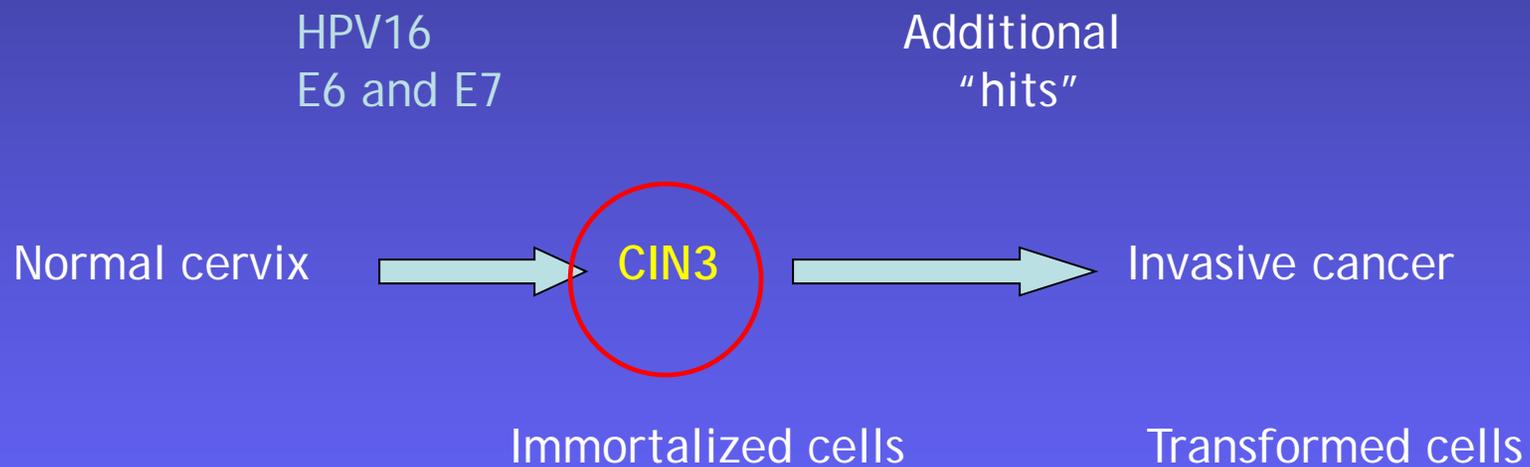


Center for Cervical
Disease
at Johns Hopkins
CL Trimble, MD

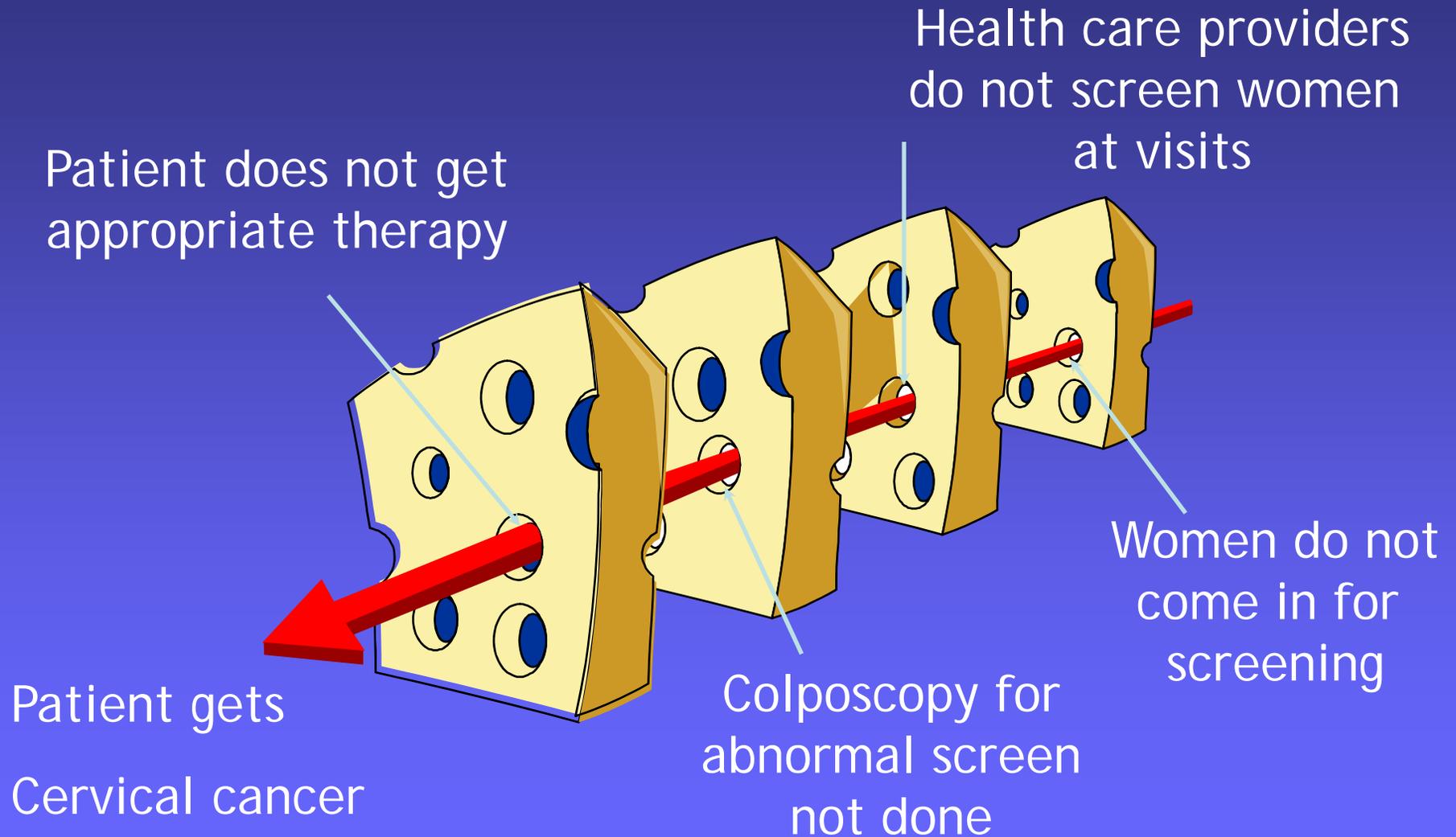
Fast facts: cervical cancer

- Cervical cancer is preventable
- Cervical cancer is the second leading cancer killer of women worldwide
- Cervical cancer happens in the setting of a common viral infection
- Cervical disease is more common in women of lower socioeconomic means
- Cigarette smoking triples the risk of cervical disease

Persistent HPV infection Cervical cancer



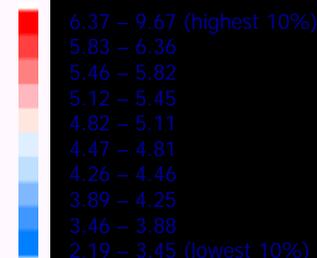
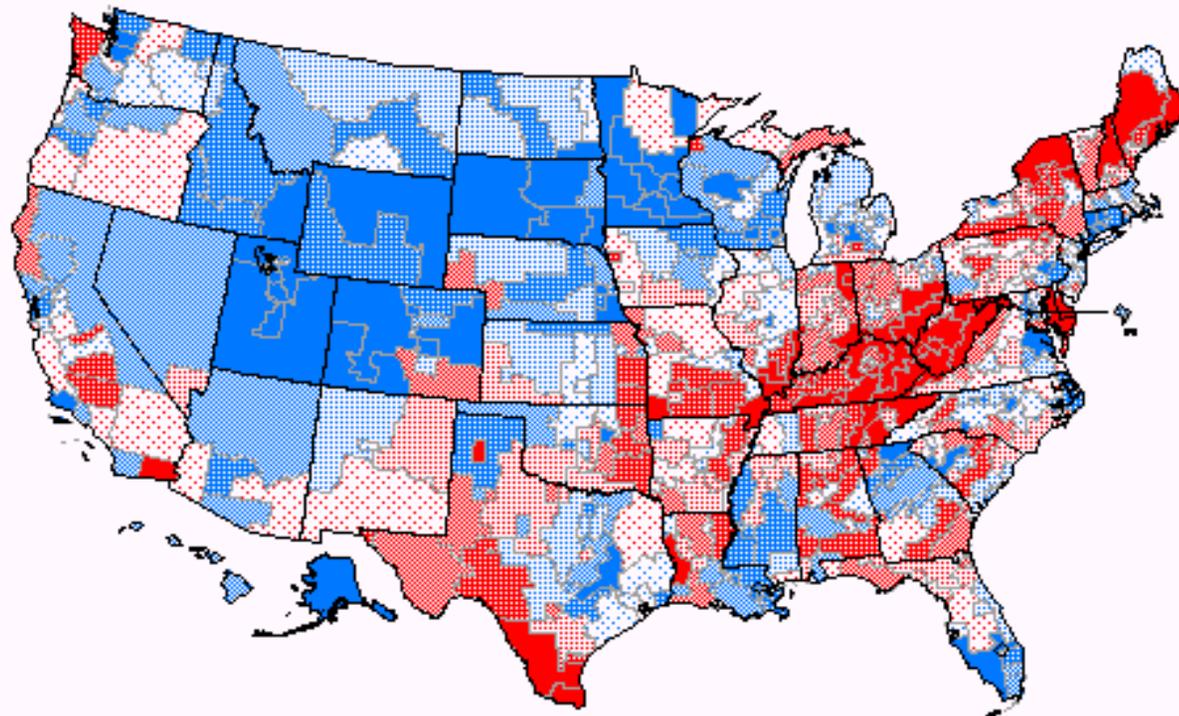
System Failures leading to Cervical Cancer Diagnosis



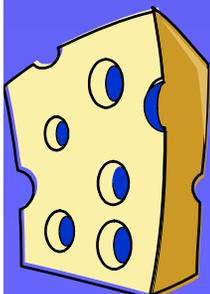
Source: P Pronovost

Cervical Cancer Mortality Rates by SEA (Age-adjusted 1970 US Population): White Females, 1950-1998

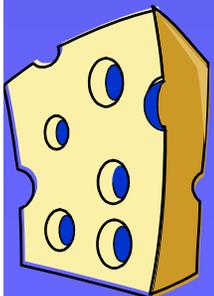
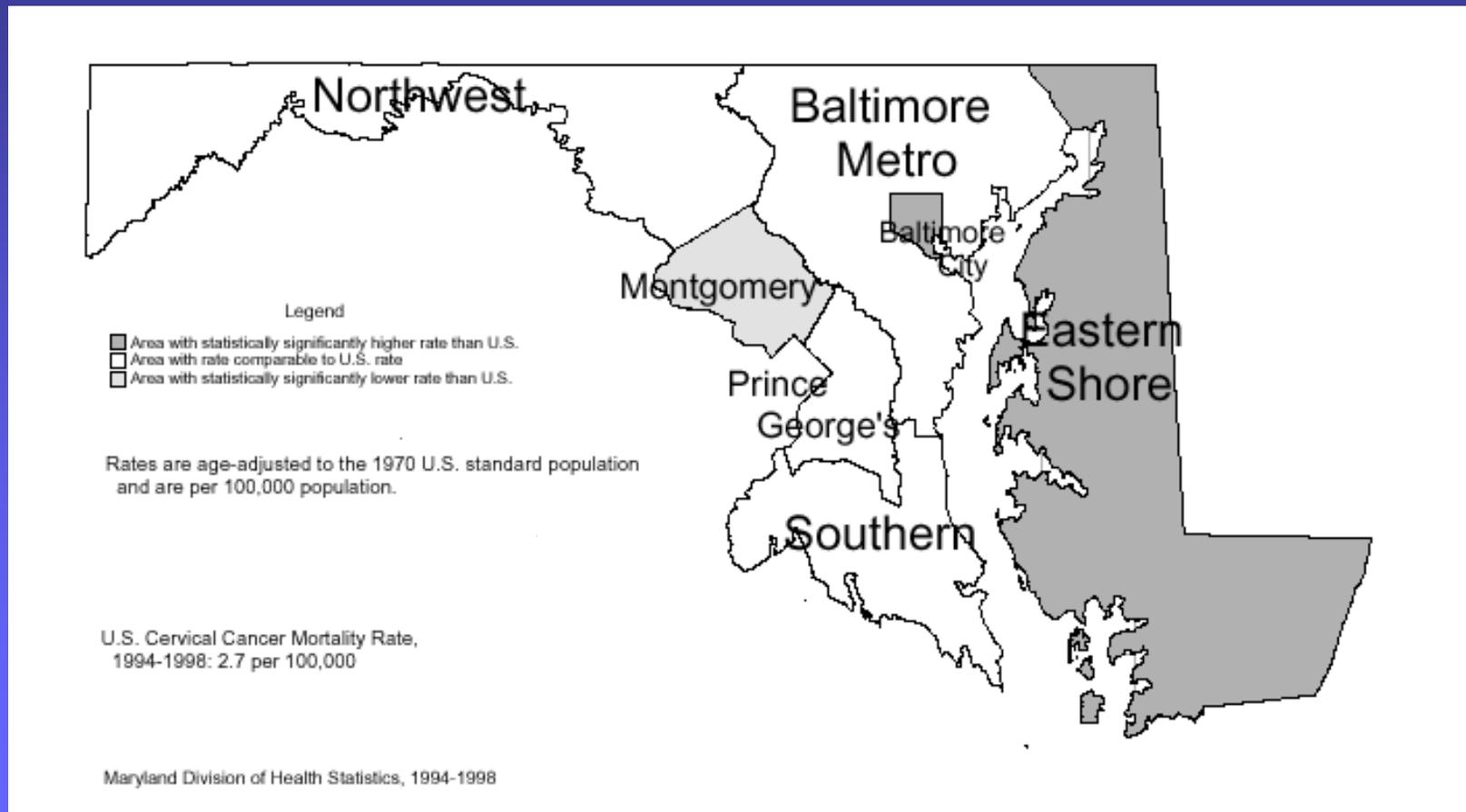
U.S. rate = 4.64 / 100,000



Jon Kerner, PhD. Division of Cancer Control, NCI



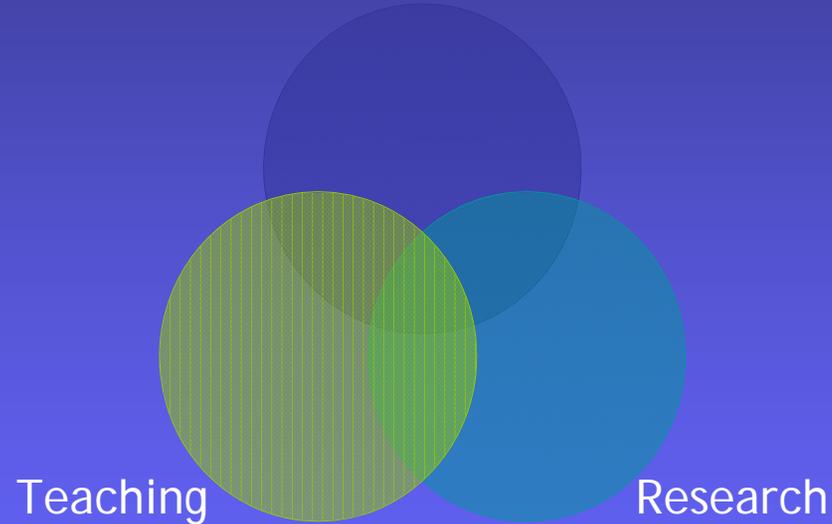
Maryland Cervical Cancer Mortality Rates by Geographical Area: Comparison to U. S. Rates, 1994- 1998



Source: Maryland Cancer Plan Web Site

Johns Hopkins Center for Cervical Disease

Patient care/outreach



Objectives: Maryland Cancer Plan

6.1: Conduct a follow-back study to determine factors that contribute to women developing and/or dying from invasive cervical cancer.

- different screening strategies
- different treatment algorithms

Retrospective Cohort Review of JHH and JHBMC patients with Squamous Cervical Cancer between 1984-2002

Women with Diagnosis
Squamous Cell
Carcinoma
Of Cervix

Socio-
Demographics?

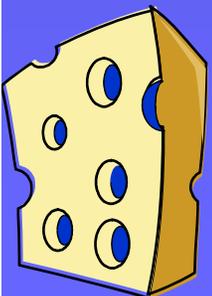
Who are they?

Medical, Gyn, and
Sexual history?

What happened?

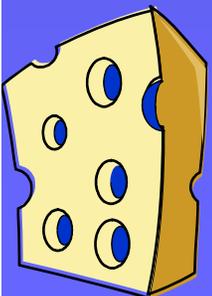
Barriers to Care /
Barriers to Access?

Why?

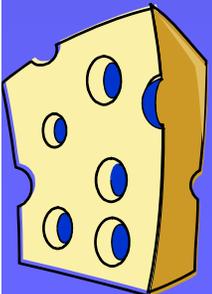
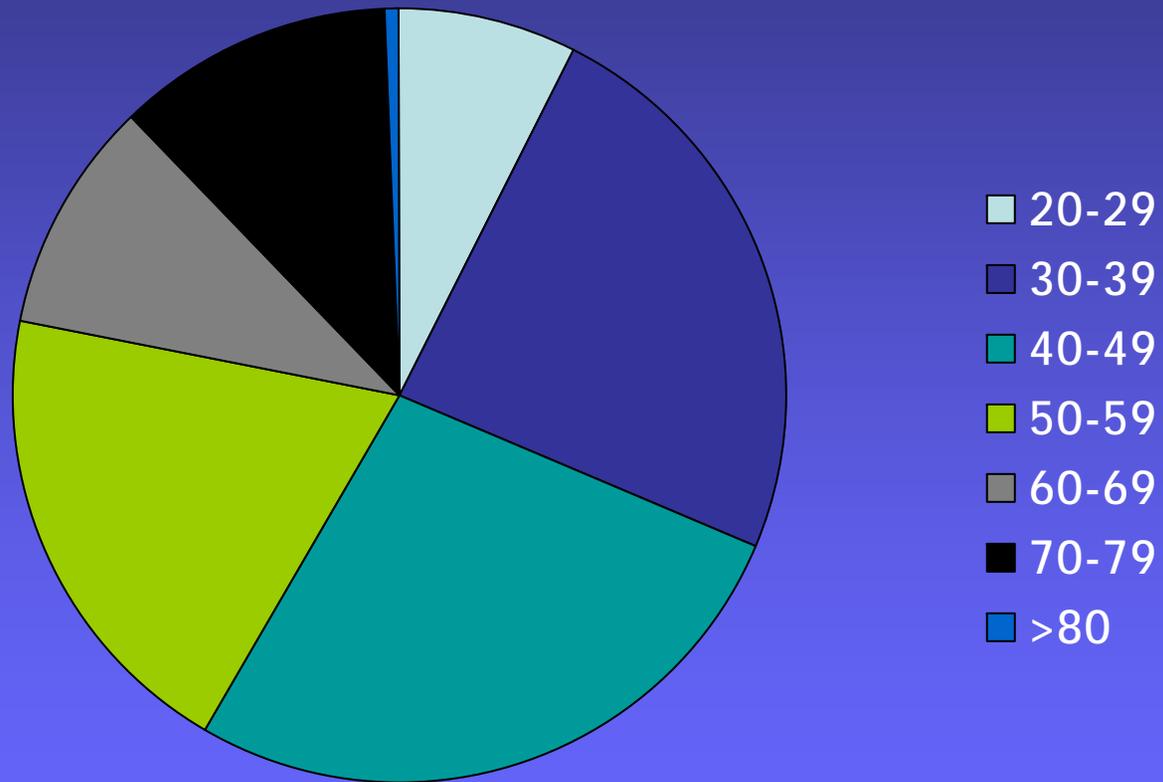


Squamous cancer of the cervix, JHH/JHB, 1984-2002

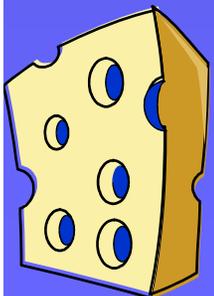
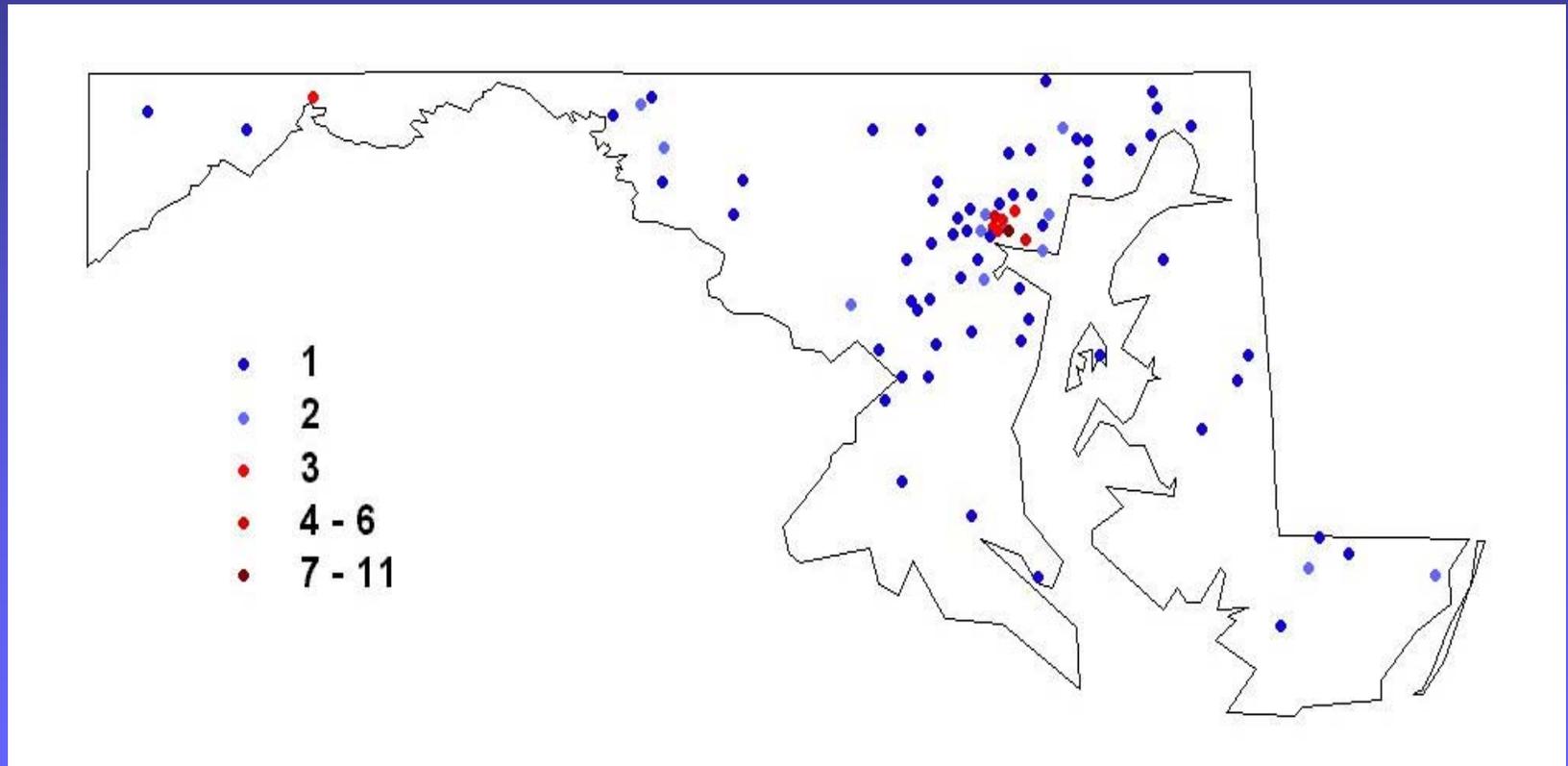
Ethnicity	
Caucasian	79%
African American	19%
Asian	1%
Other	1%
Mean age	45 (24-87)



Age distribution of cervical cancer cohort

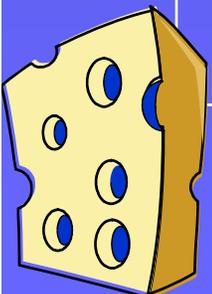


JHH cervical cancer patients: 1984 - 2002



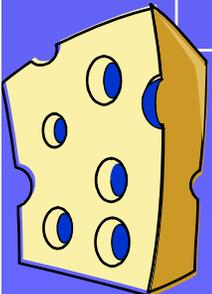
Cohort Characteristics

Exposure to Health Care system in the year prior to diagnosis	<ul style="list-style-type: none">• OB/Gyn Office (65%)• Emergency Department (22%)• Primary Care Provider (36%)
Medical Co-Morbidities	<ul style="list-style-type: none">• None reported (43%)• 1 or more (57%)<ul style="list-style-type: none">-HTN (23%)-Respiratory dz (17%)-DM (9%)-Psychiatric (8%)



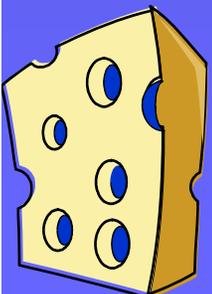
Cohort Characteristics

Insurance	<ul style="list-style-type: none">• Private Insurance (45%)• Government Aid (29%)• None (12%)
Telephone	<ul style="list-style-type: none">• Yes (97%)
Employment	<ul style="list-style-type: none">• Yes (54%)
Marital Status	<ul style="list-style-type: none">• Married (52%)• Single/Widowed (34%)



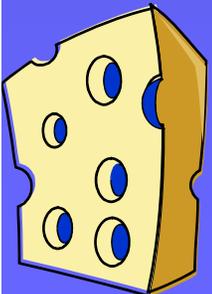
Cohort Characteristics

Transportation	<ul style="list-style-type: none">• Self (55%)• Public, arranged (4%)• Private, arranged (21%)• Unknown (20%)
Education	<ul style="list-style-type: none">• Not Completed HS (12%)• Completed HS (36%)• Unknown (52%)
Caregiver	<ul style="list-style-type: none">• Yes (59%)• No (41%)



Cohort Characteristics

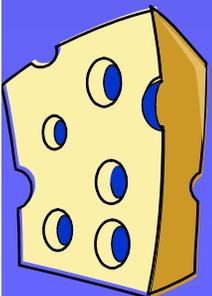
Recent Hospitalization	<ul style="list-style-type: none">• Yes (25%)• No (75%)
------------------------	--



Cohort Characteristics

Recent Hospitalization	<ul style="list-style-type: none">• Yes (25%)• No (75%)
------------------------	--

Maryland legislation mandates that women admitted to hospitals be offered a Pap test



Thinking out of the box: in-reach

- Hopkins hospital in-house screening program: 1999-2002 (n = 1,117)
- Compared with outpatient screens from all of our clinics (n= 111,933)
- Cervical cancer precursors were nearly 5-fold higher in the hospitalized patients than in our outpatient clinics

Outreach: Cervical cancer screening at the Hispanic Apostolate

- Abnormal rate is high (12.2%)
- Comparison: abnormal rate in JHH outpatient clinics is 7% (close to the national rate)
- Comparison: abnormal rate in in-reach screening program at Hopkins: is 15.5%

Making a difference, starting at home

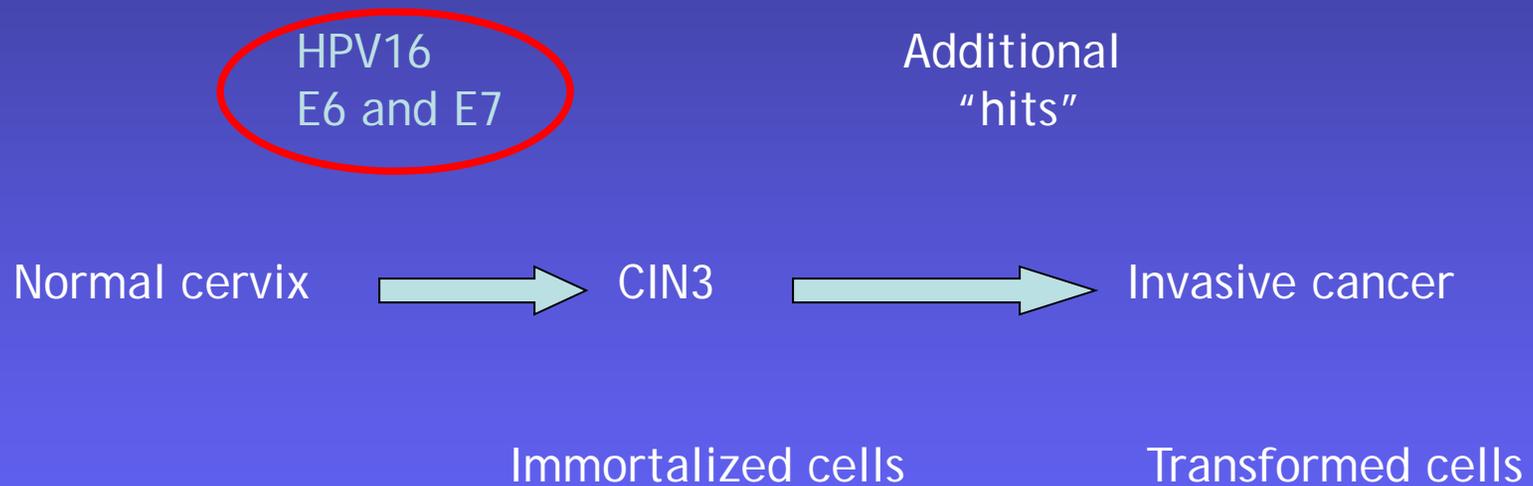
- Identify increased-risk populations in our catchment area
- Extend continuity of care to CRF sites
- Make the best treatment options available to our patients

Johns Hopkins Center for Cervical Disease

Multidisciplinary effort involving clinicians, immunologists, pathologists, virologists, oncologists, nurses, epidemiologists, biostatisticians: expertise on many levels

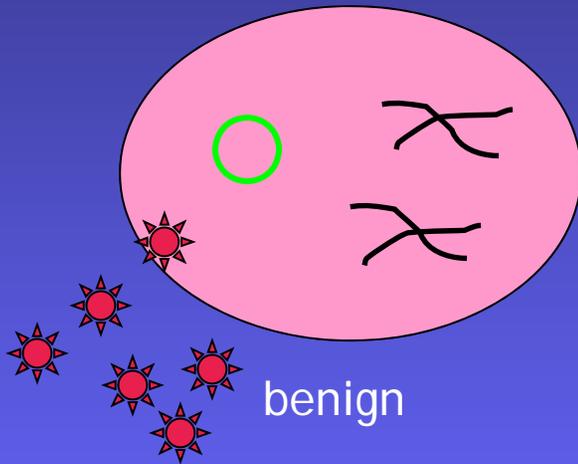
Mission: to improve screening, triage, and treatment, and to develop and evaluate interventions to prevent HPV-associated cancers of the lower genital tract

Tumor progression Cervical cancer



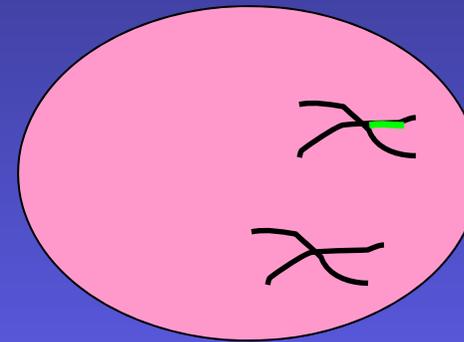
HPV Genome

CIN 1
Low grade
Preinvasive
HPV DNA is episomal



benign

CIN 2/3
High grade
Preinvasive
HPV DNA has integrated into host genome



malignant



Host genome

Host genome

HPV Genome

CIN 1

Low grade
Preinvasive

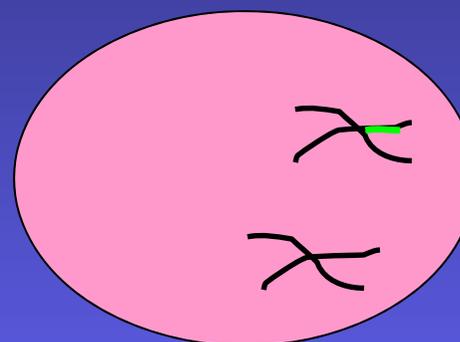
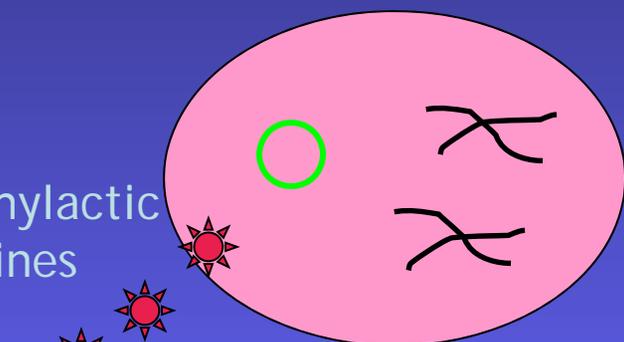
HPV DNA is episomal

CIN 2/3

High grade
Preinvasive

HPV DNA has integrated into host genome

Prophylactic
vaccines



benign

malignant

L2

E7

E1

E2

L1

LCR

E6

E2

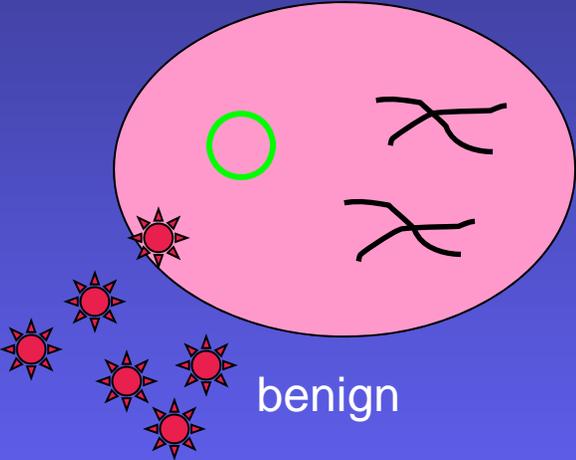
Host genome

Host genome

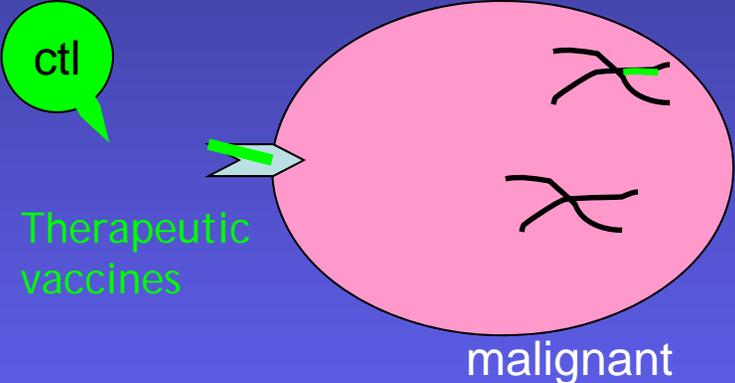


HPV Genome

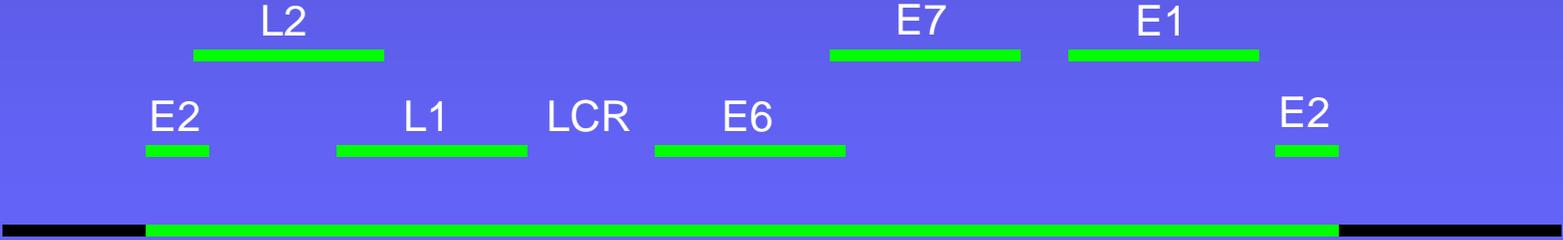
CIN 1
Low grade
Preinvasive
HPV DNA is episomal



CIN 2/3
High grade
Preinvasive
HPV DNA has integrated into host genome



Therapeutic vaccines



Host genome

Host genome

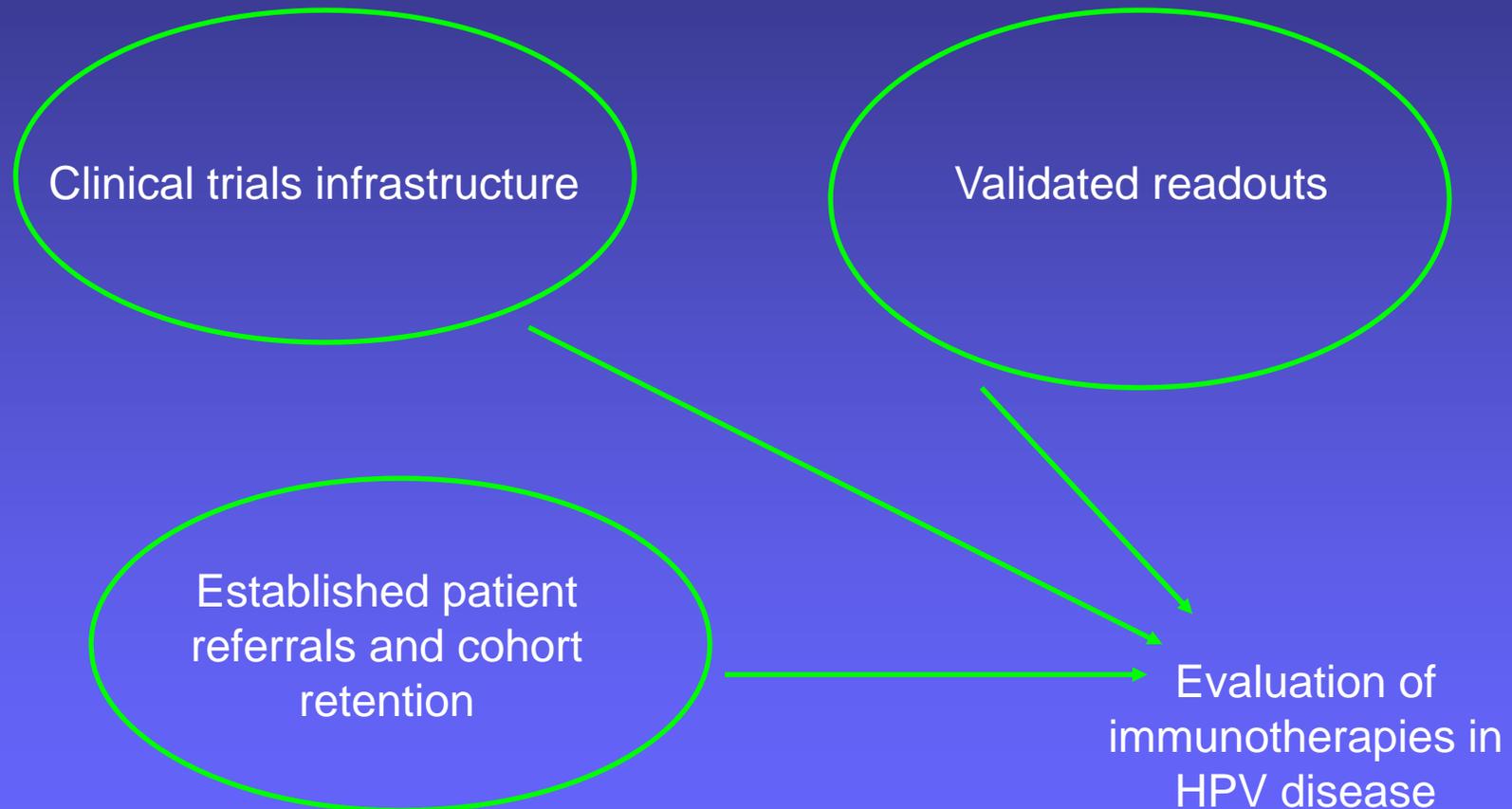
HPV vaccines: the beginning of the end of cervical cancer

- Koutsky, et al, NEJM 2002
 - 2392 women, HPV16-naïve
 - Prophylactic VLP vaccine
 - 100% efficacy at 7 months
- ICAAC 2004 42 months of follow up
 - Vaccine efficacy: 94%

HPV prophylaxis: why pursue therapeutic vaccines?

- Prophylactic vaccines will only be effective if everyone gets immunized.
- The herd burden of HPV infection is massive.
- Cultural barriers exist to vaccination for a sexually transmitted infection
- Curing early disease would also help us to figure out what is a good immune response.
- Science/discovery do not transpire out of a social context. (cancer vaccines, transplant, autoimmune diseases)

Center for cervical disease at Hopkins

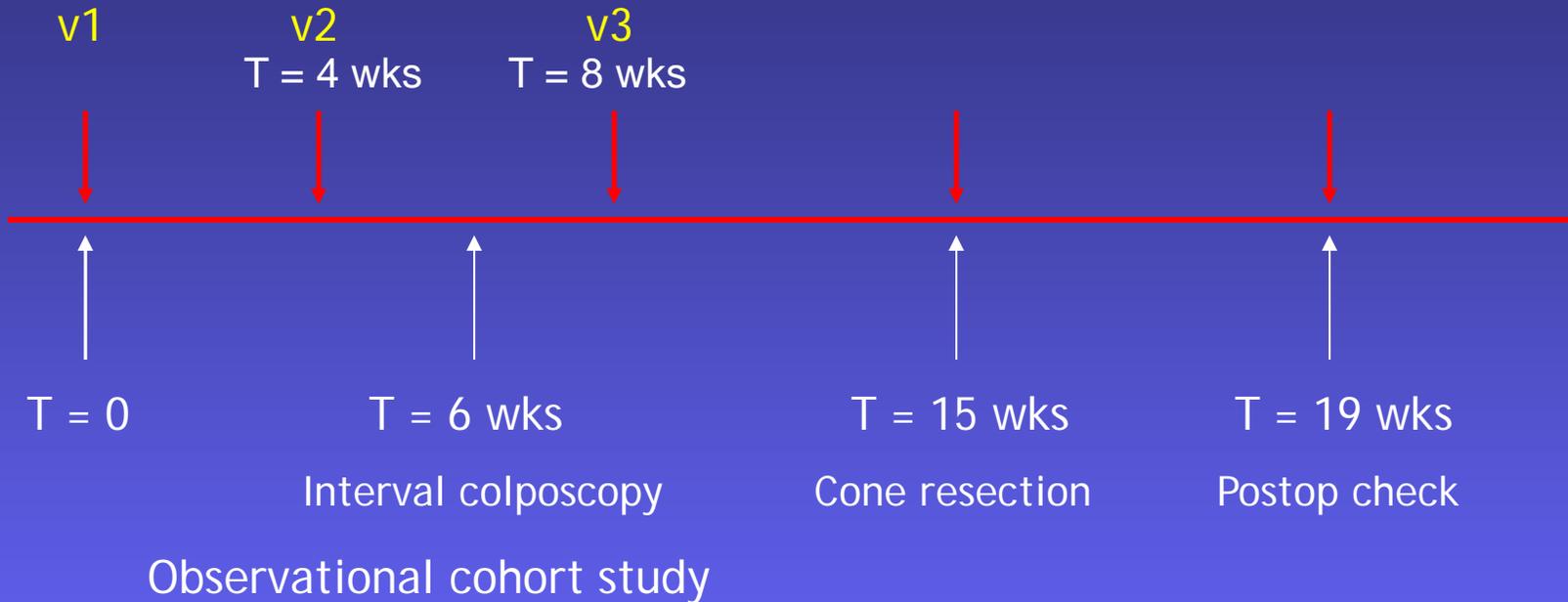


Phase I/II clinical trials: HPV 16 E7-targeted therapeutic vaccines

- Target population: healthy women with preinvasive HPV16-associated disease of the cervix
- Two parallel cohorts
 - HIV-negative
 - HIV-positive

CIN2/3 clinical trials

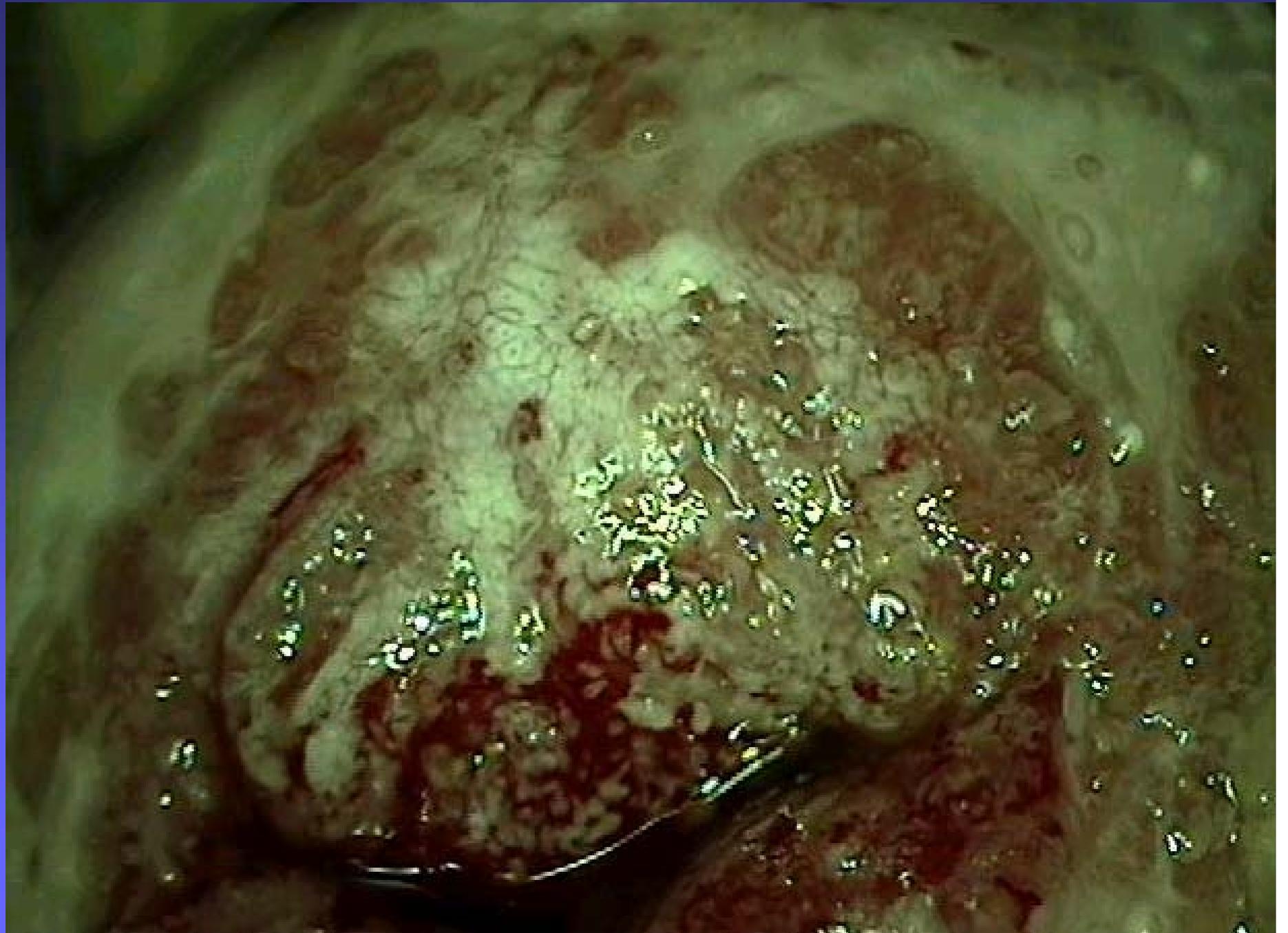
Phase I/II vaccination trial: pNGVL4a-Sig/E7(detox)/HSP70



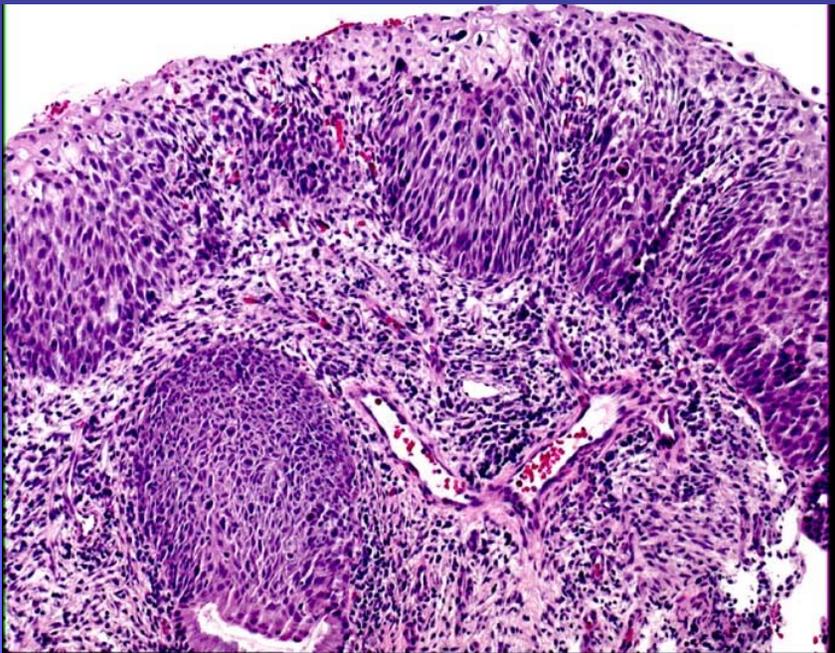
CIN 2/3 cohort study

Patient characteristics

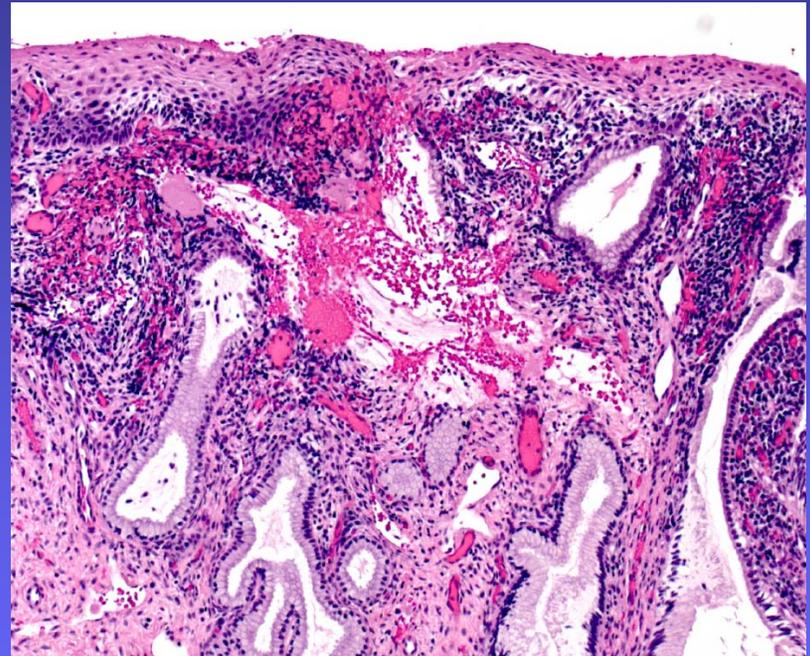
Median age (in years)	30.y (range 18-67y)
< 25	25 (25%)
25-34	53 (53%)
>35	22 (22%)
average time to resection	123.8 d
ethnicity	
African American	26 (26%)
Hispanic	3 (3%)
White	67 (67%)
Asian	4 (4%)
Reported number of partners	8.1 (1-50)
Tobacco smoking	
Current	42 (42%)
Former	2 (2%)
Never	56 (56%)
Hormonal contraceptive use	52 (52%)



Spontaneous regression over 15 weeks: CIN2/3



Week 0



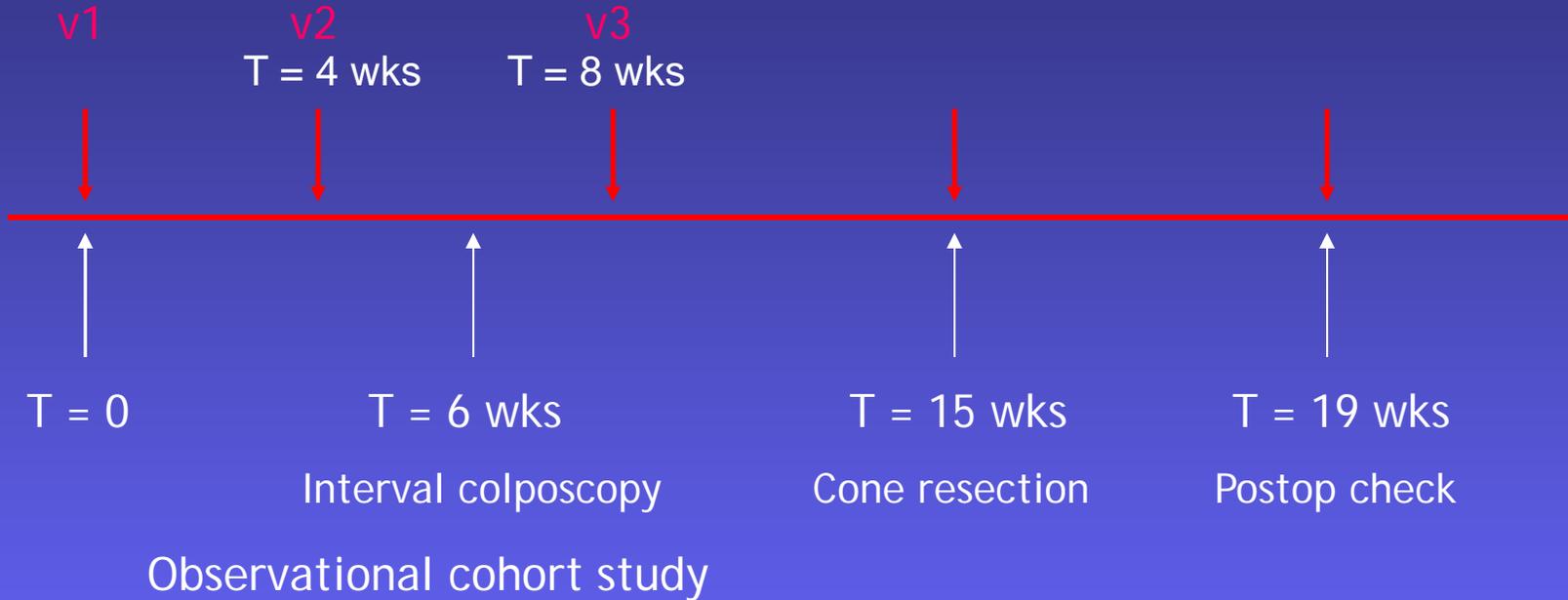
Week 15

Interaction between HLA class I and HPV : effect on disease behavior

Variable	Estimated O.R.	95% C.I.	p-value
Months	1.01	0.86-1.19	0.87
HPV16	0.20	0.06-0.73	0.01 *
HLA*A201	0.90	0.03-29.44	0.95
~HPV16*~HLA*A201	32.12	0.97->999.999	0.05 *

CIN2/3 clinical trials

Phase I/II vaccination trial: pNGVL4a-Sig/E7(detox)/HSP70



GMP-Grade pNGVL4a-Sig/E7(detox)/HSP70 DNA Vaccine



HPV vaccines at JHH

- Combination strategies
- Needle-free delivery
- Continued outreach



"Never, ever, think outside the box."

Vaccination strategies



(age 12)

Prophylactic vaccination

Vaccination strategies



(age 12)

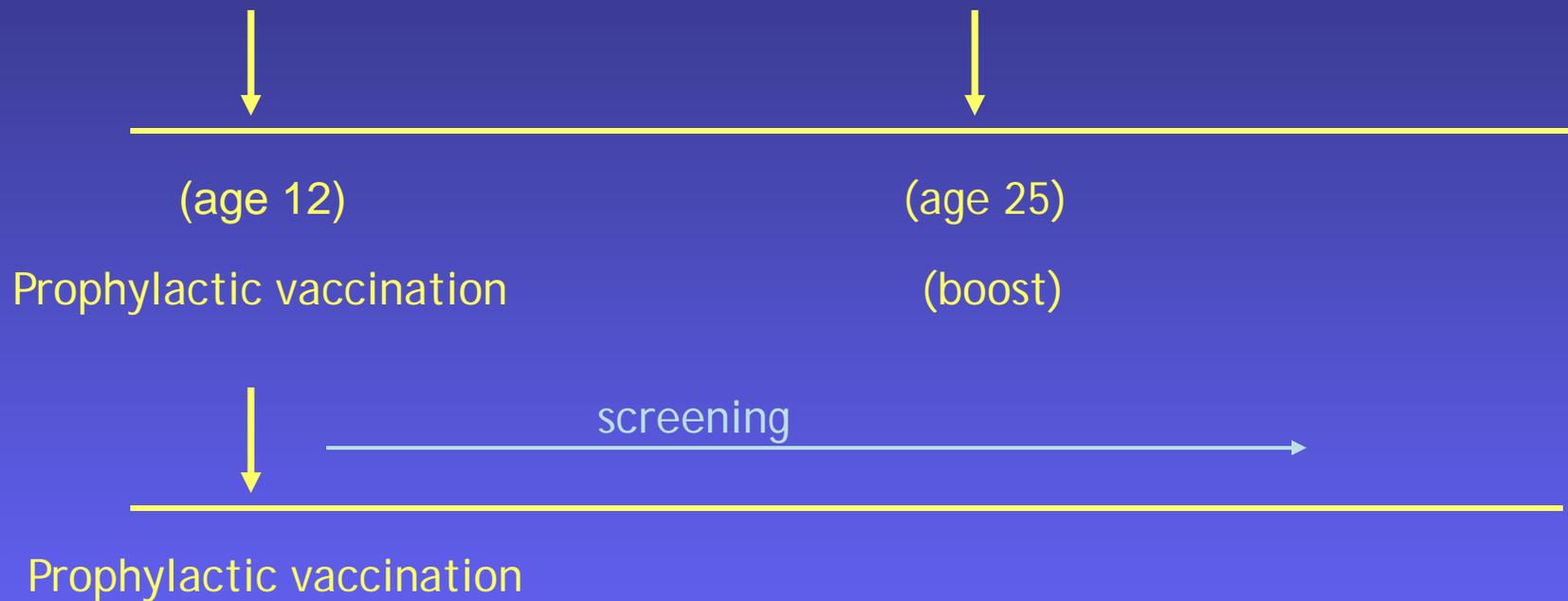
Prophylactic vaccination



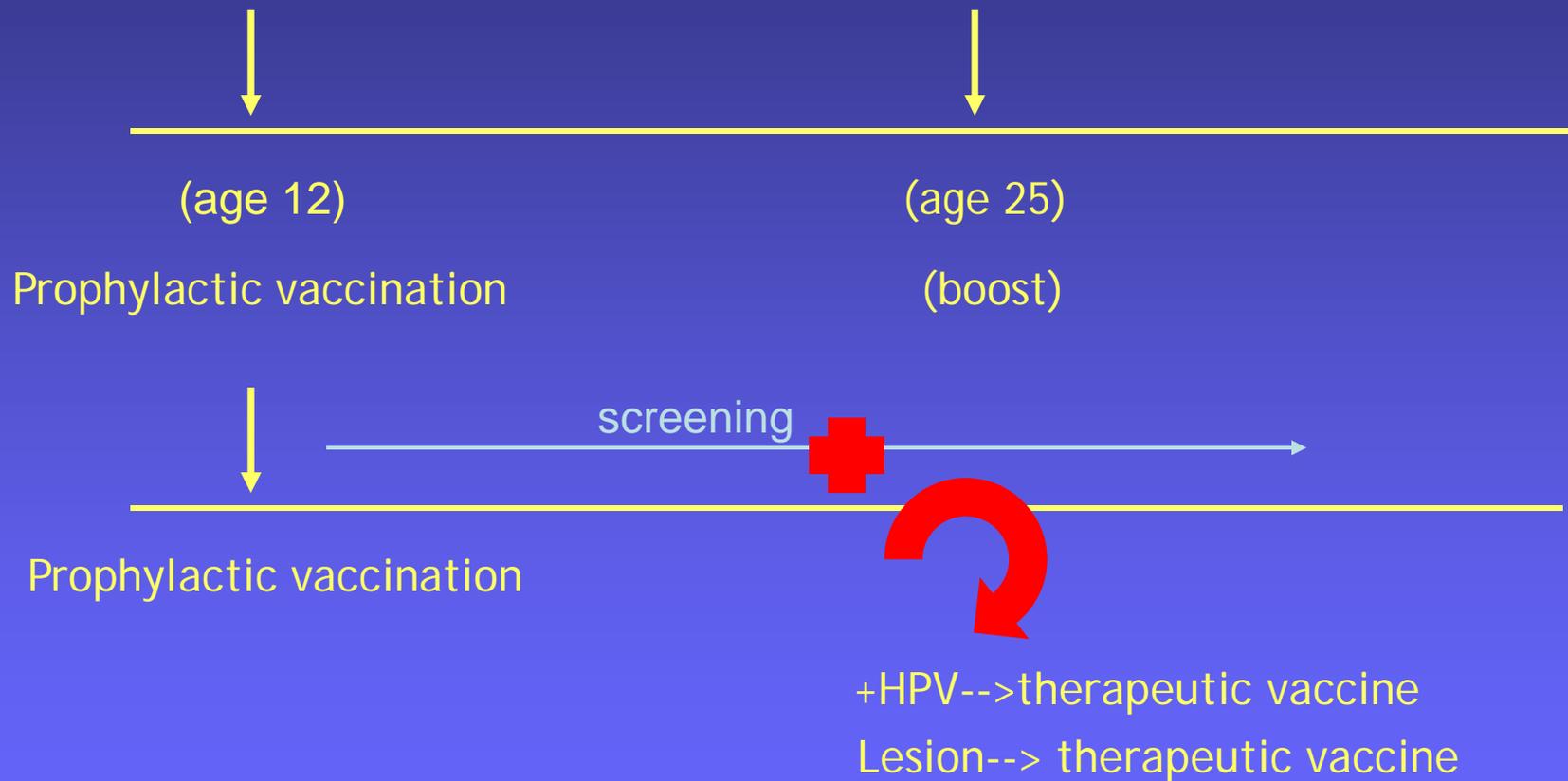
(age 25)

(boost)

Vaccination strategies



Vaccination strategies



Vaccination strategies



(age 12)

Chimeric vaccination
(combination prophylactic
and therapeutic)

(age 25)

(boost)

HPV vaccines: long-term goals

- Combine prophylactic and therapeutic approaches on a population basis
- Eliminate the need for cumbersome screening

Johns Hopkins Center for Cervical Disease

Drew Pardoll, TC Wu, Shiwen Peng, Patti Gravitt, Richard Roden, Chienfu Hung, Will Yutzy, Keerti Shah, Rick Daniel, Barbara Wilgus-Wegweiser, Cathy Wehner, Lynn Richards, Audrey Bruce, Paula Sparks, Andrea Elko, Bernice Horton, Brigitte Ronnett, Deb Armstrong, Dotty Rosenthal, Steve Piantadosi, Elizabeth Garrett, Mihaela Paradis, Judy Lee, Betty Chou, Caroline Fidyk, Chuck Drake, Cornelia Trimble

