The HPV Twilight Zone

Latency, Immune Control and Subclinical Infection - Basic Science

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The human Papillomavirus twilight zone – Latency, immune control and subclinical infection

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A B S T R A C T

The incorporation of HPV DNA testing into cervical screening programs has shown that many HPV-positive women are cytologically normal, with HPV-positivity fluctuating throughout life. Such results suggest that papillomaviruses may persist in a latent state after disease clearance, with sporadic recurrence. It appears that virus latency represents a narrow slot in a wider spectrum of subclinical and possibly productive infections. Clinical studies, and animal model infection studies, suggested a key role for host immune surveillance in maintaining such asymptomatic infections, and although infections may also be cleared, most studies have used the term 'clearance' to describe a situation where the presence of HPV DNA falls below the clinical detection level. Given our knowledge of papillomavirus immune evasion strategies and the restricted pattern of viral gene expression required for 'basal cell' persistence, the term 'apparent clearance' and 'subclinical persistence' of infection may better summarise our understanding. Subclinical infection also encompasses the lag phase, which occurs between infection and lesion development. This is dependent on infection titre, with multifocal infections developing more rapidly to disease. These concepts can usefully influence patient management where HPV-positivity occurs sometime after the onset of sexual activity, and where vertical transmission is suspected despite a lag period.

1. Chronic viral infections typically require a 'reservoir of infection' to facilitate persistence

Virus infections are generally classified as 'acute' or 'chronic', according to their infection strategies and the disease biology that they cause. Acute infections are typically characterised by the rapid development of symptomatic disease - followed by the initiation of an adaptive immune response, which over a period of days or weeks leads to virus clearance and the resolution of disease symptoms [1,2]. Many respiratory infections, including those caused by Influenza and Coronavirus follow this route, and once the initial infection is brought under control and disease symptoms subside, the protective immune response will gradually decline, allowing subsequent reinfection and disease recurrence with milder systems. Viruses which cause acute infections are typically associated with cycles of infection and clearance through life, and for many RNA viruses, this is facilitated by error prone viral replication which contributes to virus diversity [1,2].

An alternative life cycle strategy that is also commonly used by viruses, including Human Immunodeficiency virus (HIV), Human T-cell leukaemia virus (HTLV), Polyomaviruses and several members of the Herpes virus family, is to establish a chronic infection in a cell type that can act as a reservoir of infection, but which is not lysed by the virus. Typically, such 'cellular reservoirs of infection' are able to persist in the body over an extended period of time without being recognised by the immune system - a situation which facilitates the production of infectious virus particles as these cells divide to give rise to 'daughter cells' which go on to differentiate [3–5]. This is the strategy used by Epstein Barr virus and Cytomegalovirus for instance, which persist in B cell and monocytes reservoirs respectively, but is also the strategy used by papillomaviruses, who's cellular reservoir of infection is contained amongst the basal cells that make up the epithelial basal layer [6,7]. Viruses which establish chronic infections in this way are often controlled by the host's immune system, which can regulate the extent of productive infection, but which cannot clear the cellular reservoir of infection where viral gene expression is maintained at very low levels. Indeed, the so-called 'latently infected cells' that have been characterised by Herpes virus biologists, have tightly regulated latency-associated virus transcription patterns, and represent a cellular reservoir from which productive infection can be initiated when the immune environment allows it [8]. The separation of the HPV life cycle into an immunologically quiet basal cell 'reservoir compartment', and a 'productive/genome amplification compartment' which is derived from this reservoir following differentiation [9,10], we can draw analogies between papillomaviruses and other viruses which cause chronic infections and which have well established subclinical and/or latent states.

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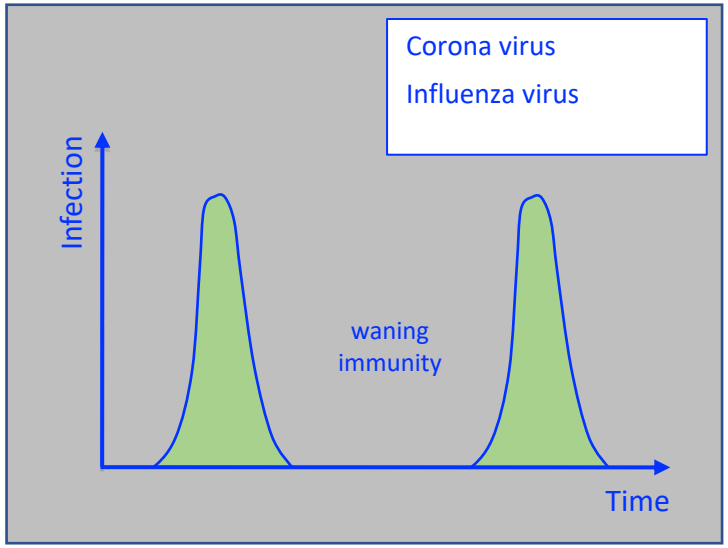
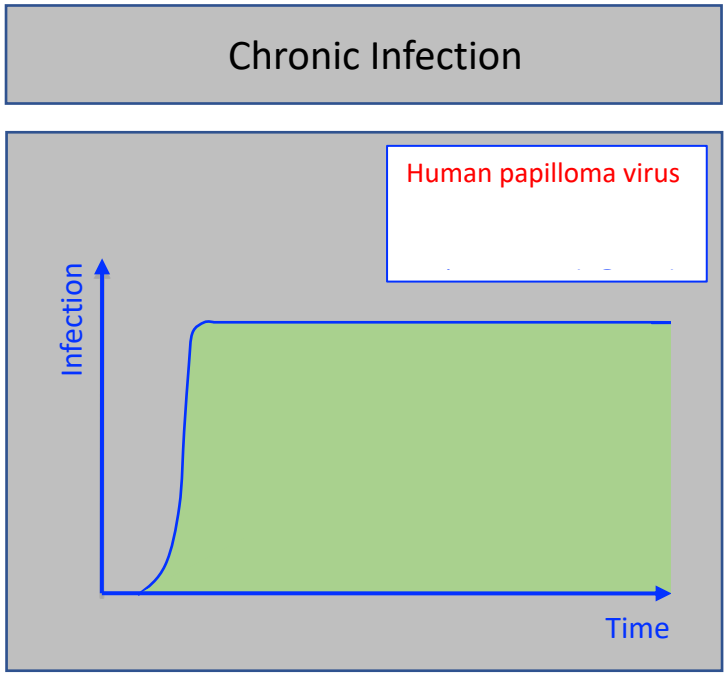
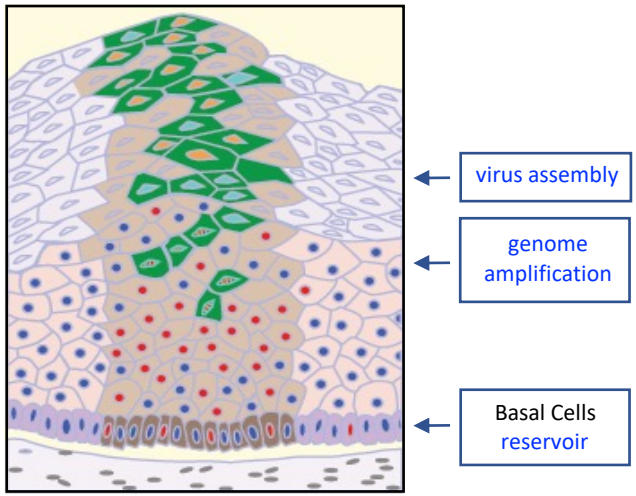
Acute Infection



Types of Virus Infection

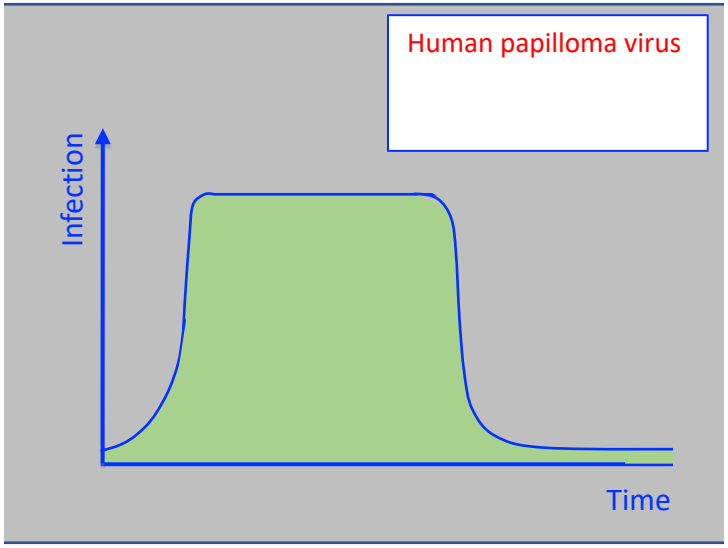


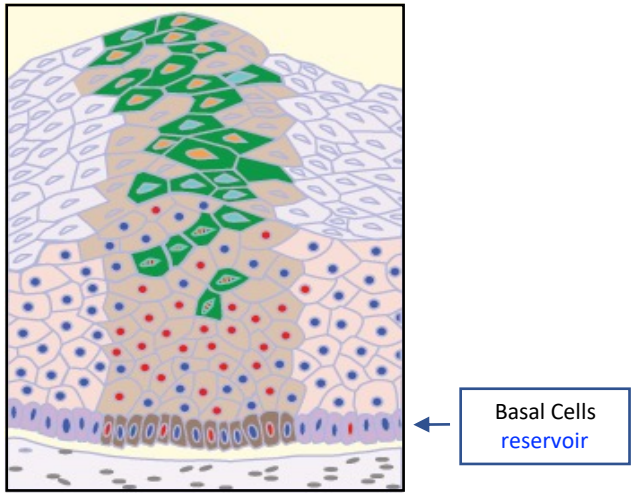


Types of Virus Infection

Roles for E1-independent replication during low-risk and high-risk human papillomavirus genome maintenance. PLOS Pathogens (2019) 15(5): e1007755. https://doi.org/10.1371/journal.ppat.1007755

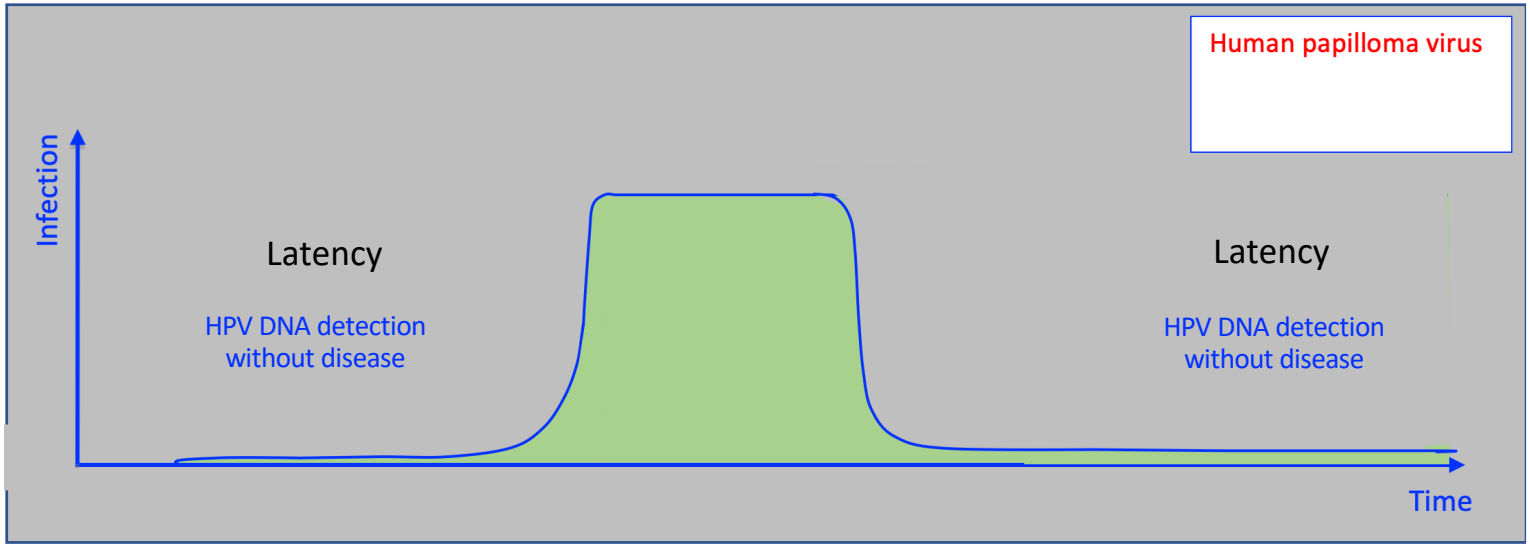
Chronic Infection



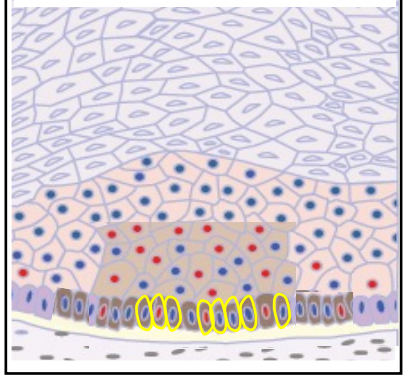


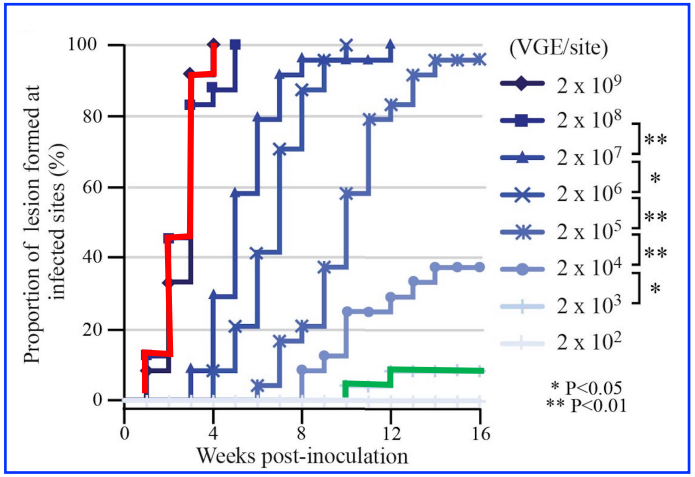
Types of Virus Infection

Chronic Infection



Duration of lag phase depends on **virus titre**





Research paper

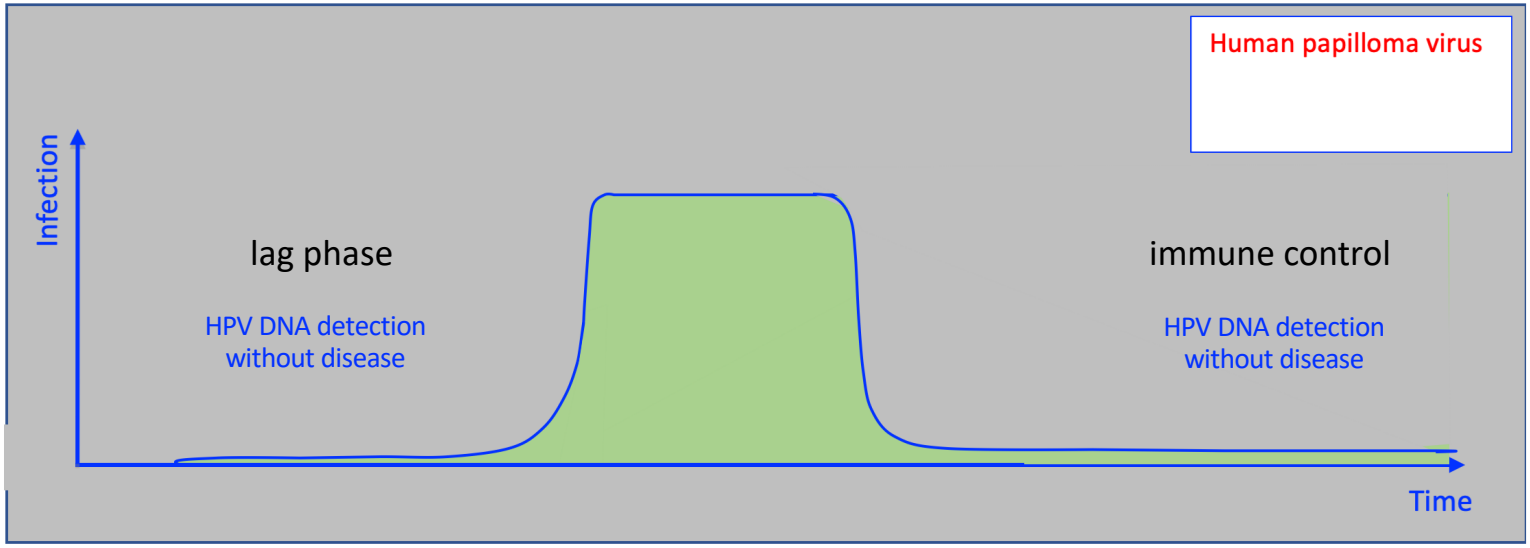
Dynamics of papillomavirus *in vivo* disease formation –Implications for transmission in clinical settings

EBioMedicine 63 (2021) 103177

Egawa, N., Shiraz, A., Crawford, R., Saunders-Wood, T., Yarwood, J., Rogers, M., Sharma, A., Eichenbaum, G.A. & Doorbar, J.

Types of Virus Infection

Chronic Infection



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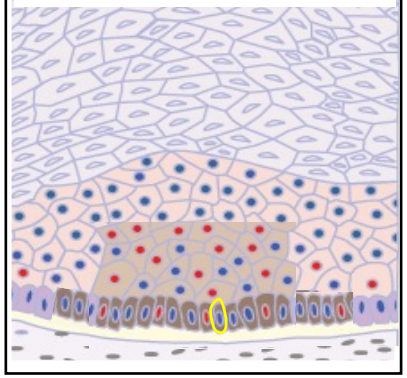
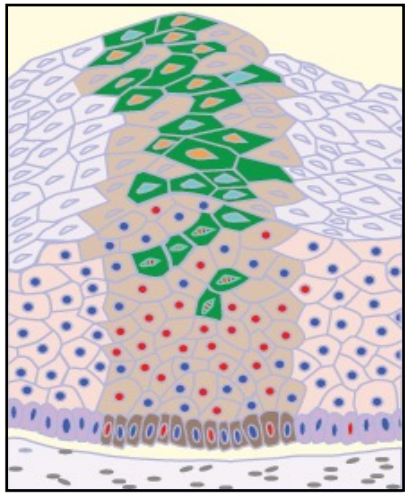




Basal Cells reservoir

Types of Virus Infection

Virus latency

Current Definitions of Virus Latency

Fields Virology ; Infection is latent if the production of infectious virus does not occur immediately, but the virus retains the potential to initiate productive infection at a later time. The process of re-initiating a productive infection from the latent state is termed reactivation. Latency is not merely a slow productive replication cycle; Latency represents a unique transcriptional and translational state of a virus in which the productive replication cycle is not operative but can become operative when the need arises.

Source; Knipe, D. M., Howley, P. (2013). Fields Virology. United States: Wolters Kluwer Health.

Wikipedia ; Virus latency (or viral latency) is the ability of a pathogenic virus to lie dormant (latent) within a cell, denoted as the lysogenic part of the viral life cycle. A latent viral infection is a type of persistent viral infection which is distinguished from a chronic viral infection. Latency is the phase in certain viruses' life cycles in which, after initial infection, proliferation of virus particles ceases. However, the viral genome is not eradicated. The virus can reactivate and begin producing large amounts of viral progeny (the lytic part of the viral life cycle) without the host becoming reinfected by new outside virus, and stays within the host indefinitely. Virus latency is not to be confused with clinical latency during the incubation period when a virus is *not* dormant.

Source; Wikipedia contributors. (2023, May 9). Virus latency. In *Wikipedia, The Free Encyclopedia*. Retrieved 12:40, May 30, 2023, from https://en.wikipedia.org/w/index.php?title=Virus_latency&oldid=1153962619

Essential Human Virology ; Some viruses enter a state, known as latency, where they no longer replicate within the cell but remain dormant until the immune system is weakened. Viral replication does not occur during latency, so there are no viral proteins produced to act as antigen and alert the immune system of the infected cell. Viruses can become latent in the initial cell type they infected or in a different cell type near the initially infected cell.

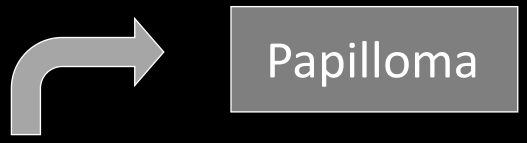
Source; Louten, Jennifer. Essential Human Virology. Netherlands: Elsevier Science, 2022.

Virus latency

From Wikipedia, the free encyclopedia

Virus latency (or **viral latency**) is the ability of a pathogenic virus to lie dormant (latent) within a cell, denoted as the lysogenic part of the viral life cycle.[1] A latent viral infection is a type of persistent viral infection which is distinguished from a chronic viral infection. Latency is the phase in certain viruses' life cycles in which, after initial infection, proliferation of virus particles ceases. However, the viral genome is not eradicated. The virus can reactivate and begin producing large amounts of viral progeny (the lytic part of the viral life cycle) without the host becoming reinfected by new outside virus, and stays within the host indefinitely.[2]

Virus latency is not to be confused with clinical latency during the incubation period when a virus is *not* dormant



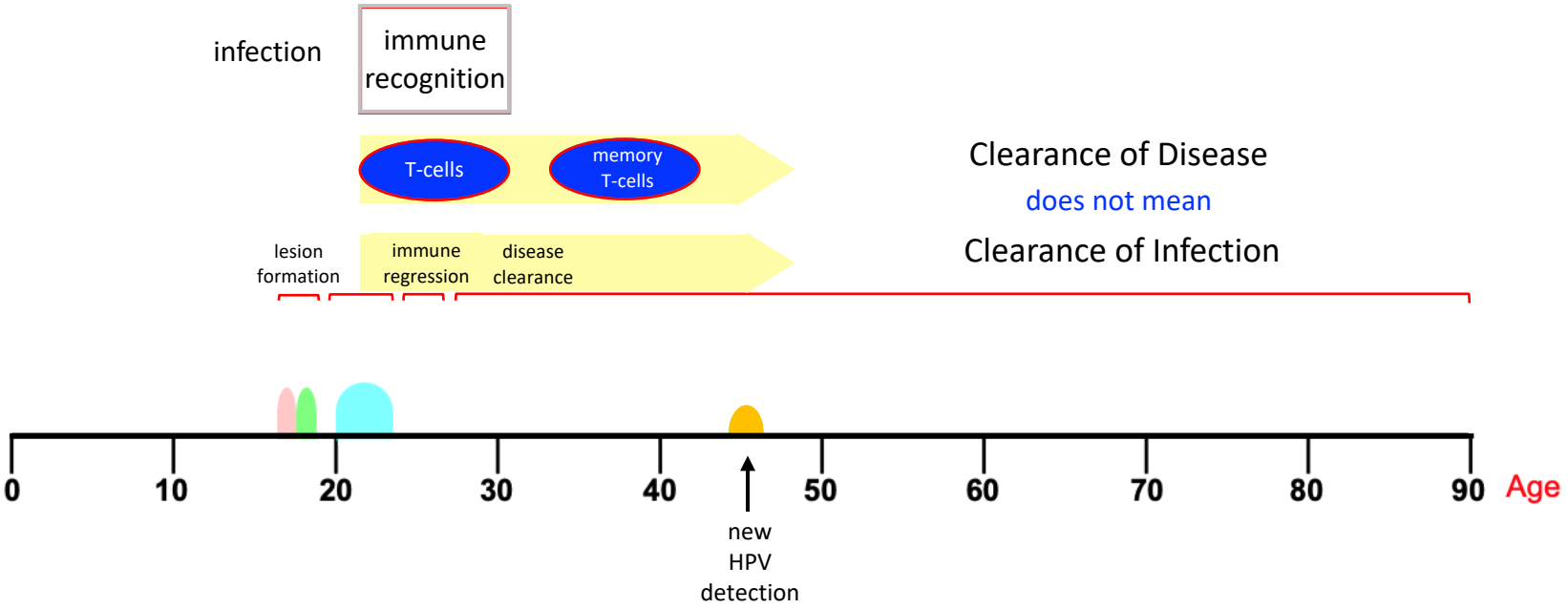
Viral Gene Expression

Alternative Outcomes following Infection

model 1

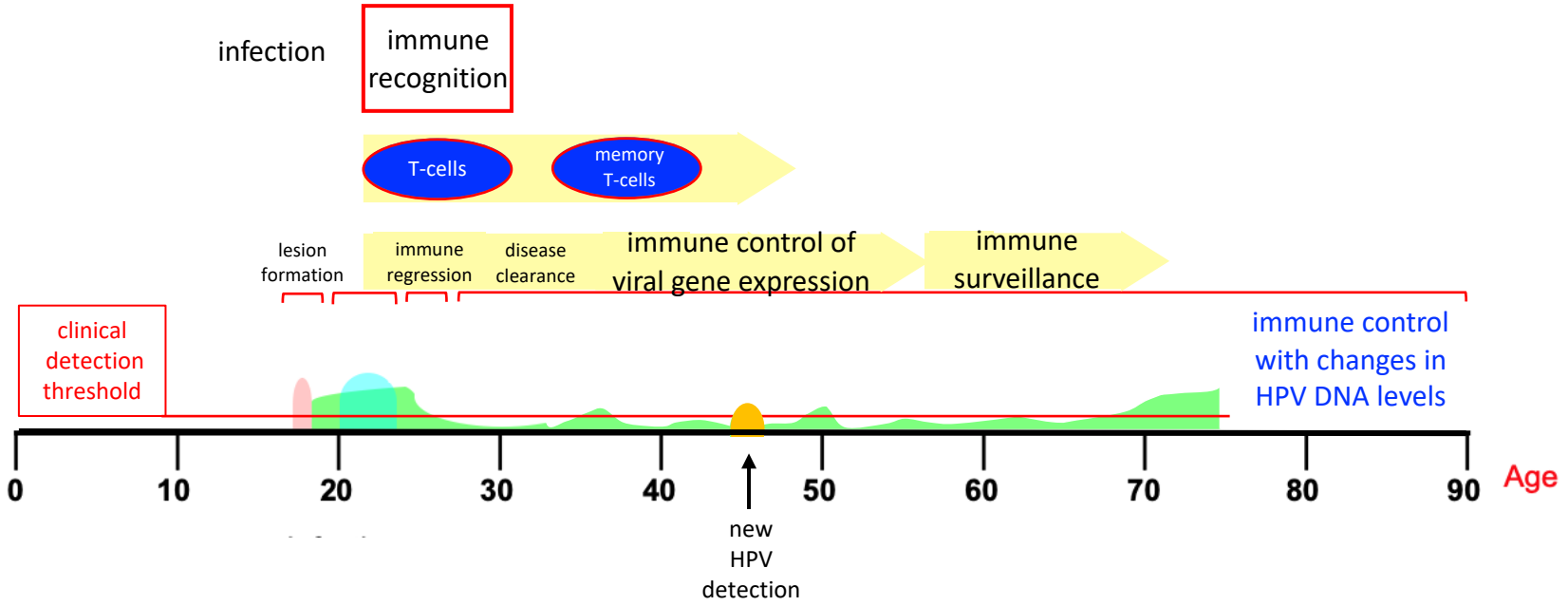
Infection & Clearance

Natural History of Infection During a Woman's Lifetime



model 2
infection & immune control

Natural History of Infection During a Woman's Lifetime

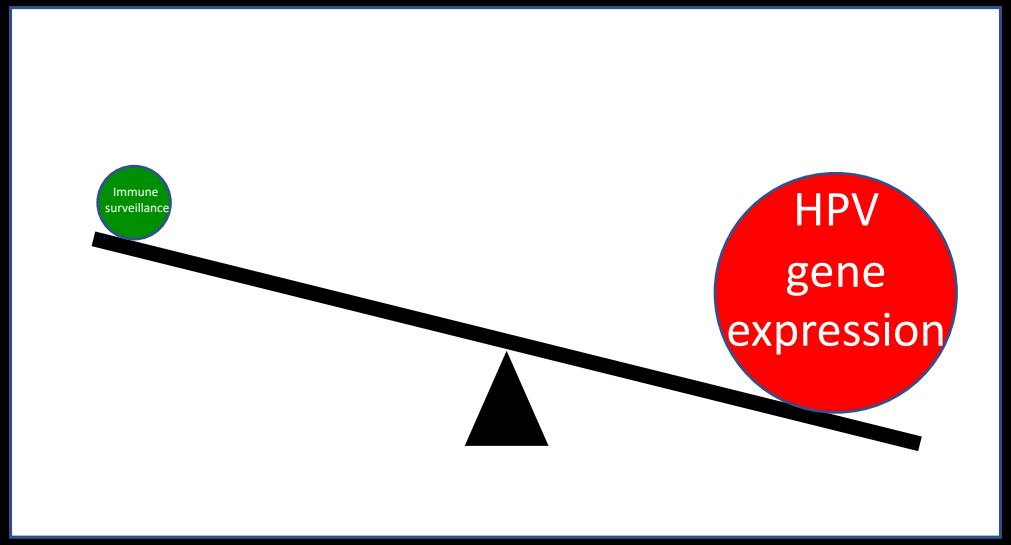


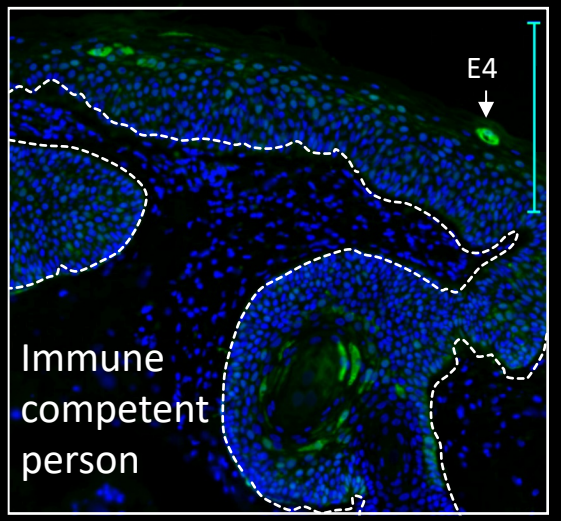
HPV Latency is a form of …

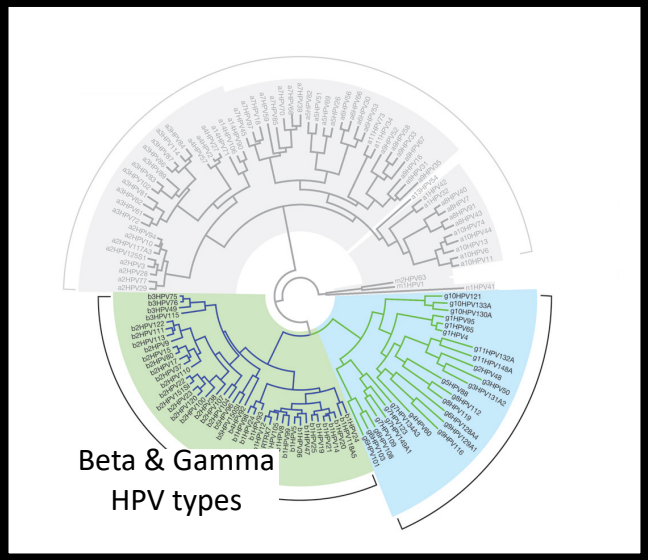
Immune control

An accurate understanding of immune control
is required for the interpretation of HPV DNA test results

Immune Control of Papillomavirus Infections



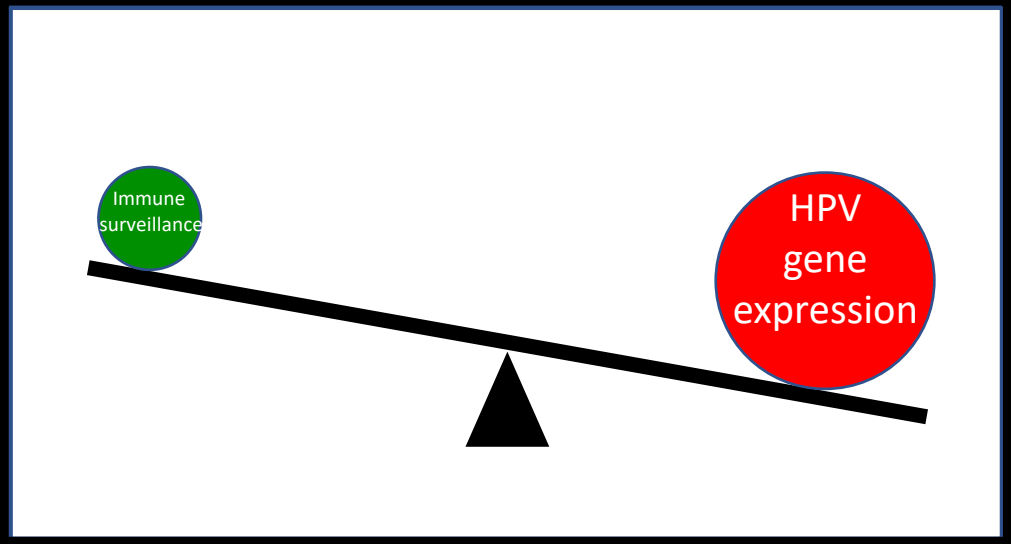


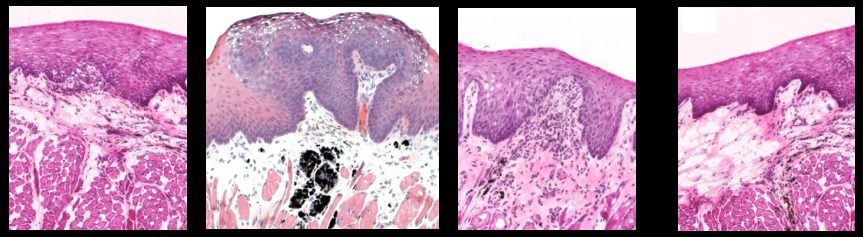


Immune deficient person

Human Beta-papillomavirus infection and keratinocyte carcinomas. **J Pathol.** (2015) 235: p342-54. PMID: 25131163
*Quint KD, Genders RE, de Koning MN, Borgogna C, Gariglio M, Bouwes Bavinck JN, Feltkamp MC. and **Doorbar** J.*

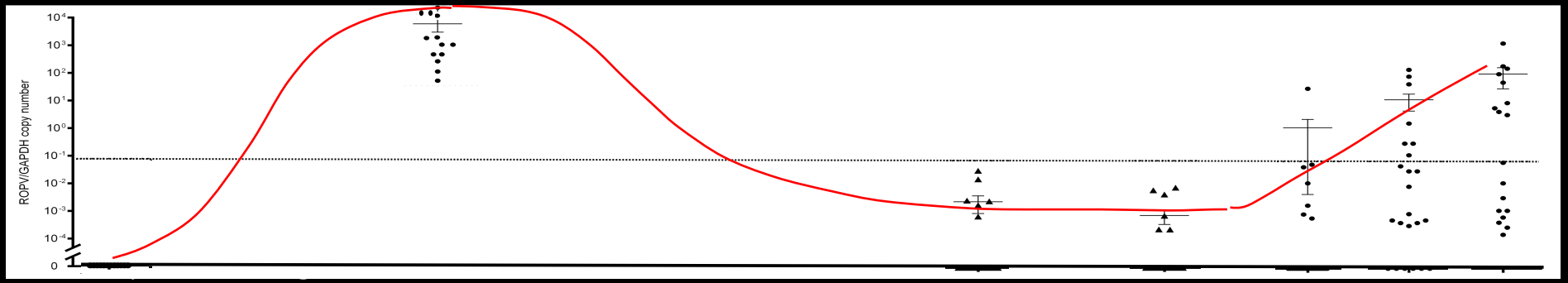
Immune Control of Papillomavirus Infections



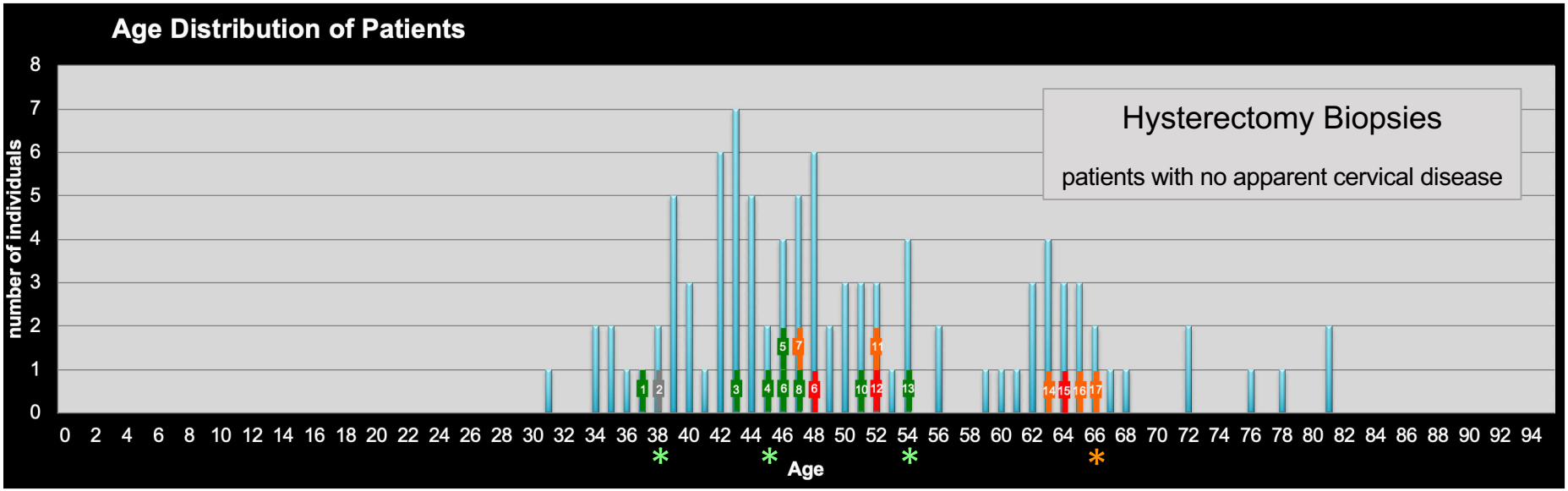


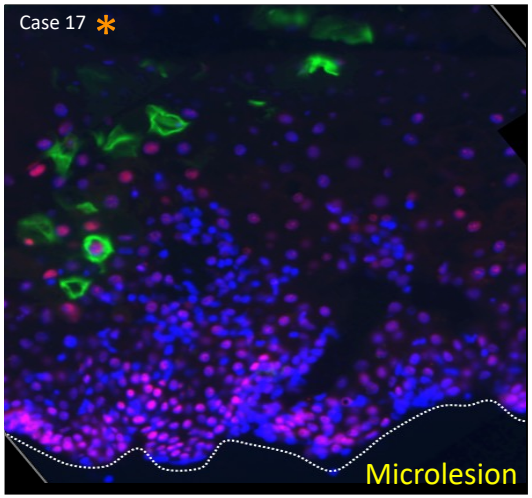
infection lesion formation lesion regression immune control

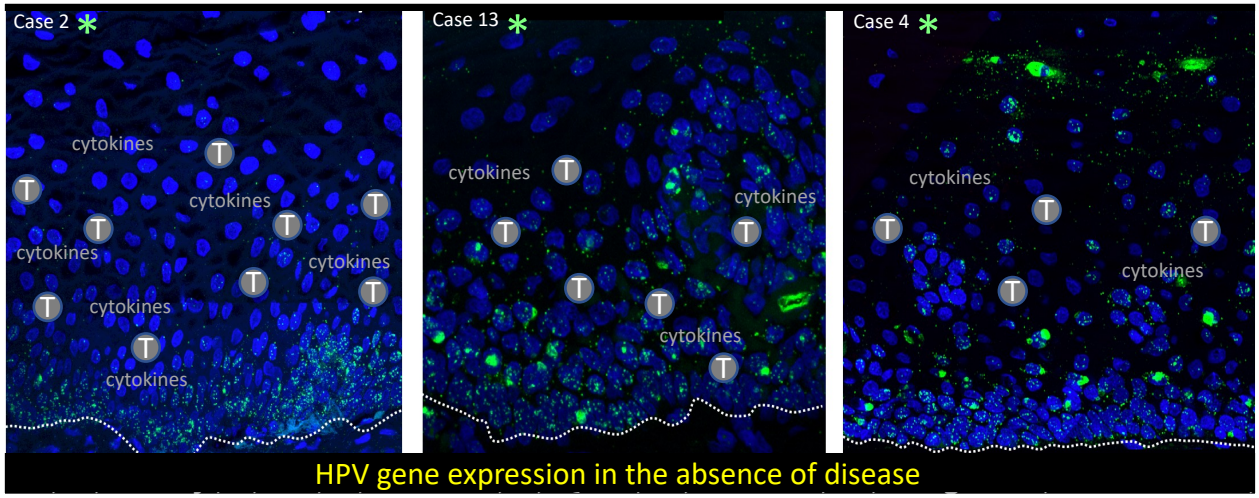
weeks → months/years →

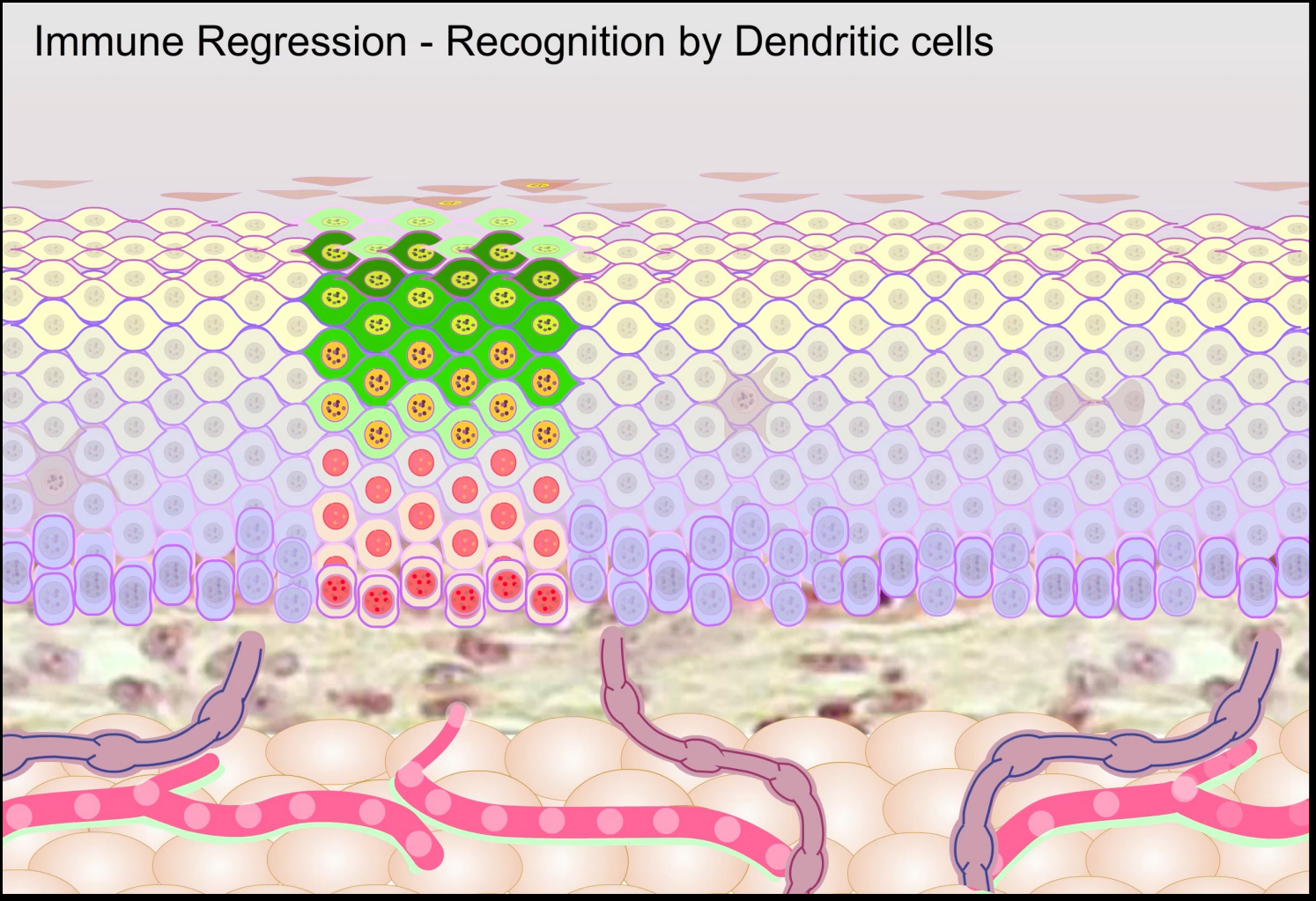


What about High-Risk HPV Infections of the Cervix ?









Immune Evasion

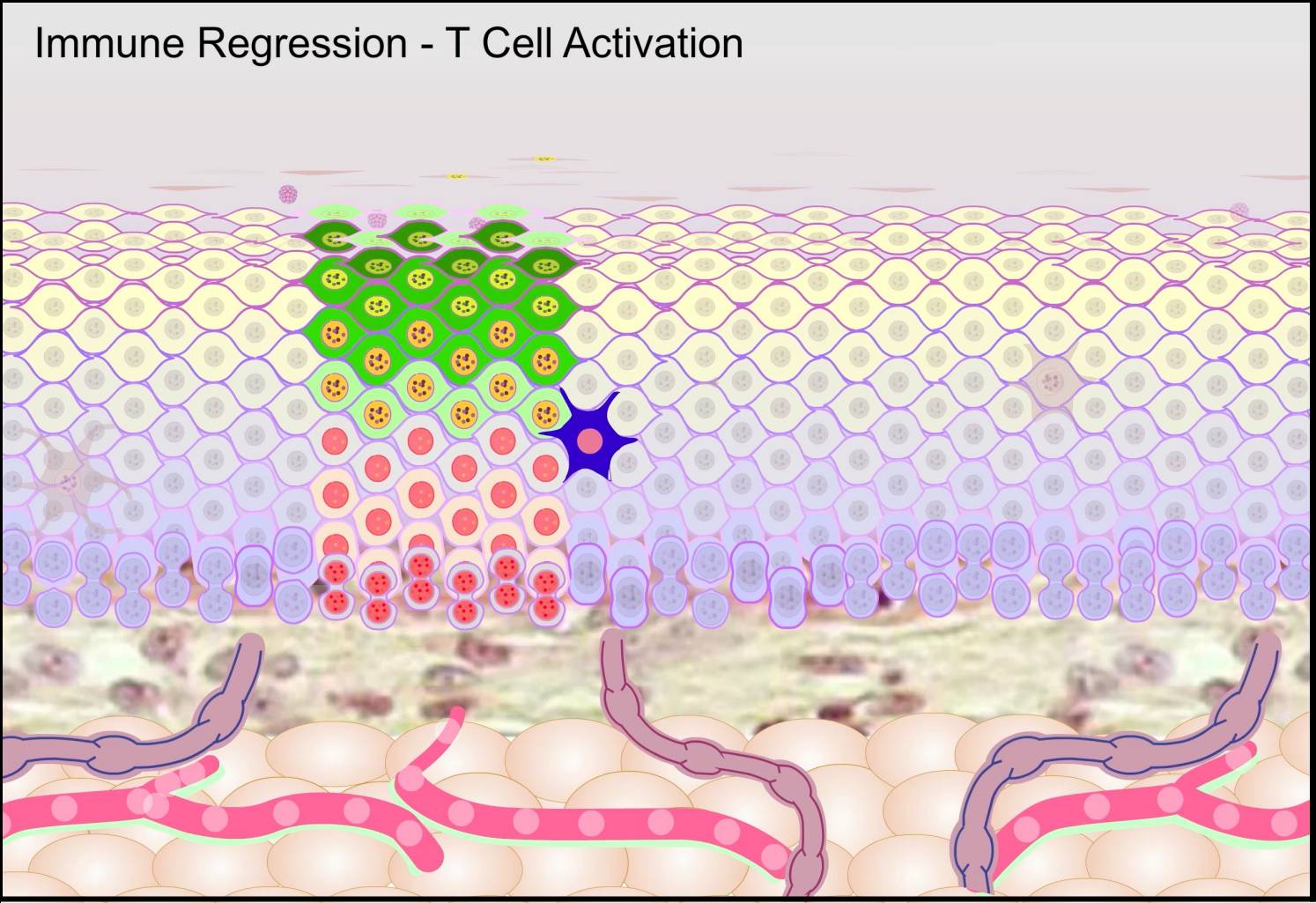
followed by…

Immune Detection

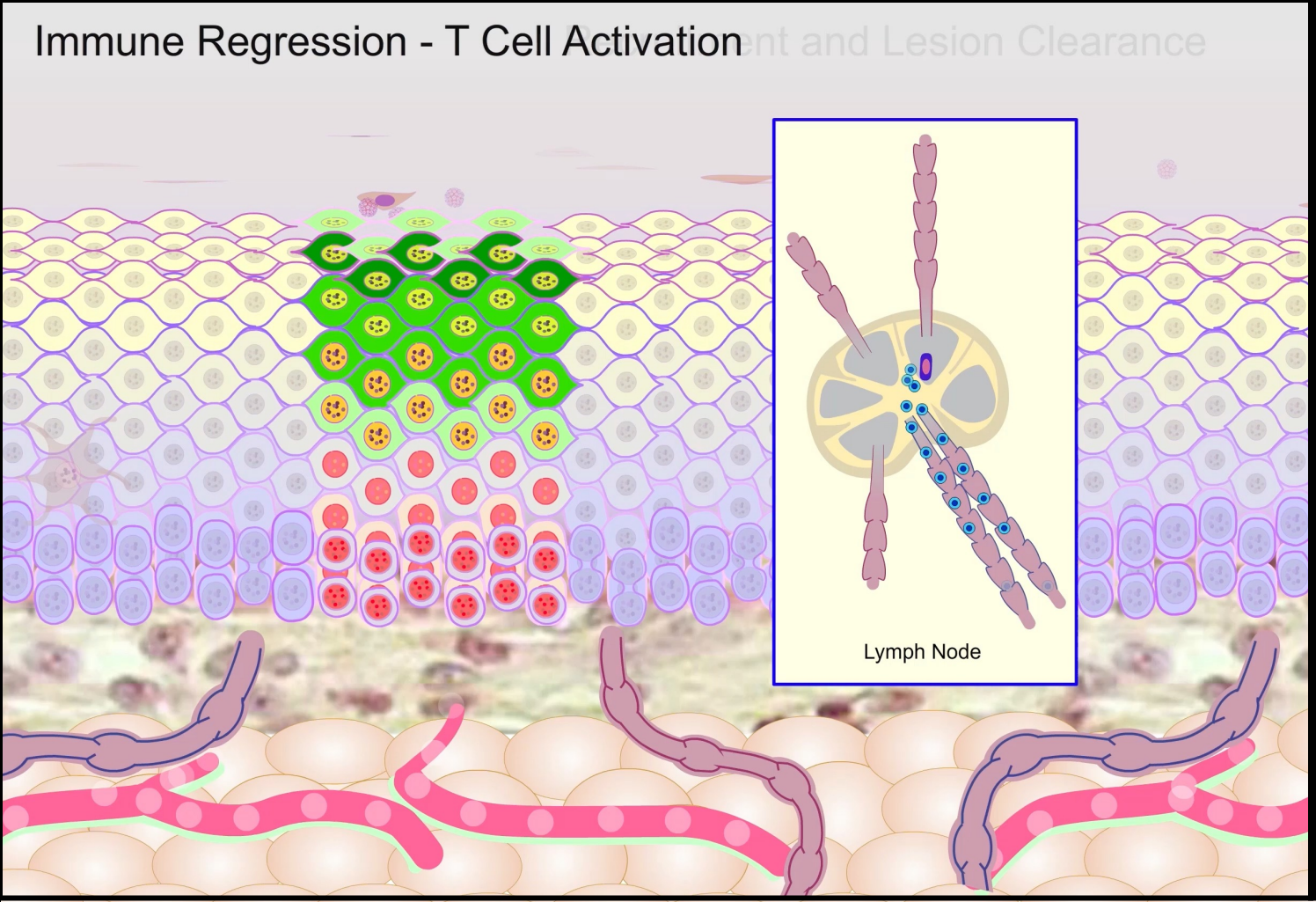
immune-competent host

immune detection

Immune Control of Infection



Immune Control of Infection



T-cell Recruitment

followed by ….

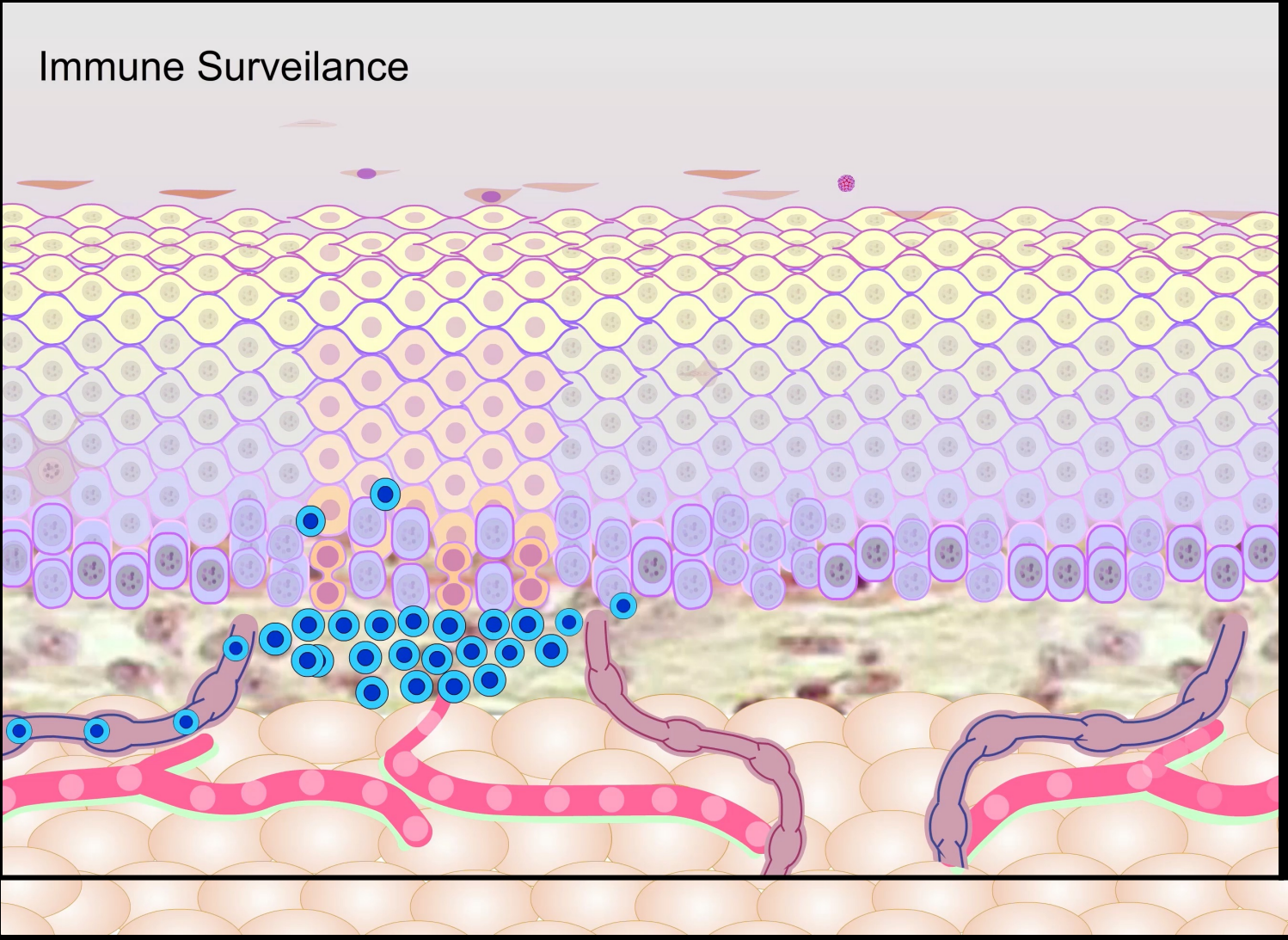
Suppression of Viral Gene Expression

lymphocyte infiltration

Suppression of viral gene expression

immunesurveillance

Immune Control of Infection



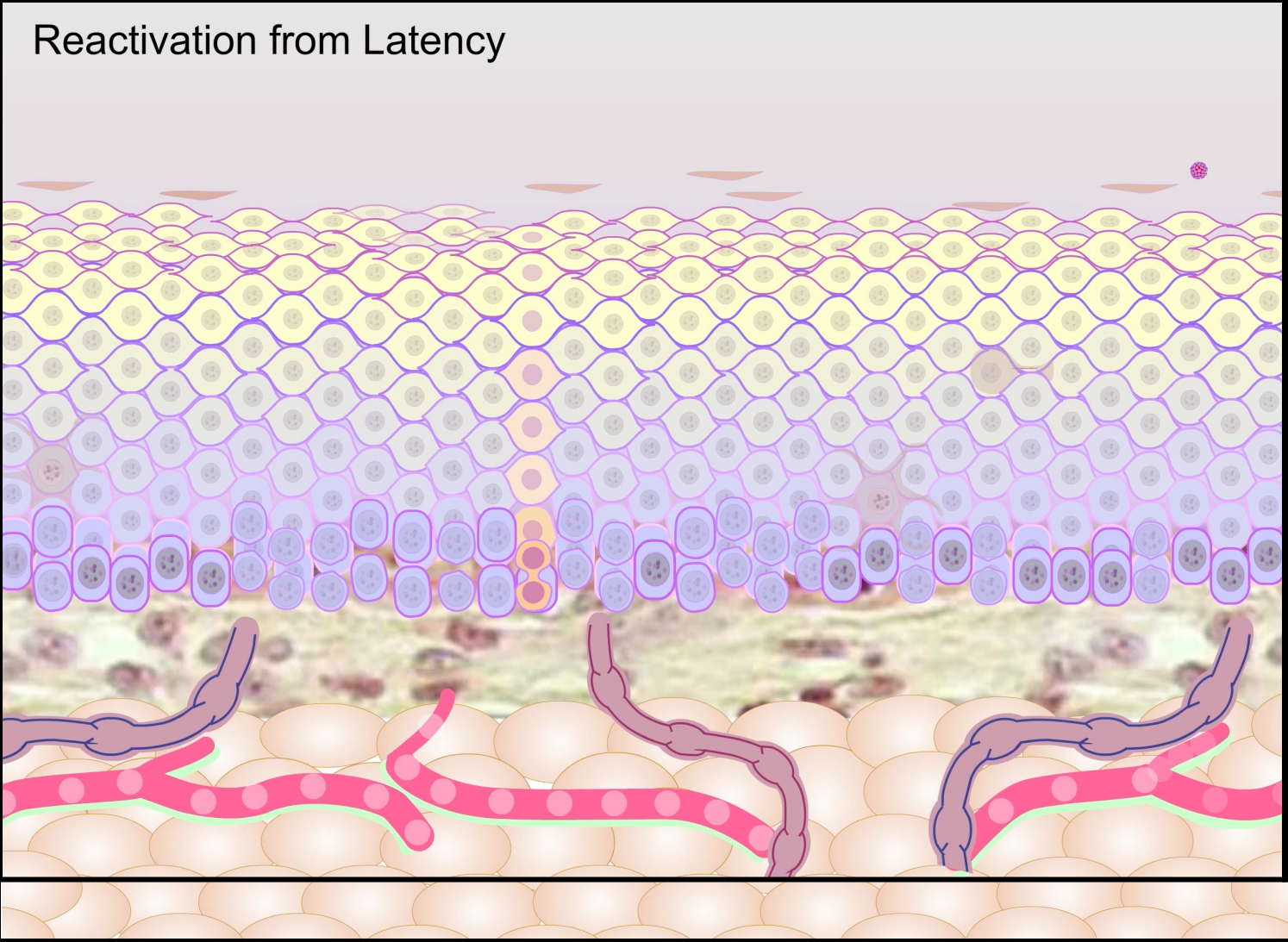
Immune Surveillance

controls

Viral Gene Expression

Decline in HPV infected cells

Immune Control of Infection



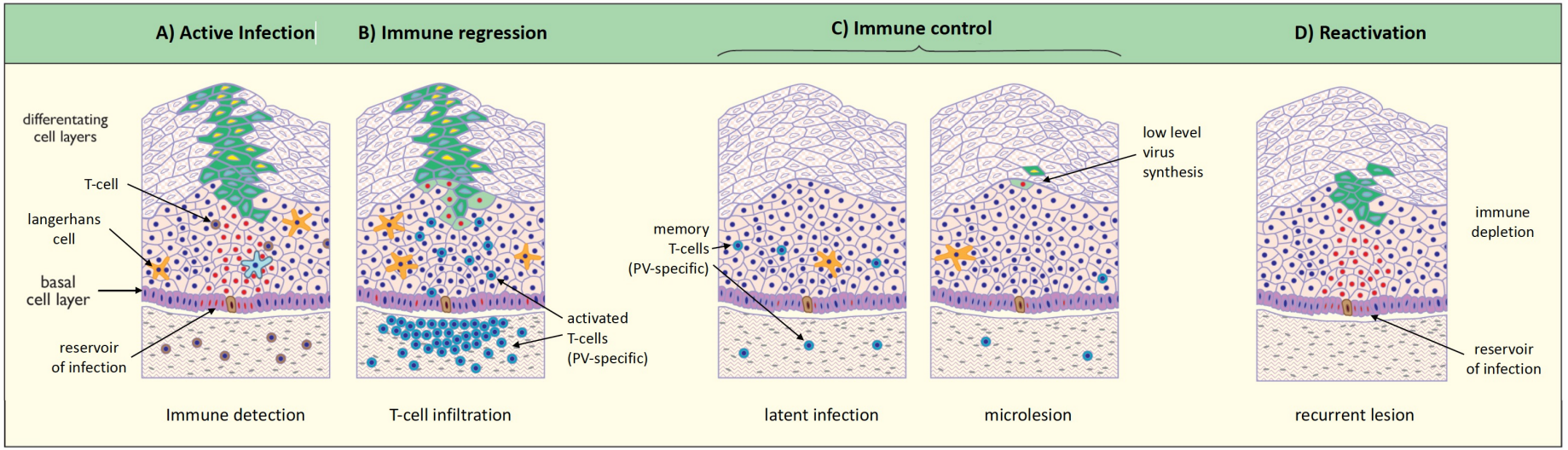
Possible Reactivation

as

Immune Control
Declines

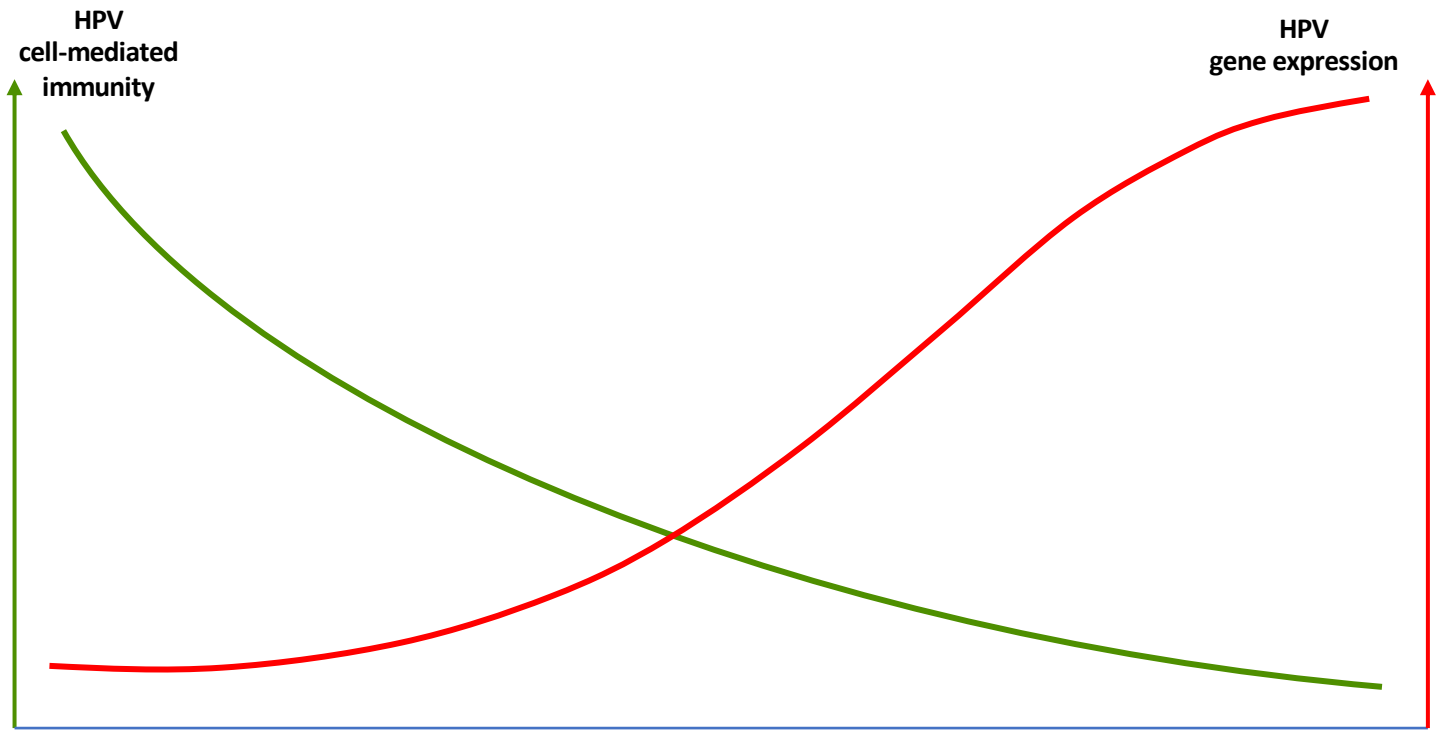
Immune Control of Infection

Current Thinking on HPV Immune Control and Subclinical Persistence



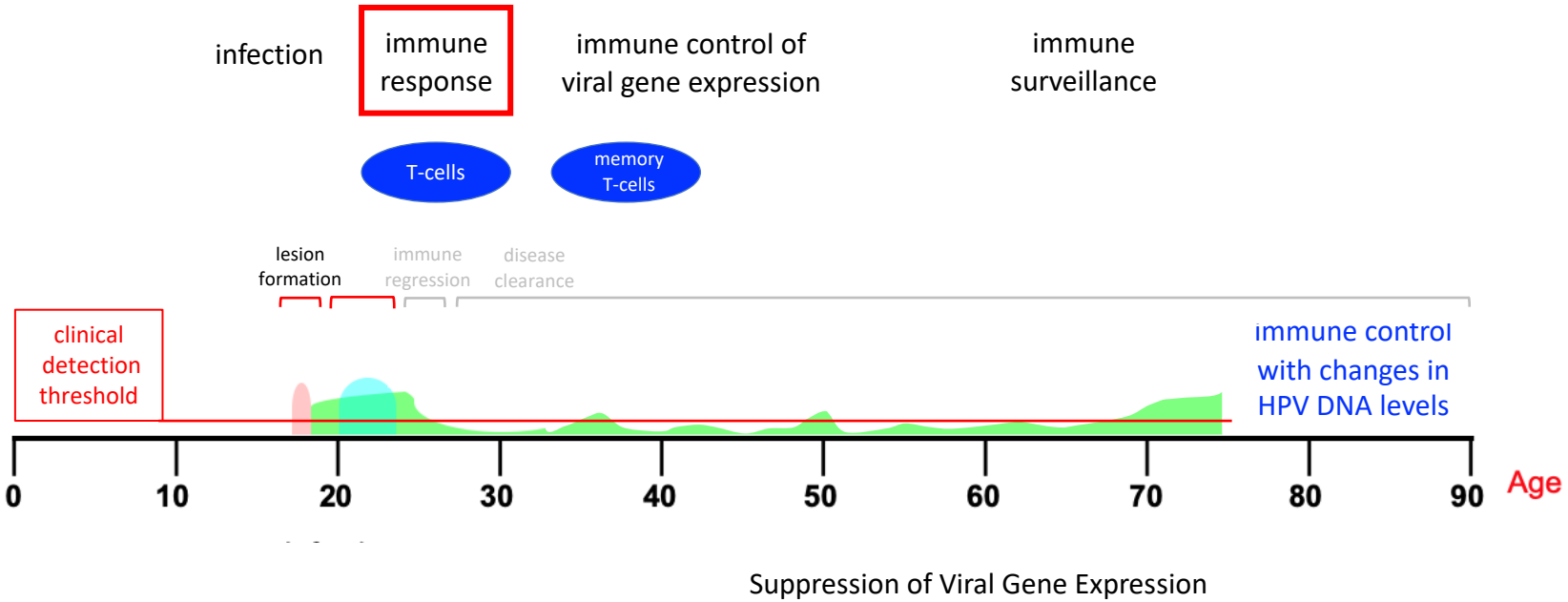
Immune Control of Human Papillomavirus Infection

Current Thinking on HPV Immune Control and Subclinical Persistence



Immune Control of Human Papillomavirus Infection

Current Thinking on HPV Immune Control and Subclinical Persistence



Suppression of Viral Gene Expression

CONCLUSIONS

1 Human Papillomaviruses cause Chronic infections

2 ….. and clearly, they can persist in the body as ….

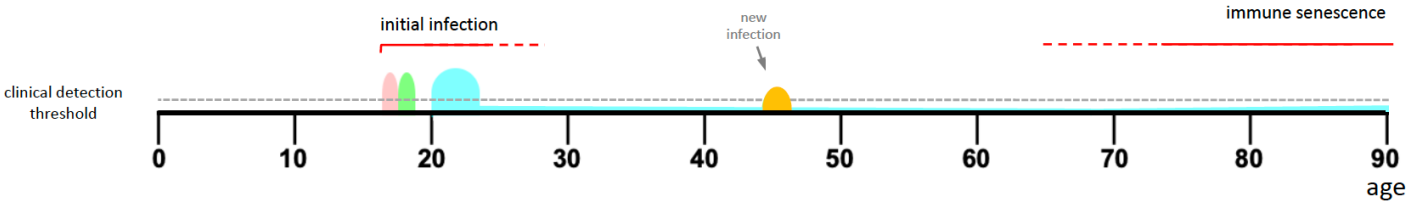
papillomas flat warts LSIL HSIL

Clinically Apparent Infections

CONCLUSIONS

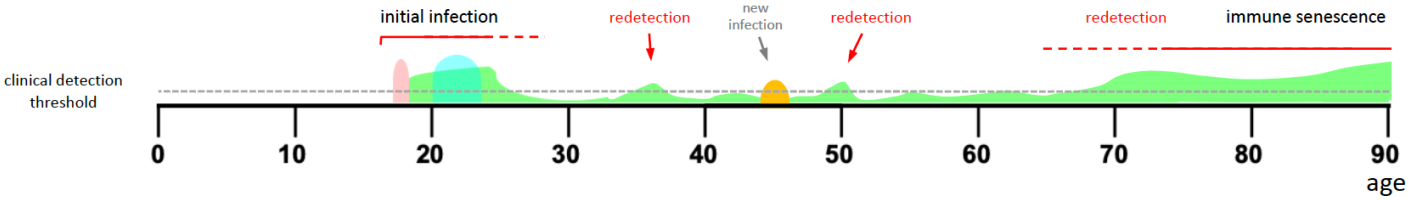
Usual Outcomes of Infection - Disease Clearance and the Immune Control of Papillomavirus Infection

i) Immune-mediated **disease clearance** is accompanied by **the apparent clearance** of infection (immune control without redetection) or **infection-clearance**



HPV DNA levels
remain below
clinical detection threshold

ii) Immune-mediated **disease clearance** is followed by **immune control of Infection**, with sporadic HPV redetection as immune surveillance fluctuates



HPV DNA levels
fluctuate above and below
clinical detection threshold

THANK YOU

Molecular Studies

Model Systems of Disease

- Nagayasu Egawa
- Heather Griffin
- Taylor Saunders-Wood
- Christian Kranjec
- Isao Murakami
- Yuwen Chen
- Sherry Yin
- Kara Zheng

Disease Biology

Silvia Sanjose

Lawrence Banks

Sheila Graham

Mark Schiffman

Clinical Studies

Cervical Tissue Tropisms

Olaf Reich

Sigrid Regauer

- Heather Griffin
- Ademola Aiyenuro

Ocular Biopsies

Hardeep Muneer

Cervical Disease Recurrence

Jaume Ordi

Marta Del Pinto

Tanvier Omar

Vulvar Biopsies

Jacob Bornstein

Mario Preti

Oropharyngeal Biopsies

Mathias Lechner

Terry Jones

Anal Biopsies

Tamzin Cuming

Gary Whitlock

Cutaneous/Beta HPV

Catherine Harwood

Animations

Caroline Walker

Joe Brock

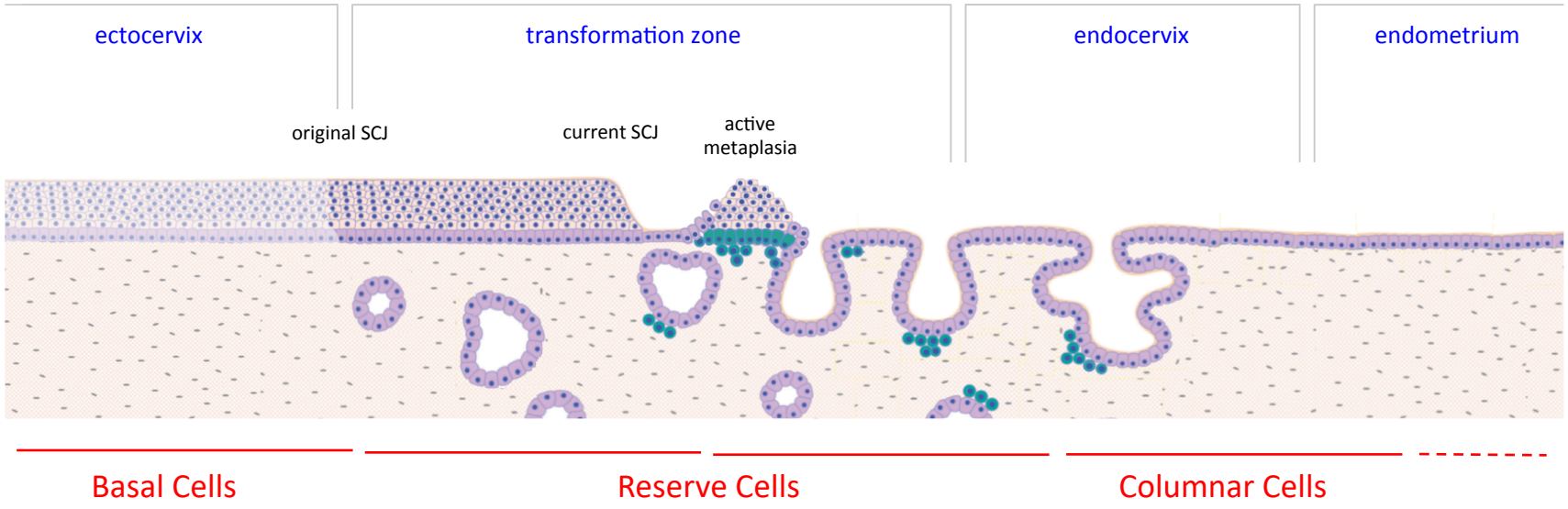
Biomarkers/Patch Sampling

Robin Crawford

Aslam Shiraz

MRC Medical Research Council
CANCER RESEARCH UK
act Addenbrooke's Charitable Trust

Summary of Our Current Thinking; How Papillomaviruses Cause Disease



Site of Infection affects Disease Outcome

Doorbar J, Griffin H. (2019) Refining our understanding of cervical neoplasia and its cellular origins. Papillomavirus Res. 2019 Jun;7:176-179. PMID: 30974183