

# Clinical Question: Ask the Experts

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## HOW SHOULD THE FIRST ABNORMAL PAP SMEAR IN AN 83-YEAR-OLD WOMAN BE MANAGED?

An 83 year-old woman, who has had regular, lifelong Pap smear screening, has her first abnormal Pap smear. The Pap smear is interpreted as low-grade squamous intraepithelial lesion (LGSIL), and she is referred for colposcopic examination.

Colposcopic examination by an expert colposcopist, including the application of the acetic acid, shows no lesion on the cervix, vagina, or vulva. The colposcopy is satisfactory; the squamocolumnar junction could not be visualized. HPV typing is performed and shows "positive for high-risk HPV type."

What would be your recommendations for further evaluation, treatment, and follow-up?

### Response 1

This is a very interesting case of a postmenopausal patient who develops a first abnormal Pap smear. Certainly, in the older population, the risk of cervical cancer is not insignificant. In general, this is related to the lack of screening in this age group.

The case presented here is a patient who has had regular lifelong Pap smear screening. I do not know the interval between her last Pap smear. This is her first abnormality and is reported as a low-grade lesion. I assume that the colposcopy is unsatisfactory as the squamocolumnar junction could not be visualized. This would not be unusual in this age group. At this point, with a Pap smear showing dysplasia and unsatisfactory colposcopy, an excisional biopsy is probably necessary.

While the clinical utility of HPV typing in this setting has not been definitively proven, I believe that this may be a case where HPV typing would be most appropriate. In a patient with a long history of normal Pap smears suddenly to have any abnormal Pap smear, is quite unusual. In the absence of the presence of HPV, I would be less likely to perform any excisional biopsy and proba-

bly would do close follow-up after performing an endocervical curettage. However, with positive HPV typing, this patient is probably at risk for preinvasive disease high in the canal.

Therefore, given this clinical case scenario, I would perform a loop excision procedure and continue appropriate follow-up from that point.

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### Response 2

The scenario doesn't say whether or not endocervical sampling was done. I assume it was. If not, a cytobrush evaluation/ECC would be appropriate. I favor the former. Because the Pap smear is LGSIL, in spite of the "high-risk HPV type," I would repeat the Pap smear in 6 months and every 6 months thereafter if the abnormality persisted. If the results were the same, I would have her partner, if appropriate, checked for HPV, too. I wouldn't be too concerned about the inability to see the SCJ unless the Pap smear worsened or persisted for some time. Obviously, if the Pap smear showed HGSIL, LEEP or cone would be appropriate.

This case also points up the necessity to continue Pap smears well into a woman's life.

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### Response 3

The first question to ask is: Why was a Pap smear performed?

In the past several years many agencies and experts have recommended that once a woman has reached the age of 65 and has had repeatedly normal Pap smears, there is no need to continue to perform them. Indeed, Medicare will presently only pay for one Pap smear every *three years* unless there is a specific indication for its

performance. Most people agree that after the age of 65 a Pap smear every 3 to 5 years is rational and sufficient.

What is the significance of a LGSIL Pap?

It is generally agreed that a Pap smear interpreted as low-grade is associated with a high-grade lesion about 18-20% of the time and with low-grade lesions about 50% of the time. This suggests that there will be no apparent lesion noted in 30% of patients with LGSIL cytology. This appears to be the case in this patient. It is stated that her colposcopic examination is satisfactory and that the squamocolumnar junction could not be visualized. These are contradictory statements since the requirement for a satisfactory colposcopy requires visualization of the entire cervical transformation zone, which means all of the T-zone from its outermost original squamocolumnar junction to the innermost border—the new squamocolumnar junction. It is not surprising that the colposcopic examination would not be satisfactory in an 83-year-old woman. One would anticipate a decrease in the size and bulk of the cervix in the late postmenopausal age group with an accompanying recession or inversion of the T-zone into the endocervical canal and, therefore, out of the field of vision. Hence, the colposcopy is unsatisfactory and our decision-making must take this into account. Should we, therefore, do a conization for this woman? I do not believe that it is needed with LGSIL cytology.

Why was HPV typing done? Does it have a prognostic significance?

It is accepted that HPV DNA testing may be an appropriate triage tool for a Pap smear that has been interpreted as ASCUS. The early reports from the ALTS trial, as well as other sources, indicate that the rate of HPV DNA high-risk and intermediate-risk positivity is about 85% and lends little triage assistance to patients with LGSIL cytology. Since there is the relatively high positive predictive value for high-grade lesions, immediate colposcopy is indicated as was properly done in this instance.

Do we have any information on this 83-year-old woman's recent sexual history? Is she still active? How long has it been since her last sexual activity? Will this information have an effect on her care? The information may help in providing a better understanding of the clinical situation but will probably not affect our behavior in diagnostic decision-making.

Knowing that an HPV DNA was done and shows "positive for high-risk HPV type": 1) is not surprising! (as noted above, this result is expected 85% of the time); and, 2) carries questionable prognostic value in the clinical setting. There are several reports in the literature, sev-

eral from European investigators, that indicate that high-grade intraepithelial neoplasia and cancer require the presence of persistent HR HPV infection with high copy numbers of the virus. Does this suggest that we should carry out aggressive diagnostic evaluation in this older woman with LGSIL and positive HR HPV? There is currently no evidence to support this approach. Should we continue to keep this woman under close scrutiny for the possible development of a progressive lesion? I believe that this is the only rational management to offer. Repeat cytology at 6-month intervals with the sample taken after 2 to 3 weeks of topical estrogen cream and subsequent repeat colposcopic evaluation dependent on the cytologic changes seems to be the correct management.

Overall, this is an uncommon occurrence but does test our clinical skills.

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#### Response 4

In my opinion, this patient should receive colposcopy again, with special attention to the transformation zone that was not adequately visualized. Her situation is too unusual and possibly too risky to ignore.

This patient presents with an HPV test indicating at least one of the 13 high-risk types of HPV known to be associated with cervical cancer. Diagnoses of HPV infections are uncommon among older women in the United States [1, 2]. She has a cytologic diagnosis of low-grade squamous intraepithelial lesion (LGSIL), which represents the semi-acute cytologic evidence of HPV infection. Approximately one-fifth of women with detectable HPV DNA are commonly diagnosed with LGSIL, but repeated cytologic and molecular signs of the same infectious process. HPV infections, with or without LGSIL, occur in only a few percent of older women in the United States. Because HPV infections are sexually transmitted, the risk is strongly related to higher numbers of recent sexual partners, typically a correlate of youth. Once detected, infections (even with one of the 13 high-risk types) typically become undetectable within 1 to 2 years [3, 4]. Rates of viral persistence tend to increase somewhat with age, but the detection of HPV and its cytologic signs still decline with age, as women have fewer new partners and most infections are cleared.

In short, this older patient presents with a clinical picture typical of young women. The explanation is not ob-

vious. She may have had a new sexual partner. She may be immunosuppressed, related perhaps to organ transplant, HIV infection, or unknown causes. Immunosuppression leads to apparently re-emergent HPV infection and SIL among women without obvious sources of new transmission [5]. HPV latency and re-emergence are poorly understood, and may account for a fraction of cervical cancers cases among older women. Of note, in some other countries, older women appear to have more HPV infections than the same age group in the United States [6, 7]. No one knows why regional variation exists in age-specific prevalences, although male sexual behavior may be involved.

Although the viral, cytologic, and colposcopic diagnoses made in this case might all be correct, a more likely possibility is that at least one is wrong. The FDA-approved Hybrid Capture 2 DNA assay is highly reproducible in competent laboratories [8], but local variations of PCR-based HPV tests are prone to false positives. The cytologic diagnosis of LGSIL is more reproducible than the histologic diagnosis of CIN1, but still can be overcalled [9]. Finding both HPV DNA and LSIL cytology suggests that both are correct, however. The suspicion falls on the normal colposcopy.

Colposcopy is not highly reproducible [10] and visual methods can be insensitive among older women [11]. In particular, in this patient the transformation zone was not seen, which implies that the colposcopic examination might not have been adequate.

The risk of a high-grade intraepithelial lesion (CIN2/3) in women with detectable high-risk HPV types followed for 5 to 10 years exceeds 20% [12, 13]. Few cases are seen in elderly women, as the median age of CIN2/3 or even cancer is high enough to motivate a re-examination of the cervix focused on better sampling of the transformation zone to rule out high-grade disease.

We should have a better understanding of this kind of case in a few years, because several cohort studies are following older women in order to understand the natural history of HPV infections in this important group.

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