



UNIVERSITY *of* MARYLAND
SCHOOL OF MEDICINE

Natural history and Epidemiology of Cervical Cancer and HPV


Patti E. Gravitt, PhD, MS

Department of Epidemiology and Public Health

University of Maryland School of Medicine

Baltimore, MD

Agenda

- What is human papillomavirus (HPV)?
 - What is the sequence of events between HPV infection and cervical cancer?
 - What are the other risk factors for cervical cancer (besides high-risk HPV infection)?
 - What is the burden of HPV and cervical cancer?
 - Secondary prevention of cervical cancer through screening
- 

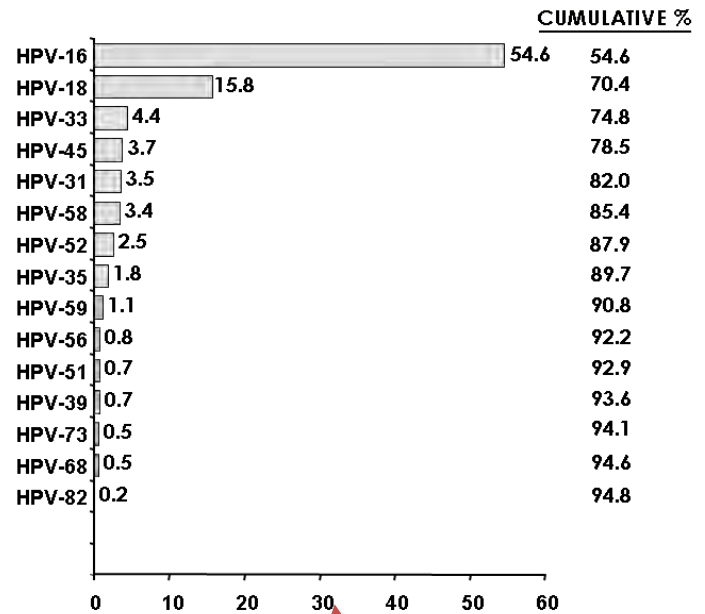
WHAT IS HUMAN PAPILLOMAVIRUS?



Human papillomaviruses



(B) META-ANALYSIS OF 14,500 CASES



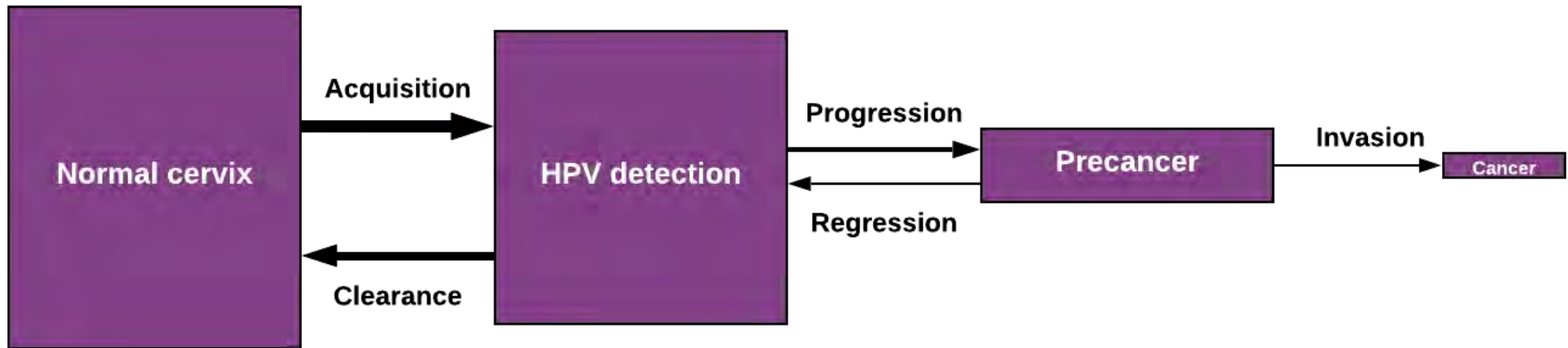
Estimates adapted from Smith LS, et al. Br J Cancer. Submitted.

Estimates adapted from Clifford GM, et al. Br J Cancer. 2003.

Sequence of events

HPV INFECTION → CERVICAL CANCER

Simple model of the natural history of HPV and cervical cancer



UNPACKING THE TRANSITIONS

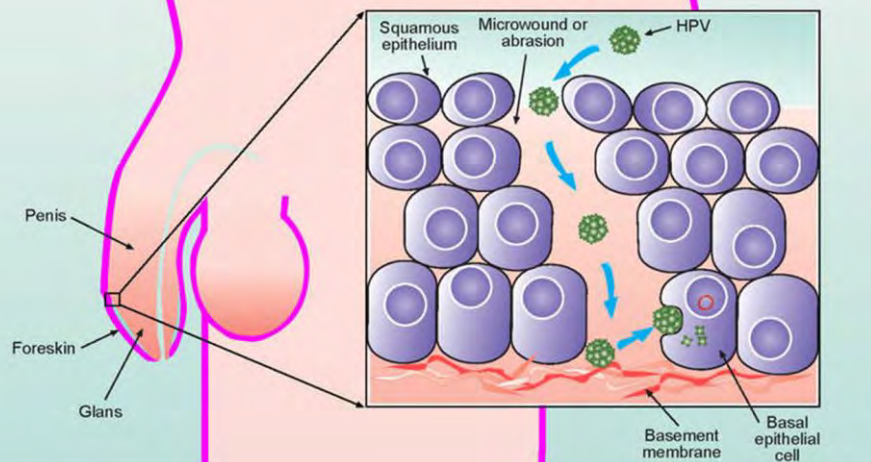
A decorative yellow wave graphic at the bottom of the slide, starting from the left edge and curving upwards towards the right edge.



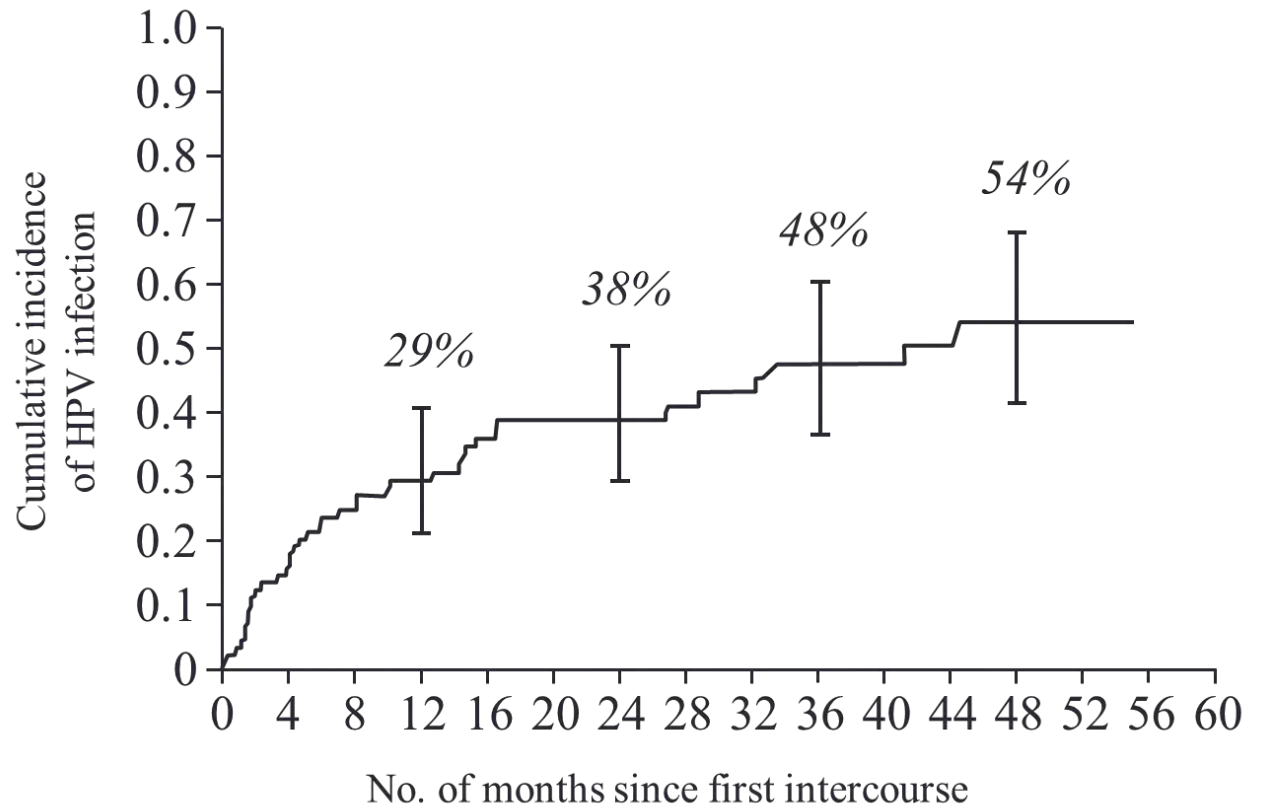
Transmission

- HPVs are EASILY transmitted through skin-to-skin contacts
- HPVs enter the basal epithelial cells through microscopic tears in the skin
- HPVs infect the basal cells, and when they are triggered to divide to repair the micro-wound, the viral life cycle is activated.

HPV infection of basal squamous epithelial cells

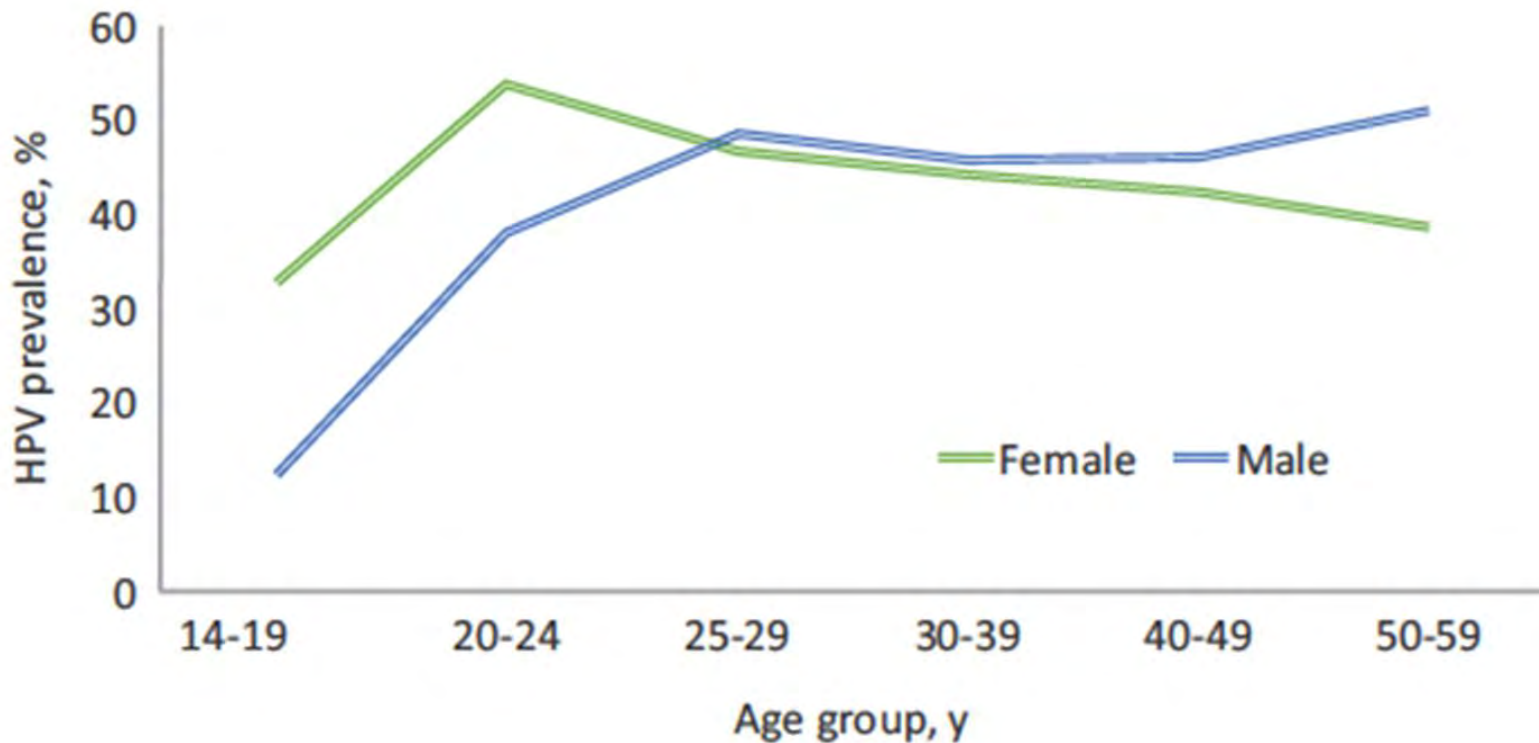


HPV transmission occurs rapidly after initiating sexual activity

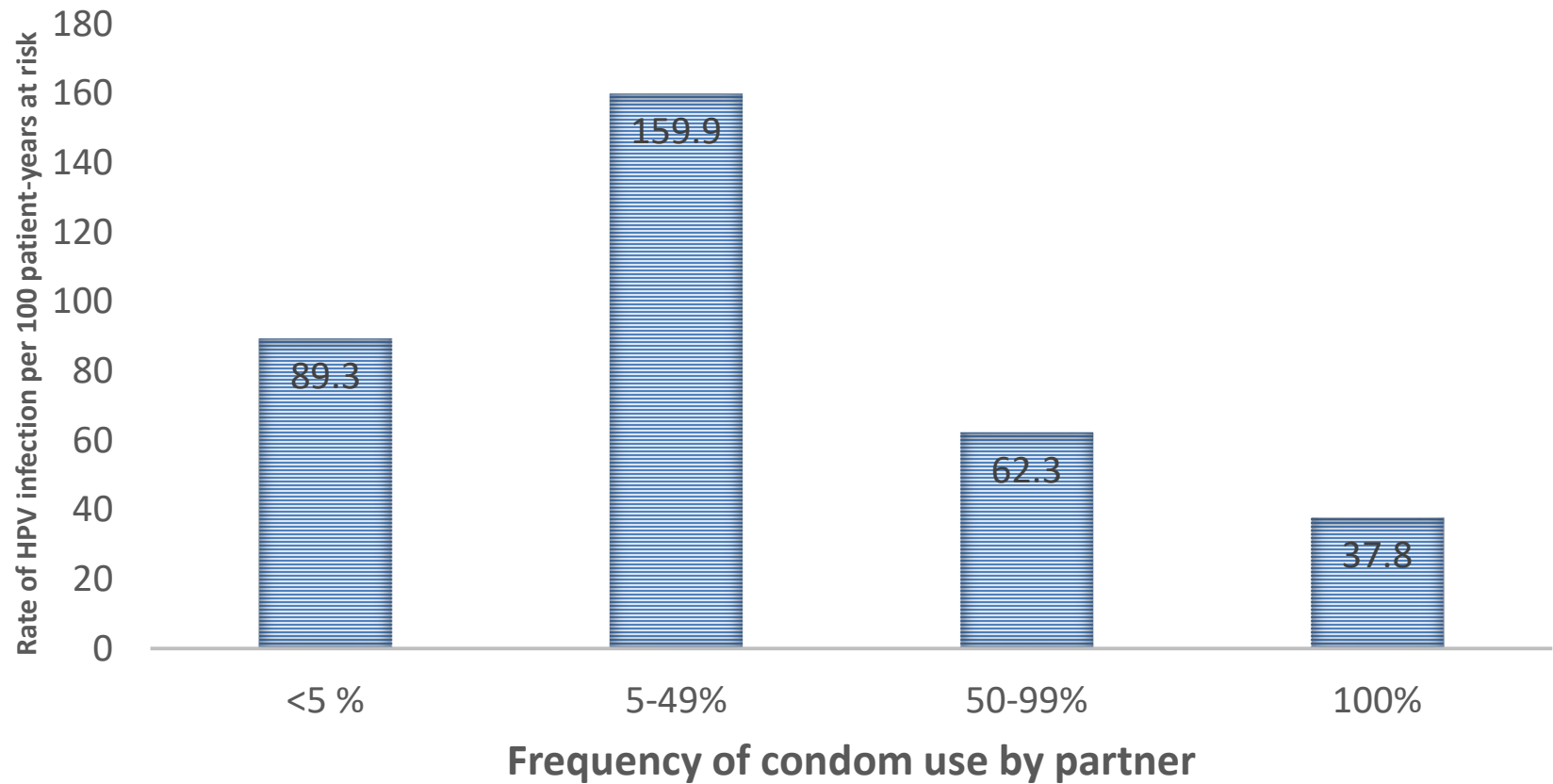


Genital HPV equally common in men and women

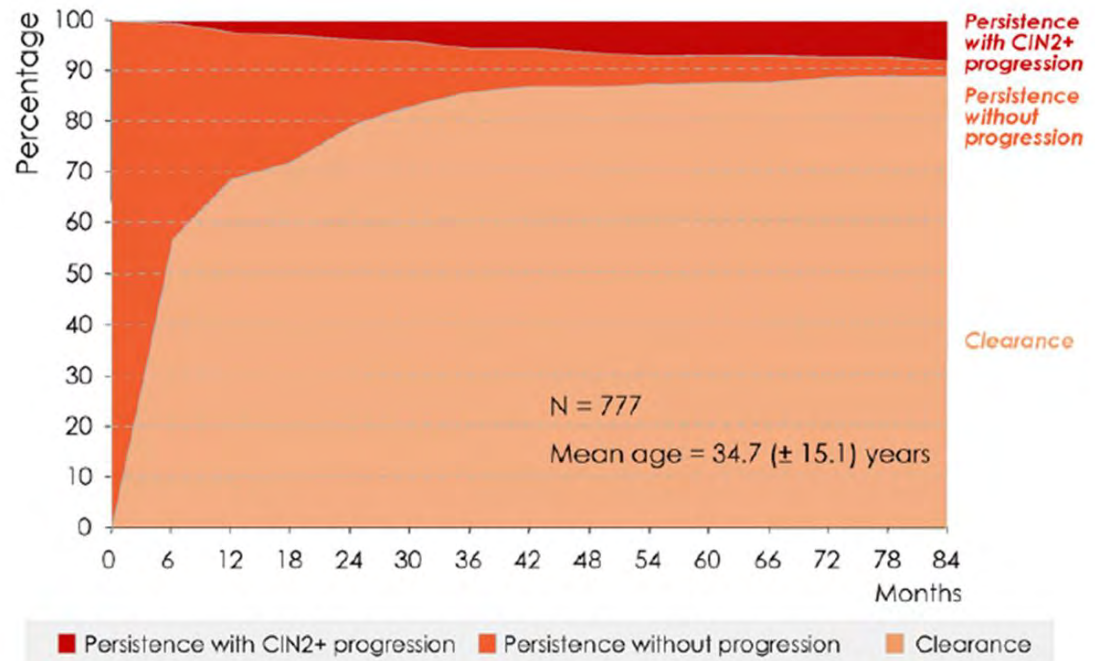
Age-specific prevalence of HPV (any type) among US female (2003-2006) and male (2013-2014) study participants. US National Health and Nutrition Examination Survey



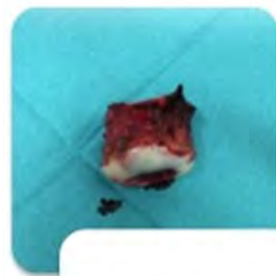
Condoms only partially protect against infection



Rapid control
of infection to
undetectable
levels is the
rule



- *Clearance* reflects loss of detectable HPV DNA from genital tract
- This happens through immune control of HPV and/or eradication of infection
- Note that absence of HPV detection *does not* imply absence of infection – HPV can become latent



a) Ex vivo separation of the cervix from the uterine corpus.

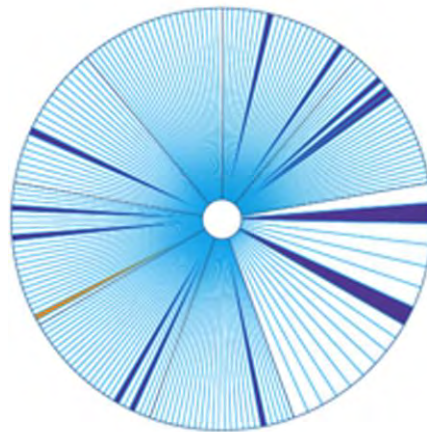


b) The cervix is sliced open in the anterior wall and fixed to a styrofoam plate.

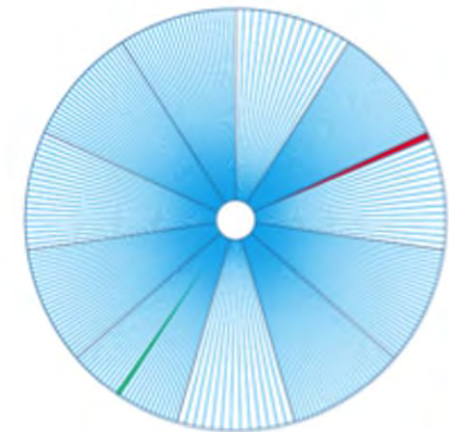


c) The formalin fixed cervix is cut into 2-3 mm sections and embedded in paraffin.

PATIENT 1



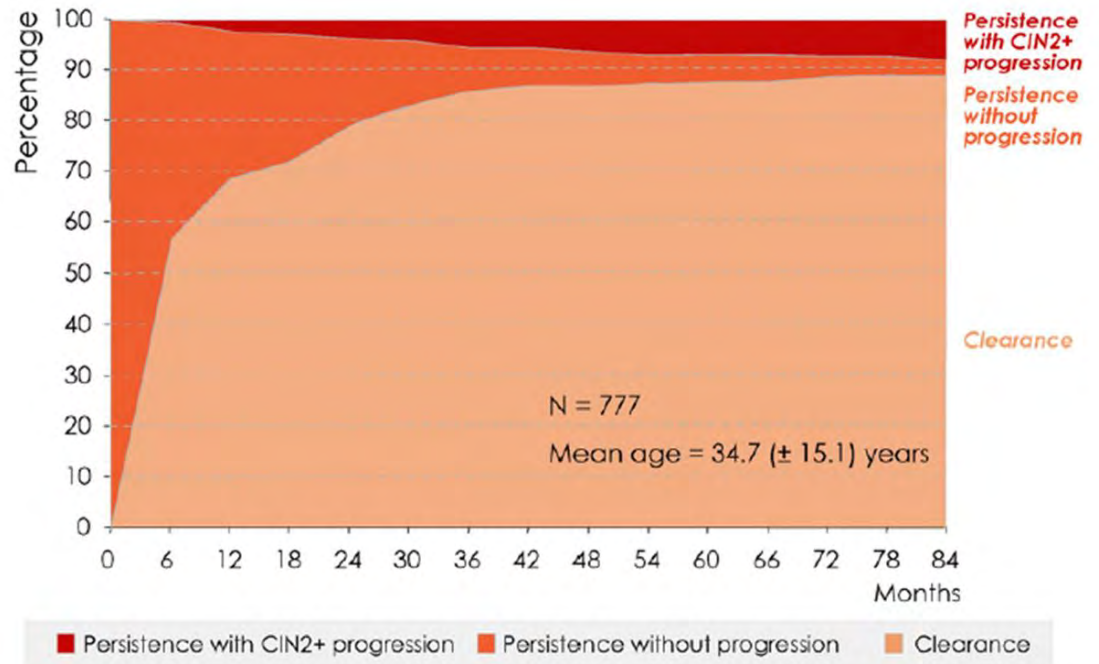
PATIENT 2



HPV deep in tissue when latent

- Animal studies show latent infection in basal cells of the epithelium
- These cells are not sampled during routine screening, but the infections are sporadically detected when sampling the entire cervical tissue

Persistent HR-HPV detection is strong risk factor for progression

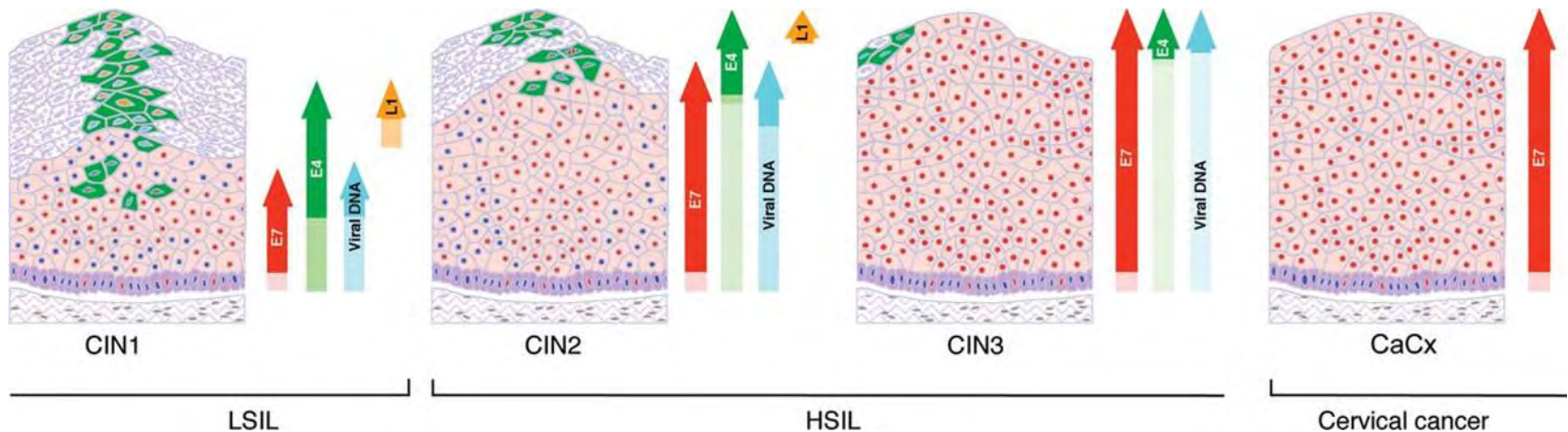


- Infections which are not controlled below limits of detection within 2-3 years are at high risk of progression to pre-cancer

What is precancer?

Cervical intraepithelial neoplasia (CIN) or squamous intraepithelial lesion (SIL) = terminology to define precancer based on Pap smear or biopsy interpretation

- **CIN1 or LSIL** = productive HPV infection with high probability of regression to normal
- **CIN2/3 or HSIL** = likely precancer with lower risk of regression → *TARGET of SCREENING*

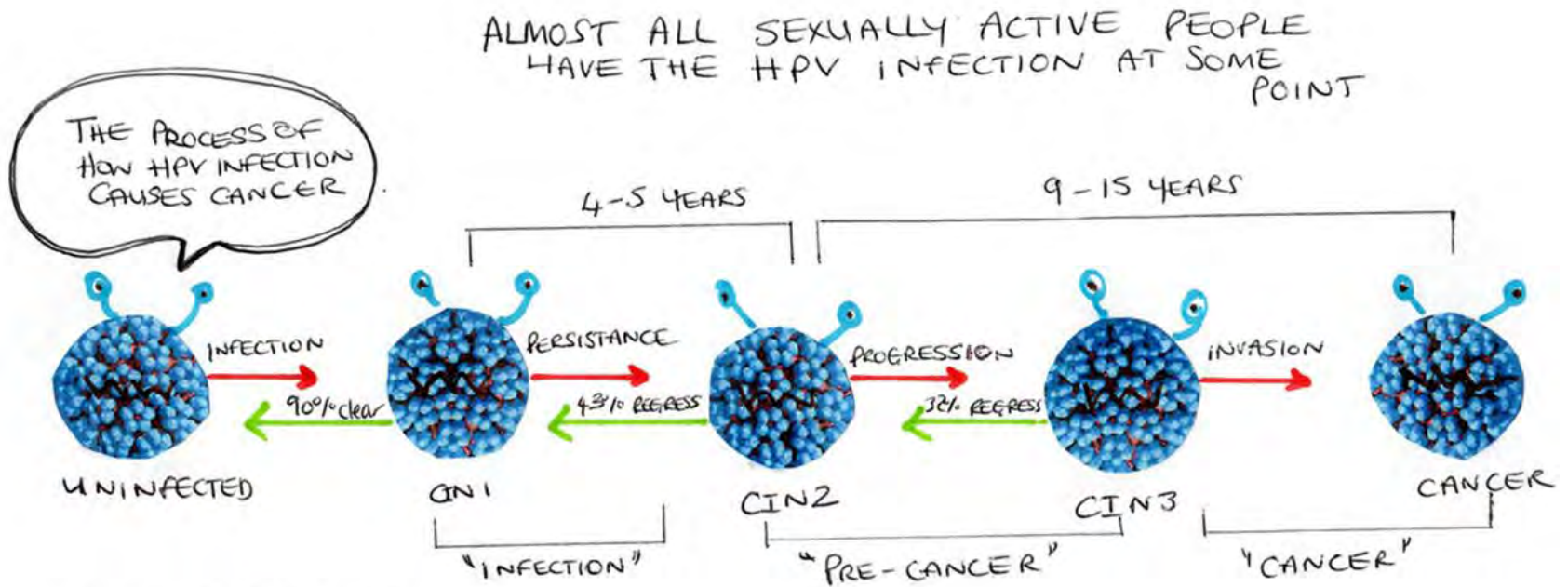


Modifiable risk factors for progression of HPV infection to cancer

- Long duration oral contraceptive use (> 5 years)
 - High parity (> 5 full-term births)
 - Tobacco smoke




Simple summary



THE BEST WAY
TO AVOID CERVICAL
CANCER? HAVE YOUR SMEAR!!

**HOW MANY PEOPLE GET HPV VS.
CERVICAL CANCER?**

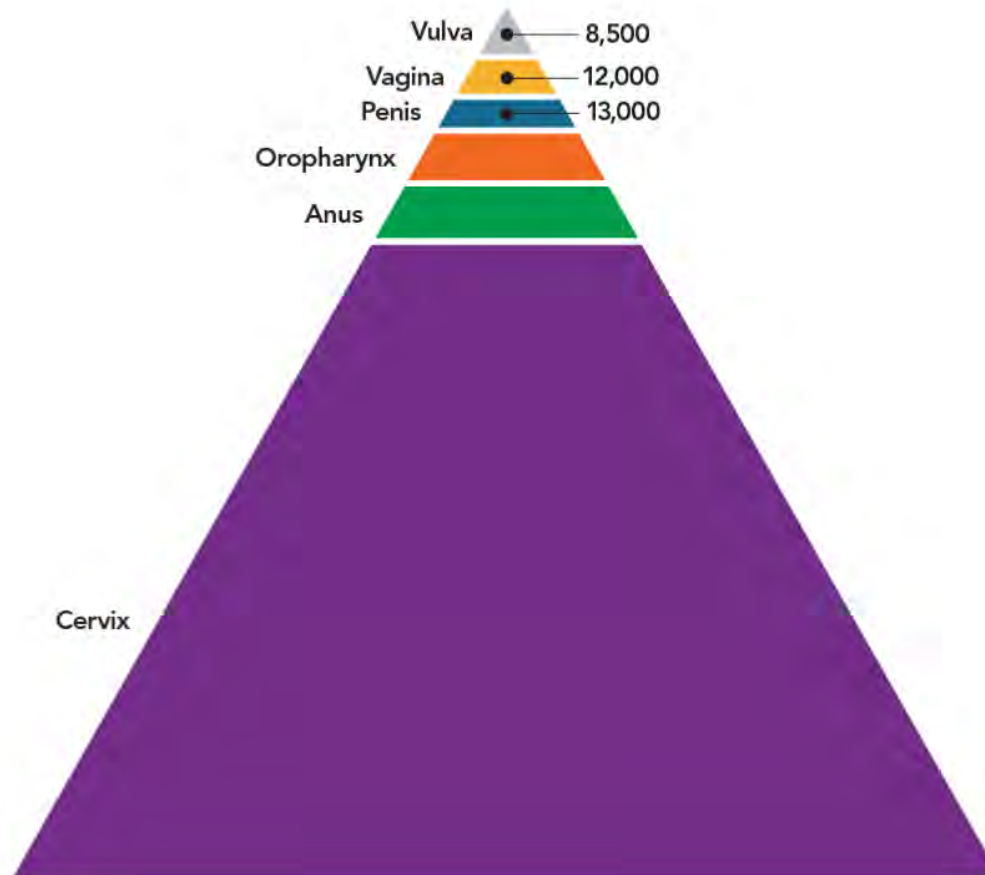


A large crowd of diverse people, seen from an aerial perspective, is arranged to form the number '100'. The crowd is composed of many small, colorful figures, creating a dense, multi-colored shape. The background is a plain, light-colored surface. In the foreground, there are several smaller, scattered groups of people, some walking and some on bicycles, providing a sense of scale to the massive crowd forming the number.

Who is at
risk for
HPV?

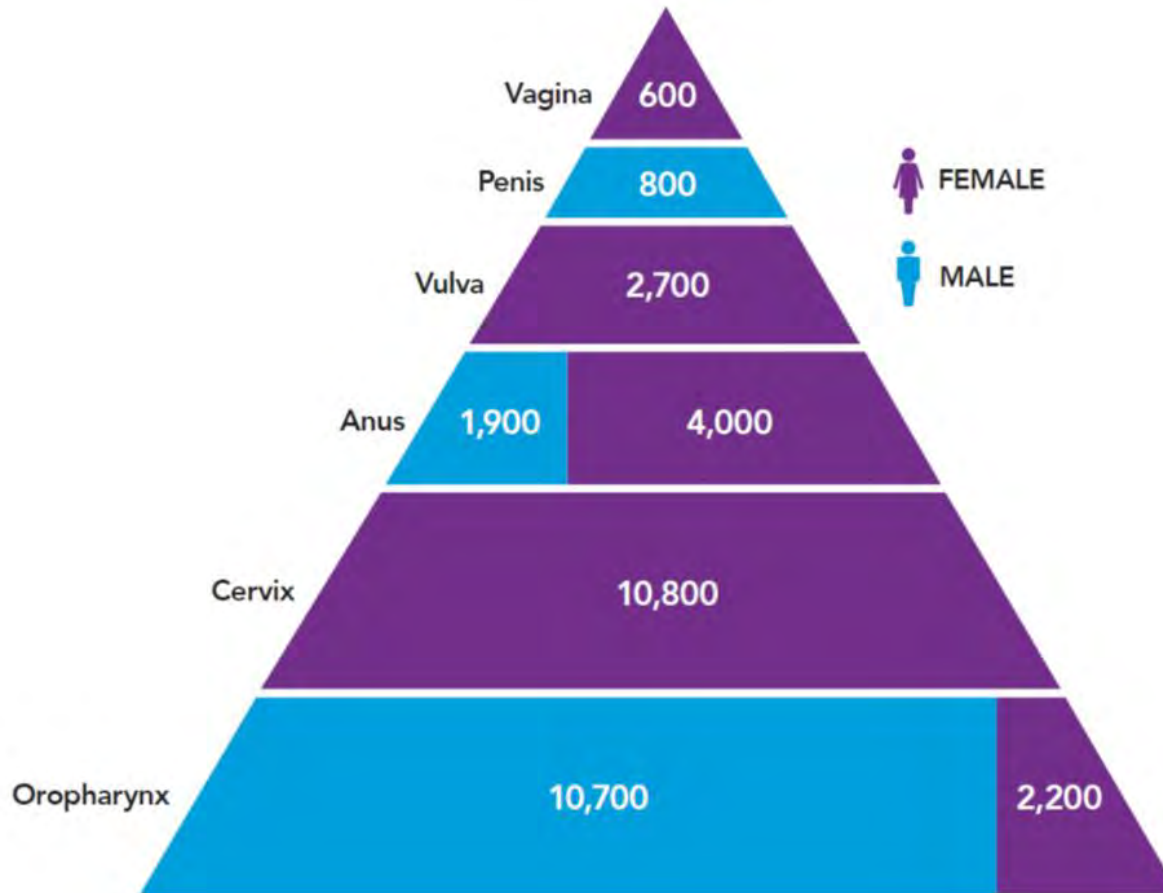
PRACTICALLY EVERYONE!

Global burden of HPV-associated cancers



Source: de Martel C, et al. Worldwide burden of cancer attributable to HPV by site, country and HPV type. *Int J Cancer*. 2017;141(4):664-70.

Numbers of US Cancers Caused by HPV



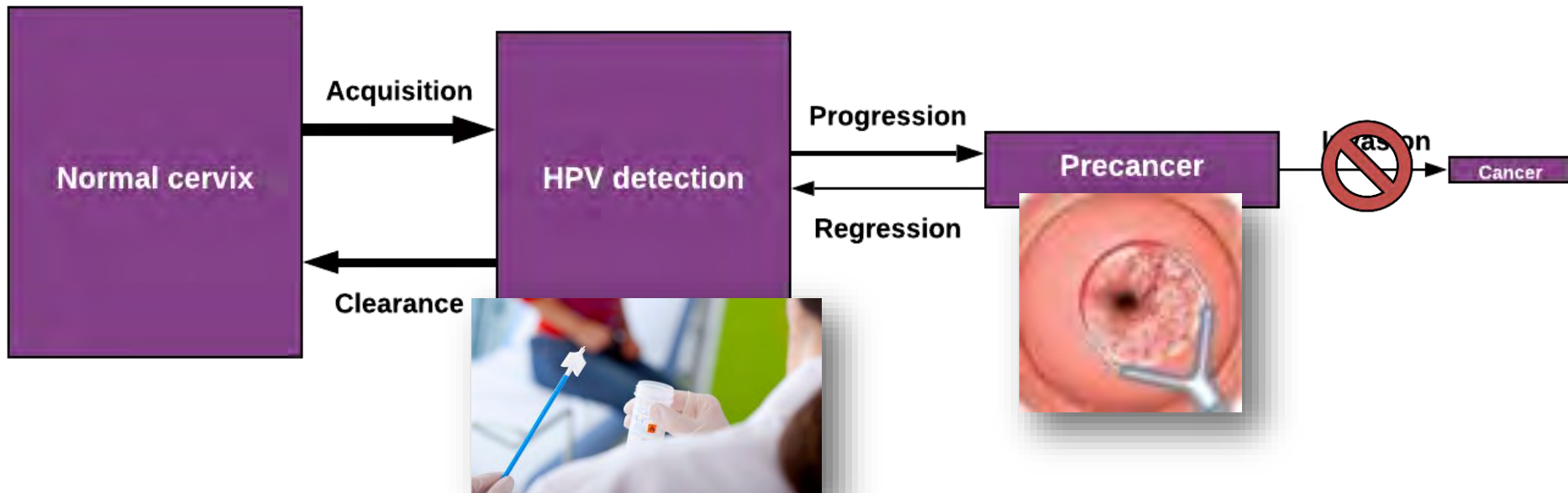
Source: Centers for Disease Control and Prevention. How many cancers are linked with HPV each year? Available from: <https://www.cdc.gov/cancer/hpv/statistics/cases.htm>.

Global vs. US burden of HPV-associated cancers – why the difference?

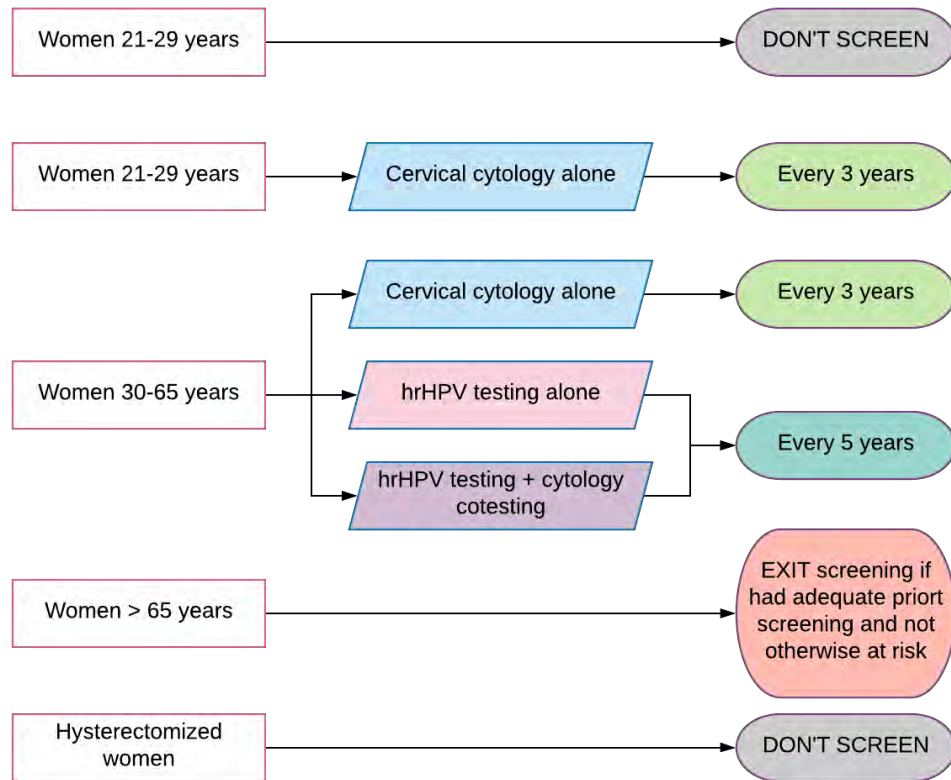
SCREENING!!

Secondary Cervical Cancer Prevention: Early detection and treatment → SCREENING

- Screening programs identify HPV infection or cellular abnormalities associated with precancer
- Diagnosis by colposcopy+biopsy and histopathologic interpretation to identify women with precancer
- Treat precancer by ablation or excision (usually outpatient procedure) to prevent progression to cervical cancer

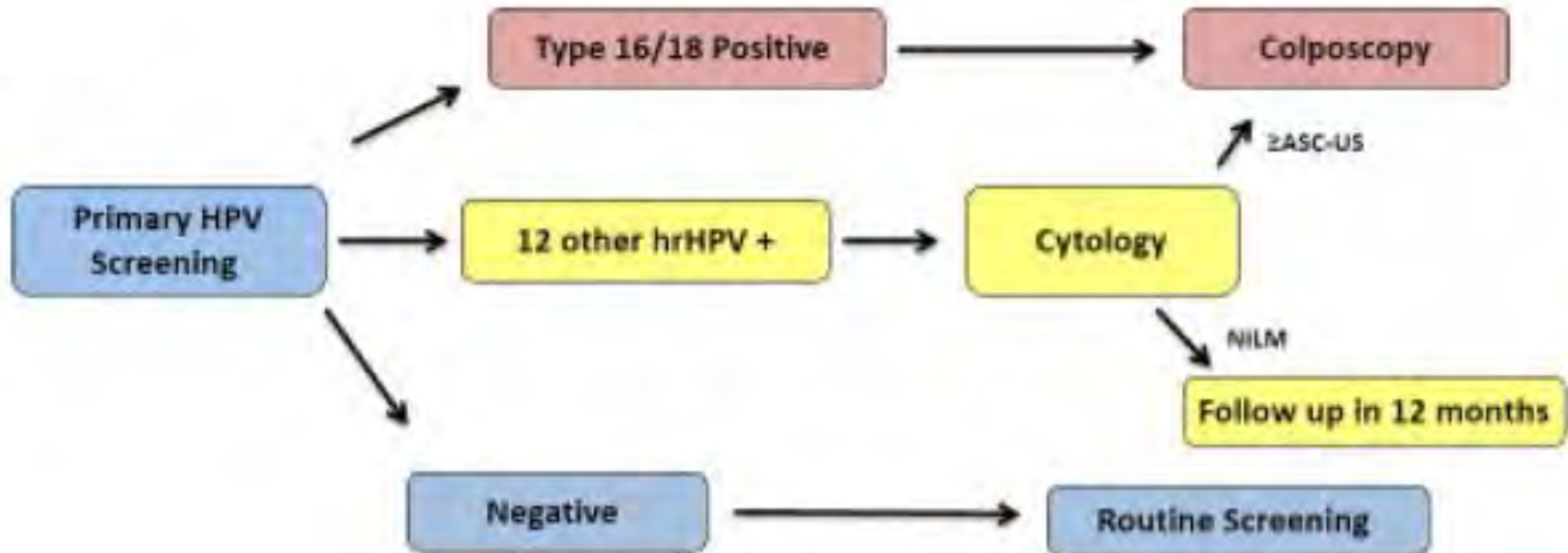


US Preventive Services Task Force (USPSTF)
Cervical Cancer Screening Guidelines:
August 2018

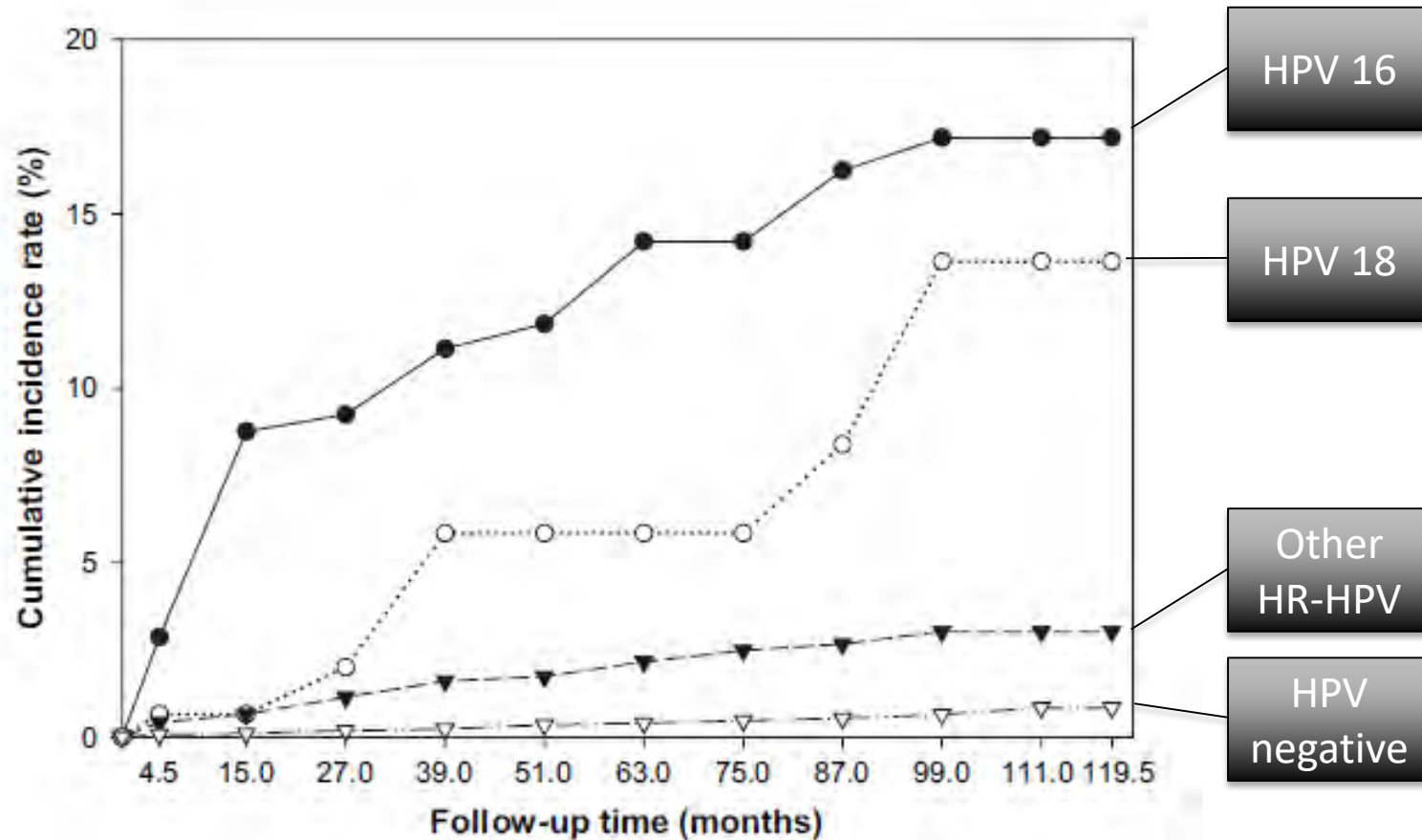


- Type and frequency of screening varies by age
- Choice of screening test in women aged 30-65 left to provider/patient

Example screening management algorithm

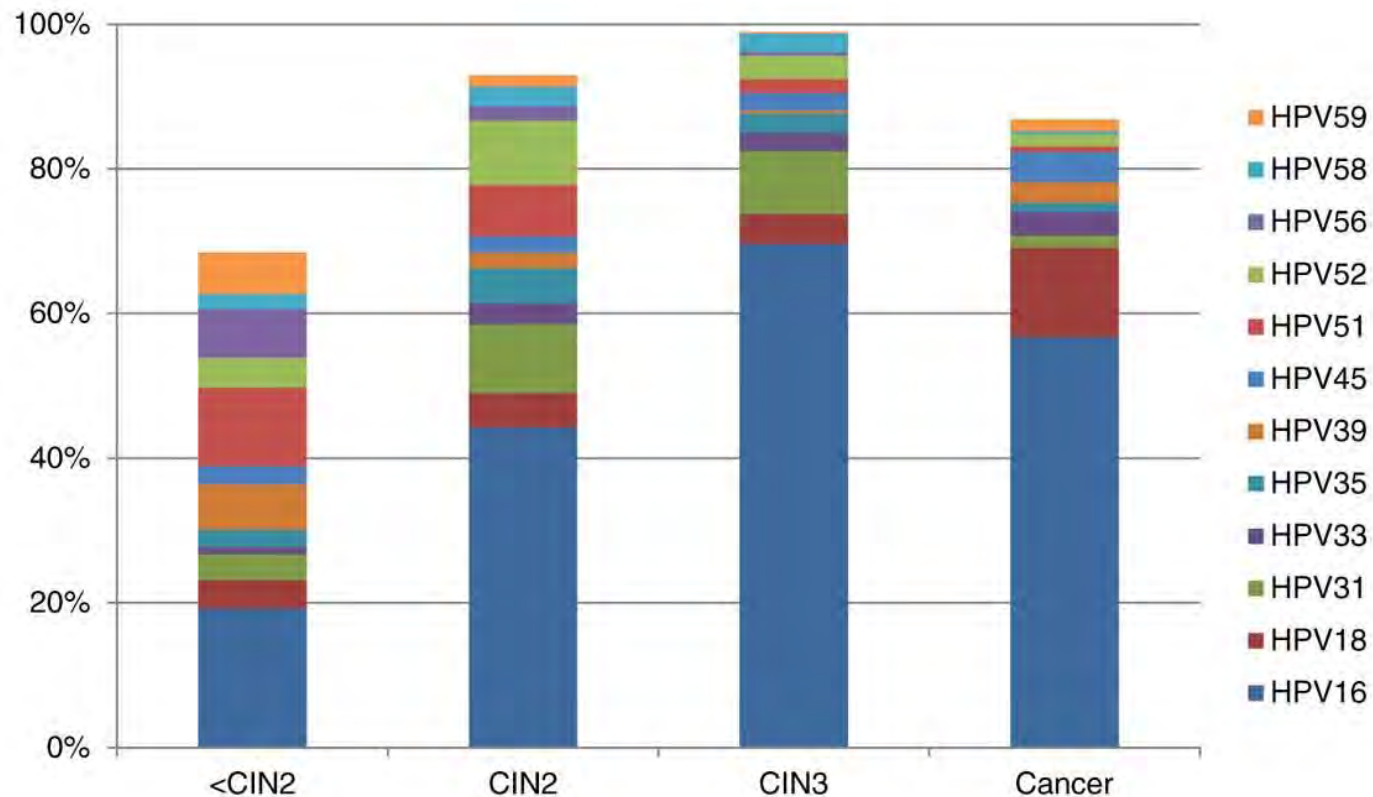


Different absolute risk of progression to precancer (CIN3+) based on HPV type



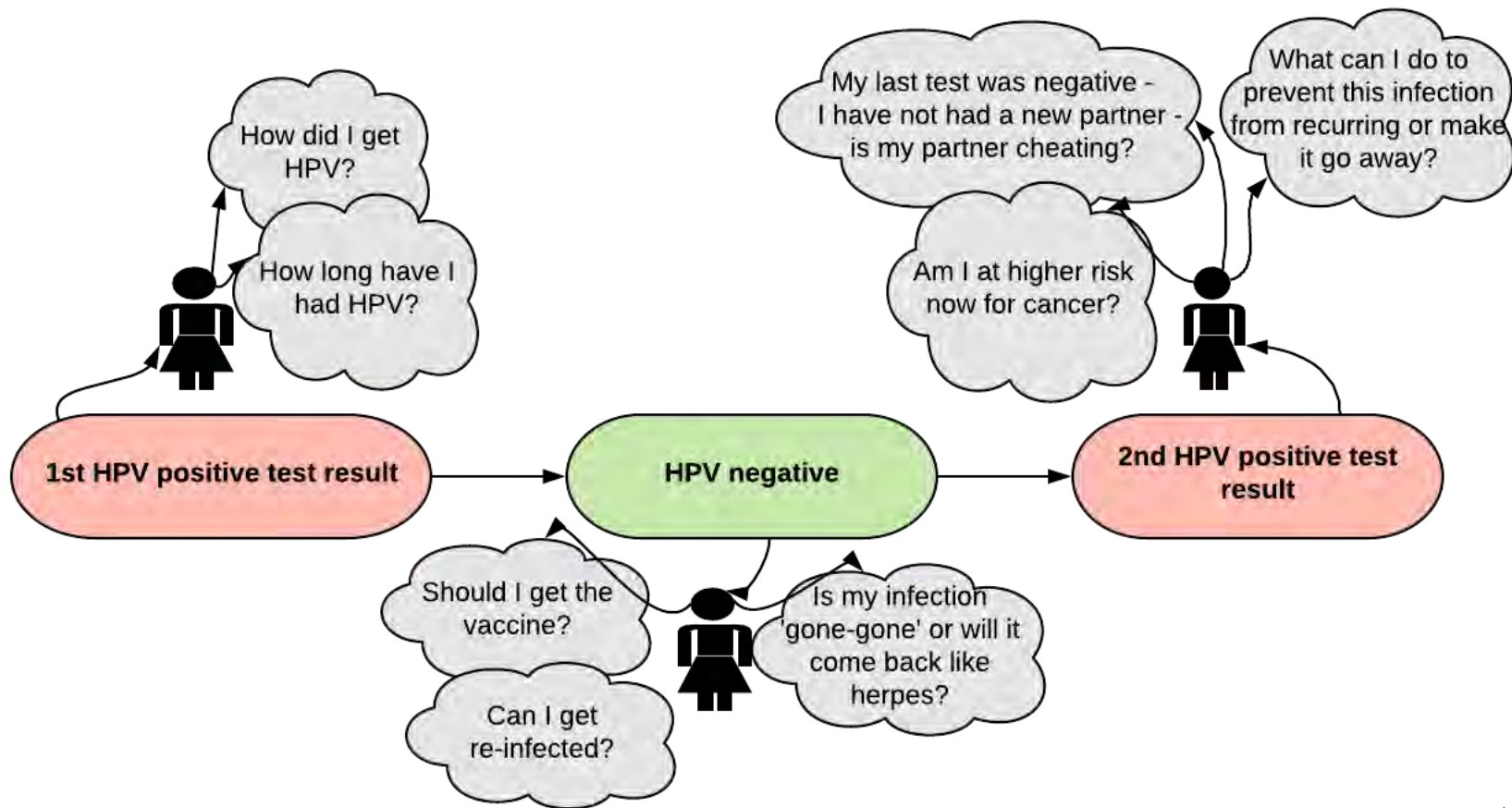
HPV 16/18 are not the most common types, they are the most common types that cause cancer

Percentage

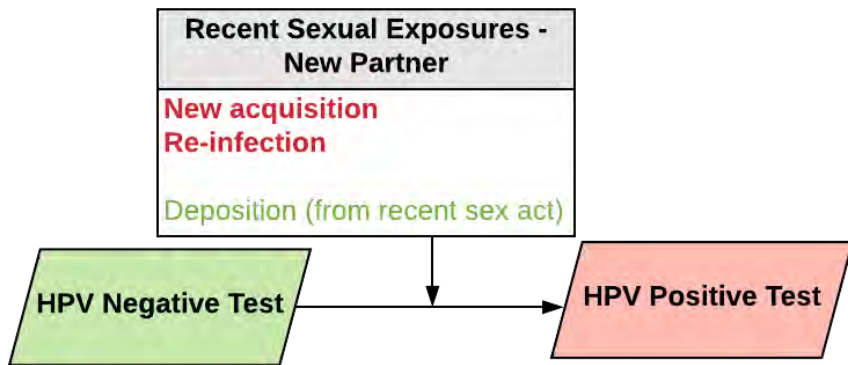


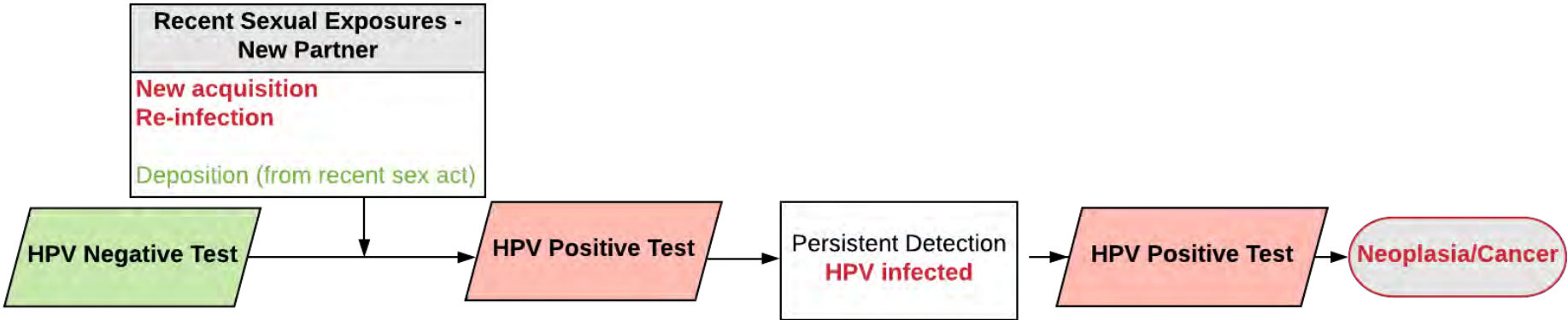
Woman-level natural history

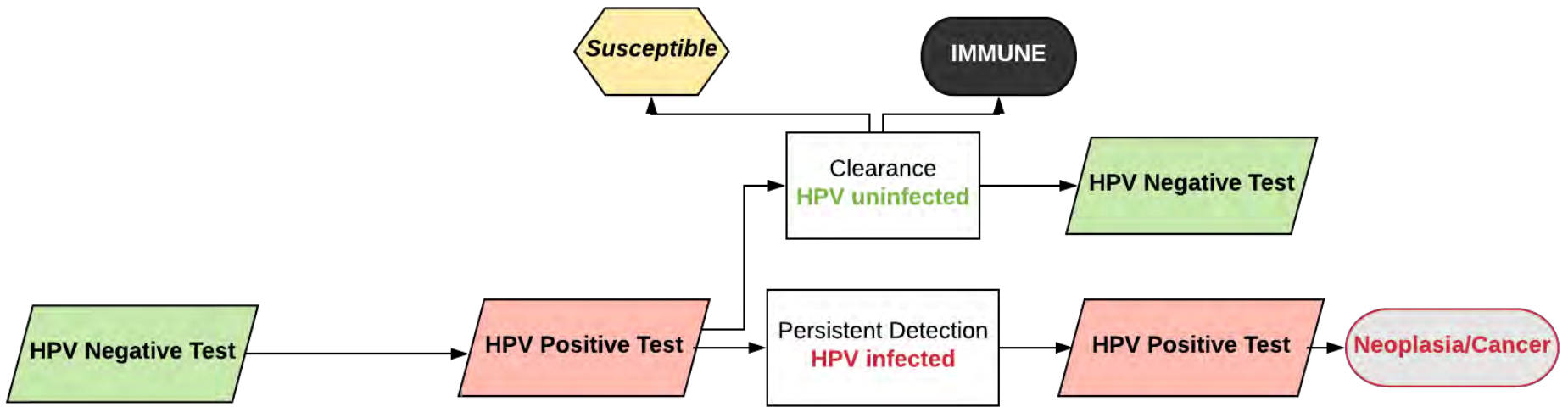
- Women participating in screening are accumulating their own personal HPV natural history
- How to counsel? How to reduce risk?

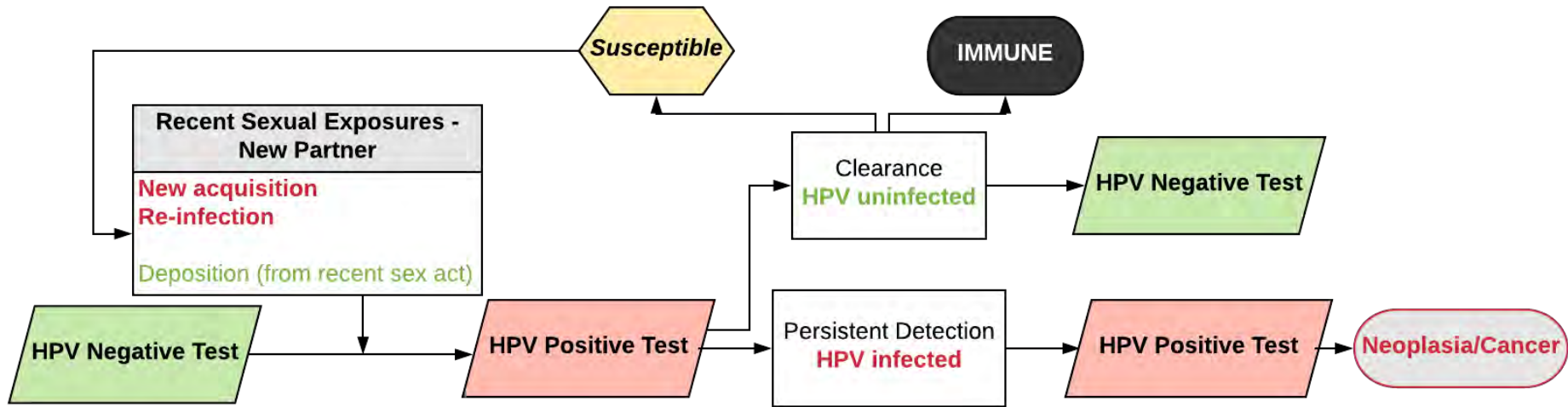


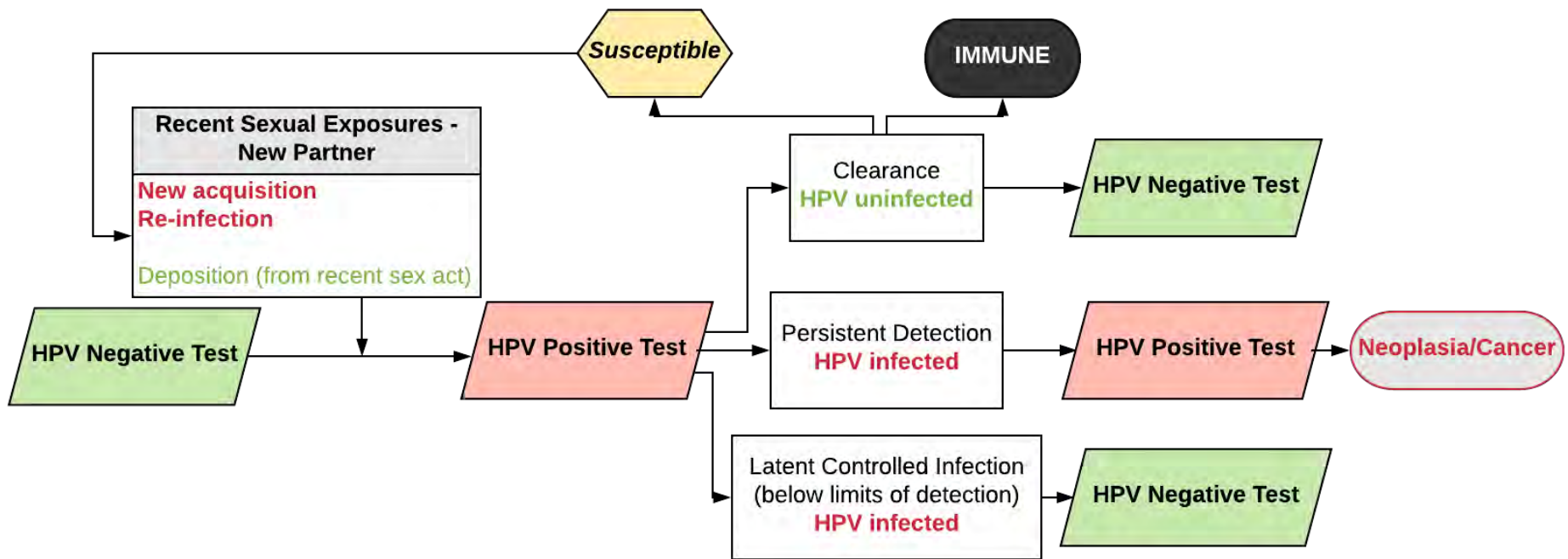
CUMULATIVE HPV SCREENING HISTORY

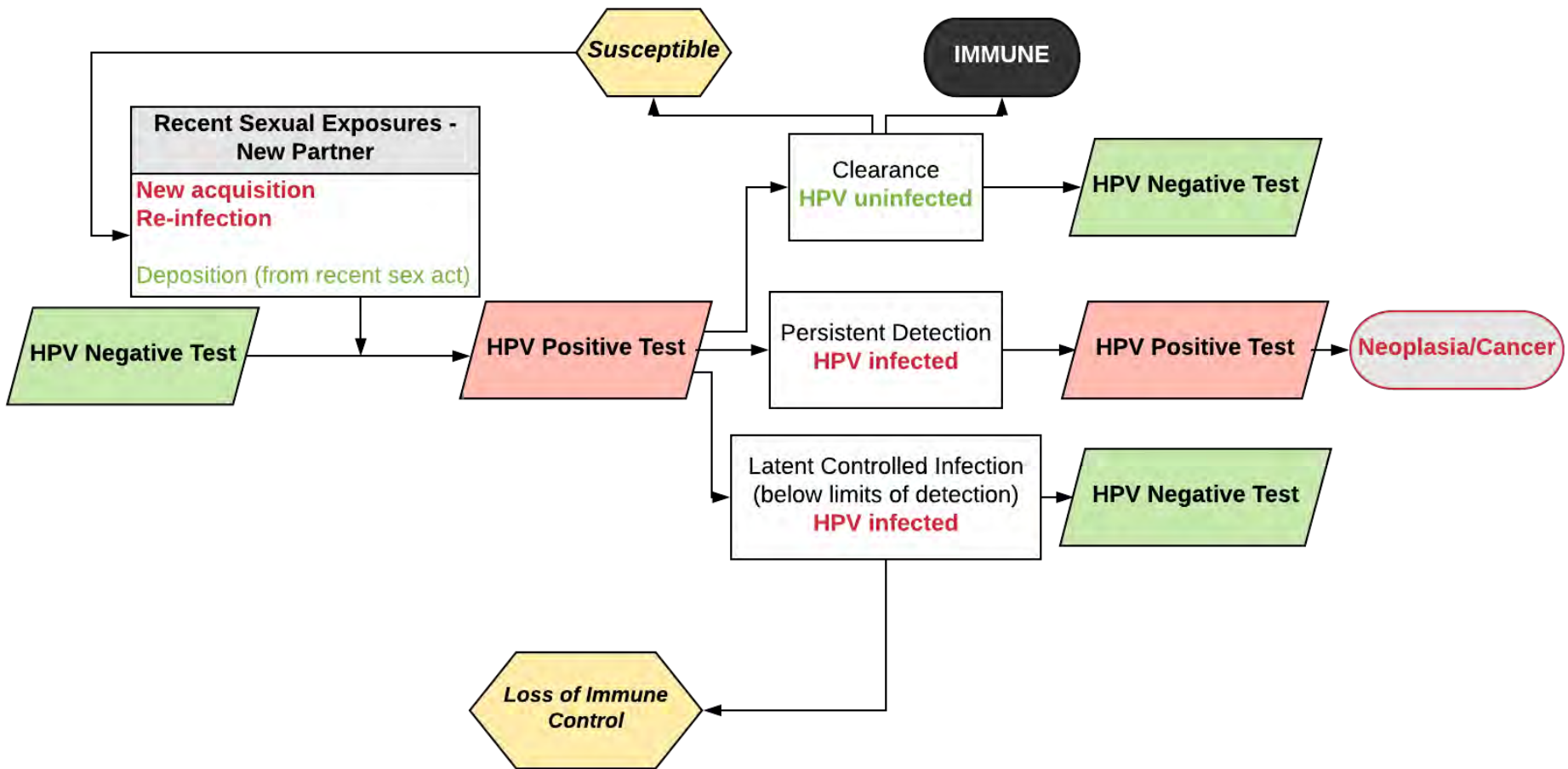


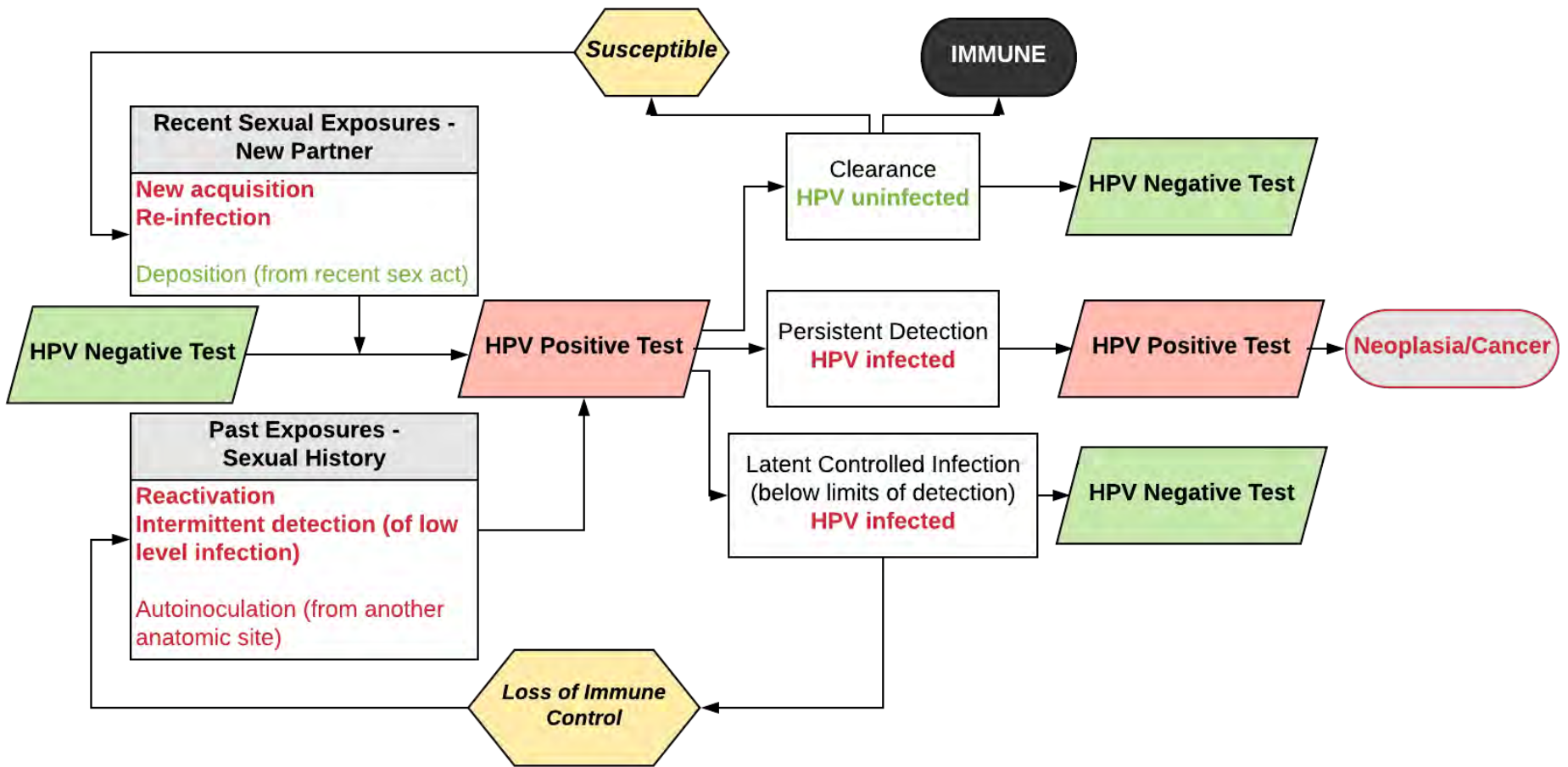




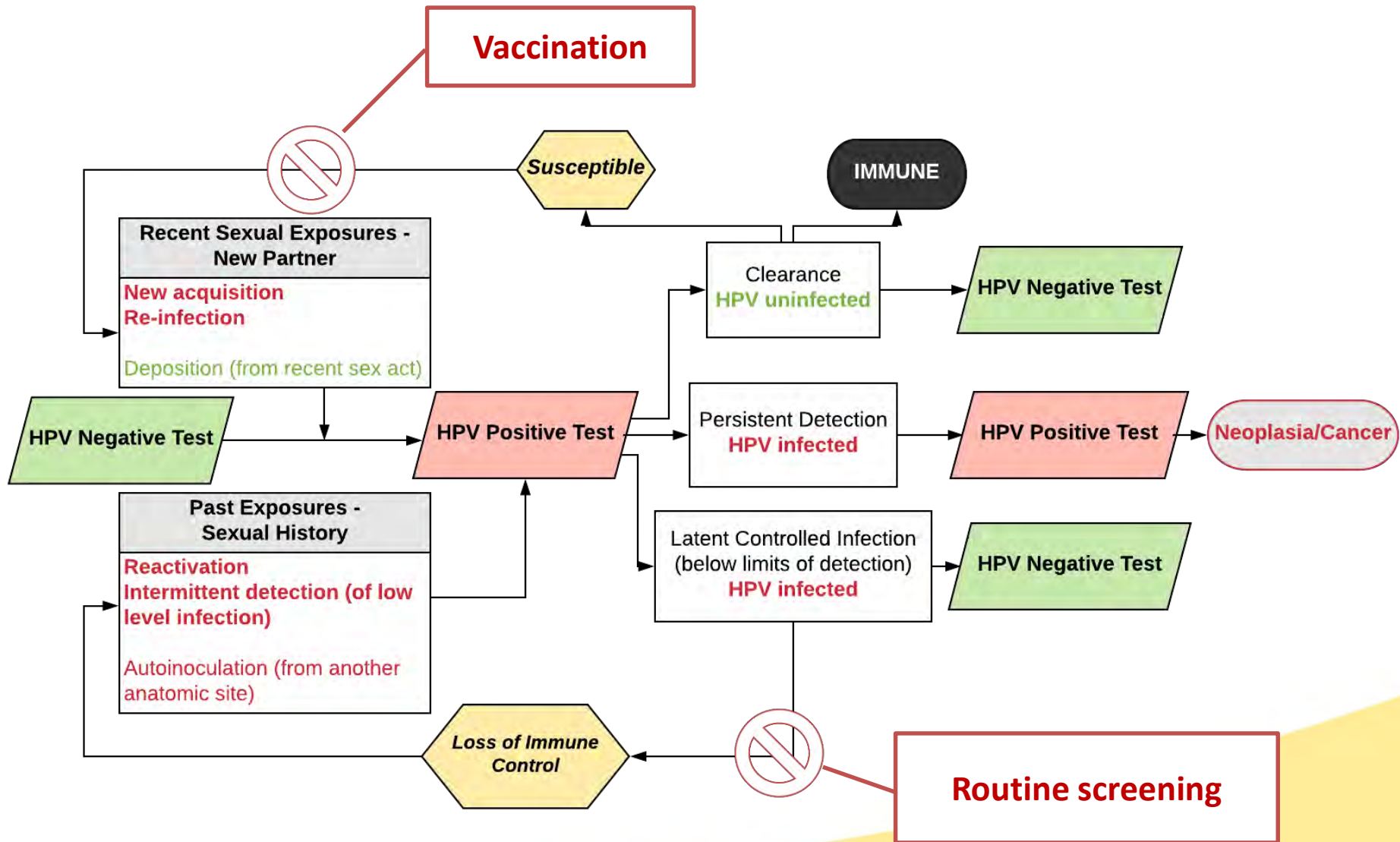






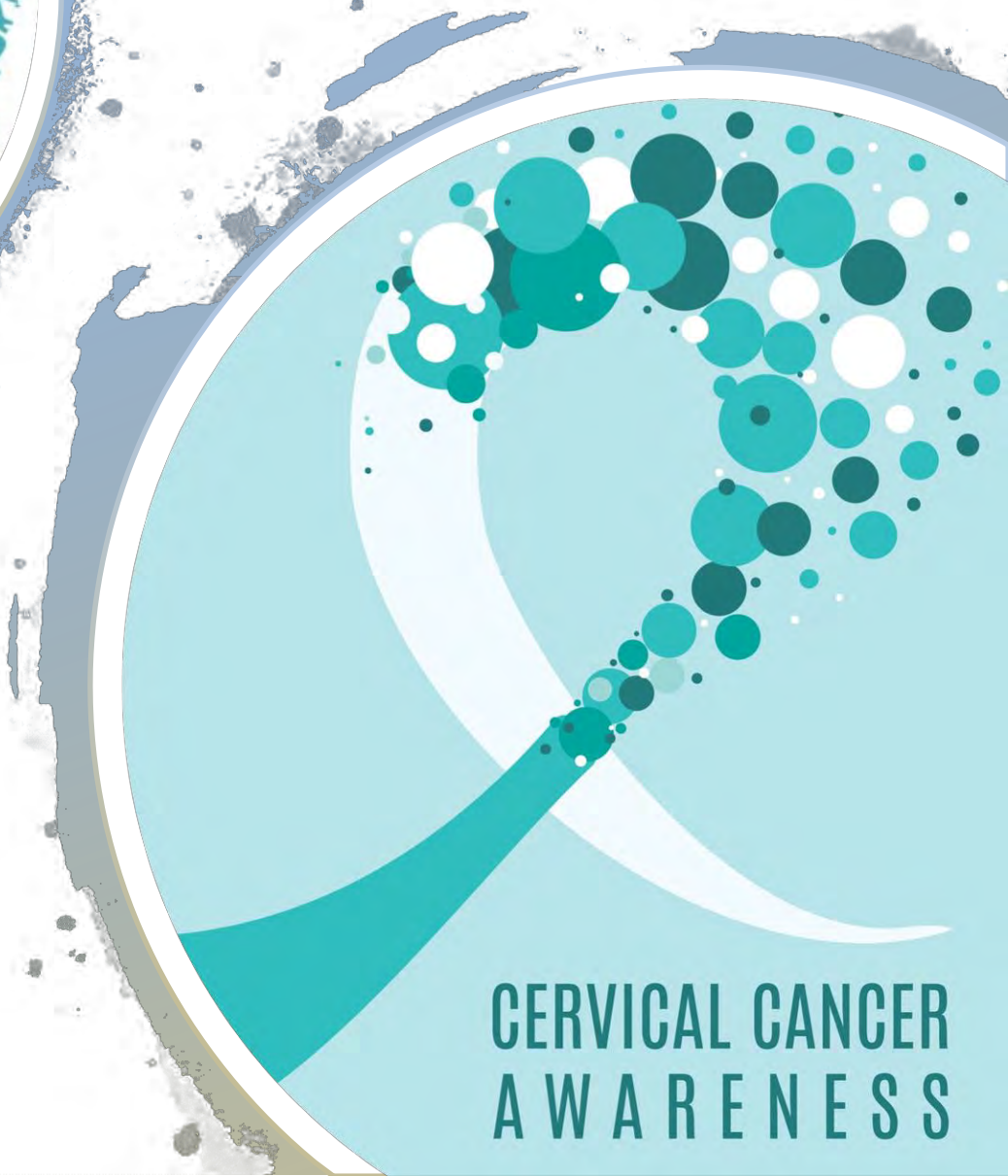


Prevention strategies





THANK YOU!



CERVICAL CANCER
AWARENESS