What is needed for implementation of a complete system from screening to treatment in LMICs?. Moving towards an organised cervical cancer screening, diagnosis and treatment in LMICs.

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HPV Prevention and Control Board
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Simms et al. estimated that In the absence of further intervention, there would be 44·4 million cervical cancer cases (25M deaths) diagnosed globally over the period 2020-69, with almost two-thirds of cases occurring in low-HDI or medium-HDI countries (1).

WHO : Implementation of **HPV-based screening twice per lifetime** between 35 years and 45 years in **all LMICs with 70% coverage** globally will bring forward the effects of prevention and avert a total of 12·5-13·4 million cases in the next 50 years

HPV-based screening

twice per lifetime

all LMICs with 70% coverage

HOW TO MAKE IT REAL?

And we need to manage all screen positive !

(1) Simms et al. 2019 Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study

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The screening situation

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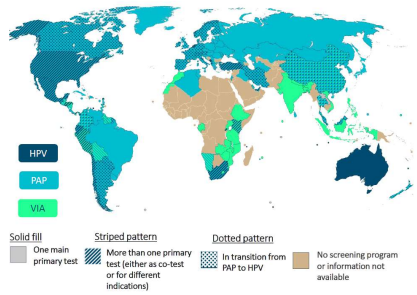
Screening situation in 2020

OFFICIALLY RECOMMENDED PRIMARY TESTS FOR CERVICAL CANCER SCREENING



Serrano and Bruni et al 2020 IPVC

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ESTIMATED SCREENING COVERAGE IN 2019, WOMEN AGED 30-49y

		COVERAGE (% - 95%CI)		
		LAST YEAR	LAST 5 YEARS	EVER IN LIFETIME
World		19% (16-21%)	33% (30-37%)	38% (34-42%)
By Income	High income	44% (38-52%)	81% (70-93%)	88% (76-100%)
	Upper middle income	25% (20-31%)	42% (36-50%)	47% (39-56%)
	Lower middle income	4% (4-5%)	10% (8-13%)	13% (9-18%)
	Low income	5% (4-7%)	12% (10-15%)	15% (12-18%)
By region	Sub-Saharan Africa	6% (5-8%)	15% (13-18%)	18% (15-21%)
	North Africa & West Asia	9% (7-12%)	19% (15-23%)	22% (18-26%)
	Central & South Asia	3% (2-4%)	9% (6-13%)	14% (8-21%)
	East & South-East Asia	16% (11-23%)	27% (20-34%)	31% (23-39%)
	Latin America & Caribbe	47% (37-56%)	76% (61-91%)	80% (65-95%)
	Oceania (excl. AUS/NZL)	3% (2-4%)	7% (5-8%)	8% (6-10%)
	Australia & New Zealand	36% (27-46%)	87% (69-100%)	98% (77-100%)
	Europe & North America	45% (38-53%)	84% (72-97%)	91% (78%-100%)

Study funded by Instituto de Salud Carlos III through project P118/01137 (Co-funded by European Regional Development Fund. ERDF, a way to build Europe).

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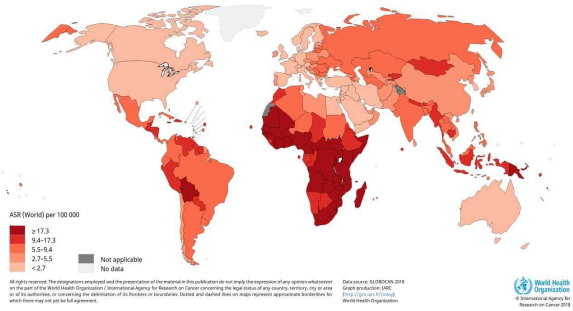
Estimated age-standardized mortality rates
OVER 280,000 DEATHS EVERY YEAR

Estimated age-standardized mortality rates (World) in 2018, cervix uteri, all ages



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Planning

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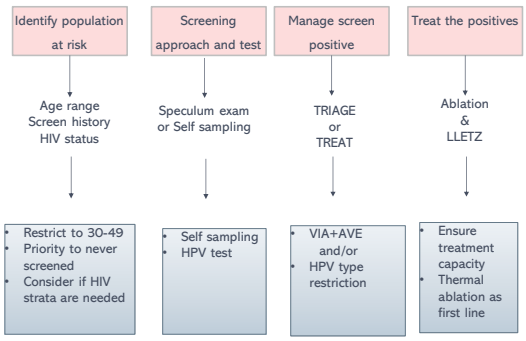
Deciding the screening strategy



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Triage and new scenarios

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Available strategies for triage of HPV- positive women in low resource settings

- Visual inspection after AA Poor reproducibility and low accuracy in many settings. Leads mainly to under treatment (1)
- VAT Visual evaluation for treatment Overtreatment (2)
- Enhanced visual inspection (with digital images) Unclear benefit
- **Visual inspection after AA with automated reading AI-based** Preliminary excellent results (3)
- **HPV genotype restriction** Scientifically strong added value (4)
- Multiplex of virological and cellular markers *(under evaluation) (5)*

(1) Catarino et al. 2017, Wentzensen 2017
(2) Toliman et al. 2018 (3) Hu et al. (4) Demarco et al.2020 (5) Gizaw et al. 2019

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Performance of VIA examination and HPV Xpert test algorithms for detection of high-grade disease.

Screening Algorithm			High-Grade Disease		Percentage %			
			Positive n (%)	Negative n (%)	Sensitivity [95% CI]	Specificity [95% CI]	PPV [95% CI]	NPV [95% CI]
Algorithm 1 (n = 462)	POSITIVE	VIA +	17 (3.7)	80 (17.3)	**51.5** [33.5–69.2]	**81.4** [77.3–84.9]	**17.5** [10.6–26.6]	**95.6** [93.0–97.5]
	NEGATIVE	VIA -	16 (3.5)	349 (75.5)				
Algorithm 2 (n = 527)	POSITIVE	Any hrHPV + (hrHPV test on self-collected specimen)	33 (6.3)	64 (12.1)	**91.7** [77.5–98.2]	**87.0** [83.7–89.8]	**34.0** [24.7–44.3]	**99.3** [98.0–99.9]
	NEGATIVE	Any hrHPV – (hrHPV test on self-collected specimen)	3 (0.6)	427 (81.0)				
Algorithm 3 (n = 529)	POSITIVE	Any hrHPV + (hrHPV test on clinician-collected specimen)	33 (6.2)	48 (9.1)	**91.7** [77.5–98.2]	**90.3** [87.3–92.7]	**40.7** [29.9–52.2]	**99.3** [98.1–99.9]
	NEGATIVE	Any hrHPV – (hrHPV test on clinician-collected specimen)	3 (0.6)	445 (84.1)				
Algorithm 4 (n = 515)	POSITIVE	Any hrHPV + and VIA + (hrHPV test on self-collected specimen)	15 (2.9)	18 (3.5)	**45.5** [28.1–63.6]	**96.3** [94.2–97.8]	**45.5** [28.1–63.6]	**96.3** [94.2–97.8]
	NEGATIVE	Any hrHPV – or Any hrHPV + and VIA - (hrHPV test on self-collected specimen)	18 (3.5)	464 (90.1)				

A 'test and treat' algorithm based HPV would have appropriately treated 92% (33/36) of all women with high-grade disease (HSIL or worse); over-treated 13% (64/491) of women without disease; and would not have detected and treated 8% (3/36) of women with high-grade disease.

Use of VIA either as primary screening or as triage would have missed 48.5% of HSIL.

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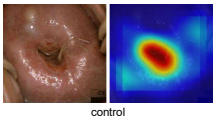
First Proof of Principle in Guanacaste Natural History Study Guanacaste, Costa Rica, use of cervigrams at baseline and follow up for CIN2+. Automated Visual Evaluation (AVE)

- AVE severity score (0 to 1) to predict precancer
- Evaluation of AVE algorithm
  - ROC curves
  - AUC statistic
- Compared well with other tests: HPV, cytology, cervicography, colpocopic impression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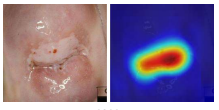
case

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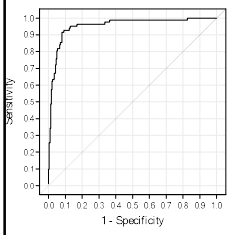
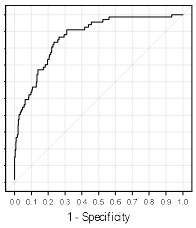
Performance of Automated Visual Evaluation (AVE) algorithms

Screening
AUC = 0.95



Triage of HPV positive
AUC = 0.87



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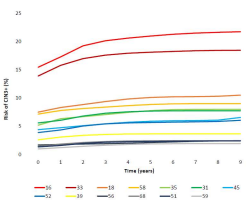
HPV type restriction

Type-specific cumulative risk of progression to CIN3+ of single HPV infections



Type group	% infections	7-yr CIN3+ risk
16	26	22
18, 45	5	>5, elevated cancer
31, 33, 35, 52, 58	39	>5
39, 51, 56, 59, 68	23	<5

Invasive cervical cancer

	N tested	% pos	95% CI
HPV16	14595	54.4	53.6–55.2
HPV18	14387	15.9	15.3–16.5
HPV33	13827	4.3	4.0–4.6

Demarco, Hyun, et al. ECM, 2020.
Schiffman, et al. Infect Agent Cancer, 2009.

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Treatment

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Treatment of precancerous lesions

- Ideally treatment should follow the triage test, if possible, in the same visit to avoid lost to FU.
- Thermal ablation is the easiest to manage and has shown to overcome many structural issues of cryotherapy with similar performance (1).
- Still a considerable proportion may not be treatable because of large lesions (2) or not visible TZ.

- Issues:
  - Logistical: Women need to accept treatment, personnel may not be available at the time of confirmation, devices may not be ready.
  - Technical: Distinction between TZ1,TZ2 and TZ3 under VIA/AVE. Management of TZ2 and TZ3 need good referral system.

(1) WHO guidelines 2019, Holme et al 2020Randal 2019, Pinder et al. 2020
(2) Gage et al. 2009

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Key issues in management

- How many cervical cancer cases can be managed?

  - Do we need to limit the screening capacity based on the availability of managing invasive cervical cancer cases detected through the screening process (aprox 0.6% of triage positive)?
  - Do we need to guarantee that treatment of precancerous lesions (about 1%) is offered with no delays and with trained personnel to run thermal ablation and LLETZ?
  - Should these 2 points be the very first questions to be answered before large scale screening is initiated?

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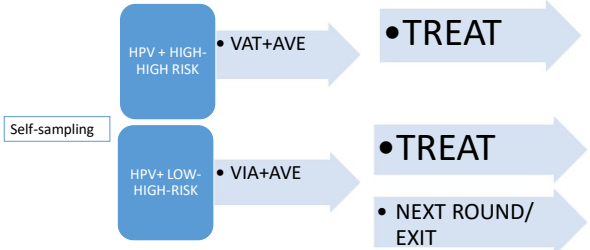
Scenario with high accuracy, minimizing overtreatment and potential low cost



VAT Visual assessment for treatment
VIA Visual evaluation necked eye
AVE Automated visual evaluation
HIGH/HIGH 16,18,45,31,33,35,52,58
LOW-HIGH 39,51,56, 59,68

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Data collection

- Minimal data collection can provide a basic measure of the impact and performance of the intervention.
- Ideally a cancer registry will be extremely useful
- Low cost approaches are available (cell phone software designed for this, DHIS2..).
- Data collection, analysis and feedback based on results are critical to re-shape efforts when needed.

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A Cervical Precancer Planning Tool was developed for country decision-makers.

Tool purpose

- The purpose of the Tool is to inform national cervical precancer screening and treatment strategies.
- The Tool enables end-users to explore trade-offs for the following:
  - **Screening approaches**
    - Number of women correctly identified
    - Number of women missed
    - Number of women incorrectly referred
    - Costs
  - **Treatment equipment deployment approaches**
    - Loss to follow-up
    - Equipment utilization
    - Cost

20 https://www.path.org/programs/market-dynamics/cervical-precancer-planning-tool/

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In summary

- Impact of screening programmes may be limited by the availability of treatment facilities.
- Self-sampling and HPV testing are key elements for high coverage and high accuracy.
- Selection of a triage strategy remains unsettled in low resource settings, but new low-cost approaches are likely to increase accuracy and affordability.
- Data monitoring can be critical to evaluate impact and may increase performance.
- While under COVID, cervical screening should be undertaken within safe environments. Otherwise delay the intervention.

8/26/2020

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THANK YOU FOR YOUR ATTENTION

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-PATH Market Dynamic team
-NCI- Mark Schiffman and the Automatic Visual Evaluation team

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