How to Manage Cases with Unsatisfactory and Satisfactory but Limited Pap Test Results with and without HPV test

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Unsatisfactory Pap Test

- An unsatisfactory Pap test either shows scant cellularity or has more than 75% of cells obscured
- The absence of an EC/TZ component and partially obscuring factors (50%-75% of the cells obscured) are considered quality indicators but do not make a Pap test unsatisfactory

Birdsong GG, Davey DD, Darragh TM, Elgert PA,Henry M. Specimen adequacy. In: Solomon D, Nayar R, eds.The Bethesda System for Reporting Cervical Cytology.Springer-Verlag: New York; 2004:1Y20.

Unsatisfactory Cytology

- Cytology results are unsatisfactory for 1% or less across all preparation types
- Unsatisfactory cytology specimens are unreliable for detecting epithelial abnormalities
- Most studies that found a higher risk of disease among women with unsatisfactory cytology employed conventional Pap tests that can be rendered unsatisfactory by obscuring blood, inflammation

Unsatisfactory Cytology

- Now that most U.S. cytology is done using liquid-based media, which can control for most obscuring factors, unsatisfactory results arise largely from insufficient squamous cells

Unsatisfactory Cytology

- Currently available HPV tests lack a control for epithelial cellularity
  - the HPV test may be falsely negative because of an insufficient sample
  - a negative HPV test cannot be relied

Specimen Adequacy

- Cellularity was assessed semi-quantitatively by counting the number of squamous cells in 25 fields using ten-fold magnification, with a minimum of 25 clearly visualised and preserved squamous cells per field of view for an adequate conventional cytology

Specimen Adequacy

- For LBC, a minimum of ten fields of view with a 40 objective should contain a minimum of seven clearly visualised and preserved squamous cells to achieve a minimum of 5000 cells per slide.

Unsatisfactory Pap Tests

- Unsatisfactory Pap tests include those that are rejected by the laboratory (due to labeling problems, specimen vial leakage, slide breakage, etc.) and those that are completely processed but are unsatisfactory due to insufficient squamous cells or obscuring (>75%) blood, inflammation
- An unsatisfactory LBP specimens are related to insufficient squamous cells
- Several studies have found that women with unsatisfactory results may be at significant risk for disease

Hock YL, Ramaiah S,Wall ES, Harris AM, Marston L, Marshall J, et al. Outcome of women with inadequate cervical smears followed up for five years. J Clin Pathol 2003;56: 592Y5.

Ransdell JS, Davey DD, Zaleski S. Clinicopathologic correlation of the unsatisfactory Papanicolaou smear. Cancer (Cancer Cytopathol) 1997;81:139Y43.

Vaginal Specimens

- The numerical criteria for squamous cellularity on Pap tests were developed for women undergoing routine cervical cancer screening and do not apply to vaginal specimens.

What Is the Recommended Follow-up for Women With an Unsatisfactory Pap Test?

- Lower cellularity specimens may be acceptable in women who have undergone hysterectomy for malignancies, chemotherapy, or radiation therapy
  - higher cellularity may not be possible in these situations
- Clinicians and laboratories should exercise judgment in determining whether the specimen is unsatisfactory and whether early repeat cytology is indicated

What Is the Recommended Follow-up for Women With an Unsatisfactory Pap Test?

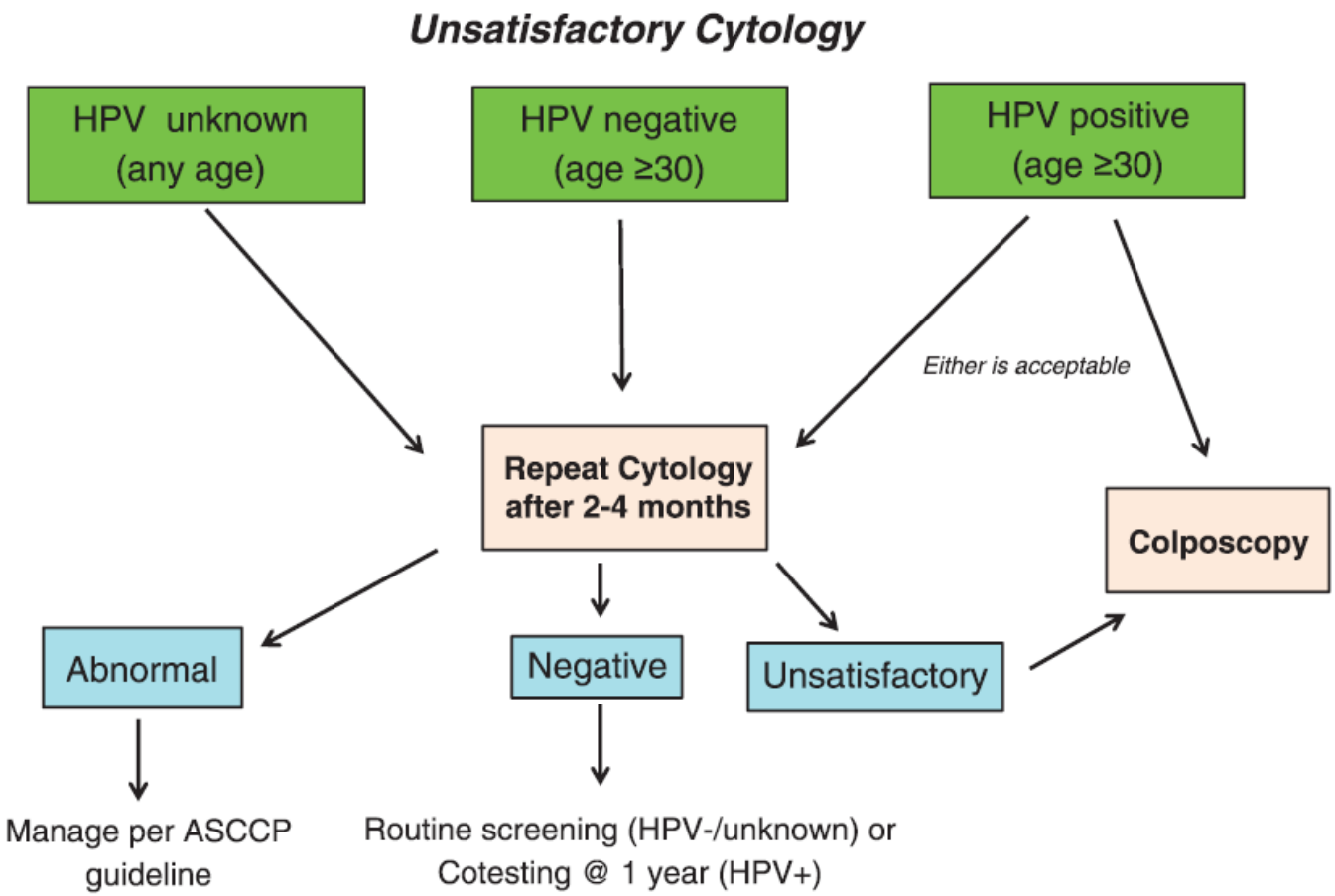
- The recommended management for most women undergoing cervical cancer screening who have an unsatisfactory Pap test result is a repeat Pap test, generally within a short time interval of 2 to 4 months (AII).

What Is the Recommended Follow-up for Women With an Unsatisfactory Pap Test?

- If the unsatisfactory result is due to obscuring inflammation and a specific infection is identified, consider specific treatment before repeating the Pap test.

What Is the Recommended Follow-up for Women With an Unsatisfactory Pap Test?

- Additional clinical evaluation is recommended in women with symptoms, abnormal examinations, and in cases where the Pap test is repeatedly unsatisfactory because of obscuring blood, inflammation, or necrosis (BIII).
- Examples are women with visible lesions, friable cervix, postcoital or abnormal bleeding, pelvic pain, and abnormal discharge; the additional evaluation may include colposcopy and/or biopsies, as appropriate.


Unsatisfactory Cytology
HPV unknown (any age)
HPV negative (age ≥30)
HPV positive (age ≥30)
Either is acceptable
Repeat Cytology after 2-4 months
Colposcopy
Abnormal
Negative
Unsatisfactory
Manage per ASCCP guideline
Routine screening (HPV-/unknown) or Cotesting @ 1 year (HPV+)

Cytology reported as negative but with absent or insufficient EC/TZ component

- Cytology reported as negative but with absent or insufficient EC/TZ component has adequate cellularity for interpretation but lacks endocervical or metaplastic cells, suggesting that the squamocolumnar junction may not have been adequately sampled.
- This raises concern for missed disease.

Cytology reported as negative but with absent or insufficient EC/TZ component

- Recently reported rates of cytology results reported as negative but with absent or insufficient EC/TZ component have ranged from 10% to 20% and are higher in older women

Huang A, Quinn M, Tan J. Outcome in women with no endocervical component on cervical cytology after treatment for high-grade cervical dysplasia. Aust N Z J Obstet Gynaec 2009;49:426-8.

Mitchell H, Hocking J, Saville M. Cervical cytology screening history of women diagnosed with adenocarcinoma in situ of the cervix. A case-control study. Acta Cytol 2004; 48:595-600

Cytology reported as negative but with absent or insufficient EC/TZ component

- Prior guidelines recommended early repeat cytology

Management of Women With Cytology Reported as Negative but With Absent or Insufficient EC/TZ Component

- A recent meta-analysis found that negative cytology had good specificity and negative predictive value despite absent or insufficient EC/TZ component

Elumir-Tanner L, Doraty M. Management of Papanicolaou test results that lack endocervical cells. CMAJ 2011;183:563-8.

EC/TZ Component, Quality Indicators, and HPV Testing The importance of the EC/TZ component in defining adequacy is controversial

- Longitudinal studies have not shown that women with Pap smears lacking an EC/TZ component are at increased risk for developing high grade squamous lesions and cancer.

Martin-Hirsch P, Lilford R, Jarvis G, Kitchener H. Efficacy of cervical-smear collection devices: a systematic review and meta-analysis. Lancet 1999;354:1763Y70.

Mitchell HS. Longitudinal analysis of histologic highgrade disease after negative cervical cytology according to endocervical status. Cancer (Cancer Cytopathol) 2001;93:237Y40.

Management of Women With Cytology Reported as Negative but With Absent or Insufficient EC/TZ Component

- HPV testing appears to be independent of transformation zone sampling and offers an added margin of safety for women aged 30-64 years
- An absent EC/TZ component is not associated with an increased incidence of cervical disease after treatment of CIN 2+

Zhao C, Austin RM. Human papillomavirus DNA detection in ThinPrep Pap test vials is independent of cytologic sampling of the transformation zone. Gynecol Oncol 2007; 107:231-5.

Huang A, Quinn M, Tan J. Outcome in women with no endocervical component on cervical cytology after treatment for high-grade cervical dysplasia. Aust NZ J Obstet Gynaecol 2009;49:426-8.

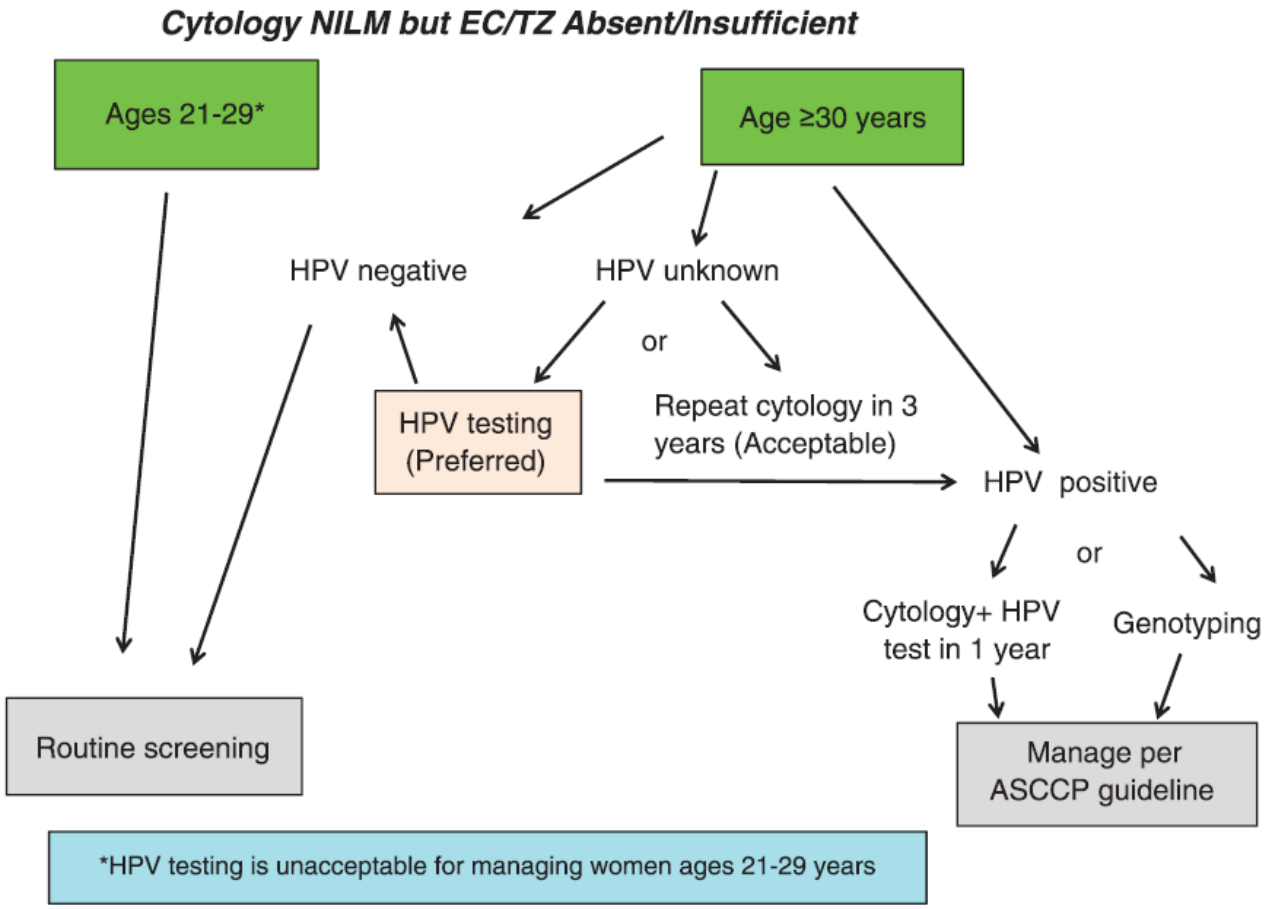
Management of Women With Cytology Reported as Negative but With Absent or Insufficient EC/TZ Component

- For women aged ≥30 years
  - cytology reported as negative and with absent or insufficient EC/TZ component
  - no or unknown HPV test result

HPV testing is preferred (BIII)

Management of Women With Cytology Reported as Negative but With Absent or Insufficient EC/TZ Component

- Repeat cytology in 3 years is acceptable if HPV testing is not performed (BIII).
- If the HPV test is done and is negative, return to routine screening is recommended (BIII).
- If the HPV test is positive, repeating both tests in 1 year is acceptable (BIII).Genotyping is also acceptable;
  - if HPV type 16 or type 18 is present, colposcopy is recommended (BII).
  - If HPV type 16 and type 18 are absent, repeat co-testing in 12 >months is recommended (BIII).


Cytology NILM but EC/TZ Absent/Insufficient
Ages 21-29*
Age ≥30 years
HPV negative
HPV unknown
or
HPV testing (Preferred)
Repeat cytology in 3 years (Acceptable)
HPV positive
or
Cytology+ HPV test in 1 year
Genotyping
Routine screening
Manage per ASCCP guideline
*HPV testing is unacceptable for managing women ages 21-29 years

CONCLUSION

- Cervical cancer prevention is a process with benefits and harms
- Risk cannot be reduced to zero with currently available strategies
- Attempts to achieve zero risk may result in unbalanced harms, including overtreatment

Thank you