2012 PRINCIPLES AND RECOMMENDATIONS THAT REMAIN FOR RISK-BASED GUIDELINES

This section summarizes principles and recommendations retained from the 2012 guidelines. Note that new data were used whenever possible to generate new guidelines. These areas represent primarily expert opinion, or areas where literature review did not reveal new evidence to change management.

PRINCIPLES RETAINED FROM 2012

1) **Balancing benefits and harms.** Providing the best care means balancing cancer prevention and overtesting/overtreatment.

2) **Equal management for equal risks.** Prior history and current test results are used to calculate an individual patient's current and future risk of CIN3+. Similar risks are managed similarly, regardless of the combination of results/history that led to that risk.

3) **Guidelines are intended for use in US or other high resource settings**. Appropriate thresholds might be different in settings with limited follow up capabilities.

4) **Guidelines apply to asymptomatic patients undergoing cervical cancer screening.** For patients with gynecologic complaints including abnormal uterine bleeding, cervical cytology and/or HPV testing as well as endocervical and endometrial biopsy may be performed as part of a diagnostic workup. (see ASCCP practice document)

5) **Guidelines apply to all individuals with a cervix.** Guidelines apply to women and transgender men who retain their cervix, and to individuals who have undergone hysterectomy for treatment of HSIL(CIN2/3) or AIS.

MANAGEMENT GUIDELINES RETAINED FROM 2012

Treatment

1. Ablative therapy is **unacceptable** under the following circumstances
    a) When the squamocolumnar junction (SCJ) is not fully visualized
    b) When the sampling of the endocervical canal demonstrates CIN 2+, or cannot be graded.

c) When the patient has had prior therapy for cervical dysplasia.
d) When there has not been histologic confirmation of cervical dysplasia.

2. If CIN1 persists for at least 2 years, either continued follow-up or treatment is ***acceptable*** (CII). If treatment is selected and the colposcopic examination visualized the entire SCJ, either excision or ablation is ***acceptable*** (AI). A diagnostic excisional procedure is recommended if the SCJ is not fully visualized; the endocervical sampling contains (HSIL) CIN2, CIN3, CIN2/3 or ungraded CIN; or the patient has been previously treated (AIII).

Rationale: In the KPNC data set of women with CIN 1 on biopsy on two consecutive visits the subsequent follow up demonstrated that 52% are HPV -, 48% are HPV +, and of the HPV + group 92% are NILM, ASC-US or LSIL. Only those with a cytology of greater than or equal to ASC-H have an immediate risk of CIN 3+ of greater than 4%. Studies have shown treatment may result in clearance of HPV, with rates varying from 43 to 95%. Therefore, treatment of persistent CIN1 is performed with the intent to clear HPV and decrease need for repeated coloposcopic exams to evaluate persistently abnormal screening tests.

Colposcopy

4) **Management of women with unsatisfactory Cytology.** Colposcopy is recommended for women with two consecutive unsatisfactory cytology tests (CIII).

Surveillance

5) For patients with an unsatisfactory cytology result and no, unknown, or a negative HPV test result, repeat cytology in 2-4 months is **recommended** (BIII). Using reflex HPV testing to determine the management of an unsatisfactory cytology is **not recommended** (BIII). Treatment to resolve atrophy or obscuring inflammation when a specific infection is present is **acceptable** (CIII). For patients aged 30 years and older who are cotested and have unsatisfactory cytology and a positive HPV test, repeat cytology in two to four months or colposcopy is **acceptable** (BII).

Rationale: Literature was reviewed for 2012-2019, and no evidence was found to change recommendations. While a negative HPV test may be adequate even when the cytology is

inadequate, interpreting this negative result as a primary negative HPV screen might constitute an off-label use of FDA tests that are currently approved only for cotesting. HPV tests without internal cellularity controls to detect the presence of squamous cells (e.g. HC2) and/or that are not FDA-approved for primary cervical cancer screening may be less reliable in a primary screening environment.

Implications: A negative HPV result from a cotest with inadequate cellularity on cytology should not be interpreted as negative primary HPV test.

6) For patients aged 21-29 years with negative cytology and absent or insufficient EC/TZ component, routine screening is **recommended**. When cervical cytology is performed for screening, HPV testing as a triage test following negative cytology and absent or insufficient EC/TZ component in this age group is **unacceptable** (BIII), though HPV testing may be used in surveillance situations following high grade abnormalities. For patients aged 30 years and older with cytology reported as negative and with absent or insufficient EC/TZ component and no or unknown HPV test result, HPV testing is **preferred** (BIII). Repeat cytology in three years is **acceptable** if HPV testing is not performed (BIII). If the HPV testing is done and is negative, return to routine screening is **recommended** (BIII). If the HPV test is positive, repeating both tests in one year is **acceptable** (BIII). Genotyping is also acceptable; if HPV type 16 or HPV type 18 is present, colposcopy is **recommended** (BII). If HPV type 16 and HPV type 18 are absent, repeat cotesting in 12 months is **recommended** (BIII).

Rationale: Literature was reviewed for 2012-2019, and no evidence was found to change recommendations.

Implications: The absence of or an insufficient EC/TZ on cytology should not affect the interpretation of the cytology result, and the test does not need to be repeated.

7) For asymptomatic premenopausal patients with benign endometrial cells, endometrial stromal cells, or histiocytes, no further evaluation is **recommended** (BII). For postmenopausal patients with benign endometrial cells, endometrial assessment is **recommended** (BII). For post-hysterectomy patients with a cytology report of benign glandular cells, no further evaluation is **recommended** (BII).

Rationale: Literature was reviewed for 2012-2019, and no evidence was found to change recommendations.

Implications: Endometrial cells on cytology in a post-menopausal patient should prompt evaluation of the endometrium.

8) If a patient undergoes screening at age ≥65 years, manage according to guidelines for patients ages 25-64 years. If surveillance testing is indicated for management of prior abnormal results, exiting a patient from surveillance is **unacceptable** (EII). Surveillance should continue for as long as the patient is in reasonably good health. Discontinuation of screening is **recommended** if they have a life-limiting condition.

Rationale: Women age 65+ with abnormal cervical cytology and/or HPV results may be at risk for cervical cancer, so abnormal results should be evaluated similarly to younger patients.

Implications: Screening for patients over age 65 should follow national screening guidelines. When present, abnormal cervical cytology or HPV testing results should be evaluated, not ignored. Patients with prior high risk for CIN3+ appear to have an elevated lifetime risk of developing cervical or vaginal cancer and thus may require surveillance testing well beyond age 65 years.

9) Management of 21-24 year olds following abnormalities on cervical cytology

<u>Initial Management</u>

For women aged 21-24 years with ASC-US, cytology alone at 12-month intervals is preferred, but reflex HPV testing is acceptable (BII). If reflex HPV testing is performed with ASC-US and the HPV result is positive, repeat cytology in 12 months is recommended (BII). Immediate colposcopy or repeat HPV testing is not recommended. If reflex HPV testing is performed and is negative, return for routine screening with cytology alone in 3 years is recommended (BII).

<u>Follow-Up</u>

For women with ASC-US who are aged 21-24 years, follow-up with cytology at 12-month intervals is recommended. Colposcopy is not recommended. (BII) For women with ASC-H or HSIL+ (HSIL, atypical glandular cells [AGC], or cancer) at the 12-month follow up, colposcopy is recommended. For women with ASC-US or worse at the 24-month follow-up, colposcopy is recommended.For women with two consecutive negative results, return to routine screening is recommended. (BII)

Rationale: Data from KPNC were reviewed for 21-24 year olds undergoing their first screening tests in 2003-2004, 2008-2009, 2011-2012, and 2016-2017. Proportions of abnormal results did not decrease over this time period, nor did the calculated CIN3+ risk for LSIL or HSIL results. Risks for ASCUS/LSIL were consistent with a 1 year return on both the first and second test (calculated immediate risk of CIN3+ approximately 2%).

Immediate CIN3+ risks of ASC-H and HSIL were approximately 9% and 20%, respectively, consistent with referral to colposcopy.