The Progesterone Challenge Test as a Functional Biomarker of Endometrial Cancer Risk: Results from a Prospective Feasibility Study

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ABSTRACT

Endometrial cancer incidence continues to increase globally, driven mainly by obesity. Current diagnostic pathways rely on symptom presentation; no validated approach exists to identify asymptomatic individuals who may benefit from targeted prevention. The progesterone challenge test (PCT) is a physiologic assessment of endometrial hormonal responsiveness that could pragmatically guide endometrial cancer prevention interventions. The RESToRE study (NCT05651282) prospectively assessed the feasibility of the PCT as a community-based risk-stratification tool for endometrial cancer prevention in British Columbia, Canada, between 2023 and 2024. Asymptomatic postmenopausal participants, defined by the absence of vaginal bleeding, with body mass index ≥34.9 kg/m^2 and an intact uterus, completed a 10-day course of oral medroxyprogesterone acetate (MPA) 10 mg daily. Feasibility, tolerability, and acceptability were evaluated. Of 96 eligible individuals, 68 enrolled, 53 initiated, and 51 completed the PCT. Sixteen participants experienced withdrawal bleeding (+PCT; 30.2% of those with evaluable results). All +PCT individuals were referred to a gynecologist for standard-of-care evaluation, including an endometrial biopsy. Among the 15 who underwent biopsy, two had a proliferative endometrium, and one had simple hyperplasia. Participants and providers found the test acceptable, citing its simplicity and low administrative burden. Side effects of the PCT were mild (median severity ≤three of 10), resulting in 3.8% (two of 53) of participants discontinuing the MPA. The PCT was feasible, well-tolerated, and acceptable among higher-risk postmenopausal individuals, supporting its use as a physiologic, functional biomarker of endometrial responsiveness. These findings provide early evidence for a scalable, low-cost strategy to identify individuals likely to benefit from targeted endometrial cancer prevention.

Prevention Relevance: This study demonstrates that the PCT is feasible and acceptable as a functional biomarker associated with the risk of endometrial cancer in asymptomatic postmenopausal individuals with obesity. As a low-cost, scalable, community-deliverable approach, our findings support validation of this test in the context of endometrial cancer precision prevention.

Introduction

Endometrial cancer is the most common gynecologic malignancy in high-income countries, and incidence continues to increase worldwide (1, 2). In Canada, endometrial cancer incidence rates increased by 54% and mortality by 25% between 1995 and 2023 (3). Endometrioid endometrial cancer, the predominant histologic subtype, is largely driven by prolonged unopposed estrogen exposure (4). Risk factors include early menarche (<12 years), late menopause (≥55 years), anovulation (e.g., polycystic ovarian syndrome), nulliparity, and obesity (5–7). In menopause, obesity further elevates estrogen levels through peripheral aromatization of androgens, producing chronic endometrial stimulation; each 5 kg/m^2 increase in body mass index (BMI) raises the risk of endometrial cancer by ~54% (8). Endometrial cancer typically presents with postmenopausal bleeding (PMB) or abnormal uterine bleeding (bleeding that is excessive, irregular, or occurs outside of expected cycles), prompting diagnostic evaluation. Although transvaginal ultrasound and endometrial biopsy are used to investigate symptomatic women and are sometimes recommended for individuals with Lynch syndrome, no screening method has been validated for asymptomatic postmenopausal women at increased risk (9, 10).

The endometrium is a hormonally responsive tissue (11). Unopposed estrogen promotes proliferation, leading to endometrial hyperplasia (EH), characterized by a thickened

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endometrium and increased glandular crowding (12). Persistent EH can accumulate somatic mutations that clonally expand to progress to atypical EH (AEH), also known as endometrioid intraepithelial neoplasia (EIN). AEH carries a 45-fold increased cancer risk (13). Most cancers arising from AEH are low-grade, estrogen receptor–positive endometrioid carcinomas (7).

Weight management strategies could reduce endometrial cancer rates but are difficult to implement at scale (14). Exogenous progesterone, delivered as combined hormone therapy (HT), progestin-only HT, and/or progestin-releasing intrauterine systems (LNG-IUS; e.g., Mirena) can reverse EH, AEH, and even early endometrial cancer (15, 16). Observational studies also suggest reduced endometrial cancer incidence among LNG-IUS users (17, 18). Although emerging evidence supports progesterone-based prevention, randomized trial data remain limited (14, 19–22), and cost-effectiveness analyses have yielded inconsistent results. The successful broader implementation of an endometrial cancer prevention strategy would benefit from improved risk stratification (23, 24).

The progesterone challenge test (PCT) is a noninvasive method for detecting a hormonally responsive endometrium. A short course of oral progestin that induces a menstrual-like ("withdrawal") bleed indicates proliferative activity and possible presence of precursor pathology (EH, AEH/EIN, or endometrial cancer; ref. 25). Long-term follow-up of +PCT women treated with progestin showed a nine-fold reduction in endometrial cancer incidence (26). A systematic review of the PCT characteristics reported a pooled sensitivity of 82% [95% confidence interval (CI), 58%–99%] and specificity of 94% (95% CI, 83%–100%) for detecting endometrial pathology, including proliferative endometrium, EH, AEH/EIN, and endometrial cancer, with a negative predictive value of 97%, supporting its use to identify those most likely to benefit from targeted prevention (27).

RESToRE (Risk Evaluation and Screening to Tailor prevention and Reduce the incidence of Endometrial cancer) was designed to assess the feasibility and acceptability of a risk-directed prevention approach in asymptomatic individuals, targeting community of postmenopausal individuals at higher risk for endometrial cancer. This article focuses on the implementation of the PCT as a risk stratification tool in this population; other components of RESToRE will be described separately.

Materials and Methods

RESToRE study overview

The RESToRE study (NCT05651282) classified participants as having a higher risk of individuals if their BMI was ≥34.9 kg/m^2. Written informed consent was obtained, and this study was conducted in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2), which is the Canadian national standard. The principles in the TCPS 2 are consistent with the ethical principles outlined in the Belmont Report and international best practices. Consenting higher-risk individuals provided self-collected vaginal swabs and completed the PCT. Participants with withdrawal bleeding, indicating a positive PCT (+PCT), were referred for diagnostic endometrial biopsy to rule out AEH/EIN/endometrial cancer, followed by standard clinical management as indicated. All consenting participants were offered a lifestyle-modification program. RESToRE was powered to detect a 75% adherence to the lifestyle intervention; the protocol was approved by the BC Cancer Agency Research Ethics Board (H22-02290).

Recruitment and risk assessment

Recruitment used a multi-pronged, decentralized approach to broadly recruit participants from the community, including a provincial research platform (REACH BC; ref. 28), paid and unpaid social media ads, online community engagement, print media (newspapers), physical posters, and recruitment through a third-party agency. Asymptomatic postmenopausal individuals from across British Columbia, Canada, were invited to participate.

Eligibility criteria included an intact uterus; no current unexplained PMB; ≥3 years since cessation of menses; no current use of any hormonal/antiendocrine agents (LNG-IUS, systemic HT, androgenic agents, antiendocrine therapy, or aromatase inhibitors); and no contraindications to oral medroxyprogesterone acetate (MPA). Consent was obtained electronically through REDCap (RRID: SCR_003445; refs. 29, 30). Baseline questionnaires captured self-reported reproductive and medical history, hormone use, risk factors, family history, and demographics based on participant recall. Participants were classified as higher risk if their BMI, calculated from self-reported height and weight, was 34.9 kg/m^2 or higher.

PCT

Eligible higher-risk participants met with the study team to review study procedures and to provide consent. Contraindications to the PCT (Supplementary Table S1) were also reviewed and contact information for the participant's primary care provider (PCP) was collected when applicable. Participants with contraindications were excluded after physician review.

Once eligibility was confirmed and consent was obtained, the PCP was contacted and invited to participate in the study. Prescriptions (10 mg MPA orally once daily for 10 days) were issued by the PCP following their independent clinical assessment for contraindications and overall suitability. Oral MPA 10 mg daily for 10 days is a widely used clinical practice for inducing withdrawal bleeding, and its use in this context is supported by prior studies of endometrial responsiveness (31, 32). For participants without a regular PCP, local gynecologists were recruited to evaluate participant suitability, prescribe the MPA, and provide follow-up as medically indicated. The estimated 10-day MPA cost was

$12 CAD. All participants were reimbursed with a $20 CAD electronic gift card.

Throughout the PCT, participants completed a daily electronic questionnaire via the MyCap mobile app for a total of 24 days, covering the 10-day MPA administration and a 14-day posttreatment monitoring phase (Supplementary Table S2; refs. 27, 29, 30). The questionnaire recorded MPA compliance, the occurrence of any withdrawal bleeding, and any side effects (SE; e.g., nausea, headache, and mood changes). A progesterone challenge was considered positive (+PCT) if any withdrawal bleeding (including spotting) was reported at any point during the 24-day period. All positive tests were confirmed by a follow-up phone call or email from the study team.

Participants completed at-home, self-collected vaginal swabs for molecular analysis prior to initiating the PCT. Those with a +PCT also collected a posttest swab. All swabs were returned by mail using prepaid envelopes. At the time of this writing, sample analysis and lifestyle intervention are ongoing and will be reported on in future publications.

Feasibility

The study aimed to assess feasibility using a *priori* target criteria of 80% enrollment and 50% to 70% retention (33, 34). Enrollment was defined as the proportion of eligible participants who consented to undergo the PCT. Retention was defined as the proportion of participants who completed the prescribed PCT regimen among those who consented to PCT (33, 34). Additional measures were calculated, including tolerability rates (as assessed by the proportion of patients completing the entire MPA regimen) and compliance with study protocols.

SEs

Participants were asked to report any SEs experienced after starting the PCT over 24 days, which included a 10-day MPA course, followed by a 14-day monitoring window. They were asked whether they experienced any symptoms, and those who reported any were given a list of common MPA SEs and asked to rate the severity of each SE on a scale of 0 (none) to 10 (extreme). Any response greater than zero was recorded as an experienced SE. A text box option was available to provide further information or to add additional symptoms.

Acceptability

The acceptability of the PCT was assessed via an online survey distributed to participants after they completed the test. The survey was developed using a modified application of the Theoretical Framework of Acceptability (TFA; ref. 35). Responses were collected using a five-point Likert Scale, and optional free-text boxes were included to capture additional participant feedback. PCPs who participated in the study were also invited to complete a separate acceptability questionnaire upon completion of their involvement.

Statistical analysis and visualizations

All analyses were conducted using R (version 4.4.3; RRID: SCR_001905). Data visualizations were generated using ggplot2 (v3.5.1; RRID: SCR_01460) and Likert (v1.3.5) packages. Differences between +PCT and −PCT participants were compared using the Mann–Whitney U test for continuous variables and the Fisher exact test for categorical variables.

A large language model (ChatGPT o4-mini, RRID: SCR_023775) was used to summarize and categorize deidentified qualitative free-text responses from exit surveys. All outputs were manually reviewed by a member of the study team to ensure accuracy and thematic fidelity (Supplementary Table S3).

Results

PCT

A total of 2,454 participants were assessed for participation between March 2023 and November 2024. Ninety-six participants met all eligibility criteria and were invited to proceed with the PCT (**Fig. 1**). Of those, 87 (90.6%) attended an intake meeting with the study team, and 68 (70.8%) consented to the PCT. Of consented participants, 53 (77.9%) initiated the 10-day MPA regimen, and 51 completed the PCT, taking all MPA doses. Supplementary Table S4 describes the representativeness of the study participants.

Withdrawal bleeding was reported in 16 of 53 participants (30.2%; +PCT). Of these, 15 (93.8%) underwent subsequent endometrial sampling. Among those sampled, two participants had a proliferative endometrium, and one was diagnosed with simple EH (**Fig. 1**); this participant was initially treated with oral progestin and elected for definitive management with hysterectomy and bilateral salpingo-oophorectomy due to EH on repeat biopsy. No treatment was initiated for the two individuals with endometrial proliferation.

Compared with the −PCT group, individuals in the +PCT group had a higher median BMI [40.2 vs. 37.4; Mann–Whitney test: 95% CI (−4.7 to −0.1); $P < 0.05$] and weight [107.9 kg vs. 102 kg; 95% CI (−13.6 to −0.91); $P < 0.05$] and a trend toward a higher median waist-to-hip ratio and weight at the age of 20 years. The overall weight difference from age 20 to 50 years was greater in the −PCT cohort (**Table 1**). A greater proportion of the +PCT group also reported a personal medical history of gynecologic conditions (fibroids, polycystic ovarian syndrome, endometriosis, and adenomyosis) compared with the −PCT group ($P < 0.05$). No other statistically significant differences in personal medical history were noted otherwise.

Lifestyle and demographics were similar between the two groups, apart from the highest attained level of education, in which a significantly higher proportion of −PCT participants reported university-level education ($P < 0.05$, Supplementary Table S5). We also assessed characteristics of those who completed PCT and those who provided consent but

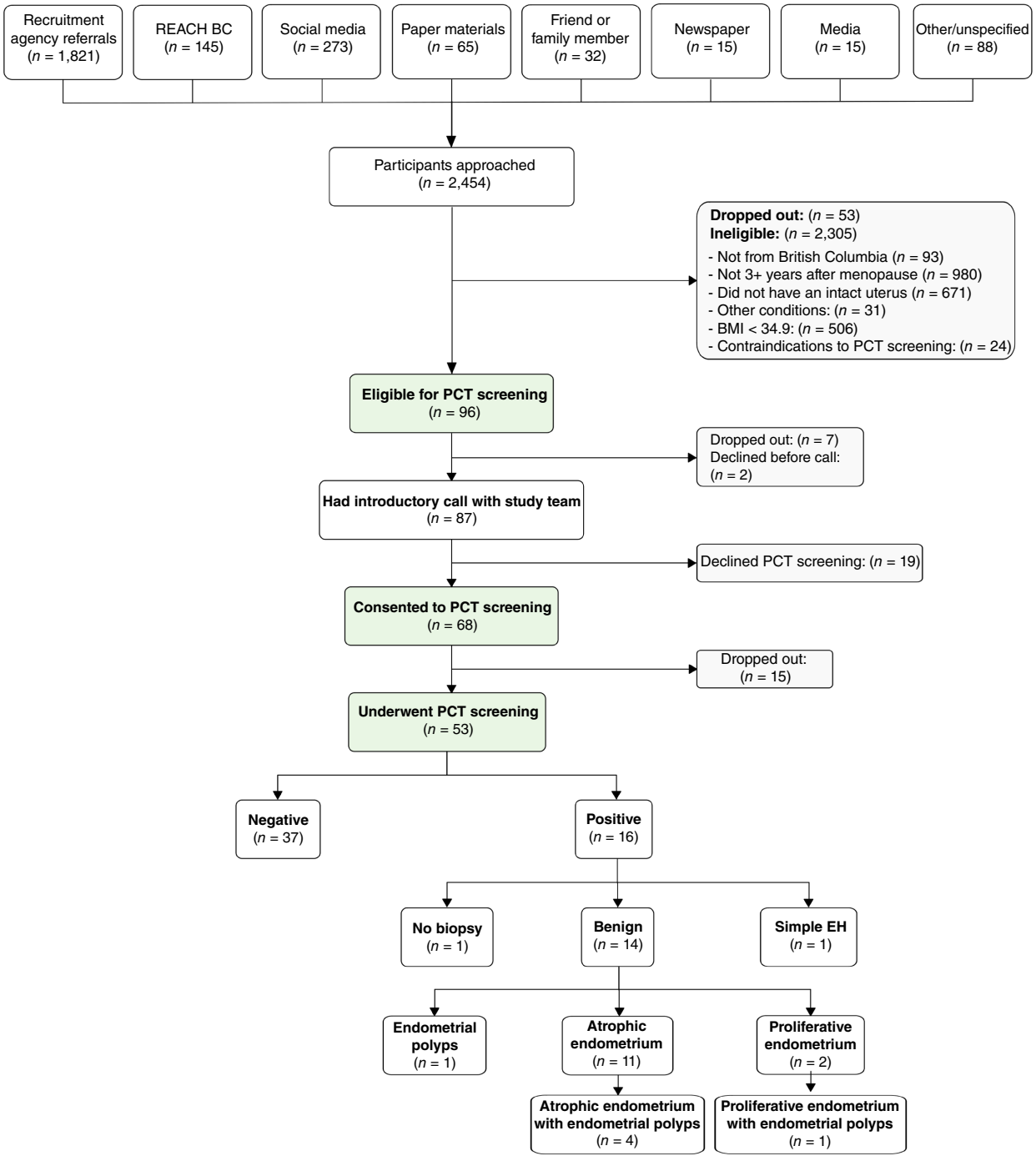

Figure 1.

Participant flow diagram illustrating enrollment, study progression, and outcomes detailing recruitment pathways, progression through the study protocol, PCT outcomes, and associated biopsy results where applicable.

did not complete, and no significant differences were noted between the two groups (Supplementary Table S6).

Feasibility

The enrollment rate was 70.8% (target 80%), and the retention rate was 77.9% (target 50%–70%; **Fig. 2**). The tolerability of the PCT regimen was 96.2%, with 51 of 53 participants taking all doses of MPA as prescribed. SE self-reporting compliance with the study protocol was 71.4% during the PCT and dropped to 52.1% during the 14-day post-PCT monitoring period. Qualitative data on reasons for declining PCT participation prior to consenting are

Table 1. Baseline self-reported demographic and clinical characteristics of participants stratified by PCT result.

	+PCT (*n* = 16)	−PCT (*n* = 37)	*P* value
Participant characteristics			
Age	61 (8.25)	62 (6)	0.48
BMI	40.2 (5.45)	37.4 (3)	**0.03***
Height (cm)	165 (8.9)	165 (8.9)	0.5
Weight (kg)	107.9 (12.1)	102 (11.3)	**0.02***
Waist-to-hip ratio	0.87 (0.07)	0.82 (0.09)	0.11
Weight at 20 years (kg)	70.3 (28.1)	63.5 (22.7)	0.08
Missing	*2*	*2*	
Weight at 50 years (kg)	104.3 (22.7)	90.7 (23.8)	0.32
Missing	*3*	*2*	
Increase in weight (50–20 years; kg)	25.1 (15.5)	27.5 (15.9)	0.64
Missing	*3*	*2*	
Estrogen exposure risk factors			
Age at menopause	52 (5.25)	53 (5)	0.41
Years after menopause	10.5 (5.75)	8 (8)	0.31
Age at menarche	12 (2)	13 (1)	0.06
Prior use of hormonal contraception			0.21
Yes	16 (100%)	30 (81.1%)	
No	0	5 (13.5%)	
I prefer not to answer	0	1 (2.7%)	
Presence of comorbid conditions			
Metabolic syndrome	9 (56.3%)	16 (43.2%)	0.55
Gynecologic conditions	8 (50%)	7 (18.9%)	**0.04***
History of abnormal vaginal bleeding	5 (31.3%)	6 (16.2%)	0.28

Metabolic conditions included diabetes, hypertension, and hyperlipidemia; gynecologic conditions included fibroids, polyps, polycystic ovarian syndrome, endometriosis, and adenomyosis. Any bleeding between menstrual cycles or postmenopausal is defined as abnormal uterine bleeding. Continuous variables are presented as median (IQR) and categorical variables are counts (percentage). Statistically significant results are bolded and indicated by an *.

summarized in Supplementary Table S7. Of the participants who consented but did not ultimately initiate PCT, the most frequently cited reasons included hesitation to take the prescribed progestin, perceived burden of study procedures, time commitment, and lack of willingness to enter a drug trial.

SEs

Of the 53 participants who underwent PCT, 34 (64.2%) reported SEs (Supplementary Table S8), with a median of three per person per day. Changes in mood, bloating, and headaches were most frequently reported with a median severity of two (on a scale of 1–10). The median severity was highest for drowsiness (three), changes in mood (2.9), headache (2.7), and bloating (2.1). Participants provided supplemental descriptions of any additional SEs not included in the daily questionnaire (Supplementary Table S9). Two participants discontinued the PCT because of SEs. One was recommended by their physician, and the other was due to symptoms affecting their mood and emotions. Overall, symptoms reported during the PCT and active monitoring periods were similar.

PCT acceptability

Most respondents reported understanding how the PCT assesses risk for endometrial cancer and felt confident undergoing the procedure (**Fig. 3**). Overall, 76.5% of participants found the PCT acceptable as a regular screening method, whereas 17.6% were neutral and 5.9% disagreed. Participants generally indicated that the PCT did not interfere with daily life or require substantial effort. Most individuals had no moral or ethical concerns about the test, and their comfort levels were largely neutral (**Fig. 3**). No qualitative data were available to explain the small proportion of individuals who disagreed with using the PCT for routine screening. Participants described the PCT as economic, easy, and noninvasive although some responses were conditional. One emphasized that acceptability depends on progestin safety, whereas others wanted to see effectiveness findings before supporting routine clinical use. Ethical concerns focused on potential hormonal disruption in postmenopausal individuals. The acceptability question had a 32.1% response rate, with 17 of 53 completing it.

PCP acceptance of the PCT

Thirty-five of 58 physicians and nurse practitioners (60%) responded to our survey. Overall, feedback was positive (**Fig. 4**). Most agreed that patients could tolerate PCT SEs (85.3%), that additional tools for identifying high endometrial cancer risk are worthwhile (94.3%), that the PCT has clinical utility, that benefits outweigh risks (88.2%), and that the PCT is safe (85.3%).

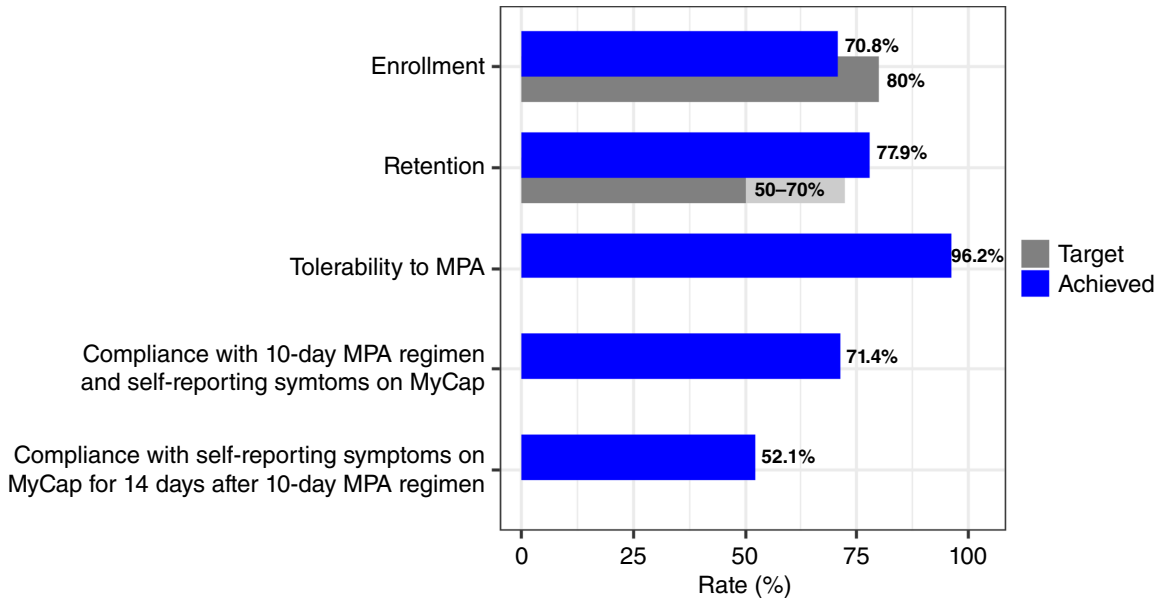

Figure 2.

Feasibility thresholds and proportions. Gray bars indicate the predefined feasibility thresholds for enrollment and retention. Blue bars represent the observed proportions for each feasibility domain, including enrollment, retention, tolerability, and compliance. Numerical values (percentage) are displayed adjacent to each bar.

Qualitative analysis of PCT acceptability for participants and providers

Thematic analysis identified three main themes. First, perceived clinical benefit and conditional support: acceptance depended more on the evidence of effectiveness. Second, perceptions of PCT effort: most indicated that required effort was acceptable. Third, hormonal impact and SE concerns: some uncertainty remained about potential hormonal disruption and bleeding. A detailed table with themes, corresponding TFA constructs, and quotes is available in the supplementary material (Supplementary Table S10).

Provider comments on acceptance were limited. Although most were supportive, concerns included an increased workload and potential SEs, which might be mitigated by alternative progestin options. Some withheld judgment, citing limited experience or waiting for trial results.

Discussion

The RESToRE study demonstrates that the PCT is a feasible and generally acceptable approach to risk stratification for endometrial cancer prevention among asymptomatic postmenopausal individuals at higher risk. The modest sample size reflects the number of participants needed to establish feasibility. Although enrollment (70.8%) did not reach the prespecified 80% feasibility threshold, retention and tolerability were high, and most participants found the intervention acceptable. These findings support the practicality of implementing the PCT in community-based settings and justify progression to larger-scale validation studies.

Earlier studies of the PCT were conducted more than two decades ago, used heterogeneous eligibility criteria and different progestin protocols, and were primarily diagnostic in intention. The test was never adopted into routine clinical use. Although some studies included asymptomatic women, definitions of "higher risk" were inconsistent and did not always reflect obesity-related endometrial cancer risk. In contrast, RESToRE provides contemporary evidence of feasibility and acceptability using a standardized protocol within a decentralized, community-based model that recruited asymptomatic postmenopausal participants with clearly defined obesity-related risk, with the intention to risk-stratify for prevention. To our knowledge, this is the only recent North American and the only Canadian evaluation of the PCT conducted across a geographically large province to capture feasibility in diverse communities with varying access to primary care. By integrating both participant and provider perspectives, RESToRE identifies behavioral and system-level considerations absent from earlier clinic-based studies. In addition to assessing feasibility as the primary objective, the study also generated key operational parameters needed to inform the design of a larger validation study.

Concerns about enrollment centered on hesitancy toward hormonal medications, particularly without direct guidance from participants' own providers. Qualitative findings pointed to mistrust of exogenous hormones, reluctance to take medication in the absence of symptoms, and confusion about the study rationale. Future research should directly address these barriers through improved communication

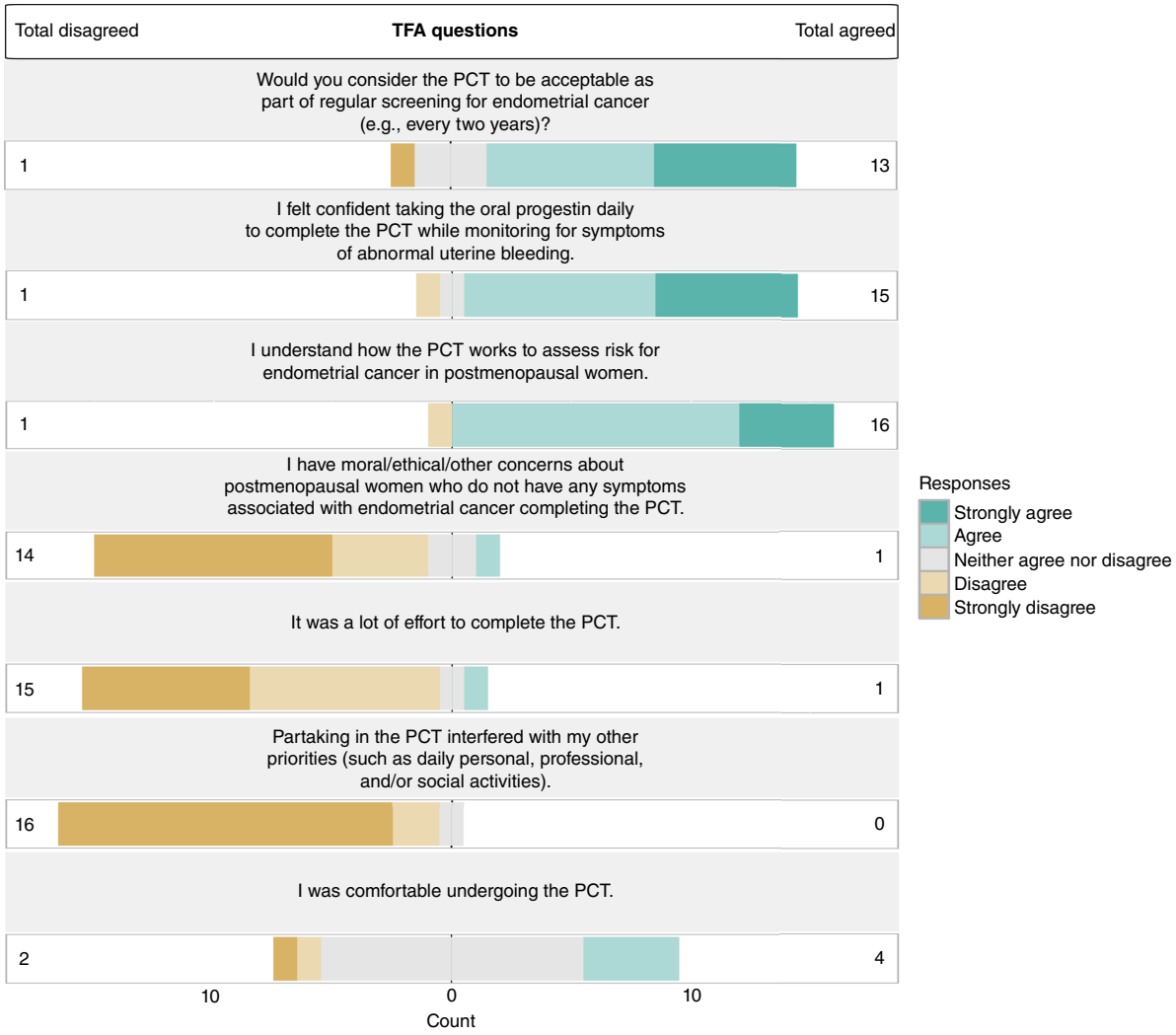

Figure 3.

Overall acceptability of the PCT as demonstrated by participant responses. Acceptability questions are displayed above each corresponding horizontal bar chart. Response categories are color-coded as follows: teal for agreement (agree or strongly agree), gray for neutral, and yellow for disagreement (disagree or strongly disagree). The bidirectional *X*-axis reflects the number of respondents (range, 0–10), with disagreement responses extending to the left and agreement responses to the right. Total counts for each response category are annotated at either end of each bar.

about the physiologic nature of the test and its distinction from HT. Enhanced education and stronger engagement of PCPs during recruitment and counseling may further mitigate reluctance.

Retention exceeded expectations (33, 34), with 78% initiating and 96.2% completing the MPA regimen. Daily symptom self-reporting declined over time, consistent with broader patterns of adherence in longitudinal studies (36). Incorporating app-based notifications, real-time feedback, and flexible symptom reporting options (e.g., via text message or email) could strengthen participant engagement and data completeness. SEs were mostly mild (median ≤3/10) although two participants discontinued because of symptoms, underscoring the importance of counseling and alternate strategies for those with hormone sensitivity or contraindications.

Acceptability was high, particularly because of the test's noninvasive, self-administered, and low-cost nature, consistent with previous reports (37). Both participants and providers emphasized that support is conditional on efficacy and safety. Some participants expressed concerns about postmenopausal hormonal disturbance and questioned the long-term benefit of the test. These perceptions mirrored the thematic findings of conditional support. Although participants valued contributing to prevention research, their willingness to adopt the PCT more broadly would depend on clear evidence of benefit and minimal risk. Providers similarly voiced support for the concept of the PCT but highlighted system-level concerns, including increased workload, as significant barriers to broader-scale implementation.

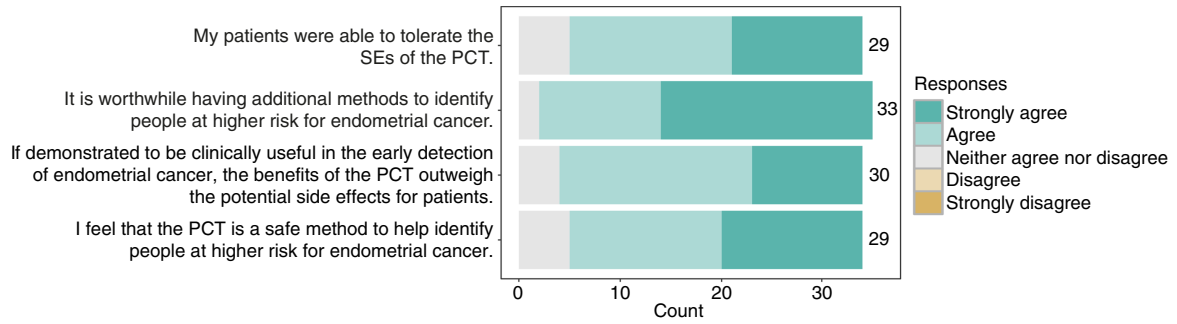

Figure 4.

PCP responses to acceptance of the PCT are shown as horizontal bar charts with the corresponding questions listed to the left. Response categories are color-coded as dark teal for strongly agree, light teal for agree, gray for neutral, and yellow for disagree (including strongly disagree). The *X*-axis indicates the total number of respondents per category. The total number of responses for each question is shown at the end of each corresponding bar.

The observed PCT positivity rate (30.2%) exceeded the anticipated 20% to 25% (27). Although one positive participant decided to forego a biopsy, 20% of those who did had a proliferative endometrium or hyperplasia. This study was not designed to assess the PCT's diagnostic accuracy; however, our findings reinforce the PCT's potential as a physiologic indicator of unopposed estrogen exposure. Given that endometrial proliferation may be associated with a fourfold increased risk of subsequent EH and cancer (38), endometrial proliferation as part of the target condition would result in a positive predictive value (PPV) of 20%. The relatively low frequency of proliferative endometrium and hyperplasia in this cohort reflects the characteristics of our community-recruited, asymptomatic population and the BMI threshold used. As shown by Crosbie and colleagues (14), even among women with a BMI greater than 40, the prevalence of hyperplasia is approximately 10%, illustrating that the underlying pathology rate varies by population risk profile. Furthermore, the biopsy provides a single-point-in-time assessment of pathology, and it would be unclear what the natural history of pathology incidence would be in this cohort. A prior meta-analysis reported a high PPV (~68%) and negative predictive value (NPV) (~97%) of the PCT (27) to detect proliferation and pathology, suggesting that the PCT compares favorably with established screening in women's health, such as mammography (PPV: 8.6%; NPV: >99.7%) and human papillomavirus testing (PPV: ~8%; NPV: >98%; refs. 39, 40). Because these measures would vary by population risk and intended use, future validation studies are necessary to define PPV and NPV for the PCT within consistently defined prevention cohorts.

Implementation insights highlight both strengths and challenges of our adopted decentralized, community-based model. Recruitment across British Columbia yielded a diverse sample but was hampered in rural areas with limited primary care coverage, requiring coordination with volunteer gynecologists. These real-world constraints highlight the need for flexible models, such as standing orders, nurse-led protocols, or pharmacist-led prescribing, in future implementation. To improve recruitment and adherence in future studies, we propose several modifications. First, streamlining eligibility assessment and using automated reminders may help retain participants throughout the whole intervention period. Second, enhanced pre-enrollment education (e.g., via videos or webinars) may reduce hormone-related anxiety and clarify the rationale for screening asymptomatic individuals. Third, ensuring cultural safety and linguistic accessibility will be key for equitable inclusion in larger-scale studies, especially among populations disproportionately affected by obesity-related cancer risk. Finally, centralizing certain study procedures (e.g., medication dispensing and follow-up monitoring) could help mitigate provider burden and enhance standardization of care.

The RESToRE study contributes to the growing body of evidence supporting the PCT as a low-burden, physiologic risk stratification tool for endometrial cancer prevention in asymptomatic individuals at higher risk (37). In combination with previous findings from the PROTEC trial and other studies showing that hormonal interventions, such as the LNG-IUS, can be both effective and acceptable in similar populations, our study shifts the focus further upstream (22). It highlights the potential to use risk stratification to direct and tailor preventive strategies at the population level, thereby enhancing the overall cost-effectiveness of efforts to reduce the risk of endometrial cancer (24).

Limitations include our modest sample size, reliance on self-reported data, the lack of long-term outcome data, and potential selection bias among self-referred participants. Nonetheless, RESToRE offers a window into the feasibility of a community-embedded individualized prevention strategy that links physiologic testing with primary care delivery. Future work should embed the PCT within randomized prevention trials (e.g., LNG-IUS or metabolic agents such as glucagon-like peptide-1 receptor agonists; NCT05829460) and cost-effectiveness analyses.

Conclusion

As endometrial cancer incidence increases, particularly among women with obesity, effective, acceptable, and scalable risk stratification tools will be essential. The PCT warrants further investigation in this context. Beyond demonstrating feasibility, these findings position the PCT as a physiologic biomarker of endometrial responsiveness. Unlike molecular assays that infer hormonal exposure indirectly, the PCT provides a dynamic functional readout of the endometrium's ability to respond to progesterone. This physiologic signal could serve as a low-cost, scalable tool to stratify cancer risk, identify candidates for preventive intervention, and anchor future biomarker validation studies that integrate molecular or microbiome correlates. Establishing the PCT as a biologically grounded screening step could redefine how endometrial cancer prevention is approached in postmenopausal populations.

Data Availability

Data used in this article are available upon request.

Authors' Disclosures

A. Neilson reports personal fees from Gynecologic Cancer Initiative during the conduct of the study, as well as grants from Gynecologic Cancer Initiative and Ovarian Cancer Canada outside the submitted work. R. Woima reports other support from Canadian Institute for Health Research and Province of British Columbia during the conduct of the study. L.C. Tindale reports grants from Michael Smith Foundation for Health Research during the conduct of the study. J.N. McAlpine reports other support from Merck, GSK, and AstraZeneca outside the submitted work. A. Talhouk reports grants from Canadian Cancer Society, Canadian Institute for Health Research, and Michael Smith BC Health Foundation during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

A. Neilson: Conceptualization, resources, data curation, investigation, writing–original draft, project administration, writing–review and editing, recruitment. **R. Woima:** Data curation, formal analysis, visualization, methodology, writing–original draft, project administration, writing–review and editing. **D. Dodani:** Data curation, software, formal analysis, validation, visualization, methodology, writing–original draft, writing–review and editing. **A. Helgason:** Data curation, formal analysis, writing–original draft, project administration, writing–review and editing. **N. Sebastian:** Data curation, formal analysis, writing–original draft, project administration, writing–review and editing. **L.C. Tindale:** Conceptualization, funding acquisition, writing–review and editing. **S. Wang:** Data curation, software, project administration, writing–review and editing. **T. Rowe:** Conceptualization, funding acquisition, writing–review and editing. **J. Kwon:** Conceptualization, writing–review and editing. **D. Miller:** Conceptualization, writing–review and editing. **L. Bernard:** Conceptualization, writing–review and editing. **J.N. McAlpine:** Conceptualization, funding acquisition, writing–review and editing. **A. Talhouk:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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Note

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