Title of Manuscript: The Feasibility of Self-Collected Screening for HPV DNA: A Systematic Review and Meta-Analysis (Protocol)

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Contributions:
EJN conceived and designed the study. EJN and BRM drafted the manuscript. BRM, LA, TL, JF and RG assisted in study design. All authors participated in editing the manuscript and approved the final protocol.
Rationale

Persistent infection with human papillomavirus (HPV) is the major cause for cervical cancer and genital warts.\(^1,2\) HPV has also been etiologically linked to other anogenital (vagina, vulva, anus and penis) and head and neck cancers, particularly oropharyngeal cancers.\(^3\) HPV is sexually transmitted, and infections are very common, with the prevalence of genital HPV infections peaking between ages 18 and 30.\(^4-6\) Most sexually active persons will acquire HPV in their lifetime.\(^7,8\) There are more than 150 different types (strains) of HPV, with over 40 HPV types that infect the genital areas of men and women, most often during vaginal or anal sex.\(^2,9\)

HPV types differ as to which type of epithelium they invade, their ability to evade immune detection, to resist immune defense mechanisms, and their oncogenic capabilities. HPV types are categorized into two groups based on their oncogenic potential: high-risk (HR-HPV) and low-risk (LR-HPV). LR-HPV types, such as types 6 or 11, can cause 1) benign or low-grade cellular abnormalities, 2) anogenital warts, and 3) recurrent respiratory papillomatosis (RRP).\(^10\) HR-HPV types, including types 16 and 18, can cause intraepithelial neoplasia of the anogenital region, including cervical, vulvar, vaginal, penile, and anal cancers as well as oropharyngeal cancers.\(^11-13\) HPV types 16 and 18 are considered the most highly oncogenic types as they collectively account for approximately 72% of HPV-related cancers.\(^11\)

It is important to emphasize that most HPV infections are asymptomatic, transient, and are cleared naturally without treatment.\(^2,6,14\) For example, the average duration of cervical HPV infection is estimated to last 4.3 months for LR-HPV and 9.8 months for HR-HPV among college aged women in the U.S.\(^15,16\) Whereas HPV infection in other sites has been observed to last between 4 and 20 months.\(^6,17\) As a result, aggressive annual testing and screening for HPV infection in the general population would be extremely expensive and impractical in order to
reduce HPV-associated outcomes. Moreover, an aggressive strategy of annual screening could lead to unnecessary procedures, treatments, and triage of infections that would otherwise clear naturally.\textsuperscript{18,19} Therefore, the current strategies to limit the long-term effects of HPV rely upon early detection and screening for disease outcomes.

Randomized controlled trials conducted over the last decade suggest that HPV DNA testing could be a more effective approach for the early detection of cervical cancer for women over the age of 30 years than cytology alone.\textsuperscript{20} HPV DNA testing is currently recommended in combination with cervical cytology for cervical cancer screening in women 30 years and older due to its high sensitivity for detecting cervical precursor lesions.\textsuperscript{21,22} Recently, the United States Food and Drug Administration approved the use of primary stand-alone type specific HPV DNA testing for cervical cancer in women aged 25 years or older.\textsuperscript{23} Currently, HPV DNA testing is typically performed in a clinic by a clinician who collects a cervical sample during a pelvic exam.\textsuperscript{24} However, HPV DNA has the potential, unlike cervical cytology, to be self-collected. Recent studies of self-collected vaginal samples for HPV testing have shown a high concordance between samples collected by patients and those obtained by clinicians.\textsuperscript{25-29} In addition, women have generally responded positively to collecting their own cervical samples.\textsuperscript{30-33} However, these studies have been conducted in clinical settings in which clinic staff has usually provided instructions for self-collection.

HPV DNA self-sampling strategies have also been adopted to detect oral, penile, and anal HPV infections, although it is not currently a recommended screening strategy for these cancers.\textsuperscript{33-35} One potential advantage of self-sampling is that screening and preventative services could be used to target specific populations who do not routinely receive them.\textsuperscript{33,34,36} Although self-sampling strategies have shown great promise in terms of detecting disease, it is unclear
whether these strategies can be implemented independent of a clinical setting in a manner that is acceptable to men and women. It is also unclear whether the acceptability of self-sampling varies by anatomical site and by sex.

**Objectives:**

The purpose of this systematic review and meta-analysis will be to examine whether or not self-collected screening for HPV DNA is feasible for large population-based screening for HPV-associated cancers. Our specific research questions are:

1. Are self-collected vaginal samples an acceptable cervical cancer screening alternative for women compared to clinician-based screening?
2. Are self-collected oral samples an acceptable screening alternative for men and women compared to clinician-based screening?
3. Are self-collected anal samples an acceptable screening alternative for men and women compared to clinician-based sampling?

In addition to the primary research questions, three secondary research questions will be examined in this review:

4. Is self-collected sampling for HPV DNA a cost-effective alternative to clinician-based sampling for population-based screening strategies compared to clinician-based screening?
5. Does self-collected sampling for HPV DNA increase access to screening and preventative services?
6. What are barriers to performing self-collected HPV DNA screening?

**Methods**

**Inclusion and exclusion criteria**
Eligible studies will include both randomized and non-randomized controlled trials, pre-and post-test designs, observational, and cross-sectional studies that examine adult male or female participant preferences and opinions or cost-benefit of self-collected vaginal, anal, or oral HPV DNA screening. Studies reporting only a kappa statistic (measuring the agreement between the self-collected sample and the clinician-collected sample) will also be reviewed. In addition to studies identified above, we will also include studies using any empirical study design that examines access and barriers of self-collected sampling for HPV DNA. Studies will not be excluded based on publication status or language. If we encounter studies written in a language other than English, we will attempt to translate the study. However, due to limited resources, if we are not able to translate the study, we will exclude the study and document this in our review.

**Search Strategy**

A comprehensive search strategy will be used to search for published and unpublished studies that meet the above inclusion criteria. Our search will be limited to studies published since 1986 based on two criteria: (1) the first study of HPV DNA testing was reported in 1986, and (2) the first known HPV self-testing article occurred in 1993. We will search the following 4 databases for potentially relevant studies: Cochrane Database of Systematic Reviews, Scopus, Web of Science, and PubMed/Medline. In addition to academic databases, we will search reference lists of included studies and prior related reviews for relevant studies as well as forward citation searching by using Google Scholar to search for studies citing included studies. The review team will also be asked to identify key articles to be screened or used for reference searching. We will also manually search the following key journals: *Sexually Transmitted Infections, Sexually Transmitted Diseases, Vaccine*, and *Sexual Health*. We will search for unpublished studies through contact with researchers working in this area, a web search of
relevant research centers, search of conference abstracts of the International Papillomavirus Society, and searching ProQuest Dissertations and Theses and OpenGrey.

**Search Terms**

MeSH headings, subject headings and keywords will be created using language that describes clinician and self-collected sampling for HPV DNA testing. The scope notes of the MeSH headings and subject headings and terms will be reviewed to identify additional terms, common usage and previous usage for terms being searched. Keywords in published journals will also be used. Search terms will include but will not be limited to: human papillomavirus; HPV; screening; DNA testing; vaginal testing; self-collected specimen; self-collected sample; self-sampling; self-screening; preferences and acceptability. Boolean operators will be used to combine search terms for more specific searches. We will document and report specific search terms and limiters used in each database.

**Study Selection and Data Extraction**

All titles and abstracts retrieved through the search strategy will be screened for relevance by one reviewer. The full text of all studies that are not obviously ineligible or are questionable at this stage will be obtained and independently screened for eligibility by two reviewers using a screening instrument. Discrepancies in screening decisions between the two reviewers will be resolved through discussion and consensus and, when necessary, a third reviewer will be consulted. Two reviewers will then independently code all reports that pass eligibility screening using a coding instrument to guide systematic examination and extraction of data. The coding instrument will first be pilot tested by two reviewers with two studies and adjustments to the coding form will be made as needed. After finalization of the coding instrument, two reviewers will then independently code the remainder of the studies.
Disagreements will be resolved by discussion and consensus and, when necessary, a third reviewer will be consulted.

The coding instrument includes categories concerning all relevant bibliographic information; study context, sample descriptors, study research methods and design; and effect size data (coding instrument may be obtained from the authors). Specifically, the following data elements will be abstracted, and if appropriate, used for stratification if heterogeneity is found: age of participants; sex; HIV status; date of study initiation and publication status (published or unpublished); country of study and author affiliation; number of specimens analyzed; number of tests per patient; any elements of blinding; location of self-collection (home, clinic and so on); community type (urban, rural); population type (stable, homeless); sexual orientation (heterosexual, gay, bisexual, transgendered); religion; location of test (clinical setting, home, other); clinician setting (outreach, primary care, referral); whether tested in conjunction with cervical cytology (yes, no); type of HPV test assay (Hybrid Capture 2, Cervista, cobas, CLART, APTIMA, etc.); type of sampling device used (cytobrush, FTA elute, Q-tip, etc.); HPV type (high-risk, low-risk or both); HPV prevalence; acceptability of self-sampling (measured on likert scales or as percentage of respondents); preference of collection method (self-collection, clinician-collected, both). If studies involve several self-sampling methods, each method described will be used in the analysis.

Quality

We anticipate several study design to be relevant to this review, including randomized or quasi-experimental studies, cohort studies and cross-sectional studies; therefore, we will assess quality using a tool appropriate to the study design. We will assess risk of bias for randomized controlled trials using Cochrane’s risk of bias tool\(^\text{40}\) and quasi-experimental studies using the
Cochran’s risk of bias assessment tool for non-randomized studies of interventions.\textsuperscript{41} For cohort and cross-sectional studies, we will use the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.\textsuperscript{42}

**Data Analysis**

**Descriptive analysis.** We will conduct descriptive analyses on all variables of interest to provide information regarding characteristics of included studies, participants and settings.

**Study level effect size estimation.** We will estimate study level effect sizes for all studies that report sufficient data to calculate effect sizes. If authors do not report sufficient data to calculate an effect size, we will contact primary study authors to request data. For studies that report results for the aggregate sample and separately for distinct subsamples (e.g., males and females; risk status), we will calculate effect sizes for the full sample. If a sufficient number of studies present subgroup data for the same subgroups, we will calculate effect size estimates for subgroups. For randomized or quasi-experimental studies that report continuous data, the standardized mean difference effect size statistic will be calculated, with adjustments made for small sample size bias (Hedges’ g). For studies reporting relative frequencies or proportions, the odds-ratio effect size statistic will be calculated. For studies that report pre-post contrasts within a group, we will use the standardized mean gain effect size statistic. For studies reporting associations between variables, the Pearson product-moment correlation will be used for continuous variables and odds ratio for dichotomous variables.

**Pooling of effect sizes.** Following the estimation of individual study level effects, we will conduct separate meta-analyses to calculate summary effects and 95% confidence intervals for studies reporting pre-post contrasts, group contrasts, and associations between variables for both
vaginal, anal and oral collection. Effect sizes will be weighted by the inverse of its variance and random effects models will be assumed.

To ensure independence of effect sizes, we will use only one effect size per study per construct in the meta-analysis. We anticipate that some studies may use multiple measures for one construct. In those cases, we will code data for each measure and create a study level average across the measures. In cases where we examine that a particular study may be reported in multiple reports, care will be taken to ensure that the study findings are represented only once in the summary effects. If it is unclear whether reports and studies provide independent findings, the authors of the reports will be contacted to clarify the discrepancy.

Following the estimation of summary effects, we will assess statistical heterogeneity using the $Q$-test and $I^2$ statistic. The $Q$ statistic is distributed as a chi-square with $k-1$ degrees of freedom ($k =$ the number of effect sizes). The $Q$ statistic is calculated by adding the squared deviations of each study’s effect size from the mean effect size, weighting their contribution by its inverse variance. A significant $Q$ rejects the null hypothesis, indicating that the variability of effect sizes between studies is greater than what would be expected by sampling error alone. The $I^2$ statistic describes the percentage of total variation across studies due to the heterogeneity rather than chance. We will also construct a forest plot displaying study-level mean effect sizes and 95% confidence intervals for the included studies to provide opportunity for visual analysis of the precision of the estimated effect sizes, detection of studies with extreme effects, and information regarding heterogeneity of studies.

Given an adequate number of studies and heterogeneity between studies, moderator analyses will be performed. We plan to examine whether the following characteristics are associated with magnitude of effect size: HPV vaccination status, race, health insurance
coverage, low income, sexual orientation.

**Treatment of qualitative research.** For the secondary research questions related to access and barriers, we anticipate the collection and analysis of qualitative data. For all studies that report qualitative data related to access or barriers, we will extract the data from studies and import the data into a Word document for analysis. We plan to employ a systematic and quantitative approach to content analysis, which allows for quantitative description of content of text. In content analysis, data (often textual material) is coded according to a classification scheme, which can be developed through inductive and/or deductive processes. For the purposes of this review, we anticipate using an inductive approach to coding, as we do not have preconceived ideas of themes or categories. Two reviewers will independently conduct open coding on a subset of at least 5 studies to develop a classification scheme to code manifest content (i.e., content that was present in the text rather than implied meanings of the text). Each reviewer will read through all qualitative data related to access and barriers extracted from included studies. After the initial review of qualitative data, a second careful read of the extracted data will be conducted and words and phrases will be highlighted to capture themes, and categories will be developed. Reviewers will meet to compare the set of preliminary categories identified by each reviewer and discuss and resolve differences. Reviewers will then develop a structured coding form that will be used to code and aggregate the data in each study.

**Conflicts of Interest and Financial Support:** The authors report no conflicts of interest. No financial support has been received by study authors for the conduct of this review.
References


