

Experience with careHPV implementation in China



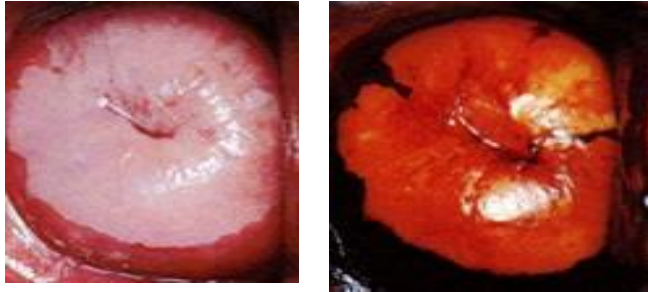
You-Lin Qiao
Professor and Director
Department of Cancer Epidemiology (DCE)
Cancer Hospital (CI)
Chinese Academy of Medical Sciences (CAMS)
Peking Union Medical College (PUMC)
National Cancer Center (NCC)

Main Content

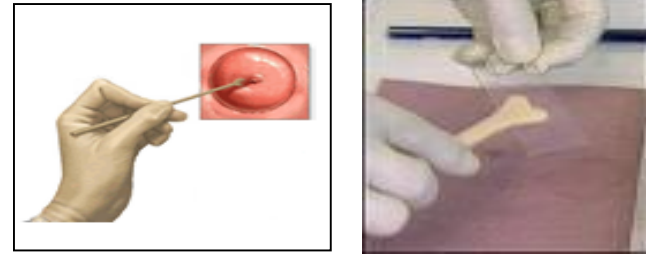
1. Introduction to HPV test for cervical cancer screening in China
2. Story of developing careHPV
3. Implementation of CareHPV in China
4. Conclusion

1. Introduction to HPV test for cervical cancer screening in China

**Visual inspection with
acetic acid & Lugol's iodine
(VIA & VILI)**



Conventional cytology



**HPV DNA tests:
Hc2, Cobas & Aptima etc.**



**Liquid-based Cytology
ThinPrep & SurePath**



Evaluation of Screening Test – SPOCCS I (N = 1997)

Screening Test	Sensitivity (\geq CIN II)	Specificity (\geq CIN II)	Accuracy (\geq CIN II)
HPV Self Test (\geq 1.0 pg/ml)	83.5% (71/85)	85.9% (1634/1903)	85.8%
HPV Direct Test (\geq 1.0 pg/ml)	95.2% (79/83)	85.9% (1507/1755)	86.3%
ThinPrep Pap (\geq LSIL)	87.2% (75/86)	93.5% (1783/1907)	93.2%
Colposcopy (\geq LSIL)	81.4% (70/86)	76.5% (1462/1911)	76.7%
Visual Inspection (\geq LSIL)	70.9% (61/86)	74.3% (1420/1911)	74.2%
Fluorescent Spectroscopy	94.0% (81/86)	9.0% (175/1934)	0.1%

HPV DNA & Liquid-based cytology Co-Testing Results from SPOCCS-I

Tests	Pathology (%)		
	≥CIN II	≥CIN III	≥Cancer
HPV (≥1.0pg/ml)	95.2	100.0	100.0
ThinPrep LBC (≥LSIL)	87.2	93.0	100.0
HPV + ThinPrep	98.0	100.0	100.0

乔友林 等. 中国医学科学院学报, 2002; 24(1): 50-53.

Belinson JL, Qiao YL, et al. Int J Gynecol Cancer. 2003;13(6):819-826.

Screening Year	Study Population	Sample Size	Age Range	CIN1	CIN2	CIN3+	Screening Tests
1999	Xiangyuan,Shanxi	1997	35-45	127	43	43	HC2, Fluorescence test, LBC, VIA, colposcopy
2001 2002	Xiangyuan and Yangcheng, Shanxi	9034	35-50	341	173	202	HC2, LBC, VIA, AFB
2003	Xiangyuan,Shanxi	1803	30-49	63	25	52	HC2, LBC, VIA
2004	Jing'an,Jiangxi	1995	30-49	82	37	62	HC2, LBC, VIA, VILI, colposcopy
2004	Shenzheng,Guangdong	1109	15-59	36	11	3	HC2, LBC, VIA, colposcopy
2004	Yangchen,Shanxi	721	15-59	41	18	14	HC2, Fluorescence test, LBC, VIA, VILI, colposcopy
2005	Wudu,Gansu	2034	30-49	34	21	11	HC2, LBC, VIA, VILI
2005	Shenyang,Liaoning	710	17-59	12	8	3	VIA, VILI, LBC
2006	Qinxian,Shanxi	2493	30-49	49	24	15	HC2, LBC, VIA, VILI, colposcopy
2006	Xiangyuan,Shanxi	884	16-54	41	8	14	HC2, LBC, VIA
2006	Beijing	795	16-54	7	3	6	HC2, LBC, VIA
2006	Hetian,Xinjiang	883	16-54	12	6	11	HC2, LBC, VIA
2006	Xinmi,Henan	879	16-54	45	6	4	HC2, LBC, VIA
2007	Shanghai	774	16-54	9	4	7	HC2, LBC, VIA
2007	Qinxian,Shanxi	818	30-50	9	5	5	HC2, careHPV, LBC, VIA, VILI
2007	Wuxiang&Xiangyuan	2388	30-54	60	47	23	HC2, careHPV, LBC, VIA, colposcopy
2008	Jiangsu	316	18-25	9	5	5	HC2, LBC, VIA
2008	Xiangyuan & QinXian	1056	30-59	32	10	14	HC2, LBC, VIA, VILI

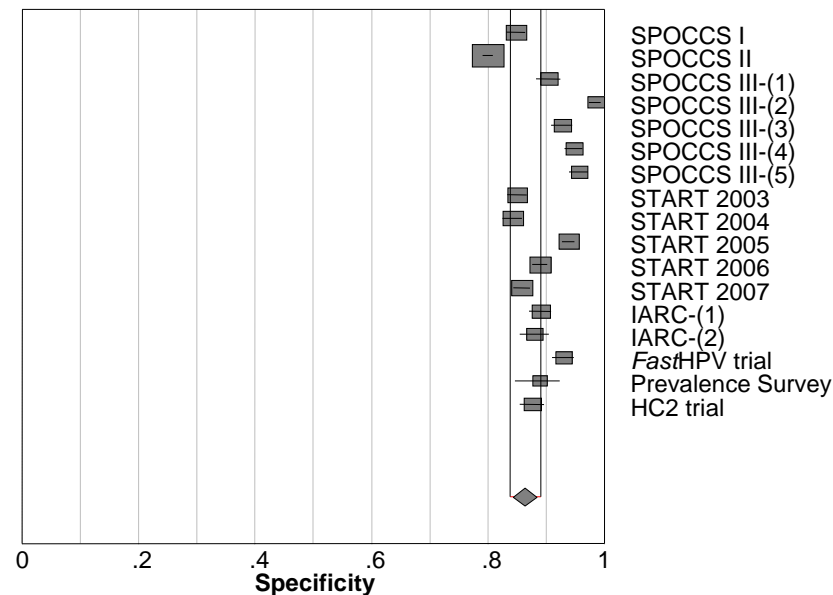
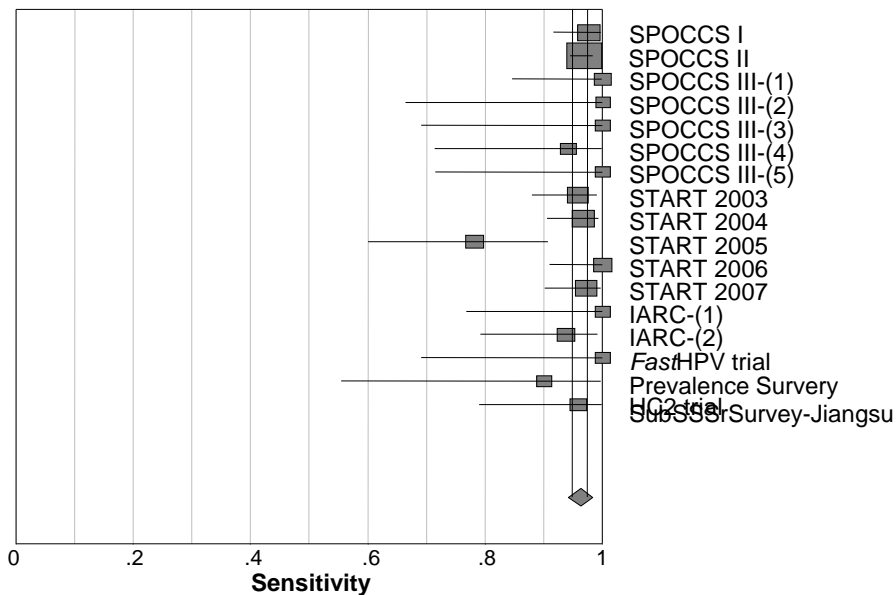
Location of Counties/cities



Note: This is not a complete map of China's territory.

Sensitivities & specificities for the high-risk HPV DNA test (hc2) (HPV DNA positivity: RLU/Co \geq 1pg/ml)

At CIN 2+ Cutoff



Pooled Sensitivity=96.3% (94.9-97.4). **Pooled Specificity=86.4% (83.8-89.0).**

Chi-square=25.55, df=16, p=0.061

Chi-square=757.21, df=16, p<0.0001

Zhao et al. *Lancet Oncology*. 2010;Dec.11(12):1160-1171. (Fast-track with commentary)

Main Content

1. Introduction to HPV test for cervical cancer screening in China
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Can we develop a cervical cancer screening test that can be easily implemented and afforded in developing countries?

- Easy-to-use, Produce a robust assay in a field setting
- Deliver high specificity and sensitivity
- Improve cost-effectiveness
- Shorten testing time; Simplify the protocol
- Adapt to high-throughput testing
- Increase portability (access to underserved women)
- Adopt self-collection of samples
- Inexpensively, rapidly and effectively screen many women at a time for cervical cancer
- Designed to meet the needs of low-resource markets.

Screening Technologies to Advance Rapid Testing for Cervical Cancer Prevention

The *START* Project

Clinical Collaborators

USA: Dr. John Sellors Program for Appropriate Technology in Health, Seattle

IARC-WHO: Dr. R. Sankaranarayanan, Screening Group, Lyon, France



Dr. Qiao You-Lin and the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS) team in Beijing, Shanxi, Jiangxi, and Gansu



Dr. K. Dinshaw, Tata Memorial Hospital, Mumbai; Dr. B. Nene, Nargis Dutt Memorial Hospital, Barshi

Grant of Bill & Melinda Gates Foundation.

From: Sellors, John [mailto:jsellors@path.org]
Sent: 2003-1-11, 3:20
To: qiao
Cc: Britton, Margaret; Shannon, Renee
Subject: letter of invitation for my China multiple-visit visa application

Hello Youlin:

Good news - we have received an official letter from the Gates Foundation that the START project is funded! Now you can tell others about it, if you want to. I am looking forward to visiting you in Beijing (arriving on Feb. 12, departing on Feb. 15) but I need to apply for a multiple-visit visa, since I may be making more than one trip to China in the next year. Thanks very much and I am looking forward to seeing you.
John

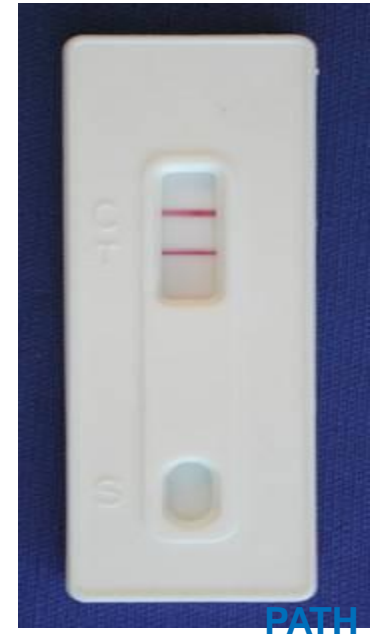
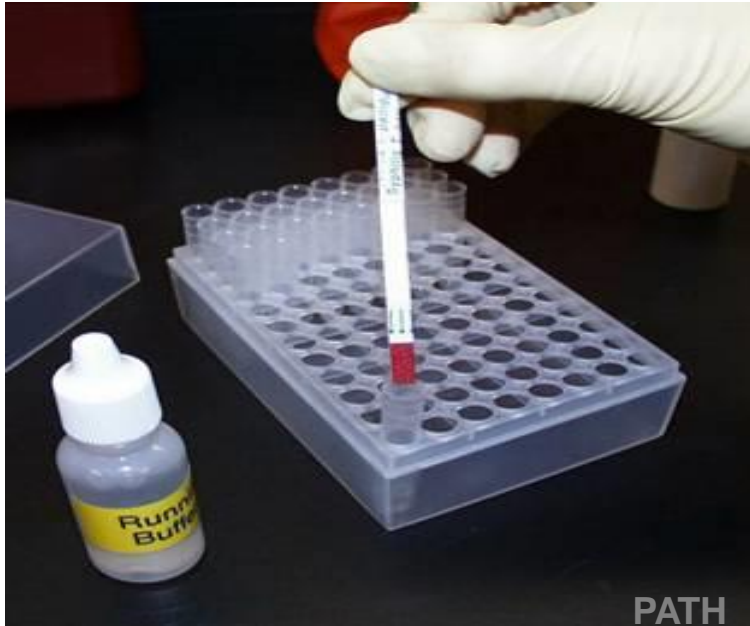
Dr. John W. Sellors
Senior Medical Advisor
Reproductive Health
Program for Appropriate Technology in Health
1455 NW Leary Way
Seattle, WA 98107 USA
Tel: (206) 285 3500; Fax: (206) 285 6619



Comparison HC2 and *Care*HPV DNA tests

	Hybrid Capture 2 (existing test) Gaithersburg, MD	CareHPV	Arbor Vita E6 strip test Sunnyvale, CA
Test format	Batch	Rapid-batch	Rapid-strip
Time	7 hours	Less than 2 hours	Less than 20 minutes
Detects	HPV-DNA	HPV-DNA	E6 protein
Setting	Lab Refrigeration needed	Static or mobile clinic No refrigeration needed	Near patient testing No refrigeration needed
Number of samples	96 well batch	24 or 48 well batch	One at a time
Number of oncogenic HPV types	13	All 13 + type 66	To be determined
Target price per specimen	US\$50 Marketed through traditional diagnostic channels (private market)	Less than US\$5 Direct public health access through governments and agencies	Less than US\$5

Immunochromatographic Strip Test



Study participants enrollment

Year	2003	2004	2005	2006	2007	Total
India	0	0	2,950	3,700	4,000	10,650
China	2,005	2,495	2,053	2,500	2,500*	11,553
Total	2,005	2,495	5,003	6,200	6,500	22,203

**The clinical accuracy trial in Shanxi, China, 2007*

*Jan Agostie, John Sellers, Phil Castle, Rosa Legood et al
in Shanxi final evaluation screening site, November, 2007*





Registration



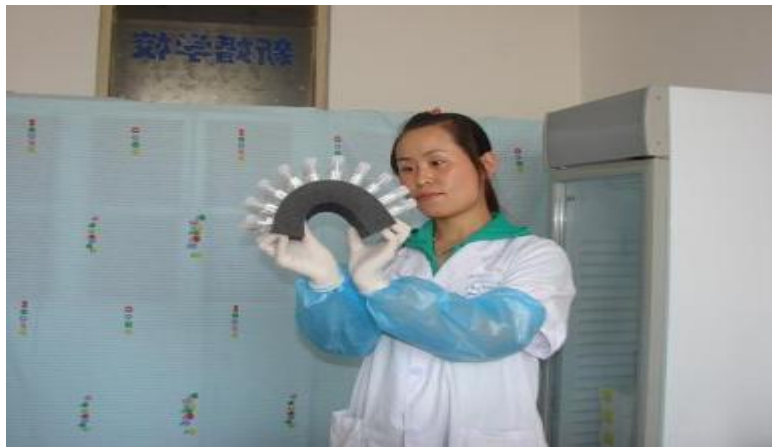
Informed consent



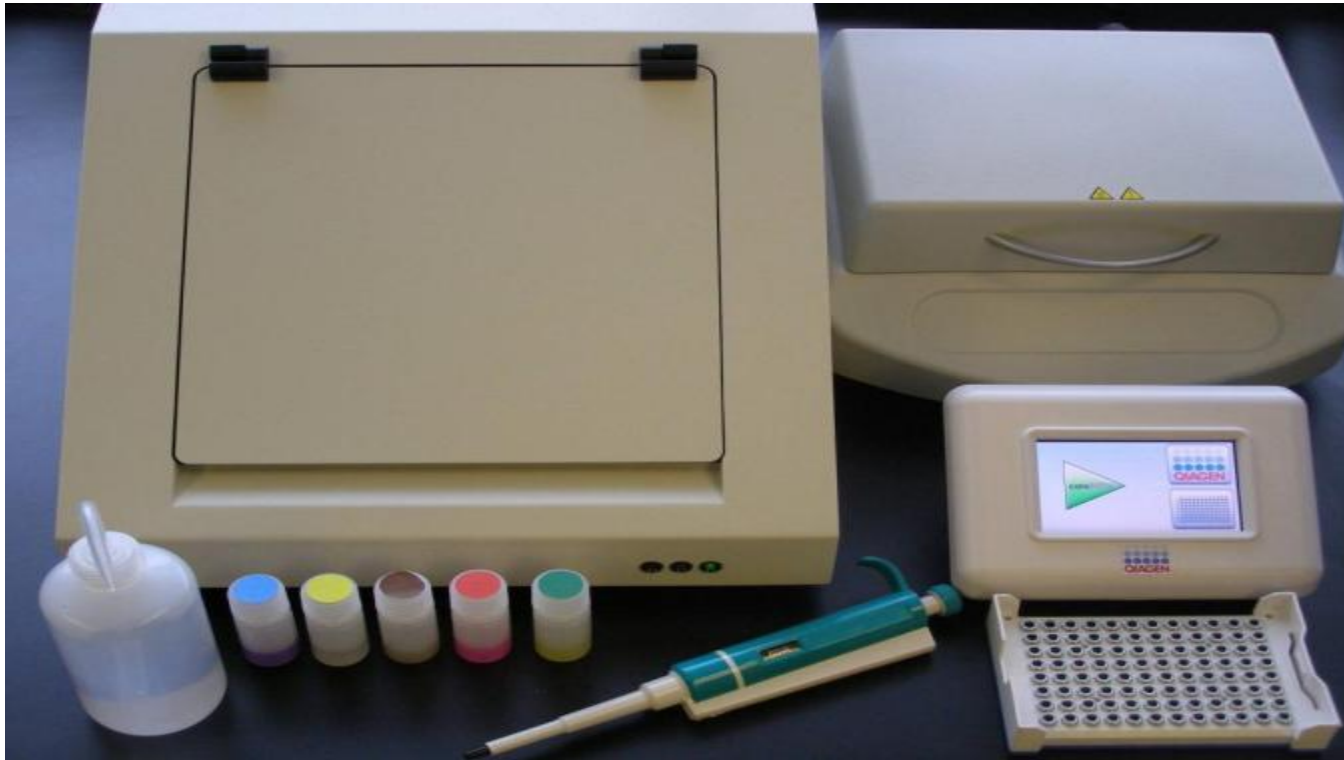
Samplers



Gynecological exam

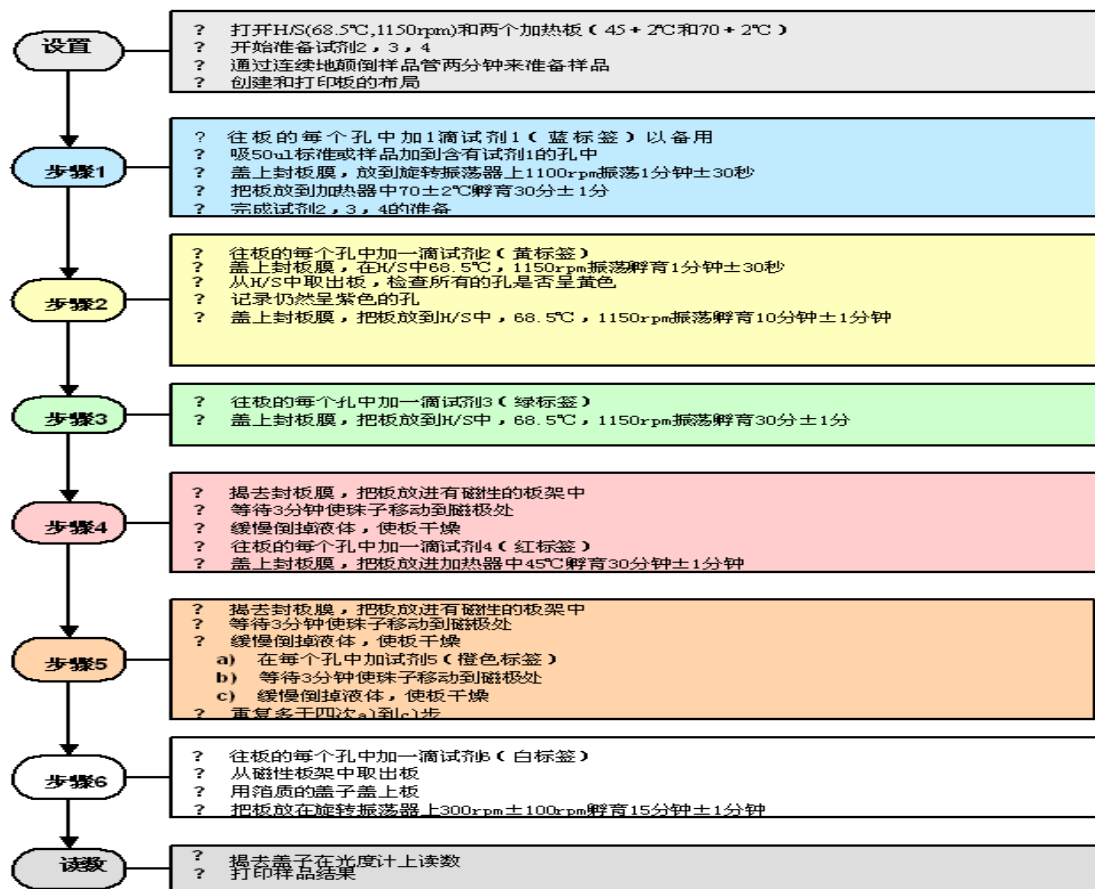


careHPV Kit and reagents

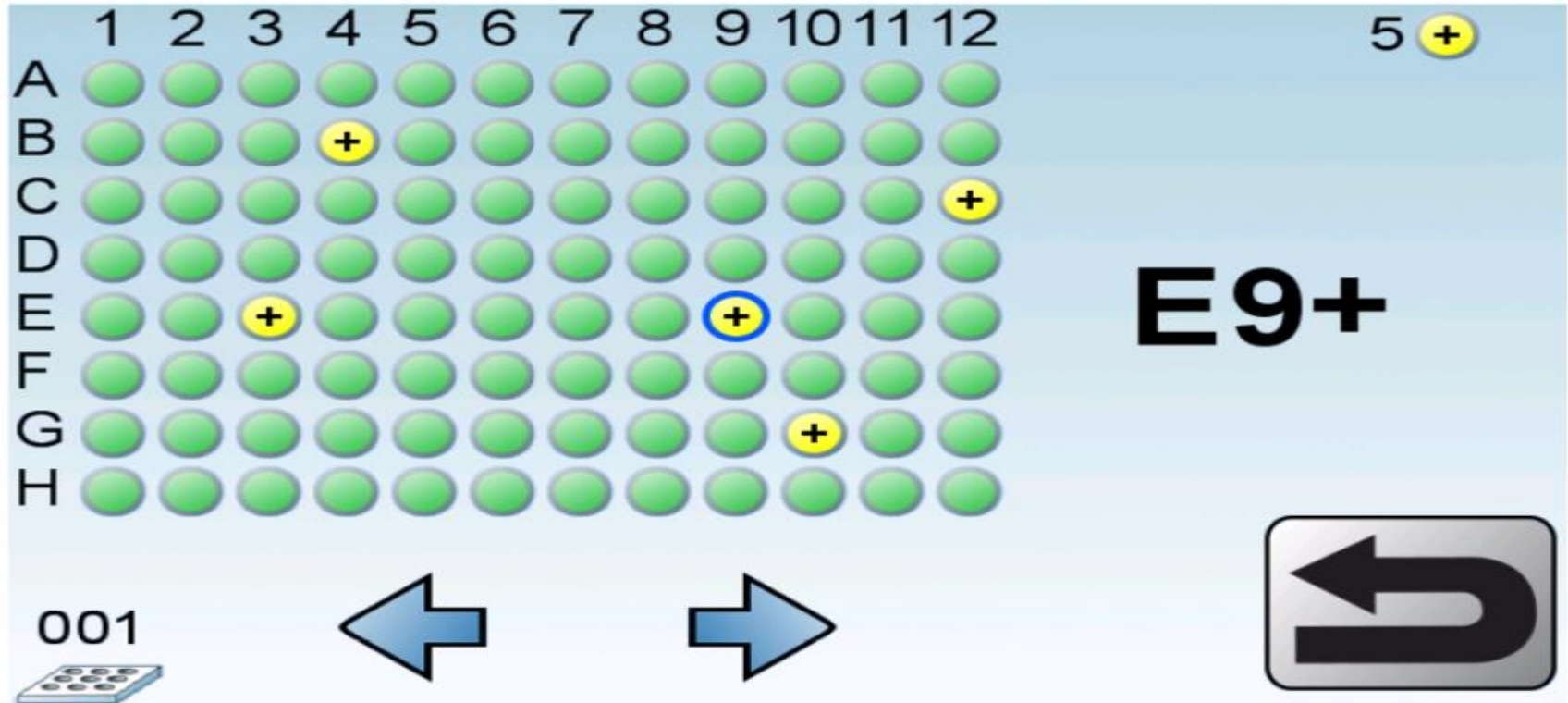


快速HPV检测流程图

注意: 用此流程图前有必要对详细的方案有充分的了解。



■ *Results readout*



THE LANCET **Oncology**

	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	Youden's index, %	Area under ROC curve (95% CI)
<i>careHPV</i>						
Cervical specimens						
0.5 RLU/cut-off ratio cut-point	90.0 (83.0–97.0)	84.2 (82.7–85.7)	14.7 (11.3–18.0)	99.6 (99.4–99.9)	74.2 (72.4–76.0)	0.93 (0.91–0.96)
1.0 RLU/cut-off ratio cut-point	84.3 (75.8–92.8)	87.5 (86.1–88.8)	16.9 (13.0–20.8)	99.5 (99.1–99.8)	71.8 (70.0–73.6)	0.93 (0.91–0.96)
Vaginal specimens						
0.5 RLU/cut-off ratio cut-point	81.4 (72.3–90.5)	82.4 (80.8–83.9)	12.2 (9.3–15.2)	99.3 (99.0–99.7)	63.8 (61.9–65.7)	0.86 (0.81–0.90)
1.0 RLU/cut-off ratio cut-point	72.9 (62.4–83.3)	87.7 (86.3–89.0)	15.1 (11.3–19.0)	99.1 (98.7–99.5)	60.6 (58.6–62.6)	0.86 (0.81–0.90)
HC2 (cervical specimens)	97.1 (93.2–100.0)	85.6 (84.2–87.1)	17.0 (13.3–20.6)	99.9 (99.8–100.0)	82.7 (81.2–84.2)	0.96 (0.94–0.97)
Liquid-based cytology (ASC-H+)	85.3 (76.9–93.7)	97.0 (96.3–97.7)	45.7 (37.0–54.3)	99.5 (99.3–99.8)	82.3 (80.8–83.8)	0.95 (0.92–0.99)
VIA	41.4 (29.9–53.0)	94.5 (93.6–95.4)	18.6 (12.5–24.7)	98.2 (97.6–98.7)	35.9 (34.0–37.8)	0.68 (0.60–0.75)
ROC=receiver operating characteristic. HPV=human papillomavirus. RLU=relative light unit. HC2=Digene High-Risk HPV HC2 DNA Test. ASC-H+=atypical squamous cells—cannot exclude high-grade squamous intraepithelial lesions. VIA=visual inspection with acetic acid.						
Table 1: Sensitivity, specificity, positive-predictive value (PPV), negative-predictive value (NPV), and area under the curve for the various methods in 2388 eligible women who were all subsequently examined by colposcopy, based on the detection of CIN2+ on histology (n=70)						

Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. Lancet Oncol. 2008;9(10):929-36.

*Aug. 20, 2010: WHO/IARC,
UICC, MOH, CICAMS et al
delegation site visit Qiagen
careHPV manufacture in
Shenzhen, China*



Mr. & Mrs. Gates visit careHPV Demo in PATH, USA

careHPV implementation progress

- Aug. 2009-Feb. 2010, CICAMS, Sun-Yat-Sen Univ Cancer Center and Nanjing Univ. Gulou Hospital did the Chinese SFDA registration trial (N=1200);
- June 2010: CE marking certification;
- Sept. 2012: SFDA licensure
- Aug. 20, 2010: WHO/IARC, UICC site visit to Manufacture in Shenzhen, China
- Mar 30, 2013: Global market launch
- WHO pre-qualification ongoing
- Implementation demo in central America sponsored by Gates Foundation;
Africa countries by FP7-CALL-FOR-AFRICA-2010 (LSHTM- Univ Montpellier),
Laos & Foundation Merieux careHPV project



CareHPV licence of SFDA
(Sept. 2012)

Main Content

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careHPV clinical evaluation—35,000人份



UPDATE ON THE CAREHPV™ PROJECTS

José Jeronimo
PATH, Seattle, WA, USA.

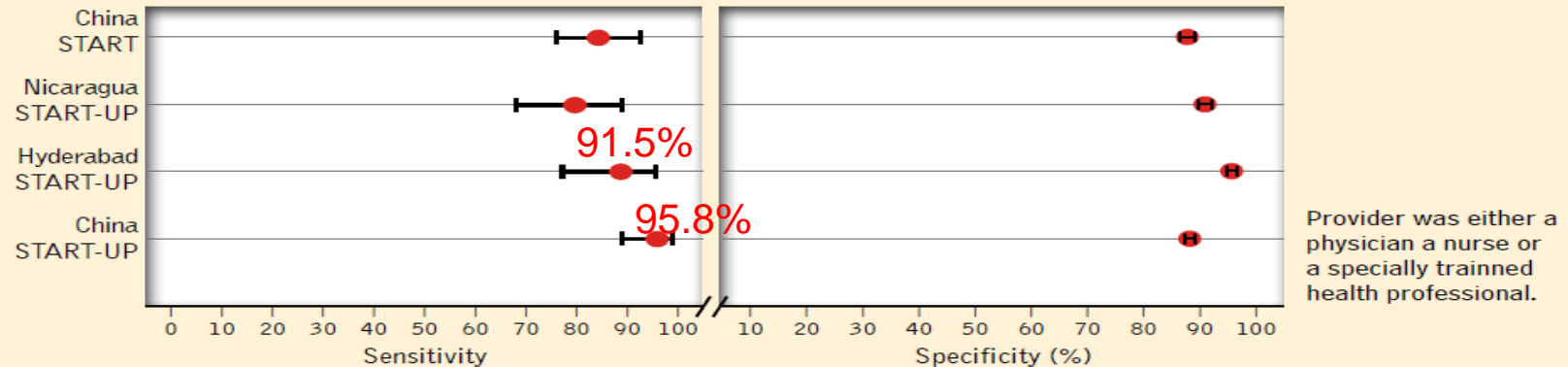


Figure 1. Sensitivity and specificity of CareHPV™ (provider-collected cervical sample).

careHPV Test in other Low resource settings (Gates Project)

Nicaragua



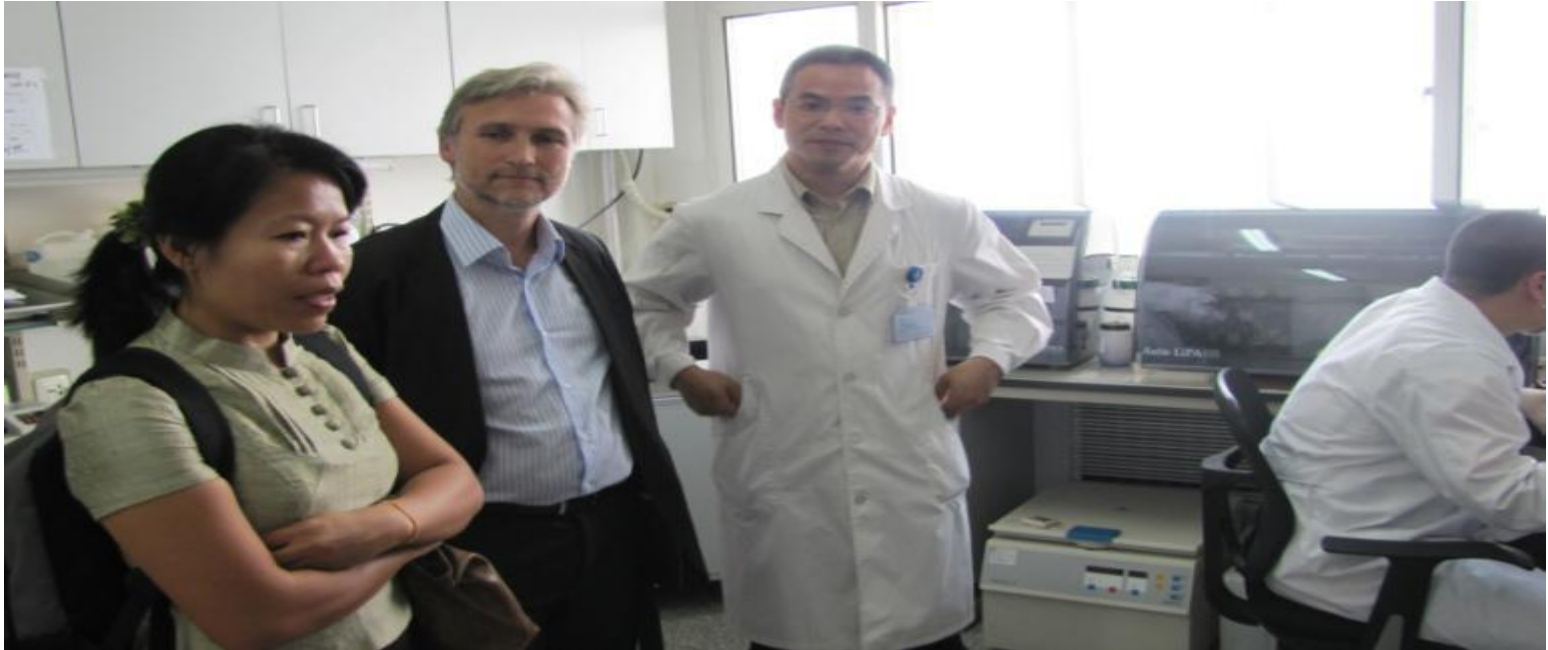
India



Uganda



Laos & Foundation-Merieux CareHPV Project: training in Dr. Qiao's Lab, CICAMS, May 31, 2013



*Dr Phimpha Paboriboune, Scientific Director, Centre d'Infectiologie
Christophe Mérieux- Ministry of Health, PO. Box 3888; Vientiane Lao PDR*

Cancer screening demo & population implementation

- **National cancer prevention & control strategy by MOH**
- **Focus on upper gastric/intestinal, cervical, nasopharyngeal cancers; Rural, poor, low resource settings;**
- **Nationwide free Cervical Cancer screening by Pap/VIA in rural women (10 million/3 years, 221 counties) =only 7% women who should be screened. Bottle-neck.**
- **20million VIA/Pap for cervical cancer screening in Year 2012-13 in 1109 counties**
- **2014-15: 20 million VIA/Pap CxCa screening (1.08 million for HPV-based screening) in 1140 counties.**

CareHPV Demo study for Cervical Ca Screening in China

□ Objectives:

- *Evaluate the accuracy of Pap smear, VIA/VILI and HPV assay in real world;*
- *Evaluate economic efficiency for screening techniques in a large-scale screening program;*
- *The awareness and attitude for CC screening in different people;*
- *Train local cancer registry workers & evaluate long-term effect of screening program.*

□ Participant:

- *3000 women each site, 63,000 in total;*
- *35-64 years-old healthy women;*
- *Cover 21 sites from 7 geographic regions across the country.*

□ *From the year 2015 to 2017*

□ *Financially supported by MOH of PRC; ¥30 million*

Location of careHPV Demo site



Support letters from Drs. Sankar and Broutet

International Agency for Research on Cancer



World Health
Organization

150 cours Albert Thomas
69372 Lyon cedex 08, France
Screening Group
Tel.: +33 4 72 73 84 88
Fax: +33 4 72 73 85 18
E-mail: scr@iarc.fr
http://screening.iarc.fr

Ref.: SCR/RS/sm

Prof. You-Lin Qiao
National Cancer Center, Cancer Hospital,
Chinese Academy of Medical Sciences,
CAMS/PUMS
Beijing, China

29 October 2013

Dear Professor Qiao,

Thank you very much for sending me the concept proposal entitled "Appropriate Technique for Cervical Cancer Screening in China: Demonstration Study of *CareHPV*" jointly prepared by Dr Hang, yourself and colleagues.

I have gone through your proposal with great interest. Your proposed study provides an exciting opportunity to evaluate the performance characteristics of three different screening approaches consisting HPV testing using *CareHPV* test, cytology and visual screening in a real world setting through routine health services in China. The study involves a substantial number of women who will be tested by health care personnel in routine health services.

The incorporation of an economic assessment involving cost-effective analysis of the three different screening approaches and a qualitative study to address the awareness and attitudes of clients, care providers and policy makers makes this study very interesting and unique in its contribution. From our perspective, your proposed study is an important initiative and of considerable public health significance in advancing cervical cancer prevention efforts in low- and middle-income countries.

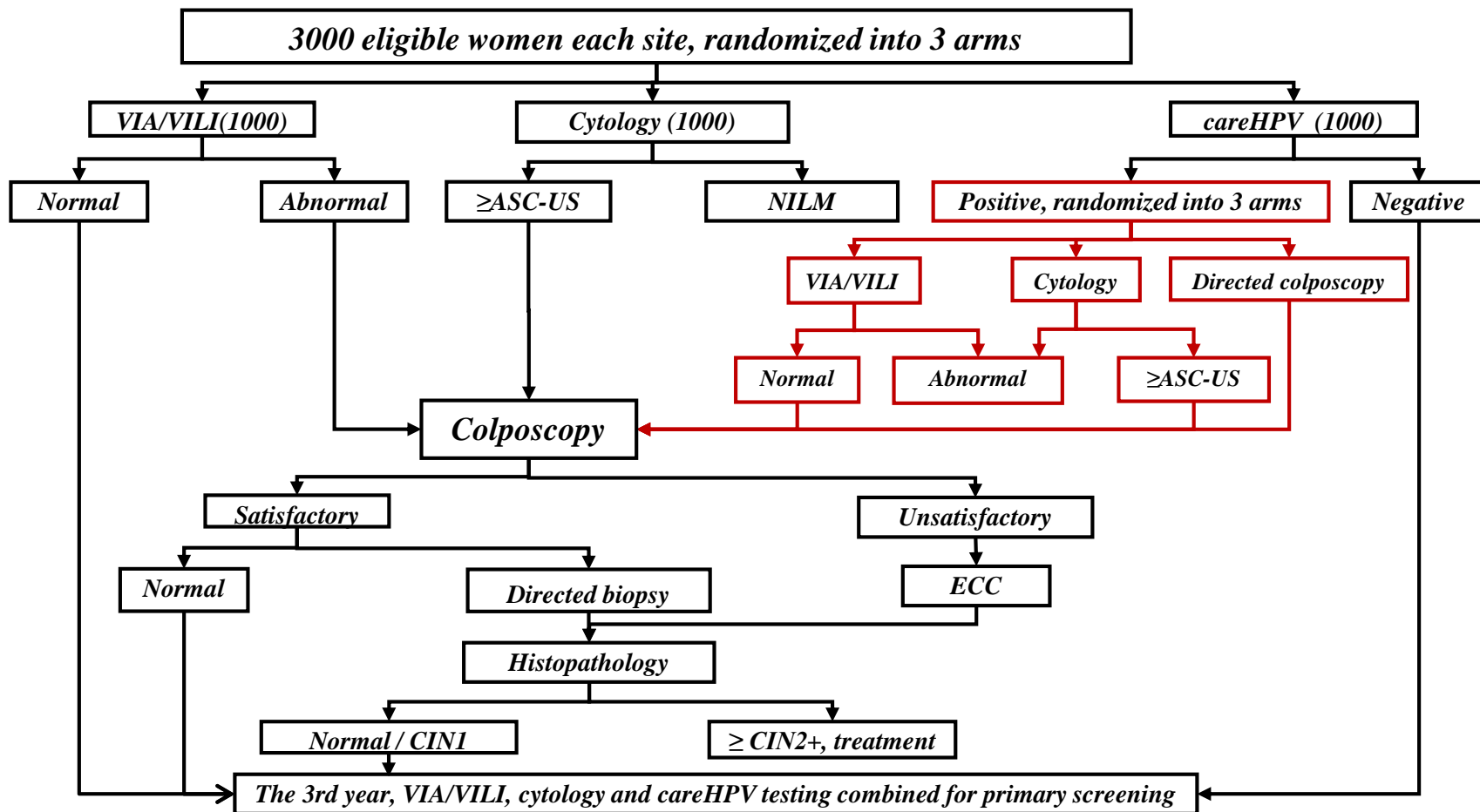
In summary, I strongly support your proposed study. I am sure that you will successfully implement this large study involving some 63,000 women and will document interesting and important findings that will further catalyze the implementation and scaling up of cervical cancer screening programs in China and in other countries in Asia, Africa and Latin America.

Wishing you all success in implementing this study and with warm regards,

R. Sankaranarayanan, MD
Head, Section of Early Detection and Prevention
e-mail: sankar@iarc.fr



Appropriate Technique for Cervical Cancer Screening in China



Flow chart of clinical protocol

*Screening Project of Cervical Cancer and Breast
Cancer in Ordos, Inner Mongolia
(2016-2020)*



12-07-2012 07:42

Study Design

1. Flowchart of Cervical Cancer Screening

fig.1:HPV test+VIA/VILI group

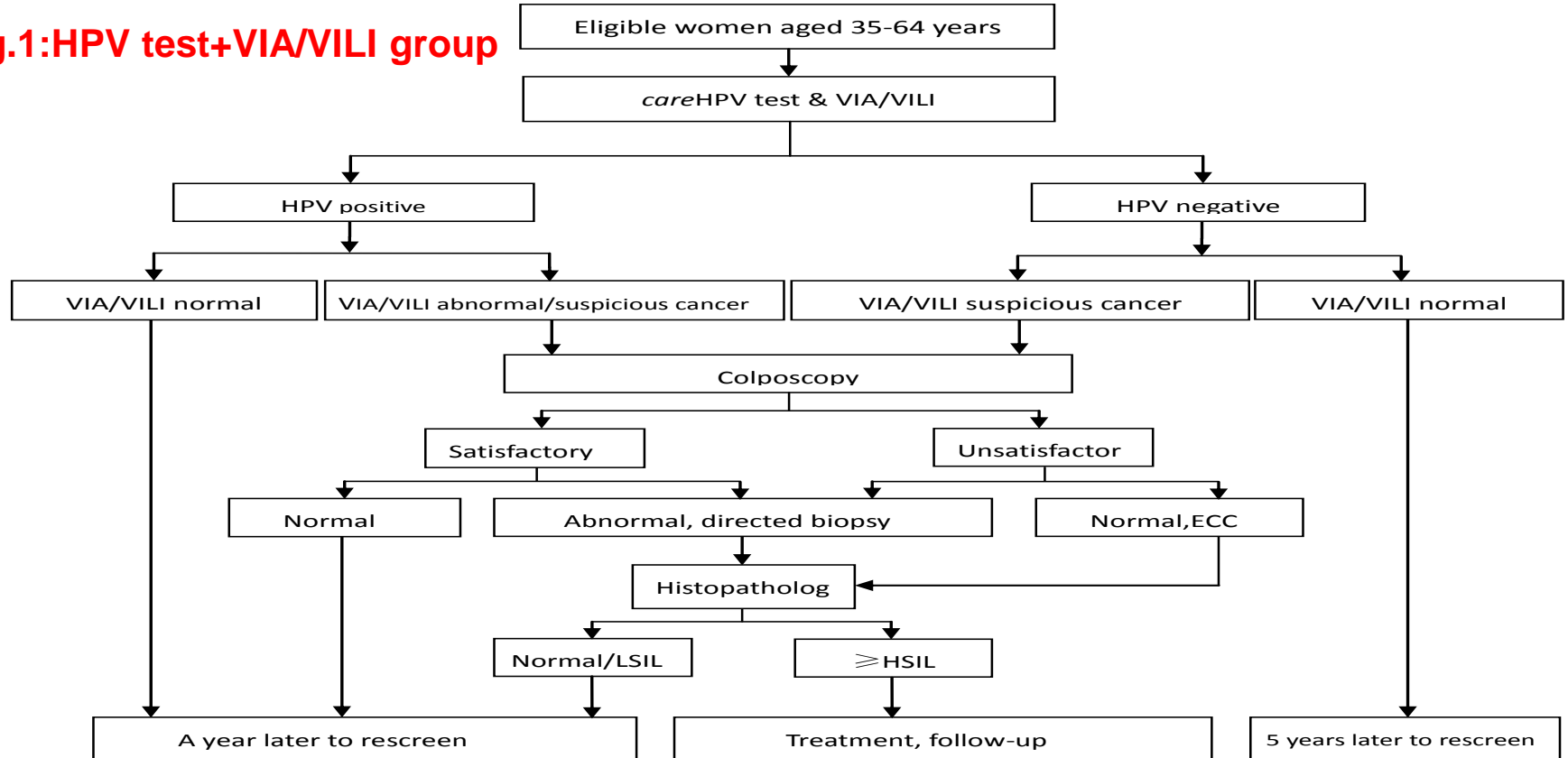
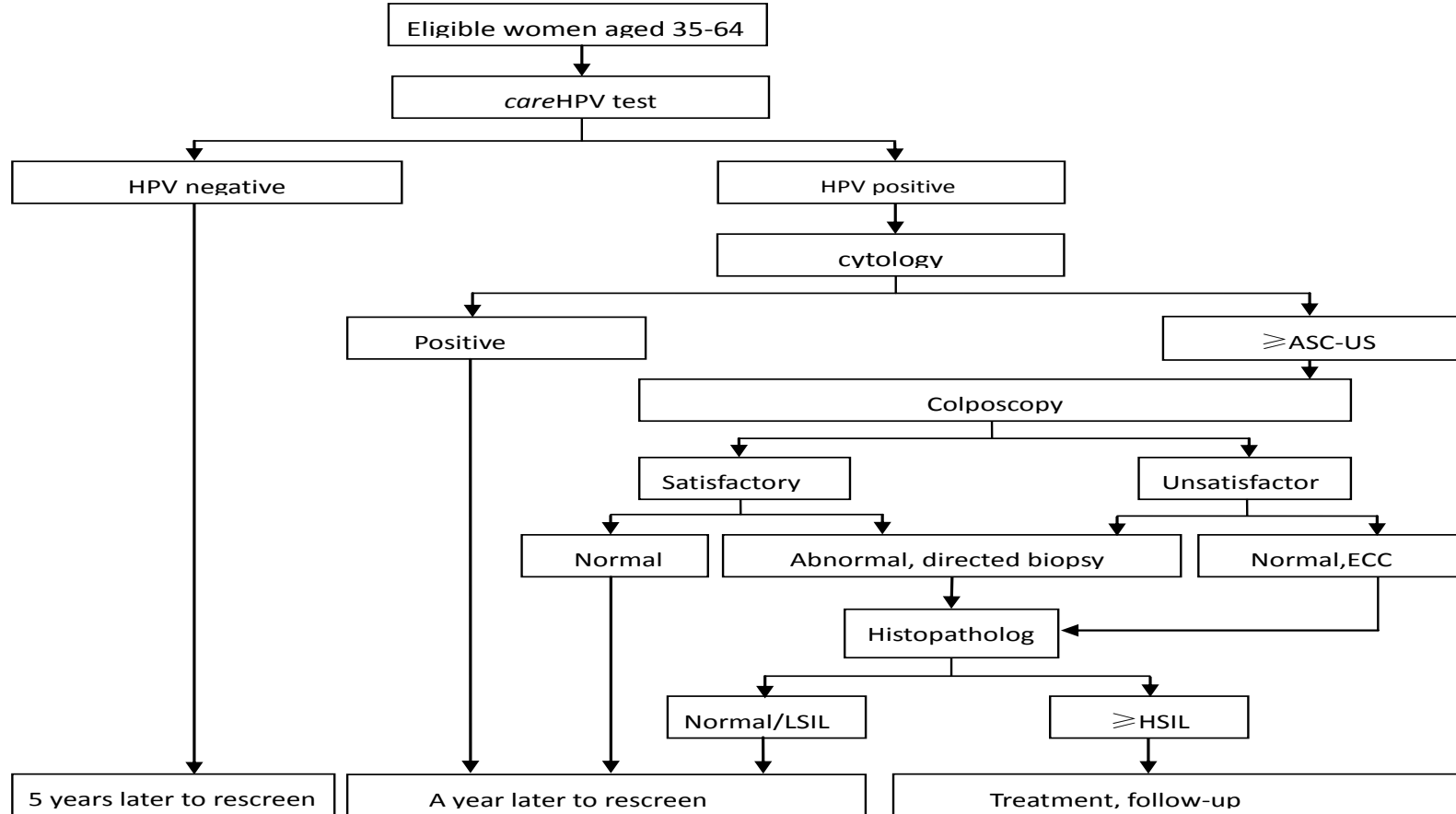


Fig.2: HPV test and cytology group



4. Conclusion & Acknowledgement

- 1. HPV DNA based tests (such as careHPV) has to implemented as the primary screening for dealing with the huge public health demand;**
- 2. Expanding & improving the capacity of demo Centers, Networks & Consortia; & move program from rural areas to cities, to whole nation**
- 3. HPV vaccination & HPV DNA screening is a good example of how vaccination and screening can be used together in a comprehensive cancer prevention fashion.**
- 4. Implementing a successful cancer prevention plan & reducing inequalities in access to screening, early diagnosis & quality care remains a challenge.**

Thanks for Listening and Welcome for Collaboration!

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