Response

We thank Lynge and Rebolj for contributing to the discussion about whether or not to replace conventional cytology screening with human papillomavirus (HPV) DNA testing. Lynge and Rebolj focus on the role of specificity measures when assessing the burden of false positives on screened women. In our study, we used the rate of recommendations for intensified screening for the same purpose. We feel that this approach was appropriate for the data because some women received the recommendation for intensified screening after a negative colposcopy and histological verification.

Borderline test results that are not clearly indicative of colposcopy caused the main burden of false positives on the women and on the health-care system in both study arms. The definition of a negative screening test suggested by Lynge and Rebolj—Papanicolaou class I or HPV viral load less than 1 pg/mL—has specifically been used as the criterion for a normal screening interval (ie, 5 years). The specificities by age group can be calculated from the published data. For instance, the specificity of the HPV DNA test with cytology triage for cervical intraepithelial neoplasia grade 2 or higher (CIN 2+) was 99.0% for 35- to 44-year-olds and was calculated as 9049 divided by 9036, in which the numerator is test-negative subjects (table 4 in Leinonen et al.) and the denominator is 9191 screened women (table 1 in Leinonen et al.) minus the 55 women with histologically confirmed CIN 2+ (table 2 in Leinonen et al.) in that age group.

We agree with Lynge and Rebolj that the price of the test plays a role in decision making. However, the number and price of lifetime tests as well as of treatments for CIN are more important than the price of
the test itself. Primary HPV DNA screening with cytology triage may actually reduce the number of lifetime tests because after a negative test, HPV screening gives an opportunity to lengthen screening intervals. At the same time, controlling spontaneous testing (opportunistic screening) is of utmost importance to avoid overuse of health-care services.

Moreover, our cross-sectional finding of fewer recommendations for intensified screening in the HPV DNA screening arm in women aged 35 years or older is promising because the referent rate in the conventional arm has been considered acceptable in the Finnish organized screening program during the last decades. Given the low lifetime risk of cervical cancer in Finland to which Lynge and Rebolj also referred, future studies should assess whether this rate of intensified follow-up, which ranges from about 6% to 10%, could be decreased with the use of new test or triage technologies.

HPV testing of young women is problematic because a positive HPV DNA test result leads to repeated testing and possibly, to overdiagnosis of regressive lesions. One option to further increase the specificity of HPV testing in population-based screening particularly in these women would be to increase the ratio of relative light units (rlu ratio) cutoff for test positivity (1–3). Another option would be to use molecular markers such as p16INK4a as a triage test (4) and base the recommendation for intensified screening on the marker. HPV DNA screening with cytology triage seems a promising screening approach, but emphasis on cost and potential adverse effects is needed before considering a national implementation. At the moment, HPV DNA screening with cytology triage cannot be recommended for women younger than 35 years.

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DOI: 10.1093/jnci/djq115
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Advance Access publication on April 1, 2010.

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