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Managing Minimally Abnormal Cervical Cancer Screening Test Results

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The approach to cervical cancer screening has changed substantially over the past decade. Current screening strategies for individuals older than 30 years include cytology (Papanicolaou tests), testing for high-risk (oncogenic) types of human papillomavirus (hrHPV), or both (co-testing).[1] However, various possible combinations of test results have led to complex management algorithms, especially for test results considered to be minimally abnormal, defined as results for which it is unclear whether the next step should be colposcopy (a magnified view of the cervix, often with biopsies) or close follow-up. This article provides an update for the approach to the initial management of minimally abnormal cervical cancer screening test results.

Supplemental content

In April 2020, 19 organizations released consensus guidelines that formalized a strategy for management of cervical cancer screening test results using a framework based on estimates of underlying high-grade precancerous lesions or cancer (known collectively as cervical intraepithelial neoplasia grade 3 or worse [CIN3+]).[2] Estimates were derived from screening outcomes observed in more than 1.5 million individuals aged 25 to 65 years enrolled in a prepaid health plan.[3] In this population, about 90% of test results were normal and about 0.75% were severely abnormal. The remainder were minimally abnormal, a category that includes an hrHPV-positive test result with a concurrent normal cytologic interpretation (negative for intraepithelial lesion or malignancy), atypical squamous cells of undetermined significance (ASC-US), and low-grade squamous intraepithelial lesion (LSIL).

Underlying risks of CIN3+ were estimated for various combinations of cytology, hrHPV testing (ie, pooled testing for ≥1 of 13 or 14 hrHPV types), and HPV genotyping (ie, testing specifically for HPV-16 and HPV-18).[4,5] Because transient hrHPV infections are associated with a lower risk of CIN3+ than persistent hrHPV infections, the effect of having an hrHPV-negative test result within the past 5 years on CIN3+ risk was also evaluated; this is a new addition to the guideline. These risks were then applied to "clinical action thresholds" defined by expert consensus[2]; 3 thresholds are relevant to individuals with minimally abnormal test results. If the immediate CIN3+ risk is 4% to 24%, colposcopy is recommended, but if the immediate risk is less than 4%, the cumulative 5-year CIN3+ risk guides the surveillance interval. Repeated testing in 1 year is recommended if the 5-year risk is greater than or equal to 0.55%, and repeated testing in 3 years is recommended if the 5-year risk is 0.15% to 0.54%. Repeated testing is specified as hrHPV testing or co-testing; if performing these tests is not feasible, cytology alone is acceptable.

The most common test abnormality is a positive hrHPV test result with a concurrent normal cytologic interpretation, comprising about 4.1% of all test results. Because the estimated immediate CIN3+ risk is 2.1% and the cumulative 5-year risk is 4.8% (eTable in the Supplement),[5] repeated testing in 1 year is recommended (**Figure**).[2] However, if a test result for HPV-16 is positive, immediate CIN3+ risk rises to 5.3%, warranting colposcopy.[4] Positive test results for HPV-18 also warrant colposcopy due to an elevated risk of adenocarcinoma.[4] Colposcopy is always recommended in individuals whose test results are positive for HPV-16 and/or HPV-18 with normal or minimally abnormal cytologic test results.

The second most common test abnormality is ASC-US, comprising about 3.6% of test results. When hrHPV testing is performed, about 44% of test results will be negative; hrHPV-negative ASC-US results have an immediate CIN3+ risk of 0.04% and a cumulative 5-year risk of 0.40%.[5] Thus, repeated testing in 3 years is recommended. In contrast, an hrHPV-positive test result confers an immediate CIN3+ risk of at least 4.4%,[5] and colposcopy is recommended. However, individuals with hrHPV-positive ASC-US test results with no evidence of concurrent infection with HPV-16 or

Figure. Initial Management for Minimally Abnormal Cervical Cancer Screening Test Results in Average-Risk Individuals[a]

Cytologic test result	hrHPV test result	hrHPV genotyping result	Recommended clinical action
NILM	hrHPV+	HPV-16+ or HPV-18+	Colposcopy
		HPV-16/18 unknown or HPV-16− and HPV-18−	hrHPV testing with or without cytology in 1 y[b]
ASC-US	hrHPV+	HPV-16+ or HPV-18+	Colposcopy
		HPV-16/18 unknown or HPV-16− and HPV-18−	Colposcopy or If hrHPV− within previous 5 y, hrHPV testing with or without cytology in 1 y[b]
	hrHPV unknown		hrHPV testing with or without cytology in 1 y[b]
	hrHPV−		hrHPV testing with or without cytology in 3 y[b]
LSIL	hrHPV+	HPV-16+ or HPV-18+	Colposcopy
		HPV-16/18 unknown or HPV-16− and HPV-18−	Colposcopy or If hrHPV− within previous 5 y, hrHPV testing with or without cytology in 1 y[b]
	hrHPV unknown		Colposcopy
	hrHPV−		hrHPV testing with or without cytology in 1 y[b]
Unknown[c]	hrHPV+	HPV-16+ or HPV-18+ or HPV-16/18 unknown or HPV-16− and HPV-18−	Colposcopy

ASC-US indicates atypical squamous cells of undetermined significance; hrHPV, high-risk human papillomavirus; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesion or malignancy.

[a] Average risk is defined as not under surveillance for a prior cervical test result abnormality, no cervical intraepithelial neoplasia grade 2 or worse within the past 25 years, and not immunocompromised.

[b] Cytology alone is acceptable if hrHPV testing or co-testing are not feasible.

[c] Cytology is recommended for risk stratification.

HPV-18 who have a documented hrHPV-negative test result within the past 5 years have a lower CIN3+ risk; therefore, repeated testing in 1 year is recommended instead of colposcopy.

Two cytologic test results include the term *atypical* and are often confused with ASC-US: atypical glandular cells and atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion. These cytologic findings are associated with higher cancer risks, and colposcopy is recommended regardless of hrHPV test results.

The third most common test abnormality is LSIL, comprising about 1.7% of all test results. When hrHPV testing is performed, only about 12% of test results will be negative. With an hrHPV-negative LSIL test result, immediate CIN3+ risk is 1.1% and the 5-year cumulative risk is 2.0%,[5] thus repeated testing in 1 year is recommended. With an hrHPV-positive test result, CIN3+ risk is at least 4.3% leading to a recommendation for colposcopy.[5] If hrHPV testing is not available, colposcopy is recommended as per previous guidelines.[6] Similar to ASC-US, when an hrHPV-positive LSIL test result is preceded by a negative hrHPV test result within the past 5 years, the risk is lower and repeated testing in 1 year is recommended instead of colposcopy, unless concurrent test results for HPV-16 or HPV-18 are positive.

The new guidelines[2] also update recommendations for abnormal test result management for primary hrHPV screening. In the setting of a positive hrHPV test result, cytology is recommended to allow for risk estimation. Colposcopy is recommended if test results are positive for HPV-16 or HPV-18. If cytology cannot be performed, it is reasonable to perform colposcopy because the estimated CIN3+ risk is 5.5%.

Risk-based management guidelines also address questions related to specimen quality. When cytology is reported as unsatisfactory, the test should be repeated in 2 to 4 months, even if the hrHPV test result is negative. Colposcopy is recommended after 2 consecutive unsatisfactory cytology test results. In contrast, the absence of endocervical cells does not increase risk, so this finding should not prompt additional testing.[2]

Although the numerous algorithms recommended by these new risk-based management guidelines have not been rigorously evaluated through comparative effectiveness studies, they bring substantial evidence to the clinical forefront, guiding clinical practice with increased precision. But, with precision comes complexity. In an effort to simplify the application of these guidelines to patients, a freely accessible interactive website[7] will be available. In addition to implementing these recommendations into clinical practice, clinicians can continue to improve cervical cancer prevention by encouraging appropriate HPV vaccination and screening of underscreened individuals.

ARTICLE INFORMATION

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