Patient- and health system-level impacts of home-based HPV screening for cervical cancer

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Abstract

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Cervical cancer screening is associated with substantial global reductions in cervical cancer incidence and mortality. However, in the U.S., screening adherence among individuals 21-65 years of age declined from 86% to 72% between 2005 and 2021. HPV self-sampling (HPV-SS), or home-based primary HPV screening, addresses well-documented screening barriers and could play a critical role in the U.S. effort to increase screening coverage. However, little is known about HPV-SS in a U.S. setting. This dissertation addresses the impacts on both U.S. patients and health systems of offering home-based HPV screening interventions. The first chapter examined adherence to clinical follow-up among individuals overdue for cervical cancer screening who were directly mailed HPV-SS kits. We reviewed the 1) recommendation of and 2) adherence to follow-up care among individuals enrolled in the HOME trial intervention (mailed HPV-SS kit) and control (usual care reminders for in-clinic screening) whose screening results (whether from HPV-SS or in-clinic screening) were abnormal and thus warranted in-clinic follow-up. We determined whether recommendation of and adherence to follow-up care varied by screening modality; kit returners were less likely than both kit recipients who screened in-clinic and control participants to receive correct follow-up care recommendations. Among the 228 HOME patients for whom follow-up was indicated, 62% of kit recipients with HPV16/18+ findings received correct follow-up recommendations for diagnostic colposcopy, with 35% ultimately completing colposcopy (vs. 81% of control). Clinician electronic health record (EHR) notes revealed uncertainty and confusion over how to correctly manage follow-up after screening via HPV-SS. In the era of primary HPV screening, this study emphasized the importance of patient and clinician education and centralized management of follow-up of abnormal results. In Chapter 2, we evaluated the role of patient education in motivating cervical cancer screening behavior. First, we conducted 8 patient focus groups to understand 1) knowledge gaps

surrounding HPV and cervical cancer screening and 2) patient risk perception surrounding cervical cancer. We then embedded a trial within a randomized clinical trial evaluating strategies to increase cervical cancer screening (the STEP trial) to understand the impact of patient education materials (PEMs) on screening completion and determine whether age-targeting of materials enhanced their effectiveness. Partway through the trial, the original PEMs were replaced with three alternatives, informed by focus group feedback: 1) a non-age-specific "optimized" version, 2) an age-targeted version for ages ≤45 years and 3) an age-targeted version for ages >45 years. We evaluated the impact of optimized and age-targeted PEMs on screening uptake across by screening history and age group. In the embedded trial, optimized and age-targeted PEMs significantly increased screening completion among individuals >45 years and those who were previously screening adherent. In the first part of the trial, the association between older age and screening completion was also significant among PEMs recipients. Across the full trial, PEMs were associated with higher screening completion rates among both younger and older individuals. Finally, in the third chapter, we expanded our understanding of the impact of HPV-SS on health systems to include an economic analysis. We extended the findings of the STEP cost-effectiveness analysis by conducting a Value of Information (VOI) analysis. Specifically, we applied a methodology of subgrouping to the VOI analytic framework that enabled us to determine whether future research around at-home cervical cancer screening interventions should focus on specific subgroups that drive heterogeneity in a patient population and, thus, render population-wide cost-effectiveness estimates suboptimal. We created subgroups according to patient age, travel time from an individual's home to a clinic, and engagement with the healthcare system in the past year. Among screening adherent and overdue individuals, VOI estimates were largely zero, indicating additional research into home-based screening programs is not warranted to reduce decision uncertainty, and private health systems can confidently deploy direct mailing of home-based HPV-SS kits (as indicated by the STEP cost-effectiveness analysis). Among participants with unknown screening histories, VOI estimates were non-zero, but low, suggesting there is additional utility in understanding more about these participants before implementing screening outreach; each health system should consider the size of their "unknown" population before investing in additional data collection or research. Across these three chapters and leveraging data from two randomized controlled trials, we generated a robust knowledge base around the

implications of at-home cervical cancer screening on 1) patient follow-up adherence and clinician management of abnormal screening results, 2) patient screening behavior and knowledge of HPV and cervical cancer, and 3) health system implementation of cost-effective, targeted screening approaches.

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ABSTRACT

Cervical cancer screening rates are declining in the U.S., and innovative screening modalities such as HPV self-sampling (HPV-SS) will be instrumental in increasing screening completion. HPV-SS enables patients to screen using home-based kits; however, for home-based testing to be successful, high adherence to recommended in-clinic follow-up procedures is necessary. The HOME study determined that directly mailing HPV-SS kits to under-screened patients was more effective at increasing screening completion compared to usual care (mailed reminder letters and ad hoc telephone outreach). Our objective was to leverage HOME data to understand and describe the challenges complicating adherence to cervical cancer screening follow-up care among patients offered HPV-SS. Our study population included HOME participants whose screening results warranted follow-up (n=228, 5.3%), including those who used HPV-SS kits (intervention-kit [n=142]), those offered kits who screened in-clinic (intervention-in-clinic [n=44]), and control participants (n=42). We evaluated follow-up adherence within six-months post screening, the definition of which varied by screening result (for HPV16/18+, adherence was colposcopy; for other HPV+ or unsatisfactory via HPV-SS, adherence was in-clinic Pap/co-test; for HPV+ or unsatisfactory via in-clinic screen, adherence was screen in one-year and thus not evaluated). We classified follow-up recommendations as correct, over, or under management; we conducted electronic health record (EHR) review of clinical procedures and, for kit returners, had access to 1) clinician-to-patient EHR messages and 2) study team-to-clinician messages (in the event of incorrect follow-up recommendations). Recommendation and receipt of follow-up care varied by screening modality; intervention-kit participants were more likely than intervention-in-clinic and control participants to receive incorrect care management. 62% of intervention-kit participants with HPV16/18+ findings received correct follow-up recommendations, with 35% ultimately completing colposcopy (vs. 81% of control). 83% of intervention-kit participants with other HPV+/unsatisfactory findings were correctly managed, with 66% ultimately completing a Pap/co-test. Clinician EHR notes revealed uncertainty and confusion over correct follow-up. This study highlights the implications of layering a new screening modality over recently updated screening guidelines; patient and clinician education is warranted, as are health system protocols that offer centralized management of abnormal screening results.

INTRODUCTION

Cervical cancer screening can prevent nearly all cervical cancers through identification and removal of cervical precancers. HPV self-sampling (HPV-SS)—an innovative modality designed to promote adherence to recommended screening intervals by eliminating established screening barriers [1–4]—has been successfully adopted internationally [5–7] and trialed in the U.S. [8, 9], where adherence to recommended screening intervals is declining [10]. However, while HPV-SS has been shown to increase screening uptake in various settings [11–13], adherence to necessary follow-up after an abnormal screening result remains a challenge [14, 15]. For home-based testing to be successful, high adherence to recommended in-clinic follow-up procedures is necessary.

Directly mailing HPV-SS kits to under-screened individuals is more effective at increasing screening uptake compared to usual care appointment reminders [11–13], and individuals who never or rarely screen are a clear intervention priority, as >50% of the 13,000 cervical cancers diagnosed in the U.S. annually are in under-screened people [16]. The HOME trial—a randomized clinical trial (RCT) set in the Kaiser Permanente Washington (KPWA) patient population from 2014 to 2018—was the first U.S. trial to evaluate the effectiveness of mailing a home-based, HPV-SS kit to patients overdue for routine screening [17]. Screening uptake was captured for up to six months following randomization and abnormal screening findings were captured for up to six months post-screening. Mailing kits increased uptake of cervical cancer screening by 50% compared to usual care, however nearly a third of participants with HPV-positive kit results did not attend recommended in-clinic follow-up [8].

Established barriers to both screening and follow-up adherence after an abnormal screen include patient, practitioner, and systems-level challenges [15]. Older individuals, those with no history of prior Pap tests, and those with no documented medical visits are less likely to complete follow-up care after an abnormal screening result [18, 19], while a lack of knowledge about screening is the most cited reason for not completing timely screening [20]. Additionally, some international evidence suggests follow-up adherence is lower among individuals who screen using self-sampling compared to those who test in-clinic, largely because underscreened individuals are both more likely to be offered the option to self-sample and to experience persistent socioeconomic and geographic barriers to seeking healthcare [21]. Barriers to follow-up adherence at the healthcare practitioner- and systems-level include clinician

awareness and adherence to screening and care management guidelines, medical record systems limitations (leading to failure to identify screening gaps), and workforce and facility capacity, particularly in low-resource settings [15]. Lack of continuity of care can result in delayed or missed follow-up (due to differing care recommendations and/or gaps in care), and this disproportionately affects patients who change health insurance providers [22, 23]. Thus, multi-level approaches designed to target poor follow-up adherence are essential to the success of cervical cancer screening programs.

Based on current U.S. management guidelines, patients with HPV16/18 positive results are referred directly to diagnostic colposcopy, whereas those positive for other high-risk (hr) HPV types require cytology to complete testing [24]. Because cytology cannot be performed on self-samples, patients with other hrHPV positive self-sampling results require an additional clinic visit to complete screening, which may be an additional barrier to follow-up adherence for HPV-SS compared to clinician testing.

Complicating the challenge of improving follow-up adherence are the logistical challenges health systems face when adopting new screening modalities (e.g., HPV-SS) and implementing updated testing guidelines. Efforts to improve U.S. screening rates have called on improvements in care team communication with screening-eligible patients [21], however this is difficult to implement in low-resource settings when ancillary support roles (like patient navigators) are under resourced [15]. Recent trends of declining primary care coverage reveal up to a third of U.S. adults lack enduring, trust-based patient-clinician relationships [25, 26], which facilitate conversations about screening and follow-up. Communication with patients about updated screening guidelines is essential; focus groups conducted in the Kaiser Permanente Southern California patient population found patients feared that the transition to primary HPV testing would result in missed cancers and was motivated by efforts to cut costs versus provide higher quality care [27], and patient surveys have found unfavorable opinions about extending screening intervals [28]. Notably, Australia's 2017 adoption of clinic-based primary HPV screening preceded a larger than expected increase in demand for colposcopies, stemming in part from reported uncertainty of proper care management and clinician distrust of the new program. This uncertainty and distrust resulted in unwarranted medical procedures for patients and unnecessary costs for the Australian healthcare system [29]. Similar over-management of care has been observed among average-risk,

commercially insured patients in the US who, despite evidence-based testing guidelines, are screened more frequently than recommended, in part due to evolving guidelines that cause confusion [30] and clinician belief that patients are uncomfortable with extended intervals between screens [31].

Although multiple studies have reported on the acceptability and uptake of HPV-SS, few have described the multi-level challenges complicating adherence to cervical screening follow-up care among patients offered HPV-SS. Therefore, we aimed to describe management and completion of follow-up care for HOME participants with abnormal cervical screening results. Additionally, to identify challenges and opportunities for resource allocation as health systems adopt HPV-SS, we also evaluated when and why study personnel intervened to encourage completion of appropriate follow-up care. Notably, when the HOME trial was initiated, screening guidelines did not yet include primary HPV screening, and thus participants were advised to attend in-clinic screening even after a negative HPV-SS result. Thus, we would anticipate the challenges apparent in HOME may differ from those observed in a health system setting that counted HPV-SS as screening.

METHODS

Setting and Participants

Study design, recruitment details, and results from the underlying clinical trial have been published previously [8, 17]. Briefly, HOME was a parallel, investigator-blinded RCT set in the KPWA patient population in which 19,851 eligible individuals were randomized 1:1 to the control (n=9891) or intervention (n=9960) group between February 2014 and August 2016, with follow-up through February 2018. Potentially eligible individuals were identified using electronic health record (EHR) data and enrolled under a waiver of informed consent. The institutional review boards (IRBs) of KPWA and the University of Washington (UW) approved all study procedures for the clinical trial.

Individuals were eligible to participate in HOME if they 1) were continuously enrolled at KPWA for >3 years and 5 months —with an assigned primary care practitioner (PCP), 2) were between the ages of 30-64 years, 3) had no documented hysterectomy, and 4) had not received a Pap test in the last 3.4 years. Individuals became eligible 5 months after receiving KPWA's annual "birthday letter" noting they had not screened in >3 years; this allowed for screening uptake without additional intervention and

ensured the study's 6-month follow-up would end before the next "birthday letter" was sent [8]. Individuals were ineligible if they 1) were currently pregnant or had a pregnancy-related procedure in the 3 months prior to randomization, 2) needed an English language interpreter, or 3) had previously asked not to be contacted for research.

Characteristics at randomization (age, travel time to primary care clinic, body mass index, tobacco use, number and type of clinic visits in the last year, and PCP specialty and degree) were derived from EHR data. Given documented racial and ethnic disparities in cervical cancer screening in the U.S. [32], data on race and ethnicity were also collected and analyzed to identify potential differences in intervention effectiveness across groups. Race and ethnicity at randomization were derived from EHR data per patient self-report at usual care patient registration via preset multiselect categorical options, with "other" allowing free text entry; IRB approval did not allow reporting of individual-level data for all participants, so to maintain consistency across all participants in categorization of race and ethnicity, free-text entries were not reviewed or coded [8].

Intervention and Procedures

The control group received usual care (annual "birthday letters" with a list of relevant upcoming or overdue preventive care needs, "gap letters" sent approximately every 60 days for individuals overdue for Pap screening, and ad hoc outreach by primary care teams). The intervention group also received usual care outreach for Pap screening, plus a mailed HPV self-sample kit. Those who received a kit could choose to return it via mail or get an in-clinic Pap test.

During the study period, KPWA followed 2012 American Society for Colposcopy and Cervical Pathology (ASCCP) management guidelines [24] for management of screening results. Guidance for management of HPV-SS tests received as part of the study were developed in conjunction with clinical leaders and aligned with ASCCP guidelines. Individuals who screened in-clinic were advised to adhere to guideline-recommended follow-up, with recommendations ranging from return to a routine screening interval to immediate colposcopy (Table 1.1).

Self-collected samples were tested with the Cobas® HPV Test (Roche Diagnostics) -- the same assay that is FDA-approved for high-risk HPV testing on clinician-collected samples. Screening results

were documented in the EHR and participants' primary care teams managed communication of results and follow-up care. Primary care teams were educated on recommended follow-up protocols, including how to notify patients of their HPV-SS results and how to manage those results, through trial information disseminated via the established infrastructure for KPWA practitioner education [17]. Results were reported per the standard protocol for usual care (Table 1.2). The patient's primary care provider was electronically notified first, and electronic test results disseminated via the Web portal included 1) a section only visible to the clinician with reminders of management guidelines, information on the HPV-SS test, and the timing of patient notification and 2) a section visible to both the patient and the clinician. Results-specific patient-visible messages were drafted for each of four possible screening results: HPV negative, HPV positive for types other than HPV-16 or HPV-18 only, HPV-16 and/or HPV-18 positive, and unsatisfactory [17]. For additional details on the flow of results from the care team to the patient, including text prepared for patient- and clinician-visible messaging, see Appendix A.

Data Sources

This analysis was restricted to HOME participants who completed screening within six months of randomization and whose screening results warranted follow-up. We used programmatic extraction and manual EHR review to capture participant characteristics and all clinical procedures that occurred within six months following an abnormal screen.

Kit Returners

Additionally, for kit returners only, we had access to documented communication between participant and their care teams. This communication included notification of abnormal results, follow-up recommendations, and notes on whether the participant responded to electronic or mailed outreach.

Outcomes

The definition of follow-up adherence varied by screening result. For participants with an HPV16/18-positive result (whether via HPV-SS or in-clinic Pap/co-test), follow-up adherence was defined as completing colposcopy. For participants with an HPV other-positive/unsatisfactory HPV-SS result, follow-up adherence was completion of an in-clinic Pap or co-test. Participants who screened in-clinic with HPV

other-positive findings were recommended to return in one year for follow-up and thus were not evaluated in this analysis.

Recommendations for follow-up care management were classified as 1) correct-, 2) under-, or 3) over-management (Table 1.1). Failing to refer patients to guideline-recommended follow-up colposcopy was considered under management by the clinician, while over management included, for example, referring to colposcopy/recommending screening on an accelerated timeline when follow-up in one year was warranted.

Details of study intervention were modeled after standard clinical practice for other at-home screening offerings (e.g., fecal occult blood testing) and are outlined in Figure 1.1. Briefly, EHRs for kit recipients were monitored weekly for HPV-SS test results. Once kit results were available, EHRs for patients with positive screening findings were reviewed regularly (weekly for those with HPV16/18-positive results, bimonthly for HPV other-positive and unsatisfactory findings). Study staff reviewed clinician communications for appropriate follow-up recommendations and referred cases of mismanagement to the study physician for clinician outreach. For those instances in which no or incorrect follow-up care was recommended, this analysis describes communication (if any) from the study team to the care team to encourage completion of appropriate follow-up.

Statistical Analysis

Analytic Groups

We evaluated follow-up adherence among three screening groups: intervention [kit], intervention [in-clinic], control [in-clinic]. *Intervention [kit]* included kit recipients who returned the kit, *intervention [in-clinic]* included kit recipients who opted to screen in-clinic, and *control [in-clinic]* included those randomized to the control group and screened in-clinic. For the purposes of this analysis, we evaluated whether participants completed follow-up as recommended within the six months post-screening.

Analysis

We described the characteristics of participants who did and did not adhere to recommended follow-up by study group (intervention [kit], intervention [in-clinic Pap], and control [in-clinic Pap]). We also described, by study group, the prevalence of care team management practices (correct, over-, and under-

management). Finally, we estimated the median time from screening (via kit or in-clinic) to follow-up, by study group. For those who screened via kit, time to follow-up was measured starting from the result date of a home kit and up to 6 months from that date; for those who screened in-clinic, the start date was the date of the in-clinic Pap/co-test. Given the small sample size and small individual cell sizes, we did not calculate effect size estimates or p-values. Additionally, intervention [in-clinic] participants were considered “non-responders,” given they did not participate in screening via kit, and thus we were unable to report on participant characteristics for any intervention [in-clinic] subgroup with fewer than five participants.

Communication between kit returners with abnormal screening results and their care teams was reviewed via EHR; the instances in which the study team intervened via practitioner outreach are described in Figure 1.1.

RESULTS

In total, 19,851 participants were included in the HOME analyses (9960 in the intervention group and 9891 in the control group). Of those who received a mailed kit, 12.1% (n=1206) returned it and 14.5% (n=1440) initiated screening in-clinic [8]. Overall, 228 (5.3%) of 4311 participants who screened (2592 in the intervention group and 1719 in the control group) had results warranting follow-up within the study observation period; of those, 142 were in the intervention group and returned a kit, 44 were in the intervention group and opted for in-clinic screening, and 42 were in the control group. Most of these individuals were White (81% of intervention [kit], 66% of intervention [in-clinic Pap], 88% of control participants) (Table 1.3). Nearly half of kit returners were 50 years of age or older, compared with 18% and 19% among those screened in-clinic in the intervention and control groups, respectively. Most individuals had attended an in-person visit (Obstetrician/Gynecologist [OBGYN] or primary care) in the 12 months prior to randomization; only 14.8% of kit returners, 18.2% of intervention in-clinic screeners and 19.0% of control participants had no visits in the last year. The majority of kit returners’ primary care clinicians specialized in Family Medicine (vs. Internal Medicine) and were Doctors (vs. Physician Assistants or Nurse Practitioners).

Characteristics of Follow-up Adherent and Non-Adherent Participants

Intervention [kit]

Two-thirds (n=95) of kit returners whose screening results warranted follow-up were follow-up adherent (Table 1.4). We compared those who were adherent to the 47 participants who were not follow-up adherent. A higher proportion of adherent participants were White (83% vs. 77% of non-adherent) and between 50-64 years of age (65% vs. 55%). One quarter (25%) of adherent participants had a body mass index (BMI) in the healthy weight range compared to 13% of non-adherent participants; 42% of adherent individuals and 53% of non-adherent individuals were obese or severely obese. While comparable proportions of adherent and non-adherent participants visited their PCP in the 12 months prior to randomization (39% vs. 40%), 26% of non-adherent individuals had no recorded clinic visits during this time, compared to only 9% of adherent individuals.

Intervention [in-clinic Pap]

Forty-four participants in this group had Pap/co-test results warranting colposcopy; of those, 70% (n=31) completed a colposcopy within the study observation period. Given these participants are considered "non-responders," we are unable to report on participant characteristics for any subgroup with fewer than five participants (e.g., non-adherent and age 40-44 years). Thus, we did not present characteristics by follow-up adherence status for intervention [in-clinic Pap] participants.

Control [in-clinic Pap]

Participants randomized to the control group had the highest follow-up adherence rate of the three study groups: 81% (n=34) of the 42 individuals whose in-clinic Pap/co-test findings warranted a colposcopy completed one. All non-adherent participants identified as White (vs. 85% of adherent participants). A higher proportion of adherent individuals were between 50-64 years of age (38% vs. 13% of non-adherent individuals). As observed in the intervention [kit] group, a larger share of non-adherent participants was obese or severely obese than adherent participants (38% vs. 12%), though cell sizes were small.

Follow-up Care Recommendation and Completion

Intervention [kit]:

HPV16/18+ Findings

Twenty-one of the 34 participants (62%) with HPV16/18-positive findings received correct follow-up recommendations from their primary care teams (Table 1.5, Figure 1.2); 12 of these participants then completed follow-up. Incorrect follow-up recommendations were made for the remaining 13 (38%) and included recommendations for Pap/co-test (n=7), re-screening in one year (n=2), or no contact with the patient (n=4) (Figure 1.2). Ultimately, 19 (56%) received a colposcopy, with four of those receiving a colposcopy only after first receiving a Pap/co-test against recommendations. Two others (6%) received a co-test—both had negative results, meaning a subsequent colposcopy would have been over-management. The study team contacted the PCP on behalf of eight participants (24%), half of whom then received a colposcopy; in total, study team intervention preceded four (21%) of the total 19 colposcopies performed. For 13 participants (38%), despite receiving guideline-informed communications, follow-up care was not received.

Other HPV+ or Unsatisfactory Findings

Ninety of 108 participants (83%) with other HPV-positive or unsatisfactory home kit results correctly received a recommendation to attend an in-clinic Pap or co-test to complete their screening episode (Figure 1.3a). The other 18 participants received incorrect care recommendations, including six who were referred to and received immediate colposcopies (over-management). Ultimately, 66% (72 of 108) of participants with other HPV+ or unsatisfactory kit findings received a Pap/co-test. Study team outreach was required in six cases in which clinicians did not communicate home kit results to participants (Figure 1.3a) and 13 cases in which clinicians failed to advise participants with normal screening findings to rescreen in one year (Supplemental Figure 1.3b).

Time to follow-up

In the intervention group, among the HPV16/18-positive participants who completed a colposcopy (n=19) and the participants with other HPV-positive/unsatisfactory findings who completed a Pap/co-test (n=72, the median time to follow-up procedure was 35 days (interquartile range [IQR]: 20-49 days) and 20 days

(IQR: 9-56 days) from the result date of the home kit, respectively (Figure 1.4). Those in the intervention group who were screened in-clinic and then completed a colposcopy (n=31) had a median time to colposcopy of 30 days from the date of the in-clinic Pap/co-test (IQR: 22-64 days). The median among those in the control group (n=34) was 39 days from the date of the in-clinic Pap/co-test to colposcopy (IQR: 23-63 days).

DISCUSSION

In this secondary analysis of randomized clinical trial data, recommendation and receipt of follow-up care after an abnormal cervical cancer screening result varied by screening modality, with participants who self-sampled using a home-based HPV kit more likely than individuals screened in-clinic to receive incorrect follow-up care management. Among HPV-SS kit returners whose findings warranted immediate colposcopy, 38% were undermanaged. Additionally, over a third of kit returners whose home-based screening results warranted a co-test to complete screening did not receive care in-clinic. These gaps in receipt of appropriate care persisted following study team intervention, highlighting the difficulties of completing necessary diagnostic follow-up in home-based screening programs.

While our sample size precluded testing for significant differences between demographic groups, our descriptive analysis suggests potential differences between individuals who did and did not adhere to prescribed follow-up. In HOME, a larger proportion of kit returners who were follow-up adherent were 40 years old or older (86%) compared to those who were not adherent (77%); a 2023 systematic review of studies evaluating failure to follow-up after abnormal cervical cancer screening results reported inconsistent findings on the association between age and occurrence of inadequate follow-up [33]. A slightly higher proportion of HOME participants who did versus did not adhere to follow-up were White (83% vs. 77%), which aligns with observational studies and meta-analyses conducted in US settings that reveal non-White and non-US born people were more likely to miss follow-up care after abnormal cervical screening [33–35]. Additionally, HOME participants who adhered to follow-up had lower rates of obesity (41% vs. 53% of non-completers), echoing prior research that suggests individuals with obesity are less likely to be screened than those of normal weight [36–38]. Several patient- and clinician-related barriers to screening exist for obese individuals, including patient delays in medical care due to stigmatization,

embarrassment, and perceived lack of clinician respect [38]. Clinician biases may make practitioners less likely to recommend and conduct screening for obese patients, and practitioners report difficulty conducting pelvic exams, particularly in severely obese individuals [39]. These factors may have prevented obese HOME participants who screened via HPV-SS from completing in-clinic follow-up with the same frequency as their non-obese peers, though breast cancer research suggests that once obese individuals access mammography, they have similar rates of follow-up after abnormal results compared to normal-weight individuals [40]. Finally, follow-up adherent individuals had higher rates of healthcare engagement compared to non-adherent individuals, emphasizing the role of strong patient-clinician relationships and suggesting additional outreach measures are required to reach under-engaged populations to ensure completion of necessary follow-up. These findings echo those of a secondary analysis of the HOME trial that found HPV-SS kits increased screening uptake among difficult-to-reach individuals who were also overdue for other recommended preventive screenings (i.e., breast, colorectal) [41]. Like our analysis, this analysis also found that, among participants who screened, the proportion who used kits was higher in older vs. younger age groups, in White vs. non-White racial groups, and among those who had not screened in ten or more years compared to those who screened less than five years prior.

Clinician and system-level factors associated with inadequate follow-up are less well known [33]. Global evidence reveals individuals are more likely to complete follow-up if they have an established relationship with a healthcare practitioner, if the clinic offers internal referral to colposcopy, and if there is direct notification of abnormal findings from pathology departments to patients [33, 42]. Regarding follow-up in the context of HPV-SS specifically, a 2018 meta-analysis found higher adherence to follow-up after an abnormal screening in settings with direct referral compared to those with triage policies [11]. Qualitative research done within US Veterans Affairs facilities concluded that clinician confusion over responsibility for test results led to gaps in indicated follow-up care (i.e., when the ordering clinician is not the one to manage or share the results with the patient) [43]. In HOME, a participant's HPV-SS kit results were sent directly to their PCP with instructions on recommended management; however, it is possible PCPs were less comfortable or familiar with managing results for tests they did not directly order, thus contributing to lower follow-up adherence among kit recipients. Clinician discomfort, knowledge gaps, and

perceived limitations of primary HPV testing have been reported [44], and this uncertainty may impact how clinicians respond to HPV-SS screening results.

Among participants who did adhere to indicated follow-up, the majority received care within 90 days, defined as timely care by the National Breast and Cervical Cancer Early Detection program (NBCCEDP) [45]. Completion of indicated colposcopy within 90 days occurred in 66% of kit returners with HPV16/18+ findings, 57% of kit recipients who screened in-clinic, and 76% of control participants who screened in-clinic. Of kit returners with other HPV+ findings, 66% completed a Pap/co-test within 60 days. This level of timely follow-up is comparable to that previously observed in a 2010-2018 study in diverse US healthcare settings, including KPWA, in which 64-73% of participants completed follow-up within three months of receiving a high-grade abnormal result [46]. Additionally, the observed result group-specific median time to follow-up in HOME of between 20 to 40 days was shorter than the median time to follow-up reported among uninsured and underinsured patients enrolled in the NBCCEDP, which ranged from 48 to 54 days [47].

This study emphasizes the complexity of layering a new screening modality (self-sampling) onto recently updated screening guidelines; as observed in other settings [29, 31, 48, 49], this can contribute to both patient and clinician confusion surrounding appropriate screening intervals and follow-up practices. In participant interviews, HOME participants with abnormal kit results expressed confusion about the purpose and meaning of HPV vs. Pap tests, as well as concern that HPV-SS is inaccurate when a subsequent Pap test is normal [14]. This suggests education at multiple times during the screening process is necessary for patients to remain engaged in HPV-SS, particularly given the need for in-clinic follow-up screening after abnormal home-based results. Clinician education is similarly important; researchers monitoring over-management of care in Australia following the country's 2017 adoption of primary HPV screening attributed higher than expected colposcopy referral rates to 1) uncertainty of proper care management during the transition period, 2) referring individuals with intermediate-risk findings to colposcopy rather than repeat screening in one year, and 3) clinician distrust of the new program and subsequent over-ordering of diagnostics [29]. EHR notes from clinicians of patients enrolled in HOME revealed similar uncertainty over follow-up procedures; the sources of greatest confusion (and the most common instances in which the study team intervened) included 1) ordering a Pap test instead

of a colposcopy for an HPV 16/18+ participant, 2) failing to contact HPV other-positive participants to schedule a Pap/co-test to complete screening, and 3) failing to notify HPV other-positive participants of the need for a repeat screen in one year vs. returning to a regular screening schedule. Kit recipients in the HOME trial who had abnormal screening results were more likely to be under-managed and similarly likely to be over-managed compared to non-kit recipients. The success of HPV-SS requires clear and frequent patient and clinician education [14, 21], particularly on the differences in follow-up of abnormal results required for clinician-collected vs. self-collected samples.

At KPWA, in response to opportunities highlighted during the HOME trial for improvements in managing individuals with abnormal screening results, a closed loop nurse position was developed and piloted in a subsequent trial [50]. The closed loop nurse protocol relieves the primary care provider of the responsibility of managing follow-up care by facilitating centralized management of abnormal screening results; one nurse directly communicates abnormal results to patients and manages follow-up scheduling, thus making it less likely patient care is incorrectly managed. Implemented in other settings, this protocol would address concerns voiced by primary care providers that limited health system support exists for following up on overdue abnormal cancer screening test results [51].

Strengths and Limitations

A strength of this secondary analysis is the inclusion of data on clinician communication to participants via the KPWA patient portal. We also included documentation of study team intervention, where applicable, including study team correspondence to clinicians regarding appropriate follow-up procedures. This qualitative data allows us to better understand common areas of confusion around screening guidelines and where practitioner education might be most useful. It also enables us to distinguish between patient follow-up care-seeking behavior in cases of documented incorrect care management vs. cases in which clinician communication was correct (and patients still did not complete timely follow-up).

We captured follow-up completed within six months post-screening. For the purposes of this analysis, we have classified all participants who completed follow-up within six months as adherent; we did not differentiate between timely (within 60 days, per the NBCCEDP [45]) and delayed screening within that window. Similarly, our follow-up window of six months prevented us from capturing follow-up data on

individuals whose screening results warranted re-screening in one year (other than for those over managed, i.e., rescreened prematurely or received colposcopy); thus, we are unable to measure correct and under management for this group. Additionally, participants with negative results were advised to attend in-clinic screenings given HPV-SS was not yet an approved screening modality, meaning we could not observe and compare to any over-management of those with negative kit results. Finally, clinician response to abnormal screening findings may have been influenced by confusion over their role in managing a screening test ordered through a study, despite study team efforts to provide clear clinician guidance.

CONCLUSION

Individuals who screened for cervical cancer using HPV-SS had lower rates of follow-up after abnormal screening results compared to those who screened in-clinic. As screening modalities and guidelines evolve, health systems should address incorrect care management (both over- and under-management) to reduce excess spending, prevent patient confusion, and optimize follow-up adherence.

Figure 1.1 HOME study team protocol for intervening in participant follow-up care following review of home-based HPV self-sampling kit results

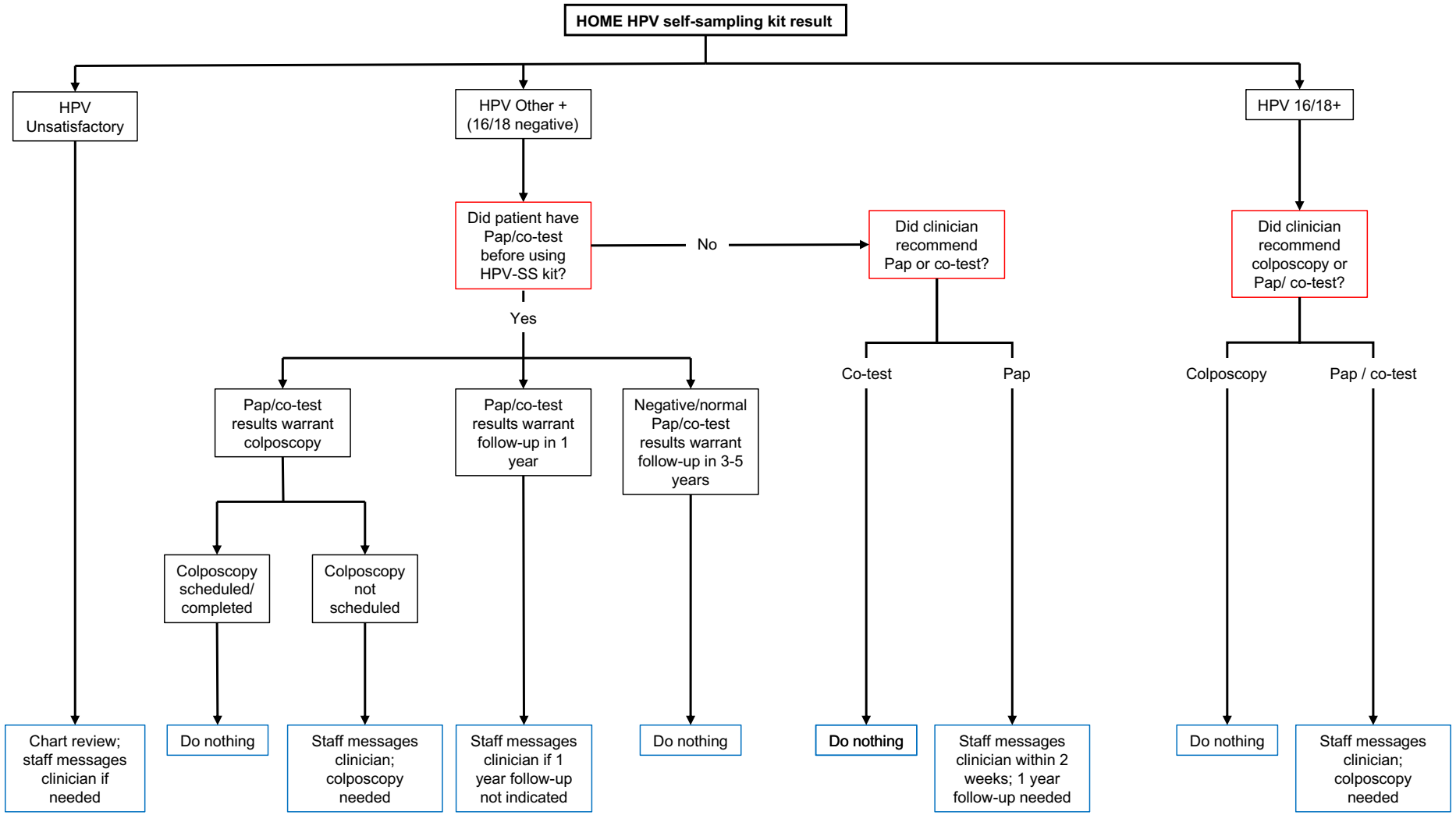
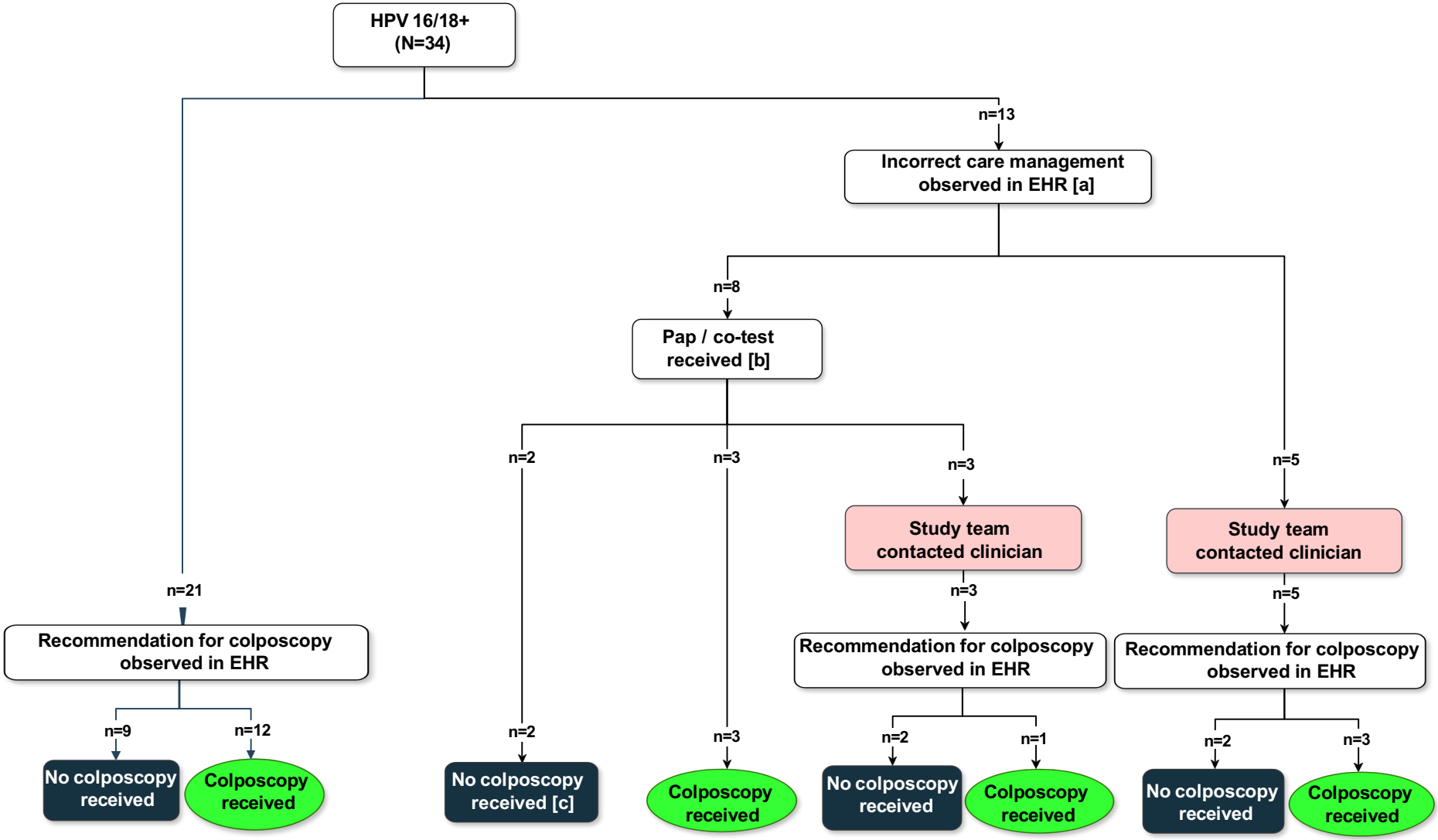
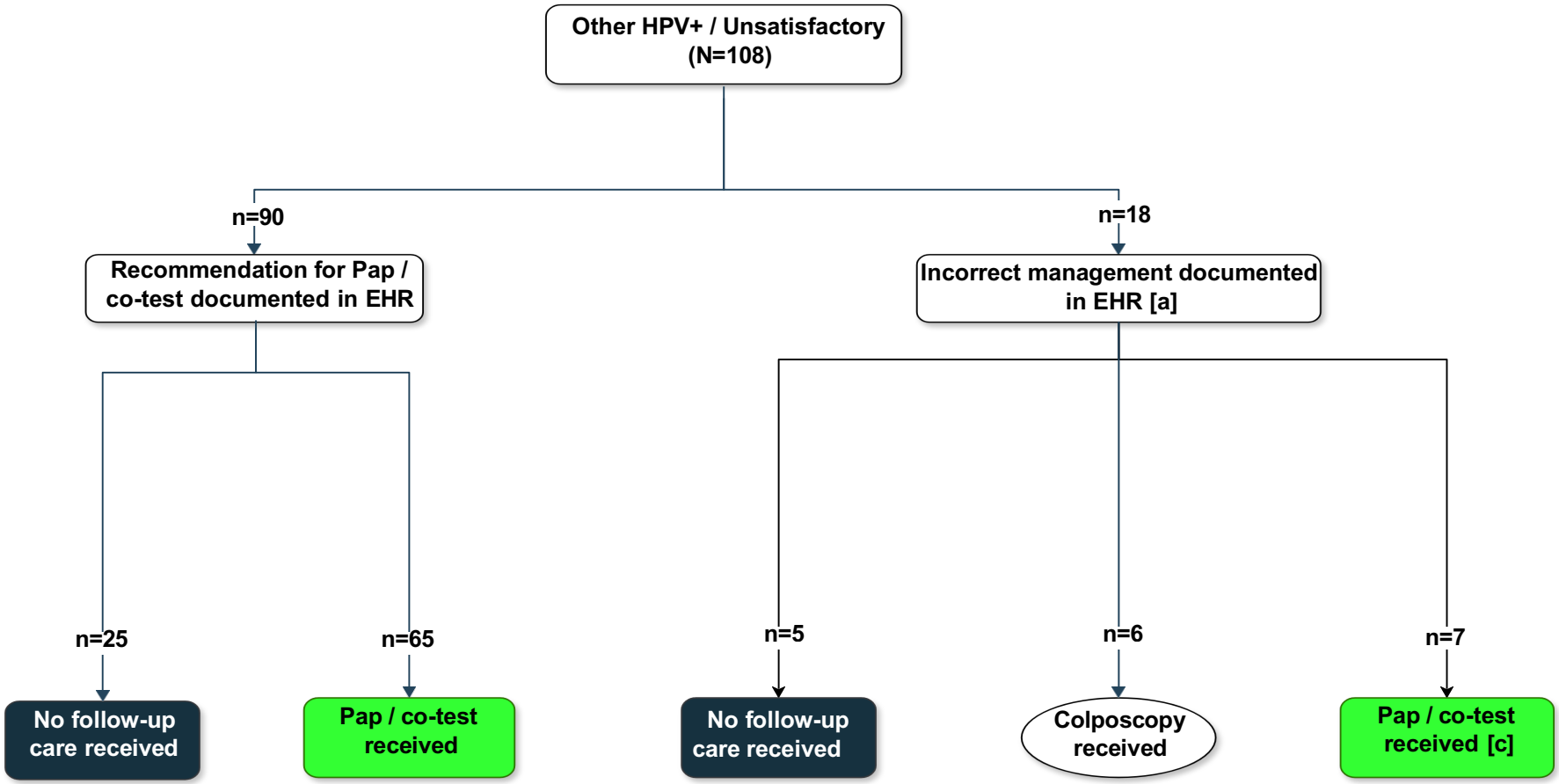


Figure 1.2 Follow-up care adherence among kit recipients with HPV 16/18-positive findings, including care recommendations, study team intervention when incorrect management was observed, and receipt of care (N=34)



[a] Incorrect care management included a recommendation for an immediate Pap/co-test (n=7; of these, 3 ultimately received a colposcopy), a recommendation for a rescreen in one year (n=2; of these, 1 ultimately received a colposcopy), or making no contact with the patient (n=4; of these, 3 ultimately received a colposcopy).
[b] Includes two participants who self-referred to Pap/co-test.
[c] These two participants had negative co-tests; given these findings, colposcopy would have been over-management.

Figure 1.3a Follow-up care adherence among kit returners with other HPV-positive or unsatisfactory findings, including care recommendations, study team intervention when incorrect care management was observed, and receipt of care (N=108)



[a] Incorrect management observed included over management (n=12) and under management (n=6). Over management included referral to colposcopy, consultation with OBGYN, and referral to OBGYN. Under management observed was failure to contact participants with results.
[b] Study team intervened for three of these participants to recommend a Pap/co-test; all three participants' physicians documented received a recommendation for a Pap/co-test, but these participants did not receive follow-up care.
[c] One of these participants self-referred to a Pap/co-test, prior to study team intervention due to no contact from clinician. Study team intervened for two other participants to recommend a Pap/co-test.

Supplemental Figure 1.3b Follow-up care adherence among kit returners with other HPV-positive or unsatisfactory findings who received a Pap/co-test, including study team intervention when no recommendation for follow-up screening in one year was noted in a HOME participant's electronic health record (N=72)

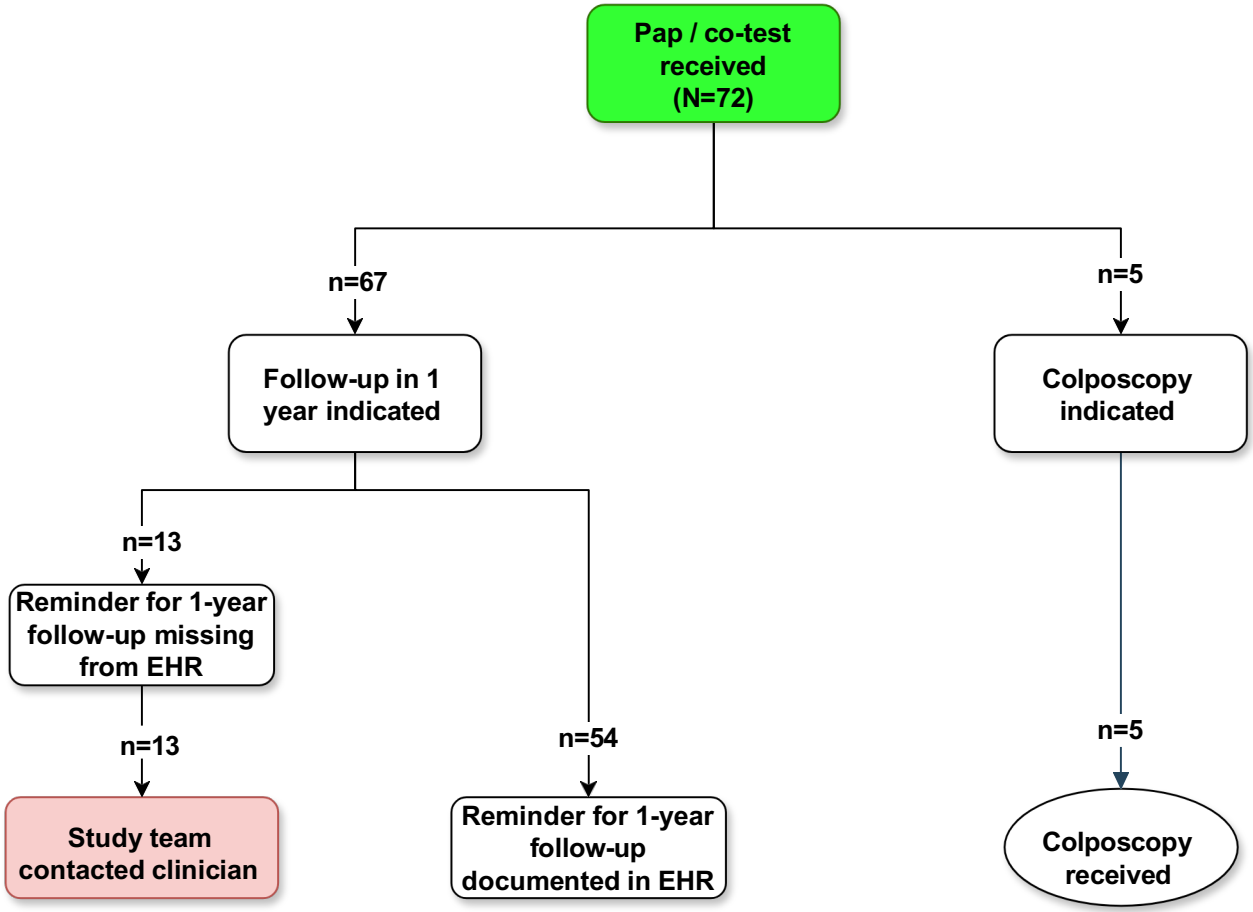
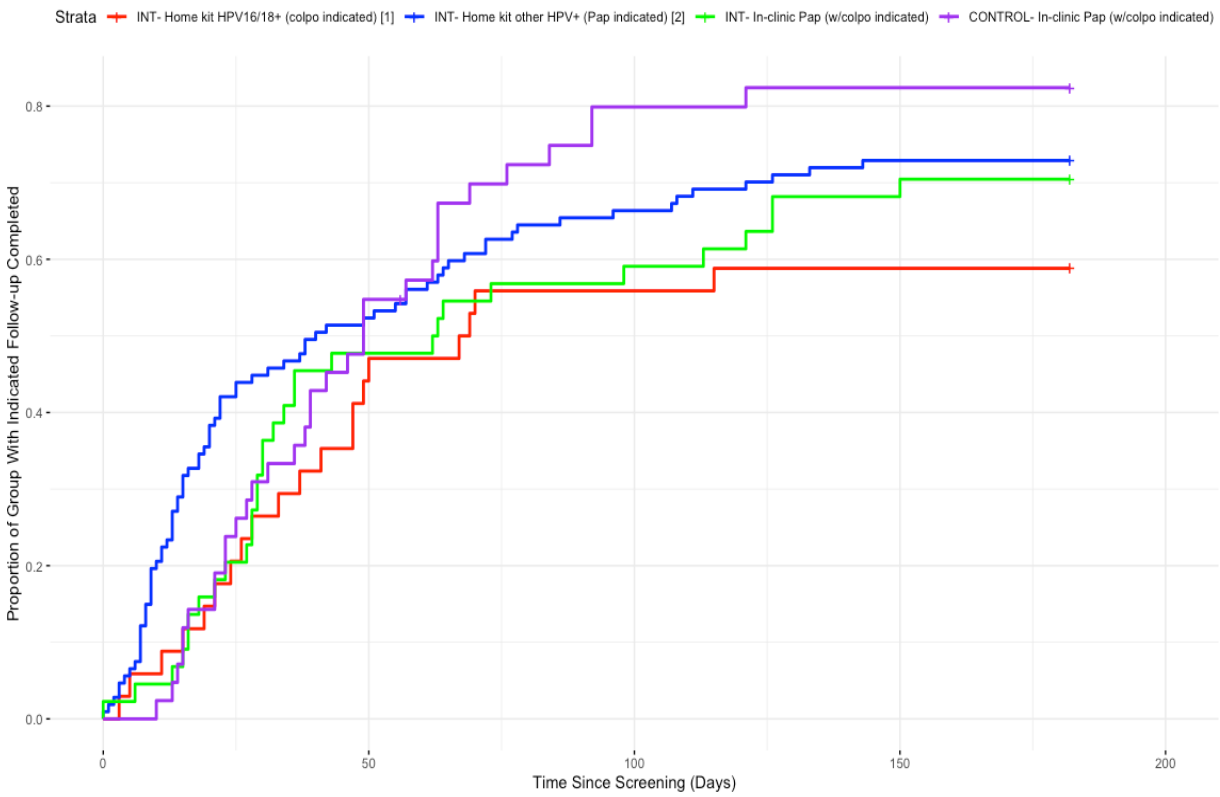


Figure 1.4 Time to indicated follow-up, by result group



[1] Individuals with home HPV results that were positive for HPV16 and/or HPV18 were censored if they received a Pap/co-test with no colposcopy (n=8), as this represented under management of care. This included n=4 individuals who ultimately did receive a colposcopy at a later date.

[2] Individuals with home HPV results that were positive for other hrHPV were censored if they received an immediate colposcopy.

Table 1.1. Classification of healthcare provider management of care in instances when follow-up care is warranted after an initial abnormal cervical screening, HOME trial data, 2014-2018, Seattle, WA

		Correct management, per 2012 screening guidelines [1]	**Incorrect management [1]**	
Screening arm	**Screening results [2]**		**Over**	**Under**
Intervention (kit)	HPV16/18 positive	Immediate colposcopy	N/A	· Pap/co-test · Surveillance screen in 1 year · No contact from provider to patient
	· Other HPV positive · Unsatisfactory	Pap/co-test	Immediate colposcopy [3]	· Surveillance screen in 1 year · No contact from provider to patient
Intervention (in-clinic), Control	· Normal cytology with HPV16/18+ co-test · ASC-US cytology [4] with HPV+ co-test or reflex test · >ASC-US cytology [5] with any or no HPV results	Immediate colposcopy	N/A	· Pap/co-test · Surveillance screen in 1 year · No contact from provider to patient
	Normal cytology with other HPV positive co-test	Repeat co-testing in 1 year	Immediate colposcopy	· Surveillance screen in 1 year · No contact from provider to patient
	ASC-US [4] cytology with HPV negative co-test or reflex test	Routine screen in 3 years	· Surveillance screen in 1 year · Immediate colposcopy	· No contact from provider to patient

[1] Throughout the HOME trial, Kaiser Permanente Washington followed the 2012 ASCCP Consensus Guidelines for management of abnormal cervical results. Care management is distinguished as correct vs. incorrect based on the follow-up procedure that immediately followed an abnormal screening result.

[2] Test results that do not warrant follow-up care (and corresponding provider management patterns) are not included in this table.

[3] Unless otherwise indicated in EHR notes, based on patient history.

[4] Atypical squamous cells of undetermined significance.

[5] Includes ASC-H (Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion), AGC (Atypical glandular cells), LSIL (Low-grade squamous intraepithelial lesion), and HSIL (High-grade squamous intraepithelial lesion).

Table 1.2. Result reporting protocol for HPV-Self Sampling (HPV-SS) test results in the HOME trial, conducted in the Kaiser Permanente Washington patient population, 2014-2018, Seattle, WA

HPV-SS test result	Patient notification of results	Recommended follow-up
Negative/normal	Patient notified immediately via the patient Web portal. If not active on portal, clinician instructed to call patient	In-clinic Pap/co-testing [1]
Abnormal		
other HPV positive	24-28 hour delay in notification via patient Web portal to allow care team time to call the patient	In-clinic co-testing [2]
HPV 16/18 positive	24-28 hour delay in notification via patient Web portal to allow care team time to call the patient	Immediate colposcopy [3]
Unsatisfactory	24-28 hour delay in notification via patient Web portal to allow care team time to call the patient	In-clinic Pap/co-testing

[1] When the HOME trial was initiated, cervical cancer screening guidelines did not yet include primary HPV screening, and thus the KPWA IRB and delivery system required that participants be advised to attend in-clinic screening even after a negative result.

[2] This was standard of care at KPWA at the time.

[3] Per ASCCP management recommendations.

Table 1.3. HOME study population baseline characteristics, by cervical cancer screening result (N= 228 participants for whom immediate follow-up was warranted following screening), 2014-2018, Seattle, WA

Characteristic	Intervention (kit) (n=142) [1]		Intervention (in-clinic) (n=44) [1]		Control (in-clinic) (n=42) [1]	
Race [2]	**N**	**%**	**N**	**%**	**N**	**%**
White	115	81.0%	29	65.9%	37	88.1%
Asian	7	4.9%	5	11.4%	2	4.8%
Other [3]	20	14.1%	10	22.7%	3	7.1%
Age at randomization, years						
30-34	13	9.2%	7	15.9%	8	19.0%
35-39	11	7.7%	8	18.2%	6	14.3%
40-44	17	12.0%	12	27.3%	10	23.8%
45-54	34	23.9%	9	20.5%	10	23.8%
55-64	67	47.2%	8	18.2%	8	19.0%
Body Mass Index (BMI) [4]						
<18.5-24.9	32	22.5%	15	34.1%	12	28.6%
25.0-39.9 or unknown	92	64.8%	24	54.5%	27	64.3%
>=40	18	12.7%	5	11.4%	3	7.1%
Smoking status						
Current or Former	67	47.2%	14	31.8%	15	35.7%
Never or Unknown	75	52.8%	30	68.2%	27	64.3%
Travel time to clinic (minutes)						
Median (IQR)	141	11.9 (9.7)	43	12.1 (12.5)	42	14.2 (12.5)
Distance to clinic (miles)						
Median (IQR)	141	5.6 (7.3)	43	6.4 (8.4)	42	6.9 (6.1)
Clinic visits in 12 months prior to randomization						
visited own PCP	56	39.4%	12	27.3%	11	26.2%
visited a PCP (other than own) or OBGYN	32	22.5%	10	22.7%	13	31.0%
any other in-person visit	33	23.2%	14	31.8%	10	23.8%
No visit	21	14.8%	8	18.2%	8	19.0%
PCP Practitioner specialty [5]						
Family Medicine	135	95.1%				
Internal Medicine	7	4.9%				
PCP Practitioner degree [5]						
Medical Doctor (MD) or Doctor of Osteopathic Medicine (DO)	123	86.6%				
Physician Assistant (PA-C)	15	10.6%				
Nurse Practitioner (ARNP)	4	2.8%				

Table 1.3. Abbreviations
PCP, Primary Care Physician

OBGYN, Obstetrician and Gynecologist
IQR, interquartile range

Table 1.3. Footnotes

[1] Results that warrant colposcopy referral include 1) Normal cytology with HPV positive co-test (HPV 16/18+), 2) ASCUS (Atypical squamous cells of undetermined significance) cytology with HPV positive co-test or reflex test, 3) ASC-H (Atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion) cytology, regardless of any or no HPV results, 4) AGC (Atypical glandular cells) cytology, regardless of any or no HPV results, 5) LSIL (Low-grade squamous intraepithelial lesion) with no or positive HPV co-test, and 6) HSIL (High-grade squamous intraepithelial lesion). Results that warrant surveillance screen follow-up include 1) Normal cytology with HPV positive co-test (HPV other+), for which repeat co-testing in one year is appropriate, 2) Unsatisfactory cytology alone or unsatisfactory cytology with HPV negative co-test, for which repeat co-testing in 2-4 months is appropriate if previous Pap test was normal, 3) Unsatisfactory cytology with HPV positive co-test, for which repeat co-testing in 2-4 months is preferred over immediate colposcopy, 4) ASCUS cytology alone, which warrants repeat cytology in one year, and 5) LSIL with negative co-test, for which repeat co-testing in one year is most appropriate.

[2] Race and ethnicity from EHR data per patient self-report at usual care patient registration via preset multi-select categorical options, with "other" allowing free text entry. The study variable was programmatically categorized into the displayed categories by coding any multiple selections as "more than one race". Manual coding of the "other" category was precluded because IRB approval did not allow individual-level data for those opting out of study participation.

[3] Due to small cell sizes in some race categories for participants in the 'Intervention (in-clinic)' group, some categories have been collapsed. These participants are considered non-responders and thus cell sizes <5 cannot be reported.

[4] Due to small cell sizes for some participants in the 'Intervention (in-clinic)' group, some categories have been collapsed. These participants are considered non-responders and thus cell sizes <5 cannot be reported. Broadly, overweight individuals (BMI=25-29.9) typically have better health outcomes than obese individuals (BMI=30-39.9).

[5] Due to small cell sizes, some categories have been suppressed.

Table 1.4. HOME study population characteristics, by receipt of indicated follow-up within six-month study follow-up window (N=184) (2014-2018, Seattle, WA).

	Intervention (kit) [1] n=142				Control (in-clinic) n=42			
	Completed indicated follow-up within window [2] (N=95, 66.9%)		Did not complete indicated follow-up within window [2] (N=47, 33.1%)		Completed indicated follow-up within window [3] (N=34, 81.0%)		Did not complete indicated follow-up within window [3] (N=8, 19.0%)	
Characteristic	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Race [4]								
White	79	83%	36	77%	29	85%	8	100%
Asian	7	7%	0	0%	2	6%	0	0%
Black	3	3%	2	4%	3	9%	0	0%
Native Hawaiian or other Pacific Islander	0	0%	1	2%	0	0%	0	0%
American Indian/Alaska Native	2	2%	0	0%	0	0%	0	0%
More than one race	3	3%	2	4%	0	0%	0	0%
Other	0	0%	3	6%	0	0%	0	0%
Unknown	1	1%	3	6%	0	0%	0	0%
Age at randomization								
30-34	7	7%	6	13%	6	18%	2	25%
35-39	6	6%	5	11%	2	6%	2	25%
40-44	12	13%	5	11%	8	24%	2	25%
45-49	8	8%	5	11%	3	9%	1	13%
50-54	15	16%	6	13%	5	15%	1	13%
55-59	23	24%	10	21%	6	18%	0	0%
60-64	24	25%	10	21%	2	6%	0	0%
Copay for visit ($)								
10	3	3%	1	2%	1	3%	1	13%
15	20	21%	10	21%	6	18%	2	25%
20	21	22%	16	34%	9	26%	2	25%
25	29	31%	8	17%	6	18%	0	0%
30	3	3%	5	11%	2	6%	0	0%
35	1	1%	0	0%	1	3%	0	0%
Unknown	18	19%	7	15%	1	3%	1	13%
Body Mass Index (BMI)								
<18.5	2	2%	0	0%	1	3%	0	0%

18.5-24.9	24	25%	6	13%	10	29%	1	13%
25.0-29.9	28	29%	12	26%	10	29%	3	38%
30.0-34.9	19	20%	9	19%	9	26%	1	13%
35.0-39.9	10	11%	8	17%	2	6%	2	25%
>=40	10	11%	8	17%	2	6%	1	13%
Unknown	2	2%	4	9%	0	0%	0	0%
Smoking status								
Current	16	17%	9	19%	5	15%	1	13%
Former	28	29%	14	30%	8	24%	1	13%
Never	49	52%	21	45%	20	59%	6	75%
Unknown	2	2%	3	6%	1	3%	0	0%
Clinic visits in 12 months prior to randomization								
visited own PCP	37	39%	19	40%	9	26%	2	25%
visited a PCP (other than own) or OBGYN	25	26%	7	15%	10	29%	3	38%
any other in-person visit	33	35%	9	19%	9	26%	1	13%
No visit	9	9%	12	26%	6	18%	2	25%
Unknown	0	0%	0	0%	0	0%	0	0%
Travel time to clinic (minutes)								
Median (IQR)	94	11.4 (7.6)	42	15.0 (21.3)	34	16.6 (12.2)	8	9.1 (7.1)
Distance to clinic (miles)								
Median (IQR)	94	5.2 (6.0)	42	8.7 (19.1)	34	8.0 (8.7)	8	3.9 (4.7)

Table 1.4. Abbreviations
PCP, Primary Care Physician
OBGYN, Obstetrician and Gynecologist
IQR, interquartile range

Table 1.4. Footnotes
[1] Participants randomized to the intervention arm who received an in-clinic Pap/co-test ("intervention [in-clinic]") were not included in this table due to small cell sizes for many of the characteristics included in this table. Intervention [in-clinic] participants are considered "non-responders" to the HOME intervention, and thus cell sizes <5 cannot be reported.
[2] Follow-up completion is considered receipt of indicated follow-up (depending on screening result, colposcopy or in-clinic Pap/co-test) captured in the six months following screening.

[3] For Intervention (in-clinic) and Control subgroups, within window follow-up can only be assessed for participants with results warranting colposcopy. Thus, this descriptive analysis includes only participants whose results warrant colposcopy and excludes those whose results warrant surveillance screening.

[4] Race and ethnicity from EHR data per patient self-report at usual care patient registration via preset multi-select categorical options, with "other" allowing free text entry. The study variable was programmatically categorized into the displayed categories by coding any multiple selections as "more than one race". Manual coding of the "other" category was precluded because IRB approval did not allow individual-level data for those opting out of study participation.

Table 1.5. Proportion of HOME trial participants within each screening arm who received correct and incorrect follow-up care management recommendations, by screening result (N=228), 2014-18, Seattle, WA

		Follow-up Care RECOMMENDED					
		Correct Management Recommended		Incorrect Management Recommended			
				Over		Under	
Study Group	Screening Results and Follow-Up Warranted	N	%	N	%	N	%
Intervention (kit)	HPV 16/18+, colposcopy indicated (n=34) [1]	21	61.8%			13	38.2%
	Other HPV+ or Unsatisfactory, in-clinic Pap/co-test indicated to complete initial screening (n=108) [2]	90	83.3%	12	11.1%	6	5.6%
	Total: All intervention (kit) (n=142)	111	78.2%	12	8.5%	19	13.4%
Intervention (in-clinic)	Colposcopy indicated (n=44) [3]	31	70.5%			13	29.5%
Control (in-clinic)	Colposcopy indicated (n=42) [3]	34	81.0%			8	19.0%

[1] For these individuals, correct management entails immediate referral to colposcopy, while under management is either referral to Pap test/co-test before colposcopy or lack of recommendation for a clinic visit entirely. Over management is not applicable for this group.
[2] For these individuals, correct management is immediate Pap/co-test to complete initial screening. Over management is referral to immediate colposcopy, while under management is either recommendation for a surveillance screen in one year, recommendation to return to regular screening, or lack of recommendation entirely.
[3] For these individuals with other HPV+ kit results and abnormal in-clinic screening findings, correct management entails immediate referral to colposcopy, while under management reflects a lack of recommendation for a clinic visit entirely. Over management is not applicable for this group.

Chapter 2: The impact of patient education materials on cervical cancer screening completion among STEP trial participants: an embedded trial

ABSTRACT

The impact of patient education materials (PEMs) on cervical cancer screening is not well known. PEMs have been shown to increase knowledge and risk perception across a variety of health outcomes, and targeting PEMs to an intended audience can increase effectiveness; however, evidence of PEMs motivating behavior change is mixed. In a pragmatic randomized clinical trial set in an integrated private health system (STEP trial), exposure to PEMs did not impact cervical cancer screening completion compared to usual care (UC). This current study is an embedded trial within STEP, in which we aimed to determine whether the impact of PEMs on screening completion can be increased through 1) patient-informed optimization and 2) age-targeting of PEMs. Participants randomized in the first 10 months of STEP received “original” PEMs. We then conducted 8 focus group discussions (FGD) within the health system to understand gaps in knowledge about HPV and risk perception regarding cervical cancer; analysis of FGD transcripts informed edits to STEP PEMs, resulting in three new PEMs (“optimized,” “age-targeted ≤45 years of age,” “age-targeted >45 years”), which were then disseminated in place of the “original” for the remainder of the trial. We used modified Poisson regression to estimate relative risk (RR) of screening completion within 6 months for the PEMs groups relative to UC. We estimated the difference in screening rates associated with 1) optimized PEMs vs UC, 2) age-targeted PEMs vs UC, and 3) age-targeted vs optimized PEMs. Primary analyses focused on the embedded trial; secondary analyses compared to 1) findings from the first part of the trial and 2) the full trial period. In the embedded trial, screening completion for PEMs recipients was significantly higher among screening adherent individuals (51.8% among optimized PEMs vs. 46.5% among UC) and adherent individuals >45 years of age (57.0% vs. 47.8%). In the first part of the trial PEMs were associated with lower screening completion (vs. UC) among participants with unknown screening history (RR:0.87, 95%CI:0.77,0.99). Age-targeting did not yield additional value beyond that achieved through optimization of PEMs. Optimizing PEMs through patient feedback proved effective in enhancing the impact of PEMs on screening completion for subgroups of patients, including those who were previously screening adherent and those adherent and >45 years of age.

INTRODUCTION

While cervical cancer screening has been instrumental in reducing the incidence and mortality of cervical cancer in the US over the past 40 years [6, 52, 53], multiple studies report that adherence to recommended screening declined from 2005 to 2019 [54, 55], with a significant increase in the number of individuals ages 30-65 reporting lack of knowledge as the primary reason for not receiving screening [21]. Additional lost screening was observed during the COVID-19 pandemic [56]. The impact of patient education materials (PEMs) on cervical cancer screening completion is not well known, particularly in the era of primary HPV screening.

PEMs can lead to significant improvement in health outcomes by changing health behaviors; written PEMs have been associated with behavior modification across a variety of health behaviors, including smoking [57], physical activity among cancer survivors [58], and colorectal, prostate, and cervical cancer screening [58–60]. A meta-analysis of 105 studies evaluating the effect of patient decision aids (a type of PEM) in people facing treatment or screening decisions-- including studies on colorectal and prostate cancer screening, influenza vaccination, and breast cancer treatment-- found the largest benefits of decision aids are better knowledge of options and outcomes and a more accurate perception of the likelihood of various outcomes, compared to usual care [61]. However, the effectiveness of patient education interventions may vary, with some leading to increased knowledge recall on a topic but failing to motivate behavioral change [62, 63].

To date, international data suggest that PEMs may be effective at increasing cancer screening uptake, but among which population(s) and in what format remains unclear [64]. Significant increases in screening uptake have been observed among individuals exposed to education materials compared to their peers receiving usual care (UC): a meta-analysis of five pooled international randomized controlled trials (RCT) found evidence that odds of screening were nearly 2.5 times higher in intervention than usual care groups (OR:2.46,95%CI:1.88,3.21), though what constituted usual care varied across studies [64]. Similar findings were observed in a cohort study in Ethiopia comparing cervical cancer screening PEMs and health education counseling to a control group that did not receive PEMs or counseling (adjusted OR:2.43,95%CI:1.58,2.90) [65]. A US-based trial evaluating the impact of education-based interventions on cervical cancer screening uptake in North Carolina measured the proportion of participants adherent to

risk-appropriate screening guidelines before and after mailing a physician letter and brochure on Pap tests; the mailing resulted in a significant increase (10.3%) in self-reported screening uptake [60]. However, null findings have been observed in several studies measuring the effectiveness of cancer education materials on screening uptake [66, 67]. A lack of association may be attributable to an inability to translate a patient's improvement in knowledge into subsequent changes in screening behavior; investigators studying the impact of prostate [68] and cervical [67] cancer education materials on screening uptake observed a significant difference in reported awareness of the importance of screening between intervention and control groups, but no significant difference in screening uptake.

Health education researchers have sought to increase the effectiveness of education materials through *tailoring* or *targeting* them to the intended audience, in which materials are personally relevant and worthy of active consideration [69, 70]. Qualitative analyses of HOME participants with HPV-positive home-based test results revealed that older individuals were more likely than their younger peers to exhibit surprise at positive results and have a low perceived risk for HPV, suggesting that targeted education materials focusing on persistent HPV infection may be of particular use among older people [14]. However, while much of the research comparing individualized to undifferentiated messaging regarding health behaviors typically shows tailoring to be more effective [71], some studies have found no difference [72–74]. An international meta-analysis of 57 randomized trials found evidence in support of targeted health communication across a host of health behaviors (e.g., physical activity, diet, mammography, seat belt use, Pap tests), but also indicated that several variables moderate the effect of targeting on health behavior change, including participant features (e.g., age, race), health behavior (e.g., cervical cancer screening), type of print material (e.g., brochure, clinic poster), and length of observation period following intervention [71]. Notably, the review determined that tailored print materials designed to persuade individuals to get a Pap test have been more effective than materials developed to encourage mammography, exercise, and smoking cessation, though only two studies on cervical cancer screening were included in this review.

Although PEMs are inherently designed to provide education, they can be viewed as a vehicle for disseminating information, facts, ideas, and (mis)perceptions that may be more/less motivating to a patient population. Designing PEMs to address known barriers may enhance their impact on patient

screening behaviors. In the HOME trial– a pragmatic RCT designed to evaluate the impact of mailed HPV self-sampling kits on screening completion among overdue individuals [8]– surveys conducted among intervention participants 6 months post-randomization showed significant knowledge gaps in HPV natural history and interpretation of HPV test results, with 82% of 235 respondents not knowing that HPV infection can clear on its own and 37% not knowing that HPV-negative results indicate a low risk of cervical cancer [75]. These results highlight the importance (and existing gap) of patient education that effectively increases knowledge about cervical cancer screening, particularly in settings with primary HPV testing. A rigorous analysis of the effect of education materials, including targeted materials, on screening completion is critical to inform US health systems, in part because targeting is inherently more expensive.

We previously reported that receipt of educational materials did not significantly impact cervical cancer screening completion among individuals enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer (STEP) trial [9]. Relative risks comparing Education to UC in STEP were 0.90 (95%CI:0.81,1.01) among individuals with unknown screening history, 0.99 (95%CI:0.87,1.13) among overdue patients, and 1.01 (95%CI:0.97,1.06) among individuals who were previously adherent and now due. Leveraging implementation science, we aimed to determine whether the impact of educational materials on cervical cancer screening can be increased through theory-driven, patient feedback-informed efforts. Given the mixed literature on tailoring and targeting, we also evaluated whether age-targeting education materials impacted screening completion and described whether any effect of age-targeting differed by screening history or age.

METHODS

The STEP trial

STEP was a parallel, investigator-blinded, pragmatic randomized clinical trial set in the KPWA patient population to evaluate the effectiveness of HPV self-sampling (HPV-SS) for increasing cervical cancer screening completion, and included individuals with previously up-to-date (adherent) and now due, overdue, or unknown cervical cancer screening histories [9]. Individuals were identified using KPWA administrative data as adherent, overdue, or having unknown screening history; through stratified randomization, individuals were assigned to one of four screening outreach interventions by screening

history group (Figure 2.1). Interventions were 1) UC (patient reminders and electronic health record [EHR] alerts), 2) Education (UC plus PEMs about screening), 3) Direct mail (UC plus PEMs plus a mailed HPV-SS kit), or 4) to Opt-In (UC plus PEMs plus the option to request an HPV-SS kit). Individuals overdue for screening were not randomized to the Opt-In intervention and those with unknown screening history were not randomized to Direct Mail. The institutional review board (IRB) of KPWA approved all study procedures. This analysis is restricted to patients randomized to the UC and Education arms.

STEP Patient Education Materials

The role of PEMs in STEP was threefold: 1) as a response to patient knowledge gaps identified in the HOME trial [14], including the importance of cervical cancer screening, key information on HPV's role in cervical cancer, and different screening strategies, 2) to provide patients with information on primary HPV screening, which had rolled out at KPWA six months prior to the start of STEP, and 3) to serve as an attention control to which the HPV-SS interventions could be compared (thus allowing estimation of the isolated impact of offering HPV-SS) [50].

STEP PEMs were packaged as an educational brochure. Intervention arm participants enrolled in the trial through early September 2021 ("Part I") received the original trial brochure (Appendix B). Broadly, the brochure focused on the importance of cervical cancer screening and recent updates to screening guidelines. The barriers to HPV testing identified in the HOME trial and addressed in the brochure are described in Table 2.1 and reflect knowledge and risk perception. The brochure was printed on a single sheet and then folded in half to form a booklet. The front page featured a stock photo and title, while the inside of the booklet was broken into four sections of text (each with a header phrased as a question, e.g., "What is HPV and how is it spread?"), a callout box featuring three relevant statistics, and another photo with a hypothetical patient quote. The back page featured a fifth section of text, another photo and patient quote, and printed reference websites.

Optimization and Targeting of PEMs Using Implementation Science and Patient Representative Feedback

From July through August 2020, we recruited 38 KPWA patients to participate in 8 virtual focus group discussions (FGD). Potentially eligible participants were identified using KPWA's EHR based on pre-defined subgroup characteristics: age (30-45 or 46-64 years) and cervical cancer screening history (previously adherent or overdue). Eligible individuals were mailed recruitment materials, including 1) an information sheet outlining study purpose, activities, risk and benefits and 2) an invitation letter detailing the focus of the study, when the virtual FGD would be held, and how to contact study staff. Study staff followed up the mailing with a telephone call, during which potential participants had the opportunity to ask questions and additional eligibility screening was conducted. If an individual was interested and eligible, they were scheduled for the FGD and received hard copy and electronic confirmation and materials, including preliminary prototypes of the outreach materials developed by the research team, who used causal pathway diagrams (CPDs) to clarify the putative mechanism to be activated by various sections of the PEM. These prototypes included comprehensive messaging options that addressed each of the key educational needs and known barriers identified in the HOME trial [8, 14] (Table 2.1). Prototypes reviewed in FGD leveraged implementation science CPDs developed in collaboration with faculty at the UW Optimizing Implementation in Cancer Control Center [76], and drew from the Health Belief Model [77], the National Academy of Medicine's dimensions of patient-centered care [78], and Epstein/Street's Patient Centered Communication Framework [79]. FGD participants provided feedback on layout, tone, and content of education materials, and each FGD had a distinct design task (Table 2.2). Participants were offered $80 to participate, with each session lasting two hours.

We employed a double coding process for FGD transcripts, ensuring reliability and consistency in the thematic analysis. Additionally, we utilized rapid qualitative analysis techniques to efficiently synthesize key findings [80], allowing for a thorough and expedited examination of the data and timely development of optimized and age-targeted PEMs. Key FGD findings included that PEMs need to clearly describe the relationship between HPV and cervical cancer and outline recent updates to screening guidelines (knowledge domain); additionally, PEMs should emphasize that HPV can persist for many years before progressing to cervical cancer and, thus, older individuals need to be screened to monitor cervical changes from infections they may have acquired when they were younger (perceived risk domain).

We used the Health Action Process Approach (HAPA) model [81] to theoretically inform and test the CPDs and, based on FGD learnings, further refine the pathways through which PEMs could target screening barriers and motivate action. The HAPA model is a theoretical framework that suggests that the adoption, initiation, and maintenance of health behaviors should be considered as a process that consists of both a *motivation* and *volition* phase (which includes planning [e.g., considering when a clinic appointment would fit in my schedule and learning about what the appointment entails], action [e.g., calling my doctor to schedule a screening or using the self-sampling kit], and maintenance phases [e.g., committing to regular screening based on recommended screening intervals]).

With fully developed CPDs and FGD themes in hand, we mapped all content (text and graphics) in the original brochure to CPD moderators, mechanisms, and barriers; where content did not map, it was marked as redundant or unnecessary. New content was generated with refinements to the FGD prototypes, informed by HAPA to optimize for possible behavior change. Following these revisions, materials were reviewed by KPWA communications and graphic design staff for further editing to ensure plain language and accessibility. This yielded an optimized, non-age-specific brochure designed to appeal to ages 30-64 (“optimized”). This process was then repeated for the age-targeted brochures (“age-targeted”). The age-targeted materials included two brochures with age-appropriate content: one for those ages 30-45 and another for ages 46-64. The age categories were selected once FGD feedback highlighted a difference in understanding of screening recommendations by HPV vaccination status. Based on current HPV vaccine eligibility guidelines [82], we selected a cut-point of 45 years, thus grouping nearly all individuals who could have received the HPV vaccine in the same subgroup. Final copies of all brochures (Appendices C, D, E) were submitted to the KPWA delivery system and, upon approval, to KPWA IRB. The process of optimizing the brochure prior to age-targeting its contents (and thus, creating a new non-age-specific baseline version) ensured comparisons between targeted and non-targeted materials would reveal solely the impact of targeting the materials.

STEP Trial: Setting, Participants, and Intervention

Study design, recruitment details, and results from the underlying clinical trial have been published previously [9, 50]. Briefly, between November 2020 and January 2022, 31,355 individuals were identified

using KPWA administrative data as eligible to be randomized to a STEP intervention. Eligible people were enrolled under a waiver of informed consent. Individuals were eligible to participate if they 1) had current KPWA insurance, 2) were current female sex, 3) had an intact cervix, 4) were between ages 30-64 years, 5) had a KPWA primary care physician, and 6) were due or overdue for screening or had an unknown screening history. Exclusion criteria were 1) current pregnancy, 2) need an English language interpreter (materials were in English only), 3) prior randomization to the intervention arm of the HOME trial [8], 4) had previously asked not to be contacted for research, or 5) an indication in EHR that the patient was not on a routine screening schedule. All eligible participants had to be paneled to a primary care practitioner because preventive care outreach is coordinated by primary care teams.

Cervical cancer **screening history** was defined as: 1) previously adherent and due now, or adherent (previously screened, due for screening in ≤3 months), 2) overdue (co-testing >5.25 years ago, Pap testing alone >3.25 years ago, or no Pap testing with continuous KPWA enrollment ≥3.25 years), or 3) unknown (no recorded screening and KPWA enrollment ≥6 months and <3.25 years).

Specifically, the **UC and Education interventions** were provision of:

1) **Usual care (UC):** At KPWA, UC includes patient outreach in the form of 1) mailed annual birthday letters with a list of applicable preventive services (including cervical cancer screening, if eligible, with dates of last and next due screening), and 2) “gap letters,” or correspondence sent 60 days before the patient’s screening due date (for adherent patients) and every 60 days for individuals with overdue or unknown screening history. UC also includes clinician-targeted EHR automated alerts for overdue patients, which persist until screening is completed [50].
2) **Education (PEMs):** UC + an education packet mailed one week after the “gap letter,” including: i) an introduction letter describing the study and the intent to determine whether education materials aid in understanding why cervical cancer screening is important, ii) a study information sheet including directions on how to “opt out”, and iii) an educational brochure about the importance of cervical cancer screening, key information on the role of HPV in cervical cancer, and different screening strategies. The educational brochure specifically addressed barriers to screening identified in the HOME trial [14] and described in detail below.

Embedded Trial Participants and Procedures

The embedded trial included all individuals enrolled in the STEP trial on or after September 14, 2021, who were randomized to receive either UC or Education. In Part I, all participants randomized to Education received the original brochure. In the embedded trial ("Part II"), participants in the Education arm were randomized to receive either an optimized brochure or an age-targeted brochure appropriate for their age group (≤45 or >45 years). All other study procedures remained unchanged from Part I through Part II.

Outcomes

The primary outcome was screening completion within six months post-randomization and was assessed using EHR data [9]. Participant characteristics at randomization were derived from EHR data, and outcome and covariate data were available for all participants, including those who did not return a kit or opted out of medical record review [50]. Care received outside of KPWA is captured in claims data.

Statistical Methods

For our primary analysis, we compared cervical cancer screening completion among those randomized to UC vs. Education according to the intention-to-treat principle, restricting to individuals enrolled during Part II of the trial. To control for the potential impact of kit receipt on screening completion, primary analyses were restricted to only those individuals randomized to UC and Education trial arms. First, we compared screening completion among recipients of 1) optimized PEMs to 2) UC, stratifying by A) screening history group (adherent, overdue, and unknown) and B) screening history and age group (e.g., adherent and ages >45 years). Second, we compared screening completion among recipients of 1) age-targeted PEMs to 2) optimized PEMs, stratifying by screening history and screening history + age. (Step 2 allowed us to estimate the overall effect of age-targeting materials.) In secondary analyses, we made these same comparisons in a) Part I of the trial, restricting to those enrolled in UC or Education and b) the full trial, restricting to those enrolled in UC or Education throughout STEP.

We used modified Poisson regression to estimate relative risk (RR) and risk difference of screening completion within 6 months for the Education groups relative to UC. We estimated the

difference in screening completion rates associated with 1) optimized PEMs relative to UC, 2) age-targeted PEMs relative to UC, and 3) age-targeted PEMs relative to optimized PEMs. Models were fit using generalized estimating equations with a working independence correlation structure and robust sandwich error estimation to account for clustering of participants with the same primary care clinician. Caution should be used when interpreting p-values in analysis results as age-stratified analyses and within-Education arm analyses (optimized vs. age-targeted) were not pre-specified in the study protocol. As the ratio of participants randomized to UC and Education arms differed by screening history, all analyses were stratified by screening history group.

Analyses were conducted using both R statistical software [83] and STATA version 15 [84].

RESULTS

Of the 31,355 individuals in the STEP trial, 12,142 were randomized to UC and 8854 were randomized to the education arm. Of those participants, 6677 (n= 3845 UC and n=2832 Education) were enrolled after the implementation of modified educational materials (September 2021) and thus were included in the embedded trial designed to test the effectiveness of age targeting education materials.

Of the 6677 randomized individuals included in the primary analyses of the embedded trial, 50 participants randomized to Education opted out of medical record review and thus data on their covariates is excluded (Table 2.3). Of the 6627 participants for whom we have access to demographic data, 2485 were screening adherent and now due (of which 1206 were randomized to UC and 1279 to Education), 2148 were overdue for screening (1709 were randomized to UC and 439 to Education), and 1994 had an unknown screening history (930 were randomized to UC and 1064 to Education). Because STEP was powered with the Education arm as the comparator group (vs. Direct Mail and Opt In), randomization ratios differed across screening history groups; for the overdue group, a smaller sample size in the Education arm was required compared to the other screening history groups.

Individuals with an unknown screening history averaged slightly younger (mean[SD] age, 43.0[10.2] years for both UC and Education participants) than screening adherent (46.1[10.2] for UC and 46.3[10.3] for Education) and overdue participants (47.1[10.2] for UC and 47.1[10.3] for Education). Across screening history groups, approximately two-thirds of participants with EHR data on race identified

as White. Most participants identified as non-Hispanic, reported no history of tobacco use, and scored zero on the Charlson Comorbidity Index. Among screening adherent and overdue participants, a higher proportion of adherent participants had been enrolled in their health plan for 10 or more years (30.8% vs. 17.6% of UC recipients, respectively), while a larger share of overdue participants receiving UC had been enrolled <3.25 years (35.0% overdue vs. 25.0% adherent). The remainder of trial participants—an additional 14,319 individuals enrolled prior to the implementation of modified education materials (n=8297 UC and n=5922 Education)—were included in secondary analyses. Demographic characteristics for participants enrolled in Part I were similar to those of participants enrolled in Part II (Supplemental Table 2.1).

Primary analysis

Screening completion in embedded trial recipients of Usual Care or Education

Screening completion was highest among screening adherent participants (ranging from 46.5% to 47.7% to 51.8% across randomization groups [UC, age-targeted PEMs, optimized PEMs, respectively]) and lower among overdue and unknown individuals (14.8% to 16.5% completion across groups). Among screening adherent individuals, screening completion rates were significantly higher in the optimized versus UC group (RR:1.11 [95% CI: 1.01,1.23]; absolute difference: 5.2% [95% CI: 0.4%,10.1%]). When we stratified by screening history and age, completion was significantly higher among recipients of optimized PEMs versus UC only for those who were adherent and >45 years of age (RR: 1.19 [95% CI: 1.05,1.35]; absolute difference: 9.2% [95% CI: 2.7%,15.8%]).

Secondary analyses

Screening uptake in Part I of the STEP trial, restricted to recipients of Usual Care or Education

In analyses restricted to STEP participants enrolled prior to the implementation of modified education materials, stratification by screening history revealed significant differences in completion by intervention among individuals with unknown screening history (RR: 0.87 [95% CI: 0.77,0.99]; absolute difference: -2.3% [95% CI: -4.5%,-0.1%]) (Table 2.5).

Screening uptake in the full trial, restricted to recipients of Usual Care or Education

In analyses that included all trial participants who received either UC or Education, screening uptake did not differ significantly by screening history (as reported in the main trial); further stratification by screening history and screening history plus age also yielded non-significant findings (Table 2.6).

DISCUSSION

In this trial embedded within a pragmatic randomized clinical trial, patient education materials were associated with higher cervical cancer screening rates compared with usual care among screening adherent participants and adherent individuals ages 46-64 years. No significant differences were observed when comparing the effect of age-targeted PEMs to non-age-specific PEMs. We compared these findings to those reported in the full STEP trial, in which screening rates among individuals who received PEMs vs. UC were not significantly different [9]. In the full trial, screening history plus age-stratified estimates were not calculated. Thus, our embedded trial analyses offer additional insight into the impact of theory-driven, patient feedback-informed PEMs on screening completion, including for patient subgroups.

To contextualize and increase interpretability of the embedded trial findings, we ran two additional analyses to present the findings from 1) Part I of the trial, during which the original brochure was in use and 2) the full trial, performing the stratified analyses that we evaluated for the embedded trial. In the embedded trial, the use of PEMs was positively associated with cervical screening among screening adherent individuals; this association was not observed in Part I or the full trial. It is likely screening adherent individuals are more likely than non-adherent patients to engage in a health behavior if prompted (given they have engaged in the behavior in the past), and it is possible the feedback-optimized PEMs sufficiently nudged these patients to action. In a trial evaluating print materials containing prostate cancer education, screening adherence was higher among individuals who believed early detection examination should be performed in the absence of symptoms (OR: 2.3 [95% CI: 1.3,4.0]) [85]. Thus, compelling print material may be sufficient in motivating to action patients who already believe in the value of preventive screening, as indicated by prior screening behavior.

In the embedded trial, optimized PEMs were also associated with higher screening completion compared to UC among adherent participants ages >45 years. This suggests the exercise of optimizing those materials through patient FGDs that test theory-driven prototypes may be beneficial in increasing the effectiveness of PEMs for this age group. Uptake of preventive health services among older adults—including influenza vaccination, mammograms, colonoscopies, and Pap tests—typically falls below recommended levels [86]. Less than 30% of adults ages 50-64 were up to date on core preventive screenings and immunizations in 2015 [87]. According to a 2020-2021 US Postal Service market research report, this age group is also the most likely to read and trust direct mail communications [88]; thus, older adults are perhaps most receptive and susceptible to the impact of mailed PEMs.

Notably, screening uptake among the UC group decreased slightly throughout the course of the STEP trial: the proportion of individuals randomized to UC who completed screening dropped from 27.8% in Part I to 25.5% during the embedded trial, while screening among those exposed to PEMs increased slightly from 30.2% to 31.4%. The decline in screening can be attributed primarily to lower completion among individuals with overdue and unknown screening histories, with the largest decrease (5.6%) observed among overdue participants ≤45 years of age (compared to 0.5% among adherent participants of the same age). It is possible this decrease in screening reflects the broader trend of declining screening rates throughout the COVID-19 pandemic, during which adherence to cervical screening within the US dropped by an estimated 15% [89]. Given the embedded trial took place later in the pandemic (September 2021 through January 2022), it is also possible individuals who avoided preventive services in the early pandemic faced scheduling delays and backlogs that plagued facilities as they re-opened for non-urgent appointments [90]. Therefore, the absolute rate of screening completion may be higher than what we observed in STEP in settings in which the COVID-19 pandemic is not a factor.

It is noteworthy that the UC group in the STEP trial received considerable outreach as part of KPWA's standard of care, including system-wide mailed birthday letters and gap letters outlining upcoming preventive services. Comparable studies frequently report UC or control groups in which less information on cervical cancer screening is shared and/or lower effort is made on behalf of the health system to encourage screening (i.e., through follow-up telephone calls, repeated mailings) [63]. It is likely that mailed PEMs may be more impactful in a health system in which the standard of care is less robust

and patients do not already receive system-wide preventive services mailings. However, the alternative is also possible: because KPWA patients regularly receive mailed preventive services correspondence, they may be more receptive to and willing to engage with it than patients who never receive screening-related mailings from their health system.

We hypothesized targeting PEMs by age would result in higher screening uptake compared to non-targeted PEMs. However, the embedded trial revealed there was no benefit of the age-targeted brochure relative to the optimized brochure, and among certain subgroups (screening adherent and adherent >45 years of age), the optimized brochure was more effective than the age-targeted brochure. These findings mirror those observed in a RCT in which patients were randomized to receive either a form letter containing generic cervical and breast cancer information, a tailored letter containing minimally tailored individualized risk factor information, or UC (no communication regarding screening services). While the form letter was associated with significantly higher cervical screening uptake relative to UC, the tailored letter was associated with decreased likelihood of cervical screening [91]. Findings such as these reflect what Kreuter et al. reported following a trial testing tailored vs. non-tailored weight loss PEMs: "good-fitting non-tailored materials" perform as well or better than tailored PEMs for several cognitive and behavioral outcomes [92]. Specifically, in cases where non-tailored materials draw on important behavioral constructs (i.e., speak to relevant barriers to behavior change), the difference in behavior change between the non-tailored and tailored groups may be minimal [92]. Thus, the optimized PEMs in our embedded trial were likely sufficient to encourage screening action; the fact they were designed with feedback collected through patient FGDs ensured a level of relevance that additional age-targeting did not meaningfully improve.

There was one notable inconsistency across our findings. In the first half of the trial, individuals with unknown screening history were less likely to screen when exposed to Education vs. UC; this association was not observed in the full trial and the trend reversed in the embedded trial (positive, though non-significant association between PEMs and screening). We considered the potential impact of age on screening completion in the unknown group: compared to the adherent and overdue groups, the mean age in the unknown group was younger (by 2.7 and 3.6 years, respectively, across the full trial). However, age-adjusted analyses showed no confounding by age (results not shown). Thus, it is more

likely that this finding is due to the fact that the unknown group consists of patients for whom we have less reliable data and an imperfect understanding of when it comes to eligibility and likelihood of engaging with STEP interventions. For example, individuals randomized to the unknown group may not yet have visited with a KPWA clinician; as such, our understanding of some patients is based entirely on the data collected during health system registration, which may not capture important details, including comfort with the English language, history of hysterectomy, etc. Given that approximately one quarter of participants at KPWA that were eligible for STEP had an unknown screening history, and that screening rates are lowest among this group [8], a better understanding of this subpopulation is essential for effective implementation of screening interventions.

Embedding a trial within STEP allowed us to compare the effectiveness on cervical screening uptake of PEMs broadly and age-targeted PEMs specifically. We were also able to draw comparisons between Part I of the trial and the embedded trial, thereby sharing findings on the impact of optimizing PEMs with feedback from patient FGD. STEP was strengthened by its pragmatic design, large sample size, and high degree of generalizability [9].

Limitations

PEMs were available only in English due to resource constraints, excluding non-English-speaking individuals, and thus results may not be generalizable to non-English speakers. STEP launched during the COVID-19 pandemic, and although routine screening resumed before STEP, screening behavior may still have been affected, with some participants avoiding in-clinic visits. Finally, to reduce any potential temporal confounding, we ideally would have simultaneously tested the original brochures disseminated during Part I of the trial against the optimized and age-targeted PEMs.

CONCLUSIONS

Educational materials administered in a pragmatic RCT set in a US healthcare system increased cervical cancer screening among subgroups of patients, including those >45 years of age and screening adherent, relative to usual care. Optimizing PEMs by leveraging implementation science including theory-driven, patient-informed data strengthened this positive association and also motivated screening

adherent individuals who received PEMs to screen at significantly higher rates. Age-targeting of PEMs did not yield additional value beyond the screening uptake achieved through optimization.

Figure 2.1. STEP embedded trial scheme. Within each arm that received education materials (all but Usual Care), participants were randomized to receive either a non-age-specific ("optimized") brochure (that incorporated focus group discussion feedback), or an age-tailored brochure (that emphasized age-relevant information and targeted age-specific barriers to care-seeking). We evaluated the effect of age-tailoring (vs. optimizing) education materials on screening completion.

Eligible individuals ages 30-64 who remained to be randomized into the STEP trial following implementation of the modified PEMs

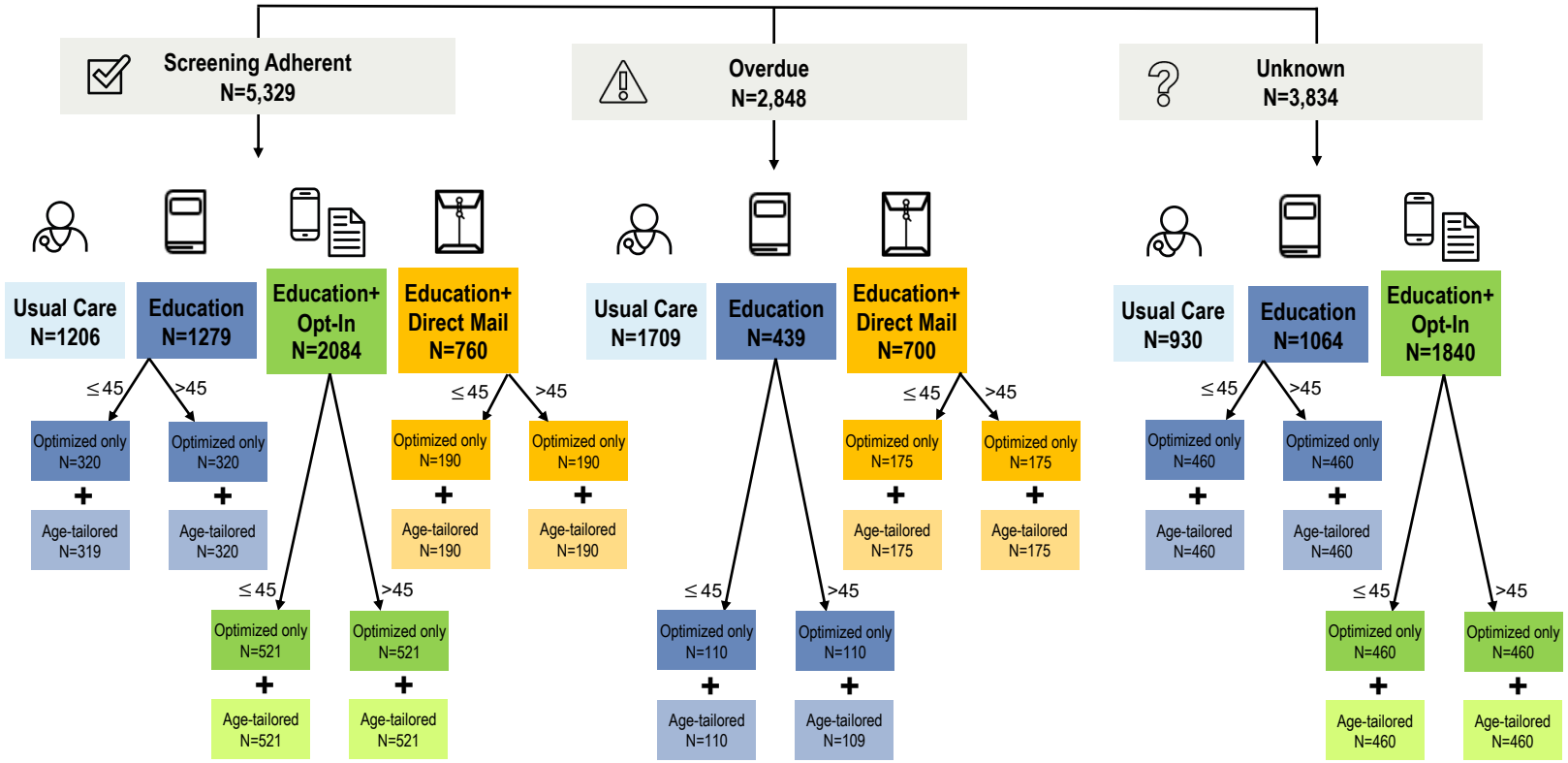


Table 2.1. Constructs addressed in educational materials disseminated to non-usual care participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial, 2021-2022, Seattle, WA

Target Barrier	Mechanism	Known Barrier Described	Expected Moderators	Proposed Messages to Enhance in Brochure Optimization
Knowledge about HPV, its role in cervical cancer, and new screening modalities	Educating, learning, understanding	Gaps in understanding: 1) the role of HPV in cervical cancer, 2) the role of HPV testing in cervical cancer screening, 3) HPV self-testing is a new, acceptable screening option 4) interpretation of HPV test results, including management of different types of positive results, and how Pap and HPV tests are used together in management decisions	1) Age: Older individuals are less knowledgeable about screening and the role of HPV in cervical cancer than younger individuals 2) Screening History: People overdue for screening are less knowledgeable about screening and the role of HPV in cervical cancer than screening adherent people	1) Role of HPV in cervical cancer, 2) How HPV and Pap screening tests work alone and in conjunction, 3) Information on new guidelines, 4) HPV self-testing is an acceptable screening option, 5) Information on next steps after possible HPV self-sampling results
Perceived risk of cervical cancer	Correcting misbeliefs, increasing relevance, developing concern	Individuals do not think they are at risk for cervical cancer, particularly if monogamous or not sexually active	1) Age: Older individuals are less likely to perceive themselves at risk for HPV and may be less inclined to think that they need HPV-based screening for cervical cancer 2) Screening History: Perceived risk for cervical cancer is lower in overdue versus adherent individuals	1) All individuals with a cervix are at risk for cervical cancer, 2) HPV can persist for many years before progressing to cancer, 3) Older individuals need to be screened to monitor cervical changes from infections they may have acquired when they were younger

Table 2.2. Design and objectives of the 8 Focus Group Discussions conducted in the Kaiser Permanente Washington patient population as part of the STEP embedded trial, July-August 2020.

Group number	Subpopulations recruited	Objective [1]
1, 2	N/A	*Co-design with the research team a universal version of the outreach materials, which could be sent to all participants, regardless of age or screening status * Select and refine messaging, as well as on the design of the materials themselves—providing feedback on layout, tone, etc. to make the materials appealing and easily understandable to the target population * The overall design of the materials created by this group will be used for the messaging developed in all subsequent groups
3, 4	Age: equal number of younger (30-45) and older (46-64) year-old individuals	* Develop 2 versions of the outreach material messaging specifically tailored to younger and older individuals * Work in age-based subgroups with members of the research team to develop messaging that is most persuasive and compelling to the respective age group
5, 6	Screening history: equal number of adherent and overdue individuals	* Develop 2 versions of outreach materials that include messaging tailored to screening status * Work in screening status-based subgroups with members of the research team to develop messaging that is most persuasive and compelling to the respective age group
7, 8	Age and screening history: ≥2 participants from each subpopulation	* This group will be seeded with the materials developed in Groups 3-6 and will be tasked with coming up with 4 different versions of outreach materials that tailor both on age and on screening status * This group will have at least 2 individuals from each subpopulation and will iteratively revise materials created in previous groups to construct versions that are best suited to the 4 age/screening status-based subpopulations

[1] All design groups had freedom to select, prioritize, order, and edit messaging to best suit the target subpopulation(s), but all resulting materials included messaging related to each of the four screening barriers identified in Table 2.1.

Table 2.3. Study population baseline characteristics, by screening history (N= 6627 participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial after implementation of modified education materials who received either Usual Care or Education materials), 2021-2022, Seattle, WA

	Screening Adherent		**Overdue**		**Unknown**	
	N=2485		N=2148		N=1994	
	Usual Care n=1206	Education n=1279	Usual Care n=1709	Education n=439	Usual Care n=930	Education n=1064
Age, mean(sd)	46.1(10.2)	46.3(10.3)	47.1(10.2)	47.1(10.3)	43.0(10.2)	43.4(10.2)
Age at randomization, y	**Frequency, Percent n (%)**		**Frequency, Percent n (%)**		**Frequency, Percent n (%)**	
30-34	185 (15.3)	204 (15.9)	248 (14.5)	63 (14.4)	263 (28.3)	268 (25.2)
35-39	198 (16.4)	210 (16.4)	234 (13.7)	62 (14.1)	151 (16.2)	201 (18.9)
40-44	189 (15.7)	163 (12.7)	224 (13.1)	57 (13.0)	127 (13.7)	151 (14.2)
45-49	161 (13.3)	185 (14.5)	238 (13.9)	68 (15.5)	117 (12.6)	115 (10.8)
50-54	146 (12.1)	177 (13.8)	266 (15.6)	60 (13.7)	110 (11.8)	118 (11.1)
55-59	177 (14.7)	175 (13.7)	251 (14.7)	59 (13.4)	83 (8.9)	124 (11.7)
60-64	150 (12.4)	165 (12.9)	248 (14.5)	70 (15.9)	79 (8.5)	87 (8.2)
Race [1]						
White	830 (68.8)	872 (68.2)	1029 (60.2)	251 (57.2)	324 (34.8)	363 (34.1)
Black or African American	58 (4.8)	67 (5.2)	73 (4.3)	25 (5.7)	37 (4.0)	39 (3.7)
Asian	152 (12.6)	156 (12.2)	188 (11.0)	57 (13.0)	105 (11.3)	96 (9.0)
Other [2]	119 (9.9)	121 (9.5)	139 (8.1)	36 (8.2)	39 (4.2)	57 (5.4)
Unknown	*47 (3.9)*	*63 (4.9)*	*280 (16.4)*	*70 (15.9)*	*425 (45.7)*	*509 (47.8)*
Ethnicity						
Non-Hispanic	1045 (86.7)	1067 (83.4)	1180 (69.0)	304 (69.2)	138 (14.8)	160 (15.0)
Hispanic	72 (6.0)	89 (7.0)	85 (5.0)	22 (5.0)	35 (3.8)	47 (4.4)
Unknown	*89 (7.4)*	*123 (9.6)*	*444 (26.0)*	*113 (25.7)*	*757 (81.4)*	*857 (80.5)*
Body mass index						
≤24.9 [3]	386 (32.0)	408 (31.9)	297 (17.4)	71 (16.2)	113 (12.2)	121 (11.4)
25-29.9	343 (28.4)	333 (26.0)	296 (17.3)	55 (12.5)	102 (11.0)	103 (9.7)
30-34.9	213 (17.7)	228 (17.8)	223 (13.0)	61 (13.9)	79 (8.5)	77 (7.2)
35-39.9	104 (8.6)	129 (10.1)	134 (7.8)	41 (9.3)	49 (5.3)	63 (5.9)
≥40	113 (9.4)	127 (9.9)	163 (9.5)	42 (9.6)	44 (4.7)	62 (5.8)
Unknown	*47 (3.9)*	*54 (4.2)*	*596 (34.9)*	*169 (38.5)*	*543 (58.4)*	*638 (60.0)*

Tobacco use						
Current	74 (6.1)	48 (3.8)	489 (28.6)	135 (30.8)	498 (53.5)	582 (54.7)
Former	281 (23.3)	890 (69.6)	822 (48.1)	197 (44.9)	306 (32.9)	340 (32.0)
Never	806 (66.8)	253 (19.8)	231 (13.5)	76 (17.3)	63 (6.8)	77 (7.2)
Unknown	*45 (3.7)*	*88 (6.9)*	*167 (9.8)*	*31 (7.1)*	*63 (6.8)*	*65 (6.1)*
Length of health plan enrollment, y						
< 3.25	301 (25.0)	343 (26.8)	599 (35.0)	159 (36.2)	930 (100)	1064 (100)
3.25 to <5	169 (14.0)	169 (13.2)	439 (25.7)	92 (21.0)		
5 to <10	365 (30.3)	365 (28.5)	371 (21.7)	124 (28.2)		
≥10	371 (30.8)	402 (31.4)	300 (17.6)	64 (14.6)		
Length of time overdue, y						
Not overdue	1206 (100)	1279 (100)				
< 3			616 (36.0)	159 (36.2)		
3+			500 (29.3)	129 (29.4)		
No prior screen			593 (34.7)	151 (34.4)		
Unknown			*0*	*0*	*930 (100)*	*1064 (100)*
Participant's US Census tract, overall US CDC/ATSDR Social Vulnerability Index						
<21.1	391 (32.4)	443 (34.6)	493 (28.8)	115 (26.2)	241 (25.9)	265 (24.9)
21.1 to <41.2	370 (30.7)	344 (26.9)	499 (29.2)	154 (35.1)	248 (26.7)	291 (27.3)
41.2 to <64.8	266 (22.1)	316 (24.7)	439 (25.7)	110 (25.1)	245 (26.3)	314 (29.5)
≥ 64.8	179 (14.8)	176 (13.8)	278 (16.3)	60 (13.7)	196 (21.1)	194 (18.2)
Participant's US Census tract, median household income						
median household income, median (IQR), $	89,792 (69,389-109,496)	90,446 (70,575-110,739)	85,779 (65,878-106,186)	86,806 (65,878-107,566)	83,285 (61,360-104,728)	85,295 (65,051-106,126)
Travel time from home to primary care clinic, min						
<10	378 (31.3)	416 (32.5)	568 (33.2)	152 (34.6)	385 (41.4)	441 (41.4)
10 to <20	460 (38.1)	480 (37.5)	615 (36.0)	160 (36.4)	324 (34.8)	375 (35.2)
20 to <30	185 (15.3)	196 (15.3)	266 (15.6)	64 (14.6)	121 (13.0)	133 (12.5)
≥30 or unknown [4]	183 (15.2)	187 (14.6)	260 (15.2)	63 (14.4)	100 (10.8)	115 (10.8)
Charlson Comorbidity Index score						
0	1024 (84.9)	1045 (81.7)	1515 (88.6)	385 (87.7)	852 (91.6)	979 (92.0)
1	125 (10.4)	151 (11.8)	117 (6.8)	41 (9.3)	57 (6.1)	56 (5.3)

2	38 (3.2)	52 (4.1)	42 (2.5)	8 (1.8)	12 (1.3)	15 (1.4)
≥3	19 (1.6)	31 (2.4)	35 (2.0)	5 (1.1)	9 (1.0)	14 (1.3)

[1] Race and ethnicity from EMR data per patient self-report at usual care patient registration via preset multi-select categorical options, with "other" allowing free text entry. The study variable was programmatically categorized into the displayed categories by coding any multiple selections as "more than one race". Manual coding of the "other" category was precluded because IRB approval did not allow individual-level data for those opting out of study participation.

[2] Race "Other" includes "Native American/Alaska native", "Hawaiian/Pacific Islander", ">1 Race", and "Other". The collapse of these distinct racial groups was the result of the inability to report the small cell sizes (<5 observations) that resulted in the "unknown" group.

[3] Due to small cell sizes (<5 observations) in the underweight category, BMI levels for underweight (<18.5) and healthy weight (18.5-24.9) were collapsed.

[4] Due to small cell sizes (<5 observations) in the "unknown" travel time category, BMI levels for "≥30 minutes" and "unknown" travel time were collapsed.

Table 2.4. Screening uptake and differences in screening rates among participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial. Restricted to participants enrolled after the implementation of modified education materials who received either Usual Care or Education alone (N=6677)

	Screening uptake rate					Difference in screening uptake rates [2]					
			Education materials								
	Usual Care (N=3845)		Optimized (N=1411)		Age-targeted [1] (N=1421)	Optimized vs. Usual Care (Referent = UC)	Optimized vs. Usual Care (Referent = UC)	Age-targeted [1] vs. Usual Care (Referent = UC)	Age-targeted [1] vs. Usual Care (Referent = UC)	Age-targeted [1] vs. Optimized (Referent= Optimized)	Age-targeted [1] vs. Optimized (Referent = Optimized)
	N	Screening completion (n (%))	N	Screening completion (n (%))	N	Screening completion (n (%))	Relative Risk (95% Confidence Interval)	Absolute risk difference (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	Absolute risk difference (95% Confidence Interval)	Relative Risk (95% Confidence Interval)	Absolute risk difference (95% Confidence Interval)
Stratified by screening history												
Adherent	1206	561 (46.5%)	657	340 (51.8%)	656	313 (47.7%)	1.11 (1.01, 1.23)	5.2 (0.4, 10.1)	1.03 (0.93, 1.13)	1.2 (-3.3, 5.7)	0.92 (0.83, 1.03)	-4.0 (-9.5, 1.4)
Overdue	1709	272 (15.9%)	219	33 (15.1%)	226	34 (15.0%)	0.95 (0.67, 1.33)	-0.8 (-6.0, 4.3)	0.95 (0.68, 1.31)	-0.9 (-5.8, 4.1)	1.00 (0.64, 1.56)	0.0 (-6.7, 6.7)
Unknown	930	148 (15.9%)	535	79 (14.8%)	539	89 (16.5%)	0.93 (0.69, 1.24)	-1.1 (-5.5, 3.2)	1.04 (0.82, 1.32)	0.6 (-3.3, 4.5)	1.12 (0.84, 1.48)	1.7 (-2.6, 6.1)

Stratified by age group and screening history												
Adherent and ≤45	597	270 (45.2%)	315	145 (46.0%)	313	141 (45.0%)	1.02 (0.88, 1.17)	0.8 (-5.7, 7.4)	1.00 (0.86, 1.15)	-0.2 (-6.8, 6.5)	0.98 (0.83, 1.16)	-1.0 (-8.7, 6.7)
Adherent and >45	609	291 (47.8%)	342	195 (57.0%)	343	172 (50.1%)	1.19 (1.05, 1.35)	9.2 (2.7, 15.8)	1.05 (0.92, 1.20)	2.4 (-4.1, 8.8)	0.88 (0.77, 1.01)	-6.9 (-14.1, 0.4)
Overdue and ≤45	758	119 (15.7%)	100	18 (18.0%)	100	17 (17.0%)	1.15 (0.73, 1.81)	2.3 (-5.8, 10.4)	1.08 (0.69, 1.70)	1.3 (-6.4, 9.0)	0.94 (0.52, 1.73)	-1.0 (-11.6, 9.6)
Overdue and >45	951	153 (16.1%)	119	15 (12.6%)	126	17 (13.5%)	0.78 (0.48, 1.28)	-3.5 (-9.8, 2.9)	0.84 (0.52, 1.36)	-2.6 (-9.2, 4.0)	1.07 (0.56, 2.05)	0.9 (-7.6, 9.4)
Unknown and ≤45	568	106 (18.7%)	320	49 (15.3%)	322	54 (16.8%)	0.82 (0.58, 1.16)	-3.3 (-8.9, 2.2)	0.90 (0.68, 1.19)	-1.9 (-6.9, 3.1)	1.10 (0.76, 1.58)	1.5 (-4.3, 7.3)
Unknown and >45	362	42 (11.6%)	215	30 (14.0%)	217	35 (16.1%)	1.20 (0.78, 1.85)	2.4 (-3.3, 8.0)	1.39 (0.90, 2.14)	4.5 (-1.5, 10.6)	1.16 (0.73, 1.84)	2.2 (-4.7, 9.1)

[1] The age-targeted brochure contained the optimized content plus language specific to age group (≤45, >45).
[2] Accounting for clustering by Primary Care Provider.

Table 2.5. Screening uptake and differences in screening rates among participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial. Restricted to participants enrolled prior to the implementation of modified education materials who received either Usual Care or Education alone (N=14,319)

	Screening uptake rate				**Difference in screening uptake rates [1]**	
	Usual Care (N=8297)		Education materials (N=6022)		Education vs. Usual Care	
	N	Screening completion (n (%))	N	Screening completion (n (%))	Relative Risk (95% Confidence Interval)	Absolute risk difference (95% Confidence Interval)
Stratified by screening history						
Adherent	2465	1164 (47.2%)	2647	1232 (46.5%)	0.99 (0.93, 1.04)	-0.7 (-3.3, 2.0)
Overdue	3779	764 (20.2%)	963	197 (20.5%)	1.01 (0.87, 1.17)	0.2 (-2.8, 3.3)
Unknown	2053	377 (18.4%)	2412	387 (16.0%)	0.87 (0.77, 0.99)	-2.3 (-4.5, -0.1)
Stratified by age group and screening history						
Adherent and ≤45	1165	531 (45.6%)	1265	572 (45.2%)	0.99 (0.91, 1.08)	-0.4 (-4.2, 3.5)
Adherent and >45	1300	633 (48.7%)	1382	660 (47.8%)	0.98 (0.91, 1.06)	-0.9 (-4.8, 2.9)
Overdue and ≤45	1656	351 (21.2%)	426	96 (22.5%)	1.06 (0.86, 1.31)	1.3 (-3.3, 6.0)
Overdue and >45	2123	413 (19.5%)	537	101 (18.8%)	0.97 (0.79, 1.18)	-0.6 (-4.5, 3.2)
Unknown and ≤45	1172	246 (21.0%)	1374	260 (18.9%)	0.90 (0.78, 1.05)	-2.1 (-5.1, 1.0)
Unknown and >45	881	131 (14.9%)	1038	127 (12.2%)	0.82 (0.66, 1.03)	-2.6 (-5.7, 0.4)

[1] Accounting for clustering by Primary Care Provider.

Table 2.6. Screening uptake and differences in screening rates among participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial. Restricted to participants who received either Usual Care or Education alone (N=20,996)

	Screening uptake rate				**Difference in screening uptake rates [1]**	
	Usual Care (N=12,142)		Education materials (N=8854)		Education vs. Usual Care	
	N	Screening completion (n (%))	N	Screening completion (n (%))	Relative Risk (95% Confidence Interval)	Absolute risk difference (95% Confidence Interval)
Stratified by screening history						
Adherent	3671	1725 (47.0)	3960	1885 (47.6)	1.01 (0.97, 1.06)	0.6 (-1.6, 2.8)
Overdue	5488	1036 (18.9)	1408	264 (18.8)	0.99 (0.87, 1.13)	-0.1 (-2.5, 2.3)
Unknown	2983	525 (17.6)	3486	555 (15.9)	0.90 (0.81, 1.01)	-1.7 (-3.5, 0.2)
Stratified by age group and screening history						
Adherent and ≤45	1762	801 (45.5)	1893	858 (45.3)	1.00 (0.93, 1.07)	-0.1 (-3.4, 3.1)
Adherent and >45	1909	924 (48.4)	2067	1027 (49.7)	1.03 (0.96, 1.09)	1.3 (-1.9, 4.4)
Overdue and ≤45	2414	470 (19.5)	626	131 (20.9)	1.07 (0.90, 1.28)	1.5 (-2.1, 5.1)
Overdue and >45	3074	566 (18.4)	782	133 (17.0)	0.92 (0.77, 1.11)	-1.4 (-4.6, 1.7)
Unknown and ≤45	1740	352 (20.2)	2016	363 (18.0)	0.89 (0.78, 1.01)	-2.2 (-4.7, 0.2)
Unknown and >45	1243	173 (13.9)	1470	192 (13.1)	0.94 (0.78, 1.13)	-0.9 (-3.3, 1.6)

[1] Accounting for clustering by Primary Care Provider.

Supplemental Table 2.1a. Study population baseline characteristics, by screening history (N= 14,319 participants enrolled in the Self-Testing options in the Era of Primary HPV screening for cervical cancer [STEP] trial prior to implementation of modified education materials who received either Usual Care or Education materials), 2021-2022, Seattle, WA

	Screening Adherent		**Overdue**		**Unknown**	
	N=5043		N=4372		N=4444	
	Usual Care n=2465	Education n=2578	Usual Care n=3779	Education n=953	Usual Care n=2053	Education n=2391
Age, mean(sd)	46.6(10.5)	46.5(10.4)	47.4(10.1)	47.3(10.2)	44.0(10.3)	44.1(10.3)
Age at randomization, y	**Frequency, Percent n (%)**		**Frequency, Percent n (%)**		**Frequency, Percent n (%)**	
30-34	398 (16.1)	403 (15.6)	533 (14.1)	138 (14.5)	503 (24.5)	570 (23.8)
35-39	372 (15.1)	392 (15.2)	489 (12.9)	112 (11.8)	355 (17.3)	413 (17.3)
40-44	335 (13.6)	387 (15.0)	514 (13.6)	146 (15.3)	270 (13.2)	324 (13.6)
45-49	332 (13.5)	323 (12.5)	516 (13.7)	133 (14.0)	245 (11.9)	290 (12.1)
50-54	314 (12.7)	340 (13.2)	573 (15.2)	133 (14.0)	237 (11.5)	303 (12.7)
55-59	348 (14.1)	355 (13.8)	591 (15.6)	144 (15.1)	240 (11.7)	264 (11.0)
60-64	366 (14.8)	378 (14.7)	563 (14.9)	147 (15.4)	203 (9.9)	227 (9.5)
Race [1]						
White	1748 (70.9)	1797 (69.7)	2444 (64.7)	627 (65.8)	800 (39.0)	934 (39.1)
Black or African American	115 (4.7)	123 (4.8)	176 (4.7)	37 (3.9)	94 (4.6)	120 (5.0)
Asian	285 (11.6)	271 (10.5)	337 (8.9)	83 (8.7)	231 (11.3)	256 (10.7)
Other [2]	202 (8.2)	250 (9.7)	307 (8.1)	84 (8.8)	151 (7.4)	175 (7.3)
Unknown	*115 (4.7)*	*137 (5.3)*	*515 (13.6)*	*122 (12.8)*	*777 (37.8)*	*906 (37.9)*
Ethnicity						
Non-Hispanic	2147 (87.1)	2211 (85.8)	2824 (74.7)	730 (76.6)	713 (34.7)	806 (33.7)
Hispanic	156 (6.3)	180 (7.0)	176 (4.7)	47 (4.9)	104 (5.1)	117 (4.9)
Unknown	*162 (6.6)*	*187 (7.3)*	*779 (20.6)*	*176 (18.5)*	*1236 (60.2)*	*1468 (61.4)*
Body mass index						
≤24.9 [3]	798 (32.4)	767 (29.8)	704 (18.6)	161 (16.9)	252 (12.3)	303 (12.7)
25-29.9	640 (26.0)	672 (26.1)	619 (16.4)	190 (19.9)	247 (12.0)	255 (10.7)
30-34.9	430 (17.4)	457 (17.7)	497 (336)	146 (15.3)	165 (8.0)	204 (8.5)
35-39.9	235 (9.5)	281 (10.9)	336 (8.9)	80 (8.4)	91 (4.4)	124 (5.2)
≥40	243 (9.9)	260 (10.1)	375 (9.9)	80 (8.4)	132 (6.4)	135 (5.6)
Unknown	*119 (4.8)*	*141 (5.5)*	*1248 (33.0)*	*296 (31.1)*	*1166 (56.8)*	*1370 (57.3)*
Tobacco use						
Current	127 (5.2)	151 (5.9)	311 (8.2)	66 (6.9)	110 (5.4)	582 (54.7)

Former	490 (19.9)	541 (21.0)	547 (14.5)	143 (15.0)	173 (8.4)	340 (32.0)
Never	1725 (70.0)	1749 (67.8)	1725 (45.6)	454 (47.6)	690 (33.6)	77 (7.2)
Unknown	*123 (5.0)*	*137 (5.3)*	*1196 (31.6)*	*290 (30.4)*	*1080 (52.6)*	*65 (6.1)*
Length of health plan enrollment, y						
< 3.25	768 (31.2)	782 (30.3)	1237 (32.7)	301 (31.6)	2053 (100)	2391 (100)
3.25 to <5	287 (11.6)	294 (11.4)	851 (22.5)	204 (21.4)		
5 to <10	635 (25.8)	718 (27.9)	928 (24.6)	244 (25.6)		
≥10	775 (31.4)	784 (30.4)	763 (20.2)	204 (21.4)		
Length of time overdue, y						
Not overdue	2465 (100)	2578 (100)				
< 3			1630 (43.1)	410 (43.0)		
3+			1075 (28.4)	265 (27.8)		
No prior screen			1074 (28.4)	278 (29.2)		
Unknown			*0*	*0*	*2053 (100)*	*2391 (100)*
Participant's US Census tract, overall US CDC/ATSDR Social Vulnerability Index						
<21.1	687 (27.9)	705 (27.3)	972 (25.7)	221 (23.2)	463 (22.6)	524 (21.9)
21.1 to <41.2	615 (24.9)	657 (25.5)	985 (26.1)	244 (25.6)	463 (22.6)	587 (24.6)
41.2 to <64.8	644 (26.1)	632 (24.5)	925 (24.5)	250 (26.2)	521 (25.4)	595 (24.9)
≥ 64.8	519 (21.1)	584 (22.7)	897 (23.7)	238 (25.0)	606 (29.5)	685 (28.6)
Participant's US Census tract, median household income						
median household income, median (IQR), $	88,333 (69,066-108,542)	88,971 (68,750-108,160)	87,200.5 (66,607-107,950)	87,227 (68,700-104,835)	84,313 (64,038-106,773)	84,172 (63,979-108,029)
Charlson Comorbidity Index score						
0	2035 (82.6)	2169 (84.1)	3333 (88.2)	824 (85.6)	1871 (91.1)	2227 (93.1)
1	276 (11.2)	267 (10.4)	276 (7.3)	89 (9.3)	119 (5.8)	114 (4.8)
2	102 (4.1)	92 (3.6)	106 (2.8)	23 (2.4)	43 (2.1)	27 (1.1)
≥3	52 (2.1)	50 (1.9)	64 (1.7)	17 (1.8)	20 (1.0)	23 (1.0)

[1] Race and ethnicity from EMR data per patient self-report at usual care patient registration via preset multi-select categorical options, with "other" allowing free text entry. The study variable was programmatically categorized into the displayed categories by coding any multiple selections as "more than one race". Manual coding of the "other" category was precluded because IRB approval did not allow individual-level data for those opting out of study participation.

[2] Race "Other" includes "Native American/Alaska native", "Hawaiian/Pacific Islander", ">1 Race", and "Other". The collapse of these distinct racial groups was the result of the inability to report the small cell sizes (<5 observations) that resulted in the "unknown" group.

[3] Due to small cell sizes (<5 observations) in the underweight category, BMI levels for underweight (<18.5) and healthy weight (18.5-24.9) were collapsed.

Chapter 3: A Value of Information analysis across patient subgroups in the STEP trial

ABSTRACT

The cost-effectiveness of home-based cervical cancer screening via HPV self-sampling (HPV-SS) has been demonstrated in both international and U.S. settings. However, cost-effectiveness analyses that do not consider heterogeneity in the patient population may lead health system decisionmakers to implement interventions that generate suboptimal outcomes. Analyses that generate subgroup-specific estimates of cost-effectiveness can identify opportunities to capture additional benefits through strategic implementation of interventions. We extended the results of a randomized controlled trial evaluating four cervical cancer screening approaches (STEP) by conducting subgroup-level economic analyses, including subgroup-level Value of Information (VOI) analyses to determine whether organizing a population according to relevant characteristics yields the greatest possible value for decisionmakers. We leveraged STEP participant electronic health record data to divide the study population by 1) patient age, 2) travel time from patient home to clinic, and 3) whether the patient had a clinic visit in the 12 months prior to study enrollment. We produced subgroup-specific incremental cost-effectiveness ratios (ICERs) to represent the relative cost-effectiveness of screening approaches. We then calculated the Expected Value of Perfect Information (EVPI) and Expected Value of Sample Information (EVSI) for each screening approach comparison, indicating the value associated with reducing parameter uncertainty in the cost-effectiveness estimate. We assumed a willingness to pay threshold of $200 and a beneficial population of 20,000. Among individuals previously adherent and overdue for cervical cancer screening, EVPI and EVSI estimates of $0 indicated there was not utility in additional research to reduce uncertainty in cost-effectiveness estimates. Among individuals with unknown screening history, VOI estimates were non-zero, but low, suggesting value for health systems in capturing and validating screening-relevant data on these individuals. Subgroup-level analyses produced comparable findings; additionally, when subgrouping by age, mailed HPV-SS interventions were more cost-effective among individuals ≥45 years vs. younger participants.

INTRODUCTION

Cervical cancer screening is associated with substantial global reductions in cervical cancer incidence and mortality [16], as most cervical cancers are preventable by addressing high-risk human papillomavirus (HPV) precancers detected during screening [93]. Recent declines in US screening adherence preceded and were exacerbated by the COVID-19 pandemic, with a decrease among individuals aged 21-65 from 86% to 72% between 2005 and 2021 [6, 21]. HPV-only (primary HPV) screening can be conducted via home-based testing because, unlike clinic-based Papanicolaou (Pap) tests, individuals can collect their own samples for HPV testing [48]. Home-based testing addresses well-documented screening barriers [1, 20] and can mitigate the impact of scheduling constraints on both patients and healthcare systems. Prior US-based [8, 94] and international research [13] has established the feasibility [8] and cost-effectiveness (vs. usual care) [94] of mailing home-based HPV kits to individuals overdue for screening.

As cervical cancer screening interventions are optimized for use across patient populations, evaluation of expanded approaches is critical. The Self-Testing options in the Era of Primary HPV screening for cervical cancer (STEP) trial evaluated home-based HPV screening among individuals enrolled at Kaiser Permanente Washington (KPWA) with varied screening histories (previously adherent and due now, overdue, and unknown history) and measured the impact on cervical cancer screening uptake of several screening approaches, including 1) usual care (UC), 2) education materials about screening, 3) education materials plus direct mail of a home HPV kit, and 4) education materials and invitation to Opt In to receive a home HPV kit [50]. Investigators determined that directly mailing kits significantly improved screening uptake among adherent and overdue individuals compared to receipt of UC (62% and 36% uptake vs. 47% and 19%, respectively) [9]. With the addition of costing data, investigators evaluated the cost-effectiveness (CE) of each screening approach; CE analysis results revealed directly mailing kits is both less costly and delivers better health outcomes (i.e., dominates) for adherent individuals and is cost-effective for overdue patients and those with unknown screening history as well [95].

CE analyses are designed to inform policy decision making; in a healthcare setting, CE analyses are instrumental in addressing whether a health system should implement a new intervention or maintain

a current program (“usual care”) [96]. However, CE analyses are based on current information and subject to inherent uncertainty (e.g., distribution around screening costs and kit uptake rates). Intuitively, making decisions based on uncertain evidence may lead to suboptimal policy recommendations, and may be more costly and less beneficial than anticipated. Ideally, additional research would be conducted to provide comfort to decisionmakers by reducing or eliminating this uncertainty; however, this additional research can be costly in both time and money. Value of information (VOI) analyses-- conducted alongside CE analyses as a quantitative basis for future research recommendations-- are designed to help policymakers address whether a decision (e.g., whether or which screening intervention to implement) should be made on existing information or if additional research to reduce uncertainty is worthwhile [97]. To be worthwhile, additional research should lead to a greater benefit (e.g., a higher rate of screening completion), and this increase in benefit should not be outweighed by the cost to conduct the research and any cost associated with waiting to make the decision [97].

The most used VOI measure for informing research and policy decisions is the expected value of perfect information (EVPI), or the value of additional information to resolve uncertainty in all parameters that inform a decision [98]. The expected value of a given research project can be quantified as the expected reduction in the probability of making the wrong decision (i.e., choosing to implement an intervention that is cost-effective based on current information, but, once implemented, proves to be the wrong choice) multiplied by the average consequence of being wrong (i.e., the opportunity loss associated with the decision) [97]. A very low EVPI indicates there is little value in conducting additional research and a decision could confidently be made based on existing evidence, while a higher EVPI suggests additional research is worthwhile; in the case of a significant EVPI, the value of reducing uncertainty by conducting another study with a specified sample size can be estimated using the expected value of sample information (EVSI). Thus, VOI analyses can inform various health policy decisions, including 1) whether to adopt an intervention/program or wait for additional evidence and 2) how to prioritize future research based on what studies (and of what sample size) are likely to yield the greatest return on research investment.

Even if population-level cost-effectiveness estimates indicate intervention cost-effectiveness, failure to account for heterogeneity in the study population may result in a suboptimal net benefit (i.e.,

leave net benefit on the table). Thus, economic evaluations that do not include subgroup analyses run the risk of obscuring key differences between groups with different characteristics, possibly leading to inequitable distribution of resources [99–101]. Structuring a subgroup analysis can be complicated by several limitations [99], but investigators that thoughtfully consider participant heterogeneity can use it to determine whether additional research could resolve uncertainty and help explain variability in costs and outcomes, possibly through strategic targeting of subgroups [100]. Ultimately, the purpose of additional research is to facilitate the design of programs that offer the greatest net benefit. Thus, patient characteristics on which subgroup analyses are conducted must be characteristics policymakers could feasibly and ethically use to tailor health interventions. For example, while the benefits and uptake of at-home cervical cancer screening may vary among participants with differing body mass indexes (BMI), it is unlikely a health system would offer patients different screening options based on BMI alone. In VOI analyses, subgroup EVPIs indicate whether all groups should be included in future research or whether research could effectively focus on particular subgroups. The methodology of layering a structure of patient demographics-based subgrouping over a VOI analysis is not well represented in the literature; however, a reduction in decision uncertainty achieved by strategically focusing future research on patient subgroups could be invaluable for health policymakers.

VOI analyses are not yet commonly conducted in U.S.-based study populations, with investigators citing complexity of calculations and lack of awareness about the approach as the two main barriers to broader application [102]. To date, the concept of CE analysis itself remains less popular in the US than in other regions [96, 101–104], in part due to Americans' hesitancy to accept rationing or limits in the delivery of health care, though health policymakers assert that some form of prioritization is unavoidable [96]. Thus, while the cost-effectiveness of home-based HPV testing has been evaluated [105, 106], to our knowledge, a VOI analysis that incorporates policy-relevant, subgroup-level stratification has not yet been conducted in the context of cervical cancer screening research. Our ability to organize the STEP study sample by subgroup enables us to explore whether integrating certain variables with specified stratifications yields additional value for healthcare systems implementing targeted cervical cancer screening interventions.

We aim to 1) describe the utility of extending the results of the STEP CE analysis with a VOI analysis, 2) highlight sources of patient heterogeneity in the STEP population and describe the ways in which this heterogeneity may impact cost-effectiveness estimates, and 3) conduct and interpret VOI analyses, contextualizing these findings for health system policymakers seeking to implement home-based cervical cancer screening interventions. As part of this analysis, we calculated both cervical cancer screening history-specific (adherent, overdue, and unknown) and subgroup-specific CE and VOI estimates to explore whether organizing a population by subgroup may yield the greatest value for health system policymakers.

METHODS

Setting, Participants, and Intervention

Study design, recruitment details, and results from the underlying clinical trial have been published previously [9, 50]. Briefly, eligible people with an intact cervix were identified using electronic health record (EHR) and administrative claims data and enrolled under a waiver of informed consent. Individuals were eligible to participate in STEP if they 1) were enrolled in KPWA, 2) were current female sex, 3) were between ages 30-64 years, 4) had a KPWA primary care physician (all patients are assigned one at health plan enrollment unless they receive care outside of KPWA), and 5) were due or overdue for screening or had an unknown screening history. EHRs were reviewed for indications of exclusion criteria, including 1) current pregnancy, 2) flag for an English language interpreter (materials were in English only), 3) prior randomization to the intervention arm of the HOME trial [8], 4) prior request to not be contacted for research, or 5) a non-routine screening schedule.

Cervical cancer **screening history** was defined as: 1) previously adherent and due now (previously screened, due for screening in ≤3 months), 2) overdue (Pap and HPV co-testing >5.25 years ago, Pap testing alone >3.25 years ago, or no Pap testing with continuous KPWA enrollment ≥3.25 years), or 3) unknown (no recorded screening and KPWA enrollment ≥6 months and <3.25 years).

Eligible individuals were allocated weekly to a STEP randomization group, stratified by screening history [11]. Groups were provision of: **1) Usual care (UC):** patient reminders and EHR clinician notifications; **2) Education:** UC + a mailed education packet; 3) **Direct Mail:** UC + Education + a direct

mail HPV-SS kit; and **4) Opt In:** UC + Education + information on how to order an HPV-SS kit, delivered one week later via mail. Adherent individuals were randomized to all four groups. Overdue individuals were not randomized to the Opt In approach and individuals with unknown history were not randomized to Direct Mail. The institutional review board (IRB) of KPWA approved all study procedures. If kits were not returned within three weeks, study staff made up to three reminder calls to participants, consistent with KPWA standard of care. Specimens were tested and results documented in the EHR and reported and followed up on per usual care [9].

Value of Information Analysis

To build on the recent findings of the STEP CE analysis [95], we conducted a VOI analysis. Fundamentally, a VOI analysis helps us understand whether the value of additional information (with which we can make decisions with greater confidence) outweighs its cost. In the context of the STEP trial, a VOI can be used to guide health system decisionmakers in determining whether to implement direct mailing of at-home cervical cancer screening kits broadly or whether it is worth investing in collecting additional information about potential subgroups to reduce uncertainty before making the implementation decision. STEP CE analysis results revealed direct mailing of home-based kits was cost-effective for screening adherent and overdue individuals when compared to UC [95]; the expected payoff for directly mailing kits (Option B) was greater than for UC (Option A). In the STEP CE analysis, investigators calculated Incremental Cost-Effectiveness Ratios (ICERs) to describe the difference in effect between Option B and Option A relative to the difference in cost between B and A. ICERs were then compared to a range of willingness to pay (WTP) thresholds, which represent the amount a health system is prepared to pay to achieve one cervical cancer screening; interventions with ICERs below the WTP threshold are cost-effective relative to the control.

While ICERs are a practical and established means of describing cost-effectiveness, for individual health systems wishing to evaluate the expected payoff of an intervention relative to usual care, the incremental net benefit (INB [Eq.1])—simply another way of stating CE analysis results—describes cost-effectiveness in terms of the system's own WTP threshold.

Incremental Net Benefit = (WTP threshold * E_T - C_C) – (WTP threshold * E_C - C_C) [Eq.1]

where: E_T = mean outcome (e.g., cervical cancer screening uptake) per participant in the intervention arm, E_C = mean outcome per participant in the control arm, C_T = mean cost of intervention per participant in the intervention arm, C_C = mean cost of intervention per participant in the control arm, and WTP threshold = amount a health system is prepared to pay to achieve one cervical cancer screening.

Thus, in the context of STEP (across a range of WTP thresholds [95]), the INB of mailing a kit was positive based on the current information that informed the STEP CE analysis, and the recommendation for KPWA and similar private health systems would be in favor of directly mailing kits for these screening history groups. However, inherent in these findings is a level of uncertainty that stems from variability in screening costs and completion rates. It is therefore possible the INB is truly negative; if this is the case, KPWA would lose money and/or screening completions ("benefit") by choosing the direct mail option. The EVPI generated through a VOI analysis represents the expected gain from eliminating the uncertainty that decisionmakers face when making decisions based solely on current information.

Figures 3.1 and 3.2 below, first developed by Wilson in his description of VOI analysis [97], illustrate the fundamental utility of VOI analysis and can be applied to the context of the STEP trial to further explain the process through which CE analysis findings are extended through VOI analysis. In Figure 3.1, the blue line is the distribution of the INB (the expected payoff associated with choosing direct mailing of kits vs. education materials); this comes from the CE analysis and is based on our current understanding of screening completion rates and costs. In this example, the mean INB is approximately $400. Based on CE analysis results, it is likely the INB is positive, and the decision should be made to adopt direct mailing. The likelihood the INB is negative is represented by the red shaded area. The more uncertain our understanding of INB is following the STEP CE analysis, the larger the red area will be. The amount the health system would lose if they adopted direct mailing is represented by the black line, or the loss function. In the event the INB is negative, the loss is equal to the value of the INB. For example, if the INB is 10£, the loss is 0£-- the decision to adopt direct mailing was 'correct', even though the benefit was less than the CE analysis predicted. However, if the INB is -$200, the loss is equal to $200-- the health

system invested in an intervention that did not deliver greater benefit than usual care and missed out on $200 of potential benefit (in the form of cost savings and/or increased screening).

Figure 3.2 illustrates the role of the VOI analysis. Suppose future research (Trial X) could be done to reduce some of the uncertainty inherent in the STEP CE analysis and displayed in Figure 3.1—this additional information would tighten the distribution of the INB and reduce the likelihood of making the 'wrong' decision. Figure 3.2 features the same distribution of INB illustrated in Figure 3.1 (blue line), while the red line indicates the likely distribution of INB given what we know from STEP data and now with the new information from Trial X. The shaded green area represents the expected reduction in probability of loss that a VOI analysis quantifies for decisionmakers (also known as the EVPI).

Figure 3.1. The blue line represents the distribution of Incremental Net Benefit (INB; expected payoff of Option B – Option A), which intuitively includes values above and below the mean INB estimated from trial data. In the event the INB is truly negative, the loss function (black line) indicates the loss incurred if Option B is adopted. The red shaded area represents the likelihood the INB is negative.

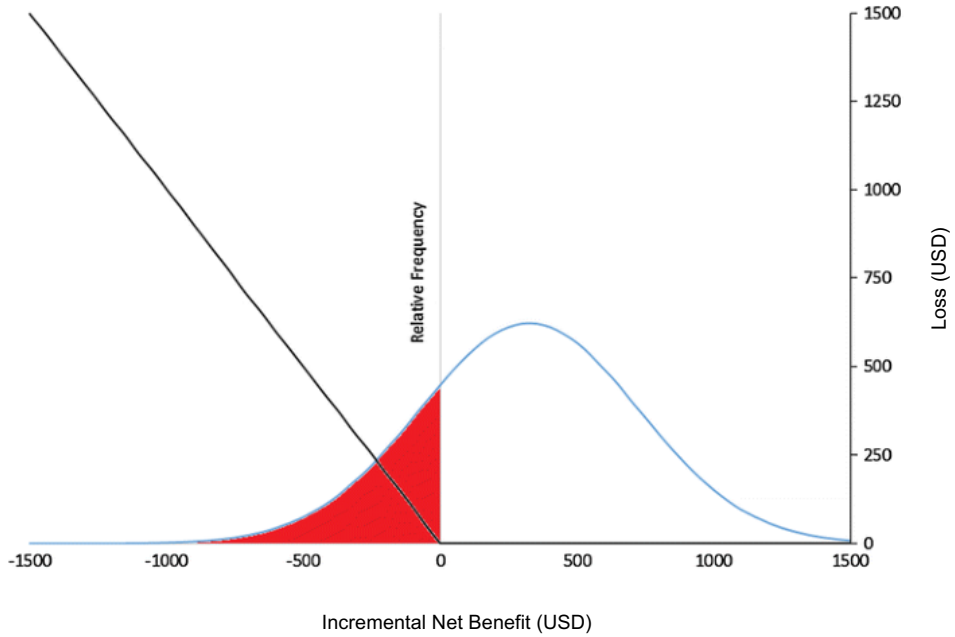
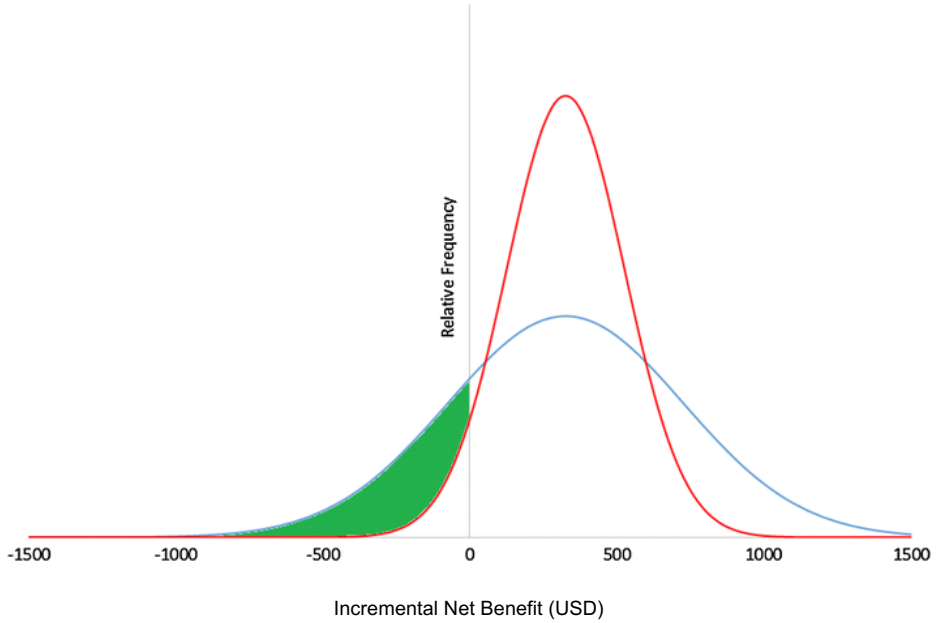


Figure 3.2. The 'tighter' distribution of INB resulting from additional data collected as part of future research (red line), when compared with the original INB distribution (blue line), reveals the expected reduction in probability of loss associated with conducting future research (green shaded area).



Outcomes

The primary STEP trial outcome was screening completion within six months after randomization defined as 1) in-clinic screening, 2) kit return with negative or HPV16-positive or HPV18-positive results, or 3) kit return with in-clinic Pap testing for other high-risk HPV-positive or unsatisfactory results. Screening completion was assessed using EHR and claims data. The primary outcome of the VOI was the EVPI; conceptually, this represents the potential gain health systems will realize through reduced parameter uncertainty. The secondary outcome was the EVSI, or the expected gain from sample information that stems from a future research study with a pre-specified sample size.

Cost Measurement

Screening intervention costs were defined as the value of resources used to implement the trial's mailed HPV kit program and were measured from the healthcare system perspective in US dollars. Intervention cost data were extracted from expense reports, KPWA's cost management database, and external sources (e.g., 2022 Medicare Physician Fee Schedule) [107]. Visit costs were estimated across two

dimensions for a total of four cost bases: 1) KPWA- or Medicare-based and 2) a wellness visit (i.e., primary care appointment to manage a comprehensive prevention plan) or a Pap-only visit. These dimensions captured cost differences between private and public funders as well as differences in the clinical context of Pap procedures. We used Current Procedural Technology codes to develop cost estimates [108].

Statistical Analysis

We calculated VOI statistics analytically, assuming normality amongst parameters, as is common for economic analyses conducted alongside clinical trials [97]. Using the approach published by E Wilson [97], we calculated both screening history-specific (adherent, overdue, and unknown) and subgroup-specific EVPI estimates. Wilson's approach utilizes an estimate of INB, and thus requires pre-specification of a WTP value. Based on acceptability curves generated as part of the STEP CEA [95], we elected to use a WTP threshold of $200 per completed cervical cancer screening; in sensitivity analyses, we varied this threshold from $1 to $75,000. Assumptions regarding the size of population that would benefit from implementation of the intervention with higher net benefit ("beneficial population") were based on the estimated annual number of screen-eligible individuals at KPWA. Regression analyses to estimate parameters used in CE and VOI analyses were conducted in Stata [84]. VOI analyses were performed in Excel [97, 109].

Typically, VOI analyses are conducted to compare two alternatives. We therefore structured our analyses such that we created dichotomous scenarios between STEP groups. We calculated EVPI for each of the five pair-wise comparisons below ("intervention comparisons"); for each comparison, we estimated the EVPI for each of the four cost-bases (KPWA wellness, KPWA Pap only, Medicare wellness, and Medicare Pap only). Analyses included all trial participants within a screening history group randomized to the specified screening approach:

1) Adherent:
    a. Direct Mail vs. UC
    b. Opt In vs. UC
    c. Direct Mail vs. Opt In

2) Overdue
    a. Direct Mail vs. UC
3) Unknown:
    a. Opt In vs. UC

We omitted the Education group from analyses based on findings that comparisons between Education and UC showed no significant relative risks and small absolute differences, regardless of screening history [9].

Concept

Subgroup Analyses

We identified three variables for use in the subgroup analyses by identifying patient characteristics 1) associated with established differences in cervical cancer screening uptake [21, 110–112] and 2) on which health policy makers could realistically and ethically target and optimize distribution of novel screening interventions. For the purposes of our analysis, characteristics also needed to be identified via EHR data, as covariate data was extracted from EHRs.

Namely, the characteristics we evaluated were: 1) age, 2) travel time from participant's home to primary care clinic (as a proxy for screening access), and 3) attending a primary care or Obstetrician/Gynecologist (OBGYN) visit in the one year prior to study enrollment (as a proxy for care utilization).

For each of the subgroup analyses, we used the following approach:

1) We evaluated how inclusion of the subgroup variable in the regression model changed the incremental cost-effectiveness ratios (ICERs) for each comparison of interventions (e.g., Opt In vs. UC), among screening history group (e.g., adherent), utilizing the KPWA wellness cost basis. This cost basis was utilized to increase generalizability of results for private health systems.
2) We subsetted the data using the subgroup variable (e.g., age). We began with the least granular approach of generating two subpopulations using a binary version of the subgrouping variable; for example, we collapsed the age variable into two groups of <45 years and ≥45 years. This cutoff

splits the population (ages 30-64 years) roughly in half, and is also groups nearly all individuals who could have received HPV vaccination in one subgroup (<45 years) [82].

3) We estimated the net benefits of Intervention A and Intervention B (i.e., Opt In and UC) using the intervention cost and effect data among each of the two subgroups. We compared the incremental net benefit (INB) (e.g., benefit of Opt In – benefit of UC) for each subgroup to the INB among the entire population for that intervention comparison.
4) Where meaningful differences in INB existed between subgroups, we returned to the full dataset and generated three subpopulations (e.g., age groups of 30-44, 45-54, and 54-64 years). We then used these subgroups to generate and compare INBs for relevant intervention comparisons.
5) We generated the EVPI and EVSI among each subgroup using Wilson's approach [97], under a WTP threshold of $200 per completed screen and assuming a beneficial population of 20,000. We compared these VOI estimates across subgroups.

RESULTS

Cost Effectiveness Analysis

The 31,355 individuals randomized in the STEP trial included 13,356 (40.8%) individuals who were screening adherent, 8,682 (26.5%) overdue for screening, and 10,733 (32.8%) with unknown screening history. Among screening adherent participants, the Direct Mail approach clearly dominated all other screening strategies [95]. Among overdue participants, Direct Mail generated an additional completed screen (relative to UC) at a cost ranging from $21.74 to $62.50 depending on cost basis and visit type. Among participants with an unknown screening history, inviting patients to opt into receiving a mailed kit dominated UC in three of four cost basis/visit type scenarios (except for Medicare Pap only).

Value of Information Analysis

Among screening adherent individuals, the incremental net benefit of Direct Mail vs. UC was $99.58; the Opt In intervention had an INB of $26.59 relative to UC and Direct Mail had an INB of $72.99 relative to Opt In (Figure 3.3). Among overdue participants, the INB of Direct Mail vs. UC was $37.72 (Figure 3.4).

Individuals with an unknown screening history had an INB of $7.97 when comparing Opt In to UC (Figure 3.5).

Among screening-adherent and overdue individuals, under a WTP threshold of $200 per screen and with a beneficial population of 20,000, all EVPI estimates were zero (Table 3.1). EVPI estimates for the comparisons among individuals with unknown screening history were all non-zero, and ranged from $529 to $10,286, depending on cost basis.

EVSI estimates for adherent and overdue screening groups were $0 for all intervention comparisons and across all cost bases, assuming 3000 observations per trial arm (Table 3.1). Among the unknown screening history group, EVSI ranged from $18 to $4841, depending on cost basis.

Subgroup Analyses

The distribution of baseline characteristics of the three variables for which we generated subgroups (age, travel time, and healthcare utilization) are presented in Table 3.2, by cervical cancer screening history and randomization group. Individuals with unknown screening history trended slightly younger than adherent and overdue individuals, and a slightly higher proportion lived <20 minutes (vs. ≥20 minutes) from a KPWA clinic compared to adherent and overdue participants. Approximately two-thirds of adherent individuals had attended at least one visit with a primary care or OBGYN provider in the 12 months prior to STEP randomization, compared to roughly one-third of individuals with overdue or unknown screening histories. Table 3.3 features screening completion rates and unadjusted relative risk estimates with 95% confidence intervals by subgroup (e.g., risk of screening for Direct Mail vs. UC recipients, among adherent individuals living <20 minutes away from a clinic). Broadly, the likelihood of screening was significantly higher among intervention vs. control participants across nearly all subgroups for adherent and overdue participants, with screening risks higher for older vs. younger participants, those living ≥20 minutes vs. <20 from a KPWA clinic, and those with no recorded clinic visit vs. ≥1 visit in the 12 months prior to STEP enrollment.

<u>AGE</u>

Screening adherent

The incremental net benefit among individuals ≥45 years of age was consistently higher than the non-age-specific estimate (and, intuitively, the INB for participants <45 years of age was below the non-age-specific estimate) across all three intervention comparisons (Table 3.4, Figure 3.3). For example, in the comparison of Direct Mail vs. UC, while the non-age-specific INB was $99.58, the INB among individuals ≥45 years of age was $109.43 and the INB among those <45 years of age was $86.53. This trend held for both the Direct Mail vs. UC and Opt In vs. UC comparisons when age was evaluated as a three-group variable (30-39, 40-49, 50-64 years of age); estimates of net benefit were higher among older individuals (40+ years of age) and lowest among younger individuals (30-39 years of age).

Subgroup-specific ICERs indicated greater cost-effectiveness of both the Opt In and Direct Mail interventions (relative to UC) among the older age group (≥45 years) versus the younger age group (<45 years) (Table 3.4). Assuming a cost basis of a KPWA wellness visit, ICERs in the younger age group ranged from $-354.24 (Opt In vs. UC) to $-528.20 (Direct Mail vs. Opt In) per completed screen. (In the context of these analyses, negative ICERs indicate lower mean costs and higher mean screening rates in the intervention group relative to the comparator.) Among participants ≥45 years of age, ICERs ranged from $-485.10 (Direct Mail vs. Opt In) to $-524.67 (Opt In vs. UC). Broadly, Direct Mail dominated all other interventions, as baseline (non-age-specific) ICERs suggested [95]. Among individuals <45 years of age, for the comparison of Opt In to UC, the EVPI was $9. All other EVPI and EVSI estimates among adherent individuals of both age groups were zero.

Overdue

The INB of Direct Mail vs. UC was higher among older overdue individuals compared to younger participants ($43.18 for >45 years and $29.06 for ≤45 years) (Table 3.5, Figure 3.4). When three age groups were used, INB was highest among the oldest individuals ($43.31 among ages 50-64) and lowest among the youngest ($24.71 among ages 30-39).

Among participants <45 years of age, Direct Mail generated an additional completed screen (relative to UC) at a cost of $20.71 (Table 3.5). Among participants ≥45 years of age, Direct Mail was cost saving (ICER $-50.62). The EVPI among younger individuals was $2 and EVSI was zero. Among older individuals, both EVPI and EVSI were zero.

Unknown

Among those with unknown screening history, younger individuals achieved a higher INB with Opt In compared to UC ($9.28 for ≥45 years of age vs. $6.39 for <45 years of age) (Table 3.6, Figure 3.5). This difference appears to be driven by a relatively low INB among the oldest age group ($4.27 among ages 50-64) and a higher INB among those ages 40-49 years ($9.99).

Among participants <45 years of age, Opt In generated an additional completed screen (relative to UC) at a cost of $1826.75 (Table 3.6). Among participants ≥45 years of age, Opt In was cost saving (ICER $-159.10). The EVPI among younger individuals was $1758 and EVSI was $346. Among older individuals, both EVPI and EVSI were higher: EVPI was $6307 and EVSI was $2589.

TRAVEL TIME TO CLINIC

Screening adherent

The INB among individuals living <20 minutes from a KPWA clinic was consistently higher than the INB among individuals living farther away (≥20 minutes) (Table 3.4). For example, in the comparison of Opt In to UC, the INB among individuals living closer was $30.01, while the INB among those living ≥20 minutes away was $19.40 (the non-location-specific INB was $26.59).

Subgroup-specific ICERs indicated greater cost-effectiveness of both the Opt In and Direct Mail interventions (relative to UC) among the group living <20 minutes from a clinic versus those living farther away (Table 3.4). Assuming a cost basis of a KPWA wellness visit, ICERs in the <20 minutes group were $-812.33 (Opt In vs. UC) and $-561.07 (Direct Mail vs. UC) per completed screen, indicating lower costs and increased screening completion in the intervention groups. Among participants living ≥20 minutes from a clinic, ICERs were $-88.57 (Opt In vs. UC) and $-416.00 (Direct Mail vs. UC). Among individuals living ≥20 minutes from a clinic, for the comparison of Opt In to UC, the EVPI was $181 and the EVSI was $25. All other EVPI and EVSI estimates among adherent individuals of both travel time groups were zero.

Overdue

The INB of Direct Mail vs. UC was higher among overdue individuals living ≥20 minutes from a clinic compared to those living <20 minutes away ($41.59 for ≥20 minutes vs. $36.66 for <20 minutes) (Table 3.5). When stratifying by travel time, Direct Mail was cost-saving for overdue participants living <20 minutes away (ICER $-33.88) and those living ≥20 minutes away (ICER $-12.60). The EVPI and EVSI for both groups were zero.

Unknown

Among those with unknown screening history, individuals living <20 minutes from a clinic achieved a higher INB with Opt In vs. UC ($8.74 vs. $5.62 among those living ≥20 minutes away). Among participants <20 minutes away, Opt In generated an additional completed screen (relative to UC) at a cost of $2059.21 (Table 3.6). Among participants ≥20 minutes away, Opt In generated an additional completed screen for $15.35. The EVPI among individuals <20 minutes away was $806 and EVSI was $70. Among those living ≥20 minutes away, both EVPI and EVSI were higher: EVPI was $20,785 and EVSI was $13,327.

HEALTHCARE UTILIZATION

Screening adherent

In the comparisons of Direct Mail vs. UC and Direct Mail vs. Opt In, the INB was higher among individuals who had attended a primary care or OBGYN visit in the 12 months prior to trial randomization (≥1 visit) compared to those who had not (no visit) (Table 3.4). For example, in the comparison of Direct Mail vs. UC, the INB among individuals with ≥1 visit was $104.88 and the INB among those with no visit was $98.28. For the comparison of Opt In vs. UC, the INB was comparable across visit groups (difference of $0.23).

Subgroup-specific ICERs indicated greater cost-effectiveness of the Direct Mail intervention (relative to UC and Opt In) among those with ≥1 visit vs. those with no visit (Table 3.4). Assuming a cost basis of a KPWA wellness visit, ICERs in the ≥1 visit group were $-603.92 (Direct Mail vs. UC) and $-765.62 (Direct Mail vs. Opt In) per completed screen. Among participants with no visit, ICERs were $-377.41 (Direct Mail vs. UC) and $-275.87 (Direct Mail vs. Opt In). In the comparison of Opt In vs. UC, the

intervention was cost-effective among individuals with no visit and with ≥1 visit; the EVPI for this comparison was $2 among those with no visit and $0 among those with ≥1 visit. All other EVPI and EVSI estimates among adherent individuals of both visit groups were zero.

Overdue

The INB of Direct Mail vs. UC was higher among those with ≥1 visit compared to those with no visit ($48.91 for ≥1 visit vs. $31.79 for no visit) (Table 3.5). Direct Mail was cost-saving for overdue participants with no visit (ICER $-17.27) and those with ≥1 visit (ICER $-44.35). The EVPI and EVSI for both groups were zero.

Unknown

Among those with unknown screening history, individuals with ≥1 visit achieved a higher INB with Opt In vs. UC ($9.06 vs. $7.50 among those with no visit). Among participants with no visits, Opt In generated an additional completed screen (relative to UC) at a cost of $2123.97 (Table 3.6). Among participants with ≥1 visit, Opt In was cost saving (ICER $-176.38). The EVPI among individuals with no visits was $1652 and EVSI was $7841. Among those with ≥1 visit, both EVPI and EVSI were lower: EVPI was $256 and EVSI was $3850.

DISCUSSION

We conducted trial-wide and subgroup-level value of information analyses using data from a cervical cancer screening trial evaluating innovative, home-based screening interventions. For individuals either previously adherent or overdue for cervical cancer screening, assuming a willingness to pay threshold of $200 per completed screen and a beneficial population of 20,000 patients, VOI estimates (EVPI and EVSI) were zero. Estimates for unknown screening history individuals were non-zero, but low. It is unlikely a private health system, equipped with these findings, would allocate research dollars to further evaluate these screening strategies among adherent and overdue patients. Rather, health systems can rely on the recommendations made using current information in the STEP trial's cost-effectiveness analysis: direct mail of HPV-SS kits is cost-effective among these screening populations. Regarding

patients with unknown screening histories, health systems may benefit from collecting and validating additional data on these patients such that they may be classified as either adherent or overdue.

Our approach to this analysis was based broadly on that which Espinoza et al. laid out [100], and it may help contextualize our findings—particularly for screening adherent and overdue individuals-- to draw comparisons between our approach and theirs. Briefly, we selected subgroups 1) for which there are established differences in cervical cancer screening completion (age [21, 110], access to a screening site [111, 112], and healthcare utilization within the last year [110]), and 2) that could ethically and feasibly be used to guide allocation of screening interventions from a health system perspective. Espinoza et al. exemplified their proposed approach to subgroup analyses with a case study: namely, they evaluated the subgroup-specific cost-effectiveness of an invasive treatment for acute coronary syndrome. In this case study, the WTP threshold was $24,714/QALY (Quality-Adjusted Life Year) and the beneficial population was 556,723 patients, given a 10-year time horizon and annual incidence of nearly 60,000 eligible patients. This is quite different from our WTP threshold of $200/screening and beneficial population of 20,000 individuals eligible to screen each year, but in line with assumptions seen in published literature. For example, a CEA done on HPV-SS vs. clinic-based sampling among Norwegian patients utilized a WTP threshold of $55,000/QALY [113]; in another VOI among Australian patients, the WTP threshold varied from $25,000 to $75,000/QALY [102]. Beneficial populations for HPV-SS trials conducted outside of the U.S., in countries with national screening programs, would be much larger than our estimate of 20,000, appropriate for a private health system. However, in sensitivity analyses, a WTP threshold of $75,000 per completed screen did not meaningfully impact EVPI or EVSI estimates for overdue and screening adherent individuals (all but one estimate remained $0), and the same was observed when manipulating the beneficial population in VOI calculations for these screening history groups.

Thus, while our analysis varied from Espinoza's approach across these key metrics, these differences are unlikely to explain the null findings of our VOI analyses in the adherent and overdue screening groups. It is perhaps more likely that the Direct Mail intervention is overwhelmingly cost-effective for these groups, such that there is not additional utility in reducing the small amount of uncertainty that informs our current state of knowledge. In Espinoza's example case, the findings from the

baseline CE analysis showed the invasive strategy was, on average, not cost-effective (at a WTP of £20,000/QALY and ICER of £21,960/QALY). The STEP CE analysis, though, was conclusive: for adherent individuals, Direct Mail is less expensive and delivers higher screening completion rates compared to UC, and for overdue individuals and those with unknown screening histories, Direct Mail and Opt In, are cost-effective, respectively [95].

The one screening group for which VOI estimates were consistently non-zero was among individuals with unknown screening histories. The low mean INB values among this group (relative to adherent and overdue history groups), combined with non-zero EVPI estimates, suggest that additional information on these patients (whether through future research or-- more realistically from a health system perspective-- additional data collection) is warranted. We can refer again to Figure 3.2 (see *Methods*): for the unknown screening group relative to adherent and overdue, the mean INB for every intervention comparison (and among every subgroup) is both closer to zero and the distribution surrounding it is wider. Thus, this is the group for which "tightening" that distribution delivers the highest value for a health system. This may be intuitive: the unknown screening history population—approximately 25% of KPWA patients eligible to be randomized to the STEP trial—is the group with the greatest inherent uncertainty. Some of the individuals with unknown screening history have never been seen by a KPWA provider; the data collected during health system registration is what informs their "unknown" status, and it may be incomplete or incorrect. To effectively target individuals within this subpopulation with cervical cancer screening interventions, it is incumbent upon a health system to invest in collecting and validating screening-relevant data (i.e., through incentive-based programs, targeted outreach, etc.).

Subgroup-specific value of information estimates (subgroup EVPIs) indicate whether all groups should be included in future research or whether research could effectively focus on particular subgroups. We conducted three subgroup analyses evaluating participant age, travel time to a KPWA clinic, and healthcare utilization within the one year prior to study enrollment. Across screening histories, Direct Mail and Opt In interventions had higher INB and were more cost-effective (relative to UC) among older (≥45 years) vs. younger (<45 years) participants. Among younger individuals with overdue and unknown screening history, although Direct Mail and Opt In interventions (respectively) were more effective at motivating screening than UC, they were also more expensive. Among older individuals in those

screening history groups, Direct Mail and Opt In were both less expensive than UC and more effective at motivating screening. STEP trial investigators did not report kit uptake [9] or cost-effectiveness of HPV-SS intervention by age [95]. However, evidence is mixed regarding acceptability of HPV-SS by age. A recent systematic review of values and preferences regarding HPV-SS found 25 studies that evaluated age and HPV-SS preferences; of these, 14 found no difference in preferences for HPV-SS vs. clinician-based sampling by age, five studies reported greater preference among younger patients, and four studies found older patients were more likely than younger patients to prefer HPV-SS [114]. Thus, health systems with very limited cervical cancer screening resources may consider targeting older patients with home-based interventions; however, additional research to reduce decision uncertainty is likely not warranted given low-to-zero EVPI estimates.

Results were similar for healthcare utilization and travel time subgroup analyses. With the exception of one non-zero EVPI and EVSI each in the Opt In to UC comparison, both of these subgroup analyses revealed that additional research aimed at reducing parameter uncertainty in cost-effectiveness estimates for screening adherent and overdue populations is unnecessary. Across screening history groups and intervention comparisons, the INB was consistently higher among individuals with one or more primary care or OBGYN visits in the 12 months prior to study enrollment. This is perhaps unsurprising: individuals who have recently engaged with a care team may be more likely to respond positively to screening outreach and, thus, a health system would achieve a greater net benefit investing in that group compared to individuals who have not recently sought care. Results for the travel time analyses were less consistent across screening history groups; among individuals with adherent and unknown screening histories, INB was higher among individuals living <20 minutes from a clinic, while among overdue individuals, INB was higher among those living farther away.

To our knowledge, this analysis is the first to apply the methodology of subgrouping to a VOI designed to aid health systems in the implementation of targeted cervical cancer screening interventions. In the context of cervical cancer screening in particular, a Norwegian modeling study determined that, while HPV-SS was cost-effective compared to clinician-collected sampling broadly, which specific self-sampling intervention is optimal (for example, Direct Mail vs. Opt In) depends on the profile and behavior of those who participate in HPV-SS [115]. This speaks to the need to not only develop and test

interventions based on screening history, but to consider other factors that contribute to patient heterogeneity and that therefore may influence the cost-effectiveness of an intervention.

Our VOI analysis required several analytic assumptions. First, we assumed a WTP threshold of $200 per completed screen based on STEP findings. As the WTP threshold influences the INB of an intervention (and thus the EVPI and EVSI), modifying WTP threshold changes the value of information for a given intervention comparison. Health systems interested in implementing home-based HPV screening should consider how their unique WTP threshold may impact their interpretation of these findings. However, in sensitivity analyses, an unrealistically high WTP threshold of $75,000 per completed screen did not meaningfully impact EVPI or EVSI estimates for overdue and screening adherent individuals, thereby highlighting that additional research is not necessary for policymakers to confidently implement home-based cervical cancer screening interventions in these subpopulations.

Second, in subgroup analyses, we assumed a cost basis that reflects the cost for a private U.S. healthcare system to conduct a preventive wellness visit that includes cervical cancer screening. In our analysis of the full STEP trial population (non-subgroup-specific), we presented four cost bases that represent a range of cost and visit type scenarios. In selecting the KPWA wellness cost basis for use in our subgroup analyses, we aimed to increase generalizability and interpretability of our findings for private healthcare systems. Third, EVPI calculations estimate the value of additional research per individual patient; to understand the implications at a population level requires assumptions about the size of the population that stands to benefit from implementation of the intervention. The “beneficial population” in our analysis was relatively small, because unlike for most other VOIs evaluating the impact of pharmaceutical interventions [102, 116], our context is a private healthcare system with a one-year time horizon, not a country or other large region with a decade-long time horizon. Intuitively, a higher beneficial population translates into a higher EVPI and EVSI. Finally, EVSI calculations hinge on an assumed number of observations (per arm) in a future trial. Our assumption of 3000 observations was based on the STEP trial [9]; modification of this number will impact estimates, though in sensitivity analyses, no differences in EVSI were observed among adherent and overdue groups with sample sizes as large as 20,000 participants per arm.

CONCLUSION

Subgroup-level value of information analyses for a pragmatic randomized controlled trial evaluating cervical cancer screening interventions revealed that additional research to reduce parameter uncertainty is not warranted among individuals with previously adherent and overdue screening histories. Health systems should consider efforts to collect and validate screening-relevant data for individuals with unknown screening histories, as VOI estimates suggested potential benefit in elimination of uncertainty for this screening history group.

Table 3.1. Value of Information (VOI) analysis for the STEP trial, 2020-2022, Seattle, WA

Screening history group	Interventions compared	Cost basis	INB (USD) [1]	EVPI (USD) [2]	EVSI (USD) [3]
Adherent	Opt-in vs. Usual Care	KPWA Pap only		-	-
		KPWA Preventive	26.59	-	-
		Medicare Pap only		-	-
		Medicare Preventive		-	-
	Direct Mail vs. Usual Care	KPWA Pap only		-	-
		KPWA Preventive	99.58	-	-
		Medicare Pap only		-	-
		Medicare Preventive		-	-
	Direct Mail vs. Opt-in	KPWA Pap only		-	-
		KPWA Preventive	77.29	-	-
		Medicare Pap only		-	-
		Medicare Preventive		-	-
Overdue	Direct Mail vs. Usual Care	KPWA Pap only		-	-
		KPWA Preventive	37.72	-	-
		Medicare Pap only		-	-
		Medicare Preventive		-	-
Unknown	Opt-in vs. Usual Care	KPWA Pap only		5,356	1,653
		KPWA Preventive	7.97	529	18
		Medicare Pap only		10,286	4,841
		Medicare Preventive		3,133	620

ICER. *Incremental Cost-Effectiveness Ratio*

INB. *Incremental Net Benefit*

EVPI. *Expected Value of Perfect Information*

EVSI. *Expected Value of Sample Information*

[1] Incremental Net Benefit calculated and displayed for KPWA Preventive cost basis to enable comparison of non-subgroup INB to subgroup INBs (see Tables 3.4-3.6).

[2] Assumes beneficial population of 20,000, based on the number of KPWA patients due for cervical screening each year.

[3] Assumes a sample size of 3000 participants per arm.

Table 3.2. Baseline characteristics by randomization group and cervical cancer screening history, STEP study, 2020-2022, Seattle, WA

		Number (%)						
		Adherent			Overdue		Unknown	
Source of patient heterogeneity (variable evaluated)	**Subgroup Delineation**	**Usual Care (N=3671)**	**Opt In (N=3949)**	**Direct Mail (N=1451)**	**Usual Care (N=5488)**	**Direct Mail (N=1399)**	**Usual Care (N=2983)**	**Opt In (N=3504)**
Age (age in years)	Age ≤45	1677 (45.7)	1802 (45.6)	596 (41.1)	2242 (40.9)	545 (39.0)	1669 (56.0)	1975 (56.4)
	Age >45	1994 (54.3)	2147 (54.4)	855 (58.9)	3246 (59.1)	854 (61.0)	1314 (44.0)	1529 (43.6)
Access to cervical cancer screening (travel time from participant's home to primary care clinic, in minutes) [1]	Travel time <20 minutes	2527 (68.8)	2739 (69.4)	1003 (69.1)	3785 (69.0)	981 (70.1)	2250 (75.4)	2594 (74.1)
	Travel time ≥20 minutes	1142 (31.1)	1208 (30.6)	448 (30.9)	1701 (31.0)	418 (29.9)	733 (24.6)	909 (25.9)
Healthcare utilization (whether participant had a primary care or OBGYN visit in the 12 months prior to STEP study randomization)	No visit	1238 (33.7)	1288 (32.6)	471 (32.5)	3475 (63.3)	862 (61.6)	2067 (69.3)	2405 (68.6)
	≥1 visit	2433 (66.3)	2661 (67.4)	980 (67.5)	2013 (36.7)	537 (38.4)	916 (30.7)	1099 (31.4)

[1] Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of US Census blocks and geocoded street address using participant's home addresses.

Table 3.3. Baseline subgroup-specific screening completion rates and risk estimates, by randomization group and cervical cancer screening history, STEP study, 2020-2022, Seattle, WA

		Screening completion (%)							Relative Risk (95% Confidence Interval)				
		Adherent			Overdue		Unknown		Adherent			Overdue	Unknown
Source of patient heterogeneity (variable evaluated)	Sub-group	Usual Care (N= 3671)	Opt In (N= 3949)	Direct Mail (N= 1451)	Usual Care (N= 5488)	Direct Mail (N= 1399)	Usual Care (N= 2983)	Opt In (N= 3504)	Direct Mail vs. Usual Care	Opt In vs. Usual Care	Direct Mail vs. Opt In	Direct Mail vs. Usual Care	Opt In vs. Usual Care
Age (age in years)	Age ≤45	45.0%	48.7%	57.7%	19.5%	35.7%	20.6%	20.0%	1.28 (1.18, 1.40)	1.08 (1.01, 1.16)	1.18 (1.09, 1.29)	1.83 (1.59, 2.11)	0.97 (0.85, 1.10)
	Age >45	48.7%	53.1%	64.4%	18.5%	35.7%	13.8%	15.6%	1.32 (1.24, 1.41)	1.09 (1.03, 1.16)	1.21 (1.14, 1.29)	1.93 (1.75, 2.13)	1.13 (0.95, 1.35)
Access to cervical cancer screening (travel time from participant's home to primary care clinic, in minutes) [1]	Travel time <20 minutes	48.9%	51.7%	63.1%	18.6%	34.3%	17.8%	17.3%	1.29 (1.21, 1.37)	1.06 (1.00, 1.12)	1.22 (1.15, 1.30)	1.84 (1.65, 2.06)	0.97 (0.86, 1.10)
	Travel time ≥20 minutes	42.8%	49.4%	58.0%	19.5%	39.0%	17.1%	20.1%	1.36 (1.22, 1.50)	1.15 (1.06, 1.26)	1.17 (1.07, 1.29)	2.00 (1.72, 2.33)	1.18 (0.96, 1.44)
Healthcare utilization (whether participant had primary care or OBGYN visit in the 12 months prior to STEP randomization)	No visit	41.1%	43.2%	58.2%	16.5%	31.1%	15.8%	15.4%	1.42 (1.28, 1.57)	1.05 (0.96, 1.15)	1.35 (1.22, 1.49)	1.88 (1.66, 2.13)	0.97 (0.85, 1.12)
	≥1 visit	50.0%	54.8%	63.2%	23.0%	43.0%	21.6%	23.8%	1.26 (1.19, 1.35)	1.10 (1.04, 1.16)	1.15 (1.09, 1.22)	1.87 (1.65, 2.12)	1.10 (0.94, 1.30)

[1] Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of US Census blocks and geocoded street address using participant's home addresses.

Table 3.4. Value of Information (VOI) subgroup analysis results for cervical cancer screening adherent participants enrolled in the STEP trial, 2020-2022, Seattle, WA

Source of patient heterogeneity (variable evaluated)	Interventions compared	Subgroup Delineation	ICER (USD)	INB (USD)	EVPI (USD)	EVSI (USD)
Age (age in years)	Opt-in vs. Usual Care [1]	Age <45	(354.24)	20.55	9.00	-
		Age ≥45	(524.67)	31.67	-	-
	Direct Mail vs. Usual Care [1]	Age <45	(477.68)	86.53	-	-
		Age ≥45	(496.10)	109.43	-	-
	Direct Mail vs. Opt-in	Age <45	(528.20)	65.98	-	-
		Age ≥45	(485.10)	77.76	-	-
Access to cervical cancer screening (travel time from participant's home to primary care clinic, in minutes) [2]	Opt-in vs. Usual Care [3]	Travel time <20 minutes	(812.33)	30.01	-	-
		Travel time ≥20 minutes	(88.57)	19.40	181.00	25.00
	Direct Mail vs. Usual Care [3]	Travel time <20 minutes	(561.07)	106.95	-	-
		Travel time ≥20 minutes	(416.00)	92.83	-	-
	Direct Mail vs. Opt-in	Travel time <20 minutes	(492.55)	76.93	-	-
		Travel time ≥20 minutes	(702.50)	73.44	-	-
Healthcare utilization (whether participant had a primary care or OBGYN visit in the 12 months prior to STEP study randomization)	Opt-in vs. Usual Care [4]	No visit	(1,139.00)	27.04	2.00	-
		≥1 visit	(345.20)	26.81	-	-
	Direct Mail vs. Usual Care [4]	No visit	(377.41)	98.28	-	-
		≥1 visit	(603.92)	104.88	-	-
	Direct Mail vs. Opt-in	No visit	(275.87)	71.24	-	-
		≥1 visit	(765.62)	78.07	-	-

ICER. *Incremental Cost-Effectiveness Ratio*
INB. *Incremental Net Benefit*
EVPI. *Expected Value of Perfect Information*
EVSI. *Expected Value of Sample Information*

[1] The cost for usual care was $395.01 among participants <45 years of age and $399.77 for participants ≥45 years of age.
[2] Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of US Census blocks and geocoded street address using participant's home addresses.
[3] The cost for usual care was $397.37 among participants living <20 minutes away from a clinic and $395.02 for participants living 20+ minutes away.

[4] The cost for usual care was $397.41 among participants with no visits and $398.12 for participants with ≥1 visit.

Table 3.5. Value of Information (VOI) subgroup analysis results for participants overdue for cervical cancer screening enrolled in the STEP trial, 2020-2022, Seattle, WA

Source of patient heterogeneity (variable evaluated)	Interventions compared	Subgroup Delineation	ICER (USD)	INB (USD)	EVPI (USD)	EVSI (USD)
Age (age in years)	Direct Mail vs. Usual Care [1]	Age <45	20.71	29.06	2.00	-
		Age ≥45	(50.62)	43.18	-	-
Access to cervical cancer screening (travel time from participant's home to primary care clinic, in minutes)	Direct Mail vs. Usual Care [3]	Travel time <20 minutes	(33.88)	36.66	-	-
		Travel time ≥20 minutes	(12.60)	41.59	-	-
Healthcare utilization (whether participant had a primary care or OBGYN visit in the 12 months prior to STEP study randomization)	Direct Mail vs. Usual Care [4]	No visit	(17.27)	31.79	-	-
		≥1 visit	(44.35)	48.91	-	-

ICER. *Incremental Cost-Effectiveness Ratio*

INB. *Incremental Net Benefit*

EVPI. *Expected Value of Perfect Information*

EVSI. *Expected Value of Sample Information*

[1] The cost for usual care was $396.94 among participants <45 years of age and $401.35 among participants ≥45 years of age.

[2] Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of US Census blocks and geocoded street address using participant's home addresses.

[3] The cost for usual care was $391.74 among participants living <20 minutes away from a clinic and $388.40 among participants living 20+ minutes away.

[4] The cost for usual care was $411.50 among participants with no visit and $399.70 among participants with ≥1 visit.

Table 3.6. Value of Information (VOI) subgroup analysis results for participants with unknown cervical cancer screening history enrolled in the STEP trial, 2020-2022, Seattle, WA

Source of patient heterogeneity (variable evaluated)	Interventions compared	Subgroup Delineation	ICER (USD)	INB (USD)	EVPI (USD)	EVSI (USD)
Age (age in years)	Opt-in vs. Usual Care [1]	Age <45	1,826.75	9.28	1,758	346
		Age ≥45	(159.10)	6.39	6,307	2,589
Access to cervical cancer screening (travel time from participant's home to primary care clinic, in minutes) [2]	Opt-in vs. Usual Care [3]	Travel time <20 minutes	2,059.21	8.74	806	70
		Travel time ≥20 minutes	15.35	5.62	20,785	13,327
Healthcare utilization (whether participant had a primary care or OBGYN visit in the 12 months prior to STEP study randomization)	Opt-in vs. Usual Care [4]	No visit	2,123.97	7.50	1,652	7,841
		≥1 visit	(176.38)	9.06	256	3,850

ICER. *Incremental Cost-Effectiveness Ratio*

INB. *Incremental Net Benefit*

EVPI. *Expected Value of Perfect Information*

EVSI. *Expected Value of Sample Information*

[1] The cost for usual care was $396.00 among participants <45 years of age and $400.66 among participants ≥45 years of age.

[2] Travel time to primary care clinic was generated with Network Analyst (ArcInfo v 9.1) using geographic centroids of US Census blocks and geocoded street address using participant's home addresses.

[3] The cost for usual care was $393.06 among participants living <20 minutes away from a clinic and $397.82 among participants living 20+ minutes away.

[4] The cost for usual care was $393.00 among participants with no visit and $390.86 among participants with ≥1 visit.

Figure 3.3. Incremental Net Benefit of screening interventions among cervical cancer screening adherent STEP patients, by number of age subgroups

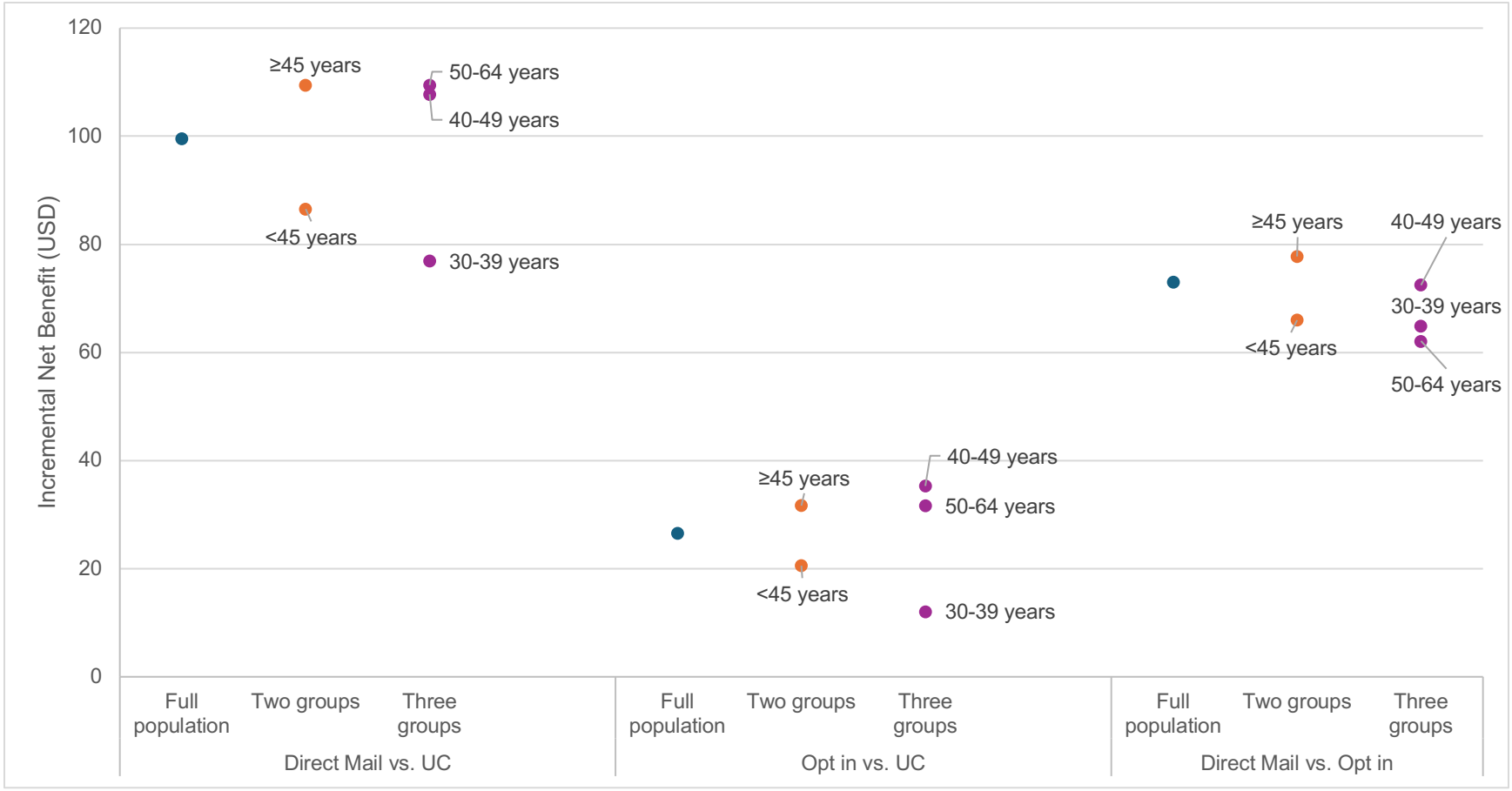


Figure 3.4. Incremental Net Benefit of Direct Mail intervention compared to Usual Care among STEP participants overdue for cervical cancer screening, by number of age subgroups

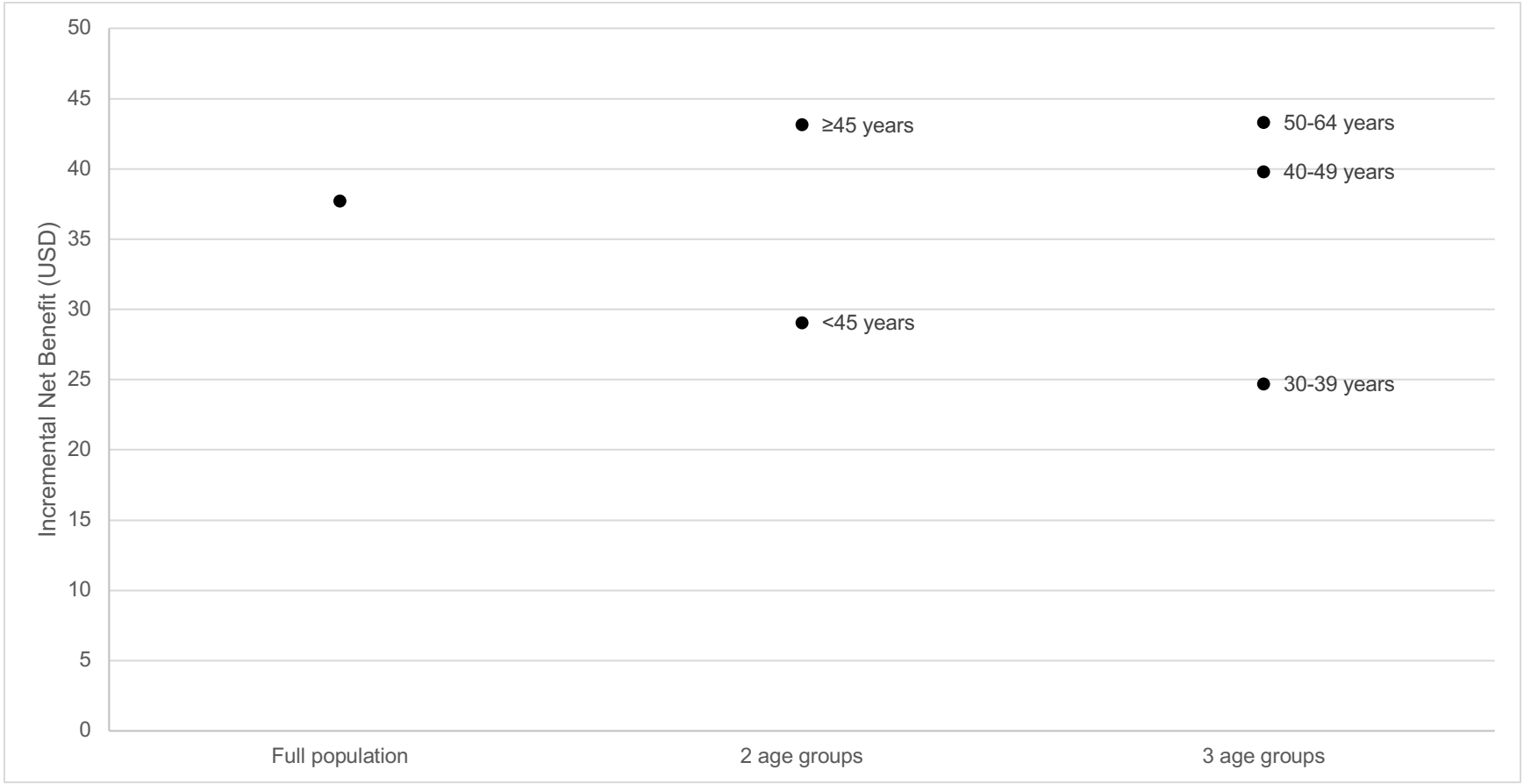
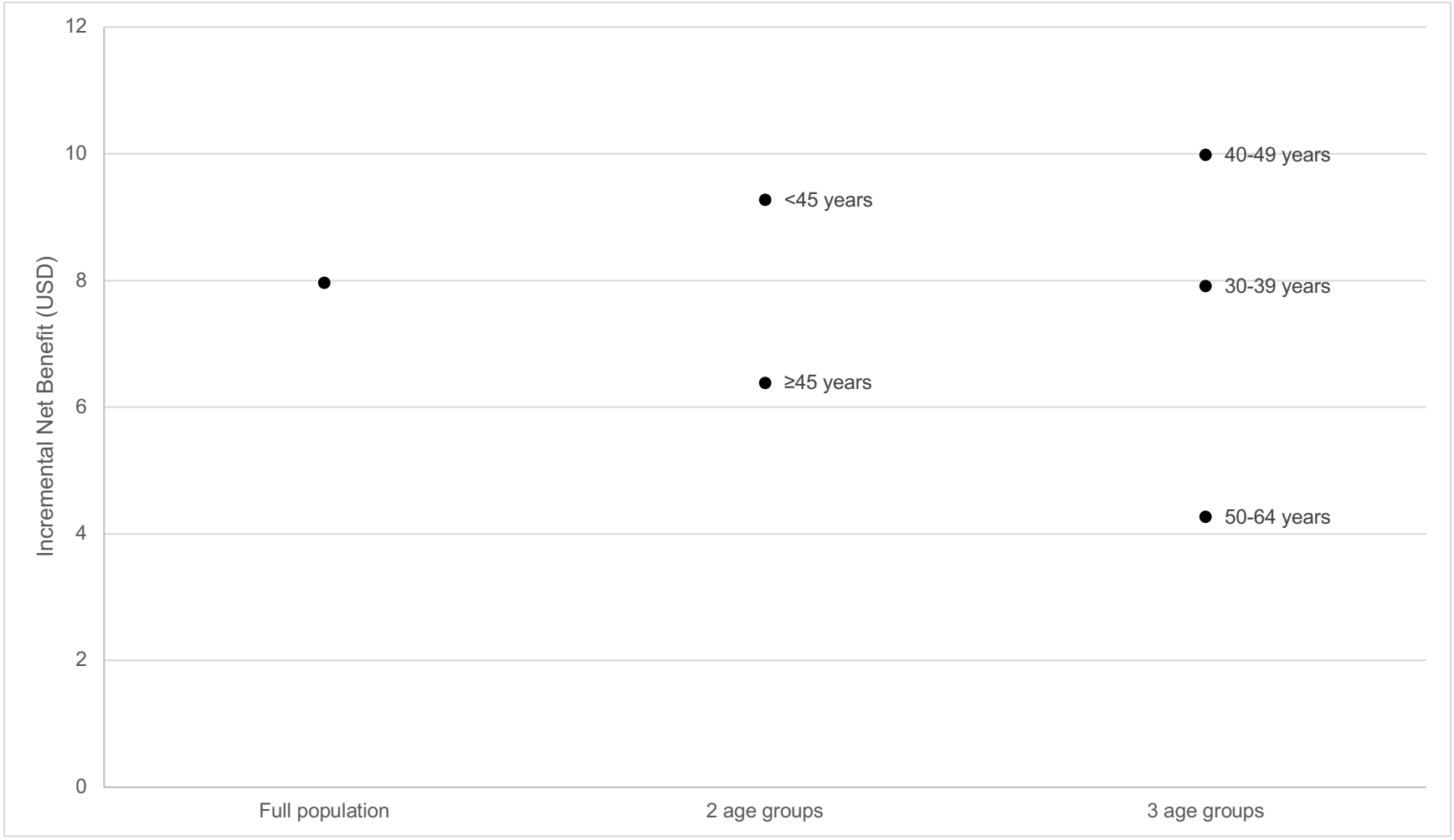


Figure 3.5. Incremental Net Benefit of Opt In intervention compared to Usual Care among STEP participants with unknown cervical cancer screening history, by number of age subgroups



Appendices

Appendix A

This appendix describes the flow of HOME study HPV self-sampling kit results– ordering of test, care team receipt of result, and dissemination of findings to study participants

Ordering of test:

After eligible individuals were randomized to the HOME intervention arm, study staff prepared kit materials for mailing. For each participant, the primary care provider (PCP) was identified using EHR, and the study team ordered the HPV test under (but without the direct knowledge of) the PCP. This ensured results from the participant's HPV-SS kit would go directly to their PCP. If participants did not return the kit within the study window, the order was not filled.

Care team receipt of result:

Electronic test results included a section visible to both the patient and their PCP, and a section for clinicians only which reminded them of management guidelines and the timing of patient notification via the portal. Messages to PCPs advised management based on the clinical co-testing result when home and in-clinic high-risk HPV results were discordant, given potential time delays between home-based and in-clinic screening (e.g., infection could have resolved causing second result to be negative).

Text visible only to clinicians included: "Please see the comments above regarding the recommended clinical management of this research study test result. As with standard HPV results, normal results will be sent to the patient via [the patient Web portal] immediately, and abnormal results will be sent after 24–48 hours. Results are not sent to the patient by mail, regardless of whether or not they are active on [the patient Web portal]. You are required to contact patients who are not active on [the patient Web portal], regardless of their test results. Please contact the patient as appropriate – note that the patient will NOT be contacted by study staff. **Patients who are HPV 16 and/or 18 positive are recommended for immediate colposcopy. We do NOT recommend that the patient get a Pap test first, or repeat the HPV test in the clinic.**"

Dissemination of findings to study participants:

All patient/PCP electronic results text included: "If you have questions about this result, please contact your health care team. If you have questions about the research that they are not able to answer, please feel free to call study staff at (toll-free telephone number)."

Text visible to patients and/or clinicians included the following:

- **For patients with HPV-negative results:**
    - "No high-risk HPV strains were found in your sample. Although this is reassuring, it's important to make an appointment with your health care team for in-clinic cervical cancer screening, since the effectiveness of home HPV testing is still being evaluated." (Starting May 2015, the phrase "home HPV testing" was changed to "home cervical cancer screening")
    - A link to an internal Kaiser Permanente Washington website with general information on cervical cancer screening was provided
- **For patients with unsatisfactory results**:
    - "There was not enough material on the swab for us to complete the test. Please make an appointment with your health care team for in-clinic cervical cancer screening."
    - A link to an internal Kaiser Permanente Washington website with general information on cervical cancer screening was provided
- **For patients with other high-risk HPV-positive results:**
    - "High-risk HPV strains were found in your sample. This result requires follow-up in the clinic with a Pap and HPV test. Please make an appointment with your health care team. You and your health care team should use the test results from the clinic to decide what steps to take next."
    - Beginning in May 2015, results text included a link to a study-specific website with information on home-based hrHPV screening. The website content reiterated the purpose of high-risk HPV tests and explained what high-risk HPV results mean and why in-clinic follow-up is recommended.

- **For patients with HPV16 and/or HPV18-positive results**:
    - "High-risk types 16 and/or 18 were found in your sample. This result requires follow-up in the clinic. Please contact your health care team to schedule follow-up."
        - **Clinicians only:** recommended follow-up (immediate colposcopy) was communicated only to clinicians in an effort to allow them to share the results with patients and avoid patient confusion or anxiety
    - Beginning in May 2015, results text included a link to a study-specific website with information on home-based high-risk HPV screening. The website content reiterated the purpose of high-risk HPV tests and explained what high-risk HPV results mean and why in-clinic follow-up is recommended.

Appendix B. Original STEP trial brochure

Page 1

Do I still need to be screened if I have had the HPV vaccine?

Yes, if you received the HPV vaccine, **you still need regular cervical cancer screening up to age 65.**

The vaccine is very effective at protecting against new HPV infections. However, **the vaccine does not help get rid of an HPV infection already in your body.** That is why it's important to start the vaccine series before being exposed to the virus.

The vaccine is recommended for girls and boys at ages 11-12 and can be given starting at age 9. It's also recommended up to age 26 for people who have not received the full series of shots. Women and men ages 27-45, who did not get the vaccine when younger, may still benefit from it. Talk with your doctor if you have questions or visit the websites below to learn more.

I thought HPV was something for teens and not people my age – but I was tested, and I had a positive HPV test. Now my doctor and I know we need to make sure I am tested on a regular schedule to make sure I don't develop cervical cancer.

For more information:

Kaiser Permanente website
kp.org/wa/paptest

Centers for Disease Control and Prevention
cdc.gov/cancer/cervical/index.htm

National Cancer Institute
cancer.gov/types/cervical
cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer

Educational Brochure Revised 15 Oct. 2020

You can prevent cervical cancer through regular screening

What's changed and why is screening so important

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Appendix B, Page 2

What is cervical cancer and why is screening important?

Cervical cancer is cancer in the cervix, or the lower part of the uterus (womb) connected to the vagina. **The most important risk factor for cervical cancer is infection with a virus called human papillomavirus (HPV).**

HPV infection can change the cells on your cervix. It takes an average of 10 years for pre-cancer cells to turn into cancer. **You can prevent cervical cancer by getting routine testing.** In most cases, screening can find pre-cancer cells that can be removed before cancer forms. Screening can also find early-stage cervical cancer that can be successfully treated.

Did you know?

90% of people have had HPV

HPV infections can come and go

You should get tested even if you're not sexually active

What is HPV and how is it spread?

HPV is spread through sexual contact. Almost all people (90%) who've been sexually active have had HPV at some time in their life. Condoms do not completely protect against HPV. For most people, an HPV infection goes away on its own. **However, when an HPV infection does not go away, it can change normal cervical cells into abnormal or pre-cancer cells.**

Some HPV infections can come and go and cause cervical cells to change at any time. Most HPV infections, pre-cancerous cells, and early-stage cervical cancers do not have any symptoms. **This is why it's so important to get screened regularly, even if you've been with the same partner or haven't been sexually active for many years.** Routine screening is important even if you have a history of negative test results.

What options do I have for cervical cancer screening?

Two tests are used to screen for cervical cancer:

- **HPV tests** look for an HPV infection that can cause pre-cancer cells.
- **Pap tests** (also called Pap smears) look for abnormal cells on your cervix.

For both tests, a doctor uses a speculum to open your vagina and then inserts a small brush inside to collect cervical cells. The tests may be used alone or together, depending on your age and health history.

Women ages 30-65 can choose to screen with one of the following:

- Pap test every 3 years
- HPV test every 5 years
- HPV and Pap test (co-test) every 5 years

In the past, doctors recommended a Pap test every year. Because testing options have improved, tests can be done less often. Talk to your doctor about which option is best for you.

I had an abnormal Pap test 5 years after I was last sexually active. I'm so glad I got tested even though I didn't think I was at high risk. You can develop cervical cancer even if you have been with the same partner for a long time.

What happens if my screening test is abnormal or positive?

An abnormal Pap or positive HPV test result does not mean you have cancer. Your doctor will use the test results along with your age and past screening history to decide on the best follow-up plan.

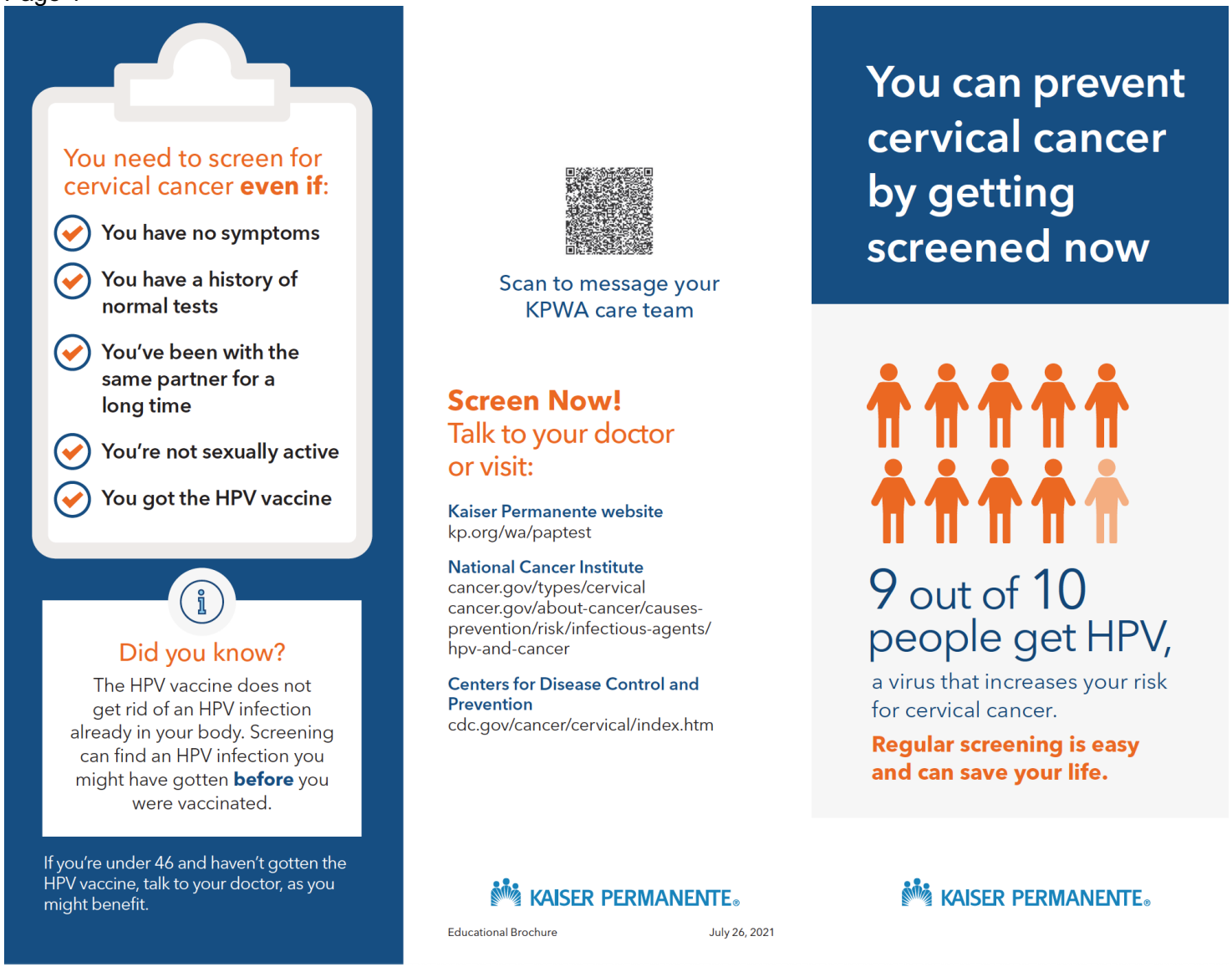
Follow-up could include:

- Having another Pap and HPV test in about a year to see if the abnormal cells or infection have gone away.
- Getting other tests, like a colposcopy that lets your doctor see your cervix more closely.

Additional procedures may be done to help diagnose and treat any cell changes on your cervix. **Follow-up care is important for preventing cervical cancer and successfully treating early-stage cervical cancer.** Complete all follow-up appointments as instructed by your doctor.

Appendix C. Optimized STEP trial brochure

Page 1



Appendix C, Page 2

Almost everyone has had HPV at some point in their life

HPV, which is short for human papillomavirus, spreads through sexual contact. Condoms don't completely protect against HPV.

HPV infections can change normal cervical cells into abnormal or pre-cancer cells.

Your body usually clears up HPV infections on its own. However, some HPV infections don't go away completely, and can come back throughout your life.

"I had an abnormal Pap test last year. I'm so glad I got tested **even though I didn't have any symptoms.** I haven't been sexually active recently, but my doctor told me HPV can come and go over time, which is why I'm on a regular screening schedule now."

Screening is easy. What to expect **during** your screening visit

A doctor will insert a small brush into your vagina to collect cervical cells.

HPV tests look for an HPV infection that can cause pre-cancer cells.

Pap tests (also called Pap smears) look for pre-cancer cells on your cervix.

Depending on your age and screening history, these tests can be used alone or together. In the past, doctors recommended a Pap test every year. Because tests have improved, screening can be done less often.

"I thought I needed to get screened every year, but my doctor told me **screening tests have improved,** and since my last test was negative, it's safe to wait a few years until my next one."

What to expect **after** your screening visit

An abnormal Pap or HPV positive test result does **NOT** mean you have cancer.

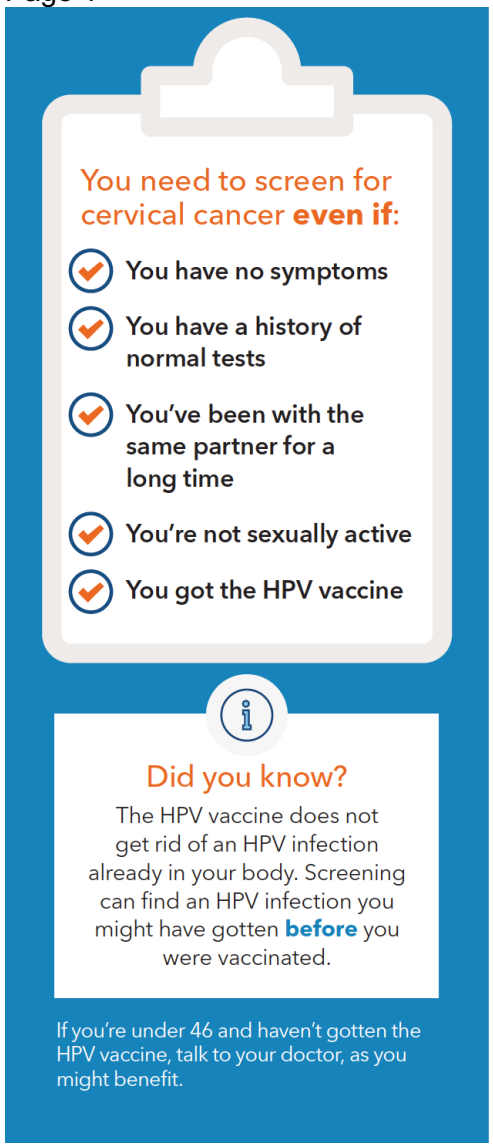
If your HPV or Pap test result is **negative (normal)**	→ You can wait 3 to 5 years before your next screening
If your HPV or Pap test result is **positive (abnormal)**	→ More testing may be needed

The most important thing you can do is follow your health care team's recommendations for the next steps.

Most HPV infections don't have any symptoms.
Regular screening can find changes to cervical cells that can be treated before they turn into cancer.

Appendix D. Age-targeted STEP trial brochure, ≤45 years of age

Page 1



Scan to message your KPWA care team

Screen Now!
Talk to your doctor or visit:

Kaiser Permanente website
kp.org/wa/paptest

National Cancer Institute
cancer.gov/types/cervical
cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-and-cancer

Centers for Disease Control and Prevention
cdc.gov/cancer/cervical/index.htm

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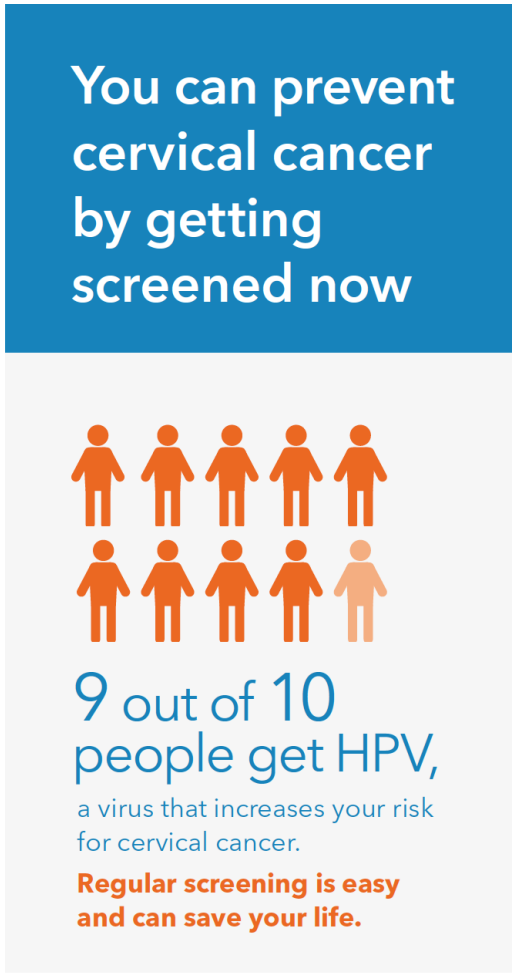

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Appendix D, Page 2

Almost everyone has had HPV at some point in their life

HPV, which is short for human papillomavirus, spreads through sexual contact. Condoms don't completely protect against HPV.

HPV infections can change normal cervical cells into abnormal or pre-cancer cells.

Your body usually clears up HPV infections on its own. However, some HPV infections don't go away completely, and can come back throughout your life.

"I had an abnormal Pap test last year. I was confused - I got the HPV vaccine in college. My doctor told me **the vaccine doesn't protect against all types of HPV**, and I might have gotten it before I was vaccinated. Now, I make sure to screen on time to prevent cervical cancer."

Screening is easy. What to expect **during** your screening visit

A doctor will insert a small brush into your vagina to collect cervical cells.

HPV tests look for an HPV infection that can cause pre-cancer cells.

Pap tests (also called Pap smears) look for pre-cancer cells on your cervix.

Depending on your age and screening history, these tests can be used alone or together. In the past, doctors recommended a Pap test every year. Because tests have improved, screening can be done less often.

"I had an abnormal Pap in my 20s, but my last few tests have been normal. My doctor told me it's important to keep screening regularly, because **HPV infections can reappear years later** and change normal cells into pre-cancer cells."

What to expect **after** your screening visit

An abnormal Pap or HPV positive test result does **NOT** mean you have cancer.

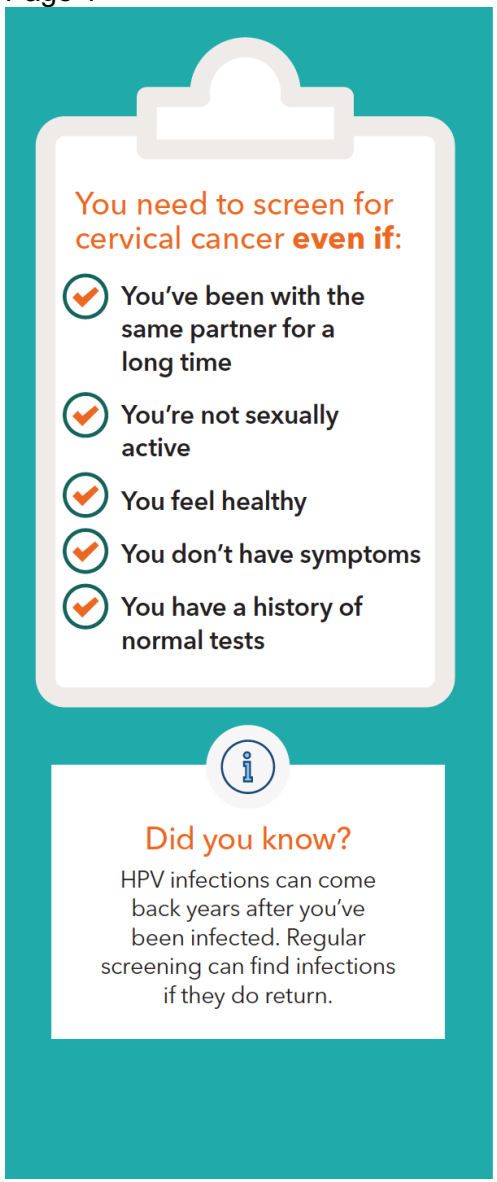
If your HPV or Pap test result is **negative (normal)**	→	You can wait 3 to 5 years before your next screening
If your HPV or Pap test result is **positive (abnormal)**	→	More testing may be needed

The most important thing you can do is follow your health care team's recommendations for the next steps.

Most HPV infections don't have any symptoms.
Regular screening can find changes to cervical cells that can be treated before they turn into cancer.

Appendix E. Age-targeted STEP trial brochure, ≤45 years of age

Page 1



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National Cancer Institute
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Centers for Disease Control and Prevention
cdc.gov/cancer/cervical/index.htm

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Educational Brochure July 26, 2021

You can prevent cervical cancer by getting screened now

9 out of 10 people get HPV,

a virus that increases your risk for cervical cancer.

Regular screening is easy and can save your life.

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Appendix E, Page 2

Almost everyone has had HPV at some point in their life

HPV, which is short for human papillomavirus, spreads through sexual contact. Condoms don't completely protect against HPV.

HPV infections can change normal cervical cells into abnormal or pre-cancer cells.

Your body usually clears up HPV infections on its own. However, some HPV infections don't go away completely, and can come back throughout your life.

"I was surprised when my last Pap test was abnormal. I've been with the same partner for years and didn't have any symptoms. My doctor told me **HPV infections can take a long time to change normal cells into pre-cancer cells** and I might have gotten HPV many years ago. I'll continue to screen on time to prevent cervical cancer."

Screening is easy. What to expect **during** your screening visit

A doctor will insert a small brush into your vagina to collect cervical cells.

HPV tests look for an HPV infection that can cause pre-cancer cells.

Pap tests (also called Pap smears) look for pre-cancer cells on your cervix.

Depending on your age and screening history, these tests can be used alone or together. In the past doctors recommended a Pap test every year. **Because tests have improved, screening can safely be done less often.**

"My last last Pap test was normal. My doctor told me **screening tests have improved, so it's safe to wait a few years until my next one.** This was reassuring to hear, and I think it will be easier to stick with regular screening."

What to expect **after** your screening visit

An abnormal Pap or HPV positive test result does **NOT** mean you have cancer.

If your HPV or Pap test result is negative (normal)	→	You can wait 3 to 5 years before your next screening
If your HPV or Pap test result is positive (abnormal)	→	More testing may be needed

The most important thing you can do is follow your health care team's recommendations for the next steps.

Most HPV infections don't have any symptoms.
Regular screening can find changes to cervical cells that can be treated before they turn into cancer.

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