High-Quality Risk-based Cervical Cancer Screening for the U.S. and the World:

A Realistic Example of Precision Prevention

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NIH NATIONAL CANCER INSTITUTE

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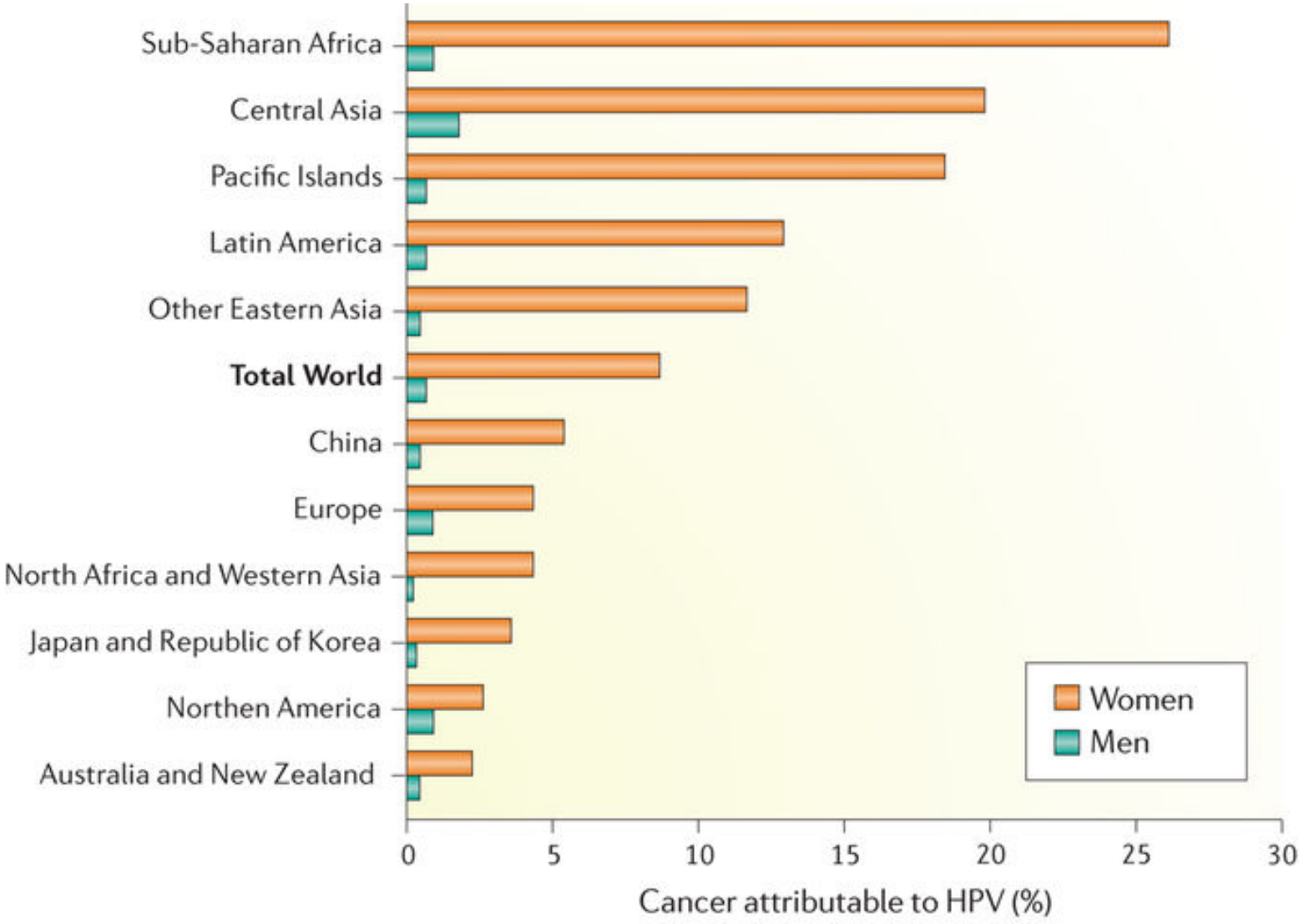
Main Message

- Cervical cancer has a uniform etiology and pathogenesis worldwide: Persistent HPV is the necessary cause
- Cervical cancer prevention already a success in some high-resource countries
  - But “precision prevention” now possible
- Worldwide burden still increasing
- New strategies can greatly increase the reach of prevention efforts

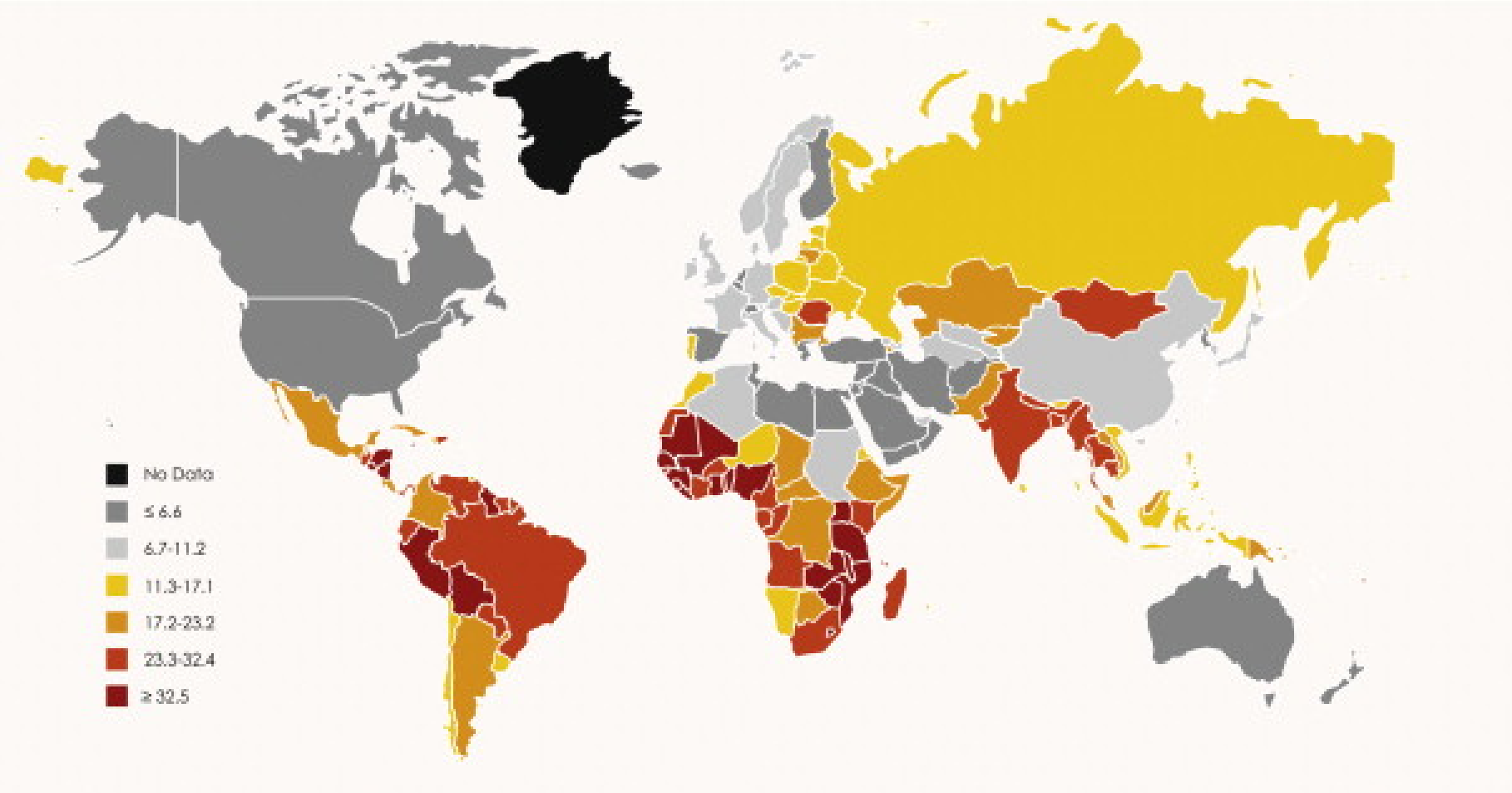
Most Of HPV-Attributable Cancer Burden in LMIC*



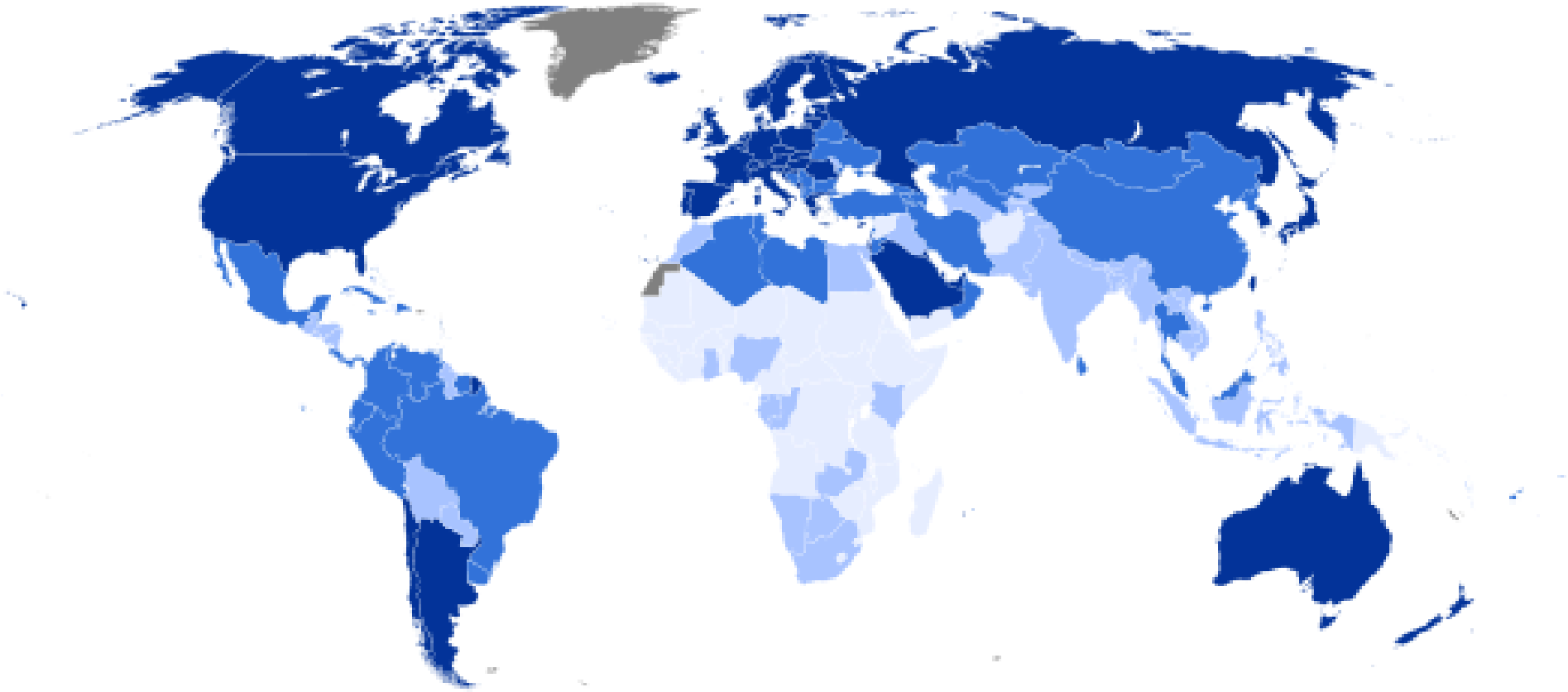
* Low and middle income countries

Nature Reviews | Disease Primers

Age-Adjusted Cervical Cancer Incidence

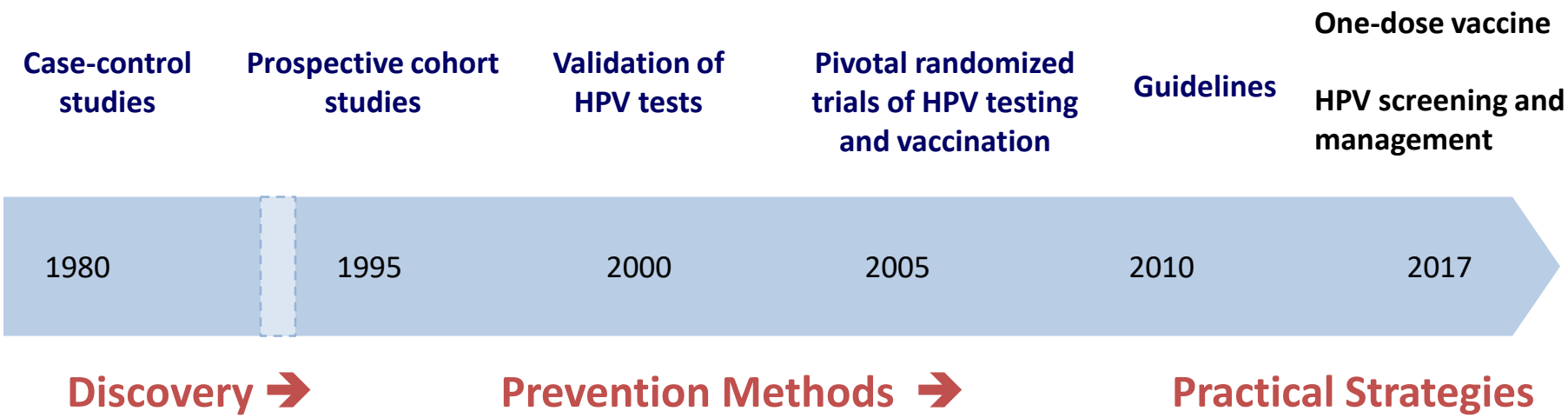


UN Human Development Index



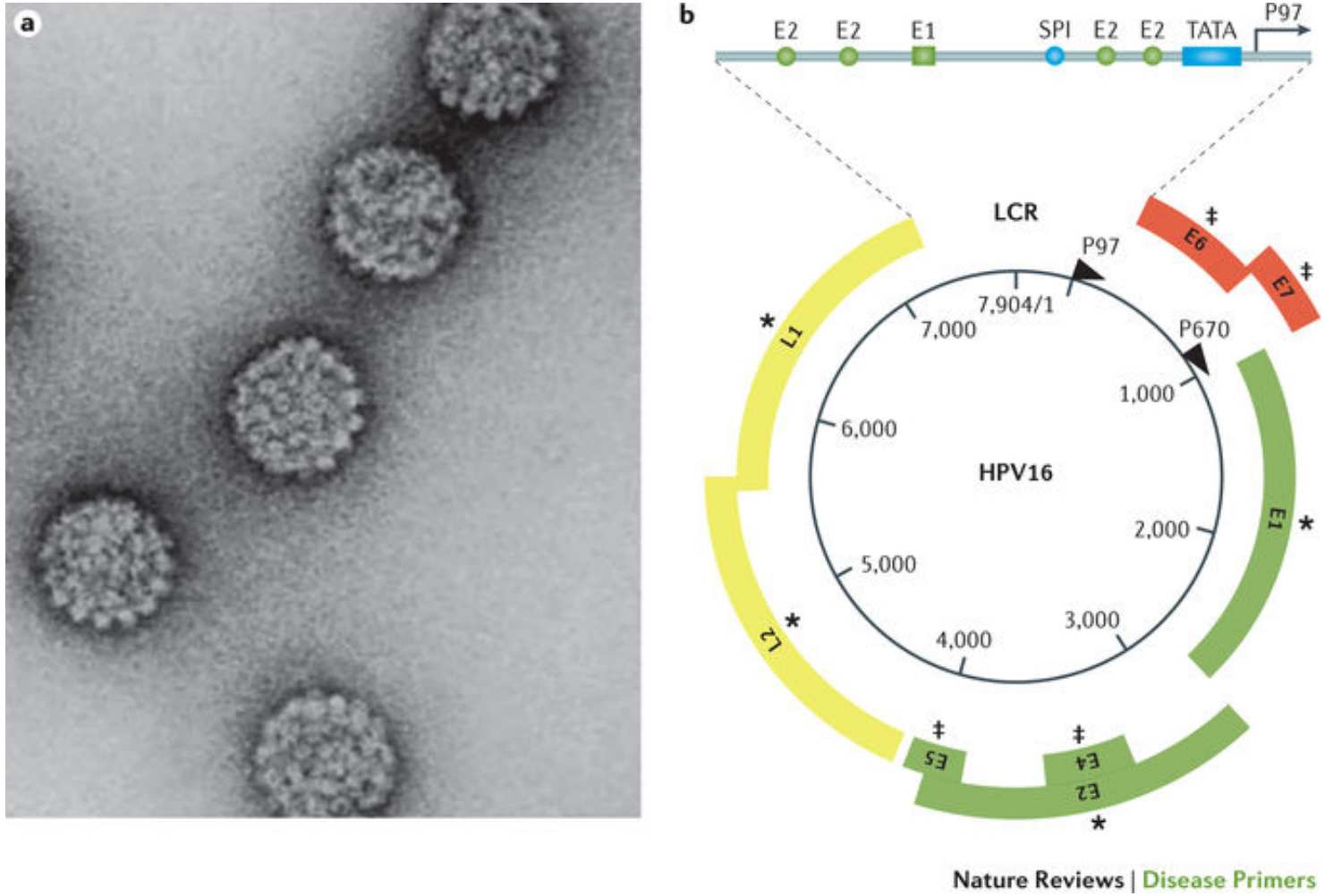
Different settings merit separate strategies, all based on same underlying science

NCI Cervical Cancer Prevention Research: From Discovery to Impact

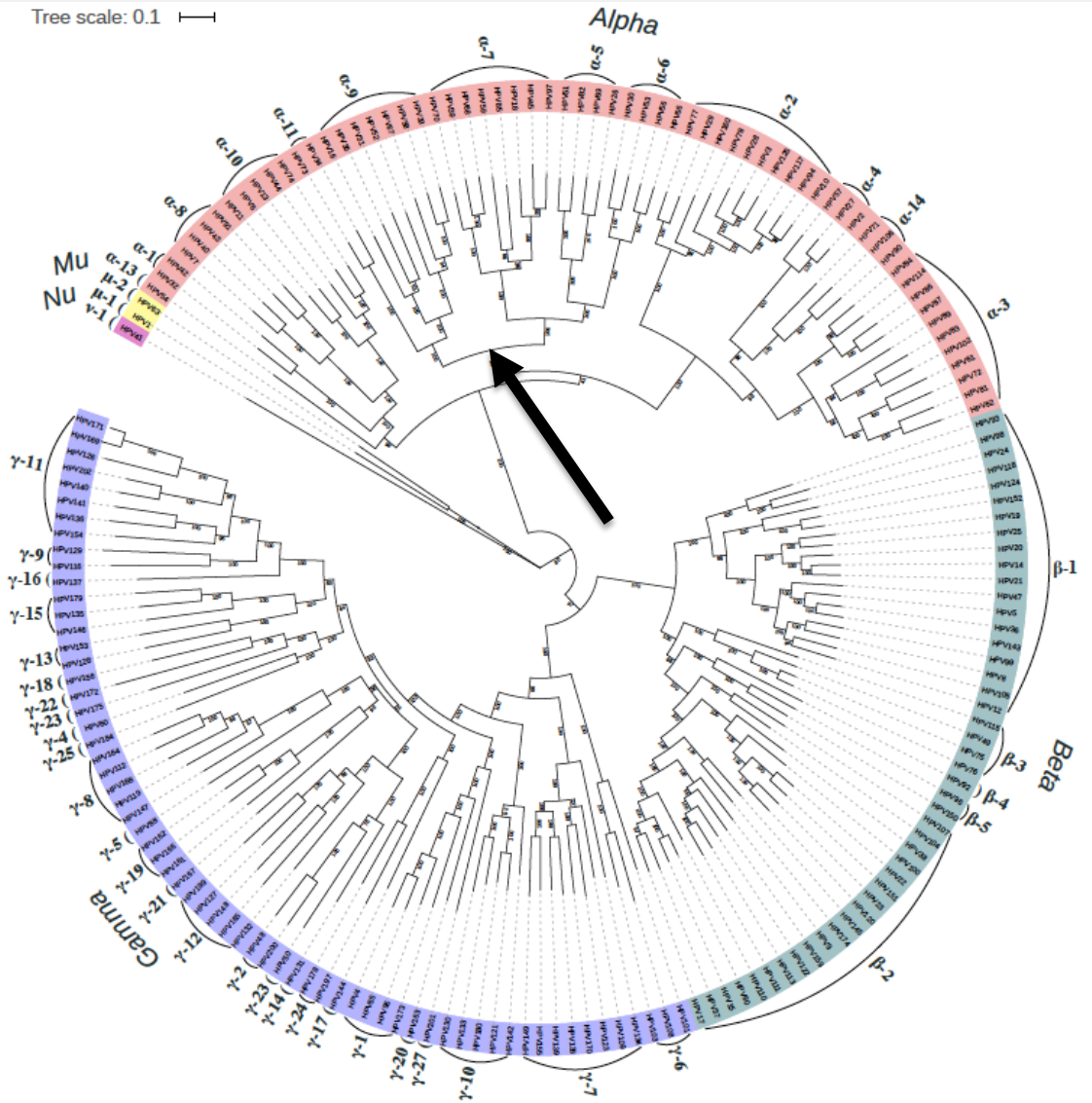


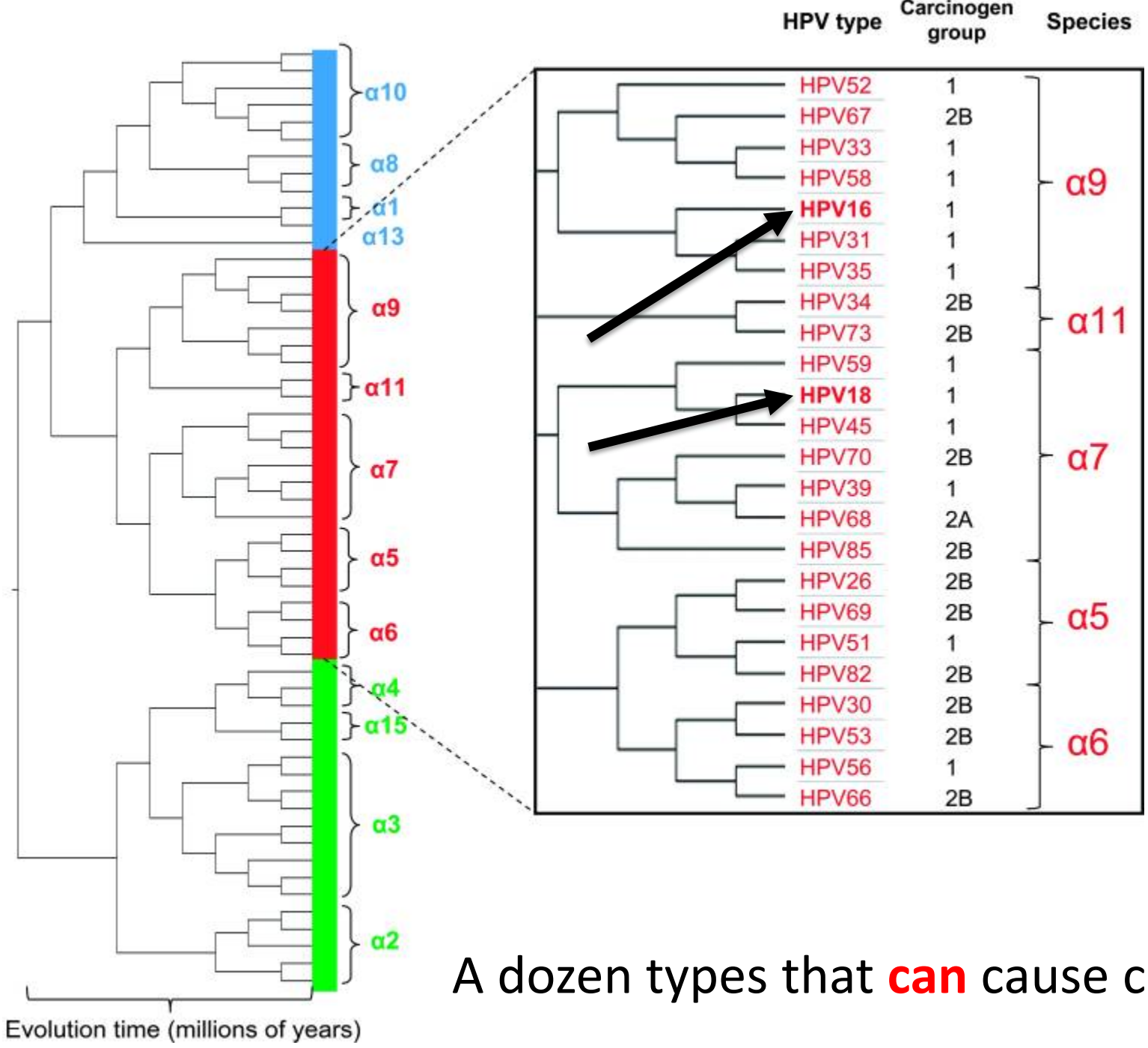
Some Basic Facts about Human Papillomaviruses

HPV Has a Relatively Small, Simple Genome

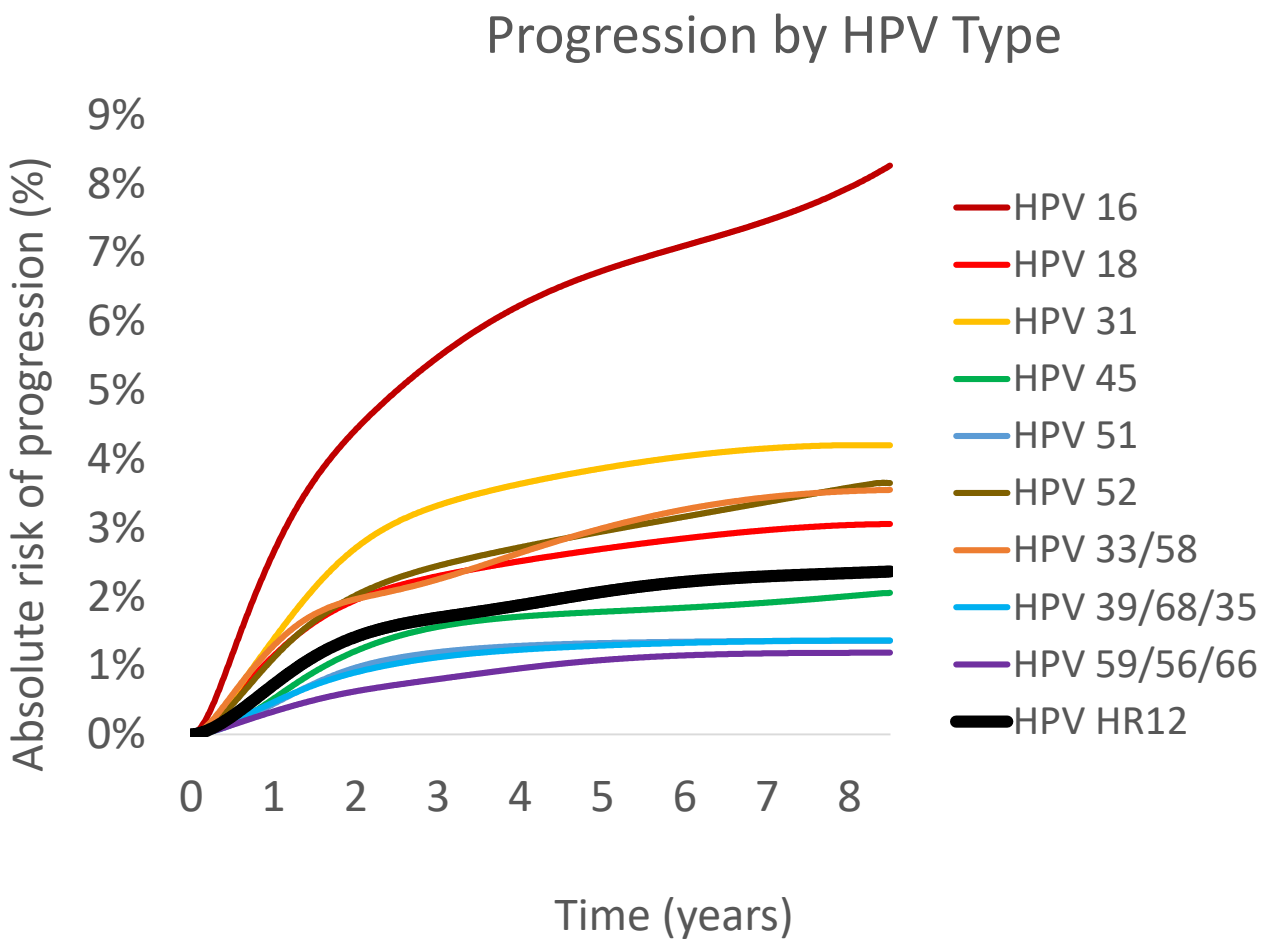


Which HPVs Cause Cervical Cancer?



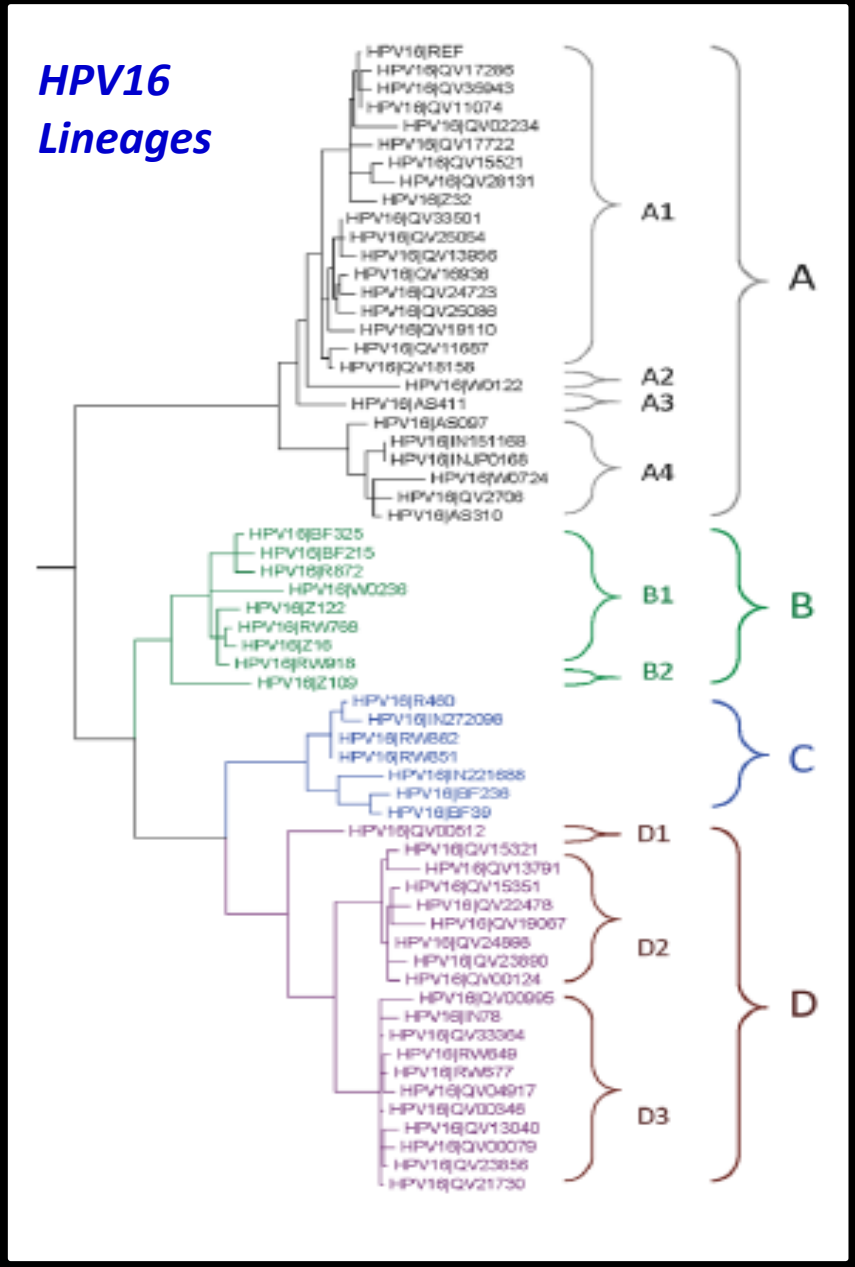


A dozen types that **can** cause cancer



Demarco et al., in preparation

HPV16 lineages/sublineages

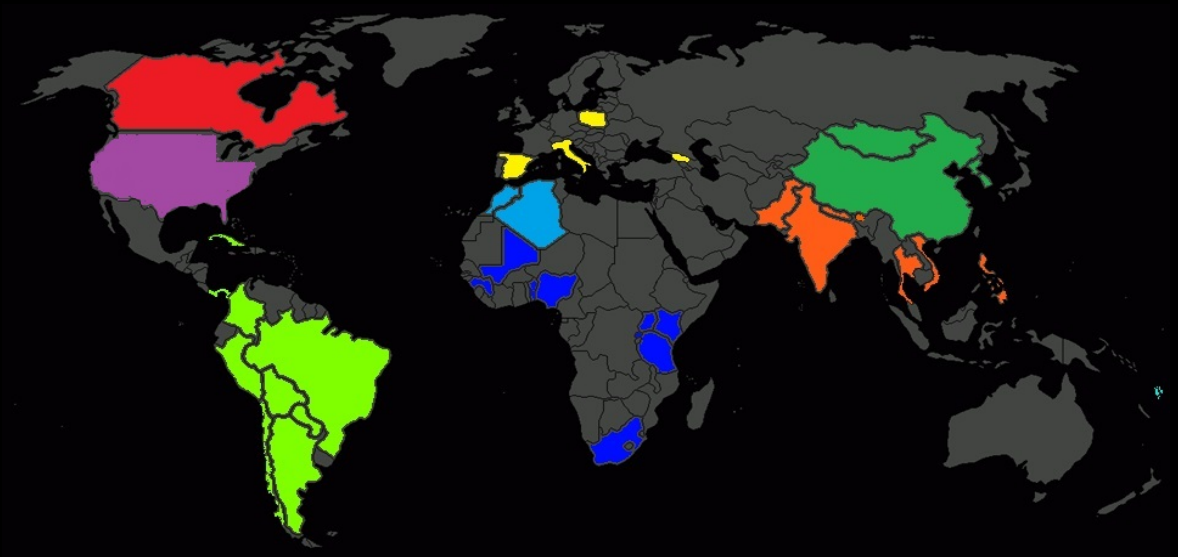


Burk et al., Virology 2013.

E7 is hypovariable in cancers around the world

- HPV16+ women in our large cohorts, and
- 1,609 cancers around the world from IARC:
- In cancers, E7 was significantly less variable than all other viral regions

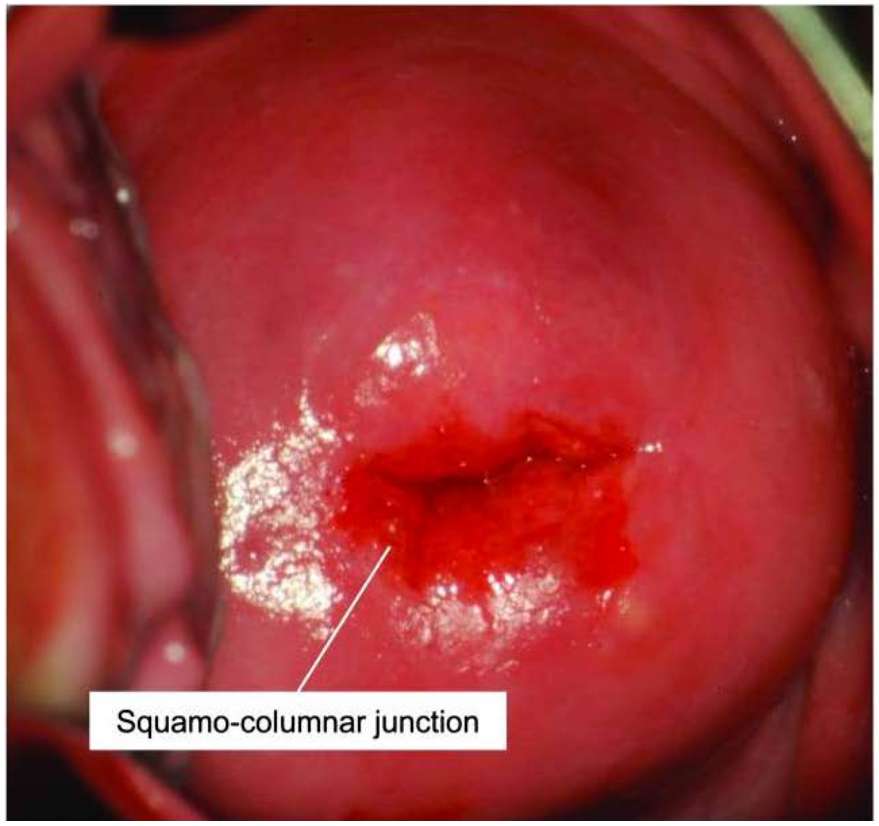
Viral region	% IARC cancers	*P*
E7	**0.8%**	**reference**
E5	6.3%	8.0E-11
E4	8.3%	1.9E-09
E6	**8.4%**	**6.1E-05**
L1	9.1%	7.0E-05
E1	22.0%	2.2E-04
E2	26.4%	5.1E-15
L2	43.6%	1.0E-14
URR	44.8%	2.2E-16

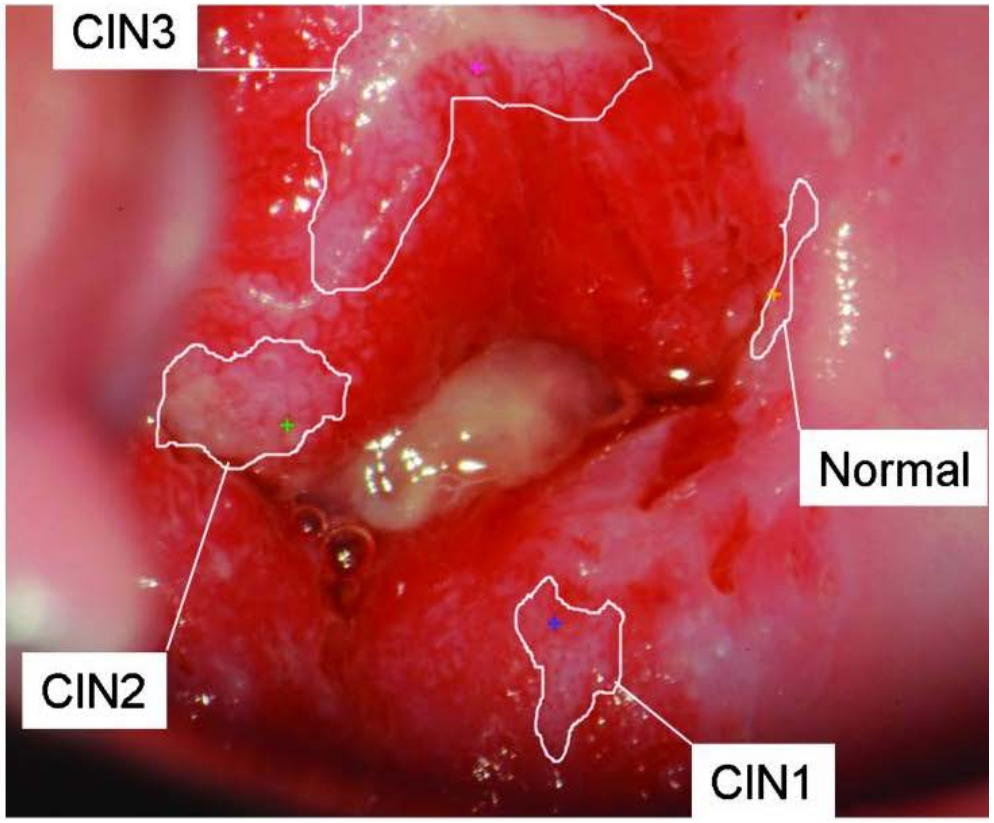


Mirabello et al., Cell 2017 Sep 7;170(6):1164-1174.

Where Do Cervical Cancers Originate?

The Cervical Squamo-Columnar Junction

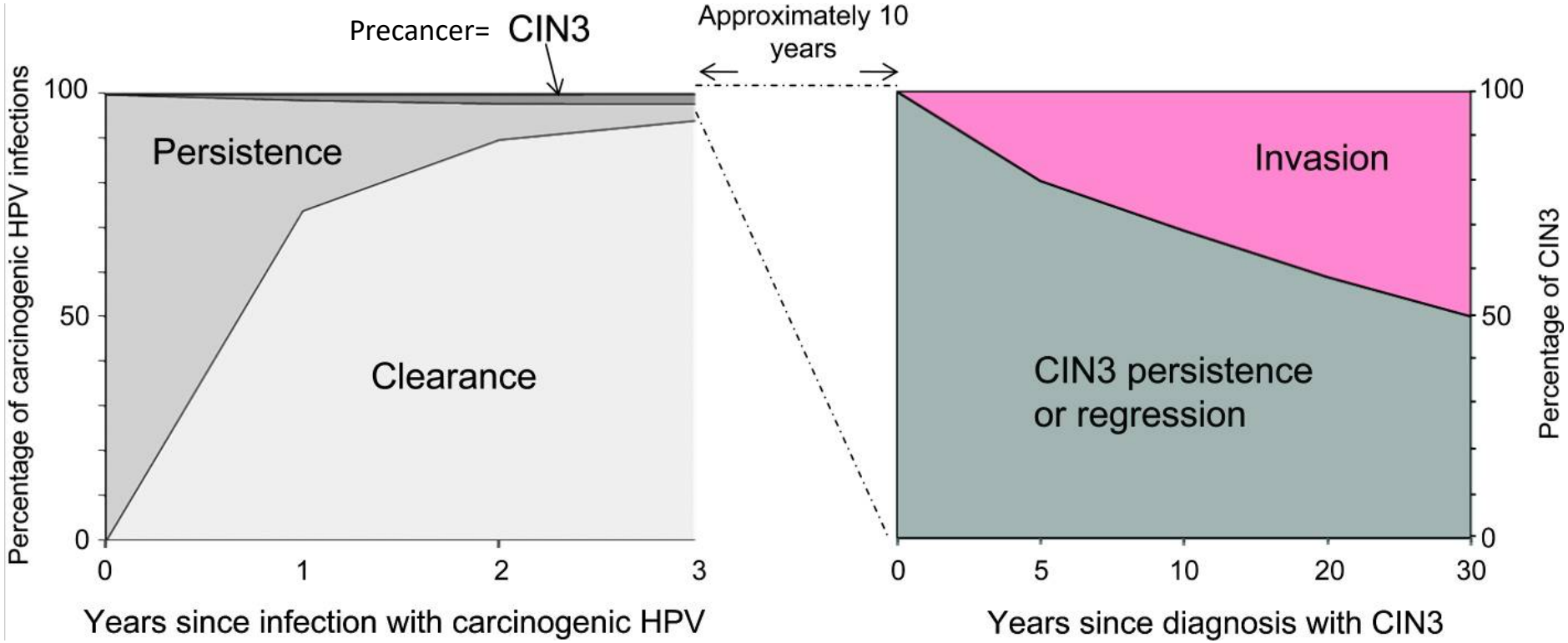




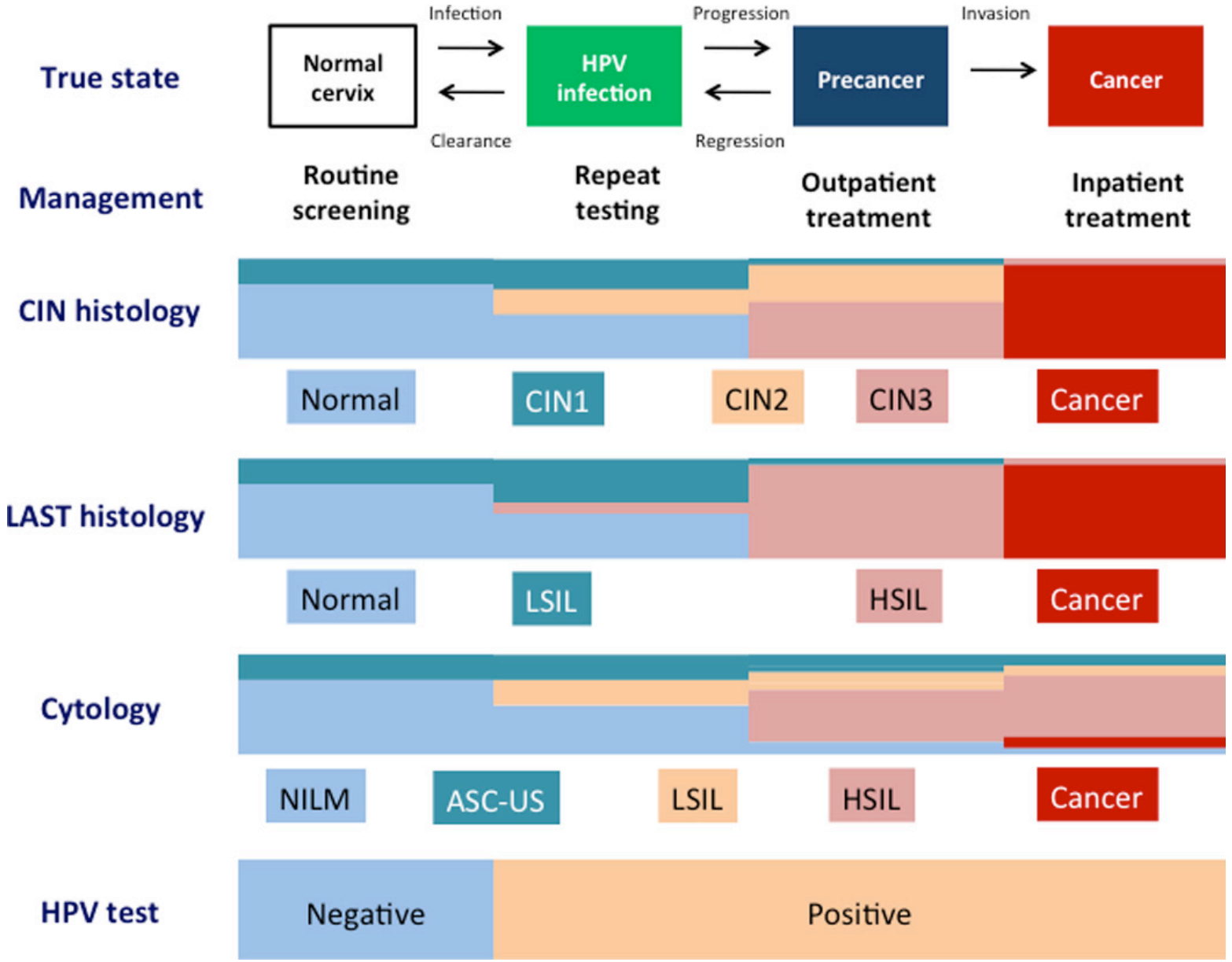
Uniquely prone to HPV-induced carcinogenesis

HPV Natural History and Steps to Cervical Cancer

Here is What We Learned



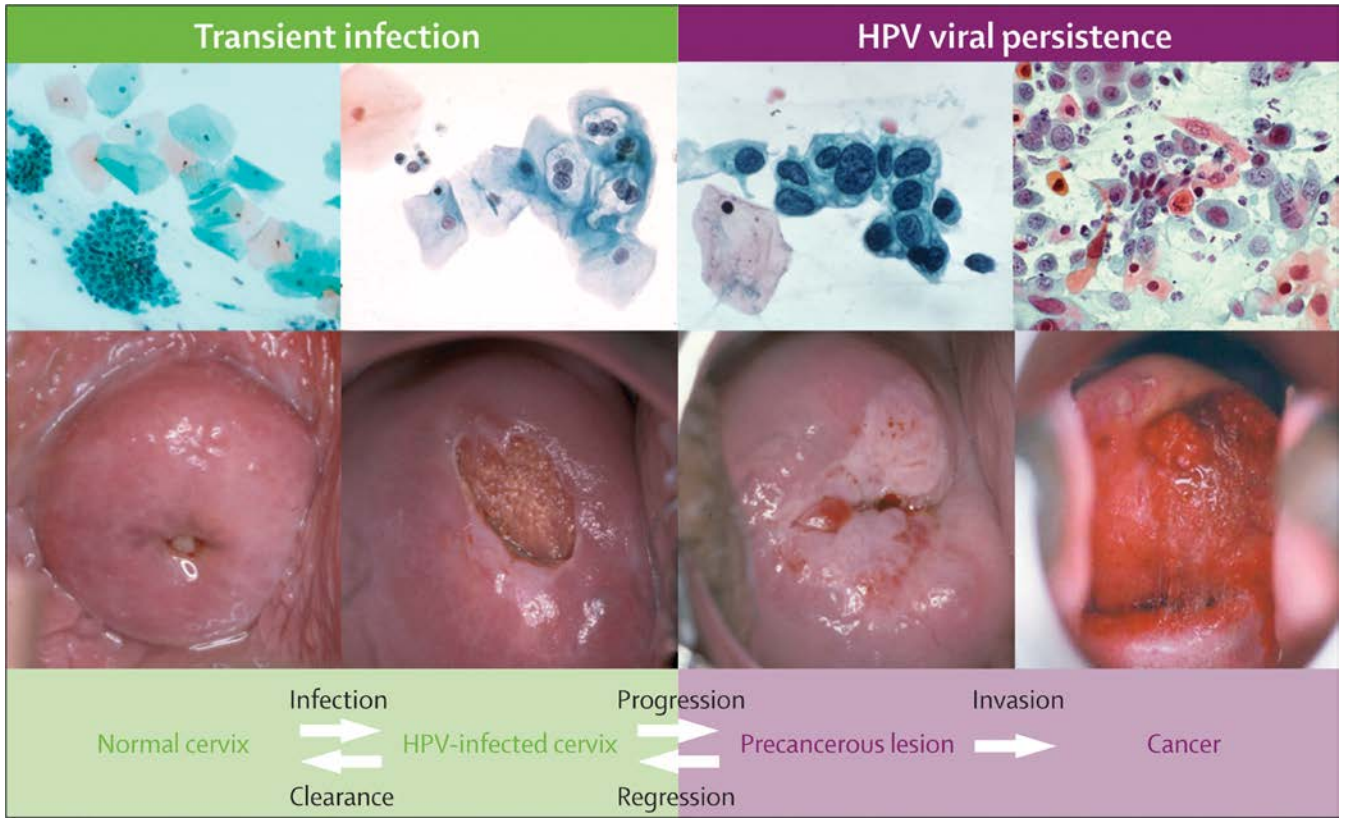
Cervical Carcinogenesis



Molecular

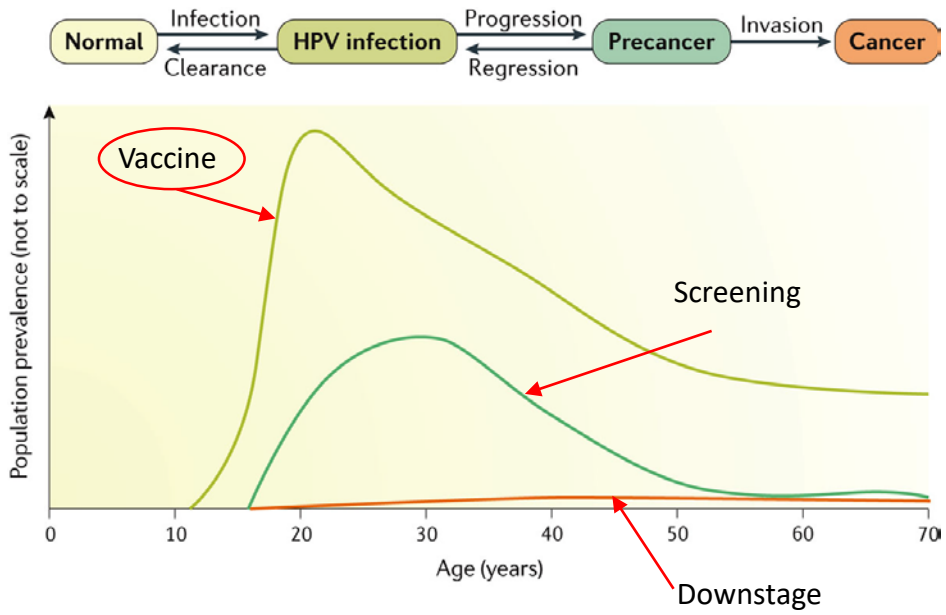
Cytologic

Visible



Prevention Methods

Preventing cervical cancer, possible interventions at each step of HPV natural history



Adapted from *Cancer Epidemiol. Biomarkers Prev.*, 2013, **22**, 553–560, Schiffman, M. & Wentzensen, N., Human papillomavirus infection and the multistage carcinogenesis of cervical cancer, with permission from AACR

Schiffman, M. *et al.* (2016) Carcinogenic human papillomavirus infection *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.86

A scientific evaluation of one or two doses of the HPV vaccines

Objectives

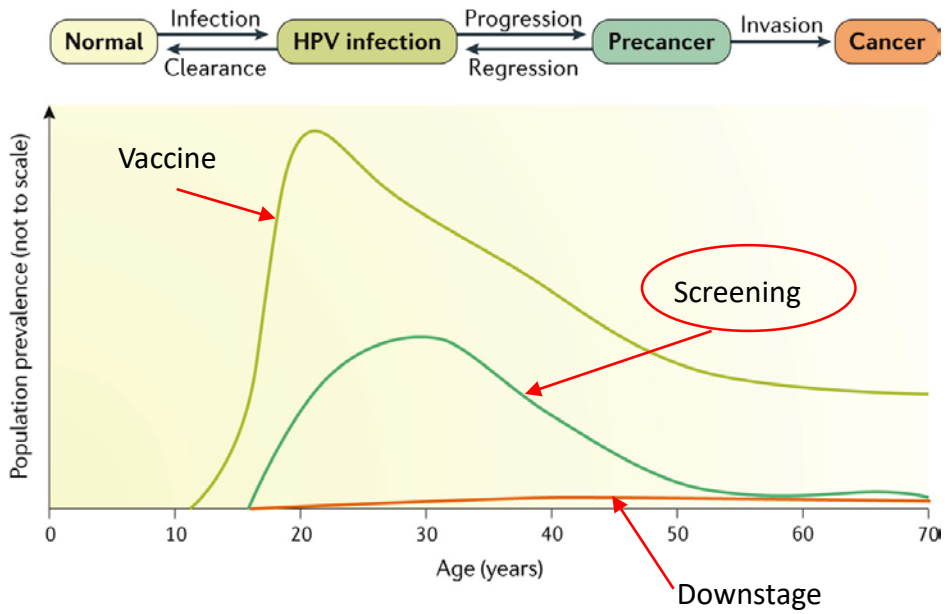
1. For each vaccine, evaluate the **non-inferiority of 1 vs 2 doses** in the prevention of new cervical HPV16/18 infections that persist 6+ months*

2. For each vaccine, evaluate **1 dose of HPV vaccination compared to 0** vaccination doses (virologic endpoint)

3. **Compare sustained immune titers** via measurement of serum antibodies between girls who received 1 and 2 doses of the HPV vaccines

*Lowy DR et al, Lancet Oncol 2015

Preventing cervical cancer, possible interventions at each step of HPV natural history



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Schiffman, M. *et al.* (2016) Carcinogenic human papillomavirus infection
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.86

The screening program

- Precision prevention: Goal to detect and treat true precancer while minimizing over-treatment
- Parts
  - Population screening (presumed normal)
  - Triage of positives
  - Treatment to prevent cancer
  - Post-treatment follow-up
- Lifetime strategy
- Must be concordant with HPV vaccination
- Cytology vs. HPV Testing vs. Cotesting

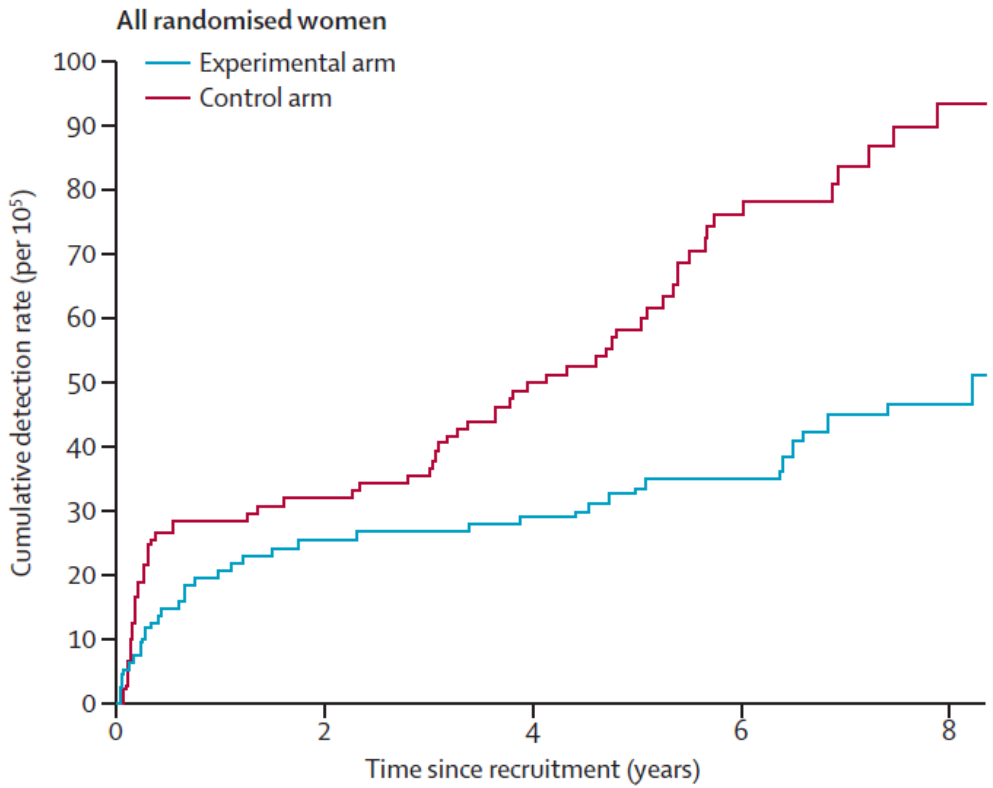
HPV as primary screen everywhere

- USPSTF draft recommendation
- Permits self sampling
- Type restriction
- High-throughput central tests vs Point-of-Care
- Existing US FDA-approved tests fundamentally similar, except for types individually identified
- Tests adapted to low-resource regions are nearly ready

RATE OF CERVICAL CANCER FOLLOWING NEGATIVE HPV TEST VS. NEGATIVE CYTOLOGY

Pooled analysis of 4 european randomized trials of HPV testing vs cytology

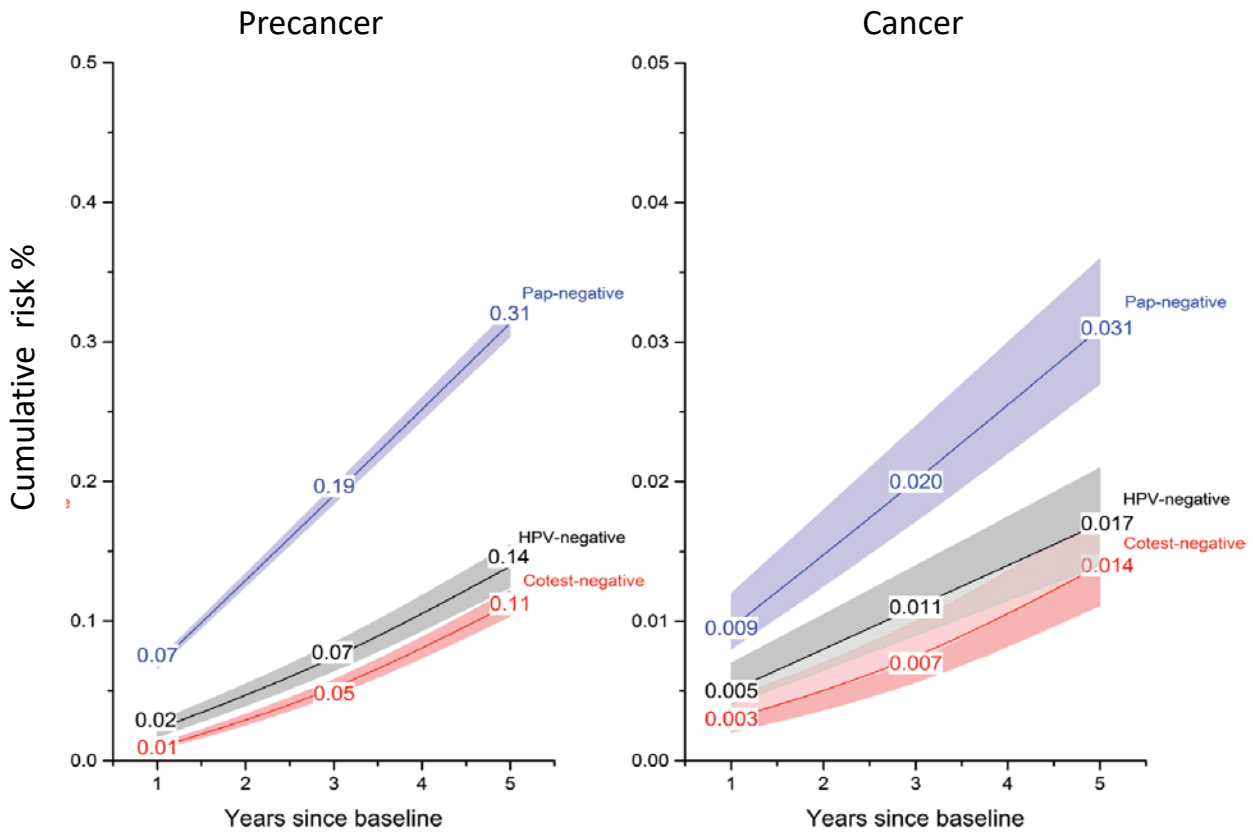
- 176,000 women 20 – 64 years old



Ronco G. et al. Lancet 2014

Why not cotesting with HPV testing and cytology?

- Kaiser Permanente Northern California (KPNC)
- 1,000,000+ women age 30-64
- HPV testing allows for extended screening intervals
- Very little additional reassurance of co-testing vs. HPV alone

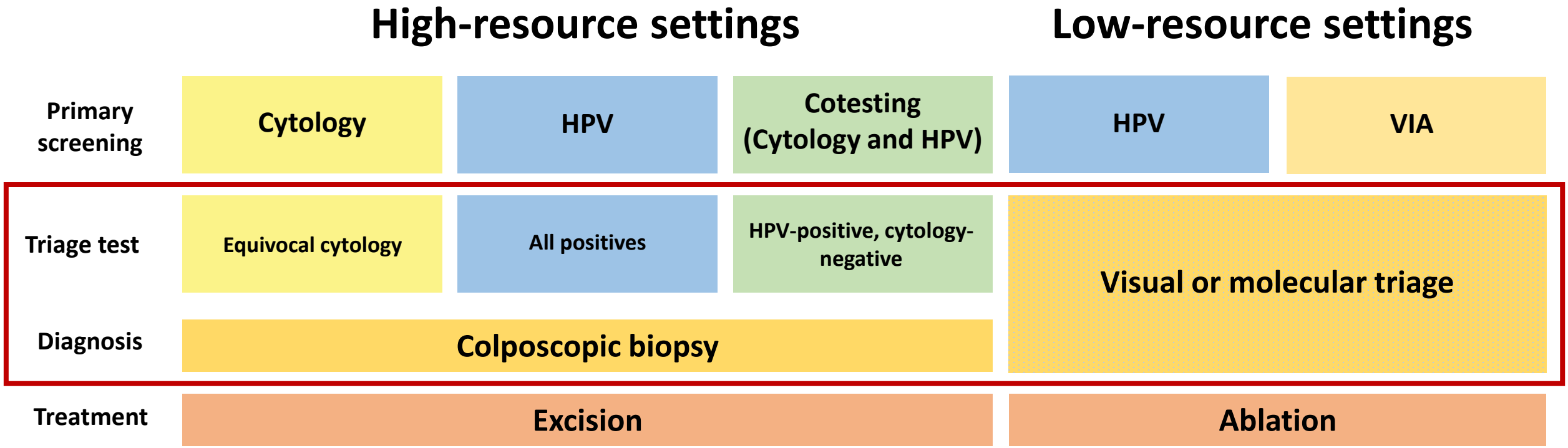


Gage et al., JNCI, 2014

The screening program

- Precision prevention: Goal to detect and treat true precancer while minimizing over-treatment
- Parts
  - Population screening (presumed normal)
    - **PRIMARY HPV TESTING AT EXTENDED INTERVAL**
  - Triage of positives
  - Treatment to prevent cancer
  - Post-treatment follow-up

Cervical cancer screening programs in different settings



- Triage and diagnosis to decide who among the screen-positives needs treatment

Wentzensen Lancet Oncol 2014, Schiffman Nat Rev Dis Primers 2016

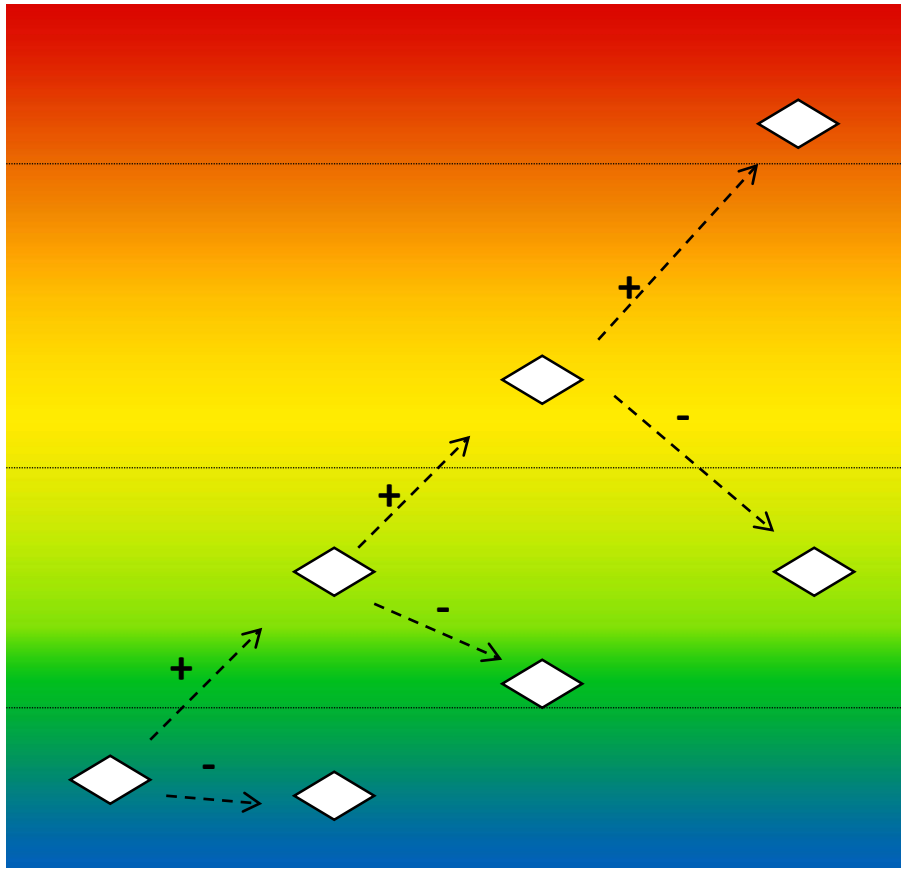
Risk-based approach to screening and management

High risk:
Treatment

Medium risk:
Colposcopy

Low risk:
Triage or repeat testing

Minimal risk:
Regular screening interval



High risk:
Treatment outweighs no treatment

Intermediate risk: Triage or surveillance?

Low risk:
No treatment outweighs treatment

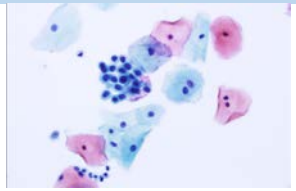
High / middle resource setting

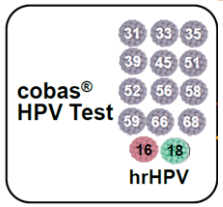
Low resource setting

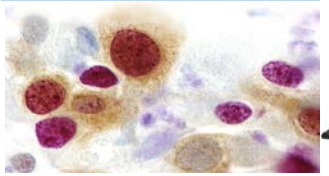
Wentzensen JCV 2016

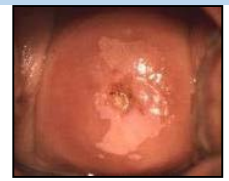
Triage strategies

Cytology-based	Molecular	Visual
Cytology / Automation	HPV genotyping	VIA / Automation
p16/Ki-67 / Automation	Methylation	Colposcopy
High / middle resource setting	Both settings	Low resource setting



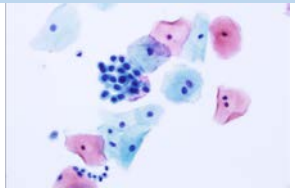




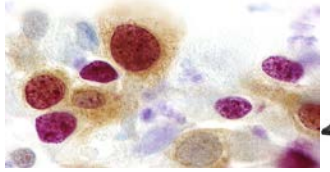


Cytology-based triage

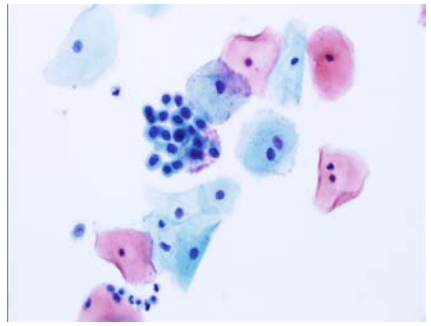
Cytology / Automation



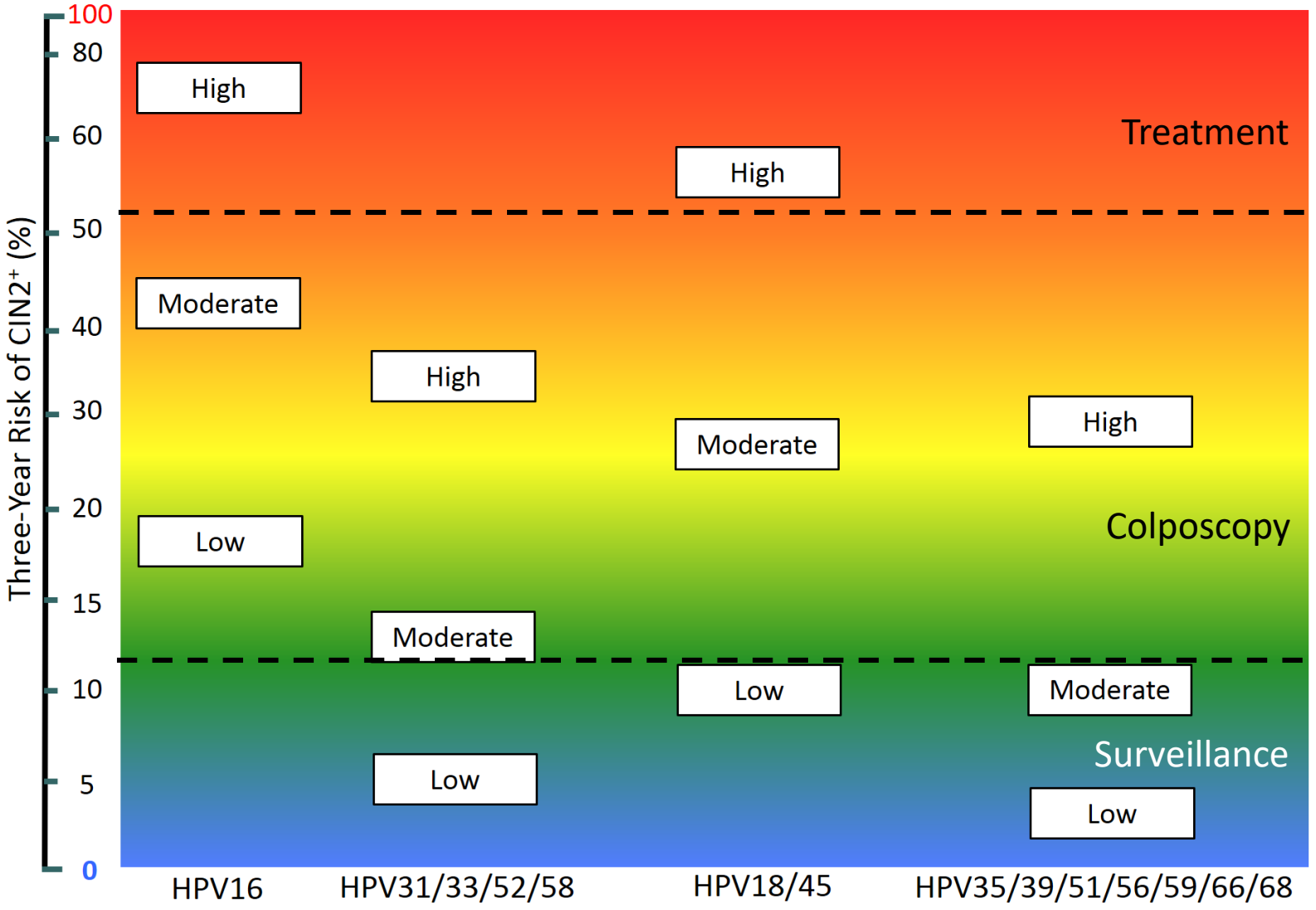
p16/Ki-67 / Automation



A new approach to automated cytology

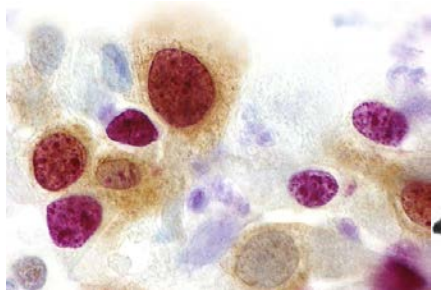


- Scanning of cytology slides (FocalPoint)
- Machine learning score indicating risk of precancer:
  - High
  - Moderate
  - Low



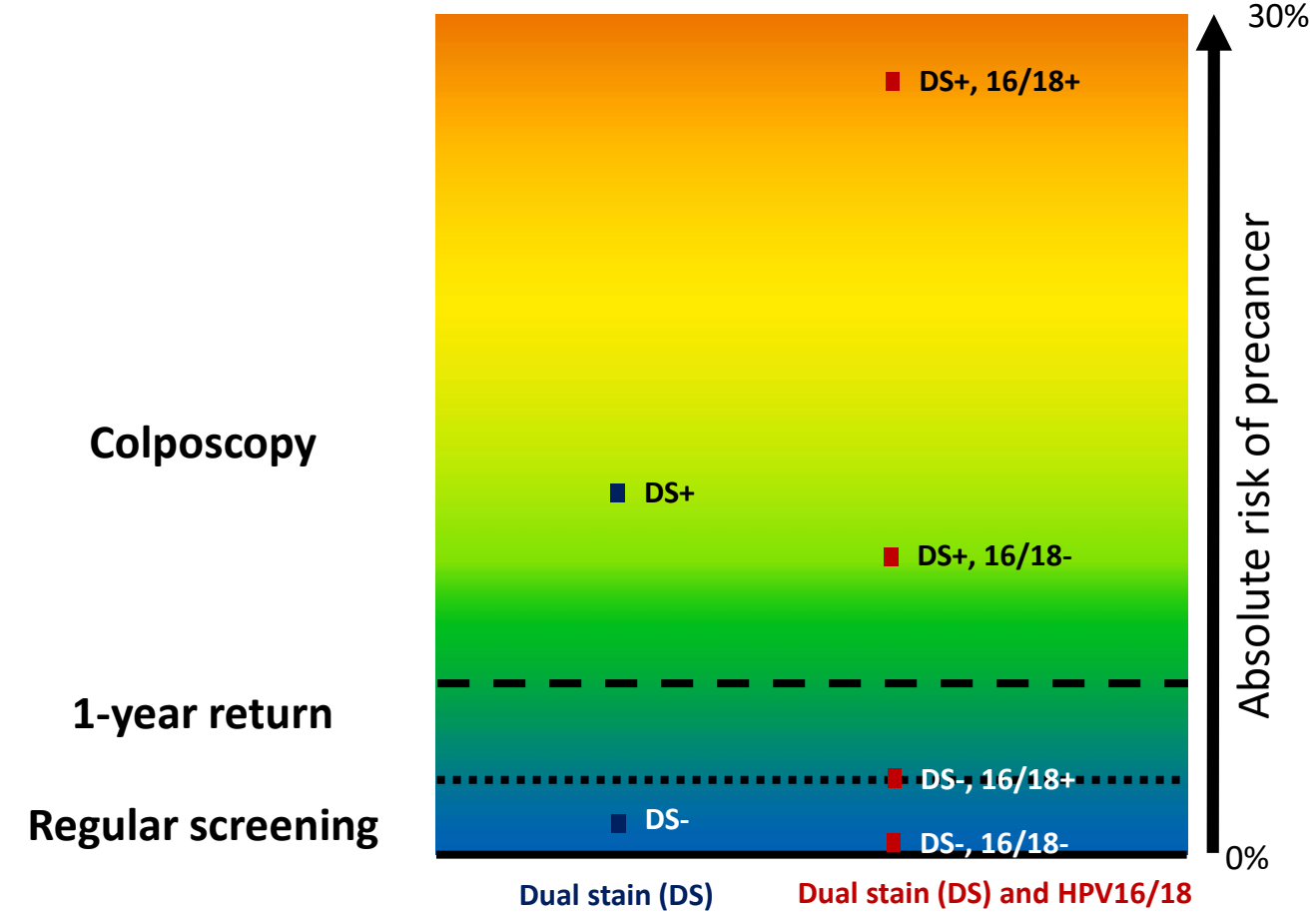
Schiffman IJC 2016

p16/Ki-67 dual stain (DS) and HPV genotyping



Kaiser Permanente

University of Heidelberg

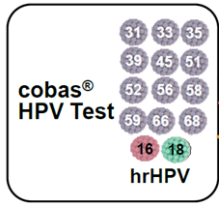


- 13,000 HPV-positive women enrolled at Kaiser Permanente Northern California
- Automated dual stain analysis feasible

Wentzensen JNCI 2015

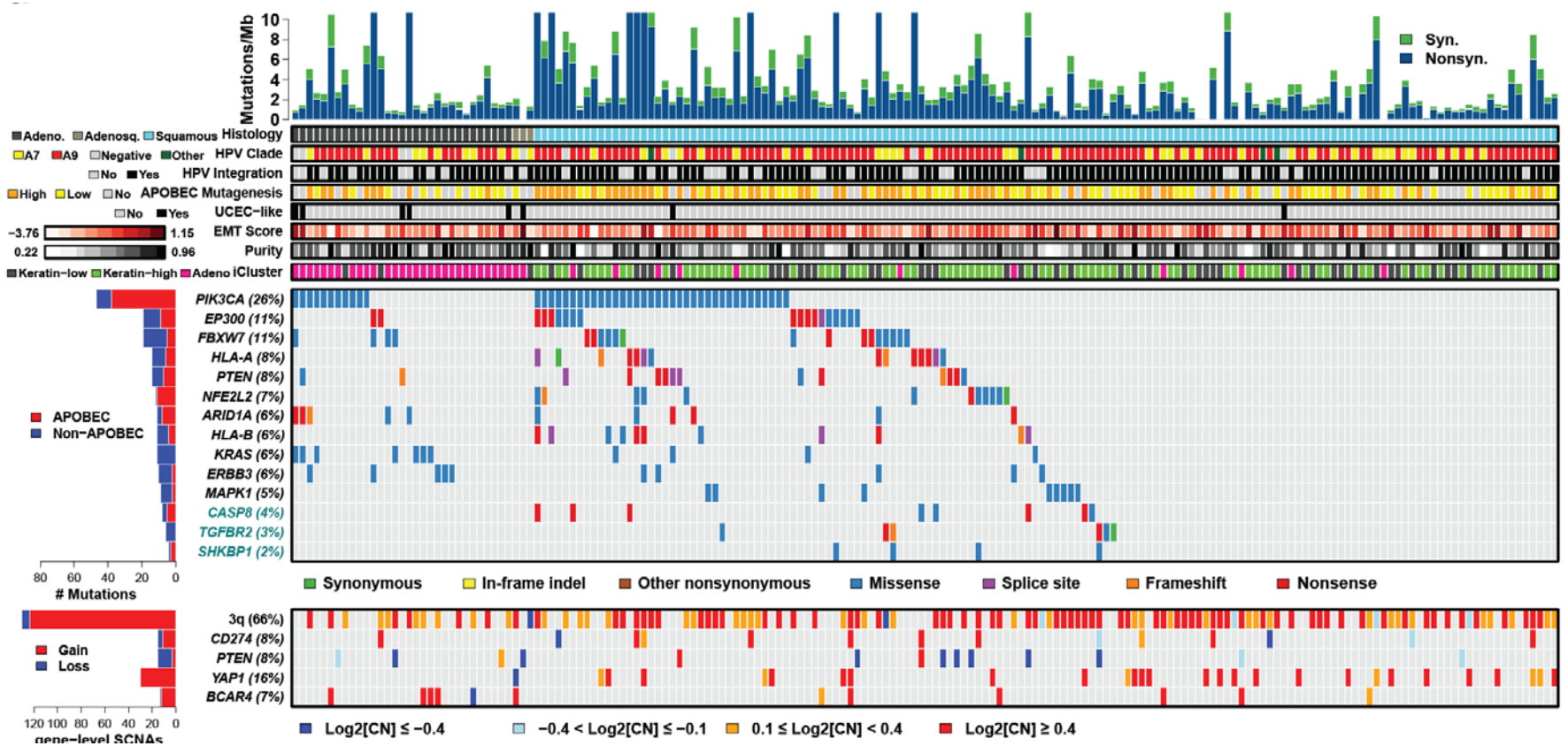
Molecular triage

HPV genotyping



Methylation

Molecular marker discovery: TCGA, SUCCEED



The University of Oklahoma

WISCONSIN

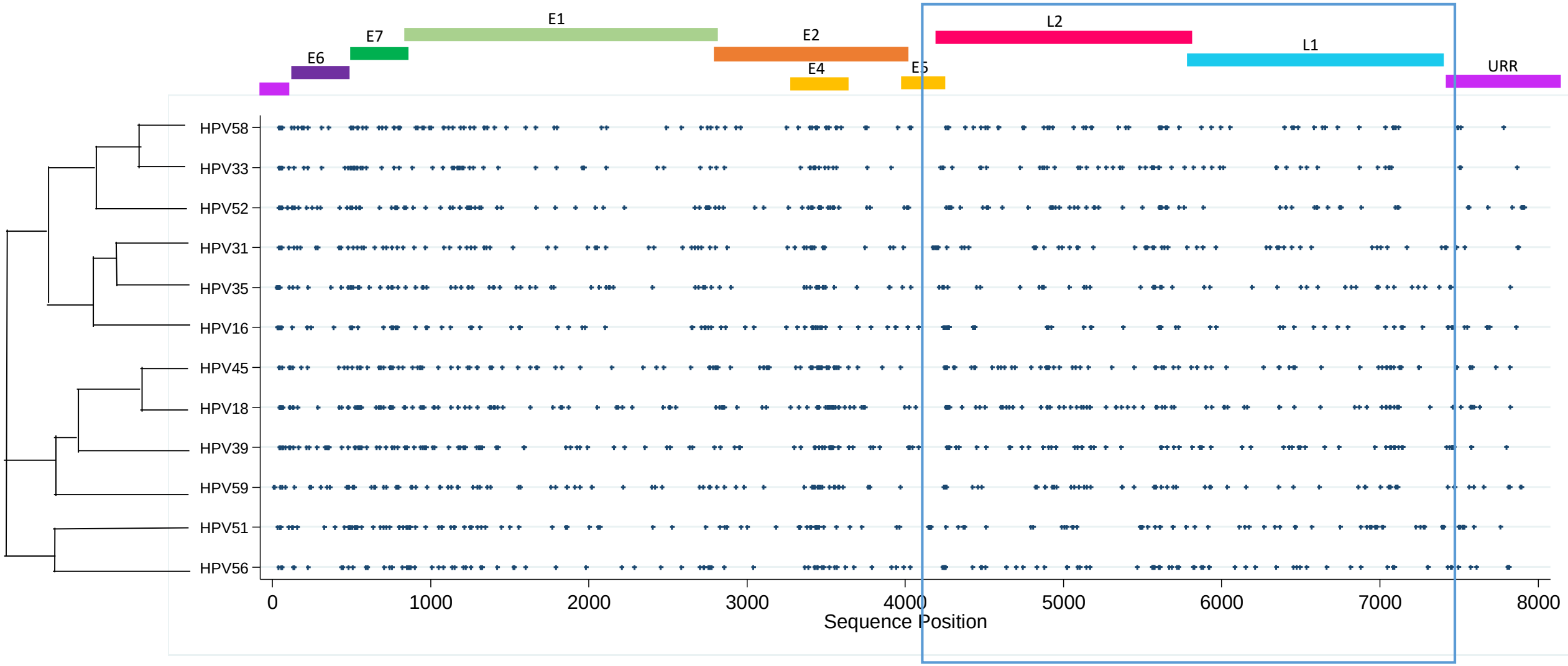
TCGA

- Somatic mutations, copy number variation, methylation, HPV integration
- **TCGA:** Integrated characterization of cervical cancers
- **SUCCEED:** Integrated characterization of cervical precancers

TCGA Group, Nature 2017

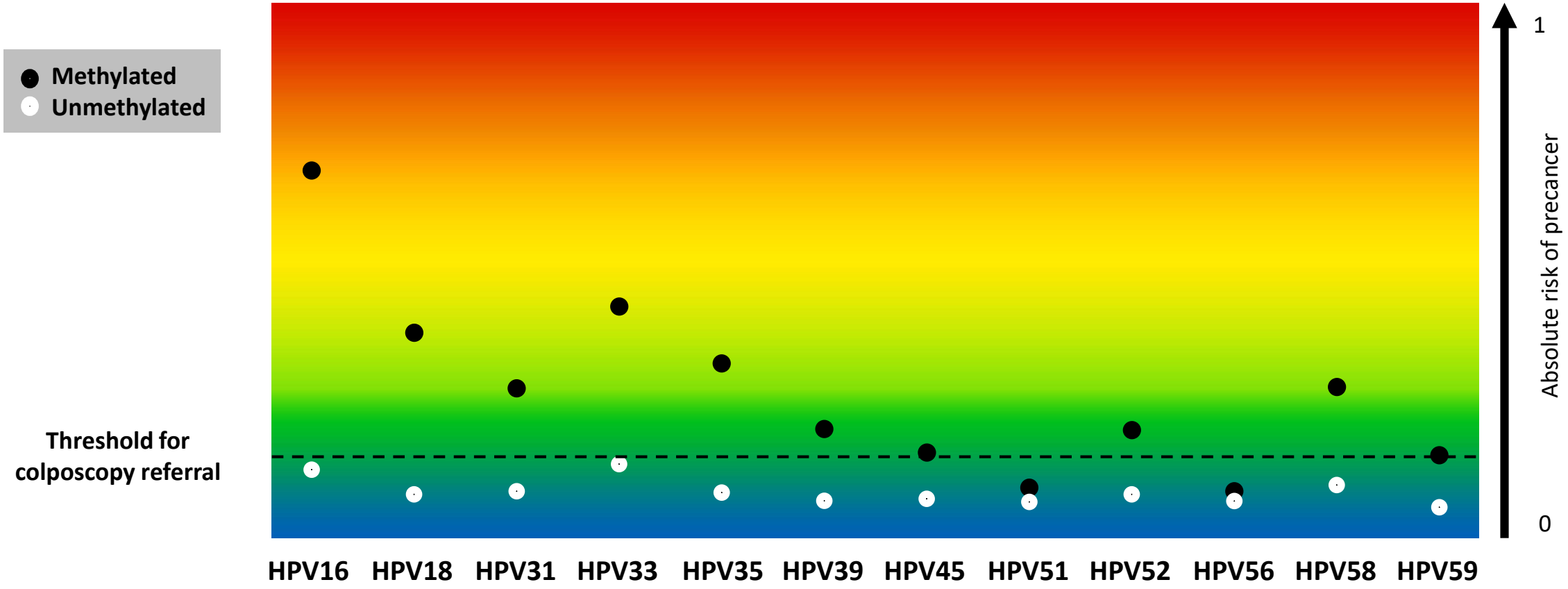
Methylation of the HPV genome

Albert Einstein College of Medicine



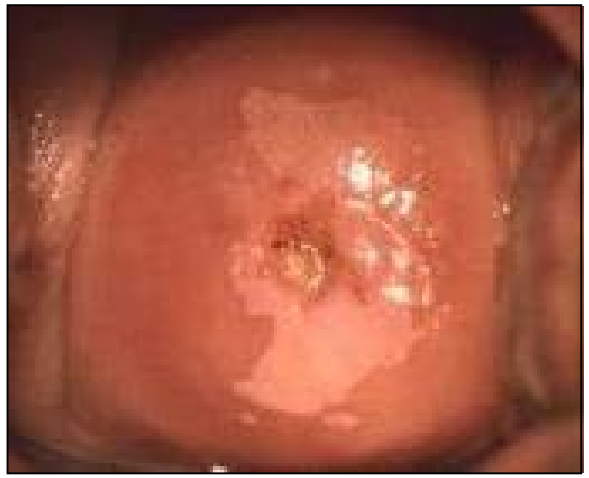
Wentzensen JNCI 2012, Mirabello JNCI 2012, Clarke CEBP 2013

Clinical performance of viral methylation



- Now developing an integrated NG-based HPV detection, genotyping and methylation assay
- Applications in high- and low-resource settings (self-sampling)

Visual triage



Low resource settings: Automated image analysis

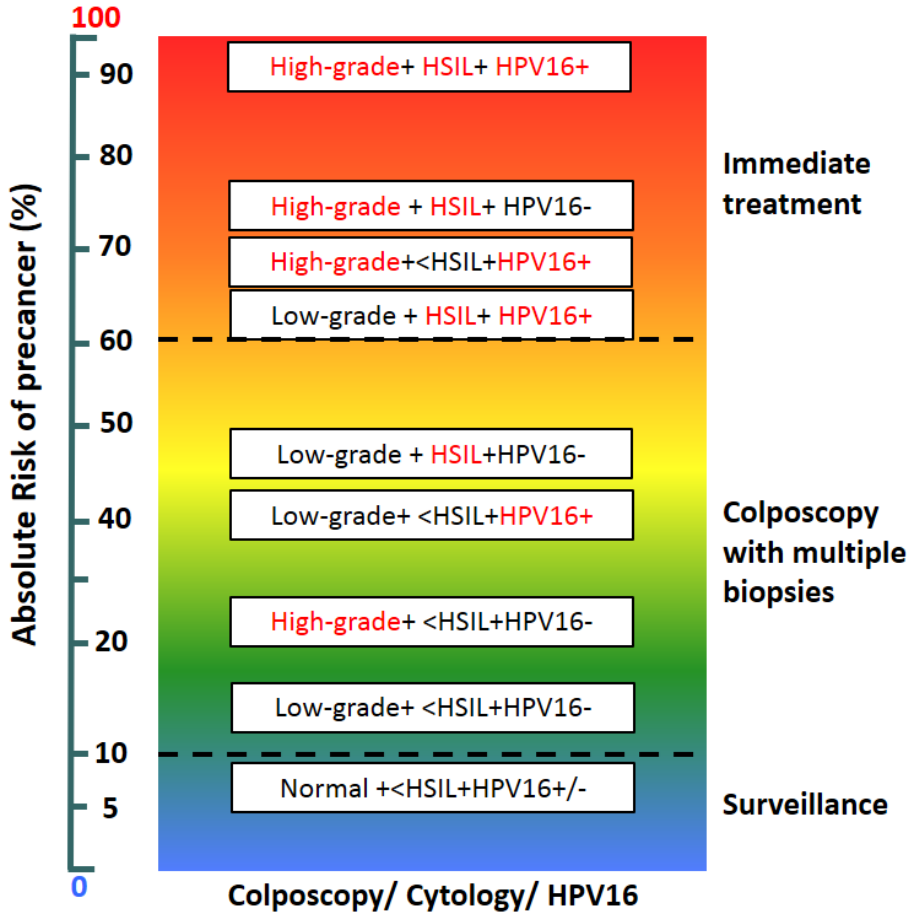
- NCI Colposcopy Image database(>100K)
  - Guanacaste Natural History Study
  - Costa Rica Vaccine Trial
  - ALTS Trial
  - Biopsy Study

- Evaluation sites
  - Rutgers University (Mark Einstein)
  - Nigeria
  - El Salvador

Machine Learning Challenge

Extramural partners, non-profits, companies

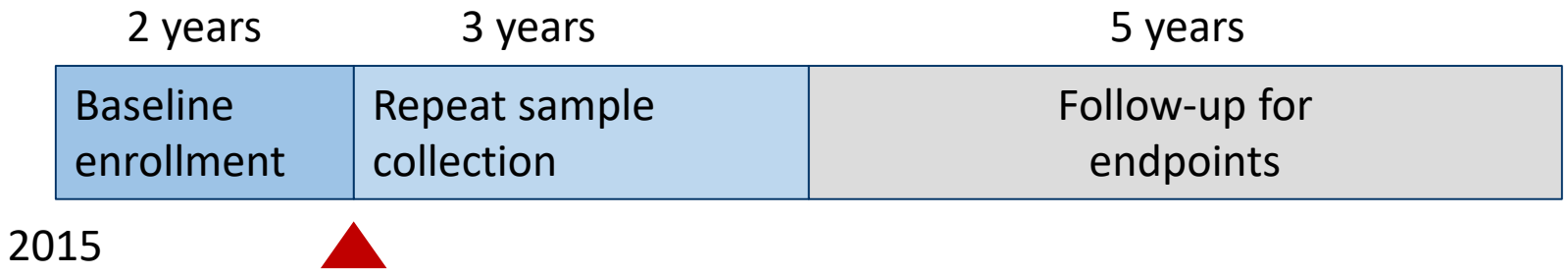
High resource settings: Improving colposcopy



- First US colposcopy guidelines were developed by a joint intramural-extramural effort and published in 2017
- NCI Biopsy Study provided key evidence for these recommendations

Large-scale evaluation of screening and triage strategies

Group	3-year risk of precancer	Sample	Expected precancers
HPV+	5%	50,000	2,500
HPV-/Pap+	0.5%	10,000	50
HPV-/Pap-	0.05%	10,000	5
Total		**70,000**	**2,555**



Improved Risk-Informed HPV Screening (IRIS): A large prospective study to evaluate biomarkers for cervical cancer screening, triage, and management nested in a large integrated healthcare system (Kaiser Permanente Northern California)

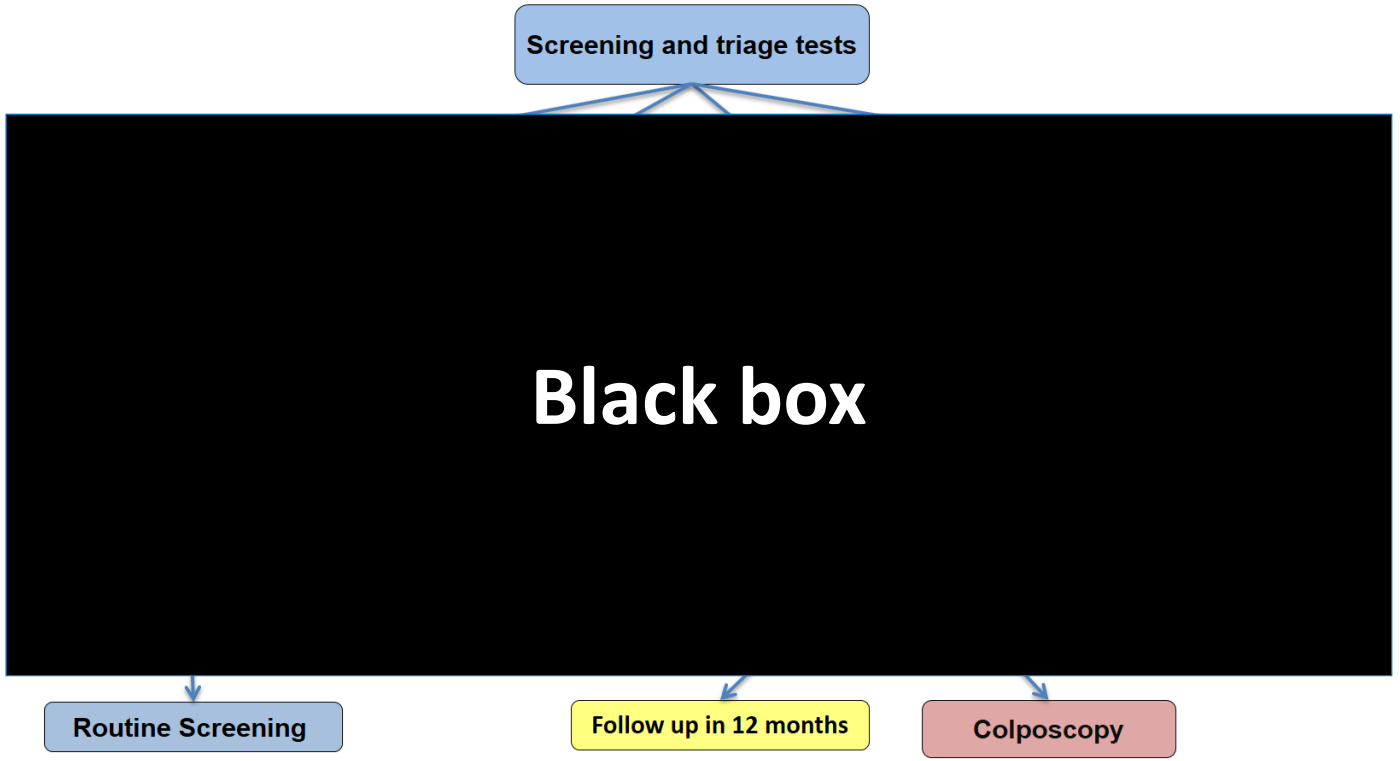
KAISER PERMANENTE®

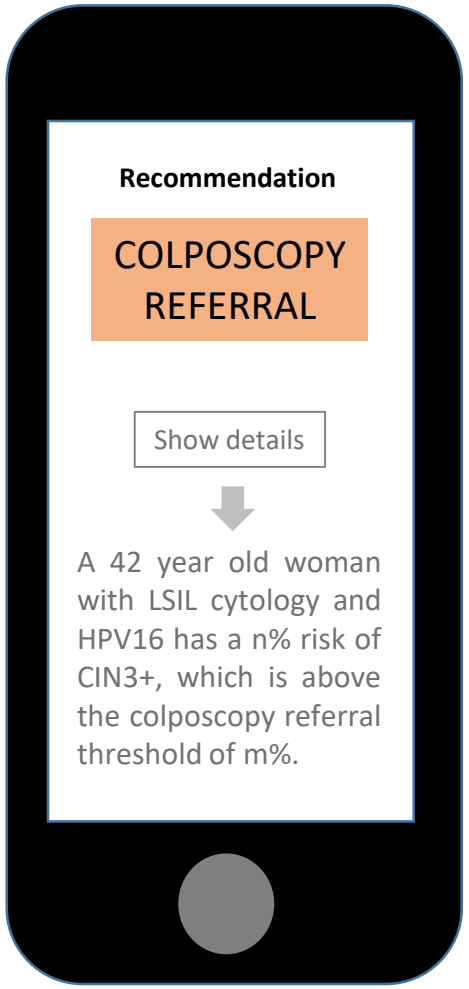
New screening and management guidelines for the US

Risk matrix:

Calculating risk of precancer for screening and triage tests

Setting risk-action thresholds

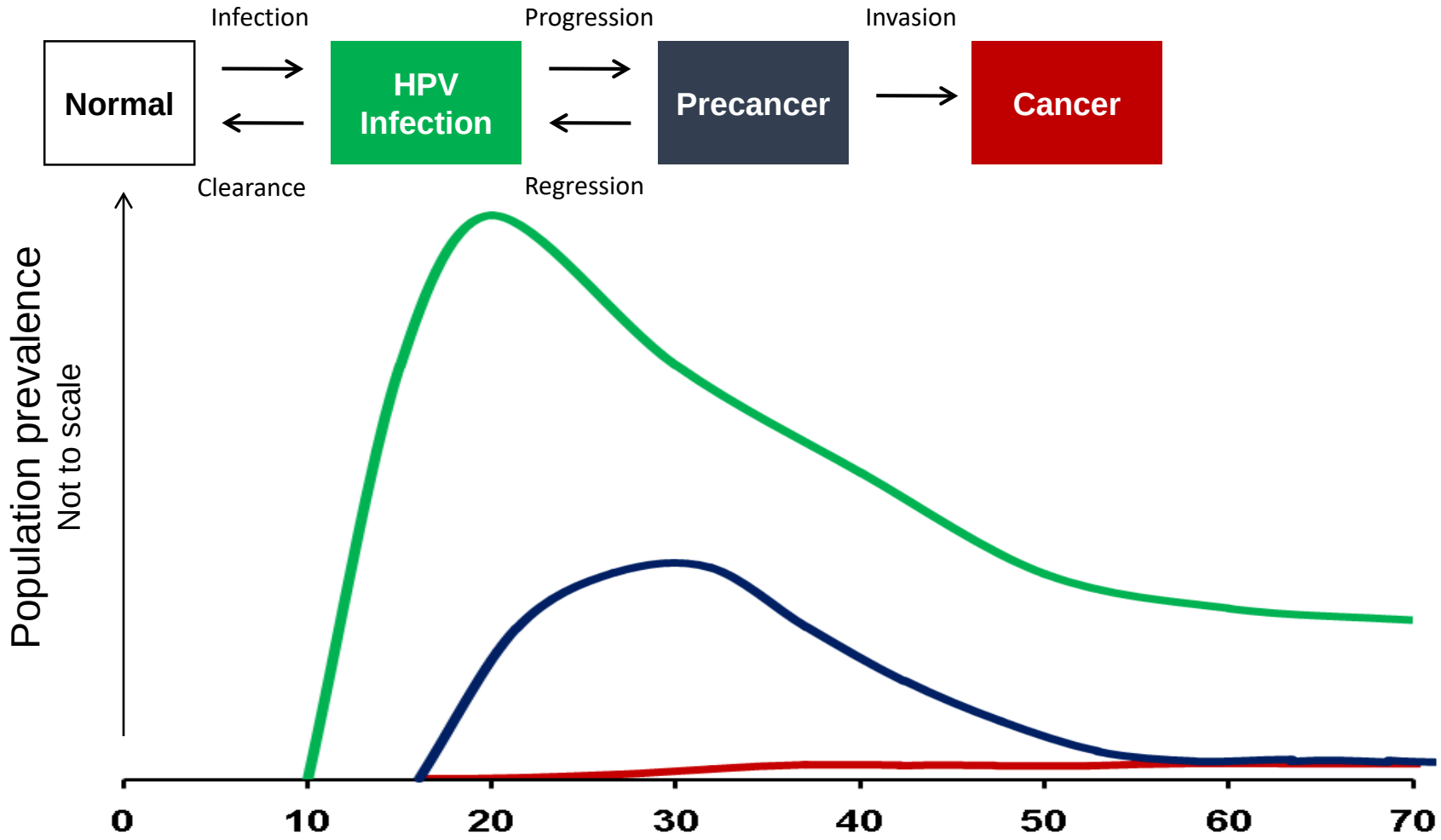




Collaboration between DCEG, ASCCP, CISNET, DCCPS

Recommendation

Integrating vaccination and screening: HPV-Faster



1-Dose Vaccination

HPV Screening and triage

Bosch 2015 Nat Rev Cancer

A comprehensive program for every setting