

eprodiate, colchicine, and their interaction, stratified according to baseline nephrotic status), indicating that eprodiate had similar benefits for patients who received colchicine and patients who did not receive colchicine. Thus, the observed differences in outcomes in the two treatment groups were not due to differential use of colchicine.

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1. Zemer D, Pras M, Sohar E, Modan M, Cabili S, Gafni J. Colchicine in the prevention and treatment of the amyloidosis of familial Mediterranean fever. *N Engl J Med* 1986;314:1001-5.

DRS. LACHMANN AND HAWKINS REPLY: Manenti and colleagues incorrectly deduced that in our study, patients with AA amyloidosis associated with diseases other than familial Mediterranean fever were likely to have been treated with colchicine.

Colchicine is of singular benefit in patients with AA amyloidosis associated with familial Mediterranean fever because it greatly suppresses this particular chronic inflammatory disease. Their suggestion that colchicine might be beneficial in kidney disease due to other mechanisms of action is not supported by the similar renal outcomes among the 20 patients with familial Mediterranean fever who received colchicine and the other 354 patients with other underlying inflammatory diseases who did not (relative risk of end-stage renal failure in the patients with familial Mediterranean fever, 1.51; 95% CI, 0.61 to 3.75; $P=0.37$). Furthermore, treatment with colchicine has the potential for severe toxic effects, the risk of which is increased in the presence of renal impairment. Even modest doses can cause diarrhea or vomiting that may precipitate irreversible end-stage renal failure in patients with amyloidosis.

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Human Papillomavirus Vaccine

TO THE EDITOR: In their editorial about the availability of a quadrivalent vaccine against human papillomavirus (HPV) (Gardasil, Merck) that was reported on by Garland et al.¹ and by the Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE) II Study Group² (May 10 issue), Sawaya and Smith-McCune³ raise concerns regarding the adequacy of cervical dysplasia as an efficacy end point, disease due to HPV types not associated with the vaccine, the lower efficacy of the vaccine among women who were previously infected with HPV than among those who had never been infected, and the need for continued Papanicolaou screening after vaccination. The approval by the Food and Drug Administration (FDA) of the quadrivalent HPV vaccine relied on the end points of moderate or severe cervical dysplasia (grade 2 or 3 cervical intraepithelial neoplasia [CIN 2/3]) or adenocarcinoma in situ, or end points reflecting more severe disease, because these histopathological findings represent precursor lesions for cervical cancer, and a diagnosis of CIN 2/3 with colposcopy results in treatment by means of excision or ablation.⁴ The FDA-approved label clearly in-

forms health care providers of the other concerns: Gardasil “does not prevent infection with the HPV types not contained in the vaccine”; it “reduced the overall rate of CIN 2/3 or AIS [adenocarcinoma in situ] caused by vaccine or non-vaccine HPV types by 12.2% (95% CI [confidence interval]: -3.2%, 25.3%)” in women, regardless of their baseline HPV status; there is “no clear evidence of protection from disease caused by HPV types for which subjects were PCR [polymerase chain reaction] positive and/or seropositive at baseline”; and women receiving “Gardasil should continue to undergo cervical cancer screening per standard of care.”⁵

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1. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928-43.

2. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.

3. Sawaya GF, Smith-McCune K. HPV vaccination — more answers, more questions. *N Engl J Med* 2007;356:1991-3.

4. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;189:295-304.
5. Gardasil [quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine]. Whitehouse Station, NJ: Merck, 2006 (package insert). (Accessed August 23, 2007, at <http://www.fda.gov/cber/label/hpvmer040307LB.pdf>).

TO THE EDITOR: In their article on introducing HPV vaccine in developing countries, Agosti and Goldie (May 10 issue)¹ suggest that “ideal” cervical-cancer prevention programs for developing countries should include HPV vaccination. This suggestion will remain premature until long-term follow-up data exclude the possibility that HPV vaccination may be ineffective for the prevention of invasive cervical carcinoma. Because it is uncertain when such data will become available, it is essential in the meantime for developing countries to allocate their limited resources toward screening, rather than vaccination.

Cytologic screening is feasible anywhere cervical screening is appropriate and is the only preventive option currently available for public-sector control of cervical cancer in developing countries.² Past and current failures of cervical-cancer prevention efforts in developed and developing countries are attributable not to factors specific to cytologic testing, but rather to lapses of political will and quality management — to which all preventive interventions, including vaccines, are vulnerable.²

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1. Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries — key challenges and issues. *N Engl J Med* 2007;356:1908-10.
2. Suba EJ, Donnelly AD, Furia LM, Huynh ML, Raab SS. Cervical cancer prevention for all the world's women: genuine promise resides in skilled quality management rather than novel screening approaches. *Diagn Cytopathol* 2007;35:187-91.

DRS. GARLAND AND KOUTSKY REPLY: Miller and colleagues discuss the widely accepted concept that CIN 2/3 and adenocarcinoma in situ are precancerous cervical lesions. In HPV-vaccine trials, such lesions serve as surrogate end points for cervical cancer because follow-up without treatment is not an

ethical option^{1,2} and appropriate excisional or ablative treatment usually prevents progression to invasion. Moreover, the World Health Organization endorses these end points for the assessment of prophylactic vaccine efficacy.³ Since rates of progression are lower for CIN 2 than for CIN 3 and adenocarcinoma in situ,⁴ it is noteworthy that a combined analysis of the data from the HPV-6/11/16/18 and HPV-16 vaccine trials showed significant, high-level efficacy (≥97%) for prevention of the separate HPV-16/18–related end points of CIN 2, CIN 3, and adenocarcinoma in situ among women who did not have infection with HPV-16/18 on day 1.⁵

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1. Garland SM, Hernandez-Avila M, Wheeler CM, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007;356:1928-43.
2. The FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med* 2007;356:1915-27.
3. Pagliusi SR, Teresa Aguado A. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine* 2004;23:569-78.
4. Wright TC Jr, Cox JT, Massad LS, et al. 2001 Consensus guidelines for the management of women with cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 2003;189:295-304.
5. The FUTURE II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. *Lancet* 2007;369:1861-8.

THE EDITORIALISTS REPLY: The FDA-approved label provided an important first look at evidence in support of vaccine efficacy and safety; recently published interim analyses from these ongoing phase 3 trials provided a second look. Our editorial raised additional unanswered questions beyond the concerns addressed by Miller et al., including overall vaccine efficacy in women unexposed to relevant vaccine HPV types, effect on cytologic abnormalities, and effect on disease caused by HPV types not included in the vaccine. The last question is particularly important, in light of the surprising report of vulvar cancer in a 22-year-old trial participant who received the vaccine¹; vulvar cancer is rare (overall incidence, 2.2 cases per 100,000 persons) and occurs at a median age of 68 years in the United States.² This finding and the

cited unanswered questions argue for a cautious approach to vaccination policy until trials have been completed and fully reported.

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1. Joura EA, Leodolter S, Hernandez-Avila M, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 2007;369:1693-702.
2. Cancer of the vulva. Bethesda, MD: National Cancer Institute, 2007. (Accessed August 23, 2007, at <http://seer.cancer.gov/statfacts/html/vulva.html>.)

DRS. AGOSTI AND GOLDIE REPLY: As we noted, the need for long-term follow-up data are important, which Suba and Raab emphasize. Furthermore, it is imperative that momentum behind efforts in the past decade to develop feasible options for cervical-cancer screening in low-resource settings continues to build. The Bill and Melinda Gates Foundation provided \$55.6 million to the Alliance for Cervical Cancer Prevention to promote screening and \$13 million toward the development of low-cost HPV DNA tests and other tests. We believe it is inequitable to exclude women in developing

countries from the potential benefits of vaccination, new technology, and screening approaches that appear to be promising.¹

We emphasized that an integrated approach that includes screening and vaccination is likely to prevent the greatest number of deaths from cervical cancer. However, countries will make their own decisions about the best strategic approach to cervical-cancer prevention, accounting for local epidemiologic factors and disease burden,² competing priorities, and the cost-effectiveness, affordability, and feasibility of vaccination programs targeting adolescents and the screening of adult women. We urge that attention be given to real-world solutions for preventing death from cervical cancer in women living in poverty.

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1. Sankaranarayanan R, Esmay PO, Rajkumar R, et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomized trial. *Lancet* 2007;370:398-406.
2. World Health Organization. WHO/ICO (Institut Català d'Oncologia) Information Centre on HPV and cervical cancer. (Accessed August 23, 2007, at <http://www.who.int/hpvcentre>.)

Human Papillomavirus and Oropharyngeal Cancer

TO THE EDITOR: The study by D'Souza et al. (May 10 issue)¹ on oropharyngeal squamous-cell carcinomas associated with human papillomavirus (HPV) provides important epidemiologic insights into a cancer that is becoming increasingly common in the United States.² However, the molecular mechanisms of carcinogenesis in HPV-associated oropharyngeal squamous-cell carcinomas remain unclear.

The integration of HPV type 16 (HPV-16) into the host genome is an important mechanism in cervical carcinogenesis,³ but there is no direct evidence that this process occurs in oropharyngeal squamous-cell carcinomas. The authors state that Southern blot, real-time polymerase-chain-reaction (PCR), and fluorescence in situ hybridization analyses⁴ have established integration sites but that these methods provide only indirect evidence. Direct evidence would require observation of the viral DNA sequence either flanked or attached to

one end of human DNA (junction sequences). Melin et al.⁵ did not observe this finding in HPV-16-positive tonsillar carcinomas. We previously used restriction-site PCR in more than 100 HPV-16 and HPV-18 cervical cancers to identify many of these junction sequences.⁶ However, when we used this same technique in 40 oropharyngeal squamous-cell carcinomas that were positive for HPV-16, we did not detect junction sequences (unpublished data). This finding, which suggests a mechanism of carcinogenesis that is distinct from that in cervical cancer, warrants further investigation.

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1. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. *N Engl J Med* 2007;356:1944-56.