Study: primary HPV test ‘merits consideration’

William Check, PhD

September 2014—With the FDA having approved use of the Roche Cobas assay for human papillomavirus as a primary standalone screen for cervical cancer in women 25 and older, expert panels are faced with the challenge of working the algorithm into current best practice recommendations for cervical cancer screening. A study published July 18 calculating the future risk of precancer (CIN2 and CIN3) and cancer among more than 1 million women who had a negative HPV test should provide valuable assistance in this task (Gage JC, et al. *J Natl Cancer Inst.* 2014;106:pii: dju153). Subjects were women who underwent routine screening for cervical cancer at Kaiser Permanente Northern California since KPNC adopted concurrent HPV and Pap testing, known as cotesting, in 2003.

The newly published study greatly expands the KPNC experience reported in 2011 (Katki HA, et al. *Lancet Oncol.* 2011;12:663–672). “Basically, with longer follow-up among more than 1 million women, we have much greater precision to calculate and estimate cancer risks,” first author Julia C. Gage, PhD, MPH, tells CAP TODAY. The analysis was conducted to provide guidance on HPV primary screening. “We looked specifically at cancer risks after negative screening results,” says Dr. Gage, a research fellow in the Clinical Genetics Branch of the Division of Cancer Epidemiology and Genetics at the National Cancer Institute.

Results from the larger, more recent study “support and extend data from the 2011 paper,” Dr. Gage says. “We found that cancer risk among women with a negative HPV test was about half of the already low risk of women with a negative Pap test and similar to the cancer risk among women who tested both HPV negative and Pap negative [cotest negative].” Similar relative risks were found for CIN3 and CIN2. “The differences in risk [for CIN2 and CIN3] between women who were HPV negative and those who were cotest negative were small although statistically significant,” Dr. Gage says. The difference in cancer risk was small and not statistically significant.

Dr. Gage

“What we have seen in these analyses going back to our 2011 paper in Lancet Oncology is that most cancers are detected by the HPV test, and that a negative Pap test provides little additional reassurance among women who test HPV negative,” Dr. Gage says. However, translating these findings into clinical practice is not simple when one takes into account the small but real differences between primary HPV testing and cotesting, as well as the “harms”—ancillary tests such as colposcopy. In addition, screening intervals have a substantive impact on the comparisons. “Which testing regimen is preferable will depend on how a woman interprets risk and how guideline committees interpret the small differences in risk,” Dr. Gage says. Thus, the cautious conclusions that she and her coauthors drew:

- “These findings suggest that primary HPV testing merits consideration as another alternative for cervical screening.”
- “In conclusion, we find that primary HPV testing every 3 years might provide as much, if not more, reassurance against precancer and cancer,

> compared to primary Pap testing every 3 years and cotesting every 5 years. Health decision analyses are now imperative to identify the optimal screening interval and preferred screening strategy."

Further complexities arise when the criteria for selecting the screening program at KPNC itself are taken into account. CAP TODAY asked Thomas S. Lorey, MD, medical director of the TPMG Regional Reference Laboratory, Kaiser Permanente Northern California Region, how he sees the problem of balancing benefits versus harms among these screening algorithms. What will Kaiser itself do with these data? Will it switch from triennial cotesting to primary HPV screening?

"It is our belief that Kaiser Permanente members are willing to tolerate the relatively minor and low-risk procedures"—i.e. additional or more frequent screening and colposcopy exams—"in order to prevent cervical cancer and its associated complications such as surgery, chemotherapy, and radiation with loss of fertility and ovarian function that ensue when a cancer is detected," Dr. Lorey says.

Dr. Lorey

KPNC uses a highly rigorous comparison to determine the differences in risk. "In the case of KPNC's Cervical Carcinoma Screening Program," Dr. Lorey explains, "we have defined the minimum level of protection required as that equal to or better than the historical benchmark protection of the annual Pap test." As a result, KPNC uses cotesting with three-year intervals, a program that is more stringent than that of professional guideline committees, which recommend triennial cytology or cotesting at five-year intervals for cervical cancer screening.

"There is a lot of historical precedent here," Dr. Lorey says. "We are maintaining a level of protection that we have always offered, as opposed to starting a new program or significantly improving the level of protection over a prior strategy." An institution that is currently doing triennial Pap screening or cotesting with five-year screening intervals would not be in the same position.

Two other analyses conducted on the same KPNC data set are relevant to cervical cancer screening policies. One analysis determined risks among women with HPV-negative/atypical squamous cells of undetermined significance (ASC-US) cytology. The authors concluded, "Women testing HPV negative/ASC-US were found to have precancer/cancer risks that were more closely aligned with women with negative Pap test results, suggesting that women testing HPV negative/ASC-US should be managed similarly to women testing negative on Pap tests with a 3-year return for screening" (Gage JC, et al. Cancer Cytopathol. Epub ahead of print July 9, 2014; doi:10.1002/cncy.21463).

In the third analysis, age-related risks were estimated. "Although the rates of HPV infection declined dramatically with age, the subsequent CIN3+ risks associated with HPV infection declined only slightly," the investigators found. They concluded that the "CIN3+ risks among older women are sufficiently elevated to warrant continued screening through age 65" (Gage JC, et al. *Int J Cancer.* Epub ahead of print Aug. 18, 2014; doi:10.1002/ijc.29143).

Currently prevailing cervical cancer screening recommendations were promulgated in March 2012 by two groups: the U.S. Preventive Services Task Force and a multidisciplinary partnership of the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology.

In brief, both groups recommended two options for screening for cervical cancer:

- For women ages 21 to 65, screening with cytology every three years.
- For women ages 30 to 65 who want to lengthen the screening interval, screening with a combination of cytology and HPV testing every five years.

With triennial Pap tests, HPV testing is recommended for triage of ASC-US results.

In the algorithm for primary HPV testing that the FDA approved, women whose specimens are positive for HPV genotypes 16/18 go directly to colposcopy. Those whose specimens are positive for one of the other 12 high-risk genotypes are triaged with a Pap test. Patients whose specimens are ASC-US or worse cytology are referred for colposcopy.

In the KPNC cotesting program, HPV testing is based on the Hybrid Capture 2 test performed from a separately collected sample. Women testing HPV positive/Pap negative or HPV negative/Pap equivocal (ASC-US) returned after one year. Women testing HPV positive/Pap ASC-US or HPV negative with a low-grade or worse Pap were referred for colposcopy. Women testing HPV negative/Pap negative returned for repeat screening in three years. For the 571,880 women who were followed beyond enrollment, the mean follow-up time was 4.36 years. (About half of women had been enrolled too recently to have a repeat visit. Also, some left the KPNC program.) Total follow-up time was 2,495,946 person-years.

Looking just at results five years after a negative screen, these were the CIN3 or worse outcomes:

- For negative Pap testing: 310 cases per 100,000 women.
- For negative HPV testing: 140 cases.
- For negative cotesting: 110 cases.

The same comparison for cancer looked like this:

- For negative Pap testing: 31 cases per 100,000 women.
- For negative HPV testing: 17 cases.
- For negative cotesting: 14 cases.

Thus, compared with cotesting, HPV testing results in an additional 30 cases of CIN3 and an additional three cases of cancer over five years per 100,000 women screening HPV negative.

Comparing results with the same interval, Dr. Gage tells CAP TODAY: “Risk estimates between HPV-negative and cotest-negative algorithms are very close. How to interpret these close risks will come down to traditional health decision analyses to understand the optimal screening interval and preferred strategy.”
What HPV testing would prevent is a large number of screening tests, the investigators wrote: “If a negative HPV test can provide the same safety (ie, reassurance against future risk of precancer and cancer) as a negative Pap or negative cotest (currently recommended strategies), most of the Pap tests now conducted in screening would no longer be required.” They estimated that over 15 years HPV screening at a five-year interval could reduce the total number of screening tests by one-third to one-half compared with primary Pap every three years or cotesting every five years.

Initially there would be fewer colposcopies with primary HPV screening, Dr. Gage says. But, she adds, “I think it’s important to consider that women who screen HPV positive/Pap negative are recommended to return in a year for rescreening, and a portion of them will also be referred to colposcopy at that time.”

Expanding on KPNC's adoption of the three-year screening interval for cotesting, Dr. Lorey called it "a progression from what was the gold standard—annual Pap smear cytology." Using annual Pap smear screening, rather than three-year cytology, as the benchmark for implementing new screening strategies resulted in a three-year, as opposed to five-year, interval for cotesting.

"When we introduced cotesting at three-year intervals in 2003," he says, "we were able to demonstrate that it provided the same or better protection against the risk of cancer and precancer with fewer tests and fewer visits compared to an annual Pap. We may evolve to a five-year interval in the future, providing we have very good data that aligns well with the risk provided by the annual Pap smear."
Adoption of the five-year interval for cotesting by the Preventive Services Task Force and the ACS/ASCCP/ASCP group, on the other hand, was based on its protection and risk being equivalent to those of the prevailing screening algorithm at that time—Pap testing at three-year intervals.

Any laboratory or health care institution could adopt cotesting at a three-year interval, and a five-year interval might be acceptable as well, Dr. Lorey says. "One of the interesting features of the HPV molecular assay is that it has superior negative predictive value," he says. He raises the possibility that cotesting at five-year intervals could approach the level of protection of annual cytology after several rounds if women experience a cumulative benefit with consecutive negative HPV results. However, he emphasizes, right now this is no more than conjecture.

Dr. Lorey attributes the slightly higher sensitivity of cotesting relative to HPV-only at the same screening interval to the small increment of additional sensitivity provided by the Pap test. "Unlike HPV-only," he says, "the Pap component of cotesting identifies a subgroup of HPV-negative/Pap-positive patients, and in this subgroup, there is a small number of patients who will have disease. However, as we know, there is a corresponding decrease in specificity due to the many HPV-negative/Pap-positive patients who do not have disease."

"We remain hopeful," he says, "that development of new screening tests, impact of vaccination, and promise of newer medical therapies will simplify the decisionmaking process when we decide to change our current testing strategy. That said, any change to our program, tests, and/or intervals will have to preserve or increase the current level of protection provided by our three-year cotesting program."

Looking into the future, he says, "Along with other tests, vaccination too will likely offer the opportunity to extend increased screening intervals."
[hr]

William Check is a writer in Ft. Lauderdale, Fla.