



April 14, 2014

Margaret A. Hamburg, M.D.
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Re: Microbiology Medical Devices Panel on Cobas HPV Test Premarket Approval Application

Dear Commissioner Hamburg,

We are writing as members of the Patient, Consumer, and Public Health Coalition and other interested experts to express our grave concerns about the March 12, 2014 FDA meeting of the Microbiology Medical Devices Panel of the Medical Devices Advisory Committee. Under consideration was the premarket approval of a new indication for the Cobas HPV test, as a first-line primary screening tool for cervical cancer in women aged 25 and older.

This is a radical change to current U.S. Preventive Services Task Force (USPSTF) guidelines, which recommend Pap smears every 3 years starting at age 21, with the option of

replacing that regimen starting at age 30 with a combination of a Pap smear and HPV test. As the American College of Obstetricians and Gynecologists (ACOG) stated in its comments to FDA regarding the lack of evidence for this proposal, “There is little comparative effectiveness data comparing primary HPV screening with co-testing, the preferred method in the ACS-ASCCP-ASCP guideline...providers will not be able to adequately counsel patients regarding the relative benefits and potential harms of primary HPV screening compared with currently accepted methods, particularly co-testing.”

Although FDA scientists and several members of the advisory committee expressed safety concerns about this radical shift, they voted in favor of approval.

The new indication is radical in several ways:

- 1) It replaces a safe and effective well-established screening tool and regimen that has prevented cervical cancer successfully in the U.S. with a new tool and regimen not proven to work in a large U.S. population, and is not supported by any evidence-based U.S. guidelines.
- 2) It interferes with the practice of medicine, by encouraging physicians to follow a positive result on the HPV test, which can identify a virus but cannot identify abnormal cells, with a colposcopy, an expensive and invasive procedure that could result in much lower compliance. For no apparent reason, the Pap smear is not used to follow-up on the HPV test to determine if cellular abnormalities have occurred.
- 3) The Pap smear is effective in detecting cellular signs of pre-malignancy that can be caused by HPV or other causes. The new indication would replace the Pap smear with the HPV test, which can only detect the virus (which usually will not cause cervical cancer) but will not detect cancers that are not caused by HPV.

We have numerous concerns about both the implications of this decision and the quality of the pivotal trial used to support it:

No U.S. guidelines currently sanction HPV testing as a first-line screening test for cancer

Current guidelines sanction HPV testing in conjunction with cytology and restricted to patients 30 and older, due to evidence of unacceptable risks among younger patients, i.e. increases in invasive follow-up procedures such as colposcopy and cervical biopsy. The latter, in cases of cone biopsy and further excisional procedures, can be associated with adverse events in pregnancy such as pre-term labor, perinatal death, low birth weight, and also subfertility, which would disproportionately affect the younger patient population being proposed in the new indication.

For these reasons, sister federal agencies and other medical associations such as the Centers for Disease Control and Prevention, USPSTF, ACOG, American Cancer Society, and American Association of Family Practitioners have not recommended HPV testing as a first-line screening tool in any patient population. The USPSTF currently gives a "D" rating for HPV testing in women under age 30 in any clinical context, citing harms which outweigh benefits among

younger women as seen in previous clinical trials, and also citing concerns regarding over-treatment of CIN2 in this patient population, where it is most likely to regress.

Interference with the practice of medicine

As was noted by the advisory committee, the new proposed indication would result in specific triage protocols for patient management following use of the Cobas HPV test. The FDA briefing materials prepared for the advisory committee explicitly stated that the advisory committee cannot "establish or recommend guidelines for medical practice." Approval of this indication would encroach on clinical practice guidelines which are outside the purview of the advisory committee and the FDA.

Significant design problems with the pivotal clinical trial

The basis for approval of this indication is a flawed clinical trial. Flaws include the design of the comparator arm, participant age and HPV vaccination status, trial duration, and testing interval.

The comparator arms were based on outdated clinical guidelines. Specifically, the main comparator arm triaged all abnormal cytology ASC-US or higher to immediate colposcopy, which is no longer current practice. As the FDA stated in its report, "this comparator was selected prior to the 2012 update of the 2006 Guidelines (2012 Guidelines), in which immediate colposcopy is no longer performed on women with ASC-US cytology and unknown HPV status." This triage design significantly increased colposcopy rates in the comparator arms, making the candidate arm colposcopy rate appear more favorable than if it had been compared to current clinical practice. In order to accurately weigh risks and benefits, the comparator arm must represent current clinical practice and guidelines.

Furthermore, given the wording of the proposed indication, this test could be used repeatedly for the majority of women's lives. Yet the pivotal trial lasted only three years with annual clinical exams, which is not consistent with current guidelines. The FDA also expressed this same concern in their questions for the panel, stating that "this study population does not have a history of screening using the newer, longer screening intervals. Disease prevalence may differ in a population that has been screened under the new intervals."

Lastly, the median trial participant age was 41, one-third were post-menopausal, and only 1% had been vaccinated against HPV, which the FDA also noted in its briefing materials. As the proposed indication poses the greatest risk of unnecessary harm to a younger age group, it is not scientifically sound to make treatment decisions for young women based on research that lacks sufficient and relevant data for this critical population.

Minimal gains in detection

Minimal gains in detection must be weighed against jeopardized patient compliance and increased harms. Most cervical cancers occur in women who have never been screened, were not screened in the last five years, or did not have appropriate follow-up treatment. The sponsor does not provide any evidence that HPV testing will increase patient compliance. On the contrary, the sponsor's plan, based on the trial population, would result in 7% of women ages 25 to 29 being advised to undergo immediate colposcopy. Are they likely to comply?

Several studies document numerous social, economic and cultural factors which contribute to reduced patient compliance with colposcopy and other longer, more invasive follow-up procedures, especially among younger, underserved populations who already suffer from disparities in cervical cancer survival. Many studies have highlighted the critical importance of screening participation in these populations in order to make any meaningful gains in cervical cancer survival. It should also be noted that HPV testing is significantly more expensive than cytology, and colposcopy is more expensive, more inconvenient, and more painful as well. This proposed indication threatens to accomplish the very opposite of its intended purpose, which should be to reduce barriers to screening and to save lives.

Clinically important information thrown away

In 2013, the Cobas test received FDA approval to use the same sample vial as the Pap test, producing a streamlined co-testing platform. The FDA stated in its questions for the panel that cytology “includes other diagnostic categories such as infectious organisms (candida sp., Trichomonas, Herpes viral changes, atypical repair, abnormal endometrial cells, etc.),” all of which the HPV test cannot identify. The Pap test can identify non-HPV cancers of the cervix, such as choriocarcinoma, melanoma, metastatic carcinoma, and some adenocarcinomas from other primary sites, which the HPV test also cannot identify. How can loss of this information be justified when it can be acquired from the same sample at little added expense?

Conclusion

This proposed indication for the HPV test would represent an unprecedented and significant shift in clinical practice that would affect millions of women for the majority of their adult lives. With the health of so many at stake, we strongly urge the FDA to reject the application for this expanded indication, until evidence clearly indicates that this will not reduce the effectiveness of screening for cervical cancer.

Sincerely,

American Medical Student Association
 American Medical Women’s Association
 American Public Health Association
 Annie Appleseed Project
 Cancer Prevention and Treatment Fund
 Community Catalyst
 Connecticut Center for Patient Safety
 Consumers Union
 Jacobs Institute of Women’s Health
 National Alliance of Hispanic Health
 National Consumers League
 National Organization for Women
 National Physicians Alliance
 Our Bodies Ourselves
 The TMJ Association
 Women Advocating Reproductive Safety
 WoodyMatters

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