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Applying Results of Extended Genotyping to Management of Positive Cervicovaginal Human Papillomavirus Test Results: Enduring Guidelines

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Objective: The Enduring Consensus Cervical Cancer Screening and Management Guidelines Committee developed recommendations for the use of extended genotyping results in cervical cancer prevention programs.

Methods: Risks of cervical intraepithelial neoplasia grade 3 or worse were calculated using data obtained with the Onclarity HPV Assay from large cohorts. Management recommendations were based on clinical action thresholds developed for the 2019 American Society for Colposcopy and Cervical Pathology Risk-Based Management Consensus Guidelines. Risk estimates were reviewed in relation to clinical action thresholds and used as the basis for draft recommendations. After an open comment period, recommendations were finalized and ratified through a vote by the Consensus Stakeholder Group.

Results: Colposcopy is recommended after positive tests for human papillomavirus (HPV) types 16 and 18. For those positive for HPV 45, 33/58, 31, 52, 35/39/68, or 51 but negative for 16 or 18, triage with cytology or dual stain testing is recommended. When screening with primary HPV testing, for patients who test positive for HPV types 56/59/66 and no other carcinogenic types, repeat HPV testing in 1 year is recommended. When screening with cotesting, for those who test positive for HPV types 56/59/66 and no other carcinogenic types, 1-year return is recommended for negative for intraepithelial lesion or malignancy, atypical squamous cells of undetermined significance, and low-grade squamous intraepithelial lesion, and colposcopy is recommended for atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion (ASC-H), atypical glandular cells, high-grade squamous intraepithelial lesion, or carcinoma. When patients without prior high-grade cytology (atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion, atypical glandular cells, high-grade squamous intraepithelial lesion, or carcinoma) or histology (cervical intraepithelial neoplasia [CIN]2, CIN3, or adenocarcinoma in situ) are being followed, use of extended genotyping results is acceptable. When high-grade cytology or histology results are present, or when patients are being followed after treatment of CIN2+, management using the 2019 guidelines is recommended.

Conclusions: Human papillomavirus extended genotyping can guide clinical management in the setting of a positive HPV test result.

Key Words: guidelines, cervical cancer, early detection of cancer, human papillomaviruses

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INTRODUCTION AND GUIDING PRINCIPLES

Essentially all cervical cancers are caused by infection with carcinogenic types of the human papillomavirus (HPV).[1] Detection of HPV or HPV-induced cytologic changes allows for triage to colposcopy for detection of cancer precursors, whose treatment reduces cervical cancer risk. However, HPV is common, and most incident infections, even with carcinogenic types, become undetectable within 3 years without sequelae.[2] Prevention guidelines must balance the benefit of avoiding cervical cancer, a rare outcome, against the potential harms of screening, diagnosis, and treatment in HPV-positive populations. Estimating benefits and harms requires study of large, diverse populations.

Human papillomavirus types vary widely in carcinogenicity. About 30 HPV genotypes infect cervical mucosae; 12 are classified as group 1 carcinogens by the International Agency for Research on Cancer (IARC).[1] Human papillomavirus 16 is the most carcinogenic, accounting for roughly half of all cervical cancers. Although HPV18 infection confers a low risk for incident cervical intraepithelial neoplasia grade 3 or worse (CIN3+), it accounts for more than 10% of cancers and is particularly associated with adenocarcinoma. Other types contribute smaller fractions to the global cervical cancer burden. This was largely validated in a recent systematic analysis of the world literature.[3] The IARC, in collaboration with international experts, has established a hierarchy of HPV genotypes based on worldwide epidemiologic data. Table 1 summarizes cervical

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L.S.M. participated in an HPV vaccine call with Merck. N.B. has served on an advisory board for Merck. D.C. is a member of the United States Preventive Services Task Force (USPSTF); this article does not necessarily represent the views and policies of the USPSTF. D.C. was recused from development of recommendations related to screening and fully participated in recommendations related to diagnosis and management. M.E. has served as a consultant for Papivax, Merck, BD, PDS. R.G. has served as a consultant for Inovio. D.H. has served as a consultant for Roche. W.H. has served as a consultant for Roche, SeeGene, and AstraZeneca. R.N. has participated in an educational meeting supported by Roche. M.C. reports legal work for Merck. The other authors have declared they have no conflicts of interest.

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TABLE 1. Contribution of Carcinogenic Human Papillomavirus (HPV) Genotypes and CIN3+ Progression Risk for Progression to Cervical Intraepithelial Neoplasia (CIN) Grade 3 or Worse

Carcinogenic HPV type	% of Cervical Cancers	9-year risk of progression to CIN3+ of incident HPV infection	Risk Group
16	60.3	6.3	16
18	10.5	3.0	18/45
45	6.1	2.2	18/45
33	3.7	4.5	16-related
31	3.6	2.2	16-related
52	2.7	2.2	16-related
58	2.2	1.9	16-related
35	2.0	2.8	16-related
39	1.6	1.1	Other
51	1.2	1.1	Other
59	1.1	0.9	Other
56	0.9	0.8	Other
68	0.6	1.0	Other

cancer attribution, that is, the proportion of cancers caused by specific HPV types, and risk of progression from infection to CIN3+, for 13 types (12 carcinogenic types and 1 probable carcinogenic type). Evidence underlying this ranking is strong and is the rationale for tailoring management by HPV genotype. Although most types have similar risk levels and cancer attributions across populations, there are notable exceptions such as HPV35, which is more common and has a higher cancer risk in persons of African ancestry compared to others.

The IARC combines carcinogenic HPV types into 4 groups based on their risk of progression and attribution to cancer: HPV16, HPV18/45, HPV16-related types (HPV33, 31, 52, 58, 35), and the remaining other carcinogenic or probable carcinogenic types (HPV 39, 51, 59, 56, 68). However, the clinical management of HPV types and type groups is not prescribed by the IARC ranking and may vary across settings, depending on specific risk-based thresholds and available triage options, as well as on colposcopy and treatment capacity. The guidelines presented here fill that gap and were specifically developed for the US setting.

Most HPV assays approved by the US Food and Drug Administration (FDA) predate the current IARC classification, so assay configurations deviate from ideal type groupings. For example, commercial US assays either individually report HPV45 or group it with the other 12 carcinogenic types (HR12). Some assays group HPV35 with types from the lowest risk group. Human papillomavirus 66 was formerly considered a carcinogen but has now been reclassified as noncarcinogenic; nevertheless, because HPV66 is reported in current assays, it is included in Enduring Consensus Cervical Cancer Screening and Management Guidelines

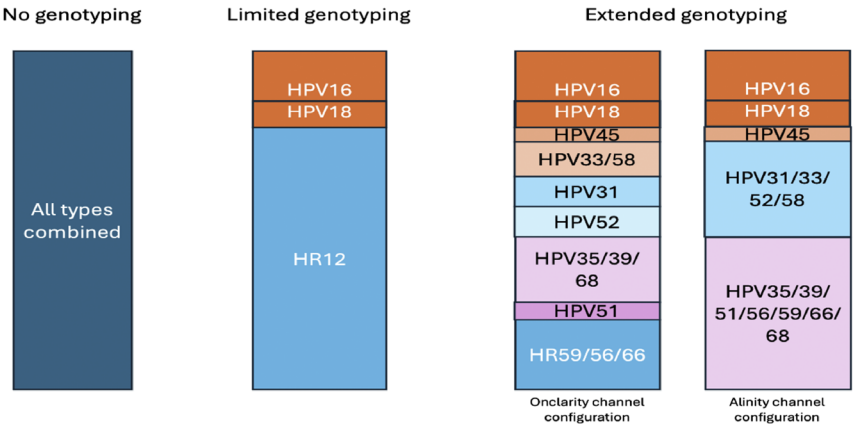

FIGURE 1. Type configurations of human papillomavirus (HPV) assays approved by the Food and Drug Administration as of May 2024.

(referred to hereafter as Enduring Guidelines) recommendations for management.

In 2015, ASCCP and the Society of Gynecologic Oncology convened a panel that developed guidance for using HPV testing with limited genotyping (16, 18, HR12, Figure 1) as a primary cervical cancer screening test.[4] Immediate colposcopy referral was recommended because of HPV16's high cancer risk and because of HPV18's high risk of endocervical glandular lesions (adenocarcinoma in situ [AIS] and adenocarcinoma) frequently missed by cytology. For individuals with HR12-positive results, cytology triage was recommended. In 2019, the ASCCP Risk-Based Management Consensus Guidelines (hereafter referred to as 2019 Guidelines) reaffirmed this approach, which constitutes the foundation for extended genotyping recommendations.[5–7]

Recently, the FDA approved 2 assays that provide extended genotyping: the Onclarity HPV Assay (Becton Dickinson, Franklin Lakes, NJ, approved April 2020) identifies HPV types 16, 18, 45, 31, 51, and 52 in individual assay channels and reports assay channels combining HPV33/58, HPV35/39/68, and HPV56/59/66; and the Alinity m High-Risk HPV Assay (Abbott, Abbott Park, IL, approved November 2023) identifies HPV types 16, 18, and 45 individually and reports combined types 31/33/52/58 and 35/39/51/56/59/66/68.

The Enduring Guidelines working group was established as a standing committee to iteratively apply the risk-based process for evaluating new technologies using previously described standardized guiding principles and processes.[8,9] Recommendations for new screening and risk stratification tests can be derived from associated CIN3 and cancer risks. For example, in 2023, guidelines were updated in this manner to provide management recommendations for the p16^{ink4}a/Ki-67 dual stain assay (CINtec Plus Cytology, Roche Diagnostics, Indianapolis, IN).[10]

METHODS

The purpose of this evidence review was to evaluate risks of CIN3+ and cancer according to extended genotyping results and to define management strategies for health systems and clinicians who choose to adopt extended genotyping. The Enduring Guidelines Risk Assessment Group, led by researchers at the US National Cancer Institute (NCI), summarized worldwide carcinogenicity data and risk data for HPV genotypes, identified US-based studies reporting on CIN3+ risks for FDA-approved extended genotyping tests, and conducted extensive data analysis to produce risk estimates from primary studies of individuals undergoing HPV testing with the Onclarity assay, as in the 2019 guidelines.[6]

Management recommendations utilized the risk threshold framework established by the 2019 guidelines[11] and the Enduring Guidelines extension for 3-year data.[9] Cytology results were reported according to the Bethesda System for Reporting Cervical Cytology as negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells cannot exclude high-grade intraepithelial lesion (ASC-H), atypical glandular cells (AGC), and high-grade squamous intraepithelial lesion (HSIL).[12] Primary data on extended genotyping were available for a subset of the cohort recruited from Kaiser Permanente Northern California (KPNC) for the Improving Risk-Informed HPV Screening (IRIS) Study.[13,14] The racial/ethnic composition of KPNC health plan members in this cohort was 44% White, 24% Hispanic, 18% Asian/Pacific Islander, and 8% Black. Improving Risk-Informed HPV Screening included individuals undergoing cotesting for cervical screening with Surepath cytology and Hybrid Capture 2 HPV testing in 2017 and followed through fall 2022.[13,14] A subset of HPV-positive samples identified on clinical routine testing with the Digene HC2 HPV DNA assay was tested with Onclarity.

To assess the performance of extended genotyping in more racially, geographically, and economically diverse populations, we also evaluated data from the STudying Risk to Improve DisparitiES (STRIDES) study. STudying Risk to Improve DisparitiES is a statewide cohort study of individuals undergoing cervical cancer screening and management as of 2018 at the University of Mississippi Medical Center or the Mississippi State Department of Health. Most study participants resided in rural Mississippi and were served by state-funded health clinics. The racial breakdown of this study group was 60% Black, 26% White, 8% other, and 6% missing. In STRIDES, individuals underwent cotesting using ThinPrep cytology and HPV testing (cobas). A subset of cobas HPV-positive residual specimens was tested using Onclarity. Follow-up continues, but for this analysis, outcomes were assessed through fall 2022.[15,16] Summary performance estimates from studies published in the literature evaluating Onclarity, including those from regulatory trials and other US-based investigations, were not included in risk assessment calculations[8] but were considered as additional supporting evidence.

The Evidence Assessment Working Group, including clinicians, pathologists, content experts, and representatives of national organizations including patient stakeholder groups, reviewed the risk estimates in relation to clinical action thresholds and drafted recommendations, considering the level and precision of risk estimators and additional appropriate information such as

cancer risk and resource utilization metrics; costs and cost-effectiveness vary across health systems and were not considered. Draft recommendations were affirmed by the Consensus Stakeholder Group, composed of representatives named by stakeholder organizations that contributed to the 2019 Guidelines; members were instructed to forward to their respective organizations for further input. In line with prior guidelines, management options were labeled recommended, preferred, acceptable, or not recommended (definitions in Box 1). To each recommendation, the Working Group assigned strength and evidence weightings (grades and definitions in Box 2). After further revision, a final online consensus stakeholder meeting was held in May 2024 to review public comment and propose additional revisions. In August 2024, each final recommendation was confirmed by a virtual affirmative vote of >90% of organization representatives, surpassing the two-thirds required majority. Recommendation terminology (recommended, preferred, acceptable, not recommended), recommendation strength (A–E), and quality of evidence (I–III) followed that of the 2019 Guidelines (Supplemental Boxes 1, http://links.lww.com/LGT/A392 and 2, http://links.lww.com/LGT/A393).[5]

Risk-Based Approach

Consistent with the processes for the 2019 Guidelines and the Enduring Guidelines, a risk-based approach was used to determine clinical actions.[8] First, risks associated with individual cytology and HPV genotype combinations were used to group results. For each clinical scenario evaluated, the Risk Assessment Working Group estimated immediate and 3-year risks of developing CIN3+ using prevalence-incidence mixture models in KPNC data.[13] In STRIDES, we estimated immediate CIN3+ risks only. Resulting clinical actions are based on risk thresholds determined by the 2019 Guidelines and the extension for 3-year risk data.[5,9,11] Using extended genotyping in combination with triage tests increases the number of possible test results substantially. For the same studies, numbers of individuals and precancer outcomes were smaller when many strata were used. These small numbers may result in unstable estimates for individual strata (eg, HPV 51 with an LSIL cytology result). For more stable estimates, HPV genotypes with similar risks were grouped together. Cytology was dichotomized as NILM versus ASC-US or worse (ASC-US+) for risk estimation for HPV genotypes of intermediate carcinogenicity and as NILM/ASC-US/LSIL versus ASC-H/HSIL/AGC for the panel with lowest risk (56/59/66).

The 2019 Guidelines committee set an immediate risk of CIN3+ of 4% as the threshold for colposcopy referral in screening tests and combinations.[5] The risk of CIN3+ among those with any carcinogenic HPV was 5.3%,[6] whereas it was 3.5% for other HR12 types (excluding HPV16 or HPV18).[6]

Recommendations

- Several key points apply when employing recommendations for extended genotyping.

1. **Recommendations only apply to FDA-approved extended genotyping assays**. At the time of writing, the BD Onclarity HPV Assay and the Abbott Alinity m High-Risk HPV Assay were the only extended genotyping tests with FDA approval. Since the grouping of HPV types differs between the 2 approved assays, recommendations here are specific for the Onclarity HPV Assay; those for groups specific to the Alinity m Assay and others may be developed as data allowing risk calculation become available. The performance of non-FDA approved extended genotyping assays may not be similar; the generalizability of these recommendations to results from such tests cannot be assumed, especially when types are grouped differently, and such assays should not be used for clinical care.
2. **The existing 2019 Guidelines and previously published Enduring Guidelines represent the standard for management recommendations. Changes are recommended when data for new tests and test combinations justify new recommendations.** When evidence is lacking or inconsistent for specific assays or type configurations in relevant populations, recommendations default to the 2019 and Enduring Guidelines,[5] as well as the 2017 ASCCP Colposcopy Standards.[17] Some recommendations for specific non-16/18 genotypes default to recommendations from the 2019 guidelines when data are inconsistent across studies or insufficiently strong.
3. **These recommendations apply only to results obtained in asymptomatic individuals with cervices undergoing screening or surveillance**. Symptomatic patients should be managed according to relevant protocols. Screening after hysterectomy should be limited to individuals with prior history of CIN2+ or cervical cancer; risks for those individuals are undetermined, and these guidelines may not apply.

The following recommendations address management of patients with positive results on cervicovaginal HPV testing for whom extended genotyping results are available as part of the screening test result. Section 1 outlines general principles for extended genotyping that will apply across all FDA-approved tests providing extended genotyping. Section 2 applies specifically to the HPV genotype groupings available in the Onclarity assay.

SECTION 1: GENERAL PRINCIPLES

Recommendation #1: HPV Extended Genotyping Is Acceptable to Guide Clinical Management in the Setting of a Positive HPV Test Result. (BII)

Rationale. Extended genotyping assays have been approved by the FDA after demonstrating safety and validity. Extended genotyping results provide more refined risk stratification than a pooled HR12 result. This in turn may facilitate more precise referral of HPV-positive individuals to colposcopy, triage, or 1-year follow-up. Extended genotyping is applicable to currently recommended screening strategies: primary HPV testing, cotesting, and cytology with HPV triage of ASC-US results. Alternative strategies for risk stratification in cervical cancer prevention are also acceptable, the recommendation development process did not compare extended genotyping to other tests, and no bias toward or against extended genotyping is implied.

Recommendation #2: When Multiple Types Are Reported, Management According to the Type With Highest Cancer Risk Is Recommended Following the IARC Hierarchy 16, 18, 45, 33, 31, 52, 58, 35, 39, 51, 59, 56, 68, 66. (BII)

Rationale. The ranking and distinction of the 4 IARC carcinogenicity groups is more important than the ranking of individual types, since differences in cancer attribution and CIN3+ risk are typically small across types from the same groups. There is no evidence for synergy between types (eg, additional risk when multiple types are present).[18] When HPV assay channels contain multiple pooled types, the specific type or types present cannot be determined. For reasons of safety, management should follow the type in the channel with the highest risk according to IARC rankings.

SECTION 2: ASSAY- AND GENOTYPE-SPECIFIC RECOMMENDATIONS

Previous Recommendation for HPV16 and HPV18

The 2019 Guidelines include recommendations for HPV16 and HPV18.[5] Data evaluated here and from the literature did not indicate a need to revise these guidelines. These recommendations are reaffirmed:

"When primary HPV screening is used, performance of an additional reflex triage test (eg, reflex cytology) for all positive HPV tests regardless of genotype is preferred (this includes tests positive for genotypes HPV 16/18) (CIII). However, if primary HPV screening test genotyping results are HPV16- or HPV18-positive and reflex triage testing from the same laboratory specimen is not feasible, referral for colposcopy prior to obtaining additional testing is acceptable (CIII). If genotyping for HPV 16 or HPV 18 is positive, and triage testing is not performed prior to the colposcopy, collection of an additional triage test (eg, reflex cytology) at the colposcopy visit is recommended (CIII)."

New Recommendations for Types Other Than HPV16 and HPV 18

The recommendations below for extended genotyping focus on HPV types other than HPV16 or HPV18, grouped according to Onclarity channels. Risks associated with individual HPV genotypes and grouped channels were examined in the IRIS and STRIDES cohorts to decide whether clinical management should differ by type or channel. Based on the combined evidence about cancer attribution and risk of progression to CIN3+: different management is warranted for HPV 45, 33/58, 31, 52, 35/39/68, and 51 versus HPV 59/56/66. When higher risk was noted in IRIS or STRIDES for a specific genotype or channel (eg, for HPV35/39/68 and HPV51, more common in the STRIDES population), management according to the current standard was recommended. Use of extended genotyping in settings of screening (Recommendations 3–5) and surveillance after prior abnormality (Recommendation 6) was considered separately.

Recommendation #3: In a Screening Setting Using Either Primary HPV Testing or Cotesting, for Patients Who Test Positive for HPV 31, 33/58, 35/39/68, 45, 51, 52, or Combinations Thereof, But Negative for HPV16 and HPV18, Triage Testing With Dual Stain or Cytology Is Recommended. If Results Are Dual Stain-Negative or NILM Cytology, Repeat HPV testing in 1 year Is Recommended. If Results Are Dual Stain-Positive or Cytology ASC-US, LSIL, ASC-H, AGC, HSIL, or Carcinoma, Colposcopy Is Recommended. (AII) for Patients With Initial Results of Dual Stain-Negative or NILM Cytology Who Undergo Repeat HPV Testing or Cotesting at 1 Year, if Results Are HPV-Positive for Any HPV Type or if Cytology of ASC-H, AGC, HSIL, or Carcinoma, Colposcopy Is Recommended. (CIII). If Results Are HPV-Negative But Cytology Is NILM, ASC-US, or LSIL, HPV-Based Testing in 12 Months Is Recommended. (CIII)

Rationale. Overall, triage testing with cytology or dual stain for patients with these HPV genotypes was a strong risk discriminator. In IARC worldwide survey data (Table 1), HPV 45, 33/58, 31, 52, 35/39/68, and 51 together were responsible for 28% of cancers, indicating carcinogenicity intermediate between types 16/18 and types 56/59/66. In the IRIS cohort of 3,757 HPV-positive patients, 2,564 (68%) tested positive for these types (Table 1). Among these, 85 were diagnosed with CIN3+ over 3 years of follow-up (68 prevalent and 17 incident cases). Adding a triage test (dual stain or cytology) enhanced risk stratification, as risks remained below the colposcopy threshold for dual stain-negative and cytology NILM but exceeded the colposcopy threshold for dual stain-positive and cytology results of ASC-US or higher (Tables 2 and 3). Findings were similar in the STRIDES cohort for HPV types other than HPV 35/39/58 and 51 (Tables 4 and 5).

Considerations for specific HPV genotypes:

HPV 35/39/68. According to the IARC carcinogenicity ranking, HPV35 is grouped with HPV16-related types, whereas HPV39 and HPV68 are in the lower risk group. For patients with

TABLE 2. Risk for CIN3+ Using Extended Genotyping and Cytology in the Improving Risk-Informed HPV Screening (IRIS) Cohort (n = 3,757)

Baseline covariate	n	CIN3+ cases	CIN3+ immediate risk	CIN3+ 3-y cumulative risk	Management recommendation	CIN3+ management confidence Probability[a]
ASC-US+/HPV16	360	74	20.5%	24.1%	Colposcopy	98%
NILM/HPV16	185	23	8.4%	11.5%	Colposcopy	99%
ASC-US+/HPV18	89	11	10.4%	16.0%	Colposcopy	98%
NILM/HPV18	56	4	4.0%	8.5%	Colposcopy	51%
ASC-US+/HPV other[b]	1,106	68	5.0%	6.4%	Colposcopy	94%
NILM/HPV other	926	15	1.8%	2.9%	1-y return	100%
ASC-US+/HPV59/56/66	297	3	1.1%	1.8%	1-y return	96%
NILM/HPV59/56/66	217	3	0.4%	0.9%	1-y return	88%

[a]The probability that the risk estimated using another random sample of individuals with the same test results from the same population would have the same recommendation.

[b]Other defined as HPV 45,33/58, 31, 52/35/39/68, and 51.

ASC-US indicates atypical squamous cells of undetermined significance or a more severe cytologic abnormality; NILM, negative for intraepithelial lesion or malignancy.

TABLE 3. Number and Risk for CIN3+ for Combinations of Extended Genotyping and Dual Stain Results in the IRIS Cohort

Baseline covariate	*n*	CIN3+ cases	Immediate risk for CIN3+	3-y cumulative risk for CIN3+	CIN3+ management	CIN3+ management confidence Probability[a]
Dual stain +/HPV16	373	90	23.4%	27.4%	Colposcopy	75.8%
Dual stain −/HPV16	172	7	1.9%	3.7%	*Special situation:* Colposcopy	N/A
Dual stain +/HPV18	94	14	11.7%	18.2%	Colposcopy	98.6%
Dual stain −/HPV18	51	1	0.8%	3.4%	*Special situation:* Colposcopy	N/A
Dual stain +/HPV other[b]	1,039	77	6.7%	8.5%	Colposcopy	100.0%
Dual stain −/HPV other	993	6	0.5%	1.1%	1-y return	98.9%
Dual stain + /HPV59/56/66	170	4	2.2%	3.2%	1-y return	93.9%
Dual stain −/HPV59/56/66	344	2	0.1%	0.5%	1-y return	100.0%

[a]The probability that the risk estimated using another random sample of individuals with the same test results from the same population would have the same recommendation.

[b]Other defined as HPV 45,33/58, 31, 52/35/39/68, and 51.

HPV35/39/68, we found differential immediate CIN3+ risks in the IRIS cohort (HPV35/39/68: 1.7%) versus the majority African American STRIDES cohort (HPV35/39/68: 5.9%), consistent with the higher prevalence and cancer attribution of HPV35 in those of African descent.[19] To ensure that individuals with HPV35 infections undergo appropriate triage, the HPV35/39/68 channel should be managed like the other HPV16-related types.

HPV 51. Immediate CIN3+ risks also differed for those with HPV51 in the IRIS cohort (1.5%) and STRIDES cohort (6.3%). Since the number of HPV51 infections with CIN3+ outcomes was limited, the evidence was insufficient to escalate management, so the Enduring Guidelines Working Group applied the 2019 recommendation for non-16/18 HPV types: to perform a triage test.

HPV 31. Risk analyses from the IRIS and STRIDES cohorts suggested that HPV31 can be successfully triaged with cytology or dual stain, supporting a triage recommendation. This is also the current standard for HR12. In contrast, the Onclarity regulatory trial data reported that individuals with HPV31 and negative cytology results had a 7.5% risk of CIN3+, which would support immediate referral to colposcopy.[20] This finding was not confirmed in other larger studies.[21] Therefore, the Enduring Guidelines group considered evidence insufficient to change current practice.

HPV 45. The utility of triage was assessed for HPV45. Human papillomavirus 45, like HPV18, is associated with increased risk of adenocarcinoma and its precursor, AIS. Both cytology and dual stain triaged HPV45 with high sensitivity for CIN3+. Of HPV45-positive participants, NILM cytology was found in 391 (54%), with no prevalent cancers and 1 incident cancer. Abnormal cytology was found in 334 (46%) and was associated with 7 prevalent cancers, plus 1 incident cancer and 1 cancer that could not be determined as incident or prevalent. This high sensitivity for triage testing supported grouping HPV45 with the intermediate-risk carcinogenic HPV group managed with triage.

Recommendation #4: In a Screening Setting Using Primary HPV Testing, for Patients Who Test Positive for HPV Types 56/59/66 and No Other Carcinogenic Types, Repeat HPV Testing in 1 Year Is Recommended. (AII) If HPV-Positive for Any HPV Type at the 1-Year Follow-Up, Colposcopy Is Recommended. (CIII)

Rationale. In the IARC worldwide survey data (Table 1), HPV 56, 59, and 66 together were responsible for 2% of cancers. In the IRIS cohort including 3,757 HPV-positive patients, 514 (11%)

TABLE 4. Number and Estimated Immediate Risk for CIN3+ for Combination of Extended HPV Genotyping and Cytology in the STudying Risk to Improve DisparitiES (STRIDES) Cohort (*n* = 1,208)

Baseline covariate	*n*	CIN3+ cases	CIN3+ immediate risk
ASC-US +/HPV16	104	38	36.5%
NILM/HPV16	99	7	7.1%
ASC-US+/HPV18	32	0	0
NILM/HPV18	57	1	1.8%
ASC-US+/HPV other[a]	245	31	12.7%
NILM/HPV other	505	1	0.02%
ASC-US+/HPV59/56/66	44	0	0
NILM/HPV59/56/66	122	0	0

[a]Other defined as HPV 45,33/58, 31, 52/35/39/68, and 51.

TABLE 5. Extended HPV Genotyping and Dual Stain in the STRIDES Cohort

Baseline covariate	N	CIN3 + [a] cases	Immediate risk for CIN3+
Dual Stain +/HPV16	**122**	**40**	**32.8%**
Dual Stain -/HPV16	**76**	**3**	**3.8%**
Dual Stain +/HPV18	**40**	**1**	**2.5%**
Dual Stain -/HPV18	**47**	**0**	**0%**
Dual Stain +/HPV other[b]	**312**	**30**	**9.6%**
Dual Stain -/HPV other	**411**	**2**	**0.5%**
Dual Stain +/HPV59/56/66	**34**	**0**	**0%**
Dual Stain -/HPV59/56/66	**126**	**0**	**0%**

[a]CIN3, adenocarcinoma in situ, or cancer.

[b]Other defined as HPV 45,33/58, 31, 52/35/39/68, and 51.

TABLE 6. Summary of Management With Extended Genotyping When Used With Cotesting or Cytology Triage of Primary HPV Testing for Patients Undergoing Screening and Follow-Up of Low-Grade Abnormalities.

	Current HPV	Current cytology	Past results	Management
HPV 16/18	16	HSIL[1]	N/A[2]	Treatment preferred; colposcopy acceptable
	16	ASC-H[3]	N/A	Treatment or colposcopy
	16	NILM,[4] ASC-US,[5] LSIL,[6] AGC[7], or no cytology	N/A	Colposcopy[8] *with collection of cytology if not already done*
	18	HSIL	N/A	Treatment or colposcopy
	18	NILM, ASCUS, LSIL, ASC-H, AGC, or no cytology	N/A	Colposcopy[8] *with collection of cytology if not already done*
HPV 45,33/58, 31, 52/35/39/68, 51 **Untyped or "other" types when 16 and 18 are not present**	45,33/58, 31, 52/35/39/68, 51 or untyped/other	HSIL, ASC-H, AGC	N/A	Colposcopy[8,9]
	45,33/58, 31, 52/35/39/68, 51	ASC-US or LSIL	N/A	Colposcopy
	Untyped/other	ASC-US or LSIL	Documented HPV negative screen in past 5 years or colposcopy <CIN2[10] in past year	Repeat HPV test in 1 year
	Untyped/other	ASC-US or LSIL	Any history other than above	Colposcopy
	45,33/58, 31, 52/35/39/68, 51 or untyped/other	NILM	Normal[11] or colposcopy <CIN2 within past year	Repeat HPV test in 1 year
	45,33/58, 31, 52/35/39/68, 51 or untyped/other	N/A	HPV+ without colposcopy (i.e. current test is 2nd consecutive HPV+)	Colposcopy
HPV 59/56/66	59/56/66	ASC-H, AGC, or HSIL[12]	N/A	Colposcopy[8]
	59/56/66	NILM, ASC-US, LSIL or no cytology[12]	Normal or colposcopy <CIN2 within past 1 year	Repeat HPV test in 1 year
	59/56/66	N/A	HPV+ without colposcopy (i.e. current test is 2nd consecutive HPV+)	Colposcopy

For patients with a history of high-grade histology or cytology or following treatment, 2019 guidelines should be followed, but for those individuals, colposcopy is recommended for any HPV+ result and for all cytology LSIL or higher (even if HPV-negative).

[a]High grade squamous intraepithelial lesion.

[b]N/A: not applicable; test result, if obtained, would not affect management.

[c]Atypical squamous cells, cannot exclude HSIL.

[d]Negative for intraepithelial lesion or malignancy.

[e]Atypical squamous cells of undetermined significance.

[f]Low-grade squamous intraepithelial lesion.

[g]Atypical glandular cells.

[h]Endometrial biopsy recommended for an AGC result if risk factors for endometrial cancer are present (eg, age 35 years or older, obesity, irregular bleeding, anovulation) or if atypical endometrial cells are present.

[i]Colposcopy or treatment is acceptable for results of untyped HPV with ASC-H or HSIL cytology.

[j]Cervical intraepithelial neoplasia grade 2 or less severe.

[k]Normal screening history per patient or documented in medical record.

[l]Cytology triage is not recommended for primary HPV screening with results positive for HPV59/56/66; this guideline may be used if cytology results are obtained.

tested positive for HPV56/59/66 (Table 2). Among those, only 6 CIN3+ cases were diagnosed over 3 years (4 prevalent and 2 incident cases). The immediate CIN3+ risk was 0.8% and 3-year risk was 1.4%, leading to a recommendation of a 1-year return. Adding a triage test with dual stain (positive or negative) or cytology (dichotomized as NILM or ASC-US+) did not change management, as risks remained below the colposcopy threshold for individuals with dual stain-positive or ASC-US+ results (Tables 2 and 3). Findings were similar in the STRIDES cohort (Tables 4 and 5). Data on CIN3+ risk after repeated positivity for HPV56/59/66 were limited; therefore, the 2019 Guidelines for colposcopy after 2 consecutive HPV-positive results were applied.

Recommendation #5: In a Screening Setting Using Cotesting, for Patients Who Test Positive for HPV Types 56/59/66 and No Other Carcinogenic Types, 1-Year Return Is Recommended for NILM, ASC-US, and LSIL, and Colposcopy Is Recommended for ASC-H, AGC, HSIL, or Carcinoma. (AII) At the 1-Year Follow-Up, Colposcopy Is Recommended if HPV Results Are Positive for Any HPV Type or if Cytology Results Are ASC-H, AGC, HSIL, or Carcinoma. (CIII)

Rationale. Risks were <4% for those testing positive for HPV types 56/59/66 with NILM, ASC-US, or LSIL cytology (Tables 2 and 4). Risk data were limited for individuals

TABLE 7. Summary of Management With Extended HPV Genotyping and p16^{ink4a}/Ki-67 Dual Stain (DS) for Patients Undergoing Screening and Follow-Up of Low-Grade Abnormalities.

	Current HPV	Current DS result	Past history	Management
HPV 16/18	16 and/or 18	N/A[1]	N/A	Colposcopy *with collection of cytology if available*
HPV 45,33/58, 31, 52/35/39/68, 51 **Untyped or "other" types when 16 and 18 are not present**	45,33/58, 31, 52/35/39/68, 51 or untyped/other	DS Positive[2]	N/A	Colposcopy
	45,33/58, 31, 52/35/39/68, 51 or untyped/other	DS Negative[3]	Normal[4] or colposcopy <CIN2[5] within past 1 year	Repeat HPV test in 1 year
	45,33/58, 31, 52/35/39/68, 51 or untyped/other	N/A	HPV+ without colposcopy (i.e. current test is 2nd consecutive HPV+)	Colposcopy
HPV 59/56/66	59/56/66	N/A	Normal or colposcopy <CIN2 within past 1 year	Repeat HPV test in 1 year[2]
	59/56/66	N/A	HPV+ without colposcopy (i.e. current test is 2nd consecutive HPV+)	Colposcopy

For patients with a history of high-grade histology or cytology or following treatment, 2019 guidelines should be followed, but for those individuals, colposcopy is recommended for any HPV+ result and for all cytology LSIL or higher (even if HPV negative).

[a]N/A: not applicable; test result, if obtained, would not affect management.

[b]If cytology is performed in a cotesting setting, colposcopy is recommended for all results including NILM.

[c]If cytology is performed in a cotesting setting, repeat HPV testing in 1 year is recommended for NILM, ASCUS, or LSIL results. Colposcopy is recommended for ASC-H, AGC, or HSIL results.

[d]Normal screening history per patient or documented in medical record.

[e]Cervical intraepithelial neoplasia grade 2 or less severe.

undergoing cotesting with cytology results of ASC-H, AGC, HSIL, and HPV56/59/66. Therefore, 2019 Guidelines apply, and colposcopy is recommended for individuals with ASC-H, AGC, or HSIL results.

Recommendation #6: During Surveillance, When Patients Are Being Followed Who Had No Preceding High-Grade Cytology (ASC-H, AGC, HSIL, or Carcinoma) or Histology (CIN2, CIN3, or AIS), Use of Extended Genotyping Results According to the Guidelines Outlined for Screening Is Acceptable. (CIII) When High-Grade Cytology or Histology Results Are Present and in the Posttreatment Setting, Management Using the 2019 Guidelines Is Recommended. (CIII)

Rationale. Estimates for HPV type-specific downstream CIN3+ risks either are not available or are insufficient to allow derivation of risk-based recommendations for persons undergoing multiple rounds of testing. In the screening setting, extended genotyping provides greater risk stratification than pooled HPV testing (Tables 2–5). It follows that extended genotyping can be used like limited genotyping in follow-up after colposcopy without high-grade cytology or histology. Data are insufficient to change management following high-grade cytology or histology or in the posttreatment setting, and therefore the 2019 Guidelines were retained. The 2019 posttreatment guidelines recommend colposcopy for all HPV-positive results (regardless of cytology or dual stain result), for HPV-negative results if cytology is ASC-H or higher, and for cytology results of LSIL or worse absent HPV testing.

TYPE-SWITCHING VERSUS TYPE-SPECIFIC PERSISTENCE. In theory, individuals who clear one HPV type and acquire a different type have a new incident infection, which would be expected to confer lower CIN3+ risk than a persistent infection. We had insufficient data on the impact of type-specific persistence or switching on CIN3+ risk to change the 2019 recommendation. Type persistence is more common than type switching.[22,23] In addition, although CIN3+ risks are highest with type persistence, type switching confers a higher CIN3+ risk than reversion to HPV-negative. Because data on CIN3+ risk after repeated positivity for HPV 45, 33/58, 31, 52, 35/39/68, and 51 are limited and distinguishing type-switch from type-persistent within a single channel with multiple types (eg, 33/58) is not possible, the 2019 guidelines for colposcopy after 2 consecutive HPV-positive results were applied. Of note, because triage testing is recommended for these HPV types, guidelines are the same in the primary HPV and cotesting settings.

In situations not covered by the recommendations above, clinical judgment and shared decision-making should consider the 2019 Guidelines and 2017 Colposcopy Standards.[5,17] In general, patients with prior abnormal HPV, cytology, dual stain, or biopsy results are at higher risk of CIN3+ and may benefit from

additional testing, whereas those with prior negative HPV test results are at lower risk and so are less likely to benefit from additional testing. Additional guidelines may follow as new data allow more robust risk estimation.

SUMMARY AND FUTURE DIRECTIONS

These recommendations from the Enduring Consensus Cervical Cancer Screening and Management Guidelines process apply to extended genotyping in cervical screening and management for clinicians and patients who choose to use the Onclarity HPV Assay (Tables 6 and 7). Extended genotyping has the potential to refine management of patients with carcinogenic HPV types, routing those with the highest risk carcinogenic types (16/18) to colposcopy and those with lowest risk (56/59/66) carcinogenic types to repeat testing in 1 year. For those with other carcinogenic types, triage using cytology or dual stain identifies high-risk patients likely to benefit from colposcopy while decreasing low-yield colposcopy. Patients who test positive for multiple carcinogenic HPV types or whose HPV infection is reported as a panel of multiple types should be managed according to the highest risk type identified. Management recommendations based on risk estimates calculated from primary data in 2 distinct, diverse populations are summarized in Tables 6 and 7.[13–16]

Extensive global data on HPV type attribution in cervical cancer form the foundation of these management recommendations, as carcinogenicity varies substantially by HPV type.[1] Four main risk groups of carcinogenic types are distinguished; these can be used to optimize management recommendations. However, current FDA-approved extended genotyping assays are not fully aligned with these groupings. For example, both Onclarity and Alinity m combine HPV35 with less carcinogenic types.

Current recommendations underscore the importance of evaluating new technologies for cervical screening and management in diverse populations. Positive Onclarity channel HPV35/39/68 results were associated with higher CIN3+ risk in the majority Black STRIDES cohort. This is likely related to higher HPV35 prevalence in individuals with African ancestry, reflecting the higher risk associated with HPV35. To avoid exacerbating racial disparities in cervical cancer risk, a triage test should be performed for patients who test positive for HPV35/39/68. Since HPV39 and HPV68 are from the lowest type group according to the IARC ranking, a channel without HPV35 would likely be recommended to have 1-year retesting, like HPV56/59/66. Assay manufacturers may consider reconfiguring how types are aggregated in reporting to provide more efficient clustering by risk. With different and optimized genotype groupings, genotype-specific recommendations may change in the future. Guidelines will require revisions when longer follow-up data become available, particularly in surveillance settings. New management approaches arising from new evidence should be welcomed. At the same time, larger datasets may still not allow precise risk estimates for rare scenarios, such as defining CIN3+ or cancer risk for uncommon combinations of HPV genotype and triage test results.

Other areas will require additional research to optimize recommendations. Currently, colposcopy is recommended for all individuals who test HPV-positive twice consecutively. In part, this recommendation arises from clustering in bundled channels of current assays, which precludes distinction among individuals with type-specific persistence and switching of types within a cluster. In addition, current data are not sufficient to precisely estimate the risk associated with type switching versus type persistence.[22,23] Until research can more accurately define risks associated with HPV genotype switching over time, the recommendation for colposcopy is a conservative measure for persistent HPV positivity.

Although risk of CIN3+ is widely accepted to benchmark clinical management recommendations, it is important to emphasize that several of the lowest risk carcinogenic types may cause CIN3 yet rarely progress to cancer, suggesting that CIN3 is not an equally strong surrogate for cervical cancer across HPV genotypes.[1]

The current recommendations are intended to guide clinical management among those choosing to use extended genotyping assays; they do not constitute a preference or recommendation for one test or combinations of tests over others. Several alternatives are currently available for risk stratification of individuals who test positive for HPV, including dual stain, cytology, and partial genotyping. We did not directly compare test accuracy, efficiency, or cost-effectiveness of various strategies when developing recommendations for extended genotyping; comparative trials would be needed to assess the accuracy and efficiency of various risk assessment strategies for individuals who test positive for HPV. Costs will vary, and laboratories and clinical practices can utilize extended genotyping risk estimates and resource utilization metrics to inform considerations about whether and how to incorporate extended genotyping into clinical practice. Importantly, extended genotyping is provided by HPV tests as part of the initial result, not as a separate test. Extended genotyping provided by screening tests can be combined with cytology or dual stain to refine management.

Self-collection for HPV testing has been proposed as an alternative to clinician collection. However, this evidence review relied on clinician-collected samples obtained at cervical speculum examination. Guidelines for self-collection are in development through the Enduring Guidelines process and will address the use of extended genotyping in these settings.

Extended genotyping is an informative risk stratification assay for managing patients with positive HPV test results in cervical cancer screening and surveillance that can be incorporated into clinical management strategies. Existing clinical decision support tools will incorporate recommendations for use of extended genotyping.

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