Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial

Pilar Hernandez Nevarez, Rodrigo Diaz Acosta, Mauricio Hernández-Avila

Summary

Background Vaginal self-sampling for human papillomavirus (HPV) DNA testing could increase rates of screening participation. In clinic-based settings, vaginal HPV testing is at least as sensitive as cytology for detecting cervical intraepithelial neoplasia (CIN) grade 2 or worse; however, effectiveness in home settings is unknown. We aimed to establish the relative sensitivity and positive predictive value for HPV screening of vaginal samples self-collected at home as compared with clinic-based cervical cytology.

Methods We did a community-based, randomised equivalence trial in Mexican women of low socioeconomic status aged 25–65 years. Participants came from 540 medically underserved, predominantly rural communities in Morelos, Guerrero, and the state of Mexico. Our primary endpoint was CIN 2 or worse, detected by colposcopy. We used a computer-generated randomisation sequence to randomly allocate patients to HPV screening or cervical cytology. Eight community nurses who were masked to patient allocation received daily lists of the women’s names and addresses, and did the assigned home visits. We referred women with positive results in either test to colposcopy. We did per-protocol and intention-to-screen analyses. This trial was registered with the Instituto Nacional de Salud Pública, Mexico, INSP number 590.

Findings 12 330 women were randomly allocated to HPV screening and 12 731 to cervical cytology; 9202 women in the HPV screening group adhered to the protocol, as did 11 054 in the cervical cytology group. HPV prevalence was 9·8% (95% CI 9·1–10·4) and abnormal cytology rate was 0·38% (0·23–0·45). HPV testing identified 117·4 women with CIN 2 or worse per 10 000 (95·2–139·5) compared with 34·4 women with CIN 2 or worse per 10 000 (23·4–45·3) identified by cytology; the relative sensitivity of HPV testing was 3·4 times greater (2·4–4·9). Similarly, HPV testing detected 4·2 times (1·9–9·2) more invasive cancers than did cytology (30·4 per 10 000 [19·1–41·7] vs 7·2 per 10 000 [2·2–12·3]). The positive predictive value of HPV testing for CIN 2 or worse was 12·2% (9·9–14·5) compared with 90·5% (61·7–100) for cytology.

Interpretation Despite the much lower positive predictive value for HPV testing of self-collected vaginal specimens compared with cytology, such testing might be preferred for detecting CIN 2 or worse in low-resource settings where restricted infrastructure reduces the effectiveness of cytology screening programmes. Because women at these sites will be screened only a few times in their lives, the high sensitivity of a HPV screen is of paramount importance.

Funding Instituto Nacional de Salud Pública, the Health Ministry of Mexico, QiAGEN Corp

Introduction The public health burden of cervical cancer in developing countries is high.1 In 2008, about 370000 deaths related to cervical cancer occurred in the Americas, costing about 545 000 DALYs.2 Findings from randomised trials of more than 200 000 women3–8 showed HPV DNA screening to be better than cervical cytology for detecting cervical intraepithelial neoplasia (CIN) grade 2 or worse, and for reducing incidence and mortality from cervical cancer. Furthermore, results of systematic reviews and meta-analyses9–11 showed that HPV testing has higher sensitivity but lower specificity than cytology. In recognition of the value of HPV DNA testing, focus has increased on assessment of HPV screening in different settings.12 The limited infrastructure of low-income countries reduces the effectiveness of cytology-based screening programmes. HPV testing of self-collected vaginal specimens could be especially useful for women with restricted access to health care9 and could increase population coverage2 because of increased acceptability and elimination of clinical examinations. Although good diagnostic performance and safety have been documented in research settings, no randomised trial has assessed the home-based performance of vaginal HPV testing.

With our Mexican Appraisal of Routine Cytology versus vaginal HPV screening (MARCH) trial—the first population-based randomised trial in a low-resource region—we aimed to assess the performance of HPV DNA testing on vaginal samples self-collected in the home versus routine cervical cytology. We postulated that HPV DNA testing of vaginal specimens would have similar or greater sensitivity and lower (but acceptable) positive predictive value than Papanicolaou (Pap) cytology in a comparison group of women.
Methods

Patients
Our community-based randomised equivalence trial was commissioned, undertaken, and monitored between March, 2006, and April, 2007, by the Mexican Ministry of Health’s evidence-based public health initiative. We began with a population-based list of 25 061 women aged from 25 to 65 years (figure). Participants came from 540 medically underserved, predominantly rural communities in Morelos, Guerrero, and the state of Mexico. Eligible women were participants in Oportunidades,7 a poverty-reduction programme involving 5 million people with limited access to health services, less formal education, and worse nutrition than the rest of the country. Exclusion criteria were previous hysterectomy and current pregnancy. Instituto Nacional de Salud Pública (INSP) Research, Biosafety, and Ethics Committees approved this study (INSP number 590). Before enrolment, all participants gave oral or written informed consent.

Procedures
Women were randomly assigned to one of two interventions: HPV DNA testing of a vaginal sample self-collected at home (the HPV group) or conventional cervical cytology smears obtained at the nearest health centre (the cytology group) by a computer-based random allocation process designed by study statisticians (webappendix). Women self-collected vaginal specimens at home with the Digene conical-shaped brush. Nurses instructed women to hold the brush midway along the shaft, insert the head as far as possible into the vagina, rotate it left

![Trial profile diagram](image_url)
and right, place it immediately into the collection tube of transport medium, and secure the cap. Local clinics did cervical cytology smears according to national guidelines. A sample was taken from the ectocervical transformation zone with an Ayre wooden spatula, and specimens from the endocervical canal taken with a cytobrush were smeared onto one slide and sent to one diagnostic reference centre in each state. We routinely collected patient safety data and recorded no adverse events. We used WHO’s classification in accordance with Mexico’s guidelines for cervical cancer screening programmes.18 We referred women who had cytological interpretations of mild dysplasia or worse or a positive HPV DNA test for colposcopy.

We detected HPV DNA with a standard commercial kit using nucleic acid hybridisation in vitro and chemiluminescent microplate-based signal amplification. We did analysis by the Hybrid Capture 2 test in a validated and accredited HPV testing laboratory at the INSP, Cuernavaca, Morelos, Mexico. We used 1 pg/mL or more as the standard cutoff point for HPV positivity. Nurses notified women of any positive test result about 1 week after testing, and scheduled their free colposcopy at mobile colposcopy units at the local health centre. Three colposcopists graded lesions using the Reid Index and took biopsies as necessary (webappendix). Identified cases of CIN 2 or worse were treated according to Mexico’s Cervical Cancer Screening Programme’s guidelines. The MARCH trial’s primary endpoint was CIN 2 or worse.

**Statistical analysis**

Based on a previous study and unpublished data, a sample size of 9500 women per group (with an assumed initial refusal rate of up to 25%) would provide 85% power to show a 40% difference (two-sided alpha of 0·05) between groups. We aimed to assess relative detection rates, relative sensitivity (ratio of the relative detection rates), and positive predictive value for CIN 1–3 and invasive cervical cancer in the HPV group versus the cytology group. We analysed data using a per-protocol approach (we considered only women assigned to the HPV group and cytology group who complied with the protocol) and an intention-to-screen approach, including all women originally assigned to the HPV group or the cytology group. We obtained relative sensitivities using Pepe’s method (webappendix) by estimating CIN detection rates per 10 000 women and dividing the endpoint detection rate in the HPV group by the rate in the cytology group. We calculated positive predictive values as a function of the probability of having a lesion (CIN 1, CIN 2, CIN 3, cancer, and CIN 2 or worse) in view of a positive HPV or Pap test. When verification is dependent on only the test result, such estimators of positive predictive value are unbiased. We obtained all estimates with Stata (version 10.1).

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Self-collected HPV (n=9202)</th>
<th>Cervical cytology (n=11 054)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25–29</td>
<td>2307 (25%)</td>
<td>2543 (23%)</td>
</tr>
<tr>
<td>30–34</td>
<td>1756 (19%)</td>
<td>2412 (22%)</td>
</tr>
<tr>
<td>35–39</td>
<td>1730 (19%)</td>
<td>2096 (19%)</td>
</tr>
<tr>
<td>40–44</td>
<td>1330 (15%)</td>
<td>1810 (16%)</td>
</tr>
<tr>
<td>45–49</td>
<td>1103 (12%)</td>
<td>1282 (12%)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>976 (11%)</td>
<td>911 (8%)</td>
</tr>
<tr>
<td>Mean</td>
<td>37.9 (9.01)</td>
<td>37.7 (8.1)</td>
</tr>
</tbody>
</table>

**Table 1: Demographic comparisons among enrolment and study population in the per-protocol set stratified by age and state of residence**

<table>
<thead>
<tr>
<th>Geographic areas</th>
<th>Self-collected HPV (n=9202)</th>
<th>Cervical cytology (n=11 054)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morelos</td>
<td>4665 (51%)</td>
<td>6955 (63%)</td>
</tr>
<tr>
<td>Mexico State</td>
<td>4034 (44%)</td>
<td>3557 (32%)</td>
</tr>
<tr>
<td>Guerrero</td>
<td>503 (6%)</td>
<td>542 (5%)</td>
</tr>
</tbody>
</table>

**Table 2: Biopsy-based rates of detection and relative sensitivity estimates for the HPV and cytology screening strategies according to the per-protocol or the intention-to-screen analyses**
Role of the funding source
The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Data are based on the per-protocol analysis unless otherwise noted. The figure shows study design and descriptive statistics. Of women randomised to the HPV group, 9202 of 9371 (98%) found at home participated, whereas 11054 of 12731 (87%) women randomised to cytology (including those not at home who left a printed invitation) attended the local clinic for a Pap smear (p=0.001). The 2959 women in the HPV group who were not at home were reassigned to the cytology group (left a printed invitation), and 2610 (88%) were tested, resulting information being used in the intention-to-screen analysis.

Both groups were similar in mean age and range of times from positive screening to colposcopy (table 1). Self-collection of vaginal samples was not associated with any adverse events. High-risk prevalence of HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 in self-collected vaginal specimens among women aged between 25 and 65 years was 9·8% (95% CI 9·1–10·4). The odds ratio (OR) of high-risk HPV infection for women younger than 30 years was 1.40 (95% CI 1.07–1.83 [reference is women older than 50 years, data not shown]). The abnormal cytology rate (any suspected dysplasia or cancer) was 0·38% (95% CI 0·23–0·45). More invasive cancers were found in the HPV group than in the cytology group (figure). The OR for CIN 2 or worse was 1·98 (95% CI 1·25–3·13) for women older than 35 years compared with those aged 25–29 years (data not shown). In the HPV group, five of the invasive cancers were stage Ia and 23 were stage Ib. In the cytology group, two cancers were stage Ia and six were stage Ib. Table 2 shows detection rates for CIN 2 or worse and other grades of cervical cancer.

HPV testing of self-collected samples had a relative sensitivity of 3·4-times greater (95% CI 2·4–4·9) than cytology for detection of CIN 2 or worse; it detected 41·1 times (15·2–111·2) more CIN 1; 3·6 times (2·2–6·0) more CIN 2; 2·4 times (1·5–5·1) more CIN 3; and 4·2 times (1·9–9·2) more invasive cancer than did cytology (table 2). Data for the intention-to-screen and per-protocol analyses were quite similar. A small decrease in HPV relative sensitivities occurred for all categories mostly because we gave cytology to 2610 women originally assigned to the HPV group, and counted detected events as being in the HPV group. In women aged 25–65 years, the positive predictive value for identifying CIN 2 was less in the HPV group than for the Pap test (table 3).

Results for per-protocol positive predictive values for the HPV and Pap tests were similar across age groups (table 3). The relative sensitivity of HPV testing versus cervical cytology for CIN 2 or more was not significantly greater with the cutoff of 1 pg/mL or more than with the 2 pg/mL or more cutoff (p=0.248), but was significantly greater than the 5 pg/mL or more cutoff (p<0.0001; table 4). For positive predictive value we recorded no significant difference for the 1 pg/mL or more cutoff compared with 2 pg/mL or more (p=0.147). However, the value was significantly lower with the 1 pg/mL or more cutoff than with the 5 pg/mL cutoff (p=0·002; table 4). For women aged between 30 and 65 years, relative sensitivity of HPV testing for CIN 2 and worse did not differ significantly for the cutoff of 1 pg/mL and more compared with the cutoff of 2 pg/mL or more (p=0·271), similarly, the positive predictive value of the two cutoffs did not differ significantly (p=0·158; table 4).

Table 3: Positive predictive value of the HPV test and Pap cytology test by age

<table>
<thead>
<tr>
<th>Age group</th>
<th>HPV (CIN 2 or worse)</th>
<th>Pap (CIN 2 or worse)</th>
<th>HPV (CIN 3 or worse)</th>
<th>Pap (CIN 3 or worse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25–65 years</td>
<td>884</td>
<td>42</td>
<td>884</td>
<td>42</td>
</tr>
<tr>
<td>CIN 2 or worse</td>
<td>108</td>
<td>38</td>
<td>48</td>
<td>18</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>12.2 (9.9–14.5)</td>
<td>90.5 (61.7–100.0)</td>
<td>5.4 (3.9–7.0)</td>
<td>42.9 (23.6–62.7)</td>
</tr>
<tr>
<td>30–65 years</td>
<td>682</td>
<td>32</td>
<td>682</td>
<td>32</td>
</tr>
<tr>
<td>CIN 2 or worse</td>
<td>99</td>
<td>30</td>
<td>45</td>
<td>16</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>14.5 (11.7–17.4)</td>
<td>93.7 (60.2–100.0)</td>
<td>6.6 (4.7–8.5)</td>
<td>50.0 (25.5–74.5)</td>
</tr>
<tr>
<td>35–65 years</td>
<td>511</td>
<td>25</td>
<td>511</td>
<td>25</td>
</tr>
<tr>
<td>CIN 2 or worse</td>
<td>85</td>
<td>23</td>
<td>37</td>
<td>13</td>
</tr>
<tr>
<td>PPV (95% CI)</td>
<td>16.6 (13.1–20.2)</td>
<td>92.0 (54.4–100.0)</td>
<td>7.2 (4.9–9.6)</td>
<td>52.0 (23.7–80.3)</td>
</tr>
</tbody>
</table>

HPV=human papillomavirus. CIN=cervical intraepithelial neoplasia. PPV=positive predictive value.

Table 4: Per-protocol relative sensitivity and PPV of HPV versus Pap for a CIN2 or worse endpoint in different age groups with different cutoffs of HPV tests

<table>
<thead>
<tr>
<th>Age group</th>
<th>≤1 pg/mL cutoff</th>
<th>≥2 pg/mL cutoff</th>
<th>≥5 pg/mL cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative sensitivity</td>
<td>PPV (%)</td>
<td>Relative sensitivity</td>
<td>PPV (%)</td>
</tr>
<tr>
<td>25–65 years</td>
<td>3.4 (2.4–4.9)</td>
<td>12.2% (9.9–14.5)</td>
<td>3.0 (2.0–4.3)</td>
</tr>
<tr>
<td>30–65 years</td>
<td>4.1 (2.7–6.1)</td>
<td>14.5% (11.7–17.4)</td>
<td>3.5% (2.3–5.4)</td>
</tr>
<tr>
<td>35–65 years</td>
<td>4.4 (2.8–7.0)</td>
<td>16.6% (13.1–20.2)</td>
<td>3.9 (2.4–6.2)</td>
</tr>
</tbody>
</table>

Data are relative sensitivity (95% CI) or PPV (95% CI). HPV=human papillomavirus. CIN=cervical intraepithelial neoplasia. PPV=positive predictive value.
Discussion

In our study in underserved Mexican women, HPV testing was more sensitive for detecting invasive cervical cancer than was cytology, with a relative sensitivity of 4.2 (95% CI 1.9–9.2). Furthermore, HPV testing was 3.4 times more sensitive than cytology for detecting CIN 2 or worse, combined with a positive predictive value of 12.2%. Our findings support a possible change to front-line large-scale application of HPV testing in different settings in Mexico, particularly in areas with restricted cervical cytology infrastructure. The high positive predictive value of cervical cytology (90–95%) indicates use of a strict classification of only mild dysplasia or worse (equivalent to the Bethesda low-grade squamous intraepithelial lesion or greater) as abnormal. The Mexican public health system rarely includes the diagnosis of atypical squamous cells of undetermined significance (ASCUS) on Pap smear in screening because it is highly irreproducible.

Other studies have noted that HPV testing of self-collected vaginal specimens is as or more sensitive than Pap testing. High sensitivity is especially important if screening is possible only a few times per lifetime. Although other findings have shown HPV testing of vaginal specimens to have a lower sensitivity for CIN 2 and worse than does HPV detection in cervical specimens collected by physicians, a high agreement exists in the HPV genotyping data, that mostly the same types are detected on the cervix and in the vagina. HPV tests of vaginal specimens in our previous study had a higher rate of positivity (lower clinical specificity) than cervical specimens, and high-risk HPV prevalence in the vaginal canal is typically 2–5 percentage points greater than in the cervix. Reports in developed countries indicate that HPV-positive women could have adverse social and psychological outcomes with no proper counselling. Hence, HPV education for women, their families, and clinicians, and counselling regarding local cultural or religious barriers to self-sampling is needed.

A limitation of our study was the large number of false-positive HPV results. Most of these HPV-positive women will not develop CIN 2 and greater, and thus, the low positive predictive value is a burden to public health-care services in view of the large number of confirmatory colposcopies required, or follow-up cytology and HPV tests. Another limitation was the absence of a confirmatory reference standard test for women testing negative in the two intervention groups. This absence was due to technical and ethical reasons, including Mexican Ministry of Health requirements that our intervention follow operating conditions and official guidelines.

Gold-standard colposcopy undertaken in a sufficiently large random sample of HPV or Pap-negative women would have allowed an adjusted estimate of true clinical sensitivity, specificity, and false positives. However, relative sensitivity is unaffected by verification bias, and positive predictive value is a useful variable for creation of policy decisions on screening programmes. Another potential limitation is the absence of masking of colposcopy to study groups. Although unmasked colposcopy is typical in community settings, absence of masking could bias study results (most likely against the HPV test). Women excluded from HPV testing because they were not at home when nurses visited were invited to Pap testing at health clinics, thus an intention-to-screen analysis was allowed that produced results similar to the per-protocol analysis. Effectiveness of cytology in our study approximates true community-based functioning. The low rate of detected cytological abnormalities, compared with higher rates in the USA and Europe, shows typical abnormality rates in Latin American public health cytology screening programmes, where ASCUS is often not considered an abnormal category.

HPV testing is lower in cost, easier to implement, and has lower false-negative rates than cytology. Testing of self-collected vaginal samples offers increased coverage...
and acceptability. However, the challenge facing such testing as a strategy for cervical cancer prevention in low-income countries is identification of the most effective triage for HPV DNA positive women because the test substantially increases the number of colposcopy referrals, associated costs, and risks of overtreatment. With our results we aim to inform policy formulation and programme implementation in deprived rural areas of Mexico (panel), but these findings could also be relevant elsewhere, including in developed countries with low participation rates and localised resource-poor settings.11

Contributors
EL-P and ATL had full access to all data and leadership responsibility for drafting and final editing and contributed equally to the study. EL-P, JS, EV-M, PU, and MH-A designed the study, led the clinical aspects and collected the raw data. PHN did the HPV tests: EL-P, AG-V, RDA, and ATL undertook and reviewed the statistical analyses. All authors contributed to and had full knowledge of the contents of the manuscript.

Conflict of Interest
ATL owns shares of and is a consultant for Qiagen Inc, the manufacturer of the Hybrid Capture 2 HPV test.

Acknowledgments
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References
Prevention of cervical cancer in women’s hands: Mexico leads the way

In The Lancet,1 Eduardo Lazcano-Ponce and colleagues report the results of the first community-based randomised trial to compare the effectiveness of HPV DNA testing of vaginal samples self-collected at home with clinician-collected cervical cytology, for detection of prevalent cervical intraepithelial neoplasia (CIN) grade 2 or greater. The trial randomly assigned 20 256 Mexican women aged between 25 and 65 years of low socioeconomic status to self-collection of samples for HPV testing (n=9202) or to clinician-collected cervical cytology (n=11 054). Women who were HPV positive or had cytological abnormalities (mild dysplasia or worse) were referred for diagnostic colposcopy and biopsies as needed.

The detection rate of cytological abnormalities was 0·38% (95% CI 0·23–0·45), which is lower than usually reported.2 This finding indicates low-quality cytology and shows the challenge of using this technique in developing countries. Absence of inclusion of atypical squamous cells of undetermined significance among the cytological abnormalities is unlikely to explain this low prevalence. That mild cytological lesions were almost completely undetected in the study is particularly noteworthy and explains the very high (90·5% [61·7–100]) positive predictive value of cytology. By contrast, the detected HPV prevalence was roughly 10%, with a correspondingly low positive predictive value (12·2% [9·9–14·5]), increasing with age as expected. HPV testing detected 3·4 times (2·4–4·9) more prevalent CIN2 and greater, and 4·2 times (1·9–9·2) more invasive cervical cancers than cytology, which clearly indicates that HPV testing of self-collected vaginal specimens is better than cytology.

Although the findings of Lazcano-Ponce and colleagues’ study largely confirm those of earlier smaller studies, this is the first community-based randomised trial to investigate the use of HPV testing of home-based self-collected vaginal specimens. The self-collection method was almost universally accepted (98%) compared with the more complex and expensive clinic-based cytology (86%), which confirms the feasibility of self-collection in this population. Self-collected sampling for HPV testing is more sensitive for detection of precancerous lesions than cytology, but the HPV test should also be able to offer a similar negative predictive value to a clinician-collected sample for HPV testing. However, several studies have shown that sensitivity and specificity of self-collected samples for HPV testing are lower than the same test when collected by a clinician directly from the endocervix.3,4 Alternative methods of self-collection have been proposed with limited success, and a study5 indicated that the sensitivity of vaginal self-collection could be improved by use of a high-throughput, low-cost, PCR-based detection method (MALDI-TOF) without much sacrifice of specificity. The performance of new methods needs to be carefully scrutinised, particularly if they will be used in deprived areas where there might be only one opportunity to screen a woman and, in this context, a false sense of security that could discredit the new approach should be avoided. The cost of the HPV test is the main factor impeding its introduction for primary screening in developing countries. A new low-cost HPV DNA test, careHPV, has comparable effectiveness to the current Hybrid Capture 2 test and is in the process of being commercialised.5

In Lazcano-Ponce’s study, all women who were HPV positive were referred to colposcopy, an unrealistic approach in view of the large number of women who would need to be referred, which would constitute a
heavy burden for public health-care systems. In reality, HPV-positive women need to be triaged using either visual inspection with acetic acid (VIA), high-quality cytology, repeat HPV testing, or other biomarkers, each method having advantages and limitations. A randomised trial done in Finland has shown that primary HPV screening with cytology triage was more sensitive than clinic-based cervical cytology for detecting precancerous cervical lesions. Furthermore, a US study has shown that primary HPV screening of home-based self-collected vaginal specimens with subsequent clinic-based cytological triage was accurate and cost effective.

This Mexican trial is an important component of a research programme established by the Mexican Instituto Nacional de Salud Pública and other institutions. The aim of the programme was to improve the limited effect achieved by previous cytology-based screening efforts, a problem that is shared by most developing regions and shown in the high burden of cervical cancer in these areas (table).

Mexico is, to our knowledge, the first country in the world to establish primary testing with HPV and subsequent cytological triage as the national policy, having already established a large network of high-technology laboratories and done several million HPV tests. As expected, this system is not free of challenges because thousands of women have HPV but no cytological lesions and need to be managed clinically, psychologically, and socially. The decision in Mexico is in agreement with what most epidemiologists view as the evidence-based way forward for control of cervical cancer, with HPV DNA testing as the primary screening test together with HPV vaccination of adolescent women.9–12

The experience in Mexico shows what can be achieved when scientific judgment guides public health policy.

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We declare that we have no conflicts of interest.