Cohort Study
Potential PURL Review Form
PURL Jam Version

PURLs Surveillance System
Family Physicians Inquiries Network

SECTION 1: Identifying Information for Nominated Potential PURL
[to be completed by PURLs Project Manager]

A. Citiation: 1: Arbyn M, Smith SB, Temin S, Sultana F, Castle P; Collaboration on Self-Sampling and HPV Testing. Detecting cervical precancer and reaching underscreened women by using HPV testing on self samples: updated meta-analyses. BMJ. 2018 Dec 5;363:k4823. doi: 10.1136/bmj.k4823. PubMed PMID: 30518635; PubMed Central PMCID: PMC6278587.
B. Link to PubMed Abstract: https://www.ncbi.nlm.nih.gov/pubmed/?term=30518635
C. First date published study available to readers: Dec 5, 2018
D. PubMed ID: 30518635
E. Nominated By: Steven Wilson
F. Institutional Affiliation of Nominator: UPMC
G. Date Nominated: 12/6/2018
H. Identified Through: BMJ
I. PURLs Editor Reviewing Nominated Potential PURL: Dean Seehusen
J. Nomination Decision Date: 12/26/18
K. Potential PURL Review Form (PPRF) Type: Cohort Study
L. Assigned Potential PURL Reviewer: Corey Lyon
M. Reviewer Affiliation: University of Colorado
A. Abstract: OBJECTIVE:
To evaluate the diagnostic accuracy of high-risk human papillomavirus (hrHPV) assays on self samples and the efficacy of self sampling strategies to reach underscreened women.

DESIGN:
Updated meta-analysis.

DATA SOURCES:
Medline (PubMed), Embase, and CENTRAL from 1 January 2013 to 15 April 2018 (accuracy review), and 1 January 2014 to 15 April 2018 (participation review).

REVIEW METHODS:
Accuracy review: hrHPV assay on a vaginal self sample and a clinician sample; and verification of the presence of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) by colposcopy and biopsy in all enrolled women or in women with positive tests. Participation review: study population included women who were irregularly or never screened; women in the self sampling arm (intervention arm) were invited to collect a self sample for hrHPV testing; women in the control arm were invited or reminded to undergo a screening test on a clinician sample; participation in both arms was documented; and a population minimum of 400 women.

RESULTS:
56 accuracy studies and 25 participation trials were included. hrHPV assays based on

polymerase chain reaction were as sensitive on self samples as on clinician samples to detect CIN2+ or CIN3+ (pooled ratio 0.99, 95% confidence interval 0.97 to 1.02). However, hrHPV assays based on signal amplification were less sensitive on self samples (pooled ratio 0.85, 95% confidence interval 0.80 to 0.89). The specificity to exclude CIN2+ was 2% or 4% lower on self samples than on clinician samples, for hrHPV assays based on polymerase chain reaction or signal amplification, respectively. Mailing self sample kits to the woman's home address generated higher response rates to have a sample taken by a clinician than invitation or reminder letters (pooled relative participation in intention-to-treat-analysis of 2.33, 95% confidence interval 1.86 to 2.91). Opt-in strategies where women had to request a self sampling kit were generally not more effective than invitation letters (relative participation of 1.22, 95% confidence interval 0.93 to 1.61). Direct offer of self sampling devices to women in communities that were underscreened generated high participation rates (>75%). Substantial interstudy heterogeneity was noted (I2>95%).

CONCLUSIONS:
When used with hrHPV assays based on polymerase chain reaction, testing on self samples was similarly accurate as on clinician samples. Offering self sampling kits generally is more effective in reaching underscreened women than sending invitations. However, since response rates are highly variable among settings, pilots should be set up before regional or national roll out of self sampling strategies.

B. Pending PURL Review Date**:** 6/20/2019

SECTION 2: Critical Appraisal of Validity
[to be completed by the Potential PURL Reviewer]

A. The study address an appropriate and clearly focused question. Well covered
Comments:

B. The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation. Well covered
Comments:

C. The study indicates how many of the people asked to take part in it in each of the groups being studied. Not applicable
Comments: This was a SR of cohort and RCTs

D. The likelihood that some eligible subjects might have the outcome at the time of enrollment is assessed and taken into account in the analysis. Not reported
Comments:

E. What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?

F. Comparison is made between full participants and those lost to follow up, by exposure status.
Not reported
Comments: SR

G. The outcomes are clearly defined. Well covered
Comments:

H. The assessment of outcome is made blind to exposure status. Not applicable
Comments:

I. Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome. Not applicable
Comments:

J. What are the key findings of the study?
In this updated SR/MA; 56 diagnostic test were reviewed; 25 RCT were reviewed

Pooled sensitivity/specificity of hrHPV of HPV self swab vs clinic collect on dx of CIN2/3

- Signal amplification
  - CIN2+ 23 studies; sens- 0.85 (0.80 to 0.89)* ; spec - 0.96 (0.93 to 0.98)*
  - CIN3+ 9 studies; sens- 0.86 (0.76 to 0.98)* ; spec - 0.97 (0.95 to 0.99)*
- PCR
  - CIN2+ 17 studies; sens- 0.99 (0.97 to 1.02) ; spec - 0.98 (0.97 to 0.99)*
  - CIN3+ 8 studies; sens- 0.99 (0.96 to 1.02) ; spec - 0.98 (0.97 to 0.99)*
  -

Efficacy of invitation scenarios – intention to treat analysis

- Mail to all; 21 studies;
  - Absolute participation (%) Self sampling; 24.8 (21.6 to 28.1);
  - Control % 11.5 (8.3 to 15.1);
  - participation difference (%) 12.8 (10.4 to 15.1);
  - RR 2.33 (1.86 to 2.91)
- Opt-in; 8 studies
  - Absolute participation (%) Self sampling; 7.7 (12.3 to 23.9);
  - Control % 13.4 (10.2 to 16.9);
  - participation difference (%) 3.3 (−0.7 to 7.3);
  - RR 1.22 (0.93 to 1.61)
- Community campaign; 1 studies;
  - Absolute participation (%) Self sampling; 15.6 (12.4 to 19.5)
  - Control % 6.0 (4.2 to 8.7);
  - participation difference (%) 9.5 (5.4 to 13.7);
  - RR 2.58 (1.67 to 3.99)
- Door-to-door; 4 studies;
  - Absolute participation (%) Self sampling; 94.6 (83.0 to 99.9);
  - Control % 53.3 (10.5 to 93.2);
  - participation difference (%) 40.5 (3.0 to 78.0);
  - RR 2.01 (0.66 to 6.15)

K. How was the study funded? Any conflicts of interest? Any reason to believe that the results may be influenced by other interests? Funded through a CDC grant

SECTION 3: Review of Secondary Literature
[to be completed by the Potential PURL Reviewer]
[to be revised by the Pending PURL Reviewer as needed]

Citation Instructions: For up-to-date citations, use style modified from http://www.uptodate.com/home/help/faq/using_UTD/index.html#cite & AMA style. Always use Basow DS on editor & current year as publication year.

Example: Auth I. Title of article. {insert author name if given, & search terms or title.} In: Basow DS, ed. UpToDate [database online]. Waltham, Mass: UpToDate; 2009. Available at: http://www.uptodate.com. {Insert date modified if given.} Accesses February 12, 2009. [whatever date PPRF reviewer did their search.}

For DynaMed, use the following style:
Depression: treatment {insert search terms or title}. In: DynaMed [database online]. Available at http://www.DynamicMedical.com. Last updated February 4, 2009. {Insert date modified if given.} Accessed June 5, 2009. {search date}

A. DynaMed excerpts

HPV DNA testing has higher sensitivity than cervical cytology for high-grade cervical dysplasia (level 1 [likely reliable] evidence), with sensitivity ranging from 87.5% to 100% in numerous studies

negative HPV DNA testing may predict very low (0.27%) risk of CIN 3+ over 6 years (level 2 [mid-level] evidence)or general population screening

a. HPV DNA-based testing may reduce invasive cervical cancer compared to cytology in women aged 25-60 years (level 2 [mid-level] evidence)
b. single round of HPV testing reduces mortality from cervical cancer compared to no screening in women aged 30-59 years (level 1 [likely reliable] evidence)
c. addition of HPV DNA testing to cytologic screening may detect cervical intraepithelial neoplasia (CIN) earlier and decrease rate of subsequent CIN 2 or greater (level 2 [mid-level] evidence)
d. addition of HPV DNA testing to liquid-based cytology screening may have limited effect on decreasing rate of subsequent CIN 3 or greater (level 2 [mid-level] evidence)

B. DynaMed citation/ Title. Author. In: DynaMed [database online]. Available at: access date www.DynamicMedical.com Last Updated:Accessed

C. Bottom line recommendation or summary of evidence from DynaMed (1-2 sentences)

D. UpToDate excerpts

HPV testing — There are several types of HPV tests available, including tests that specifically identify types 16 and 18, pool results for all high-risk types, and are for primary screening rather than for co-testing. Separate tests provide genotyping of types 16 and 18 (or a combined type 18/45 result) and can be performed as follow-up (or reflex) testing for specimens with a positive high-risk pooled result but are not used for initial screening [8,9].

Cervical testing — Specimens for HPV testing can be collected from the endocervix using a cervical spatula or cervical brush, which is then placed in HPV test transport medium [10]. With some liquid-based cytology sampling systems, the same specimen can be used for HPV testing and cytology.

In resource-limited settings, self-collection of an HPV sample by the patient is being used. Women can collect samples from the vagina using a tampon, Dacron or cotton swab, cytobrush, or cervicovaginal lavage. (See "Screening for cervical cancer in resource-limited settings", section on 'Self-collected samples'.)

Self-collected samples — For women who do not have access to a speculum examination or who are reluctant to undergo a pelvic examination, self-collected vaginal samples can be used for HPV testing [38]. Women can collect samples from the vagina using a tampon, Dacron or cotton swab, cytobrush, or cervicovaginal lavage. Self-collection can be performed under supervision at a clinic or at home. If a woman collects a sample at home, it is then placed in a collection tube with a transport medium and brought back to the clinic for processing.

Self-collected samples appear to be acceptable to women and as effective at detecting high-grade CIN as clinic screening methods.

HPV test self-collection was compared with clinician collection in a Dutch randomized trial that included 16,410 women aged 29 to 61 years.

Self-collected HPV testing (with a cervical brush) was compared with cervical cytology performed at a clinic in a randomized trial of 12,330 women in Mexico [39]. The acceptability of self-collected HPV testing was high; 98 percent of women in the HPV testing group agreed to collect the sample and performed the testing, while 89 percent of those scheduled for a Pap test had the test performed. HPV testing had a higher sensitivity for detection of CIN2+ (relative sensitivity 2.9, 95% CI 2.0-4.1) and for invasive cancer (3.6, 95% CI 1.6-7.9). The disadvantage of HPV testing was that more women underwent colposcopy and ultimately had negative findings: 28 percent in the HPV testing group compared with none in the cytology group. For CIN2+, the positive predictive value of HPV testing was 12.2 percent compared with 90.5 percent for cytology.

Self-collected samples were compared with clinician-collected samples in a meta-analysis of 18 studies with 5441 women in which women collected vaginal samples for HPV testing [40].

The analysis found a high concordance (0.87) between results of self- and clinician-collected samples. Studies that evaluated acceptability reported that women preferred self-collection versus clinician sampling. A limitation of this analysis was that many of the included studies were conducted among a referral population of women with known or suspected cervical disease; therefore, a high HPV prevalence may impact the results.

Further study is needed to determine the best method of self-collection (eg, swab, cervical brush, tampon). This question was addressed in an earlier meta-analysis, which included 12 of the same studies as the analysis described above and used clinician-collected HPV samples as a reference standard [41]. For seven studies that used a Dacron or cotton swab or a cytobrush, the pooled sensitivity and specificity for HPV detection was 78 and 90 percent. For three studies in which a tampon was used, the results are reported as a range of sensitivities (67 to 94 percent) and specificities (80 to 100 percent). These data do not allow comparison among the methods.

Given these data, self-collection appears to be a useful method for HPV testing in women who do not have access to a speculum examination.

E. UpToDate citation/ Always use Basow DS as editor & current year as publication year. Access date Title. Author. In: UpToDate [database online]. Available at: http://www.uptodate.com. Last updated: Accessed

F. Bottom line recommendation or summary of evidence from UpToDate (1-2 sentences)

G. Other excerpts (USPSTF; other guidelines; etc.)
ACOG practice bulletin

In women 25 years and older, the FDA-approved primary HPV screening test can be considered as an alternative to current cytology-based cervical cancer screening methods. Cytology alone and cotesting remain the options specifically recommended in current major society guidelines. If screening with primary HPV testing is used, it should be performed as per the ASCCP and SGO interim guidance.

H. Citations for other excerpts

I. Bottom line recommendation or summary of evidence from Other Sources (1-2 sentences)

SECTION 4: Conclusions
[to be completed by the Potential PURL Reviewer]

[to be revised by the Pending PURL Reviewer as needed]

A. **Validity**: Are the findings scientifically valid? Yes

B. If **A** was coded "Other, explain or No", please describe the potential bias and how it could affect the study results. Specifically, what is the likely direction in which potential sources of internal bias might affect the results?

C. **Relevance**: Is the topic relevant to the practice of family medicine and primary care practice, including outpatient, inpatient, obstetrics, emergency and long-term care? Are the patients being studied sufficiently similar to patients cared for in family medicine and primary care in the US such that results can be generalized?
Yes

D. If **C** was coded "Other, explain or No", please provide an explanation.

E. **Practice changing potential**: If the findings of the study are both valid and relevant, are they not a currently widely accepted recommendation among family physicians and primary care clinicians for whom the recommendation is relevant to their patient care? Or are the findings likely to be a meaningful variation regarding awareness and acceptance of the recommendation?
Yes

F. If **E** was coded as "Yes", please describe the potential new practice recommendation. Please be specific about what should be done, the target patient population and the expected benefit.

G. **Applicability to a Family Medical Care Setting**:
Is the change in practice recommendation something that could be done in a medical care setting by a family physician (office, hospital, nursing home, etc.), such as a prescribing a medication, vitamin or herbal remedy; performing or ordering a diagnostic test; performing or referring for a procedure; advising, education or counseling a patient; or creating a system for implementing an intervention? Yes

H. Please explain your answer to **G**.

I. **Immediacy of Implementation**:
Are there major barriers to immediate implementation? Would the cost or the potential for reimbursement prohibit implementation in most family medicine practices? Are there regulatory issues that prohibit implementation? Is the service, device, drug, or other essentials available on the market? Other, explain

J. If **I** was coded "Other, explain or No", please explain why.

Availability of PCR hrHPV self swab kits would be needed

K. **Clinically meaningful outcomes or patient oriented outcomes**:
Do the expected benefits outweigh the expected harms? Are the outcomes patient oriented (as opposed to disease oriented)? Are the measured outcomes, if true, clinically meaningful from a patient perspective?
Yes

L. If **K** was coded “Other, explain or No”, please explain why.

M. In your opinion, is this a pending PURL? Yes

1. Valid: Strong internal scientific validity; the findings appear to be true.

2. Relevant: Relevant to the practice of family medicine.

3. Practice Changing: There is a specific identifiable new practice recommendation that is applicable to what family physicians do in medical care settings and seems different than current practice.

4. Applicability in medical setting.

5. Immediacy of implementation

N. Comments on your response for question M.