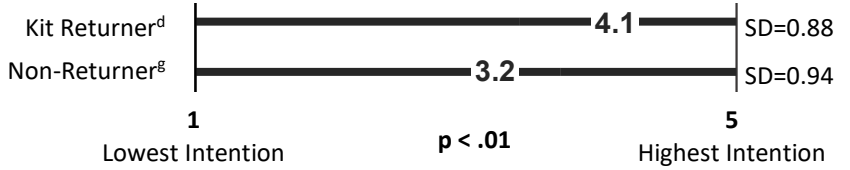



**Future HPV Self-sampling Intentions**

**Future HPV Self-Sampling Intentions Items**



**Mean Future Screening Intentions Scale Scores**
*Two items, Scale: 1-5*
*(lower to higher intention of HPV self-sampling)*




**Cervical Cancer Screening Preference**

| | | Kit Returner n=120 n (%) | Non-Returner n=94[a] n (%) |
|---|---|---|---|
| *"Which type of cervical cancer screening test do you prefer?"* | Pap test in the clinic | 13 (11%) | 34 (36%) |
| | HPV kit used at home | 79 (66%) | 28 (30%) |
| | Both tests are good-I have no preference | 25 (21%) | 12 (13%) |
| | I do not like the Pap or HPV test | 1 (1%) | 9 (10%) |
| | Missing | 2 (2%) | 11 (12%) |

HPV: human papillomavirus.
[a]21 women who did not remember receiving a kit did not receive these questions.
[b]Three respondents did not answer this question.
[c]One respondent did not answer this question.
[d]Scale scores dropped for one respondent (<80% of items answered).
[e]Scale scores dropped for three respondents (<80% of items answered).
[f]Six respondents did not answer this question.
[g]Scale scores dropped for seven respondents (<80% of items answered).

**Discussion**

By surveying underscreened women who received a mailed, unsolicited HPV-SS kit in a pragmatic trial, we found that knowledge of and perceived risk for HPV and cervical cancer, physician trust, and perceived Pap screening barriers did not differ between kit returners and non-returners. Although knowledge about HPV and its association with cervical cancer was generally high, both groups showed some knowledge gaps about HPV testing and natural history. Kit users were highly positive about their experiences and would use them again but were not as confident about trusting HPV-SS results. Non-returners lacked confidence in using HPV-SS kits and trust in the test, but half expressed willingness to use a kit in the future. To our knowledge, this is the first survey of women receiving unsolicited HPV-SS kits in a U.S. healthcare system.

As countries transition to primary HPV screening, HPV/cervical cancer knowledge has been identified as a crucial factor in women's acceptance of HPV screening.(106) Women's knowledge of the epidemiology and natural history of HPV was somewhat limited, as the majority of surveyed women did not know that most sexually active women will be infected with HPV over their lifetime, or that HPV can clear on its own. There was also a lack of clarity among surveyed women on the clinical relevance of a negative HPV test. The observed gaps in knowledge of HPV natural history and the meaning of negative HPV tests could adversely impact reactions to HPV screening (including HPV-SS) in the future. Underscreened women in our study also reported low perceived risk of cervical cancer, consistent with other studies.(107) Kit returners and non-returners reported the same low level of perceived risk, suggesting that it is unlikely that perceived risk is driving choices in this population.

Surveys conducted in countries with organized screening programs found the most powerful predictors of Pap underscreening(17) were structural/logistical factors (e.g., forgetting to make an appointment(91) and scheduling difficulties)(89) and emotional factors (e.g., embarrassment).(90,91) These factors were commonly cited by both kit returners and non-returners in our study.

Similar to other studies using convenience samples and in a trial context,(88,90,91,108) kit returners were accepting of kits, found them to be convenient and were not embarrassed to use them, suggesting that HPV-SS kits helped address some logistical barriers to Pap screening. Physician trust was high among both kit returners and non-returners. When implementing their HPV-SS program, Australia emphasized continued clinician engagement.(109,110) Our results indicate that physicians could be important as endorsers and educators in future efforts to increase HPV-SS kit uptake.

Significantly more kit returners than non-returners believed HPV-SS is efficacious; this difference could have influenced women's decisions about using the kit. Compared to other studies of unsolicited mailed HPV-SS kits, women in our survey reported lower levels of trust and confidence. Two surveys conducted within large-scale trials of unsolicited mailed HPV-SS kits in Australia(90) and Finland(89) found roughly 80% of kit returners believed they had collected a sample correctly, compared to 70% in our study. The Finnish survey found 78% percent of kit returners trusted test results,(89) compared to 58% in our study. Nonetheless, most kit returners in our study indicated they preferred HPV-SS to Pap screening and would use and recommend kits in the future. Additionally, a relatively high proportion of non-returners also reported a preference for HPV-SS and intended to self-sample in the future, indicating that

many non-returners are still open to the idea of HPV-SS. Future research should focus on ways to increase women's trust in HPV self-sampling kits.

In previous surveys of HPV-SS kit non-returners, the most common reasons for non-return had to do with women's screening eligibility (e.g., prior hysterectomy). The EHR facilitated identification and exclusion of women with recent Pap tests, hysterectomy, or pregnancy. Additional study strengths included recruiting non-returners and asking a broad range of questions to enable robust comparisons with kit returners.

As with similar surveys,(90,91) the response rate among non-returners was low (11%). We attempted to engage non-returners through mailed invitations, reminder calls, and cash incentives, but a large population of women remain unresponsive to Pap reminders, HPV-SS kits, or survey invitations. Responses from non-returners who participate in a survey may not be representative of women who are less engaged with the healthcare system. Open-ended responses revealed several additional reasons for non-return (e.g. forgetting and low perceived risk) that could be targeted in future outreach efforts. It is likely that we underestimated the frequency of these reasons by not including them as pre-specified choices. Women in our study were mostly non-Hispanic, white, and residing in urban areas; all were insured and received screening reminders. Therefore, our results cannot be generalized to all racial and ethnic groups, rural populations, or uninsured women. Individual-level data on socioeconomic barriers to screening like income(111) and education(112) were not available for our study. We waited 6 months post-randomization to mail survey invitations. This allowed us to purposively sample kit returners and non-returners, ensuring recruitment did not interfere with the HOME trial's primary outcome measures, and provided an adequate sample size among non-returners, but

also meant subsequent (post-kit) experiences, like receiving test results, knowledge-seeking, or inaccurate memory could have influenced women's responses. Our survey excluded most women with positive HPV-SS results because they had been invited to participate in an interview to learn about their experiences.(95) Interview invitees with positive HPV-SS results were similar to kit returners invited to the survey with respect to age, race, and screening history.(95) Interviewees reported intense feelings and emotions upon receiving positive HPV-SS results. Including these women in the survey would possibly have resulted in lower overall levels of trust and confidence among kit returners, although when asked similar questions, interviewees reported similar levels of trust and preferences for HPV-SS to kit returners in our study.(95)

**Conclusions**

Cervical cancer screening outreach efforts involving HPV-SS should emphasize the accuracy and reliability of self-collected samples and educate women about the high screening efficacy of HPV testing. More research is needed on ways to increase trust and confidence in HPV testing and HPV-SS kits. Women's trust in physicians suggests that physicians may play an important role in educating women and encouraging HPV-SS. The low survey response rate among kit non-returners highlights the need for continued research on new ways to engage underscreened women in screening and research. The heterogeneity in response to mailed HPV-SS kits reported in similar international trials(75) underscores the importance of research on barriers and facilitators to HPV-SS uptake. With several countries (including Australia(109,110) and The Netherlands(113)) now offering HPV-SS for underscreened women

as part of their national cervical cancer screening programs, our results suggest potential targets for education and outreach.

## Chapter 3. Cost-effectiveness studies of HPV self-sampling--a systematic review

**Abstract:**

HPV self-sampling (HPV-SS) can increase cervical cancer screening participation by addressing barriers in high- and low- and middle-income settings. Successful implementation of HPV-SS programs will depend on understanding potential costs and health effects. Our objectives were to summarize the methods and results of published HPV-SS cost and cost-effectiveness studies, present implications of these results for HPV-SS program implementation, and identify knowledge gaps. We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. One reviewer searched online databases for articles published through June 12, 2019, identified eligible studies, and extracted data; a second reviewer checked extracted data for accuracy. Eligible studies used an economic model to compare HPV-SS outreach strategies to standard-of-care tests. Of 16 eligible studies, 14 reported HPV-SS could be a cost-effective strategy. Studies differed in model type, HPV-SS delivery methods, triage strategies for positive results, and target populations. Most (9/16) modeled HPV-SS in European screening programs, 6/16 targeted women who were underscreened for cervical cancer, and 5/16 modeled HPV-SS in low- and middle-income countries. The most commonly identified driver of HPV-SS cost-effectiveness was the level of increase in cervical cancer screening attendance. Lower HPV-SS material and testing costs, higher sensitivity to detect cervical precancer, and longer duration of underscreening among HPV-SS users were also associated with increased cost-effectiveness. Future HPV-SS models in high-income settings should explore the effect of widespread vaccination and new triage

strategies such as partial HPV genotyping. Knowledge gaps remain about the cost-effectiveness of HPV-SS in low- and middle-income settings.

**Introduction:**

Pap testing in high-income countries (HICs) has dramatically reduced cervical cancer incidence and mortality in recent decades.(1,3,114) Nonattendance to regular cervical cancer screening, or "underscreening," is a key driver of continued morbidity and mortality from cervical cancer.(6,7) Despite availability, Pap screening rates in some HICs have plateaued(115,116) or even declined in recent years.(117) In the U.S., screening coverage declined from a high of 83% (2003) to 74% (2017).(4) Factors associated with underscreening in HICs include nonwhite race,(10) poor health status,[11] logistical challenges to attending clinic-based tests,[12,13] emotional/attitudinal barriers (e.g., embarrassment),(16,17) and lack of insurance coverage (in the U.S.(86) - although underscreening remains high among insured women(12)). In low- and middle-income countries (LMICs), where cervical cancer burden is highest,(118) screening coverage is much lower (estimated screening coverage=19%, on average).(119) In these settings, low Pap screening availability (due to limited resources, infrastructure, and trained personnel) and poor sensitivity of the existing low-cost cervical cancer screening option, visual inspection with acetic acid (VIA), are barriers to effective screening.(120)

Primary human papillomavirus (HPV) screening (i.e., HPV only) is a newer method with potential to expand screening coverage. Several HICs have recently transitioned their national screening programs from cytology-based to primary HPV screening,(121–123) and recently

updated U.S. national guidelines include primary HPV screening as a recommended strategy.(87) Primary HPV screening has advantages over Pap that can benefit both high- and low-income settings. HPV testing has higher sensitivity than Pap to detect cervical pre-cancers, allowing extended screening intervals,(124) and HPV testing requires less training for sample collection.(125)

HPV tests using self-collected samples have comparable sensitivity to clinician-collected samples for detecting cervical intraepithelial neoplasia grade 2 or higher (CIN2+),(75) making HPV self-sampling (HPV-SS) a feasible screening option. Women of different ages, ethnicities, and nationalities report HPV-SS to be highly acceptable.(90,95,126,127) Researchers have evaluated several methods of delivering HPV-SS in different settings. In organized screening programs, the most commonly evaluated method is mailing unsolicited HPV-SS kits to underscreened women. A recent meta-analysis of 19 randomized trials found this “direct mail” method significantly increased screening uptake among underscreened women compared to usual care Pap invitations.(75) “Opt-in” HPV-SS is a variation in which women must first respond to an invitation to receive a mailed kit. While some trials have found that opt-in HPV-SS increases uptake,(108,128) the same recent meta-analysis did not find that opt-in significantly increased screening uptake compared to usual care.(75) Trials comparing the two strategies found that direct mail results in greater screening uptake compared to opt-in.(94,129) Outside organized screening programs, some trials have studied door-to-door recruitment strategies using community health workers (CHWs). Trials in Mexico(130) and Argentina(131) found CHW-based HPV-SS strategies improved uptake over recruitment to clinic-based screening. Small-scale trials have been conducted in underserved populations in

HICs. In the U.S., two trials among ethnic minority women in Florida found that mailed(132) and CHW-delivered(133) HPV-SS increased uptake. Australia(110) and the Netherlands(113) have incorporated HPV-SS options into their national screening programs.

The potential cost-effectiveness of HPV-SS is a key consideration as health systems in other countries consider adding HPV-SS to their screening programs.(134) Several programmatic choices in HPV-SS implementation have potential cost-effectiveness implications, including target population (e.g., all women, underscreened, or never-screened), outreach method (direct mail, opt-in, or CHW), and follow-up protocols for positives. Heterogeneity in observed screening uptake from HPV-SS trials (6-34% in trials of direct-mailed HPV-SS kits)(75) has also led to concerns about costs associated with unused kits.(135) Mathematical modeling helps bring together existing evidence and informed hypotheses to determine likely health outcomes and total costs of different potential implementation scenarios.

We are unaware of any systematic review of published studies on costs and cost-effectiveness of HPV-SS. Our objectives were to conduct a systematic review of online databases to: 1) identify current published mathematical modeling studies comparing cost-effectiveness of HPV-SS with other recommended cervical cancer screening tests using a lifetime or intermediate measure of cost-effectiveness; 2) summarize model content, including target population, implementation details, modeling method, and results; 3) identify important implications to inform decision-making for health systems in the U.S. and other HICs that may be considering implementing HPV-SS; 4) identify knowledge gaps and opportunities for future HPV-SS cost-effectiveness research.

**Methods**

We designed and conducted this systematic review based on Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement guidelines.(136) The PRISMA checklist is in **Appendix A.** Eligible studies used an economic model to compare outreach strategies that incorporate HPV-SS into standard-of-care strategies. We defined standard-of-care as either the local screening guidelines for the country where the modeling study was set, or a World Health Organization approved screening strategy (clinic-collected HPV testing, Pap testing, or VIA) for countries that do not have standard screening guidelines.(137) We included studies that calculated costs from the societal or payer perspectives. Eligible studies included a lifetime (e.g., quality-adjusted life-years gained) or intermediate (e.g., detected/treated CIN2+, screening uptake) measure of clinical effectiveness. We did not restrict studies by geographic region or women's prior screening history. We excluded cost-effectiveness studies of HPV testing that included self-sampling only as a sensitivity analysis(138–143). We did not restrict searches by language, but excluded studies published in languages other than English from full-text review.

We queried Web of Science, PubMed, Embase, and Cochrane Library databases to identify eligible published reports and journal articles. Database searches included terms relating to three categories: cervical cancer, screening, and cost-effectiveness modeling. We selected databases and search terms with assistance from a research librarian. Example queries are in **Appendix B.** After running search queries, author CM reviewed study titles for potential eligibility, flagged titles of potentially eligible studies, reviewed abstracts, and selected studies for full-text eligibility review. After identifying eligible studies, author CM reviewed reference lists of full-text reviewed studies to identify any other eligible titles. Our literature search was

last updated on June 12, 2019. We did not pre-register this protocol before performing the search.

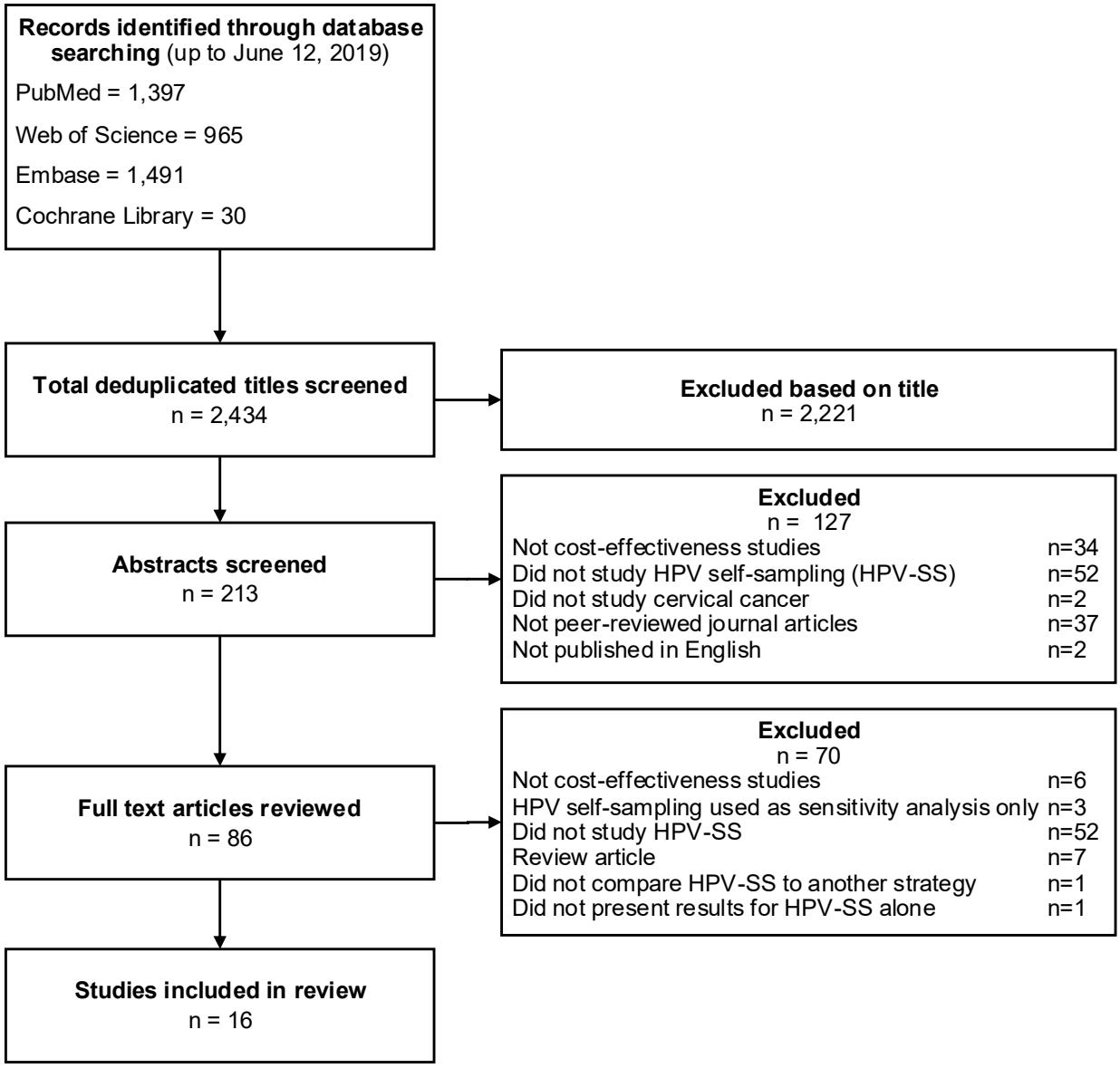
We used a data extraction form to collect data on model type, characteristics (e.g., setting, population, time horizon, perspective, outcomes, discounting), costs (payer cost sources, HPV kit/test cost), HPV test characteristics (CIN2+ detection), positive test triage strategy, primary cost-effectiveness outcome, secondary outcomes of interest (e.g., intermediate cost-effectiveness outcomes, results from payer perspective), and relevant sensitivity analysis results. If studies included additional screening promotion strategies in their cost-effectiveness analysis, we only report comparisons that include HPV-SS and standard-of-care screening strategies. Initial data extraction was performed by CM, and all extracted data points were reviewed by author RLW to ensure accuracy. This review focused on factors relevant to HPV-SS implementation for healthcare systems, especially in countries like the U.S. where costing from the payer perspective is more common than lifetime or societal costs.(144) We thus omitted detailed discussions of methods used to calculate indirect costs and quality of life estimates used to calculate quality-adjusted life-years (QALYs). To facilitate crude cost comparison among studies, we used consumer price inflation estimates for the countries of origin to inflate costs to 2017 levels, then converted costs to U.S. dollars using 2017 currency exchange rates. We developed a study quality checklist (**Appendix C**) derived from the HPV-FRAME quality framework for HPV screening models (145) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement (146). A single reviewer (CM) assessed study quality. Study quality was rated as poor, fair, good, or excellent. Because this is

the first systematic review on this topic, we specified that only studies with a poor rating would be excluded.

**Results**

Our search returned 2,434 titles after de-duplication (**Figure 3-1**). After reviewing titles, abstracts, and reference lists that came up in our search, we identified 16 eligible published cost-effectiveness studies.(128,147–161)

**Figure 3-1: Flow chart of HPV self-screening cost-effectiveness study selection**



Thirteen of 16 studies reported their model type;(148–156,158–161) the three other studies appeared to use some form of decision model (128,147,157) **(Table 3.1)**. Six studies reported using the payer perspective,(128,149,158) nine used the societal perspective (including patient and payer costs),(148,150–157) and the remaining study did not report their cost perspective, but included the cost of patient time in addition to payer costs.(147) Eleven studies reported using a lifetime horizon for model costs and outcome,.(148,150–156,158) two of the remaining analyses explicitly defined their time horizon as one year,(128) and three reported no horizon but described one cycle of HPV-SS implementation.

Studies obtained cost estimates from recent studies of local healthcare costs, national health system cost data, and micro-costing (**Table 3-1**). The only U.S.-based study estimated direct medical costs using Center for Medicare and Medicaid Services (CMS) Laboratory and Physician fee schedules.(150) Most studies derived probability estimates for HPV-SS test performance and/or HPV-SS uptake from a parent study (**Table 3-1**). Among models based on randomized HPV-SS trials, only one included CIN2+ outcomes.

Most studies reported complete information about their models. Using the study rating instrument, eleven were rated excellent, four good, and one fair (**Appendix C**). Three studies reported CHEERS checklist compliance.(146,155,156)

**Table 3-1: Model characteristics of eligible HPV self-sampling cost and cost-effectiveness studies**

| First Author Country Publication Year | Modeling Method | Model Outcomes | Time Horizon | Discount Rate | Cost Perspective | Parameter Sources | Parent Study Type | Parent Study Endpoint |
|---|---|---|---|---|---|---|---|---|
| **Vassilakos** Switzerland 2019 (158) | Decision Tree | • Lifetime cervical cancer risk<br>• Life expectancy<br>• Quality-adjusted life years (QALY)<br>• Lifetime cost | Lifetime | 3% per year | Payer | Payer Costs<br>• HPV self-sampling (HPV-SS) and healthcare costs: University Hospitals, Geneva<br>Probabilities<br>• HPV-SS uptake: Assumed<br>• Other probabilities: Literature | None | N/A |
| **Mezei** Uganda 2018 (148) | Micro-simulation | • Lifetime cervical cancer risk<br>• Life expectancy<br>• Lifetime cost | Lifetime | 3% per year | Societal | Payer Costs<br>• HPV-SS cost: Previous HPV-SS study<br>• Healthcare costs: Parent study<br>Probabilities<br>• HPV-SS uptake: Assumed<br>• Natural history transitions: Literature (parent model) | Randomized Control Trial (162) | Cryo-therapy |
| **Campos** Uganda 2017 (153) | Micro-simulation | • Lifetime cervical cancer risk<br>• Life expectancy<br>• Lifetime cost | Lifetime | 3% per year | Societal | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Micro-costing (w/ local providers)<br>Probabilities<br>• HPV-SS uptake: Assumed<br>• Natural history transitions: Literature (parent model) | Demonstration Project (163) | Cervical intra-epithelial neoplasia grade 2 or higher (CIN2+) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Kitchener/ Tsiachristas** United Kingdom 2016/2018 (155,156) | Decision Tree | • QALY<br>• Lifetime cost | Lifetime | 3.5% per year | Payer | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Previous studies, UK National Health Service<br>Probabilities<br>• HPV-SS uptake: Parent trial<br>• Other probabilities: National screening program, Meta-analysis | Cluster Randomized Trial (156) | Screening Uptake |
| **Burger** Norway 2017 (152) | Micro-simulation | • Lifetime cervical cancer risk<br>• Life expectancy<br>• QALY<br>• Lifetime cost | Lifetime | 4% per year | Societal | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Micro-costing, fee schedules<br>Probabilities<br>• HPV-SS uptake: Parent study<br>• Natural history transitions: Literature (parent model) | Randomized Control Trial (164) | Screening Uptake |
| **Virtanen** Finland 2015 (149) | Not reported | • Screening uptake<br>• Detected/ Treated CIN2+<br>• Costs (through treated CIN2+) | Not Reported (one-time analysis) | Not Applicable | Payer | Payer Costs<br>• HPV-SS cost: Parent studies<br>• Healthcare costs: Previous Finnish cost analysis<br>Probabilities<br>• Derived from parent study | Randomized Control Trial (165)<br>Cohort Study (166) | Screening Uptake<br>CIN2+ |
| **Rozemeijer** Netherlands 2015 (151) | Micro simulation | • Life expectancy<br>• QALY<br>• Lifetime costs | Lifetime | 3% per year | Societal | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Micro-costing (w/ local providers) | Randomized Control Trial (167) | Screening Uptake |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Probabilities<br>• Screening: Parent study, Dutch screening program<br>• Natural history, demographic transitions: MISCAN model | | |
| **Haguenoer**<br>France<br>2014<br>(157) | Not Reported | • Screening uptake<br>• Costs (through Pap follow-up of positive HPV result) | Not Reported (one-time analysis) | Not Applicable | Societal | Payer Costs<br>• Source not reported (Parent study assumed)<br>Probabilities<br>• HPV-SS uptake: Parent study | Randomized Trial<br>(157) | Screening Uptake |
| **Campos**<br>India, Uganda, Nicaragua<br>2015<br>(142) | Micro-simulation | • Lifetime cervical cancer risk<br>• Life expectancy<br>• Lifetime cost | Lifetime | 3%<br>per year | Societal | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Literature<br>Probabilities<br>• HPV-SS uptake: assumed<br>• Natural history transitions: Literature (parent model) | Demonstration Project<br>(163) | CIN2+ |
| **Broberg**<br>Sweden<br>2014<br>(128) | Not Reported | • Cervical cancer cases avoided<br>• Treated CIN2+<br>• Costs (one year) | One Year | Not Applicable | Payer | Payer Costs<br>• HPV-SS cost: Parent study, literature<br>• Healthcare costs: Prices in the region<br>Probabilities<br>• HPV-SS uptake: Parent study<br>• CIN and Cancer: Parent study (not self-screening arm) | Randomized Control Trial<br>(128) | Screening Uptake |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Östensson**<br>Sweden<br>2013<br>(154) | Markov | • Lifetime cervical cancer risk<br>• Life expectancy<br>• QALY<br>• Lifetime cost | Lifetime | 3%<br>per year | Societal | Payer Costs<br>• HPV-SS cost: Device cost<br>• Healthcare costs: Swedish health system<br>Probabilities<br>• Literature, Assumptions | None | N/A |
| **Shi**<br>China<br>2011<br>(161) | Markov | • Lifetime cervical cancer risk<br>• Lifetime cervical cancer mortality<br>• Life expectancy<br>• Lifetime cost | Lifetime | 3.6%<br>per year | Societal | Payer Costs<br>• HPV-SS cost: Kit cost assumed, labor costs from prior studies<br>• Healthcare costs: Microcosting with regional hospital<br>Probabilities<br>• HPV-SS uptake: Unpublished study<br>• Cervical outcomes: Literature | Cross-sectional (HPV-SS test performance)<br>(168) | CIN2+ |
| **Flores**<br>Mexico<br>2011<br>(160) | Decision Tree | • Detected/treated CIN2+<br>• Detected/treated cervical cancer | One Year | 3%<br>per year[1] | Payer | Payer Costs<br>• HPV-SS cost: Parent Study<br>• Healthcare costs: Micro-costing (w/ national screening program)<br>Probabilities<br>• HPV-SS uptake: Assumed<br>Other probabilities: Parent Study | Cohort Study<br>(169) | CIN2+ |
| **Balasubramanian**<br>USA<br>2010 | Markov | • Lifetime cervical cancer risk | Lifetime | Not Applicable | Societal | Payer Costs<br>• HPV-SS cost: Parent study | Cohort Study<br>(150) | CIN2+ |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| (150) | | • QALY<br>• Lifetime cost | | | | • Healthcare costs: Medicare laboratory and physician fee schedules<br>Probabilities<br>• HPV-SS uptake: Assumed equivalent with Pap<br>• Cervical outcomes: Literature | | |
| **Bais**<br>Netherlands<br>2007<br>(147) | Not Reported | • CIN2+ detected<br>• Cost | Not Reported (one-time analysis) | Not Applicable | Not Reported (indirect costs included) | Payer Costs<br>• HPV-SS cost: Parent study<br>• Healthcare costs: Literature estimate<br>Probabilities<br>• Parent study, assumptions | Randomized Control Trial (147) | CIN2+ |

1 Although analysis was for one-year impact, equipment and overhead costs were discounted at 3% to calculate equivalent annual expenditures

Six studies modeled strategies targeting underscreened women (**Table 3-2**).(128,147,149,151,152,157) Underscreening definitions varied, with some defining underscreening as nonresponse to reminder letters rather than a specific time since last screening (**Table 3-2**). Recommended screening intervals ranged from 3(128)-10(151) years depending on age and country. All studies in underscreened women were conducted in regional or national screening programs in European HICs.(128,147,149,151,152,157)

Six studies modeled HPV-SS targeted at all screening-age women regardless of screening history.(148,150,153,154,159,161) These included the only U.S.-based study of HPV-SS, which modeled mailed HPV-SS kits using a cohort study of clinic-based HPV-SS.(150) Five studies modeled HPV-SS in LMICs including Mexico,(160) Uganda,(148,153,159) India,(159) Nicaragua,(159) and rural China.(161)

Three studies modeled strategies targeted at never-screened women at age of first screening eligibility.(155,156,158) Two used data from the same trial, which examined whether HPV-SS could increase screening uptake among newly screening eligible 20- and 25-year-old women who did not respond to their first screening invitation.(155,156) A Swiss study modeled HPV-SS as a primary screening strategy among never screened, newly-eligible women, beginning at their first screening test at age 25 and continuing through age 70.(158)

HPV-SS delivery method:

**Table 3-2: Cost-effectiveness comparisons and select base-case results in 2017 USD, HPV self-sampling vs. standard of care screening strategies, by HPV self-sampling target group**

**Underscreened women**

| First Author Country Publication Year | Population and Cost Comparisons of HPV Self-sampling (HPV-SS) and Standard of Care (SOC) Strategies[1] | Screening Use | Screening Interval | Lifetime Cost-Effectiveness Results | CIN2+[2] Detection/ Treatment Results | Cervical Cancer (CC) Prevention Results | CC Screening Results |
|---|---|---|---|---|---|---|---|
| | Costs inflated from 2014 U.S. Dollars<br>Screening age: 25-69 years<br>Cost-effectiveness threshold: <$103,531/QALY[3] | **Screening probability** | | **ICER[4] (cost/ QALY gained)** | | **Lifetime CC risk[5]** | |
| **Burger**<br>Norway<br>2017<br>(152) | **Scenario 1: Moderately underscreened**[6] | | | | | | |
| | No screening | 0% | -- | -- | -- | 2.17% | -- |
| | HPV-SS (direct mail[7], Pap triage)[8] | SOC+10%[9] | 5 yrs | $30,673 | | 0.75% | |
| | Pap + 2 reminders (SOC) | SOC | 3 yrs | Dominated | | 0.75% | |
| | **Scenario 2: Moderate/severely underscreened**[6] | | | | | | |
| | No screening | 0% | -- | -- | -- | 2.17% | -- |
| | HPV-SS (direct mail, Pap triage)[8] | SOC+10%[9] | 5 yrs | $30,462 | | 0.72% | |
| | Pap + 2 reminders (SOC) | SOC | 3 yrs | Dominated | | 0.75% | |
| | Costs converted from 2012 Euro<br>Screening age: 30-60 years | **Population screening coverage[10]** | | | **Cost/ treated CIN2+ (payer)** | | |
| **Virtanen**<br>Finland<br>2015<br>(149) | No intervention (initial Pap invitation, SOC) | 70% | | | $20,989 | | |
| | HPV-SS (direct mail, Pap triage)[11] | 79% | 1-time | | $21,258 | | |
| | Pap reminder letter | 78% | model | | $19,798 | | |
| | Reminder+HPV-SS (direct mail, Pap triage)[11] | 83%[12] | SOC=5 yrs | -- | $19,557 | -- | -- |
| | Reminder+HPV-SS (direct mail, colposcopy triage)[11] | 83%[12] | | | $21,326 | | |
| | Costs converted from 2011 Euro (Assumed)[13]<br>Screening age: 30-65 years | **Screening uptake[14]** | | | | | **Cost/extra women screened (societal)** |
| **Haguenoer**<br>France<br>2014 | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (157) | No intervention (Initial Pap invitation, SOC)<br>HPV-SS (direct mail, Pap triage)<br>Pap reminder letter | 9.9%<br>22.5%<br>11.7% | 1-time model SOC=3 yrs | -- | -- | -- | ref.<br>$96<br>$118 |
| **Rozemeijer** Netherlands 2015 (151) | Costs converted from 2013 Euro<br>Screening age: 30-65 years<br>C/E thresholds: $27,940 and $69,850/QALY | **Screening uptake**[15] | | **ICER (cost/ QALY gained)** | **Change in CIN2+ detection** | **Change in CC mortality** | |
| | **Scenario 1: No switching to HPV-SS**[16] | | | | | | |
| | No intervention (provider-collect HPV, SOC)<br>HPV-SS (direct mail, Pap triage) | --<br>17% | 5/10 yrs[17]<br>5/10 yrs[17] | --<br>$3,180 | ref.<br>+8.9% | ref.<br>-9.6% | -- |
| | **Scenario 2: 100% switching to HPV-SS**[16] | | | | | | |
| | No intervention (provider-collect HPV, SOC)<br>HPV-SS (direct mail, Pap triage) | --<br>17% | 5/10 yrs[17]<br>5/10 yrs[17] | --<br>(Cost-saving) | ref.<br>-6.9% | ref.<br>-1.3% | -- |
| **Broberg** Sweden 2014 (128) | Costs converted from 2009 Euro<br>Screening age: 30-62 years | **Screening uptake**[15] | | | **Marginal cost per extra CIN2+ treated (payer)** | | |
| | HPV-SS invitation (opt-in[18], colposcopy triage)[19]<br>Pap invitation (SOC) | 24.5%<br>10.6% | 1 yr model SOC=3/5 yrs[20] | -- | $4,036<br>ref. | -- | -- |
| **Bais** Netherlands 2007 (147) | Costs converted from 2005 Euro<br>Screening age: 30-50 years | **Screening uptake**[14] | | | **Cost per CIN2+ detected (payer)** | | |
| | HPV-SS (direct mail, Pap triage)[21]<br>Pap recall letter (SOC) | 31.3%<br>17.6% | 1-time model SOC=5 yrs | -- | $13,803<br>$11,871 | -- | -- |
| **All women** | | | | | | | |
| **Mezei** Uganda 2018 (148) | Costs inflated from 2014 U.S. Dollars<br>Screening age: 30-50 years<br>C/E threshold $756/year of life saved | **Population screening coverage**[10] | | **ICER**[4] **(Cost/year of life saved)** | | **Lifetime CC risk reduction**[22] | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | No screening | 0% | -- | --. | | ref. | |
| | HPV-SS at home (cryotherapy for hrHPV+)[23] | 70% | 1x/Lifetime[24] | $135 | | 15.0% | |
| | VIA in clinic (cryotherapy followup) | 70% | 1x/Lifetime[24] | Dominated | -- | 7.2% | -- |
| | HPV-SS at home (VIA triage)[23] | 70% | 1x/Lifetime[24] | Dominated | | 7.6% | |
| | HPV-SS at home (cryotherapy for hrHPV+)[23] | 70% | 3x/Lifetime[24] | $248 | | 33.0% | |
| | HPV-SS at home (cryotherapy for hrHPV+)[23] | 70% | 5x/Lifetime[24] | $487 | | 42.8% | |
| **Campos** Uganda 2017 (153) | Costs inflated from 2011 International Dollars<br>Screening age: 30-49 years<br>C/E threshold $1,842/year of life saved | **Population screening coverage**[10] | | **ICER (Cost/year of life saved)** | | **Lifetime CC risk reduction**[22] | |
| | No screening | 0% | -- | ref. | | ref. | |
| | HPV-SS in-clinic (cryotherapy or colposcopy triage)[25] | 75%[26] | 1x/Lifetime | $87 | -- | 20.7% | -- |
| | Provider-collect HPV in-clinic[25] | 75%[26] | 1x/Lifetime | $131 | | 23.1% | |
| **Campos** 2015 (142) | Costs inflated from 2011 International Dollars<br>Screening age: 25-50[27]<br>India C/E threshold $5,712/year of life saved<br>Nicaragua C/E threshold $4,600/year of life saved<br>Uganda C/E threshold $1,493/year of life saved | **Population screening coverage**[10] | | **ICER (Cost/year of life saved)** | | **Lifetime CC risk reduction** | |
| India | Provider-collect HPV in clinic @45 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | $207 | | 24.1% | |
| | HPV-SS in clinic @ 45 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 20.8% | |
| | VIA in clinic @ 45 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 14.6% | |
| Nicaragua | Provider-collect HPV in clinic @35 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Cost-saving | | 25.8% | |
| | HPV-SS in clinic @ 35 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 22.2% | |
| | VIA in clinic @ 35 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 19.6% | |
| Uganda | VIA in clinic @ 40 years[28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 21.1% | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Provider-collect HPV in clinic @40 years [28](cryotherapy follow-up) | 70% | 1x/Lifetime | $131 | | 24.7% | |
| | HPV-SS in clinic @ 40 years [28] (cryotherapy follow-up) | 70% | 1x/Lifetime | Dominated | | 22.1% | |
| **Östensson** Sweden 2013 (154) | Costs converted from 2011 Euro<br>Screening age: 23-60 years<br>C/E threshold: $136,672/QALY | **Population screening coverage**[10] | | **ICER (Cost/life-year gained)** | | **Lifetime CC risk reduction**[22] | |
| | No screening | 0% | -- | ref. | -- | ref. | -- |
| | Pap reminders, then HPV-SS beginning at age 35+ (direct mail, Pap triage)[29] | 80% | 5 yrs | $65,299 | | 56.0% | |
| | Pap reminders (SOC) | 80% | 3/5 yrs[30] | Dominated | | 48.1% | |
| **Shi** China 2011 (161) | Costs converted from 2009 U.S. Dollars<br>Screening age: 35 years (1x/lifetime), 35 & 45 years (2x/lifetime)<br>C/E threshold: $3,387/life-year gained | **Screening uptake**[14] | | **CER (Cost/year of life saved)** | | **Average lifetime CC risk reduction**[32] | |
| | No intervention | -- | -- | ref. | | -- | |
| | VIA (Colposcopy triage)[31] | 71% | 1x/Lifetime | $634 | | 7.0% | |
| | HPV-SS (at mobile clinic, colposcopy triage)[31] | 71% | 1x/Lifetime | $1,092 | | 10.0% | |
| | VIA (Colposcopy triage)[31] | 71% | 2x/Lifetime | $696 | | 13.0% | |
| | HPV-SS (at mobile clinic, colposcopy triage)[31] | 71% | 2x/Lifetime | $1,175 | | 19.0% | |
| **Flores** Mexico 2011 (160) | Costs converted from 2008 USD<br>Screening age: 30-80 years[33] | **Screening uptake**[34] | | | **ICER (Cost/ detected CC and CIN2+)** | | |
| | Pap+HPV co-test in clinic (colposcopy follow-up) | 100% | 1-year model (Screening interval not reported) | -- | $3,966 | -- | -- |
| | Provider-collected HPV (colposcopy follow-up) | 100% | | | Dominated | | |
| | HPV-SS in clinic (colposcopy follow-up) | 100% | | | Dominated | | |
| | Pap in clinic (colposcopy follow-up) | 100% | | | Dominated | | |
| **Balasubramanian** USA 2010 (150) | Costs inflated from 2007 U.S. Dollars<br>Screening age: 18-85 years | **Population screening coverage**[10] | | **ICER (Cost/ QALY gained)** | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | No screening | 0% | -- | -- | | | |
| | HPV-SS (direct mail, Pap triage)[35] | 80% | 3 yrs | $11,755 | -- | -- | -- |
| | Pap screening (HPV triage, SOC) | 80% | 3 yrs | Dominated | | | |

**Never-screened women at age of first recommended screening**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Vassilakos** Switzerland 2019 (158) | Costs deflated from 2018 U.S. Dollars<br>Screening Age: 25-70 years[36]<br>C/E threshold: $48,922 | **Population screening coverage**[10] | | **CER**[37] **(Cost/ QALY)** | | **CC cases avoided (per 1,000 women)** | |
| | No screening | 0% | -- | ref. | -- | ref. | -- |
| | HPV-SS (Pap triage)[38] | 70% | 3 yrs | $10,898 | | 18.3 | |
| | HPV-SS (Colposcopy triage)[38] | 70% | 3 yrs | $12,145 | | 18.5 | |
| | Pap (HPV triage, SOC)[38] | 70% | 3 yrs | $22,003 | | 16.9 | |
| **Tsiachristas** United Kingdom 2018 (155) | Costs converted from 2014 GBP<br>Screening Age: 20-25 years<br>C/E threshold: $131,160 | **Screening uptake**[10] | | **CER**[37] **(Cost/ QALY)** | | | |
| | Pap invitation (SOC) | 15.8% | N/A one-time intervention | ref. | -- | -- | -- |
| | HPV-SS (direct mail, Pap follow-up)[39] | 22.0% | | $14,834 | | | |
| | HPV-SS invitation (opt-in, Pap follow-up)[40] | 16.8% | | $8,827 | | | |
| **Kitchener** United Kingdom 2016 (156) | Costs converted from 2014 GBP<br>Screening Age: 20-25 years<br>C/E threshold: $26,891-$40,337 | **Screening uptake**[10] | | **CER**[32] **(Cost/ QALY)** | | | |
| | Pap invitation (SOC) | 15.8% | N/A one-time intervention | ref. | -- | -- | -- |
| | HPV-SS (direct mail, Pap follow-up)[39] | 22.0% | | $10,973 | | | |
| | HPV-SS invitation (opt-in, Pap follow-up)[40] | 16.8% | | $8,656 | | | |

1 HPV-SS strategies include the triage test for follow-up of positive HPV test results. Underlined strategies were described by the authors as likely to be cost-effective.
2 CIN2+= Cervical intraepithelial neoplasia grade 2 or higher
3 QALY=Quality-adjusted life-year
4 ICER=Incremental cost-effectiveness ratio
5 Lifetime risk of developing cervical cancer among women in the model
6 Moderately underscreened = model assumed that HPV-SS users would get screened every 8 or 10 years in the absence of HPV-SS, Moderate/severely underscreened=HPV-SS users would be screened every 8, 10, 20 years, or never, in the absence of HPV-SS
7 direct = direct-mailed, unsolicited HPV-SS kit mailing
8 Pap triage compliance for positive HPV tests was set at 88% for base case
9 Model allowed women to have different time lengths between cc screenings, then specified a base-case assumption that HPV-SS would increase overall screening by 10%
10 Proportion of total population that receives initial screening test (not follow-up or triage)
11 Pap triage compliance for positive HPV tests was set at 79% for the base case, and colposcopy triage compliance was set at 90% in the base case
12 Combined screening coverage after reminder letter+HPV-SS
13 Cost year not reported, costs assumed to be the same as parent study time period
14 Screening uptake includes initial test plus any necessary triage testing
15 Initial screening test use after receiving intervention, not including triage or follow-up
16 Scenarios are defined by the estimated likelihood of underscreened HPV-SS users to have attended Pap in the future in the absence of an additional intervention – the no switching scenario estimated that no HPV-SS users would not have attended Pap in the future, and the 100% switching scenario estimated that all HPV-SS users would have attended Pap in the future.
17 Women receive screening invitations every 5 years from age 30-35 or when they do not attend last screening round, and every 10 years from age 40-60
18 Opt-in= invitation to receive an HPV-SS kit
19 Colposcopy compliance for positive HPV tests was 100% from parent study results
20 3-year screening interval for women age 23-50, 5-year interval for women age 51-60
21 Pap triage compliance for positive HPV tests was 86% from parent study results
22 Percent decrease in lifetime risk of developing cervical cancer compared to the reference group among women in the model
23 Authors estimated that 63% of women with HPV positive results would be successfully contacted in the base case, and that 97.1% of contacted women would attend follow-up at the clinic
24 1x/Lifetime screening at age 39; 3x/Lifetime screening at age 30, 40, and 50; 5x/Lifetime screening at age 30, 35, 40, 45, and 50. Additional strategies (HPV+VIA, VIA) at 3x & 5x/lifetime were dominated and not included in this summary
25 Authors assumed 85% of eligible women with HPV positive results would return to receive follow-up cryotherapy or colposcopy
26 Alternate scenario comparisons for population screening coverage (not included in this ICER comparison) ranged from 30-100%
27 The cost-effectiveness of 1x/lifetime screening was assessed for different ages at 5-year intervals.
28 Displayed strategies include the least costly ranked strategy along with adjacent comparator strategies at the same age level. All additional ranked strategies were more costly than the displayed strategies. Results for 2x and 3x/lifetime strategies are not displayed in this summary table. Cytology was also included as a comparator but was strongly dominated by all other strategies for a given age and screening frequency

29 Authors assumed 100% of HPV positive women would return for follow-up within one year
30 3-year screening interval for women age 23-0, 5-year interval for women age 51-60
31 Additional nonstandard screening comparators (VIA+Lugol's iodine, careHPV testing at lower threshold concentration) were not included in this summary. Additional screening intervals (10-yearly, 5-yearly) did not include HPV-SS and were not included in this summary.
32 Average lifetime reduction is an estimate of the reduction in CC risk for the entire region, including unscreened women.
33 Study also included cost-effectiveness estimates for the 20-80 year age range; all strategies at this age range were among the dominated strategies
34 Authors assumed 100% compliance to initial screening tests and follow-up tests
35 Authors assumed 100% compliance with follow-up for women with HPV positive results in the base case
36 Model begins with only women age 25 at first screening invitation, then screening proceeds through age 70
37 Reported as ICER in published paper, relabeled CER because ratios are calculated in comparison with the same reference strategy
38 Authors did not report the proportion of screened women who would attend recommended follow-up
39 Authors assumed 79% follow-up cytology attendance for women sent unsolicited HPV-SS kits
40 Authors assumed 94% follow-up cytology attendance for women who requested and sent back HPV-SS kits

Mailed home-based screening kits were evaluated in 11/16 studies (**Table 3-2**).(128,147,149–152,154–158) Of these, eight evaluated direct mail strategies only(147,149–152,154,157,158), one evaluated only an opt-in strategy,(128) and two compared both opt-in and direct mail strategies.(155,156) One direct mail study compared mailing an HPV-SS kit after the first unsuccessful Pap invitation letter versus first sending an additional Pap reminder.(149) One of the studies did not specify HPV-SS delivery method but included consultation costs for Pap screening and not for HPV-SS, suggesting they modeled a direct mail strategy.(158) Three studies used CHWs: one used CHWs to recruit participants to HPV-SS in-clinic,(153) one had a CHW offer HPV-SS at the home or workplace,(148) and one used mobile screening teams to visit villages to offer HPV-SS and immediate colposcopy follow-up.(161) Two studies did not model a specific outreach strategy but offered clinic-based HPV-SS.(159,160)

Standard-of-care comparison:

Of the 11 studies set in HICs, ten used Pap screening as their standard-of-care comparison test (**Table 3-2**).(128,147,149,150,152,154–158) Rozemeijer et al.(151) modeled provider-collected HPV screening as standard-of-care, in anticipation of the Netherlands' adoption of primary HPV screening. All studies targeting underscreened women, as well as the two UK-based among first-time screeners, modeled HPV-SS as an addition to existing screening programs.(128,147,149,151,152,155–157) All European studies except Vassilakos et al.(158) included some form of mailed screening invitation/reminder in their standard-of-care Pap strategy.

Among the studies set in LMICs, VIA, clinician-collected HPV, Pap, and Pap+HPV co-testing were used as comparison tests. WHO guidelines recommend ideal screening intervals of

five years for HPV screening or three years for VIA but recognize that these are not realistic for all countries, given limited infrastructure and financial resources. As such, models set in LMICs have no set screening interval for standard-of-care comparator tests, and screening frequency is as low as once per lifetime.

All studies defined HPV-SS positivity as positive for high-risk HPV. None used HPV16/18 partial genotyping for triage. Most used Pap as the triage test for a positive HPV-SS result (**Table 3-2**).(147,150–152,154–157) Three specified follow-up colposcopy for all HPV-positive tests.(128,160,161) Two studies compared both colposcopy and Pap triage strategies.(149,158) Mezei et al.(148) compared HPV-SS followed by cryotherapy for positive results (screen-and-treat) to HPV-SS followed by VIA triage, and Campos et al.,2015(159) modeled cryotherapy as the sole follow-up for positive HPV-SS tests.

**Table 3-2** displays selected base case model results. Fourteen of 16 studies reported that HPV-SS can be a cost-effective or good value-for-money strategy under certain conditions. One outlying study found that HPV-SS was only weakly dominated by clinician-collected HPV testing in three LMICs,(159) and the other found that Pap+HPV co-testing was most likely to be cost-effective in Mexico.(160) Most studies with lifetime cost-effectiveness outcomes used a country-specific willingness to pay threshold for cost-effectiveness, ranging from $756/life year gained in Uganda(148)-$103,531/QALY in Norway(152). In HICs, thresholds were taken from national guidelines, while those in LMICs used threshold values based on national(148,159,159) or provincial(161) per-capita GDP. All studies that used willingness-to-pay thresholds found HPV-SS could result in a cost-effectiveness ratio (CER) or incremental cost-effectiveness ratio (ICER) well below the threshold under base case assumptions. The two studies that compared

different triage strategies found Pap triage for HPV-SS positive women was more cost-effective than sending directly to colposcopy.(149,158) In the UK trial among never-screened women, direct mailed HPV-SS was considered the most cost-effective strategy over opt-in despite a greater cost per QALY because of higher uptake and subsequent increase in CIN2+ detection.(155,156) For studies that used intermediate cost-effectiveness outcomes, three used some measure of cost per detected CIN2+.(128,147,149) These studies considered HPV-SS to be cost-effective if it generated a substantial population reduction in untreated CIN2+ and the cost per CIN2+ treated was comparable to standard-of-care. Flores et al.(160) used a composite outcome that included the number of CIN2+ and cancer cases detected, divided by the combined costs of treated CIN2+ lesions and projected costs of treating undetected cervical cancer. Haguenoer et al.(157) used cost per woman screened as a cost-effectiveness outcome, finding it was less for HPV-SS compared to sending an additional reminder letter.

Fourteen studies reported some form of sensitivity analysis to estimate the potential for variations in model parameters or costs to affect the overall cost-effectiveness results.(128,148–158,160,161) Most studies varied uncertain model parameters univariately through a range of estimates, or simply used defensible alternate assumptions for certain parameters. Influential points (i.e., factors capable of causing a substantial swing or reversal of the cost-effectiveness comparison) included HPV-SS uptake, HPV kit cost (including device/kit, mailing, and testing costs), and relative sensitivity of HPV-SS to detect CIN2+. Burger et al.(152) explored 10-yearly vs. 5-yearly HPV-SS as a secondary analysis and found 10-yearly screening was more cost-effective only if the proportion of long-term underscreened women was low in 5-yearly screening. A concern that has arisen from randomized control trials of HPV-SS for

underscreened women is the level of background risk of CIN2+ among HPV-SS users.(134) If HPV-SS is used by too few women at high risk of CIN2+ (such as never-screened women), it could possibly lead to increased costs from false positives being sent to colposcopy for diagnosis. A related concern is the possibility of "switching," in which women who otherwise would have attended Pap decide to self-sample instead. Two studies looked specifically at these questions by modeling the risk profile of HPV-SS users. In the first, Rozemeijer et al.(151) modeled the effects of regular attendees switching from clinic-based screening to self-sampling and found that switching can cause HPV-SS to be cost ineffective when respondents have lower CIN2+ risk and HPV-SS uptake is low. Burger et al.(152) found that HPV-SS was most cost-effective when users had a longer time since last screening, although their scenario using a "moderately" underscreened population still met their cost-effectiveness threshold.

Several studies in LMICs focused on identifying a) optimal target age range for screening and b) potential cost-effectiveness of screening less frequently than 3-5 years.(148,159,161) Shi et al., 2011,(161) Campos et al. 2015,(159) and Mezei et. al. 2017(148) all found that HPV-SS was more effective than VIA, that once-in-a-lifetime screening could be cost-effective at reducing cervical cancer incidence and mortality, and that additional screening (two- or three-per-lifetime) could also be cost-effective for further reductions in cervical cancer.(148,159,161) Campos et al. 2015(159) suggested that clinic-based HPV-SS cost-effectiveness was comparable but slightly dominated by clinician-collected HPV tests due to their greater sensitivity. In a subsequent study(153) based on the same parent study(163), a more detailed model of the implementation of a hypothetical once-in-a-lifetime HPV-SS campaign in Uganda found that

HPV-SS was more effective and cost-effective than clinician-collected HPV tests when population screening coverage was >50%.

Most studies (14/16) derived HPV kit cost estimates from parent trials or previous HPV-SS research projects (**Table 3-3**),(128,148–157,159,161) while two used HPV screening kit costs from a partnering hospital.(147,158) Details reported for kit costs varied widely between studies: some itemized device costs as well as other materials such as postage(139,149,155–157), some reported the kit contents but did not separate out costs(151,152), and some did not specify kit contents at all.(147,154,158) Two studies did not separate kit costs from the cost of HPV testing.(128,154) Differences in devices, packaging, and shipping, combined with the variability in kit cost reporting, kept us from determining the degree of change in HPV-SS kit costs. Studies used a variety of collection methods, including swab(157), brush(147,148,152–156,159,161), and lavage devices(155,156,166). The cost of an HPV-SS device itself has declined since the earliest studies; Broberg et al.(128) used a device cost of $31.66 for their initial analysis to match the 2011 direct payer cost in their earlier parent trial, but also presented cost-effectiveness estimates using $2.24 to better reflect the lower costs of HPV-SS at the time of their analysis. We reported results using the lower cost to facilitate comparison with recent studies. Subsequent studies reported device costs ranging from $1.68(155,156)-$6.27(148). No HPV-SS interventions charged participants a fee for receiving or returning an HPV-SS kit.

**Table 3-3: Reported costs of HPV self-sampling kits and HPV testing in 2017 U.S. Dollars**

| First Author Country Publication Year | HPV-SS Kit and HPV Test Items[1] | Cost per kit/test[2] (2017 U.S. Dollars) | Notes[3] |
|---|---|---|---|
| **Vassilakos** Switzerland 2019 (158) | Combined Kit + Testing<br>HPV-SS kit + testing<br>HPV-SS kit + testing (sensitivity analysis range)<br>HPV-SS Kit<br>HPV kit<br>HPV Testing<br>HPV test | <br>51.86<br>29.35-71.43<br><br>2.94<br><br>48.92 | • No kit delivery method specified, assumed to be mailed<br>• No HPV-SS device or test specified<br>• Cost source: Partnering hospital |
| **Mezei** Uganda 2018 (148) | Combined Kit + Testing<br>HPV-SS kit + testing (total including staff time)<br>HPV-SS kit + testing (sensitivity analysis)<br>HPV-SS Kit<br>CareHPV kit<br>Laboratory transport costs<br>HPV Testing<br>Lab supplies/equipment/staff costs | <br>13.18<br>35.28<br><br>6.27<br>1.12<br><br>0.64 | • HPV-SS device & test: CareHPV (Qiagen, Gaithersburg, MD)<br>• CareHPV kit and test costs derived from PATH START-UP project(163) |
| **Campos** Uganda 2017 (153) | Combined Kit + Testing<br>HPV-SS intervention direct costs<br>HPV-SS intervention direct costs (sensitivity range)<br>HPV-SS Kit<br>CareHPV kit<br>Handout<br>HPV Testing<br>Testing supplies<br>Equipment | <br>9.48<br>9.03-10.37<br><br>5.45<br>0.50<br><br>0.69<br>0.28 | • Combined costs include kit, testing, outreach materials, community health worker (CHW) time, and laboratory worker time<br>• HPV-SS device & test: CareHPV (Qiagen, Gaithersburg, MD)<br>• CHW costs were not reported per kit because CHWs conducted group sessions<br>• Cost source: Parent study |

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| **Burger**<br>Norway<br>2017<br>(152) | <u>HPV-SS Kit</u><br>HPV-SS kit<br><u>HPV Testing</u><br>HPV test | <br>55.91<br><br>41.41 | • HPV-SS kit contents: self-collect device (dry brush), leaflet, resealable bag, identification sheet, return envelope, return postage, patient time (45 minutes, prorated by proportion of kit users)<br>• HPV DNA test included cost of "collection materials, disposables, facilities, and staff"<br>• No HPV-SS device or test specified<br>• Cost sources: parent study (HPV-SS kit), micro-costing and fee schedules (HPV testing) |
| **Tsiachristas**<br>United Kingdom<br>2018<br>(155) | <u>Combined Kit + Testing</u><br>HPV kit + testing (including staff time)<br><u>HPV-SS Kit</u><br>Evalyn kit<br>Evalyn postage<br>Delphi kit<br>Delphi postage<br>Clinical consumables<br><u>HPV Testing</u><br>Lab kits (cobas) | <br>18.41<br><br>1.68<br>0.94<br>3.83<br>3.50<br>1.34<br><br>9.41 | • Combined cost uses the average of both devices, plus staff time<br>• HPV-SS device: Women were offered either Evalyn Brush (Rovers Medical Devices, B.V., Oss, the Netherlands) or Delphi Lavage (Rovers Medical Devices, B.V., Oss, the Netherlands).<br>• HPV-SS kit contents: Device (either Delphi or Evalyn), return packaging, information sheet, and consent form<br>• Clinical consumables were not specified<br>• HPV DNA test: cobas (Roche Diagnostics, Pleasanton, California)<br>• Staff time was not reported per kit or per test<br>• Cost source: parent study |

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|---|---|---|---|
| **Kitchener**<br>United Kingdom<br>2016<br>(156) | <u>Combined Kit + Testing</u><br>HPV kit + testing (total including staff time)<br><u>HPV-SS Kit</u><br>Evalyn kit<br>Evalyn postage<br>Delphi kit<br>Delphi postage<br>Consumables (clinical, unspecified)<br><u>HPV Testing</u><br>Lab kits (cobas) | <br>15.50<br><br>1.68<br>0.94<br>3.83<br>3.50<br>1.34<br><br>9.41 | • All items and costs are from the same parent study as Tsiachristas et al.; total cost estimates differ because the studies used different staff time estimates |
| **Virtanen**<br>Finland<br>2015<br>(149) | <u>HPV-SS Kit</u><br>Sampling device (from parent study)<br>Sampling device (sensitivity analysis)<br>Outbound mailing and logistical costs<br>Inbound mailing costs<br>Response letter<br><u>HPV Testing</u><br>HPV test | <br>2.75<br>8.92<br>3.98<br><br>1.65<br>1.03<br><br>27.46 | • HPV-SS device: Delphi Lavage (Rovers Medical Devices, B.V., Oss, the Netherlands)<br>• HPV test: Hybrid Capture II (Qiagen, Valencia, California)<br>• Cost sources: Parent study (HPV-SS kit), literature (testing) |
| **Rozemeijer**<br>Netherlands<br>2015<br>(151) | <u>HPV-SS Kit</u><br>HPV-SS kit<br>HPV-SS kit (sensitivity analysis range)<br><u>HPV Testing</u><br>Laboratory | <br>8.38<br>4.89-13.97<br><br>40.51 | • Kit costs “estimated from contact with manufacturers of brush and lavage-based kits”<br>• Test costs were estimated for a “validated PCR test,” no other elaboration of laboratory costs was given |
| **Campos**<br>India, Uganda, Nicaragua<br>2015<br>(142) | <u>Combined Kit + Testing</u><br>HPV-SS direct medical costs (India)<br>HPV-SS direct medical costs (Nicaragua)<br>HPV-SS direct medical costs (Uganda)<br><u>HPV-SS Kit</u><br>CareHPV kit (all sites) | <br>9.70<br><br>14.69<br><br>9.24<br><br>5.45 | • HPV-SS device & test: CareHPV (Qiagen, Gaithersburg, MD)<br>• Combined costs include all direct medical costs associated with screening<br>• Cost source: Parent study, literature review (for other medical costs) |

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|---|---|---|---|
| **Haguenoer**<br>France<br>2014<br>(157) | <u>HPV-SS Kit</u><br>HPV-SS kit<br>HPV-SS kit (sensitivity analysis)<br><u>HPV Testing</u><br>HPV test + return<br>HPV test (sensitivity analysis) | <br>3.49<br>7.59<br><br>58.30<br>37.96 | • HPV-SS device: Nylon flocked swab in dry sterile tube (53080C, Copan, Brescia, Italy)<br>• HPV-SS kit contents: invitation letter, instruction leaflet, nylon flocked swab in dry sterile tube, resealable plastic bag, identification sheet, return envelope<br>• HPV test: INNO-LiPA HPV Genotyping Extra (Innogenetics, Ghent, Belgium)<br>• Base case HPV test cost included cost of return postage, HPV test analysis, and result mailing<br>• HPV sensitivity analysis test cost did not appear to include return postage & result mailing costs<br>• Cost sources not reported, assumed to be from parent study |
| **Broberg**<br>Sweden<br>2014<br>(128) | <u>HPV Kit</u><br>HPV kit (cost from study)<br>HPV kit (estimate)<br><u>HPV Testing</u><br>HPV test | <br>31.66<br>2.24<br><br>26.88 | • HPV-SS device: QvinTip (Aprovix, Uppsala, Sweden)<br>• HPV Test: Hybrid Capture 2 (Siegen AB, Solna, Sweden)<br>• HPV kits from the parent trial were purchased at higher cost; the lower cost was estimated as more realistic at the time of study analysis<br>• Study did not include further details on items in test kit or cost breakdown of HPV testing |
| **Östensson**<br>Sweden<br>2013<br>(154) | <u>Combined Kit + Testing</u><br>HPV-SS kit + testing<br>HPV-SS kit + testing (sensitivity analysis range) | <br>50.43<br>25.22-100.86 | • HPV-SS device: Viba-brush (Rovers Medical Devices, B.V., Oss, the Netherlands)<br>• From paper: “Test includes physician assessment for abnormal results and test costs.”<br>• Cost sources: manufacturer (HPV-SS device), national health system (testing) |

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|---|---|---|---|
| **Shi**<br>China<br>2011<br>(161) | <u>Combined Kit + Testing</u><br>HPV-SS kit + testing (includes labor)<br>HPV-SS kit + testing (sensitivity analysis)<br><u>HPV-SS Kit</u><br>careHPV kit | <br>10.47<br>8.20-16.17<br><br>5.69 | • HPV-SS device & test: CareHPV (Qiagen, Gaithersburg, MD) |
| **Flores**<br>Mexico<br>2011<br>(160) | <u>Combined Kit + Testing</u><br>HPV-SS direct medical costs<br>HPV-SS direct medical costs (sensitivity analysis range) | <br>16.11<br>12.08-20.14 | • HPV Test: Hybrid Capture 2 (Siegen AB, Solna, Sweden)<br>• Costs include sample collection, reagents, laboratory staff, supplies, equipment, and overhead. |
| **Balasubramanian**<br>USA<br>2010<br>(150) | <u>HPV Kit</u><br>HPV-SS kit<br>Sensitivity analysis (50%-200%)<br><u>HPV Testing</u><br>HPV test | <br>23.82<br>11.91-47.64<br><br>58.35 | • Study was based on clinic-collect HPV-SS, kit costs are an estimate, test costs came from Medicare fee schedule<br>• HPV-SS kit cost includes shipping to and from the patient<br>• HPV test: Hybrid Capture II (Qiagen, Valencia, California) |
| **Bais**<br>Netherlands<br>2007<br>(147) | <u>Combined Kit + Testing</u><br>HPV-SS kit + testing | <br>51.55 | • HPV-SS device: Viba-brush (Rovers Medical Devices, B.V., Oss, the Netherlands)<br>• HPV test: Gp5+/GP6+ PCR primer<br>• HPV-SS kit + testing costs came from parent study |

1 We included all reported costs for materials associated with HPV-SS kits or HPV testing. Costs are drawn from manuscripts and supplementary materials (when available). Combined kit + testing costs were reported when combined costs were used as the primary measure of HPV-SS kit cost in the manuscript and/or when combined costs (rather than itemized costs) were varied in the sensitivity analysis. For HPV-SS kit and HPV testing costs, when costs for materials were itemized (e.g. devices, shipping costs, invitations) we reported those item costs individually; when kit and testing costs were not itemized, they are reported here under the headings “HPV-SS kit” and “HPV test,” respectively.

2 Costs were only included in this table when they were reported per kit or per test, respectively. Whenever possible, materials costs alone were included.

3 HPV-SS device names, HPV kit contents, and HPV test types are reported when available from the manuscript, supplementary materials, or parent trial manuscripts.

HPV test type varied. Studies in high-income settings reported hybrid capture 2 (HC2)(128,150,166) or PCR-based methods(155–157) for HPV DNA testing. Flores et al.(160) modeled HC2 in Mexico, while subsequent studies in LMICs used careHPV, a signal amplification test designed for use in low-resource settings.(148,153,159,161) (**Table 3-3**) Cost reporting for HPV testing was inconsistent. Some studies used costing methods that combine the cost of test materials and equipment, some included laboratory staff costs (which vary widely), while others simply used their country's health system reimbursement amount for HPV testing. These inconsistencies make it impossible to accurately compare testing cost across settings.

**Discussion**

In this systematic review, we report on 16 studies of the cost and cost-effectiveness of HPV-SS compared to standard-of-care cervical cancer screening strategies. Eleven studies evaluated use of mailed HPV-SS kits in HICs and five studies evaluated HPV-SS strategies in LMICs. All but two reported that HPV-SS can be cost-effective, either as an addition to existing screening programs(128,147,149,151,152,155–157) or a primary screening strategy.(148,150,153,154,158,159,161) The most common driver of HPV-SS cost-effectiveness identified was the level of increase in screening attendance.(139,148,151,152,155) Additional factors that impact likelihood that HPV-SS will be cost-effective include lower costs of HPV-SS materials and testing,(128,148,157) higher relative sensitivity to detect CIN2+,(151,152,161) and attracting more never-screened or long-term underscreened women.(151,152) Modeling methods and sensitivity analyses generally became more robust and rigorous over time. The earliest study used a basic cost model embedded in a paper on randomized trial results,(147)

while some more recent studies used complex models to examine nuances like the risk profile of HPV-SS respondents,(151,152) and to model the impact of HPV-SS in different populations like first-time screeners(155,156) and women in LMICs.(148,153)

From the perspective of health systems in HICs, the studies provide insight into important decisions for program implementation. Recently, Pedersen et al.(135) described the choice of HPV-SS outreach strategy (e.g., direct mail vs. opt-in) as a key consideration for operationalizing HPV-SS. Studies in this review reported that direct mail(147,149,151,152,157) and opt-in(128) strategies could be cost-effective, but a recent meta-analysis[26] found that directly mailing kits to underscreened women resulted in higher screening uptake. Kitchener et al.(156) and Tsiachristas et al.(155) compared these two strategies and found that direct mail resulted in better screening uptake and was more likely to be cost-effective than opt-in, but with higher overall costs. Compared to direct mailed kits, requiring women to opt-in to receive an HPV-SS kit could also present a screening barrier to long-term underscreened women who are not engaged with the health system. Burger et al.(152) and Rozemeijer et al.(151) suggested that HPV-SS is most cost-effective when kit users have a longer time since last Pap. One potential "middle ground" was modeled by Virtanen et al.,(149) who found that mailing additional Pap reminders to underscreened women before directly mailing an HPV-SS kit resulted in a lower cost per treated CIN2+ than direct mailing after a single Pap invitation. Mailing additional reminders before sending HPV-SS kits could represent a way for health systems to reduce HPV-SS program costs without adding barriers to receiving an HPV-SS kit. Ultimately, the difficulty in comparing results across studies and the lack of cost-effectiveness

studies for opt-in make it difficult to determine whether opt-in HPV-SS is likely to be a cost-effective choice for health systems.

The target population for HPV-SS (e.g. cervical cancer screening status and age range) is a key choice for health systems in HICs.(135) Some early studies in this review modeled the use of HPV-SS as a replacement for clinic-based-screening among all women, but most subsequent trials and cost-effectiveness studies have targeted under- or never screened women. Age range varied widely among studies in this review, complicating comparisons across countries. For example, current U.S guidelines do not recommend primary HPV screening <age 30, but several studies modelled HPV-SS in younger women.(147,150,152,155,156,158)

Another key for successful HPV-SS program implementation is having adequate data on women's screening history when targeting underscreened women.(135) If screening history data are incomplete, screening-adherent women could be misclassified and sent an HPV-SS kit. Overscreening leads to greater patient harm and higher costs.(170) Future modelers could consider including the potential for incomplete screening histories, subsequent misclassification of screening status, and potential costs and health impacts of excess screening.

This review provides insight into other potential cost drivers for HPV-SS programs. In a screening program context, the slightly lower relative sensitivity of HPV-SS to detect CIN2+ was most problematic when HPV-SS uptake among long-term underscreened women was low. In contrast to other tests, PCR-based HPV tests have comparable sensitivity between self- and provider-collected samples,(75) suggesting PCR-based testing may be a more favorable choice for HPV-SS programs. Sensitivity analyses from multiple studies showed that lower HPV-SS kit and testing costs increased cost-effectiveness, but differences in reporting, materials, and

devices make it difficult to quantify the change in costs or to generalize across settings. Uptake among underscreened women was another frequently identified determinant of cost-effectiveness. While it is unclear what factors are responsible for the substantial variation in HPV-SS response rates in randomized trials,(75) interventions that encourage HPV-SS uptake (e.g., patient education, effective messaging and outreach strategies) could likely benefit response rates. Researchers should consider including the cost of developing such strategies in future models.

Most studies used lifetime measures of cost-effectiveness that included societal costs and quality of life weights. Future studies that include intermediate cost-effectiveness results (e.g. cost per CIN2+ treated, cost per woman screened) from the payer perspective could be more useful for healthcare system decision-making in the U.S. and other countries where QALYs are not widely used.(144) Cost-effectiveness models based on U.S. trial data are crucial, as none are currently based on U.S. randomized trial data. The only published cost-effectiveness study in the U.S.(150) did not fit the current health care context, as it did not model a HPV-SS strategy that targeted underscreened women and included women outside of the current recommended U.S. age range for screening.(171) Most studies were conducted in existing screening reminder programs and assumed availability of accurate data on prior screening history. Results from this review are not applicable for health systems that do not have screening programs already in place.

From a global perspective, there are important gaps in the HPV-SS cost-effectiveness literature. Additional models (and supporting randomized trial data) are needed in LMICs where approximately 85% of all cervical cancer mortality occurs.(118) The studies in this review

illustrate the potential for HPV-SS to impact screening coverage in these high-burden areas.(148,153) Future modeling studies in LMICs are needed, especially those that model real-world implementation scenarios to determine budget impact and cost-effectiveness of HPV-SS strategies. There is also a need for further research and modeling for HPV-SS strategies to reach underserved populations in HICs, such as immigrants, rural residents, and women with limited access to care. As new strategies are explored, such as targeting HPV-SS promotion messages to high-risk groups or combining mailed kits with in-person outreach, existing, validated models can be modified to evaluate these strategies. Cost-effectiveness models for mailed HPV-SS kits could be improved by incorporating outcomes data from recent HPV-SS trials powered to measure CIN2+ detection among HPV-SS responders. Future models should also account for effects of widespread HPV vaccination on the cost-effectiveness of HPV-SS. No studies of underscreened women in this review modeled partial genotyping (triaging HPV16/18 positives to colposcopy(172)). Future models should explore the cost-effectiveness impact of partial genotyping and other newer triage strategies (e.g., DNA methylation).

This review has several limitations. We may have missed relevant studies. Keyword searches may not have captured every potential eligible paper, title and abstract searches may have missed cost- and cost-effectiveness analyses embedded in other studies of HPV-SS, title and abstract searches were carried out by a single reviewer, and we did not review non-English full-text articles. We did not pre-register our systematic review protocol. We interpreted these studies and the operationalization of HPV-SS in the context of potential implementation in U.S. health systems; interpretations may not apply to government-based screening programs such as those in Europe and other HICs. We excluded papers that used HPV-SS as a sensitivity

analysis; this focused our review on HPV-SS implementation but meant that some studies in LMICs were not included. Despite good reporting overall, a lack of consistency and clarity in reporting presented challenges for summarizing study results. For example, the term ICER was applied inconsistently. Some studies reported ICERs by presenting screening strategies in order of increasing cost, comparing strategies to the next most cost-effective strategy, and omitting dominated strategies.[55,60,72] Others presented CER for each screening option versus a single reference strategy and referred to these as ICERs.[62,63,65] Future studies should use HPV-FRAME standards(145) to ensure consistency and thorough reporting of cost-effectiveness modeling and results. Crude conversion of costs into U.S. dollars did not account for differences in purchasing power across countries. Differences in healthcare and labor costs make it difficult to compare cost-effectiveness results across countries.

**Conclusion**

HPV-SS can be a cost-effective method to increase cervical cancer screening uptake and prevent cervical cancer under certain settings and conditions. Most studies have focused on HPV-SS targeted at underscreened women as part of a screening program; in this context, cost-effectiveness depends on factors including response rate, cost of HPV-SS materials, test sensitivity, and the cervical screening history of respondents. The broad range of potential implementation strategies makes it difficult to compare results across settings. The lack of cost-effectiveness studies outside of Western Europe, especially in LMICs, that include data on real-world implementation scenarios, represents an important gap in the literature. Future cost-

effectiveness studies within screening programs should model the impact of new triage strategies, development of HPV-SS outreach materials, and increasing HPV vaccination rates.

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## Appendix A: PRISMA Checklist

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 59 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 59 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 62-63 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 63 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 63 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 64 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 64 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Appendix B |

| | | | |
|---|---|---|---|
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 63-64 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 63-64 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 63-64 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | N/A |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | N/A |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | N/A |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | N/A |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | N/A |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 65, Figure 3-1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 67, 73, 81-84 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | N/A |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | Tables 3-1, 3-2, 3-3 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | N/A |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | N/A |

| | | | |
|---|---|---|---|
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | N/A |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 91-95 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 95-96 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 96-97 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | -- |

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

## Appendix B: Search Strategies

Our searched used queries covering three domains: screening, mathematical modeling, and cervical cancer. We allowed the database search functions to map our keyword/title/abstract searches to related subject heading terms, such as Emtree for Embase and MeSH for PubMed and Web of Science. We checked subject heading trees to ensure that search terms were mapping on to the relevant concepts. Our PubMed query is included below for reference

(HPV OR human papillomavirus OR human papilloma virus) AND (test or testing or screen or screening or self-test or self-testing or self-screen or self-screening or via or visual inspection with acetic acid) AND (math model OR mathematical model or cost-effectiveness or cost-effective or cost-benefit or cost model or economic model)
AND (cervical cancer or cervical neoplasia or cervix cancer)

## Appendix C: Ratings of Study Quality

**Scale: Excellent=13, Good=9-12, Fair=6-8, Poor=0-5**

| | **Vassilakos** 2019 (158) | **Mezei** 2018 (148) | **Campos** 2017 (153) | **Tsiachristas** 2017 (155,156) | **Kitchener** 2016 (155,156) | **Burger** 2016 (152) | **Virtanen** 2015 (149) | **Rozemeijer** 2014 (151) | **Campos** 2015 (159) | **Haguenoer** 2014 (157) | **Broberg** 2014 (128) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Described Target Population | X | X | X | X | X | X | X | X | X | X | X |
| Reported Economic Evaluation Used | X | X | X | X | X | X | | X | X | | |
| Reported Cost-Effectiveness Outcomes | X | X | X | X | X | X | X | X | X | X | X |
| Reported Time Horizon | X | X | X | X | X | X | | X | X | | X |
| Reported Cost Perspective | X | X | X | X | X | X | X | X | X | X | X |
| Described HPV-SS Strategy | | X | X | X | X | X | X | X | X | X | X |
| Described Comparator | X | X | X | X | X | X | X | X | X | X | X |
| Described Followup | X | X | X | X | X | X | X | X | X | X | X |
| Reported Parameter Source | X | X | X | X | X | X | X | X | X | X | X |
| Reported Source of Cost Inputs and Unit Costs | X | X | X | X | X | X | X | X | X | | X |
| Reported Currency and Year | X | X | X | X | X | X | X | X | X | | X |
| Conducted Sensitivity Analysis | X | X | X | X | X | X | X | X | X | X | |
| Discussed Limitations of Economic Analysis | X | X | X | X | X | X | X | X | X | | |
| **SCORE** | G | E | E | E | E | E | G | E | E | G | G |

| | **Östensson** 2013 (154) | **Shi** 2011 (161) | **Flores** 2011 [69] | **Balasubramanian** 2010 (150) | **Bais** 2007 (147) |
|---|---|---|---|---|---|
| Described Target Population | X | X | X | X | X |
| Reported Form of Economic Evaluation Used | X | X | X | X | |
| Reported Cost-Effectiveness Outcomes | X | X | X | X | X |
| Reported Time Horizon | X | X | X | X | |
| Reported Economic Perspective | X | X | X | X | |
| Described HPV-SS Strategy | X | X | X | X | X |
| Described Comparator | X | X | X | X | X |
| Described Diagnostic Follow-up | X | X | X | X | X |
| Reported Source of Parameter Inputs | X | X | X | X | X |
| Reported Source of Cost Inputs and Unit Costs | X | X | X | X | |
| Reported Currency and Year | X | X | X | X | X |
| Conducted Sensitivity Analysis | X | X | X | X | |
| Discussed Limitations of Economic Analysis | X | X | X | X | |
| **SCORE** | E | E | E | E | F |

# Vita

Colin Michael Cox Malone was born in Dallas, Texas and raised in Keller, Texas. After attending the Texas Academy of Mathematics and Science at the University of North Texas, Colin studied biology at the University of Florida, receiving a BS with highest honors in 2007. Colin then attended the University of Texas School of Public Health, Houston. In 2008 he performed his thesis research on tuberculosis at Pham Ngoc Thach Hospital in Ho Chi Minh City, Vietnam, and received his MPH in Epidemiology and Global Health in 2009. Before beginning his PhD studies, Colin led influenza and viral respiratory disease surveillance efforts for the Florida Department of Health in Tallahassee, Florida. Colin completed his PhD in Epidemiology at the University of Washington in 2020.