

Epidemiology of HPV and Cervical Neoplasia

Implications for Optimal Vaccination and Screening

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TISSUE: Cervix

- Best understood site of HPV infection
- For all sites where HPV causes cancer:

HPV +

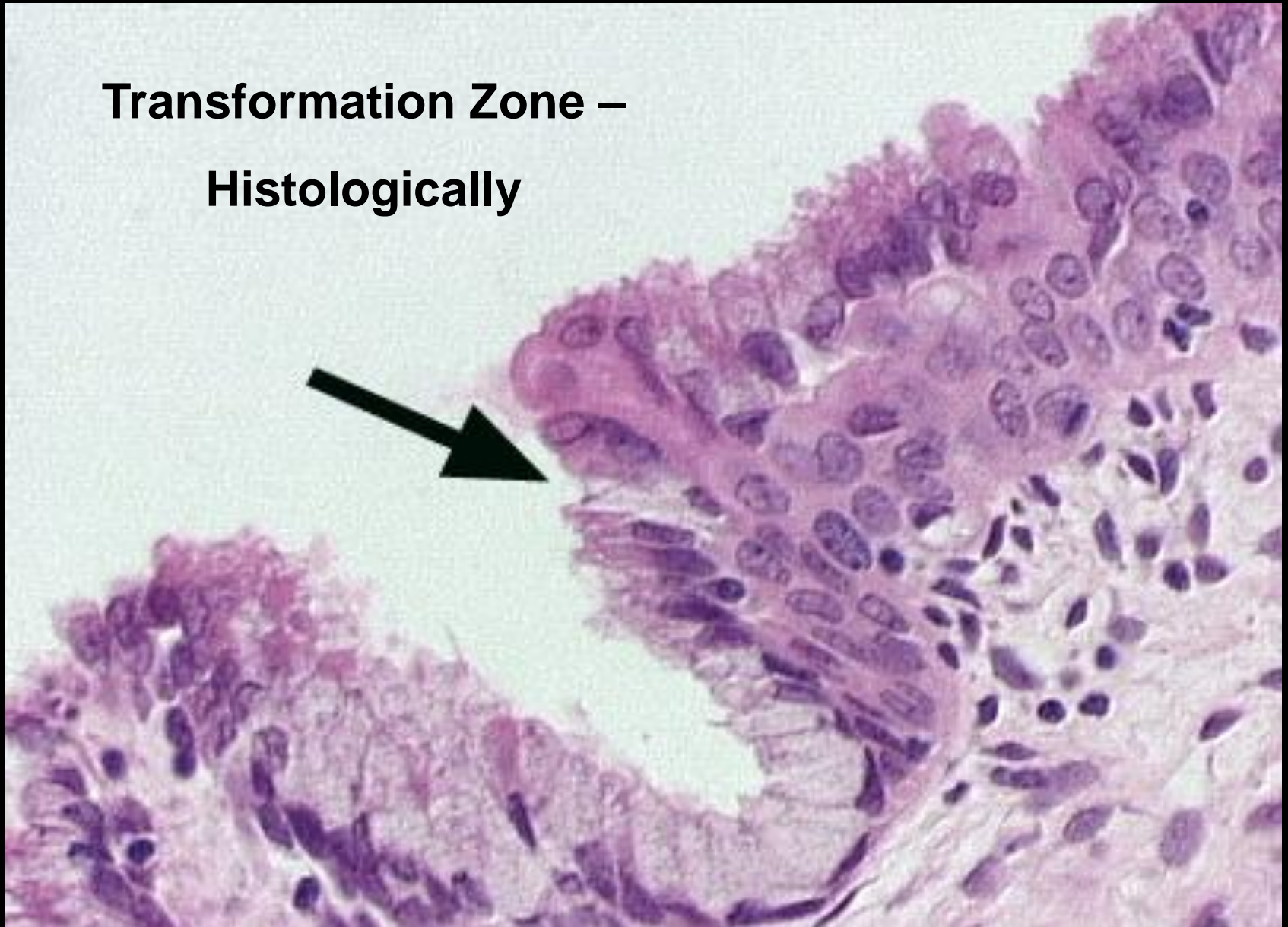
Transformation Zone =

Increased Risk of Carcinogenesis



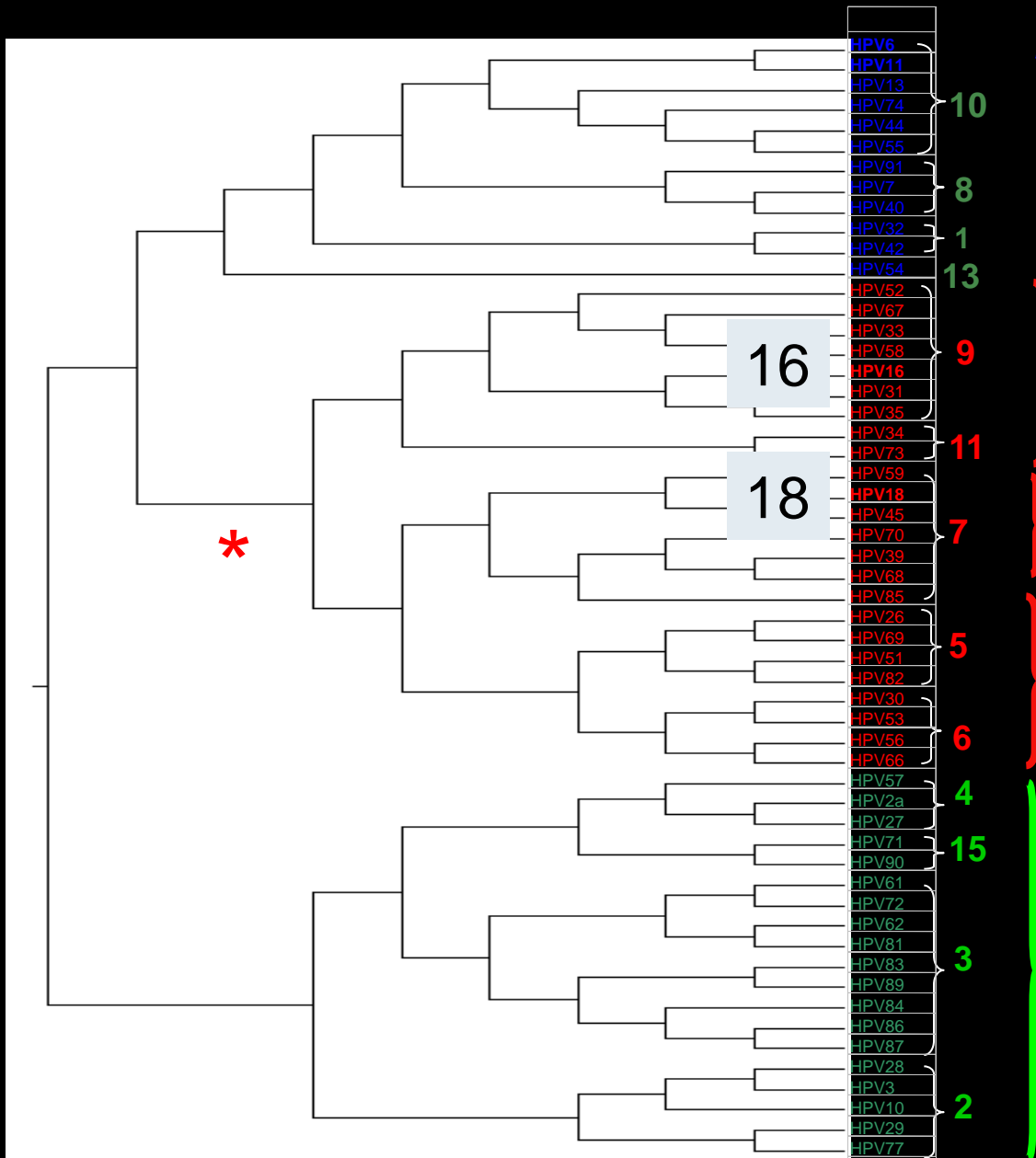
**Transformation
Zone -- Visually**

**Transformation Zone –
Histologically**



EXPOSURE: HPV

Evolutionary Tree
(millions of years) →



α1, 8, 10, 13
Genital Warts

α5, 6, 7, 9, 11
Carcinoma &
Precursors

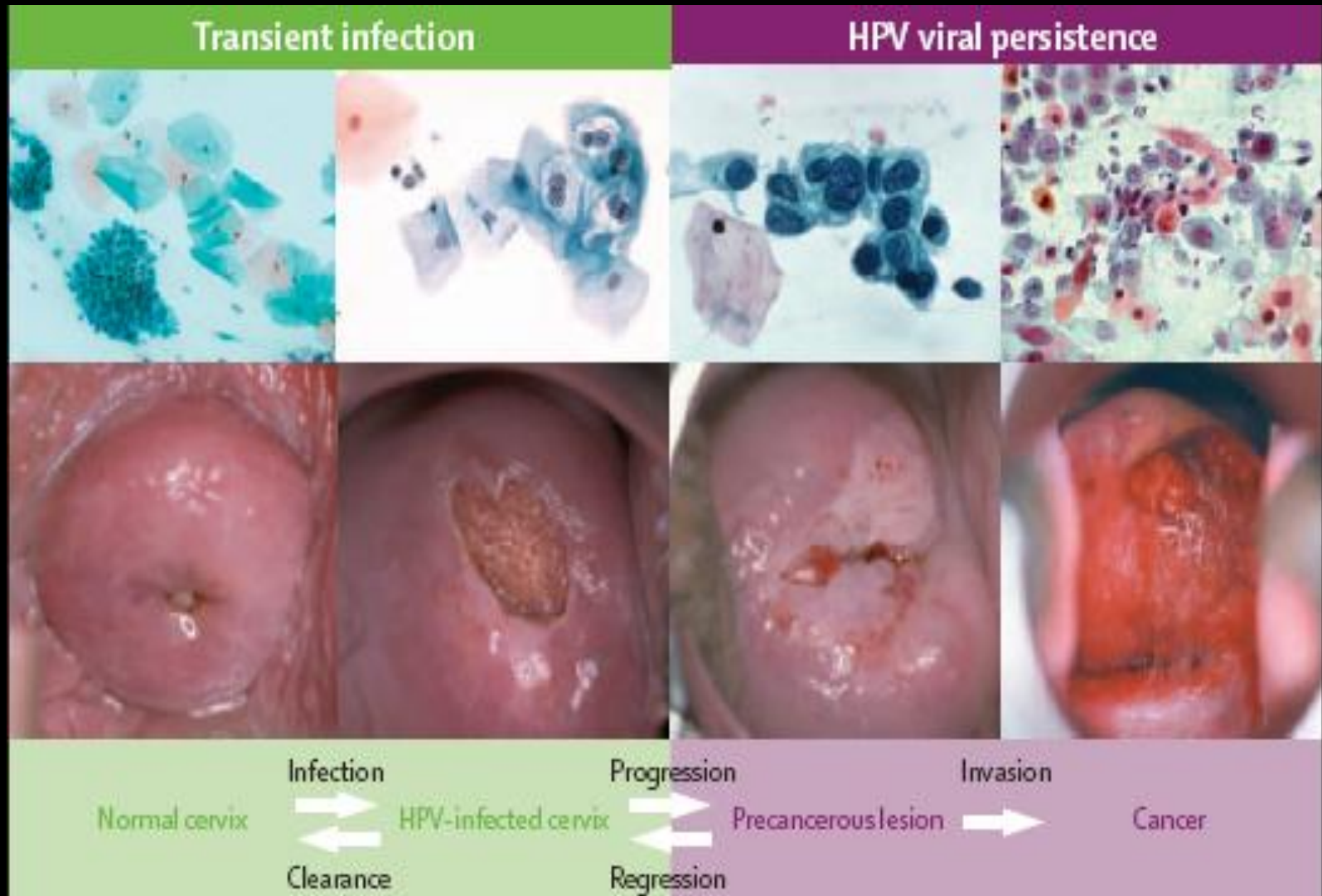
α2, 3, 4, 15
Commensal
Infections

Burk,

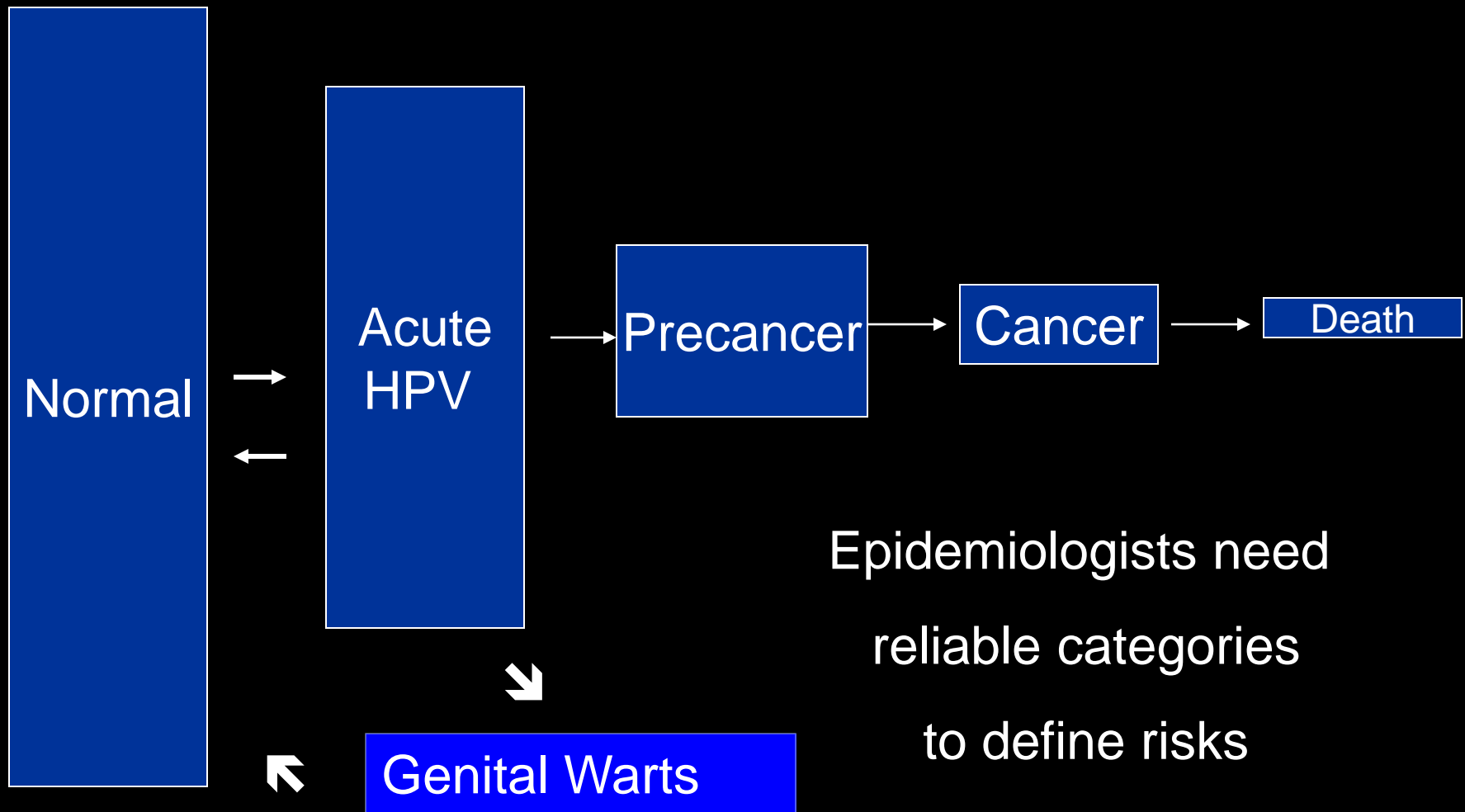
Virology 2005

DISEASE: Cervical Precancer and Cancer

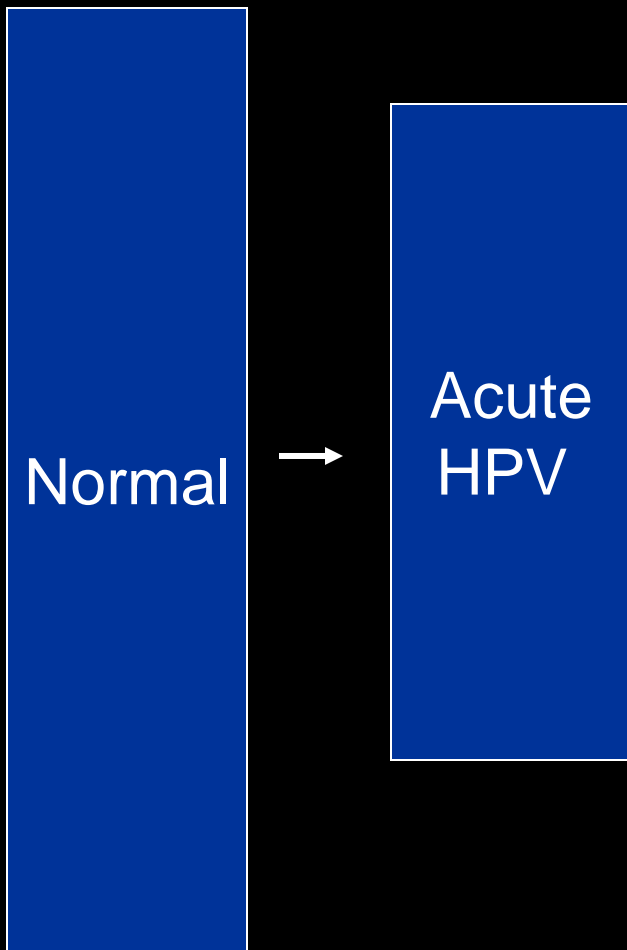
Peak Ages: 15-25 25-35 45-50



Epidemiologists Define Critical Steps From Normal to Cancer

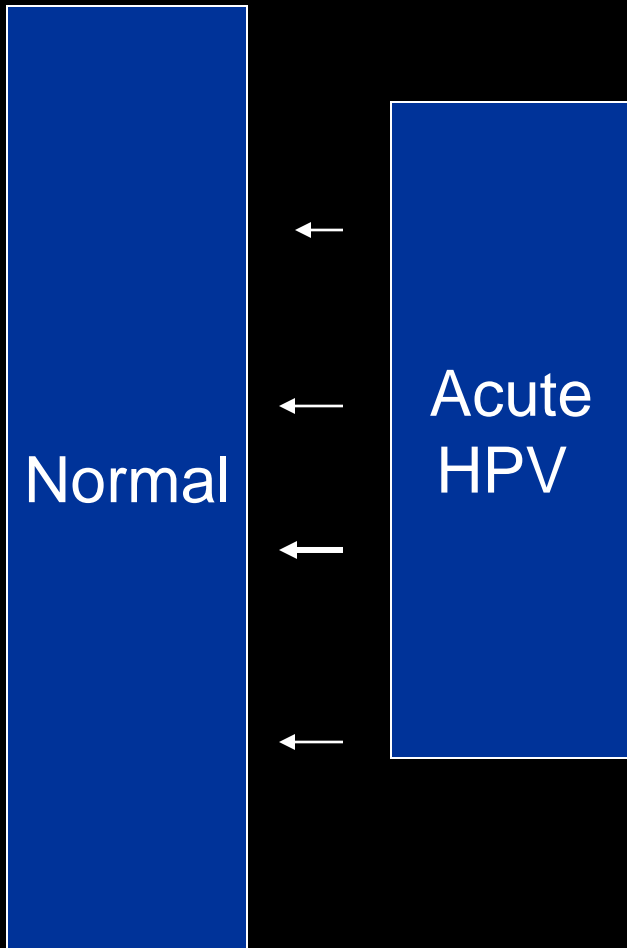


The First Step is HPV Infection

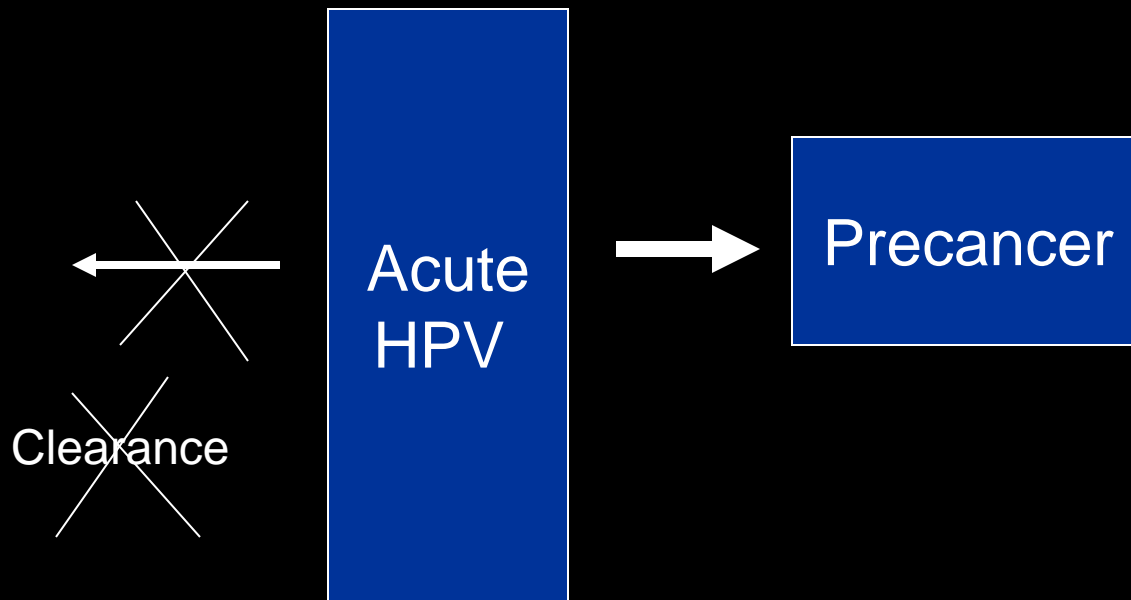


- Easily transmitted
- Each **infection** is independent
- A **woman** can have several, at the same or different times
- The peak incidence in a **population** is usually at young ages

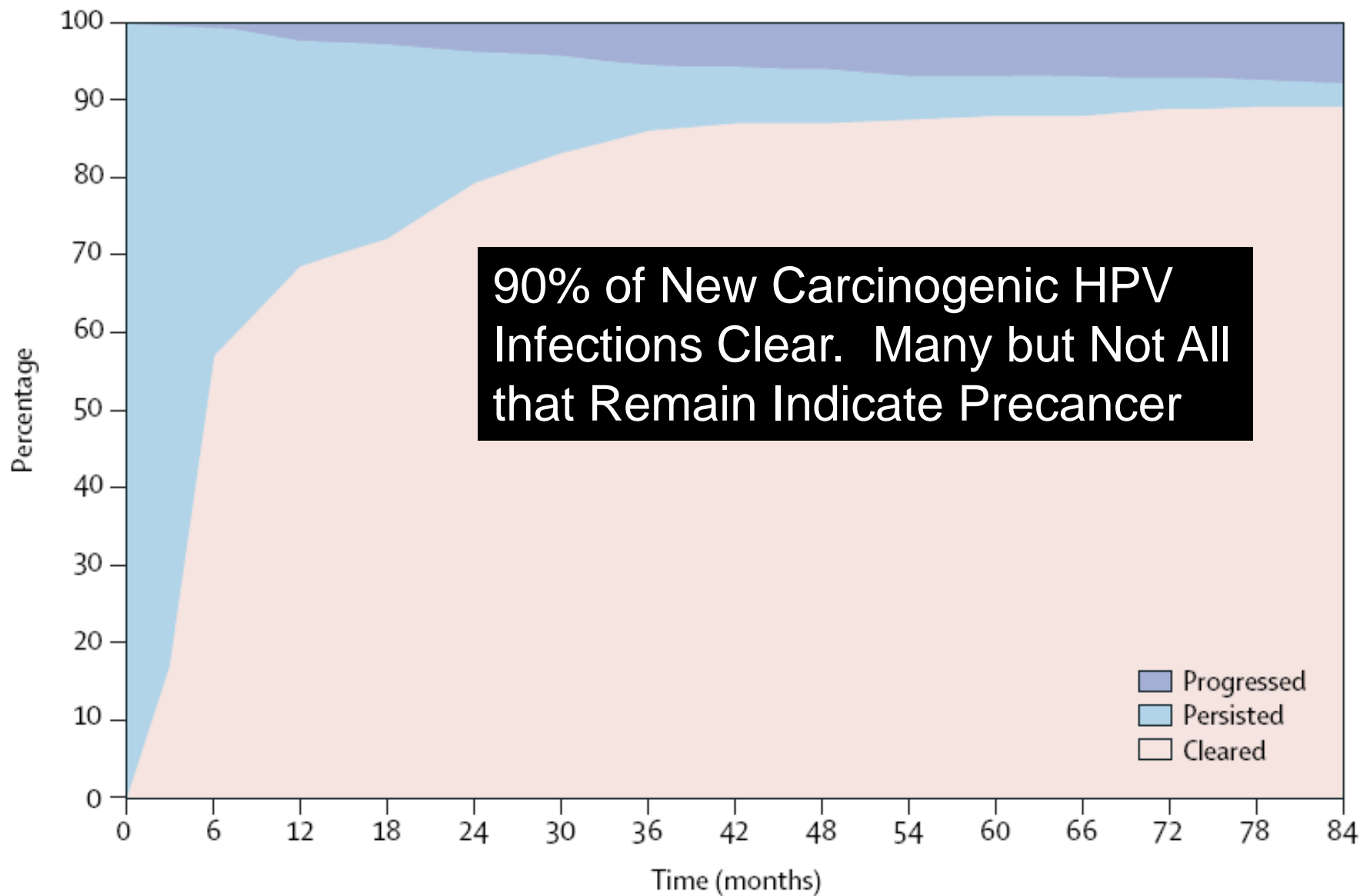
Rapid Clearance is the Rule



Persistence is Highly Associated with Risk of CIN3

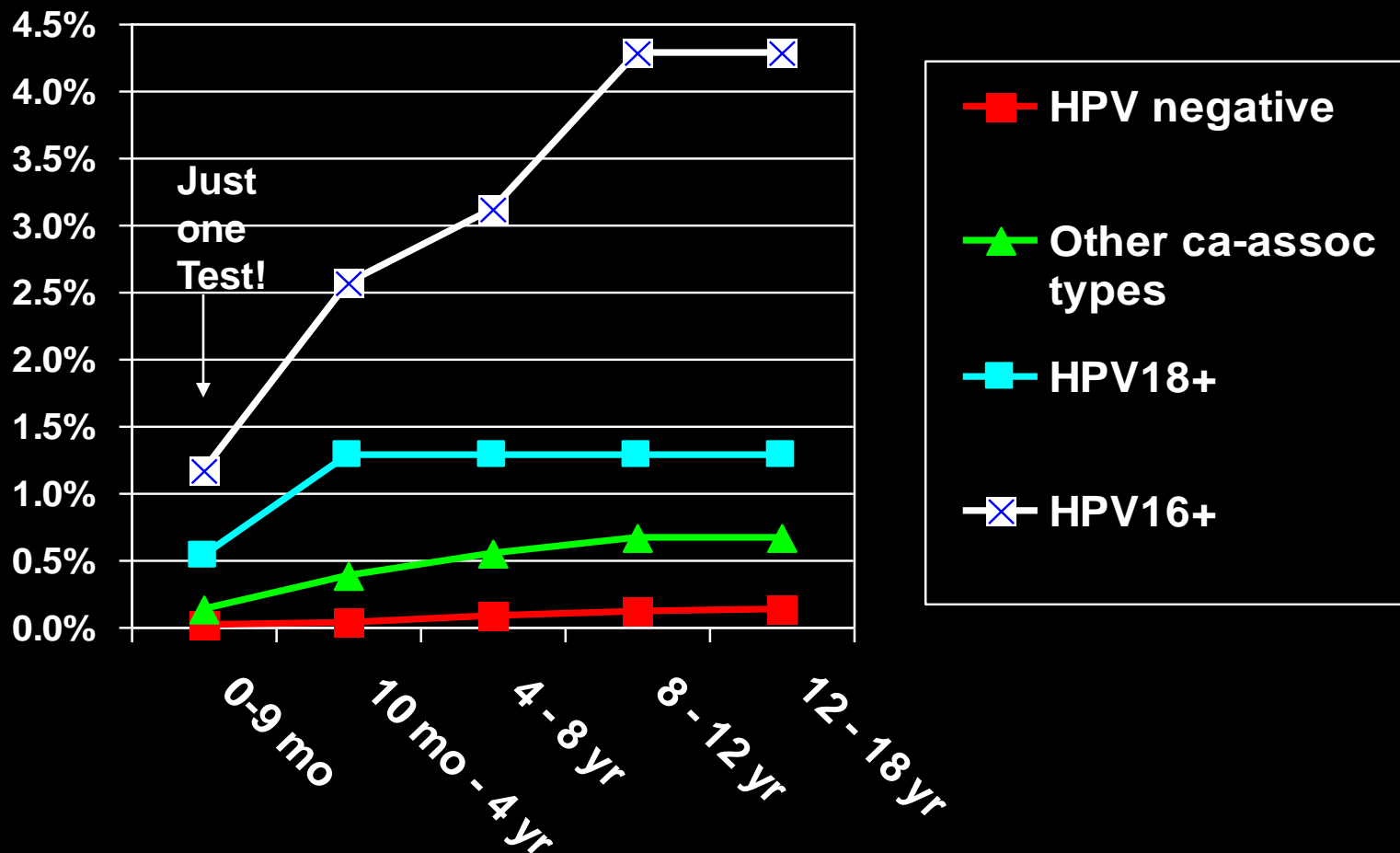


- **Overt Persistence** is key risk factor for precancer
- HPV type very important
- Co-factors like smoking or parity less important



Guanacaste Cohort (Rodriguez, JNCI 2007)

Kaiser Portland HPV Study (23,000 Women) Cumulative Risk of **Cancer**, by HPV Type



Prospective Study of Cancer **Death**

| | Cancer | Death |
|------------|------------|-------|
| HPV neg | 8 / 24,000 | 0 |
| HPV pos | 87 / 2,800 | 12 |



8 year follow-up in
randomized trial
(130,000 women)

HPV arm of trial

Sankaranarayanan,
NEJM, 2009

Clinical Viewpoint: Adapting to New Knowledge of HPV

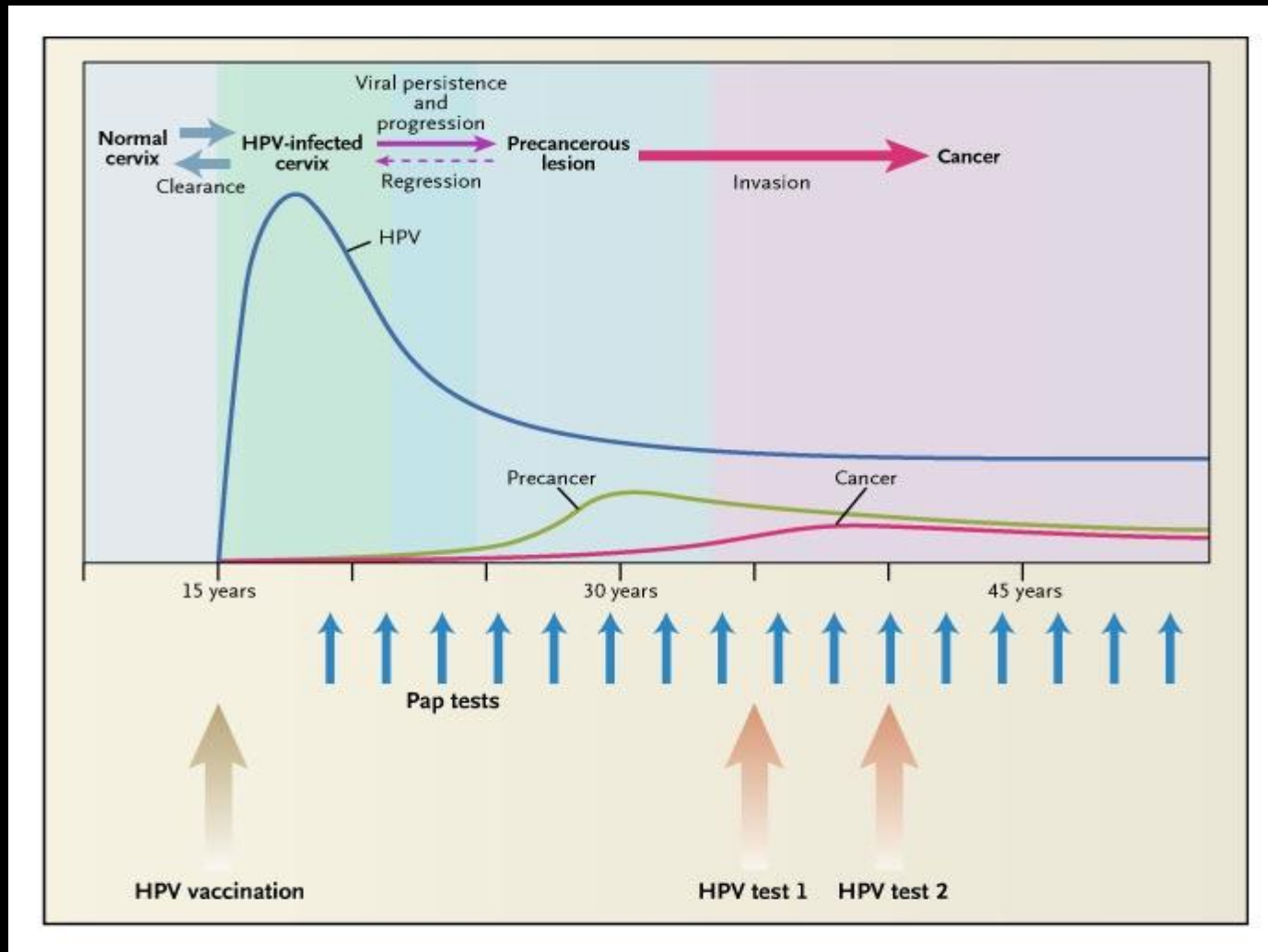
Parts of “Old” Prevention Strategy

- Pap smear
- Colposcopic impression if Pap abnormal
- Biopsy if needed
- Treatment of CIN
- Follow-up
- Cytology, colposcopy, and biopsy have been great successes. We can now do even better.

HPV Testing: Major Randomized Trials

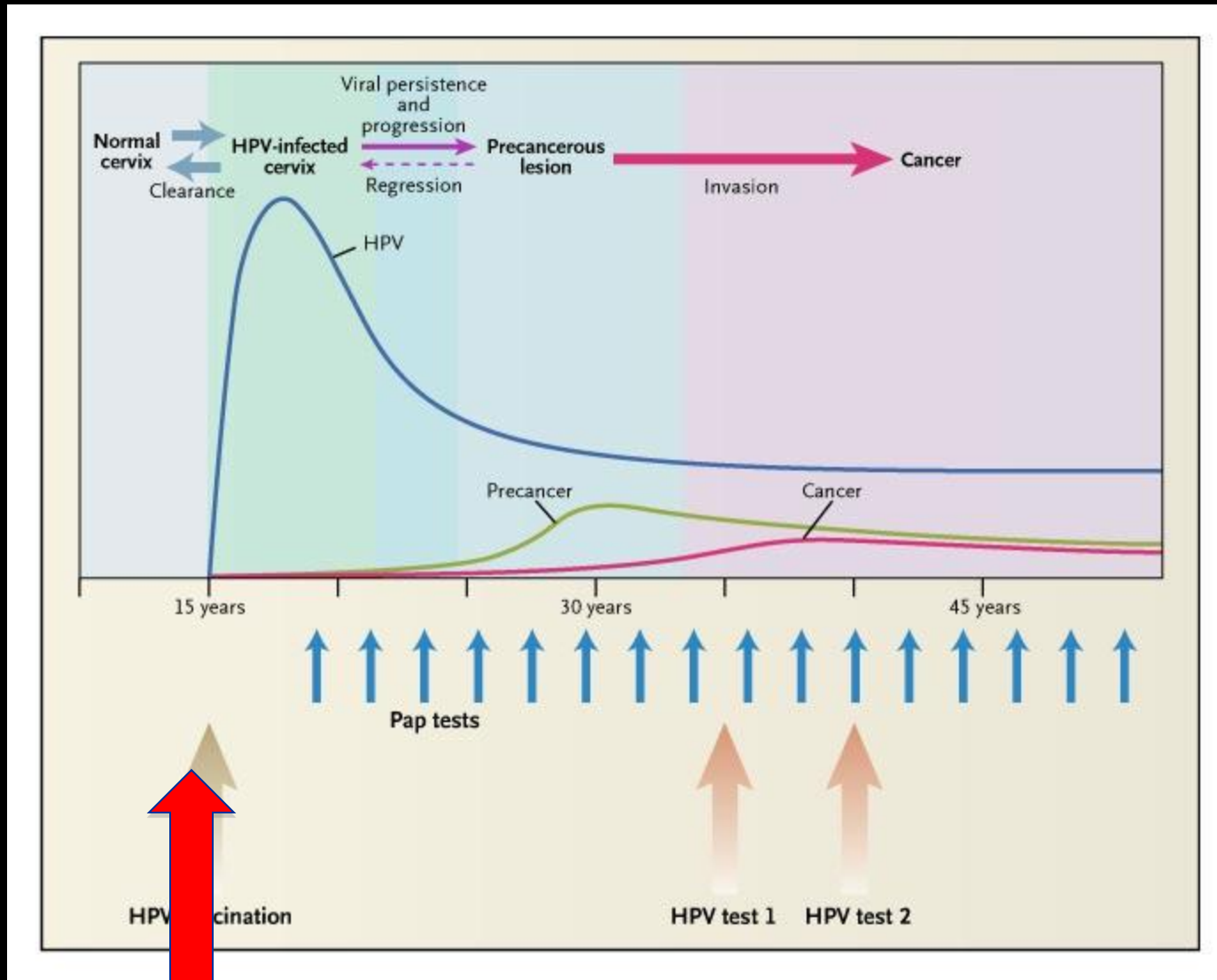
- All published in 2007-9
 - New England Journal, Lancet, J Natl Cancer Institute
- Show screening with HPV tests is more sensitive for early detection of CIN3 than cytology
- HPV testing with or followed by cytology might be useful in some places, or other triage tests might be used
- In low-resource regions, screen-and-treat?
- New IARC Study in India by Sankaranarayanan et al. is a landmark study

Cervical Cancer Prevention Efforts Should Fit Age Patterns in Natural History



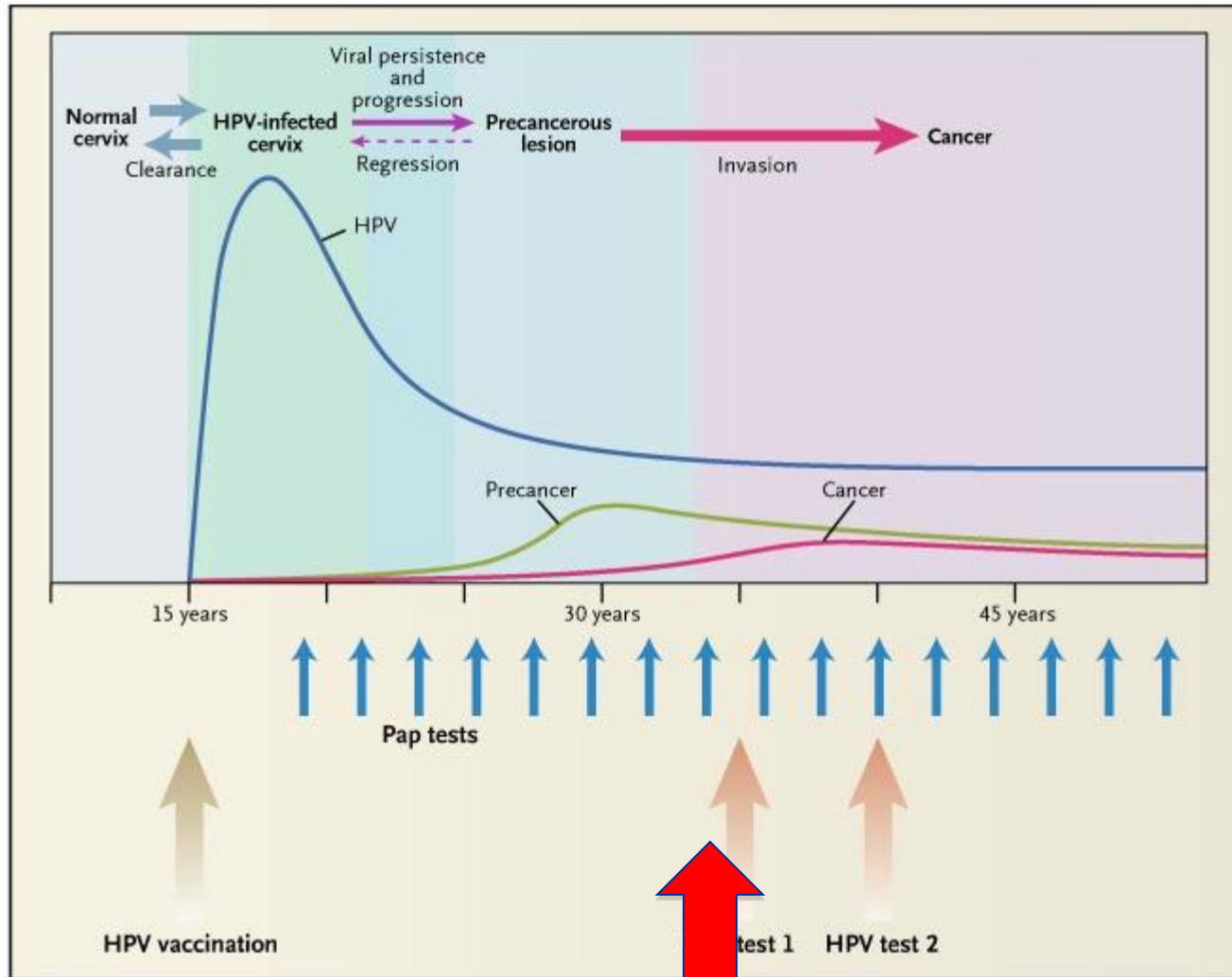
Schiffman and Castle, NEJM, 2006

If We Can Afford to Vaccinate...



Vaccinate **before** the peak of incidence, because the vaccines are preventive, and they do not work after infection occurs

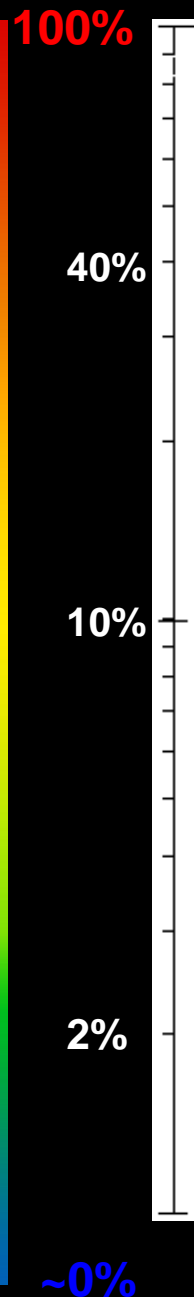
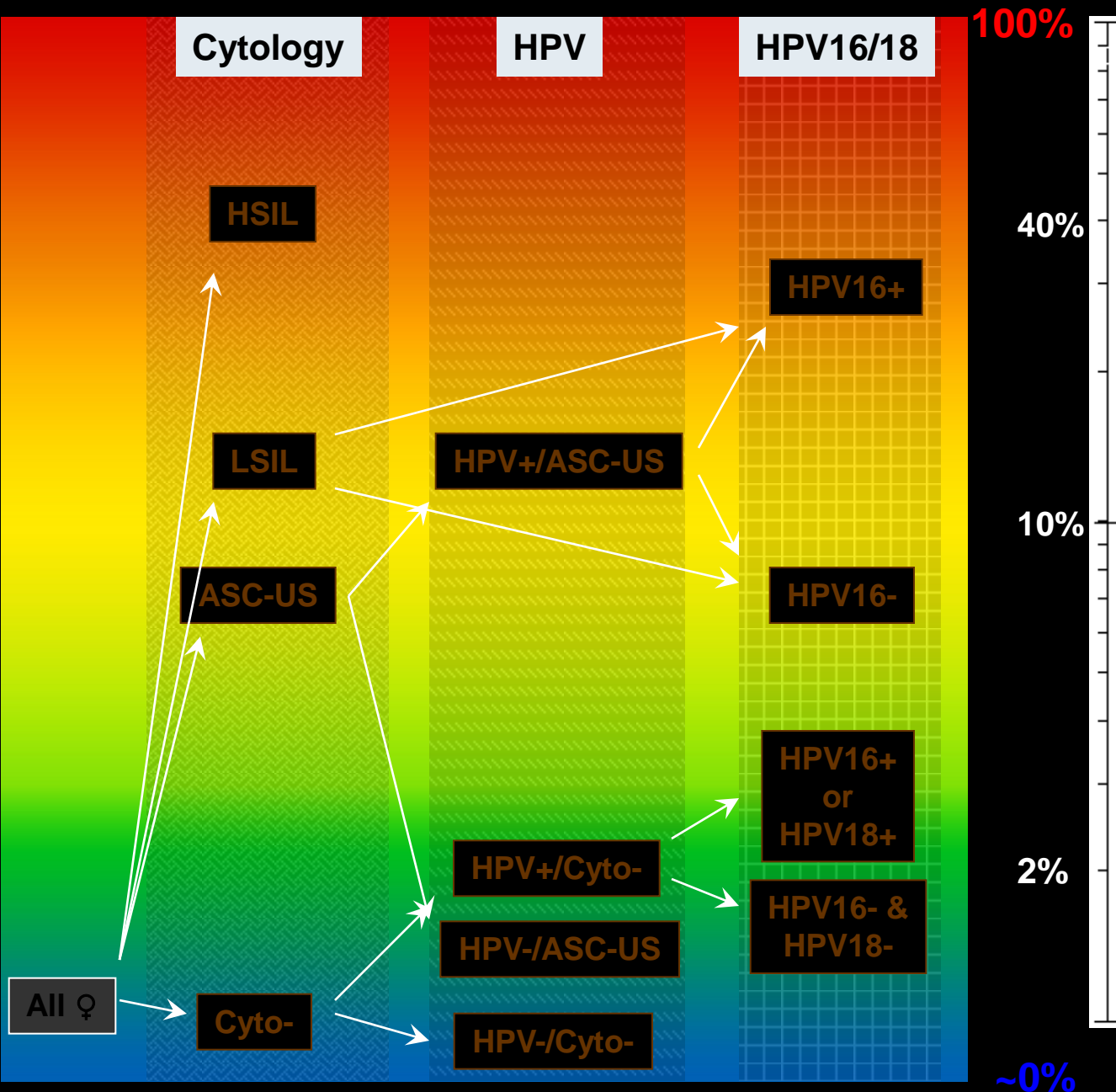
If We Screen with Limited Resources...



Screen **after** the peak of incidence, to improve specificity and positive predictive value

Defining a New Clinical View of Cervical Carcinogenesis

There are many tests which,
alone or combined, predict
similar levels of risk



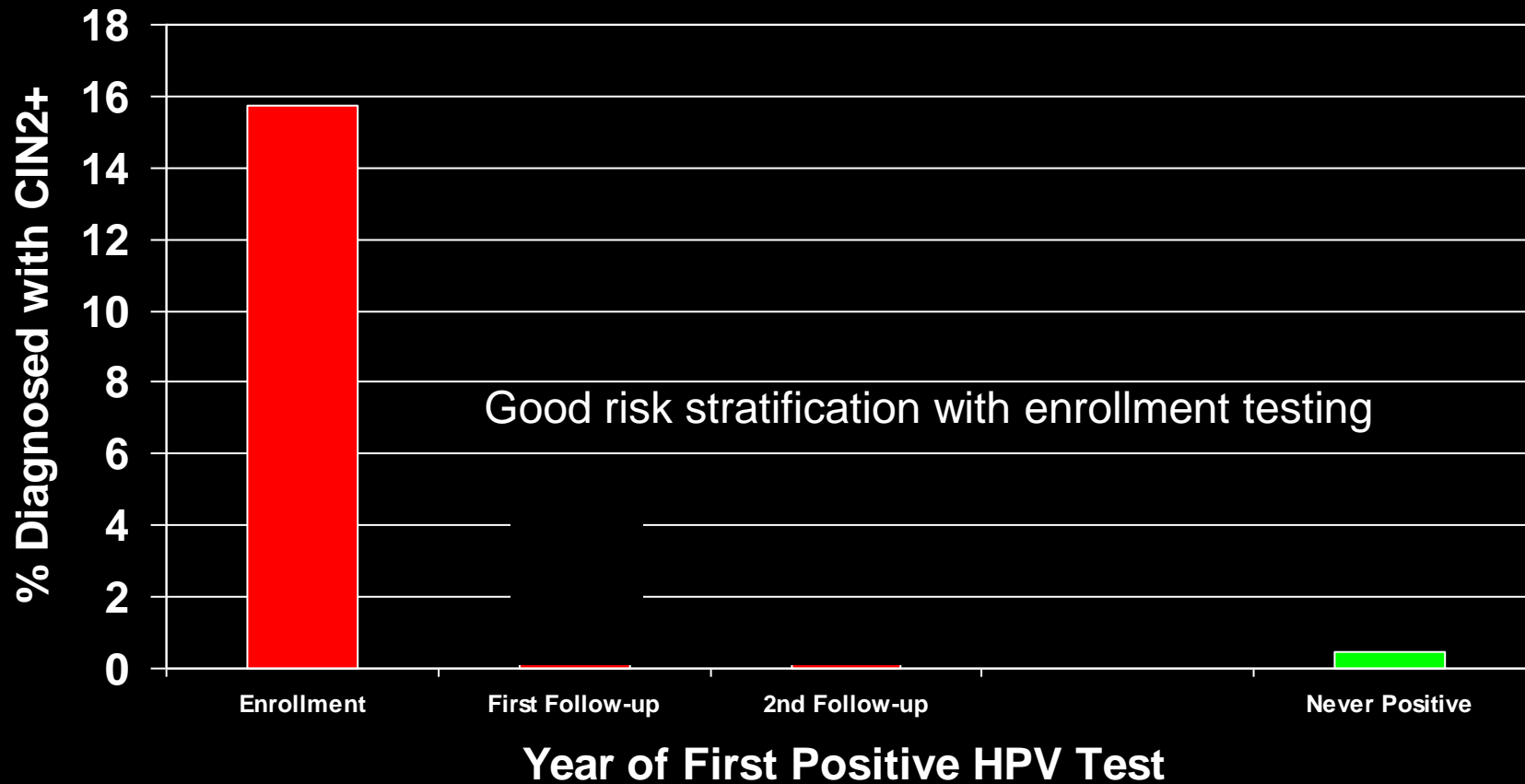
— Increasing 2-Yr. Risk of Precancer (CIN3) —>

“Risks”
Are
Simpler
To Use
Than
Algorithms

Don't Screen Too Often with HPV

(5-year cumulative incidence of CIN2+

following first HPV detection)



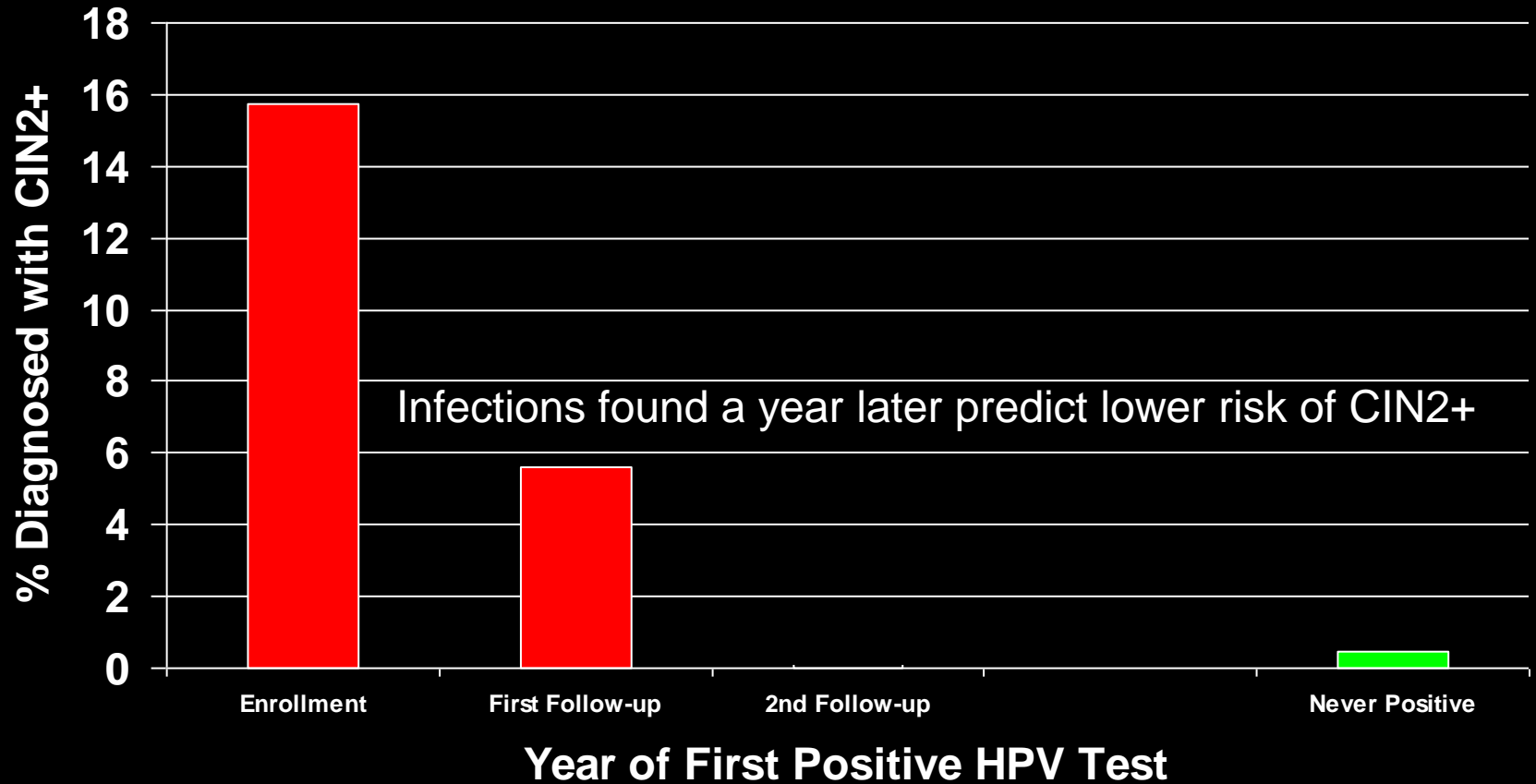
N 1324

6626

Don't Screen Too Often with HPV

(5-year cumulative incidence of CIN2+

following first HPV detection)



N 1324

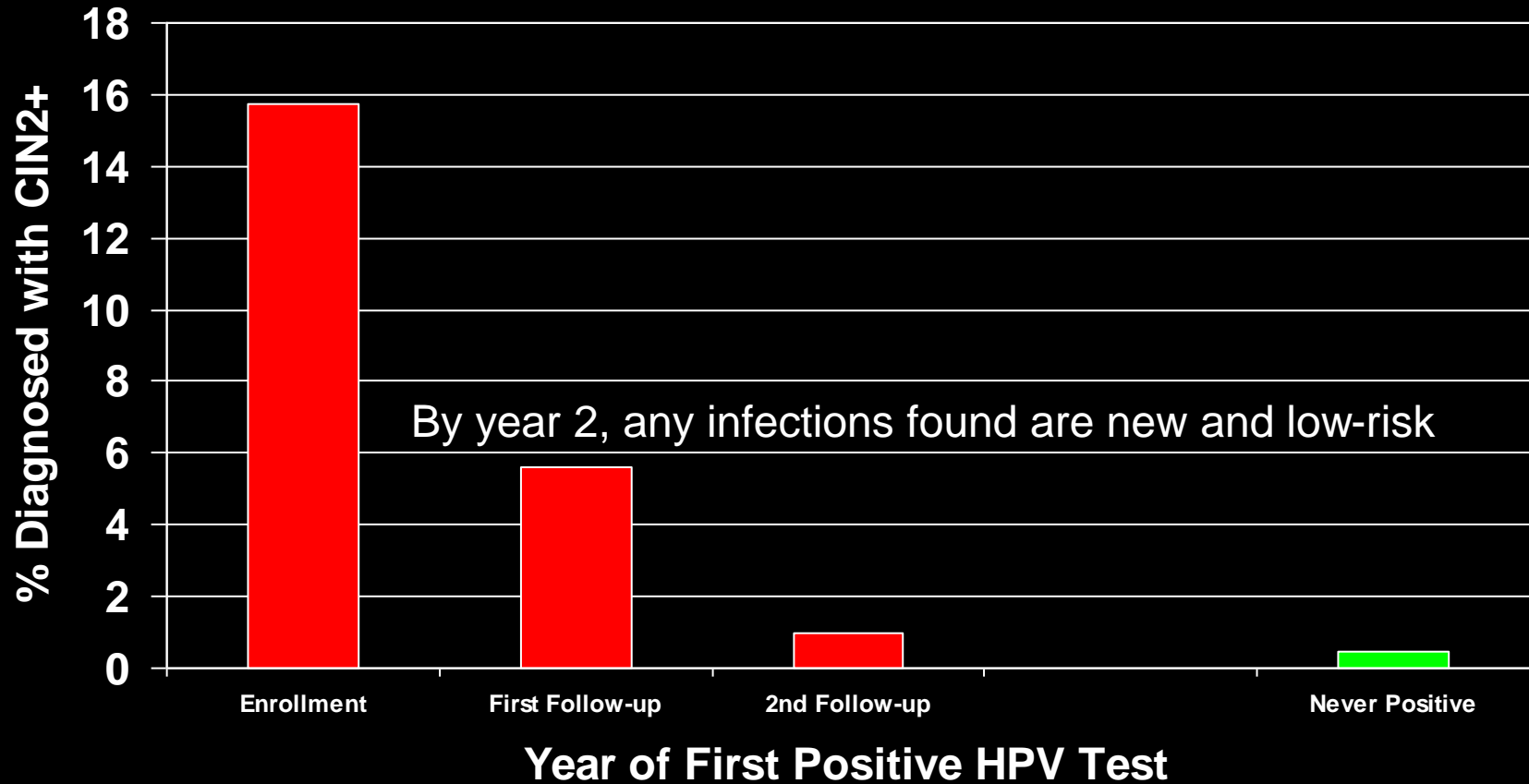
288

6626

Don't Screen Too Often with HPV

(5-year cumulative incidence of CIN2+

following first HPV detection)



N 1324

288

203

6626

Concluding Predictions

- Even better vaccines
- Decreased role for algorithms based on cytology, colposcopy and **targeted** biopsy
- More reliance on HPV-related tests and risk stratification to define management
- We need good epidemiology to inform new strategies