New Guidelines OMS and ASCO

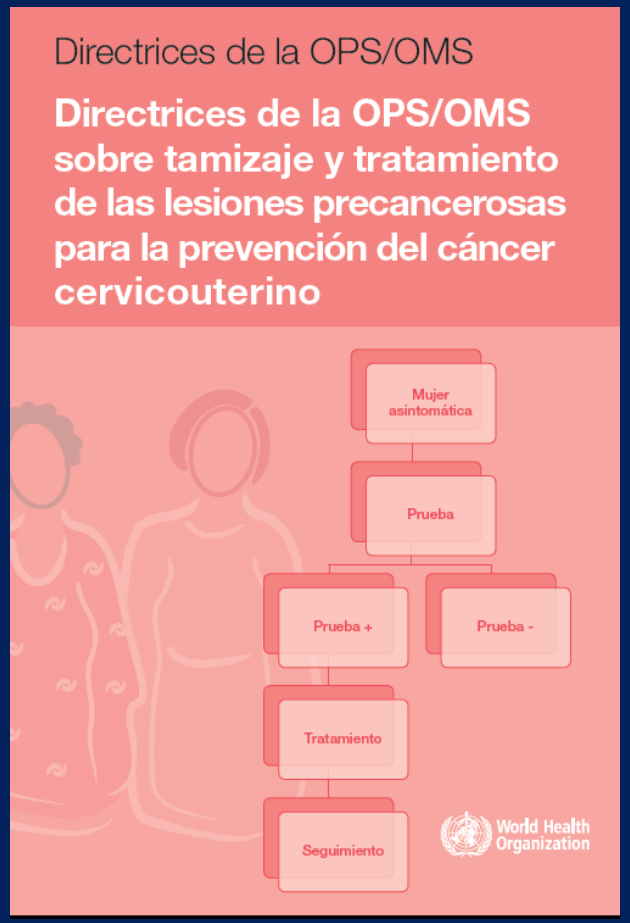
Jose Jeronimo M.D.
Associate Director Reproductive Health
PATH
Seattle, WA, USA

Disclosures

- PATH has collaborated with Qiagen in the development and validation of the careHPV test. PATH has collaborated with CryoPen and Liger in the development of new treatment devices. PATH does not receive any revenues from the commercialization of these products. We have not received any funding from those companies.

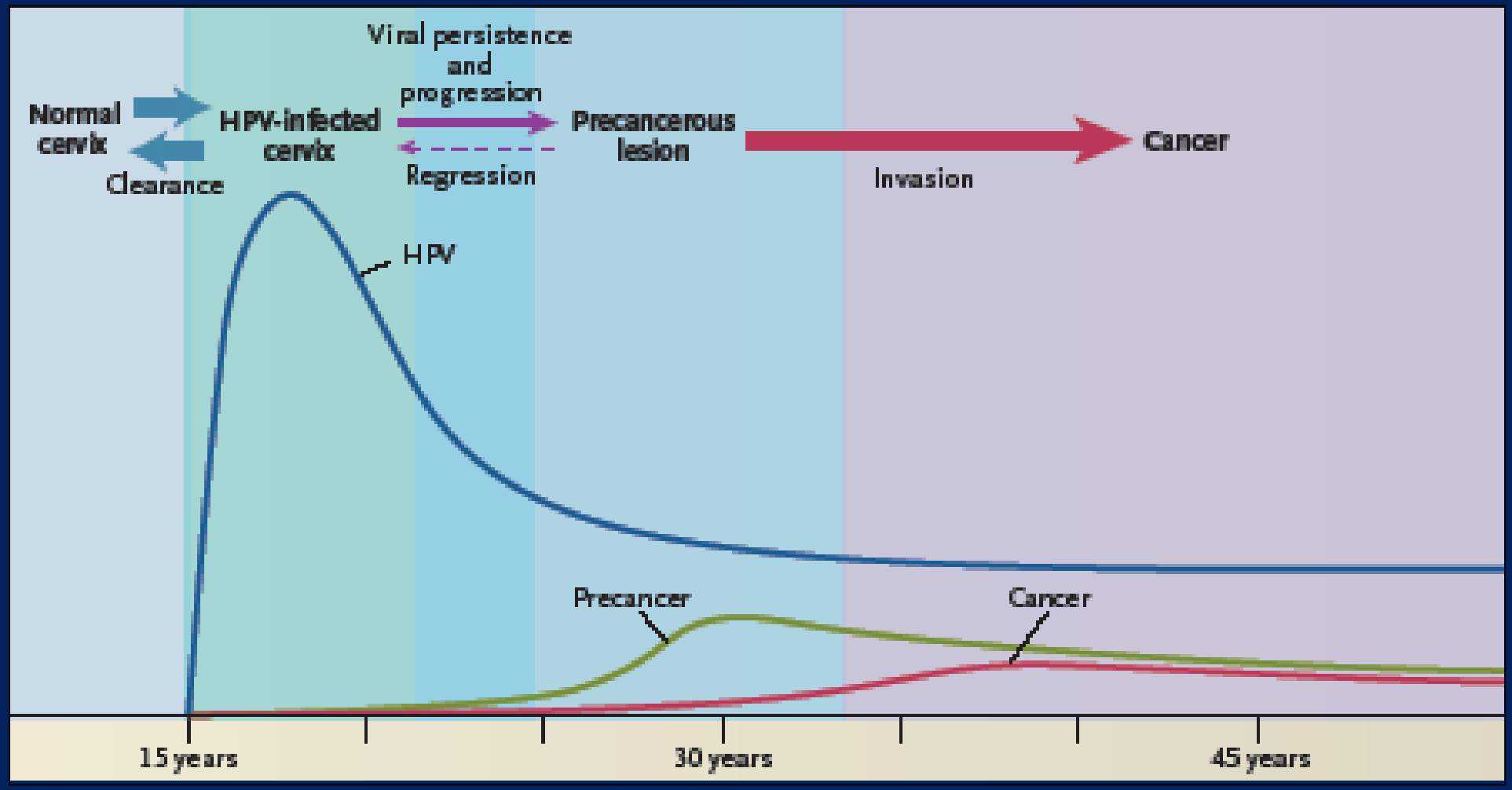
- I used to have shares in a company in Peru that provides cervical cancer screening services, and now is considering to expand its work to commercialization of medical devices. Currently I do not have any shares in that company and I do not receive any revenues from them.

NEW GUIDELINES FROM WHO



SCREENING AND TREATMENT OF PRE-CANCEROUS LESIONS FOR PREVENTION OF CERVICAL CANCER

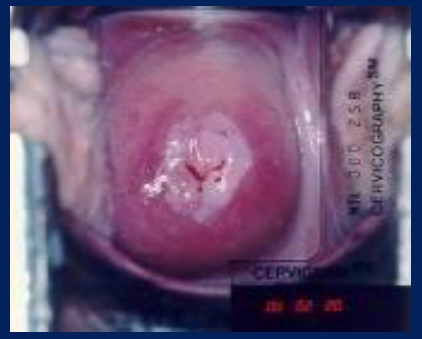
HPV and Cervical Cancer



SCREENING TESTS

Cytology: conventional and liquid-based

Visual Inspection with Acetic Acid (VIA)



HPV tests

TARGET POPULATION AND FREQUENCY

Target population: 30 - 49 y/o

Frequency: 3 - 5 years

HPV test: minimum interval of 5 years.

Priority to maximize:

Coverage: 30-49 y/o women

Completion of follow-up

Quality of screening and treatment

STRATEGIES

Screening and referral

- Screening-> colposcopy, biopsy -> treatment based on biopsy result

Screening and treatment

- screening-> treatment based on screening result

Screening, triage and treatment

- Screening-> if abnormal, second test -> treatment in women with abnormal result in both tests

Evaluation of recommended strategies

- HPV or cytology→colposcopy ?
- HPV or VIA?
- VIA or cytology →colposcopy?
- HPV or HPV → colposcopy?
- HPV or HPV → VIA?
- VIA or HPV → VIA?
- HPV → VIA or HPV → colposcopy?

METODOLOGY FOR THE DEVELOPMENT OF THE RECOMMENDATIONS.

OPTONS CONSIDERED FOR DEVELOPMENT OF RECOMMENDATIONS

Screening options	Treatment options	Results (after treatment)
1. Cytology followed by colposcopy 2. VIA 3. HPV 4. HPV followed by VIA 5. HPV followed by colposcopy	1. Cryotherapy 2. LEEP 3. Cold-knife cone	1. Mortality of cervical cancer 2. Incidence of cervical cancer 3. Prevalence of CIN2+ 4. Severe infections 5. Bleeding 6. Premature delivery 7. Fertility 8. Severe infections 9. Minor infections

EVALUATION OF SCREENING TESTS

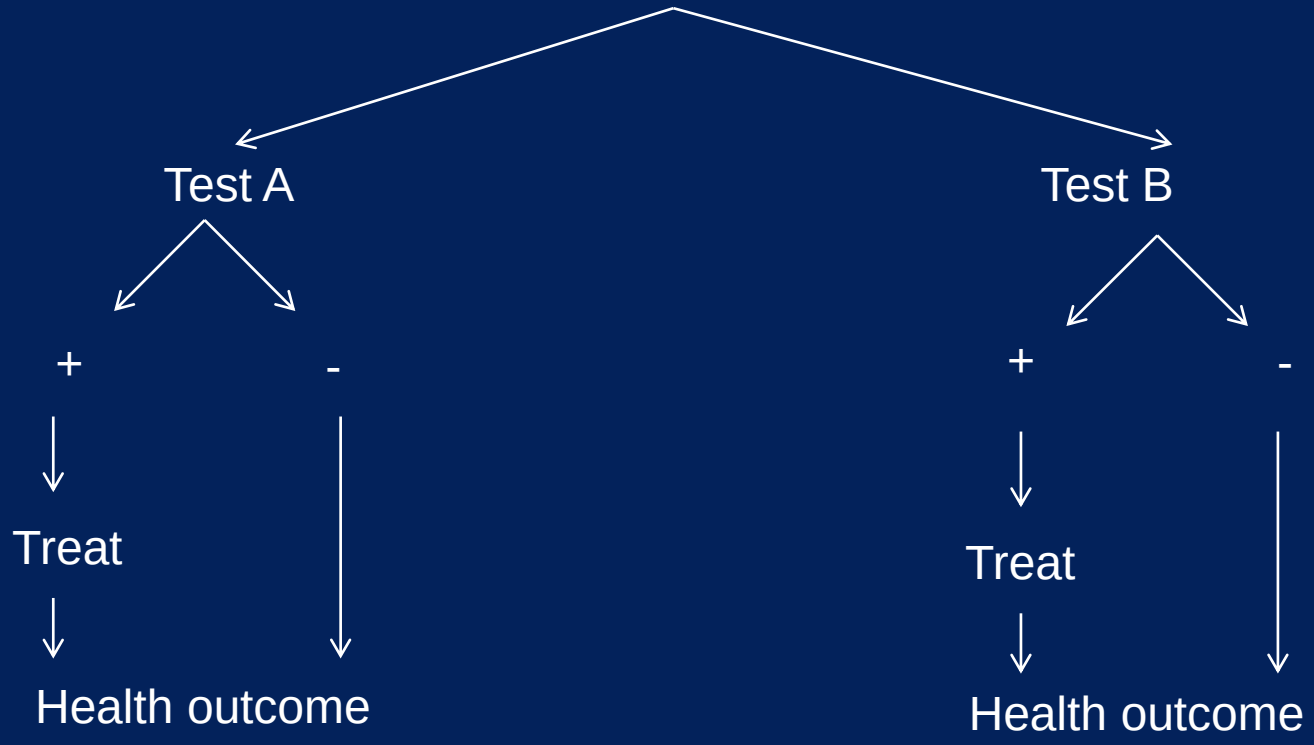
Systematic review of cohort studies

Calculation of sensitivity and specificity

	HPV	Cytology	VIA
Sensitivity	95% (95% CI: 84-98)	70% (95% CI: 57-81)	69% (95% CI: 54-81)
Specificity	84% (95% CI: 72-91)	95% (95% CI: 92-97)	87% (95% CI: 79-92)

THE BEST SCIENTIFIC EVIDENCE

Randomized studies



MODELING THE STRATEGIES

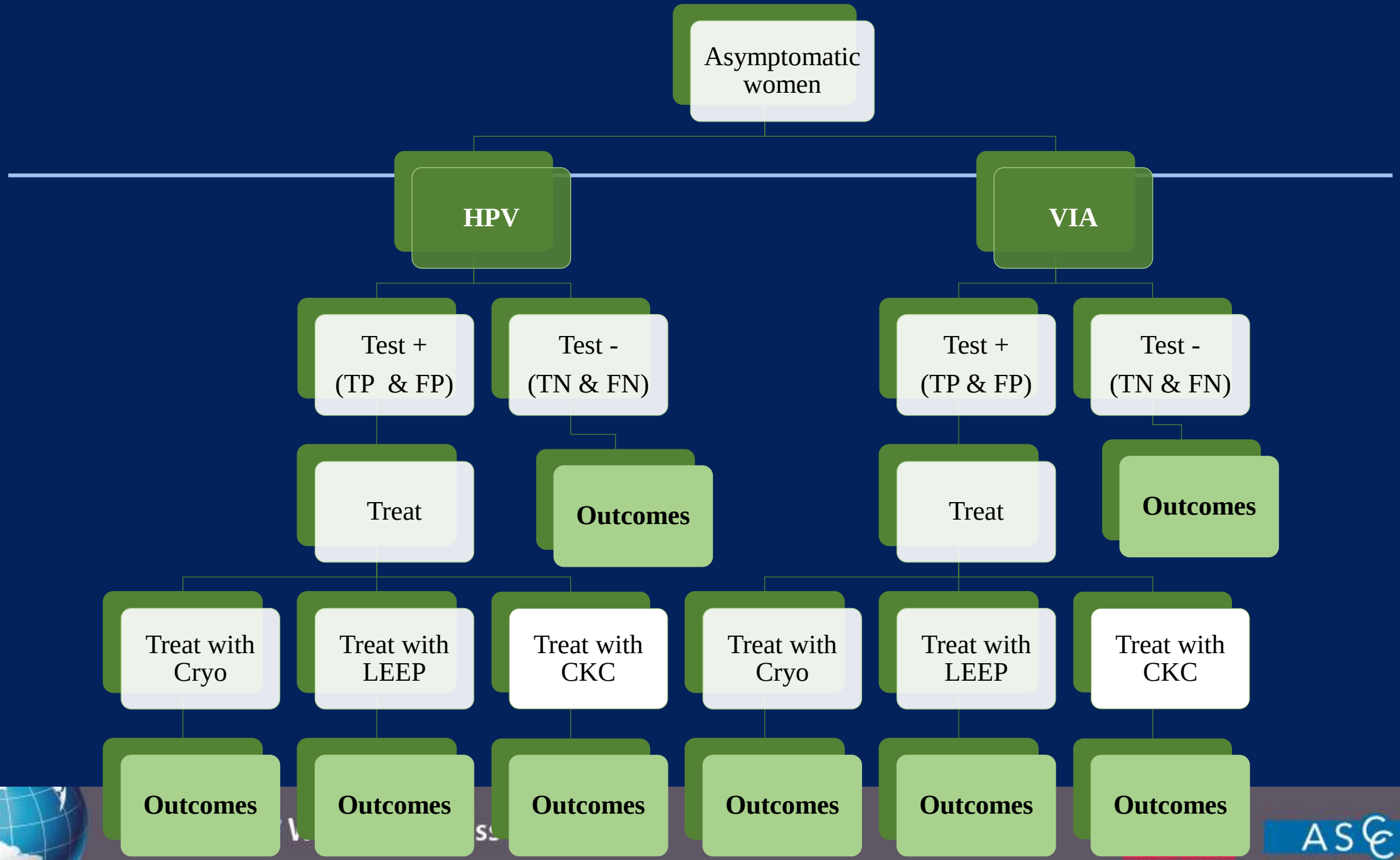
Outcomes	Events in the screen-treat strategies for patient important outcomes (numbers presented per 1,000,000 patients)*						
	HPV +/- CKC	HPV +/- LEEP	HPV +/- Cryo	VIA +/- CKC	VIA +/- LEEP	VIA +/- Cryo	NO screen[10]
Mortality from cervical cancer[1]	20	30	30	81	88	88	250
Cervical Cancer Incidence[2]	28	43	43	112	124	124	350
CIN2-3 recurrence[3]	1088	1677	1677	4328	4762	4762	13400
Undetected CIN2-3 (FN)	1000			6000			
Major bleeding[4]	1511	397	60	1210	318	48	0
Premature delivery[5]	712	575	610	670	560	588	500
Infertility[6]	-	-	-	-	-	-	0
Major infections[7]	156	225	24	125	180	19	0
Minor infections[8]	1649	1061	1139	1321	850	913	0
Unnecessarily treated (FP)	157000			127000			-
Cancer found at one time screening[9]	2454			3168			-

Consider values and preferences

Evidence to Recommendation Table

Decision domain:	Judgement	Summary of reason for judgement
Quality of evidence *Is there high or moderate quality evidence?*	Yes ☐ No ☒	There is high to moderate quality evidence for the diagnostic test accuracy data for VIA and HPV. There is low to very low quality evidence for the effects of treatment and the natural progression of CIN from observational studies often with inconsistent results across studies. The link between test accuracy data and treatment effects is very uncertain.
Balance of benefits versus harms and burdens *Are you confident that the benefits outweigh the harms and burden for the recommended strategy?*	Yes ☒ No ☐	The benefits of HPV screen and treat strategy (reduction in CIN recurrence, cervical cancer, and related mortality) may be greater than VIA, and the harms may be similar. There may also be slightly greater overtreatment and slightly fewer cancers detected with HPV compared to VIA.
Values and preferences *Are you confident about the assumed or identified relative values and are they similar across the target population?*	Yes ☒ No ☐	High value was placed on a screen and treat strategy versus no screening, since qualitative studies have shown that once women decide to be screened they find the screening tests and immediate treatment acceptable. High value was also placed on a reduction in cervical cancer and related mortality versus complications from treatment (e.g. major bleeding or infection requiring hospitalisation). Low value was placed on minor infections or bleeding, and the small number of cancers detected at screening or of women over-treated.
Resource implications *Is the cost small relative to the net benefits for the recommended strategy?*	Yes ☐ No ☒	HPV testing is resource dependent. Where HPV testing is available, affordable and implementable, the overall net benefit over VIA is worth the resources. But where not available, HPV may not be worth the benefits.

Low value on minor bleeding and infections and over- treatment

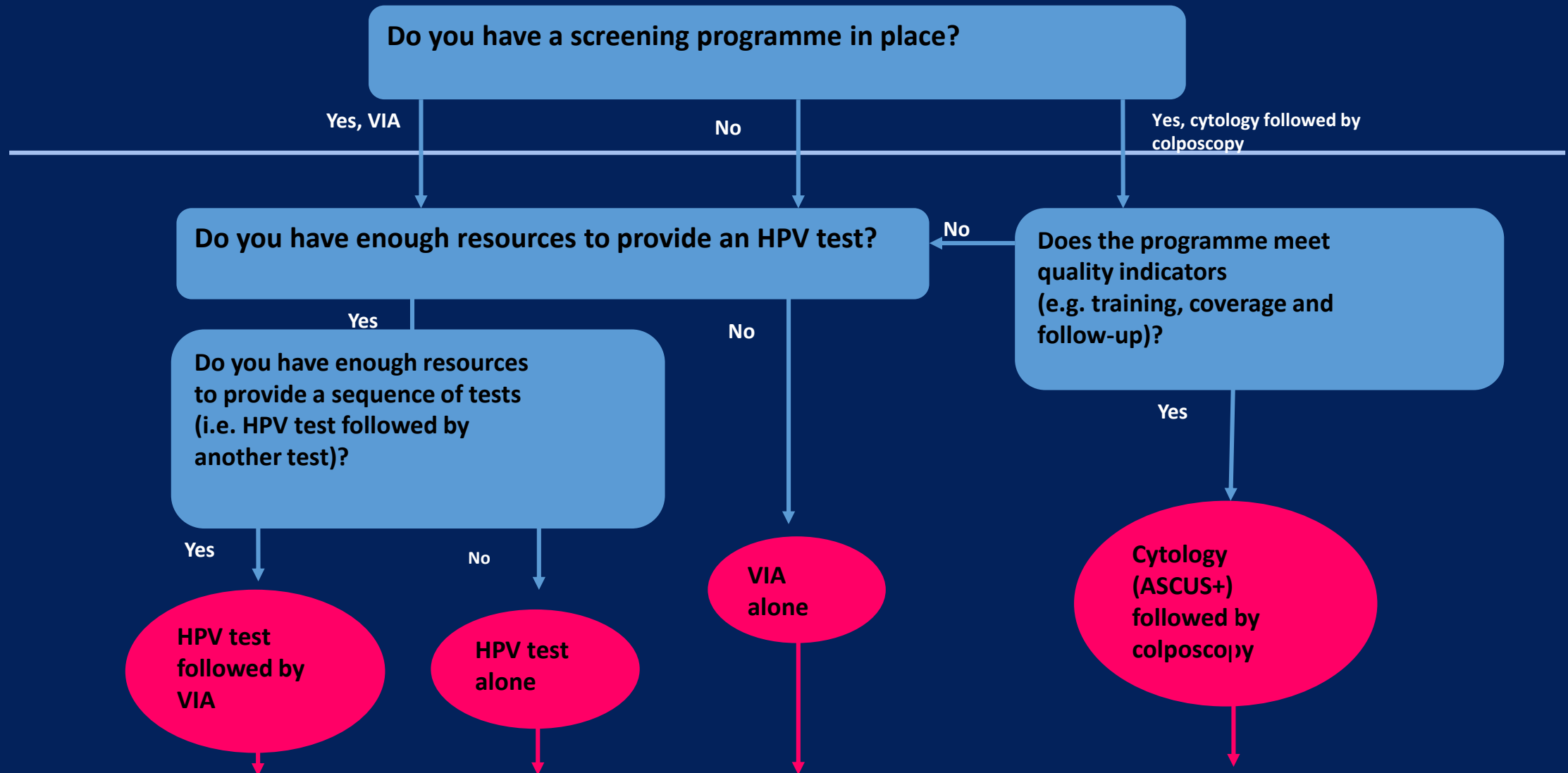

Asymptomatic women
HPV
VIA
Test + (TP & FP)
Test - (TN & FN)
Test + (TP & FP)
Test - (TN & FN)
Treat
Outcomes
Treat
Outcomes
Treat with Cryo
Treat with LEEP
Treat with CKC
Treat with Cryo
Treat with LEEP
Treat with CKC
Outcomes
Outcomes
Outcomes
Outcomes
Outcomes
Outcomes

Solution is not to ignore patient important outcomes!

Therefore had to model the numbers

- Prevalence of CIN 2+ in HIV+, HIV-, age groups
- Incidence of outcomes in the population without treatment (eg. Premature delivery)
- Natural progression rate of CIN2+ to cervical cancer without treatment
- Mortality due to cervical cancer with and without treatment
- Natural regression of CIN2+ without treatment
- Accuracy of different screening test in identifying CIN2+
- Efficacy of different treatments in stopping progression of CIN2+
- Complications and harms of each treatment

Recommendations

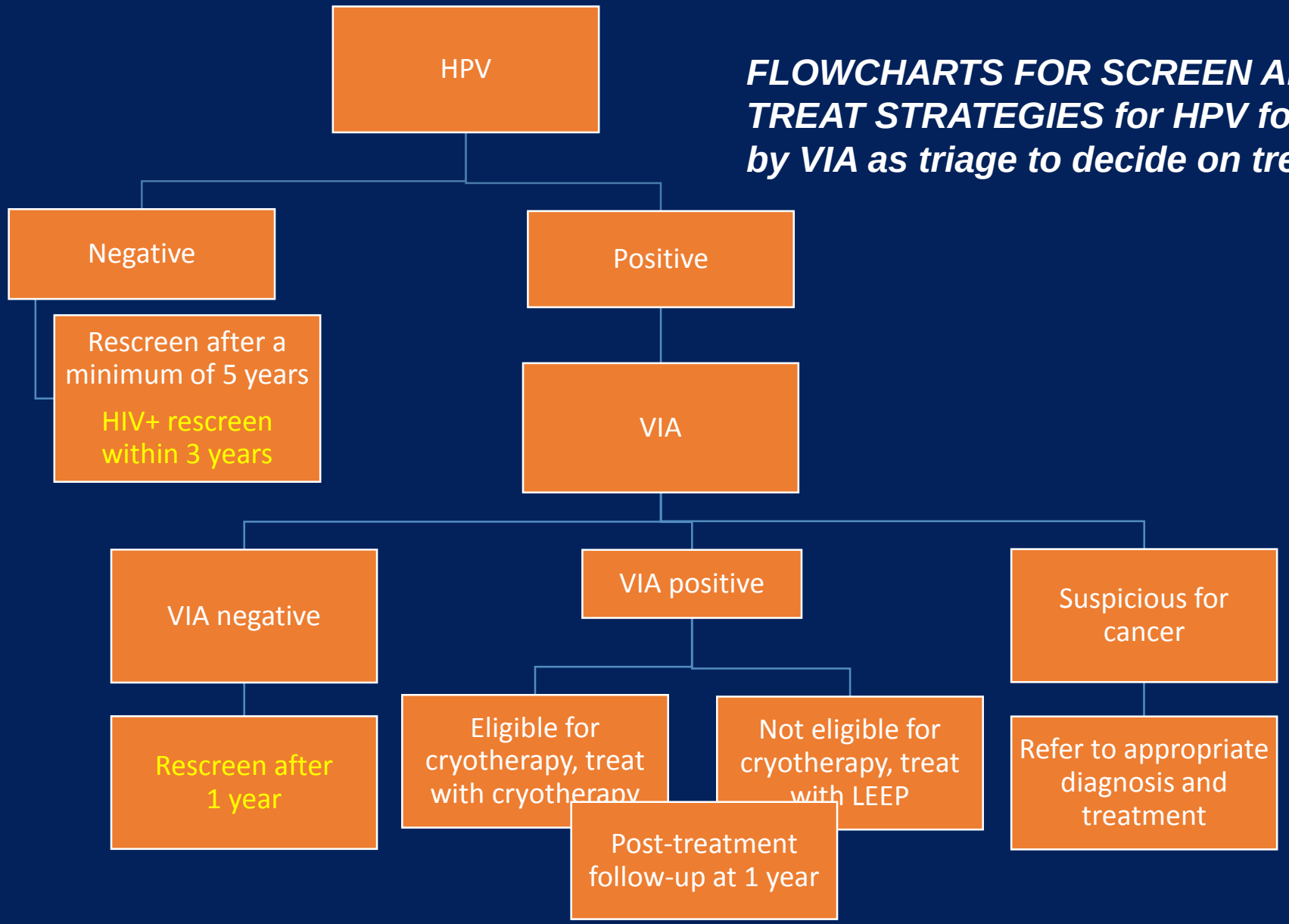

Do you have a screening programme in place?
Yes, VIA
No
Yes, cytology followed by colposcopy
Do you have enough resources to provide an HPV test?
No
Does the programme meet quality indicators (e.g. training, coverage and follow-up)?
Yes
No
Yes
Do you have enough resources to provide a sequence of tests (i.e. HPV test followed by another test)?
Yes
Yes
No
Yes
No
HPV test followed by VIA
HPV test alone
VIA alone
Cytology (ASCUS+) followed by colposcopy
Cryotherapy and/or LEEP must be part of a screen-and-treat programme

Make recommendations

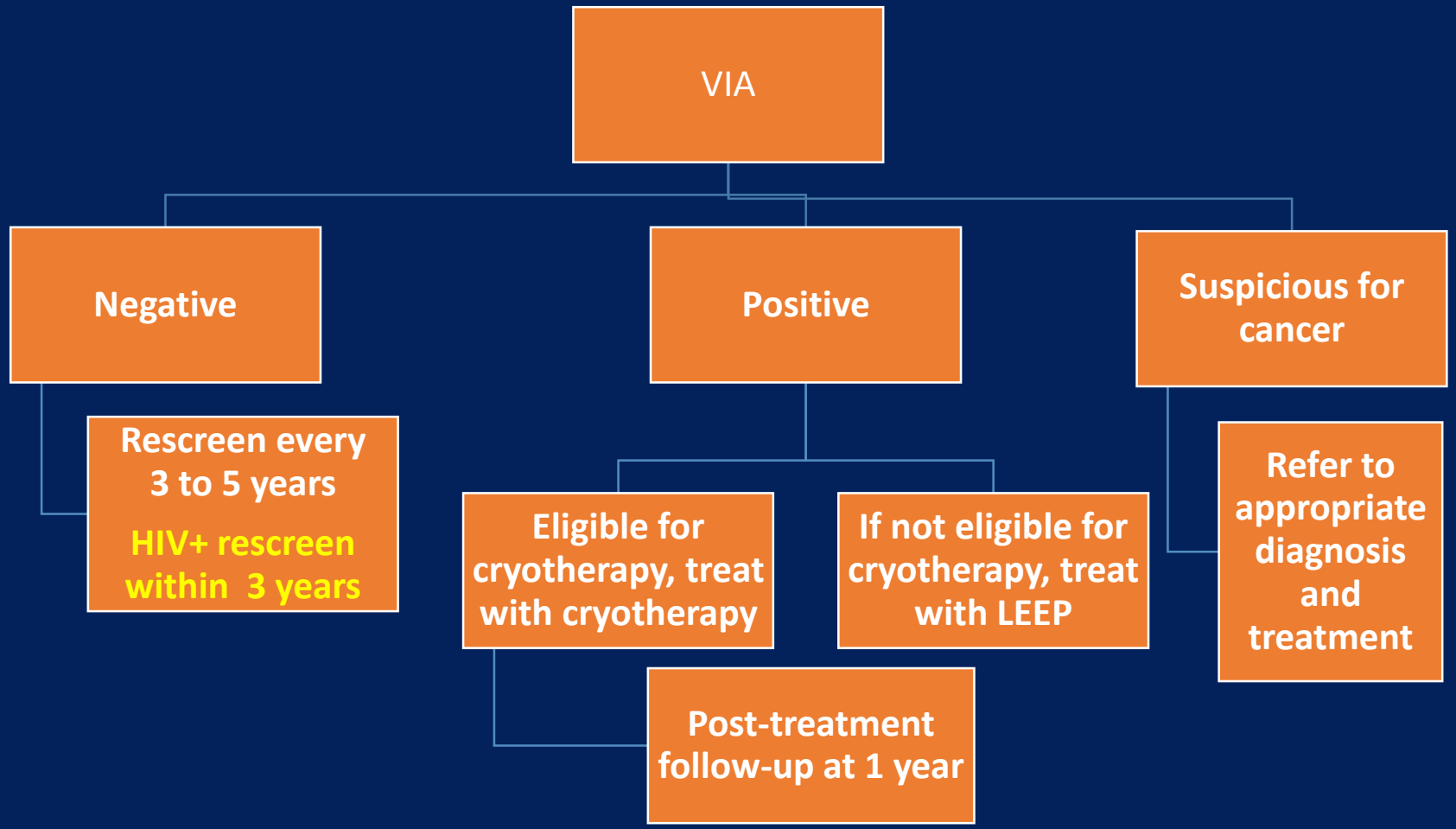
Where resources permit, the expert panel suggests a strategy of screen with **HPV and treat with cryotherapy** (or LEEP when not eligible for cryotherapy) over a strategy of screen with **VIA and treat with cryotherapy** (or LEEP when not eligible) *(conditional recommendation, ⊕⊖⊖⊖ evidence)*

Remarks: The **benefits** of screen and treat with HPV or VIA, compared to no screening, **outweighed the harms**, but the **reduction in cancer and related mortality were greater** with HPV when compared to VIA. The availability of HPV testing is **resource** dependent and, therefore, the expert panel suggests that HPV over VIA be provided where it is available, affordable, implementable and sustainable over time.

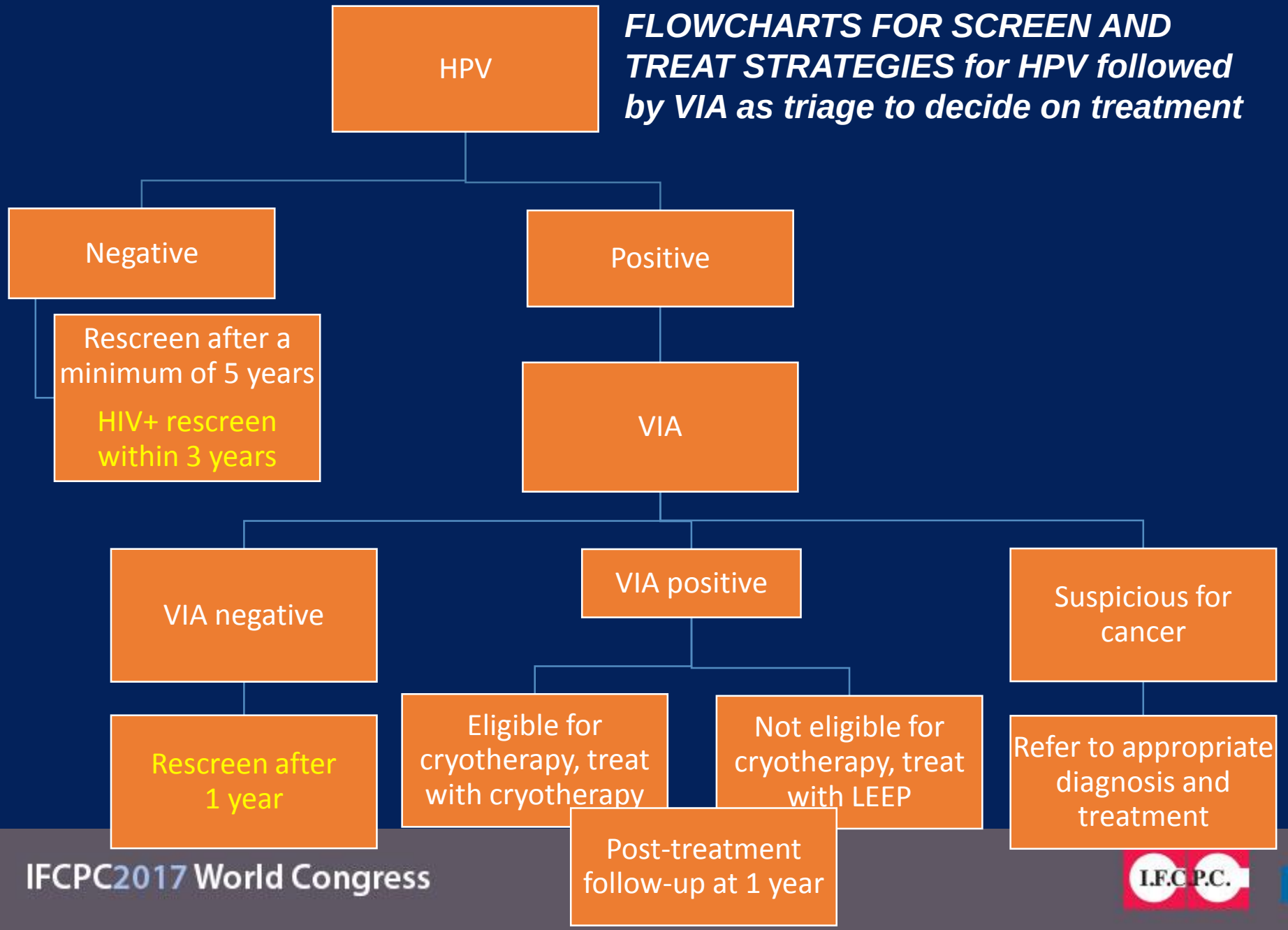
FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES for HPV followed by VIA as triage to decide on treatment



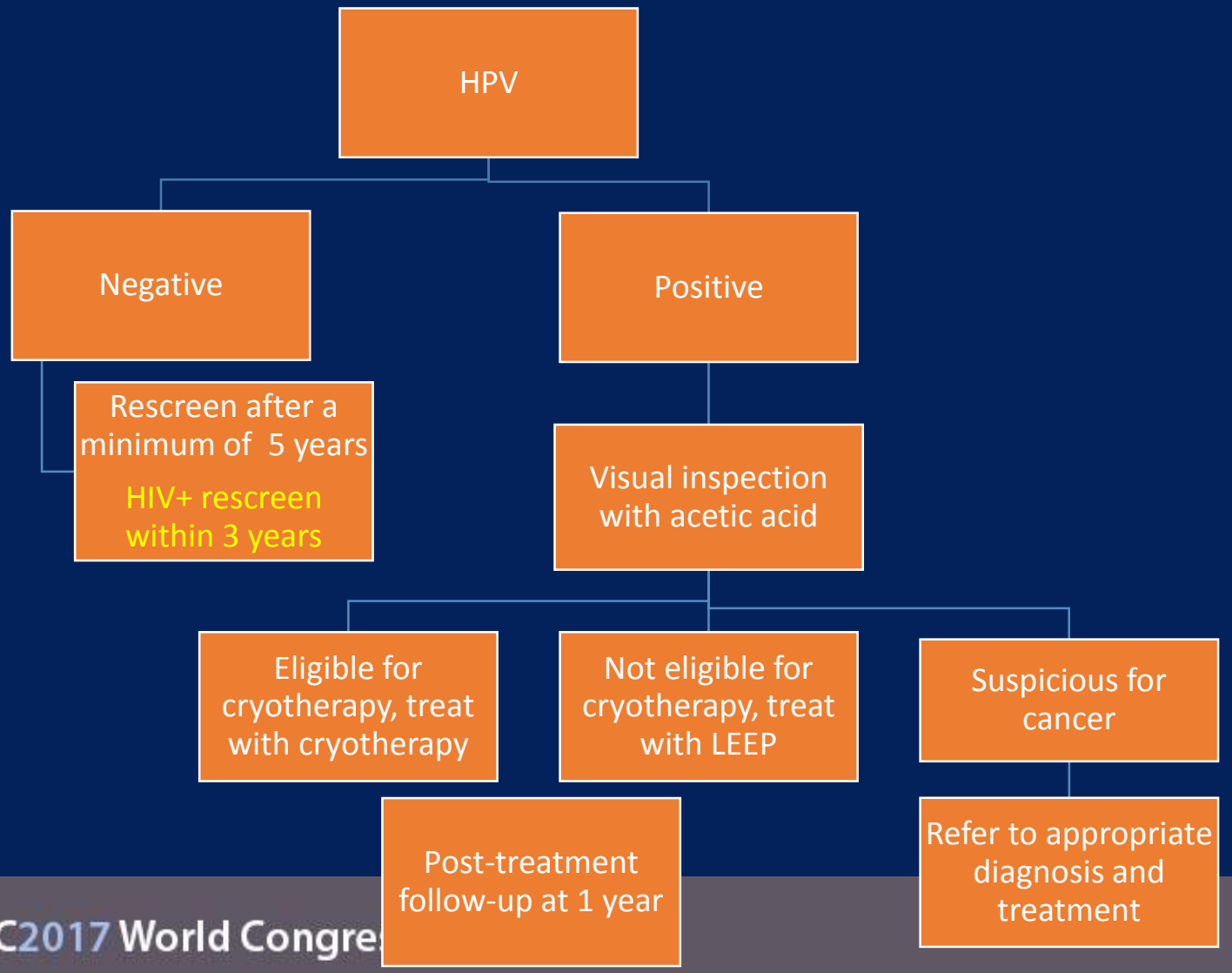
FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES WITH VIA



FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES for HPV followed by VIA as triage to decide on treatment



FLOWCHARTS FOR SCREEN AND TREAT STRATEGIES WITH HPV alone – VIA used to determine eligibility for cryotherapy



ASCO Guidelines:

American Society for Clinical Oncology

special article

Secondary Prevention of Cervical Cancer: ASCO Resource-Stratified Clinical Practice Guideline

Jose Jeronimo
Philip E. Castle
Sarah Temin
Lynette Denny
Vandana Gupta
Jane J. Kim
Silvana Luciani
Daniel Murokora
Twalib Ngoma
Youlin Qiao
Michael Quinn
Rengaswamy Sankaranarayanan
Peter Sasieni
Kathleen M. Schmeler
Surendra S. Shastri

Author affiliations appear at the end of this article.

This guideline has been endorsed by the International Gynecologic Cancer Society and the American Society for Colposcopy and Cervical Pathology (Data Supplement).

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Reprint Requests: 2318 Mill Rd, Ste 800, Alexandria, VA 22314; guidelines@asco.org

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Corresponding author: American Society of Clinical Oncology, 2318 Mill Rd, Ste 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

executive summary

Purpose To provide resource-stratified, evidence-based recommendations on the secondary prevention of cervical cancer globally.

Methods ASCO convened a multidisciplinary, multinational panel of oncology, primary care, epidemiology, health economic, cancer control, public health, and patient advocacy experts to produce recommendations reflecting four resource-tiered settings. A review of existing guidelines, a formal consensus-based process, and a modified ADAPTE process to adopt existing guidelines were conducted. Other experts participated in formal consensus.

Results Seven existing guidelines were identified and reviewed, and adapted recommendations form the evidence base. Four systematic reviews plus cost-effectiveness analyses provided indirect evidence to inform consensus, which resulted in ≥ 75% agreement.

Recommendations Human papillomavirus (HPV) DNA testing is recommended in all resource settings; visual inspection with acetic acid may be used in basic settings. Recommended age ranges and frequencies by setting are as follows: maximal: ages 25 to 65, every 5 years; enhanced: ages 30 to 65, if two consecutive negative tests at 5-year intervals, then every 10 years; limited: ages 30 to 49, every 10 years; and basic: ages 30 to 49, one to three times per lifetime. For basic settings, visual assessment is recommended as triage; in other settings, genotyping and/or cytology are recommended. For basic settings, treatment is recommended if abnormal triage results are present; in other settings, colposcopy is recommended for abnormal triage results. For basic settings, treatment options are cryotherapy or loop electrosurgical excision procedure; for other settings, loop electrosurgical excision procedure (or ablation) is recommended. Twelve-month post-treatment follow-up is recommended in all settings. Women who are HIV positive should be screened with HPV testing after diagnosis and screened twice as many times per lifetime as the general population. Screening is recommended at 6 weeks postpartum in basic settings; in other settings, screening is recommended at 6 months. In basic settings without mass screening, infrastructure for HPV testing, diagnosis, and treatment should be developed.

Additional information can be found at www.asco.org/rs-cervical-cancer-secondary-prev-guideline and www.asco.org/guidelineswiki.

It is the view of of ASCO that health care providers and health care system decision makers should be guided by the recommendations for the highest stratum of resources available. The guideline is intended to complement, but not replace, local guidelines.

INTRODUCTION

The purpose of this guideline is to provide expert guidance on secondary prevention with screening for cervical cancer to clinicians, public health authorities, policymakers, and laypersons in all resource settings. The target population is women in the general population at risk for developing cervical cancer (specific target ages depend on the resource level).

There are large disparities regionally and globally in incidence of and mortality resulting from cervical cancer, in part because of disparities in the provision of mass screening and primary prevention. Different regions of the world, both among and within countries, differ with respect to access to prevention and treatment.

Approximately 85% of incident cervical cancers occur in less developed regions (also known as low- and middle-income countries [LMICs]) around the world, representing 12% of women's cancers in those regions. Eighty-seven percent of deaths resulting from cervical cancer occur in these less-developed regions.[1] Some of the regions in the world with the highest mortality rates include the WHO Southeast Asia and Western Pacific regions, followed by India and Africa.[1] As a result of these disparities, the ASCO Resource-Stratified Guidelines Advisory Group

ASCO Guidelines

Recommendations are based on the resources available at the country or sub-country level.

Considers 4 levels of resources:

- Maximal
- Enhanced
- Limited

→ HPV screening

- Basic

→ VIA screening until HPV testing becomes available

ASCO Guidelines

Self-sampling of vaginal samples for HPV testing only:

Validated collection device, transport media and assay.

Summary

- New guidelines for cervical pre-cancer screening and treatment are evolving and will continue evolving.

- Molecular testing is becoming the preferred screening option for most guidelines.

Thank you

jjeronimo@path.org
www.path.org