Enduring Guidelines HPV Self-Collection Summary for Public Comments

Introduction
Cervical cancer is highly preventable by HPV vaccination and screening for cervical precancers. Consequently, cervical cancer is more common among those who are unscreened and underscreened. HPV self-collection provides an opportunity to expand access to screening to those who are currently unscreened or underscreened. HPV self-collection is defined as collection of a swab from the vagina without the use of a speculum by the individual who is undergoing screening. Alternatively, a vaginal collection can also be conducted by a provider, without the need for a speculum exam (e.g., for patients who cannot tolerate a speculum exam but also are not able to collect their own samples).

The FDA recently expanded the indications for use for the Roche Cobas and BD Onclarity HPV tests to "allow for the patient to self-collect a vaginal swab in a health care setting when the patient and the health care provider determine that it is not possible for the clinician to collect a cervical specimen." Following this approval, the Enduring Guidelines committee has developed draft guidelines for use of self-collection in clinical practice. As with prior guidelines, recommendations are consistent with but may expand on FDA language. The background, rationale, and specific recommendations are summarized below.

Advantages and limitations of HPV self-collection
Self-collection vaginal HPV testing for cervical cancer screening has the advantages of not requiring a speculum exam and thus overcoming barriers to screening including limited access, lack of available providers, discomfort with speculum exams, gender dysphoria, history of trauma, mobility issues, etc. The primary disadvantage of self-collection compared to provider-collected cervical sampling is that provider-collected samples that test HPV positive can be sent for reflex cytology or dual stain to determine the need for colposcopy. In contrast, most patients (68-89%) who test positive on HPV self-collection need to return for a speculum exam for collection of dual stain or cytology to determine the need for colposcopy.
Evidence summary

Clinical performance of HPV self-collection
HPV self-collection has been widely evaluated in studies in the US and around the world and compared to provider collection in the same screening participants. These studies have been summarized in large systematic reviews and meta-analyses. Overall, HPV testing from self-collected specimens has shown high agreement with HPV testing from provider-collected specimens when HPV PCR assays have been used (Table 1).

Table 1: Summary of relative sensitivity and specificity for self-collected versus provider collected HPV testing (adapted from Arbyn BMJ 2018)

<table>
<thead>
<tr>
<th>Assay</th>
<th>Outcome</th>
<th>No of studies</th>
<th>Ratio (95% CI) Sensitivity</th>
<th>Ratio (95% CI) Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signal Amplification (SA)</td>
<td>CIN2+</td>
<td>23</td>
<td>0.85 (0.80 to 0.89)*</td>
<td>0.96 (0.93 to 0.98)*</td>
</tr>
<tr>
<td></td>
<td>CIN3+</td>
<td>9</td>
<td>0.86 (0.76 to 0.98)*</td>
<td>0.97 (0.95 to 0.99)*</td>
</tr>
<tr>
<td>PCR</td>
<td>CIN2+</td>
<td>17</td>
<td>0.99 (0.97 to 1.02)</td>
<td>0.98 (0.97 to 0.99)*</td>
</tr>
<tr>
<td></td>
<td>CIN3+</td>
<td>8</td>
<td>0.99 (0.96 to 1.02)</td>
<td>0.98 (0.97 to 0.99)*</td>
</tr>
</tbody>
</table>

There was some heterogeneity across studies, with many showing equal sensitivity between self-collection and provider-collection and few suggesting slightly lower sensitivity of self-collection compared to provider-collection. A critical question related to the sensitivity of self-collection is how long a negative HPV self-collection test provides reassurance against precancer and cancer. In the current risk-based guidelines, a negative provider HPV test in a screening setting provides sufficient reassurance for a 5-year retesting interval, while a negative cytology result provides sufficient reassurance for a 3-year testing interval. Currently, long-term follow-up data after self-collection testing are very limited, but baseline performance in the context of established tests can be used to estimate return intervals. To address the retesting interval, we conducted an additional systematic review and meta-analysis of sensitivity in studies that conducted HPV self-collection, HPV provider-collection, and provider cytology (Table 2). These data demonstrate that both self-collection and clinician collection are substantially more sensitive than cytology, but self-collection was slightly less sensitive (91%) than clinician-collection (93%) (Table 2).

Table 2. Diagnostic Accuracy of Cytology, self-collection (sHPV) and clinician-collection (cHPV)

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<tr>
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</thead>
<tbody>
<tr>
<td>Cytology (n)</td>
<td>95</td>
<td>512</td>
<td>623</td>
<td>98</td>
<td>305</td>
<td>116</td>
<td>83.9 (95% CI 79.4-87.6)</td>
<td>72.0 (95% CI 59.5-81.8)</td>
</tr>
<tr>
<td>Sens/Spec</td>
<td>83.8/50</td>
<td>77.5/ 87.3</td>
<td>80.2/61.3</td>
<td>100/84.7</td>
<td>85.5/72.9</td>
<td>87.8/61.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sHPV (n)</td>
<td>94</td>
<td>512</td>
<td>623</td>
<td>99</td>
<td>305</td>
<td>114</td>
<td>91.4 (95% CI 86.5-94.6)</td>
<td>58.5 (95% CI 36.4-77.7)</td>
</tr>
<tr>
<td>Sens/Spec</td>
<td>91.9/45.6</td>
<td>82.5/93.6</td>
<td>88.5/56.5</td>
<td>100/58.1</td>
<td>95.7/43.2</td>
<td>94.1/31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cHPV (n)</td>
<td>91</td>
<td>512</td>
<td>623</td>
<td>99</td>
<td>305</td>
<td>113</td>
<td>93.1 (95% CI 89.2-95.7)</td>
<td>59.3 (95% CI 37.8-77.8)</td>
</tr>
<tr>
<td>Sens/Spec</td>
<td>94.6/46.3</td>
<td>87.5/93.2</td>
<td>91.7/60.5</td>
<td>100/57</td>
<td>95.7/44.9</td>
<td>93.8/30.3</td>
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</table>
Genotype concordance of self- and clinician-collected samples

To address whether recommendation for extended genotyping based on provider collection could be adapted to self-collection HPV testing, we evaluated type- and channel-specific concordance between HPV-self and provider collected specimen. There was good agreement for all types and channels between both sample types (Table 3). Based on this level of agreement, the guidelines developed for genotyping can also be applied to self-collected vaginal samples. (Of note, samples collected by a clinician without a speculum may also be managed this way).

Table 3. Overall agreement and type-specific agreement between self- and provider collection by Onclarity channel

<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>% agreement</td>
<td>n</td>
</tr>
<tr>
<td>Any hrHPV</td>
<td>220</td>
<td>83 (79.3)</td>
<td>278</td>
</tr>
<tr>
<td>16</td>
<td>62</td>
<td>89</td>
<td>73</td>
</tr>
<tr>
<td>18</td>
<td>15</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>31</td>
<td>21</td>
<td>97</td>
<td>55</td>
</tr>
<tr>
<td>45</td>
<td>16</td>
<td>97</td>
<td>18</td>
</tr>
<tr>
<td>33/58</td>
<td>20</td>
<td>98</td>
<td>44</td>
</tr>
<tr>
<td>35/39/68</td>
<td>37</td>
<td>94</td>
<td>50</td>
</tr>
<tr>
<td>51</td>
<td>19</td>
<td>99</td>
<td>36</td>
</tr>
<tr>
<td>52</td>
<td>30</td>
<td>97</td>
<td>42</td>
</tr>
<tr>
<td>56/59/66</td>
<td>57</td>
<td>97</td>
<td>79</td>
</tr>
</tbody>
</table>
Proposed guidelines and data summary

PROPOSED RECOMMENDATION #1: Self-collected vaginal HPV testing is acceptable for cervical screening. (AII)

Rationale: Data from other countries indicate that allowing self-collection can increase screening rates.7,8 Advantages of self-collection include avoiding barrier such as those related to health-system (e.g., lack of available clinicians, difficulty accessing primary care), clinician (e.g., clinician does not perform pelvic exams, lack of time in visit), and patient (e.g., limited mobility, vaginismus, history of sexual trauma, gender dysphoria, not comfortable with clinician, prefers self-collection). Disadvantages include the need to return for a speculum exam to obtain a triage test for most (68-89%) of patients testing HPV-positive, and a possible small decrease in sensitivity. Therefore clinician-collected sampling from the cervix remains an option for patients, and may be preferred by those who have no barriers to speculum exams and prefer to obtain all results needed to determine the need for colposcopy with a single visit (e.g., HPV with reflex cytology/dual stain results).

PROPOSED RECOMMENDATION #2: When self-collected (vaginal) HPV test results are negative in the screening setting*, repeat testing in 3 years is recommended. (AII)

*Screening setting defined as unknown history, history of all normal results, or remote history of low-grade abnormal results with at least 3 subsequent HPV-negative results and no history of high-grade abnormal results.

Rationale: Based on all data available, we have strong evidence that self-collection HPV has better sensitivity and overall accuracy compared to cytology.6 Data are somewhat heterogeneous regarding agreement between self-collection HPV and provider collection HPV performance. Some studies suggest equivalence while others suggest a small decrease in sensitivity. Heterogeneous studies with respect to populations, sampling devices, sample handling, HPV assays used. Five-year data are not currently available to estimate risks. Three-year intervals provide margin of safety while additional data accrue; the interval may transition to 5 years in the future.

PROPOSED RECOMMENDATION #3: When self-collected (vaginal) HPV test results are positive for HPV 16/18 direct referral for colposcopy is recommended. (AII)

Rationale: HPV 16 and 18 infections confer an elevated risk of CIN3+ and cancer, and therefore colposcopy is recommended.9 This is consistent with 2019 guidelines and applies regardless of setting/past history. Evidence supports concordance of self- and clinician-collected samples for HPV 16/18, therefore equivalent management is warranted. 2019 guidelines recommend collection of cervical cytology at the colposcopy visit as this would change management in the setting of AGC, ASC-H, or HSIL if colposcopic biopsy results were <CIN29; these recommendations apply to the self (vaginal) collection setting.

PROPOSED RECOMMENDATION #4: When self-collected (vaginal) HPV test results are a) HPV untyped, b) negative for HPV 16/18 and positive for HPV HR12/other; or c) negative for HPV 16/18 and positive for HPV 45, 33/58, 31, 52, 35/39/68, 51 or combinations thereof, a speculum exam for collection of cytology or Dual Stain is recommended. Subsequent management of cytology or Dual Stain results per management guidelines is recommended.

Rationale: Evidence supports concordance of self- and clinician-collected samples for partial and extended HPV genotyping. The CIN3+ risk for HR12 or untyped is above the colposcopy threshold for Dual Stain positive or cytology of ASCUS or higher, but is below the colposcopy threshold for Dual Stain negative or NILM cytology.10 Triage testing (i.e., cytology or Dual Stain) cannot be run from a vaginal sample. Therefore, a
speculum exam to collect the triage test is recommended. The 2019 guidelines are recommended for management of untyped or HR12 HPV and cytology results. The extended genotyping guidelines are recommended for management of cytology or Dual Stain results in the setting of HPV 45, 33/58, 31, 52, 35/39/68, 51 or combinations thereof. Briefly, these are: If DS-negative or NILM cytology, repeat testing in 1 year is recommended. If DS-positive or cytology ASC-US, LSIL, ASC-H, AGC, HSIL, or carcinoma, colposcopy is recommended. For patients with initial results of Dual Stain negative or NILM cytology who undergo repeat HPV testing or co-testing at 1 year, colposcopy is recommended if the repeat test is HPV-positive for any type.

**PROPOSED RECOMMENDATION #5:** When self-collected (vaginal) HPV test results are positive for HPV types 56/59/66 and no other carcinogenic types, one year repeat testing is recommended. (AII) If HPV-positive for any HPV type at the 1-year follow-up, colposcopy is recommended. (CIII)

**Rationale:** Evidence supports concordance of self- and clinician-collected samples for partial and extended HPV genotyping. The CIN3+ risk for HPV 56/59/66 is below the colposcopy threshold for Dual Stain positive or cytology of ASCUS or higher, therefore triage testing (i.e., cytology or Dual Stain) does not change management and a visit to obtain a triage test is not needed. Therefore, repeat testing in 1 year is recommended. If the patient remains HPV-positive at the 1-year follow-up, colposcopy is recommended.

**PROPOSED RECOMMENDATION #6:**

*In the surveillance setting, cervical (clinician) collection is preferred. If a cervical sample cannot be obtained, a vaginal (self) collected sample is acceptable following shared decision-making. (CIII)*

*Surveillance setting defined as: Patient with prior HPV-positive results, post-colposcopy, or post-treatment.*

**Rationale:** Sensitivity comparisons between self- and clinician-collected HPV results show near equivalence in different settings (i.e., screening and colposcopy). However, data are very limited in the post-colposcopy and post-treatment settings. In addition, the surveillance population is higher risk of CIN3+ and HPV infection, and higher HPV-positivity rates lead to more patients requiring speculum exams for triage. Therefore, the risks and benefits of self-collected (vaginal) HPV testing in the surveillance setting differ from the screening setting.

**PROPOSED RECOMMENDATION #7:**

*When self-collected (vaginal) HPV test results are negative in the surveillance setting,* repeat testing is recommended per 2019 guidelines for negative primary HPV testing results (i.e., 1 or 3 years depending on risk). (CIII)

*Surveillance setting defined as: Patient with prior HPV-positive results, post-colposcopy, or post-treatment.*

**Rationale:** If self-collected (vaginal) HPV testing is used in the surveillance setting, utilization of management guidelines as for clinician collection is recommended. Although self-collection data are not available to directly assess these scenarios, the slight decrement in sensitivity is unlikely to affect risk estimates around the 1- and 3-year thresholds, thus existing data do not indicate a change in management.
REFERENCES


GUIDELINES TERMINOLOGY, EVIDENCE EVALUATION, AND GLOSSARY

Terminology: As in prior guidelines, the following terminology is used for recommendations:

Recommended: Good data to support use when only one option is available.
Preferred: Option is the best (or one of the best) when there are multiple options
Acceptable: One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option
Not recommended: Weak evidence against use and marginal risk for adverse consequences
Unacceptable: Good evidence against use

Note: “preferred” is used when there are multiple options and some are considered preferable to others. “Acceptable” is used when there are multiple options and all are considered equally beneficial.

Evidence evaluation for Rating the Recommendations (carried forward from 2012 and 2019 guidelines processes)

Strength of recommendation
A. Good evidence for efficacy and substantial clinical benefit support recommendation for use.
B. Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.
C. Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.
D. Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
E. Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.

Quality of evidence
I. Evidence from at least one randomized, controlled trial.
II. Evidence from at least one clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III. Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Terminology used for recommendations
Recommended. Good data to support use when only one option is available.
Preferred. Option is the best (or one of the best) when there are multiple options
Acceptable. One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option
Not recommended. Weak evidence against use and marginal risk for adverse consequences
Unacceptable. Good evidence against use