

**NCC** 国家癌症中心  
 中国科学院 北京协和医学院  
 中国医学科学院肿瘤医院  
 Cancer Hospital Chinese Academy of Medical Sciences

## Secondary prevention of cervical cancer

Xue-Lian Zhao, MD, PhD  
 National Cancer Centre  
 Cancer Hospital, Chinese Academy of Medical Sciences  
 and Peking Union Medical College

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### Secondary prevention: cervical cancer screening

- Cervical cancer progresses slowly
- Feasible screening methods available
- Treatment of precancerous lesions is effective
- Screening may reduce morbidity and mortality

*Ref: Quinn M, Bubb P, James A, et al. BMJ. 1999;319(7188):964-968.  
 Chaw PA, Zhanqun A, Oubon A, et al. Lancet. 2019;393(10167):169-182.*

### Global strategy to eliminate cervical cancer

Threshold for Elimination as a Public Health Problem:  
 Age-adjusted incidence rate < 4 / 100,000 women

**2030 Targets**

- Coverage: 70%;
- Methods: high-performance test
- Population: by 35 and again by 45

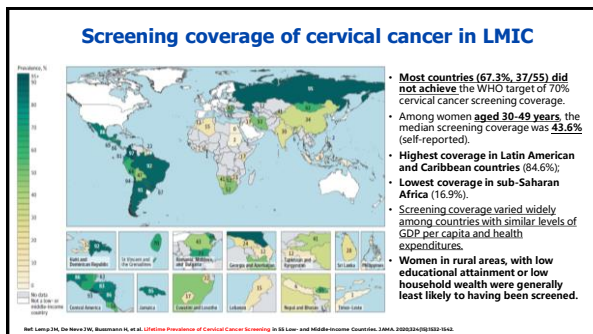
SDG 2030 Target 3.4:  
 30% reduction in mortality from NCDs

### Ever in lifetime screening coverage (2019), women aged 30-49y by country

Cov < 70 = 126 countries  
 Cov >= 70 = 76 countries

ICO  
 Generalitat de Catalunya Departament de Salut  
 hmj  
 World Health Organization

Countries with no original data for any screening method:  
 AND, BGD, BHR, BHS, BIE, BVI, CAF, CHL, CUB, DZA, GRC, HRV, IDN, JOR, KHM, KWT, LBN, LKA, MEX, MYS, NLD, NPL, PAK, PAN, PER, PHL, PRK, PSE, QAT, RWA, SLE, SVK, THA, TJK, TUN, TZA, UGZ, UZB, VNM, YEM, ZMB, ZWE

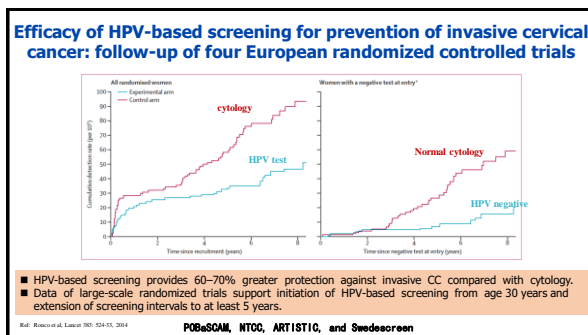


### Achieving 70% Coverage of Screening: Strategic Actions

National scale-up of screening for different settings	Increased service delivery with high quality and coverage
Sufficient, affordable supply of screen technologies & products	Monitor progress

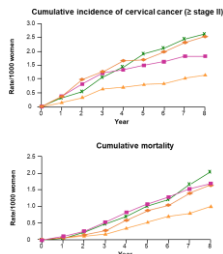
### Transition in Cervical Cancer Screening

1900 – 1950s	1950s – 2000s	2000s – Today
VIA & VILI	Pap smear / LBC	HPV tests
<ul style="list-style-type: none"> <li>• Low technology and cost</li> <li>• Easily trained</li> <li>• Point of Care</li> <li>• Subjective, low sensitivity</li> <li>• Labor cost</li> </ul>	<ul style="list-style-type: none"> <li>• 50-80% sensitivity</li> <li>• Subjective, highly depends on the qualification of cytopathologists</li> <li>• Labor cost</li> <li>• Stringent training and quality control</li> </ul>	<ul style="list-style-type: none"> <li>• High performance &gt;90% sensitivity</li> <li>• Objective and reproducible</li> <li>• High throughput</li> <li>• Availability of self-sampling</li> </ul>



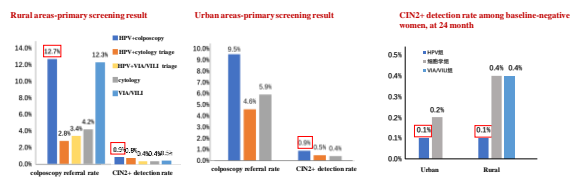
### A cluster-randomized, controlled trial of HPV Screening for Cervical Cancer in Rural India

- A total of 131,746 healthy women between the ages of 30 and 59 years
- Cluster-randomized trial
  - HPV testing (HC2)
  - Pap smear
  - VIA
  - Control (information on screening and where to obtain it)
- Women who had positive results on screening underwent colposcopy and directed biopsies.
- A single round of HPV testing was associated with a significant reduction in the numbers of advanced cervical cancers and deaths from cervical cancer.



Ref: Sukkiammarasorn R, et al. N Engl J Med 2019; 380:1385-1394.

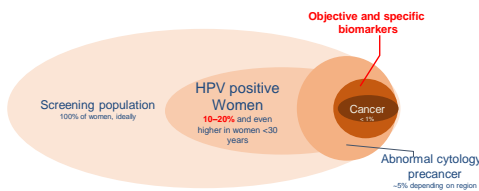
### Effectiveness of High-risk Human Papillomavirus Testing for Cervical Cancer Screening in China, A Multicenter, Open-Label, Randomized Clinical Trial



- HPV detection as a primary screening method, the detection rate of CIN2+ is about twice that of cytology or VIA/VILI.
- The colposcopy referral rate for hrHPV-positive was reduced by cytology triage, with significantly higher CIN2+ yields than cytology.
- At 24 months, baseline-negative women in the hrHPV arm had significantly lower risk ratios than those with cytology, or VIA/VIL for CIN2+.

Ref: Zhang JJ, et al. Effectiveness of High-risk Human Papillomavirus Testing for Cervical Cancer Screening in China: A Multicenter, Open-Label, Randomized Clinical Trial. JAMA Oncology. 2021;12:1016-1024. (published online first)

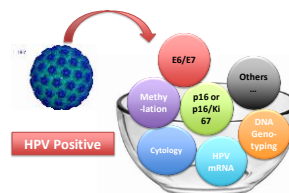
### BUT!!! HPV infection is frequent, cervical cancer is rare



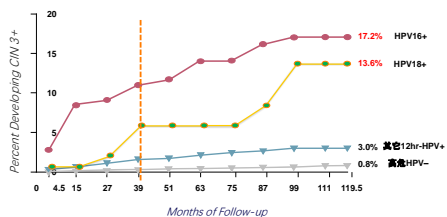
Potential harm: over diagnosis, over treatment!

Source: adapted from Dr. Johannes Schweizer' slides on the 3rd annual caacc

### Possible triage biomarkers associated with cervical lesions



### 10 Year Risk of CIN 3+ in Women >30 Yrs with NILM Cytology - Predictive Value of HPV Genotype



<sup>1</sup> Hwang ME, et al. J Natl Cancer Inst 2005; 97:1073-1078

### p16INK4a as a triage biomarker

Study	Test	Population	Sample	Outcome	Sensitivity	Specificity
1	P16 cytology	HPV-positive women	1137	CIN2+ CIN3+	88% 91%	61% 59%
2	P16 cytology	HPV-positive women	793	CIN2+ CIN3+	66.9% 77.8%	NA NA
3	P16 cytology	ASCUS LSIL	385 425	CIN2+ CIN3+	92.6% 92.0%	63.2% 37.1%
4	P16/Ki67 cytology	HPV-positive & NILM	425	CIN2+ CIN3+	91.9% 96.4%	82.1% 76.9%
5	P16/Ki67 cytology	ASCUS LSIL	361 415	CIN2+ CIN3+	92.2% 94.2%	80.6% 68.0%
6	P16/Ki67 Cytology	HPV+&ASCUS LSIL	140 264	CIN2+ CIN3+	81.8% 86.8%	62.3% 57.6%
7	P16/Ki67 cytology	ASCUS+LSIL	256	CIN2+	89.7%	73.1%

<sup>1</sup> Densit F, et al. Gynecol Oncol 2008;97:452-455; <sup>2</sup> Densit F, et al. Lancet Oncol 2011;12:158-161; <sup>3</sup> Bhatnagar S, et al. Cancer Cytopathol 2012;22:100-107; <sup>4</sup> Wang Y, et al. Gynecol Oncol 2011;121:55-61; <sup>5</sup> Schmitt D, et al. Cancer Cytopathol 2011;118:158-161; <sup>6</sup> Weissenborn N, et al. Cancer Res 2012;72:618-622; <sup>7</sup> Ijzerman M, et al. Br J Cancer 2009;101:107-109.

### HPV E6/E7 oncoprotein as a triage biomarker

OncoE6/E7 Eight HPV Type Test  
Target HPV types: 16,18,31,33,35,45,52,58 (account for ~90% of CC)

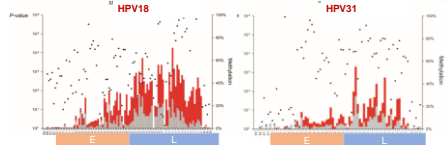
Triage tests	Screening performance of different tests for CIN2+ diagnoses among HPV positive women					
	Colposcopy referral rate (%)	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	NRR
<b>E6/E7 (8 types)</b>	17.37	87.74 (84.63-93.32)	89.47 (84.74-93.14)	88.67 (83.82-97.84)	95.33 (92.44-97.15)	2.14
<b>Geno (8 types)</b>	58.30	90.32 (74.23-97.96)	46.05 (39.45-52.76)	18.54 (16.16-21.19)	97.22 (92.21-99.04)	5.39
<b>E6(16/18)</b>	11.20	81.61 (33.06-96.85)	94.30 (90.45-96.93)	55.37 (39.63-69.76)	93.46 (90.87-95.38)	1.81
<b>Geno(16/18)</b>	20.08	54.84 (26.43-72.08)	84.65 (79.36-89.07)	32.69 (23.80-43.03)	93.24 (90.31-95.33)	3.06
<b>LBC (ASC-US+)</b>	50.97	87.10 (70.17-96.37)	53.95 (47.24-60.55)	20.45 (14.46-23.81)	96.85 (92.44-9)	4.89

- 100% sensitivity and 86% specificity for CIN3+ detection; while the specificity of LBC was 51% and DNA genotyping for respective eight types was 43%
- E6/E7 oncoprotein detection showed a good "trade-off" between sensitivity and specificity with more efficient colposcopy referrals
- This is of great importance to maximize the benefits of HPV-based screening program, especially applicable for the areas with high HPV prevalence and low-resources.

<sup>1</sup> Hwang ME, et al. J Natl Cancer Inst 2005; 97:1073-1078


### DNA methylation as a triage biomarker

Genome-wide region	CpG sites	Control (n = 28 individuals)			Paraneoplastic (n = 28 individuals)			P <sup>1</sup>
		Mean (SD)	Median (IQR)	OR (95% CI)	Mean (SD)	Median (IQR)	OR (95% CI)	
E6/E7	3413	0.01 (0.00)	0.01 (0.00)	3.46 (0.89-14.78)	0.02 (0.00)	0.02 (0.00)	0.002	
E6/E7	3415	0.01 (0.00)	0.01 (0.00)	1.49 (0.34-7.49)	0.02 (0.00)	0.02 (0.00)	0.017	
E6/E7	3420	0.01 (0.00)	0.02 (0.01)	2.79 (1.01-7.69)	0.01 (0.00)	0.01 (0.00)	0.004	
L2	4441	0.07 (0.05)	0.10 (0.07)	3.17 (1.11-9.05)	0.03 (0.00)	0.03 (0.00)	0.003	
L2	5170	0.02 (0.01)	0.04 (0.01)	4.01 (1.47-10.91)	0.01 (0.00)	0.01 (0.00)	0.002	
L2	5276	0.08 (0.06)	0.14 (0.10)	1.65 (0.71-3.86)	0.07 (0.04)	0.07 (0.04)	0.012	
L1	5811	0.05 (0.03)	0.12 (0.02)	4.18 (1.47-11.39)	0.04 (0.00)	0.04 (0.00)	0.003	
L1	6680	0.01 (0.01)	0.04 (0.01)	3.19 (1.70-6.06)	0.01 (0.00)	0.01 (0.00)	0.005	
L1	7039	0.02 (0.01)	0.04 (0.01)	3.14 (1.17-8.41)	0.04 (0.01)	0.04 (0.01)	0.003	



<sup>1</sup> Mollath L, et al. J Natl Cancer Inst 2012;104:556-561; <sup>2</sup> Weissenborn N, et al. J Natl Cancer Inst 2012;104:1738-43

### Move Toward High Performance Tests and Role of Triage test



**For the general population of women**

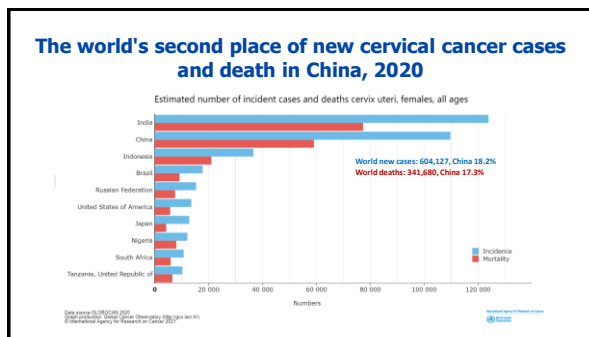
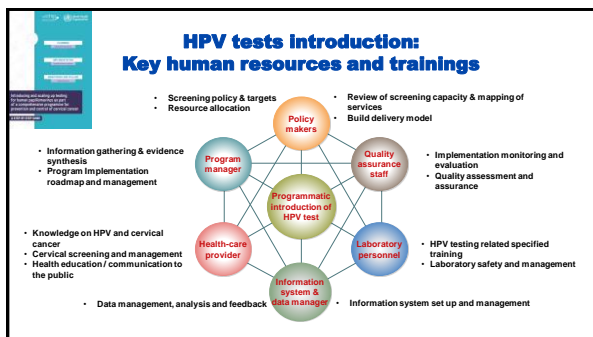
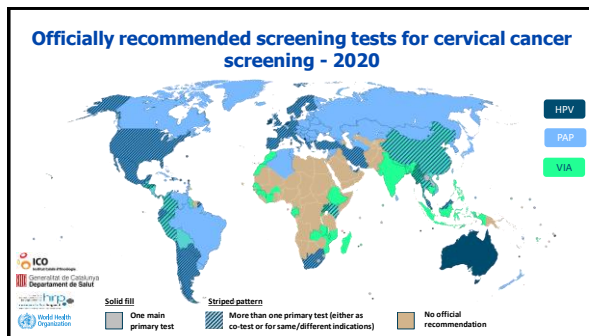
**Screen and Treat OR Screen, Triage and Treat**

- HPV DNA as primary screening test
- Starting at age 30
- Every 5 to 10 years screening interval

**For women living with HIV**

**Screen, Triage and Treat - ONLY**

- HPV DNA as primary screening test
- Starting at age 25
- Every 3 to 5 years screening interval



### Journey of HPV tests introduction in China

<p>1990s</p> <p>2006</p> <p>2015</p> <p>2017</p> <p>2020</p> <p>2019</p> <p>2021</p>		<ul style="list-style-type: none"> <li>➢ Build scientific evidence             <ul style="list-style-type: none"> <li>• High performance and feasibility of implementing multiple HPV tests in China across various settings</li> </ul> </li> <li>➢ China Food and Drug Administration (CFDA) guidelines - validating HPV tests for cervical cancer screening             <ul style="list-style-type: none"> <li>• 100+ HPV testing products available on market</li> <li>• Validators are ongoing, e.g. primary &amp; co-testing</li> </ul> </li> <li>➢ Large scale &amp; real world demonstration of HPV testing             <ul style="list-style-type: none"> <li>• Effectiveness and feasibility of HPV testing for primary screening &amp; triage strategy in rural and urban China</li> </ul> </li> <li>➢ Optimizing strategies for comprehensive cervical cancer prevention and control</li> <li>➢ Developing plans to cervical cancer elimination through tailored optimal pathway</li> </ul>
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Hu, Zhenfeng, et al., The Lancet Oncology, 2010, 11(12): 1188-1197; Chen, H., et al., Lancet Oncol, 2008, 9(10):939-950; Zhang, L, et al., JAMA Oncol, 2011, 7(2): 242-270; Xia, C, et al., The Lancet Public Health, 2015, 4(9): e462-e472; Xia, C, et al., BMC Med, 2021, 19(1): 62.

### Human resources and trainings in China

<p><b>Key stakeholders</b></p> <p>National Cervical Cancer Consortium Annual meeting since 2004</p> <p>Blue Rainbow Initiative</p> <p>HPV testing training on site</p>	<p><b>Public publicity and education</b></p> <p>GIVE LOVE NOT HPV</p> <p>Women's Day &amp; International HPV Awareness Day activities across China</p> <p>Media transmission -- World Cancer Day</p> <p>Self-sampling Training in community</p>
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COVID-19 boosted the nucleic acid PCR testing: laboratory platform and personnel's trainings

### Accelerating Cervical Cancer Elimination In China

<p><b>Scaling up of Screening</b></p> <p>National introduction of cervical cancer screening in rural women (2009)</p> <p>Demonstration of HPV testing in national program (2014)</p> <p>Cervical Cancer Screening Program incorporated into National Basic Public Health Service nationwide (2019)</p>	<p><b>Promotion on HPV vaccination</b></p> <p>Govt announces free HPV vaccination program</p> <p>Women to offer free HPV vaccinations to girls to help prevent cervical cancer</p> <p>Free HPV vaccination in Cities of Ordos, Xiamen and Guangdong province in China (2020-2021)</p>	<p><b>Supports to Elimination</b></p> <p>China supports WHO's Global Strategy to Accelerate the Elimination of Cervical Cancer</p> <p>WHO's phased strategy</p> <p>Healthy China &amp; Healthy City Initiative Innovation pilots of CC elimination (2021)</p>
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### Thanks for your attention!

<p><b>90%</b> of girls fully vaccinated with HPV vaccine by age 15 years.</p>	<p><b>70%</b> of women are screened with a high-performance test by 35 years of age and again by 45 years of age</p>	<p><b>90%</b> of women identified with cervical disease receive treatment (90% of women with precancer treated, and 90% of women with invasive cancer managed).</p>
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Global movement to eliminate cervical cancer