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Quality Improvement to Demonstrate the Lack of Reliability of the Human Papillomavirus mRNA Assay to Identify Women With Latent Human Papillomavirus Infections

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Cotton and colleagues [1] highlighted discrepancies between commercially available DNA and mRNA assays in cervical screening. They concluded that latent human papillomavirus (HPV) infections detected by DNA assays but not mRNA tests may pose a risk for cervical cancer [1]. We believe that their article incorrectly interprets what is commonly meant by *latent infection* and also fails to support the conclusion they reach. The term *latent* refers to HPV infections that are suppressed by cell-mediated immunity, such that they are undetectable by either DNA or RNA tests. They are thought to be maintained in the basal layer of the cervical epithelium with minimal replication and can re-activate following immune suppression. The subsequent role of latent infection in leading to cervical cancer is questionable and still under study. In any case, the authors are addressing a different group of infections, ie, the known percentage of HPV infections that test positive for HPV DNA but negative for mRNA. The prospective risk of mRNA-negative, DNA-positive infections is not established, in that no adequately sized cohort study has been reported to establish their rates of progression to high-grade cancer precursor lesions. The correlational study design used by Cotton et al is very inadequate to answer the question. It is important that readers realize that both HPV DNA and mRNA assays have been appropriately approved for clinical use by virtue of large-scale cross-sectional and short-term prospective studies. Whether HPV

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DNA tests confer greater long-term reassurance against risk of cervical cancer awaits the conclusion of rigorous prospective studies not yet completed. The limitations of the study design preclude drawing conclusions about the relative effectiveness of U.S. Food and Drug Administration (FDA)-cleared or approved DNA or mRNA tests for screening or surveillance. Given the strength of the initial validation data, we caution the readers of *Obstetrics & Gynecology* that the authors' conclusions are not adequately supported by their data, and that both FDA-approved mRNA and DNA HPV tests should continue to be used as outlined in screening and surveillance guidelines from the ASCCP, U.S. Preventive Services Task Force, American Cancer Society, and American College of Obstetricians and Gynecologists.

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References

1. Cotton S, et al., Quality Improvement to Demonstrate the Lack of Reliability of the Human Papillomavirus mRNA Assay to Identify Women With Latent Human Papillomavirus Infections. *Obstet Gynecol*, 2018 131(4): p. 681–687. [PubMed: 29528922]