FOCUS ON CERVICAL DISEASE

Bethesda 2001: A more usable system

Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda system. Terminology for reporting results of cervical cytology. *JAMA*. 2002;287:2114-2119.

OBJECTIVE The Bethesda 2001 Workshop updated the 1991 Bethesda System terminology for reporting results of cervical cytology. This effort represents a focus on broad participation utilizing an Internet bulletin board to collect data prior to the workshop.

METHOD AND RESULTS Eight months before the workshop convened, 9 forum groups of 6 to 10 persons developed recommendations for discussion. These recommendations were posted on the Internet to encourage discussion and commentary. More than 400 cytopathologists, gynecologists, epidemiologists, family physicians, attorneys, and patient advocates from 44 professional societies and 20 countries participated in the workshop.

After more than 1,000 comments were submitted via the bulletin board, the workshop convened in Bethesda, Maryland, from April 30 to May 2, 2001. The most clinically relevant changes to the Bethesda System are listed below.

- **Specimen adequacy.**
  - eliminates "satisfactory but limited by" (absence of endocervical cells is not considered unsatisfactory)
- **General categorization.**
  - "within normal limits" was changed to "negative for intraepithelial lesion"
- **Interpretation/result.**
  - "diagnosis" was replaced by "interpretation" or "result"
- **Epithelial cell abnormalities.**
  - ASCUS was replaced by ASC-US or ASC-H (cannot exclude HSIL)
  - 2-tiered LSIL and HSIL classifications remain
  - AGUS classification was significantly revised and changed to AGC, endocervical endometrial, or glandular cells NOS (not otherwise specified)
  - endometrial cells will be noted if present in women over the age of 40 rather than only postmenopausal patients

WHO MAY BE AFFECTED? Physicians managing patients with cytologic abnormalities.

EXPERT COMMENTARY The wide range of participants lends significance to this extraordinary effort to correct and simplify the Bethesda System recommendations. First, a 6-month Internet survey generated many recommendations. This was followed by the actual workshop, which provided another opportunity to finalize the system. The process was deemed so successful that the American Society for Colposcopy and Cervical Pathology and the American College of Obstetricians and Gynecologists used a similar process when the workshop for the management of cytologic abnormalities was held later in 2001.

Overall, this is a kinder and gentler system. Elimination of "satisfactory but limited by" was a major improvement. Narrowing the ASCUS classification to ASC-US and

CONTINUED

ASC-H makes it possible to use multiple triage methods such as immediate colposcopy, HPV testing, or repeating the smear unless the report is ASC-H, which requires immediate evaluation.

BOTTOM LINE Physicians who manage patients with cytologic abnormalities will be better served by the Bethesda 2001 System.

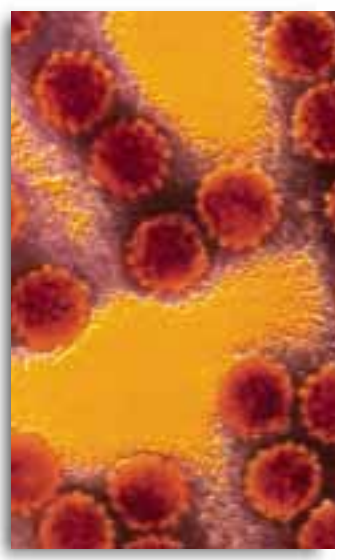
MELVIN V. GERBIE, MD
CHIEF, GYNECOLOGY
NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

Is HPV DNA testing a reliable alternative to the Pap test?

Kulasingam SL, Hughes JP, Kiviat NB. Evaluation of human papillomavirus testing in primary screening for cervical abnormalities. *JAMA*. 2002;288:1749-1757.

CONTEXT Screening women with limited access to health care is difficult—in both the United States and the third world. We now know that invasive cervical carcinoma is universally associated with persistent human *Papillomavirus* (HPV) infection, and that only a small subset of viral types place women at high risk for developing cervical intraepithelial neoplasia (CIN) 3 or carcinoma.

In an effort to increase the sensitivity of the initial encounter with the health-care system among women with limited resources and access, several researchers and agencies are investigating the use of HPV DNA testing in conjunction with standard Papanicolaou (Pap) smears, thin-layer smears, or HPV testing alone as the primary screening method.



Human *Papillomavirus*

METHOD AND RESULTS This well-designed prospective trial uses a large Planned Parenthood population to compare the sensitivity, specificity, and frequency of referral for colposcopy in patients undergoing thin-layer Pap smear, HPV testing by polymerase chain reaction (PCR), or HPV testing by liquid-based RNA-DNA hybridization capture with signal amplification.

Unfortunately, the demographics of the study population are not necessarily comparable to those of the average practicing Ob/Gyn. Therefore, it may not be appropriate to extrapolate the results universally. The mean age of participants was 25 years; more than 80% of the eligible women were under age 30. The prevalence of HPV DNA, cervical dysplasia, and carcinoma is significantly different in this age group, compared with women over 30 years of age.

Women in the trial were predominantly Caucasian, with an average of 5 sexual partners in the group under 25 years of age and 9 sexual partners in the over-30 group.

As the authors point out, another limitation of the study is the failure of some patients to return for colposcopy when recommended by the protocol. Only 72.7% of women with abnormal Pap test results and 67.9% of women with high-risk HPV DNA returned for colposcopic evaluation. This limited the reliability of the sensitivity and specificity calculations to some extent.

As expected, HPV DNA testing was more sensitive but less specific than cytology in identifying high-grade dysplasia or cervical carcinoma. HPV DNA by signal amplification identifies more intermediate- and low-risk HPV types than the PCR technique. Therefore, this method has a higher sensitivity but lower specificity for detecting high-grade lesions. All the screening strategies

were more sensitive for identifying CIN 3 or higher in women younger than 30 years of age. Specificity, however, was significantly greater for women older than 30 years of age.

WHO MAY BE AFFECTED? All sexually active women.

Persistence of high-risk HPV DNA types—not the initial presence—is a risk factor for cervical carcinoma.

EXPERT COMMENTARY Universal cervical cytology screening of sexually active women has greatly decreased the incidence of invasive cervical carcinoma in developed countries. Recently, commercialization of molecular biology techniques and cytology processing improvements have led to new products for cervical carcinoma screening.

In counseling patients, it is important to remember that it is the persistence of high-risk HPV DNA types—not the initial presence—that is a risk factor for cervical carcinoma. Most HPV infections regress spontaneously, with only about 10% of women remaining infected at 5 years. Young, recently sexually active women are likely to test positive for multiple HPV types. If they can be educated to comply with routine screening recommendations, it will not be clinically useful to employ primary screening with HPV DNA testing.

The downside to universal HPV DNA primary screening is that large numbers of women with transient high-risk HPV infections have normal cytology findings and no "disease." Labeling them as high risk would create a psychological burden on both the patient and the physician.

Until we have well-studied clinical protocols for managing these patients, we should avoid this dilemma by continuing current Pap screening in women who have good access to care and who are willing to participate in screening at appropriate intervals.

Primary HPV DNA screening is appropriate for women who are unwilling or unable to participate in routine screening.

BOTTOM LINE Screening strategies for cervical cancer are evolving. Techniques appropriate for young, sexually active women with somewhat limited access to care should not be extrapolated to a low-risk, stable, monogamous population.

If women understand the limitations of cytology screening and the need for repeated tests to capture the majority of true abnormal findings, and if they have financial and geographic access to routine care, it makes sense to use a specific but somewhat less sensitive testing strategy, i.e., cytology screening.

For women with minimal access to routine care, it is essential to use the simplest, most sensitive test to minimize false negatives. It is these women in whom primary screening with HPV DNA with or without cytology makes sense. ■

BARBARA S. LEVY, MD
CLINICAL ASSISTANT PROFESSOR OF OBSTETRICS AND GYNECOLOGY
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE
SEATTLE, WASH

SUGGESTED READING

Wright TC, Schiffman M. Adding a test for human papillomavirus DNA to cervical-cancer screening. *N Engl J Med*. 2003;348:489-901.

In the *works...*

Watch OBG MANAGEMENT for this article next month.

- Pelosi minilaparotomy hysterectomy: An effective alternative to laparoscopy and laparotomy