Objectives

- Describe our current understanding of the natural history of HPV infection and how it relates to the newest recommendations for cervical cancer screening
- Discuss the current role of HPV testing
- Describe recent recommendations from the ASCCP for management of abnormal Pap tests
Natural History of HPV Infection

- Sexual transmission (skin-to-skin)
- Enters cell through microtrauma
- Moves to nucleus of infected cell
- Infected cell exhibits koilocytosis (HPV effect, LSIL)
  - perinuclear halo
  - enlarged nucleus with clumped chromatint
Activation of Oncogenes

- E6 and E7 are oncogenes
- E7 can activate synthesis of the intracellular protein p16, normally manufactured only in miniscule amounts
- Excess p16 deregulates and stimulates the cell cycle
- Cervical neoplasia (CIN 2/3) results
Progression of Cervical Neoplasia
HPV – Usually a Transient Infection

• In 608 college-aged women
  – 70% no longer infected at one year
  – 91% no longer infected at 2 years
  – Average duration of infection - 8 months

• Manifestation of disease determined by
  – HPV subtype, viral load
  – Host cofactors
The Natural History of HPV Infection and Cervical Cancer
Current Pap Test Recommendations (ASCCP, ACS, ASCP, USPSTF, ACOG)

- First Pap test age 21
- Test every three years until age 30
- Age ≥ 30, HPV test with Pap test every 5 years
  - If HPV testing unavailable, Pap every 3 years
- No more testing after hysterectomy (if cervix has been removed) or age 65
  - With negative Pap history

Important: Pap ≠ Well Woman Exam (Still covered by WWC)
Evidence for New Guidelines

• Yearly Pap interval was chosen arbitrarily when the test was first introduced

• Now we know that
  – Cervical cancer is an STI caused by HPV
  – Most HPV infections are cleared by the body’s own immune system

• Likelihood of progression to cancer
  – \textit{Duration/persistence of infection}
Evidence for HPV Co-Testing

• Before age 30, high prevalence of HPV → Do not co-test
• In women ≥ 30, co-testing detects 17-31% more CIN 3 (pre-cancer) AND
• HPV testing is superior to cytology for detecting cervical adenocarcinoma
  – Poorer prognosis, on the rise

Exceptions to the New Guidelines

- **Continue annual Pap testing for**
  - Immunocompromised women, especially HIV+
  - Women exposed to DES *in utero*
- **Women who have had CIN 2 or CIN 3**
  - 5-10% increased risk of cervical cancer for 20 years
  - More intense screening first 5 years
  - Continue routine testing for at least 20 years
- **Women treated for cervical cancer**
  - Continue regular testing indefinitely
Exceptions to New Guidelines

- Early onset of sexual activity
- Sexual activity with multiple partners or new sex partner
- Tobacco use
Advantages of New Guidelines

• Balances benefits and harms
  – Avoids unnecessary emotional and physical trauma, especially for young women
  – LEEP may increase risk of preterm birth

• Frees up time
  – To discuss other important issues
  – To make clinic more efficient

• May increase clinic visits

• Cost savings
Who should get a Pap this year?

- A 19-year-old who has been sexually active for four years?
- A sexually active 16-year-old who is HIV positive?
- A 31-year-old who had a hysterectomy 3 years ago for endometriosis, previous Paps negative?
- A 41-year-old with a negative Pap in your clinic last year and in 2009 and 2007?
- A 67-year-old s/p LEEP for CIN III five years ago?
- A 71-year-old just returned from a cruise, where she had three sex partners?
2012 Consensus Guidelines for Management of Abnormal Pap Tests

Available (with algorithms) at www.ASCCP.org/Consensus2012
Guidance on HPV Testing
Pap Tests vs. HPV Testing

• Pap Test
  – 30-87% sensitivity
  – High specificity
  – Poor reproducibility among observers
    • ASC-US - 43%
    • LSIL - 68%
    • HSIL - 47%
    (ALTS study)

• HPV Test
  – High sensitivity
  – Low specificity
    • (only 15% of pts with + HPV and - Pap will develop + cytology within 5 years)
  – 97% reproducibility
The Role of High-Risk HPV Testing

- Low-risk HPV testing not meaningful, obsolete
- The only screening indication is for women age $\geq 30$ in addition to Pap*
  - Co-testing recommended in this group
  - If both tests negative, do not repeat for 5 years
- Primarily used for triage
  - ASCUS Paps (reflex testing)
- Minimize HPV testing in woman < age 30

*Now covered by WWC
Role of HPV 16/18 Genotyping

Positive HPV 16 or 18 linked to 14% to 17% incidence of CIN3+

The cumulative incidence of CIN 3+ over a 10-year period, as a function of a single HPV test result at enrollment. Women positive for HPV 16 or 18 had a much greater incidence of CIN 3+, compared to women negative for HPV 16 and 18 but positive for other high-risk HPV types by Hybrid Capture 2, or negative for all high-risk HPV types. Adapted from Khan et al.
Management of Women ≥ Age 30, who are Cytology Negative, but HPV Positive

- **Repeat Cotesting**
  - @ 1 year
  - Acceptable

  - Cytology Negative
  - and
  - HPV Negative

  - Repeat cotesting
  - @ 3 years

- **HPV DNA Typing**
  - Acceptable

  - HPV 16 or 18 Positive

  - HPV 16 and 18 Negative

  - Repeat Cotesting
  - @ 1 year

- **Colposcopy**

- Manage per ASCCP Guideline

- Manage per ASCCP Guideline

*WWC does not cover HPV genotyping*
Who should get an HPV test?

• A 16-year-old who is HIV positive?
• A 23-year-old with an LSIL Pap?
• A 24-year-old considering HPV vaccine?
• A 41-year-old presenting for annual exam?
• A 41-year-old with neg Pap/HPV last year?
• A 50-year-old with an ASCUS Pap?
• A 65-year-old s/p LEEP for CIN III last year?
BUT this may all be changing again soon!

We may start doing HPV testing alone on women ≥ age 25
Supporting Data

- European studies
- Kaiser of Northern California
  - 3 year risk of CIN 3 after a negative HPV test
    • HPV alone q 3 years – 0.069%
    • HPV/Pap cotesting q 5 years – 0.11%
    • Pap alone q 3 years - 0.19%
- ATHENA
  - HPV detected 50% more CIN 3 than Pap
  - BUT doubled the number of colposcopies
How might this work?

- **Primary HPV Screening**

  - **Type 16/18 Positive** → **Colposcopy**

  - **12 other hrHPV +** → **Cytology**
    - ≥ASC-US → **Follow up in 12 months**
    - NILM → **Routine Screening (q 3 years)**

  - **Negative**
Caveats

• Only one brand of HPV test (Cobas®) is approved for this indication
• Should NOT be used on women < age 25

• Not yet recommended by major organizations (including ACOG, CDC)
Guidance on Abnormal Pap Tests
Unsatisfactory Pap Tests

- With liquid-based testing, usually means not enough cells to evaluate
- Satisfactory reading implies that enough cells were seen for accurate result
  - If inflammation, etc., noted → Pap still negative
Unsatisfactory Cytology

- HPV unknown (any age)
- HPV negative (age ≥30)
- HPV positive (age ≥30)

Repeat Cytology after 2-4 months

- Abnormal: Manage per ASCCP Guideline
- Negative: Routine screening (HPV-/unknown) or Cotesting @ 1 year (HPV+)
- Unsatisfactory: Colposcopy

Note: “Manage per ASCCP Guideline” = Go to algorithm for the specific condition
Negative but
No/Insufficient Endocervical Cells

• Now shown not to be associated with missed disease
• In women ≥ age 30, HPV test gives added margin of safety
**Cytology NILM* but EC/TZ Absent/Insufficient**

- Ages 21-29+
  - HPV negative
    - HPV testing (Preferred)
  - HPV unknown
    - Repeat cytology in 3 years (Acceptable)

- Age ≥30 years
  - HPV positive or
    - HPV testing
    - Cytology + HPV test in 1 year
  - Genotyping
    - Manage per ASCCP Guideline

*Negative for intraepithelial lesion or malignancy
†HPV testing is unacceptable for screening women ages 21-29 years

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ASCUS
(Atypical Cells of Undetermined Significance)

• Two choices for management
  – HPV Test
    • Best option
    • Reflex if possible
    • ASCUS + HPV = managed same as LSIL
    • ASCUS - HPV = greater risk than negative Pap
      → repeat co-testing in 3 years, even if > age 65
  – Repeat Pap in 1 year → colpo if any abnormality
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology*

Repeat Cytology
@ 1 year
Acceptable

HPV Testing
Preferred

HPV Positive
(Managed the same as
women with LSIL)

HPV Negative

≥ ASC

Negative

Routine Screening*

Colposcopy
Endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others

Manage per ASCCP Guideline

Repeat Cotesting
@ 3 years

*Management options may vary if the woman is pregnant or ages 21-24.
*Cytology at 3 year intervals

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LSIL
(Low Grade Squamous Intraepithelial Lesion)

• Usually implies presence of HPV infection, HPV testing not needed
• But Pap is just a screening test:
  Up to 28% actually have CIN 2 or CIN 3

Colposcopy
Exception - Women Ages 21-24

- Risk of cancer 2/1,000,000 at this age
- High incidence of HPV infection
- Cervical injury has potential for harm to future pregnancies

→ Manage more conservatively
Management of Women Ages 21-24 years with either Atypical Squamous Cells of Undetermined Significance (ASC-US) or Low-grade Squamous Intraepithelial Lesion (LSIL)

Women ages 21-24 years with ASC-US or LSIL

Repeat Cytology @ 12 months Preferred

HPV Positive

Reflex HPV Testing Acceptable for ASC-US only

ASC-H, AGC, HSIL

HPV Negative

Routine Screening

Negative, ASC-US or LSIL

Repeat Cytology @ 12 months

Negative x 2 ≥ ASC

Colposcopy

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Guidelines for Colposcopy

- Always recommended for
  - HSIL (High Grade Squamous Intraepithelial Lesion)
  - ASC-H (Atypical Squamous Cells, Can’t Exclude HSIL)
  - AGC (Atypical Glandular Cells)
  - Cervical lesion or abnormal appearing cervix
    - Remove endocervical polyps*
    - Otherwise, ALWAYS SEND TO COLPOSCOPY
      - regardless of Pap results
    - Even when invasive cervical cancer present, Pap can be negative!

*WWC will cover
Further Guidelines for Colposcopy

• Colposcopy is notoriously inaccurate
  – Even “the experts” miss 18-36%¹
• Biopsies should be done with all colposcopies
  – Random biopsies +/- ECC if no lesions seen
  – 20.9% of random biopsies find CIN 2 or 3²
• All visible lesions should be biopsied
• The more cervical biopsies the better!

Management of Women with High-grade Squamous Intraepithelial Lesions (HSIL)*

Immediate Loop Electrosurgical Excision

Or

Colposcopy (with endocervical assessment)

No CIN2,3

CIN2,3

Manage per ASCCP Guideline

* Management options may vary if the woman is pregnant, postmenopausal, or ages 21-24.
* Not if patient is pregnant or ages 21-24.

*WWC will cover immediate LEEP
Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)*

Colposcopy
Regardless of HPV status

No CIN2,3

Manage per ASCCP Guideline

CIN2,3

Manage per ASCCP Guideline

* Management options may vary if the woman is ages 21-24.
Management of Women Ages 21-24 yrs with Atypical Squamous Cells, Cannot Rule Out High Grade SIL (ASC-H) and High-grade Squamous Intraepithelial Lesion (HSIL)

Colposcopy
(Immediate loop electrosurgical excision is unacceptable)

No CIN2,3

Observation with colposcopy & cytology *
@ 6 month intervals for up to 2 years

Other results

HSIL
Persisted for 24 months with no CIN2,3 identified

Diagnostic Excisional Procedure

CIN2,3
(if no CIN2,3, continue observation)

Biopsy

Manage per ASCCP Guideline for young women with CIN2,3

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The Ominous AGC Pap

Review of 3,890 AGC (AGCUS) Paps*

- 5.2% had a malignancy

- Another 23% had a significant finding
  - 8.5% LSIL
  - 11.1% HSIL
  - 2.9% AIS
  - 1.4% endometrial hyperplasia

**Initial Workup of Women with Atypical Glandular Cells (AGC)**

- **All subcategories** (except atypical endometrial cells)
  - **Colposcopy** (with endocervical sampling) and **Endometrial sampling** (if ≥ 35 yrs or at risk for endometrial neoplasia*)

- **Atypical Endometrial Cells**
  - **Endometrial and Endocervical Sampling**
  - **No Endometrial Pathology**
  - **Colposcopy**

*Includes unexplained vaginal bleeding or conditions suggesting chronic anovulation.

*The only time WWC will cover EMB
Subsequent Management of Women with Atypical Glandular Cells (AGC)

Initial Cytology is AGC - NOS
- No CIN2+, AIS or Cancer
  - Cotest at 12 & 24 months
    - Both negative: Cotest 3 years later
    - Any abnormality: Colposcopy

- CIN2+ but no Glandular Neoplasia
  - Manage per ASCCP Guideline

Initial Cytology is AGC (favor neoplasia) or AIS
- No Invasive Disease
  - Diagnostic Excisional Procedure*

* Should provide an intact specimen with interpretable margins. Concomitant endocervical sampling is preferred.
Who needs Colposcopy?

- A 23-year-old with LSIL Pap?
- A 23-year-old with AGC Pap?
- A 27-year-old with LSIL Pap?
- A 40-year-old with ASCUS, HPV positive?
- A 50-year-old with ASC-H, HPV negative?
- A 60-year-old with LSIL, HPV negative?
- A 63-year-old with AGC, HPV negative?
Treatments for CIN 2/3

- Ablative
  - Cryotherapy
  - Laser vaporization
- Excisional
  - Loop electrosurgical excision procedure (LEEP)
  - Laser excision/conization
  - Cold knife cone
- All ~90% effective
- Follow-up important
  - Cotesting q 12 mos x 2, then in 3 years
    - If negative, cotesting every 5 years for > 20 years
    - If positive, recolposcope

Risks of Treatment

- LEEP and conization may be associated with:
  - Preterm delivery
  - Premature ruptured membranes
  - Low birth weight
- Ablation appears to have fewer pregnancy risks
- In a comparative study with cryo and laser, LEEP had highest risk of complications:
  - 8% bleeding > 24 hrs post treatment
- But LEEP and cone provide histologic specimens

→ Individualize therapy

Individualized Therapy

- Avoid treating young women and nullips whenever possible, and minimize treatment for CIN I in all age groups.
- Treat CIN 2,3 in women $\geq 30$ and those who have completed childbearing.
- Can closely follow CIN 2,3 in young women (age 21-24 or who plan future pregnancy).
Management of Young Women with Biopsy-confirmed Cervical Intraepithelial Neoplasia — Grade 2,3 (CIN2,3) in Special Circumstances

**Young Women with CIN2,3**

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

**Observation — Colposcopy & Cytology**

@ 6 month intervals for 12 months

- 2x Cytology Negative and Normal Colposcopy
  - Cotest in 1 year
  - Both tests negative
  - Cotest in 3 years

- Either test abnormal

**Treatment using Excision or Ablation of T-zone**

- Colposcopy worsens or High-grade Cytology or Colposcopy persists for 1 year
- CIN3 or CIN2,3 persists for 24 months

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Individualized Therapy

• Ablative therapy preferred in women with plans for future childbearing
• Always need excisional therapy if unsatisfactory colposcopy, lesion in endocervical canal, positive ECC, or previous failed therapy
What testing is needed?

- 49 year-old with history of hysterectomy at age 39 due to CIN II/III
- 53 year-old with history of hysterectomy with ovaries removed for endometriosis. Exposed to DES in utero
- 60 year-old with negative Pap and HPV two years ago, white lesion noted on cervix at annual this year
More Questions

• 61 year-old had hysterectomy for fibroids, cervix still present. Pap neg (no ECC) but +HPV. Last Pap neg 2-3 years ago. What testing does she need? What will WWC cover?

• 52 year-old with negative Pap two years ago. Pap done again this year showed HSIL. What will WWC cover?
Importance of Meticulous Follow-up

- Abnormal Pap tests
  - WWC: time from Pap to diagnosis < 60 days
- Abnormal colposcopies
  - WWC: time from colposcopy to treatment < 60 days
- Continued follow-up after treatment (≥ 20 years)

***Tracking system more important than ever now that we are treating less and following more***

WWC: Track until patient completes treatment and F/U, informed refusal in chart, or 3 documented attempts to contact patient (one must be by certified letter)
Cervical Cancer Prevention

- Safer sexual practices
  - Condoms 70% effective in preventing transmission*
- Avoid smoking
- Healthier lifestyle

VACCINES

• Gardasil®
  – Prevents infection with HPV 16 & 18 (70% of CIN/CA) and 6 & 11 (90% of genital warts)
  – Also approved for prevention of vulvar, vaginal and anal intraepithelial lesions and CA
  – 3-dose regimen recommended for all females and males ages 11-12
    • Approved for ages 9-26
    • Does not accelerate clearance of the virus*

Coming soon: Gardasil 9® – includes HPV 31, 33, 45, 52, 58 to prevent ~ 85% of cervical cancers

• **Cervarix®**
  – Prevents infection with HPV 16 & 18
  – 3-dose regimen recommended for all females ages 11-12
    • Approved for ages 10-25
  – New adjuvant → higher antibody response
    • Likely confers longer-lasting immunity
    • Likely offers ↑ cross-protection against related viruses
Results So Far

- 16% ↓ ASCUS
- 23% ↓ ASCUS + HPV
- 35% ↓ ASCUS r/o HSIL
- 14% ↓ LSIL
- 43% ↓ HSIL

- 50% less HPV in women ages 14-19

Genital warts
Initial visits to physicians’ offices: United States, 1966–2007

Note: The relative standard error for genital warts estimates range from 17% to 29.3%.

SOURCE: National Disease and Therapeutic Index (IMS Health)
The Promise of Global Cervical Cancer Prevention