

## Advisory Board



### Gary Lee Eddy, Sr., M.D.

Professor

Director of Gynecologic Oncology

Department of Obstetrics and Gynecology Mercer University School of Medicine Medical Center of Central Georgia

Gary Lee Eddy, Sr. M.D. is Professor and Director of Gynecologic Oncology in the Department of Obstetrics and Gynecology at the Mercer University School of Medicine. He is a fellow in the American College of Obstetricians and Gynecologists and a member of the Society of Gynecologic Oncologists. Dr. Eddy is an active researcher, teacher, and clinician with interests in vulvar carcinoma, epithelial and non-epithelial ovarian tumors and gynecologic laser surgery among many others. He has been a reviewer for Obstetrics and Gynecology, Gynecologic Oncology, and American Journal of Obstetrics and Gynecology.



### Gary W. Gill, CT(ASCP), CFIAC

Corporate Compliance Officer

DCL Medical Laboratories, Indianapolis, IN

Adjunct Associate Professor

Medical University of South Carolina, Charleston, SC

Gary W. Gill, CT(ASCP), CFIAC is Corporate Compliance Officer at DCL Medical Laboratories in Indianapolis, Indiana. He is also an Adjunct Associate Professor at the Medical University of South Carolina in Charleston, South Carolina. In addition to these positions, Mr. Gill is a Consultant Cytotechnologist and an independent Consultant. He is an Associate Member of the American Society of Clinical Pathologists and the American Society of Cytopathology as well as a Fellow in the International Academy of Cytology. Mr. Gill's many honors include the Excellence in Education Award from the American Society of Cytopathology, and the International Cytotechnology Award from the International Academy of Cytology.



### Steven J. Sondheimer, M.D.

Professor

Division of Reproductive Endocrinology and Infertility

Department of Obstetrics and Gynecology

University of Pennsylvania Medical Center

Dr. Steven Sondheimer is Professor of Obstetrics and Gynecology at the University of Pennsylvania Medical Center where he is also a Reproductive Endocrinology and Infertility specialist, and Medical Director of the Family Planning Program. He has received numerous awards for excellence in teaching. Dr. Sondheimer is a Fellow in The American College of Obstetricians and Gynecologists, a Fellow in The American Society for Reproductive Medicine, and a member of The Society for Reproductive Endocrinology and Infertility as well as many other professional and scientific societies. Dr. Sondheimer has served as an ad hoc reviewer for The American Journal of Obstetrics and Gynecology, The New England Journal of Medicine Fertility and Sterility and other medical journals.



## FEATURES

Changing Guidelines for Colposcopy Use Among Adolescents? 1

Increased Access to Cervical Screening 2

Optimizing Specimen Collection for Pap Tests 4

## ABSTRACTS IN CERVICAL SCREENING

American Cancer Society Guidelines for Human Papillomavirus (HPV) Vaccine Use to Prevent Cervical Cancer and Its Precursors 5

Age-Specific Detection of High Risk HPV DNA in Cytologically Normal, Computer-Imaged ThinPrep Pap Sample 5

The Absolute Risk of Cervical Abnormalities in High-Risk Human Papillomavirus-Positive, Cytologically Normal Women Over a 10-Year Period 6

Malpractice Issue to Keep in Mind in Using Diagnostics Kits Contrary to Product Labeling 6

Cervical Cancer Incidence in a Prevalence Era in the United States, 1998-2002. 7

Prospects for Cervical Cancer Prevention by Human Papillomavirus Vaccination 7

## BIOGRAPHIES

Advisory Board 8

## Changing Guidelines for Colposcopy Use Among Adolescents

Until recently, the generally accepted attitude regarding adolescents and colposcopy was "search and destroy."<sup>1</sup> Early intervention was considered the safest way to address abnormalities in adolescents as well as in adults. However, The Consensus Guidelines of the Management of Women with Cervical Cytological Abnormalities by the American Society for Colposcopy and Cervical Pathology has updated these guidelines, shifting away from aggressive intervention, especially for younger women with HPV.<sup>2</sup>

The guidelines state that untreated CIN-1 is characterized by high rates of spontaneous regression and low rates of progression to cancer. For this reason, many experts advocate follow-up without treatment if the colposcopic examination is satisfactory. These women can be safely followed by using a program of repeat cervical cytology as can women with a cytologic diagnosis of atypical squamous cells of uncertain significance (ASC-US). However, for women with biopsy-confirmed CIN-1 and unsatisfactory colposcopic examination, regardless of the endocervical sampling results, treatment should be given.<sup>3</sup>

Spontaneous regression is also high for CIN-2, especially among adolescents. Observation with colposcopy and cytology at 4 to 6 month intervals for 1 year is acceptable for adolescents with biopsy-confirmed CIN-2, provided colposcopy is satisfactory, endocervical sampling is negative, and the patient accepts the risk of occult disease. If the lesion progresses to high grade squamous intraepithelial lesions (HSIL) or if an HSIL lesion persists for a year or more, only then should one proceed to a diagnostic and/or excisional procedure.<sup>1,2,4</sup> Ablation or excision is required for adolescent women with CIN-3.<sup>3</sup>

Guidelines for managing ASC-US in adolescents, state that the risk of invasive cancer in this population is virtually non-existent, and that HPV clearance rates are high, suggesting that conservative management is an acceptable alternative to immediate colposcopy.<sup>4</sup>

Dr. Thomas Cox, one of the authors of the guidelines said, "If you balance the risk of damage due to over-treating young women versus the risk of missing a lesion that might become cancerous later on, it weighs in favor of doing less."<sup>1</sup> The danger is that aggressive surgical or cytotoxic management of lesions in adolescents could have a negative effect on their future fertility and cervical competency, and increase the risk of cervical stenosis and preterm labor.<sup>4</sup>

## Changing Guidelines for Colposcopy Use Among Adolescents (continued)

While the guidelines state that colposcopy and surgical intervention are still appropriate in certain cases, the general recommendation is toward a more conservative approach relying more heavily on cytology as a screening and diagnostic tool.

### References:

1. Goldman EL. OB/GYN News. Feb. 15, 2003. Accessed at: [http://www.findarticles.com/p/articles/mi\\_m0CYD/is\\_4\\_38/ai\\_98165923](http://www.findarticles.com/p/articles/mi_m0CYD/is_4_38/ai_98165923). Accessed on 2.17.07.
2. JAMA. 287[16]:2120-29, 2002.
3. Wright TC, Cox JT, Massad LS, et al. 2001 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia. Am J Obstet Gynecol. July 2003;295-304.
4. American College of Obstetrics and Gynecology Committee on Adolescent Health Care. Evaluation and management of abnormal cervical cytology and histology in the adolescent. Obstet Gynecol. Apr 2006. 107;4.

## Increased Access to Cervical Screening

Since the introduction of the Pap test in the 1940s, the cervical cancer death rate has fallen by 94%.<sup>1,2,3,4,5</sup> The advent and implementation of the Pap test has had a profound impact by increasing the early detection of cervical cancer and its precursors. However, the 2000 National Health Interview Survey indicated that 1 in 5 women are not having this screening procedure.<sup>6</sup> These women tend to be indigent and uninsured.<sup>7</sup> The federal government is taking important steps to address this need.

In 1990, Congress passed the Breast and Cervical Cancer Mortality Prevention Act, which guided the Centers for Disease Control and Prevention in creating the National Breast and Cervical Cancer Early Detection Program (NBCCEDP). It provides screening support in all 50 states, the District of Columbia, 4 U.S. territories and 13 American Indian/Alaskan Native tribes or tribal organizations. It is designed to help low-income, uninsured and underinsured women gain access to breast and cervical cancer screening and diagnostic services. This includes Pap tests, surgical consultation referrals and diagnostic testing for women whose screening outcome is abnormal.<sup>8</sup> Because low-income women tend to be racial and ethnic minorities, one of the goals of this program is to reduce racial disparities in screening and early detection.<sup>9</sup>

The NBCCEDP has proven to be extremely successful. Since 1991, more than 88,000 women were diagnosed with precancerous lesions and 1,700 with invasive cervical cancer. As of 1999, the NBCCEDP provided more

than 1.1 million Pap tests to a total of more than 700,000 women, half of whom were from minority groups.<sup>10</sup>

Nonetheless, racial and ethnic disparities persist. Cervical cancer rates are highest among Vietnamese Americans, with 43 cases per 100,000,<sup>11</sup> and Hispanics, with 14.8 per 100,000, compared to 8.7 cases per 100,000 in the general population.<sup>12</sup> Regardless of income level, African American women have the highest rate of Pap screening, while Hispanic women have the lowest.<sup>13</sup> Hispanic women said they were reluctant to have Pap tests because they felt embarrassed, frightened, and feared the pain associated with a pelvic examination. Although the male partner was mentioned as a possible barrier, most women expressed that this was not an issue for them.<sup>14</sup> Community, federal and privately funded programs have targeted Hispanic women in a variety of ways. The focus is on understanding disease prevention and treatment as well as locating low-cost or free Pap screening.

The Centers for Disease Control and Prevention gave The University of California at San Francisco more than \$3.6 million over a 4 year period to improve screening and management of breast and cervical cancer among Vietnamese Americans in Santa Clara County.<sup>11</sup> Many approaches were utilized to increase understanding and communicate the importance of Pap smears. These included: conducting intensive media campaigns, training lay health workers to educate the community with culturally appropriate materials in the Vietnamese language,

## Increased Access to Cervical Screening (continued)

establishing a Vietnamese clinic (1/2 day a month) to provide Pap smears for underinsured or uninsured women in Santa Clara County and other programs.<sup>11</sup>

Preliminary results indicate the program has made great progress. By 2006, 46.8% of Vietnamese-American women had their first Pap test. Fifty Vietnamese-American physicians have been educated about cervical cancer screening and the NBCCEDP has been re-established in the county with 2 clinics and 3 providers.<sup>15</sup>

Lack of money for preventive care is the most important barrier for women of all races and ethnic backgrounds.<sup>16</sup> The NBCCEDP has helped to address this need and made great progress in increasing the number of women who are tested. In recent years, improved liquid-based Pap testing methods have also been made available to this program. Impressive strides have been made in the effort to eradicate this devastating disease, but more work lies ahead in terms of increasing awareness of the importance of the Pap test as well as awareness of access to low-cost testing. With continued momentum, this move-

ment toward better health practices may virtually eliminate cervical cancer death in America.

Suggested web sites for patients and physicians:

1. Fact Sheet about Pap smears from the National Cancer Institute, a division of the U.S. National Institutes of Health: <http://www.cancer.gov/cancertopics/factsheet/Detection/Pap-test>
2. National Cervical Cancer Coalition newsletter and information: [http://www.nccc-online.org/hpv\\_1.php](http://www.nccc-online.org/hpv_1.php)
3. American Cancer Society recommendations for cancer prevention practices: [http://www.cancer.org/docroot/ped/content/ped\\_2\\_3x\\_acs\\_cancer\\_detection\\_guidelines\\_36.asp](http://www.cancer.org/docroot/ped/content/ped_2_3x_acs_cancer_detection_guidelines_36.asp)
4. Information about the National Breast and Cervical Cancer Early Detection Program from the Centers for Disease Control and Prevention: <http://www.cdc.gov/cancer/nbccedp/>

### References:

1. OncoLink. American Cancer Center of the University of Pennsylvania. Accessed at: <http://www.oncolink.com/types/article.cfm?c=6&s=17&ss> Retrieved on 2.03.2007.
2. Braun RD. What a normal pap smear means! OBGYN.net. Accessed at: [http://www.obgyn.net/display\\_article.asp?page=/yw/articles/braun\\_PAP](http://www.obgyn.net/display_article.asp?page=/yw/articles/braun_PAP)
3. Calculations based on census of 1941 and 2006. 1941: Population Estimates Program, Population Division, U.S. Census Bureau Internet Release Date: April 11, 2000, Revised data: June 28, 2000. Accessed at: <http://www.census.gov/popest/archives/1990s/popclockest.txt> Retrieved on 2/03/07
4. U.S. Census Bureau, U.S. U.S. and World Population Clocks-POPclocks, Feb. 03,2007. Accessed at: <http://www.census.gov/main/www/popclock>. Retrieved on 2/3/07
5. American Cancer Society. What are the key statistics about cervical cancer? Accessed at: [http://www.cancer.org/docroot/CRI/content/CRI\\_2\\_4\\_1X\\_What\\_are\\_the\\_key\\_...](http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_are_the_key_...) Retrieved on 2.16.2007
6. Hewitt M, Devesa SS, Breen N. Cervical cancer screening among women: analysis of the 2000 National Health Interview Survey. Prev Med. 2004. Aug;39(2):270-8.
7. National Breast and Cervical Cancer Early Detection Program 2006-2007 from the Division of Cancer Prevention and Control. Accessed at: [http://www.cdc.gov/cancer/nbccedp/bccpdfs/0607\\_nbccedp\\_fs.pdf](http://www.cdc.gov/cancer/nbccedp/bccpdfs/0607_nbccedp_fs.pdf) Retrieved on 2.16.2007
8. National Breast and Cervical Cancer Early Detection Program Accessed at:<http://www.cdc.gov/cancer/nbccedp/about.htm> Retrieved on 2.16.2007
9. Adams EK, Breen N, Joski PJ. Impact of the National Breast and Cervical Cancer Early Detection Program on mammography and pap test utilization among white, Hispanic, and African American women: 1996-2000. Cancer. 2007 Jan 15;109(2 Suppl):348-58.
10. Lee NC. Testimony on cervical cancer before the House Committee on Commerce, Subcommittee on Health and Environment, March 16, 1999. Accessed at: <http://www.hhs.gov/asl/testify/t990316b.html> Retrieved on 2.16.2007
11. Daybreak News. University of California at San Francisco. Accessed at: [http://www.ucsf.edu/daybreak/2000/11/03\\_cancer.htm](http://www.ucsf.edu/daybreak/2000/11/03_cancer.htm) Retrieved on 2.16.2007
12. Saraiya M, Ahmed F, Krishnan S, et al. Cervical cancer incidence in a prevaccine era in the United States, 1998-2002. Obstetrics and Gynecology. 2007;109:360-370.
13. Healthy People 2010. Progress Review. U.S. Department of Health and Human Services. October 16, 2002.
14. Byrd TL, Chavez R, Wilson KM. Barriers and facilitators of cervical cancer screening among Hispanic women. Eth Dis.2007 Winter;17(1):129-34.
15. REACH — University of California, San Francisco. Accessed at: [http://apps.nccd.cdc.gov/EmailForm/print\\_table.asp](http://apps.nccd.cdc.gov/EmailForm/print_table.asp). Accessed on 2.21.07.
16. Populations at risk for cervical cancer. Accessed at: [http://www.cancermm.org/docs/pdf/Cervical\\_Handbook\\_ch2.pdf](http://www.cancermm.org/docs/pdf/Cervical_Handbook_ch2.pdf). Retrieved on 2.16.2007.

## Optimizing Specimen Collection for Pap Tests

Despite its remarkable success in cervical cancer prevention, the Papanicolaou smear is not a perfect test. Sampling errors account for a significant number of false-negative cases.<sup>1</sup> Most physicians would agree with Dr. R.W. DeMay who goes on to mention that many of the problems can be traced to inadequate sampling which, in turn, can result in diagnostic errors because the cells are too few in number, too small, or indistinct.<sup>2</sup> The growing concern over false-negative Pap tests has the potential to reduce the use and availability of this test which is still considered the most effective cancer screening test devised.<sup>3</sup> However, steps can be taken to reduce this problem.<sup>4</sup> Quality improvements have been and should continue to enhance efficacy.<sup>5</sup>

While it is vital to optimize specimen collection to diminish the number of false negatives and the potentially devastating consequences that result, it is also important to reduce the number of false positives so women do not have to undergo unnecessary testing.

Neither oral contraceptives nor intrauterine devices will diminish the accuracy of the Pap test. Menses, however, can be problematic. If the menstrual flow is heavy then the blood could obscure the cervical cell sample.<sup>6</sup> Ideally, the test should not be performed during menses; it is best to schedule the appointment two weeks after the first day of the last menstrual period.<sup>7</sup>

The physician can maximize the quality of the test by keeping the following steps in mind. First, it is critical that the Pap be done before the rest of the pelvic

exam or before getting any cultures.<sup>8</sup> An important prerequisite to the collection of the sample is a visual inspection of the lower genital tract and cervix through the speculum.<sup>9</sup> The transformation zone must be identified; the location and appearance of this area is variable depending on such factors as vaginal pH, pregnancy, hormonal milieu (age), prior therapy, and individual anatomy. An optimal cervical specimen includes sampling of the squamous and columnar epithelium, encompassing in particular the transformation zone, where the majority of cervical neoplasias arise.<sup>7</sup> The endocervical limit of the transformation zone is dynamic, defined by the leading edge of the migrating squamo-columnar junction. In post-menopausal women, it is often high in the endocervical canal and not visible.<sup>10</sup> The most accurate sampling encompasses this area.<sup>7</sup>

Warm water may be used to facilitate speculum insertion.<sup>7</sup> The liquid-based ThinPrep System allows practitioners to easily sample the ectocervix and endocervix using only one brush; or, the cervix can be sampled with a combination of a spatula and endocervical brush. In either cases, the sampling devices should be thoroughly rinsed into the vial. The preserved cells can be used for cytologic preparations or molecular testing.<sup>9</sup>

If the Pap smear is negative, but clinical signs indicating an abnormality were apparent during the collection of the specimen, the physician should proceed with follow-up testing.<sup>6</sup>

### References:

1. DeMay RM. Common problems in Papanicolaou smear interpretation. *Arch Pathol Lab Med.* 1997 Mar;121(3):229-38.
2. DeMay RM. Cytopathology of false negatives preceding cervical carcinoma. *Am J Obstet Gynecol.* 1996 Oct;175(4 Pt 2):1110-3.
3. Frable WJ. Does a zero error standard exist for the Papanicolaou smear? A pathologist's perspective. *Arch Path Lab Med.* 1997 Mar;121(3):301-10.
4. Explaining false negative results on some Pap tests. *UniSci. Daily University Science News.* Accessed at: <http://unisci.com/stories/20022/0626024.htm>. Accessed on 2.19.07.
5. Greer BE. The gynecologist's perspective of liability and quality issues with the Papanicolaou smear. *Arch Pathol Lab Med.* 1997 Mar;121(3):246-9.
6. Interviews conducted with Dr. Gary Eddy, Dr. Steven Sondheimer, Gary Hill. 2.14.07. 4 pm - 5pm.
7. NCCLS. Papanicolaou Technique: Approved Guideline. NCCLS document 15A (ISBN 1-56238-238-1) Villanova, Pennsylvania:NCCLS; 1994:14: no.8. as found in American Society of Cytopathology web site at: <http://www.cytology.org/website/article.asp?id=384> (1 of 5) Accessed on: 2.27.2007
8. Artandi M. The abnormal Pap smear in the internist's office. Publication of Stanford University. 8.14.06. Accessed at: [http://ctm.stanford.edu/06-07/Abnormal%20Pap%20Smear\\_Artandi\\_8\\_14\\_06.pdf](http://ctm.stanford.edu/06-07/Abnormal%20Pap%20Smear_Artandi_8_14_06.pdf). Accessed on 2.19.07.
9. Mayeaux EJ. Optimizing the Papanicolaou smear. Publication of the Louisiana State University School of Medicine. 7.29.05. Accessed at: <http://www.sh.lsuhsu.edu/fammed/OutpatientManual/PapSmear.htm>. Accessed on 2.19.07.
10. Gharib S, Feldman S, Hellerstein S, et al. Cervical cancer screening recommendations, with algorithms for managing women with abnormal Pap test results. Brigham and Women's Hospital, Harvard Medical School. 2004:2-12.

## Abstracts in Cervical Screening

**American Cancer Society Guidelines for Human Papillomavirus (HPV) Vaccine Use to Prevent Cervical Cancer and Its Precursors - Debbie Saslow, Philip E. Castle, J. Thomas Cox et al.** *CA A Cancer Journal for Clinicians.* 2007;57:7-28.

**Reviewed by Steven Sondheimer, MD**

In January 2007, the American Cancer Society (ACS) published recommendations on the use of the HPV vaccine. This article contains a current literature review by a diverse group of experts with recommendations on the use of the HPV vaccine. The vaccine is of greatest benefit when given to girls and young women before exposure to HPV. However, testing for HPV exposure is not required before vaccination. Pap screening programs should continue to follow ACS guidelines and are not changed or impacted by whether a woman has received the HPV vaccine. The ACS recommendations are found in Table 1 from the article and summarized below:

- Routine HPV vaccination is recommended for females aged 11 to 12 years.
- Females as young as age 9 years may receive HPV vaccination.
- HPV vaccination is also recommended for females aged 13 to 18 years to catch up missed vaccine or complete the vaccination series.
- Insufficient data exist to recommend for or against universal vaccination of females aged 19 to 26 years in the general population. Ideally the vaccine should be administered prior to potential exposure to genital HPV through sexual intercourse because the potential benefit is likely to diminish with increasing number of lifetime sexual partners.
- HPV vaccination is not currently recommended for women over age 26 years or for males.
- Screening for cervical intraepithelial neoplasia and cancer should continue in both vaccinated and unvaccinated women according to current ACS early detection guidelines.

**Age-Specific Detection of High Risk HPV DNA in Cytologically Normal, Computer-Imaged Thin-Prep Pap Sample - Edmund S. Cibas, Xuefei Hong, Christopher P. Crum, et al.** *Gynecologic Oncology.* 2006;Doi10.1016/j.ygyno.2006.10.048

**Reviewed by Gary W. Gill, CT(ASCP)**

In this well-designed study, the authors convincingly demonstrate that the high-risk (HR) HPV rates in women ages 30-45 with a cytologically negative, computer-imaged ThinPrep Pap test are low.

Age Group	N HR	HPV (1)
30-35	300	6.7%
36-40	200	3.0%
41-45	500	2.6%
30-45	1,000	3.9%

Significantly, of the 39 HR HPV positive results, 18 were likely false positives: 14 were negative by linear array HPV genotyping test and 4 were positive for low risk HPV. The 21 remaining HR HPV positive results represent infections that do not necessarily represent false negative cytology results, nor presage the development of a clinically significant cytologic lesion. Women who are HR HPV positive/cytology negative are at a relatively low risk of having high-grade squamous intraepithelial neoplasia.<sup>1</sup> Women whose cervical smears are cytologically normal only are also unlikely to develop HSIL within 3 years.<sup>2</sup> And for those who develop ASC-US, LSIL, or HSIL, only 0.25%, 0.15%, and 1.44%, respectively, are likely to progress to invasive cancer within 24 months.<sup>3</sup> Given the results of the current study, the high added cost of HPV testing with the DNAwithPap® Test, the low incidence of HR HPV positive results in cytologically negative women, and the minimal risk of developing significant lesions that progress to invasive cervical cancer, it is possible that the guidelines for routinely testing women age 30 and older with the HPV test and liquid-based cytology may be modified in the future. The authors conclude that because the incidence of HR Hybrid Capture® 2 (hc2) positivity is very low in women over age 30, imaged negative TP cytology may negate the need for hc2 co-testing.

Hybrid Capture is a registered trademark of Digene Corporation  
DNAwithPap is a registered trademark of Digene Corporation

### References

1. Wright TC Jr., Schiffman M, Solomon D, Cox JT et al. Interim guidance for the use of human papillomavirus DNA testing as an adjunct to cervical cytology for screening. *Obstet Gynecol.* 2004;103(2):304-9.
2. Sawaya GF, Kerlikowske K, Lee NC, Gildengorin G, Washington AE. Frequency of cervical smear abnormalities within 3 years of normal cytology. *Obstet Gynecol.* 2000;96(2):219-23. Free full text reprint available at: <http://www.greenjournal.org/cgi/reprint/96/2/219>.
3. Melnikow J, Nuovo J, Willan AR, Chan BK, Howell LP. Natural history of cervical squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol.* 1998;92(4pt2):727-36.

### The Absolute Risk of Cervical Abnormalities in High-Risk Human Papillomavirus-Positive, Cytologically Normal Women Over a 10-Year Period

- *Susanne Kjaer, Estrid Høgdall, Kirsten Frederiksen, Christian Munk, Adriaan van den Brule, Edith Svare, Chris Meijer, Atilla Lorinez, and Thomas Iftner. Cancer Research 2006;66:(21). November 1, 2006.*

**Reviewed by Gary Eddy, MD**

The authors assert that in spite of the success of cervical cytology as a cancer-screening tool, it has important limitations, and human papillomavirus (HPV) testing may be valuable in future screening. The majority of women in screened populations, who test HPV positive, will have a concurrent normal smear; clearly more information is needed about the risk for subsequent high-grade cervical lesions in these women. The authors examined 8,656 younger women (22-32 years old) and 1,578 older women (40-50) who were followed for development of cervical neoplasia (cytology and/or histology) through the Danish Pathology Data Bank. They estimated the proportion of women developing cervical lesions of different types before a given time point as a function of time. Among women with normal cytology and positive high-risk Hybrid Capture® 2 (hc2) test, 17.7% and 24.5% of younger and older women, respectively, had a subsequent abnormal Pap smear within 5 years. The risk of CIN3 or cancer within 10 years among younger women with positive hc2 test was 13.6% (10.9-16.2) and 21.2% (2.7-36.1) among older women. An analysis among younger women also being hc2-positive 2 years before baseline showed a subsequent 10-year risk of CIN3 of 18% (14.6-21.5). Among older women where HPV may be added to general screening, the estimated absolute risk of CIN3 in hc2-positive women was more than 20% within 10 years. The authors conclude that even a single positive HPV test in cytologically negative women is substantially predictive of high-grade CIN and suggest that hc2 testing can help stratify women into different risk categories.

The implication is clear that eliminating the Pap test from the standard screening regimen would result in substantial cost savings. While this is undoubtedly true, relying on the HPV test alone for cervical cancer screening is problematic in a number of ways. First, a Pap test confirms that the correct area has been sampled by indicating endocervical cells on the smear, while an HPV test only indicates the presence or absence of HPV. Second, the Pap test involves the physician's expertise in identifying clinical signs of pathology leading the physician to sample that particular area. This is another kind of screening that contributes to the accuracy of the Pap test. The HPV test is not reliant on

observation skills and so women will not have the benefit of this aspect of the physician's expertise. Because the HPV test is usually a blood test, it does not require the skill of the examining physician. From another perspective, if the emphasis is shifted toward HPV testing and away from Pap testing, eventually we will lose the expertise of the world class pathologists that we have now who are able to read the difficult smears. While the HPV testing has proven benefits in the screening for cervical cancer, it can be used most effectively not as a replacement, but rather as an adjunct to the Pap test.

Hybrid Capture is a registered trademark of Digene Corporation

### Malpractice Issue to Keep in Mind in Using Diagnostics Kits Contrary to Product Labeling -

*Jack R. Bierig and Seth Axelrod. CAP Today. November 2006. Available at: <http://www.cap.org/>*

**Reviewed by Gary W. Gill, CT(ASCP)**

In this timely legal opinion, the authors wisely caution physicians of the risk of a malpractice claim when using Digene's test for high-risk human papillomavirus alone—without cytology—rather than as an adjunct to liquid-based cytology as FDA-approved. According to the FDA, if physicians use a product for an indication not in the FDA approved labeling, they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.<sup>1</sup> However, using Digene's HPV test alone as a screening test is contrary to the approval statement<sup>2</sup> and safety and effectiveness data.<sup>3</sup> It is the reviewers' opinion that if using HPV testing alone results in an adverse medical outcome, the plaintiff's attorney will likely point out—among many other potential indicators of negligence from which to choose—that the quality of supporting evidence and the criteria that support the strength of recommendation on which the physician based the action are both scientifically weak. In all probability, physicians will model their approach on The 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities which does not recommend the use of the Digene HPV test without a Pap test.<sup>4</sup> Clearly, it is prudent to use the Digene HPV test in accordance with the labeling. It is the reviewers' opinion that a physician may understand why one would choose to use the Digene HPV test alone; however, if a trial results, the jury will not be comprised of medical personnel, but rather of lay citizens, who would potentially see this use as a misuse and conclude that the physician's decision constitutes negligence.

### References

1. FDA. Off-Label and Investigational Use of Marketed Drugs, Biologics, and Medical Devices, 1998. Available at: [http://www.fda.gov/oc/ohrt/irbs/off\\_label.html](http://www.fda.gov/oc/ohrt/irbs/off_label.html).
2. FDA. Digene Hybrid Capture® 2 (hc2)High-Risk HPV DNA Test - P890064/S009: Summary of Safety and Effectiveness Data. Available at: <http://www.fda.gov/cdrh/pdf/P890064s009b.pdf>.
3. PMA Number P890064/S009, 03/31/2003. Available at: <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA.cfm?ID=5907>.
4. Wright TC Jr, Cox JT, Massad LS, Twigg LB, Wilkinson EJ; ASCCP-Sponsored Consensus Conference. 2001 Consensus Guidelines for the management of women with cervical cytological abnormalities. JAMA. 2002;287(16:2120-9).

### Cervical Cancer Incidence in a Prevaccine Era in the United States, 1998-2002. - Mona Saraiya, MD, MPH., Faruque Ahmed, MD, PhD, Sheila Krishnan, MD, MPH, Thomas B. Richards, MD, Elizabeth R. Unger, MD, PhD, and Hershel W. Lawson, MD. Obstetrics & Gynecology. Vol. 109, No. 2, Part 1, February 2007.

**Reviewed by Gary Eddy, M**

This article reports the age-adjusted incidence of cervical cancer by geography, race or ethnicity, and histology. The authors examined combined data from the National Program of Cancer Registries and the Surveillance, Epidemiology, and End Results Program covering 87% of the U.S. population. The rates of invasive cancer per 100,000 females declined from 10.2 in 1998 to 8.5 in 2002. Incidence rates by state ranged from 6.6 to 12.3 per 100,000. Rates were especially high among Hispanic women aged 40 years or older (26.5 or more) and African-American women aged older than 50 years (23.5 or more). Rates of squamous cell carcinoma were significantly higher among African-American and Hispanic women than among their white counterparts. In contrast, rates of adenocarcinoma (18% of all cases) were significantly lower among African-American women than in white women (rate ratio 0.88, P<.05). Rates of adenocarcinoma were significantly higher among Hispanic women than among non-Hispanics (ratio 1.71, P<.05). Although no regional differences were noted for adenocarcinoma, rates of squamous cell carcinoma were higher in the South than in other regions.

Despite intense screening in the past decade, higher rates of cervical cancer persist among women in the South and women who are African American or Hispanic. This information could guide more focused interventions to increase access to screening with cervical cytology as well

as vaccination against human papillomavirus of lay citizens, who would potentially see this use as a misuse and conclude that the physician's decision constitutes negligence.

### Prospects for Cervical Cancer Prevention by Human Papillomavirus Vaccination - John T. Schiller and Douglas R. Lowry Cancer Research 2006; 66: (21). November 1, 2006

**Reviewed by Steven Sondheimer, MD**

This article reviews studies describing the potential of new HPV vaccines to prevent cervical cancer deaths. Of course, prevention of cervical cancer is the most important benefit of the HPV vaccine but at this time we only have data on the surrogate marker, the prevention of high grade squamous intraepithelial lesions (HSIL), a cancer precursor. Prevention of cervical cancer deaths is assumed to follow but is not certain and this article reviews areas of debate. According to Schiller, the longest follow-up to date finds close to 100% prevention of HSIL after almost four years. Though reassuring, diminution of protection over time and the need for a booster shot are still not known.

Both vaccines are structured against HPV types 16 and 18, the two most common HPV types associated with cervical cancer. Cross protection against less frequent oncogenic types is possible but unknown.

Of potentially the greatest importance will be the availability and acceptability of the vaccine in economically depressed areas of the world where there are not effective screening programs and cervical cancer remains a common cause of cancer death.

In men, unlike women, most of the surface area of the male genitalia is skin rather than mucosal membrane so that the vaccine induced antibodies may be less protective against HPV. The commonly asked question and lay assumption that the HPV vaccine will be effective in men is still not answered, but studies are ongoing.