Advances in prevention and early diagnosis of cervical cancer

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Cervical Cancer Prevention

- Primary Prevention:
  - VACCCINE
  - Limit # of sexual partners
  - Use of condoms
- Secondary prevention
  - Early identification of premalignant lesions

U.S. Estimated New Cancers Attributable to HPV *in Women* 2008–2012

Cancer Site	New Cases (n)	Attributable to any HPV type (%)	Attributable to HPV 16/18 (%)	Attributable to HPV 16/18/31/33 45/52/58 (%)
Cervix	11,771	91	66	81
Vagina	802	75	55	73
Vulva	3,554	69	49	58
Anus	3,260	93	80	91
Rectum	513	93	51	61
Oropharynx	3,100	63	51	61

LJ Viens, et al: Human Papillomavirus–Associated Cancers — United States, 2008–2012 Weekly / July 8, 2016 / 65(26);661–666

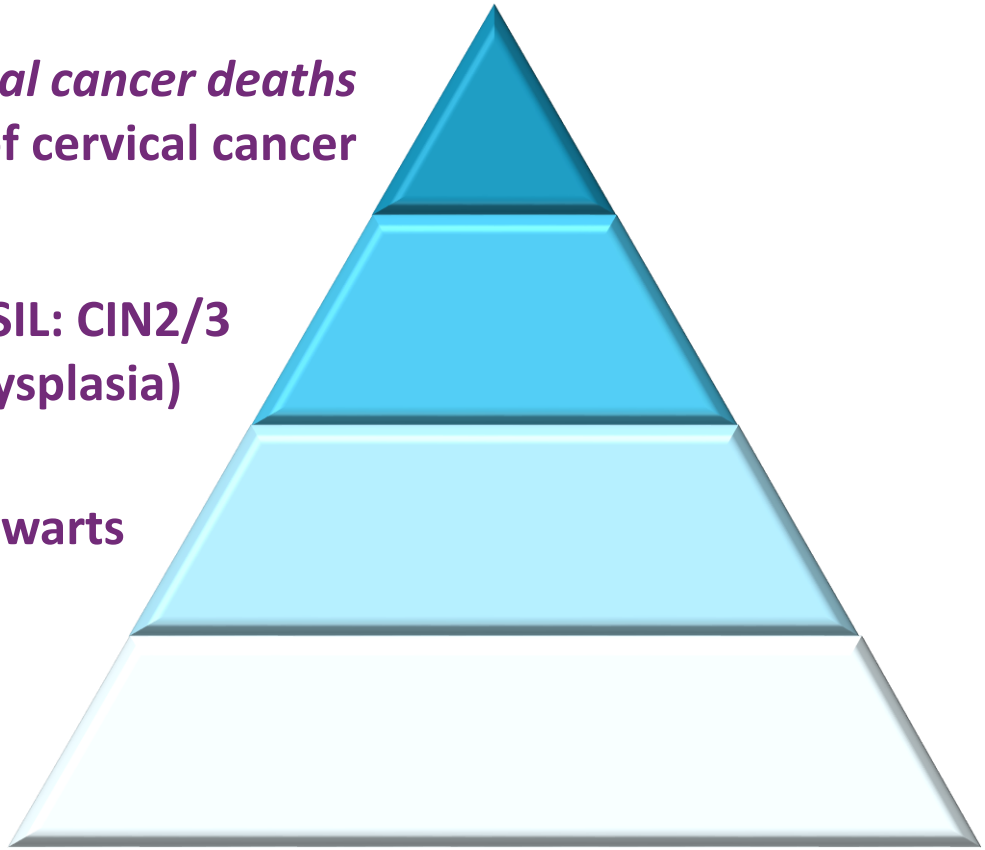
Annual burden of genital HPV-related disease in U.S. females *without vaccination*

4,000 cervical cancer deaths
10,846 new cases of cervical cancer

330,000 new cases of HSIL: CIN2/3
(high grade cervical dysplasia)

1 million new cases of genital warts

1.4 million new cases of LSIL: CIN1
(low grade cervical dysplasia)



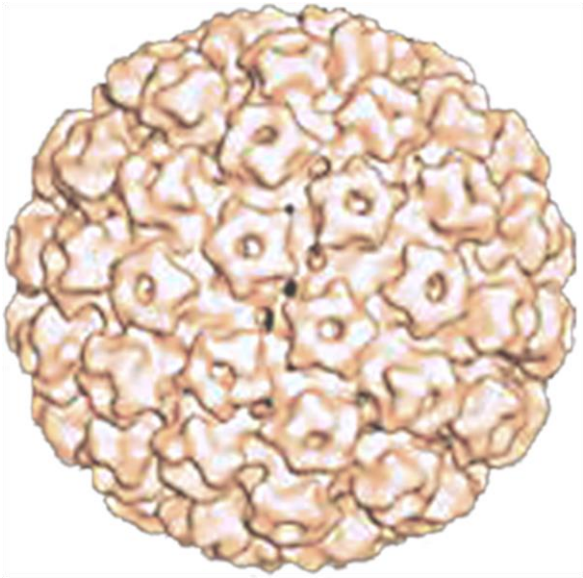
3 million cases and $7 billion

American Cancer Society. 2008; *Sex Transm Dis*. 2004; Schiffman *Arch Pathol Lab Med*. 2003; Koshiol Insinga, Pharmacoeconomics, 2005

YOU ARE THE KEY TO CANCER PREVENTION

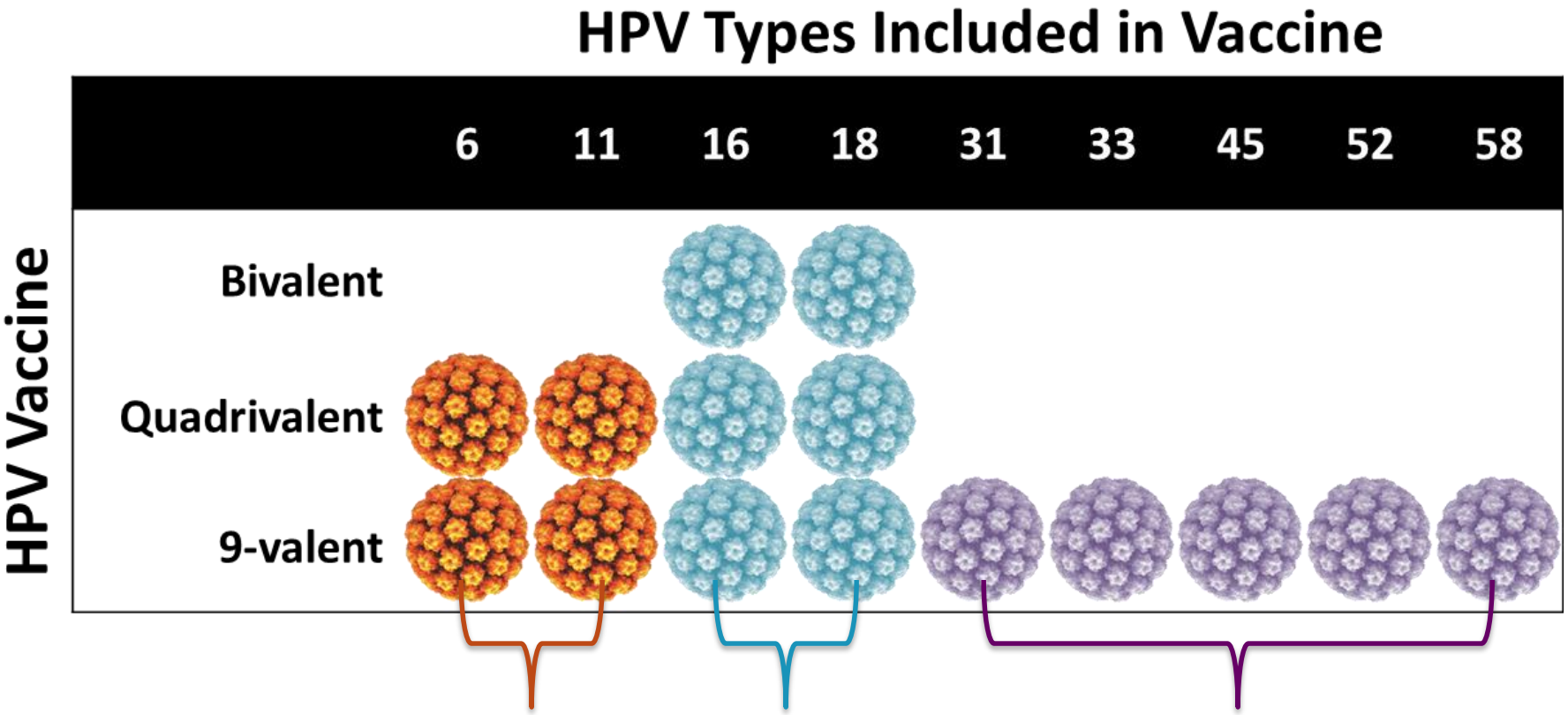
HPV Prophylactic Vaccines

- Recombinant L1 capsid proteins that form "virus-like" particles (VLP)
- Non-infectious and non-oncogenic
- Produce higher levels of neutralizing antibody than natural infection



HPV Virus-Like Particle

HPV Vaccine Comparison



Adapted from Petrosky et al. MMWR. 2015.

HPV YOU ARE THE KEY TO CANCER PREVENTION

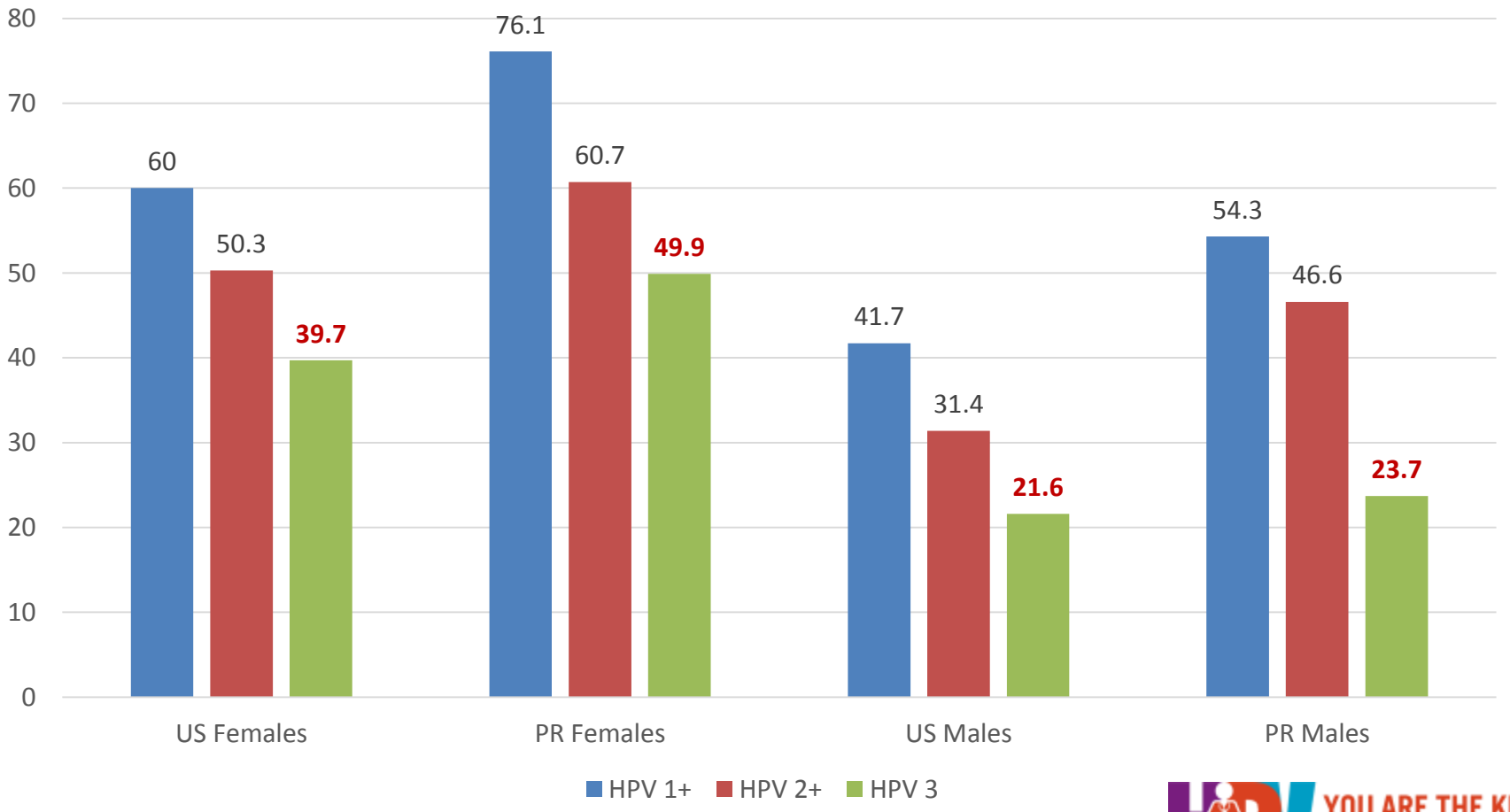
HPV Vaccines Approved by the FDA in the U.S.

Coalición para el Control de Cáncer de Puerto Rico
PROGRAMA DE CONTROL COMPRENSIVO DE CÁNCER

	Cervarix	Gardasil	Gardasil 9
Contains VLPs	HPV: 16, 18	HPV: 6, 11, 16, 18	**HPV: 6, 11, 16,18, 31, 33, 45, 52, 58**
Indicated: Women	√	√	**√**
Men		√	**√**
Cervical Pre-Cancer and Cancer	√	√	**√**
Vulvar Cancer	√	√	**√**
Vaginal Cancer		√	**√**
Anal Cancer (M/W)		√	**√**
Genital Warts (M/W)		√	**√**
Doses (Schedule)	3 (0, 1, 6 mo.)	3 (0, 2, 6 mo.)	**3 (0, 2, 6 mo.)**

HPV YOU ARE THE KEY TO CANCER PREVENTION

Estimated HPV vaccination coverage by doses among adolescents aged 13–17 years in U.S. and Puerto Rico— NIS–Teen (NIS-Teen), U.S. 2014



YOU ARE THE KEY TO CANCER PREVENTION

Dosing Schedules

Starting the vaccine series before the 15th birthday

Recommended schedule is 2 doses of HPV vaccine.

- Second dose should be administered 6–12 months after the first dose (0, 6–12 month schedule).
- Minimum interval between dose one and dose two in a 2-dose schedule is 5 months

Starting the vaccine series on or after the 15th birthday*

Recommended schedule is 3 doses of HPV vaccine.

- Second dose should be administered 1–2 months after the first dose, and the third dose should be administered 6 months after the first dose (0, 1–2, 6 month schedule).
- Minimum interval between dose one and dose three in a 3-dose schedule is 5 months

*and immunocompromised persons 9-26 years

Meites et al. MMWR. 2016.

YOU ARE THE KEY TO CANCER PREVENTION

HPV Vaccine Recommendations: Catch Up/Late

- Vaccination for females and males through age 26 years.

Meites et al. MMWR. 2016.

HPV: A Necessary but Insufficient Cause of Cervical Cancer

- Other cofactors necessary for progression from cervical HPV infection to cancer
  - Established cofactors: tobacco smoking, high parity, long-term hormonal contraceptive use, coinfection with HIV[a]
  - Probable cofactors: coinfection with *Chlamydia trachomatis*, herpes simplex virus type-2, immunosuppression, certain dietary deficiencies[a]
  - Likely important: genetic and immunologic host factors and viral factors other than type (ie, variants of type, viral load, viral integration[b]
- High number of sexual partners increases acquisition of oncogenic HPV infections[a]

a. ICO HPV Information Centre website.
b. Muñoz N, et al. *Vaccine*. 2006;24:1-10.

HPV Persistence

- **Persistent infection: Detection of same HPV type two or more times over one year and more[1]**
- **Widely accepted that persistence of high-risk types of HPV is crucial for development of cervical precancer and cancer[1]**
- **Other associated factors**
  - **Age (≥30 years)*,[2]**
  - **Infection with multiple HPV types[3]**
  - **Immune suppression[4]**
- **Currently, there are no antivirals available to treat the underlying HPV infection.[5]**

1. Schiffman M, Kjaer SK. *J Natl Cancer Inst Monogr*. 2003;31:14–19. **2.** Hildesheim A, Schiffman MH, Gravitt PE, et al. *J Infect Dis.* 1994;169:235–240. **3.** Ho GYF, Burk RD, Klein S, et al. *J Natl Cancer Inst.* 1995;87:1365–1371. **4.** Kobayashi A, Greenblatt RM, Anastos K, et al. *Cancer Res*. 2004;64:6766–6774. **5.** Stanley M. *J Natl Cancer Inst Monogr*. 2003;31:117–124.

Screening Objective

Identify Patients with:

- Persistent HPV infections
- CIN 3
- CIN 2 in older women
- Persistent CIN 2 and CIN 2/3 in non-adolescent women

Screening Modalities for Cervical Cancer

- Conventional Cytology
- Liquid Base Cytology
- Combination of cytology and HPV testing

Menses or Other Genital Tract Bleeding

- Cleaning the cervix with a large cotton swab will remove obscuring blood, and have a minimal or no effect on sample cellularity
- If obscuring blood, conventional Pap smears are more likely to be unsatisfactory
- Liquid-based methods filter out red blood cells.
- HPV testing results are not affected by bleeding

Challenges in collecting samples

- Confirm that the patient has a cervix.
- If **cervical stenosis**:
  - Perform Pap testing during menses.
  - Grasp the anterior or posterior lip of the cervix with a single-tooth tenaculum.
  - Administer a para- or intracervical block, and use small mechanical dilators to dilate the cervix.

Liquid Based Cytology

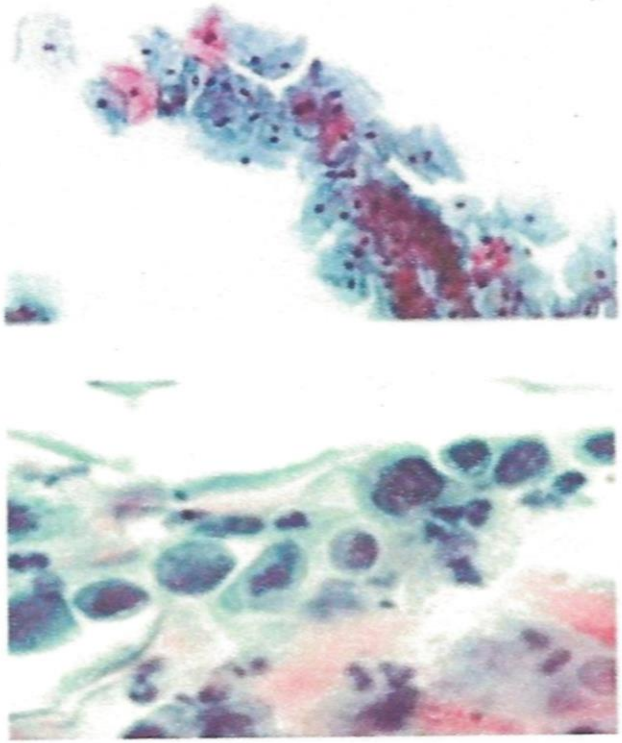
- Liquid-based cytology systems allow testing from a singe specimen for:
  - Cytology
  - HPV
  - Gonorrhea
  - Chlamydia
  - Trichomonas

Self-collected Samples

- Women can collect samples from the vagina using:
  - Tampon, dacron or cotton swab
  - Cytobrush, or cervicovaginal lavage.
- Self-collection can be performed under supervision at a clinic or at home
- Self-collected samples compared with clinician-collected samples: (meta-analysis 5441 women: High concordance (0.87)

Limitations of using cytology alone as a primary screen

- Cytology has low sensitivity for detecting CIN2 or greater[1]
- ASC-US cytology is not very specific for precancerous lesions[1]
- Highly variable results between laboratories[1]
- Poor at detecting adenocarcinoma[2]
- Requires women to be screened frequently (at least every 2–3 years)[3]



1. Castle PE, *et al. Lancet Oncol* 2011; 12:880–890 plus supplementary tables; 2. Herzog TJ & Monk BJ. *Am J Obstet Gynecol* 2007; 197:566–571; 3. ACOG Practice Bulletin no. 109: Cervical cytology screening. *Obstet Gynecol* 2009; 114:1409–1420.

ASC-US, atypical squamous cells of unc
si
LSIL, low grade squamous intraepithe

HPV Testing

- Three of the FDA-approved HPV-HR tests:
  - Reported as + if any type high risk is present, and no specific type is identified.
  - The cobas HPV:
    - Identifies types 16 and 18 and pools results for 12 other types
    - Only HPV specifically approved for primary screening.
  - Separate tests provide genotyping of types 16 and 18 (or a combined type 18/45 result) and can be performed as follow-up (or reflex) testing for specimens with a positive high-risk pooled result, but are not used for initial screening.

HPV Test

- The HPV test detects viral DNA replication:
  - False negative rate of the Hybrid Capture II HPV test for a finding of CIN grade 2/3 on biopsy is between 1 and 5%
- Type-specific testing for HPV 16 and 18 is not useful for identifying women who should not receive HPV vaccination;
  - HPV infection can be transient
  - It is not known if previous HPV infection is protective against reinfection.

Available HPV Tests

	Cobas® HPV Test[1]	QIAGEN/ digene HC2 HPV Test[2]	Hologic® Cervista HPV Test[3]	Gen-Probe APTIMA® HPV Assay	Laboratory-developed tests*
No cross-reactivity	√	-	-	-	?
Internal control	√	-	√	√	?
Small (≤1mL) sample size	√	-		√	?
3 results in 1 test	√	-	-	-	?
Detects HPV DNA	√	√	√		?
Largest U.S.-based cervical cancer clinical trial	√	-	-	-	-

HR-HPV DNA test (cobas) As Primary Screening

- Approved by FDA April 2014
  - For females 25 years and older
  - Similar protection of Annual Cytology and co-testing every 3 years
  - Superior protection to cytology every 3 years
- HPV DNA testing has a higher sensitivity in comparison with cytology for detection of CIN3.

Urine Test for HPV

- **H**as been proposed, but is not clinically available.
- The efficacy of urine testing was evaluated in a meta-analysis of 14 studies including 1443 women.
  - Most studies used commercial PCR.
  - For detection of high-risk HPV, the sensitivity was 77 percent and specificity was 88 percent.
  - Sensitivity was statistically significantly higher when urine samples were collected as first void compared with random or midstream.

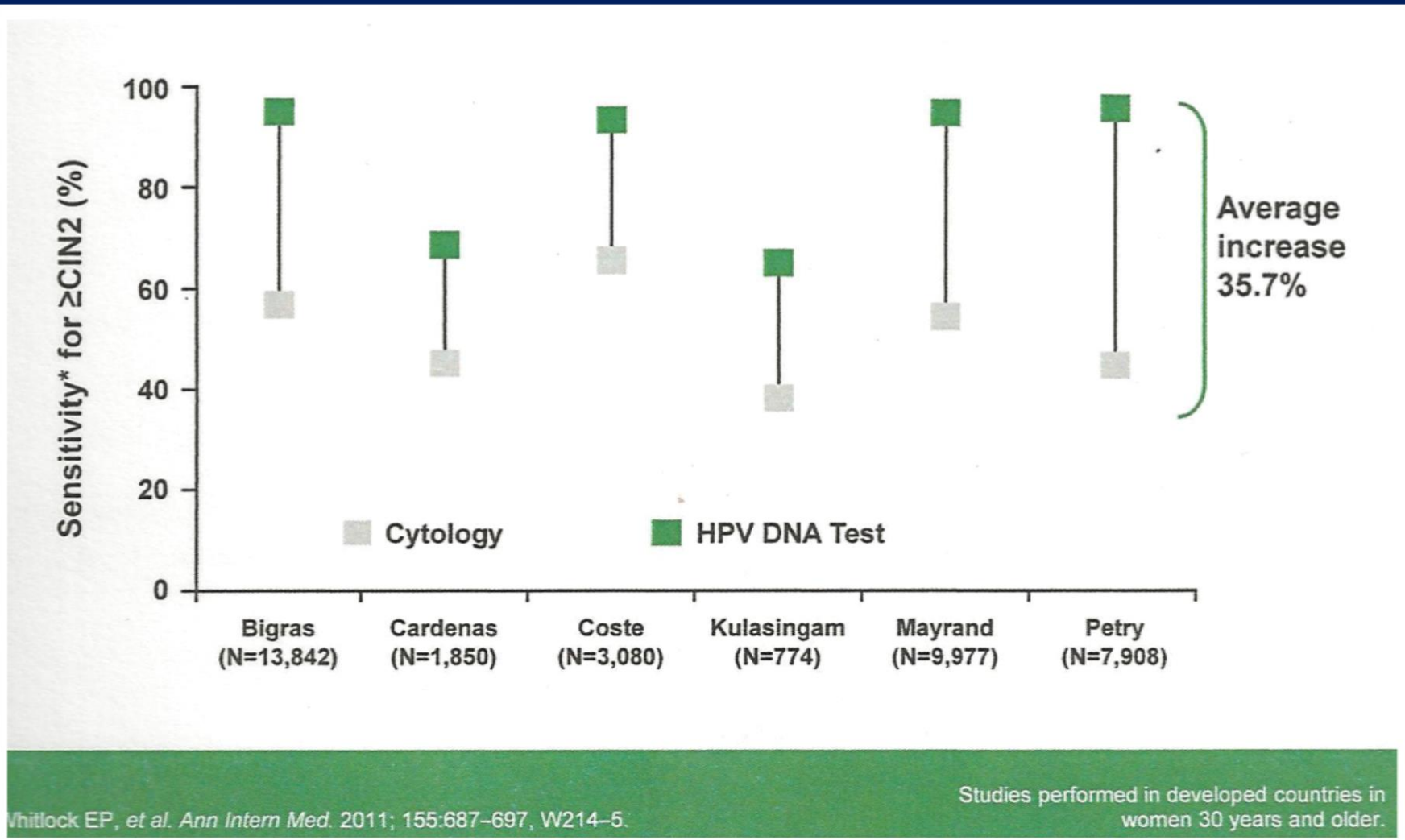
Primary hrHPV Screening

- Potential advantages:
  - Negative hrHPV test: greater reassurance of low CIN3+ risk than a negative cytology result.
- Potential disadvantage of this strategy for screening:
  - Specimen Adequacy
  - Appropriate Internal controls
  - Use of lubricants
  - lower specificity than cytology,

- ACOG: due to similar results it could be implemented as an alternative to cytology Every 3 years

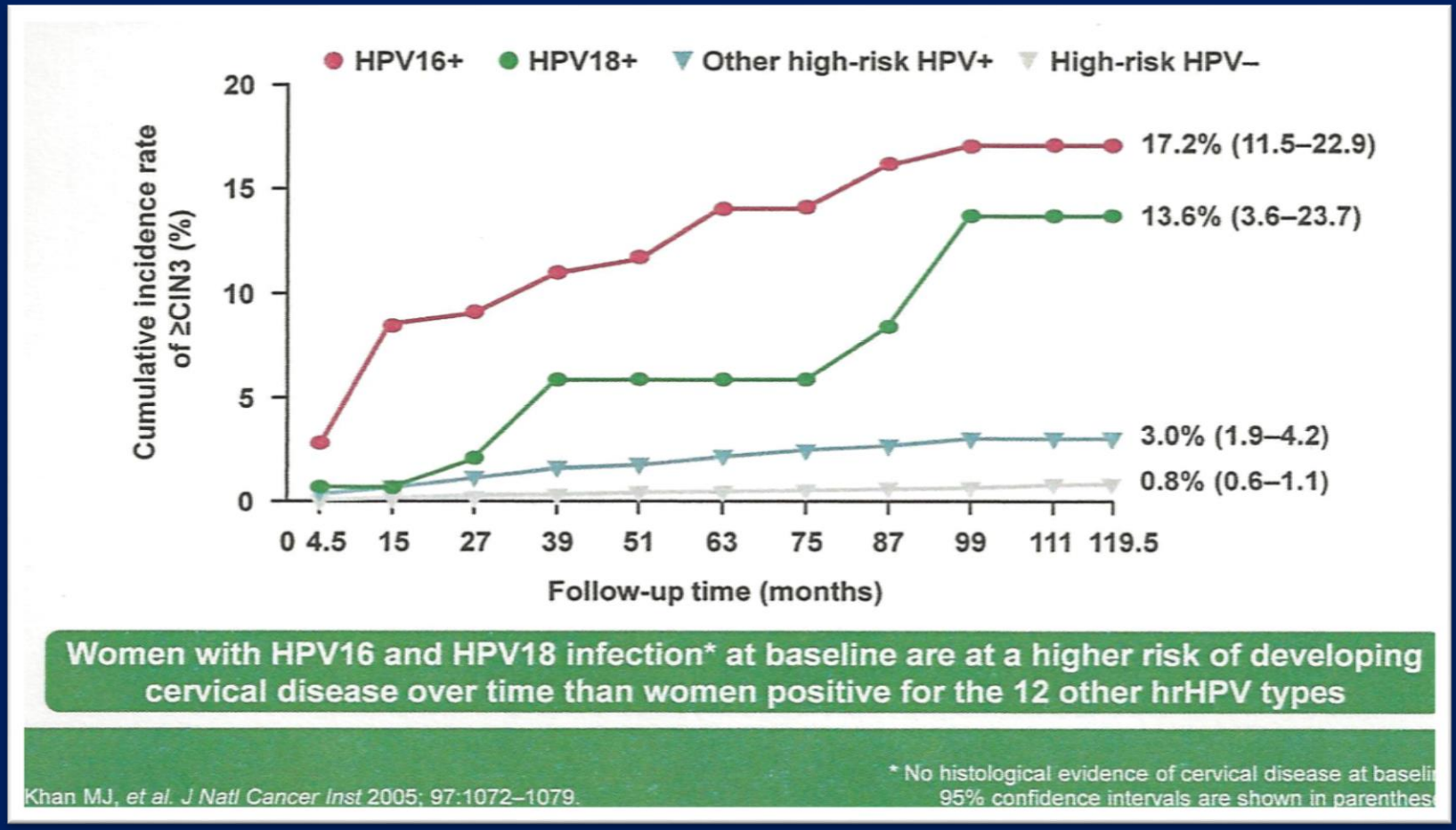
Huh Wk, et al: Use of Primary HR-HPV testing for cervical cancer screening:interim clinical guidance. Gynecol Oncol. 2015 Feb;136(2):178-82. doi: 10.1016/j.ygyno.2014.12.022. Epub 2015 Jan 8.PMID: 25579107

Sensitivity of cytology vs. HPV DNA for ≥CIN2



Whitlock EP, *et al. Ann Intern Med.* 2011; 155:687–697, W214–5.

Cumulative incidence of ≥CIN3 in women with (-) cytology over 10 years by HPV-HR + status at baseline



Future/Present of Cervix Cancer Screening

- **FDA Panel: Roche's DNA Test Can Replace Pap Smear**
- Published: Mar 12, 2014

Primary HPV Screening

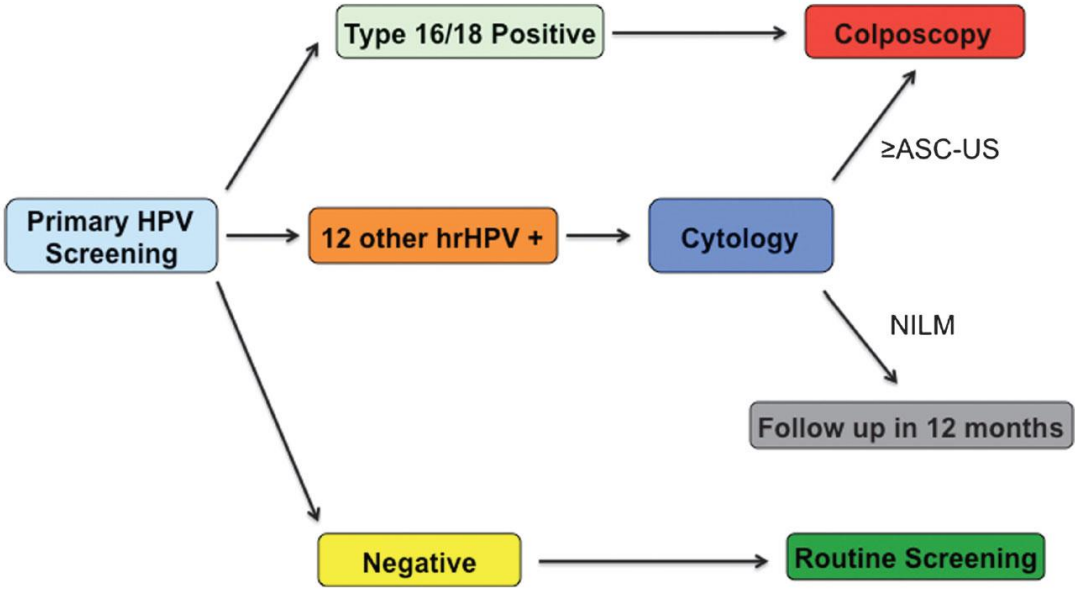
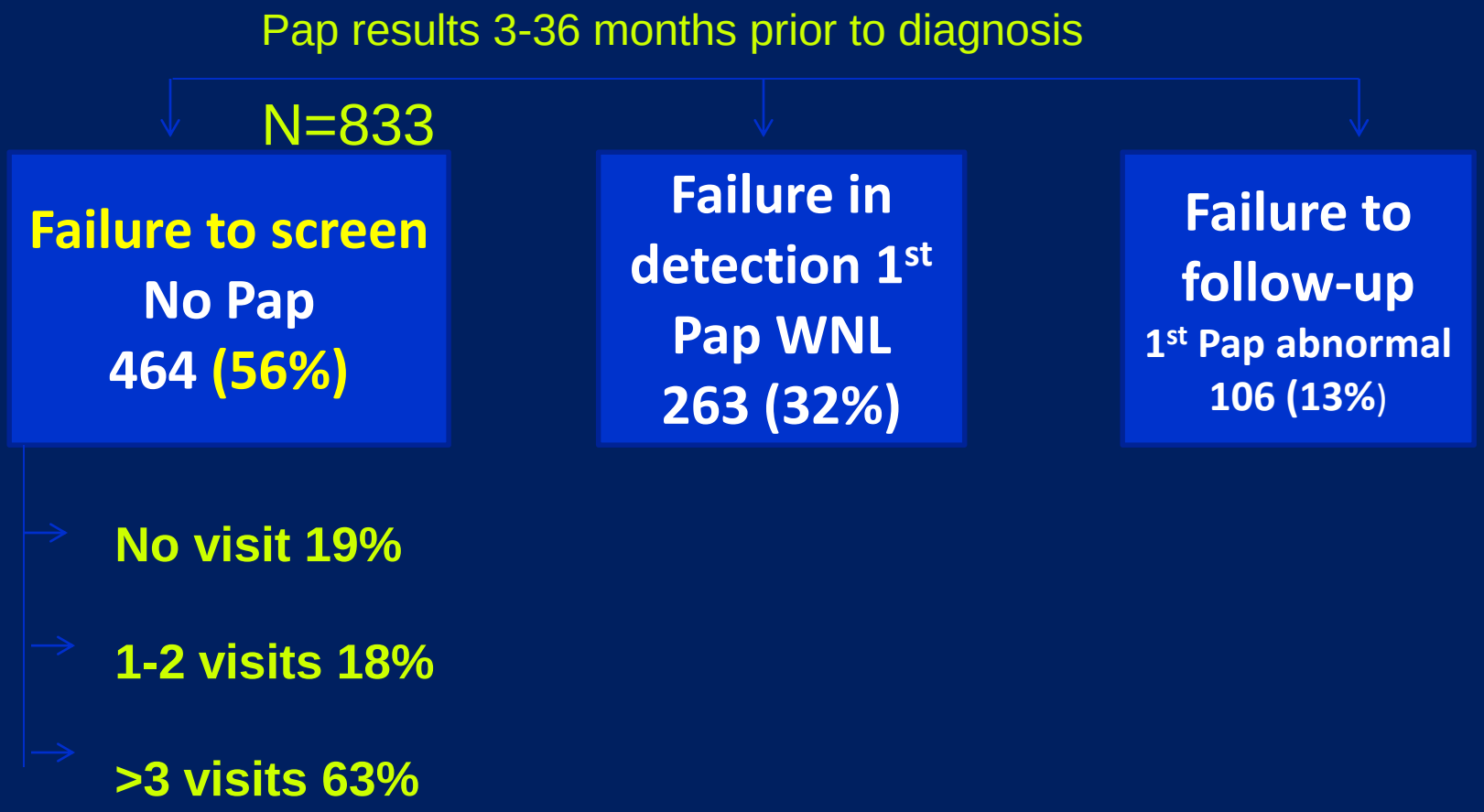


FIGURE 1. Recommended primary HPV screening algorithm. HPV, human papillomavirus; hrHPV, high-risk human papillomavirus; ASC-US, atypical squamous cells of undetermined significance; NILM, negative for intraepithelial lesion or malignancy.

Biopsy of Visible Lesions

- During Pap testing, any lesion that is raised, friable, or has the appearance of condyloma should be biopsied, regardless of previous cytology results or other risk factors for cervical cancer .
- The only visible lesions that do not require biopsy are Nabothian cysts and only when this diagnosis is confirmed by an experienced examiner.

Retrospective Study of Cervical Cancers Diagnosed at Kaiser Northern California



Leyden MA, Manos M, Kinney W et al JNCI 2005;97:67583.

USPTF Guidelines

Population	Recommendation	Grade (What's This?
Women ages 21 to 65 years	The USPSTF recommends screening for cervical cancer every 3 years with cervical cytology alone in women ages 21 to 29 years. The USPSTF recommends either screening every 3 years with cervical cytology alone or every 5 years with high-risk human papillomavirus (hrHPV) testing alone in women ages 30 to 65 years. See the Clinical Considerations section for the relative benefits and harms of alternative screening strategies for women age 30 years or older.	A
Women older than age 65 years	The USPSTF recommends against screening for cervical cancer in women older than age 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations section for a discussion of adequate prior screening and risk factors that support screening after age 65 years.	D
Women younger than age 21 years	The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.	D
Women who have had a hysterectomy	The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] grade 2 or 3) or cervical cancer.	D

When to Start Guidelines

	USPSTF	ACS/ASCCP/ASCP	ACOG
	Age 21	Age 21	Age 21
	Women aged <21 y/o should not be screened regardless of the age at sexual initiation or other risk factor. (A Recommendation) (Strong Recommendation)	Recommend against screening women Aged <21 (A Recommendation)	Regardless of the Age of onset of sexual activity. Women Aged <21 y/o should not be screened. Exception: HIV + and Immunocompromised (ACOG Updated 2018) (Level A Evidence)

USPSTF- US Preventive Service Task Force
ACS_ American Cancer Society
ASCCP- American Society for Colposcopy and Cervical Pathology
ASCP- American Society for Clinical Pathology

Screening for Ages 21 to 29

USPSTF	ACS/ASCCP/ASCP	ACOG
Cytology: Every 3 years Grade A Recommendation Strong Recommendation	Cytology: Every 3 years Grade A Recommendation	Cytology: Every 3 years Level A Evidence
HPV test not recommended Strong Recommendation	HPV test not recommended Grade A Recommendation	HPV test not recommended Level A Evidence

Annual Pelvic Exam Guidelines

ACOG	USPSTF	ACS/ASCCP/ASCP
If < 21 y/o no need for a pelvic exam in asymptomatic patients. If 21 or older, no evidence to support or refute annual exam, decision should be based on discussion with patient. External genitalia should be evaluated annually	Not Addressed, previously recommended for ovarian cancer screening but no evidence it contributes	Not Addressed.

Screening for Ages 30 to 65

ACOG	USPSTF	ACS/ASCCP/ASCP
Cytology: Every 3 years Grade A Recommendation Strong Recommendation	Cytology: Every 3 years Grade A Recommendation	Cytology: Every 3 years Level A Evidence
HPV co-testing every 5 years for women who want to extent their screening Strong Recommendation HPV test alone not recommended	HPV co-testing every 5 years Preferred HPV test alone not recommended	HPV co-testing every 5 years Preferred Method Level A Evidence HPV test alone not address

Cytology and HPV Test every 5 years rationale

- Five Years Intervals:
  - Less cervical cancer
  - Less death due to cervical cancer
  - Less Colposcopies
- Intervals < years 5:
  - Increase the Colposcopies in patients with transient infections with HPV

CERVICAL SCREENING For Older than 65

ACOG	USPSTF	ACS/ASCCP/ASCP
Stop Screening if evidence of adequate screening*	**Recommends against screening women who have had adequate prior screening* and are not otherwise at high risk for cervical cancer.** **Grade: D recommendation.**	**Women with evidence of adequate negative prior screenin* and no history of CIN2+ within the last 20 years should not be screened. Screening should not be resumed for any reason, even if a woman reports having a new sexual partner.**

* Evidence of adequate screening, Three consecutive cytology or 2 consecutive Co-testing in 10 years. Most recent done within 5 years. They are the same for ACOG, USPSTF and ACS/ASCCP/ASCP

Rational for stopping at 65 years

- CIN2+ is rare after 65
  - Most abnormal screens, even HPV+, are false +
- HPV risk remains 5-10%
- Colposcopy/biopsy/treatment more difficult
  - Harms are magnified
- Incident HPV infection unlikely to lead to cancer within remaining lifetime

When NOT to stop at age 65 years

- If History of CIN2+, CIN3, or AIS
  - Continue routine screening for at least 20 years.
  - Even if this extends screening past age 65.

Screening After Hysterectomy with cervix removal

ACOG	USPSTF	ACS/ASCCP/ASCP
Stop Screening and don't restart for any reason Level A Evidence	Recommends against screening Grade: A Recommendation	Stop screening Strong Recommendation

Screening after HPV Vaccine

ACOG	USPSTF	ACS/ASCCP/ASCP
Same screening as not immunized Level C Evidence	Same screening as not immunized	Same screening as not immunized

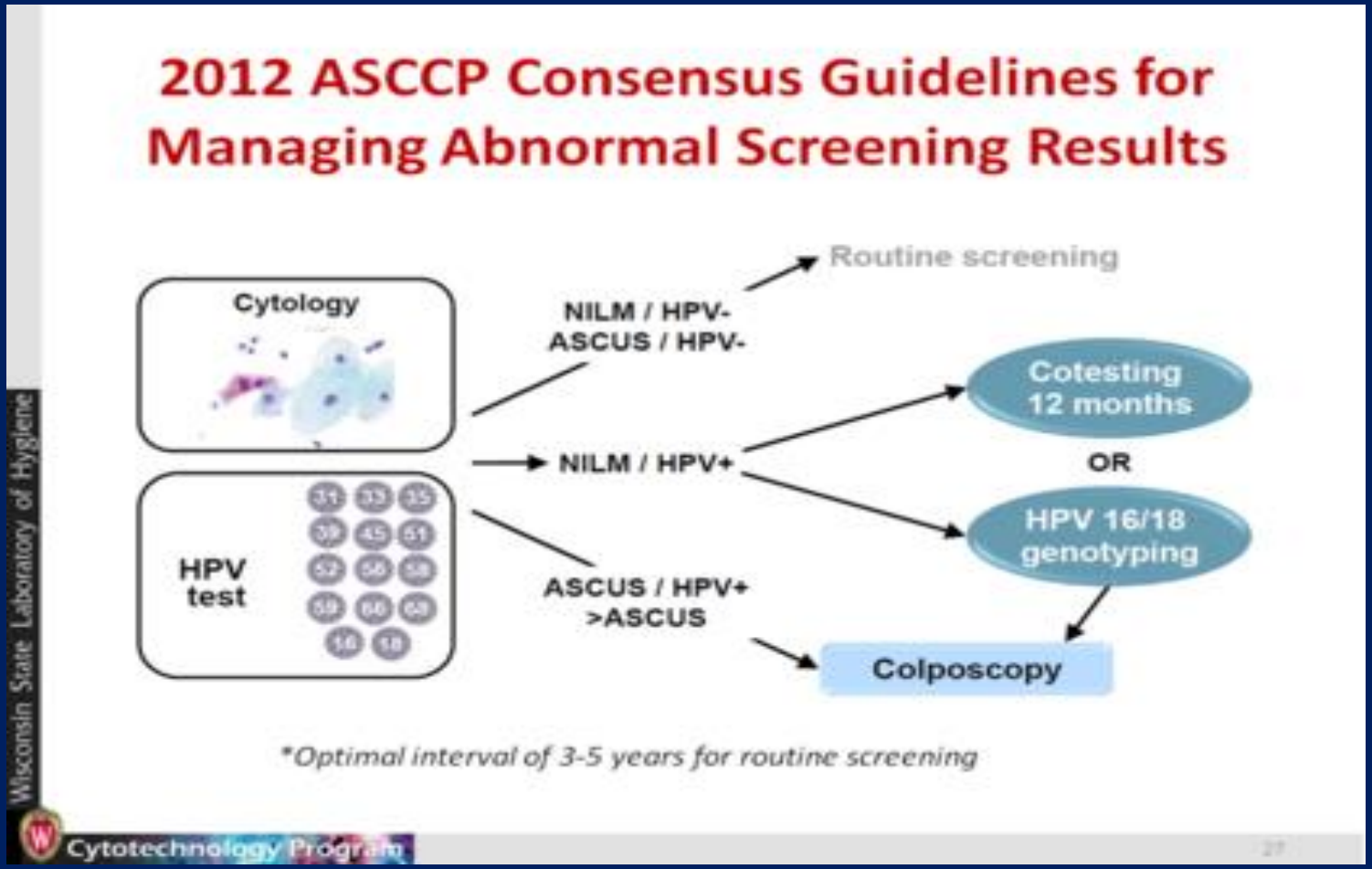
Special Populations

- HIV positive
  - Screening twice in the first year after dx and annually thereafter
- Immuno-compromised patients:

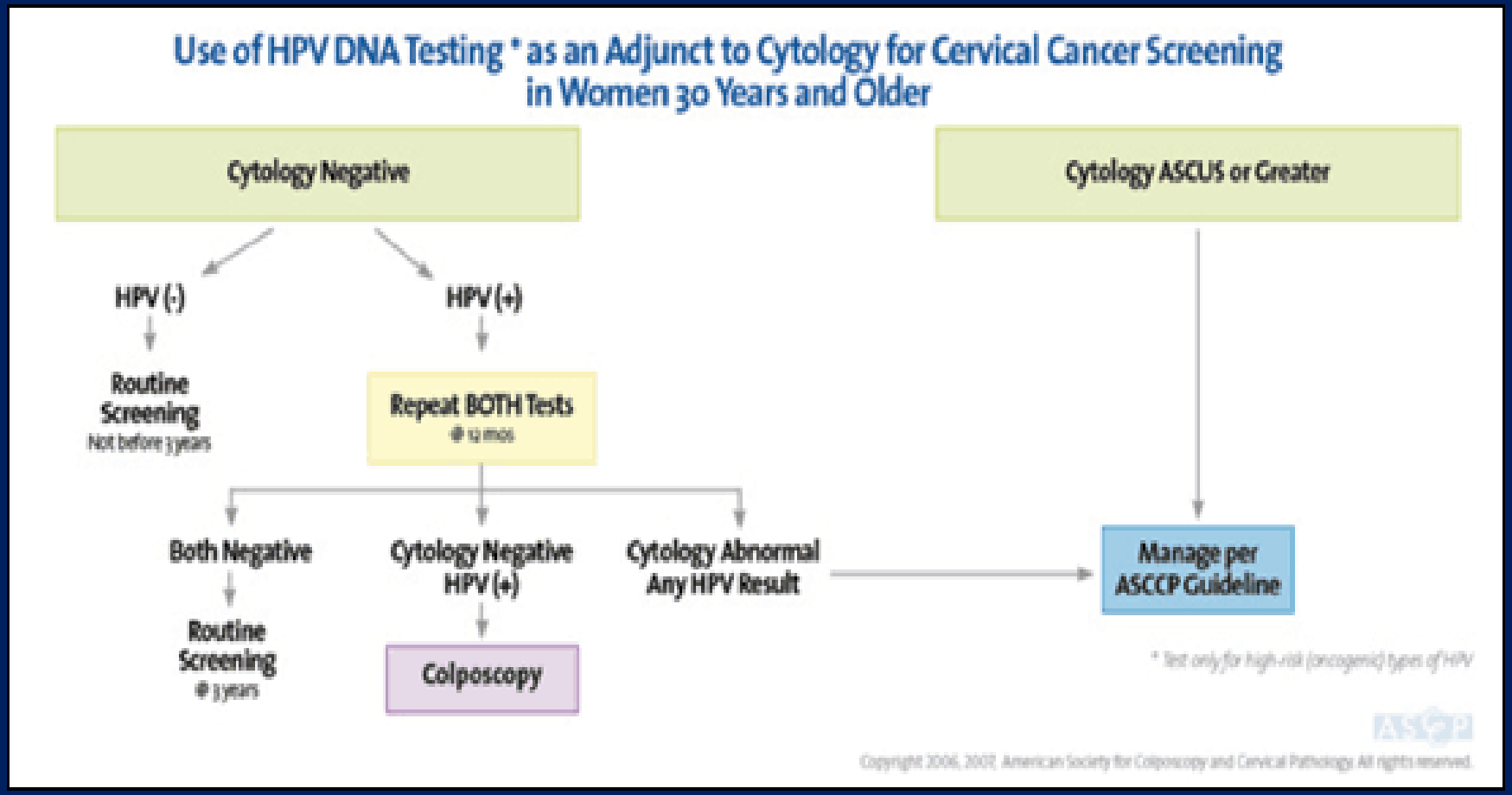
Organ Transplant & Chronic use of corticosteroids

- Screen after onset of sexual activity and NO need to wait until 21 years of age
- P/S 6 month interval during first year, then annually

Management of Abnormal Cytology and/or HPV-HR



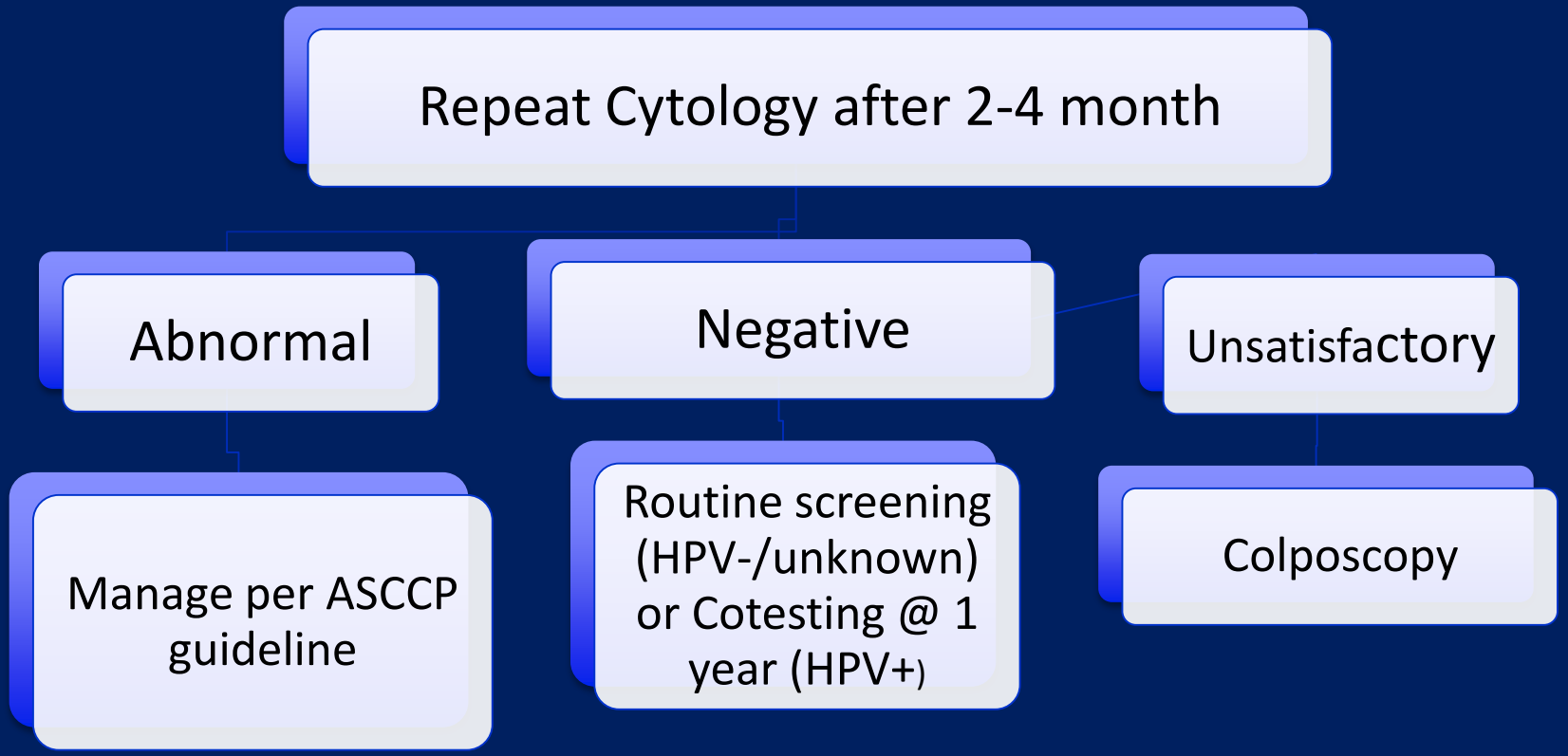
Management of HPV-HR +



ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

- Cytology reported as unsatisfactory requires to be repeated even if HPV negative.

UNSATISFACTORY CYTOLOGY: HPV UNKNOWN (ANY AGE)



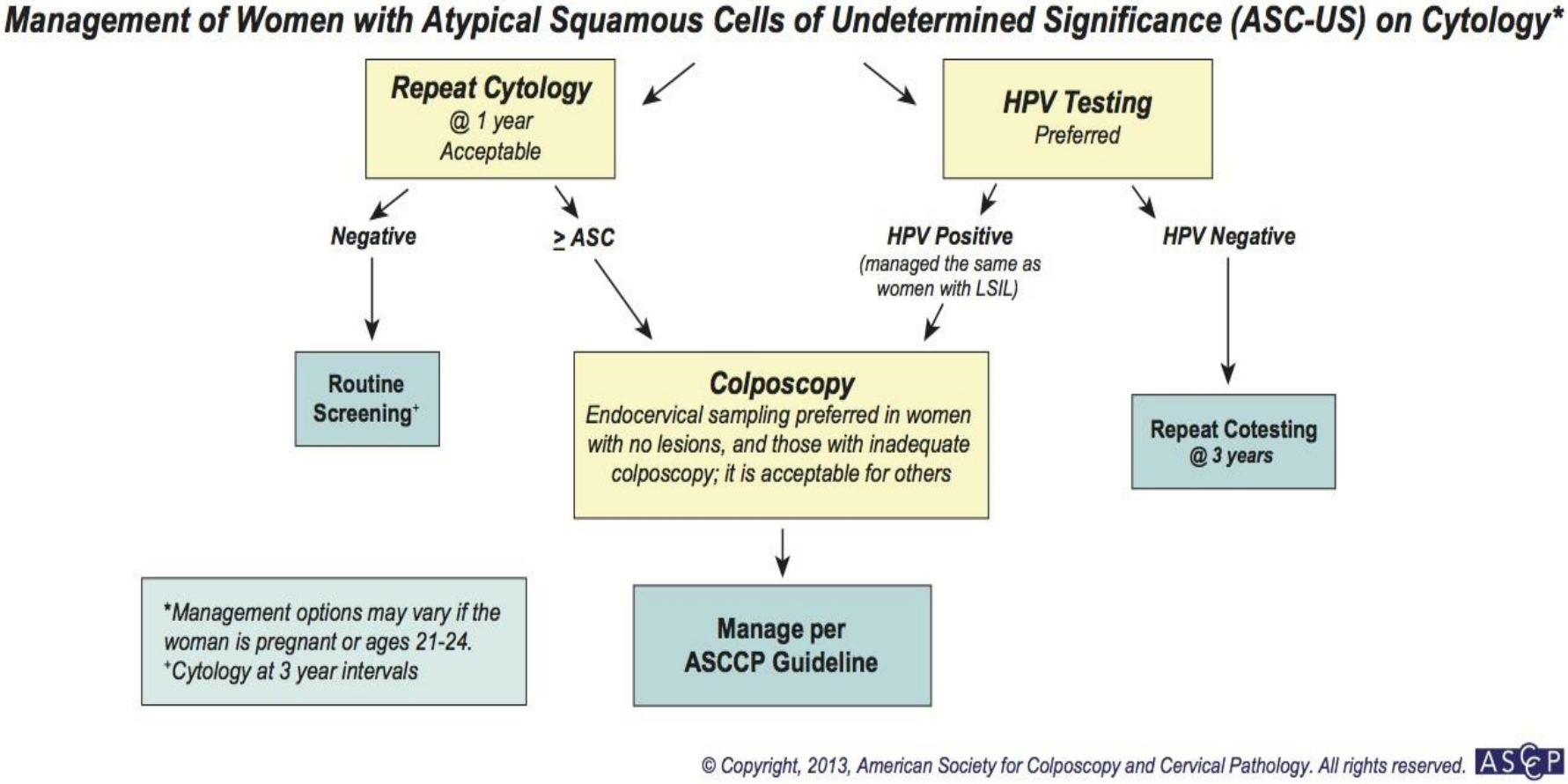
ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

- Cytology reported as negative but lacking endocervical cells can be managed without early repeat.

ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

- For ASC-US cytology, immediate colposcopy is not an option
- The alternative of HPV typing is the preferred
- The serial cytology option for ASC-US incorporates cytology at 12 months
- ASCUS and HPV negative: f/u in 3 years with co-testing

Management of ASCUS



ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

1. Colposcopy is indicated for all HPV + women and ASCUS in spite of Genotyping

2. Women with negative cytology and HPV Type 16 or type 18 goes to early Colposcopy

ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

- HPV-negative and ASC-US results should be followed with co-testing at 3 years rather than 5 years.
- HPV-negative and ASC-US results are insufficient to allow exit from screening at age 65 years.

ESSENTIALS CHANGES FROM PRIOR MANAGENET GUIDELINES

- CIN 1 on endocervical curettage should be managed as CIN 1, NOT as positive ECC.

Management of Women with ASC: Cannot Exclude ASC-H*

Colposcopy

(Regardless of HPV status)

No CIN 2,3

Manage per ASCCP guideline

CIN 2,3

Manage per ASCCP guideline

* Management options may vary if woman is pregnant or ages 21-24 years.

Initial Workup of Women with AGC

All Subcategories (except atypical endometrial cells)

Colposcopy (with ECC) and Endometrial Sampling (if ≥ 35 y/o or at risk for endometrial neoplasia *)

* Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation

Atypical Endometrial Cells

Endometrial and Endocervical Sampling

No endometrial Pathology

Colposcopy

Management of Women with Biopsy-Confirmed CIN2,3

- **Management options will vary in special circumstances or if the woman is pregnant or ages 21-24.**

- If CIN 2,3 is identified at the margins of an excisional procedures or post-procedures ECC, cytology and ECC at 4-6 mo is preferred, but repeat excision is acceptable and hysterectomy is acceptable if re-excision is not feasible.

Management of Young Women with Biopsy-Confirmed CIN2,3 in Special Circumstances <25 y/o

* **Either treatment or observation is acceptable, provide colposcopy is adequate.**
- **When CIN2 is specified, observation is preferred.**
- **When CIN3 is specified, or colposcopy is inadequate, treatment is preferred.**

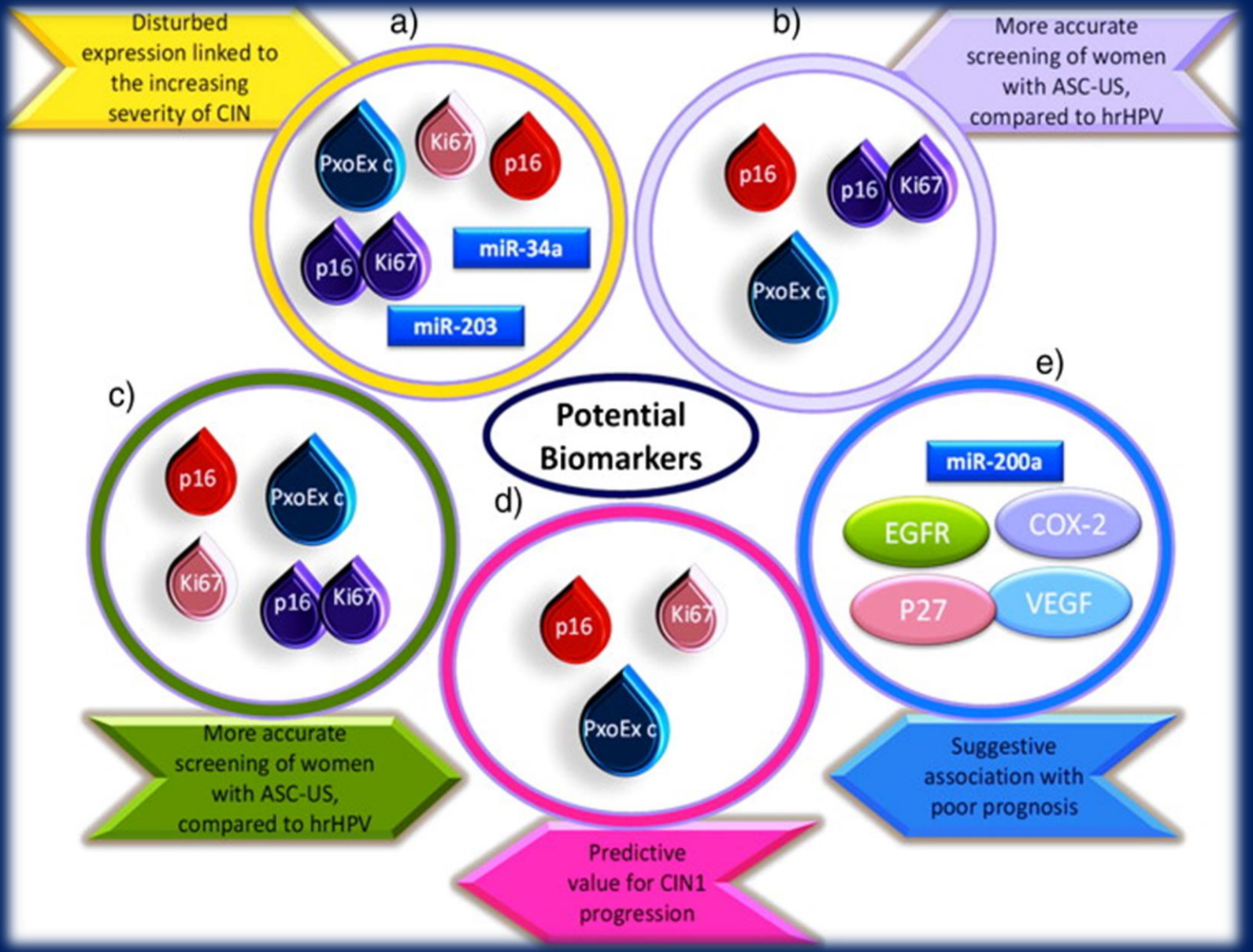
HPV test v/s Biomarkers

- **HPV Lack specificity and positive predictive value**
  - Positive hr-HPV & Negative cytology
    3-7% Risk for CIN 3
- Disease-specific biomarkers such as p16ink4a, HPV E6/E7 mRNA, or methylation assays may serve as secondary markers.

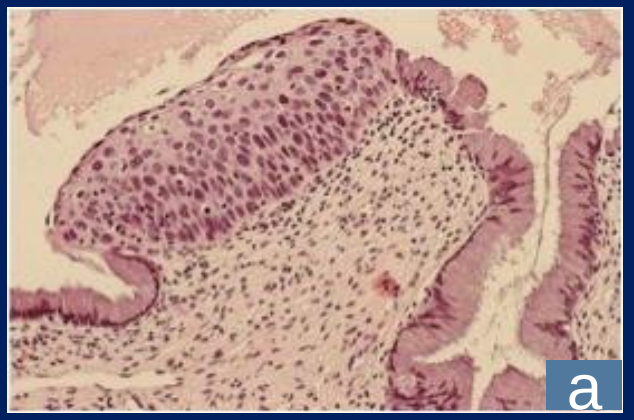
Role of Biomarkers

- CIN3 is a heterogeneous group:
  - About 30–50% of large CIN3s are estimated to invade to cancer over a long time period
  - An important area of cervical cancer biomarker research focuses on the identification of markers for cervical lesions that likely progress to cancer.

Potential Biomarkers

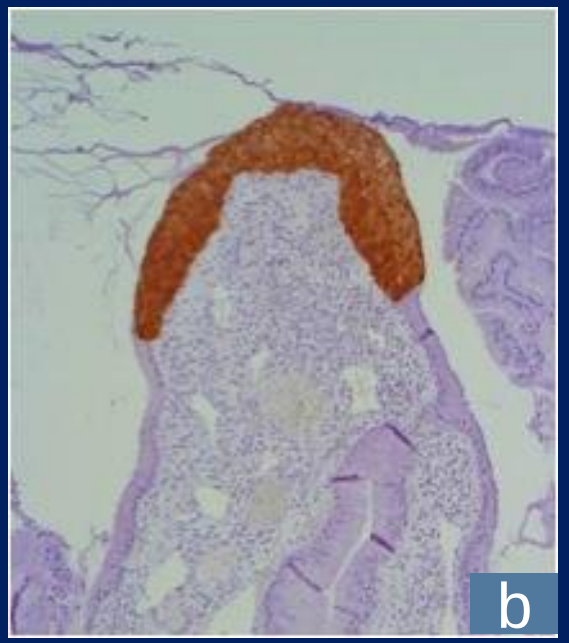


p16ink4a



- Most widely evaluated
- Markedly overexpressed in cancerous and precancerous cervical tissue.
- Cellular correlate of the

increased expression of the viral oncoprotein E7 that disrupts cycle regulator in transforming HPV infections.



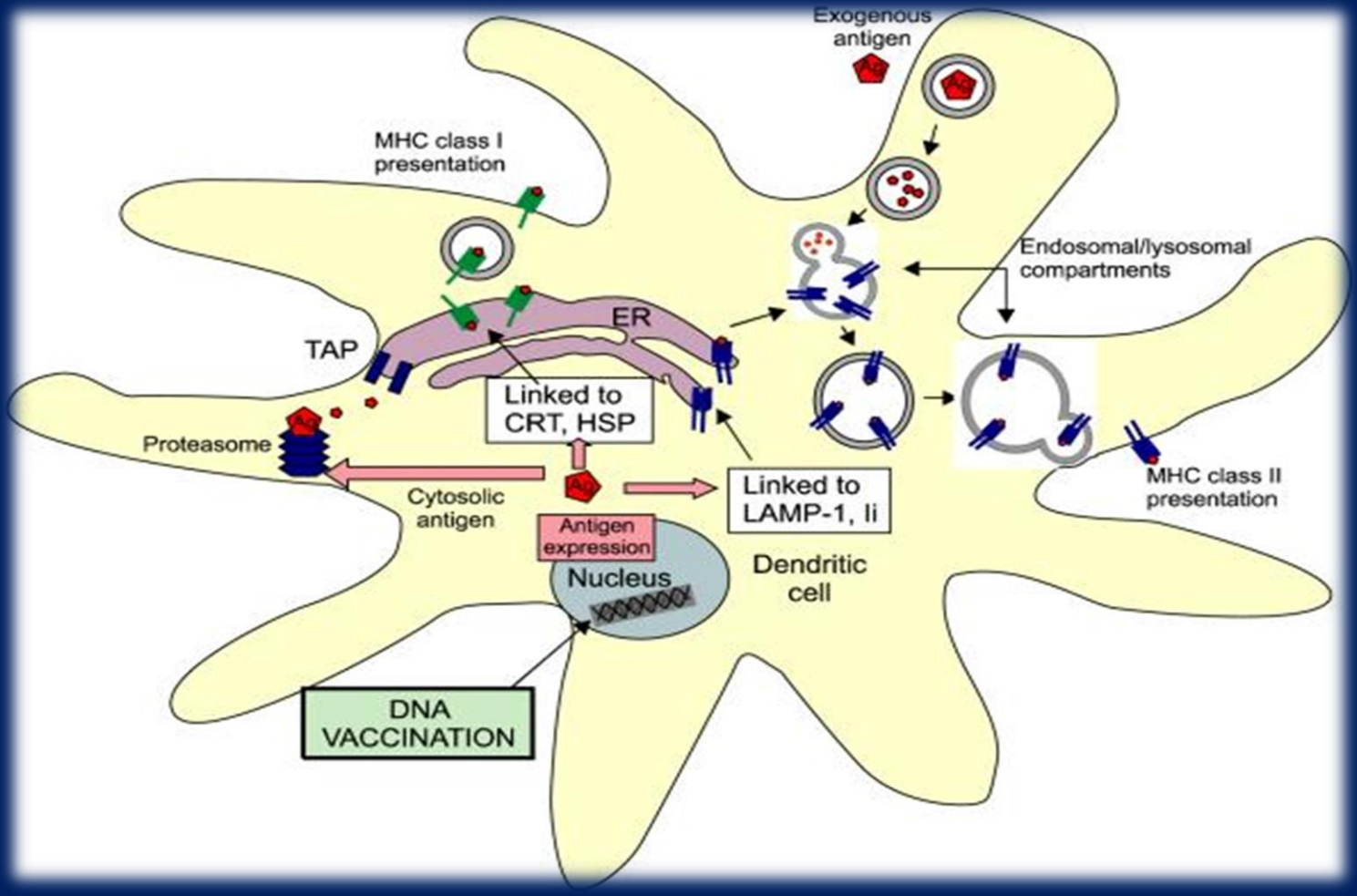
Anal Pap Test Screening in Immunodeficient Patients

- **Anal Pap tests and anoscopy**
  - There is an increased incidence of anal cancer in HIV-infected MSM.
  - Increased incidence of anal cancer in patients with previous lower genital tract severe dysplasia and cancer.
  - Some experts screen for anal intraepithelial neoplasia by cytology.
  - Anoscopy is indicated if abnormal anal cytology

HPV Related Research Projects

- Clinical Studies:
  - Microbiota and HPV disease progression
  - Incidence of Anal HPV lesions in patients with Lower Genital Tract (cervix,vagina, vulva and cervix) severe dysplasia and cancer
  - Therapeutic HPV vaccine
    - HPV HR positive with CIN 2/3 and VIN 2/3

Therapeutic HPV Vaccines



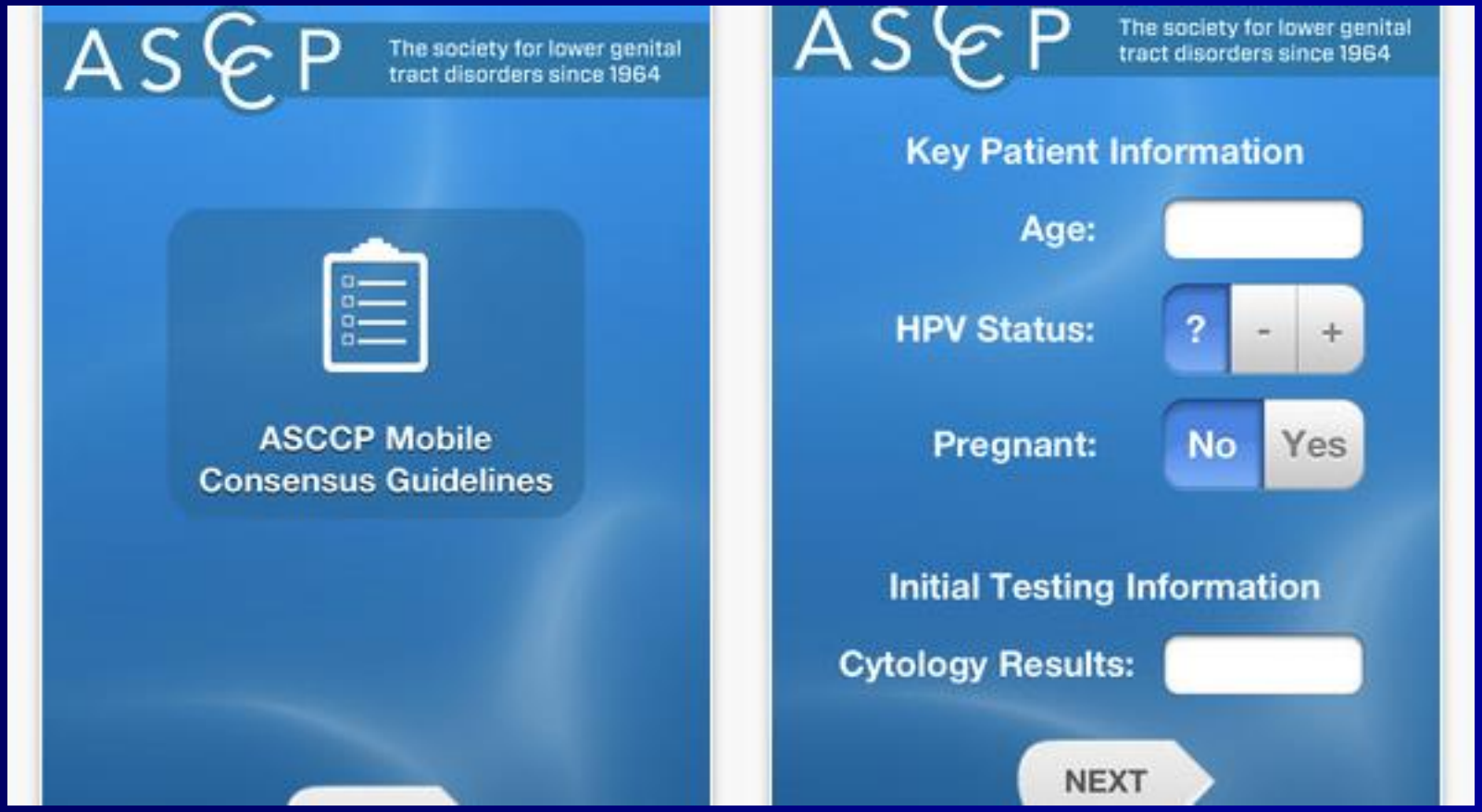
Research Projects

- Clinical Studies:
  - Endometriosis
  - Myomatous uterus
  - Polycystic Ovarian Syndrome

Información a Pacientes

- **CDC.gov**
- **SaludMujerLatina.org**
- **VOCES.org**
- **HPV Vaccination Kit**

ASCCP Application



Thanks!! QUESTIONS???

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