Cervical Cytology Screening and Evaluation

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For nearly 50 years, the gynecologist's mantra has been "Yearly Pap and Pelvic."[1] Yet, it remains unclear how the practice of annual cytology became a *de facto* standard in the United States, because there never has been an organized, national screening program. I suspect that the test became an annual ritual for many women as a result of the widespread use of oral contraceptives in the 1960s and 1970s and the need for an annual examination to obtain prescription refills. However, now there is evidence that, for some women, annual cervical cytology screening is both not necessary and may even lead to unnecessary morbidity.[2]

Although the conventional Pap test is the best cancer-screening tool ever developed–it has reduced the incidence of invasive cancer of the cervix by approximately 70%–multiple publications have documented the fact that the test is insensitive and somewhat nonspecific. The reason that it is so effective in reducing cancer is a result of the natural history of the disease, rather than the ability of a single cytology sample to detect abnormalities. In addition, there are good data to support the fact that we have been far too aggressive in our management of women with minimal disease (ie, cervical intraepithelial neoplasia grade 1 [CIN 1]).

Several national organizations, including the American College of Obstetricians and Gynecologists, the American Cancer Society, the American Society of Colposcopy and Cervical Pathology (ASCCP), and the U.S. Preventive Services Task Force, have reviewed the extensive literature that has been published about Pap tests and early lesions and have developed new guidelines for the use of Pap test screening, the evaluation of abnormal results, and management of low-grade cervical neoplasia.[3–5]

In this article, I will explain how I have incorporated some of the new guidelines into my practice, how the use of the human papillomavirus DNA (HPV-DNA) test can help us manage patients, and how I approach minimally abnormal cytology and biopsy (CIN1).

CYTOLOGY SCREENING

Because the literature (and the Food and Drug Administration) supports the concept that liquid-based cervical cytology screening can identify a few more cases of high-grade intraepithelial lesions (HSIL) than conventional testing, the majority of practices have changed to the liquid-based cervical cytology technique. In a woman who is being tested every year, there is no evidence that there is any clinical benefit, though. Probably the biggest advantage of liquid-based cervical cytology is that the same sample can be used for HPV-DNA testing, and some sexually transmitted disease testing.

Our laboratory moved to the liquid-based technique a few years ago, so I use it. However, I would have had no problem continuing to use the conventional technique for those women who are being screened yearly. It is a poor idea, though, to try to use different techniques for different women, because there is an increased risk that mistakes in labeling and collection will occur. My advice is to use 1 technique and to stick with it. In most offices that test will be liquid-based cervical cytology.

Between 1980 and 2003, all of the national organizations that took a position on cytology screening agreed that Pap testing should begin at age 18 years or at the onset of sexual activity. These same groups have now changed that guideline and recommend starting either at age 21 years or within 3 years of the onset of sexual activity.

The reason behind the change is that most women (and men, of course) become infected with

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HPV when they become sexually active.[6] If a Pap test happens to be taken while the infection is in its active phase, the report will indicate that changes consistent with a low-grade squamous intraepithelial lesion (LSIL) are present, and if a biopsy is taken, it will be interpreted as "mild dysplasia" or "CIN 1." Because more than 70% of these infections clear spontaneously, it is better NOT to know about these infections: the patient will not worry, and the clinician will not feel obliged to perform colposcopy, biopsy, and treatment.[7,8] Indeed, 1 of the strongest reasons for this change was the hope that far fewer young women would be treated for what is almost always a transient infection.[8]

Although I understand the motivation behind this change, I believe that the more proper approach would have been to educate physicians not to react to a minimally abnormal Pap test report. Even though there is no particular reason to perform a Pap test on a newly sexually active woman, the same woman does need contraceptive counseling and sexually transmitted disease counseling and testing. She needs to be encouraged to see someone who will address these issues, and that person is often her gynecologist.

The guideline is also often misinterpreted to mean that Pap tests should not be performed until a woman is aged 21 years. That is not true. Rather, the first test should be performed *within 3 years* of the onset of sexual activity. Thus, the female who begins coitus at age 15 should be regularly screened while still a teenager.

In the 1980s many guidelines also recommended that yearly Pap testing was not necessary after several normal tests if the woman was at "low risk" for cervical cancer. That recommendation never caught on. Most of us continued to perform Pap testing annually.[1] Perhaps the biggest reason we did so was that we could never identify, with any certainty, a "low-risk" population. The definition of "low risk" was a woman who began intercourse after age 18 (or 21), had only 1 lifetime sexual partner, and that partner never had another partner. Only a small number of women–fewer than 20%–fit this definition.[9] In short, the recommendation to screen based on sexual history did not work and has now been discarded.

There are only 3 factors that have been shown to be associated with cervical neoplasia that we can easily use in our offices.[3] Women with a prior history of HSIL are at increased risk. So are women who are immunosuppressed for any reason. Renal transplantation is one of the biggest contributors to this category (Fig. 1). Finally, women who were exposed to diethylstilbestrol before birth remain at higher risk of developing adenocarcinoma of the vagina at any age,

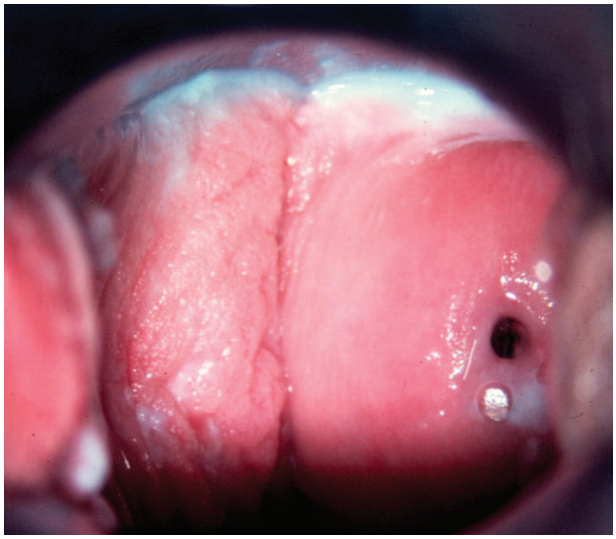

Fig. 1. Colpophotograph showing persistent human papillomavirus infection in a 31-year-old woman who had undergone renal transplantation.

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and cytology may identify early lesions, even though most are identified by palpation rather than by cytology. The new guidelines suggest that these 3 groups of women continue to have annual cytology screening.

Women who are human immunodeficiency virus positive deserve special attention. With the advent of more and better therapies, the life spans of compliant women are now close to the general population. For these women, however, annual screening is still recommended. Abnormal cytology of any degree is best evaluated by colposcopy.

Perhaps the best way to determine who needs a Pap test is to remember why we perform the test. Our goal is to identify women who have true cervical cancer precursor lesions (CIN 3, and to a lesser degree CIN 2). The most common age for these lesions to be identified is in the 20s. Therefore, we should focus our most active screening on those years. Almost all agencies now suggest annual screening to age 30. By that time most transient HPV infections have cleared, and those who are still cytology positive have a greater likelihood of harboring a true cancer precursor.[10,11]

All preinvasive neoplasia of the cervix may regress. Although many different numbers can be found in the literature, approximately 70+% of CIN 1, 50% of CIN 2, and 30% of CIN 3 (including those lesions called carcinoma in situ) disappear without treatment.[12] Nonetheless,, treatment of HSIL is recommended for most women. Therefore, it seems reasonable to test women for the first time within 3 years of coitarche and to test yearly until age 30 years. If HSIL

has not occurred by that time, it is unlikely that the woman is at risk for significant cervical neoplasia and can be tested less often.

After age 30 I believe that it makes sense to test only every 3 years. Many authorities have concluded that every 3-year testing in that age group is just as effective as annual screening and leads to fewer false-positive results, less anxiety, and less cost. I also add HPV-DNA testing to the screen (see below), and if both the cytology and the high-risk panel are negative, strongly discourage further Pap testing for at least 3 years. The data are quite clear that a woman who is 30 years of age and has a simultaneous negative cytology and high-risk HPV-DNA test is at lower risk of HSIL in the next 3 to 5 years than the woman who has 3 consecutive negative Pap tests alone.[3,13–15] A few women are not comfortable with less frequent testing, and for them I continue yearly screening, but annually raise the concept of stretching out the interval. Also, if yearly testing is continued, I do not add the HPV-DNA test.

The new guidelines also address the issue of "When to stop" cytology screening. When cervical neoplasia progresses, it does so very slowly. Few lesions progress to cancer, and several decades follow the earliest changes. From a practical standpoint, if a woman has been screened regularly and has not had HSIL by the time she reaches age 70, it is unlikely that she can live long enough to develop the disease.[16] On the other hand, she does need counseling and blood pressure testing on an annual basis.[17–29] If the Pap test is the only reason she sees her health care physician, it seems reasonable to continue to test.

For 1 group of women, all of the current guidelines strongly discourage cytology screening: women who have had a hysterectomy for nonneoplastic disease. The data show that most abnormal Pap tests in these women are falsely positive, and lead to unnecessary evaluation and treatment (Fig. 2).[21]

For years I performed annual vaginal cytology after a hysterectomy for benign disease. Quite a number of these tests were positive, especially when the vaginal epithelium became atrophic. I've performed hundreds of colposcopic examinations and biopsies in these women. Most of the biopsies were reported as vaginal intraepithelial lesions grade 1 (VAIN 1) with only a very rare VAIN 2 or 3. I've agonized many times over the best way to treat these patients, because none of our modalities are very good.

Now, I no longer perform Pap testing on any of these women unless they have a history of HSIL before their hysterectomy or are immunocompromised. Why did I change? First, I finally consciously recognized a fact that I had known for years: Vaginal cancer is exceedingly rare. Most of us think of carcinoma of the fallopian tube as a rare cancer; vaginal cancer is even less common, and occurs almost always in women with a history of HSIL of the cervix. Second, it has become clear that when the vaginal epithelium loses estrogenic stimulation, a biopsy will almost always be difficult for a pathologist to interpret, and often the report will be VAIN 1. Third, I cannot remember a single case of VAIN 3 in a woman without a history of HSIL. When I finally "put it all together," it became clear that all I had accomplished by doing Pap testing in these women was to cause needless anxiety, discomfort, and the morbidity associated with treatment. I now limit Pap testing after a hysterectomy for benign reasons to those women who previously had HSIL. If the report is VAIN 3 I still suggest treatment, but I strongly suspect that few of them would ever develop vaginal cancer.

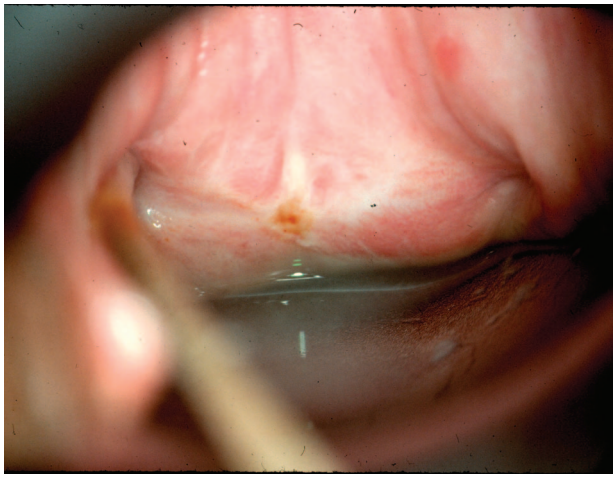

Fig. 2. Colpophotograph of the vaginal vault of a 76-year-old woman who had a Pap test reported as "Low-grade changes consistent with vaginal intraepithelial lesions grade 1." Despite negative examination findings both before and after treatment with estrogen cream, she remained very fearful of vaginal cancer.

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HPV-DNA TESTING

It has been known for some time that infection with certain types of the HPV is nearly always a requirement for the development of invasive cancer of the cervix. Unfortunately, these types have been labeled "high risk." That term scares physicians and patients alike. The truth is that the type of HPV most highly associated with cervical cancer, type 16, is both the most common (prevalent) HPV in the United States and that in the vast majority of infections it disappears spontaneously and never causes significant disease. Women with evidence of a persistent "high risk"

infection (present for more than 2 years) need to be followed up closely, because they represent the group that may develop a CIN 2 or CIN 3 lesion.[8]

In 2003 the Food and Drug Administration reported that it had determined that the "high risk" panel of the HPV-DNA test, Hybrid Capture 2, was safe and effective for cervical neoplasia screening, but added strict conditions to its use.[22–24] The test is approved only for women aged older than 30 years, only every third year, and only with a simultaneously collected Pap test, not alone. This was the second indication for the use of the test, because it had already been found to be of use in the triage of women with atypical squamous cells of undetermined significance (ASC-US) cytology reports.

EVALUATION AND MANAGEMENT OF WOMEN WITH MINIMALLY ABNORMAL PAP TESTS

The Bethesda System for the reporting of cervical cytology was necessary because many laboratories had developed their own wording for abnormal reports. Although many of us initially struggled with the new terminology, the fact that almost every laboratory in the nation now uses the same words makes referral much easier. Initially there was confusion about the meaning of the new terms, and many of us relied on "expert" opinion for patient management.[25]

INITIAL EVALUATION OF ABNORMAL CERVICAL CYTOLOGY REPORTS

Squamous Abnormalities

ASC-US →	Three equally acceptable choices: HR HPV-DNA testing (preferred) Repeat cytology in 6 months Colposcopy
ASC-H →	Colposcopy
LSIL →	Colposcopy
HSIL →	Colposcopy
Cancer →	Colposcopy

*Glandular Abnormalities**

AGC-(any modifier) →	Colposcopy
AIS →	Colposcopy
AC →	Colposcopy

ASC-US, atypical squamous cells of undetermined significance; HR HPV DNA, high-risk type of human papillomavirus DNA; ASC-H, atypical squamous cells, cannot rule out a high-grade lesion; LSIL, low-grade intraepithelial lesion; HSIL, high-grade intraepithelial lesion; AGC-US, atypical glandular cells of undetermined significance; AIS, adenocarcinoma in situ; AC, adenocarcinoma.

* Additional tests may be needed based on patient age and history.

A sufficient amount of time has now passed so that we have "pretty good" data about the meaning of the Bethesda System results. When that is coupled with what we have learned about HPV in the last decade, it is possible to design a clinically useful plan for the evaluation of every abnormal report.

ASCCP convened a consensus conference in conjunction with the American College of Obstetricians and Gynecologists, the National Cancer Institute, and others and has published the results.[26] The answer to most questions about the best plan for the evaluation of an abnormal cytology report can be found in the article. Unfortunately, it was written by a committee and is very long. I will try to hit the high points, but if your specific patient does not fit into one of the categories, you should consult the original article.

The good news is that it is relatively easy to know what to do with most abnormal results. A summary of the most appropriate action for any report that is other than normal is presented in the box. It turns out that the only result for which a decision about the first step in evaluation needs to be made is for ASC-US reports. Because this is the most common abnormal result, it is important to have a plan for these cases.

The literature has documented that some ASC-US reports are associated with HSIL.[27] Therefore, some type of follow-up is needed. Fortunately, the National Cancer Institute funded a randomized clinical trial with the purpose of determining the best way to handle these cases. It turns out that any of the 3 options shown in the box is effective.[28–29] Testing for high-risk types of HPV with HPV-DNA testing was the best by a slight margin. I believe that high-risk HPV-DNA testing is the best choice because it can be accomplished with the most ease for both the patient and the physician. The secret is to use a liquid-based technique and to ask your laboratory to perform high-risk HPV-DNA testing automatically for any ASC-US report. This so-called "reflex testing" saves the patient the time, effort and discomfort of an additional examination, and the clinician the need to arrange follow-up for all ASC-US reports. It is important to be certain that your laboratory uses only the high-risk probe set. The low-risk panel has no clinical usefulness and only adds needless expense. Consider changing laboratories if yours insists on using the low-risk probe.

Because the most common HPV type in the United States is HPV 16, up to 60% of women who have reflex testing will be high-risk positive and will need colposcopy. However, the other 40% require no further testing for 1 year. That is, they should not be rescreened for 12 months.

I see quite a large number of young women in my

referral practice who have had abnormal cytology reports and received treatment. Typically, they became sexually active and saw a physician for effective contraception. At the time of their visit they had a Pap test taken, and it was reported as either LSIL or ASC-US. By the time I see these patients they have had colposcopy, biopsy, and some form of treatment for LSIL, but remain cytology positive. On examination, many have some degree of cervical stenosis, and occasionally it is severe. There is virtually never any sign of HSIL, and I routinely recommend cytology follow-up only. I worry how many of these women will have difficulty achieving pregnancy. For these women who had a physician who overreacted to a minimally abnormal Pap test report, it would have been much better not to have had the test in the first place.

One of the interesting facts in the history of cytology screening is that cytologists acquired the ability to identify women with a few minimally abnormal cells long before we knew what such cells meant. Since Pap testing was a cancer prevention strategy, clinicians began to treat more and more women for less and less serious disease.[30]

We now have a much better understanding of the natural history of cervical neoplasia. The most important fact is that what is called "mild dysplasia" or "CIN 1" is virtually always a transient infection with the human papillomavirus (HPV), and not a cancer precursor.[31] While a tiny minority of CIN 1 lesions can progress, the light microscope cannot predict which lesions will disappear and which will not.

The good news is that it is not very important to know which lesions will go away and which ones will persist. The important thing to realize is that there are many years between CIN 1 and cancer, and that nothing is lost by waiting, as long as the patient is treated if the lesion becomes CIN 2 or 3. In teenagers, it might not be a good idea to treat CIN 2. Often I will follow up these patients, but they are most commonly treated. The ASCCP Consensus Conference agreed that follow-up without treatment could be appropriate if the patient is likely to be compliant.

All treatments for CIN 2 and 3 should be office-based. Loop electroexcision and cryotherapy can be performed with ease in the office. The use of general anesthesia only adds morbidity and expense. The only exception is the patient who has a major anxiety disorder.

Cervical intraepithelial neoplasia grade 1 infections almost always disappear within 24 months, although they can still resolve many months later.[7] I believe that CIN 1 lesions should NOT be treated unless they persist for more than 2 years. Even then, I am reluctant to treat in women aged younger than 30 years, because I know that every form of treatment can (although usually does not) lead to cervical stenosis and incompetence.

Figure 3 is a colpophotograph of a woman who had an LSIL cytology report. At the time of colposcopy the acetowhite lesion shown in the figure was seen. Although the appearance is not worrisome, there are minor mosaic changes in the transformation zone on the anterior lip of the cervix. A biopsy specimen was taken from the area of mosaic and was reported as "Mild dysplasia/CIN 1, with features of HPV infection." She represents the ideal candidate for follow-up without treatment: Her Pap test and biopsy agree, the lesion shows no features of high-grade disease, and the examination was satisfactory. She has repeat cytology at 6-month intervals. The third and all subsequent samples were negative.

Figure 4 shows a colpophotograph of a 19-year-old woman who had loop electroexcision for treatment of LSIL. After treatment her cytology specimen continued to be reported as LSIL, and she was advised to have a second procedure. At the time of her second menstrual cycle after the procedure she experienced severe cramping. At the time I saw her she had complete stenosis of the cervical canal, as shown in the figure. After several treatment attempts a patent canal was maintained.

I'm often told, "In my clinic I cannot assume that the patient will return." That's a true statement for every patient we ever see, no matter how poor or rich, or how often we have seen her previously. Of course, there are some groups that tend to have poorer

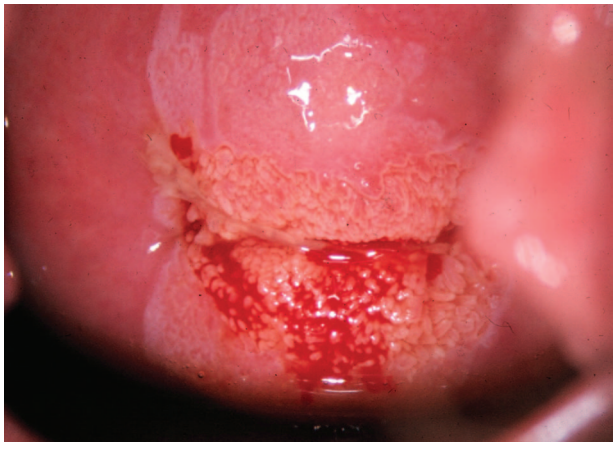

Fig. 3. Colpophotograph showing a faint acetowhite lesion with minimal mosaic changes. Cytology and biopsy were reported as low-grade squamous intraepithelial lesion/cervical intraepithelial neoplasia grade 1. The examination was satisfactory and she was followed up without treatment.

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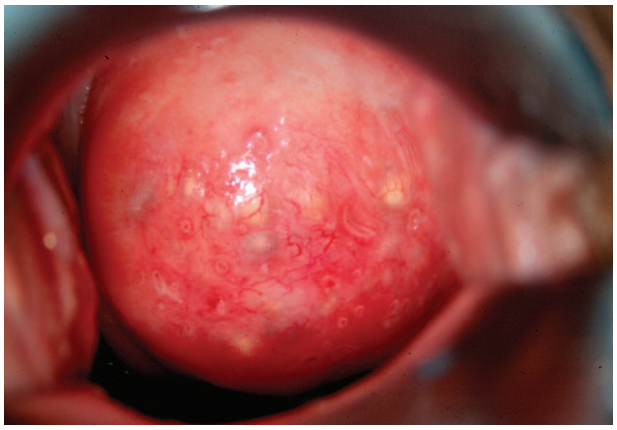

Fig. 4. Colpophotograph showing complete cervical stenosis after two loop electroexcision treatments for cervical intraepithelial neoplasia grade 1.

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records of follow-up than others. However, because it takes years for squamous cancer of the cervix to develop, it is not critical if the patient fails to appear, for example, in 6 months for another Pap test. The treatment of these early lesions is probably associated with more morbidity than follow-up failure.

The other excuse for treating CIN 1 that I hear is, "My patients won't accept follow-up. They want to be treated." Over the past twenty years I have followed up many hundreds of women with CIN 1. Perhaps there have been 3 women who demanded treatment. The others all were happy to hear that, "You have a viral infection of the cervix that is very common. Come back in six months for a repeat Pap test." I'm convinced that patients know within a microsecond whether we believe our recommendations or not. If a physician suggests following up CIN 1 without treatment, but is not convinced that it is the best way to handle the problem, the patient will recognize the lack of conviction. I'm certain that my success with follow-up without treatment is due to my personal conviction that it is the best management strategy.

The only exception to a relaxed approach to the management of minimally atypical cytology reports is if a glandular lesion is suspected. A report of "atypical glandular cells of undetermined significance" (AGC) is of much more importance than ASC-US. I once gave a talk entitled "AGUS Scares Me." It still does. While about one half of all women with such a report have no significant disease, and about another 30% or so have a squamous lesion, a significant fraction will have invasive cancer, 3% to 10%![32] All of these women deserve special attention, but it is possible to develop a plan based on what the clinician knows about the patient. Indeed, it is only the clinician who is in a position to be able to develop the best plan of action.

Atypical glandular cells reports often occur in conjunction with an HPV infection at an early age or during pregnancy. If the patient is either pregnant or aged younger than 35 years, I usually perform colposcopy to rule out an HSIL lesion and follow up with repeat cytology in 4 months. However, if the woman is aged older than 35 years, is not pregnant, and colposcopy shows nothing, an endometrial biopsy and conization is mandatory. Most pathologists prefer that the cone be performed by scalpel. If all of the tissue is negative I try to plan further steps based on the patient's history, age, and risk factors. For example, if she has chronic anovulation and/or is obese, a repeat endometrial biopsy, or even a dilation and curettage, is probably indicated. Because cancers of the uterus, tube, and ovary can all be the source of an AGC report, pelvic ultrasound might be indicated if the workup is completely negative. Even cancers of the stomach, colon, pancreas, and gall bladder have been the source of AGC on rare occasions.

Often when AGC are seen, the cytologist can determine the source of the cells. If the report indicates that the cells look like endometrial or ovarian cells, the work-up should be directed to that site.

SUMMARY

Cervical cytology screening is the best cancer-screening tool ever developed. In all countries where it has been widely used, the incidence of cervical cancer has been decreased by about 70%. In the past 2 decades there has been great progress in our understanding of the natural history of cervical neoplasia. We should now adopt changes in our practices of cytology screening and the evaluation of abnormal reports based on that new knowledge.

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