

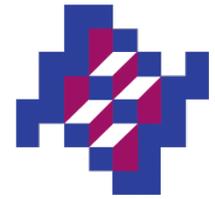
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**La segunda revolución del VPH:  
Presentando la experiencia de la  
Autotoma del Test de VPH en México.**

**Eduardo Lazcano Ponce**

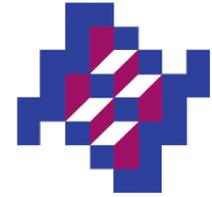
Octubre 2012

# Presentación



- 
- **Evidencia científica de utilidad de las pruebas de VPH.**
    - Un ensayo clínico aleatorizado en México
      - ◆ Pap versus autotoma.
  - **El estudio piloto de autotoma vaginal en 101,552 mujeres en el Estado de Morelos en México.**
    - La prueba en función de la calidad de colposcopia
  - **Conclusiones y recomendaciones**

**Autotoma alcanza 86% de sensibilidad y 80.7% de especificidad para CIN 2 +.**



## **Pooled Analysis of a Self-Sampling HPV DNA Test as a Cervical Cancer Primary Screening Method**

Fang-Hui Zhao, Adam K. Lewkowitz, Feng Chen, Margaret J. Lin, Shang-Ying Hu, Xun Zhang, Qin-Jing Pan, Jun-Fei Ma, Mayineur Niyazi, Chang-Qing Li, Shu-Min Li, Jennifer S. Smith, Jerome L. Belinson, You-Lin Qiao, Philip E. Castle

J Natl Cancer Inst 2012;104:178–188

**La sensibilidad para CIN 3+ fue de 94.3% en pruebas y estrategias de muestreo más eficientes.**

Int. J. Cancer: 130, 1855–1860 (2012)



## **Improved sensitivity of vaginal self-collection and high-risk human papillomavirus testing**

Jerome L. Belinson<sup>1,4</sup>, Hui Du<sup>2</sup>, Bin Yang<sup>3</sup>, Ruifang Wu<sup>2</sup>, Suzanne E. Belinson<sup>1</sup>, Xinfeng Qu<sup>5</sup>, Robert G. Pretorius<sup>6</sup>, Xin Yi<sup>7</sup> and Philip E. Castle<sup>8</sup>

**PCR-based matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF).**

Para introducir autotoma es necesario:

- Fortalecer la práctica de la atención primaria, la clínica y la participación comunitaria.
- Necesidad de fortalecer a enlaces comunitarios con grupos de abogacía.
- Generar infraestructura necesaria.



**Looking ahead: a case for human papillomavirus testing of self-sampled vaginal specimens as a screening strategy**

Int. J. Cancer: **129**, 517–527 (2011)

Patti E. Gravitt<sup>1,2</sup>, Jerome L. Belinson<sup>3</sup>, Jorge Salmeron<sup>4</sup> and Keerti V. Shah<sup>2</sup>

En un ECA en mujeres no usuarias de detección de CACU:

La autotoma incrementó la detección en 30.8% comparadas con 6.5% de mujeres que acudieron a una invitación personalizada.



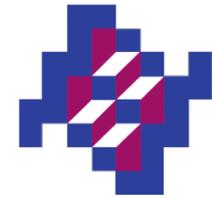
Int. J. Cancer: **130**, 1128–1135 (2012)



**Experience with high-risk human papillomavirus testing on vaginal brush-based self-samples of non-attendees of the cervical screening program**

Murat Gök<sup>1</sup>, Folkert J. van Kemenade<sup>1</sup>, Daniëlle A.M. Heideman<sup>1</sup>, Johannes Berkhof<sup>2</sup>, Lawrence Rozendaal<sup>1</sup>, Johan W.M. Spruyt<sup>3</sup>, Jeroen A.M. Beliën<sup>1</sup>, Milena Babovic<sup>4</sup>, Peter J.F. Snijders<sup>1</sup> and Chris J.L.M. Meijer<sup>1</sup>

# La prueba de VPH de AR es una nueva tecnología disponible para detección de cáncer cervical



*Cancer Causes and Control* 14: 505–512, 2003.  
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## Comparison of HPV-based assays with Papanicolaou smears for cervical cancer screening in Morelos State, Mexico

Jorge Salmerón<sup>1\*</sup>, Eduardo Lazcano-Ponce<sup>2</sup>, Attila Lorincz<sup>3</sup>, Mauricio Hernández<sup>2</sup>, Pilar Hernández<sup>2</sup>, Ahidé Leyva<sup>2</sup>, Mario Uribe<sup>4</sup>, Horacio Manzanares<sup>4</sup>, Alfredo Antunez<sup>4</sup>, Enrique Carmona<sup>5</sup>, Brigitte M. Ronnett<sup>6</sup>, Mark E. Sherman<sup>6</sup>, David Bishai<sup>7</sup>, Daron Ferris<sup>8</sup>, Yvonne Flores<sup>1</sup>, Elsa Yunes<sup>9</sup> & Keerti V. Shah<sup>9</sup>

<sup>1</sup>Unidad de Investigación Epidemiológica y en Servicios de Salud, Instituto Mexicano del Seguro Social, Morelos, México; <sup>2</sup>Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, Morelos, México; <sup>3</sup>Digene Corporation, Gaithersburg, MD, USA; <sup>4</sup>Departamento de Ginecología, Hospital Regional de Cuernavaca, Instituto Mexicano del Seguro Social, Morelos, México; <sup>5</sup>Departamento de Patología, Hospital Regional de Cuernavaca, Instituto Mexicano del Seguro Social, Morelos, México; <sup>6</sup>Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA; <sup>7</sup>Department of Population and Family Health Sciences, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA; <sup>8</sup>Medical College of Georgia, Augusta, Georgia, USA; <sup>9</sup>Department of Molecular Microbiology and Immunology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA

Received 16 July 2002; accepted in revised form 10 March 2003

**Key words:** cervical cancer, HPV assays, Mexico, pap smears.

Table 3. Performance of the Pap smear, SS-HPV and CS-HPV testing strategies for cervical cancer screening

Test	Pap	HPV-SS	HPV-CS
Relative sensitivity	59.4	71.3	93.1
(95% CI)	(49.2–68.9)	(61.3–79.6)	(85.8–96.9)
Relative specificity	98.3	89.2	91.8
(95% CI)	(98.0–98.6)	(88.5–89.9)	(91.2–92.4)
Positive predictive value	36.1	9.1	14.9
(95% CI)	(28.9–44.0)	(7.2–11.4)	(12.2–17.9)
Negative predictive value	99.5	99.6	99.9
(95% CI)	(99.2–99.6)	(99.4–99.7)	(99.78–100.0)

**Autotoma vaginal es una alternativa de tamizaje**

**Pero no es superior que la prueba dirigida por un profesional de salud**

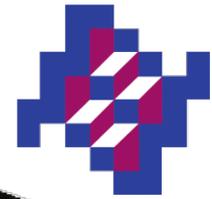
**Auto-toma vaginal en casa**

**Incremento rápido de cobertura**

**Tecnología disponible en áreas marginadas**

**Alternativa de rescate en mujeres no usuarias de los servicios de atención.**

**Seguridad aceptable**



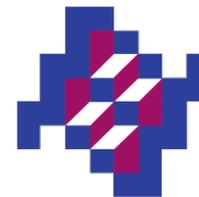
**THE LANCET**  
**November 2011**

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

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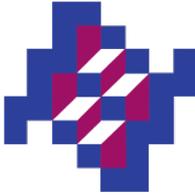
Eduardo Lazcano-Ponce\*, Attila Tibor Lorincz\*, Aurelio Cruz-Valdez, Jorge Salmerón, Patricia Uribe, Eduardo Velasco-Mondragón, Pilar Hernandez Nevarez, Rodrigo Diaz Acosta, Mauricio Hernández-Avila

# Auto-toma vaginal en casa es una invaluable herramienta de detección para áreas marginadas: Un ensayo clínico con base poblacional



	Prueba de VPH	Prueba de Pap
Número	12.330	12.731
Prueba Positiva	9.8%	0.38%
NIC 2+ x104	<b>117.4 (SR: 3.4)</b>	<b>34.4</b>
Cáncer invasor x104	<b>30.4 (SR: 4.2)</b>	<b>7.2</b>
VPP NIC 2+	12.2%	90.5%

VPH= virus de papiloma humano. NIC=neoplasia intraepitelial cervical. VPP=valor predictivo positivo  
 SR: Sensibilidad relativa comparada con Pap (sensibilidad: 1.0)



# Comparación del efecto de muestra auto-tomada en casa vs Pap en Mexicanas de zonas rurales. The March Study

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

Eduardo Lazcano-Ponce\*, Attila Tibor Lorincz\*, Aurelio Cruz-Valdez, Jorge Salmerón, Patricia Uribe, Eduardo Velasco-Mondragón, Pilar Hernandez Nevaraz, 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.<sup>1</sup> In 2008, about 37 000 deaths related to cervical cancer occurred in the Americas, costing about 545 000 DALYs.<sup>1,2</sup> Findings from randomised trials of more than 200 000 women<sup>3–6</sup> 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-analyses<sup>7–11</sup> 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.<sup>12</sup> 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 care<sup>13</sup> and could increase population coverage<sup>14</sup> 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.



**Lancet 2011; 378:**  
\*These authors contributed equally  
Centro de Investigación en Salud Poblacional, Instituto Nacional de Salud Pública, Cuernavaca, Morelos, Mexico (Prof E Lazcano-Ponce PhD, Prof A Cruz-Valdez PhD, P H Nevaraz MPH, Prof R Diaz Acosta PhD); Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London, London, UK (Prof A T Lorincz PhD); Unidad de Investigación Epidemiológica en Servicios de Salud, Instituto Mexicano del Seguro Social, Cuernavaca, Morelos, Mexico (J Salmerón PhD); Centro Nacional de Equidad Género (P Uribe MD), and Subsecretaría de Prevención y Control de Enfermedades (M Hernández-Avila PhD) Secretaría de Salud, Mexico city DF, Mexico; and Morgan State University School of Community Health and Policy, Baltimore, MD, USA (Prof E Velasco-Mondragón PhD)  
Correspondence to: Prof Attila T Lorincz, Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine, Queen Mary University of London, London EC1M 6BQ, UK; a.lorincz@qmul.ac.uk

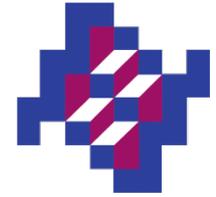
La prueba del VPH detecta **4,2 veces** más cánceres invasivos que la citología.

Tasa de Detección

Prueba VPH-AR 30.4 x 100,000

VS

Citología 7.2 x 100,000

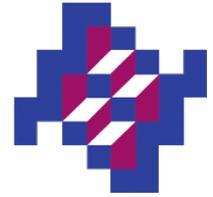


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# **Efecto de la Autotoma vaginal para detección de VPH en la prevención de cáncer cervical: *el estudio de 101,552 mujeres.***

E Lazcano-Ponce, A Lôrincz , **A Cruz-Valdez**, J Salmerón-Castro, R Rojas, P Hernández-Nevarez, M Hernández-Avila.

# Objetivos



## Primario

- **Evaluar el efecto de la prueba de VPH-AR en el ámbito poblacional mediante auto-muestreo del canal vaginal en 101,552 mujeres del Estado de Morelos.**
  - **Cuantificar pruebas diagnósticas utilizando la corrección del sesgo por verificación.**
    - ◆ Utilización de controles negativos a la prueba de VPH.
    - ◆ Determinación de sensibilidad, especificidad, VPP.
    - ◆ Cocientes de verosimilitud: Positivo y negativo.

## Secundario

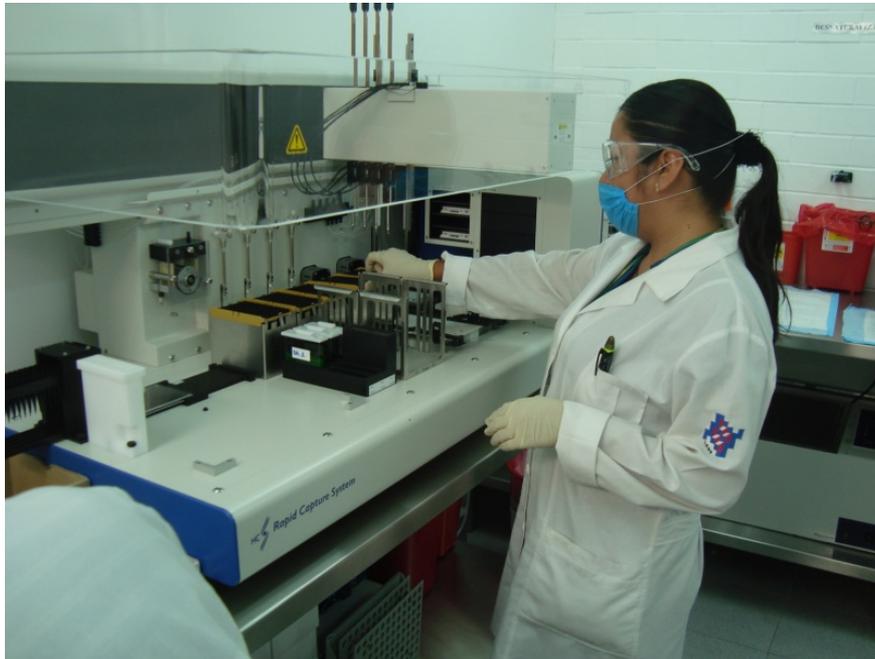
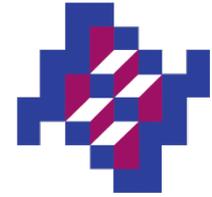
- **Evaluar la práctica de la colposcopia en condiciones reales no controladas.**

# Determinación de ADN de VPH de alto riesgo.

Instituto Nacional de Salud Pública

## Técnica de Hybrid Capture<sup>®</sup> 2 (hc2)

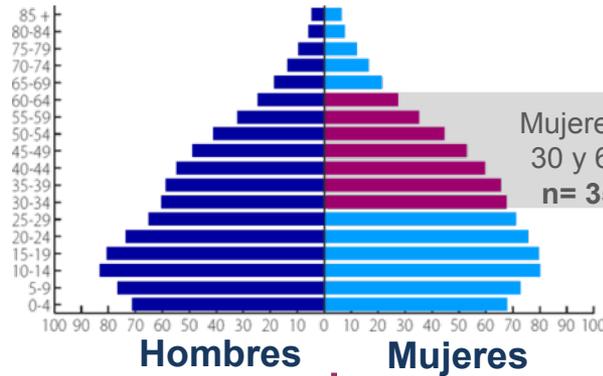
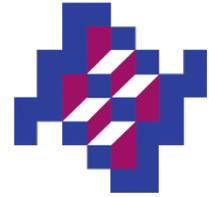
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**Detección genérica de 13 tipos de  
VPH de alto riesgo  
16, 18, 31, 35, 39, 45, 51, 56, 58, 59  
y 68**

**Rapid Capture<sup>®</sup> System**

# Pirámide de población de Morelos, 2010



Mujeres entre 30 y 64 años  
n= 352, 659

156 324 con seguridad social

196 335 sin seguridad social



## El Estudio Morelos

Intervención en mujeres entre 30 y 64 años sin seguridad social

n=121 650

1 395 comunidades de 33 municipios

Auto-toma vaginal en casa (SS)  
n=101,552(83.5%)

Muestras tomadas en clínica (CS)n=10 437 (16.5%)

VPH—  
n=98 101 (88.92%)

VPH +  
n=13 112 (11.08%)

VPH+  
n= 1 094 (10.6%)

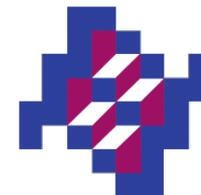
VPH —  
n=9 343 (89.4%)

Selección aleatoria por edad  
n=2 241 (2.4%)

Referidas para Pap y colposcopia, y estudios n=11 396

Selección aleatoria por edad  
n=1438 (1.8%)

# Resultados de estudios complementarios de colposcopia y determinación histológica de los casos.



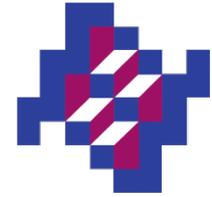
	Impresión de la colposcopia n= 11,396	
	VPH -	VPH+
<b>Satisfactoria</b>	<b>2,253</b>	<b>8,290</b>
<b>LSIL</b>	<b>140</b>	<b>608</b>
<b>HSIL</b>	<b>9</b>	<b>87</b>
<b>Cáncer</b>	<b>0</b>	<b>9</b>
<b>Total</b>	<b>2,402</b>	<b>8,994</b>



	Estudios histológicos de las biopsias	
	VPH -	VPH+
<b>Negativo</b>	<b>151</b>	<b>597</b>
<b>ASCUS</b>	<b>12</b>	<b>54</b>
<b>NIC 1</b>	<b>15</b>	<b>110</b>
<b>NIC 2</b>	<b>2</b>	<b>28</b>
<b>NIC 3</b>	<b>0</b>	<b>71</b>
<b>Invasor</b>	<b>0</b>	<b>54</b>
<b>Total</b>	<b>180</b>	<b>914</b>

# Auto-toma vaginal para determinación de VPH

Es una prueba altamente confiable y segura para detección de NIC 3+



## Pruebas Diagnósticas

### NIC 2 +

- Sensibilidad 64.9% (63.1-66.7)
- Especificidad 90.7% (90.5-90.9)
- VPP 16.9% (16.2-17.6)

### NIC 3 +

- Sensibilidad 100% (99.8-100)
- Especificidad 90.5% (90.3-90.6)
- VPP 13.8% (13.1 -14.5)

## Cocientes de verosimilitud

### NIC 2 +

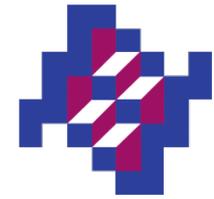
- Positiva 6.43 (6.21-6.67)
- Negativa 0.41 (0.39-0.43)

\* La sensibilidad relativa del Papanicolaou es de 24% en el ámbito poblacional.

Pruebas Diagnósticas corregidas por el sesgo de verificación\*

Begg CB, Greenes RA: Assessment of diagnostic tests when disease verification is subject to selection bias. Biometrics 1983, 39(1):207-215 .

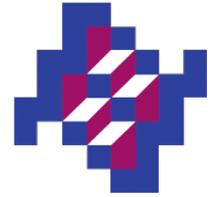
# Heterogeneidad de la práctica de colposcopia en condiciones reales



- Baja proporción de obtención de biopsias en saturación del servicio***

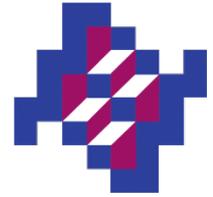
Clinicas de colposcopia	Mujeres evaluadas		Proporción de biopsias		Detección de NIC2+			
	HPV pos (n=8,208)	HPV neg (n=2,397)	HPV pos (n=899)	HPV neg (n=179)	HPV pos % (n=152)	95%CI	HPV neg % (n=2)	95% CI
1	289	127	34.3%	20.5%	3.8% (11)	1.6-6.0	0 % (0)	0
2	368	130	8.7%	3.8%	3.0% (11)	1.2-4.7	0 % (0)	0
3	843	562	14.8%	7.8%	2.9% (24)	1.7-4.0	0.18% (1)	-0.2-5.3
4	613	268	12.6%	9.0%	2.5% (15)	1.2-3.7	0 % (0)	0
5	2,323	24	12.4%	4.2%	2.0% (46)	1.4-2.5	0 % (0)	0
6	1,114	594	8.3%	5.9%	1.4% (16)	0.7-2.1	0 % (0)	0
7	2, 658	692	7.0%	6.4%	1.1% (29)	0.7-1.4	0.14% (1)	-0.1-4.3

# Conclusiones



- **Primera introducción a gran escala de la prueba del VPH en la rutina de programas de prevención y control del cáncer cervical de un país de ingreso medio como México.**
- **La prueba del VPH de muestras vaginales auto-tomadas es una buena opción de detección en condiciones de rutina a gran escala.**
- **Buena sensibilidad clínica y especificidad para NIC3+**
- **Cuando se decide enviar a colposcopia a mujeres VPH positivas se produce una elevada referencia que condiciona una menor precisión diagnóstica.**
- **Riesgo de mala clasificación de enfermedad, por un bajo**

# Propuesta actual



## ➤ Primer tamizaje con VPH

- Inicio del Tamizaje: 30-35 años

## ➤ Áreas sin infraestructura o rescate de mujeres sin Pap:

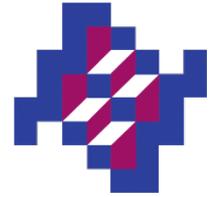
- Autotoma y protocolos de “ver y tratar”

## ➤ Triage de VPH Positivo:

- citología y/o otros biomarcadores
- biopsias múltiples en colposcopia

## ➤ *Recomendación EU 2012/ iniciado en Holanda y México, en consideración en otros*

# Políticas de prevención y control del cáncer cervical en México basadas en la prueba de VPH.



## ➤ Autotoma vaginal

- Visitas domiciliarias secundarias a campañas de salud
- Semana Nacional de Salud
- Preferencia individual al interior de los servicios de salud.

## ➤ Citología de base líquida

- Ventaja de realización de un solo muestreo y análisis posterior en VPH+
- Utilización cuando exista elevada relación costo-beneficio = Costo similar al Pap tradicional

## ➤ Esquema extendido de tamizaje

- Dos pruebas negativas de VPH en 5 años
- La tercera prueba deberá hacerse cada 10 años hasta los 64 años.