Cervical Cancer Screening – It's all about HPV

Women's Health Care: Updates for Primary Care

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Objectives

- Briefly review USPSTF cervical cancer screening guidelines
- Understand ASCCP risk-based guidelines for immediate and long-term risk for CIN3+
- Make an argument for HPV-only cervical cancer screening in average risk populations
- Bring awareness of Oregon HB 4011

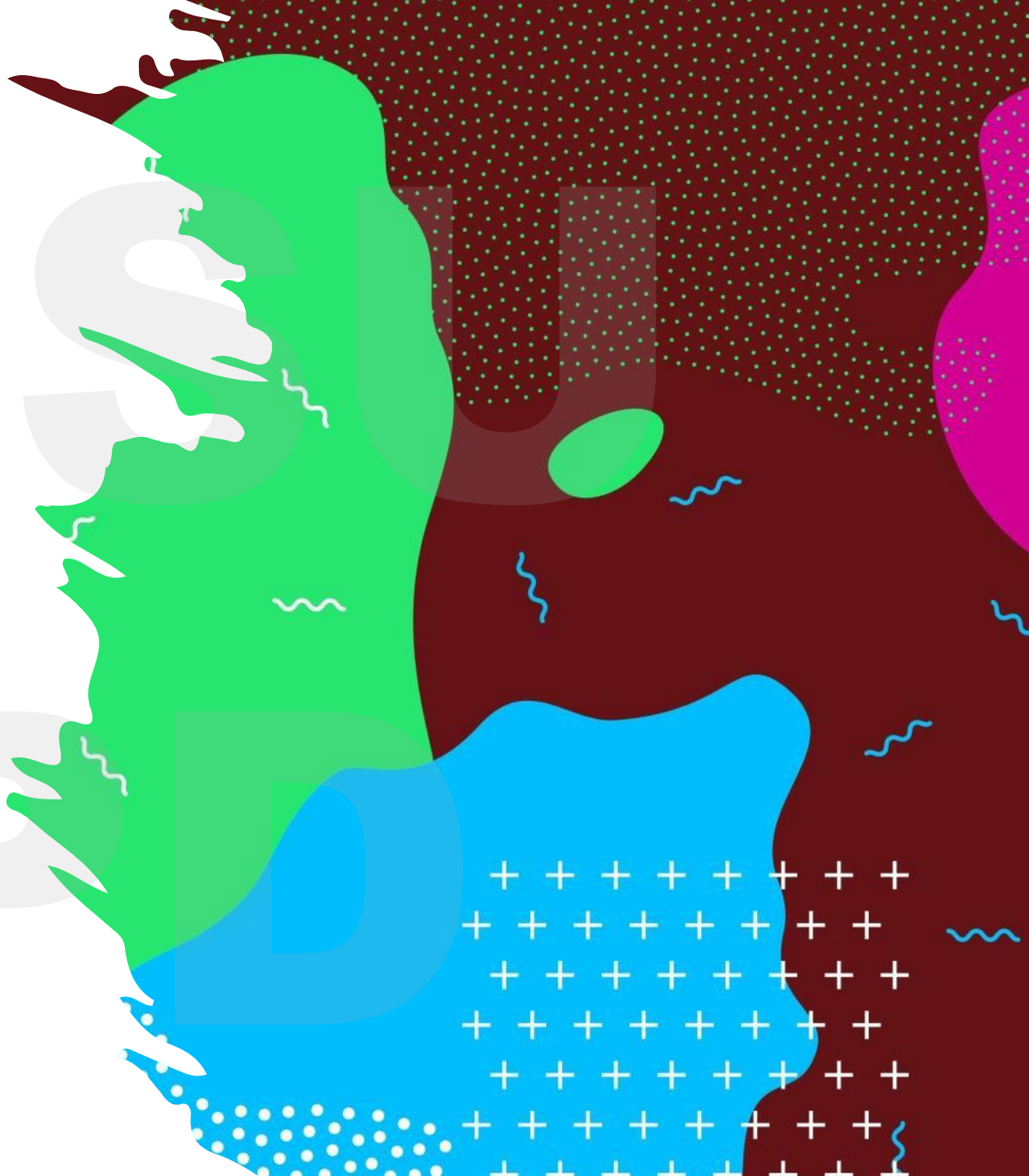
Background

- Cervical cancer disproportionally affects women of color and women of lower socioeconomic status.
  - Mortality rate from cervical cancer among African American women is 10.1 deaths per 100k women.
  - AA women are screened for cervical cancer at rates similar to those for white women, but inadequate follow-up after screening is an important contributing factor resulting in disparity in outcomes

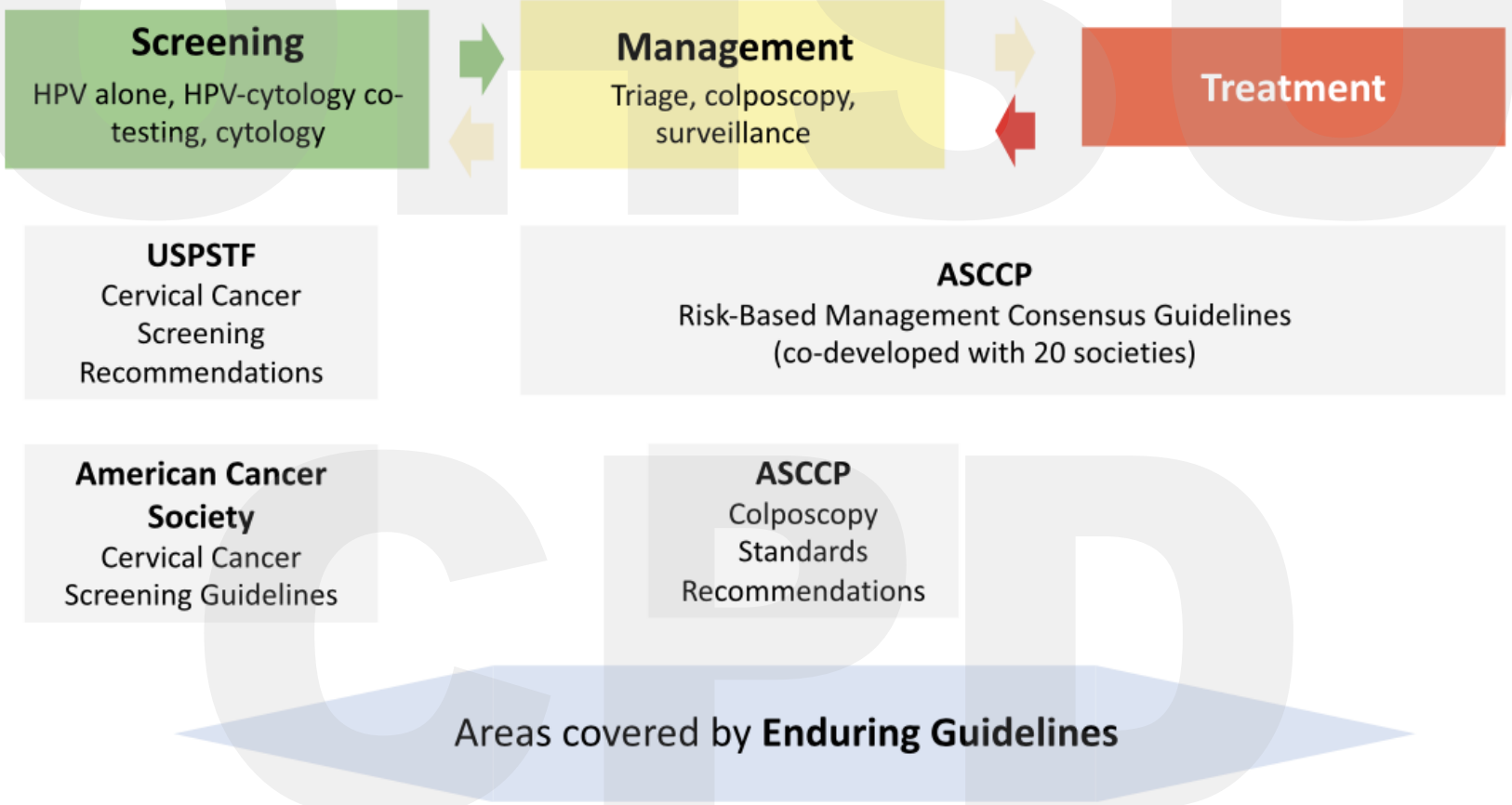
Evolution of Cervical Cancer Screening

- 1960s – switch from vaginal to cervical specimens
- 1990s – addition of HPV triage to cytology (i.e., cytology with reflex)
- 2010s – co-testing with cytology + HPV
- Today – primary HPV testing

HPV testing has high sensitivity and a strong, long-term reassurance of a low cancer risk with a negative test.



Overview of cervical screening & management guidelines in the US



J Low Genit Tract Dis 2024;28: 117–123

Table 1. USPSTF Recommendations for Routine Cervical Cancer Screening

Population*	Recommendation	USPSTF Recommendation Grade†
Aged less than 21 years	No screening	D
Aged 21–29 years	Cytology alone every 3 years‡	A
Aged 30–65 years	Any one of the following: • Cytology alone every 3 years • FDA-approved primary hrHPV testing alone every 5 years • Cotesting (hrHPV testing and cytology) every 5 years	A
Aged greater than 65 years	No screening after adequate negative prior screening results§	D
Hysterectomy with removal of the cervix	No screening in individuals who do not have a history of high-grade cervical precancerous lesions or cervical cancer	D

Abbreviations: FDA, U.S. Food and Drug Administration; hrHPV, high-risk human papillomavirus testing.

Screening Guideline Populations

- Recommendations apply to individuals with a cervix who do not have any signs or symptoms of cervical cancer, regardless of their sexual history or HPV vaccination status.
- These recommendations DO NOT APPLY to individuals who are at high risk for cervical cancer (e.g., in utero exposure to DES or those with a compromised immune system)

- Primary hrHPV testing is FDA approved for use starting at age 25 years.
- ACOG, ASCCP, and SGO endorse primary hrHPV testing q5yrs and as an alternative to cytology-only screening in average risk patients aged 25-29 yrs

- Adequate negative prior screening test results are defined as:
  - 3 consecutive negative cytology results
  - 2 consecutive negative co-testing results
  - 2 consecutive negative hrHPV test results within 10 years before stopping screening, with most recent test occurring within the recommended screening interval for the test used.

2020 ASCCP Guidelines

- Updated consensus guidelines for management of abnormal cervical cancer screening results in asymptomatic patients
- Goal: maximize cervical cancer prevention while limiting harms from overtesting and overtreatment
- *ASCCP = American Society of Colposcopy and Cervical Pathology

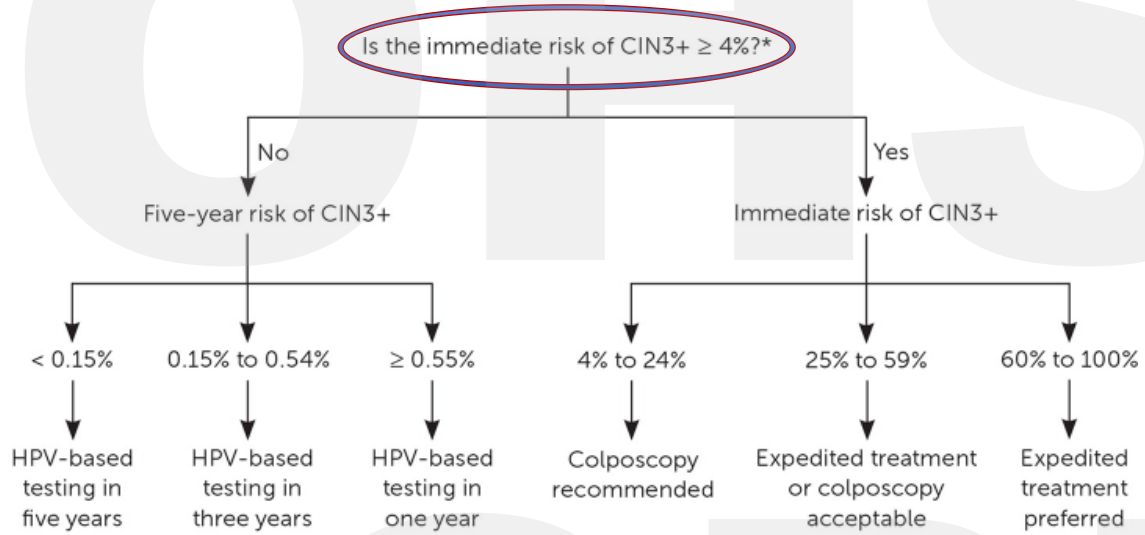
It’s all about HPV

- Persistent HPV infection is necessary for developing cervical cancer or precancer
- Observational cohort of nearly 1 million women in the Kaiser Permanente Northern California system
    - Negative HPV test (or co-test) in the past 5 years correlates with 50% decrease in risk of CIN 3+
- Adding in prior screening + biopsy results to current test result allows appropriate attention for risk of CIN 3+ AND avoids unnecessary interventions for patients at lower risk

Focus on Individual Risk for CIN3+

- ASCCP guidelines help determine risk for CIN3+
  - CIN3
  - Adenocarcinoma in situ
  - Invasive cervical cancer
- **Immediate vs Long-Term Risk**
  - **Colposcopy and treatment recommendations are based on immediate risk of CIN3+ (threshold of 4% or greater)**
  - **Longer-term surveillance recommendations are based on 5-year risk of CIN3+**
- Risk estimates based on prospective longitudinal cohort of 1.5 million+ patients followed 10+ years at Kaiser Permanente Norther California

Management recommendations based on immediate and five-year risk of CIN grade 3 or worse.



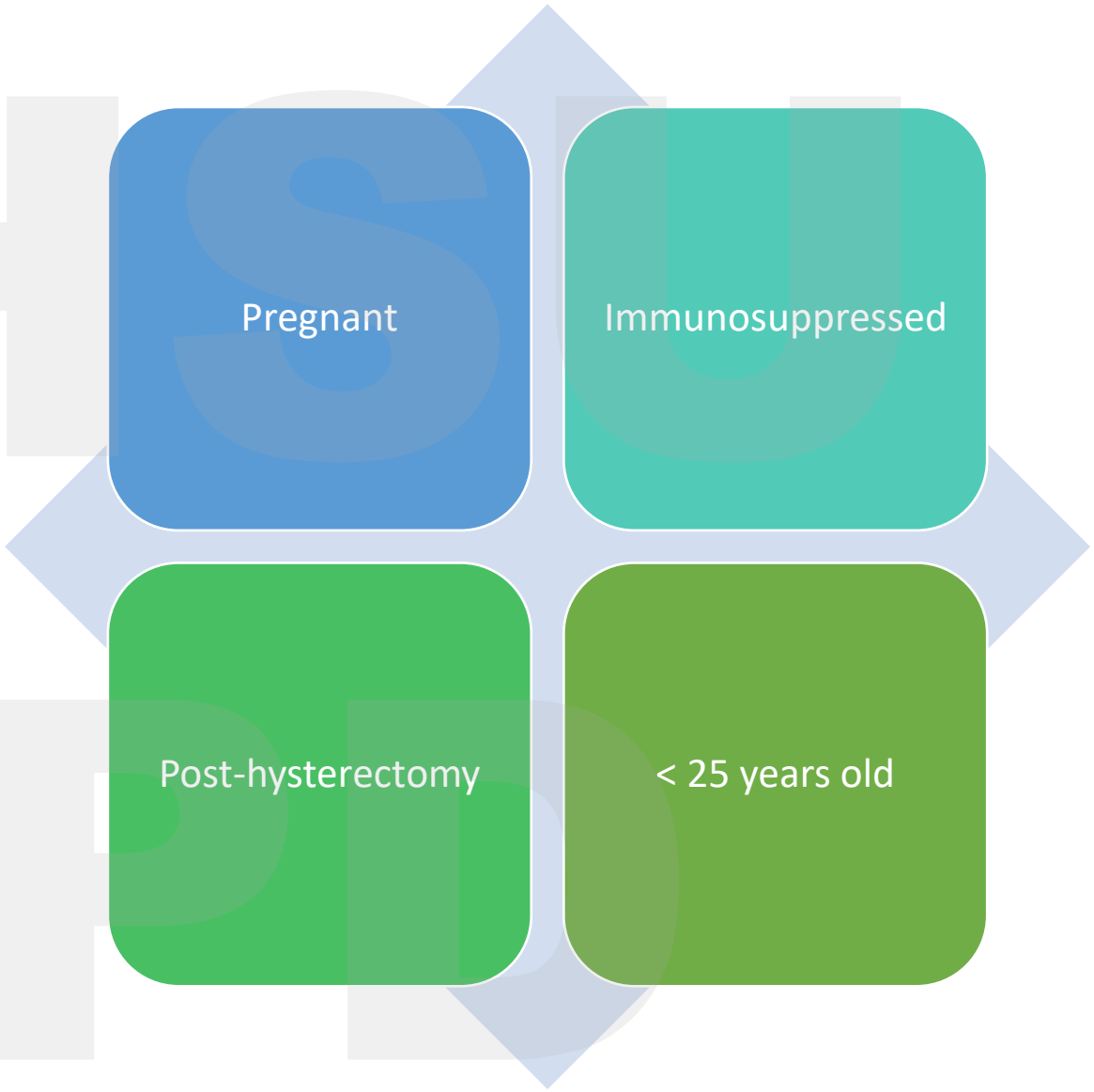
CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus.
*—To estimate the risk of CIN3+, see https://app.asccp.org.

https://www.aafp.org/pubs/afp/issues/2024/0300/pocg-abnormal-cervical-cancer-screening.html (accessed 3/31/2024)

Factors for Individualized Risk Assessment

- Patient age
- Current screening results (HPV only, co-test, cytology only)
- Prior screening and biopsy results
- History of precancer treatment

Additional Patient-Specific Considerations



eTABLE A

Risk Stratification Options for Cervical Cancer Screening

Population	Recommendation
Low risk	No testing
Patients who have had a hysterectomy (including the cervix) because of benign conditions	
Patients with a cervix but who have comorbidities and decreased life expectancy	
Average risk	Primary HPV testing
Patients 25 to 65 years of age with a cervix	
High risk*	Cotesting
Patients 30 to 65 years of age with a cervix and a high-risk condition (i.e., solid organ transplantation, chronic diseases managed by Janus kinase inhibitors or biologics, immunosuppressive drug treatment, HIV/AIDS, postcoital bleeding, or under surveillance for prior HPV-positive testing per American Society for Colposcopy and Cervical Pathology guidelines)	

HPV = human papillomavirus.

*—High risk is not defined by smoking status, drug use, number of sex partners, or age (Demarco M, Egemen D, Hyun N, et al. Contribution of etiologic cofactors to CIN3+ risk among women with human papillomavirus-positive screening test results. *J Low Genit Tract Dis*. 2022;26(2):127-134).

Harper DM, Bettcher CM, and Young AP. It Is Time to Switch to Primary HPV Scfeening for Cervical Cancer. Amer Fam Phys. Jan 2024, vol 109, no 1 (8-9c)

Details around Primary HPV Screening – current state

- Patients experience the same speculum examination; the difference is what happens in the laboratory and with the result.

- The fine print says primary hrHPV testing should be FDA-approved (Either SurePath or ThinPrep).
  - Roche Cobas – reports HPV 16 and 18 individually, and groups 12 other types
  - BD Onclarity - reports 6 individual HPV types (16, 18, 31, 45, 51, and 52) and 3 groups of combined types (33/58), (35/39/68), and (56/59/66).

- The challenge is that no self-collection method (yet) is FDA approved.
  - FDA-appoved vaginal self-sampling is coming soon!

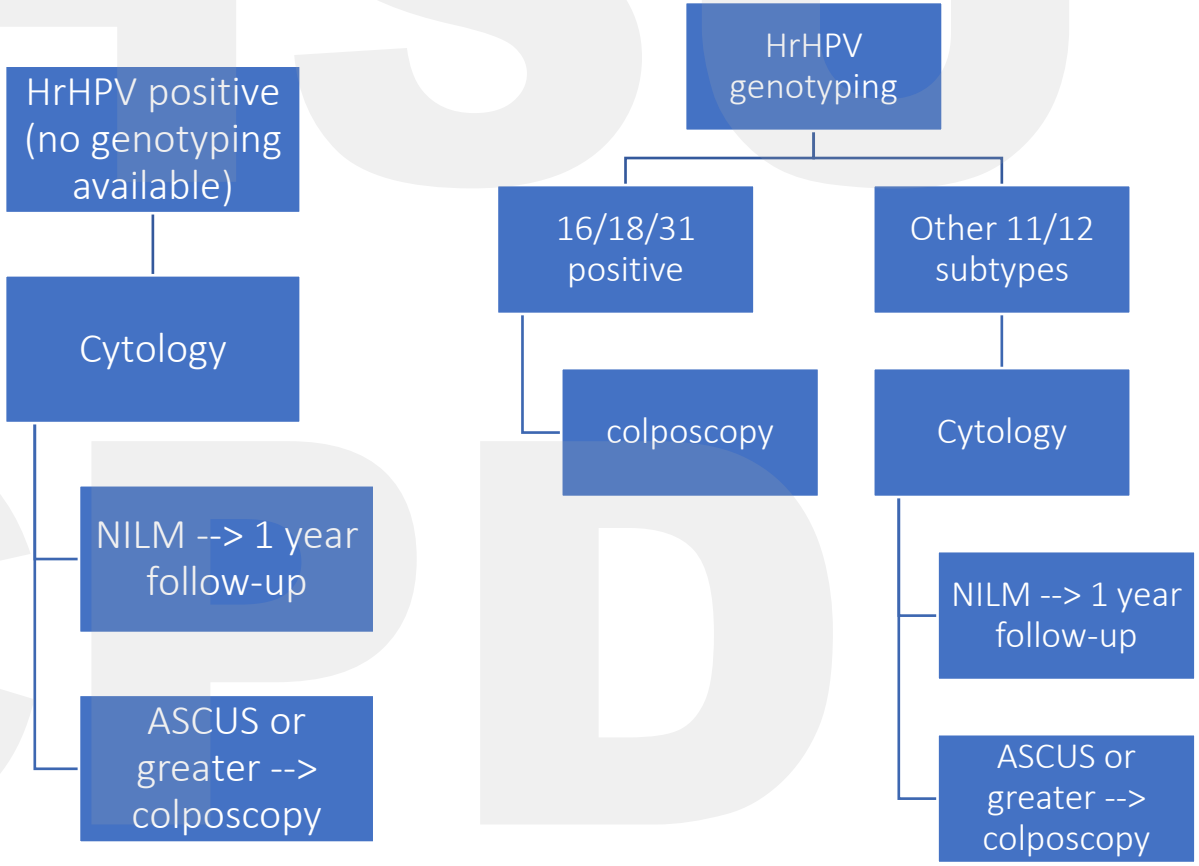
Risk Management of Primary HPV Screening Results

Pooled hrHPV test **negative**

- HPV-based testing in 5 years

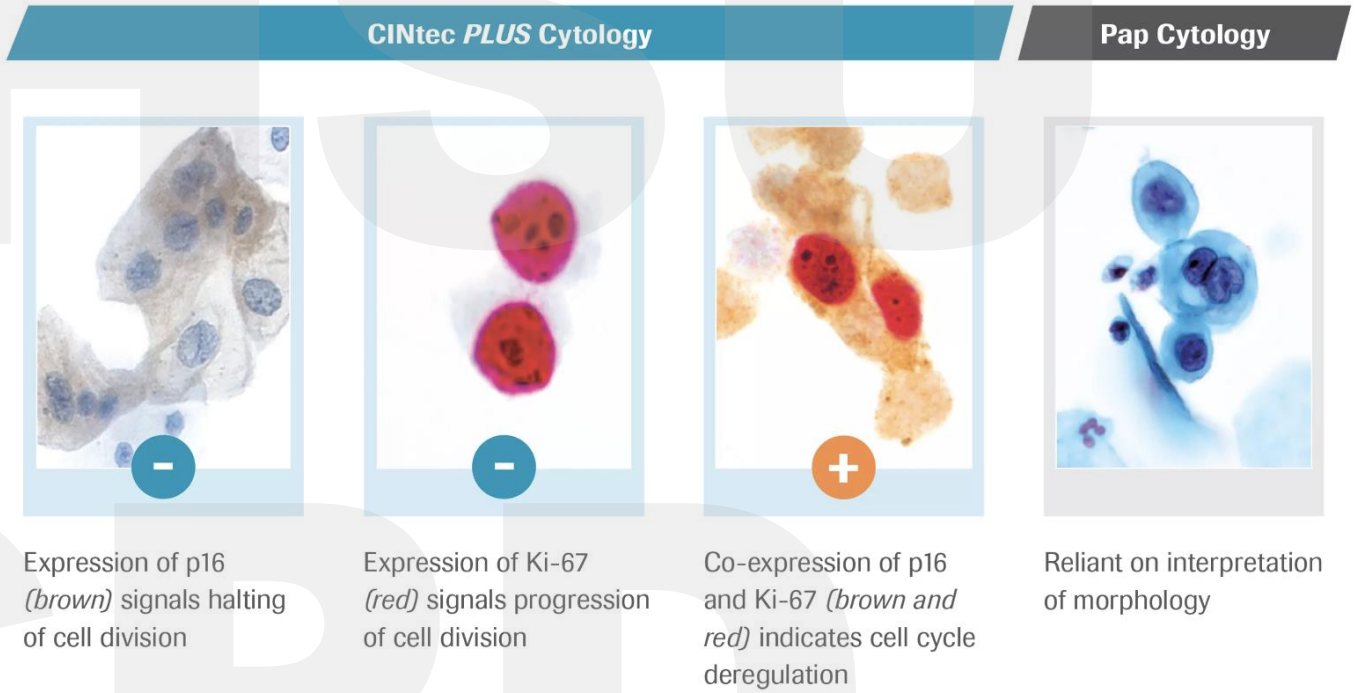
Pooled hrHPV test **positive**

- genotyping and/or use of reflex cytology

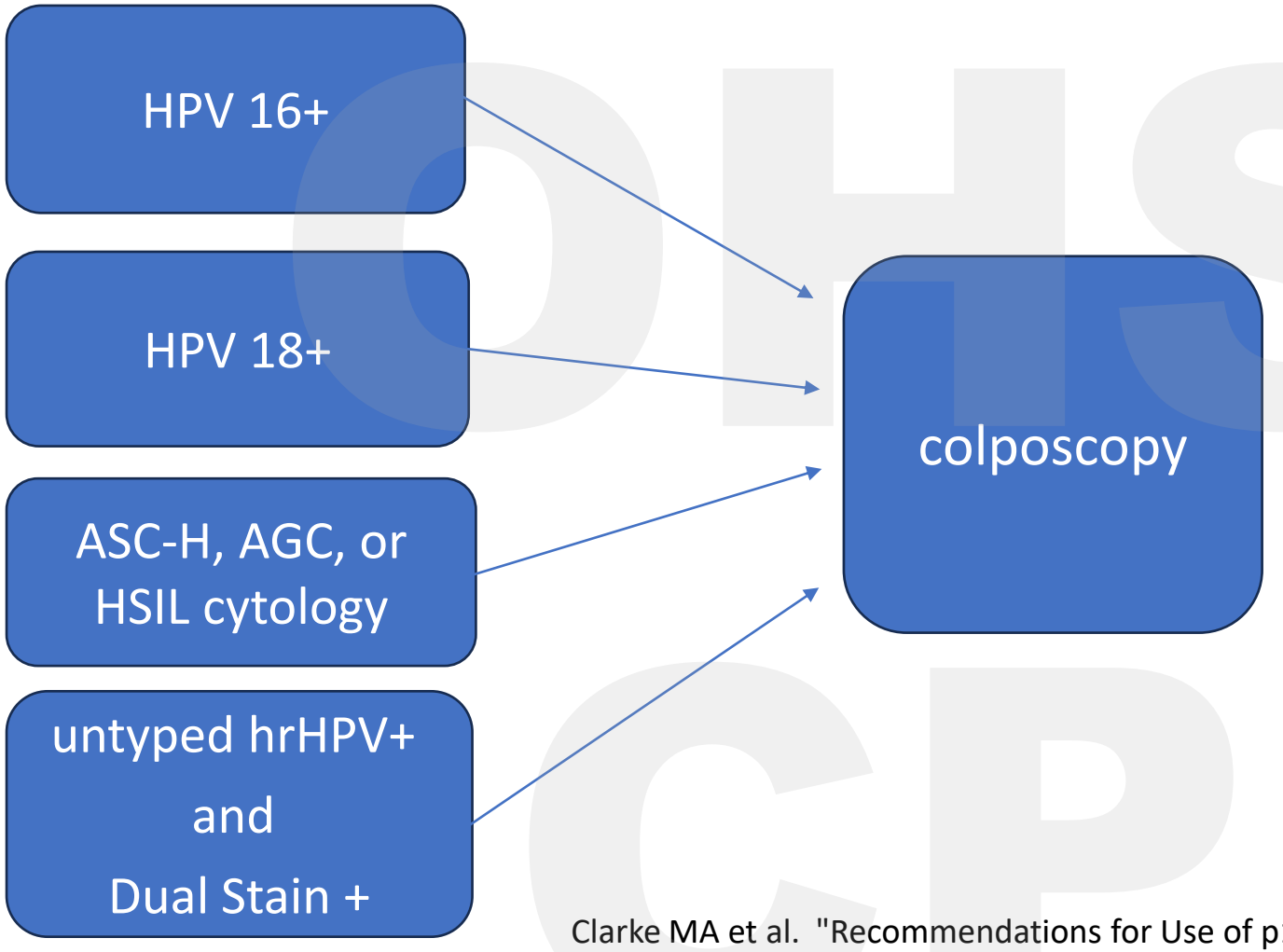


On the horizon: addition of p16/Ki67 Dual Stain

- Dual stain positive (DS+) testing will be added to triage hrHPV positive screening test results
- 2024 consensus paper calculated risks of CIN 3+ using DS results among individuals testing HPV+ using data from the Kaiser Permanente Northern California cohort and the STudying Risk to Improve DisparieiES study in Mississisppi.
- For individuals who screen positive with primary HPV testing (with or without genotyping) or with cytology co-testing, further DS testing is a way to even further stratify risk for CIN3+ and guide need for colposcopy.



https://diagnostics.roche.com/us/en/products/tests/cintec-plus.html



When compared with cytology, use of Dual Screen requires fewer colposcopies and detects CIN3+ earlier.

Clarke MA et al. "Recommendations for Use of p16/Ki67 Dual Stain for Management of Individuals Testing Positive for Human Papillomavirus." J Low Genit Tract Dis 2024;28: 124–130

Primary HPV Screening – It's Time

- As effective as cotesting at detecting cervical cancer
- Decreases the number of lifetime screenings needed
- USPSTF modeled the various screening strategies
  - Harms defined as: lifetime # tests, colposcopies, false + results, cervical cancer cases, cervical cancer deaths
  - Benefits defined as: life-years gained, disease detected, cancer averted
- Current common screening practice of cyto alone q3 yrs for individuals with a cervix age 21-29 followed by co-testing q5yrs from age 30-65 years led to the highest number of lifetime cytology tests per 1000 women.
- Primary HPV screening provides equally accurate disease detection with fewer lifetime tests

Self-sampling for Primary HPV Screening

- HPV is transmitted skin-to-skin and must travel through the vagina before reaching the cervix
- 2 self-sampling approaches have been studied:
    - Tampon-like device placed into vagina, turned several times, then placed in a transport tube and sent to the lab
    - Urine approach – gather desquamated cells coming from cervix, vagina, external genitalia in the first part of the urine stream (similar to collection for STIs)
- Both are non-inferior to clinician collection of sample at cervical os

Health Equity & Health Disparities

- Individuals can collect their own samples
- Potential to increase # individuals who complete screening

Value Proposition

- Early cost-effectiveness analyses suggest overall cost savings
  - Savings from not performing co-testing may be able to cover current out-of-pocket costs for colposcopy
  - Cytopathologists are highly trained and becoming more difficult to hire
  - Health systems may be able to utilize the limited # cytopathologists for diagnostic testing
- Affordable Care Act mandates coverage for screening tests
  - US Congress to potentially amend ACA to cover all screening and evaluation costs for cervical cancer
  - Payors could easily shift costs from routine screening cytology to cover out-of-pocket costs for colposocopy
  - Mimics what has happened with colorectal cancer screening and diagnostic colonoscopies

HB 4011

- HB4011 is the omnibus Behavioral Health and Health Care Committee Bill to eliminate deductibles, co-insurance, copayment or out-of-pocket costs for medically necessary diagnostic testing for cervical cancer under commercial insurance.
- Modeled after SB1041 (2023) which removes out-of-pocket costs for insurance coverage of diagnostic breast examinations unless required by federal or state law.
- Oregon law currently requires coverage for diagnostic follow-up for both colon cancer and breast cancer screening. It helps to eliminate obstacles to early diagnosis.
- Currently In House Committee at time of Legislature Adjournment

Bringing it back to prevention - a word about HPV vaccination

- Current CDC Guidelines recommend routine or catch-up HPV vaccination for individuals aged 9 to 26 years, and shared decision-making regarding vaccination for individuals aged 27 to 45 years.
- Multiple published studies suggest a possible benefit for adjuvant HPV vaccination in previously unvaccinated individuals aged 27 to 45 years who are undergoing treatment for CIN2+.
- How does the prophylactic HPV vaccine work?
  - may prevent HPV-related disease by inducing neutralizing antibodies directed at virus-like particles of the capsid protein, preventing the virus from entering the host cells.
  - may be beneficial if the vaccine provides protection from new future infectious with HPV types that the individual has not been previously exposed.
  - may provide cross-protection to other HPV types not covered by the vaccine and my also boost the immune response to HPV infection from the same type, providing additional protection from reinfection with the same HPV type.

Thank You

References/Resources

- Curry SJ, Krist AH, Owens DK, Barry MJ, Caughey AB, Davidson KW, et al. Screening for cervical cancer. US Preventive Services Task Force Recommendation statement. USPSTF. JAMA 2018;320:674-86
- Harper DM, Bettcher CM, and Young AP. It Is Time to Switch to Primary HPV Scfeening for Cervical Cancer. Amer Fam Phys. Jan 2024, vol 109, no 1 (8-9c)
- ASCCP Management Guidelines & Decision Aid, https://app.asccp.org
- Wentzensen N et al., Enduring Consensus Guidelines for Cervical Cancer Screening and Management: Introduction to the Scope and Process. J Low Genit Tract Dis 2024;28: 117–123.
- Clarke MA et al. "Recommendations for Use of p16/Ki67 Dual Stain for Management of Individuals Testing Positive for Human Papillomavirus." J Low Genit Tract Dis 2024;28: 124–130