2019 ASCCP Risk-Based Management Consensus Guidelines For Abnormal Cervical Cancer Screening Tests

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Disclosures

- DSMB: Inovio
- Consultant: Altum, DySiS

Objectives

1. Understand how HPV epidemiology drives risk-based cancer prevention
2. Understand why risk-based management represents an improvement in care
3. Learn fundamentals of risk-based guidelines for managing patients

How were these updated guidelines for management of abnormal screening tests and cancer precursors developed and finalized?

19 Participating Organizations

Patient Advocacy Organizations
- American Sexual Health Association
- Cervivor
- Latino Cancer Institute
- Team Maureen

Federal Agencies
- Centers for Disease Control & Prevention
- National Cancer Institute

Medical Professional Societies
- ASCCP
- American Academy Of Family Physicians
- American Cancer Society
- American College Of Nurse-Midwives
- American College Of Obstetricians and Gynecologists
- American Society For Clinical Pathology
- American Society Of Cytopathology
- College Of American Pathologists
- Nurses For Sexual And Reproductive Health
- Nurse Practitioners In Women's Health
- Papanicolaou Society Of Cytopathology
- Society Of Gynecologic Oncology
- Women Veterans Health Strategic Healthcare Group

What data were used/ how do we know they are representative?

Kaiser Permanente Northern California Data (KPNC)

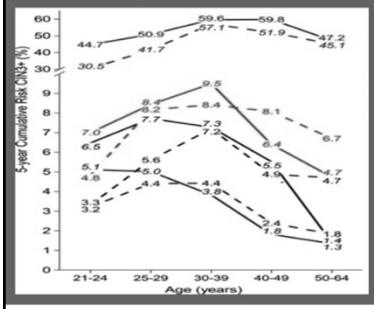
- Largest/longest real clinical experience with HPV-based screening in the world
  - Over 1.5 million women with routine cotesting from 2003-2017
  - HPV genotyping for ~19,000 patients
- Provides risk-based evidence for most of the common decision points that occur in screening
  - Long length of follow-up allows use of past-history for more personalized management

Cheung LC et al J Low Genit Tract Dis 2020;24(2):90-101.

Validation of risk and risk-based management

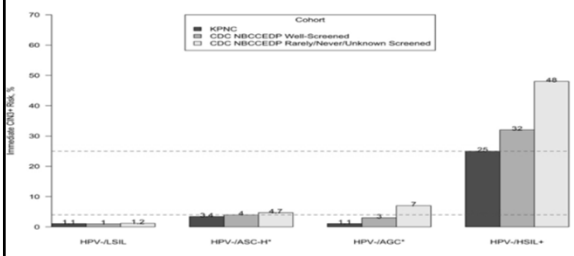
- KPNC Cohort (~1.5m)
- New Mexico HPV Pap Registry (~450k, previous study)
- CDC NBCCEDP - well-screened (~200k)
- CDC NBCCEDP - rarely/never/unknown screened (~150k)
- BD Onclarity Trial (~30k with genotyping)

Risks similar for KPNC and New Mexico



Gage...Wheeler, Obstet Gynecol 2016

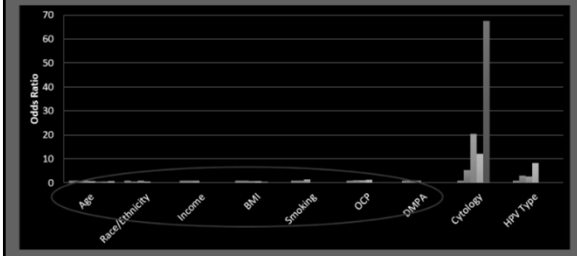
Risk-based management portable to other studies



Perkins & Guido et al, JLGTD, 2020; Saraiya, submitted

Which risk factors influence pre-cancer development?

Risk factors and Risk of CIN2+ (KPNC data)



HPV vaccination: important but NOT included (yet)

- HPV vaccination prior to age 18 reduces the CIN3+ risk by 50%

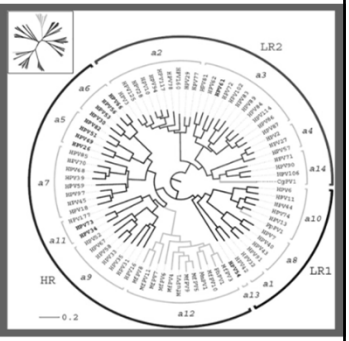
HOWEVER

- Current cohort is 21-24 years, a group already conservatively managed.
- 50% age eligible female first dose vaccine population coverage achieved 2015
- Documentation of vaccination and age at which vaccine is necessary to apply this factor correctly—*historically guidelines have not included factors clinicians can't document*
- Vaccination will impact age to start screening in the future
- Management will likely change as vaccinated cohorts age
- Target age 11-12 years, most not yet older than 25

Fundamental Concept #1

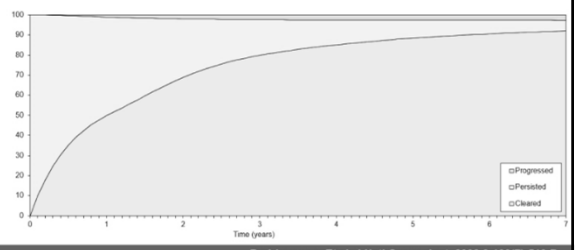
- The longer an HPV infection has been present, the higher the risk of pre-cancer and cancer
  - *Time matters*
  - *Type matters (HPV 16 most dangerous)*
  - *Other patient factors don't matter if you know about HPV*
  - *CLINICAL CORRELATE: Colposcopy is always needed following two consecutive positive HPV tests*

High Risk HPV types are related and are causally linked to cancer



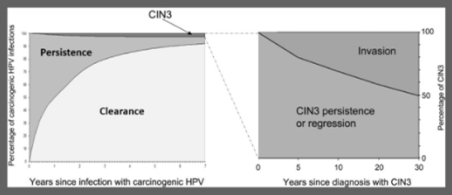
Chen Z, Schiffman M et a. Virology, 2018

Most HPV infections become undetectable in 1-3 years those that persist cause CIN3+ over time



Rodriguez ac. Et al J Natl Cancer Inst. 2008 2;100(7):513-7

Precancer and cancer increase markedly when infections persist for 5 years or more



McCredie et al., . Lancet Oncol. 2008 May;9(5):425-34.

Screening distinguishes normal from abnormal

⬇

Colposcopy with biopsy detects CIN3 ("pre-cancer")

⬇

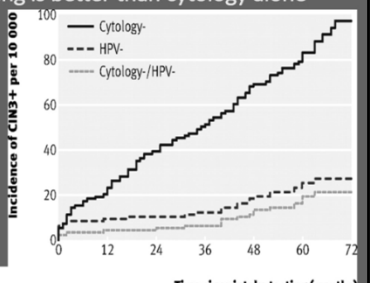
Treating CIN3 prevents cancer

⬇

Goal of screening is to detect CIN3 and *prevent* cervical cancer

HPV-based screening is better than cytology alone

- Cytology (Pap testing) is less sensitive than HPV testing
  - Detects 50-70% of CIN3+ vs >90%
- Cytology alone does not confer long-term protection against CIN3+ following a negative test



Dillner, BMJ 2008 Oct 13;337:a1754

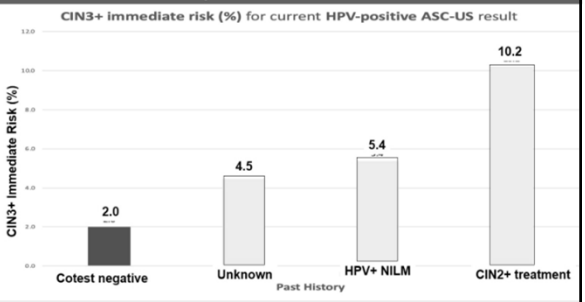
New guidelines prefer HPV testing for follow up

- Surveillance with cytology alone is acceptable only if testing with HPV or cotesting is not feasible.
- Cytology is less sensitive than HPV testing for detection of precancer, and is therefore recommended more often.
- **Cytology is recommended at 6-month intervals when HPV testing or cotesting is recommended annually.**
- **Cytology is recommended annually when 3-year intervals are recommended for HPV or cotesting.**

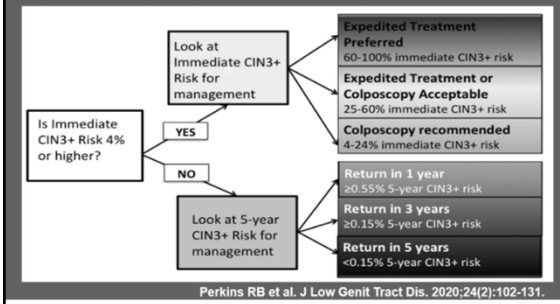
Fundamental concept #2: Management is based on risk, not results

- Recommendations of colposcopy, treatment, or surveillance are based on a patient's risk of CIN3+ determined by a combination of **current results** and **past history** *(including unknown history)*.
- The same current test results may yield different management recommendations depending on the history of recent/ past test results and other risk factors.

Past history influences current risk



Patients stratified into risk levels



Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131.

Safer for high-risk patients

Fewer unnecessary invasive procedures ***in low-risk patients***

Enduring: ***Clinical Action Thresholds allow cancer prevention to remain constant in a landscape of changing test options and decreasing HPV prevalence***

Safer: Define high risk patients to focus resources

<u>High-risk concepts similar to 2012 guidelines:</u>

- Histologic HSIL (CIN2+) on biopsy remains the threshold for treatment in the general population
- CIN3 should always be treated (except in pregnancy)
- CIN2 has the option of treatment or observation with colposcopy/biopsy for those concerned with treatment effects on future pregnancy

Safer: Define high risk patients so resources can be focused on them

- High-grade cytology with HPV 16 infections are highest risk
  - >75% risk of any precancer (histologic HSIL or CIN2+)
  - >60% risk of highest-grade precancer (CIN3+)

Demarco M. et al. J Low Genit Tract Dis. 2020;24(2):144-147.

2019 Management Guidelines
Highest risk patients receive expedited treatment

- Excisional treatment for patients at high risk of pre-cancer without requiring confirmatory biopsy

Risk /Benefit Analysis

HPV	Cytology	CIN 3+ Immediate Risk %	Number of LEEPs to treat 1 CIN3+
POS	HSIL+	48.9	2.1
POS	AGC	26.3	2.3
POS	ASC-H	25.7	2.8
NEG	HSIL+	25.2	2.8

https://CervixCa.nlm.nih.gov/RiskTables.

Clinical Action Thresholds for Expedited Treatment (without confirmatory colposcopic biopsy)

Immediate Risk of pre-cancer (CIN 3+)	
<25%	Level below which colposcopy and biopsy is preferred
≥25-59%	Immediate excisional treatment or treatment after colposcopy with biopsy confirmation are acceptable
>60%	Immediate excisional treatment is preferred, treatment after colposcopy with biopsy confirmation is acceptable

**Not recommended for patients age <25 and pregnant women*

Additional Key Changes in 2019 Guidelines

1) Excisional treatment is preferred to ablative treatment for histologic HSIL (CIN2 or CIN3) in the United States.
   - Excision is recommended for adenocarcinoma *in situ* (AIS).

2) Observation is preferred to treatment for CIN grade 1 (CIN1).
   - Treatment remains acceptable for patients with repeat diagnoses of CIN1 persisting 2 years or more.

Changes to follow-up after treatment of CIN2/3

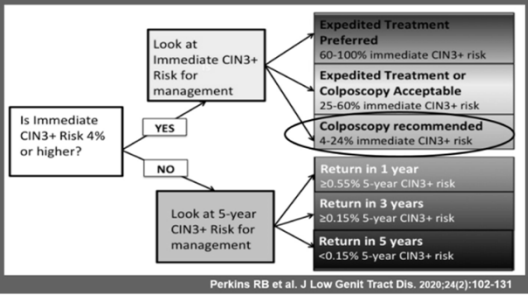
- HPV-based testing at 6 months, then annually for 3 years
- Continued surveillance with HPV testing or co-testing at 3-year intervals for at least 25 years
- Continued surveillance at 3-year intervals beyond 25 years is acceptable for as long as the patient's life expectancy and ability to be screened are not significantly compromised by serious health issues.

Note: 2012 guidelines recommended return to 5-yr screening intervals and did not specify when screening should cease. New evidence indicates that risk remains elevated for at least 25 yrs, with no evidence that treated patients ever return to risk levels compatible with 5-yr intervals.

Avoid unnecessary procedures in low-risk patients

- Colposcopy with biopsy of the cervix is recommended based on risk, not just test results
- Low-grade abnormal results (ASCUS/LSIL) have historically been the colposcopy referral threshold
  - *Is this still valid?*

Patients stratified into risk levels



Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131

Immediate CIN3+ Risk by Co-test (KPNC)

HPV	Pap	N	%	Immediate risk (%)	Colposcopies per CIN3+ diagnosis
Pos	HSIL+	3980	0.3%	48.86	2.1
Pos	ASC-H	3766	0.2%	25.73	2.8
Neg	HSIL+	183	0.0%	25.21	2.8
Pos	ASC-US	30506	2.0%	4.45	8.6
Pos	LSIL	23659	1.5%	4.27	11.3
Pos	NILM	63541	4.1%	2.13	18.3
Neg	LSIL	3300	0.2%	1.05	19.0
Neg	ASC-US	25331	1.6%	0.04	22.6
Neg	NILM	1388153	89.8%	0.002	219.4

https://CervixCa.nlm.nih.gov/RiskTables

2019 Management Guidelines Colposcopy Threshold

When individuals have an estimated immediate risk of diagnosis of CIN3+ of 4.0% or greater based on prior history and current results, referral to colposcopy is recommended.

Documented prior negative HPV (KPNC)

HPV	Pap	Immediate risk (%) after prior HPV neg	Immediate risk (%) no prior HPV test
Pos	HSIL+	32.28	48.86
Pos	ASC-H	13.56	25.73
Neg	HSIL+	13.80	25.21
Pos	LSIL	2.10	4.27
Pos	ASC-US	2.03	4.45
Pos	NILM	0.74	2.13
Neg	LSIL	0.44	1.05
Neg	ASC-US	0.014	0.04
Neg	NILM	0.001	0.002

LSIL/ASCUS no longer meets colposcopy threshold

Egemen D et al. J Low Genit Tract Dis 2020;24(2):132-143.

Impact of HPV type with prior negative HPV test (KPNC)

HPV Type	PAP Category	CIN3+ Immediate risk (%)	Cancer Immediate risk (%)
HPV16+	ASC-US	5.34	0.33
HPV 16+	LSIL	6.70	0.89

**HPV16 positive ASC-US and LSIL still exceed 4% threshold*

https://CervixCa.nlm.nih.gov/RiskTables

Special Situations: HPV18, HPV-negative AGC, and ASC-H

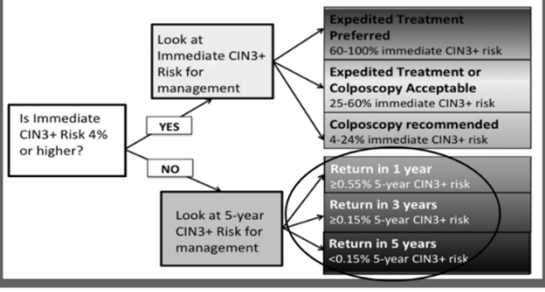
- Disproportionately important for invasive cancer
- Using medium-term risk of CIN3+ does not lead to colposcopy using Clinical Action Threshold of 4% risk.
- Consider absolute risk of cancer in addition to risk of precancer for safety

Key change in 2019 Guidelines

Colposcopy can be deferred for certain patients.

- Repeat HPV testing or cotesting at 1 year is recommended for patients with minor screening abnormalities indicating HPV infection with low risk of underlying CIN3+ (e.g., low-grade cytologic abnormalities following a documented negative screening HPV test or cotest).

Patients stratified into risk levels



ASSUMPTION: Intervals for retesting should reflect underlying risk (*equal management for equal risks*)

- Define surveillance intervals
- Define threshold to release patients back to general population screening
- Define risk thresholds for short interval follow up at 1 and 3 years
- Determine which tests to use for surveillance and at what intervals
  - HPV alone, HPV/cytology cotesting, cytology (Pap) alone

Surveillance intervals in 2019 Management Guidelines

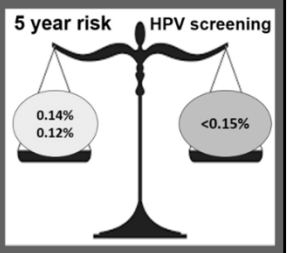
- Goal = simplicity and excellent care
- No compelling reason to change intervals
- Providers are familiar with 1, 3, and 5-year follow up intervals.
- Health systems/tracking features built around these intervals

Surveillance intervals

5-Year Return:	3-Year Return:	1-Year Return:
CIN3+ risks equivalent to general population with one negative HPV or cotest	CIN3+ risks between 3 year and 5 year return thresholds	**CIN3+ risks between colposcopy threshold and 3 year return threshold**

5-year Return Clinical Action Threshold

- Risk should be similar to that of negative HPV test or cotest in a screening population
- 5 year CIN3+ risk based on the general population at KPNC
  - HPV screening alone = 0.14%
  - Co-testing = 0.12%



Egemen D et al. J Low Genit Tract Dis. 2020;24(2):132-143

5-year Return Clinical Action Threshold

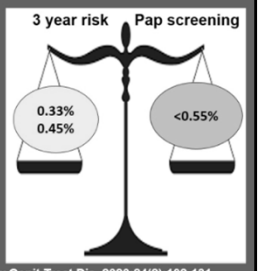
Guideline:

- **When patients have an estimated 5-year CIN3+ risk of <0.15% based on past history and current test results, return to routine screening at 5-year intervals using HPV-based testing is recommended.**

- *Note HPV-based testing is cotesting or primary HPV testing*

3-year return Clinical Action Threshold

- Risk should be similar to that of negative Pap test in a screening population
- Five-year CIN3+ risks:
  - **0.33%** estimated in KPNC
  - **0.45%** projected in CDC breast and cervical cancer screening program



Perkins RB et al. J Low Genit Tract Dis. 2020;24(2):102-131

3-year Return Clinical Action Threshold

Guideline:

- **When patients have an estimated 5-year CIN3+ risk ≥0.15% but <0.55% based on past history and current test results, repeat testing in 3 years with HPV-based testing is recommended**

- *Note HPV-based testing is cotesting or primary HPV testing*

Clinical examples of 3-year return

Result	CIN3+ risk at 5 years
HPV-negative ASC-US screening result	0.40%
HPV-negative LSIL → HPV-negative NILM cotest	0.40%
Low-grade cotest → colposcopy CIN1 → HPV-negative NILM follow-up	0.42%
CIN2/3 treated with LEEP → 3 negative cotests	0.35%

1-year Return Clinical Action Threshold

Guideline:

- **When patients have an estimated risk of CIN3+ based on past history and current results that is below the threshold for immediate colposcopy (4.0% immediate risk) and above the 3-year follow-up threshold (≥0.55% at 5 years), repeat testing in 1 year with HPV-based testing is recommended**

- *Note HPV-based testing is cotesting or primary HPV testing*

Screening results leading to *1-year Return*

Result	CIN3+ immediate risk %
HPV-positive NILM	2.1%
HPV-negative LSIL	1.0%

Egemen D et al. J Low Genit Tract Dis. 2020;24(2):132-143

Post-colposcopy results leading to 1-year return

Pre-colposcopy test result	Colposcopy result	Post-colposcopy test result	Immediate CIN3+ risk
Low-grade*	<CIN2	HPV-positive NILM	2.0%
Low-grade*	<CIN2	HPV-positive ASCUS/LSIL	3.1%

**Low-grade defined as HPV+/NILM, ASC-US, or LSIL cytology*

Egemen D et al. J Low Genit Tract Dis. 2020;24(2):132-143

Key changes to 2015 primary HPV testing interim guidance

All positive HPV tests, regardless of genotype, should have additional reflex triage testing performed from the same laboratory specimen (e.g., reflex cytology).

- Additional testing from the same laboratory specimen is recommended because the findings may inform colposcopy practice. For example, those with HSIL cytology and concurrent positive testing for HPV genotype 16 qualify for expedited treatment.
- HPV 16 or 18 infections have the highest risk for CIN3 and occult cancer, so additional evaluation (e.g., colposcopy with biopsy) is necessary even when cytology results are negative.
- If HPV 16 and 18 testing is positive, and additional laboratory testing of the same sample is not feasible, the patient should proceed directly to colposcopy.

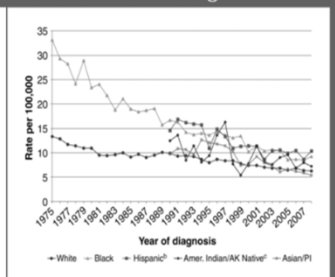
Safer for high-risk patients

Fewer unnecessary invasive procedures in low-risk patients

Enduring: Clinical Action Thresholds allow cancer prevention to remain constant in a landscape of changing test options and decreasing HPV prevalence

Enduring: designed to accommodate future changes

- Programs based on cervical cytology (Pap tests) with colposcopy referral for LSIL+ have been very successful
- Meaning of LSIL is changing: less risky following prior negative HPV test
- Risk thresholds designed around existing colposcopy referral patterns to preserve existing standard of cancer prevention while avoiding unnecessary procedures



Pierce Campbell. et al. CEPB 2012 21(9):1402

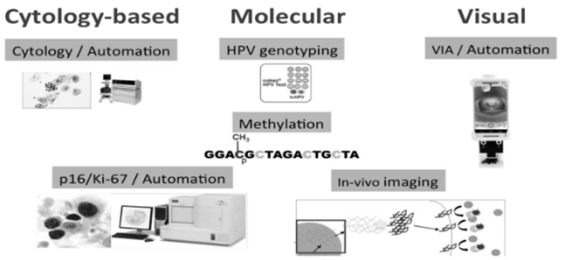
Enduring: defined risks for referral to colposcopy and treatment based on successful historical standards

- Historically, ASCUS HPV+/LSIL as a referral threshold has been very successful to detect CIN3+ and prevent cancer
  - Risks of CIN3+ for these results were historically 4-12%
- HPV-positive ASCUS/LSIL results are becoming LESS RISKY
  - Risks of CIN3+ are halved following a prior negative HPV test or on time HPV vaccination (prior to age 18)

Enduring: defined risks for referral to colposcopy and treatment based on successful historical standards

- 2019 Guidelines Framework designed to preserve cancer prevention while decreasing unnecessary colposcopy in the setting of
  - Decreasing CIN3+ prevalence as vaccinated populations age into screening cohorts
  - Decreasing CIN3+ prevalence as populations undergo multiple rounds of HPV-based screening

Enduring: accommodates new tests in development



Enduring: accommodates new tests in development

- Previously, new guidelines and interim guidance were required as each new test became clinically available
- As the nature of HPV carcinogenesis is better understood, the pace of technology development would lead to frequent interim guidance
- Frequently changing guidelines are confusing for clinicians and can create errors in patient care

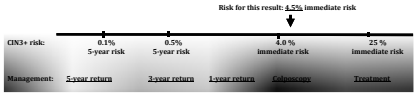
Enduring: accommodates new tests in development

- Establishment of risk-based thresholds means that new tests can be evaluated against existing thresholds instead of making new algorithms for each new test
  - Test characteristics will be objectively compared to existing Clinical Action Thresholds
  - Standardized, transparent clinical guidance will logically follow from test characteristics and existing consensus thresholds
  - Reduces the need for interim guidance and frequent consensus conferences

"A 40-year old woman (first screen with HPV), tests **HPV-positive/ASC-US**." What would be the suggested management?

A. Immediate treatment is acceptable
B. Refer for colposcopy
C. Return in 1 year
D. Return in 3 years
E. Return in 5 years
F. Don't know

HPV-positive/ASC-US

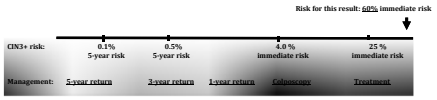


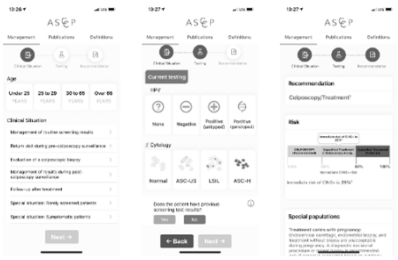
From the perspective of risk, HPV-positive/ASC-US and HPV-positive/LSIL are the same.

"A 40-year old woman (first screen with HPV), tests **HPV-positive/HSIL+**. She is **positive** for HPV type **16**." What would be the suggested management?

A. Immediate treatment is acceptable
B. Refer for colposcopy
C. Return in 1 year
D. Return in 3 years
E. Return in 5 years
F. Don't know

HPV 16-positive/HSIL+





With tremendous thanks to:

- ASCCP
- Consensus voting participants
- KPNC team
- NCI statistical team
- Steering committee members
- Working group participants