HPV Epidemiology Predicts Cost-Effective Cervical Screening

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NIH NATIONAL CANCER INSTITUTE

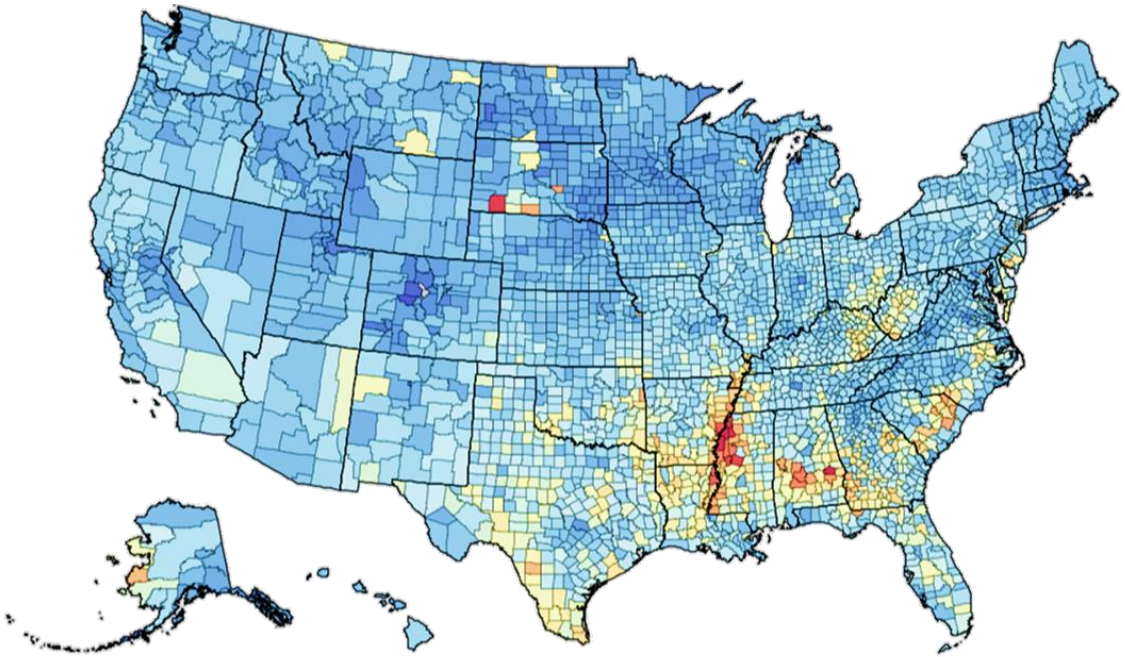
Declarations

- We have no conflicts of interest to report
- To avoid COI, we pay for commercial products, publish independently, and encourage more prevention methods/strategies designed for low-resource settings
- Personal perspective

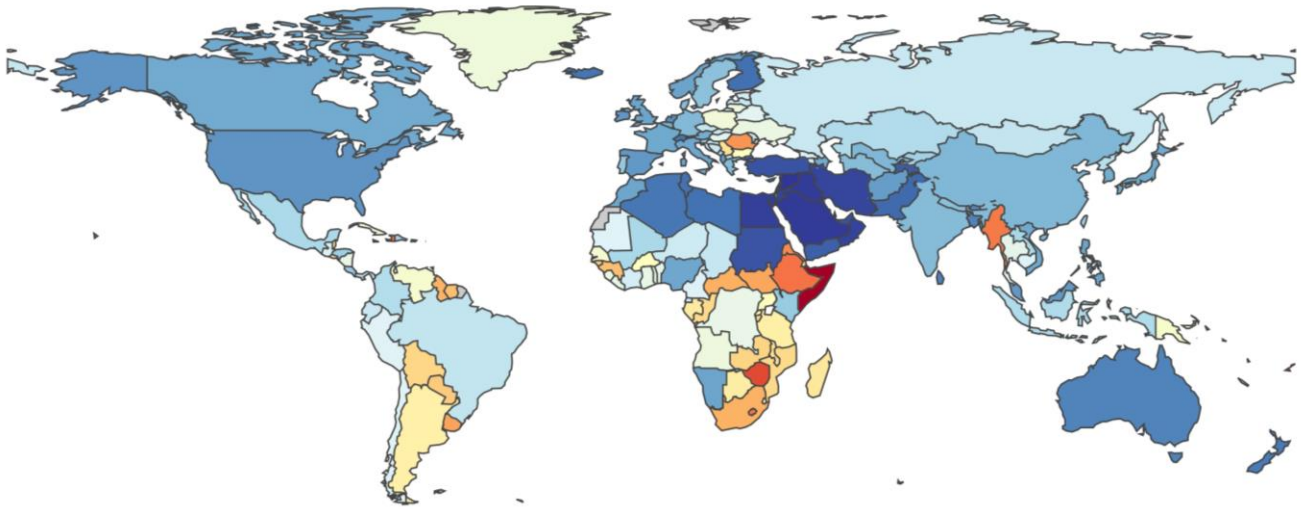
Goal and Limitations of Presentation

- To show how epidemiologic understanding of HPV and cervical carcinogenesis can guide cost-effective screening strategies
  - Focus on low-resource settings where cervical cancer burden is highest
  - Short presentation shows some key principles and gives an example of one possible strategy we are studying
  - For details, please contact schiffmm@exchange.nih.gov

Disparities in Cervical Cancer Mortality Are Increasing



0 Deaths per 100,000 6



0 Deaths per 100,000 12

Disparities are specific to settings, not countries. Practice lags behind science by decades.

World Health Organization

Dr Tedros Adhanom Ghebreyesus
Director-General

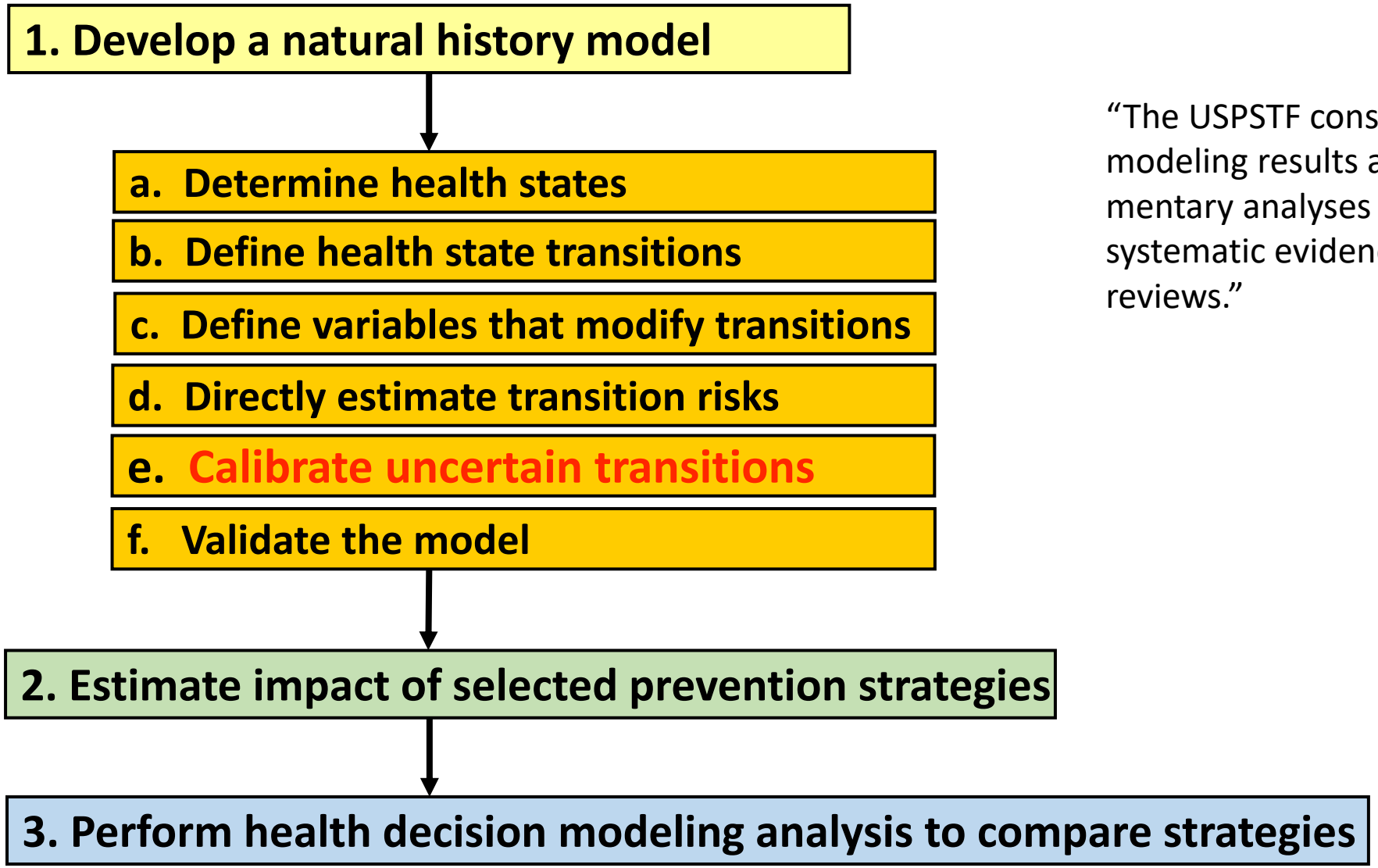
Cervical Cancer: An NCD We Can Overcome
Intercontinental Hotel, Geneva
19 May 2018

WHO call to action for elimination of cervical cancer

Need For Cervical Screening, by Age, Linked to Resources

Bruni et al., Lancet Global Health 2022

Framework for a Cost-Effectiveness Analysis



"The USPSTF considers modeling results as supple-mentary analyses to systematic evidence reviews."

Widening Scope of Cervical HPV Epidemiology, 40+ Years in the NCI IRP (Three NCAB Presentations)

Emphasis	Main Research Partners	Types of studies
Etiology and pathogenesis	Clinicians, pathologists/cytologists, molecular biologists	Looking for cause and causal pathway
Prevention methods	Immunologists, virologists, DNA diagnostics	Cohort studies and trials for vaccines and screening tests
Clinical epidemiology	Guidelines groups, optical engineers and AI, health decision scientists	Risk estimation, artificial intelligence, guidelines, prevention strategies and COST EFFECTIVENESS

Three Kinds of Cervical HPV Epidemiology, Past 40 Years in the NCI IRP (NCAB Presentation #1)

Emphasis	Main Research Partners	Types of studies
Etiology and pathogenesis	Clinicians, pathologists/cytologists, molecular biologists	Looking for cause and causal pathway
Prevention methods	Immunologists, virologists, DNA diagnostics	Cohort studies and trials for vaccines and screening tests
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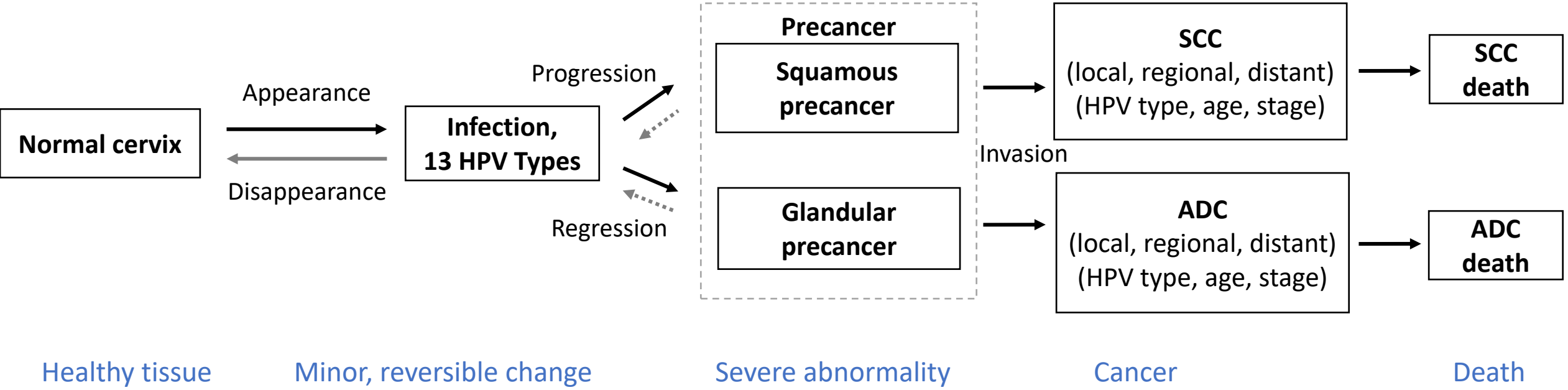
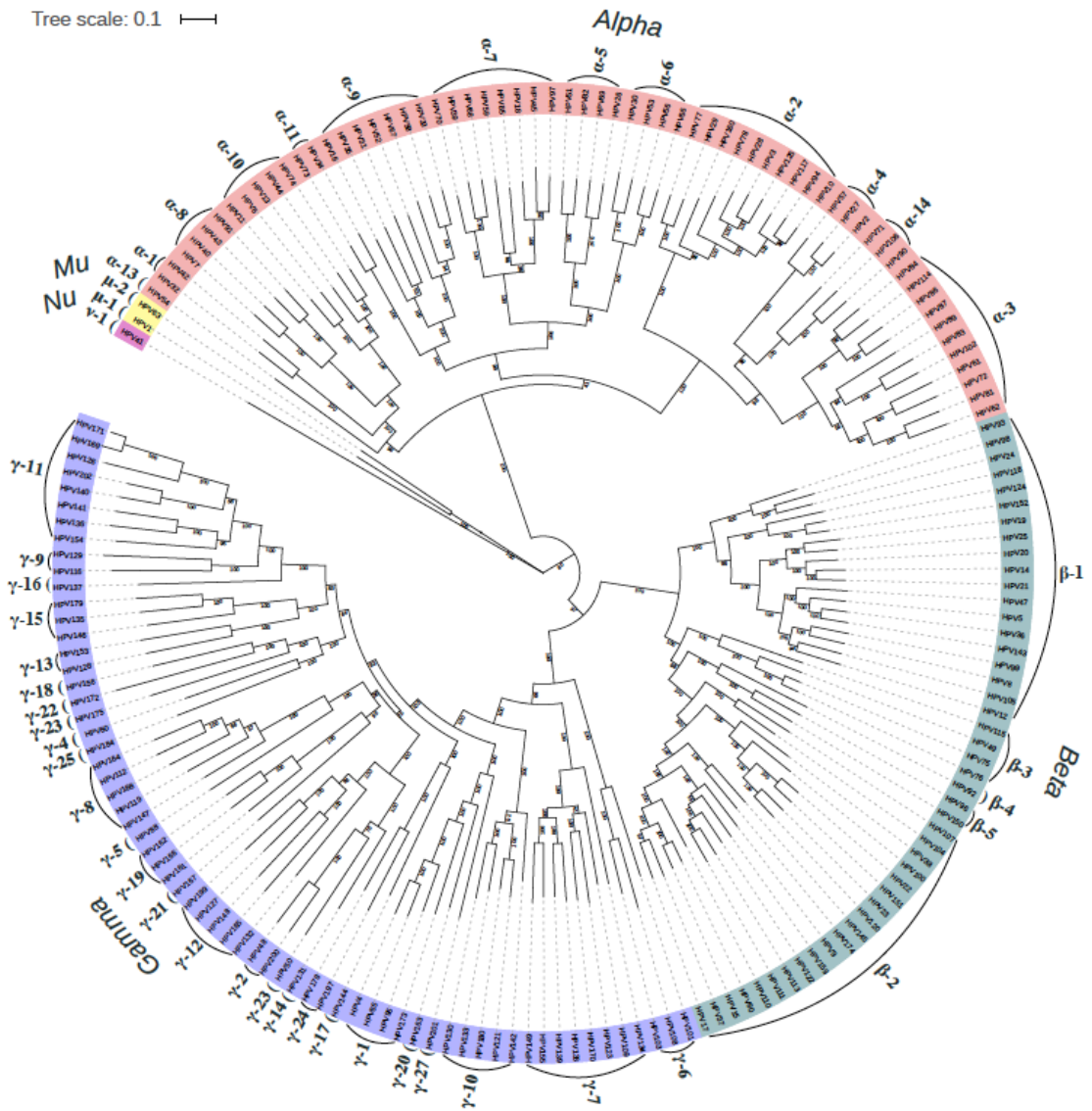
Established HPV and Cervical Cancer Causal Pathway

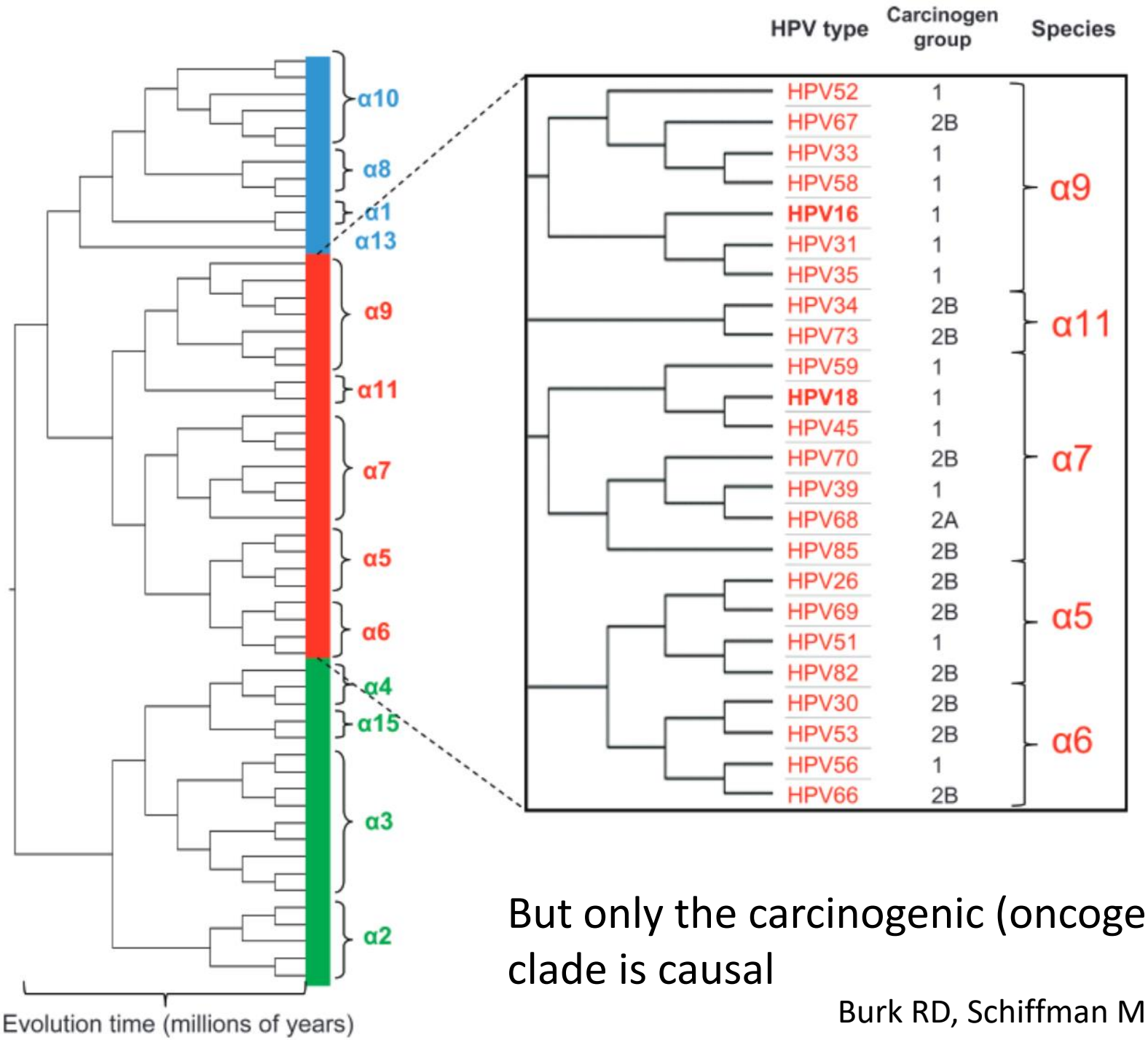


Campos et al. Preventive Med 2021

The Human Papillomaviruses Are Necessary Causal Agents



Burk RD et al., Nature Rev Dis Primers 2016



But only the carcinogenic (oncogenic or high-risk) HPV clade is causal

Burk RD, Schiffman M et al., Virology 2005

HPV Genotype Groups for Risk-Based Management

HPV type	% of Cervical Cancers
16	60.3
18	10.5
45	6.1
33	3.7
31	3.6
52	2.7
58	2.2
35	2.0
39	1.6
51	1.2
59	1.1
56	0.9
68	0.6

Cancer series and prospective cohorts reveal natural ordering among the high-risk HPV types in risk of cancer, linked to evolutionary tree

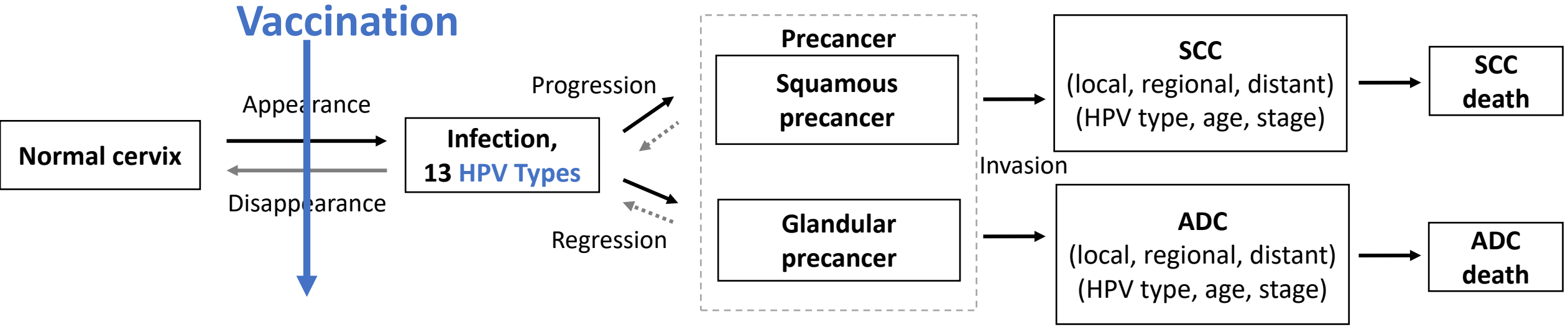
de Sanjose et al., JNCI Cancer Spectr. 2018

Demarco M. et al. EClinicalMed, 2020; De Sanjose et al. JNCI Can Spe, 2018

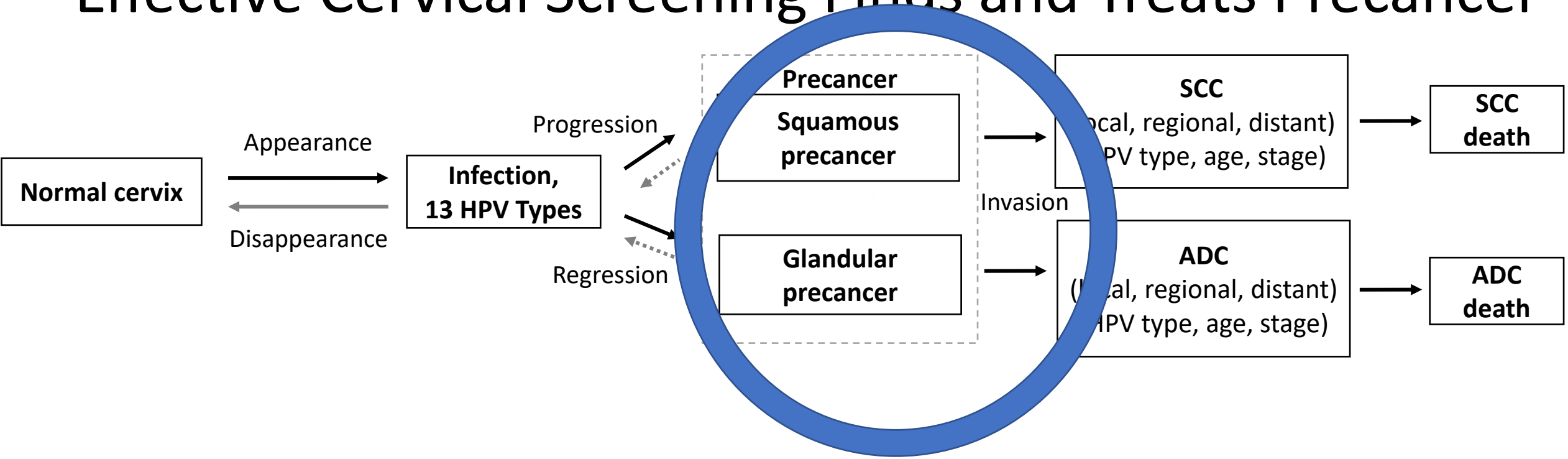
Widening Scope of Cervical HPV Epidemiology, 40+ Years in the NCI IRP (NCAB Presentation #2)

Emphasis	Main Research Partners	Types of studies
Etiology and pathogenesis	Clinicians, pathologists/cytologists, molecular biologists	Looking for cause and causal pathway
Prevention methods	Immunologists, virologists, DNA diagnostics	Cohort studies and trials for vaccines and screening tests
Clinical epidemiology	Guidelines groups, optical engineers and AI, health decision scientists	Risk estimation, artificial intelligence, guidelines, prevention strategies and COST EFFECTIVENESS

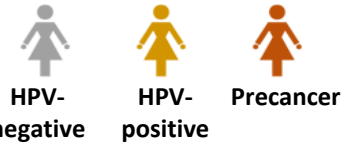
Preventive Measures Based on HPV and Cervical Cancer Causal Pathway



Effective Cervical Screening Finds and Treats Precancer



Helped design and/or validate multiple screening/triage methods



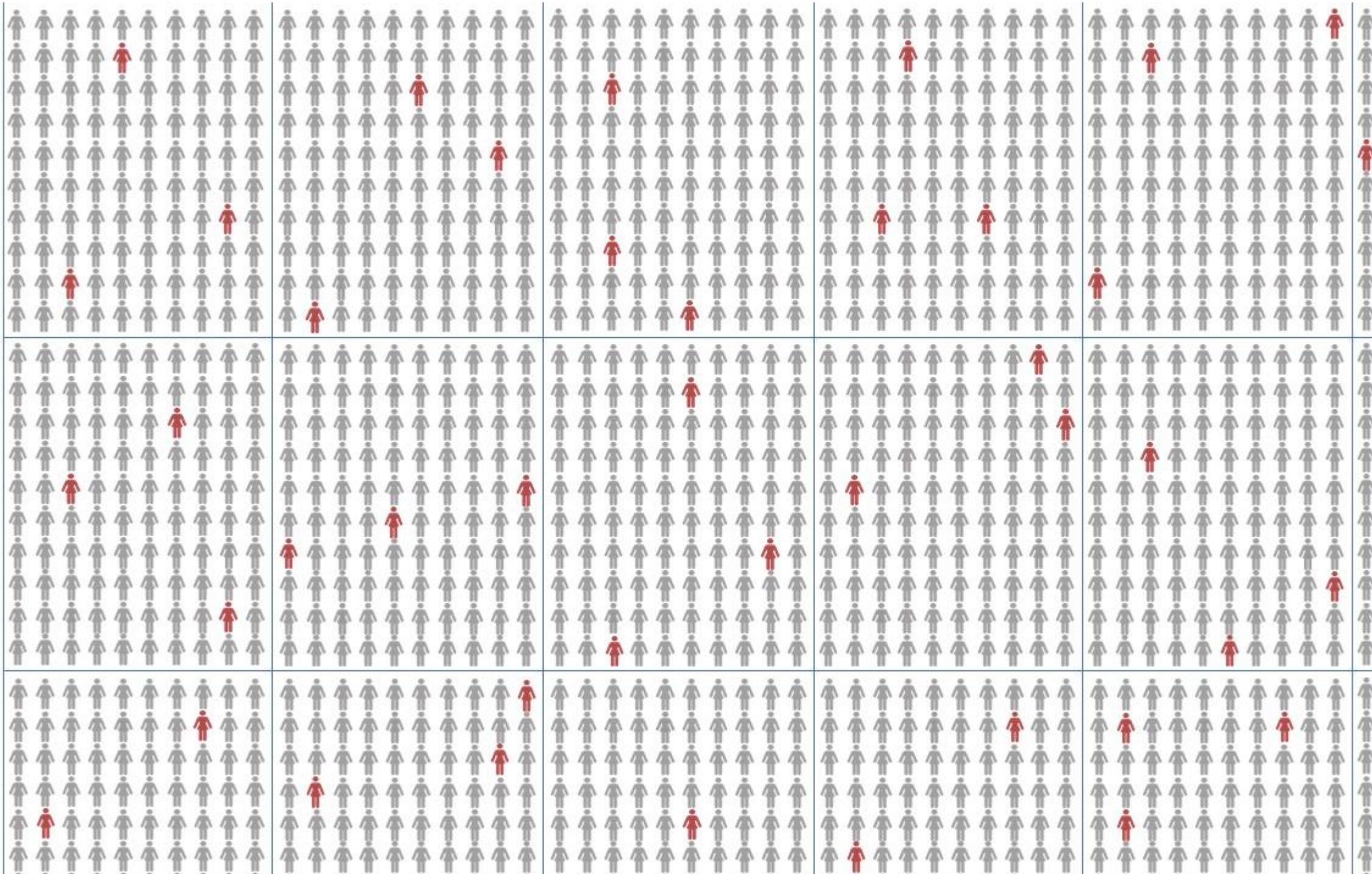
Clinical Epidemiology of Cervical HPV and Carcinogenesis, 40+ Years in the NCI IRP (Today, NCAB Presentation #3)

Emphasis	Main Research Partners	Types of studies
Etiology and pathogenesis	Clinicians, pathologists/cytologists, molecular biologists	Looking for cause and causal pathway
Prevention methods	Immunologists, virologists, DNA diagnostics	Cohort studies and trials for vaccines and screening tests
Clinical epidemiology*	Guidelines groups, optical engineers and AI, health decision scientists	Risk estimation, artificial intelligence, guidelines, prevention strategies and COST EFFECTIVENESS

* Emphasis on Absolute Risks

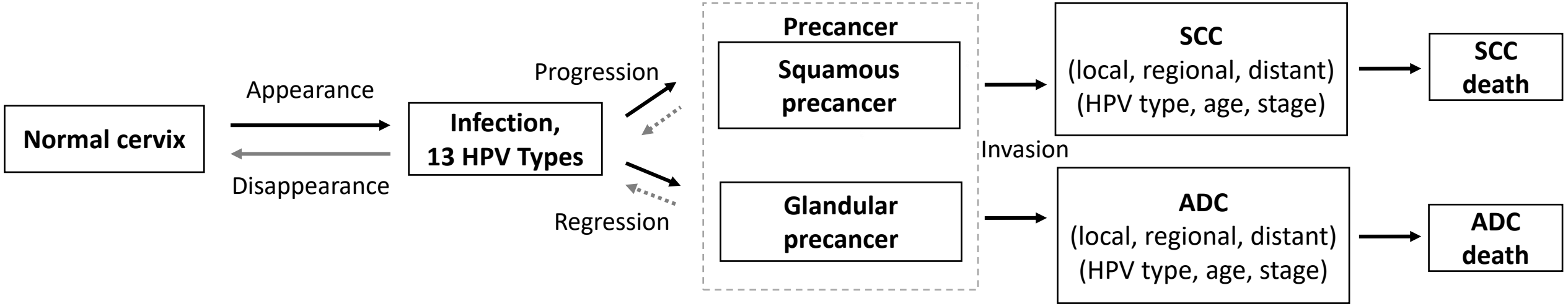
Cervical Cancers Occur In 1-5% of Women

How Does HPV Epidemiology Help to Find Them?



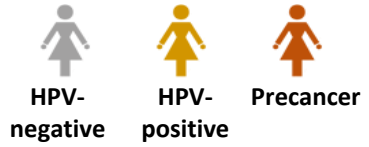
Screening population

HPV Screening Reassures Most, Alerts Those At Risk

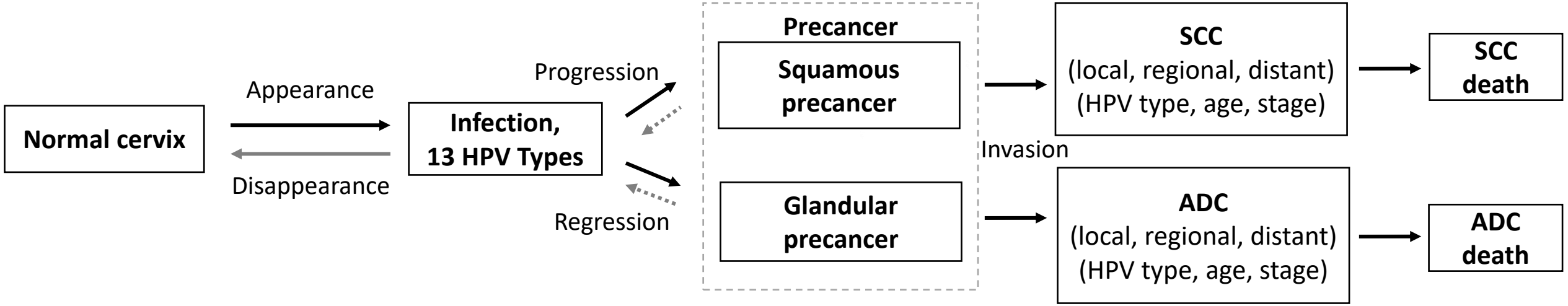


HPV negative
reassured (low risk)

HPV positive
alerted of higher
risk, need
management

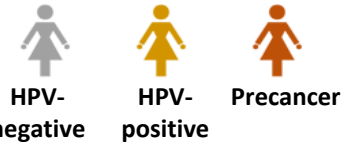


Effective Triage of HPV Positives Finds Precancer/cancer



Perfect **triage** would find only precancer among HPV-positive

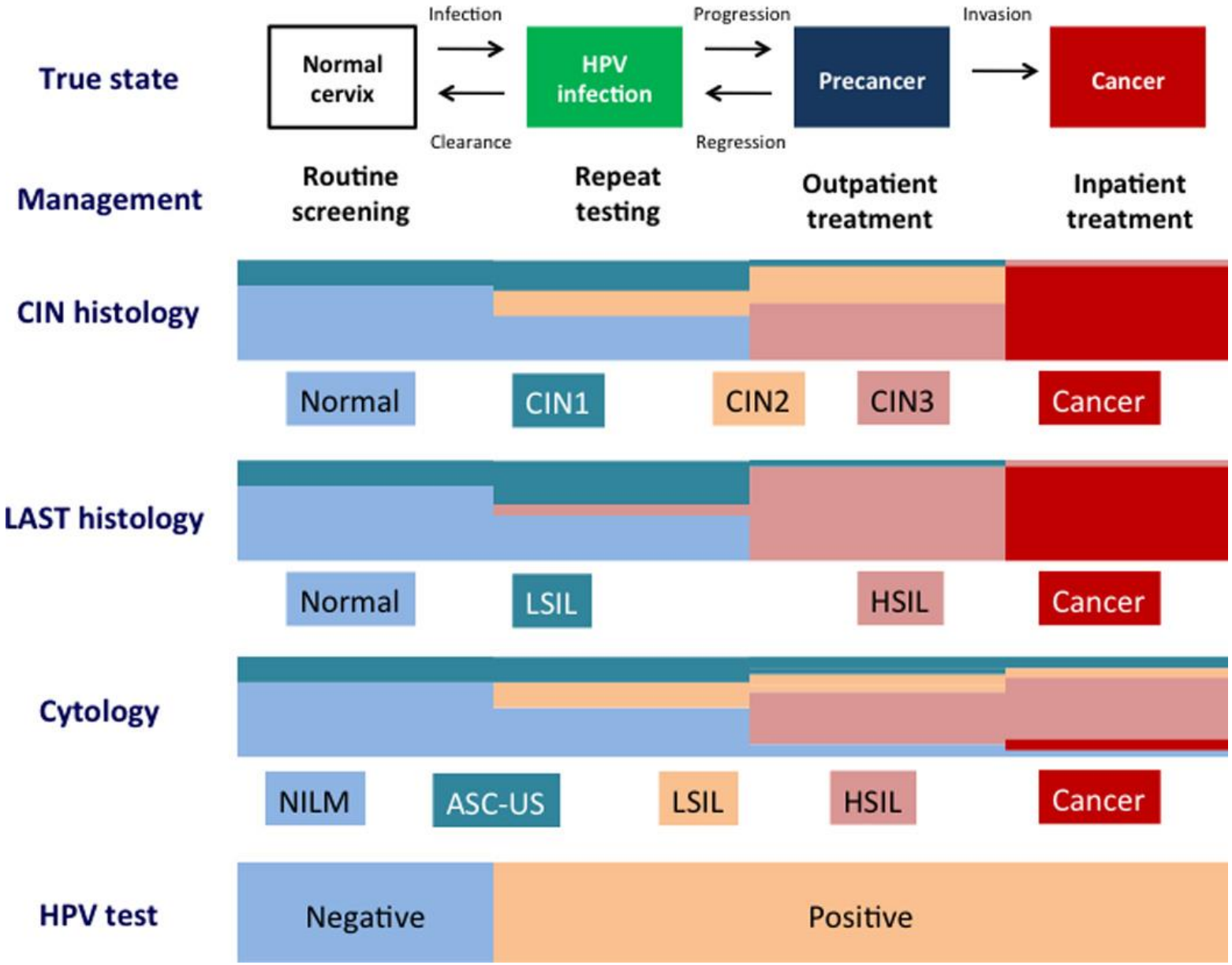
Uncommon



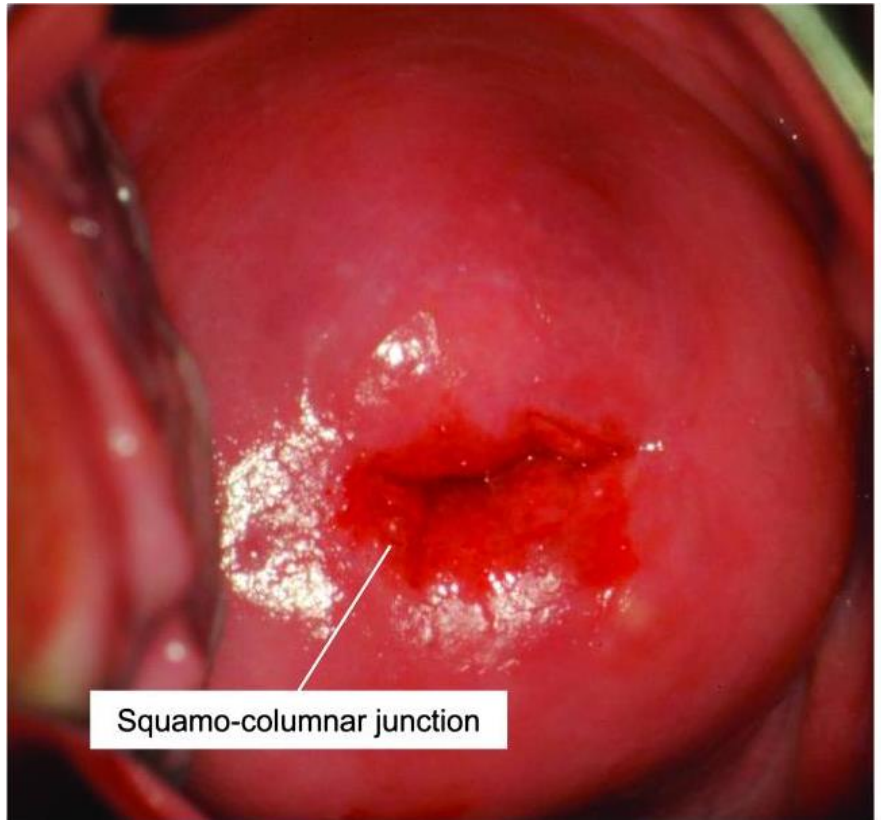
Accuracy equals effectiveness

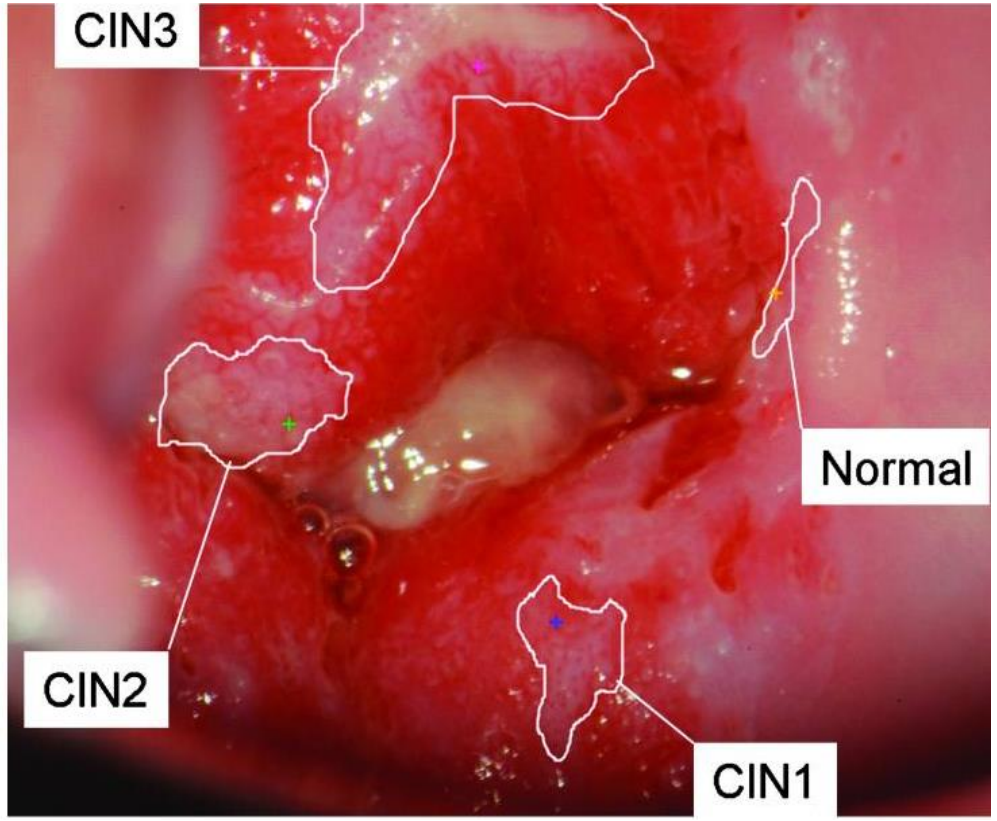
- **Older technologies** need repetition to overcome errors
- A highly accurate test, performed less often, is preferable
- This principle is true
  - In higher-resource settings for efficiency and minimal morbidity
  - In lower-resource settings for affordability and sustainability

Microscopic Approximation of Causal Pathway

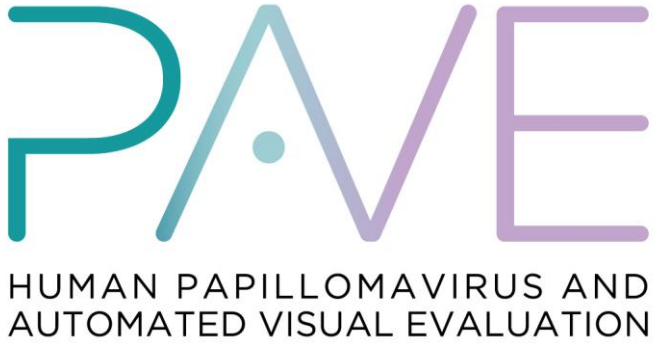


Visual Approximation of Causal Pathway





Example: Consortial Study Of a Prevention Strategy Designed to Be Cost-Effective in Low-Resource Settings



Accelerated Control of Cervical Cancer

PAVE
HUMAN PAPILLOMAVIRUS AND AUTOMATED VISUAL EVALUATION

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Imran Morhason-Bello, Nigeria

Natasha Hansen, NCI, US

Zeev Rosberger, Canada

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Michaela McCrary, NCI, USA

Lisa Finkelstein, NCI, USA

Lester Mark Solomon, NCI, USA

HIV

Helen Kelly NCI, UK

Data Integration

Sofia Granda, EHAS, Spain

Cristina Barrena, EHAS, Spain

Ignacio Prieto, EHAS, Spain

PAVE
HUMAN PAPILLOMAVIRUS AND AUTOMATED VISUAL EVALUATION

10 International PAVE Consortial Partners
(up to 100,000 to be screened by 2024)

El Salvador, Dominican Republic, Brazil (2), Nigeria, Malawi (2), Tanzania, Eswatini, Cambodia

Accurate Screening When Resources are Limited

How can we do “the right thing”
for the greatest number of women?

Achieving risk-based management
In lower-resource settings

Choice of Management Depends on Cancer Risk

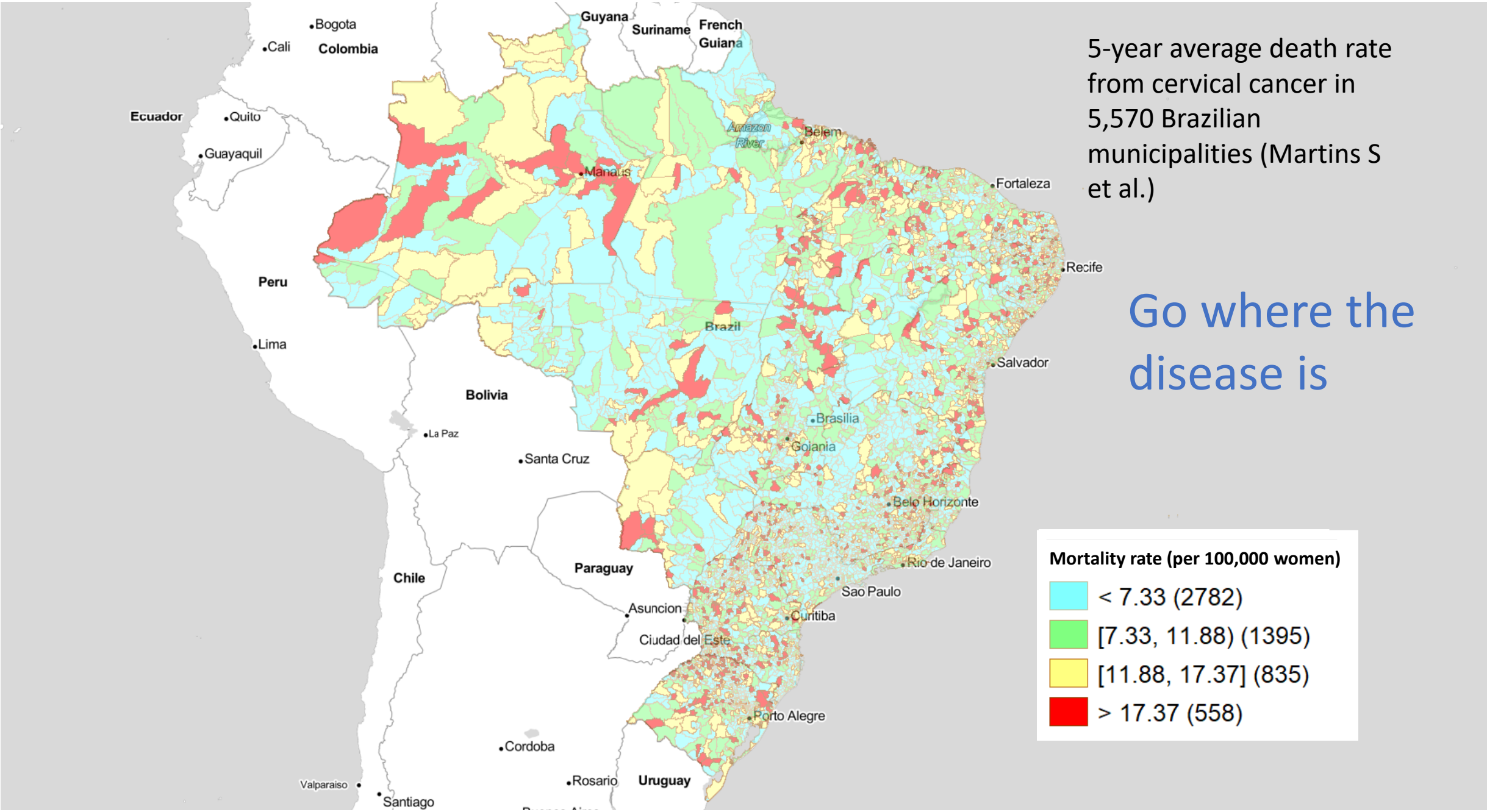
Suspect Cancer

Refer for Excision

Treat with Ablation

Reassure

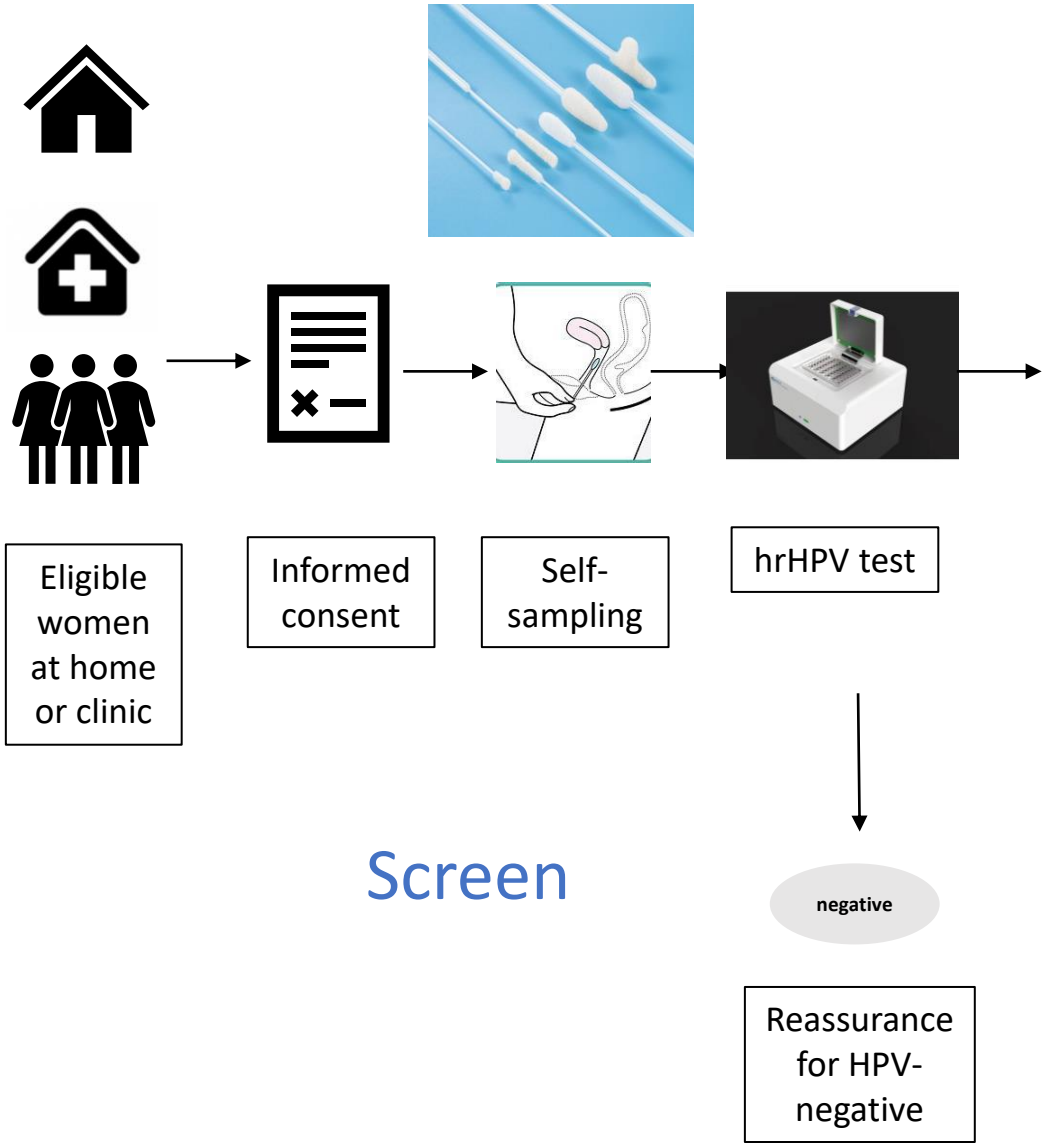
Increasing Risk of Cervical Cancer



5-year average death rate from cervical cancer in 5,570 Brazilian municipalities (Martins S et al.)

Go where the disease is

The HPV-AVE Strategy for Screen-Triage-Treat (Consortial Study Underway)



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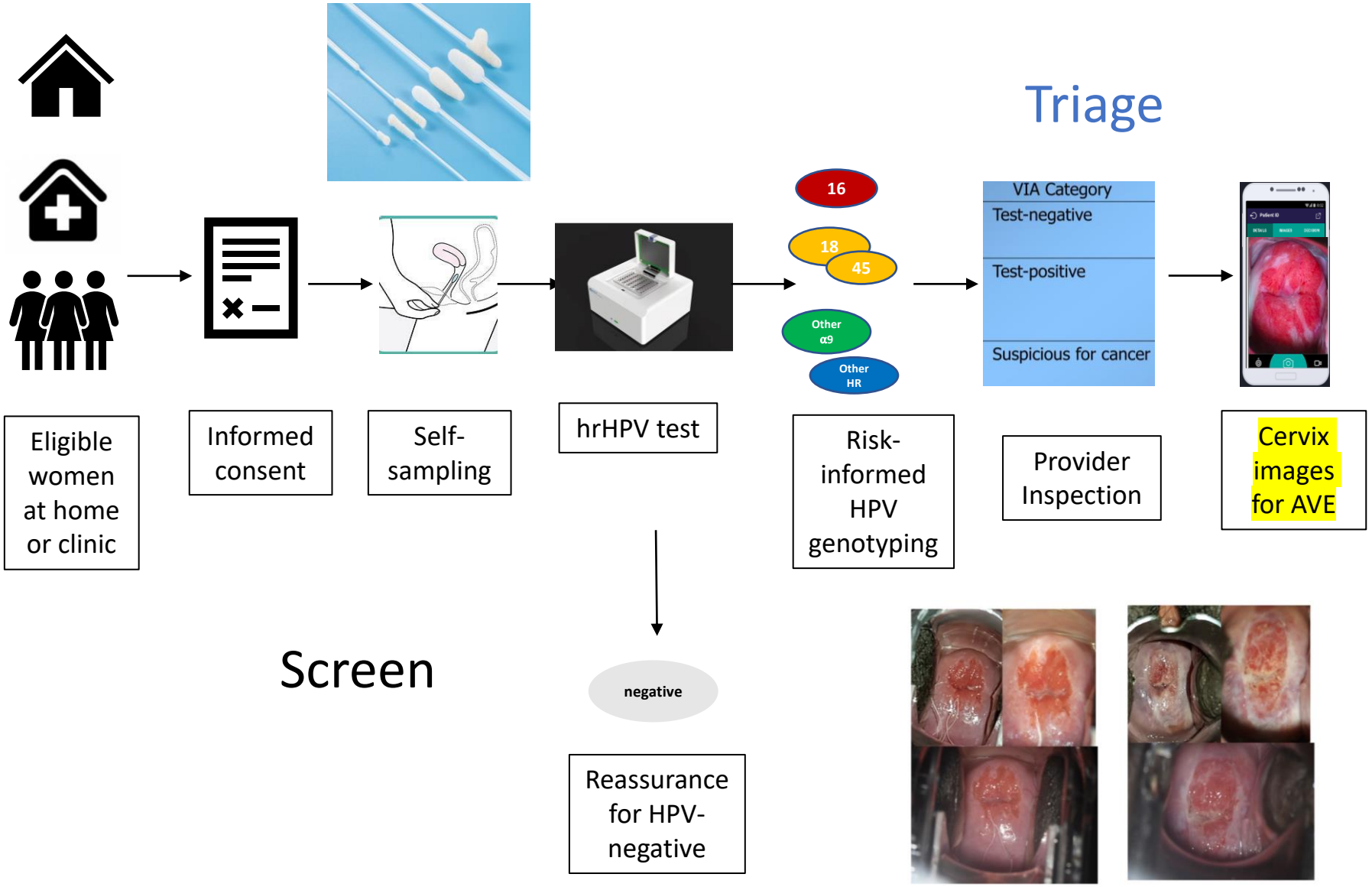

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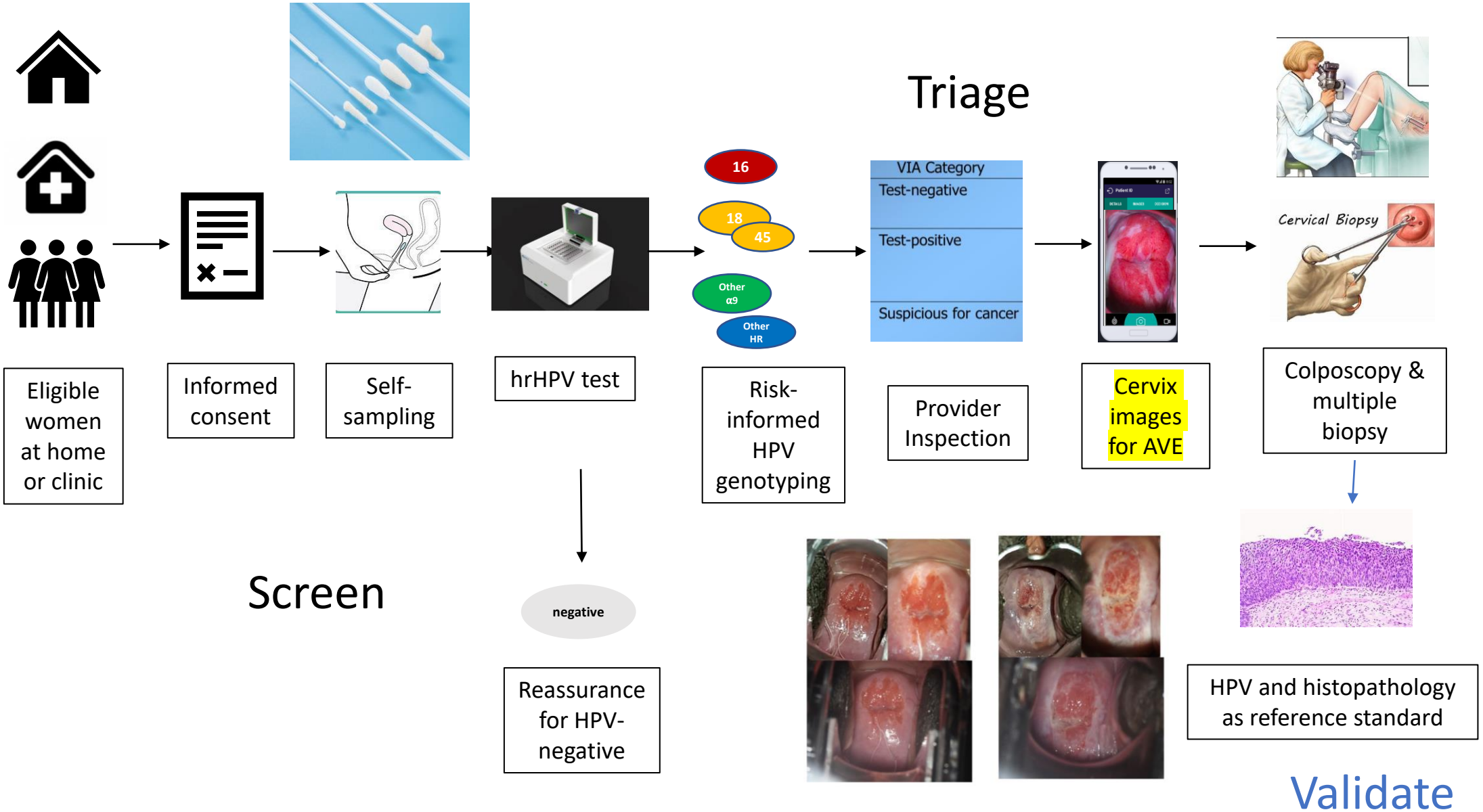
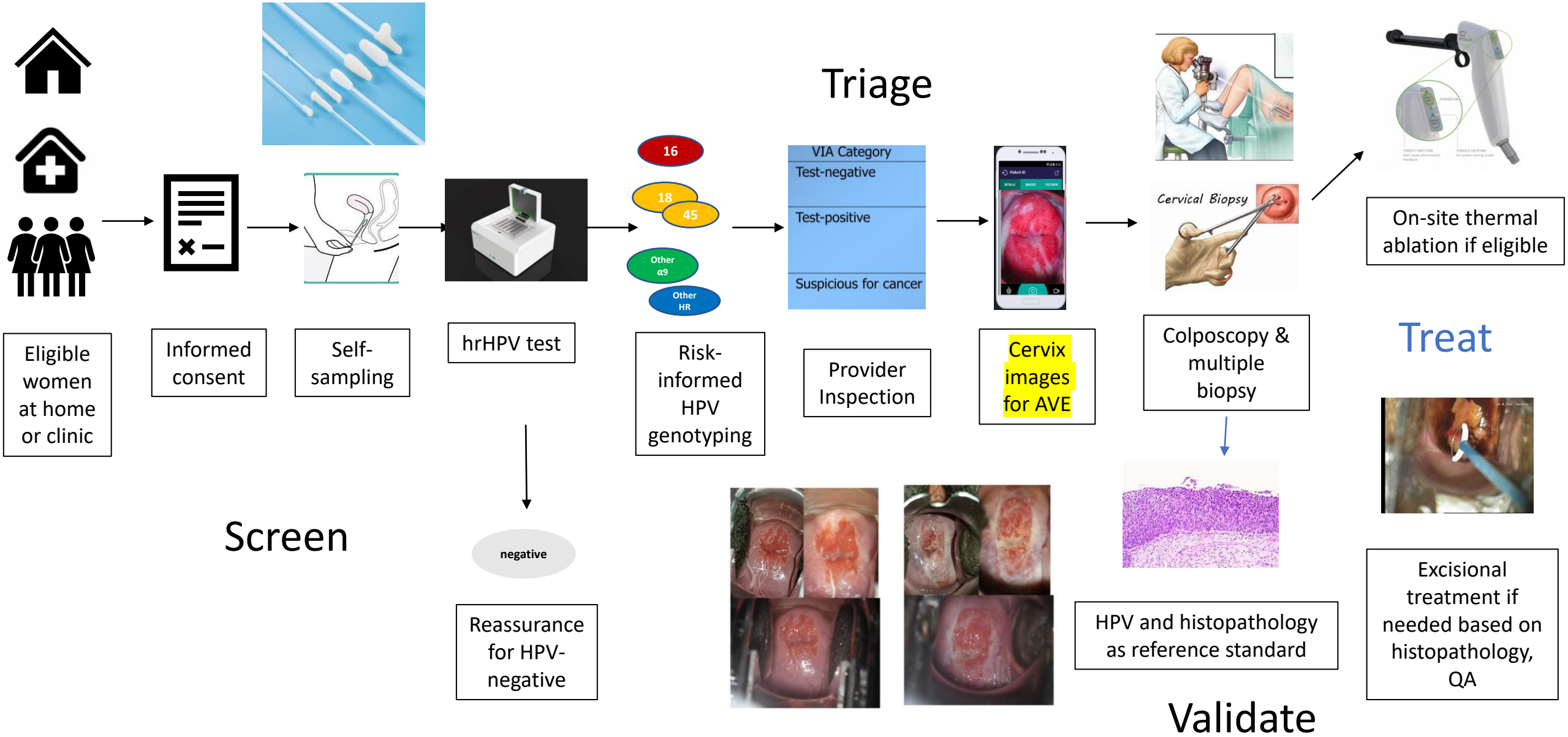


The HPV-AVE Strategy for Screen-Triage-Treat (Consortial Study Underway)



Self-sampling with HPV test. Visual Triage. Pre-pandemic.

Goldstein A. et al.

>100 women/ clinic day

Application of Artificial Intelligence

- Powerful image recognition approach
- Promising results in recognizing cervical precancer
- If it looks too good to be true… (can **not** perfectly identify precancer from HPV infection)
- Be skeptical of claims; performance declines away from training setting (see Desai et al., Int J Ca 2022)

Deep Learning Not Magic
Latent Model Acts as a Mimic

Automated Visual Examination (AVE) accepts gray zone equivocals near positive/negative cutpoint

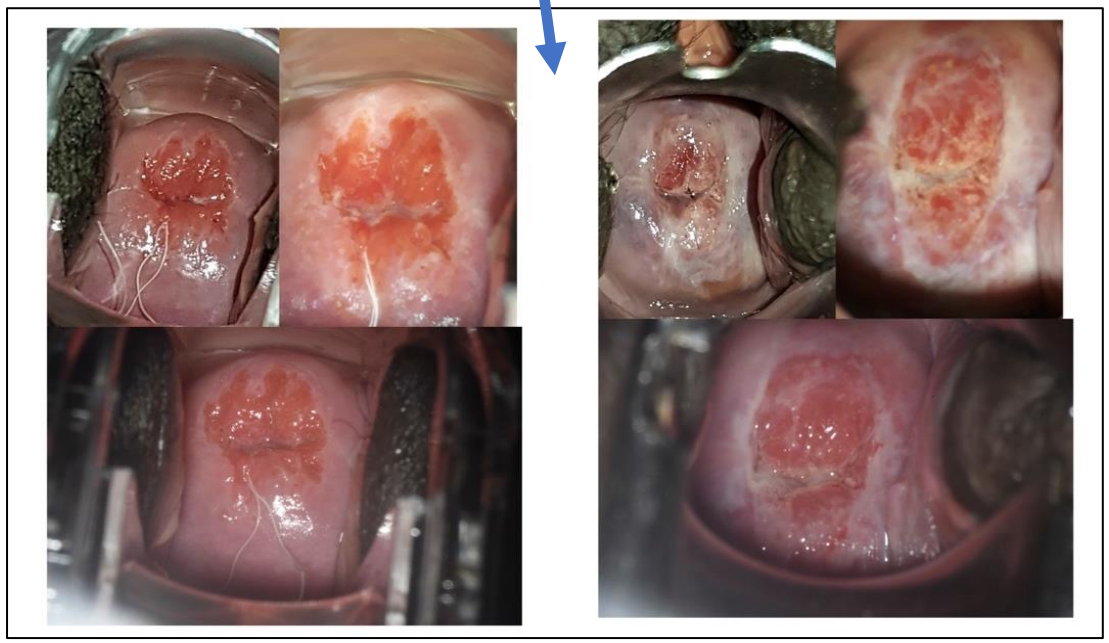
Creates an ordinal variable (positive, equivocal, negative) and minimizes grave errors by pushing uncertainty into middle group

Adapting to different image collection devices (smartphones)

Normal

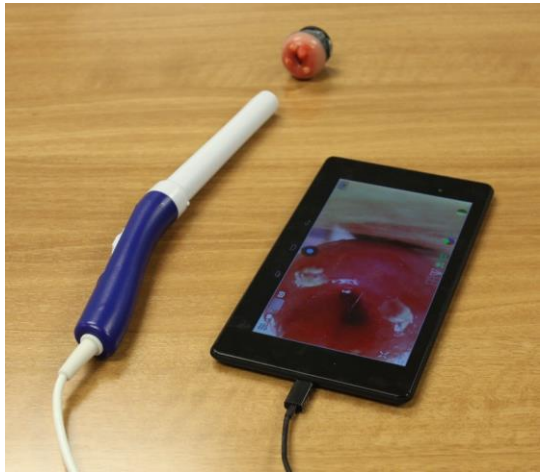
Equivocal

Precancer



OR

Creating Dedicated Device



Ajenifuja and Desai K et al. Infect Agent (2020)

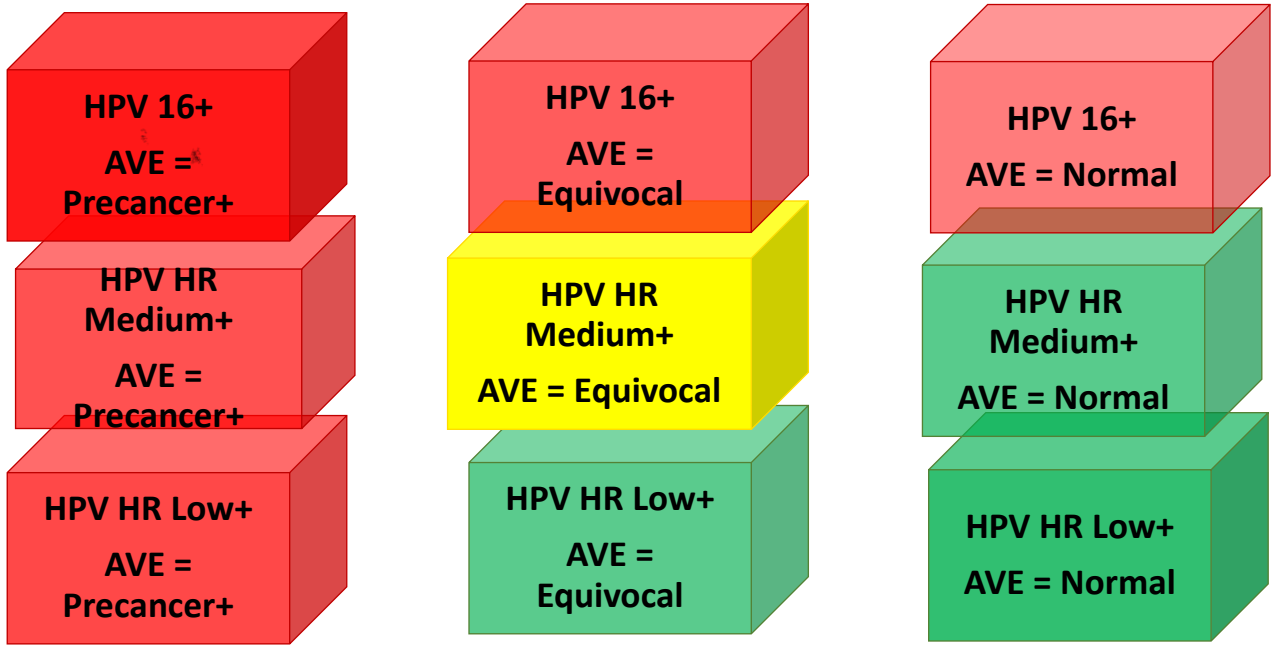
Deep Learning Diagnostic Classifiers, Systematic Study

	Algorithm design choices	
Parameter	**Level**	**Number of models**
Architecture	densenet121	70
	resnest50	36
	resnet50	30
	swin-transformers	14
Loss function	CE	83
	CORAL	27
	Weighted kappa	34
	Focal	6
Balance strategy	Balanced loss	10
	Balanced sampling	31
	Remove controls	21
	Sampling 1:1:2	12
	Sampling 1:1:4	8
	Sampling 2:1:1	4
	None	64
Drop out	First pass Monte Carlo	62
	Full Monte carlo	62
	None	26
Ground truth levels	3 level all patients	99
	3 level, subset (ex. Grey-low, Grey-high)	20
	5 level	31

Triage Of The HPV-Positive Woman When Resources are Limited

HPV type group combined with AVE classification

Risk estimates are "under the hood"



Here is what is Seen by provider

Local Management

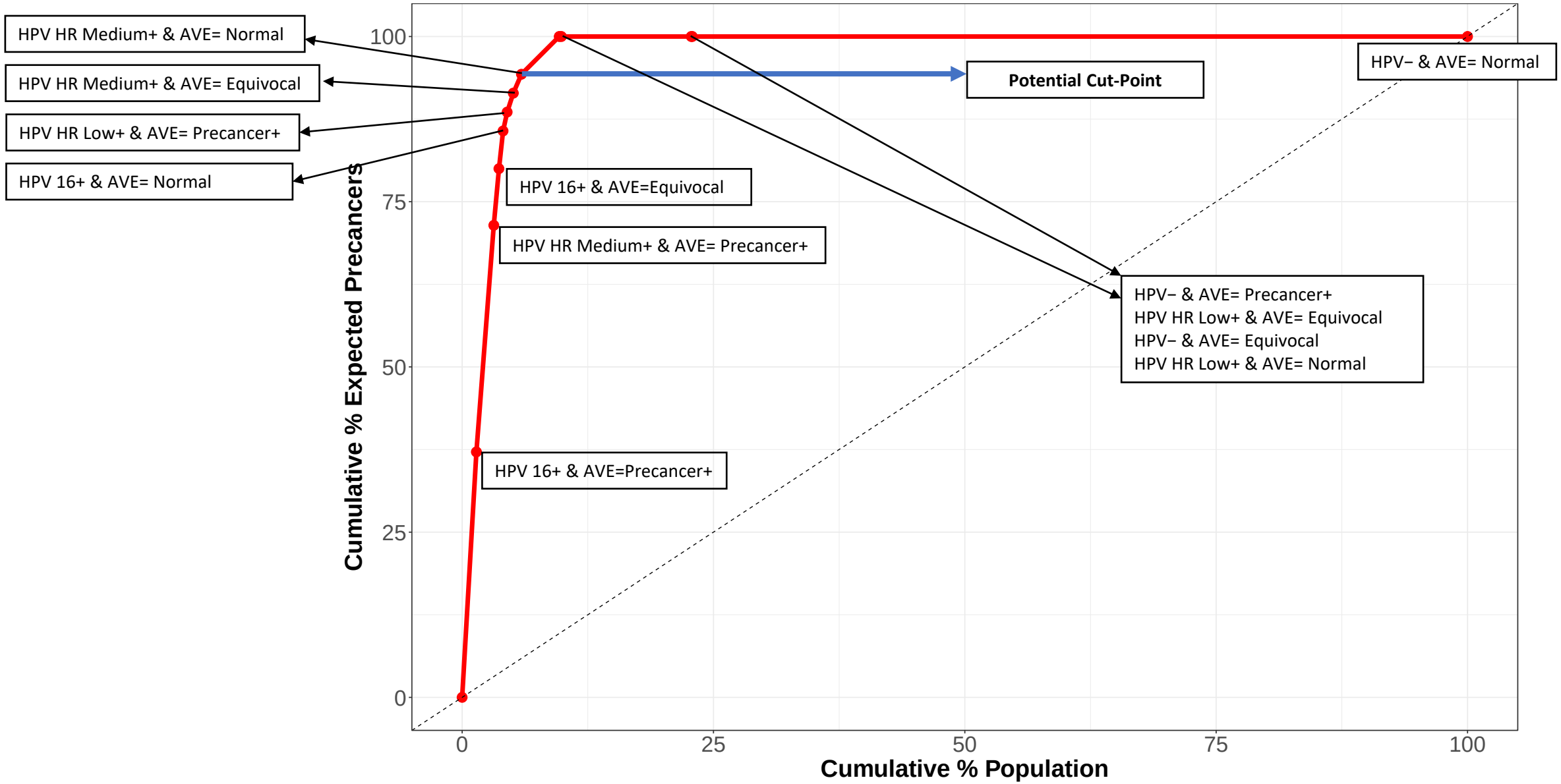
Suspect Cancer

Refer for Excision

Treat with Ablation

Reassure

Concentration Curve - For only the screened population



Framework for a Health Decision Analysis

1. Develop an HPV natural history model

- **a. Determine health states**
- **b. Define health state transitions**
- **c. Define variables that modify transitions**
- **d. Directly estimate transition risks**
- **e. Calibrate uncertain transitions**
- **f. Validate the model**

2. Estimate impact of selected strategies

3. Perform health decision modeling analysis to compare strategies

Based on improved causal pathway transition probabilities

We are assessing cost effectiveness of PAVE strategy versus others in consortial study at up to 10 sites

By Direct Measurement of Transitional Probabilities (Absolute Risk), We Need Less Calibration

Result: Increased Trustworthy Value For Health Decisions

Conclusions

- Parts of cost-effective screening program in lower-resource settings:
  - Follow HPV natural history and cervical carcinogenesis accurately
  - Screen (at correct ages) in high-risk places where prior screening is limited
  - Use HPV tests on self-collected specimens
  - Let HPV type group guide risk estimation
  - Using assistive visual method, make sure to treat the few women per 100 that make it all worthwhile
- Accurate risk estimation is achievable, but must work harder for even better affordability and sustainability
- Causal pathways, accuracy of clinical tests → trustworthy cost-effectiveness predictions → high-grade scientific evidence

Thank you