ASCCP Guidelines
Equal Management for
Equal Risk

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Cervical Cancer: Worldwide

- Second cause of cancer death in women
- Leading cause in many developing countries
- In 2002, worldwide estimates:
  - 473,000 cases
  - 274,000 deaths
- Incidence varies with availability of screening
  - 83% of cases occur in the developing world
  - 3.6% of cases in developed countries

IARC data: DM Parkin, Lancet Oncology, 2001

Figure 2: Global burden of HPV-attributable cancer in 2012.

Nature Reviews | Disease Primers
Wider Racial Gap Found in Cervical Cancer Deaths

- The death rate from cervical cancer higher than previously estimated
- Disparity in death rates between black women and white women is significantly wider
- Death rate of black American women comparable to that of women in many poor developing nations
- Hysterectomy-corrected mortality rate
  - Black women 10.1 per 100,000
  - White women 4.7 per 100,000
- Greatest mortality rates: black women 85 and older.
- Unequal access to screening and appropriate treatment, ability to pursue early-warning test results, and insurance coverage

Figure 4: HPV structure and genome organization.

From: Cervical human papillomavirus infection

Figure 5: HPV infection and the transformation zone.

From: Cervical human papillomavirus infection
Cervical Cancer + HPV

- ~15 different genital high-risk HPV types
- Persistent infection with HPV is a prerequisite for the development of cervical cancer and its precursors
- hrHPV-DNA is detected in up to 99.7% of cervical squamous carcinoma
- 94-100% of cervical adenocarcinoma and adeno-squamous carcinomas

### Natural history of CIN

<table>
<thead>
<tr>
<th></th>
<th>Regression (%)</th>
<th>Persistence (%)</th>
<th>Progression to CIN 3 (%)</th>
<th>Progression to Invasive Cancer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 1</td>
<td>60</td>
<td>10</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>CIN 2</td>
<td>40</td>
<td>10</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>CIN 3</td>
<td>33</td>
<td>55</td>
<td>N/A</td>
<td>&gt; 12</td>
</tr>
</tbody>
</table>

In young women, regression rates >90% — most caused by hrHPV
Approximately 50% of CIN2/3 is caused by HPV 16 and 18

Cervical Cancer Screening

- Optimal screening strategy should identify
  - Cervical cancer precursors likely to progress
  - Avoid detection and treatment of transient HPV infections
  - Minimize potential harms of screening

- Current screening strategies:
  - HPV as triage of cytology
  - Cytology as triage of HPV
  - Cotesting
  - Cytology at the time of HPV testing (HPV-informed guided screening)
Current Options

• Cytology-only:
  – Lower sensitivity and higher cNPV → more frequent testing
  – Triage testing needed for ASC-US results only
• Primary HPV screening:
  – Higher sensitivity and lower cNPV → safe extension of screening intervals
  – Triage testing needed for positive results to refer to colposcopy
  – Cytology as triage test for hrHPV, other than HPV 16/18
• Cotesting (cytology & HPV):
  – Highest sensitivity and lowest cNPV → longest repeat interval for negative screening
  – 2 screening tests performed up front

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Repeat interval for negative screen</th>
<th>Triage test required</th>
<th>Triage test options</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYTOLOGY</td>
<td>Highest</td>
<td>Shortest</td>
<td>For equivocal cytology results</td>
</tr>
<tr>
<td>HPV</td>
<td>Higher</td>
<td>Longer (lower cNPV)</td>
<td>For all positive results</td>
</tr>
<tr>
<td>Cotesting</td>
<td>Highest</td>
<td>Longest (lowest cNPV)</td>
<td>For all HPV positive, cytology-negative results</td>
</tr>
</tbody>
</table>

- 2 screening tests performed up front

HPV Testing

• Current HPV tests are qualitative
• Detect only high risk
• High sensitivity
• Decreased specificity → false + and overtreatment
• Allows lengthening screening intervals
• Not recommended for women between 21-29 years of age due to high false positive rate
• HPV 16: predominant type in squamous ca and adenoc; lower integration frequency than HPV18 (55-80%) → less aggressive
• HPV18: highest integration frequency in ICC, mostly adenoc (92-100%)
HPV for Primary Screening

- Detects lower number of ICC than in cytology-based screening group
- An HPV stand-alone screening algorithm misses cancer cases

- 9.4% of CIN2+ are HPV negative
- 5.7% of all CIN3 are HPV negative
- 16.6% of all ICC are HPV negative
- 26.6% of adenoca are HPV negative
- HPV screening misses more cancers than screening with cytology

Cotesting: Cytology + hrHPV

- Best and safest algorithm is cotesting
  - Cytology alone is 50% sensitive for detection of biopsy-confirmed CIN3 in women >30 years
  - Cotesting provides more protection
  - Combines a high-sensitive test (HPV test) with a higher-specificity test (cytology)
  - 91% sensitivity
- Downsides: 32% increase in colposcopies
- $39 million savings compared to HPV primary
- Greater effectiveness at lower cost

ASCCP Management Guidelines
Screening and Management Guidelines

• ASC/ASCCP/ASCP and USPSTF are screening guidelines
• ASCCP are management guidelines
  • What to do with an abnormal screening test?
  • First management guidelines in 2001
  • Revised and updated in 2006
  • Updated in 2013 incorporating HPV testing and co-testing as screening and follow up modalities

Why New Guidelines?

• Two convergent factors:
  • Reliance on Pap and HPV co-testing as primary screening modality
    • Increased sensitivity and negative predictive value useful in follow up
  • Robust database from Kaiser Permanente Northern California experience on risk after abnormal tests
    • Database of 1.4 million women with co-testing since 2003
    • Database allows age-based stratification of data

ASCCP Consensus Conference Goals

• Update on gaps not covered on previous guidelines
  • Management of abnormal co-testing results and cytology
  • Specimen adequacy limitations
  • Initial management of abnormal screening test results
  • Options for post-colposcopy management
  • Management of women aged 21-24 years
Equal Management for Equal Risk Foundation

- Premises:
  - Unachievable zero cancer risk
  - Balance between benefits and harms
    - Identify HPV-lesions likely to progress to cancer
    - Avoid overtreatment in lesions unlikely to progress to cancer
  - CIN3+ considered a reasonable substitution for cancer risk

- Tolerable risks considered:
  - CIN3+ risk in 3 years after negative cytology
  - CIN3+ risk in 5 years after negative co-testing

2012 ASCCP Management Guidelines

- Trial proved hrHPV+ ASC-US has similar risk as LSIL → recommendation for reflex-HPV testing for ASC-US (based on ASC-US-LSIL Triage Study or ALT5)
- Risk benchmarks:
  - Colposcopy referral: LSIL = HPV+/ASC-US, HPV+/ LSIL and worse, regardless of HPV results
  - 12-month return: ASC-US = HPV+ / NILM or HPV- / LSIL
  - 3-year screening interval: NILM = HPV- / ASC-US
  - 5-year screening interval: HPV- / NILM

Risk Stratification: Underlying Principle
Cytology result
Co-testing result

Similar Management for Similar Risk
Pap Test as Benchmark

Equal Management for Equal Risk

Universal thresholds summary:
• If CIN3+ risk is:
  • >5%: immediate colposcopy
  • 5-year risk CIN2+ in 30-64 with LSIL = 5.2%
  • 2-5%: 6-month to 12-month return visit
  • 0.1-2%: 3-year return visit
  • 0.1%: 5-year return visit
  • Risk comparable with negative co-testing
Equal Management for Equal Risk

- Level of risk threshold for colposcopy referral:
  - 5-year cumulative risk CIN2+ in women 30-64 with LSIL = 5.2%
- Example: A >30 y. woman with LSIL has equal risk of having precancer as a woman with ASC-US/HPV+
  - LSIL = ASC-US/HPV+ → Colposcopy
- Example: Management for a 23 yo with LSIL?
  - 5-year cumulative risk CIN2+ in women 21-24 with LSIL = 3.0%
  - Lower risk than accepted threshold of >5%
  - 2-5% → 6-month to 12-month return visit
  - Cytology surveillance recommended rather than colposcopy

Caveats

- Clinicians, patients, payers, IRBs, and the courts should never view recommendations as dictats
- Strong recommendations based on high-quality evidence will not apply to all patients
- Users of guidelines may reasonably conclude that following guidelines will be a mistake for some patients
- However, screening in excess of guidelines has been shown to cause potential harm to patients and to increase cost without sound justification

ASCCP Management Guidelines

- Gaps not covered in previous guidelines
  - Bethesda system reporting change regarding presence of TZ elements
    - Now “Satisfactory” with disclaimer “lack of TZ elements”
    - If HPV negative, no need for repeat sample
  - Only Unsatisfactory samples need to be repeated
Cytology NILM but EC/TZ Absent/Insufficient

Ages 21-29*
- HPV negative
- HPV testing (Preferred)
- Repeat cytology in 3 years (Acceptable)
- HPV positive
- Cytology/HPV test in 1 year
- Genotyping
- Manage per ASCCP guideline

Age ≥30 years
- HPV negative
- Routine screening
- HPV unknown
- HPV positive
- Manage per ASCCP guideline

*HPV testing is unacceptable for managing women ages 21-29 years

Unsatisfactory Cytology

HPV unknown (any age)
- Abnormal
- Manage per ASCCP guideline
- Routine screening (HPV/unknown) or Cotesting @ 1 year (HPV+)

HPV negative (age ≥30)
- Repeat Cytology after 2-4 months
- Negative
- Unsatisfactory
- Cervicography

HPV positive (age ≥30)
- Either is acceptable
- Colposcopy

3/30/2017
Adolescents
Young Women

Defining Adolescents

- ASCCP 2006 Consensus Conference decided that women younger than 21 years of age should be managed differently than adult women.
- HPV infection and spontaneous clearance are very common after sexual debut.
  - Only persistent HPV increases cancer risk
  - Risk declines continuously
  - Guidelines required separation of "adult" and "adolescent" groups

Defining Young Women

- Those who consider risk to future pregnancies from tx cervical abnormalities to outweigh risk of cancer during observation of those abnormalities
- ASCCP 2012 Consensus Conference decided that women aged 21-24 years should be managed differently than women aged 25-30 years.
  - HPV is common.
  - Lesions often regress.
  - Cervical cancer risk is low.
Risk of Cervical Cancer in Young Women

- 10-fold higher than risk in adolescents (1.4/100,000).
  - High enough to justify screening.
  - Low enough to allow observation for minor cytologic abnormalities.

Concepts of HPV Infection by Age

<table>
<thead>
<tr>
<th>Adolescents &amp; Young Women</th>
<th>Adult women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign and reversible disease</td>
<td>Persistent infection and a higher risk of advanced</td>
</tr>
<tr>
<td>CIN</td>
<td>&gt;&gt; Invasive Cancer</td>
</tr>
</tbody>
</table>

Updated Screening Recommendations

- When should screening begin?
  - Screening should begin at age 21.
  - Regardless of sexual history or pregnancy.
Screening Adolescents < Age 21

• Earlier screening may increase anxiety, expense from the test itself and overuse of follow-up procedures. (ACOG 2012)
• Treatment may have adverse effects on future childbearing (USPSTF 2012)
  • Risk of preterm birth.
  • Risk of delivery of SGA fetus.
• Colposcopy and other interventions should be avoided when risk for CIN 3+ is low and lesions are likely to resolve. (ASCCP 2013)

HPV in Adolescents

• HPV is an incident, not a persistent infection
  • 50% clear within 6 months
  • 90% clear within 24 months
  • 92% of LSIL regressed within 36 months
  • 3% went on to develop HSIL


Does Cervical Cancer Occur in Adolescents and Young Women?

• 2000-2004: no cervical cancer in girls < 14 years
• 0.1/100,000 cases in adolescents 15-19 years
• 1.3/100,000 cases in young women 20-24 years.
• Peak incidence of cervical cancer in US occurs in women with the lowest rates of HPV infection.
• First peak is in women aged 40-44 years (15.8/100,000).

Determining Screening Intervals

• Screening every 3 yrs. with cytology starting at age 21 confers similar number of life-years as annual screening.
• Prompts fewer than half number of colposcopies and fewer false positive test results.

ASC-US and LSIL Management

• Both are managed with repeat cytology at 12 month intervals for 2 years in adolescents.
• HPV +/-ASC-US and LSIL have similar clinical outcomes.
  – Significant change from “adult” women guidelines.
  – Based on natural history studies showing a high rate of resolution within 2-3 yrs. in adolescents.
  – HPV testing should not be done (reflex or follow-up).

2009 ACOG committee opinion, No 438, ASCCP 2013 Consensus Guidelines
Summary Guidelines for Young Women

- Biggest change in how to manage young women under 25
  - Women under 21 should not be screened
    - Risk of cancer low
  - Women age 21-24 should be screened only with Pap test
    - If minor abnormality (ASC-US or LSIL)
      - Follow with Cytology, NOT colposcopy → Fewer colposcopies in YW!
      - Repeat Pap test in 12 months
      - If abnormal → repeat Pap test in 12 months
      - If abnormal after 2 years → Colposcopy
    - If normal after 2 years → Routine screening → Pap in 3 years
    - If major abnormality (ASC-H, AGC, or HSIL) → Colposcopy
Atypical Squamous Cells of Undetermined Significance (ASC-US)

2001 Bethesda Terminology

Atypical squamous cells (ASC)

- ASC-US: Undetermined significance
- ASC-H: Cannot exclude HSIL

Cervical Cytology Screening-USA

Liquid-based (LBP) ~ 93%
Computer assisted ~ 33%

Typical Pyramid of Pap Test Interpretations

<table>
<thead>
<tr>
<th>Category</th>
<th>LBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASC-US</td>
<td>5.1%</td>
</tr>
<tr>
<td>LSI</td>
<td>2.7%</td>
</tr>
<tr>
<td>HSIL</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

CAP LAP Checklist 2014
ASC-US

- Cytologic changes suggestive of SIL but lacking specific criteria.
- Nuclear changes suggestive of but not diagnostic for SIL
- More than "reactive changes" but less than LSIL.
- 49% of ASCUS are hrHPV+ in ALTS
  - Rate of HPV+ depends on age and other factors!

ASC Interpretation

- Poorly reproducible even among expert cytologists
- 5-17% of women with ASC-US have CIN 2,3
- Risk of invasion is low (0.1 - 0.2%)


Atypical Squamous Cells

ASC-US

Atrophy

ASC-H

Endocervical cells
ASC-US

Nuclear enlargement and atypia + increase in chromatin = ASC-US

ASC-US category is reserved for cells in which a clear distinction between reactive and SIL cannot be made.

Apgar, Brotzman, Spitzer

CIN 2 + - what is the referral Pap?

HPV+ ASC-US 35%
HSIL 29%
ASC-H 5%
AGC 13%
LSIL 26%

Castle et al. Obstet Gynecol 2010;116:76-84

CIN 3 - What was the referral Pap?

HPV+ ASC-US 35%
HSIL 28%
ASC-H 13%
AGC 8%
LSIL 16%

Castle et al. Obstet Gynecol 2010;116:76-84
Risk of CIN 2,3 Among Women With HPV+/ASC-US and LSIL

- The cumulative risk of CIN 2,3 over 2 years
  - ASC-US/HPV+ 26.7%
  - LSIL 27.6%
- On initial colposcopy CIN 2,3 found in:
  - ASCUS/HPV+ 17.9%
  - LSIL 17.8%


Risk of CIN 3+ In Women with ASC-US and ASC-H

- ASC-US carries least risk of CIN 3+
- ASC-H confers substantially higher risk of CIN 3+ than ASC-US or LSIL but less than that of HSIL.

Management ASC-US

- Reflex HPV testing preferred approach
- ASC-US/HPV+ (reflex or co-testing) and LSIL are managed in the same fashion → colposcopic evaluation
- ASC-US/HPV-
  - New data indicates that risk of CIN3 is higher than a negative co-test (NILM/HPV-)
  - 2013 screening guidelines recommend 3-year repeat
Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US) on Cytology

- Repeat Cytology
  - ASC
  - HPV Positive: referred for office based colposcopy
  - HPV Negative: managed the same as women with low-grade squamous intraepithelial lesion (LSIL)
  - Colposcopy: endocervical sampling preferred in women with no lesions, and those with inadequate colposcopy; it is acceptable for others
  - Manage per ASCCP Guideline

Atypical Squamous Cells – Cannot Rule Out High Grade Lesion (ASC-H)

What is ASC-H?

- Should essentially be considered an "equivocal" HSIL
- Only a few "suspect" HSIL cells present on the slide.
- Do not have all the cytologic features of HSIL
- 5-10% of ASC cases
- Mean reporting rate: 0.43% of Paps (CAP survey 2004)
- Associated with a higher risk of CIN 2,3 lesions than ASC-US
What is risk with ASC-H?

- 2-5x greater risk of having CIN 2,3 than ASCUS
- The risk of missing CIN 2,3 is significantly higher

Management of Women with Atypical Squamous Cells: Cannot Exclude High-grade SIL (ASC-H)

- Colposcopy regardless of HPV status
- No CIN2,3
- CIN2,3
  - Manage per ASCCP Guideline
  - Manage per ASCCP Guideline
Low-grade Squamous Intraepithelial Lesion (LSIL)

What is LSIL?

- Morphologic manifestation of a generally transient viral infection
- Non-neoplastic manifestations of HPV infection
  - Raised condyloma acuminata
  - Flat acetowhite lesions
- Prevalence high among young sexually active women
  - 43% of HPV naive college women acquired HPV over 3 years

Ho et al. NEJM 1998;338:423)
Clinical Significance of LSIL

- Virtually all women with LSIL are infected with HPV but only some will develop a colposcopically visible lesion
- 118 women with LSIL followed for 53 months
  - 88.1% regressed to ASC-US or negative
  - 9.2% progressed to HSIL
- Young women more likely to have transient infections


Women with LSIL at Colposcopy

- 85% of women with LSIL will be found to have a biopsy-confirmed CIN at colposcopy
  - 14% have no lesion
  - 67% have CIN 1
  - 18% have CIN 2,3
  - 0.3% have invasive cervical cancer

Management of LSIL

- Managed same as ASC-US/HPV+
- Reflex HPV testing should not be done
- Co-testing provides an HPV result
- Colposcopy is recommended for LSIL and LSIL/HPV+
- Subsequent management is based on colposcopy and biopsy results
Guidelines’ Pearls

Updated Consensus Guidelines:
When to begin screening?

Women younger than 21 Years: No screening

3. ACOG Practice Bulletin #131, November 2012
4. NCCN Cervical Cancer Screening Guideline v. 2.2012.
www.NCCN.org

Updated Consensus Guidelines:
When to cease screening?

Women older than 65 Years: Screening should not be resumed for any reason, even if a woman reports having a new sexual partner.

3. ACOG Practice Bulletin #131, November 2012
4. NCCN Cervical Cancer Screening Guideline v. 2.2012.
www.NCCN.org
Cessation of Screening

- Adequate negative prior screening definition:
  - 3 consecutive negative cytology results
  - 2 consecutive negative co-tests within the 10 years before stopping screening
  - Most recent test within 5 years.

Updated Consensus Guidelines: Women with prior hysterectomy

Evidence of adequate negative prior screening is not required.
Screening should not be resumed for any reason, including if a woman reports having a new sexual partner.

3. ACOG Practice Bulletin #125, November 2012
www.NCCN.org

Cervical Cancer Mortality Rates after Hysterectomy

- Prevalence of hysterectomy greatest in white and black women aged 65 to 69 years
- Peak significantly higher in black women (58% vs 43% for white women)
- Corrected mortality rate for black women: 10.1 per 100,000 (5.7 per 100,000 without correction)
- Corrected mortality rate for white women: 4.7 per 100,000 (3.2 per 100,000 without correction)

**Without correction, the disparity in mortality between the races is underestimated by 44%**

- The oldest black women had the highest corrected mortality rate at 37.2 deaths per 100,000, a rate that rivals the rates of undeveloped countries
Updated Consensus Guidelines:
Women with prior HPV Vaccination

Recommended screening practices should not change on the basis of HPV vaccination

- Both liquid-based and conventional smears are acceptable
- Co-testing should NOT be performed for women under age 30
- Recommendations NOT intended for women with HIV, immunocompromised, or in utero DES exposure

Updated Consensus Guidelines:
Screening Frequency

- Age 30-65: Testing with cytology alone every 3 years or co-testing with cytology and testing for high-risk HPV types every 5 years.
- Co-testing “preferred” and cytology “acceptable” by all but USPSTF
- Recommendations NOT intended for women with HIV, immunocompromised, or in utero DES exposure
HPV Genotyping

- There is no role for testing for low risk HPV types
- Testing for HPV 16/18 was approved in March 2009 by the FDA
- Individuals with HPV 16 or 18 are at much higher risk of developing HSIL or cancer

Percent of Squamous and AdenoCa of Cervix Due to HPV 16 or 18


HPV Genotyping

Use of HPV Genotyping to Manage HPV HR Positive / Cytology Negative Women 30 Years and Older

Important Changes from Prior Management Guidelines

• Co-testing with cytology and HPV testing at 5-year intervals is the preferred strategy for women 30-64 years.
• Pap negative but lacking TZ can be managed without early repeat.
• Unsatisfactory Pap requires repeat even if HPV negative.
• HPV type 16 or type 18 triages to earlier colposcopy only after negative cytology.
• Colposcopy is indicated for HPV+/ASC-US, regardless of genotyping result.

Important Changes from Prior Management Guidelines

• For ASC-US cytology, immediate colposcopy is not an option. Management incorporates:
  • Cytology at 12 months (not 6 months and 12 months).
  • If negative, cytology every 3 years.
  • ASC-US/HPV- followed with co-testing at 3 years (rather than 5 years).
  • ASC-US/HPV- insufficient to allow exit from screening at age 65 years.
• More strategies incorporate co-testing to reduce follow-up visits.
  • Pap-only strategies are now limited to women younger than 30 years.
  • Co-testing is expanded even to women younger than 30 years in some circumstances.
  • Women aged 21-24 years are managed conservatively.

Summary of Recommendations and Evidence

<table>
<thead>
<tr>
<th>Population</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women 21 to 50 (Pap negative or 30-64 with HPV testing)</td>
<td>The USPSTF recommends screening for cervical cancer in women age 21 to 65 years with co-testing (Pap smear every 5 years) or, for women age 30 to 65 years who want to lengthen the screening interval, screening with a combination of cytology and human papillomavirus (HPV) testing every 5 years. See evidence report for discussion of cytology method, HPV testing, and screening intervals.</td>
</tr>
<tr>
<td>Women younger than 30 years, HPV testing</td>
<td>The USPSTF recommends against screening for cervical cancer with HPV testing, alone or in combination with cytology, in women younger than age 20 years.</td>
</tr>
<tr>
<td>Women younger than 21</td>
<td>The USPSTF recommends against screening for cervical cancer in women younger than age 21 years.</td>
</tr>
<tr>
<td>Women older than 65, who have had adequate prior screening</td>
<td>The USPSTF recommends against screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer. See the Clinical Considerations for discussion of adequacy of prior screening and risk factors.</td>
</tr>
<tr>
<td>Women who have had a hysterectomy</td>
<td>The USPSTF recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and who do not have a history of a high-grade precursor cervix or a second precursor lesion (CIN II) grade 2 or 3 or cervical cancer.</td>
</tr>
</tbody>
</table>
Conclusions

- Rely on the new paradigm of equal management for equal risk
- Trust that doing less is better for our patients
- Balance potential harms with potential benefits of reducing risk for cervical cancer

Conclusions

- Recognize that this is a dynamic field:
  - “New guidelines again?” “Why can they get it right the first time?”
  - Screening and management guidelines will continue to change
  - Introduction of more sensitive and specific testing modalities
  - Practice managements will need to adjust to future new developments
Conclusion

• The biggest gain in reducing cervical cancer incidence and mortality would be achieved by increasing screening rates among women who have not been screened or who have not been screened regularly. . .
  • ACS, 2002