# 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

Financial disclosure: None

#### 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

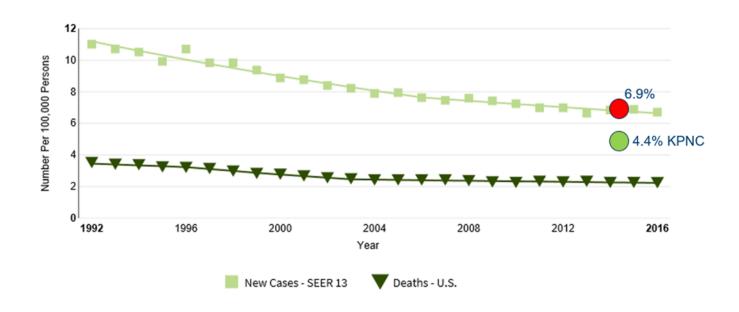
### 2. What is the sensitivity of Gyn Cytology test?

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

### 3. What is the sensitivity of HPV test?

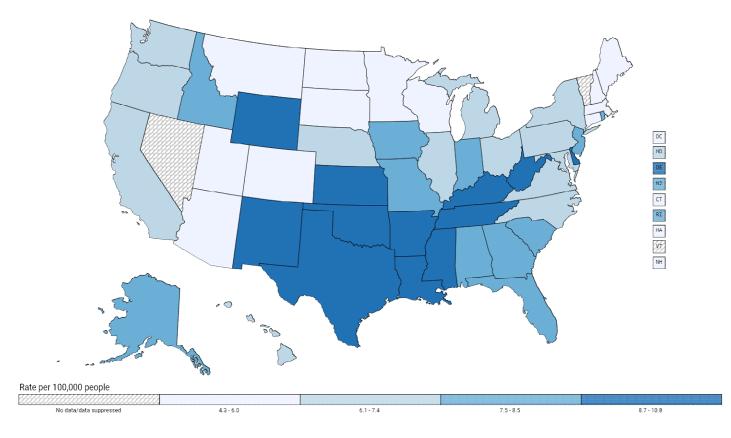
- a) 40%
- b) 55%
- c) 80%
- d) 95%

Why Now?
The Cervical Cancer rate is falling.



#### Cervical Cancer Incidence Rates – US 2018

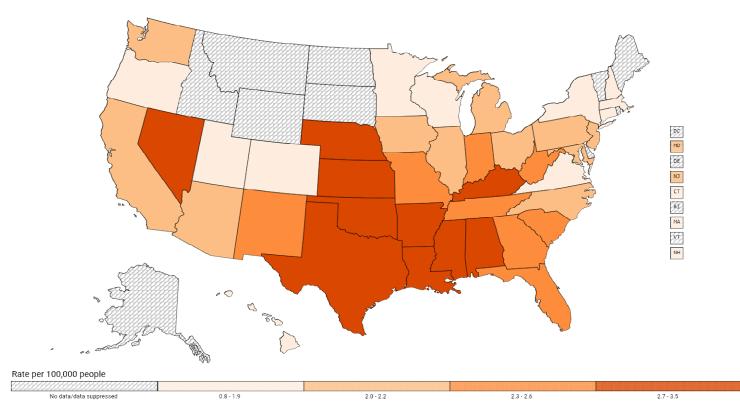
Rate of New Cancers in the United States, 2018 Cervix, All Ages, All Races and Ethnicities, Female

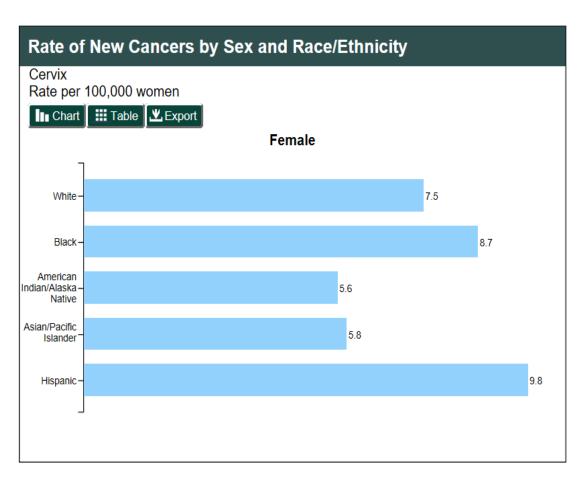


CDC Centers for Disease Control and Prevention

#### Cervical Cancer Mortality Rates – US 2018

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

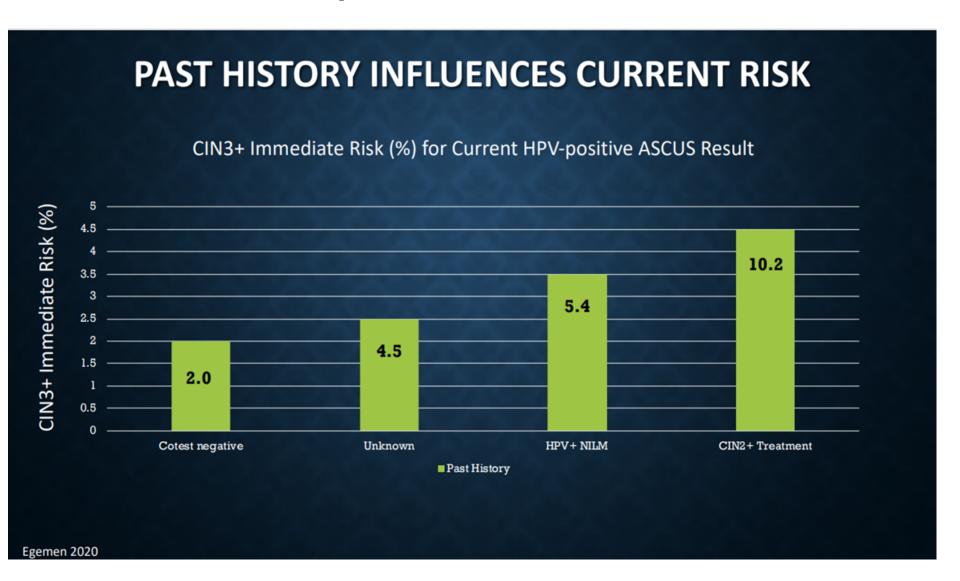




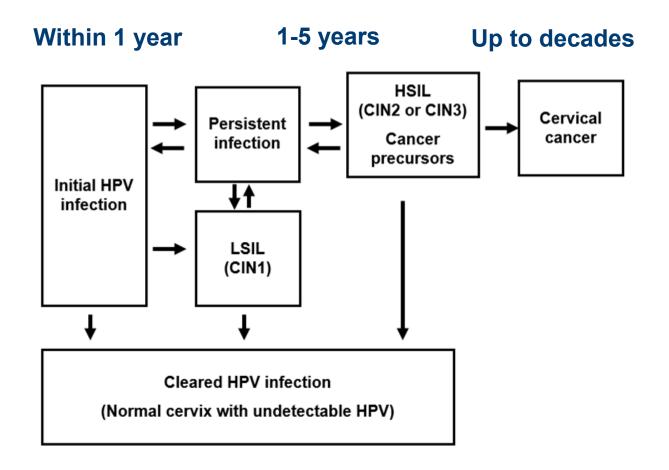
U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on November 2018 submission data (1999-2016): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; www.cdc.gov/cancer/dataviz, June 2019.

# Which Risk Factors Influence **Pre-Cancer Development?**

#### **Fundamental Concept**



#### **Natural History of HPV Infection**



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

#### **Virology – Human Papillomavirus**

Non-enveloped, double stranded, circular DNA virus Sexually transmitted HPVs falls into two categories:

Low risk can cause skin warts on or around the genitals or anus. HPV 6 &11 cause 90% of all genital wart

High risk, oncogenic HPVs, can cause cancer. HPV 16/18 responsible for the majority of HPV linked cancers



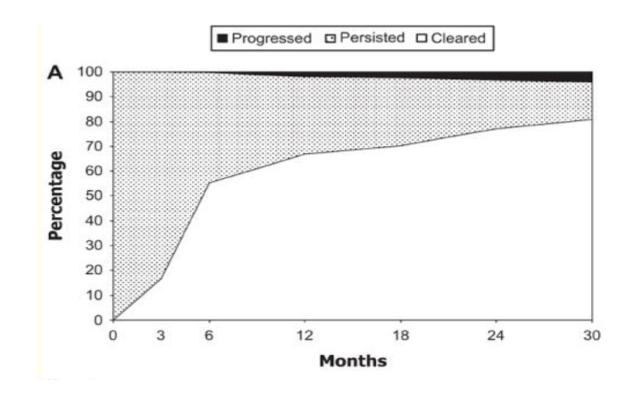
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#### **Fundamental Concept**

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

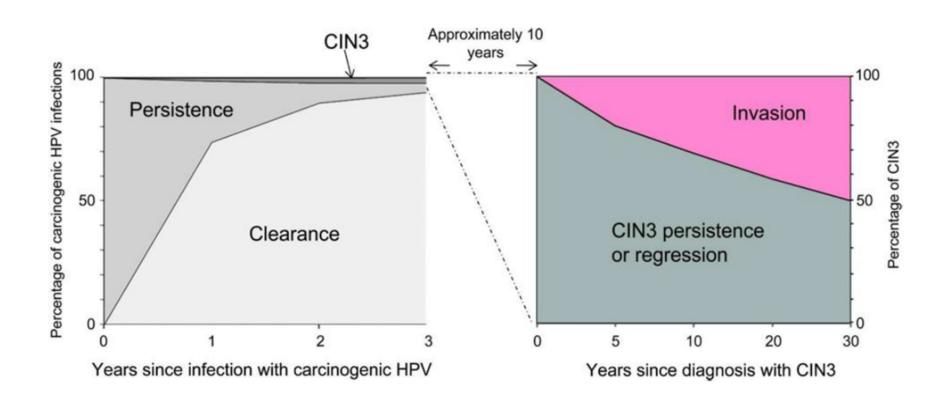
- Time matters
- Type matters (HPV 16 is most dangerous)
- Other patient factors don't matter if you know HPV status

# 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

# When HPV Infections Persist for 5 years or More, Precancer and Cancer Increase Markedly



#### **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

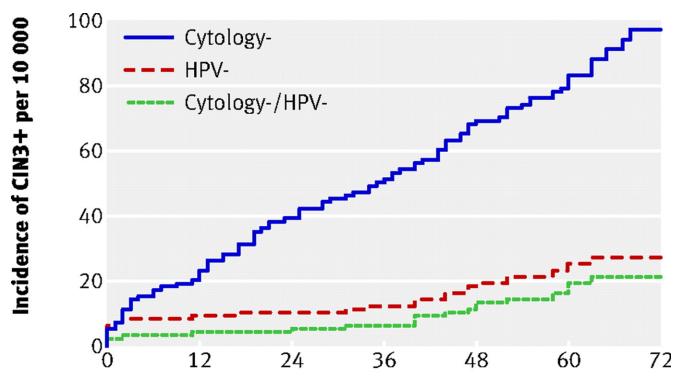
Personalized risk-based approach is possible with knowledge of current and past history

#### 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%

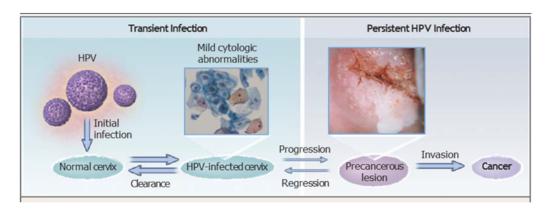


Dillner, BMJ 2008 Oct 13;337:a1754

Time since intake testing (months)
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#### **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 <u>a year earlier</u> 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

#### **High Risk HPV Types**



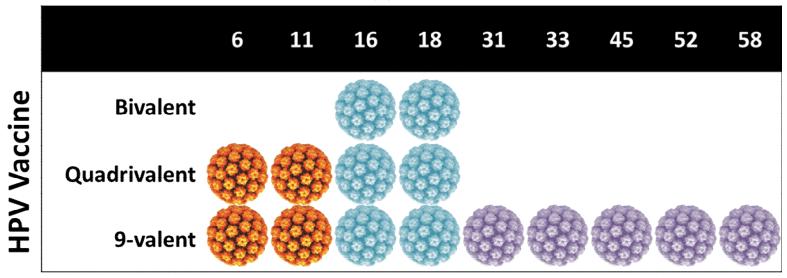
- 90% of KPNC Members are HPV NEGATIVE
- 8% are HPV 12-other POSITIVE
- Only 2% are HPV 16/18 POSITIVE

#### 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 within 12 months

#### **High Risk HPV Types**

#### **HPV Types Included in Vaccine**



These
HPV Types
Cause:

**Genital warts** 

~66% of Cervical Cancers

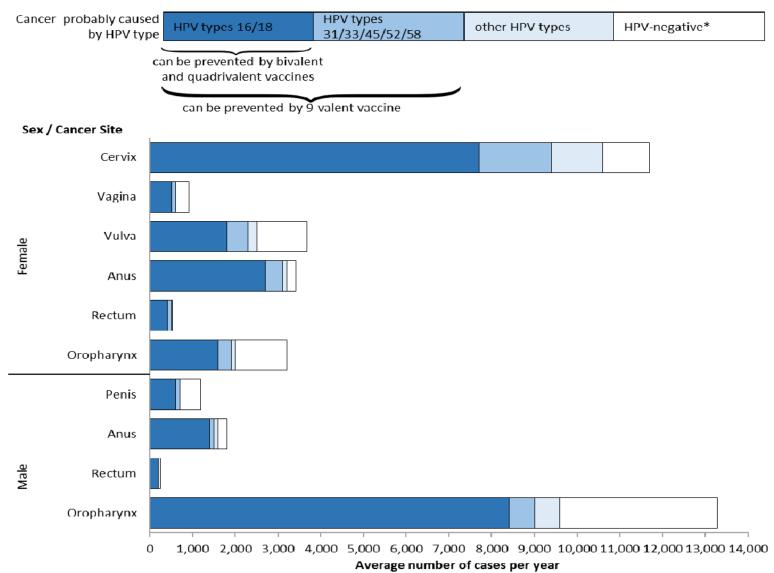
~15% of Cervical Cancers

#### 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

### When HPV persists there is increased risk for cervical CA



#### **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)

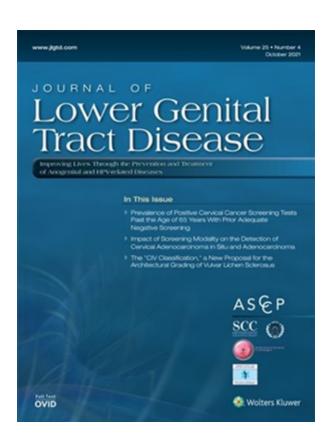


## **ACS HPV Recommendation**

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 cotest every 5 years or pap test every 3 years are still good options

# 2019 ASCCP Risk Based Management Consensus Guidelines



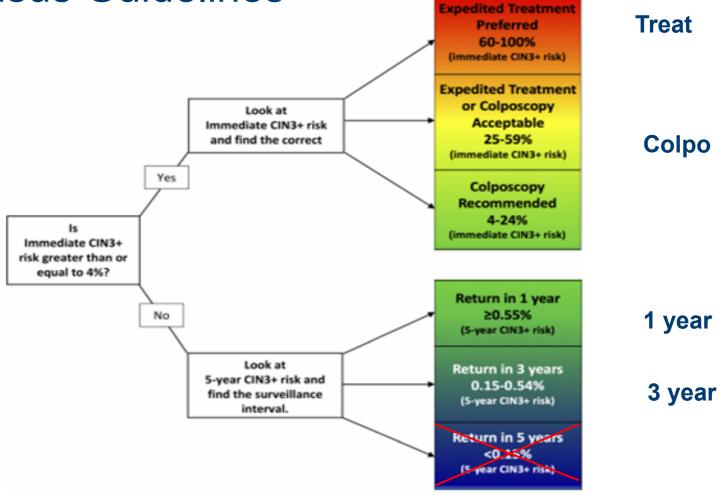
Published April 2020 Replaced the 2021/2013 Guidelines

Focus on management of cervical cancer screening results

New mobile based app released

2019 ASCCP Risk Based Management

Consensus Guidelines



#### **New KPNC Screening Guidelines**

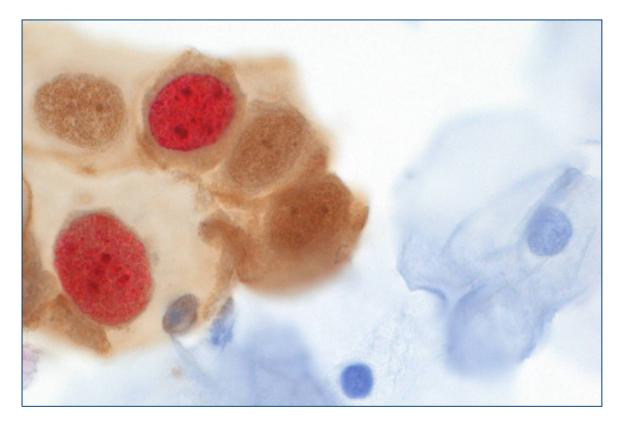
- Women 21-24: Pap alone, every 3 years
- Women 25-65: HPV primary screening, every 3 years with HPV Genotyping, and reflex Dual Stain cytology triage

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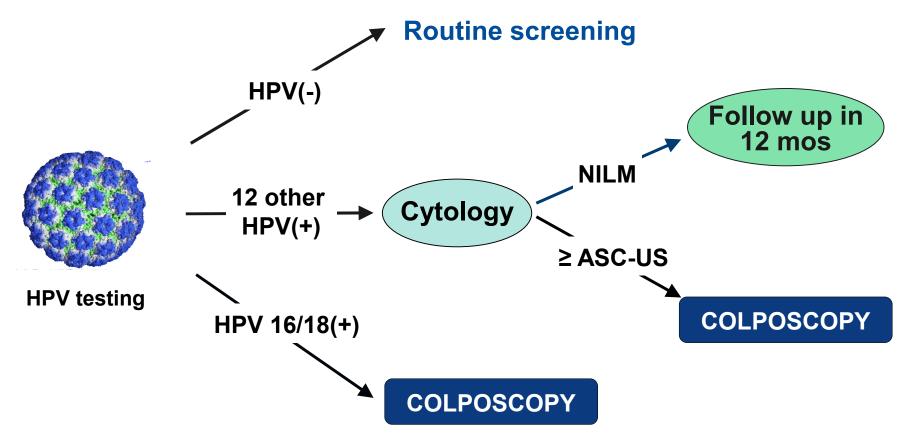
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# **Dual Stain (DS):**DS outperforms Pap in primary HPV triage in our population.



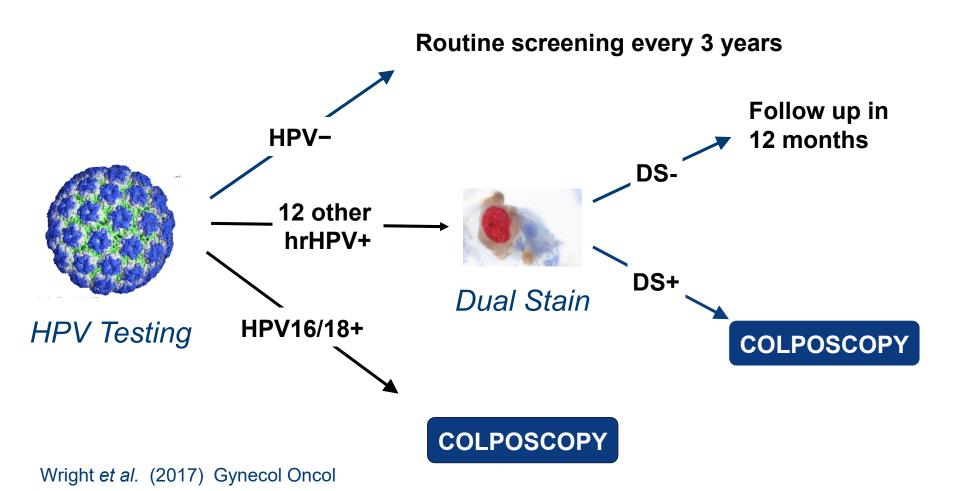
Markers of Transforming HPV infections: Brown cytoplasm indicates p16 positivity Red nucleus indicates Ki-67 positivity

## 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



#### The Key To Prevention – Vaccination



#### 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 We cannot recommend this during pregnancy at this time. during pregnancy? Yes 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? Look at outside immunizations or What if she does not know if ask patient to request records. she is vaccinated? 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

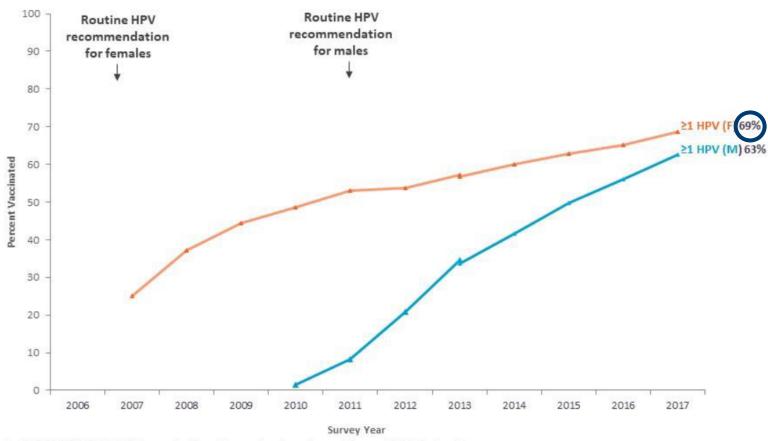
3 doses

►1<sup>st</sup> 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





Scenario	Answer
Late for 2 <sup>nd</sup> or 3 <sup>rd</sup> 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 <sup>nd</sup> dose.

## **Cotesting with HPV Genotyping**

For patients 21-24y - PAP ONLY

#### For patients 25+y:

- + HPV 16/18 with normal DS = colposcopy now regardless of HPV 12-other result or prior history
- If <u>only</u> HPV 12-other + (HPV 16/18 negative) with normal DS and no prior abnormal = <u>retest in 12-months</u>

## **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

#### **Key Takeaways:**

- New KPNC screening guidelines for women 25-65: HPV is the primary screening method, with HPV genotyping and Dual Stain as the triage instead of Pap.
- 2. Dual Stain triage is equally sensitive, but much more specific than Pap. This is how we can detect the same number of precancers with fewer colposcopies.
- 3. Patients need to be informed of the screening change at every point of contact prior to their appointment using recommended language.
- 4. Use "Cervical Cancer Screening," instead of "Pap"



#### **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 <u>not</u> 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?**

