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Home-based self-sampling vs clinician sampling for anal precancer screening: The Prevent Anal Cancer (PAC) Self-Swab Study

Alan G. Nyitray, PhD[1,2], **Jenna Nitkowski, PhD**[2], **Timothy L. McAuliffe, PhD**[2], **Bridgett Brzezinski, MA**[2], **Michael D. Swartz, PhD**[3], **María E. Fernandez, PhD**[4], **Ashish A. Deshmukh, PhD**[5,6], **Timothy J. Ridolfi, MD**[7], **Sarah J. Lundeen, NP**[7], **Leslie Cockerham, MD**[8], **Dave Wenten, RN**[9], **Andrew Petroll, MD**[2], **Brian Hilgeman, MD**[10], **Jennifer S. Smith, PhD**[11], **Elizabeth Y. Chiao, MD**[12], **Anna R. Giuliano, PhD**[13], **Vanessa Schick, PhD**[14], **The Prevent Anal Cancer Self-Swab Study Team**

[1]Clinical Cancer Center, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[2]Center for AIDS Intervention Research, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[3]Department of Biostatistics and Data Science, The University of Texas Health Sciences Center at Houston School of Public Health, Houston, Texas, USA

[4]Department of Health Promotion and Behavioral Sciences, The University of Texas Health Sciences Center at Houston School of Public Health, Houston, Texas, USA

[5]Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

[6]Cancer Control Program, Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina, USA

[7]Department of Surgery, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[8]Vivent Health, Milwaukee, Wisconsin, USA

Corresponding author: Dr. Alan G. Nyitray, Clinical Cancer Center and Center for AIDS Intervention Research, Medical College of Wisconsin, 2071 North Summit Avenue, Milwaukee, WI 53202, anyitray@mcw.edu, Ph: 414-805-3312, Fax: 414-287-4209.

Author contributions

Alan G. Nyitray: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Writing – original draft preparation, Writing – reviewing and editing **Jenna Nitkowski:** Data curation, Writing – reviewing and editing **Timothy L. McAuliffe**: Methodology, Writing – reviewing and editing **Bridgett Brzezinski**: Investigation, Project administration, Writing – reviewing and editing **Michael D. Swartz**: Methodology, Writing – reviewing and editing **María E. Fernandez**: Methodology, Writing – reviewing and editing **Ashish A. Deshmukh**: Writing – reviewing and editing **Timothy J. Ridolfi**: Writing – reviewing and editing **Sarah J. Lundeen**: Investigation, Writing – reviewing and editing **Leslie Cockerham**: Investigation, Writing – reviewing and editing **Dave Wenten**: Investigation, Writing – reviewing and editing **Andrew Petroll**: Investigation, Writing – reviewing and editing **Brian Hilgeman**: Investigation, Writing – reviewing and editing **Jennifer S. Smith**: Methodology, Writing – reviewing and editing **Elizabeth Y. Chiao**: Methodology, Writing – reviewing and editing **Anna R. Giuliano**: Investigation, Writing – reviewing and editing **Vanessa Schick**: Methodology, Writing – reviewing and editing

The work reported in the paper has been performed by the authors, unless clearly specified in the text.

Ethics Statement

Study procedures were approved by the Medical College of Wisconsin Human Research Protections Program (PROP00032999; NCT04090060). All individuals enrolled provided informed consent to participate in the study.

Conflict of Interest

None.

[9]Holton Street Clinic, Milwaukee, Wisconsin, USA

[10]Department of Medicine, Division of General Internal Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

[11]Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina, USA

[12]MD Anderson Cancer Center, Houston, Texas, USA

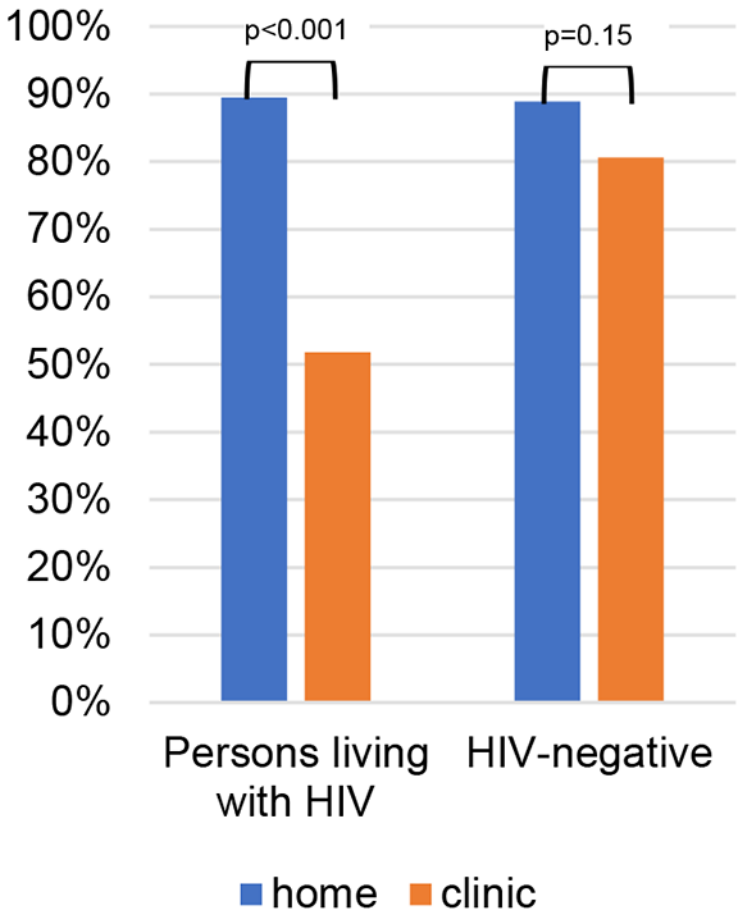
[13]Center for Immunization and Infection Research in Cancer, Moffitt Cancer Center & Research Institute, Tampa, Florida, USA

[14]Department of Management, Policy, and Community Health, The University of Texas Health Sciences Center at Houston School of Public Health, Houston, Texas, USA

Abstract

Sexual minority men are at increased risk for anal squamous cell carcinoma. Our objective was to compare screening engagement among individuals randomized to self-collect an anal canal specimen at home or to attend a clinic appointment. Specimen adequacy was then assessed for human papillomavirus (HPV) DNA genotyping. A randomized trial recruited cisgendered sexual minority men and transgender people in the community and assigned them to use a home-based self-collection swabbing kit or attend a clinic-based swabbing. Swabs were sent for HPV genotyping. The proportions of participants completing screening in each study arm and the adequacy of their specimens for HPV genotyping were assessed. Relative risks were estimated for factors associated with screening. A total of 240 individuals were randomized. Age (median, 46 years) and HIV status (27.1% living with HIV) did not differ by study arm. A total of 89.2% and 74.2% of home-arm and clinic-arm individuals returned the swab, respectively ($p=0.003$, difference between groups, 15.0% (95% CI 5.4%-24.6%). Among Black individuals, 96.2% and 63.2% in the home and clinic arms screened ($p=0.006$). Among individuals with HIV, 89.5% and 51.9% in the home and clinic arms screened ($p<0.001$). Self-collected swabs and clinician-collected swabs were comparable in adequacy for HPV genotyping (96.3% and 93.3%, respectively). People at highest risk for anal cancer may be more likely to screen if they are able to self-collect swabs at home rather than attend a clinic.

Graphical Abstract



Proportion of participants who engaged in screening by study arm stratified by HIV status.

Keywords

anal neoplasms; HIV; sexual and gender minorities; self-testing; human papillomavirus DNA tests

Introduction

Sexual minority men (SMM), especially those living with HIV, are at higher risk for anal squamous cell carcinoma (ASCC) than the overall population.[1] In addition, Black SMM have a higher incidence of ASCC than do non-Black SMM.[2] There are no commonly accepted screening guidelines for ASCC.[3]

As with cervical cancer, ASCC is typically caused by human papillomavirus and is preceded by high-grade squamous intraepithelial lesions. There is now evidence that treatment will

prevent some lesions from invading.[3] These lesions are detected with the aid of high-resolution anoscopy, a technology with limited infrastructure even in high-resource settings.[4] Thus, the development of biomarkers and screening methods for the most vulnerable populations are a high priority so that limited resources can be equitably directed toward those at highest risk for ASCC.[5]

Clinic-based cervical cancer screening programs have resulted in cancer disparities by race and ethnicity.[6] Screening disparities may be driven by access to health care, systemic racism, and stigma, in addition to cultural norms that promote or lessen the likelihood of screening.[7] To increase screening engagement of under-screened populations, cervico-vaginal self-sampling is under study and has been introduced into some countries' cervical cancer screening programs.[8] Unlike cervical Pap cytology collected by clinicians, self-sampling primarily targets HPV DNA and has comparable adequacy when compared with clinician sampling.[9]

Analogous to cervical cancer screening, anal cancer screening disparities may occur due to stigma and embarrassment associated with anogenital examinations, sexually transmitted infections, anal sex, and anal cancer.[10] It follows that anal self-sampling programs may increase access for those less likely to visit clinics or submit to ano-genital exams.

The Prevent Anal Cancer (PAC) Self-Swab Study randomized asymptomatic and community-recruited cisgender SMM, transgender women, and non-binary individuals to home-based anal canal self-sampling or clinic-based screening by a clinician. The objective of the current analysis was to estimate screening engagement in the two arms at baseline along with the adequacy of specimens for HPV DNA genotyping.

Materials and Methods

Study setting and recruitment

The full protocol [NCT04090060] has been previously described.[11] In brief, the PAC Self-Swab Study is based in Milwaukee, Wisconsin, a Midwest US city with a metro population of 1.6 million people. The study used existing health care infrastructure in that individuals randomized to the clinic arm were able to choose any one of five geographically dispersed clinics for the clinic swabbing. Each clinic had a history of providing specialized medical care to SMM, transgender individuals and/or people with HIV.

Study recruitment primarily occurred through social media but also through print materials, word-of-mouth, local presentations, and clinics. People were encouraged to join a study of anal cancer screening, with no mention of self-sampling. Interested individuals completed a short online eligibility survey before being invited to an online consenting session. Individuals were enrolled without regard to anal cancer screening history, HIV status, or HPV vaccination status. Individuals were excluded if they were younger than 25 years of age, reported no sex with men in the past five years and reported not being gay, bisexual or queer, were cisgendered women, lived outside the Milwaukee metro area, had a prior diagnosis of anal cancer, used anticoagulants, or had a diagnosis of hemophilia, cirrhosis with bleeding varices, or thrombocytopenia.

In the online consenting session, staff described all study activities in addition to discussing ASCC risk, etiology, and HPV DNA screening concerns. For example, participants were told they would be invited to engage in screening at the beginning of the study and one year later. Participants were told that a single anal HPV test did not hold value for understanding risk for anal cancer, but that persistent high-risk anal HPV might.[12] Thus, individuals would not receive baseline HPV test results, but would be notified if high-risk HPV persistence was detected after completion of the baseline and one-year screening time points.

Randomization, masking, and power

Immediately after the online consenting session, participants were sent a link to the online baseline survey. Individuals who completed the survey were randomized in a 1:1 allocation to either the home arm or clinic arm using a study-generated randomization table within Research Electronic Data Capture (REDCap) (Vanderbilt University). Given obvious differences of each arm, randomization could not be blinded to study staff or participants. Specimens sent to the laboratory for HPV genotyping were blinded as to study arm. A priori power calculations were determined for the primary question of engagement in annual screening but not for the current analysis of the initial screening period.

Intervention

Once randomized, individuals were given instructions through text, email or phone on how to screen. Individuals randomized to the home arm were mailed a “PAC Pack” which was a package lined with foam that contained instructions and supplies for self-sampling. The PAC Pack design was informed by a community advisory board of SMM and pilot testing. It included a FLOQSwab™ (Copan Italia Spa, Brescia, Italy), a vial of 2.0 mL of Standardized Transport Medium (STM) (Digene Corporation), a plastic bag, gloves, and a device to record ambient temperature (LogTag Recorders, Auckland, New Zealand). Also included were instructions for self-sampling which were adapted from existent self-sampling instructions[13] in addition to a protocol for clinician sampling,[14] e.g., twirling the swab, counting slowly to ten, and applying pressure to the anal canal walls. Then, participants were instructed to immediately immerse the swab in the vial of STM, place it back in the PAC Pack, and to overnight the postage-paid kit to the Medical College of Wisconsin Biorepository and Tissue Analytics Core (tissue bank) for processing and storage. Participants were reminded up to three times to use and return the PAC Pack after which an online computer-assisted self-interview assessed participants’ experiences with the PAC Pack. Participants in the home arm were then asked to attend a study clinic for a baseline digital anal rectal examination to screen for prevalent anal cancer after which they received a $35 incentive.

Individuals randomized to the clinic arm were instructed to make an appointment at their chosen study clinic and to attend the clinic for clinician swabbing. The attending clinician (a physician, nurse practitioner or registered nurse) was trained to collect exfoliated cells with the same sampling protocol used by study participants. The clinician then performed a digital anal rectal examination. Participants assessed the clinician sampling experience using a computer-assisted self-interview after which they received a $35 incentive. Study staff then transported the swab to the tissue bank for processing and storage.

The study consented its first participant on January 9, 2020. Enrollment was then suspended due to COVID-19 pandemic stay-at-home orders on March 14, 2020. All participants in the clinic arm who had not engaged in screening at that time (n=8) were asked to not attempt to make or attend clinic appointments until further notice. All participants in the home arm who had not returned their baseline PAC Packs (n=4) were told they should not return PAC Packs until further notice. After study resumption on November 3, 2020, the 12 individuals were invited to complete their study activities; however, none completed screening.

Assessment of specimen adequacy

Swab specimens transported to the tissue bank were aliquoted into cryovials and placed in −80℃ before batch shipping to Moffitt Cancer Center and Research Institute for genotyping. Cryovial specimens were blinded as to study arm. DNA was extracted using the robotic MDx Media Kit (Qiagen), according to the manufacturer's instructions. The HPV SPF_{10} PCR-DEIA-$LiPA_{25}$ assay was used for HPV genotyping including the detection of human RNase P by qPCR to determine sample adequacy.

Data analysis

The current analysis used screening engagement data, HPV genotyping results and survey data during the initial screening period. Engaging in screening at baseline was defined as the delivery of a swab to the tissue bank after 1) a home-arm participant returned a PAC Pack, or 2) after a clinic-arm participant completed a swabbing appointment with a clinician. The null hypothesis was that the proportion of those complying in each arm would be the same with assessment by a Pearson chi-square test for a difference in proportions. The difference in screening engagement between the two arms and its 95% Wald confidence interval (CI) was calculated. Given the increased risk for anal cancer among Black SMM[2] and persons with HIV,[1] we stratified screening engagement by these characteristics.

The median number of days from randomization to screening engagement in each arm was estimated. For individuals who engaged in screening, we compared the proportion in each arm who provided swabs that were adequate for HPV genotyping. Under the intention-to-treat principle, all participants who were randomized were included in the analyses. In addition, per protocol analyses were conducted after removing the 12 persons who were told to not engage in screening during stay-at-home orders in March 2020.

To determine exposures associated with any screening engagement, we used purposeful modeling strategies.[15] Due to numerical instability with log-binomial regression modeling, we used Poisson regression with a robust variance estimator[16] to estimate the relative risk for the association between exposures and the outcome of engagement in screening after adjustment by age. Given the suspension of the study due to the COVID-19 pandemic, the association between study arm and engagement in screening was also adjusted by time of enrollment, i.e., either prior to trial suspension or after trial resumption. Exposures with a likelihood ratio test p-value of less than 0.25 in bivariate analysis were included in the multivariable model and then were removed one at a time using backwards elimination if the p-value was ≥ 0.05. Associations in the multivariable model were considered significant when a p-value was < 0.05. Adjusted and unadjusted relative risks were reported with 95%

CIs. Analyses were conducted using SAS 9.4 TS Level 1M6 (SAS Institute, Cary, North Carolina, USA). The full protocol is available at mindyourbehind.org.

Results

From January 3, 2020 to August 31, 2022, a total of 773 individuals completed an eligibility screening online and 264 of these were not eligible. Another 256 were eligible but did not consent. The remainder, 253, were eligible and consented. A higher proportion of those who were eligible but did not consent, 58.7%, reported first hearing of the study through social media compared to 42.0% who eventually consented into the study ($p<0.001$). An additional 30.0% of those consenting first heard of the study through a flyer or advertisement, 16.4% from a friend, 9.2% from a clinic, and 2.4% through other means. A total of 240 eligible individuals who consented and completed the baseline survey were randomized (Figure 1).

Overall, participant characteristics were well-balanced by arm (Table 1). The median age was 46 years (range: 25–78 years), with a large majority (82.5%) identifying as gay. Just under two-thirds (65.8%) identified as white, non-Hispanic and 18.8% as Black, non-Hispanic. A total of 27.1% were people living with HIV (PLH).

PAC Packs were returned and clinic appointments were completed in a median of 9 and 20 days, respectively (Table 2). A total of 89.2% and 74.2% of individuals engaged in screening in the home arm and clinic arm, respectively ($p=0.003$) for a difference in proportions of 15.0% (95% CI 5.4%-24.6%). When stratified by race/ethnicity, Black, non-Hispanic individuals in the home arm were more likely to screen than those randomized to the clinic arm (96.2% and 63.2%, respectively, $p_{Fisher's\ Exact} = 0.006$, Figure 2) for a difference in proportions of 33.0% (95% CI 10.0%-55.9%). When stratified by HIV, PLH in the home arm were more likely to screen than those randomized to the clinic arm (89.5% and 51.9%, respectively, $p_{Pearson} < 0.001$, respectively) for a difference in proportions of 37.6% (95% CI 16.4%-58.8%). Finally, when results were stratified by persons enrolled before the COVID-19 pandemic-imposed trial suspension versus those enrolled after trial resumption, engagement continued to be higher in the home arm compared with the clinic arm (Supplemental Table 1).

A total of 96.3% and 93.3% of swabs used in screening were adequate for HPV DNA genotyping in the home arm and the clinic arm, respectively ($p=0.52$). There were no significant differences in swab adequacy by study characteristic in either arm.

In univariate analysis for factors associated with any screening engagement (Table 3), those in the home arm were 20% more likely to engage in screening compared to individuals in the clinic arm (relative risk (RR) 1.20, 95% CI 1.06–1.36). Individuals with a sexual orientation of bisexual or queer were less likely to screen than gay individuals (RR 0.77, 95% CI 0.61–0.98). Individuals with more years of school were more likely to screen than persons with ≤ 12 years of school (for example, RR 1.44, 95% CI 1.05–1.97 for individuals with 16 years of school compared to those with ≤ 12 years of school).

In multivariable analysis, after adjusting for potential confounders (age and COVID-19 pandemic enrollment date) and variables remaining in the model, individuals in the home

arm were 22% more likely to engage in screening compared with the clinic arm (adjusted relative risk (aRR) 1.22, 95% CI 1.08–1.38). In addition, PLH were less likely to engage in screening (aRR 0.85, 95% CI 0.73–0.98, compared to HIV-negative individuals) and individuals identifying as bisexual or queer were less likely to screen (aRR 0.76, 95% CI 0.60–0.95, compared to gay).

The per protocol analysis yielded results consistent with the intention-to-treat analysis with 92.2% and 79.5% of individuals in the home and clinic arms engaged in screening, respectively (Supplemental Table 2).

Discussion

In a randomized trial, community-based and asymptomatic SMM and transgender persons were more likely to engage in anal cancer screening when assigned to use a mailed self-collection kit in the home than when assigned to make and attend a clinic appointment. Given the increased proportion of Black individuals and PLH who engaged in screening in the home versus clinic arm, a self-sampling option may lessen potential barriers to anal cancer screening, like access to health care, stigma, and embarrassment, for those most vulnerable to disease.[17, 18] Furthermore, over 90% of individuals in this study were technically competent with self-collecting a swab that was adequate for HPV genotyping.

To our knowledge, anal cancer screening engagement has not been measured in a randomized trial that estimates uptake for home-based vs clinic-based HPV DNA collection; however, three studies have employed home-based screening among SMM with outcomes of anal cytology and *Chlamydia trachomatis* or *Neisseria gonorrhea*, although differences in study methods including recruitment of clinic populations (rather than asymptomatic community populations) and the protocol for swab return make comparisons difficult.[19–21] For example, in these studies, all swabs were brought to a clinic by a patient rather than being mailed. Two studies assessed in-home collection of cytological samples in San Francisco. In the first, of 102 SMM recruited in clinic after high-resolution anoscopy-detected anal lesions, 80% returned a home self-collected swab to a clinic.[19] In the second study, 80% of 125 SMM recruited in the community complied with instructions to self-collect a swab 1–2 days before their scheduled clinical appointment.[20] Finally, of 433 SMM in Brighton, UK who were recruited in clinics or through HIV testing efforts and then offered a home testing kit for *C. trachomatis* and *N. gonorrhea*, 47% returned the kit in-person to a clinic.[21] Our results demonstrate comparable or higher return rates from the home arm of a community-recruited sample with receipt and return of swabs in the mail.

While these results cannot substitute for an effectiveness study, we attempted to include scenarios in the screening protocol to mimic real-world screening, e.g., persons in the clinic arm had to call to make their own appointments at a study clinic. However, overall screening engagement was substantial in both arms which may reflect the study context including the enrollment of people more concerned about anal cancer.

Men have suboptimal engagement with other cancer screening,[22] and thus may not engage in anal cancer screening for a number of reasons including lack of health care access,

awareness, lack of provider recommendation, inconvenience, embarrassment and stigma.[7, 17] The potentially stigmatizing aspects of anal cancer screening are manifold including stigma associated with the anus, receptive anal sex, sexual minority status, and anal medical procedures that may violate cultural norms of masculinity.[18] Adding increased complexity is that some healthcare providers may be uncomfortable examining anuses, as suggested by PLH, and some providers have concerns about patient acceptability of anal medical procedures.[7, 23] While a majority of men with HIV report being comfortable discussing anal health with a provider, the prevalence of discussions is not optimal with only 50% of SMM with HIV, aged ≥ 50 years and receiving care in HIV clinics in Ontario, Canada, reporting ever discussing anal health with a provider.[24] Given potentially inadequate anal health communication between patient and provider, anal cancer screening that uses public education and home-based, mailed screening kits may support screening in populations vulnerable to underscreening as has been seen in cervical cancer screening.[25]

Home-based screening was particularly appealing to both Black, non-Hispanic individuals and PLH. In our prior study and in other literature, fewer Black than white SMM reported a history of anal cancer screening.[24, 26] Unease of going to a clinic may contribute to missed screening among Black SMM who may have heightened concern about sexual orientation disclosure or embarrassment of the anal exam.[7] Although there are few data assessing barriers to anal cancer screening for Black individuals, it is plausible that at least some barriers to HIV testing might also act as barriers to anal cancer screening. A comprehensive review of studies on the structural barriers to HIV testing and prevention among Black SMM found that discrimination, stigma, inadequate access to culturally competent services, and limited healthcare services where Black SMM reside all decrease their ability to receive appropriate care.[27] These structural barriers might be lessened with a mailed home-based testing kit.

Among PLH in the home arm, 89.5% returned a swab while only 51.9% of those in the clinic arm screened ($p<0.001$). In addition to convenience, the home-based option may be important to PLH due, in part, to doctor visit fatigue.[28] While not unique to PLH, other reasons that may lower engagement with anal cancer screening at clinics include poor health care utilization among males, especially for preventive care,[29] anal cancer stigma,[10] and medical mistrust, especially among Black SMM.[30] The increased risk of anal cancer among Black SMM with HIV underscores the importance of optimizing screening opportunities for both Black individuals and PLH.[2]

A plurality (42.0%) of consented persons were recruited through social media while 58.7% of eligible persons who did not consent were recruited through social media (most of these were non-responsive to making a consenting appointment). Otherwise, these two groups did not differ with regard to race, ethnicity, or sexual orientation.

Two studies have reported on the adequacy of anal self-collection for PCR-based HPV DNA genotyping among SMM in clinics or community sites.[31, 32] We observed a high 96.3% adequacy of home-based self-collected swabs, which is comparable to a study of 90 HIV-negative SMM in which adequacy was 92.2% for clinic-collected swabs.[32] Another study which involved self-collection at community sites like gay bars or festivals

observed adequacy for HPV DNA genotyping of only 66.5%.[31] Collection in the home may support adequate collection for DNA genotyping due to familiar, private and informal surroundings along with fewer time-related pressures to read instructions and then complete the swabbing. We previously found that environmental conditions like high and low temperatures encountered during mailing of the PAC Packs were not associated with adequacy of these specimens.[33] Of note is that home-based self-sampling for anal cytology rather than HPV genotyping may be considered; however, it is well-established that cervical cancer self-sampling using cell preserving transport media and HPV-associated cytological outcomes is inferior to clinician sampling while HPV DNA genotyping adequacy is comparable to clinician sampling.

Anal cancer screening using only HPV genotyping at one time point among SMM and PLH is not generally available nor currently recommended given the very high prevalence of anal HPV infection.[5] However, cancer screening is generally a repeated affair,[34] which may lend itself to repeat HPV genotyping that assesses negative persistence of high-risk HPV genotypes, possibly reassuring persons at low risk for anal cancer, or positive persistence for high-risk HPV genotypes, a necessary and biologically important event that signals increased anal cancer risk.[12]

Limitations

Screening engagement in the clinic arm may have been higher except for two situations. While we saw little impact of the COVID-19 pandemic on our conclusions, we cannot rule out potential delays or non-compliance with clinic screening due to the pandemic. Also, although we partnered with five different clinics in Milwaukee, some persons in the clinic arm still may have preferred a non-study clinic, and therefore been less likely to screen; however, a required eligibility criterion was that participants state they were willing to go to at least one of the clinics. Other limitations may have biased screening engagement estimates in both arms. Persons were excluded if they currently used a blood thinner other than non-steroidal anti-inflammatory drugs. Consequently, persons engaged in preventive medicine may be more likely to screen. Alternatively, if persons are on medication it implies they may have competing health issues which could be a barrier to screening. Participants were given a $35 debit card after completion of screening and two surveys which may have increased screening engagement.

Little is known about the implementation of anal cancer screening. Given the potential for substantial barriers to screening, the widespread acceptance of anal cancer screening programs among populations at high risk for anal cancer is not certain. Our results indicate that home-based anal self-sampling may increase engagement and make it more equitable than a program requiring clinic attendance. Subsequent research should assess if home-based self-sampling will support screening engagement among other populations at increased risk for ASCC including cis-gender women with HIV, individuals with a history of HPV-associated anogenital precancer or cancer, and persons with non-HIV-related immunosuppression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Data Availability Statement

Fully de-identified datasets and data dictionary will be shared with properly trained investigators on the study website (https://mindyourbehind.org) within one year of study completion after assessment of institutional policies, Medical College of Wisconsin Human Research Protections Program rules, as well as local, state, and federal laws and regulations. Further information is available from the corresponding author upon request.

Abbreviations:

aRR	adjusted relative risk
ASCC	anal squamous cell carcinoma
CI	confidence interval
DARE	digital anal rectal examination
HPV	human papillomavirus
IQR	interquartile range
PAC	Prevent Anal Cancer Study
PLH	persons living with HIV
RR	relative risk
SMM	sexual minority men
STM	Standardized Transport Medium

References

1. Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, de Pokomandy A, Easson AM, Stier EA. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. Int J Cancer 2021;148: 38–47. [PubMed: 32621759]
2. McNeil CJ, Lee JS, Cole SR, Patel SA, Martin J, Mathews WC, Moore RD, Mayer KH, Eron JJ, Saag MS, Kitahata MM, Achenbach CJ. Anal cancer incidence in men with HIV who have sex with men: are black men at higher risk? AIDS 2022;36: 657–64. [PubMed: 34923519]
3. Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA, Rosa-Cunha I, Arons A, Pugliese JC, Vena D, Sparano JA, Wilkin TJ, et al. Treatment of anal high-grade squamous intraepithelial lesions to prevent anal cancer. N Engl J Med 2022;386: 2273–82. [PubMed: 35704479]
4. Damgacioglu H, Lin YY, Ortiz AP, Wu CF, Shahmoradi Z, Shyu SS, Li R, Nyitray AG, Sigel K, Clifford GM, Jay N, Lopez VC, et al. State variation in squamous cell carcinoma of the anus incidence and mortality, and association with HIV/AIDS and smoking in the United States. J Clin Oncol 2022: JCO2201390.
5. Clarke MA, Deshmukh AA, Suk R, Roberts J, Gilson R, Jay N, Stier EA, Wentzensen N. A systematic review and meta-analysis of cytology and HPV-related biomarkers for anal cancer screening among different risk groups. Int J Cancer 2022;151: 1889–901. [PubMed: 35793241]
6. Wentzensen N, Clarke MA, Perkins RB. Impact of COVID-19 on cervical cancer screening: Challenges and opportunities to improving resilience and reduce disparities. Prev Med 2021;151: 106596. [PubMed: 34217415]
7. Newman PA, Roberts KJ, Masongsong E, Wiley DJ. Anal cancer screening: Barriers and facilitators among ethnically diverse gay, bisexual, transgender, and other men who have sex with men. J Gay Lesbian Soc Serv 2008;20: 328–53. [PubMed: 21165164]
8. Serrano B, Ibáñez R, Robles C, Peremiquel-Trillas P, de Sanjosé S, Bruni L. Worldwide use of HPV self-sampling for cervical cancer screening. Prev Med 2022;154: 106900. [PubMed: 34861338]
9. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, Kenter GG, Cuzick J, Snijders PJ, Meijer CJ. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol 2012;13: 78–88. [PubMed: 22177579]
10. Kutner BA, Simoni JM, DeWitt W, Gaisa MM, Sandfort TGM. Gay and bisexual men who report anal sex stigma alongside discomfort discussing anal sex with health workers are less likely to have ever received an anal examination or anal swab. LGBT Health 2022;9: 103–13. [PubMed: 35133893]
11. Nyitray AG, Schick V, Swartz MD, Giuliano AR, Fernandez ME, Deshmukh AA, Ridolfi TJ, Ajala C, Brzezinski B, Sandoval M, Nedjai B, Smith JS, et al. Rationale and design of the Prevent Anal Cancer Self-Swab Study: a protocol for a randomised clinical trial of home-based self-collection of cells for anal cancer screening. BMJ Open 2021;11: e051118.
12. Poynten IM, Jin F, Roberts JM, Templeton DJ, Law C, Cornall AM, Molano M, Machalek DA, Carr A, Farnsworth A, Tabrizi S, Phillips S, et al. The natural history of anal high-grade squamous intraepithelial lesions in gay and bisexual men. Clin Infect Dis 2020;DOI: 10.1093/cid/ciaa166.
13. Lampinen TM, Latulippe L, Van Niekerk D, Schilder AJ, Miller ML, Anema A, Hogg RS. Illustrated instructions for self-collection of anorectal swab specimens and their adequacy for cytological examination. Sex Transm Dis 2006;33: 386–8. [PubMed: 16543863]
14. Darragh TM, Winkler B. Screening for anal neoplasia: anal cytology - sampling, processing and reporting. Sex Health 2012;9: 556–61. [PubMed: 22950982]
15. Hosmer DW Jr., Lemeshow S, Sturdivant RX. Applied Logistic Regression, 3rd ed. New Jersey: Wiley & Sons, 2013.
16. Spiegelman D, Hertzmark E. Easy SAS calculations for risk or prevalence ratios and differences. Am J Epidemiol 2005;162: 199–200. [PubMed: 15987728]
17. Koskan AM, LeBlanc N, Rosa-Cunha I. Exploring the perceptions of anal cancer screening and behaviors among gay and bisexual men infected with HIV. Cancer Control 2016;23: 52–8. [PubMed: 27009457]

18. Koskan AM, Fernandez-Pineda M. Anal cancer prevention perspectives among foreign-born Latino HIV-infected gay and bisexual men. Cancer Control 2018;25: 1073274818780368.
19. Cranston RD, Darragh TM, Holly EA, Jay N, Berry JM, Da Costa M, Efird JT, Palefsky JM. Self-collected versus clinician-collected anal cytology specimens to diagnose anal intraepithelial neoplasia in HIV-positive men. J Acquir Immune Defic Syndr 2004;36: 915–20. [PubMed: 15220697]
20. Chin-Hong PV, Berry JM, Cheng SC, Catania JA, Da Costa M, Darragh TM, Fishman F, Jay N, Pollack LM, Palefsky JM. Comparison of patient- and clinician-collected anal cytology samples to screen for human papillomavirus-associated anal intraepithelial neoplasia in men who have sex with men. Ann Intern Med 2008;149: 300–6. [PubMed: 18765699]
21. Fisher M, Wayal S, Smith H, Llewellyn C, Alexander S, Ison C, Parry JV, Singleton G, Perry N, Richardson D, Brighton Home Sampling Kit Project Steering G. Home sampling for sexually transmitted infections and HIV in men who have sex with men: a prospective observational study. PLoS One 2015;10: e0120810. [PubMed: 25848769]
22. Silvestri GA, Goldman L, Burleson J, Gould M, Kazerooni EA, Mazzone PJ, Rivera MP, Doria-Rose VP, Rosenthal LS, Simanowith M, Smith RA, Tanner NT, et al. Characteristics of Persons Screened for Lung Cancer in the United States : A Cohort Study. Ann Intern Med 2022;175: 1501–5. [PubMed: 36215712]
23. Ong J, Chen M, Temple-Smith M, Walker S, Hoy J, Woolley I, Grulich A, Fairley C. The inside story. Physicians' views on digital ano-rectal examination for anal cancer screening of HIV positive men who have sex with men. J Med Screen 2013;20: 188–91. [PubMed: 24307004]
24. Gillis JL, Grennan T, Grewal R, Ogilvie G, Gaspar M, Grace D, Lofters A, Raboud JM, Saarela O, Rosenes R, Salit IE, Burchell AN. Racial disparities in anal cancer screening among men living with HIV: findings from a clinical cohort study. J Acquir Immune Defic Syndr 2020;84: 295–303. [PubMed: 32097251]
25. Fuzzell LN, Perkins RB, Christy SM, Lake PW, Vadaparampil ST. Cervical cancer screening in the United States: challenges and potential solutions for underscreened groups. Prev Med 2021;144: 106400. [PubMed: 33388330]
26. Hicks JT, Hwang LY, Baraniuk S, White M, Chiao EY, Onwuka N, Ross MW, Nyitray AG. Factors associated with self-reported anal cancer screening history in men who have sex with men. Sex Health 2019;16: 96–8. [PubMed: 30517839]
27. Levy ME, Wilton L, Phillips G 2nd, Glick SN, Kuo I, Brewer RA, Elliott A, Watson C, Magnus M. Understanding structural barriers to accessing HIV testing and prevention services among black men who have sex with men (BMSM) in the United States. AIDS Behav 2014;18: 972–96. [PubMed: 24531769]
28. Heckman BW, Mathew AR, Carpenter MJ. Treatment burden and treatment fatigue as barriers to health. Curr Opin Psychol 2015;5: 31–6. [PubMed: 26086031]
29. Mursa R, Patterson C, Halcomb E. Men's help-seeking and engagement with general practice: An integrative review. Journal of Advanced Nursing 2022;78: 1938–53. [PubMed: 35384022]
30. Eaton LA, Driffin DD, Kegler C, Smith H, Conway-Washington C, White D, Cherry C. The role of stigma and medical mistrust in the routine health care engagement of black men who have sex with men. Am J Public Health 2015;105: e75–82.
31. Gilbert M, Kwag M, Mei W, Rank C, Kropp R, Severini A, van Niekerk D, Zhou C, Press N, Ogilvie G, Wong T, the ManCount Study Team. Feasibility of incorporating self-collected rectal swabs into a community venue-based survey to measure the prevalence of HPV infection in men who have sex with men. Sex Transm Dis 2011;38: 964–9. [PubMed: 21934574]
32. Yared NF, Horvath KJ, Baker JV, Thyagarajan B, Waterboer T, Kulasingam S. Concordance of self- and clinician-collected anal swabs to detect human papillomavirus in a sample of HIV-negative men. J Low Genit Tract Dis 2019;23: 200–4. [PubMed: 30946259]
33. Nitkowski J, Giuliano A, Ridolfi T, Chiao E, Fernandez M, Schick V, Swartz MD, Smith JS, Schneider EA, Brzezinski B, Nyitray AG. Effect of the environment on home-based self-sampling kits for anal cancer screening. J Virol Methods 2022;310: 114616. [PubMed: 36096333]
34. Wilson JMG, Jungner G, Public Health Papers, #34: Principles and Practice of Screening for Disease. World Health Organization, 1968.

What's New?

Little is known about the implementation of anal cancer screening. We assessed the utility of anal canal self-sampling in a randomized trial that compared home-based self-sampling with clinician sampling among sexual and gender minorities with and without HIV. Home-based anal self-sampling was preferred to clinic-based screening while specimen adequacy for HPV genotyping was comparable and >90% in both arms. The home-based self-sampling was especially appealing to individuals who were Black and those living with HIV.

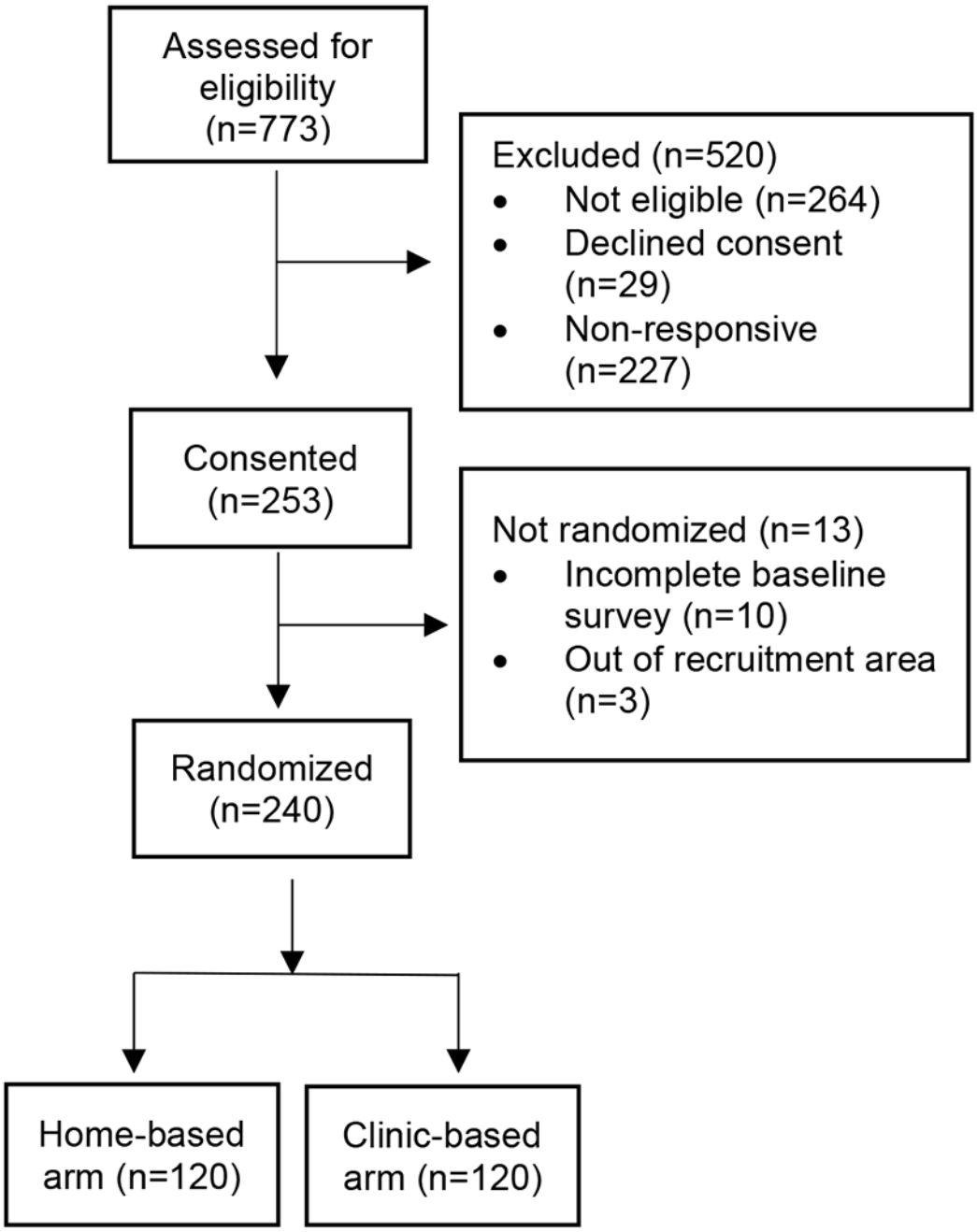

Figure 1:
Trial Profile

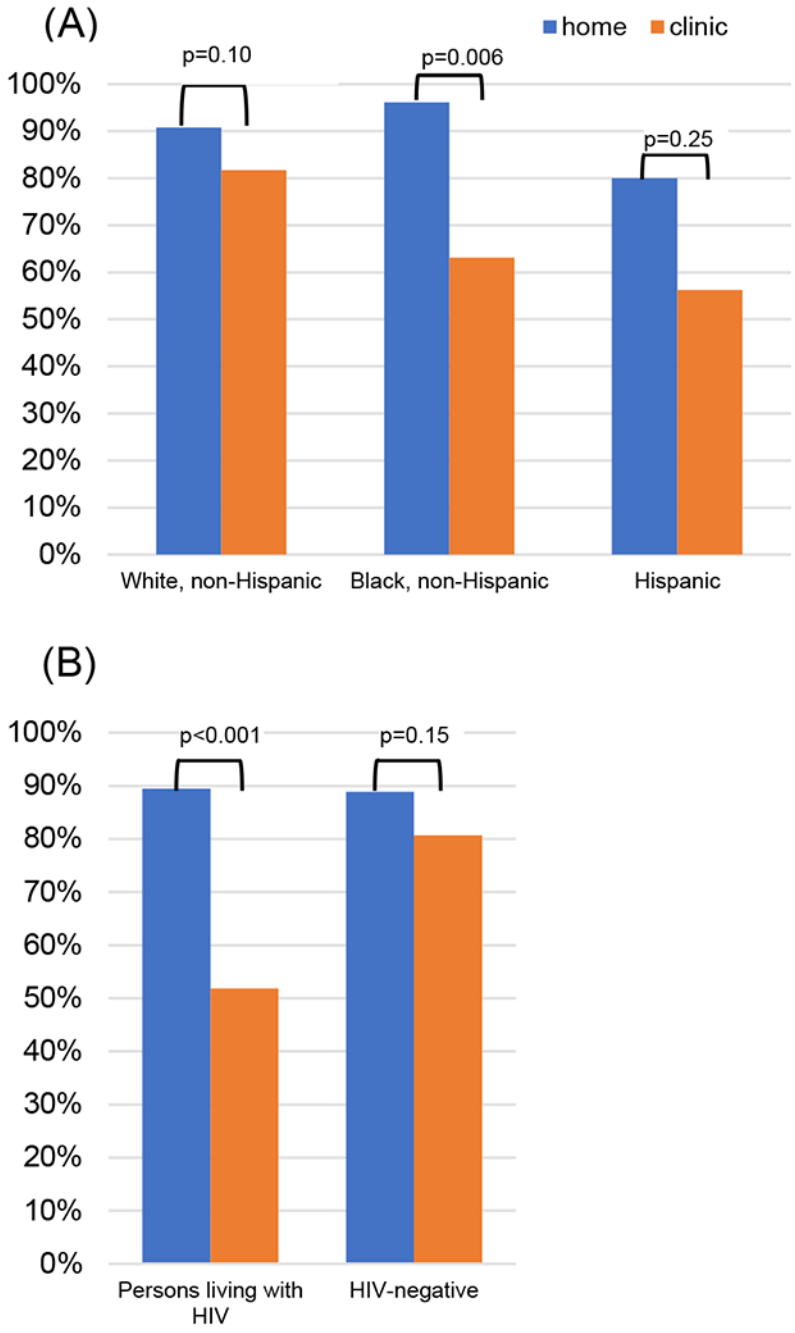

Figure 2:
Proportion of participants who engaged in screening by study arm stratified by (A) race and ethnicity and (B) HIV status. “Other” race excluded due to sparse data (n=5).

Table 1:

Characteristics of participants randomized to home or clinic arm in the Prevent Anal Cancer Self-Swab Study, Milwaukee, Wisconsin, 2020-2022, n (%)

Characteristic	Total (n=240)	Home (n=120)	Clinic (n=120)
Age, years *median (IQR)*	*46 (33-57)*	*46 (33-57)*	*45 (33-59)*
Age, years (categorical)			
25-34	71 (29.6)	35 (29.2)	36 (30.0)
35-44	43 (17.9)	20 (16.7)	23 (19.2)
45-54	45 (18.8)	24 (20.0)	21 (17.5)
55-78	81 (33.8)	41 (34.2)	40 (33.3)
Gender identity			
Man	227 (94.6)	115 (95.8)	112 (93.3)
Transgender, non-binary, or other	13 (5.4)	5 (4.2)	8 (6.7)
Sexual orientation			
Gay	198 (82.5)	99 (82.5)	99 (82.5)
Bisexual, queer	38 (15.8)	20 (16.7)	18 (15.0)
Lesbian, heterosexual or other	3 (1.3)	1 (0.8)	2 (1.7)
Missing	1 (0.4)	0	1 (0.8)
Race/ethnicity			
White, non-Hispanic	158 (65.8)	76 (63.3)	82 (68.3)
Black, non-Hispanic	45 (18.8)	26 (21.7)	19 (15.8)
Hispanic	31 (12.9)	15 (12.5)	16 (13.3)
Other, non-Hispanic[§]	5 (2.1)	2 (1.7)	3 (2.5)
Missing	1 (0.4)	1 (0.8)	0
Education, years			
≤ 12	30 (12.5)	12 (10.0)	18 (15.0)
13-15	64 (26.7)	34 (28.3)	30 (25.0)
16	44 (18.3)	22 (18.3)	22 (18.3)
> 16	101 (42.1)	51 (42.5)	50 (41.7)
Missing	1 (0.4)	1 (0.8)	0
Health insurance			
No	14 (5.8)	6 (5.0)	8 (6.7)
Yes	224 (93.3)	114 (95.0)	110 (91.7)
Missing	2 (0.8)	0	2 (1.7)
HIV			
Negative	175 (72.9)	82 (68.3)	93 (77.5)
Positive	65 (27.1)	38 (31.7)	27 (22.5)
HPV vaccination			
Never	134 (55.8)	65 (54.2)	69 (57.5)
Ever	48 (20.0)	21 (17.5)	27 (22.5)
Don’t know	57 (23.8)	34 (28.3)	23 (19.2)
Missing	1 (0.4)	0	1 (0.8)

Characteristic	Total (n=240)	Home (n=120)	Clinic (n=120)
Any anal cytology history			
No	157 (65.4)	73 (60.8)	84 (70.0)
Yes	58 (24.2)	36 (30.0)	22 (18.3)
Don’t know	25 (10.4)	11 (9.2)	14 (11.7)
Anal sex position preference			
Insertive anal sex	47 (19.6)	24 (20.0)	23 (19.2)
Versatile	111 (46.3)	55 (45.8)	56 (46.7)
Receptive anal sex	71 (29.6)	38 (31.7)	33 (27.5)
Never engaged in anal sex	8 (3.3)	2 (1.7)	6 (5.0)
Missing	3 (1.3)	1 (0.8)	2 (1.7)
History of anal warts			
No	179 (74.6)	87 (72.5)	92 (76.7)
Yes	59 (24.6)	32 (26.7)	27 (22.5)
Missing	2 (0.8)	1 (0.8)	1 (0.8)
COVID-19 pandemic-associated enrollment date *			
Prior to trial suspension	35 (14.6)	17 (14.2)	18 (15.0)
After trial resumed	205 (85.4)	103 (85.8)	102 (85.0)

Abbreviations: IQR, Interquartile range; HPV, human papillomavirus

§ Other includes Asian, American Indian or Alaskan Native, other, and “I don’t know.”

* Study enrollment was suspended due to COVID-19 pandemic stay-at-home orders on March 14, 2020 and then resumed on November 3, 2020

Table 2:

Intention-to-treat analysis of the proportion of randomized participants who engaged in screening and produced an adequate swab for genotyping in the Prevent Anal Cancer Self-Swab Study, Milwaukee, Wisconsin, 2020-2022, n (%)

	Home arm (n=120)		Clinic arm (n=120)	
	Engaged in screening	Produced an adequate swab†	Engaged in screening	Produced an adequate swab†
All participants	107 (89.2)	103 (96.3)	89 (74.2)	83 (93.3)
Days to screening engagement*median (IQR)*	*9 (6-14)*	n/a	*20 (10-36)*	n/a
Age, years				
25-34	30 (85.7)	29 (96.7)	26 (72.2)	25 (96.2)
35-44	20 (100.0)	19 (95.0)	15 (65.2)	15 (100.0)
45-54	20 (83.3)	19 (95.0)	16 (76.2)	14 (85.7)
55-77	37 (90.2)	36 (97.3)	32 (80.0)	29 (90.6)
Gender identity				
Man	104 (90.4)	100 (96.2)	84 (75.0)	79 (94.1)
Transgender, non-binary, or other	3 (60.0)	3 (100.0)	5 (62.5)	4 (80.0)
Sexual orientation				
Gay	91 (91.9)	87 (95.6)	78 (78.8)	73 (93.6)
Bisexual, queer	16 (80.0)	16 (100.0)	9 (50.0)	9 (100.0)
Lesbian, heterosexual or other	0	0	1 (50.0)	0
Race/ethnicity				
White, non-Hispanic	69 (90.8)	66 (95.7)	67 (81.7)	62 (92.4)
Black, non-Hispanic	25 (96.2)	25 (100.0)	12 (63.2)	11 (91.7)
Hispanic	12 (80.0)	11 (91.7)	9 (56.3)	9 (100.0)
Other, non-Hispanic‡	0	0	1 (33.3)	1 (100.0)
Education, years				
≤ 12	7 (58.3)	7 (100.0)	11 (61.1)	10 (90.9)
13-15	31 (91.2)	31 (100.0)	21 (70.0)	19 (90.5)
16	20 (90.9)	19 (95.0)	18 (81.8)	17 (94.4)
> 16	49 (96.1)	46 (93.9)	39 (78.0)	37 (94.9)
Health insurance				
No	6 (100.0)	6 (100.0)	4 (50.0)	4 (100.0)
Yes	101 (88.6)	97 (96.0)	84 (76.4)	78 (92.9)
HIV				
Negative	73 (89.0)	71 (97.3)	75 (80.7)	69 (92.0)
Positive	34 (89.5)	32 (94.1)	14 (51.9)	14 (100.0)
HPV vaccination				
Never	56 (86.2)	54 (96.4)	49 (71.0)	44 (89.8)
Ever	20 (95.2)	19 (95.0)	22 (81.5)	22 (100.0)
Don’t know	31 (91.2)	30 (96.8)	17 (73.9)	16 (94.1)
Any anal cytology history				

	Home arm (n=120)		Clinic arm (n=120)	
	Engaged in screening	Produced an adequate swab†	Engaged in screening	Produced an adequate swab†
No	65 (89.0)	63 (96.9)	64 (76.2)	58 (90.6)
Yes	32 (88.9)	30 (93.8)	15 (68.2)	15 (100.0)
Don't know	10 (90.9)	10 (100.0)	10 (71.4)	10 (100.0)
Anal sex position preference				
Insertive anal sex	23 (95.8)	22 (95.7)	18 (78.3)	16 (88.9)
Versatile	49 (89.1)	47 (95.9)	45 (80.4)	44 (97.8)
Receptive anal sex	33 (86.8)	32 (97.0)	21 (63.6)	19 (90.5)
Never engaged in anal sex	1 (50.0)	1 (100.0)	4 (66.7)	3 (75.0)
History of anal warts				
No	78 (89.7)	75 (96.2)	66 (71.7)	60 (90.9)
Yes	28 (87.5)	27 (96.4)	22 (81.5)	22 (100.0)
COVID-19 pandemic-associated enrollment date§				
Prior to trial suspension	13 (76.5)	11 (84.6)	10 (55.6)	8 (80.0)
After trial resumed	94 (91.2)	92 (97.9)	79 (77.5)	75 (94.9)

Abbreviations: HPV, human papillomavirus; n/a, not applicable

†The denominator is the total number of persons who engaged in screening in each arm.

‡Other includes Asian, American Indian or Alaskan Native, other, and "I don't know."

§Study enrollment was suspended due to COVID-19 pandemic stay-at-home orders on March 14, 2020 and then resumed on November 3, 2020.

Table 3:

Intention-to-treat analysis of factors associated with participants who engaged in anal cancer screening in Milwaukee, Wisconsin, 2020-2022, univariate and multivariable analysis

Characteristic	RR (95% CI)	aRR* (95% CI)
Study arm		
Clinic	1.0	1.0
Home	**1.20 (1.06-1.36)**	**1.22 (1.08-1.38)**
Age, years	1.00 (1.00-1.01)	-
Gender identity		
Man	1.0	-
Transgender, non-binary, or other	0.74 (0.48-1.15)	-
Sexual orientation		
Gay	1.0	1.0
Bisexual, queer	**0.77 (0.61-0.98)**	**0.76 (0.60-0.95)**
Lesbian, heterosexual or other	0.39 (0.08-1.94)	0.41 (0.08-2.07)
Race/ethnicity		
White, non-Hispanic	1.0	-
Black, non-Hispanic	0.96 (0.82-1.11)	-
Hispanic	0.79 (0.61-1.01)	-
Other, non-Hispanic†	0.23 (0.04-1.34)	-
Education, years		
≤ 12	1.0	-
13-15	1.35 (0.99-1.86)	-
16	**1.44 (1.05-1.97)**	-
>16	**1.45 (1.07-1.96)**	-
HIV		
Negative	1.0	1.0
Positive	**0.87 (0.75-1.02)**	**0.85 (0.73-0.98)**

Note, confidence intervals in bold do not include unity.

*Variables are adjusted for each other in addition to age (continuous) and COVID-associated enrollment date.

†Other includes Asian, American Indian or Alaskan Native, other, and “I don’t know.”