

Primary Testing with HPV Genotyping

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Agenda

- Describe how HPV epidemiology drives risk-based cancer prevention
- Review conversion to primary HPV testing
- Focus on HPV vaccination – and its importance in cancer prevention

Q. 1. What does “Pap smear” mean to our patients?

- a) STD test
- b) Pelvic exam
- c) Annual women’s check-up
- d) Cervical cancer test
- e) Painful test that Gynecologists do

2. What is the sensitivity of Gyn Cytology test?

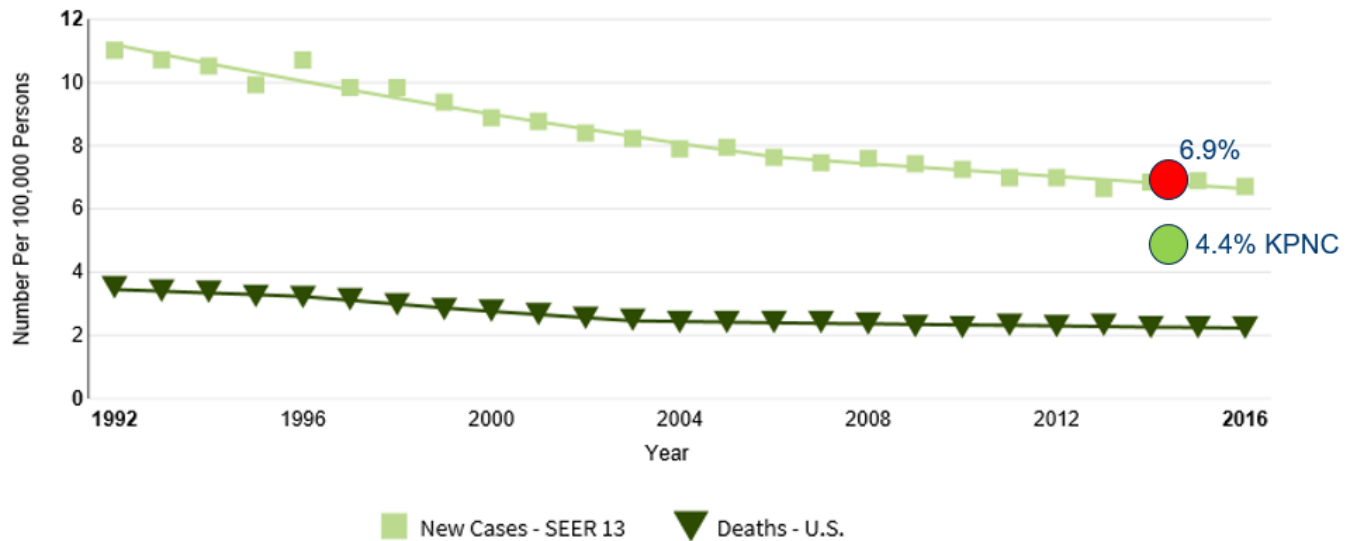
- a) 40%
- b) 55%
- c) 80%
- d) 95%

3. What is the sensitivity of HPV test?

- a) 40%
- b) 55%
- c) 80%
- d) 95%

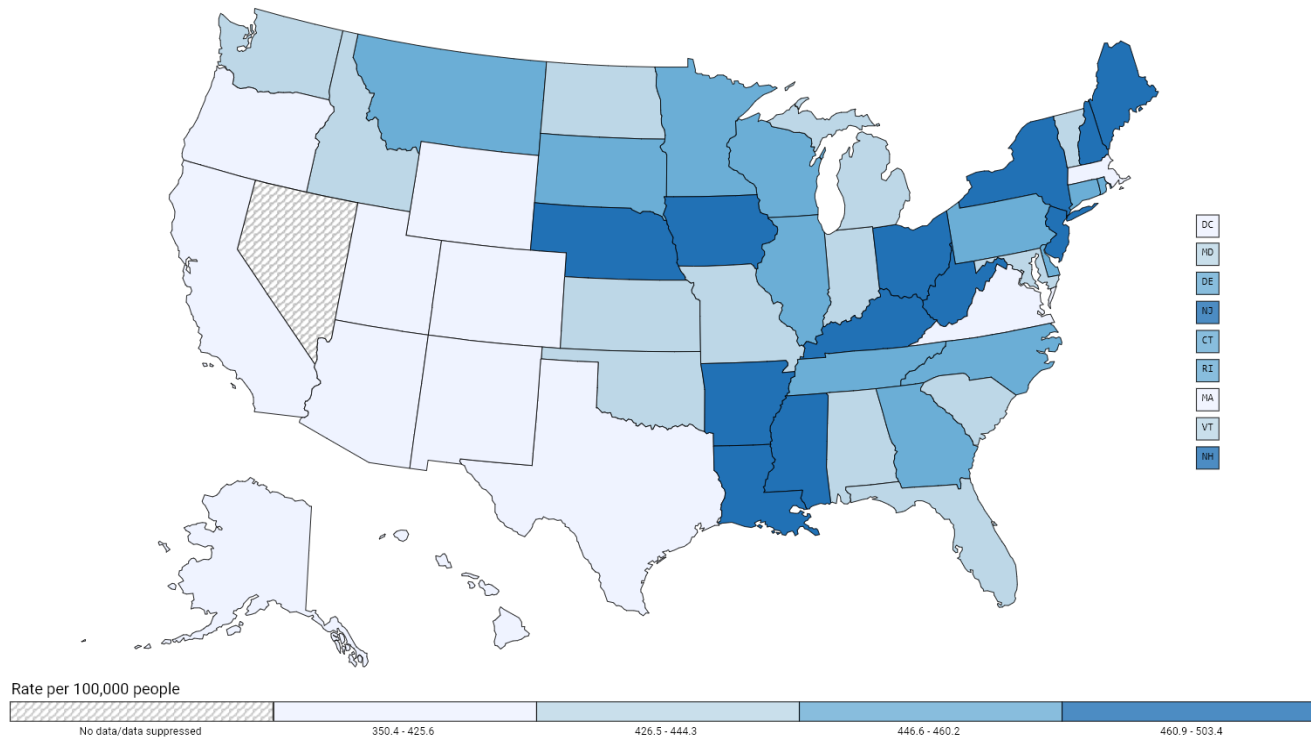
Why Now?

The Cervical Cancer rate is falling.



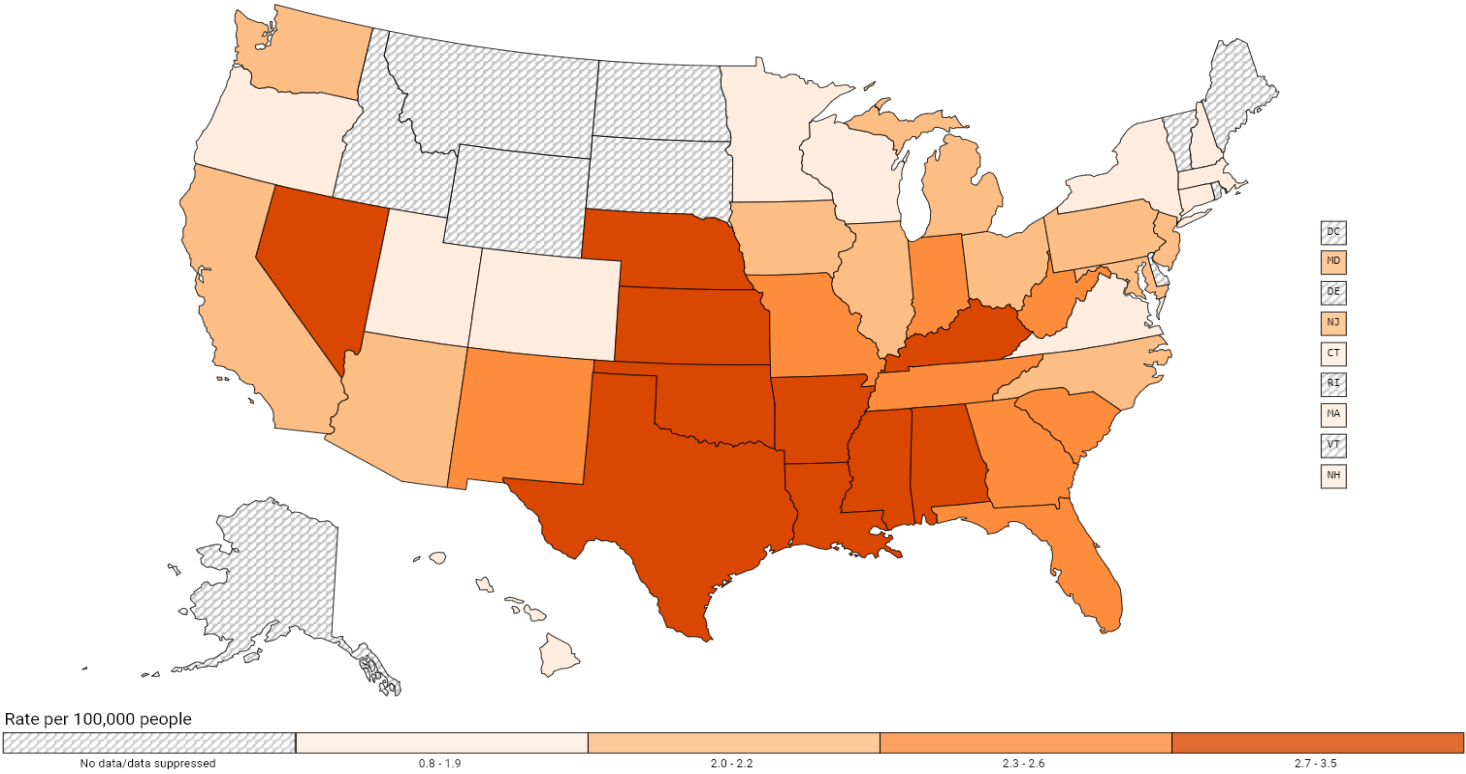
Cervical Cancer Incidence Rates – US 2018

Rate of New Cancers in the United States
All Types of Cancer, All Ages, All Races and Ethnicities, Male and Female



Cervical Cancer Mortality Rates – US 2018

Rate of Cancer Deaths in the United States Cervix, All Ages, All Races and Ethnicities, Female

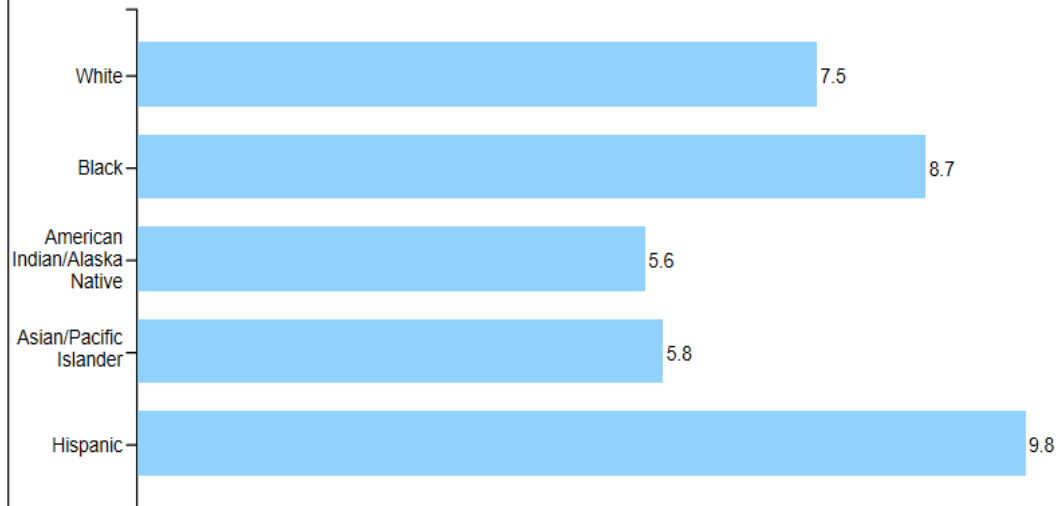


Rate of New Cancers by Sex and Race/Ethnicity

Cervix
Rate per 100,000 women

Chart Table Export

Female



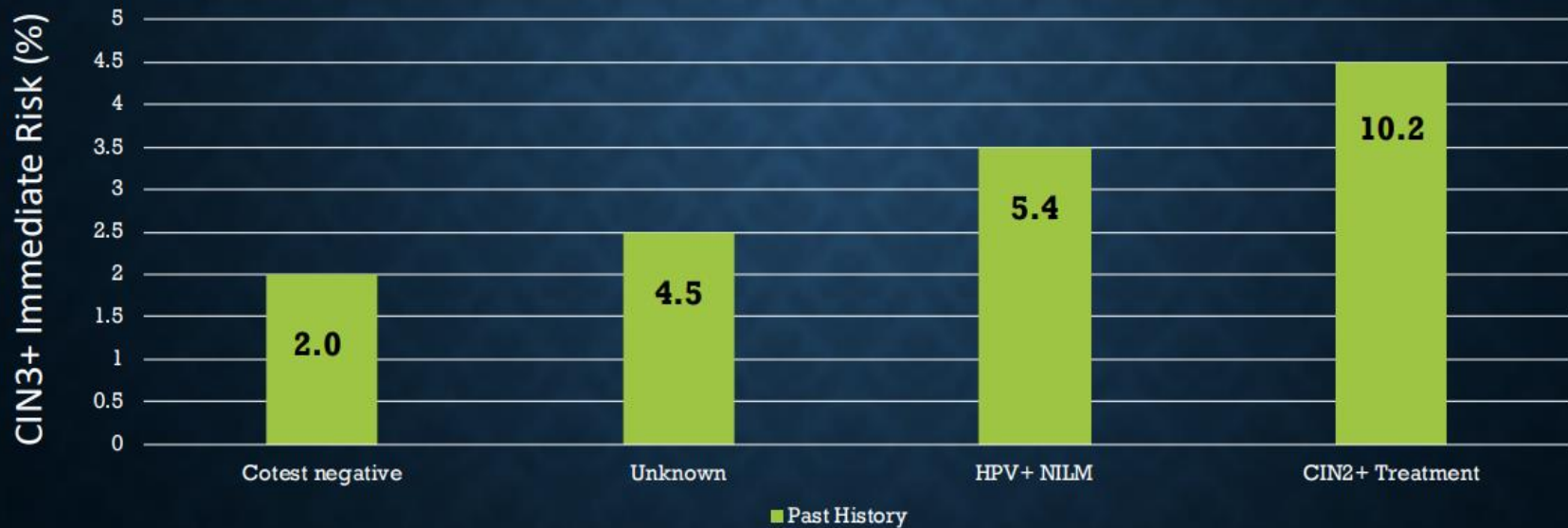
U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, June 2019.

Which Risk Factors Influence Pre-Cancer Development ?

Fundamental Concept

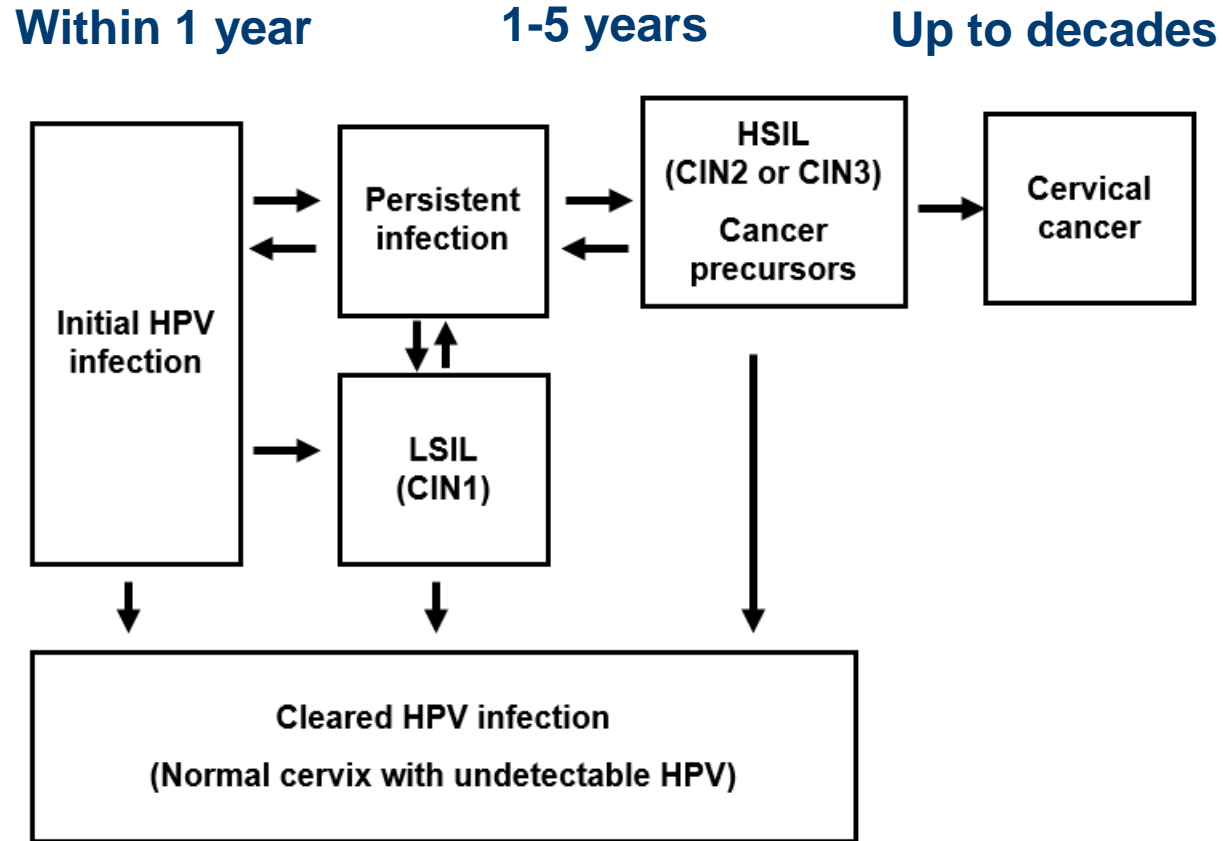
PAST HISTORY INFLUENCES CURRENT RISK

CIN3+ Immediate Risk (%) for Current HPV-positive ASCUS Result



Egemen 2020

Natural History of HPV Infection



Source: <https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/hpv.pdf>

Fundamental Concept

The longer an HPV infection has been present, the higher the risk of pre-cancer and cancer

- Time matters
- Type matters (HPV 16 is most dangerous)
- Other patient factors don't matter if you know HPV status

Guiding Principals and Approach

HPV based testing is the basis for risk estimation

Primary HPV testing or HPV and cervical cytology testing

HPV has a better sensitivity in determining long term risk

Lengthens follow up, deferring colposcopy for low-risk

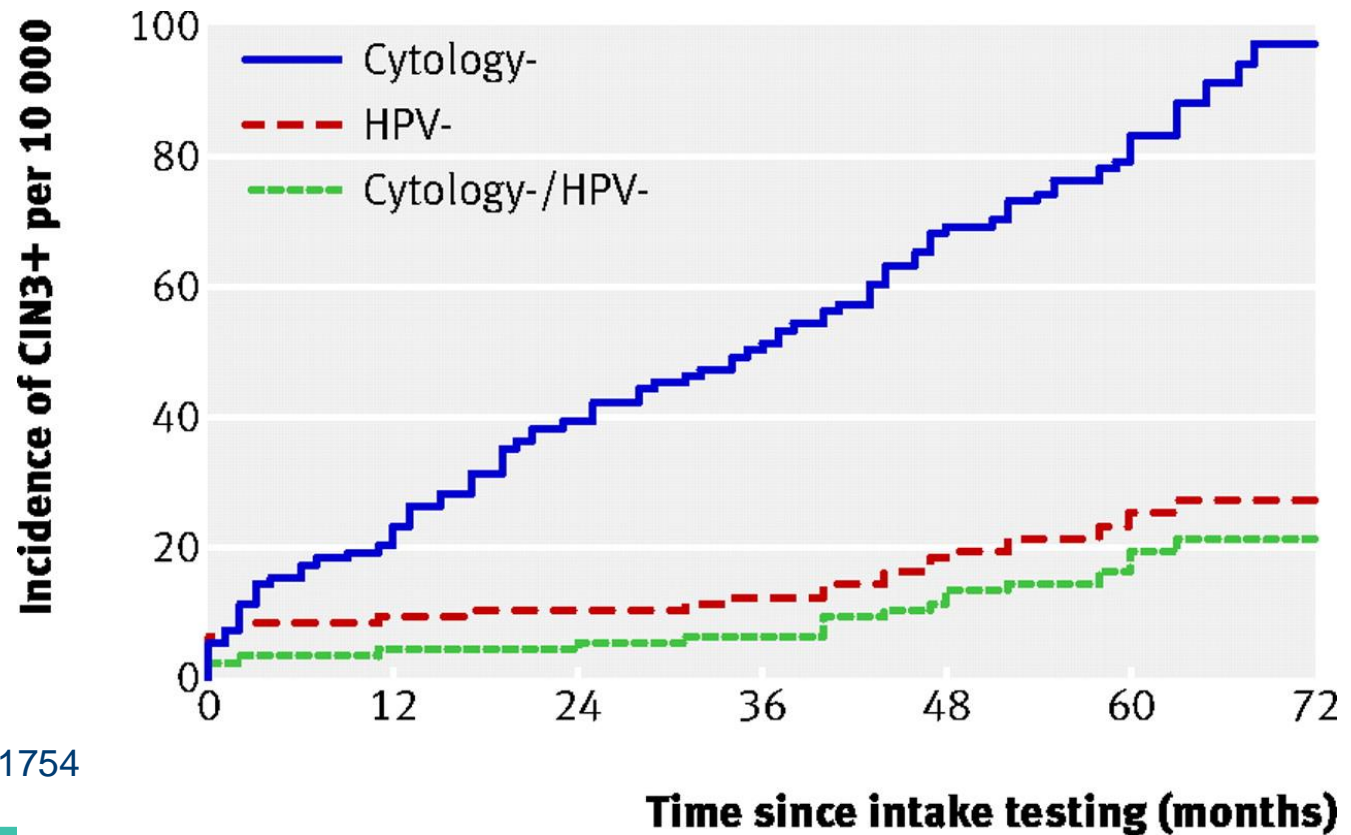
Personalized risk-based approach is possible w knowledge of current and past history

HPV- based screening is better than cytology alone

Cytology alone does not confer long-term protection against CIN3+ following a negative test

Cytology is less sensitive than HPV testing

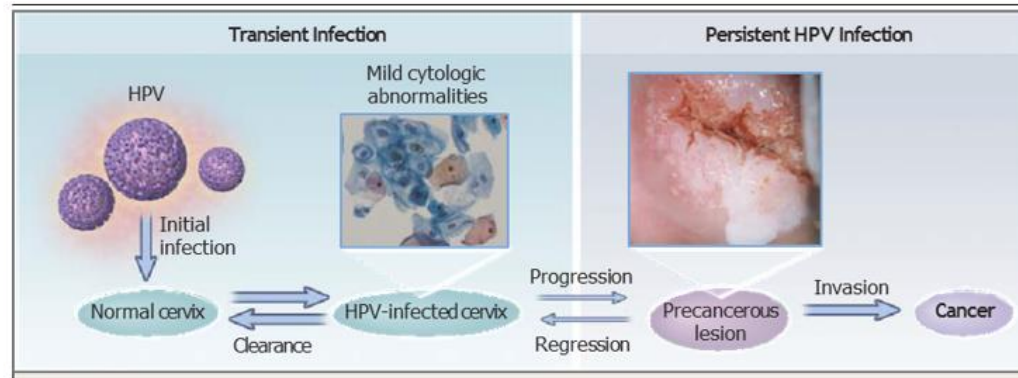
- Detects 50-70% of Cin3+ vs > 90%



Dillner, BMJ 2008 Oct 13;337:a1754

Time since intake testing (months)

HPV Progression: From Normal Cervix to Cervical Cancer



1. HPV Persists
2. HPV causes precancerous cell changes
3. Precancer progresses to cancer

Wright, T. et al., NEJM, 2003.

How does knowing the HPV Type improve care?

- The old HPV test told us one of the 14 high-risk HPV types was present, but not which one.
- The new test identifies the specific high risk genotype group
HPV 16/18 cause ~ 70% of cervical cancer.
HPV 12-other is less likely to cause cervical cancer than HPV 16/18
- If the pap is negative but HPV 16/18 is positive, we can detect pre-cancer a year earlier by doing colposcopy now

Teaching points: Natural History of HPV Infection

- Genital HPV is common in sexually active adults
- Incubation period is variable, and it is often difficult to determine the source of infection
- Natural history of HPV infection is usually benign:
 - Low risk HPV are associated with mild pap test abnormalities and genital warts
 - High risk types are associated with mild to severe Pap test abnormalized and rarely cancer of the cervix, vulva anus and penis
 - Most women infected with high- risk HPV have no pap test abnormalities and do not develop cervical CA

HPV and oropharyngeal and anal cancers

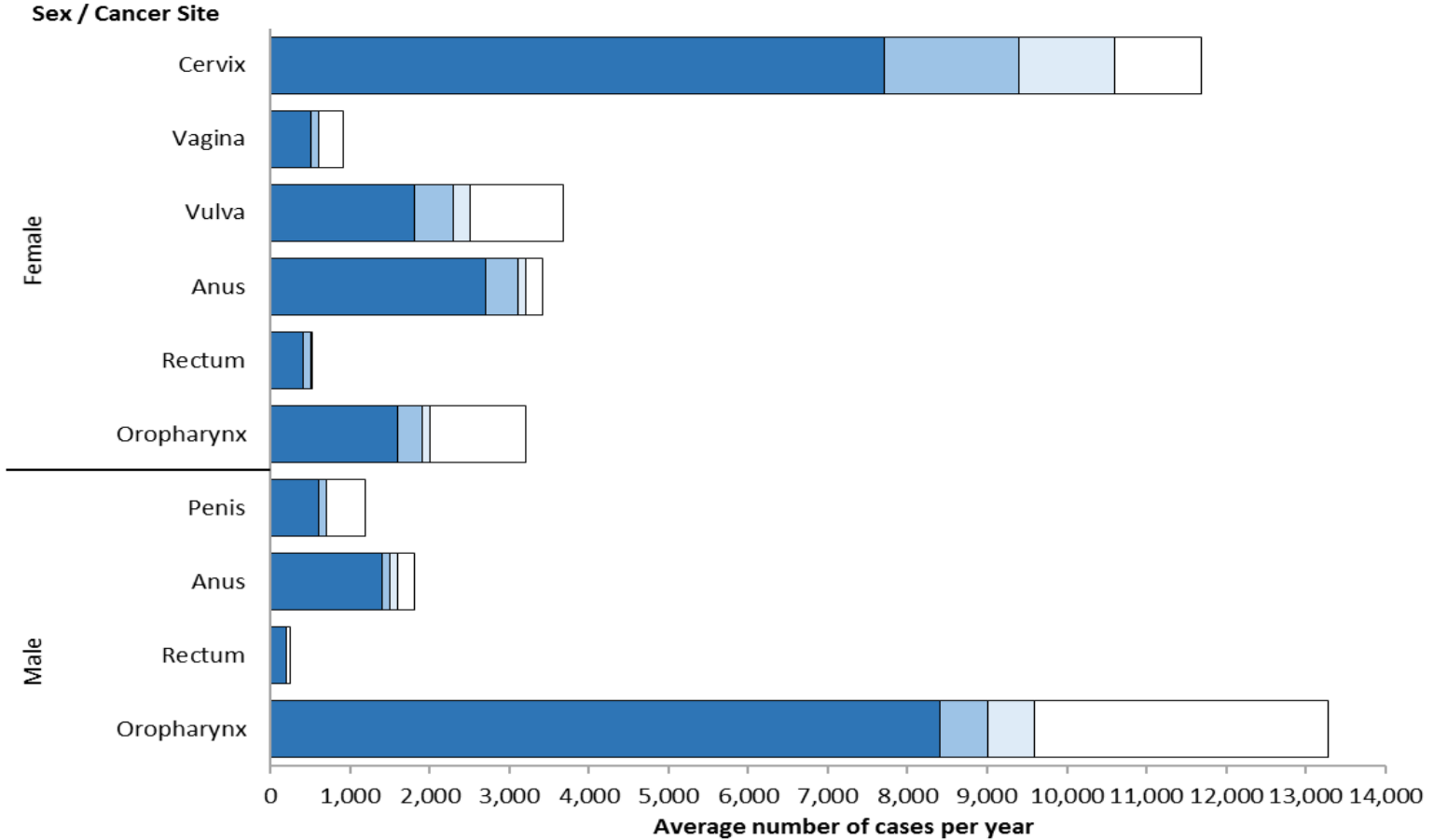
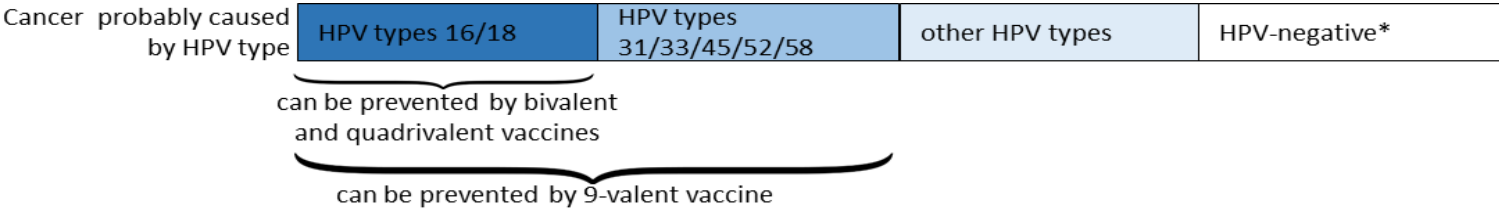
- HPV now recognized as one of the primary causes of oropharyngeal cancer
- In US, about 40-80% of oropharyngeal cancers are caused by HPV
- Increased incidence noted primarily in white men and at young ages
- Epidemiology of oral HPV infection is not well known

Marur D'Souza, Westra & Forastiere *Lancet Oncology* 2010

What about HPV 12-other?

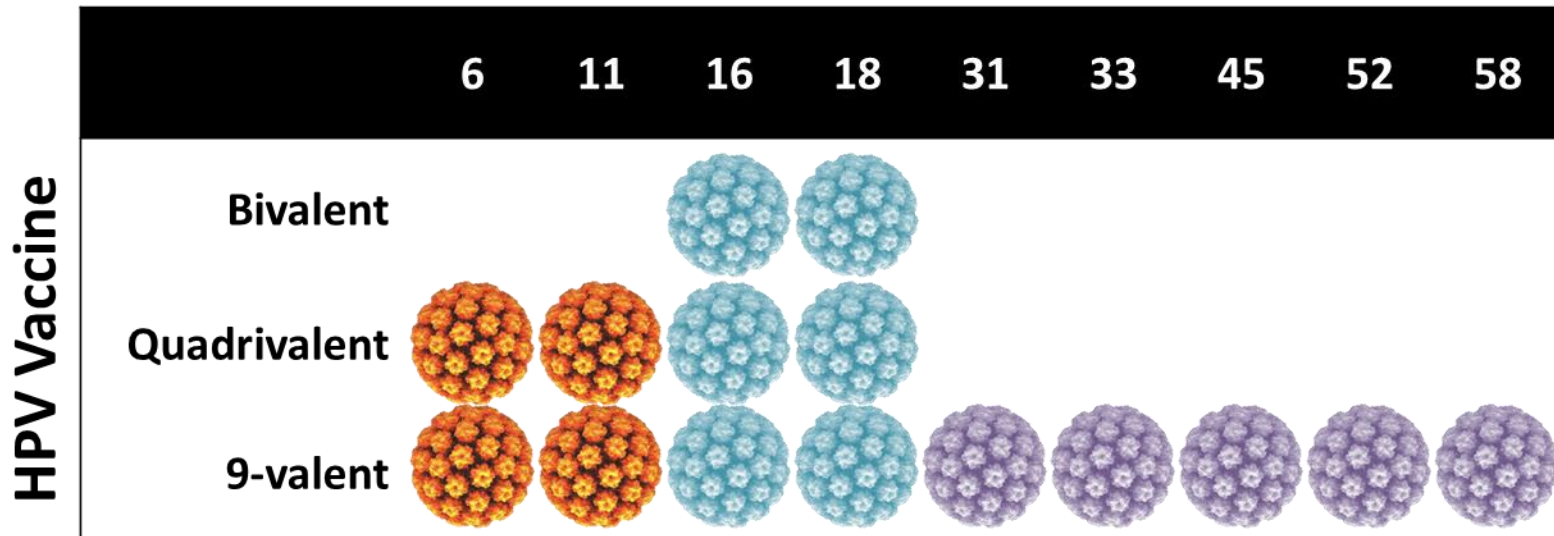
- HPV 12-other is a pool of 12 HPV types with varying risk
- HPV 12-other includes the “high-5” (HPV types 31,33,45,52,58), which cause an additional 22% of cervical cancer
 - also includes 7 more types less likely to cause cancer
- 50% of HPV clears w/in 12 months,

When HPV persists there is increased risk for cervical CA



High Risk HPV Types

HPV Types Included in Vaccine



These HPV Types Cause:

Genital warts

~66% of Cervical Cancers

~15% of Cervical Cancers

High Risk HPV Types



- *90% of KPNC Members are HPV NEGATIVE*
- *8% are HPV 12-other POSITIVE*
- *Only 2% are HPV 16/18 POSITIVE*

Current US Guidelines for Cervical Cancer Screening Methods of Average Risk Asymptomatic women (USPSTF)

- Age 21-29: Every 3 years with Pap testing.
- Age 30-65:
 - Every 5 years with HPV testing
 - OR every 3 years with Pap testing
 - OR every 5 years with co-testing (Pap+ HPV)

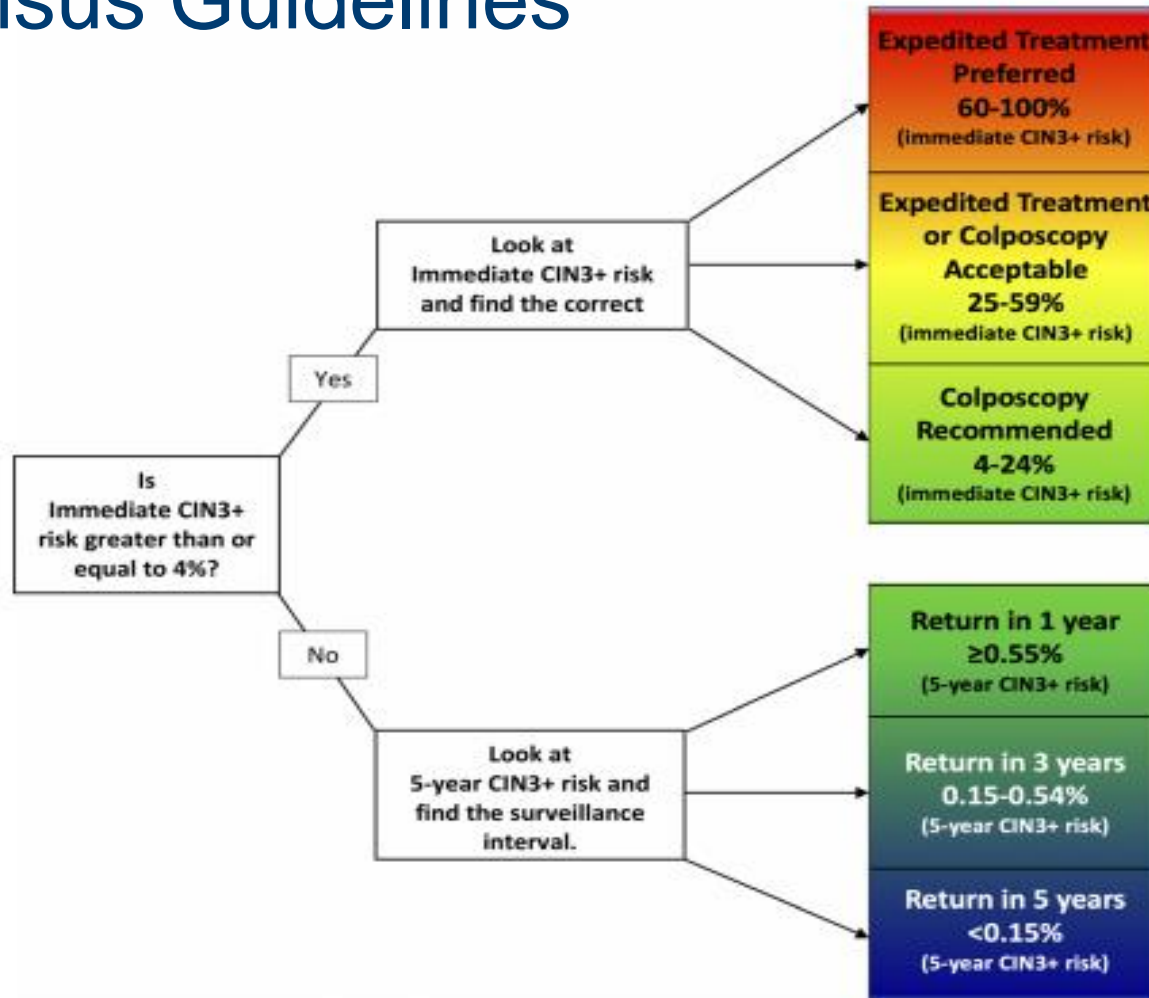


ACS HPV Recommendation

ACS Recommends the primary HPV test as the preferred test for cervical cancer screening for those 25-65 year of age

- Some HPV tests are approved only as part of the cytology/HPV co-test
- Primary HPV test may not be an option everywhere, a co-test every 5 years or pap test every 3 years are still good options

2019 ASCCP Risk Based Management Consensus Guidelines

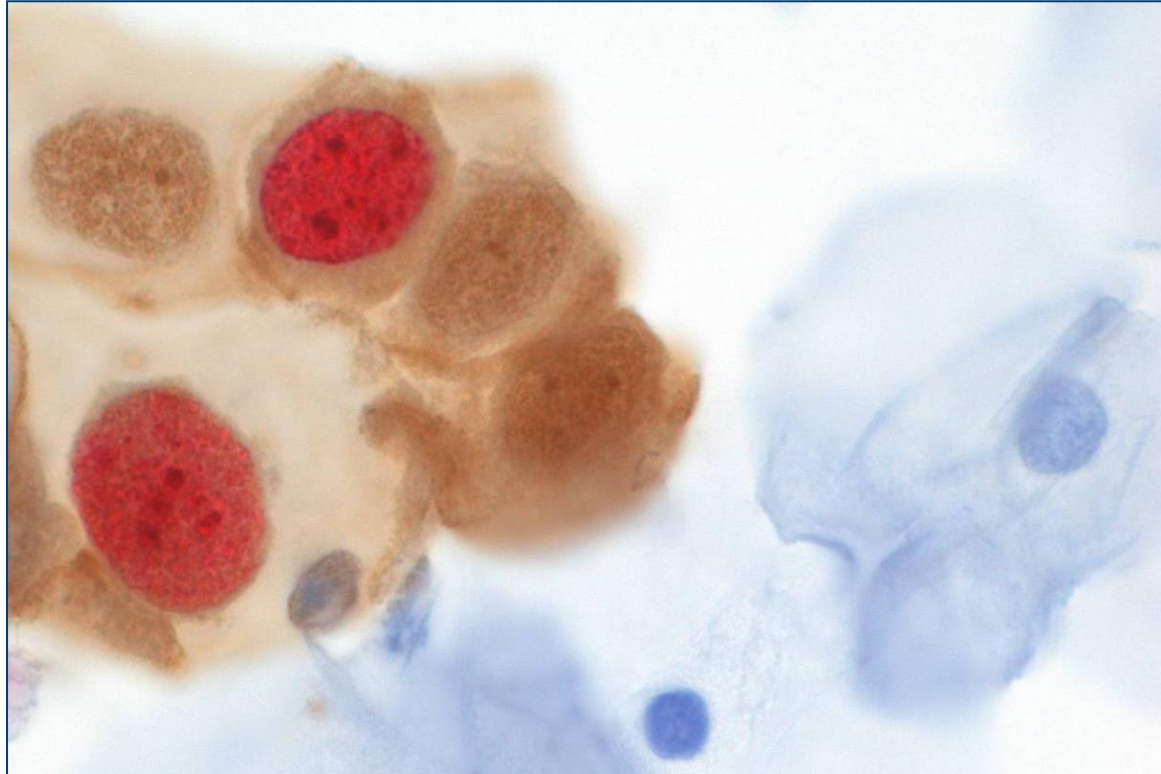


New KPNC Screening Guidelines

- Women 21-24: Pap alone, every 3 years
- Women 25-65: HPV primary screening, every 3 years with HPV Genotyping, and reflex Dual Stain cytology triage

Dual Stain (DS):

DS outperforms Pap in primary HPV triage in our population.



Markers of Transforming HPV infections:

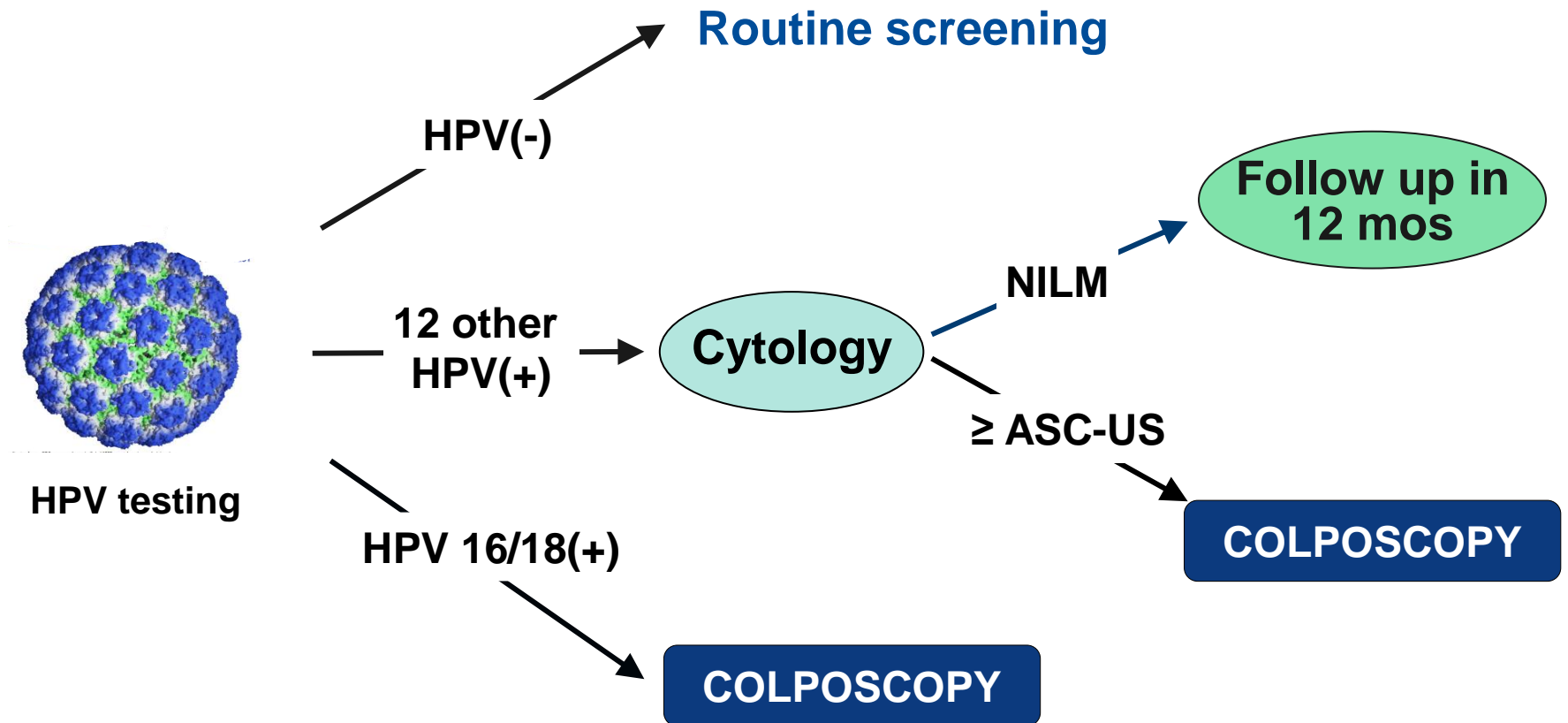
Brown cytoplasm indicates p16 positivity

Red nucleus indicates Ki-67 positivity

Slide image credit: Nicholas Wentzensen, MD, PhD; National Cancer Institute

Comparison of Screening Algorithms

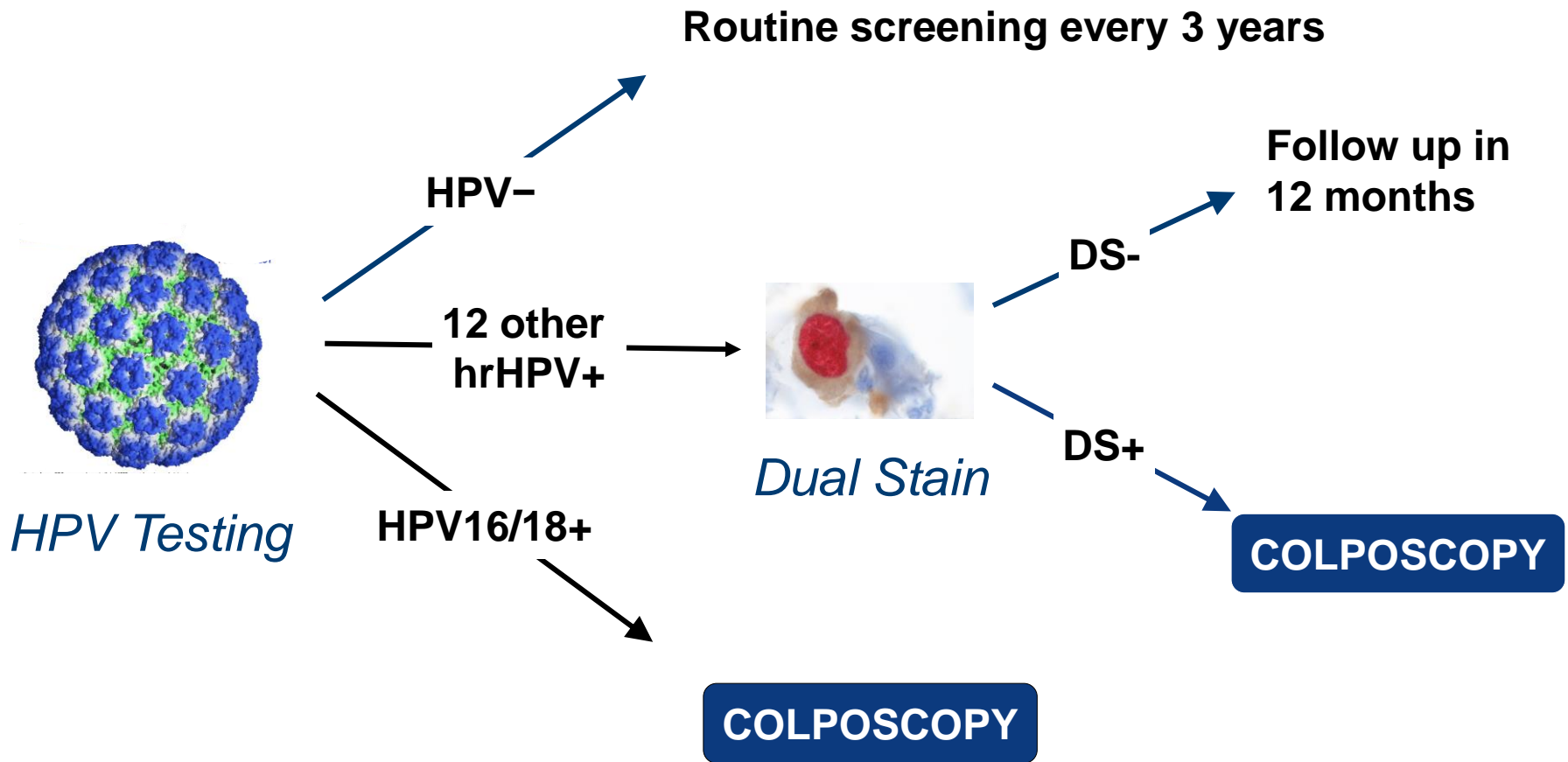
HPV primary screening (ACOG/FDA algorithm)



Algorithm image courtesy of Dr. Thomas Wright

Primary HPV Screening - ≥ 25 yrs

HPV Genotyping and Reflex Dual Stain



Wright *et al.* (2017) *Gynecol Oncol*

Screening member HPV 16/18 positive

- HPV 16/18 is Highest risk (70% of cervical cancers) → colposcopy now
- Even if Pap is normal & no prior abnormal history



66% of US teens 13-17yrs have received the HPV vaccine



Significant reductions in rates of infection & cervical neoplastic disease even in the nonvaccinated females & males aged <25 years

A single dose of vaccine still effective at 4 years, maybe longer

Herd immunity needs vaccination of 95% of boys **OR** girls. But, modeling studies suggest **60-70% OF BOTH** may be adequate.

Garland, Clin Ther 2014
Tabrizi, Lancet 2014

Pop Quiz- FAQs about HPV Vaccine

Can the HPV vaccine be given during pregnancy?

We cannot recommend this during pregnancy at this time.

Can the HPV vaccine be given if the patient is breastfeeding?

Yes

Can the HPV vaccine be given if the patient had an abnormal PAP test?

Yes

What if she does not know if she is vaccinated?

- Look at outside immunizations or ask patient to request records.
- Could re-administer.

HPV vaccination recommended through 26 years

Safe in patients 27- 45 years

Age < 15

2 doses

- 1st Dose
- 6-12 months later

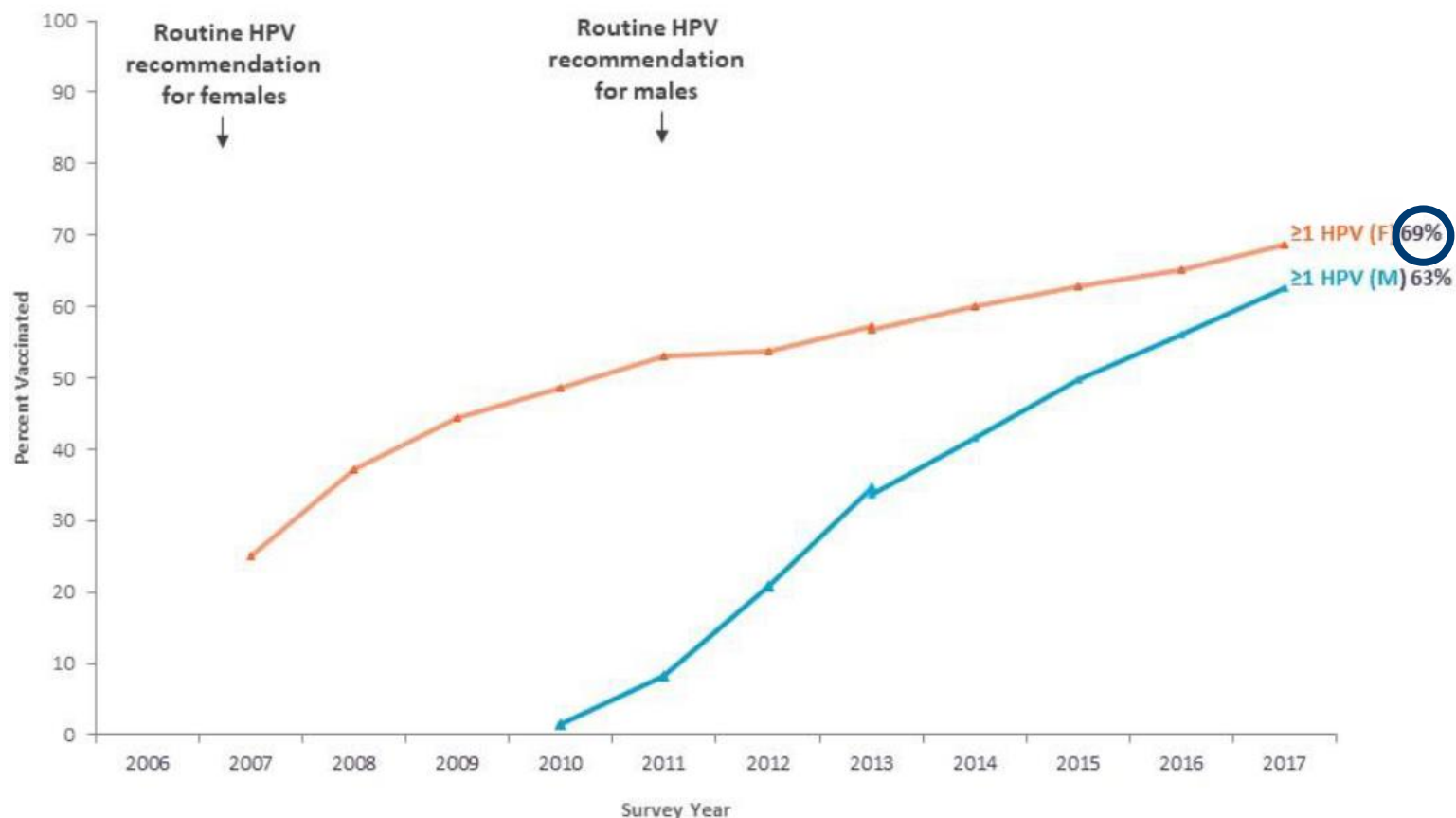
Age 15 and Older



3 doses

- 1st Dose
- 2 months later
- 6 months after 1st dose

The HPV vaccinated population comes of age.



Adapted from Walker et al. MMWR 2018; NIS-Teen, National Immunization Survey-Teen; UTD, Up-to-date

Note: revised definition of adequate provider data in 2013

FAQs about Vaccine Dosing



Scenario	Answer
Late for 2 nd or 3 rd injection	Give next dose; do not restart the series
Did not complete HPV4 series	Complete the series with HPV9
Completed HPV4 series	No not need to repeat vaccination with HPV9
Older than 26	Discuss with provider
Received COVAX	Wait 2 weeks after 2 nd dose.

Cotesting with HPV Genotyping

For patients 21-24y - PAP ONLY

For patients 25+y:

- Continue to collect two separate Pap and HPV
- + HPV 16/18 with normal Pap = *colposcopy now* regardless of HPV 12-other result
- If only HPV 12-other + (HPV 16/18 negative) with normal Pap and no prior abnormal = *retest in 12-months*

Cotesting with HPV Genotyping

Essential Management Changes

- Excision treatment is preferred to ablative treatment for CIN 2,3
- Observation is preferred to treatment for CIN1
- Histopathology recommend HGSIL should include CIN 2 or 3 qualifiers
- All primary Hpv + screening should have additional risk based screening – Dual Stain markers

Talking Points for Patients

HPV screening provides cancer protection and reduces unnecessary screening

- The HPV test separates types 16/18, from “12-other” HPV types
- No Pap screening for those 25 and older
- Dual Stain (DS) stains intracellular components, indicating precancerous risk
- Screening with Pap alone is recommended for those 21-24yo
- We recommend a 3-year CCS interval to maintain our current cancer protection.

Who Can Stop Screening?

- ✓ Do not have a history of dysplasia >CIN2 within the past 20 years, and no history of AIS or cervical cancer ever.

AND

- ✓ Are over 65 with at least 2 negative HPV tests within the last 10 years, 1 of which was in the last 5 years.

OR

- ✓ Have had a total hysterectomy and have no history of cancer of the cervix.



QUESTIONS?

