Protocol

Stress Biology, Vaginal Microbiome Dynamics, and Diagnostic Outcomes After Abnormal Cervical Cancer Screening: Protocol for a Digitally Enabled Multimodal Prospective Cohort Study

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Abstract

Background: Cervical cancer risk is shaped by interacting psychosocial, biological, microbial, and clinical processes; however, few prospective studies integrate repeated biospecimens, ecological momentary assessment, wearable data, and electronic health record information within the same cohort. This gap is especially important in populations disproportionately affected by cervical cancer inequities.

Objective: This paper describes the protocol and the current implementation of a digitally enabled prospective cohort study designed to examine how psychosocial stress, cortisol regulation, vaginal microbiome dynamics, human papillomavirus–related factors, and clinical follow-up jointly influence the resolution or persistence of abnormal cervical cancer screening findings at diagnostic evaluation.

Methods: The study is recruiting women aged 21 to 65 years after an abnormal cervical cancer screening result and before diagnostic colposcopy. The target sample is 270 women (90 Latina, 90 non–Latina Black, and 90 non–Latina White). Study procedures include electronic health record–based prescreening; in-person consent and onboarding; baseline surveys; twice-daily ecological momentary assessment for 14 days; home salivary cortisol collection; passive Fitbit monitoring; retrieval of residual Pap (Papanicolaou) material from the index abnormal screen (T0); blood, urine, saliva, vaginal pH, and a self-collected vaginal swab at baseline (T1); and provider-collected vaginal and cervical sampling at follow-up colposcopy (T2). Data are integrated across Epic, REDCap, participant-facing digital tools, biospecimen workflows, and pathology-linked outcomes. The 2 coprimary confirmatory analyses use Firth bias-reduced logistic regression to estimate the adjusted odds of persistence associated with a standardized baseline 10-item Perceived Stress Scale score and a standardized participant-level mean diurnal cortisol slope, controlling for age, race or ethnicity, and index screening risk stratum.

Results: Recruitment began in September 2025. As of July 15, 2026, 180 women had been prescreened, 25 had met eligibility criteria, 24 had been contacted, 13 had completed direct screening, 8 had declined participation, 3 participants had enrolled, and 2 had completed the study. Recruitment and longitudinal data collection are expected to continue through December 2028,

after which primary analyses will evaluate multilevel associations among stress, cortisol, vaginal microbiome features, human papillomavirus–related factors, and the resolution or persistence of screening outcomes at diagnostic follow-up.

Conclusions: This prospective cohort study provides a protocol model for equity-focused, prospective cohort research to examine multilevel drivers of women's health. By integrating psychosocial, biological, digital, and clinical data across multiple time points, the study is positioned to inform both mechanistic research on pathways underlying the resolution or persistence of abnormal cervical cancer screening results and implementation strategies for complex, participant-centered longitudinal studies.

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Introduction

Cervical cancer prevention does not end with screening. An abnormal cervical cancer screening result identifies elevated risk but does not confirm the presence of a histologically defined precancerous lesion; diagnostic evaluation through colposcopy and, when indicated, biopsy is required to determine whether clinically meaningful disease is present. Many abnormalities detected at screening ultimately resolve, regress, or do not correspond to high-grade histopathology; however, uncertainty during the interval between abnormal screening and diagnostic workup can trigger repeat testing, colposcopy, biopsy, and sometimes treatment that prove unnecessary in retrospect [1-5]. The burdens associated with this interval, including uncertainty, additional appointments, invasive procedures, and downstream reproductive consequences, are not evenly distributed.

Cervical cancer disparities are shaped by multilevel and socioecological forces rather than biology alone. Inequities in screening access, language concordance, follow-up, transportation, caregiving demands, insurance, and trust in health systems can alter who receives timely diagnostic evaluation and how burdensome abnormal-screen management becomes [1,6-8]. These structural and interpersonal stressors may be particularly salient for populations already experiencing disproportionate exposure to social disadvantage, making the abnormal-screen interval an important setting in which distal inequities can influence both care processes and biological responses.

Within this broader framework, the vaginal microbiome is increasingly understood as one potential contributor to human papillomavirus (HPV) persistence and cervical lesion behavior [9-14]. Psychosocial stress and cortisol regulation may influence microbial ecology, immune response, and vaginal homeostasis, offering one plausible mechanism through which social conditions become biologically embedded [12-19]. A prospective design that captures psychosocial experiences, physiological stress response, microbial dynamics, and diagnostic outcomes across the same interval may therefore help clarify how distal stressors and proximal biology jointly shape the resolution vs persistence of abnormal cervical screening findings.

The study was therefore developed as a prospective, digitally enabled cohort spanning the interval between an abnormal cervical cancer screening result and diagnostic evaluation. The study protocol was designed to generate a high-resolution longitudinal dataset by integrating electronic health record (EHR)–based prescreening and clinical outcomes with repeated biospecimens, patient-reported outcomes, ecological momentary assessment (EMA), and wearable data. The aim of this paper is to describe the study protocol, implementation framework, and early recruitment experience, and the study's primary scientific hypothesis is that greater psychosocial stress burden and more dysregulated diurnal cortisol patterns will be associated with the persistence of abnormal screening findings at diagnostic evaluation, with vaginal microbiome features serving as key candidate mediators or modifiers across racial and ethnic groups.

Methods

Study Aims

The study aims to examine whether psychosocial stress, cortisol regulation, vaginal microbiome dynamics, and HPV-related factors contribute to the resolution vs persistence of abnormal cervical cancer screening findings at the time of diagnostic evaluation across racial and ethnic groups; to evaluate the feasibility and acceptability of integrating biospecimen, digital, and clinical workflows during the interval between an abnormal screening result and diagnostic colposcopy; and to establish a longitudinal, multimodal data platform to support future multilevel mechanistic analyses.

For confirmatory analyses, the primary outcome is diagnostic outcome classification at T2 (resolution or nonpersistence vs persistence). The 2 coprimary participant-level exposures are the baseline 10-item Perceived Stress Scale (PSS-10) total score and the participant-level mean diurnal salivary cortisol slope across valid paired collection days. Vaginal microbiome summaries are prespecified secondary mediator and effect-modifier candidates; high-dimensional microbiome, metabolomic, HPV-related, wearable, and biomarker analyses remain secondary or exploratory. The confirmatory model specification and power assumptions are summarized in Multimedia Appendix 1.

Figure 1. Hypothesized conceptual model linking psychosocial stress, cortisol regulation, vaginal microbiome dynamics, human papillomavirus (HPV)–related factors, and the resolution vs persistence of abnormal cervical cancer screening findings at diagnostic evaluation. EMA: ecological momentary assessment.

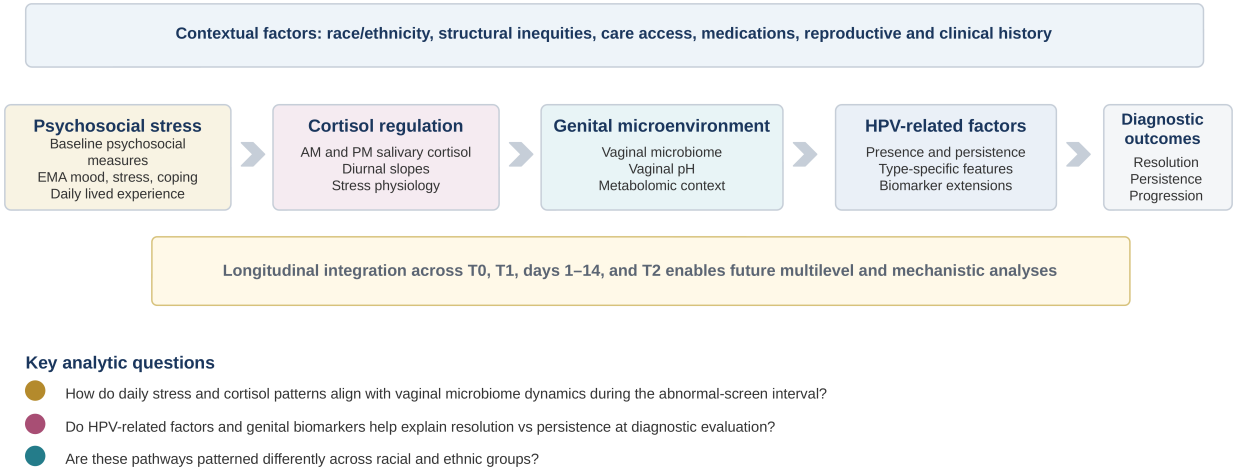


Figure 1 presents the hypothesized conceptual model linking psychosocial stress, cortisol regulation, vaginal microbiome dynamics, HPV-related factors, and diagnostic outcome classification.

Study Design and Setting

This study is an ongoing prospective cohort implemented within women's clinics and the affiliated clinical laboratory of an academic safety-net hospital. The cohort is anchored to an abnormal cervical cancer screening result, followed by planned diagnostic colposcopy. The temporal structure includes T0 retrieval of historical residual Pap (Papanicolaou) material, a T1 baseline orientation visit, a 14-day home monitoring period, and a T2 follow-up colposcopy visit.

Table 1 and Multimedia Appendix 2 summarize the study timeline, time point structure, and integrated clinical, biospecimen, and digital data streams. Study-specific operational materials, workflow summaries, the prespecified confirmatory analysis and power calculation, the protocol amendment chronology, and the study schema are provided in Multimedia Appendices 1, 3–8.

Table 1. Schedule of events and integrated data streams.

Domain	T0 historical abnormal screen	T1 orientation/ baseline	Days 1-14 home monitoring	T2 diagnostic colposcopy	Postprocessing/ outcomes
Eligibility and administration	EHR[a]/pathology prescreen	Consent, HIPAA[b], onboarding	Adherence monitoring and reminders	Visit coordination and payment	Deviation tracking, closeout
Clinical records	Index screening result and recommendation	Baseline covariates and medications	Interval contact if needed	Colposcopy and pathology results	Outcome abstraction and classification
Participant-reported and digital	—[c]	Baseline surveys; app/Fitbit setup	EMA[d] twice daily; Fitbit wear	Brief visit-specific updates	Integrated longitudinal analytic file
Biospecimens	Residual Pap[e] retrieval	Blood, urine, saliva, vaginal pH, self-swab	Home saliva AM/PM	Blood, urine, saliva, vaginal pH, provider-collected vaginal and cervical specimens	Aliquoting, storage, assay-ready files

[a]EHR: electronic health record.
[b]HIPAA: Health Insurance Portability and Accountability Act.
[c]Not applicable.
[d]EMA: ecological momentary assessment.
[e]Pap: Papanicolaou.

Protocol Evolution and Current Implementation

The current implementation reflects a sequence of institutional review board (IRB)–reviewed amendments from the original funded design. Major changes included expansion from 180 to 270 participants and addition of Latina women, extension of the age range, reduction of EMA frequency, replacement and addition of digital tools, addition or clarification of biospecimen procedures, and expansion of recruitment channels. Table 2 reports the protocol version dates, the major changes introduced, the study phase during which each version was applied, and the reconsent determination. A more detailed chronology is provided in Multimedia Appendix 8.

Table 2. Major protocol amendments, participant applicability, and reconsent status.

Protocol version/date	Major changes	Study phase and procedures applied	Reconsent
Version 1; protocol dated January 28, 2024; initial IRB[a] approval on March 4, 2024	Original design: 180 non–Latina Black and non–Latina White participants aged 21 to 44 y; 4 EMA[b] prompts/day; twice-daily saliva; original digital and biospecimen workflows	No recruitment or participant enrollment	—[c]
Version 2; April 16, 2024	Added Latina participants; increased target from 180 to 270; added Fitbit; changed PiLR[d] to Vibrent; clarified research cervical specimen, compensation, laboratories, and consent language	No recruitment or participant enrollment	—
Version 3; August 13, 2024	Reduced EMA from 4 to 2 prompts/day; revised EMA compensation; added AGE[e] assessment; updated surveys and website materials	No recruitment or participant enrollment	—
Version 4; July 7, 2025	Added blood collection and vaginal pH; revised compensation, processing locations, and recruitment workflow	Recruitment opened in September 2025. This version governed prescreening and outreach; no participant had yet been enrolled	—
Version 5; October 9, 2025	Added SMS, voicemail, in-clinic recruitment, recruitment video, pop-up banner, and eligibility/consent updates	Applied to prescreening and outreach only; no participant had yet been enrolled	—
Version 6; November 20, 2025	Added social media and revised recruitment materials; expanded/clarified self-collected swab and digital saliva-tracking procedures; extended age eligibility from 21 to 65 years	Applied to prescreening and outreach only; no participant had yet been enrolled	—
Current consolidated version; protocol dated February 12, 2026; IRB approved on March 3, 2026	Consolidated the live eligibility, recruitment, digital, compensation, biospecimen, and quality-assurance procedures; removed the prior 5-year abnormal-screen exclusion	All enrolled participants were consented and completed study procedures under this version. The recruitment tracker records the first enrollment after current-version approval	No reconsent was required because no participant had been enrolled under an earlier version

[a]IRB: institutional review board.
[b]EMA: ecological momentary assessment.
[c]Not applicable.
[d]PiLR: Personal Information and Lifestyle Research.
[e]AGE: Adverse Childhood Experiences.

All amendments that changed participant-facing procedures or compensation were accompanied by revised consent materials. Future amendments that alter risk, burden, compensation, or the scope of participant authorization will be evaluated by the IRB for reconsent requirements.

Cultural and Linguistic Adaptation

To promote equitable access and participation among Spanish-speaking individuals, all study materials underwent formal cultural and linguistic adaptation in direct collaboration with members of the Community Advisory Board (CAB). Moving beyond literal translation, the study team employed a transcreation framework [20], incorporating CAB guidance to ensure that study materials were not only linguistically accurate but also culturally meaningful and accessible.

This process involved the intentional simplification of clinical terminology and the use of culturally resonant language to bridge the gap between academic research and community understanding. Recognizing the heterogeneity of Latino populations, the adaptation prioritized linguistic neutrality by using a broadly accessible Spanish vernacular, thereby maximizing comprehension across diverse nationalities and dialects.

This approach was designed to enhance health literacy, promote cultural safety, and build trust among participants. CAB-informed messaging was integrated into recruitment, consent, and educational materials to demystify key study components, including stress biology and vaginal microbiome sampling, with the goal of increasing engagement and retention among historically underrepresented populations. In practice, these strategies were paired with bilingual recruitment, consent, onboarding, and retention-support workflows so that culturally and linguistically astute research procedures extended beyond translation alone.

Participants and Eligibility

Participants are recruited from women's health clinics within an academic safety-net hospital using EHR- and pathology-informed workflows. The live eligibility workflow prescreens women aged 21 to 65 years with abnormal cervical cancer screening results and a recommended or scheduled follow-up

colposcopy. The broader current protocol specifies female sex assigned at birth; self-identification as Latina, non–Latina Black/African American, or non–Latina White; English or Spanish proficiency; and the ability to complete digital study activities and return for follow-up within 3 months of the abnormal result.

Key exclusions include prior cervical cancer, prior pelvic radiation, hysterectomy, pregnancy, HIV infection, recent immunosuppressive therapy or antibiotic use, inability to complete online study activities, and lack of a working smartphone compatible with study procedures. Additional clinical exclusions are applied according to the live protocol when conditions would compromise the validity or safety of endocrine, microbiome, or follow-up assessments. Final eligibility is confirmed in 2 stages: prescreening through Epic and direct screening with the participant.

Recruitment and Screening

Recruitment is intentionally layered. Study staff run structured Epic reports to identify potentially eligible patients with abnormal cytology, verify abnormal result categories, and transfer limited data into a HIPAA (Health Insurance Portability and Accountability Act)–compliant university REDCap screening tracker. Pathology-linked workflows reserve residual ThinPrep material from the initial abnormal screen so that consenting participants can be linked to the historical T0 specimen. Participants are then contacted and offered study information, orientation dates, parking support, and follow-up options.

Current recruitment channels include telephone outreach, voicemail, SMS text messaging, EHR messaging, in-clinic recruitment, flyers and QR-coded materials, a recruitment video, and an official study website. This approach recognizes that recruitment occurs during a vulnerable interval in which women who have recently learned of an abnormal result may still be navigating uncertainty, work, caregiving, transportation, and follow-up clinical care. Participant-facing materials and implementation planning were also informed by community-engaged input, including feedback from advisors with lived experience relevant to abnormal cervical screening and follow-up. These strategies were designed to support culturally and linguistically responsive contact and to reduce early misunderstandings about study purpose, procedures, and expectations.

The protocol is also demanding. It requires multiple specimen types, digital onboarding, home freezer storage, repeated mobile tasks, and a return clinic visit. For that reason, the recruitment approach prioritizes clarity, empathy, flexibility, and trust building over speed.

Participant Burden, Feasibility, and Acceptability

Participant burden is a central design consideration in this study because the protocol combines digital onboarding, twice-daily EMA, twice-daily home saliva collection, passive Fitbit monitoring, multiple in-person biospecimens, home freezer storage, and return for diagnostic colposcopy. To reduce avoidable burden, the live protocol intentionally reduces EMA frequency from 4 prompts per day to 2, aligns T2 research procedures with the participant's clinical colposcopy visit, uses in-person teach-back and a run-in period for home tasks, provides bilingual and transcreated participant materials, offers scheduling and parking support, and emphasizes rapid troubleshooting rather than punitive adherence messaging.

Feasibility and acceptability are evaluated through recruitment and implementation indicators including prescreen yield, contact rate, direct-screen completion, consent and enrollment, T1 completion, EMA completion, home saliva completion, Fitbit syncing and wear, T2 completion, reasons for decline, burden-related deviations, support contacts, and visit duration when available. These indicators are used to distinguish logistical, digital, biospecimen, and acceptability barriers and are summarized in Multimedia Appendix 1.

Potential selection effects will be characterized by comparing enrolled participants with prescreened and directly screened women on EHR-available characteristics, when permitted, including age, race or ethnicity, language, index screening abnormality category, and follow-up timing. Burden-related missingness across EMA, home saliva, Fitbit, and T2 completion will be described by the study stage and incorporated into sensitivity analyses.

If recruitment remains slower than projected, the study team will monitor stage-specific losses (eg, prescreen to contact, contact to direct screen, direct screen to enrollment, and T1 to T2) and refine already approved outreach, scheduling, participant support, and visit coordination procedures accordingly. Recruitment contingency actions are limited to IRB-approved channels and workflow refinements rather than substantive protocol expansion.

Operational Readiness and Early Implementation Refinements

Operational readiness for the study required more than protocol approval alone. Early live-study implementation highlighted the importance of assigning clear staff responsibilities for recruitment, orientation, biospecimen handling, and follow-up visit coordination; conducting previsit checks for digital accounts and participant-facing materials; and using standardized reconciliation procedures to confirm that study IDs, labels, source documents, and specimen handoffs remain aligned across platforms and visits.

Early implementation also reinforced the idea that participant support is a scientific necessity in a high-burden protocol. Questions arising during onboarding, home saliva collection, and follow-up scheduling required rapid troubleshooting, flexible communication, and explicit contingency planning for missed tasks. These refinements were incorporated into the live workflow to improve protocol fidelity while minimizing disruption to clinical care and participant burden.

Consent, Orientation, and Participant Support

The T1 visit functions as both a consent encounter and a standardized onboarding intervention. The T1 consent, onboarding, and participant training workflow are summarized in Multimedia Appendix 5. Orientation materials guide staff through rapport building, informed consent and HIPAA authorization, app setup, study overview, biospecimen collection, EMA training, Fitbit training, and compensation procedures. Training is designed to reduce uncertainty and burden by combining verbal explanations, printed materials, videos, hands-on sample practice, and troubleshooting before the 14-day monitoring period begins.

Digital onboarding is supported rather than being assumed. Staff assist participants with account creation, app download, device pairing, and barcode-based saliva workflows as needed. A short run-in period is used to identify early technical or adherence problems before full data collection begins. Participants are told explicitly how to get help, what happens if a sample is missed, and how study staff will support them throughout the study window. Because the study spans a clinically and emotionally sensitive interval, participants are also provided with direct study contact information, reminders about whom to contact for technical or logistical problems, and referral information for supportive resources if study activities or the abnormal-result intervals provoke distress.

Participants may receive up to US $240 in protocol-based compensation, structured as follows: a fixed payment of US $70 for completion of the baseline/orientation visit; daily incentives for home monitoring, including US $1 per EMA survey (2 per day), with an additional US $1 bonus for completing both daily surveys; and US $1 per salivary cortisol sample (morning and evening), with the per-sample amount increased to US $2 when both samples are completed on the same day. Participants also receive compensation for completing the follow-up (T2) visit. Payments are contingent on adherence to protocol-defined criteria. In addition, participants receive a Fitbit Inspire 3 (with a retail value of approximately US $100) to support study participation.

Digital Tools

The study uses an interoperable digital ecosystem rather than a single monolithic platform. Epic supports prescreening and limited EHR abstraction; REDCap supports screening and study management; Vibrent supports participant-facing onboarding and EMA workflows; Fitbit provides passive activity and rest data; and Salimetrics OnTimePoint supports barcode-enabled scheduling of home saliva collection and sample confirmation. This layered architecture reflects pragmatic study building in which fit-for-purpose systems are linked across screening, onboarding, longitudinal prompting, and specimen verification.

The use of multiple digital tools not only creates analytic opportunities but also operational complexity. It improves time stamping, supports remote adherence monitoring, and produces dense multimodal data, but it also requires more staff training, harmonized identifiers, platform-specific troubleshooting, and explicit participant support. Evidence from e-consent research suggests that digital tools can improve comprehension, usability, and acceptability, although they do not, by themselves, solve structural barriers to participation [21]. In this study, digital tools are therefore used to augment, not replace, human facilitation.

Staff Training and Quality Assurance

Study staff are trained using standardized orientation, recruitment, and biospecimen-handling materials to promote consistency across participant contact, digital onboarding, specimen collection, labeling, transport, and documentation. Quality assurance procedures include the routine review of recruitment logs, source documentation, specimen reconciliation, and cross-platform identifier alignment across Epic, REDCap, participant-facing systems, and laboratory workflows. These procedures are intended to support protocol fidelity during the implementation of a complex cohort.

Biospecimen Collection and Processing

Biospecimen workflows were built as a central scientific infrastructure rather than as an ancillary laboratory task. Reader-facing summaries of biospecimen handling and visit workflows are provided in Multimedia Appendices 4–6. Biospecimen collection and handling are summarized in Table 3.

Table 3. Biospecimen collection and handling summary.

Specimen	Collection points	Collector	Immediate handling	Primary downstream use
Residual Pap[a]	T0 historical abnormal screen	Pathology release to study staff	Aliquot in sterile biosafety cabinet; store at –80 °C	Microbiome, metabolomics, and repository
Self-collected vaginal swab	T1	Participant with staff instruction	Preprocess promptly when applicable; store at –80 °C	Microbiome profiling
Provider-collected vaginal swab	T2 colposcopy	Clinician	Dry or protocol-defined preservation path; prompt transfer to study staff and freeze	Microbiome and genital environment analyses

Specimen	Collection points	Collector	Immediate handling	Primary downstream use
Provider-collected cervical specimen	T2 colposcopy	Clinician	Research-labeled collection during exam; clinic-to-lab transfer within 2 hours	Microbiome and HPV[b]-related analyses
Vaginal pH	T1 and T2	Participant or guided collection	Document reading immediately	Contextual genital environment measure
Saliva (visit-based)	T1 and T2	Participant passive drool	Cooler transport within 2 hours; aliquot; store at –80 °C	Metabolomics and exploratory molecular work
Saliva (home)	Days 1-14 AM and PM	Participant	Home freezer storage in prelabeled kit; barcode or time stamp confirmation; batch pickup	Diurnal cortisol
Urine	T1 and T2	Participant; residual clinical urine at T2 when available	Cooler transport within 2 hours; aliquot; store at –80 °C	DNA extraction, metabolomics, and repository
Blood	T1 and T2	Phlebotomist or clinician	Transfer to designated processing laboratory under active blood workflow	Serum, plasma, buffy coat, and PBMC[c] processing

[a]Pap: Papanicolaou.
[b]HPV: human papillomavirus.
[c]PBMC: peripheral blood mononuclear cell.

Following consent, the T0 residual Pap specimen from the index abnormal screening is retrieved, deidentified, aliquoted in a sterile biosafety cabinet, and stored at –80 °C for downstream genomics, metabolomics, and repository use. In the current implementation, T1 collection includes blood, urine, passive drool saliva, vaginal pH, and a self-collected vaginal swab. T2 collection includes clinician-collected vaginal and cervical research specimens during colposcopy, residual urine after clinical pregnancy testing, when available, blood, passive drool saliva, and vaginal pH.

Sample handling is time-sensitive. Current laboratory procedures specify transport of urine and saliva samples on ice to the principal investigator's laboratory within 2 hours, aliquoting under sterile conditions, and long-term storage at –80 °C. Blood is delivered to the institution's Clinical and Translational Research Laboratory within 1 hour of collection for serum, plasma, buffy coat, and peripheral blood mononuclear cell processing. Home saliva collection is performed twice daily for 14 days, aligned with awakening and bedtime to support diurnal cortisol estimation [22,23].

Because T2 procedures occur within an active colposcopy workflow, research collection is coordinated to minimize disruption to clinic operations. Study staff prepare labels, documentation, and materials in advance; provider-facing instructions are communicated before the visit; and specimen custody is transferred immediately to research staff for protocol-specific handling and transport. This coordination is a key operational feature of the live implementation.

This approach generates a temporally resolved biorepository: historical cervical material from the abnormal screening; in-clinic genital, blood, urine, and saliva specimens at 2 visits; and high-frequency home cortisol sampling aligned with daily stress measurements. Residual Pap material is a feasible source of cervicovaginal molecular information and supports downstream profiling as well as new collection at follow-up [24,25].

Measures

Baseline surveys assess sociodemographic context, medical and reproductive history, vaccination, medications, and validated psychosocial constructs, including depression, anxiety, resilience, perceived stress, life events, and affect. EMA captures repeated contextual data on mood, stress, coping, and daily routines. Salivary cortisol supports diurnal slope estimation. Passive Fitbit data provide activity and rest metrics. EHR variables include abnormal screening details, colposcopy timing, pathology outcomes, chronic conditions, and medications that may affect endocrine measures. Biospecimens support microbiome, metabolomic, endocrine, inflammatory, and future biomarker analyses.

Primary Outcome

The primary outcome is diagnostic outcome classification at follow-up relative to the index abnormal cervical cancer screening result. Outcome adjudication follows a prespecified source hierarchy. When histopathology from the T2 diagnostic evaluation is available and interpretable, it serves as the primary source for classification. When histopathology is unavailable, insufficient, or nondiagnostic, the classification relies on a structured review of colposcopic impression, cytology, HPV-related findings, when available, and documented management recommendations. Highest-grade interpretable pathology prevails when multiple specimens or diagnoses are available. Operational adjudication rules are summarized in Multimedia Appendix 1.

For the primary confirmatory analysis, histopathology or adjudicated diagnostic evaluation indicating no lesion, benign change, or low-grade abnormality without evidence of clinically significant disease is classified as resolution or nonpersistence. Histopathology or adjudicated diagnostic evaluation indicating persistent clinically significant abnormality, including CIN2+ or equivalent concern warranting ongoing high-grade management, is classified as persistence. Patients with unresolved discordance

among data sources, insufficient diagnostic material, or missing diagnostic evaluation are classified as indeterminate or missing for the primary analysis and are addressed in sensitivity analyses described below.

Sample Size Considerations

The target sample is 270 women (90 Latina, 90 non–Latina Black, and 90 non–Latina White). Assuming 85% retention through T2, approximately 225 participants are expected to have an adjudicable diagnostic outcome. For planning, persistence was assumed in 25% of completers, with sensitivity analyses spanning 20% to 30%; this range is consistent with the substantial variation in CIN2+ or CIN3+ detected at colposcopy across referral cytology and HPV-risk groups in contemporary cohorts [26,27]. The 25% assumption yields approximately 56 persistence events and 169 nonpersistence events; the 20% to 30% range yields 45 to 68 events. Each coprimary model contains 5 prespecified predictor parameters: 1 primary exposure, age, 2 race or ethnicity indicators, and index screening risk stratum. The expected event-to-parameter ratio is therefore 11.3 under the primary assumption and 9.0 to 13.5 across the sensitivity range. Using the multiple-logistic-regression method of Hsieh et al [28], a 2-sided per-model α of .025, 80% power, a standardized continuous exposure, and an R^2 of 0.20 between the exposure and other model terms, 225 analyzable participants provide 80% power to detect an odds ratio of approximately 1.70 per 1-SD increase when persistence is 25% (approximately 1.78 at 20% and 1.65 at 30%). Thus, the confirmatory analyses are powered for moderate participant-level associations, not small effects or interaction tests. High-dimensional and interaction analyses are designated secondary or exploratory.

Data Integration and Statistical Analysis

The psychosocial platform combines baseline surveys with twice-daily EMA over 14 days. Home saliva collection is synchronized to awakening and bedtime to estimate diurnal cortisol slopes. Fitbit data provide passive contextual information on activity and rest. Clinical data extracted from the EHR include screening findings, colposcopy scheduling, pathology outcomes, chronic conditions, medications, and relevant covariates.

Two coprimary confirmatory models are prespecified. In both, persistence at T2 is coded 1 and resolution or nonpersistence is coded 0, and estimation uses Firth bias-reduced logistic regression with a logit link [29,30]. Model 1 includes the baseline PSS-10 total score (range 0-40) as the primary exposure. Model 2 includes the participant-level mean diurnal cortisol slope as the primary exposure. For each valid day, the cortisol slope is calculated as [ln(PM cortisol) − ln(AM cortisol)] divided by the elapsed hours between collections; daily slopes are averaged across all valid paired days. At least 7 valid AM/PM paired days are required for the primary cortisol analysis, and higher values indicate a flatter diurnal decline. Each primary exposure is z-standardized so its coefficient represents a 1-SD increase.

The same covariates are included in both coprimary models: age at T1 (continuous and centered at the analytic-sample mean), race or ethnicity (non–Latina White as the reference; indicator terms for non–Latina Black and Latina), and index screening risk stratum (high-grade referral abnormality [high-grade squamous intraepithelial lesion, high-grade squamous intraepithelial lesion, atypical glandular cells, or an equivalent high-risk HPV/cytology indication] vs lower-grade referral abnormality). Continuous terms are modeled linearly in the primary analysis. No interaction term is included in either confirmatory model. The primary effect estimates are adjusted odds ratios per 1-SD increase in the exposure with 97.5% profile penalized-likelihood CIs; each coprimary test uses a 2-sided α of .025, preserving a familywise α of .05. Prespecified sensitivity analyses will assess nonlinear exposure effects using restricted cubic splines, add time from index screening to T2 and current smoking, vary the minimum number of valid cortisol days (5, 7, and 10), and compare Firth estimates with standard maximum-likelihood logistic regression when estimable.

The primary outcome and the 2 primary exposures will not be imputed. Model 1 includes participants with an adjudicable outcome and a scorable PSS-10. Model 2 includes participants with an adjudicable outcome and at least 7 valid paired cortisol days. If a prespecified covariate is missing in fewer than 5% of otherwise eligible participants, complete-case estimation will be used; if covariate missingness is 5% or greater and a missing-at-random assumption is plausible, multiple imputation by chained equations will be used for covariates only. Secondary analyses will examine the PSS-10 by cortisol-slope interaction and, in separate models, exposure by race or ethnicity interactions; these are not powered as confirmatory tests and will be interpreted as exploratory. Vaginal microbiome, metabolomic, HPV-related, wearable, p16/ki67, mediation, and multimodal trajectory analyses remain secondary or exploratory, with false discovery rate control within each omics family. The complete analytic map is provided in Multimedia Appendix 1.

Ethical Considerations

The study was initially approved by the Virginia Commonwealth University Institutional Review Board (protocol HM20028178) on March 4, 2024. Major protocol version dates and participant applicability are reported in Table 2 and Multimedia Appendix 8. Recruitment activities began in September 2025, but the recruitment tracker shows no participant enrollment before approval of the current consolidated version on March 3, 2026. Accordingly, all enrolled participants provided written informed consent and HIPAA authorization under the current version and completed the same participant-facing procedures described in this paper; reconsent was not required. Signed consent forms and study data are maintained in institutionally approved, access-controlled systems. Direct identifiers are restricted to essential study personnel; biospecimens are coded and stored using study IDs rather than direct identifiers; and EHR access is limited to IRB-approved recruitment, eligibility confirmation, and abstraction procedures.

Participants may receive up to US $240 plus a Fitbit Inspire 3, as described in the live protocol. Individual study results are not returned to participants. Because study participation occurs during a potentially stressful abnormal-result interval, participants are reminded that they may skip questions, pause activities, or withdraw at any time without affecting their clinical care, and study staff can provide referral information for supportive resources when needed. The publication of this protocol is intended to enhance transparency, improve reproducibility, and support replication or adaptation in other women's health disparity settings.

Results

Recruitment began in September 2025. As of July 15, 2026, 180 women had been prescreened through the EHR- and pathology-informed recruitment workflow. Of these, 25 had met prescreening criteria, 24 had been contacted by study staff, and 13 had completed direct screening. Eight women had declined participation, 3 had enrolled, and 2 of the enrolled participants had completed the full study protocol. Recruitment and longitudinal data collection are expected to continue through December 2028, after which primary analyses will evaluate multilevel associations among stress, cortisol, vaginal microbiome features, HPV-related factors, and screening outcomes resolution or persistence at diagnostic follow-up. Ongoing implementation includes EHR-based prescreening, pathology-linked residual Pap capture, standardized in-person onboarding, digital monitoring, and coordinated biospecimen handling across clinical and laboratory settings. Table 4 summarizes the early participant flow.

Table 4. Early participant flow snapshot as of July 15, 2026.[a]

Metric	Number, n
Women prescreened from the EHR[b]/pathology queue	180
Confirmed ineligible	142
Eligibility determination pending	13
Met prescreening criteria	25
Contacted by study staff	24
Completed direct screening	13
Completed direct screening; enrollment decision or scheduling pending	2
Declined participation	8
Enrolled	3
Completed the full study protocol	2

[a]An additional 13 women had unresolved eligibility status: 8 required rescheduling of their colposcopy, 3 were awaiting determination of whether colposcopy would be recommended, and 2 were awaiting cervical screening results.
[b]EHR: electronic health record.

Among the 180 women prescreened, 142 were confirmed to be ineligible and 13 had an eligibility determination pending at the time of the data cutoff. The most common reasons for ineligibility were no qualifying abnormal cervical cancer screening result (n=42), no recommendation for colposcopy (n=32), and a colposcopy that was scheduled too soon or had already occurred (n=25). Sixteen women had been excluded under the previous eligibility criterion concerning an abnormal screening result within the preceding 5 years; this criterion was subsequently removed from the protocol. Among the 13 women with a pending determination, 8 required their colposcopy to be rescheduled, 3 were awaiting confirmation of whether colposcopy would be recommended, and 2 were awaiting cervical screening results. Reasons for confirmed ineligibility are summarized in Table 5.

Table 5. Reasons for confirmed ineligibility among prescreened women as of July 15, 2026 (N=142).[a]

Reason for ineligibility	Participants, n (%)
No qualifying abnormal cervical cancer screening result	42 (29.6)
No colposcopy recommended	32 (22.5)
Colposcopy scheduled too soon or already completed	25 (17.6)
Prior abnormal screening result within 5 years under the former eligibility criterion	16 (11.3)
Pregnancy	13 (9.2)
Race or ethnicity did not meet eligibility criteria	6 (4.2)
Recent antibiotic use	4 (2.8)
HIV infection or immunosuppressive condition/medication	2 (1.4)

Reason for ineligibility	Participants, n (%)
Prior hysterectomy	1 (0.7)
Other	1 (0.7)
Total	142 (100)

[a]Age was applied as an automated filter during the weekly electronic health record query and therefore did not appear as a reason for exclusion among the 180 women included in the prescreening results. The historical exclusion related to a prior abnormal screening result within 5 years was subsequently removed from the study's eligibility criteria but is retained here to accurately describe cumulative recruitment outcomes.

Recruitment and longitudinal follow-up are expected to continue through December 2028, after which primary analyses will begin, following data cleaning and quality control.

Discussion

Principal Findings

This study addresses a key gap in cervical disparities research by linking mechanistic biospecimen science with participant-centered digital and clinical workflows during the interval between an abnormal cervical cancer screening result and diagnostic evaluation. The protocol is designed to support temporally aligned analyses across stress exposure, cortisol regulation, microbial ecology, HPV-related factors, and pathology-linked outcomes that would be difficult to generate in a conventional single-visit or purely retrospective design. It also treats participant burden, outcome adjudication, and missingness as methodological issues that must be measured and reported rather than assumed away.

The protocol also makes visible the implementation costs of high-resolution longitudinal cohort research. Recruitment occurs during a stressful clinical moment, and the study requires repeated biospecimen collection, digital onboarding, home monitoring, and coordinated follow-up. Accordingly, the current implementation emphasizes navigation, flexible scheduling, digital support, standardized specimen handling, and close coordination between research and clinical teams.

Comparison With Prior Work

Early implementation experience suggests that feasibility in this setting depends not only on digital tools or participant motivation but also on operational choreography across recruitment, orientation, home monitoring, specimen logistics, and colposcopy follow-up. In high-burden longitudinal studies, the coordination infrastructure itself should be treated as part of the scientific method because breakdowns in onboarding, labeling, timing, or clinic integration can directly affect data completeness, specimen integrity, and interpretability.

Evidence from e-consent and inclusive participation research suggests that digital tools may improve comprehension and usability but do not, by themselves, overcome structural barriers to participation [6-8,21]. This study responds to this evidence by pairing digital infrastructure with human facilitation, proactive troubleshooting, culturally grounded communication, and flexible outreach strategies.

Strengths

A key strength of this study is its integration of community-engaged, culturally grounded design principles within a digitally enabled research framework. In collaboration with the CAB, the research team did not simply translate study materials but transcreated them to enhance accessibility, cultural relevance, and comprehension across diverse Spanish-speaking populations. This approach prioritizes linguistic neutrality, health literacy, and cultural safety, with the goal of strengthening participant trust, engagement, and retention.

Another major strength is the study's focus on the clinically important interval between an abnormal cervical cancer screening result and diagnostic evaluation. By prospectively capturing psychosocial, biological, microbial, and clinical data during this window, the study is positioned to examine factors associated with the resolution or persistence of abnormal screening findings before the diagnostic workup is complete.

Finally, the integration of multimodal data streams—including EMA, biospecimens, wearable data, and EHRs—creates a rich longitudinal data resource capable of supporting future multilevel and mechanistic analyses. This combination of scientific depth and operational transparency positions this study as a potentially scalable model for equity-focused digital health research in women's health.

Limitations

Several limitations should be considered. First, this protocol is situated within a single academic health system, which may limit generalizability to settings with different patient populations, clinic infrastructure, or digital support resources. Second, the study is operationally complex and potentially burdensome, which may influence who enrolls, who remains adherent, and how representative the final cohort is of women undergoing abnormal cervical cancer screening follow-up more broadly. Third, the recruitment data reported here represent an early implementation snapshot from an ongoing study rather than a mature enrollment experience. For that reason, reasons for decline, stage-specific completion metrics, support-contact logs, burden-related deviations, and comparisons of enrolled vs nonenrolled women based on EHR-available characteristics are incorporated into the feasibility framework to help characterize potential selection effects. At the same time, the protocol's unusual strength lies in the integration of temporally aligned biospecimens, real-time measures, and pathology-linked outcomes. The

trade-off between complexity and scientific richness is therefore explicit and should be considered when interpreting both feasibility and future findings. Fourth, the expected event count supports parsimonious estimation of moderate main effects but not small effects, complex interaction structures, or confirmatory high-dimensional modeling; those analyses are therefore explicitly staged as secondary or exploratory. Realized power and CI precision will be reported if the final analyzable sample or persistence proportion differs from planning assumptions.

Conclusions

This prospective cohort study is designed to provide both a scientific resource and an implementation model for equity-focused, digitally enabled cohort studies in cervical cancer prevention. By documenting the integration of psychosocial, biological, digital, and clinical workflows during the abnormal-screening interval, this protocol may inform future methods papers, mechanistic analyses, and intervention-oriented studies aimed at reducing unnecessary procedures and improving equity in abnormal cervical screening follow-up.

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Generative AI Use

During manuscript revision, the authors used ChatGPT (OpenAI) to assist with organizational restructuring, plain-language editing, and drafting of revision summaries. All AI-assisted output was reviewed, revised, and fact-checked by the authors, who take full responsibility for the final manuscript. No generative AI tool was used to analyze study data or generate scientific conclusions.

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Data Availability

The study described in this paper is ongoing; therefore, deidentified participant-level data are not yet publicly available. Following study completion, data cleaning, and deidentification, data will be shared in accordance with participant consent, institutional approvals, and applicable data-sharing policies. Clinical and laboratory metadata are expected to be deposited in DASH, and sequence data in dbGaP or the Sequence Read Archive, as appropriate. Until repository deposition is complete, requests for access to deidentified data may be directed to the corresponding author and will be reviewed subject to institutional approvals and applicable data use agreements.

Authors' Contributions

Conceptualization: KT
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Investigation: BDO, SS, MJ, CR
Methodology: KT, BDO, SS, MJ, MS, JS, GB, JGL
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Visualization: ASF
Writing – original draft: KT
Writing – review & editing: KT, BDO, SS, MJ, CR, ASF, MS, JS, GB, JGL

Conflicts of Interest

None declared.

Multimedia Appendix 1

Study checklist, analytic prioritization, burden and feasibility indicators, and primary outcome adjudication rules.
[DOC File (Microsoft Word File), 118 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Study scheme.
[PNG File (Portable Network Graphics File), 353 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Operational materials.
[DOCX File (Microsoft Word File), 29 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Biospecimen framework.
[DOCX File (Microsoft Word File), 31 KB-Multimedia Appendix 4]

Multimedia Appendix 5

Onboarding workflow.
[DOCX File (Microsoft Word File), 30 KB-Multimedia Appendix 5]

Multimedia Appendix 6

Coordination workflow.
[DOCX File (Microsoft Word File), 30 KB-Multimedia Appendix 6]

Multimedia Appendix 7

Time point dictionary.
[DOCX File (Microsoft Word File), 56 KB-Multimedia Appendix 7]

Multimedia Appendix 8

Protocol amendment chronology, participant applicability, and reconsent determination.
[DOCX File (Microsoft Word File), 55 KB-Multimedia Appendix 8]

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Abbreviations

CAB: Community Advisory Board
EHR: electronic health record
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
HPV: human papillomavirus
IRB: institutional review board
Pap: Papanicolaou
PSS-10: 10-item Perceived Stress Scale
T0: historical index abnormal screen time point
T1: orientation and baseline time point
T2: follow-up colposcopy time point

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