to address each case as an "n of one experiment" requiring regular and rigorous assessment for beneficial and adverse effects.

Robert D. Gillette, MD
Poland, Ohio

References

1. Brown RL, Fleming MF, Patterson JJ. Chronic opioid analgesic therapy for chronic low back pain. J Am Board Fam Pract 1996;9:191-204.
2. Murphy TM. Chronic opioids for chronic low back pain—solution or problem? J Am Board Fam Pract 1996;9:225-8.
3. Taub A. Opioid analgesics in the treatment of chronic intractable pain of nonneoplastic origin. In: Kitahata LM. Narcotic analgesics in anesthesiology. Baltimore, Williams & Wilkins, 1981:199-208.
4. Moulin DE, Iezzi A, Amireh R, Sharpe WKJ, Boyd D, Merskey H. Randomised trial of oral morphine for chronic non-cancer pain. Lancet 1996;347:143-7.
5. Eisendrath SJ. Psychiatric aspects of chronic pain. Neurology 1995;45(12 Suppl 9):S26-34.

The Dynamically Evolving Field of Cervical Cancer Screening

Cervical cancer screening is a dynamic and changing field. At the 9th World Congress of Cervical Pathology and Colposcopy held in May in Sydney, Australia, five relatively new methods were presented as potential ancillary tools for cervical cancer screening. These included human papillomavirus (HPV) testing, cervicography, speculoscopy, polar probe, and immunofluorescence. In addition to ancillary tools, there was a prototype of a video colposcope with superior illumination. Cytology screening is also undergoing a technical revolution with automated systems for processing, quality assurance, and preliminary screening. As technology becomes more accessible and understood, and as research tools are modified, the nature of cancer screening in general changes.

Unfortunately, Holman chose to use an outdated technology for HPV typing in his study.[1] The Virapap and Viratype tests were the first commercially available prototype for HPV testing, testing for a limited number of mucosotropic HPV types. As with any technology, initially there are difficulties translating the collection and detection devices to widespread clinical practice. These difficulties have been documented previously for this first-generation HPV test.[2-10]

The second-generation HPV detection kit approved by the Federal Drug Administration, Hybrid Capture, has been available since March of 1995. This test[11-14] shows marked improvement compared with the first-generation test. The low-risk groups detectable include types 6, 11, 42, 43 and 44. The intermediate- and high-risk groups are combined together to detect types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56 and 58. In addition, the Hybrid Capture method has a chemiluminescent reaction that quantifies the amount of HPV DNA present.

The third-generation HPV detection kit is not yet commercially available, as it is still undergoing testing. It promises to improve the detection and quantification of HPV DNA oncogenic types.

Whether HPV testing is used as a triage tool[11] or as a primary screening tool,[15] the utility of HPV testing has yet to be proved in a general clinic for all age ranges. The ALTS trial sponsored by the National Cancer Institute will attempt to answer this question in the United States. Women entering this trial will be randomized to immediate colposcopy, repeat cytology, or HPV testing after an initial ASCUS or LSIL Papanicolaou smear. Two similar trials are currently being conducted in Canada. The form of the final technology for HPV testing is still evolving, as are the methods for taking Papanicolaou smears, cytologic processing, and reading. Current research must evaluate the most evolved technologies for improved clinical performance.

Diane M. Harper, MD, MPH
University of Missouri-Kansas City

References

1. Holman JR. Detection of human papillomavirus DNA in patients referred to a family practice colposcopy clinic. J Am Board Fam Pract 1996;9:162-6.
2. Lorincz AT, Temple GF, Patterson JA, Jenson AB, Kurman RJ, Lancaster WD. Correlation of the cellular atypia and human papillomavirus deoxyribonucleic acid sequences in exfoliated cells of the uterine cervix. Obstet Gynecol 1986; 68:508-12.
3. Reid R, Greenberg MD, Lorincz AT, Jensen AB, Laverty CR, Husain M, et al. Should cervical cytologic testing be augmented by cervicography or human papillomavirus deoxyribonucleic acid detection? Am J Obstet Gynecol 1991; 164:1461-9.
4. Cole HM. Human papillomavirus DNA testing in the management of cervical neoplasia. JAMA 1993;270:2975-81.
5. Moscicki AB, Palefsky JM, Gonzales J, Schoolnick GK. The association between human papillomavirus deoxyribonucleic acid status and the results of cytologic rescreening tests in young, sexually active women. Am J Obstet Gynecol 1991; 165:67-71.
6. Weintraub J, Redard M, Seydoux J. The comparative test performance of dot filter hybridization (Viratype) and conventional morphologic analysis to detect human papillomavirus. Am J Clin Pathol 1992;97:46-57.
7. Burmer GC, Parker JD, Bates J, East K, Kulander BG. Comparative analysis of human papillomavirus detection by polymerase chain reaction and Virapap/Viratype kits. Am J Clin Pathol 1990;94:554-60.
8. Meyer MP, Carbonell RI, Mauser NA, Kanbour AI, Amortegui AJ. Detection of human papillomavirus in cervical swab samples by ViraPap and in cervical biopsy specimens by in situ hybridization. Am J Clin Pathol 1993;100:12-7.
9. Corliss J. Utility of ViraPap remains to be established. J Natl Cancer Inst 1990;82:252-3.
10. Guerrero E, Daniel RW, Bosch FX, Castellsague X, Munoz N, Gili M, et al. Comparison of ViraPap, Southern hybridization, and polymerase chain reaction methods for human papillomavirus identification in an epidemiological investigation of cervical cancer. J Clin Microbiol 1992;30: 2951-9.

11. Cox JT, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am J Obstet Gynecol 1995;172:946-54.
12. Sun XW, Ferenczy A, Johnson D, Koulos JP, Lungu O, Richart RM, et al. Evaluation of the Hybrid Capture human papillomavirus deoxyribonucleic acid detection test. Am J Obstet Gynecol 1995;173:1432-7.
13. Farthing A, Masterson P, Mason WP, Vousden KH. Human papillomavirus detection by hybrid capture and its possible clinical use. J Clin Pathol 1994;47:649-52.
14. Schiffman MH, Kiviat NB, Burk RD, Shah KV, Daniel RW, Lewis R, et al. Accuracy and interlaboratory reliability of human papillomavirus DNA testing by hybrid capture. J Clin Microbiol 1995;33:545-50.
15. Meijer CJLM, Snijders PJF, Van Den Brule AJC, Helmerhorst TJM, Remmicnk AJ, Walboomers JMM. Can cytological detection be improved by HPV screening? European Research Organization on Genital Infection and Neoplasia (Eurogin) Expert's Conference. Paris: UNESCO, 1994:50-3.

The above letter was referred to the author of the article in question, who offers the following reply.

To the Editor: Dr. Harper makes some excellent points in her letter. The field of cervical cancer diagnosis and treatment is rapidly changing with new modalities being developed and introduced very quickly. Family physicians who perform colposcopy need to figure out a way to stay current with the overwhelming amount of recent literature in this field.

While the Virapap and Viratype test might now be considered outdated technology, it was the only test commercially available when the data were collected and hence constituted the most evolved technology at that time. Dr. Harper cites a number of references which she states document the difficulties with the Virapap and Viratype.[1-6] While human papillomavirus (HPV) testing is a part of the study methods of each of these reports, not all show "difficulties" with the test kit. In fact, Lorincz et al reports a sensitivity of 92 percent and a specificity of 89 percent (compared with cervical cytology).[1] The Lorincz et al paper and the article by Moscicki et al also compared HPV testing with cytology.[1,4] Cervical cytology cannot be considered a reference standard for diagnosis of HPV with its high false-negative rate. The Weintraub et al[5] study compared the Virapap/Viratype kit to polymerase chain reaction. Polymerase chain reaction might be a very sensitive method of HPV detection, but it is not the reference standard for clinicians.

A key point when evaluating a new diagnostic test is that one must compare it with the reference standard that is currently in use. Reported sensitivities and specificities for the Virapap/Viratype by Digene Diagnostics were 94.5 and 95.5 percent, respectively.[7] These results were obtained when comparing the dot blot DNA hybridization of the Virapap/Viratype kit with the laboratory reference standard of Southern blot DNA hybridization. In clinical practice, the reference standard for HPV diagnosis is a colposcopy and directed cervical biopsies with histologic evaluation. Only the Reid et al study[2] used this method as their reference standard.

Dr. Harper cites four articles that show the Hybrid Capture method has "a marked improvement compared with the first-generation test." If by "marked improvement" she means an improved sensitivity, she is absolutely correct. The study by Sun et al[8] showed a calculated sensitivity of 79 percent compared with colposcopy and cervical histology. The article by Cox et al[9] demonstrates a sensitivity of 86 percent compared with colposcopy and cervical histology. Both of these studies show a decrease in specificity (58 percent and 71 percent, respectively), but for cervical cancer screening, a test with a higher sensitivity is preferred.

New diagnostic tests are being introduced regularly. When reading articles that evaluate their performance, be sure that the reference standard is easily recognized and that it is clinically applicable. I agree with Dr. Harper that the most technologically evolved test should be used when conducting research and that the role of HPV testing in cervical cancer screening remains to be elucidated. All family physicians who care for women should be aware of the evolving nature of cervical cancer screening and the need to stay clinically current.

John P. Holman, MD
Bremerton, Wash

References

1. Lorincz AT, Temple GF, Patterson JA, Jenson AB, Kurman RJ, Lancaster WD. Correlation of cellular atypia and human papillomavirus deoxyribonucleic acid sequences in exfoliated cells of the uterine cervix. Obstet Gynecol 1986;68:508-12.
2. Reid R, Greenberg MD, Lorincz A, Jenson AB, Laverty CR, Husain M, et al. Should cervical testing be augmented by cervicography or human papillomavirus deoxyribonucleic acid detection? Am J Obstet Gynecol 1991;164:1461-9.
3. Diagnostic and therapeutic technology assessment. Human papillomavirus DNA testing in the management of cervical neoplasia. JAMA 1993;270:2975-81.
4. Moscicki AB, Palefsky JM, Gonzales J, Schoolnick GK. The association between human papillomavirus deoxyribonucleic acid status and the results of cytologic rescreening tests in young, sexually active women. Am J Obstet Gynecol 1991;165:67-71.
5. Weintraub J, Redard M, Seydoux J. The comparative test performance of dot filter hybridization (Viratype) and conventional morphologic analysis to detect human papillomavirus. Am J Clin Pathol 1992;97:46-57.
6. Burmer GC, Parker JD, Bates J, East K, Kulander BG. Comparative analysis of human papillomavirus detection by polymerase chain reaction and Virapap/Viratype kits. Am J Clin Pathol 1990;94:554-60.
7. Holman JR. Detection of human papillomavirus DNA in patients referred to a family practice colposcopy clinic. J Am Board Fam Pract 1996;9:162-6.
8. Sun XW, Ferenczy A, Johnson D, Koulos JP, Lungu O, Richart RM, et al. Evaluation of the Hybrid Capture human