CUGH & NCI Cervical Cancer Webinar Series 2: Latest scientific advances, tools, & approaches to address cervical cancer control

August 5, 2020

11:00am-12:00pm EDT

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Co-Moderator

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University of Ibadan

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Deciding How to Control Cervical Cancer in Lower-Resource Settings:
Health Decision Modeling and the Natural History of HPV Infection

Nicole Gastineau Campos, PhD

Guiding Cervical Cancer Prevention Policy in the Era of COVID-19

- Health care systems will face scarce human and economic resources.
- More than ever, cervical cancer prevention will need to be
  - Simple
  - Safe
  - Effective
  - Affordable
  - Cost-effective (high value for money)
- Health decision models will be used to identify cost-effective screening strategies in lower-resource settings.

Evaluating Complex Prevention Strategies

HPV Vaccination	Cervical Screening	Treatment of Precancer
Age at vaccination	Age(s) at screening	Eligibility for treatment / type of treatment
Valency of vaccine	Screening test	Post-treatment surveillance
Number of vaccine doses	Referral threshold for screening test result	Delivery mechanism (mobile clinics; brick and mortar clinic)
Delivery mechanism (e.g., school-based; campaign)	Triage test or co-test	
	Treatment threshold for triage test or co-test result	
	Routine screening interval / number of lifetime screens	
	Delivery mechanism (e.g., provider- vs self-collection of sample; number of visits for testing, results, and treatment; high vs. low throughput)	

Why Use Health Decision Models?

- Many complex strategies to be compared
- Long interval between HPV infection and cancer is not directly observable in clinical studies
- Models are the only tools that project lifetime costs and consequences of strategies

Parts of a Screening Program in Lower-Resource Settings

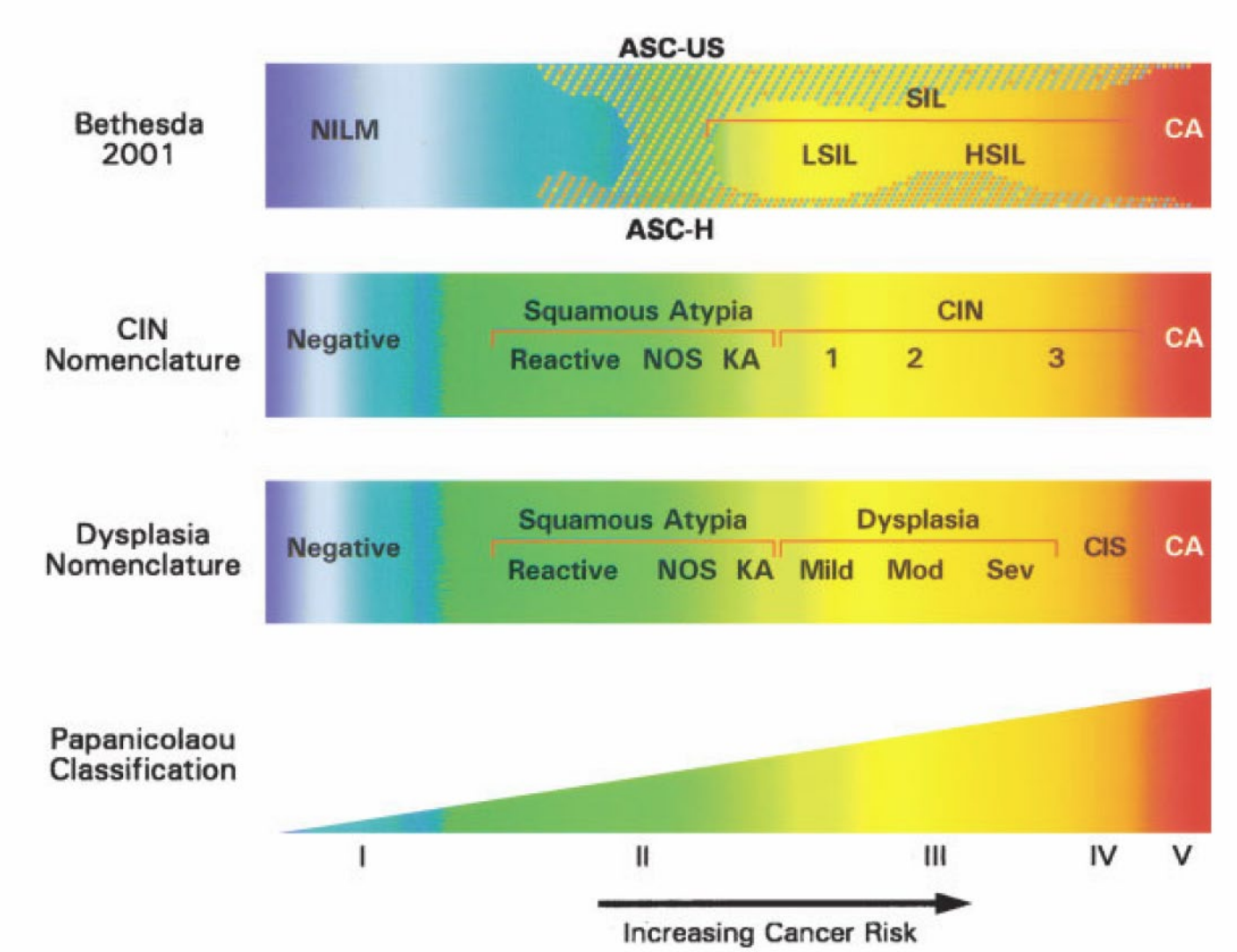
Screening:
HPV test (self-collected sample)

Triage:
HPV genotyping; AVE

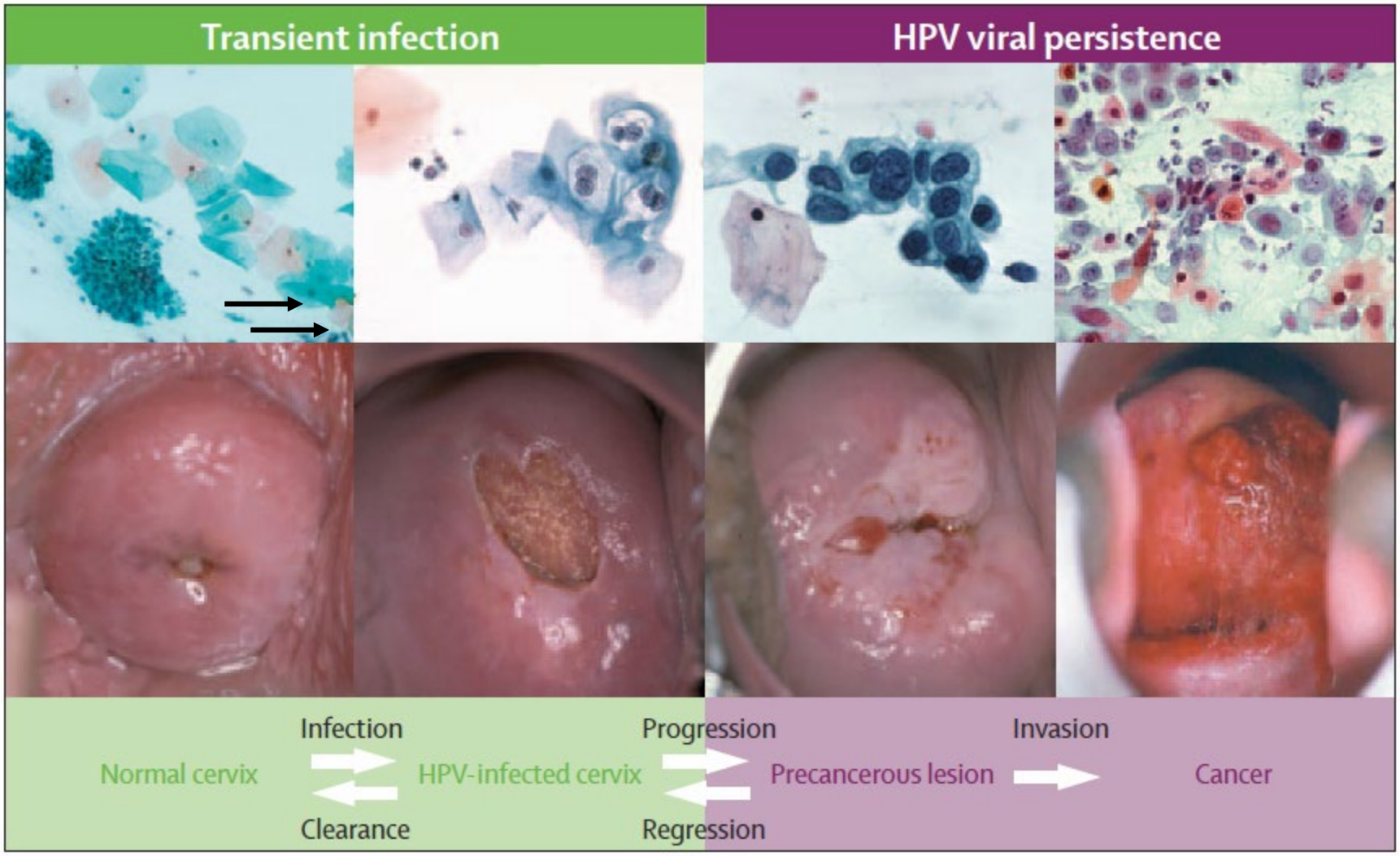
Treatment of precancer (eligible):
Thermoablation

Treatment of precancer (else):
LEEP

Past and Current Models Use Clinical Definitions for Model Health States

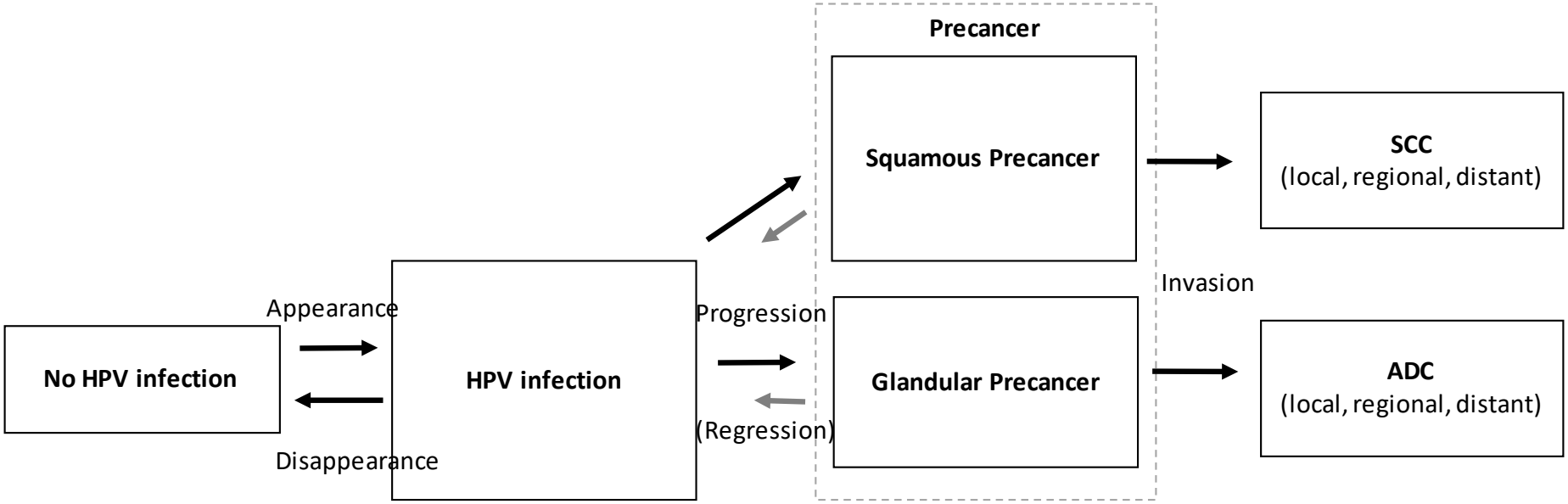


Multi-stage Causal Pathway of Cervical Carcinogenesis



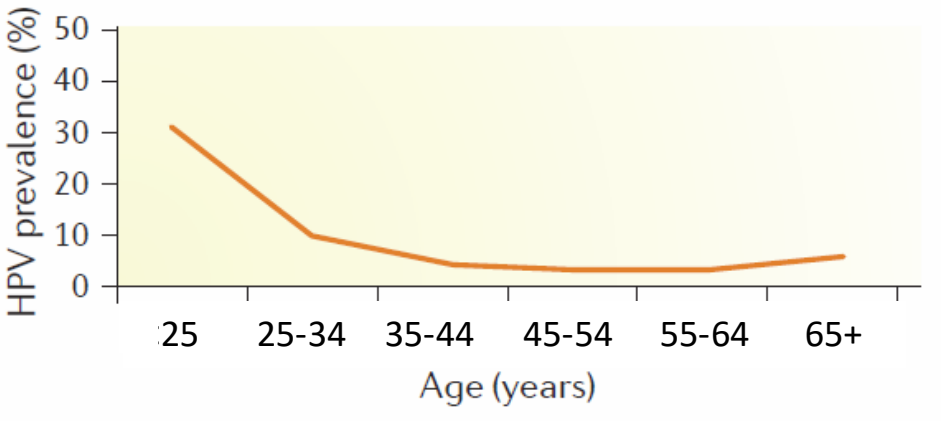
Source: Schiffman et al. *Lancet* 2007

New Health Decision Model Schematic: Universal Natural History

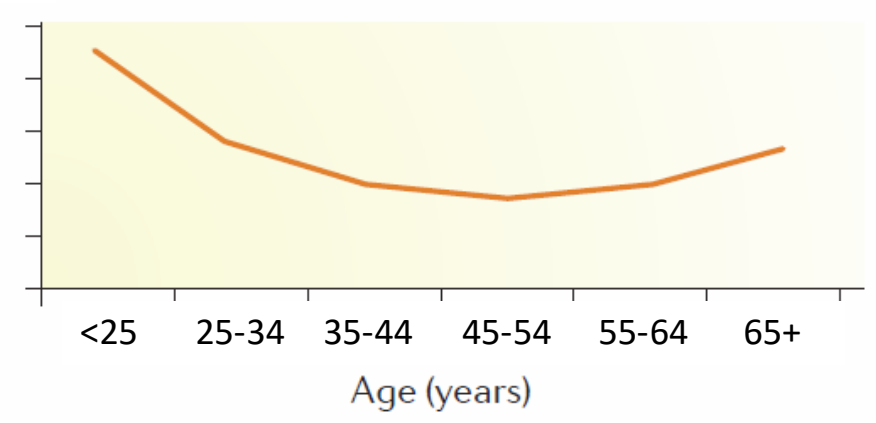


Global HPV Prevalence Patterns Vary by Region

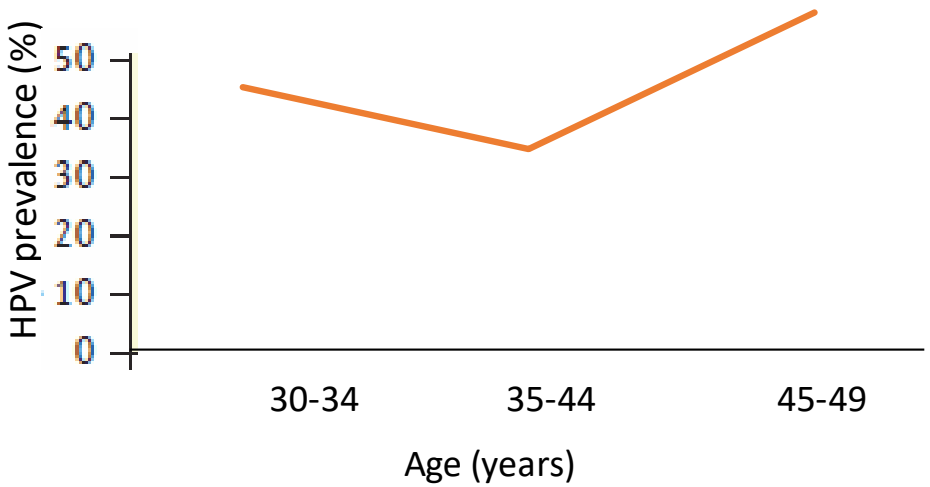
Lower prevalence at optimal screening age (25-49 years)



Higher prevalence at optimal screening age (25-49 years)



Women living with HIV (Nigeria)



Sources: Schiffman et al. *Nature Reviews* 2016; Denny et al. *JNCI* 2010.

At Least Three HPV Natural History Patterns

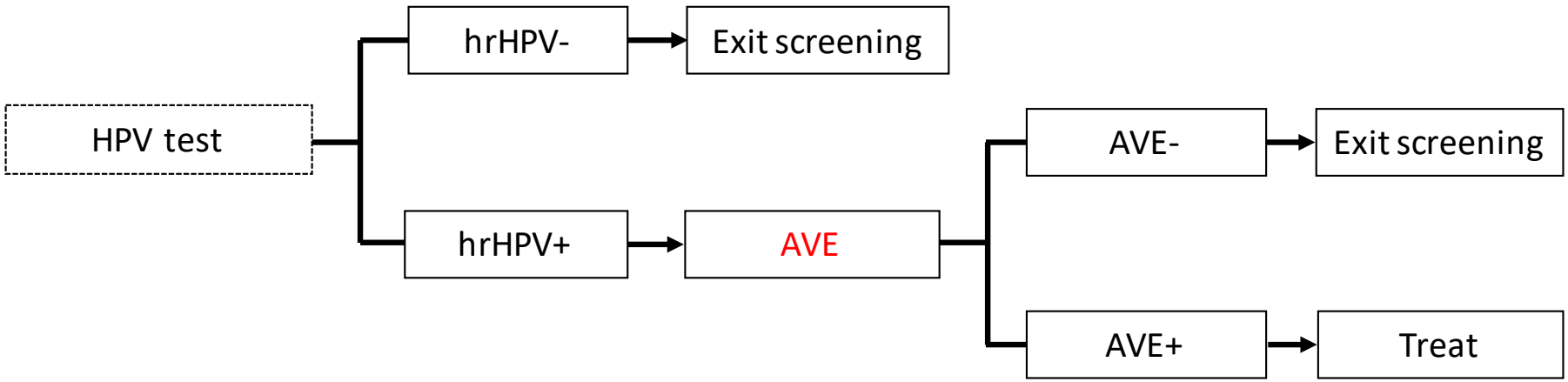
Pattern	Observed settings
Lower HPV Prevalence	**North America; Oceania; Europe; Central/South America; Asia**
Higher HPV Prevalence (non-HIV)	Sub-Saharan Africa
HIV	Women living with HIV

Data Availability for Transition Risks

Pattern	HPV Acquisition (by age, HPV type)	HPV Clearance (by HPV type, time since infection)	HPV Progression to Precancer (by HPV type, time since infection)	Invasion (by HPV type, duration of precancer)
Lower HPV Prevalence	**Available**	**Available**	**Available**	**?**
Higher HPV Prevalence (non-HIV)	Laboratory and data analysis in progress	Laboratory and data analysis in progress	Limited	?
HIV	Data analysis in progress	Data analysis in progress	Limited	?

Health decision models must account for population differences in transition risks in order to provide valid policy conclusions.

AVE Triage of hrHPV-Positive Women



Conclusions

- Health decision models are the only tool that can project cost-effectiveness over the lifetime for complex prevention strategies.
- To provide valid cost-effectiveness results, models must be based on
  - The multi-stage causal pathway of cervical carcinogenesis (universal)
  - Transition risks (vary by population HPV prevalence pattern)
- Development of a new modeling framework is underway.
- Transition risks for Higher HPV prevalence settings and WLHIV are urgently needed to inform valid health decision analyses.

New Tools and Approaches:
Accelerating Cervical Cancer Control

Mark Schiffman, MD, MPH

NIH NATIONAL CANCER INSTITUTE

August 5, 2020

Disclosure

Our NCI research group has received cervical screening supplies and assay results at no cost for our independent evaluations of test performance. I have no commercial interest in any technology, and our research and this presentation are free from commercial influence.

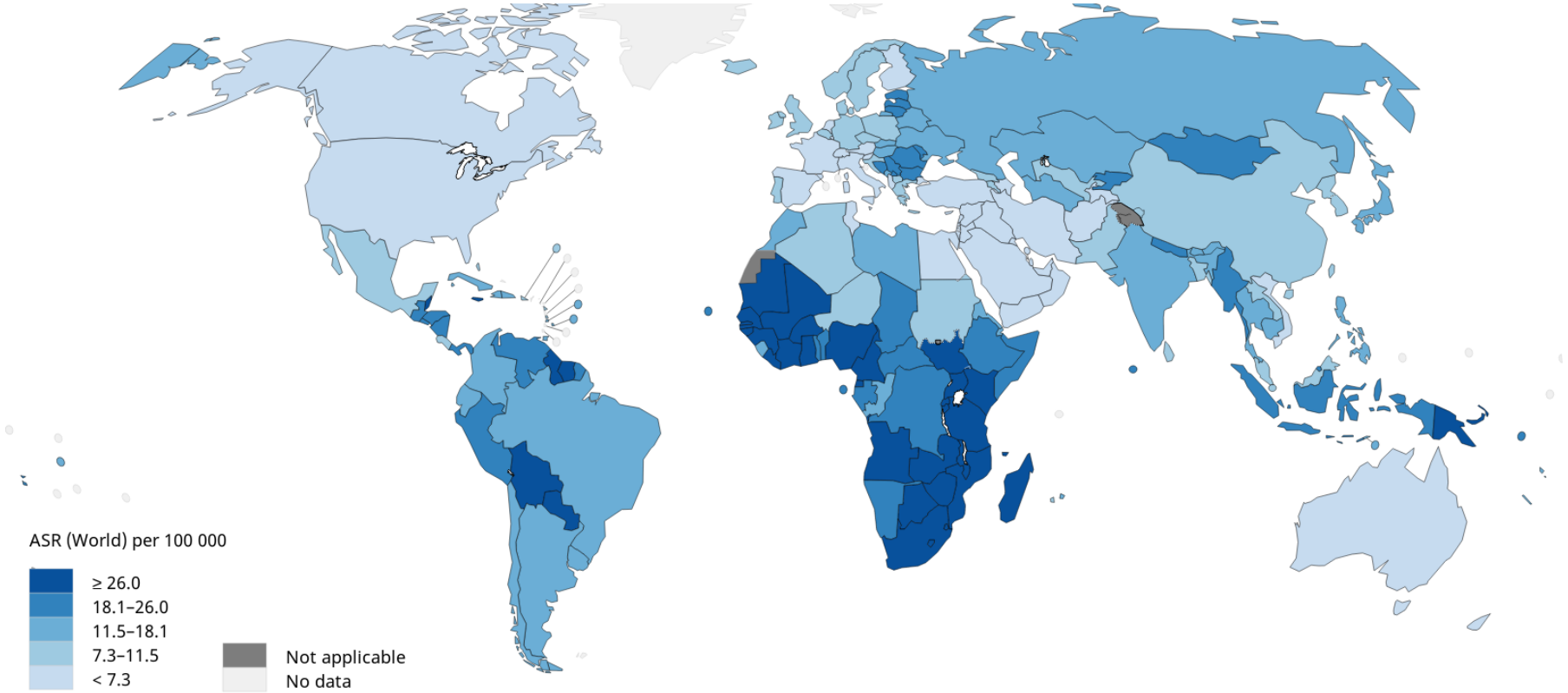
The views I express are personal and do not necessarily represent NCI or any collaborator.

Acknowledging Many Collaborating Researchers

- I wish to acknowledge the large collaborative AVE research group.
- Special thanks to Silvia de Sanjose, Nicolas Wentzensen, Doug Lowy, NCI team, National Library of Medicine group, Global Research Labs group.

MOTIVATION: Cervical cancer is an avoidable disease with gross inequities (Globocan 2018)

Progress in prevention lagging far behind our scientific knowledge



Data source: GLOBOCAN 2018
Graph production: IARC (http://gco.iarc.fr/today)
World Health Organization

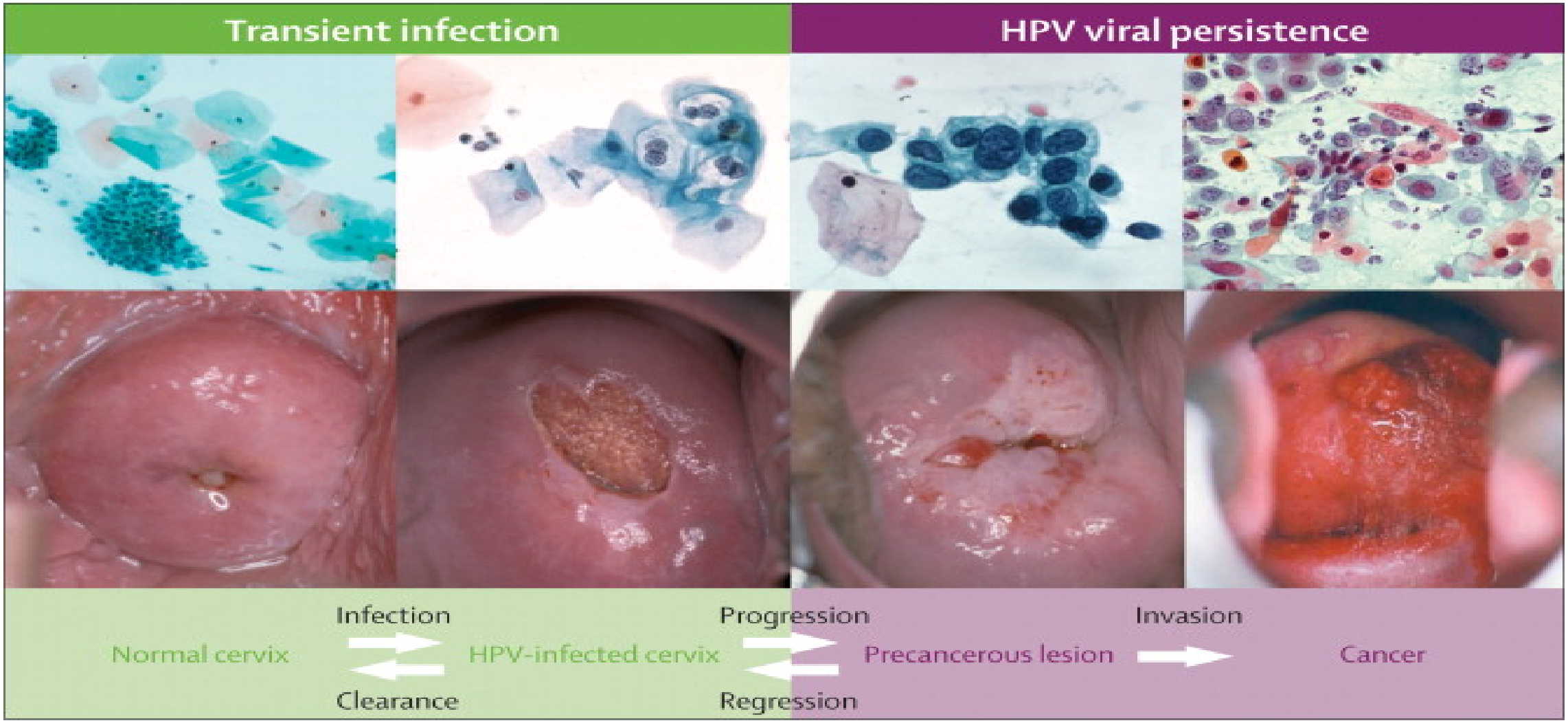
COVID-19 will tend to accentuate disparities

- Pandemic limits resources available for cervical cancer prevention
- Threat of spreading CoV-2 a serious consideration for prevention research and for screening programs
- In this environment, are currently planned programs still “better than nothing”?
- We need even better methods and strategies

The Time Lag Concern

- When we make decisions about how to control cervical cancer:
- To what degree can we anticipate improvements in prevention methods?
- Too much optimism is misleading
- What about “right around the corner” new technology?
  - There is no obvious answer but this talk is an example of high probability optimism

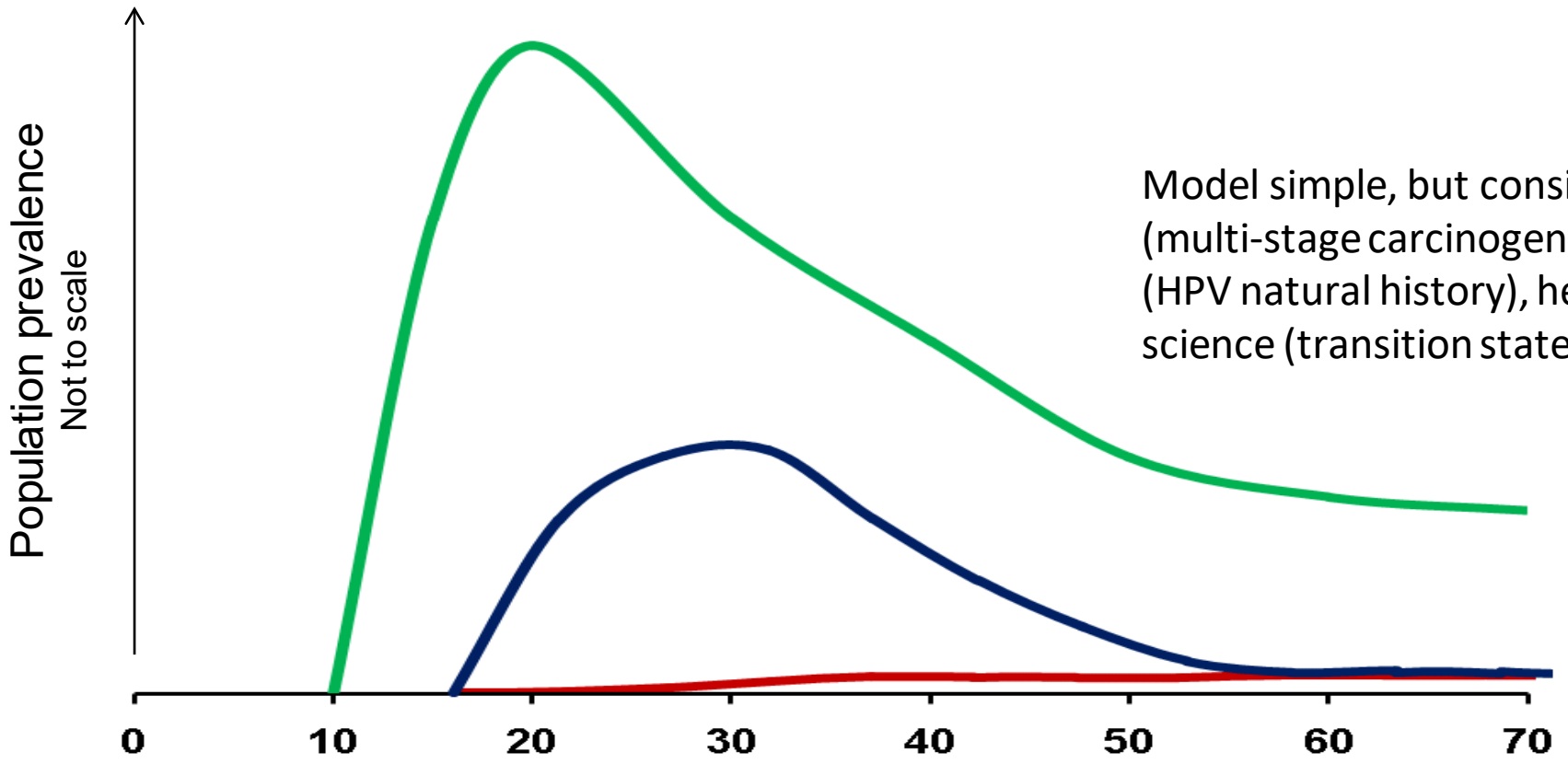
Simple View of Cervical Carcinogenesis Avoids Subjective Terms



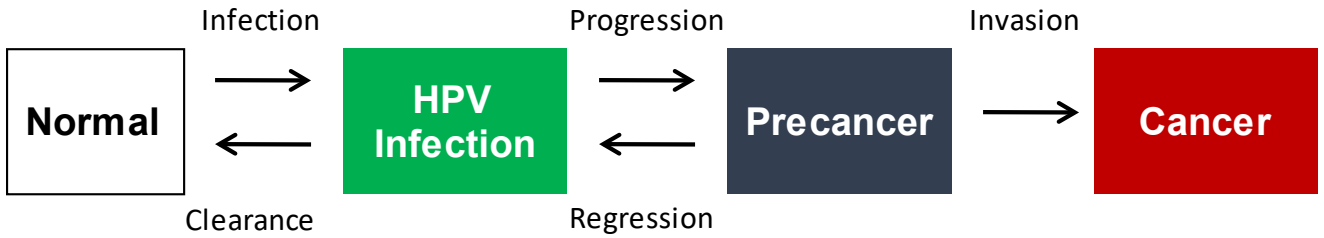
Schiffman et al. Lancet 2007

Causal Stages: Typical Age Curves

Note: Different in partly immunodeficient and WLWH populations



Model simple, but consistent with lab (multi-stage carcinogenesis), epidemiology (HPV natural history), health decision science (transition state models)



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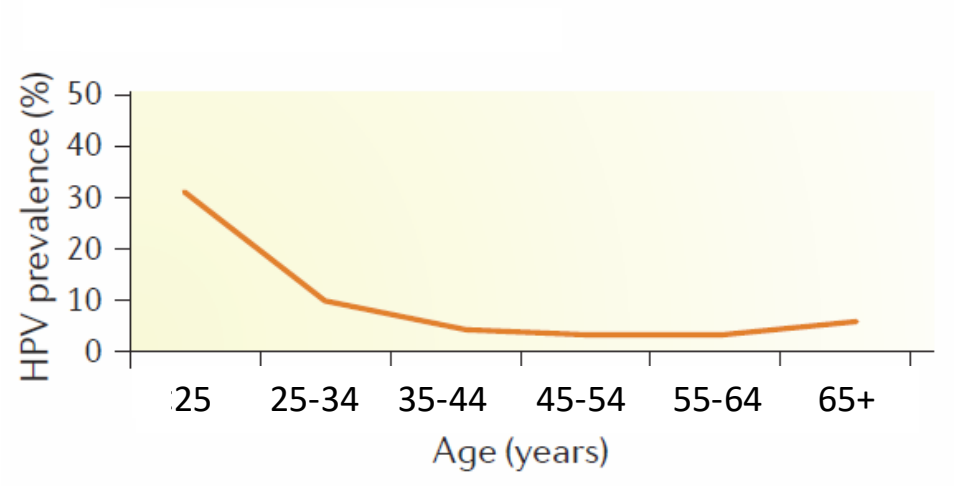

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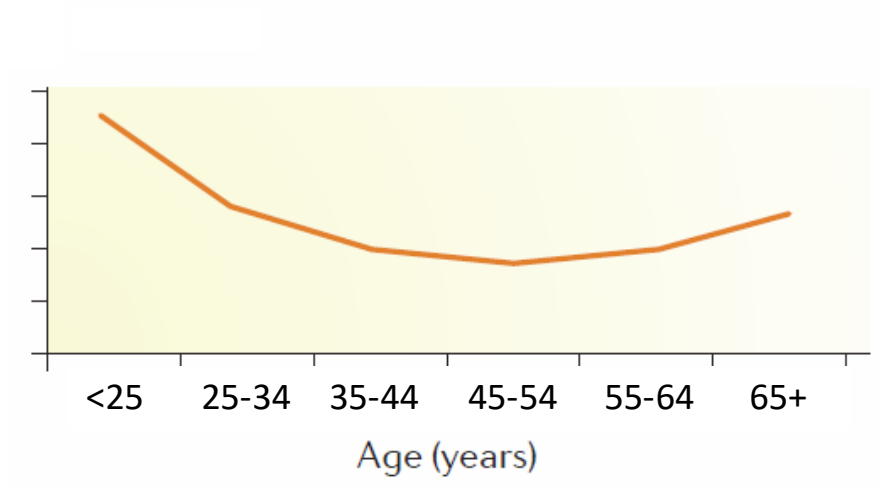

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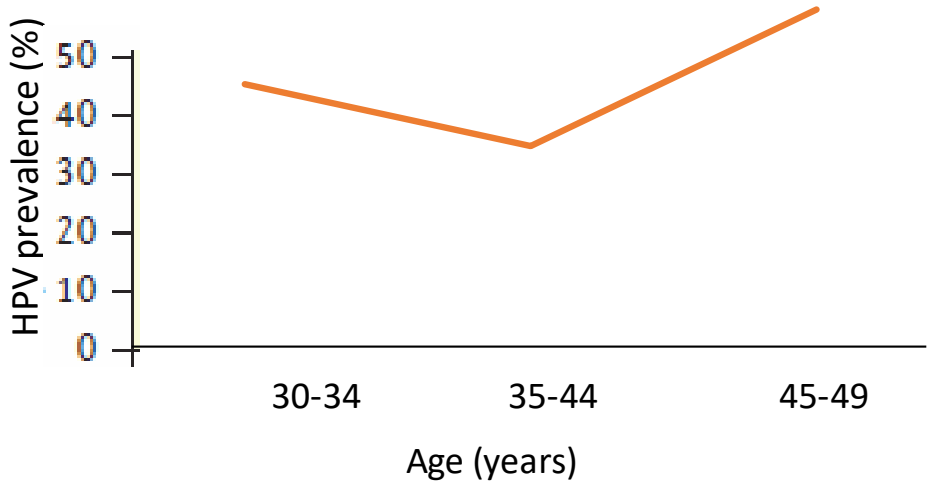
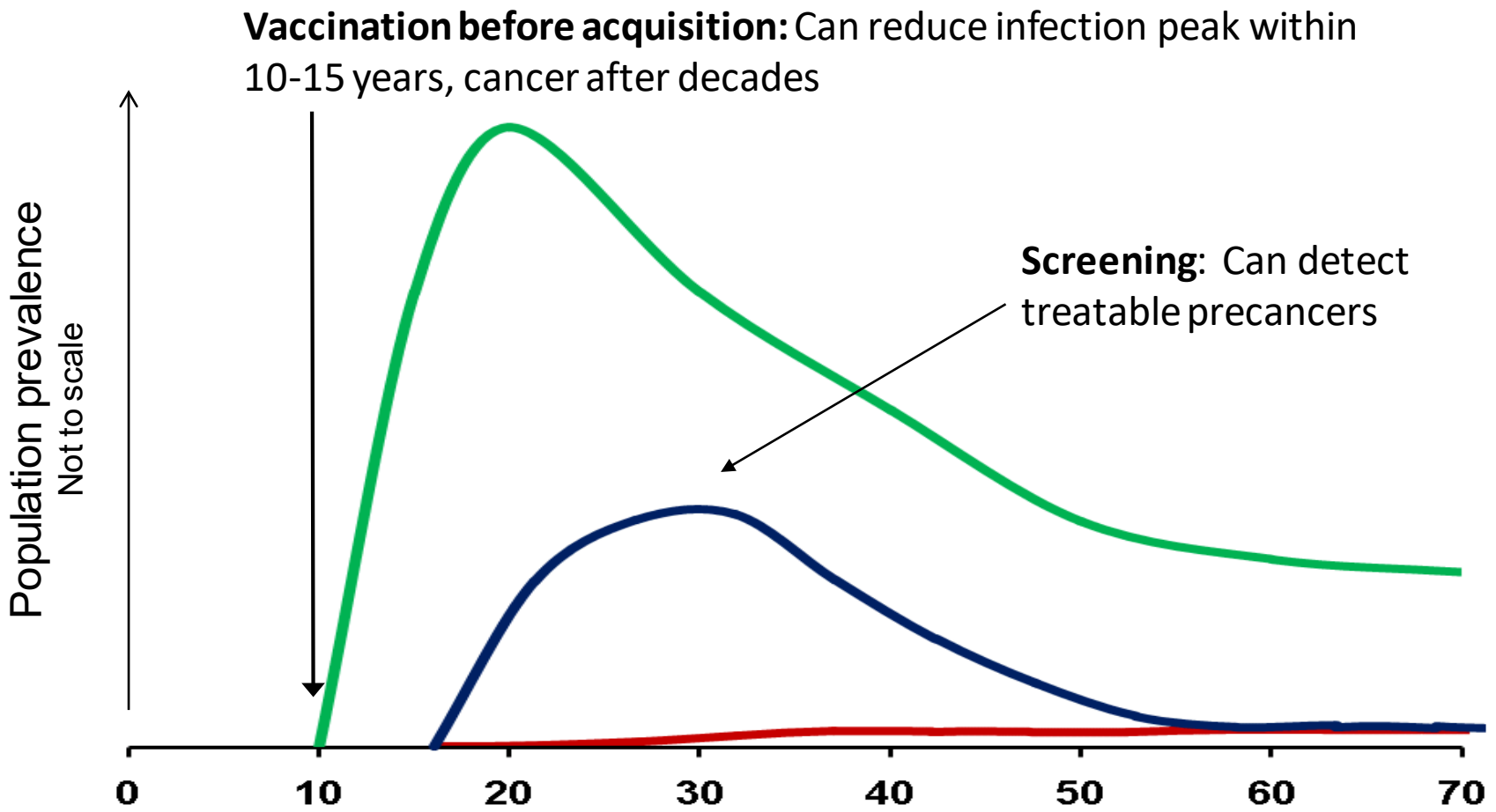
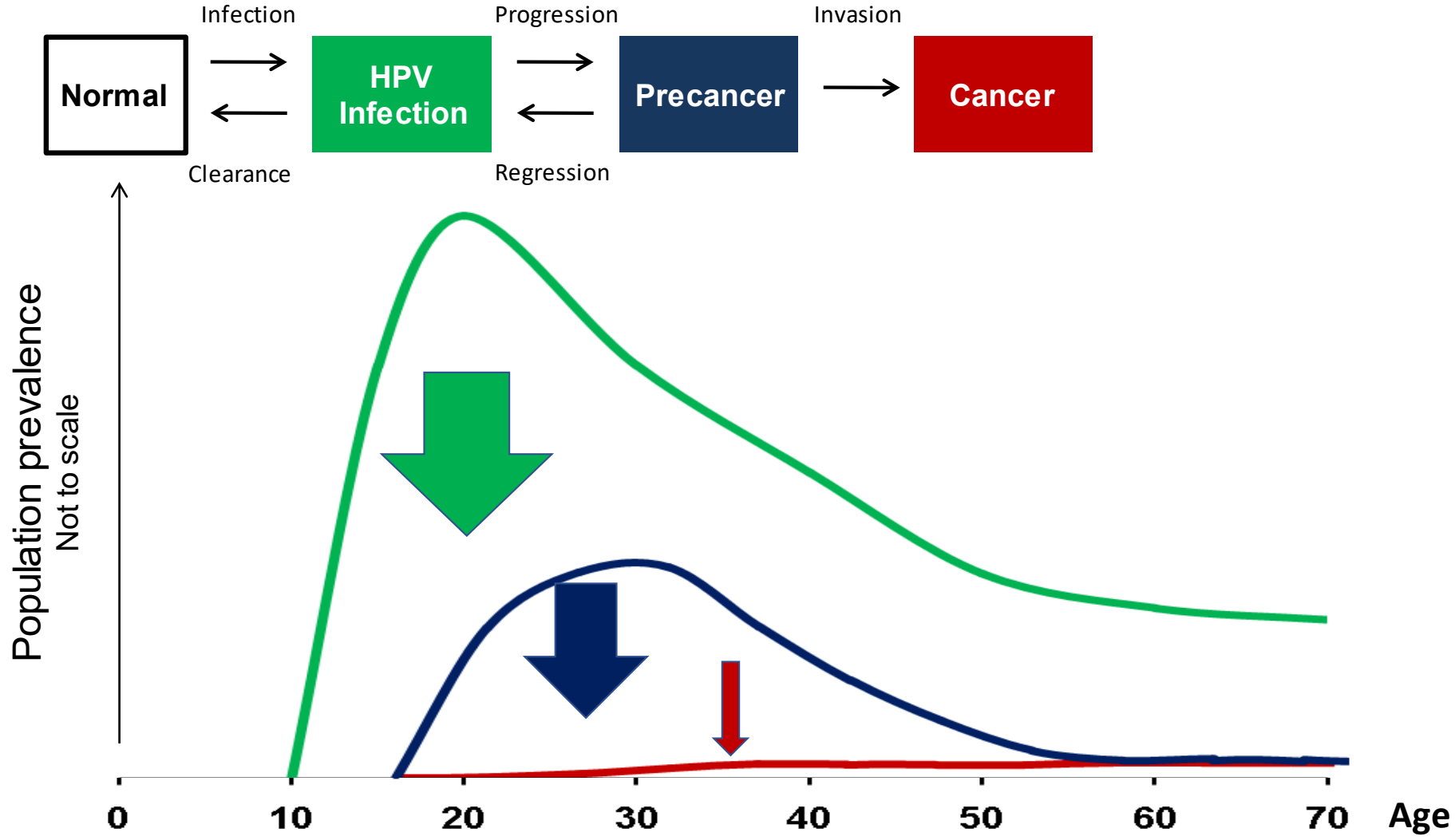


Sources: Schiffman et al. *Nature Reviews* 2016; Denny et al. *JNCI* 2010.

Prevention Methods Tailored to Natural History



Extension to make control Faster (adapted from Bosch et al.)



1-Dose Vaccination

? Until what age?

HPV Screening (with visual triage)

? Age range?

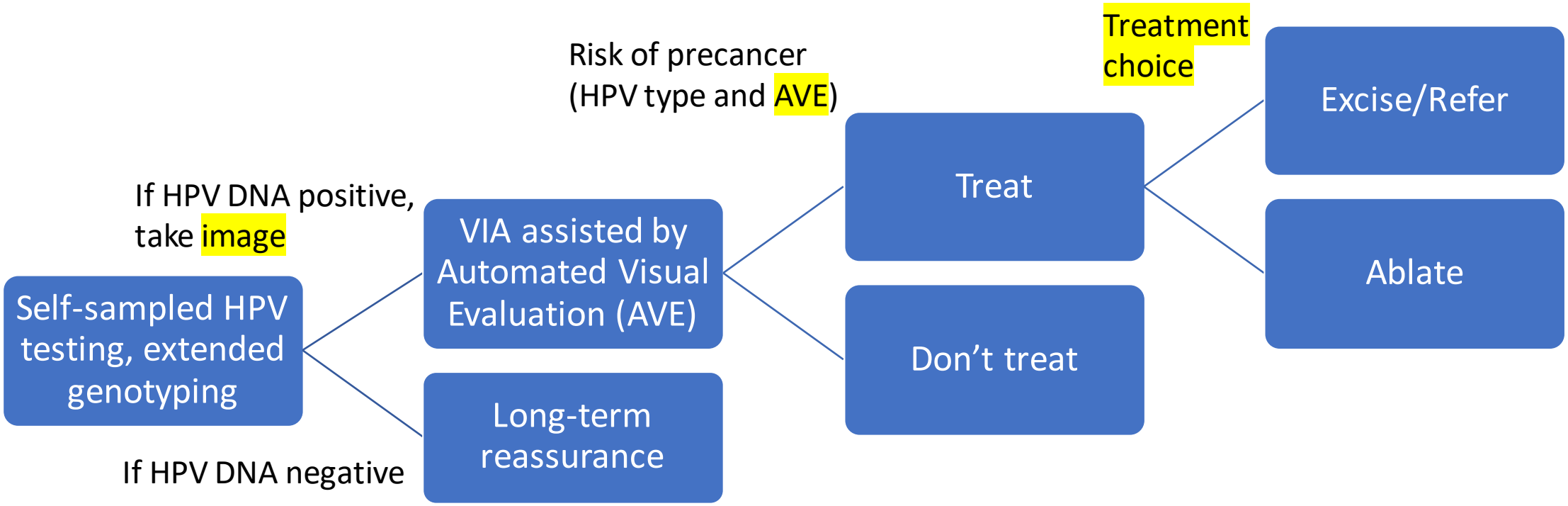
1-2 screening rounds

Wentzensen and Schiffman
Lancet Public Health 2017

Personal estimation of a promising control strategy

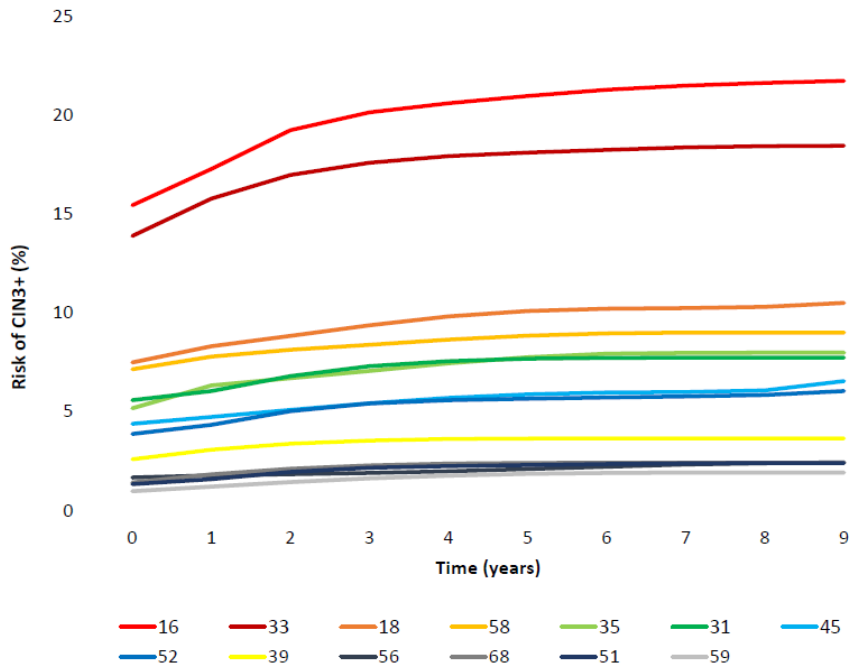
- (I predict that 1-dose HPV vaccine will protect long enough)
- Self-sampled HPV screening to provide reassurance to most women
  - Extended HPV typing using a technology like LAMP (isothermal loop mediated amplification)
  - Gives extended type group
- **Triage** using deep-learning evaluation of cervical images (**assisted VIA**)
  - Deep-learning algorithm #1 gives assurance of adequate image
  - AVE algorithm (#2) gives confidence score for whether HPV-positivity represents precancer combined with prediction from HPV typing
- Thermal ablation if feasible
  - Treatment choice algorithm (#3) gives deep-learning assistance on ablation vs. excision
- Excision restricted to those most at need

Summary of proposed strategy: HPV screening and visual triage assisted by 3 deep learning algorithms



HPV type restriction might justify "extended" genotyping for prognosis

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

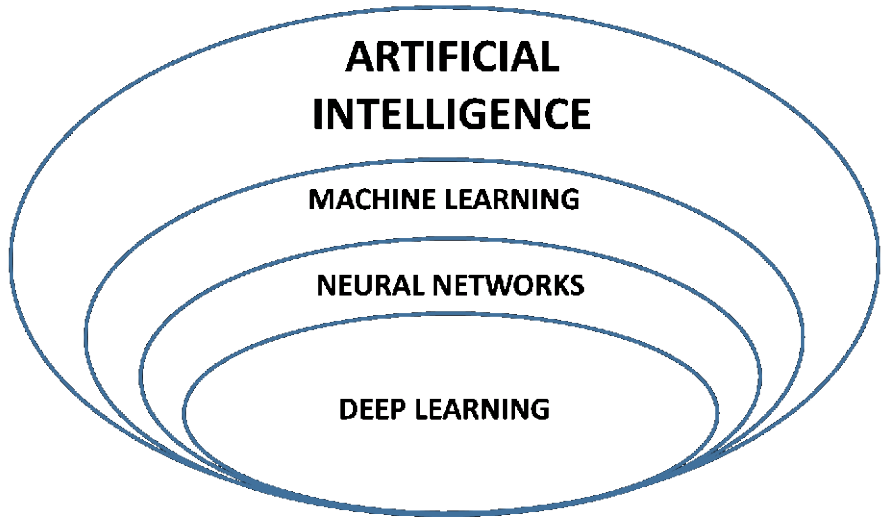
	N tested	% pos	95% CI
HPV16	14595	54.4	53.6–55.2
HPV18	14387	15.9	15.3–16.5
HPV33	13827	4.3	4.0–4.6

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

Automated Visual Evaluation (AVE) for Triage of HPV-positive women

Key Concepts

- **Artificial Intelligence** - the theory and development of computer systems able to perform tasks that normally require human intelligence, such as visual perception, speech recognition, decision-making, and translation between languages.
- **Machine Learning** – the study of algorithms that improve automatically through experience
- **(Artificial) Neural Network** – a machine learning method which learns by adjusting weights between interconnected network "layers" and "nodes"; inspired by observation of neuron networks in the human brain
- **Deep Learning** – machine learning by use of Deep Neural Networks, that is, Neural Networks with "many" layers



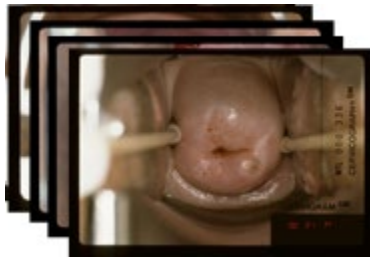
Rodney Long and National Library of Medicine colleagues

Types of NN Learning

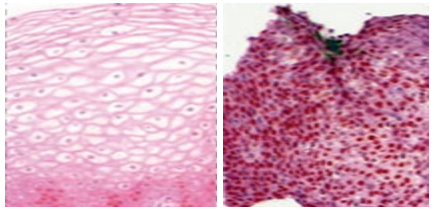
- **Supervised**
  - Two types: **classification** and **regression**
  - In either case, we provide training data points and desired outcomes to teach network
  - For classification, we call the desired outcomes the **class labels**
- **Semi-supervised** (classification)
  - We provide:
    - A small number of training data points and class labels
    - A large amount of training data points w/o class labels
  - Goal is (usually) to infer missing class labels by techniques such as clustering
  - Then apply supervised learning to the completely-labelled training data
- **Unsupervised**
  - We provide training data points only
  - Goal is to achieve a compact representation of the training data

Deep Learning: Automated Visual Evaluation (AVE)

Representative cervigram images



Training images (70%)



Ground truth histology

AVE ALGORITHM

Testing images (30%)

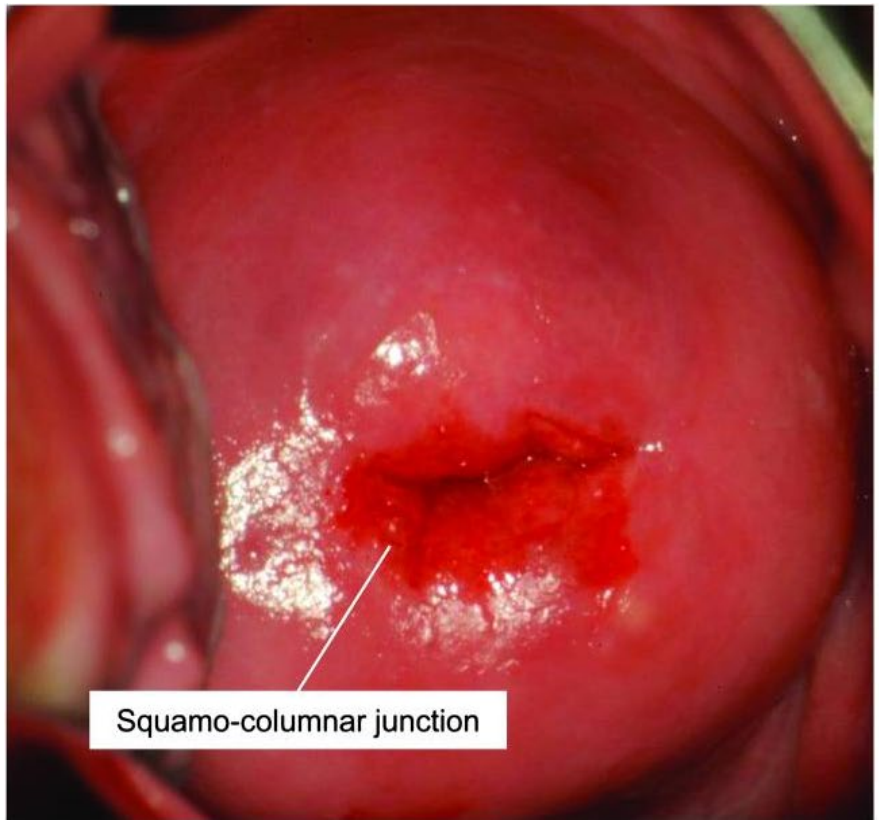
AVE severity score

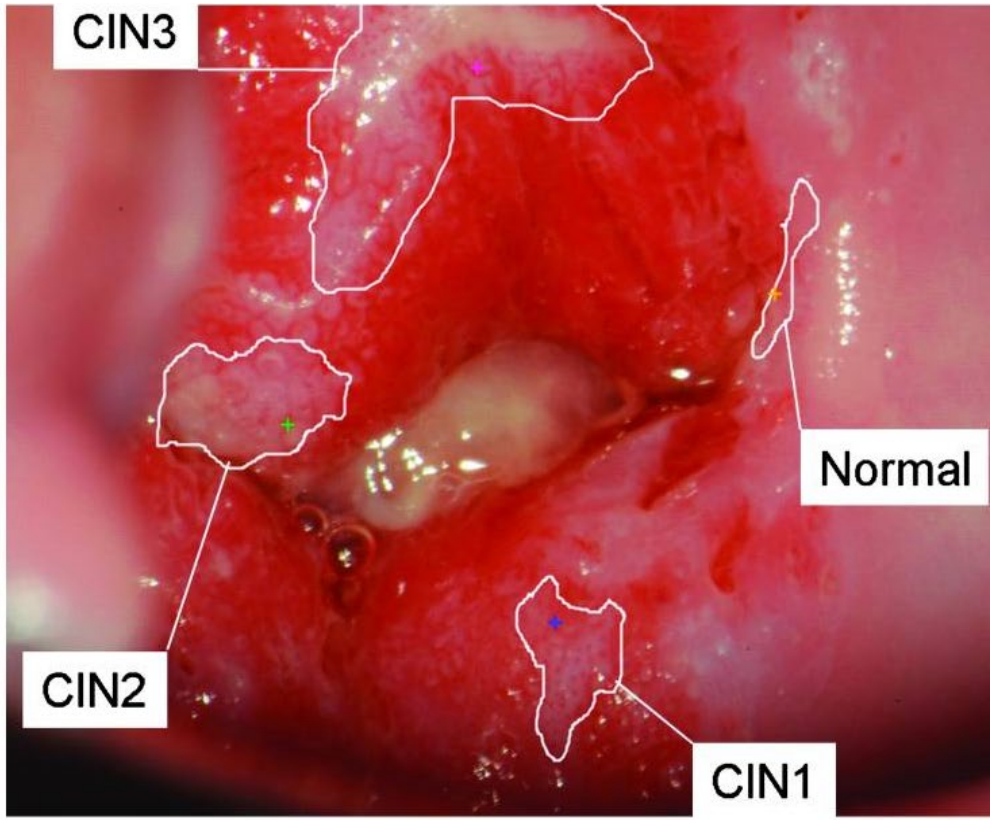
Case (CIN2+)

Control (<CIN2)

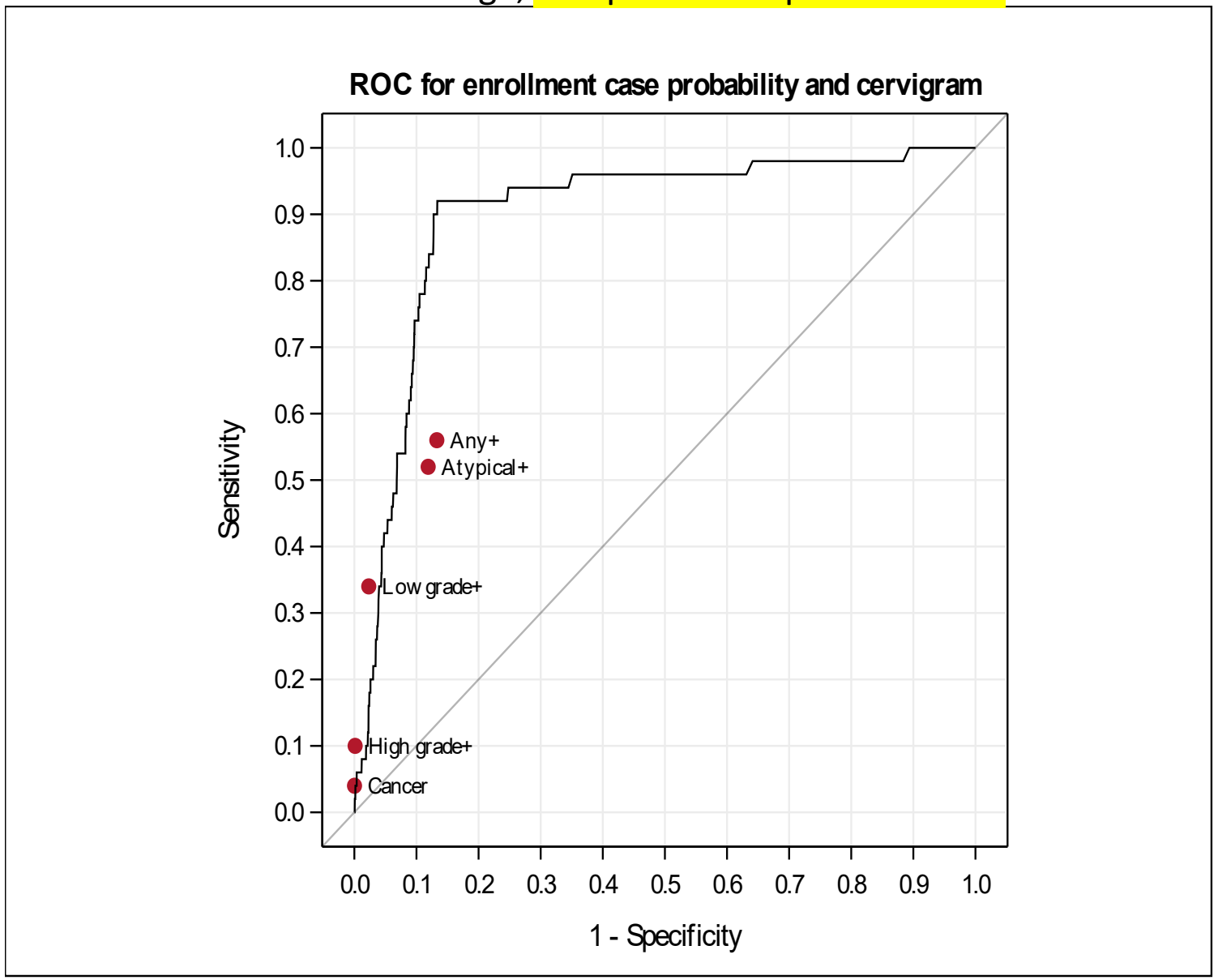
Hu…Schiffman JNCI 2019

Visual Triage Not Easy for Human Observers (Can we match or exceed human experts?)





Guanacaste Cohort, Ages 30-49, General Screening AVE Algorithm
Enrollment Image, Compared to Expert Reviewer

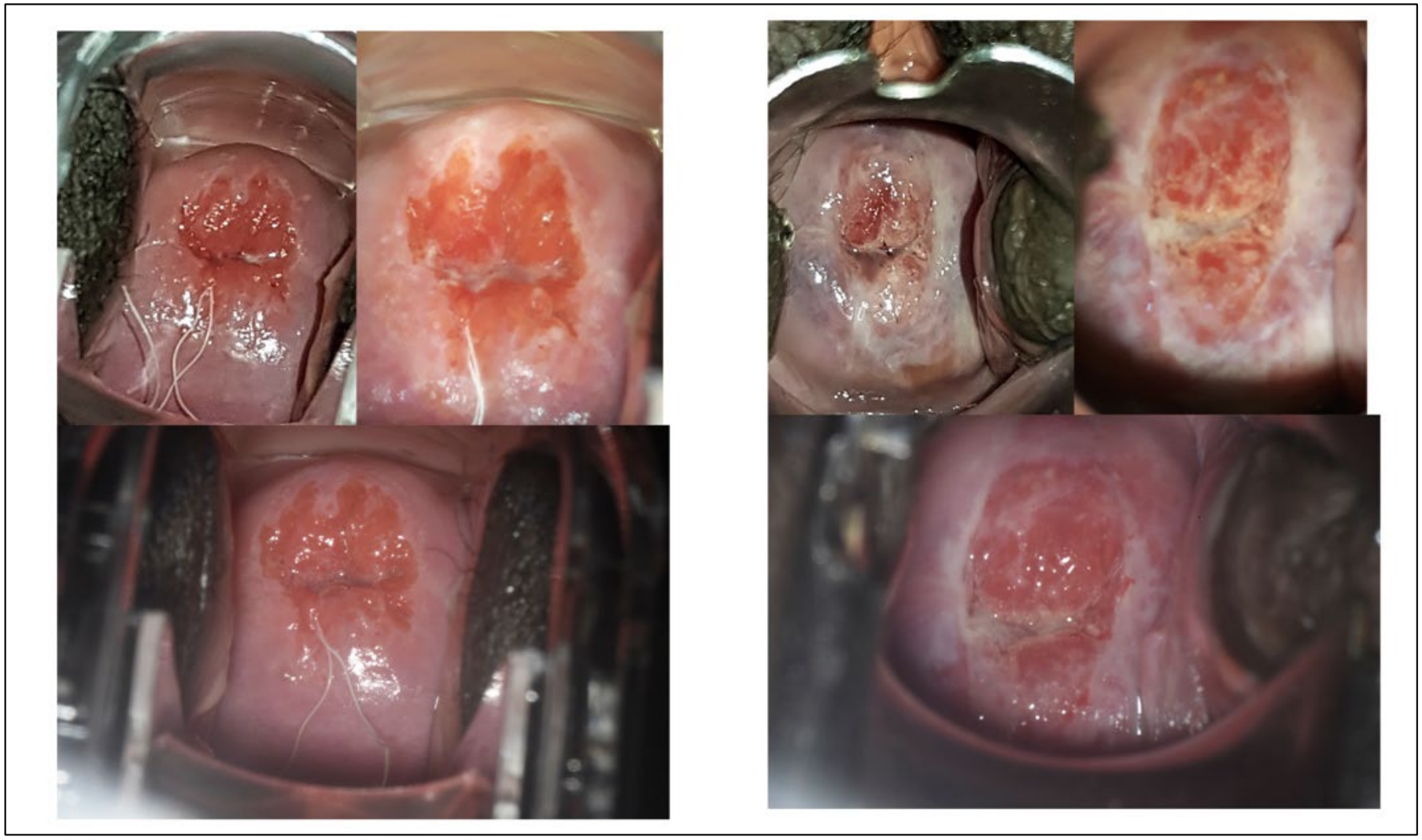


Contemporary digital image capture devices

- Proof-of-principle achieved using cervigrams
- AVE algorithm is sensitive to type of image, “fine tuning” between image types necessary and ease of “transfer learning” still not proven
- Large prospective collections of images paused due to COVID pandemic
- Confident that given enough images, we will succeed
  - We do have proof-of-principle that smartphone images can yield good AVE performance

Automated Visual Evaluation

Normal



Precancer

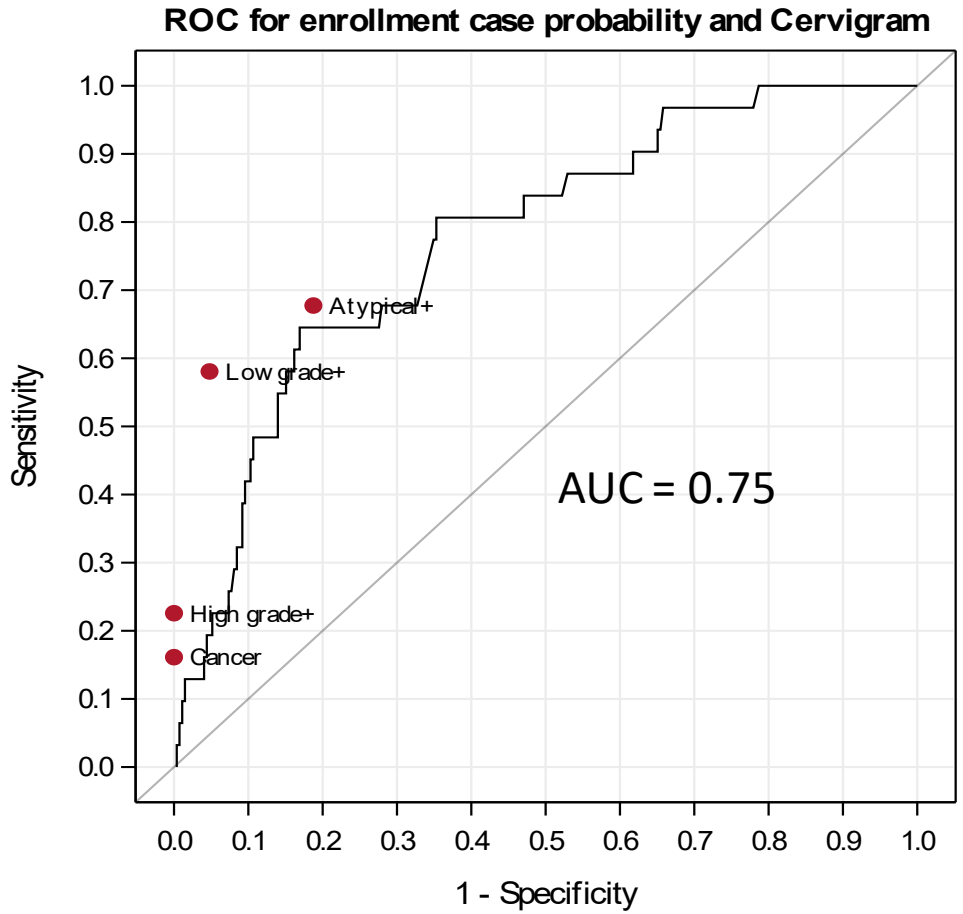
Ajenifuja and Desai et al., submitted

Adapting to different image collection devices (smartphones)

Current Limitation: AVE algorithm training needs more images than we have stored

- The more subtle the distinction we are trying to make, the more images we need
- Triage of HPV-positive women is even more difficult than general screening because the non-cases (HPV infections) are more like cases (precancer) than are HPV-negative controls
- Demonstration of why we need more images follows

Guanacaste Cohort, Ages 30-49,
Triage AVE Algorithm
Enrollment Image



Limitations of AVE discovered to date

- Preliminary evidence: AVE works mainly for classification of whether precancer is present “today”, while HPV test/type predicts future (meaning, a negative triage test does not rule out future risk)
- Like all visual methods, deep learning works best when the cervical SCJ is fully visible (age restriction, we do not have good triage or treatment answers yet for older women)

Timeline for validation and dissemination

- The deep learning approach is valid and feasible
- The faster we accrue images for AVE, the faster we can compare to VIA alone and establish value (for general screening and especially for triage)
- Ethical constraints on launching large screening efforts
  - We have converted to a “stored image” strategy

Concluding Invitation

- We invite interested colleagues to join our AVE research community
- If you have collections of archived cervical images, consider collaboration
- Or, if you are interested in hearing more, we are starting a listserv for this new public health “specialty”
- Contact Silvia de Sanjose, Farideh Almani or me (preferably all of us).
  - Silvia desanjose.silvia@gmail.com
  - Mark mark.w.schiffman@gmail.com
  - Farideh farideh.almani@nih.gov

NCI-CGH/CUGH Webinar

Global Cervical Cancer: Beyond Technology….

Ophira Ginsburg, MSc MD
Associate Professor, Department of Population Health
Director High-Risk Cancer Genetics Program, Perlmutter Cancer Center
NYU Grossman School of Medicine, NYU Langone Health

Consortium of Universities for Global Health

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I have no financial relationships to disclose.

What will it take to reach elimination targets ….
in any country?

What will it take to reach elimination targets ….
in any country?

- First, do no harm.

What will it take to reach elimination targets ….
in any country?

- Start and end with the women at risk.

What will it take to reach elimination targets ….
in any country?

- Ensure you have considered all aspects, the needs and preferences of women, what matters to them.

What will it take to reach elimination targets ….
in any country?

- Consider the whole picture, the cancer screening *journey*.

What will it take to reach elimination targets ….
in any country?

- Do they have equitable access to affordable high-quality cancer health services? Including Rx for precancer and invasive cancer? Palliative care?

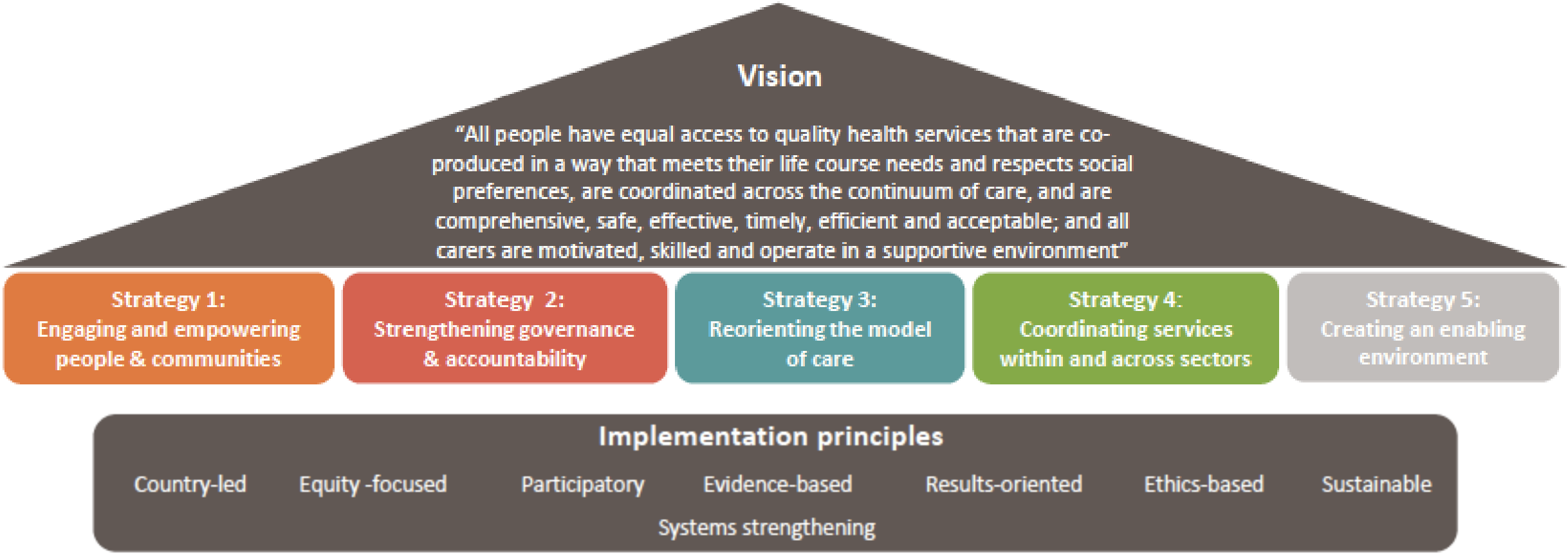
Integrated ***people-centred*** health services means putting people and communities, not diseases, at the centre of health systems, and empowering people to take charge of their own health rather than being passive recipients of services.

Evidence shows that health systems oriented around the needs of people and communities are more effective, cost less, improve health literacy and patient engagement, and are better prepared to respond to health crises.

WHO 2016

https://www.who.int/servicedeliverysafety/areas/people-centred-care/ipchs-what/en/

Framework on integrated people-centered health services: an overview



https://www.who.int/servicedeliverysafety/areas/people-centred-care/Overview_IPCHS_final.pdf?ua=1

1970’s….

1970’s….


KENYA SPECIAL
SELECTED EAST AFRICAN RECORDINGS
FROM THE 1970s & '80s

1970’s….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KENYA SPECIAL
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FROM THE 1970s & '80s


JOHN LENNON
'IMAGINE'
Released as a single
for the first time
in the UK

1973….

Martin (Marty) Cooper, Motorola, 1973

SEVENTY-FIRST WORLD HEALTH ASSEMBLY WHA71.7

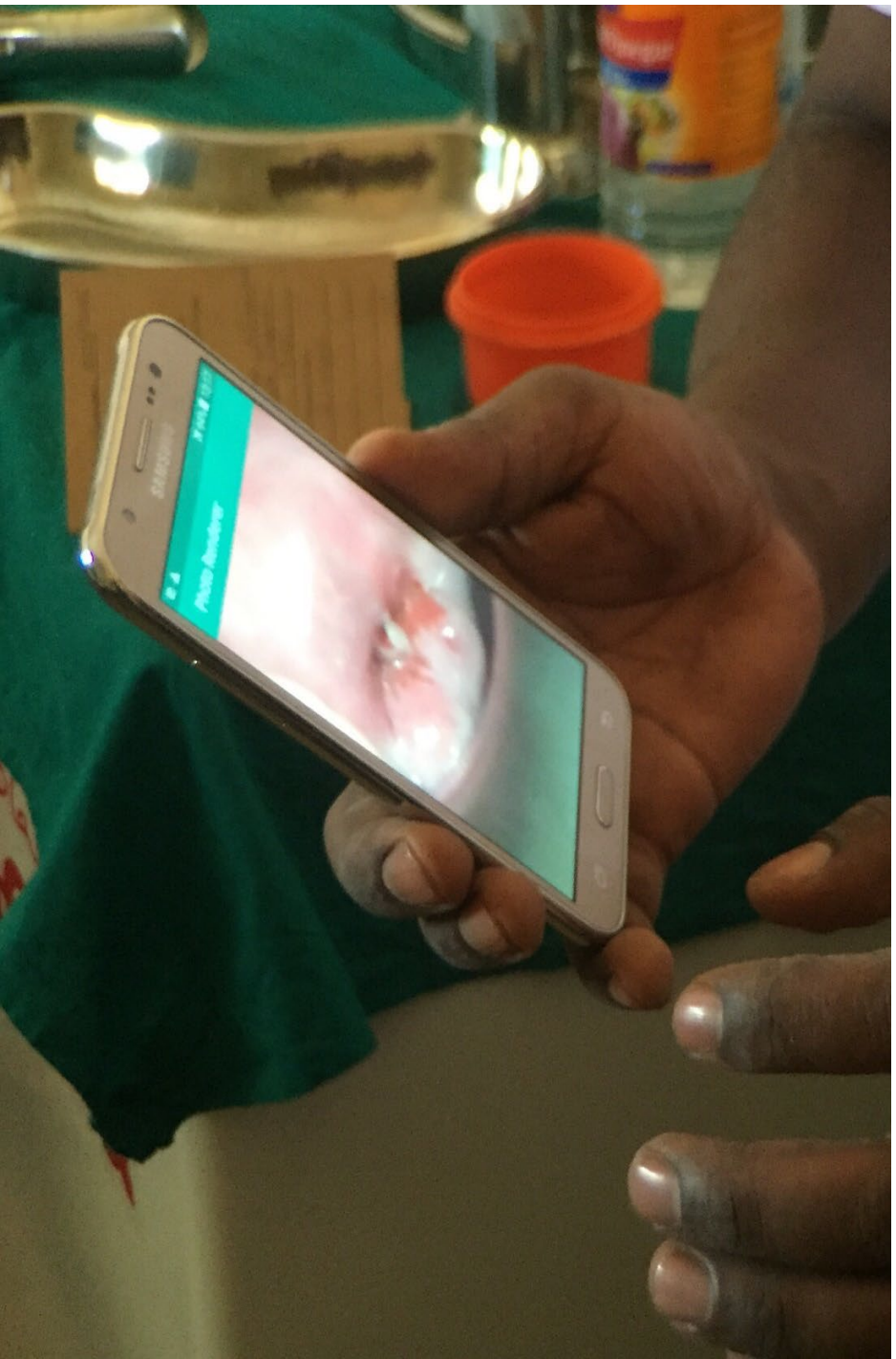
Agenda item 12.4 26 May 2018

Digital health

WHA 71/20 2018

"The spread of digital tech and global interconnectedness has significant potential to accelerate Member States' progress towards achieving universal health coverage, including ensuring access to quality health services."

from WHA 71/20



What is mHealth?

“Medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices.”

mHealth: New horizons for health through mobile technologies, WHO, 2011

“The use of mobile wireless devices for public health”

WHA 71 DG report, 2018

Background (from WHA 71/20)

- 7 billion mobile phone subscriptions, 70% in LMIC
- In many LMICs, more people have access to a mobile phone than to clean water, a bank account, or electricity.
- Digital tech including mobile tech *has the potential* to revolutionize how populations interact with health services
- mHealth can improve quality and coverage of care, increase access to health information, services, and skills, and promote positive changes in health behaviors

International Telecommunications Union (ITU) 2015

BUT….

Governments have found it challenging to assess, scale up, and integrate mHealth “solutions”.

BUT….

Many pilot studies with no process for scaling

Lack of interconnectedness between apps, and of integration with existing national eHealth & HIS infrastructures

World Heal
Organizatio

WHO r uideline on digi rventions

17 April 2019 | News rel

WHO today released ies can use digital health technology, accessib improve people's health and essential services.

Clients

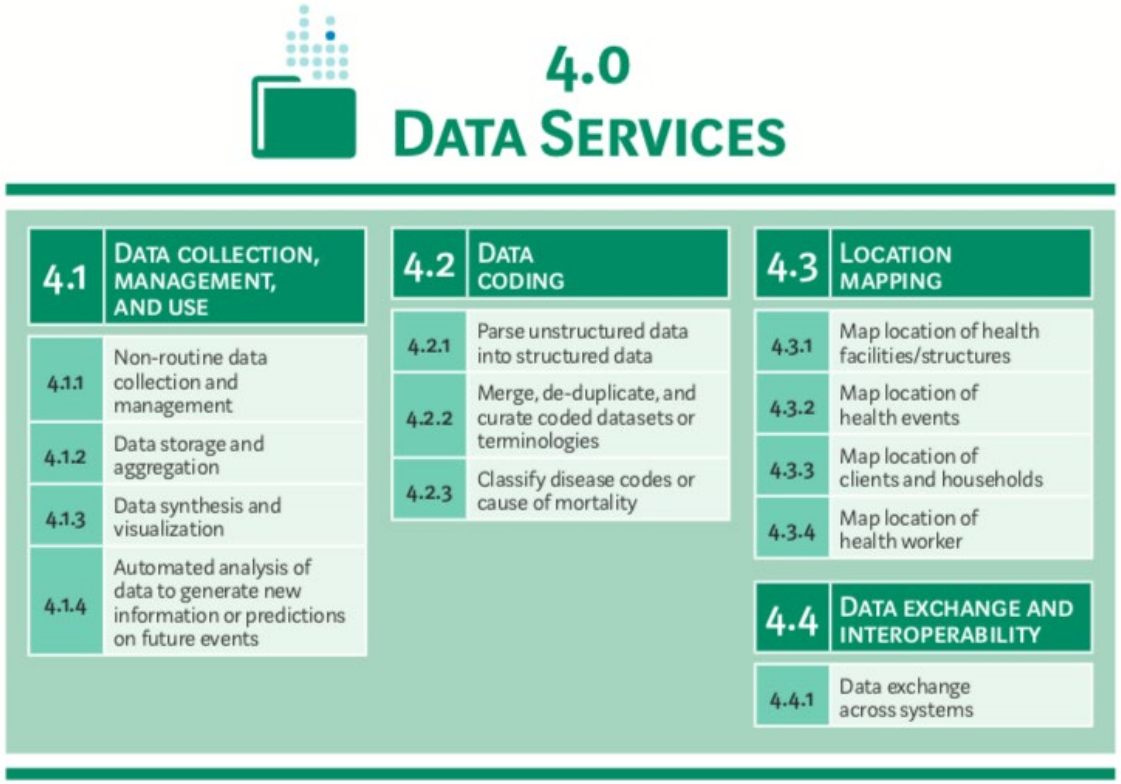
- Targeted client communication
  - i.e. health promotion, education, countering myths, etc.
- 2-way SMS or info-line with nearest services

Health workers

- Clinical decision support
- Training
- Quality assurance
- Referral coordination & tracking (navigation)

Health System Managers

- Supply chain management
- Facilities management
- HR management



Data Services

- Data collection/management/storage/ synthesis/visualization
- Location mapping: clients/patients/ facilities
- Data exchange & interoperability
- DHIS2, etc.
- Vital statistics, causes of death
- IARC: population-based cancer registries
- Cancer screening registry

WHO mERA Checklist

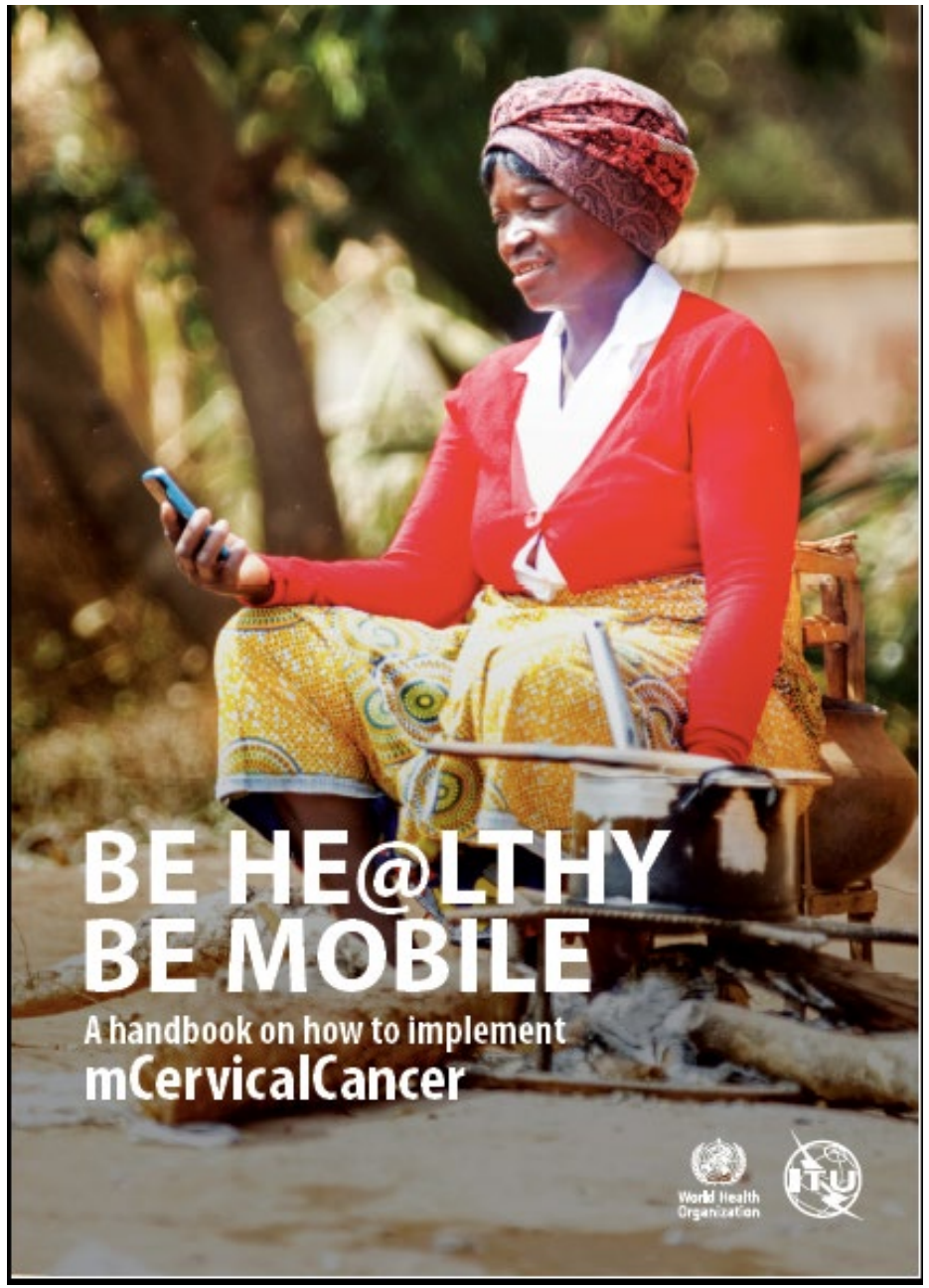
Item 1—Infrastructure: describe, in detail, the necessary infrastructure which was required to enable the operation of the mHealth programme
Item 2—Technology platform: describe, in sufficient detail to allow replication of the work, the software and hardware combinations used in the programme implementation
Item 3—Interoperability: describe how, if at all, the mHealth strategy connects to and interacts with national or regional Health Information Systems (HIS)/programme context
Item 4—Intervention delivery: elaborate the mode, frequency, and intensity of the mHealth intervention
Item 5—Intervention content: describe how the content was developed/identified and customised
Item 6—Usability testing: describe how the end-users of the system engaged in the development of the intervention
Item 7—User feedback: describe user feedback about the intervention or user satisfaction with the intervention
Item 8—Access of individual participants: mention barriers or facilitators to the adoption of the intervention among study participants

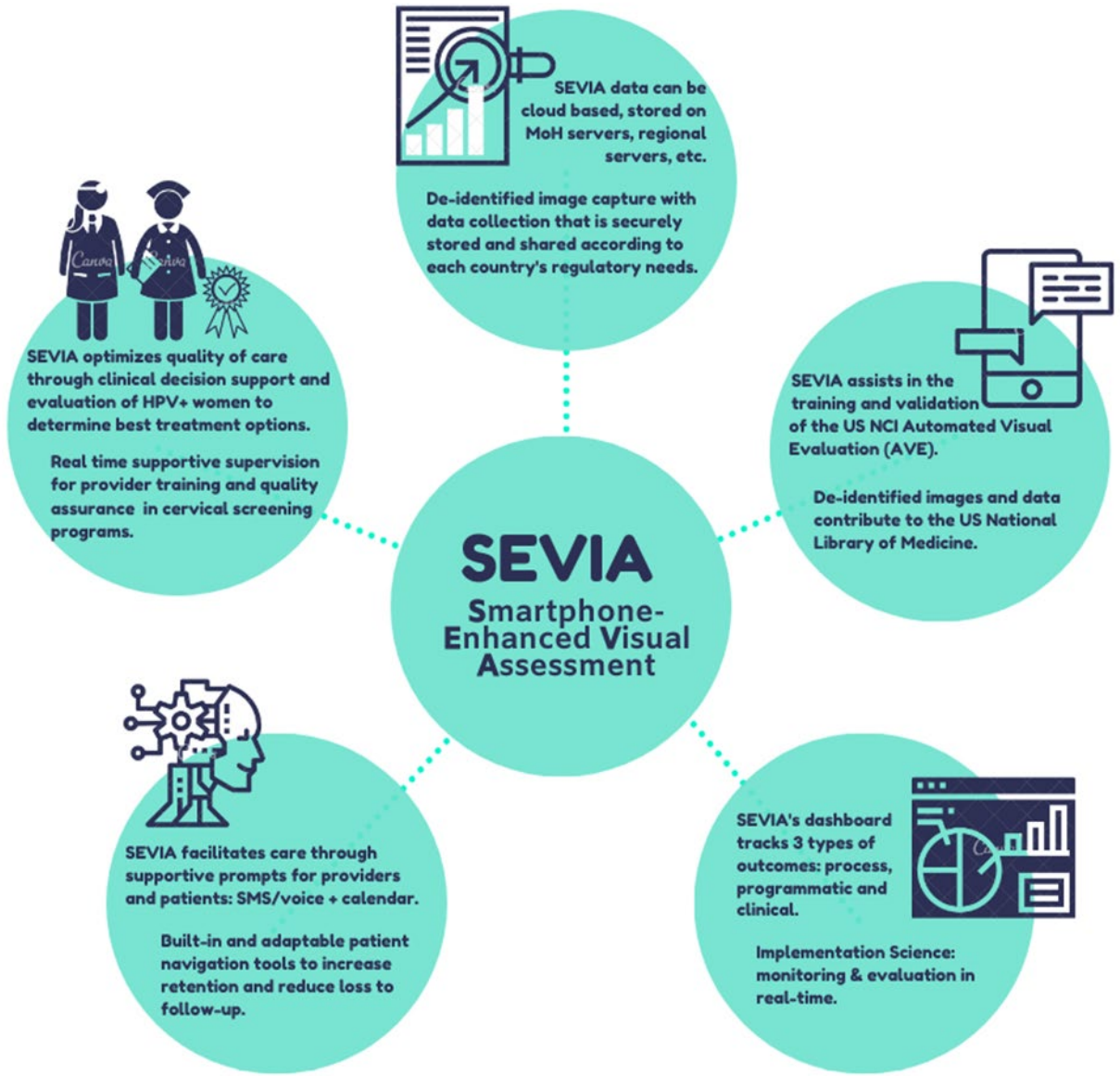
Agarwal S, LeFevre AE, Lee J, et al. BMJ. 2016;352:i1174

WHO mERA Checklist

Item 9—Cost assessment: present basic costs of the mHealth intervention
Item 10—Adoption inputs/programme entry: describe how people are informed about the programme or steps taken to support adoption
Item 11—Limitations for delivery at scale: present expected challenges for scaling up the intervention
Item 12—Contextual adaptability: describe appropriateness of the intervention to the context, and any possible adaptations
Item 13—Replicability: present adequate technical and content detail to support replicability
Item 14—Data security: describe security and confidentiality protocols
Item 15—Compliance with national guidelines or regulatory statutes
Item 16—Fidelity of the intervention

Agarwal S, LeFevre AE, Lee J, et al. BMJ. 2016;352:i1174


BE HE@LTHY
BE MOBILE
A handbook on how to implement
mCervicalCancer
World Health Organization
ITU



JCO Global Oncol 6:1114-1123. © 2020 by American Society of Clinical Oncology

Proof of Concept Study in Tanzania

Evaluation of a Smartphone-Based Training Strategy Among Health Care Workers Screening for Cervical Cancer in Northern Tanzania: The Kilimanjaro Method

Karen E. Yeates, Jessica Sleeth, [...], and Olola Oneko

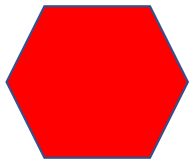
Yeates KE, Sleeth J, Hopman W, Ginsburg O, Heus K, Andrews L, Giattas MR, Yuma S, Macheku G, Msuya A, Oneko O. Evaluation of a Smartphone-Based Training Strategy Among Health Care Workers Screening for Cervical Cancer in Northern Tanzania: The Kilimanjaro Method. J Glob Oncol. 2016 May 4;2(6):356-364. doi: 10.1200/JGO.2015.001768. PMID: 28717721; PMCID: PMC5493243.

original reports

Smartphone-Enhanced Training, QA, Monitoring, and Evaluation of a Platform for Secondary Prevention of Cervical Cancer: Opportunities and Challenges to Implementation in Tanzania

Karen Yeates, MD, MPH[1,2,3]; Erica Erwin, MSc[1,4]; Zac Mtema, PhD, MSc[5]; Frank Magoti[5]; Simoni Nkumbugwa, BSc[5]; Safina Yuma, MPH[6]; Wilma M. Hopman, MA[7]; Alyssa Ferguson, MPH[8]; Olola Oneko, MD[9]; Godwin Macheku, MMED[10]; Agnes Feksi Mtei, MD[6]; Carter Smith, BSc[8]; Linda Andrews, MPH[8]; Nicola West, BScN[3,8]; Milena Dalton, MPH[11]; Ashley Newcomb, MPH[12]; and Ophira Ginsburg, MD, MSc[12,13]

JCO Global Oncol 6:1114-1123.



CAUTION!!!!

- Technology alone is never the solution to complex systems challenges.
- Beware of hype. Look for and demand the evidence.
- Ask ourselves: is there a low-tech (or non-tech) intervention that might work as well? cost-effective? Affordable?

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- Grand Challenges Canada
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- **….and most importantly the women who participated in all our studies….**

CUGH & NCI Cervical Cancer Webinar Series 2: Latest scientific advances, tools, & approaches to address cervical cancer control

August 5, 2020

11:00am-12:00pm EDT

Mark Schiffman, MD, MPH
Senior Investigator, Division of Cancer Epidemiology and Genetics
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Nicole Gastineau Campos, PhD,
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Harvard T.H. Chan School of Public Health
Boston, MA, U.S.A

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