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Perspective Editor
New England Journal of Medicine
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Re: Cervical-Cancer Screening—New Guidelines and the Balance between Benefits and Harms (09-12834).

Dear Dr. Malina:

I am writing to ask you to reconsider your decision to not accept for publication in the *Journal* my *Perspective* submission, entitled "Cervical-Cancer Screening—New Guidelines and the Balance between Benefits and Harms" (09-12834). This request is based on the provision of *Section 2.1.9 Considering Appeals for Reconsideration of Rejected Manuscripts*, published by The Council of Science Editors in its white paper (the White Paper) on the Roles and Responsibilities in Publishing. Since the New England Journal of Medicine is a leading member journal of the Council, I assume it also follows the editorial policies of the Council.

Your email of January 19, 2010 did not mention the opinion of any external reviewers on my submission. According to the White Paper, reasons for the editors to reject manuscripts without external review are usually that the manuscript is outside the scope of the journal, does not meet the journal's quality standards or is of limited scientific merit, or lacks originality or novel information. Without giving any specific comments, your email simply informed me of your decision promptly so that I *"can submit it elsewhere"* because the editorial staff seemed to be concerned about the "focus, content and interest" of the submission. I am wondering if it may help for your reconsideration if I spell out these concerns as follows, assuming that the issue is how to "*minimize screening harms*" as stated in Dr. Sawaya's Perspective.

First, the "focus" of the submission is to put on record the dissenting evidence to balance Dr. Sawaya's one-sided blanket endorsement of the American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin No. 109 for cervical cancer screening. The key components of the "content" in the submission are direct *verbatim* quotations and data cited from third-party publications in peer-reviewed scientific journals, with supportive source references

accessible through the United States National Library of Medicine website, www.pubmed.gov . The "interest" is to search for a truthful etiology for the excessive number of unnecessary colposcopic biopsies, a harmful practice which can no longer be ignored by the ACOG, evidenced by its issuing the Practice Bulletin No. 109 to replace its Practice Bulletin No. 45 issued 6 years earlier under an identical title. I believe that to convey the focus, contents and interest of my submission to the readers is consistent with the *Journal's* stated "mission to publish current, authoritative, and unbiased information about advances in medical research".

The dissenting evidence presented in my submission indicates that the real cause for the recent upsurge of unnecessary colposcopic biopsies was the introduction of the liquid-based Pap cytology and the Digene's HC2 HPV assay being used as a cancer-screening triage, both of which were first recommended as guidelines in the ACOG Practice Bulletin Number 45 entitled "Cervical Cytology Screening" published in 2003. It seems apparent that ACOG now tried to whitewash the practice leading to excessive unnecessary biopsies by blaming "over use" of Pap tests among women below 21 years of age, instead of dealing with its incorrect guidelines. The dissenting evidence indicates that ACOG's judgment might have been under the influence of the cash-rich medical device manufacturers. ACOG Bulletins No. 45 and No. 109, both recommending widespread uses of the liquid-based cytology to perform Pap test and the Digene's HPV assay as the triage to determine the need for referrals to colposcopic biopsies, were largely based on publications written by "experts" directly or indirectly receiving monetary benefits from these device manufacturers or co-authored by employees of the device manufacturers. For example, in Practice Bulletin No. 109, eight (8) references were quoted to support the statement "The utility of HPV DNA testing has been well documented for the primary triage of cervical cytology test results read as ASC-US (45, 83-88)." A little more in-depth reading of these references showed that they were largely written by paid consultants of the medical device manufacturer or its employees, or their contents did not really support a safe and effective use of HPV assays as the primary triage of cervical cytology test results read as ASC-US. In fact, **Ref.#86** concluded in **2000** the HPV triage was used to increase detection sensitivity of CIN "**at the expense of specificity"** (increased unnecessary biopsies).

The results of analysis of these 8 references quoted in ACOG Practice Bulletin No. 109 are summarized as follows.

Ref. #45 The lead author was T.C. Wright. On public record, an Editor's note in another journal stated in 2000 that "*A. Lorincz is Scientific Director of Digene Corporation, R. M. Richart holds stock in and is a consultant to Digene Corporation, and T. C. Wright conducts research sponsored by Digene Corporation and is a member of their speaker's bureau."* [1]. I have personally attended some of these manufacturer-provided Powerpoint presentations by Dr. Wright.

Ref. #83. The footnote of Ref. #83 stated: Funding/Support: This study was funded by a grant from the Kaiser Permanente Innovations Program (Drs Manos, Kinney, and Hiatt), and by grants, technical support, reagents, supplies, and equipment from Cytyc Corporation and Digene Corporation, (Dr Manos).

Financial Disclosure: Drs Manos, Kinney, and Sherman have received grants or supplies from Cytyc Corporation, Boxborough, Mass, and Digene Corporation, Beltsville, Md. Drs

Manos and Kinney have received honoraria for speaking from Cytyc and Digene. Dr Manos owns shares of Cytyc common stock.

Ref. #84. The relationship of co-authors Wright TC, Jr., Lorincz A and Richart RM with Digene Corporation was already mentioned above [1].

Ref. #85. This report only addressed the cost issue by stating "The cost of reflex HPV testing using conventional smear or liquid-based media was less than routine colposcopy ($4809 and $4308, respectively, versus $4875 per case detected)."

Ref. # 86. The CONCLUSION of this article was "Compared with repeat cytology, combined triage with HPV testing markedly improves sensitivity for detecting CIN in women with ASCUS, but **at the expense of specificity**." In fact, it predicted the rise of unnecessary colposcopic biopsies because the HPV testing was low in specificity.

Ref. #87. No authors were named in this reference. But ASCUS-LSIL Triage Study Group was largely composed of people who co-authored with A. Lorincz articles (see below) promoting Digene HPV assay to be used as triage for referrals to colposcopic biopsies.

Ref. # 88. Conflicts of Interest: C.J.L.M. Meijer is member of the advisory board of Qiagen (formerly Digene) and received lecture fee from GSK. E.L. Franco provided occasional consultation to Gen-Probe and Roche. G. Ronco provided occasional consultation to Gen-Probe. F.X. Bosch provided occasional consultation to Qiagen and Roche. J. Cuzick is member of the advisory boards of Qiagen, Roche and Gen-Probe. P.J.F. Snijders provided occasional consultation to Roche and Gen-Probe. Qiagen, Gen-Probe and Roche are companies involved with HPV diagnostics. # C Simoens and M Arbyn received travel funding from GSK and SPMSD, respectively (before 2008). P Van Damme has been principal investigator of bivalent and quadrivalent HPV vaccine trials, for which the University of Antwerp obtains contractual funding. All other authors declare no conflict of interest.

A brief online search revealed that A. Lorincz, as the senior scientific officer of Digene Corporation, recruited as company consultants from various academic institutes and government agencies as his co-authors in the following publications to promote Digene's HPV assays for detection of cancer and as the triage to colposcopic biopsies. In one of the articles which Dr. Lorincz co-authored in 2003 [11], it was concluded that **the HPV assays increased the number of colposcopy referrals** in a study conducted in Mexico, where the cervical cancer prevalence was significantly higher than in the US general population**.** Dr. Sawaya and the authors of the ACOG Practice Bulletins No. 45 and No.109 knew or should have known these dissenting data already published between 2000 and 2003, but chose to ignore them.

Reference articles (not a complete list) co-authored by A. Lorincz with paid consultant experts to promote Digene HPV testing while knowing it would increase the number of colposcopic biopsies

1. Kuhn L, Denny L, Pollack A, Lorincz A, Richart RM, Wright TC. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. J Natl Cancer Inst. 2000 May 17;92(10):818-25.

2. Castle PE, Sadorra M, Garcia FA, Cullen AP, Lorincz AT, Mitchell AL, Whitby D, Chuke R, Kornegay JR. Mouthwash as a low-cost and safe specimen transport medium for human papillomavirus DNA testing of cervicovaginal specimens. Cancer Epidemiol Biomarkers Prev. 2007 Apr;16(4):840-3.

3. Hesselink AT, Bulkmans NW, Berkhof J, Lorincz AT, Meijer CJ, Snijders PJ. Cross-sectional comparison of an automated hybrid capture 2 assay and the consensus GP5+/6+ PCR method in a population-based cervical screening program. J Clin Microbiol. 2006 Oct;44(10):3680-5.

4. Khan MJ, Castle PE, Lorincz AT, Wacholder S, Sherman M, Scott DR, Rush BB, Glass AG, Schiffman M. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. J Natl Cancer Inst. 2005 Jul 20;97(14):1072-9.

5. Castle PE, Schiffman M, Scott DR, Sherman ME, Glass AG, Rush BB, Schussler JE, Wacholder S, Lorincz AT. Semiquantitative human papillomavirus type 16 viral load and the prospective risk of cervical precancer and cancer. Cancer Epidemiol Biomarkers Prev. 2005 May;14(5):1311-4.

6. Castle PE, Garcia-Meijide M, Holladay EB, Chuke R, Payne J, Long A, Siefers H, Demuth F, Lorincz AT. A novel filtration-based processing method of liquid cytology specimens for human papillomavirus DNA testing by hybrid capture II. Am J Clin Pathol. 2005 Feb;123(2):250-5.

7. Mattosinho de Castro Ferraz Mda G, Nicolau SM, Stávale JN, Focchi J, Castelo A, Dôres GB, Mielzynska-Lohnas I, Lorincz A, Rodrigues de Lima G. Cervical biopsy-based comparison of a new liquid-based thin-layer preparation with conventional Pap smears. Diagn Cytopathol. 2004 Apr;30(4):220-6.

8. Lörincz AT. Screening for cervical cancer: new alternatives and research. Salud Publica Mex. 2003;45 Suppl 3:S376-87. Review.

9. Obiso R, Lorincz A. Digene Corporation. Pharmacogenomics. 2004 Jan;5(1):129-32.

10. Castle PE, Lorincz AT, Scott DR, Sherman ME, Glass AG, Rush BB, Wacholder S, Burk RD, Manos MM, Schussler JE, Macomber P, Schiffman M. Comparison between prototype hybrid capture 3 and hybrid capture 2 human papillomavirus DNA assays for detection of high-grade cervical intraepithelial neoplasia and cancer. J Clin Microbiol. 2003 Sep;41(9):4022-30.

11. Salmerón J, Lazcano-Ponce E, Lorincz A, Hernández M, Hernández P, Leyva A, Uribe M, Manzanares H, Antunez A, Carmona E, Ronnett BM, Sherman ME, Bishai D, Ferris D, Flores Y, Yunes E, Shah KV. Comparison of HPV-based assays with Papanicolaou smears for cervical cancer screening in Morelos State, Mexico. Cancer Causes Control. 2003 Aug;14(6):505-12. (Both HPV assays detected more cases of CIN2/3 or CC than Pap cytology alone. However, the HPV assays increased the number of colposcopy referrals. Our study suggests that HPV testing could be an effective way to improve the performance of CC screening.)

12. Lytwyn A, Sellors JW, Mahony JB, Daya D, Chapman W, Howard M, Roth P, Lorincz AT, Gafni A, Walter SD. Adjunctive human papillomavirus testing in the 2-year follow-up of women with low-grade cervical cytologic abnormalities: a randomized trial and economic evaluation. Arch Pathol Lab Med. 2003 Sep;127(9):1169-75.

13. Lörincz AT, Richart RM. Human papillomavirus DNA testing as an adjunct to cytology in cervical screening programs. Arch Pathol Lab Med. 2003 Aug;127(8):959-68. Review.

14. Gravitt PE, Burk RD, Lorincz A, Herrero R, Hildesheim A, Sherman ME, Bratti MC, Rodriguez AC, Helzlsouer KJ, Schiffman M. A comparison between real-time polymerase chain reaction and hybrid capture 2 for human papillomavirus DNA quantitation. Cancer Epidemiol Biomarkers Prev. 2003 Jun;12(6):477-84.

15. Sherman ME, Lorincz AT, Scott DR, Wacholder S, Castle PE, Glass AG, Mielzynska-Lohnas I, Rush BB, Schiffman M. Baseline cytology, human papillomavirus testing, and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst. 2003 Jan 1;95(1):46-52.

16. Castle PE, Schiffman M, Burk RD, Wacholder S, Hildesheim A, Herrero R, Bratti MC, Sherman ME, Lorincz A. Restricted cross-reactivity of hybrid capture 2 with nononcogenic human papillomavirus types. Cancer Epidemiol Biomarkers Prev. 2002 Nov;11(11):1394-9.

17. Castle PE, Wacholder S, Sherman ME, Lorincz AT, Glass AG, Scott DR, Rush BB, Demuth F, Schiffman M. Absolute risk of a subsequent abnormal pap among oncogenic human papillomavirus DNA-positive, cytologically negative women. Cancer. 2002 Nov 15;95(10):2145-51.

18. Castle PE, Wacholder S, Lorincz AT, Scott DR, Sherman ME, Glass AG, Rush BB, Schussler JE, Schiffman M. A prospective study of high-grade cervical neoplasia risk among human papillomavirus-infected women. J Natl Cancer Inst. 2002 Sep 18;94(18):1406-14.

19. Castle PE, Schiffman M, Gravitt PE, Kendall H, Fishman S, Dong H, Hildesheim A, Herrero R, Bratti MC, Sherman ME, Lorincz A, Schussler JE, Burk RD. Comparisons of HPV DNA detection by MY09/11 PCR methods. J Med Virol. 2002 Nov;68(3):417-23.

20. Flores Y, Shah K, Lazcano E, Hernández M, Bishai D, Ferris DG, Lörincz A, Hernández P, Salmerón J; Morelos HPV Study Collaborators. Design and methods of the evaluation of an HPV-based cervical cancer screening strategy in Mexico: The Morelos HPV Study. Salud Publica Mex. 2002 Jul-Aug;44(4):335-44.

21. Pretorius RG, Peterson P, Novak S, Azizi F, Sadeghi M, Lorincz AT. Comparison of two signal-amplification DNA tests for high-risk HPV as an aid to colposcopy. J Reprod Med. 2002 Apr;47(4):290-6.

22. Castle PE, Lorincz AT, Mielzynska-Lohnas I, Scott DR, Glass AG, Sherman ME, Schussler JE, Schiffman M. Results of human papillomavirus DNA testing with the hybrid capture 2 assay are reproducible. J Clin Microbiol. 2002 Mar;40(3):1088-90.

23. Terry G, Ho L, Londesborough P, Cuzick J, Mielzynska-Lohnas I, Lorincz A. Detection of high-risk HPV types by the hybrid capture 2 test. J Med Virol. 2001 Sep;65(1):155-62.

The annual financial reports published online by Digene Corporation showed that the company has rewarded Dr. A. Lorincz millions of dollars in the form of salary, bonus and stock shares/options for his efforts in organizing these publications. Based on these publications, aggressive marketing of the Digene HPV assay as the triage tool for referrals to further cancer testing, as recommended by the 2003 ACOG Bulletin No. 45 guidelines, has caused unnecessary harm to many women at any age and added more than $10 billion unnecessary health care expenditure every year in this country. After the harm of excessive unnecessary cervical biopsies was brought to public lights, the ACOG practice Bulletin No. 109 was issued to gloss over the root cause of the excessive unnecessary cervical biopsies to protect the more than $10 billion per year ASCUS/LSIL industry, which will continue to benefit ACOG's due-paying membership, Dr. Sawaya included. In his Perspective, Dr. Sawaya promoted the ACOG practice guidelines by stating *"Although cervical cancer is rare before the age of 21, cytologic abnormalities are common and can lead to labeling, anxiety, extended surveillance, and invasive procedures, such as colposcopy."* Based on the dissenting evidence, one could have easily concluded "**Although cervical cancer is rare in the United States, detections of HPV are common and can lead to labeling, anxiety, extended surveillance, and invasive procedures, such as colposcopy"**. The fundamental scientific flaw of Dr. Sawaya'a Perspective and the ACOG Bulletins No. 45 and 109 is promoting the use of a virology test result as the triage to an invasive procedure to predict a cancerous outcome. As a result, the positive predictive value (PPV) is extremely low.

The Perspective authored by Dr. Sawaya has used the space of the New England Journal of Medicine which is "*possibly the most prestigious medical journal in North America*" (Michele Landsberg, Toronto Star, Dec 21, 1997), to advance the business agenda of a trade organization at the expense of women's health and society. The readers of the *Journal* should know the dissenting evidence which contradicts Dr. Sawaya's Perspective. The right-to-know is generally recognized as one of the basic rights of society in the United States.

I hope the editorial staff of the *Journal* would agree to publish my submission so that we would not have to waste time to resolve this issue in some other formats. If external review is needed for your editorial decision, the reviewers of my submission should not be those who have co-authored publications with an employee of Digene Corporation or Qiagen Corporation due to obvious potential bias because of conflicting interests.

To disclose my competing interests, I am a hospital-based pathologist receiving a fixed salary. I have recently formed a company specializing in transferring the Sanger DNA sequencing technology to clinical laboratories to increase the specificity of HPV detection and genotyping.

I am looking forward to receiving your kind response in 10 days.

Thank you in advance.

Respectfully,

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