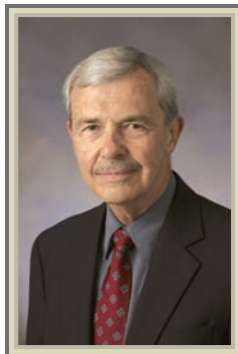


Advisory Board



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Scott A. Sullivan, MD, MSCR is an Assistant Professor and Residency Program Director in the Department of Obstetrics and Gynecology at the Medical University of South Carolina. Dr. Sullivan's career extends across both private practice and academics. He is an active researcher, clinician, and teacher, with interests in infectious disease, epidemiology, and public health. He has won several research awards. He also serves on numerous committees, advisory teams, and editorial boards.



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Dr. Edward Grendys is an Associate Clinical Professor in the Division of Gynecologic Oncology at Northwestern University, Feinberg School of Medicine. He recently moved his practice to Fort Myers from Chicago and before that was in Tampa, Florida where he was an Associate Professor in the Department of Interdisciplinary Oncology at the University of South Florida School of Medicine. Here he had a significant role in the daily instruction of medical students, obstetric and gynecology residents, and Fellows in Gynecologic and Hematologic Oncology. Dr. Grendys was recently awarded an Excellence in Teaching Award by APGO and was also awarded the Excellence in Surgical Teaching Award from the University of South Florida in 2001 and 2002.

Dr. Grendys was the Vice Chairman of the University of South Florida Institutional Review Board and Chairman of the Moffitt Cancer Center's Utilization and Information Management Committee. Dr. Grendys is a reviewer for numerous journals, including the *American Journal of Pathology*, and he has been Guest Editor of *Current Opinions in Obstetric and Gynecology*.



FEATURES

- Pap Testing and the HPV Vaccine —
The Beginning of the End for
Cervical Cancer? 1
- Adenocarcinoma of the Cervix —
The New Screening Opportunity 3
- Pap Test Imaging Provides Value
to Both Patients and the Lab 4

ABSTRACTS IN CERVICAL SCREENING

- Cervical Cancer Prevention in the Era
of Prophylactic Vaccines: A Preview
for Gynecologic Oncologists 5
- Number of Cervical Biopsies and
Sensitivity of Colposcopy 5
- Cervical Cancer Screening,
Abnormal Cytology Management,
and Counseling Practices in the
United States 6
- Comparison of Computer-assisted
and Manual Screening of Cervical
Cytology 6
- Improving Women's Experience
During Speculum Examinations
at Routine Gynaecological Visits:
Randomised Clinical Trial 7
- Incidence of Cervical Cytological
Abnormalities With Aging in
the Women's Health Initiative:
a Randomized Controlled Trial 7

BIOGRAPHIES

- Advisory Board 8

Trends in Cervical Health is an exciting new quarterly eNewsletter for healthcare professionals and laboratories. Trends in Cervical Health will deliver the latest clinical news, reflect peer opinion and examine current cervical health issues to help you stay informed. Each issue will also introduce an Advisory Board made up of opinion leaders who will provide their unique perspective on the most significant current literature published in leading cervical health journals.

Pap Testing and the HPV Vaccine— The Beginning of the End for Cervical Cancer?

The professional dialogue concerning Pap testing has intensified in recent years because of the widespread adoption of liquid-based cytology, the introduction of Human Papillomavirus (HPV) testing, and importantly, the recent FDA approval of the HPV vaccine.

The American College of Obstetricians and Gynecologists (ACOG) recently released clinical recommendations for the HPV vaccine, in which they encourage use of the vaccine in females aged 9 to 26 years.¹ It was noted that data on the vaccine in women older than 26 years and in males is insufficient to make recommendations in these populations.¹ The Advisory Committee on Immunization Practices recommends that girls routinely receive the vaccine between ages 11 and 12 years, although obstetrician-gynecologists may not see many girls in this age range. ACOG recommends that the first reproductive health care visit should occur at ages 13 to 15 years and suggests that this represents an ideal time to discuss the potential benefits of the HPV vaccine and offer it to patients.¹

The Gardasil™ (quadrivalent human papillomavirus types 6, 11, 16, 18, recombinant vaccine) HPV vaccine protects against four strains of HPV (genotypes 6, 11, 16, and 18). Types 16 and 18 are responsible for 70% of cervical cancers while types 6 and 11 are responsible for 90% of genital warts.² Because the other 30% of cancer-causing strains not covered by the vaccine, ACOG emphasizes that current cervical cytology screening recommendations remain unchanged and these should be followed regardless of vaccination

Pap Testing and the HPV Vaccine (continued)

status. ACOG states that “the vaccine is a preventative tool and is not a substitute for cancer screening.”¹ Only a cytology-based Pap test can indicate the presence or absence of disease through detection of abnormal changes in cervical cells. ACOG recommends that Pap screening should begin within 3 years of sexual intercourse (or by age 21 years) and then occur annually until age 30 years. Most women can then continue annual testing or choose to be tested every 2 to 3 years after three consecutive negative Pap tests.¹

ACOG recommends vaccination for sexually active women aged up to 26 years, although they should be counseled that it may be less effective if the patient has already been exposed to HPV. Women with previous cervical intra-epithelial neoplasia (CIN) can also be vaccinated, although they should be counseled that benefits may be limited. ACOG emphasizes the need for annual cervical cytology screening in both these patient types.¹

HPV testing as a criterion prior to vaccination is not currently recommended. ACOG guidelines state that testing provides information on current infections only and that assays can be unreliable and are not widely available.¹ Increased costs associated with including a screening requirement would also reduce the cost-effectiveness of vaccination.¹

Cervical cancer is the world’s second leading cause of cancer death in women, with an estimated 493,000 new cases and 274,000 deaths every year. The recently approved HPV vaccine represents an important advance in cervical cancer prevention particularly in countries without organized screening programs. It should be emphasized that routine cervical cytology screening still remains vital because of the other 30% of cancer-causing strains not covered by the vaccine. Thus, with widespread use of the HPV vaccine and continued routine Pap testing, there is great potential to further decrease the incidence of cervical cancer in future generations.^{1, 3, 4}

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- GARDASIL is a registered trademark of Merck & Co., Inc.

Adenocarcinoma of the Cervix—the New Screening Opportunity

The cause of the increase in cervical adenocarcinoma is unclear, but it is of particular concern as studies have shown that glandular disease is often at a more advanced stage when detected. At diagnosis, adenocarcinomas tend to be large and bulky, and local recurrence is more common in such lesions.¹ One study of high-risk patients showed that within 1 year of the initial atypical glandular cell (AGC) diagnosis, preneoplastic or neoplastic lesions were detected in 87.3% of patients.² In addition,

adenocarcinomas have been reported to have a higher fatality rate than other cervical cancers, including squamous cell lesions.³ In part, the advanced stage of these lesions is related to the difficulty associated with detecting them. Precancerous lesions are asymptomatic, and the conventional Pap smear is recognized as having a lower sensitivity for detecting glandular lesions compared with squamous cell carcinomas.⁴ Adenocarcinomas arise from endocervical glands which

Adenocarcinoma of the Cervix—the New Screening Opportunity (continued)

are less visible than ectocervix squamous cells making detection a challenge.

Fortunately, one of the liquid-based Pap tests, The ThinPrep® System, has FDA-approved labeling that references multiple peer-reviewed publications which report on the improved ability of the ThinPrep® 2000 System to detect glandular disease versus the conventional Pap smear.^{5, 6, 7, 8, 9, 10} The greater predictive value of this cytologic method is important, since a significant percentage of women with AGC will have high-grade preinvasive squamous disease, adenocarcinoma, adenocarcinoma in situ, or invasive cancers from sites other than the cervix.^{11, 12, 13}

Because of this high likelihood that AGC is associated with significant disease, aggressive follow-up has been highly recommended for these patients. If all initial evaluations (colposcopy and cone biopsy) produce normal results, follow-up should include four consecutive Pap smears every 4 to 6 months.^{11, 12, 13}

Although the cause of the increase in cervical adenocarcinoma is unclear, probable risk factors include history of uterine disease, certain hormone use, sexual history, and HPV infection. When HPV is found in AGC cases, it is predominantly HPV 18 or 16. However, unlike squamous lesions, HPV type 18 is more commonly seen with adenocarcinomas than type 16.^{2, 13, 14, 15, 16} It should be noted that the role of HPV in glandular disease has not yet been elucidated and that HPV DNA testing is not included in recommendations for AGC follow-up.¹² As stated in the Digene® HPV test Instructions for Use, “There is no known utility for HPV testing in Pap AGUS results.”¹⁷ Recent publications have cited that up to 57% of glandular abnormalities found in Pap testing may be HPV negative.¹⁴

With the rising incidence of cervical adenocarcinoma, routine cervical screening with new liquid-based Pap tests and aggressive follow-up of AGC results will play a key role in the early detection and management of this challenging diagnosis.

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Pap Test Imaging Provides Value to Both Patients and the Lab

Early detection is crucial in preventing and treating cervical cancer. There are no noticeable early-warning symptoms or physical changes, yet when it is detected early, it is one of the most treatable and curable of all cancers. As a result, the accuracy of cervical screening is crucially important.¹ In the last 10 years liquid-based Pap testing has largely replaced the Pap smear, because of the improved specimen quality and improved sensitivity. However, after the test vial leaves the physician's office, optimizing the screening process in the laboratory is key in assuring screening accuracy.

Efforts to automate cervical screening began shortly after widespread introduction of the Pap smear in the 1950s. This proved challenging due to the unique human skills required to accurately interpret the Pap smear. It was not until the late 1990s that the first computer imager for Pap smears was approved by the Food and Drug Administration (FDA) for quality-control procedures; however, it was met with little commercial success, most likely due to a lack of clinical data demonstrating a significant increase in disease detection, exclusion of high risk patients, and suspicion towards computer-only slide review.

In 2003, the FDA approved the first fully integrated, interactive computer imaging system that assists cytotechnologists in the primary screening of ThinPrep® slides. The FDA approved labeling claims include increased sensitivity and specificity (based on a statistically significant improvement in sensitivity for ASC-US+ and specificity for HSIL+).⁴ A key attribute of the ThinPrep Imaging System is "Dual Review™" technology which ensures every slide is analyzed by the Imager and also screened by a cytotechnologist. Cells of interest are

highlighted for cytotechnologists' review, helping them to better focus interpretative skills.

Independent publications have confirmed and extended the results of the FDA trials. Lozano et al. state that "Increases in the detection of LSIL and HSIL lesions are not only statistically significant but are also clinically significant," while Dziura et al. note that "Biopsy results confirmed a significant increase in the detection of HSIL."^{2,3} In addition, this technology has demonstrated a 39% reduction in false negative fraction over manual screening based on a statistically significant improvement in sensitivity for ASC-US+.⁴ Emerging data continue to substantiate claims of increased disease detection and reduced occurrence of false negative screening with the ThinPrep Imaging System with Dual Review™ vs manually screened ThinPrep slides.⁵ As summarized by Dziura et al., "The merger of mind and computer... has created a better Pap test."² In addition, in contrast to the previous imaging systems, the ThinPrep Imaging System is FDA approved for use with high-risk patients.

Cervical cancer has been described by the FDA as a "silent cancer." While many cancers cause pain, detectable lumps, or other early symptoms, cervical cancer has no associated symptoms until it is so advanced that it is usually unresponsive to treatment.¹ As a result, accurate cervical screening remains key in the early detection and prevention of cervical cancer. The introduction of computer imaging-assisted screening appears to hold great promise in increasing our ability to reduce false negatives compared to manual screening, and this represents an important advance in cervical screening technology.

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Abstracts in Cervical Screening

Cervical Cancer Prevention in the Era of Prophylactic Vaccines: A Preview for Gynecologic Oncologists

Society of Gynecologic Oncologists Education Resource Panel Writing group; Collins Y, Einstein MH, Gostout BS, Herzog TJ, Massad LS, Rader JS, Wright J. *Gynecol Oncol.* 2006;102:552-562.

by Dr. Edward Charles Grendys, Jr., MD, FACOG, FACS

The recent approval of the HPV vaccine represents the beginning of a new era in cervical health in which 70% or more of cervical cancers, as well as precancers and other genital tract malignancies, may be eradicated. This article by the Society of Gynecologic Oncologists aims to provide healthcare professionals with critical knowledge about the HPV vaccine that will allow them to act as providers, educators and policy leaders.

Collins et al. review the "outstanding" HPV vaccine efficacy data and provide clinical guidance for the use of the vaccine. They also note that physician and patient education strategies and worldwide access will be crucial in optimizing vaccine availability and use, hence producing the greatest reduction in cervical cancer.

While the HPV vaccine represents an important advance in cervical cancer prevention, Collins et al. emphasize that screening remains an important part of the comprehensive strategy to prevent cervical cancer. They state that it is "vitaly important that both vaccinated and unvaccinated women continue to fully engage in cervical cancer prevention, including cervical cancer screening, follow-up of abnormal screens, and treatment of premalignant lesions." Finally, the key role of gynecologic oncologists in promoting optimal prevention practices is emphasized.

Number of Cervical Biopsies and Sensitivity of Colposcopy

Gage JC, Hanson VW, Abbey K, Dippery S, Gardner S, Kubota J, Schiffman M, Solomon D, Jeronimo J; ASCUS LSIL Triage Study (ALTS) Group. *Obstet Gynecol* 2006;108:264-272.

by Dr. Edward J. Wilkinson, MD

The major purpose of colposcopy in the US is to improve visualization of the cervical transformation zone and direct biopsies to suspected precancerous or cancerous lesions. However, Gage et al. note that colposcopy is a subjective procedure with limited reliability. In particular, it is not optimally sensitive for detection of all cervical intraepithelial neoplasia (CIN) 3 or more severe lesions. As a result of this variation in sensitivity, it has been suggested that two or more biopsies, rather than a single biopsy, should be taken.

This analysis evaluated the factors influencing the sensitivity of the enrollment colposcopic procedure in 408 women with an adequate enrollment colposcopy and a diagnosis of CIN 3 or more severe lesions over 2 years in the ASCUS-LSIL Triage study.

Results showed that colposcopy with guided biopsy (or biopsies) detects only approximately two-thirds of CIN 3 or more severe lesions. The sensitivity of the procedure was not found to differ significantly by type of medical training, but it was greater when two or more biopsies were taken. Gage et al. conclude that as women are referred to colposcopy based on increasingly sensitive screening tests, there is a need to have an optimally accurate diagnostic examination, and taking two or more biopsies during the colposcopic procedure can improve sensitivity.

Cervical Cancer Screening, Abnormal Cytology Management, and Counseling Practices in the United States

Irwin K, Montano D, Kasprzyk D, Carlin L, Freeman C, Barnes R, Jain N, Christian J, Wolters C. *Obstet Gynecol*. 2006 Aug;108(2):397-409.

by Dr. Scott A. Sullivan, MD, MSCR, FACOG

The authors of this study evaluated surveys from 2004 in the United States regarding clinician use of the human papillomavirus (HPV) test. In addition, knowledge of and adherence to recommended HPV guidelines was assessed. A cross section of clinicians were surveyed including Ob/Gyns, internists, nurse practitioners and family physicians. A total of 2980 surveys were analyzed, which represented an 82% response rate.

Most of those surveyed indicated some knowledge of the HPV test (91%), but only 66% reported having ever used the HPV test. Only 21% of those surveyed used HPV testing as an adjunct to cytology. Those who did more frequently tested women under the age of 30 than older women. Nearly 60% of those surveyed also indicated using HPV testing for LGSIL and higher lesions. Both practices are contrary to published HPV testing guidelines.

This was a large and well designed survey study. This study is important because it provides a current look at actual practices and perceptions at the doctor-patient level. It indicates relatively high use of the HPV test in cervical cancer screening, but a variable level of understanding of the test specifics. It also shows that there is common use of HPV testing outside of published guidelines. This finding underscores the need for continued clinician education on evidence based use of the HPV test. This education will help to reduce unnecessary testing and improve cost effectiveness.

Comparison of Computer-assisted and Manual Screening of Cervical Cytology

Lozano R. *Gynecol Oncol*. 2006; doi:10.1016/j.y.gyno.2006.07.025.

by Dr. Edward Charles Grendys, Jr., MD, FACOG, FACS

The Pap smear is widely credited with having significantly reduced morbidity and mortality due to cervical cancer since its introduction more than half a century ago. Since this time, there have been efforts to automate cervical cytology screening driven mainly by a shortage of skilled cytotechnologists. This study aimed to evaluate the diagnostic performance of The ThinPrep® Imaging System in routine use in a high-volume independent laboratory.

Study results showed that the Imager increased disease detection of HSIL+ by 38% and LSIL by 46% compared with manual screening. Lozano notes that these results are not only statistically significant but are also clinically significant. Biopsy confirmation results showed that the positive predictive value for a computer-assisted HSIL diagnosis remained high, reflecting the accuracy of The ThinPrep® Imaging System.

Lozano concludes that The ThinPrep® Imaging System has “successfully combined modern computer technology and image analysis with the unique human interpretive skills of the cytotechnologist and pathologist.” He suggests that this technology will make an important contribution to the success of cervical cancer screening and patient management.

Improving Women’s Experience During Speculum Examinations at Routine Gynaecological Visits: Randomised Clinical Trial

Seehusen DA, Johnson DR, Earwood JS, Sethuraman SN, Cornali J, Gillespie K, Doria M, Farnell E 4th, Lanham J. *BMJ*. 2006 Jul 22;333(7560):171. Epub 2006 Jun 27.

By Dr. Scott A. Sullivan, MD, MSCR, FACOG

The authors attempted to compare patients’ reported discomfort, vulnerability and loss of control between pelvic examinations conducted with stirrups and without. This was a randomized clinical trial with 204 patients enrolled.

Patients reported decreased mean discomfort scores (95% CI -19.7 to -6.8) and sense of vulnerability (95% CI -16.6 to -4.4) in the study. No difference in sense of control was reported.

This trial is important as the authors have shown improved patient satisfaction with pelvic examinations when stirrups were not used. Fear has been previously shown to decrease compliance rates with cervical screening.¹ Modifications to examination technique could be a mechanism to increase compliance. A larger trial is needed to test his hypothesis and to explore the previously reported increase in inadequate specimens using this technique.

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Incidence of Cervical Cytological Abnormalities With Aging in the Women’s Health Initiative: A Randomized Controlled Trial

Yasmeen S, Romano PS, Pettinger M, Johnson SR, Hubbell FA, Lane DS, Hendrix SL. *Obstet Gynecol* 2006;108:410-419.

by Dr. Edward J. Wilkinson, MD

Yasmeen et al. note that although 25% of new cases of cervical cancer occur among the 13% of women aged 65 years or older, few studies have focused on cervical cancer screening in this population. Confusingly, current screening recommendations range from discontinuing screening at age 65 years to less frequent, lifelong screening.

This longitudinal analysis estimated the incidence of cytological abnormalities and cervical cancer on routine cytology in a prospective cohort of 16,608 postmenopausal women participating in the Women’s Health Initiative (WHI) clinical trial of estrogen plus progestin. The effects of independent risk factors for acquiring HSIL and cervical cancer were also estimated.

Results showed that use of estrogen plus progestin was associated with increased incidence of any cytologic abnormality, although it had no impact on the incidence of HSIL or cervical cancer. It was also noted that current recommendations to discontinue screening for this population do not take into account risk factors such as hormone therapy, continuing sexual activity, and associated exposure to human papillomavirus. Yasmeen et al. concluded that unmarried, sexually active, older women may benefit from continued cervical cancer screening, even if they previously had normal cervical cytology.