Pap Smear Guidelines

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Verbal Disclosure

• I have no financial relationships that may pose a conflict of interest
Outline

• Background
• Pathogenesis of Cervical Dysplasia
• Importance of HPV testing
• Summary of Consensus Guidelines 2013
• 3 Sample Cases
• Future Research
Background
Pap Smear
**Spatula/Brush Method**

- Rotate spatula 360 degrees
- Swirl the spatula 10x, then discard
- Insert brush into endocervix until only bottom bristles are visible. Slowly rotate ¼ or ½ turn. Do not overrotate
- Rinse the brush 10x, then discard
Collection: Broom Method

• Insert the central bristles into the endocervical canal until the shorter bristles are in full contact with the ectocervix. Push in gently, then rotate 5X

• Rinse the broom by pushing it into the bottom of the vial 10x, forcing the bristles apart.
• Swirl the broom vigorously to further release material
• Discard the broom
Effectiveness of the Pap

- The pap is very effective at detecting pre-cancerous abnormalities.
- It is poorly effective at detecting cervical cancer.
- The **majority of patients in the US** diagnosed with cervical cancer have either
  - never been screened or
  - have not been screened within the past 5 years.
Transformation Zone
Transformation Zone

- Transformation zone
- Most distal cervical crypt opening
- New SCJ
- Original SCJ
- Area of columnar epithelium
- Area of metaplastic squamous epithelium
- Area of original squamous epithelium
Bethesda Terminology is Preferred

<table>
<thead>
<tr>
<th>LAST System[1]</th>
<th>Cytology</th>
<th>LSIL</th>
<th>HSIL</th>
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<tbody>
<tr>
<td>Histology</td>
<td>LSIL</td>
<td></td>
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<tr>
<td>Bethesda Classification System[2]</td>
<td>Cytology</td>
<td>LSIL</td>
<td>HSIL</td>
</tr>
<tr>
<td>Histology</td>
<td>CIN 1</td>
<td>CIN 2</td>
<td>CIN 3</td>
</tr>
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<table>
<thead>
<tr>
<th>Previous terminology</th>
<th>Mild dysplasia</th>
<th>Moderate dysplasia</th>
<th>Severe dysplasia</th>
<th>Carcinoma in-situ</th>
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Histologic images

- 5%
- 12%
Pathogenesis of Cervical Dysplasia

HPV
HPV Epidemiology and Risk Factors

- 40 HPV genotypes infect the mucosa of the genital tract
- 8 types cause 95% of cervical cancers (16, 18, 45, 31, 33, 52, 58, 35)
- 2 types are responsible for 70% of cervical cancers (16, 18)
- 2 low-risk types cause 90% of benign anogenital warts (6, 11)
HPV Epidemiology and Risk Factors

- Risk α # lifetime partners
- After 1 partner, 20% infected with HPV
- 50% of young women will have a positive HPV test within 3 years of coitarche
- Up to 60% of adolescents are infected with HPV
- Most will clear within 8-24 months
- Cigarette smoking increases the risk 4-fold
HPV Genome

• Double stranded non-enveloped DNA virus
• ~ 8000 bp
• Gene consists of early and late regions
• Early genes: division, proliferation
• Late genes: virus assembly
• E6 and E7 are important oncoproteins
  – E6 binds/ inhibits p53
  – E7 binds/ inhibits pRb
Human papillomavirus infection & replication in cervical epithelial cells

Expert Reviews in Molecular Medicine
HPV Vaccine

- Quadrivalent vaccine: Types 6, 11, 16, 18
- 90-100% prevention of CIN 2/3, ACIS, cancer
- Consists of virus-like particles (VLP): empty capsid protein, i.e. no DNA, so noninfectious
- Three injections: 0, 2, 6 months
- CDC: 9-26 yrs; FDA: 13-26 yrs
- 75% greater immunity if vaccinated compared to innate immunity
The Importance of HPV Testing
HPV testing

• **Primary testing**
  – Definitions
    • a.k.a. Co-testing
    • Cytology/HPV
    • Pap/HPV together (HPV is done no matter what)
    • There is only 1 proprietary HPV test that is FDA approved for primary testing without cytology
  – Advantages
    • High sensitivity
    • High NPV
    • Picks up high grade lesions sooner
  – Disadvantages
    • Low specificity in young women (< 30 and especially adolescents)

• **Reflex testing**
  – Used as a method to **triage** abnormal cytology results
  – Useful for ASCUS
  – Not useful for LGSIL+ (will be positive anyway)
    ALTS (ASCUS-LSIL Triage Study)
HPV Testing

• In the US, 4 types of HPV tests are approved for use either as co-testing, or reflex after ASCUS
  – Hybrid Capture 2 (FDA 2003) – identifies any of 13 HR types
  – Cervista HPV HR test (FDA 2009) – identifies any of 14 HR types
    • HPV genotyping can be done with Cervista 16/18 for women who test + on original Cervista test (only for women > 30)
  – Cobas HPV test – HPV genotyping for 16 and 18 and a pooled result for 12 HR types
    • In April 2014, this was approved for primary testing in women > 25
      • Not enough data to support its use (no followup guidelines)
  – Aptima mRNA test – detects 14 HR subtypes
Screening – Identify Cancer Precursors

- Fundamental goal: prevent morbidity and mortality from cervical cancer.

- Optimal screening strategy
  - identify precursors (dysplasia)
  - avoid detection and unnecessary treatment of lesions not destined to become cancer
Diagnostic Lead Time

• Negative co-test → ↓↓ CIN3+ in next round

• Results in:
  – Lower risk of CIN3+ following a negative screen
  – Allows for a longer interval between screens
  – Incident cancer rates with co-testing is lower than annual cytology

Naucler, et al. NEJM 2007;357:1589-97
1 year → 3 years → 5 years?

- Co-testing with 5 year intervals is comparable to co-testing at 3 year intervals
- 7 observational studies involving nearly 25,000 patients, pooled to examine the long-term predictive values of cotesting.¹
  - 6-year risk of CIN 3+
    - After negative cytology alone = 0.97%
    - After negative co-testing = 0.28%
- Retrospective study 330,000 women ²
  - 3-year risk of CIN 3+
    - After negative cytology (regardless of HPV result) = 0.17% (CA 0.018%)
  - 5-year risk of CIN 3+
    - After negative HPV (regardless of cytology result) = 0.17% (CA 0.019%)
    - After negative-cotesting = 0.17% (CA 0.016%)
- Co-testing at intervals shorter than 3 years exacerbates the harms by increasing the number of colposcopic referrals and treatments.

¹ Dillner J, et al. BMJ. 2008;337:a1754
Summary of 2013 Consensus Guidelines
What are the New Guidelines?

- Cervical cancer screening guidelines in the US are issued by 3 major groups of organizations:
  - US Preventive Services Task Force (USPSTF)
  - American Cancer Society, American Society for Colposcopy and Cervical Pathology, and the American Society for Clinical Pathology (ACS/ASCCP/ASCP)
  - American Congress of Obstetricians and Gynecologists (ACOG)
# Cervical Cytology Guidelines

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<thead>
<tr>
<th></th>
<th>ACOG</th>
<th>ACS/ASCCP/ASCP</th>
<th>ACS</th>
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<tbody>
<tr>
<td>Start</td>
<td></td>
<td>age 21</td>
<td></td>
</tr>
<tr>
<td>Interval</td>
<td><strong>age 21-29:</strong> cytology alone q3yrs</td>
<td><strong>age 21-29:</strong> cytology alone q3yrs</td>
<td>age 21-29: cytology alone q3yrs</td>
</tr>
<tr>
<td></td>
<td><strong>age ≥ 30:</strong> co-testing q5yrs</td>
<td><strong>age ≥ 30:</strong> co-testing q5yrs OR cytology q3yrs</td>
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Note: these guidelines are not for women with HIV, those who are immunocompromised, those who’ve had in utero DES exposure, or those with a h/o CIN 2/ CIN 3.
Cervical Cytology Guidelines

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<tbody>
<tr>
<td><strong>Stop</strong></td>
<td>age 65 only if:</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>three consecutive negative cytology tests or two consecutive negative HPV/Pap co-tests in the 10 years prior to stopping, with the most recent test within five years</td>
<td></td>
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</tr>
<tr>
<td><strong>Post-Hyst</strong></td>
<td>Stop If have documented removal of cx with no h/o CIN 2+</td>
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</tbody>
</table>

Note: these guidelines are not for women with HIV, those who are immunocompromised, those who’ve had in utero DES exposure, or those with a h/o CIN 2/ CIN 3.
Women > 65

- 3 consecutive negative cytology results or 2 consecutive negative cotests within the 10 years before ceasing screening, with the most recent test occurring within the past 5 years

- No history of CIN2+ within the last 20 years

- TZ involutes & is less accessible to incident infection

- Screening would detect a very small number of incident CIN2+ cases and prevent very few cervical cancer deaths

- Once screening is discontinued, it should not resume for any reason, even if a woman reports having a new sexual partner

- Based on the natural history of HPV, it is improbable that incident high-risk HPV infections and newly detected CIN 3 after age 65 will have sufficient time to progress to invasive cancer. Most of them clear spontaneously
<table>
<thead>
<tr>
<th>Population</th>
<th>Recommended Screening Method</th>
<th>Management of screen results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 21 years</td>
<td>No screening</td>
<td></td>
<td>HPV testing should NOT be used for screening or management of ASCUS in this age group</td>
</tr>
<tr>
<td>21-29 years</td>
<td>Cytology alone q3 years</td>
<td>ASCUS pap with secondary HPV + or LSIL pap or more severe: Refer to ASCCP guidelines</td>
<td>HPV testing should NOT be used for screening in this age group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASCUS pap with secondary HPV negative or normal pap: Rescreen with cytology in 3 yrs</td>
<td></td>
</tr>
<tr>
<td>30-65 years</td>
<td>HPV and cytology cotesting q5 years (preferred)</td>
<td>ASCUS/HPV+ or ≥ LSIL pap: Refer to ASCCP guidelines</td>
<td>Screening by HPV testing alone is not recommended for most clinical settings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal pap/ HPV+: Option 1: cotesting in 12 mos Option 2: HPV16/18 genotyping If HPV16+ or HPV 16/18, refer to colposcopy If HPV 16 neg or HPV 16/18 neg, cotesting in 12 mos</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cotesting negative or ASCUS/HPV negative: Cotesting in 5 years</td>
<td></td>
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<tr>
<td></td>
<td>Cytology alone q3 years (acceptable)</td>
<td>ASCUS/HPV+ or ≥ LSIL pap: Refer to ASCCP guidelines</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal pap or ASCUS/HPV neg: Pap in 3 years</td>
<td></td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>No screening following adequate negative prior screening</td>
<td></td>
<td>Women with h/o CIN 2 or a more severe diagnosis should continue routine screening for at least 20 years</td>
</tr>
<tr>
<td>After hysterectomy</td>
<td>No screening</td>
<td></td>
<td>Applies to women w/o a cervix and without a h/o CIN 2 or a more severe diagnosis in the past 20 years or cervical cancer ever</td>
</tr>
<tr>
<td>HPV vacc.</td>
<td>Follow age-specific recommendations (same as unvaccinated women)</td>
<td></td>
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</tbody>
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3 Sample Cases
Patient #1

• 26 yo woman comes to your office for a well woman exam.
• You perform a pap smear and bimanual exam (normal).

1) Should you do cytology alone or a co-test?
2) Her pap returns ASC-H. What is ASC-H?
3) What is your next step?
**Patient #1**

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.

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66 yo woman comes to see you for a routine health maintenance exam. She says that she doesn’t need further gyn exams or pap smears.

Her pap history is:

- 2006: pap- negative for intraepithelial lesion (NIL)
- 2009: co-testing pap NIL/ HPV negative
- 2012: co-testing pap NIL/ HPV negative

- Do you do a pap? What about a pelvic exam?
- When do you want to see her next?
Patient #3

• **22 yo** G0 has come in today to discuss starting birth control because she is planning on have vaginal intercourse with her fiance once she is married. Her wedding is next week. She has *never had vaginal intercourse*. You talk to her about her contraceptive options and ultimately she decides that she wants the combined oral contraceptive pill.

• Does she need a pap smear?
• If yes, do you do an HPV test (co-testing) with it?
• If she outright refuses the pap smear, do you agree to prescribe the contraceptive pills?
Summary

• These guidelines are based on a systematic evidence review
  – 6 workings groups
  – Symposium sponsored by the ACS, ASCCP, ASCP and attended by 25 organizations
  – 1.4 million women in the Kaiser Northern California Medical Plan

• New age-appropriate screening recommendations address:
  – Use of co-testing after ASCUS pap
  – Less invasive strategies for younger women
  – Follow-up (e.g. management of screen positives, screening interval for screen negatives)
  – Age at which to exit screening
  – Screening strategies for women vaccinated against HPV 16/18.
Future Research

• Self-collection of cervico-vaginal specimens coupled with HPV testing can be used to address health disparities in unscreened or under-screened women
• Novel biomarkers
• How to manage HPV+ primary testing
• Screen and treat protocols in limited-resource countries.
2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors

ACOG Practice Bulletin Number 131: Screening for cervical cancer.

American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer.