ATHENA trial—an interview with Thomas Lorey, MD

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June 2014—The Food and Drug Administration on April 24 approved use of the Roche Cobas HPV test as a primary standalone screen for cervical cancer in women 25 and older. CAP TODAY writer William Check, PhD, asked questions of Thomas S. Lorey, MD, medical director, TPMG Regional Reference Laboratory, Kaiser Permanente Northern California. Their questions and answers follow. For a discussion of the ATHENA data on which the FDA based its decision, see Dr. Check's June story "Data spark new directions in cervical cancer."

CAP TODAY: What do the data show about the sensitivity of primary HPV screening relative to combined HPV and Pap cytology cotesting?

Dr. Lorey

Dr. Lorey: All else being equal, primary HPV screening is slightly less sensitive than combined HPV and Pap cytology cotesting for detection of CIN3+. However, the overall performance of any screening test(s) depends on test performance and testing intervals. It seems very likely from our data and from the modeling of Kulasingam SL, et al. (*J Low Genit Tract Dis*. 2013;17:193–201), that triennial primary HPV screening provides better cancer protection than cotesting every five years, the current recommendation for how cotesting should be used. The limited duration of the ATHENA trial precluded evaluation of such a comparison at the five-year interval.

CAP TODAY: Now the three-year data from ATHENA have been presented and the FDA has approved the Cobas HPV test as a primary screen in an algorithm along with genotyping and reflex cytology. Do you consider the ATHENA data convincing about the superiority of the primary HPV algorithm over cotesting? (By superiority I mean equally or more effective in terms of sensitivity and specificity but more efficient—a great reduction in the use of cytology.)

Dr. Lorey: Again, it depends on both the testing strategy and screening interval. From my perspective, the ATHENA trial pretty much confirmed what we already knew, that is, that most of the assessment of likelihood of CIN3+ from HPV/Pap cytology cotesting derives from the HPV component. I was not surprised that primary HPV screening provided CIN3+ diagnostic rates pretty close to that of cotesting if used at the same interval. It also seems reasonable to assume that the reason the primary HPV testing "candidate algorithm" arm of ATHENA appears to be slightly superior to the cotesting arm is because the candidate algorithm used 16/18 triage of the Pap-negative HPV-positive women, a practice not followed with the cotesting arm. This nuance didn't matter to the FDA because all the company had to do was to prove that the candidate algorithm worked as well as triennial cytology, but again, that's what we already knew. Thus, HPV 16/18 triage in primary HPV screening prevents the large loss to follow-up that invariably occurs if you send these women away for a year.

CAP TODAY: And the bottom line question—based on the ATHENA data and the review of your own experience, is Kaiser Permanente Northern California now considering shifting to the primary HPV screening algorithm? Guidelines have not yet been written recommending it, but Kaiser adopted cotesting well before the official recommendation.

Dr. Lorey: There are additional issues that need to be resolved before we will consider changing our current gold-standard testing regimen (triennial cotesting), including the lack of an optimal method for triage of the HPV-positive women, the increase in colposcopy rates required with the candidate algorithm (defined as a "harm" in the most recent national guidelines), and the lack of an FDA-approved test done out of the SurePath medium that we currently use.

In the FDA-approved approach for Cobas, colposcopy referral is higher compared to current practice, but there is also more disease detected, and the ratio of colposcopies per disease is very similar. The effect of primary HPV screening on colposcopy rates depends on the triage algorithm.

What ATHENA did not answer, and what I think amounts to a central problem with either approach, is how to triage Pap-negative HPV-positive women. Note that the vaccinated cohort is entering the screening population in increasing numbers each year. Even if HPV types 16 and 18 are helpful for triage, how well do we think that that will work for future vaccinated women, and those already present in our screening population? We should, therefore, continue to evaluate alternative triage tests.