

The Beginning Of the End of Cervical Cancer

Connie Trimble, MD

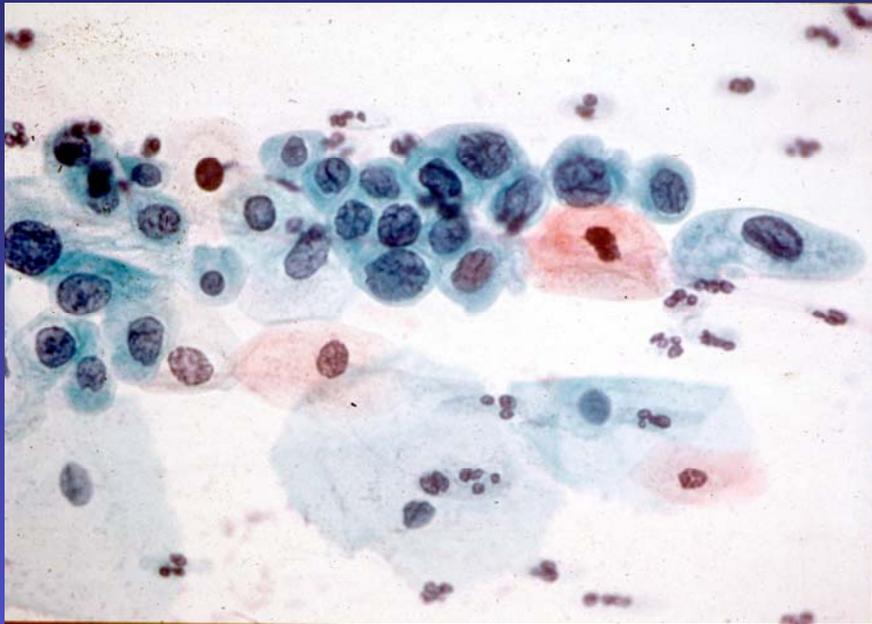
The Johns Hopkins University School of Medicine
Maryland State Council on Cancer Control

August 3, 2006

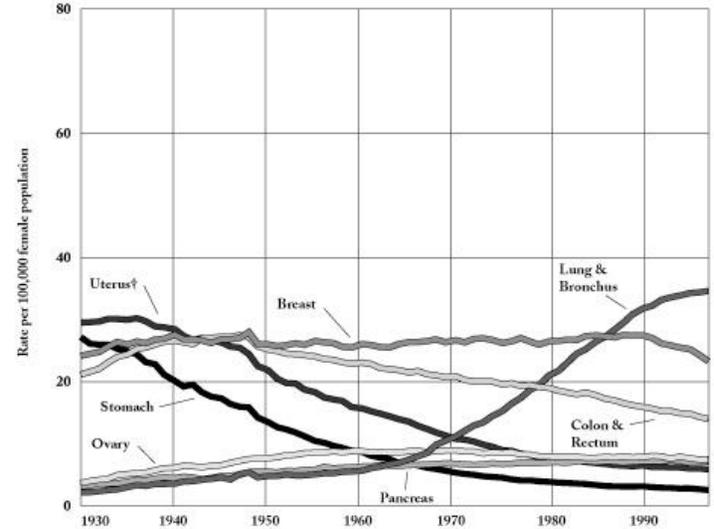


BELIEVE

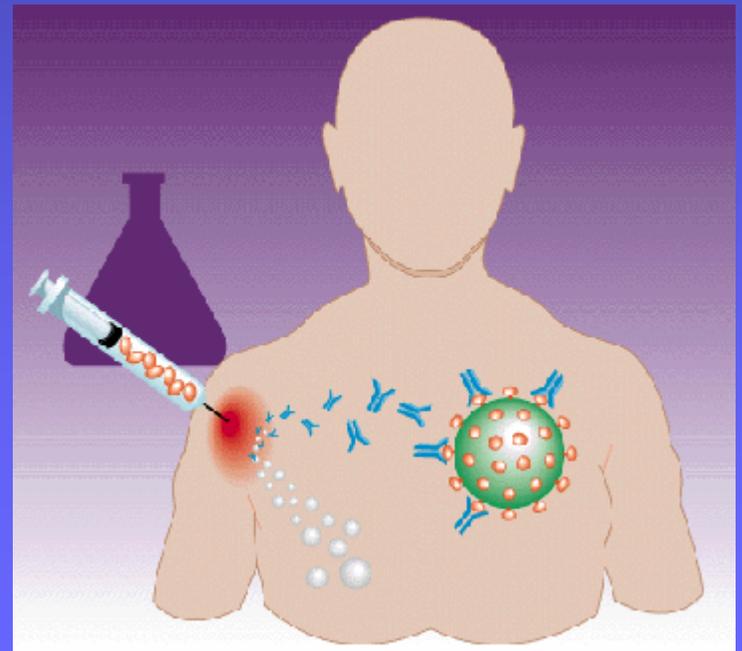
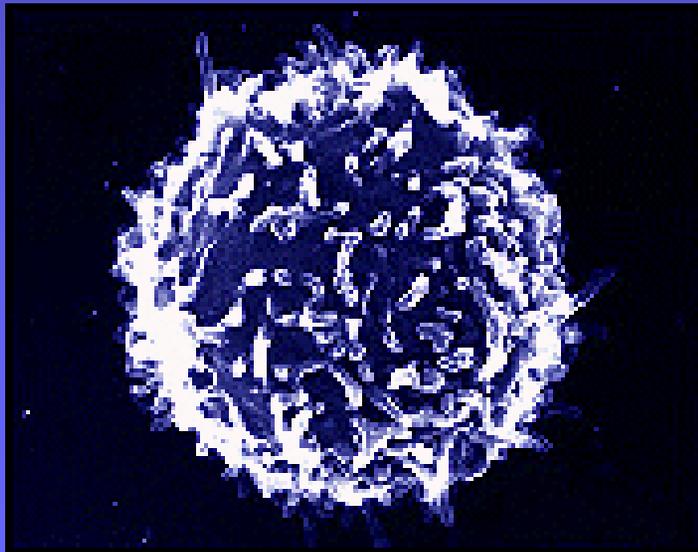




Age-Adjusted Cancer Death Rates,* for Females by Site, US, 1930-1997



*Per 100,000, age-adjusted to the 1970 US standard population. †Uterus cancer death rates are for uterine cervix and uterine corpus combined. Note: Due to changes in ICD coding, numerator information has changed over time. Rates for cancers of the uterus, ovary, lung & bronchus, and colon & rectum are affected by these coding changes. Sources: US Mortality Public Use Data Tapes 1960-1997, US Mortality Volumes 1930-1959, National Center for Health Statistics, Centers for Disease Control and Prevention, 2000. American Cancer Society, Surveillance Research, 2001.



Persistent Human Papillomavirus (HPV) Infection-> Cervical cancer



Estimated Annual Incidence of HPV Cervical Infection/Dysplasia¹

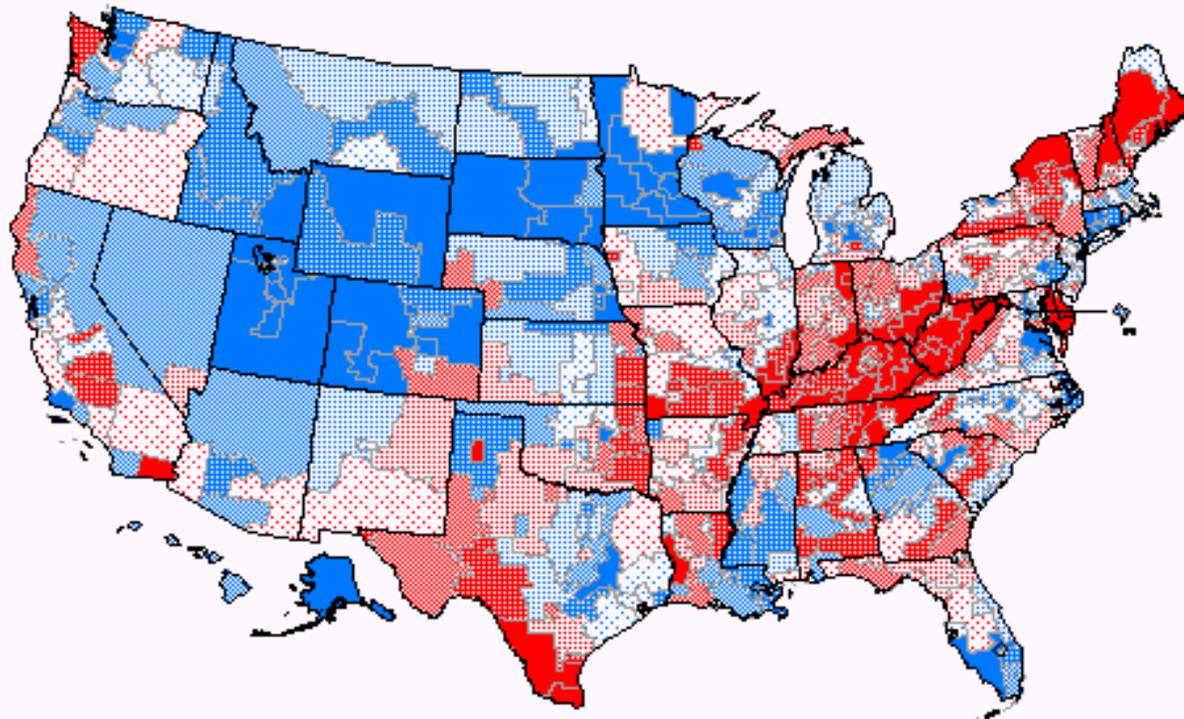
Cervical Infection/Dysplasia	United States	Worldwide
HPV infection without detectable cytologic abnormalities	10 million	300 million
Low-grade dysplasia	1 million	30 million
High-grade dysplasia	300,000	10 million

Virtually all cases of cervical cancer come from high-grade dysplasias.

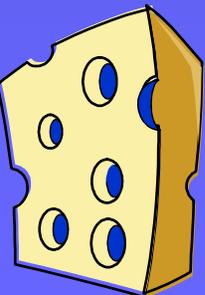
1. World Health Organization. Geneva, Switzerland: World Health Organization; 1999:1–22.

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

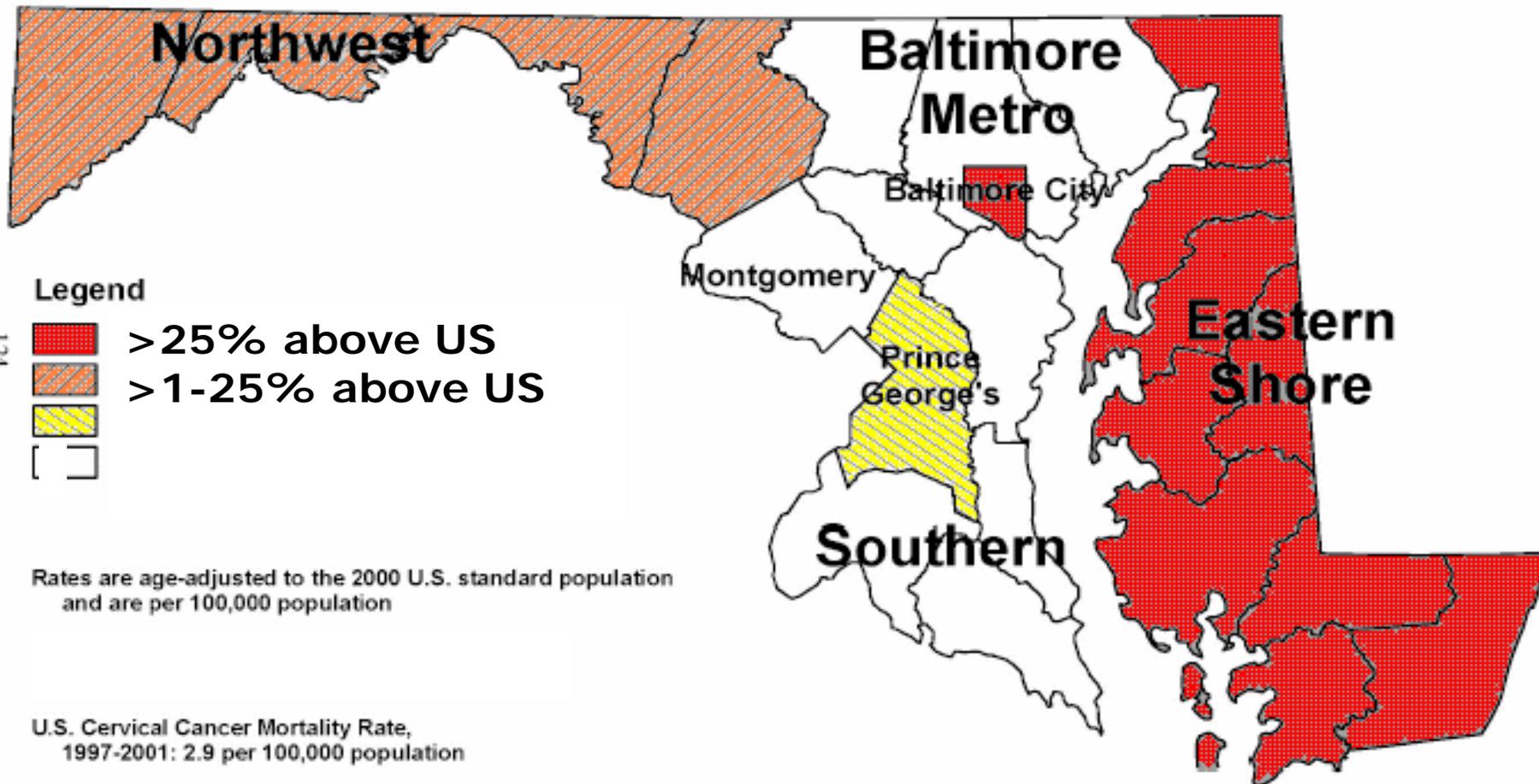
U.S. rate = 4.64 / 100,000



Jon Kerner, PhD. Division of Cancer Control, NCI

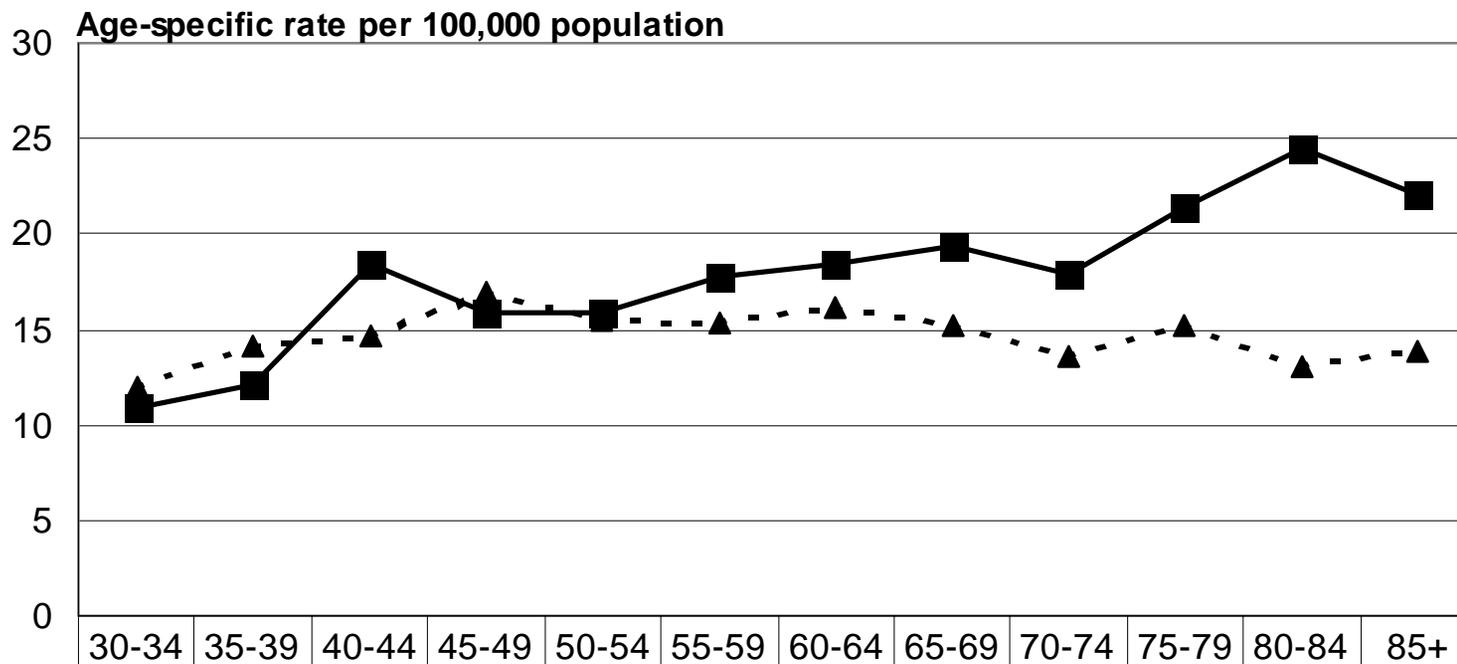


Maryland Cervical Cancer Mortality Rates by Geographical Area: Comparison to U.S. Rates, 1997-2001



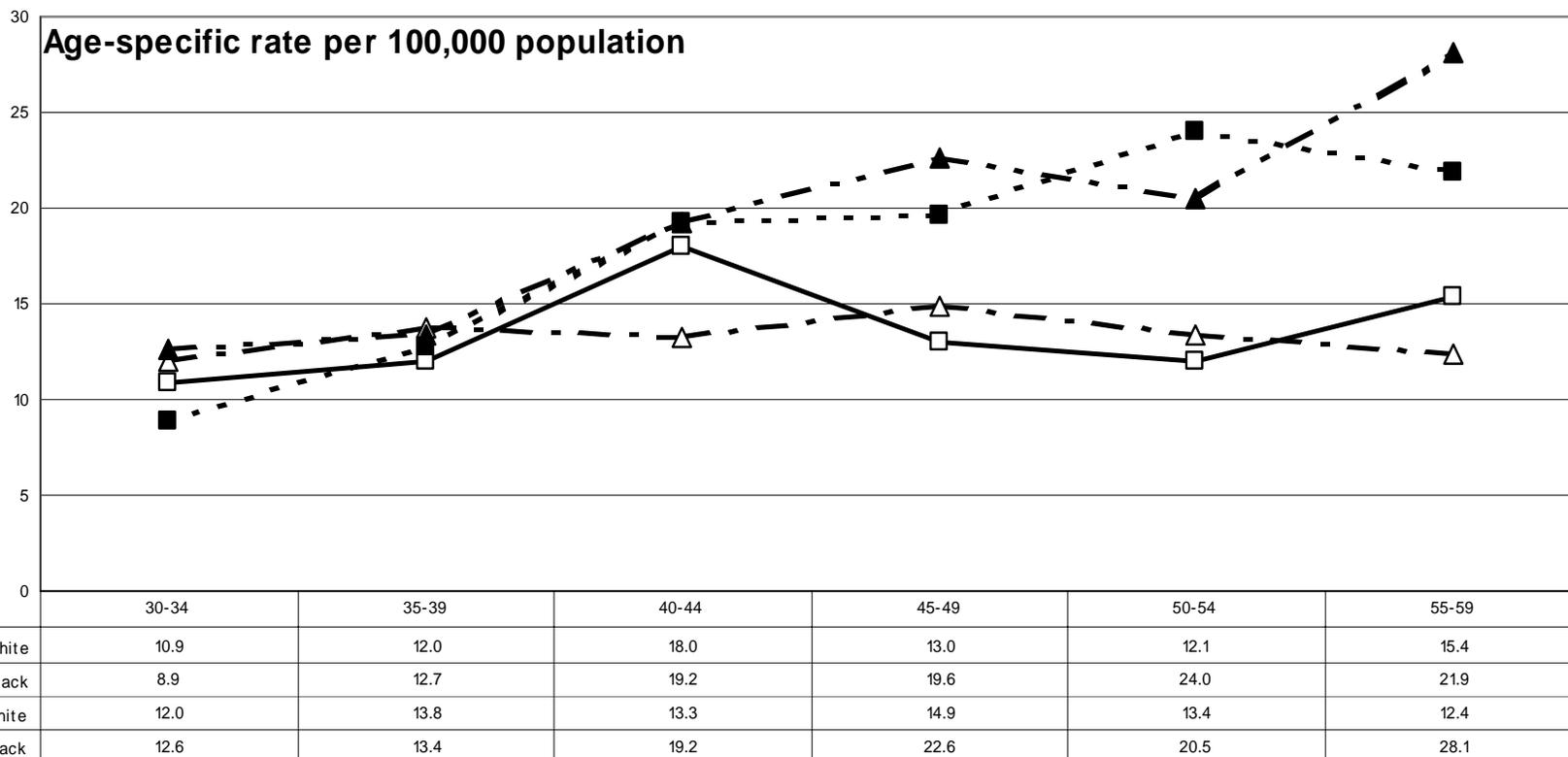
Source: Maryland Division of Health Statistics, 1997-2001

**Figure 3. Invasive Cervical Cancer Age-Specific Incidence Rates
Maryland and United States, 1994-1998**

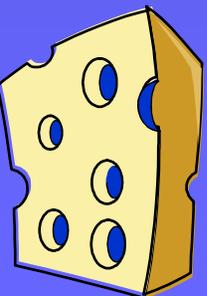
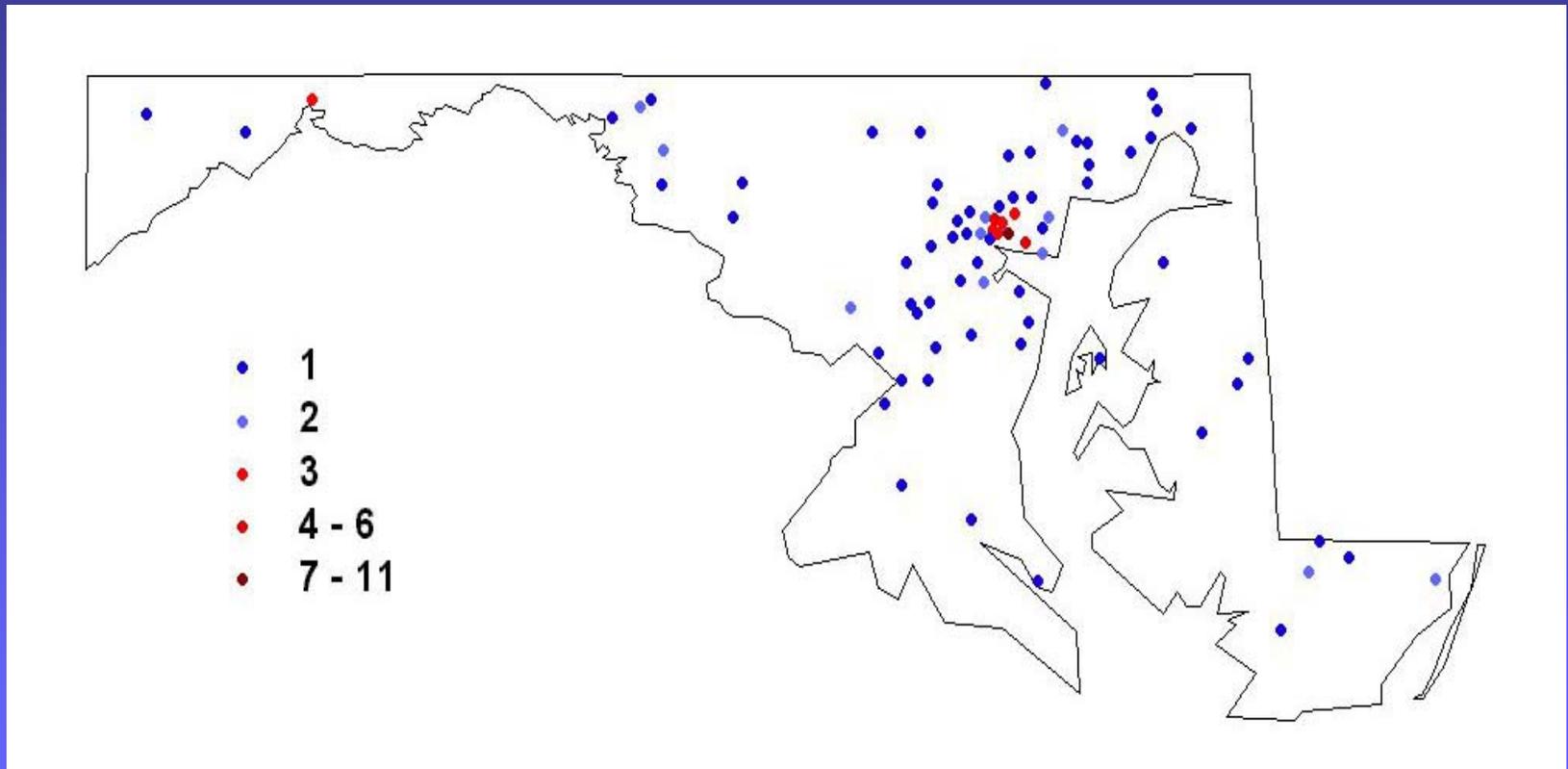


—■— MD	10.8	12.1	18.4	15.9	15.8	17.8	18.4	19.4	18.0	21.4	24.5	22.0
- -▲- - US	12.0	14.1	14.7	17.0	15.5	15.3	16.2	15.2	13.6	15.2	13.0	13.8

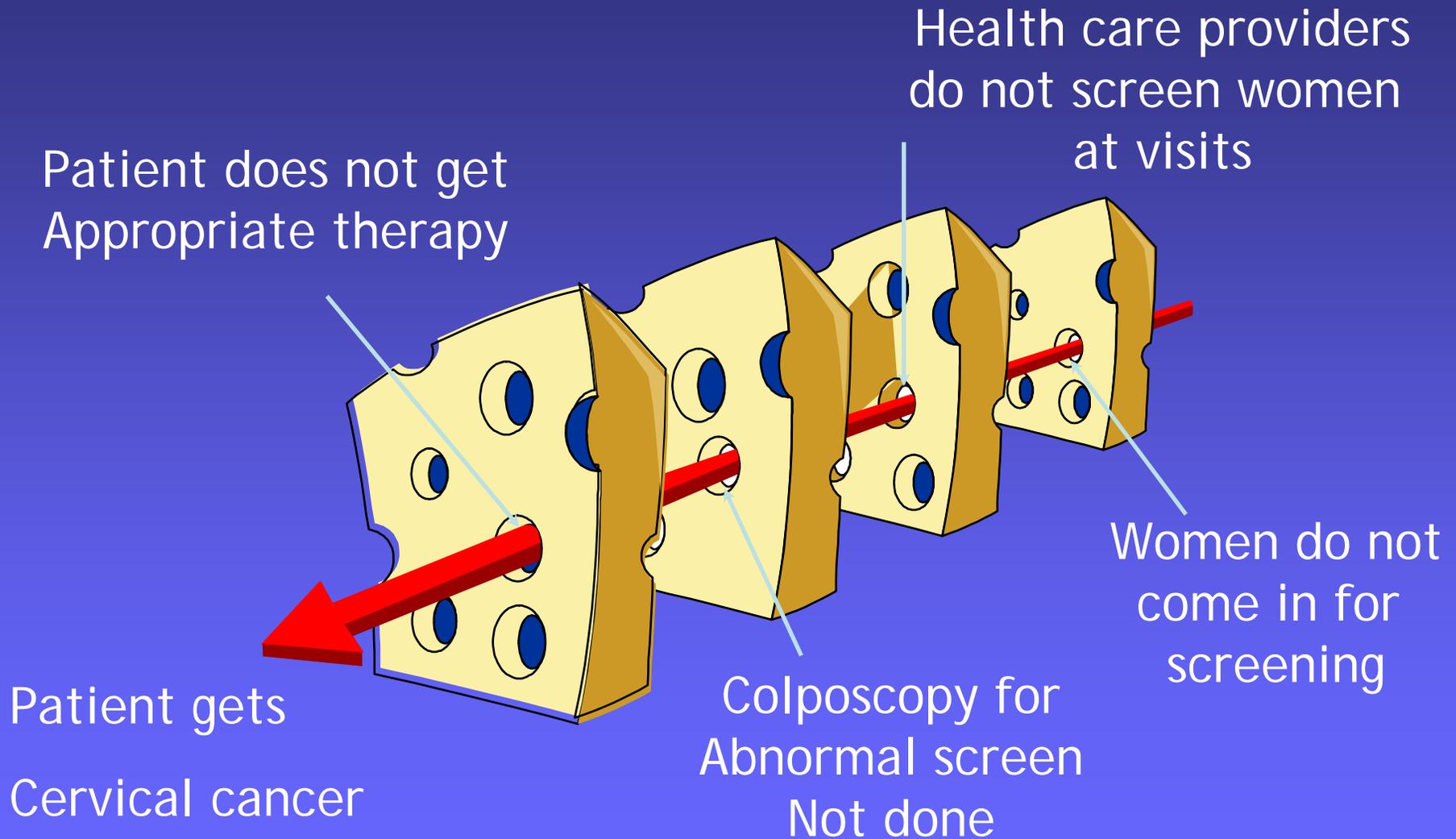
**Figure 4. Invasive Cervical Cancer Age-Specific Incidence by Race
Maryland and United States, 1994-1998**



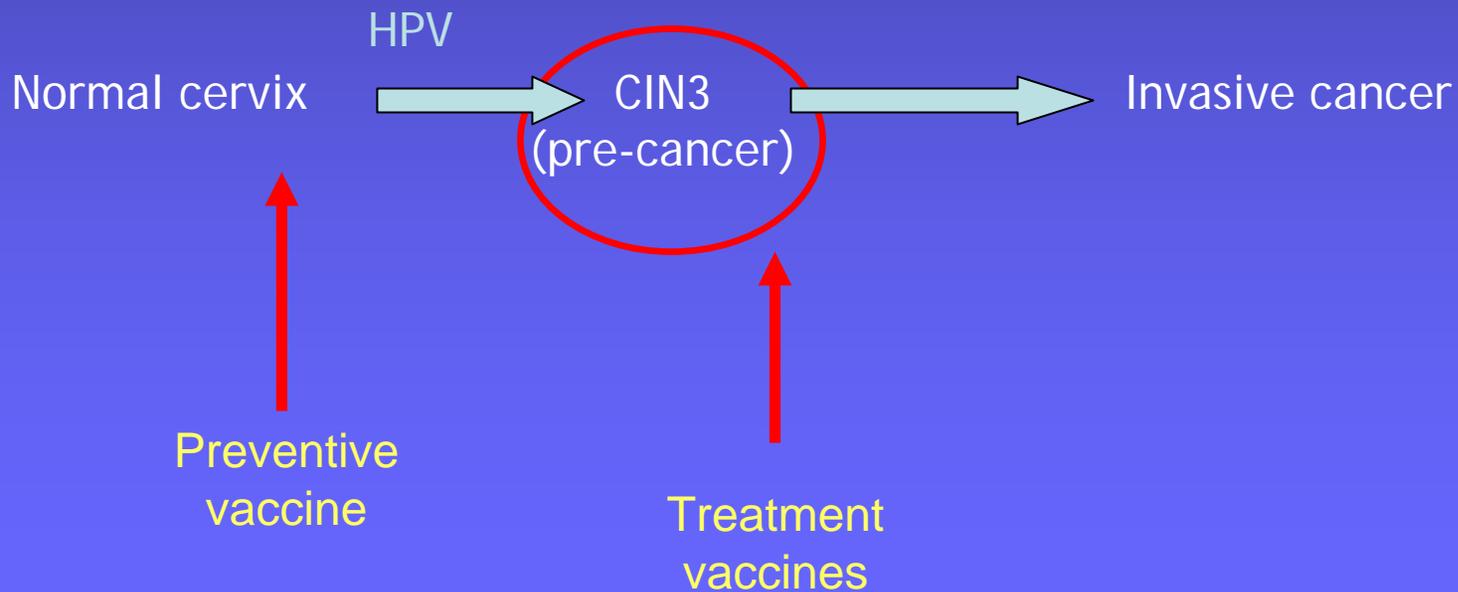
JHH cervical cancer patients: 1984 - 2002



System Failures leading to Cervical Cancer Diagnosis



Persistent Human Papillomavirus (HPV) Infection-> Cervical cancer



Prophylactic vs Therapeutic Vaccines

Prophylactic

- Inhibit infection via induction of neutralizing antibody
- Require huge test populations
- Many years for validation
- Absolutely no tolerance for possible toxicity

Therapeutic

- Elimination of infected cells requires T cell responses - Ab ineffective
- Relatively small test populations
- Viral clearance a rapid endpoint
- Greater tolerance for possible toxicity

HPV prophylaxis: why pursue therapeutic vaccines?

- Prophylactic vaccines to prevent HPV infection are available within years.
 - Vaccines are effective only if immunization programs reach people before they are infected.
 - The prophylactic HPV vaccines are \$120 a shot, you need three, over a six-month period, and you need an office visit for each shot. The barriers to getting vaccinated are the same as the barriers to getting screened.
 - The burden of HPV infection is massive.
- Cultural barriers exist to vaccination for a sexually transmitted infection
- It provides an opportunity to determine how to prevent cancer in patients with precancerous lesions.

Center for cervical disease at Hopkins

Established patient referrals and cohort retention:
>1800 visits annually

Clinical trials infrastructure

Evaluation of immunotherapies in HPV disease

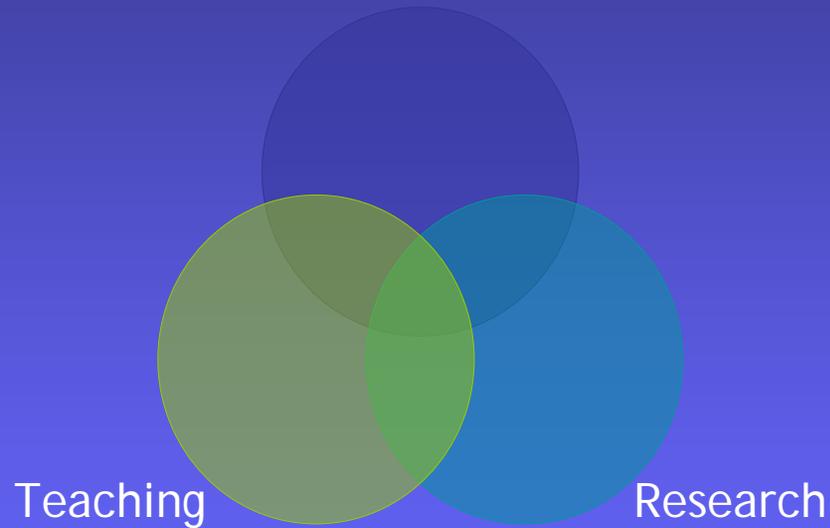
ENDPOINTS:
Histology, viral load,
Immunologic monitoring*

- Clinical care team
- Research nursing
- Data management
- Study coordinator
- Research pharmacy
- Data safety/monitoring
- Regulatory staff
- HPV typing core lab
- Tissue banking



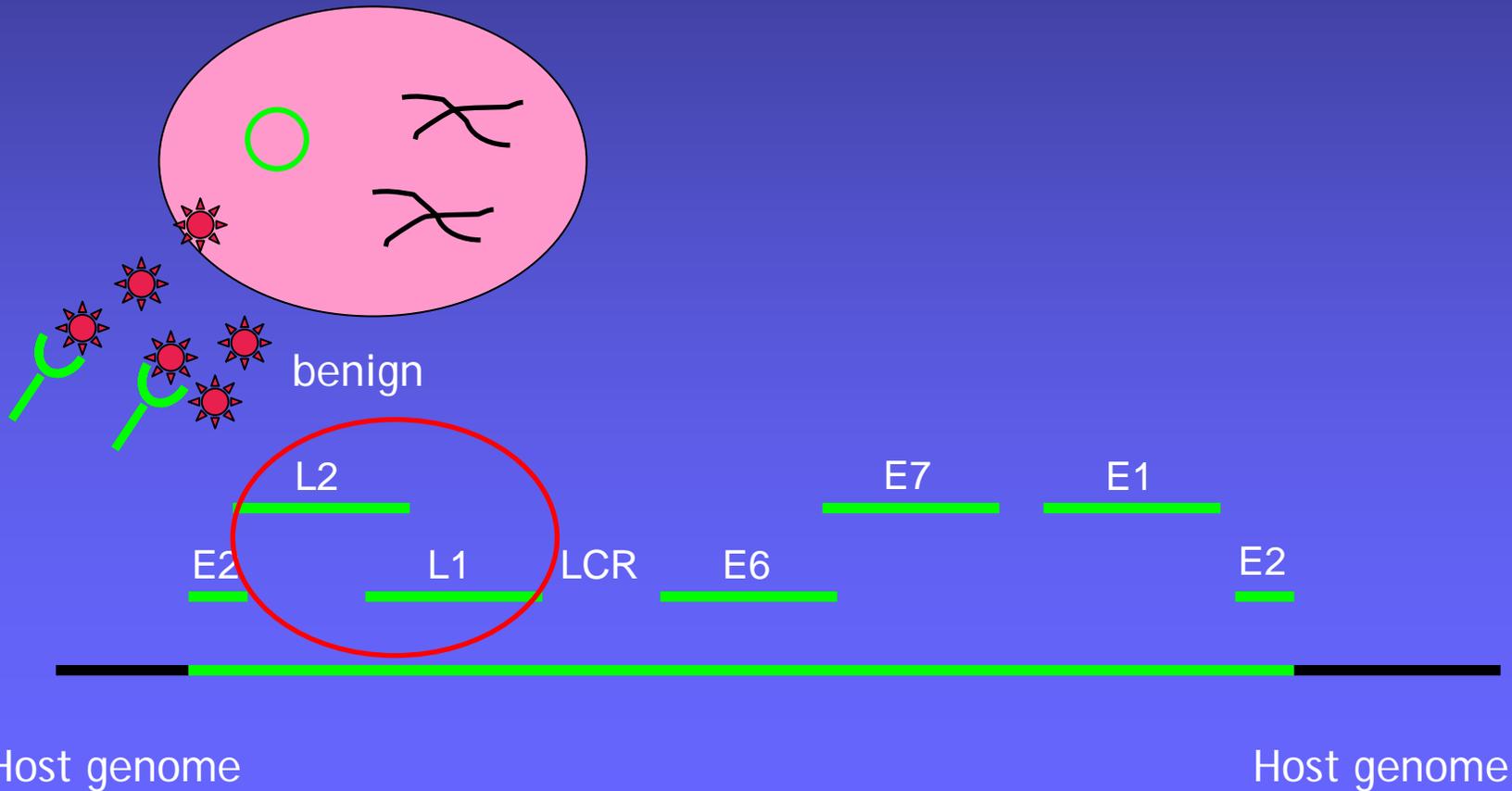
Johns Hopkins Center for Cervical Disease

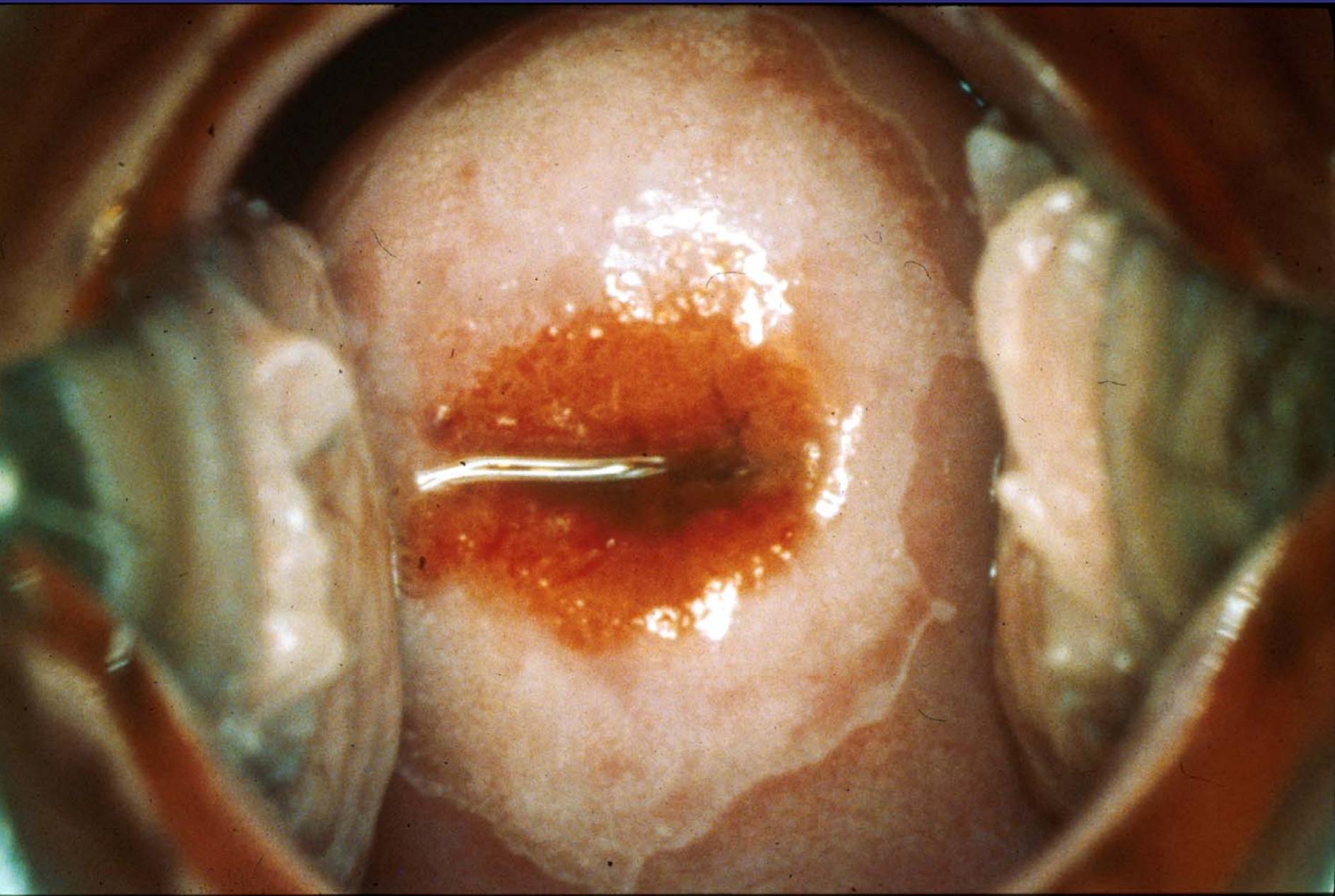
Patient care/outreach



Premalignant HPV disease: low grade dysplasia

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

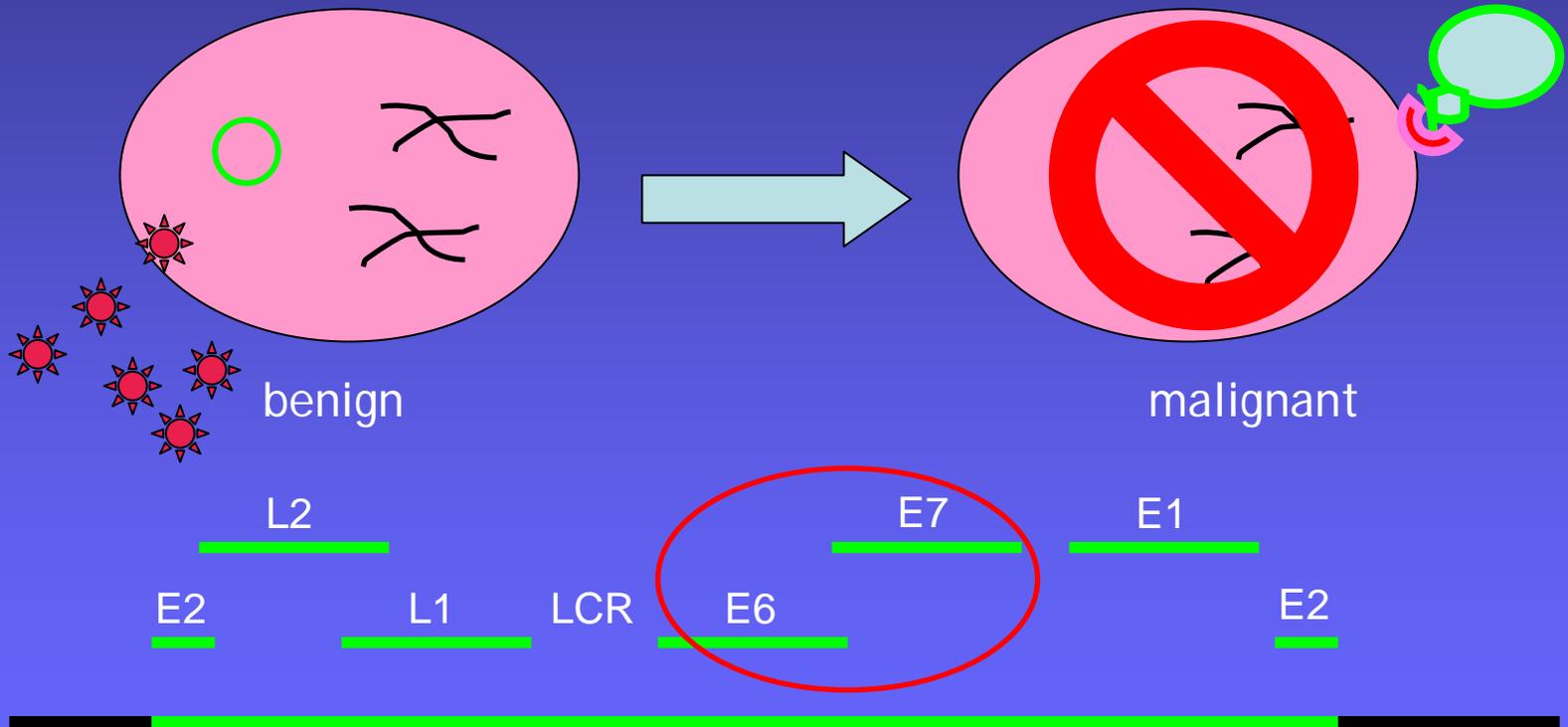




Premalignant HPV disease

CIN 1
Low grade
Preinvasive
HPV DNA is episomal

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

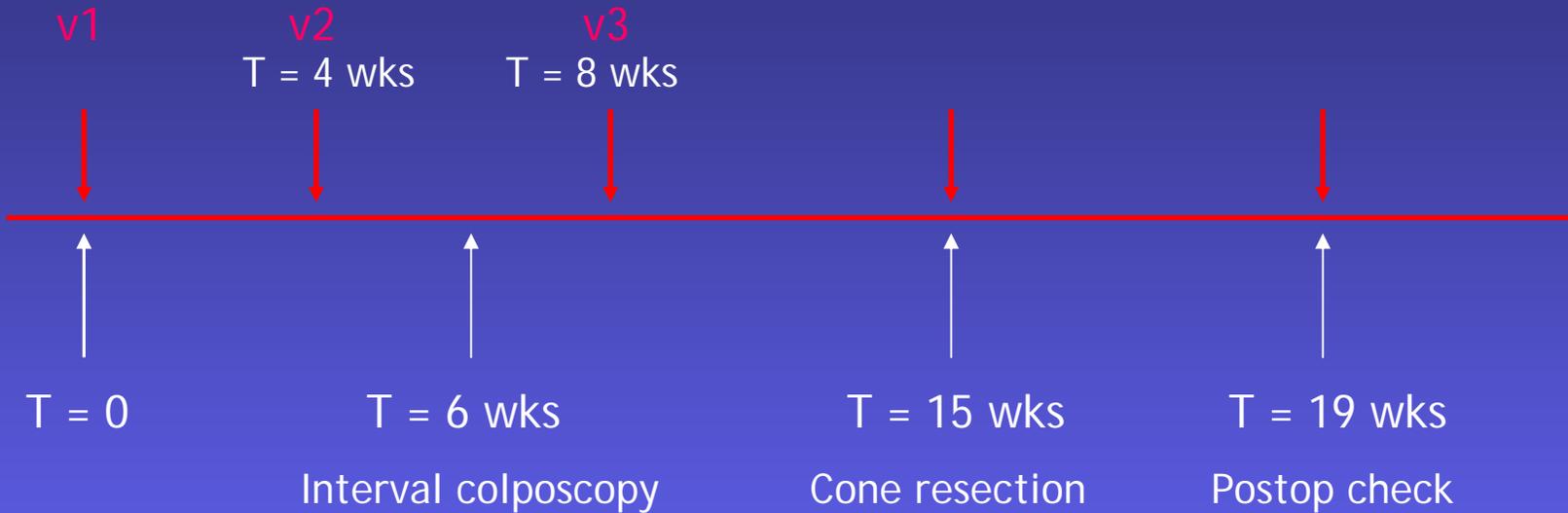


Host genome

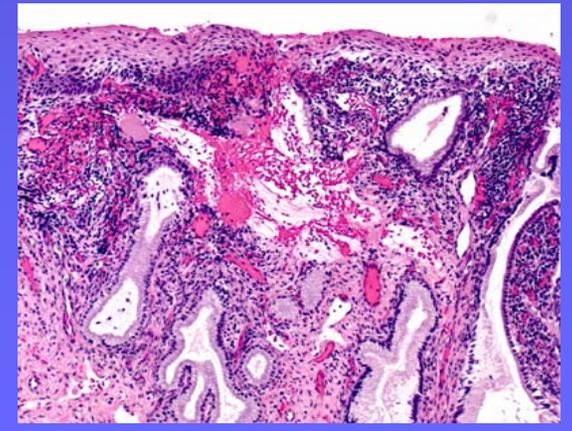
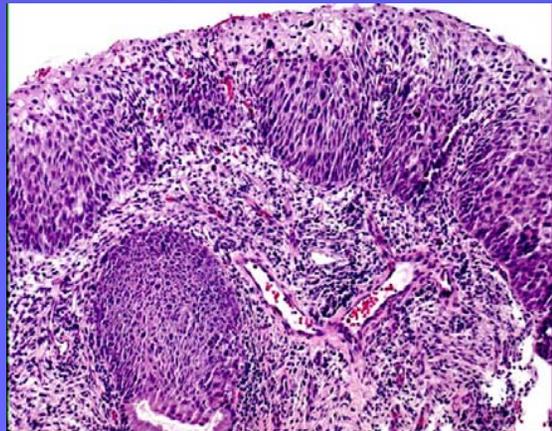
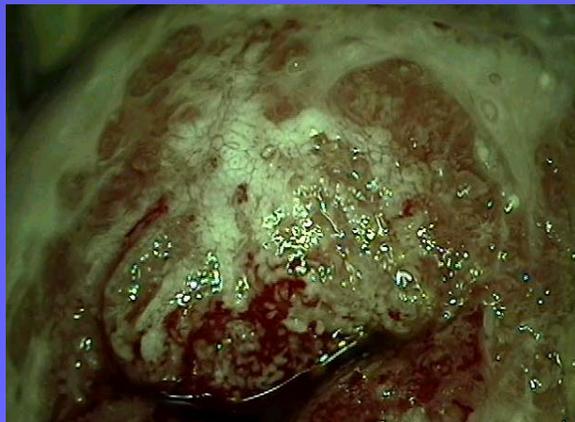
Host genome

CIN2/3 cohort clinical trials

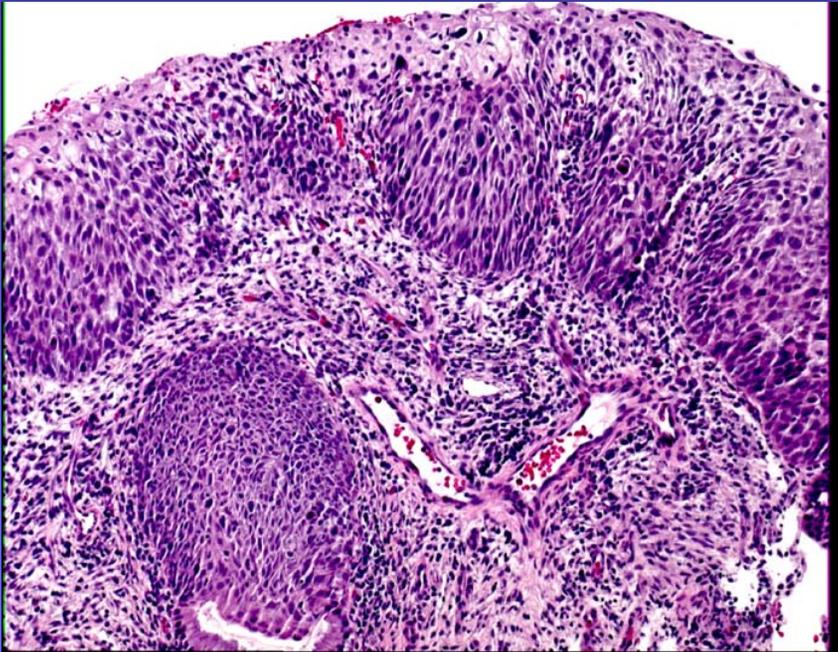
Phase I/II vaccination trial: pNGVL4a-Sig/E7(detox)/HSP70



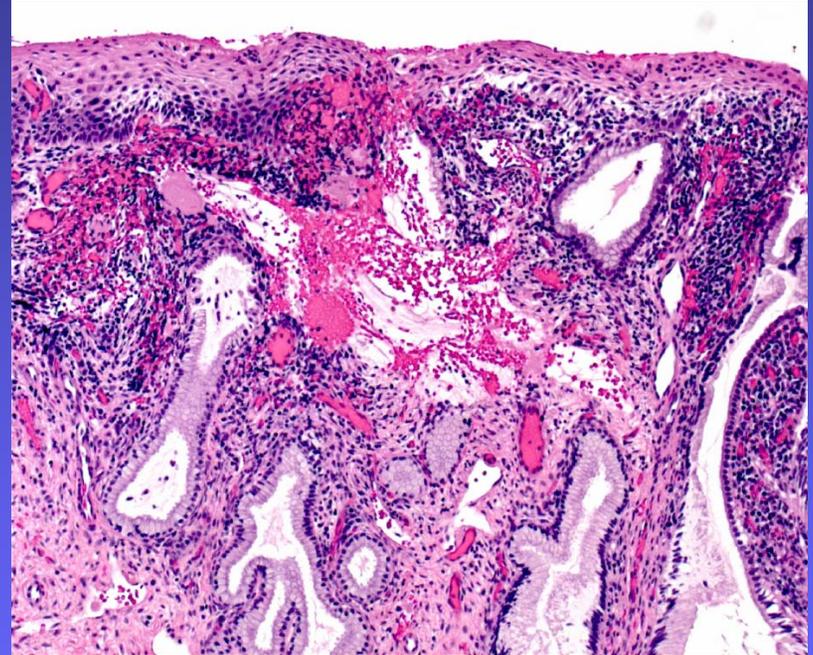
Observational cohort study



Spontaneous regression over 15 weeks: precancerous lesions

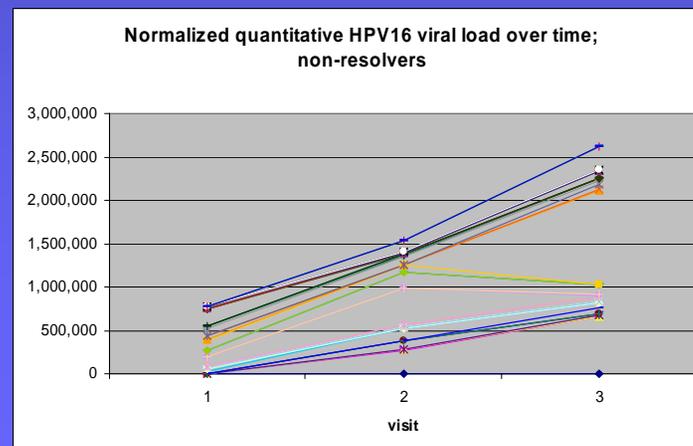
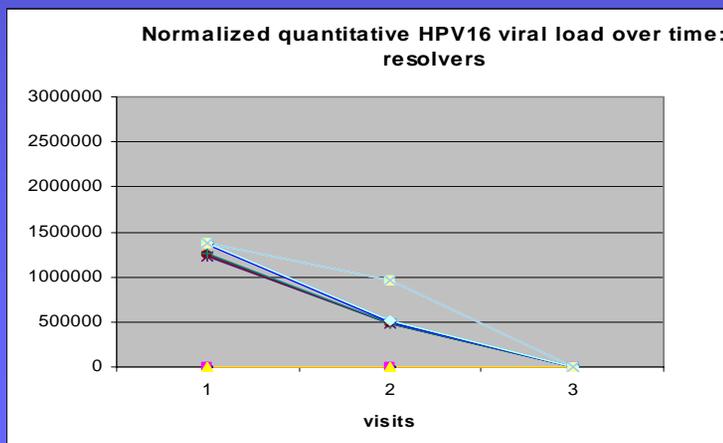
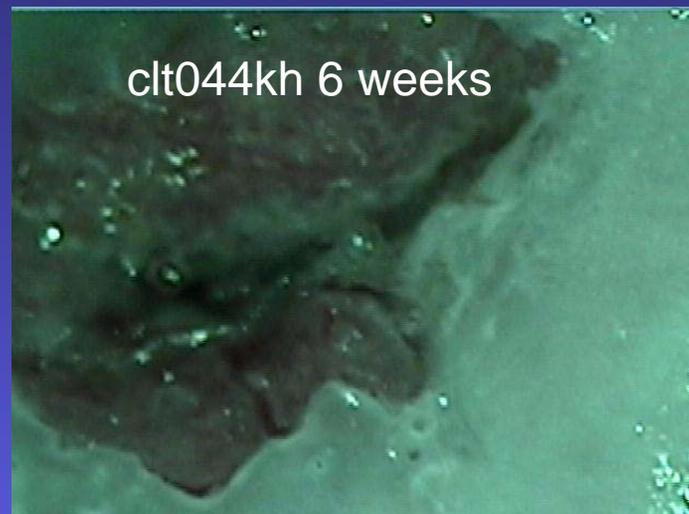
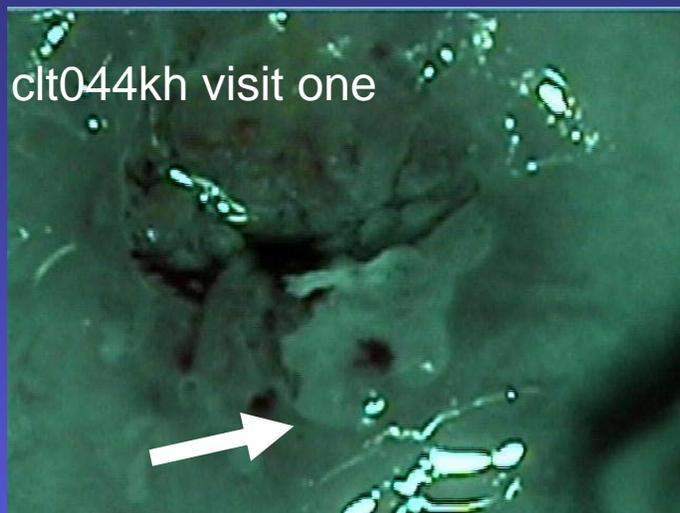


Week 0



Week 15

Spontaneous regression of CIN2/3 over a 15-week observational window

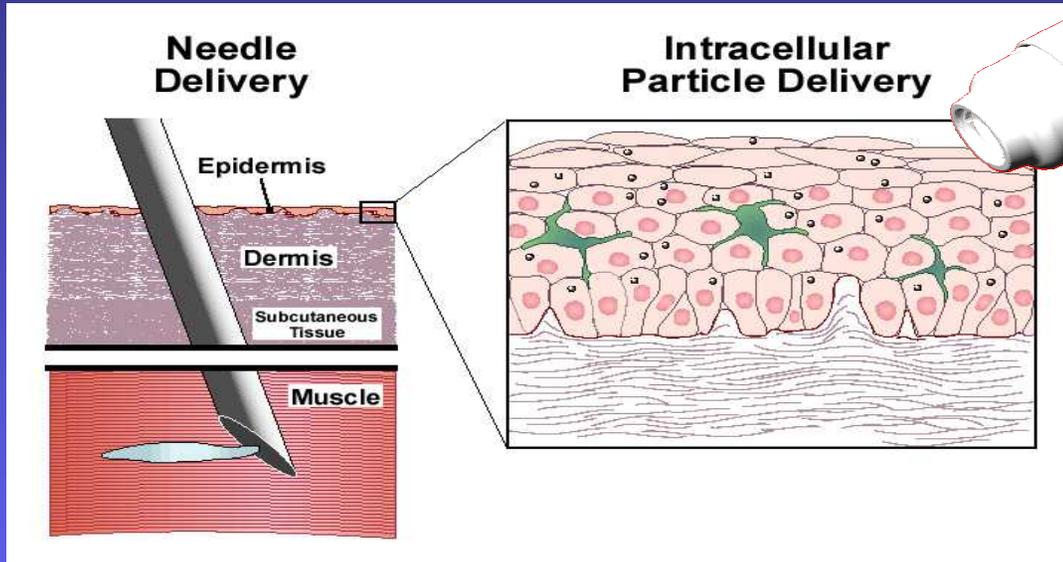


HPV vaccines at JHH

- Combination strategies
- Needle-free delivery

PowderMed Core Capability

Particle Mediated Epidermal Delivery (PMED)



- The epidermis cannot be accessed with needle and syringe
- PowderMed device is designed to deliver to the epidermis



GOG-JHU Cervical Cancer SPORE:

- GOG-SPORE collaboration to take advantage of unique clinical and scientific resources, and established, longstanding working relationships within GOG
 - Facilitate translation of promising therapeutic strategies: bench to bedside
 - Facilitate reverse translation of clinical findings: bedside to bench

GOG

- Cervix committee
- Committee on Experimental Medicine
 - Vaccine subgroup
- Cancer Prevention and Control Committee
- Pathology Committee

JHU Cervical Cancer SPORE

- Project 5: Immunotherapies in women with HPV16+ HGSIL
- Project 6: Immunotherapies in women with operable Stage IB1 Cervical Cancer

Vaccination strategies



(age 12)

Prophylactic vaccination

Vaccination strategies



(age 12)

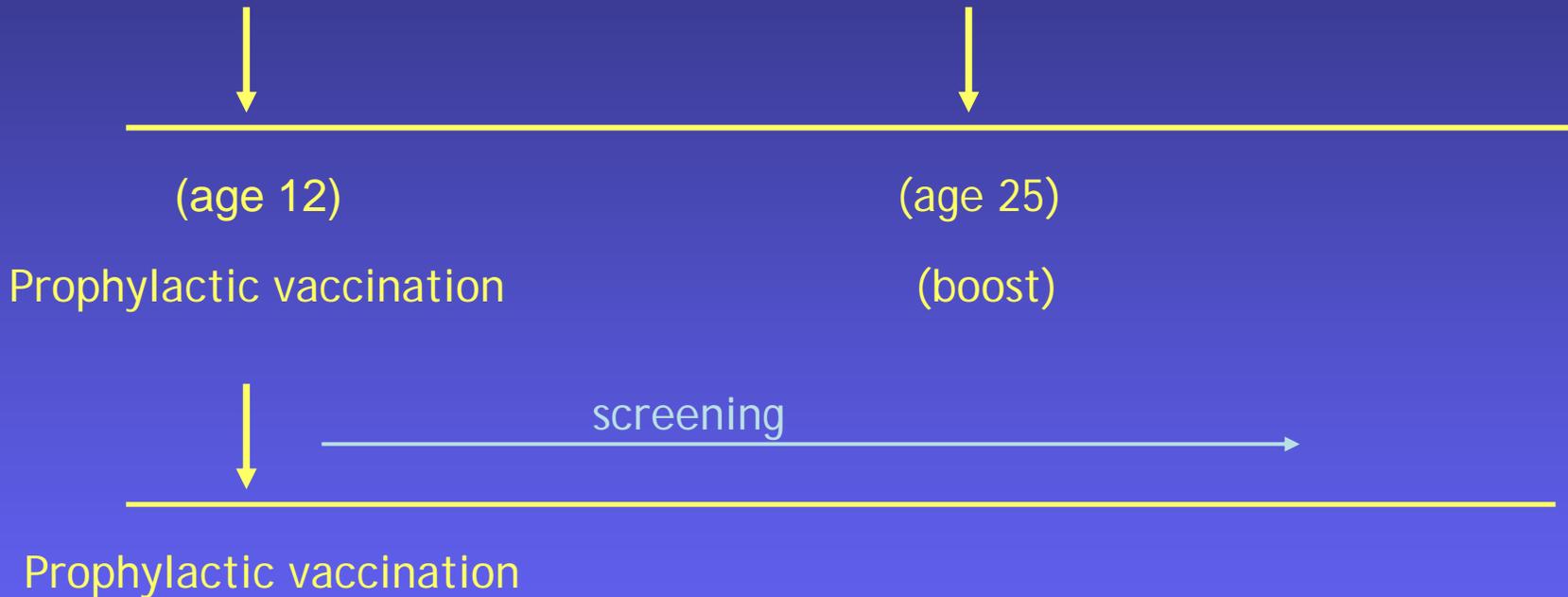
Prophylactic vaccination



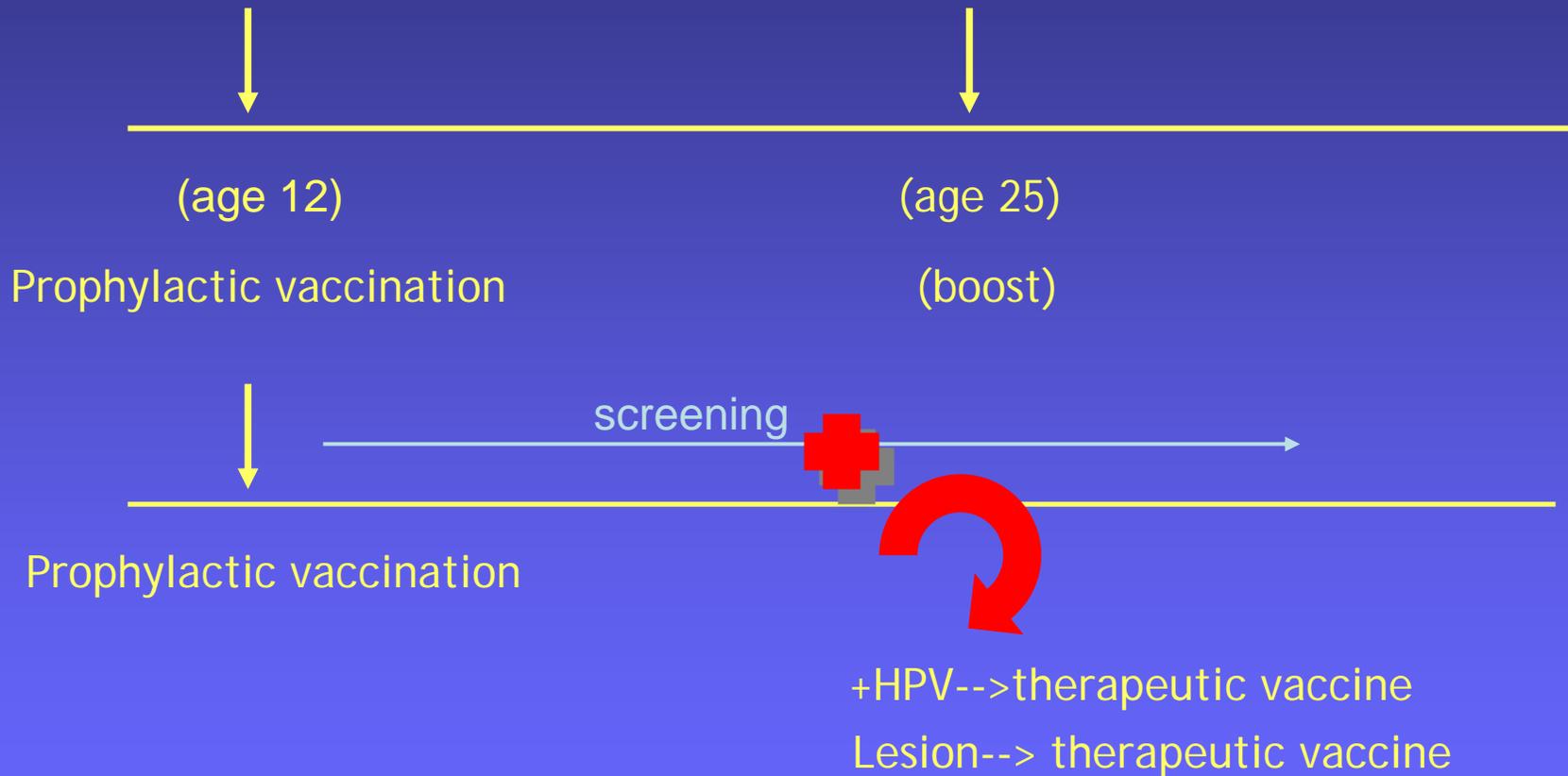
(age 25)

(boost)

Vaccination strategies



Vaccination strategies



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

