HPV45: Why does it matter?
Clinical utility in risk-stratified cervical cancer screening & management: systematic review

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ASCCP Improving Lives Through the Prevention & Treatment of Anogenital & HPV-Related Diseases

ASCCP2018 Annual Meeting

Disclosures

- Full-time employee of BD

Methods

- PubMed, Cochrane Database of Systematic Reviews, and Health Technology Assessment database were searched from 2001 through 2017 for relevant studies.
- Hand-searching of retrieved article reference lists was used to supplement the search.
- Eligible studies included prospective studies of women and retrospective studies of residual specimens from women that were screened or tested using HPV tests that reported HPV 45 individually.
- The reference standard was CIN2, CIN3, CIN2+, CIN3+, AIS, or invasive cervical cancer.
- The timeframe for screening paradigms was baseline, 1-year, 3-year, 5-year.

Results

- 17 eligible peer-reviewed published research articles
    - Kjaer 2010 JNCI, Thomsen 2015 IJC, Naucler 2007 BrJC, Smelov 2015 IJC, Elfgren 2017 AJOG, Skinner 2016 IJC, Berkhof 2006 CEBP, Kitchener 2014 NHR, Wheeler 2014 IJC, Schiffman 2015 JCM, Schiffman 2016 IJC, Schiffman 2015 GO, Sung 2016 JGO, Wheeler 2006 JID, Nakamura 2015 IJCO, Matsumoto 2011 IJC, Monsonego 2015 GO
  - 13 studied women in a screening population
    - 4 studied women in a referral population
  - 10 were prospective studies
    - 5 were retrospective analysis of a screened population, 1 was post-hoc analysis of a referral population, 1 was a retrospective analysis of a referral population
  - 13 provided data for women with NILM and hrHPV+
  - 8 provided data for women with ASCUS and hrHPV+
  - 4 provided data for women with LSIL and hrHPV+
  - 6 provided data for women with abnormal cytology and hrHPV+.

Results

Published studies of women receiving cervical cancer prevention care, with extended genotyping test and a clinical endpoint of CIN2/CIN3

Article	Study type	Population: Screening (S), Referral (R)	N	HPV genotype assay	NILM	ASC-US	LSIL	≥LSIL	Clinical Endpoints	Study Years	Follow-up duration (years)	Country
Kjaer 2010 JNCI	Prospective cohort	S	7482	line probe	√				CIN2+ CIN3+	1991-1993	13.4	Denmark
Thomsen 2015 IJC	Prospective cohort	S	33288	INNO-LiPA	√				CIN3+	2002-2014	8	Denmark
Naucler 2007 BrJC	Prospective SWEDESCREEN	S	5696	GP5+/6+ PCR	√				CIN2+ CIN3+	1997-2002	4.1	Sweden
Smelov 2015 IJC	Prospective SWEDESCREEN	S	11683	GP5+/6+ PCR	√				CIN2+ CIN3+	1997-2014	14	Sweden
Elfgren 2017 AJOG	Prospective SWEDESCREEN	S	195	GP5+/6+ PCR	√				CIN2+ CIN3+	1997-2017	13	Sweden
Skinner 2016 IJC	Prospective RCT(vaccine control arm)	S	2838	LiPAmultiplex PCR	√	√	√		CIN2+ CIN3+	2011-2016	4	multinational
Berkhof 2006 CEBP	Prospective RCT	S	21996	GP5+/6+ PCR	√	√			CIN2+ CIN3+	1999-2002	1.5	Netherlands
Kitchener 2014 NHR	Prospective cohort screening	S	8873	Roche LBA & LA	√	√		√	CIN2+ CIN3+	2007-2013	6	England
Monsonego 2015 GO	Post-hoc ATHENA clinical trial	S	40901	Linear Array	√	√	√	√	CIN2+ CIN3+	2008-2009	baseline	USA
Wheeler 2014 IJC	Screening Registry Retrospective	S	47541	Linear Array	√	√	√	√	CIN2+ CIN3+	2007-2009	3	USA
Schiffman 2015 JCM	KPNC screening Retrospective	S	4602	Linear Array	√				CIN2+ CIN3+	2007-2011	1.3	USA
Schiffman 2016 IJC	KPNC screening Retrospective	S	8664	Onclarity	√	√		√	CIN2+ CIN3+	2003-2014	3.5	USA
Schiffman 2015 GO	KPNC screening Retrospective	S	1903	Onclarity		√			CIN2+ CIN3+	2003-2014	3.6	USA
Sung 2016 JGO	Retrospective database	R	1102	HPV 9G DNA chip	√	√		√	CIN2+	2012-2015	baseline	South Korea
Wheeler 2006 JID	Post-hoc ALTS clinical trial	R	5060	L1 PCR		√	√		CIN2+ CIN3+	1996-2000	2	USA
Nakamura 2015 IJCO	Prospective cohort	R	427	CliniChip				√	CIN3+	2010-2012	baseline	Japan
Matsumoto 2011 IJC	Prospective cohort	R	570	DNA PCR			√		CIN2+ CIN3+	1998-2004	3.3	Japan

Unremarkable 45

- Prevalence by cytology
  - HPV45 is not one of the 10 most common hrHPV genotype in NILM worldwide, nor in North America.
    - [de Sanjose 2007 LID, Bulkmans 2005 IJC, Monsonego 2015 GO, ICO]
- Prevalence by CIN1,2,3
  - HPV45 is not one of the 10 most common hrHPV genotype in high-grade CIN worldwide, and is 10th most common in North America.
    - [ICO]
  - In women over 30 years with abnormal cytology, from a USA screening population of 40,901, there were no cases of CIN2+ with HPV45.
    - [Monsonego 2015 GO]

Unremarkable 45

- CIN2
  - HPV45 had the 7th highest risk
    - 4.1-year CIN2+ risk (19.2%) in a screening population of 5696 women. [Naucler 2007 BrJC]
    - 3-year risk for CIN2+ (2.5%), for all cytology results, by single genotype infection in a USA screening population of 30,596 women. [Wheeler 2014]
    - 11.32-year risk for CIN2+ (39.0%), and 7th highest adjusted increased relative risk among subjects positive for a genotype-specific high-risk HPV. [Smelov 2014]
  - HPV45 had the 5th highest hazard ratio for CIN2+, if the genotype is persistent, in the VIVIANE study, behind 33 and 16 and 31 and 18. [Skinner 2016 IJC]

Unremarkable 45

- CIN3: HPV45 had the 6th-9th highest risk
  - (9th) baseline CIN3+ in ATHENA baseline phase [Stoler 2011 AJCP]
    - (4th) baseline CIN3+ risk (3.7%), ≥30 years with NILM cytology. [Monsonego 2015 GO]
    - (6th) baseline CIN3+ risk (4.3%), ≥30 years with any cytology result. [Monsonego 2015 GO]
    - (9th) baseline CIN3+ risk (0.7%), ≥30 years with abnormal cytology results. [Monsonego 2015 GO]
  - (8th) 2-year CIN3+ risk (2.3%), LSIL/ASC-US (ALTS). [Castle 2010 CEBP]
  - (6th) 3-year CIN3+ risk (1.3%), for all cytology results, by single genotype infection. [Wheeler 2014]
  - (7th) 3-year CIN3+ risk (3.9%), ASC-US cytology & hrHPV+; a hierarchical analysis by Onclarity:
    - 16 (16%), else 18 (7.4%), else 31 (7.0%), else 33/58 (7.1%), else 52 (4.4%), else 45 (3.9%) [Schiffman 2015 GO]
  - (6th) 3-year cumulative risk for CIN3+ in 18,000 women ≥30 years, NILM+; hierarchical by Onclarity:
    - HPV16 (10.6%), 33 (5.9%), 18 (5.9%), 31 (4.5%), 52 (3.8%), 45 (1.7%) [Schiffman 2015 JCM]
  - (6th) 3-year cumulative risk of CIN3+ in women with all cytology results; hierarchical by Onclarity:
    - 16 (21.9%), else 18 (11.5%), else 33/58 (8.6%), else 31 (8.1%), else 52 (5.6%), else 45 (5.4%). [Schiffman 2016 IJC]
  - (9th) 4.1-year CIN3+ risk (7.7%) in a screening population of 5696 women. [Naucler 2007 BrJC]
  - (7th) risk for CIN3+ (6.4%), if there was persistent infection. [Kjaer 2010 JNCI]
  - (6th) 11.4-year CIN3+ cumulative incidence risk was 6th highest. [Smelov 2014]

Unremarkable 45

- Prevalence ratios, enrichment, NILM to CIN3
  - A meta-analysis of the prevalence of different HPV types in the progression of disease from normal cytology through CIN3 to ICC in 115,789 HPV-positive women demonstrated important differences in HPV type distribution between CIN3 lesions and ICC.
  - HPV45 is not enriched when CIN3 is compared to NILM, with a ratio below one. [Guan 2012, Smith 2007, Clifford 2003]

Unremarkable 45

- Persistence
  - The persistent infection risk for CIN3+ is highest for HPV16, and one-and-a-half times higher than the next highest risk (HPV18: 15.4%). [Kjaer 2010 JNCI]
  - During the follow-up period of 13.4 years, the genotype-specific risks for CIN3+ with the given HPV genotype alone were:
    - 16 – highest 26%, 18-2nd highest 15.4%, 33-3rd highest 12.8%, 31-4th highest 9.8%, 35-5th highest 9.1%, 58-6th highest 8.3%, 51-7th highest 6.9%, 45-8th highest 6.4%, 52-9th highest 4.7%, 56-10th highest 2.3%. [Kjaer 2010 JNCI]
  - Persistent HPV45 had the 5th highest risk for CIN3+, following HPV16, 18, 31, and 33. [Elfgren 2017AJOG]

Remarkable 45

- Prevalence in invasive cervical cancer (ICC) and squamous cell cancer (SCC)
  - HPV45 is the 3rd-6th most prevalent genotype in cases of invasive cervical cancer worldwide (5-6%), and 3rd in North America (5.4-6.0%), reported to vary from 3% in Eastern Asia up to 9% in Africa.
    - [deSanjose 2010 LO, Wheeler 2013 IJC, Bosch 2003 JNCI, Munoz 2003 NEJM, Clifford 2003 BrJC, IARC 2007, Wheeler 2014 IJC, Bosch 2002 JCP, Schiffman 2005 V, Hopenhayn 2014 JLGTD, Li 2011, Smelov 2014 IJC, ICO, Smith 2017 IJC]
- ICC cases in a meta-analysis were associated with HPV16 (51%), 18 (16.2%), and the next 5 most prevalent types (45, 31, 33, 58, 52) collectively accounted for 18.3% of cases
    - [Clifford 2003 BJC]

Remarkable 45

- Prevalence ratios, enrichment, NILM to Cancer, CIN3 to Cancer
  - A meta-analysis of the prevalence of different HPV types in the progression of disease from normal cytology through CIN3 to ICC in 115,789 HPV-positive women demonstrated important differences in HPV type distribution between CIN3 lesions and ICC.
  - For HPV45, ICC:normal ratio was elevated, indicating enrichment, with the 2nd -3rd highest ratio. [Guan 2012 IJC, de Sanjose 2007 LID, de Sanjose 2010 LO]

    "Based upon its level of enrichment in cervical cancer compared to cytologically normal women, HPV45 has been suggested to be the third most carcinogenic type after HPV16 and 18." [Guan 2012 IJC]
  - The relative importance of HPV45 was the 2nd highest, comparing ICC to CIN3, suggesting that HPV45 is one of the most carcinogenic genotypes. [Guan 2012 IJC]

    "HPV45 is rare in women with NILM (0.4%) and low prevalence in women with low-grade lesions (3.7%), but is consistently 3rd most common type in ICC globally and in most of the regions." [Franceschi 2005 JNCI]

    "HPV45 was significantly more prevalent in SCC than in HSIL; SCC:HSIL prevalence ratio 1.54 (95% CI: 1.20-1.98)." [Smith 2017 IJC]

Prevalence ratios, enrichment

hrHPV genotype	CIN3:NILM
16	2.85
33	1.94
31	1.46
58	1.43
52	1.28
35	1.06
18	0.88
51	0.77
45	0.75
59	0.72
68	0.65
39	0.63
56	0.48
66	NR
[Guan 2012 IJC]	

hrHPV genotype	ICC:NILM
16	3.07
18	1.87
45	1.10
33	0.94
58	0.70
35	0.51
31	0.49
52	0.44
59	0.41
39	0.27
68	0.20
56	0.17
51	0.16
66	NR
[Guan 2012 IJC]	

hrHPV genotype	ICC:CIN3
18	2.11
45	1.47
16	1.08
59	0.58
33	0.49
58	0.49
35	0.48
39	0.43
56	0.36
52	0.35
31	0.34
68	0.31
51	0.20
66	NR
[Guan 2012 IJC]	

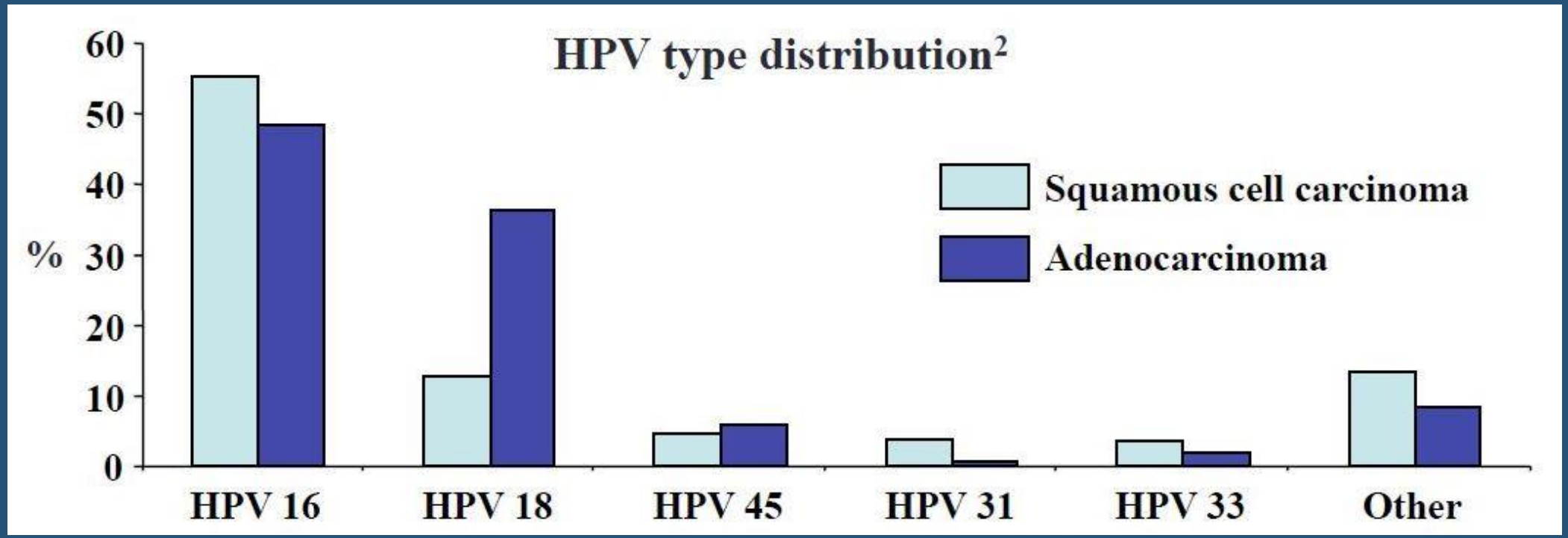
Remarkable 45

- Prevalence in adenocarcinoma
  - HPV45 is notable for being found in 5.7-12% of adenocarcinomas.
    - [deSanjose 2010 LO, Wheeler 2013 IJC, Bosch 2003 JNCI, Munoz 2003 NEJM, Clifford 2003 BrJC, IARC 2007, Wheeler 2014 IJC, Bosch 2002 JCP, Schiffman 2005 V, Hopenhayn 2014 JLGTD, Li 2011, Smelov 2014 IJC, ICO, Smith 2017 IJC]

"In women with adenocarcinoma, and mixed infections of hrHPV, HPV18 had highest prevalence (57.1%), followed by HPV16 (35.7%), and then HPV45 (11.4%). In women with adenocarcinoma, including only cases with a single GT infection, HPV18 had highest prevalence (55.4%), followed by HPV16 (33.8%), and then HPV45 (9.2%) – these three genotypes accounted for 98.4% of adenocarcinoma associated with a single hrHPV genotype infection." [Bulk 2006 BrJC]

"In women with adenocarcinoma, HPV16 had highest prevalence (50%), followed by HPV18 (32%), and then HPV45 (12%). In women with adenosquamous cell carcinoma, HPV16 had highest prevalence (39%), followed by HPV18 (32%), and then HPV45 (12%). These three genotypes accounted for 89.6-94.2% of adenocarcinoma." [de Sanjose 2010 LO]

HPV genotype distribution in squamous and adeno cervical cancer, worldwide



HPV 16, 18, 45 account for >75% of ICC [1,2]

HPV 16, 18, 45 account for >90% of adenocarcinoma [2,3]

1. Munoz Int J Cancer 2004;111:278-285
2. Bosch Vaccine 2008;26S:K1-16
3. Smith Int J Cancer 2007;121:621-32

Principles

- Under the principle of “equal management for equal risk” [Massad 2013, Katki 2013], genotypes of equal or equivalent risk should be reported to support optimal risk-based management of patients.
- Four HPV genotypes, 31,33,58,52 have the same or higher risk as types 18 or 45. Seven HPV genotypes, 35, 39, 51, 56, 59, 66, 68 have lower oncogenic risk than the other seven genotypes and this information, combined with cytology in cotesting or with triage method including cytology in primary can be used to more precisely estimate risk and choose appropriate patient management, resulting in lower invasive procedures and costs.

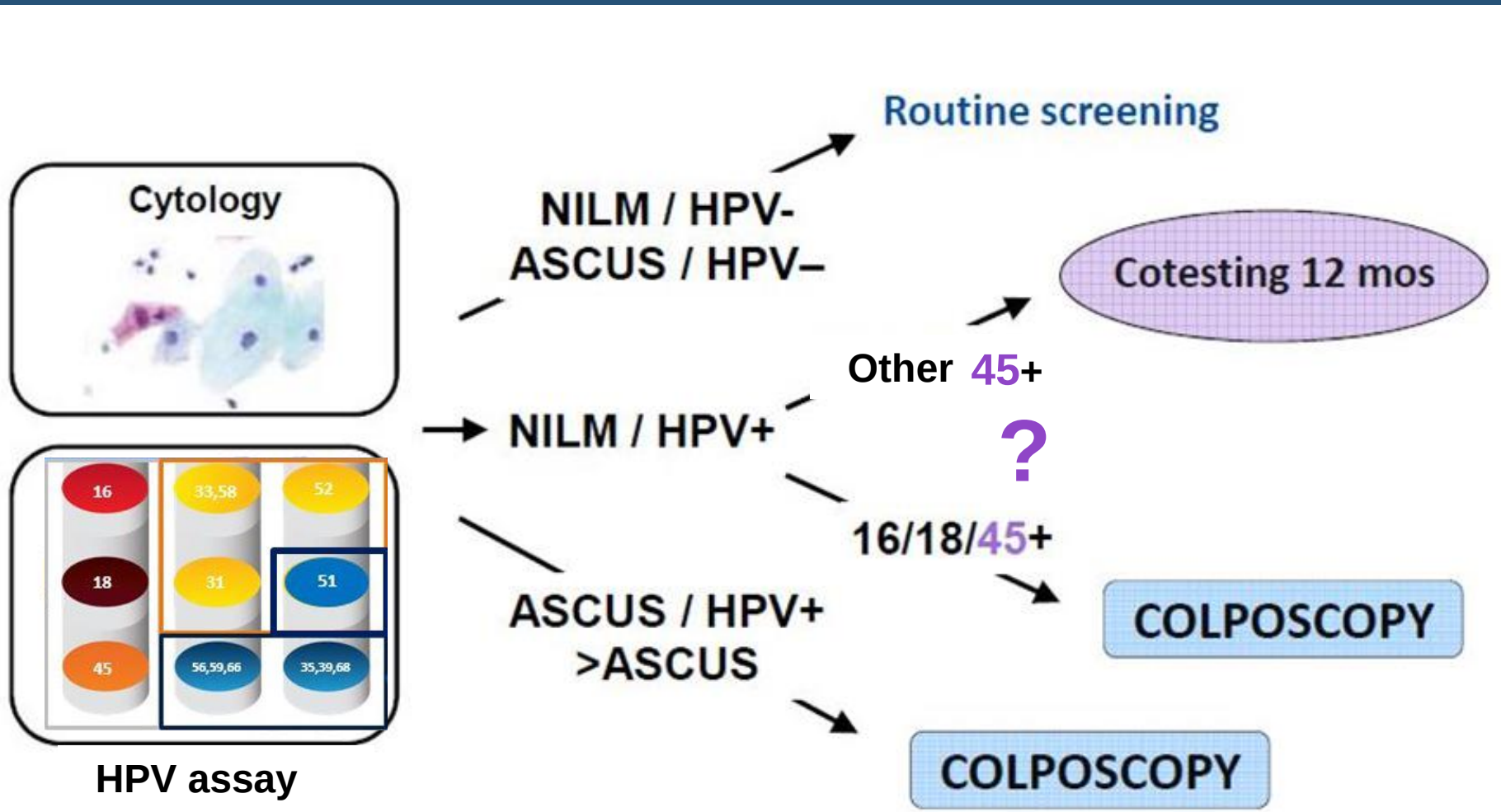
Models for different screening paradigms

- *"In the event that future cervical screening programs include HPV typing, women infected with HPV16, 18 and 45 may require closer surveillance than women infected with other hrHPV types."* [Clifford 2003 BJC]
- *"HPV 16, 18 ((substantially enriched in SCC compared with LSIL), HPV 33, 45 (approximately equal frequency between SCC and LSIL), and HPV 31, 52, 58 (slightly under-represented in SCC compared to LSIL) probably have the best trade-offs between sensitivity and specificity for cervical cancer screening prevention."* [Franceschi 2005 JNCI]
- *"Of women with LSIL cytology, those testing negative for at least eight of the highest-risk types of HPV (HPV16/18/31/33/35/45/52/58) may not need immediate colposcopy and biopsy. This would reduce the number of colposcopy referrals by approximately 40%"* [Nakamura 2105]

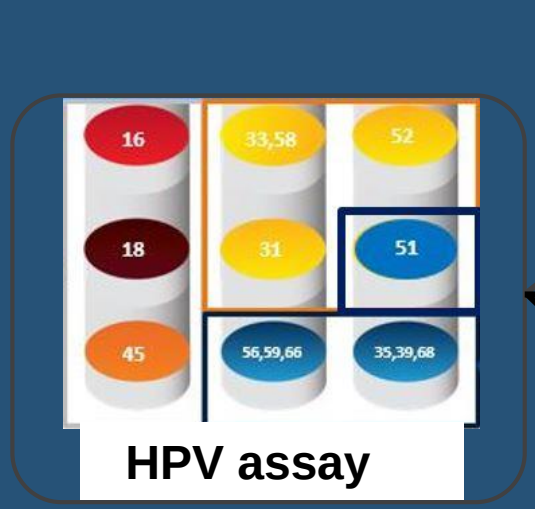
Models for different screening paradigms

- *"ASC-US linked to HPV16, HPV18, HPV31, or HPV33/58 warrants immediate colposcopy. Optimal management of women with HPV52 or HPV45 is uncertain. Risk of women with only HPV51, HPV39/68/35, or HPV59/56/66 might be low enough to recommend 1-year retesting permitting viral clearance. This strategy would defer colposcopy for 40% of women with HPV-positive ASC-US, half of whom would be cotest-negative at 1-year return."* [Schiffman 2015 GO]
- *"The 12 non-16/18 HR-HPV genotypes can be further categorized (HPV-31/33/35/45/52/58 vs. HPV-39/51/56/59/66/68) by risk stratification. The HPV-31/33/35/45/52/58 genotypes might need more aggressive action."* [Sung 2016]

Cotesting paradigm (ASCCP 2012)



Primary HPV paradigm (SGO/ASCCP 2015)



HPV−

Routine screening

12 other hrHPV+

45+

HPV16/18+

45+

?

Cytology

NILM

Follow up in 12 months

≥ ASC-US

COLPOSCOPY

COLPOSCOPY

Conclusions

Guideline panels must decide on recommendations for HPV 45 results.

Thank you

BD Associates: Charles Cooper, Salma Kodsi, Karen Eckert, Karen Yanson, Devin Gary, Edith Torres-Chavolla, Larry Vaughan, Paul Holt, Doug Malinowski, Meredith Seagraves, Giselle Bonet, Tracy Gambrell

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