Enduring Guidelines Extended Genotyping Evidence Summary and Proposed Recommendations

Introduction

The Enduring Consensus Cervical Cancer Screening and Management Guidelines effort (Enduring Guidelines) is a standing committee to provide regular updates of the 2019 ASCCP Risk-Based Management Consensus Guidelines for Abnormal Cervical Cancer Screening Tests and Cancer Precursors[1] (hereafter referred to as 2019 Guidelines) for new technologies and approaches that were not included in the 2019 guidelines process. The Enduring Guidelines effort includes experts in cervical cancer prevention, as well as representatives from 19 national organizations including patient advocacy groups.[2] More details are available at: https://dceg.cancer.gov/enduring-guidelines and at https://www.asccp.org/management-guidelines.

Risk-based approach: Following the approach of the 2019 management guidelines, a risk-based approach is used to determine clinical actions. Specifically, the immediate and 3-year or 5-year risk of developing CIN3, AIS, or cancer (CIN3+) is estimated using prevalence-incidence mixture models.[3] Resulting clinical actions are based on risk thresholds determined by the 2019 guidelines.[1] Thresholds have been developed for return in 5 years, return in 3 years, return in 1 year, colposcopy, colposcopy or expedited treatment, and expedited treatment.[1,3,4] The risk threshold that is used most throughout the remainder of this document is the colposcopy risk threshold: colposcopy is recommended when the immediate risk of CIN3+ is 4-24%. As an extension to the 2019 process, 3-year risk thresholds have been developed to accommodate data on new technologies with shorter durations of follow-up.[5] When sufficient 5-year follow-up data are available, a 5-year risk threshold is used. For technologies evaluated in studies with shorter duration of follow-up, like the extended genotyping data summarized here, 3-year risk thresholds are used.

Exceptions to risk thresholds: During the 2019 process, exceptions were made to risk thresholds for certain situations. One example is an HPV18+ test result, which has an elevated cancer risk compared to the risk of CIN3. The decision was made to recommend colposcopy for HPV18+ due to elevated cancer risk although the CIN3+ risk was below the colposcopy threshold.[1]

Terminology and evidence evaluation metrics can be found in the Glossary at the end of this document.

Background on Extended Genotyping and proposed recommendations

Background

Among over 200 known HPV genotypes, a small group of about 30 HPV genotypes may infect the cervical mucosal epithelium. Based on large world-wide epidemiologic data and mechanistic evidence, twelve of these types are considered carcinogens (IARC class 1) and one is considered a probable carcinogen (IARC class 2A).[6] The risk of cervical cancer varies substantially across these types, with HPV16 and HPV18 accounting for 60-70% of all cancers worldwide, while other types having much smaller contributions. These differences in cancer attribution are also reflected by differences in progression risk from HPV infection to precancer. In contrast, the population prevalence alone is not an indicator of carcinogenicity: there are many types that are common in the population but rarely cause cancer. Table 1 summarizes the cancer attribution and risk of progression to precancer for 13 carcinogenic types.[7] Four major groups can be distinguished, HPV16, HPV18/45, HPV16-related types, and remaining lower risk types.

Figure 1: Carcinogenic HPV genotypes with cancer attribution and risk of precancer progression

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	Lower risk
51	1.2	1.1	Lower risk
59	1.1	0.9	Lower risk
56	0.9	0.8	Lower risk
68	0.6	1.0	Lower risk

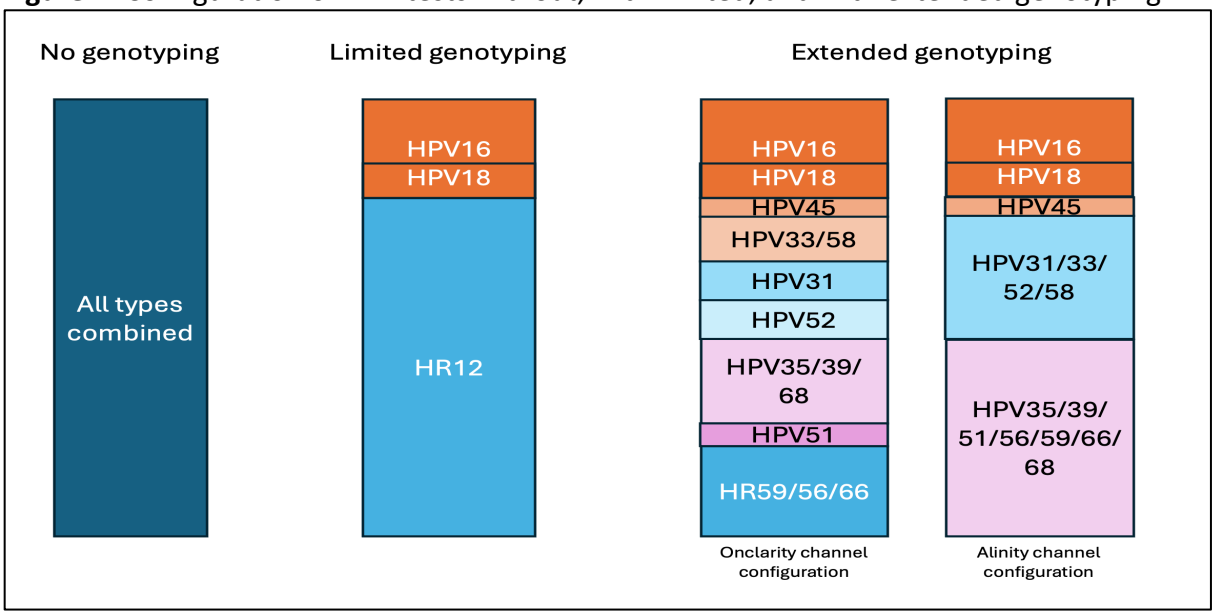
Development of cervical cancer follows a well-understood multi-step carcinogenic process. This process starts with infection of the cervical epithelium with HPV. While most infections are controlled by the host's immune system and become undetectable within 1-2 years, a small subset of infections persists longer, which can lead to transformation of epithelial cells.[7–9] With further expansion of transformed cell clones, cervical precancer develops, which is the primary

target of cervical screening programs. If untreated, a subset of cervical precancers will become invasive cancers. Generally, types accounting for a higher proportion of cancers, like HPV16, are more likely to persist, progress to precancer, and to become invasive cancer. This has important consequences for clinical management: Repeated detection of the same HPV type is associated with much higher risk of cervical precancer compared to a single time point detection. Limited data are available to evaluate management of repeated HPV-positivity where one type disappears and another type appears ("type switch"); a few studies have reported a lower risk than type-specific persistence, but higher risk than type disappearance.[10,11] Types from the lower risk carcinogenic group (blue in Figure 1) may be common in the population and may occasionally cause morphologically appearing precancers, but rarely cause cancers. Therefore, not all morphologically defined cervical precancers should be considered equal; a CIN3 caused by HPV16 has a much higher likelihood of progressing to cancer than a morphological CIN3 from the lower risk group.

HPV tests

Given these differences in cancer and precancer risk, HPV assays have been developed that can separate out different subsets of HPV genotypes. For logistical reasons, HPV assays often combine types in pooled channels. Examples of different types of carcinogenic HPV tests are shown in Figure 2. "No genotyping" refers to a test that tests for all types combined, not separating out any individual or groups of types. "Limited genotyping" refers to the separate detection of HPV16 and HPV18 (sometimes including HPV45) while all other types are detected as a pool (referred to below as HR12). "Extended genotyping" refers to identification of individual types or groups of types beyond just HPV16, 18, and 45. The two current FDA-approved versions of HPV test with extended genotyping are shown as examples.

Figure 1: Configuration of HPV tests without, with limited, and with extended genotyping



Type configurations are shown for different types of HPV assays. Types combined in the same box are included in the same channel. HR12 refers to 12 other carcinogenic types (HPV31, 33,

35, 39, 45, 51, 52, 56, 58, 59, 66, 68). Of note, the classification of carcinogenic types by the International Agency for Research on Cancer (IARC) has changed over time. HPV66 was considered a type 1 carcinogen during a period when several new assays were developed. For that reason, HPV66 is included in many of these assays. With more data available, HPV66 is no longer considered a type 1 carcinogen and should not be included in future assays.[7,12] Importantly, the extended genotyping information reviewed here is provided by the screening HPV test; extended genotyping is not intended to be run as an additional test after an initial positive HPV result. Reflex triage using cytology or dual stain can be conducted out of provider-collected samples for extended genotyping HPV testing; collection of additional samples for triage testing is not required.

Evidence review

Extended genotyping recommendations are supported by a wealth of natural history data summarized in recent reviews and systematic evidence evaluations that demonstrate the risk of cervical precancer and cancer for different HPV genotypes.[6–8] Additional supportive data come from the NCI-Kaiser Permanente collaboration that includes a large population with HPV genotyping data which informed the 2019 guidelines and provides data on type persistence and progression based on different HPV genotyping tests.[9,13]

Study populations for evaluation of Onclarity

In addition to the evidence review, risk estimates for extended genotyping based on the Onclarity assay were calculated to support the current recommendations. Risks were estimated in two distinct populations, from Kaiser Permanente Northern California (KPNC) and from Mississippi (STRIDES Cohort). There is evidence from world-wide data that the attribution of some HPV types to cancer differs somewhat across populations with different ancestry. For example, HPV35 has a slightly higher attribution to cervical cancer in women with African ancestry compared to other populations. Therefore, the inclusion of both studies, from KPNC and Mississippi, is critical to ensure that recommendations for new technologies or management approaches provide a benefit for individuals with diverse backgrounds.

Data from Kaiser Permanente Northern California (KPNC) include a subset of the IRIS Cohort[14] including individuals undergoing co-testing for cervical screening with Surepath cytology and hc2 in 2017. Individuals were followed through Fall 2022, with a high follow-up rate for baseline risk and through 3 years. The KPNC population includes a diverse population from California (44% White, 24% Hispanic, 18% Asian/Pacific Islander and 8% Black), all of whom are members of Kaiser Permanente.

The STRIDES cohort in Mississippi[15] includes individuals undergoing co-testing for cervical screening using Thinprep cytology who tested positive for HPV (cobas) in 2018-2019. Individuals were followed through Fall 2022. The STRIDES population includes a diverse population from Mississippi (60% Black, 26% White), over half of whom reside in rural areas, and two-thirds of whom receive publicly funded screening services.

Key points

- These recommendations only apply to FDA approved assays that provide extended genotyping (EG). The performance of other, non-FDA approved EG assays may not be similar, and these assays should not be used for clinical care. The generalizability may be particularly limited when other assays group HPV types differently.
- These recommendations apply only to results obtained in asymptomatic women and women with intact cervices. Symptomatic women should be managed according to relevant protocols.
- Because of limited data availability, estimates for downstream CIN3+ risk either are not available or are insufficient to allow derivation of risk-based recommendations for persons undergoing multiple rounds of testing or for specific clinical scenarios related to HPV genotyping results alone in serial samples or in combination with other tests. In situations not covered by existing recommendations, clinical judgment and shared decision making should consider the 2019 ASCCP Risk-Based Management Consensus Guidelines and 2017 Colposcopy Standards, where applicable. Additional guidelines will follow when more data become available allowing more robust risk estimation.

The evidence summary and proposed guidelines cover two areas. **Section 1** outlines general principles for extended genotyping that will apply across all FDA-approved extended genotyping tests. **Section 2** applies specifically to the HPV genotype groupings available in the Onclarity assay, which was the only FDA-approved test when the evidence review for extended genotyping started. Recently, another test (Alinity assay) has been approved by the FDA which has a different genotype configuration. Recommendations for this test may be developed when sufficient data supporting risk-based guidelines become available.

Proposed guidelines and data summary

Section 1. General Principles of Extended Genotyping

PROPOSED RECOMMENDATION #1: ***HPV extended genotyping is acceptable to guide clinical management in the setting of a positive HPV test result. (AII)***

Rationale:

Extended genotyping assays have been approved by the FDA after demonstrating safety and validity. Extended genotyping results may provide additional risk stratification beyond a pooled HR12 result. More refined risk levels may allow for more precise allocation of HPV-positive individuals to colposcopy, triage, or 1-year follow-up. Extended genotyping is applicable to currently recommended screening settings: primary HPV testing and co-testing. In addition, for settings using cytology with HPV triage of ASC-US results, extended genotyping may be applied.

PROPOSED RECOMMENDATION #2: ***When multiple types are reported, management according to the type with highest cancer risk is recommended following the hierarchy 16, 18, 45, 33, 31, 52, 58, 35, 39, 51, 59, 56, 68, 66. (AII)***

Rationale:

High risk HPV types vary in their carcinogenicity. IARC has assessed the carcinogenicity of a broad range of HPV types (Figure 1).[7] From their results this hierarchical ranking can be derived. There is no indication for synergy between types (e.g., additional risk when multiple types are present). Therefore, when channels contain multiple types, management should follow the type of highest carcinogenicity.

Section II. The remainder of this document is specific to FDA-approved assays with the following genotype groups: HPV 16, HPV 18, HPV 45, HPV 33/58, HPV 31, HPV 52, HPV 35/39/68, HPV 51, HPV 59/56/66 (e.g., the commercially available BD Onclarity assay).

General principles underlying the clinical recommendations:

Risk stratification data were available for the groupings above. Risks associated with individual HPV genotypes and type groupings were examined in the IRIS and STRIDES cohorts. When higher risk was noted in either cohort for a specific genotype or type grouping (e.g., for HPV35 and HPV51 which were more common in the Mississippi population), management according to the higher risk level was recommended to ensure safety. To simplify guidelines, channels for which risk estimates suggested similar management were grouped together.

The 2019 guidelines already include risk-based management for HPV types 16 and 18,[1] and data reviewed for these guidelines did not indicate a need to revise these guidelines. The new proposed guidelines below focus on two genotype groups beyond HPV16/18: (1) HPV 45,33/58, 31, 52/35/39/68, 51 and (2) HPV 59/56/66.

Use of extended genotyping in screening settings

PROPOSED RECOMMENDATIONS #3: ***In a screening setting using primary HPV testing, for patients who test 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: In the worldwide survey data, HPV 56, 59, and 66 together are responsible for 2% of cancers.[7] In the IRIS cohort including 3757 HPV-positive patients, 514 (11%) tested positive for HPV56/59/66 (Table 1). Among the 514, only 6 CIN3+ cases were diagnosed over 3 years of follow-up (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 ASCUS+) did not change management, as risks remained below the colposcopy threshold for individuals with Dual Stain positive or ASCUS+ results (Tables 1 and 3). Findings were similar in the STRIDES cohort (Table 2 and 4). Data on CIN3+ risk after repeated positivity for HPV56/59/66 were limited, therefore the 2019 guidelines for colposcopy in the setting of 2 consecutive HPV-positive results were used.[16]

PROPOSED RECOMMENDATION #4***: In a screening setting using co-testing, 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. (CIII)***

Rationale: Risks are <4% for those with NILM, ASCUS, or LSIL cytology (see Table 1). Risk data are limited for individuals undergoing co-testing who have cytology results of ASC-H, AGC, HSIL and are positive for HPV56/59/66. Therefore, 2019 guidelines are used, and colposcopy is recommended for individuals with ASC-H, AGC, HSIL results.[1]

PROPOSED RECOMMENDATION #5: ***In a screening setting using primary HPV or co-testing, for patients who test positive for HPV 45,33/58, 31, 52/35/39/68, 51 or combinations thereof, but negative for HPV16 and HPV18, triage with DS or cytology is recommended. 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. (AII) 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. (CIII)***

Rationale: In the worldwide survey data, HPV 45,33/58, 31, 52/35/39/68, 51 together are responsible for 28% of cancers.[7] In the IRIS cohort of 3757 HPV-positive patients, 2564 (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 with Dual Stain or cytology provided excellent 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 ASCUS or higher (Tables 1 and 3). Findings were similar in the STRIDES cohort (Tables 2 and 4). Data on CIN3+ risk after repeated positivity for HPV 45,33/58,

31, 52/35/39/68, 51 are limited, therefore the 2019 guidelines for colposcopy in the setting of two consecutive HPV-positive results are used.[16] Of note, because triage testing is recommended for these HPV types, guidelines are the same in the primary HPV and co-testing settings, and also can be used for HPV triage of ASC-US results.

Use of extended genotyping in follow-up after abnormal results, colposcopy, or treatment (surveillance settings)

PROPOSED RECOMMENDATION #6: When patients are being followed after colposcopy without high-grade cytology or histology, it is acceptable to use extended genotyping according to the guidelines outlined for screening. (CIII) When high-grade cytology or histology results are present or in the post-treatment setting, management using the 2019 guidelines is recommended. (CIII)

Rationale:

Data in the screening setting indicate that extended genotyping provides greater risk stratification than pooled HPV-positive results (Tables 1-4). Therefore, it follows that extended genotyping can be used in the settings of follow-up after colposcopy without high-grade cytology or histology.[4] Data are insufficient to change management following high-grade cytology or histology or in the post-treatment setting therefore the 2019 guidelines are used.[1]

Supporting evidence for recommendations 3-5

The tables below outline the evidence from the IRIS and STRIDES cohorts related to extended genotyping. The Onclarity assay was used in these cohorts.

Table 1 illustrates the absolute number as well as estimated immediate CIN3+ risks and 3-year cumulative CIN3+ risks for combinations of extended genotyping and cytology results in the IRIS cohort. Cytology is dichotomized as normal (NILM) and abnormal (ASC-US or higher, denoted as ASCUS+). Risk-based management recommendations are also presented, using the immediate CIN3+ risk of 4% as the colposcopy threshold. The Management Confidence Probability (calculated based on the immediate and 3-year risk in relation to risk thresholds) represents the likelihood that the same management would be recommended if the risk were to be re-estimated for a similar sample. In Table 1, risks are influenced by both genotype and cytology result, with the highest risk for ASCUS+ cytology HPV16 positive (20.5%) and the lowest risk for NILM cytology HPV59/56/66 positive (0.4%). Both ASCUS+ and NILM results meet or exceed the colposcopy threshold when HPV 16 or 18 are present. Neither ASCUS+ nor NILM results meet the colposcopy threshold when HPV59/56/66 is present. Cytology results provide meaningful risk stratification with regard to the colposcopy threshold when other types are present.

Table 1: Extended genotyping and cytology in the IRIS cohort (N= 3757)

Baseline covariate	N	CIN3+ Cases	CIN3+ Immediate Risk	CIN3+ 3yr Cumulative Risk	Management recommendation	Management Confidence Probability
ASCUS+/HPV16	360	74	20.5%	24.1%	Colposcopy	98%
NILM/HPV16	185	23	8.4%	11.5%	Colposcopy	99%
ASCUS+/HPV18	89	11	10.4%	16.0%	Colposcopy	98%
NILM/HPV18	56	4	4.0%	8.5%	Colposcopy	51%
ASCUS+/ HPV other*	1106	68	5.0%	6.4%	Colposcopy	94%
NILM/HPV other*	926	15	1.8%	2.9%	1-year return	100%
ASCUS+/HPV59/56/66	297	3	1.1%	1.8%	1-year return	96%
NILM/HPV59/56/66	217	3	0.4%	0.9%	1-year return	88%

*Other defined as HPV 45,33/58, 31, 52/35/39/68, 51; see data appendix for estimates stratified by abnormal cytology result

Table 2 illustrates the absolute number as well as estimated immediate CIN3+ risks for combinations of extended genotyping and cytology results in the STRIDES cohort. Overall, similar patterns are seen for the STRIDES and IRIS cohorts, specifically high risk for HPV 16 and ASCUS+ cytology, low risk for HPV 59/56/66 regardless of cytology result, and meaningful risk stratification to above or below the colposcopy threshold based on cytology result when other types are present.

Table 2: Extended genotyping and cytology in the STRIDES cohort

Baseline covariate	N	CIN3+ Cases	CIN3+ Immediate Risk
ASCUS+/HPV16	104	38	36.5%
NILM/HPV16	99	7	7.1%
ASCUS+/HPV18	32	0	0
NILM/HPV18	57	1	1.8%
ASCUS+/HPV other*	245	31	12.7%
NILM/HPV other*	505	1	0.02%
ASCUS+/HPV59/56/66	44	0	0
NILM/HPV59/56/66	122	0	0

*Other defined as HPV 45,33/58, 31, 52/35/39/68, 51

Table 3 illustrates the absolute number as well as estimated immediate CIN3+ risks and 3-year cumulative CIN3+ risks for combinations of extended genotyping and Dual Stain results in the IRIS cohort. Dual Stain positive results meet or exceed the colposcopy threshold when HPV 16 or 18 are present. Although Dual Stain negative results fall below the colposcopy threshold, prior Dual Stain recommendations considering these findings noted limited data on invasive carcinomas, especially adenocarcinomas, and therefore colposcopy was recommended until more follow up data become available.[17] This is represented by the *Special Situation* notation. Neither Dual Stain positive nor negative results meet the colposcopy threshold when HPV59/56/66 is present. Dual Stain results provide meaningful risk stratification to above or below the colposcopy threshold when other types are present.

Table 3: Extended genotyping and Dual Stain in the IRIS cohort

Baseline covariate	N	CIN3+ Cases	CIN3+ Immed. Risk	CIN3+ 3yr CR	CIN3+ management	CIN3+ management Confidence Probability
DS+/ HPV16	373	90	23.4%	27.4%	Colposcopy	75.8%
DS-/ HPV16	172	7	1.9%	3.7%	*Special Situation:* Colposcopy	N/A
DS+/ HPV18	94	14	11.7%	18.2%	Colposcopy	98.6%
DS-/ HPV18	51	1	0.8%	3.4%	*Special Situation:* Colposcopy	N/A
DS+/ HPV other*	1039	77	6.7%	8.5%	Colposcopy	100.0%
DS-/ HPV other*	993	6	0.5%	1.1%	1-year return	98.9%
DS+/HPV59/56/66	170	4	2.2%	3.2%	1-year return	93.9%
DS-/ HPV59/56/66	344	2	0.1%	0.5%	1-year return	100.0%

*Other defined as HPV 45,33/58, 31, 52/35/39/68, 51

Table 4 illustrates the absolute number as well as estimated immediate CIN3+ risks for combinations of extended genotyping and Dual Stain results in the STRIDES cohort. Overall, similar patterns are seen for the STRIDES and IRIS cohorts, specifically high risk for HPV 16 and Dual Stain positive, low risk for HPV 59/56/66 with any Dual Stain result, and meaningful risk stratification to above or below the colposcopy threshold by Dual Stain result when other types are present.

Table 4: Extended genotyping and Dual Stain in the STRIDES cohort

Baseline covariate	N	CIN3+ Cases	CIN3+ Immediate Risk
DS+/HPV16	122	40	32.8%
DS-/HPV16	76	3	3.8%
DS+/HPV18	40	1	2.5%
DS-/HPV18	47	0	0%
DS+/HPV other	312	30	9.6%
DS-/HPV other	411	2	0.5%
DS+/HPV59/56/66	34	0	0%
DS-/HPV59/56/66	126	0	0%

*Other defined as HPV 45,33/58, 31, 52/35/39/68, 51

Repeated HPV detection

As outlined in the background section above, repeated detection of the same HPV type is associated with highest risk of progression to precancer while single time point detection followed by disappearance is associated with lowest risk of cancer.[7,8] Fewer data are available to assess the risk of precancer associated with repeated HPV detection of different HPV genotypes ("type switch"). Furthermore, type switching cannot be excluded when a pooled channel repeatedly tests positive. Studies have shown that disappearance of one type and appearance of another type is associated with a lower risk of precancer compared to same-type persistence, but with a higher risk compared to disappearance, ranging from 1.7% to 20% short term risk of CIN3+ for individuals with a type switch.[10,11] Thus, currently, there are not sufficient data to recommend different management strategies for same-type repeat detection vs. type switch. Several efforts to pool data across multiple studies are underway to address this question and may lead to updated recommendations in the future.

Evaluation of immediate colposcopy referral versus reflex triage for HPV45

HPV45 is a genotype with relatively low population prevalence but a comparably high attribution to cervical cancer, ranked third among world-wide cancer attribution surveys. Immediate referral to colposcopy is recommended for HPV16 and HPV18, the two genotypes with highest attribution to cancers. HPV45 is also one of three HPV genotypes (HPV16, HPV18, and HPV45) strongly associated with cervical adenocarcinoma. Data for HPV16 and HPV18, but not HPV45, show that cytology performs poorly at detecting glandular precursors caused by these types (Table 5). Specifically, while HPV16+ NILM was associated with 9 prevalent cases of AIS+ cases including 3 prevalent adenocarcinomas, and HPV18+ NILM was associated with 5

prevalent AIS+ cases including 1 prevalent adenocarcinoma, no prevalent cases of AIS or cancer were observed for HPV45-positive NILM women.

Table 5. Precancer and cancer outcomes in KPNC cohort by HPV type and cytology

HPV Genotype	Cytology	N	AIS + N	AIS+ Prev	AIS+ Inc	AdCa N	AdCa Prev	AdCA Inc	CIN3 + N	CIN3 + Prev	CIN3 + Inc	SCC N	SCC Prev	SCC Inc
HPV 16	NILM	1451	65	9	56	29	3	26	257	35	222	7	2	5
HPV 16	ASC-US+	2477	79	54	25	16	10	6	844	649	195	47	41	6
HPV18	NILM	482	32	5	27	7	1	6	26	6	20	2	0	2
HPV18	ASC-US+	587	61	46	15	19	17	2	73	52	21	6	4	2
HPV 45	NILM	391	3	0	3	1	0	1	18	0	18	0	0	0
HPV 45	ASC-US+	334	14	11	3	6	5	1	49	36	13	3	2	1
HPV 31/33/35/52/58	NILM	2279	3	1	2	0	0	0	198	27	171	4	1	3
HPV 31/33/35/52/58	ASC-US+	2709	2	2	0	0	0	0	459	352	107	13	12	1
HPV 39/51/56/59/66/68	NILM	2435	2	0	2	0	0	0	56	4	52	1	0	1
HPV 39/51/56/59/66/68	ASC-US+	2472	3	1	2	1	1	0	109	74	35	2	2	0

Data Appendix: Number of CIN3+ within genotype and cytology strata (IRIS/KPNC)

IRIS/Kaiser Permanente Northern California				
Baseline covariate	**N**	**CIN3+ Cases**	**CIN3+ Immediate Risk**	**CIN3+ 3yr Risk**
NILM/HPV16	**185**	**23**	**7.8%**	**10.8%**
ASCUS+/HPV16	**360 (66%)**	**74**	**20.5%**	**24.1%**
ASCUS/HPV16	154	23	12.1%	18.6%
LSIL/HPV16	126	10	7.2%	8.4%
HSIL/HPV16	80	41	57.7%	60.4%
NILM/HPV18	**56**	**4**	**4.3%**	**8.3%**
ASCUS+/HPV18	**89 (62%)**	**11**	**10.4%**	**16.0%**
ASCUS/HPV18	47	5	6.8%	15.7%
LSIL/HPV18	31	2	3.9%	5.5%
HSIL/HPV18	11	4	41.8%	46.6%
NILM/HPV other	**926**	**15**	**1.9%**	**2.9%**
ASCUS+/HPV other	**1106 (54%)**	**68**	**5.0%**	**6.4%**
ASCUS/ HPV other	545	26	3.1%	5.4%
LSIL/HPV other	430	9	1.7%	2.1%
HSIL/HPV other	131	33	23.7%	25.3%
NILM/ HPV59/56/66	**217**	**3**	**0.5%**	**0.9%**
ASCUS+/ HPV59/56/66	**297 (58%)**	**3**	**1.1%**	**1.8%**
ASCUS/ HPV59/56/66	151	0	0.8%	1.8%
LSIL/ HPV59/56/66	126	0	0.4%	0.6%
HSIL/ HPV59/56/66	20	3	7.1%	7.9%

* Other defined as HPV 45,33/58, 31, 52/35/39/68, 51. Insufficient data in STRIDES to estimate risk by abnormal cytology category.

GUIDELINES TERMINOLOGY, EVIDENCE EVALUATION, AND GLOSSARY

Terminology: As in prior guidelines,[1,18] 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

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

GLOSSARY

Dual Stain (DS): p16/Ki-67 Dual Stain (DS) is a cytology-based test for detection of cervical precancer that has been approved by the FDA for triage of positive test results in HPV screening and HPV-cytology co-testing. DS detects a marker of HPV-related oncogene activity (p16) and a marker of cell proliferation (Ki-67) which, when detected in the same cell, are associated with precancerous cellular changes (CIN3+). Dual stain results are reported as positive or negative.

Management Confidence Probability (%): This metric describes the likelihood that, if risk estimates were recalculated in a similar population, the clinical management recommendation would be the same.

Cervical Intraepithelial Neoplasia (CIN and CIN3+) CIN is a pathologic diagnosis of squamous cervical abnormalities detected on histopathologic analysis of a cervical biopsy, endocervical curettage (ECC) or excisional biopsies such as cold knife cone or Loop Electrosurgical Excision Procedure (LEEP). CIN terminology is a 3-tiered system (CIN1, CIN2, CIN3) but a 2-tier system (LSIL/HSIL) is now recommended. Both systems are currently in use by pathology laboratories. CIN1 in the 3-tiered system corresponds to LSIL in the 2-tiered system. CIN2 (when supported by p16 immunohistochemistry) and CIN3 in the 3-tiered system both correspond to HSIL in the 2-tiered system. **CIN3+**, used as the endpoint for risk estimates in this document, includes CIN3, AIS (adenocarcinoma in situ, a glandular cancer precursor), and cervical cancer.

The *Bethesda system* is a *system* for reporting cervical or vaginal cytologic diagnoses, used for reporting cervical cytology (Pap test) results. It was introduced in 1988 and revised in 1991, 2001, and 2014. The name comes from the location (*Bethesda*, Maryland) of the conference where this terminology was developed.

Cervical cytology terms:

- Negative for intraepithelial lesion or malignancy (NILM) *normal result*
- Atypical Squamous Cells of Uncertain Significance (ASCUS) *minimally abnormal result*
- Atypical Squamous Cells of Uncertain Significance cannot exclude high grade squamous intraepithelial lesion (SIL) (ASC-H) *has features of high grade SIL but not fully developed; considered as a high-grade result in risk estimates*
- Low grade Squamous Intraepithelial Lesion (LSIL) *minimally abnormal result that is the cytologic expression of HPV infection*
- High Grade Squamous Intraepithelial Lesion (HSIL) *considered as a high-grade result in risk estimates*
- Atypical Glandular Cells (AGC) are managed *as a high grade result, AGC reporting is subclassified in Bethesda by cell type (glandular, endocervical, endometrial) and further stratified by risk as "favor neoplastic" (higher risk) or "not otherwise specified/NOS" for glandular and endocervical cell types.*

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