Women's Health and HPV: Prevention, Detection and Managment

Nicole Shields, MD

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Dates and Location of CME Activity: April 6-9, 2016, The San Juan Puerto Rico Convention Center
Your presentation**: Wednesday, April 6, 2016 from 2:00pm-3:00pm: Women's Health and HPV: Prevention, Detection and Management**

Name of Faculty/Moderator: Nicole Shields, MD

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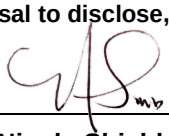
Signature:  **Date:** January 11, 2016

Nicole Shields, MD

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Deadline: Friday, January 15, 2016

Women's Health: HPV Prevention, Detection & Management

ACOFP 2016 Annual Convention and Scientific Seminars
San Juan, Puerto Rico

Nicole Shields, MD
Lincoln Memorial University – DeBusk College of Osteopathic Medicine

Objectives

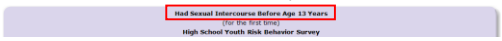
- Prevention
  - HPV vaccine – who, when and risks/benefits
  - Improving vaccination rates
- Detection
  - Screening – what, when and how often
- Management
  - Condyloma Acuminata
  - Pap Smear Abnormalities

Introduction

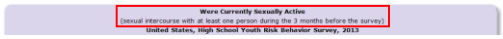
- HPV is a very common virus.[1]
  - Nearly 80 million people—about one in four—are currently infected in the US.
  - About 14 million people, *including teens*, become infected with HPV each year.
  - Genital HPV is the most common sexually transmitted infection in the US.[2]
  - Of the more than 150 HPV types, approximately 40 are linked with genital HPV infection.[2]
  - Estimated $1.7 billion spent annually in direct medical costs to treat conditions associated with genital HPV infection
- HPV infection can cause[1]:
  - cervical, vaginal, and vulvar cancers in women;
  - penile cancer in men;
  - and anal cancer, cancer of the back of the oropharynx, and genital warts in both men and women.

Introduction

- CDC Youth Risk Behavior Surveillance System (YRBSS) [3]



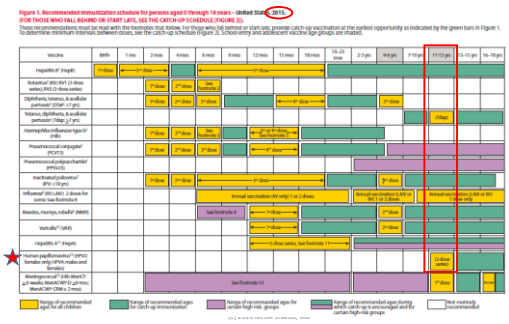
Introduction



Prevention

Prevention

- Who should be vaccinated against HPV?
  A. Females 11 – 26
  B. Sexually active females 11 – 26
  C. Males and females 11 – 26
  D. Sexually active males and females 11 – 26



Prevention

- Advisory Committee on Immunization Practices (Feb 2015)[4]
  - HPV vaccine is recommended for routine vaccination at age 11 or 12 years.
  - Females: all aged 13 through 26 years.
  - Males:
    - Aged 13 through 21 years not vaccinated previously.
    - Also recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection) if not vaccinated previously.
  - Recommended 9-valent human papillomavirus (HPV) vaccine (9vHPV) as one of three HPV vaccines that can be used for routine vaccination.

Prevention

TABLE 1. Characteristics of the three human papillomavirus (HPV) vaccines licensed for use in the United States

Characteristic	Bivalent (2vHPV)*	Quadrivalent (4vHPV)†	9-valent (9vHPV)§
Brand name	Cervarix	Gardasil	Gardasil 9
VLPs	16, 18	6, 11, 16, 18	6, 11, 16, 18, 31, 33, 45, 52, 58
Manufacturer	GlaxoSmithKline	Merck and Co., Inc.	Merck and Co., Inc.
Manufacturing	*Trichoplusia ni* insect cell line infected with L1 encoding recombinant baculovirus	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1	*Saccharomyces cerevisiae* (Baker's yeast), expressing L1
Adjuvant	500 µg aluminum hydroxide, 50 µg 3-O-desacyl-4′ monophosphoryl lipid A	225 µg amorphous aluminum hydroxyphosphate sulfate	500 µg amorphous aluminum hydroxyphosphate sulfate
Volume per dose	0.5 ml	0.5 ml	0.5 ml
Administration	Intramuscular	Intramuscular	Intramuscular

Abbreviation: L1 = the HPV major capsid protein; VLPs = virus-like particles.

* Only licensed for use in females in the United States. Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf.

† Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf.

§ Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf.

Prevention

TABLE 2. Results of a Phase III efficacy trial comparing 9-valent human papillomavirus (HPV) vaccine (9vHPV) with quadrivalent HPV vaccine (4vHPV), per protocol population* in females aged 16 through 26 years†

Endpoint-related types	Endpoint	9vHPV		4vHPV		Vaccine efficacy	
		No. participants	Cases	No. participants	Cases	%	(95% CI)
HPV 31, 33, 45, 52, 58	≥CIN2, VIN2/3, VaIN2/3	6,016	1	6,017	30	96.7	(80.9–99.8)
	≥CIN2	5,948	1	5,943	27	96.3	(79.5–99.8)
	6-month persistent infection	5,939	35	5,953	810	96.0	(94.4–97.2)
HPV 6, 11, 16, 18	≥CIN2§	5,823	1	5,832	1	—	—
	Anogenital warts	5,876	5	5,893	1	—	—

Abbreviations: CI = confidence interval; ≥CIN2 = cervical intraepithelial neoplasia grade 2 or 3 or adenocarcinoma in situ; VaIN2/3 = vaginal intraepithelial neoplasia grade 2 or 3; VIN2/3 = vulvar intraepithelial neoplasia grade 2 or 3.

Sources: Package insert available at http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM426457.pdf.

Joura EA, Giuliano AR, Iversen OE, et al. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. N Engl J Med 2015;372:711–23.

* Females who received all 3 vaccinations within 1 year of enrollment, did not have major deviations from the study protocol, were naïve (polymerase chain reaction [PCR] negative and seronegative) to the relevant HPV type(s) before dose 1, and who remained PCR negative to the relevant HPV type(s) through 1 month after dose 3 (month 7).

† Participants were enrolled from sites in 18 countries; median duration of follow-up was 40 months.

Prevention

- HPV vaccines are each administered in a 3-dose schedule.
  - The second dose is administered at least 1 to 2 months after the first.
  - Third dose at least 6 months after the first dose.
- If the schedule is interrupted, the series does not need to be restarted.

Prevention

9vHPV

- Non-inferior immunogenicity of 9vHPV compared with 4vHPV .
- No data is available on those receiving fewer than 3 doses of 9vHPV.
- 9vHPV is estimated to protect against approximately 90% of HPV-related cervical, vulvar, vaginal, and anal cancers.[5]
- One other barrier may be more difficult to overcome: cost. The older HPV vaccines, Cervarix and Gardasil, cost about $500 for three doses; the new nonavalent vaccine, Gardasil 9, currently costs about $1,100 for three doses.[6]

Prevention

- Parental safety concerns about the HPV vaccine increased from 4.5% in 2008 to 16% in 2010, although the reported adverse effects have been minor.[7]
- The most common adverse events reported were[8]:
  - Dizziness
  - Nausea
  - Headache
  - Fever
  - Injection site reactions (pain, swelling, and redness)
- Although rare, fainting was found to happen after HPV vaccination.
- HPV4 vaccine-related serious adverse events occurred in <0.1% of persons.
  - Across all clinical studies (29,323 participants), during the course of the trials, 21 deaths (0.1%) occurred among persons in HPV4 groups and 19 (0.1%) among persons in the control or placebo groups. None of the deaths was considered to be vaccine related.[9]

Prevention

- The acceptance rate for most immunizations is high (80% to 90%), especially for more well-established vaccines.[2]
- Much lower for human papillomavirus (HPV) vaccine:
  - With 57.3% of females and 34.6% of males initiating the series.[2]
  - Only 38% of females and 14% of males receiving all three doses.[7]

Table 1. Vaccination Rates

Vaccine	Population	Vaccination rate (%)
IPV (≥ 3 doses)	Children 19 to 35 months of age	93.6
Hepatitis B (≥ 3 doses)	Adolescents 13 to 17 years of age	93.2
MMR (≥ 1 dose)	Children 19 to 35 months of age	91.9
MMR (2 doses)	Adolescents 13 to 17 years of age	91.8
Varicella (≥ 1 dose)	Children 19 to 35 months of age	91.2
Hepatitis B (≥ 3 doses)	Children 19 to 35 months of age	90.8
Tdap (≥ 1 dose)	Adolescents 13 to 17 years of age	87.5
DTaP (≥ 4 doses)	Children 19 to 35 months of age	83.1
Pneumococcal conjugate (≥ 4 doses)	Children 19 to 35 months of age	82
Varicella (2 doses)	Adolescents 13 to 17 years of age	80.7
Meningococcal (≥ 1 dose of MenACWY)	Adolescents 13 to 15 years of age	77.8
Hepatitis B (birth dose)	Newborns	74.2
Rotavirus (full series)	Children 19 to 35 months of age	72.6
HPV (≥ 1 dose)	Girls 13 to 17 years of age	52.8
Hepatitis A (≥ 2 doses)	Children 19 to 35 months of age	54.7
HPV (≥ 1 dose)	Boys 13 to 17 years of age	34.6

DTaP = diphtheria and tetanus toxoids, and acellular pertussis; HPV = human papillomavirus; IPV = inactivated poliovirus; MMR = measles, mumps, and rubella; Tdap = tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis.

Information from references 4 and 6.

Prevention

Among adolescents, which of the following is one of the most important factors in the decision to vaccinate?[2]

A. CDC guidelines
B. Physician recommendation
C. Side effect profile
D. Social Media

Prevention

Impediments originating with physicians are multifactorial:

- Reluctant to recommend HPV vaccination at the suggested age based on information obtained by profiling their patients about sexual activity.[10]
- Do not see the need for HPV vaccination because cervical cancer screening, detection, and treatment are effective.[11]
- Give parents the perception that the vaccine is optional[11];
- Many parents report that their physician never offered the vaccine. [11]
- Surveys suggest that physicians who graduated more recently believe that children receive too many vaccinations.[2]

Prevention

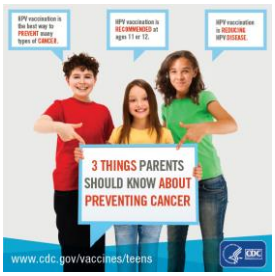
Improving HPV vaccination rates[12]:

- Instead of discussing the vaccine as a means of STI prevention, present it as a way to prevent cervical cancer in women and oropharyngeal cancer.
- Mention immunologic response is greater in younger adolescents, so earlier immunization is prudent.
- Administer HPV vaccine at the same time that other adolescent vaccines are given.
- Review immunization status at every visit, and administer the HPV vaccine at any time—including during sick visits.

It is estimated that if these procedures had been followed, the HPV vaccination rate could have reached 91.3% for 13-year-old girls who were born in 2000.

Prevention

- Physicians should continue to advocate for immunizations during routine clinical encounters, encouraging the parent(s), a factor that has been linked to overcoming vaccine hesitancy.[13]
- Resources are available to provide evidence-based education to physicians about vaccines and their effectiveness, as well as to reassure parents that vaccines are safe and effective.

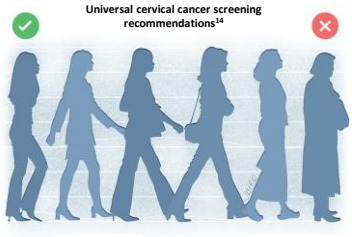


Screening

Screening

- Which of the following women should be screened for cervical cancer?
  - A. A 16 year old sexually active female with 4 lifetime male partners
  - B. A 19 year old who is 18 weeks pregnant
  - C. A 28 year old G3P2012 otherwise healthy female
  - D. A 42 year old with history of total hysterectomy for symptomatic fibroids

Universal cervical cancer screening recommendations[14]



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Screening

Common misconceptions[15]:

- Menses or other genital tract bleeding (smear vs liquid)
- Interval between Pap tests
- Gel lubricants and other contaminants
- Vaginal intercourse, douching, and tampon use

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Screening

- Cervical cancer screening in special populations[16]:
  - Total hysterectomy for reasons other than cervical dysplasia or cancer do not need pap smears.
  - Immunosuppressed (SLE)
  - HIV
    - Cervical cytology for cancer screening twice in the first year after diagnosis of HIV infection and then annually, provided the test results are normal
  - History of CIN 2, CIN 3, or adenocarcinoma in situ
    - Follow the American Society for Colposcopy and Cervical Pathology (ASCCP) guidelines
  - Recipients of HPV vaccine should undergo routine screening.
  - Pregnancy does not change screening recommendations[17].

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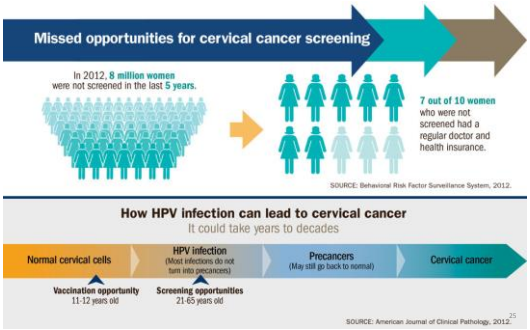


Cervical cancer screening recommendations from United States professional organizations*

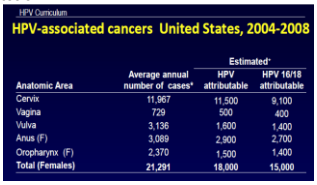
Organization	Age to initiate	Age to discontinue	Recommended screening test and frequency		Post-hysterectomy for benign disease	HPV vaccination
			Age 21 to 29	Age ≥30		
ACS/ASCCP/ASCP (2012)	21*	65†	Pap test every three years (preferred)	Co-testing (pap test and HPV testing) every five years (preferred) Pap test every three years	Not indicated‡	Same recommendations as unvaccinated women
ASCCP/SGO (2015 interim guidelines)	21	N/A	Can consider primary HPV testing every three years for women age ≥25	Can consider primary HPV testing every three years	N/A	N/A
USPSTF (2012)	21	65§	Pap test every three years	Pap test every three years Alternative: Co-testing (pap test and HPV testing) every five years‖	Not indicated‡	Same recommendations as unvaccinated women
ACOG (2016)	21	65†	Pap test every three years Can consider primary HPV testing every three years for women age ≥25	Co-testing (pap test and HPV testing) every five years (preferred) Pap test every three years Can consider primary HPV testing every three years for women age ≥25	Not indicated‡‡	Same recommendations as unvaccinated women
ACP (2015)	21	65§	Pap test every three years	Pap test every three years Alternative: Co-testing (pap test and HPV testing) every five years‖	Not indicated‡	N/A

Management

Management

HPV Disease Associations:

- Nongenital warts
- Recurrent respiratory papillomatosis
- Genital warts
- Cervical cancer[18]
- Anal cancer
- Cancer of the external genitalia
- Oropharyngeal cancer


HPV Curriculum

HPV-associated cancers United States, 2004-2008

Anatomic Area	Average annual number of cases*	Estimated* HPV attributable	Estimated* HPV 16/18 attributable
Cervix	11,967	11,500	9,100
Vagina	729	500	400
Vulva	3,136	1,600	1,400
Anus (F)	3,089	2,900	2,700
Oropharynx (F)	2,370	1,500	1,400
Total (Females)	21,291	18,000	15,000

Management

Genital Warts

- Symptoms[19]
  - Vary depending upon the number of lesions and their location.
  - Patients with a small number of warts are often asymptomatic.
  - May have pruritus, bleeding, burning, tenderness, vaginal discharge, or pain
- Location[18]
  - Most commonly occur in areas of coital friction
  - Perianal warts do not necessarily imply anal intercourse. May be secondary to autoinoculation, sexual activity other than intercourse, or spread from nearby genital wart site
  - Intra-anal warts are seen predominantly in patients who have had receptive anal intercourse.
  - HPV types causing genital warts can occasionally cause lesions on oral, upper respiratory, upper GI, and ocular locations.
  - Patients with visible warts are frequently simultaneously infected with multiple HPV types.

Management

Genital Warts-Appearance[18]

- Condylomata acuminata
  - Cauliflower-like appearance
  - Skin-colored, pink, or hyperpigmented
  - May be keratotic on skin; generally nonkeratinized on mucosal surfaces
- Smooth papules
  - Usually dome-shaped and skin-colored
- Flat papules Macular to slightly raised
  - Flesh-colored, with smooth surface
  - More commonly found on internal structures (i.e., cervix), but also occur on external genitalia
- Keratotic warts
  - Thick horny layer that can resemble common warts or seborrheic keratosis

Management[18]

- May regress spontaneously, or persist with or without proliferation.
- Frequency of spontaneous regression is unclear, but estimated at 10–30% within three months.
- Persistence of infection occurs, but frequency and duration are unknown.
- Recurrences after treatment are common.
- Choice of treatment should be guided by:
  - Patient preference,
  - Available resources,
  - Experience of the healthcare provider,
  - Location of lesion(s), and
  - Pregnancy status.

Approach to the treatment of vulvovaginal warts

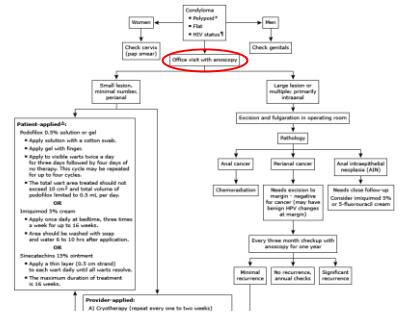
Self-administered therapies (vulva)
Podofilox 0.5 percent solution
Imiquimod 5 percent cream
Sinecatechins 15 percent ointment
Provider-admininstered therapies (vulva)
Without anesthesia
Cryotherapy with liquid nitrogen or cryoprobe
Podophyllin resin 10 to 25 percent in a compound tincture of benzoin
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent
With anesthesia
Surgical removal (sharp, electrocautery, curettage, laser)
Therapies preferred for pregnant women (vulva)
Without anesthesia
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent
Cryotherapy with liquid nitrogen or cryoprobe
With anesthesia
Surgical removal (sharp, electrocautery, curettage, laser)
Therapies preferred for treatment of vaginal warts
Without anesthesia
Cryotherapy with liquid nitrogen
Trichloroacetic acid or bichloroacetic acid 80 to 90 percent

Management

Treatment Response[18]

- Affected by Number, size, duration, and location of warts, and immune status
- In general, warts located on moist surfaces and in intertriginous areas respond better to topical treatment than do warts on drier surfaces.
- Many patients require a course of therapy over several weeks or months rather than a single treatment.
- Evaluate the risk-benefit ratio of treatment throughout the course of therapy to avoid over-treatment.
- There is no evidence that any specific treatment is superior to any of the others.
- Treatment algorithms has been associated with improved clinical outcomes

Approach to anogenital condyloma



Management

Abnormal Cervical Cytology

Management

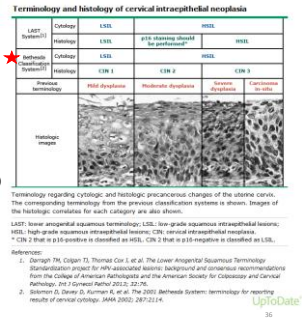
Bethesda 2014 classification system for cervical cytology[20]

- Specimen type
- Specimen adequate
- Interpretation/results
  - Negative for intraepithelial lesions or malignancy
  - Organisms
  - Epithelial cell abnormalities
    - Squamous cell
    - Glandular cell
- Other malignant neoplasms
- Adjunctive testing
- Computer-assisted interpretation of cervical cytology

Management

Epithelial cell abnormalities[20]

- **Squamous cell**
  - Atypical squamous cells
    - Of undetermined significance (ASC-US)
    - Cannot exclude HSIL (ASC-H)
  - Low-grade squamous intraepithelial lesion (LSIL)
  - High-grade squamous intraepithelial lesion (HSIL)
    - With features suspicious for invasion
  - Squamous cell carcinoma
- **Glandular cell**
  - Atypical
    - Endocervical cells (NOS *or specify in comments*)
    - Endometrial cells (NOS *or specify in comments*)
    - Glandular cells (NOS *or specify in comments*)
  - Atypical
    - Endocervical cells, favor neoplastic
    - Glandular cells, favor neoplastic
  - Endocervical adenocarcinoma in situ
  - Adenocarcinoma
    - Endocervical
    - Endometrial
    - Extrauterine



Relative incidence of cervical cytology results

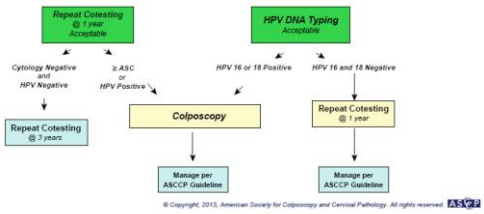
Cytology	Incidence (percent)
Negative	96
Atypical squamous cells of undetermined significance (ASC-US)	2.8
Low-grade squamous intraepithelial lesion (LSIL)	0.97
High-grade squamous intraepithelial lesion (HSIL)	0.21
Atypical glandular cells (AGC)	0.21
Atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion (ASC-H)	0.17
Squamous cell cervical carcinoma	4.5 per 100,000

Data from: Katki HA, Schiffman M, Castle PE, et al. Benchmarking CIN 3+ Risk as the Basis for Incorporating HPV and Pap Cotesting into Cervical Screening and Management Guidelines. J Low Genit Tract Dis 2013; 17:S28.

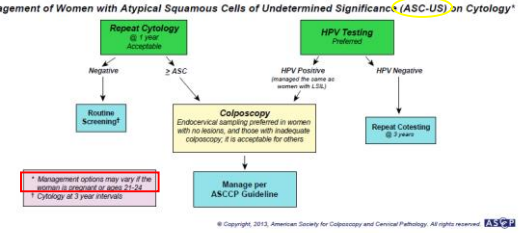
UpToDate®

Normal Cytology/HPV Positive

Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive



Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*



ASC-US

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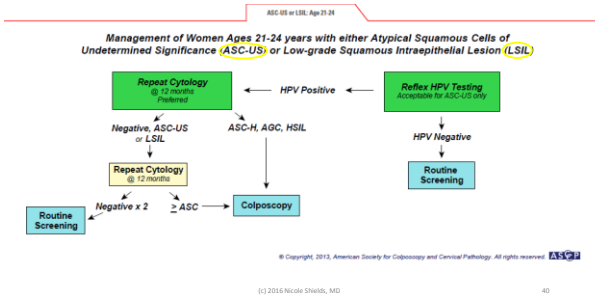

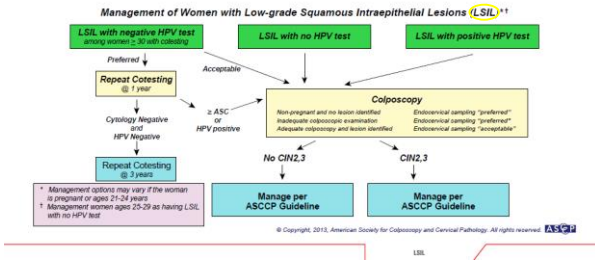

Management[20]

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Atypical glandular cells (AGC)	0.21
Atypical squamous cells: cannot exclude high-grade squamous intraepithelial lesion (ASC-H)	0.17
Squamous cell cervical carcinoma	4.5 per 100,000

Require colposcopy or other diagnostic/treatment evaluation

Data from: Katki HA, Schiffman M, Castle PE, et al. Benchmarking CIN 3+ Risk as the Basis for Incorporating HPV and Pap Cotesting into Cervical Screening and Management Guidelines. J Low Genit Tract Dis 2013; 17:S28.

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