cancer care | action cancer
ontario | ontario
program in | programme de soins
evidence-based care | fondé sur des preuves

Evidence-based Series Special Report EDUCATION AND INFORMATION 2012

Self-collected Samples for Testing of Oncogenic Human Papillomavirus

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

> **This Practice Guideline Report was reviewed in September 2011 and put in the Education and Information section in 2012. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).**
> **The reviewed report consists of:**
> **Guideline Report Overview**
> **Section 1: Clinical Practice Guideline**
> **Section 2: Systematic Review**
> **Section 3: Guideline Development and External Review: Methods and Results**
>
> **and is available on the CCO website at http://www.cancercare.on.ca**

Release Date: April 3, 2012

For information about the PEBC and the most current version of all reports,
please visit the CCO website at http://www.cancercare.on.ca/
or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca

Evidence-based Series Special Report EDUCATION AND INFORMATION 2012

Self-collected Samples for Testing of Oncogenic Human Papillomavirus

Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original version April 2006	1985-2004	Full Report	Web publication	Not applicable (NA)
Reviewed Version April 2012	N/A	N/A	Updated Web publication	Guideline ARCHIVED

Evidence-based Series Special Report ARCHIVED 2012

Self-collected Samples for Testing of Oncogenic Human Papillomavirus

Guideline Review Summary

Review Date: September 2011

The 2004 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2006. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Clinical Practice Guideline and Evidentiary Base in this version are the same as 2006 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is completed with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore no update search was conducted. The 2006 guideline and its recommendations on Self-collected Samples for Testing of Oncogenic Human Papillomavirus have been **ARCHIVED**.

Evidence-based Series Special Report: Section 1 ARCHIVED 2012

Self-collected Samples for Testing of Oncogenic Human Papillomavirus:
A Clinical Practice Guideline

Stewart DE, Johnston M, Gagliardi A, Howlett R, Barata P, Lewis N, Oliver T, and Mai V
on behalf of the HPV Self-collection Guidelines Panel

Report Date: April 6, 2006

Questions
What is the role of self-sampling for human papillomavirus (HPV) testing as an alternative to cervical cancer screening by clinicians (i.e., Pap test)? Specifically, for HPV DNA testing,
- What are the potential benefits and harms of self-sampling?
- Is it feasible for women to successfully perform self-sampling?
- With self-sampling, are samples obtained by women adequate for analysis?
- What is the accuracy of self-sampling?
- Is self-sampling acceptable to women?
- Is self-sampling appealing to women?
- Do specific characteristics of women influence preferences regarding self-sampling?
- Is self-sampling appropriate for women who are never or seldom screened by clinicians?

Background
High-risk (oncogenic) types of HPV are a necessary, but not sufficient, cause of cervical cancer. On the basis of this strong causal relationship, if equivocal cell changes are identified with a Pap test, it is important to find out if the cell changes are due to the presence of high-risk HPV. The most efficient way to determine if there is cause for concern is to test for oncogenic HPV. Cells collected from the cervix can be tested for the presence of one or more of the high-risk HPV types that are associated with cervical dysplasia and cancer. If the HPV test is positive, the risk is higher that abnormal cells may progress to more severe changes or that there is underlying pathology, either of which could result in cervical cancer. Therefore, it is important to detect HPV as cell changes caused by high-risk HPV can lead to cancer. Finding and treating HPV-related tissue changes is a way to prevent cancer.

Target Population

The target population for this guideline is women in Ontario for whom cervical cancer screening is recommended with an emphasis on those who are never or seldom (> three years) screened by clinicians. Pap testing performed by clinicians is accepted as an effective screening test for reducing mortality from cervical cancer and is the current standard practice in Ontario. The self-collection of HPV samples may offer an acceptable alternative to Pap testing by clinicians especially for women who are never or seldom screened.

Recommendations

- There is insufficient evidence to recommend for or against self-sampling for HPV testing as an alternative to cervical cancer screening by clinicians. Further research is needed to provide evidence that will allow a decision to be made about using self-sampling to increase screening rates, especially in women who are never or seldom screened.

Key Evidence

- *What are the potential benefits and harms of self-sampling?*
  In theory, this method offers benefits to women with no access to a health care provider, who are uncomfortable with physical examination, or whose values prohibit an examination by a male physician. No studies evaluated the impact of self-sampling for HPV testing on participation rates in cervical screening, early detection of cervical cancer, survival, or quality of life. Data on harms from HPV self-testing is limited and largely restricted to assessment of false-negative and false-positive rates.
- *Is it feasible for women to successfully perform self-sampling?*
  Women in many countries, across a range of ages, were successful in collecting samples for HPV testing using a variety of self-collection techniques (e.g., swabs, brushes, tampons, lavage, and pads).
- *With self-sampling, are samples obtained by women adequate for analysis?*
  The quality of the patient samples was as good as the clinician samples, with more than 95% of samples yielding HPV testing results.
- *What is the accuracy of self-sampling?*
  Evidence on the accuracy of self-sampling for HPV testing was available from 14 studies, but interpretation is hampered by incomplete colposcopy data from women with negative HPV tests. A wide range of sensitivity and specificity values were observed among both patient- and clinician-collected samples, but the sensitivity of self-collection methods appeared to be slightly lower than that for samples collected by clinicians. Eleven of 19 studies found reasonable agreement (kappa>0.6) between the HPV test results from self- and physician-collected samples.
- *Is self-sampling acceptable to women?*
  The majority of women were willing to perform self-sampling, did not find it difficult or painful, and preferred self-sampling to physician sampling.
- *Is self-sampling appealing to women?*
  One study reported that women were more comfortable and less embarrassed with self-sampling than with physician sampling but wanted assurance that self-collection of HPV samples would not make them ineligible for physician visits for other concerns.
- *Do specific characteristics of women influence preferences regarding self-sampling?*
  There is little evidence about which women are interested in, or willing to perform, self-sampling.
- *Is self-sampling appropriate for women who are never or seldom screened by clinicians?*
  Findings from one study suggested that written self-sampling instructions might be hard to follow for women with limited education; however, among that group of women, their

requests for graphics or practice sessions in the clinic were seen as possible solutions to aid sample collection.

Future Research

Further research is needed to inform a policy regarding the use of HPV self-sampling. Ideally, research in the randomized setting would compare primary outcomes for women by type of screening schedule; HPV self-sampling versus the standard practice of cervical cancer screening by clinicians. This type of trial however is not likely to occur given the known efficacy of established cervical cancer screening programs. At a minimum, well-conducted studies producing accurate estimates of sensitivity and specificity, and studies testing intermediate outcomes such as method of collection, women's preferences, participation rates, referral rates, detection of abnormalities, and cancer detection rates would be needed to develop a policy regarding the use of HPV self-sampling.

In particular, future studies should examine the accuracy of self-collection for HPV testing in a cohort of women already undergoing primary screening, as that would be most relevant to the potential use of self-collection in Ontario. Future studies should also move beyond evaluating HPV testing as an isolated test and should include data on accessibility and adherence to follow-up and treatment after HPV results are obtained.

More studies are needed that specifically target women for whom screening is recommended but who have never or seldom had cervical cancer screening. Women of low literacy, women of specific cultural groups and women living in poverty have been identified as populations who are less likely to be screened. To increase understanding about the procedure of self-sampling, a combination of graphic, verbal, and written instructions should be developed.

Evidence-based Series Special Report: Section 2 ARCHIVED 2012

Self-collected Samples for Testing of Oncogenic Human Papillomavirus: A Systematic Review

*Stewart DE, Johnston M, Gagliardi A, Howlett R, Barata P, Lewis N, Oliver T, and Mai V,
on behalf of the HPV Self-collection Guidelines Panel*

A Special Project of the Screening Guidelines Steering Committee,
Cancer Care Ontario and The Program in Evidence-based Care, Cancer Care Ontario

Report Date: April 6, 2006

QUESTIONS

What is the role of self-sampling for human papillomavirus (HPV) testing as an alternative to cervical cancer screening by clinicians (i.e. Pap test)? Specifically, for HPV DNA testing,

- What are the potential benefits and harms of self-sampling?
- Is it feasible for women to successfully perform self-sampling?
- With self-sampling, are samples obtained by women adequate for analysis?
- What is the accuracy of self-sampling?
- Is self-sampling acceptable to women?
- Is self-sampling appealing to women?
- Do specific characteristics of women influence preferences regarding self-sampling?
- Is self-sampling appropriate for women who are never or seldom screened by clinicians?

INTRODUCTION

High-risk (oncogenic) types of HPV are a necessary, but not sufficient, cause of cervical cancer. On the basis of this strong causal relationship, if equivocal cell changes are identified with a Pap test, it is important to find out if the cell changes are due to the presence of high-risk HPV. The most efficient way to determine if there is cause for concern is to test for oncogenic HPV. Cells collected from the cervix can be tested for the presence of one or more of the high-risk HPV types that are associated with cervical dysplasia and cancer. If the HPV test is positive, the risk is higher that abnormal cells may progress to more severe changes or that there is underlying pathology, either of which could result in cervical cancer. Therefore, it is important to detect HPV as cell changes caused by high-risk HPV can lead to cancer. Finding and treating HPV-related tissue changes is a way to prevent cancer.

More than half of Ontario women who are diagnosed with cervical cancer have a history of no or infrequent screening. (1,2). Those women tend to have a low level of education, live in poverty, are newcomers to Canada, are over 50 years of age, or are of Aboriginal descent (3). Among these populations, it could be beneficial to offer alternative screening methods to

prevent the burden of disease from cervical cancer. Self-collected samples for testing of oncogenic HPV holds promise for cervical cancer screening among hard-to-reach populations and for those with limited access to health care, e.g., rural and remote populations.

Cervical cancer is a common cancer-related cause of death among women worldwide. Cervical cancer is preventable through regular screening programs. The objective of screening is to reduce mortality and morbidity from cervical cancer by detecting disease at an early stage when treatment is most effective. In Ontario and much of the developed world, women are screened for abnormalities in cervical tissue that may be precursors to cancer by undergoing the Papanicolaou (Pap) test. Pap testing performed by clinicians is accepted as an effective screening test for reducing mortality from cervical cancer (4) and is the current standard practice in Ontario. The Pap test is conducted in the primary care setting by a physician, nurse practitioner (RNEC, Registered Nurse Extended Care), midwife, or specially trained registered nurses (RN) with specific competency, and the sample examined in a laboratory for specific cell types that are considered abnormal. Depending on the degree of cellular changes, an abnormal Pap result requires a follow-up test in six months or immediate colposcopy, which enables both visualization of the cervix and the taking of a biopsy.

The detection of HPV in cervical specimens may offer an alternative to population-based cytological screening because it appears to be as sensitive as the Pap test (5), and may offer an acceptable option for women who are never or seldom screened. Ongoing research is investigating HPV testing on samples collected by physicians as a primary screening test for cervical cancer (6). Consensus-based guidelines from a 2001 conference sponsored by the American Society for Colposcopy and Cervical Pathology on the management of women with cervical cytological abnormalities recommended testing for HPV in women with the Pap smear abnormalities referred to as ASCUS or atypical squamous cells of undetermined origin (7). Women with positive HPV results would be referred for colposcopic examination, while women with negative results could be followed up with repeat cytological testing at 12 months. Where liquid-based cytology is used, the preferred approach is "reflex" HPV testing, or testing carried out on the residual of the already collected Pap test sample. Revised Ontario Cervical Screening Practice Guidelines were implemented in June 2005, which recommend the use of HPV-DNA testing among women over the age of 30, whose Pap test result is ASCUS (8). Furthermore, a pilot study in Ontario is investigating how reflex HPV testing in patients with ASCUS influences colposcopy rates and compliance with colposcopy compared with usual screening care.

Loss to follow-up after abnormal Pap tests is one of the most significant impediments to the effective treatment of women with abnormal Pap tests. It is estimated that 23%-41% of women in developed countries fail to return for treatment. Literature suggests that this lack of adherence is likely due to the absence of comprehensive recall and follow-up interventions. Other relevant factors may include physician shortage, and women's misunderstanding of the importance of follow-up (9-16).

The best adherence rates for treatment are noted in those jurisdictions with comprehensive organised screening programs and/or "failsafe" mechanisms at the individual physician level (17,18).

Inadequate follow-up of abnormal Pap test results is also associated with cervical cancer. Preliminary studies suggest that HPV testing may improve loss to follow-up by producing definitive results with clear clinical management, which in turn might improve the likelihood of patient adherence. An Ontario study by Lytwyn et al showed that loss to follow-up was 17% in a group referred for immediate colposcopy (on the basis of a positive adjunctive HPV test), compared to 33% in an equivalent group with repeat cytology at 6 months (19). Reflex HPV testing may also significantly reduce the cost of population-based screening by preventing unnecessary colposcopy examinations in patients with ASCUS results who test negative for oncogenic HPV (20,21).

Underscreening is another factor that plays a role in the occurrence of cervical cancer. There are many reasons why women in both underdeveloped and developed countries do not participate in cervical screening, such as lack of access to a health care provider, discomfort with physical examination, and/or cultural, religious, or personal values that prohibit examination by a male physician. A possible application of HPV testing relates to the potential for reaching underscreened populations with self-sampling methods. Self-sampling has proved worthwhile in screening for sexually transmitted diseases in hard-to-reach populations. For example, self-administered tampons were found to be an acceptable and sensitive method for detecting sexually transmitted diseases for women living in remote regions of Australia (22). In addition, self-administered vaginal swabs produced reliable results and were acceptable to women in Southern Asia for the detection of reproductive tract infections (23). A systematic review on the role of HPV testing in cervical screening concluded that further investigation is required to evaluate self-sampling for HPV testing (24).

In 2004, Cancer Care Ontario struck a guideline panel to examine the feasibility, acceptability, and effectiveness of self-sampling for HPV testing and to formulate recommendations on the role that self-testing might play in cervical cancer screening in Ontario. Self-sampling kits for HPV testing are not yet available in Ontario, but the panel considered that it was important to evaluate this emerging technology. In theory, self-sampling has the potential to improve screening and follow-up rates in women who are never or seldom (> 3 years) screened by clinicians and, thus, contribute to reducing mortality and morbidity from cervical cancer.

METHODS

This systematic review was developed by the HPV Self-collection Guidelines Panel as a collaborative effort between the Cancer Care Ontario (CCO) Screening Guidelines Steering Committee and the CCO Program in Evidence-based Care (PEBC). Evidence was selected and reviewed by six members of the HPV Self-collection Guidelines Panel and methodologists. The six panel members interpreted the evidence, formulated recommendations, and contributed to writing the guideline report. The panel included behavioural scientists, methodologists, a gynecologic oncologist, a policy analyst, and, from Cancer Care Ontario, the Manager of the Ontario Cervical Screening Program and the Acting Vice-President of Preventive Oncology.

The PEBC and HPV Self-collection Guidelines Panel are editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Literature Search Strategy

The following databases were searched for relevant reports on HPV DNA self-testing from the years of 1985 to December 2004: MEDLINE, EMBASE, HealthSTAR, CINAHL, the Cochrane Library, Women's Studies International, Web of Science, Social Sciences Index, PsycINFO, the Campbell Library, Studies on Women and Gender Abstracts Online, Contemporary Women's Issues, the Canadian Medical Association Infobase, and the National Guideline Clearinghouse.

In addition, unpublished sources were sought through an Internet search of Google, Health Canada, the National Health Service Department of Health, the Australian Government Department of Health, the RAND Corporation, the Institute of Medicine, the World Health Organization, the Agency for Health Research and Quality, and the National Institutes of Health for relevant reports. Article bibliographies and personal files were also searched to December 2004 for evidence relevant to the guideline question.

Where sophisticated search engines were available, the literature was searched by combining disease-specific terms (cervix dysplasia/ or cervical intraepithelial neoplasia/ or cervix neoplasms/ or papillomavirus/ or papillomavirus, human/ or papillomavirus, infections/) with test-specific terms (self-collected.tw. or self-test.tw. or self-obtained.tw.) for any study design. Where limited search facilities were available, the terms (Papillomavirus AND self-

collected or self-test or self-obtained or self-administered) or simply (Papillomavirus) or (HPV) were used.

Inclusion Criteria

Articles were included in the systematic review of the literature if they reported data relating to the self-collection of HPV DNA samples as they related to any of the following:

- the potential harms and benefits of self-sampling,
- the feasibility of women successfully performing self-sampling
- the adequacy of self-collected samples for analysis
- the accuracy of self-sampling
- the acceptability self-sampling acceptable to women
- the appeal of self-sampling to women
- whether specific characteristics of women influence preferences regarding self-sampling
- whether self-sampling is appropriate for women who are never or seldom (> three years) screened by clinicians?

Randomized controlled trials, case-control studies, prospective cohort studies, retrospective cohort studies, or technical reports were considered eligible for inclusion in the systematic review of the evidence. Where reports examined the subjective outcomes of appeal, perspectives, characteristics, or acceptability of self-sampling to women, the results of surveys (interviews, focus groups, questionnaires) were also deemed eligible.

Exclusion Criteria

Studies were excluded from the evidence review if they were reported in a language other than English, were reported prior to 1985, or were abstracts, letters, or editorials. Studies were also excluded if there were no data on the research methodology used to develop the report.

Synthesizing the Evidence

Data on the design of each study were extracted and tabulated, and the methodologic quality of each study assessed using published criteria (25). Based on that first examination of the literature, a data extraction form was created, and one reviewer extracted data from each of the eligible articles. A second reviewer checked the extracted data against the primary study reports and discrepancies were discussed with the first reviewer to achieve consensus. Where outcomes of interest were not reported but source data was, the reviewers calculated sensitivity, specificity, positive predictive value, and negative predictive value (using the Predictive Value Calculator available on the Web at http://www.azzopardi.freeserve.co.uk/EasyCalc/Additions/predict.htm) or Cohen's kappa (using a statistical calculator available on the Web at http://www.niwa.co.nz/services/statistical/).

Data were not pooled across studies because of important heterogeneity among studies in design, population, technique, timing of self-sampling, and outcome measures.

RESULTS

Literature Search Results

A total of 25 studies, published in 31 papers between 1992 and 2004, were reviewed (26-56) (Table 1). The majority of those studies reported on the accuracy of self-collected samples compared with reference standards or assessed agreement with clinician-collected samples. Several studies reported on the success of self-collection, defined as the ability of women to perform the act of self-collection, their participation rate or the return of a sample providing sufficient cells for HPV testing. Some studies also examined the acceptability of self-collection to women and asked women to rate their comfort with self-testing and their preferences for self-sampling or clinician sampling.

Where multiple publications were used to compile evidence on a single study, the most relevant reference is cited in each instance below (32-40). The studies took place in a variety of geographic locations (Australia, Brazil, Canada, China, Germany, Mexico, the Netherlands, Peru, South Africa, Sweden, Taiwan, Uganda, the United States, and the United Kingdom) and settings, most commonly in colposcopy clinics. Eight studies recruited patients in colposcopy clinics (30,31,33,41,47,49,54,55), one in an internal medicine clinic (27), one in a teen health centre (28), one in a sexually transmitted infection clinic (45), two in a gynecologic clinic (26,51), and one in a dysplasia clinic (56); two studies recruited women attending a screening program (36,42) and five women from the general population (29,39,43,44,48); four assessed patients already participating in other studies, a randomized trial of sexually transmitted infection control for AIDS prevention (50), a case-control study of cervical cancer (46), a cohort study evaluating the relationship between HPV, HIV, and cervical disease (52), and a natural history study (53).

Given that the sample size ranged from 17 to nearly 8,500 participants and the methodological quality varied considerably among the studies, the larger studies and those with stronger methodological quality were accorded greater consideration in the interpretation of the data, discussions and derived conclusions.

Table 1. Evidence available from studies eligible for the systematic review.

Study	No. of pts. enrolled (# analyzed)	Study Origin	Setting	Patient Self-test Method	Accuracy	Success	Acceptability
Kim 2004 (26)	347 (340)	Korea	gynecologic clinic	pad	√		
Dannecker 2004 (27)	435 (435)	Germany	internal medicine clinic	vaginal brush	√	√	√
Kahn 2004 (28)	101 (99)	USA	teen health centre	vaginal swab	√	√	
Forrest 2004 (29)	200 (200)	UK	community	vaginal swab			√
Garcia 2003 (30)	334 (334)	USA/Mexico/Peru	colposcopy clinic	vaginal brush	√	√	
Palmisano 2003 (31)	334 (334)	USA	colposcopy clinic	vaginal swab	√	√	
Harper 2003 (32)* Harper 2002a (33)* Harper 2002b (34)*	103 (103)	USA	colposcopy clinic	vaginal swabs, tampon	√ √	√	√ √
Flores 2003 (35)** Salmeron 2003 (36)** Flores 2002 (37)** Dzuba 2002 (38)**	7876 (7732)	Mexico	screening program	vaginal swab	√	√	√ √
Belinson 2003 (39)*** Tisci 2003 (40)***	9183 (8497)	China	community	vaginal brush	√	√	√
Nobbenhuis 2002 (41)	71 (71)	Netherlands	colposcopy clinic	cervicovaginal lavage	√	√	√
Lorenzato 2002 (42)	253 (253)	Brazil	screening program	vaginal swab	√		
Chang 2002 (43)	1194 (1194)	Taiwan	community	vaginal swab	√		
Belinson 2001 (44)	2047 (1997)	China	community	vaginal swab	√		
Rompalo 2001 (45)	793 (706)	USA	STI clinic	vaginal swab	√		
Gravitt 2001 (46)	268 (268)	USA	study participant	vaginal swab			√
Sellors 2000 (47)	245 (200)	Canada	colposcopy clinic	vaginal swab vulvar swab urine specimen	√		√
Wright 2000 (48)	1415 (1365)	Africa	community	vaginal swab	√		
Hillemans 1999 (49)	247 (247)	Germany	colposcopy clinic	vaginal brush	√		√
Serwadda 1999 (50)	960 (898)	Africa	study participant	vaginal swab		√	

Harper 1999 (51)	97 (93)	USA	gynecologic clinic	tampon	√		
Coutlee 1997 (52)	230 (224)	Canada	study participant	tampon	√	√	
Moscicki 1993 (53)	114 (114)	USA	study participant	vaginal swab	√		
Forslund 1993 (54)	343 (NR)	Sweden	colposcopy clinic	urine specimen	√	√	
Morrison 1992 (55)	25 (17)	USA	colposcopy clinic	cervicovaginal lavage	√	√	
Fairley, 1992 (56)	48 (48)	Australia	dysplasia clinic	tampon	√		

NR, not reported; No. of pts., Number of patients; STI, Sexually transmitted infection.
* Three reports of one American study.
** Four reports of the Morelos HPV Study.
*** Two reports of the Shanxi Province Cervical Cancer Screening Study (SPOCCS) II Study.

There were no randomized trials or comparative cohort studies that followed patients after HPV testing to assess intermediate- or long-term outcomes from screening with self-sampling versus clinician sampling. Other than using an "experimental" procedure in the form of self-sampling, the studies were essentially observational in nature. Individual women used more than one method of self-sampling within two studies (32,34,47), and in another study, the order of sampling (self versus clinician first) was randomized (51). All studies were prospective, and informed consent was obtained from participants. A common study design involved women collecting samples for HPV testing using one or more methods of self-sampling (swab, brush, tampon, lavage, or pad), followed or preceded by a gynecological examination by a clinician (physician or nurse). The clinician collected a sample for HPV testing, obtained a cervical smear for cytology, and, in most cases, performed a colposcopic examination with cervical biopsy.

Outcomes
What are the potential benefits and harms of self-sampling?
Evidence on the benefits and harms from HPV testing is limited and largely restricted to the assessment of true-positive, false-negative, and false-positive rates (discussed under accuracy below). No studies evaluated the impact of self-sampling for HPV on screening participation rates, early detection, survival, or quality of life.

Is it feasible for women to successfully perform self-sampling for HPV testing?
A large number of women aged 14 to 88 across 25 studies in 14 countries were able to obtain samples using a variety of self-testing techniques including vaginal swab, cytobrush, pad, tampon, vaginal lavage, vulvar swab, and urine collection. Four studies reported clearly on the proportion of participants who returned samples from self-collection (34,41,50,55). In a study where women were requested to perform eight swabs and use four tampons for varying lengths of time, 15% did not complete all the sampling (34). The most common reasons reported for not doing the self-test among 15 women (21% of recruits) in the study by Nobbenhuis et al were forgetting and being too nervous about the colposcopy exam (41). Serwadda et al reported that 93% of participants in rural Uganda provided samples using vaginal swabs; the samples were collected at home and handed to a field worker (50). In the study by Morrison et al, 68% of urban American women returned samples collected by cervicovaginal lavage 10-36 days after colposcopy (55).

Five studies reported on the difficulty of performing self-sampling or understanding the instructions (27,34,38,40,41). In the trial by Dannecker et al, five of 333 women (1.5%) found it difficult to use a vaginal brush for self-collection (27). Harper et al asked women if they experienced any difficulty putting tampon samples collected at home into tubes of preservative and putting the tubes into mailing kits; of 65% of the study population who completed the survey, no one reported difficulties (34). In one trial, Mexican women rated comprehension of the self-sampling procedure with an average score of 4.5 on a five-point scale, where 1=poor and 5=good (38). Tisci et al reported that, when difficulty did occur among rural Chinese women

with low education, it was a direct result of not understanding the directions (40). Reported problems included contamination of the sampling brush, difficulty locating the vagina, spillage of the transport medium, and trouble distinguishing between the top and bottom of the container. In the trial by Nobbenhuis et al, 12% of Dutch women experienced difficulties using cervicovaginal lavage (41).

With self-sampling, are samples obtained by women adequate for analysis?
Seven papers reported on the quality of samples obtained by self-testing (28,30,31,34,52,54,55). In four studies (28,30,38,54), more than 95% of samples yielded cells for HPV testing (Table 2). In one study, it was noted that although 4% of samples were inadequately labelled and 6% of samples leaked during shipment, the samples still yielded cells sufficient for HPV testing (34). It was also reported that neither cycle stage nor recent sexual intercourse affected HPV results from self-collected samples (34). Of the remaining studies, Palmisano et al experienced difficulty with self-collected samples due to the lack of amplification (samples were considered to be amplified if the beta-high band appeared on genotyping strips), which they postulated might be due to the insufficient collection of cells using vaginal swabs (31). In the small study by Morrison et al (55), 94% of the patient-collected samples and 100% of the clinician-collected samples were adequate for analysis.

Table 2. Proportion of self-collected samples adequate for HPV analysis.

Author Year (Ref)	No. of pts.	Method of Collection	Setting	Sample Collector	Satisfactory samples
Kahn 2004 (28)	99	vaginal swab	clinic	patient	98%
		cervical swab	clinic	clinician	99%
Garcia 2003 (30)	334	vaginal brush	clinic	patient	99%
		cervical brush	clinic	clinician	98%
Palmisano 2003 (31)	334	vaginal swab	clinic	patient	~70%
		cervical swab	clinic	clinician	100%
Harper 2002 (34)	103	tampon	clinic	patient	NR
		cervical swab	clinic	clinician	NR
Coutlee 1997 (38)	224	tampon	clinic	patient	99%
		cervicovaginal lavage	clinic	clinician	99%
Forslund 1993 (54)	343	urine specimen	clinic	patient	96%
		cervical brush	clinic	clinician	100%
Morrison 1992 (55)	17	cervicovaginal lavage	home	patient	94%
		cervicovaginal lavage	clinic	clinician	100%

No. of pts., Number of Patients; (Ref), references.

What is the accuracy of self-sampling for HPV as a screening tool for cellular abnormalities of the cervix?
Most studies reported on the sensitivity, specificity, positive predictive value, or negative predictive value of self-sampling, or provided enough data for those measures to be calculated. Data related to the accuracy of self-testing for HPV were not pooled because of the variation in the studies in terms of the method used for self-collection, the test used to identify HPV (Hybrid Capture II, PCR or Southern blot analysis), the HPV strains considered high-risk, and the type of self-sampling instructions provided.

Biopsy as reference standard
Fourteen studies that reported HPV and biopsy results are listed in Table 3. The fourteen studies are presented according to patients who received colposcopy in all cases, as opposed to those who received colposcopy with a positive HPV test or finding of abnormal cytology. In one study (27), colposcopy was performed on a random sample of HPV-negative women.

In the first eight studies (seven of which recruited consecutive women referred to colposcopy clinics), all study participants underwent colposcopy (26,30,34,41,42,47,49,55). Three studies took place among previously unscreened populations (39,44,48), three at a cervical cancer screening service (36,42,43) and one at an internal medicine clinic with a focus on oncology, hematology, and gastroenterology (27). In five studies, only patients positive for HPV or with an abnormal cytology were recalled for a gynecological examination and colposcopy (36,39,43,44,48). When the reference test is not applied to all patients, including those with negative screening tests, the results are likely to suffer from verification bias. In an attempt to compensate for that design problem, Dannecker et al conducted further evaluation of a random sample of HPV-negative women (27). Seven study reports noted that biopsy samples were interpreted without knowledge of HPV results (26,28,30,34,39,47,48).

Observed positive predictive values (i.e., the proportion of patients with a positive HPV test who were found to have a cellular abnormality of the cervix) of HPV testing from self-collected samples was low (9-35%) in patients recruited for screening (27,36,39,43,44,48), compared to 38-100% in patients referred for colposcopy (29,30,34,41,42,47,49,55). While observed negative predictive values (i.e., the proportion of patients with negative HPV results who do not have a cellular abnormality of the cervix) were excellent in the screening studies, it must be kept in mind that only patients with abnormal HPV or Pap smear results were referred for further evaluation (36,39,43,44,48). Those data should be interpreted with caution because the true outcome in most women with negative HPV tests is unknown.

In a direct comparison, Sellors et al observed higher sensitivity with samples collected using vaginal swabs than with vulvar swabs or urine samples but higher specificity with urine sampling (47). HPV testing of samples collected by clinicians tended to have higher sensitivity than those collected by patients, but there is considerable variation among studies in sensitivity rates for both.

Table 3.   Accuracy of HPV test to predict cervical intraepithelial neoplasia (CIN 2/3) or cervical cancer on biopsy .

Author Year (Ref)	No. of pts.	Positive biopsy	Method	Sample Collector	Sensitivity	Specificity	PPV	NPV
All patients underwent colposcopy								
Kim 2004 (26)	340	72%	pad cervical brush	patient clinician	75% NR	100% NR	100%[#] NR	61%[#] NR
Garcia 2003 (30)	334	30%	vaginal brush cervical brush	patient clinician	49% 82%	73% 67%	44% 52%	77% 90%
Harper 2002 (34)	103	6%	tampon cervical swab	patient clinician	83% NR	89% NR	50% NR	98% NR
Nobbenhuis 2002 (41)	71	46%	lavage lavage	patient clinician	81% 91%	68% 43%	70% 58%	79% 84%
Lorenzato 2002 (42)	253	26%	vaginal swab cervical brush and spatula	patient clinician	50%[#] 75%[#]	86%[#] 88%[#]	53%[#] 69%[#]	82%[#] 91%[#]
Sellors 2000 (47)	200	24%	vaginal swab vulvar swab urine specimen cervical brush	patient patient patient clinician	86% 62% 45% 98%	54% 63% 70% 52%	43% 40% 38% 46%	91% 80% 76% 99%
Hillemans 1999 (49)	247	15%	vaginal brush cervical brush	patient clinician	92% 92%	NR NR	NR NR	NR NR
Morrison 1992 (55)	17	53%	lavage lavage	patient clinician	100%[#] 100%[#]	14%[#] 29%[#]	54%[#] 58%[#]	100%[#] 100%[#]
Colposcopy for HPV +ve or abnormal cytology or random sample of HPV –ve (data corrected for verification bias)								
Dannecker	435	6%	vaginal brush	patient	100%	71%	10%	100%

					Sensitivity	Specificity	PPV	NPV
2004 (27)			cervical brush	clinician	NR	NR	NR	NR
Salmeron 2003 (36)	7732	1.3%	vaginal swab	patient	71%	89%	9%	100%
			cervical brush	clinician	93%	92%	15%	100%
Belinson 2003 (39)	8497	4%	vaginal brush	patient	88%	77%	15%[#]	99%[#]
			cervical brush	clinician	97%	80%	18%[#]	100%[#]
Chang 2002 (43)	1194	5%	vaginal swab	patient	96%	92%	35%	99%[#]
			cervical brush or spatula	clinician	NR	NR	NR	NR
Belinson 2001 (44)	1997	4%	vaginal swab	patient	83%	86%	21%	99%
			cervical brush and spatula	clinician	95%	85%	23%	100%
Wright 2000 (48)	1365	4%	vaginal swab	patient	66%[#]	81%[#]	13%[#]	98%[#]
			cervical brush	clinician	84%[#]	83%[#]	17%[#]	99%[#]

No. of pts., Number of Patients; (Ref), references; NR, data not reported; PPV, positive predictive value; NPV, negative predictive value.
reviewer's calculation.

Cytology as reference standard

Four studies used cytology as a reference standard or reported HPV and cytology data that could be used to calculate accuracy (28,31,45,53) (Table 4). None of those studies recruited women from the general population. Sensitivity and specificity values varied among those studies, with no obvious differences between self-collected and clinician-collected samples.

Table 4.   Accuracy of HPV test to predict abnormal cytology on cervical smear.

Study	No. of pts.	Abnormal cytology	Method	Sample Collector	Sensitivity	Specificity	PPV	NPV
Kahn, 2004 (28)	99	23% ASCUS, LSIL, HSIL	vaginal swab	patient	70%	62%	36%[#]	87%[#]
			cervical swab	clinician	70%	66%	38%[#]	88%[#]
Palmisano 2003 (31)	334	phase I: 67% ASCUS, LSIL, HSIL	vaginal swab	patient	32%[#]	79%[#]	76%[#]	37%[#]
		phase II: 43% ASCUS, LSIL, HSIL	vaginal swab	patient	50%[#]	79%[#]	64%[#]	68%[#]
			cervical swab	clinician	NR	NR	NR	NR
Rompalo, 2001 (45)	706	19% ASCUS, LSIL, HSIL	vaginal swab	patient	54%[#]	68%[#]	28%[#]	86%[#]
			cervical swab	clinician	58%[#]	68%[#]	30%[#]	88%[#]
Moscicki, 1993 (53)	114	13% Atypia or LGSIL	vaginal swab	patient	80%[#]	76%[#]	33%[#]	96%[#]
			cervical swab	clinician	73%[#]	75%[#]	31%[#]	95%[#]

No. of pts., Number of Patients; (Ref), references; NR, data not reported; ASCUS, atypical squamous cells of undetermined origin; LSIL, low-grade squamous intra-epithelial lesions; HSIL, high-grade squamous intra-epithelial lesions; LGSIL, low-grade squamous epithelial lesion.
.# reviewer's calculation.

How does self-sampling for HPV compare with sampling by a clinician?

Nineteen studies reported data on agreement between self- and clinician-collected samples in the form of a kappa statistic or provided data that the reviewers could use to calculate kappa. Kappa provides a fairly crude measure of agreement beyond that expected by chance; values can range between 0 and 1, with 1 indicating perfect agreement. Although criteria vary, kappa values above 0.8 are generally considered to indicate very good agreement and values between 0.6 and 0.8 reasonable/substantial agreement (57). Kappa may vary with the prevalence of HPV in the study populations and be difficult to interpret when prevalence is very high or very low (57).

In 22 comparisons across 19 studies, agreement between results from samples collected by patients and those obtained by clinicians ranged from 0.24 to 0.96 (Table 5).

Table 5. Agreement between HPV results from self-test and clinician-test.

Studies	No. of pts.	Method of collection		Cohen's kappa (patient vs. clinician)
		Patient	**Clinician**	
Harper, 2002a (33)	103	vaginal swab	cervical swab	0.74
		tampon	cervical swab	0.63
Sellors, 2000 (47)	200	vaginal swab	cervical brush + swab	0.76
		vulvar swab	cervical brush + swab	0.55
		urine specimen	cervical brush + swab	0.41
Kahn, 2004 (28)	99	vaginal swab	cervical swab	0.72
Rompalo, 2001 (45)	706	vaginal swab	cervical swab	0.48
Gravitt, 2001 (46)	268	vaginal swab	cervical swab	0.73
Moscicki, 1993 (53)	114	vaginal swab	cervical swab	0.84[#]
Wright, 2000 (48)	1365	vaginal swab	cervical brush	0.45
Lorenzato, 2002 (42)	253	vaginal swab	cervical spatula & brush	0.62
Dannecker, 2004 (27)	435	vaginal brush	cervical brush	0.24
Garcia, 2003 (30)	334	vaginal brush	cervical brush	0.50
Belinson, 2003 (39)	8497	vaginal brush	cervical brush	0.49
Hillemans, 1999 (49)	247	vaginal brush	cervical brush	0.66[#]
Nobbenhuis, 2002 (41)	71	cervicovaginal lavage	cervical brush	0.53
		cervicovaginal lavage	cervicovaginal lavage	0.47
Morrison, 1992 (55)	17	cervicovaginal lavage	cervicovaginal lavage	0.64[#]
Harper, 1999 (37)	93	tampon	cervical swab	0.49
Coutlee, 1997 (38)	224	tampon	cervicovaginal lavage	0.76
Fairley, 1992 (56)	48	tampon	cervical spatula	0.70
Kim, 2004 (26)	340	pad	cervical brush	0.96
Forslund,1993 (54)	343	urine specimen	cervical brush	0.54

reviewer's calculation.

There was reasonable or very good agreement between patient- and clinician-collected samples (kappa>0.6) in six studies of vaginal swabs for self-collection (28,33,42,46,47,53), three studies of tampons (33,38,56), one using a cytobrush (49), one with cervicovaginal lavage (55) and one with a collection pad (26). Two of those studies were conducted in Canada (47,52). Poor agreement (kappa<0.6) was observed for collection with a vaginal swab in two studies (45,48), a tampon in one study (37), a cytobrush in three studies (27,30,39), lavage in one study (41), a vulvar swab in one study (47) and urine in two studies (47,54).

Is self-sampling for HPV testing acceptable to women?
Nine studies evaluated and reported on the acceptability of self-collection for HPV testing (27,29,33-35,38,40,41,46,47,49). Four studies used self-administered questionnaires that were completed by study participants at home (27,34,41) or in the clinic (33,46). Four studies conducted structured interviews (29,35,38,40), two of which were in a clinic setting (38,40). There were no details provided for one study (49). Inter-rater reliability (Kappa = 0.81 and 0.88 for time 1 and time 2 respectively) and test-retest reliability (Kappa = 0.71) of the questionnaire used to evaluate acceptability were assessed in only one study (40), and reliability was calculated for compilation indices in another study (Cronbach alphas = 0.74, 0.64, 0.61, 0.68) (38). No other studies reported on the development of their questionnaire or interview guides or on their validity and reliability.

Collectively, the most commonly assessed factors were test preference, acceptability, comfort level, and willingness to perform self-sampling. Outcome measures for eight studies that reported common data are summarized in Table 6 (27,29,38,40,41,46,47,49). Most often, participants were asked to select, rate, or rank either a method of collection (self versus clinician) or factors associated with the method of collection. There was considerable variation in how variables were measured and reported. Harper et al found that longer self-sampling

tampon times were increasingly bothersome, although two thirds to three quarters of women did not find the self-sampling tampons bothersome at all (34).

Table 6. Acceptability of self-collection for HPV testing.

Study	Setting	Willingness to perform	Acceptability	Preference
Dannecker 2004 (27)	internal medicine clinics (Germany)	97% willing to do at home	NR	23% -self (brush) 14% -clinician 63% - no preference
Forrest 2004 (29)	Community sample (Britain)	93.5% willing to self-test 95.5% willing as part of national screening program	NR	NR
Tisci 2003 (40)	general public (China)	91% prefer to do test at clinic	NR	NR
Dzuba 2002 (38)	Screening Program (Mexico)	79% willing to do at home if health care worker delivered kit	Significant difference between acceptability score for self (21.7) vs Pap (19.5)	68% -self (swab) 32% -clinician 4% -no preference
Harper 2002 (33,34)	colposcopy clinic (USA)	94% willing to use swab for annual screening; 97% willing to use tampon	NR	NR
Nobbenhuis 2002 (41)	colposcopy clinic (Holland)	21% did not perform self-sampling	NR	23% - Pap; 77% - self (lavage)
Sellors 2000 (47)	colposcopy clinic (Canada)	NR	98% - urine sampling 93% - vulvar sampling 88% - vaginal sampling 79% - physician sampling	Patient sampling ranking: 90% urine sampling #1 77% vulvar sampling #2 77% vaginal sampling #3 77% physician sampling #4
Hillemans 1999 (49)	colposcopy clinic (Germany)	NR	NR	94% favoured self-sampling (brush) over physician

Seven studies asked participants for their collection preference. Most found that self-collection was preferable to physician collection (29,35,38,41,46,49), but, in one study, 63% of women did not have a strong preference one way or the other (27). Two studies directly measured acceptability and reported that both self-collection and physician collected methods were acceptable to the women, although self-collection was rated higher on acceptability (38,47). In a study of 200 Canadian women, Sellors et al found that urine sampling was acceptable to 98% of women, vulvar sampling to 93%, vaginal sampling to 88%, and physician-collected sampling to 79% (47).

Harper et al, found that 97% of American women recruited from a colposcopy clinic were willing to use a tampon for annual cervical screening (33). Slightly fewer (94%) were willing to use a swab, and several expressed concerns that the swab would break. In that study, women were willing to use self-collection methods for their annual screen so long as self-sampling did not preclude an annual visit with their physician. Additional data were reported by Dannecker et al who examined the willingness to pay in a sample of German women and found that 57% of participants were willing to pay between £15 and £50 for an HPV self-test if the kit were available over the counter (27).

Two studies found a high willingness to do self-sampling at home (27,38), but a third study found that most participants (91%) preferred to perform self-sampling at the clinic (40). That preference was associated with low education, but, overall, 50% of participants felt "comfortable or very comfortable" with self-collection using a cervical brush. Two other studies reported comfort levels with self-sampling (33,34,38). One study (33,34) reported a mean discomfort score of 1.28 for self-collection using a tampon, where 1 indicated "not bothersome," and 5

indicated "extremely bothersome." Of those who self-sampled using a vaginal swab, 94% indicated that they were comfortable using swabs for self-sampling. In the other study (38), 24% of women felt no discomfort with the vaginal swab, and more reported discomfort with Pap testing than with self-sampling.

Inconsistent and scattered evidence on the immediate adverse effects of self-sampling is available from six studies. Only one superficial laceration, not requiring repair, was noted among 343 participants examined in a tri-country study using a cytobrush (30). Only three studies commented on pain or discomfort from self-sampling (38,40,45). Dzuba et al reported that 71% of 1069 women in the Morelos HPV Study reported some pain from self-sampling using a Dacron swab, but more women (95%) reported pain with a Pap test (38). That feedback was collected during interviews, using a structured questionnaire. Thirteen percent of women interviewed in the study by Tisci et al experienced pain with self-sampling using a vaginal brush, and 12% reported bleeding (40). In contrast, Rompalo reported that none of 768 participants complained of discomfort with either self-sampling using a vaginal swab or with physician sampling but did not collect this information systematically using a questionnaire (45).

What appeals to women with respect to self-sampling?
Four studies commented on what might appeal to women about self-sampling and on what they might not like about self-sampling (29,33,34,38,41).

Dzuba et al found that women reported more comfort (71%) and/or less embarrassment (55%) as reasons for preferring self-sampling (38). Vaginal dryness was the most common concern associated with self-sampling using a tampon, as reported in the study by Harper et al (33,34). A few women (13%) were concerned about toxic shock syndrome. The 21% of women who were concerned about use of a swab for self-sampling were afraid that the test would not be done properly or that the swab would break.

Participants in a study by Nobbenhuis et al found that self-sampling was difficult with the lavage method. They indicated that they were unsure if they had aspirated a sufficient quantity of fluid and questioned the efficacy of lavage as a method for self-sampling (41). Forrest et al found that a large percentage of women were concerned about doing the self-test properly (55%) and that this was particularly concerning for Indian (66%) and African-Caribbean (70%) women compared to white (33%) or Pakistani (49%) women (29). However, the vast majority of the women (96.5%) did not believe that the self-test was contrary to religious or cultural beliefs.

Those who preferred having a Pap test collected by a physician overwhelmingly cited confidence in the procedure (93%) as the reason for their preference (38). The most common explanations for preferring the Pap test was that they did not have a problem with gynaecological exams and/or that the self-test was impractical (41).

What are the characteristics of women who are interested in performing self-sampling?
Two studies examined the impact of participant demographics on acceptability outcome measures (38,40). Tisci et al found that better-educated women felt more comfortable performing self-sampling (40). Dzuba et al. reported that women in a higher income bracket were more likely to prefer the self-sampling method (38).

A third study compared British women from four ethnic groups (Indian, Pakistani, African-Caribbean, and white) as to their willingness to perform the self-test and found no significant differences among groups (29).

Will women who are never or seldom screened by clinicians perform self-sampling?
Only one study targeted women who were never or seldom screened. In the Tisci et al study, women were recruited from two counties in rural China and were only eligible to participate if they had not been screened for cervical cancer in the past 10 years (40). The authors of that study examined a number of possible barriers to self-sampling. They reported that most women

(84.7%) did not know why HPV testing was important. However, very few women (0.4% - 2.4%) agreed that they were uncomfortable touching their genital area, felt that the test might not be safe, thought that the brush was not clean, were afraid of hurting themselves while performing the test, and did not understand how to perform the test. In addition, the authors asked participants to speculate about how other women would feel about the self-sampling. A substantial number (42%) believed that other women would not perform the self-sampling test if they did not think they were ill. Other potential barriers were identified less often: the high cost of the test (12%), lack of belief in the medical sciences (10%), fear (5%), inability to read the directions (0.8%), husbands not wanting their wives to do the test (0.4%), and belief that the test may be experimental (0.4%).

Although Forrest et al included women from four ethnic groups in the United Kingdom (UK) (Indian, Pakistani, African-Caribbean, and white British), the majority in each group had had a previous Pap test, and so they cannot be considered hard-to-reach women (29).

ONGOING TRIALS
No relevant studies were listed in the National Cancer Institute database (http://www.cancer.gov/search/clinical_trials/, Accessed 2 March 2005), but one relevant study was found by a web search using the Google search engine.

The Cancer Research UK is conducting a study to assess the acceptability and performance of self-sampling for high-risk HPV types, and the psychosocial effects of HPV testing in a UK screening setting (58). The investigators have completed recruitment and are analyzing the study results (Personal communication; e-mail correspondence with Louise Cadman, Cancer Research UK Centre for Epidemiology, Mathematics and Statistics; 25 March 2005). Women were given an instruction sheet and asked to perform an HPV self-test in private before receiving an HPV test carried out by the doctor or nurse during a routine smear test. If cervical smear result showed abnormal cells or either of the HPV tests is positive, participants were invited for a colposcopy examination. One in twenty women who participated in this study was asked to have a colposcopy examination, even though all three tests were normal.

Participants were asked to complete three questionnaires:
- Before testing, women were asked how they felt about smear tests and tests for HPV.
- Directly after testing, women were asked what they thought about the HPV self-test and the HPV test that the doctor/nurse did.
- A mailed questionnaire sent a week after the participant had received the test results asked how she had been feeling since receiving the results and included specific questions on attitudes toward smear tests and HPV testing.

CONCLUSIONS
What are the benefits and harms of self-sampling for HPV testing?
There is insufficient evidence to determine if self-sampling offers the potential for increased screening participation among unscreened and underscreened populations. In theory, this method offers benefits to women with no access to a health care provider, who are uncomfortable with physical examination, or whose values prohibit examination by a male physician. However, the impact on screening participation rates, disease detection and prevention, and survival has not been determined. The harms from self-collection have not been fully evaluated, especially adverse effects associated with false-positive and false-negative test results.

Is it feasible for women to successfully perform self-sampling for HPV testing?
Women in many countries and across a wide age range were successful in collecting samples for HPV testing, using a wide variety of self-collection techniques, including swabs, brushes, tampons, lavage, and pads. Although poorly educated women experienced some difficulty with

self-collection, most women successfully collected samples. The former group asked for graphics or practice sessions in the clinic to aid sample collection.

Will samples obtained from women be adequate for analysis?
The quality of the cytology in patient samples was as good as clinician samples, with more than 95% of samples yielding HPV results.

What is the accuracy of self-sampling for HPV as a screening tool for cellular abnormalities of the cervix?
Evidence on the accuracy of self-sampling for HPV testing is available from 14 studies. The studies varied by design, method, and order of self- and clinician-collected samples; the test used to identify HPV; the HPV strains considered high risk; the reference standard employed for calculations of test accuracy; and the degree to which the women were provided with self-sampling instructions.

Interpretation is further hampered by incomplete colposcopy data from women with negative HPV tests. Colposcopy-guided biopsy is considered the "gold" or reference standard for confirming cytology results. To accurately determine sensitivity and specificity and avoid verification bias, the reference test should be conducted in all study participants or in a random sample of participants. Unfortunately, biopsies were performed only in women with abnormal cytology or HPV results in most studies of self-collection for HPV testing. Studies with high biopsy rates were conducted in colposcopy clinics and are not generalizable to the primary screening setting. A wide range of sensitivity and specificity values were observed among both patient- and clinician-collected samples, but the sensitivity of self-collection methods appeared to be slightly lower than samples collected by clinicians.

How does self-sampling for HPV compare with sampling by a clinician?
Nineteen studies examined the agreement between HPV test results from self- and physician-collected samples. Eleven of the 19 individual studies achieved a kappa statistic of 0.60 or greater, generally considered reasonable agreement. Only two studies compared different self-collection methods in the same patient (33,47); both reported higher agreement between clinician and patient samples with vaginal swabs than with tampons, vulvar swabs, or urine specimens.

Is self-sampling for HPV testing acceptable to women?
There was considerable variability across studies regarding the measurement of acceptability of self-sampling. Regardless of the outcome variable, women were quite positive about self-sampling. The majority of women were willing to perform self-sampling, did not find it difficult or painful, and preferred self-sampling to physician sampling. In most studies that evaluated acceptability, women collected vaginal samples using a swab or brush. Two studies compared the acceptability of different collection methods. In an American study, more women were willing to use a tampon than a swab for annual screening (33,34). A Canadian study found that women preferred urine sampling to vulvar or vaginal sampling using a swab (47).

These positive results are tempered somewhat by the lack of rigour used for developing the instruments (e.g., questionnaires) used to measure acceptability and by the limited generalizability of findings from the studies. The lack of attention to instrument development is explained somewhat by the focus of the studies. Acceptability was the main outcome in only three studies, two of which reported on reliability. The remainder measured acceptability as an additional and usually less important aspect of the main study.

In all but one of the studies, generalizability is limited because participants actually performed the self-sampling, thereby demonstrating their willingness. Women who would find self-sampling highly unacceptable would not have participated in those studies. In addition,

participants in all but one study also had a gynecological exam for the purpose of acquiring a physician-collected sample; women who were unwilling to undergo that exam would not have voiced their opinions about the acceptability of self-sampling.

What appeals to women with respect to self-sampling?

Only one study directly examined what might appeal to women about self-sampling (38). Women were more comfortable and less embarrassed than with physician sampling but wanted assurance that self-collection of HPV samples would not prevent access to their physicians for other concerns.

A few studies examined what women did not like about self-sampling. The most striking finding was the women's concerns about their ability to perform the test properly and suggests that education about self-sampling would have to include increasing women's confidence in their ability to perform the test correctly. Experience indicates that other factors may contribute to lack of confidence, such as the lack of awareness of anatomy, limitations of current screening practices, and lack of understanding about the importance of screening and prevention.

What are the characteristics of women who are interested in performing self-sampling?

This area has not been well studied. There is a lack of consensus as to which women are interested in or willing to perform self-sampling. Two studies suggest that women who are better educated or are in a higher income bracket are more positive about self-sampling. Thus, one might speculate that these women would be more interested in performing self-sampling. However, neither of those studies directly assessed who was actually more interested or willing to perform self-sampling, because they only included women who were willing to do the test. A third study examined the willingness to perform self-sampling across four ethnic groups and found high willingness in all groups. More research is needed to understand what appeals to women with different characteristics. This kind of research would be particularly useful to help promote cervical screening.

Will women who are never or seldom screened by clinicians perform self-sampling?

Only one study targeted women who were never or seldom screened and study findings suggest that self-sampling directions might be hard to follow for some women with very limited education (40).

Is there sufficient evidence to recommend self-sampling for HPV testing as an alternative to collection of samples by clinicians?

At present, there is insufficient evidence to make definitive conclusions for or against self-sampling for HPV testing as an alternative to sampling by clinicians. While HPV testing using self-collected samples looks promising, there are substantial gaps in the evidence. Further research is needed to provide evidence that will allow a decision to be made about using self-sampling to increase screening rates, especially in women who are never or seldom screened.

CONFLICT OF INTEREST

Prior to embarking on guideline development, members of the panel disclosed information on potential conflict of interest. No conflicts were declared. There is a relationship between the guideline panel and the Ontario HPV Pilot Study, which is funded by the Ontario Women's Health Council. Two panel members are affiliated with the Ontario Women's Health Council, and six panel members are investigators or members of the steering committee for the pilot study. The pilot study's primary objectives are to determine: i) how reflex HPV testing [by clinicians] in patients with ASCUS influences colposcopy rates and compliance with colposcopy compared with usual screening care, ii) the information needs of practitioners and women related to the topic of HPV and its use as a reflex test following a Pap test abnormality (ASCUS)

and iii) the barriers and facilitators related to physician and patient acceptance of the new follow-up protocol. As a secondary objective, the pilot study is examining the acceptability of self-collection of samples for HPV testing. To this end, the study plan included a systematic review on self-collection and several focus groups with women across Ontario.

REFERENCES

1. Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for Cervical Screening Working Group. Br J Cancer. 1996 Apr;73(8):1001-5.

2. Colgan TJ, Clarke A, Hakh N, Seidenfeld A. Screening for cervical disease in mature women: strategies for improvement. Cancer. 2002 Aug 25;96(4):195-203.

3. Ontario Cervical Screening Program. Ontario Cervical Screening Program Report 1997-2000. Toronto (ON): Cancer Care Ontario; 2002.

4. Noorani HZ, Brown A, Skidmore B, Stuart GCE. Liquid-based cytology and human papillomavirus testing in cervical cancer screening. Ottawa: Canadian Coordinating Office for Health Technology Assessment; 2003. Technology Report No.: 40.

5. Stuart G, Taylor G, Bancej CM, Beaulac J, Colgan T, Franco EL, et al. Report of the 2003 pan-Canadian forum on cervical cancer prevention and control. J Obstet Gynaecol Can. 2004 Nov;26(11):1004-28.

6. Wright TC, Jr., Cox JT, Massad LS, Twiggs LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002 Apr 24;287(16):2120-9.

7. McLachlin CM, Mai V, Murphy J, Fung-Kee-Fung M, Chambers A. Clinical practice guidelines for cervical cancer screening in Ontario Ont Med Rev [serial on the Internet]. 2005 [cited 2005 Jul 6];72(6). Accessed from: http://www.oma.org/pcomm/omr/jun/05maintoc.htm.

8. Sarfati D, Cox B, Jones RW, Sopoaga T, Rimene C, Paul C. National audit of women with abnormal cervical smears in New Zealand. Aust N Z J Obstet Gynaecol. 2003 Apr;43(2):152-6.

9. Peterson NB, Han J, Freund KM. Inadequate follow-up for abnormal Pap smears in an urban population. J Natl Med Assoc. 2003 Sep;95(9):825-32.

10. Gage JC, Ferreccio C, Gonzales M, Arroyo R, Huivin M, Robles SC. Follow-up care of women with an abnormal cytology in a low-resource setting. Cancer Detect Prev. 2003;27:466-71.

11. Hartz LE, Fenaughty AM. Management choice and adherence to follow-up after colposcopy in women with cervical intraepithelial neoplasia 1. Obstet Gynecol. 2001 Oct;98(4):674-9.

12. McKee D. Improving the follow-up of patients with abnormal Papanicolaou smear results. Arch Fam Med. 1997 Nov-Dec; 6(6): 574-7.

13. McKee MD, Lurio J, Marantz P, Burton W, Mulvihill M. Barriers to follow-up of abnormal Papanicolaou smears in an urban community health center. Arch Fam Med. 1999 Mar-Apr;8(2):129-34.

14. Mann CH, Kehoe S, Brown A, Luesley DM. A study of the follow up patterns of women treated for CIN 2 and 3 before and after the introduction of the 1992 guidelines. Br J Obstet Gynaecol. 1999 Nov;106(11):1126-9.

15. Elwood JM, Cotton RE, Johnson J, Jones GM, Curnow J, Beaver MW. Are patients with abnormal cervical smears adequately managed? Br Med J (Clin Res Ed). 1984 Oct 6; 289(6449):891-4.

16. Palm BT, Kant AC, Visser EA, Vooijs GP, van den Bosch WJ, van Weel C. The effect of the family physician on improving follow-up after an abnormal PAP smear. Int J Qual Health Care. 1997 Aug; 9(4):277-82.

17. Del Mar CB, Wright RG. Notifying women of the results of their cervical smear tests by mail: does it result in a decreased loss to follow-up of abnormal smears? Aust J Public Health. 1995 Apr;19(2):115-7.

18. Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Ellis N, et al. Comparison of human papillomavirus DNA testing and repeat papanicolaou test in women with low-grade cervical cytologic abnormalities: a randomized trial. CMAJ. 2000;163(6):701-7.
19. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. JAMA. 2002;287:2382-90.
20. Cox JT. The clinician's view: role of human papillomavirus testing in the American society for colposcopy and cervical pathology guidelines for the management of abnormal cervical cytology and cervical cancer precursors. Arch Pathol Lab Med. 2003:127(8,):950–8.
21. Tabrizi SN, Paterson B, Fairley CK, Bowden FJ, Garland SM. A self-administered technique for the detection of sexually transmitted diseases in remote communities. J Infect Dis. 1997 Jul;176(1):289-92.
22. Tanksale VS, Sahasrabhojanee M, Patel V, Nevrekar P, Menezes S, Mabey D. The reliability of a structured examination protocol and self administered vaginal swabs: a pilot study of gynaecological outpatients in Goa, India. Sex Transm Infect. 2003 Jun;79(3):251-3.
23. Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, et al. A systematic review of the role of human papillomavirus (HPV) testing within a cervical screening programme: summary and conclusions. Br J Cancer. 2000 Sep;83(5):561-5.
24. Franceschi S. The IARC commitment to cancer prevention: the example of papillomavirus and cervical cancer. Recent Results Cancer Res. 2005;166:277-97.
25. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. BMJ. 2001 Jul 21;323(7305):157-62.
26. Kim SR, Song SY, Kim DS, Lee YW, Park CS, Bae DS, et al. Evaluation of self-collected pad sampling for the detection of HPV in cervicovaginal secretion. Korean J Path. 2004;38:258-64.
27. Dannecker C, Siebert U, Thaler CJ, Kiermeir D, Hepp H, Hillemanns P. Primary cervical cancer screening by self-sampling of human papillomavirus DNA in internal medicine outpatient clinics. Ann Oncol. 2004;15:863-9.
28. Kahn JA, Slap GB, Huang B, Rosenthal SL, Wanchick AM, Kollar LM, et al. Comparison of adolescent and young adult self-collected and clinician-collected samples for human papillomavirus. Obstet Gynecol. 2004;105:952-9.
29. Forrest S, McCaffery K, Waller J, Desai M, Szarewski A, Cadman L, et al. Attitudes to self-sampling for HPV among Indian, Pakistani, African-Caribbean and white British women in Manchester, UK.. J Med Screen. 2004;11:85-8.
30. Garcia F, Barker B, Santos C, Brown EM, Nuno T, Giuliano A, et al. Cross-sectional study of patient- and physician-collected cervical cytology and human papillomavirus. Obstet Gynecol. 2003;102:266-72.
31. Palmisano ME, Gaffga AM, Daigle J, Brinkman J, Mire K, Lenczyk K, et al. Detection of human papillomavirus DNA in self-administered vaginal swabs as compared to cervical swabs. Int J STD AIDS. 2003;14:560-7.
32. Harper DM, Longacre MR, Noll WW, Belloni DR, Cole BF. Factors affecting the detection rate of human papillomavirus. Ann Fam Med. 2003;1:221-7.
33. Harper DM, Noll WM, Belloni DR, Cole BF. Randomized clinical trial of PCR-determined human papillomavirus detection methods: self-sampling versus clinician-directed – biologic concordance and women's preferences. Am J Obstet Gynecol. 2002;186:365-73.
34. Harper DM, Raymond M, Noll WW, Belloni DR, Duncan LT, Cole BF. Tampon samplings with longer cervicovaginal cell exposures are equivalent to two consecutive swabs for the detection of high-risk human papillomavirus. Sex Transm Dis. 2002;29:628-36.
35. Flores Y, Bishai D, Lazcano E, Shah K, Lorincz A, Hernandez M, et al. Improving cervical cancer screening in Mexico: results from the Morelos HPV study. Salud Publica Mex. 2003;45:S388-98.

36. Salmeron J, Lazcano-Ponce E, Lorincz A, Hernandez M, Hernandez P, Leyva A, et al. Comparison of HPV-based assays with papanicolaou smears for cervical cancer screening in Morelos State, Mexico. Cancer Causes Control. 2003;14:505-12.

37. Flores Y, Shah K, Lazcano E, Hernandez M, Bishai D, Ferris DG, et al. Design and methods of the evaluation of an HPV-based cervical cancer screening strategy in Mexico: the Morelos HPV study. Salud Publica Mex. 2002;44:335-44.

38. Dzuba IG, Diaz EY, Allen B, Leondard YF, Lazcano-Ponce EC, Shah KV, et al. The acceptability of self-collected samples for HPV testing vs. the pap test as alternatives in cervical cancer screening. J Womens Health Gend Based Med. 2002;11:265-75.

39. Belinson JL, Qiao YL, Pretorius RG, Zhang WH, Rong SD, Huang MN, et al. Shanxi Province cervical cancer screening study II: self-sampling for high-risk human papillomavirus compared to direct sampling for human papillomavirus and liquid based cervical cytology. Int J Gynecol Cancer. 2003;13:819-26.

40. Tisci S, Shen YH, Fife D, Huang J, Goycoolea J, Ma CP, et al. Patient acceptance of self-sampling for human papillomavirus in rural China. J Low Genit Tract Dis. 2003;7:107-16.

41. Nobbenhuis MAE, Helmerhorst TJM, van den Brule AJC, Rozendaal L, Jaspars LH, Voorhorst FJ, et al. Primary screening for high risk HPV by home obtained cervicovaginal lavage is an alternative screening tool for unscreened women. J Clin Pathol. 2002;55:435-9.

42. Lorenzato FR, Singer A, Ho L, Santos LC, Batista Rde L, Lubambo TM, et al. Human papillomavirus detection for cervical cancer prevention with polymerase chain reaction in self-collected samples. Am J Obstet Gynecol. 2002;186:962-8.

43. Chang CC, Tseng CJ, Liu WW, Jain S, Horng SG, Soong YK, et al. Clinical evaluation of a new model of self-obtained method for the assessment of genital human papillomavirus infection in an underserved population. Chang Gung Med J. 2002;25:664-71.

44. Belinson J, Qiao YL, Pretorius R, Zhang WH, Elson P, Li L, et al. Shanzi Province cervical cancer screening study: a cross-sectional comparative trial of multiple techniques to detect cervical neoplasia. Gynecol Oncol. 2001;83:439-44.

45. Rompalo AM, Gaydos CA, Shah N, Tennant M, Crotchfelt KA, Madico G, et al. Evaluation of use of a single intravaginal swab to detect multiple sexually transmitted infections in active-duty military women. Clin Infect Dis. 2001;33:1455-61.

46. Gravitt PE, Lacey JV, Brinton LA, Barnes WA, Kornegay JR, Greenberg MD, et al. Evaluation of self-collected cervicovaginal cell samples for human papillomavirus testing by polymerase chain reaction. Cancer Epidemiol Biomarkers Prev. 2001;10:95-100.

47. Sellors JW, Lorincz AT, Mahony JB, Mielzynska I, Lytwyn A, Roth P, et al. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papillomavirus testing to detect high-grade squamous intraepithelial lesions. CMAJ. 2000;163:513-8.

48. Wright TC, Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. JAMA. 2000;283:81-6.

49. Hillemans P, Kimmig R, Huttemann U, Dannecker C, Thaler CJ. Screening for cervical neoplasia by self-assessment for human papillomavirus DNA. Lancet. 1999;354:1970.

50. Serwadda D, Wawer MJ, Shah KV, Sewankambo NK, Daniel R, Li C, et al. Use of a hybrid capture assay of self-collected vaginal swabs in rural Uganda for detection of human papillomavirus. J Infect Dis. 1999;180:1316-9.

51. Harper DM, Hildesheim A, Cobb JL, Greenberg M, Vaught J, Lorincz AT. Collection devices for human papillomavirus. J Fam Pract. 1999;48:531-5.

52. Coutlee F, Hankins C, Lapointe N; Canadian Women's HIV Study Group. Comparison between vaginal tampon and cervicovaginal lavage specimen collection for detection of human papillomavirus DNA by the polymerase chain reaction. J Med Virol. 1997;51:42-7.

53. Moscicki AB. Comparison between methods for human papillomavirus DNA testing: a model for self-testing in young women. J Infect Dis. 1993;167:723-5.
54. Forslund O, Hansson BG, Rymark P, Bjerre B. Human papillomavirus DNA in urine samples compared with that in simultaneously collected urethra and cervix samples. J Clin Microbiol. 1993;31:1975-9.
55. Morrison EAB, Goldberg GL, Hagan RJ, Kadish AS, Burk RD. Self-administered home cervicovaginal lavage: a novel tool for the clinical-epidemiologic investigation of genital human papillomavirus infections. Am J Obstet Gynecol. 1992;167:104-7.
56. Fairley CK, Chen S, Tabrizi SN, Quinn MA, McNeil JJ, Garland SM. Tampons: a novel patient-administered method for the assessment of genital human papillomavirus infection. J Infect Dis. 1992;165:1103-6.
57. Elwood JM. Critical appraisal of epidemiologic studies and clinical trials. New York: Oxford University Press; 1998.
58. Cancer Research UK. HPV testing by self-sampling: assessment of methodology and acceptability. [cited 2004 Dec 19]. Available from: http://sci.cancerresearchuk.org/studies/mse/hart/self_samp/samp_index.html.

Self-collected Samples for Testing of Oncogenic Human Papillomavirus:
Guideline Development and External Review: Methods and Results

*Stewart DE, Johnston M, Gagliardi A, Howlett R, Barata P, Lewis N, Oliver T, and Mai V,
on behalf of the HPV Self-collection Guidelines Panel*

A Special Project of the Screening Guidelines Steering Committee,
Cancer Care Ontario and The Program in Evidence-based Care, Cancer Care Ontario.

Report Date: April 6, 2006

THE PROGRAM IN EVIDENCE-BASED CARE
The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines
Historically all the components and methodologies of the practice guidelines were packaged into one report. However, in response to feedback from Ontario clinicians and members of the PEBC panels, the end product has been restructured to better meet the information needs and preferences of that core audience. The high- quality methods and the credible developers are now part of the Evidence-based Series.

Each Evidence-based Series is comprised of the following three sections:

- *Section 1: Clinical Practice Guideline*. This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.
- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES
Development and Internal Review
This evidence-based series was developed by the HPV Self-collection Guidelines Panel of Cancer Care Ontario's Program in Evidence-based Care (PEBC). The series is a convenient and up-to-date source of the best available evidence on self-collected samples for testing of oncogenic human papillomavirus (HPV), developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

IMPLICATIONS FOR POLICY
Self-sampling for HPV testing appears to hold promise as an alternative to collection of samples by clinicians, and may help expand the reach of cervical screening programs to unscreened or underscreened women. However, more research is needed before this technology can be recommended in the Ontario setting. In particular, this guideline has highlighted the need for good quality studies to clarify:
- The accuracy of self-collection for HPV testing in a cohort of women undergoing primary screening
- The impact of self-screening on disease detection, prevention, and survival
- The relative strengths and weaknesses of the various methods of collecting self-samples
- The adverse effects of false-positive and false-negative test results
- The characteristics of women who are interested in performing self-testing
- The characteristics of self-screening that women find appealing or concerning
- The impact of self-sampling on screening participation rates for unscreened and underscreened women
- The acceptability of self-sampling for women who are never or seldom screened by clinicians?

Currently no HPV self-sampling technologies are licensed for use in Canada. Should one or more become available, a number of policy issues would arise, such as how the technologies would be dispensed to women, how they would be paid for, how samples would get to labs to be tested, how women would be informed of their results, and how they would be followed up if necessary.

For example, women could obtain the kits directly from community health centres, public health units, or pharmacies, either bearing the cost of obtaining the kits themselves, or possibly being covered by provincial or private drug plans, though this might require the kits to be a prescription product. Alternatively, health care providers could give women kits directly. The women could utilize the kits at their provider's office, allowing them to get assistance with its use if required, or take the kit home. Samples could be dropped off either at the doctor's office or the lab directly, or by mailing it to the lab. One advantage of this method of provision is that women will still have access to a regular health exam, including a pelvic exam to rule out other

gynecological problems, as is recommended in current patient education materials in Ontario. This method of provision would also maximize an existing physician-patient relationship, a factor that has been identified in studies of reflex HPV testing as an important consideration to positively influence women to be screened and to seek treatment for abnormal test results (3,4). On the negative side, hard-to-reach women and women without access to a health care provider would not be reached by this mode of distribution.

The advantage of this mode of provision is that women can obtain the test directly. Disadvantages include potential cost barriers and the current lack of public and provider awareness of the role of HPV in cervical cancer. A sustained public education campaign would be required to explain to women and their providers about the significance of HPV and the implications of a positive test result. This is of particular importance given that studies have documented significant anxiety levels among women who have been informed of positive results (5-11).

Mechanisms would need to be in place to ensure that labs could receive samples from women directly and receive payment for analyzing them; that women were informed of their results in an informative but also confidential way; and that adequate follow-up is available for women with positive HPV results.

Other essential system issues relate to appropriate guidelines for frequency and intervals for testing. Current opportunistic and organized screening guidelines recommend recall and follow-up to remind women and clinicians when a woman is overdue for screening or when no treatment has been received after abnormal test results. The availability of self-sampling, without a supportive infrastructure to include these essential components, would not likely improve screening participation. Without such an infrastructure, women may not remember to collect the required specimens, either initially or for repeat testing at the recommended frequencies.

This is a more complex issue for women who live in more remote areas of the province with limited access to Pap testing services. One of the key principles of screening is access to follow-up assessment services for individuals who screen positive. A geographic area lacking screening services, may have limited access to other medical services required for follow-up. Thus, if and when the self-test becomes available, access to other related services must be insured.

EXTERNAL REVIEW OF THE EVIDENCE SUMMARY REPORT
Developing the Draft Systematic Review and Clinical Practice Guideline
This evidence-based series was developed by the HPV Self-collection Guidelines Panel of Cancer Care Ontario's PEBC. The series is a convenient and up-to-date source of the best available evidence developed through systematic review, evidence synthesis, and input from practitioners in Ontario. The systematic review on the role of self-sampling for human papillomavirus (HPV) testing is in section 2. On the basis of that evidence and the interpretation by members of the HPV Self-collection Guidelines Panel, draft recommendations were circulated to Ontario practitioners on June 25, 2004 for feedback (Table 1).

Table 1. Draft recommendations circulated for external review.

Target Population
The target population for this guideline is hard-to-reach women in Ontario.
Recommendations
There is insufficient evidence to recommend for or against self-sampling for HPV testing as an alternative to sampling by clinicians. Further research is needed to provide evidence that will allow a decision to be made about using self-sampling to increase screening rates, especially in hard-to-reach women (for example, those who have not had a Pap test for three years or longer).

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians.

Methods
Practitioner feedback was obtained through a mailed survey of 178 practitioners in Ontario. The survey consisted of items evaluating the methods, results, and interpretive summary. Written comments were invited. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The HPV Self-collection Guidelines Panel reviewed the results of the survey.

Results
Fifty-two responses were received out of the 178 surveys sent (29.2% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 31 indicated that the report was relevant to their clinical practice and completed the survey. Results of the practitioner feedback survey are summarized in Table 2.

Table 2. Results of the practitioner feedback survey.

Item	Number (%)			
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**	**No answer**
The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	28 (90.3%)	2 (6.5%)	1 (3.2%)	0 (0%)
There is a need for a clinical practice guideline on this topic.	22 (71.0%)	7 (22.6%)	2 (6.5%)	0 (0%)
The literature search is relevant and complete	25 (80.6%)	5 (16.1%)	1 (3.2%)	0 (0%)
The results of the trials described in the report are interpreted according to my understanding of the data.	30 (96.8%)	1 (3.2%)	0 (0%)	0 (0%)
The draft recommendations in this report are clear.	26 (86.7%)	3 (10.0%)	1 (3.2%)	1 (3.2%)
I agree with the draft recommendations as stated.	26 (86.7%)	3 (10.0%)	2 (6.5%)	0 (0%)

Summary of Written Comments
Nineteen of the 31 practitioners (62.3%) provided written comments. Common themes were taken from the comments, and were addressed by the HPV Self-collection Guidelines Panel.

- It was generally agreed that the recommendation flowed from the evidence, more research was needed, and that there were insufficient evidence to inform routine self-screening at this point in time.
- A common theme was the unavailability of the self-test kits (outside of out-of-pocket expense) in Ontario, and the question of the cost involved in self-testing/follow-up versus the cost of current practice was raised.
- A major theme was the differences in practitioner ideology of the utility of HPV self-testing as an alternative to clinician-collected samples. Concerns about self-testing included:
  - Self-testing could be counterproductive with efforts to have women participate in cervical screening programs,
  - Clinicians are best qualified to collect samples,
  - There may be difficulty ensuring the follow-up of women with positive results,

- There is the concern of false-negative self-test results,
- Since most HPVs are transient and clear themselves, it was questioned how the system would handle the volume of positive self-test results,
- If hard to reach women do not avail themselves of Pap tests, they may just as well choose to not participate in self-testing.
  Alternatively there were comments that self-testing seems to be a valid screening tool and the underlying assumption that women want close assessment and follow-up by a trained clinician may not be a valid assumption. It could be that women may actually prefer self-testing options, or that self-testing may provide a valid screening alternative for hard to reach women or those without a family doctor.
- One practitioner expressed concern on how instruction pamphlets would be written, presented, and disseminated so as to be understood by groups of high-risk women who may be illiterate or who do not understand English.
- One practitioner commented that the greatest benefit from HPV self-testing would likely be for women greater than 35 years of age who have persistent low grade smear abnormalities.
- One practitioner kindly pointed out a relevant publication (12):
  - Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric W, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. Sex Transm Infect. 2005;81:207-12.
- One practitioner requested clarification over the meaning of "Diagnostic accuracy of self sampling" on page 1, questioning whether it is really the accuracy of self-sampling compared to physician-sampling in permitting the detection of HPV in the laboratory, and on page 2, "the quality of cytology in patients samples" was confusing to the practitioner because it refers to the quality of the sample to permit HPV testing not the quality of the sample to allow morphological assessment of cells as to Pap.

Modifications/Actions
- Overall, the majority of the comments did not require revisions to the evidence-series, nor did any of the comments impact the conclusions or final recommendation.
- Regarding the comment of the benefits of HPV testing for women past 35 years of age, this aspect was addressed in the introduction of the systematic review with reference to the Ontario Cervical Screening Guidelines that recommends HPV testing for women over the age of 29 with ASCUS.
- In regard to the identified report that was published after the literature search time point, the publication was retrieved and reviewed. The meta-analysis was based upon the same evidence used in the evidence series and conclusions were consistent with the present report.
- In one case where some wording was confusing, minor revisions were made to improve clarity.

Report Approval Panel
The evidence series was circulated to three reviewers, the two members of the Report Approval Panel and the Guidelines Coordinator of the PEBC. Feedback provided by the Panel and the Coordinator is summarized below. The feedback was reviewed by the HPV Self-collection Guidelines Panel, and modifications were made to the series in response (see modifications below).

Summary of Written Comments

All three reviewers agreed that the report was well written and was a topic of interest and relevance.

- It was commented that there was a disconnect between the question that asks what is the role of self-sampling, with hard-to-reach women being a subset of that inquiry, and the actual target population, which limits the discussion to hard-to-reach women only. A clarification of the target audience and an expanded definition of hard-to-reach women were requested. On a related note, from the background provided, it appears that testing for HPV is a secondary test that is to be utilized in women with an abnormal PAP smear. It was not clear whether the intended use for self testing was for this same population and whether the studies evaluated were limited to this population. As many of the reasons for being "hard to reach" could also apply to primary Pap testing, it would help if the panel would clarify whether prior Pap testing is expected of patients who would self collect, and whether it formed an inclusion criterion for the patients in the studies they evaluated.

- The panel has appropriately indicated that the outcomes of screening should include important "policy-driving" outcome measures such as the magnitude of disease prevention or survival. Presumably, there are data that support "provider-performed" HPV screening with respect to these outcome measures, and these data resulted in the cited consensus statements.

    It would be helpful if the panel would expand on the discussion related to the need to show that self-collection, if feasible and as accurate as "provider-performed" testing, improves these "policy-driving" outcome measures. From the document, it is implied that RCTs evaluating self collection with respect to these outcome measures are required before recommendations can be offered. Is this really so, if so why, and is it likely that such RCTs will be performed? An alternate view that screening for HPV is beneficial, and that "technical details" of the nature of the screening process need to satisfy more technical endpoints, rather than major outcome endpoints, could be suggested. While it is not being suggested that this is in fact the case for self collected HPV testing, further discussion by the panel to explain their position would be helpful.

- The panel has provided many details about the nature of individual reports. However, they have not included discussion about study quality, nor does there appear to be weighting by study quality in their conclusions. As the range in sample size shows great variation (17-8,497), it would be expected that considerable range in quality might exist.

- Two reviewers commented that the response rate for practitioner feedback was lower than one would expect. Further information on the types of practitioners and patterns of response was requested.

Modifications/Actions

- The question was revised to reflect that the role of HPV self-sampling as an alternative to cervical cancer screening by clinicians was the primary question of interest. The target population was also revised to reflect that the guideline applied to all women in Ontario for whom screening is recommended, but with an emphasis on those never or seldom screened by clinicians. The rationale was that Pap testing performed by clinicians reduces the mortality from cervical cancer and is the current standard practice in Ontario; however the self-collection of HPV samples may offer an acceptable alternative especially for those women who are never or seldom screened.

- The discussion on future research was expanded to indicate that, while research in the randomized setting on policy-setting outcomes for HPV self-collection would be preferable, well-conducted studies evaluating intermediate outcomes such as the method of collection, women's preferences, participation rates, referral rates, detection of abnormalities, and

cancer detection rates would be sufficient to inform a policy regarding the use of HPV self-sampling as an alternative to cervical cancer screening by clinicians.

- While a formal quality assessment was not performed, since the sample size ranged from 17 to nearly 8,500 participants and the methodological quality varied considerably among the studies, the larger studies, and those with stronger methodological quality were accorded greater consideration in the interpretation of the data, discussions, and derived conclusions. A statement to that effect was added to the results section.

- Similar to a previous guideline on cervical screening, practitioner feedback was obtained through a mailed survey of 178 physicians (127 family practitioners and pathologists [from supplied lists] and 51 practitioners from the PEBC database [30 medical oncologists, one radiation oncologist, 11 surgeons, and nine gynecologists]) across the province. Since the response rate from the cervical screening guideline was 27%, a big difference in response for the present guideline was not anticipated. It was felt that the value of disseminating the guideline to a larger group of practitioners (primarily family practitioners) outweighed the utility of targeting only those who responded to the previous cervical screening practitioner feedback survey. The pattern of practitioner responses was not tracked *a priori* as it was not a focus of the report.

Conclusion

This report reflects the integration of feedback obtained through the external review process with final approval given by the Gynecology Cancer DSG, the Report Approval Panel of the Program in Evidence-based Care, and the Ontario Screening Guidelines Steering Committee. Updates of the report will be conducted as new evidence informing the question of interest emerges.

For further information about this series, please contact:
Verna Mai; Chair, Screening Guidelines Steering Committee; Cancer Care Ontario,
620 University Ave, Toronto ON, M5G2L7;
Telephone: 416.971.5100 x2252

For information about the PEBC and the most current version of all reports,
please visit the CCO Web site at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055   Fax: 905-522-7681

REFERENCES

1. Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol. 1995;13:502-12.
2. Browman GP, Newman TE, Mohide EA, Graham ID, Levine MN, Pritchard KI, et al. Progress of clinical oncology guidelines development using the practice guidelines development cycle: the role of practitioner feedback. J Clin Oncol. 1998;16(3):1226-31.
3. Chingang LC, Bischof U, Andall-Breretion G, Razum O. 'Have a Pap smear!' – doctors, their clients and opportunistic cervical cancer screening. Int J STD AIDS. 2005 Mar;16(3):233-6.
4. McCaffery K, Irwig L. Australian women's needs and preferences for information about human papillomavirus in cervical screening. J Med Screening. 2005;12(3):134-41.
5. Anhang R, Wright TC Jr, Smock L, Goldie SJ. Women's desired information about human papillomavirus. Cancer. 2004;100(2), 315-20.
6. Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A. Psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: Cross sectional questionnaire study. Br Med J, 2004;328(7451); 1293.
7. Maissi E, Marteau TM, Hankins M, Moss S, Legood R, Gray A. The psychological impact of human papillomavirus testing in women with borderline or mildly dyskaryotic cervical smear test results: six-month follow-up. Br J Cancer. 2005;92(6):990-4.
8. McCaffery K, Forrest S, WallerJ, Szarewski A, Wardle J. Attitudes towards HPV testing: A qualitative study of beliefs among Indian, Pakistani, African-Caribbean and white British women in the UK. Br J Cancer..2003;88:42-6.
9. McCaffery K, Irwig L. Australian womens' needs and preferences for information about human papillomavirus in cervical screening. J Med Screen. 2005;12(3):134-41.
10. McCaffery K, Waller J, Forrest S, Cadman L, Szarewski A, Wardle J. Testing positive for human papillomavirus in routine cervical screening: Examination of psychosocial impact. BJOG. 2004;111(12):1437-43.
11. Waller J, McCaffery K, Nazroo J, Wardle J. Making sense of information about HPV in cervical screening: A qualitative study. Br J Cancer. 2005;92(2):265-70.
12. Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric W, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. Sex Transm Infect. 2005;81:207-12.

Review outcomes definitions.

1. **ARCHIVED** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase "ARCHIVED".

2. **ENDORSED** – An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. **DEFERRAL** – A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.